RESEARCH ACTIVITIES
Theoretical and Computational Molecular Science

The goal of the Department is understanding and prediction of static and dynamic properties, reactions, and functions in condensed phase including biomolecular and heterogeneous catalytic systems by developing novel theories and computational methodologies based on theories in quantum mechanics, statistical mechanics, and solid state physics. The Department collaborates with Research Center for Computational Science on researches.

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

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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 functions. 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.

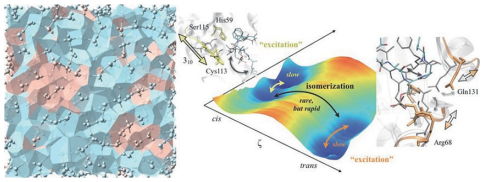

Figure 1. Snapshot of two-state model in supercooled water consisting of high- and low-density liquids (left) and schematic of 2D free energy surface for enzymatic reaction (right).

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. Conformational Dynamics in Proteins: Entangled Slow Fluctuations and Nonequilibrium Reaction Events[1)]

Proteins exhibit conformational fluctuations and changes over various time scales, ranging from rapid picosecond-scale local atomic motions to slower microsecond-scale global conformational transformations. In the presence of these intricate fluctuations, chemical reactions occur and functions emerge. These conformational fluctuations of proteins are not merely stochastic random motions but possess distinct spatiotemporal characteristics. Moreover, chemical reactions do not always proceed along a single reaction coordinate in a quasi-equilibrium manner. Therefore, it is essential to understand spatiotemporal conformational fluctuations of proteins and the conformational change processes associated with reactions. In this Perspective, we shed light on the complex dynamics of proteins and their role in enzyme catalysis by presenting recent results regarding dynamic couplings and disorder in the conformational dynamics of proteins and rare but rapid enzymatic reaction events obtained from molecular dynamics simulations.

2. Locating Transition States by a Variational Reaction Path Optimization with an Energy-Derivative-Free Objective Function[2)]

Locating transition states is essential for understanding molecular reactions. We propose a double-ended transition state search method by revisiting a variational reaction path optimization method known as the MaxFlux method. Although its original purpose is to add temperature effects to reaction paths, we conversely let the temperature approaches zero to obtain an asymptotically exact minimum energy path and its corresponding transition state in variational formalism with an energy-derivative-free objective function. Using several numerical techniques to directly optimize the objective function, the present method reliably finds transition states with low computational cost. In particular, only three force evaluations per iteration are sufficient. This is confirmed in a variety of molecular reactions where the nudged elastic band method often fails.

3. Unraveling the Dynamic Slowdown in Supercooled Water: The Role of Dynamic Disorder in Jump Motions[3)]

When a liquid is rapidly cooled below its melting point without inducing crystallization, its dynamics slow down significantly without noticeable structural changes. Elucidating the origin of this slowdown has been a long-standing challenge. Here, we report a theoretical investigation into the mechanism of the dynamic slowdown in supercooled water, a ubiquitous yet extraordinary substance characterized by various anomalous properties arising from local density fluctuations. Using molecular dynamics simulations, we found that the jump dynamics, which are elementary structural change processes, deviate from Poisson statistics with decreasing temperature. This deviation is attributed to slow variables competing with the jump motions, *i.e.*, dynamic disorder. The present analysis of the dynamic disorder showed that the primary slow variable is the displacement of the fourth nearest oxygen atom of a jumping molecule, which occurs in an environment created by the fluctuations of molecules outside the first hydration shell. As the temperature decreases, the jump dynamics become slow and intermittent. These intermittent dynamics are attributed to the prolonged trapping of jumping molecules within extended and stable low-density domains. As the temperature continues to decrease, the number of slow variables increases due to the increased cooperative motions. Consequently, the jump dynamics proceed in a higher-dimensional space consisting of multiple slow variables, becoming slower and more intermittent. It is then conceivable that with further decreasing temperature, the slowing and intermittency of the jump dynamics intensify, eventually culminating in a glass transition.

