Intelligent Nanoarchitectonics for Self-Assembling Systems
Katsuhiko Ariga* and Lok Kumar Shrestha

For the sustainable developments of life and society, various problems such as environmental, energy, and biohealth issues must be solved by a wide range of scientific and technical efforts. Therefore, the fabrication of functional materials and systems with strategic intelligence is required. As seen in the evolution processes in nature, self-assembling processes are capable of creating highly intelligent materials and systems. This task would be taken by an emerging concept, nanoarchitectonics, through the combination of nanotechnology concepts with other scientific disciplines such as materials science, supramolecular chemistry, organic chemistry, and bio-related science and technology. Herein, several examples are presented to overview intelligent nanoarchitectonics for the creation of functional materials and systems mainly through self-assembly in various scale ranges. These examples are classified into several sections according to atom-level, molecular-level, materials-level, and life-level intelligent assembly, where several key items such as atom switch devices, molecular switches, molecular machines, shape-shifting and shape-specified assemblies, and cell control at interfaces are included. Discussions on these examples show a high possibility of the nanoarchitectonics’ approach in intelligent fabrication of functional materials.

1. Introduction

For continuous improvements of life styles and sustainable developments, we have to solve various problems such as environmental,[1] energy,[2] and biohealth issues.[3] These demands are settled by a wide range of scientific and technical efforts including organic and polymer syntheses to create new molecules and polymers,[4] materials processing to fabricate functional structures,[5] energy/materials conversion and catalysis,[6] facile

Professor K. Ariga, Dr. L. K. Shrestha
World Premier International (WPI) Research Center for Materials Nanoarchitectonics (MANA)
National Institute for Materials Science (NIMS)
1-1 Namiki, Tsukuba 305-0044, Japan
E-mail: ARIGA.Katsuhiko@nims.go.jp

Prof. K. Ariga
Department of Advanced Materials Science
Graduate School of Frontier Sciences
The University of Tokyo
5-1-5 Kashiwanoha, Kashiwa, Chiba 277-8561, Japan

The ORCID identification number(s) for the author(s) of this article
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sensing and analysis,[7] energy generation and storage with advanced solar cells,[8] fuel cells,[9] capacitors,[10] and batteries,[11] and biological and biomedical treatments.[12] To accomplish low-cost, environmentally-friendly, and less-emissive systems, these scientific and technical processes have to pursue high efficiency and specificity. In some cases, the multitask nature of operating systems is desirable to achieve multiple functions together from a single or simple materials system.[13] Therefore, the fabrication of functional materials and systems with strategic intelligence has become more and more essential.

Intelligent fabrications are supported on the basis of huge facts and experiences accumulated in past histories, so far. Recent innovative developments in data processing and artificial intelligence have enabled us to get optimized solutions though machine learning.[14] A new page in the history of science and technologies is now opened by intelligence in information technology. Interestingly, such intelligent optimization of functional systems was indeed initiated in nature billions of years ago before we had created artificial intelligence. Natural selection of molecules and materials for self-assembled and self-organized systems in long evolution processes successfully created highly intelligent life forms. Therefore, self-assembling and self-organization processes have potential capabilities for the intelligent construction of functional systems.[15]

Recent developments in science and technology also initiated one distinct discipline, nanotechnology, that enabled us to observe, analyze, and fabricate nanoscopic systems and materials.[16] Developments of nanotechnology have provided lots of knowledge on nanometer-sized materials that can be also used as building blocks for self-assembling process. Therefore, the fusion of self-assembling science and nanotechnology can become a good strategy to intelligently fabricate functional systems with a wide range of materials selection. These tasks would be taken by an emerging concept, nanoarchitectonics (Figure 1).[17]

The importance of combined approaches including self-assembly both in artificial systems and in biological systems with nanoscopic features has been recognized in these decades.[18] Recently, a more comprehensive and unified concept, nanoarchitectonics, has been proposed. The nanoarchitectonics concept was initially proposed by Dr. Masakazu Aono by combining the nanotechnology concept with the other scientific disciplines such as materials science, supramolecular chemistry, organic chemistry, and bio-related science and technology.[19] Based
on the nanoarchitectonics concept, functional materials with nanoscale structural precisions can be fabricated from nanoscale building blocks intelligently using various processes including atomic-/molecular-level manipulation, chemistry-based molecular synthesis and modification, supramolecular self-assembly and self-organization, field-regulated materials arrangement, materials fabrication and processing, and bio-related treatments with crucial assistance of knowledge in nanoscience and nanotechnology. Combining several processes is sometimes advantageous for architecting hierarchic and integrated structures. However, these strategies are highly general and limited to a certain field. In contrast, the nanoarchitectonics concept is applicable for a wide range of research fields such as materials synthesis and production, structural fabrication and arrangement, catalysis, sensing, environmental remediation, energy-oriented application, physical device systems, basic biology, and biomedical applications.

