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Molecular Robots with Sensors and Intelligence

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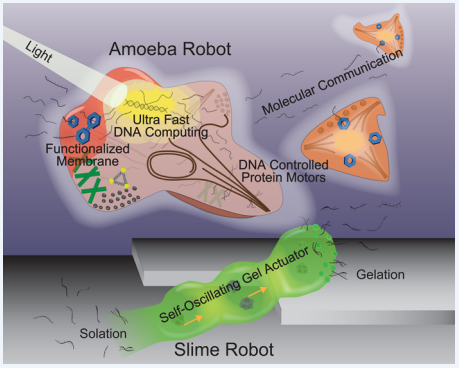
CONSPECTUS: What we can call a molecular robot is a set of molecular devices such as sensors, logic gates, and actuators integrated into a consistent system. The molecular robot is supposed to react autonomously to its environment by receiving molecular signals and making decisions by molecular computation. Building such a system has long been a dream of scientists; however, despite extensive efforts, systems having all three functions (sensing, computation, and actuation) have not been realized yet.



This Account introduces an ongoing research project that focuses on the development of molecular robotics funded by MEXT (Ministry of Education, Culture, Sports, Science and Technology, Japan). This 5 year project started in July 2012 and is titled "Development of Molecular Robots Equipped with Sensors and Intelligence".

The major issues in the field of molecular robotics all correspond to a feedback (i.e., plan−do−see) cycle of a robotic system. More specifically, these issues are (1) developing molecular sensors capable of handling a wide array of signals, (2) developing amplification methods of signals to drive molecular computing devices, (3) accelerating molecular computing, (4) developing actuators that are controllable by molecular computers, and (5) providing bodies of molecular robots encapsulating the above molecular devices, which implement the conformational changes and locomotion of the robots.

In this Account, the latest contributions to the project are reported. There are four research teams in the project that specialize on sensing, intelligence, amoeba-like actuation, and slime-like actuation, respectively. The molecular sensor team is focusing on the development of molecular sensors that can handle a variety of signals. This team is also investigating methods to amplify signals from the molecular sensors. The molecular intelligence team is developing molecular computers and is currently focusing on a new photochemical technology for accelerating DNA-based computations. They also introduce novel computational models behind various kinds of molecular computers necessary for designing such computers. The amoeba robot team aims at constructing amoeba-like robots. The team is trying to incorporate motor proteins, including kinesin and microtubules (MTs), for use as actuators implemented in a liposomal compartment as a robot body. They are also developing a methodology to link DNA-based computation and molecular motor control. The slime robot team focuses on the development of slime-like robots. The team is evaluating various gels, including DNA gel and BZ gel, for use as actuators, as well as the body material to disperse various molecular devices in it. They also try to control the gel actuators by DNA signals coming from molecular computers.

1. INTRODUCTION

Since July 2012, we have been conducting a 5 year research project titled "Development of Molecular Robots Equipped with Sensors and Intelligence", supported by a Grant-in-Aid for Scientific Research on Innovative Areas funded by MEXT (Ministry of Education, Culture, Sports, Science and Technology, Japan). The project focuses on the emerging interdisciplinary field of molecular robotics with the ultimate goal of creating a functional molecular robot.

The ultimate goal of molecular robotics is to construct robots composed of devices such as sensors, computers, and actuators, which are all implemented as molecular devices. The molecular robots are supposed to react autonomously to their environment by receiving molecular signals and making decisions with molecular computers. Building such an autonomous molecular system has long been a dream of scientists; however, despite extensive efforts, systems having all the three functions—

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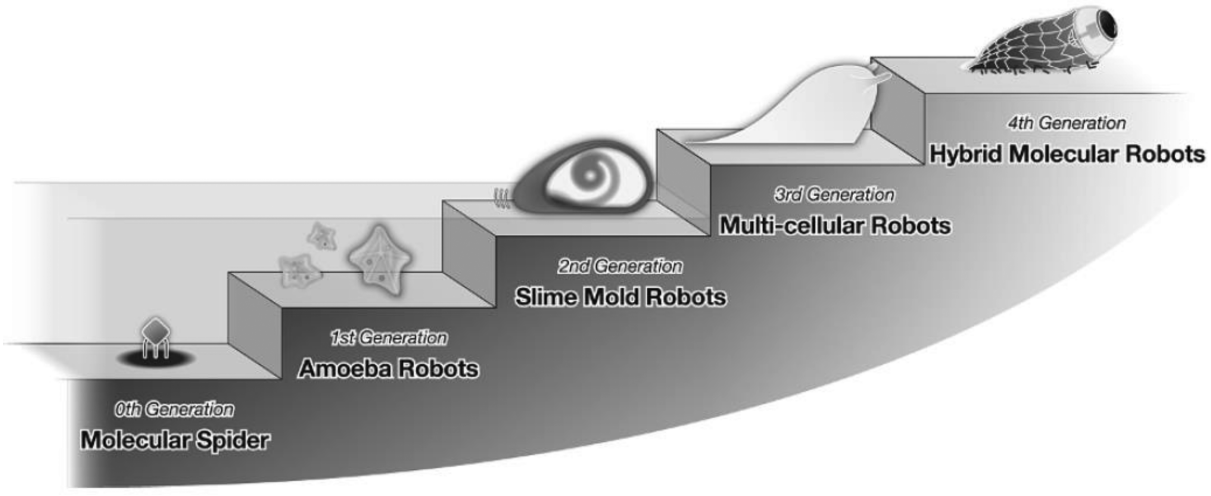

Figure 1. Evolution of molecular robots.

sensing, computation, and actuation—have not been realized yet.