4. Effect of Counterions on the Structure and Dynamics of Water near a Negatively Charged Surfactant: A Theoretical Vibrational Sum Frequency Generation Study[4)]

Charged aqueous interfaces are of paramount importance in electrochemical, biological, and environmental sciences. The properties of aqueous interfaces with ionic surfactants can be influenced by the presence of counterions. Earlier experiments involving vibrational sum frequency generation (VSFG) spectroscopy of aqueous interfaces with negatively charged sodium dodecyl sulfate (Na^+DS^- or SDS) surfactants revealed that the hydrogen bonding strength of the interfacial water molecules follows a certain order when salts of monovalent and divalent cations are added. It is known that cations do not directly participate in hydrogen bonding with water molecules, rather they only influence the hydrogen-bonded network through their electrostatic fields. In the current work, we have simulated the aqueous interfacial systems of sodium dodecyl sulfate in the presence of chloride salts of mono and divalent countercations. The electronic polarization effects on the ions are considered at a mean-field level within the electronic continuum correction model. Our calculations of the VSFG spectra show a blue shift in the presence of added countercations whose origin is traced to different relative contributions of water molecules from the solvation shells of the surfactant headgroups and the remaining water molecules in the presence of countercations. Furthermore, the cations shield the electric fields of the surfactant headgroups, which in turn influences the contributions of water molecules to the total VSFG spectrum. This shielding effect becomes more significant when divalent countercations are present. The dynamics of water molecules are slower at the interface than the bulk. The interfacial depth dependence of various dynamical quantities shows that the interface is structurally and dynamically more heterogeneous at the microscopic level.

References

1) J. Ono, Y. Matsumura, T. Mori and S. Saito, *J. Phys. Chem. B (Perspective)* **128**, 20–32 (2024).
2) S.-i. Koda and S. Saito, *J. Chem. Theory Comput.* **20**, 2798–2811 (2024).
3) S. Saito, *J. Chem. Phys.* **160**, 194506 (13 pages) (2024).
4) R. Malik, S. Saito and A. Chandra, *Phys. Chem. Chem. Phys.* **26**, 17065–17074 (2024).

Theoretical Studies of Chemical Dynamics in Condensed and Biomolecular Systems

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Keywords Quantum Dissipative Systems in Complex Molecular Systems, Quantum Optics, Light-Matter Interaction

Quantum dynamic phenomena are ubiquitous in molecular processes, and yet remain a challenge for experimental and theoretical investigations. On the experimental side, it has become possible to explore molecules on a time scale down to a few femtoseconds. This progress in ultrafast spectroscopy has opened up real-time observation of dynamic processes in complex chemical and biological systems and has provided a strong impetus to theoretical studies of condensed phase quantum dynamics.

Essentially, any quantum systems can never be regarded as "isolated systems." Quantum systems are always in contact with "the outside world," and hence their quantum natures are sometimes sustained and sometimes destroyed. In condensed phase molecular systems, especially, quantum systems are affected by the huge amount of dynamic degrees of freedom such as solvent molecules, amino acid residues in proteins, and so forth. Balance between robustness and fragility of the quantum natures may dramatically alter behaviors of chemical dynamics and spectroscopic signals. Therefore, theoretical tools to adequately describe (1) dynamical behaviors of quantum systems affected by the huge amount of dynamic degrees of freedom and (2) the interaction with radiation fields should be developed.

For this purpose, our research group has been tackling the following subjects:

(1) Developments of condensed phase quantum dynamic theories
(2) Quantum theories to describe dynamical and transport processes in materials and biological systems
(3) Theoretical investigations on measurement and control with the use of atomic-molecular-optical (AMO) physics approaches.

In recent years, specifically, special attention is devoted to the subject (3). We have been examining whether ideas and concepts in the field of quantum science and technology would provide novel control knobs that supplement classical parameters in conventional spectroscopic tools such as frequencies and time delays.

