

Chapter 7

Biologically Related Aspects of Nanoparticles, Nanostructured Materials, and Nanodevices

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INTRODUCTION

Biological molecules and systems have a number of attributes that make them highly suitable for nanotechnology applications. For example, proteins fold into precisely defined three-dimensional shapes, and nucleic acids assemble according to well-understood rules. Antibodies are highly specific in recognizing and binding their ligands, and biological assemblies such as molecular motors can perform transport operations. Because of these and other favorable properties, biomolecules, biophysics, and biology are themes that run through all of the topics of this report.

Although very promising, the bio-related aspects of nanoparticles, nanostructured materials, and nanodevices, are, for the most part, not as well developed as the nonbiological ones. However, a number of recent workshops (e.g., the U.S./EC Workshop on Nanobiotechnology), symposia (e.g., the Conference on Molecular Nanotechnology, and the Symposium on Bio-Nano Electronics), and books (e.g., *Nanofabrication and Biosystems* Hoch et al. 1996) attest to the fact that many of the novel developments in this field are poised for rapid expansion.

This chapter is organized along the lines of the main report (Figure 7.1). It first puts into perspective current research directed toward biological synthesis and assembly as it pertains to the building blocks of nanotechnology. It then focuses on the current state of the art in biological aspects of dispersions and coatings, high surface area materials, and functional

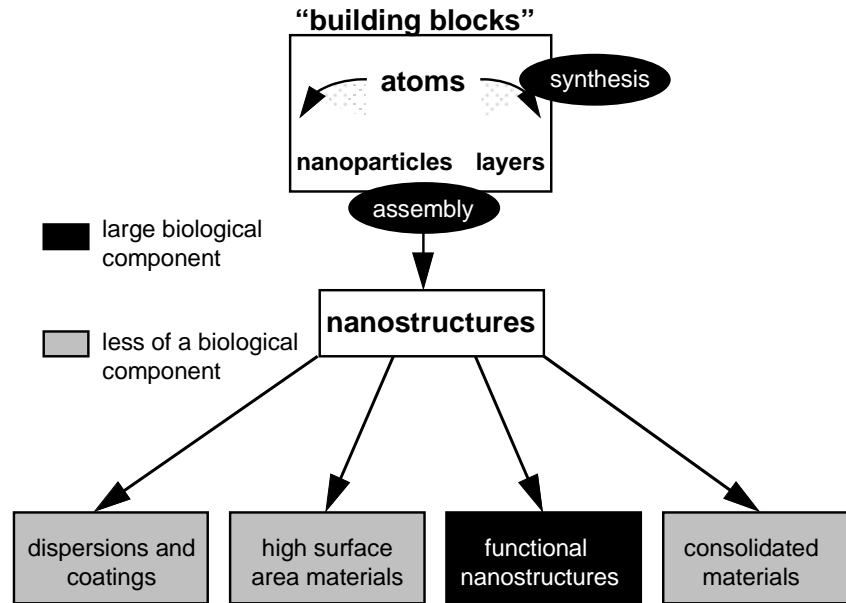


Figure 7.1. Organization of the WTEC study; sections with large biological content are indicated.

nanostructures. Finally, it ends with a section on the challenges and opportunities for the biological aspects of nanotechnology.

NANOTECHNOLOGY BUILDING BLOCKS

Synthesis

Although it seems at first that Nature has provided a limited number of basic building blocks—amino acids, lipids, and nucleic acids—the chemical diversity of these molecules and the different ways they can be polymerized or assembled provide an enormous range of possible structures. Furthermore, advances in chemical synthesis and biotechnology enable one to combine these building blocks, almost at will, to produce new materials and structures that have not yet been made in Nature. These self-assembled materials often have enhanced properties as well as unique applications.

The selected examples below show ways in which clever synthetic methodologies are being harnessed to provide novel biological building blocks for nanotechnology.

The protein polymers produced by Tirrell and coworkers (1994) are examples of this new methodology. In one set of experiments, proteins were

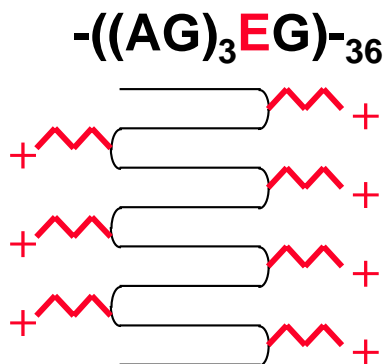


Figure 7.2. Top: a 36-mer protein polymer with the repeat sequence (alanine-glycine)₃ – glutamic acid – glycine. Bottom: idealized folding of this protein polymer, where the glutamic acid sidechains (+) are on the surface of the folds.

designed from first principles to have folds in specific locations and surface-reactive groups in other places (Figure 7.2) (Krejchi et al. 1994; 1997). One of the target sequences was $-((AG)_3EG)_{36}$. The hypothesis was that the AG regions would form hydrogen-bonded networks of beta sheets and that the glutamic acid would provide a functional group for surface modification. Synthetic DNAs coding for these proteins were produced, inserted into an *E. coli* expression system, and the desired proteins were produced and harvested. These biopolymers formed chain-folded lamellar crystals with the anticipated folds. In addition to serving as a source of totally new materials, this type of research also enables us to test our understanding of amino acid interactions and our ability to predict chain folding.