Distinct features of architectonics processes at the nanoscale region that are significantly different from constructions in macroscopic and microscopic scales would be uncertainty and unpredictability. In the nanoarchitectonics processes, molecular and materials organizations might be influenced by uncontrollable thermal fluctuations, nonuniformed statistical distributions, and complicated mutual interactions. A simple summation of individual actions might not decide final answers for the functional materials system. Harmonization of multiple actions and interactions rather than their summation is a crucial factor in the nanoarchitectonics processes. Intelligent selection including possible errors and fluctuations is possible in the production of functional materials by the nanoarchitectonics concept.

Based on these backgrounds, we have selected several examples to overview nanoarchitectonics for the creation of functional materials.
materials systems mainly through self-assembly in various length scales in this Review. These examples are classified into several sections according to atom-level, molecular-level, materials-level, and life-level intelligent assembly, where several key items such as atom switch devices, molecular switches, molecular machines, shape-shifting and shape-specified assemblies, and cell control at interface are included. Although strategies based on the nanoarchitectonics concept are not fully established yet, discussions on these examples will show high possibilities of the nanoarchitectonics approach in intelligent fabrication of functional materials and systems.

2. Atom-Level Intelligent Assembly

Motion, diffusion, precipitation, and assembly of atoms would result in the modulation of electronic properties of the body materials, which can be applied to architect intelligent devices. This conceptual paradigm has been realized by atomic switch approach in which diffusion and assembly of atoms upon electrochemical processes can switch “on” and “off” electrical devices.\(^{[31]}\) As shown in Figure 2, electrodes composed of \(\text{Ag}_2\text{S}\) and Pt are separated with \(\approx1\) nm gap. Ag ions are reduced into Ag atoms by electrons supplied from the Pt electrode through a fine tunneling current upon application of a negative bias to the Pt electrode. Assembly of the created several Ag atoms induces formation of conductive cluster bridges between the electrodes’ gap, resulting in switching “on” the device. Alternately, applying positive bias voltage to the Pt electrode causes dissolution of Ag atom bridge by the oxidation of Ag atoms to Ag ions, resulting in switching “off” the device. Atom-level assemblies can control device-level operations. Such atomic devices can be also architected as gapless electrode systems using solid polymer electrolytes as supporting materials.\(^{[32]}\)

Further intelligent operations of atom-level assemblies were realized as inorganic synaptic devices including short-term plasticity and long-term potentiation, as demonstrated by Ohno et al. (Figure 3).\(^{[33]}\) These intelligent processes can be mimicked simply by modifying the repetition frequencies of input pulse. Upon application of input pulses to the \(\text{Ag}_2\text{S}\)-based gap-type atomic switches with low frequency such as repetition with interval of 20 s, formation and dissolution of conductive Ag cluster bridges between electrodes are reversibly induced, resulting in short-term plasticity. In contrast, the application of short-interval (2 s) pulse to the same device system inputs leads to the formation of long-life stable conductive Ag bridges. Long-term potentiation can be realized by the latter operations. These examples indicate that control of atom-level assembly can even mimic the mammalian nervous intelligent systems.

Nanosopic switches with atomi-level assemblies are motifs and advantageous for brain-like intelligent computational systems by further hierarchic materials assemblies. For example, one billion atomic switches were interconnected through the entangled network of Ag nanowires, as demonstrated by Stieg and coworkers.\(^{[34]}\) The architected hierarchic assembly works as a mimic of neuromorphic device. Collective responses upon stimuli inputs were observed with the network activation and passive harmonic generation.

Atomic switches could also work in physical devices but their actual operation mechanisms are mostly working with chemical mechanisms. Hasegawa and coworkers recently reported the effect of predoping ions on operation time dependence with drastic improvements of decay behaviors in short-term plasticity operations,\(^{[35]}\) for example, the predoping of Ag ions within the ionic transfer layer (\(\text{Ta}_2\text{O}_5\)) gap of atomic switches. The concentration of Ag ions in the \(\text{Ta}_2\text{O}_5\) layer shifts the levels of electrochemical potential, which modifies necessary bias and speeds of cluster formation and dissolution upon changes in precipitation and diffusion of atoms and ions. Accordingly, the time constants of time-dependent operations can be tuned and optimized. The latter factor is indispensable for the development of artificial intelligent systems. As chemical modification of atomic switch components, thermally staticive switches were accomplished using polyvinyl alcohol film incorporated with Ag salt as a solid polymer electrolyte between Ag and Pt electrodes, as reported by Krishnan et al.\(^{[36]}\) This polymer-based assembled design exhibited operation tolerance in wider temperature ranges (20–70°C) that can be explained by water evaporation behavior and segmental mobility.