Selected Publications

- A. Ishizaki and G. R. Fleming, "Quantum Coherence in Photosynthetic Light Harvesting," *Annu. Rev. Condens. Matter Phys.* **3**, 333–361 (2012). [Invited review article]
- G. D. Scholes *et al.*, "Using Coherence to Enhance Function in Chemical and Biophysical Systems," *Nature* **543**, 647–656 (2017).
- T. P. Nguyen and A. Ishizaki, "Control of Excitation Energy Transfer in Condensed Phase Molecular Systems by Floquet Engineering," *J. Phys. Chem. Lett.* **9**, 1243 (2018).
- A. Kato and A. Ishizaki, "Non-Markovian Quantum-Classical Ratchet for Ultrafast Long-Range Electron–Hole Separation in Condensed Phases," *Phys. Rev. Lett.* **121**, 647 (2018).
- Y. Fujihashi, R. Shimizu and A. Ishizaki, "Generation of Pseudo-Sunlight via Quantum Entangled Photons and the Interaction with Molecules," *Phys. Rev. Res.* **2**, 023256 (2020).
- A. Ishizaki, "Probing Excited-State Dynamics with Quantum Entangled Photons: Correspondence to Coherent Multidimensional Spectroscopy," *J. Chem. Phys.* **153**, 051102 (2020). [Editor's Pick]

1. Dynamics of a Quantum System Interacting with White Non-Gaussian Baths: Poisson Noise Master Equation

Quantum systems are unavoidably open to their surrounding degrees of freedom. The theory of open quantum systems is thus crucial to understanding the fluctuations, dissipation, and decoherence of a quantum system of interest. Typically, the bath is modeled as an ensemble of harmonic oscillators, which yields Gaussian statistics of the bath influence on the quantum systems. However, there are also phenomena in which the bath consists of two-state systems, spins, or anharmonic oscillators; therefore, the non-Gaussian properties of the bath become important. Nevertheless, a theoretical framework to describe quantum systems under the influence of such non-Gaussian baths is not well established. Here, we develop a theory to describe quantum dissipative systems affected by Poisson noise properties of the bath, because the Lévi-Itô decomposition theorem asserts that Poisson noise is fundamental in describing arbitrary white noise beyond Gaussian properties. We introduce a quantum bath model that allows for the consistent description of dissipative quantum systems. The obtained master equation reveals non-Gaussian bath effects in the white noise regime, and provides an essential step toward describing open quantum dynamics under the influence of generic baths.[1)]

2. Pathway Selectivity in Time-Resolved Spectroscopy Using Two-Photon Coincidence Counting with Quantum Entangled Photons

Ultrafast optical spectroscopy is a powerful technique for studying the dynamic processes of molecular systems in condensed phases. However, in molecular systems containing many dye molecules, the spectra can become crowded and difficult to interpret owing to the presence of multiple nonlinear optical contributions. In this work, we theoretically propose time-resolved spectroscopy based on the coincidence counting of two entangled photons generated via parametric down-conversion with a monochromatic laser. We demonstrate that the use of two-photon counting detection of entangled photon pairs enables the selective elimination of the excited-state absorption signal. This selective elimination cannot be realized with classical coherent light. We anticipate that the proposed spectroscopy will help simplify the spectral interpretation of complex molecular and material systems comprising multiple molecules.[2)]

3. A Coarse-Grained Description of Anharmonic Lattice Environments Affecting the Quantum Dynamics of Charge Carriers

Lattice softness has a significant impact on charge carrier dynamics in condensed matter systems. Examples include the remarkable carrier lifetimes and defect tolerances of hybrid organic-inorganic perovskites. Recent studies suggest the contribution of quartic anharmonicity of the lattice vibrations. The quartic anharmonicity can be discussed with a double-well potential, and the transition between the two minima can be coarse-grained as a two-state jump stochastic process. Such a stochastic approach is typically employed to describe fluctuations introduced into a system by two-state transitions in the surroundings. To investigate charge transport in materials, however, it is crucial to describe not only the fluctuations but also the dynamic lattice distortion associated with charge transport. Therefore, there is a need for a theory to describe the charge carrier dynamics proceeding alongside the lattice distortion dynamics. In this study, we present a theory that describes quantum dynamics under the influence of an environment with two stable states, termed a bistable environment. The theory describes the effects of fluctuations and dissipation induced from the bistable environment in a reasonable manner, and the effects exhibit a different temperature dependence than the widely employed Gaussian environment. The physical implication of this temperature dependence is provided in terms of the environmental dynamics. The results of this study are expected to provide a step forward in describing charge carrier dynamics in materials with lattice softness and pronounced lattice anharmonicity.[3)]

