RESEARCH ACTIVITIES

Theoretical and Computational Molecular Science

The Department aims to advance the understanding and prediction of static and dynamic properties, reactions, and functions in condensed-phase systems, such as biomolecular and heterogeneous catalytic systems, through the development of novel theories and computational methodologies grounded in quantum mechanics, statistical mechanics, and solid-state physics. The Department collaborates with the Research Center for Computational Science on research.

Theoretical Studies on Reactions, Functions, and Fluctuations in Condensed-Phase Systems

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

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1988 B.S. Keio University
1990 M.E. Kyoto University
1995 Ph.D. The Graduate University for Advanced Studies

Professional Employment
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1994 Research Associate, Nagoya University
1998 Associate Professor, Nagoya University
2005 Professor, Institute for Molecular Science
2006 Professor, The Graduate University for Advanced Studies

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Keywords Reactions, Functions, Fluctuations

Our research centers on complex fluctuations in condensed systems, including supercooled liquids and biomolecules. These fluctuations significantly influence various properties, functions, and reactions. By investigating the dynamics and fluctuations in these molecular systems, we aim to uncover the molecular origins of these properties, functions, and reactions.

We have pioneered advanced computational methods for multi-dimensional nonlinear spectroscopy, enabling us to elucidate the molecular basis of ultrafast energy relaxation and the temporal evolution of nonuniform fluctuations in liquid water that conventional linear spectroscopy has not revealed. Additionally, we have delved into the dynamical heterogeneity of supercooled liquids, characterized by slow, inhomogeneous structural changes driven by fluctuations. Using a three-time correlation function, we unveiled the dynamic coupling of structural fluctuations across different time scales in proteins.

Our research has also focused on the anomalous properties of water, establishing a link between these anomalies and previously hidden structural and dynamical characteristics. Recently, we developed a novel analytical method for studying dynamical disorder based on stochastic process theory, elucidating the mechanisms behind slowing structural changes as systems approach the glass transition.

In the realm of biomolecular systems, structural fluctuations and conformational changes are crucial for functional expression. Our studies on enzymatic reactions underscore the importance of specific prepared conformational states that facilitate these reactions. Furthermore, we have probed the molecular origins of dynamic disorder within protein conformational dynamics, revealing the complexity of these processes. Our investigations also extend to the molecular mechanisms underlying efficient excitation energy transfer in photosynthetic systems.

Through these efforts, we are engaged in a broad spectrum of theoretical and computational studies to unravel the dynamical phenomena that govern condensed-phase systems.

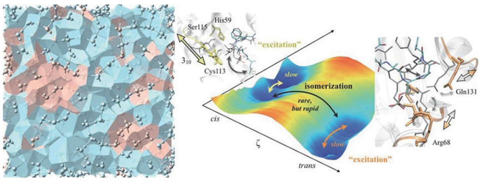

Figure 1. Snapshot of two-state model in supercooled water consisting of high- and low-density liquids (left) and schematic of 2D free energy surface for enzymatic reaction (right).

Selected Publications

- T. Yagasaki and S. Saito, *Annu. Rev. Phys. Chem.* **64**, 55–75 (2013), T. L. C. Jansen, S. Saito, J. Jeon and M. Cho, *J. Chem. Phys. (Perspective)* **150**, 100901 (17 pages) (2019), C. R. Baiz *et al.*, *Chem. Rev.* **120**, 7152–7218 (2020).
- K. Kim and S. Saito, *J. Chem. Phys. (Special Topic on Glass Transition)* **138**, 12A506 (12 pages) (2013).
- S. Saito, B. Bagchi and I. Ohmine, *J. Chem. Phys.* **149**, 124504 (8 pages) (2018), S. Saito and B. Bagchi, *J. Chem. Phys.* **150**, 054502 (14 pages) (2019), S. Saito, *J. Chem. Phys.* **160**, 194506 (13 pages) (2024).
- J. Ono, Y. Matsumura, T. Mori and S. Saito, *J. Phys. Chem. B (Perspective)* **128**, 20–32 (2024).
- S. Saito, M. Higashi and G. R. Fleming, *J. Phys. Chem. B* **123**, 9762–9772 (2019).

