

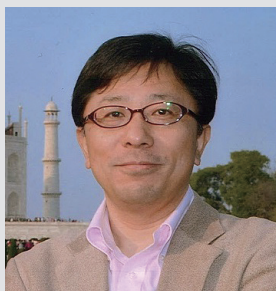
RESEARCH ACTIVITIES

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 Many-Body Molecular Systems

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



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Education

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

Professional Employment

1990 Technical staff, Institute for Molecular Science
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1998 Associate Professor, Nagoya University
2005 Professor, Institute for Molecular Science
2006 Professor, The Graduate University for Advanced Studies

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Keywords Reactions, Functions, Fluctuations

Many-body molecular systems, such as (supercooled) liquids and biomolecules, exhibit complex fluctuations. Furthermore, in these systems, various physical properties and biological functions are created and chemical reactions proceed under the fluctuations. We aim to elucidate the properties, functions, and reactions by investigating fluctuations and dynamics of the many-body molecular systems.

We have investigated fluctuations and dynamics of liquids by developing computational method for multi-dimensional nonlinear spectroscopy that can reveal detailed dynamical information not available from conventional linear spectroscopy. Consequently, we revealed the molecular origins of the ultrafast energy relaxation and time evolution of inhomogeneous fluctuations in liquid water. In supercooled liquids, rare and non-uniform structural changes, called dynamic heterogeneity, are induced by fluctuations. We elucidated the relationship between the lifetime of the dynamic heterogeneity and the fragility using the three-time correlation function of density fluctuations.

We study the molecular origin of anomalous properties of liquid water. We revealed that the anomalies of liquid water are related to the structural and dynamical instabilities hidden in the experimentally inaccessible region and the physical reason of the low glass transition of liquid water. Now we

investigate how rare but persistent structural relaxations proceed at low temperatures towards the glass transition temperature.

Complex conformational fluctuations and changes are also found in biomolecular systems. In addition, conformational dynamics are considered to be essential for biological functions. We examine the relationship between fluctuation and biomolecular function found in the robust circadian rhythm of the clock protein KaiC and the efficient excitation energy transfer in photosynthetic systems. We investigate the dynamic effects of enzymatic reactions and find the importance of prearranged states for the rare but persistent enzymatic reactions. Furthermore, we examine dynamic disorder in conformational changes of proteins at the molecular level.

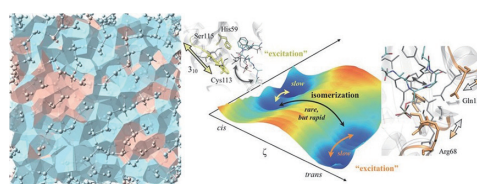


Figure 1. Snapshot of two-state model in supercooled water consisting of high- and low-density liquids (left) and schematic of 2D free energy surface for enzymatic reaction (right).

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. Multimeric Structure Enables the Acceleration of KaiB-KaiC Complex Formation Induced by ADP/ATP Exchange Inhibition¹⁾

Circadian clocks tick a rhythm with a nearly 24-hour period in a variety of organisms. In the clock proteins of cyanobacteria, KaiA, KaiB, and KaiC, known as a minimum circadian clock, the slow KaiB-KaiC complex formation is essential in determining the clock period. This complex formation, occurring when the C1 domain of KaiC hexamer binds ADP molecules produced by the ATPase activity of C1, is considered to be promoted by accumulating ADP molecules in C1 through inhibiting the ADP/ATP exchange (ADP release) rather than activating the ATP hydrolysis (ADP production). Significantly, this ADP/ATP exchange inhibition accelerates the complex formation together with its promotion, implying a potential role in the period robustness under environmental perturbations. However, the molecular mechanism of this simultaneous promotion and acceleration remains elusive because inhibition of a backward process generally slows down the whole process. In this article, to investigate the mechanism, we build several reaction models of the complex formation with the pre-binding process concerning the ATPase activity. In these models, six KaiB monomers cooperatively and rapidly bind to C1 when C1 binds ADP molecules more than a given threshold while stabilizing the binding-competent conformation of C1. Through comparison among the models proposed here, we then extract three requirements for the simultaneous promotion and acceleration: The stabilization of the binding-competent C1 by KaiB binding, slow ADP/ATP exchange in the binding-competent C1, and relatively fast ADP/ATP exchange occurring in the binding-incompetent C1 in the presence of KaiB. The last two requirements oblige KaiC to form a multimer. Moreover, as a natural consequence, the present models can also explain why the binding of KaiB to C1 reduces the ATPase activity of C1.

