From Molecular Robotics to Molecular Cybernetics: The First Step Toward Chemical Artificial Intelligence

Akinori Kuzuya, Shin-Ichiro M. Nomura, *Member, IEEE*, Taro Toyota, Takashi Nakakuki, and Satoshi Murata

***Abstract*—"Molecular Cybernetics" is an emerging research field aiming the development of "Chemical AI", artificial intelligence with memory and learning capabilities based on molecular communication. It is originated from "Molecular Robotics," which studies molecular systems that comprise of the three basic elements of robots; Sensing, Planning, and Acting. Development of an Amoeba-type molecular robot (unicellular artificial cell,) motivated the construction of multicellular artificial cell systems mimicking nerve systems. The major challenges in molecular cybernetics are molecular communication over two lipid-bilayer compartments, amplification of molecular information in a compartment, and large deformation of the compartment triggered by molecular signal, etc. Recently reported molecular devices and systems that contributes to the realization of Chemical AI are overviewed.**

***Index Terms*—Molecular cybernetics, chemical AI, molecular robotics, molecular communication, DNA computing, structural DNA nanotechnology, molecular motors.**

I. Introduction

MOLECULAR Robotics is a research field proposed by researchers in early 2010's [1], [2], [3], [4]. It aims to construct intelligent molecular systems that comprise of the three basic elements of robots; Sensing, Planning, and Acting, all implemented with functional molecules [5]. Biomolecules, especially synthesized DNA is often used in molecular robotics, not only as a structural material but also as a material capable of recording and transmitting information through its complementarity-based double helical structure. In this sense, molecular robotics is a field inspired by molecular biology but based on "DNA computing" [6] and "structural DNA nanotechnology" [7].

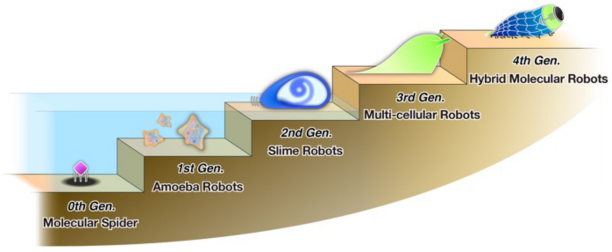

Fig. 1. Evolutionary scenarios of molecular robots (courtesy of Dr. Shogo Hamada of Tokyo Institute of Technology) [1], [2], [3].

The researchers not only study various topics of molecular robotics [8], but also propose an evolutionary scenarios in molecular robot development in terms of structural and functional complexity (Fig. 1) [1], [2], [3].

The 0th generation of molecular robots are usually realized as a single supra-molecule composed of DNA strands and other functional biomolecules. Typical example of this generation is the "molecular spiders" that "walk" along a track placed on a DNA origami presented by Lund et al. [9]. Various 0^{th} generation molecular robots that can move, recognize, and carry other molecules have been proposed, however their movement is based on random walks or Brownian motion induced by thermal fluctuation. To achieve directional motion, it is necessary to introduce "fuel" to drive molecular motion. A representative example of such a molecular robot that uses chemical energy as fuel for active movement is the "Molecular Swarm Robot" developed by Kakugo, Kuzuya, and colleagues, which combines DNA with a microtubule/kinesin molecular motor system [10], [11], [12]. Swarming, dispersion, and even coherent motion of DNA-modified microtubules gliding on kinesin-covered glass surface could be efficiently controlled by complementary DNA signals or light irradiation.

The first generation molecular robots are amoeba-type robots, which employ compartments to overcome the limitations of 0th generation. They can be regarded as a single artificial cell which contains many functional molecules and molecular actuators in it. Within a compartment, the concentration of each molecule can be defined and its change can be predicted by the law of mass action, so it is no longer

Manuscript received 31 March 2023; revised 4 August 2023; accepted 6 August 2023. Date of publication 10 August 2023; date of current version 20 September 2023. This work was supported by the Grant-in-Aid for Transformative Research, Area (A): Molecular Cybernetics – Development of Minimal Artificial Brain by the Power of Chemistry under Grant 20H05968, Grant 20H05969, Grant 20H05970, Grant 20H05971, and Grant 20H05972. The associate editor coordinating the review of this article and approving it for publication was M. Kuscu. *(Taro Toyota, Shin-Ichiro M. Nomura, and Takashi Nakakuki contributed equally to this work.) (Corresponding author: Akinori Kuzuya.)*

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Digital Object Identifier 10.1109/TMBMC.2023.3304243

a random walk. The compartments could be made by liposomes with lipid bilayer, synthetic polymer vesicles, or DNA nanostructures. These compartments are flexible and can be deformed like an amoeba by contained molecular motors. One shortcoming of amoeba robots is that they are limited in size, at most a few tens of micrometers. The first amoeba robot was reported by Sato et al. [13]. They encapsulated microtubules in liposomes together with DNA-modified kinesins, which are selectively attachable/detachable to the lipid membrane responding to light signal sensed by photo-responsive DNA moiety. Deformation of the resulting liposome was successfully controlled by adjusting the binding of microtubules to the membrane mediated by kinesins.

The second generation of molecular robots, called slime robots, extend their size to a few millimeters with the aid of polymer gels and other materials as reaction fields and actuators themselves. Polymer gels can also provide heterogenous spatiotemporal reaction fields, which enables advanced computations like slime molds in nature do. One of the most remarkable slime robots was constructed by Hamada et al. [14]. They prepared dynamic biomaterials, termed DASH (DNA-based assembly and synthesis of hierarchical materials), powered by artificial metabolism, and demonstrated programmed patterning, racing between two slime mold robots, etc.

