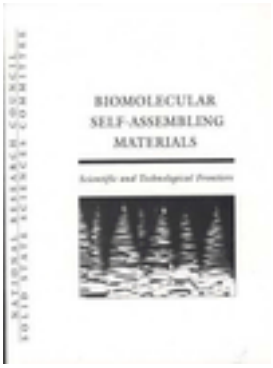

Biomolecular Self-Assembling Materials: Scientific and Technological Frontiers

Panel on Biomolecular Materials, National Research Council

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Biomolecular Self-Assembling Materials

Scientific and Technological Frontiers

Panel on Biomolecular Materials
Solid State Sciences Committee
Board on Physics and Astronomy
Commission on Physical Sciences, Mathematics, and Applications
National Research Council

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Preface

The group that prepared this report, a multidisciplinary panel with expertise in the physical sciences, the life sciences, and engineering, was formed in 1991. It operated under the auspices of the Solid State Sciences Committee of the National Research Council's Board on Physics and Astronomy. The panel met three times during the course of the study to discuss the issues and prepare drafts of this report. It also held *ad hoc* meetings in Boston, Princeton, and Los Angeles during 1992–1993 to obtain input from other members of the biomolecular materials research community.

The proposal for this study originated in the continuing efforts of the Solid State Sciences Committee (SSSC) to identify forefront developments in materials research and physical chemistry. The study plan was developed with the help of a program initiation meeting chaired by Mark Wrighton. The project was adopted by the SSSC as a priority for its program development efforts. The plan for the study called for an assessment of self-assembling materials.

Shortly after the SSSC proposed a study of self-assembling materials, the National Science Foundation decided to convene a workshop on a closely related topic, biomolecular materials. Several SSSC members attended the workshop and were impressed with the exciting developments taking place in this area. As a result, the scope of the study was broadened to include not only self-assembling but also biomolecular materials. The scope remains limited, however, to structures on scales ranging from molecules to membranes.

Cellular and tissue-scale structures have been addressed recently by another National Research Council report (*Hierarchical Structures in Biology As a Guide for New Materials Technology,* National Academy Press, Washington, D.C., 1994), prepared by the Committee on Synthetic Hierarchical Structures of the National Materials Advisory Board.

The charge to the study panel was threefold:

1. Assess the status of research on biomolecular materials in the United States.

   a. Identify the scientific forefronts and opportunities; provide a clear definition of research in the field.
   b. Identify the technological opportunities.
   c. Assess these opportunities for research using the criteria of intellectual challenge, prospects for illumination of classical research questions within specific fields, importance as a multidisciplinary research effort, and potential for applications.
   d. Assess applications using the criteria of potential for contributing to industrial competitiveness, national defense, human health, and other aspects of human welfare.
2. Identify and address the issues in the field.

   a. Assess the quality, size, and scope of the educational programs necessary to advance the field.
   b. Assess the institutional infrastructure in which research in this area is conducted and identify changes that would improve the research and educational effort.
   c. Identify small-scale instrumentation needs.
   d. Develop a research strategy that is responsive to the issues.
   e. Compare the U.S. program with those of Japan and Western Europe. Identify opportunities for international cooperation.
   f. Assess the linkage of theory and experiment.
   g. Assess manpower requirements and the prospects for meeting them.
   h. Identify the users of scientific advances in this area and their needs.
3. Make recommendations to federal agencies and to the community as to optimum funding strategies for addressing the issues.

The panel gratefully acknowledges the considerable assistance it received from the biomolecular materials research community, including substantial input from C. Safinya, G. Stucky, and J. Zasadzinski of the University of California, Santa Barbara. The SSSC is indebted to the co-chairs of the NSF workshop on biomolecular materials, Hans Frauenfelder and George Benedek, for their advice in framing the study and to Mark Wrighton for leading the program initiation effort.

Contents

Executive Summary

Research on self-assembling biomolecular materials is an exciting new discipline lying at the intersection of molecular biology, the physical sciences, and materials engineering. Biomolecular materials are those whose molecular-level properties are abstracted from biology. They are structured or processed in a way that is characteristic of biological materials, but they are not necessarily of biological origin. For example, the structure of a man-made ceramic material may be based on that of a clam shell, or a synthetic polymer may be produced using techniques from molecular biology that were originally developed for working with proteins. A key feature of biomolecular materials is their ability to undergo self-assembly, a process in which a complex hierarchical structure is established without external intervention. Self-assembly is common in biological materials. For example, long protein molecules fold themselves into complicated three-dimensional structures, and certain lipid molecules align themselves with each other to form membranes.

The focus of this report is the study and generalization of biomolecular self-assembly, with the ultimate goal being the development of new materials of technical importance. The underlying theme is the belief that there are important lessons to be learned from understanding, and perhaps mimicking, biological materials found in nature and the ways in which they self-assemble. In nature, experiments on biological materials have been ongoing for millions or even billions of years, and it is up to us to understand them better and learn how to profit from them.

If the principles of biomolecular self-assembly can be extended to the control of modern materials synthesis, they will lead to a broad range of new materials and processes with significant technological impact. The approaches used can be expected to fall into two general categories. The first involves directly mimicking biological systems or processes to produce materials with enhanced properties. An example of this approach is the use of molecular genetic techniques to produce polymers with unprecedentedly uniform molecular length. The second category involves studying how nature accomplishes a task, or how it creates a structure with unusual properties, and then applying similar techniques in a completely different context or using completely different materials. An example of this approach is the study of the laminated structure of clam shells, which has been reverse-engineered to design a metal ceramic composite twice as strong as other composites and an order of magnitude tougher, and constructed of more robust materials than its natural analogue. An important finding of this report is that successful application of biomolecular techniques could have a significant impact on materials and processes.

The Panel on Biomolecular Materials has identified a number of long-term scientific and technological opportunities in the field. Molecules that form liquid crystals can be incorporated into polymers to produce materials that have useful optical properties, are easily processed, and have good mechanical properties. Membrane-based structures can be used in applications ranging from controlled release of drugs to ultrafiltration to biosensors. It may be possible to design self-assembling electronic devices. New synthetic polymers and new polymer synthesis techniques are possible, including the production of protein-and polyester-based polymers from biomass. Biomolecular sensors may find applications in health care, agriculture, ensuring food quality and safety, and the detection of biological warfare agents. Biomotors may be developed that can construct biomolecular structures on a unit-by-unit basis.

The panel has concluded, however, that the existing infrastructure for research on biomolecular materials is not keeping pace with the development of these opportunities. As time passes, and as the record of significant results grows and the potential economic impact becomes more apparent, the need for new infrastructure only becomes more acute. The panel has therefore concluded that the existing system of disciplinary, individual-investigator-based excellence in research and education should be augmented.

Specifically, the panel has identified the following four options that could help to stimulate progress in the field:

1. Interdisciplinary collaborations could be encouraged by a new mode of research through which small numbers of scientists would come together to work on a specific problem, such as the ones identified in this report. This mechanism would encourage new collaborations while keeping their size small to help ensure accountability.
2. Consortia in biomolecular materials could be developed, i.e., groups of investigators that are focused on a specific theme or a specific instrumental capability. Such groups could involve scientists at a particular site such as a university campus or a government laboratory, or they could be consortia involving several sites. They would vary in size but would each have a well-defined focus: specific instruments, particular scientific problems, or a defined technological goal. Pre-existing collaborations with established track records of interdisciplinary activity should be favored in establishing these groups. Some of the groups could be built into existing structures such as the Materials Research Laboratories (MRLs), Science and Technology Centers (STCs), and government laboratories. Groups that have special facilities should be open to external scientists. Geographical dispersion could be a component in the selection criteria. Incorporation of the government laboratories into the groups should be strongly encouraged since the government laboratories house a broad spectrum of instruments, experience in instrument development, and relevant expertise in such areas as synchrotron radiation, neutrons, imaging (electron microscopy, scanning tunneling microscopy, atomic field microscopy, and x-ray microscopy), and chemical and biological synthesis and characterization.
3. Academic programs could be established at universities to encourage curriculum development and training in biomolecular materials. These programs would bridge biology, materials science, and the physical sciences. The multidisciplinary character of biomolecular materials research, though in many ways a great strength, can be a barrier for students pursuing an education in the field. New academic programs and curriculum development could help to overcome this problem. It is important that students are trained in one of the disciplines in depth, however, obtaining interdisciplinary breadth during the research phase of their graduate careers.

   One way to support such training could be the provision of special training grants like those that NIH has recently provided in areas related to biomaterials. Any such grants should include requirements for additional courses as well as for a program of research. The panel believes that the effectiveness of such a grant program would be enhanced if institutions receiving grants were encouraged to strengthen their ties with government and industrial laboratories. For example, they could make arrangements for outside laboratories to provide summer jobs for their graduate students, and the participating government and industrial researchers could host visitor programs and serve as guest lecturers at the universities receiving the grants.
4. A national Biomolecular Materials Institute (BMI) could be established, located at a university or a government laboratory or another site with an appropriate intellectual environment. Like options 1 and 2 above, this option is motivated by the panel's consensus that interdisciplinary collaboration requires special support and encouragement. For example, in the study of many aspects of biomolecular materials, such as those described above for molecular machines, close interaction between researchers is both difficult and very important. In addition, a national institute would broaden access to instruments and research facilities, facilitate contacts between the academic community and private industry, and enhance the visibility of the field in a way that would encourage the creation of university programs in biomolecular materials research and education.

A national BMI would act as an umbrella organization for the field. It would have four main tasks:

a. To examine research directions through workshops, meetings, and studies, giving particular attention to proposed novel initiatives;
b. To encourage interdisciplinary collaborations by bringing together scientists and engineers from different backgrounds, e.g., different disciplines or affiliations;
c. To provide instrumental facilities that would encourage interactions between experimental groups; and
d. To provide industry with a single contact point for obtaining information about biomolecular research activities and for obtaining assistance in making connections with those activities.

Structurally, the BMI might resemble the NSF-sponsored Institute for Theoretical Physics in Santa Barbara. For example, it would have quasi-independent status and be overseen by a broad-based advisory board. It would consist of a small cadre of permanent scientists, plus staff commensurate with the above-listed tasks, such as experts to assist visiting scientists in using the instruments and laboratories. Funding should if possible be provided in at least five-year increments, either by a single agency or preferably by a consortium of agencies such as NSF, NIH, the Department of Energy, and the Department of Defense. Funding should also include substantial industrial support if at all possible, probably at about the 25% level.

Although this option may be difficult to achieve in the current funding environment, the panel believes it is an important goal for the future.

1

Introduction

This report addresses the interdisciplinary emerging field of self-assembling biomolecular materials—its status, the opportunities that face it, and the research and infrastructure developments that are needed to ensure that it achieves its potential. This field is an exciting new area at the frontiers of materials science. It is based on the premise that nature has already done the critical experiments, and it is up to us to better understand them and learn how to profit from them. The focus of this report is the study and generalization of biomolecular self-assembly, as directed toward the development of new or advanced materials of technical importance. The underlying theme is the belief that there are important lessons to be learned from understanding, and perhaps mimicking, biological materials and the ways in which they self-assemble. This report conveys the relationship between materials complexity, materials self-assembly, and lessons learned from biology; it underscores the need to encourage a partnership between physical scientists, engineers, and biologists and medical researchers.

Biomolecular materials are those whose properties are abstracted from biology. They share many of the characteristics of biological materials but are not necessarily of biological origin. For example, they may be inorganic materials that are organized or processed in a biomimetic fashion. A key feature of biological and biomolecular materials is their ability to undergo self-assembly, a process in which supermolecular hierarchical organization is established without external intervention.[1]

The field of biomolecular materials is an emerging discipline at the intersection of molecular biology, the physical sciences, and materials engineering. In the words of H. Ringsdorf,[2] "the field … is now located at the interface between life-science and materials science. It applies the principles of self organization, regulation, replication, communication and cooperativity and has advanced to a promising area of applied science, undermining the borderline between scientific disciplines and offering new routes for the design of materials where the organization precedes the function." This is schematically demonstrated in Figure 1. The technological promise includes, but extends well beyond, the health applications of biomaterials and biotechnology. The stage has been set by progress in modern molecular biology, the development of powerful microscopic characterization techniques, and advances in theoretical understanding.