The similar processes of atom diffusion and assembly can be used for intelligent controls of the precise number of atoms in solid electrolyte nanodots. Hasegawa and coworkers demonstrated this nanoarchitectonics strategy using \(\alpha\)-\(\text{Ag}_2\text{S}\) nanodots with a finite number of nonstoichiometric excess dopants as the model materials with good agreements between experimental trials and theoretical expectations.\(^{[37]}\) The numbers of dopant

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**Figure 2.** An atomic switch device in which diffusion and assembly of atoms upon electrochemical processes can switch on and off electrical devices. In this example, electrodes composed of \(\text{Ag}_2\text{S}\) and Pt are separated with \(\approx1\) nm gap.

**Figure 3.** Inorganic synaptic devices including short-term plasticity and long-term potentiation functions.
Atoms can be manipulated through regulation of electrochemical potentials. The same research team also demonstrated regulations of resistivity through electrochemical removal of dopant atoms from the nanodots. As shown in Figure 4, intelligent regulation of dopant atom removal through layer-by-layer self-assembled growth of Ag nanowire is conducted under scanning tunneling microscope tip with appropriate bias condition. The Ag nanowire grows upon the reduction of Ag ion to Ag atom at the interface of Ag$_{2+\delta}$S nanodot and Ag nanowire due to electron supply from Ag nanowires. This electrochemical manipulation of atom assembly is effective to control material's resistivity upon the precise control of dopant atoms.

### 3. Molecular-Level Intelligent Assembly

Molecular machines can be regarded as molecular-level intelligent objects because of their machine-like intelligent functions such as directionally regulated rotations. Not limited to the motional molecular machines, colorimetric molecular switches and molecular receptors exhibit intelligent molecular functions. In this section, several recent examples of molecular machines and molecular switches are shortly introduced, and then dynamic operations of the assemblies of molecular machines and molecular receptors are discussed.

Molecular switch functions are not limited to responses to a single input. Molecular switches toggling between multiple states upon responses to different stimuli would be useful for intelligent switching and sensing. In this case, molecules have to take multiple states depending on signal inputs and surrounding conditions. Recently, Payne et al. successfully accomplished systems with five different optical outputs that can be induced through the coupling of two different oxidation states with two different charge transfer states within one macrocyclic scaffold. As shown in Figure 5, a resorcinarene macrocycle scaffold with mesosubstituents, 3,5-di-i-butyl-4-hydroxyphenyl groups show multiple photoresponsivity and multistability.

![Figure 4. Regulation of the dopant atom removal through layer-by-layer self-assembled growth of Ag nanowire under scanning tunneling microscope tip with an appropriate bias condition where the Ag nanowire grows upon the reduction of the Ag ion to Ag atom at the interface of Ag$_{2+\delta}$S nanodot and Ag nanowire due to electron supply from Ag nanowires.](image1)

![Switching Process](image2)

A: 2,3-Dichloro-5,6-dicyano-1,4-benzocoumarin (1 eq.) or Irradiation (285 nm)  
B: 2,3-Dichloro-5,6-dicyano-1,4-benzocoumarin (4 eq.)  
C: Trifluoroacetic acid  
D: Potassium carbonate or Pyridine  
E: Trifluoroacetic acid/Irradiation (285 nm)  
F: Zn metal/acetic acid/90 °C  
G: 2,3-Dichloro-5,6-dicyano-1,4-benzocoumarin/Trifluoroacetic acid

![Figure 5. A resorcinarene macrocycle scaffold with mesosubstituents, 3,5-di-i-butyl-4-hydroxyphenyl groups show multiple photoresponsivity and multistability.](image3)
They also accomplished shape-memory switching of assembled nanopores, using a supramolecular organic framework composed of biphenyl-3,30,5,50-tetracarboxylic acid and 1,2-bis(4-pyridyl)ethane. This porous dodecatuple intercatenated framework is formed with rather weak interaction, hydrogen bonding, and is not strong enough to maintain permanently fixed pore structures. Therefore, structural transition between the porous orthorhombic phase and porous empty tetragonal phase is regulated cooperatively upon thermal stimuli and guest inclusion. This structural transition is made via a ferroelastic transition including pyridyl ring-flipping accompanied with switchable sorption capabilities. This assembled system is also useful for the design of intelligent actuators including artificial muscles.