The third generation of molecular robots, conceived but not yet realized, are multicellular robots [1], [2], [3]. It enables the implementation of multiple functions among different cells and is expected to realize more complex systems such as natural organs and tissues. Two processes of forming such multicellular robots have been devised: artificial cell aggregation and differentiation. In the aggregation process, artificial cells with different functions are individually prepared first and then artificially combined to form an aggregate. In the process of differentiation, on the other hand, an assembly of uniform artificial cells is formed, and then individual artificial cells are functionally differentiated. This requires the development of more advanced technologies such as for self-replication of artificial cells and spontaneous symmetry breaking, etc.

Envisioned fourth generation of molecular robots are hybrids of electronic devices and molecular systems [1], [2], [3]. This may enable the realization of functions that overcome the limitations of molecular or chemical systems. There is no such analogy in natural living systems, and this is where molecular robots (artificial cells) enter a stage where they transcend natural systems.

Successful realization of unicellular molecular robots, or amoeba robots, in "Molecular Robotics" field has led to the development of multicellular molecular robots. "Molecular Cybernetics" is the next stage of development in molecular robotics [15]. The term "cybernetics" refers to the study of communication and control mechanisms common to living things and artifacts. Molecular cybernetics focuses on communication between multiple molecular robots partitioned in liposomes to construct molecule-based AI or "Chemical AI". In this paper, recent achievements that may contribute to the molecular cybernetics are overviewed. The basic concept of chemical AI in molecular cybernetics is first described

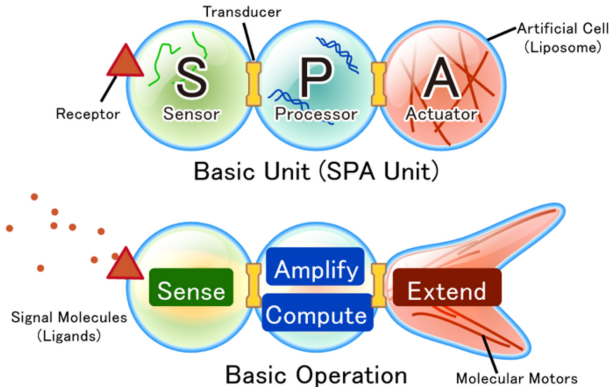

Fig. 2. Basic concept of molecular cybernetics: a chemical AI composed of three artificial cells communicate to each other using molecular information; sensor (S), processor (P), and actuator (A) cells [15].

(Section II). Then, individual studies on molecular devices that can be used to control molecular systems (Section III-A), artificial channels and transducers for molecular communication through cell compartments Section III-B, control technology of liposomes as compartment Section III-C, and finally molecular computation systems are presented Section III-D.

II. The Concept of Molecular Cybernetics

The basic "Chemical AI" is composed of three artificial cells (Fig. 2) [15]. These correspond to the three layers of nervous system in nature, and each of which has the function of sensing and amplifying chemical inputs (sensor = S), memorizing and learning (processor = P), and transforming (actuator = A). By further combining these triplets called SPA units, we aim to realize complex information processing functionalities. The SPA units are combined in microfluidic devices. Chemical information processing is initiated by inputs of various molecular stimuli to an SPA unit, mediated by chemical reactions corresponding to computation within the unit, and concluded as output of specific molecular signal. Molecular stimuli sensed by "molecular sensors" embedded in liposome membrane of S cell is transferred to P cell for the molecular information processing. Communication between each artificial cells are maintained by "transducers" or "artificial channels" that pass molecular information, typically DNA strands, through two lipid-bilayer membranes. "Molecular computation system" in P cell memorizes the molecular information and produce output molecule as a result of some chemically implemented algorithm. Amplification of the molecular signal can be held either in S or P cells. Connection between SPA units can be dynamically controlled by programmed actuation of A cell, mimicking brain plasticity based on dynamic reconnection of neurons.

III. Recent Achievements in Molecular Cybernetics

As mentioned above, the purpose of molecular cybernetics is to realize each of S, P, and A cells, and to explore the methodology to combine them into an SPA unit to realize

