# Theoretical Studies on Heterogeneous Condensed Phase Dynamics

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

**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

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

**Member**
Assistant Professor
　MORI, Toshifumi
IMS Fellow
　ONO, Junichi
Post-Doctoral Fellow
　KODA, Shin-ichi
Secretary
　KONDO, Naoko

| Keywords | Spatiotemporal Heterogeneous Dynamics, Liquids, Proteins |
|---|---|

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 dynamic 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 examined the molecular origin of anomalous temperature dependence of isobaric specific heat of water. The time scale involved in isothermal specific heat has been analyzed by analyzing complex specific heat. We examined the emergence of correlated motion in terms of the wave-number ($k$) dependent complex specific heat and the shell-wise energy fluctuation.

We currently investigate how chemical reactions proceed in biological systems, *e.g.* clock protein KaiC, under complex fluctuations. We also examine the large conformational transitions and the time-dependent couplings between conformational dynamics in proteins by using the idea of multi-dimensional spectroscopy.
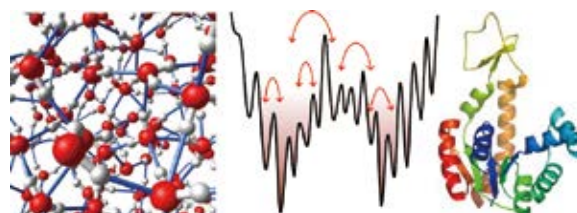


**Figure 1.** Schematic figure of rugged energy landscape (center) in supercooled water (left) and a biomolecule (right).

## 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. Chem. Phys.* **139**, 044503 (7 pages) (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).

## 1. Dynamic Heterogeneity in the Folding/Unfolding Transitions of FiP35[1]

Molecular dynamics simulations have become an important tool in studying protein dynamics over the last few decades. Atomistic simulations on the order of micro- to milliseconds are becoming feasible and are used to study the state-of-the-art experiments in atomistic detail. Yet, analyzing the high-dimensional-long-temporal trajectory data is still a challenging task and sometimes leads to contradictory results depending on the analyses. To reveal the dynamic aspect of the trajectory, here we propose a simple approach which uses a time correlation function matrix and apply to the folding/unfolding trajectory of FiP35 WW domain [Shaw *et al.*, *Science* **330**, 341 (2010)]. The approach successfully characterizes the slowest mode corresponding to the folding/unfolding transitions and determines the free energy barrier indicating that FiP35 is not an incipient downhill folder. The transition dynamics analysis further reveals that the folding/unfolding transition is highly heterogeneous, *e.g.*, the transition path time varies by ~100 fold. We identify two misfolded states and show that the dynamic heterogeneity in the folding/unfolding transitions originates from the trajectory being trapped in the misfolded and half-folded intermediate states rather than the diffusion driven by a thermal noise. The current results help reconcile the conflicting interpretations of the folding mechanism and highlight the complexity in the folding dynamics. This further motivates the need to understand the transition dynamics beyond a simple free energy picture using simulations and single-molecule experiments.

## 2. Couplings between Hierarchical Conformational Dynamics from Multi-Time Correlation Functions and Two-Dimensional Lifetime Spectra: Application to Adenylate Kinase[2]

An analytical method based on a three-time correlation function and the corresponding two-dimensional (2D) lifetime spectrum is developed to elucidate the time-dependent couplings between the multi-timescale conformational dynamics in heterogeneous systems such as proteins. In analogy with 2D NMR, IR, electronic, and fluorescence spectroscopies, the waiting-time dependence of the off-diagonal peaks in the 2D lifetime spectra can provide a quantitative description of the dynamical correlations between the conformational motions with different lifetimes. The present method is applied to intrinsic conformational changes of substrate-free adenylate kinase (AKE) using long-time coarse-grained molecular dynamics simulations. It is found that the hierarchical conformational dynamics arise from the intra-domain structural transitions among conformational sub-states of AKE by analyzing the one-time correlation functions and one-dimensional lifetime spectra for the donor–acceptor distances corresponding to single-molecule Förster resonance energy transfer experiments with the use of the principal component analysis. In addition, the complicated waiting-time dependence of the off-diagonal peaks in the 2D lifetime spectra for the donor–acceptor distances is attributed to the fact that the time evolution of the couplings between the conformational dynamics depends upon both the spatial and temporal characters of the system. The present method is expected to shed light on the biological relationship among the structure, dynamics, and function.

## 3. Ultrafast Dynamics of Liquid Water: Energy Relaxation and Transfer Processes of the OH Stretch and the HOH Bend[3]

The vibrational energy relaxation and transfer processes of the OH stretching and the HOH bending vibrations in liquid water are investigated via the theoretical calculation of the pump–probe spectra obtained from non-equilibrium molecular dynamics simulations with the TTM3-F interaction potential. The excitation of the OH stretch induces an instantaneous response of the high frequency librational motions in the 600–1000 cm$^{-1}$ range. In addition, the excess energy of the OH stretch of a water molecule quickly transfers to the OH stretches of molecules in its first hydration shell with a time constant of ~50 fs, followed by relaxation to the HOH bends of the surrounding molecules with a time constant of 230 fs. The excitation of the HOH bend also results in the ultrafast excitation of the high frequency librational motions. The energy of the excited HOH bend of a water molecule decays, with a time constant of 200 fs, mainly to the relaxation of the HOH bends of its surrounding molecules. The energies of the HOH bends were found to transfer quickly to the intermolecular motions via the coupling with the high frequency librational motions. The excess energy of the OH stretch or the HOH bend relaxes to the high frequency intermolecular librational motions and eventually to the hot ground state with a time scale of ~1 ps via the coupling with the librational and translational motions. The energy relaxation and transfer processes were found to depend on the local hydrogen bonding network; the relaxations of the excess energy of the OH stretch and the HOH bend of four- and five-coordinated molecules are faster than those of a three-coordinated molecule due to the delocalization of the vibrational motions of the former (four- and five-coordinated molecules) compared to those of the later (three-coordinated molecules). The present results highlight the importance of the high frequency intermolecular librational modes in facilitating the ultrafast energy relaxation process in liquid water via their strong nonlinear couplings with the intramolecular OH stretching and HOH bending vibrations.

### References

1) T. Mori and S. Saito, *J. Chem. Phys.* **142**, 135101 (7 pages) (2015).

2) J. Ono, S. Takada and S. Saito, *J. Chem. Phys., Special Topic: Multidimensional Spectroscopy* **142**, 212404 (13 pages) (2015).

3) S. Imoto, S. S. Xantheas and S. Saito, *J. Phys. Chem. B* **119**, 11068–11078 (2015).