Nanomedicine and biomimetics: life sciences meet engineering & physics

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NANOMEDICINE AND BIOMIMETICS: LIFE SCIENCES MEET ENGINEERING & PHYSICS

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1 Introduction

One of the fascinating aspects of nanotechnology is that on the nanometer scale all the natural sciences meet and intertwine. Physics meets life sciences as well as tribology, engineering, chemistry, materials science and computational approaches, which altogether communicate and are closely linked. This inherent interdisciplinarity of nanotechnology poses a challenge and offers enormous potential for fruitful cross-fertilisation in specialist areas. [1][2][3].

A variety of novel nanotechnological techniques such as scanning probe microscopy and scanning probe spectroscopy allows for accurate characterization and manipulation of features down to the single molecule level and below [4]. Such techniques are currently widely used and continuously being improved, and open up completely new perspectives in nearly all fields of modern science [5].

This manuscript introduces two prominent research areas at the meeting place of life sciences with engineering and physics: nanomedicine and biomimetics. The foundations of both areas are presented and current research methodologies and results are introduced. The outlook of this paper features concepts with wide ranging implications for understanding the processes in living beings as well as possible applications in engineering and medicine.

However, with the huge knowledge in different fields, nowadays it is impossible for a single person to know and understand more than just a fraction. Nevertheless, the awareness and understanding of different approaches and concepts is a paramount prerequisite of interdisciplinary work. A common language of biologists, professionals from medicine and pharmaceutics as well as engineers and natural scientists, in which descriptions at different level of detail are more compatible, is desirable.

1.1 Nanomedicine

Nanomedicine is an emerging field that is continuously gaining importance (Fig. 1). One of the pioneers of nanomedicine is Robert A. Freitas Jr. His two books on the field are recommended literature for getting introduced to basic concepts and high-flying visions and ideas [6][7].

The human body consists of ~$7*10^{27}$ atoms arranged in a highly aperiodic physical structure. Although 41 chemical elements are commonly found in the body, C, H, O and N comprise 99% of its atoms. Fully 87% of human body atoms are either hydrogen or oxygen. [6]

Atoms in the human body are generally present in combined form as molecules or ions, not individual atoms. The molecules of greatest nanomedical interest are incorporated into cells or circulate freely in blood plasma or the interstitial fluid. The typical human cell is 99.5% water and salts, by molecule count, and contains ~5000 different types of molecules. The human body is comprised of ~10^5 different molecular species, mostly proteins - a large but nonetheless finite molecular parts list. By 1998, at least ~10^4 of these proteins had been sequenced, ~10^3 had been spatially mapped, and ~7,000 structures (including proteins, peptides, viruses, protein/nucleic acid complexes, nucleic acids, and carbohydrates) had been registered in the Protein Data Bank which at that time was maintained at Brookhaven National Laboratory. Given the current accelerating pace of improving technology, it is likely that the sequences and 3D or tertiary structures of all human proteins will have been determined by the second decade of the 21st century. [6]

The Foresight Institute is a California based think tank and public interest institute on nanotechnology. Founded in 1986, the Foresight Institute was the first organization to educate society about the benefits and risks of nanotechnology.

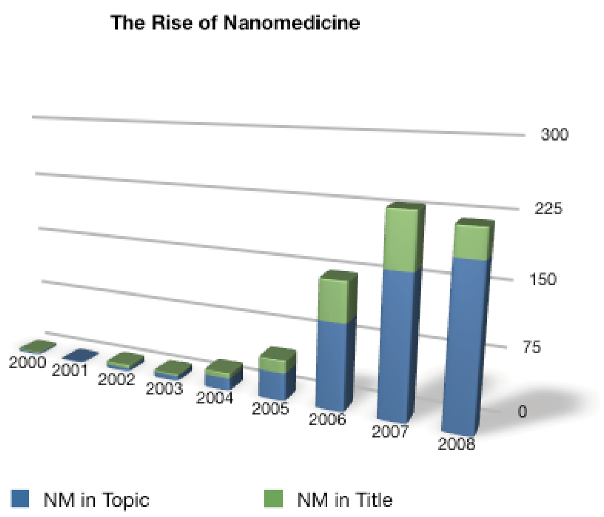

Figure 1: The number of scientific publications with "nanomedicine" as topic or in the title. Source: ISI Web of Knowledge, Thomson Reuters. http:// www.webofknowledge.com