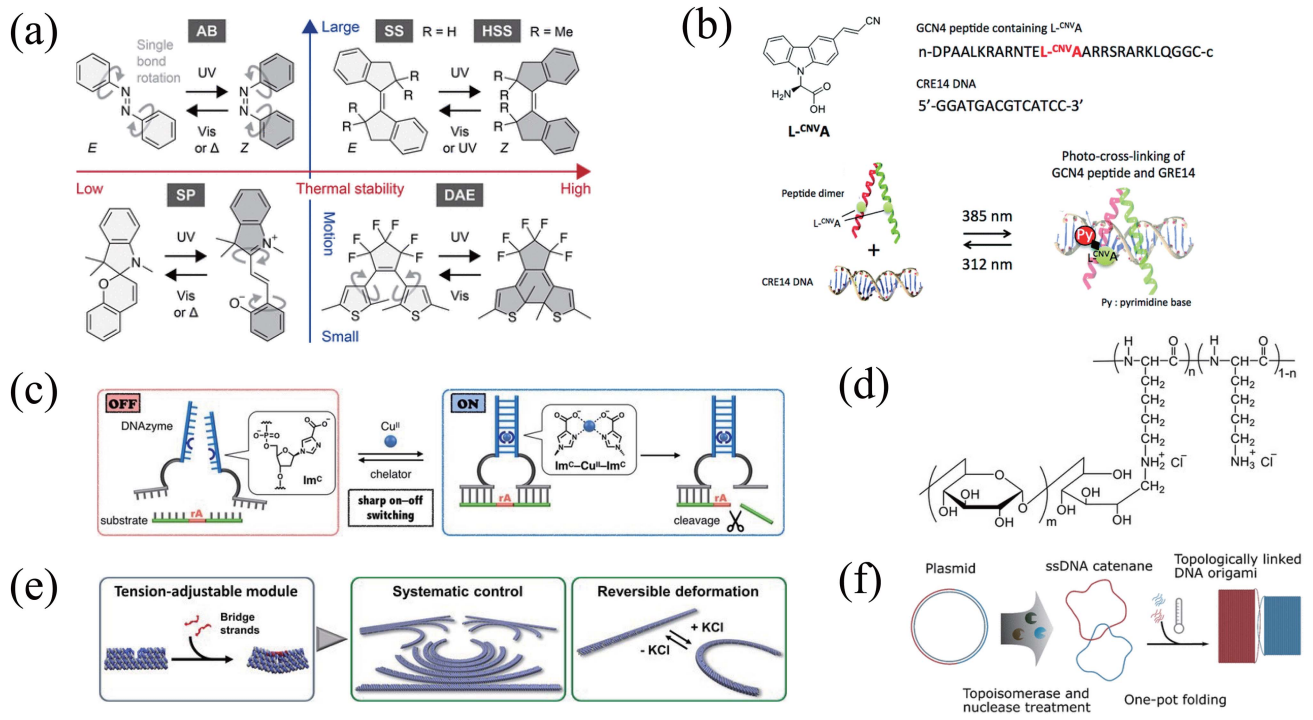

Fig. 3. Molecular devices to control molecular systems. (a) Typical photo-responsive molecules: AB, azobenzene; HSS, hindered stiff stilbene; SP, spiropyrane; DAE, diarylethene. Reprinted with permission from [19]. Copyright 2022 American Chemical Society. (b) Application of photo-crosslinking amino acid Reprinted with permission from [20]. Copyright 2019 Royal Society of Chemistry. (c) Control of DNAzyme activity by metal-responsive nucleotide. Reprinted with permission from [23]. Copyright 2020 John Wiley and Sons. (d) The structure of molecular booster (PLL-g-Dex) that accelerates DNA strand exchange by 30-folds. Reprinted with permission from [24]. Copyright 2018 John Wiley and Sons. (e) Largely deforming DNA-origami nanoarm. Reprinted with permission from [26]. Copyright 2020 John Wiley and Sons. (f) Topologically catenated scaffolds for DNA origami supramolecule (Topogami) [28].

information processing that can be called "intelligence," such as to memorize or learn. In the following sections, we introduce the main results obtained so far in the field of molecular cybernetics for each of the topics.

A. Molecular Devices to Control Molecular Systems (Fig. 3)

For precise control of molecular systems, the use of carefully designed molecular devices is essential. One of the most popular and well-studied molecular devices is photo-responsive DNA bearing azobenzene moiety (Fig. 3a) [16], [17], [18]. Azobenzene reversibly photo-isomerize between planar *trans*- and bulky *cis*-isomers upon light irradiation. DNA duplex formation can thus be efficiently photo-controlled since the *trans*-isomer stabilize DNA duplex by intercalation while the *cis*-isomer destabilize it by steric repulsion. One disadvantage of azobenzene is that it also undergoes thermal isomerization, which results in slow equilibration of *trans*- and *cis*-isomers. Imato et al. have recently developed a new photo-responsive moiety, hindered stiff stilbene (HSS) [19]. It offers larger motions than azobenzene, ca. 90% photoisomerization in both *E*-to-*Z* and *Z*-to-*E* directions, and significantly high thermal stability with a half-life of ca. 1000 years at room temperature. Although it is not yet introduced to DNA, it will be excellent photo-switch controlling duplex formation. Another possible photo-responsive molecular device useful to control molecular systems is reversible photo-crosslinker 3-cyanovinylcarbazole (CNV) moiety (Fig. 3b) [20].

Molecular systems composed of DNA can be controlled not only by photo-signal, but also by metal ions. Takezawa et al. synthesized metal-ion responsive DNA residues (Fig. 3c), and successfully controlled DNAzyme reaction by Cu(II) addition to the system [21], [22], [23]. Future use of aptamers may further enhance the variety of molecular triggers in combination with the above examples.

One of the major drawbacks of DNA computing systems is the slow reaction rate of toehold-mediated strand exchange. Shimada and Maruyama et al. found quite unique property of their cationic copolymers solving this problem [24]. They found their poly(l-lysine)-graft-dextran (PLL-g-Dex, Fig. 3d) accelerates DNA strand exchange reaction by 25- to 30-fold, and they achieved completion of two kinds of DNA molecular operations within minutes in the presence of such "molecular boosters". Similarly, polymer brush systems prepared by Mitomo and Ijiro et al. may provide useful molecular interface for DNA strand exchange when combined with such boosters [25].

Although molecular motors are the most promising source of deformation for A cells, employment of nanomechanical DNA origami devices are also feasible considering their compatibility to DNA signals. Suzuki and Murata et al. have developed stimuli-responsive DNA origami nanoarm/nanospring that can largely bend [26] or spiral [27] according to metal ion addition or pH change (Fig. 3e). Direct interaction of such DNA origami devices and lipid bilayer would trigger distortion of the liposome membrane or

formation of protrusions. To generate micrometer-scale deformation of liposomes with DNA origami devices, co-operative work by multiple DNA origami molecules are necessary despite that self-assembly of multiple DNA origami molecules are still a serious challenge. One possible solution has been proposed by Sakai et al. [28]. They catenated two circular single-stranded DNA using topoisomerase (Fig. 3f). By using such catenated DNA scaffolds, interlocked DNA origami pair has been successfully prepared.