Here, we present our vision of molecular robotics since it helps describe the direction of our project.[1] Before the start of our project, we had envisioned how molecular robots would evolve (Figure 1). The current (0th) generation of molecular robots consists of single molecules such as DNA spiders, which depend on Brownian motion for achieving their function including locomotion.[2] Molecular robots of the first generation, called "the amoeba robots", are expected to overcome this limitation of intrinsic randomness through compartmentalization. By encapsulating molecular devices in a small compartment made of a lipid bilayer, we are able to direct and accelerate molecular reactions toward an intended direction. Encapsulated molecular motors will be used to induce conformational changes of body liposomes or even their movements. The "slime mold robots" are the second generation of molecular robots. The slime robots will be made of soft matter, such as a gel, to contain various molecular devices with spatial distribution. The gel itself may work as actuator; thus, it will move on the millimeter scale with a writhing motion, thereby overcoming the scale limitation of the amoeba robots. This project focuses on developing the first and second generations within 5 years. The third and fourth generations shown in Figure 1 will be discussed in the last section.

Our project consists of four research teams: (1) The *molecular sensor team* focuses on the development of molecular sensors that can handle a variety of signals. This team also investigates methods to amplify signals from the molecular sensors. The team's contributions will be summarized in section 2. (2) The *molecular intelligence team* develops molecular computers and is currently focusing on accelerating reactions for molecular computing, a new photochemical technology for accelerating DNA-based computations. The team also introduces novel computational models behind various kinds of molecular computers and methods of numerical simulation necessary for designing such computers. These contributions will be summarized in section 3. (3) The *amoeba robot team* aims at constructing a molecular robot prototype of the first generation. The team is trying to incorporate motor proteins, including kinesin and microtubules (MTs), for use as actuators implemented in a liposomal compartment as a robot body. They also try to develop a methodology to link DNA-based computation and molecular motor control. The contributions of the amoeba team will be presented in section 4. (4) The *slime robot team* focuses on the development of second generation robots. This team is evaluating various gels, including DNA gel and BZ gel, for use as actuators, as well as the body material to disperse various molecular devices in it. The team also tries to control the gel actuators by DNA signals coming from molecular computers. The contributions of the team will be described in section 5.

2. MOLECULAR SENSORS

DNA nanotechnology, such as DNA origami, is a powerful technology for designing defined 2D- and 3D-nanostructures. For example, it has been reported that a DNA nanorobot with controllable conformation could be used for targeted drug delivery.[3] Recent studies of RNA nanotechnology also revealed that a variety of 2D- and 3D-RNA nanostructures can be constructed by employing a set of RNA structural motifs.[4] Those DNA/RNA-based nanostructures can react to several stimuli (e.g., light, nucleic acids, and proteins) and control their structures and functions depending on the environment.

The molecular sensor team is conducting research in two main directions: (1) sensing a variety of signals by employing bio-nanostructures and (2) converting sensed information to output molecular signals which can be used by computers and actuators of molecular robots. Such sensor modules generated by molecular design or in vitro evolution techniques can be used not only to control molecular actuators and other devices in molecular robots, but also to construct gene expression regulatory devices both in vitro and in living cells. The DNA origami framework together with high-speed atomic force microscopy (HS-AFM) are employed to visualize a variety of biochemical reactions with single molecule resolution.[5]

2.1. DNA Nanotechnology to Design Sensory Devices

There are several approaches to utilize designed DNA- or RNA-based nanostructures to detect environmental signals. Light is one of the most fundamental signals, and several studies have reported that DNA nanostructures can be controlled by light. For example, robust and photocontrollable DNA capsules using azobenzenes have been designed by Tanaka et al. Their DNA nanostructure can be decomposed by

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irradiation of UV-light.[6] In another example, Yang et al. demonstrated reversible assembly and disassembly of 2D-hexagonal nanostructures made of DNA origami controlled by different photoirradiation conditions.[7] This conformational control of macromolecular structures are thought be useful to design sensing devices for molecular robots.

To use molecular sensors in the amoeba robot, it is necessary to assemble DNA origami nanostructures which work as an interface on the liposomal compartment. Recently, Suzuki et al. succeeded in visualizing self-assembly and disassembly processes of photoresponsive DNA origami nanostructures on a lipid bilayer surface.[8]

The team also tries to develop a method to control biochemical reactions with DNA nanostructures triggered by sensing an input molecule. For this purpose, Endo et al. designed a T7 RNA polymerase-dependent transcription regulation system. They used single-stranded DNA as an input molecule for controlling output transcription using the toehold system.[9] Specific DNA strands, which bind to DNA attached to the tube, induce opening of the structure, which facilitates transcription reactions by exposing the promoter region of the template DNA. In this case, the tubular DNA structure contains two functions (sensing and actuation) and drives the biochemical reaction (computing) based on its conformational change.

