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 Molecular Systems

Department of Theoretical and Computational Molecular Science
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Keywords Reactions, Functions, Fluctuations

Our research focuses on the intricate fluctuations in condensed molecular systems, including liquids and biomolecules. In these systems, fluctuations affect various properties and biological functions, and reactions occur under fluctuations.

We investigate fluctuations and dynamics in these molecular systems to elucidate the molecular origins of the physical properties, functions, and reactions. To this end, we have developed advanced computational methods for multi-dimensional nonlinear spectroscopy, which allow us to extract detailed dynamical information that conventional linear spectroscopy cannot provide. Our investigations have successfully revealed the molecular origins of ultrafast energy relaxation and the time evolution of inhomogeneous fluctuations in liquid water. Additionally, we have explored the phenomenon of dynamic heterogeneity in supercooled liquids, characterized by slow and non-uniform structural changes induced by fluctuations. Using three-time correlation functions, we have also shed light on dynamic couplings of conformational fluctuations with different timescales in a protein.

Our work extends to the study of anomalous properties of liquid water, uncovering the connections between these anomalies and hidden structural and dynamical properties. Additionally, we have investigated the origin behind the low glass transition of water. We are also investigating the origin of rare but persistent structural change dynamics at low temperatures based on theories of stochastic processes and reaction rates.

In biomolecular systems, conformational fluctuations and changes are essential for function. Our investigations have explored the intricate interplay between fluctuations and biomolecular functions, exemplified by the robust circadian rhythm of the clock protein KaiC and the efficient excitation energy transfer in photosynthetic systems. Our work on enzymatic reactions has highlighted the importance of prepared conformational states with specific structures that facilitate reactions. We have also studied the molecular origin of dynamic disorder in the conformational dynamics of proteins at the molecular level, unraveling the intricacies of this phenomenon.

As seen in these studies, we aim to deepen our understanding of structural dynamics, reactions, and functions in condensed molecular systems based on theoretical and computational methods.

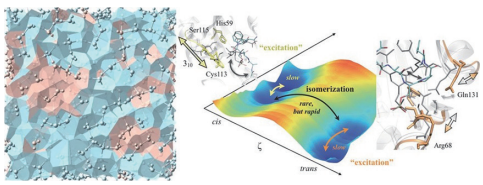

Figure 1. Snapshot of two-state model in supercooled water consisting of high- and low-density liquids (left) and schematic of 2D free energy surface for enzymatic reaction (right).

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).
- T. Mori and S. Saito, *J. Phys. Chem. Lett.* **10**, 474–480 (2019).
- S. Saito, M. Higashi and G. R. Fleming, *J. Phys. Chem. B* **123**, 9762–9772 (2019).

1. Anisotropic and Finite Effects on Intermolecular Vibration and Relaxation Dynamics: Low-Frequency Raman Spectroscopy of Water Film and Droplet on Graphene by Molecular Dynamics Simulations[1)]

The structural and dynamical properties of water can be greatly altered by the anisotropic interfacial environment. Here, we study the intermolecular vibration and relaxation dynamics of a water film and a water droplet on a graphene surface based on low-frequency Raman spectra calculated from molecular dynamics simulations. The calculated Raman spectra of the interfacial water systems show a weakened libration peak and an enhanced intermolecular hydrogen bond (HB) stretching peak compared to the spectrum of bulk water, which are attributed to softened orientation motion. We also find that the collective polarizability relaxation in the droplet is much slower than that in the film and bulk, which is completely different from the collective dipole relaxation. The slow relaxation is due to a positive correlation between the induced polarizabilities of distinct molecules caused by the global and anisotropic structural fluctuations of the water droplet. Furthermore, we find that the two-dimensional HB network by the orientation-ordered interfacial water molecules leads to different intermolecular vibration dynamics between the parallel and perpendicular components. The present theoretical study demonstrates that low-frequency Raman spectroscopy can reveal the anisotropic and finite effects on the intermolecular dynamics of the water film and droplet.