We are now ready for the development of a physical understanding of the complex but exquisite behavior manifested by biological systems, including recognition and response, self-assembly, and self-repair. These principles can be extended to the control of modern materials synthesis and will lead to new materials and processes with a broad range of technological impact. The approaches used can be expected to fall into two general categories. The first involves directly mimicking biological systems or processes to produce materials with enhanced properties. An example of this approach is the use of molecular genetic techniques to produce polymers with unprecedentedly uniform molecular length. The second category involves studying how nature accomplishes a task or creates a structure with unusual properties, and then applying similar techniques in a completely different context or using completely different materials. An example of this approach is the study of the laminated structure of clam shells, which has been reverse-engineered to design a metal ceramic composite. This composite has twice the strength of other composites, is an order of magnitude tougher, and is, of course, constructed of more robust materials than its natural analogue. Such reverse engineering, in which lessons learned from a

[1] Examples of self-assembly include protein folding, the formation of liposomes, and the alignment of liquid crystals. While this type of equilibrium self-assembly is the central focus of this report, it is important to emphasize that much biological assembly is also driven by energy sources such as adenosine triphosphate (ATP), which power biomotors for chemical transduction and other processes. These biomotors are considered to be biomolecular and are discussed in the body of this report, but strictly speaking they do not conform to the panel's definition of self-assembly.

[2] H. Ringsdorf, *Supermolecular Science* 1:5 (1994).

biological system are applied to a completely different system, is a very important concept, for in many applications the environment (e.g., temperature, pressure, corrosive chemicals) is more severe than the original biological system or material can tolerate. In addition, understanding how nature accomplishes a task or creates an unusual structure may lead to new materials or processes in which the advance is in learning to reverse nature's approach, rather than in learning to copy or modify it, so as to eliminate materials characteristics that are undesirable.

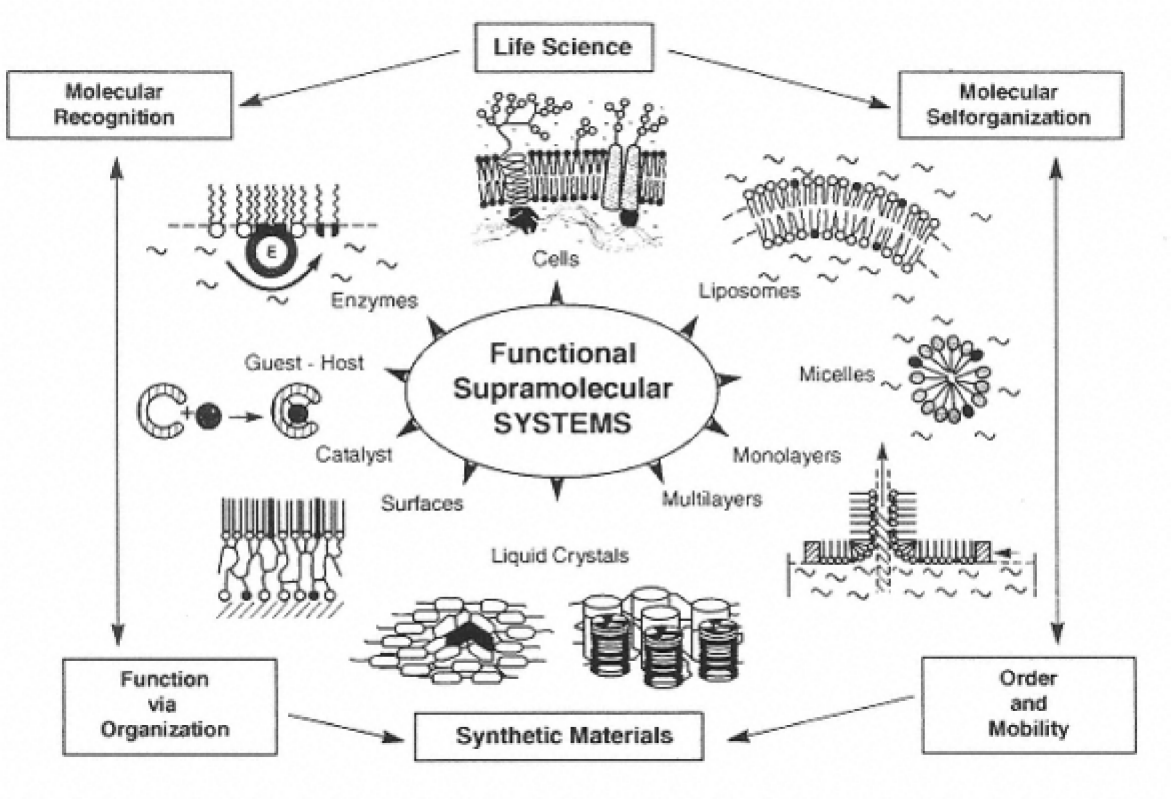

Figure 1
Illustration of the relationships among various aspects of biomolecular materials and their connections with the life sciences. (Courtesy of H. Ringsdorf, Johannes Gutenberg Universität Mainz.)

Although still in its infancy, the application of biological principles to the development of new materials has already been demonstrated. A nucleus of broad-based research already exists, involving a variety of disciplines including chemistry, physics, biology, materials science, and engineering. The field of biomolecular materials requires substantial additional basic research, however. Many significant applications are to be expected, but they may require a decade of research and development. The results of the research may not necessarily be systems that are strictly analogous or equivalent to those found in nature. It may be that payoffs will come in areas in which no functioning examples or archetypes yet exist.

The unique properties of biomolecular materials can be ascribed to certain common characteristics:

1. They are typically composed of molecules that interact by multiple, weak, orientation-dependent forces.
2. Because these molecules interact weakly, thermal fluctuations are important.
3. The materials are often self-assembled into structures on mesoscopic length scales from 100 Å to 10 mm.

4. These structures may be hierarchical;[3] i.e., they may be organized on multiple length scales with multiple functions at each scale.
5. The systems that they form consist of several components.

The following specific examples of current research may help to give the reader an idea of the character of this exciting field:

- *Polymer biosynthesis.*[4] Biosynthetic routes are being explored for the preparation of biobased polymers: natural fibers, modified versions of natural proteins, and synthetic proteins that have no close natural analogues.
- *Self-assembled monolayers and multilayers.*[5] The phase behavior of self-assembling surfactant monolayers on both fluid and solid substrates is being mapped out. These monolayers are effective in applications such as lithographic masking and high-resolution reaction templating. They also have potential as chemical sensors, as nonlinear optical elements, in neuronal networks, and for environmentally safe metal plating. Stable multilayer films of polymeric systems have been fabricated and their activity demonstrated. This approach is expected to lead to the development of functional organic films.
- *Decorated membranes.*[6] For many years, lipid bilayer membranes have been investigated as models for cell walls. Current research is focusing on active membranes that mimic natural membrane function by including bound proteins, adsorbed colloidal particles, and so on.
- *Mesoscopic organized structures.*[7] Biomolecular systems that spontaneously organize into crystalline structures with lattice constants in the mesoscopic range are being studied as molecular sieves (S-layers),[8] electrically active arrays (tubules),[9] and long-term controlled-release systems (vesicles).[10]
- *Biomineralization.*[11] Biomolecular templates are being studied as nucleation devices for the synthesis of inorganic compounds with unusual structures and high degrees of perfection. Examples include the epitaxial growth of carbonates induced by molluscan shell protein and the intracellular synthesis of CdSe semiconductors.

These specific models of contemporary biomolecular materials research have encouraged the panel to examine more speculative possible long-term goals. Some examples are discussed in Section 3 of this report, "Opportunities."

[3] The materials addressed in this report are organized on the molecular to membrane length scales. A report entitled *Hierarchical Structures in Biology As a Guide for New Materials Technology* (National Academy Press, Washington, D.C., 1994), prepared under the aegis of the National Materials Advisory Board of the National Research Council, concentrated on more complex cellular or extracellular materials.

[4] J.G. Tirrell, M.J. Fournier, T.L. Mason, and D.A. Tirrell, *Chemical and Engineering News* 72:40 (1994).

[5] L.H. Dubois and R.G. Nuzzo, "Synthesis, Structure, and Properties of Model Organic Surfaces," *Annu. Rev. Phys. Chem.* 60:437 (1992); A. Ulman, *Ultrathin Organic Films* (Academic Press, Boston, 1991).

[6] N. Unwin and R. Henderson, *Scientific American* 250(February):78 (1984).

[7] National Research Council, *Hierarchical Structures in Biology As a Guide for New Materials Technology* (National Academy Press, Washington, D.C., 1994).

[8] U.B. Sleytr and M. Sara, *Appl. Microbiol. Biotechnol.* 25:83 (1986); W. Baumeister and G. Lembcke, *J. Bioenerg. Biomembr.* 24:567 (1992).

[9] J.M. Schnur, *Science* 262:1669 (1993).

[10] D.D. Lasic, *Liposomes: From Physics to Applications* (Elsevier, Amsterdam, 1993).

[11] Stephen Mann, John Webb, and Robert J.P. Williams, eds., *Biomineralization: Chemical and Biochemical Perspectives* (VCH, New York, 1989).

2

Status

This section describes some of the important new scientific insights, novel materials, and new processing technologies that have already emerged from the interface between biology and materials science. Its purpose is to illustrate the state of the art in selected areas. It is not meant to be a complete literature survey. The examples discussed serve to establish the feasibility and underpinnings of the biomolecular materials approach.

This section is organized in order of increasing structural complexity, starting with complex fluids, whose properties, including self-assembly, mirror those of lipids. The discussion then addresses polymers, thin films, composites and templates.

COMPLEX FLUIDS AND LIQUID CRYSTALS

Complex fluids[12] are bulk multicomponent systems that self-assemble into a variety of structural forms. Such systems include: (1) amorphous composites such as polymer solutions, emulsions, and colloidal suspensions and (2) systems in which the self-assembly is based on the amphiphilic nature of surfactants and lipids. (Amphiphilic molecules are those with a polar head and a long hydrophobic tail.) Self-assembly generally involves anisotropic molecules that are driven into ordered structures by intermolecular forces and the requirements of packing. In this sense, complex fluids are closely related to liquid crystals, which are materials that possess orientational order without crystalline translational order. All these characteristics of self-assembly are nicely demonstrated in biomembranes.

Complex fluids may exhibit various types of partial ordering, i.e., the coexistence of amorphous and highly correlated structures. This concept and the rich variety of self-assembling systems can be illustrated with a few examples:

- *Colloidal suspensions* are small solid particles dispersed in a carrier fluid. Interparticle interactions may lead to a long-range crystalline order, thereby producing colloidal crystals. Such materials possess the properties of crystals, including a finite shear modulus, even though the majority component is a fluid. Indeed colloidal crystals are also interesting in that they exhibit long-range order but are disordered on short length scales.
- *Lyotropic liquid crystals*[13] exhibit a key characteristic of biomolecular self-assembly in that a local molecular feature—the amphiphilic nature of the constituent molecules—generates self-organized structures that may consist of units of mesoscopic size, which are very large compared to molecular dimensions. For example, lamellar lyotropic phases are composed of stacks of fluid lipid membranes separated by a solvent. The spacing between the membranes is well-defined and can be hundreds of nanometers even though the structure remains liquid-like at the scale of angstroms. Such systems possess quasi-long-range order but have components that are locally disordered.

As lamellar phases are increasingly diluted with solvent, a transition to the sponge phase[14] may occur. This phase is characterized by a random organization of the bilayer membranes. They divide the solvent into two distinct but interpenetrating regions, forming a bicontinuous structure.

[12] W.M. Gelbart, A. Ben-Shaul, and D. Roux, eds., *Micelles, Membranes, Microemulsions, and Monolayers* (Springer Verlag, New York, 1994).

[13] P.G. de Gennes and J. Prost, *The Physics of Liquid Crystals* (Oxford University Press, Oxford, 1993).

[14] M.E. Cates in *Observation, Prediction, and Simulation of Phase Transitions in Complex Fluids,* Proceedings of the Enrico Fermi School, 1994 [NATO ASI Series C 460, 205–242], J. Krull and J.-P. Ryckaert, eds. (Kluwer, Dordrecht, 1995).

- *Lyotropic nematic liquid crystals* are orientationally ordered fluids composed of colloidal suspensions of anisotropic rod-like particles. Such systems can undergo phase transitions as the volume

fraction of the suspended anisotropic species is varied, producing prolate colloidal particles, rod-like species such as those found in tobacco mosaic virus, cylindrical micelles, or other structures.

