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.

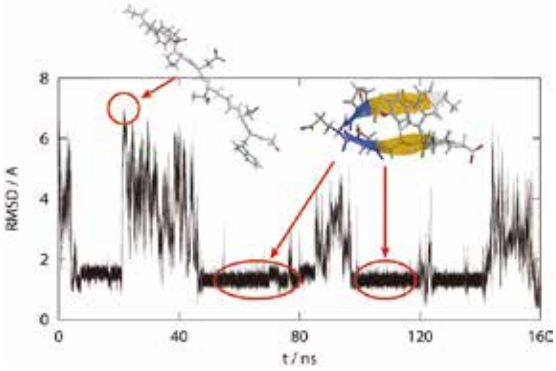

Figure 1. Time series of protein folding simulation.

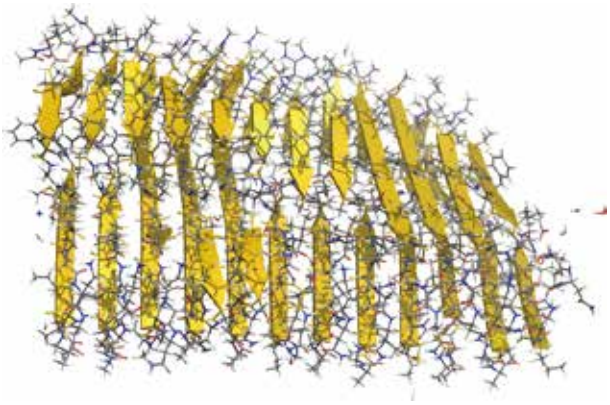

Figure 2. Snapshot of amyloid fibril.

Selected Publications

- 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).
- 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).
- 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, "Oligomer Formation of Amyloid-β(29-42) from Its Monomers Using the Hamiltonian Replica-Permutation Molecular Dynamics Simulation," *J. Phys. Chem. B* **120**, 6555–6561 (2016).

1. Molecular Dynamics Simulations Predict Only One End of Aβ Amyloid Fibril Has Open Conformations

To understand the amyloid extension mechanism, we must understand the amyloid fibril structure and fluctuation at the fibril end, which has not been revealed to date. We revealed these features by all-atom MD simulations of Aβ42 and Aβ40 fibrils in explicit water.[1] The structure and fluctuation were observed to differ between the two ends, as shown in Figure 3. At the even end, the Aβ peptide always took a closed form wherein β1 and β2 were closely spaced. The Aβ peptide fluctuated more at the odd end and took an open form wherein the two β-sheets were well separated. The differences were attributed to the stronger β-sheet formation by the β1 exposed at the even end than the β2 exposed at the odd end. Along with the small fluctuations at the even end, these results explain why the fibril extends from one end only, as observed in experiments. Our MD results agree well with recent observations by high-speed atomic force microscopy.

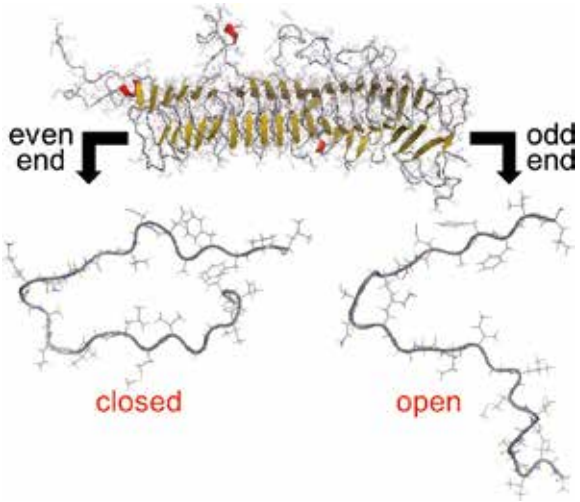

Figure 3. Typical conformation of an Aβ42 amyloid fibril and side views of the Aβ42 monomer at the even and odd ends.

2. Rapid QM/MM Approach for Biomolecular Systems under Periodic Boundary Conditions

A quantum mechanical/molecular mechanical (QM/MM) approach based on the density-functional tight-binding (DFTB) theory is a useful tool for analyzing chemical reaction systems in detail. In this study, an efficient QM/MM method was developed by the combination of the DFTB/MM and particle mesh Ewald (PME) methods.[2] Because the Fock matrix, which is required in the DFTB calculation, is analytically obtained by the PME method, the Coulomb energy is accurately and rapidly computed. For assessing the performance of this method, DFTB/MM calculations and molecular dynamics simulation are conducted for a system consisting of two amyloid-β(1-16) peptides and a zinc ion in explicit water under periodic boundary conditions, as shown in Figure 4. As compared with that of the conventional Ewald summation method, the computational cost of the Coulomb energy by utilizing the present approach is drastically reduced.

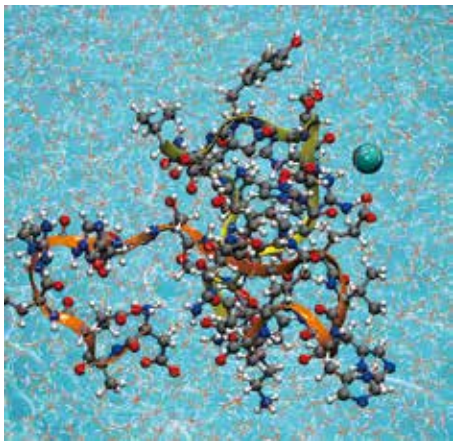

Figure 4. Test system consists of two amyloid-β(1-16) peptides, zinc ion, and water molecules.

3. Molecular Dynamics Simulation for Structural Basis of TRPA1 Inhibition by HC-030031

Pain is a harmful sensation that arises from noxious stimuli. Transient receptor potential ankyrin 1 (TRPA1) is one target for studying pain mechanisms. TRPA1 is activated by various stimuli such as noxious cold, pungent natural products and environmental irritants. Since TRPA1 is an attractive target for pain therapy, a few TRPA1 antagonists have been developed and some function as analgesic agents. Prof. Tominaga and his coworkers in National Institute for Physiological Sciences revealed that the TRPA1 antagonist HC-030031 (HC) failed to inhibit frog TRPA1 (fTRPA1) and zebrafish TRPA1 activity, but did inhibit human TRPA1 (hTRPA1). We collaborated with them and performed MD simulations of HC and hTRPA1 and found that HC stably binds to N855 in hTRPA1.[3] These findings provide novel insights into the structure-function relationship of TRPA1 and could lead to the development of more effective analgesics targeted to TRPA1.

References

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