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Functional Nanoscience
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Functional Nanoscience: Present and Future

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Fifty Years After Feynman

There have been many influences and drivers for the development of technologies that allow functional components to be constructed at smaller and smaller scale. The semiconductor revolution in the second half of the 20th century was driven by cost, speed, novel function, and power consumption. Semiconductor science and its child, large-scale integration of electronic circuitry, have been responsible for an unprecedented paradigm change in almost every aspect of human life. The change is arguably even more profound than that which resulted from the industrial revolution. As we shall see later in this paper, although the fundamental limits of Moore's Law have not yet been reached, this and the increasing energy consumption of these paradigm-breaking technologies will necessitate another paradigm shift in the near future.

In terms of the influence of individuals, the development of what we now call functional nanoscience clearly owes much to several outstanding scientists, all of whom were awarded the Nobel Prize for their work. Shockley, Bardeen and Brattain's discovery of the transistor, Kilby's invention of the integrated circuit, Krug's development of electron microscopy, Watson, Crick, and Wilkins' discovery of the structure, self-assembly of, and information processing in DNA, Prigogine's work on self-organization in dissipative structures, Cram, Lehn and Pedersen's development of self-assembled molecular structures, Smalley, Kroto and Curl's seminal discovery of buckminsterfullerenes, and Boyer and Walker's discovery of that archetypal molecular machine, ATP synthase, have all been major drivers for, and facilitators of, contemporary nanoscience.

However, it is another Nobel Laureate, Richard Feynman, who widely credited with providing essential stimulus to the development of functional nanoscience. His famous lecture, *There's Plenty of Room at the Bottom, An Invitation to Enter a New Field of Physics* was delivered at the annual meeting of the American Physical Society at the California Institute of Technology (Caltech) in December 1959. The lecture was first published in the February 1960 issue of Caltech's *Engineering and Science* [1]. It challenged scientists to think about constructing devices at the nanoscale, a possibility now brought to fruition in the early 21st century. The current paper is a summary of a series of truly inspirational and engrossing lectures, describing the state of the art of functional nanoscience, presented at the Beilstein Bozen Symposium on Functional Nanoscience. It attempts to draw together common themes in quite diverse areas of functional nanoscience, from self-assembled molecular devices and nanoscale cantilevers, through bio-inspired materials and molecular machines, to quantum electronics and lithography. Although Niels Bohr warned of making predictions, especially about the future, we also attempt to anticipate where functional nanoscience is leading in the short, medium, and long term.

Systems Chemistry and Functional Nanoscience

As the theme of the preceding Beilstein Symposium was systems chemistry [2], it is instructive to show how this new field of science overlaps with and informs functional nanoscience. Although systems chemistry is currently poorly defined, one definition is that it is the application of complex systems science to chemistry and molecular science. Complex systems science is playing an increasingly important role as an alternative, complementary approach to reductionism. Most physical and biological systems are intrinsically complex, consisting of a myriad of low-level components interacting to generate overt system (emergent) properties. Complex systems science approaches to chemistry have been reviewed recently [2]. Key elements of complexity theory are self-organization, criticality, emergent properties, and the description of interacting systems as networks. Networks describe the interactions between components of very complicated systems. Although interactions between system components may be relatively simple, they are nonetheless capable of generating extremely complex and sophisticated behaviour of the system as a whole. Network architecture influences the robustness and information flow of networks. In many robust networks commonly favoured by biological systems as diverse a social and ecological networks, gene and protein interaction networks, highly connected network nodes (hubs) play an important role in controlling network behaviour. The properties of the hubs (connectivity, etc.) and the architecture of the network in which they are embedded, contribute to network robustness and vulnerability. Hubs occur in social networks, such as citation and collaboration networks, where key researchers are highly cited and have a large number of collaborations, substantially influencing social networks of researchers in specific fields.

An example of an influential 'hub' scientist in chemistry is George Whitesides whose work has been a significant influence for some of the work presented at the Symposium. Analysis of Whitesides collaboration and citation network shows the extent of his influence, amplifying his ability to be an ''ideas catalyst'' in several major chemistry-related fields. In functional nanoscience and in the context of the Beilstein Symposium, influential hub scientists are exemplified by Nadrian Seeman (New York University, NY, U.S.A.), whose DNA origami technique is used in over 60 laboratories, and by Christoph Gerber's (University of Basel, Switzerland) seminal and hugely influential developments of the atomic force microscope (AFM), and scanning tunnelling microscope (STM)).

