RESEARCH ACTIVITIES

Theoretical and Computational Molecular Science

It is our goal to develop new theoretical and computational methods based on quantum and statistical mechanics to predict and understand structures, chemical reactions, and functions of molecules in condensed phases including nano- and biomolecular-systems.

Theoretical Studies of Reactions, Functions, and Fluctuations in Many-body Molecular Systems

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

SAITO, Shinji
Professor
[shinji@ims.ac.jp]

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

Member

Assistant Professor
  MORI, Toshifumi
  KODA, Shin-ichi
Post-Doctoral Fellow
  MATSUMURA, Yoshihiro
  ANDO, Yoshimichi
Graduate Student
  KALATHINGAL, Mahroof
  MORITSUGU, Norifumi
Secretary
  SUZUKI, Sayuri

Keywords Heterogeneous Dynamics, Reactions, Functions

In many-body molecular systems, such as liquids and bio-molecular systems, nonlinear intermolecular interactions induce complicated motions. The motions are spatially and temporally heterogeneous, and yield static, dynamic, and thermodynamic properties of the systems. The spatiotemporal heterogeneous motions known as dynamic heterogeneity are found in super-cooled liquids. In bio-molecular systems, which show slow conformational fluctuations, time-dependent reaction rates are often observed. Furthermore, biological functions are produced in complicated fluctuations with a wide range of timescales. Therefore, understanding of spatiotemporal heterogeneous dynamics is essential to the elucidation of the structure, reactions, functions, and fluctuations in these complicated systems.

We have investigated inter- and intra-molecular dynamics of water by using third-order nonlinear spectroscopy which can provide the detailed dynamics that are not available from conventional spectroscopy. We have revealed the molecular mechanism of ultrafast energy relaxation, which is one of dynamical features of water, is caused by the nonlinear strong coupling between the libration motion and other intra- and inter-molecular vibrational motions.

We have also investigated heterogeneous dynamic of supercooled liquids. In particular, we have quantified the lifetime of dynamic heterogeneity by introducing the three-time correlation function of density fluctuation. We have found that the temperature dependence of lifetime of dynamic heterogeneity obtained from the three-time correlation functions is very sensitive to the fragility, that is the three-time correlation function is sensitive to the configurational entropy.

We have also revealed the molecular origin of anomalous temperature dependence of isobaric specific heat of water by examining the so-called complex specific heat. Recently, we have investigated the structure and dynamics of deeply super-cooled water. We have found the new dynamic transitions due to the instability of high- and low-density clusters in waters and also deciphered a crucial role of specific hydrogen-bond defects in persistent structural relaxations involved in low glass transition of water.

These days, we examine complicated conformational fluctuations of proteins by using the ideas of stochastic theory. We also investigate how chemical reactions and glass transitions proceed at the molecular level and how biological functions and thermal properties of liquids are generated under complicated fluctuations with a wide range of timescales.

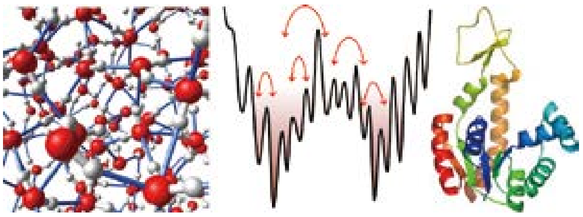


Figure 1. Schematic figure of rugged energy landscape (center) in supercooled water (left) and adenylate kinase (right).

Selected Publications

- T. Yagasaki and S. Saito, *Annu. Rev. Phys. Chem.* **64**, 55–75 (2013).
- K. Kim and S. Saito, *J. Chem. Phys. (Special Topic on Glass Transition)* **138**, 12A506 (12 pages) (2013).
- S. Saito, I. Ohmine and B. Bagchi, *J. Chem. Phys.* **138**, 094503 (7 pages) (2013), S. Saito, B. Bagchi and I. Ohmine, *J. Chem. Phys.* **149**, 124504 (8 pages) (2018).
- J. Ono, S. Takada and S. Saito, *J. Chem. Phys. (Special Topic on Multidimensional Spectroscopy)* **142**, 212404 (13 pages) (2015).

1. Conformational Excitation and Non-Equilibrium Transition Facilitate Enzymatic Reactions: Application to Pin1 Peptidyl-Prolyl Isomerase[1)]

Conformational flexibility of proteins is essential for protein function and enzyme catalysis. Yet, how proteins' conformational rearrangements and dynamics contribute to the chemical step of enzyme catalysis has remained highly controversial over decades. In order to unravel protein's role in enzyme catalysis, it is necessary to understand the static and dynamic mechanisms of enzyme catalysis simultaneously. In this respect, here we study Pin1 peptidyl-prolyl isomerase, and reveal the structural and dynamic aspects of catalytic isomerization step in molecular detail. From the static and fully-equilibrium perspective, the hydrogen bond interactions within Pin1 as well as between Pin1 and ligand are found to rearrange along the minimum free energy path of isomerization. In sharp contrast, the transition dynamics reveal that isomerization transitions are very rapid; slow protein conformational rearrangements cannot simultaneously occur with the isomerization reaction, and the reaction instead proceeds in a non-equilibrium manner. We further reveal that distinctive protein conformational rearrangements and hydrogen bonds, necessary to stabilize the transition state, need to be prepared a priori, *i.e.* as a conformational excited state within the reactant equilibrium. The present results reveal that the catalytic isomerization reaction does not occur as a simple thermal activation from the equilibrium directly to the transition state, indicating the importance of protein conformational flexibility and the presence of favorable conformations for the isomerization reactions. The current findings add a novel perspective of the Pauling's view on the enzymatic reactions in which the reactions proceed thermally from reactants to stabilized transition state and products.

2. A Reaction Model of the Cyanobacterial Circadian Rhythm Considering the Interplay among Multiple Domain-Specific Conformational Changes of KaiC[2)]

The clock proteins of cyanobacteria KaiABC constitute a biological clock with a temperature-compensated circadian period. KaiC forms a homo-hexamer with the two ring-shaped domains, C1 and C2, which allosterically communicate each other to generate the circadian rhythm. Experiments have found that several conformational changes of C1 and/or C2 are involved in the communication. However, detailed interplay among them remains elusive. We propose a mathematical model explicitly considering the interplay among the multiple domain specific conformational changes. In this model, the whole process, where the chemical reactions of ligands induce the (dis) assembly of KaiA and KaiB via the conformational changes, is represented only by the rate equations of them without any effective simplification. We show that the present model with automatically optimized rate or equilibrium constants can qualitatively reproduce various experimental data including temperature dependence of phosphorylation oscillation and ATPase activity. We also discuss a possible mechanism of the temperature compensation of period in association with the interplay among the domain-specific conformational changes, and find that some conformational changes induced by the slow and temperature-compensated ATP hydrolysis in C1 make the duration of phosphorylation temperature-compensated.