2. Vectorial Insertion of a β -Helical Peptide into Membrane: A Theoretical Study on Polytheonamide B²⁾

Spontaneous unidirectional, or vectorial, insertion of transmembrane peptides is a fundamental biophysical process for toxin and viral actions. Polytheonamide B (pTB) is a potent cytotoxic peptide with a $\beta^{6.3}$ -helical structure. Previous experimental studies revealed that the pTB inserts into the membrane in a vectorial fashion and forms a channel with its single molecular length long enough to span the membrane. Also, molecular dynamics simulation studies demonstrated that the pTB is prefolded in aqueous solution. These are unique features of pTB because most of the peptide toxins form channels through oligomerization of transmembrane helices. Here, we performed all-atom molecular dynamics simulations to examine the dynamic mechanism of the vectorial insertion of pTB, providing underlying elementary pro-

cesses of the membrane insertion of a prefolded single transmembrane peptide. We find that the insertion of pTB proceeds with only the local lateral compression of the membrane in three successive phases: “Landing,” “penetration,” and “equilibration” phases. The free energy calculations using the replica-exchange umbrella sampling simulations present an energy cost of ~ 4 kcal/mol at the membrane surface for the membrane insertion of pTB from bulk water. The trajectories of membrane insertion revealed that the insertion process can occur in two possible pathways, namely “trapped” and “untrapped” insertions; in some cases, pTB is trapped in the upper leaflet during the penetration phase. Our simulations demonstrated the importance of membrane anchoring by the hydrophobic N-terminal blocking group in the landing phase, leading to subsequent vectorial insertion.

3. Excited States of Chlorophyll *a* and *b* in Solution by Time-Dependent Density Functional Theory³⁾

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) S.-i. Koda and S. Saito, *PLoS Comput. Biol.* **18**, e1009243 (24 pages) (2022).
- 2) M. Kalathingal, T. Sumikama, S. Oiki and S. Saito, *Biophys. J.* **120**, 4786–4797 (2021).
- 3) 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 on Novel Physical Properties Arising from Many-Body Interaction

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Education

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Professional Employment

2010 Postdoctoral Fellow, Osaka University
2011 Special Postdoctoral Researcher, RIKEN
2013 Assistant Professor, The University of Tokyo
2015 Lecturer, The University of Tokyo
2019 Associate Professor, Institute for Molecular Science
Associate Professor, The Graduate University for Advanced Studies
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Awards

2008 L'Oréal–UNESCO Japan National Fellowships for Women in Science
2011 Best Poster Award in ISSS-6 Internal Symposium on Surface Science
2017 Young Scientist Award of the Physical Society of Japan
2019 The Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science and Technology
The Young Scientists' Prize
2020 The 1st Award for Early Career Women Scientists of the Japan Society of Vacuum and Surface Science
2021 The 2nd Fumiko Yonezawa Memorial Prize of the Physical Society of Japan

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Keywords Quantum Many-Body Interaction, Density Functional Theory, Quantum Field Theory

Quantum many-body interaction is a source of novel physical properties in condensed matters. In our group, we develop theoretical methods by combining quantum field theory and density functional theory, and carry out collaborative research with experimental groups. As specific targets, we focus on magnetism in nanostructure and energy dissipation.

For magnetism in nanostructure, we are interested in the Kondo effect and spin–orbit interaction. The Kondo effect arises from the interaction between the localized spin and conduction electrons, which forms a characteristic many-body state so-called the Kondo singlet state. The spin–orbit interaction originating from the relativistic effect constrains the magnetic moment direction to a specific direction. We investigate the possibility of novel physical phenomena induced by these interactions in the nanostructure and molecules on surfaces.

For energy dissipation, we focus on the effect of electron–

phonon interaction. The electron–phonon interaction is one of the most fundamental interactions in the condensed matter physics, and the quantitative evaluation in realistic materials is highly demanding. We adopt the ab-initio calculation to analyze the signal of electron–phonon coupling in surface spectroscopy and thermal properties in various kind of solids.

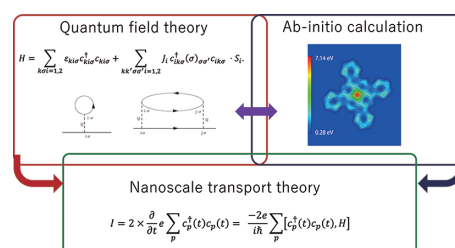


Figure 1. Schematic image of the theoretical method developed in our group.

Selected Publications

- E. Minamitani, N. Tsukahara, D. Matsunaka, Y. Kim, N. Takagi and M. Kawai, “Symmetry-Driven Novel Kondo Effect in a Molecule,” *Phys. Rev. Lett.* **109**, 086602 (2012).
- E. Minamitani, R. Arafune, N. Tsukahara, Y. Ohda, S. Watanabe, M. Kawai, H. Ueba and N. Takagi, “Surface Phonon Excitation on Clean Metal Surfaces in Scanning Tunneling Microscopy,” *Phys. Rev. B* **93**, 085411 (2016).
- R. Hiraoka, E. Minamitani, R. Arafune, N. Tsukahara, S. Watanabe, M. Kawai and N. Takagi, “Single-Molecule Quantum Dot as a

Kondo Simulator,” *Nat. Commun.* **8**, 16012 (2017).

- E. Minamitani, M. Ogura and S. Watanabe, “Simulating Lattice Thermal Conductivity in Semiconducting Materials Using High-Dimensional Neural Network Potential,” *Appl. Phys. Express* **12**, 095001 (2019).
- E. Minamitani, “Ab Initio Analysis for the Initial Process of Joule Heating in Semiconductors,” *Phys. Rev. B* **104**, 085202 (2021).
- E. Minamitani, T. Shiga, M. Kashiwagi and I. Obayashi “Topological Descriptor of Thermal Conductivity in Amorphous Si,” *J. Chem. Phys.* **156**, 244502 (2022).

