# Biomimetic Approaches to the Design of Functional, Self-Assembling Systems

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## INTRODUCTION

Successful solutions to many problems in science and technology have emerged by extracting design or strategy from biology, and applying it in a nonbiological context.[1–16] The use of biomimetic approaches is particularly well suited when designing self-assembling functional systems because life—from single cells to complex, multicellular organisms—demonstrates an enormous number of successful, functional designs and because living systems assemble themselves. Cells and organisms consist of collections of molecular and supramolecular structures that perform a range of complex functions, including molecular recognition, ligand binding, signal transduction, information storage and processing, and energy conversion. The molecular organization of biological structures also underpins their mechanical properties. In addition, certain of these structures can self-heal, self-repair, and self-replicate.

## OVERVIEW

There are two reasons for studying self-assembly. First, self-assembly is centrally important for life. Biological systems form and are sustained as a result of self-organization. Therefore understanding life requires, among other things, understanding self-assembly. Second, self-assembly can generate ordered three-dimensional (3-D) aggregates of components, ranging in size from the molecular to the macroscopic. These structures often cannot be generated by any other procedure.

In the past, self-assembly has been best known as a synthetic strategy in the molecular size regime.[17] New examples of its application to nanoscale and microscale components are now beginning to emerge.[18,19] As a consequence, self-assembly is becoming increasingly important as a strategy for the formation of useful nanoscale and microscale structures.[20]

We discuss the characteristics of self-assembly in living systems and review self-assembled functional systems designed according to biological principles. The examples include only systems that self-assemble from preexisting components larger than molecules; synthetic biomimetic approaches to molecular aggregates are reviewed elsewhere.[21–25]

## SELF-ASSEMBLY IN LIVING SYSTEMS

Self-assembly in living organisms has four distinct characteristics:

1. Programmed (coded) self-assembly: Self-assembly in living systems is based on information that is encoded into the components themselves (e.g., as sequences of nucleic acids in the genome, or of amino acid residues at the active sites of proteins). The order of monomers in these sequences and the environments they experience determine their ''shape'' (i.e., their 3-D atomic surfaces), patterns of electrostatic charge, hydrogen bonds, hydrophobicity, and other characteristics that determine their functions. Both these encoded instructions *and* features of the environment determine the outcome of self-organization in living organisms. For example, during embryonic development, cell differentiation is governed by the cell origin and by a multitude of environmental signals and cues. Neural circuits also assemble themselves from individual components (cells) following a combination of internal program and external guidance.[26]
2. Constrained (templated) self-assembly: Order and asymmetry in self-assembled aggregates of biological molecules are often achieved by imposing constraints (e.g., by ''templating'' the process of self-assembly). One mechanism that introduces constraints and is found throughout biology consists in using chains of monomers. The order of monomers in these sequences is fixed, and this constraint restricts possible 3-D structures that can form. Another mechanism that imposes constraints on biological self-assembly involves geometrical restrictions to self-assembly.[27] Undesired contacts with other molecules that might occur during the folding of linear precursors into correctly


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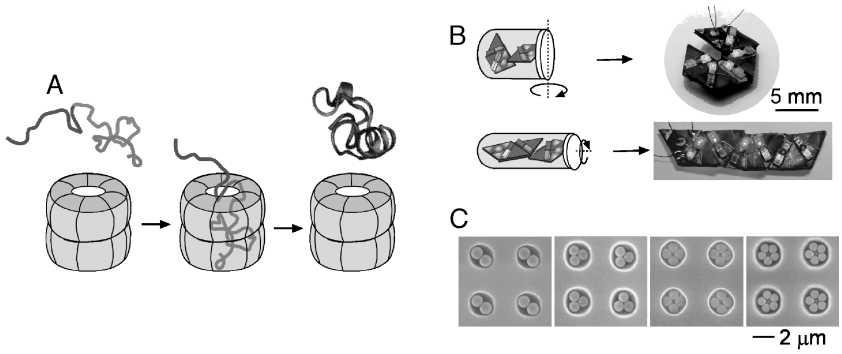