1. Flat-Bottom Elastic Network Model for Generating Improved Plausible Reaction Paths[1]

Rapid generation of a plausible reaction path connecting a given reactant and product in advance is crucial for the efficient computation of precise reaction paths or transition states. We propose a computationally efficient potential energy based on the molecular structure to generate such paths. This potential energy has a flat bottom consisting of structures without atomic collisions while preserving nonreactive chemical bonds, bond angles, and partial planar structures. By combining this potential energy with the direct MaxFlux method, a recently developed reaction-path/transition-state search method, we can find the shortest plausible path passing within the bottom. Numerical results show that this combination yields lower energy paths compared to the paths obtained by the well-known image-dependent pair potential. We also theoretically investigate the differences between these two potential energies. The proposed potential energy and path generation routine are implemented in our Python version of the direct MaxFlux method, available on GitHub.

2. Development of Molecular Dynamics Parameters and Theoretical Analysis of Excitonic and Optical Properties in the Light-Harvesting Complex II[2]

The light-harvesting complex II (LHCII) in green plants exhibits highly efficient excitation energy transfer (EET). A comprehensive understanding of the EET mechanism in LHCII requires quantum chemical, molecular dynamics (MD), and statistical mechanics calculations that can adequately describe pigment molecules in heterogeneous environments. Herein, we develop MD simulation parameters that accurately reproduce the quantum mechanical/molecular mechanical energies of both the ground and excited states of all chlorophyll (Chl) molecules in membrane embedded LHCII. The present simulations reveal that Chl *a* molecules reside in more inhomogeneous environments than Chl *b* molecules. We also find a narrow gap between the exciton energy levels of Chl *a* and Chl *b*. In addition, we investigate the nature of the exciton states of Chl molecules, such as delocalization, and analyze the optical spectra of LHCII, which align with experimental results. Thus, the MD simulation parameters developed in this study successfully reproduce the excitonic and optical properties of the Chl molecules in LHCII, validating their effectiveness.

3. Fast Diffusion of Water along Carbon Nanotube near the Wall[3]

The diffusion of water in carbon nanotubes (CNTs) is debated, particularly whether it is faster near the CNT wall or at the center and how the temperature influences this effect. Using molecular dynamics (MD) simulations, we study radially resolved water diffusion in CNT(26,26) (3.57 nm diameter) over a wide temperature range. Diffusion along the CNT axis is significantly enhanced compared to that of bulk water, with the effect intensifying at lower temperatures. Supercooling further amplifies this enhancement following near-Arrhenius behavior. Confinement has a smaller impact on the rotational dynamics. By resolving water motion into radial layers, we find that both translational and rotational dynamics are higher near the CNT wall due to weakened hydrogen bonding. The presence of dangling O−H bonds reduces friction at the CNT−water interface. Revisiting an NMR study, we suggest that the high-intensity peak corresponds to central layers, aligning with our MD results and refining our insights into confined water dynamics.

4. Correlated Flat-Bottom Elastic Network Model for Improved Bond Rearrangement in Reaction Paths[4]

This study introduces correlated flat-bottom elastic network model (CFB-ENM), an extension of our recently developed flat-bottom elastic network model (FB-ENM) for generating plausible reaction paths, *i.e.*, collision-free paths preserving nonreactive parts. While FB-ENM improved upon the widely used image-dependent pair potential (IDPP) by addressing unintended structural distortion and bond breaking, it still struggled with regulating the timing of series of bond breaking and formation. CFB-ENM overcomes this limitation by incorporating structure-based correlation terms. These terms impose constraints on pairs of atom pairs, ensuring immediate formation of new bonds after breaking of existing bonds. Using the direct MaxFlux method, we generated paths for 121 reactions involving main group elements and 35 reactions involving transition metals. We found that CFB-ENM significantly improves reaction paths compared to FB-ENM. CFB-ENM paths exhibited lower maximum DFT energies along the paths in most reactions, with nearly half showing significant energy reductions of several tens of kcal/mol. In the few cases where CFB-ENM yielded higher energy paths, most increases were below 10 kcal/mol. We also confirmed that CFB-ENM reduces computational costs in subsequent precise reaction path or transition state searches compared to FB-ENM. An implementation of CFB-ENM based on the Atomic Simulation Environment is available on GitHub for use in computational chemistry research.