3. Theoretical Approach to Dynamical Disorder of Chemical Processes: Application to Bovine Pancreatic Trypsin Inhibitor Protein[3)]

Chemical processes in many-body molecular systems proceed under thermal fluctuations over wide spatiotemporal scales. One example is the conformational dynamics of proteins, which is highly heterogeneous and closely related to their functions. Although the dynamical disorder model has been introduced to characterize and understand the process correlated with dynamical fluctuations, the molecular aspects are not well established. Recent achievements in single-molecule spectroscopy and ultralong-time molecular dynamics simulation enabled us to access rich time series data with the molecular details and encouraged us to explore the theoretical framework for the single molecule kinetics. In this study, we develop the analytical framework for the time series data based on the theory of stochastic process, to clarify the dynamical correlations of state transition processes. The framework is applied to the 1ms-length molecular dynamics simulation of the conformational dynamics of bovine pancreatic trypsin inhibitor protein in aqueous solutions. Conformational states can be detected as isomers of dihedral angles in the vicinity of a disulfide bond; experimentally three states are observed and several other transient states are also found in the simulations. The present method developed in this study can decipher that the transient states are dynamically coupled with the transitions between the three states, although complex behaviors are averaged out in experiments.

References

1) T. Mori and S. Saito, to be submitted.
2) S. Koda and S. Saito, to be submitted.
3) Y. Matsumura and S. Saito, to be submitted.

Advanced Electronic Structure Theory in Quantum Chemistry

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

YANAI, Takeshi
Associate Professor
(–March, 2018)
[yanait@ims.ac.jp]

Education

1997	B.S. The University of Tokyo
2001	Ph.D. The University of Tokyo

Professional Employment

2001	Postdoctoral Fellow, The University of Tokyo
2002	Postdoctoral Fellow, Pacific Northwest National Laboratory
2002	Postdoctoral Fellow, Oak Ridge National Laboratory
2005	Postdoctoral Fellow, Cornell University
2007	Associate Professor, Institute for Molecular Science Associate Professor, The Graduate University for Advanced Studies
2018	Professor, Nagoya University

Awards

2008	Chemical Physics Letters Most Cited Paper 2003-2007 Award
2009	The Wiley-International Journal of Quantum Chemistry Young Investigator Award
2013	Laureate, International Academy of Quantum Molecular Science
2013	Japan Society of Molecular Science
2017	Pople Medal of Asia-Pacific Conference of Theoretical and Computational Chemistry

Member

IMS Research Assistant Professor
SAITOW, Masaaki

Post-Doctoral Fellow
XIONG, Xiao-Gen

Secretary
YAMADA, Mariko

Keywords Electronic Structure Theory, Quantum Chemistry, Computational Chemistry

Computational quantum chemistry, that is, practicing quantum chemical theory using computers, is now considered to be a powerful means to provide detailed analysis of chemical phenomena. The focus of our group is to develop methods and algorithms of molecular electronic structure calculations, which are capable of supplying electronic-level interpretation and reliable prediction of chemical characters, reactivity, energetics, and spectroscopic properties of molecular systems. Also, we are interested in applying the methods to challenging chemical systems. Recently, we have developed advanced multireference methods to describe highly-correlated many-electron wavefunction, which cannot be qualitatively accounted for with mean-field or one-electron theory (*e.g.*, density functional theory). The multireference wavefunction need be represented with a quantum superposition of multiple electron configurations; however, this gives rise to a high computational expense because the degree of the superposition is in general exponentially dependent on the system size. We approach the multireference problems using the density matrix renormalization group (DMRG), which is originally a method of condensed matter physics to solve strong correlation phenomena in physical models. We developed an efficient implementation for adapting DMRG to quantum chemical calculation, in which the DMRG is exploited to describe static correlation in combination with the complete active space (CAS) model. Our DMRG-based methods have shown to be capable of handling very large correlation space, which far exceeds the limitation of conventional methods. We have further introduced a scheme to additively account for dynamic correlation on top of active-space DMRG wavefunction. Using these methods, we carried out chemical applications to multireference electronic systems, ranging from organic material molecules, such as radicals of graphene nanoribbons, to transition metal complexes, such as tetranuclear manganese cluster.

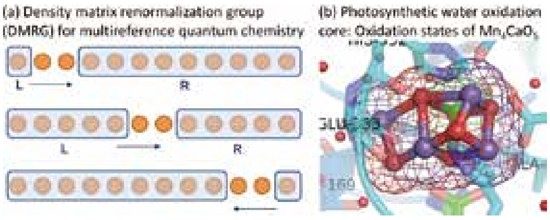


Figure 1. (a) Algorithm of density matrix renormalization group (DMRG) and (b) Its application to manganese cluster.

Selected Publications

- Y. Kurashige and T. Yanai, "High-Performance *Ab Initio* Density Matrix Renormalization Group Method: Applicability to Large-Scale Multireference Problems for Metal Compounds," *J. Chem. Phys.* **130**, 234114 (21 pages) (2009).
- W. Mizukami, Y. Kurashige and T. Yanai, "More π Electrons Make a Difference: Emergence of Many Radicals on Graphene Nanoribbons Studied by *Ab Initio* DMRG Theory," *J. Chem. Theory Comput.* **9**, 401–407 (2013).
- Y. Kurashige, G. K-L. Chan and T. Yanai, "Entangled Quantum Electronic Wavefunctions of the Mn_4CaO_5 Cluster in Photosystem II," *Nat. Chem.* **5**, 660–666 (2013).

1. Multistate Complete Active Space Second Order Perturbation Theory Based on Density Matrix Renormalization Group Reference States[1)]

We present the development of the multistate multireference second-order perturbation theory (CASPT2) with multi-root references, which are described using the density matrix renormalization group (DMRG) method to handle a large active space. The multistate first-order wave functions are expanded into the internally contracted (IC) basis of the single-state single-reference (SS-SR) scheme, which is shown to be the most feasible variant to use DMRG references. The feasibility of the SS-SR scheme comes from two factors: First, it formally does not require the fourth-order transition reduced density matrix (TRDM); and second, the computational complexity scales linearly with the number of the reference states. The extended multistate (XMS) treatment is further incorporated, giving suited treatment of the zeroth-order Hamiltonian despite the fact that the SS-SR based IC basis is not invariant with respect the XMS rotation. In addition, the state-specific fourth-order reduced density matrix (RDM) is eliminated in an approximate fashion using the cumulant reconstruction formula, as also done in the previous state-specific DMRG-cu(4)-CASPT2 approach. The resultant method, referred to as DMRG-cu(4)-XMS-CASPT2, uses the RDMs and TRDMs of up to third-order provided by the DMRG calculation (**Figure 2**). The multistate potential energy curves of the photoisomerization of diarylethene derivatives with CAS(26e,24o) are presented to illustrate the applicability of our theoretical approach (**Figure 3**).

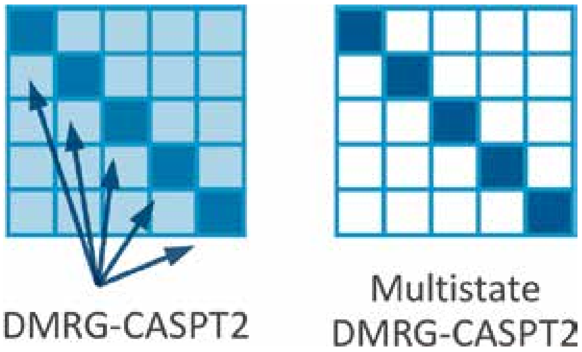
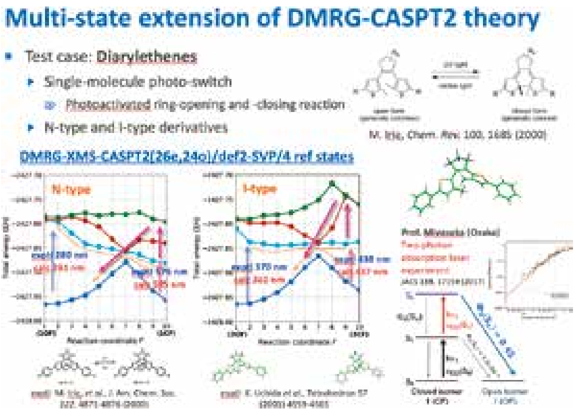


Figure 2. Development of multistate multireference perturbation theory with density matrix renormalization group references.