2.2. RNA Devices and Nanostructures

In addition to Watson–Crick base-pairing, extensive tertiary interactions are involved in the folding of RNA molecules. For instance, naturally occurring RNAs such as ribozymes often exhibit complex tertiary structures, similar to those of proteins, which are composed of many smaller structural units. To generate synthetic RNA devices that sense input molecules, induce RNA structural changes, and control biochemical reactions, Saito et al. developed a basic technology for a "synthetic RNA switch" that can regulate target gene expression (translation) in response to specific input proteins (Figure 2).[10] By using this technology, the information encoded in an input protein can be converted into that of the desired output protein. Therefore, it provides a synthetic "protein–protein information converter" in vitro. Moreover, the developed RNA switch functioned in mammalian cells and controlled cell fate (Figure 2).[11,12] Hara et al. demonstrated that synthetic RNA sensory modules can be generated by employing in vitro RNA selection techniques. The generated RNA module detected the target protein and controlled gene expression successfully.[13] Meanwhile, Ohno et al. developed a new strategy to construct synthetic RNA-protein (RNP)-based nanostructures in an equilateral triangle shape in nanometer scale (Figure 3).[14]

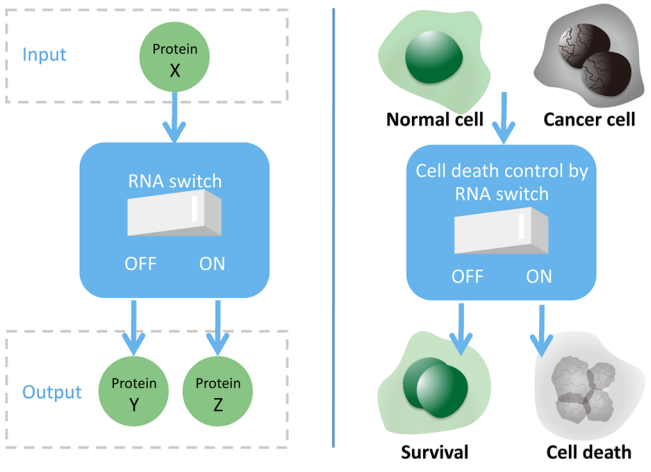

Figure 2. Synthetic RNA switches. Switch recognizes an input protein *x* to transmit its information to a desired output protein that represses the translation of protein *y* (OFF) and/or activates the translation of protein *z* (ON) (left). The system could be applied for detecting and killing cancer cells selectively (right).

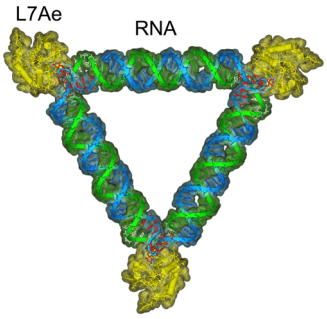

Figure 3. Protein-induced conformational change of RNA nanostructures. In the absence of L7Ae protein, two RNAs form heterogeneous structures, including triangular, linear, circular, or multimer forms. In the presence of L7Ae, the three K-turn regions are fixed at approximately 60°, which facilitates the formation of the designed triangular RNP. 3D model showing the placement of three L7Ae proteins in the triangular RNA scaffold.

Designed effector proteins can be attached to the apexes of the RNA triangle to minimize steric hindrance between the proteins. This RNP design could potentially form a multifunctional sensing agent with biological and medical applications.[15]

2.3. RNA-Based Information Converter

To substantialize information flows from sensor devices to other functional devices such as actuators and information processors, received molecular signals should be converted into information molecules after amplification. Takinoue and coworkers have constructed RNA information converters with molecular amplification of input signal, called the "Reverse-transcription-and-TRanscription-based Autonomous Computing System" (RTRACS).[16,17] By using RTRACS, the received molecular signal can be efficiently amplified and converted into RNA fragments as information molecules, which allows to transmit the signal to other molecular devices.

3. MOLECULAR COMPUTERS

Seesaw gates, proposed by Qian and Winfree, are one of the most promising molecular computing devices to construct large-scale DNA circuits.[18] For instance, Qian and Winfree have succeeded in implementing a 4-bit square root circuit of depth 7. However, each gate takes about 30–60 min to compute an output; thus, a speedup of the computing elements is crucial to realize more complex and larger circuits.[19]

The molecular intelligence team attempts to design and implement chemical reaction circuits to serve as computational components in molecular robots. Most studies in molecular computing have been focusing primarily on the DNA implementation of Boolean algebra so far. However, this approach is not always appropriate, given the physical properties of the actual chemical reactions. In order to introduce intelligence in molecular robots, it is important to explore various computational models that might be more

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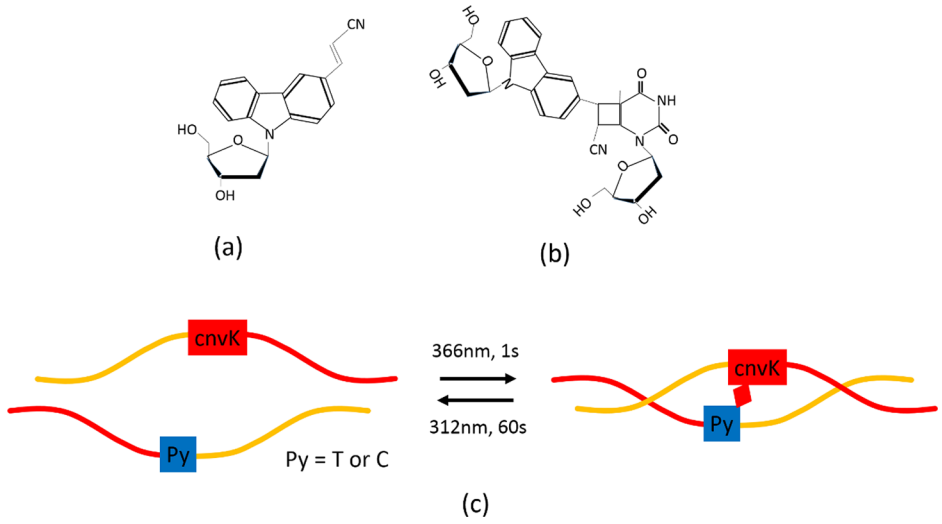