Foresight's mission is to ensure the beneficial implementation of nanotechnology. Their internet page gives sound overview on current topics in nanotechnology, and their nanomedicine part is well written.

"Nanomedicine may be defined as the monitoring, repair, construction and control of human biological systems at the molecular level, using engineered nanodevices and nanostructures.

Basic nanostructured materials, engineered enzymes, and the many products of biotechnology will be enormously useful in near-term medical applications. However, the full promise of nanomedicine is unlikely to arrive until after the development of precisely controlled or programmable medical nanomachines and nanorobots.

Such microscopic machines were first hypothesized by the Nobel-winning physicist Richard Feynman in 1959, and later were described at length by K. Eric Drexler in his popular books Engines of Creation (1986) and Unbounding the Future (1991), and in his more recent technical book Nanosystems: Molecular Machinery, Manufacturing, and Computation (1992)."

http://www.foresight.org/nanomedicine [8][9][10][11]

A deeper understanding of the fundamental principles of nature itself will provide new ways and possibilities for influence of and interaction with biological systems. Nanotechnology already has and will to an increasing degree have an impact on the medical research in the future. Although new diagnostic tools and improved ways of drug administration have already been developed as a first fruit of the upcoming nano-era, still many challenges and problems remain unsolved and the technology is far from using the wide variety of opportunities offered.

To meet this demanding task, nanomedicine like no other area of research requires a close collaboration of people from technology and biology, and only a thoroughly linked network will be able to bring this novel sector to its full potential. [12][13]

For primary literature in the field, the Elsevier Journal "Nanomedicine: Nanotechnology, Biology and Medicine" and the American Scientific Publishers "Journal of Biomedical Nanotechnology" (both founded in 2005) are recommended. These are international, peer-reviewed journals that cover basic, clinical, and engineering research in the field of nanomedicine.

1.2 Biomimetics

Biomimetics is a continuously growing field (Fig. 2) [1][14][15]. Biomimetics deals with the realization of processes and construction, as well as the development of principles of nature in technological applications and devices, i.e. there is a transfer (of knowledge) from biology to technology. It is worth noting that identical copies from nature to technology are not feasible in biomimetics. Instead, biomimetics encompasses a creative conversion into technology that is often based on various steps of abstractions and modifications, i.e. an independent successive construction that is rather a 'new invention' than a blueprint of nature [16][17].

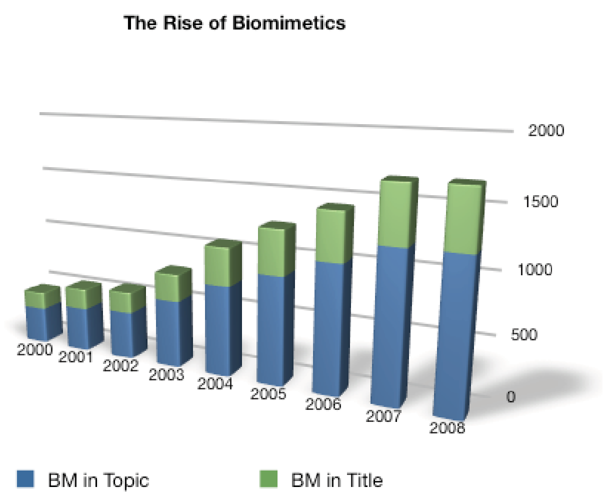

Figure 2: The number of scientific publications with "biomim" as topic or in the title. Source: ISI Web of Knowledge, Thomson Reuters. http:// www.webofknowledge.com*

The history of *biomimetics* can be traced back at least to the flying machines of L. daVinci during renaissance times. In the mid-20th century O.H. Schmitt coined the term "biomimetics". Schmitt and his wife studied natural biological processes and invented methods and machines that duplicated those actions. This new science became known as "Biomimetics" or "The Mimicry of Nature." Their research into squid nerves led to the patented "Schmitt Trigger" [18]. The word *bionics* was originally coined by J.E. Steele at about the same time and indicated a blend of biology and electronics. In German the term '*Bionik*' (blend of biology and technics) is used.

