Development of New Simulation Algorithms and its Application to Protein Aggregates

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

Award
2014 Academic Award of the Molecular Simulation Society of Japan

Member
Assistant Professor
ITOH, Satoru G.
Post-Doctoral Fellow
ISHIMURA, Kazuya
Graduate Student
YAMAUCHI, Masataka
MIYAZAWA, Kazuhisa
TACHI, Yuhei*
Secretary
KAWAGUCHI, Ritsuko

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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 protein aggregates such as spherical substances called oligomers and acicular substances called amyloid fibrils (Figure 2). These protein aggregates cause more than 30 kinds of diseases. For example, 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.

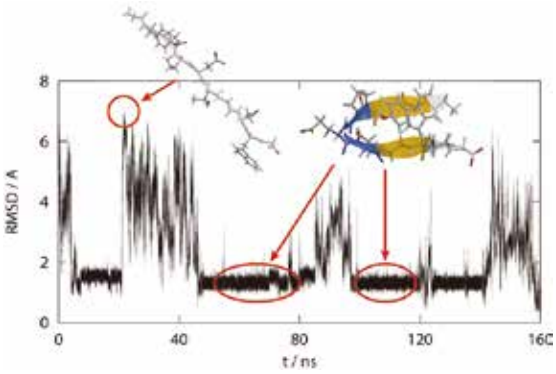

Figure 1. Time series of protein folding simulation.

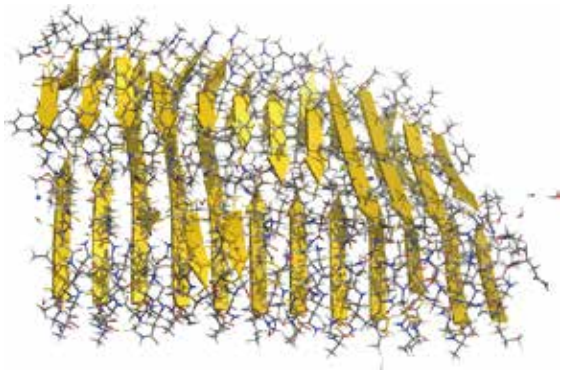

Figure 2. Snapshot of an Aβ amyloid fibril.

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. Effects of a Hydrophilic/Hydrophobic Interface on Amyloid-β Peptides Studied by Molecular Dynamics Simulations and NMR Experiments

Oligomer formation of Aβ peptides is accelerated at a hydrophilic/hydrophobic interface. However, details of the acceleration mechanism have not been elucidated. To understand the effects of the interface on oligomerization at the atomic level, we performed all-atom MD simulations for an Aβ40 monomer in the presence and absence of the hydrophilic/hydrophobic interface.[1] Nuclear magnetic resonance experiments of Aβ40 peptides with gangliosidic micelles were also carried out in collaboration with Prof. Koichi Kato. We found that the Aβ peptides tend to gather at the hydrophilic/hydrophobic interface. That is, the local concentration of Aβ at the interface is higher than that in bulk water solution. In addition, β-hairpin structures are formed more at the interface than in the bulk water solution. In the β-hairpin structure, as shown in Figure 3, a part of the Aβ peptide extends straight and forms intramolecular hydrogen bonds. Therefore, another Aβ peptide that comes close to this peptide is easy to make intermolecular hydrogen bonds and tends to aggregate. In this way, we clarified that the reason for accelerating the aggregation of the Aβ peptides on the cell membrane surface is that not only the Aβ peptide tends to have high concentration on the cell membrane surface but also it takes a structure that tends to bind to each other. This discovery enables us to elucidate the mechanism by which the Aβ peptide aggregates on the membrane surface of nerve cells.

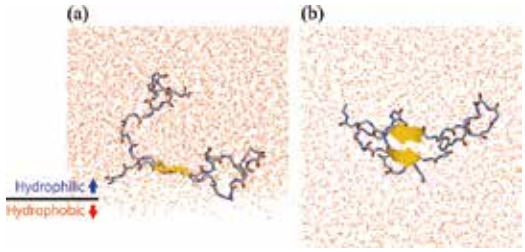

Figure 3. (a) An Aβ peptide that forms a β-hairpin structure at the hydrophilic/hydrophobic interface. (b) View from the bottom of panel (a).

2. Conformational Properties of an Artificial GM1Glycan Cluster

Recent studies showed that monosialotetrahexosyl-ganglioside (GM1) clusters induce the pathological aggregation of Aβ peptide responsible for the onset and development of Alzheimer's disease. We first performed all-atom MD simulations to characterize the conformational properties of the artificial GM1 glycan cluster. We found that more than 65% of GM1 glycans are clustered by interchain hydrogen bonds, interchain hydrogen bonds are mainly formed between Neu5Ac and Gal', and pentamers were most frequently observed in the metal-ligand complex. Our findings provide the physicochemical properties of the artificial GM1 glycan cluster under the thermal fluctuations for understanding its protein recognition.

3. Conformational Change of Amyloid-β 40 in Association with Binding to GM1-Glycan Cluster

Interaction between Aβ peptide and GM1-glycan cluster is important for the earliest stage of the toxic aggregation on GM1 cluster. We then performed all-atom MD simulations of Aβ40 on the artificial GM1-glycan cluster.[3] The GM1-glycan cluster facilitates the characterization of interactions between Aβ40 and multiple GM1-glycans. We succeeded in observing the binding of Aβ40 to the GM1-glycan cluster in all of our MD simulations. Our results indicate the importance of HHQ (13-15) segment of Aβ40 for the GM1-glycan cluster recognition. The recognition mechanism of HHQ (13-15) segment is mainly explained by non-specific stacking interactions between side-chains of histidine and rings of sugar residues, in which the HHQ regime forms coil and bend structures. Moreover, we found that Aβ40 exhibits helix structures at C-terminal side on the GM1-glycan cluster as in Figure 4. The helix formation is the initial stage of the pathological aggregation at ceramide moieties of GM1 cluster. The binding of Lys28 to Neu triggers the helix formation at C-terminus side because the formation of a salt bridge between Lys28 and Neu leads to change of intrachain interactions of Aβ40. Our findings suggest that the pathological helix formation of Aβ40 is initiated at GM1-glycan moieties rather than lipid ceramide moieties.

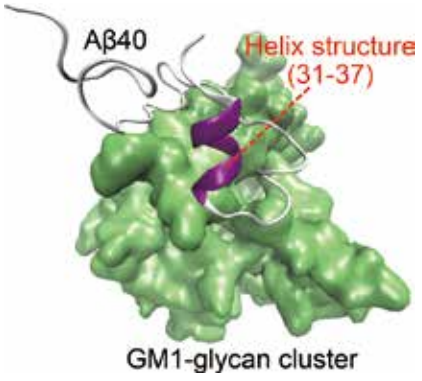

Figure 4. A typical snapshot of Aβ40 with a helix structure formed in residues 31–37. Green colored molecule is the GM1-glycan cluster.

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2) Y. Tachi, Y. Okamoto and H. Okumura, *J. Chem. Phys.* **149**, 135101 (8 pages) (2018).
3) Y. Tachi, Y. Okamoto and H. Okumura, *Sci. Rep.* **9**, 6853 (11 pages) (2019).

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