Biopolymers produced via biotechnology are monodisperse; that is, they have precisely defined and controlled chain lengths; on the other hand, it is virtually impossible to produce a monodisperse synthetic polymer. It has recently been shown that polymers with well-defined chain lengths can have unusual liquid crystalline properties. For example, Yu et al. (1997) have shown that bacterial methods for polymer synthesis can be used to produce poly(γ -benzyl α L-glutamate) that exhibits smectic ordering in solution and in films. The distribution in chain length normally found for synthetic polymers makes it unusual to find them in smectic phases. This work is important in that it suggests that we now have a route to new smectic phases whose layer spacings can be controlled on the scale of tens of nanometers.

The biotechnology-based synthetic approaches described above generally require that the final product be made from the natural, or L-amino acids. Progress is now being made so that biological machinery (e.g., *E. coli*), can be co-opted to incorporate non-natural amino acids such as β -alanine or

dehydroproline or fluorotyrosine, or ones with alkene or alkyne functionality (Deming et al. 1997). Research along these lines opens new avenues for producing controlled-length polymers with controllable surface properties, as well as biosynthetic polymers that demonstrate electrical phenomena like conductivity. Such molecules could be used in nanotechnology applications.

Novel chemical synthesis methods are also being developed to produce “chimeric” molecules that contain organic turn units and hydrogen-bonding networks of amino acids (Winningham and Sogah 1997). Another approach includes incorporating all tools of chemistry into the synthesis of proteins, making it possible to produce, for example, mirror-image proteins. These proteins, by virtue of their *D*-amino acid composition, resist biodegradation and could have important pharmaceutical applications (Muir et al. 1997).

Arnold and coworkers are using a totally different approach to produce proteins with enhanced properties such as catalytic activity or binding affinity. Called “directed evolution,” this method uses random mutagenesis and multiple generations to produce new proteins with enhanced properties. Directed evolution, which involves DNA shuffling, has been used to obtain esterases with five- to six-fold enhanced activity against *p*-nitrobenzyl esters (Moore et al. 1997).

Assembly

The ability of biological molecules to undergo highly controlled and hierarchical assembly makes them ideal for applications in nanotechnology. The self-assembly hierarchy of biological materials begins with monomer molecules (e.g., nucleotides and nucleosides, amino acids, lipids), which form polymers (e.g., DNA, RNA, proteins, polysaccharides), then assemblies (e.g., membranes, organelles), and finally cells, organs, organisms, and even populations (Rousseau and Jelinski 1991, 571-608). Consequently, biological materials assembly on a very broad range of organizational length scales, and in both hierarchical and nested manners (Aksay et al. 1996; Aksay 1998). Research frontiers that exploit the capacity of biomolecules and cellular systems to undergo self-assembly have been identified in two recent National Research Council reports (NRC 1994 and 1996). Examples of self-assembled systems include monolayers and multilayers, biocompatible layers, decorated membranes, organized structures such as microtubules and biomineralization, and the intracellular assembly of CdSe semiconductors and chains of magnetite.

A number of researchers have been exploiting the predictable base-pairing of DNA to build molecular-sized, complex, three-dimensional objects. For example, Seeman and coworkers (Seeman 1998) have been investigating these properties of DNA molecules with the goal of forming complex 2-D and 3-D periodic structures with defined topologies. DNA is

ideal for building molecular nanotechnology objects, as it offers synthetic control, predictability of interactions, and well-controlled “sticky ends” that assemble in highly specific fashion. Furthermore, the existence of stable branched DNA molecules permits complex and interlocking shapes to be formed. Using such technology, a number of topologies have been prepared, including cubes (Chen and Seeman 1991), truncated octahedra (Figure 7.3) (Zhang and Seeman 1994), and Borromean rings (Mao et al. 1997).

Other researchers are using the capacity of DNA to self-organize to develop photonic array devices and other molecular photonic components (Sosnowski et al. 1997). This approach uses DNA-derived structures and a microelectronic template device that produces controlled electric fields. The electric fields regulate transport, hybridization, and denaturation of oligonucleotides. Because these electric fields direct the assembly and transport of the devices on the template surface, this method offers a versatile way to control assembly.

There is a large body of literature on the self-assembly on monolayers of lipid and lipid-like molecules (Allara 1996, 97-102; Bishop and Nuzzo 1996). Devices using self-assembled monolayers are now available for analyzing the binding of biological molecules, as well as for spatially tailoring the

