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)

Award
2014 Academic Award of the Molecular Simulation Society of Japan
2023 Best Author Award, Japan Society for Simulation Technology

Member
Assistant Professor
ITOH, Satoru G.
Post-Doctoral Fellow
TANIMOTO, Shoichi
Graduate Student
OTAWA, Masaki
SUZUKI, Hinako*
Secretary
KAWAGUCHI, Ritsuko

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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.

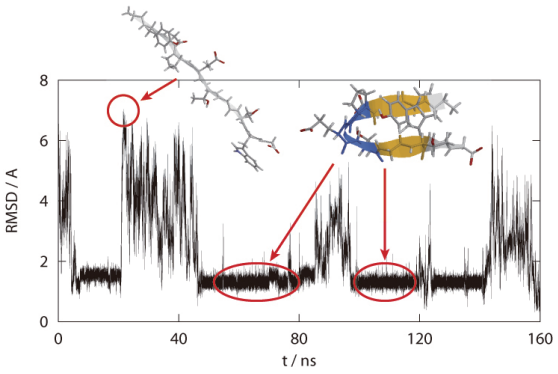

Figure 1. Time series of protein folding simulation.

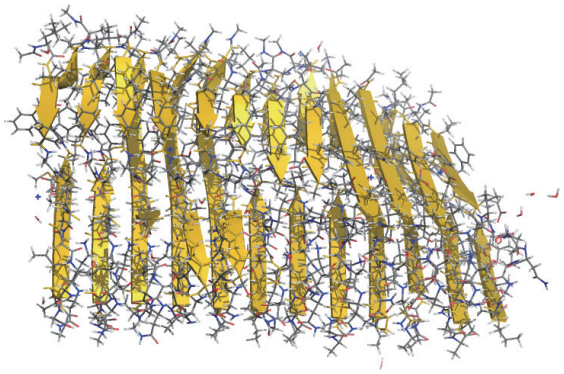

Figure 2. Snapshot of an Aβ amyloid fibril.

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. Why Is Arginine the Only Amino Acid that Inhibits Polyglutamine Monomers from Taking on Toxic Conformations?

Polyglutamine (polyQ) diseases are devastating neurodegenerative disorders characterized by abnormal expansion of glutamine repeats within specific proteins. The aggregation of polyQ proteins is a critical pathological hallmark of these diseases. Arginine was identified as a promising inhibitory compound because it prevents polyQ-protein monomers from forming intra- and intermolecular β-sheet structures and hinders polyQ proteins from aggregating to form oligomers. Furthermore, such an aggregation inhibitory effect was not observed in other amino acids. However, the underlying molecular mechanism of the aggregation inhibition and the factors that differentiate arginine from other amino acids, in terms of the inhibition of the polyQ-protein aggregation, remain poorly understood. We performed replica-permutation MD simulations to elucidate the molecular mechanism by which arginine inhibits the formation of the intramolecular β-sheet structure of a polyQ monomer.[1] We found that the intramolecular β-sheet structure with more than four β-bridges of the polyQ monomer with arginine is more unstable than without any ligand and with lysine. We also found that arginine has 1.6–2.1 times more contact with polyQ than lysine. In addition, we revealed that arginine forms more hydrogen bonds with the main chain of the polyQ monomer than lysine. More hydrogen bonds formed between arginine and polyQ inhibit polyQ from forming the long intramolecular β-sheet structure. It is known that intramolecular β-sheet structure enhances intermolecular β-sheet structure between proteins. These effects are thought to be the reason for the inhibition of polyQ aggregation. This study provides insights into the molecular events underlying arginine's inhibition of polyQ-protein aggregation.

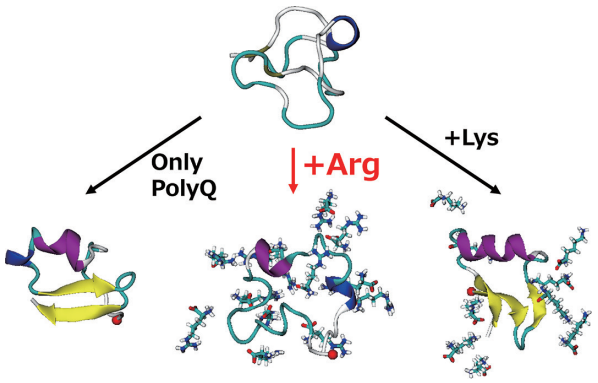

Figure 3. Arginine inhibits polyQ-proteins from forming intra- and intermolecular β-sheet structures. However, lysine, which also has a positive charge, does not have such an effect.

2. Dissociation Process of Polyalanine Aggregates by Free Electron Laser Irradiation

Polyalanine (polyA) disease-causative proteins with an expansion of alanine repeats can be aggregated. Although curative treatments for polyA diseases have not been explored, the dissociation of polyA aggregates likely reduces the cytotoxicity of polyA. Mid-infrared free electron laser (FEL) successfully dissociated multiple aggregates. However, whether the FEL dissociates polyA aggregates like other aggregates has not been tested. We applied MD simulation to follow the dissociation process by FEL.[2] We successfully observed how the intermolecular β-sheet of polyA aggregates was dissociated and separated into monomers with helix structures upon FEL irradiation. After the dissociation by FEL, water molecules inhibited the reformation of polyA aggregates. We recently verified the same dissociation process using FEL-treated amyloid-β aggregates. Thus, a common mechanism underlies the dissociation of different protein aggregates that cause different diseases, polyA disease and Alzheimer's disease. However, MD simulation indicated that polyA aggregates are less easily dissociated than amyloid-β aggregates and require longer laser irradiation due to hydrophobic alanine repeats.

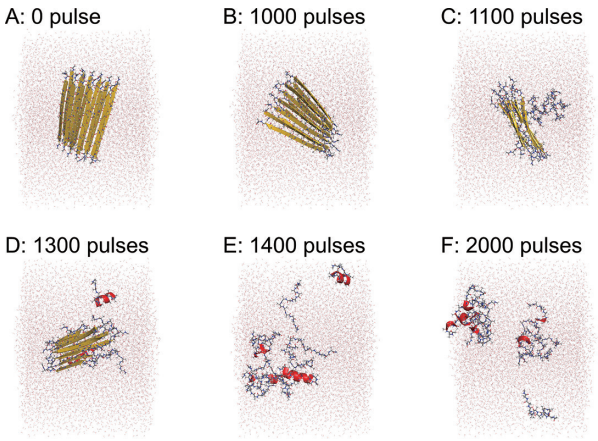

Figure 4. Snapshots of polyA amyloid fibril during a nonequilibrium MD simulation. Snapshots (A) before FEL irradiation, (B) after 1000 pulses, (C) after 1100 pulses, (D) after 1300 pulses, (E) after 1400 pulses, and (F) after 2000 pulses.

References

1) S. Tanimoto and H. Okumura, *ACS Chem. Neurosci.* **15**, 2925–2935 (2024).
2) H. Okumura, S. G. Itoh, H. Zen and K. Nakamura, *PLoS One* **18**, e0291093 (2023).

Award

TANIMOTO, Shoichi, ITOH, Satoru G. and OKUMURA, Hisashi; Best Author Award, Japan Society for Simulation Technology (2023).

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