2. Conformational Dynamics in Proteins: Entangled Slow Fluctuations and Nonequilibrium Reaction Events[2)]

Proteins exhibit conformational fluctuations and changes over various timescales, ranging from rapid picosecond-scale local atomic motions to slower microsecond-scale global conformational transformations. In the presence of these 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 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.

3. Molecular Insights into the Intrinsic Dynamics and Their Roles During Catalysis in Pin1 Peptidyl-prolyl Isomerase[3)]

Proteins are intrinsically dynamic and change conformations over a wide range of time scales. While the conformational dynamics have been realized to be important for protein functions, *e.g.*, in activity–stability trade-offs, how they play a role during enzyme catalysis has been of debate over decades. By studying Pin1 peptidyl-prolyl isomerase using extensive molecular dynamics simulations, here we discuss how the slow intrinsic dynamics of Pin1 observed in the NMR relaxation dispersion experiment occur and couple to isomerization reactions in molecular detail. In particular, we analyze the angular correlation functions of the backbone N–H bonds and find that slow conformational transitions occur around the 3_{10} helix in the apo state. These events at the helical region further affect the residues around the ligand binding site. Unfolding of this helix leads to a tight hydrogen bond between the helical region and the ligand binding loop, thus forming a stable coiled structure. The helical and coiled structures are found to be characteristic of the Pin1–ligand complex with the ligand in the *trans* and *cis* states, respectively. These results indicate that the changes in the slow dynamics of Pin1 by the isomerization reaction occur via the shift in populations of the helical and coiled states, where the balance is dependent on the ligand isomerization states.

4. Excited States of Chlorophyll *a* and *b* in Solution by Time-Dependent Density Functional Theory[4)]

The ground state and excited state electronic properties of chlorophyll (Chl) *a* and Chl *b* in diethyl ether, acetone, and ethanol solutions are investigated using quantum mechanical and molecular mechanical calculations with density functional theory (DFT) and time-dependent DFT (TDDFT). Although the DFT/TDDFT methods are widely used, the electronic structures of molecules, especially large molecules, calculated with these methods are known to be strongly dependent on the functionals and the parameters used in the functionals. Here, we optimize the range-separated parameter, μ, of the CAM-B3LYP functional of Chl *a* and Chl *b* to reproduce the experimental excitation energy differences of these Chl molecules in solution. The optimal values of μ for Chl *a* and Chl *b* are smaller than the default value of μ and that for bacteriochlorophyll *a*, indicating the change in the electronic distribution, *i.e.*, an increase in electron delocalization, within the molecule. We find that the electronic distribution of Chl *b* with an extra formyl group is different from that of Chl *a*. We also find that the polarity of the solution and hydrogen bond cause the decrease in the excitation energies and the increase in the widths of excitation energy distributions of Chl *a* and Chl *b*. The present results are expected to be useful for understanding the electronic properties of each pigment molecule in a local heterogeneous environment, which will play an important role in the excitation energy transfer in light-harvesting complex II.

References

1) T. Inagaki, M. Hatanaka and S. Saito, *J. Phys. Chem. B* **127**, 5869–5880 (2023).
2) J. Ono, Y. Matsumura, T. Mori and S. Saito, *J. Phys. Chem. B (Perspective)*, accepted.
3) T. Mori and S. Saito, *J. Phys. Chem. B* **126**, 5185–5193 (2022).
4) Z. Zhu, M. Higashi and S. Saito, *J. Chem. Phys. (Special topic on Photosynthetic Light-Harvesting and Energy Conversion)* **156**, 124111 (13 pages) (2022).

