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
Post-Doctoral Fellow
MATSUMURA, Yoshihiro
ANDO, Yoshimichi
Graduate Student
KALATHINGAL, Mahroof
MORITSUGU, Norifumi
Secretary
SUZUKI, Sayuri

Keywords Heterogeneous Dynamics, Reactions, Functions

In many-body molecular systems, such as liquids and bio-molecular systems, nonlinear intermolecular interactions induce complicated motions. The motions are spatially and temporally heterogeneous, and yield static, dynamic, and thermodynamic properties of the systems. The spatiotemporal heterogeneous motions known as dynamic heterogeneity are found in super-cooled liquids. In bio-molecular systems, which show slow conformational fluctuations, time-dependent reaction rates are often observed. Furthermore, biological functions are produced in complicated fluctuations with a wide range of timescales. Therefore, understanding of spatiotemporal heterogeneous dynamics is essential to the elucidation of the structure, reactions, functions, and fluctuations in these complicated systems.

We have investigated inter- and intra-molecular dynamics of water by using third-order nonlinear spectroscopy which can provide the detailed dynamics that are not available from conventional spectroscopy. We have revealed the molecular mechanism of ultrafast energy relaxation, which is one of dynamical features of water, is caused by the nonlinear strong coupling between the libration motion and other intra- and inter-molecular vibrational motions.

We have also investigated heterogeneous dynamic of supercooled liquids. In particular, we have quantified the lifetime of dynamic heterogeneity by introducing the three-time correlation function of density fluctuation. We have found that the temperature dependence of lifetime of dynamic heterogeneity obtained from the three-time correlation functions is very sensitive to the fragility, that is the three-time correlation function is sensitive to the configurational entropy.

We have also revealed the molecular origin of anomalous temperature dependence of isobaric specific heat of water by examining the so-called complex specific heat. Recently, we have investigated the structure and dynamics of deeply super-cooled water. We have found the new dynamic transitions due to the instability of high- and low-density clusters in waters and also deciphered a crucial role of specific hydrogen-bond defects in persistent structural relaxations involved in low glass transition of water.

These days, we examine complicated conformational fluctuations of proteins by using the ideas of stochastic theory. We also investigate how chemical reactions and glass transitions proceed at the molecular level and how biological functions and thermal properties of liquids are generated under complicated fluctuations with a wide range of timescales.

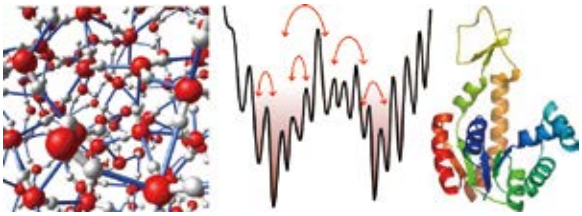

Figure 1. Schematic figure of rugged energy landscape (center) in supercooled water (left) and adenylate kinase (right).

Selected Publications

- T. Yagasaki and S. Saito, *Annu. Rev. Phys. Chem.* **64**, 55–75 (2013).
- K. Kim and S. Saito, *J. Chem. Phys. (Special Topic on Glass Transition)* **138**, 12A506 (12 pages) (2013).
- S. Saito, I. Ohmine and B. Bagchi, *J. Chem. Phys.* **138**, 094503 (7 pages) (2013), S. Saito, B. Bagchi and I. Ohmine, *J. Chem. Phys.* **149**, 124504 (8 pages) (2018).
- J. Ono, S. Takada and S. Saito, *J. Chem. Phys. (Special Topic on Multidimensional Spectroscopy)* **142**, 212404 (13 pages) (2015).