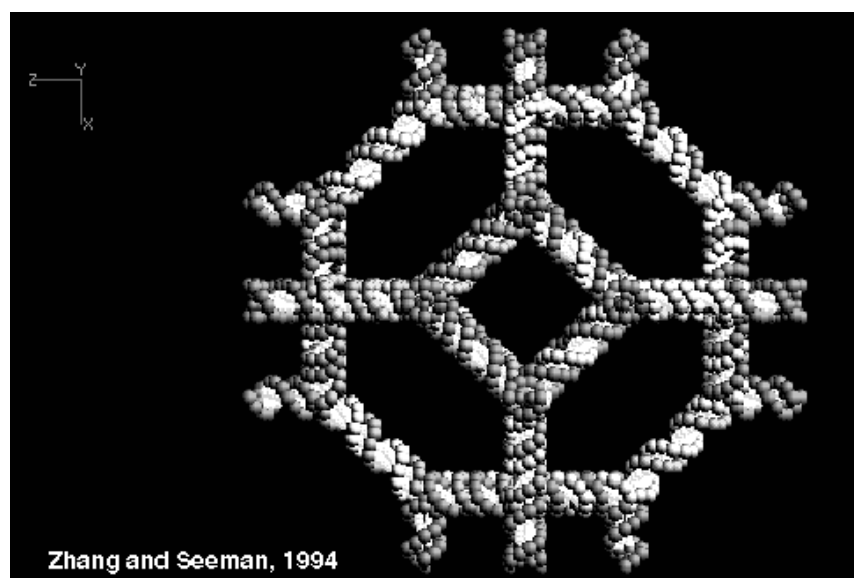


Figure 7.3. Idealized truncated octahedron assembled from DNA. This view is down the four-fold axis of the squares. Each edge of the octahedron contains two double-helical turns of DNA.

surface activity. The technology to make self-assembled monolayers (SAMs) is now so well developed that it should be possible to use them for complex electronic structures and molecular-scale devices.

Research stemming from the study of SAMs (e.g., alkylthiols and other biomembrane mimics on gold) led to the discovery of “stamping” (Figure 7.4) (Kumar and Whitesides 1993). This method, in which an elastomeric stamp is used for rapid pattern transfer, has now been driven to < 50 nanometer scales and extended to nonflat surfaces. It is also called “soft lithography” and offers exciting possibilities for producing devices with unusual shapes or geometries.

Self-assembled organic materials such as proteins and/or lipids can be used to form the scaffolding for the deposition of inorganic material to form ceramics such as hydroxyapatite, calcium carbonate, silicon dioxide, and iron oxide. Although the formation of special ceramics is bio-inspired, the organic material need not be of biological origin. An example is production of template-assisted nanostructured ceramic thin films (Aksay et al. 1996).

A particularly interesting example of bio-inspired self-assembly has been described in a recent article by Stupp and coworkers (Stupp et al. 1997). This work, in which organic “rod-coil” molecules were induced to self-assemble, is significant in that the molecules orient themselves and self-assemble over a wide range of length scales, including mushroom-shaped clusters (Figure 7.5); sheets of the clusters packed side-by-side; and thick films, where the sheets pack in a head-to-tail fashion. The interplay between hydrophobic and hydrophilic forces is thought to be partially responsible for the controlled assembly.

DISPERSIONS AND COATINGS

Drug Delivery Systems

Nanoparticles and nanospheres have considerable utility as controlled drug delivery systems (Hanes et al. 1997). When suitably encapsulated, a pharmaceutical can be delivered to the appropriate site, its concentration can be maintained at proper levels for long periods of time, and it can be prevented from undergoing premature degradation (see Chapter 3). Nanoparticles (as opposed to micron-sized particles) have the advantage that they are small enough that they can be injected into the circulatory system.

Highly porous materials are also ideal candidates for controlled drug delivery (Schnur et al. 1994) and for tissue engineering (Hubbell and Langer 1995). An example of a controlled drug delivery system comes from the area of microtubules. Phospholipid bilayers can self-assemble into long cylindrical tubes with diameters usually below a micron and lengths up to hundreds of microns (Schnur 1993). During synthesis, drugs can be entrained

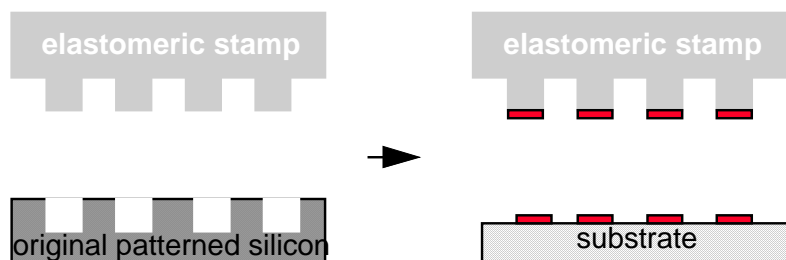


Figure 7.4. An elastomeric stamp (top left) is made from an original master (bottom left). The stamp is dipped into the biological material (top right) and the pattern is transferred to the substrate (bottom right).

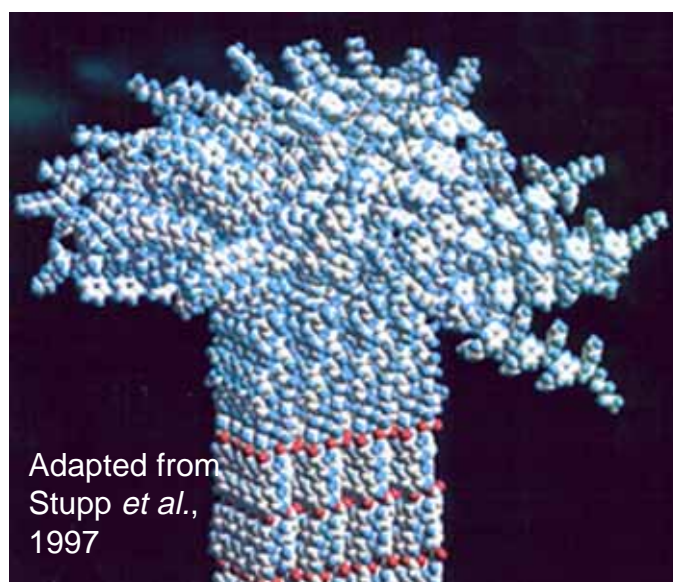


Figure 7.5. Mushroom-shaped clusters formed from self-assembly of rod-coil molecules; these clusters can undergo further packing to form sheets.

in these nanotubes, and the final product can be used as a controlled delivery system. Tubules prepared from phospholipid bilayers are ideal for such applications because they are biocompatible.