Significant developments of probe microscopes enabled us to observe molecular shapes, structures, and motions. As typical examples, the observations of vehicle-like molecules (molecular cars/nanocars) are now hot research targets, leading to a worldwide race between molecular cars. Accordingly, evaluations on the motions of molecular machines also become highly possible, for example, Hill coworkers visually demonstrated surface chiral directionality switching of current-driven supramolecular motor (Figure 6). The supramolecular motor is composed of assembled dimers of platinum–porphyrin derivative molecules. Bias application to the supramolecular motor on a Au(111) surface using the tunneling current of a scanning tunneling microscope can rotate the supramolecular motor to a particular direction (clockwise and counterclockwise). Rotational directions are decided by the surface chirality of the assembled dimer, which is inverted through in situ intramolecular rearrangements. Although this motor is simple dimer assembly, it may mimic biological supramolecular motors. Significance of this research can also be seen in the demonstration of reconfiguration of molecular motors upon surrounding environments and applied stimuli, which may lead to ways to architect intelligent molecular machines from simple molecular units with less extensive efforts of organic synthesis.

Playgrounds of molecular machines are not limited to solution and solid surfaces. Research on molecular machines on soft surfaces such as liquid interfaces and membrane surfaces would be attractive targets with environmental similarity to biological applications. We have been working on the regulation of molecular machines at the air–water interface with and without matrix amphiphiles. Molecular machines and molecular receptors embedded at the air–water interface are working within their monolayer assembly. Therefore, their motional features are much influenced by the surface dynamic nature and viscoelasticity. As shown in Figure 7, rotational behaviors of the molecular rotor, composed of 4-farnesyloxyphenyl-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (BODIPY rotor), were investigated at various interfacial conditions with mixed amphiphilic monolayers. The BODIPY rotor emits fluorescence without rotation at its locally exited state. In contrast, the BODIPY rotor has intramolecular rotation without fluorescence emission in the twisted intramolecular charge transfer state. Fluorescence emissions become sensitive indicators of intramolecular rotation of the molecular rotor. For example, free rotation of the BODIPY rotor in solution accompanies with no fluorescence emission, but motional freezing of the BODIPY rotor deep within lipid bilayer membranes can be confirmed by fluorescence emissions. At the air–water interface with the matrix amphiphile monolayer, monitoring of fluorescence emission from the surfaces sensitively indicates intramolecular rotational activities of the BODIPY rotor molecule depending on surface

![Figure 6](image-url). Bias application to the supramolecular motor on a Au(111) surface using the tunneling current of a scanning tunneling microscope can rotate the supramolecular motor to a particular direction (clockwise and counterclockwise).
pressures. The systematic research revealed various influential factors such as 2D surface pressures and compressibility of the matrix monolayer. The accumulated knowledge would be also useful for consideration of necessity factors on the use of intelligent molecular machines in biological membrane media.

Comparisons of the BODIPY rotor behaviors with other molecular machine behaviors at the air–water interface notice the importance of machine molecular designs. In case of another amphiphilic molecular rotors, julolidine derivatives, their intramolecular rotation is not restricted by the compression

Figure 7. Rotational behaviors of molecular rotor, composed of 4-farnesyl oxyphenyl-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (BODIPY rotor), investigated at various mechanical media such as solution, lipid bilayer, and amphiphilic monolayer.
of monolayer (Figure 8).[52] The rigid rotating part is smaller than the julolidine moiety of the molecule, and thus the freedom of intramolecular rotation is preserved even under tightly assembled conditions.

For some molecular motions other than rotation, motions and deformation of molecular machines embedded at the air–water interface can be controlled by 2D mechanical processes when motional moiety is sterically large enough. For example, dihedral angles of a rigid binaphthyl moiety of amphiphilic binaphthyl molecules can be tuned by 2D surface pressures, leading to molecular pliers functions.[53] Confirmations of a xylose molecule with pyrene arms can be drastically controlled with the modulation of optical properties by compression of its monolayer.[54] Motions and functions of molecular machines at the air–water interfaces depend strongly on the intrinsic flexibility of the molecular machine themselves.[55]

