New Generation Computing, 31(2013)27-45
Ohmsha, Ltd. and Springer

Invited Paper

Molecular Robotics: A New Paradigm for Artifacts

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Received 19 July 2012

Abstract The rapid progress of molecular nanotechnology has opened the door to *molecular robotics*, which uses molecules as robot components. In order to promote this new paradigm, the Molecular Robotics Research Group was established in the Systems and Information Division of the Society of Instrument and Control Engineers (SICE) in 2010. The group consists of researchers from various fields including chemistry, biophysics, DNA nanotechnology, systems science and robotics, challenging this emerging new field. Last year, the group proposed a research project focusing on molecular robotics, and it was recently awarded a Grant-in-Aid for Scientific Research on Innovative Areas (FY2012-16), one of the large-scale research projects in Japan, by MEXT (Ministry of Education, Culture, Sports, Science and Technology, JAPAN). Here, we wish to clarify the fundamental concept and research direction of molecular robotics. For this purpose, we present a comprehensive view of molecular robotics based on the discussions held in the Molecular Robotics Research Group.

Keywords: Molecular Robotics, DNA Nanotechnology, Robotics, Self-organization, Bottom-up Approach, Nano-devices, Grant-in-Aid for Scientific Research on Innovative Areas.

§1 Introduction

A robot is an artifact exhibiting intelligent behaviors by sensing-processing-actuating cycles. In other words, a robot requires the facilities of sensors, actuators and intelligence as well as a body to integrate these facilities. Is it possible to develop a compartment, sensors, actuators and intelligence in molecules? If it is possible, what is different from an ordinary mechanical robot such as a humanoid robot? What kinds of technologies can be applied for molecular robotics? What is the ultimate goal of molecular robotics? How can we reach this goal? These are fundamental questions discussed in the Molecular Robotics Research Group, which was established in the Systems and Information Division of the Society of Instrument and Control Engineers (SICE) in 2010.[1)]

Nowadays, almost all robots are developed in a top-down fashion. Robots are mechanical systems designed for specific purposes. A robot's body, arms and legs are assembled by electronic and mechanical parts by considering the balance of performance and costs. The energy driving the robot must be supplied directly through its power plugs or batteries. The mechanical parts are replaced when broken. However, in this sense, even a state-of-the-art humanoid robot is no different from an electric kettle, no matter how well the robot mimics human behavior.

The subject of this paper is to introduce the concept of molecular robotics. It extends beyond these conventional definitions of robots and even reshapes the concept of artifacts. This new paradigm allows robots with more flexible structures and introduces more dynamic relationships involving exchange of matter between the robot and its environment. In other words, the robot's structure will not be fixed in advance; instead, it will be ever-changing like Play-Dough. Also, the robot parts are not assembled in a factory but are autonomously assembled into a robot structure, which adapts to its environment.

Until recently, systems possessing such properties were thought to be limited to living beings. That is to say, the ability to maintain their own systems in a changing environment, the ability to self-replicate, and the ability to evolve. Our strategy is to borrow the mechanisms found at the molecular level of living systems and modify them to bring life to our robots. Our goal is not only to realize the sensing-processing-actuating functions at the molecular level, but also to create systems that possess the flexibility and adaptability that are thought to be characteristic of living beings.

Last year, we proposed a five-year research project focusing on molecular robotics, and fortunately, our proposal "Development of Molecular Robots Equipped with Sensors and Intelligence" was awarded a Grant-in-Aid for Scientific Research on Innovative Areas by MEXT (Ministry of Education, Culture, Sports, Science and Technology, JAPAN). This scheme not only allows us to do core projects but also allows us to accept applications of related research projects from the public. This should be used as an opportunity for especially young scientists wishing to pursue a research career in this field. Therefore, it is crucially important at this moment to clarify the concept and research direction of molecular robotics. For this purpose, here, we present a comprehensive view of molecular robotics based on the discussions held in the Molecular Robotics Research Group.

This paper is organized as follows. First, the design philosophy of molecular robotics is discussed from the viewpoint of the architectural differences between mechanical robots and living systems in section 2. Next, we propose a molecular robotics evolution plan driving molecular robot research activities in section 3. Then, we describe the state of the art and future perspectives of molecular robot research in sections 4 and 5, respectively. Finally, our conclusion is given in section 6.

