Molecular Dynamics Simulations of Disease-Related Biomolecules

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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 disease-related biomolecules. For example, protein aggregates such as spherical substances called oligomers and acicular substances called amyloid fibrils (Figure 2) cause more than 30 kinds of diseases. Alzheimer's disease is thought to be caused by aggregated amyloid-β (Aβ) peptides. To overcome these diseases, it is essential to understand the aggregate genesis and disruption of Aβ peptides. We perform such MD simulations of oligomers and amyloid fibrils.

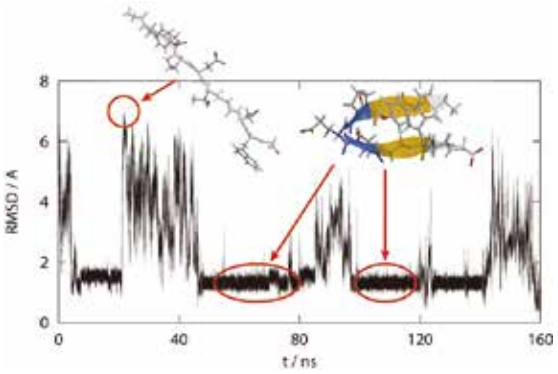

Figure 1. Time series of protein folding simulation.

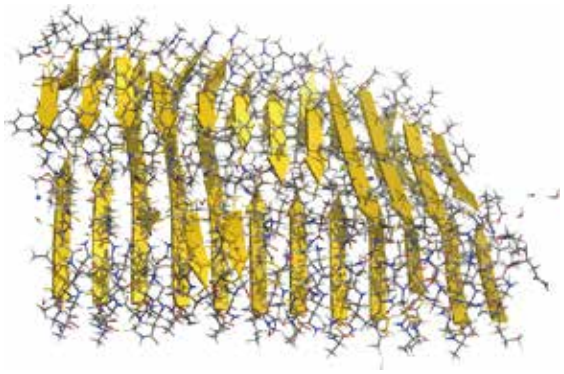

Figure 2. Snapshot of an Aβ amyloid fibril.

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).
- H. Okumura and S. G. Itoh, "Structural and Fluctuational Difference between Two Ends of Aβ Amyloid Fibril: MD Simulation Predicts Only One End Has Open Conformations," *Sci. Rep.* **6**, 38422 (9 pages) (2016).
- 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).
- 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. Role of Water Molecules in the Laser-Induced Disruption of Amyloid Fibrils Observed by Nonequilibrium Molecular Dynamics Simulations

Water plays a crucial role in the formation and destruction of biomolecular structures. The mechanism for destroying biomolecular structures was thought to be an active breaking of hydrogen bonds by water molecules. However, using non-equilibrium molecular dynamics simulations, in which an Aβ amyloid fibril was destroyed via infrared free-electron laser (IR-FEL) irradiation, we discovered a new mechanism, in which water molecules disrupt protein aggregates,[1] as shown in Figure 3. The intermolecular hydrogen bonds formed by C=O and N–H in the fibril are broken at each pulse of laser irradiation. These bonds usually spontaneously reform after the irradiation in many cases. However, when a water molecule happens to enter the gap between C=O and N–H, it inhibits the reformation of the hydrogen bonds. Such sites become defects in the regularly aligned hydrogen bonds, from which all hydrogen bonds in the intermolecular β-sheet are broken as the fraying spreads. This role of water molecules is entirely different from other known mechanisms. This new mechanism can explain the recent experiments showing that the amyloid fibrils are not destroyed by laser irradiation under dry conditions. Additionally, we found that helix structures form more after the amyloid disruption; this is because the resonance frequency is different in a helix structure. Our findings provide a theoretical basis for the application of IR-FEL to the future treatment of amyloidosis.

