Biomimetic Materials: Properties and Processing

The concept of biomimesis has long been used in chemistry in the context of compounds with enzyme-like catalytic action. Since the mid-1980s it has been applied to materials, particularly with a view to producing ceramic and composite materials with improved toughness, analogous to shell, tooth, and bone. There was some discomfort in the materials community with the idea of mimicking biological materials in the sense of producing an indistinguishable copy.

However, mimesis more generally refers to copying some essential aspects of a thing rather than duplicating or faking it. The phrase "bioinspired materials" is also used to express the idea in more familiar terms, but is grammatically less desirable as it is a Greek/Latin hybrid. The field has now spread to include a group of loosely linked goals in new materials and processes. These are surveyed below.

It should be kept in mind that materials development is considerably upstream from the development of new products. It is quite typical for new materials to find their way into commercial products about 20 years after their discovery (Calvert 1994). Examples include Kevlar, high-T_c ceramic superconductors, piezoelectric polymers, and gallium arsenide. It is also typical for the first applications to be quite different from those originally proposed, and for their impact to be modest compared to that suggested during the initial excitement. A personal view of the status and prospects for biomimetic materials is given at the end of this article.

1. Inorganic Particle Formation

Coccolithophores—single-celled marine algae—assemble an external skeleton from single crystals of calcite with very complex shapes, such as that shown in Fig. 1. The growing crystal is surrounded by a lipid membrane that controls the growth orientation in the crystal, but it is not known exactly how this is achieved. As shown in Fig. 1, a series of overgrowths on the initial ring lead to the whole calcite assembly. Sponges and diatoms show similar close control of the shape of silica particles on the micron scale. Magnetotactic bacteria form single-domain iron oxide (magnetite) crystals with a very closely controlled size of a few nanometers, which then aggregate into magnetic chains (Fig. 2). These biological examples all involve growth within a compartment surrounded by a membrane. For sponge spicules there is an organic template

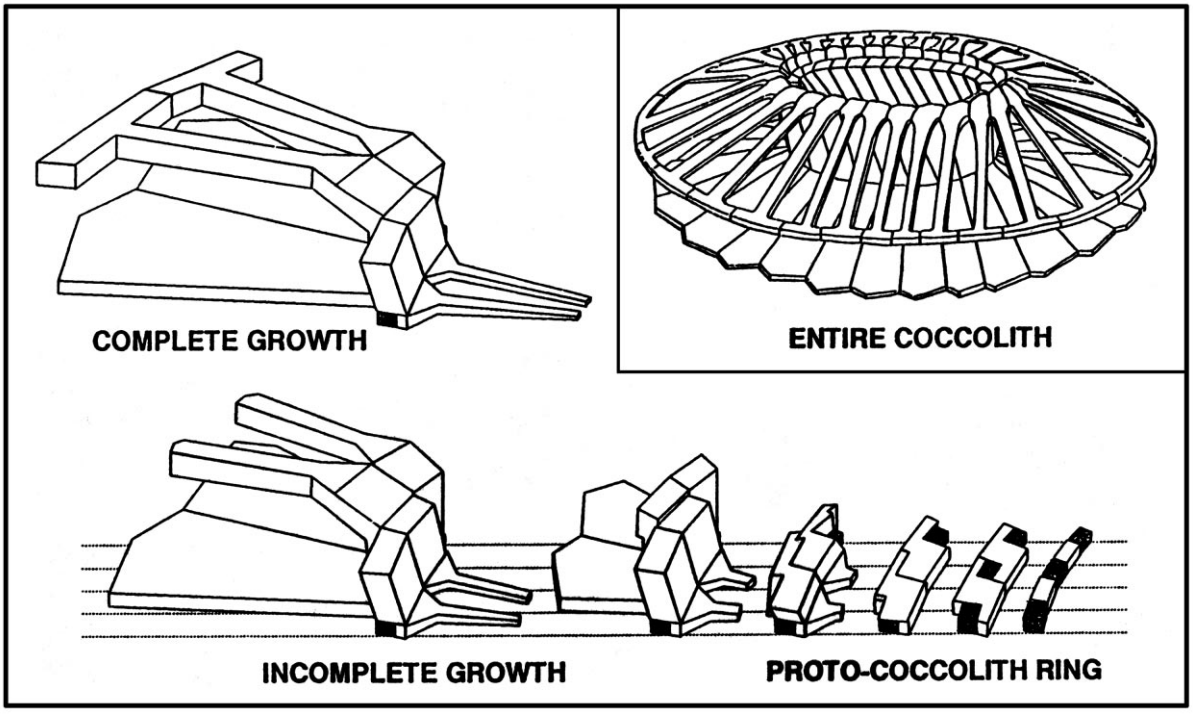

Figure 1
Assembly of a coccolith from calcite crystals (reproduced by permission of Macmillan from *Nature*, 1992, **356**, 516–8).

