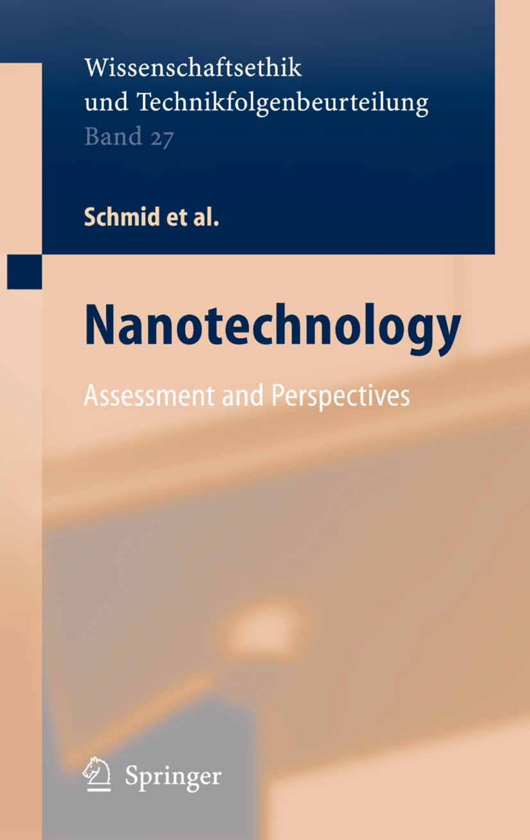

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Band 27

Schmid et al.

Nanotechnology

Assessment and Perspectives

Springer

Wissenschaftsethik und Technikfolgenbeurteilung
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U. Simon · V. Vogel · D. Wyrwa

Nanotechnology

Assessment and Perspectives

With 189 Figures

Springer

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Europäische Akademie

zur Erforschung von Folgen wissenschaftlich-technischer Entwicklungen
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The Europäische Akademie

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Acknowledgement

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Preface

The Europäische Akademie zur Erforschung von Folgen wissenschaftlich-technischer Entwicklungen Bad Neuenahr-Ahrweiler GmbH is concerned with the study of the consequences of scientific and technological advance both for the individual and social human life and for the natural environment. It intends to contribute to finding a rational way for society to deal with the consequences of scientific and technological developments. This aim is mainly realised by proposing recommendations for options of action with long-term social acceptance. The results of the work of the Europäische Akademie is published in the series "Wissenschaftsethik und Technikfolgenbeurteilung" (Ethics of Science and Technology Assessment), Springer Verlag.

This book is dedicated to Nanotechnology, considered by many as a key to the 21st century. This fascinating field of research and development is driven by inputs from different academic disciplines. Accordingly, conformal with its acknowledged work principle, the Europäische Akademie set up an interdisciplinary project group of recognised scientists from various European universities and other institutions to tackle the issue. I would like to give my thanks to Professor Dr. Günter Schmid (group chair), Professor Dr. Harald Brune, Professor Dr. Holger Ernst, Professor Dr. Armin Grunwald, Dr. Werner Grünwald, Professor Dr.-Ing. Heinrich Hofmann, Professor Dr. Harald Krug, Professor Dr. Peter Janich, Professor Dr. Marcel Mayor, Professor Dr. Ulrich Simon and Professor Dr. Viola Vogel for their cooperation as well as to Dr.-Ing. Wolfgang Rathgeber for coordinating the project on behalf of the Europäische Akademie and to Dipl.-Chem. Daniel Wyrwa for assisting the group. Special thanks go to Katharina Mader and Friederike Wütscher for the editorial work in preparing the text for print.

Bad Neuenahr-Ahrweiler, January 2006 Carl Friedrich Gethmann

Foreword

Technological challenges, resulting from political, social, economic or ecological demands, can nowadays only be mastered by a strong integration of different scientific disciplines. This is especially the case in Nanotechnology, where the situation is arbitrarily complex due to the fact that Nanotechnology ranges over all disciplines of natural sciences including medicine and engineering. In nanoscience and -technology the classical differences between physics, chemistry and biology lose their significance, synonymous with a novel view of natural sciences. Nanotechnology is therefore much more than an other kind of discipline, based on nanoscaled products in the sense of a simple continuation of microtechnology. This description is by far too simple. The incredible chances and possibilities offered by Nanotechnology make it indeed the key technology of the new century, as is frequently reported.

Faced with the accelerating developments in nanoscience and, in consequence, in nanotechnology, the Europäische Akademie Bad Neuenahr-Ahrweiler GmbH started an initiative with the aim to evaluate the state of the art in nanoscience and nanotechnology, considering not only the natural sciences, but – to the same extent – philosophical, ethical, toxicological and, last but not least, economic aspects. Besides the description of the state of the present situation, the book also considers possible future developments as far as they can be foreseen and gives recommendations to decision makers.

The working group, consisting of internationally acknowledged experts from all fields of nanoscience and -technology, began its activities on 1st July 2003 and organized from this time on monthly working sessions. The project was finished on 31st December 2005. On 8th October 2004, a Mid-Term Meeting was held in the Academy with prominent representatives of all fields of nanotechnology for getting response and valuable critics on the project at that stage. For this unrenouncable help the group would like to thank Dr. Gerd Bachmann (VDI-Technologiezentrum Düsseldorf), Professor Dr. Peter Bäuerle (Universität Ulm), Professor Dr. Paul Borm (CEL Technohouse, Hogeschool Zuyd), Professor Dr. Harald Fuchs (Universität Münster), Professor Dr. Uwe Hartmann (Universität des Saarlands, Saarbrücken), Professor Dr. Christoph Hubig (Universität Stuttgart), Professor Dr. Martin Möhrle (Universität Bremen), Professor Dr. Reinhard Nesper (ETH Zürich), Professor Dr. Andreas Offenhäuser (Forschungszentrum

Jülich), Dr. Markus Pridöhl (Degussa AG, Hanau), and Dr. Eberhard Seitz (Forschungszentrum Jülich).

Personally, I am anxious to thank the members of the working group for the enthusiastic cooperation over two and a half years, the valuable contributions during the numerous intense discussions, the patience, and the absolute will to bring this difficult task to a successful end. Special thanks go to Dipl.-Kfm. Nils Omland (WHU Koblenz) for his assessment of patent data used in this study.

The group's work was exemplarily supported by the co-workers and members of the Europäische Akademie, among numerous others especially Mrs. Margret Pauels, Dr.-Ing. Wolfgang Rathgeber and Dr. Gerd Hanekamp. Their overwhelming hospitality contributed substantially to the effective study progress. The excellent working atmosphere caused regular anticipation of the next meeting by each group member.

Essen, December 2005 Günter Schmid

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Appraisal and Recommendations

By meeting at the nanoscale, the differences between classical disciplines, from physics via chemistry to biology, from engineering to medicine, are disappearing. Due to this merger of disciplines, our approaches to science and technology are fundamentally changing. The newly created knowledge base and resulting technological advances will revolutionize many sectors of our society. Consequently, the challenges and opportunities are multidimensional: scientific, technical, economical, cultural, ethical, educational and risk related.

Scientific and Technical Needs

Research and development at the nanoscale will be key drivers to innovation and ultimately economic vitality. Central to such innovations are (a) nanotools to explore, analyze and manipulate at the nanoscale, (b) molecular assembly processes to construct novel materials and devices from nanoscale building blocks, (c) new concepts for information technology, (d) technologies to interface biological and synthetic systems and finally, the creation of a new knowledge base that will lead to major innovations in biological sciences and medicine.

Nanotools: The improvement of existing and the development of new tools is of decisive importance for any kind of techniques, however, it is the more the case for Nanotechnology. The state of the art in Nanotechnology could only been reached by fundamentally new tools. Analytic tools are the driving forces in Nanotechnology. For instance, without the development of scanning tunnelling microscopy (STM) and subsequently a dozen or more other scanning probe techniques, Nanoscience and -technology on the present level are unthinkable. Improved spectroscopic tools have become as important as modern high resolution electron microscopic devices allowing us the observation of biosystems in unexpected details. Modern nanotools in bionanotechnology will allow us to quantitatively understand how cells work. Intensive further research and development of nanotools is an unrenounceable condition for further progress in Nanoscience and -technology.

Molecular assembly: The assembling strategies are in part inspired by natural processes, from where we can learn how molecular systems interact in a predictable way in order to generate manifold structures and functionalities which range from simple control and molecular recognition to complex properties. Hence, future research should not only be focused on the duplication of biotic design principles, but nature's strategies shall inspire new solutions how to engineer at the nanoscale. Technologically relevant problems that could be addressed by bioinspired approaches include the self-assembly of three-dimensional electronic circuits or the development of new concepts of information technology beyond optics and solid state electronics. Going beyond biology, self-assembly strategies further need to be combined with micro- and nanofabrication tools which will ultimately result in materials and devices with integrated nanoengineered building blocks. A particular challenge in assembling nanoscale building blocks is to generate functions that go beyond the capabilities of the individual building blocks. Research on this topic has to aim at the development of quantitative and synthetic molecular construction techniques that lead to novel physical, chemical and biological functions. This will enable to combine the complex functionalities of large organic or bioorganic molecules with the size specific properties of inorganic nanoscaled objects following reliable design rules resulting in new emerging systems and properties.

Information technology: Information technology and enhanced miniaturization will profit from the understanding of nature's design and system's integration principles. Future nanoelectronics will essentially depend on the development of design rules for the set-up of complex architectures compatible with scalable technologies for the synthesis of the respective building blocks. This will by far exceed the present day paradigm of information exchange, since three-dimensional architectures will enable fundamentally new logical concepts. Furthermore, quantitative simulations and model building, as well as the integration of the myriad of digital information require major computational efforts.

Interfacing biology with engineered systems: Of particular interest is the interface between synthetic and living systems. Interfacing living cells with engineered nanosystems is needed for many biomedical applications, from tissue engineering, drug delivery to sensors implanted within human tissues to obtain real-time information on biological processes and functions. Considering the cost explosion of the health care sector, microfabricated platforms with integrated nanoscale systems are needed to build portable devices at low cost to analyze samples from body fluids and gases without major time delays.

Nanotechnology in biosciences and medicine: Today's medicine is often focused on developing therapies for preexisting diseases, often treating symptoms rather than curing the disease. In part, this is due to the lack of a comprehensive understanding of how cells work and how cell functions are regulated. Advances in Nanotechnology provide new tools to bring about major changes leading to a transitioning of biology into a quantitative science. This includes how cellular building blocks are chemically modified typically in a spatiotemporal dependency, how they facilitate and interact in signaling pathways and other cellular processes, and how these building blocks are assembled and disassembled into larger functional units. Deciphering the hierarchical architecture of molecular networks and understanding the regulation is needed for the comprehension of biological systems on the nanometer scale. The technological advances will come from various disciplines and include the development of new nanoscale probes and imaging techniques in combination with intelligent computational tools to analyze molecular events in living cells with high spatial and temporal resolution. They will be complemented by new devices for in- and exvivo sensing and diagnostics. The goal is to ultimately derive the engineering principles that control and regulate cellular functions, from growth, differentiation, motility, contractility, to apoptosis. The biggest longterm pay-off for society might come from the early detection of diseases and their more effective treatment.

Commercial Needs

The patent analyses have shown that Europe is lagging behind Japan and the US in many fields of Nanotechnology. This finding could result from different perceptions about the effectiveness of patents as an important instrument for the creation of competitive advantages. Managers and policy makers must understand that professional intellectual property management is essential for the successful commercialization of Nanotechnology. Policy makers can give support by 1) creating a strong and attractive intellectual property regime, and 2) by providing the right intellectual property infrastructure at research institutions:

A strong intellectual property regime makes it possible for inventors to get an effective patent protection in all fields of Nanotechnology. Inventors can only leverage the advantages of patents (e.g., by means of licensing or the exclusive offering of products) in the field of Nanotechnology, if patent protection is legally strong. The attractiveness of patent protection is further impacted by the efficiency (time and money) of the patenting process at the various patent offices. The European patent system is not favorable to inventors, start-up firms and SMEs, because a common European patent does not exist and the costs of obtaining a European patent are too high, especially compared to the US. This institutional obstacle puts European inventors in an unfavorable position when it comes to protecting and commercializing new discoveries in the field of Nanotechnology.

Patents are an important instrument for knowledge protection and the creation of competitive advantages in many industries. Empirical research suggests that professional patent management and a strong portfolio of high-quality patents are important drivers of business performance in high-tech industries (Ernst et al. 2005; Shane 2001). These findings should raise the awareness of the value of intellectual property among scientists and managers and must lead to initiatives to improve patent management in firms and research institutions. Professional patent management especially requires the establishment of the right organizational structures and the corresponding processes to handle patent-related matters in the R&D process. Start-up firms, SMEs and research institutions should benchmark their patenting activities against existing best practices in order to increase the proficiency of their patent management (Ernst et al. 2005).

The relatively low patenting activity in Europe should not be viewed as an indicator of inferior research performance. The analysis of scientific Nanotechnology publications clearly revealed that European scientists produce the most scientific publications in many fields of Nanotechnology. This finding leads to the conclusion that Europe faces the problem of transferring research results consequently and effectively into development and subsequently into commercial applications. European research institutions must therefore increase their willingness and their possibilities to move research results into the subsequent development of new products. This requires a change in culture, incentives and structures in many research institutions. A critical aspect in this regard is that it takes good management to turn research results into a successful new product (Brockhoff 1999; Hauschildt 2004). A scientist may not have the motivation or the capabilities to build up a management team or to found a start-up to commercialize research results. To avoid this pitfall, the formation of cross-disciplinary teams (esp. scientists and business people) at research institutions must be encouraged in order to successfully found and to spin-off start-up firms. New forms of collaborations between established firms and research institutions should be established in order to get market feedback early in the research and development process and to foster the knowledge transfer from research institutions into firms. Finally, the establishment of professional and capable technology transfer centers at research institutions, as e.g. in the US, can further improve the transfer of Nanotechnology from research into commercial applications.

Societal and Ethical Aspects

The further development of Nanotechnology should be accompanied by continuous research on the impact on environment and health as well as on ethical and political questions associated with possible risks, but also in view of the expected benefits.

Currently, classical risk assessment is – according to knowledge gaps concerning hazards resulting from nanoparticles – not applicable in the field of Nanotechnology. Quantitative measures of the probability of damage and of the extent of possible hazards are not yet available. Insofar it is not surprising that lively discussions about the applicability of the “strict precautionary principle” take place in the industrialized countries. According to our analysis and to the review of the state of the art in toxicological research on nanoparticles given above we do not see a “reasonable concern” which would legitimate hard measures, like a moratorium, but with respect to responsibly dealing with artificially designed, new nanoparticles specific caution is required. Such particles should be handled analogously to *new* chemicals even in case that the chemical composition is well-known beyond the nano character. Dealing with new nanoparticles is still based on a case by case approach because established nomenclature and classification schemes are not well-prepared to be applied to nano-particles. Beyond risk management and regulation the level of public risk communication has to be observed carefully because irritations in this communication could have dramatic impact on public acceptance and political judgment. It is necessary to distinguish between scientifically assessed risks and the public perception of risk, which has to be taken seriously even in case that it seems to be inadequate against the results of scientific risk assessment.

Knowledge about risks includes knowledge about the validity and the limits of that knowledge. Communicative and participative instruments of technology assessment could help improving mutual understanding and public risk assessment. Scientists should not leave these discussions to the mass media and politicians but should engage themselves in those debates.

Education

Education in the field of Nanotechnology is established on the level of bachelor, master and doctoral schools at only a few places. The reason for this can be found in the fact that Nanotechnology is a young research field with a very high degree of interdisciplinarity. Therefore, the content of teaching is not well defined and a job description for a nanoscientists or an engineer in Nanotechnology is also missing. Because the content of teaching depends very often on the background of the institute or department responsible for the courses, curricula focused on Nanoscience like physics of small systems, or on nanostructured materials and finally such that try to fulfil the demand for an interdisciplinary program in Nanotechnology are offered. The latter have the difficult problem to select the right courses as well as the right level of difficulty and of being too large and, because of time limitations, too superficial.

Recommendations

1. The project group defines Nanotechnology based on effects and functions independently of any longitudinal measure. Size is relevant only derivatively and thus is not addressed in the definition. It is recom-

mended that this definition as Nanotechnology in the narrower sense be used to specify the field. This narrowing of the scope is not supposed to preclude priority settings in research funding (s. chapter 2).

2. *Funding in Nanotechnology in Europe is mainly restricted to top-down target oriented programs. However, diversity of research approaches is a crucial requirement for knowledge creation and innovation. Therefore, funding priority should be given to basic research on a broad level and basic knowledge has to be better transferred by engineering science and technology into products.* This step has not yet been taken over by most of the industrial partners and the gap between basic research and application is still existing for many of those nanosystems with new functions. *It is therefore recommended to strengthen the efforts of transient research in this field and to encourage industry to better close the information gap between basis and practice* (see chapter 3).
3. *It is also recommended to encourage the change in culture and incentives at universities and research institutions which are dealing with Nanotechnology versus new forms of collaboration to stimulate the transfer between scientific institutions and facilitate the contact to the industry (s. also chapter 4).*
4. Materials (section 3.1) and their specific properties in the nanoregime create novel applications preferentially in the field of information storage systems (section 3.2), in biology and in medicine (section 3.3). The research in each of these fields needs profound knowledge of the experts, but for applying the materials an interdisciplinary knowledge exchange is indispensable. *It is recommended to create a pool of experts from the different branches who are acquainted with research and development and the industrial needs to support decision makers in politics and enterprises.* This kind of proceeding could also be developed for other potential fields of application (s. section 3.4) and *would help (s. recommendation 2) to close the gap between basic research and industry.*
5. Many more of the inventions and innovations which have been and will be made in Nanoscience and Nanotechnology have to be patented to secure the intellectual properties of the inventor, the university and/or the industry. *As in Nanotechnology patents already have to be applied in the early stage of research and development, it is therefore recommended to establish a more attractive European Intellectual Property regime in order to foster the commercialization of Nanotechnology inventions and to improve the competitive position of European inventors and firms (s. chapter 4). In regard to recommendation 2 it is also recommended to encourage and facilitate a professional Intellectual Property Management at universities and research institutions to support researchers in their business venture to transfer knowledge into application.*
6. There is a tendency to reduce research activities at the universities. This is problematic for two reasons: Firstly, excellence in teaching is tightly cou-

pled with excellence in research. Secondly, diversity in basic research originates mainly from universities. Consequently, politics must provide sustainable strengthening of research capabilities at the universities (s. chapter 7).

7. The many and engaged debates about societal and moral aspects of Nanotechnology show a high degree of uneasiness among the population. Possibly adverse effects of nanotechnological products are presently discussed in the public mostly on the basis of speculations and many of these debates are very emotional and not based on facts. It is therefore recommended to identify risks in studies performed in related institutions and to place future debates on "facts and figures" so that society is informed in a transparent and understandable way by experts who are trained for this (s. also recommendations 8–10).
8. Knowledge on the behavior of nanomaterials in living organisms and in the environment is largely missing. Research is now starting only at selected institutes and rarely as a combined activity between materials and bio-, medical research. *It is recommended to foster a common research based on similar standards so that results can be compared and industry can use the recommendations in their production of Nanotechnology based products. Regulations have to be reconsidered according to the outcome of research (s. chapter 5).*
9. *ELSI (Ethical, Legal and Social Implications) activities should be specifically dedicated to recognisable ethical concern in specific areas of nanotechnological advance (chance/risk considerations, enhancement of human performance) and should be a parallel research activity to basic, materials/engineering research, industrial application and the medical observation of Nanotechnology risks (s. chapter 6).*
10. The future of education in Nanoscience and Nanotechnology depends on the acceptance of Nanotechnology in the industrial environment. The more research activities can be transferred into products and the daily life, the more a profound education in all fields of Nanotechnology will be required. *It is recommended at this stage to educate students in one of the established domains like physics, chemistry, biology or engineering and to superimpose in a second stage the truly multidisciplinary education in Nanotechnology, for example at the master level or in graduate schools. In a parallel step, it is recommended to improve the continuous education of engineers, medical doctors and other people dealing with Nanotechnology so that nanomaterials are used in an adequate way without any healthy risks and by exploiting all the new and interesting functions of these materials* (s. chapter 7).

1 Introduction and Summaries

1.1 Introduction

Since Nanotechnology is considered a key to the 21st century, its promises have been assessed by various scientific communities. By meeting at the nanoscale, various disciplines, from physics via chemistry to biology, from engineering to medicine contribute synergetically to the newly created knowledge base and the resulting technological advances. Considering that large societal sectors will be impacted, the unique aspect of this 2-year study was to assess Nanotechnology from various interrelated perspectives: scientific progress, industrial relevance, economic potential, educational needs, potential adverse health effects, and philosophical aspects.

The goal of this study is to derive recommendations which consider the large range of societal implications reflecting the different views in an integrative manner. The study attempts to link previously isolated statements, bundling the various concepts and giving unified recommendations to decision makers in relevant society sectors as politics, economy and research. Special attention was given to the European situation with respect to commercial consequences, an aspect that turned out to have serious consequences.

The world is facing major challenges that cannot be sufficiently addressed by current technologies. These challenges include environmental protection, exploding health care expenses, as well as energy and resource limitations. While the large range of emerging nanotechnologies will not bring universal solutions, as sometimes misleadingly expressed in the public, Nanotechnology will most likely make essential contributions to addressing those challenges. In contrast, being of enormous societal relevance, Nanotechnology and its consequences are also subject of intense public debate. Fuelled by fears, anti-“Nano” campaigns and calls for a moratorium on any kind of Nano research are getting started. An early fact-based debate and risk assessment will enable society to get involved in addressing relevant questions and concerns, helping to avoid mistakes committed with the treatment of nuclear energy or genetically modified organisms, where lack of adequate public communication has led to broad front rejection of these technologies. Neither must risks be denied, nor must chances be overestimated – otherwise much harm could be done. An honest and transparent discussion is the basis for widespread acceptance of any new technology.

The Europäische Akademie GmbH has adopted the aim of discussing matters of technology assessment rationally, seeking an independent discourse with society. In accordance with the insight that technology assessment should be carried out in an interdisciplinary way, the group consists of chemists, physicists, engineers, biologists, toxicologists, philosophers and economists. Its scheme of work was to lead a dialogue across the borders of the disciplines. While desirable in any scientific endeavour, this way of operating was *essential* for the assessment of Nanotechnology where the traditional borderlines between established disciplines are disappearing.

The group's starting point was first to ask which properties and functions of materials are changing at the nanoscale in accordance with our definition (s. chapter 2) and then how those unique properties can be exploited for technological applications as summarized in table 3.1. Due to the endless range of potential applications, we then focused on emerging technologies in information storage (table 3.2) and major biomedical challenges (table 3.3). These tables served as a basis to organize our chapters, to highlight relevant technologies and comment on their respective relevance. The consequences following from these considerations are reflected in our recommendations. This structural organization is unique and gives fundamentally new insights into the treated matter. The book's overall setup becomes apparent by the summaries in the next subchapters.

There exist numerous other reports on Nanotechnology. These reports, however, stretch different aspects of Nanotechnology and take approaches that are not comparable to ours. Usually, they follow a descriptivistic line, not questioning the label "Nano" attributed to various fields of science and technology by various actors, and examine typical or exemplary application areas and related societal implications (Paschen et al. 2004). This conception is adequate for giving a survey of Nanotechnology in a wider sense. In contrast to that, we introduce our own definition and concentrate on Nanotechnology in a stricter sense. This enables us to set an orientation mark throughout the whole book.

There are topics we did not consider in our study. For example, Intellectual Property (IP) problems of Nanotechnology have not been treated due to the fact that the corresponding legal questions remain unsettled so far. Besides, they are not of decisive importance for the ends of this study. However, the authors are aware that this topic will play a significant role in the further commercial development of Nanotechnology. Neither were the juridical aspects of risk management treated in chapter 5 due to size limitations. Also, the tables of chapter 3 may miss some entries. This is either because we do not know them – due to conscious or unconscious lack of knowledge – or because we feel that they will not play a significant role in the further development of Nanotechnology. Besides, this work was not driven by an encyclopaedical impetus. We just tried to discuss subjects we consider representative for this fascinating field of science. Hopefully, this will contribute to a clearer picture of what Nanotechnology is today and what it could or should be tomorrow.

1.2 Summaries

Chapter 1: Introduction and Summaries

The general idea of the study was a multi-perspective treatment of Nanotechnology leading to integrated acting recommendations. Public perception of Nanotechnology with its hopes and fears entails the goal of a transparent technology discussion which is based on facts. Technology Assessment (TA) can be carried out in a variety of ways. The approach of the Europäische Akademie zur Erforschung von Folgen wissenschaftlich-technischer Entwicklungen Bad Neuenahr-Ahrweiler GmbH (European Academy for the Study of Consequences of Scientific and Technological Advance) is an interdisciplinary treatment by experts from different science branches. The way of work and the methodology of the project group "Nanomaterials, Nanodevices, Nanocomputing. Determination of Present Position and Perspectives" determine the structure and contents of this book. No claim for completeness is stated, instead only selected aspects of Nanotechnology of exemplary character are treated.

Chapter 2: Nanotechnology and Philosophy of Science

Theory of science reflects research practice of sciences and their results with the aim of critically checking subjects and methods (technical laboratory methods as well as term and theory formation procedures) relatively to the claims and aims of the researchers. Questions of different subject determinations of the nano domain, of measurement techniques in the nanoscale (against the background of historical controversies), different forms of (constructive or empirical) progress and the principle of methodical order for the orientation of theory along laboratory techniques have to be treated as well as aspects of discovery, invention and application, which can be judged as researchers' actions following purposes and means. Known distinctions include the ones between nature and technology or between top-down and bottom-up approaches. Conclusions with respect to the understanding of traditional disciplines and of new microscopy techniques arise. Further conclusions refer epistemically to the character of Nanotechnology as paradigm change, ethically to the acceptability of research consequences and side effects, and politically to the question where research aims and purposes come from.

> On the basis of these considerations, the authors suggest a new, recursive definition of Nanotechnology: *Nanotechnology comprises the emerging applications of Nanoscience. Nanoscience is dealing with functional systems either based on the use of sub-units with specific size-dependent properties or of individual or combined functionalized subunits.*

Conceptually different from Nanotechnology as defined above are *scaling effects*, where laws that already hold in the macroscopic world are just transformed to other size scales by miniaturization of existing structures. Nevertheless, many of these effects are designated as Nanotechnology in common language use and play an important role. Thus, some of them are mentioned in the course of the book. The authors of this study agree that lateral dimensions between 1 and 100 nm can be a good indicator of Nanotechnology, but decided not to include this size specification in their definition to stress the decisive importance of specific size-dependent properties.

Chapter 3: Fields of Research and Technology

In chapter 3 all physical, chemical, material, and biological effects and connections, summarized in tables 3.1-3.3, are discussed and assessed in appropriate length. From these texts result the recommendations presented in "Appraisal and Recommentations". The explanations concerning table 3.1 are dealing with the detected nano-effects in agreement with the definition in chapter 2, resulting from the combination of physical and chemical properties. Important developments in this sense are, for instance, high-strained and transparent ceramics based on nanoscopic building blocks. Other forward-looking developments are linked with quantum size effects. Table 3.1 also contains molecular units that are either functionalized units by themselves like molecular magnets or that are used as building blocks for the construction of more complex systems from which, for instance, molecular motors, machines or switches can be developed. Also the so-called supramolecular chemistry offers great opportunities to generate nanoscaled systems with hitherto unknown properties.

The evaluation of the effects captured in table 3.2 is of special future relevance, since they all open novel opportunities on the field of data storage and future computer generations, respectively. There exist already technologies in the test phase, for instance the Millipede system. Others, like the quantum dot computer or even the quantum computer are still in the state of fundamental research. This is also valid for storage capable and switchable molecular systems or optical computing. Further developments of the Atomic Force Microscopy (AFM) promise numerous applications. Examples are the Magnetic Force Microscopy (MFM) and the Magnetic Resonance Force Microscopy (MRFM), promising candidates for the optimization and practical applications of nanosized magnetic systems. Scanning-Near-Field Optical Microscopy (SNOM) and Scanning-Near-Field Magneto-Optical Microscopy (SNMOM) represent new optical procedures with a dispersion below the wavelength of light.

The consequences from table 3 reflect the possibilities for the use of biosystems in combination with artificial building blocks. These lead to completely new approaches in medicine, whereby the further development of nano-tools is of considerable importance. The dominating tendency in the living nature for self-assembling can be utilized to transfer artificial nano-building blocks with biomolecular units into novel hybrid systems. The interaction of nanoparticles with biosystems also gives rise to critically assess toxicological aspects. Here, transport mechanisms through living systems play a dominant role. A better understanding of transport mechanisms will help to reliably assess the health risks originating from nanoparticles.

In contrast to the strict scientific definition in chapter 2, the expression "Nanotechnology" is commonly also used for proceedings which would be better described by "Scaling Effects". It is the matter of size-dependent behaviour that develops continuously from microscopic to nanoscopic dimensions without coming to a significant change of properties at a distinct dimension. Possibly, in the nanometer regime the phenomena may become stronger or even weaker. Examples of successful scaling effects are, for instance, the self-cleaning (Lotus effect) or the antireflection behaviour (moth eye effect) of micro-/nanostructured surfaces. In order to take these developments into account, some relevant examples are listed at the end of the chapter, but are not part of the tables and the related texts.

Chapter 4: Commercial Perspectives of Nanotechnology

Technological and economic opportunities in the field of Nanotechnology are assessed based on the analysis of patent data. Such patent data analyses are an adequate approach to analyze development trends in the field of Nanotechnology. Patents have been found to correlate significantly with the level of R&D expenditures and the probability for successfully commercializing these R&D results. There are different tools and methods for the assessment of patent data. The meaningfulness of information gained hereby depends largely on the specific analytical tool used for the examination. Multiple indicators for analyzing the patenting behavior of inventors, companies, regions, countries etc. exist. Such patenting indicators and portfolio illustrations are used for the presentation of the results gained by the study.

The patent analyses differentiate according to the specific sub-fields of Nanotechnology as defined and explained in the previous chapters of this book. The patent analyses are based on the number of patent families filed between 1983 and 2002 in the major industrialized countries in the field of Nanotechnology. The patent analyses indicate the importance, the growth dynamic and the patent position of European inventors relative to other countries for each sub-field of Nanotechnology.

One important result of the patent analyses is that Europe's patent position is weaker compared to the USA and also Japan in many fields of Nanotechnology. Especially the USA have a dominating patent position in almost every field of Nanotechnology. Europe should therefore take initiatives to improve its patent position. This includes in particular strengthening basic research in Nanotechnology to create long-term and sustainable competitive advantage; increasing the awareness of the value of intellectual property rights for creating a competitive advantage and for attracting venture funding for Nanotechnology enterprises; establishing an attractive European Intellectual Property regime for inventors and entrepreneurs; introducing and supporting a professional Intellectual Property Management at research institutions and in firms and improving the effective transfer of basic research results into development and commercial applications.

Chapter 5: Risk Assessment and Management

The European Commission has stated in a communiqué in 2004 that "any potential public health, safety, environmental and consumer risk has to be addressed upfront by generating the data needed for risk assessment" and this should be achieved by "integrating risk assessment into every step of the life cycle of nanotechnology-based products, and adapting existing methodologies and, as necessary, developing novel ones" (European Commission 2004). Exactly these important issues as well as already known problems are being discussed intensely. As in any other technology, first of all risks of Nanotechnology must be identified. Hence, the characterization of potential risks plays an important role but the positive acquisitions of new nanotechnological products regarding environment and health have to be considered as well. One important aspect of a possible risk of nanomaterials or nanoparticles is their distribution in the environment and the associated exposure of living organisms or the direct exposure of humans at working places that will increase during the expected large-volume production within the next years. With regard to such an exposure the ultrafine particles that reach the deepest parts of the lung will play the most important role especially within the discussion about possibly induced diseases. Besides some first evidences for biological or medical relevant effects within organisms, there exists only a small number of studies that demonstrate possible negative effects on living organisms or the environment, on the basis of which a risk characterization could be achieved. Mainly the present knowledge on the effects of ultrafine particles results from environmental and laboratory studies on unintentionally released particles derived generally from combustion processes. An extrapolation of these results on newly produced nanoparticles with surprising new features and properties gives rise for the assumption that they exhibit potentially negative effects in biological systems that have to be addressed in the near future. For such studies various models are introduced and discussed that are useful for the characterization of adverse effects of nanomaterials. Nevertheless, until the knowledge has reached a reasonable level, the precautionary principle requires that nanoparticles are handled in a very careful way, that systematic long-term monitoring activities are conducted and that continuous and comprehensive processes of analysis and assessment of the knowledge available will be performed.

In the societal debate on Nanotechnology during the last years the ambivalence of speculative visions has become clear. The point of departure of the societal risk debate on Nanotechnology has been the "dark side" of far-ranging visions which initially have been regarded as positive visions. In spite of the situation that such visions (self-replicating nanobots, as an example) are merely speculative in nature, from a scientific point of view, the societal risk debate led to negative consequences concerning the public reputation of Nanotechnology. In the fields of possible risks of nanoparticles for the environment and health as well as concerning the communication about far-reaching visions, our analysis shows that a rational discussion about possible risks is required as a transparent process accompanying the scientific advance. Fears against possible new hazards must be taken seriously, as well as new positive expectations and benefits, against the background of the scientific knowledge have to be announced.

Chapter 6: Ethical Aspects of Nanotechnology

Parallel to the public discussion on the benefits and risks of Nanotechnology, a debate on the ethics of Nanotechnology has been hesitatingly begun. It has been postulated that a new "nano-ethics" was necessary. In this debate, the – positive as well as negative – visionary and speculative innovations which are brought into connection with Nanotechnology stand in the foreground. It turns out that there are hardly any genuinely new ethical aspects raised by Nanotechnology. It is much rather primarily a case of gradual shifts of emphasis and of relevance in questions which, in principle, are already known and which give reason for ethical discussions on Nanotechnology. Major moral challenges from nanotechnological advance are (1) the impact of the precautionary principle on various development paths of Nanotechnology, (2) research and development at the interface between biological (especially human) and technical systems or to bridge the gap between both types of systems, and (3) enhancement of human performance via the concept of "converging technologies". New questions are mainly posed by the fact that previously separate lines of ethical reflection converge in the field of Nanotechnology. Ethics in and for Nanotechnology needs cooperation between various sub-disciplines of ethics and philosophy as well: bioethics, ethics of technology, philosophy of science, philosophy of technology, health care ethics, and anthropology. The proposal of an independent "nano-ethics", however, seems exaggerated.

Novel aspects are emerging via the big factual importance of visions and utopia in public debate. The possible postponement or abolishment of aging, crossing the borderline between humans and technology or other futuristic visions, are leading to challenging ethical questions. Therefore, such visions should – independent from their plausibility – be subject to ethical reflection. Analysing and assessing such visions requires developing a new methodology towards a "vision assessment".

However, in spite of ethical concern about specific aspects of Nanotechnology, a fundamental objection against Nanotechnology, based on moral convictions, cannot be recognised. There is no "core argument" against Nanotechnology which would be necessary to catalyst a broader movement. Such dramatic and singular technological interventions into society and nature as the Hiroshima bomb or the Cernobyl accident will not be related with Nanotechnology. Also the secular dimension of the technical possibility of manipulating the human genome cannot be reached by Nanotechnology (except in some of the more futuristic visions, but that is a different topic). Such singular events or revolutionary developments (revolutionary with respect to human self-understanding, not to economic factors) show the potential to create great movements, proponents as well as opponents. But the debates show that Nanotechnology – up to now – does not have this secular dimension – in spite of the fact that many people talk about its revolutionary character. With regard to the question for a possible objection against Nanotechnology on the basis of moral convictions this means that the heterogeneity of Nanotechnology – many people prefer to speak about nanotechnologies – *protects, in a certain sense, against coherent objection*, focussed on one specific line of argumentation.

The many and engaged debates about societal and moral aspects of Nanotechnology show a high degree of uneasiness among the population with the many proclamations of the revolutionary nature of Nanotechnology. Such uneasiness is no objection but a call for more open debate, more explanation and more deliberation. However, uneasiness could develop into opposition if it would not be taken seriously. Therefore, problems with the nanotechnological advance which express themselves via certain debates in the public or in the media should be taken seriously. Nanoscientists should engage themselves, together with ethicists, in such discussions in order or contribute to preventing irrational and fundamentalistic biases.

Chapter 7: Knowledge Transfer in Nanotechnology

Nanotechnology and Nanoscience are present in the curriculum of universities, especially in universities with a strong orientation towards science and engineering. During the last years more than 100 universities have started education in this field. It is very interesting to note that roughly two different approaches can be observed: i) The curriculum is very strongly focused on physical, material or engineering aspects of Nanoscience/-technology; ii) education programs with a very large interdisciplinarity. The most challenging approach is the second one, because the danger to teach too superficial because the content of the curriculum is too large is relatively high. It is therefore proposed to teach Nanoscience/-technology only at the master or even better at a doctoral school level. The time necessary before the students of this new field enter the job market is too long for the industry. To fulfil their needs, universities or other organisation active in the postgraduate formation has to establish training courses similar to that given for patent attorney. Universities can also introduce minors in Nanoscience to increase in short term the numbers of academics educated in Nanoscience. For the interested citizen, balanced information, which shows the high potential as well as the risk and social impact of this new technology has to prepared in a continuous way.

1.3 Zusammenfassungen

Kapitel 1: Einleitung und Zusammenfassungen

Das Grundprinzip der vorliegenden Studie ist eine multiperspektivische Behandlung der Nanotechnologie, die zu integrierten Handlungsempfehlungen führt. Die öffentliche Wahrnehmung der Nanotechnologie mit ihren Hoffnungen und Befürchtungen bedingt das Ziel einer transparenten, faktenbasierten Technologiediskussion. Technikfolgenabschätzung (*technology assessment)* kann mit verschiedenen Methoden betrieben werden. Der spezifische Ansatz der Europäischen Akademie zur Erforschung von Folgen wissenschaftlich-technischer Entwicklungen Bad Neuenahr-Ahrweiler GmbH ist eine interdiszipinäre Betrachtung durch Experten unterschiedlicher Fachbereiche. Arbeitsweise und Methodik der Projektgruppe „Nanomaterials, Nanodevices, Nanocomputing. Standortbestimmung und Perspektiven“ bedingen Struktur und Inhalt des vorliegenden Buches. Dabei wird kein Anspruch auf Vollständigkeit erhoben, stattdessen werden ausgewählte Aspekte der Nanotechnologie exemplarischen Charakters behandelt.

Kapitel 2: Nanotechnologie und Wissenschaftstheorie

Wissenschaftstheorie reflektiert die Forschungspraxis der Fachwissenschaften und deren Ergebnisse mit dem Ziel, Gegenstände und Methoden (technische Labormethoden ebenso wie Verfahren der Begriffs- und Theoriebildung) relativ zu den Ansprüchen und Zielen der Forscher kritisch zu prüfen. Fragen der verschiedenen Gegenstandsbestimmungen des Nanobereichs, der Messtechnik im Nano-Maßstab (vor dem Hintergrund historischer Kontroversen), verschiedene Formen des (konstruktiven oder empirischen) Fortschritts und das Prinzip der methodischen Ordnung zur Orientierung der Theorie an der Labortechnik sind dabei ebenso zu behandeln wie Aspekte des Entdeckens, Erfindens und Anwendens, die sich als Handeln der Forscher nach Zwecken und Mitteln beurteilen lassen. Bekannte Unterscheidungen sind die von Natur und Technik, top-down oder bottom-up-Vorgehen. Es ergeben sich Folgerungen für das Verständnis der traditionellen Disziplinen ebenso wie für das Verständnis neuer Mikroskopiertechniken. Weitere Folgerungen betreffen epistemisch den Charakter der Nanotechnologie (NT) als Paradigmenwechsel, ethisch die Verantwortbarkeit von Folgen und Nebenfolgen der Forschung und politisch die Frage nach der Herkunft der Forschungszwecke und -ziele.

Auf Grundlage der angestellten Überlegungen schlagen die Autoren der Studie eine neue, rekursive Definition der Nanotechnik vor: *Nanotechnologie umfasst die aufkommenden Anwendungen der Nanowissenschaften. Nanowissenschaften beschäftigen sich mit funktionalen Systemen, die entweder auf dem Gebrauch von Untereinheiten mit spezifischen größenabhängigen Eigenschaften oder von einzelnen oder kombinierten funktionalisierten Untereinheiten basieren.*

Konzeptionell von der so definierten Nanotechnologie sind *scaling effects* abzugrenzen, bei denen bereits im Makroskopischen geltende Gesetzmäßigkeiten durch Miniaturisierung bestehender Strukturen lediglich in anderen Größenordnungen überführt werden. Viele solcher Effekte werden im täglichen Sprachgebrauch aber trotzdem als Nanotechnologie bezeichnet und spielen eine wichtige Rolle. Daher finden einige von ihnen im weiteren Buch Erwähnung. Die Autoren der Studie stimmen darin überein, dass laterale Abmessungen zwischen 1 und 100 nm ein guter Indikator für Nanotechnologie sein können, haben sich aber entschieden, diese Größenangabe nicht in ihre Definition aufzunehmen, um die herausragende Bedeutung der spezifischen größenabhängigen Eigenschaften zu unterstreichen.

Kapitel 3: Forschungs- und Technologiefelder

In Kapitel 3 werden sämtliche in den dortigen Tabellen 1-3 gesammelten physikalischen, chemischen, materialwissenschaftlichen und biologischen Effekte und Zusammenhänge in angemessener Ausführlichkeit diskutiert und bewertet. Aus diesen Texten resultieren die entsprechenden Empfehlungen im vorgeschalteten Kapitel „Appraisal and Recommendations".

Die Ausführungen zu Tabelle 1 behandeln aus der Kombination physikalischer und chemischer Eigenschaften resultierenden „Nanoeffekte" im Sinne der Definition in Kapitel 2. Wichtige Entwicklungen in diesem Sinne sind etwa neuartige Effekte im Bereich hochfester und transparenter Keramiken, die auf nanoskopischen Bausteinen basieren. Andere zukunftsweisende Entwicklungen sind mit Quantum Size-Effekten verbunden. Tabelle 1 beinhaltet auch molekulare Einheiten, die entweder selbst funktionalisierte Nanosysteme darstellen wie z.B. molekulare Magnete, oder die als Bausteine zum Aufbau komplexerer Systeme verwendet werden, woraus beispielsweise molekulare Motoren, Maschinen und Schalter entwickelt werden können. Auch die sog. supramolekulare Chemie bietet großartige Möglichkeiten zum Aufbau nanoskaliger Systeme mit zuvor ungekannten Eigenschaften.

Die Auswertung der in Tabelle 2 erfassten Effekte ist von besonderer Zukunftsrelevanz, da sie allesamt neuartige Möglichkeiten auf dem Gebiet der Datenspeicherung bzw. zukünftiger Computergenerationen eröffnen. Es existieren bereits in der Erprobung befindliche Technologien wie z. B. das Millipede-System. Andere wie Quantenpunktcomputer oder gar Quantencomputer befinden sich dagegen noch in der Grundlagenforschung. Dies gilt auch für speicherfähige und schaltbare molekulare Systeme oder das Optical Computing. Weiterentwicklungen der Atomic Force Microscopy (AFM) versprechen vielfältige Einsatzmöglichkeiten. Beispiele sind die Magnetic Force Microscopy (MFM) und die Magnetic Resonance Force Microscopy (MRFM), viel versprechende Kandidaten zur Optimierung und Nutzung nanoskaliger Magnetsysteme. Scanning-Near-Field Optical Microscopy (SNOM) und Scanning-Near-Field Magneto-Optical Microscopy (SNMOM) stehen für neuartige optische Verfahren mit einer Auflösung unterhalb der Lichtwellenlänge.

Die Konsequenzen aus Tabelle 3 reflektieren die Möglichkeiten zur Nutzung von Biosystemen in Kombination mit künstlichen Bausteinen. Diese führen zu völlig neuartigen Ansätzen in der Medizin, wobei die Weiterentwicklung von Nano-Werkzeugen von großer Bedeutung ist. Die in der belebten Natur vorherrschende Tendenz zur Selbstorganisation kann sinnvoll genutzt werden, um künstliche Nanobausteine mit biomolekularen Einheiten in neuartige Hybridsysteme zu überführen. Die Wechselwirkung von Nanopartikeln mit Biosystemen gibt auch Anlass zur kritischen Bewertung toxikologischer Aspekte. Hierbei spielt der Transportmechanismus von Nanopartikeln durch lebende Systeme eine dominierende Rolle. Ein besseres Verständnis der Transportmechanismen wird helfen, die von Nanoteilchen ausgehenden Gesundheitsrisiken zuverlässiger abschätzen zu können.

Entgegen der streng wissenschaftlichen Definition im Kapitel 2 wird der Begriff „Nanotechnologie“ gemeinhin auch für Vorgänge benutzt, die besser mit „Skalierungseffekte“ beschrieben würden. Es handelt sich größenabhängige Erscheinungen, die sich kontinuierlich von mikroskopischen zu nanoskopischen Dimensionen entwickeln, ohne dass es bei einer bestimmten Dimension zu einem signifikanten Eigenschaftswechsel käme. Im Nanometerbereich verstärken sich allenfalls die Phänomene oder werden sogar schwächer. Beispiele für erfolgreiche Skalierungseffekte sind etwa die Selbstreinigung (Lotus-Effekt) oder das Antireflexverhalten (Mottenaugeneffekt) mikro-/nanostrukturierter Oberflächen.

Um diesen Entwicklungen Rechnung zu tragen, sind relevante Beispiele am Ende des Kapitels angeführt, jedoch nicht Bestandteil der Tabellen und der zugehörigen Texte.

Kapitel 4: Kommerzielle Perspektiven der Nanotechnologie

Die Entwicklungspotentiale der Nanotechnologie werden anhand einer Patentanalyse aufgezeigt. Patente sind geeignete Indikatoren für die Untersuchung technologischer Entwicklungstrends. Sie korrelieren signifikant mit der Höhe der Forschungs- und Entwicklungsaufwendungen und der Vermarktung der daraus resultierenden Erfindungen. Es existieren verschiedene Ansätze und Methoden zur gezielten Auswertung von Patentdaten. Die Aussagekraft von Patenten hängt entscheidend von den eingesetzten Auswertungsmethoden ab. Kennzahlen erleichtern die Analyse der Patentierungsaktivitäten von Erfindern, Unternehmen, Regionen, Ländern etc. Solche Kennzahlen und Portfolio-Darstellungen werden für die Präsentation der gewonnenen Ergebnisse verwendet.

Die Patentanalyse differenziert nach verschiedenen Technologiefeldern innerhalb der Nanotechnologie, wie sie auf Basis der Definition von Nanotechnologie in den vorausgehenden Kapitel dieses Buches beschrieben werden. Die Auswertungen basieren auf den zwischen 1983 und 2002 auf dem Gebiet der Nanotechnologie angemeldeten Patentfamilien in den wesentlichen Industrieländern. Die Patentauswertungen führen jeweils in den verschiedenen Technologiefeldern der Nanotechnologie zu Erkenntnissen über die Bedeutung verschiedener Technologiefelder, über die zunehmende oder abnehmende Patentierungsdynamik und über die Position europäischer Erfinder im internationalen Vergleich.

Ein wesentliches Ergebnis ist, dass Europa, gemessen an seiner Patentposition, auf dem Gebiet der Nanotechnologie hinter den USA und Japan zurückliegt. Insbesondere die USA haben eine dominierende Patentposition in vielen Feldern der Nanotechnologie. In Europa sind daher Maßnahmen zu ergreifen, um die Patentposition auf dem Gebiet der Nanotechnologie zu verbessern. Dazu gehören insbesondere die Stärkung der Grundlagenforschung, die Verbesserung des Patentmanagements in allen F&E-betreibenden Institutionen, die Schaffung von optimalen Rahmenbedingungen zur Erlangung von gewerblichen Schutzrechten sowie die Verbesserung des Transfers von Ergebnissen der Grundlagenforschung in die Entwicklung und Vermarktung von Innovationen.

Kapitel 5: Risikobewertung und -management

Die Europäische Kommission hat in einem Communiqué aus dem Jahr 2004 festgestellt, dass „die potentiellen Risiken bezogen auf die Gesundheit, Sicherheit, Umwelt und den Konsumenten stärker berücksichtigt werden müssen, indem vor allem die schwache Datenlage in dieser Hinsicht verbessert werden muss. Dies sollte geschehen, indem der gesamte Lebenszyklus der nanotechnologischen Produkte betrachtet werden soll und die bereits existierenden Methoden darauf angewendet oder neue entwickelt werden sollen“ (European Commission 2004). Wie bei jeder neuen Technologie müssen auch im Zusammenhang mit der Nanotechnologie zuerst einmal die Risiken identifiziert werden, um ihnen dann auf geeignete Weise zu begegnen. Wichtige Aspekte bei der Diskussion um eine Gefährdung durch Nanopartikel oder Nanomaterialien sind deren Verteilung in der Umwelt und die damit einhergehende Exposition lebender Organismen als auch die direkte Exposition am Arbeitsplatz, die sich bei der zu erwartenden Produktionssteigerung in den kommenden Jahren mit großer Sicherheit ebenfalls erhöhen wird. Daher spielen in diesem Zusammenhang mögliche Erkrankungen eine bedeutende Rolle, die durch Feinstpartikel, welche bis in die tiefsten Bereiche der Lunge vordringen können, ausgelöst werden. Neben einigen Hinweisen auf solche medizinisch relevanten Effekte gibt es allerdings nur wenig belastbares Material zu negativen Einflüssen auf Lebewesen oder die Umwelt, die bereits eine vernünftige Risikocharakterisierung zulassen würden. Im Wesentlichen gehen die aktuellen Erkenntnisse auf Untersuchungen von unbeabsichtigt in die Umwelt emittierten ultrafeinen Stäuben zurück, die meist aus Verbrennungsprozessen stammen. Eine Extrapolation dieser Ergebnisse lässt allerdings erwarten, dass Nanopartikel aus technischen Produktionen, die mit außergewöhnlichen Eigenschaften ausgestattet sind, auch im biologisch/medizinischen Bereich nachteilige

Effekte haben werden, die frühzeitig erkannt werden müssen. Dazu werden verschiedene Modelle diskutiert, die für die Charakterisierung solcher Effekte von Bedeutung sind. Bis die Datenlage sich verbessert hat, gebietet das Vorsorgeprinzip (precautionary principle) einen besonders sorgsamen Umgang mit Nanopartikeln und eine systematische Langzeit-Beobachtung sowie eine kontinuierliche Auswertung des verfügbaren Wissensstandes.

In der gesellschaftlichen Diskussion zur Nanotechnologie wurde in den vergangenen Jahren die *Ambivalenz* von spekulativen Visionen deutlich. Die Risikowahrnehmung der Nanotechnologie entzündete sich zuerst an der „dunklen Seite“ von eigentlich als positiv gedachten Visionen. Sind diese Visionen (z.B. selbst replizierende Nanoroboter) zwar wissenschaftlich rein spekulativ, hat die daran ansetzende Risikokommunikation dennoch zu negativen Folgen für das Ansehen der Nanotechnologie geführt. Sowohl zur Frage der möglichen Gefährdung von Umwelt und Gesundheit durch Nanopartikel als auch im Umgang mit weit reichenden Visionen zeigt sich, dass begleitend zu den Forschungsaktivitäten eine rationale Diskussion und Kommunikation zu den möglichen Risiken der Nanotechnologie durchgeführt werden muss. Dabei müssen Ängste vor neuen Gefährdungen ebenso ernst genommen werden, wie neue positive Errungenschaften vor dem Hintergrund belastbaren wissenschaftlichen Wissens herausgestellt werden müssen.

Kapitel 6: Ethische Aspekte der Nanotechnologie

Parallel zur öffentlichen Diskussion über Chancen und Risiken der Nanotechnologie ist zögerlich eine Debatte über Ethik in der Nanotechnologie angelaufen. Eine neue „Nano-Ethik“ wird als dringend bezeichnet. Im Vordergrund stehen dabei die – positiven wie negativen – visionären und spekulativen Entwicklungen, die mit der Nanotechnologie in Verbindung gebracht werden. Es stellt sich heraus, dass es kaum genuin neue ethische Aspekte der Nanotechnologie gibt. Vielmehr sind es zumeist graduelle Akzent- und Relevanzverschiebungen in prinzipiell bereits bekannten Fragestellungen (wie z.B. Fragen des gerechten Zuganges zur Nutzung der Nanotechnologie oder der Sicherung der Privatsphäre), die zu ethischen Diskussionen der Nanotechnologie Anlass geben. Neue Fragen werden vor allem dadurch aufgeworfen, dass sich im Feld der Nanotechnologie bislang getrennte ethische Reflexionslinien treffen, so vor allem Bioethik, Medizinethik, Anthropologie und Technikethik sowie die Überlegungen zur Künstlichen Intelligenz. Besondere Relevanz werden diese ethischen Fragen im Umfeld der Diskussion um „Konvergierende Technologien“ und die mögliche „technische Verbesserung des Menschen“ erhalten. Die Forderung nach einer eigenen „Nano-Ethik“ erscheint jedoch übertrieben.

In gewisser Weise strukturell neuartige ethische Aspekte entstehen durch die große Rolle der nanotechnologischen Visionen in der öffentlichen Diskussion. Die Abschaffung des Alterns, die Möglichkeit der Überwindung der

Grenze zwischen Mensch und Technik oder andere Visionen werfen teils dramatische Fragen auf – allerdings zu eben mehr oder weniger zurzeit rein hypothetischen Erwägungen. In diesem Feld stellt sich die Notwendigkeit, in methodische Entwicklungen eines „Vision Assessment“ zu investieren, um die Fehlallokation von Ressourcen (seien dies Forschungsgelder oder das knappe Gut „öffentliche Aufmerksamkeit“) aufgrund bloßer „Hypes“ zu vermeiden.

Angesichts der Felder, in denen moralische Aspekte der Nanotechnologie thematisiert werden, stellt sich die Frage, ob sich hier grundsätzliche ethische Vorbehalte gegenüber der Nanotechnologie verbergen oder sich ihre eventuelle Formierung ankündigt. Hinweise darauf, dass sich eine moralisch motivierte Ablehnungsfront gegenüber der Nanotechnologie ausbildet, gibt es nach der vorgenommenen Analyse jedoch nicht. Es fehlt das Spezifische, das den motivierenden Kern einer solchen bilden könnte, wie es das in manchen Vorstellungen Ungeheuerliche des Eingriffs in die Erbsubstanz durch Gentechnologie oder die durch Hiroshima und Cernobyl illustrierten Katastrophenbefürchtungen in der Kernenergie waren. Die Heterogenität der Nanotechnologie in sich selbst ist in gewisser Weise ein Schutz vor fokussierenden und kohärenten Gegenpositionen.

Was aber aus den verschiedenen Thematisierungen ethischer Aspekte der Nanotechnologie spricht, ist ein eher allgemeines Unbehagen – nicht nur gegenüber der Nanotechnologie, sondern allgemeiner gegenüber Wissenschaft und Technik angesichts der erheblichen Innovationsgeschwindigkeit. Unbehagen ist noch keine Ablehnung, sondern ein Ruf nach Erklärung, Diskussion, Auseinandersetzung etc. Gleichwohl kann Unbehagen in Ablehnung umschlagen, wenn sie nicht ernst genommen wird. Dies bereits sollte – über die fachlichen Notwendigkeiten im Einzelfall hinaus – Anlass genug sein, den ethischen Fragen und ihrer offenen Austragung im weiteren Verlauf der gesellschaftlichen Diskussion um Nanotechnologie genügend Aufmerksamkeit zu widmen.

Kapitel 7: Wissensvermittlung in Nanotechnologie

Nanotechnologie und -wissenschaft ist an vielen Universitäten, speziell in technischen, stark in den Vorlesungsplänen vertreten. Mehr als 100 Universitäten bieten entsprechende Kurse an. Es können 2 unterschiedliche Ansätze für die Lehre in diesem Bereich beobachtet werden: 1.) Die Ausbildung ist stark auf ein Gebiet wie zum Beispiel Physik, Biologie, Materialwissenschaften oder Ingenieurwisenschaften fokussiert, 2.) es wird eine sehr breite interdisziplinäre Ausbildung angestrebt. Die größte Herausforderung stellt sicher dieser interdisziplinäre Ansatz dar. Es ist sehr schwierig angesichts der Größe des Gebietes und der nur beschränkt zur Verfügung stehenden Zeit nicht in eine zu oberflächliche Lehre zu kommen. Dies ist der Grund für die Empfehlung, keine eigenständige Lehrgänge „Nanotechnologie“ anzubieten, sondern die Nanotechnologie ab dem Niveau des Masters oder noch besser ab dem Doktorat zu vermitteln. Da es noch länger dauern wird, bis die ersten Abgänger dem Arbeitsmarkt zur Verfügung stehen und der Bedarf der Industrie und Behörden vor allem in den nächsten Jahren größer sein wird als das Angebot, sollten von den Universitäten zusätzliche Nachdiplomskurse angeboten werden. Zudem ist eine sachliche und verständliche Information der interessierten Bevölkerung notwendig, damit auf einer sachlichen Basis die Vor- und Nachteile der Anwendung der Nanotechnologie in alltäglichen Produkten diskutiert werden kann.

2 Nanotechnology and Philosophy of Science

2.1 *Icons of Nanotechnology*

No new development in science is exclusively limited to lab work. Rather, it must attract public attention in order to plausibly present itself as important, promising and, above all, worth of being funded. Informing and self-advertising is part of the scientific business. Where public attention seeking gains priority over actual research, occasions arise for submitting self-understandings – or for creating them in the first place. These are mechanisms that give shape and contents to scientific communities through reference to commonly shared objects, methods, terminologies, interpretations, promises, etc. Where representatives of a new enterprise go public, attractive pictures, symbols and signals are needed. They serve as brands with a high recognition value. They are the "icons" of the new trend.

Typical icons most frequently encountered in both popular and scientific presentations of Nanotechnology are the famous title of Richard P. Feynman's paper "There's Plenty of Room at the Bottom", the letters "IBM" formed by singular Xenon atoms (Donald M. Eigler 1989), and the figure of a small man formed by a few particular molecules. While the latter two refer to the possibility of manipulating and visualizing atomic or molecular objects, and promise new products, atom by atom, into a "bottom-up" way, the Feynman phrase is the heading of a programmatic talk which, as both vision and order, is carried like a banner for the advancing group of nano research soldiers. This Feynman program not only is of historical importance for science and technology, but it also matters for philosophy of science. This program, at a first glance, appears to grow from technological challenges with regard to demands of new technologies through progressive miniaturization. On closer inspection, however, this program touches upon many questions relating to basic research and philosophical interpretation.

The starting point of Feynman's talk does not refer to "fundamental physics" but rather focuses on "solid state physics in the sense that it might tell us much of great interest about strange phenomena that occur in complex situations" where "the problem of manipulating and controlling things at a small scale" turns up.

In a first step, Feynman discusses the technology of reducing the size of letters by a factor of 25,000 in both writing and reading. As an answer to the question "How do we write small?" Feynman proposes to reverse the lenses of an electron microscope "to demagnify as well as magnify". But why only demagnify the *Encyclopedia Britannica* and not the holdings of the Library of Congress joined with those of the British Museum Library and the National Library of France – "some 24 million volumes of interest in the world" – to fit them on a pin-head?

Roughly estimated using a body's entire material (about 100 atoms per bit) rather than its surface for information storing could demagnify the book holdings of those libraries and write them "in a cube of material one two-hundredth of one inch wide – which is the barest piece of dust that can be made out by the human eye. So there is plenty of room at the bottom!" The storage of information in the nucleus of the tiniest cell that organizes complex creatures such as us, with about 50 atoms in the DNA coding one bit in the cell, is hardly puzzling to a biologist. Feynman mentions a number of technical tasks which, according to the physical knowledge of his time, did not conflict with known physical laws: improvement of electron microscopes, making single atoms visible, answering fundamental questions of molecular biology by "seeing" the processes in the DNA, and the synthesis of materials or objects on the atomic level.

Given the very small, highly active biological units, biology, according to Feynman's initial thoughts, has indicated a strategy for demagnifying computer components to molecular size in order to achieve any desired high performance with a minimum expense of material and energy. Of course, radical miniaturization produces a range of new problems: If a car were demagnified to the length of 1 millimeter, are its wheels sufficiently round when they consist of atomic "balls"? On the other hand, problems with friction and lubrication would disappear. Where mass and inertia become irrelevant due to the reduced size, important new problems would arise with regard to electric and magnetic properties, thus requiring new constructive principles. A hierarchy of self-producing machines with iterative miniaturization could realize the miniaturization of mobile working machines like "the surgeon to be swallowed".

> *So you have a scheme by which you can do things at one-quarter scale anyway – the little servo motors with little hands play with little nuts and bolts; they drill little holes; they are four times smaller. Aha! So I manufacture a quarter-size lathe; I manufacture quarter-size tools; and I make, at the one-quarter scale, still another set of hands again relatively one-quarter size! This is one-sixteenth size, from my point of view… Thus I can now manipulate the one-sixteenth hands… At each stage, it is necessary to improve the precision of the apparatus... We can make flats by rubbing unflat surfaces in triplicates together – in three pairs – and the flats then become flatter than the thing you started with... Where am I going to put the million lathes that I am going to have? ... For instance, if I made a billion little lathes, each 1/4000 of the scale of a regular lathe, there are plenty of materials and space available because in the billion little ones there is less than 2 percent of the materials in the big lathe. (Feynman 1960)*

With reduced size, new interesting problems will arise. "All things do not simply scale down in proportion." Materials are held together through Van der Waals attraction on a molecular level. On the other hand, what could be realized by rearranging atoms one by one? Purified, singular-atom-type substances? Controlled construction of mono-atomic or monomolecular layers? "Atoms on a small scale," to be sure, "behave like nothing on a large scale, for they satisfy the laws of quantum mechanics." But "if we go down far enough, all of our devices can be mass produced so that they are absolutely perfect copies of one another."

Feynman finally affirms that he is not attempting "to violate any laws; it is something, in principle, that can be done; but in practice, it has not be done because we are too big.

> *What then might be the aim of this new enterprise? He points out a few potential economic applications, "but I know that the reason that you would do it might be just for fun. But have some fun! Let's have a competition between laboratories. (Feynman 1960)*

Feynman phrased his program in an impressive, even enthusiasm-inspiring way, which anticipated many details of current Nanotechnology at least in the form of a goal. Included in his program are many questions relevant to present-day Nanotechnology (compare chapter 3):

- How large or small is the area covered by this new kind of research? Feynman's paper provides indications of relevant sizes by referring to objects of everyday life (such as letters, pages in books, or the surgical robot that can be swallowed) on the one hand and by reference to objects like atoms or molecules in chemical contexts on the other. What, then, defines the new realm of nano objects? Is it really measures of size or scale that properly define or limit Nanoscience or Nanotechnology? Or should Nanoscience and Nanotechnology rather be defined (as is attempted in the present study) by referring to characteristic properties of materials or processes, which only in a subsequent step are identified as belonging to the nano scale? To put it differently, is the unit of "nano meter" decisive for scientific description? In any case, measurement plays an important role in this field as well. How should an art of measurement be designed or conceived that catches up with the miniaturization and at the same time is more precise by orders of magnitude as compared to the objects to be measured?
- What are the driving forces behind this new kind of research? Is innovation more like a consequence of casual discoveries of new effects, laws or properties of substances that may ultimately lead to further technical application? Or does (and should) progress rather happen through the continuation of available technologies, e.g. in the form of industrial product development as in the automobile or computer industries? So who is needed, the discoverer or the inventor, the engineer? Are we deal-

ing with results of fundamental research in search of new and economically profitable technical application or rather with new technical problems in search of solutions through scientific research?

- What does prevail in this new field? New scale-dependent natural laws or new technical procedures easily compatible with well-known laws? Is it an inquiry into nature or rather extension of the art of engineering?
- How do strategies of miniaturization relate to the strategies of bottom-up construction? How are problems arising from these two strategies relying on each other?
- How can the improvement of microscopy that Feynman requested be accomplished? Are mapping procedures to be replaced by techniques for the production or creation of new images that are not defined by the principle of optical imaging?
- Do Nanoscience or Nanotechnology have consequences for the traditional understanding of physics, chemistry or biology? Does the new field of research constitute a “paradigm change” or a “scientific revolution” in the Kuhnian sense with far-reaching consequences such as the development and establishment of a new scientific community, a new identity for researchers and, possibly, a new curriculum? (In this place, the widespread popular use of the term “paradigm change” in fields such as politics or advertising needs to be distinguished from the scientific use of the term: in the latter, the two conflicting paradigms have to be identified and their mutual exclusion, their incommensurable concepts, etc. must be demonstrated.)
- Who, after all, are the ones who are going to ask the new questions, to establish the new goals, to define the new criteria, to pay the fresh money, and who is to be held responsible for the consequences, especially of unforeseen possible side effects ranging from poisonous substances to structural economic change?

To put it in a nutshell, the icon “There is Plenty of Room at the Bottom” provokes a wide range of questions and problems which by no means are scientific or technological ones, since they do not concern atoms and molecules, machines and organisms, but the practice of the human researcher. Rather, these questions are philosophical ones. The language in which they are phrased does not refer to objects of laboratory research but to acting human subjects, to persons. Dealing with these questions and problems is the proper task of philosophy of science in the field of Nanoscience and Nanotechnology. Therefore, a clarification is needed of what “philosophy of science” is all about.

2.2 The Approach

With regard to the effects mentioned, philosophy of science is trying to contribute to the relevant disciplines in a job-sharing manner, which is not very different from comparable cooperative examples such as the collaboration between physicists and mathematicians, between biologists and chemists, and so on. It is obvious that philosophers' special competence in matters of logic, concept formation, theory building, development of methodologies, images of man or the world that are invested in or resulting from research, criteria of being scientific, etc. can be useful both for research and the presentation of its results.

For philosophy of science Nanotechnology is a particularly worthwhile and maybe even a unique subject, because, given the novelty of Nanotechnology, a pertinent philosophy of the field does net yet exist. There are hardly any relevant publications, Nanotechnology being not a "mature" disclipline but rather a juvenile enterprise. The prospective thinking of scientist and the reflective thinking of philosophers might support each other in order to prevent the field from getting on a wrong track or to encourage or to promote novel ideas. This philosophical contribution by itself is obliged to being "critical" in the sense not of everyday language (refusal or rejection) but in a sophisticated philosophical sense of promoting sharp conceptual distinctions or well-founded judgments (compare Immanuel Kants' three famous critiques which, of course, also are no documents of refusal or rejection).

Pursuing these aims, the following might be the leading questions for the following philosophical investigation:

- What are the tacit assumptions and their technical realization that enter into the quantitative determination of "nano"? Here the alternative needs to be considered whether (a) the size of objects is supposed to *define* Nanoscience and Nanotechnology, or (b) *the novelty of properties and effects* limits the nano domain. Of course, in this domain, no less than in any other field of experimental science, measurements are performed (and raise questions as to the technical realizeability of procedures and tools at the proper scale).
- How, and to which ends, do new technical means develop relative to known and recognized scientific theories? Which *forms of progress*, technical or scientific, takes place in current nano research and development? And how do they depend on the invested aims and purposes?
- What determines the relation between research and application? If (like in this study) a distinction is drawn between Nanoscience and Nanotechnology (i.e., between fundamental research and applied technology), the *concept of application* must be clarified. Who sets the aims for applications, and how do they influence basic research?

- In which way does basic research depend on the *technical laboratory equipment* and on the theory behind it? How do basic concepts and theories interact with methods and their applications?
- Are there proper nano laws? Should Nanotechnology be considered naturalistically or culturalistically, i.e., as new images of nature or just as a new form of technical know how? Does the project of progressive miniaturization lead to new natural laws?
- Do Nanoscience and Nanotechnology represent a paradigm change, or do they display cumulative growth of knowledge? (Which concept of "paradigm change" is applied when Nanotechnology is labeled in the former way by representatives of that research?) *(Epistemological implications)*
- Are consequences and side effects of Nanoscience and Nanotechnology predictable and therefore matters of responsibility? *(Ethical implications)*
- Can Nanoscience and Nanotechnology be objects of rational preplanning in terms of political or economic decision-making? *(Political implications)*

2.3 The Nano Domain as a Product of Non-Linguistic and Linguistic Human Action

Nobody among the nano scientists would deny, of course, that natural science as a whole and Nanoscience/Nanotechnology in particular, are brought about by human activities including both manufacturing and talk. Even if some nano scientists enjoy the idea that they were immediately dealing with Nature herself, at least Nanoscience and Nanotechnology form part of cultural history, not of nature. Briefly, Nanoscience and Nanotechnology require reflection in terms of culture.

As is well known, "nano" is derived from the ancient Greek word *"nanos"* (dwarf) – as almost all introductory texts assure us. This neglects the fact, though, that "technology" contains the roots "techno" from ancient Greek *"techne"* (art, man-made as opposed to natural), and "-logy" from the ancient Greek *"logos"* (word, language, ratio, doctrine) which itself is derived from the verb *"legein"* (to speak, to say, to read). Literally, "nano technology" means "doctrine (or: theory) of the artificial mastery (or: ruling) of tiny things". That is to say that even the very name of the new field appositely refers to the artificial character of the objects in question. Hence, even the inclination to think of nature or of natural "nano objects" in the case of Nanotechnology should be considered suspicious.

At a first glance, this conceptual diligence might be considered of minor importance, if not completely irrelevant. Isn't it obvious that it is people who bring about Nanotechnology? So, why care? Taking a closer look at the problem of Nanotechnology demarcation will be helpful and instructive: The unit "nano meter", i.e., the millionth part of a millimeter, of course is a mere linguistic convention, and it does not seem to imply any philosophical problem. It refers to the technical reproducibility of a measuring unit according to the legal definition of "meter" by the *Bureau International des Poids et Mesures (Paris).* However, except for elementary mathematics, the ratio "a millionth" invariably refers to the well-established practice of relying on a publicly approved system of measuring units. The reproducibility of units, according to the legal definitions, forms a delicate epistemic problem, however. This is because a huge amount of empirical knowledge is invested into those definitions in the first place; knowledge, to be sure, which itself is based on measurement. In this sense, the nano meter carries along a problem of circularity as well: What does one need to know in order to reproduce a measuring unit, and how does this knowledge itself depend on measurement using the units as reference magnitudes?

Referring to certain objects as examples of size, such as (chemically identified) molecules, proteins, viruses, or the like, as we are used to do in everyday practice when we, e.g., indicate the size of an object with the help of our own fingers or arms, does not serve to circumvent this circularity, because those exemplars have to be measured for size beforehand.

That is to say that conventions to establish the nano meter as a measuring unit depend on the mastery of technical reproducibility, and they do not imply, but presuppose a wide range of nano know how. (It will be remembered that, in the present study, the definition of Nanoscience and Nanotechnology is not done via the demarcation of a domain through size and its measured extension, but rather via new phenomena hitherto unknown in familiar domains.) Whatever definition of the nano scale is chosen, it remains clear that measurement has to take place and poses technical problems that are as yet unsolved. Therefore, the following question will be discussed in more general terms:

2.3.1 What defines a Measurement?

What measurement is, and how measuring procedures are justified as compared to different ways of collecting observational data, cannot itself be a matter of measurement. Rather, this is a philosophical or a meta-theoretical question. To the question, "What is measurement?" a scientist is likely to answer: "Determining a rational number indicating the ratio between a given unit and the object measured". That procedure includes the use of a measuring tool, the function of which relies on the natural laws realized in the instrument. This is the prevailing opinion originating from a 19th century empiricist tradition.

More precisely, it was the empiricist Hermann v. Helmholtz who explained, in his famous article "Counting and Measuring, Regarded Epistemologically" ("Zählen und Messen, erkenntnistheoretisch betrachtet", 1887), how to establish a system of operations that he paralleled to the construction of the system of numbers in arithmetic, starting with integers and leading over rational and irrational numbers all the way up to the real numbers. He used the symmetric balance as a simple example. Equal weight of two bodies confirmed by the horizontal position of the balance levers corresponds to arithmetical equality. The equality of the numbers gained by measurement operationally defines the equality of weight. Consequently, all the arithmetical operations such as adding, subtracting and multiplying measuring numbers are related to certain operations carried out with bodies that are either put into or taken away from the balance bowls.

This plain, intuitive understanding of how mathematics comes in into the management of the bodily world through the use of instruments became dominant in philosophy of science in its mainstream empiricist form (Vienna Circle and its successors). Its prominent representatives, like Rudolf Carnap and Carl Gustav Hempel, elaborated on this Helmholtzian approach by means of formal logic. This doctrine also governs scientific textbooks in those rare cases where they exhibit any concern at all for basic concepts and their formation. But this theory contains a decisive mistake. (It is therefore named "empiricist" doctrine here.)

To point out that mistake, the process of attributing numbers to objects through measurement must be considered in more detail. Arithmetical equality is an equivalence relation, which means that it is symmetric and transitive. Therefore, the equality of weight of bodies that are compared with the help of balances also has to prove symmetrical and transitive. Since this statement is meant to apply to all bodies, the empiricists considered it an empirical hypothesis. In other words, symmetry and transitivity of weight (as an exemplar of all measured magnitudes) has to be tested by measuring tools.

2.3.2 A Critique of the Empiricist Theory of Measurement

Following the assumption that only experience can decide whether weight is a concept that proves symmetric and transitive with regard to equality, a corresponding measuring tool is needed. This, of course, assumes that the balance is working properly. Philosophers say that the balance is "undisturbed". If a person disturbed the balance by putting a finger on one side of the balance, thus pushing down the bowl, this alters what the balance would show without human intervention. Therefore, any empirical test for symmetry and transitivity of weight with balances requires a general criterion for the undisturbedness of the balance (or any other measuring tool).

Empiricist v. Helmholtz still knew what later empiricists such as Carnap and Hempel disregarded: that it properly is symmetry and transitivity that define the undisturbed function of the balance. But, then, mathematical properties of the concept of weight cannot conceivably be tested by empirical means; such a test would only lead to a trivial tautology: If the balance shows symmetry and transitivity for any suitable pair or triplet of bodies, then those bodies prove to be equal in weight in the sense of symmetry and transitivity. (If bodies of equal weight are exchanged on both sides of the balance, a horizontal position of the levers will result; the same holds for three bodies A, B, and C when pairs AB, AC, and BC, respectively, are compared).

Therefore, the assumption is wrong that the function of the symmetric balance is causally effected or explained by a law of nature (the law of levers), because that law can be controlled empirically only by means of bodies whose weights have already been established through prior measurement. The undisturbed function of a balance, thus, is not an empirical matter but a technical aim of purposively acting persons who invent, produce and use balances. Disturbed measuring tools do not falsify any natural law but rather miss a human purpose. Therefore, this holds for all measurement-controlled parameters: The criteria imposed on the function of the corresponding measuring tool must be known in order to operationally define a physical magnitude (and to subject it to factual control).

The empiricist view of measurement simply ignores the fact that measuring tools (like tools and laboratory equipment in general) are not natural objects but artificially, “technically” produced ones. It is their respective purpose that defines their function. And it is up to the competence of the individual scientist to know both that purpose and how it can be realized technically. (Some sensitivity for the words involved, such as “instrument”, “apparatus”, and “tool” would provide sufficient clues as to the dependence of those technical products on the purposes that are invested.)

2.3.3 What Defines Nano Size?

Wherever the size of nano objects can be given only by means of quantitative concepts and measurement, a complex system of technical purposes always has to be invested. This forms the basis of any empirical statement. (Again be reminded that the definitions of Nanoscience and Nanotechnology in the present study do not rest on size or scale readings but on certain effects and phenomena.)

The purposes that are being invested of course must to be made explicit in cases of doubt or controversy. Generally speaking, any art of measurement must be based on a system of explicit norms that are to be technically realized. The theory developing those normative systems is called “protophysics” (derived from the ancient Greek *“protos”*, first).

Protophysics comes first in the sense of methodical order, which refers to the sequence in which laboratory work is actually performed: Some actions must precede (or be preceded by) others in order to be performable or successful. Protophysics makes explicit what scientists are implicitly pursuing if they are doing successful scientific research and measurement.

With regard to nanotechnology (NT), some questions still remain open and cannot be answered in this place. Consider, for instance, the problems pointed out by Feynman with regard to the process of progressive miniaturization that has to be controlled through measurement. Or think of the problem of specifying the magnification rate by electron and other NT-based microscopes. The logical structure of the concepts used in presenting quantitative results of Nanotechnology is one side, the ideal one, as it were, of the norms that guide measurement. On the other side, there is the question whether technical realization in nano size depends on concepts that lose their meaning in the process of reducing the size of tools or artificial objects. Taken for granted that protophysics can repair the empiricist view of measurement, the following problem may still arise: The prefix “nano” simply indicates a mathematical proportion. As mentioned before, the unit of “nano meter” refers back to the legal definition of the meter (1,650,763.73 times the wave length of the spectral line of the krypton isotope Kr 86 changing from the 5d5 state to the 2p10 state in the vacuum), which is based on extensive physical research and experience. The intrinsic circularity of this reference was already noted above and described as an epistemic problem.

Understandably, the introduction of units and their legal definition by a suitable international institution is not guided by the philosophical interest in founding and explaining measurement, but it serves a quite different purpose: that of providing a reliable basis for communication among scientists. It avoids exchanging samples for magnitudes – a problem that cannot be handled as elegantly in, say, microbiology, because here the reproduction of certain standard organisms is not possible in the same way as it is in the case of measuring units. The formulation of the so-called laws of nature becomes much easier if it can be related to units communicable among persons or institutions. Else, natural laws could only be given through proportions as is the case in Johannes Kepler's famous laws of planetary motion: Kepler compared the paths, velocities, and times of planets in a way that allowed him to state his laws in terms of ratios rather than by naming units such as meter, second, etc.

Measurement in NT, however, cannot be considered as being of the same type as Kepler's laws given the legal definition of the meter, because it is questionable whether the knowledge and technology invested into that legal definition are still valid when it comes to nano scales. A case taken from analytical chemistry that is roughly analogous may illustrate this: The concentration of one substance in another one, for instance with regard to volume, can be given in a mathematically trivial way. The concept of volume is independent of huge proportional factors. Mathematically, a concentration of 1:10 is not simpler than one of $1{:}10^{1000}$. But the real measurement does not live up to this ideal situation. Inevitably, any tool for volume measurement meets a natural limit of tool precision. In other words, those extremely small concentrations lose operational meaning. Any attempt to realize such an extreme ratio would find its limits at the atomic structure of the measuring vessel. This analogy makes plausible that measurement in Nanotechnology is not at all well reflected at the present time. Does the nano meter (and parts thereof), simple as it is mathematically, have any operational meaning at all? We must content ourselves here with having raised the problem. Obviously, there is still quite a bit of work to do for the philosopher of science in the fields of Nanoscience and Nanotechnology. This much is clear at least: Simple confidence on the part of the scientist is lacking good reasons.

To briefly summarize the problems of measurement in the nano domain: What the field is dealing with is not natural laws or natural objects or phenomena, but rather artificially produced situations that depend on technical purposes. This provides perspectives for answers to the question in how far our everyday measuring procedures in the laboratory also can be used on nano scales.

2.4 Epistemology of Innovation and Progress

The public attention that Nanotechnology has attracted centers on the concepts of innovation and progress. Novelty follows upon novelty. Technical progress is permanently announced, promised, or stated. Even new concepts or forms of innovation are supposed in order to comprehend or propagate Nanotechnology. There is undifferentiated talk about both *discoveries* and *inventions* despite the fact that, in everyday language at least, Christopher Columbus is usually called a discoverer whereas Thomas Alva Edison is known as an inventor, and not the other way around. There is an important difference between discovering something and inventing something, at least with regard to patent options. Here, again, some philosophical clarification is needed.

First of all, wherever new developments occur in NT, there is only *technical* innovation involved in spite of claims to the effect that there was pure progress in basic research, which, so the argument goes, was either far removed from any application or neutral with regard to be applicable. (The words "application" and "to apply" then usually are considered reliable concepts of everyday language, which will be shown to be wrong in the next paragraph.) Developments representing technical innovation and the progress caused by them are subject to certain constraints. Two examples of everyday technology size will illustrate this.

2.4.1 Constructive Progress

The proverbial invention of the wheel is historically so remote that its author(s), place and time have remained unknown. The wheel of a vehicle, either freely revolving around a fixed axis or fixed on a freely revolving axis, is not a natural object. Presumably, it was invented as an ingenious improvement of the technique of drawing heavy loads by putting round timber underneath. Historically speaking, the origin of the invention to turn the use of the wheel on a vehicle into a rope-pulley is unknown as well. Instead of leading a rope over a beam in order to lift a heavy load, friction is reduced through the use of pulleys. This invention, thus, can be re-described as finding a new purpose for an old means. The wheel of a vehicle is used as a means for changing the direction of a rope that is drawn.

Once the rope-pulley was invented the inventions of the double pulley and the block-and-tackle could follow. (The double pulley consists of two pulleys of different diameter fixed to each other in order to continually gear down or gear up forces exerted on or by a rope.) These two machines can be interpreted as tools that progressively "apply" the law of levers.

The next step in the technical development leads to the transmission of forces by transmission bonds with different gearing ratios. This technique has been widely used at the beginning of the industrial revolution and is still in use today for changing gears in lathes and drilling machines. The next developmental step was the invention of toothed wheels and of the gearbox that, in turn, was needed before the worm drive could be invented. This does not only allow the gearing down at a very high rate but also functions like a valve that transports force only in one direction. Further inventions such as the synchronized or the automatic gear in cars carried on this developmental history.

Apparently, the direction these steps have taken, the *order* and the *sequence* of these inventions, cannot be reversed. Earlier inventions are indispensable for the later ones. Nobody would have been able to invent pairs of toothed wheels without prior knowledge of the wheel itself. In other words, technical innovation (of that type!) builds on each other in a methodical order. And every step that is taken in this methodical order includes a new interpretation of means for an earlier purpose as the means for a new purpose. The latter inventions represent *progress* relative to the older ones. This can also be described as developments on the way towards *increased height of technology and culture.*

2.4.2 Empirical Progress

Before the philosophical distinctions assembled so far are applied to Nanotechnology, there is an important *second type of technical progress* that deserves mention. To provide a simple example: The history of metalworking brought about the art of producing wire. It was used for mechanical purposes, for bondages to fix blades on handles or for embellishment purposes. A modern mechanical application of wires is displayed, for instance, in fences or in cable cars.

Wires had to be available for a particular discovery to be made: that these wires are electrically conductive. The ancient Greek word for amber (*elektron)* provides a hint. Amber that was polished with a piece of fur showed unusual phenomena like attracting dust or hairs. And it was discovered that connecting a piece of amber with earth would neutralize this static electric charge by a metal wire. Here, again, *a methodical order* can be identified: That discovery would not have been possible without the availability of metal wires even though they were developed for quite different purposes.

Even so, empirical progress is not in the same sense constructively enforceable as the constructive progress discussed before. A discovery by chance – “casual”, to some extent – of a certain, hitherto unknown state of affairs must occur.

Both types of progress rest on the re-interpretation of known means for new ends. Also, the electric use of wires goes beyond their mechanical use. This provides a new philosophical distinction that allows differentiating between new developments in Nanotechnology that are pre-planned (or at least could have been brought about by following a plan) and ones that cannot be planned in advance.

In the case of both constructive and empirical progress, coherent developmental steps can be distinguished from others. The coherence of developments that had led from the wheel of a vehicle to the automatic gearbox, or from archaic wire to electric circuits can only be judged *ex post.* Questions regarding the earlier stages and conditions of an observed historical development can be asked and answered. Even for intermediate steps the conditions that made it possible can be identified. This, no doubt, is a theoretical reflection with the wisdom of hindsight: A development is considered as a chain of steps that consists of human actions with the *rationality of means and ends* as the leading principle.

In a less reflected language one might term earlier states of Nanotechnology "presuppositions" of later ones. However, this description has plausibility only at a first glance. While it properly covers the non-reversible order of steps, it erroneously implies that things can be the "presuppositions" of things. As our analysis has shown, only the usage of an object might methodically be presupposed by another usage. Only in the context of practice, of the practical production and use of objects, the terms "innovation" and "progress" make any sense. This places objects in the context of human action and does no longer consider technical products "as such" or as instances or applications of natural laws.

2.4.3 The Principle of Methodical Order

The *ex post* analysis requires a *"principle of methodical order"*. This principle prescribes that the linguistic representation of a chain of actions has to observe the sequence in which these actions are performed. It rules out descriptions in an order or sequence that deviate from the sequence the actions take in order to gain technical success. The compelling power of this principle does not reflect any natural constraints but rather the rationality of technical chains of productive actions. For any technical product (in the broadest sense) there are chains of actions that will invariably fail when their sequence is reverted. As in familiar cases such as building a house (and consider metaphors about "ground", "construction", "keystone", "foundation", etc.) this order of steps taken by the craftsman to produce something is not a matter of the psychology of the persons involved but one of the objective dependence of actions on each other. One can also learn that not all actions are related in a methodical way: Wherever different components are needed to assemble a product these components must be produced before the assemblage can be effected; but the sequence in which those components are produced is quite arbitrary. It does not matter whether the carpenter produces the windows first and the doors afterwards, or the other way around. But at a certain point they have to be available.

This principle appears pretty obvious in everyday contexts. No one appreciates recipes, manuals, or instructions for use or construction that, if observed, would ensure failure instead of success. In the theory-generating sciences, however, things are different. Wherever initial formulations of theories are at hand, they can (and regularly will) subsequently be rephrased in equivalent ways. A simple example may explain what counts as "equivalent": The theory of classical mechanics contains basic concepts of space, time and matter. It has become "classical" to think of operational definitions of length, duration and (inert) mass. The simple relations between length, duration and velocity (or between mass, volume and density) are usually considered explicit definitions of velocity (or density, respectively) on the basis of measurement of space and time (or, respectively, of mass and volume). But it is mathematically equivalent to prefer instead the direct measurement of velocity by a tachometer (or of density by a swimmer), or of one of the other parameters involved, and, consequently, to define duration as the ratio of length and velocity (or mass as the product of density and volume, as Newton proposed).

As theories are usually considered formal syntactical structures only (quite separate from their material interpretation, according to David Hilbert's understanding of geometry), all types of definitions mentioned count as equivalent; they are truly equivalent only in a syntactical, not a methodical sense, though. Which explicit definition should be chosen depends on the principle of methodical order. The technical availability of measuring procedures is the decisive criterion of which steps (of operational definitions) come first, and which can be added later on as mere linguistic definitions of further parameters.

Therefore, the principle of methodical order – superfluous as it is in everyday life, since there it is never violated anyway – becomes important in science where theories undergo syntactic permutations of both axioms and definitions, of propositions and instructions. Violations of this principle are consequential for the validity of theorems and even of entire theories since the order of actions in controlling theories through laboratory research are ignored. (It will be shown that, to a certain extent, this problem also exists in Nanotechnology.)

2.4.4 The Foundation of Nanotechnology

A further aspect of the metaphorical chain of human actions that bring about scientific results is its limited length. Since a methodical order exists in those chains, both a first and a last step can be identified. There is no problem with the last step. It is defined as the latest stage in a development that can be subjected to an analysis of its history, or the last product that comes about. But what about the first step? In the examples given above (the invention of toothed wheels and the electric use of metal wires) those first steps lie buried in the vaults of unknown and unrecorded cultural history. In the case of modern technologies, however, going back to everyday life and its practices one can identify first steps. The mobile telephone, for instance, can be traced back via the electric net telephone to the initial invention by Johann

Philipp Reis (1834–1874) (and its improvement by Alexander Graham Bell, 1847–1922). The transformation of spoken language into electric oscillation was preceded by electric telegraphy as invented by Samuel Morse (1833, patent 1837) and succeeded by Guglielmo Marchese Marconi and his invention of wireless telegraphy. This technological history goes back at least to military and political systems of transportation of news by couriers (literally: runners) and express riders that served the need for fast transportation of information. In this sense, all technologies are based in needs and practices of everyday life. This also holds for Nanotechnology. Philosophers like to say that the objects of technical and scientific development are "constituted" in the "life world" ("Lebenswelt"). Sciences, then, are considered as "styled-up" everyday practices grown, for instance, from craftsmanship, farming, the trade, or public organization. We will to come back later to the practices (like miniaturization) for Nanotechnology.

The metaphor of the chains of actions that bring about technologies also suggests a potential error. It suggests (and again it does so in the examples mentioned earlier: the chain leading from the primitive wheel to the synchronized automatic gearbox in cars, or from the primitive mechanical wire to electronic chips) that there are only linear chains without ramification. In fact, non-ramified chains usually result from restricted descriptions of historical developments that often concentrate either on a certain starting point or on a certain product. A less biased view reveals branching out with regard to both the starting and end points. Developments are often interlaced. Only consider the chemical or metallurgic improvement of materials for the construction of machines. The picture of a tree that grows in its roots as well as in its branches matches this fact. However, the principle of methodical order always allows distinguishing developmental directions, as it were, from a particular root to a particular branch (or even to a single leaf). That is to say that methodically reflecting science in its technical form must focus on certain aspects or questions.

Nanotechnology as we encounter it today is a complex, disordered collection of different technologies, questions, options, findings, accidental progress, etc. This conglomerate has to be structured by applying the principle of methodical order if a systematic survey is intended. (The results that are offered in this book and elaborated upon by scientific experts from different traditional disciplines in the first place had to come up with criteria and aspects for the tables presented in the following chapters. It had to be decided, for instance, whether needs or trends of research or methods or yet something different should serve to classify present Nanotechnology and Nanoscience research.)

2.4.5 Techniques, Technology, and Theory

Another potential source of error must be taken into account: Philosophical reflection on topics like Nanoscience and Nanotechnology is concerned with linguistic entities, viz., with descriptions of non-linguistic technical and technological development. Any improvement of a technique that is already mastered basically consists of the elimination or avoidance of technical disturbances. Any technological knowledge is know-how, that is, the knowledge how to eliminate or avoid disturbances. The very definition of disturbance, of course, depends on the technical purpose of the enterprise.

As any knowledge aspires to the form of theories as the best intellectual organization for surveying, teaching and using knowledge many believe that the philosophy of Karl Popper is best adapted to the problem of the growth of knowledge: It appears as a cumulative way to collect and augment knowledge by the piecemeal elimination of contradicting cases. In other words, does Popperian falsificationism provide an understanding of technical progress in Nanotechnology through the elimination of false hypotheses?

The technical examples do not support this assumption. When, for instance, toothed wheels substituted older techniques like transmission bonds not the slightest proposition of mechanics was falsified. When mechanical calculators were replaced by electronic ones no theory of either mathematics or physics applied in the machines proved to be wrong. The advantages a novel technique has over an older one does not at all depend on the falsification of the theory that supported the old technology. It is a bundle of advanced technologies and advantages such as reduced costs, faster function, increased reliability, and others that govern technical progress. This must be taken into account when judgments are made on Nanoscience and Nanotechnology: As it turns out, not basic research in the sense of progress of knowledge as conceived by Popper (that is supposed to eventually approach some metaphysical truth or “the laws of nature”) is decisive, but technology in the sense of constructive or empirical progress (cf. 2.4.1 and 2.4.2).

This situation calls for a closer look at the distinctions made in the nano scientists’ everyday language, where they are speaking about discovery, invention, and application. These words, common and unsuspicious as they may be in everyday life, disguise some implicit philosophical presuppositions that turn out to be quite problematic.

2.5 Discoveries, Inventions, and Applications: The Role of Purposes in Nanotechnology

A highly influential cliché has gained prominence in the discussion of the natural and engineering sciences: Researchers into nature and technology are utterly curious persons who like to play, to make *discoveries* "just for fun" (as R. Feynman would have it); they dispense with any utility considerations and are obliged only to the form of truth or validity (or success) that they consider typical of scientific knowledge. Their discoveries, above all, are quite unconstrained by ends, purposes or similarly inferior motives. Only after new facts of nature, new laws, insights, or understandings, etc. are established, *applications* (and their economic pay-off) become legitimate additional tasks for the scientist. The *inventor* is a person, and he performs a function, somewhere in between discovery and application. On the one hand, so the argument goes, inventions may sometimes count as applications of purpose-independent knowledge about nature, on the other hand, they may be considered aids for basic research in the laboratory – such as, for instance, the invention of novel microscope types in Nanotechnology that facilitate new discoveries in, say, molecular biology. Concepts like discovery, invention and application are omnipresent in discussions about the novelty and the importance of Nanotechnology.

2.5.1 What Does it Mean to Apply Knowledge?

The difference between "to discover" and "to invent" something, which is of considerable relevance to the discussion of NT, may rest on the backburner for a moment. We shall first discuss the question: "What does it mean *to apply knowledge*?" What does "application" refer to when the results of Nanoscience and Nanotechnology research are said to be applied in, for instance, medicine, information technology, or cognitive science? The usage of phrases such as "to apply something" or "application" seems quite clear in everyday language; so where is the problem?

It is claimed, for instance, that *Aspirin* is not only effectively applied as an analgesic but also proved to be useful for decreasing blood coagulation and therefore helps against tinnitus as well. Or consider the screwdriver as another very simple example taken from everyday contexts: a screwdriver can also be applied as a can opener. These examples show that the application of something to something else implies the re-interpretation of an object with respect to its purpose: what initially was used as an analgesic turned out to be a successful means toward the new end of curing tinnitus. Or in terms of the theory of action: Application denotes the new interpretation or re-interpretation of ends of available means. Something is turned into a means for new ends.

This use of application language does not quite seem to fit the cases where, for instance, carbon nano tubes are said to be applicable for the storage of certain gases as well as in electronics. Because carbon nano tubes, so we are told, initially were produced just for fun, as objects that lacked any definite purpose, they represented a discovery (the discovery, at least, of their own possibility, of a way of producing them). So in the beginning they were considered free of any purpose, end or goal – and therefore could not possibly serve as means.

However, this way of talking reveals a naturalistic background: In a first approach, the scientists are thought to make discoveries beyond any practical use, application, or goal-oriented invention. They "endeavor into nature" (even though no scientific textbook has ever ventured to define or analyze or explain the concept of nature!). Discoveries are considered purpose-free whereas applications (and inventions) clearly must be oriented towards ends – the tacit assumption behind this view being that only craftsmen, constructors, engineers and, of course, business people act in pursuance of purposes, whereas pure science is devoted to learning about nature, to acquiring knowledge as an end in and of itself.

This is not the place to discuss the historical roots of this understanding of knowledge and science in ancient Greek philosophy. (The English word "banausic" is derived from the Greek *banausos*, meaning craftsman, a person who works with his hands. According to this philosophy, bodily labor was considered unacceptable for the free citizen; it was left to slaves, women and banauses.) Also technology was not considered worth the efforts of free men; slaves rendered technical support superfluous. There was little appreciation then of the artificial or the technical, which has lead to lacking appreciation of means-and-ends rationality in our days. The concept of knowledge that is free of ends, purposes and usefulness is still leading astray our current understanding of the discovery versus invention issue.

2.5.2 Discovery versus Invention

Although the phrases "to discover" (or discovery) and "to invent" (or invention) often are used to characterize the results of science and to distinguish science from engineering, no explications or definitions of them are found anywhere. The debate about cloning humans, for instance, often is burdened by the argument that scientists only did or intended to do what nature did or does. Scientists just do not *invent* anything new; they only discover how nature works. Cloning therefore is only an imitation of nature. Hence, no inventor may legitimately be requested to morally or legally justify anything. The scientist is a discoverer, not an inventor. Even the patent acts that are of considerable relevance to Nanotechnology (which nano discoveries can be protected by patents?) lack definitions of invention vs. discovery that satisfy philosophical criteria. They tend to be flatly naturalistic.

Earlier the names of Columbus and Edison were mentioned as easily recognized labels for the everyday distinction between discovery and invention.

The point of that distinction is that Columbus was able to discover America only because it "was there" (westward from Portugal to India) independently of his journey, his orders, plans, etc. The electric bulb, as invented by Edison, on the other hand, did not exist beforehand. However, everyday language is not very reliable.

Certainly, no one would say that Columbus invented America, and that Edison discovered the light bulb. But one can claim with some justification that Edison discovered a way to produce electric light without burning something, e.g., a wire or the electrodes in light-bow lamps. One also might say that Columbus invented a way of traveling to a new continent unknown at the time. Hence, everyday language is insufficient to tackle the questions whether nano scientists invent or discover something, and whether, accordingly, a distinction between Nanoscience and Nanotechnology can be based on the distinction between discovery and invention. A closer look is needed at research as it is (and not as it appears according to a popular psychology).

What happens in laboratories in general and in nano research in particular decisively depends on the use of instruments and apparatuses with a wide variety of types. Measuring tools that were discussed earlier only represent a part of them. Without sophisticated technology provided by specialized workshops modern scientific research would not be possible. The factual "discoveries" (again, according to everyday language) are only discovered as effects or states or properties of manufactured objects or events; they do not refer to natural objects or events at all. Those objects or events are not "there" in the same sense as America was "there" for Columbus (or even for us since we are equipped with marvelous maps, satellite photographs and globes that show continents and oceans in any desired detail). Hence, "discoveries" made in scientific laboratories always discover possible technical procedures. They are concerned with human actions, which are successful in the sense that they realize events or states that match the (theoretical or hypothetical) expectations of the experimenter. Discoveries, for short, always are bound up with the scientist's own proper actions. In other words, only in terms of means-and-ends rationality lab research can be understood and reconstructed. The scientist makes discoveries by means of his or her inventions. This also holds for all those famous "lucky" discoveries: only if they are reproducible, they count as scientific findings.

One further pitfall deserves mention that, again, can be traced back to ancient Greek philosophy: Purposes (ends, aims) should not be confused with use(fullness). Things that are very appropriate for certain purposes still may be either useful or useless. For instance, many poisons, acts of violence or weapons may be highly rational in the sense of means-and-ends rationality, yet they turn out to be obnoxious, harmful, destructive, and not useful at all. This immediately shows that the criteria of usefulness and lack thereof are quite different from those that distinguish between appropriate means for certain ends and inappropriate ones. Also, it is immediately apparent that only the latter, means-and-ends rationality, provides criteria of scientific truth or falsehood, because the *experimentum crucis* for every scientific statement depends on the successful realization of ends through the choice of the suitable means. To develop a philosophical understanding of what happens in lab research that research must be analyzed in terms of proper ways of speaking about actions, means and ends.

2.5.3 Acting Nano Scientists

Acting, as contrasted by (natural) behavior, has to be learned. That is to say that people, considered as organisms from a scientific point of view, display a tremendous amount and variety of innate "natural" reactions, ranging from metabolic processes over simple reflexes (like the lid-closing reflex) to complex patterns of behavior as when a person runs into an obstacle and falls into a water. But there also are "cultural" motions, which can only be acquired through exercise and learning such as ways of walking, running, jumping, dancing, running a bicycle or a car, skiing, playing tennis, writing by hand, using cutlery, piano playing, etc. With reference to a Greek root, those actions are called "kinetic".

In addition to those actions of motion we have to acquire the abilities to produce or manufacture things. Yet even the most elementary routine actions such as dressing and undressing, preparing and taking a meal, or arranging books in a sideboard are manufacturing or (derived from a Greek root) "poietic" actions. Poietic actions no doubt are indispensable for lab research, measurements, experimentation, and so on. And, finally, there are "practical" actions (from the Greek words *prattein*, to act, and *praxis*, practice, meaning actions that represent or concern relations to other persons). NT, needless to say, is not a private endeavor of an isolated person but a common enterprise.

Actions are distinguished from ("mere") behavior by the criterion that they can be mutually attributed by persons in terms of merit or guilt. We are responsible for our actions while we cannot be held responsible for our behavior (again everyday language use is not sufficiently consequent in this respect). This is one of the indispensable moral and legal fundamentals of free societies – independently of any naturalistic theories about human beings since these theories, again, may claim scientific character only relative to the responsibility persons have for their actions. It makes sense to attribute merit or guilt to what a person does, because actions (and only actions as opposed to mere behavior) can succeed or fail.

The English language unfortunately cannot give adequate expression to an important distinction that is drawn by the German word pairs *gelingen/misslingen* and *erfolgreich/erfolglos*, respectively. The latter pair of words indicates that the purpose of an action is either realized or not realized. "Success" (*Erfolg*) thus is defined as realizing a purpose, "lack of success" (*Misserfolg*) as failure to realize a purpose, to achieve the intended end. Actions themselves, however, also can be judged as either successful or failing independently of their purposes: A person may succeed or fail, for instance, to perform a certain motion (such as in the context of sports, regulated games, dancing, etc). The person acts "correctly" or "wrongly"; the action itself succeeds (in German: *gelingt*) or fails (in German: *misslingt*). This distinction between the two pairs of concepts indeed is essential since, as everybody knows, purposes sometimes are not realized although the person performed correctly and according to established rules. A different person's act may have interfered and prevented the action of the first person from reaching its goal, or else a natural event may have had a disturbing influence on the action. If someone aims, say, at throwing a snowball at a target, a different person may inadvertently cross the trajectory of the ball, or a blow of wind may deflect it from its way. A medical doctor may have done his best to cure a disease and acted in full accordance with the accepted rules of the medical arts, and yet his patient died.

These prototypes of actions and results, exemplified by means of everyday cases, are central to empirical research as well. The experimenter acts while constructing, building and running his experiment according to his knowledge and expectation – but if the experiment does not run as expected, his "experience" then is an occurrence (German: Widerfahrnis) that happens to him; and it does only happen to him relative to the purposes realized in the experimental equipment. Thus, purposes or ends are necessary for any scientific experience. They are not metaphysical entities but simply projected states of affairs towards which our actions are directed. This also implies that things (objects) do not represent purposes or ends; only states of affairs do, which are linguistically represented in the form of propositions. I do not act pursuing a cake as the purpose of my action but in order to eat it or to have it at my disposal.

Planning is an action of the second order in the sense that designing a plan is acting in order to act. Thus, when Nanotechnology research starts out from technical problems in search of a solution, or when, alternatively, it starts out from available techniques in search of possible applications; two entirely different types of action are performed. Someone who performs an action really is doing something different than to describe an action. Sociologists, philosophers in ethics, and others use to distinguish observer perspectives from participant perspectives. For the natural and technical sciences, another difference is more pertinent: that between performance and description. It is not the description of actions that brings about the objects of Nanotechnology but their performance. This probably sounds trivial, but philosophically this issue is essential because traditional philosophy of science has been done with a descriptive attitude: as much as the physicist is considered as facing objective reality or nature, the philosophers is conceived as facing scientists as his objective reality. However, Nanotechnology exists as a social practice only by doing it, not by considering it philosophically. Therefore, doing, acting, performing (and not some theory of nature or science) is the final authoritative instance for the decision as to what is possible or not possible in Nanotechnology.

To sum up the discussion about discovery and invention on the basis of action theory, it is not the nano object, its ontological status, or its properties within the limits set by the laws of nature that decide what can be discovered, invented, or applied. Judgment about Nanotechnology and about the validity of its theories, its purposefulness and its utility can be found only within the realm of the means and ends of human actions. This holds for Nanotechnology as well as for science in general: Its scientific character is independent of individual persons (authors of techniques or theories) which usually is described as "*transsubjectivity*"; and claims of validity for all objects under consideration are usually termed "*universality*". Results, therefore, must be repeatable and reproducible in order to be considered transsubjectively and universally valid. Thus, not natural laws but cultural skills ensure that nano phenomena are technically mastered in this sense. Nanotechnology should stay away from naturalistic pseudo philosophies; Nanotechnology consists of technical know how. Confessions volunteered by nano scientists to the effect that they were imitating or learning from nature belong to the realm of science folklore, and they fall victim to "Occam's razor", the philosophical principle of parsimony.

2.6 Nanotechnology – Technical Know-How or Basic Scientific Research?

Physicist Feynman sees physics challenged by the question how known techniques might be miniaturized (like fitting the *Encyclopedia Britannica* on top of a pin). A new range of phenomena appears at the border between classical and quantum physics. Here Feynman clearly moves to and from between technology from the perspective of physics and the laboratory practice of chemistry that he thinks should be made up by quantum theory. In particular, the manipulation of objects, atom by atom, is seen as being not excluded by the known laws of physics. But before that can be actively endeavored one first needs "to learn to understand the special physics" (Bushan 2004) that governs the nano domain – as B. Bushan requests in his "Introduction to Nanotechnology" in the *Springer Handbook of Nanotechnology*. According to Bushan, R. Feynman had envisioned a technology that employs "the ultimate toolbox of nature" (Bushan 2004) in order to build up nano (and bigger) objects, atom by atom and molecule by molecule – as nature did in the early days of the universe or in the growth of life.

2.6.1 Technical or Natural?

Those lines must not be read in a literal sense. A "toolbox" contains tools but not the materials from which something is produced by means of tool use. We will have to forgive the author for failing to distinguish manipulations from the objects of manipulation. The original meaning of words according to which tools of craftsmen are used to produce something out of natural materials – like a cottage from timber, from trees – must not be forgotten. Only when human actions are distinguished from their objects the distinction between nature and culture (or technology) makes sense. The technical always is the artificial that depends on human ends or purposes. ("Culture" is derived from the Latin words *"cultura"* and *"cultivare"* which mean human intervention into given circumstances – a meaning still viable in phrases such as "agriculture" and "bacteria cultivation" in the lab.)

"Nature", as understood by Feynman, is the material from which something (atoms and molecules, in our context) is built. "[W]e must always accept some atomic arrangement that nature gives us," he explains. And "the physics" which, according to Bushan, we yet have to fully understand in order to apply it to new technologies seems to consist of natural laws that, again, are provided by nature. We are confronted here with a type of *naturalism* that is characterized by two aspects:

- "Physics" is understood as something attached to micro or nano objects independently of humans. Physics stands for natural properties of natural objects. Historically, physicist Heinrich Hertz formulated this view for the first time. He advocated a philosophy of physics (in his famous 1894 book, *Die Prinzipien der Mechanik*) according to which causal relations between natural objects have to be mapped onto logical relations between mental pictures. The structure of mental pictures he referred to as "models" (in fact, it was Hertz who introduced the term "model" into science) and, surprisingly, as "theory" whereas what nowadays is called theory, i.e., a system of propositions, in Hertzian terms is called "the representation of a theory" (in the German original: "Darstellung der Theorie").

– Only after scientists have found a "theory" of a certain range of phenomena engineers can start to apply theories by inventing, constructing, and building new revolutionary machines. Natural laws thus provide the ground, the *fundamentum*, for technical application. But if the explication of the concept of "application" given above can be maintained according to which any application consists of a reinterpretation of (technical) means for a new, hitherto unforeseen purpose, then the leading purpose according to Feynman would be neutral physical knowledge as such, neutral with respect to technical application. Nature has to be "uncovered" (as a form of discovery: taking away a cover that hides the laws of nature) as some kind of business that has to be completed before any idea of applying the findings to human purposes even can turn up. This naturalistic view of physics, and of science in general, ignores *the technical character of any scientific research.*

Only if this technical character and its dependence on the ends of human practices are taken into account scientific efforts can be judged in terms of their successes or failures. Achieving or missing purposes defines the criteria of the validity of scientific results. In this respect, the crucial question of Nanotechnology regarding the proper direction of approaches ("top-down" or "bottom-up") acquires rational meaning.

2.6.2 Top Down or Bottom Up?

The alternative of "top down" and "bottom up" approaches was first discussed in the context of different types of software development in the information sciences. These terms were transferred to Nanotechnology in order to facilitate a distinction between the way down from macro and micro objects through miniaturization to the molecular level (and in some sense from physics down to chemistry) and a strategic handling of atoms, molecules, and nano objects considered as natural entities. The latter ought to be aware of quantum physical laws, and it leads to certain new situations somehow located between quantum and classical physics. Some experts entertain the hope that these new ways of building up new objects will be added to the familiar methods of synthetic chemistry.

This understanding entails considerable philosophical problems that must be pointed out in order to discuss the bottom-up approaches independently of the problems that were described, for instance, as "the argument of the thick fingers" by Richard E. Smalley: Scientists, physicists and chemists alike, speak about atoms and molecules as if these were simple objects available to everyday experience, comparable to stones found in nature. One can take them into ones hands, look at them, describe them, crush and grind them or throw them away. The question about the sources of that familiarity and confidence is usually answered with reference to results of scientific research in the form of theories. They are claimed to have proven successful with regard to explanations and predictions and certainly to encompass the correct picture of those elemental objects. In physics, elementary particles are treated by an extensive experimental practice that is held to support the known atomic models. In chemistry, the periodic system of elements somehow presents the climax of a science by offering an exhaustive survey of all natural substances as sources also for any artificial synthetic matter. Consequently, the physics of atoms and their parts forms the basis of chemistry, because on a lower level physics is able to explain what is observed in chemical reactions. This, briefly, represents the widespread, commonly shared understanding of successful reductionism in the natural sciences.

This view, however, is an *ex post* view, and it violates the principle of methodical order (s. section 2.4.3 The Principle of Methodical Order, above). From the point of view of the historian of physics and chemistry theories are rearranged in such ways as to form a picture in which parts of the historical development depend on each other in ways that never would have lead to the very results accepted today as the (temporary) end of that development. At first, of course, chemists had to identify substances step by step that cannot be split up by chemical procedures. Along this way, they had to learn the differences between dissolving, decomposing and other techniques – or in terms of chemistry: they had to learn the differences between mixture, solution, compound, etc. No doubt, chemistry had become a science in the modern experimental sense by adopting the methods of measurement and experimentation developed by physicists. But the physics of atoms already presupposes the results of the chemical distinctions between substances and the systematic periodic order of elements. In a methodical sense, chemistry provides the foundation of atomic physics, not *vice versa.* This is of some significance for the understanding of what is happening in Nanotechnology. The supposed access to atoms or molecules by physical methods remains dependent on their definition in terms of traditional chemical laboratory techniques. So if properties of substances such as color, melting point, electric conductivity, and others change as they are reduced to nano size, any question about what substances are treated makes sense only relative to the basic chemical definitions.

2.6.3 Historical Development versus Methodical Foundation

According to the natural scientist's self-conception, history of science is irrelevant for the validity or the acceptability of the results of scientific research. Knowledge is seen as being properly controlled by experience, which, if necessary, can be repeated by everyone upon request – so why care about history of science and its casual events, discoveries, etc.? Being able to tell historical stories may mark the difference between the erudite scientist and his colleague of lesser education, but it certainly should not serve to distinguish the successful researcher from the less successful one. Historical knowledge even of one's own discipline frequently (and regrettably) is considered luxury rather than competence in the field itself.

It is not at all surprising to find that scientists share this view. Science is taught that way. The student is made familiar with the state of the art and the latest results, the most recent output of laboratories and publications. This, of course, tacitly assumes that up-to-date data and theories represent the most sophisticated knowledge one ever could hope to obtain at the present stage. What the student has to learn about methods, laboratory equipment, etc. only is presented in this tacit understanding. Consequently, critical questions about the validity of results, the rationality of distinctions, the quality of the terminology, or the logic of theory structure simply cannot turn up. Everything seems to be justified just because, historically, it has prevailed and led to the results supposed to be the best ever.

This burden is most striking in chemistry (and apparently it explains why chemistry is the science that has developed the lowest culture of scientific discussion). A student entering the chemistry classroom for the first time is confronted, on the one hand, with the periodic system of elements fixed to the wall (and tacitly suggesting that this is the complete and latest survey of just about everything there is to know about chemistry) and, on the other hand, with substances and arrangements the teacher has made for demonstrations of what is the case in chemistry. However, these substances in no way are pure bottled nature but rather technical products that already contain advanced chemical know how, as it were. They are in fact produced by an industry specialized on reactants and can be mail-ordered from a catalogue that indicates degrees of purity and other properties of the substances. The devices used by the teacher are no natural objects either but sophisticated tools. And the skills of a good chemistry teacher are also shown in his ability to make all demonstrations look easy, obvious and self-explanatory. So the typical scientist, and the typical chemist in particular, just lacks the practice of asking pertinent questions as to the scientific character of his discipline. Worse still, the aspiring chemist even is trained not to ask those questions. Therefore, philosophical questions use to appear strange, sometimes far-fetched, and slightly outlandish to scientists. They often seem bothered rather than challenged by questions concerning the familiar terminological language, or the believes, metaphors, and images connected with their own scientific activity: How can an outsider dare to assert that he better understands what is done by the trained expert than the expert himself? One essential difference usually is disregarded: While the scientist speaks about the objects of his laboratory practice, the philosopher is concerned with the scientists, their actions and their successes or failures.

Therefore, questions need to be asked about the principles, methods, stipulations, and definitions that carry the results reported, or, in short, about what makes scientific results valid? Philosophy of science has established *protochemistry* as a theory of methods and concept and theory formation in chemistry. It does not only consider the factual development of chemistry in the classification of substances with regard to criteria such as melting and boiling point, specific weight, color, smell, hardness, electric conductivity, and others. Rather, it shows that the very concept of a chemical element is intimately connected with certain methods of separating components, which then serve to prove that the laws of constant and multiple proportions are principles rather than empirical propositions. They are fulfilling the role of definitional constraints. Only presupposing them, on the other hand, leads to ratios of bulks of substances that can be reproduced by certain analytic procedures and, thus, to the assumption that, eventually, the ultimate natural building blocks of all matter might be accessed.

2.6.4 Classes of Substances, Nano-Scale and Protochemistry

If particles or dusts of particles on the nano scale show unexpected properties that differ from those of the original material, and if, say, the color or the melting point change, the original substance and the procedure of changing it through the production of nano particles can be looked into. Methodically speaking, in a first step one must know that a certain piece of material is, say, gold in the sense of the chemical element Au. Then a physical process is initiated in order to produce nano particles of that material. Taking the powder to be gold indeed even though it looks and behaves quite differently than bulk gold only is legitimate by virtue of the powder's "history" or "descent". The question which methods of identifying substances with novel nano properties can be used in order to render Nanoscience coherent and consistent with good old bulk chemistry cannot be answered in this place. Also, methodically speaking, the common methods of mass spectroscopy are secondary because they must be calibrated relative to classical distinctions and methods for identifying chemical elements or compounds.

What is striking to the philosophical observer of the Nanoscience and Nanotechnology discourse is the apparent confusion of models with descriptions of reality. No objections will be raised here against successful chemical or quantum physical concepts or theories for the description of, for instance, chemical reactions or the stability of compounds. However, in their everyday routines scientists tend to use their conceptions of model as if they conformed to the type of description that we normally use in everyday contexts, quite independently of theories, modeling and important basic decisions. Also, nano objects exist for the Nanotechnology scientist only because of theoretical contexts. They cannot be accessed as something "given" without the respective framework of hypothetical theories, basic methodological decisions and purposes that function as the domain of phenomena that is to be modeled.

2.6.5 Pictures or Artifacts Through Nano-Microscopy?

This confusion of models with depictions of nature is also apparent in Feynman's suggestion that microscope technology be refined up to the point where atoms can be made visible. This clearly follows everyday-life experience where we use immediate sight of something in order to describe it. By implication, then, when objects become smaller and smaller, lenses for the generation of optical pictures and, in a further step, light microscopy is used. The principle idea is this: When we look at a far remote object we use a telescope in order to optically approach the object. This technical remedy works (and accordingly defines the criteria of "good" mapping) as if we were personally approaching the respective object. Likewise, with small objects and light microscopy we are tempted to imagine that the instrument is approaching the object. And we appear to see the visible features that the object provides; we see its real properties in all its aspects such as form, shape, size, and color as we know them from the everyday business of seeing and describing objects of familiar size.

Procedures of nano microscopy, however, just cannot be properly understood this way. They do not represent a continuous transformation of the blow-up factor from the immediate 1:1 sight by the 1:2 and 1:n enlargement through lenses or light microscopes of up to 1:1,000,000 magnifications. They simply do not "map" or "portray" the visible properties of the object in the sense of geometrical similarity and the realistic depiction of colors. Geometric similarity is an ideal concept independent of the ratio of sizes of similar figures. (The concept of similarity of geometric entities is independent of the size ratio only in an ideal sense: It holds for figures such as triangles but not, for instance, for the diagrams, i.e. the representations of triangles by lines drawn with a pencil on a piece of paper. An analogous problem with the concentration of one substance in another one in analytical chemistry was mentioned above. There the mathematics also is very trivial, but the operational realization of extreme concentrations confronts the limits of preciseness of technical measuring devices.) Therefore, geometric similarity and geometric picturing are restricted to applications to objects of the same type. The picture and the depicted must potentially be subjected to the same possible description. This situation very much resembles that of photography. We speak of a "good" photograph of, say, a flower *if we use the very same words* for the description of both the real flower and the flower in the photograph. This is the linguistic form of the condition that allows calling something a picture of something else.

The "pictures" of the different types of nano microscopy do not, however, fulfill this criterion. The techniques that are being used up to now (e.g., scanning force microscopy, atomic force microscopy, scanning tunneling microscopy) are *methods of producing artifacts* for which not only the physical principles of data production are different but also the types of effects between a sensor and the target. This is still very much a question of what kind of presuppositions (sometimes depending on other micro or nano theories) enters into the construction of the immediate data-producing devices, and which software constructions are responsible for the resulting visible pictures that are produced from the data thus collected. Although the different types of effects between the sensor and the target (and, again, their quantitative limitations) are being discussed among the scientists as the appropriate theory of microscopy, those problems always run the risk of using false models of direct sense perception. This cannot be discussed here in depth and in scientific terms. However, the following analogy may be instructive:

Imagine blind persons visiting a collection of statues. They are asked to "picture" the statues that are exhibited. Touching the statues with their bare hands is prohibited, however. Imagine further that one of the blind persons brings along different sets of gloves that he uses interchangeably, starting, say, with rather crude street-worker's gloves and then replacing them in turn by very fine leather kid gloves and, eventually, by the thinnest available type of latex gloves as they are used by surgeons. We immediately would assume that this sequence of glove materials represents successive improvements because the rough gloves cannot possibly convey the same information as the surgeon's gloves about the surface of a statue. But this, again, would be a false assumption because it is inadvertently smuggling in knowledge of both our optical sense perception as a control mechanism for our haptic sense perception which itself is modeled after a geometric model of spatial similarity. The thinner and more elastic the material of the glove, the more information is transported. But this, precisely, does not hold for nano microscopic techniques: The corresponding knowledge that would be required just is unavailable.

Let us drive the analogy even further: Another blind person may "scan" the statues with the aid of a small stick. He varies the size and the form of the stick, especially of its tip. He also varies the materials the sticks are made of because he realizes that slightly hitting on the statue provides acoustic in addition to the haptic data, and different materials produce different sound patterns. Again, another blind person, the third one, does not use his stick to tip onto the statues and probe different patterns of tipping but keeps his stick in continuous contact with the object following its surface; again, this strategy also can be varied between a regular scanning pattern to one that is guided by the particular form of a statue starting out, say, with "looking" for extreme points or edges. Here the analogy with picture production software gains relevance: Is there a predefined coordinate system that is invested, or does the object to be detected or recognized define the "coordinates" or the paths of the stick exploring the statues?

Imagine now that the blind persons with their different techniques and approaches to the exploration of the statues communicate about their findings. Which language should they use? Do the particular choices of materials for gloves and sticks, the scanning patterns, etc. influence or even determine this language? Do the blind persons have a means of controlling the correct translation from language into another?

At least it appears that they might employ a strong test of the validity of their respective descriptions: Can they identify the statues or their parts? It is tempting immediately to insist on the introduction of a realistic truth criterion: The statue is as it is; it is the object of exploration. Hence, the results of the different explorative methods must be checked against objective facts: Do the descriptions match the features of the object? This supposes, however, that the object is independently accessible beyond the blind-scanning process. We, the people with normal eyesight, invest something like good eye perspective – an Archimedian observer, as it were – i.e., the museum's clerk who can see both the statues and the blind persons. In other words, there are ways, even strong criteria, for the "translation" of pictures obtained by different methods only if we adopt a naively realistic position. We assume that the objects of microscopy in fact have the properties which are observed or scanned and which computer calculation then transforms into visible pictures. These assumptions, however, are unsupported by any scientific or philosophical knowledge.

Wherever the assumption is shared that we can "portray" objects like atoms or molecules quite a few things are presupposed, such as that all atoms of a certain substance as they are classified and identified by traditional laboratory chemistry are indistinguishable. This is obvious since the question how two atoms of the same sort (and in the same compound) might look different does not make sense within chemistry (of course, "different" not with respect, say, to their place or any other relation with a third object, but "different" in the sense in which we use to compare two apples in everyday life). Two atoms being indistinguishable cannot, however, be the result of an observation by means of a nano-microscope. Rather, this is a theoretical investment into the production of pictures by the machine. Chemists and physicists handle atoms and molecules in the same way biologists handle species or genus in taxonomy: Although the individuals of course are different in many respects they are considered samples of the same taxon. When, for instance, experts on nano microscopy discuss how kind and magnitude of forces at a tip of an atomic force microscope depend on the material on which the detected objects are fixed (besides other effects of chemical or physical secondary conditions), the entire discussion again applies relative to strong assumptions about the objects that are visualized.

This analogy of nano microscopy with the blind persons' visit to a museum was supposed to draw attention to the fact that nano-microscopy is as misleading as it is informative. While it serves and supports certain models, it does not simply generate an empirical data base (as the astronomer's look through the telescope does). The microscopic "pictures" are artifacts not only in the obvious philosophical sense of being purposefully produced by humans, but also in the more sophisticated sense that they are telling us more about the tool of observation than about the objects that are observed. One ought to be aware of naturalisms inherent in scientific terminology: When a scientist labels something an "artifact" he or she is going to say that an observation or a measurement result is disturbed or adulterated for instance by pollution or a systematic deviation of the tool of observation. This way of describing it assumes that the "real" or "true" value or finding, "the real nature of the object", as it were, cannot be observed or measured due to an unintended or unforeseen circumstance or influence. Overcoming or circumventing the disturbance must avoid the "artefact" but keep intact what is considered "the natural" or "the real". However, the undisturbed situation – if achieved eventually – itself of course is the product of technical intervention and intellectual performance and, hence, artificial instead of "natural" in its own right. Only an explicit theory of the instruments that are employed (cf. *protophysics*, as mentioned in section 2.3.3) allows for a sharp distinction between the conceptual and technical investment into observation – and hence between the artificial (the "natural" part, if one prefers to stick to the traditional metaphysical interpretation of nature as the source of the experienced) and the empirical result.

Returning to the problem of identification of substances and objects on a nano scale in terms of traditional chemical concepts (elements, compounds, atoms, molecules), any visualization suffers from the same difficulties as the other methods: When models are confused with what is being modeled, pragmatic coherence gets lost. It is indispensable for NT, therefore, to introduce sharp distinctions between that which is invested and what is considered the outcome. A leading principle for this distinction may lie in the question, which circumstances would empirically falsify what is accepted, considered likely, or believed. Mainly it is the failing experiment, or the failing realization of an object, as well as the technical know how for overcoming the disturbing factors and conditions, that reliably contributes to the growth of knowledge. In short, for Nanoscience and Nanotechnology knowledge takes the form of knowledge how to avoid or overcome disturbances relative to the aims and purposes that are invested. This also holds for the theoretical side of nano-microscopy.