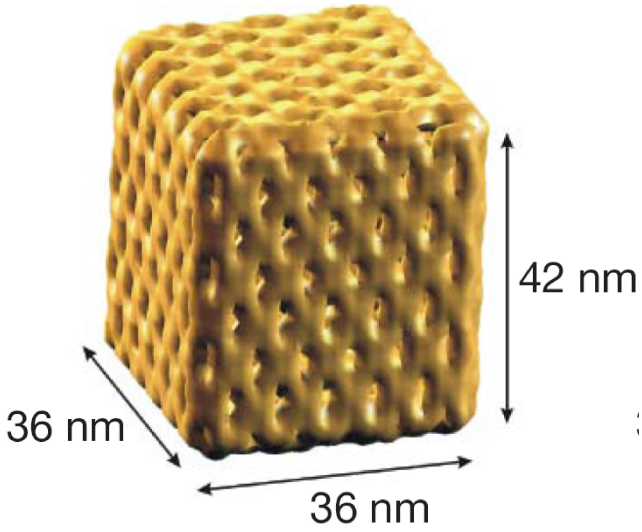

Figure 1. Self-assembled DNA cube.

Like scientists, molecules can also be influential hubs in research fields. In functional nanoscience molecular hubs include buckminsterfullerenes, nanotubes, and DNA. We shall see later in this chapter when discussing the work of Keith Firman (University of Portsmouth, UK), Nadrian Seeman, Jørgen Kjems (Åarhus University, Denmark), and William Shih (Harvard Medical School, Boston, MA, U.S.A.) the pivotal role that DNA plays in design and self-assembly of precisely assembled molecular objects.

Complex systems science concepts like self-organization, self-assembly, emergent properties, criticality, and network properties will play increasingly important roles in functional nanoscience in the future.

The Present

Chemists would argue that we have been doing 'nanoscience' for a long time. Although it is perhaps the ultimate reductionist science, chemistry has developed a remarkable suit of capabilities over the past century. Current chemical synthesis methods allow exceedingly complex molecules to be assembled via precise control of atom placement, as the total synthesis of ciguatoxins (Figure 2) by Hirama illustrates [3]. Essentially any atom that obeys the laws of chemical reactivity and valence can be placed at will in any position to obtain complex synthetic molecules, which are often designed to have a specific purpose. The main limitations are time and cost.

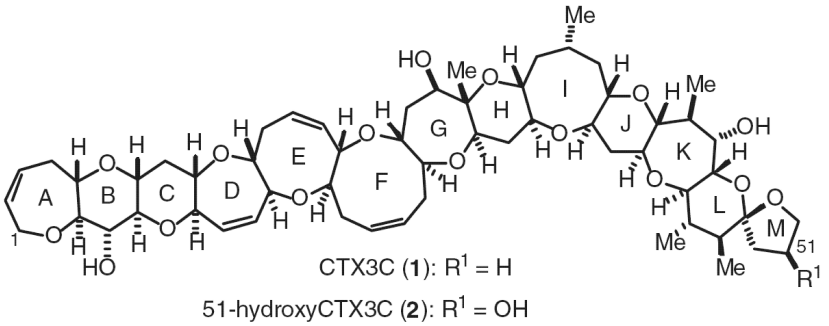

Figure 2. Structures of ciguatoxins.

Nanoscience draws heavily on organic chemistry, colloid and surface science, inorganic chemistry, molecular biochemistry, and macromolecular chemistry in particular. These fields have provided a source of knowledge about biological nanomachines, and the means for constructing, visualizing and characterizing very small objects. Functional nanoscience, *the ability to create, move and image nanoscale objects*, is now moving from the era of 'passive' nanoparticles, towards 'active' nanomachines with multiple functions and capabilities, increasing autonomy and complexity.

Contemporary functional nanoscience can be essentially subdivided and several different ways. Top down and bottom up nanoscience generally describe nanodevices that are engineered either by micromachining of a larger substrate material, or that self-assemble spontaneously via precisely designed molecular interactions as in biological systems for example.

Like all new, exciting scientific fields, nanoscience stimulates imaginative and sometimes overly optimistic or fanciful images of its possibilities. This is captured in the graph in Figure 3 that shows the history of scientific discoveries. The period of exaggerated

expectations is followed, when these high expectations go unmet, with a period of disappointment. A return to the fundamentals of the technology allows science to link with applications and real commercial investment begins [4].

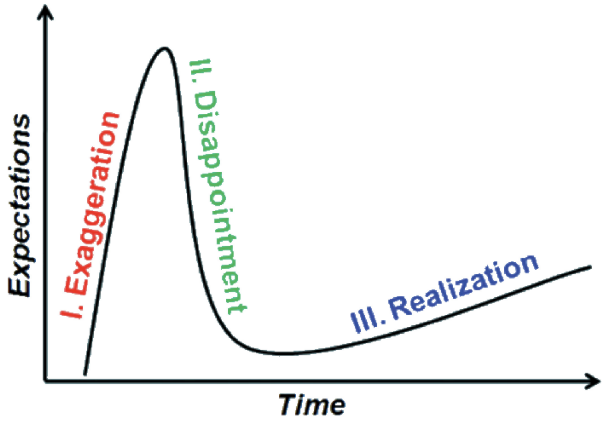

Figure 3. The expectations of a new technology as a function of time [4].

