

*Review*

# Robust dynamics of synthetic molecular systems as a consequence of broken symmetry

Yoshiyuki Kageyama <sup>1,\*</sup><sup>1</sup> Faculty of Science, Hokkaido University; y.kageyama@sci.hokudai.ac.jp

\* Correspondence: y.kageyama@sci.hokudai.ac.jp; Tel.: +81-11-706-3532

**Abstract:** The construction of molecular robotic-like objects that imitate living things is an important challenge for current chemists. Such molecular devices are expected to perform their duties robustly to carry out mechanical motion, process information, and make independent decisions. Dissipative self-organization plays an essential role in meeting these purposes. To produce a micro-robot that can perform the above tasks autonomously as a single entity, a function generator is required. Although many elegant review articles featuring chemical devices that mimic biological mechanical functions have been published recently, the dissipative structure, which is the minimum requirement, has not been sufficiently discussed. This article aims to show clearly that dissipative self-organization is a phenomenon involving autonomy, robustness, mechanical functions, and energy transformation. Moreover, the author details the recent experimental results of an autonomous light-driven molecular device that achieves all of these features. In addition, a chemical model of cell-amplification is also discussed to focus on the generation of hierarchical movement by dissipative self-organization. By reviewing this research, it may be perceived that mainstream approaches to synthetic chemistry have not always been appropriate. In summary, the author proposes that the integration of catalytic functions is a key issue for the creation of autonomous microarchitecture.

**Keywords:** dissipative structure; energy conversion; mechanical work, self-oscillation; collective dynamics; autonomous motion; self-replication; autocatalysis; molecular motor; molecular robot

## 1. Introduction

It is one of the dreams of chemists to create life or its imitative system using a synthetic chemical method.[1,2] Life is thought to be a collection of nanomachines, and their cooperative behavior is capable of performing work continually in a stationary environment. The process termed ‘dissipative self-organization’ is one of the key processes involved in this framework.[3] On the other hand, typical inanimate objects in which modules are not self-organized can only perform work passively under transient environmental conditions. Here, work is broadly defined to denote the transfer of energy to the surroundings in a form other than thermal motion; the mechanical work this involves is defined in Section 2. The function of continuously developing in a stationary environment is defined as an autonomous function: autonomy is the realization of continuity by the internal factors of the system.

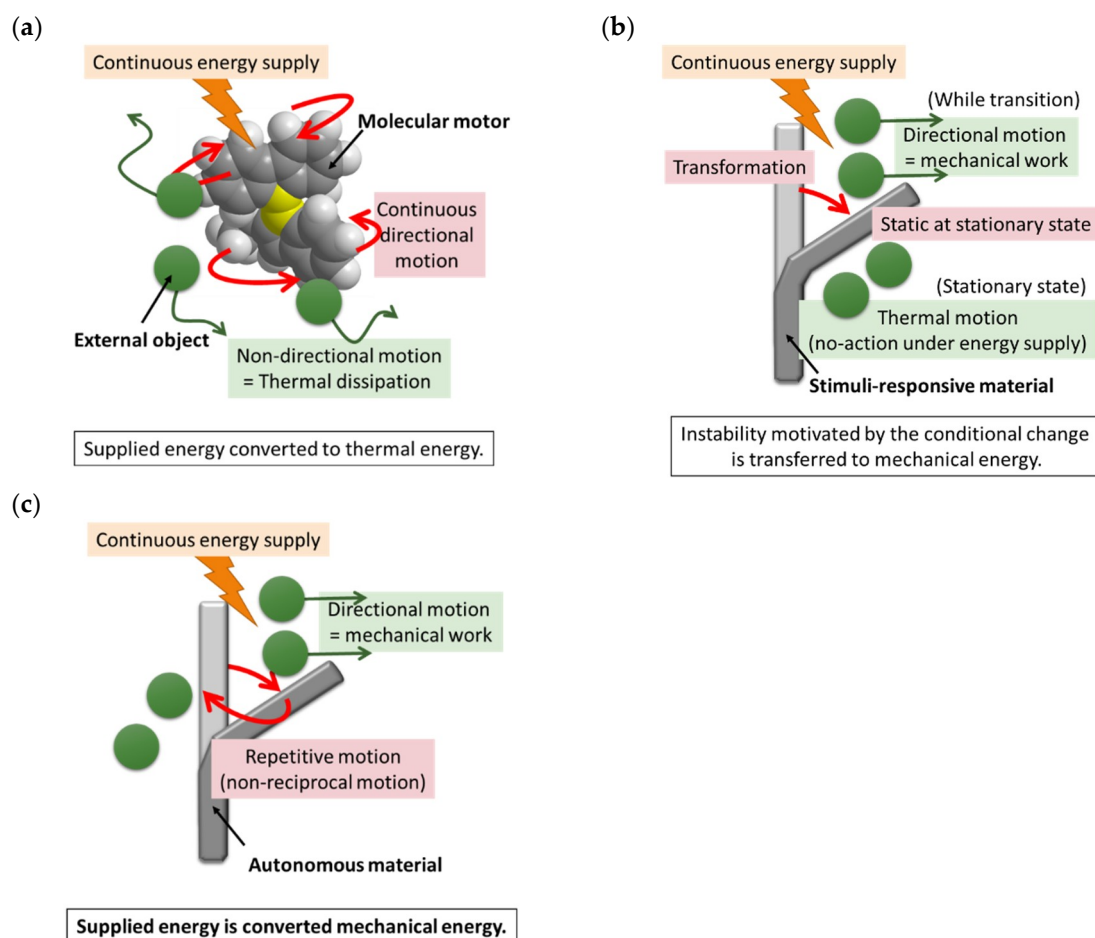
For example, fluorescent molecules emit light continuously in a photostationary state; catalyst molecules continuously convert reactive substrates into reaction products. The continuous function of these molecules (broadly defined as ‘work’) is derived from the fact that the molecules consist of self-organized nuclei and electrons. Focusing on such electronic characteristics on the molecular scale, a substantial number of chemical studies have been conducted. Because molecular structures well represent the self-organized forms of nuclei and electrons, chemists can predict and consider various functions by looking at molecular structural formulas and calculating the density of their electron distributions, while studying phenomena from the perspective of these electronic properties.