2.7 Consequences

Philosophy of science as applied here to Nanoscience and Nanotechnology is supposed to provide valuable hints for experts (in an attitude that enjoys the division of labor), on the one hand, and to contribute to the public debate (in the interest of avoiding errors through conceptual clarification) on the other. Therefore, a couple of conclusions have to be drawn here in order to focus the self-understanding of nano scientists that flourishes at the borderline between the actual scientific work and its public presentation. This self-understanding and self-definition is neither accessory with respect to the choice of projects and methods by the scientist, nor it is irrelevant for the relation between science and the public. Therefore, several conclusions may be drawn and presented in the form of brief epistemological, ethical, and political theses:

2.7.1 Is Nanotechnology a "Paradigm Change"? (An Epistemic Consequence)

The almost epidemic use of the phrase "paradigm change" goes back to Thomas S. Kuhn's theory of scientific progress (and it can be traced further back to the writings of Polish medical micro-biologist Ludwik Fleck). Kuhn, a disciple of Karl R. Popper, had developed doubts about Popper's understanding of cumulative rational progress in science through the stepwise elimination of errors that contradict singular experience. Instead, he emphasized historical and social aspects of scientific development such as the scientific community's support of certain opinions, the competition of schools and persons, and the dependence of research on leading ideas. Kuhn developed a kind of law of states or levels that science is passing through, from a pre-normal and a normal state to a revolutionary one: A "paradigm" eventually will be replaced by a new one in a revolutionary act. A "paradigm", as opposed to a "theory" (a system of hypotheses) in the philosophy of Popper, is considered a complex set of leading ideas, stiles, exemplary cases, leading texts, methods, etc. – all of them aspects that are essentially shared by a community of scientists working in the same problem areas at a given time.

There is an important, scientific reason for discouraging Nanoscience and Nanotechnology scientists to refer to their field as a paradigm change: The Kuhnian theory suffers from a severe defect which intrinsically matters in the context of technically-based fields such as Nanoscience and NT: it again focuses (as the Popperian theory it criticizes did) on linguistic aspects of a paradigm while it neglects the technical and technological aspects of scientific laboratory research. It has never happened that a lab was shut down as a paradigm change in Kuhn's sense occurred. No equipment was thrown away; no people (least of all the clerks who produce the required lab equipment) were fired. Across all registered paradigm changes, the number and the preciseness of effects or measurable parameters have increased. The Kuhnian denial of cumulative growth of knowledge is mistaken with respect to the technical side of science. Even his central thesis that asserts that two competing paradigms are always incommensurable (i.e., contain concepts that cannot be translated into each other) goes astray: Since they share the same technical basis they always can be made commensurable.

This decidedly holds for Nanoscience and Nanotechnology as well: Miniaturization and bottom-up techniques both have brought enormous progress to technologies. Both constructive and empirical progress as defined in this chapter occurs (s. section 2.4). But that progress should not be designated as a paradigm change, because it takes place without any brake or collision in the higher-ranking aims and purposes of natural science. No scientist is confronted with a situation that forces him to decide to which of two hostile communities he wants to belong. There are no quasi-religious belief systems obliging its adherents to renounce their faith in the older paradigm. Neither classical nor quantum nor chemical laws really have been falsified by Nanoscience and NT; only the focus has shifted to new, admittedly unknown phenomena and their scale range. R. Feynman's famous headline, "there is plenty of room at the bottom", precisely depicts what holds for technical know how and its consequences in physics and chemistry: Its "room" can be claimed without competing approaches. The revolutionary new in Nanoscience and Nanotechnology lies in the prospect of new, even unexpected and of course unplanned technical possibilities they hold out. For those, however, it is still an open question whether they are due to access possibilities induced by technology or by problems of basic research. We therefore should take a look at the responsibilities of nano scientists:

2.7.2 Responsibility for Effects and Side Effects (an Ethical Consequence)

Nanoscience and Nanotechnology are products of human actions of the means-and-end rationality type. Therefore, the actions involved can and must be accounted for. The aspects of discovery, invention and application and their interrelations were discussed above. This will be supplemented now by a look at planning in Nanoscience and Nanotechnology. Public or political critics often exaggerate the claim that research must be properly planned because they misunderstand science as far as its foundation in human actions is concerned. As we have seen, progress is intimately connected with the new interpretation of a means for new ends (like to use a gearbox as a calculator).

It is beyond the scope of any rational planning possibilities to foresee or predict any conceivable changes of interpretations of means for unforeseen ends that human fantasy may eventually come up with. Also the examples of empirical progress referred to above (e.g., the electric use of wires that were originally intended for mechanical purposes) were not predictable, much less predicted. Empirical progress can only be identified after the fact. In this very sense the electric use of wires is a side effect (and, historically, a secondary effect) of its mechanical use (accordingly, the purposes of the electric use are side purposes relative to the original mechanical ones). What holds for these simple examples also is true for comparatively far-reaching impacts of complex scientific results and their technical realization.

People can be held responsible only for consequences that can reasonably be foreseen or at least cautiously imagined, presumed, or suspected. There are of course suitable ways for proper risk assessment and for taking necessary precautions. But the misuse of certain means, foreseeable or not, always has to be identified. Above all, the misuse of otherwise useful means for dangerous or noxious ends is less a matter of responsible planning but rather one of the power to prevent misuse. That is to say that an appropriate understanding of Nanoscience and Nanotechnology as products of human actions is not only a matter of academic philosophy of science but also an important resource for the rejection of false claims nano scientists may be confronted with (cf. section 7.5 of the Springer Handbook).

2.7.3 Where do the Aims and Purposes Come From? (A Political Consequence)

Ends and purposes turned out top from the litmus test for both epistemic and ethical questions. Means-and-ends rationality was invested here as the prototype of rationality to reconstruct what nano scientists do or ought to do. This may appear somewhat idealistic given the complex mechanisms that govern the distribution of money, instruments of rewarding, public interest, and intra-scientific institutional and psychological influences. Where do the aims and purposes come from? Who decides about them? How are they shown to be legitimate? Are there certain authorities (such as in the case of Feynman's visionary talk) that not only put forward a certain program but also offer motivation ("I know that the reason that you would do it might be just for fun") and institutional incentives ("High school competition")?

A first answer concerns an obvious dialectics of ends and means. Dealing with certain problems in science by pursuing certain aims and by offering certain means for problem solving always has effects on the aims as well through the modification or reinterpretation of the available means that was mentioned before. There are no simple non-branching ways of human practices but rather ways that resemble trees with roots and branches. Policy making in the field of science policy, even if it occurs under rational conditions and with the use of economic knowledge (s. the chapter on "Economic Perspectives of Nanotechnology"), depends on a rational appraisal of possible or expectable results and developments. A philosophical understanding of Nanoscience and Nanotechnology may contribute some knowledge about the limiting factors of visions of the future, and it may prevent some mistaken strategies. Yet, policy is acting under risk and with limited knowledge.

Therefore, ends, aims, and purposes themselves must develop in the social and political process. Scientists as experts should be invited to contribute to this process, and they ought to contribute. But in doing so they should abstain from odd philosophies.

2.7.4 A Definition of Nanotechnology

The Definition

The understanding of Nanotechnology and Nanoscience respectively on which this study is based follows from the above considerations that a scientific endeavor always follows a specific purpose that is linked to a specific ability, not only to a certain thing of a particular size. The size is a coincidental or instrumental property at best. This is why Nanotechnology is definitorily linked to new functions that can be used as new means to reach established ends or to reach ends that can be established only with the new functional systems at hand:

> Nanotechnology comprises the emerging applications of Nanoscience. Nanoscience is dealing with functional systems either based on the use of sub-units with specific size-dependent properties or of individual or combined functionalized subunits.

With respect to the many definitions available (Schmid et al. 2003), the extensions of which determine a Nanotechnology in the wider sense, the definition here determines Nanotechnology in the narrower sense thereby capturing the essence of a technology that relies on new functions.

The question whether Nanotechnology (in the narrower sense) is linked to a particular lateral scale becomes an empirical one. In fact, one can find effects that are within the interval between 0.1 nm and 100 nm and do not satisfy the definition and effects that occur above 100nm (or even 1000nm) but show these "specific size dependent properties" (Schmid et al. 2003).

The term "system" is used to separate a specific part of a larger subject area (in nature, society, technology or in the life-world) being under special consideration. The constitution of the system boundaries in a concrete case is guided pragmatically by scientific or technological objectives and purposes. Functional systems are systems where the (technological or natural) functionality to be considered provides the criteria for defining system boundaries. A functional system may be described as a collection of a certain number of interacting subunits forming a new entity with system specific properties. The subunits are ideally combined in a directed manner and are hierarchically organized on different levels of complexity leading to new qualities of the functional system which can not be achieved by uncontrolled combination of the subunits.

An example of a functional system for information storage could be a DNA molecule consisting of individual base pairs as subunits or even a decorated copper surface with individual carbon monoxide molecules as subunits. Another example of a functional system would be a single electron transistor consisting of nanoparticles attached to electrodes both acting as subunits. In contrast, silica particles in Ketchup improving the rheological behavior are not combined in a directed manner while the same silica particles forming a super-lattice in a photonic crystal fulfill these criteria.

Material properties cover magnetic, mechanic, electronic, optical, thermodynamic and thermal features as well as the abilities for self assembly and recognition.

The specific-size dependence of these properties becomes evident when they

- no longer follow classical physical laws but rather are described by quantum mechanical ones;
- are dominated by particular interface effects;
- exhibit properties due to a limited number of constituents, since the usual term "material" refers to an almost infinite number of constituents (e.g. atoms, molecules) displaying an averaged statistical behavior.

These properties have no equivalent in the macroscopic world. For example, the nature of electronic properties roots in quantized features based on the wave character of the electrons that becomes solely relevant in typical length scales. Such length scales are the De Broglie wavelength, the mean free path, and the phase relaxation length of an electron.

The term "functionalized" in conjunction with sub-units is to be understood in the sense either of a chemical functionalization of and by molecules or molecular fragments, causing an ability for special interactions with environmental species. It can also be a kind of physical functionalization, e. g. magnetization, structurization, coating etc.

In contrast to that, scaling laws which hold for macroscopic objects and also keep their validity in the nanometer range continuously do not imply new size specific properties. The examples of the following chapter should clarify this distinction (Schmid et al. 2003).

Clarifying Examples

Nano-effects Dominated by Quantum Mechanical Behavior. For electronic and optical properties, the well known "*quantum confinement effect*" apparent in Quantum dots, Quantum wires and Quantum wells is the most important effect. The quantum confinement effect can be observed when the diameter of the particle is of the same order of magnitude as the wavelength of the wave function of electrons. In this case, the energy spectrum changes from continuous to discrete. Most simply an electron in a nanoparticle can be imagined as an "electron in a box" where energy levels are considered as the solutions of the Schrödinger equation for the box of a given size and geometry. The critical length is reached if the size of the crystal is smaller than the exciton's Bohr radius (i.e. radius of lowest energy Bohr orbital). For Si this is reached at 4.9 nm, for CdSe at 6.1 nm. For metals, this value is even smaller. Consequently, this example fulfills the definition as a quantum size effect.

Ferromagnetism is caused by magnetic fields generated by the electrons' spins in combination with a mechanism known as exchange coupling, which aligns all the spins in each magnetic domain. This coupling is quantum mechanical in nature and not purely due to the magnetic forces acting between neighboring atoms. The energy related to this exchange energy can be expressed as $C \cdot V$, where C is a constant including all energy related to this interaction and V is the volume of the magnetic material or structure. In the case of $C \cdot V <$ thermal energy, a randomizing of the ordered magnetic moments will occur and the ferromagnetic material will show a paramagnetic behavior. From the above relation, a critical size can be determined. Similar to this effect, known as the ferro-paramagnetic transformation, a ferroelectric-paraelectric transformation is possible. Consequently, this example fulfills the definition as a quantum size effect.

Nano-effects Dominated by Particular Interface Effects. In bulk semiconductors an increase of the energy levels near the surface can be observed. The reason for this phenomenon is a surface charge (effected by defects, adsorbed molecules, etc.) which generates a space charge region in the bulk near the surface (in the thermal equilibrium the Fermi level of the bulk must be the Fermi level of the surface). This surface depletion layer can be expressed by the Debye length, which is a material constant and depends on the carrier concentration, in the material. Under standard conditions, the Debye length in silicon is 41.5 nm. For a particle or structure smaller than the Debye length an increase of the band gap can be observed, because of the overlap of the space charges. Consequently, this example fulfills the definition as a particular interface effect.

An illustrative counter-example not fulfilling our definition is the influence of the grain size on the strength of ceramics. Because no dislocations are active, a deformation occurs mainly via grain boundary sliding. Decreasing grain sizes will increase the amount of grain boundary areas and phases just to the extreme case of an amorphous material and will therefore change the strengths of the ceramics in a monotonous way. This reflects a continuous change of physical properties passing from the macroscopic world down to the atomic level. Similar conclusions are valid for nanocomposites.

Nano-effects Resulting from a Limited Number of Constituents. As an example, the design of a supramolecular system consisting of a well defined number of constituents may include a pigment molecule to quench an excited state of a subunit in close vicinity. Therefore, an ideal spatial arrangement between the pigment molecule and the excited subunit is required. The function of the pigment molecule is to quench the excited state and to radiate light of a particular color. This event is the last step of a series of events in the supramolecular assembly. Such a complex architecture of several subunits represents Nanotechnology as defined above, since its function results from the spatial order of a limited number of constituents.

In contrast to that, an arbitrary collection of the same pigment molecules in a bucket serving as color paint is obviously not considered to belong to Nanotechnology, as the color of the wall results from their averaged statistical behavior.

3 Fields of Research and Technology

This chapter deals with the current situation in Nanosciences and -technologies with respect to the definition of the previous chapter. Apart from a supplementary short section (3.4) with some exceptional examples of high technological relevance, only those effects that strictly follow the definition are considered. To the best of the authors' knowledge this is the very first approach to collect and to treat nanoeffects in such a systematic and, regarding the selected fields, quantitative manner. The treatment is concise and corresponds to the importance and the available knowledge of the particular effect. The specialist will gain an overview of the field that is up to the state of the art. Yet the text is also available for researchers of other disciplines and for those that have to assess the field in order to make policy decisions. The following investigation is structured along the line of three tables:

- Materials (with size-dependent properties and engineered functions)
- Information Storage
- Biomedical Opportunities and Applications

First of all an overview of materials is presented. *Materials* with size-dependent properties and engineered functions are the indispensable presumption to realize physically or chemically based nanoeffects and to transfer them into practical applications.

In a second step a highly promising field of application of the effects treated in the first part is assessed and discussed – information storage. It is a physical fact that present systems of information storage are more or less exclusively based on silicon technologies. However, the necessary semiconductor properties are linked with a minimum size of the building blocks. To overcome this limitation novel chemical or physical principles have to be found and intensively tested for future generations of *information storage systems.*

The relevant processes in *Biology* and herewith in *Medicine* take place on the nanoscale with functionalized subunits as characteristic elements. The size of a cell is in the micrometer dimension, the interplay between cells and especially the interactions of the cell building blocks happen by functionalized sub-units on the nanoscale. The treatment of this field, thus, widens the view in terms of the second part of our definition.

It is likely that the basic research as well as the existing and evolving fields of application that is systematically assessed here will develop in the course of the next few decades with a speed, not to be compared with any other technological development in the history of mankind with dramatic consequences for our daily life. Of course, it is difficult to predict which of the numerous fields in the three tables will succeed and which will fail, since numerous of the effects that have become known in the recent past only describe a physical or chemical nanoeffect, however, can not yet be used for predictions. Others already have come along so well that applications can be foreseen or even have been realized. Independent of these different states of development it is the claim of this chapter not to neglect any kind of nanoeffect that might become of interest in future. The three sections are organized by three tables. The handling of the three tables will be explained in detail in the heading of each of the tables.

The exceptions of section 3.4 mentioned above are mostly already established techniques that are generally assigned to Nanotechnology and belong to Nanotechnology in the wider sense. They do not follow the definition. Rather they represent useful scaling effects, i. e. effects that do not appear spontaneously, but can be observed already on the microscale. Reaching the nanoscale the effects may get improved however, they are not limited to it. The inclusion of those examples is to be considered as a concession to those readers who would like to also get an impression of Nanotechnology in the wider sense.

3.1 Materials

3.1.1 Metals

A1: Ferrofluids and Superparamagnetism (also A3)

At the size of magnetic elements scales below 20 nm, a transformation from ferromagnetic to superparamagnetic behaviour occurs (Herzer C. and Warlimont H., 1992). In the superparamagnetic state of the material the room temperature thermal energy k, where k is the Boltzmann constant, overcomes the magnetostatic energy of the domain or particle, resulting in zero hysteresis. In other words, although the particle itself is a single-domain ferromagnet, the ability of an individual magnetic "dot" to store the original magnetization orientation is lost when its dimension is below a threshold. Consequently, the magnetic moments within a particle rotate rapidly in unison, exhibiting the superparamagnetic relaxation phenomenon. This superparamagnetic relaxation is descripted by the relaxation time which depends exponentially on the volume of the particle and the magnetic surface anisotropy. Typically particle sizes for the ferrro- to superparamagnetic phase transformation are between 10 and 20 nm for oxides and 1-3 nm for metals (X. Battle and A. Labarta, 2002). The phenomenon can also be described by a blocking temperature T_B. At temperatures lower than the blocking temperature or at measuring times shorter than the relaxation time the material shows still ferromagnetic behaviour. However, at $T>T_B$, or for relaxation times longer than the measuring time, the time averaged value of the ferromagnetic characteristics (e.g. magnetization and coercivity) vanish within the measuring time. Then the system is in an apparent paramagnetic or superparamagnetic state, even though within each particle the magnetic moments remain ferromagnetically aligned. Because of the superparamagnetic relaxation, the value of remanent magnetization (M_R) and coercivity (H_c) decrease with increasing temperature and vanish at the blocking temperature (T_B). On the other hand, the saturation magnetisation is slightly decreased, a consequence of the relative large volume of a randomly magnetized surface layer of few atoms of thickness.

This unique combination of high magnetization and paramagnetic behaviour opens this material to a very large field of application, especially for medical biotechnology (for details s. table 3). Superparamagnetic particles can be dispersed in a liquid, e.g. oil, without any agglomeration. By applying an external magnetic field the superparamagnetic particles are arranged in chains of particles along the magnetic field and thus the viscosity of the fluid is increased considerably within milliseconds. When the magnetic field is switched off the originally maintained viscosity is reproduced (S. Odenbach 2004). Magnetorheological fluids can be used in gaskets of bushings or in suspension control systems of automotive vehicles.

B1–3: High Strength Materials and Composites (also B5)

Grain refinement has been a research field during the past decades and has proved to be a powerful tool to improve materials properties such as mechanical strength, the ability to withstand plastic deformation. The upcoming of nanostructured materials in the late 1980s opened new chances for further improvement. Advances in the development of tools for characterization of materials with respect to force in the range of pN (10^{-12} N), displacement in the nanometer regime (1 nm = 10^{-9} m) and spatial resolution in the Angstrøm range (1 Angstrøm = 0,1 nm) have provided unprecedented opportunities to investigate materials properties. Furthermore improvements in computational simulation of properties are nowadays available in a performance which could not be imagined a few years ago.

The mechanical properties of nanocrystalline materials on the one hand and of nanocomposites on the other hand will be discussed in the following.

Nanocrystalline Materials. The mechanical properties depend strongly on the type of bonding in the material. Metals with non-directional bond are highly ductile. Ceramics have strong directional bonds and are subject to brittle fracture while some metals are soft and easily deformable due to dislocations. In the nano regime both types of bulk like behavior are altered. Some appealing properties of nc metals and alloys include high yield and fracture strength, superior wear resistance and possibly enhanced superplastic formability at faster strain rates and lower temperatures.

In metals with grain sizes > 100 nm strengthening is attributed to the pile-up of dislocations at grain boundaries and can be described by the semi-empirical Hall-Petch-relation (equation 1):

$$\sigma = \sigma_0 + k * d^{-1/2} \text{ (eq. 3.1)}$$

This model breaks down as grain size is reduced down to the 10 nm range (Wertman 2002), as it is shown schematically in figure 3.1. Below the 10 nm grain size range even an inverse Hall-Petch-relation has been observed in some experiments.

As published by Josell et al. (1999) also freestanding Al/Ti-multilayer thin films seem to follow the Hall-Petch relation although there is still some controversy debate on the results.

Grain boundaries are highly effective dislocation sinks and sources and it is generally accepted that traditional dislocation sources cease to operate in the nanometer regime (s. e.g. Arzt 1998). This is evident due to the fact that the smallest dislocation loop no longer fits into a grain of size d. Additionally it is assumed that the influence of the soft amorphous grain boundary phase is increased when with decreasing grain size the number of atoms in the grain boundary come into the order of magnitude of atoms in crystalline arrangement. The observed superplasticity in nc ceramics which are otherwise brittle relies possibly also on such an effect, although this effect at lower

Table 1: Materials

Materials, playing a role in Nanoscience, are usefully distinguished into two categories:

- materials with size dependent properties and
- materials characterized by engineered functions.

Table 1 is therefore divided into two parts, representing these two fields. The left part (columns 1-3) presents materials with size dependent properties. They are split into metals (1), semiconductors (2), and insulators (3). So, any kind of material, independent of its composition, is considered. The properties, listed in the first column, do not only consider any kind of physical property (A–F) but, and this is of special relevance in Nanoscience, also the capability of nanosized materials to recognize neighbors and environment (G, H). Based on this ordering system, one can easily find any existing property of a material caused by nanoeffects in the sense of the definition. The description of the corresponding effects in the following text sections follows strictly the numbering system A1–H1 (metals), A2–H2 (semiconductors), A3–H3 (insulators). Recognition capabilities (H) are not found to exist with these materials that are throughout of inorganic nature.

Table 1	**Size Dependent Properties**		
Properties	**Metals (1)**	**Semiconductors (2)**	**Insula**
magnetic (A)	Ferrofluids and Superparamagnetism	Quantum (Anti)dots	Ferrofluids a mag
mechanic (B)	High Strength Materials		
electric/ electronic (C)	Quantum Size Effects (QSE); Materials with Switchable Fermi Levels Thermoelectric Materials	Quantum Size Effect (QSE); Thermoelectric Materials	Quantum Siz Ferro- and ele Thermoele
optical (D)	Formation of Discrete Energy Levels/QD; Plasmonics	Formation of Discrete Energy Levels/QD; Photoluminescence (QD/QSE)	Transpare
thermodyn. (E)	Size as Additional Variable in Thermodynamics		
thermal (F)		Phonon Engineering	
Ability for self assembly/ Adaptation (to the environment) (G)	Magnetic Dipole-Dipole Interaction		
Recognition Ability (H)			

The right part of Table 1 (columns 4–6) summarizes materials that are characterized by engineered functions. Materials of this claim are either of molecular or of hybridic nature. Furthermore, nanoeffects can happen on boundary surfaces and so determine their behaviour decisively. From A4–H6, via A5–H5, up to A6–H6 the effects are described in the subsequent sections. Some boxes contain identical catchwords, since the corresponding effect is to be observed for various materials. The detailed description of the phenomenon is then performed at the field it appears for the first time. In order to follow consequently the instructions to handle the table, the other fields containing the same catchwords are only mentioned at the appropriate positions with a reference to the number of the field with the description.

On the basis of the definition, Table 1 presents a more or less quantitative survey over the presently existing material-related nanoeffects, as far as they have been described in the literature. It is not only, as has frequently been done before, a list of actual examples.

	Engineered Functions		
tors (3)	**Molecules/Assemblies/ Biomolecules (4)**	**Hybrids/Compos. (5)**	**Boundary Surf. (6)**
nd Superpara- etism	Molecular Magnetism	Giant Magneto Resistance (GMR)	Proximity Effect
	Molecular Motors & Machines	High Strength Composites	
Effects (QSE); Super para- trics; tric Materials	Molecular Switches		Gas Sensors and Catalysts
nt Ceramics		Photochromism; Plasmonics	Plasmonics
	Brownian Ratchets		
	Nanoarchitectures	Self Assembly of Metal Nanoparticles; Coordination Polymers	Patterns by Phase Separated Block Copolymers
	Shape Complementarity	Biosensors	

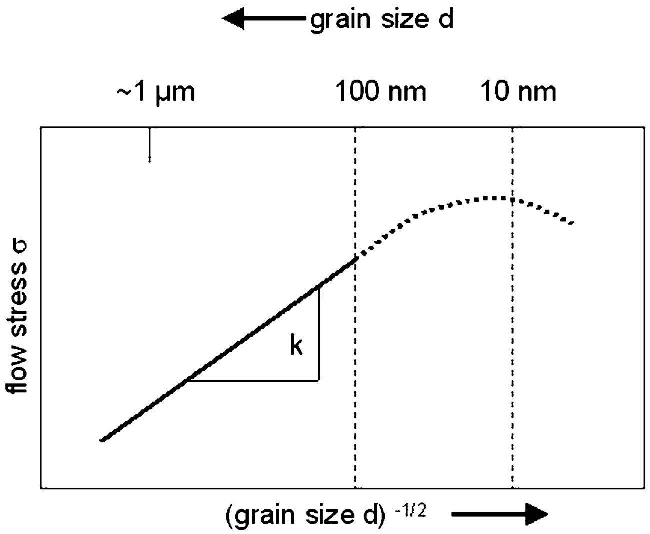

Figure 3.1: Hall Petch relation, flow stress inverse square root of versus grain size.

temperatures may be also due to incomplete consolidation of the nc ceramic material (Mayo 1997).

Peak broadening in X-ray diffraction profiles occurs as a result of both limited scattering volume and the presence of inhomogeneous lattice strains. The latter is often related to dislocation storage and can be used as indirect measures of dislocation densities, arrangement parameters, dipole polarisation and dislocation character. The results of Budrovic et al. (2004) on coarse grained Copper are in agreement with previous studies, but on nc electrodeposited Nickel they found that peak broadening completely recovered upon unloading. They also could show that the deformation process does not build up a residual dislocation network. Two important implications have been concluded from these experiments (Hemker 2004):

- The dislocation activity in Ni-nanocrystallites is fundamentally different in comparison with micro structured Nickel.
- The X-ray peak broadening which is observed under load is an indirect measure of the as yet undiscovered process, or processes, that lead to plastic deformation in nc Nickel.

Further information on the deformation process is provided by Molecular Dynamic (MD) simulations (van Swygenhoven and Derlet 2002). These simulations make it evident that nc metals accommodate externally applied stresses by means of grain boundary sliding and the emission of partial dislocations that run through the grain and are absorbed into the opposite grain boundary. These emitted and reabsorbed dislocations can not be observed by TEM, because their life time is extremely short.

An unsolved problem still is the fabrication of bulky nc materials. Typical methods are

- mechanical alloying (including cryomilling) and consequent compaction (Koch 1997, Zhou et al. 2003);
- severe plastic deformation (Valiev et al. 2000);
- crystallization of amorphous materials (He et al. 2003);
- gas-phase condensation of particulates and compaction (Gleiter 1989);
- sol-gel processing and compaction;
- electrodeposition of metal layers (Erb 1995).

All these methods display problems in fabrication of real high density solids without structural defects. Hot isostatic pressing or vacuum sintering has proved to be one of the most reliable processes. But unfortunately these processes are by far too expensive. Figure 3.2 shows examples of densification in various processes during sintering of various 40 nm ceramic materials in comparison with conventional Yttrium stabilized Zirconia:

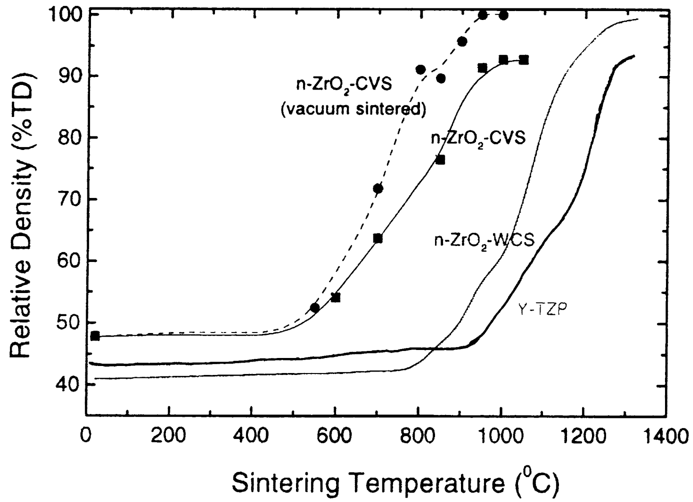

Figure 3.2: Density in % of theoretical density as a function of sintering temperature of chemical vapor synthesized (CVS) n-ZrO_2, wet-chemical synthesized (WCS) n-ZrO_2 and commercial Y-TZP (Hahn 1998, with permission of H. Hahn, Forschungszentrum Karlsruhe).

The difference in the sintering behaviour of the 40 nm wet chemical synthesized and the 40 nm vapour synthesized Zirconia material is striking. The reason for this is not clear. The reduction of the sintering temperature at about 400°C is rather impressive.

In contrary to the behavior of metals the hardness of bulk nc ceramics at room temperature is independent of grain size. Practically, the hardness is unchanged up to those temperatures at which diffusion and grain boundaries deformation by sliding become considerable. These temperatures are lower for nanostructured ceramics in comparison with coarse-grained ceramics of the same composition by the increased content of the "soft" grain boundary phase. At higher temperatures hardness decreases. This behavior is attributed mostly to diffusion and creep flow.

Nanocomposite Materials. Inorganic composites. The problems in avoiding grain growth during the sintering process makes it advantageous to incorporate a second phase of well distributed nanoparticles in a ceramic matrix. For high strength high temperature materials the most favorite materials are Al_2O_3 /SiC and Si_3N_4/SiC composites. But other systems with other components like e.g. ZrO_2, TiO_2, TiN, MgO, W or Mullite/SiC are also being investigated. It should be emphasized that the properties of composites strongly depend on the system under investigation and may vary considerably. Processing also plays a major role. The results reported here are to be seen only as examples and demonstrate the trend of materials improvement of nanocomposite materials.

One of the most important parameters influencing the mechanical properties is sintering density. The best results in the system Al_2O_3/5 vol % SiC with a density of 99,9% have been achieved by hot-pressed materials (Niihara and Nakahara 1991a) while Zhao et al. (1993) achieved a density of only 98,3% by pressureless sintering of material with the same constitution with much less increase in strength. The differences in fracture strength and toughness shown in figure 3.3 published by different authors (from Sternitzke 1997) are possibly due to different processing. The high values of Niihara (filled circles) especially with 5 vol% SiC-addition could not be confirmed by the other authors. Possibly this is due to different processing of the materials. In all works it seems that above SiC contents of about 10 vol% a plateau value is reached which is about twice the value of pure alumna.

Annealing of polished samples at higher temperatures under Argon resulted in a strong increase of bend strength (Niihara and Nakahara 1991b; Zhao et al. 1993). It is suspected that this is due to healing of machining introduced cracks.

The high fracture toughness reported by Niihara in figure 3.3, lower picture, is still discussed controversially. Zhao et al. 1993 reported that depending on the measuring method an increase of fracture toughness between 22 and 100% compared to monolithic Alumina was found. The fracture mode is changing from mixed inter/transgranular in pure Alumina to transgranular within the nanocomposites (Sternitzke 1997).

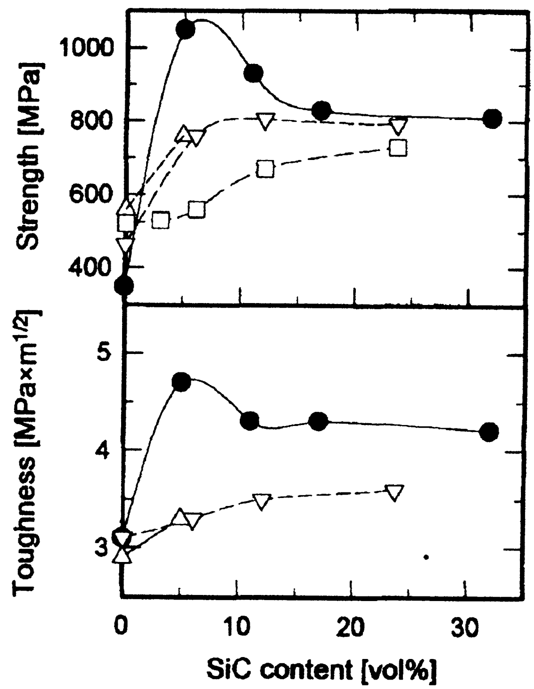

Figure 3.3: Fracture strength and toughness of Al_2O_3/SiC composites as a function of SiC content; comparison of the results of various authors. Reprinted with permission of Sternitzke (1997), "Review: Structural Ceramic Composites". J. of the European Ceramic Society 17 (1997): 1061-1082. Copyright 1997, with permission from Elsevier.

The addition of SiC in an Alumina matrix results in an increase in wear resistance, creep resistance and high temperature strength. Concerning wear two effects have to be considered. First, by the addition of the nano-SiC grain size and thus wear is reduced. Second, grain boundary fracture is inhibited. It appears that processes including plastic deformation are also reduced.

Creep mechanism can be changed by the nanoparticles in the matrix (Thomson et al. 1995). While in the reference sample Alumina showed secondary creep, the nanocomposite material with 5 vol% SiC predominantly was observed at the tertiary creep. It could be demonstrated that cavities at the grain boundaries associated with SiC particles lead to failure. Ohji et al. (1994) observed that the SiC particles at grain boundaries rotate while small cavities are formed. The most important grain boundary sliding of creep mechanism and dislocation movement are blocked by a clamping and riveting mechanism at the nanoparticles on grain boundaries. The improved creep resistance can be seen from figure 3.4. It displays the results of Thomson et al. (1995) and Nakahira et al. (1993) for samples with different com-

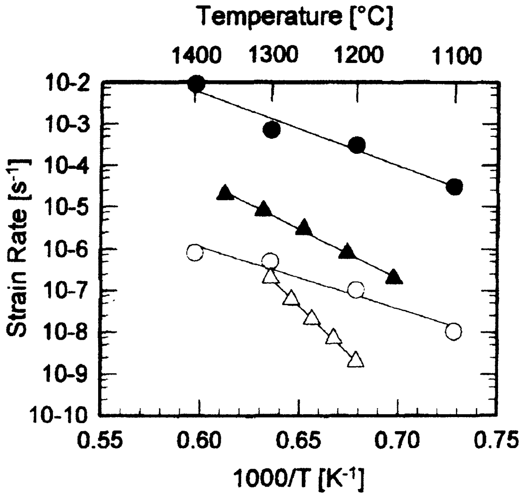

Figure 3.4: Comparison of the results from Thomson et al. 1995 (triangles) and Nakahira et al. 1993 (circles). The figure shows creep rates as a function of temperature for monolithic Alumina (solid symbols) and Alumina with 5 vol% SiC. Reprinted with permission of Sternitzke (1997), "Review: Structural Ceramic Composites". J. of the European Ceramic Society 17 (1997), 1061-1082. Copyright 1997, with permission from Elsevier.

positions of Al_2O_3/SiC under a constant load of 100 MPa for 1% strain as a function of temperature. The results are shown together with the values for monolithic Alumina.

Despite of some differences in performance of the experiments the results are in pretty good agreement and demonstrate the improvement in creep resistance.

The high temperature strength of monolithic Alumina starts to decrease at about 800°C to about 30% of the room temperature strength at 1000°C. Depending on the composition Al_2O_3 /SiC nanocomposites maintain their strength up to 1000°C. At higher temperatures a rather abrupt drop of strength is observed (Niihara and Nakahira 1991a and 1991b). They also report a strongly improved thermal shock resistance.

Polymer Nanocomposites (PNC's). The reinforcement of polymers using fillers, whether inorganic or organic, is common in the production of modern plastics. PNC's represent a new alternative to conventional fillers or polymer blends. In contrast conventional systems with reinforcements of the order of microns in PNC's constituents of a few nanometer or even in the molecular scale are applied.

The characteristic property of the nanoscaled fillers in comparison with conventional fillers is their large interfacial area between the filler and the host polymer. Host polymer can be thermoset or thermoplastic material. As nanofiller materials like e.g. nanopowders, exfoliated silicate layers or Carbon nanotubes are used. This provides new opportunities for new materials with outstanding properties, also in the field of mechanical reinforcement. Small amounts (<10 vol%) of layered silicate additions effect an increase of tensile strength by 40% compared with the neat material. Also the glass temperature of the polymer is considerably increased.

The key of any fabrication process is the uniform distribution of the nanofillers and the engineering of the polymer-nanoparticle interface. Commonly surfactants are used to achieve a good adherence between filler and host polymer. These surface modifiers mediate interlayer interaction by lowering the interfacial energy. For fabrication three main routes are being developed: in situ routes and exfoliation.

In situ routes have not yet reached the state of development for large scale application. But interesting progress may be achieved by self-organization of the in situ produced nanoparticles in the polymer (Pomaglio and Rosenberg 2004). Advantageous in this method is the technology which facilitates uniform distribution of the particles coming into existence. Goal of the exfoliation method is to uniformly disperse and distribute the inorganic within the polymer. The final PNC structure results from the transformation of an initially microscopically heterogeneous system to a nanoscopically homogeneous system. Different approaches have been investigated to fabricate PNC's using exfoliation (AFRL 2004). Each methodology has advantages with respect to the processing steps depending on further processing (powder, film, paste fiber, bulk, monolith).

Because of its outstanding properties Carbon nanotubes (CNT) may become a major important filler material in the future. The Youngs modulus in the TPa-range (Wong et al. 1997, Treacy et al. 1996) is about twice the value of SiC. The tensile strength of CNT is ten to one hundred times stronger than the tensile strength of steel. Furthermore CNT have a very low density (~ 2,1 g/cm^3) so that by adding CNT to the polymer material no density increase will occur. Two main problems are hindering the introduction of CNT. First, CNT are still rather expensive and second, processing with a uniform distribution and good adherence of the CNT in the polymer matrix is not satisfactory at all.

Conclusion. The excellent mechanical properties of nanostructured materials and nanocomposites will make this class of materials indispensable for structure materials. Further work will be necessary for a better understanding on the molecular level, appropriate processing and cost reduction. Although a series of new materials with superior striking properties are on its way the potential of nanostructured materials can be explored only insufficiently without further funding.

The appearance of some effects like the inverse Hall-Petch-relation comes due to the nanostructure of the material. So they can be considered as real

Nano-effect in the sense of our definition. Other properties like the reduced sintering temperature of nano grained powders or the enhanced strength of Nanocomposites can be described by mere scaling down the components.

C1: Quantum Size Effects (also C2/3, D1/2)

Since the time chemistry and physics have provided nanoscale materials, scientists in these fields are focused on a set of fundamental questions, like: How small a number of atoms have to be to loose the properties of the original mater? How does an ordered assembly of atoms behave, when it is no longer embedded into an almost infinite volume of the respective bulk material? And perhaps most important for "nanoscientists": What are the future directions for Nanotechnology and the applications of nanomaterials e.g. in optical or electronic devices?

The fundamental research in Nanoscience has shown impressively that nanoscale materials show many properties that are somehow in-between that of a macroscopic solid or a bulk material and that of a single atom or a molecule. This has revolutionized in many ways our understanding of what is meant by "material specific properties". If, for example, one looks to the melting point of a certain element for which well established and repeatedly proved data can be found in handbooks and tables collecting physical constants, one has to keep in mind that the values are bulk values obtained on macroscopic samples. For the noble metal gold the melting point is 1063°C. But as the diameter of a small piece of gold becomes smaller than 20 nm, the melting point becomes size dependent and it drops down to ca. 200 °C in particles as small as 2 nm (Castro et al. 1990).

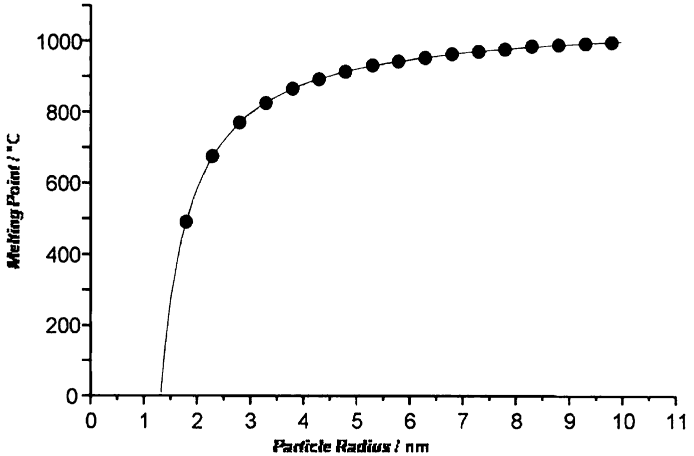

Figure 3.5: Relationship between particle size and melting point of gold nanoparticles (reproduced with kind permission from Castro et al. 1990).

It results from the fact that with decreasing particle size the ratio between surface atoms to inner atoms increases. The surface atoms have a lower coordination number and therefore become increasingly mobile. For smaller particles where the number of surface atoms exceeds the number of inner atoms, the term "melting point" according to its macroscopic definition, i.e. temperature, at which the liquid and the solid phase of a compound are in the thermodynamic equilibrium at 1013 hPa, cannot be applied. These particles now have to be regarded as molecular objects consisting of a limited number of constituents.

Therefore one can start to look on the properties of a nanoparticle from the point of view of a chemist, regarding the particle as a large molecule or even as a superatom or artificial atom with discrete electronic states. Students in their first chemistry course learn to describe the atomic structure by electrons with defined orbits or wave functions around a single nucleus, whereas the nature of the element is defined by the number of protons in the nucleus and therefore by the number of electrons, as long as the atom remains in a non-charged state. The simplest case is the hydrogen atom with one proton as the nucleus and one electron in a spherically shaped atom orbital, the so called s-orbital. For larger atoms, where more electrons come into play, in addition to the nucleus-electron interaction electron-electron interaction needs to be taken into account, leading to a set of quantum numbers, which describe the individual state of each electron in a atom. If atoms interact to form a molecule, linear combinations of electron orbitals lead to the formation of the same number of molecular orbitals, which are bonding or anti-bonding and which are shared between the interacting atoms. In the case of hydrogen a molecule is formed due to the full occupation of the bonding σ-orbital and the empty anti-bonding σ^*-orbital. This concept can be extended to larger assemblies of atoms, i.e. molecules or clusters of atoms, which are still described by a distinct number of molecular orbitals with discrete levels.

Regarding now a piece of matter, under unifying boundary conditions, like perfect order or translational symmetry and infinity, i.e. surface effects are neglected, the periodic combination of atom orbitals leads to the description of extended plane waves. Now the electronic structure consists of broad energy bands, which have its analogue in the bonding and antibinding molecular orbitals. Each band is filled with a limited number of electrons and the energetically highest band, which is fully occupied, corresponds to the highest occupied molecular orbital (HOMO) and is called valence band. Accordingly the energetically lowest band remaining unoccupied, corresponds to the lowest unoccupied molecular orbital (LUMO) and is called conduction band. In metals valence and conduction band overlap, while in non-metals (semiconductors and insulators) they are separated by an energy gap or a band gap.

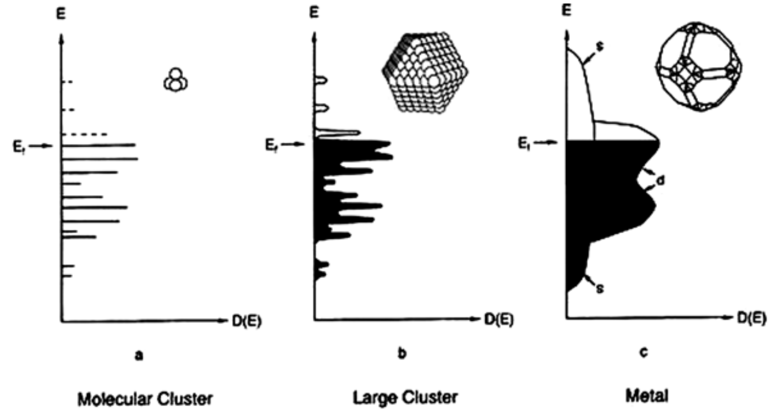

Figure 3.6: Electronic structure of a metal (plot of energy E vs. density of states D(E)) depending on the number of interacting atoms. In a molecule or molecular cluster (a) the electronic states are discrete according to the molecular orbital theory. In a macroscopic piece of metal (c) the electrons occupy energy bands with a continuous density of states. In the intermediate range, represented by nanoparticles or large clusters (b) the energy levels tend to become discrete. Ef denotes the Fermi level and the energy of the highest occupied molecular orbital (reproduced with kind permission from Schmid 2001).

In the intermediate size range between molecule and macroscopic solid for nanoparticles with a diameter between one and several tens of nanometers in diameter the electronic structure is now something in between the discrete electronic levels of an atom or molecule and the band structure of a bulk material. The concept of band structure can still be applied, however, these nanoparticles show a size dependent band gap and tend to form *discrete energy levels* replacing the continuum of the energy bands. In this intermediate state matter reveals new physical properties which now depend on the size of the object under consideration. This leads us to a new understanding of materials specific properties, which are restricted to the macroscopic length scale. Having its origin in the quantization of electronic states this size dependent change of materials properties is called *quantum size effect* (QSE) or *size quantisation effect.* Nanoparticles reflecting these size dependent properties are called *quantum dots.*

Several techniques are known how to prepare quantum dots, each with its individual advantages and disadvantages. Ideally, an ultimate technique should provide significant amounts of a certain material, where each quantum dot has the same size, shape and composition. In that case the single particle properties are not averaged by sample inhomogenities of structural disorder. Which of the present day techniques is favoured for the preparation of quantum dots depends on the scientific question or on the application. Among these the most common techniques are

- lithographic fabrication;
- fabrication by epitaxially self-assembly;
- chemical synthesis.

As an example, lithographically defined quantum dots are formed when a two-dimensional electron system (2DES) or a two-dimensional electron gas (2DEG), as can be found in metal-oxide-semiconductor field effect transistors (MOSFETs) or in so-called semiconductor heterostructures, is separated by tunnelling barriers from its electronic environment. Such heterostructures are formed by layer-by-layer deposition of different semiconductor materials using molecular beam epitaxy (MBE). Depending on the materials chosen (usually GaAs/AlGaAs), a single layer can form a 2DES. Periodic repetition of this sequence leads to the formation of a superstructure, which is also called *multiple quantum wells*. Quantum dots formed by this technique are usually larger than 10 nm and even at the present resolution limits the quantum dots cannot be formed with atomic precision (Davies 1998).

Quantum dot self-assembly from epitaxially grown semiconductor layers, which are typically formed by deposition from the gas phase using MBE or metal-organic chemical vapour deposition (MOCVD) results from lattices mismatch between the substrate or support and the deposited semiconductor layer. Another route is surface treatment by ion bombardment or by sputtering. In both cases a transformation from a two-dimensional layer to a two- or three-dimensional assembly of nano-objects (e.g. dots, truncated pyramids, rings, wires) is induced. However, these structures usually suffer from the strain field in the proximity of the island-substrate interface, which modify the band structure of the quantum dots etc. at the interface. Actually, there are a lot of efforts dedicated to the defined positioning of these objects as well as to the sharpening of size distribution (Petrov et al. 2001).

The chemical preparations of quantum dots or nanoparticles are based on the classical routes of colloid or organometallic chemistry. These techniques are suitable for various metals, usually transition metals, as well as for many semiconductors which have technologically applications in the bulk state. Besides radiolytic and photochemical techniques, typical ways of preparation are

- the reduction of soluble metal salts or complexes by suitable reducing agents (e.g. hydrogen, boronhydride, methanol, citric acid)
- and the reaction of metal ions or complexes with group V, VI or VII anions in the presence of typical colloid chemical stabilizers or of electron donor ligands (e.g. phosphines, thioles) which give an electrostatic or steric stabilisation and enable controlling the particle size.

Consequently, the size of most nanoparticles, which are obtained by these methods, is well defined. In some cases the size is even determined by the so-called geometric magic numbers. This model is developed from a simple geometric consideration and it explains the formation of the well defined size and stability of many nanoparticles. Examples for such structures are $[Au_{55}(PPh_3)_{12}Cl_6]$, $[Pt_{309}phen^*_{36}O_{30}]$ or $[Pd_{561}phen_{36}O_{200}]$ (phen* = bathophenantroline and phen = 1,10-phenantroline).

Various examples for semiconductor nanoparticles, synthesized by the method described above have been developed and the syntheses of uniform quantum dots as well as their arrangement in one-dimensional or two-dimesional assemblies or even in solids or three dimensional super lattices have been demonstrated. A comprehensive overview about synthetic aspects, including polymer-matrices, micellar structures, host-guest chemistry as well as electrochemistry, about the structure and the characterisation of these highly developed materials is given in Simon and Schön (1999), by Schmid (2004), and Schmid and Simon (2005).

Quantum Size Effects in Metals. In metal nanoparticles the quantum size effect is represented by the average levels splitting ΔE in the valence and conduction band. It can roughly be estimated with the formula of Kubo or of Halperin $\Delta E \sim 4E_F/3N$, where E_F is the Fermi energy and N is the number of valence electrons per atom in a nanoparticle (Halperin 1986, s. figure 3.7).

In 1986 results on the size-dependent electrical conductivity of Indium nanoparticles have been reported (Marquardt et al. 1986). The authors speak of the so-called *Size Induced Metal-Insulator Transition* (SIMIT). This refers

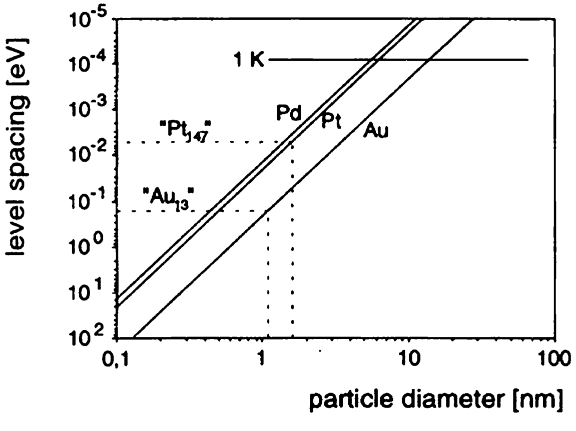

Figure 3.7: Average levels spacing as a function of particle diameter for some metallic elements according to the formula of Halperin (reproduced with kind permission from Schön and Simon 1995). The level spacing of small nanoparticles can be estimated.

to a transition due to a geometrical confinement of delocalized states with a corresponding de Broglie wavelength, when the volume of metallic particles is strongly reduced by fractionation, beginning with a diameter of 1 μm, down to an experimental limit of less than 20 nm, which was given in these experiments.

This effect was detected by measuring the dielectric absorption in the microwave range of small particles of solid or liquid indium metal dispersed in a liquid dielectric. Its explanation claims that the boundaries of these particles confine the electrons into localized states with wave lengths of multiples of half of the de Broglie wavelength $\lambda/2$, thus leading to the picture of "particles in a box". The corresponding level splitting was assumed to be smaller than the characteristic thermal energy k_BT, as the conductivity of these particles is only slightly affected by temperature. This means that the particles still exhibit metallic conductivity, but even with a limited number of electrons determined by the particle size. This effect may be regarded as the onset of the metal-to-non-metal transition, according to Mott's terminology (Mott and Davis 1971).

Clear evidence of discrete energy levels in a 1.4 nm Gold nanoparticle of composition $Au_{55}(PPh_3)_{12}Cl_6$ was given by means of low temperature tunneling spectroscopy (Zhang et al. 2003). This cluster belongs to the family of the so-called full shell clusters, which consist of a defined number of atoms, like a molecule. Based on a simple geometrical consideration these particles ought to gain their stability from the full coordination of a central atom with twelve atoms, forming a closed shell structure around the center. The resulting cluster of atoms now consists of 13 atoms with a defined geometry. To build up a new closed shell around the 13 atom cluster 42 atoms are needed. The new cluster now consists of 55 atoms, which is again a structurally and electronically well defined object with enhanced stability. Generally, a nanoparticle following this construction principle with n full shells consists of $10n^2 + 2$ atoms. To prevent these particles from aggregation or Ostwald ripening and to stabilize them in solution or even in the solid state, the clusters are surrounded by a protecting ligand shell. In the case of $Au_{55}(PPh_3)_{12}Cl_6$ the ligands are Triphenylphosphine (PPh_3) and Chlorine (Cl).

The plot of the differential conductivity shows conductivity oscillations with an average spacing of 135 meV. If this value is compared to the simple estimation of the levels splitting ΔE, the "electronically apparent" diameter is ca. 1.0 nm. This is significantly smaller than the geometrically determined diameter of 1.4 nm for a nanoparticle consisting of 55 atoms, and slightly larger than the expected value of 0.84 nm for a nanoparticle consisting of 13 atoms. However, the difference is assumed to be most likely caused by the six Cl atoms located at the six square faces of the cuboctahedral Au_{55} surface. Since Cl has high electronegativity it removes one electron from the Au_{55} core.

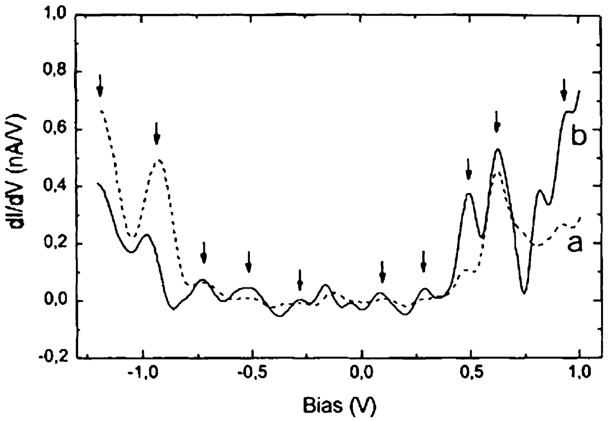

Figure 3.8: Differential conductivity (plot of dI/dV vs. V) of a 1.4 nm cluster, recorded by scanning tunnelling spectroscopy. The two curves (a and b) have been taken at two different positions above the cluster, both reflecting the discreteness of the electronic states by the appearance of conductivity peaks (reproduced with kind permission from Zhang et al. 2003).

On a much larger energy scale than the quantum size effect in metals the so-called Coulomb blockade effect exists, which originally was observed in experiments on small metallic and superconductor particles (Simon and Schön 1998). The Coulomb blockade results from the increase of the potential energy when one electron is added to an initially uncharged particle. This potential energy needs to be overcome by the charging energy to add an extra electron and it roughly scales with 1/r (r = radius of the nanoparticle). Since it can be estimated from the charging energy of a macroscopic metallic sphere scaled down to the nanometer range the Coulomb blockade sometimes is regarded as a "classical size effect". It can be measured by means of tunneling spectroscopy or by using nanocontacts, which are small enough to electrically address single nanoparticles.

A reliable technique, which is called electrostatic trapping, allows the controlled deposition of a single nanoparticle between two metal nanoelectrodes, as shown by Bezryadin et al. (1997). The method is based on the attraction of a polarized metal nanoparticle to the point of the strongest electric field, which is formed when being applied to two Pt electrodes. From solution the particles can be immobilized in the gap between the Pt electrodes. The size of the gap, i.e. the electrode spacing, can be reduced down to 4 nm. In this gap Pd nanoparticles have been trapped to study the electrical transport properties of this double-barrier system. A typical I(U)-curve is shown in figure 3.9. At 4.2 K, the most pronounced feature is the Coulomb gap, i.e. the suppression of a tunneling current below the Coulomb blockade, at a voltage of about 55 mV, which disappears at 295 K, where k_BT leads to thermal smearing of the localized charges.

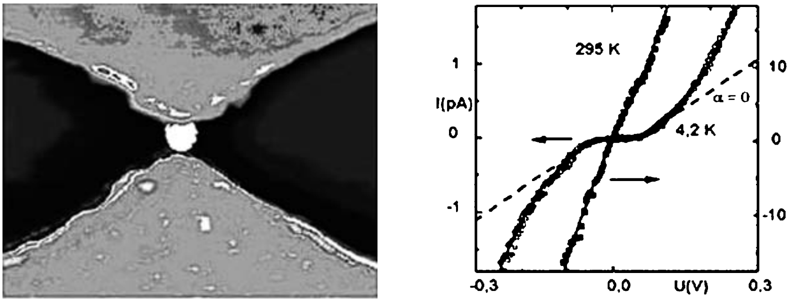

Figure 3.9: (Left) Scanning electron microscopy image of a 17 nm Platinum particle trapped between the tips of two nanoelectrodes. (Right) Current-voltage curves measured at 4.2 Kelvin and at 295 K. The dashed line ($\alpha=0$) represents the hypothetical I(V) curve of a conventional voltage independent tunnel barrier (reproduced with kind permission from Bezryadin et al. 1997).

The Coulomb blockade of metal nanoparticles can be utilized for the set-up of so called single electron devices, which will be explained in *section 3.2.* Thus, metal nanoparticles can be used individually as building blocks in complex nano-architectures for different types of application in switching and memory elements.

Quantum Size Effect in Semiconductors. In semiconductor nanoparticles size quantization effects are predominantly reflected by the optical absorption and emission spectra. According to the band structure model the decreasing of the size of a semiconductor leads to the widening of the optical bang gap E_g between the valence band and the conduction band, or in terms of molecular orbitals, between the HOMO and the LUMO. Thus the energy needed to excite an electron from the valence band into the conduction band, i.e. the formation of an electron-hole pair (an exciton) in such a quantum dot is no longer a property depending only on the chemical composition of the semiconductor, but also on the lateral size. This repeatedly has demonstrated an emission spectra for many different semiconductor materials by means of absorption, showing the so-called blue-shift of the characteristic excitation energies by reducing the particle size (Schmid 2004). This again illustrates that for example the color of a semiconductor, which is a material specific property, becomes size dependent, so that one and the same material can change its color over the whole visible electromagnetic spectrum by changing the size of the particles on the scale of a few nanometers. Furthermore it is apparent that the lowest absorption energy, i.e. the wavelength of the lowest peak of optical excitation and the emission energy, i.e. the wavelength of fluorescence, are not identical. This red-shift is called the “Stokes shift” and is depending on the surface properties of the particles.

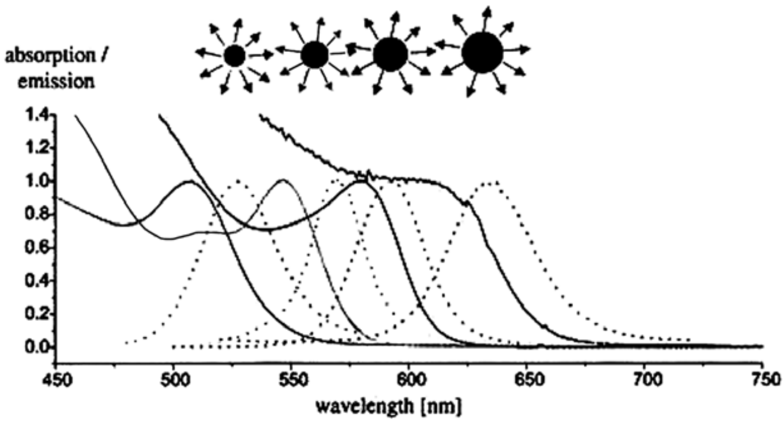

Figure 3.10: Absorption (plain lines) and emission spectra (dotted lines) of CdSe nanoparticles of different sizes (2.3, 3.0, 3.8, 4.6 nm from left to right) showing the shift of the excitation and emission maximum, respectively to shorter wave lengths form smaller quantum dots as compared to larger quantum dots or to the bulk material (reproduced with kind permission from Schmid 2004).

The more pronounced level splitting as well as the widening of the band gap semiconductor quantum dots also has consequences for the electrical properties of the system. Additionally to the charging energy one has to take into account the discreteness of the electronic states. While E_C scales with $1/r$, the quantization energy scale roughly with $1/r^2$, indicating that the quantum effect is more pronounced in smaller system, and that even metals behave as semiconductors at very small particle sizes ($\leq$ 1.4 nm).

In general, there are different ways how to fabricate metal or semiconductor nanoparticles. This ranges from mechanical or tribological methods, like ball milling, via gas phase methods, like sputtering or thermal evaporation, as it is used in molecular beam epitaxy, via lithographic methods (e-beam, UV, soft/imprinting) up to chemical methods. Which method will be the most relevant for technical applications depends on the special purpose as well as on the financial efforts. Nevertheless, chemical synthesis together with a distinct surface modification by ligands or by the formation of core-shell structures seems to be the most flexible approach for the design of properties of the nanoparticles.

Design of Material Properties. The size dependent single particle properties led us to regard nanoparticles as artificial atoms. This raises fundamental questions about the design of "artificial molecules" or "artificial solids" built up from nanoscaled subunits finally leading to a new state of matter. Therefore one could start to look again to the H_2 molecule, which is formed due to the overlap of the electron wave function centered on the individual hydrogen atoms. Correspondingly, the wave functions of the artificial atoms can overlap, too, and electrons can exchange coherently and reversibly between them to form a covalent bond. In continuation the ordered assembly of identical nanoparticles of one, two or three dimensions represents the formation of an artificial solid or super lattice. The fabrication of two- and three-dimensionally ordered super lattices has been demonstrated in several works. Furthermore it is possible to mix nanoparticles of different chemical compositions, of bimodal sizes or of different shapes to obtain tailored nanoalloys. A comprehensive overview is given in (Rao et al. 2004). Remacle and Levine called them new “designer materials” with tunable properties (Remacle and Levine 2001). Such artificial solids exhibit delocalized electron states depending on the strength of the electronic coupling between the adjacent nanoparticles. The electronic coupling depends on the size of the nanoparticles, on the nature and the covering density of the organic ligands, on the particle spacing, and on the packing symmetry.

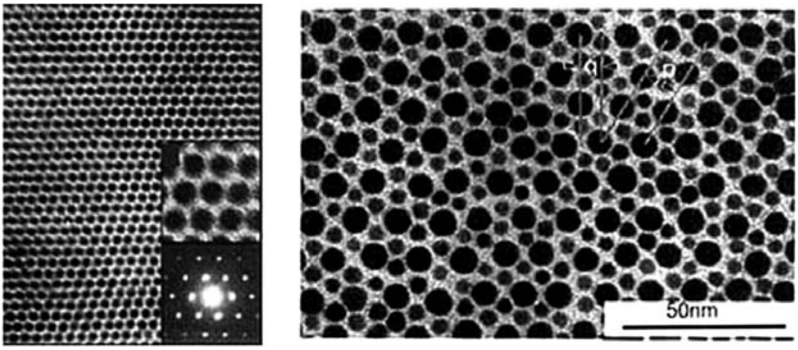

Figure 3.11: Three-dimensional superlattice of 4.8 nm CdSe nanoparticles (left) and bimodal hexagonal array of Au nanoparticles (right) (reproduced with permission from Murray et al. 1995 and from Kieley et al. 1998).

As it is known from solid state physics, any kind of disorder affects the electronic structure of a solid. Accordingly, size distribution, packing defects as well as chemical impurities lead to a modification of the electronic structure of the quantum dot super lattice. Even in the case that the size of the nanoparticles is identical over larger domains (several micrometers), slight deviations in the ligand density or orientation induce that the nanoparticles are not strictly the same at each lattice site, as it would be in the case of atoms. Therefore solids consisting of nanoparticles are inherently disordered and the loss of translational symmetry affects the extended states in the solid, which is immediately reflected in the optical and the electrical properties.

It will be one of the greatest challenges for the next decades to develop strategies for the controlled assembly of inorganic nanoparticles with large functional organic molecules to lead to a new class of tailor-made materials. From the actual point of view the combination of the large recognition capability of biomolecules, like DNA, proteins or supramolecular complexes with the size specific function of inorganic nanoparticles appear to be most promising to achieve this goal. This requires a directed assembly of nanoparticles over distinct characteristic lengths scales (atomic-molecular-supramolecular).

C1: Materials with Switchable Fermi Levels

Most recently it has been reported that some nanoporous metals with high specific surface area, fabricated by aggregation of metal nanoparticles, show a charge-induced reversible strain, as it is known from other materials, like ceramics, polymers or carbon nanotubes (Weissmüller 2003). Their dimensions change in response to an applied electric field are approximately 0.1% or even more. The strain amplitudes are comparable to those of commercial piezo ceramics and can be induced in an electrochemical set-up by switching the Fermi-levels of the metal and, by this, controlling the surface electronic charge density through an applied potential relative to an electrolyte impregnating the pores of the metal.

This effect turns out to be a nanoeffect as a particular interface effect, following a non-continuous trend with the particle size. These new materials have potential applications as substitutes of conventional piezo ceramic components, e.g. in actuators. Besides the control over strain, this effect may lead to applications for materials with tunable electrical conductivity, optical absorption, and magnetic interactions.

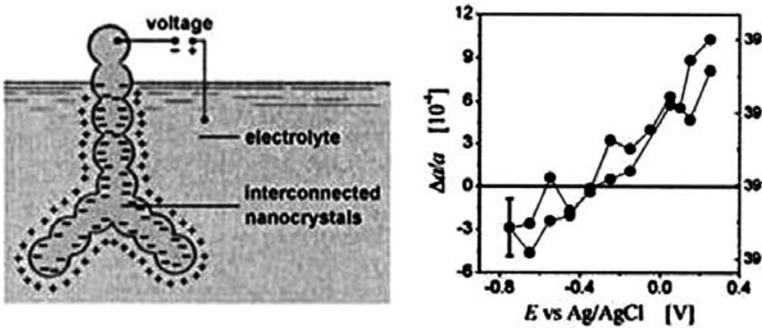

Figure 3.12: (left) Schematic representation of an interconnected array of charged nanoparticles immersed in an electrolyte. (right) Lattice parameter a (right ordinate) and lattice strain Δa/a0 (left ordinate) as a function of the applied potential (reproduced with permission from Weissmüller 2003).

C1: Thermoelectric Materials (also C2/3)

Some materials with confined geometries, like one-dimensional nanowires, two-dimensional superlattices or even zero-dimensional quantum-dots inserted into segmented nanowires can exhibit substantially higher efficiencies in the thermoelectric power (i.e. electrical voltage generated by a temperature gradient in a conductor) as compared to the respective three dimensional bulk materials (Dresselhaus 1999). This is due to an enhanced density of states (DOS) at the energy band edges caused by quantum confinement effects, since the thermoelectric power factor increases with DOS. Together with the increased phonon scattering from the surfaces in low-dimensional systems, this will lead to a reduction in the lattice thermal conductivity and hence to an increase in *ZT*, i.e. the dimensionless figure of merit of a thermoelectric solid.

According to

$$ZT = \sigma S^2/\kappa$$

it depends on the Seebeck coefficient S, the specific electrical conductivity σ, and the thermal conductivity κ of the respective material. *T* denotes the temperature. Thus, a good thermoelectric performance can be achieved with a material having a high electrical conductivity, a high Seebeck coefficient, and a low thermal conductivity. Bulk materials with high S normally have a low σ and according to the Wiedemann-Franz law, σ is proportional to κ. Therefore, the classical way to achieve an enhanced DOS and an increased σ, e.g. by electron donor doping, results in a decrease of the Seebeck coefficient and in an increase of the thermal conductivity.

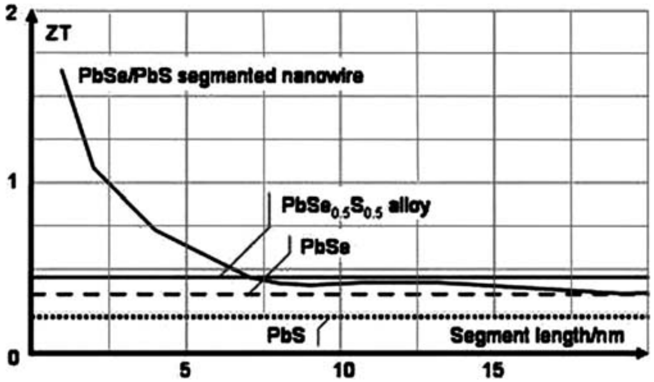

Figure 3.13: Optimal ZT calculated for 10-nm diameter PbSe/PbS nanowires at 77 K as a function of segment length, where "optimal" refers to the placement of the Fermi level to optimize ZT. The optimal ZT for 10-nm diameter PbSe, PbS, and $PbSe_{0.5}S_{0.5}$ nanowires are 0.33, 0.22, and 0.48, respectively (adapted from Bhushan B 2003, according to Lin YM, Dresselhaus MS 2003).

The high electronic density of states together with the increased phonon scattering from the surfaces in quantum-confined structures as well as with the ability to tailor the band structure and electronic transport behaviour allow to optimize *ZT* based on a true quantum size effect. In this course, the most important thermoelectric materials are Bi metal as well as Bi-Te, Bi-Sb and metallic Pd-X (X = Te, Se, S) compounds. So far, the best bulk material is $Bi_{0.5}Sb_{1.5}Te_3$. With nanowires of these materials an enhancement of the thermoelectric performance could be achieved. The proposed application of those nanostructures are elements for thermoelectric cooling, e.g. for the development in solid state refrigerators as well as for cooling elements on integrated microelectronic chips and for the conversion between thermal and electrical energy.

D1: Formation of Discrete Energy Levels/QD (also D2)

S. "Quantum Size Effects" (C1)

D1: Plasmonics (also D5/6)

Plasmons are collective electron oscillations which can be excited by external electromagnetic radiation such as light or by the impact of electrons on conductive systems (cf. cell D1). Surface electrons as a subset of plasmons are bound to the surface or interfacial region of a metallic object and thus can be used for probing the vicinity of interfaces and surfaces due to the presence of evanescent electromagnetic fields close to these interfaces.

In two-dimensional metallic layers, these plasmons are representing guided non radiative electromagnetic waves. Since the dispersion relation of surface plasmons is different from freely propagating electromagnetic waves such as light, special setups need to be used to satisfy energy and momentum conservation. This can be done for example by using the so-called Kretschmann setup, consisting of a transparent (glass) prism and a thin metallic coating (thickness typically 50 nm) allowing to excite surface plasmons by means of total reflection of the incoming light at the basis of the optically transparent prism. Such prisms can be used as a tetrahedral tip for a scanning near-field optical microscope to obtain images of metal nanostructures with a lateral resolution in the order of 25–50 nm (Maas et al. 2003).

The surface plasmon resonance of metal nanoparticles is based in the confined electron gas of the particles: the surface electrons are oscillating with respect to the positive metal core. Due to the excitation of plasmon resonances in the electron gas by visible light, nanoparticles of numerous transition metals show intensive absorption maxima in the UV-visible spectra. For instance, gold, silver and copper nanoparticles of ca. 20 nm exhibit plasmon resonances at ca. 520 nm, 385 nm, and 560 nm, respectively. These absorption phenomena are quantitatively described by the Mie theory (Mie 1908; Kreibig and Vollmer 1995), in which the theoretical absorption spectrum of dilute spherical particles is related to their size and relative dielectric properties compared to the surrounding medium. The wavelength of the absorption

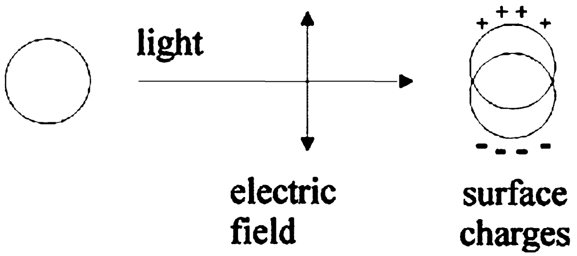

Figure 3.14: Excitation of a dipolar surface plasmon polariton by the electric field of an incident light.

maximum is also dependent on the size and shape of the particles and on their proximity to each other. It has been shown that the absorption spectrum for gold nanoparticles in water changes characteristically with changes in the aspect ratio of the particles. For instance, if the ratio of the major to the minor axes changes from 1 to 4, the absorption maximum splits into two peaks, one corresponding to the transverse resonance and a second corresponding to the longitudinal resonance which shifts from 520 nm to 770 nm.

The surface plasmon band is also sensitive to changes in the surface composition of the particles and to the presence of adsorbates. Deposition of a second metal at the surface also has a marked effect on the spectra. The amplifying effect of two combined appropriate metals constitutes new knowledge.

The field enhancement normal to the surface on small metal particles together with the high sensitivity of the surface plasmons to the index of refraction of the surrounding medium can be used to probe changes in the chemical or dielectric environment of the particle. Furthermore, this effect can be used for the coloring of glasses, ceramics, etc. and for the tuning of the color by the kind of metal, shape and size of the nanoparticles and of the surrounding medium.

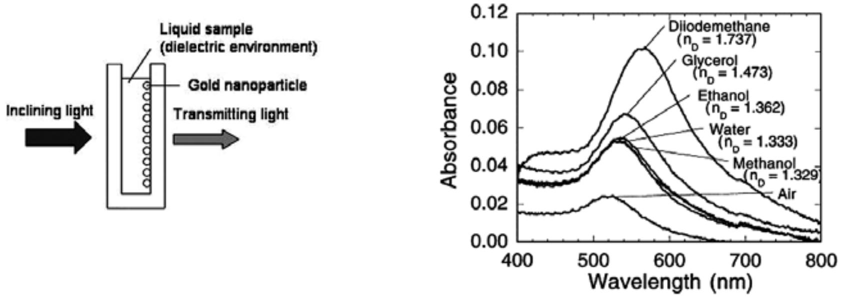

Figure 3.15: Schematic configurations for absorption measurements of a liquid sample and measured absorption spectra of a 20.2-nm gold nanoparticle monolayer immersed in liquid samples of various indices of refraction (with kind permission from Okamoto 2000).

Field localization effects can be used by means of arranging plasmon resonators to guide surface plasmon polaritons. In this way, nanoscopic devices can be made which allow us to generate optical waveguide structures exhibiting spatial dimensions far below the wavelength of light. This has lead to great technological interest and created the field of surface plasmon photonics or plasmonics.

The application of surface plasmons effects ranges from the generation of interference lithography patterns by using resonant surface plasmons to the set-up of optical guides in nanooptical devices as well as to sensor devices based on the interaction of molecular systems at the plasmon guiding metal surface or a nanoparticle. The latter effect can be used, for example, for the generation of highly sensitive and specific biosensors (cf. section 3.3) by modifying the metal surface with biologically active molecules. Another application is in the field of nearfield optical applications as well as the generation of novel nearfield optical probes making use of surface plasmons at glass/metal interfaces (tetrahedral tip). These systems can then be used to generate novel nearfield optical probes with high transmission factors.

E1-3: Size as Additional Variable in Thermodynamics

In the nano-regime the interface and surface energy is comparable to that of the nanoparticles volume energy. Therefore, below a critical size the often simplified definition of thermodynamic functions must be modified to take into account the effect of the surface on the energy balance. Typical values for this characteristic length are ~ 10 nm. Phase diagrams with one of the constituent phases being a nanophase are quite new. Simplest estimates of phase equilibrium may be obtained by taking into account the contribution of surface energy to the free energy. Melting temperature, temperatures of polymorphous transformations and other characteristics of phase diagrams depend on the nanophase size. Thus, the phase diagram of binary nanophase materials become three-dimensional, the third coordinate being the size. One particular phenomenon of interest is the size-dependent melting point depression in nanomaterials – small particles have a lower melting point than the bulk. First attempts for a theoretical understanding of the melting of small particles were made within a macroscopic frame-work, using thermodynamic concepts such as surface energy. While this approach is found for mesoscopic particles with thousands of atoms, its applicability to much smaller clusters (where most if not all atoms are on the surface) is obviously tenuous. An application of this “nanoeffect” is low temperature sintering. Nanometer-sized CeO_2 can be sintered at low temperatures to dense ceramics with nanometer-scaled grain size by the additions of transition metal oxides. The rapid densification may be attributed to size-dependent melting of the dopant in the neck region of the particle contacts. With decreasing nanoparticles size the phase with lower surface energy (packed more tightly) becomes energetically favored in the solid state. For example, in the case of the common body-centered cubic (BCC) and face-centered cubic (FCC) crystal lattice, the latter may become energetically more favorable, since its specific volume and surface energies are less than those of the bcc lattice. Other well known phase changes with decreasing crystallite size are observed for alumina and zirconia. It is interesting to note that Hill (1964) has developed a thermodynamic model of small systems which goes much further than only to stay in the macroscopic approach and to add a surface term. The work was not developed any further by him, but since 1994, after re-publication of earlier books, thermodynamics play an ever growing role in understanding mesoscopic phenomena (Hill 1994; 2001a; 2001b).

Cell G1: Magnetic Dipole–Dipole Interaction

Recently, ensembles of nanosized magnetic particles dispersed in different carrier liquids, have been used as experimental model systems for random magnets. The direction of the magnetic moment in a monodomain ferromagnetic particle is determined by the magnetic potential, which for a noninteracting magnetic particle is formed by the magnetic anisotropy and magnetic field energies. A nontrivial problem appears when the dipole fields due to neighboring magnetic particles become of importance. Effects of the interaction are investigated by studying the change in the magnetic relaxation going from a noninteracting system to a system of a sizeable interparticle interaction increasing the concentration of particles and therefore the distance in-between (Jonsson et al. 1998). It has been shown that the magnetic relaxation of an interacting nanosized magnetic particle system at low temperatures is extended towards longer time scales as compared to the relaxation of a noninteracting particle system. At temperatures higher than 45 K the magnetic relaxation is best described using a model based on single-particle dynamics. Colloidal forces or capillary forces which are generated during drying processes are very often responsible for the ordered array of particles. Therefore, one must distinguish between such common effects and intrinsic forces leading to an ordered arrangement of particles. Ferromagnetic particles or superparamagnetic particles in a magnetic field rather interact via magnetic forces than via capillary forces. If the particle size is much smaller than the interparticle distance, they may be approximated by short magnetic dipoles with the pair-interaction energy which depends directly from the magnetic moment of the particles and of the inverse of the distance between the particles. For identically oriented particles, the interaction is repulsive; therefore, a confinement like a topological or chemical structured surface is required to hold particles together. When few hundreds of particles are confined within the walls of a trough the particles in the center exhibit an ordering of a hexagonal symmetry. Formation of crystalline like structures with the preference of hexagonal over square ordering in large 2D arrays of interacting particles is quite a general phenomenon and has been theoretically demonstrated for several isotropic long-range and short-range interaction potentials. Experiments on colloidal particles with electric dipole interactions and magnetic holes in ferrofluids also demonstrate hexagonal ordering (Golosovsky et al. 1999).

3.1.2 Semiconductors

A2: Quantum Antidots

A quantum antidot (*qad*) is formed, when a potential barrier is introduced into a two dimensional electron system subjected to an external magnetic field (Karakurt 2001). *Qads* can be produced by lithography or by self organization processes resulting in arrangements of electronically and optically inactive or hole structures (nano-rings), which localize electronic states. This is complementary to conventional quantum dot structures which confine an electronic system to the size of extension of dot. Thus, *qads* represent regions of electronic exclusion rather than confinement as in the case of quantum dots. The effect only occurs when the Debye length of the electronic system under consideration is comparable to or larger than the spatial extension of the antidot structure and can therefore be regarded as a quantum size effect.

The structures can be used for inducing resonant tunneling and also for fundamental many body quantum mechanical effects. They may find application in electronic and optical devices such as for building a novel highly sensitive electrometer device for the observation of fractionally quantized electrical charges (quantum Hall regime). Due to many body interactions around *qad* magnetic effects such as Kondo behavior may be induced (Kataoka 2002).

Up to now studies on *qads* have only been reported on lithographically fabricated semiconductor devices. Besides, in solid state chemistry different materials have been synthesized, which in principle fulfill the structural requirements to show *qad* behaviour. One example are the so-called cetineites, which are nanoporous semiconductors with a 1-dimensional channel structure, where the channels may act as *quads* (Simon et al. 1997). Due to the small size of the channels, a magnetically induced electronic current may circulate around multiples of the channels.

B2: High Strength Materials and Composites

(s. B1)

C2: Quantum Size Effects

(s. C1)

C2: Thermoelectric Materials

(s. C1)

D2: Formation of Discrete Energy Levels/QD

(s. "Quantum Size Effects in Nanoparticles" C1)

D2: Photoluminescence (QD/QSE)

(s. "Quantum Size Effects" C1)

E2: Size as Additional Variable in Thermodynamics

(s. E1)

F2/3: Phonon Engineering

Heat transfer in isolators and semiconductors strongly depends on the behavior of phonons, e.g lattice vibration, and therefore differs at the nanoscale from that at the macroscale due to several fundamental reasons. In bulk materials, internal phonon-phonon scattering dominates the heat transfer processes. As size shrinks, the frequency of the phonon-grain boundary or phonon-surface collision increases. The interface scattering of phonons and the associated thermal boundary resistance can dominate heat conduction in nanostructures (Klemens and Gell, 1998). Additionally size effects are not only limited to the thermal processes inside nanostructures. In the vicinity of small devices or particles, phonons become rarefied when their mean-free-path is comparable or larger than the device size, which effectively increases the thermal resistance for removing heat from the devices (Chen et al. 2000). Understanding these physical processes is important not only for the prediction of the microelectronic device temperature rise and reliability, but can also enable new technology development such as low dimensional thermoelectrics.

Apart from thermal conductivity, the influence of the nano-regime on the specific heat is of interest. The phonon scattering at the boundary of the nanocrystals generates new phonon frequencies in a nanocrystal, which contributes to the specific heat. The well known Debye law for the specific heat at low temperature will be suppressed by this kind of boundary scattering if there are a large number of small particles. Compared to bulk material, the specific heat of nanocrystalline material is enhanced by 10 to 20% for temperature lower than the Debye temperature.

Assisted by recent advances in materials processing and techniques for phonon generation and control, phonon engineering can significantly enhance the performance of nanostructure solid-state devices (Cahill at al. 2003). Of special interest today is the development and implementation of device configurations in which phonons and the coupling of phonons to electrons and holes leads to enhanced device performance. Unlike in bulk materials, the phonon properties of these low-dimensional systems and, in particular, the phonon frequency, group-velocity, spectral density, as well as the strength of the interaction with carriers can be widely modified in phonon engineered materials as well as in carbon nanotubes (Dresselhaus et al. 2004).

Another interesting field of application is the use of nanostructured layers for improved thermal barriers for gas turbine blades. Calculations as well as experimental investigations have shown that the thermal conductivity of nanostructured ceramic layers can be decreased by a factor of 10 (Braginsky et al. 2002 and 2004).

3.1.3 Insulators

A3: Ferrofluids and Superparamagnetism

(s. A1)

B3: High Strength Materials and Composites

(s. B1)

C3: Quantum Size Effects

(s. C1)

C3: Ferro- and Superparaelectrics

In contrast to normal dielectrics, ferroelectrics (e.g. perovskites) show a spontaneous electrical polarization and in which the direction of the polarization can be reoriented between crystallographically defined states by an external electric field (Richter, Trolier-McKinstry 2003). This results in a hysteresis-loop with a saturation polarization at high field strength and a remanent polarization P_r.

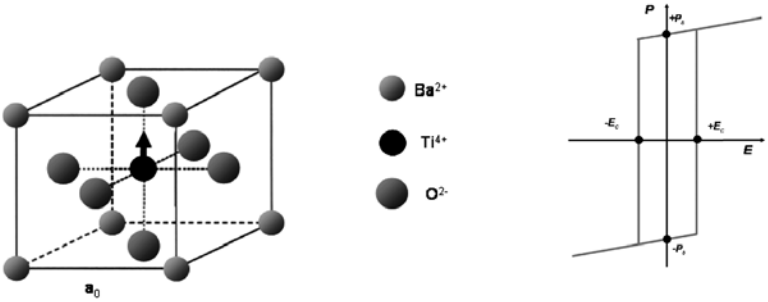

Figure 3.16: (left) Unit cell of cubic $BaTiO_3$ (perovskite structure). The central Ti^{4+}-ion is coordinated by six O^{2-}ions in octahedral configuration. The arrow at the Ti^{4+}-ion illustrates the possible displacement of the central ion at the transition to the tetragonal ferroelectric structure that leads to a spontaneous polarization and, hence, to the ferroelectricity of tetragonal $BaTiO_3$. (right) Idealized hysteresis-loop of the polarization P as a function of the field E for a ferroelectric material, when recorded in the polar direction. The remanent polarization P_r and the spontaneous polarization P_s are identical. An electrical field amplitude $E > E_c$ is needed to reverse the polarization.

The polarization appears in a uniform direction and extends over domains. The domains are separated by domain walls, which have a typical size of 1-10 lattice parameters. The domain size itself depends on the material and can be as small as 20 nm, whereas the orientation of neighboring domains is anti-parallel. Below this size a transition from the ferroelectric phase to the superparaelectric phase analogous to the superparamagnetism in ferromagnetics, which has no spontaneous polarization, appears.

Ferroelectrics are already very widely applied. In the course of further miniaturization they turned out to be very promising materials for logic devices, i.e. ferroelectric field effect transistors as well as in ferroelectric random access memories (cf. section 3.2).

C3: Thermoelectric Materials

(s. C1)

D3: Transparent Ceramics

Conventional translucent alumina ceramics exhibit poor mechanical properties and a low in-line transmission of unscattered light (<15%) because of coarse micro-structures (grain size > 20µm); in fact, they are optically not clear. The new alpha-Al_2O_3 ceramics with a nanosized grain structure avoid these shortcomings and can be manufactured with relatively complex shapes. Such materials show in-line transmission (wave length = 640 nm) > 70% at thickness 0.8 mm, the same high infrared transmission as sapphire in the 3-5 µm range. The strength of this ceramic is extremely high (600-850 MPa) because the defect size is in the nm range. The hardness, scratch and wear resistance are also very high (Krell et al. 2003). Many different reasons for scattering events in an alumina ceramics exist: rough surfaces, pores, inclusions and grain boundaries. Of these mentioned reasons, only scattering at the grain boundary and pores is of interest in the framework of the discussion of nanosized effects. The other scattering effects can be eliminated by optimized processing or the use of very high purity powder. At grain boundaries, the scattering has two reasons: reflection and refraction. The reflection at grain boundaries of alumina is caused of its hexagonal crystal structure, alumina is birefringent. The Raleigh-Gans-Debye Theory shows that at grain sizes smaller than 1 nm, the scattering of light caused by refraction is negligible. The scattering at pores shows a maximum in the region of the wavelength of the light (Mie theory); nearly no scattering can be observed at pore sizes smaller than 10 nm. Between these extreme values, significant scattering of light occurs because the refractive index of pores (air) and the ceramics bulk material is too different. Therefore, for transparent ceramics, submicron sized grains and pores with sizes smaller than 10 nm are necessary. The economic importance of transparent ceramics is relatively low, only some niche markets like lamps or watches exist, but the development in this field can stimulate the improvement of technical ceramics like the investigation of super-fast densification of nanocrystalline MgO powders by spark plasma sintering (SPS) between 700°C and 825°C under applied pressures of 100 and 150 MPa shows. With this method fully-dense transparent nanocrystalline MgO with a 52-nm average grain size was fabricated at 800°C and 150 MPa for some minutes (Chaim et al. 2004).

E3: Size as Additional Variable in Thermodynamics

(s. E1)

F3: Phonon Engineering

(s. F2)

3.1.4 Molecules/Assemblies/Biomolecules

A4: Molecular Magnetism

Unpaired electrons in particular molecular subunits cause small magnetic moments. Organic stable radicals or open spin metal complexes are typical members of such subunits. Modern chemistry allows to assemble several such subunits to larger molecular architectures as nano-objects. However, the control of the interactions between such subunits and the design of larger assemblies with tailor-made magnetic properties is a very active current research field (Miller and Drillon 2001). Of particular interest is to combine the subunits in a way that adds up the small magnetic moments of each subunit to a larger over-all moment of the nano-object, entitled "single

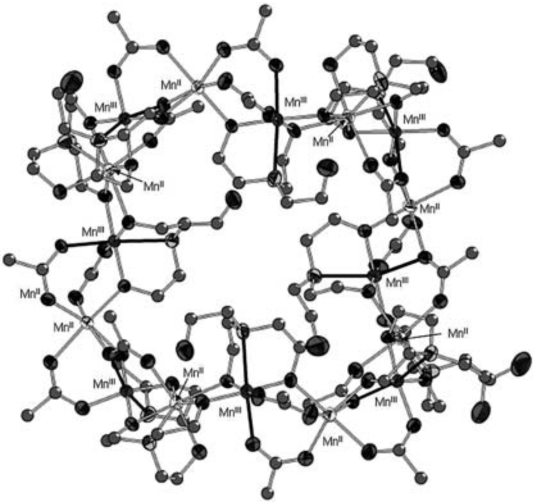

Figure 3.17: Model of the cyclic spin cluster $[Mn_{16}(O_2CMe)_{16}(teaH)_{12}]\cdot 16MeCN$ consisting of 16 manganese atoms that are assembled by small ligands. Reproduced from Murugesu et al. 2005 with permission from Wiley-VCH.

molecule magnet" (Barbara and Gunther 1999; Sangregorio et al. 1997). Considerable progress has been made by combining several open spin metal complexes to so-called spin clusters. While first spin clusters combined 12 open spin manganese atoms (Sessoli et al. 1993; Gatteschi et al. 1994), the number of maganese atoms has been increased. The figure bellow displays a cluster containing a total of 16 manganese atoms of the oxidation states II and III (Murugesu et al. 2005).

Such single molecule magnets are well defined magnetic particles in size and shape which display a slow relaxing magnetic moment. Molecular Magnets are based on the tailored coupling of molecular subunits. Due to the nm scale-length of the building blocks, the interaction between subunits and the magnetic behaviour of the resulting "Molecular Magnet" can only be described with quantum mechanical rules instead of classical physical laws.

Molecular magnets are of particular interest as nanoscale objects which may serve in future as very small memory units. Potential applications are low cost short time memory devices.

B4: Molecular Motors & Machines

Molecular motors and machines are systems consisting of molecules or molecular subunits that display mechanical motions and/or movements. The vision to profit from designed molecular devices to transport material or to perform mechanical motion is very promising and leads to various research activities. While complex systems performing mechanical motion have been found and isolated in nature, the number of synthesized devices is rather limited due to the required complexity of working systems.

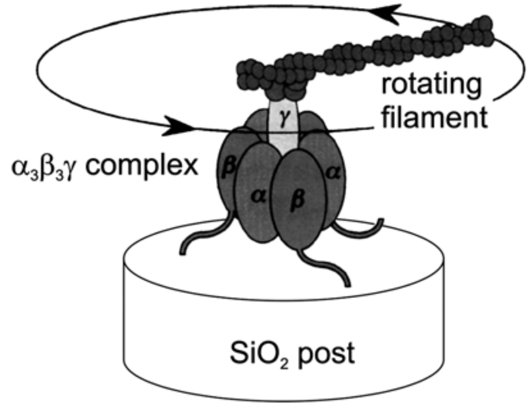

Figure 3.18: Schematic representation of a F_1ATP synthase immobilized on a SiO_2 post. The γ subunit as the axis of the $\alpha_3\beta_3\gamma$ complex is functionalyzed with a fluorescent filament to visualize the rotation upon exposure to ATP.

The most prominent examples of biological mechanical motors are rotation systems like the F_1-ATPase (Noji et al. 1997; Elston et al. 1998) or the bacteria flagella motor (Berry and Armitage 1999) and "walking" systems like kinesin proteins (Hirokawa 1998) or dynein protein complexes (King 2000) transporting cargo along microtubules in cells. Even the translocation of proteins on chains of nucleic acids like RNA and DNA polymerases can be considered as molecular motions, even though their movement is not directed as in the case of transport proteins like kinesin and myosin (Julicher and Bruinsma 1998). Several of these biological systems have already been implemented on artificial platforms to investigate and even to profit from their motions (Hess et al. 2004). Prominent examples are the immobilization of an F_1-ATPase rotor (Noji et al. 1997) or kinesin functionalized surfaces as traffic platforms for microtubules (Hess et al. 2004). The F_1-ATPase rotor was mounted on a prefabricated post and was functionalized with a fluorescent actin filament. Subsequent optical investigations proved the rotation of the filament in the presence of ATP, the "fuel" of the F_1-ATPase rotor. A schematic representation of the experiment is displayed below.

Kinesin functionalized surfaces have shown to move microtubules in the presence of ATP. Microtubules are rather stiff rod-like objects and do not like strong curvatures. Hence their tracks on substrates can be predefined by channels made by lithographical methods. The concept has already been applied in several model systems e.g. for light-controlled cargo transport (Hess et al. 2001) or to control the direction of the motion of the microtubules (Hiratsuka et al. 2001).

In contrast to these from nature extracted systems, man-made molecular motors consist of smaller molecules or molecular subunits performing mechanical motions. These objects consist of at least two parts, of which one can be moved relative to the other. These parts are either molecular subunits that are linked by a covalent bond which is at the same time the rotation axis of the motor, or the parts of the molecular motor are supramolecular subunits (individual molecules) assembled by supramolecular interactions. The design and synthesis of molecular subunits and the subsequent assembly of the molecular motor is a very challenging current research topic and the number of synthesized "working" systems is still very limited. Some pioneering examples are redox switchable catenanes, which will be discussed in the subsection on nanoarchitectures. A few examples of synthetic molecular motors with rotations based on sequences of chemical reactions have been reported (Koumura et al. 1999; Balzani et al. 2000). Even though these motions are not fast and their working mechanisms and principles are subjects of current investigations, there already exist first applications. A rotaxane consisting of a ring annealed on a rod has been placed between two electrodes. As the ring has two stable positions on the rod and its actual position can be triggered

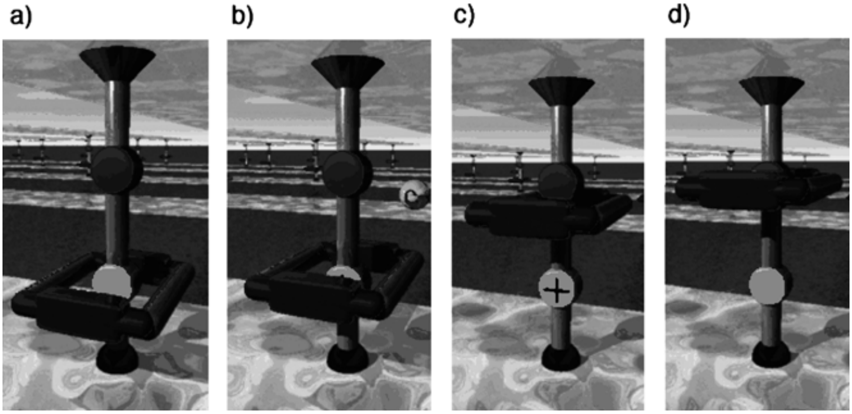

Figure 3.19: Graphical representation of the working mechanism of a molecular switch tunnel junction. The rotaxane axis provides two positions for the interlocked ring. a) Due to electrostatic interactions the ring prefers the lower position. b) The lower position is oxidised electrochemically and the resulting repulsion moves c) the ring to the upper position as shown in d). Reproduced from Luo et al. 2002 with permission from Wiley-VCH.

electrochemically, the potential of the device as memory cell has been investigated (Luo et al. 2002). The suggested working principle of the device is displayed below.

Molecular Motors and *Machines* display motions of (supra)molecular subunits relative to each other that are inspired by the engines of the macroscopic world. These motions are properties that evolve from a limited number of constituents and their interactions.

C4: Molecular Switches

A molecular switch is a molecular or supramolecular system which is to a reasonable extend stable in two different states. Ideally, both states are interconvertible by external stimuli and display different physical properties for the read out of the actual state. Of particular interest are molecular switches displaying good control of the addressing, switching and reading of the actual state (large differences of physical properties and long lifetimes of both states), as such systems may serve as molecule based information storage devices. Some possibilities of such bistable molecular switches are (Mayor et al. 2003).

- A reduction-oxidation (redox) process may change between neutral and ionized acceptor/donor groups of a given molecule.
- A configuration change may take place through a reversible re-arrangement reaction.

- A conformation change may be controlled in a manner that both conformations are sufficiently stable at the operation temperature of the designated storage element.
- Electronically excited state R* and ground state R can be used as pair of different states, if the lifetime of excited state R* is sufficiently high.
- Spin magnetic moments may also be used as states for switchable devices.

In all cases, the bistable switches are characterized by double well potentials concerning their energy and exhibit a hysteresis when driven between the two states. Often only the combination of more than one of the above described effects results in the desired hysteretic properties.

An example of a supramolecular system as a molecular hysteretic switch is the catenane synthesized by Asakawa et al. (1998). It consists of two interlocked rings (definition of a catenane) that are decorated with electrochemically active subunits. Temporary charging of particular subunits by an applied electric potential results in a controlled motion of one ring relative to the other to another stable configuration due to coulombe interactions. It is noteworthy that the system can hence be considered as *Molecular Machine* (see subsection before) as well. Both configurations are stable at zero volt. However, immobilized between two electrodes as monomolecular layers (Collier et al. 2000), they differ considerably in the observed tunnel currents, an effect that allows to observe the actual state of the switch. However, the origin of the observed switching behaviour is still under investigation. Lately, a comparable system displayed switching on a carbon nanotube as electrode, reducing the number of discussed potential switching mechanisms in these devices (Diehl 2003). In view of the application potential of a properly working device, the large number of activities in this research area is not surprising.

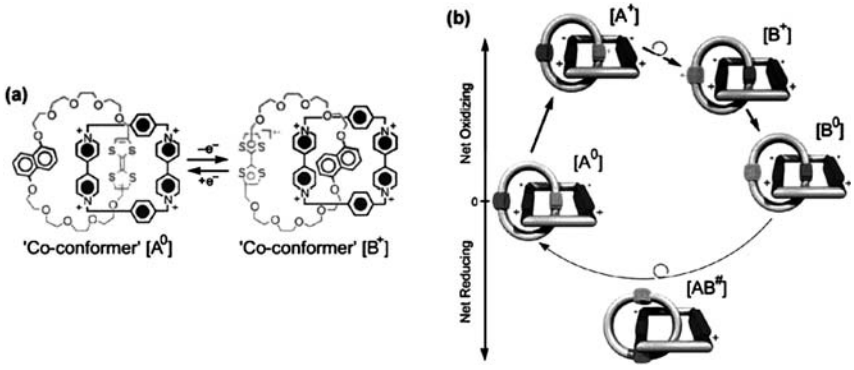

Figure 3.20: (a) Schematic representation of both stable configurations of the supramolecular catenane switch. (b) Switching by temporary charging of particular electrochemical active subunits on the rings.

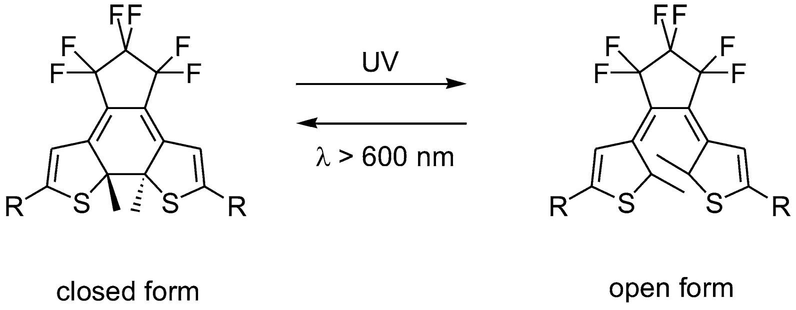

Figure 3.21: The "Irie"-switch based on two light induced ring-closure and ring-open reactions. Charge can be moved much easier between the thiophene units in the closed conjugated state on the left side.

An example of a molecular system as switch is the light driven system first described by Irie (1993). The switch is based on the fact that the forward and back reaction of an intramolecular ring-closure can both be triggered by light of different wave-length. As both states display pronounced differences in their electron transport abilities, the system as switchable molecular subunit has already been integrated in numerous experiments.

An overview of molecular switches is given in the recent book "molecular switches" by Ben Feringa (2001). Supramolecular switching systems like e.g. the catenane described above may be considered as molecular machines. Switching systems based on e.g. a chemical rearrangement reaction can only be described by quantum chemical laws. Very promising application of molecular switches is their use as memory cells in the near future. Companies like Hewlett Packard, Infineon, etc. already have signalized their considerable interest in such systems by increasing their research activities and cooperations related to the field.

E4: Brownian Ratchets

A *Brownian Ratchet* is a device that allows random *Brownian* motion only in one direction, thereby leading to directional motion from random *Brownian* motion. A typical example is shown in figure 3.22 bellow. The *Pawl machine* consists of two parts. An asymmetric cogwheel with a pressed on a mechanical lever that allows for rotation in only one direction and a vane which is randomly bombarded by small objects. As the device allows for only one sense of rotation it becomes selective concerning the bombardment events and hence should lead to a unidirectional rotation.

However, this spontaneous motion is violating the second law of thermodynamics (at equilibrium the effect of thermal noise is symmetric, even in an anisotropic medium) and is thus very unlikely to happen as was cited already by W. Smoluchowski in 1914: "No automatic, permanently effective perpetual motion machine can violate the second law by taking advantage of

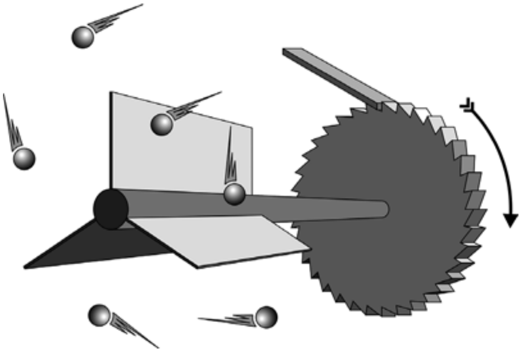

Figure 3.22: The Pawl machine, consisting of a vane and a wheel that can only turn in one sense of rotation. The vane is in a thermal bath of gas molecules at equilibrium. The whole device is considered to be reduced to microscopic size, so gas molecules can randomly bombard the vane to produce motion.

statistical fluctuations." However, R. Feynman was anew raising some hope with his statement: "Such device might perhaps function if operated by intelligent beings." (Smoluchowski 1914) Even though that statement was countered by W. H. Zurek: "The second law is safe from intelligent beings as long as their abilities to process information are subject to the same laws as these of universal Turning machines", models for Brownian ratchets are objects of current research. The unidirectional rotation of a *Molecular Machine* based on the principle of a *Pawl* machine has been published (figure 3.23) (Kelly et al. 1997), but these objects were not able to overcome the second law of thermodynamics (Davis 1998).

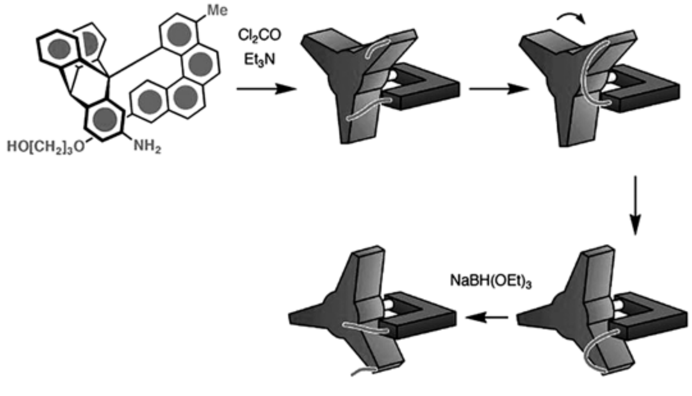

Figure 3.23: A molecular model of a Pawl machine allowing for unidirectional rotation (Kelly et al. 1997). The rotation is assisted by the formation of a covalent chemical bond that occurs only in one direction.

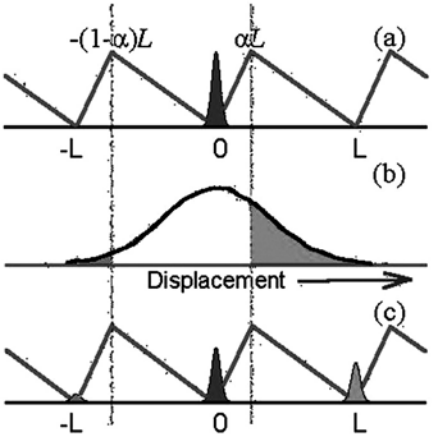

Figure 3.24: The mechanism of the ratchet potential: The Gaussian distributions of the particles' energy should result in a directional movement to the right side.

Another approach to *Brownian Ratchet* is focused on lateral random motion exposed to a saw tooth profile. As schematically shown in figure 3.24, the setup is designed to result in a directional movement of the particles.

Currently there are several approaches to investigate biomolecules in combination with nano- and micro-patterned arrays (Bader et al. 1999; Oudenaarden and Boxer 1999). For example, the transport of DNA molecules on a micromachined *Brownian Ratchet* silicon-chip device has been reported recently (Bader et al. 1999).

The devices are designed to profit from the *Brownian* motion of particles. Thus, to have a directional selectivity in a rotation device, for instance, the numbers of events acting on the device during an action step must be reduced enormously (ideally to one). On the other hand, the few numbers of events must provide enough energy to perform the action step. Hence, such concepts may work either theoretically or in reality at most for ultimate small devices.

G4: Nanoarchitectures

Nature's building blocks to assemble complex living systems are molecules (consisting of covalently linked atoms) and ions. Two molecules may react with each other by forming one or several new bonds in-between their atoms and hence, a new larger molecule is formed in that case combining most atoms of both molecules (in most cases two new molecules are formed and hence, some atoms get lost to form the second molecule). To understand and to control these reactions between molecules to create new structures or to break down existing molecules in a controlled fashion is ever since the topic of preparative synthetic chemistry. In over more than two centuries, chemists have developed amazing skills to design and to build up (synthesize) tailor-made molecular structures. The rich toolbox of chemical reactions and the permanently increasing number of available building blocks allows to assemble infinite numbers of new molecules and a current concept in chemistry is to profit from this amazing variety by synthesizing huge numbers of different molecules and to subsequently screen for promising candidates for particular tasks. The ability to control the connection between molecular building blocks enables to build up fairly large molecular systems. In the beginning of the last century, a whole branch of chemistry has developed the expertise to assemble long chain-like molecules ranging up to the sub-micrometer regime (macromolecular chemistry). As these chains are assembled by a large number of one or several similar subunits (monomers) they were entitled polymers. The polymer chemistry has become one of the economically most important branches of materials chemistry, however, polymers are not considered as well defined molecular compounds but rather as mixtures of chain-like molecular structures with a certain chain length distribution. To investigate correlations between chain length and physical properties similar chain-like molecules with well-defined length (oligomers) have been synthesized (Müllen and Wegner 1998; Martin and Diederich 1999). Their studies showed that many physical properties like colour, transparency, conductivity, redoxpotentials etc. depend on the chain length. Most investigated systems display a threshold chain length upon which the parameter of interest remains unchanged, the so-called effective conjugation length. However, recently the first, and up to my knowledge so far the only system, that did not display similar saturation effects with increasing length has been reported. The monomer units are zinc porphyrins, which are connected with three car-

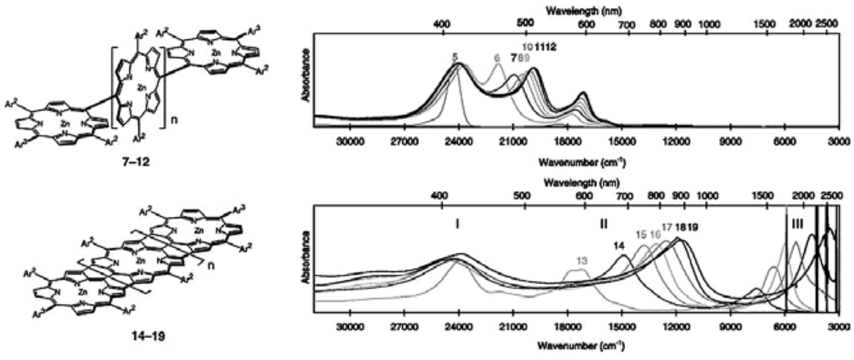

Figure 3.25: Rigid rods based on porphyrin building blocks. (Left) Molecular structures and (Right) ultraviolet-visible-infrared absorption spectra. (Top) Meso-meso linked Zn-porphyrin oligomers 7 (n = 1), 8 (n = 2), 9 (n = 3), 10 (n = 4), 11 (n = 6), 12 (n = 10). (Bottom) Meso-meso-, β-β- and β-β-linked Zn-porphyrin oligomers 14 (n = 1), 15 (n = 2), 16 (n = 3), 17 (n = 4), 18 (n = 6), 19 (n = 10).

bon-carbon bonds to each neighbour to form tape like structures (Tsuda and Osuka 2001). Porphyrin tapes consisting of 1024 monomers with a length in the order of several hundred nanometres have already been synthesized and did not display an effective conjugation length.

But not only chain-like oligomers have been developed as model compounds for polymers. More than two decades ago the pioneering concept to use branched monomer units to assemble spherical oligomers with well-defined molecular size and weight was introduced (Buhleier et al. 1978). The term denrimers has been created a few years later for this new family of oligomers. Originally intended as standards for polymer characterization, these spherical Nanoscale objects displayed a variety of very promising properties, mainly due to spatial separation of chemically well-defined compartments.[1] Furthermore, the stepwise building up allows the integration of specific functional subunits in the centre, on the dentritic branches or at the periphery of these spherical molecules. Numerous functional systems based on dendrimers combining particular subunits are reported (Fischer and Vögtle 1999). Meanwhile, even hyperbranched polymers are made as dendrimer mimics to perform actions and functions, which have originally been found with dendrimers (Sundar et al. 2000).

Large molecular structures are not only limited to organic building blocks. By careful adjustment of the reaction conditions large inorganic clusters, often protected by a shell of organic ligands, have been synthesized (Schmid 2004). The size of these metallic and/or semiconducting clusters can be adjusted by appropriate choice of the reaction conditions, and hence, a number of in size and composition well defined clusters have been prepared in the past. Furthermore, the organic surface chemistry of these inorganic clusters can be adjusted for particular tasks. The variety in size of robust inorganic units, enriched by designable surface chemistry and size dependent physical properties,[2] make them very promising building blocks for future devices. While the genesis of these inorganic clusters depends on the organic additives, which cover the surface and thereby prevent a particular stable combination of cluster size and surface coverage from further growth, approaches to nanoscale objects exclusively depending on inorganic components also have been reported. Beautiful examples of inorganic macromolecules without organic templates are large rings, balls and other objects made of molybdenum oxides with sizes up to several nanometres (Müller and Serain 2000). The variety of possible oxygen connection geometries between two neighbouring molybdenum centres, given by the fact that different numbers of oxygen atoms can be shared by two neighbouring molybdenum centres and that molybdenum itself provides several oxidation states resulting in different numbers and also different geometries of sur-

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[1] See also section on drug delivery, table 3.

[2] See also sections on quantum size effects and formation of discrete energy levels, table 1.

rounding oxygens, provide the system the potential of a construction kit with an almost infinite number of possible objects of different sizes.

A relatively new approach to nanoscale and/or nanostructured inorganic objects, entitled biomineralization, is profiting again from well-ordered organic structures. Mimicking principles of nature, the growth of inorganic material due to organic structures of well-defined surfaces and/or interfaces is investigated (Mann 2001; Baeuerlein 2004). The influence on the resulting inorganic object of layers of organized organic molecules at the interface of growth is of particular interest, as for example the enormous mechanical stability of muscle and snail shells results from the micro and nano structuring as well as the structural phase of the calcium carbonate.

All these examples are beautifully well-defined nanoscale objects or nanostructured materials, which have been synthesized from smaller molecules as building blocks that have been connected to larger molecules or materials applying the principles of preparative organic and/or inorganic chemistry. However, since the seventies of the last century a new comprehension of working with molecules as building blocks has emerged. Instead of using strong chemical bonds between molecular subunits to build up larger molecules, rather weak interactions between molecules have been investigated. These weak interactions allow to assemble larger and well-defined objects consisting of several molecules – so called supermolecules, too. This chemistry beyond the molecule, building up nanoscaled objects based on intermolecular interactions, is called supramolecular chemistry (Vögtle 1992; Lehn 1995). Even though weak interactions result in less robust objects, their use turned out to be particular powerful to assemble large structures with dimensions in the order of several nanometers. Molecular building blocks are designed to organize themselves in the network of neighbouring molecules. Supermolecules are formed spontaneously after its molecular building blocks are mixed in appropriate reaction conditions and thus, the term "molecular self assembly" is used to describe the supermolecule's formation. Thereby the construction plan for the nanoscale object is already an intrinsic property of its building blocks, as it is stored in the individual molecules' structures. After meeting each other, the formation of the super molecule is driven by intermolecular interaction and the arrangement is optimised either thermodynamically (the most stable arrangement of the molecular building blocks) or kinetically (the fastest arrangement of the molecular building blocks). However, a kinetically formed arrangement must be separated from the reaction conditions to prevent further rearrangements to a more stable thermodynamic minimum and thus, its belonging to the family of supermolecules may be debated. However, numerous well-defined nanoscale objects are based on quenched kinetically optimised structures, like e.g. metallic clusters with organic ligand shells already mentioned above.

The lability of the interactions between the molecular building blocks of a supermolecule turned out to provide these objects with very promising properties. Supermolecules can easily adapt to changes in the environment. For example, depending on the presence of particular guests, they may adjust the number of subunits and hence the size of the supermolecule as host for the available guest. Furthermore, an individual molecule as subunit of a supermolecule can easily be exchanged and as the correct molecular structure fits best and strongest between its neighbours, a defect building block is automatically exchanged, providing the object with self-healing properties.

The amazing potential of weak intermolecular interactions to assemble well-defined large objects can best be shown with an example from nature, the tobacco mosaic virus (TMV). The virus consists of a well-defined large number (2130) of identical polypeptide molecules. To some extent its shape resembles a wedge. These building blocks spontaneously assemble to small starting oligomers, larger disc like structures and finally to a helical arrangement, giving the nanoscale-object a rod-like shape. Furthermore, in the case of the native virus, the number of molecular subunits that assemble, and hence the length of the rod like object, is determined by a chain like molecule, a ribonucleic acid (RNA) strand. This single RNA strand is wrapped in the helix of the polypeptide monomers and thus its length determines the final object length. It has been shown, that the dissociated molecular building blocks of the TMV reassemble in vitro leading to the reconstitution of the intact virus (Fraenkel-Conrat and Williams 1955). The assembly processes of the TMV are displayed in the picture below.

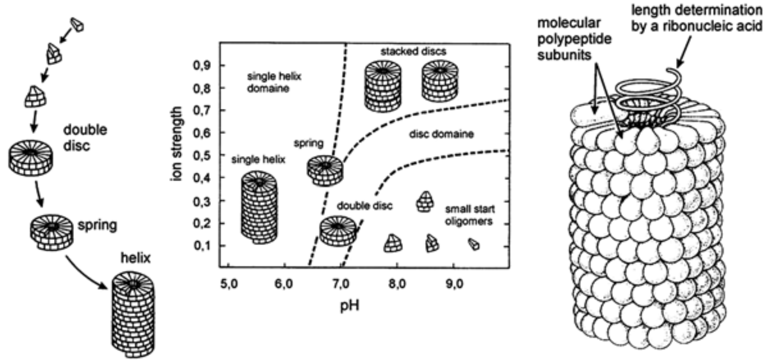

Figure 3.26: The self assembly of the tobacco mosaic virus (TMV): (Left) Assembly of wedge-shaped polypeptide molecules to discs, springs and helices. (Centre) The assembled objects based on the wedge-shaped polypeptide molecules depend on the ion strength and the pH. (Right) Representation of the final tobacco mosaic virus, some wedge-shaped polypeptide molecules are removed to display the length determining ribonucleic acid (edited presentation from the biochemistry book by A. L. Lehninger 1987).

The rather weak interaction that enable to build up supermolecules range from very weak van der Waals[3] interactions, over electrostatic interactions like ion-dipole[4] or dipole-dipole[5] interactions to directed hydrogen bonds[6] and coordinative[7] interactions. As these interactions have their relatively weakness in common, supermolecules are often assembled by the parallel and cooperative action of numerous small interactions, sometimes even of different kinds of interactions.

While van der Waals interactions are crucial for the assembly processes of organic molecules at surfaces and interfaces like membranes and self assembled monolayers (SAM), they are rarely used to assemble monodisperse well-defined nanoscale objects. Only micelles may be considered as such objects, however, they generally display a fairly wide size distribution. Ion dipole and dipole-dipole interactions are of great interest in biological and medical systems, as the information processing of the living species is mainly based on ion concentration gradients. However, these interactions are seldom used to build up nanoarchitectures.

On the other hand hydrogen bonds are ideal tools to design the assembly of molecules. The functional groups providing hydrogens (hydrogen donor) and the functional groups being greedy for hydrogens (hydrogen acceptor) can be placed in particular positions of a molecular structure by chemical synthesis and accordingly, the interaction of the molecular building block with its neighbours can be tailor-made. The concept to use hydrogen bonds to control the assembly of molecules has been applied for million years in nature. For example the base pairs of a DNA double strand are based on hydrogen bonding interactions of two sets of complementary bases (Watson and Crick 1953), enabling living systems to code and to reproduce their construction plan. The base pairs of DNA and their hydrogen bonding interactions will be displayed schematically in figure 3.34 as a particular example of shape complementarity. The DNA double strand is by far not the only self-assembled nanoscale object in nature; biologically active large molecules like proteins are made of one or more large chainlike biooligomers which wrap-up to a well-defined nanoscale structure by supramolecular interactions. The crucial importance of the final shape of the nanoscale structure for its biological activ-

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[3] Attraction between two neighbouring molecules, due to the attraction of an accidentally unsymmetric distribution of electrons resulting in a dipol in one molecule that induces an opposite distribution of electrons and hence an opposite directed dipol in the neigbouring molecule.

[4] The solvatation of ions in a dipol solvent like water comes due to the ion-dipol interaction.

[5] Attraction between two dipol molecules to average out the local charging.

[6] The sharing of a hydrogen atom between two molecules; one providing the hydrogen atom and the second a functional group with a large electron density attracting the partially positive charged hydrogen.

[7] Weak directed electron pair bonding.

ity has been demonstrated in numerous cases. A particular impressive one is the protein causing the mad cow disease (Prusiner 1997). The biomolecule responsible for the disease turned out to be the chemically correct connected subunits in the biooligomer, but the wrong assembly to the final nanoscale object. Finally, the poor solubility of the wrong assembly together with the ability to induce the rearrangement to the wrong assembly in the correct biologically active protein turned out to have deadly consequences.

These impressive nanoscale objects based on hydrogen bonding have inspired numerous designed and synthesized nanoarchitectures. The variety of the supramolecular approach can easily be demonstrated by building blocks containing hydrogen-bonding patterns mimicking nucleic acids. For example a system of two bifunctional molecular building blocks (s. figure below) enables to build up two different objects, both driven by the formation of hydrogen bonds (dashed lines below). The barbituric acid derivative (BA) on the left side with its hydrogen bonding pattern acceptor-donor-acceptor and the 2,4,6-triaminopyrimidine derivative (TAP) with the complementary pattern donor-acceptor-donor form polymer tape-like structures or cyclic oligomers consisting of three units of both molecular building blocks (Lehn 1995).

The strength of intermolecular hydrogen bonding interactions strongly depends on the surrounding, in particular on the presence of competing hydrogen donors and acceptors from other molecules or the solvent. The

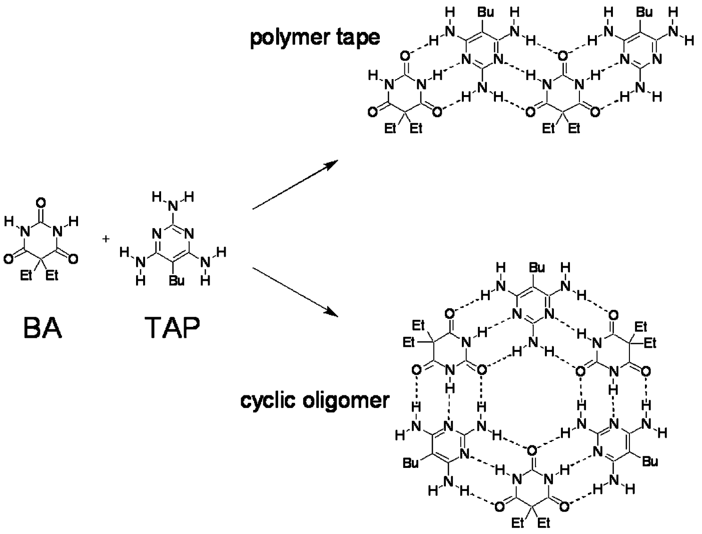

Figure 3.27: Self-assembly of either a supramolecular ribbon (top) or a supramolecular macrocycle (bottom) from barbituric acid (BA) and 2,4,6-triaminopyrimidine (TAP) units (Lehn 1992).

assembly of these structures can thus be triggered by appropriate choice of solvents. Furthermore, their sensitivity to competing molecules provides them the potential to act as selective sensors. As these structures mimic natural hydrogen bonding patterns, numerous approaches try to profit of these structures to address specific binding sites of natural systems. Medical application of hydrogen bonding molecules for example intercalating in DNA double strands has been proposed.

Hydrogen bonding patterns have been used to build up polymer strands. In particular the dynamic exchange of the building blocks of such a hydrogen-bonded polymer may provide new and interesting adaptation and healing features (Sijbesma et al. 1997). Three-dimensional nanoarchitectures have been designed and synthesized. For example cages based on hydrogen-bonded subunits have been made by appropriate connection of several planes made of a comparable structure as the cyclic oligomer displayed above. In a recent example, such a cage-like structure with four recognition planes to increase the stability, selectively complexed a particular sacharide (Ishi-I et al. 2003). The use of chiral subunits in hydrogen bonded polymers lead to helical ropes of hydrogen bonded polymer strands (Lehn 1995).

