# Molecular Dynamics Simulations of Disease-Related Biomolecules


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

**OKUMURA, Hisashi**
Associate Professor
[hokumura@ims.ac.jp]


**Education**
1998 B.S. Keio University
2002 Ph.D. Keio University

**Professional Employment**
2002 Postdoctoral Fellow, The University of Tokyo
2002 Research Associate, Institute for Molecular Science
2004 Research Associate, The Graduate University for Advanced Studies
2006 Research Lecturer, Nagoya University
2008 Research Assistant, Rutgers University
2009 Assistant Research Professor, Rutgers University
2009 Associate Professor, Institute for Molecular Science
Associate Professor, The Graduate University for Advanced Studies
2018 Associate Professor, Exploratory Research Center on Life and Living Systems (ExCELLS)

**Awards**
2014 Academic Award of the Molecular Simulation Society of Japan
2023 Best Author Award, Japan Society for Simulation Technology
2024 Biophysics and Physicobiology Editors' Choice Award, The Biophysical Society of Japan

**Member**
Assistant Professor
ITOH, Satoru G.
Graduate Student
OTAWA, Masaki
MORI, Joe
TSURUMA, Ryohei
SUZUKI, Hinako*
Secretary
KAWAGUCHI, Ritsuko

**Keywords** Molecular Dynamics Simulation, Protein, Amyloid

Biomolecules such as proteins and peptides have a 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 the 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.

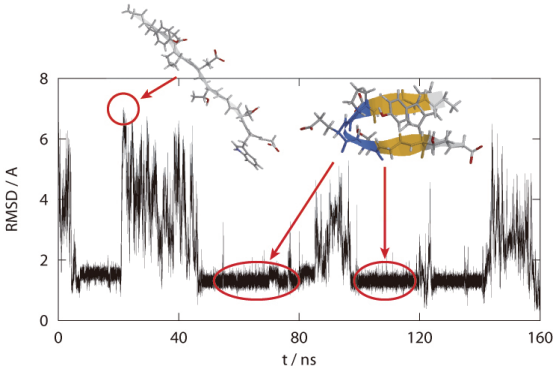


**Figure 1.** Time series of protein folding simulation.

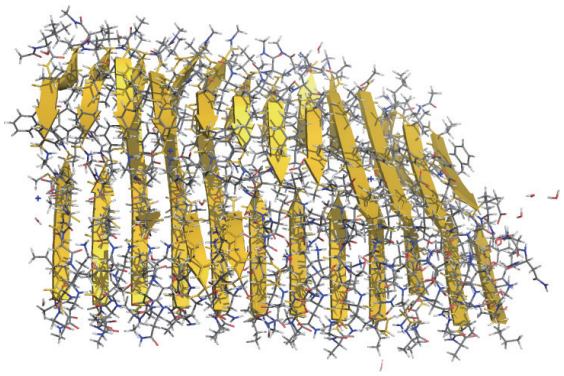

**Figure 2.** Snapshot of an Aβ amyloid fibril.

## 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, S. G. Itoh, K. Nakamura and T. Kawasaki, "Role of Water Molecules in the Laser-Induced Disruption of Amyloid Fibrils Observed by Nonequilibrium Molecular Dynamics Simulations," *J. Phys. Chem. B* **125**, 4964–4976 (2021).
- S. Tanimoto, S. G. Itoh and H. Okumura, ""Bucket Brigade" Using Lysine Residues in RNA-Dependent RNA Polymerase of SARS-CoV-2," *Biophys. J.* **120**, 3615–3627 (2021).
- S. G. Itoh, M. Yagi-Utsumi, K. Kato and H. Okumura: "Key Residue for Aggregation of Amyloid-β Peptides," *ACS Chem. Neurosci.* **13**, 3139–3151 (2022).

