Advancing Nonequilibrium Chemistry by Clarifying Misconceptions

Yoshiyuki Kageyama, Faculty of Science, Hokkaido University
y.kageyama@sci.hokudai.ac.jp

Nonequilibrium supramolecular chemistry has garnered significant interest. Although Prigogine[1] and other researchers developed theoretical perspectives in this area of chemistry, many recent studies have not aligned with these perspectives. Although updating old ideas into new ones is beneficial, their interrelationships must also be examined. Herein, recent discussions on supramolecular chemistry under nonequilibrium conditions are re-evaluated from a basic standpoint.

Contradictory comprehension of equilibrium in nonequilibrium contexts

In its *Gold Book*, IUPAC defines chemical equilibrium as a state in which the rates of forward and reverse reactions in a reversible chemical reaction are identical, and the chemical composition is static, at which the Gibbs free energy, G, is minimum. However, explanations for using the term "equilibrium" to describe behaviors in open systems are not available. Prigogine[1] applied the term "equilibrium structure" or "near-equilibrium behavior" to a state in which the chemical composition is static because the reaction rates are equilibrated within a subject system or subsystem. The opposite phenomenon, in which the chemical compositions are never equilibrated, as observed in dissipative structures and chaos, is regarded as behavior far from equilibrium. In contrast, many supramolecular chemists regard the stationary state reached in an open system as far from equilibrium, even if the chemical composition of the state is constant. Furthermore, a state in which the detailed balance is disrupted and a molecule with a highly unstable conformation is occasionally referred to as a state far from equilibrium. As shown here, the term "far from equilibrium" has been used differently by researchers. This complicates the understanding of the relevant science.

Far from equilibrium in the context of living organisms

Why is being alive considered far from equilibrium? Here, we refer to Shrödinger's perspective, which is described in his article, "What is Life?" Schrödinger perceived life as a piece of matter in which activities were performed continuously. Molecules generally undergo repeated thermal motion and transformations, particularly in the case of catalysts, which are continuously involved in chemical reactions with accompanying continuous conformational transformations. These well-known inanimate behaviors of individual molecules do not reflect what Schrödinger identified as characteristics of life. He stated that the piece of matter formed by many molecules continues to be a characteristic of life. This view has been echoed by other scientists and remains central to discussions

on life. The term “far from equilibrium” in the context of life describes a phenomenon that self-sustains movement and evolution, transcending simple thermal behavior in a chemical system composed of multiple molecules.

Here, we consider the mechanical action of chemical material in the solution phase. When a material undergoes a change in chemical composition, it often experiences instantaneous distortions followed by spontaneous deformations. If the deformation does not immediately lead to a stable structure, distortion energy may be temporarily stored within the material, resulting in significant morphological changes with dissipating the stored energy. In cases where little or no distortion energy is stored for the material’s deformation, the external object subjected to the deformation does not acquire any inertial force, and the object simply moves in tandem with the deformation. To exert force on an external object and separate it, the material must undergo salient deformations that release sufficient energy. Similarly, for the material itself to move through the solvent during deformation, coordinated energy dissipation is required to generate cooperative solvent flows.[2] In short, achieving repetitive mechanical work through energy conversion necessitates the material self-sustaining movements accompanied by the release of adequate energy. For a system at a smaller molecular scale, whether there is a mechanism to attain practical work is uncertain owing to the predominance of thermal motion. However, a mechanism that generates an action force that is sufficient to move a coherent set of molecules is required.

Next, we consider self-sustaining behaviors. In chemistry, dissipative structures and chaos are known as cooperative molecular self-sustaining systems. These show self-continuous changes in the chemical potentials and chemical compositions within a system owing to several cooperative phenomena induced by reactions within the target system. Previously, scientists explained dissipative structures using a virtual model of reactions in which diffusions conveniently occur, known as the Brusselator.[1] It should be noted that this model has faced criticism for being unrealistic. However, the author believes that it aids in understanding chemical behaviors under nonequilibrium systems and introduces it here. Additionally, while some critics argue that reverse reactions should be considered and equations assuming stationary states should be used, it should be emphasized that such assumptions cannot accurately capture nonstationary behavior. For a reaction scheme with a balance broken under nonequilibrium conditions (Fig. 1a), whether the chemical composition is equilibrated or not depends on whether a certain parameter (herein, k_2[B], which depends on the condition of the system) is smaller or larger than a threshold value (Figs. 1b and c).[3] In other words, a set of reaction schemes or kinetic equations does not indicate whether the system will reach a stationary state or an oscillating state. Therefore, to claim far-from-equilibrium behavior, one must demonstrate observed phenomena such as compositional oscillations or repetitive mechanical behavior, or prove it through modeling.