A particular interesting approach is the design of hydrogen-bonded nanoarchitectures based on designed chains of nucleic acids. The hydrogen bonding properties of the subunits is studied in detail, the interactions of two chains can be adjusted by choice of the sequence of building blocks pro-

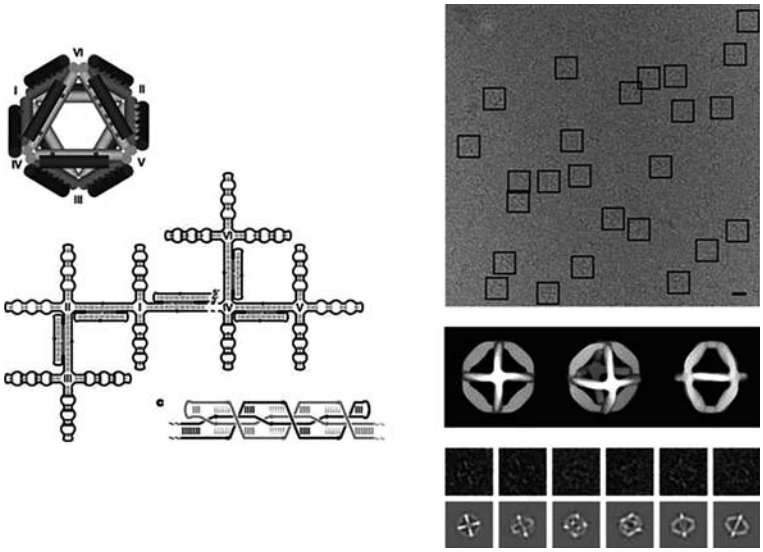

Figure 3.28: (Left) Design considerations for a octahedron based on a 1700 bases long DNA strand. (Right) Cryoelectron microscopy pictures of the resulting octahedron together with a computational simulation of the observed objects (Shih et al. 2004).

viding particular bonding patterns and the synthesis of the chains with required sequences is fully automatized today. Hence, well-defined nano-objects have been proposed and synthesized based on synthesized strands of nucleic acids (Seeman 1998). A beautiful recent example is a huge single-stranded DNA consisting of 1700 bases that fold into an octahedron by designed intramolecular interactions between different DNA double helical subunits (Shih et al. 2004).

Another supramolecular approach to assemble nanoscale objects is based on the merging of coordination chemistry with synthetic ligand design. This hybrid approach turned out to be a very powerful tool to assemble large functionalized nanoscale architectures. It merges huge expertises of both classical domains of chemistry. Large organic structures are designed and synthesized providing subunits that allow for coordination with particular ions. Furthermore, the variety of coordination geometries elaborated in inorganic chemistry is used to assemble the large molecular subunits together. Moreover this approach beautifully combines both features of labile equilibrium conditions (required to assemble a supermolecule) and stability of the resulting supermolecule as nanoarchitecture. Equilibrium conditions and hence the thermodynamic minimum structure (the supermolecule) is reached at elevated temperature and the supermolecule is frozen out as rather stable nanoarchitecture by cooling to room temperature. The availability of interesting nanoarchitectures via this approach seems to be unlimited and hence, the here displayed examples are only a very brief view of the field. An additional particular beauty of this supramolecular approach to nanosacle structures is the combination of the rich photophysical properties of inorganic coordination chemistry with the huge modular structural variety of organic chemistry.

Rather complex three-dimensional nanostructures have been synthesized using organic molecules with several binding sites and appropriate metal ions to coordinate two or more of the organic molecules. Thereby, the coordinated metal centre acts not only as glue that holds the organic building blocks together, it controls to some extent the relative geometry of the coordinated organic subunits. The designed organic building blocks comprising several multidental coordination sites on the other hand contain most of the blueprint for the resulting supramolecular architecture as intrinsic property.

First pioneering structures were based on strand-like oligomers of coordination sites that were flexibly linked. These oligomers formed together with corresponding metal centre helical structures. The recognition potential was amazing: starting from a mixture of oligomers, depending on the geometry of the coordinating metal ion, each n-mer found one or two additional molecules of exactly the same length and together, they were coordinating n-metal centres (Krämer 1993). While first studies have been made with oligomers of linked bipyridine units and copper(I) or nickel(II) salts, formation of multimetal helical complexes has meanwhile been observed for other combinations of coordination sites and metal centres. Due to their photophysical properties, a particularly interesting example is helical structures containing lanthanides (Floquet et al. 2003). Furthermore, similar to the topological objects described above for DNA-strands (Seeman 1998), such oligomer strands have been designed and synthesized to form convoluted and knotted nanoscale objects together with corresponding metal ions. As the coordination geometry of the metal centres depends on their oxidation state, the resulting supermolecule may be triggered by electrochemically adjusting the redox state of the coordinating ions. For example a chain-like oligomer with six coordination sites for metal ions is designed to form either a cyclic interwoven supermolecules (8 pentacoordinating ions, Cu(II) and 4 tertacoordinating ions, e.g. Cu(I)) or a cross shaped nano-structure (4 hexacoordinating ions, e.g. Cu(II) and 8 tetracoordinating ions, e.g. Cu(I)), depending on the coordination geometry of the ions present (Funeriu et al. 2000). As for example cooper ions may serve all the required coordination geometries depending on their redox state, one might consider to switch between both supermolecules electrochemically (Boulas et al. 1998).

The concept of metal centre redox state dependent switching in supermolecules has already been shown beautifully by systems, consisting of mechanically interlocked molecules, like e.g. the catenane from Sauvage (1998) displayed below. A catenane consists of two interlocked ring molecules, similar to two chain links. The particular catenane has a bidental phenantren coordination site in both rings. However, one ring is further

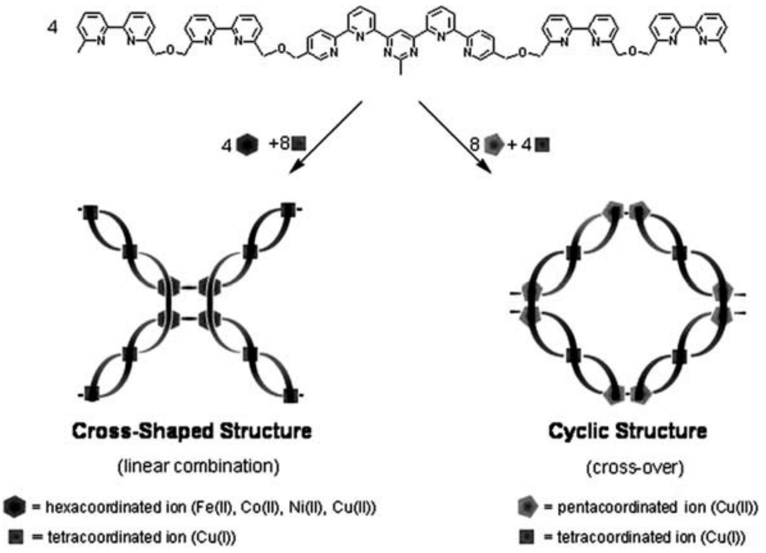

Figure 3.29: Depending on the coordination geometries of metals, four ligands form a cross-shaped structure (left) or a supermolecular interwoven macrocycle (right).

functionalized with a tridental terpyridine coordination site. As copper (I) ions prefer fourfold coordination, the two rings are held together by the Cu(I) ion via complexes of both phenantren units. Oxidation of the metal centre results in Cu(II), which prefers a fivefold coordination sphere and hence, the catenane rearranges to coordinate the Cu(II) ion via a complex of the phenantren and the terpyridine subunit. The redox state of a coordinating metal centre dependent rearrangement of two mechanically linked molecules has as well been used to assemble molecular shuttles based on rotaxanes (molecular ring annealed on a molecular rod) and for molecular muscles (Collin et al. 2001). To assemble molecular muscles the concepts of a rotaxane shuttle and a catenane have been merged beautifully. For that purpose a molecule consisting of a ring attached to a rod like axis has been synthesized. Furthermore, the molecule is functionalised with a bidental coordination site in the ring part and with a bi- and a tridental coordination site in the rod part. Complexation of the molecule yields in a dimer with two metal centres in which the rod part of one molecule is thread in the ring of the other and vice versa (s. picture below right side). Depending on the coordination geometry of the metal centres, the rings are fixed to one or the other coordination site of the axis and hence, the penetration depth of the rod like structure varies. This results in a shrinking or extending of the length of the supermolecule and the assembly displays the properties of a muscle.

Redox switchable catenanes, rotaxanes and shuttles have also been assembled solely based on organic subunits (Paese et al. 2001). The supramolecular assembly of the molecular components mainly was driven in that case by

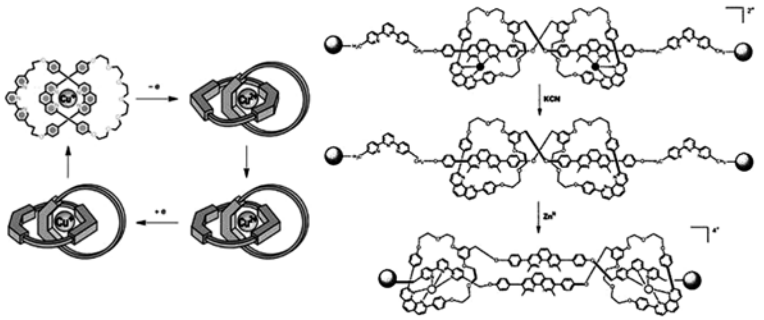

Figure 3.30: (Left) Redox switchable catenane: depending on the redox state of the copper ion, the ring on the left side coordinates with its bidental phenantren unit or with its tridental terpyridine unit. (Right) Redox switchable molecular muscle: Depending on the coordination geometry of the available ion, the interlocked molecular structure prefers an elongated conformation with a fourfold coordination sphere (top) or the supermolecule shrinks to a more compact conformation with a fivefold coordination sphere for the metal ions (bottom).

donor-acceptor π-stacking interactions. Charging of subunits in both rings leads to coulomb interactions resulting in rearrangements of the molecules to each other. A prominent example is the catenane by Stoddart and coworker Collier et al. (2000) consisting of a ring with two paraquat units and a second ring with a tetrathiofulvalene and a naphtyl subunit. The structure of the catenane and the redox state dependent rearrangement of the interlocked supermolecule are displayed in figure 3.20. Of particular interest is the fact that for this catenane two stable conformations exist at zero potential, depending whether the point is reached from a reducing or an oxidising environment. As both states are supposed to differ in their tunnel currents, a Langmuir-Blodget film of the catenane supermolecule has been deposited between two electrodes as memory cell (Collier et al. 2000). The device indeed displayed two different states with respect to the tunnel current as a function of the prior applied potential. However, the origin of the observed switching behaviour is a topic of current debates. To further support the hypothesis of the rearrangement in the supermolecule as the switching mechanism, advanced systems based on immobilized shuttles between two molecules have been investigated between two electrodes as films (Luo et al. 2002) and on a single molecule level (Yu et al. 2003).

Another amazing example of nanoscale structures based on organic ligands held together by coordinating metal centres are huge grid-like structures, which have been designed, synthesized and investigated in detail. They consist of rigid-rod like organic molecules with several (n) multidental-binding sites. In general, 2n organic rod-like ligands with n coordination sites together with n x n metal centres form an n x n grid like structure. An example of a 3 x 3 grid is displayed bellow (Lehn 1995).

Numerous structures based on such grid motives have already been synthesized and studied in detail. Of particular interest are the interactions

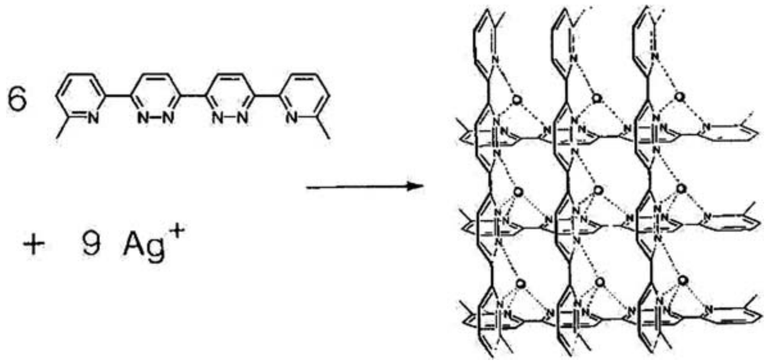

Figure 3.31: Self-assembly of six rigid rod like ligands each comprising three bidental coordination sites and nine silver(I) ions to a supramolecular 3 x 3 grid.

between the spatially very close metal centres in these structures (Ruben et al. 2004). For example a 2 x 2 Fe(II) grid displayed amazing spin cross over properties.[8]

Many more nanoscale objects like ladders, cages, boxes etc. have been synthesized based on similar multidental coordination sites. However, the multidental coordination site is not a crucial requirement to form nanoscale objects. An amazing variety of supermolecules are based on organic structures containing pyridines as monodental coordination sites. To give an impression of the available objects the picture below displays some possible nanostructures as interplay between the spatial arrangement of the monodental coordination site in the organic molecule and the coordination geometry of the complexing metal centre (Stang and Olenyuk 1997).

A huge variety of two dimensional objects like squares and cycles of different diameters have been synthesized based on pyridine terminated organic ligands and platinum ions by Stang and co-workers (Stang and Olenyuk 1997). Also three dimensional supramolecular objects have been

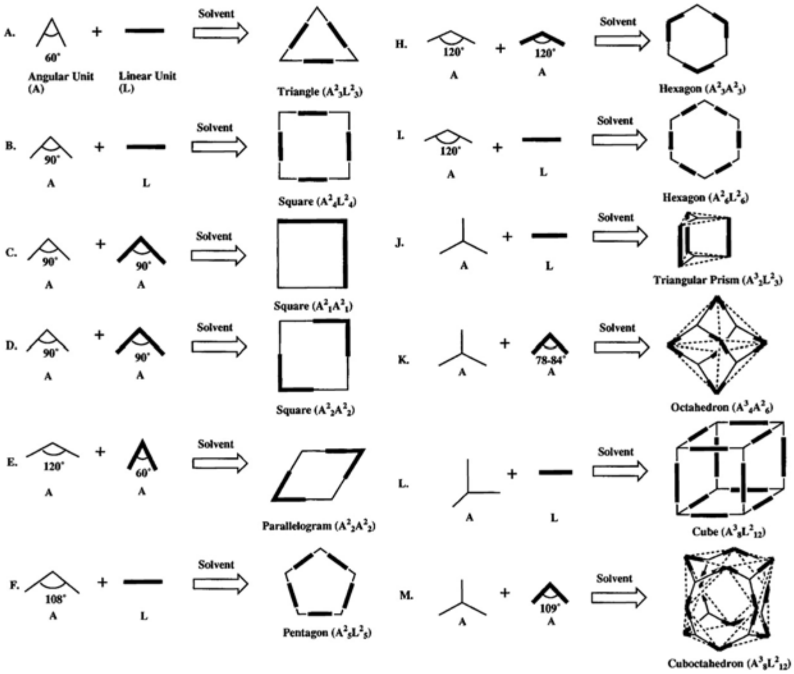

Figure 3.32: Design considerations for two- and threedimensional supermolecular structures based on the interplay between bridging monodental ligands and coordination geometry at the metal centers.

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[8] See also section on hs-/ls-complexes, table 2.

synthesized based on monodental coordination subunits. Prominent examples in the literature are the cage-like supermolecules synthesized by Fujita and coworkers (Fujita 1996, Kusukawa et al. 2001). The adaptation potential of these cages has been beautifully demonstrated. A system consisting of different building blocks allowing for a variety of cages of different size displayed an impressive adaptation potential to the presence of different guests. The cages with cavities of sizes that the guest fits inside have been produced preferentially under appropriate conditions (Kubota 2002).

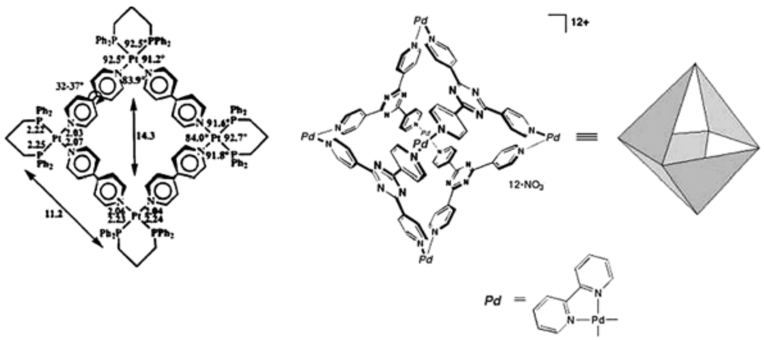

Figure 3.33: (Left) A supramolecular square based on the self-assembly of for 4,4'-bipyridine ligands and four platinum ions. (Right) A coordination nanocage consisting of four triangular organic ligands and six paladium ions (Kusukawa et al. 2001).

Based on the combination of organic ligands with coordinating metal centres not only nanoscale object can be designed and synthesized. A very promising approach to functional materials that combines the advantageous features of organic and inorganic chemistry are coordination polymers.[9] These structures consist of regular three dimensional frameworks of metal centres connected to each other by organic molecules with two or more coordination sites (Kitagawa et al. 2004; Rao et al. 2004). In particular the design of the nanoscale holes and channels in these porous materials has attracted much interest as potential tailor-made materials for storage purposes and sensors. Open framework materials are not restricted to organic ligands. The most prominent and technically important materials are inorganic mesoporous structures (Cheetham 1999) like zeolites or Al_2O_3.

As already mentioned in the beginning, the cited examples are only a very small part of the current research in the field of nanostructures based on supramolecular chemistry. The intention is rather to provide a feeling of the potential, the features and the promises of this truly bottom-up approach to

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[9] See also section on coordination polymers, table 1.

nanoscale objects than to provide a detailed overview. The amazing property of these structures is their sensitivity to surrounding conditions. Subtle changes in reaction conditions may lead to another supramolecular assembly. Hence these objects display adaptation properties allowing for new approaches to functionality like selectivity based on dynamic combinatorial libraries.

H4: Shape Complementarity

In the previous section on nanoarchitectures, the outstanding self-assembling features of molecules in general and of biomolecules in particular have already been discussed. Closely related is the ability of molecular structures to recognize shapes and chemical properties of other molecules or surfaces. The most prominent example to illustrate this amazing properties are the base pairs of the DNA double helix, which encode our genome by shape complementarity of the arrangement of hydrogen bond donors and acceptors (s. figure 3.34 below; Watson and Crick 1953).

Numerous supramolecular recognition processes are known to be size selective. A typical example is the complexation of ions in crown ethers and cryptands, both molecular structures with cavities for ions (Lehn 1995). The stability of the formed molecule- ion-complexes is drastically increased, when the size of the cavity is adjusted to the size of the particular ion. These

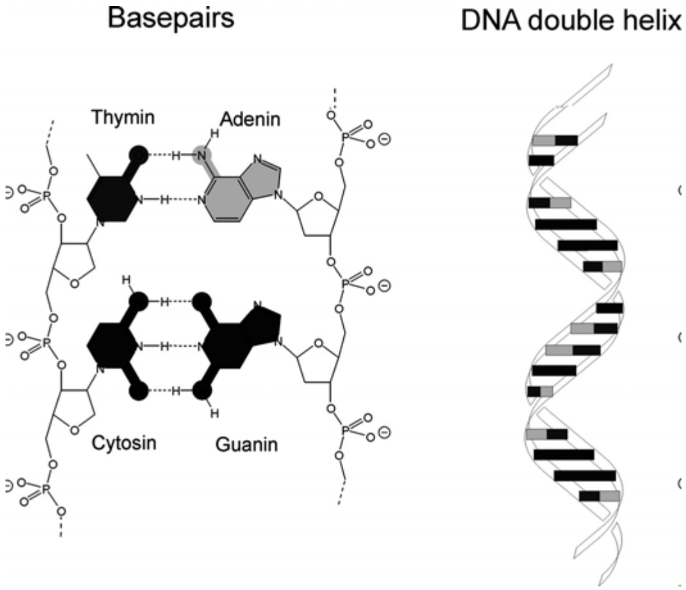


Figure 3.34: (Left side) The two base pairs encoding the whole genome in a DNA double helix. (Left side) Schematic representation of a DNA double helix.

selective complexation properties are known to be crucial in natural systems. For example the information exchange in nerve cells is based on ion gradients which are build up by selective complexation and the resulting transport events through the membrane of the nerve cell. The selective recognition of shape, size and function is based on interactions on the molecular level, which can only be described by quantum mechanical laws.

The main field of application of these recognition events is in life-science. For example, already the first known antibiotics were based on an increased ion transport through the bacteria's membrane. Diseases due to imperfections in the DNA, in particular inheritable ones, are known. An example is SCID (Severe Combined Immunodeficiency). It is a very nasty disease which in effect disables the immune system – leading to very ill patients. It has been clear for quite a while now which letters in the DNA need to be fixed in order to cure these people. Numerous attempts where made to patch running people, using viruses that insert new DNA into living organisms, but this proved to be very hard. The genome is guarded far too well for such a simple approach to work. Recently, however, the right virus was found which was able to breach the protection of the genome and fix the broken characters. It then lead to apparently healthy people. DNA is the executing code of living organisms and numerous diseases, but also many currently investigated therapies are related to its binding properties and shape complementarity.

3.1.5 Hybrids/Composites

A5: Giant Magneto Resistance (GMR)

Introduction

The GMR-effect has become the first real success story of Nanotechnology. The effect has been discovered independently from each other in 1988 by Peter Grünberg in Jülich and by Albert Fert in Paris (IBM-Research-Homepage; Fert 1995; Levy 1994; Barthelemy 1999). Fert and Grünberg investigated the electrical resistance of 2-dimensional (2-D) multilayer systems of very thin alternating layers of various metallic elements. They found very large changes in the electrical resistance between 6 and 50 percent when a magnetic field was applied to a system with alternating ferromagnetic and nonferromagntic, either metallic or insulator, layers. This change of the resistance was enormous high in comparison with the then known Anisotropic Magnetic Resistance (AMR) with values in the range of <3% resistance change in a magnetic field. The AMR effect had been discovered in 1857 and is an anisotropic effect which can be observed also in thick layers and which depends on the angle between the direction of current and magnetisation. On the contrary the GMR-effect is isotropic and is confined to multilayers with layers of a few nanometer thickness. For this reason it is real Nanotechnology in the sense of our definition.

The whole topic has been comprehensively treated e.g. by the script of FZJ-Ferienkurs (1999).

Phenomenology of the GMR-effect

An electrical current can flow in the plane of the layers (CIP Current In Plane) as well as perpendicular to the layer plane (Current Perpendicular Plane CPP). In both cases a GMR-effect can be observed. Dependant on the applied external magnetic field the electrical resistance decreases in a magnetic field continuously. Figure 3.35 shows this behaviour for the CIP-case in the original curves.

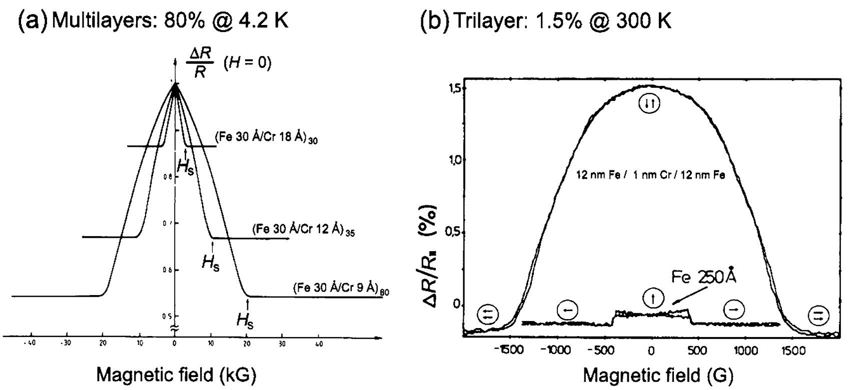


Figure 3.35: First observations of the GMR effect: (a) in Fe/Cr multilayers (Baibich, Fert et al. 1988), (b) Fe/Cr/Fe trilayers compared with AMR-effect (lower curve): (Binasch, Grünberg et al. 1989; from Bürgler DE and Grünberg PA (2003): "Magnetoelectronics-Magnetism and Magnetotransport in Layered Structures" In Nanoelectronics and Information Technology, Wiley VCH 2003, ISBN 3-527-40363-9,111-128; reproduced by permission of Wiley VCH, STM-Copyright & licenses.

The lower curve in figure "First observation b" shows the resistance change of the so called Anisotropic Magnetic Resistance (AMR) in a magnetic field. As can be seen the AMR effect is much smaller than the GMR effect. Measuring temperature in figure "First observation a" was 4.2 K, in figure "First observation b" 300 K. In figure a) the observed maximum GMR-effect is in the range of 80% while in figure b) at room temperature in a trilayer the effect is about 1.5%. This strong temperature dependency of the effect was confirmed in the following years by further investigations with further improvements of the maximum GMR effect.

For the appearance of the GMR effect it is necessary that configurations of the ferromagnetic layers can be established in which the directions of magnetization can be arranged parallel (ferromagnetic coupling) or antipar-

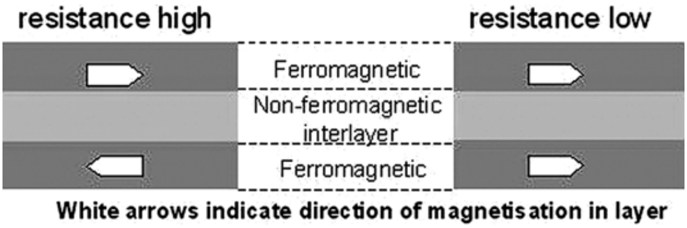


Figure 3.36: Ferromagnetic layers separated by non-ferromagnetic layers with and without parallel magnetisation (schematically). White arrows indicate direction of magnetisation.

allel (antiferromagnetic coupling) dependant on the external magnetic field. This is shown schematically in figure 3.36.

This behaviour can be achieved either in “Interlayer Exchange Coupled” systems with free magnetic layers or by “Spin Valve Systems” (SVS) where one magnetic layer is pinned by a bias layer. In the following the Internal Exchange Coupling (IEC) will be considered first.

The arrangement of the magnetisation directions is dependant on the Energy E_{IEC} of the IEC. E_{IEC} can be described phenomenologically in a first order approach by the areal energy of the IEC:

$$E_{IEC} = -J_1 * \cos\Theta - J_2 * \cos^2\Theta \quad \text{(eq. 3.2)}$$

Θ describes the angle between the direction of magnetisations in the magnetic layers. J_1 and J_2 are Parameters which depend on the layer material and the thickness of the nonferromagnetic interlayer. They describe the type and strength of the coupling between the ferromagnetic layers. If the first term on the right side in equation 3.2 dominates then the coupling is ferromagnetic for positive J_1 and antiferromagnetic for negative values of J_1 in the absence of an magnetic field, which means that without external magnetisation the arrangement of neighboured layers is antiparallel. Thus the GMR effect can be observed only for $J_1 < 0$. The IEC can be enhanced significantly by additional nanometer thick ferromagnetic layers (Co) adjacent to the nonferromagnetic interlayer (Peng et al. 2002).

Figure 3.37 (a) schematically shows how J_1 oscillates with increasing thickness of the nonferromagnetic interlayer. Figure 3.37 (b) displays the GMR in a Co/Cu/Co system. As can be seen the GMR only appears when J_1 becomes negative. When in equation 3.2 the second term with J_2 is dominating and J_2 is negative then a 90 degree coupling occurs.

This kind of coupling is very sensitive to temperature and it is believed that it is mainly due to interface roughness (Bürgler and Grünberg 2003) and will not further be discussed here. A detailed discussion of the interlayer exchange coupling (IEC) can be found at Mathon et al. (1993), Bruno (1995), Stiles (1999) and Grünberg (1999).

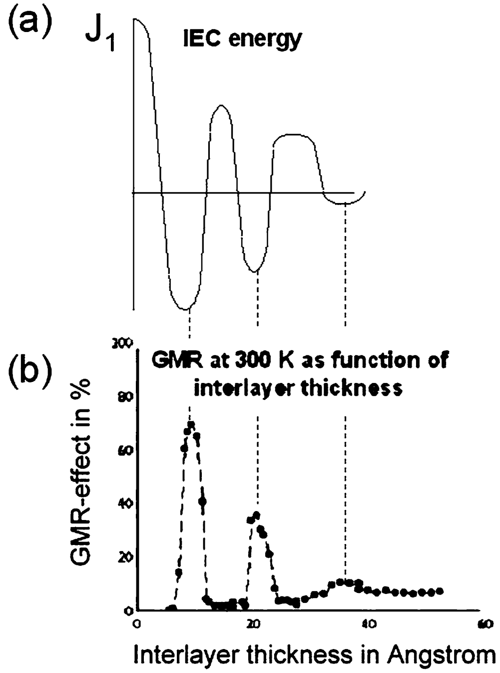


Figure 3.37: Oscillation of J1 (schematically; figure 3a) and of the GMR effect (figure 3b) with interlayer thickness. The GMR effect has its first maximum at 9 Angstrom interlayer thickness (Stoner 2004).

Decoupled Layer System (Spin Valve Systems SVS). In this structure an antiferromagnetic pinning layer (FeMn) pins a magnetic film (CoFe) with a fixed magnetic orientation. A second softmagnetic (NiFe) is stacked above the other separated by a nonferromagnetic interlayer, e.g. Cu. This free layer is decoupled from the pinned layer. The arrangement is shown in figure 3.38a.

If the external field is not too large the antiferromagnetic pinning layer keeps the magnetisation of the pinned CoFe-layer in a fixed direction. Separated by a nonferromagnetic layer (e.g. Cu) a softmagnetic free layer is deposited. In the absence of an external field the magnetisation of this layer will be the same as that of the pinned layer.

Figure 3.38b shows the slope of magnetisation of the system with external field, figure 3.38 (c) displays the resistance change with an increase of the GMR when the magnetisations become antiparallel in an external field. When the external magnetic field increases and becomes larger than the exchange bias field then the magnetisation of the pinned layer rotates and eventually also becomes parallel to the external field. The more the magnetisations of the pinned and the free layer become parallel the more

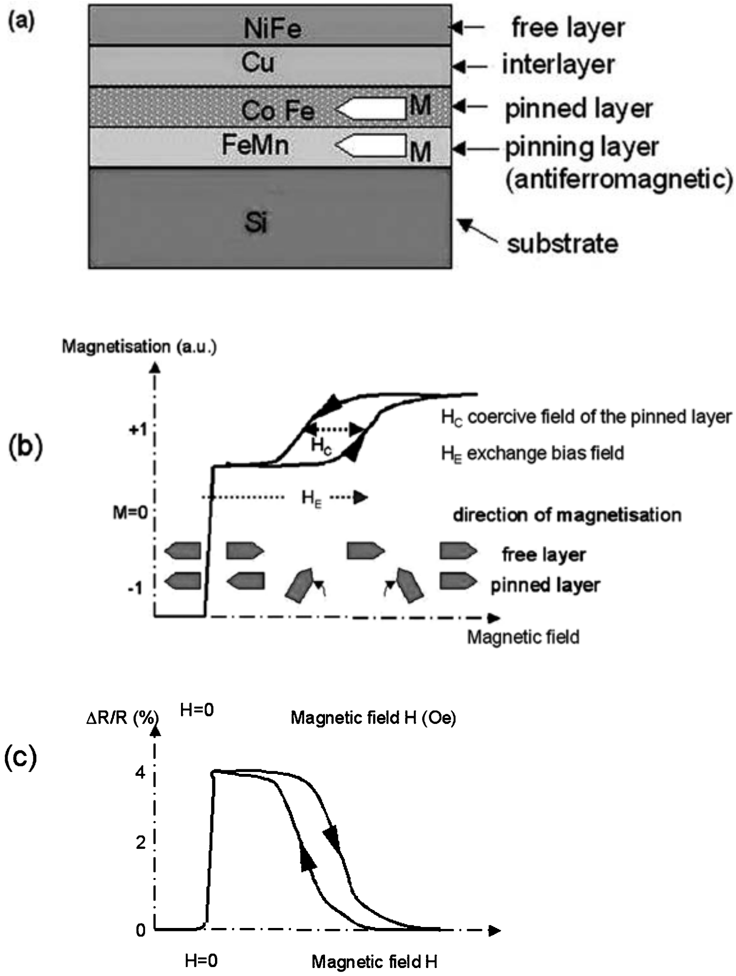


Figure 3.38: a: Arrangement of layers in a decoupled system; b: Characteristic curves of normalised magnetisation in layer systems; c: ΔR/R during cycling in an external magnetic field (Bürgler and.Grünberg 2003).

the GMR decreases. When the external field is reduced again the magnetisation of the pinned layer rotates once more with a hysteresis into the direction of the bias field. The GMR follows the slope as shown in figure 3.38c. The GMR in SVS is especially appropriated for reading digital "0-1"-information as even for small external fields a big change in the resisitivity appears.

Theoretical background of the GMR-effect

The GMR-effect can be explained by Sir Neville Mott's two current model. Two kinds of conduction electrons are responsible for the current transport in a ferromagnetic 3d-metal: electrons with spin parallel and others with spin antiparrallel to the local magnetisation (spin up and spin down electrons). Near the Fermi-energy the density of states of electrons in ferromagnetic 3d-materials is different for spin up and spin down electrons. By the lowering of the spin up energy the number of spin up electrons at the Fermi level is higher (majority carriers) than that of spin down electrons (minority carriers). This is shown schematically in figure 3.39.

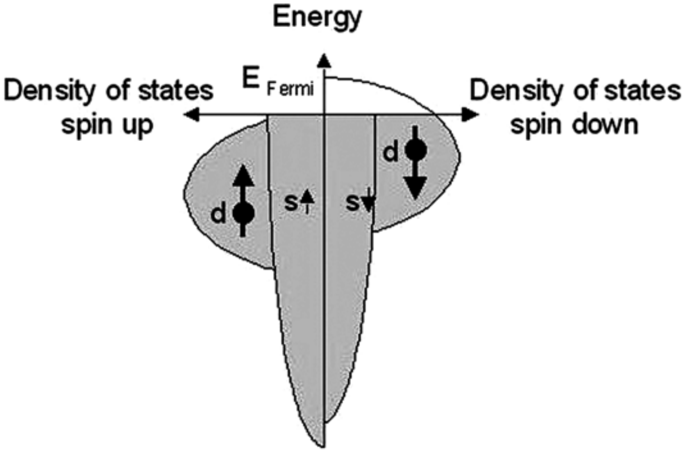


Figure 3.39: Spin up and spin down electrons with respect to the Fermi level.

Without external electric field electrons move itinerant with Fermi-velocity in the layer with no resulting electric current. The electrical resistance is determined by the density of conduction electrons and by scattering processes during the movement of electrons in the electrical field. The observed GMR effect is related to different scattering processes for spin up and spin down electrons in the different layers.

Figure 3.40 schematically shows that scattering of electrons when crossing the interfaces of neighbouring layers for parallel and antiparallel direction of spin with respect to the directions of magnetization in the ferromagnetic layers (after Bürgler and Grünberg 2003). Due to the asymmetry of the density of states the scattering probability of d-electrons for both kinds of electrons is different.

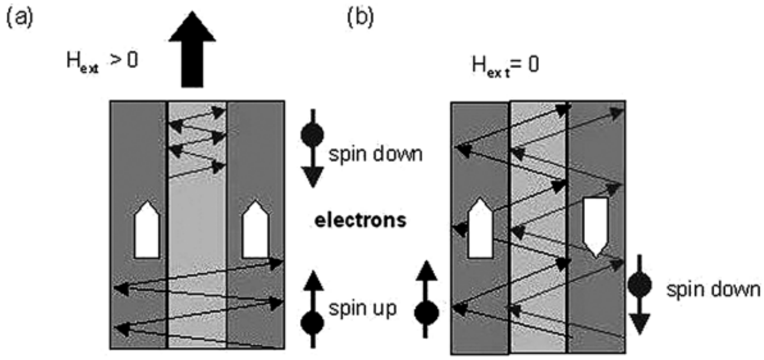


Figure 3.40: Spin dependent scattering of electrons with spin directions parallel and antiparallel to directions of layer magnetization (spin up straight lines, spin down dashed lines) after Bürgler and Grünberg 2003.

An electric current results from the drift of electrons in the direction of an applied electric field. This drift velocity of the electrons caused by the electric field is much smaller than the Fermi velocity. The electric resistance results from scattering of the electrons at inner and outer surfaces and defects in the layer system. Only electrons near the Fermi-energy with spin down magnetisation can be scattered because only they can find unoccupied states above the Fermi-level after scattering. The scattering probability is much higher for the minority carriers (spin down) than for the majority carriers (spin up). The movement of electrons in the layers with the drift in an electric field is shown schematically for parallel (a) and antiparallel (b) direction of layer magnetization. For simplification, scattering at internal defects like impurities or vacancies is not considered here.

This changes when the magnetization in the layers becomes antiparallel (b) in a zero external field (H = 0). Now electrons with both spin directions experience scattering processes when passing an interface with magnetization direction opposite to the spin direction. The overall resistance then will no be longer near zero but finite. The slope of resistance in figure 3.35 with a maximum of resistivity for zero external field can thus be understood in principle.

Realization of GMR-systems

The discovery of the GMR in 1988 found special interest by the manufacturers of magnetic hard disc drives (HDD). Since about 1970 the AMR effect with the rather poor sensitivity had been applied in magnetic reading heads (MRH). An effect like the GMR seemed to be especially appropriate for MRH with improved sensitivity. The first investigations and experiments on the GMR had been carried out at very low temperatures and high magnetic fields which were not practicable for any application. Another critical point was the production of the GMR layers. The first layers had been produced by molecular beam epitaxy (MBE) which is an extremely expensive process. For any application of the GMR a much cheaper production process had to be developed.

All over the world many research groups in academia and industry recognized the potential of the effect very quickly and several teams of researchers started intensive investigations to design a sensor which would operate at low magnetic fields and at room temperature for reasonable costs. By the time many different systems have been explored. At IBM e.g. more than 30000 different multilayer combinations and layer dimensions have been made and tested (IBM Homepage/research GMR). Some selected examples of the investigated systems will be described in the following chapters.

Two Dimensional Magnetoresistive Systems, Multilayer Systems with Current in Plane (CIP)

The focus of the development of GMR has been on two dimensional systems with CIP-geometry all the time. Thus most results have been published about this arrangement. As already mentioned before we have to distinguish here between free layer systems where the magnetization is free without any external pinning force. On the contrary there are (next section) so called spin valves, where one layer with a preoriented magnetisation pins the adjacent ferromagnetic layer.

Systems with free magnetic layers (IEC). Table 3.01 shows the results of GMR measurements for some representative sample structures (values from Baibich and Grünberg 2003). The higher values for a higher number of layers in table 3.01 and also in figure 3.35 (a) can be explained by increased

Table 3.1: GMR effect as function of number of layers at various temperatures for different layers.

Sample structure	ΔR/R in %	Temperature (K)
$[Fe(4.5)/Cr(12)]_{50}$	220 42	1.5 300
$[Co(15)/Cu(9)]_{30}$	78 48	4.2 300
$[Co(8)/Cu(8.3)]_{30}$	115 65	4.2 300
$[Co(10)/Cu(10)]_{100}$	80	300
NiFe(100)/Cu(25)/Co(22)	4.6	300

Table 3.1 Remarks: Number in Brackets indicates layer thickness in Angstrom (Bürgler and Grünberg 2003).

scattering probability as electrons have to pass a higher number of interfaces with increasing number of layers.

Costs are of major importance for the application of the GMR effect. A first step has been the successful application of sputtering instead of MBE. Another step in cost reduction is the reduction of the number of multilayers. In this field progress has been reported by Egelhoff et al. (1996; 1997). He achieved smoothing of a Co-metal surface by annealing in oxidizing atmosphere. Preferably the peaks of the metal surface where oxidized to CoO. The result was reduction of scattering by improvement of the specular reflectivity of the electrons at the external surfaces.

A well-functioning GMR-system is a combination of NiFe magnetic layers and Ag. The layer system can be easily produced by sputtering. The optimum layer thickness is in the range between 1 and 1,5 nm. During an optimization process by annealing between 200 and 300°C an Ag-Ni-Fe-alloy is formed at the layer interfaces. The annealing is reducing the roughness of the interface. In dependence of the magnetic and the non-magnetic layer thickness these systems display a good antiferromagnetic coupling at moderate magnetic saturation fields in the range of up to 1 Tesla combined with reasonable detectable MR-effect of up to more than 20% at room temperature.

Spin Valve Systems (SVS)

IBM has developed special magnetic reading head based on spin valve systems. Figure 3.41 shows the principal design.

The whole multilayer structure is about 10 nm thick on a Si-surface.

The advantage of this system is that it is very sensitive to external fields, e.g. the magnetic hard disc, with a very low saturation field of 10 to 30 Oe.

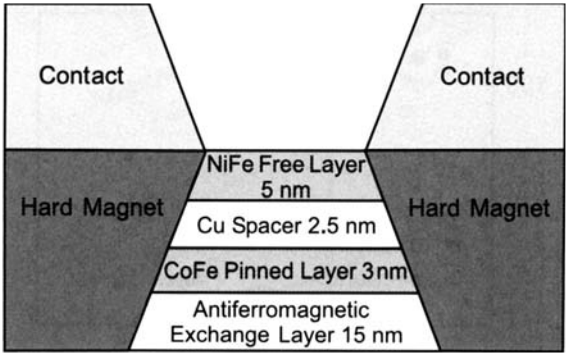


Figure 3.41: Principal design of a GMR reading head (Dietzel, Andreas) In: Nanoelectronics and Information Technology, Wiley VCH 2003, ISBN 3-527-40363-9, "Hard Disk Drives" 618-631; reproduced by permission of Wiley VCH, STM-Copyright & licenses.

For this reason spin valve system are now commonly used in magnetic reading heads.

One Dimensional Magnetoresistive Systems, Multilayers in Nanowires (CPP)

One dimensional MR-wires can be easily produced by intermitting galvanic deposition of ferromagnetic and non-ferromagnetic layers consisting of a few atoms in nanoporous templates (Ansermet 1996; Piraux 1994). The templates can be produced in different ways, e.g. in Polycarbonate (Martin 1994) or in Alumina (e.g. Jessinsky et al. 1998).

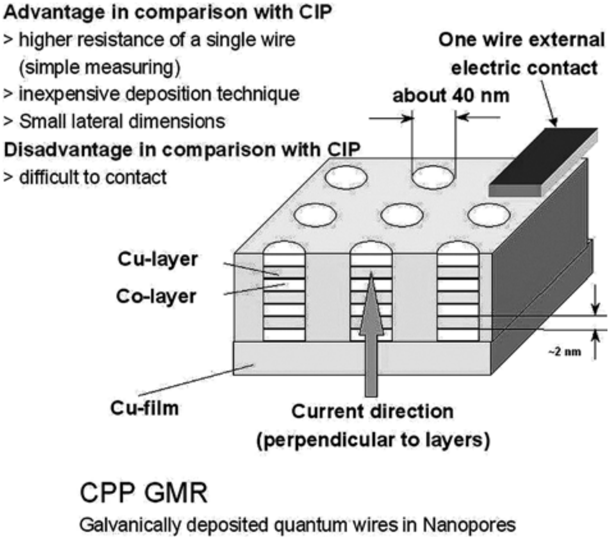


Figure 3.42: GMR effect (CPP) in one-dimensional systems (Ansermet 1996).

The arrangement of the system is shown in figure 3.42. The external magnetic field is applied perpendicular to the current direction.

Table 3.2: CPP-GMR effect in some representative sample structures (CPP); data from Bürgler and Grünberg (2003); Number in Brackets indicate layer thickness in Angstrom.

Sample structure	ΔR/R in %	Temperature (K)
$[Co(12)/Cu(11)]_{180}$	55	300
$[Co(8)/Cu(12)]_n$	170	4.2

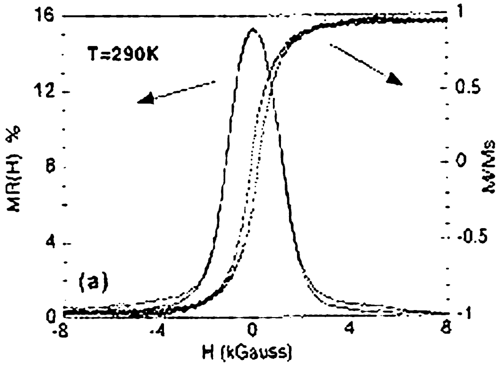


Figure 3.43: CPP-GMR and magnetisation in nanowires. Reprinted with permission from L. Piraux, J. M. George, J. F. Despres, C. Leroy, E. Ferain, R. Legras, K. Ounadjela, and A. Fert, "Giant magnetoresistance in magnetic multilayered nanowires". Applied Physics Letters, 65, 2484 (1994). Copyright 1994, American Institute of Physics.

The electrical resistance of a single nano wire is in the range of some 10 Ohms. This value is much higher than that in 2-D-systems which facilitates the evaluation of the GMR. But contacting discrete nano wires is much more difficult as it is in two-dimensional systems. Also the required magnetic fields are higher than in the CIP case (figure 3.43). This reduces sensitivity of the effect.

Advantageous for applications could be the possible miniaturization of the system. According to table 3.02 it should be expected that the GMR in nanowires with CPP should be rather higher than in CIP geometry. But it seems that the galvanic deposition of the layers with constant thickness is not as reproducible as required. Another disadvantage which prevents application is that with lower dimensionality higher magnet fields are required equivalent to a reduced sensitivity of the GMR effect. Further research will be necessary for improvement.

Zero dimensional Magnetoresistive Systems (Granular Systems)

Granular systems with a mixture of powders of non magnetic and ferromagnetic materials can be easily produced e.g. by thick film technology (TFT) or by sputtering. The advantage could be the extremely inexpensive production

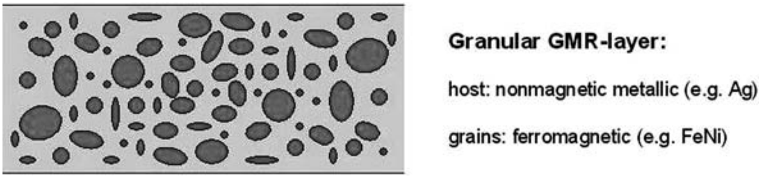


Figure 3.44: Granular GMR layer (schematically).

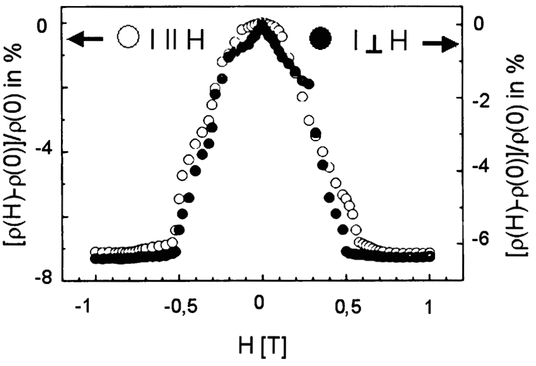


Figure 3.45: GMR effect in a sputtered Ag/Ni granular layer (Hahn 1996, reproduced by permission of Horst Hahn).

of granular systems e.g. by thick film technology. Figure 3.44 displays the schematic design.

Figure 3.45 displays a measuring curve on a sputtered Ag/Ni granular system (Hahn 1996). The powder had been produced by gas phase condensation and had been consolidated afterwards by pressure at room temperature.

Layers with granular powders can have a large MR-effect up to 60%. The scale on the left side of figure "Granular curve" is for current I parallel to the magnetic field, while the scale on the right is for perpendicular current direction. As can be seen, the scales are almost the same for both current directions because scattering occurs anisotropically. But reproducibility with all available technologies up to now is rather poor and not sufficient for introduction to any products. Usually the required magnetic field strength are pretty high.

Colossal Magneto Resistance (CMR)

Some Perovskites like Lanthanum Strontium Manganese Oxide display a resistance change of up to 600% at low temperatures at about 100 to 200 K when high external magnetic fields are applied (VDI 1997). In Manganese based systems a CMR effect up to room temperature has been observed, too (v. Helmolt et al. 1993). The limitations to high magnetic fields and to small temperature ranges prevent the application of the effect in industrial products up to now. Also the theory of this effect is not yet completely understood.

Tunnel Magnetoresistance (TMR)

The TMR configuration consists of two ferromagnetic electrodes, normally in form of thin films. The electrodes are separated by a thin dielectric (e.g. AlO_x) or semiconducting layer with a thickness of about 1 nm. If a small voltage (< some hundred mV) is applied to the electrodes a small tunneling current will flow across the barrier. This corresponds to a CPP-geometry. The TMR is found to be dependent on the magnetization of the electrodes on both sides of the layer (Moodera and Mathon 1999). Record TMR values have been found in the order of 50%. The effect is not yet really understood.

Applications of the GMR

The 2-dimensional GMR is being used extensively in magnetic recording heads, because the GMR effect can be made much more sensitive than the formerly used AMR effect (IBM-Homepage 2004). Figure 3.41 shows the principal design of a reading head using a spin valve layer system with CIP geometry which is most advantageous for this application. The NiFe free layer can rotate its magnetization in the presence of an external field, e.g. from the magnetic storage disc.

Other applications under investigation are contactless working position sensors, e.g. for automotive steering wheel position or in anti-lock systems (ABS). The requirements there concerning the temperature range of application, robustness and costs are very hard to meet, especially in the mass market for "automotive application". This prevents further introduction into products up to now. Support by funding should still be granted for further development of systems like the CMR and the TMR which up to now are not completely understood. In systems like these there may be room for further improvements for products.

B5: High Strength Composites

(s. "High Strength Materials and Composites" B1)

D5: Photochromism

PhChr has been defined as a reversible change in the color, or darkening, of a material caused by absorption of ultraviolet (UV) or visible light (Crano 1993). The reversion of the system to its original state can be driven either by thermal or photochemical energy ("photobleaching"), or both.

PhChr systems are naturally separated into two principal categories: inorganic and organic. There are several types of organic photochromic systems (Bouas-Laurent and Dürr 2001) involving a multitude of mechanisms. The photochromic reactions can be uni- or bimolecular.

Within the inorganic category, the systems which are studied and commercially utilized mostly are those containing silver halide nanocrystallites dispersed throughout a glass matrix. The mechanism of the silver halide PhChr is the reversible formation of the silver metal atoms with subsequent formation of silver clusters on the halide crystallite surface. Both the photochemical formation of the metal and the reformation of silver halide are catalyzed by copper ions.

Silver halide glass systems have been used in photochromic eyewear. Other possible applications in the future could be smart windows, displays and memories (Fujishima 2002). The photochromic reaction is controlled essentially by diffusion processes. Therefore in it is rather a scaling effect and not real Nanotechnology the sense of our definition.

D5: Plasmonics

(s. D1)

G5: Self Assembly of Metal Nanoparticles

Self assembly of molecules and nanoparticles is a well known phenomenon. If it happens in three dimensions it is traditionally called crystallization. In connection with this chapter the two-dimensional (2D) self assembly is of special interest, since those arrangements are of decisive relevance in Nanoscience and -technology. As in the case of three dimensions, self assembly happens due to weaker or stronger attractive forces between the particles to be organized, linked with the natural tendency to form dense packings. In the 2D case the substrate on which the monolayer shall be deposited is also of great relevance. There should exist attractive forces between the particles and the surface, however, these have to be weak enough that deposited particles can move around to form densely packed structures. However, too weak interactions prevent well organized structures due to redissolution.

The final goal in generating and investigating 2D arrays of metal nanoparticles is their use in nanoelectronics, optoelectronics, storage systems etc., based on their size-quantized electronic properties. Most important for a successful self assembly of nanoparticles is a dispersity that should be as small as possible. Deviations of up to 10% are tolerated. Appropriate chemical modification of the nanoparticles' surface, the substrates surface or

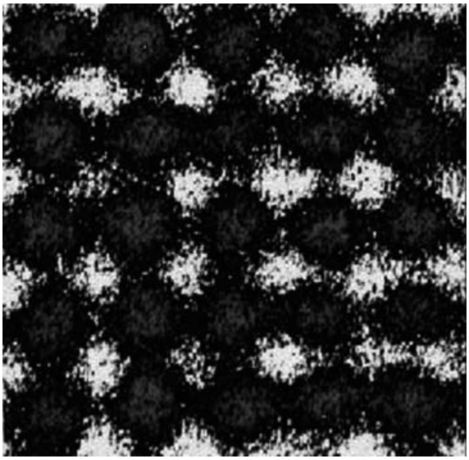


Figure 3.46: TEM image of square packed ligand protected 1.4 nm Au particles. With permission from Wiley-VCH, Weinheim.

of both has turned out to give the best results. Figure 3.46 shows a transmission electron microscopy (TEM) image of 1.4 nm ligand stabilized gold nanoparticles on an appropriately modified surface.

One-dimensionally organized structures of metal or semiconductor nanoparticles are still very rare. They require appropriate templates to arrange the particles in one dimension. First approaches look promising; however, 1D organization is much more difficult compared to formation of 2D arrangements.

2D, with some respect also 1D and 3D organized metal and semiconductor nanoparticles, are the basic systems for applications in nano- and optoelectronics, storage systems and many other future applications. This field of Nanoscience and -technology is still at the very beginning. Intensive further developments are necessary.

G5: Coordination Polymers

Coordination polymers are metal-ligand compounds of one- (1D), two- (2D) or three-dimensional (3D) structures, as can be seen in figure 3.47.

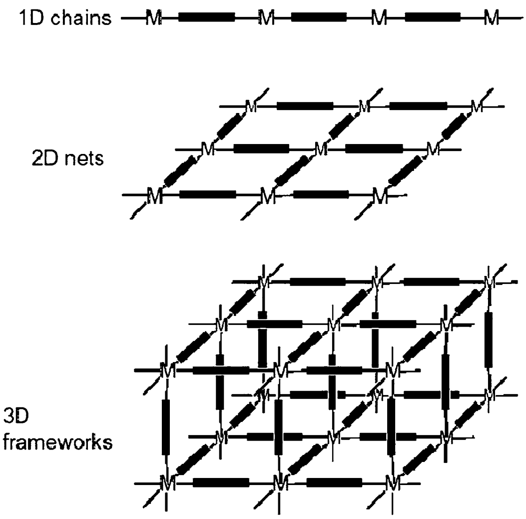


Figure 3.47: Principles of 1D, 2D and 3D coordination polymers.

Coordination polymers have gained an enormous interest during the last decade. The formation of coordination polymers follows self-assembly processes ending up in novel systems with highly interesting properties.The bonds between metal and ligand usually are, but do not have to be of covalent character. A discrete example for 1D is shown in figure 3.48.

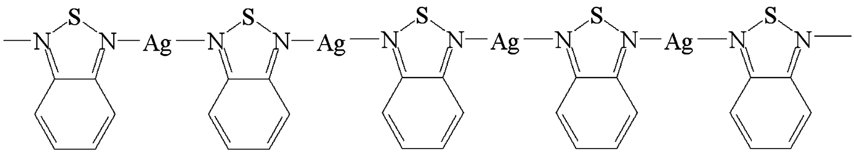


Figure 3.48: Sketch of a 1D coordination polymer consisting of 2,1,3-benzothiadiazole molecules, linked by silver ions.

The use of appropriate building blocks allows the construction of an almost infinite number of 1D, 2D and 3D systems with individual properties depending on the nature of the buildings blocks, the dimensionality and the kind of cooperation.

Applications of coordination polymers in future nanotechnological devices can especially be expected on the fields of non-linear optics (NLO), molecular magnets, catalysis, spin-crossover processes, sensors, zeolite analogs and many more. In so far this chemically based scientific development is worth to be intensively supported. For representative literature s. Janiak (2000) and Munakata et al. (1994).

H5: Biosensors

Semiconductor and metal nanoparticles with their unique and size dependent properties are useful labels for biomolecular detection. In conjunction with biomolecules with their highly specific recognition abilities (oligonucleotides, proteins, anti-bodies, enzymes) they represent functional hybrid systems, whereas bimolecular reactions and binding events can be detected by means of electrical, optical or magnetic measurements. This covers the fields of simple detection, sensing, imaging, diagnostics and therapy. Thus, the hybrid systems can be applied in vivo or, at least, can be immobilized on solid supports, applicable for high throughput experimentation as well as chip technologies. In this sense, miniaturization down to the nanometer scale will be one of the great challenges within the next years and will contribute essentially to the field of home-care diagnostics. Furthermore, those systems can be relevant in the self-organized assembly of electrical circuits.

The fields of applications range from biomedical applications and diagnostics to micro- and nanoelectronis (chemical information technology). A detailed analysis of the technological potential of these developments will be given in section 3.3, which will acquaint the reader with the biomedical challenges of Nanotechnology.

3.1.6 Boundary Surfaces

A6: Proximity Effect

The proximity effect is a so-called nearfield effect. It generally occurs when a current carrying system is brought in close vicinity of another conducting sample. These currents can either be macroscopic external currents induced by an external source or can also be based on the electronic system of two bodies interacting via fluctuating electromagnetic fields. This interaction gives rise to van der Waals and dispersion forces.

In nanocrystalline systems consisting of small non-magnetic particles embedded in a magnetic matrix or in a non-magnetic interacting system exhibiting strongly differing Fermi levels, magnetism can be induced in otherwise diamagnetic system. This results from the shifting of the Fermi level of a non-magnetic component. Thus, under these conditions magnetic properties of diamagnetic systems such as copper can be induced.

This requires a precise control of the particle sizes and distribution of nanoparticles in an appropriate inducing matrix. The local electric fields may than be much higher than the corresponding dielectric breakthrough fields. The effect occurs when the electronic screening length becomes

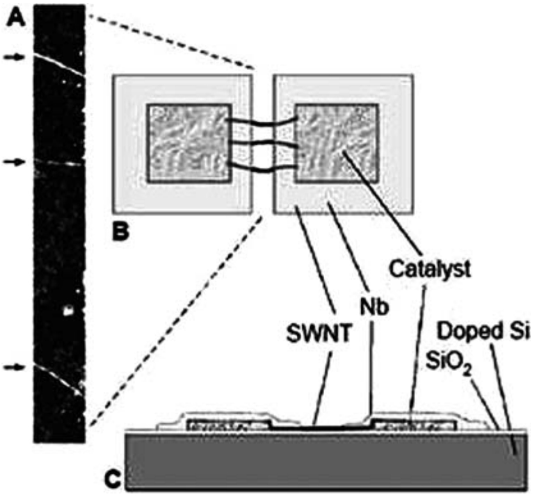


Figure 3.49: Schematic of sample layout, showing SWNTs grown from two 5 mm by 5 mm catalyst islands, then covered with 60 nm of sputtered Nb, producing a 300-nm gap between Nb pads. (A) Atomic force microscope image of gap region between Nb pads, with three SWNTs (marked with arrows) visible. (B and C) Top and side views of a schematic device layout. Atomic force microscope images show that the diameters of all SWNTs are 1.6 nm (except for one SWNT in one of the samples measured, which has a diameter of 1.8 nm) (with kind permission from Morpurgo et al. 1999).

smaller than the range of the inducing local fields and coherence lengths involved. This can be adjusted by choosing particles in the nanometer size.

A similar effect can be induced in the area of superconductivity where the investigation of small particles between nanoelectrodes and electronic influence of the superconducting electrons on normal conducting systems is to be expected. Using small particles in the close vicinity of superconducting materials may thus induce superconductivity in the nearfield regime of the inducing elements. Morpurgo et al. demonstrated the superconducting proximity effect also in single-walled carbon nanotubes (SWNTs) connected to niobium electrodes. Using a gate electrode, the niobium-nanotube transparency could be tuned at 4.2 Kelvin (Morpurgo et al. 1999).

Hence, this effect only occurs below a certain particle size and can not be induced in macroscopic samples and therefore has to be regarded as a quantum size effect.

Applications of the proximity effect are in the field of inducing magnetism in diamagnetic metals and also shift electronic states of magnetic particles such that they become non-magnetic. In addition, the effect can also be used to induce superconductivity on small particles or thin layers in otherwise non-superconducting materials such as gold. Applications include switchable magnetic materials and sensor devices based on superconductivity.

C6: Gas Sensors and Catalysts

Sensor technology is one of the most important mass-markets of the future with a constantly increasing number and variety of applications in both the industrial and domestic sectors. Ever more sensors and sensor arrays are being used in the control of technical processes, within environmental protection, applications in health care, for use in automobiles and aircraft and the control of (chemical) production processes.

Semiconductor nanoparticles as well as nanoporous solids are increasingly used for the fabrication of highly selective gas sensors. The nanoparticles used are typically metal oxides, among the best-understood prototype of oxide-based gas sensor is the SnO_2 sensor (Barsan et al. 1999). This material has repeatedly been tested by changing the preparation and deposition techniques. These range from powder preparation techniques, e.g. via precipitation from solution, milling of bulk material or by laser pyrolysis up to gas phase methods via chemical vapour deposition (CVD) or physical vapour deposition (PVD). According to the presently most accepted model for the working principle of a metal oxide gas sensor, the particle size of the sensor material plays a crucial role. Below a certain grain or particle size, the radius approximately reaches the Debye-length, which corresponds to the length of the space-charge or depletion zone. At this size the sensitivity reaches its maximum. At the same time nanoparticles provide an increased surface area as compared to micrometer sized particles, making the materials more accessible towards the applied gases. This will allow the further miniaturization and integration of single sensor elements and sensor arrays. The development of new material compositions on the nanometer scale, i.e., semiconductor nanoparticles with variable compositions and huge variety in volume and surface doping will be essential for this design routes. For this purpose, high-throughput experimentation and combinatorial chemistry will be powerful methods, as it was demonstrated just recently (Franzen et al. 2004).

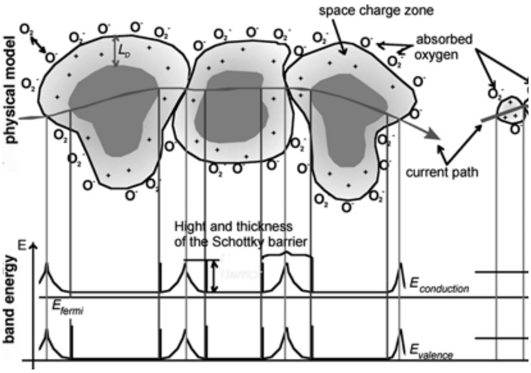


Figure 3.50: Physical model and band structure of a gas sensor material, illustrating the meaning of the Debye-lengths for the sensitivity. In nanoparticles the Debye-length extends over the entire volume of the particles.

Surface doping provides the opportunity of utilising size effects of the respective catalytically active material, when it is applied as nanoparticles with a narrow size distribution. With this method the sensitivity of a sensor can be tuned via the particle size.

Nanoporous sensor materials, like zeolites, have a great potential in terms of selectivity (Franke et al. 2003). A prominent example is a zeolite-based NH_3 sensor, which will enter the market as an exhaust gas sensor for NO_x-rich diesel exhausts in commercial vehicles. Comparable to the shape selectivity of heterogeneous catalysts one might expect new materials with high selectivity. This can be utilised in applying the material as gas sensing materials as well as filters in combination with conventional sensor materials.

In heterogeneous catalysis most effects are related to the microstructure of the catalyst as well as on the topology and topography of the catalytically active sites on the nanometer or even atomic length scale. The technical relevance of nanomaterials in catalysis cannot be underestimated. But it will be an impossible task to foresee those fields of technical application, which will profit from a rational design of nanomaterials, since the complex interplay of the multiple reaction parameters in catalysis (as well as in sensor development) need at least an empirical or semi-empirical strategy for system opti-

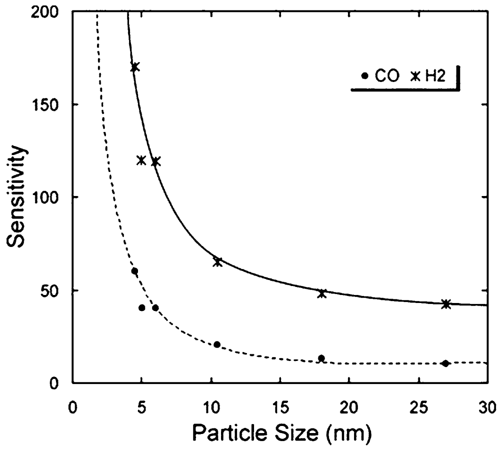


Figure 3.51: Sensitivity of a nanoparticle doped SnO_2 sensor expressing the increasing sensitivity with decreasing particle size (adapted from Yamazoe 1991).

mization. Here again the use of high-throughput experimentation and combinatorial chemistry will be a promising approach. Modern literature on catalysis more and more focuses on size effects. A comprehensive discussion of the different aspects would by far exceed the limits of the present study, so that the interested reader might be guided by a new text book edited by Zhou, Hermans and Somorjai (2004) and the references therein. With the title "Nanotechnology in Catalysis" it emphasizes the fundamental understanding of catalysis on the nanoscale, the synthesis of different nanomaterials (particles, porous materials, nanotubes, dendrimers etc.) and gives a lot of instructive examples for the application of nanomaterials in a variety of catalytic processes.

D6: Plasmonics

(s. D1)

G6: Patterns by Phase Separated Block Copolymers

Block-copolymers are macromolecules consisting of at least two parts, generally differing in their hydrophilicity. As generally these molecular subunits prefer to interact with the similar substructures of the neighbouring molecule, ordered structures of nanoscale dimensions emerge. This organization of macromolecules can result in very regular patterns in nanoscale dimensions in two dimension on surfaces and in three dimensions in materials (Hamely 2003). The regularity of the structure allows for physical effects (optical properties) that are typical for periodic nanoscale structures. The figure below shows two structures that have been made by phase separation of a diblockpolymer (Park et al. 1997).

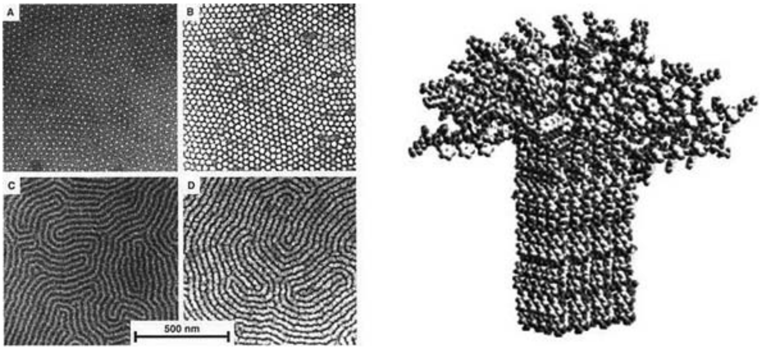


Figure 3.52: Left side: TEM picture of a surface structure made by a diblockpolymer. Both surface structures have been used as lithographical masks resulting in the structures on the right side (Park et al. 1997). Right side: Schematic representation of the mushroom shaped object formed by a diblockpolymer (Stupp et al. 1997). The picture is reproduced from the internetpage stupp.northwestern.edu.

These interactions can not only be used to organize two dimensional patterns. Phase separation also allows for the engineering of nanoscale three dimensional objects, like the mushroom shaped objects from Stupp et al. (1997) shown in the figure above on the right side. These structures and objects in nanoscale dimension result from selective recognition interactions on a molecular level and thus must be described by quantum mechanical laws. In addition, these patterns provide typical physical (optical) properties for periodic nanoscale structures.

The potential applications of such materials are manifold. Their use as lithographical mask has already been demonstrated in the figure above. Large antireflection surfaces have been prepared by phaseseparation as well. An envisaged application of nanoscale objects is their use as artificial body compatible polymers for surfaces of prostheses.

3.2 Information Storage

3.2.1 Stimulus: Electric/Electronic

A1: Magnetic Random Access Memory (MRAM) (also B1)

Magnetic random access memories are non-volatile memories with access times independent of the address. Thereby they combine the advantages of computer hard disks, keeping the information stored without power supply, with the ones of current DRAMs, having fast and constant access times. The core of an MRAM cell is a junction between two ferromagnetic layers separated by an oxide spacer layer, s. figure 3.53. Such a junction is known as magnetic tunnel junction and its transport is characterized by the tunnel-magneto-resistance (TMR). The conductance differs for parallel and anti-parallel configuration of the magnetizations in the ferromagnetic layers due to the spin polarization of the ferromagnets. Typically, one of the two ferromagnets is pinned such that only one of the two electrodes switches when applying a magnetic field enabling one to go from parallel to anti-parallel and back again. While the state of the cell can be sensed with a very small sense current by the TMR, writing the cell requires high currents injected simultaneously into bit and word lines producing high magnetic fields at the intersection which one wants to address.

Demonstrators and prototypes of MRAMs have been produced at Cypress, Motorola, and IBM, collaborating with Infineon. The majority of

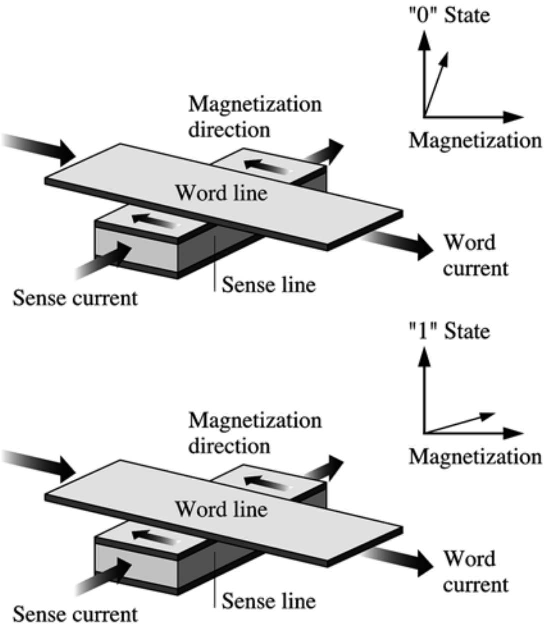


Figure 3.53: MRAM cell.

observed in nanowires and contacts to nanoparticles. Using this effect for writing a MRAM cell directly yields to addressing in the very same way as the read-out, only with different current magnitudes. Another promising progress has been achieved in the TMR values obtained at room temperature. While 1000% have been predicted, only 80% were obtained (Reohr et al. 2002, Parkin et al. 2003), until very recently single crystalline (Yuasa et al. 2004) and polycrystalline (Parkin et al. 2004) samples have demonstrated more than 200% at 300 K.

Altogether the MRAM is greatly benefiting from fundamental studies and presumably it will soon be an alternative to DRAMs. This will imply that we don't have to boot our computers any more and that they do not contain mechanically moving parts any longer. An additional advantage of MRAMs is the high speed with which magnetization can be reversed. Field pulses of 2 ps duration have been demonstrated to reverse the magnetization of a thin film (Back et al. 1999).

A1: Semiconductor-Spintronics (also A2/B2)

While conventional semiconductor devices use electrical fields to manipulate the flow of the charge carriers, electrons and holes, spintronics (or magnetoelectronics) exploit their spin. Here we briefly discuss semiconductor thin films and nanostructures which may possibly be employed in spintronic circuits fulfilling memory or logic functions. For metal/oxide spintronics we refer to the chapters on spintronics–GMR and on MRAMs. We note that in addition to memories also reconfigurable logic gates can be realized with spintronics using metallic components (Cowburn et al. 2000, Allwood et al. 2002).

Since metallic components are considered to be incompatible with current CMOS technology there is a desire to realize spintronics also with semiconductors. This involves the creation of ferromagnetic semiconductors and the injection of spin-polarized currents into non-magnetic semiconductors. Groups working on the first issue have achieved Curie temperatures up to 110 K in GaAs by growing thin films where 7% of the gallium atoms have been replaced by manganese (Ohno et al. 1996). Despite the effort put into understanding and optimizing these diluted magnetic semiconductors (DMS), no concise theoretical picture of the physics giving rise to ferromagnetism could be put forward so far. Most of the uncertainty originates from the state of the magnetic impurities in the semiconducting host, in particular it is unclear whether the Mn is there in the form of clusters or of single atoms. This influences the magnetic state of the individual impurities and their coupling establishing the long-range ordered ferromagnetic ground state. The issue of spin injection has been solved for the interface between a non-magnetic and a magnetic semiconductor, where an efficiency of 90% was achieved (Fiederling et al. 1999, Ohno et al. 1999). At the interface semiconductor/metal spin injection is most effi-

Table 2: Information Storage

Table 2 and the corresponding sections take up effects that are to a certain extent already covered by Table 1. Regarding the enormous importance of new information storage systems with a great future, this chapter is dedicated exclusively to physical and chemical nanoeffects offering principles that can be used for information storage. This chapter pursues two goals. First, it gives a brief introduction into key technologies to probe nanostructures and second, the potential of effects and concepts for envisaged, planned or even partly realized technological applications is discussed.

			Retr
		electric/electronic (1)	
Stimulus	**electric/ electronic (A)**	Magnetic Random Access Memory (MRAM); Semiconductor- Spintronics; Single Charge Storage; Ferroelectrics; Molecule Based Memory/NDR; Chemical Atomic Force Microscopy	Semic
	magnetic (B)	Magnetic Random Access Memory (MRAM); Magneto Resistance (MR)	Semic
	optical (C)	Molecular Switches	Spin- Switcha
	mechanic (D)	Chevron-Scanning Tunneling Microscopy	Spin-
	thermal (E)	Optically and Electrically Switched Phase Change	Spin-

the problems encountered have to do with the writing process consuming too much energy, and being not sensitive enough since the write current produces half of the magnetic field of the crossing point all along the word and write lines, and it is difficult to adjust the switching field of the cells to a factor of two. Therefore neighbouring cells sometimes switch, too.

All of this can possibly be solved by a recently discovered phenomenon known as current-induced magnetization reversal. Injecting a spin-polarized current into a ferromagnet may exert torque onto the magnetization of the ferromagnet by which it can be reversed. This effect is restricted to nanoscale junctions since it requires high current densities. It has been

In the first column Table 2 lists the physical kind of the stimulus that triggers the state of the storage device (A-E) against the physical kind of the retrieval of the stored information in the upper row (1-4). The individual fields are treated row by row, i. e. from A1-A4, B1-B4 etc.

In numerous cases, the state of the storage device differs in several physical properties allowing to read the information in different (physical) ways. Hence, some concepts are mentioned in several boxes of Table 2 but are only discussed in detail in the box with the most advanced or the one technological information retrieval concept most likely to be realized.

ieval		
magnetic (2)	**optical (3)**	**mechanic (4)**
nductor- Spintronics	Electrochromism	Molecular Actuators; Chemical Atomic Force Microscopy
nductor- Spintronics	Scanning Nearfield Magneto-Optical Microscopy (SNMOM)	Magnetic Force Microscopy (MFM); Magnetic Resonance Force Microscopy (MRFM)
Crossover Processes, ble Biradical Coupling	Scanning Nearfield Optical Microscopy (SNOM); Optical Computing; Optically and Electrically Switched Phase Change	Optically Triggered Mechanics
Crossover Processes		Chevron-Scanning Tunneling Microscopy Rotaxanes; Chemical Atomic Force Microscopy
Crossover Processes	Optically and Electrically Switched Phase Change	

cient through a tunnel barrier (LaBella et al. 2001). Due to low Curie temperatures and due to the spin injection efficiency decrease of temperature, there is still some way to go before all-semiconductor room temperature magnetoresistance devices will be realized. Part of these problems can be solved with magnetic oxides which can be compatible to CMOS technology and may therefore present valuable alternatives to DMS (Wolf et al. 2001).

The quantum mechanical nature of the spin makes it an ideal candidate for the quantum bits (Qbits) needed for quantum computing. The concept of quantum computing requires the creation of coherent spin carriers, i.e., spins which are not simply aligned, but are coupled in a collective quantum state described by a single wavefunction (Ball 2000). The lifetime of such a state is linked to the spin coherence time, which, in magnetic semiconductors, can be as high as 100 ns (Kikkawa et al. 1997). This is sufficiently long to drag a coherent spin packet of electrons over a distance comparable to typical device dimensions (Kikkawa et al. 1999).

Semiconductor nanostructures, so-called quantum dots (QDs), are particularly interesting for the realization of Qbits (Engel et al. 2001, 2002). Coherent spin packets could be confined for example in CdSe quantum dots with 2 to 8 nm diameter (Gupta et al. 1999). Arrays of QDs have been proposed to be used to implement a large scale quantum computer (Loss et al. 1998). In these proposals each QD is a Qbit interacting with its neighbours by the exchange interaction, the strength of which can be switched by gate voltages enabling for instance the realization of exclusive OR quantum gates. The read out of a spin Qbit can be performed with a spin-polarized current passing through the dot (Engel et al. 2001).

While the spin degree of freedom is already implemented in industrial metallic devices, such as hard disk read heads, semiconductor spintronics will still need a few years before being put into practice, however, currently it is a prosperous field of fundamental research focusing on understanding and manipulating spin in semiconductors. Quantum computers are still far from being realized.

A1: Single Charge Storage

Since the late 1970s, CMOS (complementary metal-oxide-semiconductor) technology is the leading technology for device fabrication in computer industries and there is no doubt that this dominance will continue for the next 10–15 years, at least for the set-up of logic elements. At the end of 1970s, in the early stage of this technology, the complexity of the chip-design appeared as a limiting factor, which had been overcome by computer-aided design. More than ten years later the increased integration rates lead to new problems concerning the power- and heat-management, which are still remaining. Nevertheless, optical lithographic fabrication techniques allow mass fabrication down to 50 nm and new techniques, like extreme ultraviolet lithography, X-ray proximity lithography, imprinting lithography and focused electron- and ion-beam techniques will guarantee the exponential down scaling according to the famous Moore's law. This has already been illustrated by the fabrication of transistor elements with feature size of less than 10 nm (Kagan et al. 2003).

However, fundamental limits require the development of new technologies, which will replace CMOS technology in course of further miniaturization. From the present point of view elements for a spin-based information technology (e.g. magnetic RAMs) and chemically based concepts (e.g. molecular switches), carbon nanotube based elements (e.g. carbon nanotube field effect transistor) and single electron tunneling (SET) devices appear to be most promising. Each of these approaches has its own advantages and disadvantages, but it seems to be non-realistic that one of these techniques will exhibit the versatility and stability of CMOS logic. But besides logic elements, single electron devices will have a great impact in the development of memory devices in the future, which consist of hybrid circuits of SET elements and CMOS devices.

In the following, the working principle of SET-based elements is briefly described: Electric current in a macroscopic metallic conductor is associated with motion of a huge amount of free electrons over the entire conductor. In spite of the discrete nature of the charge carriers the current flow in a metal is quasi-continuous. In contrast, in an isolated nanoscaled piece of metal (islands), the number of electrons in there is always integer and at least countable. An electrical circuit of such islands should present a number of reservoirs for free electrons, which should be small and well-conducting and which are separated by poorly permeable tunneling barriers. As long as the size of these islands is larger than the atomic scale, they certainly comprise a huge amount of free charge carriers. But, however, handling of individual charges is still possible if the characteristic electric capacitance of the island C is small enough, i.e. the charging energy is large enough to overcome thermal fluctuations. Such a circuit deals with a small and defined amount of excess electrons on islands changing their distribution over the islands in time in a desirable way. This is the concept of single charge storage (SCS) and the respective electronic transport process is called single electron tunneling (SET).

In order to realize this practically the following two principal conditions must be fulfilled:

– the insulating barriers separating the conducting islands from each other should be much higher than the characteristic resistance expressed via fundamental constants, the so-called resistance quantum, $R_q = h/e^2 = 25.8\ k\Omega$. Then the electrons in the island can be considered as to be localized and their number already behaves classically, although they undergo thermodynamic fluctuations as every statistical variable.

- in order to have these thermal fluctuations small enough and consequently to make the exchange of electrons controllable, the energy associated with charging by one extra electron should be essential with respect to the characteristic thermal energy k_BT. This is the charging energy E_C and it depends on the charge Q, on the size, and on the charge of capacitances of junctions, gates, conductors etc. in the vicinity of the island. The smaller the island the smaller the capacitance and the larger E_C as well as temperature, at which single electron charging can be observed experimentally.

The simplest storage device is the single-electron box for injected/ejected electrons, i.e. a device, which can control the numbers of electrons in a quantum dot (island).

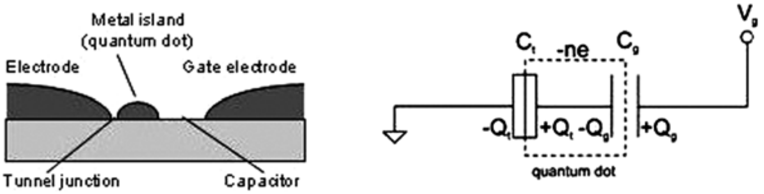


Figure 3.54: Schematic structure of a single-electron box, consisting of a quantum dot (island), an electron connected to the dot through a tunneling junction, and an electrode coupled to the dot through an ideal, infinite-resistance, capacitor (left). Equivalent circuit of the single-electron box (right).

Such an element can be implemented into a charge-state logic, which bases on the bistable or, if more than one charge is deposited on the metallic island, multi-stable configurations. Since one electron represents one bit, which can be transferred from one island to the next, power consumption of such a device is extremely small. This will be of great advantage with respect to minimize the power loss and the heat development in future nanoscale devices. However, the unavoidable drawbacks of SET logis devices are actually the large out-put impedance, which makes the elements intrinsically slow, as well as the extreme charge sensitivity. Thus, the application of SET elements will apparently be restricted on sensing and memory elements.

As a switching device capable for ultra-large-scale integrated circuits (ULSIs), the single-electron transistor can be utilized in the set-up of devices with nonvolatile memory function as well as in SET/CMOS hybrid circuits, working even at room temperature (Uchida 2002). Such transistor elements can be fabricated with different techniques, ranging from silicon-based technology up to chemical self-assembly. While single-electron transistors with multiple nanoparticle charge-storage have a great potential to replace Flash-memories as non-volatile memories, the highest integration rate might be expected from chemically based concepts, where metal or semiconductor nanoparticles assembled at nanocontacts form simple or complex elements with single or multiple SET function.

In order to utilize the opportunities of these molecularly based approaches, principally two different routes have been followed up to now with respect to the experimental design. On the one hand techniques have been developed to fabricate metallic electrodes by electron beam lithography which enable the addressing of a few or even single nanoparticles. On the other hand scanning electron tunneling (STS) techniques have been developed further for chemical control of gating of the central island in a SET transistor or far the chemical switching of the tunneling barrier, i. e. the insulating organic molecules, separating the nanoparticles from the underlying support. This will be illustrated by the following two examples:

Alivisators and coworkers realized an electrode structure scaled down to the level of a single Au nanoparticle (Klein et al. 1997). To fabricate such a device, they combined optical lithography and multi-angle metal evaporation techniques. They yield in a narrow gap of a few nanometers between two Au leads on a Si substrate. The Au leads have been functionalized with hexane-1,6-dithiol, which binds linearly to the Au surface. At the free ends 5.8 nm Au nanoparticles were bound from solution. The resulting device reflects slight current steps in the I(U)-characteristic at 77 K. In further development of this device, a gate electrode to externally control the current flow through the central island a CdSe nanoparticle could be applied to realize a SET transistor.

Since the current flow through such a device thus will be very sensitive to any charges and impurities that reside on the nanoparticles or in the ligand shell, the "transparency" of the ligand shell can be switched by chemical modification. This control is called a "chemical gate", which allows to control the SET current. This has been demonstrated most recently by Schiffrin and coworkers by means of an STS experiment (Git-

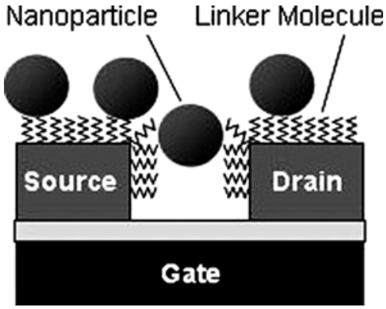


Figure 3.55: Sketch of a chemically fabricated single electron transistor (adapted: Klein et al. 1998).

nis et al. 2000). They used a bipyridyl moiety (viologen group, V^{2+}) as a redox group incorporated in the ligand shell of the particle. Electrons were incorporated into this group under electrochemical control, while the transparency of the insulating barrier was measured by STS. They found that reduction of V^{2+} to the radical $V^{\bullet+}$ leads to a significant decrease of the barrier height. Further reduction to V° results in a very large increase of the barrier hight. This result reflects the supporting effect of a half-filled molecular ortbital in $V^{\bullet+}$. This might lead to an extension of the electronic wave function from the nanoparticle to the substrate via the orbitals of the radical $V^{\bullet+}$. As soon as V° is formed, electron pairing in the LUMO (lowest unoccupied molecular orbital) suppresses the direct electronic interaction.

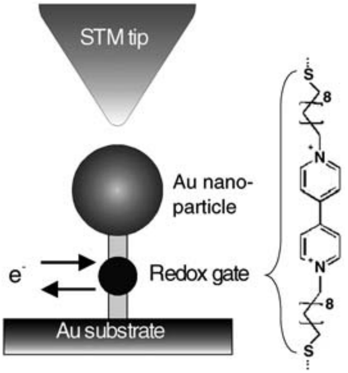


Figure 3.56: Scheme describing the redox switch, which is based on a viologen redox center incorporated within the nanoparticles ligand shell. For simplification the counterelectrode is not shown (adapted from Gitnis et al. 2000).

These results impressively show that switching of the SET current through a ligand stabilized nanoparticle can be induced by electron injection to a specific redox group within the barriers of the tunnel junction. While the configuration, which was studied in this work, requires the reduction by at least 30 electrons to change the transparency of the barrier in the nanoparticle layer, a great challenge will be to integrate those switching elements into a self-assembled SET circuitry.

In order to further develop this approach, there is a big need to advance strategies for the controlled assembly of inorganic nanoparticles with large functional organic molecules to build up SET devices. Actually, the combination of the large recognition capability of biomolecules, like DNA, proteins or supramolecular complexes with the size dependent charging energy of metal nanoparticles seem to be most promising to achieve this goal.

Analogous to SET devices, tunnel junctions can be fabricated from superconducting materials. The tunneling events that appear in these junctions are due to the transport of Cooper pairs, which have an integer spin and which follow the Bose statistics. These so called Josephson junctions or elements essentially need to be cooled down, e.g. as it is typical for a SQUID (*Superconduction Quantum Interference Device*). With respect to SET devices the recharging time in superconducting junctions is of orders of magnitude smaller, which can increase the clock frequency in digital circuits, so that operation frequencies above 100 GHz become realistic.

A1: Ferroelectrics

Introduction

The triumphal march of information technology based on Silicone semiconductors is a consequence of the continuous improvement of the technologies to store information. The storage density on a chip has grown exponentially during the past four decades. The slope follows the well known Moore's law according to which, since the early sixties, the storage density is doubled every two years.

Two principal types of storage information systems are used in information technology:

- Volatile memories: The information is kept in the Dynamic Random Access Memory (DRAM) only as long as the supply voltage is applied. The information is used only for processing the information.
- Non-volatile memories: The information is stored after switching off the external power supply.

DRAM's have been realized since its introduction to the market by Intel in 1972 by large scale integration in Silicone chips with increasing requirements. As progress in lithography was not sufficient to achieve the high storage densities advanced technologies for a three dimensional integration of components, especially capacitors, had to be developed. With the next generation of DRAMS the limits of the existing technologies and materials are dawning at the horizon and new ways and materials for further integration are necessary.

For non-volatile data storage common hard disc drives (HDD) with magnetic storage media are used. They were being developed to highly perfect systems with still increasing storage densities. But for special applications as e.g. in hand held devices like a PDA, digital video cameras magnetic storage is not preferred due to high power consumption.

High permittivity materials with and without hysteresis of the polarisation-voltage loop may be promising materials to overcome the problems of volatile and non-volatile storage devices. The following discussion will focus on material properties and processing of high permittivity materials with respect to their integration in electronic memory circuits. This means that the field cannot be considered as Nanotechnology in the sense of our definition but only as a miniaturization by scaling down layer thickness and structure dimensions. The circuit design will be considered only schematically. A more detailed excellent review of the whole field has recently been given by Kohlstedt and Ishiwara (2003), Schroeder and Kingon (2003), Böttger and Summerfelt (2003).

High Permittivity Material for DRAM Volatile Memory Devices

Principal Design of DRAM's

The principle of a DRAM storage cell is shown in figure 3.57:

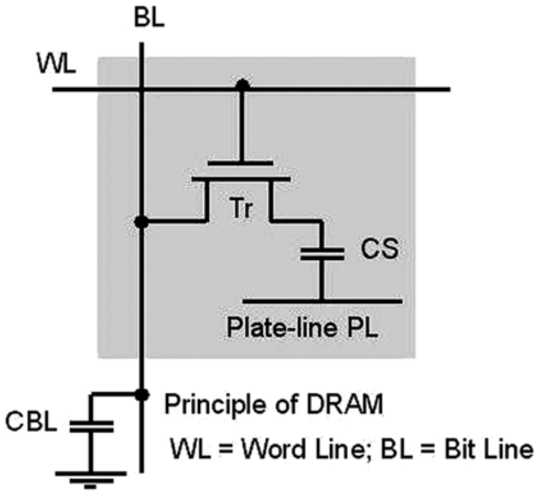


Figure 3.57: Principle of DRAM storage cell (after Schroeder and Kingon 2003).

Heart of the memory cell is the storage capacitor CS with a capacitance of about 25 fF which is connected to the bit line via the transistor Tr as a switch. The switch is controlled by the word line WL. The corresponding charge on CS represent the binary information "1" or "0".

The size of one memory cell is essentially determined by the geometrical size of the storage capacitor CS. The capacitance can be described by the following equation:

$$CS = \varepsilon_0 * \varepsilon_r * \frac{A_C}{t} \quad \text{(eq. 3.3)}$$

where ε_0 and ε_r represent the absolute and relative permittivities, A_C is the area of the dielectric in the capacitor and t its thickness. For a prefixed capacitance CS different ways for reducing the projected required area of the capacitor on the chip have been investigated and applied.

The simplest way is to reduce the layer thickness t. This has been done in the past down to values of a few nanometers. Further thinning makes no sense because it must be guaranteed that the layers are pin hole free to avoid short circuits.

Another way is increasing the dielectric area in 3D perpendicular to the chip surface while the lateral dimensions of the capacitor on the chip surface can be reduced. This can be achieved by growing columns of dielectric and plugs into the interior of the chip (trench technology). In this way the projected memory cell area can be reduced down to the range of about 10% of the dielectric area. Another more complicated way is using a capacitor as a multilayer stack (stack technology; Mitsubishi 1994). The stack is arranged on the surface of the chip above the wiring of the memory cell (Capacitor over Bit-line COB). Both methods are schematically displayed in figure 3.58 and result in smaller lateral dimensions with higher storage densities.

According to equation 3.3 the third possibility to reduce capacitor dimensions is using a dielectric with a higher permittivity. In the first memory cells in the 1960's SiO_2 with a permittivity of about 3 had been used as dielectric. This has been improved by introducing Silicone-Oxi-Nitride (SON) compatible with the CMOS process. SON has a permittivity of about 7. While all the other ways described before have already been developed almost to their technical limits it seems that this could be the big chance for high permittiv-

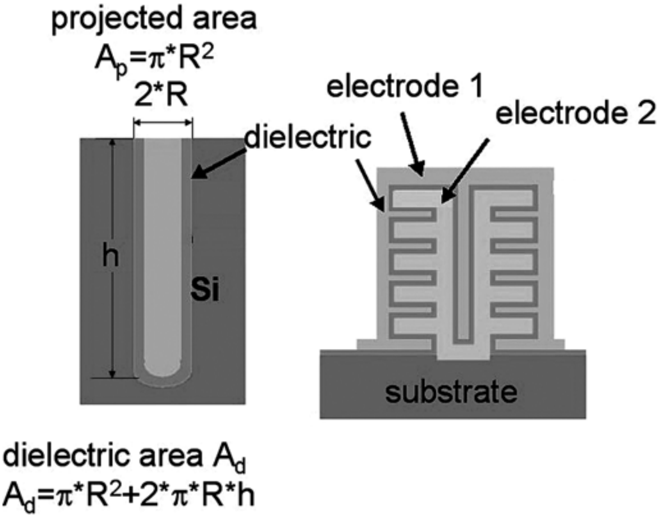


Figure 3.58: Schematical design of 3D capacitors; (a) trench technology; (b) stack technology (H. Schroeder and A. Kingon, "High-Permittivity Materials for DRAM's in Nanoelectronics and Information Technology". Waser, Rainer (ed) Wiley-VCH 2003. ISBN 3-527-40363-9, chapter 22:564-589 (reproduced by permission of Wiley VCH, STM-Copyright & licenses).

ity materials for future Gbit generations of DRAM's. The properties of high permittivity materials as thin films will be presented in the next chapter.

High Permittivity Materials for DRAMS

Requirements to high permittivity films for FeDRAM's
The most important requirements to the dielectric of the storage capacitor with enhanced permittivity in advanced Gbit generations are (Schroeder and Kingon 2003):

- No hysteresis;
- High permittivity ($\varepsilon > 200$) to reduce the folding factors in 3D designs;
- Material must be deposited homogeneously as a thin film (<30 nm) also on 3D structures over large areas (e.g. a 12 inch wafer);
- For read/writing times down to ~1 ns the material should display no considerable dispersion up to frequencies up to ~1 GHz;
- Low leakage currents and charge loss due to polarization;
- All processes for the dielectric material itself and the electrodes have to be compatible with CMOS technology;

It will be discussed in the following in how far high permittivity materials can meet these requirements.

Materials Properties
The following results are shown for BariumStrontiumTitanate $Ba_xSr_{(1-x)}TiO_3$ (BST), which has been extensively investigated by Bascerie et al. (1997) and from which most data are known. The Ba/Sr-ratio was kept at 70:30 while the (Ba+Sr)/Ti-ratio was controlled at ~ 47:53. This was important as it proved that this ratio has some influence on the properties. The BST films were deposited by MOCVD (Metallo Organic Chemical Vapor Deposition) at a temperature of approximately 640°C. The electrodes were made of Platinum.

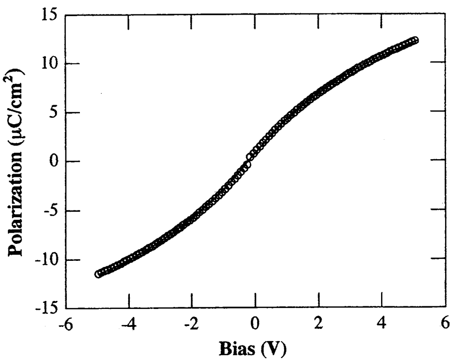


Figure 3.59: Polarization versus applied voltage. Reprinted with permission from Cem Basceri, S. K. Streiffer, Angus I. Kingon, and R. Waser, Journal of Applied Physics, 82, 2497 (1997). Copyright 1997, American Institute of Physics.

BST as bulk material is ferroelectric with a transition temperature of about 0°C.

But in thin films phase transition from the paraelectric to the ferroelectric state is suppressed (Bascieri et al. 1997). Figure 3.59 shows the polarisation of a 61 nm thick BST layer in dependency of the applied voltage. As required no hysteresis is observed.

In figure 3.60 the relative permittivity is plotted versus the nominal electric field for various temperatures. Figure 3.61 shows the slope of ε_r versus temperature for zero applied field.

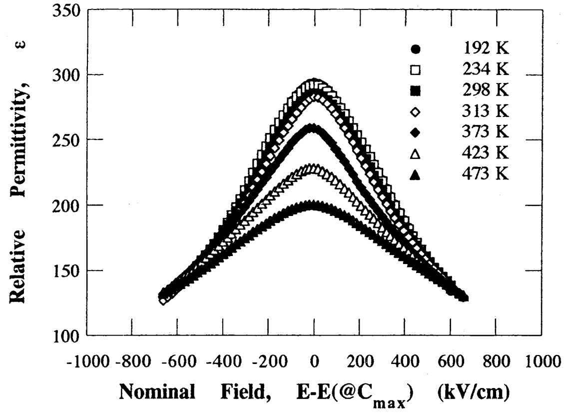


Figure 3.60: Permittivity versus applied electric field strength. Reprinted with permission from Cem Basceri, S. K. Streiffer, Angus I. Kingon, and R. Waser, Journal of Applied Physics, 82, 2497 (1997). Copyright 1997, American Institute of Physics.

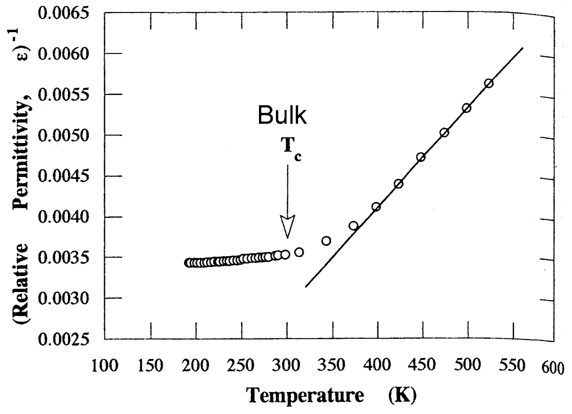


Figure 3.61: Relative permittivity as function of temperature. Reprinted with permission from Cem Basceri, S. K. Streiffer, Angus I. Kingon, and R. Waser, Journal of Applied Physics, 82, 2497 (1997). Copyright 1997, American Institute of Physics.

The maximum of permittivity decreases from about 290 at 192 K to about 190 at 473 K. For temperatures higher than 373 K the slope follows the Curie-Weiss-law (straight line). Permittivity figures for films are much smaller than the figures for bulk material.

The variation of the capacitance area density with film thickness is displayed in figure 3.62. It shows the inverse capacitance area density $(C/A)^{-1}$ versus layer thickness t.

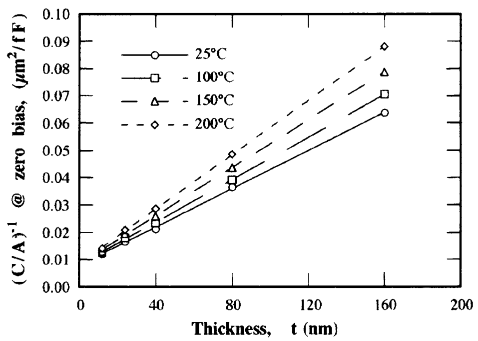


Figure 3.62: Inverse capacitance area density versus thickness layer. Reprinted with permission from Cem Basceri, S. K. Streiffer, Angus I. Kingon, and R. Waser, Journal of Applied Physics, 82, 2497 (1997). Copyright 1997, American Institute of Physics.

According to equation 2.1 the expected linear relationship between $(C/A)^{-1}$ and t is shown. It is striking, however, that for t→0 the inverse capacitance area density displays an offset and does not become zero as it would be expected. This indicates that the measured permittivity is an effective one. An explanation can be derived from figure 3.63 by the assumption of additional capacitance caused by low permittivity interlayers near the electrodes in series with the BST layer.

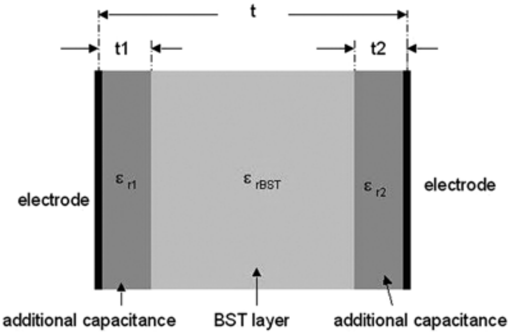


Figure 3.63: Schematic presentation of interlayers between electrodes and ferroelectric layer.

$(C/A)^{-1}$ of the whole arrangement in figure 3.63 can be described by equation 3.4:

$$\left(\frac{C}{A}\right)^{-1} = \frac{t1}{\varepsilon_0 * \varepsilon_{r1}} + \frac{t-t1-t2}{\varepsilon_0 * \varepsilon_{BST}} + \frac{t2}{\varepsilon_0 * \varepsilon_{r2}} \quad \text{(eq. 3.4)}$$

t1 and t2 describe the thickness of the interlayers adjacent to the electrodes. For t→0 there remain terms with t1 and t2 by which the offset in figure 3.62 can be explained. The microscopic reason for this behavior is not yet really understood. It should be mentioned that by using conducting oxide electrodes (e.g. RuO_2) instead of Pt the offset is reduced.

The frequency dependence of the permittivity ε_r (ω) is shown in figure 3.64 as a function of frequency normalized to the value at very low frequencies:

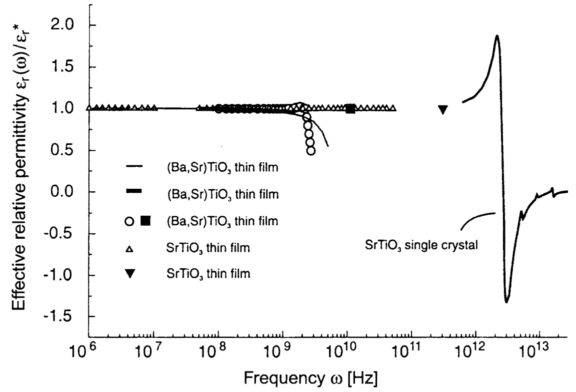


Figure 3.64: Normalized relative permittivity (referred to values at low frequencies) versus frequency. From H. Schroeder and A. Kingon, “High-Permittivity Materials for DRAM’s” In: Nanoelectronics and Information Technology. Waser, Reiner (ed). Wiley-VCH 2003. ISBN 3-527-40363-9, chapter 21:540-563 (reproduced by permission of Wiley VCH, STM-Copyright & licenses).

It can be seen that up to frequencies of more than 1 GHz almost no variation is observed.

The current leakage is strongly dependent on the pretreatment of the layer. Annealing in oxygen at higher temperatures yields the best results. The mechanism is far from being well understood (Banieki et al. 1999).

Integration of High Permittivity Layers in DRAMS

As described before, many of the requirements for an application of BST layers in DRAM’s seem to be fulfilled. Integration aspects of the layers in CMOS technology have not been discussed yet. In comparison with the geometries of figure 3.58 capacitors with high permittivity layers can be

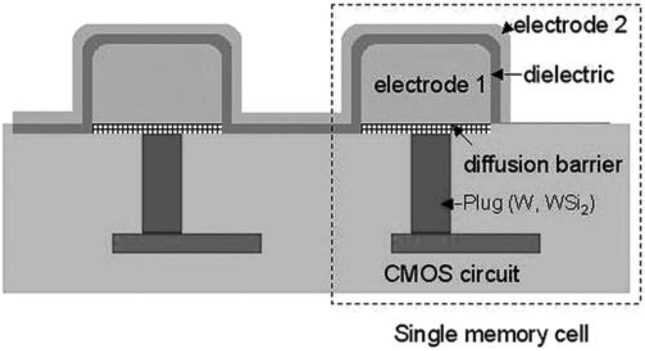


Figure 3.65: Integration of high permittivity capacitors in CMOS circuits (schematically adapted from Schroeder and Kingon 2003).

designed much more simplified with moderate aspect ratios. This is shown schematically in figure 3.65. The CMOS-circuit is only indicated schematically. The capacitor is arranged on top of the Si-chip (COB=Capacitor Over Bit-line). But technically there arise some problems from the materials and the processing of the materials.

- Plug connection to the capacitor: Due to the design the plug connection of the capacitor to source/drain of the cell transistor. The plug material, usually Platinum, should have high electric conductivity, compatible with CMOS processing and form no high resistivity or insulating layers at the interface to the capacitor electrode.
- Diffusion barrier: To avoid formation of brittle silicides with low conductivity between Pt bottom electrode and the Silicone a diffusion barrier has to be deposited. The barrier should display good oxidation resistance and also good electric conductivity to guarantee high conductivity between the plug and the bottom electrode. Up to now no material is known which might be an acceptable compromise.
- Bottom electrode: A series of requirements must be fulfilled by the bottom electrode. The electrode must adhere to the diffusion barrier, maintain a low resistivity to the underlying plug and it must remain conductive after the deposition of the dielectric. Furthermore structuring by reactive dry etching should be possible. Noble metals such as Platinum are favorized because of their chemical inertness which on the other hand aggravates structuring. As an alternative also conducting oxides like RuO_2 are being discussed, mainly because the interface capacity to the high permittivity dielectric is minimized. Another point of interest is the adhesion between the layers. Adhesion can be decreased due to thermal stress by different thermal expansion coefficients and due to the deposition conditions.

- Deposition of the dielectric layer: This process requires uniform deposition of the dielectric on the 3D structure of the bottom electrode (s. figure 3.65). MOCVD (Metallo Organic Chemical Vapor Deposition) is the most suitable technology. The process requires the optimized tuning of all processing parameters e.g. precursor material, evaporation and flow in the reactor vessel, partial pressures of the reactants and temperature. Optimization is also necessary with respect to uniformity of the layer, grain size distribution and orientation of the layer. Typical deposition temperatures for BST are in the range between 850 to 900 K. Somewhat lower deposition temperatures are possible with plasma assisted MOCVD (>720 K). At lower deposition temperatures the dielectric properties of the layer diffusion barrier deteriorate while the oxidation resistance of the conductive diffusion barrier and the uniformity are improved.
- Top electrode: Except the adhesion on the dielectric the requirements are less severe for the top electrode.
- Final processing of the chip: A final step in the CMOS process is annealing in a reducing Ar-4%H_2 forming gas mixture while mixed oxide layers like BST are usually deposited and post annealed under oxygen to minimize oxygen vacancy defects. On the contrary the annealing in forming gas creates oxygen vacancies yielding in an increase of the leakage current (Banieki et al. 1999). As expected after the annealing process in reducing the results for the leakage current are not acceptable. To prevent the deterioration of the dielectric properties an encapsulation of the whole capacitor by a Hydrogen diffusion barrier has been proposed. But this means a complication of the whole manufacturing process with a considerable increase of costs.

To sum up, it can be stated that conventional capacitor integration technologies (trench and multilayer stack) have almost reached their technical limits and thus no further improvement will be possible with reasonable expense. A new technology jump is required which hopefully will be achieved by high permittivity dielectrics. According to the forecast of researchers from Samson (Park and Kim 2001) the incorporation of BST is inevitable for DRAM technology nodes below 70 nm. A timetable for the introduction is not existent yet. More progress and more investigations also on other high permittivity thin layer systems are necessary.

Ferroelectric Layers as Storage Medium in Random Access Memories (FeRAM's)

Essential general demands on non-volatile memories are:

- low power consumption,
- fast write/read times,
- near infinite number of write/read processes,
- non-volatility,
- high storage density.

In chapter 1 it has already been mentioned that especially for some applications storage density is a less relevant requirement so that magnetic storage systems like HDD become disadvantageous due to their high power consumption and sensitivity to shock and vibration. A current trend in chip design is the use of embedded non-volatile memories with the memory integrated on-chip. One product, recently introduced, are smart cards with a size range from 1 to 4 kb (Böttger and Summerfelt 2003).

Principle of Operation

The most simple ferroelectric non-volatile memory cell is a ferroelectric capacitor as is schematically shown in figure 3.66.

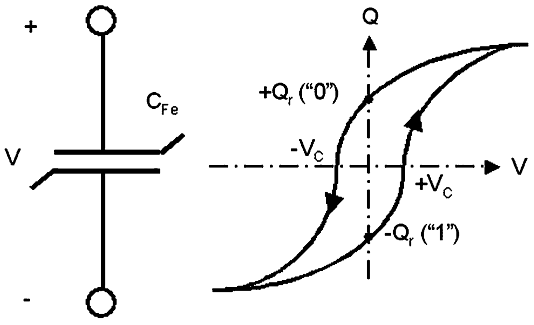


Figure 3.66: Ferroelectric capacitor as memory cell (schematically adapted from Sheikholeslami and Gulak 2000).

The remanent polarization $+Q_r$ and $-Q_r$ at external voltage 0 represent the logical states "0" and "1". Reading and writing the information is achieved by applying voltage pulses. With a voltage pulse in the same direction as the remanent polarisation no charge from the capacitor is transferred (except the small amount due to the difference of saturation polarisation and remanent polarisation). When the voltage pulse is opposite to the direction of polarisation, polarisation direction will change which results in measurable current response. Unfortunately this reading process destroys the information on the capacitor and its no real non-volatile memory. These

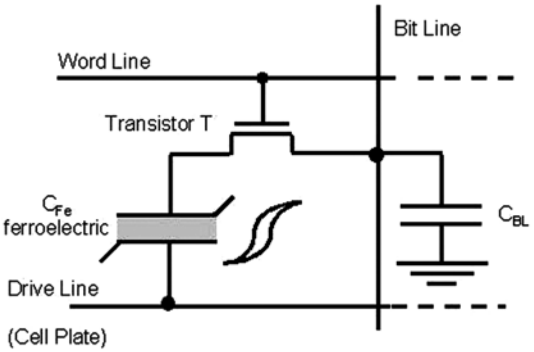


Figure 3.67: Ferroelectric 1-Transistor-1Capacitor memory cell (schematically adapted from Böttger and Summerfelt 2003).

problems can be overcome by using more transistor switched circuits. An example for a 1 Transistor-1 Capacitor (1T-1C) cell is displayed in figure 3.67.

The transistor T is called the access transistor which controls the access to the capacitor. When T is off the bit line is disconnected from the Fe-capacitor and the stored information remains undisturbed. When T is on (switched by the word line) the Fe-capacitor is connected to the bit line and information can be written or read via the plate line. More sophisticated circuits with detailed description of the read/write process are described by Sheikholeslami and Gulak (2000). As in the case of DRAM's we will not go into details of the memory architecture but focus more on the material and processing problems with respect to the ferroelectric capacitor.

Ferroelectric Films for Application in RAMS

Requirements to Ferromagnetic Films in FeRAM's

With two exceptions the requirements to ferroelectric thin films for FeDRAMS's (s. chapter above)

- For storing information by the state of polarisation the films should show a hysteresis. On the other hand coercivity should not be too high so that switching of the polarisation can be achieved with reasonable electrical fields (only low voltages should be necessary). This requires layer deposition with preferred orientation.
- To avoid read failure the switched charge $\Delta Q = A*\Delta P$ (A = capacitor area, ΔP change of polarisation) with reversal of polarisation should exceed 30 fC (Böttger and Summerfelt 2003). Thus with decreasing area polarisation must increase.

Favorite materials for FeRAM application are $Pb(Zr_xTi_{1-x})O_3$ (PZT) and $SrBi_2Ta_2O_9$ (SBT). SBT has a lower coercivity than PZT.

Properties of Ferroelectric Thin Films

- Thickness dependency of coercivity: Dependent on the system under consideration (ferroelectric dielectric, electrodes, pretreatment) the behavior is quite different. For PZT with Pt electrodes a strong increase of coercivity with decreasing thickness has been found (Ren et al. 2001, Larsen et al. 1994, Lin et al. 2001, Cillessen et al. 1997). The effect for SBT with Pt electrodes is somewhat smaller, but still considerable. Only for oxide electrodes (e.g. RuO_2) weak or no dependency was observed. The effect can be explained by low permittivity interlayers adjacent to the metallic electrodes (similar as shown in figure 3.63 for non-ferroelectric high permittivity layers). Zhu et al. (1998) found on film with the composition $0.8SrBi_2Ta_2O_9$-$0.2Bi_3TiNbO_9$ (BST+BTN) that rather the grain size than the film thickness determines the dielectric properties.
- Ferroelectric switching: Switching time depends on many parameters like e.g. domains structure and mobility of domain walls. The lower limit is given by the time for a domain wall to propagate from one electrode to the other. It can be assumed, that propagation occurs with approximately sound velocity c. The time t_0 to cross a layer with thickness t is given by the relation $t_0 = t/c$. For c = 4000 m/s and a thickness t = 200 nm the switching time is about 50 ps. Experimental values have been found near this theoretical limit.

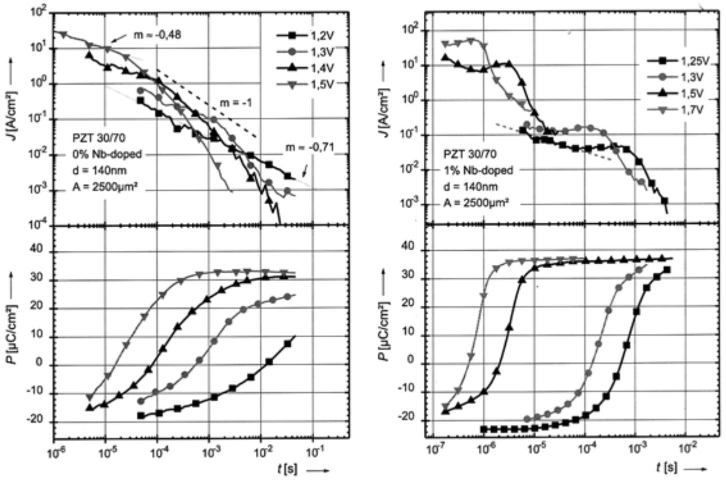


Figure 3.68: Current response on a voltage step above coercivity voltage for undoped and 1% Nb-doped PZT. (Böttger U, Summerfelt SR 2003: "Ferroelectric Random Access Memories." In: *Nanoelectronics and Information Technology.* Waser, Reiner (ed). Wiley-VCH 2003. ISBN 3-527-40363-9. chapter 22:564-589 reproduced by permission of Wiley VCH, STM-Copyright & licenses).

Current response can behave in different ways when a voltage step above the coercivity voltage is applied. Figure 3.68 shows this behavior for undoped (left side) and 1 mol% Nb doped PZT (right side). The upper pictures show the polarisation switching current for various voltages, the lower show the calculated polarisation for different electric fields versus time. The undoped film shows a continuous decrease of current versus time without a maximum. The maximum in the slope which can be recognized for the doped films is characteristic for ferroelectric behaviour with a marked hysteresis.

This behaviour was explained by Lohse (2001). He assumed an ideal ferroelectric capacitor in series with an interlayer capacitor with high dielectric losses represented by a parallel resistor. The equivalent circuit is shown schematically in figure 3.69. Lohse showed that the dielectric interface has an extremely strong influence on the switching behaviour. The delay of polarisation reversal time is determined to a high degree by dielectric dispersion losses in the interlayer at the electrodes.

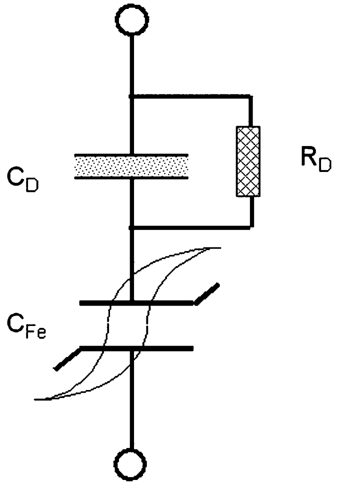


Figure 3.69: Equivalent circuit of a ferroelectric capacitor with dielectric losses (Lohse et al 2001).

An assumed distribution of relaxation times results in a smear of depolarization current versus time as observed in figure 3.68.

- Polarisation fatigue is also very dependent on the layer system which can be seen in figure 3.70. The fatigue behavior for different electrode-layer-systems has been investigated by Wersing (2000). The figure was taken from Boettger and Summerfelt (2003). It shows the decrease of polarisation over the number of cycles (logarithmic scale). It can be seen that the

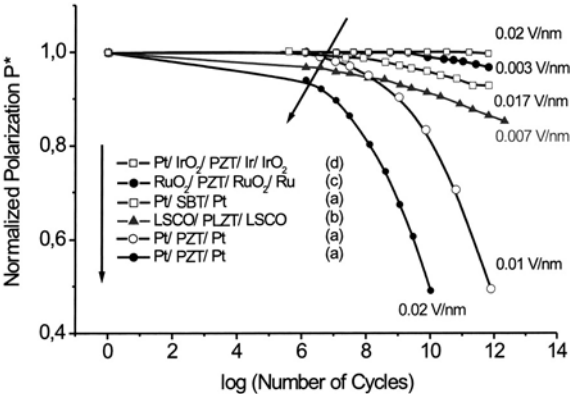


Figure 3.70: Normalized polarization versus number of hysteresis cycles from (Böttger U, Summerfelt SR 2003: "Ferroelectric Random Access Memories." In: *Nanoelectronics and Information Technology.* Waser, Reiner (ed). Wiley-VCH 2003. ISBN 3-527-40363-9. chapter 22:564-589 reproduced by permission of Wiley VCH, STM-Copyright & licenses).

decrease strongly depends on the dielectric / electrode layer system. Polarisation fatigue up to now cannot be explained satisfactorily. According to one model the effect is caused by oxygen vacancies as defect traps in the interface between Pt-electrodes and ferroelectric film (Desu and Yoo 1993). To some degree oxide electrodes are capable to compensate these defects.

The change of the hysteresis by fatigue is displayed in figure 3.71.

- Another effect influencing life time is the observed shift of the ferroelectric hysteresis loop with cycling combined with a continuous decrease of polarisation (figure 3.71). This effect is observed in polycrystalline and

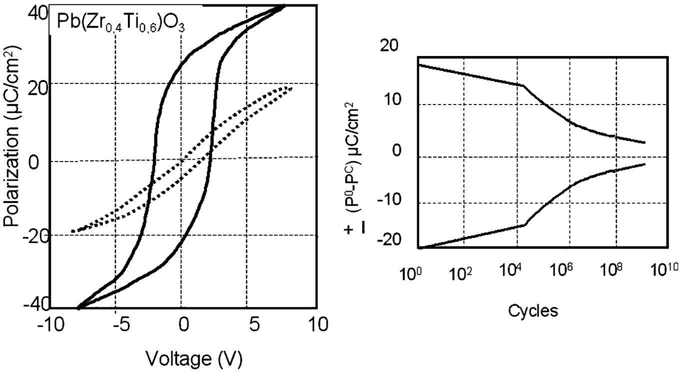


Figure 3.71: Fatigue behavior of polarization (VDI 2003).

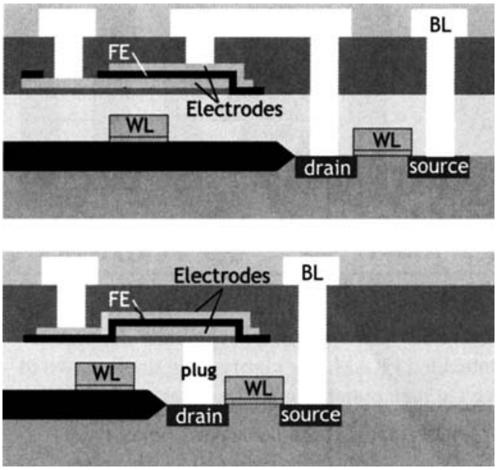


Figure 3.72: Schematic presentation of integration of ferroelectric thin films in different systems of stacked cells. From (Böttger U, Summerfelt SR 2003: "Ferroelectric Random Access Memories." In: *Nanoelectronics and Information Technology.* Waser, Reiner (ed). Wiley-VCH 2003. ISBN 3-527-40363-9. chapter 22:564-589 reproduced by permission of Wiley VCH, STM-Copyright & licenses).

single crystalline bulk material as well as in ferroelectric thin films. Several models have been proposed to understand the effect (Lohkämper et al. 1990, Robels et al. 1995, Grossmann 2001).

Integration of Ferroelectric Thin Films

The integration aspects for ferroelectric layers in RAMS are in some respects similar as the integration of non ferroelectric high permittivity layers (s. section 2.3). The problems concerning plug connection, diffusion barrier, bottom electrode, deposition of the ferroelectric layer and back end processing are rather the same. Figure 3.72 shows schematically two examples for non-volatile 1T-1C-memory cells. As can be seen, that the mentioned problems are very similar Therefore this topic will not be discussed here any further.

Conclusion and Outlook

Key features for future application of ferroelectric layers in non volatile RAM's will be a further decrease of cell size and a lower operation voltage. For dimensions below about 100 nm folded 3D structures will become necessary which will complicate the design. Further improvements with respect to life time are necessary.

First applications of FeRAM's have been presented in smart cards with storage capacities up to 4 kb. Functional structures with cell dimension < 100 nm have been reported (VDI 2003). For further applications e.g. in mobile phones, public transportation and travelling, electronic banking, PDA's and Palm PC's further improvement of layer properties and processing is required. The design of 3-dimensional circuits with smaller lateral capacitor dimensions will be a special challenge.

It should be noted that the FeRAM's are competing with other technologies. FeRAM-technology, however, has a good chance to become the ultimate memory technology.

A1: Molecule Based Memory and Negative Differential Resistance (NDR) Devices

To write and read the state of a memory both by electric/electronic means is of particular interest, as it would allow for straightforward integration of the memory cell in the existing electronic based information technology. However, to perform both, the writing and the reading via the same physical parameter requires hysteretic behaviour of the physical property changed by the stimulus to enable a read out without messing up the memory state. Different concepts have been presented for bistable memory cells performing hysteretic switching between both states.

Ferroelectric materials consisting of ion lattices with two well-defined lattice positions for a particular kind of ions are one example. An applied electric field arranges all ions on one preferred of both positions. The resulted asymmetric distribution of the ions is subsequently observed by a tunnel current at a lower potential, not allowing for switching of the ion's position. However, these properties are not limited to nanoscale units and have already been observed in several devices of micro- to actually millimetre sizes. The motivation for miniaturization is solely the reduction of the required potentials to switch between both states. Hence these ferroelectric memory cells would not obey our definition of Nanotechnology.

Another concept for hysteretic switches is based on the relative arrangement of two molecules that are mechanically linked with each other. Particular examples of such supramolecular arrangements (supermolecules) are two interlocked rings resembling two segments of a chain (catenane) or a ring annealed on an axis (rotaxane). Often, the synthesis of such mechanically linked molecular components profits from intermolecular interactions that range from rather weak donor-acceptor stacking or hydrogen bonding to strong covalent or coordination bonds that are subsequently broken by chemical means. These intermolecular interactions may also be triggered after the supermolecule is formed. Of particular interest are such supermolecules when two different conformations of both molecular components relative to each other can be triggered by external stimuli like e.g. light, applied electronic potential or mechanical pressure. However, for a straightforward integration in existing microelectronic technology, to address two different states electronically is most promising.

For that purpose, catenanes and rotaxanes have been functionalised with electrochemically active subunits whose redox state can be addressed individually in the group of Fraser Stoddart (Asakawa et al. 1998, Pease et al. 2001, Luo et al. 2003). The appropriate charging of subunits allows switching the supermolecule between two different conformations that are both also stable in the supermolecule's neutral state. These redox-switching processes have been investigated thoroughly in solution with several spectroscopic methods and their conformational changes have been proofed without doubt (Asakawa et al. 1998, Pease et al. 2001).

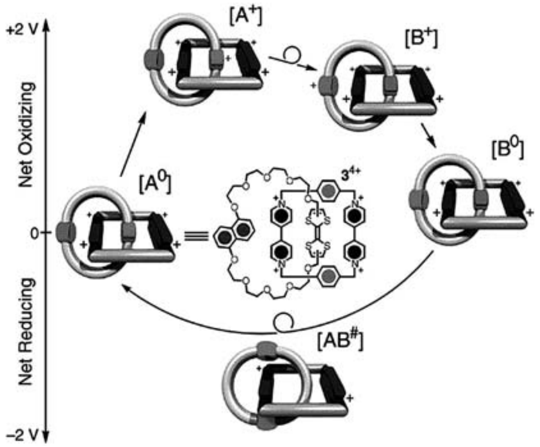


Figure 3.73: Proposed mechanochemical mechanism for the switching between both conformations of a catenane consisting of two interlocked rings with appropriate redox active subunits (Pease et al. 2001).

However, to profit from the switching on a molecular level the supermolecules have to be integrated in a solid-state device. A multilayer architecture has been suggested, developed and investigated by a cooperation of the groups of Fraser Stoddart, James Heath and Stanley Williams. They have reported from both catenanes (Collier et al. 2000) and rotaxanes (Luo et al. 2003) sandwiched between either two metal electrodes or one metal and one doped semiconductor electrode. When triggered by corresponding voltage pulses, these devices displayed reversible and reproducible switching properties witch have been assigned to the rearrangement of the sandwiched supermolecule. However, control experiments with long chain carboxylic acids between two platinum electrodes displayed comparable switching properties, even though they are neither mechanically interlocked molecules nor bear electrochemically active subunits. As these experiments are performed at higher voltages than the investigations with a semiconductor bottom electrode, it may be that there is another switching mechanism involved. However, these control experiments show that the nature of the switching mechanism in the solid state is not fully understood and that further investigations are required. Recent publications of the Stoddart/Heath groups are geared in that direction. They investigate supermolecules in mechanically controlled platinum break junctions (Yu et al. 2003) or between crossed carbon nanotubes as electrodes (Diehl 2003).

