シンポジウム3: 「物質間境界層に於ける環境適応機能の発現」

水溶液中における生体分子自己組織化過程の統計熱力学

Statistical thermodynamics of biological self-assembly in aqueous solution

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1. Introduction

A material element exhibits high function when it is in contact or mixed with other material elements rather than when it is independently present. We refer to a system comprising multiple material elements as a "complex system". For example, a complex system is formed by the contact of a metal with aqueous electrolyte solution or the dissolution of solute molecules in solvent. The biological system is a typical complex system. Biomolecules, a great diversity of molecular and ionic species, or water is simply *material* when each of them is separately present. When they form a system, however, their complicated correlations can lead to *life*. In this talk, though the principal subject is the microscopic self-assembly or ordering process in the biological system, it is argued that studies on general complex systems are quite challenging and important.

2. Nonlinear behavior of complex system

The behavior of a complex system is far from the superposition of behavior of its individual elements. It is often highly advanced and beyond imagination. When solute molecules are immersed in solvent, for example, the interface region whose structure and properties are quite different from those of the bulk solvent is formed near each solute molecule. The structure and properties of the solvent confined between two solute molecules are even more different. Moreover, the presence of a solute molecule generates a space from which the centers of solvent molecules are excluded. Upon the formation of a complex system, drastic changes such as the appearance of these matters occur, leading to the exhibition of nonlinear behavior. In studies on any complex system, it is necessary to combine the concepts and approaches which have been developed independently in different fields. Take the metal-aqueous electrolyte solution interface, for example. The metal is a quantum system treated in solid-state physics. By contrast, the solution is a classical system requiring liquid-state theory. It presents a new, difficult problem where these two systems must be combined in a self-consistent manner. The studies enlighten the creation of innovative areas. A complex system is a treasure house of exhibition of novel and high functions leading to the development of new functional materials and technology. I am a biophysicist with the skill of liquid-state theory and collaborated with metal physicists, electrochemists, and structural biologists. In these collaborations, we could construct a new theory of the metal-aqueous electrolyte interface [1], develop a new method for constructing electrode structure for a fuel cell using the concept of "surface-induced phase transition" [2], and elucidate the mechanism of molecular recognition [3].

3. Biological system

Multilevel problems must be solved in studies on life phenomena: a molecular-level problem related to the structure and function of a biomolecule, properties and functions exhibited by an ensemble of biomolecules, a cell-level problem, an organ or system comprising a number of cells, and a living body. Multiscale analyses are thus required. A variety of self-assembly and ordering processes are sustaining life. They are microscopic, mesoscopic, or macroscopic. We have been investigating those of a microscopic scale which occur only by a single biomolecule or several biomolecules. Typical examples of biological processes occurring at microscopic levels are protein folding, protein traffic, ordered aggregation of proteins, molecular recognition, unidirectional movement of a linear-motor protein along a filament, and exclusion of toxic solutes from a cell by a protein complex. These processes can be argued on the basis of equilibrium thermodynamics for a closed system. By contrast, the problems of the cell level and larger scales are expected to require the concept of "dissipative structure" formed in a nonequilibrium and open system, just like the macroscopic self-assembly in the plasma system.

The features of our study are as follows. We emphasize the crucial importance of "entropic effect" and "entropic force" originating from the translational displacement of water molecules. Upon the biological self-assembly, the number of accessible translational configurations of water in the system increases considerably, leading to a large gain in water entropy. The concept of the entropically driven self-assembly is then suggested. We have developed very efficient statistical-mechanical approaches treating water and biomolecules in atomic details [4-6] and succeeded in elucidating a variety of biological processes [7]. As an interesting example, in this talk I give some informative calculation results obtained for the extrusion of toxic solutes (drugs) from a cell by ABC transporter [8].

4. Extrusion of toxic solutes (drugs) from a cell

The transporter first inserts the solute and then releases it. It is quite mysterious that the two apparently *opposite* events, insertion and release, successively occur in the same system. The structural change caused by the ATP binding to the transporter should play essential roles in the switch from insertion to release. In the bulk solvent, there is no spatial distribution of the potential of mean force (PMF) formed. However, in the solvent confined on the scale of a nanometer, there is a spatial distribution in which the PMF becomes largely positive and largely negative with the periodicity of the solvent diameter d_S. Here we analyze the entropic component of the

PMF scaled by k_BT (k_B is Boltzmann's constant and T is the absolute temperature), $-\Phi_S/k_B$. $-\Phi_S$ is rather insensitive to the properties of the solute and vessel surface (i.e., hydrophobic or hydrophilic). Figure 1 illustrates the entropic insertion of a solute into a cylindrical vessel. In the figure, $-\Phi_S$ becomes lower as the color approaches dark blue and it becomes higher as the color approaches dark red. The solute motion is severely influenced by the distribution of $-\Phi_S$, and the solute is spontaneously inserted into the vessel and confined within its cavity without contacting the vessel surface. Once the solute is inserted, as illustrated in Fig. 2, it can be released by changing the spatial distribution of $-\Phi_S$ using continuous variation of the vessel geometry caused by the ATP binding. In this case, the exit of the vessel is opened, and the diameter of a portion in the entrance side is made smaller by $2d_S$ and the portion is continuously lengthened. After the solute release, Pi and ADP (products of hydrolysis of ATP) are dissociated, the transporter structure returns to the other one, and the next solute insertion occurs. We have shown that a variety of solute sizes can *entropically* be handled.

