REVIEW

What are the emerging concepts and challenges in NANO? Nanoarchitectonics, hand-operating nanotechnology and mechanobiology

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Most of us may mistakenly believe that sciences within the nano regime are a simple extension of what is observed in micrometer regions. We may be misled to think that nanotechnology is merely a far advanced version of microtechnology. These thoughts are basically wrong. For true developments in nanosciences and related engineering outputs, a simple transformation of technology concepts from micro to nano may not be perfect. A novel concept, nanoarchitectonics, has emerged in conjunction with well-known nanotechnology. In the first part of this review, the concept and examples of nanoarchitectonics will be introduced. In the concept of nanoarchitectonics, materials are architected through controlled harmonized interactions to create unexpected functions. The second emerging concept is to control nano-functions by easy macroscopic mechanical actions. To utilize sophisticated forefront science in daily life, high-tech-driven strategies must be replaced by low-tech-driven strategies. As a required novel concept, hand-operation nanotechnology can control nano and molecular systems through incredibly easy action. Hand-motion-like macroscopic mechanical motions will be described in this review as the second emerging concept. These concepts are related bio-processes that create the third emerging concept, mechanobiology and related mechano-control of bio-functions. According to this story flow, we provide some incredible recent examples such as atom-level switches, operation of molecular machines by hand-like easy motions, and mechanical control of cell fate. To promote and activate science and technology based on these emerging concepts in nanotechnology, the contribution and participation of polymer scientists are crucial. We hope that some readers would have interests within what we describe.

INTRODUCTORY MESSAGE: WHAT ARE THE NEXT CHALLENGES?

Undoubtedly, nano is an important key term for developments in science and technology. Under the names of nanotechnology and nanoscience, various research efforts have been made for the fabrication, control and functionalization of ultrasmall objects and/or materials with ultrasmall interior and exterior structural precision, which can make extensive contributions to a wide range of fields from fundamental physics to practical biomedical applications. Rapid progress in technologies for essential targets such as energy and environmental problems are mostly based on nano-level science and technology. Nano may be believed to solve any problems in various occasions, and hence nano has become a magic word in recent science and technology. Of course, such positive effects of nano in recent science and technology are greatly appreciated. However, we need to re-think the true meaning,[1] effect and value of nano to resolve emerging challenges.

The central concepts of nanotechnology and nanoscience include their operation and functional size. It is basically defined to the nanometer scale, which generally denotes a scale ranging from nanometer to submicron (10^{-9} to 10^{-7} m range). Most of us may be under the misconception that sciences within the nano regime are simple extensions of what is observed for micrometer regions. We may be misled to think that nanotechnology is merely a far advanced version of microtechnology. However, many factors including uncertainties, thermal fluctuations, quantum effects and statistical distributions may result in nano-specific phenomena that are not expected or easily controllable. For true developments in nanosciences and related engineering outputs, the simple transformation of technology concepts from micro to nano may not always be the appropriate solutions. As Aono *et al.* proposed, a novel concept, nanoarchitectonics,[2–4] has to emerge next to the well-known nanotechnology. In the first part of this review, the concept and examples of nanoarchitectonics will be introduced.

Next, methods of controlling nanostructures and nanometer-scale functions are re-considered here. These controls may be roughly classified into the following three types: (i) fabrication and preparation of nano-sized objects and/or materials having nano-sized structures; (ii) direct manipulation of nano-sized structures and objects; and (iii) control of nano-sized functions within well-designed organized

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structures by access of stimuli from the macroscopic scale. If materials and objects can be created under nanoscale control, the synthesized materials would be different from materials produced by nature and current human manufacturing according to approach (i). In current science, research efforts along this line are apparently successful, as seen in the production of nano-sized objects such as quantum dots,[5,6] nanoparticles,[7–9] nanorods wires[10,11] and nanosheets,[12–15] as well as their assemblies,[16,17] and materials with internal nanostructures such as mesoporous materials[18–24] and metal–organic frameworks (of porous coordination polymers).[25–28] However, most of them have regular, simple structures, which offer a limited level of nano-sized control. Although the polymer sciences have created various ways to control the polymer size and sequence,[29–34] naturally occurring polymers including peptides/proteins, DNA/RNA and oligosaccharides have superior capabilities in nano-sized structural control.[35,36] Therefore, the directions of nanoscience and nanotechnology would overlap in approaches to biological systems.

With respect to the approach (ii) mentioned above, the manipulation of nano-sized objects including clusters, molecular assemblies and even a molecule/atom is one of the ultimate goals of nanotechnology. Various designs of molecular machines such as molecular rotors and motors represent a novel concept in using synthesized molecules as molecular-level mechanisms.[37–40] In many examples, molecular machines are dissolved in solutions, and the application of external stimuli such as light irradiation, redox reactions, pH changes and the addition of chemicals induces machine motions that can be monitored by various types of spectroscopy. Although the former examples would be regarded as novel controls of molecular motions, they are far from machine operation at a specified and well-defined location. The direct manipulation of individual molecules and molecular pairs can be achieved with sophisticated devices such as the highly sharpened tips of scanning tunneling microscopy. One example, shown in Figure 1, is the successful operation of molecular motors on a metal substrate using molecular pairs of designed porphyrin molecules, with their rotational reversion through rearranging the molecular pairing.[41] The surface chirality of the molecular pair determines the rotational direction of this molecular motor that can be inverted through a process involving an intra-pair rearrangement that is also modulated by bias voltages
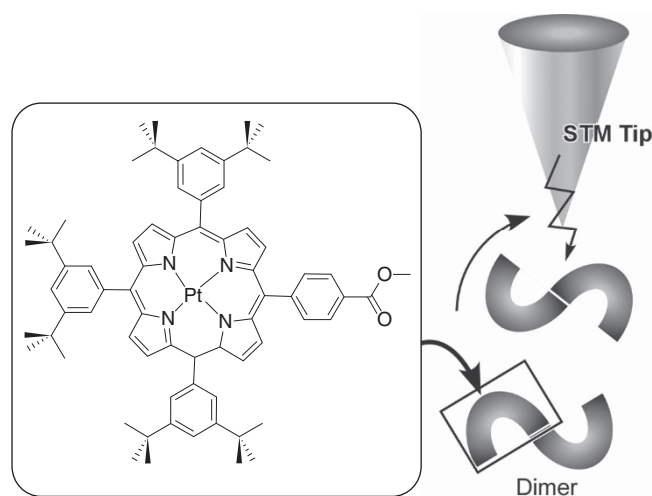
from the scanning tunneling microscopy tip. The application of positive voltages forces the pinned molecule to rotate together with its counterpart. In contrast, the vibration mode within the pinned molecule is excited by negative voltage application, leading to the independent motion of the pinned molecule accompanied by intra-pair rearrangement for chirality switching.

Although such an example represents the highly advanced status of current techniques for nano-sized manipulation, such techniques cannot be well generalized to a wide range of molecules. Sophisticated techniques would promote forefront-level science and technology but are not useful for general cases. High-tech-driven strategies must be replaced by low-tech-driven strategies. In this case, the use of the above-mentioned approach (ii), nano-control through nano/molecular organization, would provide solutions because the manipulation of a larger size of molecular organization would be driven by lower-technical-level actions such as macroscopic mechanical motions.[42] On the basis of significant curiosity in the relationship between molecular organization and function, various types of molecular organizations have been well investigated by self-assembly processes, supramolecular chemistry and polymer chemistry. The introduction of a novel concept to the mature molecular organization science would make low-tech-driven nano-manipulation possible.

As the required novel concept, we recently introduced an unusual concept, hand-operation nanotechnology,[43,44] which can control nano and molecular systems through incredibly easy actions, hand-motion-like macroscopic mechanical motions. This will be described in this review as the second emerging concept and technique. As described in detail later in this chapter, this new concept uses an interface as an operation media because interfacial environments can bridge two extremely different-sized media, with a macroscopic dimension in the lateral direction of the interface and a nano/molecular dimension in the thickness direction. We actually demonstrated the manipulation of molecular machines to catch and release molecular targets in surface-organized systems on macroscopic mechanical manipulation of film compression and expansion of several tens of centimeters in size. With this concept, manipulation of nano-sized objects becomes possible under ambient conditions without using any highly sophisticated machines or apparatuses, leading to the popularization of nanotechnology for everyday life activities.

The further development of such mechanical control systems would extend to bio-related systems. As most organized structures in biological systems are soft and deformable materials, it is no wonder that their organizations as well as functions are highly dependent on mechanical stimuli from both exterior and interior bodies. Biological systems are often composed of interfacial structures such as cell membranes and the interior surfaces of enzyme pockets. Therefore, a new research field must be emerged in mechanobiology[45,46] by exploiting the aforementioned mechano-nanotechnology concept at the interface. In this review, we also focus briefly on recent examples in mechanobiological research as an emerging concept.

Technological developments based on nano concepts have demonstrated great success in various areas including catalysts,[47–52] energy conversion,[53–57] sensors[58–62] and biomedical applications.[63–66] All of them are promising targets and will undoubtedly bring certain success in the near future. This review, however, does not include such currently promising and future strategies. We are looking one step forward and searching for emerging possibilities. To elucidate emerging concepts and new challenges in nano-related science and technology, we discuss the following three unusual topics:

Figure 1 Manipulation of molecular pairs by highly sharpened tips of scanning tunneling microscopy (STM) with chiral control of rotational direction.

(a) nanoarchitectonics: thinking about nano again; (b) hand-operating nanotechnology: for popularization of nanotechnology; and (c) mechanobiology: applications of the above concepts to biology. This review is not merely an assembly of well-known and mature popular science, but we also address new directions in nano-related science and technology.

NANOARCHITECTONICS: THINKING ABOUT NANO AGAIN

Nanoarchitectonics concept

Some successful examples of nanotechnology in its initial stage are those for microfabrication, as seen in silicon-based device technologies. Although several top-level examples for atom-size and nano-level fabrication and manipulation were recently reported,[67,68] most of the other promising fabrication structures were prepared with only micrometer-scale precision. Such microtechnology provides a great contribution to the device industry with the incredible miniaturization of various device structures. These devices and machines are actually working in our daily life with considerable success. Therefore, an extension of the fine strategies of microtechnology to the nano-region may simply provide more advanced functions with the same working principles. However, this expectation is not really true. The micro-worlds and nano-worlds are actually very different.

Fabrication on the micrometer-level is basically the same as that on the macroscopic scale. As seen in building construction and handcrafted work, connecting correctly shaped parts according to the proposed design drawing and blueprints leads to successful construction. This working principle can be applied to structural fabrication on the micron scale. Simply using advanced methodologies such as various lithographic techniques, any types of microstructure can be fabricated, which led to the current great success of miniaturized and high-information-density devices.