The assembling systems of molecular machines at the dynamic interface such as the air–water interface provide another intelligent feature, operation of molecular machines by macroscopic mechanical motions.[56] The air–water interface has totally different dimensions in the lateral direction and thickness direction. Therefore, macroscopic motion at lateral direction can be connected with molecular nanoscopic motions in the thickness direction. Through placing molecular machines as their monolayer assembly at the air–water interface, the macroscopic motions of compression and expansion of the monolayer in tens of centimeter levels can be converted into the control of nanometer-scale conformational changes of machine molecules confined within nanometer-level thin films. As shown in Figure 9, repeated reversible captures of aqueous guest molecule by the molecular machine, so-called steroid cyclophane, with a central ring (1,6,20,25-tetraaza[6.1.6.1]-paracyclocphane cyclic core) and four rigid cholic acid walls were demonstrated upon macroscopic mechanical deformation of their monolayer.[57] The steroid cyclophane machines adopt open conformation through contacting their hydrophilic faces of colic acid walls. Conversion from open to cavity conformation was induced by mechanical compression of the monolayer. Accordingly, naphthalene-type guest molecule can be captured in the cavity of the steroid cyclophane machine. In turn, mechanical expansion

Figure 8. Intramolecular rotation of amphiphilic molecular rotors, julolidine derivatives, is not restricted by compression of monolayer. The rigid rotating part is smaller than the julolidine moiety of the molecule, and thus the freedom of intramolecular rotation is preserved even under tightly assembled conditions.
of the monolayer converts the cavity to open conformation, accompanying the release of the guest molecule. Molecular-level functions of guest capture and release are controlled by visual-size material motions. The proposed interfacial systems for molecular machine operations would be regarded as intelligent connections between human-level motions and nanotechnological functions.

Conformational controls of functional molecules by macroscopic mechanical motions at the air–water interface can be used for more delicate tuning of molecular receptors (Figure 10). Mechanical tuning of chiral molecular receptor, N-substituted cyclen containing a 1,4,7,10-tetraazacyclododecane core with four cholesteric, at the air–water interface resulted in continuous shifting of the chiral environment at the aqueous surface of the monolayer.[58] Accordingly, enantiomeric binding of amino acids from aqueous subphase exhibited sensitive pressure dependence. In the case of valine guest, binding preference between L- and D-isomer was inverted upon the changing of applied 2D surface pressures. The same concept was applied to another molecular receptor, cholesterol-substituted triazacyclononane, at the air–water interface to discriminate uracil and thymine derivatives.[99] Optimization of the molecular receptor conformation upon mechanical tuning recognizes that uracil over thymine achieved 64-time difference although these two nucleic acid bases have only one-methyl-group difference.

The exemplified mechanical tuning of molecular receptors can be regarded as a new mode of molecular recognition systems, as shown in Figure 11. The most fundamental mechanism for molecular recognition is based on the formation of one most stable state between guest and host (receptor) (Figure 11A), as typically seen in molecular recognitions by crown ethers, cyclodextrins, and the other traditional hosts.[60] The switching mechanism on molecular recognition was introduced by Shinkai et al., using the photoisomerization of azobenzene in receptor structures (Figure 11B).[61] A few multiple states (two or three) of the receptor structures are toggled upon inputs of external stimuli. Switching of molecular structures by external stimuli such as light irradiation, redox, and chemical reactions is also the basics of molecular machine controls by external factors.[62] Unlike these two former modes, molecular tuning modes for molecular recognition rely on the continuous shifting of receptor structures (Figure 11C).[63] The most desirable answer (molecular recognition with purpose) can be selected from numerous candidates of receptor conformers tuned at nanoscopically confined media. This mode is also regarded as a new approach to utilize a wide range of conformational flexibility of organic molecules.

Molecular-level nanoarchitectonics is of course not limited to such chemistry-based approaches. Sophisticated physical fabrication to handle molecules such as molecular beam epitaxy would also have important contributions.[64] Various biological machineries such as proteins and biological motors can be excellent components to architect intelligent functions.[65] Combining these approaches from different fields would create molecularly organized systems with intelligent functions.

4. Materials-Level Intelligent Assembly

Materials formed through molecular assembly often show flexible and stimuli–responsive intelligent functions. In this section, several examples on material-level intelligent assemblies are introduced. Seki has summarized photoinduced materials motions at the surface of thin-layer assemblies of photochromic molecules in his recent review article.[66] The research targets of photochromic molecules are mainly focused on their color changes. Because photoisomerization often accompanies changes of various molecular status such as conformation and dipole moments as typically seen in cis–trans isomerization of azobenzene units, collective changes at their assemblies can induce materials’ motions even in the visible range upon molecular photoisomerization. As shown in Figure 12, Ichimura et al. successfully controlled materials motion both in lateral and in vertical direction. In case of lateral motion control (Figure 12A), on-demand lateral motions of a droplet of olive oil on the azobenzene-functionalized self-assembled monolayer were realized only upon photoirradiation of the surface.[67] To provide enough spaces for photoisomerization, azobenzene units were immobilized on a cyclic calix[4]:resorcinarenes scaffold. Irradiation of ultraviolet (UV) and visible light fluxes in designed patterns resulted in a gradient in the surface energy (surface tension). The continuous modulation of the irradiation patterns induces lateral sliding motion of a visible-size droplet of
olive oil. Because this motional control is based on remote light irradiation, the similar system can be applied to a liquid system in various shapes. For example, sliding motions of liquids within a cylinder are obtained by modifying the interior of a cylinder by the azobenzene-containing self-assembled monolayers.