Theoretical Studies of Chemical Dynamics in Condensed and Biomolecular Systems

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2016 18th Sir Martin Wood Prize
2017 The Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science and Technology
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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. Control and Enhancement of Single-Molecule Electroluminescence through Strong Light-Matter Coupling

The energetic positions of molecular electronic states at molecule/electrode interfaces are crucial factors for determining the transport and optoelectronic properties of molecular junctions. Strong light-matter coupling offers a potential for manipulating these factors, enabling to boost in the efficiency and versatility of these junctions. Here, we investigated electroluminescence from single-molecule junctions in which the molecule is strongly coupled with the vacuum electromagnetic field in a plasmonic nanocavity. We demonstrated an improvement in the electroluminescence efficiency by employing the strong light-matter coupling in conjunction with the characteristic feature of single-molecule junctions to selectively control the formation of the lowest-energy excited state. The mechanism of efficiency improvement was discussed based on the energetic position and composition of the formed polaritonic states. Our findings indicated the possibility to manipulate optoelectronic conversion in molecular junctions by strong light-matter coupling.[1)]

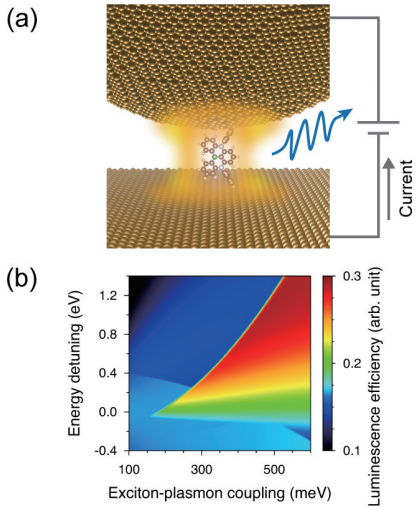

Figure 1. (a) Schematic illustration of electroluminescence from a dye molecule in a plasmonic nanocavity. (b) Two-dimensional plot of the electroluminescence efficiency as a function of the exciton–plasmon coupling strength and energy detuning.

2. Probing Exciton Dynamics with Spectral Selectivity through the Use of Quantum Entangled Photons

Quantum light is increasingly recognized as a promising resource for developing optical measurement techniques. Particular attention has been paid to enhancing the precision of the measurements beyond classical techniques by using nonclassical correlations between quantum entangled photons. Recent advances in quantum optics technology have made it possible to manipulate the spectral and temporal properties of entangled photons, and the photon correlations can facilitate the extraction of matter information with relatively simple optical systems compared to conventional schemes. In these respects, the applications of entangled photons to time-resolved spectroscopy can open new avenues for unambiguously extracting information on dynamical processes in complex molecular and materials systems. Here, we proposed time-resolved spectroscopy in which specific signal contributions are selectively enhanced by harnessing the nonclassical correlations of entangled photons. The entanglement time characterizes the mutual delay between an entangled twin and determines the spectral distribution of the photon correlations. This characteristic allows us to filter out specific frequency regions of spectra while temporally resolving the state-to-state dynamics in the time region longer than half of the entanglement time. Therefore, the entanglement time plays a dual role as the knob for controlling the accessible time region of dynamical processes and the degrees of spectral selectivity. The results demonstrated that the application of quantum entangled photons to time-resolved spectroscopy leads to monitoring dynamical processes in complex molecular and materials systems by selectively extracting desired signal contributions from congested spectra. We anticipated that more elaborately engineered photon states would broaden the availability of quantum light spectroscopy.[2)]

3. 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.[3)]

References

1) K. Miwa, S. Sakamoto and A. Ishizaki, *Nano Lett.* **23**, 3231 (2023).
2) Y. Fujihashi, K. Miwa, M. Higashi and A. Ishizaki, *J. Chem. Phys.* **159**, 114201 (2023).
3) 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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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)

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NAKATANI, Kaho
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Keywords Quantum Chemistry, Photochemistry, Heterogeneous Catalysis

We develop the accurate electronic structure theories and investigate the photochemistry and catalysis theoretically. Currently, our focuses are 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, R. Morooka, P. Zhao, D. Uchida, Y. Konno, M. Yamada and M. Ehara, "Controlling Near-Infrared Photoluminescence Properties of Single-Walled Carbon Nanotubes by Substituent Effect in the Stepwise Chemical Functionalization," *J. Phys. Chem. C* **127**, 2360 (2023).

