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

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Effective samplings in the conformational space by Monte Carlo and molecular dynamics simulations are necessary to predict the native structures of proteins. In the conventional canonical-ensemble simulations, however, it is difficult to realize effective samplings in complex systems such as proteins. This is because the usual canonical-ensemble simulations tend to get trapped in a few of many local-minimum states. To overcome these difficulties, we proposed new generalized-ensemble algorithms.

1. Replica-Exchange Method in van der Waals Radius Space: Overcoming Steric Restrictions for Biomolecules[1)]

The replica-exchange method is one of the most well-known methods among the generalized-ensemble algorithms. For large systems such as proteins in aqueous solution, however, the usual replica-exchange method has a difficulty. We need to increase the number of replicas in proportion to $O(f^{1/2})$, where f is the number of degrees of freedom. Large biomolecular systems, therefore, require a large number of replicas in the replica-exchange method and hence huge amount of computation time. In order to overcome this difficulty, Hamiltonian replica-exchange method is somtimes employed.

We present a new type of the Hamiltonian replica-exchange method, where the van der Waals radius parameter and not the temperature is exchanged. By decreasing the van der Waals radii, which control spatial sizes of atoms, this Hamiltonian replica-exchange method overcomes the steric restrictions and energy barriers. Furthermore, the simulation based on this method escapes from the local-minimum free-energy states and realizes effective sampling in the conformational space. We applied this method to an alanine dipeptide (Figure 1) in aqueous solution and showed the effectiveness of the method by comparing the results with those obtained from the conventional canonical and replica-exchange methods.

2. Optimization of Partial Multicanonical Algorithm for Molecular Dynamics and Monte Carlo Simulations

The multicanonical ensemble algorithm is another one of the most well-known generalized-ensemble algorithms. A non-Boltzmann weight factor is employed in this ensemble so that a free one-dimensional random walk can be realized in the potential-energy space. Thus, a simulation with this algorithm can escape from the free-energy-minimum states and sample a wide range of the conformational space. Because of this advantage, the multicanonical algorithm has been frequently applied to a biomolecule, which has a free-energy surface with many local minima. However, the non-Boltzmann weight factor in the multicanonical algorithm is not *a priori* known and has to be determined by a preliminary simulation. As the

system size increases, the distribution of the total potential energy gets narrower. Thus, the determination of the multicanonical weight factor to give a flat distribution becomes difficult in a large system.

In order to alleviate this difficulty, we proposed recently the partial multicanonical ensemble algorithm for molecular dynamics and Monte Carlo simulations. The partial multicanonical algorithm samples a wide range of an important part of the potential energy. Although it is a strong technique for structure prediction of biomolecules, the choice of the partial potential energy has not been optimized. In order to find the best choice, partial multicanonical molecular dynamics simulations of an alanine dipeptide in explicit water solvent were performed with 15 trial choices for the partial potential energy. The best choice was found to be the sum of the electrostatic, Lennard-Jones, and torsion-angle potential energies between solute atoms. In this case, the partial multicanonical simulation sampled all of the local-minimum free-energy states of the P_{II}, C_5, α_R, α_P, α_L, and C_7^{ax} states and visited these states most frequently. Furthermore, backbone dihedral angles ϕ and ψ rotated very well. It is also found that the most important term among these three terms is the electrostatic potential energy and that the Lennard-Jones term also helps the simulation to overcome the steric restrictions. On the other hand, multicanonical simulation sampled all of the six states, but visited these states less time. Conventional canonical simulation sampled only four of the six states: The P_{II}, C_5, α_R, and α_P states.

3. Conformational Populations of Ligand-Sized Molecules by Replica Exchange Molecular Dynamics and Temperature Reweighting[2)]

The use of the replica exchange molecular dynamics method for the efficient estimation of conformational populations of ligand-sized molecules in solution is investigated. We compare the computational efficiency of the traditional constant temperature molecular dynamics technique with that of the parallel replica exchange molecular dynamics method for a series of alkanes and rilpivirine (TMC278), an inhibitor against HIV-1 reverse transcriptase, with implicit solvation. We show that conformational populations are accurately estimated by both methods; however, replica exchange estimates converge at a faster rate, especially for rilpivirine, which is characterized by multiple stable states separated by high-free energy barriers. Furthermore, convergence is enhanced when the weighted histogram analysis method is used to estimate populations from the data collected from multiple replica exchange temperature replicas. For small drug-like molecules with energetic barriers separating the stable states, the use of replica exchange with the weighted histogram analysis method is an efficient computational approach for estimating the contribution of ligand conformational reorganization to binding affinities.

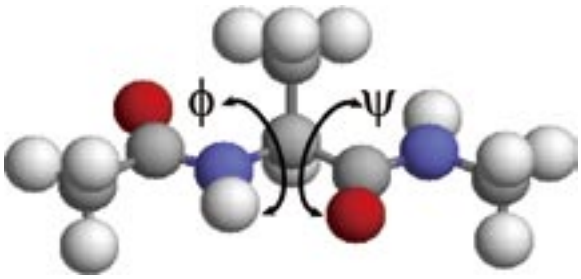

Figure 1. The initial conformations of alanine dipeptide for the molecular dynamics simulation.

References

1) S. G. Itoh, H. Okumura and Y. Okamoto, *J. Chem. Phys.* **132**, 134105 (8 pages) (2010).

2) H. Okumura, E. Gallicchio and R. M. Levy, *J. Comput. Chem.* **31**, 1357–1367 (2010).