Theoretical Studies of Reactions, Functions, and Fluctuations in Many-Body Molecular Systems

Department of Theoretical and Computational Molecular Science
Division of Theoretical Molecular Science I

SAITO, Shinji
Professor
[shinji@ims.ac.jp]

Education
1988 B.S. Keio University
1990 M.E. Kyoto University
1995 Ph.D. The Graduate University for Advanced Studies

Professional Employment
1990 Technical staff, Institute for Molecular Science
1994 Research Associate, Nagoya University
1998 Associate Professor, Nagoya University
2005 Professor, Institute for Molecular Science
2006 Professor, The Graduate University for Advanced Studies

Member
Assistant Professor
MORI, Toshifumi
KODA, Shin-ichi
JSPS Post-Doctoral Fellow
MATSUMURA, Yoshihiro
Post-Doctoral Fellow
MAURYA, Manish
Graduazte Student
KALATHINGAL, Mahroof
ZHU, Zhe
Secretary
CHIBA, Fumika

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Many-body molecular systems, such as (supercooled) liquids and biomolecules, exhibit complex fluctuations. Furthermore, in these systems, various physical properties and biological functions are created and chemical reactions proceed under the fluctuations. We aim to elucidate the properties, functions, and reactions by investigating fluctuations and dynamics of the many-body molecular systems.

We investigate fluctuations and dynamics of liquids by developing computational methods for multi-dimensional nonlinear spectroscopy that can reveal detailed dynamical infomation not available from conventional linear spectroscopy. Consequently, we revealed the molecular origins of ultrafast energy relaxation and time evolution of inhomogeneous fluctuations in liquid water. In supercooled liquids, rare and non-uniform structural changes, called dynamic heterogeneity, are induced by fluctuations. We elucidated the relationship between the lifetime of the dynamic heterogeneity and the fragility using the three-time correlation function of density fluctuations.

We study the molecular origin of anomalous properties of liquid water. We revealed that the anomalies of liquid water are related to the structural and dynamical instabilities hidden in the experimentally inaccessible region and the physical reason of the low glass transition temperature of liquid water. We currently investigate how rare but persistent structural relaxation of liquid water proceeds towards the glass transition temperature.

Complex conformational fluctuations and changes can be observed in biomolecular systems. Such conformational dynamics are considered to be essential for biological functions. We examine the relationship between fluctuation and biomolecular function found in the robust circadian rhythm of the clock protein KaiC and the efficient excitation energy transfer in photosynthetic systems. We investigate dynamic effects of enzymatic reactions, and find the importance of prearranged states for the rare but persistent enzymatic reactions. Furthermore, we examine dynamic disorder in conformational changes of proteins at the molecular level.

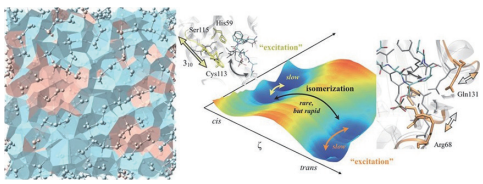

Figure 1. Snapshot of two-state model in supercooled water consisting of high- and low-density liquids (left) and schematic of 2D free energy surface for enzymatic reaction (right).

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- T. Mori and S. Saito, *J. Phys. Chem. Lett.* **10**, 474–480 (2019).
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1. Dissecting the Dynamics during Enzyme Catalysis: A Case Study of Pin1 Peptidyl-Prolyl Isomerase[1)]

Free energy surfaces have played a central role in studying protein conformational changes and enzymatic reactions over decades. Yet, free energy barriers and kinetics are highly dependent on the coordinates chosen to define the surface, and furthermore, the dynamics during the reactions are often overlooked. Our recent study on the Pin1-catalyzed isomerization reaction has indicated that the isomerization transition events remarkably deviate from the free energy path, highlighting the need to understand the reaction dynamics in more detail. To this end, here we investigate the reaction coordinates that describe the transition states of the free energy and transition pathways by minimizing the cross-entropy function. We show that the isomerization transition events can be expressed by the concerted changes in the improper torsion angle ζ and nearby backbone torsional angles of the ligand, whereas the transition state of the free energy surface involves changes in a broad range of coordinates including multiple protein–ligand interactions. The current result supports the previous finding that the isomerization transitions occur quickly from the conformational excited states, which is in sharp contrast to the slow and collective changes suggested from the free energy path. Our results further indicate that the coordinates derived from the transition trajectories are not sufficient for finding the transition states on the free energy surfaces due to the lack of information from conformational excited states.

2. An Alternative Interpretation of the Slow KaiB-KaiC Binding of the Cyanobacterial Clock Proteins[2)]

The biological clock of cyanobacteria is composed of three proteins, KaiA, KaiB, and KaiC. The KaiB–KaiC binding brings the slowness into the system, which is essential for the long period of the circadian rhythm. However, there is no consensus as to the origin of the slowness due to the pre-binding conformational transition of either KaiB or KaiC. In this study, we propose a simple KaiB–KaiC binding scheme in a hexameric form with an attractive interaction between adjacent bound KaiB monomers, which is independent of KaiB's conformational change. We then show that the present scheme can explain several important experimental results on the binding, including that used as evidence for the slow conformational transition of KaiB. The present result thus indicates that the slowness arises from KaiC rather than KaiB.

3. Site-Dependent Fluctuations Optimize Electronic Energy Transfer in the Fenna-Matthews-Olson Protein[3)]

Light absorbed by light-harvesting antennae is transferred to the reaction center (RC). The excitation energy transfer (EET) to the RC is known to proceed with nearly perfect quantum yield. However, understanding of EET is still limited at the molecular level. Here, we examine the dynamics in the Fenna–Matthews–Olson (FMO) protein by developing an efficient molecular dynamics simulation that can properly describe the electronic properties of bacteriochlorophylls. We find that the FMO protein consists of sites with heterogeneous fluctuations extending from fast to slow modulation. We also find that efficient EETs are facilitated by site-dependent fluctuations that enhance the resonance condition between neighboring sites with large site energy differences and circumvent exciton trapping on the pathway to the RC. Knowledge of site-dependent fluctuations is an important component of understanding optimization of EET in photosynthetic systems.

4. Molecular Mechanism of Acceleration and Retardation of Collective Orientation Relaxation of Water Molecules in Aqueous Solutions[4)]

The collective orientation relaxation (COR) of water molecules in aqueous solutions is faster or slower with the increase in concentration of the solutions than that in pure water; for example, acceleration (deceleration) of the COR is observed in a solution of sodium chloride (tetramethylammonium chloride) with increasing concentration. However, the molecular mechanism of the solution and concentration dependence of the relaxation time of the COR has not yet been clarified. We theoretically investigate the concentration dependence of the COR of water molecules in solutions of tetramethylammonium chloride (TMACl), guanidinium chloride (GdmCl), and sodium chloride (NaCl). Based on the Mori-Zwanzig equation, we identify two opposing factors that determine the COR of water molecules in any aqueous solution: The correlation of dipole moments and the single-molecule orientation relaxation. We reveal the molecular mechanism of the concentration dependence of the relaxation time of the COR in the TMACl, GdmCl, and NaCl solutions in terms of these two factors.

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4) N. Moritsugu, T. Nara, S.-i. Koda, K. Tominaga and S. Saito, to be submitted.