1. Inverse Design of Molecule–Metal Nanoparticle Systems Interacting with Light for the Desired Photophysical Properties[1)]

Molecules close to a metal nanoparticle (NP) have different photophysical properties from those of the isolated one. To harness the potential of molecule–NP system, appropriate design guidelines are expected. In this work, we propose an inverse design method of the optimal molecule–NP systems and incident electric field for desired photophysical properties. It is based on a gradient-based optimization search within the time-dependent quantum chemical description for the molecule and the continuum model for the metal NP. We designed the optimal molecule, relative molecule–NP spatial conformation, and incident electric field of a molecule–NP system to maximize the population transfer to the target electronic state of the molecule. The present method is promising as the basis for designing molecule–NP systems and incident fields and accelerates discoveries of efficient molecular plasmonics systems.

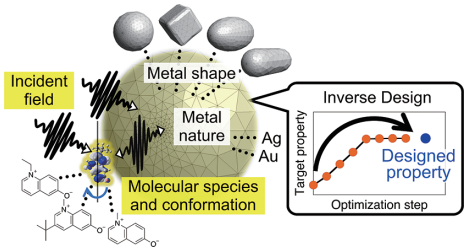

Figure 1. Inverse design of the photophysical properties of molecule–nanoparticle system.

2. *N*-Heterocyclic Carbene-Based *C*-Centered Au(I)-Ag(I) Clusters with Intense Phosphorescence and Organelle-Selective Translocation in Cells[2)]

Luminescent metal nanoclusters are expected to exhibit unique physical properties in the cluster structure depending on the ligand structure, metal type, number of nuclei and arrangement. In this study, carbon-centered gold-silver (CAu_6Ag_2) clusters with *N*-heterocyclic carbene (NHC) ligands were designed and synthesized, and it was found that these clusters emit strong phosphorescence in solution, and the contribution of NHC ligands to phosphorescence emission was revealed by theoretical calculation. The luminescence rate constant was calculated by an analysis including spin–orbit interactions, and the quantum yield was discussed in terms of the energy barrier to the minimum energy crossing point. Furthermore, the phosphorescent gold-silver clusters with long luminescence lifetime were used for cellular imaging, which revealed the pathway of uptake into the cell and selective localization to specific organelles, confirming their superior functionality, which is different from the non-selective uptake of conventional phosphine ligands.

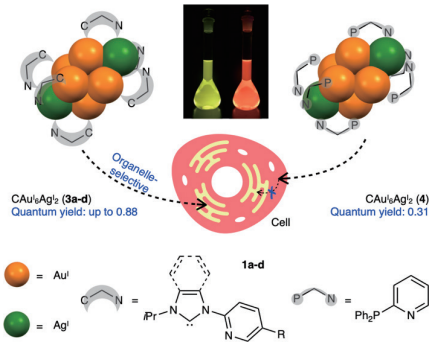

Figure 2. Schematic diagram of Carbon(*C*)-centered Au(I)-Ag(I) clusters with *N*-heterocyclic carbene (NHC) ligands with intense phosphorescence and their ligand-specific, organelle-selective translocation in cells.

3. Controlling Near-Infrared Luminescence of Single-Walled Carbon Nanotubes by Substituent Effect in Stepwise Chemical Functionalization[3)]

Introducing the quantum defects into single-walled carbon nanotubes (SWNTs) enhances their photoluminescence (PL) with red-shifted peaks. In this work, the stepwise chemical functionalization of SWNTs was shown to be useful for controlling site-specific functionalization and PL. Dialkylated and hydroalkylated SWNTs were selectively synthesized. The ^{n}Bu-SWNTs-^{n}Bu and ^{n}Bu-SWNTs-H adducts of the (6,4), (6,5), (8,3), and (7,5) SWNTs that were separated using gel chromatography showed dominant E_{11}^{**} PL and E_{11}^{*} PL, respectively. The systematic assignments of the PL were performed based on the thermodynamic stability and transition energy of 1,2- and 1,4-adducts of SWNTs using DFT and TD-DFT calculations. It was shown that the steric hindrance of the added group and the *R* value, *i.e.*, mod(*n*-*m*, 3) in an (*n*,*m*) chiral nanotube are key factors that control the addition site and the magnitude of the local bandgap.