In this context, it is interesting to revisit the initial expectations of functional nanoscience as summarized in the recent review by Whitesides and Lipomi [4].

- revolutionary electronics (including devices constructed from single organic molecules)
- ultra-dense microprocessors and memories, and quantum computers;
- futuristic speculations concerning nano robots and nanoscale machines;
- revolutionary materials with extraordinary applications (*e.g.*, buckytubes and the space elevator, or quantum dots and cancer-targeted drugs);
- applications in biomedicine relying on particles small on the scale of the cell.

We can now contrast these with the nanoscience applications that have emerged [4].

- information technology and nanoelectronics. Developments in conventional microfabrication, like short-wavelength light sources and immersion optics, have moved microfabrication into the deep nanoscale region (~45 nm). Extreme ultraviolet lithography, double patterning lithography, and multiple maskless electron-beam writing will push the limit lower.
- an enormous range of opportunities for nanoscience in energy production, These range from heterogeneous catalysis to improved membranes for separation of water and gases

- soft nanotechnology in biology. The role of nanoscience in fundamental biology is still to be established, but is discussed at length in this paper.
- the physical chemistry of systems containing small numbers of molecules or particles, and having most of these particles on or close to a surface, is just beginning to be explored.
- quantum effects that emerge in small systems are very much unexplored.

Where is functional nanoscience now? Passive nanodevices have essentially formed the bulk of past and contemporary nanoscience research. They are generally particles that have controllable properties but are still essentially 'simple' with no inbuilt intelligence, energy source, or means of propulsion. Passive nanoscience is approaching maturity. There were > 1000 nano products on market in U.S. at the end of 2009 [5].

The other, more challenging class of nanodevices that form the theme of this workshop are the active or functional nanodevices. Compared with the passive nanodevices, the field is embryonic but is developing rapidly and has great promise.

Issues/concepts/constraints from the Beilstein Bozen Symposium on Functional Nanoscience

The research presented at the Symposium contained a number of common themes, threads, constraints, and methodologies. We have summarized the presentations in terms of these general attributes so that the possible interconnections and interdependencies are drawn out.

Learning from, and instructing biology

Biology provides vivid proof that self-assembling functional nanodevices of immense sophistication and complexity are possible. We are surrounded by (and indeed composed of) a myriad of examples. As well as providing extremely compelling proof of concept, understanding how biological functional nanomachines operate provides a fast track to developing synthetic analogues. These may not have the current constraints of biology in requiring a controlled environment, physiological conditions, and an aqueous environment (extremophiles notwithstanding). As well as providing extremely useful mechanistic ideas, the biological machines themselves can be adapted to perform useful functions. The elegant experiments described by Firman show how DNA helicases can be used to construct functional nanomachines with very useful properties. Biology shows us what is possible if we are clever enough to understand it

We have been tackling difficult problems related to biological nanomachines, wittingly or unwittingly, for a very long time. Historically, this has largely involved disrupting biological processes for medical purposes. Examples include the modulation of DNA replicative machinery by antimicrobial [6, 7] or anticancer drugs (Figure 4), inhibition of enzymes, and artificial activation or inhibition of receptors.

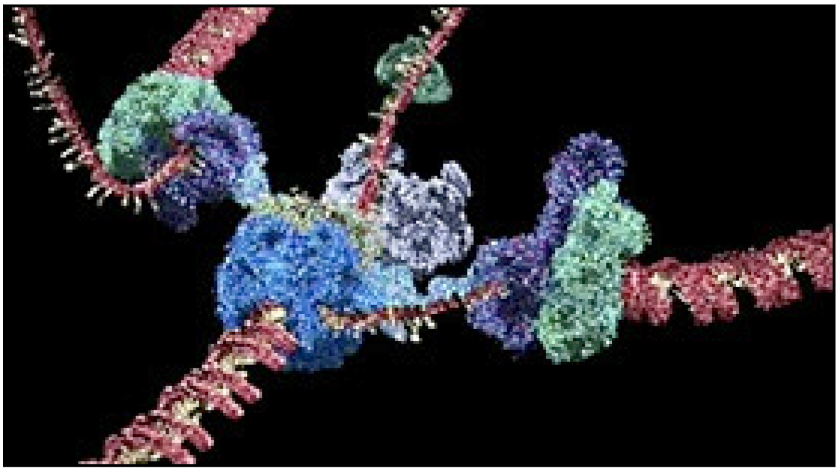

Figure 4. DNA polymerase molecular machine (DNA Replisome image by Drew Berry, the Walter and Eliza Hall Institute).