§2 Design Philosophy

What are the main gaps between mechanical robots and living systems? What is required to fill the gaps? What is lacking in conventional mechanical robotics? In order to answer these questions, we firstly clarify the differences between typical mechanical robots *i.e.*, humanoids and living systems. Then, we focus on the main features of molecular robotics: selfness and bottom-up development.

2.1 Comparison of Mechanical Robots and Living Systems

One of ultimate goals in robotics is to develop a mechanical robot walking on two legs, speaking in natural language, and working for human beings. In order to achieve this goal, a robot must be equipped with sensors and actuators and have some degree of intelligence. Conventional robotics realize these facilities by the integration of mechanical and electrical devices controlled by embedded micro-computers with sophisticated software, so-called "artificial intelligence."

Rapid progress of computer and control technologies has enabled us to develop mechanical humanoids which perform human-like actions. Sooner or later, humanoid robots will appear in our daily life, like in science fiction novels and movies. However, there still remain intrinsic differences between current humanoids and living things. We have plenty of examples to show such gaps. For instance, humanoids are created by a designer under particular criteria, whereas there is no designer for the living things. Each part of a humanoid robot is produced from different materials by different manufacturing methods in different factories, whereas living things reproduce themselves from the materials available in their environment. When a humanoid is broken, the broken part should be replaced by a human being, whereas living things have the ability of self-repair. Such differences can be represented by the term "self-X" property, such as self-organization, self-repairing and self-reproduction. Is it possible to fill the gaps by improving the engineering of mechanical robotics? Or shall we develop a new methodology to overcome these gaps? Molecular robotics is the latter approach which fills the gaps by means of molecular devices and a bottom-up development, similar to that observed in living systems.

In the living systems, parts are usually made of biomolecules such as proteins and lipids. All these parts degrade as time goes by. In order to keep the quality and quantity of functional parts, new parts are constantly synthesized to replace the old parts. The energy and materials that are necessary for this replacement are taken in from the external environment while the by-products of this process are excreted. In short, a living system is an autonomous open system maintained by metabolism and catabolism. Autonomy in energy consumption and part maintenance is one of the characteristics that ordinary robots are still missing and for which they require human intervention.

The above can be summarized by what Schrödinger wrote in *What is Life?*[2]; namely, that the essence of life is *information* and *metabolism* in the end. The goal of molecular robotics is to design artifacts with the properties of living systems. In a broader context, we can say that the ultimate goal of molecular robotics is to establish the next generation of engineering to design *evolvable systems*; that is, to create architectures that maximize a system's potential. Molecular robotics is one of such paradigm shifts from *engineering in order to do something* to *engineering in order to let things become something.*[3]

2.2 Selfness

In molecular robotics, the notion of *self* is a key concept. In life, a self is expressed through a unit called "individuals." An individual contains all the information necessary for developing, maintaining and reproducing the self. The goal of molecular robotics is to construct an artifact containing a description of such a self.* (Footnote: Description or representation of the robot is necessary, when the robot repairs itself or replicates itself without external help.) More specifically, the goal is to realize the above *self-X* properties, such as self-reconfiguration, self-assembly, self-repairing and self-replication, according to the description of the self.

To address these issues, a new way of thinking that differs from conventional approaches in robotics and mechanical engineering, is required. The difficulty here is how to describe self-X properties in an artifact. In conventional engineering, an artifact consists of objects whose behavior can be expressed by a mathematical model such as differential equations. However, in order to realize the self-X properties, one has to take into account that the model must have an ability to describe the change of the model in itself.* (Footnote: For example, imagine expressing a self-replicating system through differential equations. Once the system self-replicates, the dimension of the model equations doubles.) In other words, in order to realize these self-X properties, we must devise a methodology encoding the description of the *self* within the system, like reflective programming in computer science. In general, such a description is very difficult, especially when the system possesses a certain level of complexity.

Living systems solved this problem by separating the representation of the *self* into genotypes and phenotypes connected by bottom-up processes, the so-called "self-organization." Instead of describing the *self* directly, living things encode the physical properties of the system in DNA sequences as genotypes. Phenotypes, *i.e.*, the physical properties, emerge when living things mature by means of self-organization processes at various levels, such as self-assembly of molecular complex, controlled cell replication, differentiation and apoptosis. As a result, description of the *self* becomes very simple: it is a one-dimensional base sequence on DNA which can be easily replicated by complementarity of DNA. In this sense, we strongly believe that the "bottom-up" system development is a key concept in molecular robotics to realize self-X properties.