The classification of the single subfields within biomimetics is not yet standardized. Based on the work of Nachtigall [17], the field can be subdivided as follows: construction biomimetics, process (or procedure) biomimetics, and information biomimetics.

The structure and function of biological systems are studied as models for the design and engineering of materials and machines. Principles and abstract ideas of natural phenomena and model systems are extracted and applied to technical applications and design (Fig. 3).

General principles that can be applied by engineers who are not at all involved in biology are

- integration instead of additive construction,
- optimization of the whole instead of maximization of a single component feature,
- multi-functionality instead of mono-functionality,
- energy efficiency and
- development via trial-and-error processes.

Systematic technology transfer from biology to engineering thereby becomes generally accessible.

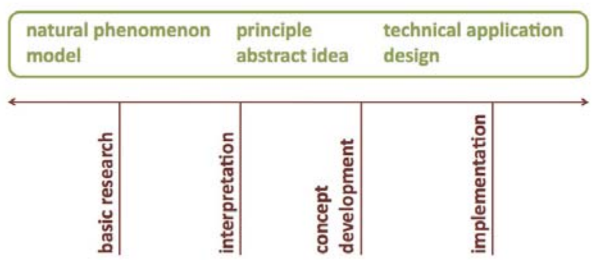

Figure 3: Biomimetics: principles and abstract ideas of natural phenomena and model systems are extracted and applied to technical applications and design. © 2008 by P. Gruber, transarch.

Strategies and technologies for entering an ecological age comprise the following biomimetics principles:

- Use waste as a resource,
- use materials sparingly and do not draw down resources,
- diversify and cooperate,
- gather and use energy efficiently,
- clean up not pollute,
- remain in balance with the biosphere and
- use local resources.

In June 2008 the Center of Excellence for Biomimetics, TU BIONIK (for logo see Fig. 4) was founded at the Vienna University of Technology by Herbert Stachelberger from Chemical Engineering, Heinz-Bodo Schmiedmayer from Mechanical Engineering, Petra Gruber from Architecture and Ille C. Gebeshuber from Physics Engineering.

TU WIEN BIONIK BIOMIMETICS

Figure 4: Logo of TU BIONIK, the Center of Excellence for Biomimetics at the Vienna University of Technology.

TU BIONIK comprises more than 30 researchers from all faculties, covering an impressive range of fields:

Architecture and Planning:
Architectural Design, Architecture Theory, Biomimetics, Sustainable and efficient Building Construction, Biomaterials in Architecture, Digital Architecture and Planning.

Civil Engineering:
Biomechanics, Dynamic Behaviour of Biomechanical Systems.

Electrical Engineering and Information Technology:
Biocompatibility of Surfaces, Micro-und Nanostructure Technology, Microsystems Technology, Construction Methodology, Cognitive Information Processing, Industrial Sensor Systems.

Informatics:
Evolutionary Computation.

Mechanical and Industrial Engineering:
Nanoarchitecture of Biomaterials, Biomineralisation, Biomechanics, Non Metallic Materials, Simulation of dynamic Multibody Systems, Interaction Human-Technical System.

Mathematics and Geoinformation:
Spatial cognition, Computational Neuroscience and Biomedical Engineering.

Physics:
(Bio)Nanotechnology, Tribological Micro- and Nanosystems of the Biosphere, Engineering Biology.