The stages of maturity in understanding controlling and emulating biological nanomachines may be summarized as follows:

- disrupting/destroying biological nanomachines (drug discovery, > 100 years)
- understanding biological nanomachines (often to learn better how to disrupt them, molecular biology and related sciences, > 50 years)
- emulating/mimicking biological nanomachines (synthetic biology, tissue engineering, present and future of functional nanoscience)
- improving/reprogramming/repurposing biological nanomachines (molecular biology, cell biology (stem cells), functional nanoscience

Disrupting biological nanomachines – drug development

Nanoscience has an important role to play in increasing efficiency of drug design and delivery

Nano approaches to drug targets

Rational drug design often requires detailed knowledge of the 3D structures of relevant molecular targets, usually receptors or enzymes. Although techniques for generating this information using X-ray crystallography has improved greatly, the rate determining step is still the crystallization of the target protein. This is particularly problematic for membrane bound proteins like many of the important receptor targets. Several of the speakers at the Bozen Symposium addressed these and related issues.

Paul Weiss (UCLA, Los Angeles, CA, U.S.A.) described a general technique for immobilizing neurotransmitters on surfaces, and using them to capture membrane receptors for identification, mapping, and structural studies. This may ultimately allow single molecule structural analysis, with no crystallization required [8]. The use of DNA type 1 restriction enzymes and DNA helicases for detecting drug-target, and drug-drug interactions, was described by Firman. The detector he described used the ability of helicase to unwind dsDNA, causing bead movement and a signal. Small molecule inhibitors stopped the helicase from functioning, generating no or low signal. This method may have single molecule sensitivity. Seeman made novel use of DNA origami to generate self-assembled crystal arrays for proteins. These employed a tensegrity triangle [9], and proof of concept was shown by organizing gold nanoparticles into a precisely constructed arrays. He proposed that such arrays might be used as frameworks to solve the protein crystallization problem. Kjems also described how DNA origami might be used to tackle the protein crystallization problem. He demonstrated how DNA arrays or objects could be generated by precisely controlled self-assembly, and how points on DNA objects can be addressed with proteins to make patterns on surface [10]. Shih used DNA origami to generate nanofibres as an NMR alignment medium for solving solution phase structures of membrane-bound proteins. The aligned DNA nanofibres generate a slight alignment bias of proteins allowing structure to be determined [11].

Nano approaches to drug delivery

Presentations by Bozen Symposium speakers described a diverse range of drug delivery methods that aim to approach the ‘‘ideal’’ drug delivery nanoparticle (Figure 5). Jonathan Posner (Arizona State University, Tempe, AZ, U.S.A.) described the properties of motile hybrid Au/Pt nanorods driven by a peroxide reaction. These nano-objects can carry payloads thirty times larger than the nanoparticle, and have potential applications in wound healing, and drug delivery [12]. Kjems’ work on DNA origami produced programmable, selective DNA boxes for drug delivery. These have an openable box with a lock closed by hybridization and opened by competing off the DNA oligonucleotide using a free complementary strand that is longer than the lock oligo. The DNA box delivery system can get into cells and appear to be stable in the intracellular environment, but they cannot yet be opened in cells on demand [10]. Tim Clark (University of Erlangen-Nürnberg, Germany) described how theory could lead experiment in design of persistent micelles for drug delivery [13], while Peter

Seeberger (Max Planck-Institute for Colloids and Interfaces, Berlin, Germany) showed examples of carbohydrate targeted nanoparticles. He exploited carbohydrate recognition to allow nanoparticles to be recognized by specific cells and internalized [14]. He has shown proof of concept of the technique applied to siRNA or antisense delivery. Carbohydrate treated quantum dot experiments in live rats showed very good delivery to liver, no obvious toxicity, and the particles were cleared in a few hours.

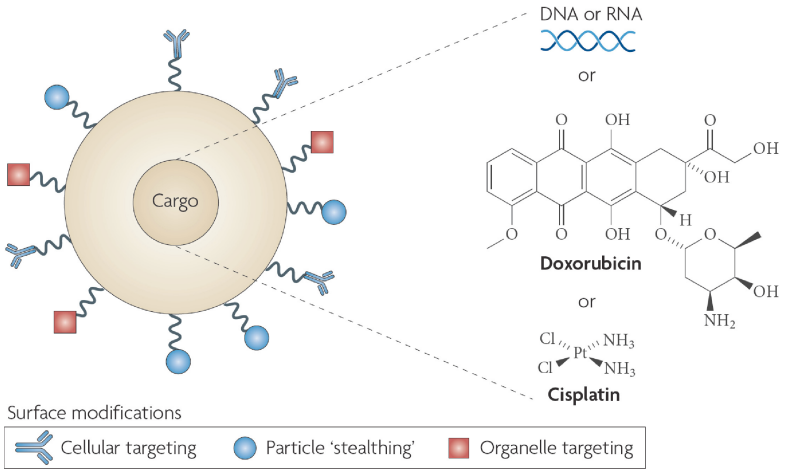

Figure 5. Ideal drug delivery nanoparticle. Petros and de Simone [15] use with permission.