2.3 Bottom-up Development

The paradigm of bottom-up development allows a robot to be more flexible in structure and to increase its ability to adapt to its environment. In other words, the robot structure will be perpetually reconfigured, and the robot parts are not assembled in a factory but are assembled autonomously. Such robots may differ from what we usually imagine, but we can still call them "robots" as long as they execute a cycle of sensing-processing-actuating.

Until recently, living systems were the only ones which had the property of bottom-up development. In some sense, the bottom-up development is a source of "life"-like systems; the ability to maintain their own systems to a changing environment (adaptability), ability to self-replicate, and the aforementioned abilities. It is this ability that most man-made artifacts have not achieved yet.

Rapid progresses in molecular biology, or rather in genome science, have revealed mechanisms at the molecular level since the discovery of the DNA double-helix structure in the mid-20th century. Our strategy is to apply the mechanisms found in living systems to artificial robots in system design ranging from the level of individual molecular device designs, such as DNA sequence designs, to the level of molecular robotic systems. In system design, the following aspects are essential:

1. Modular design of molecular devices: modularity, interface and library of molecular devices;
2. Dynamics design: control of spatio-temporal molecular reaction dynamics, crosstalk in stochastic molecular device interactions, and assembling

of molecular devices to gain desired dynamic characteristics;

3. Higher-order functionality design: architecture for decision-making, learning, adaptation, and evolution.

Our goal is to engineer molecular robotics with flexibility and adaptability comparable to those exhibited by living systems as well as with sensing-processing-actuating functions. Molecular robots will survive in a changing environment by adapting themselves to this environment. As a result, the molecular robots may become artifacts capable of evolving.* (Footnote: Molecular robotics is reminiscent of a past movement of bio-inspired engineering. The first wave was brought to us by Norbert Wiener, known as the initiator of cybernetics[4] followed by communication engineering and control engineering. The second wave came up with the advance of computer science in the fields of artificial intelligence and mechanical robotics. In this context, molecular robotics can be considered a third wave driven by molecular nanotechnology.)

§3 Molecular Robotics Evolution Plan

Chemistry has made amazing strides in the last few decades. Much progress has been made in various technologies to design and utilize molecular devices based on biochemistry, organic metal chemistry, supra-molecules, polymer chemistry, inorganic chemistry, and so on and so forth. In parallel, a new technology called "molecular programming" that is a technology to create molecular devices by designing the base sequences of DNA and RNA evolves at a rapid pace.* (Footnote: This technology will be explained in detail in section 4.) Altogether, the ever-increasing inventory of available molecular devices allows us to make one more step toward creating "systems" including many molecular devices. This trend is most evident in DNA-based molecular devices. According to Winfree, the complexity of DNA-based molecular systems in terms of the number of bases has doubled every three years since the first DNA nanostructure was created by Seeman in 1983. This means that similar to Moore's law in the semiconductor industry, an exponential innovation is happening in the world of DNA nanotechnology as well. We think it is important to envision the future of molecular systems at the early stage of development. As mentioned before, the goal of molecular robotics is to derive new paradigms for artifacts by learning from living systems.

To be concrete, we can take the frame of reference from the evolutionary process of life. The evolution of organisms is a natural process shaped by various environmental factors. Similarly, the evolution of artifacts is also swayed by various factors, such as technological limitations and social needs at a given time. In this vein, the section below will explore one conceivable evolutionary scenario for molecular robotics. Similar to the many epochs in the evolution of living organisms, the development of molecular robotics faces many technological hurdles. When these hurdles are overcome, new possibilities will arise (Fig.1).

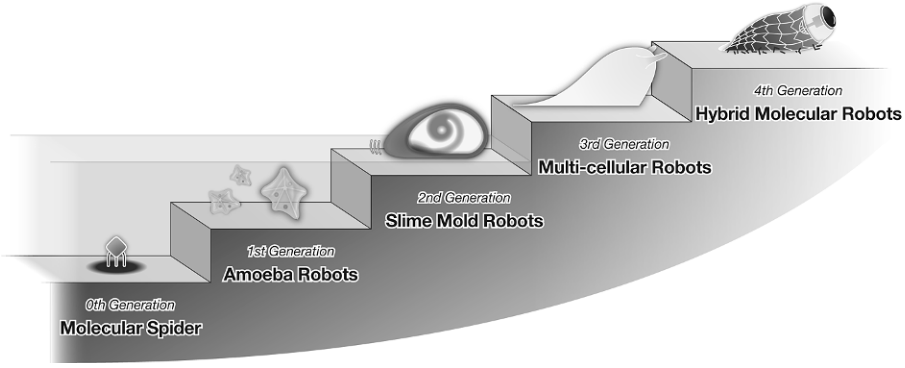


Fig. 1 Evolution of Molecular Robots

1) 0th Generation (current generation): DNA Molecular Robots

DNA molecular robots consist of a supra-molecular assembly of DNA fragments and other bio-molecules. Typical examples are the DNA molecular spiders constructed by DNA nanotechnologies.[5)] Some DNA molecular robots can move, recognize and carry other molecules. However, their movement is based on a random walk, and their functionalities are limited by the ability of molecular recognition.