**Fig. 1** Templating of the structure of biological (A) and artificial (B, C) self-assembled aggregates using geometric restrictions. (A) Scheme illustrating chaperonine-assisted protein folding. The limited volume within a chaperonine molecule in which the folding process takes place ensures the correct folding of a polypeptide chain into a functional 3-D protein by preventing undesired contacts with other molecules. (B) Geometric templating of the structure and function of 3-D aggregates self-assembled from millimeter-sized components. Self-assembly in containers of different shapes generated topologically different 3-D structures—helices (top) or zigzags (bottom); these structures had different patterns of electrical connections among LEDs carried by the components. (From Ref. [34]. ©Wiley-VCH, 2003.) (C) Geometric templating of the morphology of aggregates self-assembled from micrometer-sized spherical colloids. The structure of the aggregates was determined by the ratio between the dimensions of the colloids and the cylindrical holes templating their self-assembly. (From Ref. [35]. ©American Chemical Society, 2001.) (*View this art in color at www.dekker.com.*)

folded 3-D structures can be prevented by geometrically restricting the volume in which the folding process takes place, as happens, for example, during chaperonin-assisted protein folding.[28] Local geometrical factors are also important at the supramolecular level (e.g., for templating crystal growth during biomineralization,[29] for regulation of cell growth and viability,[30] and for exchange of materials between cells and their environment.[31]).

3. Hierarchical self-assembly: Living organisms form by bottom–up, hierarchical self-assembly—the primary building blocks (molecules) associate into larger, more complex secondary structures, which are, in turn, integrated into increasingly more complex structures in hierarchical designs. Thus, the organization of biological structures is integrated across length scales from the molecular to the organismic. For example, tendons have six discrete levels of hierarchical organization, starting from the triple helices of tropocollagen, and proceeding through microfibriles, subfibriles, fibrils, fascicles, and tendons.[32]
4. Static and dynamic self-assembly: Self-assembly in biological systems may generate equilibrium structures; examples include molecular recognition and folding of globular proteins. Other biological processes and systems are dynamic, that is, they exist out-of-equilibrium, and the systems maintain their characteristic order only while dissipating energy.[19,33]

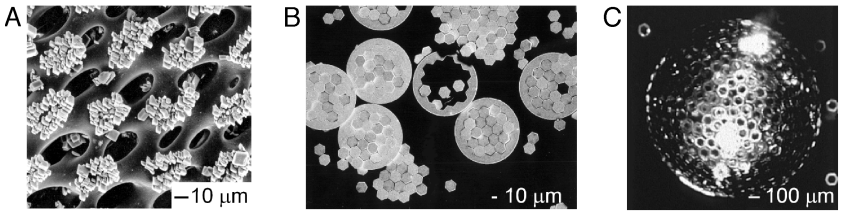


**Fig. 2** Templating of the structure of biological (A) and artificial (B, C) self-assembled aggregates using preformed templates. (A) Epitaxial overgrowth of calcite crystals on the spine surface of the brittle star *Ophiocoma wendtii*. (From Ref. [39].) Nucleation of the newly formed calcite crystals occurs at and is templated by specific sites on the surface. (Courtesy of J. Aizenberg.) (B) Two-dimensional, close-packed arrays of metal hexagons. The size and the shape of the assemblies were determined by the boundaries of the metal cavities used as templates. (From Ref. [40]. ©American Chemical Society, 2002.) (C) Three-dimensional, spherical structure formed by self-assembly of hexagonal metal plates on the surface of a drop of perfluorodecalin in water. The surface of the liquid drop acts as a template for the structure. (From Ref. [41]. ©American Chemical Society, 1998.) (*View this art in color at www.dekker.com.*)