Figure 4. Ultrafast and reversible photo-cross-linking reaction via cnvK.

suitable for molecular implementation as well as analysis and simulation methods for complicated chemical reaction systems. With these issues in mind, the molecular intelligence team defined the research objectives as follows: (1) improving the speed of molecular circuit elements, and (2) establishing computational models of chemical reaction systems to provide computational technologies for the analysis and simulation of complex chemical reaction systems. Some recent results of the team will be described in the following section.

3.1. Photochemical Technology toward Fast Circuit Devices

Photochemical technology for manipulating DNA can be an effective tool for developing novel devices for molecular computing. The advantages are that the reaction is enzyme-free, and it requires neither additional reagents nor intricate control of buffer conditions. Also, the computing reactions are controllable in space and time by an appropriate choice of irradiation methods. One of the most promising photochemicals for the speedup of molecular computation is a DNA interstrand photo-cross-linking reaction via 3-cyanovinylcarbazole nucleoside (cnvK, Figure 4a) developed by Yoshimura and Fujimoto.[20] The reaction is ultrafast and reversible; cnvK contained in oligonucleotide (ODN) can be photo-cross-linked to a pyrimidine base of complementary DNA by irradiation at 366 nm for 1 s, and the photo-cross-linked ODN can be split by irradiation at 312 nm for 60 s (Figure 4c). To devise a high-speed element with the use of cnvK, it is important to investigate the details of the kinetics of photo-cross-linking reaction. Fujimoto et al. evaluated the *cis*–*trans* isomeric effect of the cyanovinyl group from the viewpoint of kinetics and the structure of the products.[21] NMR analysis of the photoadduct consisting of cnvK and dT strongly suggested that the *trans* isomer of cnvK reacted with the thymine base, forming a cyclobutane ring (Figure 4b). They also measured the rate constant of *cis*–*trans* photoisomerization of cnvK and that of the photo-cross-linking reaction.

3.2. Computational Models and Simulation

As one of the efforts to establish a novel theoretical framework for molecular computing, Okubo et al. proposed a new model, called "reaction automata", inspired from chemical reaction systems with small molecular counts, where the number of counts of each molecular species plays an essential role.[22,23] They showed that the proposed system is Turing universal; that is, it is able to compute anything that computers can.

As for a numerical analysis and simulation methodology for molecular computing, Kobayashi developed a novel theory that efficiently computes the chemical equilibrium of complex reaction systems, based on graph theory and optimization theory in a coupled manner.[24] The key idea of the theory is the *enumeration* of all molecular species using a graph, which results in drastic reduction of the number of variables needed to compute chemical equilibrium. A similar enumeration technique was also applied to realize an efficient simulation of the complex reaction systems by Kawamata et al.[25] They proposed a graph-based model to formulate reaction rules, and they used it to reduce the number of variables necessary for approximate or exact simulation. They applied the theory to a DNA hybridization system and an RNA interference as case studies. Aubert et al. developed a computer-assisted design software for the construction of DNA based circuits.[26]

4. AMOEBA ROBOTS

In our vision of amoeba robots, giant liposomes are thought to be a component for the compartmentalization, and DNA devices and other molecular devices will be encapsulated in the compartment. Motor proteins such as microtubules (MT) and microfilaments conjugated with DNA tags could be used as a controllable actuation device for molecular robots, which requires ATPs as chemical energy supply. The objectives of the amoeba team are summarized as (1) developing containers and components for amoebThe integration of biological motorsa robots, (2) developing molecular actuators controllable with DNA computing circuits, and (3) developing energy supply methods for the devices.

4.1. Containers and Components

As a container for amoeba robots, (giant) liposomes could be our first choice because the liposomal membrane is fluidic (e.g., allows molecular diffusion) and can be transformed into various shapes by external stimuli. Toyota and co-workers have developed methods to fabricate liposomes that can encapsulate a variety of molecular devices (Figure 5).[27,28] A method to transform the shape of giant liposomes with membrane-deforming proteins such as septins, F-BARs, and melittins is

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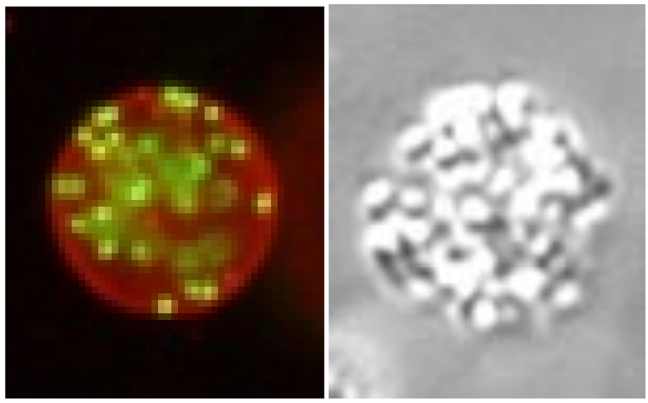