References

1) S.-i. Koda and S. Saito, *J. Chem. Theory Comput.* **20**, 7176–7187 (2024).
2) Z. Zhu, M. Higashi and S. Saito, *J. Chem. Theory Comput.* **21**, 413–427 (2025).
3) G. R. Kahn, S. Saito and S. Daschakraborty, *J. Phys. Chem. B* **129**, 6561–6573 (2025).
4) S.-i. Koda and S. Saito, *J. Chem. Theory Comput.* **21**, 3513–3522 (2025).

Theoretical Studies of Functional Molecular Systems and Heterogeneous Catalysts

Department of Theoretical and Computational Molecular Science
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Education

1988	B.E. Kyoto University
1990	M.E. Kyoto University
1993	Ph.D. Kyoto University

Professional Employment

1993	Postdoctral Fellow, Institute for Fundamental Chemistry
1994	JSPS Postdoctoral Fellow
1994	Visiting Researcher, Heidelberg University (–1995)
1995	Assistant Professor, Kyoto University
2002	Associate Professor, Kyoto University
2006	Theoretical Research Division Supervisor, Kyoto University (–2008)
2008	Professor, Institute for Molecular Science Professor, The Graduate University for Advanced Studies
2012	Professor, Elements Strategy Initiative for Catalysts and Batteries (ESICB), Kyoto University (additional post, –2022)

Awards

2009	APATCC Pople Medal
2009	QSCP Prize CMOA

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ZHAO, Yao-Xiao

Secretary
SUGIMOTO, Yukari

Keywords Quantum Chemistry, Photochemistry, Heterogeneous Catalysis

We develop the useful electronic structure theories and investigate the photochemistry and catalysis theoretically. Currently, we focus on the following research subjects.

(1) Inverse design and theory for complex electronic states

We are interested in improving the various functions of molecular systems. Inverse design approach can optimize the functions in the “functional space.” Recently, we adopted the inverse design approach and succeeded in maximizing various photofunctions of the molecular aggregates and molecule-nanoparticle systems. We also work on developing electronic structure theories for complex electronic states such as CAP/SAC-CI method for locating metastable resonance states.

(2) Nanocluster and heterogeneous catalysts

We proceeded the national project of Element Strategy Initiatives for Catalysts and Batteries (ESICB) where we focused on the developments of the platinum-group metal (PGM) reduced or PGM-free catalysts. We also investigated the nanocluster and heterogeneous catalysts for the fuel cells and fine chemicals like Pt, PtCo and PtNi sub-nanoclusters for oxygen reduction reaction (ORR), Pd-Au alloy nanoparticle for hydrosilylation, Niobium oxide surface for direct synthesis of various amides and imides.

(3) Functions of *C*-centered Au(I) based clusters

We theoretically investigate the various functions of metal nanoclusters. In the recent project, we worked on *C*-centered Au(I) based clusters such as chiral induction of $C\mathrm{Au^I_6}$ cluster with monodentate *N*-heterocyclic carbene (NHC) ligands, intense emission of $C\mathrm{Au^I_6Ag^I}_n$ (n = 2–4) and $\mathrm{CAu^I_6Cu^I_2}$ clusters and its biological application, vapochromism of $C\mathrm{Au^I_6}$ cluster, and the generation of $C\mathrm{Au^I_5}$ cluster and its red-shifted PL as well as catalytic activity.

(4) Photofunctional materials: Perovskite solar cells and modified single-walled carbon nanotubes (SWCNTs)

Recently, we worked on the method to fabricate high-quality multi-junction Sn-Pb perovskite semiconductor films. We elucidated the mechanism of how the phenylalanine cation interacts with the constituent ions of perovskite and their composed species during the solution stage. We also have investigated the selective PL from modified SWCNTs which enhances their PLs with red-shifted peaks. Previously, we proposed the substitution rule using Clar-sextet theory. We achieved the control of near-IR PL, the selective $\mathrm{E}_{11}{}^{**}$ PL (~1,200 nm) by tether alkyl functionalization, and the PL in telecommunication wavelength (>1,300 nm) by perfluoroalkyl functionalization.