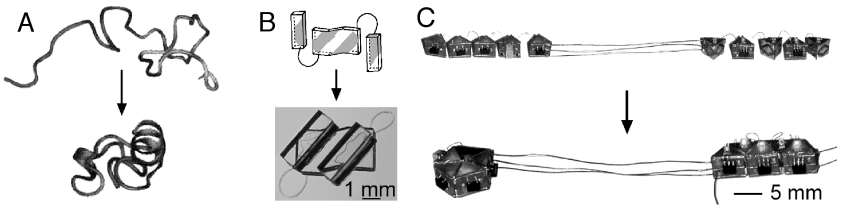


**Fig. 3** Templating of the structure of biological (A) and artificial (B, C) self-assembled aggregates by using sequence-restricted folding of linear precursors. (A) Scheme illustrating the formation of the functional 3-D structure of a protein molecule by folding of a linear chain of amino acid residues. (B) Compact 3-D structure formed by folding of a string of tethered, polymeric polyhedra. (From Ref. [50]. ©American Chemical Society, 2002.) (C) Self-assembled, asymmetric device formed by folding of a linear string of electronic components. (From Ref. [51]. ©National Academy of Sciences, USA, 2002.) (*View this art in color at www.dekker.com.*)

Living cells and organisms are examples of such systems—they die when the flow of energy through them stops. In many animate systems, new properties and patterns emerge as a result of interactions between autonomously moving components (e.g., bacteria in swarming colonies, fish in schools, and birds in flocks).

## ARTIFICIAL SELF-ASSEMBLING SYSTEMS DESIGNED USING BIOLOGICAL PRINCIPLES

In analogy to biological self-assembled structures, the shape and functionality of artificial self-assembled aggregates are governed by the shapes of their components, by the interactions between them, and by the environments and constraints imposed on them (e.g., the degree of order and the symmetry of a crystalline lattice of microspheres determine its optical properties, and the shape and connectivity in aggregates that form electrical circuits determine the type of electronic functionality that they exhibit). Control over the structure—and, thereby, the properties—of self-assembled aggregates has been achieved in several ways by borrowing strategies from biological systems.

### Constrained Self-Assembly

Fig. 1 illustrates templating of the structure of self-assembled aggregates using geometric restrictions. In these systems, the geometry of the volume available for the self-assembly of components determined the morphology and the pattern of functional connections formed between self-assembled components. The same principle has been used in colloidal[36,37] and macroscopic[38] systems.

Fig. 2 illustrates templating of the structure of self-assembled aggregates by preformed templates. In a system without constraints, self-assembly of micron-sized hexagonal plates resulted in the formation of sheetlike aggregates containing undefined numbers of components (plates). Self-assembly of the same plates in the presence of templates (holes with complementary shapes,[40] or drops of immiscible liquid,[41–44]) led to the formation of new types of structures: planar aggregates with defined shapes, or spherical aggregates. In other examples, preassembled colloidal structures[45] chiral kernels,[38] encapsulating host molecules,[46] and micropatterned scanning Auger microscopy (SAM)[30,47,48] have also been used as templates.

Fig. 3 illustrates templating of the structure of self-assembled aggregates by using sequence-restricted folding of linear precursors,[49–51] in analogy to the sequence-restricted folding of proteins and RNA into 3-D