However, while this requirement can be easily met in macroscopic systems, it is challenging in small systems. Even in small systems such as a biomolecular motor at the ten-nanometer scale, mechanical work beyond thermal motion can be generated. A deeper understanding of the origin of mechanical work in such small systems is a crucial issue in nonequilibrium chemistry.

Is the discussion of Brownian ratchets in molecules for mechanical work?

Brownian ratchets are often discussed as a concept in the mechanism of molecular motors.[4] Originally, Brownian ratchets were understood as a behavior in which the thermal motion of a small object with an asymmetric structure becomes biased in the presence of nonthermal factors.[5] This mechanism is considered to contribute to determining the driving direction and improving the efficiency of long-distance transport by biomolecular motors.

Building on this concept, Leigh *et al.* proposed a molecular motor[6] and pump[7] driven by information ratchets, a Brownian ratchet mechanism in which chemical reactions determine the bias in the driving directionalities. The directional change of the rings in their catenanes and pseudo-rotaxanes was the result of thermal motion with a ratchet mechanism generated through the degradation of FmocCl. In the case of the pump, the standard chemical potential of the set of molecules increased. A question arises: Did the molecules exert mechanical forces on external objects? The kinetic discussions in their paper are based on a stationary state assumption. In this regard, process of mechanical forcing with energy conversion was not investigated in these studies. Nonlinear processes for achieving molecular coherence must be designed to perform autonomous mechanical tasks. This will be the next target of research on artificial molecular motors.

In contrast, in biological motors such as F-type ATPases, the consumption of chemical substrates is associated with the generation of mechanical forces as well as unidirectional conformational change.[8] It has been proposed that ATP hydrolysis in two different subunits is interconnected. When nonlinear molecular cooperation is triggered by chemical reactions, mechanical motion that surpasses the level required to move a coherent number of molecules may occur. Therefore, it is considered that interconnected hydrolysis is the key to mechanical work performance. In addition, ATPases function synergistically in biological systems such as flagella to generate higher power levels.

Difficulty in drawing energy diagrams for nonequilibrium systems

Recently, researchers have attempted to explain the behavior of nonequilibrium systems by constructing potential surfaces that resemble reaction coordinates. In molecular-level chemistry,

reaction-coordinate potential surfaces follow a specific format: the vertical axis represents the standard-reaction molar Gibbs free energy ($\Delta_r G^o$), whereas the horizontal axis represents the coordinate of all atoms involved in the target reaction, spanning from the initial structure through the transition structure to the product structure.[9] In the target reaction, the atoms constituting the molecules move left and right repeatedly due to thermal motion, which we refer to as a conformational change or a chemical reaction (**Fig. 1d**). Although the molecules continuously changed their conformations, the system achieved an equilibrated state of the various conformers (**Fig. 1e**). In the cases of catalysts, we can draw a reaction coordinate-like diagram with closed coordination if we omit the atoms of the reactants (if we do not omit the reactants, we can draw a reaction coordinate diagram in a general manner). Broken detailed balance is the behavior in which the frequency of transitions from left to right is different from that from right to left on the pseudo-reaction coordination diagram because of the presence of factors (reactants in this case) that are not represented on the pseudo diagram (**Fig. 1d**). Even in this case, the system generally exists in a state in which various conformations are equilibrated (**Fig. 1e**). The behavior that leads to a stationary state, including that of artificial molecular motors, can be understood in this manner.

On the other hand, a reaction coordinate diagram is not helpful for understanding far-from-equilibrium behaviors. A dissipative structure may be realized when the conditions of the system change cyclically because of the reactions. The emergence of new reaction processes, such as autocatalysis, variation of the activation energies or kinetic coefficients by phase transition, and modulation of the flow rate of the reactants by morphological changes, are examples of nonlinear self-governed changes in system conditions. Drawing such cooperative effects on the reaction coordination is difficult. Clarifying the thermodynamics of molecular cooperative effects is a cutting-edge issue in nonequilibrium thermodynamics, and our current limited knowledge hinders the construction of appropriate straightforward potential curves. One way to show the dynamics is shown in **Fig. 1e**; however, it is doubtful whether the vertical axis can also be adequately depicted in this figure.