Technical Chemistry:
Characterisation of Biopolymers, Natural Products and Food Chemistry, Fibre technology, Mechanical Process Engineering.

The aim of TU BIONIK is to combine existing competencies and to develop new ones. A trans-disciplinary research facility shall be established, and the existing activities at the TU Wien shall be crosslinked. Furthermore, sponsorship for the network as well as project funding shall be acquired, and cross-linking with Austrian and international activities such as the BIONIS network in the UK shall take place. The joint internet appearance of the groups involved is http://biomimetics.tuwien.ac.at/ and will feature background information as well an ongoing projects and research attempts.

2 Methods

2.1 Nanosized Drug Delivery Systems: Particle Mediated Delivery Strategies

The roots of particle aided drug delivery range back to the beginning of the 20th century, when Paul Ehrlich introduced the concept of '*magic bullets*' that should be able to attack selectively the "bad cells" in a diseased human body, leaving the healthy parts of the organism undisturbed. Inspired by the plot of a classical opera he established the principle of targeted drug delivery, and for the first time he pinpointed the problematic issues that up to now occupy scientists working on the field. What was merely a visionary idea in the days of Paul Ehrlich has meanwhile come to practical realization, greatly fostered by the striking advancements on the (bio)nanotechnological sector of engineering and life science. While at present being still in its infancies, particle mediated delivery strategies will finally open the way for a far more specific and compliant treatment of numerous diseases.

The technology available today facilitates the entrapment of pharmaceutically active ingredients or imaging markers in the matrix of micro- or nanometer sized carriers, which then release their content at the site of disease. In addition to temporally controlled liberation behaviour, the unique advantage lies in the possibility to modify the particles' surface so they adhere selectively to an intended target tissue [19]. This allows for addressing a multitude of problematic therapeutic questions, ranging from uptake-enhancing formulations for poorly bioavailable drugs to the highly specific targeting of bacteria or cancer cells [20].

Malignant tumours can thus be identified in an earlier stage of progression and patients be provided with a more fortunate prognosis. Shielding the healthy tissue from adverse effects, higher potent antiproliferative drugs can be administered. In future, the treatment of cancer may further be improved by applying the concept of '*theranostics*' that comprises simultaneous diagnosis and medication of diseased cells via multifunctional carriers [21].

Clinical trials on superparamagnetic nanoparticles that can be used to image and externally heat up tumour tissue have led to promising initial results [22].

Conceptual designs of higher complexity suggest the development of nanosized functional entities that dynamically respond to changes in the physiological state while circulating in the human body. Someday, medical nanorobots could be in use to monitor certain parameters of their environment and release encapsulated substances upon pathological stimulation. Insulin containing reservoirs that automatically react to the blood glucose level or drug carriers that sense the acidic microenvironment in cancer tissue might become available by the future advancement of bionanotechnology. However, much developmental work remains to be done before these ambitious goals will be reached.

2.2 Biomimicry Innovation Method

The large biodiversity in rainforests holds enormous potential for inspiring emerging technologies as well as optimising existing ones. Biomimicry is an innovation method that seeks sustainable solutions by emulating nature's time-tested patterns and strategies, e.g., a solar cell inspired by a leaf or noise reduction in aircraft inspired by parasitic flies of cicadas. The goal is to create products, processes, and policies - new ways of living - that are well adapted to life on earth over the long haul.

The Biomimicry Innovation Method (© Biomimicry Guild, Helena, MT, USA 2008) involves specifically trained biologists as well as engineers, natural scientists, architects and/or designers from universities or companies. The Biomimicry Innovation Method is for example used in the rainforest (high species variety, high innovation potential) to learn from and emulate natural models (http://www.biomimicryguild.com/).

The steps in the biomimicry process are as follows:

- Identify function,
- biologize the question,
- find nature's best practices and
- generate product ideas.

Identify Function:
The biologists distil challenges posed by engineers/natural scientists/architects and/or designers to their functional essence.