This paper describes the autonomous function of molecular assembly generated by molecular self-organization. This concept realizes continuous work at a larger level than the molecular level. It is a concept of nanotechnology that is expected to be applied to material transfer devices, molecular robots and computers, and to drive innovation in the field of energy research. Dissipative self-organization remains an attractive keyword for current chemistry. On the other hand, the present author is uncertain whether or not our community genuinely values the concept of dissipative self-organization. One reason for this doubt lies in the fact that the conceptual vocabulary and approaches of nonequilibrium thermodynamics are challenging for chemists who perform their experiments in a flask. Another reason is that clearly realized studies of dissipative self-organization in synthetic chemistry are limited in number. Besides, capturing a temporally developing phenomenon in a printed research paper is not easy. In addition, the terms of self-organization and self-assembly are frequently synonymous; in Japanese, for instance, they are the same word. In this paper, the basic concept of dissipative self-organization is defined in order to underline its importance to current chemical research, and recent developments in synthetic studies are reviewed.

## 2. Dissipative self-organization is a concept for autonomous mechanical work

Atkins' *Physical Chemistry* describes mechanical work as 'the transfer of energy that makes use of organized motion in the surroundings'[4] and distinguishes it from the transfer of energy to disordered thermal motion. In other words, to create molecular devices capable of performing useful work, it is necessary to provide the devices with proportions that will create organized movements in the surroundings (Figure 1a). Hence, a single synthetic molecular motor is too small to achieve beneficial mechanical work independently and, therefore, the motor molecule must either be positioned in a heterogeneous field, or the molecules must be assembled.[5] This text considers the latter approach in detail. If a large number of molecules are merely assembled to increase the device's size, the movement of molecules is time-averaged, and the molecules show no macroscopic changes under a steady condition (Figure 1b). This state is referred to as chemical or near-chemical equilibrium, and under it, the molecules cannot create organized movements in their surroundings. In other words, to create molecular devices capable of performing beneficial work, it is necessary to introduce 'a mechanism in which the devices continually demonstrate macroscopic changes even if the environment is in a steady state' (Figure 1c). This mechanism is referred to as dissipative self-organization. In short, it is a mechanism for generating macroscopic motions via movement at the molecular level. The generated motion also has the potential to create intensive motion in a larger hierarchy. Furthermore, due to the ability of the self-continuous action to an external object, the devices that exhibit dissipative self-organization can act as an oscillation generator to actuate repetitive motion of equilibrial materials. The creation of such molecular technology will lead to the invention of autonomous molecular robots, autonomous molecular pumps and autonomous molecular information processors.



**Figure 1. How to compel molecular materials to work.**

(a) A small molecular motor cannot carry out mechanical work for several reasons, one of which is that the transferred energy is converted to thermal energy immediately. (b) A Stimuli-responsive material can perform work only while relaxing the instability motivated by a shift in an external condition. (c) Autonomous transformation of a molecular system can perform work via energy transformation. The green circles denote objects subjected to force in the surroundings.

### 3. Dissipative self-organization for robustness and energy conversion

In chemistry, transient aspects of the system are generally described by reaction rate equations. Here, we consider chemical reactions in a homogeneous solution, where (a) the symmetry of reactions are broken, and (b) the kinetic constants ( $k_s$ ) are consistent. An autocatalytic reaction, in which the  $A \rightarrow B$  reaction is accelerated by B, is introduced as a symmetry-broken reaction.[6] The reaction with the co-existence of a non-autocatalytic process, the kinetics equation of which termed as a logistic equation. An example is shown in Figure 2a. After introducing the logistic curve, general textbooks of nonlinear chemistry describe Lotka-Volterra type dynamics. The open reaction of  $A \rightarrow B \rightarrow C \rightarrow D$  with two autocatalytic steps demonstrates oscillatory behavior in composition (Figure 2b).[3,7] On the other hand, we consider a triangular type reaction of  $A \rightarrow B \rightarrow C \rightarrow A$ , aiming to distinguish the system's boundary.