Beyond the boundary

Drawing the changes in the assembly structure in the form of reaction coordinate diagrams is also challenging, particularly when defining suitable horizontal axes. In studies of dissipative self-assembly in chemistry, science was developed based on these difficult-to-draw energy diagrams: in many research articles, horizontal axes were not indicated in their energy diagrams. Therefore, several misconceptions remain. Most studies pertaining to dissipative self-assembly claim stationary-state behaviors, reported as processes that spontaneously proceed towards a balanced state. Only a few papers reported self-continuous dynamics.[10] Approaches to dissipative self-assembly hold promise for the creation of autonomous dynamics by discovering conditions that cross the boundary between

stationary and far-from-equilibrium states; however, most researchers terminate their experiments without exploring the boundary, probably due to misconceptions.

The theoretical framework and insights derived from macroscopic reaction kinetics, as developed by Prigogine, remain helpful in contemporary chemistry for addressing nonequilibrium systems. However, molecular-level aspects have not been fully revealed. A stationary state with a constant composition and a dynamic state with varying compositions differ significantly despite both resulting from a broken detailed balance under nonequilibrium conditions. Instead of being content with misinterpreting the breaking of the detailed balance as the ultimate goal for systems far from equilibrium, chemists are encouraged to develop nonequilibrium dissipative behaviors beyond the bifurcation point by designing a nonlinear cooperative effect. This approach will advance our understanding of life-like behaviors from a molecular science perspective. In conclusion, the distinction between the terms “stationary state” and “far from equilibrium” is essential for the proper use of academic terminology and the appropriate setting of our research objectives.

Note

Herein, ΔG denotes the Gibbs free energy of reaction, which is generally denoted as $\Delta_r G$ and represented on the vertical axis of a graph, with the horizontal axis representing the reaction extent (ξ). To avoid the misunderstanding that $\Delta_r G$ and $\Delta_r G^o$ share the same horizontal axis, the subscript is omitted.

The stationary state assumption in this paper refers to a method of solving the rate equation by assuming that the chemical composition of the system remains equilibrium. This is distinct from the steady state approximation and is more closely related to the pre-equilibrium assumption.

Acknowledgements

The author, who attended the 2024 workshop ”Dissipative Processes in Molecular Systems” in Padua, appreciates the ongoing efforts of researchers to foster meaningful discussions despite language barriers and other challenges. The author thanks Dr. Goro Maruta and others for their input on this topic.