Selected Publications

- T. Shiraogawa, G. Dall’Osto, R. Cammi, M. Ehara and S. Corni, “Inverse Design of Molecule-Metal Nanoparticle Systems Interacting with light for the Desired Photophysical Properties,” *Phys. Chem. Chem. Phys.* **24**, 22768 (2022).
- H. Miura, K. Imoto, H. Nishio, A. Junkaew, Y. Tsunesada, Y. Fukata, M. Ehara and T. Shishido, “Optimization of Metal-Support Cooperation for Boosting the Performance of Supported Gold Catalysts for Borylation of C–O and C–N Bonds,” *J. Am. Chem. Soc.* **146**, 27528–27541 (2024).
- X.-L. Pei, P. Zhao, H. Ube, Z. Lei, M. Ehara and M. Shionoya, “Single-Gold Etching at the Hypercarbon Atom of *C*-Centred Hexagold(I) Clusters Protected by Chiral *N*-Heterocyclic Carbenes,” *Nat. Commun.* **15**, 5024 (2024).
- S. Hu, J. Wang, P. Zhao, M. Ehara, R. A. J. Janssen, A. Wakamiya, H. J. Snaith *et al.*, “Steering Perovskite Precursor Solution for Multijunction Photovoltaics,” *Nature* **639**, 93–101 (2025).

1. Developing Interface Structure Control for Tin-Containing Perovskite Semiconductors and Elucidation of Mechanism: Realization of High-Performance Multi-Junction Solar Cells[1)]

Multi-junction solar cells demonstrate superior performance, achieving photovoltaic conversion efficiencies that surpass the radiative limits of single-junction cells. Furthermore, developing high-performance Sn-Pb perovskite semiconductor films is of great importance for thin-film devices. We have developed a method to fabricate high-quality Sn-Pb perovskite semiconductor films by incorporating phenylalanine hydrochloride, a simple compound bearing both amino acid and carboxylic acid groups, into the precursor solutions. Through various spectroscopic measurements and theoretical calculations, we elucidated the mechanism of how the phenylalanine cation interacts with the constituent ions of perovskite and their composed species during the solution stages, providing a global improvement in the bulk and surface quality of the as-deposited films. Single-, double-, and triple-junction solar cells incorporating these high-quality Sn-Pb perovskite layers achieved remarkable open-circuit voltages of 0.91 V, 2.22 V, and 3.46 V, respectively, and power conversion efficiencies of 23.9%, 29.7% (certified value: 29.26%), and 28.7%. Additionally, triple-junction devices with an area of 1 cm^2 demonstrated power conversion efficiencies of up to 28.4% (certified value: 27.28%). Furthermore, for the first time, all-perovskite four-junction devices were fabricated, achieving an impressive open-circuit voltage of 4.94 V and power conversion efficiencies of up to 27.9%.

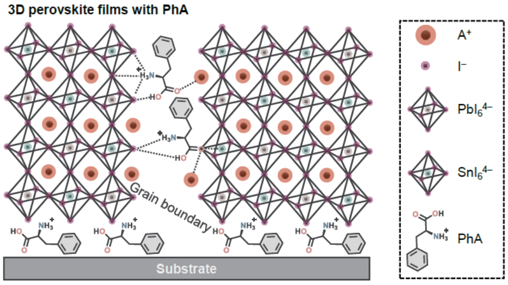

Figure 1. Structural modification at the perovskite bottom interface.

2. Oxidation of *para*-Substituted Benzyl Alcohols by $PdAu_{12}$ Cluster Catalysts: Effect of Pd Atom Doping[2)]

Single-atom doping of atomically size-controlled metal nanoclusters is useful for elucidating doping effects in catalysis. MAu_{12} (M = Au, Ir, Rh, Pt, Pd) nanoclusters were synthesized on a double metal hydroxide composed of Co and Ce. The catalytic activity and activation mechanism for benzyl alcohol oxidation were analysed through both experimental measurements and theoretical calculations. $PdAu_{12}$ exhibited 4.4 times the catalytic activity of Au_{13}, while other MAu_{12} catalysts (M = Ir, Rh, Pt) showed activity comparable to Au_{13}. Periodic DFT calculations based on slab model revealed that oxygen molecules are activated more efficiently on $PdAu_{12}$ than on Au_{13}, indicating that a different mechanism involving an activated oxygen molecule emerges with Pd single doping.