As controls of macroscopic-level materials orientation in vertical direction, they also reported a pioneering concept, command surface (Figure 12B).[68] This concept is based on transfer of structural information from ultrathin monolayer to the liquid crystalline layer with visible-size thickness. The photosensitive azobenzene ultrathin film such as its Langmuir–Blodgett film and self-assembled monolayer was first immobilized on a solid surface with a thick layer of bulk nematic liquid crystals. Photoirradiation onto the azobenzene thin film induces isomerization of azobenzene and its alignment. Photoisomerization of azobenzene from cis form to trans form with vertical orientation of azobenzene assembly with respect to the substrate leads to the orientation transition of the azobenzene layer from planer to homeotropic. The orientation of much thicker liquid crystalline films can be controlled upon command of the ultrathin surface monolayer of azobenzene units.

The intelligent design of self-assembled structures with multiple components sometimes makes the resulting materials express intelligent functions. Leong and coworkers fabricated intelligent assemblies for cancer-targeted drug delivery systems through the heterogeneous assembly of 2D material, MoS$_2$ nanosheet, biological deoxyribonucleic acid (DNA) components, anticancer drug upon layer-by-layer assembly, sequence-specific DNA hybridization, and the selective accommodation of drug molecules.[69] The assembled structures form stacked Testudo-like-layered MoS$_2$ superstructures, and DNA assembly can carry cancer drugs and their responsive release. The MoS$_2$ nanosheets have defect sites of S atom to which S-atom-terminated DNA strands can be anchored stably. The addition of mutually complementary DNA oligonucleotides induces spontaneous layer-by-layer assembly of DNA-appended MoS$_2$ nanosheets. The formed layer-by-layer structure of rigid 2D nanosheets and soft DNA layers are suitable for accommodation of guest drugs such as doxorubicin with high protection as nano-Testudo superstructures from in vivo and intracellular degradative enzymes. In addition, the linker DNA oligonucleotides were designed to have ATP aptamer sequence. When these assemblies were exposed to ATP-rich conditions at the vicinity of cancer cells, the layer-by-layer assembled structures were disassembled to release drug molecules. These designed assemblies of rigid 2D materials and stimuli-response DNA accomplish two necessary factors of protection and stimuli-selective release of drugs.

Molecular assembly processes have surprising capabilities to produce materials with a huge variety of shapes only from very simple molecular sources. For example, liquid–liquid interfacial precipitation[70] of 0D fullerene molecules (C$_{60}$ and C$_{70}$) provides 1D tubes, rods, or whiskers.[71] 2D nanosheets with hexagonal and other shapes,[72] 3D cubes[73] and ellipsoids,[74] and more hierarchic and integrated structures.[75] As an example of microstructures with surprising shapes, hole-on-cube structures were prepared by the one-step self-assembly of C$_{70}$ molecules (Figure 13).[76] In addition, intentional opening and closure of the holes on the surface of cubes and selective particle trapping
to the holes were demonstrated as intelligent functions. The hole-on-cube C\textsubscript{70} assemblies were synthesized by dynamic-type liquid–liquid precipitation through the rapid addition of a mesitylene (good solvent) solution of C\textsubscript{70} into tert-butyl alcohol (bad solvent). Although the conducted procedure is very simple, assemblies with intergraded shape, one big hole on every face of the regular cubic structure, can be obtained. The open holes can be intentionally closed by addition of excess C\textsubscript{70} molecules. The closed holes can be again intentionally opened by local irradiation of electron beams. Because the interior of these holes have hydrophobic natures with sp\textsuperscript{2} π-electron-rich carbons, the selective inclusion of carbonized microparticles over conventional polymer resin microparticles was demonstrated. The hole-on-cube C\textsubscript{70} assemblies would be capable of selectively removing toxic particles such as PM 2.5.