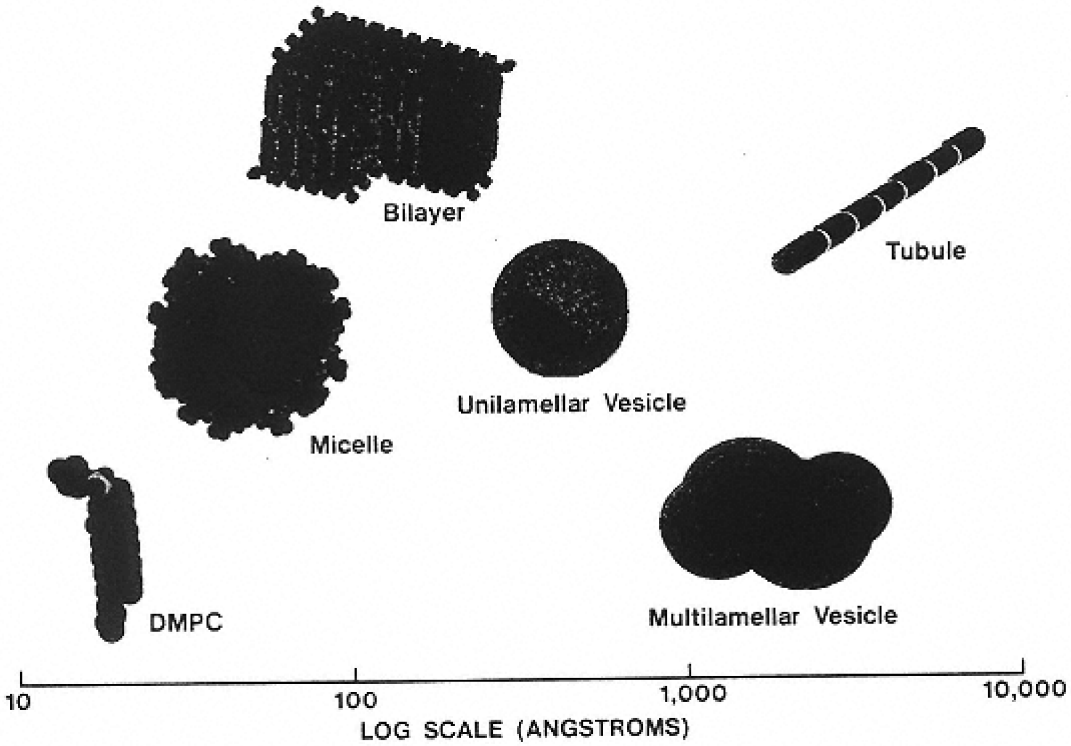

Figure 2
Schematic representation of some self-assembled lipid-based microstructures. (Reprinted, by permission, from J. Schnur, Science 262:1670 (1993). Copyright © 1993 by the American Association for the Advancement of Science.)

SURFACTANT-BASED SELF-ASSEMBLY

Surfactant molecules (e.g., phospholipids, soaps, detergents, and block copolymers) self-assemble[15] in selective solvents (e.g., water) to form bilayer membranes and micelles of several structures (Figure 2). The membranes also organize in a variety of patterns. Such self-assembled structures may be swollen by adding an organic solvent to the system, which remains stable as a clear single phase. Such two-solvent composites are called microemulsions. Surfactant bilayers have been investigated for many years as model systems for biological membranes.

Repulsive forces between the surfactant head groups organize the bilayers on longer length scales. This process may form lamellar stacks, sponge phases, or microemulsions, depending on whether there are one or two solvents. Even more relevant to biomolecular systems is the formation of closed-film structures called vesicles (Figure 3), which are already being employed as simple containers to transport drugs within the blood system.

The self-organizing micelles may form in different shapes depending on the specific chemistry and on solvent conditions such as pH, ionic strength, and temperature. The most common form is spherical, but cylindrical micelles also occur. In fact, entropic optimization drives long cylindrical micelles into the form of flexible polymer-like chains. These polymeric micelles have many of the rheological properties of polymers with covalently bonded backbones, but their lengths are determined by equilibrium thermodynamics rather than being fixed.

An interesting example of a self-assembling structure is the tubule, a hollow phospholipid bilayer cylinder morphologically similar to a soda straw (Figure 4). The length of these ultrasmall cylinders is

[15] S.A. Safran, *Statistical Thermodynamics of Surfaces, Interfaces, and Membranes* (Addison-Wesley, New York, 1994).

typically tens or hundreds of microns.[16] The diameter can vary from 0.1 mm or less to over 0.7 mm, with the wall thickness varying from less than 100 Å to well over 500 Å. A number of applications using both metal-clad and non-clad tubules are currently being evaluated for commercial application. A hollow tubule is essentially a "microvial" in which a solid or liquid can be encapsulated. The use of such microvials has led to controlled-release applications for marine antifouling (release over many years) and drug delivery (release over several days to months).[17] These applications are now at the advanced development stage in several commercial firms both in the United States and abroad. The metal-clad structures also have interesting electromagnetic properties. Applications based on their dielectric properties (miniaturized microwave circuits) and as absorptive filters are currently under development in several universities and government laboratories. While several of the technical issues critical to successful commercialization of tubule applications have been solved, other issues (such as scale-up and a satisfactory cost/performance ratio) remain to be addressed prior to successful marketing.

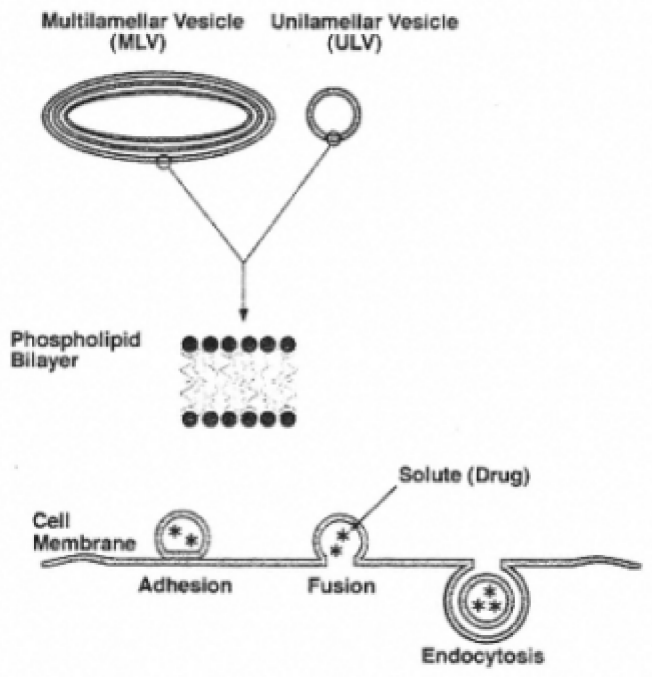

Figure 3
Vesicles: (top) sketch of multilamellar and unilamellar vesicles and the phospholipid bilayer of which they are made; (bottom) sketch of a mechanism whereby drug-containing vesicles adhere to a cell surface and present drugs for uptake by endocytosis.

POLYMERS.

Since much of biology is based on the special properties of macromolecules, it is widely anticipated that the area of polymeric biomolecular materials will be rich.[18] Two of the tools of molecular biology, namely recombinant DNA and genetic engineering techniques, now make it possible to construct monodisperse, highly specific polymers. For example, both polyesters and polyamides (i.e., protein polymers) have been produced in this manner. A current area of investigation is to understand those features of protein polymers that confer high tensile strength, high modulus, and other advantageous properties. Once those features are understood, the tools of biotechnology will make possible entirely new paradigms for synthesis and production of materials. If they can be made economically viable, these new approaches will help reduce our dependence on petroleum and furthermore will enable making materials that are biodegradable.

[16] See footnote 9.
[17] Microstructure Controlled Release Group, *Pharmaceutical News* 2(1):10 (1995); J.M. Schnur, R. Price, and A.S. Rudolph, *Journal of Controlled Release* 28:3 (1994).
[18] See footnote 4.

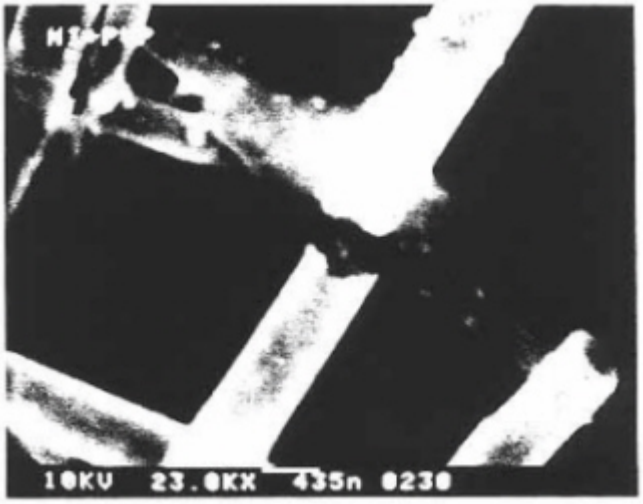

Figure 4
Electron micrograph of nickel-coated tubules approximately 0.4 μm in (inner) diameter and with walls approximately 500 Å thick.
(Reprinted, by permission, from J. Schnur, Science 262:1673 (1993). Copyright © 1993 by the American Association for the Advancement of Science.)

In the last few years it has become possible to produce designer polymers comparable to those produced naturally. Use of genetic engineering techniques to obtain new polymer molecules provides the polymer scientist with model, controllable, synthetic proteins for the first time. Two aspects of this approach are biomimetic: targeted molecules are produced by biosynthesis, and they then self-assemble into desirable structures that have new or improved properties. Efforts in biosynthesis have been directed toward the preparation of precisely defined polymers of three kinds: (1) natural proteins such as silks, elastins, collagens, and marine bioadhesives, (2) modified versions of these biopolymers, such as simplified repetitive sequences of the native protein, and (3) synthetic proteins designed *de novo* that have no close natural analogues. Although such syntheses pose significant technical problems, these difficulties have all been successfully overcome in recent years.

Figure 5 shows the key steps in the *in vivo* synthesis of protein-like polymers under direct genetic control in bacteria. The first requirement is that the amino acid sequence of interest must be encoded into a complementary sequence of DNA. For natural proteins, the requisite DNA sequence is obtained by isolating the appropriate gene from the natural host organism. *De novo* design and synthesis require chemical synthesis of an artificial coding sequence. In either case, the isolated DNA fragment is ligated into a loop of DNA (a plasmid) that can be replicated in a microbial host and that includes the signals needed for controlled transcription and translation. The resulting recombinant DNA is then introduced into the host cell population, cells are grown in large numbers, and protein production is induced. To date, this approach has been used successfully to produce a variety of natural proteins, as well as dozens of wholly artificial protein-like polymers. [19]

It is now relatively routine to use bacterial hosts to produce multigram quantities of polymers with degrees of polymerization up to 1000 and molecular weights up to 100,000. The first commercial product based on this technology, an artificial cell attachment protein that can be used to coat polystyrene culture dishes, has already appeared. Although the anticipated structural regularity has been thoroughly demonstrated in several instances, mutations have also occurred that have led to an altered chain sequence. There have also been examples of enzymatic degradation, which leads to chain length heterogeneity. Such problems have as yet unknown consequences for targeted secondary and tertiary structures.

Biological synthesis is also being used to prepare important classes of polymers other than proteins. Bacterial polyesters have attracted particular attention because of their biodegradability.[20] They are

[19] D.P. Mobley, ed., *Plastics from Microbes: Microbial Synthesis of Polymers and Polymer Precursors* (Hanser, Munich, 1994).
[20] Y. Doi, *Microbial Polyesters* (VCH, New York, 1990).

already finding commercial application in specialty packaging uses. Costs are still high in comparison to those for commodity polymers, but increasing volume seems likely to bring production costs down to levels that are economically competitive in a wider range of applications. Furthermore, it has recently been demonstrated that the production of bacterial polyesters can be transferred to plants, opening the way for their production from biomass. Natural polysaccharides are under development for biodegradable packaging applications. Several companies have recently commercialized starch-based polymer blends that can be processed using existing thermoplastic methods.

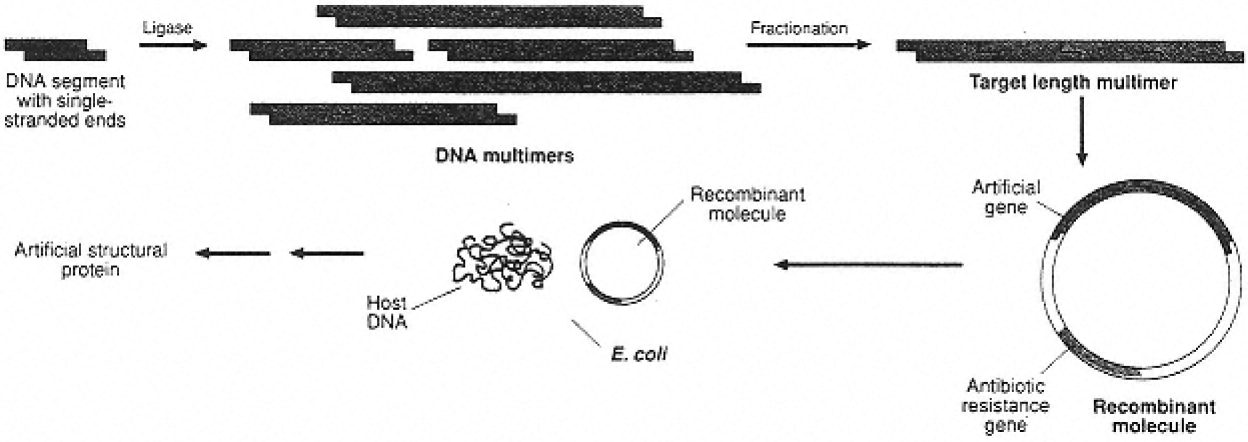

Figure 5
Key steps in the in vivo synthesis of protein-like polymers under direct genetic control in bacteria. First a DNA sequence is produced that codes for the desired polymer. This DNA is then inserted into a plasmid. When the plasmid is inserted into E. coli bacteria, the bacteria produce the polymer. (Reprinted with permission from J.G. Tirrell, M.J. Fournier, T.L. Mason, and D.A. Tirrell, Chemical & Engineering News 72(51:December 19):43 (1994). Copyright © 1994 by the American Chemical Society.)

