Theoretical Studies on Reactions, Functions, and Fluctuations in Many-Body Molecular Systems

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Many-body molecular systems, such as (supercooled) liquids and biomolecules, exhibit complex fluctuations. Furthermore, in these systems, various physical properties and biological functions are created and chemical reactions proceed under the fluctuations. We aim to elucidate the properties, functions, and reactions by investigating fluctuations and dynamics of the many-body molecular systems.

We have investigated fluctuations and dynamics of liquids by developing computational method for multi-dimensional nonlinear spectroscopy that can reveal detailed dynamical infomation not available from conventional linear spectroscopy. Consequently, we revealed the molecular origins of the ultrafast energy relaxation and time evolution of inhomogeneous fluctuations in liquid water. In supercooled liquids, rare and non-uniform structural changes, called dynamic heterogeneity, are induced by fluctuations. We elucidated the relationship between the lifetime of the dynamic heterogeneity and the fragility using the three-time correlation function of density fluctuations.

We study the molecular origin of anomalous properties of liquid water. We revealed that the anomalies of liquid water are related to the structural and dynamical instabilities hidden in the experimentally inaccessible region and the physical reason of the low glass transition of liquid water. Now we investigate how rare but persistent structural relaxations proceed at low temperatures towards the glass transition temperature.

Complex conformational fluctuations and changes are also found in biomolecular systems. In addition, conformational dynamics are considered to be essential for biological functions. We examine the relationship between fluctuation and biomolecular function found in the robust circadian rhythm of the clock protein KaiC and the efficient excitation energy transfer in photosynthetic systems. We investigate the dynamic effects of enzymatic reactions and find the importance of prearranged states for the rare but persistent enzymatic reactions. Furthermore, we examine dynamic disorder in conformational changes of proteins at the molecular level.

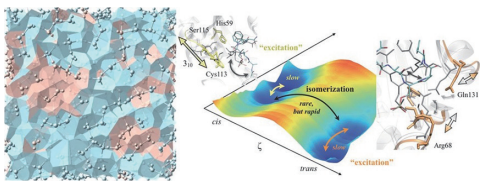

Figure 1. Snapshot of two-state model in supercooled water consisting of high- and low-density liquids (left) and schematic of 2D free energy surface for enzymatic reaction (right).

Selected Publications

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1. Multimeric Structure Enables the Acceleration of KaiB-KaiC Complex Formation Induced by ADP/ATP Exchange Inhibition[1)]

Circadian clocks tick a rhythm with a nearly 24-hour period in a variety of organisms. In the clock proteins of cyanobacteria, KaiA, KaiB, and KaiC, known as a minimum circadian clock, the slow KaiB-KaiC complex formation is essential in determining the clock period. This complex formation, occurring when the C1 domain of KaiC hexamer binds ADP molecules produced by the ATPase activity of C1, is considered to be promoted by accumulating ADP molecules in C1 through inhibiting the ADP/ATP exchange (ADP release) rather than activating the ATP hydrolysis (ADP production). Significantly, this ADP/ATP exchange inhibition accelerates the complex formation together with its promotion, implying a potential role in the period robustness under environmental perturbations. However, the molecular mechanism of this simultaneous promotion and acceleration remains elusive because inhibition of a backward process generally slows down the whole process. In this article, to investigate the mechanism, we build several reaction models of the complex formation with the pre-binding process concerning the ATPase activity. In these models, six KaiB monomers cooperatively and rapidly bind to C1 when C1 binds ADP molecules more than a given threshold while stabilizing the binding-competent conformation of C1. Through comparison among the models proposed here, we then extract three requirements for the simultaneous promotion and acceleration: The stabilization of the binding-competent C1 by KaiB binding, slow ADP/ATP exchange in the binding-competent C1, and relatively fast ADP/ATP exchange occurring in the binding-incompetent C1 in the presence of KaiB. The last two requirements oblige KaiC to form a multimer. Moreover, as a natural consequence, the present models can also explain why the binding of KaiB to C1 reduces the ATPase activity of C1.

2. Vectorial Insertion of a β-Helical Peptide into Membrane: A Theoretical Study on Polytheonamide B[2)]

Spontaneous unidirectional, or vectorial, insertion of transmembrane peptides is a fundamental biophysical process for toxin and viral actions. Polytheonamide B (pTB) is a potent cytotoxic peptide with a $\beta^{6.3}$-helical structure. Previous experimental studies revealed that the pTB inserts into the membrane in a vectorial fashion and forms a channel with its single molecular length long enough to span the membrane. Also, molecular dynamics simulation studies demonstrated that the pTB is prefolded in aqueous solution. These are unique features of pTB because most of the peptide toxins form channels through oligomerization of transmembrane helices. Here, we performed all-atom molecular dynamics simulations to examine the dynamic mechanism of the vectorial insertion of pTB, providing underlying elementary processes of the membrane insertion of a prefolded single transmembrane peptide. We find that the insertion of pTB proceeds with only the local lateral compression of the membrane in three successive phases: "Landing," "penetration," and "equilibration" phases. The free energy calculations using the replica-exchange umbrella sampling simulations present an energy cost of ~4 kcal/mol at the membrane surface for the membrane insertion of pTB from bulk water. The trajectories of membrane insertion revealed that the insertion process can occur in two possible pathways, namely "trapped" and "untrapped" insertions; in some cases, pTB is trapped in the upper leaflet during the penetration phase. Our simulations demonstrated the importance of membrane anchoring by the hydrophobic N-terminal blocking group in the landing phase, leading to subsequent vectorial insertion.

3. Excited States of Chlorophyll *a* and *b* in Solution by Time-Dependent Density Functional Theory[3)]

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, μ, 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 μ for Chl *a* and Chl *b* are smaller than the default value of μ 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.

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