Improving known technologies would enable the construction of microscale structures exactly obeying design drawings. On the microscopic scale, architectures can be products of assembled technologies. Therefore, micro-level architectonics (methodology for architecting microscale structures) has almost identical features to micro-level technology. However, further reducing the construction size to nanometer scale drastically changes the situation. In the nanoscale region, the phenomena and properties of objects and materials include several uncontrollable factors such as thermal/statistical fluctuations, mutual inevitably occurring interactions and even quantum effects. Inputs of effects and signals to a desired target are often disturbed by surroundings or neighboring components, which causes additional mutual interactions. Accordingly, the material structures and properties as outputs are not decided by simple assemblies of inputs. In this situation, design drawings are not decisive guides. Unexpected disturbances and uncontrollable fluctuations introduce uncertainties into material fabrication and construction systems in the nanoscale region. The simple assembly of technologies cannot reach architectonics in nanoscale worlds. Known nanotechnology cannot simply advance to an architecting strategy in the nanoscale region. A novel paradigm, nanoarchitectonics, has to emerge for the creation of advanced functional systems in the nanoscale.[69] Nanoarchitectonics requires the concerted harmonization of various effects and interactions, including various technologies to accomplish material organization and the stimulation of spontaneous processes. Some of them may be regarded as expanded concepts of self-assembly/organization.[70–72]

This novel terminology nanoarchitectonics (nano+architecto+nics) was proposed by Masakazu Aono in the year 2000 as a new paradigm of nanoscale materials science and technology at the '1st International Symposium on Nanoarchitectonics Using Suprainteractions' in Tsukuba, Japan.[73] Later, Hecht first used this terminology in a title in the scientific literature in 2003.[74] Nanoarchitectonics doctrine as stated by Aono indicates the use of the following strategies: (i) fabrication and preparation of nanomaterials and nanosystems through the organization of nanoscale building blocks, even with possible and unavoidable unreliability and (ii) origination of functions on the basis of their mutual interactions (not by the simple summation of the individual nanoparts).

The nanoarchitectonics concept can be fundamental in nanoscale science and technology and widely applicable to various research fields. It must not be too strict but rather must be adjustable for a range of purposes. Accordingly, the use of this terminology is now spreading to a wide range of research fields, including supramolecular chemistry and self-assembly science,[75–78] preparation of nanostructured and hybrid materials,[79–81] structure fabrication methodologies,[82–87] energy and environmental technology,[80–89] physical device and related applications[90,91] and biological and medical applications.[92–96] Nanoarchitectonics is an emerging concept that represents the next step of nanotechnology.

Nanoarchitectonics examples

Although the nanoarchitectonics concept has only recently emerged and has not yet been fully realized, some examples can be presented to show the effectiveness and uniqueness of this concept. Here, several examples of functional systems that exhibit features and bare essences of nanoarchitectonics are presented from atomic-scale mechanisms to unusual mesoscale phenomena.

The initial examples are a series of atomic switches that have been developed by Aono and colleagues.[97,98] The mechanisms of atomic switches are based on the manipulation and precipitation control of atoms across very small gaps, which can be regarded as the smallest stage of nanoarchitectonics. One typical example of atomic switches is shown in Figure 2, where the basic mechanisms of switching by atom manipulation are exemplified. Using a set of Ag_2S and Pt electrodes with an approximately 1-nm gap, the application of a negative voltage to the Pt side induces the reduction of Ag cations to Ag atoms on electron supply by a tunneling current flow, and the formed Ag cluster creates an electrical conduction path (switch ON). This atomic switching can be reversed to OFF on a positive bias application to re-establish a high resistance across the gap between the electrodes.

The most important feature of the atomic switch systems is not their ultrasmall size. Their similarity to biological synapses rather than
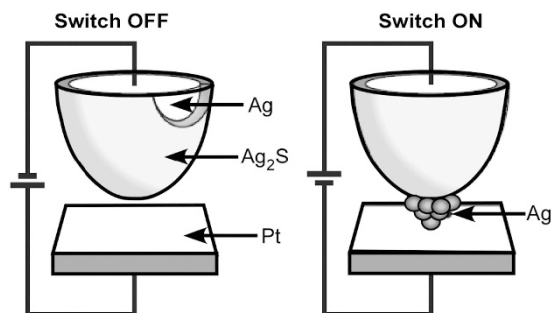
Figure 2 Basic mechanism of an atomic switch, where the application of a negative voltage to a Pt electrode induces the reduction of Ag cations to Ag atoms by forming an electrical conduction path (switch ON). This atomic switching can be reversed to OFF on a positive bias application to re-establish high resistance at the gap between the electrodes.
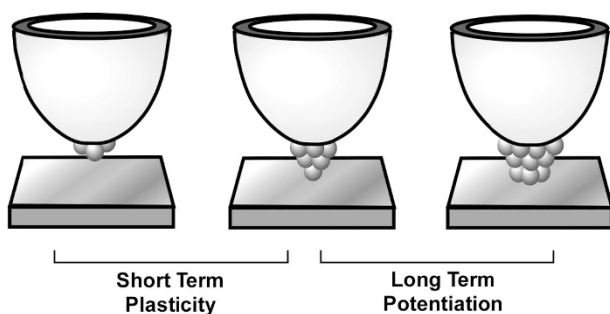
Figure 3 Short-term plasticity and long-term potentiation can be regenerated by gap-type Ag_2S-based atomic switches. Repeated pulses with a rather long interval results in the reversible formation of a highly conductive channel. However, pulse signals with a much shorter interval lead to the formation of a long-lasting conducting path to achieve long-term potentiation.

conventional physical switches has to be emphasized. As recently demonstrated by Ohno et al.,[99] the short-term plasticity and long-term potentiation characteristic of a synapse can be mimicked by the gap-type Ag_2S-based atomic switches (Figure 3). These memory modes can be adjusted by modifying the repetition time of an input pulse with only a single atomic switch. When the inputs of the pulses are repeated with a rather long interval such as 20 s, the formation of a highly conductive channel and a return to a highly resistive state are repeated at every interval. This behavior is regarded as a mimic of short-term plasticity. In turn, setting the pulse interval to a much shorter value (for example, 2 s) leads to the formation of a long-lasting conducting path to achieve long-term potentiation. These behaviors are totally different from the macroscopic mechanical switches in our rooms. According to the nanoarchitectonic concept, atoms behave differently under modified conditions, resulting in more bio-like switching mechanisms. These systems therefore correspond to inorganic synapses.

More elaborate neuromorphic networks of atomic switches were investigated both theoretically and experimentally by Sillin et al.[100] On the basis of their numerical model, it was clarified that even the random assembly of numerous atomic switches into network-like architectures can lead to the formation of dynamics analogous to bio-like neural networks. Surprisingly, billions of atomic switches can be interconnected through the entanglement of silver nanowire networks, as demonstrated by Stieg and colleagues.[101] Collective responses to stimulus inputs can be realized through network activation along with passive harmonic generation, which may represent self-organized neuromorphic devices. These examples strikingly represent the heart of nanoarchitectonics: the harmonization of nanostructures can create unexpected higher functions.

The next example, shown in Figure 4, is the automatic regulation of material releases from layered films of silica capsules with nanostructured pore channels.[102,103] Hierarchic pore architectures of silica capsules, which have an internal submicron-scale empty reservoir surrounded by silica walls with nanostructured pore channels, were assembled from silica nanoparticles and polyelectrolytes in a layer-by-layer manner. The release of liquid molecules such as water showed a step-wise ON/OFF profile, even without any external stimuli. This automatic regulation of material release is surely beyond our expectation and results from non-equilibrated concurrent actions of evaporation from the nanoscale pore channels and capillary penetration into the pores from the central reservoir.

The number of ON/OFF release steps is determined by the volume ratio between the nanopore channels and the amount of the guest

liquid in the central reservoir space. In the initial process, only liquid molecules entrapped in the nanopore channels are selectively evaporated as the evaporation speed gradually slows down. Only after the nanopore channels are close to empty and the evaporation speed becomes zero (automatic OFF) does the supply of the guest liquid from the central reservoir to the nanopore channels become possible on compensation of air penetration from the outside to the reservoir space through some of the empty nanopore channels. With this liquid supply from the inside space to the nanopore channel, the filled nanopore channels resume the release of guest liquid molecules. Further functional tuning such as setting the number of release steps and the release speed can be achieved by nanoarchitecture modulation, including the polymer coating of capsules and the size selection of particle co-adducts. Nanoarchitectonic structural design can achieve harmonized functions of automatic material release.

HAND-OPERATING NANOTECHNOLOGY
The second example of emerging challenges in nano-level research is the mechanical control of molecular machines. Mechano-chemistry has currently become popular, with the study of rather difficult processes such as bond breaking.[104–106] However, organic molecules should have potential delicate functions in their soft structural changes. Therefore, the subtle control of the structures of organic molecules would create unexplored functions and become a new challenge in nanoscale science. Below, the controls of molecular machines by macroscopic mechanical actions such as hand-motion-like stimuli are introduced as a novel concept named hand-operating nanotechnology.

Specific natures of interfacial supramolecular chemistry
As described later in detail, the interfacial environment is a key to achieve hand-operating nanotechnology. Before the description of molecular machine controls by macroscopic motions, the specific nature of interfacial supramolecular chemistry is explained below.