Multi-state extension of DMRG-CASPT2 theory

- Test case: Diarylethenes
  - Single-molecule photo-switch
    - Photoactivated ring-opening and -closing reaction
  - N-type and I-type derivatives

M. Irie, Chem. Rev. 100, 1685 (2000)

DMRG-XMS-CASPT2(26e,24o)/def2-SVP/4 ref states

Figure 3. Application of DMRG-XMS-CASPT2 theory for studying potential energy curves of S_0–S_3 states of two types of diarylethene derivatives with use of large active space, CAS(26e,24o), considering four reference states.

2. Robust and Efficient Relativistic Complete Active Space Self-Consistent Field[2)]

We report a highly efficient algorithm using density fitting for the relativistic complete active space self-consistent field (CASSCF) method, which is as efficient as, but significantly more stable than, the algorithm previously reported. Our algorithm is based on the second-order orbital update scheme with an iterative augmented Hessian procedure, in which the density-fitted orbital Hessian is directly contracted to the trial vectors. Using this scheme, each microiteration is made less time consuming than one Dirac–Hartree–Fock iteration, while macroiteration converges quadratically. In addition, we show that the CASSCF calculations with the Dirac–Gaunt and Dirac–Breit interactions can be sped up by means of approximate orbital Hessians computed with the Dirac–Coulomb interaction. It is demonstrated that our algorithm can also be applied to systems under an external magnetic field, for which all of the molecular integrals are computed using gauge-including atomic orbitals.

References

1) T. Yanai, M. Saitow, X.-G. Xiong, Y. Kurashige, J. Chalupský, S. Guo and S. Sharma, *J. Chem. Theory Comput.* **13**, 4829–4840 (2017).

2) R. D. Reynolds, T. Yanai and T. Shiozaki, *J. Chem. Phys.* **149**, 014106 (2018).

Award

SAITOW, Masaaki; 2017 Molecular Physics Early Career Researcher Prize.

Theoretical Studies of Chemical Dynamics in Condensed and Biomolecular Systems

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

ISHIZAKI, Akihito
Professor
[ishizaki@ims.ac.jp]

Education

2008	D.Sc. Kyoto University

Professional Employment

2006	JPSP Research Fellow, Kyoto University
2008	JPSP 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	Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science and Technology The Young Scientists' Prize

Member

Assistant Professor
NGUYEN, Thanh Phuc

Post-Doctoral Fellow
KATO, Akihito
FUJIHASHI, Yuta

Secretary
AKABA, Atsuko

Keywords Quantum Dissipative Systems, Energy/Charge Transfer Dynamics, Photosynthetic Light Harvesting

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. Quantum dynamics of energy/charge transfer dynamics in condensed phase molecular systems such as protein environments are remarkable examples of such phenomena.

Photosynthetic conversion of the energy of sunlight into its chemical form suitable for cellular processes involves a variety of physicochemical mechanisms. The conversion starts with the absorption of a photon of sunlight by one of the light-harvesting pigments, followed by transfer of electronic excitation energy to the reaction center, where charge separation is initiated. At low light intensities, surprisingly, the quantum efficiency of the transfer is near unity. A longstanding question in photosynthesis has been the following: How does light harvesting deliver such high efficiency in the presence of disordered and fluctuating dissipative environments? Why does not energy get lost? At high light intensities, on the other hand, the reaction center is protected by regulation mechanisms that lead to quenching of excess excitation energy in light harvesting proteins. The precise mechanisms of these initial steps of photosynthesis are not yet fully elucidated from the standpoint of molecular science. Particularly, recent observations of long-lived beating phenomena in two-dimensional electronic spectra of photosynthetic pigment-protein complexes stimulated a huge burst of activity in an interdisciplinary community of molecular science and quantum physics.

Selected Publications

- A. Ishizaki and Y. Tanimura, "Quantum Dynamics of System Strongly Coupled to Low-Temperature Colored Noise Bath: Reduced Hierarchy Equations Approach," *J. Phys. Soc. Jpn.* **74**, 3131–3134 (2005).
- A. Ishizaki and G. R. Fleming, "Unified Treatment of Quantum Coherent and Incoherent Hopping Dynamics in Electronic Energy Transfer: Reduced Hierarchy Equation Approach," *J. Chem. Phys.* **130**, 234111 (10 pages) (2009).
- A. Ishizaki and G. R. Fleming, "Theoretical Examination of Quantum Coherence in a Photosynthetic System at Physiological Temperature," *Proc. Natl. Acad. Sci. U.S.A.* **106**, 17255–17260 (2009).
- A. Ishizaki, T. R. Calhoun, G. S. Schlau-Cohen and G. R. Fleming, "Quantum Coherence and Its Interplay with Protein Environments in Photosynthetic Energy Transfer," *Phys. Chem. Chem. Phys.* **12**, 7319 (2010). [Invited perspective article]
- 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).

1. Control of Excitation Energy Transfer in Condensed Phase Molecular Systems by Floquet Engineering

Excitation energy transfer (EET) is one of the most important processes in both natural and artificial chemical systems including, for example, photosynthetic complexes and organic solar cells. The EET rate, however, is strongly suppressed when there is a large difference in the excitation energy between the donor and acceptor molecules. We have demonstrated both analytically and numerically that the EET rate can be greatly enhanced by periodically modulating the excitation energy difference. The enhancement of EET by using this Floquet engineering, in which the system's Hamiltonian is made periodically time-dependent, is found to be efficient even in the presence of strong fluctuations and dissipations induced by the coupling with a huge number of dynamic degrees of freedom in the surrounding molecular environments. The shift of the optimal driving frequency as moving from the homogeneous to the inhomogeneous broadening limits can be used to probe the nuclear motion dynamics of the environment.1)

2. Control of Quantum Dynamics of Electronic Excitation Transfer in Molecular Loop Structures: Spontaneous Breaking of Chiral Symmetry

Manipulation of quantum systems is the basis for many promising quantum technologies. How quantum mechanical principles can be used to manipulate dynamics of quantum dissipative systems is, however, still elusive because of strong decoherence effects arising from the interaction with the surrounding environment. We have demonstrated that electronic excitation transfer dynamics in molecular loop structures can be manipulated with the use of the Floquet engineering, in which the Franck-Condon transition frequency is temporally modulated in a periodic manner. Despite strong dephasing, the system's dynamics spontaneously breaks the chiral symmetry of the loop in a controllable fashion, followed by the generation of a steady-state current of electronic excitation. The breaking of chiral symmetry and the consequent controllable unidirectional flow of electronic excitations could be employed to construct functional molecular circuits for energy transport.2)