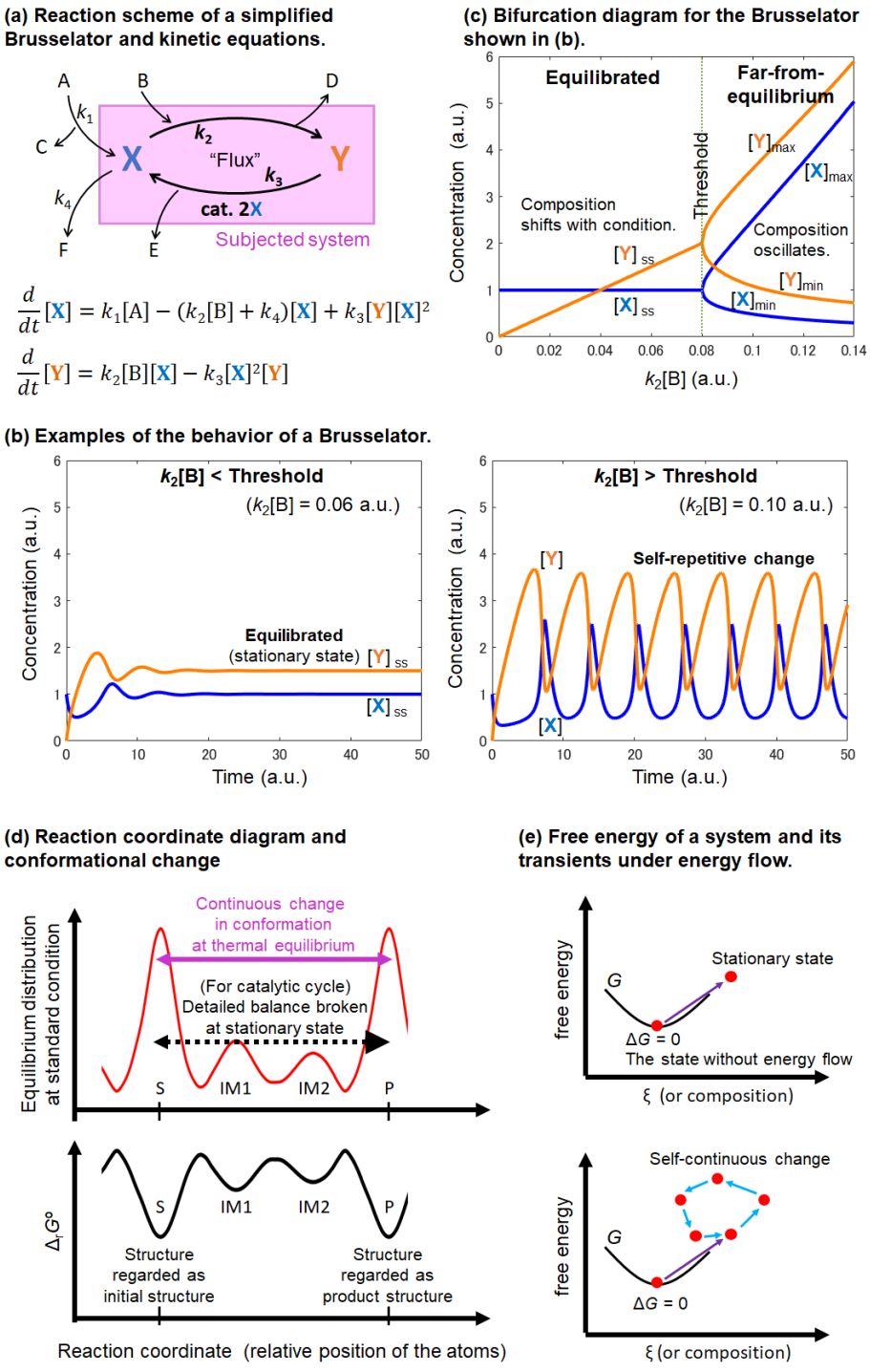

Fig. 1. Behaviors under nonequilibrium conditions. (a,b,c) Explanation of conventional concept of far from equilibrium using a Brusselator model. In the model, 0.002, 0.04, 0.04, and 20 were used for the constants k_1, k_3, k_4, and [A], respectively, and 1 and 0 were used for initial value of [X] and [Y], respectively. (d, e) Reaction coordination diagram and free energy diagram, respectively. (Abbreviations) SS: steady state; G: Gibbs free energy; ξ : extent of reaction; IM: intermediate, S and P: Starting and product material, respectively.

References

1. Nicolis, G., Prigogine, I. (1977). Self-organization in nonequilibrium systems — from dissipative structures to order through fluctuations (John Wiley & Sons, Inc.).
2. Lauga, E. (2011). Life around the scallop theorem. Soft Matter 7, 3060-3065. DOI: 10.1039/C05M00953A.
3. Tyson, J.J. (1973). Some further studies of nonlinear oscillations in chemical systems. J. Chem. Phys. 58, 3919–3930. DOI: 10.1063/1.1679748.
4. Astumian, R.D. (2015). Irrelevance of the power stroke for the directionality, stopping force, and optimal efficiency of chemically driven molecular machines. Biophys. J. 108, 291–303. DOI: 10.1016/j.bpj.2014.11.3459.
5. Magnasco, M.O. (1993). Forced thermal ratchets. Phys. Rev. Lett. 71, 1477–1481. DOI: 10.1103/PhysRevLett.71.1477.
6. Wilson, M.R., Solà, J., Carlone, A., Goldup, S.M., Lebrasseur, N., and Leigh, D.A. (2016). An autonomous chemically fuelled small-molecule motor. Nature 534, 235–240. DOI: 10.1038/nature18013.
7. Amano, S., Fielden, S.D.P., and Leigh, D.A. (2021). A catalysis-driven artificial molecular pump. Nature 594, 529–534. DOI: 10.1038/s41586-021-03575-3.
8. Junge, W., and Nelson, N. (2015). ATP Synthase. Annu. Rev. Biochem. 84, 631–657. DOI: 10.1146/annurev-biochem-060614-034124.
9. Fukui, K. (1970). Formulation of the reaction coordinate. J. Phys. Chem. 74, 4161-4163. DOI: 10.1021/j100717a029.
10. Leira-Iglesias, J., Tassoni, A., Adachi, T., Stich, M., and Hermans, T.M. (2018). Oscillations, travelling fronts and patterns in a supramolecular system. Nat. Nanotechnol. 13, 1021–1027. DOI: 10.1038/s41565-018-0270-4.