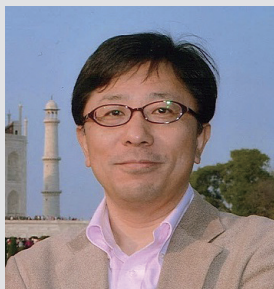


# Theoretical Studies on Reactions, Functions, and Fluctuations in Condensed Molecular Systems

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Our research focuses on the intricate fluctuations in condensed molecular systems, including liquids and biomolecules. In these systems, fluctuations affect various properties and biological functions, and reactions occur under fluctuations.

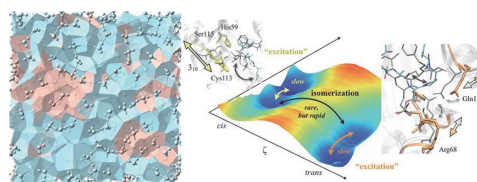
We investigate fluctuations and dynamics in these molecular systems to elucidate the molecular origins of the physical properties, functions, and reactions. To this end, we have developed advanced computational methods for multi-dimensional nonlinear spectroscopy, which allow us to extract detailed dynamical information that conventional linear spectroscopy cannot provide. Our investigations have successfully revealed the molecular origins of ultrafast energy relaxation and the time evolution of inhomogeneous fluctuations in liquid water. Additionally, we have explored the phenomenon of dynamic heterogeneity in supercooled liquids, characterized by slow and non-uniform structural changes induced by fluctuations. Using three-time correlation functions, we have also shed light on dynamic couplings of conformational fluctuations with different timescales in a protein.

Our work extends to the study of anomalous properties of liquid water, uncovering the connections between these anomalies and hidden structural and dynamical properties. Additionally, we have investigated the origin behind the low glass transition of water. We are also investigating the origin of rare but persistent structural change dynamics at low temperatures

based on theories of stochastic processes and reaction rates.

In biomolecular systems, conformational fluctuations and changes are essential for function. Our investigations have explored the intricate interplay between fluctuations and biomolecular functions, exemplified by the robust circadian rhythm of the clock protein KaiC and the efficient excitation energy transfer in photosynthetic systems. Our work on enzymatic reactions has highlighted the importance of prepared conformational states with specific structures that facilitate reactions. We have also studied the molecular origin of dynamic disorder in the conformational dynamics of proteins at the molecular level, unraveling the intricacies of this phenomenon.

As seen in these studies, we aim to deepen our understanding of structural dynamics, reactions, and functions in condensed molecular systems based on theoretical and computational methods.



**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).

#### Selected Publications

- T. Yagasaki and S. Saito, *Annu. Rev. Phys. Chem.* **64**, 55–75 (2013), T. L. C. Jansen, S. Saito, J. Jeon and M. Cho, *J. Chem. Phys. (Perspective)* **150**, 100901 (17 pages) (2019), C. R. Baiz *et al.*, *Chem. Rev.* **120**, 7152–7218 (2020).
- K. Kim and S. Saito, *J. Chem. Phys. (Special Topic on Glass Transition)* **138**, 12A506 (12 pages) (2013).
- S. Saito, B. Bagchi and I. Ohmine, *J. Chem. Phys.* **149**, 124504 (8 pages) (2018), S. Saito and B. Bagchi, *J. Chem. Phys.* **150**, 054502 (14 pages) (2019).
- T. Mori and S. Saito, *J. Phys. Chem. Lett.* **10**, 474–480 (2019).
- S. Saito, M. Higashi and G. R. Fleming, *J. Phys. Chem. B* **123**, 9762–9772 (2019).

## 1. Anisotropic and Finite Effects on Intermolecular Vibration and Relaxation Dynamics: Low-Frequency Raman Spectroscopy of Water Film and Droplet on Graphene by Molecular Dynamics Simulations<sup>1)</sup>

The structural and dynamical properties of water can be greatly altered by the anisotropic interfacial environment. Here, we study the intermolecular vibration and relaxation dynamics of a water film and a water droplet on a graphene surface based on low-frequency Raman spectra calculated from molecular dynamics simulations. The calculated Raman spectra of the interfacial water systems show a weakened libration peak and an enhanced intermolecular hydrogen bond (HB) stretching peak compared to the spectrum of bulk water, which are attributed to softened orientation motion. We also find that the collective polarizability relaxation in the droplet is much slower than that in the film and bulk, which is completely different from the collective dipole relaxation. The slow relaxation is due to a positive correlation between the induced polarizabilities of distinct molecules caused by the global and anisotropic structural fluctuations of the water droplet. Furthermore, we find that the two-dimensional HB network by the orientation-ordered interfacial water molecules leads to different intermolecular vibration dynamics between the parallel and perpendicular components. The present theoretical study demonstrates that low-frequency Raman spectroscopy can reveal the anisotropic and finite effects on the intermolecular dynamics of the water film and droplet.