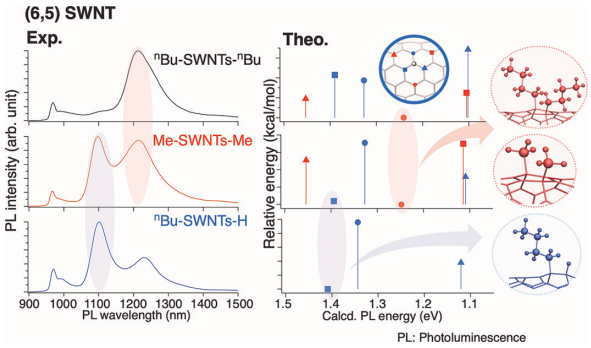

Figure 3. Control of near-IR photoluminescence (PL) of substituted SWNTs regarding E_{11}^{**} PL, and E_{11}^{*} PL.

References

1) T. Shiraogawa, G. Dall'Osto, R. Cammi, M. Ehara and S. Corni, *Phys. Chem. Chem. Phys.* **24**, 22768–22777 (2022).
2) 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, *Nat. Commun.* **13**, 4288 (2022).
3) Y. Maeda, R. Morooka, P. Zhao, D. Uchida, Y. Konno, M. Yamada and M. Ehara, *J. Phys. Chem. C* **127**, 2360–2370 (2023).

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.

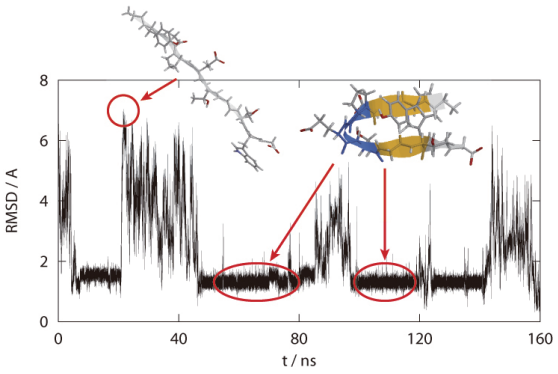

Figure 1. Time series of protein folding simulation.

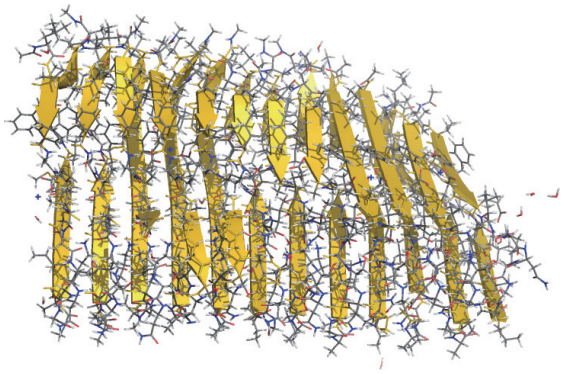

Figure 2. Snapshot of an Aβ amyloid fibril.

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).
- 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).
- 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).