Recently, Minami coworkers reported the living-creature-like behaviors of self-assembled objects simply composed of two fullerene deliveries, pentakis(phenyl)fullerene and pentakis(4-dodecylphenyl)fullerene (Figure 14).\textsuperscript{[77]} Under well-considered conditions, egg-like spherical structures were first formed, and tails grew on the surface of spheres after the appropriate incubation time period. This behavior resembles well-known biological events, shape shifts from eggs to tadpoles of frogs. Therefore, the observed phenomenon is regarded as a novel phenomenon, supramolecular differentiation, as analogous with embryonic development. This supramolecular differentiation is based on time-programmed assembly at the liquid–liquid interface followed by homogeneous growth. Spherical microparticles were spontaneously formed from these two fullerene derivatives at the interface between isopropyl alcohol and toluene. A patch-like domain of pentakis(4-dodecylphenyl)fullerene phase separated gradually on the surface of the sphere body of pentakis(phenyl)fullerene. Appearance and the numbers of the phase-separated patch domains are time dependent, i.e., the phase separation occurred in a time-programmed fashion. From one patch domain, one tubular tail of pentakis(4-dodecylphenyl)fullerene then grew, resulting in the formation of a tadpole shape. This example indicates that even fundamental spontaneous processes such as self-assembly and phase separation in time-controlled modes can mimic intelligent biological phenomenon, shape differentiation, only from simple molecular components.

5. Life-Level Intelligent Control on Self-Assembly

Higher intelligent functions are often seen in biological events where multiple processes and their equilibrium are integrated.
through self-organization. Self-organization sometimes works far from equilibrium with the consumption of external energy whereas self-assembly occurs toward thermodynamic equilibrium. As recently reviewed by He and Xu, intermediate process between self-assembly and self-organization can be referred as instructed assembly. Instructed assembly corresponds to the formation process of ordered supramolecular structures, including at least one triggered event such as chemical reaction, enzymatic reaction, and ligand–receptor interaction (Figure 15). The resulting assembled structures often depend on the path and history of triggered events but remain even after energy dissipation past unlike self-organization. Because the instructed assembly of proteins is important key in processes, the concept of instructed assembly often becomes an intelligent strategy for biological controls including cell fates and the resulting therapy. Natural biological systems utilize the instructed assembly, as seen in the formation of apoptosomes triggered by dephosphorylation reaction. As an artificial approach, they demonstrated instructed self-assembly of cholesterol conjugates with the trigger of enzymatic reaction toward selectively inhibiting cancer cells.

Cell regulation can be done by various self-assembled materials, but they are not limited to small molecular assemblies within cells. Macroscopic contact with larger self-assembled materials is also an effective method to control cell differentiation and cell fate, depending on mechanical properties, orientation, and arrangement of the surface materials. Minami et al. investigated C2C12 myoblast cells on a surface with highly aligned fullerene nanowhiskers for their cellular orientation and differentiation to muscle cells (Figure 16). Rigid fullerene nanowhiskers were made by liquid–liquid interfacial precipitation of C60 molecules, followed by transfer to a solid surface by the Langmuir–Blodgett method to form a highly aligned 2D arrangement. Aligned 1D fullerene nanowhiskers significantly affect the direction of muscle fibers formed during myogenic differentiation. Because myotubes and muscle fibers work as linear actuators, parallel 1D growth of myoblasts and myotubes was promoted. Cell fusion index values estimated from the ratio of multinuclear myosin heavy-chain positive cells to the total number of nuclei became 23.2% on the aligned fullerene nanowhiskers, whereas the corresponding value on a bare glass remained only at 12.3%. The aligned fullerene nanowhiskers would be capable of myoblast fusion. Further investigation on cell differentiation revealed that significant upregulation of myogenic genes was induced through contact with microscopically assembled objects, aligned fullerene nanowhisker arrays. Because microscopic objects prepared through self-assembly nanoarchitectonics have high potentials to have various structures and arrangements, it can overcome the drawbacks of limited shape selections in the other nanocarbons such as carbon nanotubes and graphenes. Approaches based on self-assembly nanoarchitectonics would be promising strategies for cell controls and tissue engineering.

In sharp contrast to the previous example, Minami et al. investigated cell behaviors at liquid–liquid interfaces without...
any solid objects as the opposite case (Figure 17). Interactions between cells and substrate (interface) are expected to be reduced at the microenvironment of a fluidic liquid–liquid interface, which would provide much different effects on cellular differentiation. In fact, the suppression of myogenic differentiation of mammalian cells was observed in cultures of C2C12 myoblast cells at interface between aqueous culture solution and fluorocarbon organic layer. The expression level of myogenin, myogenic regulatory factors family gene, was significantly suppressed, implying that fluidic liquid interfacial environments induce the attenuation of myogenic differentiation. Physical modification of contacting environments can be effective control for cellular adhesion, proliferation, and differentiation. These interfacial experiments also indicate that interfacial processes are strategies efficient for investigation of effects of mechanical forces on cells for the field of mechanobiology.