3. Non-Markovian Quantum-Classical Ratchet for Ultrafast Long-Range Electron–Hole Separation in Condensed Phases

In organic photovoltaic systems, a photogenerated molecular exciton in the donor domain dissociates into a hole and an electron at the donor–acceptor heterojunction, and subsequently separates into free charge carriers that can be extracted as photocurrents. The recombination of the once-separated electron and hole is a major loss mechanism in photovoltaic systems, which controls their performance. Hence, efficient photovoltaic systems need built-in ratchet mechanisms, namely, ultrafast charge separation and retarded charge recombination. In order to obtain insight into the internal working of the experimentally observed ultrafast long-range charge separation and protection against charge recombination, we theoretically investigate a potential ratchet mechanism arising from the combination of quantum delocalization and its destruction by performing numerically accurate quantum-dynamics calculations on a model system. We demonstrate that the non-Markovian effect originating from the slow polaron formation strongly suppresses the electron-transfer reaction back to the interfacial charge-transfer state stabilized at the donor–accepter interface and that it plays a critical role in maintaining the long-range electron–hole separation.3)

4. Intramolecular Vibrations Complement the Robustness of Primary Charge Separation in the Photosystem II Reaction Center

The energy conversion of oxygenic photosynthesis is triggered by primary charge separation in proteins at the photosystem II (PSII) reaction center (RC). Several time-resolved spectroscopic studies have reported that the primary charge separation in the PSII RC take place on subpicosecond time scale. However, it is one order of magnitude faster than the time constant of the charge separation starting from the special pair in the well-investigated purple bacterial RC, despite similarities in their arrangement of the pigments. As the coupling strengths between electron donors and acceptors are usually thought to be on the order of tens of wavenumbers, the precise mechanisms that enable subpicosecond charge separation in the PSII RC are to a large extent unknown.

To address the above question, we investigated the impacts of the protein environment and intramolecular vibrations on primary charge separation at the PSII RC. This was accomplished by combining the quantum dynamic theories of condensed phase electron transfer with quantum chemical calculations to evaluate the vibrational Huang-Rhys factors of chlorophyll and pheophytin molecules. We reported that individual vibrational modes play a minor role in promoting charge separation, contrary to the discussion in recent publications. Nevertheless, these small contributions accumulate to considerably influence the charge separation rate, resulting in subpicosecond charge separation almost independent of the driving force and temperature. We suggested that the intramolecular vibrations may complement the robustness of the charge separation in the PSII RC against the inherently large static disorder of the involved electronic energies.4)

References

1) T. P. Nguyen and A. Ishizaki, *J. Phys. Chem. Lett.* **9**, 1243–1248 (2018).

2) T. P. Nguyen and A. Ishizaki, preparation.

3) A. Kato and A. Ishizaki, *Phys. Rev. Lett.* **121**, 026001 (2018).

4) Y. Fujihashi, M. Higashi and A. Ishizaki, *J. Phys. Chem. Lett.* **9**, 4921–4929 (2018).

Theoretical Study on Photochemistry and Catalysis

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

EHARA, Masahiro
Professor
[ehara@ims.ac.jp]

Education

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

Professional Employment

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

Awards

2009	APATCC Pople Medal
2009	QSCP Prize CMOA

Member
Assistant Professor
    ITO, Soichi
JSPS Invited Fellow
    ZHAO, Xiang
Post-Doctoral Fellow
    ZHAO, Ruisheng
    SADHUKHAN, Tumpa
    ZHENG, Hong
    VELLOTH, Archana
Visiting Scientist
    JUNKAEW, Anchalee
    NAMUANGRUK, Supawadee
    CHIRAWAT, Chitpakdee
    ZHAO, Pei*
    TEANWARAWAT, Jitpinan†
    BOEKFA, Bundet
Graduate Student
    KANAZAWA, Yuki
    SHIRAOGAWA, Takafumi
Secretary
    KAWAGUCHI, Ritsuko
    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 H_2 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).
- N. Berrah, M. Tashiro, M. Ehara *et al.*, "Double Core-Hole Spectroscopy for Chemical Analysis with an Intense X-Ray Femtosecond Laser," *Proc. Natl. Acad. Sci. U.S.A.* **108**, 16912–16915 (2011).
- M. Ehara and T. Sommerfeld, "CAP/SAC-CI Method for Calculating Resonance States of Metastable Anions," *Chem. Phys. Lett.* **537**, 107–112 (2012).
- P. Hirunsit, K. Shimizu, R. Fukuda, S. Namuangruk, Y. Morikawa and M. Ehara, "Cooperative H_2 Activation at Ag Cluster/θ-Al_2O_3 Dual Perimeter Sites: A DFT Study," *J. Phys. Chem. C* **118**, 7996–8006 (2014).

1. Frenkel-Exciton Decomposition Analysis of CD and CPL for Multichromophoric Systems$^{1)}$

Recently, a method to calculate the absorption and circular dichroism (CD) spectra based on the exciton coupling has been developed. In this work, the method was utilized for the decomposition of the CD and circularly polarized luminescence (CPL) spectra of a multichromophoric system into chromophore contributions for recently developed through-space conjugated oligomers. The method which has been implemented using rotatory strength in the velocity form and therefore it is gauge-invariant, enables us to evaluate the contribution from each chromophoric unit and locally excited state to the CD and CPL spectra of the total system. The excitonic calculations suitably reproduced the full calculations of the system, as well as the experimental results. We demonstrated that the interactions between electric transition dipole moments of adjacent chromophoric units are crucial in the CD and CPL spectra of the multichromophoric systems, while the interactions between electric and magnetic transition dipole moments are not negligible.

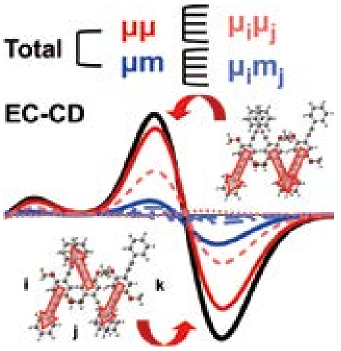


Figure 1. Frenkel-exciton decomposition analysis (FEDA) of CD spectra for through-space conjugated trimer.

2. Fluorescent Imaging Biological Probes of Nucleic Acids$^{2)}$

Photophysical properties of exciton-controlled hybridization-sensitive fluorescent oligonucleotide (ECHO) probes which show strong emission in the near-infrared region via hybridization to the target DNA and/or RNA strand have been investigated using the SAC-CI and TD-DFT calculations. The monomer and dimer (H-aggregate) of fluorescent cyanine chromophores whose excitation is challenging for TD-DFT methods, have been examined. The present results support for the experimentally suggested mechanism of strong fluorescence and suppression of the probe. The SAC-CI method well reproduced the experimental transition energies, while the quantitative prediction by TD-DFT calculations was difficult for these chromophores. Stokes shifts of these chromophores were qualitatively reproduced by the theoretical calculations.

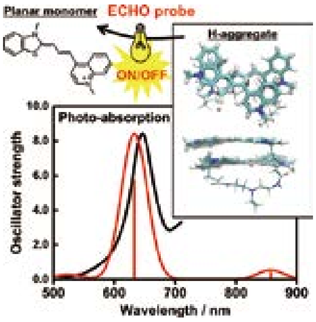


Figure 2. Photophysical properties of exciton-controlled hybridization-sensitive fluorescent oligonucleotide probe.