1. Key Residue for Aggregation of Amyloid-β Peptides

Aβ mainly has two isoforms, Aβ40 and Aβ42. Although the difference between Aβ40 and Aβ42 is only two additional C-terminal residues, Aβ42 aggregates much faster than Aβ40. It is not known what role the C-terminal two residues play in accelerating aggregation. Since Aβ42 is more toxic, its oligomerization process needs to be clarified. Moreover, clarifying the differences between the oligomerization processes of Aβ40 and Aβ42 is essential to elucidate the key factors of oligomerization. To investigate the dimerization process, which is the early process of the oligomerization, Hamiltonian replica-permutation molecular dynamics simulations were performed for Aβ40 and Aβ42.[1] We identified the key residue, Arg5, for the Aβ42 dimerization, as shown in Figure 3. The two additional residues in Aβ42 allow the C-terminus to form a contact with Arg5, and this contact stabilizes β-hairpin. This β-hairpin promotes dimer formation with formation of intermolecular β-bridges. To approve this theoretical prediction, experiments on Aβ aggregations were also conducted. We confirmed that the aggregation of Aβ42 is remarkably suppressed by a mutation of Arg5. Moreover, mutation of Arg5 also suppresses the Aβ40 aggregation. It was found by analyzing the simulations that Arg5 is important for Aβ40 to form the intermolecular contacts. Thus, it was clarified that the role of Arg5 in the oligomerization process is changed by the two additional C-terminal residues.

The fact that we could predict the experimental results from the simulation results means that the differences seen in the formation of dimers make a difference in the formation of much larger aggregates, such as amyloid fibrils observed in experiments. Thus, it is essential to elucidate the process of small oligomer formation to fully understand the Aβ aggregation.

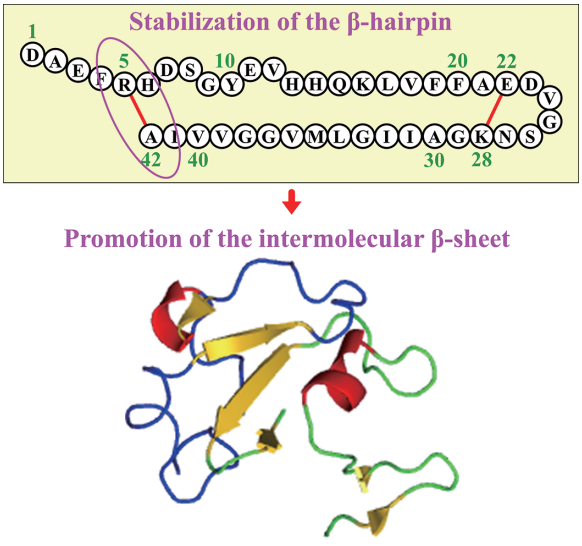

Figure 3. The key residue for the aggregation of amyloid-β peptides is Arg5, which stabilizes the β-hairpin structure and promotes the intermolecular β-sheet.

2. Ingenuity in Performing Replica Permutation: How to Order the State Labels for Improving Sampling Efficiency

Replica-exchange method (REM) is one of the generalized ensemble algorithms and is widely used for systems with many local minima, such as biomolecules. In this method, copies of the systems, call replicas, are prepared. The temperatures are excahnged between two replicas, as shown in Figure 4. As an advanced alternative to REM, the replica-permutation method (RPM) has been developed. In this method, all combinations of replicas and parameters are considered for parameter permutation, and a list of all the combinations is prepared. We reported that the temperature transition probability depends on how the list is created, especially in replica permutation with solute tempering (RPST).[2] We found that the transition probabilities decrease at large replica indices when the combinations are sequentially assigned to the state labels as in the originally proposed list. To solve this problem, we propose to modify the list by randomly assigning the combinations to the state labels. We performed molecular dynamics simulations of amyloid-β(16–22) peptides using RPST with the "randomly assigned" list (RPST-RA) and RPST with the "sequentially assigned" list (RPST-SA). The results show the decreases in the transition probabilities in RPST-SA are eliminated, and the sampling efficiency is improved in RPST-RA.