B. Artificial Channels and Transducers (Fig. 4)

Channel proteins that transport ions across cell membranes play important roles in many biological processes such as energy conversion and signal transduction [29]. Among them, mechanoreceptor channels have an interesting property of transmitting non-negligible physical forces in the molecular environment on a scale larger than a cell as changes in the ionic environment across the membrane [30]. However, there are few reports of synthetic channels that artificially emulate this mechanism [31], even though a variety of synthetic ion channels have been reported [32].

Recently, Sato et al. were inspired by a natural potassium-selective ion channel that can respond to mechanical forces applied to the membrane, and designed a molecule that satisfies the two conditions of mechanoreceptivity through dynamic changes in channel structure and formation of a pore with a fixed size (Fig. 4a) [33]. The molecule is a cyclophane, a cyclic amphiphilic molecule composed of a flexible hydrophilic OEG chain and a fluorinated aromatic unit (Fig. 4a, lower) that forms a supramolecular transmembrane ion channel by self-assembly in the lipid bilayer. Current recording measurements and ion transport assays using pH-sensitive fluorescent dyes revealed that the channel responds to mechanical forces on the membrane and exhibits ion selectivity. This study is the first example of a synthetic mechanosensitive potassium channel, and its introduction into artificial lipid membranes will play an important role not only as a model for ion channel research and material purification techniques, but also for molecular information processing across membranes using artificial cell structures.

Synthetic peptides that form channels in lipid membranes have been designed based on natural membrane proteins, such as transmembrane αHelix model [34], cylindrical β-sheet model [35] and β-hairpin model [36]. Their structure-function relationships and stimulus responsiveness have been studied. Taira et al. designed a disulfide dimer of an amphiphilic αHelix peptide and reported their ion channel-forming ability in artificial lipid membranes [37], focusing on the helix-helix interaction, in which the assembly state changes depending on electrostatic interactions (Fig. 4b). Electrophysiological analysis showed that the peptide exhibited strong affinity for the lipid membrane under neutral conditions (Fig. 4b, lower), and that the association of three molecules formed a stable channel from six peptide helices. Intramolecular electrostatic interactions between the helices can be achieved by designing anionic/cationic peptide helices, and the channel activity is found to be pH-dependent. The molecules form ion-permeable channels with a single conductance at concentrations as low as 1 nM, suggesting their potential use as pH-responsive artificial cell membrane devices. This research has further progressed to the design of peptide-peptide interactions to control higher-order structure.

Next, let us discuss some applications of membrane channels. Scanning ion conductance microscopy (SICM), which uses a nanopipette as an imaging probe, is expected to be a powerful tool for high-resolution and information-rich live cell imaging. This technique enables non-contact, nondestructive imaging with high spatial resolution ($\sim$nm) and also provides electrochemical information by measuring the ion current flowing between two electrodes, one in the nanopipette and the other in the external solution [38], [39], [40].

Shoji et al. proposed a probe-type artificial cell membrane system in which membrane channels (nanopores) on an artificial lipid membrane are constructed on the nanopipette surface [41], [42]. The artificial cell membrane is formed on the tip of a microelectrode or nanopipette with a hydrophilic surface to detect molecules by nanopore sensing (Fig. 4c). They first used Ag/AgCl microelectrodes encapsulated in glass pipettes as probes to control the cavity volume between the α hemolysin (αHL) nanopores embedded in the artificial lipid membrane. By doing so, the relationship between the attenuation of the channel current through the nanopores was investigated, and an evaluation method for artificial membrane devices incorporating nanopores was established [41]. Next, as a method to reduce the tip diameter of the probe, the usage of a hydrogel-filled nanopipette to construct a lipid bilayer membrane has been proposed [42]. This method provides highly sensitive chemical sensing because the lipid bilayer is more stable than the one prepared with conventional tip-dip method and the hydrogel at the pore opening reduces the migration rate of the analyte through the nanopore. When the target single-stranded DNA passes through the nanopores, it can be detected as an ion current change (inhibition current). By analyzing this inhibition current, it is possible to obtain information (size, charge, concentration, etc.) on the molecules that have passed through. The SICM system using nanopore probes not only provides a powerful analytical system for biological phenomena, but also leads to a system to monitor the results and progress of molecular calculations provided by artificial cell structures, converting molecular information into electronic information using nanopores.

These membrane channel device-based interface technologies provide a possible picture for future progress in molecular cybernetics research, in which artificial cells use molecular information to compute and make decisions with each other. The environment would consist of a group of artificial cells with membrane devices that exchange molecular signals with each other, and nanopore sensors that are attached onto the artificial cell's membrane to monitor changes in state.

As an example of the application of such membrane devices, Sato et al. have developed an artificially synthesized ultra-fast