Molecular recognition at interfaces has been researched since the late 1980s.[107] Kunitake and co-worker highlighted molecular recognition at aqueous interfaces as an important key issue to solving the mystery of biological molecular recognition.[108] As seen in the recognition of specific substrates by enzymes and the highly selective pairing between DNA strands, hydrogen bonding and electrostatic interactions have crucial roles in biomolecular recognition. However, these interactions are highly weakened in polar media such as water. The rather weak hydrogen bond has extreme difficulty in forming in aqueous systems. In fact, most mimics of biological recognition with capabilities of hydrogen bonding are actually studied in non-aqueous media, and hydrogen-bond-based molecular recognition in aqueous media still represents a great challenge.[109,110] Biological recognition occurs in aqueous media, but these environments are highly disadvantageous for biological recognition. This fact remains a mystery, but research efforts on molecular recognition at interfaces have provided reasonable answers.[111]

Although molecular recognition based on organic chemistry often uses homogeneous solution media to examine recognition behaviors, actual molecular recognition in biological systems occur at heterogeneous interfaces such as cell membrane surfaces, inner surfaces of proteins and macromolecular interfaces of nucleic acid strands. Therefore, including an interfacial concept in molecular recognition would be a key to solving the mystery of biological recognition. In fact, the highly efficient molecular recognition of biologically important molecules such as nucleotides,[112] nucleic acid bases,[113] amino acids,[114] peptides[115] and sugars[116] has been
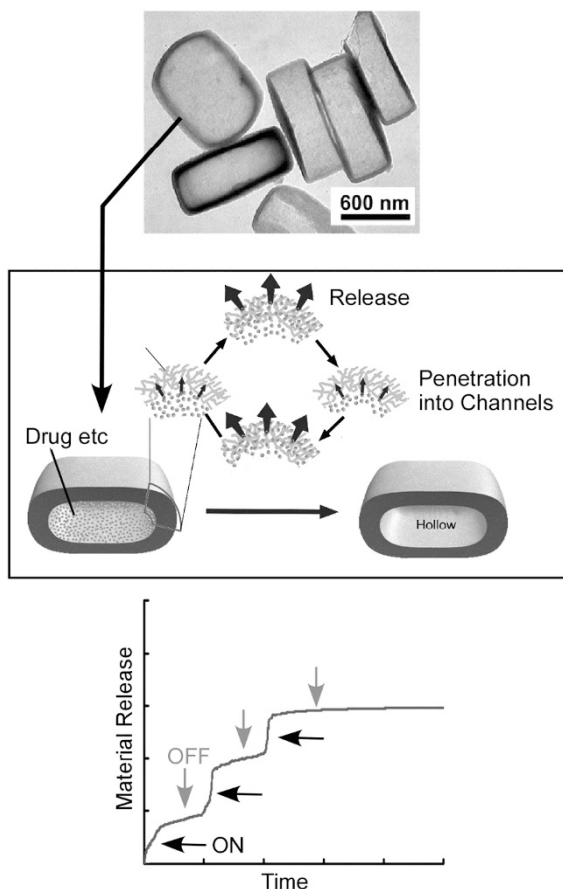
Figure 4 Hierarchic pore architectures of silica capsules exhibiting automatic regulation of material release with a step-wise ON/OFF profile, even without any external stimuli.

demonstrated at water interfaces, such as the air–water interface. Even in environments rich in water molecules, the achievement of hydrogen-bond-based molecular recognition has been experimentally proven (Figure 5).

For a more systematic understanding of molecular recognition in the interfacial media, one model recognition pair, phosphate–guanidinium, was evaluated at three different aqueous interfaces: a molecular-level interface, mesoscopic-level interface and macroscopic interface.[117] Although the phosphate–guanidinium pair can be formed through the contributions of electrostatic interactions and hydrogen bonding, its binding constant remains only $1.4\,M^{-1}$. In sharp contrast, embedding the same pair at mesoscopic interfaces (that is, surfaces of aqueous micelles and bilayers) and macroscopic interfaces (that is, the air–water interface) surprisingly increases the corresponding constants to 10^2–$10^4\,M^{-1}$ and 10^6–$10^7\,M^{-1}$,[118] respectively (Figure 6). These facts prove the striking enhancement of the molecular-recognition efficiency at interfaces. We generally attempt to modify molecular structures to obtain a better capability for molecular recognition. However, changing the interfacial environment would be a more optimal step for improving the molecular-recognition efficiency rather than structural optimization by traditional organic synthesis.

Physical and chemical constants have also been theoretically investigated. In the models reported by Sakurai et al.,[119] a guanidinium derivative molecule and a phosphate molecule are placed at various locations at an interface between a high dielectric medium ($\varepsilon = 80$, aqueous phase) and low dielectric phase ($\varepsilon = 2$, lipid/air phase;

Figure 7). The binding energy was calculated from an energy diagram as a function of the distance between the guanidinium and phosphate. The obtained binding constant significantly depends on the location of the binding pair at the interface. The binding pair located deep in the low dielectric medium showed a large binding constant, whereas the binding pair located deep inside the high dielectric medium exhibited a significantly small binding constant. It should be noted that a reasonably high binding constant was obtained even for the guanidinium–phosphate pair in aqueous media very close to the interface. Even when the moieties of hydrogen bonding are embedded in the aqueous phase, they are influenced by the low dielectric medium. Therefore, molecular recognition in the aqueous binding medium becomes efficient. Simulation based on the Poisson–Boltzmann equation with the Debye–Hückel approximation also suggests the promotion of molecular interactions at the air–water interface.[120]

In addition to promoting the binding constant, confining the binding sites within an interfacial two-dimensional media also results in entropic advantages in architecting binding sites based on self-organization. As exemplified in Figure 8, several biomolecules such as the flavin mononucleotide[121] and dipeptides[122,123] are specifically recognized by complicated recognition sites constructed by rather simple recognition pieces. The synthesis of complicated recognition sites to distinguish small differences in biomolecules is often a difficult task. However, self-assembling supramolecular processes at the interface would overcome these difficulties. This methodology includes the concept of nanoarchitectonics.

The above-mentioned supramolecular formation of binding sites can be used for nanostructure fabrication.[124] As illustrated in Figure 9, two-dimensional patterned motifs with sub-nanometer structural precision can be architectured on the basis of specific molecular recognition and subsequent supramolecular assembly at the air–water interface.[125] In this case, the specific binding of flavin adenine dinucleotide to amphiphilic orotate and guanidinium molecules at air–water interfaces can create regular height difference patterns with several angstrom precision. In another case, the binding of aqueous template molecules of dicarboxylic acid to guanidinium amphiphiles leads to the control of two-dimensional ordering and crystallinity depending on the spacer length of the former template molecules.[126] The linear formation of complementary hydrogen bonding between amphiphilic melamine molecules and aqueous barbituric acid derivatives results in the formation of one-dimensional molecular tapes within a two-dimensional geometry.[127] Controlled nanoscopic phase-separated structures can be created through balancing the attractive interactions between carboxylate and guanidinium and the repulsive interactions between hydrocarbon and fluorocarbon chains.[128] The aggregation of oligo(p-phenylene vinylene) derivatives at the air–water interface leads to the formation of well-defined nanorods that can be used for detailed studies on the mechanism of excitation energy migration for one-dimensional supramolecular nanostructures.[129]

New role of interfaces

As mentioned above, interfacial environments have significant effects on supramolecular chemistry. Molecular recognition with specific interactions is emphasized at the air–water interface compared with that observed in bulk aqueous phases. Molecular assembly at interfaces as confined spaces occurs with the restriction of material diffusion and molecular motion, resulting in the formation of highly oriented structures and patterns with nano- and molecular-scale precision. These significant effects are based on the fact that phenomena at
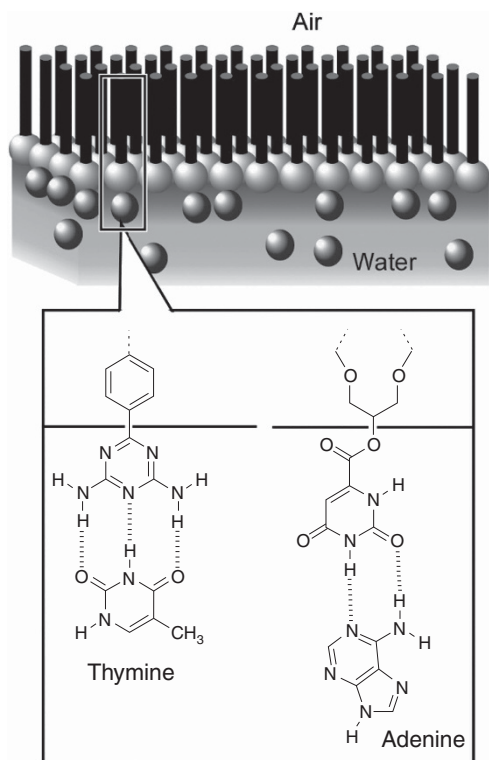
Figure 5 At the air–water interface, the hydrogen-bond-based molecular recognition of biomolecules such as nucleic acid bases can be achieved in environments rich in water molecules.

interfaces are different from those in a bulk phase. The latter fact is commonly used in surface science, as seen in chemical reactivity in catalysis and the anisotropies of various physical properties. Most of the surface science is about differences between interfacial (or surface) and bulk states.

In this part, we would like to emphasize a new role of interfaces and a novel task of surface science as emerging concepts and challenges in nanoscience. The new role of the interface would be as a medium for bridging phenomena between visible-size macroscopic events and nano/molecular-scale phenomena.[130–134] We can prepare bulk-size functional materials through assembling molecular-scale unit parts. Such assembly processes mostly occur in three-dimensional bulk phases, where the nano-level features of the resulting materials are usually buried deep in the three-dimensional bulk materials. For example, the direct mechanical control of functional nano-units is usually difficult because such assembled materials do not have a logical connection between macroscopic actions and molecular functions. This failure originates from methods of material architecting. The three-dimensional construction of materials loses its nano-size dimensions in all directions.