Figure 5. Water-in-oil emulsion centrifugation method for encapsulating information polymers or surface functionalized particles at a high density.

also developed by Tanaka-Takiguchi and co-workers (Figure 6).[29,30]

4.2. Molecular Actuators

Motor proteins, such as the actin−myosin system and MT−kinesin/dynein system, have been proposed as the building blocks of ATP-fueled biomachines. The greatest challenge is to determine how to exploit the sophisticated functions that motor proteins show in real biological systems. As an example of such a research, Aoyama et al. reported a method for the bottom-up assembly of a functional protein motor system combined with artificial microstructures fabricated by photolithography.[31] In their "artificial melanophore" inspired by the fish pigment cell, motor proteins are stored in a microchamber array. In each chamber, the pigment granules are transported by dynein along radially grown microstructures made of MTs. The researchers successfully demonstrated that arbitrary patterns can be displayed on the array.

The integration of biological motors into an ordered structure plays an essential role to realize amoeba robots. The molecular recognition between biotine and streptavidine provides an effective path toward this goal. Inoue et al. reported that a large ring-shaped bundle of MTs with a diameter of 1−12 μm can be obtained by modifying tubulines with biotine/streptavidine tags. When an MT slides on the surface coated with kinesin, it simultaneously cross-links with other MTs through biotine/streptavidine interaction (Figure 7). They are now developing a similar tag system by using DNA hybridization.

In general, DNA can be attached to various molecular motors or cytoskeletons, either by amide coupling, click reaction, or specific tags such as SNAP or CLIP tags. Then they can subsequently be assembled on DNA origami nanostructures. Such an assembly is precisely controllable by programming the DNA sequences. Nanomechanical DNA origami devices will add further sophisticated movements to the system. Kuzuya and co-workers developed a nanomechanical DNA-origami device (called DNA origami pliers), which consists of two lever portions with a length of 180 nm that are connected at a Holliday junction fulcrum.[33−35] The device can steer the mechanical movement of these levers, thereby transporting their ends to a distance of 200 nm. Such a mechanical movement can be triggered by specific interactions with various biorelated compounds, ranging from small metal ions to giant proteins. Han et al. developed a method to automatically recognize DNA nanostructures in atomic force microscopy (AFM) images, which is useful for the quantitative evaluation of

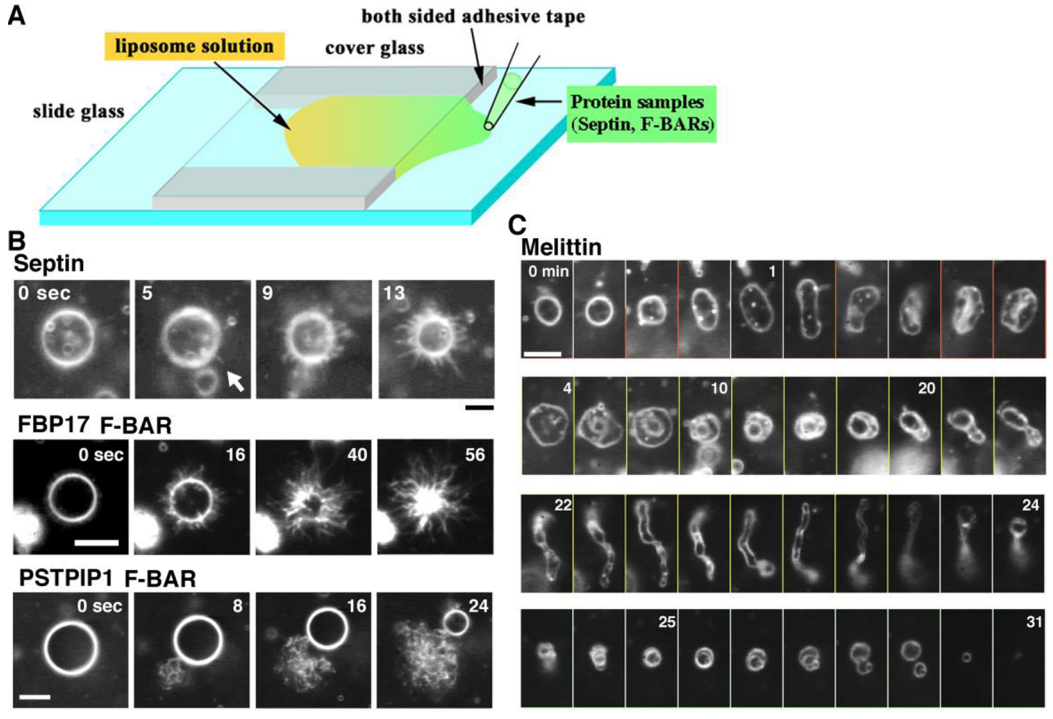

Figure 6. Membrane-deforming proteins and peptides. Giant liposomes morphologically changed by adding membrane-deforming protein/peptides from the outside using a mixing chamber (A). Robust tubulation could be caused by adding septin or F-BAR domain proteins to the giant liposome (B). Depending on the type of F-BAR, different tubulation processes could be induced. By adding membrane perturbation peptides, such as melittin, various deformations, for example, inflation, fluctuation, or elongation, could be induced into spherical liposome (C). Bars indicate 10 μm.