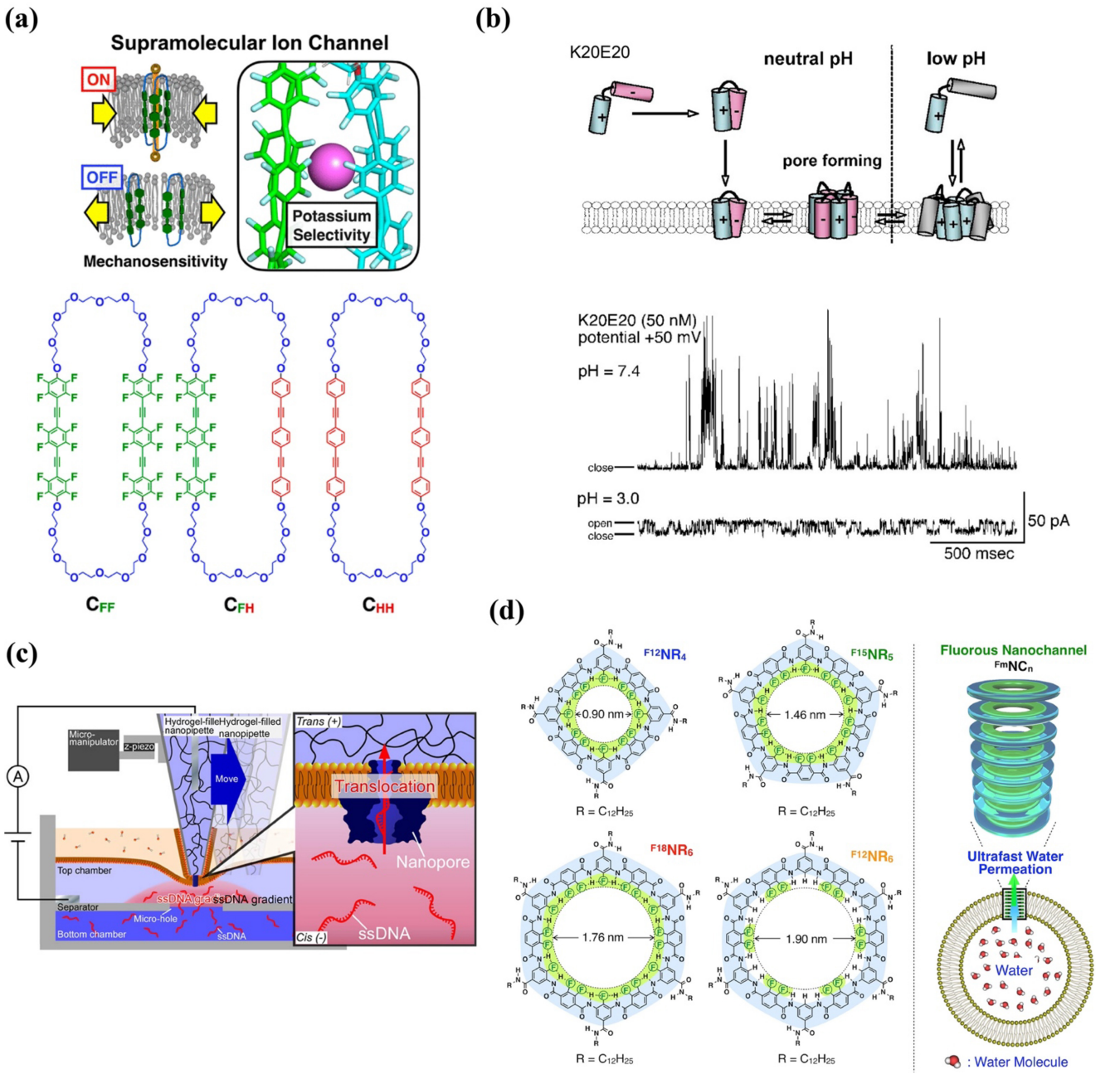

Fig. 4. Artificial Channels and Transducers. (a) (Upper) The supramolecular ion channels formed by highly fluorinated cyclophane CFF was responsive to the mechanical forces applied to the membranes, with potassium ion selectivity. (Lower) The structures of the developed fluorinated amphiphilic cyclophanes. Reprinted with permission from [33]. Copyright 2022 American Chemical Society. (b) (Upper) Suggested scheme for the pore-forming mechanism and pH-sensitive behavior of the designed peptide (K20E20) with their electrostatic interactions. Reprinted with permission from [37]. Copyright 2008 American Chemical Society. (Lower) pH effects on ion-channel activities of the peptides. Erratic conductance patterns with large ion conductivity were recorded in the neutral pH conditions, and the patterns were converted to single-state conductance patterns in the acidic conditions. (c) Spatially resolved chemical sensing using a hydrogel-filled nanopipette and the formation of a planar bilayer lipid membrane at the tip of the pipette. A concentration gradient of ssDNA generated by diffusion from a bottom chamber is measured by manipulating the nanopipette using an SICM system. Reprinted with permission from [42]. Copyright 2022 American Chemical Society. (d) Synthetic water channel. (Left) Molecular structures of a series of fluorous nanorings. (Right) Schematic representation of the supramolecularly polymerized FmNRn into a fluorous nanochannel embedded in a vesicular phospholipid bilayer membrane. Reprinted with permission from [43]. Copyright 2022 The American Association for the Advancement of Science.

and selective "water channel" (Fig. 4d) [43]. Their synthetic oligoamide fluoride nanorings self-assemble in an artificial lipid membrane and form nanochannels with strong water repellency due to their inner walls densely covered with fluorine atoms.

C. Liposome Handling Techniques (Fig. 5)

Methods for preparing liposomes with uniform particle size and reduced concentration variation of each chemical species inside have recently attracted considerable attention as a technology for constructing artificial cells. In