As illustrated in Figure 10, the construction of materials into reduced dimensions such as two-dimensional interfacial media leads to the connection of the macroscopic dimensions and nanoscopic dimensions. In these interfacial media or interfacial materials, lateral dimensions, as denoted by the *xy* plane, can spread infinitely in the macroscopic scale, where common macroscopic actions such as compression, expansion and bending are freely allowed. In contrast, the thickness direction along the *z* axis remains at the nano/molecular-level. Therefore, macroscopic actions can be logically connected with nano/molecular functions at interfaces.
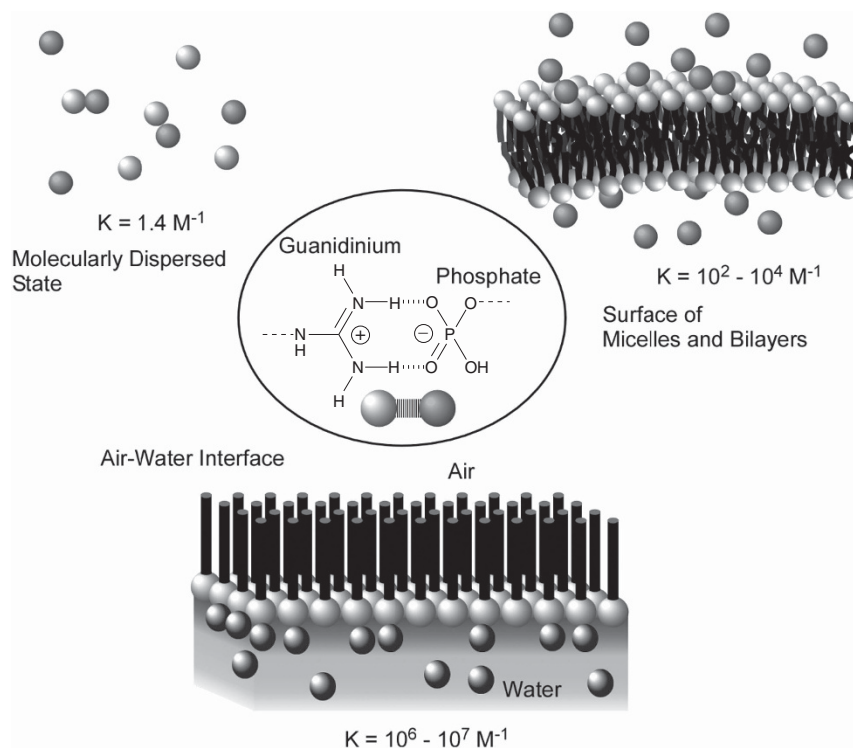
Figure 6 A model recognition pair, phosphate–guanidinium, was compared at three different aqueous interfaces: molecular level, mesoscopic level and macroscopic level. Huge enhancements of the molecular-recognition efficiency were observed in the interfacial media.
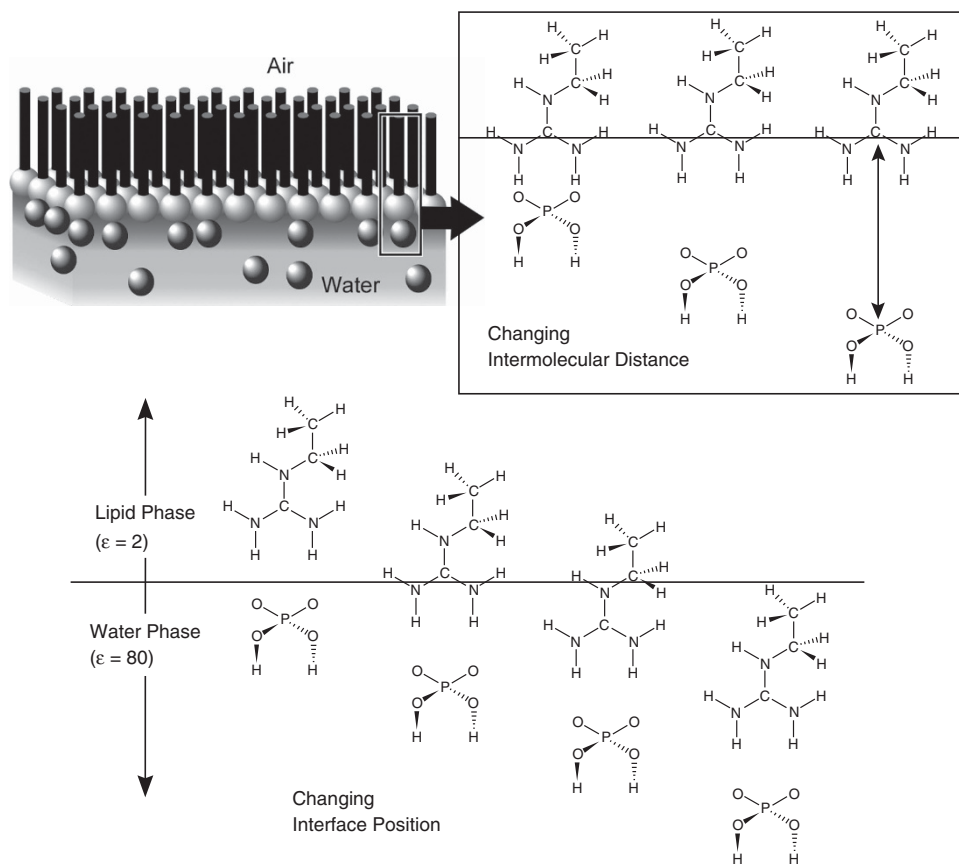
Figure 7 Energies between a guanidinium derivative molecule and a phosphate molecule in an interfacial medium were calculated as a function of the distance between the guanidinium and phosphate to provide binding constants. Even when the moieties of hydrogen bonding are embedded in the aqueous phase, they are influenced by the low dielectric medium and sufficiently high bonding constants.

We can control nano/molecular-level functions by macroscopic actions through the judicious use of interfacial environments. It is possible that fine nanotechnological functions and mechanisms could be handled and operated by common actions such as hand motions. Therefore, we named this emerging concept 'hand-operating nanotechnology'.[135,136] This concept would also connect our daily life and forefront nanotechnology. In most top-level nanotechnology, atoms, molecules and nanomaterials are controlled using sophisticated tools such as highly sharpened probe tips, often under well-adjusted environments such as high-vacuum inert atmospheres. Such high technological conditions are not applicable to the circumstances of our daily life. With the emerging concept of hand-operating nanotechnology, the control of nanophenomena would become possible within daily life activities, in economically developing countries and regions, and even in emergency disaster situations.

Mechano-tunable molecular machines
For a clear demonstration of hand-operating nanotechnology, the control of molecular machines by macroscopic mechanical motions has been investigated. In many examples of molecular machine studies, stimuli such as light, redox and chemical reactions have been used.[137–139] These stimuli have separate units, photons, electrons or molecules, through which they can have direct contact with the molecular machine. More common mechanical stimuli cannot be applied to these systems because mechanical actions cannot be divided into nanoscale units. In contrast to this common sense, the following examples based on hand-operating nanotechnology demonstrate

molecular capture-release and molecular discrimination by macroscopic mechanical motions.

In the first example (Figure 11), a molecular machine, the so-called steroid cyclophane, was embedded at an air–water interface.[140,141] This molecular machine has a central ring of a 1,6,20,25-tetraaza[6.1.6.1]-paracyclophane, to which four rigid walls of a cholic acid moiety are connected via a flexible L-lysine linker. Because the rigid cholic walls have hydrophobic and hydrophilic faces on the reverse side, this molecular machine adopts an open conformation by contacting the hydrophilic face to the water phase at low pressures. On high-pressure lateral compression, this molecular machine converts to its cavity conformation. The pressure-molecular isotherm indicates a shift of the molecular area at the air–water interface from 7 to 2 nm^2, corresponding to a conformational change from the open to cavity conformation of the molecular machine. When a model guest molecule 6-(p-toluidino)naphthalene-2-sulfonate is dissolved in the aqueous phase, fluorescence changes owing to guest inclusion are observed on the lateral compression of the monolayer of the steroid cyclophane machine. The florescence intensity abruptly increases when the cavity formation of the molecular machine is completed at high pressure. The increase in the binding constant from the open conformer (approximately 3×10^2 M^{-1}) to the cavity conformer (approximately 1×10^6 M^{-1}) induces this guest molecule capture.

The dynamic control of the cavity-forming molecular machine was also examined by the repeated mechanical compression and expansion of the molecular machine monolayer below the transition pressure from the two-dimensional phase to the three-dimensional phase.
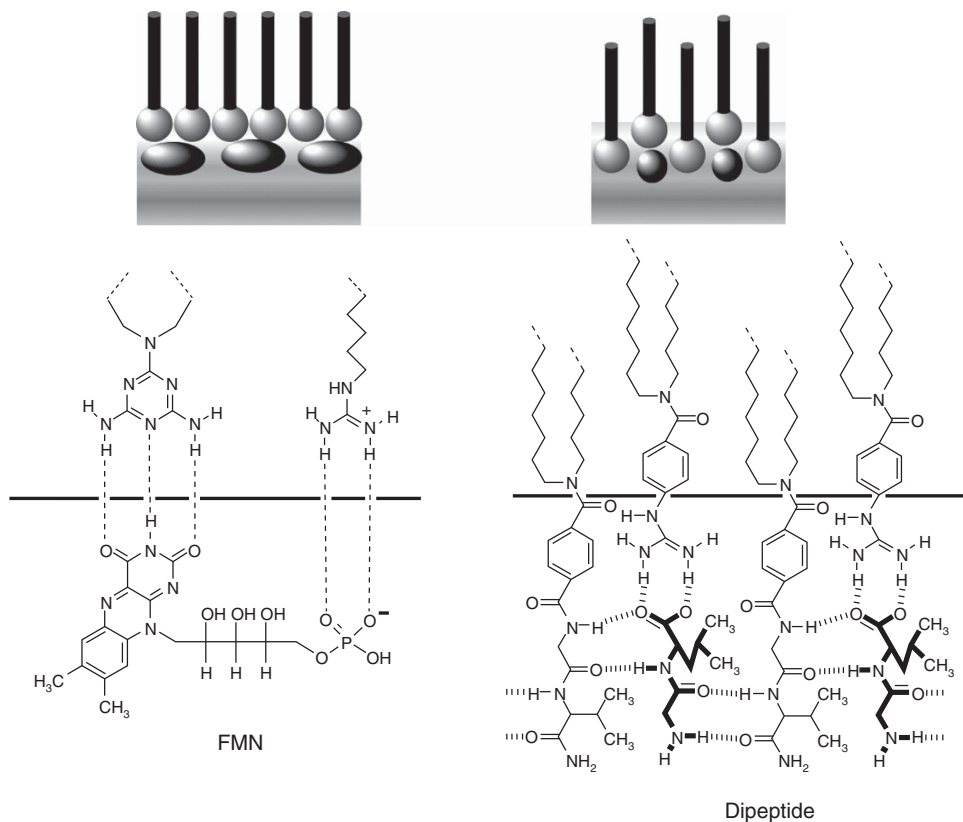
Figure 8 Self-organized binding sites at the air–water interface: recognition of flavin mononucleotide (FMN, left) and dipeptides (right).

The repeated increase and decrease of the guest-capture-based fluorescence was confirmed on synchronization of the compression and expansion of the molecular machine monolayer. These observations indicate that the molecular capture and release on conformational changes of the molecular machine are induced by hand-motion-like macroscopic mechanical motions. Although these experiments were conducted with a computer-controlled film-balance machine to collect precise experimental data, the working principles of operation are the same as those of human-motion-based operation. This demonstration confirms the operation of a molecular machine by hand-motion-like macroscopic actions using an interfacial media and appropriate molecular design.

