Development of New Molecular Dynamics Algorithms for Biomolecular Systems

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Biomolecules such as proteins and peptides have complicated free-energy landscape with many local minima. The conventional canonical-ensemble molecular dynamics (MD) 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 replica-permutation method. We apply these methods to proteins and peptides and try to predict the native structures of proteins as in Figure 1.

We are also interested in amyloid fibrils, which are insoluble aggregates of misfolded fibrous proteins and associated with more than 20 human neurodegenerative diseases (Figure 2). For example, Alzheimer's disease is related to amyloid-β (Aβ) peptides. To overcome these diseases, it is essential to understand amyloid genesis and disruption. We perform such MD simulations of amyloid fibrils.

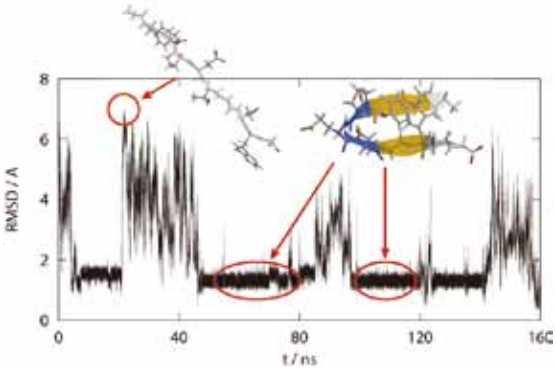

Figure 1. Time series of protein folding simulation.

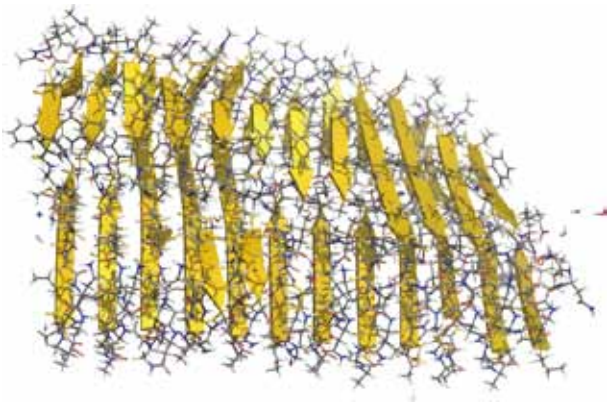

Figure 2. Snapshot of amyloid fibril.

Selected Publications

- H. Okumura and S. G. Itoh, "Amyloid Fibril Disruption by Ultrasonic Cavitation: Nonequilibrium Molecular Dynamics Simulations," *J. Am. Chem. Soc.* **136**, 10549–10552 (2014).
- S. G. Itoh and H. Okumura, "Replica-Permutation Method with the Suwa-Todo Algorithm beyond the Replica-Exchange Method," *J. Chem. Theory Comput.* **9**, 570–581 (2013).
- Y. Mori and H. Okumura, "Pressure-Induced Helical Structure of a Peptide Studied by Simulated Tempering Molecular Dynamics Simulations," *J. Phys. Chem. Lett.* **4**, 2079–2083 (2013).
- H. Okumura, "Temperature and Pressure Denaturation of Chignolin: Folding and Unfolding Simulation by Multibaric-Multithermal Molecular Dynamics Method," *Proteins* **80**, 2397–2416 (2012).

1. Amyloid Fibril Disruption by Ultrasonic Cavitation: Nonequilibrium Molecular Dynamics Simulations

There are some experimental reports that cavitation disrupts amyloid fibrils. However, it is still unknown how the cavitation or bubble in water disrupts the amyloid fibrils at atomic level. In order to answer this problem, we performed nonequilibrium molecular dynamics simulations of an Aβ fibril in explicit water.[1] We used twelve Aβ(17–42) peptide molecules, 10169 water molecules, and twelve sodium ions as counter ions. The simulation was started from the experimentally-known amyloid oligomer structure in the amyloid fibril. To express supersonic wave, sinusoidal pressure was applied between –100 MPa and 300 MPa. Snapshots of this simulation are illustrated in Figure 3. When the pressure was decreased to a negative value of –100 MPa from a room pressure, a bubble formation was observed around the transmembrane region, in which all the amino acid residues were hydrophobic. Even after the bubble size increased, the secondary structures of the oligomer were maintained. When the pressure was increased to a positive value, the bubble shrank and collapsed, and the oligomer was disrupted. At this time, most water molecules attacked the hydrophilic residues in nontransmembrane region.