2) 1st Generation: Amoeba Robots

The first generation molecular robots, called amoeba robots, introduce a compartment and an actuator to overcome the limitation of 0^{th} generation. A compartment can be made from a lipid bilayer, such as liposome or vesicle, or capsules made of DNA nanostructure. A compartment allows to encapsulate various functional and computational molecular devices to realize higher functions by means of molecular-device-circuitry like metabolic pathways and signal transduction pathways in organisms. An actuator controls the movement of an amoeba robot. The goal of the first generation molecular robots is to mimic the behavior of an amoeba. Amoeba robots, however, have a scale limit which prevents their sizes to be beyond several micrometers.

3) 2nd generation: Slime Mold robots

The second generation molecular robots, called slime mold robots, increase the scale of their sizes by means of functionalized polymer gels that work as both reaction field and actuator at the same time. Their sizes expand to the range of several millimeters. Polymer gels also create a heterogeneous spatio-temporal reaction field that causes macroscopic anisotropy in shape. As a result, the robots move like slime molds.* (Footnote: A corresponding organism with similar characteristics is *Physarum polycephalum.*) However, slime mold robots are similar to amoeba robots in the sense that both of them are categorized as unicellular organisms.

4) 3rd generation: Multi-cellular Robots

The third generation molecular robots, multi-cellular robots, can remarkably increase their complexity by means of a combination of heterogeneous cells like organs and tissues. There are two ways to create multi-cellular robots: the cell aggregation method and the cell division method. The cell aggregation method develops a multi-cellular robot by fabricating various molecular robot cells separately and then assembling them later. The cell division method requires higher technologies, including cell-replication and spontaneous symmetric breaking, to name but a few. These technologies enable us to develop various kinds of multi-cellular molecular robots and accelerate the diversity of molecular robots, so to speak, a Cambrian explosion of molecular robots. In this generation, we might be able to say that artifacts have *selfness*. However, multi-cellular robots cannot surpass living systems in performance and complexity due to the intrinsic limitations of bio-molecular reactions.

5) 4th generation: Hybrid Molecular robots

The fourth generation molecular robots, hybrid molecular robots, can make use of electronic devices to go beyond the limitations of molecular reactions. The fusion of electronic and molecular devices makes it possible for molecular robots to use advanced information processing technologies, such as high performance computation and high-speed communication. There is no such living system that corresponds to hybrid molecular robots. From this stage, the boundary between traditional artifacts and molecular robots gradually begins to blur.

In the molecular robotics evolution outlined above, there is no doubt that DNA will play important roles in molecular robots as a material to build compartments and molecular devices. However, there is nothing that prevents the use of materials other than DNA fragments. The desired properties suitable for molecular robot materials are the following. The materials should consist of polymers so that they can hold information in the arrangement of sequences. The materials should also have suitable chemical characteristics with respect to affinity and selectivity. In addition, accurate predictability in kinetics is also required, as well as the prediction of higher-order structures.

§4 Technologies for Molecular Robotics

In this section, the current status of molecular nanotechnology related to molecular robotics is described. Modern chemistry has made it possible to synthesize molecules with great complexity. Many of those synthetic molecules possess properties not found in nature. Those molecules with useful features are called molecular devices. Molecular robots are combination of such molecular devices formed into well-organized systems.

The number of molecular devices that can combine with others is very limited, because in order to combine them, not only their reaction conditions must be compatible, but they also must have a property called orthogonality.*

(Footnote: In the molecular system, molecule-wise orthogonality may be almost impossible to realize; instead, orthogonality at a certain level of reaction system should be considered.) Namely, the devices do not interfere with each other, and only desired coupling takes place. No matter how useful a device's features are, if these conditions are not met, it cannot be used as a component for molecular robots.