It is worth mentioning that the principle of these switches is not limited to supermolecules. A molecular compound with two different conformations leading to two different transport states would result in comparable properties. The crucial requirement however is a high enough energy barrier for the switching between the two states to allow for a hysteretic current/voltage characteristic of the resulting device.

Reed and Tour have reported another interesting concept (Chen et al. 1999). In a lateral limited silicium nitride pore with a diameter of about 30 nm a gold film of a molecular rod has been immobilized between two gold electrodes. These devices display at low temperature a so-called NDR-effect (negative differential resistance), an increase of the current with increasing voltage until a certain threshold where suddenly the current breaks down. The effect as such is very promising as it allows already for the construction of first logic circuits. However, the nature of the effect is not fully understood yet and the topic of current debate.

A1: Chemical Atomic Force Microscopy (AFM) (also A4/D4)

Introduction

Atomic Force microscopy has become one of the most important tools for investigations of nanostructured surfaces and nanoparticles, due to its relatively easy operation and comparably low costs of acquisition. Nanoscience and Nanotechnology would never have reached the present state of the art without the availability of AFM. Apart from this unrenouncable application for the characterization of nanoarchitectures, AFM is going to develop to a novel tool for doing chemistry on the nanosize scale.

The following 2 chapters will deal with novel techniques that might be suited to overcome fundamental difficulties in structurization of surfaces in such a way that they alternatively can be used for the positioning of nanoparticles of various natures for future storage systems. The first one uses the AFM tip as a pen to write structures on appropriate surfaces using molecules as an "ink", called dip-pen nanolithography. The second one takes advantage of metallized tips to emit electrical pulses to chemically create functions on molecular monolayers for successive usage.

Dip-Pen Nanolithography (DPN)

Dip-pen nanolithography is inevitably linked with the name C. A. Mirkin (Piner and Mirkin 1999, Hong et al. 1999, Demers and Mirkin 2001, Demers et al. 2001). This method uses the water meniscus between an AFM tip and a surface that is unavoidably formed under usual laboratory conditions by atmospheric humidity, as sketched in figure 3.74.

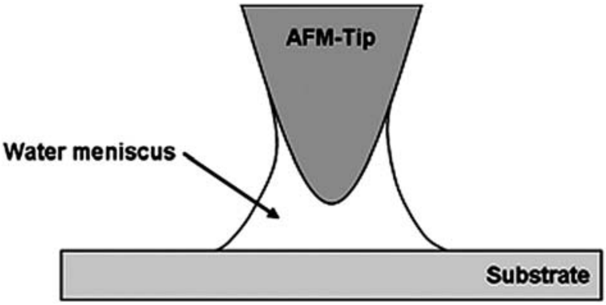


Figure 3.74: Sketch of an AFM tip with water meniscus.

If the tip has been loaded with appropriate water-soluble molecules by simple dipping it into a solution of those molecules with successive drying, the molecules are transported by the water meniscus to a flat surface over which the tip is scanning. An important condition is the chemical attraction of the molecules by the surface. An ideal molecule-surface combination is that of thiols with gold, since S-Au bonds are known to be strong and spontaneously formed if SH functions contact gold atoms. A software conducted tip thus decorates the surface with molecules at distinct positions. The extension of an individual point or line depends on the tip`s geometry and the herewith linked water meniscus. Figure 3.75 illustrates the technique how to deposit nanospheres on a pattern of molecules generated afore.

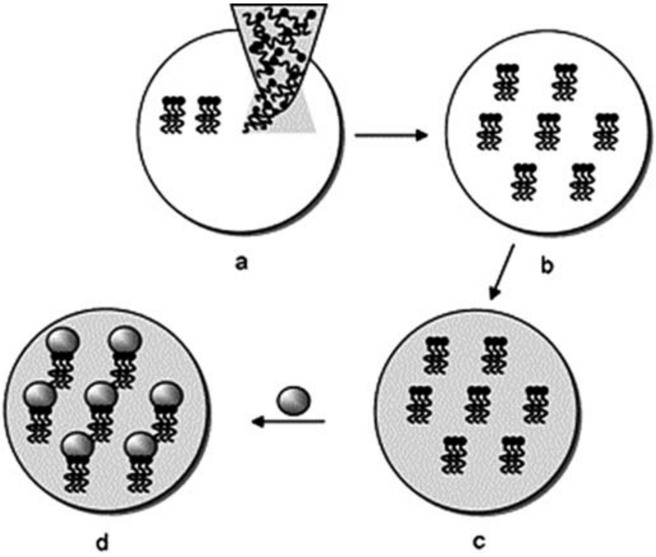


Figure 3.75: Illustration of transport of thiol molecules from the AFM tip to a surface via water meniscus and decoration with nanoparticles.

Thiol molecules, for instance 16-thiohexadecanoic acid, are used to draw the pattern on an atomically flat gold surface (a, b). Thus, the top carboxylic groups can be used to interact with suited nanoparticles or could be further chemically treated to generate other than COOH functions. Before that, it is appropriate to passivate the unpatterned regions by alkylthiols in order to avoid particles depositions in between the functionalized dots (c). To interact nanoparticles with the carboxylic groups (d), they have to be functionalized with basic ligand molecules. Although not yet realized in all cases, it can be assumed that quantum dots of metallic or semiconducting nature can be used to be deposited on top of functionalized positions.

An interesting version of DPN has also been described by the Mirkin group. It is illustrated in figure 3.76.

After patterning a gold surface with 16-thiohexadecanoic acid molecules and passivation with 1-octadecanethiol, alkylamine-modified oligonucleotides, e. g. TCTCAACTCGTAA$_{10}$ (a), has been chemically fixed to the

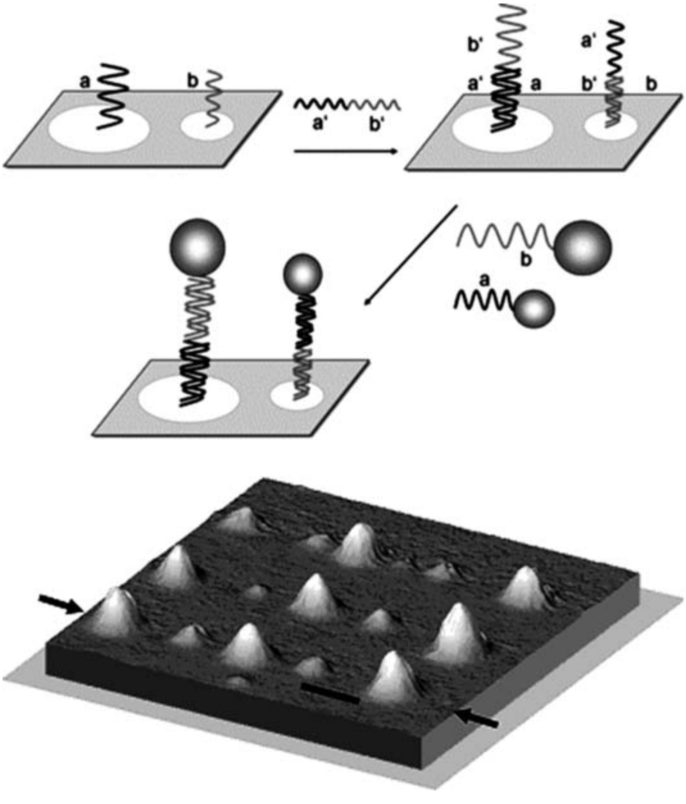


Figure 3.76: Illustration of complementary oligonucleotides linked with different gold nanoparticles and AFM image of an as-prepared surface. With permission from Wiley-VCH, Weinheim.

COOH groups. DPN then allows a tricky next step: a 16-hexadecanoic acid loaded tip can replace 1-octadecanethiol molecules at elected positions and so to create a second orthogonal structure to the first one. An alkylamine modified A_{10}CGCATTCAGGAT (b) nucleotide is then combined with the second series of COOH functions. The a, b decorated surface is then treated with the oligonucleotide a′b′ = TACGAGTTGAGAATCCTGAATGCG with a′ and b′ complementary to a and b. Gold nanoparticles, if wanted of different size, can then be coordinated using a- and b- substituted nanoparticles. Finally, the procedure ends up with a pattern as shown in figure 2-3b. Of course, instead of using gold nanoparticles of two different sizes, two different kinds of metal or any other suited nanoparticles could in principle be involved.

Nanoelectrical Use of AFM

The AFM tip has meanwhile developed to a multifunctional tool. Therefore metallized and thus conducting tips have been used to change the end groups of self-assembled monolayers chemically. Sagiv et al. (Maoz et al. 1999, 2000, Liu et al. 2002) developed a technique to transform CH_3 groups into COOH functions by emitting electrical pulses from the tip to the methyl groups of a C_{18} alkyl monolayer using atmospheric oxygen and water as reactants. Herewith he installed a novel method to inscribe chemical information into appropriate surfaces. The COOH groups could either be used itself for further applications or can chemically be transferred into other functions. Figure 3.77 explains the process how COOH functions have been modified to SH functions that offer ideal conditions to bind gold nanoparticles.

Starting with a self-assembled monolayer, the generation considered as routine nowadays, the CH_3 end groups are oxidized to COOH at predetermined positions. Functionalization of only the carboxylic groups with

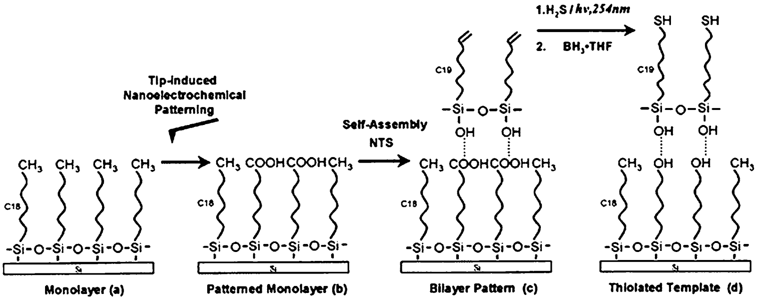


Figure 3.77: Formation of thiol-functionalized patterns by tip-induced nanoelectrochemical treatment of a methyl-terminated monolayer. With permission from The American Chemical Society, Washington DC.

alkene terminated silanes, followed by a photochemical radical addition of H_2S to the C=C double bonds. Successive treatment with $BH_3{\cdot}THF$ aims at the reduction of S-S bonds formed during the hydrosulfurization of the C=C double bond. Finally, a thiol terminated pattern of any kind of structure is available.

With respect to the generation of storage systems, the use of 1.4 nm Au_{55} clusters which have been found to act as single electron switches at room temperature is suggesting itself. Figure 3.78 shows a pattern of parallel wires of Au_{55} clusters that have been introduced in a ligand stabilized form as $Au_{55}[(C_6H_5)_2PC_6H_4SO_3Na]Cl_6$. The part of phosphine ligand molecules will be substituted by the thiol groups.

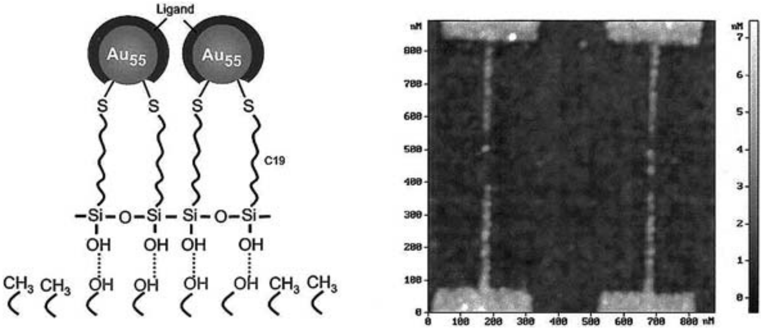


Figure 3.78: Sketch of cluster decorated thiol terminated positions and AFM image of strictly one-dimensional cluster wires, artificially interrupted by positioning of 1 and 2 individual quantum dots. With permission from The American Chemical Society, Washington DC.

Figure 3.79 shows an AFM image of an array of 16 dots, fabricated by the same principle.

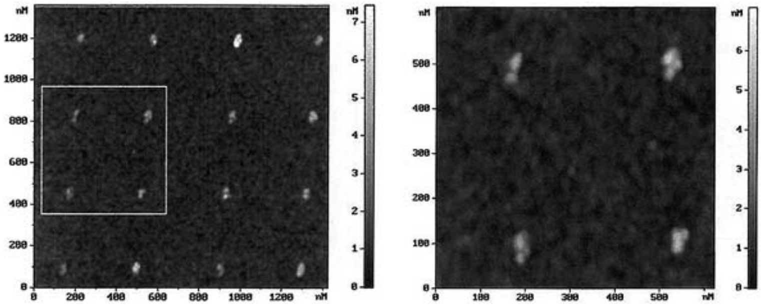


Figure 3.79: AFM image of an array of 16 Au_{55} quantum dots. With permission from The American Chemical Society, Washington DC.

Summarizing the results described in this chapter it can be stated that the use of AFM tips for the generation of artificial patterns of nanoparticles is very promising with respect to future storage systems. Dip pen nanolithography as well as the nanoscale chemistry using electric pulses from a conductive AFM tip open the door to alternate storage systems. Of course, they are still quite far from practical application, however, they indicate remarkable chances, if fundamental research is intensively continued in the near future!

A2: Semiconductor-Spintronics

(s. A1)

A3: Electrochromism

Electrochromism is a reversible colour change of a material caused by the application of an electrical current or potential (Kalyanasundaram and Graetzel 1998, Gerfin et al. 1997). The large interest for electrochromic systems evolves from their broad application potential including windows for the modulation of incoming light or displays, a field in which competition with LCD is possible. Of particular interest are bistable systems, which means, that once the colour has been switched, the state of the device remains even if in absence of applied voltage. Currently, such systems are based on electrodes made of conducting glass coated with an organic or inorganic polymer which colour is different in the reduced and in the oxidized state. Preferably, the two materials must display complementary electrochromism: the colour change that occurs by oxidation on the first electrode must be the same that occurs by reduction on the second electrode. This type of assembly is used for instance in elctrochromic windows. However, these systems suffer from intrinsic limitations like the slowness of the colour change due to the low migration rate of the counterions in the bulk polymer or the difficulties to obtain strong and bright colours. Electrochromic systems in solution are not limited by these problems. However, they have the strong drawback that an electrical current is needed to maintain the coloured state, because the two types of coloured molecules diffuse through the system and react with each other to restore the bleached states. Therefore, it cannot be used for large area devices or for battery-powered displays.

Nanotechnology may allow combining the advantages of both systems, the bistability of the polymer-type electrochromism and rapidity and efficiency of the molecular electrochromism. Therefore glass electrodes are covered with semiconductor nanoparticles which are subsequently functionalized with molecular layers of the electrochromic molecules. Such architectures enable the fast switching of the molecules as they are immobilized on the electrode on one hand and the bistability of the system as recombination of the immobilized charged species on different electrodes is impossible. In these set-ups, the main task of the nanoparticles is to increase the electrodes surface to enlarge the number of coloured molecules.

Liquid crystalline systems profit from the ability of liquid crystals to align along an electrical field. Between two sheets of polarizing materials, liquid crystals act as optical shutter that allow light to pass or not depending on the applied electrical field. The action resulting in the change of the materials properties is of molecular nature and hence clearly on the nanometre scale. However, to the best of our knowledge, there are currently neither applications or investigations nor postulated advantages to reduce the size of these systems to Nanotechnology.

A4: Molecular Actuators

Rotaxanes are supramolecular arrangements consisting of two mechanically linked molecules: a molecular axis with two terminal stoppers and an annealed macrocycle as ring on the axis. The interactions between both molecular building blocks of a rotaxane are dominated by intermolecular forces ranging from rather weak like e.g. electrostatic interactions or hydrogen bonds to stronger forces like coordination bonds. If the building blocks of a rotaxane are appropriately functionalized, these interactions can be triggered by electrochemical means. For example, the electrochemical charging of subunits on the building blocks is leading to electrostatic interactions that may alter the position of the ring relative to the axis. Thereby, mechanical motion on the molecular level evolves from an electric trigger. Typical examples are the rotaxanes and catenanes synthesized by Fraser Stoddart et al. (Pease 2001).

A particularly beautiful example is a molecular actuator described by Jean-Pierre Sauvage et al. (Collin et al. 2001). In a designed molecule the rotaxane's ring and axis are covalently linked to each other. For sterical reasons the axis and the ring are unable to react with each other in an intramolecular reaction and hence, two molecules are reacting with each other to dimmers because the axis of one molecule is satisfying the needs of the ring of the other one and vice versa. In this particular example, the ring is functionalized by a phenantrolin unit while the axis is functionalized with a phenantrolin unit and a terpyridine unit. These subunits are well known for their complexation properties with metal ions. As the complexation properties of particular ions depends on their redox state, the preference of the ions redox state for a particular combination of complexation partners from the subunits is used to switch between two different conformations electrochemically. In the particular example, Cu(I) prefers four complexation partners and it forms a complex with the four nitrogen atoms from both phenantroline units from the ring and from the axis. After oxidation, Cu(II) prefers five binding partners and hence the molecules rearrange so that the complexes between both nitrogen atoms of the ring-phenantroline and the three nitrogen atoms of the terpyridine subunit on the axis becomes possible. Both conformations drastically differ in the distance between the endstoppers of the axis and hence, the system acts as molecular actuator – an artificial muscle that tears together by an electrochemical stimulus.

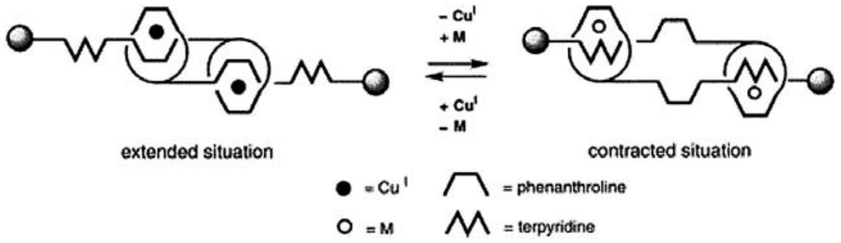


Figure 3.80: Functioning principle of the molecular muscle. The two-component rotaxane dimer contains identical ring-and-string conjugates. Both different coordination sites on the string allow a particular ion to select the complementary coordination partner to the fixed coordination site on the ring to satisfy its coordination geometry (Collin et al. 2001).

A4: Chemical Atomic Force Microscopy (AFM)

(s. A1)

3.2.2 Stimulus: Magnetic

B1: Magnetic Random Access Memory (MRAM)

(s. A1)

B1: Magneto Resistance (MR)

(s. GMR, table 1)

B2: Semiconductor-Spintronics

(s. A1)

B3: Scanning Near-Field Magneto-Optical Microscopy (SNMOM)

Scanning near-field magneto-optical microscopy (SNMOM) uses magneto-optical effects in a scanning near-field optical microscope (SNOM). By applying the Kerr or the Faraday effect, one obtains quantitative information on the magnetization vector field at the surface of a sample in the very same way as in classical magneto-optical microscopy, but here with sub-wavelength resolution (Betzig et al. 1992, Hartmann 2005). Like in other magneto-optical techniques SNMOM also offers the advantage of very good temporal resolution enabling direct access to the dynamics of magnetization reversal processes.

Figure 3.81 shows that one feeds polarized light into the SNOM fiber and detects the reflected or transmitted light with polarization analysis (Wiesendanger 1998). One also recognizes the usual SNOM beam deflection setup detecting the tip lateral oscillation amplitude and frequency used for dis-

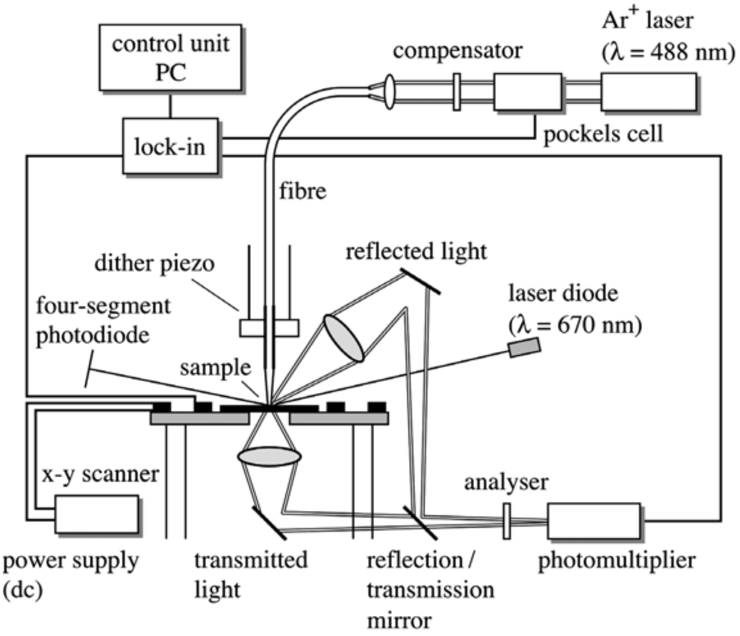


Figure 3.81: Setup of a scanning near-field optical microscope for magnetic imaging.

tance regulation (670 nm laser diode and four quadrant detector). The setup shown here has no external magnetic field and therefore reveals the samples remanent state. As can be seen in the following figure, the resolution is clearly below 100 nm.

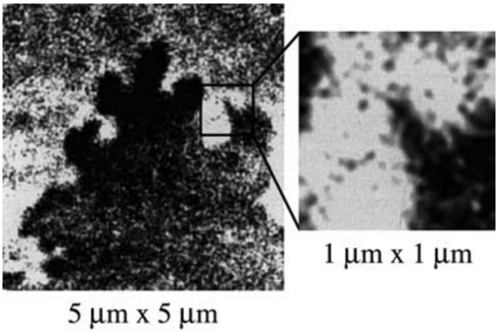


Figure 3.82: Faraday near-field image of a CoPt multilayer, field of view 5 µm. The right-hand image shows a close up of the left-hand image giving an idea of the lateral resolution.

B4: Magnetic Force Microscopy (MFM)

Magnetic force microscopy is performed with an instrument very similar to the atomic force microscope (AFM). One uses tips coated with ferromagnetic material mounted to soft AFM cantilevers with spring constants of 0.01–0.1 N/m. The information obtained is the stray field at a distance of about 30 nm above the sample surface and with a lateral resolution down to 10 nm. The magnetic forces are with typically 30 pN two orders of magnitude smaller than the forces detected in conventional AFM (Abelmann et al. 2005). Therefore MFM generally requires dedicated instruments which are, however, commercially available.

The magnetic forces are detected either in static mode by measuring the cantilever deflection, or in dynamic mode by measuring the frequency shift of a forced cantilever oscillation. In both cases the tip is scanned at constant average distance above the surface. The ideal distance is given by the compromise between lateral resolution and the influence of forces other than magnetic; both do increase upon approaching the surface. The influence of non-magnetic forces caused, e.g., by surface roughness, is reduced by keeping the tip-sample distance constant. This allows obtaining topography-free stray field images. In the simplest case distance control is being done with non-contact AFM using the same detector than the one measuring the magnetic forces (beam deflection, interferometry, or piezoresistivity of the cantilever). More sophisticated approaches have a dedicated detector optimized for tip-sample distance measurement. The signal can be derived from the capacitance between cantilever or tip and sample, the field emission current between tip and sample, or finally, for smallest distances the tunneling current, which might be employed in the future. Distance control can either be done in an image by image, line by line or even pixel by pixel way. In the line

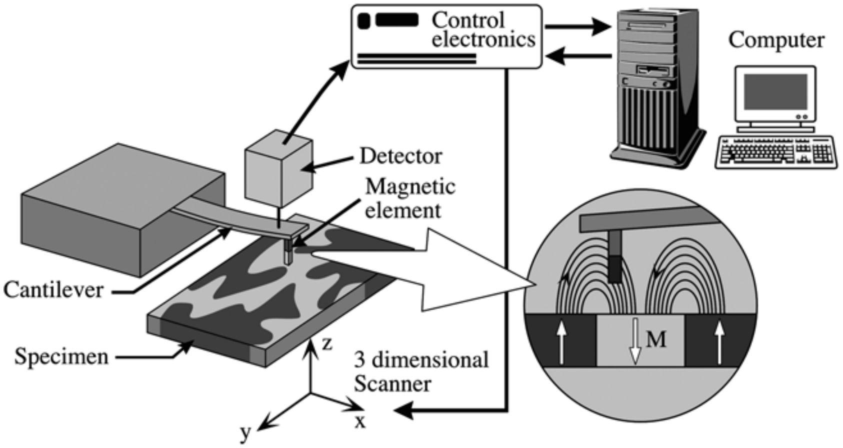


Figure 3.83: Principle of magnetic force microscopy.

by line way for instance the tip is scanned across the sample in order to record the topographic profile and then it is scanned a second time following this profile at the desired distance to record the MFM image. Typical image sizes are 1 to 200 μm a side with acquisition times of 5 – 30 minutes. The stray field of the tip may influence the magnetization of the sample therefore limiting the method to magnetically hard specimens.

MFMs operate best in vacuum ($p < 0.1\,\text{Pa}$) since this improves the quality factor of the cantilever by orders of magnitude, removes noise due to molecules impinging onto it, eliminates the formation of water capillaries between tip and sample (Stifter et al. 2000), and finally reduces sample and tip contamination. MFMs may equally be operated in air, where they are typically in sound proved cupboards equipped with wire mesh to provide a Faraday cage protecting against electromagnetical noise. In addition, the instruments are isolated from building vibrations and from temperature variations.

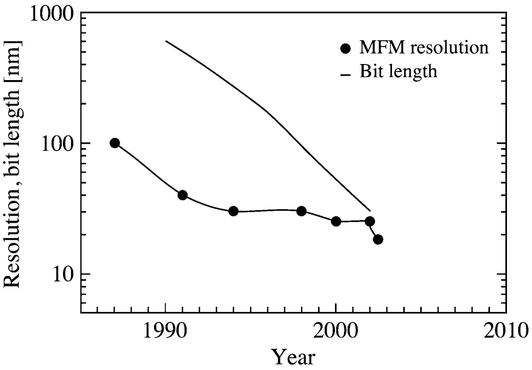


Figure 3.84: Evolution of bit length (along the track direction) on a magnetic computer hard disk compared to the MFM resolution.

The applications of MFM are situated in the development and control of magnetic and magneto-optical recording media (Porthun et al. 1998), where MFM complements scanning electron microscopy with spin analysis (SEMPA). The resolution of MFM is going to be challenged by the rapid decrease of bit sizes, see the two slopes in figure 3.84. Ideally, one would like to resolve individual magnetic grains comprising a bit, which are of the order of 4 nm in diameter. MFM may equally well be used in the development of the magnetic electrodes used in magnetic random access memories (MRAMs). In fundamental research, MFM is employed to study ordered layers of magnetic colloid particles, magnetic domains in ultrathin films (Moser et al. 1995), and magnetic properties of nanostructures at single crystal surfaces (Demand et al. 2002).

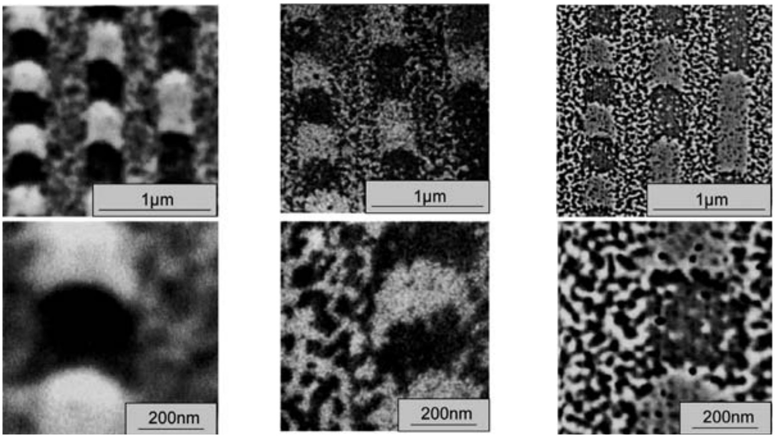


Figure 3.85: Comparison of resolution between today's standard commercial MFM (Digital Instruments 3000 at Hitachi Global Storage Technology, San Jose, USA), SEMPA (Hitachi CRL, T. Kohashi), and latest commercial MFM developments (SwissProbe). The sample is a test pattern written into a state-of-the art magnetic hard disk material. Kindly from H. Hug.

B4: Magnetic Resonance Force Microscopy (MRFM)

Magnetic resonance force microscopy (MRFM) is a combination of atomic force microscopy with magnetic resonance, such as electron spin resonance (ESR), and nuclear magnetic resonance (NMR). We also discuss ferro-magnetic resonance (FMR) of a small sample volume, equally using AFM-related detection schemes.

ESR and NMR are powerful methods for molecular structure analysis. A break through has been achieved recently in detecting the precession of a single electron spin (Rugar et al. 2004). It is anticipated that this technique will eventually also enable detection of magnetic resonance of single nuclei and thus enable structural analysis for example of a single biomolecule. Particularly interesting are membrane proteins, which do not form 3D crystals required for diffraction techniques. In the context of storage these techniques will enable to investigate single molecule magnets and individual magnetic nanoparticles.

Figure 3.86 explains the principle of ESR–AFM. The electron spin precesses with the Larmor frequency given by the magnetic field and the gyromagnetic ratio. In the experimental setup, the field is a superposition of the homogeneous background field B_0 and the inhomogeneous field produced by the magnetic tip. The tip field has spherical symmetry and decays with distance creating a bowl-shaped slice as constant field region in space. Electrons in this slice are resonant with the external high frequency field produced by the coil. As the cantilever carrying the tip vibrates, the slice swings

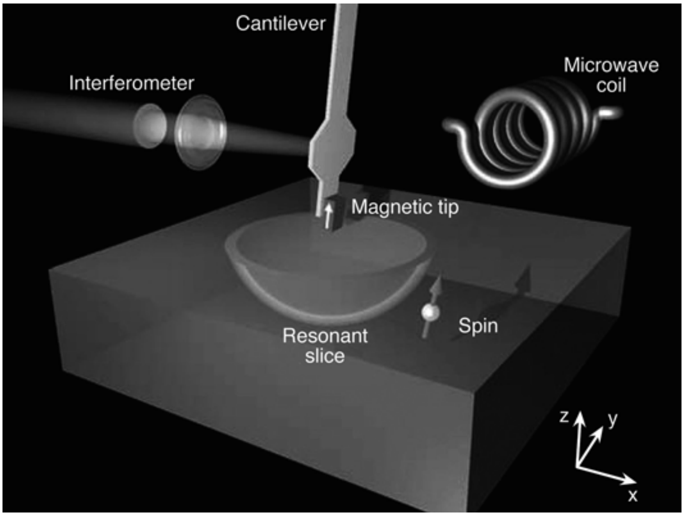


Figure 3.86: The principle of magnetic resonance force microscopy here applied to an unpaired electron spin in SiO_2.

back and forth through the sample causing adiabatic inversion of the spin. This leads to a detectible shift in cantilever frequency due to the force exerted by the spin on the tip. We note that detection of these signals is far from trivial which can be rationalized by following the improvements from the first references (Rugar et al. 1992, Wago et al. 1997) to reaching single spin sensitivity (Rugar et al. 2004). The advantage of the technique: It allows detecting spins located until 100 nm below the sample surface. We note that one is still far from reaching NMR sensitivity, requiring a 10^3 improvement of magnetic moment sensitivity, however, seen the 10^7 increase achieved by the group of D. Rugar from 1992 until 2004 it is not out of reach. A second issue where future research will have to focus, is to detect single spins in cases when put close to each other.

While the experiments discussed above require ideal conditions, such as low temperature, high vacuum, and special cantilevers, mechanical detection of ferromagnetic resonance in small sample volumes displayed in figure 3.87 works also under ambient conditions and with standard cantilevers. In both possible operation modes one applies, in addition to the background field B_0, an additional rf magnetic excitation creating an adjustable precession of the spins around the B-axis (Hartmann 2005).

In the present context we also mention attempts of ESR with an STM. The work realized so far largely goes back to Y. Manassen, who detected peaks in the tunnel current at frequencies corresponding to the Larmor frequency of the electrons (Manassen et al. 1989, 1993, 2000; Balatsky et al. 2002). Durkan et al. (2002) have reported the first reproduction of such

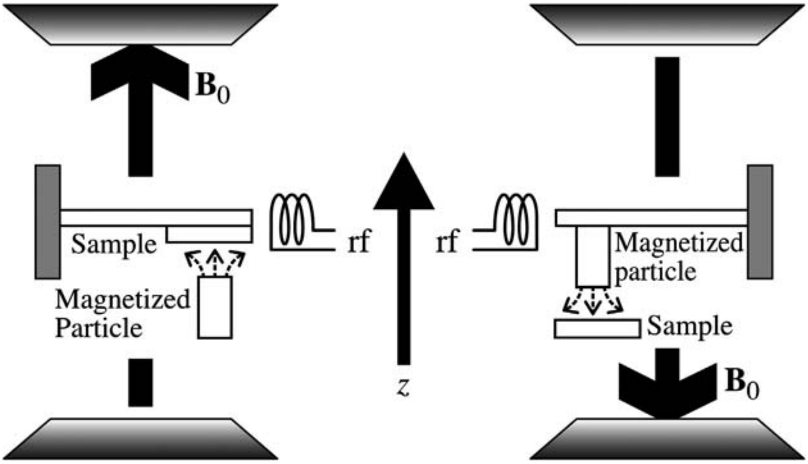


Figure 3.87: Sample on cantilever and magnet on cantilever configurations of the mechanical detection of ferromagnetic resonance.

peaks, and in particular the linear shift of the peak position with applied magnetic field (Durkan et al. 2002). Although this technique being very promising, there are issues that have to be clarified before it can be considered as established. These are the theoretical interpretation of the signal but also the variation of the frequency with tip-sample distance which is not expected.

The described research efforts are worthwhile to be pursued since nanometer scale magnetic resonance is expected to revolutionize chemical, physical, and biological research.

3.2.3 Stimulus: Optical

C1: Molecular Switches

The integration of molecular systems in electronic circuits is a topic of great current interest – often referred to as "Molecular Electronics". The amazing development is that the nanoscale analysis tools like scanning probe methods or advanced lithographic techniques resulted in a revival of the visionary concept of the 1960s as the investigation of small molecular junctions became feasible for the first time. Current activities in the field are rather exploring the potential of components based on molecules in electronic circuits than already designing devices. Photoreactions in molecules have been known for more than a century and to profit from photoreactions to change the electric transparency of a molecular system is not surprising. The use of mechanically interlocked supramolecular systems like rotaxanes and catenanes has already been discussed. A particularly beautiful molecular photoswitch has been developed by Irie and coworkers (2000). The switch has been investigated in solution extensively integrated in many systems and is displayed in figure 3.88 below.

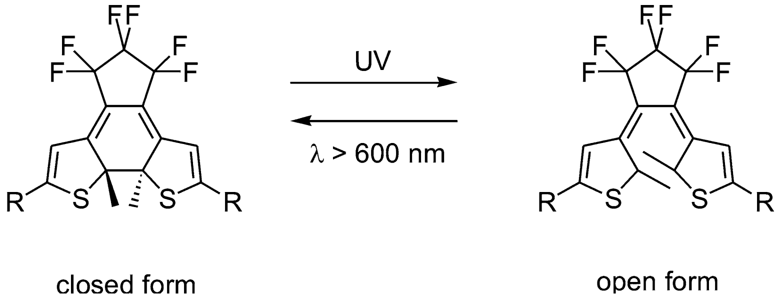


Figure 3.88: Light of appropriate wavelength enables the switching from the closed form to the open form and back in the displayed molecular system developed by Irie (2000).

Two appropriately functionalized thiophene units are covalently linked with each other via a hexafluorocyclobutane bridge. A photoreaction allows to form or to break an additional covalent link between both thiophene respectively depending on the used wavelength. Only with the additional covalent bond the π-systems of both thiophenes are parallelly leading to an increased transparency for electric currents. Integrated between two electrodes, the system is an optically triggered electric switch that can be considered as memory device as well. As subunit for particular experimentally designed molecules, the switch has already been integrated as a monomolecular film between a flat gold surface and a mercury top electrode or even on a single molecule level between both electrodes of a mechanically controlled break junctions.

Numerous other bistable molecular systems can be triggered by an external stimulus between two different conformations. Examples have recently been collected by Feringa (2001).

Another particular interesting chemical photoreaction is the conformational change of azobenzenes and stilbenes. Upon irradiation with appropriate light, they switch along the central double bond between a rod like trans- and a bent cis-configuration. This conformational change has not only already been investigated to build up mechanical pull, it also enables to vary the distance of a molecule or a molecular film from an electrode and hence it's tunnelling currents. While single molecule investigations by AFM (Hugel et al. 2002) and STM techniques have already been reported, molecular films are currently studied.

C2: Spin-Crossover Processes (also D2/E2)

Transition metal complexes either exist in the high-spin (HS) or in the low-spin (LS) configuration. The high-spin state is characterized by a maximum of unpaired electrons in the d-orbitals, whereas the low-spin case exhibits a maximum of spin-paired electrons, i. e. the total spin S is 0 for an even number of electrons and ½ for an odd number of electrons. The decision whether HS or LS will take place mainly depends on the chemical nature of the ligands in the complex. Weak ligands cause a small ligand field splitting so that single electrons occupy all d-orbitals before spin pairing happens. In case of strong ligands electrons first occupy the lower lying orbitals, if necessary as electron pairs, before higher states begin to become occupied. Figure 3.89 illustrates the two situations for an octahedral d^6 system, for instance a Fe(II) complex (Gütlich et al. 2000).

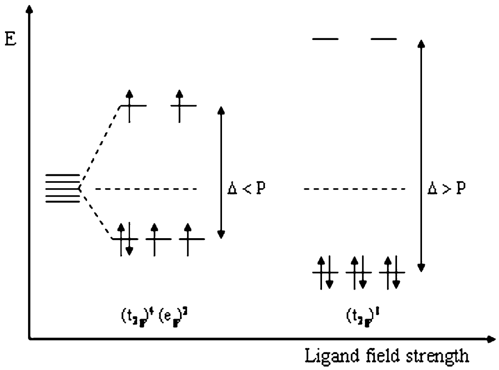


Figure 3.89: High-Spin/Low-Spin situations for an octahedral d^6 complex.

The HS/LS alternative in octahedral complexes is only possible for d^n configurations with $4 \leq n \geq 7$, since in case of 3 or less electrons the degenerated t_{2g} orbitals are singly occupied in any case, whereas in case of 8 d-electrons the e_g levels are also first singly occupied, followed by a first (d^9) and a second (d^{10}) pair of electrons, independent of the ligand field splitting. Most of the known ligands in complex chemistry differ sufficiently from each other for unambiguously generating either HS or LS complexes. However, some $3d^n$ complexes exhibit cooperative transitions between HS and LS state. Such molecular bistabilities are of greatest interest, since they can be used for information storage or signal processing, especially if the transition is abrupt. An ideal complex should be sensitive for an external perturbation P and should spontanously switch from the ground state into the excited state if appropriately disturbed. The value of P to switch from the ground state to an excited state is P_c. Of course, the transition between both states must be detectable; i. e. a response function R must be measurable for any value of the corresponding perturbation. The abruptness of the transition can be defined as R = *f*(P). Perturbations can consist of temperature, pressure or light. The situation is illustrated in figure 3.90 (Gütlich et al. 2000, Zarembowitch and Kahn 1991).

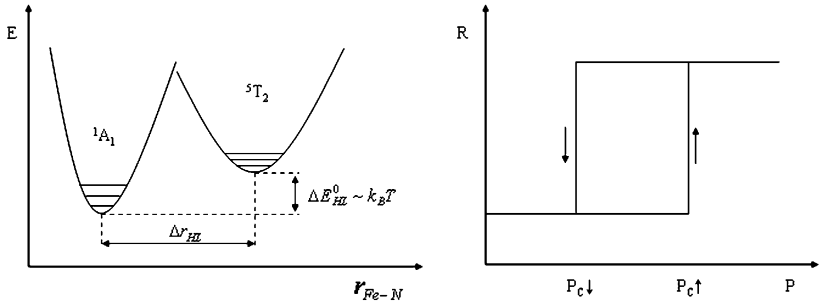


Figure 3.90: LS and HS potential energy curves for a spin transition complex (left) and an idealized R/P relation.

Some examples of bistable transition metal complexes shall be given to show the practicability of this promising concept.

The Co(II) complex ($3d^7$) of figure 3.91 can be switched between HS and LS by temperature. The HS/LS change is observed by the change of the magnetic susceptibiliy. The high-spin configuration has a total spin S = 3/2, whereas in the low-spin version S = 1/2. From the hysteresis curve in figure 3.91 (Zarembowitch, Kahn 1991) it can be calculated that the lower lying states in the HS alternative are energetically higher than than those of the LS configuration, as is already generally indicated in figure 3.90.

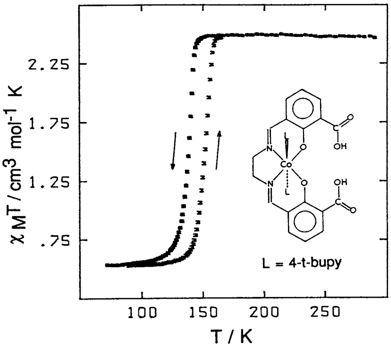


Figure 3.91: Temperature dependance of the magnetic susceptibility χ_{MT} for the octahedral Co(II) schematically drawn in the insert. The arrows indicate decreasing and increasing temperatures, respectively.

Figure 3.92 shows an example of an Fe(II) complex, switchable with green light at 30K (Konigsbruggen et al. 2003).

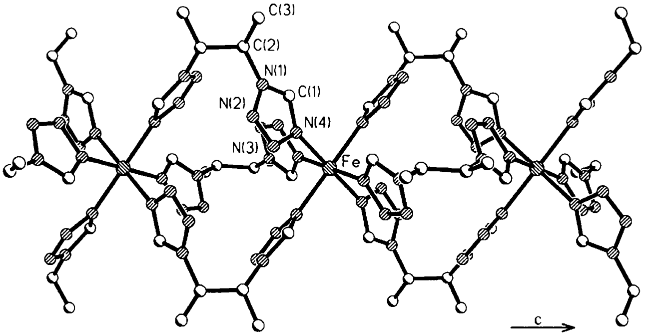
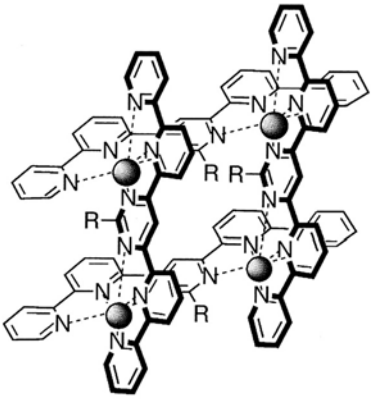


Figure 3.92: Molecular model of $[Fe(btzb)_3](ClO_4)_2$ (btzb = 1,4-bis(tetrazol-1-yl) butane). With permission from Springer-Verlag GmbH, Wien.

It undergoes light-induced excited spin-state trapping (LIESST effect).

The tetranuclear complex, imaged in figure 3.93 (Lehn et al. 2000) is an example of an Fe(II) d^6 complex that is switchable by temperature, pressure as well as by light.



$[Fe_4L_4](ClO_4)_8$

Figure 3.93: A tetranuclear Fe(II) complex, switchable between LS and HS by temperature, pressure or light. With permission from Wiley-VCH, Weinheim.

Due to its tetranuclear character the complex can be switched in over three magnetic steps: 3HS/1LS, 2HS/2LS and 1HS/3LS and thus opens completely novel fields of molecular storage and switching systems. As has been shown, there exist 3 HS states at room temperature, whereas the 4th is inbetween HS and LS. At 100 K 3 of the 4 iron ions are near the LS state, the 4th ion stays in the HS state.

Pressure has a similar influence on the electronic situation since it causes changes in the metal-ligand bond lengths like temperature does. The bond lengths are directly linked with HS and LS configurations, since HS is linked with longer, LS with shorter metal-ligand distances.

The LIESST effect can be observed at 4.2 K with green light ($\lambda = 514$ nm, 15 mWcm^2). However, a reverse LIESST effect by red light could not be observed.

The electronic bistability of transition metal complexes belongs to one of the most interesting research fields in Nanoscience with respect to future storage media. Presently, the investigations are still part of fundamental research. However, very first approaches have been made to bring the fundamental knowledge at least onto a nanoengineering level. Some iron complexes have been investigated exhibiting both magnetic and optical changes when they undergo a HS/LS transition. It is especially the optical behavior that might be used for future developments. Two types of displays are under investigation, based on writing steps with local warming in a spin-transition polymer as active element. Therefore it can be foreseen that spin-crossover systems will develop to promising alternatives in the field of future storage systems, however, there must be done considerable basic research during the next one or two decades.

C2: Switchable Biradical Coupling

High-spin organic molecules are of particular interest for novel magnetic materials, particularly organic magnets. Molecular designs are aimed at π-conjugated organic molecules with half-filled topologically degenerated or nearly degenerated non-bonding molecular orbitals (NBMOs). Such degeneracies are usually required (but not always sufficient) for a molecule to possess high-spin ground state. To enlarge the ground state's spins of organic materials the high-spin subunits must be connected with a ferromagnetic coupling unit. The first historical example of such a ferromagnetic coupling unit is the meta-benzene linker in Schlenk's hydrocarbon in 1915. Since then, this structural motive has been investigated to structure sizes of cross-linked polymers where several hundred radicals are ferromagnetically coupled with each other.

However, the nature of the coupling between two radicals depends on the linker between them. Currently, the correlation between the chemical structure of the linker and the magnetic coupling of radicals is investigated by several groups in detail (Martin et al. 1998). Of particular beauty would be a bistable molecular linker, displaying two different conformations with different magnetic coupling. Similar to the optical switches for electric currents, the most likely stimuli to trigger the magnetic coupling of a molecule is probably based on a photoreaction. To the best of our knowledge, such systems are currently under investigations but not published up to date.

C3: Scanning Near-Field Optical Microscopy (SNOM)

The probe of a scanning near-field optical microscope (SNOM) consists of an optical fiber with a conical end being coated with a thin metal film (Al), leaving an aperture at the fiber end with a diameter of about 50 nm, see right hand side of figure 3.94 (Bozhevolnyi et al. 1997). Light is fed into the fiber and exits it as evanescent wave confined to the diameter of the aperture, thereby overcoming the diffraction limit. This light may interact with the sample. The fiber tip can equally be used for collecting light emitted from the sample. The distance between fiber tip and sample is controlled in a way very similar to non-contact AFM (Hartmann 2005). The fiber end is vibrated laterally with respect to the sample surface and this vibration is regulated to a constant frequency shift resulting from tip-sample interactions (left hand side of figure 3.94).

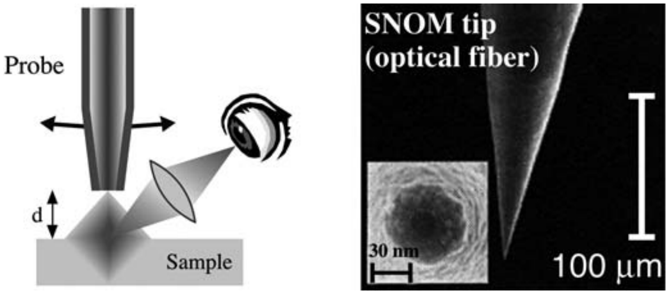


Figure 3.94: Principle of scanning near field optical microscopy (SNOM). Typical SNOM tip.

Since SNOM uses a nanometer sized optical probe, ordinary optical recording mechanisms, such as magneto-optical (MO) and phase change (PC) recording, can be investigated and performed with this technique. In figure 3.95 we show SNOM-based storage using PC recording (Hosaka 2004). Light irradiation from the SNOM tip gives rise to a well localized temperature increase driving a phase transition from amorphous to crystalline in the recording medium (a 30 nm thick GeSbTe film).

The associated reflectivity increase is localized roughly to the area of the aperture and can be detected in the reflected light. In the example shown the sample was irradiated by 5 ms long pulses of 7.3 mW laser input power with 785 nm wavelength. In the reflection of SNOM images this yielded feature sizes of 60 nm in diameter corresponding to 170 Gbits/in^2.

SNOM enables also *in-vivo* investigations of biological samples. However, care has to be taken since local heating due to the deposited power from the laser light may damage the biological samples.

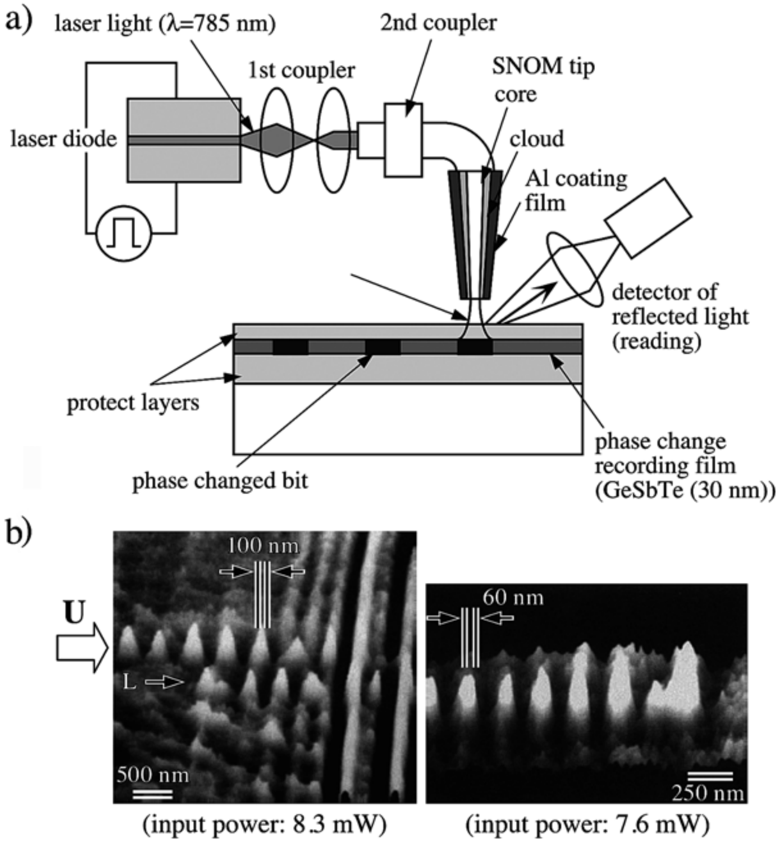


Figure 3.95: a) Schematic diagram of SNOM based PC storage with reading and writing. b) Reflection SNOM image showing 60 nm diameter features at 7.6 mW laser input power.

C3: Optical Computing

Today's computers are limited in speed by the restriction of the electrons travelling in the solid-state semiconductor materials. A vision, already postulated in the 1980s, is to change the media and to use light instead of electrons for information exchange and processing (Feiteslson 1988; Arsenault et al. 1989). The concept is of intrinsic beauty, as it would increase the processing speed by several orders of magnitude. In addition, it would allow for completely new circuit architectures as with light, two signals could cross without any interaction or even short circuit. However, the realization of optical computing turned out to be scientifically extraordinary challenging and the enthusiasm faded away because of materials limitations that seem to prevent optochips from getting small and cheap enough to ever be more than laboratory curiosities. However, the increasing control in size and space attainable with today's Nanotechnology lead to a revival of the ideas of optical computing and to first realizations of milestones on the way to optochips.

Photonic crystals or optic band gap materials are made to control the light by not offering a mode or a pathway to the light to leave a predefined structure. Smallest silver clusters are used as nanometer scale optoelectronic devices that can act as logic gates. These clusters are electroluminescent and act like a transistor with light as an output instead of electrical current.

Even though these current activities are only the first steps to control light they are of fundamental interest to investigate the potential and to further push the limitations of optical computers in particular and optical devices in general.

Photons can also respond to electrons through media like e.g. lithium niobate leading to another promising field of current investigations: electro-optical hybrids. These devices may help to pave the way to optical computing. The most likely devices in the near future will probably be switches and relays e.g. based on photonic band gap materials for optical fibre technology.

C3: Optically and Electrically Switched Phase Change (also E1/E3)

Generally, phase change information storage utilizes the thermally induced reversible transformation between the crystalline and the amorphous state. In an optically switched phase change device, the respective active materials are typically heated by a focused laser beam. Over a restricted area, which is determined by the size of the laser spot (typically 150-200 nm), the active material melts and keeps in the amorphous state after rapid cooling (cooling

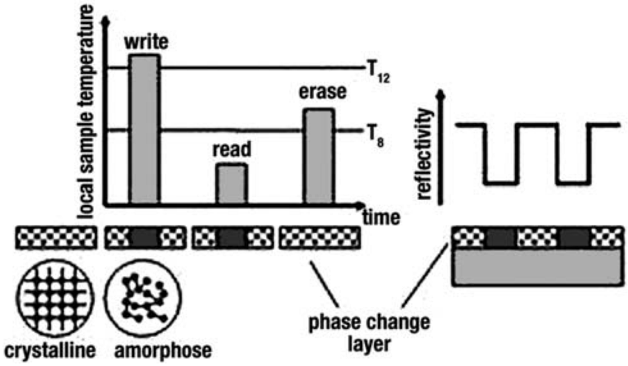


Figure 3.96: Principle of optical data storage with phase change media: To write a bit, the crystalline layer is locally molten. Recrystallization is prevented by very high cooling rates, leading to the amorphous region. The amorphous and the crystalline regions have different reflectivities. By a laser beam of intermediate intensity the material is heated above the glass transition temperature to recrystallize and thus to erase the bit (adapted from Wuttig 2000).

rates of 10^9 K/s) as soon as the laser is switched off. Although the amorphous state is meta-stable, the system keeps trapped in this state. Since the optical properties (refractive index, absorption and reflectivity) of both states differ significantly, the phase change can be probed by a weak (non-erasing) laser beam. With inter-metallic compounds, like $Ge_2Sb_2Te_5$, writing and erasure can be realized faster than 10 ns. Materials design is actually realized by combinatorial methods using gradient libraries accompanied by density functional calculations.

Therefore phase change materials are promising to develop high-density optical storage media in multimedia applications and system optimization promises to compete with storage range and density of magnetic hard discs.

In strict sense of our definition, this technology cannot be regarded as a Nanotechnology, since the optical reading without near field optics will not reach down to the true atomic scale. Nevertheless, optically switched phase change media will increasingly gain applications in optical non-volatile data storage.

In an electric phase change element, electric current of different magnitudes are passed from a heater element to a phase change material (again typically GeSbTe alloys). The local heating (s. scheme of a current memory structure) is used to change the programmable volume around the contact region. Rapid cooling keeps the material in the amorphous high temperature state with an increased electrical resistance (s. temperature dependent resistance).

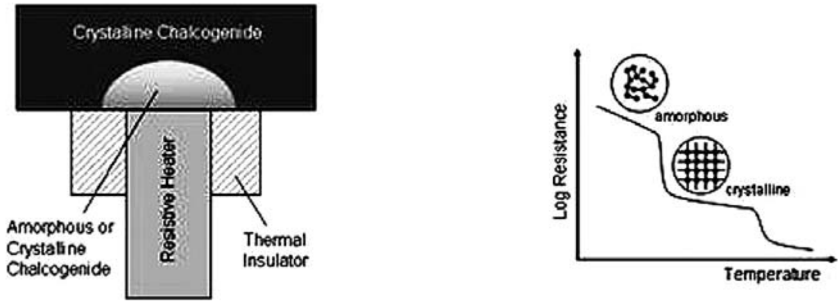


Figure 3.97: Schematic presentation of a current memory structure (left: adapted from www.intel.com, 2002) and temperature dependent resistance of a phase change material during annealing of an initially amorphous sample (adapted from www.ex.ac.uk/Projects/pcram/).

The time required for switching to the amorphous state by a high current pulse is less than 20 ns, while the re-crystallization appears by a longer medium current pulse. Non-destructive reading low-current measurements are performed. The stability of the material allows ~ 10^{12} write/erase cycles with an actual integration size of about 22 nm. According to an actual statement of Intel corp., this concept has no known physical scaling limit, and therefore it has the potential to continue Moore's law scaling beyond transistor memory scaling, whereas the main application may be as non-volatile data storage (phase change random access memory/PC-RAM) in mobile applications and in space technology, due to the low power consumption and the low sensitivity toward radiation. Thus, phase change memories have reached a high technological level and commercialisation is already expected for the near future. But in the near term, projected cost is highly compared to NOR/NAND flash. The challenge is now how to lower cost faster.

An alternative route may be the use of semiconductor/polymer hybrid elements, which have been developed as a write-once read-many-time memory (WORM) devices (Möller et al. 2003). It turns out to be a reliable and low-cost concept for storage, utilizing a current-controlled thermally activated un-doping of a two-component electrochromic conducting polymer, i.e. polyethylene-dioxythiophene (PEDT) and styrene sulphonic acid (PEDOT).

C4: Optically triggered mechanics

Azobenzenes are bistable molecules, possessing two stable configurations an elongated rod-like transform and a more compact cis form. The transconfiguration is typically thermally more stable with a thermal barrier between both states of about $\Delta G^* \sim 40$ kT. Selective excitation of one of both forms result in the first excited singulett state S_1, which calms down to one of both forms. As light of a wavelength of 420 nm only excites the cis-form and light of a wavelength of 365 nm only excites the trans-form, switching between both states by light of appropriate wavelength is possible.

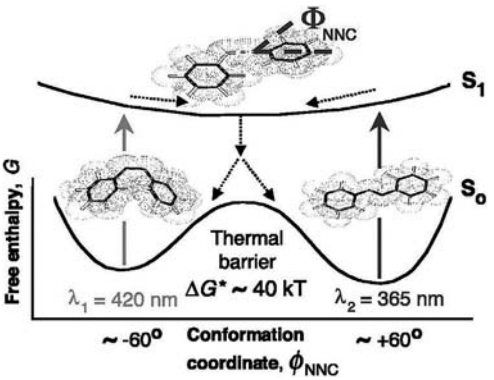


Figure 3.98: Switching between the cis-form (left) and the trans-form (right) of an azobenzene by light of the corresponding wavelength to excite in from the ground state singulett S_0 to the first excited singulett S_1 (with kind permission of Hugel et al. 2002).

In an atomic force microscope (AFM) experiment, Gaub and coworkers (Hugel et al. 2002) managed to immobilize single polymer strands containing azobenzene subunits between the tip of the AFM and the substrate. The set-up allowed exciting the polymer strand in total internal reflection to avoid thermochemical disturbance of the cantilever. Elongation and shrinking of the polymer as a function of the excitation wavelength has been observed. Periodic cycles of both wavelengths even allowed to investigate the mechanical work of the polymer stimulated by light as an optical stimulus.

3.2.4 Stimulus: Mechanic

D1: Chevron – STM (also D4)

Low-temperature scanning tunneling microscopy observations of CO molecules chemisorbed on the single crystal metal surface Cu(111) have revealed arrangements of three molecules showing bi-stable behavior (Heinrich et al. 2002). When three CO molecules are placed at roughly second neighbor substrate lattice distances one can create a metastable state where the three molecules form a chevron, and a stable state where the three molecules form a regular triangle. One may switch from the first to the second state by external undirected excitation, such as heat, whereas one has to put work, *i.e.* a force acting into a given direction, into the system in order to come back from the stable to the metastable state. The left and right hand side of figure 3.99 show the metastable and stable state, respectively.

Setting up the molecules initially, and bringing them back to the initial (metastable) state after they have switched, is performed by manipulation with the STM tip (Eigler et al. 1990) which is evidently a slow process.

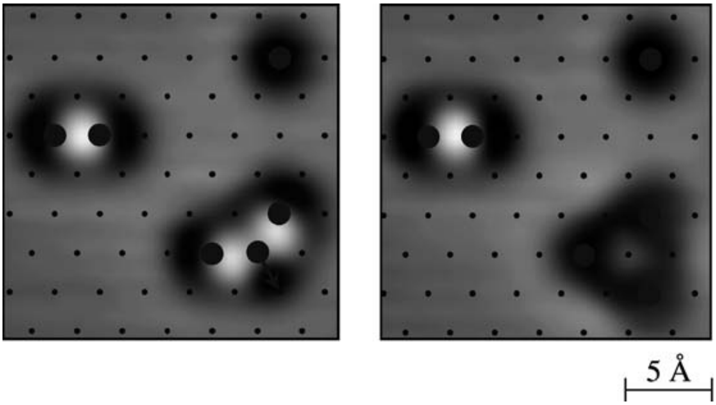


Figure 3.99: STM images of CO molecules on a Cu(111) surface. Large circles indicate locations of CO molecules and small ones substrate atoms. The bottom right of the figures show the trimer, once in the chevron configuration (left), and once after the central CO molecule in the chevron has hopped to its more stable site (right).

Conversion from the chevron to the stable state can in addition to heat also be initiated by environmental changes at low temperature (5 K). This means, a molecule may jump to its more stable site by the move of one of its neighbors. This enabled to construct molecular cascades where molecular jumps propagate, very much as in rows of dominoes. Figure 3.100 shows the realization of an AND gate by combining two such cascades.

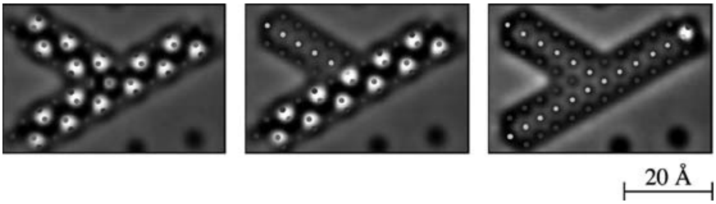


Figure 3.100 Logic AND gate built with cascades of CO molecules. Left: initial state, middle: after one of the inputs has been triggered and the cascade has propagated to the central connection where its fate depends on the state of the other input, right: case where the other input was high, cascade can go through the gate all the way to the output.

Very complex circuits have been demonstrated, such as the 3-input sorter cascade shown in figure 3.101.

Chevron-STM is an exciting demonstration of the currently smallest logic circuits. However, the instrument around the circuit fills an entire room, works at low temperature, and circuit operation (such as reset) involves macroscopic times and in particular directed force from the out-

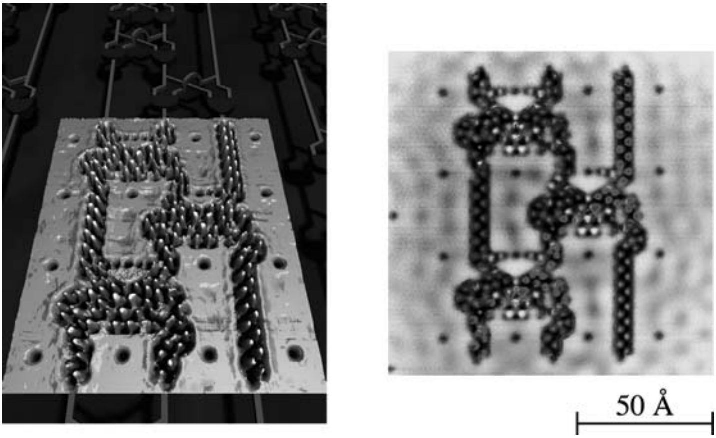


Figure 3.101 3-input sorter realized by CO cascades on Cu(111). Left: schematic and 3D representation of the STM image, right: topview of the STM image.

side. Nevertheless it is fascinating to see these circuits at work, even if applications will certainly not arrive in due course.

D2: Spin-Crossover Processes

(s. C2)

D4: Chevron – STM

(s. D1)

D4: Rotaxanes

Recently, David Leigh and co-workers have reported a new strategy for information storage (Cavallini et al. 2003). The strategy is based on a rotaxane molecule that displays two conformations of comparable free energy, which can be addressed by external stimuli. A few nanometer thick films of the rotaxane molecule were grown by drop casting on a flat substrate (mica or graphite). These films were imaged by AFM in contact mode with a set point force below a threshold value of 2 nN. By increasing the load force above the threshold value of 2 nN a mechanical perturbation of the film is observed. A continuously scanned tip along a line results in a string of regularly spaced dots. These dots are uniform in height, width and pitch. As the numbers of dots is proportional to the length of the line scan, any predetermined number of dots can be written by AFM on a line. The proof of concept of the method for information storage has been done by writing the hexadecimal code of 968616 (ec7a8) in a field of approximately 500 x 700 nm (s. figure 3.102 below).

D4: Chemical Atomic Force Microscopy (AFM)

(s. A1)

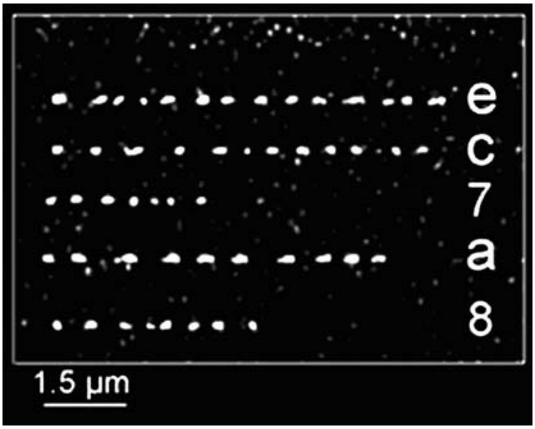


Figure 3.102: Proof of concept for the information storage: the sequence "e c 7 a 8" is written by AFM in a film consisting of the rotaxane.

3.2.5 Stimulus: Thermal

E1: Optically and Electrically Switched Phase Change

(s. C3)

E2: Spin-Crossover Processes

(s. C2)

E3: Optically and Electrically Switched Phase Change

(s. C3)

3.3 Biomedical Opportunities & Applications

Introduction

Major innovations in biomedicine and in our understanding how cells work was made possible throughout the last decades by a series of new technologies, from biochemistry starting in the 1970s, biotechnology, and finally through the deciphering of the human genome at the end of the 1990s. While these technologies have provided impressive knowledge identifying and characterizing many of the molecular players, Nanotechnology now promises to deliver the needed tools to learn more about the rules of the molecular chess game by which cells control the assembly and disassembly of their molecular building blocks into larger functional units, including organelles. This will contribute in a major way to transitioning biology from a descriptive to a quantitative science. Beyond providing new insights into how cells and organs work, the biggest pay-off for society might come from utilizing these quantitative insights combined with advanced imaging and analytical technologies for the early detection of diseases and their more effective treatment.

A combination of these and other emerging tools will greatly impact the quantitative understanding of how biological systems work on the nanometer scale, and of how these systems are integrated within cells thus making essential contributions to the field termed "systems biology". The goal is to ultimately derive the engineering principles that control and regulate cellular functions, from growth, differentiation, motility, contractility, to apoptosis. Another biomedical challenge is to interface living cells with engineered nanomaterials. Interfacing living cells with engineered nanosystems is needed for many medical applications – from tissue engineering to sensors implanted within human tissues – to obtain real-time information on biological processes and functions. Considering the cost explosion of the health care sector, microfabricated platforms with integrated nanoscale systems are needed to build portable devices at low cost to analyze samples from body fluids and gases without major time delays. Additional to the biomedical application of nanotechnological tools, the nanosized building blocks can be used for the "construction" of tailor made materials using biological principles.

3.3.1 A: Nanoparticles and their Biomedical Applications

Nanoparticle design

Quantum-dots and other nanosized particles with unique physical properties (s. table 1) have a large impact on some important developments in different medical areas like diagnostic tools (magnetic resonance imaging, MRI), in in-vitro and in-vivo detection and analysis of biomolecules, development of nonviral vectors for gene therapy, as transport vehicles for DNA, protein, drugs or cells and finally in different therapeutic tools for cancer treatment. Beside the unique physical properties of the nanoparticles, the size of the particles which is with 2 to 30 nm comparable to the size of biological building blocks (protein, DNA) allows to investigate the cellular machinery without too much functional interference (Taton 2002). Understanding of biological processes on the nanoscale level is one of the strong driving forces behind the developments of Nanotechnology. Out of the impressive number of size-dependent physical properties available for practical use of nanoparticles as presented in table 1, optical and magnetic effects are the most interesting for biological applications. In this chapter, the use of such particles as analytical tools, as transport vehicles and for cancer treatment will be presented.

In order to interact with biological targets, a biomolecular coating which acts as a bioactive and selective interface should be attached to the nanoparticles. Examples of such coatings may include antibodies, biopolymers like collagen, or monolayers of molecules that make the nanoparticles biocompatible and stable as colloids in a biological environment. The approaches used in constructing nanoparticles for biomedical and/or biotechnological applications are shown schematically in figure 3.103. The inorganic core of the nanosized particles allows the user to apply different external fields so that specific nano effects can be used for there detection or active therapeutic tasks. For example, using gold as core material is ideal to employ surface plasmon resonance in biosensing applications, whereas semiconducting core materials (ZnS, CdSe) are useful to utilize their photoluminescence, and superparamagnetic iron oxide particles are used for imaging and drug delivery using the strong saturation magnetisation of these nanoparticles.

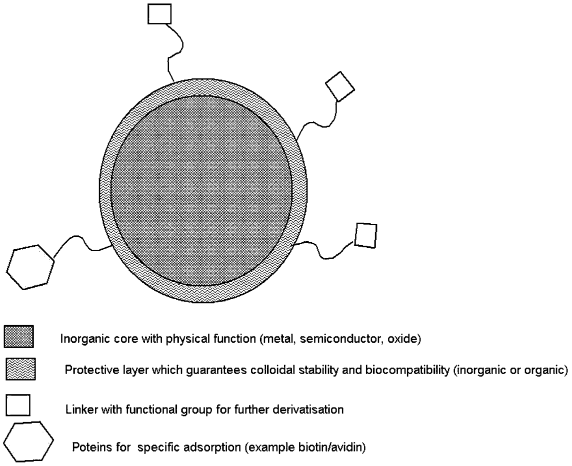


Figure 3.103: Typical configuration used for nanoparticles for biomedical application.

Table 3.3: Biomedical Opportunities & Applications

The construction of Table 3 differs characteristically from that of Table 1 and Table 2. With respect to the definition forming the basis for the whole chapter 5, the matter to be considered in this section mainly refers to that part of the definition saying that Nanoscience is dealing with functional systems based on the use of a system of functionalized subunits.

The matter to be treated is divided into *in vivo* and *ex vivo* (1. row) and, as can be seen, the *in vivo* part is remarkably more voluminous than the *ex vivo* part. This has to do with the fact that *ex vivo* experiments with biological systems are restricted by nature. Only modelling reactions on a molecular level, analyses, biomineralization studies and some other limited areas can be performed *ex vivo*. However, independent on the *in vivo* or the *ex vivo* situation, fields of interest are in principle the same. Thus the first column informs on the relevant activities (A–D). The reason that nanoanalytical tools (B) take up such a broad scope is to be seen in the fact that, especially in the in vivo experiments, studies on the nanoscale have to be performed with special

<table>
<tr><th></th><th colspan="2">**Subcellular/Cellular
In Vivo (1)**</th></tr>
<tr><td>(A)
Nanoparticles and Nanosystems</td><td colspan="2">Drug Delivery Systems
Contrast Agents For Functional Imaging (Ultrasound, PET, etc)</td></tr>
<tr><td rowspan="2">(B)
Nano Analytical Tools
(Scanning Probes, Optical Tweezers, Single Molecules Spectroscopy, Optical Imaging)
Computational Tools</td><td>(1a) **Imaging at Nanoscale**</td><td>(1b) **Tracing, Tracking and Kinetics**</td></tr>
<tr><td>High Resolution Imaging And Manipulation of Single Molecules in Biological Environments
Microscopy at the Nanoscale
Time-resolved, High-resolution Imaging In 3d
Pattern Recognition And Image Analysis;
Nanometer Resolution</td><td>Tracing Single Molecules/Pa in Time and Space
Cell-Cell Interactions and I Pathways (Viruses And Bact Infections)
Subcellular Dynamics</td></tr>
<tr><td></td><td colspan="2">← Systems Biology —</td></tr>
<tr><td>(C)
Biomimetics And Nanoengineered Cell Environments</td><td colspan="2">Deriving Bioinspired Engineering Design Principles
Controlling Cell Shape By Nanoengineered Structures And Patterns, Spatial Patterning Of Synapse Formation, Engineering Of Interactio
Tissue Engineering, Engineering Interactions Of Cells With Syntheti</td></tr>
<tr><td>(D) **Adverse Health Aspects**</td><td colspan="2">Effect Of Nanoparticles On Function Of Biomolecules (Proteins); Tr Signaling And Degradation Of Nanoparticles In Cells</td></tr>
</table>

analytics on the nanoscale without destruction of the matter to be investigated. The progress in nanobiology is therefore strongly linked with the development of appropriate analytical tools.

Another important point in relation with Table 3 has to be commented. Health aspects (D) are mainly dealing with the toxicity of nanoparticles. These are often not well defined, neither with respect to their size nor to their chemical composition. Furthermore, it can not be neglected that also microparticles may damage living systems. So, it could be concluded that these health aspects are not such typical nanoeffects as the definition demands, rather they might be assigned to scaling effects. This is correct with respect to the particles, but not regarding their interactions with cell materials. The basic steps, for instance transport mechanisms into and inside the cells etc. must be considered as chemical interactions between boundary surfaces (particles) and biomolecules on the nanoscale. In so far these health aspects have become part of this chapter.

		Ex-Vivo **(2)**
		– Diagnostic Devices – NEMS/MEMS
	(1c) Manipulation and Mechanical Force	
rticles nfection erial	Manipulation of Single Molecules/ Molecular Complexes Combined With Force Measurements Manipulation of Subcellular and Cellular Systems Mechano Transduction: How Cells Sense Force	Imaging And Analysis Of Isolated Biological Nanosystems Single Molecule Spectroscopy Single Molecule Mechanics Dynamics And Kinetics Of Single Molecules And Molecular Assemblies
		→
ns And Communication With Cells c Systems		Biomineralization
ansport Across Cell Membranes, Trafficking,		Transport, Signalling And Cell Activation In Cell Co-Cultures And Organs; Isolated Organs, Biopsies

Because the physical properties depend strongly on the size of the particles, it is evident that the size as well as the size distribution of the core particles has to be controlled carefully during the synthesis.

The protective layer which gives to the particles the necessary biocompatibility often consists of biodegradable polymers or silica. Beside the biocompatibility, the protective layer has to prevent particle aggregation and ensure its longterm stability in water or even more important in blood or body liquid. The development of such layers is still challenging because the physical properties of the core material will be also influenced by the coating. Finally, linkers (long chain polymers) with functional groups like thiol, amino or carboxylic groups or proteins which allow for site specific binding to the cell membrane or even the translocation of the particles through the membrane (endocytosis), have to be attached to the protective layer. The molecules chosen to functionalize the protective layer depend on the application and cell types that have to be specifically addressed. Some examples will be given in the chapters describing the application of the particles (for reviews s. Bailey et al. 2004; Parak et al. 2003; Schmid 2004).

Beside single particles beads, multiple nanoparticles embedded in biocompatible matrices are of considerable interest. Such particles can display several functions in parallel at the same time, for example superparamagnetic properties that are exploited for transport in a gradient of a magnetic field and photoluminescence for particle tracking or local treatment of diseases (s. figure 3.104). Such multifunctional particles are mainly used for biosensors or for separation tasks. In-vivo applications are difficult because

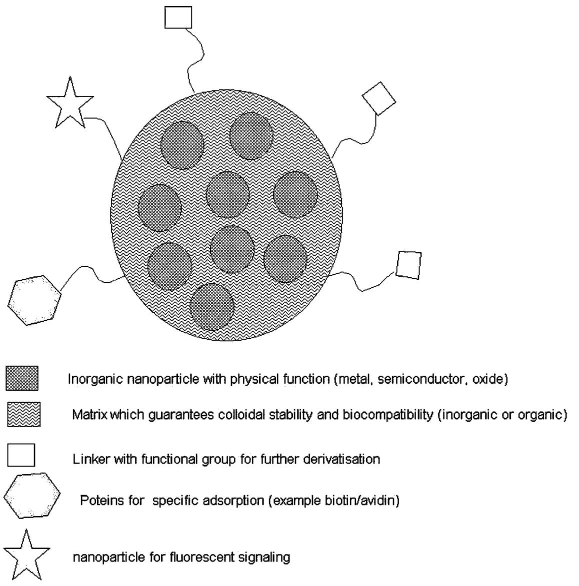


Figure 3.104: Typical configuration used for beads for biomedical application.

the size of the beads is very often several 100 nm and therefore to large for translocation, but still small enough for transport tasks in blood vessels.

A1/2: Nanoparticles for biomedical imaging and biological detection

Using nanosized particles and their specific properties, cellular or molecular events can be detected *in vivo* (also called molecular imaging) by three main formats: magnetic detection, optical detection and still in development, electrical detection.

Magnetic detection

Superparamagnetic nanoparticles as contrast agents for magnetic resonance imaging (MRI): MRI is a tomographic imaging technique, able to produce an image of the nuclear magnetic resonance (NMR) signal in a thin slice through the human body using hydrogen nuclei which show a strong NMR signal. In the early seventies, magnetic resonance was extended to the *in vivo* study of human organs. This was made possible by new, practical methods for obtaining signals from limited volumes which opened the door for spatial imaging. Relying primarily on the differential decay and recovery characteristics of the proton NMR signal (generally termed relaxation behavior), this technology can generate images with high contrast among various soft tissues and organs. As a result, magnetic resonance imaging (MRI) has become the modality of choice in many diagnostic studies of the head, spine, and joints. With ongoing developments to improve the image quality, acquisition speed and quantitative accuracy of related measures of local signal characteristics, the range of clinical applications for MRI, like functional MRI which can visualise metabolic processes in vivo at real time, continues to expand rapidly. Although MRI was initially hoped to provide a means of making definitive diagnoses non-invasively, it is known that the addition of contrast agents, which changes locally the magnetic field and therefore the relaxation time, in many cases improves the sensitivity and/or specificity. Superparamagnetic iron oxide nanoparticles (SPION) used as contrast agent for MRI are magnetically saturated in the normal range of magnetic field strengths used in MRI scanners, thereby establishing a substantial locally perturbing dipolar field which leads to a marked shortening of the spin-spin relaxation (T_2) along with a less marked reduction of the spin-lattice relaxation (T_1). MRI contrast relies on the differential uptake of the SPION by different tissues. SPION for liver MRI are commercially available whereas coated SPION which adsorbs specifically at different cells types are still under development. Nanoparticles with diameters of 30 nm or more are rapidly collected by the liver and spleen, while particles smaller than 10 nm are not so easily recognized by the macrophages. The smaller particles therefore have a longer residenz time in the blood stream and are collected by reticuloendothelial cells throughout the body, including those in the lymph nodes and bone marrow (Harisinghani et al. 2003). Iron oxide nanoparticles also lend themselves to encapsulation into target-specific agents, such as liposomes that are known to localize in the bone marrow (Bulte et al. 1999). The ability to label stem cells with magnetic resonance imaging (MRI)-visible contrast agents was shown recently (Himes et al. 2004). This allowed tracking and quantification of stem cell transplantation non-invasively with high spatial resolution in a swine model. Trafficking of dextran coated SPION from brain to lymph nodes are used to detect routes for fluid drainage from the central nervous system (Muldoon et al. 2004).

The examples above show that coated superparamagnetic iron oxide particles with covalently linked proteins are capable to bind cell-type specific and show therefore a considerable potential for further application in medical imaging. The superparamagnetic effect is important to assure the colloidal stability of the particle in blood and body liquid. On the other hand the high saturation magnetisation of the nanoparticles leads to a strong contrast. The combination of these properties can lead to more advanced application like single molecule tracing or combination of tracing and treatment, for example in drug delivery and hyperthermia (Pankhurst et al. 2003).

Superparamagnetic nanoparticles for diagnostics: Development in the last 10 years in MEMS (microelectromechanical systems) has brought a new and interesting analytical concept which is based on sandwich immunoassay and electrochemical detection (Niwa 1993), also called "Lab on the chip". As illustrated in figure 3.105 in a microfluidic device magnetic beads are used as both substrates of antibodies and carriers of target antigens. Antibody-coated beads consisting of superparamagnetic iron oxide particles embedded in a polymer matrix are introduced on the electromagnet and separated by applying a magnetic field. In a second step, while holding the antibody-coated beads, antigens are injected into the channel. Target antigens are

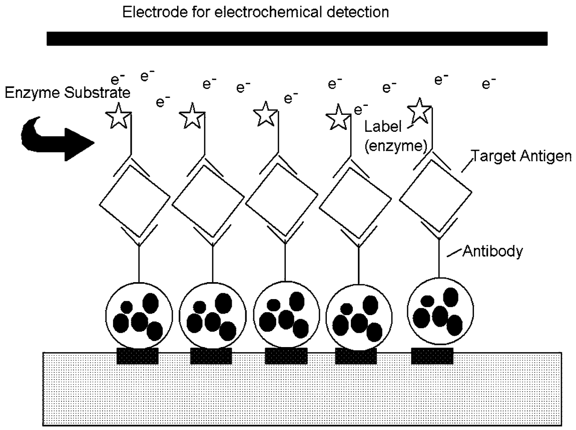


Figure 3.105: Bio-MEMS using superparamagnetic beads for antigen detection (from Choi, Ahn et al. 2000).

immobilized on the magnetic bead surface due to specific antibody/antigen reaction whereas nonbonding antigens get washed out with the flow.

In a third step, enzyme labeled secondary antibodies are introduced and incubated, along with the immobilized antigens, followed by a rinse to remove all unbound secondary antibodies. An electrochemical detection can be performed injecting a substrate solution which will react with the enzymes. Finally, the magnetic beads are released to the waste chamber, and the bio-separator is ready for another immunoassay.

Labeled SPION or labeled beads with SPION can be used for DNA detection if the magnetic field of the beads or the SPION is detected in a careful way. The latter is possible with magnetic field sensors based on the giant magneto resistance, which is also based on a nanoeffect. Recently (Baselt et al. 1998) have developed a bead array counter, a magnetic-label-based system for the detection of biomolecules. Central to this system is a microfabricated sensor chip containing giant magnetoresistance (GMR) magnetic field sensors that detects the presence of magnetically-labeled DNA samples. In these assays, magnetic bead labels are used like fluorescent labels except that the beads are excited and detected with magnetic fields and changing electrical resistivity rather than with light. For example, thiolated, single-stranded DNA capture probes were fixed on a gold surface above the embedded GMR sensors. When adding biotinylated DNA samples to the probe, hybridization with the complementary probes occurs. The hybridised DNA can be finally detected by the GMR sensor binding Streptavidin-coated magnetic microbeads utilizing the strong and specific biotin-avidin coupling. An important advantage of this method is that the means for excitation and detection are easily integrable on a silicon circuit.

Optical imaging and detection

For optical detection of biological molecules with nanoparticles, various principles are used, including luminescence and surface plasmon resonance both of which are based on nanoeffects as described in table 1. Nanosized semiconducting particles, also called quantum dots like cadmium selenide or cadmium sulphide, are attractive candidates to exploit their photoluminescence, whereas for surface plasmon-based sensors, metallic nanoparticles, normally gold, are of interest.

Quantum Dots: Following the nearly simultaneous reports of using QDs as labels in biological experiments in 1998 (Bruchez et al. 1998; Chan and Nie 1998), the number of QD biological studies has increased rapidely. Quantum dot labels have been successfully used for a variety of bioanalytical purposes, such as DNA hybridization detection (Parak et al. 2003), immunoassays (Goldman et al. 2002), and binding assays using fluorescence resonance energy transfer (FRET) to probe for target events (Tsourkas and Bao 2003). Quantum dots are also very interesting nanomaterials for increasing the assay sensitivity. Additionally, the lifetime of the photoluminescence of quantum dots is significantly longer than the autofluorescence of biological tissue. The lifetime of quantum dots, which is on the order of some hundreds of microseconds, is also advantageous in diagnostics since the electronics to probe lifetimes on the micro- rather than the nanosecond timescale are much cheaper.

Quantum dots are highly light absorbing, luminescent nanoparticles whose emission maximum is shifted to higher energy with decreasing particle size due to quantum confinement effects (s. table 1). Nanosized semiconductors emit much brighter light and are much more photostable than fluorescent oganic dyes. In contrast to molecular fluorophores, which typically have narrow excitation spectra, semiconductor nanocrystals absorb light over a broad spectral range. This makes it possible to excite a broad spectrum of quantum dots using a single excitation laser wavelength, which may enable to simultaneously probe several markers in biosensing and assay applications emitting different colors. CdSe-CdS or CdSe-ZnS core-shell nanocrystals have been shown to span the visible region from green to red. Other materials, such as InP and InAs, provide quantum dot fluorophores in the near-infrared region of the optical spectrum, a region where transmission of light through tissues and blood is maximal. Coating of the particles with silica or organic layers permits the nanoparticles to be biocompatible as long as they are not digested or degraded. Quantum dots can also be embedded within polymer nano- or microparticles to improve biocompatibility while maintaining the interesting fluorescence. Specific binding of these nanosized particles to cell surfaces, cellular uptake, and nuclear localization have all been demonstrated following conjugation of semiconductor nanocrystals to appropriate targeting proteins, such as transferrin or antibodies (Chan et al. 2002). Two typical applications of photoluminescent quantum dots are given below.

Molecular tagging with photoluminescent quantum dots: Because the photon emission wavelength of different nanocrystal species can be tuned by varying the particle size, microbeads with varying colors and intensities, so called microscopic bar-codes can be prepared (Han et al. 2001). When attached to DNA probes or to antibodies, these beads can tag each individual molecules or particles with a different bar code whereby combinations of colours and intensities could tag up to a million different molecules. As they can be easily mixed into biological samples, the beads are also ideal for high-throughput screening applications.

Molecular beacons: Molecular beacons as described by (Tsourkas and Bao 2003) and (Tyagi and Kramer 1996; Tyagi et al. 2000) are single-stranded oligonucleotide hybridization probes that form a stem-and-loop structure. The loop contains a probe sequence that is complementary to a target sequence, and the stem is formed by the annealing of complementary arm sequences that are located on either side of the probe sequence. A fluorophore or a semiconducting quantum dot (Kim et al. 2004) is covalently linked to the end of one arm and a quencher is covalently linked to the end of the other arm. Molecular beacons do not show fluorescence in solution because the quencher on one arm is in contact with the fluorophore on the other arm. However, when they hybridize to a nucleic acid strand containing a target sequence they undergo a conformational change that enables them to fluoresce brightly (s. figure 3.106).

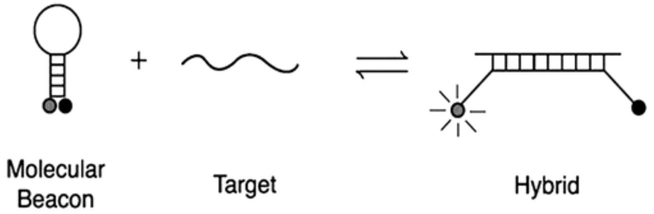


Figure 3.106: Molecular beacon (from Tyagi, Marras et al. 2000).

Molecular beacons are highly specific. They easily discriminate target sequences that differ from one another by a single nucleotide substitution. Molecular beacons are designed so that their probe sequence is just long enough for a perfectly complementary probe-target hybrid to be more stable than the stem hybrid. Molecular beacons have been used for the detection of RNAs within living cells, for monitoring the synthesis of specific nucleic acids in sealed reaction vessels or for identification of single nucleotide variations in DNA and for the detection of pathogens.

Surface plasmon resonance for biosensor applications: Conjugates of gold nanoparticles-oligonucleotides systems (AuNPs) are of great interest because of the versatility by which they can provide changes in their optical signatures upon binding of specific DNA sequences. Applications in the fields of biosensors, disease diagnosis, and gene expression are documented in the literature. The group of Mirkin (Mirkin 2000) pioneered strategies for the functionalization of AuNPs with oligonucleotides. Two non-complementary oligonucleotide sequences are thereby immobilized on the surfaces of two sets of *gold nanoparticles*, and if mixed, do not recognize one another (red in color due to surface plasma resonance). Upon hybridization with a complemtary strand that recognizes both of the immobilized DNA sequences, the gold particles aggregate and their distance is determined by the length of the oligonuleotides. As the gold particles assemble, a red shift in the plasmon band occurs, which correlates to a red-to-blue color change as detected by the naked eye (figure 3.107).

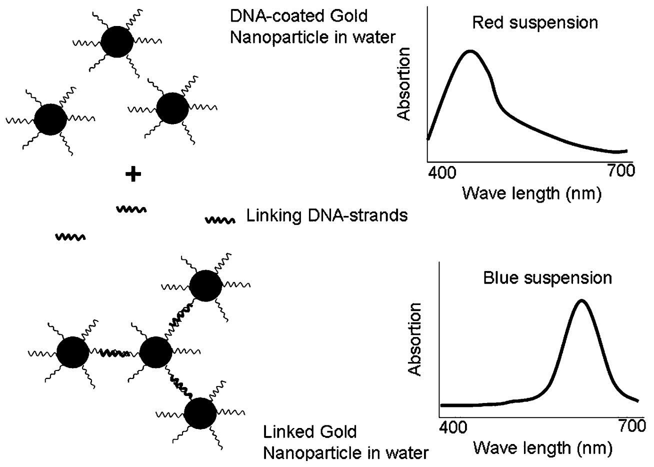


Figure 3.107: Surface plasmon resonance shift caused by specific binding of DNA (from Mirkin 2000).

Immunolabeling with AuNPs and imaging of cells, biomolecules, and other biological components have been subject of extensive research. The investigated AuNP-protein conjugate architectures involve either direct binding of antigen-AuNP-biocongugate to an antibody-modified surface or vice versa. This classic type of immunoassay allows the evaluation of AuNP tags in a standard mode of antigen detection. Since the aggregation of gold nanoparticles leads to the formation of a new absorption band at longer wavelengths as a result of electric dipole-dipole interaction and coupling between the plasmons of neighboring particles, the rate of aggregation of the protein A-coated gold nanoparticles in the presence of anti-protein A can be monitored by measuring the absorption of the gold colloid suspension at 620 nm (Thanh and Rosenzweig 2002).

Nanoparticles for drug delivery

At the beginning of drug delivery in the late 1960s, the dimensions of the first drug delivery systems were in the range of several centimeters and often needed an electric supply, so that the implantation and later on its replacement was connected with considerable stress for the patient (as reviewed in Earl E. Bakken 1991; Tricumed 1999). Later, microsystems made possible a considerable reduction of the geometrical size which implies (e.g. debiotech 2003; Santini et al. 1999). With the rise of Nanotechnology new approaches have been explored to develop non-toxic scaffold materials to serve as drug carriers, to create structural nanoarchitectures that allow for controlled drug release rates, to potentially link the drug release with biodegradation of the scaffold, and to ensure target specific delivery.

Various nanostructures are currently explored for future application in drug release. They have in common that drugs are entrapped or encapsulated in a nanostructure from which the drug can be released uniformly over an extended time period. While a high dose of drugs is needed at the location of the diseased tissue or organ, conventional medication is distributed over the entire body often with high peak concentration if conventional medication is taken orally or is injected. It is often the high peak concentration of the drug or its action on healthy tissue that causes adverse and sometimes dangerous side effects. One prime example is chemotherapy where the drugs are not specifically delivered to the cancer cells. Efforts are thus under way to decorate nanostructured drug carriers with antibodies on their surface to target the deceased cell specifically such that the carrier can deliver its payload which minimizes the toxification of the surrounding. The drugs are normally ingested or implanted. Recently it has also been attempted to develop drugs for oral uptake (Duncan 2001; CEN 2004). We will now highlight a few selected supramolecular systems which have been explored recently as scaffolds for drug delivery.

Guest-host systems: One idea was to create guest-host systems as shown in figure 3.108 where complementary stereochemistry or bonds are tailored to form a stable complex with the drug.

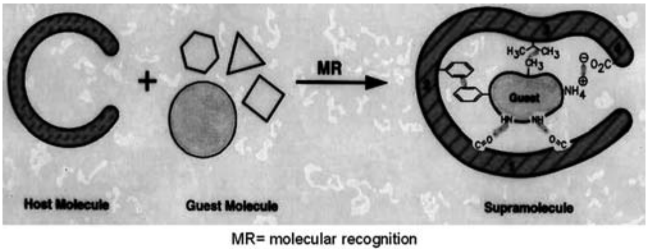


Figure 3.108: Principal design of Supramolecules (with permission of Prof. F. Vögtle, University of Bonn).

The bonding mechanism between guest and host can be based on hydrogen bonding, π-stacking, van der Waals bonding, or electrostatic interactions.

Dendrimers: Dendrimers as shown in figure 3.109 have been introduced as drug carrier systems.

The active substance, including drugs, pesticides or other substances, are either encapsulated in the dendrimer (figure 3.109 A), entrapped within a network composed of dendrimers (figure 3.109 B), or linked to the surface of the dendrimer by a labile (figure 3.109 C) or stable bond (figure 3.109 D). Each drug delivery system requires its own host-guest-system (s. figure 3.110 and e.g. Khopade et al. 2002; Jeong et al. 2002; Sakharov et al. 2001; Aida et al. 2001).

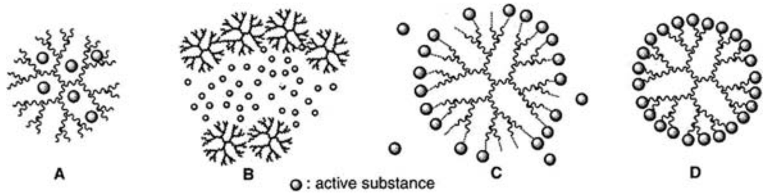


Figure 3.109: Principal ways to use dendrimers as drug carriers. Reprinted from Tetrahedron Letters, Vol.42, 2001, R Göller, JP Vors, A-M Caminade and J-P Majoral; pp 3587-3590, "Phosphorous dendrimers as new tools to deliver active substances", Copyright 2001, with permission from Elsevier.

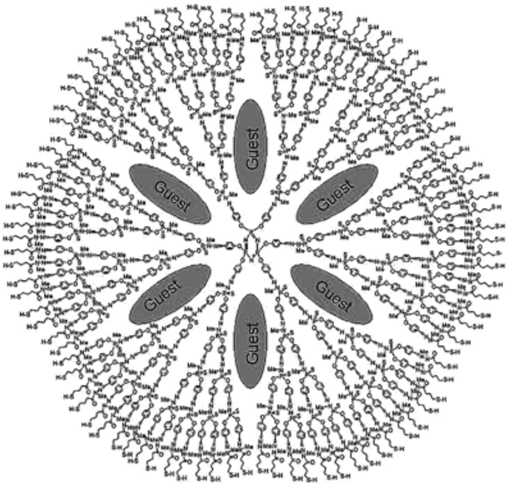


Figure 3.110: Encapsulation of a guest molecule (drug) in a supramolecule. From Prof. Vögtle, University of Bonn, private communication 1998.

Fullerenes and Fullerites: Also other molecular nanostructures like fullerenes and fullerites are under investigation for drug delivery (Breslau 2002). Because their dimensions are somewhat smaller than those of dendrimers, the drug together with the steering system is usually attached to the outer surface of the carrier. Other approaches include entrapping Co^{60}-atoms within fullerenes and then to decorate the fullerenes surface with antibodies to target cancer cells to achieve precisely localised radioactive irradiation of cancer cells.

Gold Nanoshells: Nanoshells are another platform being developed for nanoscale drug delivery. These are hollow spheres made of Silica coated with Gold. The nanoshells are embedded into a drug containing polymer and injected into the human body. The nanoshells can be effectively heated by an infrared laser such that the heat directly damages surrounding tissue, or is utilized to activate site specific drug release. One application is in cancer treatment, another potentially in treating diabetes. Instead of taking an injection of insulin a patient would use a ball-pen-size infrared laser to heat the skin where the polymer containing drugs had been injected. The heat from the nanoshell could cause the polymer to release a pulse of insulin. Unlike injections the polymer could remain in the body for month.

Magnetic particle systems: In another similar system, the drug is embedded in a thermosensitive polymer carrier together with magnetic nanoparticles (Müller-Schulte and Schmitz-Rode 2004). "Thermosensitive" means that the polymer particles above a discrete threshold temperature loose a great part of their bounded water content combined with a considerable reduction of particle size up to 70%. Simultaneously during the shrinking process the encapsulated drug is released. The co-encapsulated magnetic particles work as contactless controllable heater elements via inductive heating with frequencies in the Megahertz range. The temperature during the heating is controlled at a temperature of 42°C as shown schematically in figure 3.111.

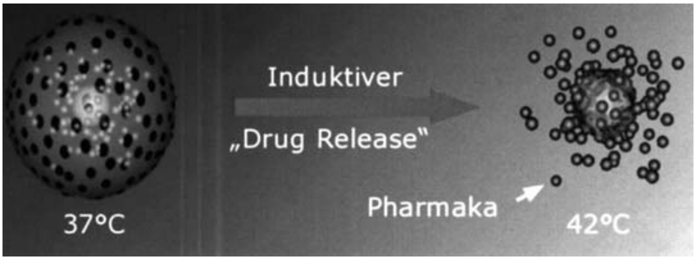


Figure 3.111: Thermally activated drug release by shrinkage of polymer carrier (schematically). From D Müller-Schulte and Th Schmitz-Rode "Neue Trägermedien für Therapeutika und Pharmaka." In: RWTH Themen "Vielfalt des Nanokosmos" Rheinisch-Westfälische Hochschule Aachen; Ausgabe 1/2004 ISSN-Nr. 0179-079X, 51-53 with permission of the Pressestelle Rheinisch-Westfälische Hochschule Aachen.

pH responsive systems: Here, advantage is taken from the observation that the pH in normal and pathological tissues can vary significantly (Engin et al. 1995; Ojugo et al. 1999; van Sluis et al. 1999; Stayton 2003). For example the extracellular pH of tumors is slightly more acidic than in the blood and in normal tissues. It is proposed that micellar or supramolecular nanoparticles are taken up by cells via an endocytic process (Kabanov et al. 1992; Luo et al. 2002). The endocytic pathway begins near the physiological pH value 7.7 and drops to pH values 5.5-6.0 in endosomes and approaches pH 4.5-5.0 in lyosomes (Mellamn et al. 1986). Therefore, supramolecular nanoparticles that are responsive to pH can be designed to selectively release their payload in tumor tissue or within tumor cells.

Such pH-responsive polymeric carriers mimic the transport mechanism of a variety of viruses and toxins which are directing cellular uptake and transport to the cytoplasm from the low pH endosomal compartment by the use of synthesized pH-responsive polymeric carriers ("encrypted polymers") (Murthy et al. 2003). The pH sensitivity is provided through acid-degradable acetal bonds. Beside the cellular uptake, cytosolic delivery by disrupting endosomal membranes in a pH dependant fashion is enhanced. Encrypted polymers also significantly enhance the delivery of oligonucleotides and peptides to the cytoplasm of cultured macrophages. Another approach with acid-sensitive micelles uses polyethyleoxide (PEO)-dendrimer hybrids for the delivery of doxorubicin (DOX) (Gillies and Frechet 2005). Hydrophobic groups are thereby attached to the periphery of the core forming dendrimer block by the use of acid-sensitive acetal linkages such that the parameters for the release of DOX can be tuned.

In vaccine-development, controlled-release systems represent the second wave of strategies after direct-injection approaches (Stayton 2003). The biodegradable polymeric microencapsulation technology for timed protein-release has been extended to several polymer compositions and micro-particle processing technique (Hanes et al. 1997). These microspheres can be designed for sustained and controlled antigen release and for the incorporation of multiple antigens and adjuvants. They can also be synthesized with acid-sensistive groups to increase release at lower pH-values.

Drug delivery and tissue engineering: Drug release from engineered tissue scaffolds (as reviewed in Lavik and Langer 2004) can be used to manipulate the biochemical environment found at the interface of the scaffold with the surrounding tissue. The controlled release of drugs and growth factors aims at promoting wound healing, tissue formation and angiogenesis. Growth factors, for example, have been successfully incorporated into hydrogels to augment the development of tissues including bone (Burdick et al. 2002) and cartilage (Elisseeff et al. 2001) by releasing growth factors from microspheres (Nam and Park 1999; Benoit et al. 2000; Fu et al. 2003). Drug filled microspheres themselves have been assembled into scaffolds for generating tissue (Mahoney and Saltzman 2001) and, by combining microspheres containing different drugs, combinatorial release profiles can be generated to emulate the complex biochemical environment seen by cells in their native environment. This might become important to regulate the differentiation of stem cells for tissue engineering applications.

It must be emphasized that most of the processes and materials discussed above are still under development. They still have to pass clinical trials before they might enter the market in the next five to ten years.

Nanostructured membranes for drug delivery: Alternatively to releasing drugs from supramolecular structures, nano- and microcontainers sealed with semipermeable membranes of defined nanopore sizes are explored as delivery systems. Pores with diameters in the range of 10 to 500 nm and with high aspect ratios, for example, have been generated by anodic oxidation of alumina membranes (e.g. Jessinsky et al. 1998; Masuda et al. 1998; Heilmann et al. 1999; Kipke 2003; Diggle 1969), as shown in figure 3.112.

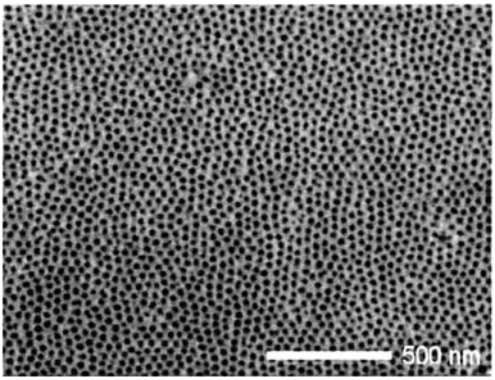


Figure 3.112: Top view of nanotubes in a porous Alumina membrane (with permission from S. Kipke 2003).

Such membranes regulate the diffusion controlled release of drugs from the container, whereby the diffusion rate is dependent on the number of pores and the pore size for particle sizes is smaller than the pore diameter

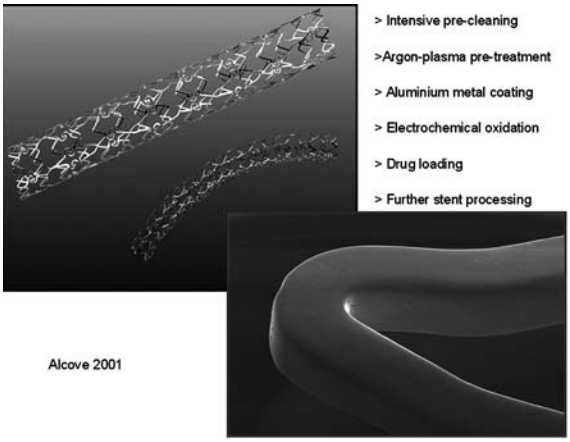


Figure 3.113: Stent coated with anodic oxidized Aluminum; Alcove GmbH 2001. With permission of Alcove GmbH.

(Kipke et al. 2003). Alumina nanopores have also found applications as drug delivery systems for stents (Alcove 2001) as displayed in figure 3.113 with the hope to prevent stent rejection after bypass surgery.

Microcontainers sealed by nanopores membranes can also be used to encapsulate enzymes, catalysts, adhesives, polymers, inorganic nanoparticles, latex particles or even biological cells. For example, nanoporous membranes with uniform and well controlled nanostructured pores with pore diameters down to 7 nm were used to encapsulate cells, for example pancreatic islets (Desai et al. 2004). If the cells can be kept vital for extended time periods in such synthetic microcontainers, the cells could be exploited to synthesize drugs of interest. Applications of the nanoporous membranes may thus range from cellular delivery to cell-based biosensing in vitro cell-based arrays.

Drug delivery coupled to magnetic nanoparticles: In biomedicine it is often advantageous to separate out specific biological entities from their native environment in order to concentrated samples. The two-step process involves (i) the tagging or labeling of the desired biological entity with superparamagnetic particles or beads, and (ii) the separation of these tagged entities via a fluid-based magnetic separation device. Superparamagnetic behavior is necessaries to assure the dispersion of the particles after separation. Magnetic separation has been successfully applied to many aspects of biomedical and biological research. It has proven to be a highly sensitive technique for the selection of rare tumor cells from blood, and is especially well suited to the separation of low numbers of target cells (McCloskey et al. 2003). A similar application is the use of superparamagnetic iron oxide nanoparticles (SPION) for drug delivery (Mornet et al. 2004; Pankhurst et al. 2003). Therapeutic drugs are administered intravenously leading to their general distribution, resulting in deleterious side-effects as the drug attacks normal, healthy cells in addition to the target tumor. Therefore, the objective of magnetically target drug delivery is to limit the systemic distribution of the cytotoxic drug by localizing the drug, which will also reduce the overall dosage required. In magnetically targeted therapy, a drug is attached to a biocompatible magnetic nanoparticle carrier which is mostly a bead with superparamagnetic nanoparticles embedded in a polymer matrix. When the particles have entered the blood vessels, external, high-gradient magnetic fields are used to concentrate the drug loaded beads at a specific target site within the body. Once the drug/carrier is concentrated at the target, the drug can be released using different methods like temperature, pH change or via enzymatic activity. Furthermore, SPION single particles have been used for transfection (Huth et al. 2004) by loading positively charged SPIONs with DNA. Such particles, with a hydrodynamic diameter of 50 to 80 nm can easily enter the cells using receptor mediated endocytosis mechanisms and a magnetic field gradient. Inside the cell, the DNA is liberated and might enter the nucleus. This method is called non-viral transfection and is under development for gene therapy.

In all these cases, a force has to act on the particles so that they move into the desired direction, for example across a blood vessel wall or into a tumor. The magnetically induced force has to be much larger as the hydrodynamic forces acting on a particle. According to equation 3.5 the superparamagnetic particles must show a high magnetization and additionally a high gradient of the magnetic field strengths is necessary to assure a movement of the beads:

$$\vec{F}_m = V_m \Delta\chi \nabla\left(\frac{1}{2}\vec{B}\times\vec{H}\right) \quad \text{(eq. 3.5)}$$

where $\vec{F}_m$ is the Force on the particle based on the external magnetic field, V_m is the magnetic active volume of the superparamagnetic particles inside the beads, H the magnetic field strength and B the magnetic flux density. The magnetization of the particles, expressed in equation 3.5 via the susceptibility χ depends for nanosized superparamagnetic particles also from the size as well as from the magnetic interaction between the particles.

On the other hand the hydrodynamic drag force, described by Stoke's equation, has to be overcome if the particle has to move in the desired direction. Taking this in account, the velocity u_z of a particle in a liquid like body fluid or blood is

$$u_z = \frac{V_{mag} M}{12\pi\eta r_{hydr}} \frac{dB}{dz} = \frac{r_{mag}^3 M}{9\eta r_{hydr}} \frac{dB}{dz} \qquad \text{(eq. 3.6)}$$

where r_{mag} is the magnetic active radius of the particle, r_{hydr} is the hydrodynamic radius of the coated particles and η the viscosity of the fluid. In the nanosized regime, the hydrodynamic radius of a particle can be much larger than the magnetically active radius. The reason for this is that the adsorbed molecules of the different layers are in the size range of nanometers. For example, a protein might have a diameter of 2.5–5 nm, or a DNA is 100 nm long whereas the single superparamagnetic iron oxide particle often has a radius of only 4 nm. In other words, the magnetic active core is too small to generate a force high enough to move the particle in the direction of the gradient of the magnetic field. This is the reason, why very often beads instead of single particles are used in separation devices and especially if the particles are designated to be injected in the blood stream. On the other hand, the transfection efficiency is strongly influenced by the size of the particles. Particles larger than 100 nm show a very low transfection rate.

Magnetic nanoparticles for cancer treatment: Magnetic materials for hyperthermia of biological tissue have been explored in principle for more than four decades in order to manifest a therapeutic effect on several types of tumors in animal experiments or by using cancer cells (Jordan et al. 2003; Jordan et al. 2000; Jordan et al. 2001; Jordan et al. 1999). Magnetic media were applied in several ways using glass ceramics, microcapsules, or suspensions of superparamagnetic nano particles. Preferentially, several types of magnetic oxides were used, among which, magnetite and maghemite are very promising candidates since there biocompatibility was already proven. In any case, a large heating power of the material is desirable in order to reduce the amount of material to be applied to the patient.

The physical basis of the heating of SPION particles by an alternate magnetic fields (as reviewed by Rosensweig 2002) is can be described by the Debye model. The dielectric dispersion in polar fluids and the observation that the finite rate of change of M in a suspension of SPION particles in a liquid or solid matrix imply that M will lag behind H. For small field amplitudes and well dispersed particles with negligible interactions between the SPION, the response of the magnetization of such a material to an alternate magnetic field can be described in terms of its complex susceptibility, where both χ' and χ'' are frequency dependent. The out-of-phase χ'' component results in heat generation given by

$$P_{SPION} = \mu_0 \pi f \chi'' H^2 \quad \text{(eq. 3.7)}$$

with P_{SPION} = Power Loss; μ_0= permeability of free space; f = frequency; H = magnetic field strength which can be interpreted physically as meaning that if M lags H there is a positive conversion of magnetic energy into internal energy. χ'' itself depends strongly from the frequency and shows a maximum if the frequency of the applied field similar to $1/\tau$ where τ is the magnetic relaxation time. This relaxation time is a function of the magnetic anisotropy energy K and of the volume of the particle V:

$$\tau = \tau_0 \exp(KV / k_B T) \quad \text{(eq. 3.8)}$$

Equation 3.8 shows that the relaxation time of superparamagnetic particles depends strongly on the size of the particles. Best results for medical applications were observed with monosized particles in the size range of 12 to 15 nm. The frequency and strength of the externally applied AC magnetic field used to generate the heating is limited by deleterious physiological responses to high frequency magnetic fields (Reilly 1992). These include stimulation of peripheral and skeletal muscles, possible cardiac stimulation and arrhythmia, and non-specific inductive heating of tissue. Generally, the useable range of frequencies and amplitudes is considered to be λ = 0.05-1.2MHz and H = 0-15 kA/m. The amount of magnetic material required to produce the required temperatures depends to a large extent on the method of particle administration. For example, direct injection allows greater quantities of material to be localized in a tumor than methods employing intravascular administration or antibody targeting, although the latter two may have other advantages like a much lower danger to disturb the tumor and to initiate metastases. Choosing high power magnetic particles combined with appropriate technical parameters of the external radio-frequency-field, very small amounts of magnetic nano particles in the order of tenth of milligrams per ml tissue may easily be used to rise the temperature of biological to induce cell apoptosis.

3.3.2 B: Nanoanalytical Tools

B 1a: In vivo Optical Imaging at the Nanoscale

To learn more about the spatial organization of molecules in living cells, novel tools are needed that allow to image molecules and supramolecular assemblies at the nanoscale in living cells. Optical microscopy has been the major workhorse harnessed by biologists for imaging and probing dynamic cellular events since visible light probes living cells noninvasively. The versatility of optical techniques is due to the large selection of fluorescent markers combined with their specificity in molecular staining and tagging. In addition to revolutionizing structural studies, functional studies have been made possible by tagging fluorophores to molecules of interest, by utilizing the varying responses of fluorescent probes to local environments, and by using green fluorescent protein and its derivatives as fusion-protein tracers.

Since 1989, single molecule spectroscopy has evolved from initially demonstrating the possibility to detect the emission of single molecules at low temperatures, to probing single molecules in biological samples (for reviews s. Kulzer and Orrit 2004; Peterman et al. 2004). Single molecule detection techniques provide a direct way to quantify biological events in single cells with a high spatial and temporal resolution (Sako and Yanagida 2003). Imaging single molecules in biological samples is frequently done by combining far-field fluorescence microscopy with total internal reflection (TIR):

Far-field optical microscopy using visible light has been limited in the past to a resolution of about 250 nm, as determined by the diffraction limit of light, and does therefore not allow to spatially resolve the shape of subcellular nanosystems. Accordingly, a single fluorescent molecule produces a diffraction limited light spot in the image plane with a Gaussian intensity profile while any particle shape information is lost. Fitting intensity profiles of single molecules does provide their center positions with accuracies below 100 nm, even using far-field optics, but only if the molecules are spaced far enough apart such that their intensity profiles do not overlap. Fluorescence resonance energy transfer (FRET) is then widely used to probe distances between adjacent particles which are labeled with energy donors and acceptors. The energy transfer efficiency is highly sensitive to the distance of the fluorophores in the 1-10 nm range which makes FRET an ideal tool to probe distances, and distance changes *in vitro* or in living cells, including conformational changes and molecular binding events, even at the single molecule level (for reviews s. Kulzer and Orrit 2004; Zhuang and Rief 2003).

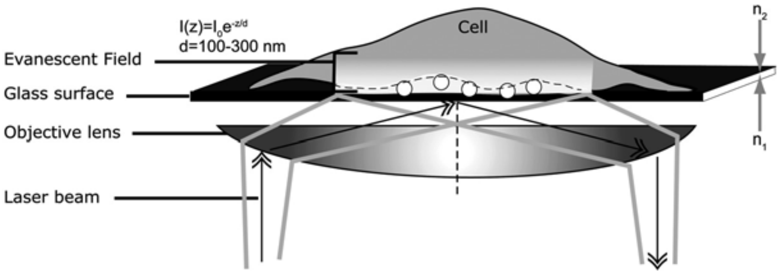


Figure 3.114: Total internal reflection fluorescence microscopy (Adopted from Sako and Yanagida, 2003).

In total internal reflection fluorescence (TIRF) microscopy a light beam illuminates the interface between two media at an angle greater than the critical angle of total internal reflection (which is 61° at the glass/water interface). The 'evanescent field' that penetrates the aqueous medium exponentially decays with distance from the interface with a typical decay length of several hundreds of nanometres. In contrast, the height of various cellular regions varies from ~0.1 μm in lamellipodia to ~10 μm at the nucleus. Typical spacings between the ventral cell surface and the glass surface are ten to a few hundred nanometres. The red and purple circles represent fluorescent molecules that are visible and invisible in TIRF.

Total internal reflection fluorescence (TIRF) microscopy is a widely used technique for single molecule detection both *in vitro* and *in vivo.* By limiting the number of excited fluorophores to those that are in close proximity to the surface as shown in figure 3.114, the TIRF geometry reduce significantly the background noise since the evanescent optical field that penetrates the opposing medium under the total internal reflection geometry decays exponentially with the distance from the interface, typically within a few hundreds of nanometres. In combination with FRET, TIRF also gave insights into the dynamics of enzymatic reactions and of DNA-protein interactions (Sako and Yanagida 2003). Furthermore, in 2000, the biological reactions of ligand and receptor proteins and the movements of lipid molecules were first visualized as single molecules on the surface of living cells. Since then, ion channels, small G proteins and their effectors, cell-adhesion proteins, viral proteins and components of the cytoskeleton have been visualized as single molecules in living cells (as reviewed in Hess et al. 2004).

To resolve structural features of biological samples at the nanoscale, more refined optical imaging schemes with nanometer resolution are required that circumvent the diffraction limit of light. Several novel schemes have been realized recently (for reviews s. Bastiaens and Hell 2004). (1) Scanning near-field optical microscopy (SNOM) circumvents the diffraction limit of conventional light microscopy by scanning samples with the evanescent tail of light passing the aperture and is able to achieve optical resolutions substantially below 100 nm. However, in the field of cell biology SNOM has been rarely applied, probably because previous techniques for sample-distance control are less sensitive in liquid than in air (Hoppener et al. 2005). Recently, development of a distance control based on a tuning fork in tapping mode allowed to visualize single nuclear pore complexes kept in physiological media (Kubitscheck et al. 2005). (2) Optical imaging at the nanoscale has recently been made possible with far-field optics. Combining wide-field collection with interference in the emission and excitation leads to an axial resolution better than 100 nm (Gustafsson et al. 1995), and by coherently adding the spherical wavefronts of two opposing lenses, two-photon excitation 4Pi-confocal fluorescence microscopy has achieved three-dimensional imaging with an axial resolution 3-7 times better than confocal microscopy (Bahlmann et al. 2001). Hell and co-workers then used the stimulated emission depletion (STED) technique to quench the fluorescence surrounding a very small volume, thus, effectively increasing the resolution in both lateral and axial directions (Hell 2003). Recently, they combined the use of 4Pi microscopy with STED and achieved an unprecedented optical resolution of 28 nm (Gugel et al. 2004). Accordingly, images of live cells reveal far greater details (Gugel et al., 2004). (3) Scanning surface confocal microscopy was developed for simultaneous nanoscale imaging of surface topography and fluorescence of living and fixed cells (Gorelik et al. 2002). In this confocal setting, a nanopipette was scanned over the cell surface and the ion current between the pipette and the sample was used to control their distance. This method enables to image the surface of living cells with high topographic resolution both laterally and vertically, typically 75-150 nm and 10-20 nm, respectively. This method was applied to record the interaction of single virus-like particles with the cell surface and demonstrated that single particles sink into the membrane in invaginations reminiscent of caveolae or pinocytic vesicles (Gorelik et al. 2002). Finally, (4) Swan and co-workers introduced a new interferometric technique, spectral self-interference fluorescence microscopy, that determines the axial position down to less than a nanometer by using the spectral signature of fluorescent markers placed above a reflecting surface (Swan et al. 2003). While scientists have recognized for decades that either energy transfer, the modulation of the excitation field by standing waves, or the interference in the emission can lead to significant modulation of fluorescence emission intensities due to constructive or destructive interference effects perpendicular to the surface, spectral self-interference fluorescence microscopy is based on a similar scheme. It interrogates the spectral intensity distribution of interference fringes instead of the variation of intensity with distance to the surface. It also requires a different configuration of the substrate: the separation between the fluorophore and the reflecting substrate is much greater, with typically 10 wavelengths as shown schematically in figure 3.115.

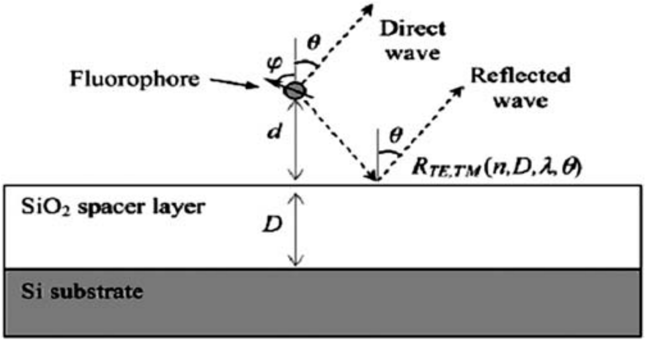


Figure 3.115: Spectral self-interference fluorescence microscopy. Schematic drawing of the geometrical arrangement of the fluorophore and the reflective substrate.

The silicon dioxide layer thickness D is typically 5 μm, while d is a few nanometers. Note that, while the dimension of interest is on the nanometer scale, the spacer layer thickness is large (on the order of 10 wavelengths) and the dominant reflection takes place at the SiO -Si interface. A long path length difference between direct and reflected light means that only a small change in the wavelength is needed to go from constructive to destructive interference. The effect of the long path difference is included in the wavelength-dependent reflection coefficient defined for the system. This results in oscillations or fringes in the emission spectrum – a unique spectral signature of the height of the emitter above the reflector. Small height differences produce shifts in the fringes and changes in the period of oscillation, although the latter are less apparent. The broader the emission spectrum, the more information is collected and the more precise the height determination. The distance above the mirror can be determined solely from the oscillations within the spectrum (from Swan et al. 2003).

In summary, fluorescence microscocopy at the nanoscale will play a dominant role for the exploration of subcellular processes. The advances will come from combining numerous ways of specific labelling to visualize dynamic molecular events with advanced single molecule detection and nanoscale imaging schemes to analyse complex intracellular events in living cells.

B 1a: Other Nanoscale Imaging Techniques

Imaging with Angstrom resolution is currently only possible under *in vitro* conditions by various techniques, including scanning probe microscopy as discussed in earlier chapters, as well as electron microscopy and holography which we will now be discuss briefly. When a potential exists in the path of an electron beam, the phase of the electron wave varies in proportion to the distance of the potential that the beam passes through. With a specimen

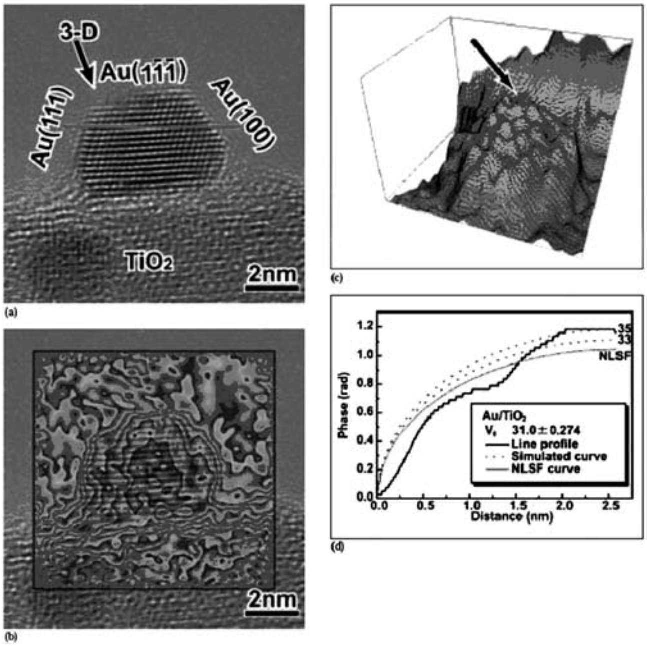


Figure 3.116: High resolution electron microscopy image (a) and the phase image (b) reconstructed from the hologram of the Au/TiO_2 catalyst with a size ~5 nm. The phase image (b) was amplified 30 and overlapped on the HREM image (a). (After Ichikawa et al. 2003).

without an electric or a magnetic field, the electron wave is affected by the mean inner potential, i.e. the thickness of the specimen. The conventional transmission electron microscopy (TEM) methods use only the information on the amplitude component of an electron beam, and mostly neglect the information on the phase change by the mean inner potential. The spatial resolution can be enhanced towards the Angstrom scale by recording the phase shift in a hologram, i.e. electron holography, and reconstructing the phase image. This also provides 3D resolution that is difficult to obtain using the HREM technique. Images of the 5 nm gold particle supported on TiO_2 are shown in figure 3.116. With respect to biological applications, it should be noted that although electron holography provides Angstrom resolution, it is limited to using dried or frozen samples, and so cannot probe dynamic events.