3. Nickel-Catalyzed Coupling Reaction of Alkyl Halides with Aryl Grignard Reagents in the Presence of 1,3-Butadiene: Mechanistic Studies of Four-Component Coupling and Competing Cross-Coupling Reactions$^{3)}$

We investigated the mechanism, substituent effects, and origins of the selectivity of nickel-catalyzed four-component coupling reaction of alkyl fluorides, aryl Grignard reagents, and two molecules of 1,3-butadiene that affords a 1,6-octadiene carbon framework bearing alkyl and aryl groups at 3- and 8-positions, respectively, and the competing cross-coupling reaction. The C–C bond formation of alkyl fluorides with the γ-carbon of anionic nickel complexes leads to the four-component coupling product, whereas the cross-coupling product is yielded via nucleophilic attack of the Ni center toward alkyl fluorides. These steps are found to be the rate-determining and selectivity-determining steps of the whole catalytic cycle, in which the C–F bond of alkyl fluorides is activated by Mg cation rather than Li or Zn cation. ortho-Substituent(s) of aryl Grignard reagents suppressed the cross-coupling reaction leading to the selective formation of the four-component products. Such steric effects of the ortho-substituent(s) were clearly demonstrated by crystal structure characterizations of ate complexes and DFT calculations. The present mechanistic study offers new insight into anionic complexes, which are proposed as the key intermediates in catalytic transformations though detailed mechanisms are not established in many cases, and demonstrates their synthetic utility as promising intermediates for C–C bond forming reactions, providing useful information for developing efficient and straightforward multi-component reactions.

References

1) T. Shiraogawa, M. Ehara, S. Jurinovich, L. Cupellini and B. Mennucci, *J. Comput. Chem.* **39**, 931–935 (2018).
2) T. Shiraogawa, G. Candel, R. Fukuda, I. Chiofini, C. Adamo, A. Okamoto and M. Ehara, *J. Comput. Chem.*, in press.
3) T. Iwasaki, A. Fukuoka, W. Yokoyama, X. Min, I. Hisaki, T. Yang, M. Ehara, H. Kuniyasu and N. Kambe, *Chem. Sci.* **9**, 2195–2211 (2018).

---

* IMS International Internship Program

† IMS International Internship Program in Asia

Development of New Molecular Dynamics Algorithms for Biomolecular Systems

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

OKUMURA, Hisashi
Associate Professor
[hokumura@ims.ac.jp]

Education

1998	B.S. Keio University
2002	Ph.D. Keio University

Professional Employment

2002	Postdoctoral Fellow, The University of Tokyo
2002	Research Associate, Institute for Molecular Science
2004	Research Associate, The Graduate University for Advanced Studies
2006	Research Lecturer, Nagoya University
2008	Research Assistant, Rutgers University
2009	Assistant Research Professor, Rutgers University
2009	Associate Professor, Institute for Molecular Science Associate Professor, The Graduate University for Advanced Studies
2018	Associate Professor, Exploratory Research Center on Life and Living Systems

Award

2014	Academic Award of the Molecular Simulation Society of Japan

Member

Assistant Professor
ITOH, Satoru G.

Post-Doctoral Fellow
ISHIMURA, Kazuya
NISHIZAWA, Hiroaki

Graduate Student
YAMAUCHI, Masataka
TACHI, Yuhei*
MIYAZAWA, Kazuhisa†

Secretary
KAWAGUCHI, Ritsuko

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 replica-permutation method. We apply these methods to proteins and peptides and try to predict the native structures of proteins as in Figure 1.

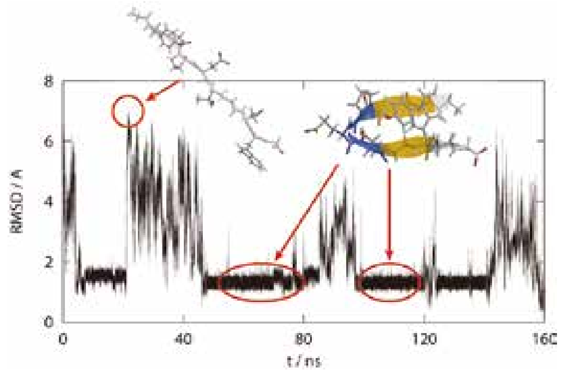


Figure 1. Time series of protein folding simulation.

We are also interested in amyloid fibrils, which are insoluble aggregates of misfolded fibrous proteins and associated with more than 20 human neurodegenerative diseases (Figure 2). For example, Alzheimer's disease is related to amyloid-β (Aβ) peptides. To overcome these diseases, it is essential to understand amyloid genesis and disruption. We perform such MD simulations of amyloid fibrils.

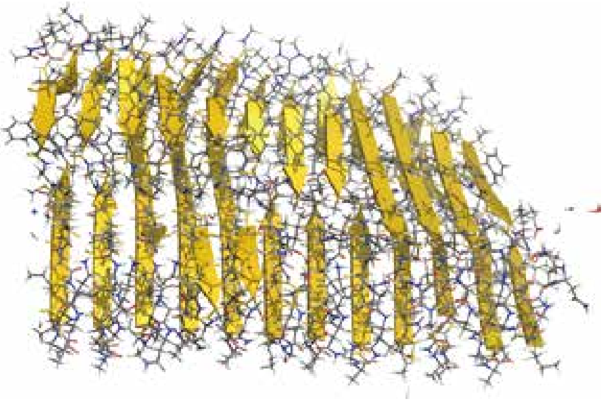


Figure 2. Snapshot of amyloid fibril.

Selected Publications

- Y. Mori and H. Okumura, "Pressure-Induced Helical Structure of a Peptide Studied by Simulated Tempering Molecular Dynamics Simulations," *J. Phys. Chem. Lett.* **4**, 2079–2083 (2013).
- S. G. Itoh and H. Okumura, "Replica-Permutation Method with the Suwa-Todo Algorithm beyond the Replica-Exchange Method," *J. Chem. Theory Comput.* **9**, 570–581 (2013).
- 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).

1. Development of Isothermal-Isobaric Replica-Permutation Method and Its Application to Chignolin

We developed a two-dimensional replica-permutation molecular dynamics (MD) method in the isothermal-isobaric ensemble.1) The replica-permutation method is a better alternative to the replica-exchange method. It was originally developed in the canonical ensemble. This method employs the Suwa-Todo algorithm, instead of the Metropolis algorithm, to perform permutations of temperatures and pressures among more than two replicas so that the rejection ratio can be minimized. We showed that the isothermal-isobaric replica-permutation method performs better sampling efficiency than the isothermal-isobaric replica-exchange method. We applied this method to a β-hairpin mini protein, chignolin. In this simulation, we observed not only the folded state but also the misfolded state. We calculated the temperature and pressure dependence of the fractions of the folded, misfolded, and unfolded states. Differences in partial molar enthalpy, internal energy, entropy, partial molar volume, and heat capacity were also determined, and agreed well with experimental data. We observed a new phenomenon that misfolded chignolin becomes more stable under high-pressure conditions. We also revealed this mechanism of the stability as follows: TYR2 and TRP9 side chains cover the hydrogen bonds that form a β-hairpin structure as in Figure 3. The hydrogen bonds are protected from the water molecules that approach the protein as the pressure increases.