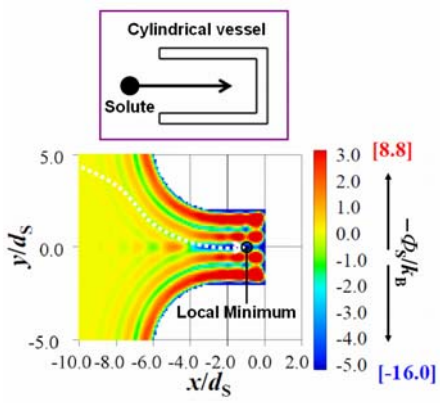

Fig. 1. Solute insertion driven by solvent entropy.

A serious problem in medical practice is that a drug quickly looses its efficacy. The "multidrug efflux", which means that the transporter is capable of extruding a variety of drugs, can be elucidated when the entropic component dominates as described above. However, our result may imply that even useful solutes such as sugar and amino-acid molecules are extruded. To solve this problem, we have to account for the energetic component of the PMF scaled by k_BT, $\Phi_E/(k_BT)$, as well. Φ_E is largely dependent on the properties of the solute and vessel surface. If the solute is hydrophilic and the vessel surface is not, for example, the solute insertion does not occur because the solute prefers to be hydrated in the bulk [9]. We intend to perform a systematic analysis accounting for both of $\Phi_E/(k_BT)$ and $-\Phi_S/k_B$ so that we can design a drug which cannot be extruded.

5. Future outlook

Though intimate collaboration by experts in different fields is required in studies on the complex systems, such collaboration cannot readily be realized. Therefore, the studies have lagged behind. In other words, there are lots of unresolved, important problems which are solvable only by interdisciplinary research. The research leads to the systematization of new fields, exploration of innovative areas, and development of novel functional materials, drugs, and technology. The biological system, electrochemical system, and first wall-plasma interface in a fusion reactor are typical complex systems. To accomplish the biological research, the connection between problems of the molecular level and those of the cell level and larger scales is required. The theoretical approach toward the formation of macroscopic ordered structure and spatiotemporal pattern in the biological and electrochemical systems are relevant to those in the plasma system. Biophysicists, electrochemists, and plasma physicists could collaborate on such subjects as the treatment of highly nonlinear problems, theoretical methods for the interfaces, self-assembly in a nonequilibrium and open system, and multiscale analyses and simulations. For example, some aspects of the theoretical approach for the metal-aqueous electrolyte solution interface might be applicable to that for the first wall-plasma interface. Such collaboration, which has never been performed, presents very much challenge.

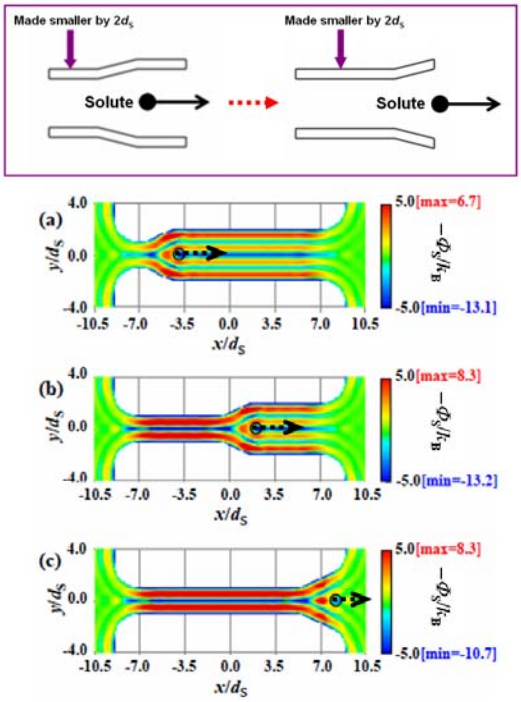

Fig. 2. Solute release driven by solvent entropy.

References

[1] M. Yamamoto, M. Kinoshita, and T. Kakiuchi, Electrochim. Acta, **46**, 165 (2000).

[2] K. Fukami, R. Koda, T. Sakka, Y. Ogata, and M. Kinoshita, J. Chem. Phys. **138**, 094702 (2013).

[3] T. Hayashi, H. Oshima, T. Mashima, T. Nagata, M. Katahira, and M. Kinoshita, Nucleic Acids Res. **42**, 6861 (2014).

[4] M. Kinoshita, J. Chem. Phys. **116,** 3493 (2002).

[5] R. Roth, Y. Harano, and M. Kinoshita, Phys. Rev. Lett. **97**, 078101 (2006).

[6] T. Yoshidome, Y. Ito, M. Ikeguchi, and M. Kinoshita, J. Am. Chem. Soc. **133**, 4030 (2011).

[7] M. Kinoshita, Biophys. Rev. **5**, 283 (2013).

[8] H. Mishima, H. Oshima, S. Yasuda, K. Amano, and M. Kinoshita, J. Chem. Phys. **139**, 205102 (2013).

[9] K. Amano, H. Oshima, and M. Kinoshita, J. Chem. Phys. **135**, 185101 (2011).