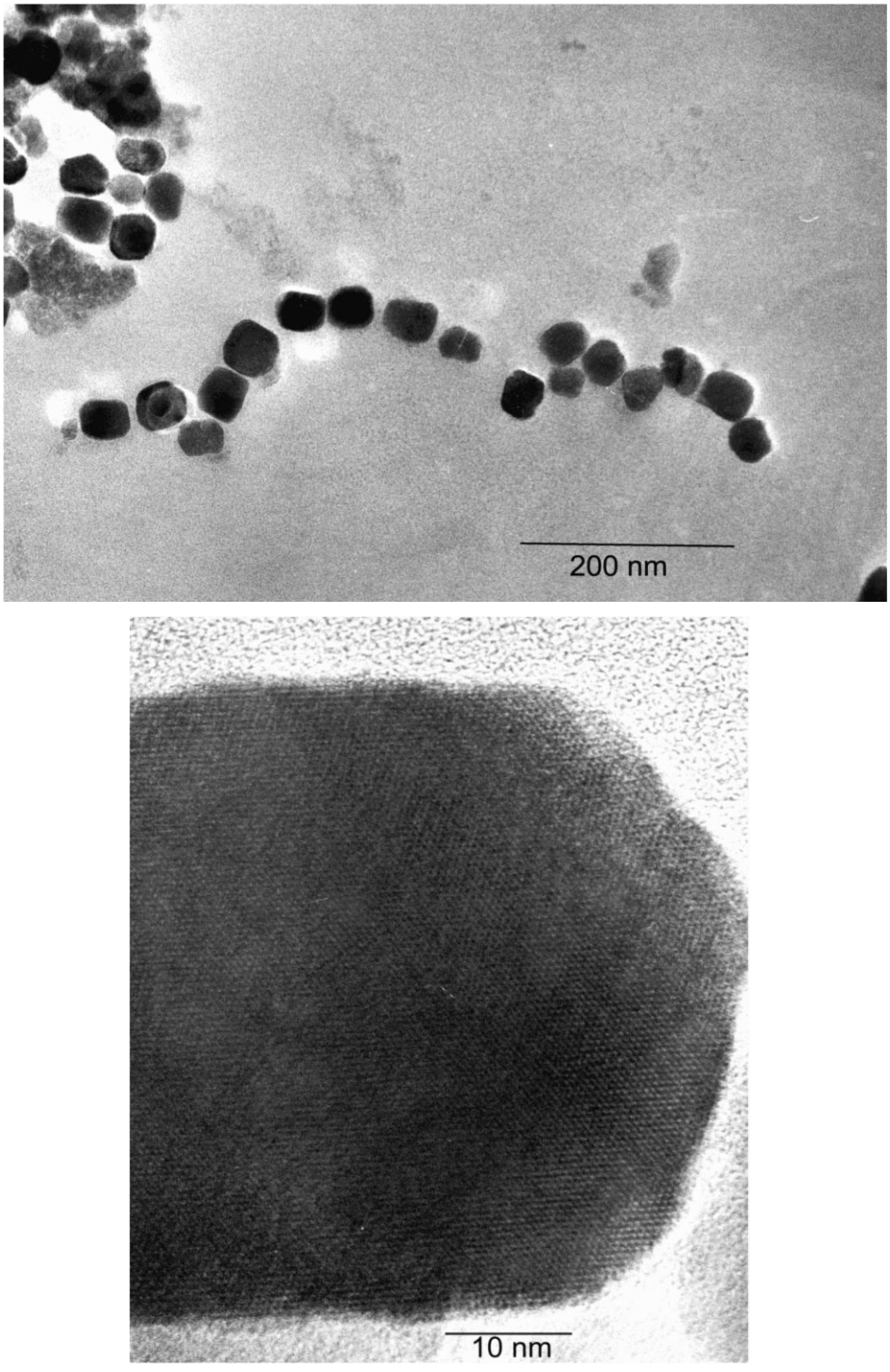

Figure 2
Magnetic particles from a magnetotactic bacterium, showing chain formation (courtesy of Professor S. Seraphin, University of Arizona).