1. Topology and Machine Learning Reveal a Hidden Relationship between Thermal Conductivity and Amorphous Structure

The structure of amorphous materials is characterized by the absence of long-range order (LRO) and the presence of some medium-range order (MRO) beyond the short-range order (SRO). Revealing the quantitative correlation between the structural and physical properties of amorphous materials remains a challenging task. Thermal conductivity is a fundamental physical property that shows unique behavior in amorphous materials owing to the strong interaction between lattice vibrations and disorders. The lack of LRO reduces the lattice thermal conductivity by several orders than that of a crystal with the same stoichiometry. The heat carriers, vibrational modes, in amorphous materials are generally classified into propagating and non-propagating modes. The former is exhibited in the low-frequency range and has characteristics similar to those of phonons in the crystal. In contrast, the latter carries heat in a diffusive manner rather than propagating energy as phonons do in the crystal. It is expected that the MRO affects the propagation and diffusion of these vibrational modes, and thus the thermal conductivity.

Previous studies indicated that determination of the atomic structure corresponding to the MRO and extraction of the correlation between the MRO and the lattice thermal conductivity is essential to precisely control the thermal properties of amorphous Si. However, these tasks remain challenging because determining the essential features of MRO from the traditional structural analysis is difficult, such as the pair distribution function and bond-orientation order analysis.

Recently, persistent homology, an emerging technique in the field of topological data analysis, has been employed to describe the atomic structures corresponding to MRO in SiO₂ glass, metallic glass, and amorphous ice. The advantage of persistent homology is that multiscale topological information can be extracted from complicated structures. For the analysis of persistent homology, we considered a growing sequence of network structures for given data points with different scale lengths defined by the filtration procedure. A schematic of the filtration procedure is shown in Figure 2. As can be seen, we considered spheres centered at the respective data points. Subsequently, the radius of each sphere gradually increases. The sequence of increases in radius is often referred to as “time.” At some radius, the spheres start to intersect with each other, and we set an edge between the centers of the spheres. When the edges form a closed ring, this corresponds to a topological feature called a “cycle.” As the radius further increases, the ring gets fully covered by circles. This is interpreted as the cycle converting into another class of topological features called a “boundary.” The topology of the data is represented by the pairs of birth and death times at which the cycle appears and is converted into a boundary. The two-dimensional visualization of birth and death time pairs is called a persistence diagram (PD).

In this study, using persistent homology, we constructed reliable descriptors for lattice thermal conductivity, reflecting the topological features of the MRO in amorphous Si.

A structural model of amorphous Si was generated via the

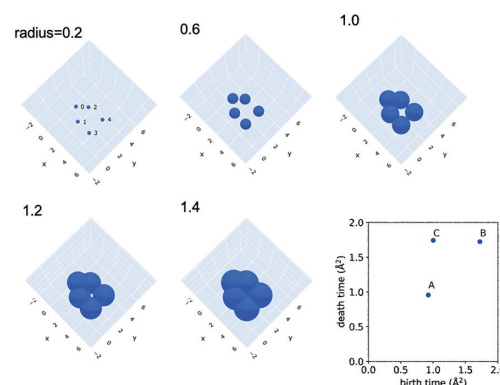


Figure 2. Schematic of the filtration procedure used to obtain a PD from data points.

melt–quench method using classical molecular dynamics (MD), where the system temperature was increased above the melting temperature and then gradually cooled to room temperature. The difference in structural characteristics was introduced by changing the cooling rate in the MD simulation from 10^{14} to 10^{11} K/s. We selected 570 snapshots from the equilibrated MD simulation after the melt–quench procedure, and the thermal conductivity mediated by non-propagating modes and the PD were evaluated for each structure.

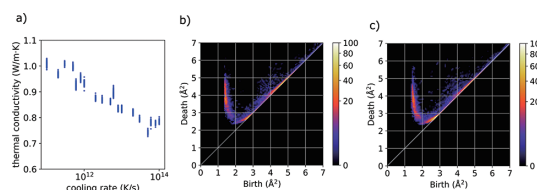


Figure 3. a) and b) Persistent diagrams for amorphous structure generate by the cooling rate of 10^{14} and 10^{11} K/s, respectively.

As shown in Figure 3, both thermal conductivity and PD depend on the cooling rates. Therefore, we constructed a descriptor of the topological features using the persistent image of the PD. We demonstrated that supervised training for the dataset of these descriptors and lattice thermal conductivities could achieve accurate predictions. In addition, from the inverse analysis by volume-optimal cycle, we determined the typical ring features correlated with the thermal conductivity and MRO.¹⁾ Our study demonstrates that the physical properties of amorphous Si can be predicted based on topological features. In addition, our results illustrate the hidden relationship between MRO and the physical properties of amorphous Si. This study could open an avenue for controlling material characteristics through the topology of nanostructures.

2. Other Ongoing Projects:

- Mechanical Properties in Amorphous Solids

Reference

- 1) E. Minamitani, T. Shiga, M. Kashiwagi and I. Obayashi, *J. Chem. Phys.* **156**, 244502 (2022).