4. Network Analysis with Quantum Dynamics Clarifies Why Photosystem II Exploits both Chlorophyll *a* and *b*

In land plants, chlorophyll-*a* and chlorophyll-*b* in light-harvesting proteins are responsible for absorbing solar energy. While the individual characteristics of these pigments are well-understood, the advantages of their coexistence have not been fully elucidated. Here, we presented a principled framework based on complex network analysis and quantum dynamics to investigate and quantify the features of this coexistence during excitation energy transfer in a photosystem II supercomplex. By using model networks with diverse chlorophyll compositions, our analysis revealed that the excited energy preferentially flows through specific domains, where excessive energy can be controlled, solely in those supercomplexes with a natural chlorophyll-*a*/*b* ratio, resulting in a moderate charge separation yield. Our findings suggested that light-harvesting proteins with the natural chlorophyll-*a*/*b* ratio are optimized to safely and efficiently capture light energy across various light intensities. By leveraging our framework, we could gain valuable insights into the mechanisms by which light-harvesting proteins harvest light energy and adapt to changing environmental conditions.[4)]

References

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2) Y. Fujihashi, A. Ishizaki and R. Shimizu, *J. Chem. Phys.* **160**, 104201 (2024).
3) K. Miwa, S. Sakamoto, K. Funo and A. Ishizaki, submitted.
4) E. Kim, D. Lee, S. Sakamoto, J.-Y. Jo, M. Vargas, A. Ishizaki, J. Minagawa and H. Kim, submitted.

Theoretical Studies of Functional Molecular Systems and Heterogeneous Catalysts

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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 elucidated the mechanism of various three-way catalysts like PGM-free tandem catalyst. We also investigated the nanocluster and heterogeneous catalysts for the fuel cells and fine chemicals like Pt sub-nanoclusters for oxygen reduce 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 CAu^{I}_{6} cluster with monodentate *N*-heterolytic carbene (NHC) ligands, intense photoluminescence (PL) of $CAu^{I}_{6}Ag^{I}_{n}$ (n = 2–4) clusters and its biological application, vapochromism of CAu^{I}_{6} cluster, and the generation of CAu^{I}_{5} cluster and its red-shifted PL as well as catalytic activity.

(4) Photoluminescence of modified single-walled carbon nanotubes (SWNTs)

In the series of works, we have investigated the selective photoluminescence (PL) from photofunctional molecular systems. Introducing the quantum defects into single-walled carbon nanotubes (SWNTs) enhances their PLs with red-shifted peaks. Previously, we proposed the substitution rule using Clar-sextet theory. Recently, we have achieved the control of near-IR PL by the stepwise chemical functionalization, the selective E** 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).
- P. Hirunsit, T. Toyao, S. M. A. H. Siddiki, K. Shimizu and M. Ehara, "Origin of Nb_2O_5 Lewis Acid Catalysis for Activation of Carboxylic Acids in the Presence of a Hard Base," *ChemPhysChem* **19**, 2848 (2018).
- Z. Lei, M. Endo, H. Ube, T. Shiraogawa, P. Zhao, K. Nagata, X.-L. Pei, T. Eguchi, T. Kamachi, M. Ehara, T. Ozawa and M. Shionoya, "*N*-Heterocyclic Carbene-Based C-Centered Au(I)-Ag(I) Clusters with Intense Phosphorescence and the Organelle-Selective Translocation in Cells," *Nat. Commun.* **13**, 4288 (2022).
- Y. Maeda, Y. Suzuki, Y. Konno, P. Zhao, N. Kikuchi, M. Yamada, M. Mitsuishi, A. T. H. Dao, H. Kasai and M. Ehara, "Selective Emergence of Photoluminescence at Telecommunication Wavelengths from Cyclic Perfluoroalkylated Carbon Nanotubes," *Commun. Chem.* **6**, 159 (10 peges) (2023).