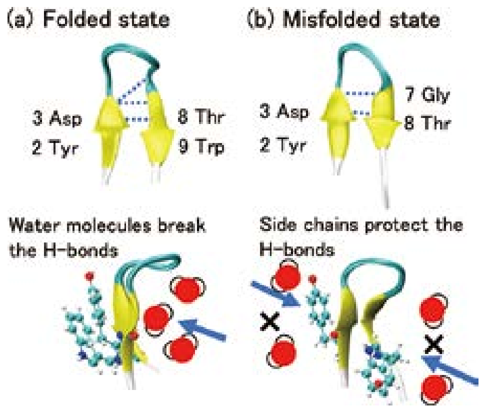


Figure 3. Schematic figure of the mechanism by which misfolded chignolin becomes stable under high-pressure conditions.

2. Classical Molecular Dynamics Simulation to Understand Role of a Zinc Ion for Aggregation of Amyloid-β Peptides

Metal ions such as those of copper and zinc are considered to accelerate initial formation of amyloid fibril of Aβ peptides. In this study, the role of a zinc ion for Aβ peptide aggregation was investigated by the classical MD simulations.2) The MD results indicated that the negatively-charged residues gained large stabilization in the existence of a zinc ion. On the other hand, histidine and tyrosine which were reported as making a bond with a metal ion were slightly stabled. Therefore, a zinc ion is thought of as combining with histidine or tyrosine after being attracted by negatively-charged residues, because these residues exist near negatively-charged residues. These results indicate that the metal-containing system needs to be treated by quantum-mechanical techniques.

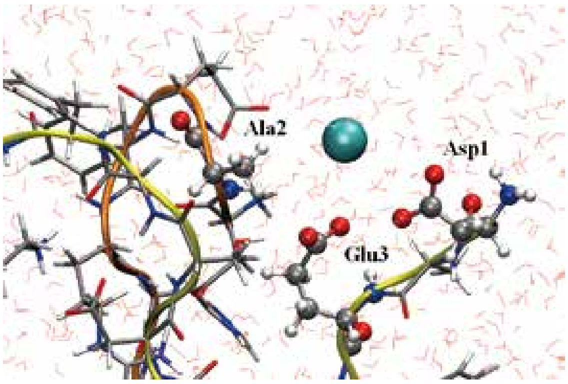


Figure 4. A snapshot around the zinc ion. Asp1 and Glu3 of one Aβ(1–16) peptide and Ala2 of the other Aβ(1–16) peptide exist near the zinc ion.

3. Antigen-Dependent Fluorescence Response of Anti-c-Myc Quenchbody Studied by Molecular Dynamics Simulations

We performed metadynamics MD simulations to reveal mechanism of antigen-dependent fluorescence response observed for site-specifically fluorescent-labeled single-chain antibody against c-Myc peptide antigen.3) We found that V_H and V_L bind with each other only when the antigen exists and that the fluorophore labeled at the N-terminus of V_H interacts with Trp103 most stably. These results support the mechanism proposed from previous experiments: In the absence of antigen, Trp residues are partially exposed at the interface of V_H and quench the fluorophore. In the presence of antigen, the Trp residues are buried in the interface between V_H and V_L, and the quenching is eliminated.

References

1) M. Yamauchi and H. Okumura, *J. Chem. Phys.* **147**, 184107 (15 pages) (2017).
2) H. Nishizawa and H. Okumura, *J. Comput. Chem. Jpn.* **17**, 76–79 (2018).
3) Y. Mori, H. Okumura, T. Watanabe and T. Hohsaka, *Chem. Phys. Lett.* **698**, 223–226 (2018).

---

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

† carrying out graduate research on Cooperative Education Program of IMS with Shinshu University

Theoretical Studies on Molecular Aggregates

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

FUJITA, Takatoshi
Research Associate Professor
[tfujita@ims.ac.jp]

Education

2006 B.H.D. Kobe University
2008 M.S. Kobe University
2011 Ph.D. Kobe University

Professional Employment

2010 JSPS Research Fellow (DC2)
2011 JSPS Postdoctoral Fellow (PD)
2012 Postdoctral Fellow, Harvard University
2015 Postdoctral Fellow, Kyoto University
2016 Research Associate Professor, Institute for Molecular Science

Member
Secretary
SUZUKI, Sayuri

Keywords Exciton, Energy and Charge Transfer, Organic Semiconductors

Organic molecules can assemble into an ordered structure by non-covalent interactions, forming various types of aggregates. Molecular aggregates can exhibit remarkable optical and electronic properties that are not observed in isolated molecules. We study optoelectronic properties and quantum dynamics of molecular aggregates. More specifically, we focus on energy and charge transfer dynamics, and energy conversions, and structure-property relationship. Our research also include the developments of theoretical and computational methods.

It is still challenging to simulate quantum dynamics of energy or charge transfer in condensed systems. An exciton or electron wave functions can be delocalized over many molecules by intermolecular electronic couplings. By contrast, the wave functions can be localized because of the static disorder and interactions with nuclear degree of freedom. Therefore, successful theoretical descriptions require the inclusions of electronic couplings, static disorder, and electron–phonon or electron–vibration interaction. We develop a method to simulate quantum dynamics in condensed phase by combining molecular dynamics simulations, electronic structure theories, and quantum dynamics methods, as shown in Figure 1. Electronic states of an aggregate is obtained from a large-scale electronic structure calculation, and the model Hamiltonian for an exciton or a charge carrier is derived. The model Hamiltonian is used for simulating energy or charge dynamics by a quantum dynamics method, which incorporates finite-temperature effects and electron–vibration interactions. The combine computational approach allows for bottom-up descriptions of energy or charge transfer dynamics in realistic molecular aggregates.

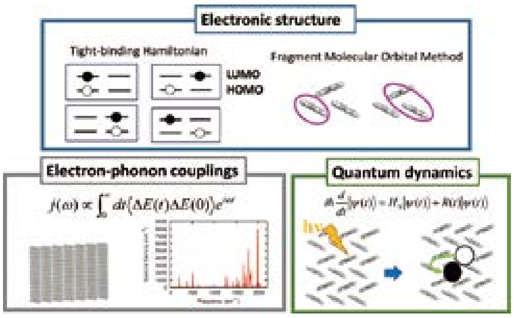


Figure 1. A combine approach to quantum dynamics in molecular aggregates.

We currently investigate electronic states and quantum dynamics at organic interfaces. We also develop the many-body perturbation theory to predict electronic levels at higher accuracy.

Selected Publications

- T. Fujita, S. Atahan-Evrenk, N. P. D. Sawaya and A. Aspuru-Guzik, "Coherent Dynamics of Mixed Frenkel and Charge Transfer Excitons in Dinaphtho[2,3-*b*:2'3'-*f*]thieno[3,2-*b*]-thiophene Thin Films: The Importance of Hole Delocalization," *J. Phys. Chem. Lett.* **7**, 1374–1380 (2016).
- T. Fujita and Y. Mochizuki, "Development of the Fragment Molecular Orbital Method for Calculating Nonlocal Excitations in Large Molecular Systems," *J. Phys. Chem. A* **122**, 3886–3898 (2018).

1. Interfacial Charge-Transfer States at Organic Bilayer Heterojunction[1)]

The electronic structures at organic–organic interfaces comprising electron-donor and electron-accepter materials are of great importance in the performance of the organic solar cells. In particular, the interfacial charge-transfer (ICT) state—an electron-hole pair formed across the donor/acceptor interface—plays an essential role in charge photogeneration because it is an intermediate for both charge separation and charge recombination processes. Despite their critical importance, it is difficult to experimentally investigate the interfacial CT states.