Theoretical Studies of Chemical Dynamics in Condensed and Biomolecular Systems

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Education

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Professional Employment

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2008 JSPS Postdoctoral Fellow for Research Abroad, University of California, Berkeley
2010 Postdoctoral Fellow, Lawrence Berkeley National Laboratory
2012 Research Associate Professor, Institute for Molecular Science
2013 Fellow 2012–2013, Wissenschaftskolleg zu Berlin
2016 Professor, Institute for Molecular Science
Professor, The Graduate University for Advanced Studies
Visiting professor, Nagoya University

Awards

2015 10th Condensed-Matter Science Prize, Japan
2016 10th Young Scientist Award of the Physical Society of Japan
2016 18th Sir Martin Wood Prize
2017 The Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science and Technology
The Young Scientists' Prize
2020 JSPS Prize
2020 Japan Academy Medal

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AKABA, Atsuko

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 spec-

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

Quantum light, such as entangled photons, are promising resources for the development of new spectroscopic techniques. For example, non-classical correlations between entangled photons can be potentially exploited to enhance the precision of optical measurements beyond classical techniques or to extract matter information with simpler optical systems compared to conventional schemes. In this respect, the entangled photons may open new avenues for unambiguously extracting information about dynamic processes in complex molecules such as photosynthetic light-harvesting systems, in which multiple electronic states are present within a narrow energy range, from the congested spectra. However, to date, only a few theoretical studies have been reported on the application of entangled photons to time-resolved spectroscopic measurements. Hence, there is no comprehensive understanding of what non-classical states of light are suitable for implementing real-time observation of dynamical processes in condensed phases.

Here, we propose a novel time-resolved spectroscopy technique that selectively enhances specific signal contributions by harnessing the non-classical correlations between entangled photons generated via parametric down-conversion (PDC) pumped with a monochromatic laser. The key feature in the proposed technique is that the entanglement time, which is the hallmark of the non-classical photon correlations, works as a spectral filter in signal processing to selectively resolve a specific region of spectra, while it simultaneously offers a knob for controlling the accessible time region of dynamics in molecules. For demonstration purposes, we apply the proposed spectroscopic scheme to the Fenna-Matthews-Olson (FMO) pigment-protein complex from the photosynthetic green sulfur bacterium. The results show that the phase-matching functions of the PDC in the nonlinear crystals such as periodically poled KTiOPO_4 (PPKTP) crystal and $\beta\text{-BaB}_2\text{O}_4$ (BBO) crystal allow one to separately measure specific peaks of spectra in the FMO complex by tuning the entanglement time and the central frequencies of the entangled photons. It is also found that the spectral filtering can be implemented in the range of currently available entangled photon sources. Moreover, the results indicate that the spectral filter effects can be easily adjusted by changing nonlinear crystals and/or their properties because the spectral distribution of the phase-matching function strongly depends on the properties of the nonlinear crystal. Since, in addition to the BBO and PPKTP crystals considered in this study, there is a wide range of nonlinear crystals that have been used for PDC in the near-infrared and visible regions, the proposed technique is expected to be applicable not only to the FMO complex but also to other light-harvesting systems by finding an appropriate nonlinear crystal corresponding to the spectral range of the molecular system of interest. We thus anticipate that the proposed technique can be a useful tool for monitoring step-by-step energy transfer pathway in the light-harvesting systems by selectively extracting desired signal contributions from the congested spectra.¹⁾

2. Benefit of Coexistence of Chlorophyll *a* and *b* in Antenna of Photosystem II

Chlorophylls (Chls) in the photosystem II (PSII) play essential parts in the initial process of oxygenic photosynthesis, *i.e.*, the solar light is collected by Chls embedded in the light-harvesting complexes termed antenna, and then the excitation energy is transferred to Chls in the reaction center, where the charge separation takes place. The antenna includes two distinct types of Chls, Chl *a* and *b*, whereas the reaction center possesses a single type Chl *a*. As the transition energy of Chl *b* is higher than that of Chl *a*, the excitation energy flows from Chl *b* to Chl *a*. Hence, if all the pigments in the antenna are composed of Chl *b*, higher efficiency of the excitation energy transfer to the reaction center could be expected [H. Kim, *et al.*, *arXiv:2101.04848* (2021)]. Even though such an ‘all-*b*’ system would offer an advantage in photosynthesis, the naturally occurring antenna binds both Chls *a* and *b* throughout the green plants. The reason why the mixed Chl system is adopted in the antenna found in nature has yet to be understood clearly.

In this work, we investigated the role of Chl *a* existed in the antenna during the excitation energy transfer (EET). The rate constants of the EET within and between domains, each of which comprises strongly coupled Chls forming delocalized excited states, were calculated with the aid of the Redfield and generalized Förster theory. To discuss how the ratio κ of Chl *b* to *a* in the antenna affects the time evolution of the excitation energy distribution, we considered the hypothetical models of the PSII where κ was equal to or different from that in the natural PSII. The results show the quantum yield of the EET to the reaction center is improved with increasing κ , as expected. Moreover, it is found that in the case of the natural PSII, the excitation energy was localized at particular pigment-protein complexes in the antenna, termed CP26 and CP29, where the occurrence of non-photochemical quenching during the photoprotection was suggested in the previous study [T. K. Ahn, *et al.*, *Science* **320**, 794 (2008)]. The results indicate the natural PSII possesses the optimal structure not only for collecting the light energy into the reaction center but also for balancing the EET and the other processes, such as photoprotection.