This interfacial mechanical concept can be coupled with photo-emission based on controlled interaction between chromophores (Figure 12).[142] The receptor molecule at the air–water interface possesses a phenylboronic acid as a recognition part and a carboxy-fluorescein as an indicator moiety. In the initial state, the coumarin-based chromophore 4-methylesculetin is bound to the phenylboronic acid moiety. The efficiency of the FRET (fluorescence resonance energy transfer) between 4-methylesculetin and carboxyfluorescein depends on the distance and conformation of these fluorophores. The macroscopic mechanical compression of the monolayer controls the distance between these chromophores. The blue fluorescence emission at around 450 nm directly from 4-methylesculetin fluorophore on exciting the 4-methylesculetin chromophore at 373 nm (FRET OFF) is changed to green fluorescence at around 530 nm from neighboring carboxyfluorescein fluorophore through the FRET ON process. The addition of glucose as a guest molecule to the water phase induces the replacement of 4-methylesculetin by glucose through binding to phenylboronic acid, accompanied by the intensity decrease of the

green fluorescence (FRET OFF). This fluorescent glucose recognition is activated only on the application of mechanical stimulus. Therefore, glucose can be detected only at a place with mechanical stress. This new mode of detection is called a mechanically controlled indicator displacement assay.

Molecular tuning concept
The examples mentioned above mainly demonstrate mechanical molecular operations with drastic changes of the target molecules. However, organic molecules have a soft and flexible nature in their structures and conformations unlike inorganic molecules. Therefore, organic molecules have good potential for functional modulations with minimal tuning of the molecular conformation. As explained in the next example, mechanical processes at interfaces are actually low-energy processes compared with other processes in conventional mechano-chemistry. In two-dimensional systems, the system size (lateral area) can be significantly changed while keeping the main orientation. Even a tiny input of mechanical energy of less than 1 kcal mol^{-1} can lead to a huge variation of the area of the molecules, inducing the modification of the molecular conformation. Therefore, two-dimensional systems such as the air–water interface can be regarded as ideal media for the investigation of soft mechano-chemistry, both through experimental and theoretical analyses.

For this purpose, novel amphiphilic binaphthyl molecules as molecular pliers were embedded at the air–water interface, and changes of the torsional behavior at their binaphthyl hinge were evaluated by both experimental and theoretical approaches (Figure 13).[143] The used molecule has circular dichroic activity that can be combined with simulation for optimized structures with the use of time-dependent density functional theory to estimate the
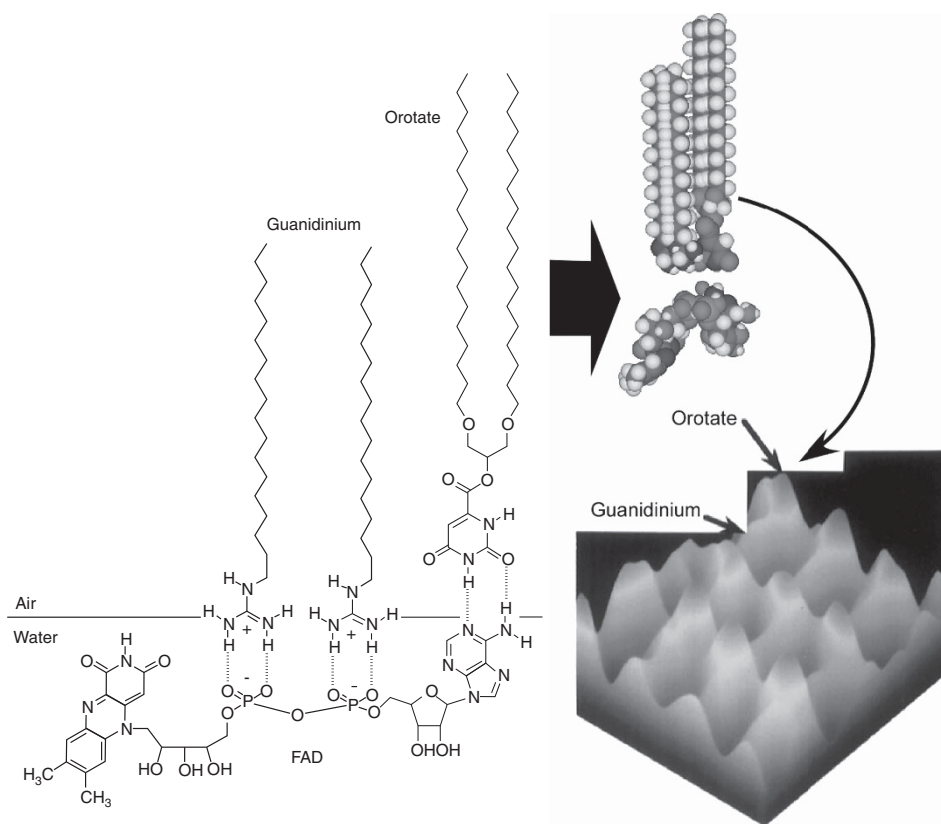
Figure 9 Two-dimensional patterned motifs with sub-nanometer structural precision can be architectured on the basis of specific molecular recognition and subsequent supramolecular assembly at the air–water interface, where flavin adenine dinucleotide (FAD) has the role of a structural template.
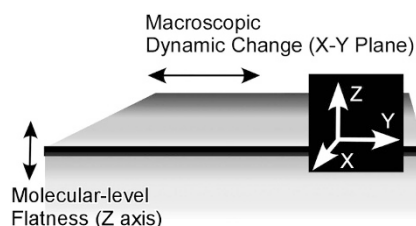

Figure 10 An interfacial medium can bridge macroscopic scale (*xy* plane) and nano-size (*z* direction) functions.

torsion angle of the naphthalene planes. This process reveals a shift of the corresponding torsional angle from $-90°$ to $-80°$ in the chiral binaphthyl molecular pliers. In addition, single-molecule simulations on the basis of individual molecules floating in large molecular areas and standing in small molecular areas (both at low pressures) confirmed similar changes of the binaphthyl torsional angles. The energies necessary for these structural changes were also determined by density functional theory calculations, and the single-point energies were evaluated by spin-component-scaled MP2 calculations. Considering that thermal energy is estimated to be $kT \sim 0.6$ kcal mol^{-1} at ambient temperature, the chiral binaphthyl molecular pliers fluctuate with a torsion angle in the range $-110°$ to $-70°$.

The thermodynamic energies supplied by macroscopic motions were separately obtained through the integration of the isotherms of the surface pressure as a function of molecular area, which provides a precise evaluation of the energy used in the compression process.

From these calculations and comparisons, the macroscopic mechanical energy is converted proportionally to molecular torsional energy. Except in high-pressure regions, the conversion efficiency seems to be approximately 100%. At the air–water interfacial media, the mechanical forces remain small, but the conversion efficiency from macro to nano would be high. Soft mechano-chemistry with small forces would be important both for soft chemical processes and biological systems, in the latter of which pN-level forces are known to induce conformational changes important for biological function, such as protein properties. Mechano-chemistry and related processes at appropriate interfaces would become a key for molecular conformational control for the fine-tuning of functions.

The tuning of the structure of molecular receptors at the air–water interface is also useful for the fine control of recognition for biological guest molecules. In the example illustrated in Figure 14, the mechanically controllable twisting motion of a cholesterol-armed cyclen molecule having a hydrophilic tetraazacyclododecane central core and hydrophobic cholesterol residues is used for the enantioselective recognition of aqueous amino acids.[144,145] In the cholesterol-armed cyclen molecule, the four chiral cholesteryl residues form helical structures depending on the external environment, such as the presence of chiral guest molecules and the packing states of their assemblies. In the assembled states, the calculated molecular cross-sectional area of the four cholesterol residues is 1.6 nm^2, which is sufficiently larger than that of the cyclen moiety (0.35 nm^2). Therefore, the cholesterol-armed cyclen molecule has a certain void space for the accommodation of guest amino acids from the water phase. The volume and chiral environment of the void space for external guests can be tuned by the mechanical compression of the
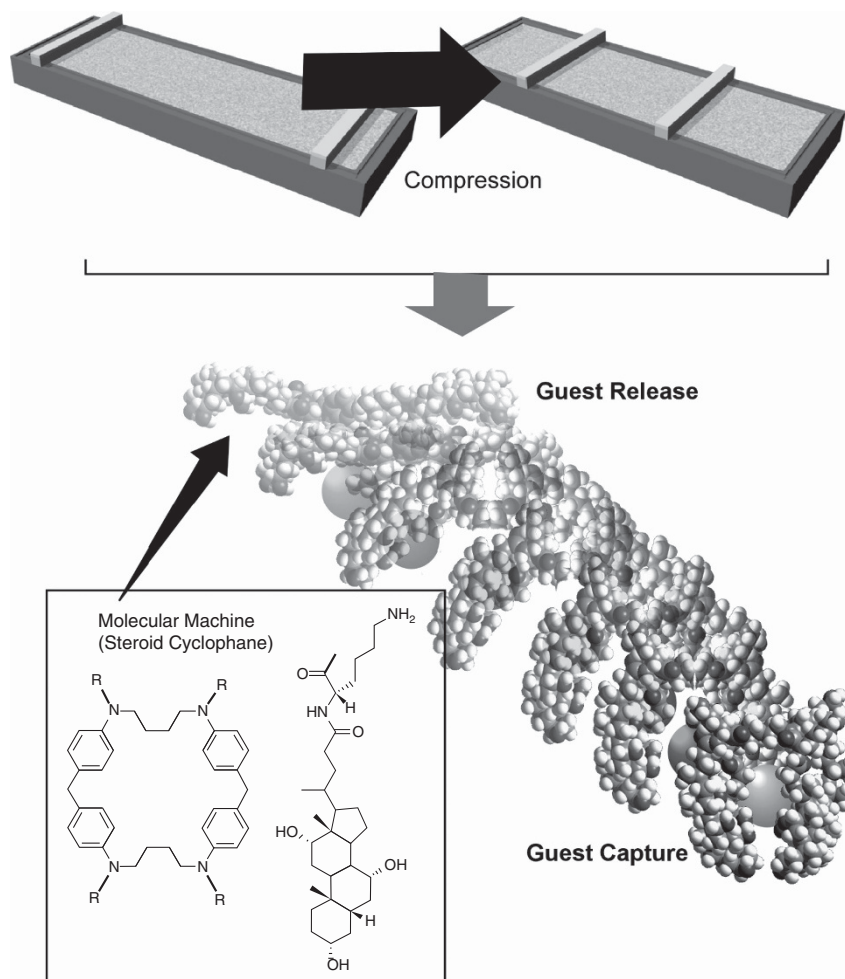
Figure 11 Capture and release of guest molecules by a molecular machine, so-called steroid cyclophane, on macroscopic-scale mechanical compression and expansion of its monolayer at the air–water interface.

monolayer. Lateral pressure application to the monolayers has an especially critical influence on its helical structure, with unavoidable influence on the diastereomeric stability of complex structures formed with aqueous guest molecules.