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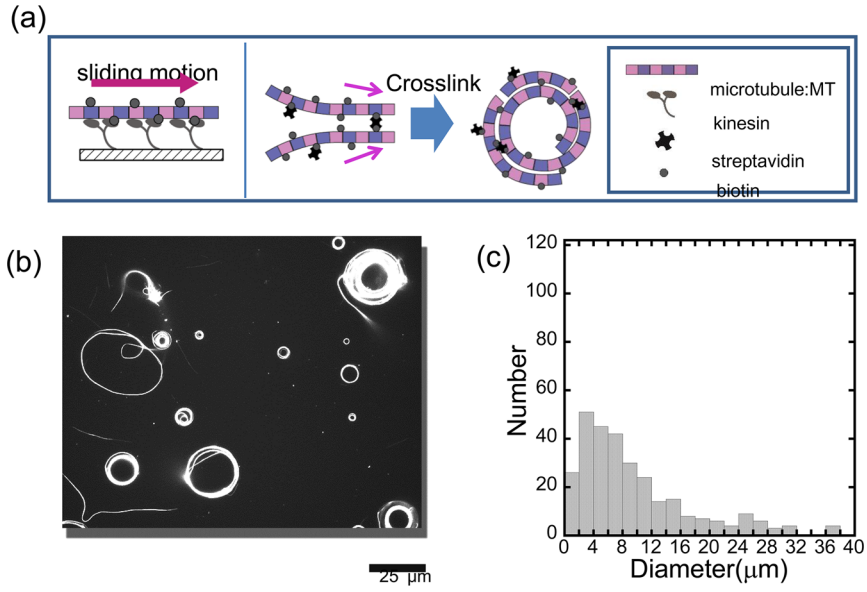

Figure 7. Ring-shaped microtubule (MT) assemblies formed through biotine/streptavidine interaction on a kinesin-coated surface.

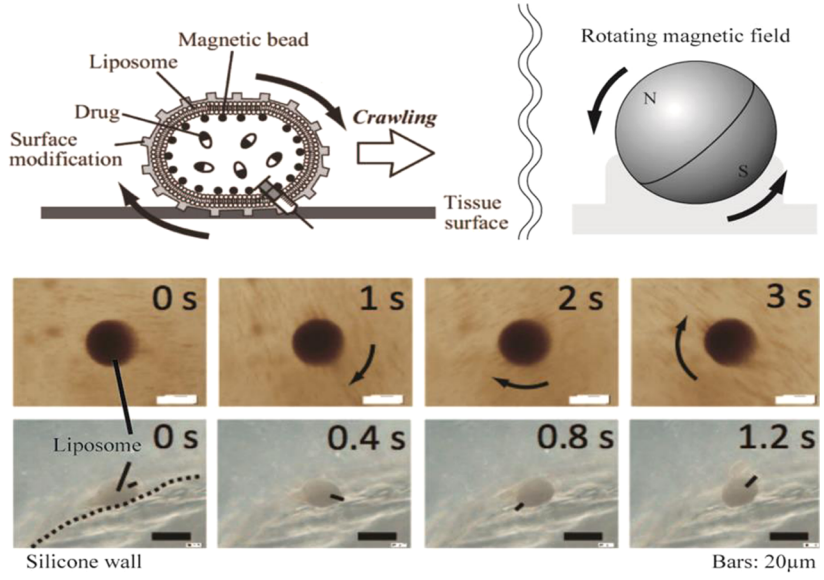

Figure 8. Rotational behaviors of a microcrawler liposome. Top: Schematic illustration. Bottom: Time-lapse images of rotating liposome on a glass (middle) and silicone substrates (bottom).

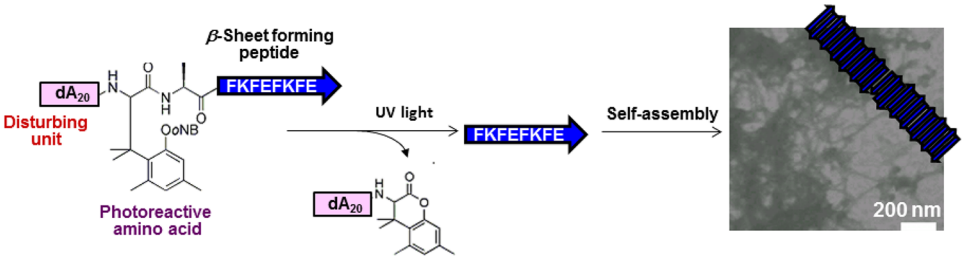

Figure 9. Phototriggered formation of β-sheet peptide fibril.

the mechanical properties of flexible nanostructures.[36] This combination of motor proteins and DNA structures is expected to provide a novel type of molecular actuation mechanism for molecular robots.

4.3. Energy Supply

There are several ways to supply the energy necessary for actuation and shape transformation of amoeba robots: optical, magnetic, or chemical power supply, and combinations thereof.