3. Dynamics of the Coupled System Composed of Electrons and Anharmonic Lattice Vibrations in Solid

Anharmonicity of lattice vibrations is responsible for a large quantity of phenomena including thermal conductivity, structural phase transition, and so forth. Moreover, recent studies suggested lattice anharmonicity would have a dominant role in the carrier dynamics of some sort of soft semiconductors, *e.g.*, lead-based halide perovskites which exhibit novel optoelectronic properties. Here, we theoretically investigate the dynamics of the coupled systems composed of electrons and anharmonic lattice vibrations. We highlight the importance of the timescale difference between electron and lattice dynamics in determining the materials properties.

Reference

1) Y. Fujihashi *et al.*, to be submitted.

Theoretical Studies of Functional Molecular Systems and Heterogeneous Catalysts

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Education

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

Professional Employment

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

Awards

2009 APATCC Pople Medal
2009 QSCP Prize CMOA

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KANAZAWA, Yuki
INAI, Naoto

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HATORI, Atsuya

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SUGIMOTO, Yukari

Keywords

Quantum Chemistry, Photophysical Chemistry, Heterogeneous Catalysis

We develop the accurate electronic structure theories and investigate the photochemistry and catalysis theoretically. Currently, our focuses are following research subjects.

(1) Coupled cluster theory for excited states of large system

We develop the coupled cluster theories and their efficient computational algorithm aiming at large-scale calculations of molecular excited states. We also develop the basic theories and methodologies that are useful for fundamental chemistry and applied chemistry; for example, PCM SAC-CI method for effectively describing the solvent effects on excited states, CAP/SAC-CI method for locating metastable resonance states, general-R method for multiple excited states, and active-space method for efficiently describing complex electronic states.

(2) Heterogeneous catalysis

Metal nanoclusters supported by metal oxides or polymers achieve highly efficient catalytic reactions. We study the catalytic activity of these complex systems by means of quantum chemical calculations and informatics theories. We have elucidated the importance of the perimeter sites at hetero-junction of Ag nanocluster supported by alumina surface in terms of H₂ activation, the mechanism of methanol oxidation on Au:PVP and the unique coupling reactions on Au/Pd:PVP. We proceed these works in the project of Elements Strategy

Initiative for Catalysts and Batteries (ESICB).

(3) Photophysical chemistry

Our accurate electronic structure theories are applied to wide varieties of theoretical studies and sometimes in cooperation with experiments on the photophysical properties and excited-state dynamics of nano-bio systems like photo-electronic devices, photofunctional molecules, and biosensors. Target molecules include nanocarbons like fullerenes, near-IR absorbing phthalocyanine congeners, dye-sensitized solar cells, organometallic compounds for artificial photosynthesis, biological chemosensors, and bio-imaging probes.

(4) Theoretical spectroscopy

New quantum states, single-site and two-site double-core hole states, have been observed owing to the recent development of free electron laser and coincidence spectroscopy. We have proposed new chemical concept regarding the physical properties or relaxation processes of these quantum states in cooperation with experiments. We also perform accurate theoretical analysis for the state-of-the-art molecular spectroscopy; for example, the electronic transitions in the FUV region by ATR-FUV spectroscopy and the excited-state relaxation processes by pump–probe spectroscopy.

Selected Publications

- R. Cammi, R. Fukuda, M. Ehara and H. Nakatsuji, “SAC-CI Method in the Polarizable Continuum Model-Theory for Solvent Effect on Electronic Excitation of Molecules in Solution,” *J. Chem. Phys.* **133**, 024104 (24 pages) (2010).
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- M. Ehara and T. Sommerfeld, “CAP/SAC-CI Method for Calculating Resonance States of Metastable Anions,” *Chem. Phys. Lett.* **537**, 107–112 (2012).
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1. Aggregation-Induced Phosphorescence of Platinum(II) Complexes: The Role of the Metal–Metal Interactions on Emission Decay in the Crystalline State¹⁾

Discerning the origins of the phosphorescent aggregation-induced emission (AIE) from Pt(II) complexes is crucial for developing the broader range of photo-functional materials. In this work, we describe phosphorescence and deactivation processes of four class of AIE active Pt(II) complexes in the crystalline state based on experimental and theoretical investigation. These complexes show metal-to-ligand and/or metal–metal-to-ligand charge transfer emission in crystalline state with different heat resistance against thermal emission quenching. The calculated energy profiles including the minimum energy crossing point (MECP) between S_0 and T_1 states were consistent with the heat resistant properties, which provided the mechanism for AIE expression. Furthermore, we have clarified the role of metal–metal interaction in AIE by comparing two computational models.

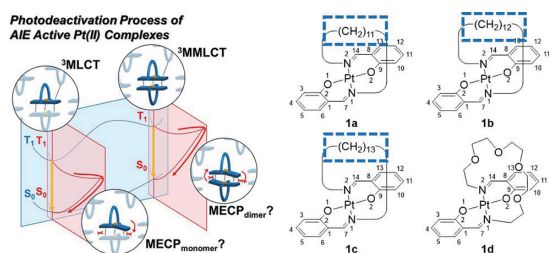


Figure 1. The mechanism of phosphorescent AIE by estimating the MECP of four Pt(II) complexes in crystalline state, along with an investigation of the role of metal–metal interaction on AIE.