Biologize the Question:
In the next step, these functions are translated into biological questions such as "How does nature recover fresh water from salt water?" or "How does nature bond two dissimilar materials?" The basic question is "What would nature do here?"

Find Nature's Best Practices:
Scientific data bases as well as the surrounding rainforest are used to obtain a compendium of how plants, animals and ecosystems solve the specific challenge.

Generate Process/Product Ideas:
From these best practices (90% of which are usually new to clients), the biologists generate ideas for cost-effective, innovative, life-friendly and sustainable products and processes.

3 Application of the Methods

3.1 Biomimicry in Nanomedicine

In the sense of emulating naturally given structures and construction principles in order to profit from the related functional behaviour, many tasks in nanomedicine may be regarded as a specialized subdivision of in-body biomimicry.

For the growing fields of tissue engineering and endoprosthesis technology, durable engraftment still poses a major problem as artificial surfaces often show insufficient biological compliance. Pioneering recent studies found that the configuration of nanometer surface features can greatly facilitate cell adhesion, with an increasing extent the closer the surface structure resembles the natural microenvironment [23].

The regulation of cells in terms of growth and differentiation is remarkably affected by the structural and mechanical constitution of their underlying substrate, and nanopattering will thus be of primary importance for the successful development of cell-based therapies [24][25]. As cells “feel” their surrounding at the micro- and submicrometer length scale, also a manipulation of the respective surface features to influence cellular behaviour has to be carried out at this dimension.

In an attempt to counteract the rapid clearance of nanometer sized drug delivery devices by the immune system, it has been recognized that a coating with macromolecular hydrophilic chains such as polyethylene glycol prevents opsonisation and thus macrophagic uptake. Strikingly, it was found that certain types of biomolecules can intercalate with these chains and thus result in a particle that closely resembles the structure of endogenous low-density lipoprotein spheres, which finally leads to an enhanced uptake across the blood brain barrier [26]. By mimicking the physicochemical appearance of endogenous structures, artificial carriers may thus be able to utilize physiological transport mechanisms present in the human body.

3.2 Applying the Biomimicry Innovation Method: The BioScreen Project

The TU BIONIK project BioScreen analyses the rich flora in South East Asia (especially Borneo) concerning its biomimetic inspirational potential for technological applications.

A central aspect in the implementation of the project is the cooperation between institutions in the European Union, especially in Austria, with local institutions in South East Asia, especially Malaysia. Increasing awareness about the technological innovation potential of the rainforest and its abundance of species might cause a paradigm shift in the way locals view the pristine forests.

BioScreen is a pilot project with one major task: the installation of collaborations between key institutions that shall then serve as base for further projects.

BioScreen is conducted by Herbert Stachelberger from the Institute of Chemical Engineering at the Vienna University of Technology, and Ille C. Gebeshuber, who is currently on leave from the Vienna University of Technology, working as Professor of Nanotechnology and Biomimetics at the Institute of Microengineering and Nanoelectronics (IMEN) at the Universiti Kebangsaan Malaysia. Both are founding members of TU BIONIK.

BioScreen is performed in cooperation with the Forest Research Institute Malaysia (http://www.frim.gov.my) and Prof. Burhanuddin Yeop Majlis, chairman of the National Nanotechnology Association of Malaysia and director of IMEN.

4 Future Perspectives

The high degree of specialization in current science and technology requires a cross-disciplinary dialogue to prevent re-invention of the wheel. Nanomedicine and biomimetics are rapidly growing interdisciplinary fields. However, there is still a cleft in the conceptual worlds and in the attitudes as well as languages of researchers in the fields involved (in many cases originating from early education). Educating a number of people in a more interdisciplinary way is a promising first step towards reaching the goal of a common language.