Here, we performed ab initio excited-state calculations to investigate the ICT states formed at a pentacene/C_{60} bilayer heterojunction modeled by molecular dynamics simulations. The model bilayer heterojunction structures contain approximately 1.8×10^5 atoms, and their local interface regions containing 2,000 atoms were treated quantum mechanically, embedded in the electrostatic potentials from remaining parts. Therefore, the charge delocalization effect, structural disorder, and the resulting heterogeneous electrostatic and polarizable environments were taken into account in the excited-state calculations. The computed energies of the low-lying ICT states are in reasonable agreement with experimental estimates. By comparing the edge-on and face-on configurations of the pentacene/C_{60} interfaces, we highlight the influence of interfacial morphologies on the energetics and charge delocalization of ICT states. We found that, in the edge-on configuration, the pentacene absorption region is resonant with dense delocalized ICT states, resulting in the formation of hybridized states. The hybridization enhances the delocalization of ICT states, owing to their electron wave functions extending across the pentacene/C_{60} interface. In addition, the delocalized ICT state can be directly accessed by photoexcitation, borrowing absorption intensity from pentacene excited states. Such the optically-bright delocalized ICT states enable photoinduced long-range electron transfer through the extended electron wave functions, giving rise to rapid charge separations.

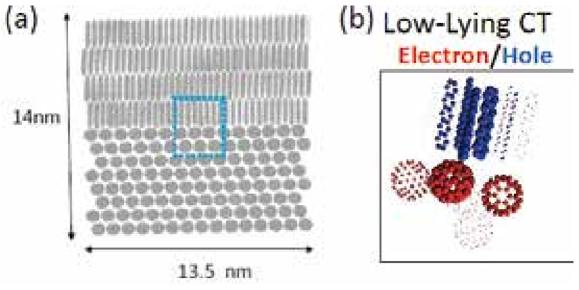


Figure 2. (a) The atomic structure of pentacene/C_{60} bilayer heterojunction. (b) Visualization of electron (red) and hole (blue) wave functions that constitute the low-lying CT state.

2. Development of Many-Body Green's Function Method for Large Molecular Systems[2)]

The GW many-body Green's function approach has been established as an accurate and efficient method to predict the electronic levels. Within the GW method, the dielectric function is computed for screened Coulomb interaction, and the self-energy is approximated from the Green's function and the screened Coulomb potential. The GW method can be combined with the Bethe-Salpeter equation to obtain electronically excited states. The GW/BSE method have been applied to isolated molecules or periodic systems. However, they were not applied to interface systems because large and disordered system must be treated.

We develop the fragment-based GW method suitable to treat large molecular systems in heterogeneous polarizable environments, on the basis of the fragment molecular orbital (FMO) method. The Green's function of a total system is approximated from fragment Green's functions that are calculated by fragment molecular orbitals and is expanded up to two-body terms. The screened Coulomb potential is approximated from the sum of intrafragment density-response functions, with interfragment polarization terms being neglected. The approximations of the Green's function and screened Coulomb potential lead to the many-body expansion of the self-energy; this expansion is essentially equivalent to the many-body expansion of the Fock matrix in the FMO method. To deal with large molecular systems, the present implementation relies on the Coulomb hole plus screened exchange (COHSEX) approximation, which is the static limit of GW. The accuracy of the FMO-COHSEX method is demonstrated in comparison to conventional COHSEX results for organic molecular aggregates. We confirmed that the present fragmentation approach can provide resonantly accurate results, and the mean absolute errors of quasiparticle energies less than 0.1 eV have been achieved for valence orbitals. We also investigate the accuracy of the COHSEX approximation for describing the effects of molecular aggregation of electronic states, by comparing them to the GW method. Although the COHSEX fails to quantitatively determine quasiparticle energies, it was found to successfully describe the molecular aggregation effects on electronic states, such as induced polarization and dispersion effects. As an illustrative application of the present method, we consider the electronic states of the pentacene thin film. We discuss the impact of induced polarization effect in the heterogeneous environment, highlighting the gap renormalization and the polarization-induced localization. The application shows that our fragment-based GW method is useful to study electronic structures of molecular aggregates in complex environments.

References

1) T. Fujita, Md. K. Alam and T. Hoshi, submitted.
2) T. Fujita and Y. Noguchi, in preparation.

Functional Dynamics of Biomolecular Machines Revealed by Theoretical Methods

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

OKAZAKI, Kei-ichi
Research Associate Professor
[keokazaki@ims.ac.jp]

Education

2004	B.S. Kyoto University
2006	M.S. Kobe University
2009	Ph.D. Kobe University

Professional Employment

2007	JSPS Research Fellow (DC2)
2009	JSPS Postdoctoral Fellow (PD)
2009	Postdoctoral Fellow, Waseda University
2010	Part-time Lecturer, Waseda University
2011	Postdoctoral Fellow, National Institutes of Health, U.S.A.
2012	JSPS Postdoctoral Fellow for Research Abroad
2013	Postdoctoral Fellow, Max Planck Institute of Biophysics, Germany
2016	Research Associate Professor, Institute for Molecular Science

Award

2014	Early Career Award in Biophysics, Biophysical Society of Japan

Member
Post-Doctoral Fellow
MAHMOOD, Md Iqbal
Secretary
SUZUKI, Sayuri

Keywords Theoretical Biophysics, Molecular Motors, Molecular Simulations

Functional dynamics plays an important role when biomolecular machines fulfill their functions. For example, motor proteins walk on the rail or rotate relative to the stator by using ATP hydrolysis energy. Transporter proteins transport their substrates across the membrane by changing their conformation between inward-open and outward-open conformations. We aim to understand design principles of these precise, yet dynamic nano-machines developed by nature.

Functional dynamics of biomolecular machines involve wide spectrum of intricate motions and reactions. In order to understand such dynamics, we need a multiscale approach to cover full range of these motions and reactions. Conventional atomistic molecular dynamics simulations alone cannot cover millisecond-long (or even longer) functional dynamics, especially for a large system like typical biomolecular machines with more than hundreds of thousand atoms including water molecules. Thus, we use both atomistic and coarse-grained molecular simulations, as well as kinetic models based on statistical mechanics, to tackle this problem.

We have been working on ATP synthase that produces most of ATP required for living activities. The ATP synthase is composed of two rotary motors, F_o and F_1. The F_o motor is embedded in membrane and its rotation is driven by proton gradient. The F_1 motor is a catalytic part that produces ATP from ADP and P_i. However, the F_1 motor by itself (F_1-ATPase) rotates the central stalk, γ-subunit, in the opposite direction by hydrolyzing ATP. Thus, the two motors are driven by different energy sources and rotate in the opposite directions. In order to understand how ATP synthase works, we have to look into both individual motors and ATP synthase as a whole.

We are also working on other types of biomolecular machines like chitinase that shows a unidirectional motion by hydrolyzing chitin, Na^+/H^+ antiporter that exchanges sodium ions and protons inside and outside the cell. Methodological development and application of sampling rare events are our interests too.