One of the remarkable aspects of living system is their ability to invent a variety of molecular devices that satisfy these constraints by simply combining relatively few kinds of different elements; namely, only four different bases in DNA and 20 kinds of amino acid in the case of protein. Are there any technologies capable of systematically producing various molecular devices that can combine with one another? At present, the field thought to be closest to the answer is DNA nanotechnology.

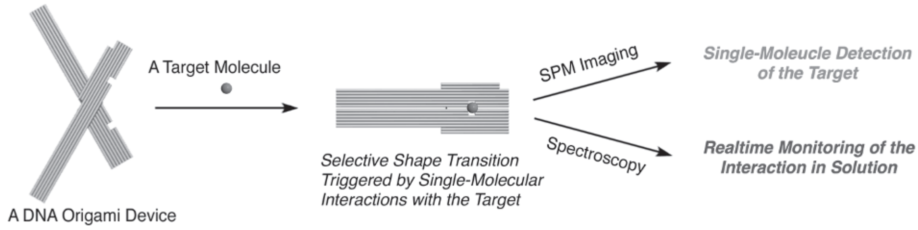
While DNA is obviously a very important molecule in living systems, it also makes for useful nanotechnology material. It is natural to use it to build molecular devices for our molecular robots. Thanks to the progress in biotechnology, it is now possible to synthesize DNA molecules with arbitrary base sequences, and the cost for the synthesis is continuously decreasing. DNA nanotechnology is the technology of using such artificial DNA to create molecules that self-assemble into any desired structure or into molecular devices with various functions, such as performing logical operations.

The main operating principle of DNA devices is DNA hybridization. Hybridization is the process in which single stranded DNAs containing complementary base sequences combine with each other through hydrogen bonding to form a double helix section. Hybridization takes place wherever there are mutually complementary single stranded sections, either within the same molecule or between different molecules. What makes hybridization special is its high selectivity. Furthermore, it is possible to predict which parts undergo hybridization to what degree of stability, even when a great number of arbitrary base sequences coexist. A number of software tools for making such predictions have been developed and are available to the public. By using such design tools, it has become possible to use DNA molecules as building blocks to create molecular devices with a variety of features.

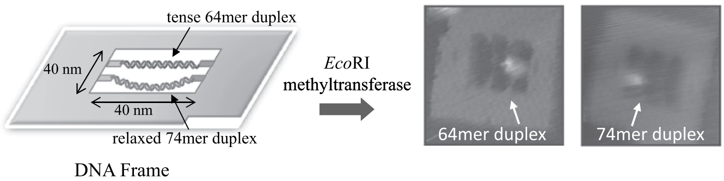
DNA nanotechnology originated from two ideas. The first one was to use DNA molecules as building blocks to build structures, which gave birth to the field of structural DNA nanotechnology. Another one was the idea that molecules can compute by using hybridization. This led to the development of a new field of study, called DNA computing. Below, we will provide an overview of the current state of DNA nanotechnology and describe related studies.

4.1 Structural DNA Nanotechnology

The idea of building nanostructures with DNA molecules was proposed by Seeman in 1983,[6)] who realized that it should be possible to create nanostructures by combining DNA junctions. Later on, the development of DNA tiles based on this idea caused a surge of interest in DNA nanotechnology.



a. Nanomechanical DNA origami used as a single-molecule beacon.



b. DNA origami test bed to visualize enzymatic reaction.

Fig. 2 Structural DNA Nanotechnology

Broadly speaking, there are two methods of building DNA nanostructures: DNA motifs and DNA Origamis. In the DNA motif method, the main idea is to construct complex DNA structures by connecting sticky ends of branched DNA fragments. Many types of DNA motifs have been proposed. Typical examples among them are double crossover (DX) molecules,[7)] cross tiles,[8)] 3-point star motifs[9)] and T-motifs.[10)]

The other method called DNA Origami is a way of DNA folding with a long single-stranded DNA molecule. Rothemund came up with the idea of folding a 7000-base single stranded DNA into a planar shape in 2006,[11)] followed by studies folding a planar shape into a 3D box shape[12)] and solid 3D shapes.[13)] Like protein folding, DNA Origami uses an optimization process of DNA structures with regards to free energy. Applications of DNA Origami include molecule sensing devices using DNA Origami structures that open and close like scissors (Fig. 2a),[14)] and enzymatic single-molecule characterizations (Fig. 2b).[15)] These high-sensitive techniques will be used for sensing for molecular robots.