Biology often combines very different materials in closely interwoven patterns to develop unique properties that stem from the co-continuous nature of the assembly. The liquid-crystalline state in polymers, first viewed as unusual, is now becoming accepted as a normal state occurring between the crystalline and isotropic liquid states. High-performance fibers based on solution processing of lyotropic liquid-crystalline polymer solutions (e.g., Kevlar) have contributed to a host of high-technology composites developed for their light weight, high strength and stiffness, and high temperature stability (service temperatures of up to 500°C). Certain insects, including spiders, take advantage of the low viscosity in the liquid crystalline regime. Spider dragline silk is a versatile engineering material that performs several demanding functions. The mechanical properties of dragline silk exceed those of many synthetic fibers. Moreover, dragline silk exhibits the unusual behavior that the strain required to cause failure actually increases with increasing deformation.[21] This property is particularly advantageous because webs need excellent energy-absorbing capability to capture flying prey. Spiders extrude an aqueous solution of silk protein to spin the molecules into oriented fibers. The female garden cross spider can use seven different glands, each containing silk with a unique amino acid sequence, to

[21] D. Kaplan, pp. 176–184 in *Silk Polymers: Materials Science and Biotechnology,* American Chemical Society Symposium Series 544, D. Kaplan, W.W. Adams, B. Farmer, and C. Viney, eds. (American Chemical Society, Washington, D.C., 1994).

produce fibers with different properties. Figure 6 illustrates a proposed model for the structure of spider silk.

There is renewed interest in the structure-property relationships of such structural biological materials because the fibers have outstanding tensile as well as compressive properties. Work is under way to fully characterize the molecular weight and sequence distribution; the nature of the *in vivo* solution (speculated by some to be liquid crystalline); the structure, size, and orientation of the crystalline regions; and their interconnection to the amorphous regions. The consensus crystalline repeat in two silk proteins has recently been identified. [22] Cloning and expression of the gene for spider dragline silk to facilitate production of large quantities of synthetic silk are now under investigation.[23]

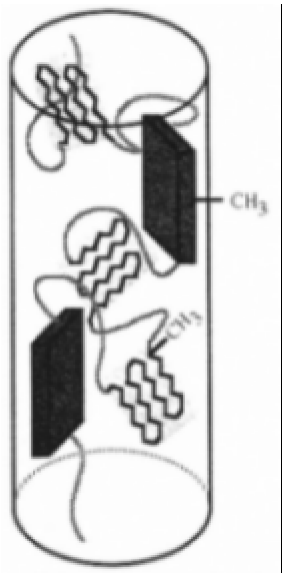

Figure 6
Diagram of the proposed model for the molecular arrangement of alanine residues in a fiber of spider dragline silk. Highly oriented alanine-rich crystals of -sheets (rectangles) and weakly oriented yet crystalline unaggregated sheets (canted sheet-like structures) are depicted in an amorphous glycine-rich matrix (curved lines). In reality, the glycine-rich matrix composes about 70 percent of the fiber; in this drawing it has been largely suppressed for clarity. (Reprinted, by permission, from A.H. Simmons, C.A. Michal, and L. W. Jelinski, Science 271:84–87 (1996). Copyright © 1996 by the American Association for the Advancement of Science.)

Another important use of polymers is adding them to hydrocarbon-and water-based fluids to control rheological properties.[24] Advances in functionalization chemistry have enabled the engineering of synthetic polymers with associating groups. Ionomers, oil-soluble polymers containing ionic functionality such as sulfonate or carboxylate groups, have been synthesized in a variety of architectures including random, block, and telechelic structures. In hydrocarbon solvents, the polar ionic groups interact to create self-assembled or aggregated polymer chains, which appear to have much higher molecular weights than the non-functionalized polymers. Conversely, hydrophobically associating polymers are water-soluble but contain a small amount of oil-soluble or hydrophobic functionality. These two classes of polymers have been called associative thickeners. The association of the functional groups in fluids enables these synthetic polymers to mimic the secondary and tertiary interactions and structures found in biomolecules such as proteins and polysaccharides. The inter-and intra-molecular interactions of the polymers define their conformation and assembly in solution, and in turn, the solution's rheological properties. Unique and useful rheological properties such as dilatancy or shear thickening, enhanced viscosification, and compatibility with other fluid components can be designed into fluids using associating polymers.

[22] M. Xu and R.V. Lewis, *Proc. Nat. Acad. Sci. USA* 87:7120–7124 (1990); M.B. Hinman and R.V. Lewis, *J. Biol. Chem.* 267:19320–19324 (1992).
[23] J.T. Prince, K.P. McGrath, C.M. DiGirolamo, and D.L. Kaplan, *Biochem.* 34:10879–10885 (1995).
[24] D.N. Schulz and J.E. Glass, eds., *Polymers As Rheology Modifiers,* American Chemical Society Symposium Series (American Chemical Society, Washington, D.C., 1991).

Designer fluids with controlled rheological and interfacial properties, with potential applications for processing composites, can be prepared by combining polymers and microemulsions.[25] Water-soluble synthetic polymers such as polyacrylamides or polyethylene oxides and biopolymers such as xanthan or scleroglucan have both been studied in water continuous microemulsions. Polymers and surfactants may not be compatible in such complex fluid mixtures, and separation into polymer-rich and surfactant-rich phases may therefore occur. This phenomenon is similar to the coacervation observed in mixtures of two polymers in a common solvent. The compatibility between the polymer and the surfactant or microemulsion phase may be enhanced by replacing the water-soluble polymer with an associating polymer that contains hydrophobic groups. Single-phase fluids with controlled rheological and interfacial properties can thus be prepared.

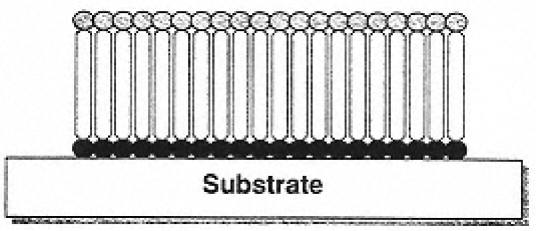

Figure 7
Schematic illustration of the molecular structure of a self-assembled monolayer (SAM) on a substrate surface. The properties the SAM are determined both by the physical properties of the molecules from which they are formed and by the nature of their packing interactions.

MOLECULAR THIN FILMS

The study of molecular thin films obtained via the self-assembly of small molecules on surfaces (Figure 7) has witnessed enormous growth. Most recent work has been directed at a series of model phases, for which structural characterizations have been made in considerable depth. Monolayer phases supported on a variety of substrates have been explored. Notable among these are alkane thiols supported on coinage metal surfaces (gold, silver, and copper), alkyl silanes bound to a variety of metal oxide surfaces (especially SiO_2), and carboxylic acids adsorbed on basic oxides (e.g., Al_2O_3). Polymer brushes formed by amphiphilic block copolymers make up a conceptually related but structurally distinct set of phases. The structures of monolayers at the air-water interface have also been very extensively studied. There is a clear relationship between the behavior of these systems and the unique phase behaviors of very thin films of liquid crystals.

Multilayer assemblies have not been as extensively studied. Perhaps the most significant examples of current research on multilayer assemblies are systems based on zirconium phosphonates. Polymeric adsorbates, i.e., polymer films that are sufficiently thin as to be completely dominated by the structural perturbations of an interface, remain very poorly understood for the most part, although very recent work has explored ordering near solid surfaces of block copolymer films whose thicknesses are on the order of several radii of gyration or more.

Some significant progress has also been made in building function into these thin film phases, albeit primitive function by the standards of biology. Electroactive centers have been incorporated into ordered thin films. So has photochromic functionality with vectorial optical response. There have also been several reports[26] of the construction of molecular thin films with significant abilities for molecular recognition, though again of a fairly rudimentary sort.

[25] K. Siwadasan and P. Somasundaran, *Colloids and Surfaces* 49:229 (1990); S. Biggs, J. Selb, and F. Candau, *Langmuir* 8:838 (1992).

[26] For example, E.U. Thoden van Velzen, J.F.J. Engbersen, P.J. De Lange, J.W.G. Mahy, and D.N. Reinhoudt, *J. Am. Chem. Soc.* 117:6053 (1995); E.U. Thoden van Velzen, J.F.J. Engbersen, and D.N. Reinhoudt, *J. Am. Chem. Soc.* 116:3697 (1994); K.D. Schierbaum, T. Weiss, E.U. Thoden van Velzen, J.F.J. Engbersen, D.N. Reinhoudt, and W. Göpel, *Science* 265:1413 (1994); I. Willner, M. Lion-Dagan, S. Marx-Tibbon, and E. Katz, *J. Am. Chem. Soc.* 117:6581 (1995); G.B. Sigal, C. Bamdad, A. Barberia, J. Strominger, and G.M. Whitesides, *Anal. Chem.* 68:490 (1996).

Considerable attention has been given to the influence of thin boundary layer films on the properties of interfaces. Self-assembled monolayers (SAMs) make it possible to functionalize surfaces in well-defined ways, and it is only natural that they have found considerable application in research on friction, lubrication, and wetting. It is now understood, as a direct result of the study of SAMs, that wetting phenomena on molecular solids depend sensitively on near-surface structure and composition. An understanding is now emerging from this work of how molecular structure drives the macroscopic properties of surfaces. This understanding is enabling the development of surface modification schemes for technological applications that are based on reason rather than empirical experience alone.

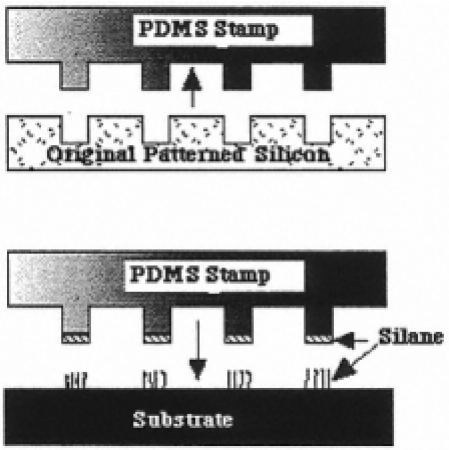

Figure 8
Chemical patterning of surfaces: (top) patterned stamps are prepared from lithographically patterned silicon; (bottom) silane-based self-assembled monolayers are then "stamped" onto a surface. PDMS is poly (dimethylsiloxane). (Reprinted with permission from P.T. Hammond and G.M. Whitesides, Macromolecules 28:17569 (1995). Copyright © 1995 by the American Chemical Society.)

SAMs are also beginning to find applications in the biological sciences. There has long been an interest in the interaction of cells with surfaces. SAMs have allowed the tailoring of surface properties in ways that allow considerable control over the ability of cells to bind to a solid. Several recent papers[27] have demonstrated that spatially defined SAMs can be used to pattern cell attachment to a substrate. Neural synaptic integration in planar neural arrays can also be mediated by SAMs, and the pattern of their interconnections can be controlled by the modification of surface properties. The affinities of surfaces for protein adsorption are also easily modifiable using SAMs.

There is considerable interest in the applications of SAMs in the area of sensors. Their potential utility is being demonstrated very powerfully in electrochemical applications. They have been used to control the redox tunneling properties of gold surfaces by allowing the homogeneous placement of electroactive materials at known densities and distances from the surface. More recently, photoexcited vectorial electron transport has been demonstrated in both monolayer and multilayer assemblies. Several general sensor designs have also been described that involve the use of SAM-modified microelectrode grids.

