

論文審査の結果の要旨および担当者

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論 文 題 目 Thermal energy transport and signal transduction of biomolecular machines: Molecular dynamics simulation study of proteins

(生体分子機械の熱エネルギー輸送と情報伝達：タンパク質の分子動力学シミュレーション)

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論文審査の結果の要旨

Proteins, molecular machines in the cell, play crucial roles in a broad range of biological processes. In particular, thermal energy transport is among the essential biophysical properties of proteins; however, its relationship with protein structures, dynamics, and functions is still elusive.

The structures of folded proteins are highly inhomogeneous with various interactions such as hydrogen bond (H-bond), electrostatic interaction, and van der Waals contact. Accordingly, we expect that the flow of thermal energy is also anisotropic and non-uniform under protein conformational fluctuations. To address the issue, the doctoral candidate has developed a theoretical framework for analyzing the local transport properties of thermal energy based on the autocorrelation function formalism using equilibrium molecular dynamics (MD) simulation. Furthermore, she employed machine learning techniques to identify key determinants for protein thermal transport.

First, she examined the properties of an α -helical protein, HP36, with a special emphasis on the heat flow along the polypeptide main-chain. She introduced a residue-base partition scheme and assumed that heat currents occur only within each individual amino acid residue and between residues adjacent in sequence. Also, she considered short-range cross-correlations of heat currents between different parts. As a result, this model (linear-homopolymer-like model) reproduced the exact value of the protein thermal conductivity of the entire molecule, derived from the total heat current, with an error of $< 1\%$, indicating that the heat currents along the chain dominate the thermal transport process. Also, residue-wise thermal conductivity demonstrated distinct residue-type dependence, i.e., their values decreased in the order of charged $>$ polar $>$ hydrophobic residues.

Second, the doctoral candidate examined the roles of non-bonded interactions in the thermal transport of HP36 by calculating the heat currents between residue pairs in non-bonded native contacts. As a result, the inter-residue thermal conductivity, λ_{inter} , of contact residue pairs exhibited interaction-type dependence, i.e., λ_{inter} decreased in the following order: H-bond $>$ π -stacking $>$ electrostatic $>$ hydrophobic. Among them, the λ_{inter} values of the H-bonded pairs exhibit a positive linear correlation with the H-bond occurrence probability, P_{HB} , a measure of the average number of H-bonds calculated using MD trajectories. To identify key determinants for λ_{inter} , she used the random forest regression algorithm. She found three key factors, i.e., the contact distance, variance in contact distance, and P_{HB} .

As an application, the doctoral candidate examined the allosteric signaling mechanism of the oxygen sensory domain of FixL protein by computing its vibrational energy transport network, which mediates heat dissipation. It has been widely accepted that essential cellular processes are controlled not only by well-structured proteins but also by fully or partially disordered proteins, whose structural and dynamical characterization, however, is known to be a challenging problem. To address the issue, she developed a hybrid approach of deep learning, MD simulation, Small-angle X-ray scattering (SAXS), and Electron paramagnetic resonance (EPR)/Double electron-electron resonance (DEER) to characterize the ensemble of a chloroplast protein, CP12, which contains intrinsically disordered regions (IDRs).

In summary, the doctoral candidate established a computational method of site-selective heat current analysis of proteins. Furthermore, she demonstrated a possible interplay between allosteric signal transduction and thermal energy transport. By using machine learning techniques, she characterized complex biophysical properties of proteins such as non-uniform thermal energy transport and conformational ensemble of highly flexible proteins including IDRs. Her method of site-selective heat current analysis provides a unique approach for the study of protein properties, and her finding of the controlling factors for the local thermal transport coefficients in proteins is highly evaluated. Considering the above, we concluded that she deserves to be awarded a doctoral degree Doctor of Science.