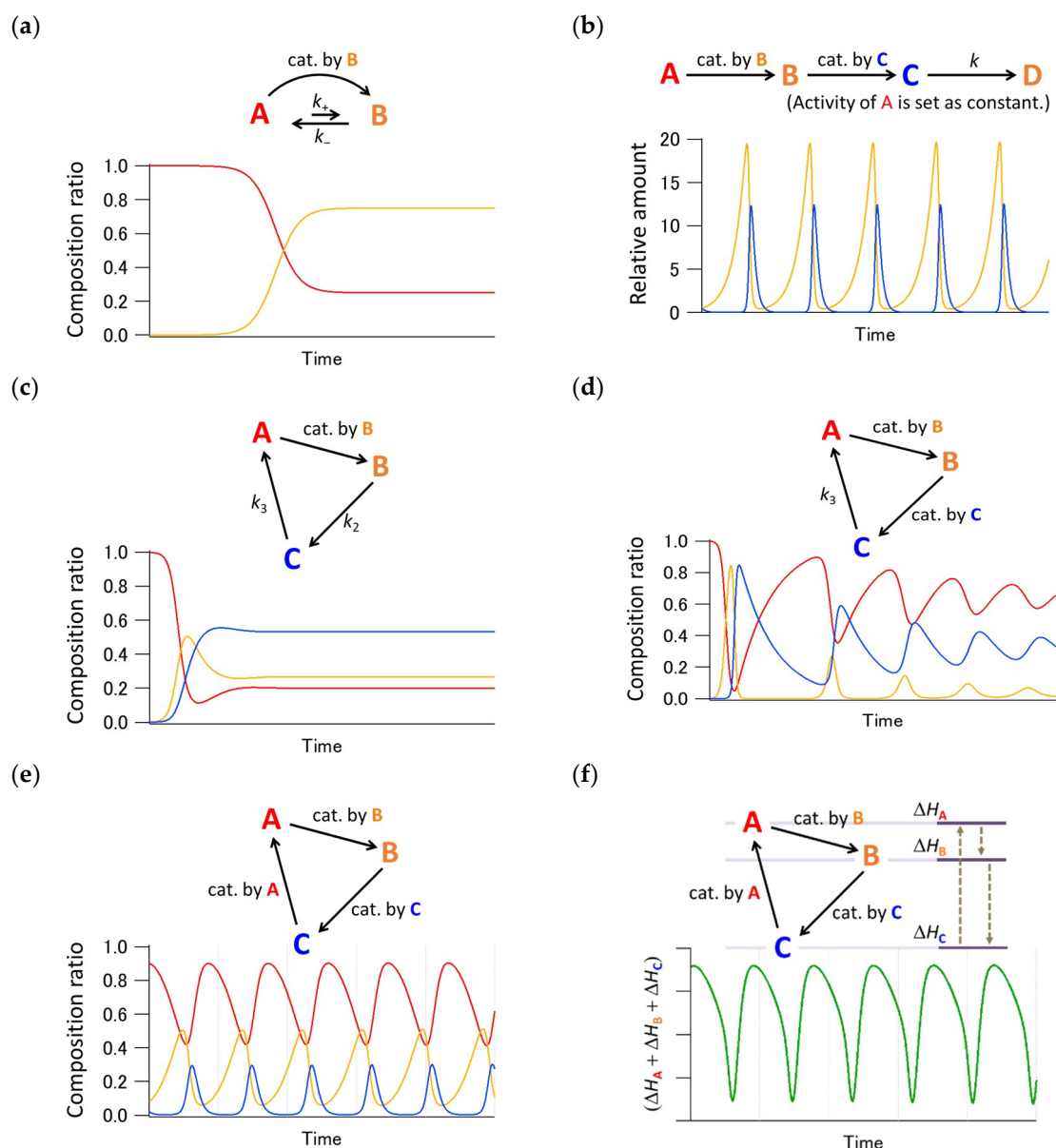
In triangular-type reactions with one autocatalytic step, it is easy to achieve equilibrium, as shown in Figure 2c. In reactions with two autocatalytic steps, the reaction achieves equilibrium with oscillatory composition changes, as shown in Figure 2d. On the other hand, in reactions with three autocatalytic processes, periodic oscillation in the composition ratio is autonomously demonstrated, as shown in Figure 2e. As described here, the kinetic equations indicate that multi-molecular oscillations may be generated by the contribution of plural nonlinear processes. Note that

autocatalysis is employed only because it is a well-known and significant nonlinear chemical process—other symmetry-broken phenomena may contribute to realizing the oscillatory system.