Nano approaches to diagnostics

Functional nanoscience has the potential to revolutionize medical diagnostics. Several novel engineered nanodevices described by the speakers may lead to single molecule detection systems. Firman described the coupling of restriction endonucleases to magnetic beads to generate nanodetectors for quantifying ligand-receptor interactions in an analytical device. Christoph Gerber (University of Basel, Switzerland) described how micro-fabricated silicon cantilever array technology could be used to detect drugs, antibodies, bacteria, and to analyze breath for disease diagnosis. He also illustrated how nanomechanical holography can image live cells and track nanoparticles in them.

The cantilever sensor arrays are based on an AFM without tip, where inkjet technology is used to functionalize cantilever directly. The methods can be used to monitor transcription factors, transcription, and protein synthesis, and can be applied to proteomics by using antibody/antigen interactions. He also described the fast detection of microorganisms by cantilever arrays. These can easily detect resistant versus wild-type microbes (*e.g.* MRSA) where resistance is due to deletion of a *single* hydrogen bond. Seeberger discussed the manufacture of fast, cheap, carbohydrate-based nanodetectors. These exploit automated

carbohydrate synthesis, and printing technology applied to the rapid manufacture of glycomic chips [16]. He used nanotechnology to detect pathogenic bacteria quickly and cheaply using surface recognition and a fluorescent polymer. He also described using supramolecular chemistry (cyclodextrans on dendrimers) to make easy cheap detectors for, for example, bacteria and single molecules.

Understanding biological nanomachines

Are living things irreducibly complex?

There is a role for complementary reductionist and complexity-based approaches to understanding properties of biological systems.

Linear scaling quantum mechanical, and fine and coarse-grained MD modelling were described by Clark as useful techniques for understanding properties of biological systems. They provide an appropriate level of scale for modelling biological systems that is coupled to the complexity of the system and the amount of information available from experiments. Petra Schwille (TU Dresden, Germany) discussed experimental models of biological systems such as cells and cell division processes. She is constructing coarse-grained models of cells and genes. This work was informed by single molecule experiments in live organisms to deduce how nanoscale objects in biology self-organize [17]. The aim was to reproduce cellular processes in a simpler way than the cell uses. She adopted a bottom up approach to cell division, starting with a simple cell-like membrane, adding ion channels and skeleton and ATP. Sylvia Speller (Radboud University Nijmegen, The Netherlands) studied real biological systems (magnetoreception and bionavigation in fish) to understand how information is transduced to the nervous systems. Using AFM to study bio-magnetite within the nasal epithelium of salmon, she showed how the observed structures are compatible not only with mechanosensitive gating, but also with voltage gating of ion channels.

What is the basis for the incredibly low error rate with which biological machines operate?

This robust behaviour is a function of high fidelity operations, and editing of errors. In some cases (*e.g.* microtubule assembly) the robustness and self-editing are a function of self-organization, dynamic instability or equilibrium. We need to understand these processes well enough to exploit them in artificial nanomachines. Fraser Stoddart (NWU, Evanston, IL, U.S.A.) tackled this problem by designing ''intelligent interactions'' into his functional nanodevices [18]. Non-covalent intramolecular interactions can generate precise robust structures, such as catenanes and rotaxanes that can be used to build functional molecular devices. Weiss also worked with precise chemical systems, and attempted to use defects to advantage. Soft lithography developed by Whitesides' group, led to microdisplacement printing that uses adamantanethiols as a stamp ''resist'' easily displaced by stronger binding alkanethiols or amide substituted versions [19].

Emulating or mimicking biological nano objects

Biological nanomachines have both restrictions and advantages compared to synthetic versions that functional nanoscientists may construct. Primarily, the disadvantages are the need for physiological temperatures, neutral pH, and an aqueous environment. Biological nanomachines can, however, exploit readily available energy currency (ATP) and tap into sophisticated waste disposal processes in organisms. Biological nanomachines are often self-organized, autonomous, and robust. Artificial functional nanodevices, particularly those that move, will require a source of energy. This is a challenging problem, given the extremely small scale of the devices, but experiments described by Paul Weiss, Jonathan Posner, Petr Kràl (University of Illinois, Chicago, IL, U.S.A.), and William Shih show how this may be achieved by exploiting resources in the environment. Peter Dimroth's (ETH Zürich, Switzerland) presentation showed how we might learn from biological motors, ATP synthase being the archetypal example. We may be able to construct artificial nanodevices that exploit ATP and also use the body's waste disposal processes to remove the waste products of their operation.