1. Elucidating Electronic Structure of Anion-Templated Silver Nanoclusters by Optical Absorption Spectroscopy and Theoretical Calculations[1)]

Electronic structures of anion-templated silver nanoclusters (Ag NCs) have not been well understood compared with conventional template-free Ag NCs. In this work, we developed three new anion-templated Ag NCs, that is $[S@Ag_{17}L_{15}(PPh_3)_5]^0$, $[S@Ag_{18}L_{16}(PPh_3)_8]^0$, and $[Cl@Ag_{18}L_{16}(PPh_3)_8][PPh_4]$, where L = 4-chlorobenzene methanethiolate for which single-crystal X-ray crystallography revealed that they have $S@Ag_6$, $S@Ag_{10}$, and $Cl@Ag_{10}$ cores, respectively. Investigation of their electronic structures by optical spectroscopy and theoretical calculations elucidated the following unique features; (1) their electronic structures are different from those of template-free Ag NCs described by the superatomic concept; (2) optical absorption in the range of 550–400 nm for S^{2-}-templated Ag NCs is attributed to the charge transitions from S^{2-}-templated Ag-cage orbitals to the s-shaped orbital in the S^{2-} moiety; (3) the Cl^--templated Ag NCs can be viewed as $[Cl@Ag_{18}L_{16}(PPh_3)_8]^0[PPh_4]^0$ rather than the ion pair $[Cl@Ag_{18}L_{16}(PPh_3)_8]^-[PPh_4]^+$; and (4) the singlet-coupled singly occupied orbitals are involved in the optical absorption of the Cl^--templated Ag NC.

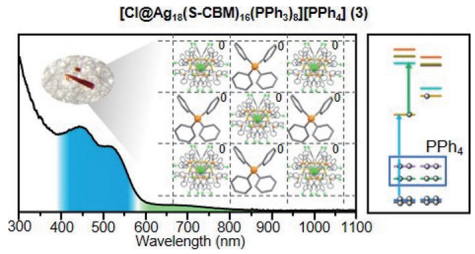

Figure 1. Photophysical properties and electronic states of $[Cl@Ag_{18}L_{16}(PPh_3)_8][PPh_4]$.

2. Single-Gold Etching at the Hypercarbon Atom of *C*-Centred Hexagold(I) Clusters[2)]

Etching is an excellent top-down synthesis method for controlling the structures and chemical and physical properties of nanomaterials. Chemical etching at the atomic level is a particularly challenging task for the precise synthesis of nanosized metal clusters. The synthesis of metal clusters containing smaller metal nuclei and potential surface vacancies will further elucidate the details of structure–function relationships and facilitate future materials design. In this work, we report the successful single-gold etching at a hypercarbon centre in gold(I) clusters. Specifically, *C*-centred hexagold(I) clusters protected by chiral *N*-heterocyclic carbenes were etched with bisphosphine to yield *C*-centred pentagold(I) (CAu^I_5) clusters. The CAu^I_5 clusters exhibit an unusually large bathochromic shift in luminescence, which is reproduced theoretically. The etching mechanism was experimentally and theoretically suggested to be a tandem dissociation-association-elimination pathway. Furthermore, the vacant site of the central carbon of the CAu^I_5 cluster can accommodate AuCl, allowing for post-functionalisation of the *C*-centred gold(I) clusters.

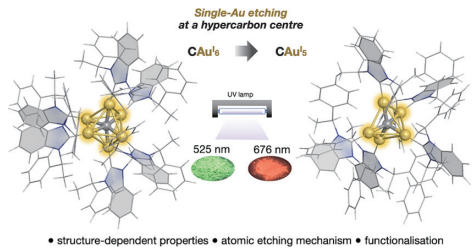

Figure 2. Schematic diagram of single-Au etching at a hypercarbon center.