However, the enthalpy of the system varies with oscillation (Figure 2f). The actual system dissipates thermal energy outside the system when the enthalpy decreases, and the periodic behavior is relaxed and terminated. This fact suggests that a supply of convertible energy from outside the system is required to develop the oscillation. In summary, a system with autonomous multi-molecular oscillation can be realized as shown in Scheme 1. The reaction scheme is somewhat similar to a catalytic reaction and a fluorescence scheme: the difference is that the nonlinear phenomena are involved in the scheme and act inter- or intra-molecularly.

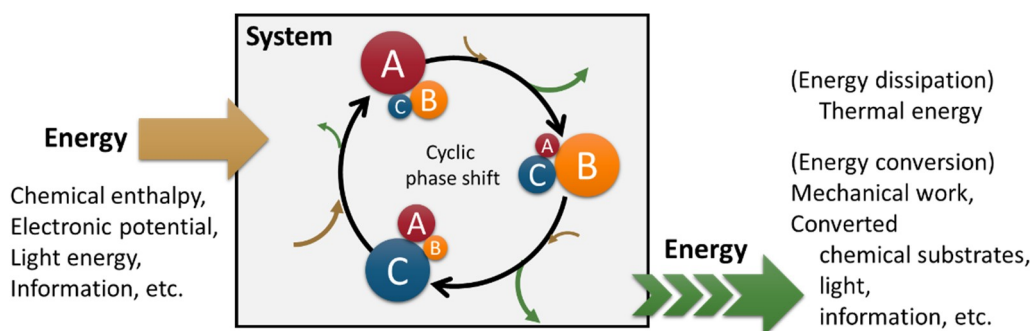
This temporal pattern in a multi-molecular system under continuous energy supply and periodic energy dissipation is referred to as a dissipative structure: while making cyclic transitions ( $A \rightarrow B \rightarrow C \rightarrow A$ ) on the molecular level, periodic behaviors are generated as a molecular ensemble, the time-scale of which is larger than molecular-level conversion. Although we cannot predict when a chemical reaction happens at the molecular level, we can predict when the macroscopic change occurs by observing the robust temporal pattern. Even if the reaction solution is reduced by half or is frozen temporarily in the middle of the reaction, the autonomous oscillation is robustly maintained. These features are characteristic of dissipative structures.

In a homogeneous system, the variation of the system's enthalpy is dissipated as thermal energy because the system cannot form organized motion. Regarding devices with shapes (such as molecular assemblies), variation in enthalpy can be used to apply mechanical work to the surroundings. This energy-conversion function at the multi-molecular scale is the essential attraction of dissipative self-organization with molecular self-assembly.



**Figure 2. Composition curves of autocatalysis involving reactions.**

(a) Logistic-type composition curve. (b) Lotka-Volterra-type composition oscillation. (c) Composition curve for a triangle reaction including one autocatalytic process: the system tends to equilibrium even if the curve sometimes shows oscillatory behavior. (d) Composition curve for a triangle reaction including two autocatalytic processes. (e) Oscillatory composition curve in a triangle reaction including three autocatalytic processes. (f) The variation in total heat of formations of A, B and C while the change is shown in (e). Because the exteriorization of energy from the system occurs when the sum of the heat of formations decreases, an external energy supply is required to maintain the oscillation. The red, orange and blue lines denote compounds A, B, and C, respectively. The equations for the numerical analysis are described in Appendix A.



Scheme 1. Conceptual scheme for an autonomous system.