Functional nanodevices designed for non-biological applications are potentially more problematic. Mimics would be required to operate in a wider range of environments, but need the energy and waste issues resolved. Kràl described how other types of nanopropulsion devices such as propellers, motors, and wheels can be modelled and designed by molecular dynamics calculations (Figure 6) [20]. He also discussed motors driven by electron tunnelling. Nanowheels can be driven by oblique light that generates charges in illuminated regions that drive wheel across water surface. Molecular graphene paddles can also pump liquids.

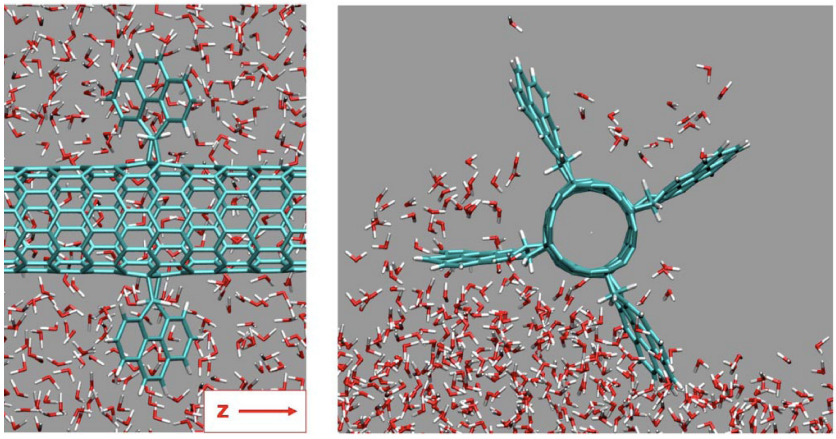

Figure 6. The bulk (left) and surface (right) water propellers that pump water along the tube (z) axis and orthogonal to it, respectively. Both systems are based on carbon nanotubes with covalently attached aromatic blades [20].

However, Kerstin Koch (Rhine-Waal University, Kleve, Germany) showed that nano objects generated by plants have simpler but useful functions that can be emulated. Her studies of the superhydrophobic, self-cleaning surfaces of leaves of plants such as the Lotus, largely due to the nanostructure of the leaf surface, have led to synthetic materials with very useful, self-cleaning properties that can function in diverse environments.

Improving, reprogramming, repurposing biology

Although not specifically covered by the Bozen Symposium presentations, the new research fields of synthetic biology, stem cell science, in addition to functional nanoscience, are beginning to adapt existing biological machines. Reprogramming somatic cells and stem cells to generate induced pluripotent stem cells (iPS cells) are high-level examples of manipulation of very complex biological systems. Directed evolution of enzymes to gain optimized or new functions, or to allow enzymes to operate in non-physiological environments, and the design and delivery of siRNA are additional example. Functional nano-objects that rely on adapting biological systems include nanoactuators based on restriction endonucleases described by Firman, and the exploitation of the properties of DNA to build novel nanostructures discussed by Seeman, Kjems, and Shih.

Self-organization and Self-assembly

The terms self-assembly and self-organization are used interchangeably and differently in different scientific disciplines. A recent publication has attempted to provide clear definitions for these terms that are generally applicable [21]. Self-assembly is a non-dissipative structural order on a macroscopic level, because of collective interactions between multiple (usually microscopic) components that do not change their character upon integration into the self-assembled structure. This process is spontaneous because the energy of unassembled components is higher than the self-assembled structure, which is in static equilibrium, persisting without the need for energy input. In contrast, self-organization is a dissipative non-equilibrium order at macroscopic levels, because of collective, nonlinear interactions between multiple microscopic components. This order is induced by interplay between intrinsic and extrinsic factors, and decays upon removal of the energy source. In this context, microscopic and macroscopic are relative. Both forms of programmable pattern formation are useful, but chemists tend to be more familiar with self-assembled objects that essentially form spontaneously using specific interactions between the components that are 'programmed into' the structures. The most mature and robust example of this is the DNA origami discussed in the presentations by Seeman and Shih, although the bottom up work described by most presenters also involved self-assembly. Weiss and Shih emphasized robustness, and precise placement in self-assembled nano objects in their presentations. Stoddard, Seeman, Kjems, and Shih discussed reliable, deterministic rules that result from programmed interactions in self-assembled objects. Quite complex self-assembled nanodevices have been designed, as the photonic device in Figure 7 illustrates [22, 23].