These situations create fine control of the enantiomeric selection of aqueous amino acids that can be tuned by macroscopic mechanical forces. The binding constants for D-valine to the monolayer of cholesterol-armed cyclen are slightly greater than those for L-valine at low-pressure conditions. The binding constant of L-valine significantly increases as the surface pressure increases, whereas the increase of the binding constant of D-valine is moderate. Accordingly, the enantiomeric selectivity to aqueous valine is inverted at approximately 22–23 mN m^{-1}, that is, D-valine is preferentially recognized at low pressures over L-valine. When we think about host–guest complex structures with traditional methods such as X-ray crystallography, one host (receptor) molecule provides the most stable complex structure, resulting in a single guest selectivity value. In contrast to the traditional host–guest chemistry, the continuous mechanical tuning of receptor structures at interfaces can give numerous possibilities of binding structures. Therefore, the optimization and condition selection of guest binding can be performed simply by the application of lateral pressures.

The inversion of enantiomeric selectivity was similarly observed for phenyl alanine, but enantioselective inversion was not observed in the case of leucine. In the latter case, the binding constant for D-leucine is higher than that of L-leucine under all pressure conditions. These results indicate that the control of weak intermolecular interactions can sense small structural differences of the guest (only a single methylene group difference in the cases of valine and leucine). A plausible mechanism for these behaviors of fine molecular recognition may be the interaction modes and the freedom of molecular motion at the interfacial media. At the lower pressure, the helical structures of cholesterol-armed cyclen have dynamic motion freedom, and the formation of thermodynamically stable helical structures would determine the guest selectivity. However, the packing of hydrophobic groups including cholesterol arms and the side chains of guest amino acids becomes crucial under the limited molecular motions possible at high pressures. The balancing of these factors would result in the fine-tuning of the enantiomeric selectivity. These processes can be regarded as the discrimination of chiral compounds by macroscopic mechanical forces. This would be only the second successful example of chiral separation by hand-motion-like actions since Professor Pasteur's separation of crystals of tartaric acid by tweezers.

The same concept of mechanically controlled molecular recognition was also applied to another challenging fine discrimination, that of thymine and uracil.[146,147] These nucleic acid bases form the same hydrogen bonding pairs with adenine in DNA and RNA, respectively,
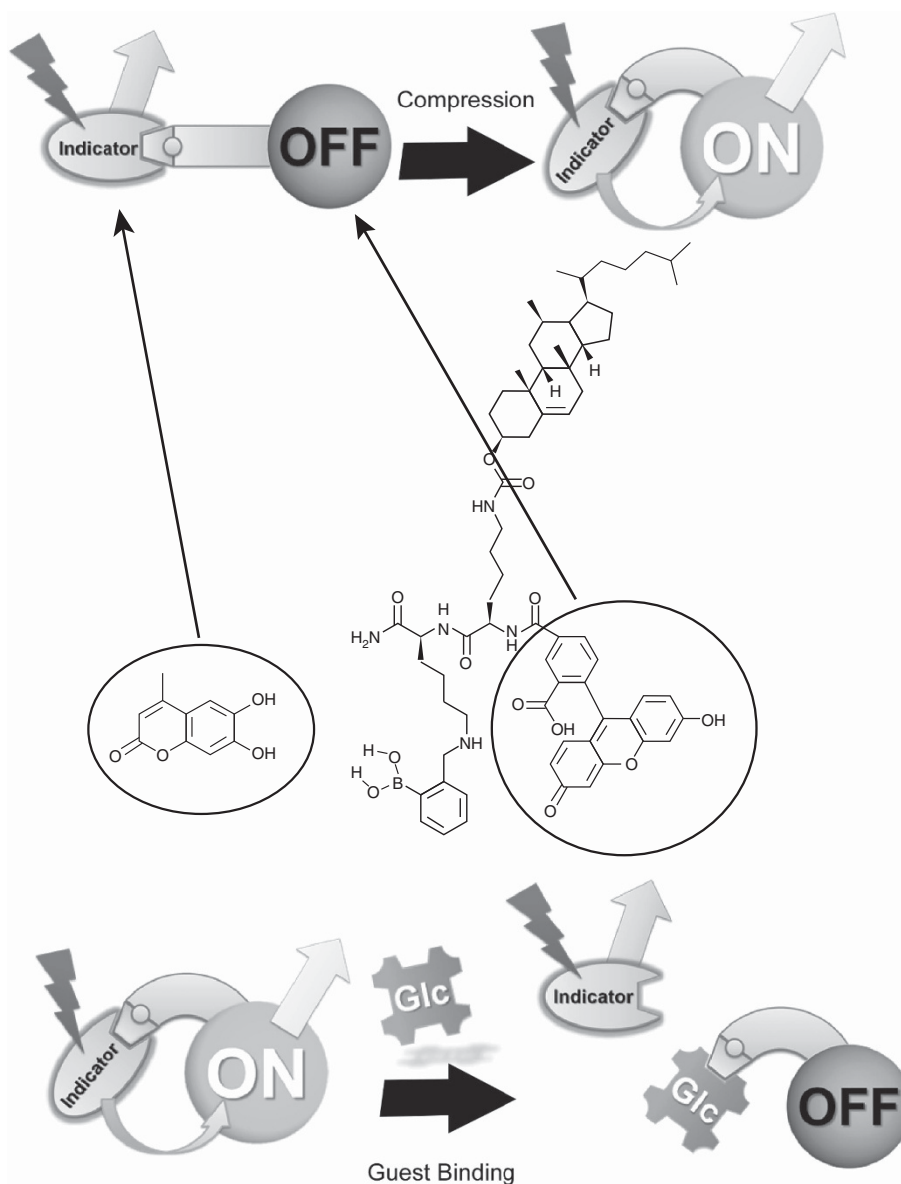
Figure 12 Mechanical control of fluorescence resonance energy transfer (FRET) at the air–water interface and detection of glucose (Glc in the illustration) through a mechanically controlled indicator displacement assay (MC-IDA).

and are not distinguishable at the nucleic acid level. In natural systems, only a special enzyme with a sophisticated three-dimensional recognition site can discriminate between them. As shown in Figure 15, only a simple array of molecules with carbonyl groups and amino groups show distinct differences in their binding constants to these nucleic acid bases. The used molecular receptor is cholesterol-substituted triazacyclononane, which is spread at the air–water interface as a compressible monolayer. The binding behaviors of aqueous thymine and uracil derivatives were systematically measured under various surface pressures and the presence or absence of the reinforcing ion Li$^+$. Under optimized conditions, the binding constant for uracil recognition becomes 60–70 times as high as that of thymine, although uracil and thymine have only a tiny structural difference of one methyl group. This example demonstrates a new strategy to optimize the recognition of a guest molecule structure through the structural tuning of an array of molecular structures, which is a rather

simple design. This approach can avoid difficult and tedious processes in the design and synthesis of complicated receptor structures.

In Figure 16, the above-mentioned emerging concept of mechanical molecular tuning is compared with past traditional modes of molecular recognition and molecular machines. Molecular recognition systems in the initial stages, including host–guest pairs with crown ethers, cyclodextrins, other artificial host molecules and naturally occurring host molecules such as some antibiotics, basically use one stable state of the host–guest complex. The modulation of the host–guest structure by external stimuli was demonstrated by Shinkai et al.[148] in their pioneering work on photo-switchable azo-benzene hosts. This can be regarded as a switching concept in molecular recognition and could also be thought of as the second-generation concept in molecular recognition. The switching of molecular recognition and molecular states has been widely used in advanced host–guest systems and molecular machine operations. The

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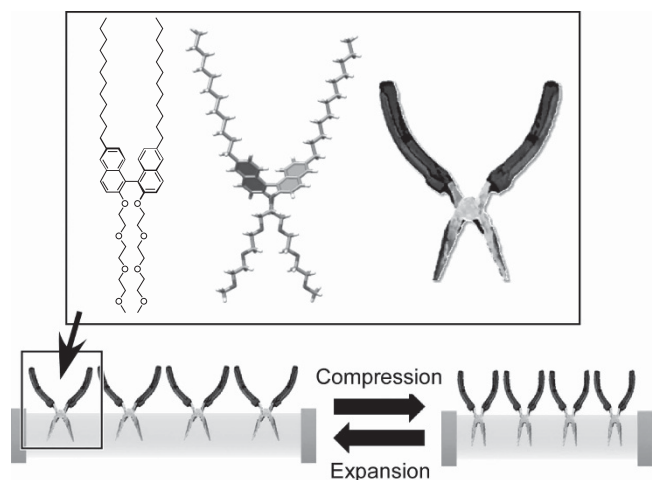
Figure 13 Changes of torsional behaviors at a hinge moiety in amphiphilic binaphthyl molecules as molecular pliers embedded at the air–water interface were evaluated by both experimental and theoretical approaches.

switching concept creates two, three or more stable states for molecular interaction to change the molecular state. In fact, most current molecular machines are operated by this switching concept. Unlike these two traditional modes, we propose a tuning concept as an emerging generation of molecular recognition. In our tuning concept, the molecular states and energy states of molecules can be continuously shifted through the application of macroscopic mechanical forces. The optimization of the systems to particular purposes can be achieved by the selection of conditions from numerous candidates because structural candidates can be continuously created. On the basis of the softness and flexibility of organic molecules, molecular tuning can be accomplished with mechanical motions as weak non-digital stimuli.

MECHANOBIOLOGY AND MECHANICAL ACCESS TO BIO-RELATED FUNCTIONS

In the previous sections, two emerging concepts, nanoarchitectonics and the mechanical control of nanosystems, were introduced. Nanoarchitectonics shares architecting strategies and a functional flexibility with biological systems, where nano and molecular components are assembled and work together in balanced functional harmony. However, the mechanical control of nanosystems is an important task that provides access for macroscopic mechanical motions to nanostructured materials and systems. Combining these emerging concepts would lead to the third emerging concept, mechanobiology and mechanical access to biological functions.

