

# Theoretical Studies of Heterogeneous Dynamics and Protein Functions

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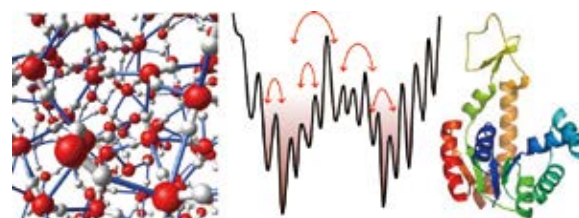
Nonlinear intermolecular interactions cause complicated motions in condensed phases, *e.g.* liquids and biological systems. These motions are spatially and temporally heterogeneous with a wide range of time and spatial scales and yield both static and dynamic properties of the systems. The spatiotemporal 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, thermodynamics, dynamics, and functions 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 IR spectroscopy. We have examined the detailed fluctuations in water by calculating two-dimensional IR spectra of water. 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 dy-

namic 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  $\alpha$ -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 complex specific heat.

We currently investigate how chemical reactions proceed in biological systems, *e.g.* clock protein KaiC, under complex conformational fluctuations. We also examine heterogeneous conformational dynamics of proteins by exploiting the ideas of multi-dimensional spectroscopy and glassy dynamics.



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

#### Selected Publications

- T. Yagasaki and S. Saito, *Acc. Chem. Res.* **42**, 1250–1258 (2009), *Annu. Rev. Phys. Chem.* **64**, 55–75 (2013).
- S. Imoto, S. Xantheas and S. Saito, *J. Phys. Chem. B* **119**, 11068–11078 (2015).
- 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).
- J. Ono, S. Takada and S. Saito, *J. Chem. Phys. (Special Topic on Multidimensional Spectroscopy)* **142**, 212404 (13 pages) (2015).

## 1. Quantitative Evaluation of Site Energies and Their Pigment Fluctuations in the Fenna-Matthews-Olson Complex with an Efficient Method for Generating Potential Energy Surfaces<sup>1)</sup>

We develop an efficient method to generate an accurate semi-global potential energy surface of a molecule in condensed phases with low computational cost. We apply the method to the analysis of the site energies and their fluctuations of bacteriochlorophyll (BChl) a pigments in the Fenna-Matthews-Olson (FMO) complex using the density functional properly describing the ground and excited states of BChl a in solution in our previous work (*J. Phys. Chem. B* **118**, 10906–10918 (2014)). The errors of the potential energies calculated from the present and QM/MM methods are small:  $\sim 1$  kcal/mol for both the ground and excited states. The calculated site energies are in good agreement with the experimentally fitted results. The calculated spectral density also agrees with the experimentally available data. The spectral densities of BChl 2 and BChl 5 are much larger than those of the other five sites. The present method is expected to reveal the efficient excitation energy transfer in light-harvesting antennas.

## 2. Molecular Mechanism behind the Fast Folding/Unfolding Transitions of Villin Headpiece Subdomain: Hierarchy and Heterogeneity<sup>2)</sup>

Proteins involve motions over a wide range of spatial and temporal scales. While the large conformational changes such as folding and functioning are slow and appear to occur in a highly cooperative manner, how the hierarchical dynamics over different timescales play a role during these slow transitions has been of great interest over the decades. Here we study the folding mechanism of the villin headpiece subdomain (HP35) to understand the molecular mechanism behind this prototypical fast-folding protein. The  $\sim 400$   $\mu$ s molecular dynamics (MD) trajectories obtained by Piana *et al.* [Piana, S. *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **109**, 17845 (2012)] are analyzed in detail. By extracting the slowest mode from the trajectories, which is responsible for the folding/unfolding transitions, and by analyzing the transition events along this mode, we find that the transitions occur in a heterogeneous manner. Detailed analysis of the individual transition events shows that the folding/unfolding transitions occur via two qualitatively different pathways, *i.e.* the unfolding triggered from the C-terminal ( $\alpha_3$  helix) and from the N-terminal ( $\alpha_1$ – $\alpha_2$  loop). Non-native contacts are also found to contribute in slowing down the transitions. The folding of HP35 thus proceeds in a segmental manner rather than cooperatively at the sub-microsecond timescale. The Lys  $\rightarrow$  Nle mutation is found to speed up the transitions by rigidifying the  $\alpha_3$  helix, *i.e.* suppressing one transition pathway. The analysis of the microsecond dynamics in the single-molecule Förster resonance energy transfer efficiency trajectories, which are calcu-

lated from the MD data, reveals that the folding/unfolding transitions in the NleNle mutant can be fitted with a two-state model, whereas those in WT appear to be more complex and involves multiple timescales. This may be due to the similarity in the timescale of the transition events and overall folding/unfolding transitions in WT. The present study demonstrates that a protein as small as HP35 already involves heterogeneous characters during folding/unfolding transitions when the hierarchical dynamics at molecular level is considered, thus heterogeneity can be a general characteristic in protein folding.

## 3. Multiple Transitions of Water on Its Path to Low Density Amorphous Ice<sup>3)</sup>

Amorphous ice is ubiquitous in the Universe, being a major constituent of meteorites and asteroids. It is mechanically stable at very low temperatures and is different from its crystalline counterpart, ice Ih. However, the mechanism of its formation from low temperature water is still not understood. The amorphous ice, when heated from below, undergoes a glass transition to a highly viscous liquid at 136 K, then crystallizes at 150 K, while liquid water when supercooled below its freezing temperature itself freezes at 227 K. Our difficulty to understand the formation of amorphous ice stems from the inaccessibility of liquid water to experiments between 227 K and 150 K, a temperature range well-known as “no man’s land.” We study the entire process of vitrification of water by extensive molecular dynamics simulations. We find that vitrification of water occurs in three distinct stages, accompanied by two sharp changes in fragility. A large scale density fluctuation between the high density liquid (HDL) and the low density liquid (LDL) that appears near 220 K, profoundly influences the entire transformation process. It undergoes a further dynamical transition at  $\sim 195$  K where we find the dynamical heterogeneity to decrease sharply, and rather suddenly. This transition occurs by a fragmentation of macroscopic HDL, leading to the formation of a state where small, non-spherical, fast relaxing, high density droplets containing 3- and 5-coordinated defects exist in the slow low density network of 4-coordinated water molecules. The fragmentation scenario explains well the observed density minimum of water at 190 K. We also find that particular 3-coordinated defects with two HB acceptors and one HB donor are involved in structural changes in water. It is found, furthermore, that the presence of LDL predominantly formed by 4-coordinated molecules leads to a significant decrease of the glass transition temperature of water.

### References

- 1) M. Higashi and S. Saito, *J. Chem. Theory Comput.* **12**, 4128–4137 (2016).
- 2) T. Mori and S. Saito, *J. Phys. Chem. B* **120**, 11683–11691 (2016).
- 3) S. Saito, B. Bagchi and I. Ohmine, to be submitted.