Self-organization has not yet been exploited significantly in functional nanoscience, but examples in nature show that is can be very useful. For example, the dynamic assembly of microtubules from tubulin is partly spontaneous but partly driven by the energy released when GTP is hydrolyzed by tubulin, which is an enzyme as well as a structural component [24]. One paper at the Bozen Symposium focused specifically on self-organization. Schwille described her experiments aimed to emulate some aspects of self-organization in cells. Her work exploits nonlinear dynamical systems reaction diffusion phenomena in biological systems.

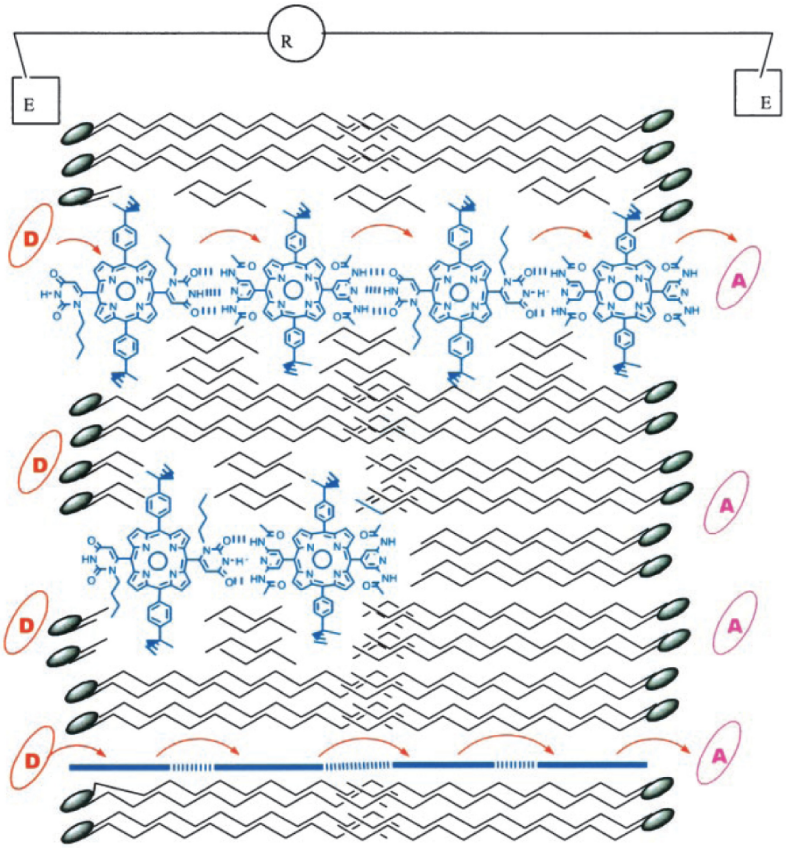

Figure 7. Schematic of one of four self-assembling porphyrin systems self-organized into bilayers to form a functional, self-assembled photonic device [22]. Used with permission.

Recent publications have described a new way to assemble nanostructures by exploiting dynamic instability and incorporating self-healing/editing [25]. Bouchard *et al*. show how to harnessing microtubule dynamic instability for nanostructure assembly. In nature intracellu-

lar molecular machines synthesize molecules, dissemble others, transport materials, and transform energy into different forms. Bouchard *et al*. proposed emulating these molecular machines to build nanostructures. Biological nanomachines work in a stochastic, noisy fashion. As described above, microtubules switch randomly between growing and shrinking in a process known as dynamic instability, but the final outcome is a very robust construction of microtubule bundles. A related example is given by kinesin movement along microtubules, which is randomly interrupted by these motor proteins falling off the microtubule. The error recovery afforded by dynamic instability allows these motor proteins to perform their functions autonomously and reliably. Bouchard *et al*. suggested gaining control over these highly dynamic, stochastic processes by eliminating some of them [25]. They show how the natural dynamic instability of microtubules can be exploited to build nanostructures, and described strategies for ensuring that ‘‘unreliable’’ stochastic processes yield a robust outcome. They made extensive use of simulation to understand how to harness dynamic instability, an important component of functional nanoscience discussed in the next section.

Design, computation, simulation and modelling

Most papers presented at the Bozen Symposium stressed the valuable contribution that computational modelling and simulation makes to functional nanoscience. The ability to model the properties of nano objects by molecular dynamics methods was illustrated by Clark (micelles) and Kràl (graphene propellers). Deterministic computational design is tractable, useful, and reliable at least for DNA as illustrated by Seeman, Kjems, and Shih. Stoddart emphasized the importance of ‘‘making, modelling, measuring’’, and Posner successfully modelled nanorod behaviour using simple scaling rules. However, Clark identified important caveats on molecular dynamics calculations for micelle self-assembly. Dimroth showed how modelling can be used to unravel the mechanisms of biological machines like ATP synthase. Athel Cornish-Bowden (CNRS-BIP, Marseilles, France) describes some elegant mathematical modelling to emulate or improve biology, and Michael Huth (University of Frankfurt, Germany) using the Hubbard model to predict the properties of granular metals.