4.2 DNA Computing

DNA computing was originated by Adleman, who in 1994 demonstrated that combinatorial optimization problems can be solved by combining DNA hybridization and enzymatic reactions of DNA.[16)] Unfortunately, massive parallelism in molecular computing could not compete directly with silicon computers due to the inherently slow operations such as DNA hybridization and electrophoresis. Instead, the DNA computing has changed its direction from performance competition to the study of autonomous computing models in which computation takes place spontaneously after the molecular ingredients are mixed in. Nowadays, DNA molecules turned out to be essential molecules to realize molecular logic circuits, because DNA molecules facilitate digitalization property and high selectivity. Again, DNA hybridization plays an essential role to guarantee high-yield reaction products and to suppress crosstalk between molecules when building multi-variable and multi-stage molecular logic gates. Examples of DNA-based molecular logic gates include: finite-state automata using restriction enzymes,[17] single-molecule finite-state automata based on DNA polymerization (Fig. 3a)[18, 19] by Komiya et al., various types of DNA memory,[20] and DNAzyme-based logic gates.[21] Also, in order to implement hundreds of logic gates in a single DNA hybridization reaction, toe-hold mediated branch migration has been developed.[22–24] Recently, Rondelez developed dynamic oscillators using logic gates that combine DNA polymerization with nicking enzyme and exonuclease (Fig. 3b).[25] These techniques are necessary to implement intelligence in molecular robots.

4.3 Related Molecular Nanotechnology

So far, molecular devices that use DNA as their building blocks have been described. However, while devices built of DNA molecules have good mechanical or chemical stability, they lack in further functionalities. In order to overcome this problem, the strategies of exploiting other molecular species, and combining those species with DNA devices, are being considered.

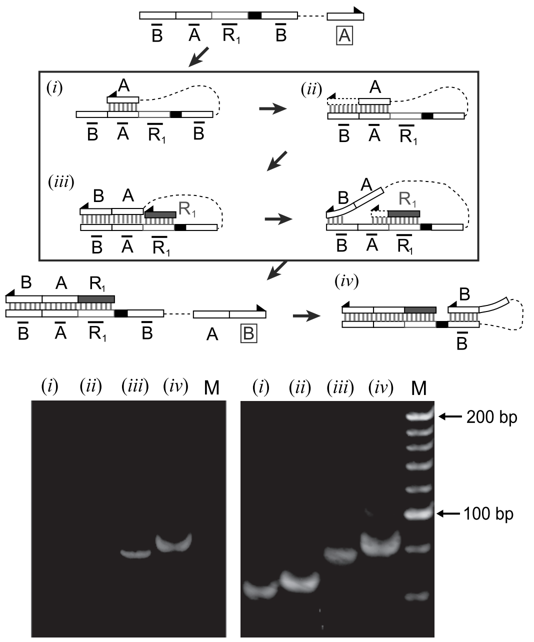
1) RNA devices

Various enzymatic functions of RNA such as ribozyme and riboswitch should be exploited for molecular robots. Because RNA and DNA can be hybridized, coupling RNA with DNA devices is a relatively straightforward procedure.

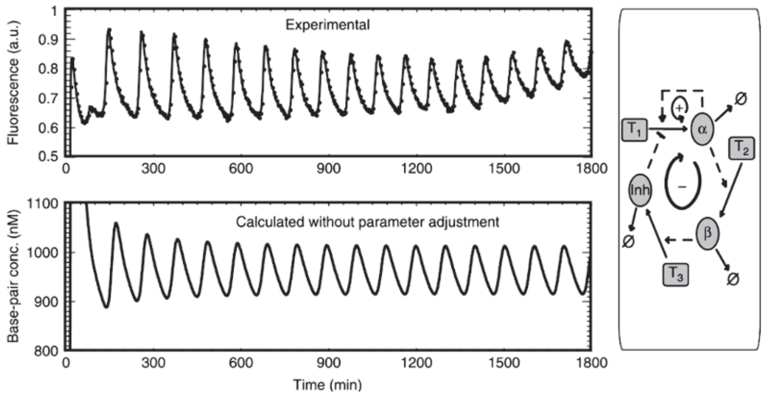
One variety of RNA nanostructure is referred to as the RNA jigsaw puzzle.[26] Predicting the structure of RNA is significantly more difficult than in the case of DNA, and therefore, only a certain portion of all known configurations of RNA structures are utilized as tiles when designing such puzzles. Sensing devices consisting of a complex of RNA and proteins have been proposed.[27] As for computing devices, a computational system called RTRACS[28] by Suyama et al., combining enzymatic reactions of RNA and DNA is currently under development.