3. Optimization of Metal-Support Cooperation for Boosting the Performance of Supported Gold Catalysts for the Borylation of C–O and C–N Bonds[3)]

Supported metal catalysts have interfacial sites between metal nanoparticles and their supports, where multiple catalytic elements can work in cooperation to efficiently promote intermolecular reactions. In this work, we performed kinetic and theoretical studies to elucidate the effect of metal-support cooperation for the borylation of C–O bonds by supported gold catalysts and revealed that the Lewis acid density of the supports determined the number of active sites at which metal nanoparticles (NPs) and Lewis acid at the surface of the supports work in cooperation. DFT calculations revealed that strong adsorption of diborons at the interface between Au NPs and supports and lowering the LUMO level of adsorbed diboron were responsible for efficient C–O bond borylation. Supported Au catalysts with the optimized metal–metal oxide cooperation sites, namely Au/α-Fe_2O_3 catalyst, showed excellent activity for C–O bond borylation, and also enabled the synthesis of organoboron compounds by using continuous flow reactions. Furthermore, Au/α-Fe_2O_3 showed high activity for direct C–N bond borylation without the transformation of amino groups to ammonium cations. The results described herein suggest that the optimization of metal–metal oxide cooperation is beneficial for taking full advantage of the potential performance of supported metal catalysts for intermolecular reactions.

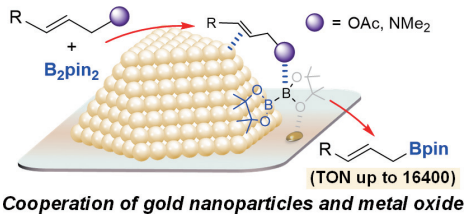

Figure 3. Borylation of C–O and C–N bonds on the supported gold catalysts: Optimization of metal-support interaction.

References

1) Y. Horita, S. Hossain, M. Ishimi, P. Zhao, M. Sera, T. Kawawaki, S. Takano, Y. Niihori, T. Nakamura, T. Tsukuda, M. Ehara and Y. Negishi, *J. Am. Chem. Soc.* **145**, 23533–23540 (2023).

2) X.-L. Pei, P. Zhao, H. Ube, Z. Lei, M. Ehara and M. Shionoya, *Nat. Commun.* **15**, 5024 (2024).

3) H. Miura, K. Imoto, H. Nishio, A. Junkaew, Y. Tsunesada, Y. Fukata, M. Ehara and T. Shishido, *J. Am. Chem. Soc.* **146**, 27528–27541 (2024).

Molecular Dynamics Simulations of Disease-Related Biomolecules

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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.

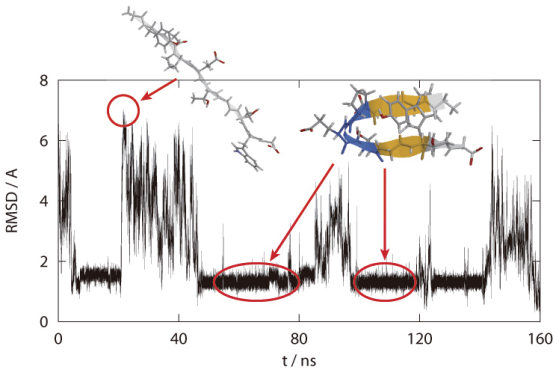

Figure 1. Time series of protein folding simulation.

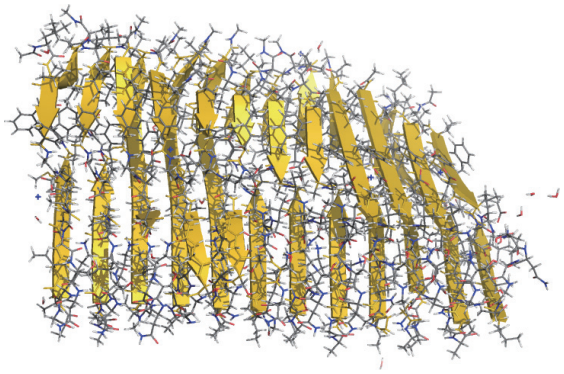

Figure 2. Snapshot of an Aβ amyloid fibril.