Strengths of Hybrid Top down / Bottom up Approaches

Limitations of conventional top-down techniques like photolithography and scanning beam (or maskless) lithography include high capital and operating costs, difficulty in accessing these facilities. However, some of these can be overcome by moulding, stamping, and templating methods, and other often simple and elegant methods. An example of the latter is the manufacture of aligned and dimensionally controlled gold nanowires using ice described in Thomas Schimmel’s (Karlsruhe Institute of Technology, Germany) presentation.

It was clear from the presentations at the symposium that both top down and bottom up methods of constructing functional nanodevices are capable of yielding very useful and elegant devices. However, the strengths obtained by incorporating techniques and concepts from both approaches came out strongly. Each approach has strengths and weaknesses and these can often be reduce or eliminated by using hybrid approaches.

The Future

While extrapolation is dangerous and many incorrect projections often result, we have nonetheless attempted to predict where functional nanoscience may lead in the short, medium and long time frames. These extrapolations are based on presentations of the speakers at the Bozen Symposium, discussions with these scientists, and other input provided by nanoscientists not present at the symposium. The predictions will clearly be less accurate as the time frame extends out from 2010.

Extrapolations (2 – 5 years)

Most presenters agree that there will be an increasing move from passive to active nanomachines, for example, nanomachines used as pumps and valves in microfluidics (Gerber). Development of low energy, environmentally benign nanomaterials and manufacturing processes was identified as important drivers by Cornish-Bowden and Schimmel. Coupled to this will be community concern about the safety of nanoparticles and nanodevices, and methods for predicting the impact of nano-objects on cells will begin to appear. Improved methods to control defects will continue to develop, aided by increasingly powerful design, modelling, simulation, and informatics tools. Top down and bottom up fabrication methods will also combined more often in new devices, exploiting the advantages of both techniques (Stoddart). Cantilever devices will grow into larger device arrays and will gain additional functions and speed increases. AFM cantilever devices will begin to be developed for personalized medicine (Gerber). Single molecule structure determination methods, single molecule biosensors (Firman), and single atom quantum switches (Schimmel) will become more robust and begin to be developed into practical devices. Proof of concept for an artificial cell that divides symmetrically will be reported (Schwille), and better modelling of EBID processes, and new metals will be developed (Hans Mulders, FEI Electron Optics, Eindhoven, The Netherlands).

Predictions (5 – 10 years)

Nanomaterials and devices will become increasing complexity and multifunctional. 'Smart materials' such as structural materials with embedded sensors and distributed intelligence will appear, and passive and active nanomaterials will be incorporated into apparel for health monitoring, and sensor networks (Drummond). Faster, larger nanoswitch arrays will be developed (Stoddard, Schimmel) and direct experimental demonstration of a Turing machine

may be achieved (Stoddard). The first proof of concept demonstrations of self-organized nanomachines may also be achieved (Winkler). Reliable, targeted drug, vaccine, DNA/RNA delivery systems, with multiple payloads will be demonstrated (multiple, Caruso), and oral delivery of drugs using DNA boxes (Kjems). Very significant progress will be made on solution of the protein crystallization problem using precisely defined nanoarrays decorated with proteins (Seeman), and improved NMR protein structures will be obtained using nanoalignment (Shih). In this time frame, cryoEM images will yield atomic details (Shih), lithographic features as small as to 1 nm will be routinely generated (Huth), and precise control of functionality in carboranes will be possible (Weiss). The glycome will be understood sufficiently to allow precise and reliable targeting of nanoparticles and drugs to specific organs (Seeberger)

Dreams (10 – 20 years)

The increasing level of knowledge about biological systems, and improved nanoscience tools will facilitate the construction of adaptive, self-optimizing nanodevices. Engineered medical nanomachines will be designed that exploit endogenous ATP as a power source. Multiple energy sources such as miniature fuel cells, methods for tapping biological energy for nanodevices will be developed. Nanofabrication defects will be greatly reduced or eliminated by improved fabrication or dynamic self-healing methods, and effective control of self-organization for use in nanoscience will be achieved. Design and constriction of complex, diverse self-assembling nano objects will become routine, and nano-enabled diagnostic devices make personalized medicine a reality. Nano methods of target identification and drug delivery will create new paradigm for successful treatments of diseases. The first commercially useful self-assembled electronic devices will be developed and the estimated market for nanoscience will be US$1 trillion [26].

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