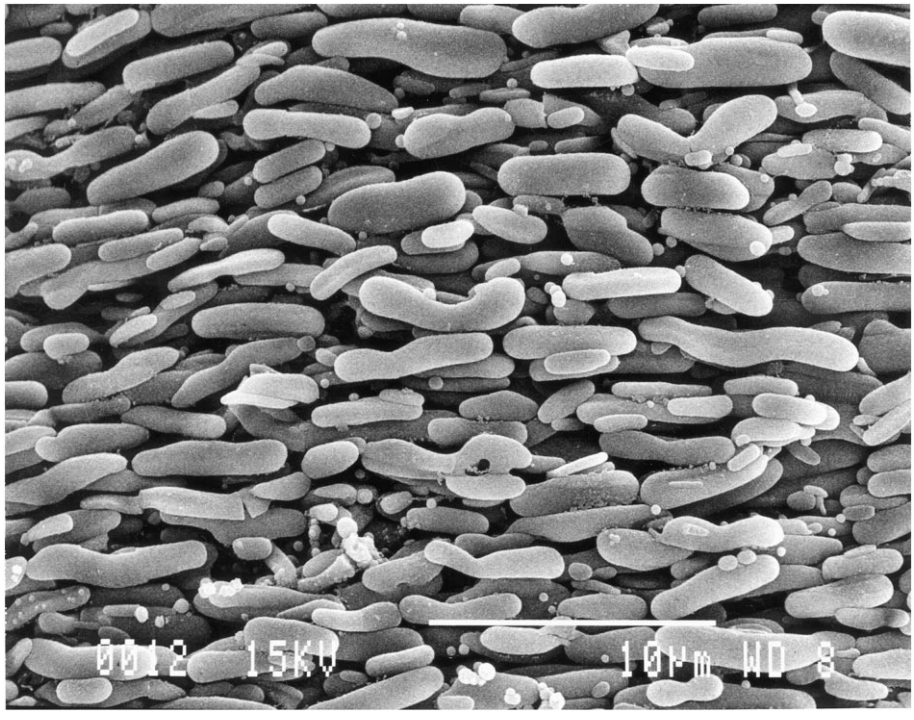

Figure 3
Elongated titania particles formed by impregnation of a stretched two-phase polymer with titanium alkoxide, followed by hydrolysis.

on which the mineral grows. In other cases there may be specific nucleation sites on the membrane surface. This suggests synthetic approaches where inorganic particles are grown within a micromold—a predefined space.

There have been many efforts to grow particles in liposomes, i.e., spherical shells with a lipid bilayer wall (Mann *et al.* 1997). One solution is trapped when the liposome is formed, and precipitation occurs when a second reagent, often a base, diffuses in through the wall. Generally the trapped solution must be quite dilute in order to avoid destabilizing the liposome. As a result, the precipitate therefore only occupies a small part of the internal volume. A method is needed to introduce a continuous feed of both reagents through the membrane.

There have also been many efforts to grow particles in multiphase polymer systems, such as block copolymers (Kane *et al.* 1996). For instance, a two-phase polymer can be soaked in one reagent, which selectively absorbs into one phase. A cadmium salt could be taken up by a polyether phase. Subsequent treatment with hydrogen sulfide results in precipitation of cadmium sulfide within the polyether. While the volume fraction of sulfide formed is quite small, repeated cycles can give rise to higher fractions of the mineral.

Work on precipitation in lyotropic liquid crystalline amphiphile solutions has led to composite structures (see Sect. 4).

One characteristic of biological minerals is their elaborate shapes. For mechanical reinforcement of soft matrices, a filler should consist of high-aspect-ratio rod or plate particles. These may grow as a natural outcome of differing crystal growth rates along different crystal axes. However, most simple minerals are not sufficiently anisotropic to form such elongated particles. The shape of biological crystals is probably controlled by selective inhibition of growth on specific crystal faces. Very elongated silica particles are also formed in lipid vesicles, but it is not known how important these are for controlling shape in crystals. While synthetic methods offer many ways of controlling particle size, good methods for controlling shape are lacking. One route is to form long micromolds by phase separation in a two-phase polymer, which is cold-drawn to elongate the included phase. The included phase is then swollen with a metal alkoxide, which is hydrolyzed to oxide, Fig. 3 (Calvert 1996).