SAMs have also been shown[28] to act as effective masks for the lithographic patterning of metals (Figure 8). These studies have demonstrated that microstructures can easily be fabricated in shapes and architectures that are hard to implement flexibly with conventional multistep lithographic patterning. An exciting application has been demonstrated in the growth of thin films by chemical vapor deposition:

[27] C. O'Neill, P. Jordan, P. Riddle, and G. Ireland, *J. Cell Sci.* 95:577–586 (1990); D. Kleinfeld, K.H. Kahler, and P.E. Hockberger, *J. Neurosci.* 8:4098–4120 (1988); C.S. Dulcey, J.H. Georger, V. Krauthamer, D.A. Stenger, T.L. Fare, and J.M. Calvert, *Science* 252:551–554 (1991); D.A. Stenger, J.H. Georger, C.S. Dulcey, J.H. Hickman, A.S. Rudolph, T.B. Nielson, S.M. McCort, and J.M. Calvert, *J. Am. Chem. Soc.* 114:8435–8442 (1992); T.G. Vargo. P.M. Thompson, L.J. Gerenser, R.F. Valentini, P. Aebischer, D.J. Hook, and J.A. Gardella, *Langmuir* 8:130–134 (1992); K.L. Prime and G.M. Whitesides, *J. Am. Chem. Soc.* 115:10714–10721 (1993); K.L. Prime and G.M. Whitesides, *Science* 252:1164–1167 (1991).

[28] A. Kumar, N.L. Abbott, E. Kim, H.A. Biebuyck, and G.M. Whitesides, *Accounts of Chemical Research* 28:219–226 (1995).

SAMs were very effective in improving the adhesion of the deposited film, and in several systems it has been demonstrated that they can be used to influence the activated nucleation of thin-film growth. [29]

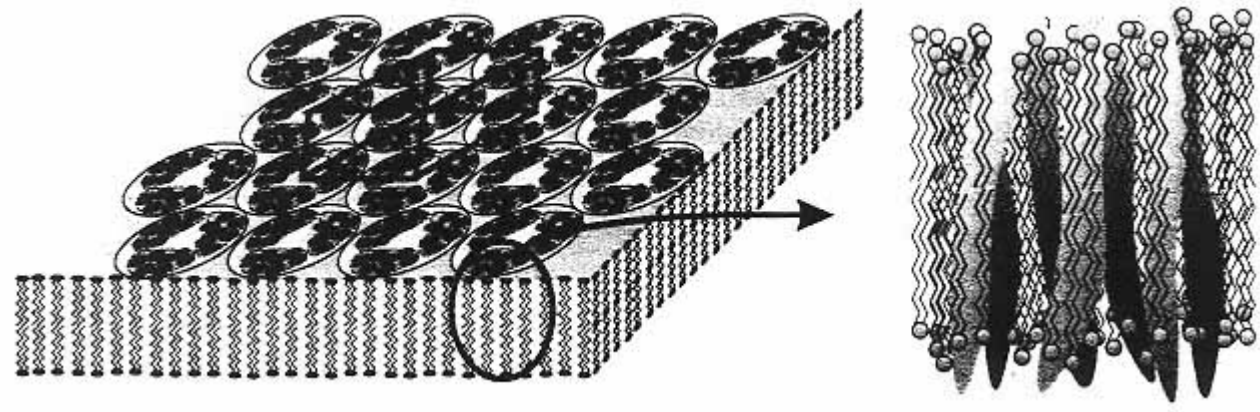

Figure 9
Schematic view of a bacterial membrane with a hexagonal lattice of bacteriorhodopsin trimers. The expanded view on the right shows one bacteriorhodopsin molecule, illustrating the seven -helices that span the membrane. (Reprinted, by permission, from Y. Shen, C.R. Safinya, K.S. Liang, A.F. Ruppert, and K.J. Rothschild, Nature 366 (6450):48 (1993). Copyright © 1993 by MacMillan Magazines Limited.)

Membrane-associated Proteins

In contrast to phospholipid molecules, which form the passive permeability barrier in biomembranes, membrane-associated proteins serve as active components to facilitate important cellular processes such as nerve conduction, energy conversion, active-ion and molecular transport, and cell-cell adhesion. Integral membrane proteins are intercalated and firmly tethered to the two-dimensional host lipid membrane plane, in which they are free to diffuse. Research has begun to develop new types of materials that incorporate the functional activity of such proteins into chemical and biological sensors, materials with controlled interfacial properties, and optoelectronic materials.

A notable example of a membrane-associated protein is bacteriorhodopsin (bR),[30] which embodies two functions of membrane proteins, energy transduction and active ion transport.[31] This protein, which acts as a photon-induced proton pump, self-assembles into a two-dimensional crystalline patch in the lipid bilayer plane of the plasma membrane of the bacterium *Halobacterium halobium.* The structure of bR has been determined to near-atomic resolution of 3.5 Å parallel to the membrane and 10 Å perpendicular to the membrane; each bR molecule consists of a polypeptide chain that traverses the membrane, forming seven folded a-helices as shown in Figure 9.

The detailed mechanism by which bR absorbs light energy and transports protons against an electrochemical gradient is becoming clear. Several features make bR attractive from the standpoint of biomolecular materials development. At low temperatures, bR can function as an optically driven bistable switch. For example, when the light-adapted form of bR, which absorbs at 570 nm, is irradiated with green light at 77 K, it is converted to the stable K form, which absorbs near 630 nm. Recent studies[32] using genetic engineering techniques suggest that mutant forms of the protein can be produced that exhibit optical bistability at room temperature.

[29] A.R. Bishop and R.G. Nuzzo, *Current Opinion in Colloid and Interface Science* 1:127–136 (1995) and references therein.
[30] W. Stoeckenius, *Scientific American* 234(July):38–46 (1976).
[31] R.R. Birge, "Protein-Based Computers," *Scientific American* 272(March):90–95 (1995).
[32] M. Dunach, S. Berkowitz, T. Marti, Y.W. He, and S. Subramaniam, *J. Biol. Chem.* 265:16978 (1990); P.L. Ahl, L.J. Stern, T. Mogi, H.G. Khorana, and K.J. Rothschild, *Biochemistry* 28:10028 (1989).

Laminates and Templates

Biomineralization[33] is precisely controlled by complex templating relationships and coordinated secretory processes that are ultimately encoded in genes. During formation of abalone shell, for example, secreted proteins self-assemble into two-dimensional polyanionic b-pleated sheets that serve as templates for the nucleation and epitaxial growth of calcium carbonate crystalline domains (Figure 10). A microlaminate composite is formed that has exceptional regularity, strength, and crystalline ordering. The organizing organic polymers typically contribute less than 1% of the composite material by weight, yet the material's strength and fracture resistance far exceed those of the crystals themselves. The unique properties of biosynthetic microlaminates are due to the organic matrix layers' capacity for flexible deformation and to the retardation of crack propagation at each mineral-organic interface.

The biological templating process that controls the structure of molluscan shell has been mimicked in the formation of sub-micron structures built up on tubules. The cylindrical structure of a tubule is intrinsically interesting as a template. It leads directly to a large degree of shape anisotropy, which can be tuned by adjusting the dimensions of the tubules either by manipulating the molecular structure of the protein or other molecule attached to the substrate or by changing the processing conditions under which the tubules form.

A beautiful example of the use of spontaneously self-assembled mesoscopic ordering to produce new materials is the use of the lyotropic hexagonal phase as a template to make mesoporous solids. These materials have periodic arrays of nanometer-sized pores of unprecedented regularity and density. Mesoporous metallic surface films have also been generated via molecular templating, by employing the self-assembled two-dimensional crystalline protein arrays of bacterial cell walls as patterning elements.

Biomotors

Much of the molecular transport in biological systems occurs not by diffusion but by active transport by biomotors.[34] Such systems do not conform to our definition of self-assembly because the biomotors are driven by chemical energy input

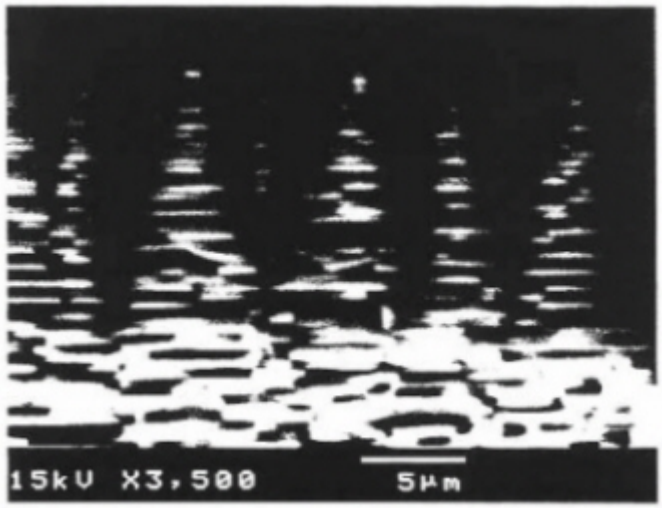

Figure 10
Scanning electron micrograph of the growth front of abalone shell. The aragonite ($CaCO_3$) crystals in the shell form very regular stacking and interdigitating plates. A combination of polyanionic proteins and matrix proteins produces this hierarchical structure, which gives the shell its unique optical properties and its increased strength. (Courtesy of A. Belcher, D. Morse, and G. Stucky, University of California, Santa Barbara.)

[33] See footnote 11.

[34] "Seventh Biophysical Discussions: Molecular Motors: Structure, Mechanics and Energy Transduction," *Biophysical Journal* 68 (April 1995).

in the form of ATP. Biomotors often involve "walking" carrier proteins along "rails" that are themselves biopolymers, such as tubulin or actin (Figure 11). These systems are receiving increased attention in the context of studying molecular-level transport with modern probes such as optical tweezers (magnetic beads with fluorescent labeling). There are also several theoretical groups modeling biomotors in the framework of the statistical mechanics of irreversible processes.

3

Opportunities

Section 2, "Status," provides many examples of current research in biomolecular materials and its applications, from which the immediate direction of the field can be discerned. In this section the panel suggests a few possibilities for the longer term and describes ways in which biomolecular materials can have an impact on national needs. For example, it appears likely that it will be possible to produce self-repairing composites of biologically active molecular arrays with passive structural materials, using the same chemistry that nature uses to produce operational devices and structures. Much of the content of this section is speculative. The developments described are meant to represent a vision of what might occur in the field over the next 10 to 20 years.

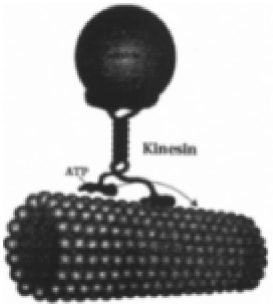

Figure 11
Kinesin "walking" along a microtubule, transporting a vesicle. (Courtesy of P. Pincus, University of California, Santa Barbara.)

LIQUID CRYSTALLINE POLYMERS[35]

Monomers similar in structure to the molecules that form liquid crystals can be linked together in a large number of ways, including linear and comb-like arrays, to form polymer liquid crystals. Liquid-crystal-forming molecules are beginning to be incorporated into polymer hosts to form anisotropic gels. These, in turn, can be cross-linked or used to form composites with structures on larger length scales. Polymer liquid crystals can combine the optical properties of liquid crystals with the ease of processing and good mechanical properties of polymers.

LYOTROPIC SYSTEMS[36]

Surfactant-based lyotropics will play a basic role in self-assembling and self-repairing systems. For example, lipid-water systems are known to display cubic phases that are bicontinuous; i.e., the entire aqueous region of the sample is divided by the lipid bilayer into two disconnected regions that are

[35] National Research Council, *Liquid Crystal Polymers* (National Academy Press, Washington, D.C., 1990).
[36] See footnote 12.

simultaneously continuous. The bilayer has been shown to be an infinite periodic minimal surface. It has cubic symmetry and long-range three-dimensional periodicity, even though the lipid molecules within the bilayer possess no positional order. Although the structures of biological cell membranes most often resemble those of the liquid-crystalline lamellar phase exhibited by phospholipids, there are several examples of organelles with structures very similar to bicontinuous cubic phases. Cell membranes resembling periodic minimal surfaces have been observed in cytoplasmic organelles such as mitochondria and chloroplasts. It has been suggested that in certain invertebrates the endoplasmic reticulum (a system of interconnecting membranes inside the cell) may exhibit gyroid (spiral) cubic structures.

Electron micrographs show that nature has elevated these structures to a high level of sophistication. The lamellar-like body of chloroplasts has revealed a structure in which the pore sizes of the two intertwining aqueous channels are different, suggesting a difference in osmotic pressure between them. It is believed that these two channels act as reaction chambers for the synthesis of chlorophyll. Even though the formation of these saddle surfaces in lipid-water systems is determined by the balance of forces between the polar head groups and the nonpolar tails, in biological membranes the periodic curvature may be due to the presence of some membrane-spanning proteins.