Komatsu et al. developed a microrobot that can crawl on contact surfaces in biological environments.[37] The prototype

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chassis of the micro-bot consists of a lipid membrane that encapsulates micrometer-sized magnetic particles. By applying a rotating magnetic field, they succeeded in generating a crawling motion (Figure 8).

Takiguchi et al. demonstrated the shape transformation of actin filament and heavy meromyosin complexes with ATP supply through α-hemolysins, a bacterial membrane pore-forming toxin forming a channel to transfer ATPs into the inside of the liposomes.[38]

Matsuura et al. developed an artificial protein which self-assembles into a large fibril complex by external stimuli. They found a β-sheet-forming peptide (FKFEFKFE) that can be conjugated with a single-strand DNA moiety as the disturbing unit through a photoreactive amino acid.[39] Photoirradiation triggers cleavage of the conjugate, and it causes subsequent formation of the peptide nanofibers (Figure 9). The combination with an FKFEFKFE-conjugated kinesin could enable MTs to move along the nanofibers through the kinesin–MT interaction, which would lead to deformation of the corresponding part of an amoeba robot.

5. SLIME MOLD ROBOTS

In a slime mold robot, sensors, actuators, and information processing devices should be all distributed in the medium, and their spatiotemporal pattern development must reveal functionalities such as locomotion.[40] DNA-functional hydrogels are one of the most feasible media for implementing various DNA devices, gates, and circuits with spatial distribution.[1] Moreover, various mechanisms of gel–sol transitions of a DNA-functional hydrogel have been demonstrated, based on DNA hybridization/denaturation reactions,[41] which can be utilized for slime-like locomotion. One type of such a hydrogel is made of polyacrylamide cross-linked with complementary DNA strands, which can solate with the addition of a DNA strand that displaces the linker DNA.[42] Another kind of hydrogel, fully constructed of DNA using an enzymatic polymerization reaction, does not require a high concentration of DNA.[43] These types of gel are prime candidates for the slime mold robot because the gel–sol transition can be driven with a small amount of output DNA from the molecular computation circuitry.

With the framework mentioned above, the following challenges are addressed in the slime mold team: (1) developing appropriate mathematical models and efficient simulation methods with high precision to describe diffusion-reaction kinetics including gel–sol transitions, (2) investigating effective reactions for changing physical properties of gels (e.g., causing gel–sol transitions or shrinking and swelling gels) in response to outputs of molecular computations, and (3) embedding anisotropic structures in gels for spatial control of the gel actuator. In the following, we mention some results from the team.

5.1. Mathematical Models and Simulation

Morita and Hara constructed a model of self-oscillating gel based on DPD method.[44] This model can be applied to the dynamics of both swelling and shrinking processes as indicated by their previous results combined with the stress–diffusion coupling theory. In our project, the peristaltic motion of a gel is simulated by using the OCTA system (http://octa.jp). Figure 10 shows snapshots of the simulation results. The simulated gel robot consists of a cross-linked polymer gel (e.g., BZ gel) and solvent particles, where the bottom layer of the gel is fixed at the floor. The polymer particle in each colored area has a different interaction parameter compared to the solvent particle, which induces swelling/shrinking of the gel, where the parameter in each layer is shifted holizontally corresponding to the propagation of the chemical reaction wave in the self-oscillating BZ gel.

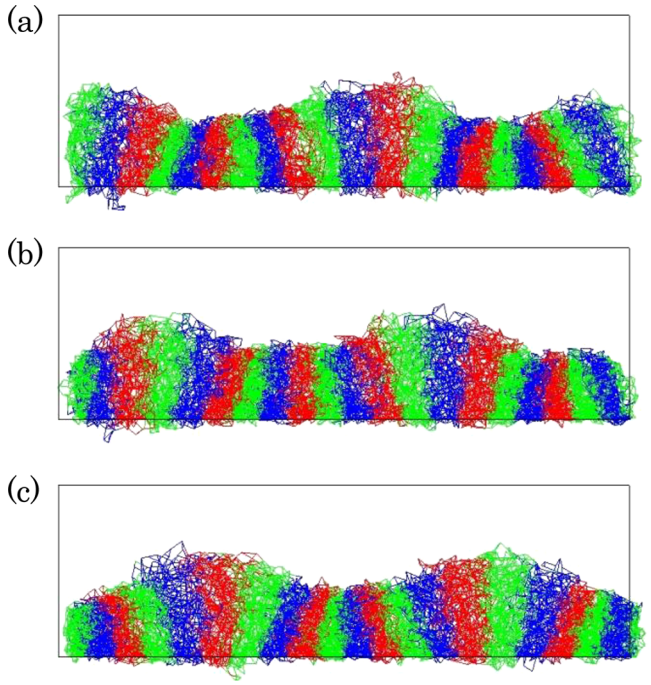

Figure 10. Snapshots from DPD simulation. Simulation proceeds from (a) to (c), where the swelling region is shifted from left to right.

5.2. Controlling Physical Properties of Gels

Kandatsu et al. have proposed a photocontrollable gel made of a DNA motif with designed base sequences and photo-responsive artificial bases for slime robots.[45] The motif is a cross-shaped DNA junction with a self-complementary sticky end and a photolinking artificial base (cnvK[20,21]) at each arm. Under UV–vis irradiation, they have realized the sol–gel state transitions in a repetitive manner (Figure 11). The physical properties such as swelling degree and diffusion coefficient have been evaluated in both sol and gel states.