B 1b: Tracking Molecules and Probing Molecular Dynamics and Kinetic Events in Living Cells

An understanding of how biological nanosystems work together synergistically within cells, thus enabling the sensing and processing of a myriad of spatiotemporal stimuli, which ultimately result in coordinated responses within and between cells requires the development of an integrated model of the cell. This includes the development of a physical picture how the molecules involved in signaling cascades and in other cellular processes cooperate, knowledge that goes far beyond mapping intermolecular binding strengths and their overall molecular concentrations. Pieces to the puzzle of how cells work can only be derived from a range of techniques that probe biophysical and chemical characteristics of molecules and their interactions under in vivo conditions. Recently developed nanotools as partially discussed in previous sections are beginning to promise major progress in establishing a quantitative and physical model of the cell as demonstrated already for a few selected biological systems:

Tracing single molecules and particles: It is highly desirable to trace single molecules and particles with high spatial and temporal resolution as they move through the cell, from their synthesis to degradation, and potentially to probe the local interactions and forces that they encounter. Single-molecule techniques in biological systems and living cells have allowed probing the location and movements of molecules and particles. A few selected examples will highlight recent progress derived from nanotools.

The determination whether molecules are subject to random Brownian motion, diffusion, or active transport, is essential to establish spatiotemporal trajectories of single molecules within living cells. Tracking single molecules also provides insights how their often heterogeneous environments in which they are embedded affect their spatial position and function. For example, the movement of single sodium-driven rotors from a bacterial ATP synthase within a membrane was tracked at the subnanometer resolution using time-lapse AFM topographs (Muller et al. 2003). Within one trajectory, individual rotors can undergo movements assigned to either free or obstacled diffusion. Optical tweezers and single particle tracking revealed that the lateral mobility of single transmembrane receptors (λ-receptor) within the outer membrane of a living *Escherichia coli* bacterium is restricted presumably due to the fact that its periplasmatic domain is physically coupled to the underlying peptidoglycan layer (Oddershede et al. 2002). Even single copies of RNA molecules were tracked for many hours in living Escherichia coli cells revealing distinct characteristic dynamics of RNA molecules, all consistent with the known life history of RNA in prokaryotes (Golding and Cox 2004): localized motion consistent with the Brownian motion of an RNA polymer tethered to its template DNA, free diffusion, and a few examples of polymer chain dynamics that appear to be a combination of chain fluctuation and chain elongation attributable to RNA transcription. Finally, QDs were used to study the lateral movement of individual GlyRs, the main inhibitory neurotransmitter receptor in the adult spinal cord in living neurons (Dahan et al. 2003).

The emerging possibilities to optically trace single particles in living cells also provide novel insights into the pathways of viral infections (Gorelik et al.

2002; Lakadamyali et al. 2004). Most viruses enter cells via receptor-mediated endocytosis and then progress to late endosomes where viral fusion leads to the release of the viral genome. However, the entry mechanisms used by many of them remained unclear. Also largely unknown was the way in which viruses are targeted to cellular endocytic machinery. By tracking the interaction of single viruses with cellular endocytic structures in real time using fluorescence microscopy (s. figure 3.117), the entry mechanisms of influenza viruses was studied virus by virus thereby revealing multiple influenza entry pathways (Gorelik et al. 2002; Lakadamyali et al. 2004; Lakadamyali et al. 2003).

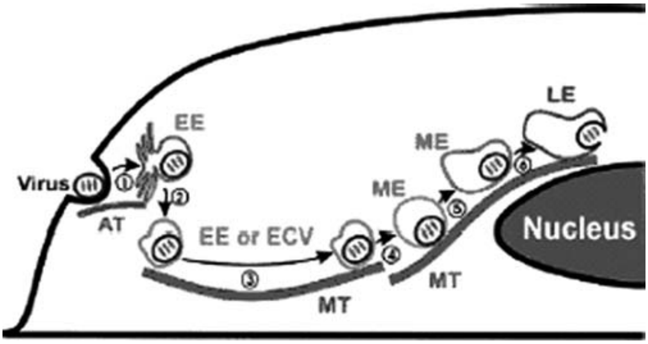


Figure 3.117: Tracking single virus particles in a cell allowed to refine the model of the endocytic viral pathway toward late endosomes.

(permission granted: Lakadamyali M et al. (2003) Visualizing infection of individual influenza viruses. National Academy of Sciences, U.S.A.)

(1) The virus is internalized and transported to the early endosome (EE) in an actin (AT)-dependent way (stage I movement). *(2)* The virus-containing endocytic compartment leaves the EE, still at the extracellular pH. This may occur either through a virus-bearing endocytic carrier vesicle (ECV) budding from the EE or the membrane-rich tubular region of the EE recycling to leave a more vesicular EE that contains the virus. *(3)* The ECV or vesicular EE is transported to the perinuclear region via a dynein-directed movement on a microtubule (MT) (stage II movement). *(4)* The ECV or vesicular EE matures into a maturing endosome (ME) by changing the membrane-bound motor protein activity (transition from stage II to stage III movement). *(5)* The endosome further matures by changing its pH from the extracellular value to about pH 6 (initial acidification as indicated by the change in fluorescence ratio between CypHer 5 and Cy3 conjugated to viruses). *(6)* Further acidification brings the pH of the endosome to the late endosomal (LE) value, pH 5 (second acidification as indicated by viral fusion) (from Lakadamyali et al. 2003).

Single-molecule visualization in living cells thus opens new avenues for quantifying cellular reactions and will be indispensable for further understanding the molecular mechanisms of cellular responses. This also includes tools to observe molecular events and to track the distribution and kinetics of molecular probes, drugs, and environmental agents within cells, organs or humans under physiological conditions.

High resolution structural models derived from molecular dynamics (MD) simulations: molecular dynamics simulations are essential to study the conformational dynamics of biomolecules and molecular complexes. Simulations on ion channels, for example, revealed detailed structural insights into the mechanisms of hydrophobic gating in K channels where a narrow (<0.4 nm) hydrophobic region can form a functionally closed gate in the channel and can be opened by either a small increase in pore radius or an increase in polarity (Beckstein et al. 2003). MD also allows investigations of the microscopic mechanisms by which ions and molecules pass through transmembrane pores. The bacterial pore OmpF from the outer membrane of Escherichia coli, for example, is considered to be the main pathway for certain antibiotics. MD revealed insights into the reaction path for the translocation of an antibiotic through the pore protein, insight that may help in the design of more efficient antibiotics (Ceccarelli et al. 2004). Another example is the flagellar motor of bacteria where simulations provide detailed insights into how a passing ion can generate torque in the protein structure, how this torque is then transmitted to the rotor surface and can trigger the motor to rotate (Schmitt 2003). Simulations are thus essential to understanding the complex dynamics of biological nanosystems.

Kinetics of molecular processes: Equally important is to obtain quantitative information of the kinetics of local transport, of molecular assembly and disassembly processes and of chemical modifications of all molecular constituents associated with a given pathway. Such information is essential to establish quantitative models how signaling and metabolic pathways cross-talk and how they are regulated in hierarchical manners. An example of the advances that come with single molecule detection capabilities is the following: bacteria are equipped with effective means for withstanding damages from hazardous chemicals – namely, actively extruding such chemicals to lower their intracellular concentrations. By following single fluorescent-labeled drugs as they enter and leave a bacterial cell, the kinetics, efficiency, and regulation of the cell's extrusion pump machinery could be probed (Xu et al. 2003). In contrast, averaged ensemble measurements cannot distinguish between extrusion-mediated efflux rates and the influx rate arising from passive diffusion into cells. Moreover, many regulatory molecules such as transcription factors are often present in vanishingly small quantities so that the number and location of individual molecules is important and cannot be approximated by an average measurement over time or space. Such experimental and theoretical insights need to be integrated into computational models in an interactive process to ultimately establish quantitative predictions how cells respond to internal and external stimuli.

Fluorescence correlation spectroscopy (FCS): Beyond probing motion by tracking single molecules or particles in living cells, FCS can measure dynamics of fluorescent molecules in cells over a large dynamic range, from the GHz- to the Hz-region (for reviews s. Elson 2001; Dittrich et al. 2001; Medina and Schwille 2002; Gosch and Rigler 2005). The foundations for FCS were laid in the early 1970s, but this technique did not become widely used until single-molecule detection became routine. FCS measures spontaneous fluctuations in the fluorescence emission of small molecular ensembles illuminated by a thin beam of excitation light. These fluctuations are processed statistically to yield an autocorrelation function thus providing information about a multitude of parameters, such as local concentrations, molecular mobility, chemical reactions, and state of aggregation and molecular interaction of fluorescently labeled molecules. Performed within diffraction-limited confocal volume elements, FCS provides an attractive alternative to photobleaching recovery methods for determining intracellular mobility parameters of very low quantities of fluorophores.

Fluorescenece speckle microscopy (FSM): FSM uses low levels of fluorescent proteins to create fluorescent speckles in high-resolution fluorescence images of living cells. The dynamics of speckles over time have been used to encode subunit turnover and motion of the cytoskeletal polymers and focal adhesion proteins (GFP-vinculin) (Adams et al. 2004). Furthermore, cell migration is initiated by extension of the actin cytoskeleton at the leading edge. Computational analysis of FSM movies of migrating epithelial cells revealed that this process is mediated by two spatially colocalized but kinematically, kinetically, molecularly, and functionally distinct actin networks (Ponti et al. 2004). A lamellipodium network assembled at the leading edge but completely disassembled within 1 to 3 micrometers. It was weakly coupled to the rest of the cytoskeleton and promoted the random protrusion and retraction of the leading edge. Productive cell advance was a function of the second colocalized network, the lamella, where actomyosin contraction was integrated with substrate adhesion.

B 1c: Force Measurements on single molecules, particles and cells

Force is an important regulator of cell and tissue function, but how is mechanical force transduced into biochemical signals? Recent advances in atomic force microscopy, optical laser tweezers and computational tools now allow probing the response of single molecules to force and to establish how structure, force and function are interrelated. Figure 3.118 shows the range where the mechanical properties of single molecules can be probed by force spectroscopy. The lower and upper force range is given by the region of limited thermal stability of molecular structures and by the rupture of covalent bonds, respectively.

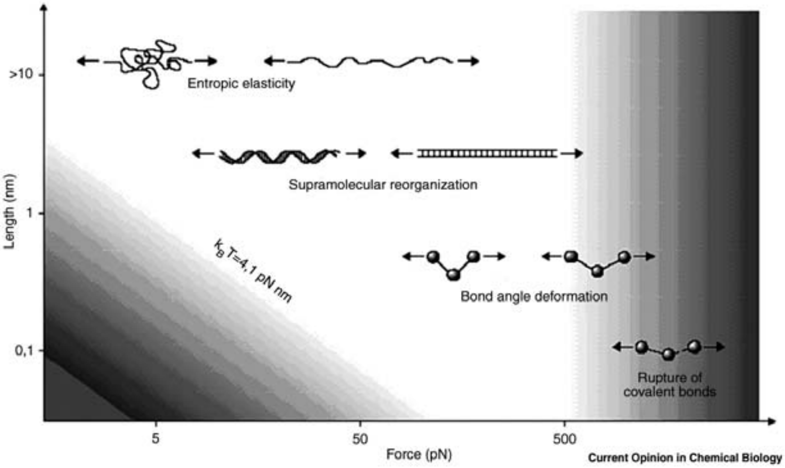


Figure 3.118: Typical forces and length scales in single molecule force spectroscopy. (permission granted: reprinted from Current Opinion in Chemical Biology, 4, Clausen-Schaumann H et al. (2000) Force spectroscopy with single bio-molecules, 524–530, with permission from Elsevier)

The experimentally accessibility of mechanical information is limited to the light areas of the plot. The shaded area in the lower corner indicates the region of limited thermal stability of molecular structures (length multiplied by force = thermal energy, k_BT = 4.1 pN at room temperature). The upper limit to the accessible experimental force range is determined by the rupture of covalent bonds at several nanoNewton (Clausen-Schaumann et al. 2000).

Quantification of intra- and intermolecular interactions: Quantification of biomolecular interaction by studying their response to controlled mechanical perturbations has evolved into a powerful tool for materials and life sciences. Single-molecule manipulation using fine glass needles, optical tweezers or atomic-force microscopy has become widely applied to the study of the single molecule mechanics of RNA, DNA (Zhuang and Rief 2003; Clausen-Schaumann et al. 2000; Rief et al. 1999) and proteins (Engel and Muller 2000). *In vitro*, the unfolding trajectories of RNA and many proteins have been mapped experimentally (Engel et al. 1999; Carrion-Vazquez et al. 2000; Oberhauser et al. 2002; Carrion-Vazquez et al. 2003) and by computer simulations (Lu et al. 1998, Harlepp et al. 2003, Isralewitz et al. 2001; Thomas et al. 2002; Craig et al. 2004). Force measurements also allowed to map various intermolecular interactions, including protein-ligand (Moy et al. 1994; Merkel et al. 1999; Strunz et al. 2000), protein-protein and protein-DNA interactions (Fotiadis et al. 2002; Kuhner et al. 2004; Parbhu et al. 2002). As shown in figure 3.119, the force-induced unfolding pathway can differ from that induced by thermal or chemical denaturisation (Carrion-Vazquez et al. 1999; Zhuang and Rief 2003).

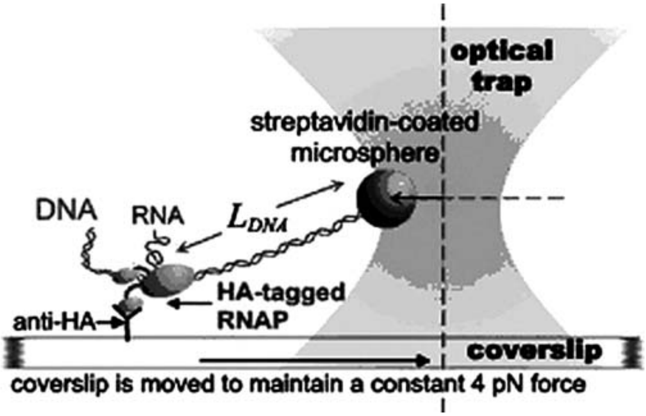


Figure 3.119: Study of RNA polymerase (RNAP) in action by optical tweezers. (permission granted: reprinted from Molecular Cell, 14, Adelman K et al. (2004) Molecular Mechanism of Transcription Inhibition by Peptide Antibiotic Microcin J25, 753–762, with permission from Elsevier)

A stalled ternary elongation complex composed of *E. coli* RNA polymerase (RNAP) an HA-epitope tag, template DNA, and a short RNA was specifically immobilized on a coverslip surface through interaction with a nonspecifically adsorbed anti-HA antibody. A streptavidin coated microsphere was attached to a biotin located on the downstream end of the DNA. The microsphere was held at a fixed position relative to the optical trap throughout elongation. During transcription, the template DNA was pulled through the RNAP, leading to a decrease in length of downstream DNA (*L*DNA). Feedback control moved the coverslip toward the optical trap so that a constant force of 4 pN was maintained on the RNAP (from Adelman et al. 2004).

In vivo, the force acting on single molecules has been tracked, for example, by attaching molecules of interest to a bead, which serves as a handle for trapping the particles within optical tweezers and then tracing both position and forces acting on the bead and its attached molecules with microsecond resolution (s. 3.2). Optical tweezers allow to apply loading forces to nano- and micro-scale objects in a controlled manner and then to record the response of the object. Figure 3.119 shows how the rates by which single *E. coli* RNA polymerase (RNAP) molecule elongates RNA has been measured by immobilizing a RNAP molecule bearing an HA-epitope tag, template DNA, and a short RNA on a coverslip. A streptavidin coated microsphere was then attached to a biotin located on the downstream end of the DNA and trapped by the optical tweezers.

Alternatively, the tip of an atomic force microscope, while often used to measure the topography of an object, can operate in a similar way to measure the response of the system to mechanical perturbations (for review s. Fotiadis et al. 2002). For example, by first contacting a single membrane protein embedded in a bacterial surface layer with the tip of the AFM and then pulling the tip back, the target protein can be unzipping in a controlled manner and ultimately removed while measuring force/extension curves as seen in figure 3.120 (Engel and Muller 2000). Nanodissection with the cantilever and high-resolution imaging of a single photosynthetic core complex in native membranes by AFM allowed the demonstration that the L and M subunits exhibit an asymmetric topography which may influence the energy transfer within the core complex (Scheuring et al. 2003). The next challenge is to develop molecular force probes that can be employed in cell cultures to visualize force-induced protein unfolding events in living systems. Several ideas are currently explored how to design such molecular force probes, for example, they could be based on fluorescence resonance energy transfer (Baneyx et al. 2002), on proteins that change their spectroscopic signature upon unfolding, e.g. derived from green fluorescent proteins (Dietz and Rief 2004), or they could serve as differential reference bonds of known strength such as short DNA duplexes (Albrecht et al. 2003).

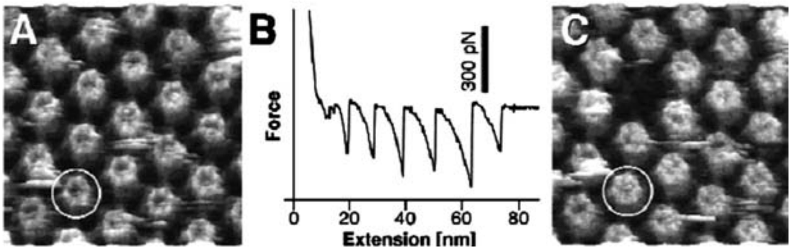


Figure 3.120: Dissecting a single protein from a membrane by atomic force microscopy.

(permission granted: Engel A, Müller DJ (2000) Observing single biomolecules at work with the atomic force microscope. Nat Struct Biol, 7 (9), 715–718)

Conformational change and single molecule force spectroscopy of the HPI layer. *a*, Inner surface of the HPI layer showing hexameric pores. Individual pores exist in plugged or unplugged conformations. *b*, After taking the image the AFM stylus was pushed onto the HPI surface and retracted. Occasionally, the force extension curve recorded showed a sawtooth like pattern with up to six force peaks of ~300 pN each. *c*, The same surface area imaged after recording the force extension curve shows that an entire hexameric pore was removed. The emanating arms of the adjacent pores to which the unzipped hexamer was connected are clearly visible. A few individual pores have changed their conformations between recording the first and the second topographs (circled). This conformational change is fully reversible and can be observed over hours. The topographs exhibit a vertical range of 3 nm, while the center-to-center distance between hexamers is 18 nm (Engel and Muller 2000).

While the above mentioned tools typically probed one molecule at the time, future studies need to be conducted in a highly parallel fashion on large arrays of spatially isolated molecules to improve the overall throughput. First steps have been taken using optical tweezers and the AFM. While conventional tweezers use Gaussian light beams, which cannot trap particles in multiple locations more than a few microns apart in the axial direction because of the beam distortion by the particle and subsequent strong divergence from the focal plane, the simultaneous micromanipulation in multiple planes was accomplished by using a self-reconstructing light beam (Garces-Chavez et al. 2002). In AFM, the development of cantilever arrays, namely the multipede as discussed in sections 3.2 and 3.4 will allow to fabricate surface textures in a highly parallel fashion, as well as to probe or actuate biological samples in many locations at the same time. Such an approach lends itself also for the quantification of single-molecule binding forces in parallel assays (Blank et al. 2003).

Insights how bacteria adhere to surfaces: Nanotools also provided fundamentally new insights into the mechanics how bacteria adhere and move along interfaces. While synthetic adhesives weaken if strained, E. coli has evolved bonds whose strength can increase under force. *E. coli* is coated by long hair, so-called fimbriae, each of which carries an adhesin at its outer tip that specifically recognizes and binds to carbohydrates. If shear flows that were initially thought to wash off bacteria from surfaces are applied, the bacterial adhesin switches from low to strong binding resulting in tight binding of bacteria to the surface (Thomas et al. 2002; Thomas 2004). Bonds that strengthen under force are also referred to as “catch bonds” (Dembo et al. 1988; Barsegov et al. 2005; Konstantopoulos et al. 2003; Marshall et al. 2003). Computer simulations how force impacts the structure of this adhesion, combined with tools of molecular biology where point mutations were introduced at specific locations of FimH, allowed to gain first insights into a sophisticated engineering principle how E. coli bacteria might circumvent the force-weakening of bonds that is so common for most receptor-ligand interactions (Evans et al 1999; Thomas et al. 2004; Thomas et al. 2002).

Optical tweezers provided insights into a flagellum-independent mechanism by which some bacteria move across surfaces. This so-called “twitching” mobility is involved in bacterial colonization of surfaces during vegetative growth and enables bacteria to form complex colonial structures in biofilms and fruiting bodies (Merz et al. 2000). Specifically, twitching entails extending, tethering, and then retracting type IV pili (Maier et al. 2004). Each pilus retracts at a constant speed unless there is a resisting force, in which case it slows down and stalls. Although individual pili likely depolymerize into subunits within the membrane, how these changes generate force remains to be determined. AFM and optical tweezers thus provide sensitive new means for studying the physical properties and dynamics of such biomolecules and their assemblies.

Mechanosensing of cells: The physical aspects of many cellular functions, including cell migration, cell shape dependent and physical aspects regulating gene expression, are not understood despite the fact that genome sequencing was critical to identify the molecular players involved in various cellular processes. The emerging tools of Nanotechnology and modern cell biology are beginning to provide the means to investigate many of the physical aspects of complex cellular processes. Understanding at the molecular level how cells sense and respond to mechanical forces, a field to which the development of nanotools can bring about significant progress, requires measurements of the mechanical properties of biomolecules and their unfolding pathways (as reviewed above) and how forces acting on proteins change their functional states (Gao et al. 2003; Sukharev and Corey 2004; Tamada et al. 2004; Vogel and Baneyx 2003). At the systems level, new tools are emerging to probe with high spatial and temporal resolution the forces cells apply to their environments (Balaban et al. 2001; Tan et al. 2003; du Roure et al. 2005), to learn how the linkage between the extracellular matrix and the cytoskeleton is stabilized by mechanical force (Choquet et al. 1997; Riveline et al. 2001; Geiger and Bershadsky 2001; Mack et al. 2004, Katsumi et al. 2005), and to identify major intracellular players that are involved in force sensing and force generation (Khan and Sheetz, 1997, Choquet et al. 1997, Giannone et al. 2003; Geiger et al. 2001) and how these players are physically connected to each other. Forces generated by the interplay of cells with their surrounding matrices (Vogel et al 2003; Geiger and Bershadsky 2001; Georges and Janmey 2005) are transmitted through protein-protein interactions that rely upon formation of integrated networks between matrix, membrane and cytoskeletal components (as further reviewed by Charras and Horton, 2002; Janmey and Weitz 2004). Thus they are susceptible not only to biochemical transformations, but also to functional changes imposed by mechanical forces. Deciphering how cells sense and respond to mechanical forces is thus a major future challenge (mechanotransduction).

One of the key challenges is to learn at the molecular level how mechanical forces are converted into biochemical cues. This requires the development of high resolution structural models how force changes the structure of proteins involved in mechanosensing and thus regulates the exposure of otherwise cryptic molecular recognition sites. Steered molecular dynamic (SMD) simulations have been successfully applied in the past to study the mechanical properties of proteins and their unfolding pathways, and many SMD predictions have already been experimentally verified. For example, SMD allowed identification of the positions of critical force-bearing backbone hydrogen bonds that have to be broken in order to unravel single titin modules (Lu et al. 1998). These positions were later confirmed by atomic force microscopy (Carrion-Vazquez et al. 1999). AFM also confirmed SMD predictions regarding the relative mechanical stability of various FnIII modules, verifying that SMD and AFM probe the same energy barriers (Krammer et al. 2002) (Craig et al. 2004; Oberhauser et al. 2002). Other experiments were successfully guided by SMD predictions. This includes a structural model of how the bacterial adhesion FimH is mechanically switched into a long-lived catch-bond state (Krammer et al. 2002). Experimentally, it was demonstrated that cell contractility is sufficient to mechanically unfold the extracellular matrix protein fibronectin (Baneyx et al. 2001; Baneyx et al. 2002), as well as the intracellular protein p130Cas (Tamada et al. 2004). In case of p130Cas, unfolding is needed to expose cryptic tyrosine phosphorylation sites which triggers further downstream cell signaling events. Once more information is available how proteins and protein complexes deform if stretched mechanically, experimentally testable models can be established how force affects outside – in cell signaling and force is used by cells to regulate the coupling of force –sensitive intracellular molecules to cell signaling networks.

In the future, combining various nanoanalytical tools, including single-molecule visualization, single-molecule-manipulation and single-molecule-electrophysiology techniques will be important to allow us to further understand the complex interplay of various nanosystems within living cells. Ultimately, the goal is to address one of the major challenges, how all the components are integrated to work in synchrony in the "cell as a machine". Integration of molecular components requires that they are physically coupled to each other. Thus they are susceptible not only to biochemical transformations, but also to functional changes imposed by mechanical forces.

3.3.3 B & C: Nanotechnology and Systems Biology

The Medicine of today is still mainly focused on developing therapies for preexisting diseases, typically late in their progression (Hood et al. 2004). Addressing symptoms more efficiently or detecting early onsets of diseases, however, requires a far better and quantitative understanding of how cells work and advances in many fields of Nanotechnology are beginning to provide urgently needed new tools. High throughput gene expression analyses revealed that transcriptional controls regulate only a fraction of cellular activities. Going from molecules to the next level of biological organization requires a quantitative understanding of how molecular components in cells interact with each other and how they are organized into functional modules for doing discrete tasks that any single classes of molecules cannot accomplish. While the tools of biochemistry and molecular biology have provided impressive knowledge about cellular components, an important challenge in biology is to decipher the hierarchical architecture of molecular networks and how they work. One of the most important unifying principles to have emerged from the past decade of cell signaling research concerns the physical location of the proteins involved (Bray 1998). Most molecules that carry and process messages inside and across living cells are associated with molecular clusters attached to cell membranes or the cytoskeleton. These clusters, variously termed signaling complexes, signaling cassettes, signaling modules, signalosomes, or transducomes, operate as computational units. Each receives one or more inputs and generates one or more specific outputs (Bray 1998). Nanotech tools now open completely new possibilities for the study of the hierarchical organization of functional modules under in vivo conditions by providing increasing spatial and temporal resolution. General principles that govern the structure and behavior of modules may be further discovered with help from engineering and computer sciences, from stronger interactions between experiment and theory in cell biology, and from an appreciation of evolutionary constraints (Hartwell et al. 1999). Biophysical constraints that result from macromolecular crowding, rates of diffusion, and the energy-cost of information have an important and perhaps controlling influence on the design of cell signaling pathways (Bray 1998). Proteins, nucleic acids, and small molecules are all part of this dense network of molecular interactions in a cell (Spirin and Mirny 2003). The architecture of molecular networks can reveal important principles of cellular organization and function, similarly to the way that protein structure tells us about the function and organization of a protein (Spirin and Mirny 2003). Comparison with experimental data and functional annotation of genes showed two types of modules that constitute "building blocks" of molecular networks: (i) protein complexes (splicing machinery, transcription factors, etc.) and (ii) dynamic functional units (signaling cascades, cell-cycle regulation, etc. (Spirin and Mirny 2003).

Central components are thereby genetically programmed networks (circuits) within cells (Heath et al. 2003). Within this context, disease is considered as a genetic or environmental reprogramming of cells to gain or lose specific functions that are characteristics of disease. Systems approaches to disease are grounded in the idea that disease-perturbed protein and gene regulatory networks differ from their normal counterparts which might be reflected in differences within multiparameter measurements of the blood (Hood et al. 2004). Such concepts are transforming current diagnostic and therapeutic approaches to medicine and, together with new technologies, will enable a predictive and preventive medicine that will lead to personalized medicine (Hood et al. 2004). Furthermore, quantitative insights into how networks work might come from the construction of artificial networks of transcriptional control elements in living cells which represents a new frontier for biological engineering (Yokobayashi et al. 2002). A combined rational and evolutionary design strategy for constructing genetic regulatory circuits already allowed to fine-tune the biochemical parameters of genetic networks and revealed that a nonfunctional simple genetic circuit containing improperly matched components can evolve rapidly into a functional one (Yokobayashi et al. 2002).

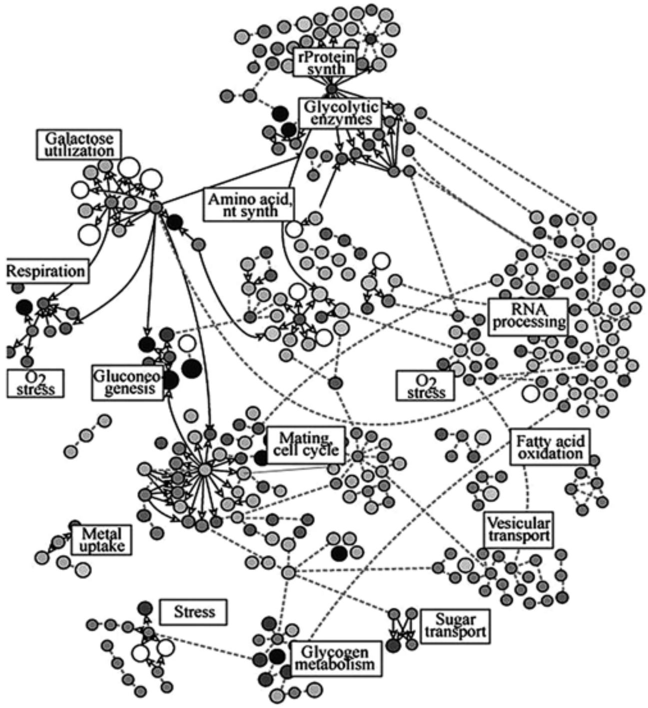


Figure 3.121: A network perturbation model of galactose utilization in yeast.
(adopted, reprinted with permission from Hood L et al. (2004) Systems Biology and New Technologies Enable Predictive and Preventative Medicine, Science, 306, 640–643, AAAS)

This model reflects the integration of mRNA levels for the 6000 yeast genes in each of 20 different genetic and environmental perturbations, as well as thousands of protein/protein and protein/DNA interactions from the literature. The software program Cytoscape integrated these data into a network where the nodes represent proteins (encoded by genes) and the lines represent interactions (blue straight lines, protein/protein interactions; yellow lines with arrows, protein/DNA interactions). A gray scale represents the levels of mRNA, with black being abundant levels and white very low levels. The red node indicates that this network model reflects the knockout of the corresponding gene (and protein) gal 4 – a key transcription factor. rProtein, ribosomal protein; nt, nucleotide; synth, synthesis (Hood et al. 2004).

Much insight into function of biological nanosystems and network regulation currently comes from the study of bacteria (as reviewed by Bray 1998; Vogel and Thomas 2004). For example, three transcriptional repressor systems of Escherichia coli that are not part of any natural biological clock were used to build a synthetic oscillating network (Elowitz and Leibler 2000). The network periodically induced the synthesis of green fluorescent protein as a read-out of its state in individual cells. The resulting oscillations, with typical periods of hours, were slower than the cell-division cycle, so the state of the oscillator has to be transmitted from generation to generation. This artificial clock displays noisy behavior, possibly because of stochastic fluctuations of its components. Such 'rational network design may lead both to the engineering of new cellular behaviors and to an improved understanding of naturally occurring networks (Elowitz and Leibler 2000). Networks of interacting proteins orchestrate the responses of living cells to a variety of external stimuli, but how sensitive is the functioning of these protein networks to variations in their biochemical parameters (Alon et al. 1999)? One possibility is that to achieve appropriate function, the reaction rate constants and enzyme concentrations need to be adjusted in a precise manner, and any deviation from these 'fine-tuned' values ruins the network's performance. An alternative possibility is that key properties of biochemical networks are robust; that is, they are insensitive to the precise values of the biochemical parameters. This issue was addressed in experiments using chemotaxis of Escherichia coli, one of the best-characterized sensory systems (Alon et al. 1999). They focused on how response and adaptation to attractant signals vary with systematic changes in the intracellular concentration of the components of the chemotaxis network. While some properties, such as steady-state behavior and adaptation time, showed strong variations in response to varying protein concentrations, the precision of adaptation was robust and did not vary with the protein concentrations. This is consistent with a recently proposed molecular mechanism for exact adaptation, where robustness is a direct consequence of the network's architecture (Alon et al. 1999). Finally, a fraction of a genetically homogeneous microbial population may survive exposure to stress such as antibiotic treatment (Balaban et al. 2004). Unlike resistant mutants, cells regrown from such persistent bacteria remain sensitive to the antibiotic as studied in microfluidic devices. Persistence was linked to preexisting heterogeneity in bacterial populations. Quantitative measurements led to a simple mathematical description of the persistence switch (Balaban et al. 2004; Kussell et al. 2005). The persistence phenotype is acquired via a spontaneous, reversible switch between normal and persister cells and that fitness loss due to slow persister growth pays off as a risk-reducing strategy (Kussell et al. 2005). Inherent heterogeneity of bacterial populations may be important in adaptation to fluctuating environments and in the persistence of bacterial infections.

Needs for new tools: Networks of interacting biomolecules carry out many essential functions in living cells, but the 'design principles' underlying the functioning of such intracellular networks remain poorly understood, despite intensive efforts including quantitative analysis of relatively simple systems (Elowitz and Leibler 2000). In illustration of a network is given in figure "A network perturbation model of galactose utilization in yeast". Biologists would thus like to analyze individual cells for the key measurements of systems biology, so that network hypotheses could be generated from individual cells (Hood et al. 2004). The mRNAs from single cells have been analyzed after polymerase chain reaction (PCR) amplification, but there is no similar amplification technique for proteins. Thus, techniques are needed that are highly parallel, allow for multiple types of measurements (genes and proteins) and operations (such as cell sorting) to be integrated, are miniaturized (to analyze single cells and single molecules), and are automated (Hood et al. 2004). Advances in various technologies, including microfluidics, nanotechnologies, and molecular imaging methods have to be adapted to the needs of systems biology. For example, multilayer elastomer microfluidics is a powerful new technology that allows for the integration of many pumps, valves, and channels within an easily fabricated microchip. This means that multiple operations, such as cell sorting, DNA purification, and single-cell gene expression profiling, can be executed in parallel providing a bridge between biological materials and systems biology through large-scale multiparameter analysis, with applications ranging from molecular dissections of single cells to the rapid sequence analysis of individual DNA molecules (Hood et al. 2004).

New technologies are thus also needed to develop a quantitative understanding of how individual cells process and integrate a myriad of spatiotemporal stimuli. Analyzing the top-down controls that operate in living cells entails studying how regulatory modules are coupled to one another and to gene transcription. NT tools are already advancing our understanding of how cells work, while providing new opportunities to probe the dynamic and physical aspects of molecules, molecular assemblies, and intact cells, whether in isolation or under in vivo conditions. Beyond determining how individual molecules behave, it is important to understand how they cooperate synergistically. In the cellular environment, molecules and functional modules are densely packed which has profound implications on how they work. Proximity mediates cooperative effects at all levels of functional organization. Consequently, as molecular biotechnology now makes it possible to build elaborate systems models, but the systems biology community needs information standards if models are to be shared, evaluated and developed cooperatively. The Systems Biology Markup Language (SBML), a free and open, XML-based format for representing biochemical reaction networks is available (Hucka et al. 2003) for describing models common to research in many areas of computational biology, including cell signaling pathways, metabolic pathways, gene regulation, and others (http://www.sbml.org/). As computational approaches are being developed to simulate the responses of molecular networks, physiochemical parameter sets derived from equilibrium data alone might be insufficient to correctly predict the behavior of a cooperative system. One solid proof of whether we truly understand any particular biomolecular chess game, with all its rules and exceptions, would come from our ability to reconstitute specific supramolecular entities and their functions ex vivo. Doing so would provide additional benefits beyond learning more about how biological systems work. We might also learn from these schemes how to develop new bioinspired technologies.

With the development of appropriate technologies and the inherent gain of knowledge, medicine can move from a reactive symptom oriented mode to a more quantitative and preventive mode over the next 10 to 20 years (Hood et al. 2004). New technologies will then allow individuals to have the relevant portions of their genomes sequenced, and multiparameter informative molecular diagnostics via blood analysis will become a routine procedure for assessing health and disease status.

3.3.4 C: Bioinspired Engineering, Biomineralisation and Tissue Engineering

Between 1993-1996 several research groups started to investigate similar methods as nature for the formation of inorganic-organic nanocomposites like bone, teeth, diatoms and sea shells (Aksay et al. 1996; Firouzi et al. 1995; Mann et al. 1993). These structure are formed through template assisted self-assembly processes, in which biomolecules such as proteins, peptides, DNA or lipids form the structural scaffold for the in-situ precipitation or deposition of inorganic materials. A classic and widely studied example of such biomimtic material is the nacre of abalone shell, in which thin films of organic (> 10 nm) and inorganic (<500 nm) phases are coupled together to produce a laminated structure with interesting mechanical properties. Traditionally, biomimetics was done by emulating or duplicating biosystems, whereas with the recent development of molecular and nanoscale engineering and advances in molecular biology biomimetics is entering the molecular scale. By combining molecular tools with syntetic nanoscale constructs like nanosized particles or self-assembeld supramolecules, molecular biomimetics is emerging as a hybrid methodology (Sarikaya et al. 2003). As shown in section 3.1, nanoscaled materials can have unique functional properties at nanometre-scale dimensions which could lead to novel engineering systems with highly useful characteristics like mechanical properties of nanostructured composites, electronic properties of low-dimensional semiconductors, magnetic properties of single-domain particles, and solution properties of colloidal suspensions, are all attractive and interesting. The realization of the full potential of new nanosized materials and systems needs controlled and reproducible methods for the construction of useful functional systems and devices. New nanosized building blocks combined with principles of molecular biomimetics methods could solve the still existing problem of synthesis of 2 and 3-D nanoscaled functional structures. Molecular biomimetics can help to overcome some of these difficulties, because inorganic surface-binding biomolecules like polypeptides have the potential to specifically bind to a material based on its chemical characteristics.

In molecular biomimetics, inorganic-binding proteins could potentially be used as (i) linkers for nanoparticle immobilization; (ii) functional molecules assembled on specific substrates; and (iii) acting directly as seed for crystallisation of inorganic compounds (Sarikaya et al. 2003). (Brown et al. 2000) characterized the effects of genetically engineered polypeptide for inorganics (GBPI) on the morphology of gold particles. Using the well-known Faraday technique, monodispersed nanogold particles 12nm in diameter can be formed by reducing AuCl3 with sodium citrate under ambient conditions. Reducing the gold concentration and temperature allows particle formation at a slower rate, giving the protein time to interact with surfaces during growth, and provides conditions to examine the effect of gold-binding during colloidal gold formation.

Mao et al. (2004) report the general synthesis of 1D nanostructures based on a genetically modified virus scaffold for the directed growth and assembly of crystalline ZnS, CdS, CoPt or FePt nanoparticles into 1D arrays, followed by annealing of the particle assemblies into high aspect ratio crystalline nanowires. Screening of the above mentioned systems systems with commercially available bacteriophage libraries has yielded to a clear identification of petide with very specific sequences, like CNNPMHQNC (termed A7) for ZnS. The incorporation of these peptides into the highly ordered, self-assembled capsid of the M13 bacteriophage virus provides a linear template that can simultaneously control particle phase and composition. Mineralization of the ZnS and CdS systems involves incubating the viral template with metal salt precursors at reduced temperatures to promote uniform orientation of the peptide molecules during nucleation which leads to the preferred crystallographic orientation of nucleated nanocrystals.(Mao et al. 2004).

The crystallisation induced by biological molecules like peptides or proteins is used in biology for fabrication of very different composite materials (also called biomineralisation) like bone tissue which is a particularly complex example of such a biological composite because it contains several levels of hierarchical organized inorganic and organic layers on the nanoscale (Hartgeringk et al. 2001). The controlled nucleation and growth of inorganic bone-like material from templates built up from organic molecules has been demonstrated by in-vitro experiments and in a large number of natural biomineralizing systems (Fendler 1997; Mann 1993). Very often nucleation occurs on surfaces which show repetitive patterns of anionic groups which are able to attract enough dissolved cations creating local supersaturation which can lead to heterogeneous nucleation. Are the proteins in a regular manner assembled, a preferred orientation of the crystallites in respect to the assembled molecules on the substrate is observed.

The principle biomineral in mammalian skeletal tissues is a substituted calcium hydroxyapatite ($Ca_{10}(PO_4)_6OH_2$; HAP). The size and form of the crystals within mineralised tissues reflect the controls and constraints imposed during tissue morphogenesis (Robinson et al., 1998). The phosphophoryns (PPs) are a family of highly phosphorylated proteins with a unique composition and amino acid sequence. The PPs have been considered to be the archetype of macromolecules that might regulate biomineralization processes by binding to the matrix of structural proteins nucleating mineralization and controlling crystal growth (Veis A 1972; Veis and Sabsay 1982). In bone, osteocalcin (bone γ-carboxyglutamic acid protein) is the predominant Gla protein with contributions up to 20% of noncollagen bone tissue proteins.

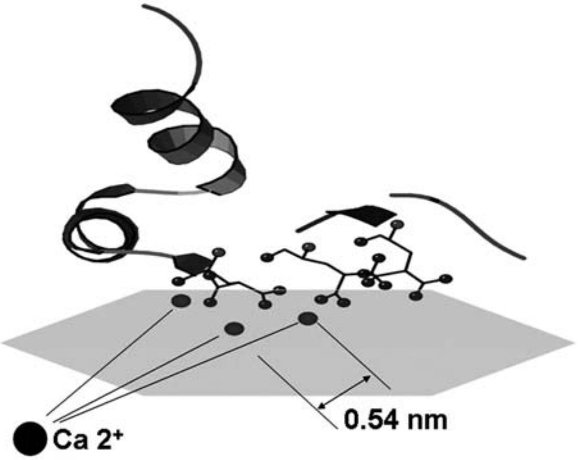


Figure 3.122: Schematic representation of the osteocalcin-HAP interaction. After Flade, Lau et al. 2001 and Houang, Sicherl et al. 2003).

The osteocalcin molecule contains 46-50 amino acid residues and conformational studies have shown that osteocalcin consists of α-helical and β-sheet structures. Two antiparallel α-helices, the "Gla helix" (residues 16-25) and the "Asp-Glu helix" (residues 30-41), are framed by β-sheet structures (Houang et al. 2003). Because of its content of three Gla residues in each molecule, osteocalcin has a strong Ca^{2+} binding effect. The carboxyl groups of Gla residues are the main binding sites for Ca^{2+}. The α-helix has a periodicity of 5.4 Å, which is remarkably similar to the interatomic lattice spacing of Ca^{2+} in the (0001) planes of HAP, which is 5.45 Å. The effect of osteocalcin on hydroxyapatite formation has been investigated in several studies elucidating the nucleation and inhibition functions of the bone-specific protein. Studying a dissolution-reprecipitation process from brushite to hydroxyapatite under biomimetic conditions, (Flade et al. 2001) have found an experimental proof for the assumed nucleation and inhibiting effect of osteocalcin. By SFM measurements the osteocalcin activity during DCPD dissolution and HAP precipitation has been imaged directly. They observed an effect on HAP nucleation, especially an osteocalcin-induced acceleration of the dissolution-reprecipitation process. Osteocalcin interacts specifically with the (0001) plane of the grown apatite phase, and subsequently the proteins inhibit crystal growth perpendicular to this plane.

Instead of precipitation of inorganic crystals at assembled protein or other biomolecules with charged surfaces, similar structures can be fabricated using assembled proteins as support for controlled adsorption of nanosized particles. The interesting difference between these two method is, that in the latter case the particles can be synthesized independently of the environmentally conditions needed for stable protein configurations, and therefore more structures with interesting physical properties could be realized.

Since (Mirkin 2000) and (Alivisatos A. P. 1996) demonstrated DNA mediated-assembly of gold nanoparticles; there has been a strongly increasing interest and many reports describing the use of DNA to specifically assemble nano-size particles for chemical and biological detection are published. Patterned assemblies of nanosized gold particles were not active devices, rather passive Au pads that were not suitable for any electronic applications. Active devices such as carbon nanotubes and nanorods for interconnect systems have been assembled, but still additional work is required to bring these systems to application (McNally et al. 2003). In the case of DNA, hydrogen bonding provides the specificity behind the matching of complementary pairs of single-stranded (ss) DNA to hybridize into a double strand (ds) of helical DNA. In the case of antibodies/antigens and ligands/receptors, binding takes places by a combination of electrostatic forces, chemical bonding, and shape-mediated effects. As an example, avidin is a large protein that has binding sites for four biotin molecules. The affinity of the biotin-avidin complex is with 84 kJ/mol one of the highest binding

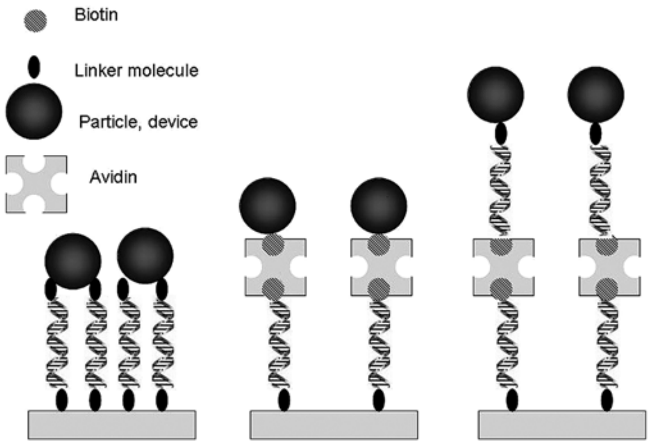


Figure 3.123: Single stranded DNA and quantum dots as building blocks for the construction of complex 3-dimensional structures which can be used for biosensors (after Sarikya, 2003).

in biochemistry, but still lower than covalent bonds like the Au–S thiolate covalent bond, with an energy of around 180 kJ/mol. These energies are still low but sufficiently high to fabricate stable structures. Different approaches can be taken to particle assembly, as shown in figure 3.123. For all three cases, the particles could be nano-scale objects like particles (quantum dots), gold or superparamagnetic iron oxide or devices. In the first case of figure 3.123, presents an approach that uses DNA only and relies on hybridization for attachment of the islands to the surface. The substrate surface is functionalized with single strand DNA while the complementary strand is attached to the gold surface of the particle. Direct hybridization into a double strand DNA would result in capture of the islands onto the patterned gold surface. In the second case DNA and ligand/receptors for the capture of avidin-coated particles are used. A double stran DNA is attached to a surface presenting a biotin. The strong affinity between avidin and biotin is relied upon to ultimately capture the particle. In the third case the particles are captured with a thin layer of gold so the particles could be functionalized with DNA via the Au–S bond. The single strand DNA is attached to the gold surface and subsequently hybridized just as the patterned surface is functionalized. Again, the double strand DNA presents biotin molecules for attachment to the avidin molecule. Generating such devices, it is very important that the reaction sequences allow fulfilling the requirements of colloidal stability of the particles. Avidin/biotin as well as electrostatic interaction can lead to flocculation and uncontrolled stuctures morphology.

Structures like shown in figure 3.123 are the starting point for more sophisticated structures which are finally useful for electronic devices. The basic idea is to learn from nature's solution to storage and process information and to fabricate suitable pattern in or on a microengineered template providing I/O communication. Building blocks for such biodevices are peptides, proteins, DNA strings etc., and combinations of them as well as inorganic quantum dots or other nanosized particles with size selective properties. On the other hand the signalling processes in living systems, (Bioelectronics) is still only at the very early, explorative research stage and it is too early to judge if it will or will not become a practical reality in the future (Bhalla and Iyengar 1999). However, biomimetic structures that have the quantum efficiency, sustainability, and a self-repair ability approaching those of natural systems.

Much further developed is the knowledge regarding the interaction of cells, protein or other biological molecules with the surface of inorganique or organic materials used as implants. This knowledge combined with Nanotechnology and cell biology knowledge led to the promising area of tissue engineering. To synthesise successfully artificial tissue the structures, bonding, dynamics and kinetics of biomolecules at surfaces has to be known and to be combined with the knowledge how biofunctional surfaces participate in the communication system of cells and tissue. In other words, biofunctional surfaces needs advanced design combining topographic, chemical and visco-elastic patterns and preparation in order to match the sophisticated recognition ability of biological systems like proteins at the nanometer scale and cells at the micrometer scale (Kasemo 2002). Examples are antibody-antigen, enzyme-substrate, and receptor-transmitter recognition (e.g. in cell membranes). The recognition is realized through the combination of the morphology and confinement of the molecules and the dynamic properties. Figure 3.123 shows in a simplified way the sequence of events takening place if a surface is coming in contact with a biological environment. It is important to note that cells arriving at the surface they "see" a protein-covered surface whose protein layer shows properties that were determined by the preformed water shells at the surface as well a attached to the biomolecules. Thus, the cell-surface interaction is finally an interaction between cells and surface bound proteins (or other biomolecules). In the framework of this book, only the important interactions at a nanosize levels are of interest where as building blocks proteins, DNA's, vesicles (phospholipids) or other biomolecules are used. A typically surface structure used as support for further tissue growth is prepared from phospholipids vesicles with a hydrophopic and hydrophilic tail spread on the surface. It is possible to incorprate proteins, DNA or inorganic nanoparticles as marker into that layer. Different layers can build up using the biotin/ avidin coupling mechanism. Additional topological or chemical structuring applying methods developed in microtechnology like self-assembly lithography or stamping, can help to orient the cell growth.

3.3.5 D: Interaction of Nanoparticles with Biosystems

Biology exists as a natural form of "Nanotechnology", because all elements of living cells fulfill the criteria of size and technology in this regard. Most proteins, nucleic acids, lipids and other molecules are in a nanometer scale, cellular organelles represent units in a comparable size, organizing functionality and production, leading to self-reproduction and their regulation. Man-made Nanotechnology or Nanosciences, however, design small structures that can interact or influence the biological systems on this nanometer scale. This is in most cases the implication of investigation and development with respect to medical uses and other biological relevant applications. On the other hand, production and use of nanoscale materials in all fields of chemistry, industry, medicine or biology may enforce problems for organisms in all parts of our environment. This has already been published in a great number of biological and epidemiological studies, dealing on the monitoring and distribution as well as on the effects of ambient air particles, coming from natural sources or the combustion of fossil fuel. Moreover, since the 1970s investigations are continually increasing that analyze the use of nanoscale structures, e.g. synthetic liposomes, for drug transport and comparable applications (Agrawal et al. 1987; Clark 1998; Desmukh et al. 1978;

Fendler and Romero 1977; Gabizon 1989; Gregoriadis 1973; Gregoriadis et al. 1974; Kshirsagar et al. 1995; Speiser 1991). Additionally, not only liposomes but also nanoparticles produced from other materials come into the focus of physicians for various treatments of diseases (Allen and Cullis 2004; Chen et al. 2003; Gupta and Curtis 2004; Jordan et al. 1996; Li et al. 2002; Shi Kam et al. 2004). The main purpose in that connection is to design inert auxiliary accompanying materials and to use body-friendly and biodegradable excipients. These new materials should miniaturize the drug carrier systems dramatically in order to get good stability, excellent absorption, quantitative tissular transfer and, therefore, the expected pharmacodynamic activity of the drug. Furthermore, side effects and foreign body irritation should be avoided and a good local and systemic tolerance during and after medication should be a condition *sine qua non.* On the other hand, nanostructured materials are used not only for drug delivery or gene transfer but also in technical production, food and cosmetic chemistry and many other applications. Therefore, it is of great interest how these materials, whenever reaching living organisms, were taken up, transported in or through cell layers and possibly alter biological functions.

Real particles in the range of 10 to 100 nm diameter of the primary particle normally adhere and form clusters. Such small clusters will be described by physical analytical measurements as single spheres. The same is true for larger aggregates in the range of 500 nm up to several μm that will be described as bigger spheres, whereas in reality they exhibit roughly the same properties as the single primary particles (such as active surface etc.). Engineered primary particles in the nanometer range normally form aggregates or agglomerates shortly after their synthesis or production. These bigger clusters were classified by state-of-the-art detection methods as single particles with spherical characteristics. Real agglomerates or aggregates, however,

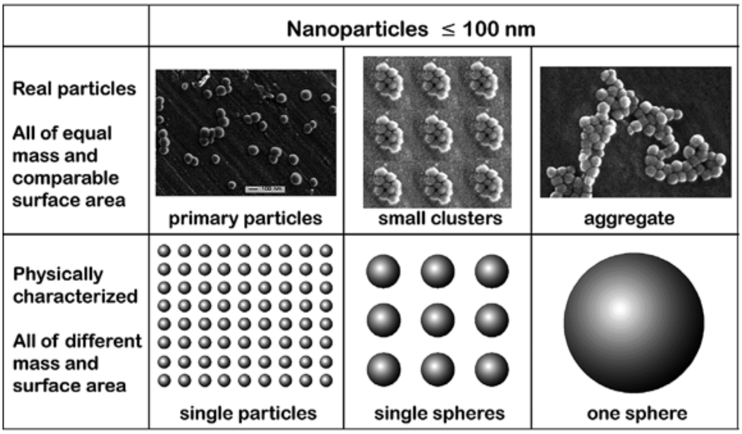


Figure 3.124: Size and morphology of nanoparticles.

exhibit a much greater surface area as suggested by a spherical particle in the range of the sum of all primary particles they consisted of (figure 3.124). As the actual discussion point to the active surface area as an important parameter of nanoparticles for determination of their biological interaction, solely measuring the particle number and overall size should not be a representative value for the characterization of nanoparticles and the biological effects.

D 1: Transport across cell membranes, trafficking, signalling and degradation of nanoparticles in cells

As an organism we are separated from the environment via different surfaces. These surfaces have to protect us from uncontrolled incorporation of non-wanted materials as well as from foreign organism as bacteria or viruses and parasites or others. Each different surface has its own strategy to fulfill these criteria. First of all the skin is the barrier that is directly exposed to the atmosphere or clothes or all materials we manipulate with. Having 2 m? of total area this is the smallest interior/exterior but the tightest barrier. Covered with several layers of dead keratinocytes (*stratum corneum*), it is for most chemicals as well as particles and materials insuperable. Nevertheless, lipids or lipophilic chemicals can easily penetrate through these cell layers and reach the blood stream. But this route is restricted only to such hydrophobic and small molecules; particles, even nanoparticles, have been shown not to penetrate into the deeper layers or viable cells of the skin (Lademann et al. 1999; Pflücker et al. 2001; Puccetti and Leblanc 2000). The second important barrier and the greatest in area is the gastro-intestinal tract. With its 40 m^2 of surface which is enlarged by the microvilli on top of each epithelial cell up to 2.000 m^2 this is the main surface having contact to material coming from outside. Here the decision is made which components or molecules are taken up and will be transported to the liver. Nanoparticles coming with the food or the water this route were found not to be absorbed from the gut (Kreyling et al. 2002). On the other hand, nanoparticles synthesized for drug delivery or other systemic purposes were taken up and transported to the liver, dependent on the surface markers used (Florence et al. 1995; Florence and Hussain 2001; Hussain et al. 1997; Hussain 2001; McClean et al. 1998; Yang et al. 1999). An earlier study has shown that polystyrene microspheres between 50 and 100 nm in diameter were taken up by the rat gastrointestinal tract and were transported to the liver and the spleen, whereas bigger particles have not reached the blood (Jani et al. 1990). The most important route where nanoparticles can reach the organism and the interior compartments is the respiratory tract. At working places in nanomaterial production plants as well as in the environment where particulate matter is directly produced by combustion processes or traffic activities, for instance, many people will have contact to ultrafine particles (UFP $\leq$ 100 nm) via inhalation. Inhalation offers fundamentally two further routes for chemicals or particles to penetrate into the body, the epithelium of the upper respiratory tract including the olfactory epithelium and the lower respiratory tract with the alveolar sacs. Human lungs have an active surface of around 90 m^2 and each day a total volume of about 15–18 m^3 of air is inhaled. Together with the air every other gaseous component reaches the deepest parts of the lung (e.g. ozone) as well as the smallest particles ($\leq 1\ \mu m$).

The application of nanoparticles for medical purposes imposes high demands on the nanomaterials: they should not accumulate, have to be biodegradable, should reach the region of interest within the body thereby crossing different tissue barriers and leave their cargo right at the position they should do it. A possibility to direct nanoparticles to the brain from the blood stream for instance seems to be coating them with polysorbates that lead to the adsorption of apolipoprotein E from blood plasma onto the nanoparticle surface. The particles then seem to mimic low density lipoprotein (LDL) particles and could interact with the LDL receptor leading to their uptake by the endothelial cells of brain capillaries (Kreuter 2001; Kreuter et al. 2002). For carbon particles labeled with ^{13}C, it could not be demonstrated that transcytosis across the blood-brain barrier is responsible for their appearance in some regions of the brain. Thus, the consistent post-exposure increase of in the olfactory bulb is unlikely to be of bloodborne origin.

It is discussed not only by Oberdörster (2004) but also directly demonstrated by others that another pathway exists as direct access to the central nervous system (CNS) for inhaled or nasally-instilled soluble metal compounds, the olfactory nerve (Arvidson 1994; Dorman et al. 2002; Tjalve and Henriksson 1999). Since inhalation exposure to nanoparticles results in significant deposition in the nasal area (ICRP 1994), a reasonable interpretation of the results after inhalation of carbon particles is that inhaled solid ultrafine particles translocate via this route. This is further corroborated by several studies that provide convincing evidence for such a translocation of particles via the olfactory nerve.

1941: Bodian and Howe (1941) showed olfactory axonal transport of Poliovirus (30 nm) after intranasal instillation in chimpanzee; transport velocity: 2.4 mm/h.

1970: De Lorenzo (1970) determined olfactory axonal transport of 50 nm colloidal gold after intranasal instillation in squirrel monkey; they reached olfactory bulb 30-60 min after inoculation; transport velocity: 2.5 mm/h.

1983: Adams and Bray (1983) determined the axonal transport of microinjected solid particles (up to 500 nm) to be in the range of 2.5 mm/h in crabs.

1984: Katz and coworkers measured axonal transport of micro-injected rhodamine labeled nanospheres (20 - 200 nm; optimal size ~30 nm) in cortical neurons of rats and cats (Katz et al. 1984).

1998: Hunter and Dey (1998) demonstrated in rats with the same nanoparticles after intranasally instillation the translocation to the trigeminal ganglion inside the cranium via uptake into the ophthalmic and maxillary neurons of the trigeminus nerve. The trigeminus supplies sensory nerve endings throughout the nasal mucosa, including the olfactory mucosa.

2002: Oberdörster and coworkers studied the inhalation of 13C-UFP (25 nm) and found them translocated into the olfactory bulb, cerebellum and cerebrum of rat brains during the week after exposure (Oberdörster et al. 2002, 2004).

2002: Calderón-Garciduenas and her coworkers investigated healthy stray mongrel dogs that were daily exposed to high levels of ambient air pollutants (particulate matter with an effective aerodynamic diameter less than 10 µm = PM_{10}, ozone, etc.) in Mexico City and in a control city and found persistent pulmonary inflammation, deteriorating of olfactory and respiratory barriers, brain neuropathology as damage of blood-brain-barrier, degeneration of neurons and glial cells as well as neuronal plaques (Calderon-Garciduenas et al. 2002).

Collectively, these studies show that solid nanoparticles of different materials can effectively be taken up by sensory nerve endings at several sites in the respiratory tract and gain access to the CNS and ganglionic structures. In particular the studies by De Lorenzo (1970) demonstrate unequivocally the existence of a neuronal olfactory pathway to the CNS for nasally deposited solid UFP.

The adsorption of particles into organisms presupposes their uptake mainly by epithelial cells or phagocytes. This process is strongly dependent on the size and the surface characteristics of the appropriate nanoparticles. Several studies have been published using specifically coated nanoparticles to direct these particles to particular target structures or organs (Chen et al. 2003; Gupta and Curtis 2004; Kreuter 2001; Mo and Lim 2004; Stevens et al. 2004). Dependent from these parameters the transport through or within living cells called trafficking is managed comparably (Gumbleton 2001; Jones et al. 2003; Panyam and Labhasetwar 2003; Paul et al. 1998; Sundstrom et al. 2004). Especially for the direct use in the body for medical purposes or sensor systems nanoparticles were used that show a biodegradable behavior. Mainly drug delivery systems were build out of such materials that can be dissolved or degraded by the cells of the target organ (Alonso and Sanchez 2003; Aukunuru et al. 2003; Chawla and Amiji 2002; Florence and Hussain 2001; Kaul and Amiji 2002; McClean et al. 1998; Panyam et al. 2003; Panyam and Labhasetwar 2003; Potineni et al. 2003; Prabha et al. 2002; Qaddoumi et al. 2004; Sang and Gwan 2004). Nevertheless a multitude of various nanoparticles made from different materials is produced not directly for biological or medical use but reaches living organisms as well and exhibit a variety of signaling mechanisms or adverse effects that will be discussed in more detail in chapter 5. The fundamental mechanisms by which nanoparticles can be taken up and transported in and through cells will be explained below.

Cellular uptake

In any case nanoparticles have various possibilities to find their way across cell membranes. Because of their small size all mechanisms of endocytosis are theoretically possible. Although most of the mechanistic aspects of nanoparticle-uptake into cells are still unclear a minimum of five different options exist for this transport: phagocytosis, endocytosis via caveolae or clathrin-coated pits, pinocytosis or an unspecific, non-endocytic mechanism so-called "adhesive interaction" (figure 3.125).

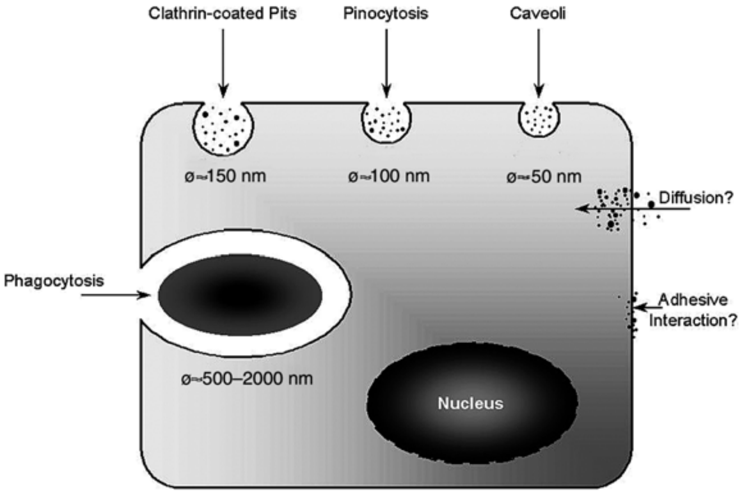


Figure 3.125: Possible cellular uptake pathways for particles of different sizes.

Endocytosis

The uptake of a larger part of the surrounding media by a cell is called endocytosis. During this process the cell engulfs some of its extracellular fluid including material dissolved or suspended in it. The plasma membrane is invaginated and pinched off forming a membrane-bound vesicle called an endosome. Some special aspects can be discriminated firstly for various cell types and secondly for the elements involved in this process. Therefore, different types of endocytotic mechanisms can be distinguished.

Phagocytosis

This process is normally mediated by macrophages and other phagocytic cells specialized on the uptake of bigger structures as microorganisms, insoluble particles, damaged or dead host cells, cell debris and other aggregates like activated clotting factors or antibody/antigen-complexes. After having recognized the structure to internalize the cells form pseudopodia and flow round their "prey". When these cell protrusions start to fuse with the cellular membrane a structure called "phagosome" is build, containing the target structure. This vesicle moves deeper into the cell and fuses with lysosomes to form a phago-lysosome that now contains some special enzymes to digest their content.

Pinocytosis

Pinocytosis is the very special form for single cells to "drink". During this operation a relatively small drop of extracellular fluid is engulfed. Pinocytosis occurs in almost all cells continuously. During this mechanism the cells acquire a representative sample of the molecules and ions dissolved in the surrounding fluid. Pinocytosis also provides an elegant method for cells to pick up critical components of the extracellular fluid that may be in scant supply.

Coated Pits (Clathrin)

Clathrin-coated pits are the major ports of entry into the cell. These pits are responsible for the internalization of a variety of biologically important macromolecules as well as other foreign material. Clathrin-coated pits are specialized structures formed at the plasma membrane with a striking lattice morphology that results from the polymerization of clathrin from the cytosol on to the membrane. Within this lattice a clathrin-binding adapter complex links transmembrane receptors destined for cellular uptake in this region.

Smooth- or non-coated Pits (Caveolae)

Caveolae or caveolae-like structures are prominent morphological features in a variety of cell types, e.g. endothelial cells and type I alveolar epithelial cells. A characteristic component of these structures that forms not only a striated coat of such pits but also is a principal constituent of the so-called "lipid-rafts" of cellular membranes is the protein caveolin.

Transcytosis

Transcytosis is a special process of transport of fluids or very small particulate matter across an epithelium by uptake into and release from coated or non-coated vesicles (figure 3.126). This process might play a role in trafficking of nanoparticles through the alveolar epithelium to the blood stream (Gumbleton 2001).

Particles coming from the alveolar airspace may penetrate into vesicles on the surface of epithelium cells (e.g. caveoli) and can be transported through the cell and leave the cell at the basolateral side after fusion of the vesicle with the membrane.

For nanoparticles built from physiological materials as human serum albumin it has been demonstrated by electron microscopy that they were

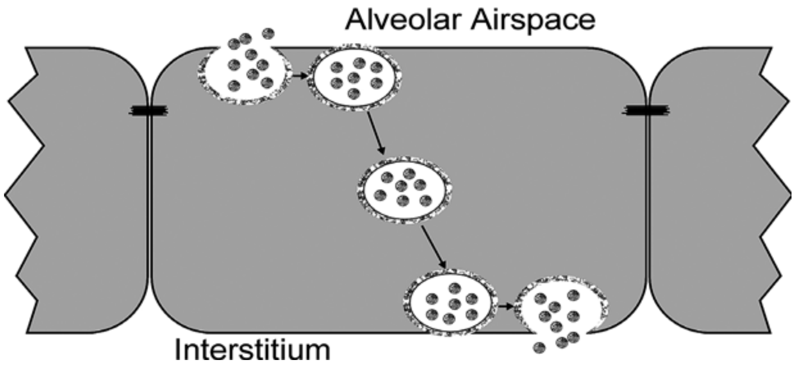


Figure 3.126: A putative mechanism for particle transcytosis.

taken up via phagocytosis (Roser et al. 1998; Schäfer et al. 1994). Comparable polymethacrylate particles showed low cytotoxicity and were located within phagocytotic vesicles (Paul et al. 1998) which fused with primary lysosomes to form secondary lysosomes. Other groups investigated the uptake mechanism in more detail and described a non-phagocytic route taken by poly(N-isopropylacrylamide-co-methacrylic acid) nanoparticles (Moselhy et al. 2000). Nevertheless, in their studies they used additionally more hydrophobic polystyrene particles and showed evidences for phagocytosis of these particles claiming differing pathways for different surface characteristics. There is first evidence that in the lung inhaled nanoparticles may be taken up by alveolar epithelial cells via caveolae (Gumbleton 2001). The alveolar epithelial cell type I has an average surface area of about 5.000 μm^2 and an average cell thickness of 0,4 µm. The number of non-coated plasmalemmal invaginations is estimated to be around 600.000 to 900.000 per cell with a vesicle diameter of 50 to 60 nm. This great number of steadily formed caveolae leads to 150 to 600 vesicles per μm^3 in the cell (Gumbleton 2001). Such a high number of possible transport units leads to the assumption that nanoparticles smaller than 60 nm can be rapidly taken up and transported through lung epithelial cells. Moreover, somehow bigger nanoparticles ($\leq$ 100 nm) may penetrate the cells through clathrin-coated pits (figure 3.125). This uptake-pathway is temperature sensitive and Huang et al. (2002) demonstrated that the internalization of chitosan nanoparticles by human alveolar A predominantly by adsorptive endocytosis initiated by non-specific interactions between nanoparticles and cell membranes, and was in part mediated by a clathrin-dependent process. Recently, it has been shown that biodegradable and biocompatible nanoparticles consisting of the polymer poly (D,L-lactide-*co*-glycolide) are internalized efficiently through an endocytic process and that this uptake is concentration- and time-dependent (Davda and Labhasetwar 2002; Panyam and Labhasetwar 2003). They further stated that the uptake of these nanoparticles was rapid and they were localized mostly in the cytoplasm. Furthermore, this uptake has been shown to depend on the temperature of incubation, with relatively lower uptake at 4°C than at 37°C, suggesting that the uptake is an energy dependent process (Qaddoumi et al. 2000, 2004). The efficiency of the uptake process decreased at higher doses, suggesting that the uptake pathway is saturable. The same group described for these particles that their internalization is in part through fluid phase pinocytosis and in part through clathrin-coated pits. On the other hand, they also observed that caveolae and phagocytosis are not involved in nanoparticle uptake. Following their uptake, nanoparticles were shown to be transported to primary endosomes and then probably to sorting endosomes. From these the nanoparticles escaped after surface charge alterations into the cytoplasm. Particles that were not able to change their surface charges in a surrounding of low pH as polystyrene particles do not leave the endo-lysosomes. In these studies it has been demonstrated that a massive drop of the intracellular fraction of nanoparticles could be determined when the external concentration gradient was removed and serum or proteins were present in the medium.

Furthermore, it has been shown that coating of nanoparticles with proteins or other naturally components alters their behavior totally and that they uptake characteristics by cells. Whereas non-coated superparamagnetic iron oxide nanoparticles were taken up irreversibly by cells, lactoferrin or ceruloplasmin coated nanoparticles attached to the cell membrane, most likely to the cell expressed receptors and were not endocytosed (Gupta and Curtis 2004). A comparable effect has been shown for carbon nanotubes (CNTs) that have been derivatized by attachment of small molecules and proteins. These functionalized CNTs enter cells and were shown not to be acute cytotoxic (Shi Kam et al. 2004). The uptake pathway is suggested to be endocytosis and the observed biocompatibility may be the basis for drug, protein, and gene delivery applications with this new class of material (Shi Kam et al. 2004). Multiple sidewall derivatization of single- and multiwall carbon nanotubes (SWCNT/MWCNT) may open a wide field of applications (Chen et al. 2003; Dyke and Tour 2004; Peng et al. 2003; Shi Kam et al. 2004). As an example, these modified CNTs may serve as biosensors (Chen et al. 2003) or can be applied for specific and sensitive analysis of environmental samples for contaminants (Li et al. 2004). Moreover, functionalized CNTs are able to cross cell membranes, accumulate in the cytoplasm and reach the nucleus without being toxic up to 10 μM (Pantarotto et al. 2004). Despite these first studies with CNTs and their possible biological applications, direct use in biological systems has to be made with caution because other investigations revealed adverse effects in cellular systems (Krug et al. 2004a; 2004b; Monteiro-Riviere et al. 2005; Shvedova et al. 2003) as well as in animal studies (Lam et al. 2004; Warheit et al. 2004).

The differences in uptake shown by several laboratories can mainly be explained by the diverse cell types used for these experiments. Some groups use lung epithelial cells, whereas others have investigated smooth muscle cells, vascular endothelial cells, or phagocytes. Moreover, toxicological studies were mostly carried out with macrophages and related cell types. It remains still unclear if the uptake of nanoparticles by various cell types follows the same or different rules dependent on the chemical and physical properties. During the last decade the number of studies is permanently increasing in which various nanoparticles were used as sensors or probes for biological mechanisms in cells or microbes. It has been demonstrated that the uptake of silver-nanoparticles by bacteria is size-dependent and that these particles can be followed in real-time investigating the uptake mechanisms and its influence by antibiotics (Xu et al. 2004). By coating luminescent semiconductor quantum dots with biomolecules (e.g. peptides) the uptake via receptor-mediated mechanism can be directly followed (Chan and Nie 1998; Lidke et al. 2004). Thus, especially prepared nanoparticles provide an amazing tool for the monitoring of fluctuations and alterations in the distribution of biomolecules and the possibility for the direct observation of signaling processes (Zorov et al. 2004).

D2: Transport, Signaling and Cell Activation in Cell Co-cultures and Organs; Isolated Organs or Biopsies

For the application as well as for the investigation of biochemical effects of nanoparticles several biological systems can be used. The simplest model is a single living cell. As mentioned above, such studies have been done with mammalian cells as well as with bacteria. Mainly fluorescent particles were used for molecular imaging of special events in the cells. But not only the usage as sensors or tools is of great interest but also the questions concerning the uptake and transport mechanisms of synthetic nanoparticles that come unintentionally in close contact with cells or organs and might have adverse effects on health or environmental compartments. This is the reason that several laboratories are engaged in investigations of the intercellular transport of particles and their systemic uptake. Due to these questions several approaches have been established to investigate the transition of small particles through cellular barriers. Besides the lung-vascular barrier the blood-brain and the placental barriers are of great interest, both for the medical application of drugs and due to possible hazard especially during fetal development. Fundamentally, three different possibilities exist to investigate the biological effects of nanoparticles: the whole animal model, the isolated organ model and the cellular *in vitro* model. Each of these models has its specific advantages and disadvantages. In order to permit extrapolation to humans of results obtained in animal studies *in vivo* and *in vitro* and in human tissues or cells *in vitro*, increasing use is being made of models that take account of physiological and biochemical differences between species (figure 3.127). Nevertheless, most experimental animals differ greatly from human beings in terms of the anatomy of the respiratory tract, the absorp-

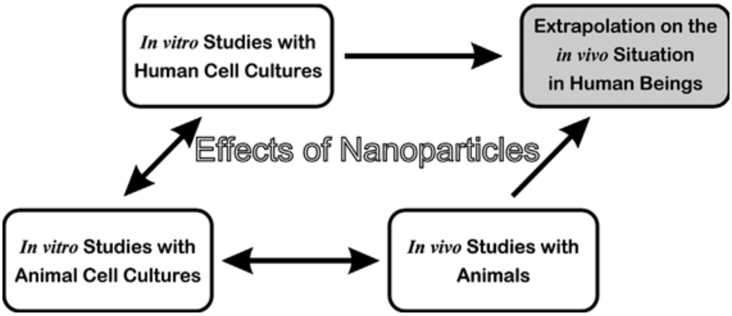


Figure 3.127: Extrapolation of experimental results from animals to humans.

tion, distribution, accumulation and elimination of nanoparticles. The effect by a given amount of nanoparticles can therefore vary greatly between different animal species and humans, on the organismic as well as on the cellular level.

Animal models
Whole animals are most representative and the results from such experiments will supply profound knowledge. Even though the extrapolation from animal studies to the human situation is not possible for all situations or species it is one of the most important models used. Actually a project funded by the European Community called NanoDerm investigates the skin as a barrier for nanoparticles. Within this project skid mice with human skin transplants were used to test for a translocation of particles through the skin, but during the first period of the project, no evidence was found that nanoparticles penetrate into the deeper, viable layers of the skin (http://www.uni-leipzig.de/~nanoderm/index.html). The second and most important exposure system is the lung. Mostly rats (Elder et al. 2000; Gallagher et al. 2003; Gilmour et al. 2004; Oberdörster et al. 2002; Semmler et al. 2004; Takenaka et al. 2004; Warheit et al. 2004) or mice (Elder et al. 2000; Heinrich et al. 1995; Khandoga et al. 2004; Lam et al. 2004; Oberdörster et al. 2000; Shukla et al. 2000) were used for inhalation studies with ultrafine particles or nanoparticles (figure 3.128), but in some cases dogs too (Kreyling et al. 1990; Möller et al. 2002).

The majority of these studies look for inflammation processes or possible DNA-damaging reactions, but actually more and more experiments were done to clarify a possible translocation of inhaled nanoparticles into the bloodstream, inducing systemic effects on the cardiovascular system or the brain. These translocation investigations have to use particles that are chemically modified to identify that part which is translocated into remote organs. ^{13}C or other rare isotopes have been used as well as radioactively labeled particles, but none of the so far published data are strongly convincing that a substantial amount of the inhaled dose is translocated systemically

Figure 3.128: Three adult Wistar Kyoto rats in single-cages integrated into a small whole-body exposure chamber (Photo Courtesy Dr. Wolfgang Kreyling, GSF).

(Khandoga et al. 2004; Kreyling et al. 2002; Nemmar et al. 2004; Oberdörster et al. 2000; Oberdörster et al. 2002; Semmler et al. 2004). The most prominent difficulty is the detection of such low amounts of translocated material in the various organs, therefore it might be easier to study these and comparable mechanisms in tissue slices or isolated organs.

Isolated Organs

For studying the interaction of nanoparticles with special organs or the penetration through several cell layers tissue slices could be used. As the classical techniques of cell suspension preparation did not allow to isolate without damage for example spleen macrophages, which are tightly bound to a well-developed reticular meshwork, Demoy and co-workers (1999) designed a tissue slice incubation method, in order to study *in vitro* the interaction of nanoparticles with these particular macrophages, in conditions close to *in vivo*. A mixed method at the interface of *in vivo* to *in vitro* was established earlier to study the uptake of particles in hamsters through the respiratory system (Geiser et al. 1990). Within these experiments hamsters were exposed via the air to polystyrene particles and subsequently the lungs were cut into slices for quantification of the particle number in the different parts of the respiratory tract as well as in specific cell populations. But more and more new techniques were developed for keeping whole isolated organs alive under controlled conditions using them for transport and translocation experiments. Whereas the isolated perfused liver from rats, hamsters, mice, or guinea pigs are well characterized experimental models, the lung is much more complicated to stabilize under isolated conditions. This is connected to the difficulty to control on the one hand the air pressure and breathing cycles and on the other hand the pressure of the blood substitute. Recently, it has been published that nanoparticles of different size and surface modifications affect the microvascular response in isolated perfused rabbit lungs (Hamoir et al. 2003). The used polystyrene particles of different diameters on the nanometer scale induce an increase in the microvascular permeability depending on the number and surface composition of intratracheally instilled particles. The authors considered the number of particles as an important parameter and suggested this value to be an alternative to total particle surface area measurements in monitoring particle impacts. Moreover, they found that particle surface charges must be taken into account to compare possible adverse health potency of various particles since amine-modified particles induce more marked changes than carboxylate-modified particles, independently of all other parameters. Continuing these experiments the same group observed in the same lung model that fluorescent polystyrene particles of different diameters (24, 110 or 190 nm) and surface chemistry (carboxylate or amine modified) could not penetrate after intratracheal instillation to the perfusion liquid or after intravascular administration could not penetrate into the bronchoalveolar lavage fluid (Nemmar et al. 2005). Only after an increase of microvascular permeability by pharmacological treatment with histamine in the vascular compartment, a fluorescent signal in the bronchoalveolar lavage fluid could be recorded, suggesting a translocation of particles through the alveolo-capillary barrier. They conclude that ultrafine polystyrene particles cannot significantly diffuse from lung into the vascular compartment in this lung model, but they are able to

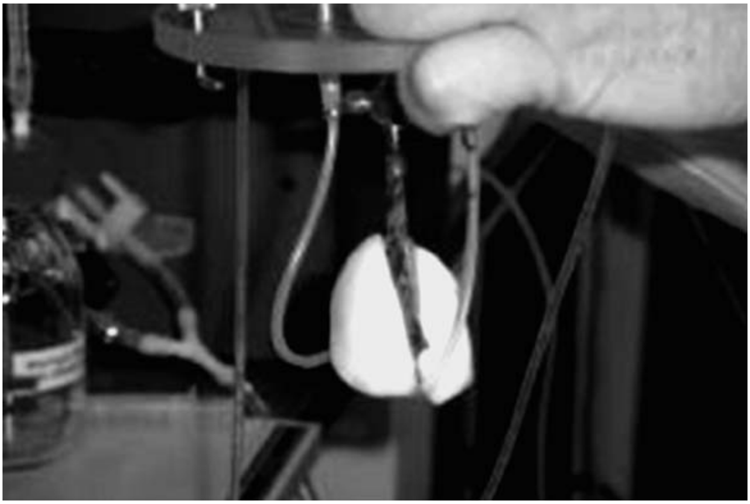


Figure 3.129: Perfused rat lung model for the investigation of aerosols of ultrafine particles.

translocate in the opposite direction when the microvascular permeability is increased. This result is confirmed by another group using the isolated perfused rat lung as a model (Meiring et al. 2004). Initial experiments within this model (figure 3.129) showed no detectable translocation of several types of particles, including latex fluorescent beads (50, 250 nm), ultrafine TiO_2 (20 nm) and radioactive iridium particles (18 nm).

Isolated rat lung is prepared for an inhalation chamber. The white-colored blood-free lung (middle) is ventilated under negative pressure in a plethysmograph type chamber. During perfusion the medium was monitored for CC16, a clara cell specific protein, as index of performance. After the inhalation of particles lung tissue and perfusate were analysed for distribution of nanoparticles and the possible translocation into the blood flow (Meiring et al. 2004; picture: courtesy of P. Borm and W. Kreyling).

Isolated Cells

During the last two decades a multitude of studies has been published dealing with the biological effects of particles investigated in cell cultures *in vitro.* Some of these examinations already analyzed the effect of nanoparticles especially in human cells isolated from the blood (Leroux et al. 1994; Schäfer et al. 1994) or in tumor cells from different species (Colin et al. 1994). Freshly isolated bovine alveolar macrophages have been chosen for several investigations on the adverse effects of various particles, e.g. fullerenes or superconducting materials, coming from industrial productions (Baierl et al. 1996; Wilczek et al. 1989; Wilczek et al. 1990).

Nowadays, sophisticated cultivation and exposure techniques enhance the efficiency of *in vitro* studies. Especially the treatment of cultured cells to particulate matter necessitates ingenious methods. Whereas exposure of cells usually takes place simply in culture medium in which the particles are resuspended (submers exposure; examples cited in the previous paragraph), these newly developed techniques provide the possibility to study the biological effects of an aerosol which directly contacts the cells at the air-liquid interface. Such an exposure system is technically challenging, but it better reflects, however, the situation in the lung during inhalation of atmospheric particulate matter. Until now only a few systems are described in the literature for this type of exposure to study the effects of gases or aerosols. The classical method is described by Voisin et al. (1977) who placed lung cells on special holding devices in temperature conditioned exposure chambers. But this system is suited for gas exposure solely. Modifications have been applied by different groups (Aufderheide and Mohr 1999; 2000; Cheng et al. 2003) which allow direct exposure of cells to particulates in an aerosol at the air/liquid interface (figure 3.130).

The module consists of two separate parts, both of which are temperature-controlled (water 37°C). The upper part (A) contains the gas or aerosol in- and outlets and can be fixed on top of the lower part (B). Herein the cell

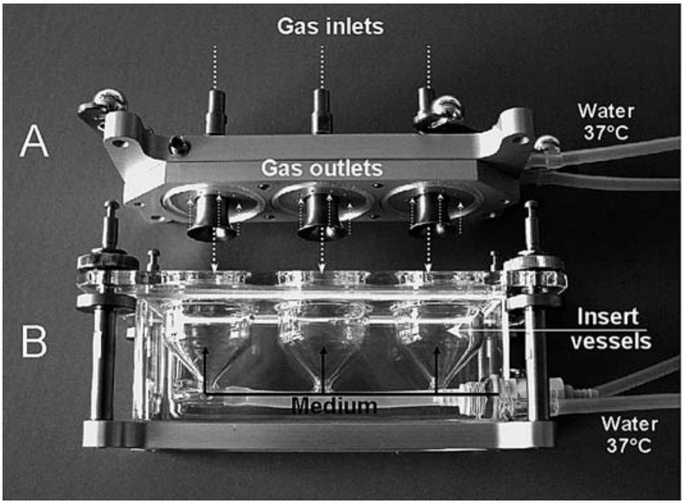


Figure 3.130: Culture and exposure module for the treatment of cell cultures to aerosols.

culture inserts (insert vessels) are placed. During the exposure time the cell cultures can be supplied with medium (courtesy of M. Aufderheide).

In such a system cells of the respiratory tract can be grown on porous membranes in cell culture inserts. After removal of the medium, the cells can be treated on their superficial surfaces with the aerosols or normal air, and at the same time they are supplied with nutrients through the porous membrane below. In comparison with the so-called submers-approach (s. above), the goal of this experimental design is to analyze the biological effects of test atmospheres under physiological relevant conditions. The system shown here (figure 3.130) is small and flexible, independent of a cultivation chamber and thus offers the opportunity for onsite study of indoor and outdoor atmospheres or the aerosols at working places of nanotechnological production plants/labs. The efficacy of this exposure device has already been demonstrated in the analysis of dose-dependent cytotoxic and genotoxic effects of exposure of epithelial lung cells to complex mixtures such as native diesel exhaust and side-stream smoke (Aufderheide et al. 2003a, 2003b; Ritter et al. 2003).

3D Cellular Model

Great efforts will be made to adapt the cellular model to the *in vivo* conditions. The described exposure system can be improved by using a more realistic cell culture model. It is a common paradigm that monolayers of a single type of cells reflect only poorly the situation in a whole organ. Therefore, co-culture systems have been developed to consider the communication and amplification mechanisms between cells of different types after exposure to nanoparticles (Diabaté et al. 2004; Ito et al. 2004; Mögel et al. 1998; Omidi et al. 2003; Soma et al. 2000; Wottrich et al. 2004). One example of such systems is shown in figure 3.131 and the cell culture inserts can combined with the exposure system shown above. This reflects a more realistic situation where the epithelial cells and the macrophages can be exposed directly to the air flow as in a normal lung.

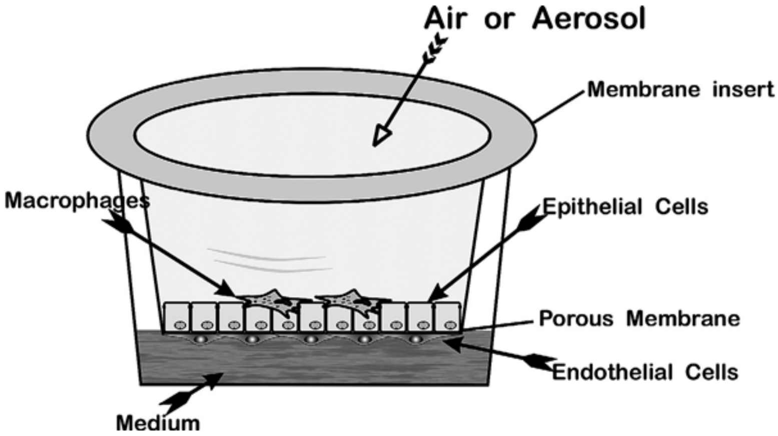


Figure 3.131: 3D-Cell Model close to the situation in a lung alveolus.

The cell system for exposure experiments at the air/liquid interface consist of a transwell plate insert with a synthetic membrane containing pores of 400 nm in diameter. On top epithelial cells and below endothelial cells were seeded. Alveolar macrophages were cultured on top of the epithelial cells. This system can be exposed directly to an aerosol containing ultrafine particles (Wottrich et al. 2004). Additionally, the communication of different cell types with each other in one culture system may enhance the collective response inducing higher activation levels as single cell culture systems may reach. Such co-cultures are more realistic with regard to their biological function. This has already been demonstrated in some culture systems (Mögel et al. 1998; Omidi et al. 2003; Soma et al. 2000; Wottrich et al. 2004).

D1: Effects of nanoparticles on function of biomolecules

For ambient air particulate matter it is well known that they can enter the cells and interact with cellular structures and elements thereby inducing occasionally adverse health effects. Meanwhile more and more studies document a comparable behavior of synthetic nanoparticles. Cells exposed to various kinds of nanoparticles incorporate these materials more or less easily, independent from the functionality of the cells. Besides macrophages, phagocytes that are physiologically adapted to the uptake and handling of

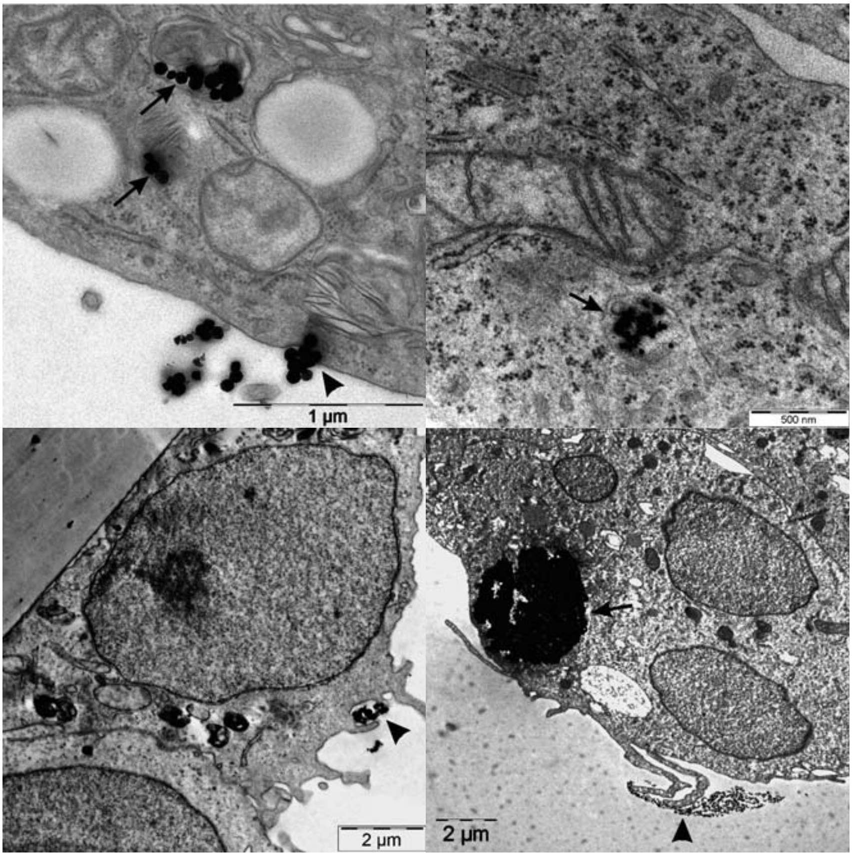


Figure 3.132: Uptake and distribution of nanoparticles in human lung epithelial cells.

foreign material, epithelial or endothelial cells can take up nanoparticles as well (figure 3.132a–d).

Human lung epithelial cells in culture (BEAS 2B) were exposed with different types of nanoparticles. After 10 to 20 h of exposure cells were fixed and analyzed by transmission electron microscopy. Shown are cells with 70 nm Ø hematite (a), 20 nm Ø palladium (b), 25 nm Ø TiO_2 (c), and a bundle of nanotubes (d). Given are the diameters of primary particles. Arrows: particles in the cytoplasm or within vesicles; arrow heads: particles at the surface of the cells (all pictures were taken in the Institute of Toxicology and Genetics, Forschungszentrum Karlsruhe, Germany, by T. Detzel and S. Meixner).

Once these particles have entered the cells they may interact with various intracellular structures or molecules. There is first evidence for the interference with cellular signaling processes, but nevertheless there is not enough data so far to understand transport and biological effects of nanoparticles in

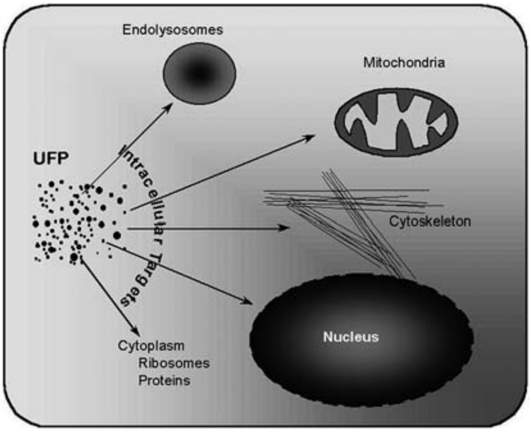


Figure 3.133: Possible intracellular targets of nanoparticles (UFP).

living cells, despite the fact that most types are taken up very good. Although the dynamics of endocytosis and exocytosis *in vivo* could be different from that observed *in vitro*, it is important to understand the parameters affecting the cellular uptake of nanoparticles as well as their intracellular trafficking and sorting mechanisms to further explore the drug delivery applications of nanoparticles as well as the toxic properties of unintentionally internalized ultrafine particles.

Possible negative consequences and, moreover, intended effects during nanoparticle application can be the result of a more direct interaction of particles with various cellular targets (figure 3.133):

- Cell membrane proteins/adhesion molecules; integrins and extra-cellular matrix (ECM), receptor molecules, transporters (Berry et al. 2004; de Campos et al. 2004; Gualbert et al. 2003; Gupta and Curtis 2004; Kristl et al. 2003; Lidke et al. 2004; Maye et al. 1997; Pryhuber et al. 2003);
- Phospholipid turnover and lipid mediator release (Beck-Speier et al. 2001; Beck-Speier et al. 2003; Oberdörster 2004);
- Ion channels (Park et al. 2003);
- Endolysosomes (Kreyling 1992; Lundborg et al. 1995; Panyam et al. 2002);
- Mitochondria (Cruz et al. 1997; Knaapen et al. 2004; Thibodeau et al. 2003);
- Nucleus and DNA (Carlisle et al. 2001; Gallagher et al. 2003).

Of course there exist more structures or single elements in each cell like the Golgi apparatus or ribosomes, endoplasmic reticulum or cytoskeleton but most of these structures have not been investigated in detail to interact with nanoparticles or may be influenced negatively by these.

Nanoparticles have been intensely tested for drug targeting purposes during the last 20 years and it has been shown that, after intravenous administration, they were quickly cleared from the bloodstream by mononuclear phagocytes mainly localized in liver and spleen (Grislain et al. 1983; Jani et al. 1990; Kreuter 1994; Li et al. 1993; Verdun et al. 1990). The liver capture, involving the Kupffer cells, has been well documented (Chiannilkulchai et al. 1990; Fernandez-Urrusuno et al. 1996; Lenaerts et al. 1984) whereas only few investigations were carried out to better understand the mechanisms of spleen uptake (Demoy et al. 1999; Moghimi et al. 1993). The directed application of nanoparticles to the spleen for instance is related to the nanoparticle size and charge (Moghimi et al. 1991, 1993) and could be modified by treatment with different hydrophilic block-copolymers, such as poloxamer 407 and poloxamine 908 (Davis et al. 1993; Moghimi et al. 1991, 1993), which decreased protein fixation on nanoparticle surface (Norman et al. 1993). However, the precise investigation of factors such as the nature of plasma proteins or macrophage receptors responsible for the nanoparticle adhesion which is the first step of phagocytosis, remains difficult. Indeed, most of the nanoparticles are retained by marginal zone macrophages. As these particular cells, actively involved in the capture, are tightly bound to neighboring lymphocytes and reticular cells, it is almost impossible to obtain pure suspensions of these unaltered cells for *in vitro* studies and have to be investigated in tissue slices (Demoy et al. 1997).

Protein adsorption onto solid interfaces from aqueous solution is a well-known phenomenon. Proteins may change their conformation when they

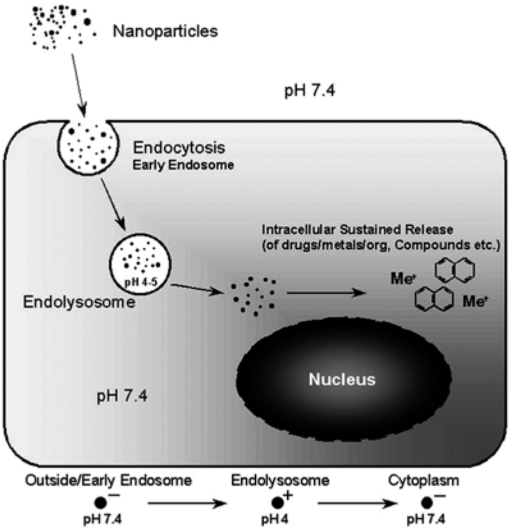


Figure 3.134: Schematic diagram of possible intracellular trafficking pathways of nanoparticles.

adsorb from solution onto flat surfaces. Important questions that concern the adsorption process and structural alterations in the adsorbed proteins remain unanswered. For example, structural changes may be forced upon the protein by adaptation to the chemistry of the solid surface. On the other hand, structural changes may also occur due to intrinsic properties of the protein, roughly independent of the surface chemistry. Moreover, the pH-value in the surrounding solution is important for a possible release of compounds or ions bound to the surface of the nanoparticles. Biodegradable nanoparticles formulated from synthetic or natural polymers have been shown to change their surface charge dependent on the compartment in which they were transported. In smooth muscle cells it could be demonstrated that such nanoparticles were taken up via pinocytosis and clathrin-coated pits that fuse with intracellular sorting vesicles and lysosomes to form endolysosomes with a low pH-value. Changing their surface charge inside these organelles many of these nanoparticles can escape the lysosomes into the cytoplasm (figure 3.134).

Following their uptake, nanoparticles are transported through early endosomes to the sorting endosomes. A fraction of nanoparticles recycles back to the cell exterior (exocytosis or transcytosis) while another fraction is transported to secondary endosomes (endolysosomes) from where nanoparticles may escape into the cytoplasm. Nanoparticles that can escape into the cytoplasm could act as intracellular reservoirs for sustained release of encapsulated therapeutic agent but also for materials from the surface on nanoparticles as bound organic compounds or metal ions (adapted from Panyam and Labhasetwar 2003).

All the above described mechanisms of uptake, transport and distribution of nanoparticles in cells of different species and organs are important for their implications and applications. Some of the relevant functions are mentioned in the chapters before and will be listed here again:

- Imaging and microscopy
- Diagnostics and analysis (research and therapy)
- Production of bio-active compounds and materials (Lab-on-a-Chip)
- Targeting and dosing of drugs
- Intervention in biological processes (cell growth)
- Nutrition (bioavailability, stability, optics)
- Cosmetics (UV-filter, liposomal formulations)
- Sensors and detectors
- Biomolecules for information and communication technology (ICT; DNA computing).

3.4 Scaling Effects

As variously mentioned, scaling effects, even if they happen on the nanoscale, are not in agreement with the definition of Nanoscience and Nanotechnology in chapter 2. In spite of this knowledge, this chapter summarizes some of the best known scaling effects due to the fact that they have long ago become part of what commonly is called "Nanotechnology". In this connection it should be referred to chapter 2 where some less exact former definitions are commented. Several of them allow scaling effects to be considered as "nanoeffects" although they do not follow strict scientific criteria. The everyday usage of the expression "Nanotechnology" in the public and in politics may justify this chapter containing descriptions of phenomena, which have indeed partially developed to technical processes of enormous relevance.

Field Emission and Field Emission Display (FED)

Conducting carbon nanotubes and inorganic nanorods have excellent materials properties which make them ideal emitting units for field emission applications.

These properties are:

- Large aspect ratio > 1000
- Atomically sharp tips
- High chemical stability
- High temperature stability
- High electrical and thermal conductivity.

They are hence capable of producing very high current densities at low operating voltages. Most of the studies on field emission from carbon nanotubes have focused on two terminal devices, which have limited potential for electronic device application.

A new kind of flat screen device called "field emission display" (FED) is based on the idea of using CNTs as emitting units. In contrast to conventional liquid crystal devices, FED displays should have higher image quality, a broader field of view and lower production and operation costs.

In principle, FEDs work just like conventional cathode-ray tubes (CRTs). There's a grid of coloured phosphor dots, which emit light when stimulated by an electron beam. In the conventional CRT, there's a single source of electrons – the electron gun – whose aim is scanned across the screen. In order for the gun to have enough room to "see" the whole area of the screen, it needs to be mounted far enough away, a fact that causes the very obvious non-flatness of CRTs. An FED, however, doesn't have a single electron gun. Instead, every pixel in the display has its own private gun, mounted just behind it. An electric field applied to the screen pulls electrons out of the guns. The design calls for the tiny guns to have sharply-pointed tips, so they emit coherent, focussed streams of electrons. Due to the above listed field emission characteristics, nanotubes are perfect for this. The main difficulty of fabrication is to grow an array of nanotubes on a glass substrate, making sure they're all perfectly aligned in the array, and all pointing perfectly forwards. Recently, researchers at Samsung's Korean labs demonstrated a working prototype, and several other Japanese companies are known to be working on the technology – in secret.

Lowered Percolation Threshold

By using electrically conducting nanoparticles as fillers in polymer composites, the percolation threshold can be considerably reduced down to the range of contents between 5 and 10 Vol%. From the agglomerated nanostructured powder different sieve fractions have been investigated. This property is not yet completely understood in theory. But it seems that this is achieved by scaling down the grain size of the powder filler and thus not a real Nano effect in the sense of our definition.

With decreasing grain size, a higher filling volume with decreasing overall density of the filling material can be achieved. This is already evident in macroscopic systems.

On account of the higher filling volume, many small particles are brought together so close that the electrons can tunnel from one grain to the other.

The effect can be advantageously applied in conductive adhesives which can be used for the mounting of Silicon chips on a substrate.

Diffusion limited electrode reactions

When diffusion processes become rate determing for a chemical reaction, the velocity of the reaction can be enhanced considerably by the use of nanostructures. This is clearly a scaling down effect and thus not Nanotechnology in the sense of our definition. Examples for the use of nanostructured reaction partners to reduce diffusion path ways are considered in the following sections.

Lithium-Ion-Batteries with nanostructured Electrodes

Batteries with Lithium Anodes have the highest electrical storage capacity with respect to weight and the highest standard potential which makes them interesting for application in batteries. The cathode in these batteries is made of Lithium-Cobaltate(II) or Lithium-Manganate(II). During the charging and discharging process Lithium-ions are migrating between the electrodes due to the following reaction (Blumes 2004):

The constitution of the element in the discharged state is as follows:

Discharged state:

$$Li_2MnO_2|Li - salt,\ organic - solvent|Graphite$$

Charging:

Lithium-Manganate (connected to the plus pole):

$$Li_2MnO_2|Li \longrightarrow MnO_2 + 2Li^+ + 2e^-$$

Graphite (connected to the minus pole)

$$Graphite + 2e^- + 2Li^+ \longrightarrow Graphite^{2-} + 2Li^+$$

Discharging:

Manganate electrode (now cathode): $MnO_2 + 2Li^+ + 2e^- \longrightarrow Li_2MnO_2$

Graphite electrode (now Anode): $Li_2\ Graphite \longrightarrow Graphite + 2e^- + 2Li^+$

Figure 3.135 shows the discharging process schematically.

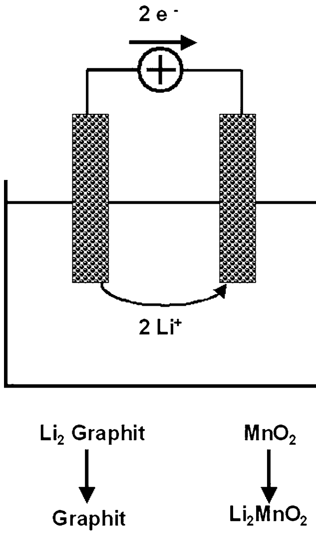
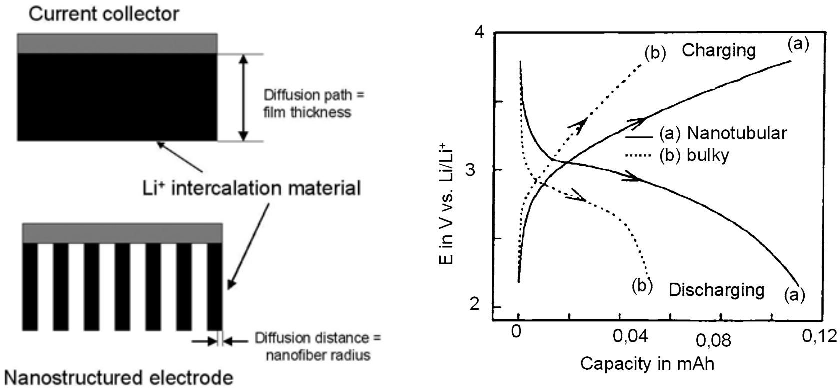


Figure 3.135: Charging and discharging process of a Lithium Ion Battery (schematically, from Prof. Blumes, University of Bielefeld; http://dc2.unibielefeld.ded/dc2/echemie/li-ion-b.htm).

The Lithium-ions are intercalated in the Carbon anode and embedded in the Lithium-Manganate cathode by a diffusion process. Figure 3.136 (left) displays that the diffusion path in nanostructured electrodes is much shorter than in bulky electrodes. This means that charging and discharging processes are facilitated (figure 3.136 right) and the capability of loading of the battery is considerably increased.



a) b)

Figure 3.136: a) Diffusion path in conventional and in nanostructured electrode (from Charles Martin 1996, private communication); b) Charge and discharge curves (from Charles Martin 1996, private communication).

The nanostructured electrodes can be produced e.g. by using nanoporous templates made by anodic oxidation of Alumnium. Also Carbon nanotubes seem to be promising as cathode material.

Electrochromic systems with nanoporous electrodes

In electrochromic systems the chemical reaction of an electrolyte cell of alkaline ions e.g. Lithium with Tungstentrioxide (WO_3) is used to switch the optical transparency of the cathode layer.

The reaction in the cathode can be described by

$$Li^+ + e^- + WO_3 \leftrightarrow LiWO_3$$

This reaction switches reversibly the colour of the cathode from transparent to dark blue.

Normally the cathode layer is a compact polycrystalline layer with the consequence that the Lithium-ions have rather long diffusion paths for this reaction which means that the switching times can be in the range of minutes.

By using nanoporous electrodes the diffusion paths can be decreased by orders of magnitude as it is shown schematically in the figure 3.137 below.

Applications:

- *Alkaline batteries* can be used for electrical energy storage with very high storage capacities and storage densities for mobile and stationary applications.
- *Electrochromic systems:* Switching times can be reduced to the range of some ten milliseconds. So a many applications of this effect are imaginable, e.g. to switch the transparency of windows in a house or in a car. Other possible applications could be flat displays even for TV which can store the information after switching off the external applied voltage.

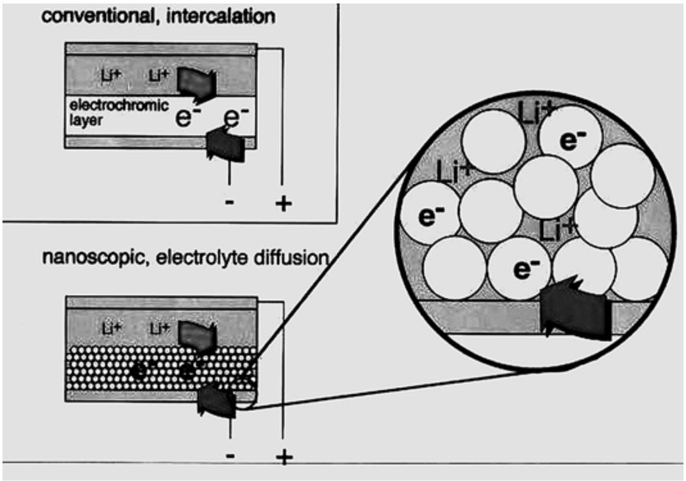


Figure 3.137: Intercalation of Li-ions in conventional and in nanostructured electrodes (with permission of H. Weller, University of Hamburg 1996, private communication).

As these systems have a high potential for special applications, e.g. the above mentioned fields of energy storage and displays, funding may be helpful for further improvement to get new products with a high market volume.

Nanostructured Surfaces

The reasons to structure surfaces are to be seen in the change of physical and chemical properties when smooth surfaces are micro- and/or nanostructured. Two relevant aspects shall be discussed in the following. While one concerns the change of wettability compared with unstructured surfaces, the other one is dealing with the influence on optical properties. Both effects will be described in principle and will be elucidated be means of typical examples. It should be mentioned that both phenomena do not hit on the crux of the definition, given in chapter 3, since changes of wettability as well as those of optical properties do not exclusively depend on a distinct dimension of the structure units. Rather they have to be considered as typical scaling effects, the consequences of which are observed in qualitative changes when going from micro- to nanoscale. In spite of that these effects shall be considered here, since they are meanwhile accepted as belonging to Nanotechnology by the community.

Wettability behaviour of structured surfaces

Surface tension is defined as the force acting perpendicular to the phase boundary of a liquid with the goal to reduce the surface (Israelachvili 1995). It is measured as force per length in millinewton per meter ($mN \cdot m^{-1}$). Measurements are carried out indirectly via the interactions with liquids, since surfaces of solids can not reversibly be enlarged and reduced, respectively. To mention only three examples: water has a surface tension, sometimes also named as surface energy, of 72.8 mN·m^{-1}, aluminum of 683 mN·m^{-1}, whereas the value for Teflon is only 19.1 mN·m^{-1}. Interfacial tension describes the interaction of two adjacent surfaces. Its value is determined by the surface tension of the participating materials. The expression wettabilty describes the interaction of a liquid with a solid surface (Israelachvili 1995). The wettability can be calculated via the interfacial tensions of a system. Figure 3.138 shows a three-phase system existing of a solid, a liquid and a gas, indicating the corresponding interfacial tensions.

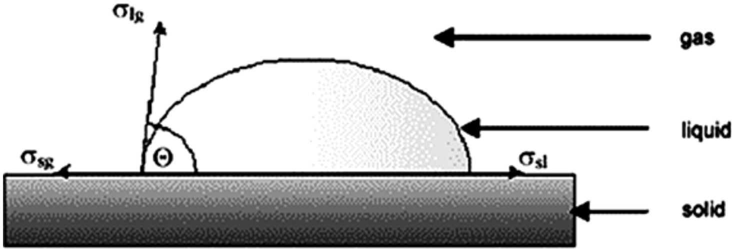


Figure 3.138: Sketch of the three-phase system gas/liquid/solid (σ_{sl} = interfacial tension solid/liquid; σ_{sg} = interfacial tension solid/gas; σ_{lg} = interfacial tension liquid/gas; θ = contact angle solid/liquid).

The contact angle θ describes the angle between the solid surface and a tangent applied at the surface of a liquid droplet. The determination of this angle is performed by the Young Equation (Israelachvili 1995): $\sigma_{sg} - \sigma_{sl} = \sigma_{lg} \cdot \cos\theta$. The theoretical limits of the contact angle are 0° and 180°. 0° means perfect wettability, whereas the value of 180° corresponds with a perfect non-wettability. The theory of wetting is rather complex and is extensively discussed in a review paper of de Gennes (de Gennes 1985). The treatment of details would by far go beyond the purpose of this chapter.

The changed wettability properties of structured surfaces can also be described by means of the Young Equation. For instance, the surface tension of Teflon of 19.1 mN·m^{-1} results in a contact angle of water in air of 110° (Chen et al. 1999). In order to reduce the wettability of a surface, the surface tension has to be lowered. This can be reached by coating processes. The more promising route however, is to micro-/nano-structure the surface, since interchange activities with the surface can dramatically be improved with respect to wettability. Figure 3.139 shows a sketch of a droplet of water on a smooth and on a structured surface.

If a water droplet contacts a hydrophobic surface with a nanostructure it is unable to wetten the surface to such an extent as on a flat surface due to the rather high surface tension of water, compared to the low interfacial ten-

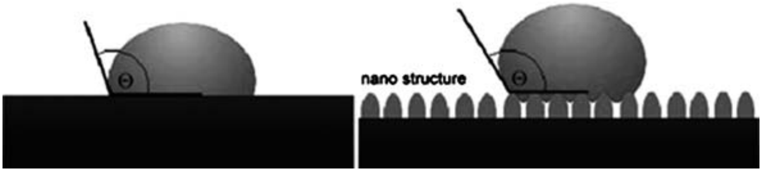


Figure 3.139: Elucidation of the wetting of hydrophobic surfaces by a water droplet without (left) and with nanostructured surface (right).

sion of the surface. The energy necessary to distribute the water between the surface pillars would extend the energy gain by the additional interactions with the surface. Since the contact angle is calculated from the averaged surface energy of the contact area of the support, those parts where the droplet has only contact with air must be considered too. So, the effective surface energy of the hydrophobic material is lowered, though the material dependent value is not changing. Substituted in the Young Equation, a higher contact angle results and herewith a decreased wettability. The reduction of wettability can additionally be increased if the hydrophobic surface is equipped with a double structure, consisting of micro- and nanosized structure units, as is indicated in figure 3.140.

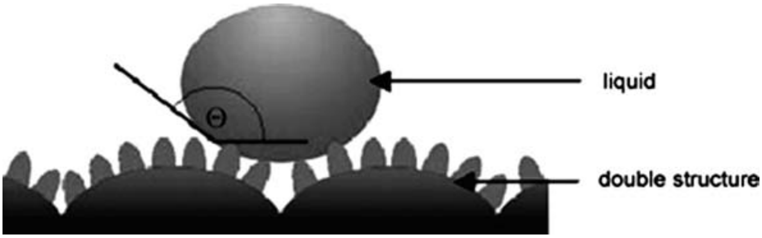


Figure 3.140: Wetting of a doubly structured surface.

On the contrary, wettability is increased if the surface energy of the solid is larger than that of the liquid. In this case a droplet can wetten the interspaces between the structure units, linked with a gain of energy. Technically relevant examples are appropriately structured glass windows that are able to form thin water films minimizing the formation of water stains after drying.

Since formation of hydrophobic surfaces is of remarkable practical relevance, examples based on this effect will exclusively be considered in the following.

Natural systems – The Lotus-Effect

All primary parts of plants are covered by a cuticle, formed of lipids in a polyester matrix (Holloway 1994). Usually such cuticles are of hydrophobic nature. As has been shown in the course of the last 23 decades, many plant surfaces are composed of a variety of microstructures of different materials. Wax crystalloids seem to play an important role to cover the cuticular surface. In spite of numerous investigations since 1940 and an increasing of knowledge on the relation of plant surfaces and environment, only from 1990 on Barthlott et al. found out the decisive function of leaf surfaces by investigations of some 10,000 plant species by means of Scanning Electron Microscopy (SEM) (Barthlott 1990, 1993; Barthlott and Neinhuis 2004). They found out that leaves having epicuticular wax crystals on their surface had not to be cleaned before doing microscopy in contrast to smooth leaves. These observations finally led to the so-called Lotus-Effect, since Lotus leaves attracted special attention due to the permanent clean surface of their huge leaves. Figure 3.141a shows a typical SEM image of a cutout of a Lotus leaf showing a double structure of microsized cells covered by nanosized wax crystallites. Figure 3.141b shows a droplet of water rolling down a structured surface, assembling all dust particles on its way. Figure 3.141c gives an impression of the enormous effect that not only allows cleaning from dust, but even strong glue does not adhere to the leaf surface.

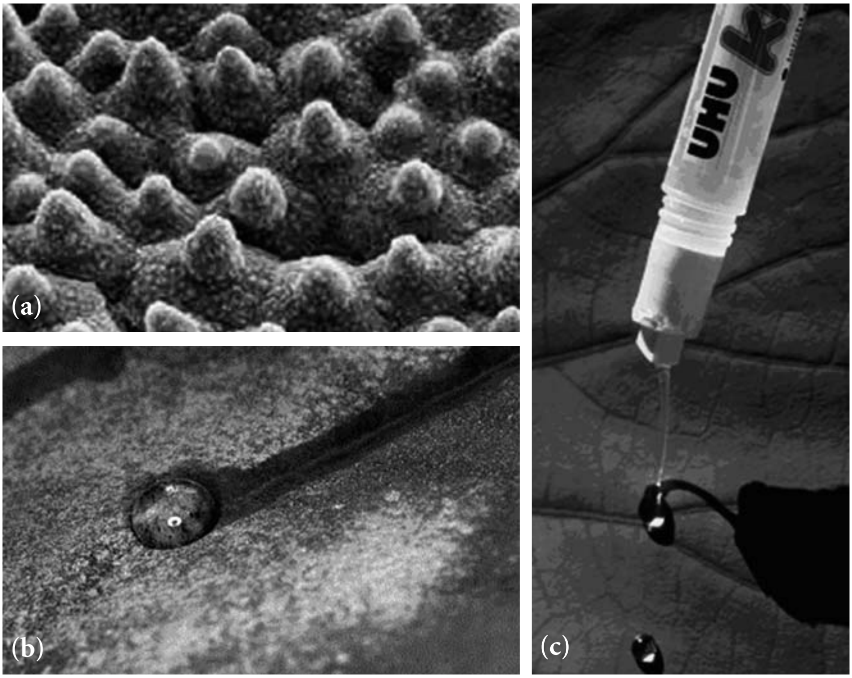


Figure 3.141: (a) SEM image of Lotus leaf surface showing the effective double structure. (b) Image of a water droplet collecting dust on a Lotus leaf surface. (c) Droplets of glue do not adhere on the Lotus leaf. With permission from Prof. W. Barthlott, Bonn.

As could be expected, the discovery of the Lotus-Effect led to important practical consequences. Techniques to nanostructure surfaces of different surfaces have been developed in order to imitate the Lotus-Effect with the consequence that so-called self-cleaning surfaces have become available on very different practical fields. Some of these examples will be discussed.

Nanostructured artificial surfaces

The imitation of the Lotus-Effect requires appropriate techniques to nanostructure surfaces of different nature. Lithographic methods are quite common to structure surfaces however, usually in the microregime or in the upper nanoregime. Other routes to structure surfaces are starting out from coating processes with appropriate materials. Sol-gel reactions have been applied to gain nanostructured surfaces using Al- and Si- nanoparticles as additional components of the sol-gel mixtures (Sporn 1999). Inorganic-organic copolmers (ORMOCERs®) on various surfaces have been used to be imprinted and so to give structured surfaces. Injection molding is the way to shape generated structured surfaces (Ballweg 1999). Some of those nanostructured surfaces have been developed to fabricate antireflex behaviour of glasses, a procedure that is also based on micro- and nanostructured surfaces.

A quite different technique to generate structured surfaces is Physical Vapour Deposition (PVD). It is based on a cathode spray process of appropriate materials onto the surface to be structured (Burr et al. 2004). An ultrahydrophobic surface has been generated by simultaneous etching of polypropylene and etching/sputtering of poly(tetrafluoroethylene) (PTFE) by inductively coupled radio frequency argon plasma (Youngblood and McCarthy 1999; Chen et al. 1999). The semicrystalline polypropylene surface becomes roughened due the differential rates at which the crystalline and the amorphous parts ablate. The degree of roughness is controlled by the time of plasma etching. Fractal structures consisting of alkylketene dimers (AKD) were found to form superhydrophobic structures with contact angles for water of 174o (Shibuichi et al. 1996; Onda et al. 1996). AKD is a kind of wax forming fractal structures when solidified from melted mixtures of AKD and a dialkylketone. Very actual developments to really nanostructure surfaces are to cover them with aligned carbon nanotubes (ACNTs) (Li et al. 2001; Wang et al. 2000). ACNTs can, for instance, be prepared by pyrolysis of metal phthalocyanines on quartz glass plates. The length of the ACNTs can be varied over a wide range by changing the experimental conditions. Contact angles for water up to about 160o could be reached. Nanostructured coatings of quite different nature became available by means of polyelectrolytes and fluorinated amphiphiles (PEFA) (Thünemann 2000). PEFAs are easily to be prepared, and there exists a broad variability in the possible adjustments of their bulk properties. Figure 3.142 shows the principle of this novel and innovative hydrophobic nanostructure.

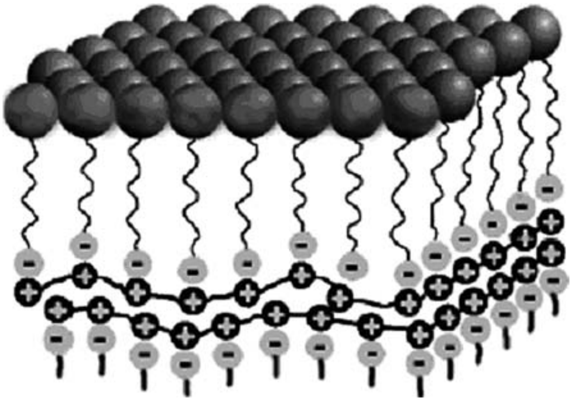


Figure 3.142: Principle of a PEFA complex. The interface towards air is dominated by the very hydrophobic CF_3 groups.

Positively charged polyelectrolyte chains interact with the negative ends of CF_3-terminated amphiphile molecules. The negative charges result from functions such as SO_3^- or COO^-.

Last, but not least a very promising procedure to nanostructure very different surfaces consisting of imprinting techniques shall be mentioned, since it promises successful practical applications in the near future (Sawitowski et al. 2001). This imprinting process is based on the use of nanoporous alumina as stamp material which can easily be fabricated in any size and shape by anodic oxidation of appropriate aluminum surfaces in polyprotic aqueous solutions. Among other advantages, it is the variability of the pore diameters in the range of 10 to 200 nm which is simply depending on the applied voltage. The anodization processes are frequently described in literature and have been developed to routine (Schmid 2002) For imprinting processes the use of massive aluminum that can directly be used as stamp or of aluminum foils is possible. Due to their small thickness, the rupture of the oxide layer is drastically reduced compared to those on compact aluminum stamps. Figure 3.143a shows an Atomic Force Microscopy (AFM) image of an alumina surface with 50 nm pores, whereas figure 3.143b shows a piece of a PMMA (Plexiglass) surface, nanostructured by exactly the same part of the stamp surface of figure 3.143a.

The imprinted part is the exact negative image of the stamp. The averaged density of piles can be calculated as $10^{10} \cdot cm^{-2}$. Their diameter agrees perfect with the pore diameter as well as their distance from each other.

Generally, the results of the imprinting processes are mainly determined by the mechanical properties of the used masks and substrates. The alumina masks, of course must be harder than the material to be imprinted. This is the case for polymers, many metals and coatings. If a substrate is too hard or brittle, warming up during the imprinting process allows successful structurization in spite of great hardness (Levering 2003).

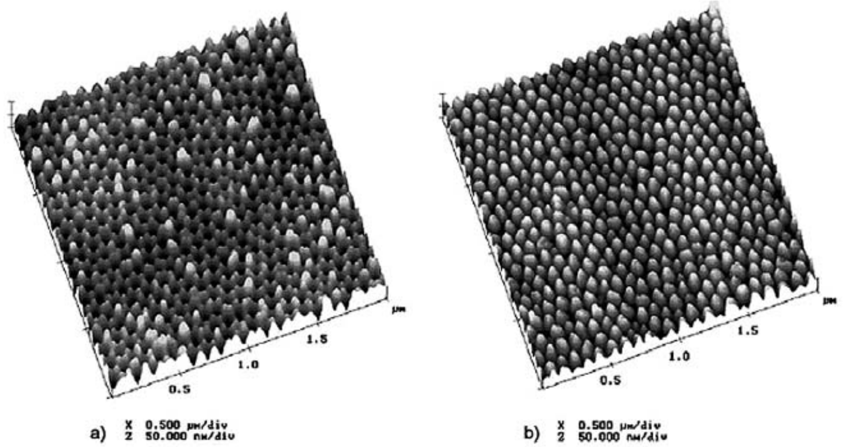


Figure 3.143: (a) AFM image of an alumina membrane surface with 50 nm pores, (b) AFM image of the inverse structure in PMMA, generated by imprinting.

