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

Department of Theoretical and Computational Molecular Science
Division of Computational Molecular Science

OKUMURA, Hisashi
Associate Professor

ITOH, G. Satoru
Assistant Professor

MORI, Yoshiharu
IMS Research Assistant Professor

NOMURA, Hitomi	Graduate Student
KHUNTAWEE, Wasinee	Graduate Student
KAWAGUCHI, Ritsuko	Secretary

Biomolecules such as proteins and peptides have complicated free-energy landscape with many local minima. In the conventional canonical-ensemble simulations, it is difficult to realize efficient samplings in such systems because the simulations tend to get trapped in a few of the local- minimum states. To overcome these difficulties, we have proposed new generalized-ensemble algorithms, such as helix-strand replica-exchange method and replica- permutation 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. Transformation of a Design Peptide between the α-Helix and β-Hairpin Structures by a Helix-Strand Replica-Exchange Molecular Dynamics Simulation

We investigated the transformation between the α-helix and β-hairpin structures of an 18-residue design peptide, whose sequence is INYWLAHAKAGYIVHWTA.[1] This peptide has both α-helix and β-hairpin structures in aqueous solution. For this purpose, we proposed the helix-strand replica-exchange method. This is one of the Hamiltonian replica-exchange methods in which we exchange parameters for umbrella potentials to enhance the α-helix or β-strand structure formation, as in Figure 1. We performed an all-atom helix-strand replica-exchange molecular dynamics (MD) simulation of this peptide in explicit water solvent with five replicas. Because the suitable umbrella potential was applied, the helix-strand replica-exchange MD simulation reproduced conformations closer to experimental conformations than a temperature replica-exchange MD simulation when the same numbers of the replicas were used, while the temperature replica-exchange MD simulation does not require bias along any specific order parameter. We calculated its free-energy landscape and revealed the transformation pathways between the α-helix and β-hairpin structures and the folding pathways from an extended structure. The free-energy difference between the two structures is calculated to be almost zero, which agrees with the experimental results.

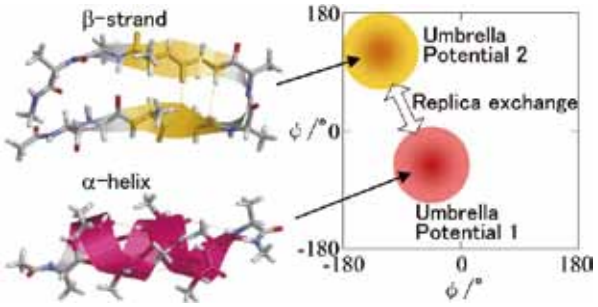

Figure 1. Schematic illustration of the helix-strand replica-exchange method.

2. Replica-Permutation Method with the Suwa-Todo Algorithm beyond the Replica-Exchange Method

We proposed a new method for MD and Monte Carlo simulations, which is referred to as the replica-permutation method, to realize more efficient sampling than the replica-exchange method.[2] In replica-permutation method, not only exchanges between two replicas but also permutations among more than two replicas are performed, as in Figure 2. Furthe-

rmore, instead of the Metropolis algorithm, the Suwa–Todo algorithm is employed for replica-permutation trials to minimize its rejection ratio. We applied RPM to particles in a double-well potential energy, Met-enkephalin in a vacuum, and a C-peptide analog of ribonuclease A in explicit water. For comparison purposes, replica-exchange molecular dynamics simulations were also performed. As a result, replica-permutation method sampled not only the temperature space but also the conformational space more efficiently than REM for all systems. From our simulations of C-peptide, we obtained the α-helix structure with salt bridges between Gly2 and Arg10, which is known in experiments. Calculating its free-energy landscape, the folding pathway was revealed from an extended structure to the α-helix structure with the salt bridges.

