Development of New Algorithms for Molecular Dynamics Simulation and Its Application to Biomolecular Systems

Department of Theoretical and Computational Molecular Science
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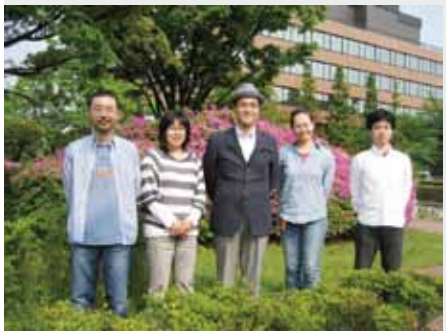

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In the conventional canonical-ensemble simulations, it is difficult to realize efficient samplings in proteins because the simulations tend to get trapped in a few of many local-minimum states. To overcome these difficulties, we have proposed new generalized-ensemble algorithms, such as multibaric-multithermal algorithm, partial multicanonical algorithm, van der Waals replica exchange method, and Coulomb replica exchange method. It is important to realize efficient samplings in the conformational space and to predict the native structures of proteins. We apply these methods to proteins and peptides.

1. Temperature and Pressure Denaturation of Chignolin: Folding and Unfolding Simulation by Multibaric-Multithermal Molecular Dynamics Method

We performed a multibaric-multithermal molecular dynamics (MD) simulation of a 10-residue protein, chignolin and discussed its folding thermodynamics last year. We further investigated the denaturation mechanisms this year.[1)]

All-atom model for the protein with Amber parm99SB force field were employed in explicit TIP3P water. This MD simulation covered wide ranges of temperature between T = 260~560 K and pressure between P = 0.1~600 MPa and sampled many conformations without getting trapped in local-minimum free-energy states.

Radial distribution function $g(r)$ between the chignolin heavy atoms and the water oxygen atoms, the first peak position of $g(r)$, r_1, the number of hydration water molecules, and the number of hydrophobic contacts were calculated. As the temperature increases, r_1 increases and the number of water molecules around chignolin decreases. It represents that chignolin gains more space to move around and is transferred to a high entropy state, even if it losses potential energy by breaking hydrogen bonds between the protein atoms or between the protein and water. Entropy of the transition state and the unfolded state is higher than the native state. This is the reason why the probabilities of not only the unfolded state such as the extended structure but also the transition state increase as the temperature increases.

On the other hand, the number of hydration water molecules increases with the increasing pressure. There are fewer water molecules near the hydrophobic residues when the protein is folded at the room pressure. As the pressure increases, more water molecules come closer to the hydrophobic residues and the number of hydrophobic contacts decreases. The hydrophobic residues then get separated from one another and the protein is unfolded.

2. Coulomb Replica-Exchange Method: Handling Electrostatic Attractive and Repulsive Forces for Biomolecules

We propose a new type of the Hamiltonian replica-exchange method for molecular dynamics (MD) and Monte Carlo simulations, which we refer to as the Coulomb replica-exchange method. In this method, electrostatic charge parameters in the Coulomb interactions are exchanged among replicas while temperatures are exchanged in the usual replica-exchange method. By varying the atom charges, the Coulomb replica-exchange method overcomes free-energy barriers and realizes more efficient sampling in the conformational space than the

replica-exchange method. Furthermore, this method requires only a smaller number of replicas because only the atom charges of solute molecules are employed as exchanged parameters.

We performed Coulomb replica-exchange MD simulations of an alanine dipeptide in explicit water solvent and compared the results with those of the conventional canonical, replica-exchange, and van der Waals replica-exchange methods. Two force fields of AMBER parm99 and AMBER parm99SB were employed. As a result, the Coulomb replica-exchange method sampled all local-minimum free-energy states more frequently than the other methods for both force fields. Moreover, the Coulomb, van der Waals, and usual replica-exchange methods were applied to a fragment of an amyloid-β peptide (Aβ) in explicit water solvent to compare the sampling efficiency of these methods for a larger system. The Coulomb replica-exchange method sampled structures of the Aβ fragment more efficiently than the other methods. We obtained β-helix, α-helix, 3_{10}-helix, β-hairpin, and β-sheet structures as stable structures and revealed pathways of conformational transitions among these structures from a free-energy landscape, as shown in Figure 1.