#### 4. Research aiming mechanical work with energy conversion

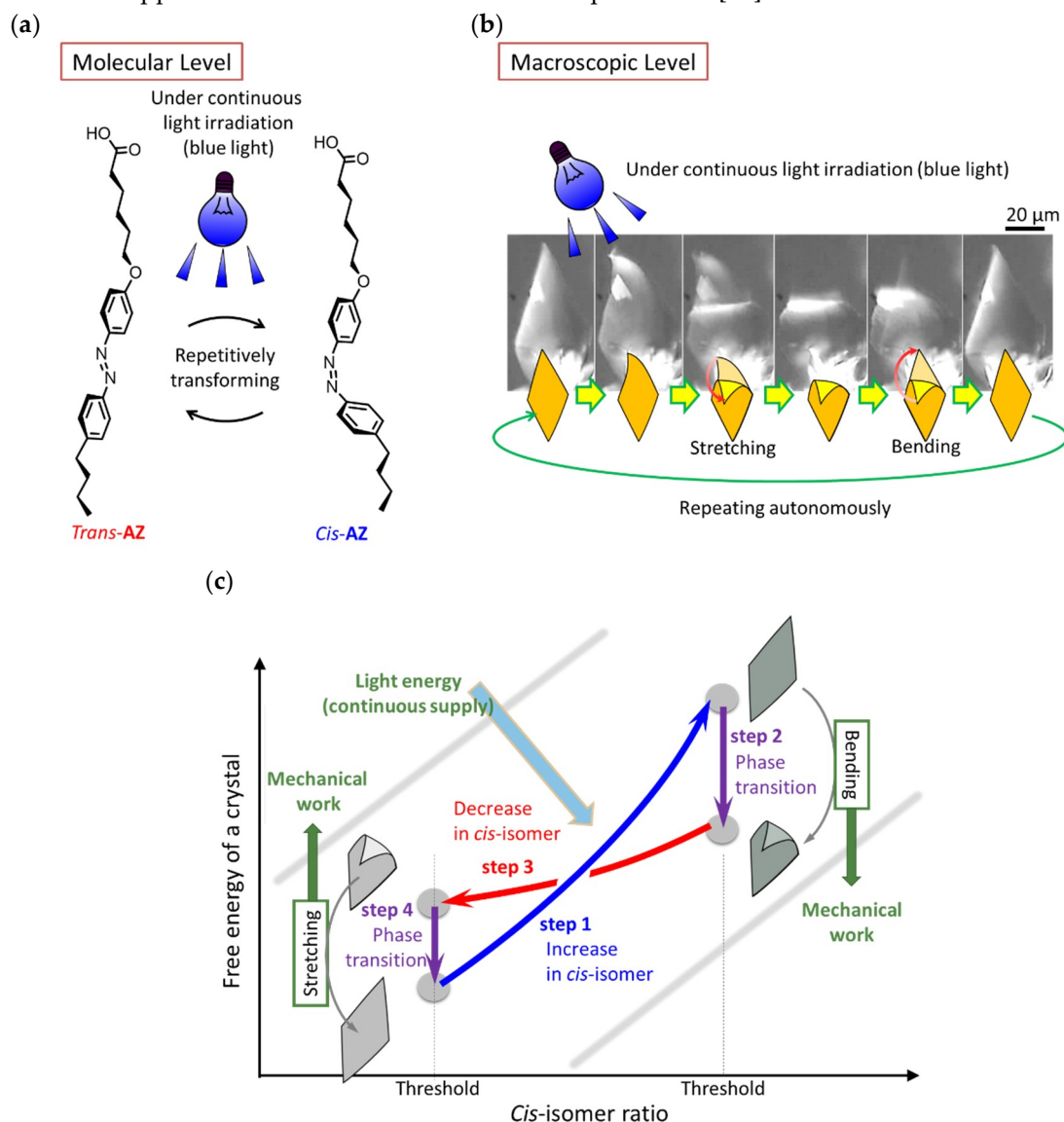
Molecular machines and motors, which are defined as molecules that are expected to convert supplied energy into mechanical forces and motion, have attracted considerable attention among chemists.[8-12] Molecules that reversibly alter their equilibrium structures triggered by shifts in external conditions are known as molecular machines, distinguishing them from molecular motors, a term denoting molecules that maintain their symmetry-broken motion under the continuous supply of energy.[11] In contrast to the molecular machines, the symmetry-broken motion of molecular motors may perform autonomous work in molecular-level space if in contact with another object. Feringa's research into nano-cars may be an example, although the experiment was conducted using an intermittent electric current.[13] Photoinduced ion or electron transportation across membranes[14,15] are also examples.[5] However, to attain more significant autonomous work at the multi-molecular scale, the concept of dissipative self-organization is required. Even if we gather molecular motors and supply energy, the motions are time-averaged and the energy is dissipated as thermal energy. In fact, according to Feringa's report, the motion of a glass-rod on a molecular motor-containing liquid crystal was terminated despite the continuous energy supply,[16,17] similar to the system employing molecular machines.[18,19] Therefore, his collaborators are currently directing their efforts to the design of multi-molecular systems where the motors are synchronized to realize mechanical work at the macroscopic level.[20]

As mentioned here, the synthetic challenge towards active work is in the creation of macroscopic and self-continuous motion. This consideration has been often pointed out recently,[12,21] and one successful example was published already.[14] The way without using a chiral molecule was different from the mainstream method. Molecular-level chirality (e.g., chirality due to an asymmetric carbon) is not the requirement for the motions of macroscopic objects, although symmetry-breaking is a critical factor in the motion of materials. Herein, the autonomous flipping and swimming of a submillimeter-size molecular-assembly is introduced.[22-24]

The submillimeter-size assembly of an achiral azobenzene derivative (**AZ**) showed autonomous bending-unbending motion under continuous light irradiation (Figure 3). The photochromic compound repetitively changes its molecular structure between *trans*- and *cis*-isomers under light irradiation. Ordinarily, repetitive photoisomerization yields a mixture of isomers, the composition ratio of which is constant and depends on the photoreaction rates. However, in the study, a phase transition occurred before the ratio achieved the equilibrium value, switching the reaction rates. Coupling the sets of photoisomerization and its induced phase transition led to the periodic transition of the increase in *cis*-isomer, the morphological change, the decrease in the *cis*-isomer, and the morphological recovery.[22,25] The enthalpy also changed periodically with the cyclic process:[23] the cycle enabled autonomous energy conversion from light to mechanical work. At the bending motion, another asymmetry defines the direction of the transformation. According to the single-crystal analysis,[23] the space group of the assembly was  $P_1$ , and it was assumed that the asymmetry concerns the direction of bending. In addition, some break in symmetry is required to produce an autonomous swimming motion: if the bending-and-unbending motion is spatially reciprocal, it is impossible for the assembly to swim in water, as the Scallop theorem indicates.[26] The directional



swimming of the assembly indicated that the morphological changes occurred in a non-reciprocal manner.[24] Further, the authors also demonstrated signal-dependent pattern formation, a concept that can be applied to molecular-based information processors.[23]