Arimura and co-workers have been developing self-oscillating polymer gels, which exhibit autonomous cyclic shrinking–swelling oscillation behavior without external stimuli in water solution.[46,47] Intercalation moieties were successively introduced and functionalized into the self-oscillating polymer gels to recognize the DNA sequences. The optimization of a molecular design to control the oscillation by using DNA sequences or external electric signals is under investigation.

To improve actuation properties of the gel, Miyamoto and co-workers seek for inorganic nanocomponents as "molecular springs" as an ingredient for the gel. They also examine mesoporous ingredients to store fuel molecules in the gel actuators[48,49]

5.3. Toward Spatial Control of Gels

In slime robots, computing devices are supposed to be distributed in the gel medium. One possible demonstration of such a distributed computing system is to construct a reaction-diffusion field whereby a gel state gradually moves in one

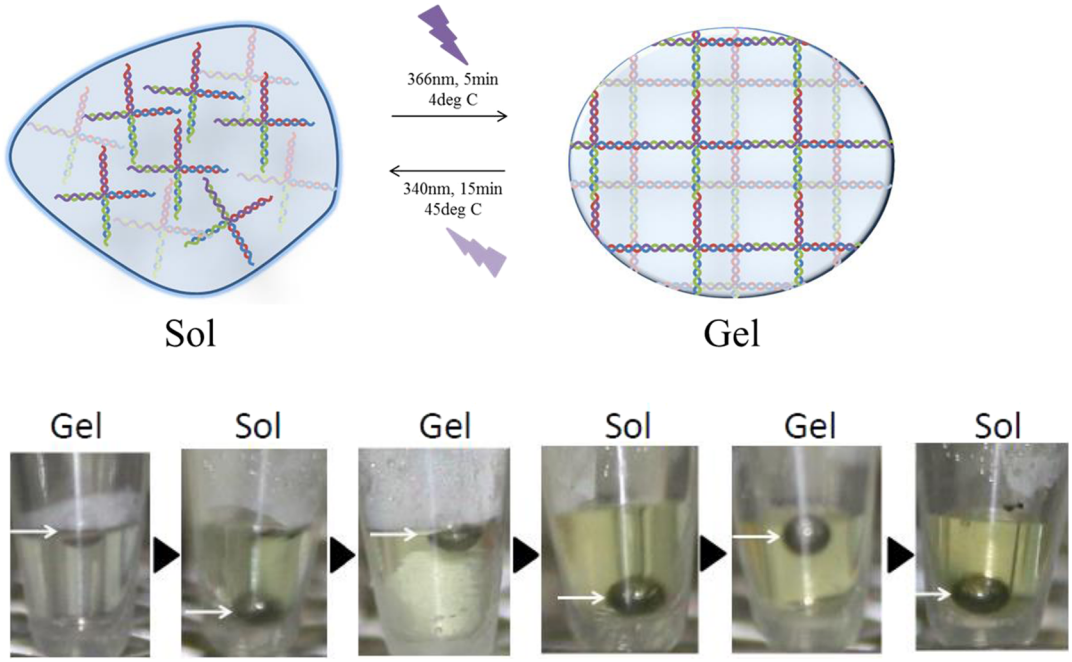

Figure 11. Reversible gel−sol transition of DNA gel controlled by UV irradiation.

direction, which we have set as a midterm goal for the slime mold team.

Kawamata et al. have confirmed the spatial and temporal solation of a DNA cross-linked hydrogel, which is achieved by diffusion of a displacement strand.[50] To propagate a gel state in a sol solution, one must implement a mechanism whereby only the part of the sol near the boundary of a gel turns into a new part of the gel.

The anisotropic and hierarchical structures inside the gel are also the key for triggering macroscopic-scale motions by a trace amount of information-carrying molecules. Miyamoto and co-workers approach this problem by hybridization of polymer hydrogels with inorganic nanomaterials that have a controllable, well-defined hierarchical structure.[51,52]

6. PERSPECTIVES

Let us consider again Figure 1. As described in the previous sections, we are now focusing on developing the first two generations of molecular robots. Here, we would like to give a brief explanation of the latter generations. The third generation molecular robots will be multicellular and will exhibit much more complex behaviors than those in a group of cells. The fourth generation will merge molecular robots with electrical circuits. We hope that these hybrid molecular robots will overcome the limitations of molecular reactions in general and, ultimately, even outperform living systems in certain domains.

This evolution process shows just one of the many possibilities, and it does not need to be followed sequentially. For example, the first and second generations may be developed simultaneously. Although the molecular robotics project is currently focusing on amoeba and slime mold robots, we have already recognized new challenges leading to the next generation of molecular robots, for instance, a swarm of amoeba or slime mold robots, which requires us to construct molecular robots that are able to communicate each other. For such a purpose, methods for bioprinting are expected to enable us to construct a complex multicellular structure for molecular robots.[53] Some pioneering work along those lines has already been accomplished.[54]

As for the applications of molecular robotics, we strongly believe that molecular robotics or molecular-based bottom-up fabrication will open the doors to innovative engineering fields including medical and pharmacological technologies. Drug delivery and tissue engineering are examples of such pioneering fields, although many hurdles still need to be overcome in basic research before the research results can be translated into various applications with tangible impact.[3]

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Notes

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