The bicontinuous cubic phases provide thermodynamically stable structures on the nanoscale whose characteristic size can be precisely controlled. They are not rigid, however. If these structures could be stabilized, they would provide continuous, triply-periodic pore space with very uniform nano-sized pores. Such structures could find many useful technological applications in such areas as controlled release and ultrafiltration. “Smart” release vehicles can be envisioned that would allow first-order drug release in response to stimuli. These phases can also be used as templates for synthesizing nanoporous materials and nanocomposites. Another important property of the cubic phase that can be harnessed is the large bilayer surface area that it provides (10^3 to 10^4 m^2/g). Immobilization of proteins can be envisaged, either by covalent attachment to the head group or by simple incorporation into the bilayer, which could lead to the development of biosensors. It is believed that the functionality of the integral proteins will be optimal since the fluid bilayer provides an environment closest to the natural condition *in vivo.*

FABRICATION OF DEVICES BY SELF-ASSEMBLY[37]

The potential for fabrication of electronic devices by self-assembly has often been cited as a long-term goal of research in organic thin films. It is attractive to consider devices in which the components are individual molecules or molecular complexes self-assembled on substrates from solution or by deposition from interfaces. There are three steps that must be accomplished in order to achieve this goal. Functioning molecular units must be designed and synthesized, they must be organized on a surface into defect-free structures, and they must be interconnected to form functioning networks. While progress needs to be made in each of these areas, the last one is the most difficult and needs to be addressed in the long-term. It is clearly possible to make connections by photolithography, but this cannot be accomplished at the molecular scale. Methods based on scanning microscopy, especially with chemically active tips, may provide a solution, but it is difficult to envision how such a process can be carried out on a practical scale. A biomimicking process of self-assembly, in which connections are made by enzyme-like molecules that either form bonds or activate functional groups so that they can be photochemically linked, is more attractive.

[37] See footnote 7.

POLYMERS—SYNTHESIS AND PROCESSING.

The biosynthesis of polymers is discussed in Section 2 of this report. The generality of this approach remains uncertain. Although it seems clear that it is possible to use the technique to make virtually any copolymer of the 20 naturally occurring amino acids, extension to other classes of monomers is not simple. To date, two successful approaches to this problem have been reported. The first involves chemical acylation of transfer RNAs and *in vitro* protein synthesis. This is an elegant approach and has been shown[38] to succeed not only with non-natural amino acids but also with lactic acid, a hydroxyacid related to the natural amino acid alanine. This result suggests that templated ribosomal catalysis might be extended to polymerization reactions other than polyamidation and that other classes of polymers might be prepared with the exquisite architectural control that is the hallmark of protein biosynthesis. On the other hand, the scale of these reactions is limited by the cost and inefficiency of cell-free biosynthesis, and the modest efficiency of incorporation of artificial monomers limits the *in vitro* method's utility in the preparation of periodic chains that require high levels of substitution. A second approach to the preparation of protein-like polymers of non-natural amino acids relies on the observation in the 1950s that bacteria can utilize as substrates a surprising number of amino acid analogues, including several with functionally interesting side chains.[39] The scope of this second approach remains to be defined, but it appears likely that *in vivo* protein biosynthesis will prove to be a more versatile route to new materials than was previously anticipated.

Although the morphologies so far discovered in polymer systems are already quite diverse, it is nevertheless expected that advances in synthetic capabilities for greater control and complexity will lead to macromolecules with new structural geometries. Control of the morphology of polymers, and thereby control of their physical properties, has been well demonstrated in the anionically synthesized A/B block copolymers; biosynthesis will provide greater opportunities to tailor-make such materials.

Some possible future directions are to use block copolymer architecture to produce liquid-crystalline domains of prescribed size and shape embedded in a matrix of high-temperature thermoplastic. Such an approach could generate materials of novel mechanico-optical properties.

There is much additional scope for the production of advantageous materials by the coupling of dissimilar molecules. Not only are flexible-stiff combinations of interest (including the combination just mentioned), but so also is tailoring of the polymer backbone (persistence length and chemical bonding), which controls subsequent physical structure. Structural control could be of special interest for materials with rheological applications, because chain geometry can influence the nature of entanglements and the motion of the chain.

Control of molecular diffusivity is a critical factor in the organization of molecules at different length scales, but as yet it is almost unused. As an example, consider a blend of an A homopolymer and a B/C diblock copolymer. At high temperature or with sufficient solvent the system is in a single homogeneous phase. Depending on the interactions of A with B, A with C, and B with C, and on the relative selectivity of the solvent, macrophase separation of A liquid from B/C liquid or microphase separation of swollen B from swollen C may occur first, followed at some later stage by aggregation of A within the existing structure. Depending on the various chemical interactions, and especially on the relative mobilities of the components, a vast range of morphologies is possible. Arresting the evolving structure can be done thermally (via quench below the glass transition temperature T_g) or through a chemical trigger.

[38] C.J. Noren, S.J. Anthony-Cahill, M.C. Griffith, and P.G. Schultz, *Science* 244:182–188 (1989); J.D. Bain, C.G. Glabe, T.A. Dix, and A.R. Chamberlin, *J. Am. Chem. Soc.* 111:8013–8014 (1989); D. Mendel, J.A. Ellman, and P.G. Schultz, *J. Am. Chem. Soc.* 113:2758–2760 (1991); D. Mendel, J.A. Ellman, Z. Chang, D.L. Veenstra, P.A. Kollman, and P.G. Schultz, *Science* 256:1798–1802 (1992).

[39] M.H. Richmond, *Bacteriol. Rev.* 26:398–420 (1962).

Another opportunity in this area is the challenge of inserting polymer genes into plants and then using biomass conversion to make protein-and polyester-based polymers. This would be an entirely new method of polymer production that might be more environmentally benign than present techniques.

Materials with highly specialized functions are likely candidates for the first applications of polymer biosynthesis. The major advantage of polymers is their easy and versatile processing into useful shapes such as fibers and films. Single-step processing in which the overall shaping of a part is achieved simultaneously with its detailed structural arrangements (possibly on several length scales) will be an important factor in acceptance into the marketplace. Likely early candidates for thin film applications are those in which surface, optical, electrical, or transport characteristics are critical. Because of the small quantities of materials required, the first specialty applications of biosynthesized materials will probably be biocompatible coatings.

SENSORS

Perhaps the earliest example of a biosensor is the use of canaries to detect lethal fumes in mines. Even today animals are the method of choice to search for the highly prized truffle, and dogs are used to track missing persons and to search for earthquake victims.

One of the goals of biomolecular materials research is to couple the sensitivity and selectivity of biosensing with the robustness and mass-production attributes of silicon and the reliability of electronics.[40] To this end, optical-fiber-based and microelectronics-based biosensors have been fabricated to detect a large number of chemicals, including glucose, nerve gas, and ethanol.[41] Many of these devices take advantage of highly selective antigen-antibody recognition events, others employ receptors as the sensing element, and yet others use catalytic selectivity of enzymes such as horseradish peroxidase to produce a detectable byproduct.

One of the major as yet underexplored opportunities in sensor research is the coupling of biological sensing units, whether they be receptors, antibodies, or enzymes, with microelectromechanical machines (MEMs). MEM devices have been fabricated with free-standing components that can be made to oscillate at a frequency that changes with the binding of a very small number of molecules.

Biomolecular-based sensors will have a wide range of applications, including the detection of low levels of toxic or harmful chemicals, the detection of biological warfare agents, and diagnostic applications in health care, agriculture, and food quality and safety. For example, one can envision nanoscale reactors and sensors that are safe and reliable parts of artificial organs, depending on the seamless integration of biomaterials with other high-performance materials.

MOLECULAR MACHINES

Active transport by biomotors (discussed in Section 2, “Status”) suggests the possibility of molecular-level bioengineering and construction on a unit-by-unit basis. This capability would require the use of in situ biorecognition sensors. In other words, integrated systems might be fabricated that would use biomotors to build up supermolecular assemblies much as children construct tinker toy models.

Other examples of molecular machines are discussed elsewhere in this report, such as bacteriorhodopsin in the subsection titled “Membrane-associated Proteins” and RNA polymerases in the subsection titled “Polymers—Synthesis and Processing.” The idea of combining such machines presents a number of interesting opportunities. For example, one might couple a biomotor with an energy

[40] “Nanofabrication and Biosystems—The Frontiers and Challenges,” in *Nanofabrication and Biosystems: Integrating Materials Science, Engineering, and Biology,* H.C. Hoch, L.W. Jelinski, and H.G. Craighead, eds. (Cambridge University Press, New York, 1996).

[41] J.S. Schultz, “Biosensors,” *Scientific American* 265(August):64–69 (1991).

transducing machine such as the bacteriorhodopsin "solar cell," producing a light-powered machine for specialized transport of chemicals to a specific desired location.

Such work would require expertise in several different molecular machines, a combination of specialties rarely found within a single laboratory. This area is thus a good example of the need to encourage collaboration among groups of researchers involved in biomolecular materials research.

4

Needed Developments

OVERVIEW

Certain needs must be addressed to effectively take advantage of the important scientific and technological opportunities that this report and other studies[42] have documented. The strong multidisciplinary skills required to make progress in the field, as well as the broad potential technological impact, present special challenges for research, infrastructure, and funding. The basic features of these challenges have also been documented in the studies referred to above. In this report the panel draws from these other studies, many of whose findings it shares, and provides additional input based on the panel's efforts.

Although the research needs documented below are particular to the area of biomolecular materials, the infrastructure and funding challenges contain many features common to other frontier areas that are emerging at the interfaces between established disciplines. Biomolecular materials is centered at the interface between materials science and biology, two fields that are themselves experiencing strong intellectual and technological progress. Materials science is itself highly multidisciplinary; it bridges the sciences and engineering. Thus, providing the needed infrastructure and funding that will successfully and effectively bring materials scientists and biologists together, and will supply them with the supporting infrastructure for research, education, technology transfer, and funding, represents a significant challenge to existing mechanisms.

In this section, after proposing broad research priorities and mid-term research goals for the field, the panel suggests some options with respect to infrastructure and funding mechanisms.

RESEARCH PRIORITIES

This subsection discusses broad research priorities for the field. It gives specific examples of research areas that should be pursued over the next five to seven years. Success in accomplishing these research goals will provide a measure of the extent to which the possibilities outlined in Section 3, "Opportunities," can be realized within a reasonable time.

Colloids

Because they are mechanically rigid (i.e., have a shear modulus) colloidal particles can serve as substrates for molecularly thin films of biopolymers or other surface-active agents. In applications in which film orientation is not important, coated colloidal particles provide an efficient means to pack these films. Extensive use has been made of silica and latex particles as substrates to which antibodies and antigens could be attached for assaying and in drug delivery applications. Lock-and-key protein

[42] National Science Foundation, *Biomolecular Materials: Report of the University/Industry Workshop, October 10–12, 1990,* NSF 91–142 (National Science Foundation, Washington, D.C., 1991); National Research Council and Institute of Medicine, *Interdisciplinary Research: Promoting Collaboration Between the Life Sciences and Medicine and the Physical Sciences and Engineering* (National Academy Press, Washington, D.C., 1990); G.M. Whitesides and M.S. Wrighton, *Report on the La Jolla Workshop on Self-Assembly of Materials, July 23–24, 1986* (private communication, 1986); *Synopsis and Workshop Results, Self-Assembling Molecular Materials Conference, Princeton University* (Princeton Materials Institute, Princeton, N.J., 1991).

systems such as the biotin-avidin couple may be used as controllable strong adhesives. Colloidal dispersions have also been used as a solvent for self-assembling lamellar phases of surfactants. In particular, superparamagnetic grains have been used to allow orientation of the smectic liquid crystal phase in magnetic fields as low as a few gauss. The physics of the phase behavior of these amphicolloids is just now beginning to be studied. It is likely that there will be increasing activity in the study of colloid-surfactant interactions. Other studies, [43] mostly carried out in Europe, have investigated colloidal particles in polymer solutions. They have demonstrated that under appropriate conditions the particles may adsorb on the polymers, forming "pearl necklaces" that have the potential to combine the excellent mechanical properties of polymers with useful electronic or optical properties of the solids. In the future, we may expect biomolecular applications based on such "necklaces."