Liquid–liquid interface between aqueous culture layer and fluorocarbon organic layer also provides media for tailored protein self-assembled monolayers. At the surface of the spontaneously formed protein monolayers, mechanosensing properties of mesenchymal stem cells can be modulated for cell spreading, as reported by Jia et al. (Figure 18). At the liquid interface between aqueous culture medium and perfluorocarbon fluid layer, a monomolecular protein nanosheet is spontaneously self-assembled. The protein nanosheet is suspended at the liquid–liquid interface and does not have any vertical constraint. Based on combined interactions of hydrophobic interaction and hydrogen bonding, an anisotropically developed network with...
strong in-plane interaction and weak out-of-plane interaction supports the freestanding protein monolayer film. Although the formed protein nanosheets have a soft nature, they are capable of fine regulation of cell spreading depending on their packing status. Appropriate stiffness of the assembled protein nanosheets can trigger cell spreading, adhesion growth, and yes-associated protein nuclear translocation on the basis of the molecular clutch model. Because integrin and the protein nanosheet move together, any resistances do not work between integrin and the focal adhesion molecules. Tensionless interaction results in a much softer interaction for cells as compared
with the other solid substrates. Cell culturing at solidless liquid–liquid interfaces may give unique intuitions for materials’ designs for implants and regenerative therapies.

6. Perspectives

Biological systems use long-time processes for billions of years on the natural selection and optimization of spontaneously occurring huge possibilities and successfully create highly intelligent systems of highly evolved life forms. The evolution processes rely on self-assembly and self-organization of molecules and their aggregates. Self-assembly and self-organization processes are highly capable of constructing intelligent systems; however, it may need long time. Therefore, the addition of artificial and intentional essences from nanotechnology to these spontaneously occurring self-assembling systems much accelerates the creating process of intelligent systems. Therefore, the nanoarchitectonics concept including essences and features of nanotechnology and supramolecular assembly might be the methodology highly suitable for the production of functionally intelligent materials.

In this short Review, various possibilities of intelligent functional materials based on nanoarchitectonics processes including atom-level assemblies, molecular-level assemblies, material-level assemblies, and life-level assemblies are exemplified (Figure 19). Intelligent functions can be observed with features of self-responsive output and systematic relays of...
functions in all the size regions. Even with precipitation, diffusion and assembly of atoms can mimic brain-like functions of the mammalian nervous intelligent, short-term plasticity and long-term potentiation. A single molecule is intelligently working as a machine depending on external stimuli and its assemblies at dynamic interfaces can be operated by hand-motion-like macroscopic mechanical actions. Controlled assembly of molecules exhibits a novel phenomenon, supramolecular differentiation, as analogous with embryonic development. Intentionally prepared molecular assemblies of fullerene nanowhiskers and spontaneously assembled weak monomolecular protein nanosheets can regulate cell spreading, adhesion growth, proliferation, and differentiation. The nanoarchitectonics concept based on self-assembly under uncertainties and thermal fluctuations can work for the creation of life-like intelligent systems and is capable of controlling intelligent life activities.

The nanoarchitectonics approaches with self-assembling processes would be much more intelligent than it used to be expected. From atoms to life forms, they assembled as the integration of various physicochemical integrations and processes and sometimes result in an optimized system on the basis of wise natural selections from huge possibilities. These processes may somehow resemble the approaches of artificial intelligence to estimate optimum solutions using huge sets of data. So far, research approaches on self-assemblies and their extensions have been done within the limited size ranges separately. Total architectonics approaches bridging from the atom-/molecular-level unit to life-level macroscopic organization have not been fully explored although nature uses this size-bridged approach in long-time evolution processes. Some approaches combining atomic-/molecular-level motions and materials’ systems have been somehow initiated[83] that would lead to the creation of size-bridged artificial intelligent systems.

Instead of long evolution, we now have computer-based technology to handle the huge amount of information in surprisingly short periods. Intelligent approaches for materials’ design and functionalization have been widely proposed on the basis of big data science and sophisticated computation. This can be somehow regarded as a rapid selection process from huge amounts of possibilities. Therefore, introduction of the artificial intelligent approach to experimental efforts would lead to the significant developments on the creation of functional materials systems with the nanoarchitectonics concept with total construction of intelligent materials from nanosized bottom units.

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Conflict of Interest
The authors declare no conflict of interest.

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