2) Artificial bases

Thanks to the nucleic acid chemistry, various chemical modifications of nucleic acids to extend the functionality of nucleic acids are now available. Bases other than A, C, G, and T called "artificial bases" can be given properties not found in natural nucleic acids. For example, it is possible to optically control hybridization by using photo-reactive bases. A photo-reactive DNA actuator using this mechanism is currently developed by Asanuma.[29] Photo-reactive DNA linkers by Fujimoto[30] have a wide range of applications to build devices for molecular robots.



a. Finite state automata implemented on a single molecule of DNA.



b. Oscillating circuitry implemented by enzymatic reaction of DNA.

(K. Montagnue, Y. Rondelez et al., *Molecular Systems Biology*, 2011,7,466 ©2011 NPG)

Fig. 3 DNA Computing

3) Peptides

The main substance that builds living systems is not DNA, but protein. Designing proteins is difficult, but by taking a hint from the structure of virus capsids, it has become possible to create artificial nanostructures. For example, a capsule-like structure is being made capable of controlling its conformations through artificially synthesized peptides.[31] It is possible to synthesize copolymers of peptide and DNA, allowing the various activities of peptides to be systematized by combining these peptide devices with DNA nanotechnology.

4.4 Necessary Devices for Molecular Robots

In the previous section, the current state of related nanotechnologies was summarized. Those technologies and devices will be used as a basis to make necessary components for molecular robots. Here, we look ahead to discuss what is important or necessary to realize such components.

1) Compartment

A molecular robot requires a compartment to integrate multiple molecular devices in it. DNA nanostructures explained above and artificial liposomes can be used for this purpose. Recently, the latter have gained increasing attention in the context of artificial cells and synthetic biology. Molecular robotics can make use of such an artificial liposome as a compartment. Recently, Kurihara et al. has achieved the self-replication of artificial liposome,[32] and Nomura has already succeeded to attach connexins, or gap junction proteins, on an artificial liposome, suggesting the possibility of a multi-cellular organization.[33]

2) Sensors

Sensing devices capable of detection, amplification, and conversion of input signals are required for molecular robots to detect weak input signals in noisy environments. In mechanical robots, sensors are realized by electric devices such as optical devices. The sensors transfer input signals to central computers via electric lines. The computers process the input signal, and then control actuators such as arms and legs as the reaction to sensing. In contrast, in living systems, sensors are realized by receptors on the cell membrane. The receptors transfer input signals to the nucleus via signal transduction pathways. The pathways trigger new gene expression necessary for cell actuation as the reactions of sensing.

In order to realize the above mechanism, molecular robots use DNA/RNA fragments, aptamers and DNA logic gates as information molecules, molecular switches and control logics, respectively. In DNA logic gates, DNA/RNA fragments work as information molecules which carry digitalized information encoded in nucleic acid sequences. DNA/RNA fragments also work as high signal-to-noise ratio detectors due to the high selectivity to complementary strands. Aptamers are nucleic acid sequences which recognize specific small molecules. Due to their high sensitivities, we can use them as molecular switches recognizing the existence of certain molecules, differences of environmental parameters such as pH, ion concentration and temperature.

3) Actuators

A number of DNA actuators have been proposed so far, including DNA tweezers,[28] DNA walkers[29] and DNA motors.[30] Further, it is possible to control DNA walkers by means of DNAzymes.[31]

The DNA actuators mentioned above are driven by hybridization and enzymatic reactions. However, when it comes to improving their operating speeds, this method is proving to be problematic. In contrast, biomolecular motors made of microtubule-kinesin and actin-kinesin are of interest as they are much faster and more efficient. There is an attempt to combine DNA origami with such microtubule-kinesin motors. Self-organization of microtubule-kinesin complex is also investigated as an engineered molecular motor system.[34)]

The objectives of actuators are to achieve certain motions at the macro-level; for example, to be able to sense the gradient of particular chemical substances concentration, and to control chemotaxis for a specific direction. To scale-up the motion, spatially distributed gel actuators with molecular computational circuits should be considered.