4.1 Nanomedicine

Nanotechnology is beginning to change the scale and methods of medical imaging and drug delivery. The American National Institute of Health states in its “Nanomedicine Initiative Roadmap” that the development of nanoscale laboratory-based diagnostic and drug discovery platform devices such as nanoscale cantilevers for chemical force microscopes, microchip devices, nanopore sequencing, etc. shall yield generally usable devices within less than ten years [27]. Nanometer scale multifunctional entities that can diagnose, deliver therapeutic agents, and monitor cancer treatment progress are current hot topics of research [28]. These include design and engineering of targeted contrast agents that improve the resolution of cancer cells to the single cell level, and nanodevices capable of addressing the biological and evolutionary diversity of the multiple cancer cells that make up a tumor within an individual.

Thus, for the full *in vivo* potential of nanotechnology in targeted imaging and drug delivery to be realized, nanocarriers have to get smarter [29]. Pertinent to realizing this promise is a clear understanding of both physicochemical and physiological processes. These form the basis of complex interactions inherent to the fingerprint of a nanovehicle and its microenvironment. Inherently, carrier design and targeting strategies may vary in relation to the type, developmental stage, and location of the disease. Toxicity issues are of particular concern but are often ignored. Therefore, it is essential that fundamental research be carried out to address these issues if successful efficient application of these technologies is going to be achieved [30][31].

Rapid progress in the recent years gave proof of the benefits and enormous potential lying in the implementation of nanotechnology in the biomedical sector, but many promising approaches have so far not been able to exceed beyond the conceptual stage. This can be attributed to a still insufficient understanding of the basic principles that govern the interaction behaviour of nanosized entities and living tissue, which is also associated with a certain fear for 'nano'-toxic side effects. Further elucidation on this issue - preferentially conducted by interdisciplinary overlapping research collaborations - is thus urgently required to set the solid basis for a successful development of novel nanomedical therapy concepts in the future.

4.2 Biomimetics

Biomimetics can help to create products and processes that are sustainable, perform well, save energy, cut material costs, redefine and eliminate "waste", heighten existing product categories, define new product categories and industries, drive revenue and build unique brands:

Sustainability:
Biomimetics that follows "life's principles" [32] (i.e. build from the bottom up, self-assemble, optimize rather than maximize, use free energy, cross-pollinate, embrace diversity, adapt and evolve, use life-friendly materials and processes, engage in symbiotic relationships, and enhance the bio-sphere) yields sustainable products and processes.

Performance:
In nature, if a strategy is not effective, its carrier dies. Nature has been vetting strategies for 3.8 billion years. Biomimetics helps to study the successful strategies of the survivors and to perform well.

Energy:
Energy in the natural world is even more expensive than in the human world. Plants have to trap and convert it from sunlight and predators have to hunt and catch it. As a result of the scarcity of energy, life tends to organize extremely energy efficient designs and systems, optimizing energy use at every turn. Emulating these efficiency strategies can dramatically reduce the energy use of biomimetic devices.

Materials Costs:
Nature builds to shape, because shape is cheap and material is expensive. By studying the shapes of nature's strategies and how they are built, biomimetics can help minimize the amount spent on materials while maximizing the effectiveness of products patterns and forms to achieve their desired functions.

Waste Management:
By mimicking how nature transitions materials and nutrients within a habitat, units and systems can be set up to optimally use resources and eliminate unnecessary redundancies. Organizing habitat flows more similarly to nature's will drive profitability through cost savings and/or the creation of new profit centers focused on selling waste to companies who desire "waste" as a feedstock (e.g. plastic bags from waste disposal sites are valuable feedstock material for the cement industry).

Heighten existing product categories:
Biomimetics might help to see stale product categories in a radically different light, creating opportunities for innovation.

Define new product categories and industries:
Biomimetics can help to create disruptive technologies that transform technology or help build entirely new industries.

Drive Revenue:
Biomimetics can help create whole new growth areas, reignite stale product categories and attract both customers who care about innovation and sustainability.

Build Unique Brands:
Creating biomimetic products and processes will help to become known as both innovative and proactive about the environment.

Pursuing a biomimetic approach may be a path for realizing simultaneously 'smart', dynamic, complex and environmentally friendly products and processes.

5 Acknowledgements

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