**Figure 3. Self-sustaining mechanical motion of azobenzene assembly under continuous blue-light irradiation.**[22,23](a) Molecular-level repetitive transformation of the component molecule (AZ). (b) Micrographs of the macroscopic autonomous flipping motion under light irradiation. (c) Schematic energy diagram for the autonomous cycle: mechanical work was performed at the steps of exergonic morphological change. All figures were reproduced from the original data with permission from Wiley-VCH 2016.

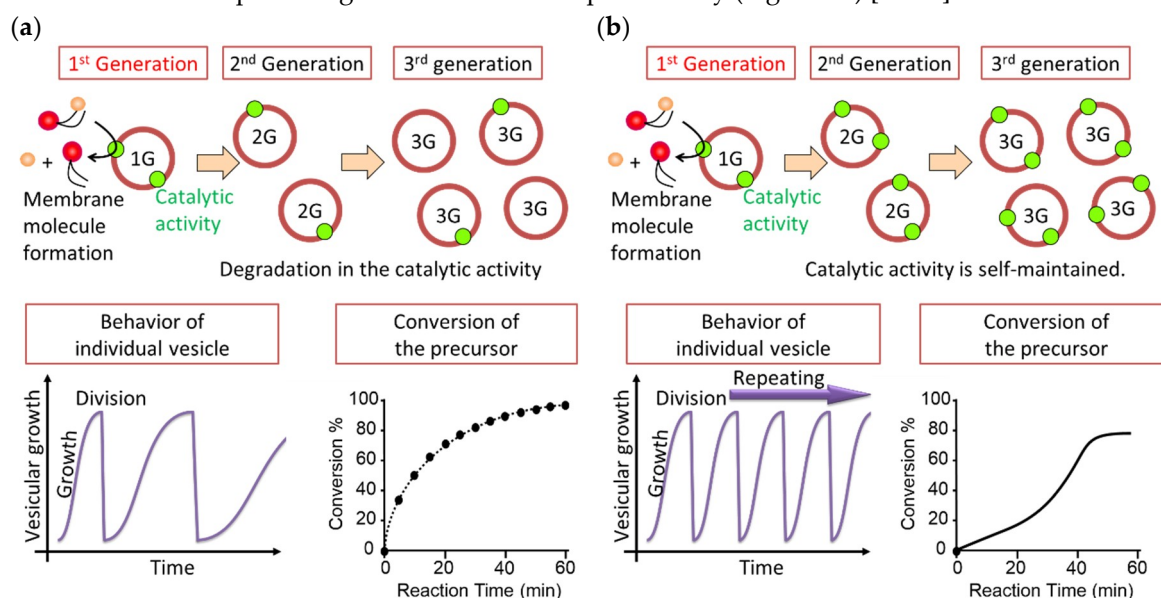
Applying stimuli-responsive materials, oscillatory motions and directional motions have also been reported.[27-39] Stimuli-responsive materials generally terminate their motion when the systems achieve equilibrium. The oscillations in those studies were motivated by the coupling of the directionality of external energy-supply and the time-delayed transition of materials.[25,37] Therefore, we can anticipate that the motions are characterized and controllable by the external conditions, but the motions lack robustness: for example, adjustment of the energy source position seriously affects the mechanical behavior.[25] Some researchers wrongly regard the feature as taxis, but the feature is owing to the lack in self-excitation. On the other hand, dissipative self-organized materials possess the feature of autonomy. The sustainability and directionality of the movements are guaranteed by the internal factors of the materials. The series of studies of BZ-hydrogels, which

are hydrogels periodically repeating swelling and unswelling through the Belousov-Zhabotinsky (BZ) reaction, clearly indicated the superiorities of dissipative self-organization for mechanical device applications.[40,41]

## 5. Research into self-developing molecular systems: the chemical model of cell amplification

Cell amplification is also intrinsic to living things.[1,2,42-44] The pioneering study of the chemical model of cell amplification was reported by Luisi.[45,46] The team monitored the increase in oleate assembly in water following the addition of oleic anhydride and concluded that the autocatalytic hydrolysis of the anhydride occurred in the oleate assembly to form oleic acid.[46] Inspired by the study, Sugawara's group designed a system where a membrane molecule formed from a bipolar amphiphile via hydrolysis catalyzed by a molecule embedded in the vesicular membrane and, thereby, captured the growth-and-division dynamics of vesicular assemblies.[47,48] In addition, they succeeded in demonstrating the amplification of DNA via polymerase chain reaction within the vesicles.[49,50] Furthermore, the group firstly realized autocatalytic vesicular amplification systems, via organic synthesis.[51,52] Following these studies, Devaraj's group[53] also reported the production of an autocatalytic membrane amplification system, where a molecular catalyst formed spontaneously.

