Theoretical Studies on Reactions, Functions, and Fluctuations in Condensed-Phase Systems

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Our research centers on complex fluctuations in condensed systems, including supercooled liquids and biomolecules. These fluctuations significantly influence various properties, functions, and reactions. By investigating the dynamics and fluctuations in these molecular systems, we aim to uncover the molecular origins of these properties, functions, and reactions.

We have pioneered advanced computational methods for multi-dimensional nonlinear spectroscopy, enabling us to elucidate the molecular basis of ultrafast energy relaxation and the temporal evolution of nonuniform fluctuations in liquid water that conventional linear spectroscopy has not revealed. Additionally, we have delved into the dynamical heterogeneity of supercooled liquids, characterized by slow, inhomogeneous structural changes driven by fluctuations. Using a three-time correlation function, we unveiled the dynamic coupling of structural fluctuations across different time scales in proteins.

Our research has also focused on the anomalous properties of water, establishing a link between these anomalies and previously hidden structural and dynamical characteristics. Recently, we developed a novel analytical method for studying dynamical disorder based on stochastic process theory, elucidating the mechanisms behind slowing structural changes as systems approach the glass transition. In the realm of biomolecular systems, structural fluctuations and conformational changes are crucial for functions. Our studies on enzymatic reactions underscore the importance of specific prepared conformational states that facilitate these reactions. Furthermore, we have probed the molecular origins of dynamic disorder within protein conformational dynamics, revealing the complexity of these processes. Our investigations also extend to the molecular mechanisms underlying efficient excitation energy transfer in photosynthetic systems.

Through these efforts, we are engaged in a broad spectrum of theoretical and computational studies to unravel the dynamical phenomena that govern condensed-phase systems.



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).

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1. Conformational Dynamics in Proteins: Entangled Slow Fluctuations and Nonequilibrium Reaction Events¹⁾

Proteins exhibit conformational fluctuations and changes over various time scales, ranging from rapid picosecond-scale local atomic motions to slower microsecond-scale global conformational transformations. In the presence of these intricate 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 the 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.

2. Locating Transition States by a Variational Reaction Path Optimization with an Energy-Derivative-Free Objective Function²⁾

Locating transition states is essential for understanding molecular reactions. We propose a double-ended transition state search method by revisiting a variational reaction path optimization method known as the MaxFlux method. Although its original purpose is to add temperature effects to reaction paths, we conversely let the temperature approaches zero to obtain an asymptotically exact minimum energy path and its corresponding transition state in variational formalism with an energyderivative-free objective function. Using several numerical techniques to directly optimize the objective function, the present method reliably finds transition states with low computational cost. In particular, only three force evaluations per iteration are sufficient. This is confirmed in a variety of molecular reactions where the nudged elastic band method often fails.

3. Unraveling the Dynamic Slowdown in Supercooled Water: The Role of Dynamic Disorder in Jump Motions³⁾

When a liquid is rapidly cooled below its melting point without inducing crystallization, its dynamics slow down significantly without noticeable structural changes. Elucidating the origin of this slowdown has been a long-standing challenge. Here, we report a theoretical investigation into the mechanism of the dynamic slowdown in supercooled water, a ubiquitous yet extraordinary substance characterized by various anomalous properties arising from local density fluctuations. Using molecular dynamics simulations, we found that the jump dynamics, which are elementary structural change processes, deviate from Poisson statistics with decreasing temperature. This deviation is attributed to slow variables competing with the jump motions, *i.e.*, dynamic disorder. The present analysis of the dynamic ment of the fourth nearest oxygen atom of a jumping molecule, which occurs in an environment created by the fluctuations of molecules outside the first hydration shell. As the temperature decreases, the jump dynamics become slow and intermittent. These intermittent dynamics are attributed to the prolonged trapping of jumping molecules within extended and stable lowdensity domains. As the temperature continues to decrease, the number of slow variables increases due to the increased cooperative motions. Consequently, the jump dynamics proceed in a higher-dimensional space consisting of multiple slow variables, becoming slower and more intermittent. It is then conceivable that with further decreasing temperature, the slowing and intermittency of the jump dynamics intensify, eventually culminating in a glass transition.

4. Effect of Counterions on the Structure and Dynamics of Water near a Negatively Charged Surfactant: A Theoretical Vibrational Sum Frequency Generation Study⁴⁾

Charged aqueous interfaces are of paramount importance in electrochemical, biological, and environmental sciences. The properties of aqueous interfaces with ionic surfactants can be influenced by the presence of counterions. Earlier experiments involving vibrational sum frequency generation (VSFG) spectroscopy of aqueous interfaces with negatively charged sodium dodecyl sulfate (Na⁺DS⁻ or SDS) surfactants revealed that the hydrogen bonding strength of the interfacial water molecules follows a certain order when salts of monovalent and divalent cations are added. It is known that cations do not directly participate in hydrogen bonding with water molecules, rather they only influence the hydrogen-bonded network through their electrostatic fields. In the current work, we have simulated the aqueous interfacial systems of sodium dodecyl sulfate in the presence of chloride salts of mono and divalent countercations. The electronic polarization effects on the ions are considered at a mean-field level within the electronic continuum correction model. Our calculations of the VSFG spectra show a blue shift in the presence of added countercations whose origin is traced to different relative contributions of water molecules from the solvation shells of the surfactant headgroups and the remaining water molecules in the presence of countercations. Furthermore, the cations shield the electric fields of the surfactant headgroups, which in turn influences the contributions of water molecules to the total VSFG spectrum. This shielding effect becomes more significant when divalent countercations are present. The dynamics of water molecules are slower at the interface than the bulk. The interfacial depth dependence of various dynamical quantities shows that the interface is structurally and dynamically more heterogeneous at the microscopic level.

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