1. Conformational Excitation and Non-Equilibrium Transition Facilitate Enzymatic Reactions: Application to Pin1 Peptidyl-Prolyl Isomerase[1)]

Conformational flexibility of proteins is essential for protein function and enzyme catalysis. Yet, how proteins' conformational rearrangements and dynamics contribute to the chemical step of enzyme catalysis has remained highly controversial over decades. In order to unravel protein's role in enzyme catalysis, it is necessary to understand the static and dynamic mechanisms of enzyme catalysis simultaneously. In this respect, here we study Pin1 peptidyl-prolyl isomerase, and reveal the structural and dynamic aspects of catalytic isomerization step in molecular detail. From the static and fully-equilibrium perspective, the hydrogen bond interactions within Pin1 as well as between Pin1 and ligand are found to rearrange along the minimum free energy path of isomerization. In sharp contrast, the transition dynamics reveal that isomerization transitions are very rapid; slow protein conformational rearrangements cannot simultaneously occur with the isomerization reaction, and the reaction instead proceeds in a non-equilibrium manner. We further reveal that distinctive protein conformational rearrangements and hydrogen bonds, necessary to stabilize the transition state, need to be prepared a priori, *i.e.* as a conformational excited state within the reactant equilibrium. The present results reveal that the catalytic isomerization reaction does not occur as a simple thermal activation from the equilibrium directly to the transition state, indicating the importance of protein conformational flexibility and the presence of favorable conformations for the isomerization reactions. The current findings add a novel perspective of the Pauling's view on the enzymatic reactions in which the reactions proceed thermally from reactants to stabilized transition state and products.

2. A Reaction Model of the Cyanobacterial Circadian Rhythm Considering the Interplay among Multiple Domain-Specific Conformational Changes of KaiC[2)]

The clock proteins of cyanobacteria KaiABC constitute a biological clock with a temperature-compensated circadian period. KaiC forms a homo-hexamer with the two ring-shaped domains, C1 and C2, which allosterically communicate each other to generate the circadian rhythm. Experiments have found that several conformational changes of C1 and/or C2 are involved in the communication. However, detailed interplay among them remains elusive. We propose a mathematical model explicitly considering the interplay among the multiple domain specific conformational changes. In this model, the whole process, where the chemical reactions of ligands induce the (dis) assembly of KaiA and KaiB via the conformational changes, is represented only by the rate equations of them without any effective simplification. We show that the present model with automatically optimized rate or equilibrium constants can qualitatively reproduce various experimental data including temperature dependence of phosphorylation oscillation and ATPase activity. We also discuss a possible mechanism of the temperature compensation of period in association with the interplay among the domain-specific conformational changes, and find that some conformational changes induced by the slow and temperature-compensated ATP hydrolysis in C1 make the duration of phosphorylation temperature-compensated.

3. Theoretical Approach to Dynamical Disorder of Chemical Processes: Application to Bovine Pancreatic Trypsin Inhibitor Protein[3)]

Chemical processes in many-body molecular systems proceed under thermal fluctuations over wide spatiotemporal scales. One example is the conformational dynamics of proteins, which is highly heterogeneous and closely related to their functions. Although the dynamical disorder model has been introduced to characterize and understand the process correlated with dynamical fluctuations, the molecular aspects are not well established. Recent achievements in single-molecule spectroscopy and ultralong-time molecular dynamics simulation enabled us to access rich time series data with the molecular details and encouraged us to explore the theoretical framework for the single molecule kinetics. In this study, we develop the analytical framework for the time series data based on the theory of stochastic process, to clarify the dynamical correlations of state transition processes. The framework is applied to the 1ms-length molecular dynamics simulation of the conformational dynamics of bovine pancreatic trypsin inhibitor protein in aqueous solutions. Conformational states can be detected as isomers of dihedral angles in the vicinity of a disulfide bond; experimentally three states are observed and several other transient states are also found in the simulations. The present method developed in this study can decipher that the transient states are dynamically coupled with the transitions between the three states, although complex behaviors are averaged out in experiments.

References

1) T. Mori and S. Saito, to be submitted.
2) S. Koda and S. Saito, to be submitted.
3) Y. Matsumura and S. Saito, to be submitted.