Theoretical Studies of Reactions, Functions, and Thermodynamic Properties in Biomolecular and Liquid Systems

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Nonlinear intermolecular interactions cause complicated motions in condensed phases, *e.g.* liquids and biological systems. These motions are spatially and temporally heterogeneous and produce both static and dynamic properties of the systems. The spatiotemporal non-uniform motions known as dynamic heterogeneity are considered to be a clue to understand supercooled liquids and glass transition. Furthermore, heterogeneous reaction rates have been found in biological systems. Therefore, understanding of spatiotemporal heterogeneous dynamics is essential to the elucidation of the structure, reactions, functions, and thermodynamic properties of the condensed phase 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, *i.e.* the fast energy relaxation is caused by the nonlinear strong coupling between the libration motion and other intra- and inter-molecular vibrational motions.

We have also investigated the dynamics of supercooled liquids. We quantified the lifetime of dynamic heterogeneity by introducing the three-time correlation function of density fluctuation, which is sensitive to the time evolution of heterogeneity. Our systematic analysis for various systems shows that the lifetime of dynamic heterogeneity is intimately related to configurational entropy and thus the temperature dependence of lifetime of dynamic heterogeneity is more sensitive to the fragility than that of α-relaxation time determined by one-time correlation function. In addition to the analysis of dynamic heterogeneity with multi-time correlation function, we have revealed the molecular origin of anomalous temperature dependence of isobaric specific heat of water by examining the spatiotemporal fluctuations in terms of specific heat.

We examine heterogeneous conformational dynamics in proteins by exploiting the ideas used in multi-dimensional spectroscopy and glassy dynamics. Currently, we investigate how enzymatic reactions proceed at a molecular level under complicated environmental fluctuations. In addition, we elucidate the emergence of functions, *e.g.* the circadian rhythm in Kai system, as a result of dynamics over a wide range of spatiotemporal scales.

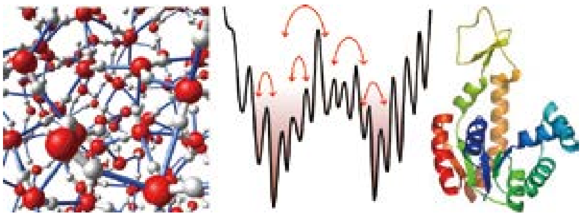

Figure 1. Schematic figure of rugged energy landscape (center) in supercooled water (left) and adenylate kinase (right).

Selected Publications

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1. Crucial Role of Low-Populated Conformations Facilitating Enzymatic Reactions: Example in Catalysis in Pin1 *cis-trans* Isomerase[1)]

Protein flexibility is essential for enzymes to function, yet the mechanism of catalysis has been highly controversial. Here we elucidate how protein and ligand conformational changes occur along the reaction by examining the *cis-trans* isomerization reaction catalyzed by Pin1 as an example. While free energy profiles can explain the catalytic effect, we show that the enzymatic reaction proceeds through specific conformations, which hereafter we call excited conformational state formed in the reactant. The transition trajectories therefore do not overcome the barrier in a simple stochastic manner. Furthermore, since the excited conformational state is formed by specific hydrogen bonds, the reaction occurs via bond-alternations and the excess energy is efficiently dissipated. As a result, the reaction path is direction-dependent and possesses directionality, *i.e.* different paths are used depending on the reactant character. We expect that the excited conformational states and specific bond switching mechanisms are embedded in broader enzymes.

2. A Reaction Model of Circadian Rhythm in Kai Proteins by Considering Elementary Reactions and Conformational Changes[2)]

Circadian clocks are biological timing system used in various organisms to anticipate daily changes in environment and to adjust their biological activity to the changes. Cyanobacteria are known as the simplest organisms showing a circadian rhythm, where the core oscillator is composed of only three proteins, KaiA, KaiB, and KaiC. KaiC consisting of two domains plays a central role in the circadian rhythm of Kai system, and has autokinase and autophosphatase activities. A periodic phosphorylation and dephosphorylation occur at Ser431 and Thr43 in KaiC. This periodic oscillation is generated with the help of KaiA and KaiB: KaiA promotes the phosphorylation, on the other hand KaiB inhibits KaiA to act on KaiC. Several important elementary processes have recently been unveiled, for example, the phosphorylation and dephosphorylation reactions and conformational changes that might switch between phosphorylation and dephosphorylation phases. It is, however, an open question to integrate these detailed experimental results and explain how the circadian phosphorylation occurs. In almost all previous mathematical models, only the phosphorylation/dephosphorylation reactions have been focused for the circadian rhythm of Kai system. In the present study, we propose a mathematical reaction model of the circadian rhythm in the Kai system based on conformational changes in KaiB and KaiC as well as elementary processes, such as ATP hydrolysis, ADP/ATP exchange, and phosphorylation/dephosphorylation reactions. As a result, an allosteric effect in the domains in KaiC is also considered in the current model. We find that the optimized parameters determined to reproduce the experimental data of the periodic phosphorylation can quantitatively reproduce not only the data of phosphorylation used in the optimization, but also various experimental data not used in the optimization, such as ATPase activity even when KaiA and/or KaiB are absent. In addition, the current model can successfully reproduce the synchronization of oscillation caused by environmental changes. The present study demonstrates that the circadian rhythm is regulated by conformational changes as well as elementary reactions.

3. Crucial Role of Fragmented and Isolated Defects in Persistent Relaxation of Deeply Supercooled Water[3)]

Water is the most common and the most intensively studied liquid in nature. Characteristic properties of water have been well elucidated for temperature above ~200 K. And yet a mystery still remains about the deeply supercooled region: Why and how can water stay in the liquid state even at very low temperature? Experiments show that amorphous ice when heated from very low temperature. undergoes a transition to a highly viscous liquid at 136 K and then crystallizes to ice at 150 K. This water glass transition temperature, T_{G} = 136 K, almost half of the ice melting temperature T_{M}, is much lower than what is expected from the general $T_{\mathrm{G}}/T_{\mathrm{M}} \approx 2/3$ rule of glass formers. The present study, performing extensive trajectory calculations, attempts to clarify what molecular mechanisms could be involved in promoting molecular motions in deeply supercooled water. We find that the structural and dynamical instabilities hidden behind the so-called “no man’s land” the experimentally inaccessible region for liquid water between 235 K and 150 K, strongly influence the properties of deeply supercooled water, through the fragmentation and the consequent isolation of high density (HD) clusters. The fragmentation that starts below 220 K, makes each larger HD cluster scattered into smaller clusters. When the fragmentation is completed at ~190 K, each scattered HD cluster contains only one or two defects. These isolated defects are hardly annihilated in the well-formed hydrogen bond network of low density (LD) molecules. We find that specific 3-coordinated defects play a crucial role to induce slow but persistent structural relaxations and thus lower the T_{G} of water. These defects are exactly the same ones essential in melting ice. The fragmentation of LD clusters in HD network takes place at the temperature of density maximum. The fragmentation scheme provides a unified picture on water properties in a wide temperature range.

References

1) T. Mori and S. Saito, to be submitted.
2) S. Koda and S. Saito, to be submitted.
3) S. Saito, B. Bagchi and I. Ohmine, submitted.