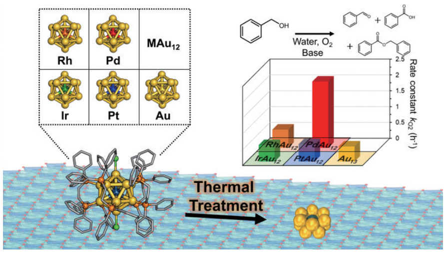

Figure 2. Supported size selective MAu_{12}/Co_3Ce catalyst for alcohol oxidation.

3. Control of Luminescence Wavelength in Modified Single-Walled Carbon Nanotubes Utilizing Steric Hindrance in Reductive Arylation[3)]

To control the luminescent properties of single-walled carbon nanotubes (SWCNTs), we have developed modified SWCNTs. In this study, emission wavelength control was achieved via reductive arylation using monosubstituted and disubstituted iodobenzene derivatives. Chemical modification with substituted iodobenzenes altered the functionalization depending on the position of the substituent on the aryl group, enabling control of both luminescence intensity and wavelength. Introducing a Me or MeO group at the 2-position and Me groups at the 3,5-positions of the phenyl ring increased the selectivity of E_{11}^{**} PL (~1230 nm) and E_{11}^{*} PL (~1100 nm), respectively. Theoretical calculations indicated that the effect of ortho-substituted groups on the relative stability of isomers is greater for diarylated SWCNTs than for hydroarylated ones. Experiments and theoretical calculations revealed that the substitution position on the benzene ring regulates the emission wavelength, influencing the favorable binding configuration of the SWCNT adduct, the relative stability of conformational isomers, and the emission wavelength.

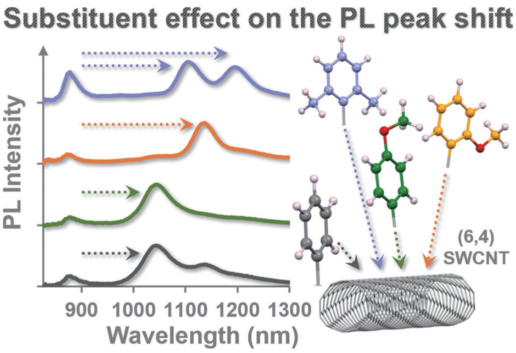

Figure 3. Control of photoluminescence of modified SWCNTs by steric hindrance in reductive arylation.

References

1) S. Hu, J. Wang, P. Zhao, M. Ehara, R. A. J. Janssen, A. Wakamiya, H. J. Snaith *et al. Nature* **639**, 93–101 (2025).

2) S. Masuda, H. Hirai, P. Zhao, S. Takano, M. Ehara and T. Tsukuda, *ACS Catal.* **14**, 17123–17131 (2024).

3) Y. Maeda, Y. Iguchi, P. Zhao, A. Suwa, Y. Taki, K. Kawada, M. Yamada, M. Ehara and M. Kako, *Chem. –Eur. J.* **31**, e202404529 (2025).

Molecular Dynamics Simulations of Disease-Related Biomolecules

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Education

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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

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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.

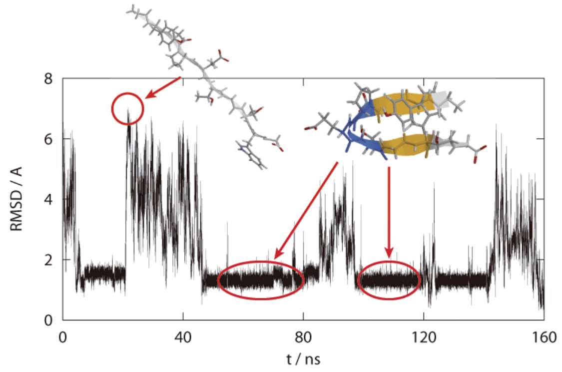

Figure 1. Time series of protein folding simulation.

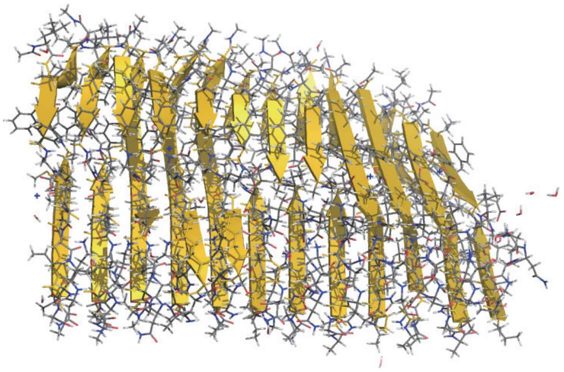

Figure 2. Snapshot of an Aβ amyloid fibril.