2. Asymmetric Twisting of C-Centered Octahedral Gold(I) Clusters by Chiral N-Heterocyclic Carbene Ligation²⁾

Asymmetric induction of metal clusters by ligation of chiral ligands is intriguing in terms of the mechanism of chirality transfer and the stability of the resulting chiral structure. In this work, we report the asymmetric induction of C-centered hexanuclear CAu_6^I clusters into an asymmetrically twisted structure through monodentate, chiral benzimidazolylidene-based N-heterocyclic carbene (NHC) ligands. X-ray diffraction analysis revealed that the NHC-ligated CAu_6^I cluster was diastereoselectively twisted with directionally-selective, bond length expansion and contraction of the Au–Au contacts, and that the original cluster with high symmetry was transformed into an optically pure, asymmetric CAu_6^I cluster with C_1 symmetry. The circular dichroism (CD) spectroscopy confirmed that the asymmetrically twisted CAu_6^I structure was maintained even in solution. The TD-DFT calculations provided the detailed assignments of the CD spectrum and clarified the origin of the chiroptical properties of this cluster. Such asymmetric induction of configurationally stable metal clusters would greatly expand the molecular design possibilities of asymmetric catalysts and chiroptical materials by utilizing library chiral NHC ligands.

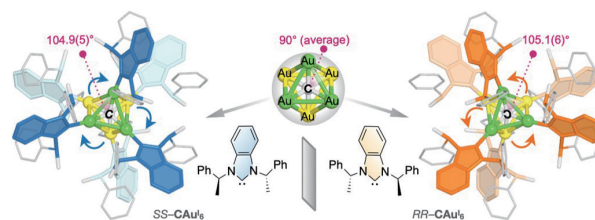


Figure 2. C-centered octahedral gold(I) clusters (CAu_6^I) monoligated by N-heterocyclic carbene (NHC) ligands. Asymmetrically twisted CAu_6^I core structures were induced by NHC ligands.

3. Enhanced Oxygen Reduction Activity of Size-Selected Platinum Subnanocluster Catalysts: Pt_n ($n = 3–9$)³⁾

Nanoclusters (NCs) are promising candidates to improve catalytic activity despite of the controversial size specificity, because the atomicity is a crucial parameter that determines the activity of platinum (Pt) NCs. In this work, we show the enhanced catalytic activity based on the charge redistribution in Pt sub-NCs containing three to nine Pt atoms (Pt_n ; $n = 3–9$) on a glassy carbon substrate. The sub-NCs show 1.6–2.2 times higher activity than the standard Pt/C catalysts with a Pt crystallite diameter of 2 nm. The geometric structures are identified using structure analyses by X-ray absorption fine structure spectroscopy and density functional theory, and the activity origin within the supported Pt sub-NCs is theoretically discussed from viewpoints of energetics for reaction intermediates in the electrochemical processes. It should be possible to use sub-NCs in future fuel cell technologies as an active catalyst with a high atomic efficiency.

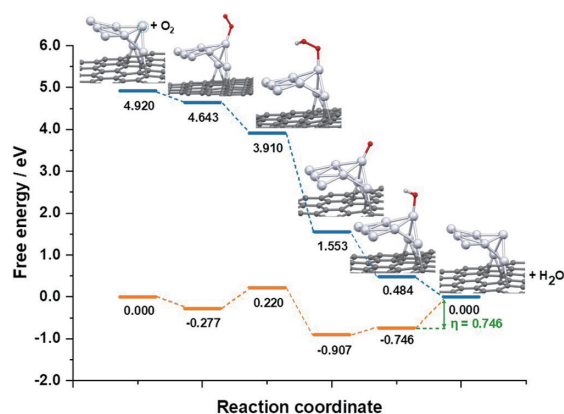


Figure 3. Oxygen reduction reaction (ORR) free energy diagrams for sequential reactions of Pt_8/Gr isomer between O_2 reactants and H_2O products with applied potentials of 0 V (blue) and 1.23 V (orange).

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Molecular Dynamics Simulations of Disease-Related Biomolecules

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Keywords Molecular Dynamics Simulation, Protein, Amyloid

Biomolecules such as proteins and peptides have complicated free-energy landscape with many local minima. The conventional canonical-ensemble molecular dynamics (MD) simulations tend to get trapped in a few of the local-minimum states. To overcome these difficulties, we have proposed new generalized-ensemble algorithms, such as 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.

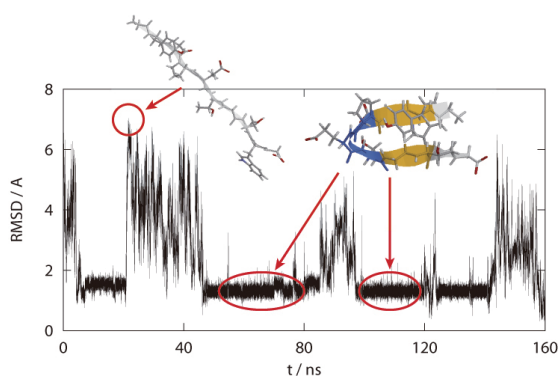


Figure 1. Time series of protein folding simulation.

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 ($A\beta$) peptides. To overcome these diseases, it is essential to understand the aggregate genesis and disruption of $A\beta$ peptides. We perform such MD simulations of oligomers and amyloid fibrils.