2. Toughness and Layered Structures

Large organisms operate in an environment that subjects them to fluctuating forces—from the action of wind and water on plants, and from the locomotion of

animals. These fluctuating forces and collisions will often result in local damage that should not lead to catastrophic failure. As a result, many biological tissues contain structural features that add toughness without severely compromising stiffness or strength.

In mollusk shells and teeth, toughness may arise from added polymeric layers or from very fibrous structures (see *Shell: Properties* and *Marine Teeth* (*and Mammal Teeth*)). The addition of polymer could be especially effective if the polymer structure is capable of a large extension to break after yield, such as occurs in folded β-sheet proteins, where the unfolding of the chains leads to a large energy absorption, as has been discussed by Smith *et al.* (1999). However, polymer layers will also lead to a significant loss of elastic modulus when compared to a wholly inorganic material.

Much effort has gone into increasing the serviceability of ceramic materials by improving their toughness. Much work was initially devoted to fibrous materials (see *Fibrous Ceramics*), particularly silicon nitride, but the need for reliable, cheap processing methods was not met. Attention then switched to ceramic composites with fibrous reinforcements that would add toughness. These mostly proved to be unstable or reactive at the temperatures needed for turbine engines, while still being hard to process. Since then there have been many studies of ceramic/metal-layered structures, where the metal layers take the role of the polymers in mollusk shell. Such materials are of interest for use in engines and for armor. There is also interest in incorporating structured porosity into materials to improve fracture properties, or to modify elastic properties such as Poisson's ratio or piezoelectric response (Sigmund *et al.* 1998).

In the case of metal/ceramic-layered materials, the key problem is to absorb as much energy as possible within the metal layers. Hwu and Derby (1999) showed that the major energy absorption is due to metal drawing across the gap after the crack has passed. However, the extent of deformation occurring during the drawing was limited by the thinness of the metal layers. As a result, substantial increases in toughness were only seen when the volume fraction of metal was quite large. In contrast, mollusk shells show significant toughness with only a small percentage of polymer. It is likely that some combination of embedded metal, porosity, and interfacial debonding can give much enhanced toughness or impact resistance to ceramics. However, current methods for modeling fracture do not provide enough guidance for these designs and the biological models are only just being interpreted.

Recent studies on the influence of polymers on the crystallization of calcium carbonates *in vitro* has shown that metastable liquid complexes with anionic polymers can be formed which subsequently transform to calcite. Studies of carbonate biomineralization have shown that amorphous calcium carbonate does form either transiently or as a stable phase. It has also been shown that absorbed proteins do modify the fracture properties of carbonates. In particular, fracture surfaces show smooth conchoidal fracture, like glass, rather than the faceted fracture characteristic of normal crystals. This suggests that we have much to learn about the modification of the properties of crystals and amorphous solids by entrained polymer. In the example shown in Fig. 4, the polymer coating may serve to protect the surface from weakening cracks, and the entrained polymer may increase toughness. There are parallels with the Lanxide process for toughening alumina ceramic by entrained aluminum metal particles.

3. Polymers

The core difference between proteins and synthetic polymers is that protein synthesis provides total control of the sequence of units along a chain while the best-controlled polymerizations can only provide several blocks of functional units on a chain (see *Biosynthesized Materials: Properties and Processing*). One obvious goal is the formation of synthetic polymers with enzyme-like catalytic activity. Many enzyme active sites have an array of active groups held in close proximity so as to interact with the substrate (target molecule), and to reduce the activation energy for reaction by a precise spatial array of ionic or hydrogen-bonding interactions. To achieve such a precise spacing of active groups on a synthetic polymer would require a rigid structure, which would in turn normally render the material insoluble and so inactive. Studies of dendrimer molecules (see *Dendrimers: Polymerization and Properties*) with highly branched structures may lead to the required combination of flexible and soluble outer structures combined with a highly structured core. Many proteins also go through large changes in shape in response to the binding of substrates or other energy inputs. This seems to require a structure where two well-defined conformations are closely balanced in energy, so that the molecule can flip from one to another. Such a change is not likely in a wholly flexible system, and again some subtle combination of flexible segments and rigid units is required. There is still much to learn about these aspects of macromolecular design, but both the synthetic tools and the understanding are being acquired.