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.

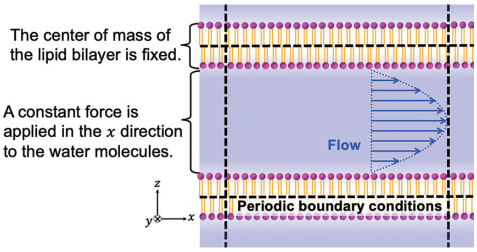

Figure 3. Schematic illustration of the method to generate a flow on bio-membranes.

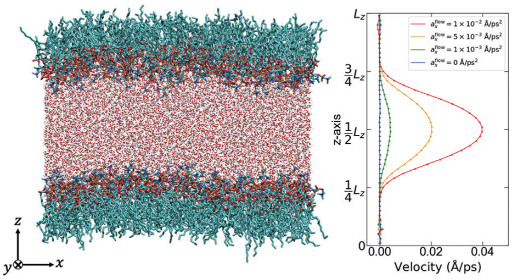

Figure 4. Snapshot during the NEMD simulation and flow velocity profile.

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.

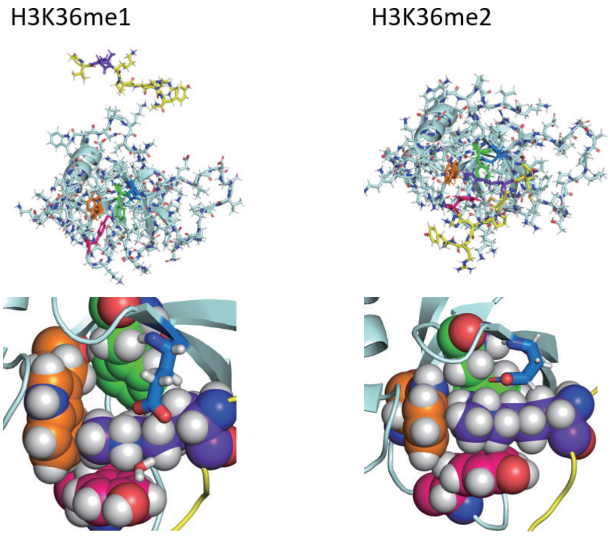

Figure 5. Typical binding structures of H3K36me1 and H3K36me2.

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).

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Dynamics of Biomolecular Machines in Function Revealed by Theoretical Methods

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Education

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2009	Ph.D. Kobe University

Professional Employment

2007	JSPS Research Fellow (DC2), Kobe University
2009	JSPS Postdoctoral Fellow (PD), Waseda University
2010	Part-time Lecturer, Waseda University
2012	JSPS Postdoctoral Fellow for Research Abroad, National Institutes of Health, U.S.A.
2014	Postdoctoral Fellow, Max Planck Institute of Biophysics, Germany
2016	Research Associate Professor, Institute for Molecular Science
2020	Associate Professor, Institute for Molecular Science Associate Professor, The Graduate University for Advanced Studies

Award

2014	Early Career Award in Biophysics, Biophysical Society of Japan

Member

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MAHMOOD, Md Iqbal

Graduate Student
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GUYOT, Constantin

Secretary
CHIBA, Fumika

Keywords Theoretical Biophysics, Biomolecular Machines, Molecular Simulation

Biomolecular machines, such as molecular motors and transporters in the cell, are known to change their structure when they function. For example, ATP synthase, which synthesizes ATP in mitochondria, is a molecular motor that uses chemical energy to rotate unidirectionally. Transporters, which transport substrate molecules across the cell membrane, perform substrate transport by changing their structure between inward-open and outward-open states relative to the membrane. We aim to elucidate the mechanisms of these elaborate and dynamic nanomachines created by nature at the atomic and molecular levels and to control their functions based on our findings.

We would like to understand the mechanisms of biomolecular machines by "seeing" the motion of biomolecular machines at the moment they function at the molecular level on a computer. However, this is not an easy task because biomolecular machines are huge molecules, and their functioning time scale is slow (for a molecular scale) at milliseconds or longer. Conventional atomistic molecular dynamics (MD) simulations cannot cover millisecond-long dynamics, especially for a large system like typical biomolecular machines. Therefore, we have developed and applied methods such as coarse-grained modeling and enhanced sampling to capture the motion at the moment of function.