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. 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.

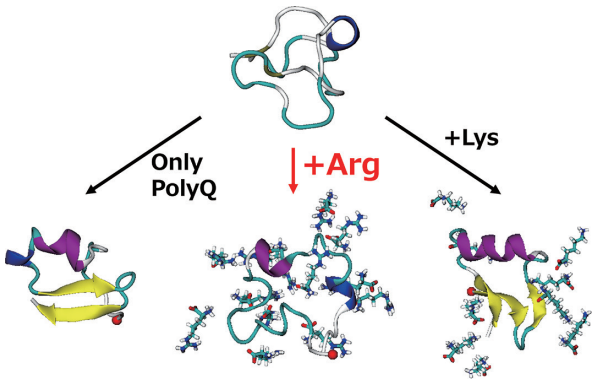

Figure 3. Arginine inhibits polyQ-proteins from forming intra- and intermolecular β-sheet structures. However, lysine, which also has a positive charge, does not have such an effect.

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.

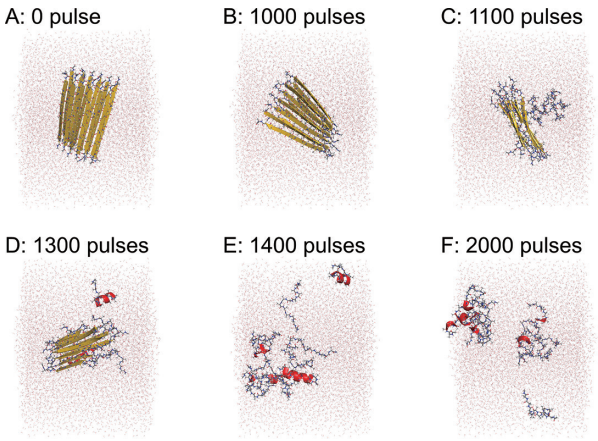

Figure 4. Snapshots of polyA amyloid fibril during a nonequilibrium MD simulation. Snapshots (A) before FEL irradiation, (B) after 1000 pulses, (C) after 1100 pulses, (D) after 1300 pulses, (E) after 1400 pulses, and (F) after 2000 pulses.

References

1) S. Tanimoto and H. Okumura, *ACS Chem. Neurosci.* **15**, 2925–2935 (2024).
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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

Dynamics of Biomolecular Machines in Function Revealed by Theoretical Methods

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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 Oxalate Transporter

Oxalate is contained in our daily food, such as spinach and nuts. Excess amounts of oxalate form insoluble salts with calcium ions, causing kidney stone disease. *Oxalobacter formigenes*, an oxalate-degrading bacterium that lives in the intestine, absorbs oxalate as its sole carbon source and excretes formate, a metabolic degradation product. As a result, *Oxalobacter formigenes* contributes to reducing the risk of kidney stone disease by lowering the oxalate level. The oxalate transporter (OxlT) in the bacterium's membrane is responsible for oxalate uptake and formate efflux. The crystal structures of the two different conformations taken by OxlT during its transport cycle have been determined by our collaborators.[3] One structure is in the outward-open conformation, while the other is in the occluded conformation with the bound oxalate.

We have identified the inward and outward gates of OxlT using MD simulations from the experimental structures.[3] An unresolved inward-open conformation was obtained by performing accelerated MD simulations, in which boost potential was applied to residues around the inward gate (Figure 1A). The obtained inward-open conformation was validated by an additional simulation observing the substrate formate binding from the inside of the membrane (Figure 1B). The contact analysis was performed to identify key interactions that change during the conformational change (Figure 1C). The residues that break contacts include D280 at the cytoplasmic side. The S162 and T258 formed a contact at the periplasmic side.

Then, we used the state-of-the-art structural prediction AI AlphaFold2 to see how mutations of the identified residues affect AlphaFold prediction (Figure 1D). While AlphaFold predicted only the outward-open conformations with the wild-type sequence, the mutation D280L or S162C/T258C made AlphaFold also predict the inward-open conformation. These mutations likely stabilize the inward-open conformation.