As discussed in the articles on silk (see *Silk Produced by Engineered Bacteria* and *Natural Protein Fibers*), structural proteins include regular and random regions in the chain structure that would be expected to give rise to crystalline and amorphous material (Calvert 1998). In contrast, the amorphous component of synthetic polymers arises from entanglements of the coiled chains that cannot be resolved during the crystallization process. New polymer properties may be achievable once polymer chains can be designed with such controlled sequences.

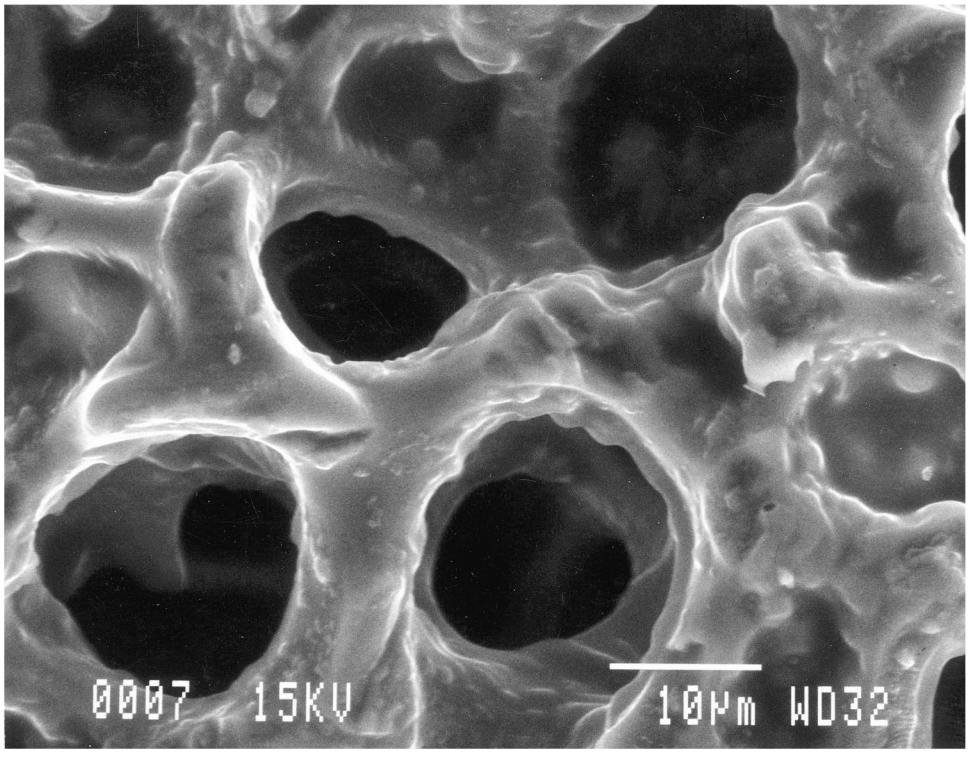

Figure 4
Porous interior of a sea urchin spine (calcite single crystal).

There has been a report of enzyme-like activity in a block co-polypeptide which enhances the rate of hydrolysis of tetraethoxysilane (TEOS; a standard reagent in sol-gel chemistry) as a suspension in water (Cha *et al*. 2000). If this block structure is made up of a sequence of units of a hydrophilic amino acid followed by units of a hydrophobic amino acid, it would be expected to be active at a water-solvent interface. The morphology of the silica that forms is dependent on the structure of the copolymer. This system is biomimetic both in the sense of employing a polypeptide catalyst and in the sense of it functioning in a multiphase system, since biological processes rarely occur in homogeneous solutions.

Many tissues, such as cartilage, arterial wall, and the walls of soft marine organisms, are swollen polymer structures. Swollen polymers, such as plasticized polyvinylchloride (PVC), do occur in artificial structures but they are usually avoided because loss of plasticizer leads to shrinkage and cracking. Even the swelling of wood with changes in humidity is a major impediment to its use in structures—though years of experience have taught us how to design around this problem. Skin does change in volume and properties as it takes up or loses water. The structure of amphibian skin keratin is apparently different from mammalian keratin for this reason.