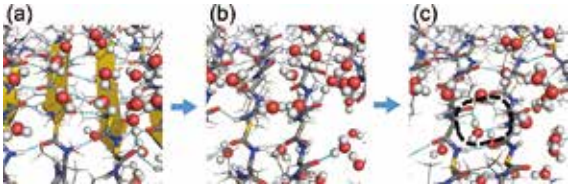

Figure 3. Snapshots of the disruption process of the hydrogen bonds between the Aβ peptides. (a) Hydrogen bonds are formed between Aβ peptides. (b) These hydrogen bonds are broken by the IR-FEL. (c) Water molecule enters the gap between C=O and N–H, it inhibits the reformation of the hydrogen bonds.

2. Replica-Permutation Molecular Dynamics Simulations of an Amyloid-β(16–22) Peptide and Polyphenols

Polyphenols are known to inhibit the aggregation of Aβ peptides. We performed all-atom replica-permutation molecular dynamics simulations of an Aβ fragment, $A\beta_{16-22}$, and two kinds of polyphenols, myricetin and rosmarinic acid in explicit water solvent.[2] We found that glutamic acid E22 of the $A\beta_{16-22}$ peptide has the highest probability to bind to the polyphenols and specified the hydroxyl groups and carboxyl groups of polyphenols that contribute to the binding.

3. "Bucket Brigade" Using Lysine Residues in RNA-Dependent RNA Polymerase of SARS-CoV-2

The RNA-dependent RNA polymerase (RdRp) of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a promising drug target for coronavirus disease 2019 (COVID-19) because it plays the most important role in the replication of the RNA genome. Nucleotide analogs such as remdesivir and favipiravir are thought to interfere with the RNA replication by RdRp. More specifically, they are expected to compete with nucleoside triphosphates, such as adenosine triphosphate (ATP). However, the process in which these drug candidates and nucleoside triphosphates are taken up by RdRp remains unknown. We performed all-atom molecular dynamics simulations to clarify the recognition mechanism of RdRp for these drug candidates and ATP that were at a distance.[3] The ligand recognition ability of RdRp decreased in the order of remdesivir, favipiravir, and ATP. We also identified six recognition paths. Three of them were commonly found in all ligands, and the remaining three paths were ligand-dependent ones. In the common two paths, it was observed that the multiple lysine residues of RdRp carried the ligands to the binding site like a "bucket brigade," as shown in Figure 4. In the remaining common path, the ligands directly reached the binding site. Our findings contribute to the understanding of the efficient ligand recognition by RdRp at the atomic level.

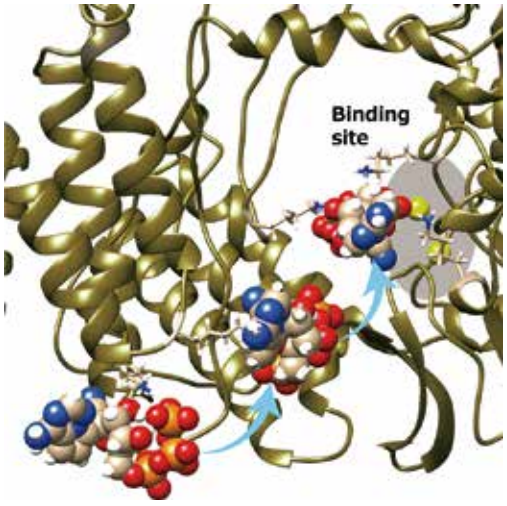

Figure 4. Remdesivir (shown in the sphere model) is transferred to two Mg^{2+} ions (yellow-green spheres) at the binding site of the RNA polymerase while being passed from one lysine residue (shown in the stick model) to another.

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1) H. Okumura, S. G. Itoh, K. Nakamura and T. Kawasaki, *J. Phys. Chem. B* **125**, 4964–4976 (2021).
2) L. Le Nguyen Ngoc, S. G. Itoh, P. Sompornpisut and H. Okumura, *Chem. Phys. Lett.* **758**, 137913 (7 pages) (2020).
3) S. Tanimoto, S. G. Itoh and H. Okumura, *Biophys. J.* **120**, 3615–3627 (2021). DOI: 10.1016/j.bpj.2021.07.026