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主　論　文　の　要　旨

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　内　容　の　要　旨

Proteins are crucial macromolecules in living organisms, performing various essential functions. Thermal energy transport is among the essential biophysical properties of proteins, but its relationship with protein structures, dynamics, and functions is still elusive.

The structures of folded proteins are highly inhomogeneous, giving rise to an anisotropic and non-uniform flow of thermal energy through different types of pathways and interactions. To illustrate such transport nature of proteins, I developed a theoretical framework for analyzing the local thermal transport properties of thermal energy based on the autocorrelation function formalism using equilibrium molecular dynamics (MD) simulations. In addition, advanced machine learning-based methods were utilized to illustrate the contributing factors of thermal transport in protein and the structural characterization of intrinsically disordered regions.

First, the overall thermal conductivity of an α-helical protein (HP36) was calculated as 0.26 ± 0.01 W/(m K) based on the linear response theory using equilibrium MD simulations. The local heat transport properties along peptide chains were studied using a linear-homopolymer-like model, where the entire protein was divided into small pieces by residues and heat flows only within each residue (intra-) and between two peptide-bonded residues

(inter). Short-range cross-correlation corrections were introduced and employed to correct the model for redistributing the overestimated contributions from partial heat currents to the total heat current of the model due to the non-neglectable independent fluctuations between residues. The model reproduced the exact value of the protein thermal conductivity, derived from the total heat current, within 1% error. The local thermal transport calculation indicates that intra-residue thermal transport has a dominant contribution to the overall heat current and residue-wise thermal conductivity demonstrated distinct residue-type dependence: their values decreased in a order of charged, polar, and hydrophobic residues.

Second, the local thermal transport properties of non-bonded contacts in proteins were studied by introducing a derived physical quantity of *inter-residue thermal conductivity* (λ_{inter}). As a results, λ_{inter} of non-bonded contacts exhibited a decreasing trend on interaction types: hydrogen bonding > π-stacking > electrostatic > hydrophobic. Furthermore, the λ_{inter} values are proportional to the hydrogen bond occurrence probability (P_{HB}), a measure of the average number of hydrogen bonds during MD simulations. The random forest regression prediction model was used to investigate the non-linear relationship between λ_{inter} and various static and dynamical properties of the protein. The contact distance, variance in contact distance, and P_{HB} were found to be the three most important factors.

As a case study, the allosteric signaling process of the oxygen sensor domain of *Bj*FixL protein was investigated by constructing the vibrational energy exchange network (EEN) model. In addition, a hybrid approach of deep learning algorithms, MD simulation, small angle X-ray scattering (SAXS), and double electron-electron resonance electron paramagnetic resonance (DEER/EPR) spectroscopy, was developed to characterize the ensemble of a chloroplast protein, CP12, which contains intrinsically disordered regions (IDRs).

In summary, a theoretical framework of site-selective heat current analysis for analyzing the local thermal transport was developed based on the linear response theory using equilibrium MD simulations. The role of thermal energy transport in the signaling mechanism was investigated by using the energy exchange network model. Furthermore, machine learning methods were employed to solve complicated problems, such as the non-linear relationship between heat transfer pathways and static and dynamical properties of protein and the structural characterization of proteins with IDRs and their complexes in structural biology.