There have been many suggestions that designers should make more use of soft structures. These could take the form of composites of hard fibers with rubbers. In which case, tires (National Materials Advisory Board 1994) and reinforced plastic tubing could be considered as examples. Liquid-swollen soft structures could also be used more in the synthetic world. For purely mechanical systems this may not make much sense, but in active systems such as batteries or muscle-like actuators, a liquid component is necessary and should probably be viewed as a soft material rather than simply as a liquid to be contained.

4. Surfactants and Self-assembly

Self-assembly is a hallmark of biological systems, including assembly of protein subunits into holoenzymes, of proteins and nucleic acids into virus particles, and of tropocollagen into collagen fibers. There has been increasing interest in synthetic self-assembly. In addition to the assembly of molecules with complementary hydrogen bonding to form supramolecular clusters (Lehn 1990), there are many papers on the assembly of charged polymers and particles to form multilayers (Bertrand *et al*. 2000), and on the

assembly of particles or particles and films coated with complementary biological recognition molecules, such as the biotin-streptavidin system. Synthetic peptide self-assembly is discussed further in *Molecular Self-assembly* and *Self-assembly by Phase Separation in Polymer Thin Films*.

Work at the Mobil Corporation showed that mesoporous silica could be formed by hydrolysis of TEOS entrained in a highly concentrated water/silane/surfactant system. In this regime, the three-component mixture forms ordered structures with a range of symmetries. In one hexagonal phase, rods of water are surrounded by surfactant and embedded in a hydrophobic silane matrix. Hydrolysis of the silane under suitable conditions followed by drying and sintering, results in a porous silica with aligned pores of a few nanometers in diameter.

Growth of the lyotropic liquid crystal precursor is very sensitive to the environment. Ozin and co-workers have shown that complex particle morphologies can result from growth of these mesoporous structures in quiescent solutions as diffusion fields and surface forces interact (Yang *et al*. 1999). Several workers have shown how the direction of the rods or plates of silica can be controlled. Polymers can be introduced to form composite structures very reminiscent of some biological composites (Sellinger *et al*. 1998). This does seem to parallel the proposed importance of liquid crystals in the growth of many biological structures.

While one would expect that this approach could be extended to many other material combinations, the rules are not understood. Efforts to form similar structures, other oxides such as titania or various crystalline materials, have been only partly successful. Any rapid or localized conversion process possibly also disrupts the liquid crystalline organization.

Stupp and co-workers have produced a range of amphiphiles, which assemble into various ribbon and wedge structures, and have explored their catalytic activity (Stupp *et al*. 2000).

5. *Muscles*

There is a clear need for actuators for robot arms with properties comparable to human muscle. Unlike human muscle, an artificial muscle ought to respond to an electrical impulse by a change in length, since any chemical energy source must involve a system of pipes. There are many candidate materials, but all have considerable drawbacks at the moment. Piezoelectric actuators have a rapid response but the total strain is small, less than 0.1% and, as a result, complicated linkages are needed to obtain significant motion. Electrically conducting polymers show volume changes of a few percent, but this is still much below that needed for a muscle. Shape memory alloys are promising but the response is slow and the cycle life is limited. Motorized or hydraulic arms tend to be heavy and clumsy. A soft polymer actuator is the obvious analog for a muscle for fast but gentle manipulations.

Ionizable gels that respond to electrical fields and demonstration devices are discussed in *Synthetic Muscle*. There is also much interest in composites of metal and ionic polymer as synthetic muscles (Shahinpoor *et al*. 1998).

6. *Processing Methods*

Freeform fabrication methods allow objects to be built as a series of layers directly from a three-dimensional computer representation. Current methods are described in *Freeform Fabrication*. These allow only one material, or a material plus a soluble support structure, to be used at a time. It is clearly feasible to combine several different materials into a single object, which would allow the building of something much closer to an organism. A recent report on simple robots, which were allowed to evolve in a virtual environment and then were built by freeform fabrication, shows how evolutionary methods might be applied to manufacturing (Lipson and Pollack 2000).

To build a crude organism would require resolution at the scale of about 10 microns. Most current freeforming methods allow resolution down to about 100 microns and a limited materials set. Microcontact printing and related methods allow much higher resolution—down to about 1 micron but effectively are restricted to one layer (Xia and Whitesides 1998). There is much current interest in ink-jet printing methods which could provide the required 10 micron resolution while allowing many layers to be deposited (Fan *et al*. 2000).