Dendrimers can be prepared so they are of discrete size and contain specific functional groups (Karak and Maiti 1997). They can be functionalized and used in biomedicine. Examples include gene transfer agents for gene therapy, made to carry and control the relaxivity of paramagnetic MRI (magnetic resonance imaging) contrast agents (Toth et al. 1996), and to deliver drugs on a controlled release basis.

Role of Nanoparticles in Health and Pollution

Although beyond the scope of this review, it is important to keep in mind the potential role of atmospheric nanoparticles in photocatalytic and thermal production of atmospheric pollutants. Atmospheric aerosols in heavily polluted areas have the potential to accelerate ozone formation reactions. Furthermore, because they are respirable, they could represent a health hazard. Two controversial studies (the Harvard University six-city study and the American Cancer Society study) have linked the presence of fine particular matter to premature mortality (*Chemical and Engineering News* 1997).

Atmospheric aerosols generally contain two major components: one is composed of amorphous carbon that has fullerene-like particles dispersed in it; the second is inorganic and consists of oxides and sulfides supported on clay minerals. In particular, the iron oxide, manganese oxide, and iron sulfide nanoparticles have band-gaps that could enhance the photocatalytic adsorption of solar radiation. In addition, these materials are acidic and may be coated with water, which would enhance their catalytic ability to crack hydrocarbons and create free radicals (Chianelli 1998). At present this is an underexplored area of research that bears scrutiny.

It is interesting to note that some microorganisms produce and sequester CdSe and CdS nanoparticles in response to high levels of toxic Cd⁺⁺ in their environment (Brus 1996). A large number of organisms also have the ability to precipitate ferrimagnetic minerals Fe₃O₄ and Fe₃S₄ (see Consolidated Materials, below).

HIGH SURFACE AREA MATERIALS

Membranes for Biological Separations

Supported polymeric membranes can be used to remove low molecular weight organics from aqueous solution (Ho et al. 1996). They work by filling the pores of microfiltration or ultrafiltration membranes with functional, polymeric, or oligomeric liquids that have an affinity for the compound of interest. These ideas can be extended to microemulsions and used for separations of large biological molecules. For example, non-ionic microemulsions (i.e., oil-water systems) have been used for hemoglobin extraction. These results augur well for the separation of other biological materials (Qutubuddin et al. 1994). Molecular imprinting can also be used to produce high surface area adsorbents that are enantioselective for amino acids and other biological molecules (Vidyasankar et al. 1997).

Bacterial Cell Surface Layers as Patterning Elements

Crystalline bacterial cell surface layers (S-layers) are composed of repeating protein units. These layers self-assemble and have a high binding capacity. They have been explored as patterning elements for molecular nanotechnology. For example, they have been used to pattern cadmium sulfide superlattices (Shenton et al. 1997).

FUNCTIONAL NANOSTRUCTURES

Molecular Computation

The smallest possible computer would ideally be able to perform computations on a molecular scale. Even though the computation may be carried out on that scale, the issue becomes one of having enough molecules to obtain sufficient signal-to-noise ratio to read out the answer. Consequently, at least at present, these computations must be carried out in bulk or with extremes in temperature. There has been a recent development along this line. Adleman (1994) has shown how the rules of DNA self-assembly, coupled with polymerase chain reaction (PCR) amplification of DNA, can lead to a molecular computer of sorts. The system was used to solve the Hamiltonian path problem, a classic and difficult (NP complete) mathematical problem that involves finding a path between vertices of a graph. The starting and ending vertices of each edge of the graph were encoded as the first and second halves of a strand of DNA. A solution to the problem (what is the path between two specific vertices?) was obtained by using PCR primers for the two vertices. Others have extended these ideas and shown that it is possible to make DNA add (Guarnieri et al. 1996). Although these are exciting demonstrations, at present this technology has a number of drawbacks, including the labor and time it takes to analyze the results of the computation, and the uncertainties associated with wet chemistry.

Optoelectronic Devices

Biological molecules and assemblies, such as the photochemical reaction center, are capable of capturing light with good quantum efficiency and transforming it into chemical energy. If properly exploited, such assemblies have potential applications as biomolecule information processing units.