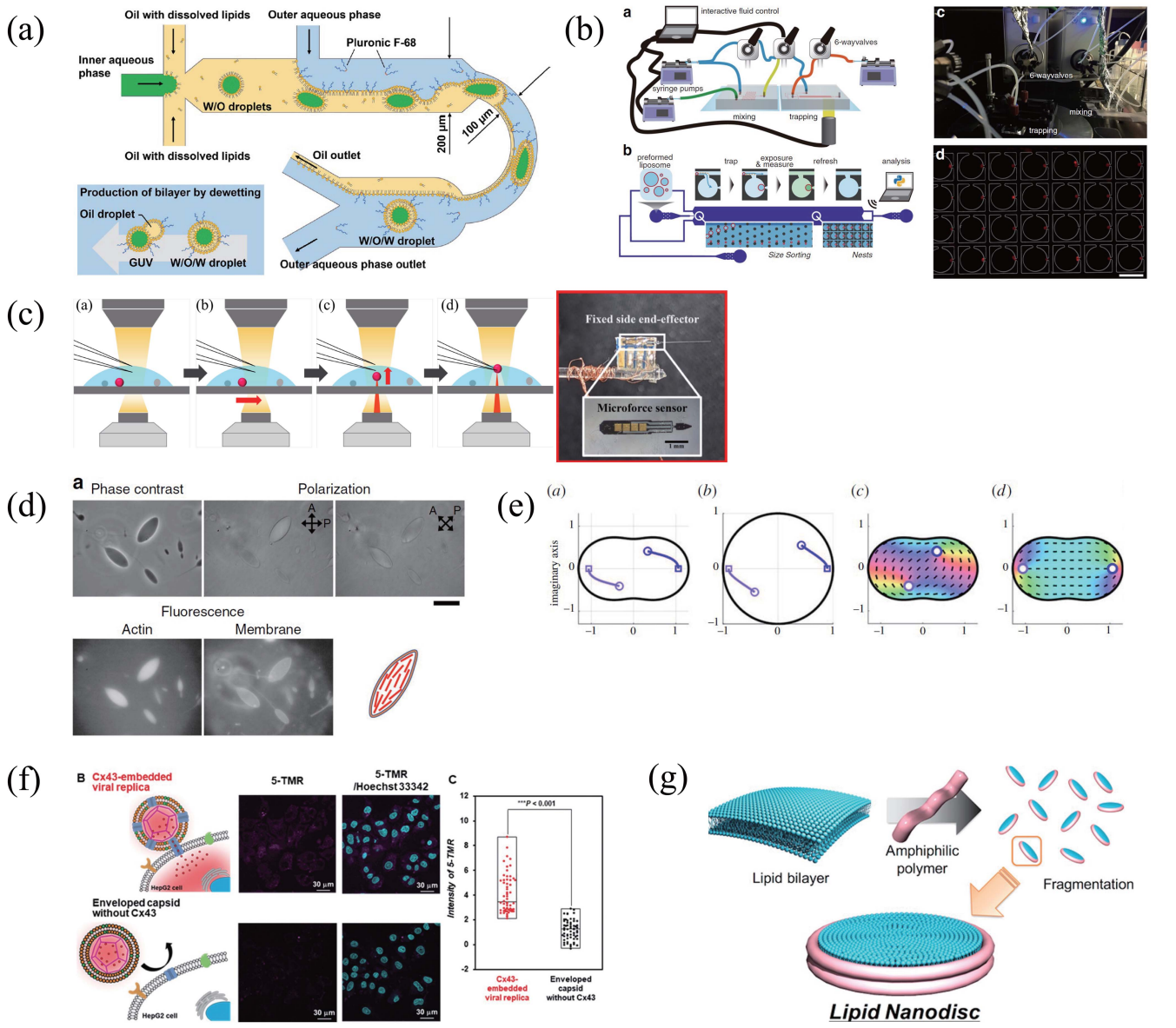

Fig. 5. Liposome handling techniques. (a) Microfluidic device that can fabricate W/O/W double emulsions with surfactant stabilizer Reprinted with permission from [47]. Copyright 2022 Elsevier. (b) Microfluidic device that can sort liposomes by size and capture them individually and automated observation platform for trapped liposomes [50]. (c) Micro-hand system for evaluating the stiffness of a cell by fixing it with a fixation end-effector and directly crushing it. Reprinted with permission from [55]. Copyright 2022 IEEE. (d) Large liposome deformation due to the nematic phase inside liposome by encapsulating actin at high concentration [57]. (e) Theory that can precisely estimate the causal relationship between defects in the liquid crystal and cell morphology [58]. (f) Connexins-loaded enveloped artificial viral capsid composed of β-Annulus-EE peptide [60]. (g) Amphiphilic polymer for lipid nanodisc formation. Reprinted with permission from [61]. Copyright 2017 American Chemical Society.

the Water-in-oil-water (W/O/W) double emulsion template method, three kinds of liquids (water or buffer as the inner aqueous phase, oil and lipid, and water or buffer as the outer aqueous phase) are poured into the channels of a microfabricated fluidic device to form W/O/W double emulsion droplets. The oil phase separates from each droplet to form a lipid bilayer, resulting in the formation of liposomes. Devices used in this method have been reported, including glass capillary combinations [44], photoengineered devices by 3D printers [45], and microfluidic devices fabricated by optical lithography techniques [46], [47]. For example, Dekker's group successfully formed liposomes by coating the relevant wall surface with polyvinyl alcohol and dissolving a thickening agent such as glycerol in the inner/outer aqueous phase and an amphiphilic stabilizing agent in the outer phase [46]. However, uneven flow in the coating process may result in low yield, and the use of thickening agents may reduce the rate of chemical reactions inside the GUV. Therefore, Suzuki's group developed a microfluidic device that does not use coating, but only amphiphilic stabilizers in the outer aqueous phase, and can fabricate W/O/W double emulsions only by controlling the fluid device structure design and temperature (Fig. 5a) [47]. In the future, it is expected to make a significant contribution to the development of methods for the fabrication of functionalized liposomes that can encapsulate DNA nanostructures, fibrous proteins

that form the cytoskeleton, cell-free protein synthesis reaction solutions, etc.

In order for cell-sized liposomes, which are regarded as artificial cells, to function as chemical AI, S, P, and A liposomes should be arranged in that order and adjacent to each other. To achieve this, a technique is required to make the particle size of each liposome uniform and manipulate it to a specific location. Although there have been reports on techniques for creating liposomes with uniform particle size [46], [47], [48], it is difficult to create different types of liposomes and then arrange them adjacent to each other. Therefore, Toyota's group has developed a microfluidic device that can sort liposomes by size and capture them individually, even if they are polydisperse in size at the liposome production stage (Fig. 5b) [49]. The microfluidic device made it possible to capture more than 100 liposomes with a monodisperse size distribution in the range of 10 to 20 micrometers, with a coefficient of variation of about 10%, and observe them simultaneously under a microscope. The group has further developed an automated observation platform that couples the microscope stage, camera, and pump and valve control programs with image identification software to significantly increase the throughput of liposome dynamics measurements [50], [51]. Currently, technology development is underway to design the capture structure in this device to allow three liposomes to be captured, making it a single unit with three adjacent liposomes.