In both synthetic and biological structures, it is useful to keep in mind the distinction between design and patterning. Phase separation, crystallization, and aggregation processes can give rise to patterns in two and three dimensions on a scale, from millimeters to nanometers, which reflects the kinetics of the separation and diffusion processes. To form working devices or organisms, we need to build to a non-recurring design, which may include patterned elements. If we seek to adopt biomimetic processes, we will need to exploit self-assembling structures and patterns but within an overall design.

In current silicon technology, photolithographic methods can form two-dimensional designs down to less than 1 micron. Much finer resolutions are achievable in laboratory methods. Three-dimensional designs can be formed to below 1 micron using two-photon methods (Cumpston *et al*. 1999), but commercial freeforming methods are limited to about 100 microns resolution. In biology there are many examples of patterns forming at the nanometer level, but most designs are on the scale of individual cells, i.e., a few tens of microns. There are structures, such as

sensing hairs, which are much finer but the spacing between them is still on the 10 micron scale.

7. Cell Adhesion and Tissue Engineering

Biomedical engineering is becoming more concerned with the problems of the long-term biocompatibility of synthetic implants. Material wear and degradation, and tissue loss or chronic inflammation due to changing mechanical loads will limit the lifetime of most implants to about 10 years. In addition, biocompatibility is not a material property but is very dependent on the specific environment of the implant—in terms of implant site in the body, animal species, and animal age. Strategies to eliminate these problems include the use of biodegradable materials that will eventually be replaced by natural tissue, and tissue-engineered implants where as much of the device as possible is formed from tissue grown *in vitro* on a synthetic support before implantation.

Tissue engineering imposes a need to understand the interaction between neighboring cells, and between cells and synthetic surfaces. Cell binding to a biological surface proceeds through a series of stages including physical adsorption, interaction between surface macromolecules and specific binding sites on the surface, reorganization of the macromolecules in the cell membrane to bring more binding sites into contact with the surface, and then specific changes in the cell induced by the surface.

At the physical adsorption level, studies of cell attachment to self-assembled monolayers on silicon or glass have shown that attached polyethylene oxide chains form a structureless hydrophilic barrier layer and will thus prevent adsorption. Different polar end groups allow cells to absorb, and printed surface patterns with binding and non-binding areas can be used to control cell shape (Zhang *et al*. 1999). Cells recognize and bind to simple short sequences of amino acids in a protein exposed on a surface. Arginine-glycine-aspartic acid (RGD) and arginine-alanine-aspartic acid-serine (RADS) are sequences that can be used to induce strong cell attachment (see *Molecular Self-assembly*). Thus suitable polymers can be produced which will promote attachment of particular cell types on the surfaces for tissue engineering.

In the case of bone implants, there has been much interest in the use of bone morphogenic proteins (now produced from cloned bacteria). These constitute one group of a family of cell-signaling proteins known to induce the development of bone or other tissues when released locally in the body. A similar set of signals induces the growth of small blood vessels and is an important factor in the development of many cancers. By allowing implants to release such signaling proteins, it should be possible to speed up the integration of the implant. However, much remains to be learnt about the appropriate concentrations, gradients, and the timing of these signals. All these efforts take us in the direction of making synthetic organs that look more like a natural organ transplanted from an identical twin.

Belcher and co-workers (Whaley *et al*. 2000) have demonstrated that a phage library, displaying 10^9 different peptide sequences at the surface, can be used to identify short peptide sequences that selectively bind to inorganic semiconductor surfaces. Sarikaya and co-workers (Brown et al. 2000) have developed a similar method for the control of gold precipitation using *Escherichia coli* genetics.

8. Applications

Vogel has discussed the importance of biomimesis in engineering, asking whether it is possible to unequivocally attribute any engineering advance to a biological inspiration (Vogel 1998). There are no unambiguous examples and there are cases, such as attempts to imitate flapping flight, where a biological analogy may have inhibited progress. At the same time, many engineering advances clearly drew some inspiration from biology. In chemistry and materials, studies of the structure and properties of biological materials do suggest alternative approaches to particular problems and illustrate new properties that should be achievable in synthetic materials.

Biomimesis clearly will have an important role in new biomedical devices, and in new devices that try to combine biological structures or organisms with electronics in sensors and actuators. In structural materials, the obvious place for advance is the introduction of greater toughness into synthetic composites and ceramics. In electronics, there are not yet many signs of a conjunction between the hard, high-resolution, two-dimensional world of silicon and the soft, larger-scale, three-dimensional design of the brain and nervous system.

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