## 2. Conformational Dynamics in Proteins: Entangled Slow Fluctuations and Nonequilibrium Reaction Events<sup>2)</sup>

Proteins exhibit conformational fluctuations and changes over various timescales, ranging from rapid picosecond-scale local atomic motions to slower microsecond-scale global conformational transformations. In the presence of these fluctuations, chemical reactions occur and functions emerge. These conformational fluctuations of proteins are not merely stochastic random motions but possess distinct spatiotemporal characteristics. Moreover, chemical reactions do not always proceed along a single reaction coordinate in a quasi-equilibrium manner. Therefore, it is essential to understand spatiotemporal conformational fluctuations of proteins and conformational change processes associated with reactions. In this Perspective, we shed light on the complex dynamics of proteins and their role in enzyme catalysis by presenting recent results regarding dynamic couplings and disorder in the conformational dynamics of proteins and rare but rapid enzymatic reaction events obtained from molecular dynamics simulations.

## 3. Molecular Insights into the Intrinsic Dynamics and Their Roles During Catalysis in Pin1 Peptidyl-prolyl Isomerase<sup>3)</sup>

Proteins are intrinsically dynamic and change conformations over a wide range of time scales. While the conformational dynamics have been realized to be important for protein func-

tions, *e.g.*, in activity–stability trade-offs, how they play a role during enzyme catalysis has been of debate over decades. By studying Pin1 peptidyl-prolyl isomerase using extensive molecular dynamics simulations, here we discuss how the slow intrinsic dynamics of Pin1 observed in the NMR relaxation dispersion experiment occur and couple to isomerization reactions in molecular detail. In particular, we analyze the angular correlation functions of the backbone N–H bonds and find that slow conformational transitions occur around the  $3_{10}$  helix in the apo state. These events at the helical region further affect the residues around the ligand binding site. Unfolding of this helix leads to a tight hydrogen bond between the helical region and the ligand binding loop, thus forming a stable coiled structure. The helical and coiled structures are found to be characteristic of the Pin1–ligand complex with the ligand in the *trans* and *cis* states, respectively. These results indicate that the changes in the slow dynamics of Pin1 by the isomerization reaction occur via the shift in populations of the helical and coiled states, where the balance is dependent on the ligand isomerization states.

## 4. Excited States of Chlorophyll *a* and *b* in Solution by Time-Dependent Density Functional Theory<sup>4)</sup>

The ground state and excited state electronic properties of chlorophyll (Chl) *a* and Chl *b* in diethyl ether, acetone, and ethanol solutions are investigated using quantum mechanical and molecular mechanical calculations with density functional theory (DFT) and time-dependent DFT (TDDFT). Although the DFT/TDDFT methods are widely used, the electronic structures of molecules, especially large molecules, calculated with these methods are known to be strongly dependent on the functionals and the parameters used in the functionals. Here, we optimize the range-separated parameter,  $\mu$ , of the CAM-B3LYP functional of Chl *a* and Chl *b* to reproduce the experimental excitation energy differences of these Chl molecules in solution. The optimal values of  $\mu$  for Chl *a* and Chl *b* are smaller than the default value of  $\mu$  and that for bacteriochlorophyll *a*, indicating the change in the electronic distribution, *i.e.*, an increase in electron delocalization, within the molecule. We find that the electronic distribution of Chl *b* with an extra formyl group is different from that of Chl *a*. We also find that the polarity of the solution and hydrogen bond cause the decrease in the excitation energies and the increase in the widths of excitation energy distributions of Chl *a* and Chl *b*. The present results are expected to be useful for understanding the electronic properties of each pigment molecule in a local heterogeneous environment, which will play an important role in the excitation energy transfer in light-harvesting complex II.

### References

- 1) T. Inagaki, M. Hatanaka and S. Saito, *J. Phys. Chem. B* **127**, 5869–5880 (2023).
- 2) J. Ono, Y. Matsumura, T. Mori and S. Saito, *J. Phys. Chem. B (Perspective)*, accepted.
- 3) T. Mori and S. Saito, *J. Phys. Chem. B* **126**, 5185–5193 (2022).
- 4) Z. Zhu, M. Higashi and S. Saito, *J. Chem. Phys. (Special topic on Photosynthetic Light-Harvesting and Energy Conversion)* **156**, 124111 (13 pages) (2022).