Among the functionalized liposomes used in chemical AIs, those corresponding to actuators are responsible for coupling chemical signals to physical deformations and transmitting signals to adjacent chemical AIs. Although the liposome membrane itself has deformability, it is expected to promote directed elongation by deforming through state changes inside the liposome that receive chemical signals from the P cell. For this purpose, it is considered promising to apply atomic force microscopy [52], microfluidic devices [53], and laser trapping [54], which are widely used to study cells, to evaluate the viscoelasticity of actuators. However, the problem with these techniques is that the dynamic range of forces that can be applied to the entire liposome from the outside is narrow. Kojima's research group overcame this problem by developing a micro-hand system (Fig. 5c) [55]. This system can evaluate the stiffness of a target cell by fixing it with a fixation end-effector and directly crushing it. The resolution of the reaction force measurement is about 1 nN, and the time resolution of the measurement is 10 ms, which enables data acquisition. By applying this method to the direct evaluation of artificial cells that serve as actuators, this method will make a significant contribution to improving the yield of actuators for chemical AI.

For A cells, the mechanism of asymmetric structure formation and expansion/contraction inside liposomes is important. Studies have attempted to induce large deformation of liposomes by internalizing proteins that form cytoskeletons. Although polymerization and depolymerization of tubulin has been the dominant mechanism for liposome deformation into spherical and spindle-shaped liposomes [56], Hayashi's group has reported a large deformation of liposomes due to the nematic phase inside the liposome by encapsulating actin at high concentration (Fig. 5d) [57]. While tubulin can induce deformation according to temperature and pressure change, deformation by the actin in the nematic phase could be induced by forming defects in the actin caused by light irradiation. This mechanism can contribute significantly to chemical AI,

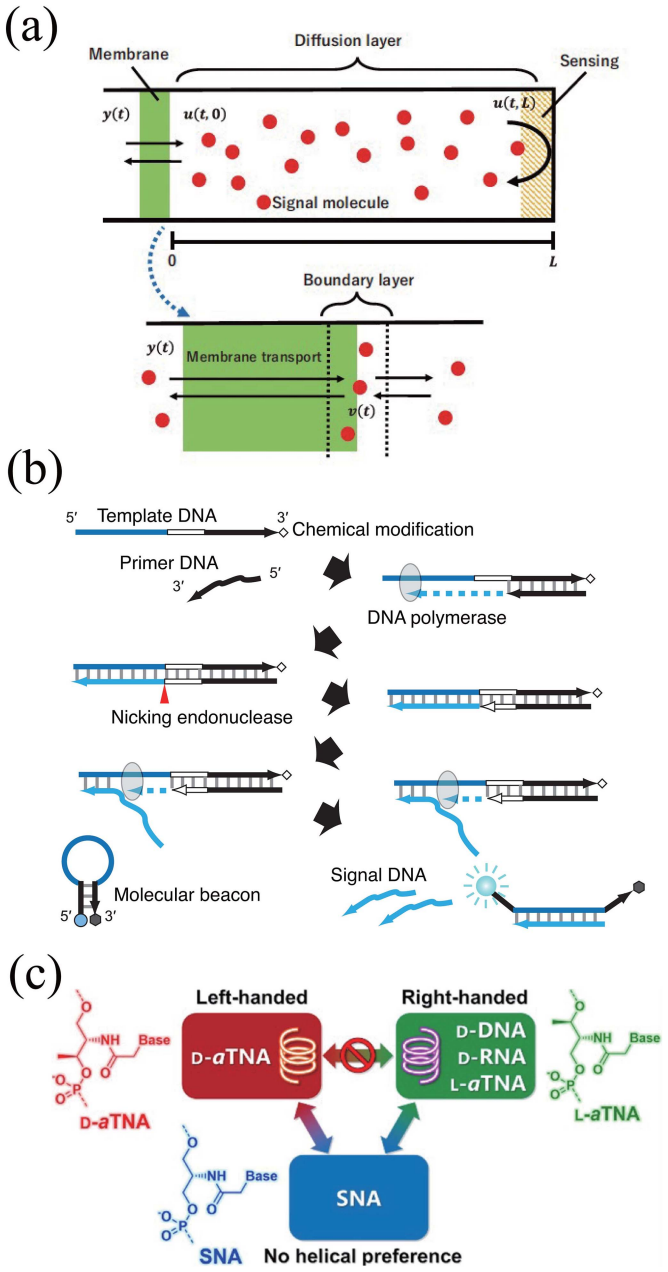

Fig. 6. Molecular computing systems. (a) Outline of the diffusion-based molecular communication channels in bounded environment [65]. Signal molecules (denoted by red circles) bidirectionally diffuse through the membrane (denoted by green area) toward the sensing area (denoted by orange area), in which these two units are L apart. (b) Outline of one-layer single-stranded DNA generation reaction (courtesy of Dr. Ken Komiya of Japan Agency for Marine-Earth Science and Technology) [69], [70]. Input DNA (described by "Primer DNA") binds to the template DNA, and induces a series of reactions denoted by big arrows, where two enzymes (DNA polymerase and nicking endonuclease) facilitate the reactions. (c) Chemical structures, helicities, and hybridization compatibilities among backbone-modified artificial nucleic acids. Left-handed D-aTNA and right-handed L-aTNA do not bind each other, but can communicate via no-helical-preference SNA. Reprinted with permission from [71]. Copyright 2022 American Chemical Society.

in which actuators function with minimal impact on sensors and processors.