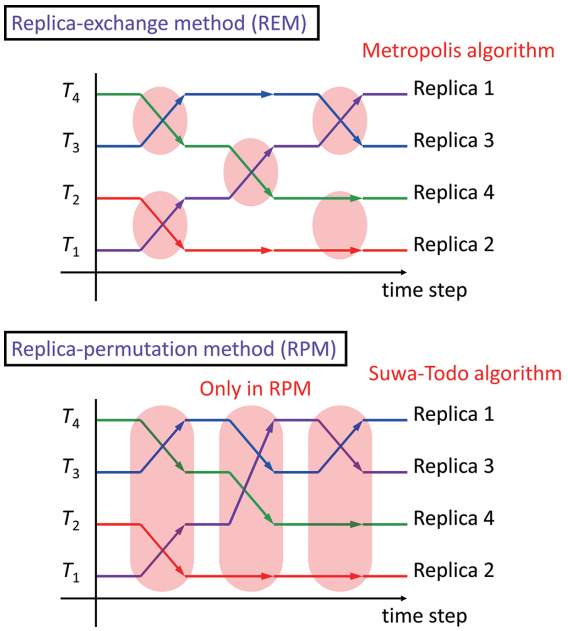

Figure 4. Schematic illustration of replica-exchange method (REM) and replica permutation method (RPM).

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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 an inwardly and outwardly open structure relative to the membrane. Our goal is to elucidate the mechanism of these elaborate and dynamic nanomachines created by nature at the atomic and molecular level, and to control their functions based on our findings.

We would like to understand the mechanism 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 functional dynamics, especially for a large system like typical biomolecular machines. Therefore, we have developed and applied methods such as coarse-grained modeling, enhanced sampling and importance 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 ATP required in the cell. It is composed of two rotary motors: F_o and F_1. F_o motor is embedded in the membrane and driven by proton gradient, while F_1 motor is driven by ATP hydrolysis reaction. We clarified how the rotation of F_1 motor is driven by a key chemical step, P_i release after 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 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 transition path sampling technique to capture the moment of the ion transports. The simulations predicted the mutation that can speed up the 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 mechanism obtained from simulations.[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 oxalate forms 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), which exists in the membrane of the bacterium, is responsible for oxalate uptake into and formate efflux out of the bacterium. 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 structure is in the occluded conformation with the bound oxalate.

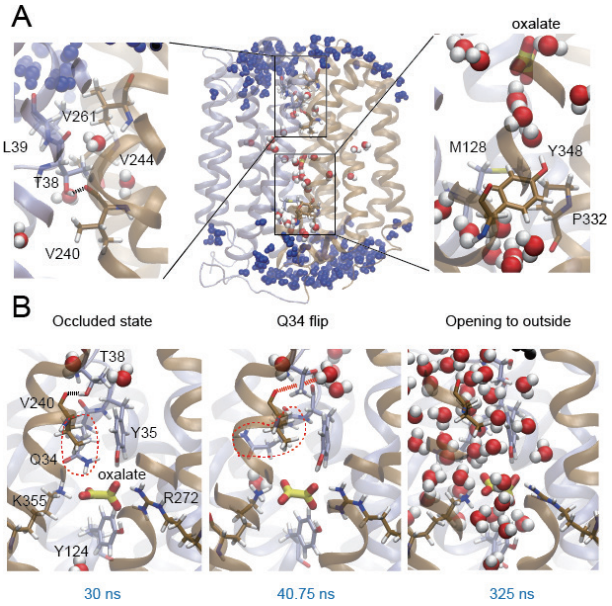

Figure 1. (A) The determined periplasmic and cytoplasmic gates. (B) The conformational transition from the occluded to the outward-open state.[3]

The atomistic MD simulation from the occluded conformation of OxlT and analysis of the water molecule density revealed the presence of gates above and below the substrate binding pocket that control the influx of water and substrate molecules.[3] The periplasmic gate consists of a hydrogen bond between Thr38-Val240 and a hydrophobic structure around it (Figure 1A left). The cytoplasmic gate consists of a hydrophobic structure composed of Met128, Pro332, and Tyr348 (Figure 1A right). Furthermore, in microsecond-scale simulations, OxlT undergoes a conformational change from the occluded conformation to the outward-open conformation.[3] The overall conformational change was preceded by a localized change in the flip of the Gln34 side chain at the oxalate binding site and the dissociation of the Thr38-Val240 hydrogen bond mentioned above, followed a few hundred nanoseconds later by the opening of the periplasmic gate to the open conformation (Figure 2B). Thus, the Gln34 side chain and the Thr38-Val240 hydrogen bond are considered to be "latches" for the periplasmic gate.