## 1. Non-Equilibrium Molecular Dynamics Method to Generate a Poiseuille-Like Flow on a Lipid Bilayer

There are various flows inside and outside cells *in vivo*. It was shown recently that such flows enhance the protein aggregation. Non-equilibrium molecular dynamics (NEMD) simulation is a useful tool for understanding the effects of these flows on the dynamics of biomolecules. However, there was no NEMD simulation to handle a flow on a membrane surface. We thus proposed a NEMD method to generate a Poiseuille-like flow on a lipid bilayer.[1)] We extended the conventional equilibrium MD method to produce a flow by adding constant external force terms for the water molecules (Figure 3). Using the Lagrange multiplier method, the center of mass of the lipid bilayer is constrained so that the flow does not sweep away the lipid bilayer but the individual lipid molecules fluctuate. The temperature of the system is controlled properly in the solution and membrane using the Nosé–Hoover thermostat. We found that the flow between two lipid bilayers is slower than the analytical solution of the Navier-Stokes equations between rigid parallel plates due to fluctuations and deformation of the membrane (Figure 4). This method can be applied not only to a flow on lipid membranes but also to a flow on soft surfaces generally.

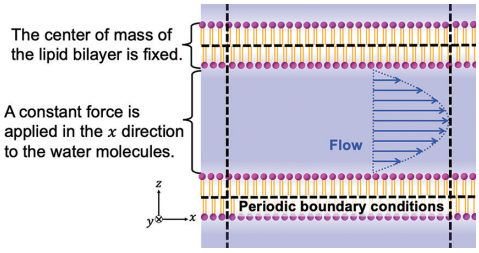


**Figure 3.** Schematic illustration of the method to generate a flow on bio-membranes.

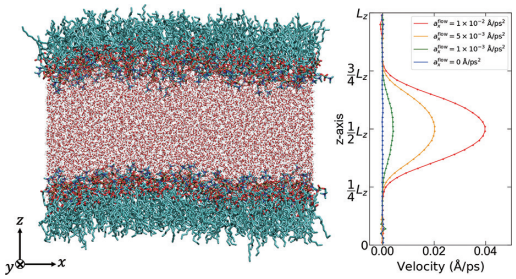


**Figure 4.** Snapshot during the NEMD simulation and flow velocity profile.

## 2. Why Do Histone Monomethylation and Dimethylation Cause a Significant Difference in Binding to LEDGF?

Lens epithelium-derived growth factor (LEDGF) is a chromatin-binding protein. It regulates gene transcription and is associated with AIDS and cancer. Its PWWP domain binds to histone H3 at K36 (H3K36). The binding affinity depends on H3K36 methylation. To investigate this dependency, we performed molecular dynamics simulations of the PWWP domain and histone fragments (Figure 5). We found not only hydrophobic interaction but also electrostatic interaction is important. The binding isn't maintained with nonmethylated and monomethylated H3K36 because the tips of these H3K36s form hydrogen bonds with water molecules, while dimethylated and trimethylated H3K36 form no such hydrogen bond, making this binding stable.

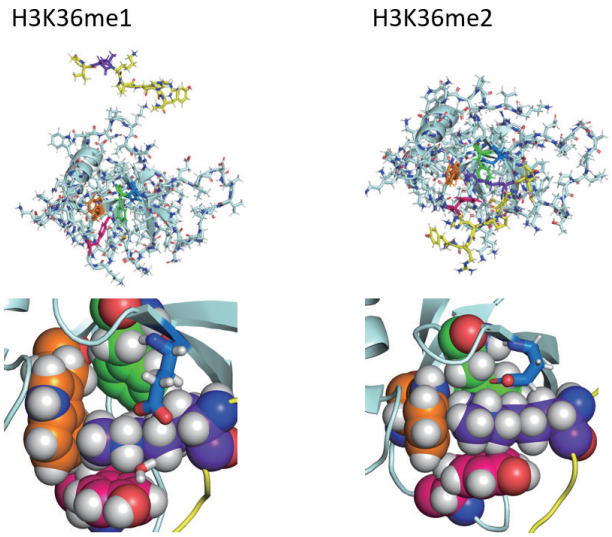


**Figure 5.** Typical binding structures of H3K36me1 and H3K36me2.

### References

1) M. Otawa, S. G. Itoh and H. Okumura, *J. Chem. Theory Comput.* **20**, 10199–10208 (2024).
2) H. X. Suzuki, H. Okumura and S. G. Itoh, *J. Chem. Phys.* **162**, 185102 (8 pages) (2025).

### Award

OKUMURA, Hisashi; Biophysics and Physicobiology Editors' Choice Award, The Biophysical Society of Japan (2024).

* carrying out graduate research on Cooperative Education Program of IMS with Shinshu University