Bacteriorhodopsin, from the purple membrane bacterium *Halobacterium halobium*, is one such system that has been studied extensively and has been

commercialized into optical holographic memories (Birge 1995). In the bacterium, the protein bacteriorhodopsin self-assembles into ordered lipid patches. The protein absorbs light and undergoes a cycle involving a complex series of intermediates, resulting in a proton being pumped across the membrane. It was information developed from understanding the basic science behind the way that bacteriorhodopsin works that led to the use of bacteriorhodopsin as a biomolecule information processing unit. To be used for information storage, the protein is placed under nonbiological conditions. It is dispersed and immobilized into a matrix (e.g., collagen or another polymeric substance) and held at liquid nitrogen temperatures. At this low temperature, the protein acts as an optically-driven bistable switch. One form, the light-adapted form of bacteriorhodopsin, absorbs light at 570 nm. When irradiated with green light at 77 K, it switches to a different stable form that absorbs at 630 nm. Using light of different colors enables one to read and write images onto these memories. By subtracting one memory from the other, these memories are especially useful for realtime, rapid comparison of images.

Molecular Motors

The molecular motors found in biology provide for bacterial locomotion, as well as for the active transport and delivery of molecules. For example, the bacterial flagellar motor is about 20 nm in diameter, and is comprised of a complex assembly of more than 10 different proteins (Imae and Atsumi 1989). The role of the motor is to rotate the helical flagella of the bacterium so that it is able to swim. Chemical energy (in this case protons or sodium) is transduced into mechanical energy.

Other examples of molecular motors include RNA polymerase (Yin et al. 1995), F₁-ATPase (Noji et al. 1997), myosin, and kinesin (Seventh Biophysical Discussions 1995). The fuel that powers these motors is ATP (adenosine triphosphate). A number of researchers have proposed schemes by which such motors could be used to deliver molecules, one at a time, for the purpose of the ground-up assembly of nanoscale devices (NRC 1996). It is envisioned that the highways could be actin or tubulin, which would need to be immobilized onto a surface. Myosin or kinesin, which naturally travel along these highways, could be used to deliver molecular “packages” to a specific assembly site.

Other Forms of Biological Transport Using Nanoparticles

In the human body, the function of the high density lipoproteins is to transport cholesterol. The ~ 7.5 nm discoidal lipoprotein assemblies are sandwiched between discs of phospholipids and stacked, poker-chip style.

The lipoproteins stabilize the cholesterol particles and assist in their transport. Current research involves manipulating and fusing the assemblies and particles with an atomic force microscope (ATM) tip (Sligar 1998).

Bioelectronics

There has been considerable research activity in molecular electronics and bioelectronics, particularly in Japan (Aizawa 1994). Although this area of nanotechnology is still not as well developed as others in this report, it bears watching. For example, Shionoya and coworkers at the Institute for Molecular Science of the Okazaki National Research Institutes in Japan (see site report, Appendix D) have proposed that novel combinations of DNA, metal ligands, DNA templating, and proteins could produce molecular wires; molecular hoops through which DNA could be threaded; and double-stranded peptides whose helix pitch could be controlled by an entrained metal (Figure 7.6). The active site containing the metal could be induced to go from $\text{Cu(I)}_{\text{tetrahedral}}$ to $\text{Cu(II)}_{\text{square planar}}$, perhaps by electrons delivered by a scanning tunneling microscope (STM) tip.

CONSOLIDATED MATERIALS

Ceramics

Biomolecule/inorganic interactions can be used to produce ceramics with increased toughness. Fundamental studies of biomineralization, in which an organic substance (usually protein or peptide or lipid) interacts with an inorganic phase (e.g., calcium carbonate or hydroxyapatite) have led to the bioinspired synthesis of composite materials.

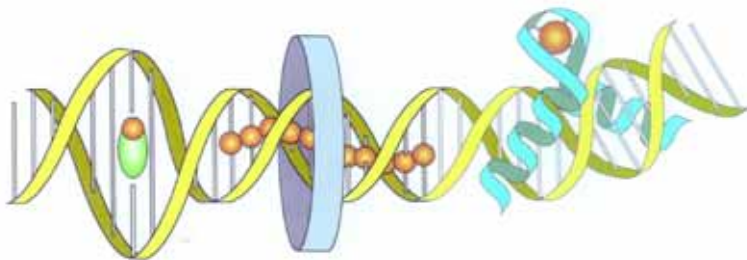


Figure 7.6. Novel combinations of DNA, metal ligands, DNA templating, and proteins are being investigated for molecular wires, inductors, and switches (photo courtesy of Shionoya and coworkers, Inst. for Molecular Science).

The structure and porosity of the inorganic phase can be controlled by templating with an organic surfactant, vesicular arrays, or liquid crystalline materials. Micelle-templated synthesis can produce ceramics with 20-100 Å pore dimensions (Ying 1998). These tailored pores can be used as catalysts and absorbents, and for gas/liquid separations and thermal and acoustic insulation. Their selectivity makes them very useful for biochemical and pharmaceutical separations. Bioceramics can also be made that are more compatible with teeth and bone.

An interesting example of an organic/inorganic composite is the new packaging material that has been developed to replace the polystyrene “clam-shell” for fast food products. Composed of potato starch and calcium carbonate, this foam combines the advantages of good thermal insulation properties and light weight with biodegradability (Stucky 1978).

Biological Bar Magnets

It has been well documented that a very large number of organisms have the ability to precipitate ferrimagnetic minerals such as Fe_3O_4 and Fe_3S_4 . In addition, linear chains of membrane-bound crystals of magnetite, called magnetosomes, have been found in microorganisms and fish (Kirschvink et al. 1992). For example, the Fe_3O_4 domain size in the organism *A. magnetotactum* is about 500 Å, and a chain of 22 of those domains has a magnetic moment of 1.3×10^{-15} . It is not immediately clear how these particles could be exploited for nonbiological applications.