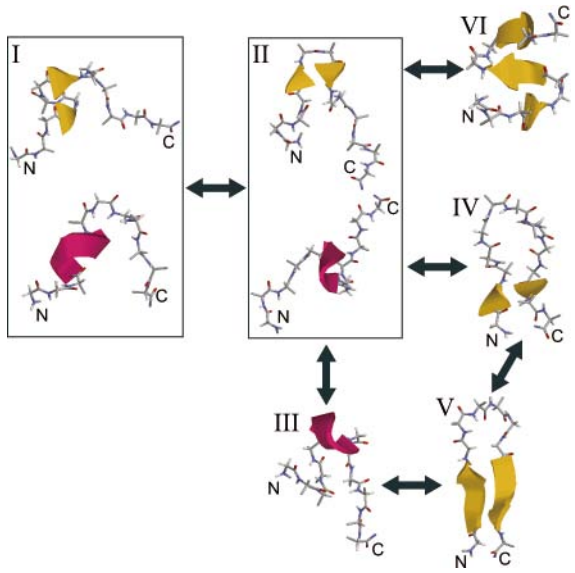

Figure 1. Folding pathways of amyloid-β peptide obtained from Coulomb replica-exchange MD simulations.

3. Replica Exchange Molecular Dynamics Simulation of Chitosan for Drug Delivery System Based on Carbon Nanotube

Chitosan is an important biopolymer in the medical applications because of its excellent biocompatibility. It has been recently highlighted in the targeted drug delivery system (DDS) by improvement of the carbon nanotube (CNT) solubility. To investigate the effect of chitosan length, the two targeted DDSs with 30 and 60 chitosan monomers were performed by replica-exchange molecular dynamics simulations at temperatures in the range of 300–455 K. Each DDS model contains the epidermal growth factor (EGF), chitosan (CS) of 30 (30CS) and 60 (60CS) monomers, single-wall CNT (SWCNT) and gemcitabine (Gemzar) as the model payload anticancer drug, called EGF/30CS/ SWCNT/Gemzar and EGF/60CS/SWCNT/Gemzar, respectively. The SWCNT confines gemcitabine inside its cavity, while the outer surface is wrapped by chitosan in which one end is linked to the EGF. The results showed that in the EGF/30CS/SWCNT/Gemzar DDS the 30CS chain was not long enough to wrap around the SWCNT, and consequently the EGF was located so close to the tube as to potentially cause steric inhibition of the binding of EGF to its receptor (EGFR), which is highly expressed on the surface of cancer cells. On the other hand, this phenomenon is not observed in the EGF/60CS/SWCNT/Gemzar DDS in which the 60CS was found to completely wrap over the CNT outer surface using only 50 chitosan units. Although an increase in the temperature is likely to influence the overall DDS structure, and especially the orbit of helical chitosan on the SWCNT and the EGF conformation, gemcitabine is still encapsulated inside the tube.

4. Monte Carlo Simulation for Isotropic–Nematic Phase Transition of Infinitely Thin Liquid Crystal Molecules

We are also interested in isotropic–nematic phase transition of liquid crystal molecules. We gave a criterion to test a non-biaxial behavior of infinitely thin hard platelets based upon the components of three order parameter tensors. We investigated the nematic behavior of monodisperse infinitely thin rectangular hard platelet systems by this criterion. Starting with a square platelet system, and we compared it with rectangular platelet systems of various aspect ratios. For each system, we performed equilibration runs by using isobaric Monte Carlo simulations. Each system did not show a biaxial nematic behavior but a uniaxial nematic one, despite of the shape anisotropy of those platelets. The relationship between effective diameters by simulations and theoretical effective diameters of these systems was also determined.

Reference

1) H. Okumura, *Proteins: Struct., Funct., Bioinf.* **80**, 2397–2416 (2012).

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