We have been working on biomolecular motors such as ATP synthase. ATP synthase is a rotary motor that produces most of the ATP required in the cell. It is composed of two rotary motors: F_o and F_1. The F_o motor is embedded in the membrane and driven by a proton gradient, while the F_1 motor is driven by the ATP hydrolysis reaction. We clarified how the rotation of the F_1 motor is driven by a key chemical step, Pi release after the ATP hydrolysis reaction, by accelerating atomistic MD simulations with external forces.1)

Transporters are membrane proteins that transport their substrates across the membrane. We have studied a Na^+/H^+ antiporter, which exchanges sodium ions and protons inside and outside the cell. The ion transport process by the Na^+/H^+ antiporter was simulated in atomic detail with a transition path sampling technique to capture the moment of the ion transport. The simulations predicted the mutation that could speed up ion transport. The mutation was tested in experiments and shown to speed up the ion transport twice faster than the wild type. Therefore, we succeeded in controlling the function of the transporter based on the mechanism obtained from simulations by creating the faster transporter.2)

Selected Publications

- K. Okazaki and G. Hummer, "Elasticity, Friction, and Pathway of γ-Subunit Rotation in F_oF_1-ATP Synthase," *Proc. Natl. Acad. Sci. U.S.A.* **112**, 10720–10725 (2015).
- K. Okazaki, D. Wöhlert, J. Warnau, H. Jung, Ö. Yildiz, W. Kühlbrandt and G. Hummer, "Mechanism of the Electroneutral Sodium/Proton Antiporter PaNhaP from Transition-Path Shooting," *Nat. Commun.* **10**, 1742 (2019).
- R. Kobayashi, H. Ueno, K. Okazaki and H. Noji, "Molecular Mechanism on Forcible Ejection of ATPase Inhibitory Factor 1 from Mitochondrial ATP Synthase," *Nat. Commun.* **14**, 1682 (2023).

1. Mechanism of the Inhibitor Protein IF_1 for Mitochondrial ATP Synthase

ATPase inhibitory factor 1 (IF_1) regulates mitochondrial F_oF_1-ATP synthase by inserting into the rotor–stator interface and blocking F_1 rotation. Single-molecule experiments showed that rotation only in the ATP-synthesis direction ejects IF_1, but the atomic mechanism is unclear. Using all-atom MD simulations with torque applied on the γ subunit, we found that rotation proceeded further in the synthesis than hydrolysis direction. At 120° synthesis rotation, IF_1 contacts were disrupted, destabilizing its helices, and by 240° rotation, the β subunit pulled IF_1 outward. These stepwise changes appear key to IF_1 ejection. Simulations also revealed how hydrolytic rotation is nullified by steric clash between IF_1 and β_{TP}. We further discuss the proton motive force needed to release IF_1 inhibition.

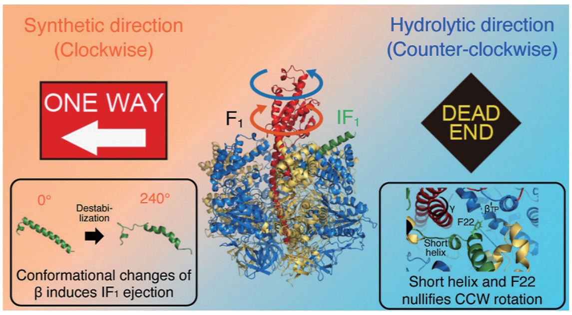

Figure 1. Rotation-direction-dependent mechanism of IF_1 inhibition for mitochondrial ATP synthase from atomistic molecular dynamics simulation.$^{3)}$

2. Rotary Mechanism of the Prokaryotic V_o Motor Driven by Proton Motive Force

ATP synthases use the proton motive force (pmf) to rotate their c-ring and drive ATP synthesis. However, the mechanism of how pmf converts into c-ring rotation remains unclear. This study presents a 2.8 Å cryo-EM structure of the V_o domain of V/A-ATPase from *Thermus thermophilus*, revealing precise orientations of glutamate (Glu) residues in the c_{12}-ring with possible locations of water molecules that form the half channels for protons. MD simulations identified the channels and possible proton transfer pathway, and showed that protonation of specific Glu residues triggers unidirectional Brownian motion of the c12-ring towards ATP synthesis.$^{4)}$