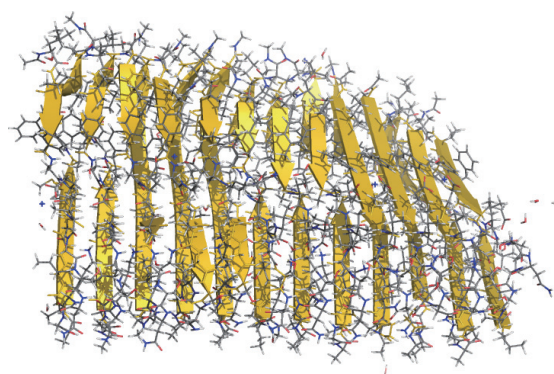


Figure 2. Snapshot of an $A\beta$ amyloid fibril.

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).
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1. Replica Permutation with Solute Tempering for Molecular Dynamics Simulation and Its Application to the Dimerization of Amyloid- β Fragments

We proposed the replica permutation with solute tempering (RPST)¹ by combining the replica-permutation method (RPM) and the replica exchange with solute tempering (REST), as in Figure 3. Temperature permutations are performed among more than two replicas in RPM, whereas temperature exchanges are performed between two replicas in the replica-exchange method (REM). The temperature transition in RPM occurs more efficiently than in REM. In REST, only the temperatures of the solute region, the solute temperatures, are exchanged to reduce the number of replicas compared to REM. Therefore, RPST is expected to be an improved method taking advantage of these methods. For comparison, we applied RPST, REST, RPM, and REM to two amyloid- β (16–22) peptides in explicit water. We calculated the transition ratio and number of tunneling events in the temperature space, and the number of dimerization events of amyloid- β (16–22) peptides. The results indicate that in RPST, the number of replicas necessary for frequent random walks in the temperature and conformational spaces is reduced compared to the other three methods. Additionally, we focused on the dimerization process of amyloid- β (16–22) peptides. The RPST simulation with a relatively small number of replicas shows that the two amyloid- β (16–22) peptides form the intermolecular antiparallel β -bridges due to the hydrophilic side-chain contact between Lys and Glu and hydrophobic side-chain contact between Leu, Val, and Phe, which stabilizes the dimer of the peptides.

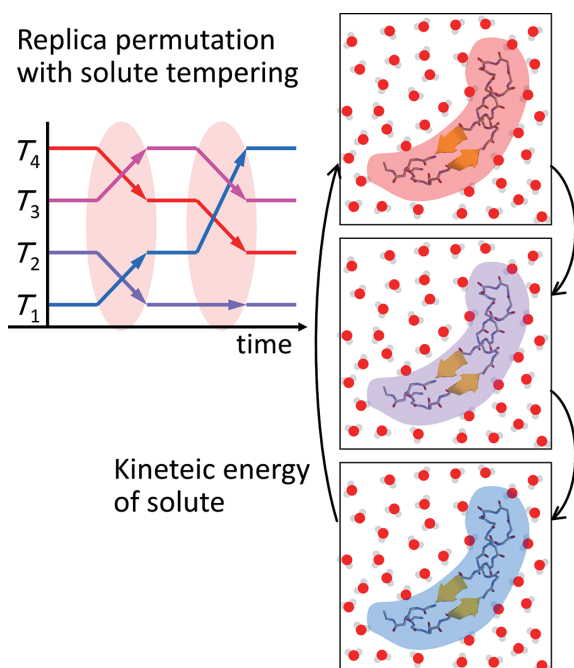


Figure 3. Schematic illustration of replica permutation with solute tempering. Temperatures in the solute region are permuted among more than two replicas.

2. Implementations of Replica-Permutation and Replica Sub-Permutation Methods into LAMMPS

The replica-permutation method (RPM) and the replica sub-permutation method (RSPM) have been proposed as improved alternatives to the replica-exchange method (REM). We implemented the RPM and RSPM in the canonical and isothermal-isobaric ensembles into an open-source classical molecular dynamics package, LAMMPS.² We applied the RPM and RSPM to a polyethylene chain in a vacuum and an alanine dipeptide in explicit water to test the implemented codes. We demonstrated that the RPM and RSPM by our codes achieved higher transition ratios of temperatures and faster convergence of physical quantities than the REM. We also validated that the RPM and RSPM generate statistical ensembles correctly.

3. Dimerization of α -Synuclein Fragments Studied by Isothermal-Isobaric Replica-Permutation Molecular Dynamics Simulation

Aggregates and fibrils of intrinsically disordered α -synuclein are associated with Parkinson's disease. Within a non-amyloid β component (NAC) spanning from 61st to 95th residues of α -synuclein, an 11-residue segment called NACore is an essential region for both fibril formation and cytotoxicity. Although NACore peptides alone are known to form aggregates and amyloid fibrils, the mechanisms of the aggregation and fibrillation remain unknown. We investigated the dimerization process of NACore peptides as the initial stage of the aggregation and fibrillation process by isothermal-isobaric replica-permutation molecular dynamics simulation.³ The simulation succeeded in sampling a variety of dimer structures. An analysis of secondary structure revealed that most of NACore dimer forms intermolecular β -bridges. In particular, more antiparallel β -bridges were observed than parallel β -bridges. We also found that intramolecular secondary structures such as α -helix and antiparallel β -bridge are stabilized in the pre-dimer state. However, we identified that the intermolecular β -bridges tend to form directly with no specific structure because the NACore peptides have a low propensity to form the intramolecular secondary structures.