Polymers differ considerably from each other depending on their structure. Polymer chains in thermoplastics are, in contrast to elastomers and duroplasts, not interlinked and so are better suited for imprinting than the others. Plexiglass (PMMA) is one of these polymers that can easily be imprinted, as has been shown above. Best results are obtained, if it is warmed up before imprinting slightly over the so-called glass point. The glass point of polymers indicates beginning softening; sharp melting points do not exist. So, PMMA is perfectly nanostructured with alumina membranes having pores from 10 nm up to hundred or more nm at 110 ± 5 °C and a pressure of 100 MPa. Polycarbonate, polyethylene, and poly(tetrafluorethylene) (PTFE) have successfully been nanostructured. The hydrophobizing of PTFE by a surface structure consisting of ca. 180 nm piles can be seen from figure 3.144.

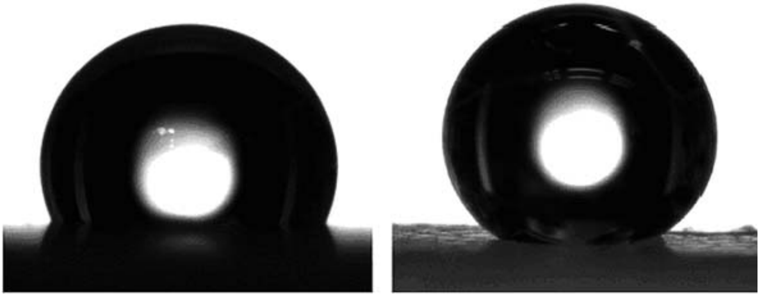


Figure 3.144: Water droplet on a smooth (left) and on a nanostructured (ca. 180 nm) PTFE surface (right).

The contact angle for water increases from 112° for an untreated surface to 145° in case of the nanostructured surface. The resulting contact angle depends sensitively on the dimensions of the structure units, as is to be seen from figure 3.145, where the results of measurements of contact angles in dependence on the structure size are summarized.

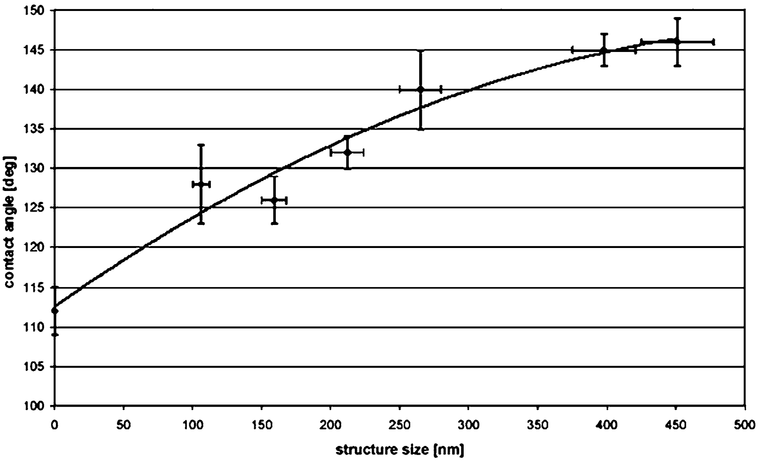


Figure 3.145: Contact angles of water droplets on PTFE surfaces in dependence of the structure size.

A series of metals have also been nanostructured using this imprinting technique (Levering 2003). Aluminum, lead, zinc, brass, iron, nickel, palladium, platinum, copper, and silver could be imprinted by alumina masks with aspect ratios between 0.9 and 1.5. The applied pressures for metals varied between 250 MPa for aluminium and 985 MPa for iron, copper, palladium, platinum and silver. The highest pressure had to be used for nickel (1450 MPa). Nanostructured metal surfaces can not only be used for their changed hydrophobicity/hydrophilicity towards water, but also for the change of their adhesive behaviour towards polymers with possible practical consequences. For instance, an aluminium surface, imprinted by 200 nm pores, looses its tendency to adhere to polystyrene foils completely, compared to non-treated aluminum. This observation may have practical consequences for macroscopic imprinting of polymer foils by aluminum stamps, where adhesion between both materials must be avoided.

Finally, the possibility to nanoimprint coatings shall be mentioned. Coatings of very different nature play increasing roles not only for changing wettability properties, but also for improving transparency of glasses. Coatings may consist of organic and inorganic polymers. Silicon-polyester resins (Silikoftals) on metals have been tested successfully, an attractive perspective to hydrophobize metals by a nanostructure in an hydrophobic coating, since metals tend to get hydrophilized when nanostructured due to their high surface energy. However, other materials like ceramics and glasses, generally household utensils, can also be considered in this connection. Important inorganic coatings are generated by means of sol-gel techniques. Hardened coatings from sol gel processes usually are hard and brittle. Therefore, imprinting has to be performed at the appropriate time before final hardening. Altogether, imprinting procedures for the nanostructurization of surfaces seem to become the dominating techniques. Using nanoporous alumina membranes, the advantage to be able to choose between pores of varying diameters, makes this material to a very promising tool for the future.

Optical Antireflection Behaviour

If an electromagnetic wave changes from a medium with the refraction index n_α into another one with the refraction index n_β with $n_\alpha \neq n_\beta$, two effects can be observed. According to the Snellius refraction law, the direction of the wave will change and part of the beam is reflected. Figure 3.146 elucidates the process.

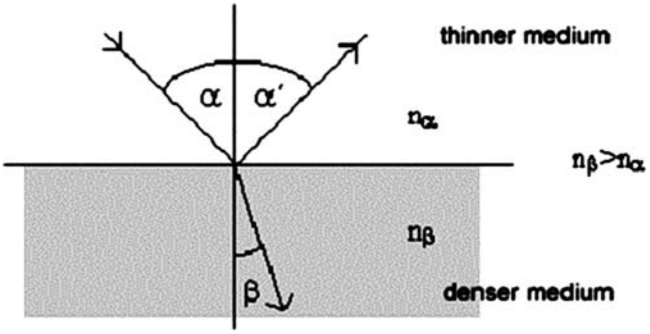


Figure 3.146: Sketch of the reflection of light at the transition into an optical denser medium.

The deflection of the entering light beam at the phase boundary corresponds to $\sin\alpha/\sin\beta = n_\beta/n_\alpha$. The reflection at the phase boundary is described by the Fresnel law. In case of identical magnetic permeabilities of both phases and of no absorption of a perpendicularly entering beam, the reflection coefficient $r = (n_\alpha - n_\beta)/(n_\alpha + n_\beta)$. For the example of a glass surface with $n_\beta = 1.52$, $r \cong -0.21$. The reflection R can be calculated as $R = r^2$, i. e. $\cong 0.04$. In other words, 4 % of the incident light is reflected. For the second phase transition from glass to air the intensity loss is repeated and a total amount 8 % results (Kaiser 2001).This is the reason why antireflection techniques are to be developed.

A frequently used method to reduce reflection of light is to cover the surface with films of defined refraction index and defined thickness. If the refraction index of the film is smaller than that of the substrate, first reflection happens at the phase transition from, usually air, into the coating film and then from the film into the substrate. Assuming that the film thickness is λ/4 of the wavelength and light hits the surface perpendicularly, then the wave reflected at the second phase transition exhibits a phase shift of λ/2 in comparison with the first reflection. This leads to a destructive interference between the both reflected waves, combined with a quantitative extinction of the reflected wave (Thelen 1989; Kaiser 2001).

These discussions on reflections are based on two simplifying conditions: they assume monochromatic light and an angle of incidence of 90° . Practically those conditions are not realistic. One possible way out is the use of several thin layers, linked with adhesion problems. The most promising attempts to solve the problems are derived from nature: the so-called motheye effect is a perfect system to avoid reflection, especially used by night active insects. Their eye surface is nanostructured, consisting of hemispheres of 200–300 nm in diameter. These hemispheres are smaller than the wavelength of visible light, resulting in continuous increase of the refraction index. Figure 3.147 elucidates the physical background of this phenomenon.

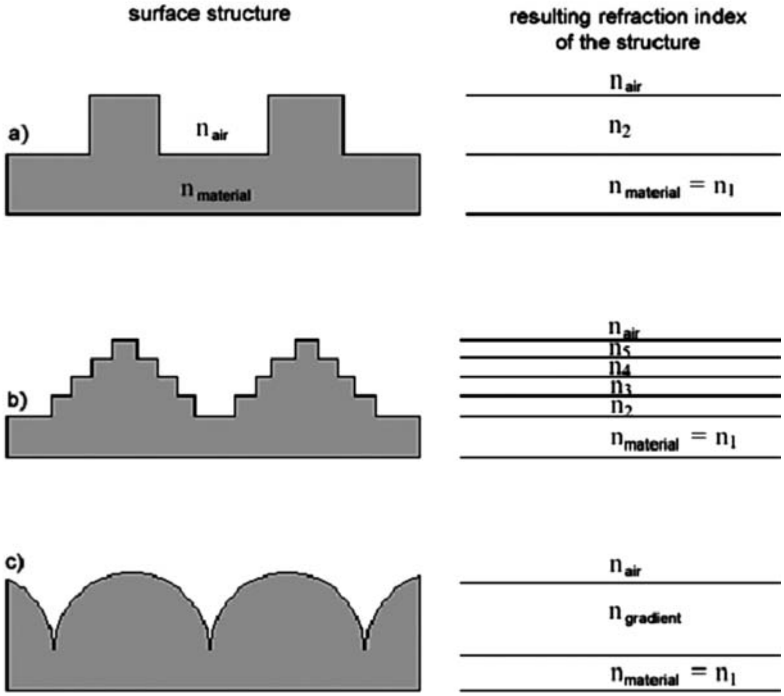


Figure 3.147: Elucidation of the motheye effect.

In figure 3.147a a two-phase system is indicated, consisting of a bottom layer with a refraction index $n_{material} = n_1$. The structured upper layer has, if the structure units are smaller than the wavelength, a refraction index n_2 ($n_1 > n_2$) acting at any point and resulting from the refraction indices of $n_{material}$ and the surrounding gas, usually air. Figure 3.147b shows a more complicated structure with a stair-case structure on top of the support. The part of air is reduced continuously resulting in a step by step increasing refraction index $n_5 < n_4 < n_3$ etc. An ideal structure would behave like in figure 3.147c avoiding a sharp transition between the individual phases. Here, the refraction index increases continuously until reaching that of $n_{material}$.

In order to reduce reflection; for instance of windows, solar cells etc. several large scale techniques have been developed. So, porous sol-gel coatings on glass are rather cheap and can be applied in any dimension (Fraunhofer Gesellschaft 2000). Reflection of glass so could be reduced from 8 % to 1 %. By means of holography stamps with motheye structures can be realized which then can be used to imprint polymer foils. In principle, most of the techniques to nanostructure surfaces, described in the first subchapter of this section, can also be applied for antireflection systems and have not to be repeated here. As an example, results by imprinting of PMMA with nanoporous alumina stamps with respect to antireflection shall be discussed. Figure 3.148 shows the UV-vis transmission spectra of untreated and various imprinted PMMA windows in dependence on the structure size.

Compared with untreated PMMA, all nanostructured samples show an increased transmission of visible light with maxima at 520 nm, 720 nm and 870 nm, independent on the structure size. A maximum transmission is reached with the smallest structure units, namely those of about 70 nm.

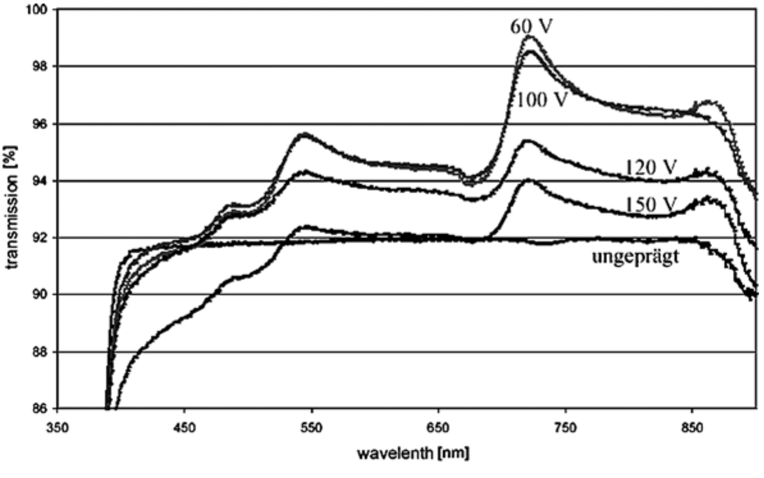


Figure 3.148: UV/vis transmission spectra of PMMA glasses imprinted by alumina masks with different pore sizes.

Summarizing this chapter it can be stated that nanostructured surfaces, in some cases combined with microstructured surfaces, exhibit best results with respect to self-cleaning properties, if the material is of hydrophobic nature. Antireflection behaviour can also considerably be improved using nanostructured surfaces. Both effects are of enormous practical relevance. That is why Nanoscience on that field already has developed to real technologies of increasing importance. Besides self-cleaning of house fronts, self-cleaning windows, cars, roofs, ceramics etc. seem possible or have already been realized. Improved antireflection properties will become of increasing importance, especially for technical uses were light is to be absorbed in a maximum manner like in solar cells and other light consuming processes.

On the other hand, it has to be stated, that the described effects not conclusively meet our definition of Nanotechnology that is based on effects clearly linked with nanosized effects. Self-cleaning of surfaces, as well as improved antireflection behaviour, happens already in the microregime. In combination with nanosized structure units the effect can be improved, however they are not a condition to release them. In spite of that both effects are considered here, following less restricted opinions in the public eye.

Low-k Dielectrics Field

The further miniaturization of electrical circuits require new materials with extraordinary low dielectric constant and high breakdown voltage to allow an effective electrical insulation of neighboring and crossing leads on a chip. The materials must suppress the leakage currents and unwanted cross-talk in electrical circuits. Therefore, semiconductor industry is forced to look for alternatives to SiO_2, i.e. for materials, which have a lower dielectric constant than $\varepsilon_r \approx 4$. Promising materials are fluorinated SiO_2 and polymers, such as PTFE ($\varepsilon_r = 2 - 2.5$). To further decrease the dielectric constant, nanoporous materials, either silica-based (e.g. so-called *Nanoglas®*) or polymer-based (e.g. so-called *Nanofoam®*) are currently studied. To increase the porosity, molecularly linked silica-oligomers (e.g. silsequioxanes) forming a network with nanometer sized pores and channels may be very promising for this application.

The decrease of the dielectric constant with decreasing material density is not restricted to the nanometer range and is therefore not a pure nanoeffect. Nevertheless, such materials are already applied as dielectrics for electrical circuitry on integrated chips. Here they are essential for further miniaturization.

Self Cleaning Surfaces, Photo-Catalysis

Semiconductor photo-catalysis has proven to be a promising technology for use in the clean-up of water contaminated with hazardous industrial by-products. Particular semiconductors have shown to be light harvesting materials and mediators in the photochemical degradation of environmental contaminants (Bems et al. 1999; Vautier et al. 2001). The size and shape dependent optical and electronic properties of nanoparticles make it possible for exploiting them in light induced chemical reactions. When a semiconductor is brought in contact with an electrolyte, the migration of charge carriers occurs until the Fermi level of the semiconductor is equilibrated with the chemical potential of the electrolyte. These result in the formation of a space charge layer in the surface region of the semiconductor and a Helmholtz double layer in the electrolyte adjusted to the semiconductor surface. The space charge region in a semiconductor is relatively large, extending up to 100 nm. When the size of the semiconductor particle is smaller than the space charge region, the particle is too small to develop a space charge layer and as a consequence, the position of the band edges of semiconductor nanoparticles will shift and the band gap will increase (Kisch and Macyk 2002). Most of the published work on photocatalysis are done with titania (TiO_2) (Kamat and Meisel 2002). Its large bandgap energy 3.2 eV necessitates UV-excitation to induce charge separation within the electrons and holes. The ability of oxides to act as catalysts in the radiolytic degradation of contaminants such as chlorinated aromatics (Cl-Ar) has recently been demonstrated (Zacheis and Kamat 2001). Only reductive pathways involving dechlorination was found to occur on oxide surfaces. Semiconductor nanoparticles offer interesting advantages in the heterogeneous photocatalysis process: high absorption cross section of the incident photons, fast carrier diffusion and suitable redox levels of the valence and conducting band edges that can yield high efficiencies in converting light energy to interesting and useful redox reaction. For example, if the reduction of a particular species in the solution is of interest, the conduction band of the semiconductor must be more negative than the relevant redox level, while the oxidation of the particular species by valence band holes must be more positive than the relevant redox potential. All redox couples having a standard redox potential more positive than that of the conduction band and more negative than that of the valence holes can, in principle, be reduced and oxidized respectively on the colloidal surface.

The photocatalytic activity of titanium results in thin coatings of the material exhibiting self cleaning and disinfecting properties under exposure to UV radiation (Antimicrobial Coatings). These properties make the material a candidate for applications such as medical devices, food preparation surfaces, air conditioning filters, and sanitary ware surfaces.

Electromechanical Data Storage (IBM Millipede)

Introduction

While magnetic data storage systems with storage densities in the range of about 70 to 100 Gigabits per square inch approach their technical limit, since a couple of years IBM scientists have been investigating a highly innovative data storage system, called "Millipede". When a new technology like the Millipede is going to substitute the older one some preconditions have to be fulfilled: Naturally it should exhibit considerable superiority to magnetic storage in its technical specification especially storage density and writing/reading time. To remain competitive over a long time, it should have potential concerning further technical improvement and cost reduction. The Millipede developed by IBM researchers might have the perspective to become the data storage method of the next generation. An excellent review on the whole topic has been presented by Vettiger (2003).

The Millipede Concept

Design and function of the Millipede

The Millipede from IBM is in principle nothing else but a miniaturized perforated card, as they were used as storage media in the first computers some decades ago. It is in principle nothing else but a scaling down of a well known storage technology and thus in the sense of our definfition only a miniaturization and not a real Nanotechnology. The principle is shown in figure 3.149:

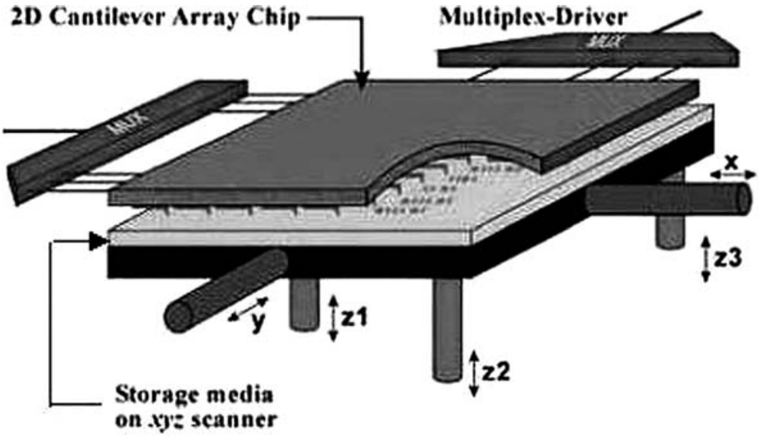


Figure 3.149: Principle of micromechanical scanning device of Millipede (from IBM homepage 2004 by permission of IBM Research GmbH Zürich).

The storage medium is a thin PMMA polymer layer of about 50 nm thickness on a wafer substrate which is located on a xyz-scanner. Above the polymer layer a two dimensional array of STM tips positioned on U-shaped Silicone cantilevers is arranged as displayed in figure 3.150:

Figure 3.150: Two-dimensional of multi-cantilever array of a Millipede (from IBM homepage 2004 by permission of IBM Research GmbH Zürich).

As described more detailed in section 3.2, the information in the storage layer is written and read out parallel by the AFM tips by scanning in contact with the storage layer. The scanning of the tip is displayed in figure 3.151a for a large area and more detailed in figure 3.151b. The information is represented by pits, produced by local melting of the storage medium by heating the AFM tip, or by the absence of pits in the storage layer underneath the AFM tip. The approach of the Millipede AFM tips to the surface of the storage layer in z-direction is not controlled individually for each individual AFM tip but for the entire chip. This requires accurate control and uniformity of height and shape of the tip and the cantilever bending. This is achieved by three sensors, the fourth being a spare, which provide an signal with feed back control in the z-direction. By this vertical position control tip and storage medium wear resulting from large force variations and geometrical nonuniformities can be avoided to a large extend.

The cantilever array has been produced with Silicone microsystemtechnology (MST). The scanning distance is currently 92 µm in x- and y-direction (Vettiger 2003). This is exactly the distance equivalent to the cantilever x/y-pitch. So each cantilever-tip-system has its own storage field.

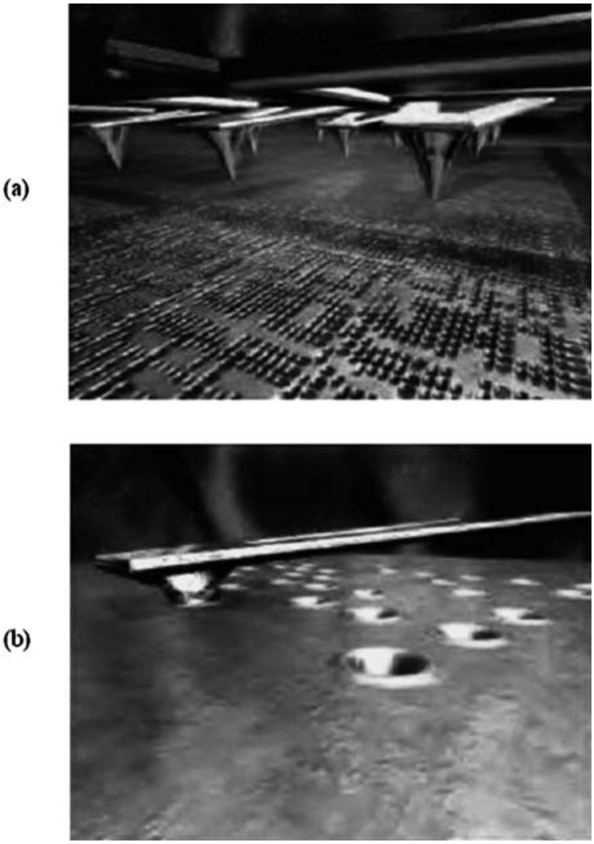


Figure 3.151: Scanning process with pits which represent the storage information (from IBM homepage 2004 by permission of IBM Research GmbH Zürich).

The IBM researchers have realized a demonstrator with a matrix of 32 x 32 = 1024 cantilevers and a chip area of about 3 x 3 mm^2 which is shown in figure 3.152.

To avoid difficulties in lateral tracking between write and read cycles by different thermal expansion of cantilever chip and substrate the temperature of chip and substrate is held within a temperature range of 1 °C.

The IBM researchers have realized a demonstrator with a matrix of 32 x 32 = 1024 cantilevers and a chip area of about 3 x 3 mm^2 which is shown in figure 3.152. The reading/writing time of a single tip is limited to the range of some microseconds mainly due to the mechanical properties of the cantilever and the thermal transfer from the AFM tip to the substrate. This problem can be overcome by parallel processing of the AFM tips during reading and writing which enhances writing and reading velocity by orders of magnitude.

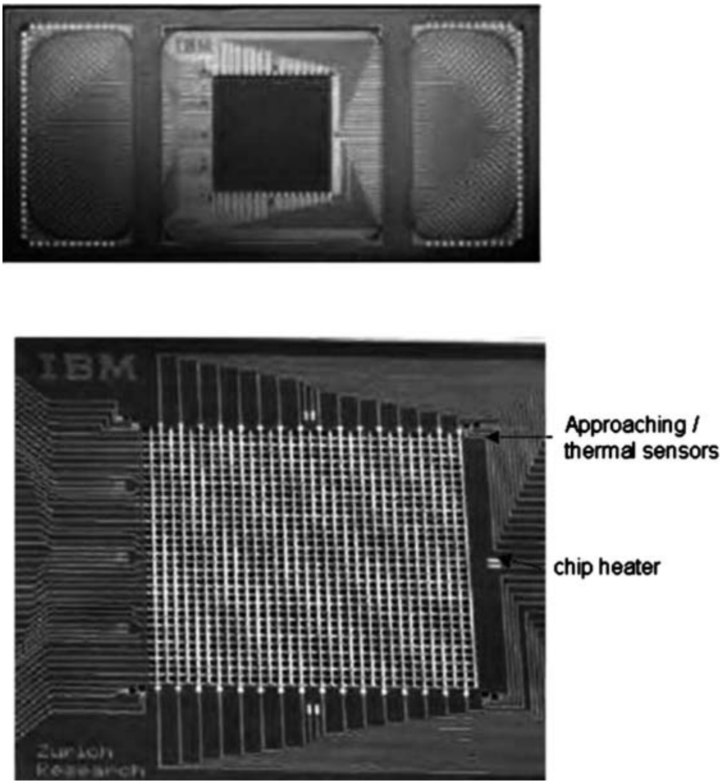


Figure 3.152: Chip with 32 x 32 = 1024 cantilevers (from IBM homepage 2004 by permission of IBM Research GmbH Zürich).

The Process of Writing and Reading the Information

Both, writing and reading with the Millipede is a thermomechanical process. But these processes work at different temperatures.

Design of a Single Sensing Element
The design of a single element is shown in figure 3.153 below.

The whole element is made from Silicone fabricated in MST compatible with CMOS technology. At the end of the cantilever legs a heater platform is positioned with the AFM tip on top. The wiring for heating the tip and for multiplexing is integrated. The electric resistance of the heater platform is in the range of some kOhms while the resistance of the highly doped cantilever leg is about 400 Ohms.

Writing information with the Millipede
The principle of the writing process of one single tip is displayed in figure 3.154.

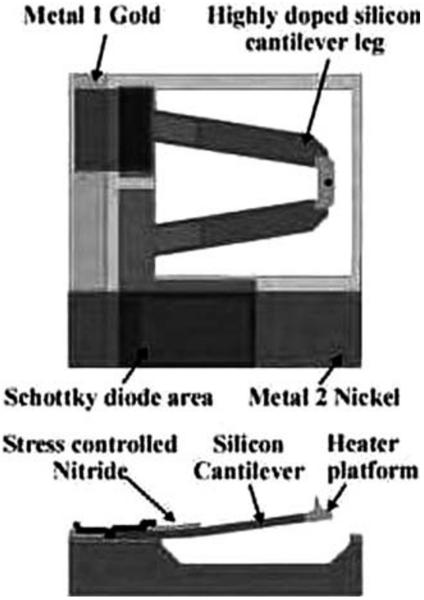


Figure 3.153: Cantilever design (from IBM homepage 2004 by permission of IBM Research GmbH Zürich).

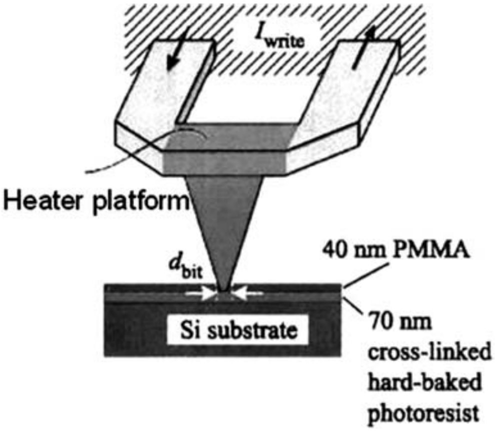
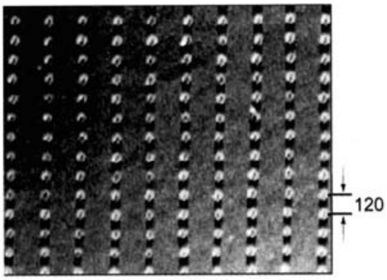


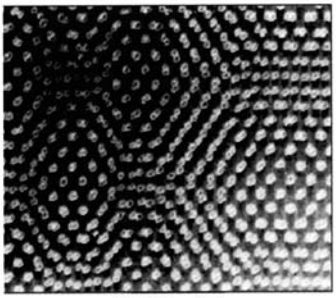
Figure 3.154: Schematic presentation of the writing process (from Vettiger P, Despont M, Dürig, U Lantz MA, Rothuizen HE, Binnig GK:"AFM-Based Mass storage- The Millipede Concept" in "Nanoelectronics and Information Technology", Wiley VCH 2003, ISBN 3-527-40363-9, chapter 28, 689-701; (reproduced by permission of Wiley VCH, STM-Copyright & licenses).

While the tip is scanned over the substrate surface it is pressed with a loading force of about 50 nN against the substrate. For writing a bit the tip is heated via the heater platform to a temperature >400°C at which the PMMA polymer layer is molten and the tip intrudes into the polymer layer (s. figure 3.151). Viscosity and thickness of the polymer layer, writing velocity have to be tuned very accurate.

In order to reduce wear of the tip a hard baked cross linked photoresist layer is deposited between the storage medium layer and the Silicone substrate. Figure 3.155 shows two examples of pit patterns. Figure 3.155a displays a regular alignment of 40 nm pits with pitch 120 nm. In figure 3.155b the pits were written with variable pitch very close to each other but without merging although with still a degraded quality. Theoretically this corresponds to a bit areal density of 400 Gbit per square inch. First results with the formerly described 32 x 32 cantilever array chip resulted in storage densities better than 100 Gbit per square inch.



Pitch 120 nm
(a)



Variable pitch
(b)

Figure 3.155: a) Regular arrangement of pit pattern; b) Irregular arrangement of pit pattern with higher areal density. From Vettiger P, Despont M, Dürig, U Lantz MA, Rothuizen HE, Binnig GK:"AFM-Based Mass storage- The Millipede Concept" in "Nanoelectronics and Information Technology", Wiley VCH 2003, ISBN 3-527-40363-9, chapter 28, 689–701; (reproduced by permission of Wiley VCH, STM-Copyright & licenses).

With single tips 10 nm pits have been demonstrated which is equivalent to a storage density of 1 Tbit per square inch.

It is also possible to erase and to rewrite bits in the polymer layer. It has been shown that by heating the deformed volume above the glass temperature of the polymer the surface flattens back by internal stresses and surface tension as driving forces to its unstressed original state.

Reading information with the Millipede

Reading with the Millipede is a thermomechanical process similar to writing; the principle can be seen in figure 3.156.

While reading the information in the storage layer the temperature dependent resistor in the heating platform is kept at a constant temperature of about 300°C which is below the softening temperature of the polymer. Dependent on the position of the cantilever different amounts of energy are necessary to maintain a constant resistor temperature.

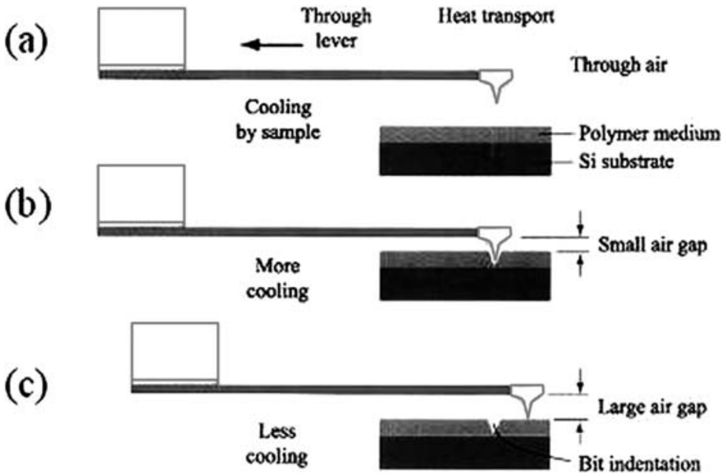


Figure 3.156: Schematic description of the reading process. From Vettiger P, Despont M, Dürig, U Lantz MA, Rothuizen HE, Binnig GK:”AFM-Based Mass storage- The Millipede Concept” in “Nanoelectronics and Information Technology”, Wiley VCH 2003, ISBN 3-527-40363-9, chapter 28, 689-701; (reproduced by permission of Wiley VCH, STM-Copyright & licenses).

With the tip not in contact with the substrate heat loss is mainly due to heat conduction through the legs of the cantilever (figure 3.156a). An increased heat loss to the substrate will be observed when the tip gets into contact with the layer surface. However, as long as the tip does not “fall” into a pit the polymer layer effects a thermal insulation (figure 3.156c). But when the tip in a pit gets into direct contact with the substrate a much higher heat loss will be observed and much more energy is required to maintain a constant temperature in the heating resistor and which can be taken as a measure for a bit information (figure 3.156b).

According to the first reported results from the first demonstrators the Millipede concept might be a very promising novel technology. The up to now observed storage densities with more than 100 Gbits per square inch are by far not the limit. Further development with much higher areal densities at the molecular or atomic scale seem to be possible.

Due to the demands for further improvements the current activities focus mainly on the following topics (Vettiger 20003):

- Overall system reliability including bit stability, tip and medium wear, erasing/overwriting;
- Limits of data rate (signal/noise ratio, areal density, array and cantilever size);
- CMOS integration;
- Optimization of write/read multiplexing scheme.

The IBM researchers have already some visions on possible further applications of the Millipede in the farther future (Vettiger 2003). When the Millipede could be provided with some intelligence a smart Millipede would push open the door to much more applications like e.g. in imaging devices for pattern recognition.

It will be very interesting to look at the further development of the Millipede.

Beside the thermomechanical Millipede concept of IBM there exist some alternative ideas how by means of multicantilever systems high density non volatile storage can be achieved. Examples are

- Use of a magnetic storage medium instead of the polymer storage layer. Writing and reading is done with magnetic tips.
- Use of ferroelectric storage layer. The information is stored by local polarisation of the ferroelectric storage medium by means of the AFM tip.
- Phase change material as storage medium (Hewlett Packard). It is believed that the resolution can be brought down to the atomic scale (ARS = atomic resolution storage).

Very little is being known on the state of the art of these interesting ideas. Even if it seems that the IBM concept is by far ahead in the development, these alternatives should be looked at more intensively with respect to their potential. For this reason, interesting alternatives to the IBM concept should be investigated.

4 Commercial Perspectives of Nanotechnology – An Assessment Based on Patent Data

4.1 Introduction

Because of its potentially large impact on many industries, Nanotechnology is widely considered to be a revolutionary technology that could obliterate business models and restructure vast parts of the economy (BMBF 2002; CMP Cientifica 2002; Luxcapital 2003). The world market for Nanotechnology in 2001 was estimated to be worth EUR 54 billion (National Science Foundation 2001; DG-Bank 2001). The total market for Nanotechnology is expected to grow by 15%-17% p.a. leading to a total market value of EUR 220 billion in 2010 (DG-Bank 2001). According to the more optimistic forecast of the NanoBusiness Alliance, the market volume of EUR 220 billion will already be reached by 2005 and will have passed US$ 1 trillion in 2015 (National Science Foundation 2001). These very optimistic market forecasts explain why Nanotechnology has attracted great attention in the public and private sector (BMBF 2002; CMP Cientifica 2002; Luxcapital 2003). Increasing venture capital funding, the growing number of start-up businesses and private research and development (R&D) and patenting activities indicate that private companies and investors see a significant business opportunity in the field of Nanotechnology.

These forecasts face some fundamental problems that cast significant doubts on their validity (Schmid et al. 2003). A first fundamental problem of existing market forecasts is that they are often based on the assumption that applications depending on Nanotechnology will eventually replace existing technologies and thus capture large shares of an existing market. Market estimates for Nanotechnology are often based on forecasts for already existing markets assuming that the entire or large shares of the future market will belong to nanotech products. However, only the share of nanotech products in the relevant value chain could be used as a meaningful indicator for the commercial value of Nanotechnology. Second, a high degree of technological uncertainties make market forecasts at this stage difficult. Nanotechnology is still in its infant stages of technological development (BMBF 2002; CMP Cientifica 2002; Luxcapital 2003; WGZ-Bank 2002). Thus, in many areas of Nanotechnology it is yet uncertain, if the technological objectives will eventually be achieved in the predicted time frame and if these technologies will finally lead to commercially viable products on the market. In addition, advances in complementary technologies, e.g. manufacturing technologies, and improvements of existing or newly upcoming alternative technologies can impact the commercial viability of Nanotechnology. Third, a superior technology may not necessarily become an innovation (Brockhoff 1999; Hauschildt 2004). A technology, which is superior from a technical standpoint, may fail in the market because the customer does not recognize the benefit of the technology or is not willing to pay a higher price for the more expensive technology (Ernst 2002; Montoya-Weiss and Calantone 1994). Due to a lack of customer acceptance, the technology fails in the market and can therefore not be called an innovation. A commercially successful technology, i.e. an innovation, must either offer additional benefits to the customer that justify higher prices or it must deliver the same functionality as existing technologies or products at a lower price. In both instances, the added value to the customer is higher for the innovation than for the existing product. Nanotech products can only be successful from a commercial perspective, if they offer a higher added value to customers than competing products. This effect is extremely difficult to assess in a very early stage of technological development.

This discussion leads to the conclusion that valid market forecasts for Nanotechnology are hardly feasible at this stage of technological development (Schmid et al. 2003). One should rather aim for assessing technological and economic opportunities in the field of Nanotechnology based on more reliable and objective information. A promising approach for this objective is the analysis of patent activity in Nanotechnology. The basic notion is that patent activity reflect the present research and development (R&D) activities in the field of Nanotechnology. Patenting priorities and patenting growth rates should reflect those fields within Nanotechnology, which promise – based on the perception of patentees – more immediate and significant economic returns. Taking patents as an indicator of R&D is justified because extensive empirical research has shown a positive correlation between R&D, patents and innovation (Griliches 1990; Ernst 1996; Ernst 2001). A further advantage is that patents can be assigned to subfields of Nanotechnology as discussed in this book (chapter 3). This allows a very detailed analysis of R&D activities in the field of Nanotechnology.

Summarizing, the objective of this chapter is to assess the attractiveness of various subfields of Nanotechnology as defined in this book by means of a patent analysis. Patent activity reflects levels, priorities and dynamics of R&D activities in the field of Nanotechnology (Ernst 2003). The results show the patent positions of countries, firms, research institutions and inventors in sub-fields of Nanotechnology and the dynamics of patent growth in these technology fields. They have implications for setting further R&D priorities, both in the private and the public sector.

The chapter is organized as follows: section 4.2 discusses the suitability of patents as indicators of R&D. Section 4.3 introduces important indicators for assessing patenting behavior at multiple levels of analysis. The procedure and the results of the patent analysis in the field of Nanotechnology are described in section 4.4. The chapter ends with a brief summary of key findings and a discussion of implications in section 4.5.

4.2 Patents as Indicators of Technological Developments

Following Schmookler's (1966) groundbreaking studies in the 50s and 60s, the status of patents in innovation processes has attracted much attention in the literature (Griliches 1990). The innovation process describes activities and their results which lie between the conception of a new idea and its introduction to the market (Brockhoff 1999). If technical requirements of an idea are realised successfully through research and development (R&D), the result is an invention (Brockhoff 1999). One expression of technical success may be a ´patent application` (Hauschildt 2004). Launching an invention on the market requires resources from other parts of the organisation, e.g., production and marketing. The successful introduction of an invention into the market or into production is termed a ´product` or ´process innovation` (Hauschildt 2004).

Pursuing this notion to its logical consequence, patents can be regarded as the result, or output of technically successful R&D activities. There have been extensive discussions in the literature as to whether patents do in fact measure the output of inventive activities, or whether they are merely an indicator of R&D input. The latter view is based on the argument that patents only reflect the extent of R&D expenditures and therefore represent an input into the innovation process (Schmookler 1966). This should be distinguished from the notion of invention output, which considers patents as the result of R&D activities, which is directly associated with economic output variables of innovation success, such as growth in productivity, profitability or the market value of firms (Griliches 1990). Consequently, patents represent a qualitative weighting of R&D output and thus reflect those elements of technological progress that lead to economic growth. Griliches (1990) summarises these aspects as follows:

> *Ideally, we might hope that patent statistics would provide a measure of the output of such [inventive] activity, a direct reading on the rate at which the potential production possibilities frontier is shifted outward. The reality, however, is very far from it. The dream of getting hold of an output indicator of inventive activity is one of the strong motivating forces for economic research in this area. (Griliches 1990:1669)*

This quote already implies that the use of patents as an indicator of both the input and the output of R&D activities is faced with problems. The meaningfulness of patents is generally restricted by the fact that not all inventions are patentable, that not all patentable inventions are patented and that the economic significance of inventions varies enormously (Basberg 1987; Griliches 1990).

The conceptual relationship between inventions, patents and innovations is sketched in figure 4.1. First, not all inventions resulting from R&D are patentable. This applies in particular to basic research due to a lack of immediate commercial use of this type of research (Brockhoff 1997). It is therefore suggested in the literature to measure the outcome of basic research rather by means of scientific publications (Hauschildt 2004). Furthermore, not all patentable inventions lead to a patent application, for example where other tools to assert the appropriability of R&D earnings are available, as for example trade secrets (Franke 1993; Levin et al. 1987). The share of all patentable inventions that are actually patented can be seen as an indicator of a company's propensity to patent (Mansfield 1986). In industries where patents provide effective protection, firms are likely to be more patent-active. This is typically the case in high-tech industries with high R&D expenditures, especially in the pharmaceutical, biotechnology, chemical and electronics industry (Ernst and Omland 2003). Thus, the suitability of patents as an indicator of R&D activities largely depends on the nature of technology and the effectiveness of patent protection in various industries.

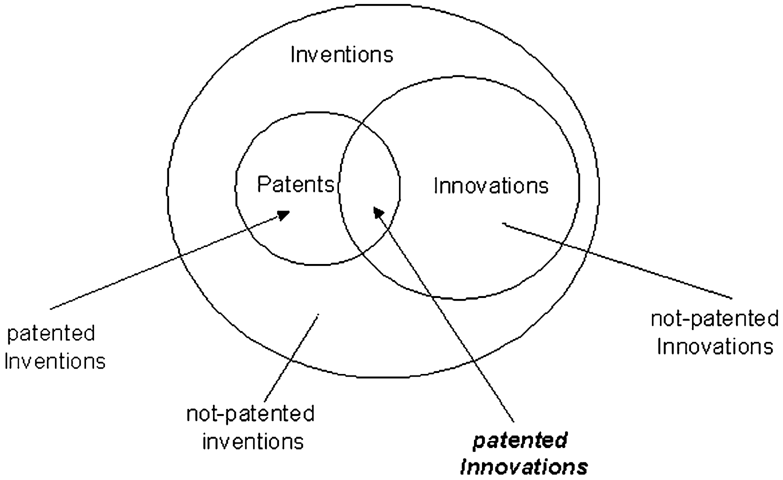


Figure 4.1: The Relationship between Patents, Inventions and Innovations. Source: Basberg (1987: 133).

The technological and economic quality of patents is extremely heterogeneous; evidently, a few patents are of high quality and while the vast majority is of low quality (Schankerman and Pakes 1986). Patent citations, patent applications at foreign patent offices and patents granted can be used as indicators of patent quality (Basberg 1987; Ernst 2003). Figure 4.1 demonstrates this effect in the relatively small intersection between patented inventions and innovations actually found on the market. Patented innovations are clearly of greater economic significance, so these patents meet the previously described conditions for use as a measure of R&D output.

Empirical research has frequently shown that the level of R&D expenditures is positively correlated with patenting (Griliches 1990; Hall et al. 1986; Pakes and Griliches 1984). It has been further shown that even the level of research expenditures is positively related to patenting output (Ernst 1998).

It can therefore be argued that patents are an effective input indicator to reflect the level of R&D activities (Griliches 1990).

Further empirical studies have shown a positive correlation between patents and economic performance parameters, if patents are differentiated according to their technological and economic quality (Austin 1993; Deng et al. 1999; Ernst 1995; Ernst 2001; Hall et al. 1999; Lerner 1994; Narin et al. 1987; Shane 2001). Suitable indicators of patent quality are patent citations, the international and technological scope of patents and the number of patents granted (Ernst 2003; Ernst 1996).

These results have significant implications for both business practice and empirical research. The more patents reflect the economic results of R&D activities, the more meaningful they become as an indicator of the output of R&D activities (Ernst 2003; Griliches 1990). The information contained in patents has a particular advantage because patent data are easily accessible via databases, are not subject to the problems of imprecise definition and lack of comparability, are objective information, allow the coverage of international developments, can be allocated directly to more detailed fields of analysis, e.g., fields of technology, products or inventors and are often a timely indicator of technological changes (Brockhoff 1992; Ernst 1997; Ernst 1998; Ernst 2003). Figure 4.2 summarizes the advantages of patent data as an information source about technological developments.

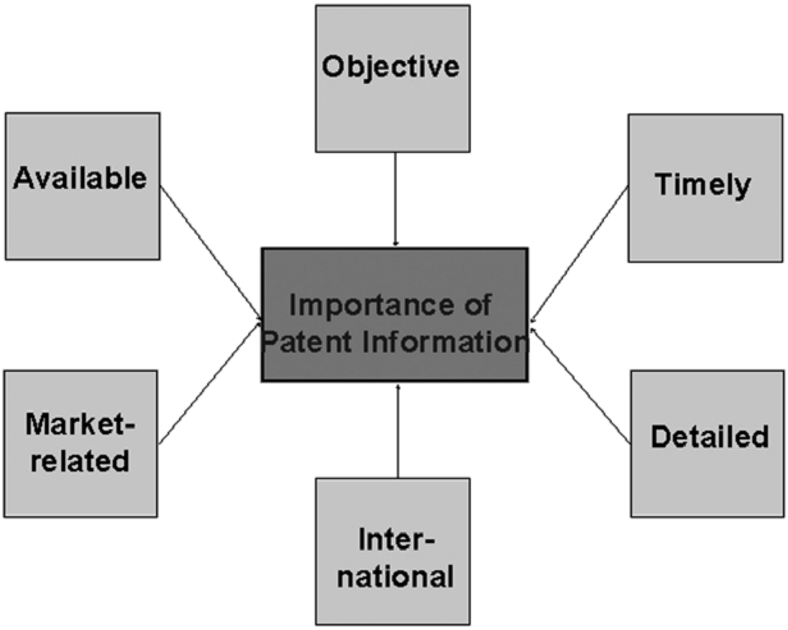


Figure 4.2: Advantages of Patents as an Information Source.

Despite theses obvious advantages and the positive statistical correlations between R&D, patents and innovation, it should not be overlooked that patents are an imperfect indicator of technological developments. Patent statistics should therefore be analysed very carefully and – if possible – they should be complemented by other indictors, such as scientific publications: "We have the choice of using patent statistics cautiously and learning what we can from them, or not using them and learning nothing about what they alone can teach us" (Schmookler 1966:56). With regard to Nanotechnology it can be argued that overall patenting activity has increased significantly in the last decade (Bachmann 1998; Luxcapital 2003). Patenting has a very prominent role for start-up firms in the field of Nanotechnology, because a strong patent position is important to secure competitive advantage and to attract venture funding (Ernst and Omland 2003; Luxcapital 2003). It can therefore be argued that patents are a good indicator of R&D activities in the field of Nanotechnology. Patents may reflect more these R&D activities, which look most promising regarding commercially viable applications of Nanotechnology. Patents may not fully reflect those R&D activities in Nanotechnology, which are in the stage of pure science in an exploratory stage of development. Here, further indicators such as publications, can be used. However, for the main purpose of this paper patents are believed to be an adequate indicator of R&D, because this analysis has a strong focus on assessing the commercial potential of Nanotechnology. This is best reflected in the patenting activities of all institutions and inventors, which conduct R&D in the field of Nanotechnology. Beyond that, patents can be assigned to sub-fields on Nanotechnology as listed in this book (chapter 3), which allows a consistent and more detailed analysis.

4.3 Indicators and Tools for Systematic Patent Analyses

4.3.1 Patenting Indicators

Table 4.1 summarizes an important set of indicators which can be used to analyze patent data at various levels. Generally, these patenting indicators can be developed at the individual inventor level (Ernst et al. 2000), the organizational level (Ernst 2003), the industry level (Glissmann and Horn 1988) or the country level (Furman et al. 2002). Here, the firm level is taken to illustrate the various patenting indicators. The data necessary to calculate these patenting indicators can be retrieved from available patent databases such as Derwent Information's World Patent Index (WPI) or Micropatent. All indicators are most informative if their dynamic development is analyzed over time (Ernst 1999).

A firm's 'patent activity' in certain technological fields is a fundamental patenting indicator and decreasing or increasing a firm's patent activity in a technological field can be interpreted as changing levels of R&D activity and thus future technological and commercial interest. The 'technology share', based on patent applications, measures a firm's competitive position in a technological field. Conceptually, the technology share captures a firm's competitive position in R&D, as does the market share in the marketing domain. A significant drop in a firm's technology share should lead to a reassessment of its R&D strategy (Brockhoff and Chakrabarti 1997). 'R&D emphasis' illustrates the importance placed on a specific technological field within the firm's entire R&D portfolio and highlights differences in companies' R&D strategies.

The value of patent information is greatly enhanced if varying levels of a patent's quality is taken into account. It has been suggested in the literature to use the following indicators of patent quality: (1) ratio of granted to filed patents; (2) international scope; (3) technological scope and (4) citation frequency (Austin 1993; Deng et al. 1999; Ernst 2003; Hall et al. 1999; Lerner 1994; Shane 2001). The weights for each indicator of patent quality can be determined empirically, where the weights reflect the indicator's relative impact on the commercial value of a patent (Ernst 2003). Based on the weights, an index on average 'patent quality' can be calculated (Ernst 2003).

Once patent quality is determined, overall 'patent strength' can be calculated (table 4.1). A better measure of 'technology share' including aspects of patent quality can be derived for each technological field in a similar manner as described above. It shows the competitive position of a firm in a technological field. The 'relative patent position' transforms the 'technology share' into a range of values between 0 and 1; this facilitates the identification of leading firms and the assessment of technological distances between competitors.

Table 4.1: Important Patenting Indicators for Competitor Monitoring Patent Indicator Definition Meaning

Patent Indicator	Definition	Meaning
Patent activity	Patent applications (PA) of firm i in technological field (TF) F (PA_{iF})	Extent of R&D expenditures in TF F; Interest of firm i in TF F
Technology share (based on patent applications)	PA_{iF} / PA of all competitors in TF F	Competitive position regarding technology (quantitative)
R&D emphasis	PA_{iF} / Number of firm's (i) total patent applications	Importance of technological field for the firm (R&D emphasis)
Co-operation intensity	Number of joint patent applications with partners in TF F / PA_{iF}	Access to external knowledge (plus identification of partners)
Share of granted patents (Q_1)	Granted patents of firm i in TF F / PA_{iF}	Technological quality of patent applications
Technological scope (Q_2)	Diversity and number of IPC classes in a patent application	Technological quality of patent applications
International scope (Q_3)	Size of patent family and share of triad (US, JP and EPO) patents of PA_{iF}	Economic quality of patent applications
Citation frequency (Q_4)	Average citation frequency of PA_{iF}	Economic quality of patent applications
Average patent quality (PQ_{iF})	Sum of all indicators of patent quality ($Q_1 - Q_4$)	Average total quality of all patent applications of firm i in TF F
Patent strength (PS_{iF})	Product of average patent quality (PQ_{iF}) and patent activity (PA_{iF})	Technological strength of firm i in TF F
Technology share (based on patent strength)	PS_{iF} / PS of all competitors in TF F	Competitive position regarding technology (qualitative)
Relative patent position (Relative technology share)	PS_{iF} / Max. patent strength of a firm in TF F	Distance to the technological leader in TF F

Source: Ernst (2003:235)

4.3.2 Patent Portfolios

One of the most important decisions to be made in technology management is the investment of R&D resources; senior management must decide how much of the R&D resources will be spent on which type of technology. Portfolio concepts have been developed in order to facilitate this decision making process (Ernst and Soll 2003). Portfolios have the advantage that they structure and visualize complex problems while focusing on the most relevant decision making criteria. Portfolios have thus gained popularity over the years among managers; technology portfolios are used to support strategic R&D planning (Ernst 1999). However, these approaches have three major drawbacks: they are based on subjective assessments made by respondents; they fail to incorporate the competition due to a lack of necessary information; they are static, not allowing for the analysis of dynamic technological developments (Ernst 1999; Ernst and Soll 2003). To overcome these problems, patent portfolios, which are technology portfolios using patent data, have been developed (Brockhoff 1992; Ernst 1998; Ernst 1999).

The allocation of patents to technological fields is the prerequisite for creating portfolios. In Figure 4.3, two technological fields TFa and TFb are considered. The patent portfolio has the same basic structure as most two-dimensional portfolio illustrations. On the abscissa a firm's 'relative patent position' is measured by relating its 'patent strength' (table 4.1) to the highest 'patent strength' in the specific technological field. This allows for the speedy identification of the leading firm per technological field (which receives a value of 1), as well as to assess the distances between each competing company and the leading company. As in other portfolios, the abscissa value is determined predominately by the behavior of the firm under consideration (Ernst 1998; Ernst 1999).

On the ordinate we observe that the attractiveness of each technological field is measured by using relative growth rates of patent applications. Patent growth in recent years relative to patent growth in preceding years is measured because it emphasizes recent developments in patent growth. It is assumed that technological fields with high relative patent growth rates will be more attractive in the future than those fields with low patent growth. The ordinate values are influenced by all of the companies that file patents in

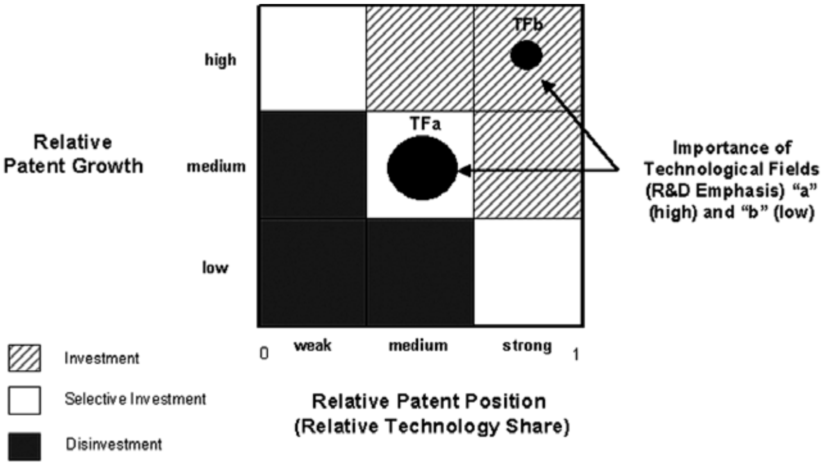


Figure 4.3: The Patent Portfolio. Source: Ernst (2003:237).

the respective technological fields (Ernst 1998; Ernst 1999). Empirical studies show a positive and lagged relationship between patent growth and competitive changes in the market (Ernst 2001).

The size of the circles in figure 4.3 indicates the importance of each technological field within the company's R&D portfolio ('R&D emphasis'; table 5.1). The company puts a high emphasis on TFa and a low emphasis on TFb. The 'R&D emphasis' is calculated by the number of patent applications in a technological field divided by the total number of patent applications filed by the respective company. 'R&D emphasis' is an internal variable impacted only by the firm itself (Ernst 1998; Ernst 1999).

The rankings in a patent portfolio provide senior management with valuable information regarding their R&D investment decisions. In general, firms should increase R&D spending in fields with medium to high relative patent growth, especially where they also have medium to strong 'relative patent positions'. Firms should also tend to spend less in areas with lower relative patent growth and weaker 'relative patent positions'. Positions on the diagonal require a careful examination before a final decision is made. For example, in a situation in which the 'relative patent position' in a technological field with high rates of relative patent growth is weak, various strategic options need to be considered. The firm may chose to develop the technology in-house because it is considered to be of high competitive importance in the future. Alternatively, the firm may consider acquiring this technology from the leading company which can easily be identified in the patent portfolio ('relative patent position' = 1). Finally, the firm may decide to ignore this technology because it is classified as a non-core area according to the overall business strategy (Ernst 1998; Ernst 1999).

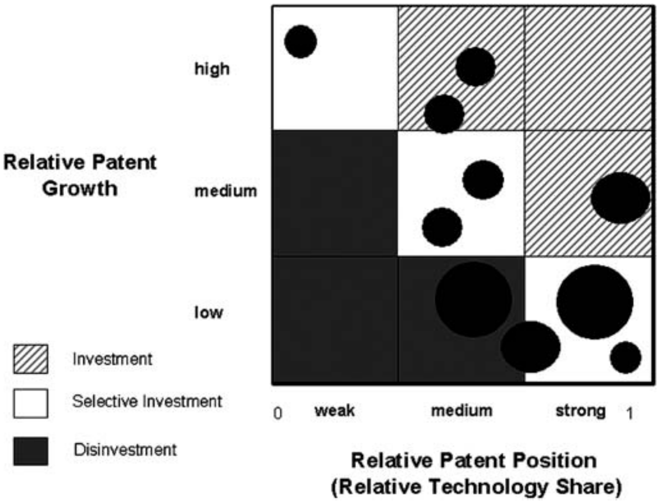


Figure 4.4: An Example of a Patent Portfolio. Source: Ernst (2003:237).

Figure 4.4 shows an example of a patent portfolio for one firm. This particular company holds strong patent positions in many of the technological fields under consideration although the focus is on the technological fields with the lowest relative patent growth rates and a competitor dominates the fastest growing technological field. Management should, therefore, consider shifting R&D resources from slower to faster growing technological fields.

In sum, the proposed patent portfolio method can be used to evaluate the strengths and weaknesses of competing companies with regard to different technological fields. Patent portfolios provide valuable information for decision makers regarding strategic R&D investments, i.e. how much of the R&D budget should be spent on which technological field. Furthermore, patent portfolio analyses can be used to identify and assess opportunities for external knowledge creation and licensing opportunities. Finally, it should be stressed that any portfolio analysis should be conducted with caution. Portfolios display only a limited amount of information required to make final decisions. Portfolios should, therefore, be viewed as a valuable tool to structure and visualize a complex situation to facilitate discussions among senior management to support decision-making (Ernst and Soll 2003).

The patent portfolio approach can also be applied at other levels of analyses. With respect to our analyses in the field of Nanotechnology, we are not only interested in analyzing the patent position of organizations, as for example firms, universities and research institutions. A further focus will be on the assessment of countries' positions in the field of Nanotechnology by means of patent portfolio analyses.

4.4 Patent Analysis in the Field of Nanotechnology

4.4.1 Patent Data Collection

An appropriate patent search string was developed and subsequently refined by this group of experts for most of the fields of functional Nanotechnology covered in tables 3.1 and 3.2 (chapter 3). Primarily, fields of Nanotechnology consistent with our definition have been considered. Scaling effects have been analyzed if the corresponding phenomena are well-known in public or commercially important. The analysis can thus be seen as referring to Nanotechnology in a wider sense with a focus on functional Nanotechnology. The definition of Nanotechnology used in this book has an impact on the definition of technology sub-fields of Nanotechnology and hence on the results of the patent analyses. Patent statistics based on other definitions may therefore lead to other results and are difficult to compare (Paschen et al. 2004). Each search string for a specific technology field consists of multiple key words as shown in tables 3.1 and 3.2. Preliminary patent searches showed that too many patents not related to Nanotechnology were found, when the search strategy was unfocused. In order to avoid this problem, the truncated term “nano” was added to each search string for each technology field. The downside of this procedure can be that some Nanotechnology patents were not found due to the narrower search strategy. However, this procedure has the advantage that patents are related to Nanotechnology and that the results are not distorted by a high number of irrelevant patents that are unrelated to the field of Nanotechnology.

In total, 47 sub-fields of Nanotechnology are covered by the patent analysis. These subfields do not always exactly match the corresponding entries of tables 3.1 or 3.2, since patent filers may use various descriptions of their work contents. A patent search for the key words in patent titles, claims and abstracts in the Micropatent full-text database was performed. To focus the patent analyses on the most important markets for Nanotechnology, patents filed at the patent offices of the US, Europe, Japan, Germany, Great Britain and France were retrieved. The analysis is based on patent families in order to avoid multiple patent counts of similar or technically related patents that were filed at more than one of these patent offices simultaneously. The patent family information comes from the international patent database INPADOC.

Patent families are assigned to the year of origin according to the priority date. The priority date of a patent family is the date of the first patent application filed in the entire patent family. The analysis covers patent families filed from 1983 to 2002. Only a small number (approximately 700) of patent families in the field of Nanotechnology was found before the year 1983. After 2002, no meaningful analysis can be made because patents are published only 18 months after the priority date of the first patent filing. Hence, the database is not complete for patents filed in 2003 or later.

Table 4.2: Degree of Technological Overlap in Fields of Nanotechnology (% of Patent Families Assigned to the same Technological Field)

	High Strength Composites	Molecular Switches	Field Emission	Transparent Ceramics	Nanostructured Surfaces	Shape Complementarity	Scanning Probe	Molecular Switches
Discrete Energy Levels / QD					38%	21%		
High Strength Materials	55%		36%					
Field Emission Display			100%					
Self-Organized Complex Patterns			24%		29%	22%		
Phonon Engineering					30%			
Shape Complementarity					26%			
Magnetic Dipole Interaction			24%					
Discrete Energy Levels / QSE			21%		23%			
Lowered Percolation Threshold			28%					
Transparent Ceramics					29%			
Phase Change					36%			
Gas Sensors					20%			
Molecular Actuators					20%			
SNOM							52%	
Rotaxanes								21%

Only substantial overlaps (>20%) are shown.
The number shown is the percent of horizontal TF's patents that are also attributed to the vertical TF.

The scope of the search strings used in this analysis represents a compromise between finding all Nanotechnology patents and not finding too much non-Nanotechnology patents. Often patents do not use the typical terms of their technology field and are difficult to find. The absolute number of Nanotechnology patents found in our study therefore has to be interpreted with some care. We believe, however, that we can suppose a comparable error over all technology fields and are therefore able to make observations on the relative development and importance of the various sub-fields within Nanotechnology.

In principle, each patent family could be assigned to multiple sub-fields of Nanotechnology. In most cases, however, patent families could be clearly assigned to one unique technology field only. In 10% of the cases, patent families were members of two or more technology fields. The technology fields 'Field Emission/Nanotubes', 'Gas Sensors', '(Anti)reflection', and 'Shape Complementarity' have a substantial overlap with many other fields of Nanotechnology. As can be expected, all 'Field Emission Display' patents were also contained in the technology field 'Field Emission'. Half of the patents in the technology fields 'SNOM' and 'High Strength Materials' were also assigned to the technology field 'Scanning Probe Techniques' and 'High Strength Composites', respectively. Cross-assignments between other fields are of much smaller magnitude and do not need to be analyzed any further here. Table 4.2 summarizes the areas with the highest degree of technological overlap based on the cross-assignment of patents.

4.4.2 Results

Overall Patenting Activity

A total number of 25.425 Nanotechnology patent families in a wider sense were filed at these patent offices over the covered time period from 1983 to 2002. Figure 4.5 shows that the overall patenting activity in Nanotechnology has increased exponentially since 1983. This indicates a significant and increasing amount of R&D expenditures by public and mainly private organizations in the field of Nanotechnology. Obviously, increasing quantities of patent applications reflect the rapidly growing interest in Nanotechnology from a technological and a commercial perspective. The cumulative development of the number of patent families is a good indicator for the accumulated knowledge stock in a technology field (Ernst 1996). A large knowledge stock has been accumulated in the field of Nanotechnology since 1983 and it continues to grow exponentially. One can therefore assume that significant technological advantages in the field of Nanotechnology have either been made or will be made in the near future. New developments can build on this accumulated stock of knowledge, which can increase the effectiveness and efficiency of future R&D in Nanotechnology.

The technology field 'Scanning Probe Techniques' (used here as a term collecting various technology fields) is by far the largest sub-field of Nanotechnology. Patents in this technology field used to account for more than 50% of total Nanotechnology patents (approx. up to 1995). This technology field can therefore be considered to be a basic field within Nanotechnology. However, patent activity in the other sub-fields of Nanotechnology has been growing much faster in recent years. By 2002, 33% of cumulated nanotech patents fell into the technology field 'Scanning Probe Techniques'.

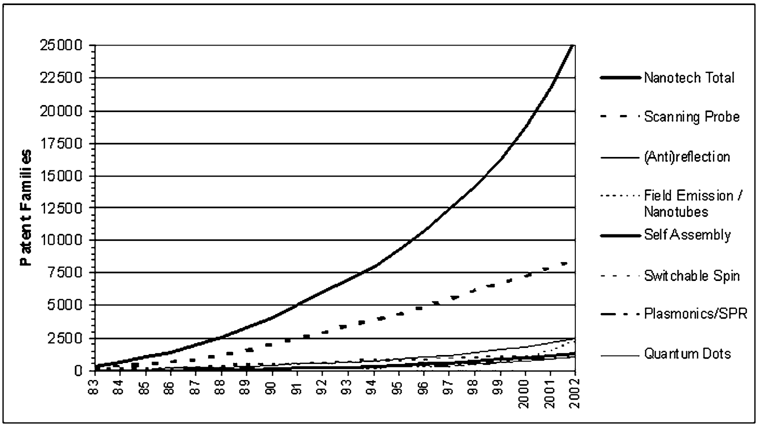


Figure 4.5: Cumulative Number of Annual Patent Families in the "Top 7 Nanotechnology Fields".

Figure 4.6 illustrates the annual development of patent families in the most important (according to the total number of patent families) Nanotechnology fields excluding the largest sub-field 'Scanning Probe Techniques'. Patent activity was very dynamic in the technology fields '(Anti)reflection', 'Self Assembly', 'Plasmonics', 'Quantum Dots (QD)' and particularly in 'Field Emission/Nanotubes'. The rapid growth of patenting activity in the technology field 'Field Emission/Nanotubes' began in 1998. By 2002, the technology field 'Field Emission/Nanotubes' had reached the third largest cumulated patent or knowledge stock in the field of Nanotechnology. Figure 4.6 further shows that patenting quantity remained high and grew linearly in the technology field 'Switchable Spin/Spintronics'.

Table 4.3 summarizes the number of patent families in each sub-field of Nanotechnology and its development over four time periods between 1983 and 2002. The structure of table 4.3 is identical to the one of table 3.1. To give an example, the numbers for the technology field 'Hard Magnets' need to be read as follows: one patent family was filed in the period 1983 to 1987, two cumulative, i.e. including the patent family from the first time period, patent families were filed in the period 1983 to 1992, 18 cumulative patent

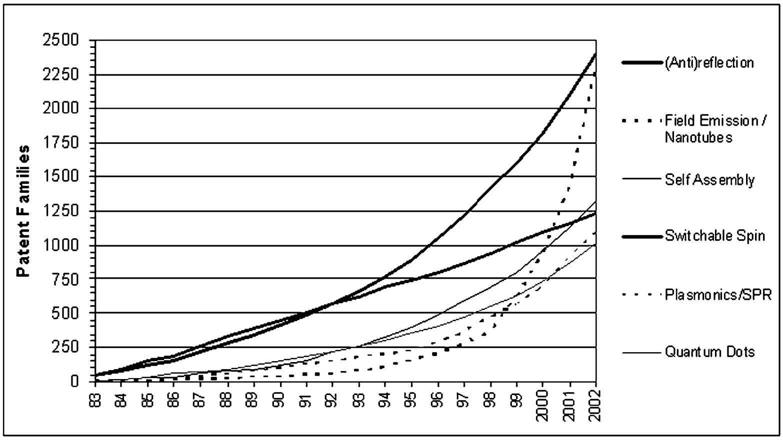


Figure 4.6: Cumulative Number of Annual Patent Families in the Top 2-7 Nanotechnology Fields.

families were filed in the period 1983 to 1997 and 53 cumulative patent families were filed in the period 1983 to 2002.

In the category 'Magnetic (A)', the technology fields 'Quantum Antidots' and 'Ferrofluids/Superparamagnetism' are most important. Patenting activity has been high and has increased substantially since 1993. Other technology fields like 'Hard Magnets', 'Giant Magneto Resistance' and 'Proximity Effect' are less important in terms of patent numbers, however, patenting activity has increased significantly in the former two technology fields since 1993. In comparison, the category 'Mechanic (B)' is less attractive than the category 'Magnetic (A)' as indicated by a much lower patenting activity.

Within the category 'Electric/Electronic (C)', the two technology fields 'Field Emission/Nanotubes' and 'Gas Sensors' have the highest patenting activity. Patenting activity was extremely high in the technology field 'Field Emission/Nanotubes' in the last two time periods from 1983 to 1997 and from 1983 to 2002, in which the cumulative number of patent families increased by almost 4000% from 57 to 2.303 patent families. It appears as if this technology field is very attractive from a technological and commercial point of view. Overall, the distribution of patent families over the technology fields in the category 'Electric/Electronic (C)' seems to indicate that the category 'Engineered Functions' receives more R&D focus than the category 'Size Dependent Properties'. Within the latter category, the technology fields 'Ferro- and Superparaelectrics' and 'Quantum Size Effect' have the highest number of patent families. The recent patent growth has been very high in the former technology field.

In the category 'Optical (D)', the most important technology fields are 'Plasmonics' and '(Anti)reflection'. Whereas patenting activity has been relatively high over all time periods in the latter technology field, patent growth

Table 4.3: Cumulated number of patent families in four time periods: 1983-1987, 1983-1992, 1983-1997 and 1983-2002

	Size Dependent Properties			**Engineered Functions**		
Properties	**Metals (1)**	**Semiconductors (2)**	**Insulators (3)**	**Molecules/ Assemblies Biomolecules (4)**	**Hybrids/ Compos. (5)**	**Boundary Surf. (6)**
magnetic (A)	Ferrofluids and Superparamagnetism 78 - 212 - 398 -707	Quantum (Anti)dots 73- 220 - 440 - 1014	Ferrofluids and Superparamagnetism 78 - 212 - 398 -707	Molecular Magnetism 49 - 82 - 119 - 165	Giant Magneto Resistance 0 - 2 - 59 - 213	Proximity Effect 0 -1 - 3 - 8
mechanic (B)	High Strength Materials 1 -3 - 6 - 10			Molecular Motors 2 - 7 - 19 - 54	High Strength Composites 5 - 19 - 54 - 109	Self Cleaning Surfaces 15 - 29 - 55 - 143
electric/ electronic (C)	Switchable Fermi Levels 0 - 1 - 4 - 4		Ferro- and Super paraelectrics 5 - 14 - 41 - 133	Molecular Switches 34 - 82 - 129 - 269 Field Emission / Nanotubes 18 - 57 - 276 - 2303 Field-Emission Display 3 - 8 - 62 - 272	Lowered Percolation Threshold 2 - 2 - 15 - 45	Low-loss DK 2 - 6 - 12 - 29 Gas Sensors and Catalysts 47 - 116 - 268 - 636
	Quantum Size Effect 17 - 63 - 81 - 95 Thermoelectric Materials 0 - 0 - 2 - 17					
optical (D)	Formation of Discrete Energy Levels/QD 19 - 45 - 92 - 181 Plasmonics 9 - 151- 361 - 1090	Formation of Discrete Energy Levels/ QD/QSE 6 - 28 - 66 - 213	Transparent Ceramics 5 - 17 - 41 - 142		Photochromism 4 - 15 - 60 - 116 Electrochromism 1 - 6 - 14 - 69	(Anti) reflection 214 - 565 - 1216 - 2404
thermodyn. (E)				Brownian Ratchets 0 - 1 - 2 - 4		

	Size Dependent Properties			**Engineered Functions**		
thermal (F)		Phonon Engineering 1 - 8 - 33 - 94				
ability for self assembly / Adaptation (G)	Magnetic Dipole-Dipole Interaction 6 - 15 - 36 - 98			Nanoarchitectures 6 - 35 - 195 - 827	Self Assembly of Metal Nanoparticles / Polymers 57 - 214 - 590 - 1332	Self-organized Complex Patterns 16 - 37 - 109 - 281 Phase Separated Block Copolymers 15 - 39 - 109 - 227
recognition Ability (H)				Shape Complementarity / Biosensors 28 - 104 - 286 - 600		

Reading example: In technology field A1+A3 (ferrofluids), from 1983 to 1987 78 patent families have been applied for; from 1983 to 1992 212 patent families have been applied for. Only patent families with at least one member in WO/US/JP/EP/DE/GB

has been particularly high in the former technology field in recent time periods, especially after 1997. The number of patent families is much lower in the other five technology fields in the category 'Optical (D)'; however, patenting activity has increased substantially in recent time periods in these fields too.

'Energy Conversion' is the most important technology field in the category 'Thermodynamic (E)'. Patenting activity can be observed in all four time periods, where the number of patent families doubled in both the third (1983-1997) and the fourth (1983-2002) time period compared to the respective subsequent time periods. The other technology fields in this category are of minor importance as far as patents are concerned. The technology field 'Phonon Engineering' in the category 'Thermal (F)' has experienced relatively high patent growth in recent time periods, however, the absolute number of patent families filed in this technology field is rather low.

Overall, the category 'Ability for Self-Assembly/Adaptation (G)' is an important field within Nanotechnology as indicated by high numbers of patent families in the multiple sub-fields of this category. Within this category, the technology fields 'Self Assembly of Metal Nanoparticles/Polymers' and 'Nanoarchitectures (Nanostructures)' are most important. The number of patent families in these technology fields is high and patent growth in recent time periods was very dynamic. Obviously, the technological attractiveness as measured by patents seems to be very high in these two sub-fields of Nanotechnology. In addition, the technology fields 'Self-Organized Complex Patterns' and 'Phase Separated Block Copolymers' have experienced high patent growth in recent time periods, which indicates an increased interest in these areas of Nanotechnology.

The category 'Recognition Ability (H)' is an important technology field of Nanotechnology. Patent growth was high in the last two time periods indicating an increased interest in this technology field.

Table 4.4 summarizes the number of patent families in each sub-field of Nanotechnology and its development over four time periods between 1983 and 2002. The structure of table 4.4 is identical to table 3.2. Only some of the technology fields were included in the patent analyses due to a high degree of overlap between table 3.1 and table 3.2. The technology field 'Scanning Probe Techniques' is outstanding due to its high patenting activity in all four time periods. The next two most important and most dynamic technology fields are 'Switchable Spin' and 'Actuators'.

Table 4.4: Cumulated number of patent families in four time periods: 1983-1987, 1983-1992, 1983-1997 and 1983-2002

	electric/electronic (1)	**magnetic (2)**	**optical (3)**	**mechanic (4)**
electric / electronic (A)	Scanning Probe Techn. 826 - 2859 - 5433 – 8488 Nano/Quantum Metrology 7 - 20 - 45 - 100			Actuators 35 - 106 - 251 - 646
magnetic (B)				
optical (C)		Switchable Spin 258 - 561 - 865 - 1230	SNOM 0 - 3 - 18 – 61 Phase Change 9 - 25 - 59 - 159	
mechanic (D)	Local Probe Array for Mass Storage 0 - 2 - 8 - 8			Rotaxanes 0 - 2 - 12 - 48
thermal (E)	Phase Change 9 - 25 - 59 - 159		Phase Change 9 - 25 - 59 - 159	

Reading example: In technology field A1 (scanning probe t.), 2859 patent families have been applied for from 1983 to 1992.
Only patent families with at least one member in WO/US/JP/EP/DE/GB

International Patenting Activity

Figures 4.7 and 4.8 show the international origin of the patenting activity in the field of Nanotechnology in a wider sense. The illustration in figure 4.7 is based on the cumulated number of patent families between 1983 and 2002. Substantially higher number of patent families have originated from the US and Japan. Recent patent growth (starting approximately in 1993) has been highest in the US. The US surpassed Japan as the country with the highest cumulative stock of Nanotechnology patents in 2001. Prior to that, Japan had the highest cumulated patent stock in Nanotechnology. Patenting activity in Europe is much lower compared to the US and Japan. It started increasing in the mid 90ies, however, by the year 2002, cumulated priority patent filings in Europe (approx. 4.000 patent families) were still significantly lower than in the US (approx. 11.000 patent families) and in Japan (approx. 10.000 patent families).

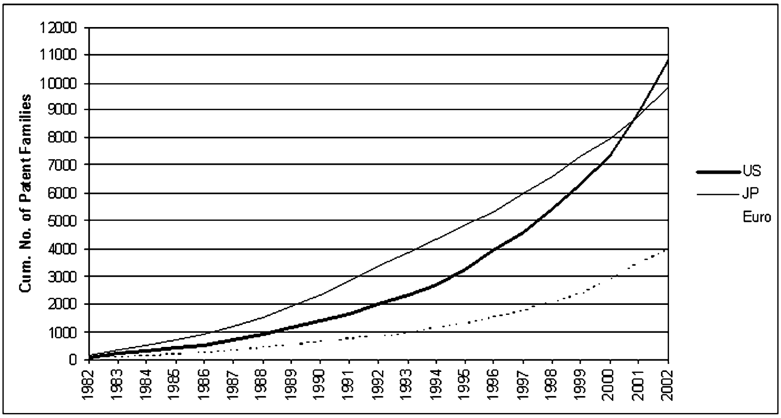


Figure 4.7: Cumulated Number of Annual Patent Families with Origin of Priority Patent Application in the US, Japan and Europe

Figure 4.8 illustrates the number of new patent families by region of origin over time. The strong position of Japan in Nanotechnology results from an older patent stock, which was build between 1986 and 1994. On a yearly basis, more new Nanotechnology patent families originated in the US from 1995 until 2002. The annual number of new patent families filed in the US increased dramatically in 1999 leading to an increased gap between Japan and Europe. Patenting activity picked up significantly in Japan in 2000, whereas patenting activity in Europe has increased between 1997 and 2000 and basically remained constant in subsequent years. In 2002, more than triple the number of new patent families are filed in the US (approx. 1.900 new patent families) and almost double the number of new patent families are filed in Japan (approx. 1.000 new patent families) compared to Europe (approx. 550 patent families).

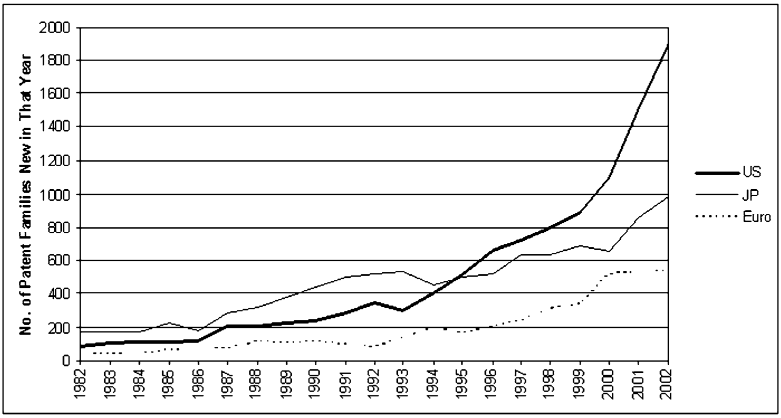


Figure 4.8: Number of New Patent Families with Origin of Priority Patent Application in the US, Japan and Europe.

The high number of Japanese priority patent filings is caused by a large number of domestic patent applications, which is significantly higher compared to other countries due to peculiarities of the Japanese patent system and the patenting behavior of Japanese inventors (Ernst 1996). In order to compare international patent statistics in a better way and to account for patent quality, it is recommended to look at triad patent families (Ernst 1996). Triad patent families have patents, which are filed in the US, Japan and Europe simultaneously. These triad patent families better reflect the economic quality of patents because the share of triad patent families correlates significantly with the economic value of a patent family (Ernst 2003; Ernst and Soll 2003).

Figure 4.9 shows the cumulated annual number of patent families by region based on triad patent families only. As expected, Japan looses some of its patent positions because a large number of domestic patents is excluded. The US clearly is the dominating player in the field of Nanotechnology. Most of the important Nanotechnology patent families with a large international scope originate in the US. Europe improves its position and its stock of valuable international Nanotechnology patent families is higher compared to Japan. Europe's position looks even more favorable in figure 4.10, which shows only the number of new triad patent families. In 2000, the number of new triad patent families originating in Europe increased sharply and almost reached the level of new triad patent families filed in the US. It remains to be seen, however, if this annual observation will continuously go on to become a sustainable development.

Table 4.5 shows the patent position of the US, Japan and Europe in subfields of Nanotechnology associated with table 3.1. The first figure refers to the share of patent families first filed in the US, whereas the second and the third figure refer to the share of patent families first filed in Japan and

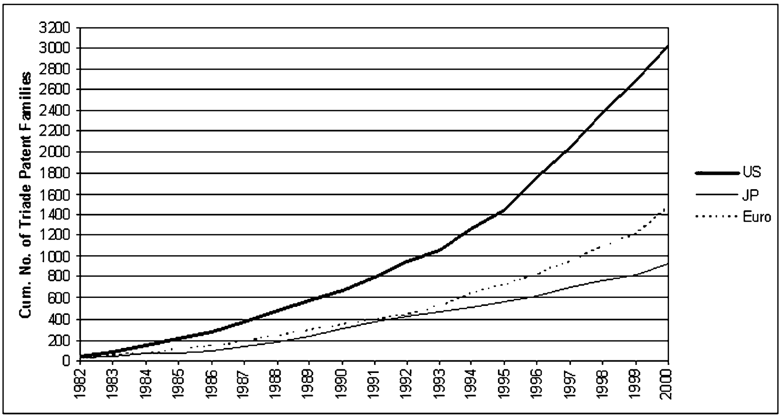


Figure 4.9: Cumulated Number of Annual Patent Families with Origin of Priority Patent Application in the US, Japan and Europe (Triad Patent Families Only).

Note: No data available after 2000 due to time-lag in the publication of international patent applications. A 'triad patent family' has simultaneous patent applications in the US, Japan and Europe.

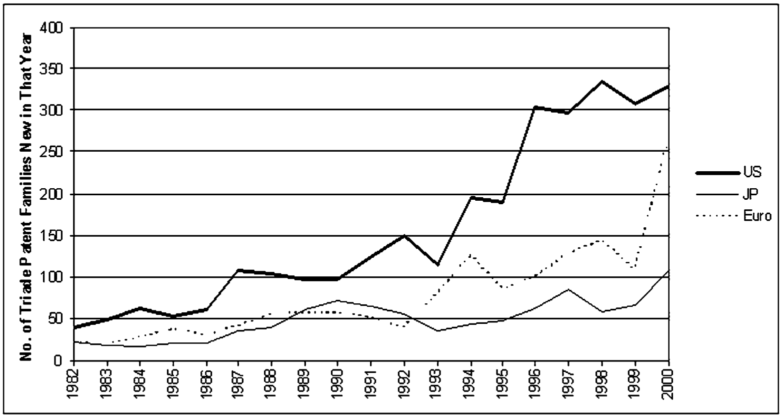


Figure 4.10: Number of New Patent Families with Origin of Priority Patent Application in the US, Japan and Europe (Triad Patent Families Only).

Note: No data available after 2000 due to the time-lag in the publication of international patent applications. A 'triad patent family' has simultaneous patent applications in the US, Japan and Europe.

Europe, respectively. To give an example, 43% of patent families in the technology field 'Hard Magnets' are from the US, 41% of all patent families come from Japan and 14% of all patent families are from Europe. Some technology fields were dropped from this analysis because they have less than 30

Table 4.5: Share of patent families (in % of all patent families in the technology field) that were first filed in the US, Japan and Europe*

	Size Dependent Properties			Engineered Functions		
Properties	**Metals (1)**	**Semiconductors (2)**	**Insulators (3)**	**Molecules/ Assemblies/ Biomolecules (4)**	**Hybrids/ Compos. (5)**	**Boundary Surf. (6)**
magnetic (A)	Ferrofluids and Superparamagnetism 56 - 7 - 33	Quantum (Anti)dots 31 - 50 - 13	Ferrofluids and Superparamagnetism 56 - 7 - 33	Molecular Magnetism 24 - 65 - 8	Giant Magneto Resistance 35 - 39 - 24	Proximity Effect n/a**
mechanic (B)	High Strength Materials n/a**			Molecular Motors 63 - 16 - 21	High Strength Composites 61 - 27 - 10	Self Cleaning Surfaces 40 - 29 - 20
electric/ electronic (C)	Switchable Fermi Levels n/a**		Ferro- and Super paraelectrics 63 - 11 - 17	Molecular Switches 45 - 33 - 16 Field Emission / Nanotubes 40 - 38 - 11 Field-Emission Display 55 - 28 - 9	Lowered Percolation Threshold 51 - 6 - 38	Low-loss DK 44 - 16 - 31 Gas Sensors and Catalysts 66 - 5 - 23
	Quantum Size Effect 17 - 80 - 3 Thermoelectric Materials n/a**					
optical (D)	Formation of Discrete Energy Levels/QD 81 - 2 - 16 Plasmonics 38 - 34 - 26	Formation of Discrete Energy Levels/QD/ QSE 62 - 8 - 25	Transparent Ceramics 68 - 3 - 23		Photochromism 73 - 7 - 16 Electrochromism 28 - 24 - 40	(Anti) reflection 73 - 8 - 15
thermodyn. (E)				Brownian Ratchets n/a**		
thermal (F)		Phonon Engineering 66 - 6 - 21				
ability for self assembly / Adaptation G)	Magnetic Dipole-Dipole Interaction 71 - 3 - 21			Nanoarchitectures 57 - 10 - 25	Self Assembly of Metal Nanoparticles / Polymers 61 - 12 - 23	Self-organized Complex Patterns 79 - 6 - 8 Phase Separated Block Copolymers 55 - 7 - 20
recognition Ability (H)				Shape Complementarity / Biosensors 71 - 4 - 20		

Reading example: In technology field A1+A3 (ferrofluids), from 1981 to 2002 56% of all patent families originated from the USA, 7% from Japan and 33% from EURO* countries.

* = EURO includes DE, GB, EP, FR, SE, CH, NL, AT, IT, FI, DK, ES, NO (in order of significance for total nanotech)

** = Technology fields having less than 30 patent families (total 2002) are omitted.

patent families. The US is the most important region for Nanotechnology. The US has the highest shares of patent families in 26 out of 31 technology fields shown in table 5.5. Japan has the highest shares in four fields of Nanotechnology. These are the technology fields ‘Quantum Antidots’, ‘Molecular Magnetism’, ‘Giant Magneto Resistance’ and ‘Quantum Size Effects’. Furthermore, patents from Japan are relatively more frequent in the technology fields ‘Field Emission/Nanotubes’, ‘Field Emission Display’ and ‘Hard Magnets’. Overall, Japanese patents have a clear focus on the two categories ‘Magnetic (A)’ and ‘Electric/Electronic (C)’. Europe has the highest share of patent families in the technology field ‘Electrochromism”. Furthermore, patents from Europe are relatively more frequent in the technology fields ‘Ferrofluids and Superparamagnetism’, ‘Lowered Percolation Threshold’, ‘Low-loss DK’, ‘Gas Sensors’ and ‘Nanoarchitectures (Nanostructures)’.

Table 4.6 shows the patent position of the US, Japan and Europe in subfields of Nanotechnology associated with table 3.2. The US has the highest shares of patent families in 7 out of 9 technology fields. This confirms the overall leading position of the US in the field of Nanotechnology. Japan has the highest shares in two technology fields. These are the technology fields ‘Scanning Probe Techniques’ and ‘Switchable Spin’. The Japanese position is remarkable because both technology fields are among the five most important technology fields in terms of the number of cumulated patent families (figure 4.5). Patents from Europe are relatively more frequent in the technology fields ‘Rotaxanes/Catenanes’ and ‘Nano/Quantum Metrology’.

Table 4.6: Share of patent families (in % of all patent families in the technology field) that were first filed in the US, Japan and Europe*

	electric/electronic (1)	**magnetic (2)**	**optical (3)**	**mechanic (4)**
electric / electronic (A)	Scanning Probe Techn. 22 - 66 – 10 Nano/Quantum Metrology 47 - 1 - 39			Actuators 76 - 3 - 14
magnetic (B)				
optical (C)		Switchable Spin 19 - 65 - 12	SNOM 45 - 29 - 19 Phase Change 72 - 13 - 11	
mechanic (D)	Local Probe Array for Mass Storage n/a**			Rotaxanes 45 - 26 - 28
thermal (E)	Phase Change 72 - 13 - 11		Phase Change 72 - 13 - 11	

Reading example: In technology field D4 (rotaxanes), until 2002 45% of all patent families originated from the USA, 26% from Japan and 28% from EURO* countries.

* = EURO includes DE, GB, EP, FR, SE, CH, NL, AT, IT, FI, DK, ES, NO

** = Technology fields having less than 30 patent families (total 2002) are omitted.

Table 4.7: The relative importance of sub-fields within Nanotechnology in four time periods: 1983-1987, 1988-1992, 1993-1997 and 1998-2002

	Size Dependent Properties			**Engineered Functions**		
Properties	**Metals (1)**	**Semiconductors (2)**	**Insulators (3)**	**Molecules/ Assemblies/ Biomolecules (4)**	**Hybrids/ Compos. (5)**	**Boundary Surf. (6)**
magnetic (A)	Ferrofluids and Superparamagnetism 4,0 - 3,6 - 3,2 - 2,8	Quantum (Anti)dots 3,7 - 3,7 - 3,8 - 4,0	Ferrofluids and Superparamagnetism 4,0 - 3,6 - 3,2 - 2,8	Molecular Magnetism 2,5 - 1,4 - 1,0 - 0,6	Giant Magneto Resistance 0,0 -0,0 - 0,5 - 0,8	Proximity Effect 0,0 - 0,0 - 0,0 - 0,0
mechanic (B)	High Strength Materials 0,1 - 0,1 - 0,1 - 0,0			Molecular Motors 0,1 - 0,1 - 0,2 - 0,2	High Strength Composites 0,3 - 0,3 - 0,4 - 0,4	Self Cleaning Surfaces 0,8 - 0,5 - 0,4 - 0,6
electric/ electronic (C)	Switchable Fermi Levels 0,0 - 0,0 - 0,0 - 0,0		Ferro- and Super paraelectrics 0,3 - 0,2 - 0,3 - 0,5	Molecular Switches 1,7 - 1,4 - 1,0 - 1,1 Field Emission / Nanotubes 0,9 - 1,0 - 2,2 - 9,1 Field-Emission Display 0,2 - 0,1 - 0,5 - 1,1	Lowered Percolation Threshold 0,1 - 0,0 - 0,1 - 0,2	Low-loss DK 0,1 - 0,1 - 0,1 - 0,1 Gas Sensors and Catalysts 2,4 - 2,0 - 2,2 - 2,5
	Quantum Size Effect 0,9 - 1,1 - 0,7 - 0,4 Thermoelectric Materials 0,0 - 0,0 - 0,0 - 0,1					
optical (D)	Formation of Discrete Energy Levels/QD 1,0 - 0,8 - 0,7 - 0,7 Plasmonics 2,0 - 2,5 - 2,9 - 4,3	Formation of Discrete Energy Levels/QD /QSE 0,3 - 0,5 - 0,5 - 0,8	Transparent Ceramics 0,3 - 0,3 - 0,3 - 0,6		Photochromism 0,2 - 0,3 - 0,5 - 0,5 Electrochromism 0,1 - 0,1 - 0,1 - 0,3	(Anti) reflection 10,9 - 9,5 - 9,8 - 9,5
thermodyn. (E)				(Anti) reflection 10,9 - 9,5 - 9,8 - 9,5		
thermal (F)		Phonon Engineering 0,0 - 0,1 - 0,3 - 0,4				

Reading example: In technology field A1+A3 (ferrofluids), the patents applied for from 1983 to 1987 represented 4% of all Nanotechnology patent families found in this study. In 1992, the patents applied for in this technology field since 1983 represented 3,6% of all Nanotechnology patents of that period.

Relative Importance of Nanotechnology Fields

Tables 4.7 and 4.8 show the relative importance of each subfield of Nanotechnology over time. The relative importance is measured as the subfields' share of the total number of cumulative patent families in Nanotechnology. These shares were calculated for all four time periods in order to illustrate changes of importance over time. To give an example, the relative importance of the technology field 'Quantum (Anti)dots' was 3.7 between 1982 and 1987; i.e., 3.7% of all cumulated patent families in Nanotechnology were filed in the technology field 'Quantum (Anti)dots'. The relative importance of this technology has remained constant over the entire period until 2002 (table 5.7). While table 4.7 reflects the Nanotechnology fields associated with table 3.1, table 4.8 corresponds to the Nanotechnology fields associated with table 3.2.

The seven technology fields with the highest share of the total knowledge stock in 2002 are those that have already been identified in figure 4.5. Except for the largest sub-field, 'Scanning Probe Techniques' (33% patent share between 1998 and 2002), Nanotechnology knowledge is widely distributed among many sub-fields: The second largest technology field '(Anti)reflection' has a share of only about 10% of the total Nanotechnology knowledge (table

Table 4.8: The relative importance of sub-fields within Nanotechnology in four time periods: 1983-1987, 1988-1992, 1993-1997 and 1998-2002

	electric/electronic (1)	**magnetic (2)**	**optical (3)**	**mechanic (4)**
electric / electronic (A)	Scanning Probe Techn. 41,9 - 47,9 - 43,9 - 33,4 Nano/Quantum Metrology 0,4 - 0,3 - 0,4 - 0,4			Actuators 1,8 - 1,8 - 2,0 - 2,5
magnetic (B)				
optical (C)		Switchable Spin 13,1 - 9,4 - 7,0 - 4,8	SNOM 0,0 - 0,1 - 0,1 - 0,2 Phase Change 0,5 - 0,4 - 0,5 - 0,6	
mechanic (D)	Local Probe Array for Mass Storage 0,0 - 0,0 - 0,1 - 0,0			Rotaxanes 0 - 0 - 0,1 - 0,2
thermal (E)	Phase Change 0,5 - 0,4 - 0,5 - 0,6		Phase Change 0,5 - 0,4 - 0,5 - 0,6	

Reading example: In technology field A1 (scanning probe t.), the patents applied for from 1983 to 1992 represented 47,9% of all Nanotechnology patents of that period.

Table 4.9: The science-base of patent families in fields of Nanotechnology in four time periods: 1983-1987, 1988-1992, 1993-1997, 1998-1999*

	Size Dependent Properties			**Engineered Functions**		
Properties	**Metals (1)**	**Semiconductors (2)**	**Insulators (3)**	**Molecules / Assemblies / Biomolecules (4)**	**Hybrids / Compos. (5)**	**Boundary Surf. (6)**
magnetic (A)	Ferrofluids and Superparamagnetism 3,1 - 2,1 - 1,4 - 0,9	Quantum (Anti)dots 1,1 - 2,8 - 1,6 - 1,7	Ferrofluids and Superparamagnetism 3,1 - 2,1 - 1,4 - 0,9	Molecular Magnetism 0,9 - 3,2 - 1,6 - 3,0	Giant Magneto Resistance n/a - n/a - 0,3 - 0,2	Proximity Effect n/a**
mechanic (B)	High Strength Materials n/a**			Molecular Motors n/a**	High Strength Composites n/a - n/a - 1,4 - 0,5	Self Cleaning Surfaces n/a**
electric/ electronic (C)	Switchable Fermi Levels n/a**		Ferro- and Super paraelectrics n/a**	Molecular Switches 6,4 - 4,9 - 3,3 - 1,9 Field Emission / Nanotubes n/a - 4,2 - 2,8 - 2,0 Field-Emission Display n/a - n/a - 2,2 - 2,2	Lowered Percolation Threshold n/a**	Low-loss DK n/a** Gas Sensors and Catalysts 1,9 - 4,4 - 3,1 - 1,8
	Quantum Size Effect n/a - 3,4 - n/a - n/a Thermoelectric Materials n/a**					
optical (D)	Formation of Discrete Energy Levels/QD n/a - n/a - 1,8 - 4,1 Plasmonics 2,6 - 5,0 - 2,6 - 3,8	Formation of Discrete Energy Levels/QD/ QSE n/a - n/a - 1,8 - 2,8	Transparent Ceramics n/a**		Photochromism n/a - n/a - 1,6 - 1,5 Electrochromism n/a**	(Anti) reflection 1,6 - 3,4 - 1,9 - 1,9
thermodyn. (E)				Brownian Ratchets n/a**		
thermal (F)		Phonon Engineering n/a***				

	Size Dependent Properties			**Engineered Functions**		
ability for self assembly / Adaptation (G)	Magnetic Dipole-Dipole Interaction n/a**			Nanoarchitectures n/a - n/a - 3,2 - 1,9	Self Assembly of Metal Nanoparticles / Polymers 9,5 - 10,7 - 7,6 - 3,8	Self-organized Complex Patterns n/a - n/a - 3,7 - 2,4 Phase Separated Block Copolymers n/a - n/a - 2,6 - 0,6
recognition Ability (H)				Shape Complementarity / Biosensors n/a - 9,3 - 4,1 - 8,0		

Reading example: In technology field A1+A3 (ferrofluids), the US patents applied for from 1988 to 1992 cited 2,1 times more non-patent documents than the average US patent.

* = Due to a lag in publication of patent grants, the number cannot be calculated from 2000 on.

** = Cases with less than 30 patents are omitted.

4.7). While the share of this field remained stable since 1987, the field "Switchable Spin" constantly lost relative significance and its patent share dropped from 13% in 1987 to 4.8% until the end of 2002 (table 4.8) – despite an increasing number of patent families in this technology field. Two other important technology fields, 'Ferrofluids and Superparamagnetism' and 'Molecular Magnetism' grow slower than the other technology fields and their patent share therefore drops accordingly. The many smaller fields are not discussed any further. Other important technology fields with increasing relative importance are 'Self Assembly', 'Plasmonics' and 'Field Emission/Nanotubes' (patent share of 9% between 1998 and 2002; table 4.7). Smaller technology fields that increased their patent share include 'Nanoarchitectures (Nanostructures)', 'Shape Complementary/Biosensors' (table 4.7) and 'Actuators' (table 4.8).

Science Base of Nanotechnology Fields

The number of non-patent documents (publications) a patent cites as prior art is a good measure of the science-intensity of the underlying technology (Ernst, 1996). This publication citation intensity of patents is an appropriate patenting indicator for science-based technologies as it is the case for Nanotechnology in its stage of development. The science-base of Nanotechnology is determined on the basis of US patents only in order to avoid distortions caused by differences in national citation policies. Overall, Nanotechnology patents from the US in this study cited 4.6 non-patent documents on average. In comparison, random samples of US patents taken from the years

1987, 1992, 1997 and 1999 had, on average, only 2.2 non-patent citations. Thus, the prior art of Nanotechnology patents has a stronger science orientation than the average US patent.

Table 4.9 shows the science-base of patent families in sub-fields of Nanotechnology over time. Table 4.9 contains the average number of non-patent citations in a subfield's patent family relative to the average number of non-patent citations in all fields of Nanotechnology associated with table 3.1. Table 4.10 contains similar information on the science base for the technology fields associated with table 3.2. The highest science intensities can be observed for the technology fields 'Self Assembly', 'Shape Complementarity/Bio Sensors', 'Molecular Switches' and 'Gas Sensors' and 'Plasmonics'. In some technology fields such as "Ferrofluids and Superparamagnetism", "Nanotubes" and "Self-Assembly", sience-intensity is highest when the technology field emerges and it drops when more and more patents are applied for and the knowledge stock increases. This can be seen as an indicator that the technology advances from science to applied science and development. In other technology fields such as 'Scanning Probe Techniques' and 'Quantum (Anti)dots', the science intensity has remained relatively constant with a slight increase in the second time period.

Table 4.10: The science-base of patent families in fields of Nanotechnology in four time periods: 1983-1987, 1988-1992, 1993-1997, 1998-1999*

	electric/electronic (1)	magnetic (2)	optical (3)	mechanic (4)
electric / electronic (A)	Scanning Probe Techn. 1,3 - 2,4 - 1,5 - 1,2 Nano/Quantum Metrology n/a**			Actuators 2,4 - 3,3 - 2,0 - 1,6
magnetic (B)				
optical (C)		Switchable Spin 1,0 - 1,7 - 1,1 - 0,4	SNOM n/a*** Phase Change n/a - n/a - 1,3 - 0,6	
mechanic (D)	Local Probe Array for Mass Storage n/a**			Rotaxanes n/a**
thermal (E)	Phase Change n/a - n/a - 1,3 - 0,6		Phase Change n/a - n/a - 1,3 - 0,6	

Reading example: In technology field A1 (scanning probe t.), the US patents applied for from 1988 to 1992 cited 2,4 times more non-patent documents than the average US patent.

* = Due to a lag in publication of patent grants, the number cannot be calculated from 2000 on.

** = Cases with less than 30 patents are omitted.

4.4.3 Bionanotechnology: Exploratory Patent Analysis in the Subfield Drug Delivery

As the application areas in bionanotechnology are only gradually emerging, an exploratory patent analysis was performed only for one important subfield of bionanotechnology, namely ‘drug delivery’ (for an explanation of how Nanotechnology enables new avenues for drug delivery s. chapter 3). The patent analysis was carried out following the same procedure described in section 4.4.1. Since the word “nano” is not necessarily used in all patents whose methods of engineering the drug carrier system are based on nano-approaches, particularly if the patents date back before the term “nano” became popular in the middle of the 1990s, additional search terms were used. Figure 4.11 shows the development of the cumulated number of patent families between 1984 and 2002. The total number of patent families in bionanotechnology is relatively low compared to other fields of Nanotechnology described in earlier sections. This confirms results from other patent analyses in the technology field ‘drug delivery’ (BMBF, 2004). As many drug delivery systems are self-assembled from molecular building blocks, the subfield ‘assembly’ is the most common key word in the technology field ‘drug delivery’. The cumulated number of patent families in the subfield ‘assembly’ is higher than the number of patent families in all other subfields combined. Patent growth in the subfield ‘assembly’ started growing fast in 1989 and 1993. Since 1993, growth has remained constantly high in the subfield ‘assembly’. Patent growth in the other 11 subfields in the technology field ‘drug delivery’ picked up in the mid 1990s.

Figure 4.12 illustrates the international development of the cumulated number of patent families in the technology field ‘drug delivery’ in Europe,

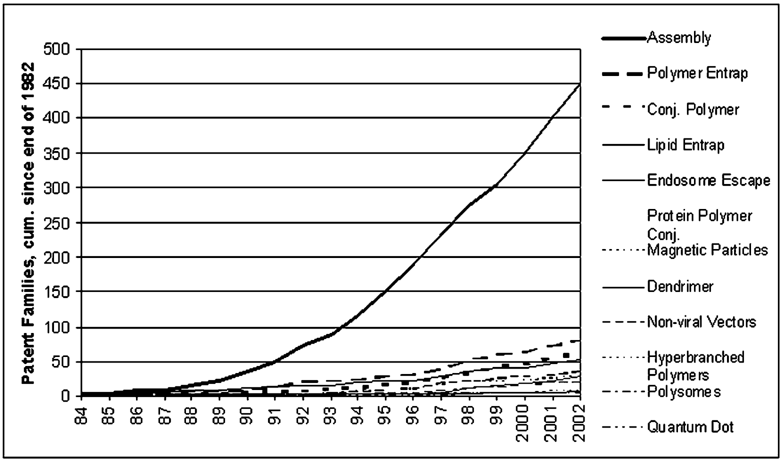


Figure 4.11: Development of the cumulated number of selected patent families in bionanotechnology between 1984 and 2002.

the US, Japan and Germany. As already observed in the other fields of Nanotechnology, the US is the dominating country also in the field of 'drug delivery'. It is remarkable that patents in the field of 'drug delivery' in the US were already filed in the 1980s, whereas European patents appeared only later in the early and mid 1990s. Patent growth has been much stronger in the US compared to Europe and Japan; the US had already reached the 2002 European level of overall cumulated patent families in 1993. One can therefore conclude that US researchers and inventors were first to identify the opportunities in the field of 'drug delivery' and to transfer research results into subsequent applications and to protect them by means of patents. As also observed in biotechnology, the US is leading by about 10 years in the field of drug delivery. The early filing of patents gives US companies a leading edge to convert scientific discoveries into new products.

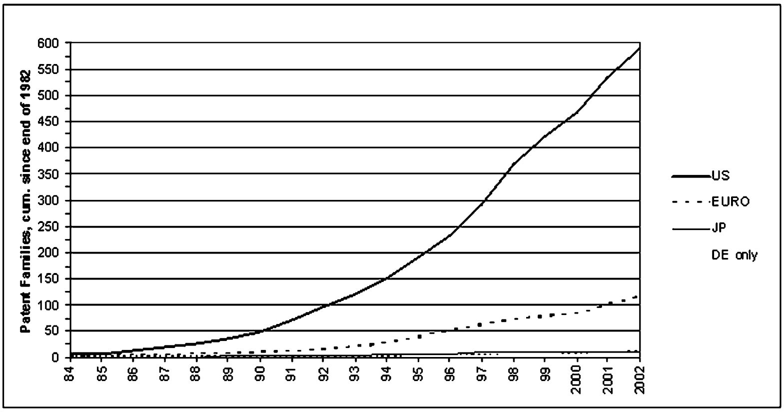


Figure 4.12: International development of the cumulated number of patent families in the technology field 'drug delivery' in Europe, the US, Japan and Germany.

4.5 Summary of Important Results and Implications

The patent portfolios in figures 4.13 – 4.16 are an adequate way to summarize and to visualize the position of the USA, Japan and Europe in important fields of Nanotechnology (refer to section 4.2 and figure 4.3 for a description of the patent portfolio method). The patent portfolio illustrations focus on the top ten technology fields with the highest number of cumulative patent families in Nanotechnology in a wider sense. For better illustration, only five technology fields are shown in each portfolio.

The patent portfolio in figure 4.13 is based on the number of total cumulative patent families and shows the results for the top five Nanotechnology fields. The USA is the leading country in four out of the five top Nanotechnology fields. These are the technology fields 'Nanotubes', 'Plasmonics', 'Self-Assembly' and '(Anti)reflection'. Japan is the leading country in the technology field 'Scanning Probe Techniques'. Overall, Europe is significantly behind the USA and Japan in all five technology fields except in the technology field 'Plasmonics'. The USA is far ahead in the technology fields 'Self-Assembly' and '(Anti)reflection', whereas Japan is close to the US position in the technology fields 'Nanotubes' and 'Plasmonics'. All three regions have almost identical R&D or patenting priorities as reflected by the circle size in the portfolio illustrations (the circle size shows the importance of a technology field (R&D emphasis) as

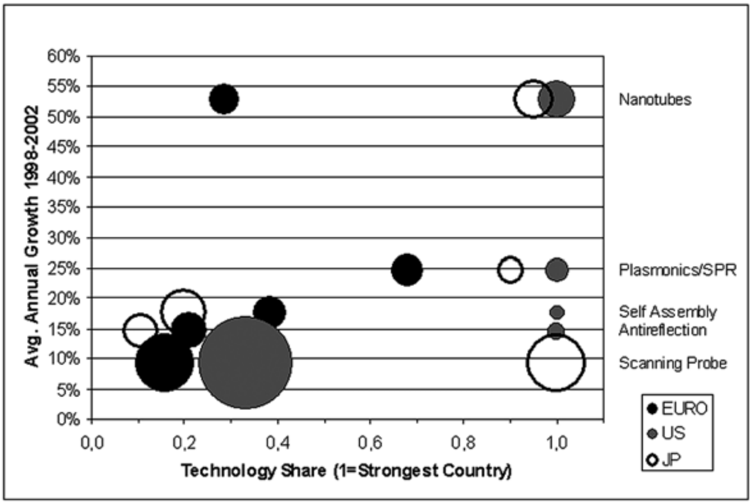


Figure 4.13: Patent Portfolio – The Patent Position of the US, Japan and Europe in the Top 5 Nanotechnology Fields.

Note: The size of the bubbles reflects the share of a country's total number of Nanotechnology patent families that are assigned to the specific technology field. Patent families are assigned to the respective region based on the first priority patent application.

explained in section 4.2 and illustrated in figure 4.3). The technology field 'Scanning Probe' is the most important field, especially for Nanotechnology patents originating in the USA. Slight differences between the USA and Japan/Europe can be observed for the technology fields 'Self-Assembly' and '(Anti)reflection'. Japan and Europe have a relatively stronger patenting focus on these technology fields than the USA. The ordinate of the patent portfolio shows the dynamic of recent patent growth in the various technology fields (section 4.2 and figure 4.3). In figure 4.13, the average annual growth rate of patent families between 1998 and 2002 is shown. It can be seen that all five technology fields had been growing at least at an average of 10% each year during this time period. This indicates the dynamic development of patenting in the field of Nanotechnology. The most dynamic patent growth occurred in the technology field 'Nanotubes'. The average patent growth rate was more than 50%. This indicates a high level of R&D activities in this technology field and an increasing technological and commercial interest in 'Nanotubes'. In this most dynamic technology field, the USA and Japan are best positioned.

Figure 4.14 shows the position of the US, Japan and Europe in the remaining top six to ten technology fields based on cumulative patent families up to 2002. The USA leads in the technology fields 'Nanostructures', 'Actuators' and 'Gas Sensors'. Japan leads in the technology fields 'Quantum Dots' and 'Switchable Spin'. Europe is far behind the USA and Japan in all

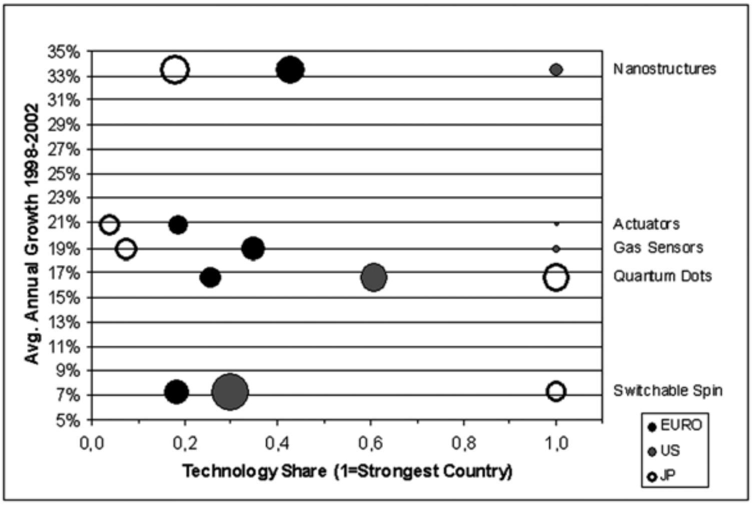


Figure 4.14: Patent Portfolio – The Patent Position of the USA, Japan and Europe in the Top 6-10 Nanotechnology Fields.

Note: The size of the bubbles reflects the share of a country's total number of Nanotechnology patent families that are assigned to the specific technology field. Patent families are assigned to the respective region based on the first priority patent application.

five technology fields. Japanese patent families have a strong focus on the technology fields 'Quantum Dots', 'Switchable Spin' and 'Nanostructures'. US patent families have a strong focus on the technology fields 'Quantum Dots' and 'Switchable Spin'. European patent families have a strong focus on the technology fields 'Gas Sensors' and 'Nanostructures'. Patent growth was high in all technology fields, particularly in the technology field 'Nanostructures'. This again proves the growing technological and commercial interest of patentees in the field of Nanotechnology.

The patent portfolios in figures 4.15 and 4.16 differ from the patent portfolios in figures 4.13 and 4.14 because the former portfolios use triad patents only. The impact of this procedure is apparent in the new patent portfolios in figures 4.15 and 4.16. The use of triad patents as the data base for the portfolios leads to a change within the top Nanotechnology fields. The formerly top technology fields 'Nanostructures', 'Actuators' and 'Quantum Dots' are replaced by the technology fields 'Shape Complementarity/Biosensors', 'Energy Conversion' and 'Ferrofluids/Superparamagnetics' (figures 4.14 and 4.16). The strength of the Japanese patent position decreases because a large quantity of national patents are excluded from the portfolio illustrations. Japan looses parts of its formerly very strong patent position in the technology fields 'Nanotubes' and 'Plasmonics'; however, Japan remains strong in the technology fields 'Scanning Probe' and 'Switchable Spin' (figures 4.15 and

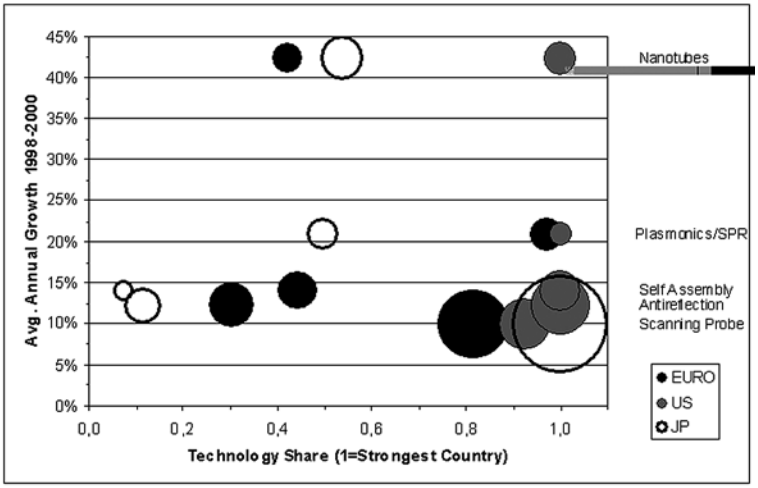


Figure 4.15: Patent Portfolio – The Patent Position of the US, Japan and Europe in the Top 5 Nanotechnology Fields (Triad Patent Families Only).

Note: The size of the bubbles reflects the share of a country's total number of Nanotechnology patent families that are assigned to the specific technology field. Patent families are assigned to the respective region based on the first priority patent application.

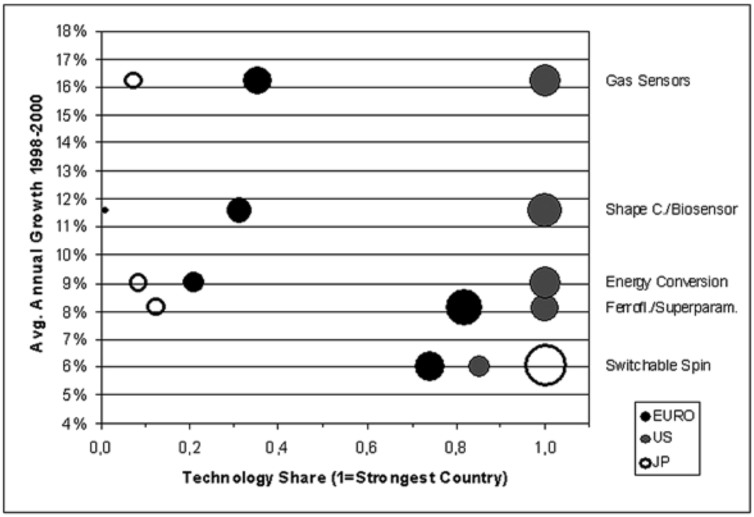


Figure 4.16: Patent Portfolio – The Patent Position of the US, Japan and Europe in the Top 6-10 Nanotechnology Fields (Triad Patent Families Only).

Note: The size of the bubbles reflects the share of a country's total number of Nanotechnology patent families that are assigned to the specific technology field. Patent families are assigned to the respective region based on the first priority patent application.

4.16). The US position improves further; in eight out of ten technology fields, most Nanotechnology patent families have originated in the USA. The European position also improves when the patent portfolio analysis is based on international and economically more valuable triad patent families. Europe gains more strength in its patent position in the technology fields 'Plasmonics', 'Scanning Probe', 'Self-Assembly' and 'Switchable spin' (figures 4.15 and 4.16). Regarding the three new fields among the top ten Nanotechnology fields, the USA is in the leading position in all three technology fields (figure 4.16). The European position is close to the USA position only in the technology field 'Ferrofluids/Superparamagnetics' (figure 4.16). The patent growth rates of triad patent families are as high as the growth rates based on the overall number of patent families. This result further proves the initial observation that the top fields of Nanotechnology seem to be very attractive for pattentees. This leads to the assumption that technological and commercial perspectives are very promising in these fields of Nanotechnology.

Tables 4.11 and 4.12 complement the portfolio illustrations. They summarize three important key patenting indicators per subfield of Nanotechnology: the relative importance of each technology field (share of a subfield's patent families of the total number of patent families), the recent patent growth in the technology field (increase of relative importance in the period 1998 to 2002 compared to the previous time period) and the leading region in each technology field (share of a region's cumulative patent families in the technology field of the total number of patent families in the technology field). To give an example, Japan is the leading region in the technology field 'Giant Magneto Resistance' (38% share of patent families in this technology field). This technology field has an 0.8% share of total patent families in Nanotechnology. Its importance slightly increased (1.2%) in the time period between 1998 and 2002. Tables 4.11 and 4.12 confirm earlier analyses and can be used to assess in particular those technology fields that are not included in the portfolio illustrations.

The patent analyses have shown that overall patenting in the field of Nanotechnology has increased substantially, particularly over the last ten years. This reflects continued and increasing interest of patentees in Nanotechnology. Since there is a correlation between patenting activity, R&D expenditures and market developments (Ernst 1996; Griliches 1990), one can assume that technological advances in Nanotechnology leading to marketable products have been made and continue to be made. The technology field 'Nanotubes' seems to be most attractive as indicated by very high growth rates of patent applications. The other fields of Nanotechnology have all been growing at least with an annual growth rate of 10% between 1997 and 2002. The most important technology field 'Scanning Probe Techniques' with a share of 33% of total Nanotechnology patents remains a core area, in which fundamental advances have been made allowing subsequent technological breakthroughs in multiple fields of Nanotechnology. The increasing relevance of commercial applications in various areas of Nanotechnology is further reflected in large and growing numbers of patent families with a large international scope. Patentees would not take the risk and spend the money to protect their inventions globally, if they did not expect high returns from this up-front investment (Basberg 1987; Ernst 2003).

A large stock of knowledge has been accumulated over time in Nanotechnology, which will eventually be used in subsequent developments. This knowledge base, if used correctly, will increase the future effectiveness and efficiency of R&D in Nanotechnology. Important knowledge is captured in the patent documents analyzed in this study and it can be used for better R&D management (Ernst 1996; Ernst 2003). Firms, research institutions, inventors etc., who have already accumulated important shares of this knowledge stock, have a strong competitive advantage. In addition, regional knowledge clusters can facilitate the process of knowledge creation and dissemination. These clusters of Nanotechnology knowledge can have an important impact on R&D location and investment decisions and hence on the future development in Nanotechnology.

The US is best positioned and has the strongest patent position in eight out of ten of the most important technology fields (based on the analysis of triad patents). The USA therefore continues to be the most attractive location for R&D in Nanotechnology. If this R&D leads to new products, the

Table 4.11: Summary of important key patenting indicators: Relative importance, recent growth trend and leading region per sub-field of Nanotechnology

<table>
<tr><th></th><th colspan="3">Size Dependent Properties</th><th colspan="3">Engineered Functions</th></tr>
<tr><th>Properties</th><td>Metals (1)</td><td>Semiconductors (2)</td><td>Insulators (3)</td><td>Molecules/ Assemblies/ Biomolecules (4)</td><td>Hybrids/ Compos. (5)</td><td>Boundary Surf. (6)</td></tr>
<tr><th>magnetic (A)</th><td>Ferrofluids and Superparamagnetism 2,8% -2,4%- US56%</td><td>Quantum (Anti)dots 4,0% - 4,2% - JP50%</td><td>Ferrofluids and Superparamagnetism 2,8% - 2,4% - US56%</td><td>Molecular Magnetism 0,6% - 0,4% - JP65%</td><td>Giant Magneto Resistance 0,8% - 1,2% - JP38%</td><td>Proximity Effect 0,0% - 0,0% - n/a</td></tr>
<tr><th>mechanic (B)</th><td colspan="3">High Strength Materials 0,0% - 0,0% - n/a</td><td>Molecular Motors 0,2% - 0,3% -US63%</td><td>High Strength Composites 0,4% - 0,4% - US61%</td><td>Self Cleaning Surfaces 0,6% - 0,7% - US40%</td></tr>
<tr><th rowspan="2">electric/ electronic (C)</th><td>Switchable Fermi Levels 0,0% - 0,0% - n/a</td><td></td><td>Ferro- and Super paraelectrics 0,5% - 0,7% - US63%</td><td rowspan="2">Molecular Switches 1,1% - 1,1% - US45%
Field Emission / Nanotubes 9,1% - 15,5% - US40%
Field-Emission Display 1,1% - 1,6% - US55%</td><td rowspan="2">Lowered Percolation Threshold 0,1% - 0,2% - US51%</td><td rowspan="2">Low-loss DK 0,1% - 0,1% - US44%
Gas Sensors and Catalysts 2,5% - 2,8% - US66%</td></tr>
<tr><td colspan="3">Quantum Size Effect 0,4% - 0,1% - JP80%
Thermoelectric Materials 0,1% - 0,1% - US83%</td></tr>
<tr><th>optical (D)</th><td>Formation of Discrete Energy Levels/QD 0,7% - 0,7% - US81%
Plasmonics 4,3% - 5,6% - US38%</td><td>Formation of Discrete Energy Levels/QD/ QSE 0,8% -1,1% - US62%</td><td>Transparent Ceramics 0,6% 0,8% - US68%</td><td></td><td>Photochromism 0,5% - 0,4% - US73%
Electrochromism 0,3% - 0,4% - EU*40%</td><td>(Anti) reflection 9,5% - 9,1% - US73%</td></tr>
<tr><th>thermodyn. (E)</th><td colspan="3"></td><td>Brownian Ratchets 0,0% - 0,0% - n/a</td><td></td><td></td></tr>
<tr><th>thermal (F)</th><td></td><td colspan="2">Phonon Engineering 0,4% - 0,5% - US66%</td><td></td><td></td><td></td></tr>
</table>

	Size Dependent Properties			Engineered Functions		
ability for self assembly / Adaptation (G)	Magnetic Dipole-Dipole Interaction 0,4% - 0,5% - US71%			Nanoarchitectures 3,3% - 4,8% - US57%	Self Assembly of Metal Nanoparticles / Polymers 5,2% - 5,7% - US61%	Self-organized Complex Patterns 1,1% - 1,3% - US79% Phase Separated Block Copolymers 0,9% - 0,9% - US55%
recognition Ability (H)				Shape Complementarity / Biosensors 2,4% - 2,4% - US71%		

Reading example: The technology field A1+A3 (ferrofluids) represented 2,8% of all Nanotechnology patents from 1983 to 2002. In the period 1998-2002, 2,4% of all new patent families in Nanotechnology concerned this field. 56% of patent families in this field were first applied for in the USA.