Considering the intrinsic feature of cell amplification, the concept of autocatalysis is fundamental,[54,55] and all self-reproductions occur in an autocatalytic manner.[6,56-69] In the vesicular self-reproduction system without autocatalysis, the generated vesicles were different from the original ones – the catalytic ratio decreased proportionally in each generation, and the system tended to equilibrium, even if the precursor for the membrane molecule was continuously supplied (Figure 4a).[47,48,50] This behavior is the same as inanimate systems. On the other hand, in the autocatalytic system, the catalytic ability is maintained across generations. When the precursor is supplied continuously, or an excess amount of precursor is presented, or under both conditions, the individual vesicle repeats its growth and division periodically (Figure 4b).[51-53]

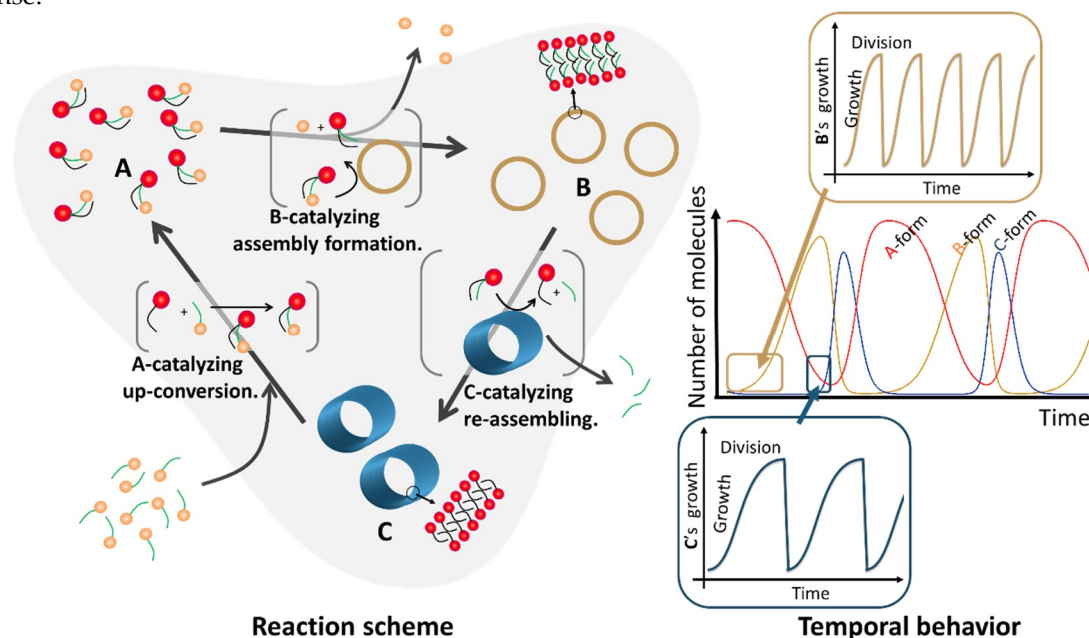


**Figure 4.** The difference between (a) non-autocatalytic and (b) autocatalytic vesicular self-reproduction.

Besides, as Fletcher comments on his autocatalytic micellar system,[70,71] a cyclic reaction with an autocatalytic vesicular formation maintains the vesicle numbers in an open system: the scheme is represented in Figure 2c (and Figure 2a). Developing the concept, we would like to consider the existence of one additional autocatalytic reaction: the system where the vesicle becomes prey to a larger self-assembly (the consumption ratio is proportional to the number of the larger assembly), and the larger self-assembly decomposes. The reaction equation of the system is complicated because



of the diversity in molecular numbers in each vesicle. Nevertheless, it can be expected that the behavior can be represented by the Lotka–Volterra model (if the decomposition is exhausted to the exterior of the dispersion: Figure 2b) or the similar model shown in Section 3 (if the exhaust is recycled autocatalytically by accepting energy from outside the system: Figure 2e). Under such conditions, a spatially and temporally larger oscillation than the vesicular growth–division periodicity will be generated (Figure 5). This predator–prey concept is linked to the robustness of nature in an overall sense.



**Figure 5.** Conceptual illustration for a hierarchical system composed of autocatalytic assembling processes. Spatially and temporally larger oscillation generating a molecular assembly that appears and disappears repetitively.

## 6. Conclusions and perspectives

Dissipative self-organization is the concept of the cooperation of dynamics to form larger dynamic systems.[3] At the nano level, the coupling of thermal fluctuation and a symmetry-breaking phenomenon with energy supply forms a tiny but organized dynamic system. Once organized dynamics are generated, more robustness and more significant organized motion are formed if symmetry-breaking processes are involved. Through iterative self-organization, a highly hierarchical molecular world is constructed. The symmetry-breaking phenomena contribute to making the system differ from the equilibrium structure. Here, a supply of convertible energy is required to realize self-organization, and both the reception and the dissipation of the energy occur autonomously. The concept of dissipative self-organization is directly linked to the chemical energy conversion to achieve autonomous mechanical functions.