Biosynthesis of Polymers

Although there has been impressive progress in the development of new polymeric materials by biosynthetic pathways, important challenges in synthesis remain. Artificial DNAs, especially those with highly repetitive sequences, can be so unstable in microbial hosts that they are rapidly deleted from the cellular population or are rearranged. Artificial messenger RNAs can be rapidly degraded or translated into protein with unacceptably low efficiency. Even after a protein product is formed, it may be toxic to the host cell or subject to rapid metabolic turnover. Bioprocess engineering for the separation and recovery of products from genetic engineering is, at present, a time-consuming and expensive step that is often rate-limiting. Further work on each of these problems will be required to make protein biosynthesis a tool of broad utility in materials science and technology.

Processing of Biosynthetic Polymers

As novel *in vivo* synthesized polymers become increasingly available, researchers need to address processing issues. The principles of self-assembly imply slow processing in order to achieve equilibrium. Practical situations may demand assisted assembly, however, and indeed the modification of self-assembly by external controls may in certain cases prove beneficial. Alternatively, the use of processing techniques that have worked well with synthetic polymers may prevent realization of the inherent properties present in precision-built biosynthetic materials. Processing of biosynthetic materials demands detailed investigation.

Surfactant-based Self-Assembly.

In order to realize the potential of self-assembled tubules for applications such as those mentioned in the "Status" section, the dimensions of the tubules need to be engineered for optimal performance for each application. Such an effort will require a better fundamental understanding of basic tubule phenomena. In addition, the cost of the tubule-based approach must be consistent with operational requirements and the competitive marketplace.

Multicomponent Self-Assembly

A high priority should be assigned to learning to control the processes by which multicomponent self-assembling systems evolve for homogeneous states.

Multicomponent self-assembly can yield structure at several length scales. The patterns that can be formed by a suitable quench from an initially homogeneous state can vary over several orders of magnitude in size. This variability arises from the many possible combinations of phase transition mechanisms (e.g., spinodal decomposition versus nucleation and growth), including phase transitions of one or more components. For example, the transition of one of the components from liquid to liquid

[43] For example, B. Cabane and R. Duplessix, *Colloids and Surfaces* 13:19 (1985).

crystal, homogeneous liquid to microphase-separated liquid, or liquid to crystal can arrest the overall phase separation process at an intermediate stage. It is apparent that such multiple combinations of phase transitions give an extremely rich variety of possible structures, all of which should be accessible with a suitable choice of components and processes.

An illustrative example from the laboratory of Hashimoto[44] demonstrates how a binary blend of isotactic polypropylene (PP, a crystalline polymer) and ethylene-propylene rubber (EPR, a random amorphous copolymer) can result in a novel morphology with two important length scales. A blend of PP and EPR was cooled from the high-temperature single-phase melt state to a temperature above the melting point of the PP but below the spinodal curve of the blend. After spinodal decomposition took place for some time, the blend was again quenched, now to below the melting point of the PP, whereupon crystallization of the PP effectively pinned the structure. This process history resulted in volume-filling PP spherulites approximately 100 mm in diameter with a fine-scale (0.1-mm) internal periodic bicontinuous structure of packets of PP lamellar crystals and amorphous EPR-rich regions from the initial spinodal decomposition. Thus the two-stage quench process produced and fixed a dual morphology consisting of spherulites and bicontinuous domain structures.

Several possibilities exist for pinning (fixing) an evolving system. These include crystallization, vitrification, and chemical cross-linking. Further morphological control can be added by imposing an electric, magnetic, or flow field during processing. For example, one can couple the shear deformation rate with the rate of chain relaxation, the rate of phase separation, and the crystallization rate to achieve structures with strong shape anisotropy that arises from the phase separation, phase elongation, and crystallization of flow-oriented molecules.

Establishing Design Rules for the Development of Advanced Molecular Materials

Improved understanding of the role that molecular structure and self-assembly have in determining molecular architectures leads researchers to be optimistic about the possibility of designing new materials with novel function starting at the level of the molecule, i.e., from the bottom up. Advances in computational techniques have led to a clearer understanding of protein folding. New insights in statistical physics have led to a better understanding of the role of chirality in determining the molecular architecture that leads to microstructure formation and novel properties in heteropolymers. Coupled with these recent theoretical and computational advances, the advent of new characterization tools that can successfully probe molecular architectures (e.g., atomic force microscopy (AFM), scanning tunneling microscopy (STM), and near-field microscopy) suggests that it will soon be possible to design advanced materials based on their engineering requirements by appropriately designing their molecular or polymeric structures.

Imaging on Mesoscopic Scales

A variety of techniques exist for examining the structure of materials on molecular and macroscopic length scales. Fewer methods exist, however, for mesoscopic length scales, i.e., 5 nm to 1 μm, the scale relevant for many of the systems discussed here. The development of scanning microscopies such as AFM, STM, and lateral force microscopy (LFM) has been a major advance, but these powerful methods have limited application.

Recent developments in soft x-ray optics, such as multilayer mirrors and high-resolution zone plates, have stimulated work on a new class of microscopes: x-ray high-fidelity optical microscopes and high-resolution and lower-fidelity electron microscopes. These will provide images of soft materials at high-resolution in their natural environment. A reflection imaging soft x-ray microscope is based on the fact that surfaces of different materials have reflection coefficients for soft x-ray radiation near 10 to 20 nm

[44] N. Inaba, K. Sato, S. Suzuki, and T. Hashimoto, *Macromolecules* 19:1690 (1986).

that differ by up to several percent. At these wavelengths the resolution of such a microscope can be an order of magnitude better than that of an optical microscope. The reflection coefficient is strongly dependent on the material and the angle of incidence of the radiation, and thus provides sufficient contrast for imaging microscopy. The soft x-ray reflection microscope, when fully developed, will make it possible to view the surface and near-surface structure of soft biomolecular materials at a relatively high-resolution—not as high as that obtained with a scanning electron microscope, but achievable in a natural state without staining. The technique will add significant new information to data obtained with the atomic force microscope and the near-field scanning microscope, especially for those cases in which subsurface structural information is important.

Vesicle Adhesion and Fusion

Many of the interactions between membranes leading to vesicle adhesion are reasonably well understood and are similar to the Derjaguin-Landau-Verwey-Overbeek (DLVO) interactions between simple colloidal particles. As a result, vesicle stabilization methods based on classical colloidal schemes have been successful, including steric stabilization by end-grafting polymers to lipid molecules in the bilayer,[45] or electrostatic stabilization, as in the case of equilibrium vesicles made from cationic-anionic surfactant mixtures.[46] However, there exist interactions unique to membranes that are less well understood, such as repulsion due to membrane undulations or protrusions, which depend sensitively and in unknown ways on membrane composition, lipid properties, and other factors. Additional experimental and theoretical work needs to address the dependence of membrane elasticity on membrane composition and how that dependence affects membrane adhesion.

The mechanism of fusion is still elusive from both an experimental and theoretical viewpoint. Many proteins and ions are known to enhance fusion, but the detailed pathway of fusion is not yet known. On the experimental side, new light-sensitive calcium chelators[47] might be used to examine the early steps of calcium-induced fusion in membranes. Biochemical and biophysical studies are necessary to examine the effects of cell fusion proteins and their mechanisms.[48]

Membrane Proteins

Membrane-associated proteins offer exciting opportunities for the development of advanced materials. Membrane proteins serve as active components and as such facilitate some of the most important cellular processes, including nerve conduction, energy conversion, active ion and molecular transport, and cell-cell adhesion.

A future goal is the development of new types of materials that incorporate the functional activity of membrane-associated proteins. For example, functionalized biomolecular interfaces that incorporate receptor proteins could form the basis for developing advanced materials that serve as chemical and biological sensors, or materials with controlled interfacial properties (e.g., adhesion and lubrication). Membrane proteins with photoactivity could be used to develop a new class of optoelectronic materials in the nascent field of molecular electronics.

Bioactive gels based on membrane proteins incorporated in lipids (Figure 12) are expected to become increasingly important. The bioactive gel would combine (1) the optimal mechanical integrity and processability properties of the host polymer together with (2) the particular intrinsic activity of the protein macromolecule, leading to a new class of gels suitable for a variety of purposes including chemical and biological sensors. For example, many biotechnology companies are anxious to improve

[45] Dan Lasic, ed., *Stealth Liposomes* (CRC Press, Boca Raton, 1995).
[46] E.W. Kaler, A.K. Murthy, B. Rodriguez, and J. Zasadzinski, *Science* 245:1371 (1989).
[47] A.M. Gurney, P. Charnet, J.M. Pye, and J. Nargeot, *Nature* 341:65 (1989).
[48] A.E. Sowers, ed., *Cell Fusion* (Plenum, New York, 1987).

skin-healing gels that are used on burn patients. One technique that has been developed is the incorporation of a peptide in the disordered gels that acts as a glue for the incoming white blood cells that are needed for the initial scavenging of dead cells. These bioactive gels have been found to significantly shorten skin healing times. Membrane-based bioactive gels would have the advantage (over disordered gels) of having a natural membrane environment for the needed peptide or protein to attach to via an anchor.

Opportunities for the development of new biomolecular materials based on membrane proteins also stem from the natural tendency of some membrane proteins, such as bacteriorhodopsin and gap junctions, and proteins constituting the outermost wall of bacterial surface layers (S-layers), to self-assemble into two-dimensional lattices. For example, given their molecular sieving ability derived from their microscopic pore structures, ranging typically between 2.0 to 5.0 nm for different strains, specifically processed multilayer stacks of S-layers will result in a tortuous molecular path with potential for use in separations technology.

Membrane protein self-assembly is expected to play an increasingly important role in obtaining increased temperature stability for the development of heat-proof proteins and enzymes. Proteins that are stable at high temperatures will find utility in numerous present-day and future biotechnology applications, such as biosensors (e.g., toxin detectors), bioreactors (for purifying genetically engineered proteins with high-temperature sieves), and catalytic applications (e.g., current polymerase chain reaction (PCR) machines, which use enzymes at high temperatures).

The recent finding that the membrane protein bacteriorhodopsin may be stabilized to 140°C through higher-order self-assembly in dry films[49] suggests the generalization of the technique for temperature stabilization, through higher-order self-assembly, of a variety of functional proteins. A promising approach[50] to higher-order self-assembly is via schemes involving the specific binding of macromolecules to functionalized interfaces, e.g., by using the biotin-avidin scheme pioneered by Uzgiris and Kornberg.[51]

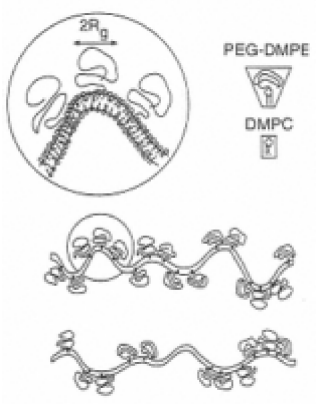

Figure 12
Two undulating fluid membranes [composed of dimyrithristoyl phosphatidyl choline (DMPC) and cosurfactant pentanol (single chain)] with poly(ethylene glycol)-derived polymer (PEG-lipid) hydrophobically anchored but freely diffusing within the membrane. This system forms a gel. (Reprinted, by permission, from H.E. Warriner, S.H.J. Idziak, N.L. Slack, P. Davidson, and C.R. Safinya, Science 271:969–973 (1996). Copyright © 1996 by the American Association for the Advancement of Science.)

Gene Therapeutics

Genetic engineering, gene therapy, and gene therapeutics depend on the transfer of different size nucleic acids to the cytoplasm of bacteria or within the cytoplasm or nucleus of eukaryotic cells. Retroviral vectors are currently the most common method of gene delivery in gene therapy because of their efficient and stable integration of nucleic acid into the host genome.[52] The conventional non-viral

[49] Yi Shen, C.R. Safinya, K.S. Liang, A.F. Ruppert, and K.J. Rothschild, *Nature* 366:48 (1993); N. Hampp, News & Views, *Nature* 366:12 (1993).
[50] C.R. Safinya and K.J. Rothschild, *Nature* 370:105 (1994).
[51] E.E. Uzgiris and R.D. Kornberg, *Nature* 301:125 (1983).
[52] F. Bushman, *Science* 267:1443 (1995).

transfer methodologies, which have transfection rates significantly lower than viral transfection rates, include anionic liposomes that encapsulate nucleic acid, calcium-phosphate precipitation, use of polycationic reagents (DEAE-dextran or polylysine), and electroporation. An important recent development involves the use of cationic liposomes as non-viral vectors of nucleic acids and recombinant DNA molecules. While the transfection rates and reproducibility in many cells have been found to be significantly enhanced as compared to the other chemical methods involving non-viral vectors, the mechanism of transfection via cationic liposomes remains unknown.

An important future development in gene therapy and therapeutics will come about through an increased understanding at the molecular level of the mechanisms of transfection via chemical methods such as those involving liposomes.