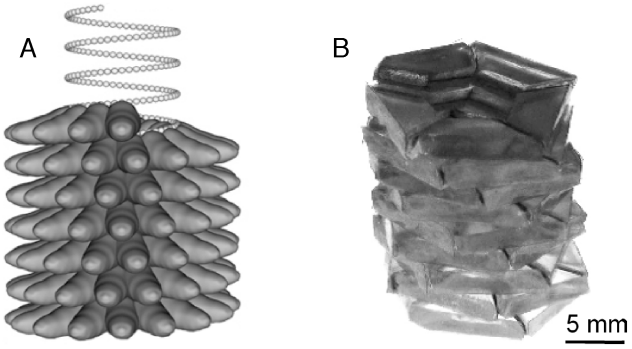


**Fig. 4** Biological (A) and artificial (B) aggregates self-assembled by the concerted action of multiple types of weak interactions between molecular or millimeter-sized components. (A) The structure of tobacco mosaic virus. Protein molecules and a strand of RNA assemble into a right-handed helical structure via hydrogen bonds, electrostatic interactions, and hydrophobic interactions. (B) Helical aggregate formed by millimeter-sized polyurethane polyhedra interacting via two orthogonal capillary interactions acting in parallel. (From Ref. [56]. ©American Institute of Physics, 2002.) (*View this art in color at www.dekker.com.*)

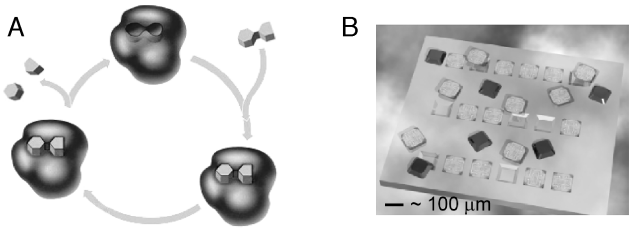


**Fig. 5** Biological (A) and artificial (B) self-assembling systems in which the components interact by 3-D complementary surfaces. (A) Scheme of interaction between an enzyme and its substrate. The binding pocket of the enzyme molecule adopts a geometrical shape complementary to the shape of the substrate. (B) Silicon chips self-assemble into indentations of complementary shapes on a substrate. (From Ref. [60].) (*View this art in color at www.dekker.com.*)

structures. In these examples, the sequence of millimeter-sized components in a chain and the properties (e.g., topology and flexibility) of the connections between them templated the structure and function of the self-assembled aggregates.

## Self-Assembly Based on Multiple Driving Forces

Biomolecular systems usually self-assemble by the concerted action of multiple types of weak interactions. In most artificial systems, self-assembly of the components involves not more than two types of interactions: fluidic and gravitational,[52] vibrational and gravitational,[53] magnetic and hydrodynamic,[54] or magnetic and electrostatic.[55] By using several types of interactions between the components, it is possible to form independently different types of connections between the components: structural connections, functional connections, or connections combining both tasks. Fig. 4 shows one such system, modeled on the structure of tobacco mosaic virus.[56] The millimeter-sized components forming the helical aggregate interacted via two orthogonal capillary interactions: a strong interaction based on drops of liquid solders was responsible for the growth of the aggregates and resulted in electrical connectivity between the components, and a weaker interaction based on drops of hydrophobic liquid stabilized the aggregates laterally.

## Recognition by Shape Complementarity

This principle has been used to design components that interact in both molecular[57] and mesoscale[58–60] self-assembling systems. Three-dimensional surfaces enable high specificity in recognition, and contribute to the structural stability of self-assembled aggregates. Fig. 5 shows a mesoscale system in which polyhedral, micron-sized electronic components self-assemble onto a common substrate by shape recognition and shear forces.

## Hierarchical Self-Assembly

Bottom–up, hierarchical self-assembly has been used to build nanostructures for application as optical and magnetic materials,[61] tunable nanoporous[62] and microporous[63] materials, nanomaterials with anisotropic properties,[64] metal nanostructures on diblock copolymer scaffolds,[65] and extended arrays of polymeric objects at a fluid–fluid interface.[66] Fig. 6 illustrates the use of hierarchical self-assembly to form three-dimensional lattices of spheres.[67] Unrestricted and templated self-assemblies of spheres have been shown to give access to only a limited range of structures. The use of a hierarchical approach (i.e., the confinement of spheres in rods, followed by assembly of these rods) makes it possible to generate 3-D structures with a variety of 3-D lattices.