* = EURO includes DE, GB, EP, FR, SE, CH, NL, AT, IT, FI, DK, ES, NO (in order of significance for total nanotech)

commercial impact of US-based inventions looks very promising. The USA should therefore be an attractive market for venture investments in Nanotechnology firms. The patent position of Japan is very strong, if domestic patents are included in the analyses. Japan had the largest cumulative patent stock in Nanotechnology until 2001, when it was surpassed by the USA. This knowledge stock is important and represents a good position for future developments in the field of Nanotechnology in Japan. Based on the overall number of patent families, Japan has relatively strong patent positions in the most dynamic technology field 'Nanotubes', the largest and core technology field 'Scanning Probe Techniques' and in the top ten technology fields 'Plasmonics', 'Quantum Dots' and 'Switchable Spin' are placed. The European position is rather weak if the patent analyses are based on the total number of patent families. In this case, the dynamics of patent growth is also lower compared to the US and Japan. The picture changes when only triad patents with a high international scope are used for the patent analyses. In this case, Europe's patent position improves, especially relative to Japan, in many fields of Nanotechnology. Europe has a relatively strong patent position based on triad patents in the technology fields 'Plasmonics', 'Scanning Probe', 'Switchable Spin' and 'Ferrofluids/Superparamagnetics'. However, patent growth based on triad patents has only recently increased substantially in

Table 4.12: Summary of important key patenting indicators: Relative importance, recent growth trend and leading region per sub-field of Nanotechnology

	electric/electronic (1)	**magnetic (2)**	**optical (3)**	**mechanic (4)**
electric / electronic (A)	Scanning Probe Techn. 33,4% - 23,4% - JP66% Nano/Quantum Metrology 0,4% - 0,4% - US47%			Actuators 2,5% - 3,0% - US76%
magnetic (B)				
optical (C)		Switchable Spin 4,8% - 2,8% - JP65%	SNOM 0,2% - 0,3% - US45% Phase Change 0,6% - 0,8% - US72%	
mechanic (D)	Local Probe Array for Mass Storage 0,0% - 0,0% - n/a			Rotaxanes 0,2% - 0,3% - US45%
thermal (E)	Phase Change 0,6% - 0,8% - US72%		Phase Change 0,6% - 0,8% - US72%	

Reading example: The technology field A1 (scanning probe t.) represents 33,4% of all Nanotechnology patents filed from 1983 to 2002. In the period 1998-2002, this field represented only 23,4% of the new Nanotechnology patents. 66% of patent families in this field were first applied for in Japan.

* = EURO includes DE, GB, EP, FR, SE, CH, NL, AT, IT, FI, DK, ES, NO (in order of significance for total nanotech)

Europe and it remains to be seen if this trend has continuity and if Europe will eventually close the gap to the USA.

The patent analyses have shown that Europe is lagging behind Japan and the USA in many fields of Nanotechnology. This finding could result from different perceptions about value and effectiveness of intellectual property rights, especially patents, as an important instrument for knowledge protection and the creation of competitive advantages. Empirical research suggests that professional patent management and a strong portfolio of high-quality patents are important drivers of business performance in high-tech industries (Ernst et al. 2005; Shane 2001). This is especially the case for small and medium firms. A strong patent portfolio is particularly relevant for start-up companys that require venture funding. High-tech start-ups that have a strong patent portfolio raise significantly more venture capital, receive higher valuations by investors and go faster IPO (initial public offering) than firms with weaker patent positions (Lerner 1994; Shane and Stuart 2002; Stuart et al. 1999). Managers, researchers and policy makers must therefore understand that professional intellectual property management is essential for the successful commercialization of Nanotechnology.

Patents may not fully reflect all research activities in the field of Nanotechnology (s. chapter 3). A valuable additional indicator for research output is the number of scientific publications. A literature search based on the same search strings as for the patent analyses was carried out. Figure 4.17 and table 4.13 summarize the most important results. The first figure in table 4.13 refers to the share of scientific publications from the USA, whereas the second and the third figure refer to the share of publications from Japan and Europe, respectively. To give an example, 32% of publications in the technology field 'Hard Magnets' are from the USA, 24% of all publications come from Japan and 44% of all publications are from Europe.

The dynamic growth of research activity in Nanotechnology and many of its sub-fields is further validated by the publication intensity. Regarding the position of Europe in comparison to the US and Japan it becomes strikingly evident that Europe significantly improves its position in many fields of Nanotechnology based on the criterion publication output. Taking this as an indicator of high European research activity in the field of Nanotechnology, one can attribute the much weaker European patent position in the same fields of Nanotechnology to a transfer problem from research to development and to commercial applications in Europe. It should therefore be the task of policy makers and managers to improve Europe's capabilities to effectively convert research excellence into successful commercial applications in the field of Nanotechnology (s. recommendations).

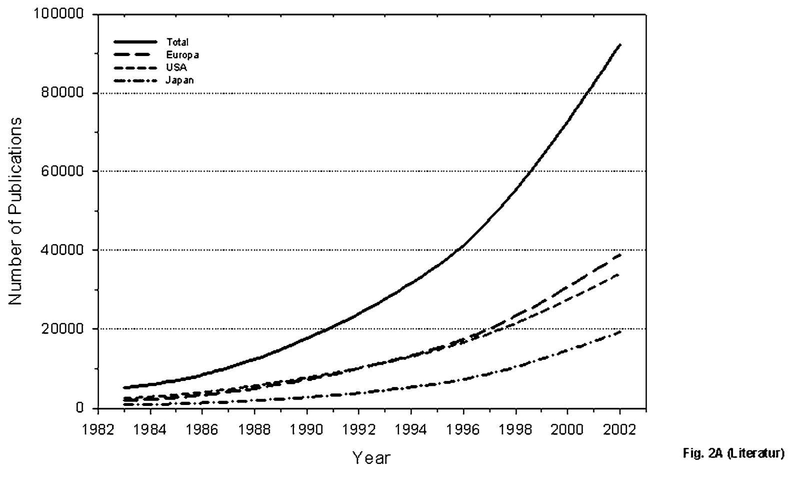


Figure 4.17: Cumulative annual publications with origin in the USA, Japan and Europe (Incl. sum of all Publications world-wide).

Table 4.13: International Origin of Scientific Publications in Nanotechnology (% of Overall Number of Scientific Publications)

	Size Dependent Properties			**Engineered Functions**		
Properties	Metals (1)	Semiconductors (2)	Insulators (3)	Molecules/Assemblies/ Biomolecules (4)	Hybrids/ Compos. (5)	Boundary Surf. (6)
magnetic (A)	Ferrofluids and Superparamagnetism 423-659-1499-2265	Quantum (Anti)dots 48-743-3755-10827	Ferrofluids and Superparamagnetism 423-659-1499-2265	Molecular Magnetism 105-108-274-1189	Giant Magneto Resistance (GMR) 0-1-1-0	Proximity Effect 0-18-57-212
mechanic (B)	High Strength Materials 0-0-11-15			Molecular Motors 920-2504-4051-4530	High Strengths Composites 0-1-1-3	Self Cleaning Surfaces 0-0-3-30
electric/ electronic (C	QSE 193-219-600-1023 Materials with Switchable Fermi Levels 0-0-0-0 Thermoelectric Materials 0-0-13-50	QSE 193-219-600-1023 Thermoelectric Materials 0-0-13-50	QSE 193-219-600-1023 Ferro- and Super paraelectrics 0-0-0-0 Thermoelectric Materials 0-0-13-50	Molecular Switches 34-120-361-833 Field Emission (Nanotubes) 21-91-1405-8155 Field-Emission Display (FED)	Lowered Percolation Threshold 9-15-117-362	Low-loss DK 19-34-67-82 Gas Sensors 4-9-101-485
optical (D)	Formation of Discrete Energy Levels/QD 0-3-10-48 Plasmonics 1435-1990-3626-6323	Formation of Discrete Energy Levels/QD/QSE 54-273-1549-2806	Transparent Ceramics 0-3-2-3		Photochromism 10-18-73-122 Electrochromism 1-0-23-59	(Anti) reflection 174-432-1374-3210
thermodyn. (E)				Brownian Ratchets 0-1-8-65		
thermal (F)		Phonon Engineering				
Ability for self assembly/ Adaptation (to the environment) (G)	Magnetic Dipole-Dipole Interaction 26-54-193-715			Nanoarchitectures 360-1591-12200-27753	Self Assembly of Metal Nanoparticles / Polymers 606-2142-5828-11292	Self-organized Complex Patterns 0-0-0-1 Phase Separated Block Copolymers 6-5-42-136
Recognition Ability (H)				Shape Complementarity / Biosensors 50-181-597-1544		

5 Risk Assessment and Risk Management

In the last years, a worldwide risk debate on Nanotechnology has risen. Surprisingly to most nanotechnologists and nanoscientists, issues of concern and fear have been expressed in the public and have been communicated via the mass media. At the side of science this risk debate has mostly been regarded as a danger for further development of Nanotechnology, remembering the histories of nuclear power technology and of biotechnology. In this chapter, we address both of these types of concern and uneasiness and we attempt at giving hints how to avoid destructive developments in public debate. To this end, we start by explaining some general aspects of technological risks and their perception and management, and ask the question, what specific challenges of Nanotechnology might be there (5.1). Then we will go into the details of possible risks of Nanotechnology, focussing on nanoparticles, their transportation and proliferation possibilities and their possible impacts on health and the environment (5.2). This directly leads to questions of risk assessment and risk management, especially regarding the precautionary principle (5.3). Beyond this scope of rather concrete questions for risks of Nanotechnology and their management, it has to be taken into account that in public debate fears and concerns have been expressed which are related to the more visionary and speculative issues related to Nanotechnology, like nanobots or self-replicating nano-machines. We will investigate the role of such topics in public risk debate and analyze the implications for communication between science and the public (5.4). Finally, we will give some conclusions and some recommendations for dealing with possible risks of Nanotechnology (5.5).

5.1 Introduction: Risks of New Technologies

Scientific progress and technical innovations are necessary in order to secure and to raise, respectively, the present level of prosperity, and to uphold the competitiveness of national economies, but also for further progress, e.g. in medicine and for sustainable development. On these points, there is, to a great extent, consensus. Necessary scientific and technical progress and increasing mechanisation of society produce, however, not only positive aspects. Unintended side effects of technology, such as, above all, hazards of new technologies for the natural environment, for human health or for our common social life, can influence the balance considerably. The ozone hole, long unrecognized carcinogenic effects of asbestos, and historical catastrophes like Bhopal or Chernobyl are well-known examples (Harremoes et al. 2002). This ambivalence of science and technology is today acknowledged to a great extent and has led to the result that risk research, technology assessment, and ethical reflection accompany technological progress (Slovic 2000; Grunwald 2002).

5.1.1 Risk Issues of New Technologies

Technology is developed with regard to the future: for a presumed need, to solve foreseeable problems, or for a future market. Objectives – *intended* effects – of technology are an essential element of decisions on technology. The objectives related to a certain course of technology development might be reached, partly reached or missed. Furthermore, besides such *intended effects* (i. e., the purposes or functions of the technology and the goals connected with them) also *unintended* effects ("side effects", which also include misappropriation and misuse) might occur and might influence the overall balance. In principle, the differentiation between intended and unintended effects has to be distinguished from the differentiation between societal desirability of technology effects and their undesirability: intended effects can meet with society's rejection, just as unintended effects can be perceived as positive. Technological risks belong to the *unintended and undesirable side effects.*

"Risk" is a notion showing a large internal complexity and forming a considerable challenge to interdisciplinary work (s. Banse and Bechmann 1998; Streffer et al. 2004). There exist two completely different perspectives on risk. The "objective" perspective (coming from natural and engineering sciences) tries to quantify the probability of the occurrence of a damage as well as to quantify the extent of the damage itself. Risk then is defined as the product of both, allowing for an "objective" comparison of different risks. The "subjective" perspective claims that objectivity in this sense is not reachable in risk analysis. Instead, normative and evaluative judgments inevitably would already enter risk analysis, not only risk assessment. Therefore, from this perspective risk assessment is not only business of experts but also subject to public debate and societal processes. While from the "objective" line of thought public perception of risk is often seen as irrational and arbitrary and should, therefore, not be taken into account, public risk perception is, from the "subjective" perspective, taken as it shows itself – which corresponds to a social sciences' point of view (Slovic 2000).

The differentiation between "subjective" and "objective" risks is somewhat illustrative but misleading in other respects. The main problem is that the notion of an "objective" risk ignores the fact that also in using quantitative measures for risk assessment normative and evaluative elements necessarily will enter the process and influence the results. The "objectivity" of risks is, therefore, misleading and might cause severe misunderstandings. On the other side, the notion of a "subjective" risk puts risks in the sphere of merely private beliefs without any claim for inter- and transsubjectivity. Instead of using these notions we will speak in the following about risks in general and will distinguish between perceived and calculated risks – bearing in mind that both of them could inherently transport subjective as well as objective aspects.

Ethical analysis asks for the normative and evaluative aspects involved, challenges the range of validity of the normative presuppositions involved, and distinguishes between "acceptance" of risks which could be described empirically and their "acceptability" which constitutes a normative concept in nature (Gethmann and Mittelstraß 1992). It insists – following the argumentative pattern that "naturalistic fallacies" do not provide legitimate reasons for orientation and action – that the normative acceptability cannot be derived from empirically measurable acceptance (Grunwald 2000a).

Further, we have to distinguish between the "proximity" of the effects interpreted as risks and the technology bringing them about: immediate effects (primary effects) are directly connected with the technology and are an inseparable aspect of its use. The expulsion of combustion residues by a jet turbine belongs in this category. The actual problematic aspects of technology effects, however, concern the indirect, the consequential effects (secondary effects), which spread by way of various and partially only insufficiently known cause/effect-relationships. Here we could name, e. g., the effects of the combustion residues mentioned above on the climate and on the atmosphere – in general, the impacts and second-order effects of the direct effects of technology on the natural environment and on society. Not only environmental or health risks are subject to such a risk assessment but also economic risks and potential social problems like technology conflicts as well as risks for sustainable development in a general sense (Kopfmüller et al. 2001). Classical types of technical or technologically-initiated risks are (Grunwald 2002, sec. 1.2):

Accidents in technical facilities: accidents in technical facilities are disruptions of normal operation. Above all, the incidents in nuclear power plants (Three Miles Island in 1979, and, still much more strongly, Chernobyl 1986) lastingly shook confidence in this method of producing energy, but also trust in technology and in the experts and politicians concerned with it in a fundamental way. The poisonous-gas catastrophes in Seveso und Bhopal point to the extremely high danger potential of certain chemical plants.

Consequences for human health: new materials or completely new emissions can affect human health, for example in the production or use of technology. To these belong the known risks and side effects of medicines (one recall, for example, the Lipobay affair), but also the dramatic history of asbestos (Gee and Greenberg 2002). Entire chapters of modern regulations for handling hazardous substances are reactions to actual health problems. Special problems of risk assessment arise in case of low dose exposures (for example, to radioactive or EMF radiation).

Consequences for the natural environment: air pollution, the ozone hole, chemical residues in ground water and in the soil are well-known, unintended consequences of the use of technology. Other than in the case of the accidents in technical facilities alluded to above, these are often *gradual* processes. They are not always readily recognizable, and there is dissent on the question of tolerance limits or "cut-off-" or "threshold values", from which point on protective or remedial measures would have to be taken. A special problem arises from anthropogenic modifications on living organisms which could be – as in the GMO case – neither reversible nor containable in case of release.

Social and cultural effects of technology: social risks connected with technology are, for instance, the loss of many jobs through rationalization and automation, especially as far as less highly qualified work is concerned. Further risks can also be a tendency towards a "police state" through the use of modern surveillance technologies, such as tapping systems for listening in on fixed network- or mobile telephone conversations, for following users' tracks in the internet, video monitoring of many public places, and registration of the genetic traits of population groups. Ethical "slippery slopes" on biomedical questions are also felt to be "cultural" risks by segments of the population (positive eugenics is an example).

Intentional misuse of technology: the terrorist attacks on September 11th, 2001 have directed our attention to a completely new type of technological risk, namely, to the intentional misappropriation and misuse of technology. This is neither a case of gradual side effects nor of accidents, but of a re-definition of the purposes of technology. Modification of chemical plants for the production of toxic agents, or of biological laboratories for breeding anthrax pathogens, and the misuse of Uranium isotopes intended for nuclear power plants to make nuclear weapons would be further examples.

Vulnerability of society: modern societies are strongly dependent on a functioning technical infrastructure. Electric power supply as well as information and communication infrastructure (telephone, Internet) are obvious examples. As a consequence, society becomes vulnerable: technical failure as well as terroristic attacks might cause severe problems to society and economy.

Such technological risks show certain characteristics which influence the approaches to their anticipative investigation and evaluation through risk research and technology assessment. Among these are, in particular:

- spatially far-reaching effects up to global effects (above all, the emissions into the atmosphere and their effects there cross one´s mind first; but also the global water cycle);

- increase of the temporal scope of consequences of technology (a classical example is the final disposal of radioactive wastes, which possibly requires careful observation for thousands of years);
- immense enlargement of the group of those possibly affected by hazards (up to all of present and future humanity);
- the problem of delayed effects: often, perceptible damage appears only decades after its cause (examples are the ozone hole, but also the asbestos case, cf. Harremoes et al. 2002);
- the difficulty of ascertaining the chain of causes in view of highly complex and hardly reproducible causal relations (example: the mad cow disease BSE);
- poor or insufficient perceptibility of the risks (e. g., of radioactivity) with normal human sensory organs;
- a high degree of damage potential due to society's vulnerability on technical dysfunction (cp. the case of the dependency of the economy on a well-functioning Internet);
- diffuse distribution of responsibility – often there are millions of people causing negative side-effects (for example, the ozone hole), but who could be made responsible or accountable?
- in many cases, irreversibility of risks (for example: genetically manipulated organisms, once released, can no longer be completely retrieved from the natural environment);
- precise knowledge of the probability of an event or the extent of damage is not available, but only as – often themselves uncertain – probabilities.

In summary, in the past decades it has turned out that side effects can interfere with or even counteract the goals pursued by means of technology. This ambivalence of technology, the greater discrepancy between the intended and the (then) actually realized effects constitute a *conditio humana* of technological civilization. Both positions are senseless: the demand for absolute safe and risk-free technology ("zero risk"), as well as disregarding or denying the "dark side" of technology. The challenge consists much rather in addressing the risks, in analyzing them, and in evaluating them rationally, in comparing them with the expected benefits, and in taking the results of these deliberations into consideration in decision-making processes.

5.1.2 Risk Assessment and Risk Management – General Aspects

Risk management concerning the implementation of new technologies and the introduction of new materials has a long tradition. Often, a quasi "experimental" approach has been taken in earlier times. New substances and technologies have been introduced assuming that either probably no negative developments and impacts would occur or that – in case of unexpected negative effects – *ex post* repair and compensation strategies would be appropriate to deal with those unexpected situations. For example, concerning the asbestos case, knowledge about toxic impacts of high asbestos dust concentration on the lung – leading to asbestosis – came up in the 1920s and led to first regulations which limited the asbestos dust concentration at the working places in the asbestos industry (which could indeed prevent asbestosis but was not sufficient to prevent lung cancer and mesothelioma, cp. Gee and Greenberg 2002). Experiences with hazards caused by new materials, radiation, or by new technologies led to regulations in different fields, in order to prevent negative impacts on health and the environment. Important areas are:

- regulations for working places with specific exposures showing specific risks (nuclear power plants, chemical industry, aircraft personnel etc.);
- procedural and substantial regulations for nutrition and food (concerning conservation procedures, maximally allowed concentrations of undesired chemicals like hormones etc.);
- environmental standards in many areas (concerning ground water quality, maximum of allowed rate of specific emissions of fabrication plants, power plants, heating in households, etc.);
- safety standards and liability issues (in the field of automobile transport, for power plants, engines, technical products used in households etc.).

In the meantime, due to many experiences (like in the asbestos case, Gee and Greenberg 2002, or in the CFC case, Farman 2002), risk management strategies have been developed and implemented (cp. for example the Toxic Substances Control Act in the United States, Wardak 2003). In the last years debates about the precautionary principle – which has been implemented in the environmental policy of the European Union (von Schomberg 2004) –

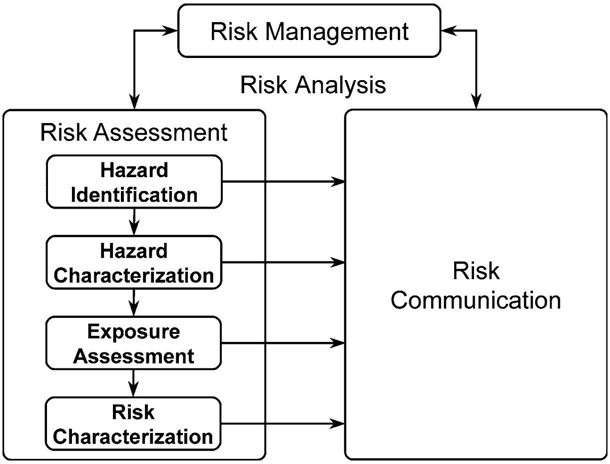


Figure 5.1: The three interconnected components of risk analysis (Official Journal of the European Union L, 031, 01/02/2002, pp. L31/0001–L31/0024).

and its consequences have been discussed for many fields (for example, in climate policy, Schröder et al. 2002, or in the regulation of the production and use of new chemicals in the European Union REACH, which is still in a deliberation stage).

Figure 5.1 illustrates the three interconnected components of risk analysis – risk assessment, risk management, and risk communication, which will also be treated in subchapter 5.4 – as identified and defined by the so-called EU "Food Law". The scheme also highlights hazard identification as the first step in risk assessment. Because of lack of knowledge (sec. 5.2) it is an open question whether established mechanisms of risk analysis and risk regulation, based on the above-mentioned "objective" understanding of risk and following the scheme in figure 5.1, may be applied to Nanotechnology. A lively debate focuses on the question whether the precautionary principle as a means of "uncertainty-based" regulation should be used in this case instead (s. tab. 5.1; Haum et al. 2004).

Regulatory systems have been established in many areas following the concept of calculable risk (as product of the extent of harm and the probability that harm could occur). In case that risk may not be calculated in this (quasi-objective) way there is uncertainty about the extent of harm and the probability of the occurrence of harm remaining. In this case "uncertainty-based" regulation applies (tab. 5.1) which, in case of possible severe harm, leads to the precautionary principle (s. section 5.3.2).

Table 5.1 Characteristics of regulatory systems (modified following von Schomberg 2004)

Risk-based regulation	**Uncertainty-based regulation**
identifying risks	Assessing uncertainties/state of affairs in science
applying normative standards of acceptable risks, supported by ethical analysis (Gethmann and Mittelstraß 1992) and public debate	applying transformable (deliberations-based) standards of acceptable uncertainties
applying definitions of harm	appealing to normative transformable standards
calculating the chance of occurrence of probable effects (for example, by means of classical risk assessment)	assessing the plausibility of possible adverse effects
policy objective: minimizing risks; prevention of damage, protection of the population's health and of the environment	policy objective: reducing uncertainties; enabling precautionary and learning practice etc
possibility of avoidance of predictable long-term effects by prevention	prospective long-term effects can only be identified to some extent, precautionary measures such as monitoring enable possibly the early identification of adverse effects over time

5.1.3 Risk Management of Nanotechnology – Specific Aspects

Humans have been exposed to airborne particles, especially to nano-scaled particles, during their total developmental period, but this exposure has increased enormously over the last century due to anthropogenic sources. Whereas this increase mainly comes from combustion processes where these particles reach the environment unintended, the rapidly growing field of Nanotechnology is likely to become yet another source for such very small particles in the near future. As a first approximation, there is no difference between risk assessment for nanomaterials produced for technical use or those with unique surface functionalities for a more direct application in biological systems. Nevertheless, those particles coming in close conctact with living organisms and with special surface characteristics to interfere with biological elements deserve closer attention.

Present scientific knowledge about substances and devices produced using nanotechnologies precludes going further than identifying hazards – the first step of risk assessment – and providing some elements of hazard characterization – the second step of risk assessment. Research on the behaviour of nanoparticles in different compartments of the environment as well as research on the impacts of nanoparticles on animals and humans, depending on different ways of assimilation of nanoparticles (via the lung, via digestion, or via the skin) are on the agenda (s. 5.2). Together with assessments of the exposure of humans to nanoparticles at different locations (exposure at working places in industry, or for consumers of nanoparticle-based products) – which would require prospective analyses of the production and distribution of nanoparticle-based products – the risk management chain (figure 5.1) could be completed by scientific knowledge.

The question might arise why and to which respect Nanotechnology could be the source of completely new or modified challenges to risk analysis, risk management and risk communication. What is specific about nanotechnologies which would legitimate and motivate a corresponding specific risk debate, perhaps also specific regulatory regimes or measures? Why does it – at the moment – seem to many experts and people concerned, who are involved in this debate, that established strategies and measures of dealing with risks might be inadequate or insufficient?

One reason might be that nanotechnologies and their products do not fit into the classical classification systems, especially of chemistry (in the following argumentation we will restrict our considerations to artificially designed nanoparticles as described in chapter 3, tables 1-3 in contrast to other particulate matter that normally is unintendedly released into the environment and is under intense investigation. Besides, this is an area that will also be a topic of ethical considerations in section 6.2.1). Nanoparticles might consist of well-known chemical substances or might fit into established classes of chemicals. But because of the new properties and functionalities they show and which are closely related to the nanoscale (cp. our definition in chapter 3) there might be new classes or types of risk and uncertainty in spite of the fact that the basic chemicals and their toxic properties might be well-known. The traditional classification systems and regulatory regimes take care of the particle size only in a rather rough manner (distinction between PM_{10}, $PM_{2,5}$ and in some future $PM_{0,1}$) and ignore completely the surface properties of particles which are decisive in the nano-particle case.

In order to allow for a more rational debate differentiating approaches are necessary. Facing the manifold nanoparticles and their which could be imagined and which are already subject to ongoing research, a categorization of nanoparticles and possibly related risk types would be highly desirable. Typical categories could be (s. also Haum et al. 2004, p. 15)

- particle size (mobility and diffusion issues, detectability),
- particle morphology,
- surface properties (adhesion, cohesion, agglomeration),
- active surface areas,
- surface charges.

Furthermore, the possibilities to learn from experiences with other types of risk should be exhausted to the largest possible extent. Especially experiences in dealing cautiously with new chemicals should be taken into account. In order to establish criteria for comparing possible nanoparticle risks to other (well-known) types of risks it would be very useful to get reliable orientation what could be *really new* about nanoparticle risks.

5.2 Risk Characterization in Nanotechnology

"*There are risks and costs to a program of action (or a technology, author's remark) but they are far less than the long range risks and costs of comfortable inaction*" (John. F. Kennedy) or in other words "whenever we invent new processes and technologies there will be some risk, but without any risk, nothing will happen anymore". This is *one possible* viewpoint to initiate a new technology. But on the other hand, there always exist possible risks coming from most new technologies and influences may be perceivable in the environment or in living organisms and we have to consider this as well. Moreover, we can state that there is "*no innovation without risk*". Whenever mankind has developed a new and intriguing technique, this technique has had its impacts on environment and health (and, often, on society in a more general manner (s. section 5.1). In this chapter, however, we will focus on possible toxicological effects). Nowadays the main purpose of environmental health and toxicological studies is to minimize these impacts and protect living organisms from adverse effects coming from products or processes or from new technologies.

The first step in managing risks is to identify potential risks and their causes. Risk identification should consider all areas of a technology and both internal and external factors. Research is therefore needed with respect to the environmental health and safety (EHS) on the following topics:

- Particle uptake into living organisms
- Accumulation of nanoparticles in specific organs (e.g. liver, spleen, brain, fetus)
- Specific effects of nanoparticles in the respiratory system (e.g. inflammation)
- Fate of nanomaterials in the environment (e.g. mobilization of heavy metals, binding of toxic substances)
- Possible entry into the food chain: accumulation
- Desorption/adsorption
- Surprising effects.

One of the most important points in assessing risks of Nanotechnology is to distinguish between free nanomaterials, especially nanosized particles, and fixed nanoparticles, because of the tremendous differences in mobility. Next, we have to discriminate between nanoparticles from technological processes and those that were unintentionally produced and released into the environment by several conventional technologies (e.g. diesel exhaust particles, fly ash, catalyst emissions, candle light). Furthermore, we have to take into account that some engineered nanomaterials possibly exhibit critical characteristics when emitted into the environment or taken up by living organisms (Krug 2003, Krug and Diabaté 2003, Krug et al. 2004). Based on the knowledge that newly synthesized nanomaterials possess totally new properties with respect to chemical, physical or electronic applications, they may exhibit totally new effects in living systems as well. Therefore, it will not be possible to extrapolate the effects of bulk material down to nanomaterial and a valid prediction for the toxicity of nanoparticles on the basis of conventional materials cannot be made. The situation will be much more complicated because of the following reasons:

- the multitude of different substances;
- the multitude of different structures, surfaces and sizes;
- the expected totally different behavior in living systems and the environment.

Consequently it might be legal requirement that each nano-particle type or nanomaterial must be evaluated in its own right. Nevertheless, the technical feasibility to produce ultrafine materials at the nanometer scale is not the basis for a totally new and unique exposure of humans and the environment. Long before we invented this new technology and the manipulation of single atoms was achieved, we were imperiled by smallest particles coming from forest fires, sand storms, volcanic eruptions, combustion processes, and mechanical procedures that do not only produce visible particles but also a huge amount of ultrafines. Thus, the exposure against coarse, fine and ultrafine dust is part of our life and it is widely known that this exposure is harmful for our health. Since the middle ages it has been well documented in special books that there exists a risk for occupationally exposed workers at specialized working places. In particular, miners will suffer from pneumoconiosis after long-term inhalation of silica-containing dust. Today most ambient air particles of non-natural source are coming from

- technical combustion processes;
- traffic (diesel exhaust particles, catalyst particles, abrasion of tyres, couplers and brakes);
- private domain (candle light, fireside);
- kitchen work (cooking, roasting, barbecuing);
- smoking.

The experience with these exposure conditions will possibly express reservations against new techniques that enhance the contact to very small particles in a great number. Several products are introduced onto the market containing nanoparticles for different purposes:

- cosmetics/tooth past/vanishing crème;
- printer/copier;
- sunscreen;
- paint/varnish/glue;
- car tires;
- food additives;
- surface coatings.

Many of these applications will result in an enhancement of particle numbers in the environment despite the fact that only a minor number of these will be in the nanometer range. The technical use as well as the daily utilization of such materials during normal life will pose several questions: is there an increasing exposure to nanomaterials and which pathways are involved, where will the particles go and where do they remain, is there an unacceptable risk coming from these new materials? It is discussed that ultrafine particles have increased in the air during the last decades and there is evidence not only for an induction of lung injury but also for cardiovascular diseases and adverse effects in the nervous system. But such discussions mostly concern the totality of all ultrafine particles in the ambient air and until now there have been no nanoparticles in the air coming from new nano-technological developments. For this reason the public discussion and the opinion in the newspapers are mostly speculations based on irrelevant or statistically not significant data (however, this diagnosis – reasons will be given below – does not legitimate to ignore public uneasiness or concern).

5.2.1 Production and Use of Nanomaterials

As mentioned earlier, production and use of nanomaterials and nanoparticles will increase dramatically over the next years (chapter 3). No area within our society or the individual life will be excluded; all organisms will have contact to nanomaterials or will be more or less exposed to nanoparticles. To estimate possible consequences we have to discriminate between "coated engineered nanoparticles" and "uncoated engineered nanoparticles". Coatings change the characteristics of nanoparticles and will possibly render such particles inert, depending on the characteristics of the particle, the properties of the coating, and the environment of the nanoparticle. Another important difference with far-reaching effects is the possible life span of nanomaterials. The environmental as well as the health impact is mainly determined by the fact, if these particles are "short-lived engineered nanoparticles" or "long-lived/durable engineered nanoparticles". This difference will acquire special importance for particles that penetrate the body, because the possible accumulation of nanoparticles in special remote organs is a critical issue. Nanoparticles produced as drug delivery system for instance should be either excretable or biodegradable once they have fulfilled their mission. It must be a legal demand to ask for precautionary measures during and after nanoparticle production processes.

Generally, in a recent report from the Institute of Occupational Medicine in Great Britain (Aitken et al. 2004), it has been postulated to consider

- the existence of potential routes for human exposure;
- possible industrial sources of occupational exposure;
- the levels of exposure;
- means of and effectiveness of control measures;
- potential numbers of humans exposed;
- trends in the (potential) use of Nanotechnology;

views concerning the likely impact of the implementation of the change from research use to full-scale industrial use.

Occupational and Environmental Implications: Impacts and Aspects

The environment could benefit from the technical possibilities of Nanotechnology to create new types of miniature sensors, pollutant filters and fuel cell catalysts. However, this technology is still at its beginning to start production on a large scale and thus there is nonetheless uncertainty about the possible impact of releasing nanoparticles into the environment (figure 5.2). The benefits are expected to rise from better end-of-pipe technologies for cleaning of air emissions, wastewater discharges and polluted soil and other hazardous wastes as well to more efficient energy production and storage technologies. Some examples for such potential benefits are:

- Synthetic or manufacturing processes may occur at ambient temperature and pressure to safe energy.
- The use of non-toxic catalysts with minimal production of resultant pollutants reduces material needs and emission.
- The use of aqueous-based reactions can safe solvents, contaminants and a technique for building molecules as needed "just in time" can help to avoid overproduction.
- Nanoscale information technologies will help to identify products and tracking them to manage recycling, remanufacture, and end of life disposal.
- Iron walls used in groundwater treatment can be made more efficient using nanosized iron that enhances the reaction. This can be further enhanced by coupling with other metals (e.g. Pd) on the nanoscale. Nanoscale FeO is more reactive and effective than the microscale bulk material.
- Several nanomaterials can serve as semiconductor films to be used as a sensor and photocatalyst: special nanosized materials "senses" organic pollutants indicated by changes in visible emission signals and the same or other nanomaterials "shoot" the pollutants via photocatalytic oxidation to form more environmentally benign compounds.
- Single molecule detection sensors may enhance the recognition of pollutants early before damages can occur.
- Nanodevices can be used to detect chemicals using either a specific reaction between analyte and sensor layer or chemical/physisorption processes. Such applications can be adapted to bio-toxins as well.

On the other hand, based on today's knowledge on occupational hygiene, for nanoparticle production it can actually be concluded that (following Aitken et al. 2004)

- of the main groups of nanoparticle production processes (gas-phase, vapor deposition, colloidal and attrition) all may potentially result in exposure by inhalation, dermal or ingestion routes:
- these processes are not different from existing chemical production processes;

- only the gas-phase processes have the potential to cause exposure to primary nanoparticles by inhalation during the synthesis stage. All processes may give rise to exposure (by inhalation, dermal and ingestion) to agglomerated nanoparticles during recovery, powder handling and product processing;
- for exposure by inhalation, control approaches and methods are available which should be effective in nanoparticle processes; however, this is not valid for other exposure routes;
- the most appropriate metric in most cases for assessment of adverse health effects after inhalation exposure to nanoparticles is particle surface area. There are no effective methods currently available by which particle surface can be assessed in the workplace, even the number of nanoparticles and their agglomerates are not definitely detectable;
- current knowledge is inadequate for risk assessment purposes;
- less information has been gathered about workers′ exposures to nanoparticles in the university/research sector or in the new nanoparticle production companies;
- the number of people in the university/research sector, and in new nanoparticle production companies may increase drastically over the next decade.

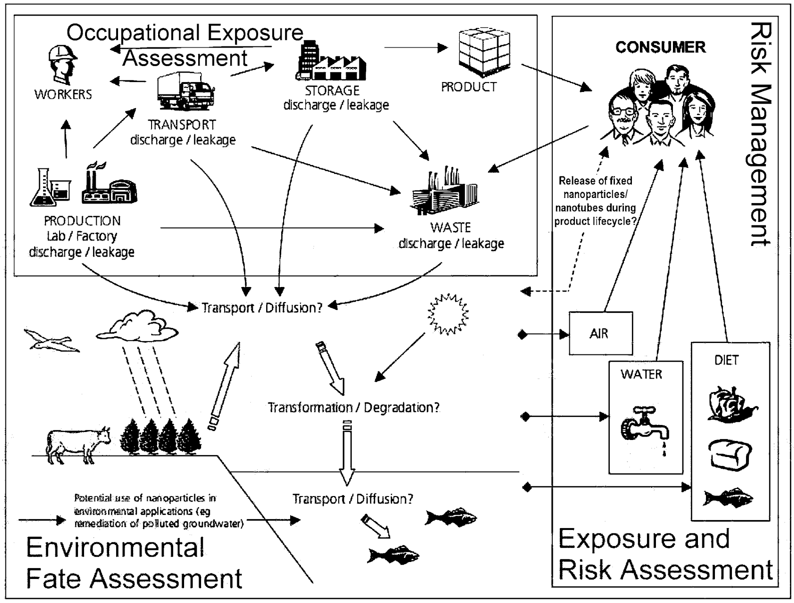


Figure 5.2: Possible exposure routes for nanoparticles/-materials based on current and potential future applications (adapted from National Institute for Resources and Environment, Japan http://www.nire.go.jp/eco_tec_e/hyouka_e.htm; adapted from: Royal Society 2004).

Nanoparticles can occur naturally, through combusting for instance, but as mentioned above they are increasingly being manufactured for industrial and medical applications. The question is how many people will be exposed to nanoparticles, and more precisely to engineered nanoparticles and in what quantities? Where will these particles go and how do they distribute in the environment?

First studies dealing with the direct investigation of an exposure to nanoparticles and the effect on mortality were carried out. Until now no significantly increased standardized mortality ratio (SMR) was found for any specific cause of death in rats exposed to high levels of TiO_2 as well as in a group of workers (Fryzek et al. 2003).

Nevertheless, it is being discussed in the public more and more, but also between toxicologists and occupational physicians, that Nanotechnology may create contaminants whose tiny size makes them ultra-hazardous or these very small materials may bind or react with other contaminants in the air or in the water that are harmful and facilitate their transport into living organisms leading to adverse effects. Because most developments of new materials at the nanometer scale are rather at the scientific than on the production level, the actual release of nanomaterials into the environment is basically low or negligible. With an increasing number of applications and users, however, the produced amount will grow dramatically and the chance of environmental contamination and exposure of living organisms will grow in parallel (Health and Safety Executive 2004; VDI-TZ 2004).

Distribution via the Air

Depending on the production process and the use of nanomaterials nanoparticles can reach the water or the air and may finally be deposited in soil or ground water. Moreover, their usage within one-way-products makes it mandatory to recycle or depollute such waste. Most of the airborne fine and ultrafine particles came from unintended sources like combustion or abrasion processes. But as production of nanomaterials will increase dramatically during the next years they may serve as a totally new class of non-degradable pollutants in the air with long distribution distances. The long-term effects of these materials are not calculable at present. Since the air is one of the best analyzed compartments and the atmospheric load and the exposure of organisms have been intensely investigated for decades, there exist a lot of studies dealing with adverse effects of particulate matter. Nevertheless, the disproportionate activity of the smallest particles has been recognized only during the last 10 years (Ibald-Mulli et al. 2002; Wichmann et al. 2000). We may reckon that during the following years the number of ultrafine particles will increase in the air, especially at work places. Figure 5.3 illustrates the three different size classes of particles in the air. Whereas particles coming from combustion, e.g. from diesel exhaust, will coagulate and aggregate to form fine and coarse fractions that will sediment during days, engineered nanoparticles are often sur-

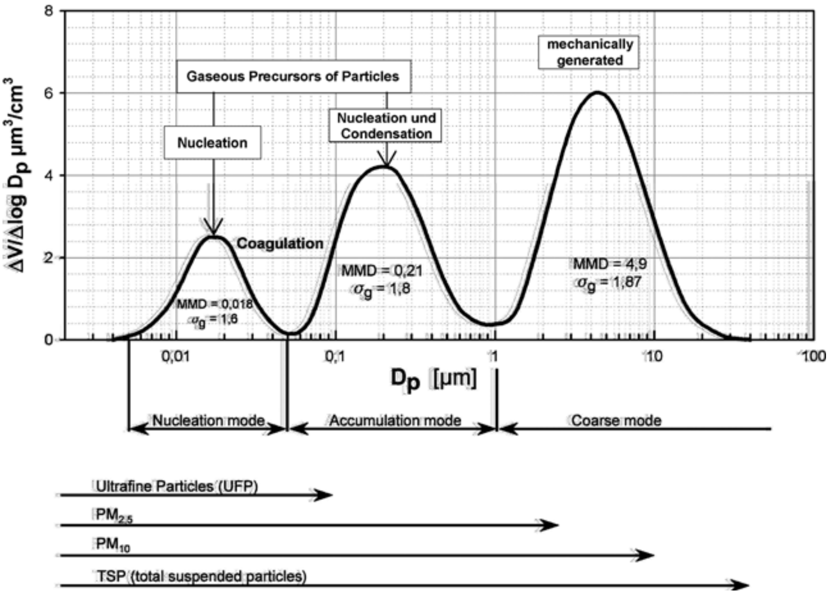


Figure 5.3: Particle-volume distribution in the atmosphere (adapted from: John 1993 and Whitby 1978; the absolute values in this graph were taken from figure 1 in Cyrys et al. 2002).

face-treated and therefore do not aggregate and their life-time in the air is drastically enhanced, because they do not sediment due to their low mass.

When freshly prepared in the gas phase nanoparticles will behave more like a gas or a vapor because diffusional forces dominate. Particles with high diffusion coefficient have high mobility and mix rapidly in aerosol systems. This is an important fact with implications for the ease in which they can be controlled. In closed manufacturing systems which have a leak, nanoscale particles would be much more likely to escape than larger particles because of their higher mobility. Therefore systems have to be applied that normally are used to contain gaseous emissions. Moreover, leaking nanoparticles will distribute very rapidly with two major aspects: at the site of leakage the concentration will fall rapidly, but their distribution could end up at great distance from the source potentially leading to larger numbers of individuals being exposed.

Diffusion of smaller particles at higher velocities will enhance the number of collisions leading to coagulation and agglomeration, causing a growth in size. The rate of this process is dependent on the number and the mobility (proportional to size) of the particles.

Taking into account the relatively short half-life of nanoparticles (Table 5.2) one should envision that the outcome of such a coagulation process is still a nanoparticle, albeit a slightly larger one (compare figure 5.1). But airborne particles do never constitute a uniform population, various types of

Table 5.2: Coagulation half-life (original values: Preining 1998)

Particle diameter	**Half life at concentrations**			
[nm]	1 g x m^{-3}	1 mg x m^{-3}	1 µg x m^{-3}	1 ng x m^{-3}
1	2.20 µs	2.20 ms	2.20 s	36.67 min
2	12.00 µs	12.00 ms	12.00 s	3.34 hrs
5	0.12 ms	0.12 s	2.00 min	33.34 hrs
10	0.70 ms	0.70 s	11.67 min	8.10 days
20	3.80 ms	3.80 s	63.34 min	43.98 days

particulate air pollution have been addressed in epidemiological studies, the main ones being TSP (total suspended particulate) and PM_{10} (particulate matter with an effective aerodynamic diameter less than 10 µm). Recently, many studies have targeted fine particles with an aerodynamic diameter less than 2.5 µm (Becker et al. 2003; Kappos et al. 2004; Murphy et al. 1998; Nemmar et al. 2004; Pekkanen et al. 2002; Penttinen et al. 2001; Pope, III et al. 1995; Schwartz et al. 1996; Schwartz and Neas 2000). Based on evidence coming from epidemiologists and results from animal studies on the potential toxicity of very small particles, several studies actually focus on the health effects of particles which are less than 100 nm in diameter (Brown et al. 2004; Campbell et al. 2005; de Hartog et al. 2003; Gilmour et al. 2004; Kapp et al. 2004; Nemmar et al. 2004; Nemmar et al. 2005; Timonen et al. 2004; von Klot et al. 2002). Primary ultrafine particles are formed during gas-to-particle conversion or during incomplete fuel combustion. Car traffic is one of the most important sources of particulate emissions (Cyrys et al. 2003; Hoek et al. 2001b; Wehner et al. 2002; Wiedensohler et al. 2002). Whether ultrafine particles come from unintended sources or were emitted from production processes, their contribution to the total mass concentration is relatively low. For future evaluation of exposure doses improvement of measurement techniques is important to calculate number size distributions down to a few nanometers (Wichmann et al. 2000; Wiedensohler et al. 2002). With regard to nanoparticles or ultrafine particles most of the actual studies are ongoing and very few results on their biological activity are available so far (Donaldson et al. 2002; Hamoir et al. 2003; Hohr et al. 2002; Ibald-Mulli et al. 2002; Kleinman et al. 2003; Lam et al. 2004; Oberdörster et al. 2004; Rehn et al. 2003; Warheit et al. 2004; Wottrich et al. 2004).

Direct measurements of concentrations in the air in production areas of nanomaterials are much less frequent (Kuhlbusch et al. 2004; Maynard et al. 2004) and such studies have to be encouraged intensely. Two recently published books/reports summarize the knowledge on the distribution of ultrafine particles in the atmosphere and at workplaces (Brown et al. 2003; Möhlmann 2003).

Distribution via the Water

In the longer term, there is the opportunity for a wide exposure of the entire ecosystem to engineered nanomaterials through water and soil. If nanomaterial applications develop as projected (i.e. very quickly), the increasing concentrations of nanomaterials in groundwater and soil could present the most significant exposure avenues for assessing environmental risks (Colvin 2003) because these materials are already making their way into consumer products ranging from nano-engineered titania particles for sunscreens and paints to carbon nanotube composites in tires and alumina nanoparticles in shampoos. Several varieties of bimetallic or polymeric nanoparticles have been proposed as products for groundwater remediation (Lecoanet and Wiesner 2004; Tungittiplakorn et al. 2004; Wang and Zhang 1997). Keeping this in mind there is little doubt that at least some portion of the materials marketed as products of a growing nanochemistry industry will ultimately find their way into our environment. Based on this knowledge there are two essential needs for information: firstly, regarding the environmental implications of nanomaterials and secondly, regarding the transport, deployment, and potential efficacy of transporting engineered nanoparticles introduced to porous media in environmental applications such as groundwater remediation. Recent work has considered the transport properties of a variety of nanomaterials in porous media and have found that there is profound difference between oxide nanoparticles and carbon particles like fullerenes or carbon nanotubes (Lecoanet et al. 2004; Lecoanet and Wiesner 2004). Moreover, during transport in water or soil, nanoparticles themselves possibly not

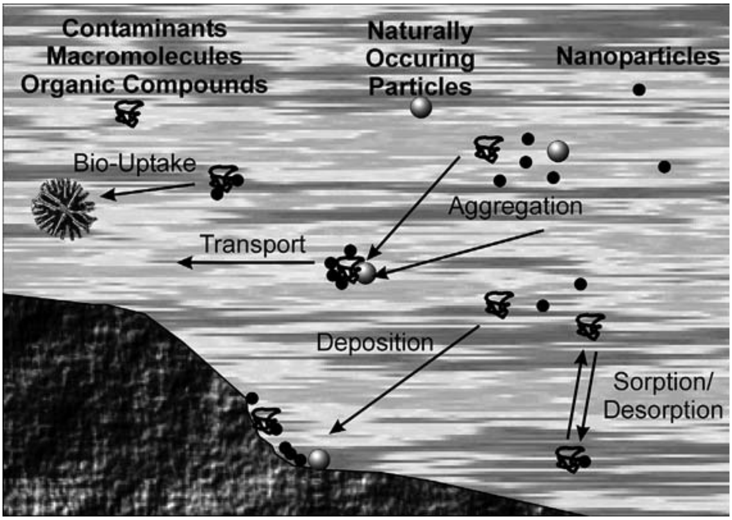


Figure 5.4: Distribution and possible reactions of nanoparticles in aquatic systems.

dangerous could bind or react with other chemicals, substances and contaminants that are harmful and thereby mediating adverse effects in biological systems (Gerde et al. 2001; Johnston et al. 2000; Knaapen et al. 2004; Moore and Willows 1998; Xia et al. 2004). Many types of molecules will adsorb to nanoparticles in complex aqueous environments (De Jesus et al. 2004; Mudroch et al. 1994) and these adsorbed molecules may dictate biological interactions, especially bio-uptake and adverse effects, of the nanoparticles (figure 5.4). The direct effects of the particles as well as of the bound pollutants may be harmful, e.g. via lysosomal damage and augmented autophagy with subsequent cell injury as described by Moore (2002).

As the movement of nanomaterials in the environment is very case-specific and strongly dependent on the material properties surely not all nanomaterials are mobile in water or soil. Regarding their potential impact in water, for instance, the movement of different nanomaterials in aqueous systems has been investigated (Lecoanet et al. 2004; Lecoanet and Wiesner 2004). In this study the mobilities of three fullerenes under pH and ionic strength conditions similar to those in many groundwater aquifers were tested. The fullerene mobilities were compared with those of four oxide nanomaterials and a "widely differing transport behavior" was found. While the transport of mineral nanoparticles is well described by current models for particle transport in porous media such as ground waters, the transport of fullerenes cannot be described by these models and shows some unusual properties. Moreover, the form of buckyballs, that has received the most attention in recent toxicity studies (Oberdörster 2004), is the least mobile form of fullerenes tested, thus the potential for environmental risk should be somewhat reduced. Such studies dealing with the transportation phenomena of nanoparticles in water and soil will help to understand the potential efficiency of using such materials to clean up groundwater pollution, as well as aiding the assessment of any environmental risks that nanomaterials might present. Ultimately for every material a decision criterion must be the possible availability to ground water and its distribution within this compartment (figure 5.5).

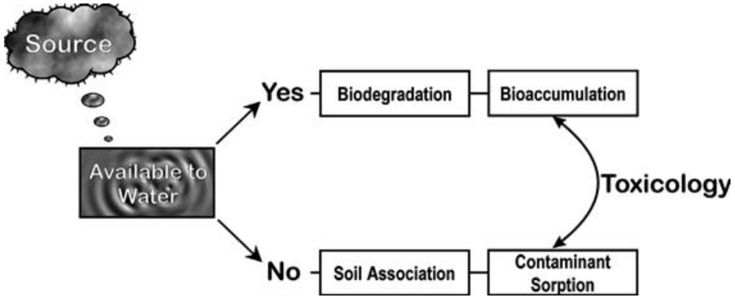


Figure 5.5: Scheme of decision for nanoparticle evaluation.

First evidences that these synthetic carbon nanoparticles may exhibit adverse effects in aquatic organism arose from work with manufactured fullerenes in water (Oberdörster 2004). After exposure of juvenile largemouth bass to 0.5 ppm water-soluble buckyballs (C_{60}) for 48 h the animals developed significant alterations in their brains particularly lipid peroxidation. Additionally, the same group looked for altered gene expression especially in the liver of the exposed animals and found a variety of genes that were turned on or off, indicating a systemic activity of the fullerenes in the whole body. Besides the biological mechanism of action two further questions have to be asked in this matter: how many particles have been taken up by the fish (dosage) and may such materials accumulate throughout the food chain, affecting not just fish, but other animals, plants and possible people.

Therefore great efforts have to be undertaken to clarify possible bio-accumulation processes, as many nanomaterials are non biodegradable and may behave like an persistent pollutant.

On the basis of the above mentioned considerations Moore (2002) defines four important challenges for ecotoxicological risk management which are definitely relevant for nanotechnological products as well: (1) much of the toxicological research to date has been descriptive; a profound change in current thinking for better tools to understand the mechanisms of molecular and subcellular interactions with pollutant chemicals or nanoparticles, including genomic and proteomic aspects, is required; (2) the development of predictive simulation models to study the toxic effects of chemicals or nanoparticles on complex cellular and physiological processes, taking into account that different types of cells or different organisms communicate and interact with each other; (3) linking molecular, cellular and pathopysiological 'endpoints' with higher level of ecological consequences; and (4) precautionary anticipation of possible harmful impacts of novel developments in industrial processes, including biotechnology and Nanotechnology.

Health Aspects

The most important point with regard to health effects, at the actual stage of Nanosciences, is the identification and characterization of possible hazards coming from manufactured nanomaterials and engineered nanoparticles. Secondly, there must be a situation where an exposure can be assumed, as without any exposure there is no risk for health (figure 5.6).

Risk = Exposure x Hazard

If we postulate that an increasing production of nanomaterials will be associated by an increasing amount of nanoparticles being emitted into the air at working places or in the environment we next have to calculate the possible doses living organism are possibly exposed to (figure 5.7).

Health Impact Extrapolation: Dose-Response Relationships

To understand the correlation between environmental noxes and their influence on living systems and the way how to estimate the risk coming from such xenobiotics we have to define the terms with which occupational physicians and toxicologists describe these processes.

Hazard is defined as the potential of a noxious matter to cause harm: hazard is typically assessed by (occupational) toxicologists testing the harmful potential on cultured cells or isolated organs (*in vitro*) or directly on laboratory animals (*in vivo*).

Exposure is the presence of the noxious matter in a relevant medium (air, food, water, soil) multiplied by the duration of contact.

Risk (s. above) is a quantification of the two above explained terms: if a noxious matter is demonstrated to be harmful (hazard) and there can be situations defined where an exposure can occur (exposure), then there exists a possible risk for adverse effects induced by this xenobiotic. The height of the calculated risk is further dependent on the concentration of the noxious matter and the time of exposure dose, see next. In the case of materials to which exposure has already occurred, risk may be measured directly by the techniques of epidemiology (this is risk in the sense of the "objective" notion, s. 5.1.1).

Dose is defined as the amount or concentration (e.g. for nanoparticles μg or number per m^3 air) of the noxious matter that will reach a specific biological system (e.g. μg/kg bodyweight). The dose is directly dependent on the exposure, taking account of the fact that part of the xenobiotic is eliminated by the body's natural defenses and does not reach the target organ.

In correlation to risk analysis all these factors are important for characterization and assessment of special risks. Moreover, specific properties of xenobiotics may enhance the occurrence of adverse effects and thereby the likelihood harm.

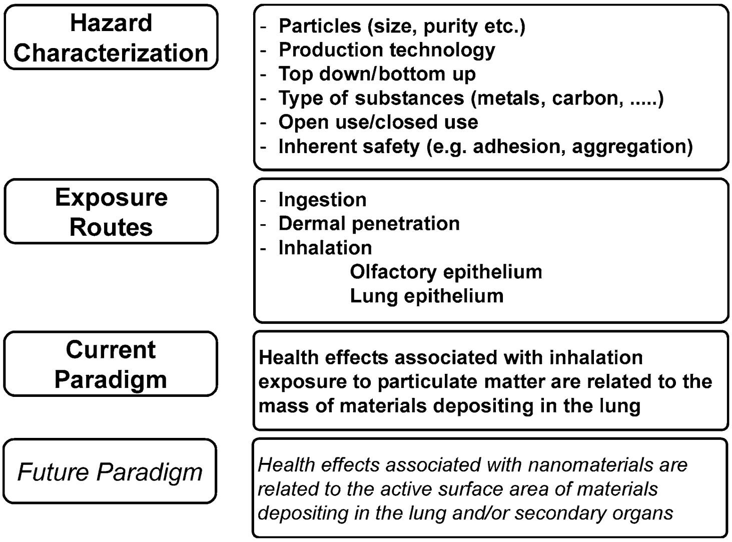
Persistence: Chemicals or materials that do not decay or that either take a long time to decay are most threatening; because of their persistence the chance to burden living organisms will drastically increase.

Bioaccumulation: Dependent on stability and persistence, many chemicals or materials have the capacity to accumulate in specific organisms and in specific organs. Such bioaccumulation is valid mostly for lipophilic xenobiotics that have a strong tendency to be taken from solution or the air into the fatty tissues or other target organs of the body where they remain. This tendency is the basis for the accumulation within the food chain.

Toxicity: Noxious matter that is toxic causes direct damage to organisms that are exposed to them. Toxicity is generally defined as a concentration of a given substance or material in a given matrix that will induce direct effects on living organisms in that compartment: severe (acute) toxic chemicals are defined as having a LD_{50} (the dose at which 50 % of the exposed organisms will die) via oral uptake $\leq 25\,mg/kg\,BW$, via dermal uptake $\leq 50\,mg/kg\,BW$, and via inhalation $\leq 0.25\,mg/l \times 4\,h$.

Ultrafine particles and disease

For inhaled particulate matter it has been shown that both acute and chronic health effects can be induced. Concerns about these effects primarily derive from epidemiological studies that associate short-term increases in particle concentration with increases of respiratory and cardiovascular diseases. The effects of variations in daily air pollutants on the morbidity and mortality of the population is well documented and investigated all over the world, e.g. from Europe (Hoek et al. 2001b; Ibald-Mulli et al. 2002; Kappos et al. 2004; Pekkanen et al. 2002; Penttinen et al. 2001; Wichmann et al. 2000) as well as from the United States (Fryzek et al. 2003; Laden et al. 2000; Samet et al. 2000; Schwartz and Neas 2000) but also from China (Chen et al. 2004; Kan et al. 2004; Kan and Chen 2004; Wong and Lai 2004), Japan (Choi et al. 1997; Omori et al. 2003), India (Chhabra et al. 2001; Joseph et al. 2003; Pande et al. 2002; Srivastava and Kumar 2002) and Australia and New Zealand (Hales et



Hazard Characterization	**- Particles (size, purity etc.)** **- Production technology** **- Top down/bottom up** **- Type of substances (metals, carbon, ...)** **- Open use/closed use** **- Inherent safety (e.g. adhesion, aggregation)**
Exposure Routes	**- Ingestion** **- Dermal penetration** **- Inhalation** **Olfactory epithelium** **Lung epithelium**
Current Paradigm	**Health effects associated with inhalation exposure to particulate matter are related to the mass of materials depositing in the lung**
Future Paradigm	*Health effects associated with nanomaterials are related to the active surface area of materials depositing in the lung and/or secondary organs*

al. 2000; Jalaludin et al. 2004; McGowan et al. 2002; Morgan et al. 1998; Roberts 2004; Scoggins 2004; Scoggins et al. 2004; Sharman et al. 2004; Simpson et al. 2000). The current paradigm for the association of adverse health effects with the amount of particles in the air is the mass of material depositing in the lung. As new nanotechnological materials exhibit totally new properties, and for ambient air particulate matter it is shown as well that the smaller particles are much more toxic when compared to their bigger counterparts, a new paradigm should be appointed for the nanosized materials, considering the active surface area of the particles reaching the lung tissue or remote organs (figure 5.8).

In the concert of potential adverse effects of nanoparticles, they can deliver fundamentally dual possibilities of threatening, firstly they can serve as vehicles for attached toxic chemicals, microorganisms or endotoxins from the air bound to their surface, and secondly, they may induce adverse effects by itself via their chemically active surfaces, soluble constituents or binding properties. Taking into account only the second variant the following scenarios are conceivable for their biological fate.

Nanoparticles may enter living organisms via the digestive tract by ingestion, via the respiratory tract by inhalation, and possibly via the skin through direct exposure. Iatrogenic exposure by injection of nanoparticles in the body for medical purposes is another exposure route. Once in the body, nanoparticles may behave as xenobiotics, they can translocate to specific organs or tissues of the body distant from the portal of entry. Such a translocation is facilitated by the propensity of nanoparticles to enter cells, to cross cell membranes, and to move within cells. These transport routes may include the crossing of tissue barriers as the blood/brain barrier (Alyaudtin et al. 2001; Chen et al. 2003; Gumbleton and Audus 2001; Koziara et al. 2003; Kreuter 2001; Kreuter et al. 2002; Lockman et al. 2003a, 2003b; Omidi et al. 2003; Schroeder et al. 1998; Speiser 1991), which opens new therapeutic possibilities on the one hand, but launch radically novel health concerns on the other. Ultrafine particles were additionally found to enter the brain via the *Nervus olfactorius* after deposition on the olfactory mucosa of the nose following instillation or inhalation (Calderon-Garciduenas et al. 2002; De Lorenzo 1970; Oberdörster et al. 2004; Tjalve and Henriksson 1999).

The olfactory epithelium is situated in the upper nasal region and represents a short-cut from the air to the brain, because only one cell serves as barrier in between. The olfactory sensory neuron links the air space directly with the olfactory bulb laying underneath the brain. It has been demonstrated that animals inhaling great amounts of ambient air particles show a high degree of these particles in this region of the brain indicating such a transport route as a valid exposure pathway (Calderon-Garciduenas et al. 2003). Oberdörster et al. (2004) confirmed this observation with animal studies and ^{13}C-labeled ultrafine carbon particles (Ø 36 nm). They provided some evidence against the circulatory route of CNS translocation of nanoparticles, but as mentioned above and shown by other groups specially coated nanoparticles are able to cross this tissue barrier (Gulyaev et al. 1999).

With regard to possible adverse health effects the most important entry of nanoparticles is certainly the lung. The deposition of inhaled particles in the respiratory tract is governed by diffusional processes. With respect to the efficiency of maximal deposition in different regions of the respiratory tract of humans there exist significant differences within the ultrafine particle size range. About 90% of inhaled ultrafine particles around 1 nm in size deposit in the nasopharyngeal region (Cheng et al. 1996; Swift et al. 1992). Only 10% of this size deposit in the tracheobronchial and essentially none in the alveolar region. In contrast, 5-10 nm particles deposit in all 3 regions with about 20-30% efficiency, whereas 20 nm particles are predicted to be deposited in the alveolar region up to 50% and only about 10 to 20% each in the nasopharyngeal and tracheobronchial regions (ICRP 1994). Thus, each of the three regions of the respiratory tract is targeted differently by a given size of ultrafine particles (figure 5.9).

The neuronal uptake and translocation in the respiratory tract discussed above is found to be especially important for the smallest nanoparticles from ambient air in the range of 10-20 nm generated at very high number concentrations from traffic-related sources and photochemical nucleation events

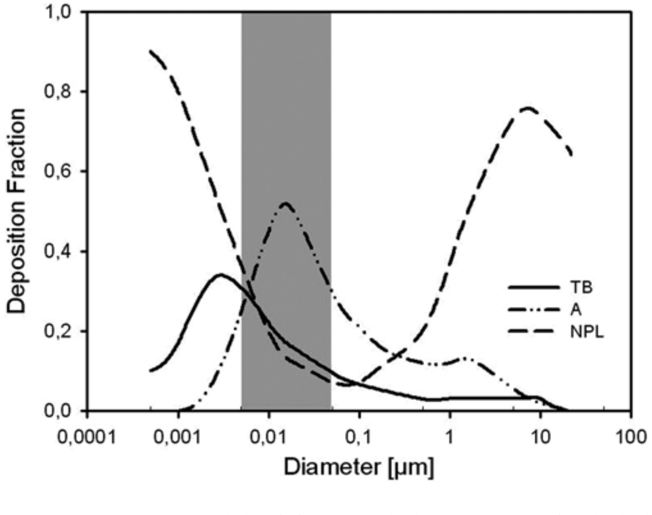


Figure 5.9: ICRP (1994) model of fractional depositions of inhaled particles ranging from 0.6 nm to 20 µm in the nasopharyngeal/laryngeal (NPL), the tracheobronchial (TB) and the alveolar (A) regions of the human respiratory tract during nasal breathing. Note that within the ultrafine particle size range (< 100 nm) there are significant differences in each of the 3 regions with regard to their deposition probabilities and between 5 and 50 nm (shaded area) deposition is highest for the alveolar region (the absolute values in this graph were taken from figure 2 in Oberdörster et al. 2004).

(Kittelson 1998; McMurry et al. 2000; Woo et al. 2001). Otherwise engineered nanomaterials (e.g. quantum dots; Ø 1-10 nm) should translocate via the same route when they become airborne and were inhaled. The smaller the nanoparticles, the more they could be subjected to a neuronal clearance pathway in the nose because nasal deposition increases with decreasing particle size.

To summarize the above discussed exposure routes the majority of fine and ultrafine particles from ambient air will reach the body via the respiratory tract. Depending on particle size the deposition takes place at different parts of the respiratory tract defining the further fate of these particles (figure 5.10): uptake into alveolar macrophages or epithelial cells or the direct translocation into nerve endings and their transport to the CNS.

Some *in vivo* inhalation studies with rats using nanosized particles from polymer fumes (polytetrafluoroethylene, median diameter 26 nm) have demonstrated severe lung damage within hours at "low doses" (60 µg/m?), resulting in the death of the treated rats (Oberdörster et al. 1995). Even so, the nanosized particles used in these experiments should not be considered "engineered" and there is probably no justification to extrapolate these results obtained with rats to humans. Studies with engineered carbon nanotubes carried out with mice or rats showed measurable effects only after instillation of high doses (Lam et al. 2004; Warheit et al. 2004).

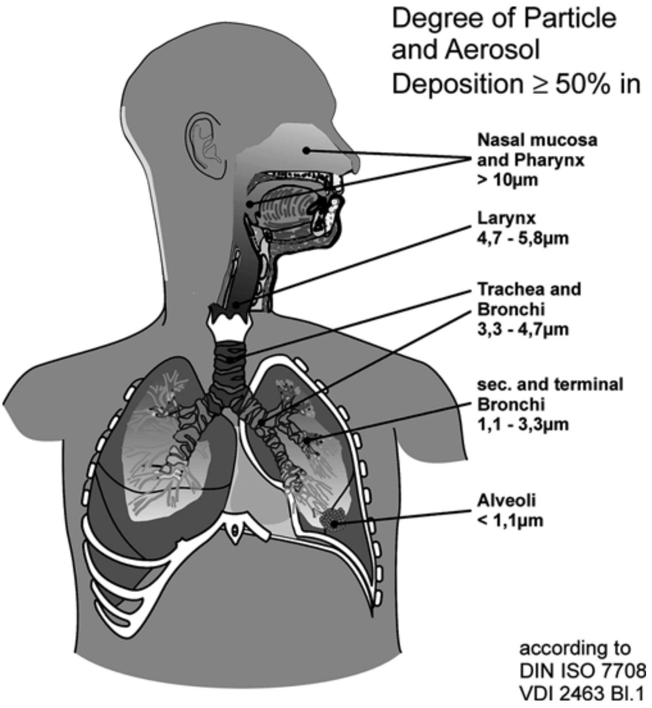


Figure 5.10: Deposition rate of particles in various regions of the lung.

From all these studies and discussions the main target organs of nanoparticle exposure can be described as follows:

organs of intake:	skin, gastro-intestinal tract, respiratory tract;
secondary organs:	central nervous system, liver, cardiovascular system, immune system.

As mentioned above the mass of particulate matter is probably not the relevant reference value for estimation of their toxicity. Some studies have additionally calculated the surface area of the applied nanoparticle dose and discovered that the inflammatory effect of various particles of different sizes is strongly dependent on the surface instead of the mass (Borm et al. 2004; Hohr et al. 2002; Oberdörster et al. 2000; Oberdörster 2001).

This has been demonstrated in a study with mice and rats where titanium dioxide in two different sizes was investigated. In both species it was observed that the smaller particles (20 nm), given at the same mass dose as the bigger particles (250 nm), have a much higher potency to induce inflam-

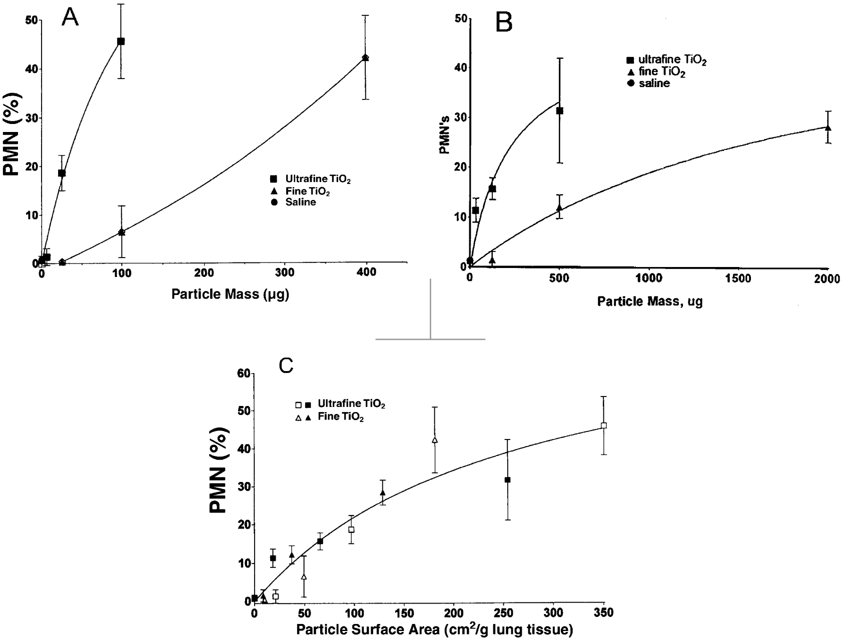


Figure 5.11: a – c: Dose-response relationship for instilled nanoparticles (20nm TiO_2) and fine particles (250 nm TiO_2) 24h after intratracheal instillation in mice and rats. Top: correlation between instilled particle mass and lavaged polymorphonuclear cells (PMNs) for mice (a) and rats (b); bottom (c): correlation between instilled particle surface area and lavaged PMNs for both animal models (open symbols: mice; closed symbols: rats) (Reproduced by permission of Springer Verlag from Oberdörster 2001).

matory processes. When particle surface area is plotted against the inflammatory potency all particles can be described with the same function as the biological effect is directly proportional to the particle surface area (figure 5.11a–c).

Apart from some minor exceptions the knowledge about the biological effects of synthetic nanoparticles is marginal. There already exist some important relevant studies on the toxicity of fullerenes (Baierl et al. 1996; Oberdörster 2004; Sayes et al. 2004), carbon nanotubes (Lam et al. 2004; Monteiro-Riviere et al. 2005; Shvedova et al. 2003; Warheit et al. 2004), and metal oxides (Dick et al. 2003; Renwick et al. 2004; Tran et al. 2000), but these studies often have been carried out with very high amounts or concentrations of nanoparticles and were done in totally different biological systems. Thus, these experiments are not significant for all species and of course can not be extrapolated to humans. It is strongly recommended that during the next decade many studies in more or less standardized systems are carried out to corroborate the hypotheses already published and mentioned above. These studies can be done under the following aspects:

Exposure studies

- Occupational hygiene studies at the site of production and use to determine the sizes and concentrations of nanoparticles and carbon nanotubes (CNT) likely to be present at the workplace;
- Especially for CNT it must be clarified, if these structures were taken up and cleared by lung macrophages and/or whether they behave like fibres.

In vitro studies

- Are nanoparticles stable even in a surfactant-like surrounding and in cells and do they persist in lung tissue?
- Do nanoparticles provoke inflammation and the production of free radicals and are cells killed by these mechanisms?
- Can metal ions or other material be solved or extracted from the surface of the nanoparticles into biological fluids?
- Are all these effects dependent on size, form, surface area or surface charge or other properties of the nanoparticles?

In vivo studies (mammals, aquatic organisms)

- Estimation of the biological half-life of nanoparticles in lung tissue or other organs;
- Possible systemic translocation of nanoparticles after inhalation or instillation or from the surrounding water;
- Which parameter of the nanoparticles determines the inflammatory potency in the lung?
- Are there effects on cell proliferation and the DNA, in other words are specific nanoparticles genotoxic or do they induce fibrosis after long-term exposure?

Models for Hazard Characterization

In vitro studies in cell cultures

Most of the questions asked may be answered *in vitro*. Ultrafine particles from ambient air (particulate matter $< 10\,\mu m = PM_{10}$) came into focus because new epidemiological evidence has demonstrated a short-term relationship between increases in PM_{10} and deaths from cardiovascular/cardio-respiratory causes (Hoek et al. 2001a) or hospital admissions for cardiovascular causes (Zanobetti et al. 2000). Because of the cardiovascular effects it has been discussed that such diseases may be the result of a possible transfer of ultrafine particles into the bloodstream and a transfer from the lung to the heart, but toxicological data in this regard is limited and conflicting (Kreyling et al. 2002; Nemmar et al. 2001, 2002; Oberdörster et al. 2002b; Oberdörster and Utell 2002). Nevertheless, these hints suggest a similar if not stronger effect of nanoparticles with specialized surfaces and smaller size. Before such particles can reach an epithelial cell surface in the alveoli of the lung they interact with a special coating named “surfactant”. This surfactant film at the air-liquid interface in the airways and the alveoli is the first fluid structure hit by inhaled particles during their deposition on the inner pulmonary surface. Due to tension forces exerted on the particles by this surfactant film, they were displaced underneath into the liquid phase (Gehr et al. 2000). At this stage the particles come into close association with the surface of epithelial cells or cells of the defense system. Their possible fate then is to be taken up by macrophages and carried away or to be cleared off by mucocilliar activity, others enter the epithelium where they may come into contact with dendritic cells or other cells of the immune system. During this displacement process the surface of the particles may be modified by surfactant components. The coating of particles by surfactant lipids and/or proteins may play a crucial role in the clearance of particles, as well as for their toxic potency. Besides the particle-cell interactions and the possible influence that surfactant may have on this process the main open question is how the different cells communicate with each other when they interact with particles (Geiser et al. 2003; Kiama et al. 2001).

The assessment of cytotoxicity of air contaminants such as gaseous or particulate compounds and complex mixtures has traditionally involved animal experiments, due to the difficulties in exposing cell cultures directly to these substances. During the last three decades culture techniques were developed to overcome most of these difficulties. As the lung is the most important organ in connection to exposure to particles *in vitro* studies often were carried out with cells derived from the respiratory tract. One of the best investigated cellular models is the alveolar macrophage that is exposed *in vivo* and *in vitro* to gases and particles in a multitude of studies (Baierl et al. 1996; Beck-Speier et al. 2001; Beck-Speier et al. 2003; Brown et al. 2004; Donaldson et al. 2002; Höckele et al. 1998; Möller et al. 2002; Müller et al. 1989; Pätzold et al. 1993; Polzer et al. 1994; Renwick et al. 2004; Stone et al. 2000; Wilczek et al. 1989; Wilczek et al. 1990).

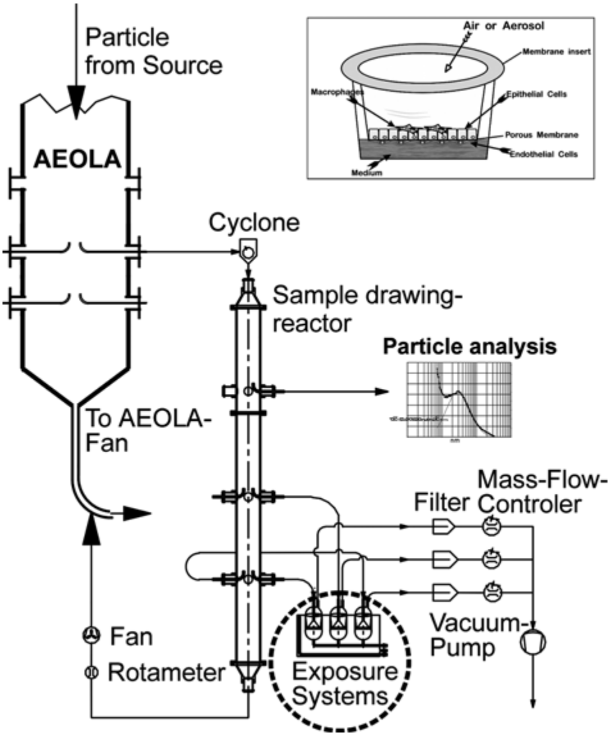


Figure 5.12: Technical extension of the 3D-Cell Model (insert, s. chapter 4) for exposure to work-place relevant aerosols. Aerosols were prepared in an aerosol generating tube (AEOLA, 8m high), distributed through various outlet valves, homogenized in a cyclone and injected into a sample drawing reactor from which the aerosol passes through pipes to the exposure chambers (dashed circle) as well as to the analytical equipment (adapted from: Mülhopt et al. 2004; courtesy H.R. Paur, Institute of Technical Chemistry, Forschungszentrum Karlsruhe).

Exactly for the analysis of aerosols at workplaces or in laboratories new culture system are developed to expose cell cultures at the air/liquid interface (compare figure 5.7). At the Forschungszentrum in Karlsruhe this system is extended via the connection to an aerosolgenerator that is fully controlled with regard to mass flow, particle number and humidity (figure 5.12). In a situation directly comparable to the lung the effects of nanoparticles on cells can be analyzed (Mülhopt et al. 2004). For particles of greater aerodynamic diameter it is well-known that they can accumulate in the lung inducing chronically effects on the level of fibroblast proliferation finally resulting in a fibrosis or comparable diseases (Borm et al. 1990; Jorna et al. 1994; Oberdörster 1995a; 1995b). In most cases such altered proliferation pattern is the result of inflammatory processes dependent on overloaded lung cells that start to produce inflammatory mediators or on oxidative stress medi-

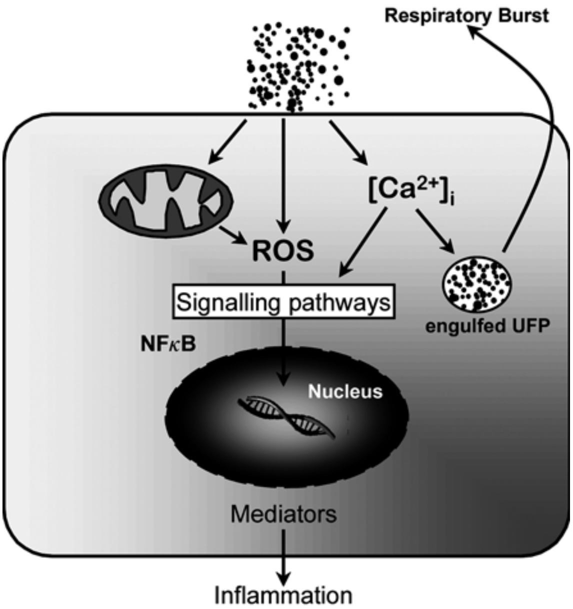


Figure 5.13: Sequence of reactions leading to inflammation by particle uptake. After contact and uptake of the particles by the cell the production of reactive oxygen species (ROS) starts and often an increase of the intracellular calcium concentration [Ca2+]i can be measured. This and further involvement of lysosomal and mitochondrial elements enhances various signaling pathways including transcription factors (e.g. NF?B) leading to the activation of gene programs and the production of peptide mediators that induce inflammation (adapted from: Donaldson and Stone 2003; MacNee and Donaldson 2003).

ated by particles phagocytized by different lung cells (Brown et al. 2000; Brown et al. 2001; Brown et al. 2004; Dick et al. 2003; MacNee and Donaldson 2003). These biological endpoints can be investigated in the new exposure system and will provide more insight into the adverse effects of nanoparticles on the molecular level (figure 5.13). A summary of the toxicity of ultrafine particles and the various endpoints of interest has recently been published (Kreyling et al. 2004).

One very important mechanism shown to be influenced by various types of particles is the alteration of the intracellular calcium concentration $[Ca^{2+}]_i$. Increases in $[Ca^{2+}]_i$ may underlie the cellular effects of ultrafines via direct effects of nanoparticles or carbon nanotubes on membrane channels for Ca^{2+} or other ions (Park et al. 2003) probably involving oxidative stress by a mechanism not yet understood (Brown et al. 2004; Donaldson and Stone 2003; Stone et al. 2000). Increased Ca^{2+} in cells can lead to the transcription of key pro-inflammatory genes such as IL-8 and IL-2 (Dolmetsch et al. 1998) and this might happen when cells are exposed to nanoparticles.

Changes in $[Ca^{2+}]_i$ could also have priming effects, e.g. on macrophages, that are important in susceptibility.

In vitro studies in organ cultures
As mentioned earlier in this book (s. 3.3), Borm and his coworkers established a new model of the isolated perfused rat lung (Meiring et al. 2004). Initial experiments within this model showed little to no translocation of several types of particles, including latex fluorescent beads (50, 250 nm), ultrafine TiO_2 (20 nm) and radioactive iridium particles (18 nm). Another group has established a comparable model with rabbit lungs (Hamoir et al. 2003; Nemmar et al. 2005). They found that polystyrene particles between 24 nm and 190 nm induce an increase in the microvascular permeability depending on number and surface composition of intratracheally instilled particles. They stated that the number should be considered as an important parameter and could be an alternative to total particle surface area measurement in air quality monitoring. Moreover, particle surface charges must be taken into account to compare the adverse health potency of various particles since amine-modified particles induce more marked changes than carboxylate-modified particles, independently of all other parameters (Hamoir et al. 2003). The newest study was engaged in analyzing the translocation of the polystyrene particles from the alveolar side as well as from the vascular side (Nemmar et al. 2005). However, without further chemical treatment to enhance the microvascular permeability no translocation could be detected.

In vivo studies in animal models
On the one hand the investigation of whole animals is the most realistic exposure system but on the other hand it is not practicable to address all problems (compare 3.3). After incubation with ultrafine materials it is often not possible to find the nanoparticles within the organism, the various tissues or target organs or to measure specific alterations induced by the nanoparticles. How difficult these studies may be is demonstrated by two groups which investigate the toxic effects of carbon nanotubes in mice or rats. After instillation of the CNTs into the lungs of the animals, up to 15% of the animals died from mechanical blockage of the upper airways by the instillate (Warheit et al. 2004). Nevertheless, both studies concerning the lung toxicity of carbon nanotubes found an essential formation of so-called granulomas consisting of macrophages laden with black particles, and had very few lymphocytes, neutrophils, eosinophils, or other inflammatory cells (Lam et al. 2004; Warheit et al. 2004).

Some years ago two studies were released at the University of Warsaw investigating the dermatological and inhalation effects of carbon nanotubes. In the study on dermatological effects of fullerenes and carbon nanotubes, rabbits were treated and the researchers "did not *find* any signs of health hazards related to skin irritation and allergic risks". This study recommended no special precautions with respect to both, fullerenes and carbon nanotubes, in the working environment; in fact, the articles were titled "Carbon Nanotubes: Null Risk of Skin Irritation and Allergy" and "Fullerenes: Null Risk of Skin Irritation and Allergy" (Huczko et al. 1999; Huczko and Lange 2001). The second study concentrated on the question, if carbon nanotubes may behave asbestos-like (Huczko et al. 2001). The experiments with guinea pigs revealed that carbon nanotubes do not exhibit effects similar to asbestos and it is suggested that working with soot containing carbon nanotubes is unlikely to be associated with any health risks. Nevertheless, it must be answered if carbon nanotubes are toxic or not and some more studies have to be undertaken to clarify this question additionally in long-term assessment experiments.

Other studies with rats focusing the translocation of nanoparticles from the lung into the blood stream demonstrated only a very small portion of the particles to be translocated and some of these data are already under suspicion (Kreyling et al. 2002; Oberdörster et al. 2002b).

When ultrafine particles were intravenously injected they have been shown to accumulate in the liver as the major organ of their uptake from the blood circulation. The more realistic exposure via inhalation of nanoparticles and the measurement of their translocation to extrapulmonary organs via the blood compartment is, however, hampered by several methodological difficulties. Using labeled particles, the label may be released, the particles may partially be solved in the mucus, the blood or other fluids or the label alters the "normal" behavior of the particles, resulting in a totally different distribution within the body. Moreover, analytical limitations have to be taken into account, because very small amounts of the nanomaterials have to be measured in the different target organs. In experiments with ^{13}C-carbon particles or ultrafine insoluble iridium only a very small amount of these particles was translocated systemically and could be found in the liver

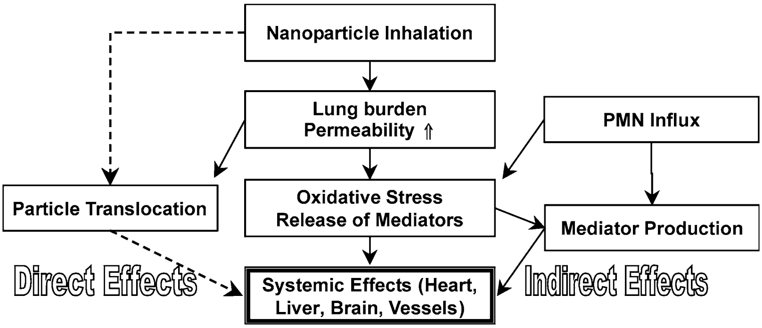


Figure 5.14: Possible relations between nanoparticle lung burden, alteration of lung permeability and pro-inflammatory mediator release leading to systemic effects (adapted from: Borm and Kreyling 2003). PMN: polymorphonuclear cells (leukocytes/neutrophils) mediating inflammation.

(Kreyling et al. 2002; Oberdörster et al. 2002b). Another explanation for possible systemic effects concerning health hazards is the pulmonary inflammation and the activity of mediators translocated into the blood stream. Ultrafine carbon particles as well as nanoscale titanium dioxide are demonstrated to cause an increase of leukocytes within the bronchoalveolar lavage fluid as well as in the blood and some other pro-inflammatory markers are enhanced as well (Gilmour et al. 2004; Oberdörster 2001). In this connection it is discussed that nanoparticles induce specifically oxidative stress within lung cells provoking pro-inflammatory effects that might lead to systemically problems (Donaldson and Stone 2003).

The mechanistic hypothesis behind these studies (figure 5.14) is that inhaled nanoparticles may activate resident inflammatory cells leading to oxidative stress and production of cytokines, and that this primary response is further amplified through inflammatory cell recruitment and elaboration of both inflammatory and epithelial cell-derived cytokines. Such an amplification of the pulmonary response can possibly lead to a parallel induction of the systemic acute phase response with associated changes in blood coagulability and cardiac events.

Besides an enhancement of inflammatory reactivity, nanoparticles may impair the phagocytic capacity of alveolar macrophages, especially after infections that induce an increased production of interferon gamma (IFN-γ). Consequently, there might be a risk for additional infections after an episode of high nanoparticle inhalation (Lundborg et al. 2001).

The overall objective of the animal studies is to identify factors which are causally associated with adverse pulmonary and cardiovascular health effects after exposures to ultrafine particles from the environment or at work

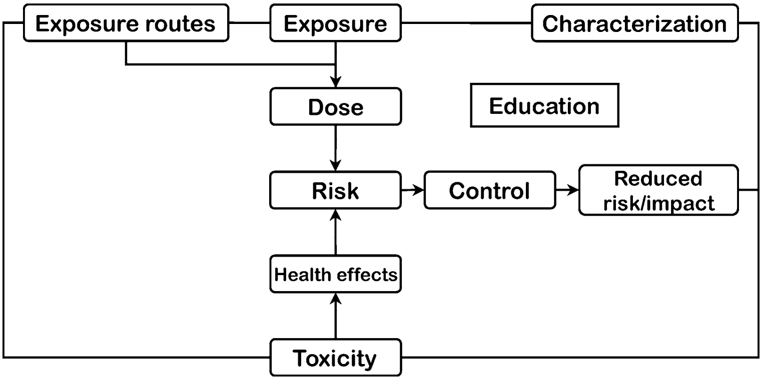


Figure 5.15: Flow diagram showing the input in risk identification and the output for risk characterization and education. The risk can be estimated on the basis of knowledge of exposure, dose, and toxicity of nanoparticles leading to necessary control measures to reduce the risk at the working places by education of the producers.

places. The main focus will be concentrated on risk estimation (figure 5.15) on the basis of particle characteristics (inhalation and accumulation; content of transition metals or other contaminants), dosimetric aspects (lung deposition and disposition), host susceptibility (young and elderly people, predisposition for disease as cardiovascular disorders or respiratory tract sensitization), cellular mechanisms (role of Clara cells, macrophages or dendritic cells), and co-exposure to other air pollutants (such as ozone, NO_x or other fibers and particles).

In the overall debate on toxicity of nanoparticles one should be cautious in discussing published data not relevant for the problems that have to be solved. To give an example: in a Danish Report on the environmental and risk aspects of Nanotechnology (written on behalf of the Danish Ministry of Science, Technology and Innovation, June 2004, http://teknologiskfremsyn.dk) V. Colvin was cited with the statement: *"Examples of health impacts could be that ingested nanoparticles may cause liver damage as ingested nanoparticles (i.e. oral drug delivery) have been found to accumulate in the liver. Excessive immune/inflammatory responses cause permanent liver damage."* Most of the studies found in the literature (only a small number is cited here) dealing on the liver accumulation of nanoparticles have administered the particles (s. 3.3):

subcutaneously	(Reddy et al. 2004)
intravenously	(Borchardt et al. 1994; Chen et al. 2003; Chiannilkulchai et al. 1990; Fernandez-Urrusuno et al. 1996; Gipps et al. 1986; Kreuter 1994; Lenaerts et al. 1984; Lode et al. 2001; Peracchia et al. 1999; Simon et al. 1995; Violante 1990)
intra-arterially	(Khandoga et al. 2004)
intraperitoneally	(Simeonova et al. 1994)

One study examined the amount of radioactively labeled nanoparticles that reached the liver after instillation into the lung, but within these experiments only a diminutive number of label could be found in the liver (Kreyling et al. 2002). Another study which tested nanoparticles as a drug delivery system and administered these particles orally could only find the drug systemically represented but not the particles (Pandey et al. 2003). Florence and Hussain (2001) reviewed the transcytosis within the gastrointestinal tract for dendrimer delivery systems and found no publications which demonstrate a noteworthy accumulation of such particles within the liver. Thus, an accumulation of nanoparticles within remote organs like the liver has still to be proven and there is no indication until now that nanoparticles of which material ever may induce liver damage as stated above.

As a result of the toxicological issues described above, addressing the potential risks of nanotechnologies to human health and the environment

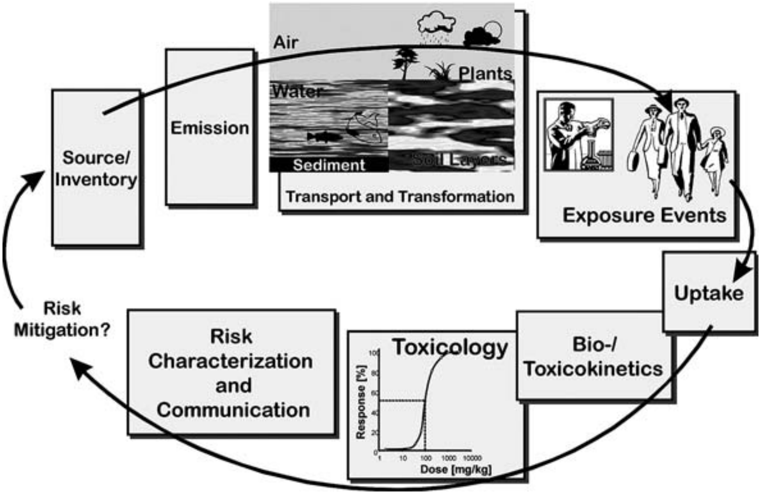


Figure 5.16: Schematic presentation of life-cycle assessment of nanomaterials. From source to dose, an evaluation loop to the reduction of emission of nanomaterials.

the generating of new, Nanotechnology-specific data on toxicology and ecotoxicology is required (including dose response and exposure data). This also calls for examining and, possibly, adjusting risk assessment methods. The European Commission (2004a) recommended that "in practice, addressing the potential risks associated with nanotechnologies necessitates that risk assessment be integrated into every step of the life cycle of nanotechnology based products" (figure 5.16).

In support of a high level of public health, safety, environmental and consumer protection, the following needs are highlighted (European Commission 2004b):

- to identify and address safety concerns (real or perceived) at the earliest possible stage;
- to reinforce support for the integration of health, environmental, risk and other related aspects into R&D activities together with specific studies;
- to support the generation of data on toxicology and ecotoxicology (including dose response data) and evaluate potential human and environmental exposure

and it is further recommended that:

- the adjustment of risk assessment procedures has to take into account the particular issues associated with Nanotechnology applications and
- the integration of assessment of risk to human health, the environment, consumers and workers at all stages of the life cycle of the technology (including conception, R&D, manufacturing, distribution, use, and disposal).

With direct regard to human health the following key questions have to be addressed by toxicological and occupational health studies:

- by which mechanism do nanoparticles induce lung diseases (if they do)?
- which components or properties of the nanoparticles/-materials are responsible for the adverse health effects?
- which type of particle or material is most effective?
- which part of the population (children, elderly) is most sensitive against nanoparticle exposure?

With regard to the most important hypothesis, the induction of oxidative stress by nanoparticles, the following important points have to be clarified:

- do pro-oxidative surfaces on nanoparticles exist?
- by which mechanism have reactive oxygen species been produced?
- is subsequently a pro-inflammatory answer provoked?
- do nanoparticles have a potency to induce chronic inflammation?

As the first step in risk assessment and risk management is the identification of the main hazards the following possibilities have to be ruled out or confirmed for nanoparticles:

- can they translocate systemically from the lung or the gut to other organs including liver, kidney, placenta, heart and brain?
- do they cause blood coagulation and thrombosis?
- do they destabilize plaques and which ones causes lipid peroxidation?
- which ones can cause rapid lung inflammation?
- do they affect mitochondrial (and nuclear?) function?
- can they directly interfere with Ca-transport and signaling?
- do they – and if they do, which ones – can cause persistent inflammation – and lung cancer upon chronic exposure?
- are manufactured nanoparticles as ultrafine ambient air particles associated with increased morbidity and mortality in susceptible parts of the population?

Despite the fact that all these questions are unanswered in connection to newly manufactured nanomaterials it must be acknowledged that such problems will arise with all new developed materials and science and research are responsible for sustainability.

Transport, Depots and Accumulation in Organisms

As mentioned above and described in detail in chapter 4 nanoparticles can possibly enter the body via the digestive tract by ingestion and to some extent it can be expected that some may cross the lung/blood barrier in the respiratory tract after inhalation. So far, there is no evidence for their penetration through the skin. At the actual state the most relevant exposure route will be injection of nanoparticles in the body for medical purposes. Once in the body, nanoparticles can translocate to organs or tissues of the body distant from the portal of entry. Such translocation is facilitated by the propensity of nanoparticles to enter cells, to cross cell membranes, and to move along the axons and dendrites that connect neurons. Notably, under certain conditions, some nanoparticles can cross the blood/brain barrier (cf., e.g., Kreuter et al. 2002) – which opens therapeutic possibilities as well as radically novel health concerns – and were found to enter the brain via the *Nervus olfactorius* after deposition on the olfactory mucosa of the nose following instillation or inhalation, but these phenomena are explained in detail above. There exist only a limited number of studies that have investigated the persistence and accumulation within organisms. Mainly durable nanoparticles may be biopersistent and can accumulate in the body and this has been shown in particular in the lungs (Elo et al. 1972; Renwick et al. 2004), the brain (Bodian and Howe 1941; De Lorenzo 1970; Oberdörster et al. 2004), and the liver (Khandoga et al. 2004; Oberdörster et al. 2002a). Moreover, some data are available for an uptake of specific polystyrene nanoparticles within the gastrointestinal tract. This process is strongly dependent on the size of the spheres and after having reached the blood they accumulate in the liver and in the spleen (Florence et al. 1995; Jani et al. 1990).

During development of new drugs and more specialized therapies several new strategies have been tested to target nanoparticles to specific organs leading to an intended accumulation to reach a high dose of the delivered drug (Akerman et al. 2002; Gao et al. 2004). Moreover, for drug delivery or comparable biological or medical applications nanomaterials are produced that are biodegradable (Alonso and Sanchez 2003; Fattal et al. 1998; McAllister et al. 2003; Panyam and Labhasetwar 2003; Qaddoumi et al. 2004; Sang and Gwan 2004). There exist no relevant data so far on accumulation or biodegradation of nanomaterials that unintentionally have reached the lung, the gut or other organs or biological systems during production processes at working places or elsewhere.

We can discriminate at this position between two major problems: the first is the gap of knowledge when biological effects of technical important materials on the nanometer scale should be evaluated and the second is the general discussion on consequences of this new technology without a scientific background or fundamental information. This leads to the requirement on the one hand to intensify the efforts in research on the toxicology of nanoparticles and on the other hand to a more sensitive discussion with the public and NGOs on possible hazard or risks of this new technology. Despite the fact that nanobots and grey goo are more fiction than science the fears must be taken as real.

Military Use

With regard to human health and possible risks it must be taken into account that Nanotechnology can improve not only multiple peaceful uses but also military and future arms systems. It is predicted that Nanotechnology will bring revolutionary changes in these areas as well, with the potential for both great benefits and great risks (Altmann and Gubrud 2002; Altmann 2004). Military research and the use of nanotechnological products is expanding and potential future applications will span all areas of warfare. Most of the developments with military background will include augmentation of human performance and information processes. In 2002 the MIT and the US Army established a new section within the MIT, the so-called Institute for Soldier Nanotechnologies (http://web.mit.edu/isn/) to enhance soldier survivability. This obviously makes clear that Nanotechnology has its applications within the military field. Nevertheless, new progress in a new technology will not only improve survival and healing, it always implies its use to enhance the efficacy of weapons, surveillance systems and other military equipment. In several countries the Departments or Ministries of Defense have arranged nanotechnological programs and it might happen that, if they continue to follow current trends, it could give rise to an arms race similar to that of nuclear weapons.

Besides soldier protection, the investigation of various weapons is of course an important military aspect that will not be presented on the internet homepages of these institutions. It may be that Nanotechnology helps to improve weapons of mass destruction. On the one hand the storage, transport and dissemination of chemical or biological weapons will be improved and the exposure of humans, animals and plants will be much more effective. On the other hand existent weapons of mass destruction like nuclear weapons can be improved considerably. As Nanotechnology will provide materials and products that are stronger, lighter, smaller or more sensitive, there exist many options for miniaturization. The result may be projectiles with greater velocity and smaller precision-guidance systems. Moreover, Nanotechnology will influence the processing in energy generation and storage, displays and sensors, logistics and information systems, all being important elements of warfare.

It must be possibly discussed that all areas of international agreements must be reconsidered. To these belong the arms control agreements (e.g. Biological Weapons Convention; limits on conventional forces by new types of weapon outside of treaty definitions) or the international law of warfare (e.g. through introduction of autonomous fighting systems not reliably discriminating between combatants and non-combatants). Furthermore, the stability (arms races from technological innovation, pressure for preventive attack and fast action, proliferation of cheap microsystems), as well as humans, the environment, or society (microrobots for eavesdropping, crime, and terrorism; implanted systems altering human nature) may be affected. In the end dealing with peacetime civilian life, military research and deployment of systems could create “facts” before an open debate about the desirability of such developments has been launched.

5.3 Risk Management

Present scientific knowledge about substances and devices produced with nanotechnologies precludes going further than identifying hazards – the first step of risk management – and providing some elements of hazard characterization like dose-response assessment – the second step of risk management (s. 5.2 for the case of nanoparticles). Indeed, there is little or no data on dose responses and exposure to engineered nanomaterials – the third step of risk management. Figure 5.17 provides a visual rendition of the four interconnected components – hazard, dose-response and exposure assessment as well as risk characterization – building the fundament and having implications on the different stages of risk management. In this chapter, we will take this situation as point of departure for an analysis of the consequences for regulation issues. Starting with a brief overview about recent studies on regulation of nano-materials (5.3.1) we will investigate the applicability of the precautionary principle (5.3.2) and draw conclusions for regulatory measures which should be taken (5.3.3).

5.3.1 The Debate on Regulation Issues in Nanosciences

"The new element with this kind of loss scenario is that, up to now, losses involving dangerous products were on a relatively manageable scale whereas, taken to extremes, Nanotechnology products can even cause ecological dam-

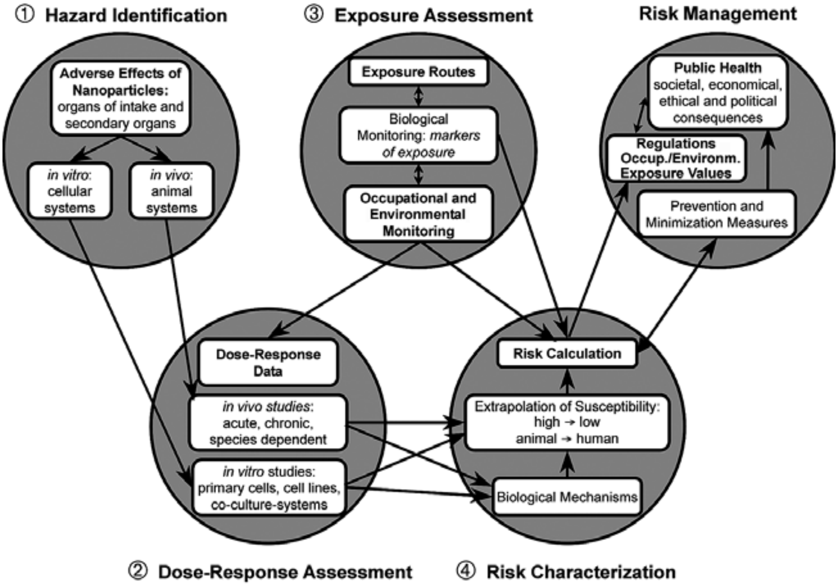


Figure 5.17: The four steps of risk assessment leading to risk management (adapted from Oberdörster 1994).

age which is permanent and difficult to contain. What is, therefore, required for the transportation of Nanotechnology products and processes is an organisational and technical loss prevention programme on a scale appropriate to the hazardous nature of the products" (Münchener Rück 2002:13). Such "alarmistic" postulate has been expressed in the course of the "Bill-Joy-debate" and is a remarkable document demonstrating the impact of such speculative discussions.

In the following, however, we aim at a more "back-to Earth" approach by focussing on the regulation of the production and use of nanoparticles, building upon the comprehensive review of the current state of knowledge given in section 5.2. In the following, some already published thoughts will be reviewed, aiming at – at this stage of our analysis – giving an overview about recent and ongoing activities in this field.

The position on Nanotechnology regulation which has been most widely perceived and discussed is probably the postulate of the ETC-group (2003) for a moratorium:

> *Regulatory bodies in OECD countries have thus far established no policies or protocols for considering the safety of step 1 Atomtechnology which includes nanoparticles in products already on the market and new forms of nano-scale carbons. At this stage, we know practically nothing about the possible cumulative impact of human-made nano-scale particles on human health and the environment. Given the concerns raised over nano-particle contamination in living organisms, ETC group proposes that governments declare an immediate moratorium on commercial production of new nanomaterials and launch a transparent global process for evaluating the socio-economic, health and environmental implications of the technology (ETC 2003:72).*

We will come to a rather different conclusion, in spite of a comparable point of departure consisting in the diagnosis of a massive lack of knowledge (s. 5.2) and the application of the precautionary principle (s. 5.3.2 and 5.3.3). However, one should acknowledge that the ETC work gave a significant push to many discussions on Nanotechnology regulatory issues in many countries. NGOs and other groups of civil society often act as a monitoring and early warning system concerning new technologies. They often "give a voice" to a widely distributed but not focussed uneasiness in the broader population (Weingart 2004). Therefore, there is no reason to ignore such statements of proposals assuming that only a small degree of population is engaged in such organisations. They also act as multipliers as well as detectors (and amplifiers) of concerns. Facing this background, it would, in most cases, be prudent for scientists, science managers and science policy to agree in starting an open debate with those organisations (like the ETC-group).

An also rather strict result has been given by Phoenix and Treder (2003) of the Center for Responsible Nanotechnology CRN. Their application of the precautionary principle led them to the recommendation:

> *CRN has identified several sources of risk from MNT (molecular nanotechnology), including arms races, gray goo, societal upheaval, independent development, and programs of nanotech prohibition that would require violation of human rights. It appears that the safest option is the creation of one – and only one – molecular nanotechnology program, and the widespread but restricted use of the resulting manufacturing capability (Phoenix and Treder 2003:4).*

This proposal would imply a secret and strictly controlled nanotech development which seems to be unrealistic (who should control and fund such unique program?), unsafe (because knowledge proliferation will not be avoidable) as well as undemocratic (because it would leave the development to closed experts circles).

The debate on regulatory issues of Nanotechnology responding to possible risks started in the United States (as also did the public risk debate, compare 5.4.1). Today, there is an intensive debate between representatives of the Nanotechnology business companies and concerned regulatory bodies like the US Food and Drug Administration. The debates take a product-based approach and decide pragmatically in each case which is related to the high importance of product liability in the States. The Toxic Substances Control Act (TSCA) as the US Regulatory Act for Chemical Substances (passed in 1976) aims at regulating production and use of chemicals with risk or risk potential to the environment (Wardak 2003). Main element is the TSCA Chemical Substance Inventory which is a database of about 80.000 chemical substances from which about 50.000 have been reviewed and about 5.000 have been subject to rigorous testing (Wardak 2003). Ideas of the precautionary principle are not implemented in the TSCA. Regulatory action can only be undertaken if any scientific uncertainty about possible hazards has been resolved. The "burden of proof" applied requires that there is clear scientific evidence for the existence of adverse effects. With regard to Nanotechnology there are three types of possible relevant exemptions: the Low Volume Exemption, the Low Release and Exposure Exemption, and the Test Marketing Exemption. The Low Volume Exemption frees a manufacturer from full reporting in accordance with the TSCA regulations if less than 10 tons of a particular substance are produced per year (in the envisaged and not yet passed new European system for the regulation of chemicals REACH this threshold will be lowered to 1 ton/year). Probably many nanomaterials will be below this exemption condition. Also the Test Marketing Exemption might apply to many nano developments because in many cases small amounts will be produced in order to exploit its market potential (s. Wardak 2003).

In the future European REACH system a different perspective is taken. It aims at testing all known chemical substances and including the data in a central database while new chemicals will be reviewed only optionally (Haum et al. 2004). This *prima facie* strange approach is motivated by the diagnosis that new substances are only a small portion compared to the complete set of existing chemicals – its features, side-effects and risks are often only partially known. In case of nanoparticles this situation is ambivalent: on the one side there is a chance to carefully check the impacts of nanoparticles based on well-known chemicals (differing only with respect to particle size and/or morphology), but on the other side there might be a gap if such nanoparticles might be declared as new chemicals – with only optional review within REACH. This unclear situation should be clarified in the process of passing and implementation.

In the United Kingdom in intensive debate on Nanotechnology issues also took place rather early. The widely perceived study of the Royal Society and the Royal Academy of Engineering (2004) resulted in a lot of statements and recommendations in the field of regulation aiming at closing the knowledge gaps and at minimising the risks possibly resulting from production and use of nanoparticles before this has happened. In the meantime the UK Government responded to these recommendations (UK Gov 2005) and promised to promote more research on Nanotechnology risks, to conduct reviews of existing regulations with respect to their applicability to Nanotechnology, and to enforce public debate. These promises, however, did satisfy neither members of the responsible Academy's commission nor the public (Peplow, news@nature.com:25.2.2005).

There exist first recommendations of experts in handling of nanomaterials for the EC (Community Health and Consumer Protection, Haum et al. 2004). Special emphasis is given to developing a nomenclature for nanoparticles, assigning a new Chemical Abstract Service (CAS) registry number to engineered nanoparticles and to grouping and classification of nanomaterials with respect to categories of risk, toxicity, and proliferation. Furthermore, a lot of requirements apply to advancing science and developing instruments for risk assessment methods, screening and testing. Also institutions to monitor nanotechnologies and the knowledge about them are seen as an important step. A dialogue with both the public and the industry shall be initiated (s. 5.4.3). Free engineered nanoparticles should be contained and production and unintentional release of waste of nanosized particles shall be avoided whenever possible and otherwise minimized.

5.3.2 The Precautionary Principle

Dealing with classical risk regulation is adequate if the level of protection is defined, and the risk (e.g. the probability of the occurrence of the adverse effects multiplied by their impact) can be quantified. In such situations thresholds can be set, informed by ethical analysis because of their normative nature (Gethmann and Mittelstraß 1992; Janich 1996), risks can be either minimised or kept below a certain level, and also precautionary measures can be taken to keep particular effects well below particular thresholds by employing the ALARA (as low as reasonably achievable) principle. The situation becomes completely different when we can no further rely on scientific information and thus possible adverse effects have to be estimated (s. table 5.3). This is notably the case when an epistemic debate is going on in science: different disciplines use competing models or analogies or basic assumptions to disclose the subject matter under investigation in order to acquire new knowledge (compare 5.2). As soon as the conditions required for the risk management approach are no longer fulfilled, controversies and ambivalent situations under uncertainty are the consequence. This is the case

– if scientific knowledge concerning possible adverse effects is not available at all or is itself controversial and hypothetical, or if empirical evidence is still missing (for example, if the knowledge is based on models which could not yet be validated to a sufficient extent);
– if adverse affects could have catastrophic dimensions with respect to their amount or to their specific impacts and consequences (possible situations of this type have been the point of departure for the "future ethics" of Hans Jonas 1979).

The observation that in many cases severe adverse effects in the course of implementing new materials or technologies had not been detected in an early stage but rather led to immense damage on human health, on the environment, and also on economy (cp. impressive case studies in Harremoes et al. 2002) motivated debates about stronger regulation measures. These debates resulted in the implementation of the precautionary principle in the European Union (von Schomberg 2004). In the last consequence, its objective is to prevent such developments as the asbestos story (Gee and Greenberg 2002) or the ozone hole story (Farman 2002).

A wide international agreement on the precautionary principle was reached during the Earth Summit (United Nations Conference on Environment and Development UNCED) in Rio de Janeiro 1992 and became part of Agenda 21. Principle 15 of the Rio Declaration states:

> *In order to protect the environment, the precautionary approach should be widely applied by States according to their capabilities. Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation.*

Since then the precautionary principle has been implemented in various environmental instruments, and in particular in areas of global climate change (Schröder et al. 2002), ozone depleting substances and biodiversity conservation (s. von Schomberg 2004 for the following descriptions of the implementation of the precautionary principle in the European Union and of its core elements).

The precautionary principle has been incorporated in 1992 in the Treaty on the European Union. Article 174 states: "Community policy on the environment shall aim at a high level of protection taking into account the diversity of situations in the various regions of the Community. It shall be based on the precautionary principle...” It is apparent from the Treaty that Community policy on the environment is to pursue the objective *inter alia* of protecting human health, and that the policy, which aims at a high level of protection, is based particularly on the precautionary principle.

The precautionary principle establishes a rationale for action: it substantially lowers the (threshold) level for action of governments. It implies a breakthrough in comparison with the previous context in which politicians could use or abuse a persistent dissent among scientists as a reason (or excuse), simply not to take action at all (von Schomberg 2004). For cases for which the accumulation of relevant scientific evidence can take decades, this implies that political action simply would come too late if today’s plausible assumption based on incomplete or contested scientific knowledge would turn out to be true: the area of climate change is an obvious example (Schröder et al. 2002).

Table 5.3: Overview of State of Affairs in Science and the possible corresponding responses by Risk Management (modified by von Schomberg 2004)

Circumstances	State of Affairs in Science	Policy Framework/ Regulatory action/ Examples
Risk (classical approach)	Known effects, quantifiable probabilities, remaining uncertainties may have statistical (e.g. stochastically) nature	Risk Management by defining thresholds on the basis of chosen level of protection, exercising prevention, minimalisation of risk: applying the ALARA principle etc.
Unquantifiable Risk, lack of knowledge	Known effects/unknown or uncertain cause-effect relations, therefore unknown probabilities	Antibiotics in feeding stuff/Protection of the North Sea. Invocation of PP is justified; preventive measures to take away the possible causes can be justified.
Epistemic uncertainty: scientific controversies, lack of knowledge)	Unknown scope of effects, however, degree and or nature of their "seriousness” (in relation to the chosen level of protection) can only be estimated in qualitative terms.Arguments on the basis of a fully conjectural knowledge base, no scientific indication for their possible occurrence	Invocation of the PP is justified: example: GMOs, Climate Change, Ozone depletion
Hypothetical effect/ imaginary risk	Arguments on the basis of a fully conjectural knowledge base, no scientific indication for their possible occurrence	Invocation of PP is not justified.

The following characterisation of the precautionary principle (modified by von Schomberg 2004) shows – in spite of it still does not cover all relevant aspects – the complex inherent structure of the precautionary principle:

> *Where, following an assessment of available scientific information, there is reasonable concern for the possibility of adverse effects but scientific uncertainty persists, measures based on the precautionary principle may be adopted, pending further scientific information for a more comprehensive risk assessment, without having to wait until the reality and seriousness of those adverse effects become fully apparent.*

The first important point is that the application of the precautionary principle generally starts with a scientific examination. There is a need to have an assessment of the state of affairs in science and of the types of uncertainties involved. Drawing the borderline with classical risk management practice or the situation of a purely conjectural risk involves making normative choices which need to be made explicit. But even more importantly, in the case of epistemic uncertainty, a normative relationship between the nature of the uncertainties and the possible adverse effects needs to be established in order to justify policy and regulatory intervention. In assessing the uncertainty involved, *normative* qualifiers come into play while applying the precautionary principle. It does namely make a difference if the application of the precautionary principle needs to be established in relation to the anticipated adverse effects: a "reasonable ground for concern" (EC communication on the PP), the identification of possible harmful effects on health following an assessment of available information (Regulation EC 178/2002, general principles and requirements of food law) or "sufficient evidence for safety" (WTO Agreement on the Application of Sanitary and Phytosanitary Measures). However it is difficult to precisely outline the normative constraints of the type of scientific information needed which is "sufficient" to trigger it of. Some argue that there is a "degree" of likelihood associated with those qualifiers. von Schomberg (2004) suggests to relate the normative qualifiers to the "quality of the available information" which especially relates to the fact what type of information is known or should be known and of which we are ignorant: for example the knowledge concerning established cause-effect relationships and their degree of necessity to know those relationships in order to make a judgement. The qualifier "reasonable concern" as employed by the EC guidelines makes no prejudice about the degree of likelihood, but this qualifier relates in fact to a judgement on the quality of the available information (von Schomberg 2004).

Furthermore, after the application of the precautionary principle corresponding measures need to be regularly reviewed when scientific information either calls for relaxation or strengthening of those measures. Precautionary measures can be lifted if scientific knowledge has progressed to a point that we would be able to translate (former) uncertainties in terms of risk and adverse effects in terms of defined, consensual levels of harm/damage, moving from the second or third to the first line of table 5.3. Consequently, the central questions at the current situation are:

- Is there "reasonable concern" in Nanotechnology to legitimate the application of the precautionary principle?
- If yes, what would follow out of this judgment with respect to adequate precautionary measures?

The first question has to be answered, following table 5.3 and having in mind the results from section 5.2, *positive.* There are unknown or uncertain cause-effect relations and still unknown probabilities of risks resulting from production, use and proliferation of nanoparticles. The scope of possible effects, their degrees and the nature of their "seriousness" (in relation to the chosen level of protection) can currently only be estimated in qualitative terms. Therefore, we are witnessing a typical situation of uncertainty (see table 5.1) where established risk management strategies are not to be applied (in the same sense also summary of Royal Society 2004).

With regard to resulting measures (the second question above) the precautionary principle regularly has an impact at two levels (Haum et al. 2004:26): at the level of improving the knowledge base in order to enable usual risk management strategies as well as at the level of elaborating regulatory mechanisms to be better able to deal with the uncertainties involved. While the first level has been tackled in section 5.2 we will now focus on possible consequences for regulation or other types of action.

5.3.3 Dealing responsibly with Uncertainty about Nanotechnology Risks

Facing the "precautionary situation" we identified above, the first question which would have to be answered is whether there is, according to present knowledge, "reasonable concern" about possible adverse effects of Nanotechnology which could serve as legitimating reason for very strict measures (like a moratorium on nano-particle use in products, a strict regulation of the release of nanoparticles or even a ban on nanoparticles). Remember that the precautionary principle requires a scientific assessment of the state of the art to be conducted as a basis for further thought, and that the "quality of the information available" (von Schomberg 2004) serves as a normative qualifier in order to assess the "reasonability of concern". This scientific assessment of the knowledge available has been provided in section 5.2 in a comprehensive manner, going up to the frontier of present research (usually, such a comprehensive analysis and overview is not included in studies on Nanotechnology and society, cp. Haum et al. 2004, Royal Society 2004, Nanoforum 2004). The result is that there are indications for nanoparticle risks for health and environment in some cases but that there is *no reason for serious concern.*

This result coincides with results from other studies: "Taking into account our present-day knowledge, there is, with regard to nanospecific effects (excluding self-organisation effects and cumulative effects of mass production), no reason for particularly great concern about global and irreversible effects of the specific technology "per se", with it being on a par with the justifiable apprehension concerning nuclear technology and genetic engineering" (Haum et al. 2004:16). Scientific uncertainty is, following the precautionary principle, not a sufficient reason for strict measures though the situation cannot guarantee that there will be no serious harm implied by a wider use of nanoparticles. It will always be possible to create speculative scenarios with highly adverse effects – this situation, however, does not legitimate to use the precautionary principle as argument for a moratorium or other prohibitive measures. There is a considerable difference between

- the future ethics of Hans Jonas (1979) which put into the foreground the "priority of the negative prediction" and postulated to refrain from new technologies already in case of mere hypothetical catastrophic developments existing only in imagination without "reasonable" scientific basis, and
- the precautionary principle where some scientific indications for considerable damage and serious concern about their probability is required. The precautionary principle consists of a combination of precautionary thought and "sufficiently reasonable" evidence of harm.

The next question then is what other (and weaker) types of measures are required facing the precautionary situation. These could be

- self-organisation of science, applying and strengthening established forms of the responsibility of science (mainly in this sense, cp. Reynolds 2002, based on experiences in genetic engineering in the course of the famous Asilomar conference in 1973);
- adaptation of existing regulation schemes to special features of nanoparticles;
- systematic monitoring of the development of the knowledge base on possible Nanotechnology risks in order to learn from disastrous experiences like the asbestos case (Gee and Greenberg 2002).

It seems helpful to reconsider, as an example, the first comprehensive implementation of the precautionary principle which has been performed in the genetically modified organisms (GMOs) case:

> *The European Directive 2001/18 (superseding directive 90/220), concerning the deliberate release of GMOs into the environment, is the first piece of international legislation in which the precautionary principle is translated into a substantial precautionary framework. There is no experimental scientific evidence for harm to humans or the environment caused by GMOs but ecologists consider it plausible that single releases of GMOs could cause for instance irreversible effects on the natural vegetation (decrease of biodiversity) or resistant weeds. There is scientific uncertainty whether GMOs pose an additional risk in comparison to conventional cultivation methods. In the framework of this directive the precautionary principle is translated into a regula-*

> *tory framework which is based on a so-called case by case and a step by step procedure. The case by case procedures facilitates a mandatory scientific evaluation of every single release of a GMO. The step by step procedure facilitates a progressive line of development of GMO's by evaluating the environmental impacts of releases in decreasing steps of physical/biological containment (from greenhouse experiments, to small scale and large scale fields tests up to market approval). This procedural implementation of the precautionary principle implies an ongoing scientific evaluation and identification of possible risks. The procedure also results in the accumulation of scientific data, which provides input into new evaluations. Such a framework can thereby bypass scientific inconclusive deliberations on whether GMOs can be considered as generally safe or not, and shifts the discussions to the micro-level of scientific information and deliberations whether a particular GMO can be considered safe for a particular application, for a particular limited time frame, and particular post-approval monitoring and management requirements (regulatory requirement such as monitoring, labelling, traceability, time-limited licenses, are measures that are consistent with and enable a precautionary practice; it also enables a "learning practice" in which we enable us to collect information in due course and acknowledge the innovative aspects of GMOs and their possible benefits) (von Schomberg 2004).*

This model could serve as a framework of reference also for other cases like dealing with the situation of uncertainty concerning nanoparticles. The precautionary principle would imply "that there is a need for a cautious step-by-step diffusion of risk-related activities or technologies until more knowledge and experience is accumulated" (Haum et al. 2004:6).

Against this background our first conclusion is that the existing measures of regulation *need not to be extended* for dealing with possible nanoparticle risks. Established mechanisms in the regulation of chemicals are sufficiently prepared to cover also the nano case. Though there are particular points of criticism (for example towards the TSCA, Wardak 2003), these points may be taken into account with little modifications. Major points of criticism (for example the TSCA showing too few elements of precaution, Haum et al. 2004) do not apply to nanoparticles in a specific way but are concerning the "philosophy" of those regulatory measures as a whole. Presently, there is a wide consensus that no additional regulatory measures are needed: "… the existing regulative framework is adequate to deal with the introduction of new substances in the nanotechnology sector" (Haum et al. 2004:27). Treating nanoparticles as new chemicals seems to be the adequate risk management approach.

This result also holds for companies and entrepreneurs using nanoparticles for designing, producing, and providing new technical products. The responsibility of managers and engineers in dealing with nanoparticles, therefore, should be oriented along the established codes of conduct and the existing regulation measures. Special awareness about possible side-effects should be applied because still only little knowledge on side-effects is available, and especially because there are no long-term studies about possible effects of nanoparticles on health and environment. This special awareness, however, should also and always be given to the use of new chemicals and their impacts. Consequently, from the view of engineering ethics and ethics in economy, there is no principally new situation.

However, this statement should not be misused. There are urgent tasks to be done by science, especially in order to close the large knowledge gaps. Within the framework presented the main task is to improve the knowledge base by research in several respects, mainly by means of human and environmental toxicology (see 5.2). A second line of activities required consists of collecting systematically all relevant knowledge and regularly conducting comprehensive evaluation of the respective state of knowledge and what would follow out from that state (in the asbestos case the situation was that a lot of separated knowledge pieces existed but no instance felt responsible for performing systematically a kind of synopsis, Gee and Greenberg 2002).

Consequently, we arrive at the following steps for further action, thereby meeting several of recommendations by other groups (Haum et al. 2004, European Commission 2004b, Royal Society 2004):

- develop a nomenclature for nanoparticles
- assign a new Chemical Abstract Service (CAS) registry number to engineered nanoparticles
- group and classify nanomaterials with respect to categories of risk, toxicity, and proliferation
- treat nanoparticles as new substances
- develop and approve tools for screening and testing
- improve the knowledge base in toxicology
- creating institutions to monitor nanotechnologies and the knowledge about possible risks
- establish a dialogue with the public and the industry
- develop guidelines and standards for good practices in cautiously dealing with nanoparticles
- avoid or minimize production and unintentional release of nanosized waste particles
- establish comprehensive evaluation of the state of knowledge and its evaluation with respect to implications for risk management as well as for identifying knowledge gaps which should urgently be closed.

This step-by-step approach conforms to present knowledge and will be the adequate way of applying the precautionary principle in a pragmatic way. However, it should not be forgotten that there is no guarantee of preventing all kinds of possible risks by applying these steps. The present situation “no reasonable evidence of harm” does not mean “evidence of no harm” (Gee and Greenberg 2002). This situation (s. also section 5.4.3) implies that science and industry should deal with nanoparticles (in research and industry) in a cautious way, due to their responsibility and accountability.

5.4 Risk Communication

The history of some technology conflicts has shown that scientific risk assessment and dealing with the "objective risks" is only part of the game. Especially in the fields of nuclear power and of genetic engineering it became clear that risk perception in society and public risk communication did not simply follow the scientific assessments but rather went their own course, frequently leaving back confused scientists who could no longer understand what was been going on. Severe communication problems between science and society have been the consequence with serious impacts on the further development and use of those technologies: nuclear power technologies have not been developed further and will, in some countries, not be used in future, and genetically modified food is still not accepted in many countries. Facing this situation, a new type of research emerged in the 1980s: risk research in social sciences, in psychology and in the political sciences (Slovic 2000). Such research activities aim at uncovering the mechanisms of public risk perception and the patterns of risk communication, frequently applying the basic distinction of expert communication and lay communication (Bechmann and Hronszky 2003). Presently the hope is that such severe communication problems as in the cases mentioned above might be avoided in new technology debates – as in Nanotechnology, while some media already put Nanotechnology in one row with nuclear technology and genetic engineering (NZZ 2003).

5.4.1 Emergence of the Public Risk Debate on Nanotechnology

For many years Nanotechnology has been a seemingly non-risk technology. In the 1990s, Nanotechnology became a growing field not only for scientific advance but also in public awareness. Public perception has been, in the first years, exclusively positive. The prefix "nano" absolved a career in the media as a synonym for "good" science. In contradiction to large power plants or to big chemical factories – which have frequently been regarded as problematic in several respects – Nanotechnology promised a better and "clean" technological future based on the very positive appreciations of "the small".