3. Integration of AlphaFold with MD Simulation

The computational cost of all-atom MD simulations for biomolecular machines is so high that direct simulation of the functional motions is impossible. We introduce a method that integrates AlphaFold with MD simulation to overcome this difficulty.$^{5)}$ This method first generates broad structures by AlphaFold with reduced MSA depth, including multiple stable conformations and intermediates. Then, MD simulations are conducted from these structures to cover the broad conformational space that is involved with the function. The method was tested with the transporter protein NarK. It successfully uncovers a missing conformational state and transition dynamics between stable states.

4. Machine Learning of Reaction Coordinates

It is a challenging task to identify reaction coordinates for biomolecular systems with many degrees of freedom. Unlike order parameters or collective variables, a reaction coordinate should describe the progress of a reaction between two metastable states. We have developed a machine learning method to identify reaction coordinates based on the committor function.$^{2,6)}$ We have applied a deep neural network (DNN) and Explainable Artificial Intelligence (XAI) for this problem.$^{6)}$ We also developed a hyperparameter tuning approach to this problem.$^{7)}$

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Award

SEKI, Takehito; Young Presentation Award, 50th Meeting of Japan BioEnergetics Group (2024).

Visiting Professors

Visiting Professor

TSUCHIMOCHI, Takashi *(from Shibaura Institute of Technology)*

Theoretical and Computational Chemistry for Degenerate Electronic Structures

Our research focuses on quantum chemistry to compute the electronic structure of materials. We are particularly interested in chemical systems where electrons are strongly correlated, making them notoriously difficult to compute with traditional approaches due to either the inappropriate treatment of quantum entanglement or prohibitively large computational costs. To tackle this conundrum, we have proposed several methodologies based on symmetry-breaking of the underlying wave function as well as its restoration by means of symmetry-projection. While these methods primarily fall within the realm of wave function theory, we are integrating these concepts into the more affordable density functional theory. We have also been extensively exploring the potential of quantum computer to address such challenging electronic structures; recently, we have proposed a novel quantum-classical hybrid algorithm that mitigates the quantum measurement in optimizing the ground state energy. Finally, we actively collaborate with experimental groups to elucidate real chemical systems where quantum mechanical effects become important.

Visiting Professor

FUJII, Keisuke *(from The University of Osaka)*

Theoretical Research on the Fundamentals and Applications of Quantum Computers

Our research explores both theoretical foundations and applications of quantum computing. While recent advances have realized cloud-accessible devices with over 100 qubits, current noisy intermediate-scale quantum computers (NISQ) remain strongly affected by noise. We investigate how such devices can still be applied to meaningful tasks, such as machine learning and quantum many-body simulations, through noise mitigation. In parallel, we study architectures and physical systems for realizing large-scale fault-tolerant quantum computers (FTQC) with quantum error correction and estimate the resources required for practical problems. Recently, we have proposed new protocols for magic state distillation that significantly reduce FTQC resource requirements, and we are investigating how compiler-level optimizations can further reduce overhead.

Visiting Associate Professor

ABE, Minori *(from Tokyo University of Agriculture and Technology)*

Development of Relativistic Quantum Chemistry Software and Its Applications, and Generative AI Models for Chemistry

We have developed relativistic quantum chemistry software to compute molecular electronic structures involving heavy atoms. The CASPT2 method is employed in our program to treat multireference electron correlation effects, and relativistic effects are accurately incorporated by connecting to the DIRAC software. The software is publicly available on GitHub (https://github.com/RQC-HU/dirac_caspt2), and its application to the spectra of UO_2^{2+} has been published in the *Journal of Chemical Theory and Computation*.

In parallel, we have also developed generative machine learning models for chemical tasks based on the Bayesian Flow Network (ChemBFN). This model learns molecular structures from SMILES representations and generates new molecules in SMILES format. Furthermore, it can be fine-tuned for regression and classification tasks, enabling the generation of molecules with desired physical properties (N. Tao and M. Abe, *J. Chem. Inf. Model.* **65(3)**, 1178–1187 (2025)).