## Self-Healing Structures

Designing materials and structures that can self-repair in ways modeled on living systems is an emerging goal for materials science.[68] Self-healing in living systems involves complex cascades of out-of-equilibrium processes that are impossible to reproduce in current man-made systems. However, self-assembly may offer an interesting alternative for the design of self-healing, steady-state systems. After disruption, equilibrium self-assembled

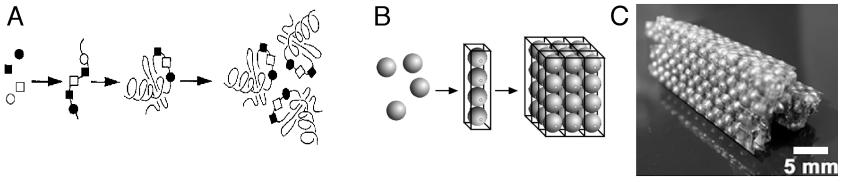


**Fig. 6** Biological (A) and artificial (B, C) self-assembling systems in which the components are organized at several hierarchical levels of structural complexity. (A) Hierarchical self-assembly of a viral capsid. Amino acids (shown as squares and circles) form a disordered polypeptide chain; the chain folds (self-assembles) into a functional protein; several protein molecules aggregate into the viral capsid. (From Ref. [66]. ©Wiley-VCH, 1999.) (B) Hierarchical self-assembly of millimeter-sized spheres. The spheres are packed into rods, which subsequently self-assemble into 3-D structures (C). (From Ref. [67].) (*View this art in color at www.dekker.com.*)

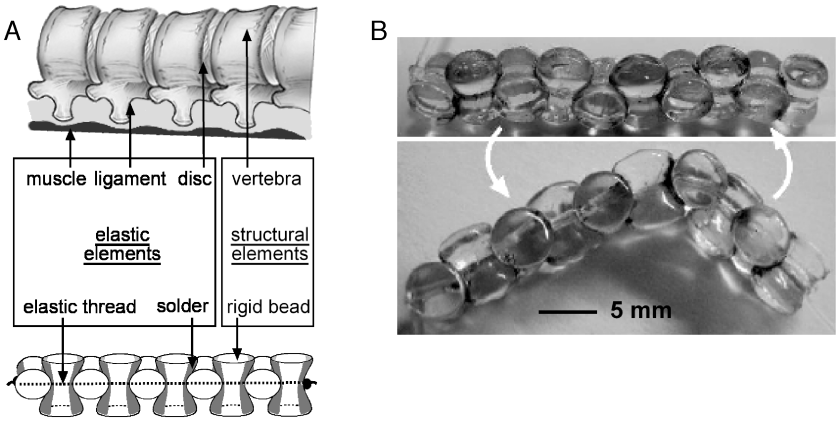


**Fig. 7** Self-healing structures in biology and engineering. (A) Common features of the design of a vertebrate spine (top) and a self-assembling system of millimeter-sized components (bottom). Both systems consist of rigid structural elements connected by elastomeric elements. (B) The structure loosely mimicking the organization of vertebrate spine spontaneously realigns and heals after breaking and dislocation. (From Ref. [69]. ©Wiley-VCH, 2003.) (*View this art in color at www.dekker.com.*)

systems return to their ordered state, provided that this state corresponds to a thermodynamic minimum. Fig. 7 shows a self-healing system loosely mimicking the spine of vertebrates, based on self-assembly of a string of millimeter-sized components interacting via capillary forces.[69]

## Dynamic Self-Assembling Systems

The central importance of dynamic systems for life has prompted the development of simple out-of-equilibrium systems with which to model complex behavior and emergence.[54,55,70,71] Fig. 8 shows two examples of dynamic, mesoscopic self-assembling systems. The first system consists of millimeter-sized metallic objects rotating at the liquid–air interface. The objects self-organize into a variety of patterns. The second system consists of polymer plates floating at the surface of an aqueous solution of hydrogen peroxide. The individual components can move autonomously and can interact with one another. Obviously, these systems are too primitive to mimic the complex biological dynamic systems; the studies of dynamic self-assembly are just beginning.