OPPORTUNITIES AND CHALLENGES

This section of the review describes current limits on the biological aspects of nanotechnology. It outlines selected broad areas of research opportunity, and it sets forth challenges for the intermediate and long-term future.

Enabling Technologies

We owe much of the recent progress in the biological aspects of nanotechnology and nanoparticles to important enabling technologies. Many of these enabling technologies are described in other parts of this report. Those that have had a significant impact on biological measurements include techniques and instrumentation such as optical traps, laser tweezers, and “nano-pokers” to measure femtoNewton forces (Svoboda and Block 1994), and AFM and STM (Wildoer et al. 1998).

There is also a need to move detection away from the ensemble, to the single molecule scale. This includes driving instrumentation toward single-molecule spectroscopy; single-spin detection (Rugar et al. 1994); chemical analysis of nanoliter volumes (Hietpas et al. 1996, 139-158); nuclear magnetic resonance microcoils; nanoscale electrode arrays and chemical sensing and detecting technology (McConnell 1996, 97-102); separations technology; chemical analysis of single cells (Hietpas et al. 1996); new biological transformations; and chemical probes of nanostructures.

Enhanced computational infrastructure, both hardware and algorithm development, will also be required to investigate supramolecular assemblies and to understand interactions that occur over a wide variety of time and length scales. At present, we are fairly well equipped to handle quantum mechanical calculations. At the next level of computational complexity, the molecular dynamics force fields and atomic charges can presently handle up to about a million particles and still retain their accuracy. The next scale of complexity, mesoscale modeling, currently requires the use of pseudo atoms. Much more research is required to improve the accuracy of finite element calculations and the modeling of materials applications (Goddard 1998).

Surface Interactions and the Interface Between Biomolecules and Substrates

Much of the progress in the biological aspects of nanotechnology has come from research on surface interactions. It will be important to continue to develop a better understanding of the interface between biomolecules and surfaces. Of particular interest are questions about whether surfaces cause biomolecules to denature, the optimum length of linker groups, and ways to communicate from the biomolecule, through the linker, to the substrate. Another challenge is to produce nanometer ultrathin films that have stable order (Jaworek et al. 1998).

Robustness of Biomolecules and Their Interactions in Aqueous Solution

Although much progress has been made on ways to confer additional robustness on biomolecules, it will be necessary to continue to improve the stability and reliability of biomolecular assemblies. Such research may be along the lines of understanding the thermal stability of biomolecules, perhaps by examining extremophiles and molecules produced by directed evolution. It will also be necessary to produce molecules that can work in the absence of water, or to devise ways in which aqueous solutions can be used reliably.

Assemblers or Templating

The hierarchical self-assembly of biomolecules is often touted as one of their key attributes for nanotechnology applications. However, there remains much to be learned about how to make periodic arrays of biomolecular assemblies, how to use biological templating in an efficient manner, how to mimic biological self-assembly with nonbiological molecules, and how to exploit differences between biological and nonbiological self-assembly.

Combinatorial Approaches to Nanotechnology

Combinatorial chemistry has had an enormous impact on drug discovery and development in the past several years. Ability to develop molecularly sensitive screening techniques is one of the limiting factors of combinatorial chemistry. It would be intriguing to discover screening methods that are particularly sensitive for picking up new phenomena exhibited by biological nanoparticles.

Biomimetics and Polymer-Biopolymer Chimeras

The largest impact of biological sciences on nanotechnology may prove to be through the lessons one can learn from biology, rather than from directly employing the biological molecules themselves. To this end, it is important to support research on various aspects of biomimetics, including activities in which synthetic and biologically-based molecules are combined in chimeric fashion.

TECHNOLOGICAL COMPARISONS

Table 7.1 makes subjective comparisons, weighted by level of effort, impact of research, etc., between the state of biology-related nanotechnology work in Japan, Europe, and the United States.

TABLE 7.1. Comparisons Between Japan, Europe, and the United States in Biologically Related Aspects of Nanotechnology

Synthesis	US/Eur/Japan			
Assembly	US/Eur		Japan	
Dispersions and Coatings		US	Eur	Japan
High Surface Area Materials		Eur/Japan	US	
Functional Nanostructures		US/Japan		Eur
Bio-electronics		Japan		US/Eur
Level	1	2	3	4
	Highest			