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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_0 and F_1 . F_0 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.

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.

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- K. Okazaki and G. Hummer, “Phosphate Release Coupled to Rotary Motion of F_1 -ATPase,” *Proc. Natl. Acad. Sci. U.S.A.* **110**, 16468–16473 (2013).
- K. Okazaki and G. Hummer, “Elasticity, Friction, and Pathway of γ -Subunit Rotation in F_0F_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).

1. Mechanism of Na⁺/H⁺ Antiporter and Engineering of a Faster Transporter

Na⁺/H⁺ antiporters control pH and Na⁺ concentration in the cell by exchanging sodium ions and protons across lipid membranes. They belong to the cation/proton antiporter (CPA) superfamily, and prevail in all domains of life. The archaeal Na⁺/H⁺ antiporters PaNhaP and MjNhaP1 as well as human NHE1, which is linked to a wide spectrum of diseases from heart failure to autism and has no structure solved yet, are electroneutral antiporters of the CPA1 family, exchanging one proton against one sodium ion. As a model system in mechanistic studies of electroneutral Na⁺/H⁺ exchange, we studied the transport mechanism of PaNhaP.¹⁾

Na⁺/H⁺ antiporters use the gradient of either sodium ion or proton to drive the uphill transport of the other ion (Figure 1A). The conformational transition of the transporter makes the ion-binding site accessible from either side of the membrane in the alternating manner. For PaNhaP, the inward-open conformation was obtained by X-ray crystallography, while the outward-open conformation is not known experimentally. We modelled the outward-open conformation by MDFF flexible fitting to the low-resolution outward-open structure of the homologous MjNhaP1 from cryo-EM, followed by the long equilibrium MD simulations. It was shown that the transporter domain moves ~3.5 Å in the direction normal to the membrane to take the outward-open state.

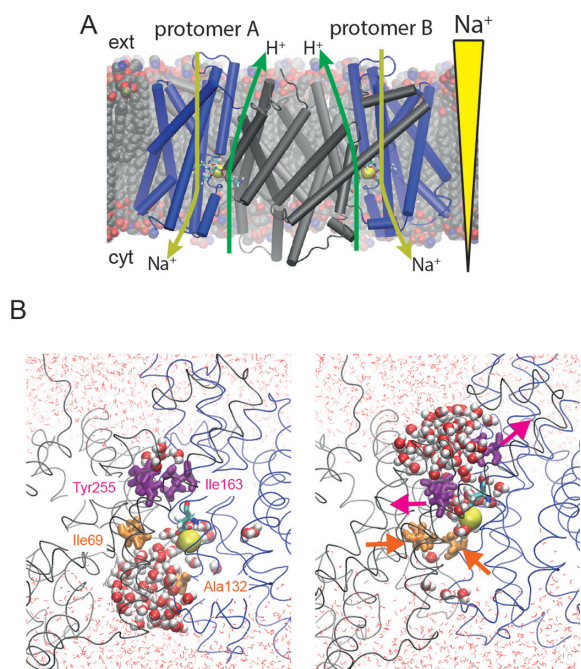


Figure 1. (A) PaNhaP dimer structure. (B) The outside (purple) and inside (orange) gates found in the transition path simulations.

By applying the transition path sampling technique, we sampled unbiased transition paths between the inward- and outward-open states. In analysis of the transition paths, we found hydrophobic gates above and below the ion-binding site, which open and close in response to the domain motions (Figure 1B). From the reaction coordinate analysis, it was

shown that open-close motion of the outside gate (Ile163-Tyr255) is a rate-limiting step of the alternating-access conformational change. Based on this result, we weakened the outside gate by mutating the residues to both alanine. It was expected that this mutation lowers the barrier and makes the ion transport faster. It was confirmed by experiments that the ion-transport speed of the mutant is indeed twice faster than the wild-type transporter.

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.²⁾ 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.³⁾

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.⁴⁾ By matching structural fluctuations between AA and CG simulations, a CG protein model called “Gō-MARTINI” was developed and optimized.⁵⁾ The 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 theories in quantum chemistry and statistical mechanics and on 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 computations and the local spin structures. (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. The phenomena at the electrode interface were systematised based on molecular dynamics simulation.



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, we have developed an accurate pKa prediction method for molecules in solution based on a hybrid method of integral equation theory and quantum chemical methods. Related to the method, in collaboration with the Institute for Molecular Science, we are developing an efficient structural sampling method for the pH-dependent protonation state of dissociative amino acid residues in proteins. We are also developing a novel integral equation theory that takes into account the electronic polarization of the solvent and applies it to electron-transfer reactions in solution.



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 using mean-field theory and coarse-grained membrane simulations. We clarified the difference between laterally anisotropic and isotropic proteins in the curvature sensing and generation. In particular, the sensing curvature of the anisotropic proteins depends on the protein density, whereas that of the isotropic proteins is constant. Traveling waves of chemical reactions containing curvature-inducing proteins change the membrane shapes and vice versa. Moreover, we investigated cavitation and bubble oscillation in sound-wave propagation using massively parallel simulations.