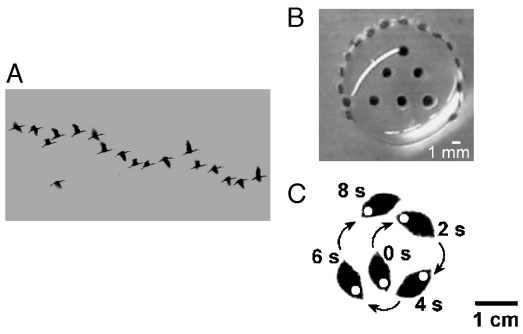


**Fig. 8** Biological (A) and artificial (B, C) dynamic self-assembling systems. (A) A flock of ibises (Image J. -M. Bettex). (B) Magnetized disks rotating on the top surface of a droplet of perfluorodecalin covered with water. (From Ref. [70]. ©Macmillan Magazines Limited, 2000.) (C) A system of millimeter-scale objects that move autonomously across the surface of a liquid powered by the catalytic decomposition of hydrogen peroxide. The numbers indicate time elapsed during change between two positions of the objects at the fluid–air interface. (From Ref. [71]. ©Wiley-VCH, 2002.) (*View this art in color at www.dekker.com.*)

## CONCLUSION

Self-assembly is an efficient, and often, practical way to organize components ranging in size from molecular to macroscopic into functional aggregates. Biomimetic approaches to the design of self-assembling systems have been immensely stimulating in solving critical problems in the design of artificial self-assembling systems; they might be the key to many of the unsolved problems facing the future of self-assembled functional systems in different size regimes.

In the molecular size regime, supramolecular self-assembly based on biomimetic principles has delivered many types of complex molecules[17,46] and useful materials.[5,22,72] The synthesis and assembly of large molecules and molecular aggregates with intricate structure and functionality (e.g., analogs of integrated circuits or viruses) remain unsolved problems.[73] Templated and hierarchical self-assembly—concepts familiar from many biological instances—may offer a solution.[46]

In the nanoscale size regime, principles extracted from biology have been applied to the fabrication of functional

materials (e.g., photonic bandgap crystals and self-healing materials). Much of the current research in the nanoscale is focused on achieving electronic functionality, notably on the problems of electrically connecting the components, organizing them into arrays, and establishing the best architectures for nanoscale devices.[74] Biological systems have demonstrated the utility of templating and hierarchical self-assembly in ordering components of similar sizes (macromolecules and organelles) into functional entities (cells). Dynamic, reconfigurable biological systems offer examples of a different approach to self-assembly: dynamic systems are currently of purely academic interest, but may become useful in the future.[75]

In the microscale and macroscale size regimes, self-assembly can generate functions that are not possible at smaller scales (e.g., electric connectivity and electronic functionality).[20] In addition, self-assembling systems may be useful in solving problems in robotics and microfabrication. Biomimicry might help to solve the most significant problem in this size range—the fabrication of small, functionalized components. Self-folding and hierarchical self-assembly—two strategies widely used by biological systems—are among the most promising approaches to this problem.[76,77]

Some of the most important problems in current technology include: 1) better systems for information processing (i.e., systems that are fast, cheap, and can be cooled efficiently); 2) systems that use and store energy efficiently; 3) materials and structures with internal organization leading to valuable properties (e.g., capability to self-repair, self-heal, and self-replicate); and 4) small, three-dimensional, functional structures. All of the materials and functions in this list are found in biological systems.[78] The self-assembled, living world provides examples of some of the most efficient functional systems known. To the extent that one can understand and model the designs and strategies used in these systems, the biomimetic approach will stimulate new designs for self-assembled functional systems.

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