A directional deformation of A cells is required for efficient network propagation such that the adjacent P cell can connect to the S cell of the adjacent chemical AI with minimal deformation. In order to induce such specific dynamics, it is an urgent issue to construct a theoretical model for deformation induction as well as to conduct repeated experiments. Miyazako's research group has created a theory that can precisely estimate the causal relationship between defects in the liquid crystal and cell morphology, based on the proposition of what kind of liquid crystal state the cytoskeleton inside the cell is in (Fig. 5e) [58]. According to this theory, one can construct a function of the orientation angle of the cytoskeleton by physically modeling the artificial cytoskeleton enclosed in the actuator as a nematic liquid crystal. Based on this function, the position of defects in equilibrium can be determined by optimizing the elastic energy. This is expected to establish a control method for actuators to deform only in a given direction.

In chemical AI, it is required to implement a reset function for each S, P, and A cells against stepwise responses to chemical stimulus, since they are fractionated by liposomal membranes. One of the most important functions is a system to supply the consumed contents externally (without disrupting the liposomal membrane) for each artificial cell. For this purpose, a method utilizing membrane fusion of negatively charged artificial cells with positively charged small liposomes has been reported [59], but the selectivity of fusion of small liposomes to artificial cells has been low. In contrast, Matsuura's group recently succeeded in loading connexins onto an enveloped artificial viral capsid composed of β-Annulus-EE peptide and positively charged lipids using a cell-free expression system (Fig. 5f) [60]. Such connexin-loaded enveloped viral replica enables molecular transport into cell-sized liposomes.

Furthermore, it is important to connect multiple artificial cells by transducers so that the output from each artificial cell is transmitted to the neighboring cell. The transducers will also have a reset function, but if they cannot be completely reset, initialized transducers must be added and supplied to each artificial cell. At this time, Yasuhara's group has developed a membrane fusion technique using lipid membrane "nanodiscs" [61] in addition to liposome membrane fusion technology (Fig. 5g). Simply by changing the physicochemical environment (temperature change, salt concentration, dilution, etc.), lipid nanodiscs can be fused to target liposomes to deliver additional hydrophobic molecules such as transducers. This is expected to lead to not only addition and replenishment, but also in situ recombination of membrane properties and logic circuits of S, P, and A cells.

D. Molecular Computing Systems (Fig. 6)

The construction of molecular communication systems using biomolecules that diffuse in liquids as carriers of information is advancing. Molecular communication is a reliable method of information transfer that is used universally in biological systems, both inside and outside of the cell [62]. Recent developments in nanotechnology have made it possible to construct artificial molecular communication systems using microfluidic devices [63]. In general, signals transmitted to a receiving device in a liquid are related to the concentration of molecules (intensity) and the concentration change (frequency). However, artificially designing a reliable molecular communication system is difficult because of the spatio-temporal transmission of molecules, where the waveform of the signal molecular concentration is smoothed by diffusion, resulting in loss of information [64]. Further technological breakthroughs require theoretical improvements in molecular communication. A method has been proposed to analyze the effects of the diffusion coefficient and membrane transit velocity of communication molecules on the signaling characteristics between transmitting and receiving devices that bidirectionally communicate (Fig. 6a) [65].

DNA computing, which attempts to compute information through designed DNA reaction systems, is still developing [66]. In principle, it is possible to construct more sophisticated molecular systems by "connecting" multiple DNA reaction systems into a single module (circuit) in series or parallel [67]. In many cases, appropriate amplification of molecular signals is required when multiple devices are linked together, and nucleic acid amplification circuits are considered to be one of the main basic circuits in DNA computing. It is important to select an amplification circuit with the appropriate gain and response time for the intended use and specifications. Attention has increased for designing amplification circuits with DNA strand displacement reactions without enzymes [68], million-fold gain [69], [70] (Fig. 6b), and XNA-HCR [71] (Fig. 6c), which uses backbone-modified artificial nucleic acids to suppress nonspecific amplification independent of the input molecules.

IV. Perspective

In line with the increasing popularity of AI research in many scientific fields, various excellent results have been reported in the first few years since the concept of "molecular cybernetics," which aims to develop chemical AI is proposed. In addition to those described in this paper, other promising technologies, such as a new method for constructing transmembrane DNA and a counting DNA circuit, for use as transducers and processors are being developed. By bringing together these technologies, the transfer of molecular information across two lipid bilayers, which should be the first milestone of the field, may be realized within a span of a few years.

Individual achievements presented above are expected to contribute to other fields, not only to the development of chemical AI. For example, Sato's water nanochannels are expected to exhibit nearly perfect salt reflectance for desalination of salt water [43]. Matsuura's viral replica has great potential for application in vaccination [60].

The field of molecular cybernetics, which emerged from the development of molecular robotics, is steadily taking its first steps.

ACKNOWLEDGMENT

The authors thank Prof. Dr. Akihiko Konagaya, Prof. Dr. Hideyuki Nakashima, Prof. Dr. Masami Hagiya, and Prof. Dr. Mizuo Maeda, for their supports with stimulus discussions for the establishment of the concept of the field.

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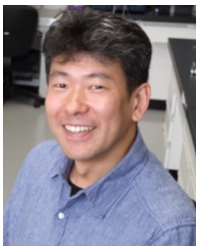

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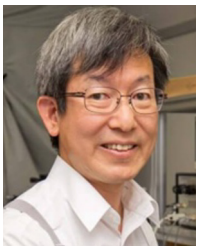

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