Mechanobiology: cell control

Our living system is constantly exposed to various mechanical stimuli. In a similar fashion to the regulation of various biological activities by cytokines and growth factors, mechanical stimuli direct cells to proliferate, differentiate and even die through mechanotransduction. For example, the differentiation of stem cells, such as neurogenic, myogenic and osteogenic lineages, can be determined by the elasticity of their culture matrices.[149,150] Mechanobiology research examines how biomolecules, cells and tissues respond to mechanical stresses. The field also covers the measurement of forces and mechanical parameters in biological systems and the development of materials for mechanical control of biological activities. We believe that mechanobiology is a promising output of the two above-mentioned
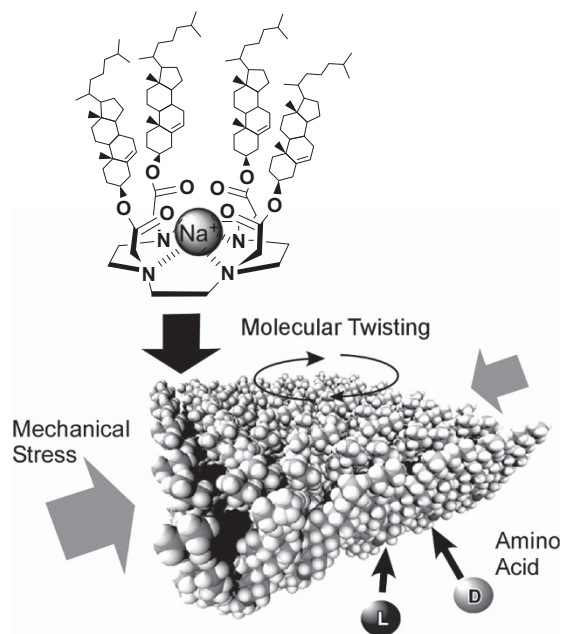
Figure 14 Tuning of structure of molecular receptors of cholesterol-armed cyclen molecules at the air–water interface realized mechanically controllable enantiomeric discrimination of aqueous amino acid guests.

emerging concepts—nanoarchitectonics and interfacial mechanical control.

From the viewpoint of materials research, the development of mechano-structural stimulus-responsive polymeric materials for cell fate control is an attractive target. As the extracellular matrix dynamically changes its stiffness, gel materials can be used for cell culture. For example, Frey and Wang[151] synthesized a crosslinking poly(acrylamide) hydrogel with a UV-cleavable component that is capable of rigidity modulation by UV-light irradiation. They become much softer on UV irradiation, resulting in a substantial decrease of the spread area of NIH fibroblast cells. Kloxin et al.[152] also developed photodegradable hydrogels for the dynamic and external control of cell-material interactions by light. Uto et al.[153] synthesized temperature-responsive poly(ε-caprolactone) films with dynamically tunable elastic properties. The stiffness of the used polymer films decreased from 20 to 1 MPa when the temperature was elevated above the melting point. Accordingly, the shape of the myoblasts on the surface of the film changed to a rounded one on the drastic increase of the temperature above the melting point.

The control of the surface morphology and the nature of the matrix polymer material are also effective to dynamically modulate cell behavior. For example, Mosqueira et al.[154] recently reported the regulation of intracellular localization of YAP/TAZ (YAP: Yes-associated protein, TAZ: transcriptional coactivator with PDZ-binding motif) in cardiac progenitor cells by the nanotopographical control of poly(ε-caprolactone) films (Figure 17). On a temperature shift from 32 to 37 °C, the nanostructured film morphology with 300 nm of line ridge, 500 nm of groove and 120 nm of height was converted to flat. The nuclear expression of YAP/TAZ significantly decreased after 90 min, and the degree of YAP nuclear-positive cells returned to its original value after 180 min. These proteins are sensitive to dynamic changes in the surface nanotopography, and the relocalization of YAP/TAZ occurred with a response to the stiffness change of the base polymer. The related mechanical factors have unavoidable influences.

The stiffness of the substrate is also related to mechanotaxis. Kidoaki and colleagues demonstrated the control of cell migratory behavior by microelastically patterned hydrogel matrices.[155–158] The

Figure 15 Mechanical tuning of a molecular receptor, cholesterol-substituted triazacyclononane, results in highly efficient discrimination between thymine and uracil, which usually cannot be achieved by DNA and RNA.

hydrogel matrices with large varieties of elasticity boundaries are fabricated by the photolithography of a poly(*N*-isopropylacrylamide) hydrogel by changing the stiffness from 3 to >500 kPa. On these microelastically patterned hydrogel substrates, the fibroblast migrations are induced with respect to the stiffness as well as the micropatterned structure of the soft–hard elasticity boundaries, such as sharp/diffuse, straight and convex/concave boundaries.

The differentiation of stem cells is usually induced by the addition of specific soluble factors, which can directly activate lineage programs. The differentiation and lineage specifications of stem cells are also influenced by the microenvironment stiffness of the substrate. Engler *et al.* demonstrated the control of the lineage specification using the elasticity of the microenvironment.[159] Three substrates with different elasticities were fabricated with poly(acrylamide) gel. On optimized matrices varying in elasticity (0.1–1, 8–17 and 25–40 kPa), the lineage specification of mesenchymal stem cells is selectively activated to express β3 tubulin for neurogenic, MyoD for myogenic and CBFα1 for osteogenic differentiation.

Materials used for the mechanical control of biological processes are not limited to soft polymer materials. Arrays of rigid nano/micromaterials are also applicable to this research field. As demonstrated in recent research results, fullerene crystals as supramolecular nanocarbon materials can be formulated in various shapes and assembled into aligned arrays through interfacial processes.[160,161] One example is fullerene whiskers prepared through a liquid–liquid precipitation technique,[162] which have a high stiffness of 30–50 GPa.[163] Unlike other nanocarbon materials such as carbon nanotubes, the fullerene whiskers have a submicron-level width (not in the nano range) and are basically harmless to biological systems. In fact, the fullerene whisker materials exhibit good biocompatibility with macrophages performing phagocytosis.[164]
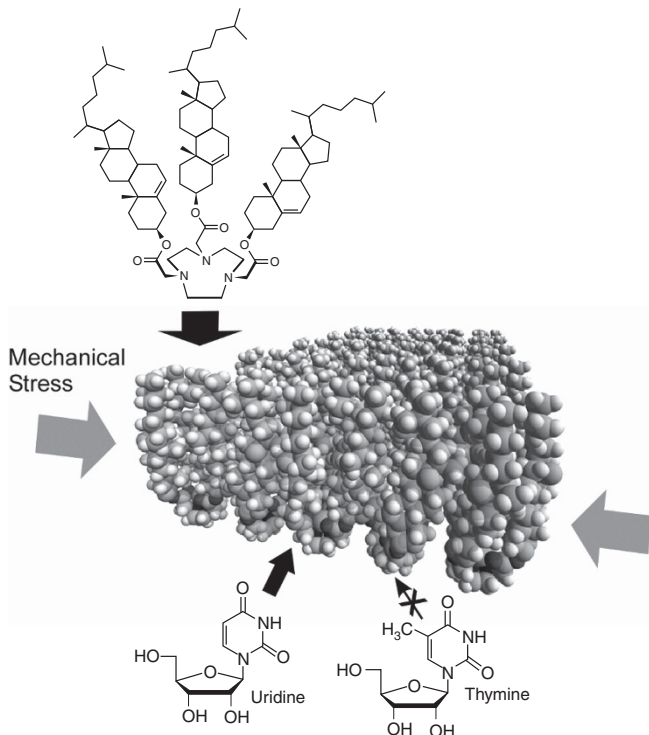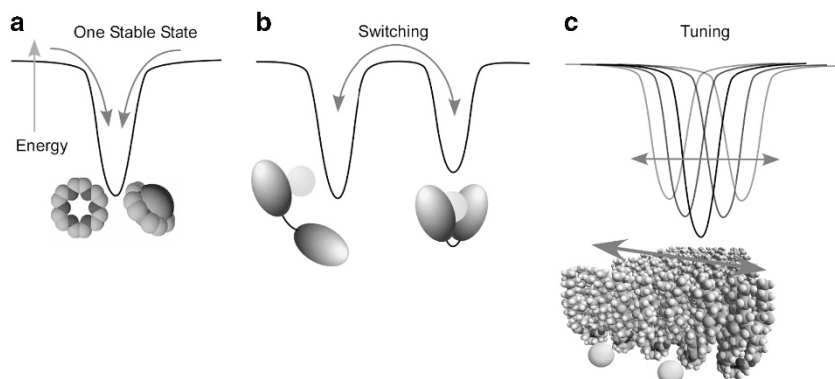
Figure 16 Three major historical methodologies for molecular recognition: (**a**) traditional molecular recognition considers only a single stable state; (**b**) switching mechanism can modify the molecular-recognition efficiency within a few possible candidates; (**c**) tuning strategies use all possibilities for conformational changes as candidates for selecting the best solution for the desired recognition.
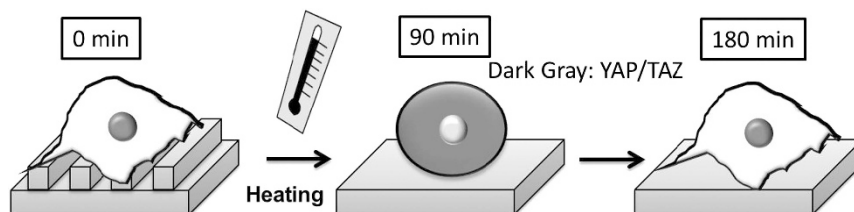
Figure 17 Regulation of intracellular localization of YAP/TAZ (YAP, Yes-associated protein; TAZ, transcriptional coactivator with PDZ-binding motif) in cardiac progenitor cells by nanotopographical control of poly(ε-caprolactone) films.
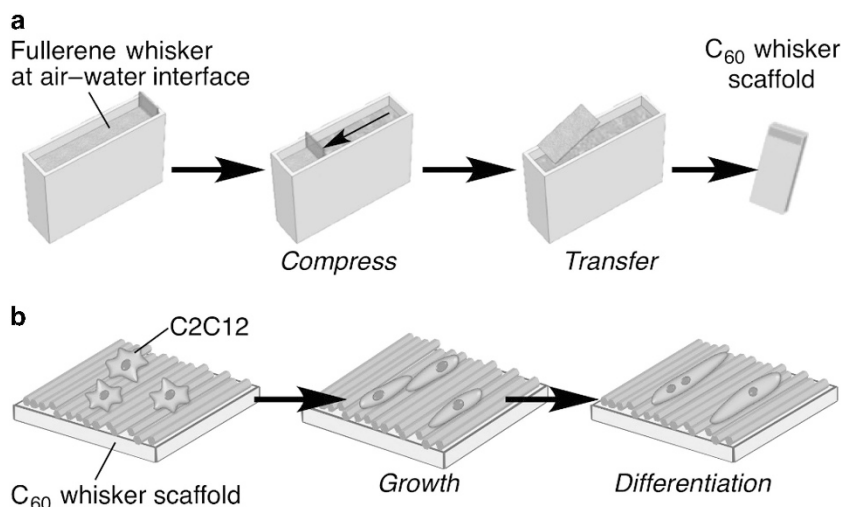
Figure 18 Using the Langmuir–Blodgett technique, fullerene whiskers were assembled into highly aligned arrays that regulate the growth, alignment and differentiation of target cells. (**a**) Preparation of aligned fullerene whisker array. (**b**) Control of cellular differentiation.
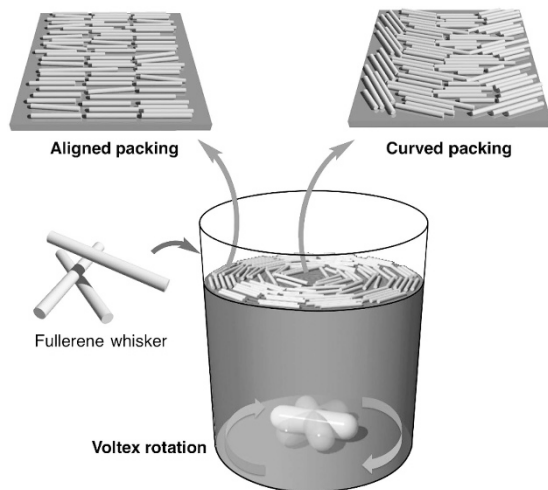
Figure 19 Vortex-mode of Langmuir–Blodgett (LB) transfer (vortex-LB), in which vortex flow can make fullerene whiskers oriented along direction of flow of centrifugal rotation at liquid surface.