Biological Computation

Discovery of the polymerase chain reaction (PCR) as a method for amplifying very small amounts of DNA has ushered in a wide variety of possible new applications. Although used primarily for genetic engineering and forensics, the PCR reaction has also been used in a "biological computation," in which DNA recognition was the basis for solving the Hamiltonian path problem, an important mathematical problem in combinatorics that involves finding a path between vertices of a graph.[53] The path was encoded in strands of DNA. The first half of a particular DNA strand encoded the starting vertex of a link in the graph, and the second half encoded the target vertex. A complete solution was deduced by using PCR primers for the initial and final vertices.

Sensor Development

Mid-term research goals for biosensors include the development of better methods for interfacing biomolecule-sensing units with the device. Achieving this goal will require a better understanding of surface chemistry and surface interactions, and perhaps the development of better transduction mechanisms.

Biological molecules are often non-robust, and one of the challenges in biomaterials research for sensors is to understand what factors contribute to thermal and oxidative stability of biomolecules. Furthermore, the response of a biosensing device is often quite slow, and research is needed to improve response times.

Processing Using Templates.

Spatial and temporal *in vivo* characterization of biomineralization growth processes is providing insight into biomolecular templating of inorganic phase structure, phase transformations, crystallographic orientation, and metamorphosis through growth stages. Studies of this type are leading to the "bioinspired" synthesis of composite materials that are structurally designed at nano-, meso- and micro-length scales by templating inorganic growth with surfactants and vesicular arrays. An example is the condensation of calcium hydroxyapatite phases with mesoporosity induced by liquid crystal-like surfactant array templating to generate mesoporosity and a hierarchical longer-range structure generated through a second vesicular-like templating component. Multicomponent cooperative assembly of this type, involving organic and inorganic phases, can be expected to lead to polyphasic materials with nano-structured regions that are spatially well-defined and, if desired, chemically accessible for modification during and after the initial synthesis processing.

[53] L.M. Adleman, *Science* 266:1021–1024 (1994).

INFRASTRUCTURE

Two previous studies have recognized the challenge that multidisciplinary research presents to the existing infrastructure. The 1990 National Science Foundation (NSF) study of biomolecular materials reached the following conclusion:[54]

Research in biomolecular materials requires expertise in both biological and materials sciences. Researchers must be capable of working across a variety of disciplines. Furthermore, organizational structures have to be created within industry, government, and universities that facilitate synergistic interactions among scientists, each of whom may have outstanding individual skills.

In the National Research Council study on interdisciplinary research, a similar theme was presented but with a more focused target:[55]

The conclusions and recommendations on policy strategies are all directed toward advancing the following goals:…

- forging new links between disciplines through educational programs and institutions and through professional activities,…
- ensuring that the most productive and beneficial areas of interdisciplinary research are well supported, and
- identifying factors that create respectable and productive environments for interdisciplinary research collaboration.

Both studies also recognized the need to couple research in biomolecular materials to technology that could benefit the economy and quality of life:

National competitiveness in a number of areas will, to a large extent, hinge on the support for education, research and knowledge transfer in this research area.[56]

The creation of effective mechanisms for the flow of knowledge and invention between academic institutions and industry is becoming an increasingly important factor in funding for university research and in improving the competitiveness of U.S. business in biotechnology, medical devices, and pharmaceuticals.[57]

The studies found further that academic-industrial interaction has become a significant stimulus for interdisciplinary research.

The panel's deliberations led it to agree with the above conclusions, with the added emphasis that as time passes, and as the record of significant results grows and the potential economic impact becomes more apparent, the need for providing the new infrastructure is becoming even more acute. Put simply: **The existing infrastructure is not keeping pace with scientific and technological opportunities in the field of biomolecular materials and in other fields that are emerging at the interfaces between established disciplines.**

[54] National Science Foundation, *Biomolecular Materials: Report of the University/Industry Workshop, October 10–12, 1990,* NSF 91–142 (National Science Foundation, Washington, D.C., 1991), p. 1.

[55] National Research Council and Institute of Medicine, *Interdisciplinary Research: Promoting Collaboration Between the Life Sciences and Medicine and the Physical Sciences and Engineering* (National Academy Press, Washington, D.C., 1990), p. 19.

[56] See footnote 54, p. 1.

[57] See footnote 55, p. 22.

The panel considered at length what course it should suggest to overcome these well-documented barriers to interdisciplinary biomolecular materials research. The outcome of its deliberations was greatly influenced by the successful approach that led to the establishment of university programs in materials science and engineering over the last decade. The situation for materials science and engineering a few decades ago was similar to that for the field of biomolecular materials today. Namely, the field was clearly recognized as important for the United States, but capturing its potential required bringing physical scientists and engineers together. Two parallel and related approaches were taken that managed to successfully overcome the barriers that existed at that time: (1) specific organizations and funding programs directly targeted at materials science and engineering were established by the relevant federal agencies, and (2) centers were created at major research universities at a scale that was sufficient to influence the university culture to establish academic programs in the field. By all accounts, these efforts have been very successful in providing the United States with the expertise, trained students, and knowledge base that have been so essential to progress in both the scientific and the technological aspects of materials science and engineering.

As documented throughout this report, there now exists a need to extend this approach to include the biological sciences, as well as engineering and the physical sciences, by creating organizations and funding mechanisms that are directly targeted at biomolecular materials research.

In 1995 a first step was taken toward addressing this need when the NSF Directorate for Mathematical and Physical Sciences created its Office of Multidisciplinary Activities. This is a very positive development, but in the panel's opinion it should be extended to other agencies, particularly the National Institutes of Health (NIH). Furthermore, to have a significant impact specifically on the field of biomolecular materials there need to be directly targeted funding mechanisms that can create on a smaller scale the critical mass of activity that has been created over the last decade in materials science and engineering. Only then can we be sure that in the 21st century the United States will have the experience and knowledge needed to capture the scientific and technological opportunities that this report describes.

ACTION OPTIONS

The panel has identified four options that could help to stimulate progress in the field:

1. Interdisciplinary collaborations could be encouraged by a new mode of research through which small numbers of scientists would come together to work on a specific problem, such as the ones identified in this report. This mechanism would encourage new collaborations while keeping their size small to help ensure accountability.
2. Consortia in biomolecular materials could be developed, i.e., groups of investigators that are focused on a specific theme or a specific instrumental capability. Such groups could involve scientists at a particular site such as a university campus or a government laboratory, or they could be consortia involving several sites. They would vary in size but would each have a well-defined focus: specific instruments, particular scientific problems, or a defined technological goal. Pre-existing collaborations with established track records of interdisciplinary activity should be favored in establishing these groups. Some of the groups could be built into existing structures such as the Materials Research Laboratories (MRLs), Science and Technology Centers (STCs), and government laboratories. Groups that have special facilities should be open to external scientists. Geographical dispersion could be a component in the selection criteria. Incorporation of the government laboratories into the groups should be strongly encouraged since the government laboratories house a broad spectrum of instruments, experience in instrument development, and relevant expertise in such areas as synchrotron radiation, neutrons, imaging

(electron microscopy, scanning tunneling microscopy, atomic field microscopy, and x-ray microscopy), and chemical and biological synthesis and characterization.

3. Academic programs could be established at universities to encourage curriculum development and training in biomolecular materials. These programs would bridge biology, materials science, and the physical sciences. The multidisciplinary character of biomolecular materials research, though in many ways a great strength, can be a barrier for students pursuing an education in the field. New academic programs and curriculum development could help to overcome this problem. It is important that students are trained in one of the disciplines in depth, however, obtaining interdisciplinary breadth during the research phase of their graduate careers. One way to support such training could be the provision of special training grants like those that NIH has recently provided in areas related to biomaterials. Any such grants should include requirements for additional courses as well as for a program of research. The panel believes that the effectiveness of such a grant program would be enhanced if institutions receiving grants were encouraged to strengthen their ties with government and industrial laboratories. For example, they could make arrangements for outside laboratories to provide summer jobs for their graduate students, and the participating government and industrial researchers could host visitor programs and serve as guest lecturers at the universities receiving the grants.
4. A national Biomolecular Materials Institute (BMI) could be established, located at a university or a government laboratory or another site with an appropriate intellectual environment. Like options 1 and 2 above, this option is motivated by the panel's consensus that interdisciplinary collaboration requires special support and encouragement. For example, in the study of many aspects of biomolecular materials, such as those described above for molecular machines, close interaction between researchers is both difficult and very important. In addition, a national institute would broaden access to instruments and research facilities, facilitate contacts between the academic community and private industry, and enhance the visibility of the field in a way that would encourage the creation of university programs in biomolecular materials research and education.

A national BMI would act as an umbrella organization for the field. It would have four main tasks:

a. To examine research directions through workshops, meetings, and studies, giving particular attention to proposed novel initiatives;
b. To encourage interdisciplinary collaborations by bringing together scientists and engineers from different backgrounds, e.g., different disciplines or affiliations;
c. To provide instrumental facilities that would encourage interactions between experimental groups; and
d. To provide industry with a single contact point for obtaining information about biomolecular research activities and for obtaining assistance in making connections with those activities.

Structurally, the BMI might resemble the NSF-sponsored Institute for Theoretical Physics in Santa Barbara. For example, it would have quasi-independent status and be overseen by a broad-based advisory board. It would consist of a small cadre of permanent scientists, plus staff commensurate with the above-listed tasks, such as experts to assist visiting scientists in using the instruments and laboratories. Funding should if possible be provided in at least five-year increments, either by a single agency or preferably by a consortium of agencies such as NSF, NIH, the Department of Energy, and the Department of Defense. Funding should also include substantial industrial support if at all possible, probably at about the 25% level.

Although this option may be difficult to achieve in the current funding environment, the panel believes it is an important goal for the future.

Appendix: Biomolecular Materials Research in Other Countries

Research on biomolecular materials is becoming increasingly evident in the international arena. The 1990 workshop on biomolecular materials sponsored by the National Science Foundation documented several international programs,[1] but there are as yet no standard inventories that correlate and quantify the levels of research funding in this relatively young field. The following examples of programs in Japan and Western Europe are typical of the level of activity in the field.

JAPAN

There are several organized Japanese programs that involve substantial efforts in biomolecular materials.

The New Energy and Industrial Technology Development Organization (NEDO) is a semigovernmental agency supervised by the Ministry of International Trade and Industry (MITI). It sponsors international joint research programs. International teams of between three and six scientists in areas of materials research are supported at a level of approximately $200,000 per year for up to three years. At present there are about six such teams active in subjects related to biomolecular materials.

The Institute of Physical and Chemical Research (RIKEN) is a corporation sponsored primarily by the Science and Technology Agency. It carries out in-house research in the physical and biological sciences. It is also jointly responsible for SPring 8, a new 8-GeV synchrotron x-ray source scheduled to begin operation in 1998. RIKEN operates the Frontier Research Program at a level of approximately $20 million per year. In this research effort, young scientists are drawn together (about one-third of them from outside Japan) for initial five-year periods. At the moment, one of the three research areas in this program is Frontier Materials, and roughly two-thirds of this effort involves biomolecular activities.

The Research Development Corporation of Japan (JRDC) is another governmental corporation. It sponsors the Exploratory Research for Advanced Technology (ERATO) program, whose goal is the "creation of advanced technologies and advancing future interdisciplinary scientific activities." There are currently 17 ERATO projects, each of which involves 15 to 20 scientists and is funded for five years at a level of approximately $20 million. The projects bring together personnel from academia, industry, and government laboratories (including foreign scientists) at temporary sites throughout Japan. Roughly one-third of the current projects are related to biomolecular materials.

GREAT BRITAIN

The LINK Molecular Electronics Program is concerned with the "systematic exploitation of molecular—including macromolecular—materials in electronics and related areas such as optoelectronics." LINK provides matching government support (up to $20 million for five years) for collaborative industry, government, and university research projects. These include programs in biomolecular electronics.

GERMANY

There are several programs in Germany that have substantial biomolecular materials components. They include large university-based groups in Mainz and Munich and a Max Planck Institute in Mainz. A new Max Planck Institute, located in Potsdam, focuses on interfaces in biomolecular materials.

[1] National Science Foundation, *Biomolecular Materials: Report of the University/Industry Workshop, October 10–12, 1990,* NSF 91–142 (National Science Foundation, Washington, D.C., 1991).

FRANCE

In France, the efforts in biomolecular materials are focused on individual professors and programs at various CNRS (Centre National de Recherche Scientifique) laboratories. Notable among these are the activities in the College de France and the Ecole Normale Superieure in Paris, the Charles Sadron Institute for Macromolecules in Strasbourg, and the Paul Pascal Research Center in Bordeaux. The Physics and Chemistry Department at the Curie Institute in Paris has been reorganized and has as its charter the development of research in biomolecular materials.