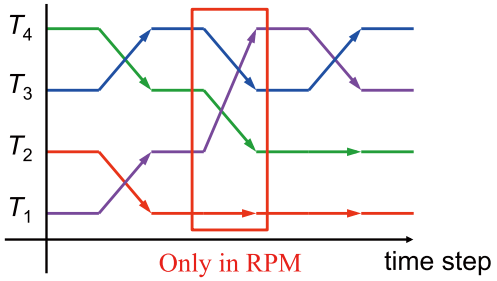

Figure 2. An example of time series of temperatures in replica-permutation method (RPM). The transitions of replicas in the red square frame are not realized in replica-exchange method (REM).

3. Pressure-Induced Helical Structure of a Peptide Studied by Simulated Tempering Molecular Dynamics Simulations

It is known experimentally that an AK16 peptide forms more α-helix structures with increasing pressure while proteins unfold in general. In order to understand this abnormality, MD simulations with the simulated tempering method for the isobaric–isothermal ensemble were performed in a wide pressure range from 1.0×10^{-4} GPa to 1.4 GPa.[3] From the results of the simulations, it is found that the fraction of the folded state decreases once and increases after that with increasing pressure. The partial molar volume change from the folded state to unfolded state increases monotonically from a negative value to a positive value with pressure. The behavior under high pressure conditions is consistent with the experimental results. The radius of gyration of highly helical structures decreases with increasing pressure, which indicates that the helix structure shrinks with pressure. This is the reason why the fraction of the folded state increases as pressure increases.

4. Decomposition-Order Effects of Time-Integrator on Ensemble Averages for the Nosé-Hoover Thermostat

Decomposition-order dependence of time development integrator on ensemble averages for the Nosé-Hoover dynamics is discussed.[4] Six integrators were employed for comparison, which were extensions of the velocity-Verlet or position-Verlet algorithm. Molecular dynamics simulations by these integrators were performed for liquid-argon systems with several different time steps and system sizes. The obtained ensemble averages of temperature and potential energy were shifted from correct values depending on the integrators. These shifts increased in proportion to the square of the time step. Furthermore, the shifts could not be removed by increasing the number of argon atoms. We show the origin of these ensemble-average shifts analytically. Our discussion can be applied not only to the liquid-argon system but also to all MD simulations with the Nosé-Hoover thermostat. Our recommended integrators among the six integrators are presented to obtain correct ensemble averages.

5. Cutoff Effect in the Nosé-Poincaré and Nosé-Hoover Thermostats

We performed MD simulations of a Lennard-Jones system and investigated the effect of potential cutoff in the Nosé–Poincaré and Nosé–Hoover thermostats.[5] The Nosé–Poincaré thermostat is the symplectic algorithm of the Nosé thermostat, while the Nosé–Hoover thermostat is not a symplectic algorithm. If the potential energy is twice or more differentiable, the Hamiltonian was conserved well in the Nosé–Poincaré thermostat. If the potential energy is once or less differentiable, however, the Hamiltonian was not conserved, but increased because the continuity of potential energy is required in a symplectic MD simulation. The increase in the Hamiltonian caused the increase in instantaneous temperature, and physical quantities cannot be obtained correctly. It is because the difference in the Hamiltonian effectively increases the set temperature in the equations of motion. On the other hand, the Hamiltonian was not conserved for any cutoff method in the Nosé–Hoover thermostat because it is not a symplectic algorithm. However, temperature was controlled appropriately because the Hamiltonian deviation does not affect the set temperature.

References

1) H. Okumura and S. G. Itoh, *Phys. Chem. Chem. Phys.* **15**, 13852–13861 (2013).
2) S. G. Itoh and H. Okumura, *J. Chem. Theory Comput.* **9**, 570–581 (2013).
3) Y. Mori and H. Okumura, *J. Phys. Chem. Lett.* **4**, 2079–2083 (2013).
4) S. G. Itoh, T. Morishita and H. Okumura, *J. Chem. Phys.* **139**, 064103 (10 pages) (2013).
5) T. Sakaguchi and H. Okumura, *J. Phys. Soc. Jpn.* **82**, 034001 (7 pages) (2013).