4) Intelligence

"Intelligence" is one of the keywords that distinguish robots from other machines like aircrafts and cars. Rapid progress of computer technologies enables artifacts to compete with human intelligence in specific areas such as vision, natural language processing, games, question-answer systems and so on. *Watson, Siri* and *Wolfram Alpha* are such examples that may demonstrate the abilities of the state-of-the-art question-answer systems. In some sense, the amount of total knowledge encapsulated in these systems is truly immense and beyond the human capability. However, no matter how much knowledge the artificial intelligence systems have, the knowledge is constructed by human beings, thus it is not gained by the artificial intelligence systems themselves in principle. In other words, conventional artificial intelligence lacks autonomy. In order to overcome this problem, we have to develop artifacts which gain their knowledge by themselves.

All the conventional AI systems have been designed top-down, and thus do not have the ability to reconfigure themselves. True intelligence, however, should be capable to handle a variety of "unstructured" knowledge, and this requires the ability to change the system structure itself according to the given constraints and context. This is very difficult for the conventional top-down design approach.

Our brains do this job, although we do not know the design principles yet. And the mechanisms of the brain must be based on molecular reactions. This is our motivation to incorporate "intelligence" in our molecular robots. The intelligence of molecular robots may not exceed the intelligence of bacteria at the first stage. However, we believe that once molecular robots can gain such facilities to gain knowledge autonomously, it would only be a matter of time to see more and more intelligent molecular robots emerge.

§5 Future Perspectives

Molecular robotics is classified as a branch of engineering. It strives towards the establishment of a systematic methodology for developing artifacts from molecular devices in a bottom-up approach. Molecular robotics design

DNA logic gates on the basis of DNA fragments, analogously to semiconductor technology that designs transistors on the basis of silicon devices. In this sense, we can consider a molecular robot itself as a kind of non-conventional computer. Instead of numerical calculus in silicon computers, molecular robots repeat sensing-processing-actuating cycles.

Then, what changes will this new paradigm bring us? A promising application of molecular robots is pharmacology such as drug delivery systems (DDS) and regenerative medicines. Molecular robots may also be applicable to problems related to energy, food, and the environment. Molecular robots will play crucial roles which are difficult to fulfil by traditional technologies alone.

If we foresee the age of inter-planet space trips, molecular robots might be the only technology launching terrestrial life into outer space. Because terrestrial life has been nurtured in the limited environment of our planet, its various properties are optimized to survive on earth. However, this optimization becomes meaningless when moving to planets other than the earth. In the near future, when molecular robotics will be highly developed, we shall be ready to release the restraints of life on earth. In other words, we will be able to equip a molecular robot with the ability to choose the most suitable molecular material depending on the environment it is located in, as well as embedding the ability to self-transform and self-replicate. In short, we will be able to make a system that configures and adapts itself according to the given environment. Only such an evolvable system will be able to survive on an unknown planet.

Fusion of electronics and molecular devices is a final stage of the molecular robot evolution. We will be able to embed all cultural heritages of human beings into hybrid molecular robots. The hybrid molecular robots can be super-vital artifacts enduring long and harsh interstellar travel.* (Footnote: These flights would expose the traveler to intense cosmic radiation for tens of thousands of years) Then, we will be able to entrust the essence of our existence to the super-vital artifacts. Sending seeds through space in such a way may be the only hope that we, as terrestrial organisms, have to provide a future for our descendants.

The current activities in molecular robotics are still in their infancy. However, we believe molecular robotics is the only way to go beyond the limitation of conventional technologies. Learning from the elaborate and complicated phenomena of nature called life, molecular robotics is nothing but an attempt to exploit that knowledge to create intelligent artifacts with life-like properties. It is about the creation of new artifacts with all the intellectual heritage we have accumulated outside of our genome. This signifies that we have reached a critical stage never before experienced in the history of life.

Acknowledgements

This paper is based on the discussions held in the Molecular Robotics Research Group, SICE. We appreciate all the participants to the discussions. We are also thankful to Prof. Shogo Hamada of Tohoku University for making an illustration, and Prof. Masayuki Endo of Kyoto Univ., Prof. Akinori Kuzuya of Kansai Univ., Prof. Ken Komiya of Tokyo Institute of Technology and Prof. Yannick Rondelez of the University of Tokyo for permitting use of figures. This work was supported by a Grant-in-Aid for Scientific Research on Innovative Areas "Molecular Robotics" (No. 24104001-5) of The Ministry of Education, Culture, Sports, Science, and Technology, Japan.

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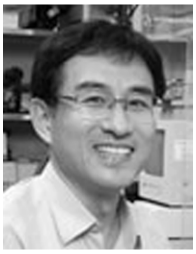

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