2. 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 progress of a reaction between two metastable states. We have developed a machine learning method to identify reaction coordinates based on the committor function. Assuming a linear combination of many collective variables, reaction coordinates are optimized via likelihood maximization or cross-entropy minimization.[4] From coefficients of the optimized reaction coordinates, we can also identify rate-limiting variables, which play an important role in transition state area. We have also applied a deep neural network and Explainable Artificial Intelligence (XAI) for this problem.[5]

3. Mechanism of Membrane Remodeling by F-BAR Protein Pacsin1

F-Bin/Amphiphysin/Rvs (F-BAR) domain proteins play essential roles in biological processes that involve membrane remodelling, such as endocytosis and exocytosis. Notably, Pacsin1 from the Pacsin/Syndapin subfamily has the ability to transform the membrane into various morphologies: Striated tubes, featureless wide and thin tubes, and pearling vesicles. We clarified the membrane curvature induction and sensing characteristics of Pacsin1 by combining all-atom (AA) and coarse-grained (CG) MD simulations.[6] By matching structural fluctuations between AA and CG simulations, a CG protein model called "Gō-MARTINI" was developed and optimized.[7] This model should prove useful for describing protein dynamics that are involved in membrane remodeling processes.

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Visiting Professors

Visiting Professor
SATO, Hirofumi *(from Kyoto University)*

Theoretical Study of Electronic Structure and Statistical Mechanics for Molecular Systems

Our research focuses on developing new quantum chemistry and statistical mechanics theories and analysing chemical phenomena in condensed matter systems consisting of polyatomic molecules.

(1) Based on biorthogonal second quantisation, we proposed a method to extract the resonance structures embedded in molecular orbital and the local spin structures. A geminal theory for a molecule's electronic structure is also proposed based on generalised electron pairing. (2) The statistical mechanics of molecular liquids is an analytical and systematic approach to understanding liquids' structure and thermodynamic properties. In addition to hybrid methods with quantum chemistry, we have developed many novel methods, including density functional theory and diffusion equations for polyatomic molecular systems. Recently, we proposed an ab initio theory for NMR chemical shifts based on the RISM-SCF-SEDD method. (3) The mechanisms of various chemical reactions and phenomena have been clarified at the molecular level. For example, the self-assembly process of the transition metal complex system was clarified.

Visiting Professor
YOSHIDA, Norio *(from Nagoya University)*

Theoretical Study of Chemical and Biological Processes in Solution

We are interested in the chemical and biological processes in solution with a particular focus on the role of solvents in these processes. Our group is studying the role of solvents in these processes based on the integral equation theory of molecular liquids. Recently, based on a multiscale hybrid method of integral equation theory and quantum chemical methods, we have elucidated the mechanism of pKa shift due to molecular recognition in solution. In addition, using a hybrid Monte Carlo framework, we developed a method for structural sampling of biomolecules in solution that satisfies the Hamiltonian based on integral equation theory.

Visiting Associate Professor
NOGUCHI, Hiroshi *(from University of Tokyo)*

Theoretical Study on Soft Matter and Biophysics

We study soft-matter physics and biophysics using theory and simulations. Our main targets are the structure formation of biomembrane and the dynamics of complex fluids under various conditions. This year, we investigated the shape transformation of membrane induced by curvature-inducing proteins. We estimated the anisotropic bending rigidity and spontaneous curvature of crescent curvature-inducing proteins from tethered-vesicle experimental data using a mean-field theory. Our coarse-grained simulations revealed that reaction waves of curvature-inducing proteins can induce large shape transformations, such as membrane budding and necking, that erase or divide the wave. Moreover, we demonstrated that the occasional disappearance of the waves can alter the pathway of wave propagation on a membrane network.