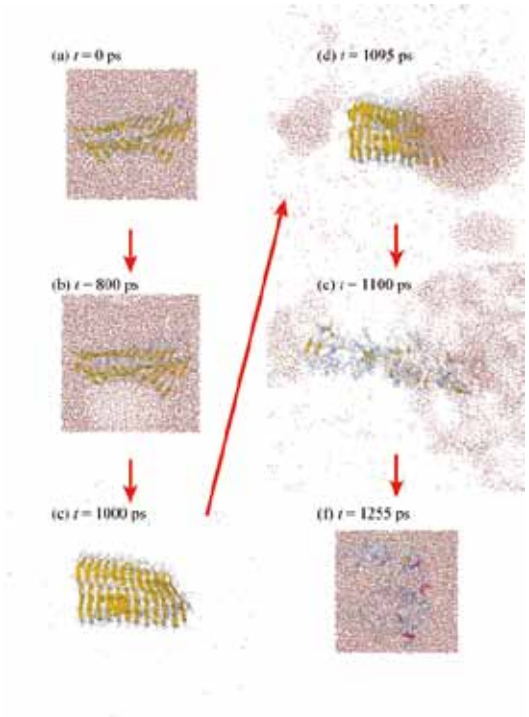

Figure 3. Snapshots of the non-equilibrium MD simulation of the amyloid-β fibril in explicit water.

2. Development of Hamiltonian Replica-Permutation Method

We propose the Hamiltonian replica-permutation method (RPM) (or multidimensional RPM) for molecular dynamics and Monte Carlo simulations, in which parameters in the Hamiltonian are permuted among more than two replicas with the Suwa-Todo algorithm.[2] We apply the Coulomb RPM, which is one of realization of the Hamiltonian RPM, to an alanine dipeptide and to two amyloid-β(29–42) molecules. The Hamiltonian RPM realizes more efficient sampling than the Hamiltonian replica-exchange method. We illustrate the protein misfolding funnel of amyloid-β(29–42) and reveal its dimerization pathways.

3. Manifold Correction Method for the Nosé-Hoover and Nosé-Poincaré Molecular Dynamics Simulations

We introduce the manifold correction method to MD simulations with the Nosé-Hoover and Nosé-Poincaré thermostats.[3] The manifold correction method was originally developed in astronomy, as an accurate numerical method for many body systems. Because the Nosé-Hoover thermostat is not a symplectic algorithm, the quantity which is conserved analytically is not conserved but increases in actual MD simulations. Using the manifold correction method, this quantity is completely conserved, and it makes the MD simulation stable. Because the conservation of this quantity is required in the proof that the Nosé-Hoover thermostat gives the canonical ensemble, the manifold correction method guarantees to provide the correct statistical ensemble. Although the time development of the Nosé-Poincaré thermostat is described as a symplectic algorithm, if the interatomic potential energy is truncated, the Nosé-Poincaré thermostat is no longer symplectic. In this case, the Hamiltonian increases, and temperature cannot be controlled. Applying the manifold correction method to the Nosé-Poincaré thermostat, the Hamiltonian becomes conserved and temperature can be appropriately controlled.

References

1) H. Okumura and S. G. Itoh, *J. Am. Chem. Soc.* **136**, 10549–10552 (2014).
2) S. G. Itoh and H. Okumura, *J. Comput. Chem.* **34**, 2493–2497 (2013).
3) H. Okumura, S. G. Itoh, A. M. Ito, H. Nakamura and T. Fukushima, *J. Phys. Soc. Jpn.* **83**, 024003 (5 pages) (2014).

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