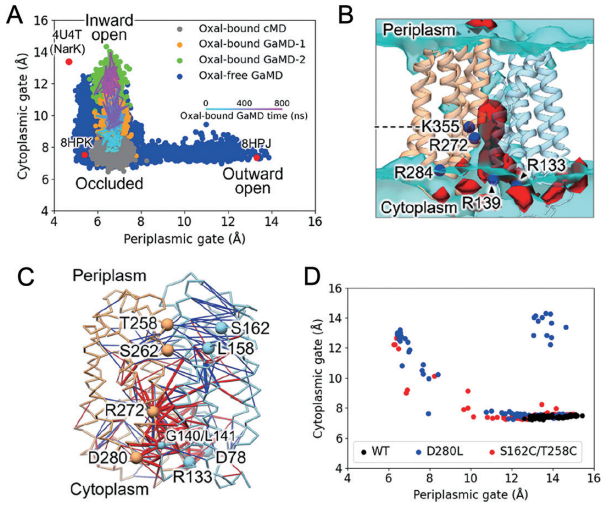

Figure 1. (A) Accelerated MD simulations discover an inward-open conformation. (B) Formate density in the inward-open state. (C) Contact analysis to identify important residue pairs. (D) AlphaFold structures for wild type and mutants.[4]

2. 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.

3. 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 and Explainable Artificial Intelligence (XAI) for this problem.[6]

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1) K. Okazaki and G. Hummer, *Proc. Natl. Acad. Sci. U. S. A.* **110**, 16468–16473 (2013).
2) K. Okazaki, D. Wöhlert, J. Warnau, H. Jung, Ö. Yildiz, W. Kühlbrandt and G. Hummer, *Nat. Commun.* **10**, 1742 (2019).
3) T. Jaunet-Lahary *et al*., *Nat. Commun.* **14**, 1730 (2023).
4) J. Ohnuki, T. Jaunet-Lahary, A. Yamashita and K. Okazaki, *J. Phys. Chem. Lett.* **15**, 725–732 (2024).
5) J. Ohnuki and K. Okazaki, *J. Phys. Chem. B* **128**, 7530–7537 (2024).
6) T. Kikutsuji, Y. Mori, K. Okazaki, T. Mori, K. Kim and N. Matubayasi, *J. Chem. Phys.* **156**, 154108 (2022).

Awards

OHNUKI, Jun; Young Scientist Excellence Award of the Protein Science Society of Japan (2024).
KOBAYASHI, Ryohei; Early Career Award, The Biophysical Society of Japan (2023).

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 with each other, 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. Recently, we have also been extensively exploring the potential of quantum computer to address such challenging electronic structures; we have proposed novel quantum-classical hybrid algorithms for accurately determining both ground and excited states in fermionic systems.

Visiting Professor
FUJII, Keisuke *(from Osaka University)*

Theoretical Research on the Fundamentals and Applications of Quantum Computers

Our research interests include theoretical foundations and applied research related to quantum computing. The development of quantum computer hardware has made remarkable progress in recent years. Quantum computers with 50 to over 100 qubits have already been realized and quantum computers can be used from the cloud. However, current quantum computers are known as noisy intermediate-scale quantum computers (NISQ), suffering from noise. In the future, it is hoped to realize a larger-scale quantum computer and a fault-tolerant quantum computer (FTQC) with quantum error correction. Our group is investigating how quantum computers of the scale currently realized can be used for useful tasks, such as machine learning and quantum many-body simulations, by mitigating noise. At the same time, we are also analyzing what physical systems can be used to construct a large-scale FTQC and how much resources are needed to solve problems of practical interest.

Visiting Associate Professor
ABE, Minori *(from Hiroshima University)*

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. Our program was used to elucidate the ground and excited electronic states of several actinide compounds, such as UO_2^{2+} and $Cm(phen)_2^{3+}$. Our calculated excitation energies agree with experimental data and previously reported theoretical results. We will make our program publicly available on GitHub.