We chemists ordinarily encounter self-organized phenomena. If we consider a molecule to be a thermodynamic system composed of electrons and nuclei, the system demonstrates self-organized behavior whether the molecule is termed a machine or not. However, such systems are too small to perform mechanical work, and the assembly of molecules is, thus, proposed to meet this function. However, controlling the symmetry-breaking in multi-molecular level is a complex task: the artificial system of a molecular assembly tends to form its equilibrium structure. The BZ reaction which was applied to mechanical gel,[40,41] and the recent azobenzene-assembly system[22–24] are successful examples. The creation of chemically fueled mechanical work is particularly challenging: if we outdistance the system from the thermal fluctuation level by consuming the dilute energy of chemical compounds, we have to recruit effective ratcheting phenomena.

A recently proposed concept, ‘dissipative self-assembly’ seems to share the same issues.[72–77] However, from the author’s standpoint, the claims of dissipative self-assembly are still unclear and

weak in the aspect of the distancing from equilibrium: most of the papers reported consecutive reactions where the intermedium products were assemblies and claimed that the assembled state can be maintained through continuous substance supply.[70,71,78-85] The structure of such systems is not dissipative structure but equilibrium structure, according to the definition by Prigogine.[3,86] In this context, the supplied energy is consumed to sustain the assembly, but not for autonomous tasks.[87,88] To imitate the living dynamics clearly, we have to employ one or more symmetry-breaking effects to replace the system from the equilibrium structure at the tentative state to a nonequilibrium resume.

However, a negative attitude to the current difficulties in imitating the intrinsic features of living dynamics is misplaced. One of the reasons for the struggle to reproduce autonomous dynamics is that chemists attempt to create mechanical materials using switchable molecules, so-called molecular machines. Such molecules are convenient for chemists, because their status is easily controlled. Yet in living things, not switching motions but continuous motions do power autonomous work. In other words, enzymes work with ratcheting mechanisms to prevent the system from attaining equilibrium. By imitating the function of enzymes[89-91] – molecular-recognition with nonlinear adaptation, and repetitive transformation with energy conversion – and by assembling the synthesized products, the author believes that we chemists will attain breakthroughs in nanotechnology; indeed, research based on this perspective has recently begun.

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## Appendix A

Each graph in Figure 2 was the result of numerical analyses of Equations A1–A7. The symbols of  $\chi_s$ ,  $k_s$ , and  $t$ , denote the molar fractions, kinetic constants, and time, respectively. The calculated timespan was from 0 to 1000 (arbitrary unit). The 'N's denote the relative number of portions. To solve the ordinary differential equation, the ODE45 method was used and operated by Matlab 2020a software provided by The Mathworks Inc, USA. For Figure 2a the following equations were used:

$$\frac{d}{dt}\chi_B = (k_1\chi_B + k_+)\chi_A - k_-\chi_B, \quad (\text{A1})$$

$$\chi_A = 1 - \chi_B. \quad (\text{A2})$$

For the demonstration, 0.04,  $4 \times 10^{-7}$ , and 0.01 were assigned for  $k_1$ ,  $k_+$ , and  $k_-$ , respectively, and 1 was assigned for the initial molar fraction of A. For Figure 2b the following equations were used:

$$\frac{d}{dt}N_B = k_1N_B - k_2N_BN_C, \quad (\text{A3})$$

$$\frac{d}{dt}N_C = k_2N_BN_C - k_3N_C. \quad (\text{A4})$$

For the visualization, 0.03, 0.02, and 0.1 were assigned for  $k_1$ ,  $k_2$ , and  $k_3$ , respectively, and 0.5 was assigned for the initial numbers of B and C. For Figure 2c, 2d, and 2e the following equations were used:

$$\frac{d}{dt}\chi_B = (k_{AB}\chi_B + k_1)\chi_A - (k_{BC}\chi_C + k_2)\chi_B, \quad (\text{A5})$$

$$\frac{d}{dt}\chi_C = (k_{BC}\chi_C + k_2)\chi_B - (k_{CA}\chi_A + k_3)\chi_C, \quad (\text{A6})$$

$$\chi_A = 1 - \chi_B - \chi_C. \quad (\text{A7})$$

The subscriptions of AB, BC, and CA indicate the kinetic constants of autocatalytic steps of  $A \rightarrow B$ ,  $B \rightarrow C$ , and  $C \rightarrow A$ , respectively. Each value for the calculations is indicated in Table A1.

**Table A1.** Values assigned to each parameter for the numerical analysis.

Entry	$k_{AB}$	$k_1$	$k_{BC}$	$k_2$	$k_{CA}$	$k_3$	$\chi_B(\text{initial})$	$\chi_C(\text{initial})$
Figure 2c	0.1	0	0	0.02	0	0.01	0.001	0.001
Figure 2d	0.15	0	0.3	0	0	0.01	0.001	0.001
Figure 2e	0.3	0	0.1	0	0.03	0	0.08	0.02

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