REFERENCES

- Adleman, L.M. 1994. Molecular computation to solutions of combinatorial problems. *Science* 266:1021-1024.
- Aizawa, M. 1994. Molecular interfacing for protein molecular devices and neurodevices. *IEEE Engineering in Medicine and Biology* (Feb./March):94-102.
- Aksay, I.A., M. Trau, S. Manne, I. Honma, N. Yao, L. Zhou, P. Fenter, P.M. Eisenberger, and S.M. Gruner. 1996. Biomimetic pathways for assembling inorganic thin films. *Science* 273:892-898.
- Aksay, Ilhan. 1998. Nanostructured ceramics through self-assembly. In *R&D status and trends*, ed. Siegel et al.
- Allara, D.L. 1996. Nanoscale structures engineered by molecular self-assembly of functionalized monolayers. In *Nanofabrication and biosystems*, ed. Hoch et al.
- Birge, R.R. 1995. Protein based computers. *Sci. Am.* (Mar.):90-95.
- Bishop, A.R., and R.G. Nuzzo. 1996. Self-assembled monolayers: Recent developments and applications. *Current Opinion in Colloid & Interface Sci.* 1:127-136.
- Brus, L. 1996. Semiconductor colloids: Individual nanocrystals, opals and porous silicon. *Current Opinion in Colloid & Interface Science* 1:197-201.
- Chemical Engineering News.* 1997. Particulate matter health studies to be reanalyzed (August 18):33.
- Chen, J. and N.C. Seeman. 1991. The synthesis from DNA of a molecule with the connectivity of a cube. *Nature* 350:631-633.
- Chianelli, R.R. 1998. Synthesis, fundamental properties and applications of nanocrystals, sheets, and fullerenes based on layered transition metal chalcogenides. In *R&D status and trends*, ed. Siegel et al.

- Conference on Molecular Nanotechnology. 1997. 2nd Annual International Conference, December 8-9. La Jolla, CA.
- Deming, T.J., M.J. Fournier, T.L. Mason, and D.A. Tirrell. 1997. Biosynthetic incorporation and chemical modification of alkene functionality in genetically engineered polymers. *J. Macromol. Sci. Pure Appl. Chem. A* 34:2143-2150.
- Goddard, W.A. 1998. Nanoscale theory and simulation. In *R&D status and trends*, ed. R. Siegel et al.
- Guarnieri, F., M. Fliss, and C. Bancroft. 1996. Making DNA Add. *Science* 273:220-223.
- Hanes, J., J.L. Cleland, and R. Langer. 1997. New advances in microsphere-based single-dose vaccines. *Advanced Drug Delivery Reviews* 28:97-119.
- Hietpas, P.B., S.D. Gilman, R.A. Lee, M.R. Wood, N. Winograd, and A.G. Ewing. 1996. Development of voltammetric methods, capillary electrophoresis and tof sims imaging for constituent analysis of single cells. In *Nanofabrication and biosystems*, ed. Hoch et al.
- Ho, S.V., P.W. Sheridan, and E. Krupetsky. 1996. Supported polymeric liquid membranes for removing organics from aqueous solutions. 1. Transport characteristics of polyglycol liquid membranes. *J. Membrane Sci.* 112:13-27.
- Hoch, H.C., L.W. Jelinski, and H.G. Craighead, eds. 1996. *Nanofabrication and biosystems*. New York: Cambridge University Press.
- Hubbell, J.A., and R. Langer. 1995. Tissue engineering. *Chem. Eng. News* (March 13): 42-54.
- Imae, Y., and T. Atsumi. 1989. T. Na⁺-driven bacterial flagellar motors: A mini-review. *J. Bioenergetics and Biomembranes* 21:705-716.
- Jaworek, T., D. Deher, G. Wegner, R.H. Wieringa, and A.J. Schouten. 1998. Electromechanical properties of an ultrathin layer of directionally aligned helical polypeptides. *Science* 279:57-60.
- Karak, N., and S. Maiti. 1997. Dendritic polymers: A class of novel material. *J. Polym. Mater.* 14:105.
- Kirschvink, J.L., A. Koyayashi-Kirschvink, and B.J. Woodford. 1992. Magnetite biomineralization in the human brain. *Proc. Nat'l. Acad. Sci. USA* 89:7683-7687.
- Krejchi, M.T., E.D.T. Atkins, A.J. Waddon, M.J. Fournier, T.L. Mason, and D.A. Tirrell. 1994. Chemical sequence control of beta-sheet assembly in macromolecular crystals of periodic proteins. *Science* 265:1427-1432.
- Krejchi, M.T., S.J. Cooper, Y. Deguchi, E.D.T. Atkins, M.J. Fournier, T.L. Mason, and D.A. Tirrell. 1997. Crystal structures of chain-folded antiparallel beta-sheet assemblies from sequence-designed periodic polypeptides. *Macromolecules* 30:5012-5024.
- Kumar, A., and G.M. Whitesides. 1993. Features of gold having micrometer to centimeter dimensions can be formed through a combination of stamping with an elastomeric stamp and an alkanethiol ink followed by chemical etching. *App. Phys. Lett.* 63:2002-2004.
- Mao, C., W. Sun, and N.C. Seeman. 1997. Construction of Borromean rings from DNA. *Nature* 386:137-138.
- McConnell, H.M. 1996. Light-addressable potentiometric sensor: Applications to drug discovery. In *Nanofabrication and biosystems*, ed. Hoch et al.
- Moore, J.C., H.M. Jin, O. Kuchner, and F.H. Arnold. 1997. Strategies for the in vitro evolution of protein function: Enzyme evolution by random recombination of improved sequences. *J. Mol. Biol.* 272:336-347.
- Muir, T.W., P.E. Dawson, and S.B.H. Kent. 1997. Protein synthesis by chemical ligation of unprotected peptides in aqueous solution. *Meth. Enzymol.* 289:266-298.
- NRC (National Research Council). 1996. *Biomolecular self-assembling materials: Scientific and technological frontiers*. Washington, DC: National Academy Press.
- _____. 1994. *Hierarchical structures in biology as a guide for new materials technology*. Washington, DC: National Academy Press.
- Noji, H., R. Yasuda, M. Yoshida, and K. Kinosita, Jr. 1997. Direct observation of the rotation of F-1-ATPase. *Nature*. 386:299-302.