Recently, Minami *et al.*[165] successfully demonstrated the control of the cell alignment and differentiation using an array of fullerene whiskers as a scaffold (Figure 18). Using the Langmuir–Blodgett technique, fullerene whiskers were assembled into highly aligned arrays. On these mechanically aligned supramolecular carbon materials, the incubation of mouse skeletal myoblast C2C12 cells resulted in aligned cell growth highly correlated with the direction decided by fullerene whisker arrays. In addition, myogenic differentiation in both the early and late stages is promoted, and cell fusion along the directions of cell growth was induced to form oriented myotubes. Mechanically manipulated nanocarbon arrays would be a useful scaffold for the regeneration of skeletal muscle tissues.

As a more advanced mechanical method for nanomaterial alignment, the vortex-flow Langmuir–Blodgett technique has been recently proposed.[166] As illustrated in Figure 19, the vortex flow can be activated by the mechanical stirring of the medium. Fullerene whiskers were actually oriented along the flow of the centrifugal rotation at the liquid surface, depending on the position of the surface. These aligned whiskers can be transferred onto a wide range of substrates including paper, mica, glass, boron nitride and gold. Cell culture experiments on the transferred fullerene whiskers reveal that the adhesion of human osteoblast MG63 occurs preferentially at the surface of the aligned fullerene whiskers. The adhered cells tend to grow along the direction of the aligned whiskers. The low toxicity of the aligned fullerene whiskers was also confirmed by cell proliferation experiments.

Mechanically controlled bio-related events: enzymatic reaction and drug delivery

Not limited to cell culture matters, mechanical control of the polymer matrix can regulate various bio-related processes. For example, Voegel and colleagues successfully demonstrated the activation switching of an enzymatic reaction by mechanical stimuli (Figure 20).[167,168] As a model enzyme, alkaline phosphatase was incorporated within polymer thin films that were prepared using layer-by-layer assembly. The layer-by-layer assemblies of polymer multilayers, in which the alkaline phosphatase molecules were embedded, were first assembled, followed by the assembly of capping multilayers. The latter polymer layers have a key role of a mechanically sensitive nanobarrier. When the capping layer is over the enzyme layers, the alkaline phosphatase stayed catalytically inactive. The enzymes deeply embedded in the polymer films cannot easily access the fluorescein diphosphate as a reaction substrate. However, the enzyme can be accessible to the substrate molecules and initiate the corresponding reaction by the mechanical stretching of the polymer films. Above a critical stress, the enzymatic activity of the alkaline phosphatase becomes positive, which can be confirmed through the enhancement of the green fluorescence because of the hydrolysis of fluorescein diphosphate to phosphate and fluorescein components. The increase of the product concentration exhibits a negative feedback on the enzymatic activity. As a result, stopping the stretching turns off the enzymatic reaction. Because the used system can be regarded as interfacial materials, this example shares the same concept as the mechanical control of molecular machines in interfacial media, with the transduction of macroscopic forces to molecular phenomena using interfacial media.

When we apply the mechanical control concept to three-dimensional materials, materials with flexible and soft structures have to be used in response to external mechanical stimuli. Gels are the most suitable materials for this purpose. In gel materials, non-covalent
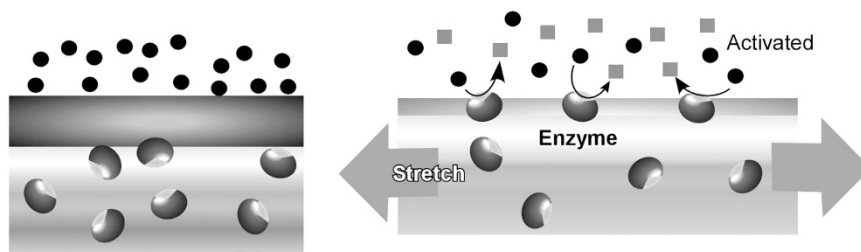
Figure 20 Mechanical stretching of an LbL film containing enzyme molecules (alkaline phosphatase) can initiate the enzymatic reaction. LbL, layer-by-layer.
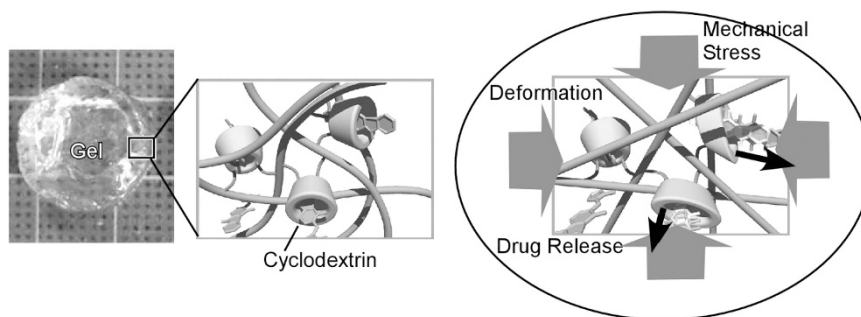
Figure 21 Supramolecular inclusion (host–guest complex) for controlled drug release can be controlled mechanically using gel materials of alginate polymer chains cross-linked with supramolecular host, β-cyclodextrin, as a junction point. Mechanical stresses would be concentrated at the β-cyclodextrin junctions, and their deformation induces release of drug molecules such as ondansetron.

and/or covalent networks develop as interior structures that can transmit external mechanical stimuli to the molecular network. Such structures can be regarded as integrated three-dimensional structures of interface-like networks. Gel materials are widely known as useful drug carriers for controlled release. For example, controlled drug release from gel materials on the application of osmotic pressures are well reported, in which volume and structural changes including shrinkage and swelling induce selective drug release.

Unlike the well-known examples, the example illustrated in Figure 21 uses a novel concept, the mechanical control of supramolecular inclusion (host–guest complex) for controlled drug release.[169,170] The used gel materials were made from alginate polymer chains cross-linked with a supramolecular host, β-cyclodextrin, as a junction point for integrated polymer chains. Therefore, the stresses may be concentrated to the β-cyclodextrin junctions when the entire gel structures are mechanically deformed. The cyclodextrin parts can accommodate shape/size-selected guest drug molecules, which are far different from those used for gel-based drug delivery with rather ambiguous void structures. Ondansetron molecules as a model drug were entrapped within the cyclodextrin cavities linked within alginate gels. The drug-entrapped gel materials were mechanically compressed with up to 50% strain with one-time and five-cycle compression modes. When the gel was repeatedly compressed with the one-time mode at intervals of 1, 4, 7 and 10 h, the release of the guest ondansetron molecules was accelerated. Similarly, five-cycle compression processes after 25, 28, 31, 34, 49 and 52 h resulted in pulsatile releases of ondansetron. Apparently, compression actions (macroscopic mechanical actions) are linked with supramolecular phenomena (guest release from cyclodextrin).

For a more detailed investigation, the binding constant of ondansetron to the cyclodextrin core was evaluated at various strain conditions. The obtained binding constant remains almost the same up to 30% strain. However, higher strain application (to 50% strain) resulted in a drastic decrease of the binding constant, accompanied by a rapid increase in stress. According to molecular dynamics simulation, the release of guest ondansetron from the cyclodextrin core can result from even a small deformation and motional restriction of the cyclodextrin moiety. These calculations and simulations also support the controlled drug release from supramolecular host structures on macroscopic mechanical stimuli.

FUTURE PERSPECTIVES

In this review, we introduce three emerging concepts in nanoscience: (i) nanoarchitectonics; (ii) mechanical control of nano/molecular systems; and (iii) application of these concepts to biology, as seen in mechanobiology. These concepts will allow us to construct functional materials from nano/molecular units to create harmonized functions. Macroscopic mechanical control of nanosystems and molecular functions will bridge motions and actions in our daily life with forefront nanotechnology. We believe that these two different approaches, the bottom-up construction of functional materials from nano/molecular units and the top-down macroscopic mechanical control of nanosystems and molecular functions, would have deep relations to the regulation of biological functions such as cell control and drug delivery. Although the three topics are separately discussed in this review, they are well connected. An important unified concept is the integration between advanced nanotechnology and our daily biological life. These emerging concepts would provide ways to use specialized advanced technology in our life activities.

If we think about the realistic success of these emerging concepts, the contributions of polymer science cannot be avoided. For example, nanoarchitectonics-based fabrications from only small molecular and atomic units would be a difficult process. The utilization of polymer chemistry to extend structural units from small molecules to polymer units through synthetic procedures would provide more comfortable building pieces for nanoarchitectonic construction. One successful

example may be the structural formation of the DNA-origami strategy.[171–174] The appropriate design of DNA strands and their assembly results in well-expected nanostructures. If we expand this methodology to more general polymers, more flexible and ambiguous interactions between polymer units would create soft and adjustable functional nanostructures, which may express smarter and self-adjustable (even self-thinking) functions. The application of polymeric materials to two-dimensional media through assembly within confined media is a good strategy to prepare highly anisotropic, well-designed structures. These possibilities were already demonstrated in illustrative works on polypeptide assemblies[175] and interfacial metal–organic framework structures.[176,177]

To promote and activate science and technology based on these emerging concepts in nanotechnology, the contribution and participation of polymer scientists are crucial. We hope that this description will be of interest to some readers.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

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