This situation came to an end in 2000. The paper "Why the future doesn't need us" by Bill Joy (2000) inverted the positive utopia of "the small" into horror scenarios, based on the same "small" technologies. It showed the ambivalence of technology-based visions in a dramatic way. Other authors followed, as well as feuilletons of important newspapers. The public risk debate on Nanotechnology emerged using issues of visionary and speculative developments. The topics of "grey goo", "nanobots" and "cyborgs" became well-known to many people within few months. As a result, concerned groups began to draw parallels between Nanotechnology and other technology lines with a specific history of public risk debate: nuclear technology and biotechnology (ETC-group 2003). Also newspapers put Nanotechnology in the category of risky technologies, and re-assurance companies followed this line of thought (Swiss Re 2004).

We could witness, in the mirror of public perception and mass media communication, the fall of Nanotechnology from a synonym for the "good" scientific and technological progress to a technology line that is currently expected to bear a lot of still unknown risks. The former perception of Nanotechnology as being highly attractive – because of dealing with the very small instead of building large factories – turned into fears exactly because of its smallness: replicators, nanobots and nanoparticles frequently are regarded as dangerous because they could bring harm without humans being able to observe them. We are not able to see or feel them, neither to smell or taste them.

Currently, the speculative visions seemingly loose importance in public risk debate. Instead, nanoparticles are in the centre of interest (s. 5.2). The most important reason for this shift might be that nanoparticles are closer to the integration in concrete products (some are already used). Therefore, consumers and citizens could easier come in contact with nanoparticles, and the probability of directly having contact with artificially produced nanoparticles will increase considerably in the next years because of the expanding market of products based on Nanotechnology. Headings in newspapers of the type "small particles – large risks" appeared rather frequently in the last years.

One special observation is that – in contradiction to most expectations – the risk debate on Nanotechnology did not arise in Europe (especially not in Germany) but in the United States. The European public has been a latecomer compared to the States, concerning Nanotechnology risk perception. The moratorium has been postulated by a Canadian group, not by European sceptics. Also ELSI issues of Nanotechnology have been discussed rather early in the States. Thus, in case of Nanotechnology, the usual opinion that the States are chance-orientated and Europe is more risk-orientated has been proven a prejudice.

5.4.2 Futuristic Visions in Public Debate

Visions are an established (and perhaps, in some respect, necessary) part of the scientific and technological progress as well as an important element of the communication between science and the public. In general, they shall create fascination and motivations among the public but also in science; they shall increase public awareness on specific research fields; motivate young people to choose science and technology as fields of education and career and help gaining acceptance in the political system and in society for public funding.

Nanotechnology visions based on early dreams of Richard Feynman (1959; s. chapter 2) and on more concrete utopia published by Eric Drexler (1986) have been perceived as positive utopia, and have contributed to the career of Nanotechnology in political and public debate. In this sense, those visions also contributed considerably to the strong increase of public funding of Nanotechnology. Starting with the Bill-Joy-debate, however, those visions also showed completely different faces: that positive expectations also might have a “dark side”. Therefore using scientific visions in public debate to a considerable extent shows specific risks of communication at the interface between science and society. In the following, we will briefly sketch the most prominent examples of such “dark sides”, we will analyse what can be said to those visions from the viewpoint of science and we will identify the most problematic aspects of speculative visions in public communication.

Fears and Negative Utopia

(1) The "grey goo" scenario

Media coverage of nanotechnologies has invariably raised the spectre of the ‘grey goo’: a doomsday scenario in which nanoscale robots self-replicate out of control, producing unlimited copies of themselves, consuming all available material and ultimately laying waste to the planet: “Tough, omnivorous “bacteria” could out-compete real bacteria: they could spread like blowing pollen, replicate swiftly, and reduce the biosphere to dust in a matter of days” (Drexler 1986, p. 172). Whereas most of the scientific community considers this to be science fiction, others have argued that it is a possible outcome of unregulated Nanotechnology. This scenario motivated the Munich Reassurance company (2002:15) to far reaching postulates on risk management: Specifically, risk management should cover the following:

- Technological assessment and an appraisal of the effect of each nanotechnologically produced article.
- Differentiation between passive (e.g. passive surfaces) and active (e.g. robots in the human cell) Nanotechnology products.
- Active Nanotechnology manufacturing only under controlled, high security laboratory conditions (HPR approach).
- Use of active Nanotechnology products with guaranteed, continuous monitoring.
- Lifecycle monitoring obligation on the manufacturer and devising of recall strategies and technical options.
- Decoupling of function and power supply for active Nanotechnology products.
- Compulsory tagging of products which incorporate active and passive nano components.
- Setting up of discussion and decision-making organs on social, corporate, ethical and political levels, to give all interested parties a chance to voice an opinion.

Public risk perception frequently used the grey goo scenario in arguing for more cautiousness in scientific and technological progress. This scenario reminded many people of the large apocalyptic fears, based on technological innovations, which have been brought up in the 1970s, and which motivated Hans Jonas (1979) to the famous "imperative of responsibility". Apocalyptic illustrations of future developments have been accompanying the scientific and technological advance since the Industrial Revolution while their role and influence varied considerably over time. The level of public and media interest in Nanotechnology therefore justifies the following question: Is 'grey goo' a real concern, or is it a distraction from the important issues?

(2) The "prey" scenario

The "prey" scenario is built on the same basic idea, the self-replicating nanorobots. Initially, the idea of these robots has been invented to describe positive utopia expected from Nanotechnology: they could, following the imagination of the vision promoters, invade the human body and act there as an improved health maintenance system. Each failure of a cell or a process should instantaneously be detected and be repaired by such nanorobots: "In the hunt for pathogens, doctors send tiny machines into the furthest recesses of the body. These "mini-submarines" are so small that they are not visible to the naked eye even as a speck of dust. Rotating cutting devices from the same dwarf world burrow their way through blocked blood vessels to eliminate the causes of heart attacks and strokes" (Münchener Rück 2002:3). The vision of slowing down or even abolishing ageing is closely related to this basic technological idea. However, Bill Joy (2000) drew a completely different picture. He argued that the "converging technologies" (in fact, he did not use this notion but pointed to developments which are currently discussed under this topic) Nanotechnology, biotechnology and information technology could indeed lead to the possibility of "intelligent" nanobots. His concern is that humans easily might loose control over those armadas of nanorobots (in a certain sense, such nanorobots are the "inorganic equivalent of genetic engineering" (Haum et al. 2004:4). Instead of being servants to human needs nanorobots could start acting independently from human orders and could gain control over the world. The completely technical civilization which could emerge from such a development then would no longer need humans.

Loosing control over technology is, as the above-mentioned category of apocalyptic fears, an old momentum of societal thought about technology. The concern that technology could invert the traditional relationship between humans and technology – technology serving human needs – is also a Leitmotiv of philosophical and general debates on future prospects in the technicalized civilization. The more capabilities could be given to technology the more fears in this respect arise. Accordingly, the emergence of such scenarios as "prey" is not surprising at all. In future, we will be confronted with scenarios of loosing control over technology to an increasing extent, in public communication as well as in scientific reflection itself. At the moment, the relevant question is: what can be said to the prey scenario from the perspective of science?

(3) The "cyborg" scenario

There is intensive work in nanobiotechnology on connecting the world of molecular biology with that of technology and engineering. An interesting field of development is nanoelectronic neuro-implants (neurobionics), which aims at making direct interfaces between technical systems and the human nervous system possible (for example, to compensate damage to sensory organs, or to the nervous system, or to increase the performance capacity of these organs and broaden the spectrum of human perception). Technical access to the nervous system is, due to the possibilities of manipulation and control, a particularly sensitive issue (s. section 7.2.5).

Extrapolating these lines of development into the realm of speculation, the convergence of technology and humanity, the conceivability (in the sense of a pure thought possibility) of "cyborgs" as technically enhanced humans or humanoid technology could be problematized (Paschen et al. 2004). In nanotechnological visions, aspects repeatedly occur which blur the boundary between what human beings are and what they create with the help of technical achievements and applications. The "Foresight Institute" and the "extropian movement" have developed futuristic visions which include the possibility of the technological storage of human consciousness. Furthermore, some researchers who participate in the National Nanotechnology Initiative (NNI) of the United States assume that artificial brains might be created within the next 25 years (Cauller and Penz 2002). Such visions pose the question, to which extent even technical or partly technical, partly biologically constructed man-machine chimeras can lay claim to the status of a person. An entire spectrum of anthropological and ethical questions follows out of this aspect. In some US-American churches precisely this aspect of Nanotechnology is a central theme, too – from the opposite point of view compared to the Transhumanism discussion: "When God fashioned man and woman he called his creation very good. Transhumanists say that, by manipulating our bodies with microscopic tools, we can do better. Are we ready for the great debate?" (Hook 2004). Nanotechnology currently acts as a playing-field on which various philosophies of life compete.

The idea of cyborgs is not a new one. Starting with Science Fiction (SF) literature of earlier times (Golem and Frankenstein) there is an ongoing debate on the relation between humans and technology and on the borders between them. The technicalisation of humans on the one side, and the growing capabilities of autonomous robots (Christaller et al. 2001) seemingly are challenging traditional convictions.

The perspective of science on the feasibility of those visions

The grey goo as well as the prey scenario is grounded on the same technological idea: molecular manufacturing with the potential of developing self-replicating nano-units. The original concept of molecular manufacturing described by Eric Drexler, Chairman of the Foresight Institute, imagined the synthesis of materials and objects by a mechanical 'assembler'; that is, a machine with the ability to make any object by selecting atoms from the environment and positioning them, one at a time, to assemble the object. This assembler can be programmed and is powered independently: "Eric Drexler … believes nanoassemblers could make steaks out of "grass, water and foodstuffs", avoiding the cumbersome process involving the cow" (Münchener Rück 2002:3). As it can make any object, it can reproduce itself. If the process malfunctions or is corrupted, intentionally or not, the self-replication process could continue indefinitely. Over the past 20 years or so, Drexler and his colleagues have continued theoretical studies of the feasibility of such machines, but as far as we are aware of there is no research in this field that has been supported by funding agencies, and there has been no practical experimental progress over this period. The reason is simple: there are many serious fundamental scientific difficulties and objections, to the extent that most of the scientific community believes the mechanical self-replicating nanorobot proposal to be impossible.

The scientific issues have been debated in open correspondence between Eric Drexler and Rick Smalley, corecipient of the Nobel Prize for Chemistry in 1996 for the discovery of carbon 60 – so called buckyballs. In summary, there are two major difficulties: first, to lift and position atoms one needs very fine manipulators, of similar size to the atoms being worked with; second, the atoms being manipulated must first attach – i.e. chemically bind – to the manipulator, and then unbind from the manipulator and bind to the object. Although scientists have used atomic force microscopes to manipulate a restricted group of individual atoms and molecules into simple structures on surfaces, the properties of matter on this lengthscale appear to be incompatible with the requirements for a mechanical self-replicating technology. These objections have been termed by Smalley as 'thick fingers' and 'sticky fingers'. "My argument is that I believe that it is so implausible that I wouldn't worry about it … proving an impossibility is a very difficult thing to do and I've only done it in small parts" (Smalley in evidence to the Working Group of the Royal Society 2003).

George Whitesides has questioned the feasibility of the energy management system that would be needed to handle the large energy input and release that occurs at the different stages of the construction process. Because the assembler is a nano-machine, its positioning accuracy is severely limited by the intense bombardment it receives from atoms in the environment – whether gaseous or liquid – which causes Brownian motion. It is quite clear: making a mechanical self-assembler is well beyond the current state of knowledge: 'I think there is no such thing as the assembler.' (Whitesides in evidence to the Working Group; with reference to the mechanical molecular assembler proposed by Drexler). Even Eric Drexler expresses the opinion that there might be other, more urgent developments to take care of: "... when people say 'this [grey goo] isn't what we should be worrying about' I think they are right. I believe it's very much the wrong issue to focus on for a variety of practical and sensible reasons" (Eric Drexler in evidence to the Working Group of the Royal Society 2003).

Our experience with chemistry and physics teaches us that we do not have any idea how to make an autonomous self-replicating mechanical machine at any scale, let alone nanoscale. However, in the world of biology we can find self-replicating machines. The cell, thousands of nm in size, is the smallest unit we know that contains all the machinery essential for the process of reproduction, given a suitable environment. In fact, the planet we know today is quite different from its earliest form: biology evolved and turned a desert into the ecosystem we are now part of. At present however, the complete details of operation of even a simple cell are far beyond our understanding.

Given the above, we have heard no evidence to suggest that mechanical self-replicating nanomachines will be developed in the foreseeable future, and so we would direct regulators at more pressing concerns. Also public risk debate should be focused on more relevant issues. The "grey goo" as well as the "nanobot" scenario belongs to SF literature instead to serious visions of the next steps in scientific advance.

The situation looks different in the "cyborg" field. There are a lot of research activities towards making direct connections between technical systems and the human nervous system possible (s. section 3.3). Micro-implants could restore the functions of hearing and eyesight. Even today, simple cochlear or retina implants, for example, can be realized. With progress in nano-informatics, these implants could approach the smallness and capabilities of natural systems. It seems to be rather probable that traditional borders between humans and technological systems will be transgressed in the next decades, and new interfaces will be established. The "cyborg" scenario only points to the possible negative consequences of such developments. However, there will also be a lot of positive and highly desired developments, at least in the medical and health area. New interfaces between humans and technology will, without doubt, considerably challenge society and human self-understanding. But there is no reason to exclusively look on possible negative consequences and to use such one-sided perspectives as points of departure for public risk debate. In spite of this approach, ethical reflection of such developments (s. section 6.2.5) and technology assessment should contribute to an open societal discourse weighing benefits and risks.

But even if these visionary assertions actually were mere speculations, speculations often have – publicly communicated and debated – real effects in society, e. g., on public opinion or on the societal atmosphere and on acceptance in public. For example, the nanorobot scenario motivated the Munich Re-Assurance Company to postulate a lot of precautionary measures against risk implications of that scenario (Münchener Rück 2002; s. the quote in section 5.4.2). Sometimes they are instrumentalized to create public acceptance and political support (Paschen et al. 2004). Negative visions could be used to mobilise resistance against specific technologies. The factual impact of visions on public and political debate is the strongest argument for the need for Vision Assessment (Grunwald 2004). As result from the analysis given above, the following essentials may be drawn:

- occupation with futuristic visions, speculations and risks is not only sensible, but necessary because of their impacts on really ongoing societal discussions;
- most scientists do not assume futuristic visions like the molecular assembler to be feasible;
- however, a statement that they would be completely impossible in the future, cannot be proven – new scientific knowledge might change our feasibility judgments;
- the visions mentioned will not be feasible in the short or medium-term;
- thus, there would be enough time for society to reflect on those developments and to establish regulations according to ethical and political lines of argumentation (for example, safety standards, prevention of misuse etc.);
- there is absolutely *no need* for regulation today (risk management or application of the precautionary principle) in these fields;
- speculative visions should no longer determine public risk debate; nanoscientists should engage themselves in these discussions in order to deviate public awareness to more relevant fields.

Risks of Vision Communication in Public Debate

As has been demonstrated the usage of speculative visions in public debate raised, after some years without any problems, severe communication problems at the interface between science and society. From our point of view, there are mainly two problematic aspects of speculative visions in public communication: the *ambivalence* issue and the *frustration* issue.

(1) The ambivalence of positive visions

Dramatic and deep-ranging changes in society as a consequence of nanotechnological advance are seen by some visionary scientists and science writers. In economic respect Nanotechnology might be the basic technology for the 3rd industrial revolution. Expectations have been expressed that

Nanotechnology could allow for much more longevity of humans, up to an abolition of ageing – which would be one of the more radical societal visions. Other visions have been put forward in the context of "converging technologies", considering the vision of "enhancing human performance":

> *Rapid advances in convergent technologies have the potential to enhance both human performance and the nation's productivity. Examples of payoff will include improving work efficiency and learning, enhancing individual sensory and cognitive capacities, revolutionary changes in healthcare, improving both individual and group efficiency, highly effective communication techniques including brain to brain interaction, perfecting human-machine interfaces including neuromorphic engineering for industrial and personal use, enhancing human capabilities for defence purposes, reaching sustainable development using NBIC tools, and ameliorating the physical and cognitive decline that is common to the aging mind (Rocco and Bainbridge 2002:1).*

These visions make use of rather ancient ideas of improving or "optimising" humans but put them into the context of ongoing scientific and technological developments, therefore claiming the future feasibility of such visions.

But indeed, the ambivalent nature of futuristic visions is evident. Revolutionary changes and developments towards completely new technologies do not only create fascination and motivation but also concern, fear, or objection. Traditional convictions and values could be challenged and existing societal structures could change radically. There might be, in the course of time, winners as well as losers, there might be unexpected and possibly negative consequences, and, in any case, there will be a large degree of uncertainty. Revolutionary prospects do not automatically lead to positive associations but might cause negative reactions. As an example: the promise of a "New Renaissance" by the promoters of "Improving Human Performance" (Rocco and Bainbridge 2002) shall obviously be understood as a pure positive prospect. But, looking closer to what happened in the real Renaissance, things might appear very different. The historic Renaissance has been a time of war, crudelity and violence. There have been few winners but many, many losers of societal revolutions. Today, we think of Leonardo da Vinci and Michelangelo Buonarotti but we tend to forget the victims. As soon as somebody points to the many victims the positive idea of "New Renaissance" would turn into a negative one. Using futuristic visions might, as a consequence, lead to a backlash and rejection instead of fascination and acceptance. Recent discussions in Nanotechnology (Joy 2000) are an excellent example for such "risks" of vision communication.

Therefore, positive visions could be re-interpreted as negative ones at the same time, hopes of some people may be fears of others, judgements may change over time. Besides the positive visions of "enhancing human performance" or goals like treating diseases new fears arise. For example, one of the concerns is that nanoparticles, due to their microscopic size, could invade the human body unhindered, and could cause unforeseeable effects there. Many of the more technical visions also show such "dark aspects":

> *Replicators can be more potent than nuclear weapons: to devastate Earth with bombs would require masses of exotic hardware and rare isotopes, but to destroy all life with replicators would require only a single speck made of ordinary elements (Drexler 1986).*

Also warnings have been put forward against mankind's presumptuousness in wanting to improve the physical or psychic endowments predetermined by nature (as in the program of the "converging technologies"). Specific concerns are expressed about blurring the boundaries between humans and technology on the basis of new interfaces between technical systems and the human organism (cyborg discussion, s. above) made possible by Nanotechnology, for example in the direction that such developments might allow more technological control over humans. The more speculative and revolutionary the vision, the more interpretations are possible – a wide field for public debate and occasions for ideological use of them.

Applied to the three negative scenarios mentioned in section 5.4.2, we can see that in the beginning there has been a positive vision (molecular assembler, new access interfaces to the human brain for medical purposes mainly) with positive effects in public communication. But as soon as someone detected "dark sides" of those visions and used an effective communication strategy public perception may change rapidly to the opposite side of the spectrum. This "fragility" of public perception makes the usage of highly speculative visions in public debate an approach with high inherent risk. Rise and fall of public perception of new technologies sometimes are close together. The use of speculative visions increases the erratic course of public perception between high fascination and deep fears.

(2) The frustration issue

A second problematic issue of positive visions has not yet been virulent in Nanotechnology but might gain increasing relevance in the upcoming years. Visions with high promises and expectations could be regarded, after some years, as having been only a means of selling science and gaining political support. As a rule, some media will ask, after a certain period of time, for the real results of the technology line under question. High public awareness and high public funding will motivate questions for the measurable utility of that technology (for everyday life, for economic welfare, for employment, for security, for the objective of sustainable development etc.). The public and the media will not be able to wait for a long time but they want to see concrete results. The time scales of scientific-technological innovation (often even concrete developments take 10–15 years of time, calculated from first steps in scientific laboratories to concrete products at the marketplace being available) and of public expectation are considerably different.

In the past, we could witness some developments of "frustration" comparing public and political expectations and scientific advance and its technological use. One well-known field is space. The promoters of space technologies used far-reaching visions of settling at the Moon, going to Mars, exploring the solar system, building factories in the Lower Earth Orbit, or using Solar Power Satellites for energy supply on the Earth. For some decades, such visions created considerable fascination and led to large public funding (surely supported by the special situation of the Cold War). The visions considerably contributed to the technological progress in space transportation. However, in the 1980s, critical voices began to ask for the "real" benefits. Because it had been difficult to give answers space technologies and activities lost public support in the meantime. Another field is micro systems technology which started in the 1980s with large expectations but did not yet lead to the expected outcomes.

Overselling science has become a problem in the last years because of lower public budgets. There are tendencies to exaggerate the expected outcomes and to assume too short times for their realisation (research as well as their diffusion into the marketplace). Overselling, however, may cause frustration and in case of delays or in case of missing the expectations and, in the following, might have negative consequences for the line of development under consideration as well as for science as a whole. In the field of Nanotechnology, such disappointments following exaggerated expectations can already be observed (Die Zeit, Ausgabe 20/2004).

Issues of Trust

In certain circles, particularly in economy, but also among scientists, it is unpopular to talk about the potential risks of new technologies. They are afraid that the eternal pessimists and technology-enemies prevent making use of technological advances through excessive fear of technical risks. These people would try (often successfully) to mobilize public opinion in their own favour and against innovative technologies by means of campaigns and spectacular public appearances. In this manner, politicians would be coerced to delay scientific and technical progress through regulation or restructuring of research funding, often in the name of a very extensively interpreted precautionary principle. In this manner, it is rendered impossible to make early use of the advantages of new technologies, to increase prosperity, or to heal diseases. And afterwards, these people say, it often turns out that the hazards feared don't materialize (pithy on this aspect, Gannon 2003).

There actually have been occurrences of this sort. But there have also been other developments in which things came just the reverse: early and extensive utilization of technology without thorough investigation of the risks, ignoring, e. g., the first cases of disease or of environmental problems, trivializing statements on the part of science and industry, very slow reaction on the part of politics (impressive case studies in Harremoes 2002). The result was not only a great deal of human suffering and economic losses, but often, also the end of the technology made responsible. The example of asbestos is, in this respect as well, a unique warning (Gee and Greenberg 2002).

It is also possible to formulate an antithesis to Gannon´s thesis (2003): addressing the risks of technology doesn't necessarily have to mean wanting to hinder or prevent scientific or technical progress. Rather, an early and open discussion of possible technological risks contributes, in the medium and long run, towards upholding and strengthening confidence in science and technology. There are cases enough in which risks were denied at first, then played down, and then – much too late –, openly admitted. This is the classical history of many incidents, for instance, in chemical industry or in nuclear power plants. The trust of the public in the ability of science and technology to deal with risks is not actually confirmed in such a fashion – on the contrary: trust which had been painstakingly built up is immediately destroyed by this sort of risk communication.

This also applies for nanotechnologies. It generally holds true that innovative technology can always also be connected with risks, early knowledge of which is, in fact, desirable, but is possible only to a limited extent. Trying to ignore or conceal this circumstance would fall back on its originator at some time, because – in an open society – these risks would inevitably be discovered and made public. Declaring technological risks to be non-existent is possible only in totalitarian states (as it was also actually practiced in the Communist nations; there were – officially – as a rule neither mishaps nor environmental problems). If these risks are discovered only in later phases of technological development, moderate correction is no longer possible. Often, all that remains is only the complete abandonment of the technology in question (good examples are the chlorofluorinated hydrocarbons (CFC) in refrigerators (Farman 2002), but also – again – asbestos). Early consideration of the risks and correspondingly careful management could have helped, not only to avoid serious negative consequences, but would possibly also have saved the products, the branches concerned, and jobs. It turns out, therefore, that there are pertinent cases in which not excessive discussion of risks was detrimental, but rather ignoring or lack of knowledge of risks had disastrous consequences. Visionary promises of positive effects of technological progress which ignore technology's ambivalence, collapse when this ambivalence becomes apparent – quite concretely, for example, in risks for health or for the natural environment. In this manner, those who ignore the existence of technological hazards are playing directly into the hands of the technology sceptics.

If one, on the contrary, proceeds carefully from the beginning, neither ignores nor denies the existence of risks, but addresses them openly and tries to analyze them more closely through scientific research, then subsequent disappointment and loss of confidence can be prevented. If it is openly acknowledged that new technology can always also be connected with risks, then the mere possibility of risks can no longer be used as an argument for stopping technological progress (for instance, in the sense of a moratorium on Nanotechnology). Risks are so self-evidently connected with technology *that no argument against technology can be derived out of their mere possibility*. To this end, a more detailed investigation is necessary: how great are the risks, what type of risks are they, which possible damage would occur if they actually became reality, and in which relation do these risks stand to the expected benefit? Also the question for possible risks of *not* implementing the technology under consideration has to be answered.

It comes out that the best way to achieve a "sustainable" trust between science and society would be an open-minded relation to the question of risk. Science, driven by curiosity and interests, should direct its own focus on possible risks by taking them as research fields. In this way, science demonstrates responsibility and also follows the imperatives of rationality which include *reflexivity*: scientific knowledge – of highest importance for future sustainability, health, welfare etc. – can be regarded as rational if together with the knowledge also the "meta-knowledge" about premises, risks and uncertainties of the knowledge itself is provided (Grunwald 2000b). Thinking simultaneously in both of these categories and frankly communicating this approach to advance and progress seems to be the best way of trust-building.

5.5 Prospective Risk Assessment as Concomitant Process

The further development of Nanotechnology should therefore be accompanied by continuous research on toxicology as well as on ethical and political questions associated with possible risks, but also in view of the expected positive effects. Elements of this work are:

- further analyses of the behaviour of nanoparticles in the human body and in the environment as well as of possible toxic effects from nanoparticles;
- prospective scientific occupation with the opportunities and risks of nanotechnologies and with their evaluation in the sense of technology assessments, dedicated to different lines of development (Fleischer 2002);
- accompanying monitoring the developing state of knowledge about opportunities and risks, as well as about the conditions under which they can become reality;
- performing "vision assessments" (Grunwald 2004, cp. section 7.4) to investigate the positive and negative utopias with regard to their cognitive content and their evaluative aspects but also with respect to their "risk" potential in public debate (s. 5.4);
- an open societal dialogue with the participation of nanoscientists, toxicologists, and of technology assessment.

Currently, classical risk assessment is – according to knowledge gaps concerning hazards resulting from nanoparticles – not applicable in the field of Nanotechnology. Quantitative measures of the probability of damage and of the extent of possible hazards are not yet available (s. 5.2). Insofar it is not surprising that lively discussions about the applicability of the precautionary principle take place in the industrialised countries (s. 5.3).

For the precautionary principle to be applied there must be a "reasonable concern" about possible hazards, based on scientific investigation. According to our analysis and to the review of the state of the art in toxicological research on nanoparticles given above we do not see such a "reasonable concern" which would legitimate hard measures (like a moratorium) according to the precautionary principle. Currently no additional regulatory measures are required.

However, with respect to dealing responsibly with artificially designed, new nanoparticles, specific caution is required. Such particles should be handled analogously to *new* chemicals even in case that the chemical composition is well-known beyond the nano character. Dealing with new nanoparticles is still based on a case by case approach because established nomenclature and classification schemes are not well-prepared to be applied to nanoparticles. This situation should be changed as soon as possible.

Beyond risk management and regulation the level of public risk communication has to be observed carefully because irritations in this communication could have dramatic impact on public acceptance and political judgment. It is necessary to distinguish between scientifically assessed risks and the public perception of risk. Public perception of risk has to be taken seriously even in case that it seems to be inadequate against the results of scientific risk assessment. The following text shows that those horror scenarios are being taken seriously:

> *If set free uncontrolled nano robots could, with the necessary constant power supply, transform organic substances in the environment into new materials or penetrate into the soil, causing permanent damage to crop cells or even destroying them. These would be totally new loss scenarios likely to go far beyond anything experienced up to now in today's hi-tech world (Münchener Rück 2002:4).*

Assessments like this one show that the risk situation would completely change in case molecular replicators would become feasible. This, however, seems to be pure Science Fiction at the moment and in the next future.

Innovation and progress are inevitably related to risk but also inaction carries risk. There is no choice between risk and no risk but only between different types of risk, between different degrees of risk, and between different rations between risks and benefits. This simple message must be a "ceterum censeo" part of the communication between science and the public.

Completely denying the existence of risks of Nanotechnology often causes mistrust and suspicion instead of creating optimism. To speak frankly about possible risks increases the chance for a trusty relation between science and society: "Taking risks seriously will help to foster public support" (Hermerén 2004). Building trust in public debate needs an open debate about chances and risks, and often requires schemes for comparing different types and amounts of risk to be available. Transparency about the premises of different risk assessment exercises is urgently required. Knowledge about risks includes knowledge about the validity and the limits of that knowledge. Communicative and participative instruments of technology assessment (Decker and Ladikas 2004) could help improving mutual understanding and public risk assessment (Schütz et al. 2004). Scientists should not leave these discussions to the mass media and politicians but should engage themselves in those debates.

To allow a more rational communication about chances and risks requires openmindedness, tolerance, and knowledge about communication issues on both sides. Scientists are not pure scientists but in many cases also science managers and science communicators. In order to deal adequately with the challenges of risk communication researchers should also learn some basics about risk perception, risk management and risk communication. This leads to specific requirements for interdisciplinarity in higher education (s. chapter 9).

Because innovations inevitably are related to risks the scientific and technological progress always shows some aspects of an experiment: there is no ex ante guarantee that all objectives will be met and that all hopes will be fulfilled. Furthermore, there is no guarantee that non-intended side-effects, especially risks, might occur. The question then poses itself, how such "experiments" can be carried out as responsibly and as legitimately as possible. The contributions of science, technology, and technology assessment consist in first taking care to provide as good a preparation of the "experiments" as possible (through analyses of the situation, innovative technology, modelling and simulation of the projected measures, etc.); in accompanying the painstaking performance of the "experiment"; and then in observing the effects of implementation (monitoring); in comparing the results with the goals pursued; and in investigating the causes of deviations. Precisely this is the principle of long-term monitoring, which explicitly acknowledges the incompleteness and uncertainty of knowledge of the effects of technology, as well as the possible existence of risks, and draws the corresponding conclusions. In this "experimental" situation, it is decisive to grasp a maximum of opportunities for *learning*. This means that the introduction of Nanotechnology products and processes is to be understood as an open process, in which the experiences which are made during realization co-determine the further course. In this sense, an accompanying, prospective risk assessment based on scientific research as well as on ethical thought is an indispensable element of a responsible development of Nanotechnology.

6 Ethical Aspects of Nanotechnology

In view of the revolutionary potential frequently attributed to Nanotechnology (Paschen et al. 2004), it is not surprising that this technology has found great interest in the media and in the public at large. Ethical, legal, and social implications (ELSI) are already being elaborated by commissions and study groups (Coffrin and MacDonald 2004; NanoForum 2004). Ethical reflection on Nanotechnology has, in fact, already coined new terms such as "nanoethics" (Moor and Weckert 2003; Robison 2004), but has, to date, hardly accomplished more than to proclaim a need for ethics in and for Nanotechnology (Mnyusiwalla 2003, Khushf 2004a). The ethical aspects discussed in the – to the present, few – treatises are much rather evidence of a tentative approach to a relatively new field of science and technology than of systematic analysis. Criteria for determining why certain aspects, such as self-replicating nanorobots or nanoparticles should be ethically relevant, are not given. The normative fuzziness of unclear criteria joins the cognitive fuzziness caused by a lack of knowledge of the real possibility of the technical innovations concerned. This situation shows, above all, a diffuse uneasiness in parts of society regarding rapid scientific advances in Nanotechnology. A broad and ethically motivated objection against Nanotechnology, however, is not to be expected to arise, as will be one of the results of this investigation (6.3).

In the face of this situation, the purpose of this chapter primarily consists in studying current and foreseeable developments in Nanotechnology from the viewpoint of ethics. Which are the ethically relevant developments, which questions have already been answered by current discussions on the ethics of technology or bioethics, and which developments pose completely new questions? To work out this programme, it is necessary – besides inquiry into the present state of the discussion – to first look for criteria for deciding when something is ethically relevant (6.1). These criteria are then applied to the field of Nanotechnology, and the ethical challenges are "mapped out", answering the above-mentioned questions (6.2) on the basis of an evaluation of the current literature, and of pertinent references in the Internet. These answers allow for the conclusion that many of the ethical issues of Nanotechnology are not that new but frequently have already been discussed in other areas (6.5). The most challenging and rather new topic for ethical reflection consists in the field of "improving human performance" which has been brought up in the discussion on "Converging Technologies"

(Roco and Bainbridge 2002). This issue and many of the other ethically relevant developments of Nanotechnology show visionary character. Therefore, it seems to be important to have a look on the use and the consequences of visions from the viewpoint of an ethics of responsibility (6.4). Finally, comments are subsequently made on the role to be played by ethics in the further development of Nanotechnology.

This approach differs considerably from the approaches chosen in the preceding chapters. The point of departure is not defined by the tables of nanotechnological research fields (chapter 3) and the explanations of the entries given there but by the already ongoing ethical discussion and the topics discussed there. This approach has been selected because of the following reasons:

- The entries in the tables are closely related to physical, chemical or biological effects while ethical aspects are related mostly with application fields of such effects and the consequences which might occur there. Therefore, the tables do not provide an ideal starting point for investigating ethical questions.
- Beginning with ongoing ethical discussions of Nanotechnology shows the advantage that we can benefit from results and analyses which have been already made there.

Nevertheless, the tables are also very valuable for the ethical discussion because they allow to establish links between Nanotechnology R&D and ethical reflection. It becomes more transparent which basic effects and processes are related to which application fields (via chapter 3 of this book), and which ethically relevant questions could arise there. To this end, there are links to certain table fields or groups of them included in the following chapter (especially in section 6.2).

6.1 The Relation between Science, Technology and Ethics

In the modern discussion the distinction between factual morals, on the one hand, and ethics as the reflective discipline in cases of moral conflicts or ambiguities on the other has widely been accepted (Gethmann and Sander 1999). This distinction takes into account the plurality of morals in modern society. As long as established traditional moral convictions (e.g. religious ones) are uncontroversial and valid among the relevant actors, and as long as they are sufficient to deal with the respective situation, ethical reflection does not have a relevant objective. Morals are, in fact, the action-guiding maxims and rules of an individual, of a group, or of society. Ethics, on the other hand, concerns itself with the justification of these rules of action, which can lay claim to validity above and beyond the respective, merely particular morals. Individual ideas of the good life, resulting from individual moral conceptions and preferences, have to be assessed, weighed and compared if there are conflicts arising between particular morals. In particular, ethics serves the argumentative management of conflict situations which result out of the actions or plans of actors based on divergent moral conceptions.

In a morally pluralistic society normative aspects of science and technology unavoidably lead to societal debates at the least, often – further – also to conflicts over scientific advance and innovative technologies. As a rule, what is held to be desirable, tolerable, or acceptable is controversial in society. Open questions and conflicts of this type in the context of science and technology are the point of departure for the ethics of technology (Grunwald 1999). Technology conflicts are, in the rule, not only conflicts over technological means (e. g., in questions of efficiency), but are also conflicts over visions of the future, of concepts of humanity, and on views of society (this is in particular the case in Nanotechnology, compare chapter 5 and section 6.4). The role of the ethics of technology in analysis consists of the normative structure of technology conflicts, and in the search for rational, argumentative, and discursive methods of resolving them.

Even if technology is basically beset with values, most of the technically relevant decisions can be classified as the "standard case" in the following sense (Grunwald 2003b): they do not subject the normative aspects of the basis for the decision (criteria, rules or regulations, goals) to specific reflection, but assume them *to be given* for the respective situation, and accept the frame of reference they create. In such cases, no explicit ethical reflection is, as a rule, necessary, even if normative elements self-evidently play a vital role in these decisions – the normative decision criteria are clear, acknowledged, and unequivocal. It is then out of the question that this could be a case of conflict with moral convictions or a situation of normative ambiguity – the information on the normative framework can be integrated into the decision-making process as an axiological information, without analyzing it or deliberating on it. The (national and international) legal regulations, the rules of the relevant institutions (e. g., corporate guidelines), where applicable, the code of ethics of the professional group concerned, as well as general societal usage, are elements of this normative framework.

It was, in fact, controversial for a long time, whether science and engineering have any morally relevant content at all (and could therefore at all be a subject of ethical reflection). Into the 1990s, technology was held to be *value-neutral.* In numerous case studies, however, the normative background of decisions on technology (even those made in the laboratory) has since been recognized and made a subject of reflection (Rapp 1999). The basic assumption of this development is not to see technology solely as a sum of abstract objects or processes, but to take its embeddedness in societal processes seriously (Majer 2002). Technology isn't nature, and doesn't originate of itself, but is consciously produced to certain ends and purposes – namely, to bring something about which would not happen of itself (Weizsäcker 1962). Technology is therefore always embedded in societal goals, problem diagnoses, and action strategies. In this sense, there is no "pure" technology as a technology completely independent of this societal dimension. Technology, therefore, is morally relevant concerning its purposes and goals, the measures and instruments used, and the side-effects evolving. Currently, technology is recognised as an appropriate subject to moral responsibility (Jonas 1979, Durbin 1982) and to ethical reflection (Grunwald 1999). To develop orientational knowledge about the requirement or necessity for ethical reflection in the various steps and processes of research and technology development the question shall be answered which types of decision-making situations can be declared as "standard situations" and which criteria for classifying them in this way may be applied. Following examples may lead to a preliminary understanding of "standard situations":

- Consider an engineer within a typical engineering process working in a team at a laboratory improving some technical features, for example, of an automobile, or improving the quality of materials of some substances, for example designing a special steel to decrease the weight of some automobile components. Engineering activities of this type, so the hypothesis, does not need ethical reflection as long as some conditions are fulfilled (s. below).
- In the management of a company the decision about a new production chain has to be taken. It consists of the choice between two alternatives differing in some technical features, in the cost/benefit-ratio and in some long-term strategic factors. Actors and decision-makers in this type of situation are often or even mostly, so the hypothesis, not obliged to perform ethical reflection – of course, the same as above, only if some conditions are given (s. below).

The most important question behind these examples for assumed spaces free from the necessity for ethical reflection in technology development is, therefore, the question concerning the criteria defining the boundaries for such “standard situations”. If these can be given in a transparent and justified manner it can then be investigated empirically whether the conditions are fulfilled or not. In such a way defining the criteria is a task of ethical reflection itself, reflecting its own limits to practice while the investigation of the fulfilledness has to be performed empirically by means of the social sciences.

Which conditions have to be fulfilled to enable us to identify a specific situation as a standard situation in moral respect? The hypothesis can be, as a proposal, sharpened to the following formulation of a principle (Grunwald 2000b): steps, decisions and processes in shaping technology are free from the demand or necessity for ethical reflection if, and only if, they take place in a “standard situation” with respect to moral issues. A standard situation is given if there is a comprehensive, clear, consistent, commonly accepted and factually followed normative framework, which has to be and factually is followed in the specific context. The requirements to be set on the normative framework in order that it can be accepted as a “standard case” can be operationalized according to the following criteria (Grunwald 2003b):

Comprehensiveness: The norms, principles and customs included in the normative framework must be comprehensive in the sense that they are sufficient to handle the problem under consideration.

Clearness: (a) There shouldn’t be any ambiguity in the understanding of the normative framework between the various persons and groups involved and (b) a clear ascription and distribution of responsiblities among them has to be guaranteed.

Local Consistency: The normativity governing a specific context must avoid contradictions because otherwise no orientation could be derived.

Acceptance: The normative framework must be commonly accepted by the persons or groups involved. This point ensures that a technology developed according to the accepted normative framework should find acceptance, too. The framework must be accepted not as an eternal truth but as some kind of *morale provisoire,* being valid until some change occurs (Hubig 1993).

Compliance: The normative framework must not only be established and commonly accepted but also be followed in practice. This means that laws, regulations, moral codes and customs are, in fact, followed by the participating persons or groups.

The *comprehensive, clear, consistent, commonly accepted and factually acknowledged* normative framework serves as an “axiological information” for people involved in shaping technology. It is constituted by the sum of all action norms, principles or other kinds of customs, generally accepted guiding the concrete actions relevant to shaping technology. In general, the normative framework consists of

- all obligations given by political regulation, such as, to acknowledge environmental or safety standards in designing new technologies and technological systems or other kinds of regulation by law relevant to technology development like waste disposal stipulations;
- all obligations below the level of regulation by law resulting from other societal regulation or quasi-regulation by generally accepted customs or traditions (here the various and presently intensively discussed professionalities‘ "Codes of ethics" can be mentioned as well as the "Hippocratic Oath").

It has to be taken into account very carefully that the ascription "ethics-free" to specific decision situations is valid only relative to the assumed validity of the specific and contextually valid normative framework governing that "standard situation". If, however, questions concerning the validity of this framework have to be dealt with, then explicit ethical reflection is indispensable. This is the case if there are moral ambiguities, ambiguities in the distribution of responsibilities, infringements of regulations or doubts on or insufficiencies of the normative framework. In this way an only seeming paradox emerges: namely that though ethical reflection is – principally – indispensable for "reasonable" technology development, in many situations it may be replaced by referring to a normative framework governing the morals of the problem concerned. This is taking away the burden of reflecting each step in engineering under ethical regard. On the other hand, however, it emphasizes the role of ethics in cases where such a commonly agreed and followed normative framework does not cover all relevant aspects in a sufficient manner.

There are such well-established "standard" situations in many fields (e. g., in decision-making processes in public administration or in private business). Technical innovations and scientific progress, however, can "disturb" such situations by presenting new questions or by shaking views previously held to be valid. Standard situations in modern society are highly fragile (Stehr 2004). It is of great importance but also very difficult to recognise the point of development which denotes the break-down of a standard situation. This is then the "entry point" for ethical reflection in questions of science and engineering, for the explicit confirmation, modification, or augmentation of the normative framework.

Summarising this line of argumentation, we may state: ethical relevant aspects of Nanotechnology arise as soon as the (concrete or hypothetical) developments in Nanotechnology would lead to moral conflicts or ambiguities which could weaken or challenge existing "standard situations" in moral respect.

6.2 Ethically Relevant Fields of Nanotechnology

In practical philosophy and in ethics, Nanotechnology has hitherto seldom been made a subject of discussion. "While the number of publications on NT [*NT = Nanotechnology*; the authors] per se has increased dramatically in recent years there is very little concomitant increase in publications on the ethical and social implications to be found" (Mnyusiwalla et al. 2003, R10). Some postulate a need for ethics (Khushf 2004a) and make reference, above all, to remote visions (for example, the abolition of ageing or "runaway nanorobots", cp. Mnyusiwalla et al. 2003; Weckert 2002). Certain terms, such as privacy, man-machine relationship, or equity are often cited (e. g., Hermeren 2003/2004, Baumgartner 2004). Systematic studies, which could do justice to the diversity and breadth of Nanotechnology, haven't yet been presented, as has also been one of the results of a recent BMBF-funded project: "An independent ethical perception of nanotechnology is currently nearly not recognizable" (Farkas and Monfeld 2004, 49; translation A.G.). At the same time, concern over the detrimental consequences of this deficit grows [NT = nanotechnology]: "The lack of dialogue between research institutes, granting bodies and the public on the implications and directions of NT may have devastating consequences, including public fear and rejection of NT without adequate study of its ethical and social implications" (Mnyusiwalla et al. 2003, R11).

Whether there are new challenges for ethics in Nanotechnology and what they might be will be investigated starting at the systematic point of view which has been elaborated above (6.1). The guiding questions in this study were

- What are the genuine ethical aspects in Nanotechnology?
- Which of them are – in some respect – *new* topics for ethical reasoning?
- Which of the ethical aspects of Nanotechnology are *specific* for Nanotechnology?
- Is relevant and sufficiently evident knowledge available for the assessment of scientific and technical developments in Nanotechnology or of their use, as addressed with regard to ethics?

The results presented below have been derived by a stepwise methodical approach. Firstly, an overview about current discussions has been assembled by literature search and a web recherché in order to identify relevant discussions interrelating "Nanotechnology" and "ethics" (cp. Coffrin and MacDonald 2004). This "raw material" then has been evaluated against the criteria given in section 6.1 in order to identify ethically relevant issues and to answer the above-mentioned questions. Finally, the Nanotechnology tables (chapter 3) have been used as a scheme for identifying possible gaps in the literature available on ethical aspects of Nanotechnology.

This procedure permits a clear determination of the questions to which ethical reflection can make a real contribution. It then also permits an estimation, to which extent an independent "nano-ethics" would be justified. The resulting "map" of ethical aspects described below is a survey of the use of Nanotechnology as regards aspects of content, and includes partially overlapping fields of content. These fields have the fact in common that Nanotechnology will play a constitutive role in the foreseeable advances in their areas.

The current discussion on ethical aspects of Nanotechnology is still rather general. Mostly, it covers Nanotechnology as a whole or focuses on some revolutionary aspects. Concrete and individual applications and their impacts are – with the exception of nanoparticles, compare section 6.2.1 – still not under discussion. In some fields this situation – which is often the usual situation in case a new field of philosophical thought opens up – is changing at the moment (primarily with respect to medical applications of Nanotechnology, cp. Baumgartner 2004 and section 6.2.4). In this chapter, concrete examples for relations of ethical reflections to concrete nanotech developments and applications will be given as far as possible.

6.2.1 Nanoparticles – Chances versus Risks

A vast potential market for nano-based products is seen in the field of new materials (Paschen et al. 2004). By means of an admixture or specific application of nanoparticles, some new properties of materials can be brought about, for instance, in surface treatment. If making new technical functions and performance factors is a common motivation for scientific and technological progress, ethical questions on these advances pose themselves as the "classical" question of the possible *side effects* of these developments. And precisely on this aspect a discussion about possible consequences of nanoparticles for health and ecology has evolved (Paschen et al. 2004).

Artificially produced nanoparticles can be disseminated into the environment or enter the human body as emissions during production or by the daily use of products including nanoparticles. Nanoparticles could eventually be transported as aerosols over great distances and be distributed diffusely. They could enter the human body by way of the lungs, through the skin, or the digestive tract. How they interact in spreading and their effects on health and on the environment, and, in particular, potential long-term effects, are, to the present, almost unknown. This applies also and above all for substances which do not occur in the natural environment, such as fullerenes or nanotubes that have already been discussed in chapter 3. As far as the potential proliferation of nanoparticles is concerned, aspects such as mobility, reactivity, persistence, lung infiltration, solubility in water, etc., have to be taken into consideration (Colvin 2003; Krug et al. 2004; compare section 5.2 in this volume).

Questions of toxicity for the environment and for humans, on nanomaterial flow, on their behaviour in spreading throughout various environmental media, on their rate of degradation, and their consequences for the various conceivable targets are, however, not ethical questions. In these cases, the pertinent scientific disciplines, such as toxicology or environmental chemistry, are competent (Krug et al. 2004; compare chapter 5 in this volume). The possibility of nano-particle risks is not an ethically relevant question *per se.* There are established mechanisms of risk analysis, risk assessment and risk management in many areas of science, medicine, and technology, for example in dealing with new chemicals or pharmaceuticals. Laws like the Toxic Substance Control Act in the United States of America (Wardak 2003) determine what has to be done in the case of risk. Insofar as such mechanisms are able to cover new challenges sufficiently, there is a "standard situation" in moral respect (in the sense of section 6.1). Consequently, ethical reflection is not necessary and the problem under consideration may be faced directly using the established risk regulation measures. However, it might be a problem to judge whether the word "sufficiently" does apply to the situation or not.

Ethics comes into the game as soon as this will be not the case, so that existing risk regulation may be insufficient or inadequate. The main question then is about the applicability of the precautionary principle and its consequences for practical action. The normative (and therefore potentially ethically relevant) aspects of the precautionary principle are (following Schomberg 2004):

- The *political dimension*: should the precautionary principle be applied to a certain political field of action, and which are the criteria for decision-making? The question has to be answered: what does it mean that we have only little knowledge about nano-particles?
- The *epistemic dimension* concerning the validity, reliability, comprehensiveness or uncertainty of the scientific knowledge available and the judgment in corresponding scientific controversies: what can be said about the quality of the knowledge available and the knowledge gaps?
- The *dimension of acceptability*: Which criteria are determining the societal acceptability of certain technological developments or technical products or their side-effects? These criteria must be sufficiently open in order to allow for negotiation, adaptation and modification due to deliberative communication and societal learning processes.

Accordingly, ethical reflection about possible risks by nanoparticles could take place in the following fields:

- What follows out of our present lack of knowledge about the possible toxic side effects of nanoparticles? One radical consequence, namely, a moratorium on putting nanoparticles onto the market, as it would probably follow out of Hans Jonas' ethics of responsibility (Jonas 1979) according to the priority of the negative prognosis in his approach, has already been demanded (ETC-group 2003). Do we have a "sufficient" suspicion that there might be "serious" risks?

- More generally formulated: is the precautionary principle (Harremoes et al. 2002; Schomberg 2004) relevant in view of a lack of knowledge about nanoparticles, and what would follow out of the answer? It should not be forgotten that the application of the precautionary principle does not automatically result from a situation of non-knowledge but rather a plausible and well-founded expectation of possible serious damage should be part of the diagnosis (for the climate problem cp. Schröder et al. 2002).
- Which role do the – doubtlessly considerable – *opportunities* of nanoparticle-based products play in considerations of this sort? Upon which criteria could benefits and hazards be weighed against each other when the benefits are (relatively) concrete, but the hazards are hypothetical?
- Are comparisons of possible risks of nanoparticles to types of risk known from other areas justified, in order to learn from them, and in which respect may they be compared? Can criteria for assessing the nanoparticle-risks be gained from experience in developing new chemicals or medicines? What's about nanoparticles of natural origin like volcano eruptions? Could they be used as a term of reference, analogously to the field of radioactive radiation where sometimes the natural exposition is used as term of reference? We also have to think about artificial nanoparticles from sources like smoking or barbecue (Krug et al. 2004). Which normative premises enter into such comparisons?
- Some voices point to the analogy of artificial nanoparticles created in industry to asbestos: "Some people have asked whether the ultra-small particles and fibres that Nanotechnology produces, such as carbon nanotubes, might become the new asbestos" (Ball 2003). Could we learn something from the asbestos story (Gee and Greenberg 2002), and under which conditions could we transfer that knowledge to the nanoparticle case? Ethics would ask here for the normative criteria of transferring knowledge and building analogies.
- Is the discussion on threshold values and environmental standards (Gethmann/Mittelstraß 1992) transferable to nanoparticles? What about the acceptability or tolerability of risks? Which methods of determining critical values come into question, and how do they relate to ethical questions or questions of democratic theory?

Contribution of ethics to this subject therefore lie in a value judgement of the situation (values involved, possible moral conflicts, applicability of the precautionary principle), in a clarification of the comparability of nanoparticle risks to other types of risk, and in disclosing the normative presuppositions and implications entering into it, as well as in investigating the normative basis for practical consequences. These questions of the acceptability and comparability of risks, the advisability of weighing up risks against opportunities, and the rationality of action under uncertainty are, without doubt, of great importance in Nanotechnology. A new field of application is developing here for the ethics of science and technology, where close cooperation with toxicology on the one and jurisprudence on the other side is necessary; the type of questions posed, however, is not a new one but is well-known from other fields of risk (exposure to radiation; new chemicals; cp. Streffer et al. 2000).

6.2.2 Equity

Possible side effects of Nanotechnology of a completely different type result from considerations of equity. In particular, ethical questions of the *distribution* of the opportunities for the use of as well as the spatial and temporal distribution of the opportunities and risks of Nanotechnology are relevant in connection with the imperative of sustainability (Fleischer 2003):

> *Nanotech offers potential benefits in areas such as biomedicine, clean energy production, safer and cleaner transport and environmental remediation: all areas where it would be of help in developing countries. But it is at present mostly a very high-tech and cost-intensive science, and a lot of the current research is focused on areas of information technology where one can imagine the result being a widening of the gulf between the haves and the have-nots (Mnyusiwalla et al. 2003).*

In respect of the requirements of sustainable development, we have to distinguish between (1) *inter*generational and (2) *intra*generational aspects (Kopfmüller et al. 2001).

The distribution of the use of natural resources between present and future generations belongs to the *intergenerational* aspects. Appreciable relief for the environment is expected from the use of Nanotechnology: savings of material resources, reduction of the incidence of environmentally detrimental by-products, improvement of the efficiency of energy transformation, reduction of energy consumption, and the elimination of ecologically deleterious materials from the environment (s. several of the table fields in section 3.1 and 3.2; Paschen et al. 2004). There is a strong ethical recommendation to perform R&D on the exploitation of these chances for saving natural resources.

Decisive for the assessment of Nanotechnology or, resp., the corresponding product lines, from the viewpoint of ecological sustainability is that technology accumulates positive and negative contributions to sustainability throughout its entire "lifetime", which extends from the primary sources of raw materials via transportation and processing to consumption, and finally ends with their disposal as waste (Fleischer and Grunwald 2002). The entire life cycle of a technology is therefore decisive for the assessment of the technology's sustainability.

Nanotechnology, however, is at present in many branches still in an early phase of development. For this reason, we can only speak of Nanotechnology's *sustainability potentials* (Fleischer 2003), and we could use the knowledge about potentials to orientate the future path of development, asking for the conditions to realise the potentials, or asking for obstacles against the realisation. There is no guarantee that technical sustainability *potentials* will turn out to be real contributions to sustainable development. The discussion of sustainability potentials can, however, be employed constructively with regard to technological development, if further development is accompanied by ethical reflection on questions of distribution between present and future exploitation of nature.

Intragenerational problems of distributive justice present themselves basically in every field of technical innovation. As scientific and technical progress requires considerable investments, it usually takes place where the greatest economic and human resources are already available. Technical progress increases existing inequalities of distribution. This can be illustrated on the example of Nanotechnology in medicine (Fleischer 2003). Nanotechnology-based medicine will, in all probability, be expensive medicine, at least in certain areas. Questions of equity and of access to (possible) medical treatments could become urgent in at least two respects: *within* industrialized societies, existing inequalities in access to medical care could be exacerbated by a highly technicized medicine making use of Nanotechnology, and with regard to less developed societies, because, likewise, already existing – and partially dramatic – inequalities between technicized and developing nations could be still further increased. Apprehensions with regard to both of these types of a potential "nano-divide" (after the well-known "digital divide") are based on the assumption that Nanotechnology can not only lead to new and greater options for individual self-determination (e. g., in the field of medicine), as well as to considerable improvement of the competitiveness of national economies. There are also far-reaching expectations that especially developing countries might benefit from Nanotechnology (Court et al. 2003). Consequently, it has already been postulated to involve developing countries in decisions about the future path of Nanotechnology (Mnyusiwalla et al. 2003). Current discussions on distributive justice on the national and on the international level (in the context of sustainability as well) are therefore likely to gain new relevance with regard to Nanotechnology.

Both of the aspects described above are, however, not really new ethical aspects of technology, but rather intensifications of problems of distribution already rife. Problems of equity principly belong to the ethical aspects of modern technology (Gethmann 2000). Obviously, they express themselves also in the field of Nanotechnology, in parts even in a specific way – but questions of this type have not been brought up by Nanotechnology.

6.2.3 Privacy and Control

Another field regularly mentioned among the ethical aspects of Nanotechnology is the threat to privacy through new monitoring- and control technologies (e.g. EU-Commission 2004; Moor and Weckert 2003; Nanoforum 2004). Nanotechnology offers a range of possibilities for gathering, storing, and distributing personal data to an increasing extent. In the course of miniaturization, a development of sensor and memory technology is conceivable which, unnoticed by its "victim", drastically increases the possibilities for acquiring data (Moor and Weckert 2003; "invisibility of Nanotechnology", Suchmann 2002). Especially the new developments offered resp. promised by nanotechnologies for information storage and retrieval technologies at the nanoscale (compare table 3.2 in section 3.2) point to the necessity of reflecting also possible side-effects and misuse scenarios. Mehta (2002) considered "nano-panopticism" as considerable danger for social trust and involvement of citizens in public life. Furthermore, miniaturization and networking of observation systems could considerably impede present control methods and data protection regulations, or even render them obsolete. For the military, new possibilities for espionage are opened (Altmann et al. 2003). Passive observation of people could, in the distant future, be complemented by actively manipulating them – for instance, if it would be possible to gain direct technical access to their nervous system or brain.

These scenarios are regarded by some to be not only realistic, but even certain: "But what is not speculation is that with the advent of nanotechnology invasions of privacy and unjustified control of others will increase" (Moor and Weckert 2003). Underlying this opinion is an only thinly veiled technological determinism (Ropohl 1982): "When new technology provides us with new tools to investigate and control others we will use them" (Moor and Weckert 2003).

Within the private sphere, health is a particularly sensitive area. The development of small analyzers – the "lab on a chip" (s. section 3.3; table field D1) – can make it possible to compile comprehensive personal diagnoses and prognoses on the basis of personal health data. Stringent standards for data protection and for the protection of privacy therefore have to be set. Without sufficient protection of their private sphere, people are rendered manipulable, their autonomy and freedom of action are called in question (Paschen et al. 2004). The "lab-on-a-chip"-technology cannot only facilitate medical diagnoses but can also make fast and economical comprehensive screening possible (op. cit.). The rapid decoding of complete individual genetic dispositions can come within the reach of normal clinical work or of clinic-external services. Everyone could let him- or herself be tested, for example, for genetic dispositions for certain disorders – or could be urged by his/her employer or insurance company to do so. In this manner, individual persons could find themselves put under social pressure; their freedom of action would be impaired. In addition, it would have to be clarified, how one has to deal with results which possibly depress the patients affected over longer periods of time, fearing the impending outbreak of a serious disease (which possibly never occurs). How to deal with – presumably sometimes considerable – uncertainties of diagnoses is, in this connection, also an important aspect.

Questions of privacy, of monitoring and controlling people are doubtlessly ethically relevant. The current discussions on restricting civil liberties for the sake of combatting terrorism are taking place against a background in which normative criteria play a pivotal role, and in which there are conflicts over this subject. On the other hand, the *political* dimension of these questions stands prominently in the foreground, for instance, on estimations of the immediacy of the danger and on statements on the assumed problem-solving capacity of measures proposed. If it should come to an endangerment of the private sphere through Nanotechnology, the ethical dimension would be more tangible. And nonetheless, it would even in this case be more likely to be kept in the background, while the central discussion would certainly much rather be concerned with the context of data protection, in which we have already gained considerable experience.

But all of these questions of monitoring and of data protection are not posed exclusively by Nanotechnology. Even without Nanotechnology, observation technologies have reached a remarkable stage of development which poses questions on the preservation of the private sphere. Even today, so-called smart tags, based on RFID-technology (Radio Frequency Identification), are being employed for access control, as ticketing, e. g., in public transportation and in logistics. These objects have at present a size of several tenths of a millimetre in each dimension, so that they are practically unnoticeable for the naked eye. Further miniaturization will permit further reduction in size and the addition of more functions – without Nanotechnology being needed –, but Nanotechnology will promote and accelerate these developments.

The ethically relevant questions on a right to know or not to know, on a personal right to certain data, on a right to privacy, as well as the discussions on data protection and on possible undesirable inherent social dynamisms, and, in consequence, of a drastic proliferation of genetic and other tests, have been a central point in the bio- and medical-ethical discussions for quite a while. Nanotechnological innovations can accelerate or facilitate the realization of certain technical possibilities, and therefore increase the urgency of the problematics of the consequences; in this area, however, they do not give rise to qualitatively new ethical questions (cp. in this sense Baumgartner 2004, while Moor and Weckert 2003 contradict this statement).

6.2.4 Medical Applications

With the help of Nanotechnology-based diagnostic instruments, diseases or predispositions for diseases could possibly be discovered earlier than at present. Through development of the “lab-on-a-chip”-technology, the emerging tendency towards personalised medicine would be further promoted. In therapy, there is the prospect, with the help of Nanotechnology, to develop targeted treatments free of side effects. The broad use of nanoparticle-dosage systems could lead to progress in medicinal treatment. Through nanotechnological methods, the biocompatibility of artificial implants can be improved. Drug-delivery systems could considerably enhance the efficiency of medication and minimise side-effects.

> *Although many of the ideas developed in nanomedicine might seem to be in the realm of science fiction, only a few more steps are needed to make them come true, so the ‘time-to-market’ of these technologies will not be as long as it seems today. Nanotechnology will soon allow many diseases to be monitored, diagnosed and treated in a minimally invasive way and it thus holds great promise of improving health and prolonging life. Whereas molecular or personalised medicine will bring better diagnosis and prevention of disease, nanomedicine might very well be the next breakthrough in the treatment of disease (Kralj and Pavelic 2003:1012).*

Addressing symptoms more efficiently or detecting early onsets of diseases – which is promised by research on systems biology, especially towards a far better and quantitative understanding of how cells work and how molecular components in cells interact with each other and how they are organized into functional modules for doing discrete tasks (s. section 3.3) – is undoubtfully recommended by ethics. These potentials are so remarkable that ethical reflection almost seems to be superfluous – if one looks solely at the potentials. A comprehensive analysis, however, has to include – as noted above – also possible side-effects, especially risks. There is probably no field of science in which dealing with risks is so natural and so reliable as in medicine and pharmaceutics. In medical research, it is a self-evident fact that new medicinal treatments involve risks, and that, for that reason, at first often animal experiments, then experiments with human volunteers are carried out. For new medicines, there are established and officially supervised approval procedures. Advances in medicine (diagnosis and therapy) are evidently related with risks, and there are a lot of established mechanisms for dealing with them. Therefore, this is a “standard situation” in the above-mentioned sense. Against this background it seems to be not probable that direct applications of Nanotechnology for medical purposes (for example, drug delivery, compare section 3.3) might lead to completely new ethical questions (cp. in this sense also Farkas and Monfeld 2004 on the basis of an expert survey).

However, new types of responsibility and new tasks for weighing pros and cons might occur. New forms of drug delivery based on Nanotechnology (using fullerenes, nanostructured membrans, gold nanoshells, dendrimers, for example; s. section 3.3) could also have consequences which are not expected and might not be welcome. According to the present knowledge, however, there are no indications that such side-effects would endanger the whole line of developments. Of course, careful observations of the advance of knowledge and early investigations of possible side-effects have to be conducted. HTA (Health Technology Assessment) offers several established approaches for early warning.

In this sense, the use of Nanotechnology in medical applications seems to be a "standard situation" in the sense of section 6.1. The boundaries of such "standard situation" would, however, be transgressed in some more visionary scenarios as in the vision of longevity or the abolition of ageing. Nanotechnology could, in connection with biotechnology and, perhaps, neurophysiology, build the technological basis for realising such visions. Some writers assume that we will become "posthumans" with our minds uploaded into computers, our bodies becoming redundant, and we would gain real immortality (Broderick 2001). In this respect, the idea has been proposed that nano-machines in the human body could permanently monitor all biological functions and could, in case of dysfunction, damage or violation, intervene and re-establish the "correct" status. Thus, an optimal health status could be sustained permanently (Drexler 1986) which could considerably enlarge human lifespan. Such methods, however, would require dramatic technological progress (Paschen et al. 2004). According to the state of present knowledge neither a prediction of the time needed for such developments nor an assessment of their feasibility at all can seriously be given.

Besides the speculative nature of such visions ethical reflection has already been started (Moor and Weckert 2003). Surprisingly, the realisation of the vision of slowing down or stopping ageing is taken as given. The authors think about the question what quality of life could mean in a society where humans can expect a lifespan of 500, 5000 or 50.000 years. Considering the postulate of "pragmatic relevance" of ethical thought (section 6.1), such reflections merely seem to be an artificial intellectual game. The "ethics first" perspective is exaggerated to an extent so that any relevance will be lost.

Summing up, in the field of medical applications of Nanotechnology there are, regarded from the standpoint of today's knowledge, no ethical concerns which are specifically related with the use of Nanotechnology. There are a lot of positive potentials which probably also will bear risks – theses risks, however, might be dealt with by "standard" measures of risk analysis and management in medical practice (Baumgartner 2004). However, things might change in the further future (for example, if there would be a shift from the classical medical viewpoint to the perspective of "enhancing" human performance, s. section 6.2.6 below).

6.2.5 Crossing the Border between Technology and Life

Basic life processes take place on a nano-scale, because life's essential building-blocks (such as proteins, for instance) have precisely this size. By means of nanobiotechnology (VDI 2002; Roco and Bainbridge 2002), biological processes are made nanotechnologically controllable. Molecular "factories" (mitochondria) and "transport systems", which play an essential role in cellular metabolism, can be models for controllable bio-nanomachines (s. section 3.3). Nanotechnology on this level could permit the "engineering" of cells. An intermeshing of natural biological processes with technical processes seems to be conceivable. The classical barrier between technology and life is increasingly being breached, resp., crossed. In classical mechanics' language One speaks of elements of living organisms: as factories, rotors, pumps, and reactors. Prominent examples of biological mechanical motors are rotation systems like the F_1-ATPase or the bacteria flagella motor and "walking" systems like dynein protein complexes transporting cargo along microtubules in cells (s. section 3.3). Several of those biological systems have already been implemented on artificial platforms to investigate and even to profit from their motions.

This is, at first glance, a cognitively and technically extremely interesting process, with a great deal of promise. The technical design of life processes on the cellular level, direct links and new interfaces between organisms and technical systems – all of this portends a new scientific and technological field with a high rate of dynamics. Diverse opportunities, above all, in the field of medicine, stimulate research and research funding (Paschen et al. 2004).

New ethical aspects are certainly to be expected in this field. Their concrete specification, however, will only be possible when research and development can give more precise information on fields of application and products. The corresponding discussions of risks could have structural similarities to the discussion on genetically modified organisms. Discussions about safety standards for the research concerned, about the risks of experiments outside the laboratories, and release problems could arise. The danger of misuse will be made a topic of debate, such as, for example, technically modifying viruses in order to produce new biological weapons. A wide range of future ethical discussions is opening, for which at present there is insufficient practical background for concreter reflections. In this field of Nanotechnology (not in that of the nanoparticles, compare section 6.2.1 above), similar developments concerning resistance in society could be feared as in the case of genetic engineering (s. section 5.3 and 6.3 for this analogy and its problems).

A special and practically as well as ethically interesting area consists in making direct connections between technical systems and the human nervous system. There is intensive work on connecting the world of molecular biology with that of technology. An interesting field of development is nanoelectronic neuro-implants (neurobionics), which compensate damage to sensory organs, or to the nervous system, or increase the performance capacity of these organs and broaden the spectrum of human perception. Microimplants could restore the functions of hearing and eyesight. Even today, simple cochlear or retina implants, for example, can be realized. With progress in nanoinformatics, these implants could approach the smallness and capabilities of natural systems. Because of these undoubtedly positive goals, ethical reflection could, in this case, concentrate above all on the definition and prevention of misuse. Technical access to the nervous system, because of the possibilities for manipulation and control it opens, is a particularly sensitive issue.

Extrapolating these lines of development into the realm of speculation, the convergence of technology and humanity, the conceivability (in the sense of a pure thought possibility) of "cyborgs" as technically enhanced humans or humanoid technology could be problematized (s. section 6.4). Developments of this type raise the question of humanity's self-concept and are of extremely high ethical relevance. In nanotechnological visions, aspects repeatedly occur which blur the boundary between what human beings are and what they create with the help of technical achievements and applications. The "Foresight Institute" and the "extropian movement" have developed futuristic visions which include the possibility of the technological storage of human consciousness. Furthermore, some researchers who participate in the National Nanotechnology Initiative (NNI) of the United States assume that artificial brains might be created within the next 25 years (Cauller and Penz 2002). Such visions pose the question, to which extent even technically or partly technically, partly biologically constructed man-machine chimeras can lay claim to the status of a person. An entire spectrum of anthropological and ethical questions follows out of this aspect. In some US-American churches precisely this aspect of Nanotechnology is a central theme, too – from the opposite point of view compared to the Transhumanism discussion: "When GOD fashioned man and woman he called his creation very good. Transhumanists say that, by manipulating our bodies with microscopic tools, we can do better. Are we ready for the great debate?" (Hook 2004). Nanotechnology currently acts as a playing-field on which various philosophies of life compete.

In spite of the speculative nature of the subject, ethical reflection doesn't seem to be premature. One need not see the main concentration of Nanotechnology's ethical aspects in this area, but one can certainly find enough indications that scientific and technical progress will intensify the – at present non-existent – urgency of these questions in the coming years. In particular, advances in brain science and developments in "converging technologies" (Roco and Brainbridge 2002) lead to this expectation – and would justify ethical reflection "in advance". But the insight that the questions raised are not really specific for Nanotechnology also applies here. Since the 1980s, these subjects have been repeatedly discussed in the debates on artificial intelligence and on artificial life (e.g. Christaller et al. 2001 for the case of autonomous robots).

6.2.6 Improving Human Performance by Converging Technologies

With the transgression of the boundary between technology and living beings from both sides (s. section 3.3), our understanding of what distinguishes human beings and which relationship mankind assumes to its natural physical and psychic constitution, is also called into question. Well in the tradition of technical progress, which has, at all times, transformed conditions and developments which, until then, had been taken as given, unalterable fate (not standing at our disposition) into influenceable, manipulable, and formable conditions and developments, the human body and its psyche are rapidly moving into the dimension of the Formable. The vision of "enhancing human performance" has been conjured up, above all, in the field of "converging technologies":

> *Rapid advances in convergent technologies have the potential to enhance both human performance and the nation's productivity. Examples of payoff will include improving work efficiency and learning, enhancing individual sensory and cognitive capacities, revolutionary changes in healthcare, improving both, individual and group efficiency, highly effective communication techniques including brain to brain interaction, perfecting human-machine interfaces including neuromorphic engineering for industrial and personal use, enhancing human capabilities for defence purposes, reaching sustainable development using NBIC tools, and ameliorating the physical and cognitive decline that is common to the aging mind (Roco and Bainbridge 2002:1).*

If the wish to "improve humanity" – probably in view of the experience of the cultural and social deficits of "real human beings" – has been often expressed in history, the approach of bringing about these improvements by technical means – assuming that this is realizable – is apparently new (science fiction, as a rule, does not lay any claim to future realizability). Formerly, improvement utopias were founded rather on the basis of "soft" methods – above all, upbringing and education. Technology had its place outside of human beings, as a means of augmenting mankind's capacities for action. Technical enhancement of human beings themselves – if this would be possible at all – would in any case pose a series of new ethical questions.

Nanotechnology, in combination with biotechnology and medicine (s. section 3.3 for ongoing research activities in these fields) opens perspectives for fundamentally altering and rebuilding the human body. At present, research is being done on tissue and organ substitution (s. the descriptions of bioinspired engineering, biomineralisation and tissue engineering in section 3.3), which could be realized with the help of the nano- and stem cell technologies. Nanoimplants would be able to restore human sensory functions or to complement them, but they would also be able to influence the central nervous system. While the examples of medical applications of Nanotechnology cited remain within a certain traditional framework – because the purpose consists in "healing" and in "repairing" deviations from an (ideal) condition of health, which is a classical medical goal – here, chances (or risks) of a remodelling and "improvement" of the human body are opened up. This could mean extending human physical capabilities, e. g., to new sensory functions (for example, broadening the electromagnetic spectrum the eye is able to perceive). It could, however, also – by means of the direct connection of technical information storage systems with the human brain – give rise to completely new interfaces between man and machine, with completely unforeseeable consequences. Even completely technical organs and parts of the body (or even entire bodies) are being discussed, which, in comparison with biological organisms, are supposed to have advantages such as – perhaps – increased stability against external influences (Paschen et al. 2004).

There are, for the first, anthropological questions of our concept of humanity and of the relationship between humanity and technology (Baumgartner 2004). With them, however, and at the same time, the question poses itself, how far human beings *can*, *should*, or *want to* go in remodelling the human body. The difference between healing and enhancing interventions is on conceptual grounds – especially the terms "health" and "illness" have not been clarified to date – and for practical reasons, gradual (Habermas 2001). Possible answers would probably be controversial in a pluralistic society – indicating that this situation would be far away from being a "standard situation" in moral respect (section 6.1).

The improvement of mankind could also include the – to a great extent – postponement of death. According to the definition of health formulated by the World Health Organization (WHO), according to which health is a "state of complete physical, mental, and social well-being, and not merely the absence of disease or infirmity" (Charter of the WHO), aging could also be interpreted as a disorder. Overcoming aging with the help of Nanotechnology would, then, in the sense of medical ethics, be nothing other than fighting epidemics or other diseases. Aging "as a disease" would be combatted medically as if it were the flu. Seen against the background of continuing and controversial discussions on the concept of illness in medical theory and in medical ethics, this is, however, not undisputed. Whether aging as a process and death are, in principle, acknowledged as a predetermined initial condition of human existence, and should only be made subject to medical treatment in their extreme expression, or whether aging and death are seen as conditions which are, whenever possible, to be abolished, depends on fundamental normative presuppositions, which, in view of the conflicts connected with them, are of great ethical relevance (Moor and Weckert 2003).

Possible answers from ethics could, according to the respective school of thought, turn out quite differently. Liberal eugenics based on utilitarian ethics could draw the conclusion that it doesn't acknowledge any difference between therapeutic and enhancing interventions and leave "the choice of purposes of interventions which alter characteristic traits to individual preferences" (Habermas 2001), Kantian ethics would thematize the instrumentalization of human beings, religious morals would bring traditional human self-concepts (which are deeply rooted in culture) as a limited being (in time as well) to bear (Hook 2004).

The practical relevance of such ethical questions in view of a – at least in the eyes of some protagonists – possible technical improvement of human beings (with the substantial participation of Nanotechnology) may, at first sight, seem limited. Two considerations, however, contest this estimation: first, the vision of the technical enhancement of human beings is actually being seriously advocated. Research projects are being planned in this direction, and milestones for reaching this goal are being set up (NBIC, Roco and Bainbridge 2002), whereby Nanotechnology takes on the role of an "enabling technology" (Fleischer 2003). Furthermore, technical enhancements are by no means completely new, but are – at least in rudiments – actually established, as the example of plastic surgery as a technical correction of physical characteristics felt to be imperfections shows, and as is the case in the practice of administering psycho-active substances. It isn't difficult to prognosticate that the possibilities and the realization of technical improvements of human beings will increase; demand is conceivable. In view of the moral questions connected with this development and of their conflict potential, ethical reflection is needed in this field which seems to be the Nanotechnology research area with the highest degree of ethical questions involved (Khushf 2004b).

6.3 Are there Indicators for an Ethically Motivated Objection of Nanotechnology?

Some promoters or proponents of Nanotechnology and also parts of the community are afraid that there might be an upcoming, broad objection against Nanotechnology in the public or in large parts of the population. Such broad objections could have several motivations, moral reasons being one of them. As could be observed in the case of GMO, moral arguments played and still play an important role. Positions coming from religions like "humans should not take the role of God" or other moral convictions like the suspicion of human hybris have been put forward in the GMO debate. The question has already been raised whether there might emerge a similar movement objecting Nanotechnology. According to the preceding broad analysis of ethical aspects of Nanotechnology based on an overview on literature and Internet debates, it will be tried here to give an answer to this question. In a first step it is necessary to give an interpretation of the overall picture of the state of the debate on moral and ethical aspects of Nanotechnology. The following aspects seem to be of some importance in this respect:

- moral problems of Nanotechnology are currently discussed in very heterogeneous fields, like risk, privacy, equity, and human enhancement (sections 6.2.1-6.2.6);
- nearly all of the currently discussed ethical aspects of science and technology are touched in these debates;
- the types of arguments put forward (pro and con) also cover a wide range (from the sustainability discussion to anthropological discourse, from political philosophy to medical ethics, etc.);
- there are no completely new moral topics and arguments to be discussed but rather the concerns and issues dealt with already have had a longer or shorter history in preceding debates on impacts of the scientific and technological advance (like the Artificial Intelligence debate, the equity debate or the privacy debate);
- the degree of specificity to Nanotechnology is, in many cases, rather small. Mostly, technological developments behind the moral challenges are accelerated by Nanotechnology with the consequence that moral challenges become gradually more urgent.

In this situation, a fundamental objection against Nanotechnology, based on moral convictions, cannot be recognised. There is no "core argument" against Nanotechnology which would be necessary to catalyst a broader movement. Such dramatic and singular technological interventions into society and nature as the Hiroshima bomb or the Cernobyl accident will not be related with Nanotechnology. Also the secular dimension of the technical possibility of manipulating the human genome cannot be reached by Nanotechnology (except in some of the more futuristic visions, but that is a different topic, s. section 6.4). Such singular events or revolutionary developments (revolutionary with respect to human self-understanding, not to economic factors) show the potential to create great movements, proponents as well as opponents. The debates show, however, that Nanotechnology – up to now – does not have this secular dimension – in spite of the fact that many people talk about its revolutionary character. With regard to the question for a possible objection against Nanotechnology on the basis of moral convictions this means that the heterogeneity of Nanotechnology – many people prefer to speak about nanotechnologies – *protects, in a certain sense, against coherent objection*, focussed on one specific line of argumentation.

At the core of Nanotechnology is the ability to technically manipulate matter at the level of atoms and molecules (Nordmann 2003). At this level of abstraction such an activity seems to be morally irrelevant: atoms and molecules cannot claim special moral rights. An argumentation structure analogously to the field of stem cells, where the ethical discussion focuses on the moral status of stem cells, seems to be unthinkable in Nanotechnology: there is no moral status of atoms and molecules. This situation seems to be the main difference to other discussions in society and ethics, and it could prevent Nanotechnology against objection movements based on this kind of argumentation. Going beyond this level of abstraction, then immediately "the" Nanotechnology" separates into many "nanotechnologies" (look at the tables in chapter 3) with all different moral aspects and ethical discussions where there seems to be no longer a focus for a coherent ethically motivated objection of the entire Nanotechnology.

This result should not lead to ignoring social debates around moral aspects of nanotechnologies or to judging them as of minor importance. The many and engaged debates about societal and moral aspects of Nanotechnology show a high degree of uneasiness among the population with the high innovation rate of Nanotechnology and, perhaps, also with the many proclamations of the revolutionary nature of Nanotechnology. Also some mistrust against science and technology as a whole, against the possibilities of politics to ensuring safety and social compatibility can be derived from the discussions. Such uneasiness is no objection but a call for more open debate, more explanation and more deliberation. However, uneasiness could develop into opposition if it would not be taken seriously.

6.4 Ethical Vision Assessment

The point of departure of this section consists of an observation in the societal debate on science and technology of the last years. The career of Nanotechnology as a metaphor for revolutionary advance of science in general and as an important issue in societal debate is related, according to this observation with a specific role of visions. Visions emerging from nanotechnological advance or from expectations concerning the convergence of Nanotechnology and other technology fields like biotechnology, cogno-science and information technology (NBIC, Roco/Bainbridge 2002) have been put forward by visionary scientists and by science managers.

Mid-term and long-term visions have, in general, been of increasing importance in the scientific, political and public debates on future technologies in the last years, for example in highly dynamic fields of scientific research and innovative technology like stem cell research, brain research or Nanotechnology. In contrast compared to the discussion on *Leitbilder* and "guiding visions" in the 1990s (Dierkes et al. 1992; Grin/Grunwald 2000), we are now witnessing a growing use and relevance of more speculative and longer-term visions (positive expectations and fears, cp. Coenen 2004). In this paper, we will call those visions "futuristic". Futuristic visions can be separated in technical visions and in visions for society or humankind which often are mixed up but would have to be analysed differently by TA. Some examples of more scientific-technical visions from the fields of Nanotechnology and nano-biotechnology are the famous "replicators", the vision of molecular assemblers enabling engineering at the level of atoms, or nano-bionic visions. Dramatic and deep-ranging changes in society are seen by some visionary scientists and science writers. In economic respect Nanotechnology might be the basic technology for the 3rd industrial revolution. Expectations have been expressed that Nanotechnology could allow for much more longevity of humans, up to an abolition of ageing – which would be one of the more radical societal visions. Other visions have been put forward in the context of "converging technologies", considering the vision of "enhancing human performance" (s. section 6.2.6 above). A new paradise has been announced:

> *People will possess entirely new capabilities for relations with each other, with machines, and with the institutions of civilisation. […] Perhaps wholly new ethical principles will govern in areas of radical technological advance, such as the routine acceptance of brain implants, political rights for robots, and the ambiguity of death in an era when people upload aspects of their personalities to the Solar System Wide Web. With proper attention to safeguards, ethical issues and societal needs, quality of life could increase significantly (Roco/Bainbridge 2002:19).*

The importance of futuristic visions in ongoing debates – in the debate on the chances of scientific-technological advance as well as in the ongoing risk debate, compare sections 5.3 and 5.4 – is the main argument for postulating an early vision assessment in order to allow for more rationality, reflexivity, and transparency in these debates (Grunwald 2004 for the case of vision assessment as part of technology assessment). This rough analysis emphasises the importance of an early assessment of such visions in ethical regard, in order to allow for more transparent discussions about the premises, especially about the normative content and about potentials for moral conflicts. Such ethical vision assessment will also have to tackle the "pragmatics" of dealing with futuristic visions: in which way do such visions emerge, which role do they play in the communication between science, politics, and society, which consequences and impacts might their use show, including non-intended consequences, and what does this mean in terms of *responsibly* dealing with such futuristic visions, according to a code of conduct or established standards of good scientific practice. Obviously, this issue can, in the framework of this chapter, only be sketched in a brief and programmatic way.

6.4.1 The Need for an Early Vision Assessment

Mid-term and long-term ("futuristic") visions have been of increasing importance in scientific, political and public debates on future technologies in the last years, the best example being Nanotechnology. Occupation with such futuristic visions, speculations and risks is not only sensible, but necessary. While their content often is near to fictions and might be rather far away from facts it is a fact that visions can have real impact on scientific and public discussions. We have to distinguish between the degree of facticity of the content of the visions and the fact that they are used in real communication processes with their own dynamics. Even a vision without any facticity at all might cause real impact on debates, on opinion-forming, on acceptance, and even on decision-making.

Sometimes futuristic visions are instrumentalized to create public acceptance and political support (Paschen et al. 2004). Negative visions, however, could be used to mobilise resistance against specific technologies. The factual impact of visions on public and political debate is the strongest argument in favour of stating a need for vision assessment, including ethically relevant aspects. Futuristic visions are of high relevance for technology assessment, ethical discussion and risk communication because:

- they have great impact on the way in which the political and the public debates on future technologies are currently conducted, and they will probably also have a great impact on the results of those debates – and they will, therefore, considerably influence the pathways to the future;
- the societal and public debate about chances and risks of new technologies will be structured around those visions to a considerable extent (as is currently the case in the field of Nanotechnology, cp. Paschen et al. 2004);

- they motivate and enable public debate because the impact of those visions on everyday life and the future of social areas like military, work or health care is obvious;
- facts and values are mixed up in futuristic visions which forms an obstacle to a transparent discussion;
- therefore, futuristic visions might be easily instrumentalised in public debate;
- visions show – in spite of their speculative nature – *possible* paths of future technology developments and their impacts on society and individuals which have to be scrutinised carefully;
- they provide some insights into the ways scientists and engineers are thinking about their products, developments, and perspectives.

Therefore, new methodical approaches are needed to analyse and assess such futuristic visions, especially their reliability, their degree of reality and expectability, their normative aspects and their impact on public and political debate (Grunwald 2004).

6.4.2 Characteristics of Futuristic Visions

An established category of future technology projections are the *Leitbilder* in the sense of the "Leitbild assessment" (Dierkes et al. 1992). Leitbilder (or guiding visions) are more technical in nature and close to ongoing technological development. They show a close relation with designing, planning and implementing new technologies, they are more or less "realistic" and do not cover such a large time frame. Two examples are:

- the paperless office, a vision closely related to the advance in information and communication technologies which assumed that digital communication and data storage could considerably reduce the need for printouts (in a certain sense, a reasonable and imaginable idea, in spite of the fact that it has been proven false in the meantime);
- the city designed to the needs of the automobile which has been a vision in urban planning in the 1960s (we all can observe realisations of this Leitbild in many European and American cities – often wishing that this vision should not have been that successful).

On the other side, we are familiar with radical and "fantastic" visions without any claim for feasibility. SF in literature and TV brought up a large set of fantastic technologies. The famous "beaming" as a means for transport of human beings, used in the TV series "Enterprise" or utopian technologies for inter-galactical spacecrafts or SF types of weapons for "Star Wars" are fictions, well-known to the broader public. There is, however, no relation to ongoing technology developments science and technology in these fields, neither a motivation for a scientific analysis nor for reflections on the impacts (chances and risks) of those fictionary technologies.

The visions of the new type ("futuristic visions") show aspects from SF as well as from *Leitbilder*. They include long-term, utopian aspects as well as the claim for feasibility by scientific and technological means: "Although many of the ideas developed in nano-medicine might seem to be in the realm of science fiction, only a few more steps are needed to make them come true, so the ´time-to-market` of these technologies will not be as long as it seems today" (Kralj/Pavelic 2003:1012). Accordingly, futuristic visions in the sense of this paper are intermediate between *Leitbilder* and SF. They are describing specific *hybrids* between facts and fictions (Schmidt 2003) – this situation asks for new analysis and assessment methods. The following hierarchy of future-oriented notions is proposed:

- fantastic visions: SF ideas without serious claim for feasibility;
- futuristic visions: far-reaching and futuristic technological or societal prospects with claim for feasibility but with a high degree of uncertainty;
- *Leitbilder* or "guiding visions": more technical and plannable technological futures and
- goals as concrete aims for technology development or science and technology policy and political programmes.

A rather important distinction may consist of the degree of facticity of the different types of visions: very low or not existing at all in the fantastic case, plausible with good reasons in the case of aims and goals with some steps in between. Futuristic visions claim to show some aspects of "fact" and reliable knowledge but also include large parts of fiction. There is no sharp borderline between fantastic, futuristic and guiding visions. The following characteristics may, however, illustrate the specific nature of futuristic visions:

- futuristic visions are referring to the more distant future of at least one but mostly of some decades;
- they show revolutionary aspects in technological respect as well as in terms of culture, human behaviour, individual and social issues (compare the issue of "enhancing human performance", section 6.2.6);
- the driving factors of the developments outlined in the visions are scientific and technological advances (compare the NSF report on Converging Technologies which sees science and technology not only as main drivers of societal evolution but, a fortiori, as the *only* drivers while society only can react;
- the authors of the visions are scientists, science writers and science managers;
- futuristic visions are showing *normative* aspects (the developments proposed *shall* come into reality, according to the author's convictions) as well as *predictive* aspects (following the convictions of the proponents, they *will* come into reality);

- futuristic visions are claiming feasibility which is demonstrated by giving milestones bridging the gap between today's state and the visionary future state. In the study on convergent technologies (Roco and Bainbridge 2002) milestones have explicitly been used to relate the future ideas to the current agenda of the sciences. Some of them are:

  > *Fast, broad-bandwidth interfaces directly between the human brain and machines will transform work in factories, control of automobiles, ensure superiority of military vehicles, and enable new sports, art forms and modes of interaction between people; Robots and software agents will be far more useful for human beings, because they will operate on principles of human goals, awareness and personality; The human body will be more durable, healthy, energetic, easier to repair, and resistant to many kinds of stress, biological threat and aging process (Roco and Bainbridge 2002:4ff.).*

- these milestones are also relating the visions with the current agenda of affected scientific disciplines and show the factual involvement of scientists and engineers in realising the visions;
- therefore, there is, in spite of the long-term nature of the visions, relevance to the current scientific agenda claimed;
- all of these projections are showing a high degree of uncertainty;
- especially, often there is no consensus among the scientists themselves about the feasibility of the visionary technologies (cp. the Smalley/Drexler-debate).

It is essential for futuristic visions that future feasibility is claimed and that reasons for this assumption are given. To argue in favour of feasibility requires bridging the gap between the current state of knowledge and skills on the one hand, and the knowledge and skills needed to realise those visions on the other. To this end it is familiar in the engineering sciences to propose milestones which are demarcating intermediate steps between today and the future. By using milestones, a kind of roadmap for the way to realising the visions is given (cp. Roco and Bainbridge 2002 for NBIC).

6.4.3 Vision Assessment with Respect to Ethical Issues

Vision assessment can be divided analytically in several steps which are not sharply separated and not linearly ordered but which serve different subobjectives and involve different methods (cp. Grin et al. 2000; Grunwald 2004). These steps are vision *analysis* which itself separates into a *substantial* part (what is the content of the respective vision?) and a pragmatic part (in which way is it used in concrete communication?), the vision *evaluation* (in which way could the content of the vision be evaluated and judged?) and the vision *management* (in which way should the persons and groups affected deal with the visions?). Vision assessment with regard to ethical questions will follow the general scheme proposed but probably focus on specific steps. At this point – ethical vision assessment only being a programmatic idea – it seems not adequate to already establish an own procedure, separated from the proposed procedure in more general vision assessment (Grunwald 2004). This should be task of subsequent case studies.

(1) Vision Analysis: what is the content of the visions and how are they used in social communication? In answering these questions the following subtasks will play a role:

- empirical investigation of the visions used in the debates (by recurring on established techniques like discourse analysis and expert interviews);
- analysis of the differences between alternative visions;
- analysis of the roles of science and technology on the one hand and of societal advance on the other in the respective visions;
- identification of the basic features of the desired final state, denoted in the respective visions;
- identification of relevant experts: a broad range of experts should be involved who are able to shed light on a particular technology from various angles, and not the limited set of experts who are directly involved in developing and using technology;
- investigation of the actors involved and establishing a "map" of the debate (by established methods of empirical social sciences);
- investigation of the roles of scientists and science managers and identification of possible expert dilemmas (intermediate visions are created and promoted by science and technology itself, not "co-shaped" in an interactive way as has been regarded as an ideal point of departure for social shaping of technology (Grin/Grunwald 2000);
- analysis of the strategic instruments used by the actors to influence public debate via long-term visions.

(2) Vision Evaluation: how to judge visions according to their cognitive and ethical content. In answering this question the following subtasks will play a role:

- analysis of the direct and indirect origins of the vision (is it a traditional vision in new clothes, does it have deep cultural or religious backgrounds etc.);
- uncovering and discussing underlying assumptions and premises, especially moral pre-occupations and convictions, imaginations of future society, positions concerning human self-understanding; comprehensive analysis of the moral and ethical status of the visions;
- analysis of the epistemological status of the visions (what can be said about their degree of "cognitive rationality", where is the borderline between the fictionary and the more reliable elements of the visions);
- investigation of the degree of uncertainty involved in the visions themselves but also in the analyses of the visions;
- analysis of possible divergent expert opinions on the assessment of visions with respect to different underlying assumptions and values.

(3) Vision Management: how to deal "rationally" with visions?

- Identify stakeholders apart from those who push visions forward. This is one of the basic questions in technology assessment, and one that has not been resolved satisfactorily up to now (Grin et al. 2000).
- Discuss alternatives: Discuss standards of performance and criteria of merit, as well as methods to assess these standards and criteria. Thus one sheds lights on various dimensions of the problem definition. Different visions possibly entail different problem definitions and different ways to assess proposed solutions (Grin et al. 2000).
- Compare objects central to the vision with alternative ones, perhaps with alternatives that fit more naturally in alternative visions, is a way to get stakeholder perspectives to the surface. This of course refers to the empirical and normative assumptions from which stakeholders look upon reality and set the problem. Visions may fundamentally differ from each other on that level.
- Vision communication: Discuss the relations between a technological artefact and the human and procedural factors that are envisaged to form its application context. This, of course, uncovers assumptions concerning the degree to, and the conditions under which technology may contribute to solving societal problems.
- Maximise the transparency for supporting democratic debate.
- Ensure reflectivity: communicate not only the vision but also the "meta-knowledge" about the visions (results from steps 1 and 2).
- At this point only the question may be raised: Do we need "Codes of Conduct" for Vision Communication? Vision communication might be misused or used for short-ranged goals which could hinder longer-term goals. It is risky to promise too much because of frustration disappointment afterwards.

Currently, this approach – which is a relatively general one despite the fact that its motivation has been the use of futuristic visions on the field of Nanotechnology – is being applied to concrete examples in the field of Nanotechnology (Fiedeler et al. 2005).

6.4.4 Responsibly Handling Futuristic Visions

Visions are an established (and perhaps, in some respect, necessary) part of the scientific and technological progress. In general, they shall

- create fascination and motivations among the public but also in science;
- create or increase public awareness on specific research fields;
- help motivating young people to choose science and technology as fields of education and career;
- help gaining acceptance in the political system and in society for public funding;

- motivate colleagues from other scientific disciplines to engage themselves in new fields;
- contribute to forming a broad movement in science to address new fields of research and development.

In this way, visions are a usual part of communication in science as well as between science and society. However, inevitably there is also an ambivalent nature of futuristic visions. Revolutionary changes and developments towards completely new technologies do not only create fascination and motivation but also concern, fear, or objection. Traditional convictions and values could be challenged and existing societal structures could radically change. There might be, in the course of time, winners as well as losers, there might be unexpected and possibly negative consequences, and, in any case, there will be a large degree of uncertainty. Revolutionary prospects do not automatically lead to positive associations but might cause negative reactions. Using futuristic visions might, as a consequence, lead to a backlash and rejection instead of fascination and acceptance: "Tough, omnivorous ´bacteria` could out-compete real bacteria: they could spread like blowing pollen, replicate swiftly, and reduce the biosphere to dust in a matter of days" (Drexler 1986:172). Recent discussions in Nanotechnology (Joy 2001) are an excellent example for such "risks" of vision communication.

Therefore, positive visions could be re-interpreted as negative ones at the same time, hopes of some people may be fears of others, and judgments may change over time. Besides the positive visions of "enhancing human performance" or goals like treating diseases new fears arise: the concerns of Bill Joy (*Why the future doesn't need us*, 2002) may be interpreted as the "dark side" of the "New Renaissance" expected in the Convergent Technologies debate. Many of the more technical visions also show such "dark aspects": "Replicators can be more potent than nuclear weapons: to devastate Earth with bombs would require masses of exotic hardware and rare isotopes, but to destroy all life with replicators would require only a single speck made of ordinary elements." (Drexler 1986:174). Also warnings have been put forward against mankind's presumptuousness in wanting to improve the physical or psychic endowments predetermined by nature (as in the program of the "converging technologies"). Specific concerns are expressed about blurring the boundaries between humans and technology on the basis of new interfaces between technical systems and the human organism (cyborg discussion) made possible by Nanotechnology, for example in the direction that such developments might allow more technological control over humans. The more speculative and revolutionary the vision, the more interpretations are possible – a wide field for public debate and occasions for ideological use of them. Against this background, it is not surprising that the public risk debate emerged from the conversion of positive utopia to negative dystopia (s. section 6.3).

This situation asks for guidelines how should be dealt with futuristic visions, especially by scientists and science promoters. Without extensive investigations of "vision communication" already being available, some recommendations may be derived from the diagnosis given above. Important aspects are

- *hybrid nature*: futuristic visions are combinations of expectations and facts but not only grounded in scientific knowledge;
- *uncertainty*: there is a high degree of uncertainty (feasibility, time scales, applications etc.);
- *ambivalence*: positive visions – from the standpoint of science – might be perceived as negative in the media or in the public;
- *risk of backlash*: even visions which are perceived as mainly positive could lead to backlash situations if too much would be promised to come into reality in too short time.

In general, the recommendation is to not communicate futuristic visions without pointing to the "meta-knowledge" about the visions: premises, presuppositions, values involved, uncertainties etc.

6.5 Consequences and Conclusions

6.5.1 Do We Need a New "Nano-Ethics"?

Some scientists and philosophers already called for a new sub-discipline of ethics named "nano-ethics" (Moor and Weckert 2003; Robison 2004; Hermeren 2004). Their diagnosis is that Nanotechnology will bring up a lot of completely new ethical questions the answering of which would be extremely important for the further successful advance of Nanotechnology. The analysis given in this study, however, presents a different picture.

The propagation of nano-ethics overlooks the fact that many of the ethical questions raised by Nanotechnology have already been posed in other fields of ethical reflection. The ethics of technology, bioethics, the ethics of medicine or also the theoretical philosophy of technology concern themselves with questions of sustainability, of risk assessment, of the interface between human beings and technology, resp., between living beings and technology. These questions are in themselves not new (in this line of thought cp. also MacDonald 2004; Baumgartner 2004), as the analyses of the problem have shown.

Partially new, however, is their overlap, even their convergence in the field of Nanotechnology. Analogous to the well-known fact that Nanosciences and Nanotechnology are fields in which the traditional borders between physics, chemistry, biology, and the engineering sciences are crossed, various traditional lines of ethical reflection also converge in ethical questions in Nanotechnology. The fashionable creativity in coining terms, as it precipitates itself in designations like "neuro-philosophy" or "nano-ethics", obscures the integrative and cross-sectional nature of many ethical challenges, rather than being particularly helpful. We don't need any new sub-discipline of applied ethics called "nano-ethics" but there is a need for *ethics in and for Nanotechnology* because some topics and questions gain larger urgency and will converge in Nanotechnology, and because Nanotechnology accelerates scientific and technical progress. Presupposition is, in particular, willingness on the part of the ethicists for an open reflection of ethical aspects of Nanotechnology beyond the scope of classical "hyphenated ethics" and to a dialogue with natural and engineering scientists.

Also the heterogeneity of Nanotechnology would be an obstacle for an own "nano-ethics". This heterogeneity at the scientific side (chapter 3) corresponds to the obvious diversity of ethical questions around Nanotechnology (section 6.2). It would be very artificial to use the term "nano-ethics" as an umbrella. Consequently, we need ethical consideration of nanotechnologies in some fields – following the criteria of relevance given in section 6.1 – but we do not need a new field called "nano-ethics".

6.5.2 Ethics as Concomitant Reflection of Nanotechnology

Since the very beginning of ethical reflection in science and technology there is an ongoing discussion about the adequate relation in time between the scientific-technological advance and ethics. Ethics often seems to pant helplessly behind technical progress and to fall short of the occasionally great expectations. The rapid pace of innovation in technicization has the effect that ethical deliberations often come too late: when all of the relevant decisions have already been made, when it is way too late for planning technology. Technological and scientific progress sets facts which, normatively, can no longer be revised (Habermas 2001). Ethics in this perspective could, at best, act as a repair service for problems which have already arisen.

The above is, however, a one-sided view. Ethics actually can provide orientation in the early phases of innovation, e. g., because even the scientific and technical basis includes certain risks which are ethically unacceptable. The opinion that one has to wait with ethical reflection until the corresponding products are on the market and have already caused problems, can easily be refuted. Because the technical knowledge and capabilities are known, as a rule, long before market entry, and can, with the reservation of the well-known problems of the uncertainty of prognosticating the future, be judged as to its consequences and normative implications. Due to Nanotechnology's early stage of development (many prefer to call it Nanoscience), we thus have a rare case of an advantageous opportunity: there is the chance and also the time for concomitant reflection, as well as the opportunity to integrate the results of reflection into the process of technology design, and thereby to contribute to the further development of Nanotechnology (Moor and Weckert 2003; Fleischer 2002).

These two complementary concerns are sometimes related to as either the "ethics last" or the "ethics first" model:

(1) The "ethics last" model means that first there have to be concrete technological developments, products and systems which then could be reflected by ethics. Ethical reflection then would always be late, compared to the technical developments. The concern is that this might be too late with the consequence that ethical reflection then would have no impact because the respective technology is "already in the world", and ethics could not change this *ex post*: "It is a familiar cliché that ethics does not keep pace with technology" (Moor and Weckert 2003; s. also Habermas 2001). There are already concerns that this situation might occur in Nanotechnology (NT) because of the extreme high innovation speed: "We believe that there is danger of derailing NT if serious study of NT's ethical, environmental, economic, legal and social implications [...] does not reach the speed of progress in the science." (Mnyusiwalla et al. 2003:R9). In order to avoid such derailing, it is necessary that ethics starts early in the development chain, not waiting until there are products at the marketplace.

(2) The “ethics first” model postulates comprehensive ethical reflection on possible impacts already *in advance* to the technological developments. But, ethical reflection at a very early stage of development could only be speculative because there would be only little knowledge, if ever, about the application fields, about the acceptance at the marketplace, about the reactions of the consumers and the consequences for individuals and society. Therefore, ethical reflection in this model has to deal with the situation that the knowledge about technology and its consequences is uncertain and preliminary.

In Nanotechnology, the second model seems to be more adequate. Nanotechnology is still at an early stage of development but ethics is required, due to many voices in science and society (Mnyusiwalla et al. 2003). However, the concerns about the difficulties of ethical reflection in regard of the uncertain and preliminary nature of knowledge about the use of Nanotechnology and its impact have to be taken seriously. Some questions are

- Ethical reflection of Nanotechnology needs resources (time, persons engaging themselves, funding) which could be missing by dealing with other, perhaps more relevant questions. Which degree of urgency should moral concerns show to justify comprehensive ethical reflection?
- Ethical reflection is related with moral conflicts which can, in early stages of development, often only be assumed hypothetically to appear in the future. A question could be to which degree such hypotheses should be plausible to give rise to ethical reflection.
- In many cases the reliability of knowledge (about technology conflicts or other societal impacts) decreases if the time span into the future is increased. Does this imply that the relevance of ethical reflections should also decrease considering developments in the farer future?

Because of questions of this type the answer to the above mentioned dilemma between the “ethics last” and the “ethics first” model cannot simply be that ethical reflection should always start as early as possible (as postulated by Joy 2001). Exaggerating this approach could lead to wasting or badly allocating resources and to irrelevant ethical analyses because arbitrary science fiction stories could be subject to ethical investigation. However, ethical reflection is obliged to show pragmatic relevance (Grunwald 1999). Therefore, criteria should be identified to allow differentiating possible situations according to their relevance and urgency with respect to ethical reflection. Such criteria have to balance the “ethics first” postulate with the knowledge available and the pragmatic relevance of the respective topic. If, for example, in discussions about implications of Nanotechnology, the question is analysed in ethical respect, what would be the consequences of an abolition of ageing (Moor and Weckert 2003), there might be a big question mark (compare section 6.4.4). The analysis of ethical aspects of Nanotechnology (section 6.2) has to take into account such arguments in order to distinguish between more and less relevant issues in ethical respect. The answer to the dilemma mentioned between the "ethics last" and the "ethics first" model can be resolved by following the approach of ethical reflection as an accompanying process: "Our position is that the ethics first model and the ethics last models are popular but poor solutions to a false dichotomy" (Moor and Weckert 2003).

Therefore, these considerations don't necessarily mean that ethical deliberations have to be made for absolutely every scientific or technical idea. The problems of a timely occupation with new technologies appear most vividly in the diverse questions raised by the visions of salvation and horror as regards Nanotechnology. What sense is there in concerning oneself hypothetically with the ethical aspects of an extreme lengthening of the human life-span, or with self-replicating nanorobots (Moor and Weckert 2003)? Most scientists are of the opinion that these are speculations which stem much rather from the realm of science fiction than from problem analysis which is to be taken seriously: "If discussions about the ethics and dangers of Nanotechnology become fixated on a worry that exists only on science fiction, we have a serious problem." (Ball 2003). We shouldn't forget that ethical reflection binds resources, and there should therefore be a certain evidence for the realizability of these visions, if resources are to be invested in them which could then be lacking elsewhere. Ethical reflection is not necessary "in advance" nor just for the sake of the intellectual diversion it provides. In this respect, ethical analysis needs its own "vision assessment" (s. above).

Ethical reflection and policy advice building upon it are neither senseless nor premature in early phases of development if there are at least certain possibilities for the practicability of the technology concerned. Then, there are possibilities for designing ethical assessments as concomitant processes of technological development. If at first only rather abstract considerations on lines of technological development are possible, valuable advice for the further path of development can nonetheless already be given (e. g., by means of timely allusions to potential technology conflicts and to methods of de-escalation). Further, ethical judgement makes orientation for planning the *process* of technological development possible (for example, with regard to questions of equity). In the course of the continuing concretization of the possibilities for application of Nanotechnology, it is then possible, to continuously concretize the – at first abstract – estimations and orientations on the basis of newly acquired knowledge, and finally, to carry out an ethically reflected technology assessment: "Nanoethics is not something one can complete satisfactorily either first or last but something that needs to be done continually updated." (Moor and Weckert 2003).

The added value in comparison with a later start for ethical reflection is obvious: even the process of technological development profits from the assessment of the consequences, and ethics avoids "coming too late", which it is occasionally accused of doing (Ropohl 1995). Technology assessment and ethics have the responsibility, in view of the rapid and momentous developments in Nanotechnology, to make the societal process of learning which is always connected with the introduction of a new technology as constructive, transparent, and effective as possible by means of timely investigation and reflection: "As a result, the ethics of nanotechnology have not really been addressed even when funds have been specifically allocated for doing so. In 2001 the US National Nanotechnology Initiative allocated between $16 and $28 million for the study of its societal implications but only about half that budget was used." (Ball 2003).

6.5.3 Ethics for Nanotechnology – Outline for Further Activities

As has been shown there are relevant ethical questions concerning the advance of Nanotechnology which have to be tackled. However, the statement "The only way to avoid such a moratorium[10] is to immediately close the gap between the science and ethics of NT. Either the ethics of NT catch up or the science will slow down." (Mnyusiwalla et al. 2003:R12) seems to be one-sided. It does not take into account the heterogeneity and multi-dimensionality of Nanotechnology which brings up a lot of different ethical questions with different relevance in various fields. In this sense, it does not make any sense to postulate an undifferentiated "catching-up" of ethical thought.

According to the analysis given above, we can derive some more concrete conclusions for the next steps in ethical reflection of Nanotechnology:

– The many and engaged debates about societal and moral aspects of Nanotechnology show a high degree of uneasiness among the population with the many proclamations of the revolutionary nature of Nanotechnology. Such uneasiness is no objection but a call for a more open debate, more explanation and more deliberation. However, uneasiness could develop into opposition if it would not be taken seriously. Therefore, problems with the nanotechnological advance which express themselves via certain debates in the public or in the media should be taken seriously. Nanoscientists should engage themselves in such discussions in order or contribute to preventing irrational and fundamentalistic biases.
– This "uneasiness" frequently focuses on visionary or utopian developments. According to the big factual importance of visions and utopia in public debate such visions should – independent from their plausibility – be subject to ethical reflection. Analysing and assessing such visions requires developing a new methodology towards a "vision assessment".
– Facing the ambivalence of visions scientists and science managers should be very careful in bringing up visions into public debate. There are two types of risks in "vision communication": (1) promising revolutionary

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[10] That has been proposed by the ETC group 2003.

advances might cause fear and concern instead of fascination and (2) raising high expectations might lead to disappointment and frustration in case the developments would need more time than promised.

- Appropriate funding of ELSI activities is not necessary in a broad sense (ethical aspects of Nanotechnology in general) but should be dedicated to recognisable ethical concern in specific areas of nanotechnological advance.
- Major moral challenges of nanotechnological advance are (s. section 6.2): (1) the impact of the precautionary principle on various development paths of Nanotechnology, (2) research and development at the interface between biological (especially human) and technical systems or to bridge the gap between both types of systems, and (3) enhancement of human performance via the concept of "converging technologies".
- Most ethical reflections on Nanotechnology are still at a rather general level (s. sections 6.2.2–6.2.6). As soon as the application scenarios and pathways of Nanotechnology will become clearer, ethical work on more concrete issues will be on the agenda.
- These activities require interdisciplinary cooperation between experts in ethics and other disciplines as well as transdisciplinary collaboration of sciences and humanities with the political system (e.g. regulators in applying the precautionary principle).
- Ethics in and for Nanotechnology needs co-operation between various sub-disciplines of ethics and philosophy as well: bioethics, ethics of technology, philosophy of science, philosophy of technology, health care ethics, and anthropology. Traditional barriers between different systems of reasoning have to be overcome.
- This should be done in worldwide cooperation, bringing together people from different cultural backgrounds as well as from developed and developing countries (Mnyusiwalla et al. 2003:R12). According to the situation that Nanotechnology will become a globally distributed technology, ethical reflection should be performed in an adequate manner.
- Ethical reflection takes place at different levels of communication: as philosophical discourse, as interdisciplinary exchange, as well as stakeholder and public debate. Platforms for bringing together these different debates should be provided by funding agencies or foundations.

7 Knowledge Transfer in Nanotechnology

Taking our definition of Nanotechnology of chapter 2 in consideration, it is evident that the knowledge transfer in these fields must address different groups of the society in very different manner. An aggravating factor is that compared to other established scientific domains, nanosience and Nanotechnology are still young research fields which are at least in public discussions not very well defined. On the other hand the creation of centres conducting research in these fields as well as the creation of the curriculum for bachelors and masters in Nanotechnology gives the impression that Nanotechnology is accepted as an independent field in research and development. Therefore the question is raised in which way the new generation of researchers and engineers has to be educated in Nanotechnology. Another question which takes in account the short term demand of industry deals with the transfer of knowledge generated in Nanotechnology research programs: this has to be transferred as fast as possible into successful applications. It is well known that this last question is strongly related to the first one because technology transfer needs educated collaborators at each level of research and application including standardisation and regulation issues. Finally, the balanced evaluation of risks and benefits of Nanotechnology which includes a public discussion needs also to have well adapted information of the policy makers and interested citizens. This chapter gives a description of the concepts of education in Nanoscience and Nanotechnology for academic people and a discussion of the transfer of knowledge to industry and to the interested public. Finally, conclusions and recommendation regarding the education at academic level as well as for the knowledge transfer will be presented.

7.1 Education at Academic Level

Chapter 3 of this book shows very clearly that Nanotechnology, which includes also Nanoscience in this definition, encompasses an unusually large number of different disciplines including physics, chemistry, biology, medicine and different kinds of engineering sciences. It is also important to note that in many cases the scientific level of the above mentioned fields are extremely high, especially in physics (applied quantum mechanics) or especially in biology where Nanotechnology opens the door to new characterisation methods on molecular level and that very rarely only one discipline is involved. As a simple example we can take a Biosensor which allows the detection of DNA sequences by tuning the surface plasmon resonance of nanosized gold particles in a suspension. It can be easily seen that in such a problem quantum physics, chemistry, biology and finally microtechnology are involved. This multi-disciplinarity is even larger than in material science and engineering and the big challenge for education is to transfer this multidisciplinarity in an interdisciplinary education. Especially the problem how to transfer an education which is at this time an assembly of different aspects of the disciplines involved to a new interdisciplinary education offering the students added values.

In the following, we tried to classify the existing undergraduate and graduate programs which claim to give education in Nanotechnology. The information, existing in the Web, is not exhaustive, but will give a detailed enough picture of the situation and will allow formulating some valid conclusions. The information found in the Web is presented here in a portfolio using the

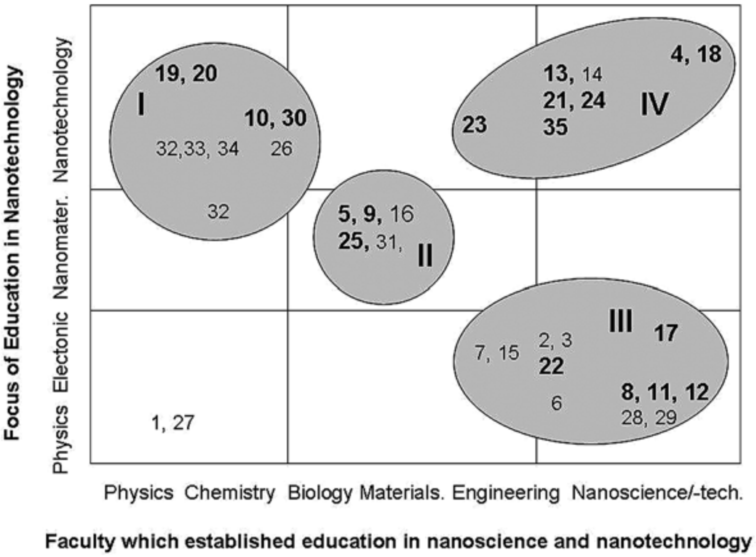

Figure 7.1: Nanotechnology related courses at Universities in North America, Australia and Europe. (Numbers in bulk: Master courses (full program), other numbers indicates couses in the framework of other Master programs; 1 TU Munich, 2 Uni Washington, 3 Uni Oregon, 4 Uni Toronto, 5 Pennstate, 6 Uni Copenhagen, 7 Purdue, 8 TU Delft, 9 Darmstadt, 10, Clarkson, 11 Harvard, 12 Leiden, 13 Flinders (Australia), 14 Helsinki, 15 Cork, 16 RWTH, 17 Leeds, 18 Imperial College, 19 Würzburg, 20 Basel, 21 Buchs (Applied University), 22 Standford, 23 Twente, 24 Sydney, 25 Rennselar, 26 Arizona State, 27 Lipköping, 28 Rice, 29 Lund, 30 Siegen, 31 EPFL, 32 Kassel, 33 Saarland, 34 Erlangen, 35 Int. Uni Bremen).

origin of the initiating group of the course (for example department of physics or a Nanotechnology research centre) as parameters and on the other hand the focus of education, for example if engineering or basic science aspects are more important. Very interdisciplinary courses are located at the top of the portfolio, whereas courses focused on the specialities of the home faculty are placed near the bottom line. Similar the situation for the origin of the education programs: courses presented from a Nanotechnology centre at the university, are posted on the right end of the diagram whereas courses origin from pure physics or chemistry are on the left side. This allows characterizing the courses in a relatively easy manner; Nanoscience courses with a strong focus on basic science are located in the lower left corner, whereas interdisciplinary courses given from a multidisciplinary faculty are located in the upper right corner. Important is to note that not quality of the courses was judged, the focus and character of the courses are of interest. It is also evident, that the courses located in the lower left corner are more science oriented, whereas the courses in the opposite corner are more engineering oriented. Figure 7.1, which presents the results of this investigation, shows clearly that four clusters regarding the above mentioned criteria can be identified.

I These courses are initiated from natural science departments and aim to cover most of the aspects of Nanotechnology and physical or biological aspects very often have first priority. These courses are therefore more focused on scientific aspects of Nanotechnology than the engineering ones. The admission to the master courses is mostly related to a bachelor degree in physics (for physics oriented Nanotechnology programmes) or in biology, respectively. Therefore, the courses in cluster I are not really interdisciplinary. They correspond more to a larger education in solid state physics with some introduction in biological and chemistry or vice versa. The engineering part, if present, is focused on molecular monolayers, self assembly of organic molecules at surfaces and surface investigation with atomic force microscopy or other scanning force microscopy.

II This cluster represents the material science and engineering (MSE) community. Courses are based on material science and engineering as well and are focused on properties and synthesis of nanostructured materials, mostly nanosized particles, self-assembled supramolecules, surface modification and fabrication methods. Depending on the origin of the ME education (e.g. mechanical engineering or physics), a more profound education in solid state physics, introduction in quantum mechanics, biology, or supramolecular chemistry is provided. Admission to such a Master or PhD-program is given to students with a BS in MSE. It is important to note that the education is more focused on nanostructured materials, which is a part of Nanotechnology, therefore, the aspect of interdisciplinarity is at the same level as in material science.

III The courses represented in cluster III are typical for courses initiated from Nanotechnology research centres, which are very often based on a close cooperation between researchers coming from natural science and/or from microtechnology. This fact is reflected in the orientation of the proposed master courses which are more physics and electronic oriented. The courses are very often focused on the top-down approach for the fabrication of new devices using nanoeffects. To follow the courses, students should have a basic knowledge in electronics, microtechnology or experimental physics.

IV The highest amount of courses and master programs is located in group IV. They are based on a large diversity of involved departments (natural science, engineering, biology etc.) and offer an education which encompasses as many aspects of Nanotechnology as possible. Because Nanotechnology is a very large field, each program for masters or doctoral schools shows always some aspects which are highlighted stronger than other ones. Admission to these courses depends on the home disciplines participating in the program. The courses in this cluster show the highest degree in interdisciplinary, but this must be compensated by a low level in some of the disciplines.

This systematic overview on education programs on the master level in Nanotechnology shows very clearly that education in Nanotechnology covering at the same time all aspects of Nanotechnology and Nanoscience is not possible. A master course following the Bologna rules (1 year or 60 credits courses and 1 semester project work) will never give enough time for a satisfying education in Nanotechnology which fulfils also the requirements on interdisciplinarity. Therefore, an academic education in Nanotechnology has to be organized in three steps:

- Bachelor degree in one of the existing directions like physics, biology, or engineering;
- Master in Nanotechnology or Nanoscience;
- PhD or other graduate programs in Nanotechnology/Nanoscience.

Comparing the detailed curriculum in Nanotechnology of the universities mentioned in figure 7.1 shows that the curriculum is not very different from the usual curriculum of the corresponding home faculty which is responsible for the education: a physics curriculum and a Nanoscience curriculum established by a school of basic science is very similar. This is not surprising because as shown in chapter 3, dealing with Nanoscience needs a very solid knowledge in basic science and/or engineering. This does not exclude introduction courses in a field outside the faculty which is concerned, especially courses like “Introduction in Nanotechnology” are of interest, especially to enforce the motivation of students and to attract students to Nanotechnology. It seems that in most cases the name “Nanotechnology” or “Nanoscience” for a bachelor degree is chosen to attract students to basic science or engineering or in other words Nanotechnology degrees on bachelor level is often a deceptive package.

On the Master level the possibilities to create a curriculum which fulfils the requirements for a master in Nanotechnology/-science are much better than at the bachelor level. Using the opportunity to split the formation in a major (60 credits) and minor (30 credits) opens for the interested university the freedom to adapt the curriculum to the speciality of the home faculty and at the same time to profit from the experience of other faculties at the university or research centres. Master programs at national or European level are also possible. Examples for a curriculum in Nanotechnology at master level can be a major in solid state physics or experimental physics with minor in microtechnology or selected courses in life science like cell biology, tissue engineering etc. It is evident that the minor courses have to be adapted to the knowledge of the students, for example a physicist needs another type of cell biology than for example a student coming from chemistry or engineering. This leads also to the conclusion that teaching in Nanotechnology needs an academic environment which allows to give such diverse and well adapted courses, otherwise, the danger to provide only introduction and overviews is very high and finally the scientific level of the master students will not fulfil the needs of industry or academia.

Only on the third level, doctoral schools or other graduate programs, a further specialization can start. We believe that only at this level an interdisciplinary education can take place. International summer schools, provided by universities, research centres, EU networks or other research organisation exist today and the offer have to be enlarged.

Academic education in Nanotechnology has to be based on a strong fundament in one of the “classical” disciplines of natural science and engineering, even at the master level. The education in one of these disciplines must be the fundament for a more specialised education which can finally lead to a interdisciplinary education encompasses from physics to device design or medicine all interesting field of Nanotechnology.

7.2 Knowledge Transfer to Industry and Regulatory Authorities

The installation of new courses at the academic level needs time and additionally it needs again 5 to 9 years that scientists and engineers with a specialisation in Nanotechnology are available on the employment market. During the mean time, and this is especially true for Nanotechnology, industry and regulatory authorities have a large need for collaborators educated at a sufficient level in Nanotechnology. This type of collaborators is needed for the transfer of research results to industrial application, but also for the elaboration of standards and rules (s. section on toxicity), the evaluation of patents and social aspects regarding the application of Nanotechnology. To fulfil the requirements in this area, education profiles similar to that of patent attorney, industrial engineer etc. which have a solid education in natural science or engineering completed with patent law or economic science, respectively, but with a focal point in education on Nanotechnology have to be installed. In view of the special situation of Nanotechnology, like new combination of scientific and engineering domains, a still ongoing discussion of risk and benefits of this technology and missing rules regarding application regarding work safety aspects, it seems obvious that tools for a fast and efficient knowledge transfer from science to industry and regulatory authorities must be installed. Examples for such tools could be:

Post-graduate courses in Nanotechnology: Centres for Nanotechnology or Universities with an important activity in Nanotechnology must offer courses for industrial engineers, patent attorneys or medical doctors. The level of the courses has to be well adapted to the long as well as short term needs of industry and authorities.

Minors in Nanotechnology: Minors are packages of courses which are taken in parallel to the main education. In the European BS/MS system, a minor corresponds to 30 credits (a semester) where the education is focused on Nanotechnology. Such programs have to be tailor made, as the students would have a very different background.

Both types of education have the advantages that after a short time educated collaborators can be engaged from industry or governmental institutions. Such educated scientists would also be able to treat questions regarding the social impact of Nanotechnology and can play an important role regarding the communication with the scientifically interested public.

7.3 Knowledge Transfer to the Public (Science Goes Public)

A third group which needs information regarding new results in science and engineering of Nanotechnology is the interested public. On one side, we can observe a very intensive use of the word "Nano" or "Nanotechnology" in TV or in print media. Mostly it is related to electronics, coatings (self cleaning walls) or new therapeutic methods, especially in the domain of cancer treatment and analytical tools. This type of information increased enormously the pressure on the scientific community to communicate interesting results and to promise useful application in a short time. On the other hand, a short circuit is used between the danger of nanosized exhaust particles (e.g. diesel soot), man-made nanoparticles (e.g. used in biomedicine, sensors or paints) and finally Nanotechnology (like lithography, AFM, surface coatings). In the public, a dyadic recognition of Nanotechnology exists. It is therefore an obligation of all researchers as well as of the authorities to prepare and spread information regarding Nanotechnology carefully to allow an objective discussion of the benefits and risks of Nanotechnology and to compare and combine this with the real short and long term economic potential.

It is also interesting to see how similar problems were handled in the human genome project. In this project, similar questions regarding risks and benefits were discussed and also only limited knowledge regarding genomics and biology exists in the world outside the involved academia. We have to learn from the errors and positive experience with the public dialogue in gene therapy and biotechnology. In the framework of the gene technology discussion, special financial support for "Ethical, Legal, and Social Implications" (ELSI-domain) was foreseen. This fund was used for the in-deep discussion of the impact of the results on ethical and legal consequences. Such a discussion has to be conducted from the interested academia for special fields in Nanotechnology, including toxic aspects of particles, the use of Nanotechnology in gene therapy and diagnostics or in the field of sensors to allow an objective and profound information of the citizens.

7.4 Conclusions

Education and knowledge and information transfer in Nanotechnology is still inconsistent: At academic level, a huge and still increasing number of courses and master programs called "Nanotechnology" exist. The diversity of the contents is as large as the field of Nanotechnology itself. Therefore it is very difficult for students to choose the optimal course. It is also obvious that Nanotechnology is used as a marketing instrument to enlarge the enrolment of students. To educate students correctly in the field of Nanotechnology, a strong first education in natural science; engineering or biotechnology/biology is necessary for the basic understanding of processes and functions. Nanotechnology can only be a specialization of master programs or the topic of doctoral schools. An interdisciplinary education in a BS/MS cycle is not possible or will stay on a very superficial level. For the education of future collaborators in regulatory authorities or as patent officers, post-graduated courses have to be installed encompassing different domains of Nanotechnology (Nanotechnology in electronics, Nanotechnology in bio-engineering…).

In the public area, Nanotechnology has a two edged image: key to the future technology *versus* toxicity of nanoparticles. It will be the task of each researcher in this field to use well established communication channels to inform the public in an objective manner.

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