- Qutubuddin, S., J.M. Wiencek, A. Nabi, and J.Y. Boo. 1994. Hemoglobin extraction using cosurfactant-free nonionic microemulsions. *Sep. Sci. and Technology* 29:923-929.
- Rousseau, D.L., and L.W. Jelinski. 1991. Biophysics. In *Encyclopedia of Applied Physics* Vol. 2. New York: VCH Publishers.
- Rugar, D., O. Zuger, S. Hoen, C.S. Yannoni, H.M. Veith, and R.D. Kendrick. 1994. Force detection of nuclear magnetic resonance. *Science* 264:1560-1563.
- Schnur, J.M. 1993. Lipid tubules: A paradigm for molecularly engineering structures. *Science* 262:1669-1676.
- Schnur, J.M., R. Price and A.S. Rudolph. 1994. Biologically engineered microstructures—Controlled release applications. *J. Controlled Release* 28:3-13.
- Seeman, N.C. 1998. DNA nanotechnology. In *R&D status and trends*, ed. Siegel et al. Seventh Biophysical Discussions. 1995. Molecular motors: Structure, mechanics and energy transduction. *Biophys. J.* 68:Supplement S.
- Shenton, W., D. Pum, U.B. Sleytr, and S. Mann. 1997. S. synthesis of cadmium sulphide superlattices using self-assembled bacterial S-layers. *Nature* 389:585-587.
- Siegel, R.W., E. Hu, and M.C. Roco. 1998. *R&D status and trends in nanoparticles, nanostructured materials, and nanodevices in the United States*. Proceedings of the May 8-9, 1997 workshop. Baltimore: Loyola College, International Technology Research Institute. NTIS #PB98-117914.
- Sligar, S. 1998. Molecular and electronic nanostructures. In *R&D status and trends*, ed. Siegel et al.
- Sosnowski, R.G., E. Tu, W.F. Butler, J.P. O'Connell, and M.J. Heller. 1997. Rapid determination of single base mismatch mutations in DNA hybrids by direct electric field control. *P. Natl. Acad. Sci. USA* 94(4)(Feb. 18):1119-1123.
- Stuckey, G.D. 1998. High surface area materials. In *R&D status and trends*, ed. Siegel et al.
- Stupp, S.I., V. LeBonheur, K. Wlaker, L.S. Li, K.E. Huggins, M. Keser, and A. Armstutz. 1997. Supramolecular materials: Self-organized nanostructures. *Science* 276:384-389.
- Svoboda, K., and S.M. Block. 1994. Biological applications of optical forces. *Ann. Rev. Biophys. Biomol. Struct.* 23:247-285.
- Symposium on Bio-Nano Electronics. 1997. Proceedings. November 15, Toyo University, Japan.
- Tirrell, J.G., M.J. Fournier, T.L. Mason, and D.A. Tirrell. 1994. Niomolecular materials. *Chem. Eng. News* 72(January 30):40-51.
- Toth, E., D. Pubanz, S. Vauthey, L. Helm, and A.E. Merbach. 1996. The role of water exchange in attaining maximum relaxivities for dendrimeric mri contrast agents. *Chemistry—A European Journal* 2:1607-1615.
- US/EC Workshop on Nanobiotechnology. 1999. Workshop of September 23-24, 1997, Washington, D.C. (report available from the National Science Foundation, Washington, DC, in 1998).
- Vidyasankar, S., M. Ru, and F.H. Arnold. 1997. Molecularly imprinted ligand-exchange adsorbents for the chiral separation of underivatized amino acids. *J. Chromatography A* 775:51-63.
- Wildoer, J.W.G., L.C. Venema, A.G. Rinzler, R.E. Smalley, and C. Dekker. 1998. Electronic structure of atomically resolved carbon nanotubes. *Nature* 391:59-62.
- Winningham, M.J. and D.Y. Sogah. 1997. A modular approach to polymer architecture control via catenation of prefabricated biomolecular segments: Polymers containing parallel beta-sheets templated by a phenoxathiin-based reverse turn mimic. *Macromolecules* 30: 862 - 876.
- Yin, H., M.D. Wang, K. Svoboda, R. Landick, J. Gelles, and S.M. Block. 1995. Transcription against an applied force. *Science* 270:1653-1657.
- Ying, J.Y. 1998. Nanostructure processing of advanced catalytic materials. In *R&D status and trends*, ed. Siegel et al.

- Yu, S.J.M., V.P. Conticello, G.H. Zhang, C. Kayser, M.J. Fournier, T.L. Mason, and D.A. Tirrell. 1997. Smectic ordering in solutions and films of a rod-like polymer owing to monodispersity of chain length. *Nature* 389:167-170.
- Zhang, Y., and N.C. Seeman. 1994. The construction of a DNA truncated octahedron. *J. Am. Chem. Soc.* 116:1661-1669.