Selected Publications

- 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_oF_1-ATP Synthase,” *Proc. Natl. Acad. Sci. U.S.A.* **112**, 10720–10725 (2015).
- M. Sugawa, K. Okazaki, M. Kobayashi, T. Matsui, G. Hummer, T. Masaike and T. Nishizaka, “F_1-ATPase Conformational Cycle from Simultaneous Single-Molecule FRET and Rotation Measurements,” *Proc. Natl. Acad. Sci. U.S.A.* **113**, E2916–E2924 (2016).
- H. Jung, K. Okazaki and G. Hummer, “Transition Path Sampling of Rare Events by Shooting from the Top,” *J. Chem. Phys.* **147**, 152716 (2017).
- A. Nakamura, K. Okazaki, T. Furuta, M. Sakurai and R. Iino, “Processive Chitinase is Brownian Monorail Operated by Fast Catalysis after Peeling Rail from Crystalline Chitin,” *Nat. Commun.* **9**, 3814 (2018). doi:10.1038/s41467-018-06362-3

1. Mechanochemical Coupling Mechanism of F_1-ATPase

Many single-molecule studies as well as crystallographic studies have clarified how the γ-subunit rotation is coupled to ATP hydrolysis reactions at three catalytic sites of F_1. As summarized in Figure 1B, main points are, 1) 120° step inferred from three-fold symmetry is further divided into 80° and 40° substeps, 2) the 80° substep is driven by ATP binding and ADP release, 3) the 40° substep is driven by P_i release and ATP hydrolysis reaction, 4) typical crystal structures correspond to catalytic dwell (before 40° substep). There are still some remaining questions, though. What is the timing of P_i release: Just after the hydrolysis reaction or after ADP release? What conformation does it take in ATP-binding dwell (before 80° substep)?

We resolved the timing of P_i release by using atomistic molecular dynamics simulations.[1] The question is, essentially, from which catalytic site, DP-site or E-site, P_i is released. Since the P_i release takes ~millisecond, a biasing method called metadynamics was employed to facilitate the functional dynamics. Different pathways were observed depending on the site P_i was released. From the E-site it went through P-loop toward outside of the ring structure, while from the DP-site it went through switch II toward inside of the ring structure (Figure 1C). We estimated mean first-passage time from free energy profile (Figure 1D) and diffusion coefficient and concluded that P_i is release from the E-site. That is, P_i is released after ADP release, which is unique among other members of ATPases.

We also identified conformational state of the ATP-binding dwell by combining single-molecule FRET measurements and systematic structural analysis.[2] We found that an ε-inhibited *E. Coli* structure that has half-closed β_{DP} and loose $\alpha\beta_E$ interface is consistent with the conformation taken in the ATP-binding dwell.

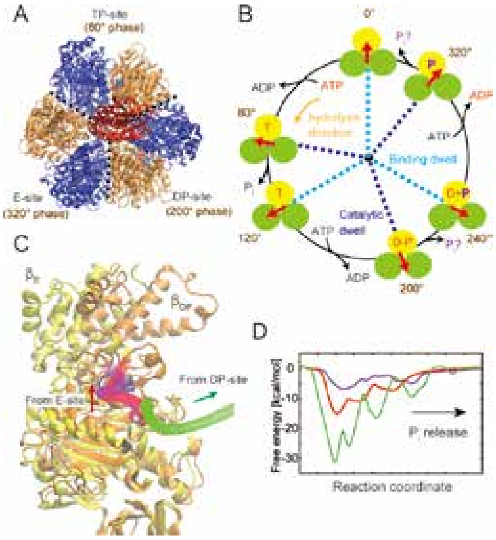


Figure 1. Mechanochemical coupling scheme and P_i release in F_1-ATPase.

2. Torsional Elasticity and Friction of Rotor in F_oF_1-ATP Synthase

It has been known that there is a symmetry mismatch between F_o c-ring and F_1 $\alpha_3\beta_3$ ring. The F_1 $\alpha_3\beta_3$ ring has (pseudo) three-fold symmetry, while the F_o c-ring in animal mitochondria has 8-fold symmetry. Thus, the common rotor, γ-subunit, has to rotate by 120° steps (or 80°+40° substeps) in F_1 part, while it has to rotate by 45° steps in F_o part. Therefore, it has to have torsional elasticity to solve the mismatch. In order to estimate torsional elasticity as well as viscosity of the γ-rotation, we built a simple viscoelastic model (Figure 2B) and fitted it against atomistic simulation trajectories in which external torque was applied on γ.[3]

The estimated torsional elasticity is consistent with values from single-molecule experiments. By using this elasticity, we identified pathways and associated free energies of the coupled F_oF_1 rotation (Figure 2C). It turned out that with the two-substep F_1 the pathway is blocked by high-energy states. To solve this situation, F_1 needs three substeps as was measured for human mitochondrial F_1 recently. From the estimated torsional friction, we predict that γ-rotation can rotate as fast as 1 MHz and this fast rotation can be observed with an attached bead as small as 20 nanometer diameter.

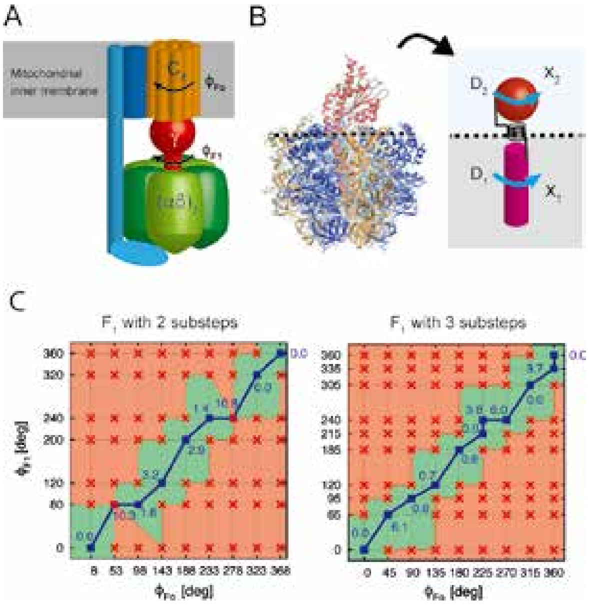


Figure 2. Viscoelastic model of F_oF_1-ATP synthase.

References

1) K. Okazaki and G. Hummer, *Proc. Natl. Acad. Sci. U.S.A.* **110**, 16468–16473 (2013).

2) M. Sugawa, K. Okazaki, M. Kobayashi, T. Matsui, G. Hummer, T. Masaike and T. Nishizaka, *Proc. Natl. Acad. Sci. U.S.A.* **113**, E2916–E2924 (2016).

3) K. Okazaki and G. Hummer, *Proc. Natl. Acad. Sci. U.S.A.* **112**, 10720–10725 (2015).

Electronic Properties of Heterostructures Controlled by Applied Bias and Light

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

IIDA, Kenji
Assistant Professor

Heterostructures under applied bias and/or light irradiation have been extensively investigated in relation to the development of optical and electronic devices. To reveal their electronic functions, it is required to clarify the details of the electronic structure under applied bias and the photoinduced electronic interactions at the atomic scale.

1. Optical Response of Heterostructures

We have studied optical response of heterostructures using a first-principles computational program in which electron dynamics is directly calculated in real-time and real-space. This program can be applied to complex optical phenomena such as optical near-field excitation of nanostructures by carrying out massively parallel calculations. Using the program, we have shown that the photoexcitation of a MoS_2-graphene heterostructure induces the electron transfer from graphene to MoS_2. It is revealed that the photoexcitation causes the electron dynamics inherent in atomically-thin interfacial regions.1)

2. Electronic Structure Change by Applied Electrode Bias

We have been developing a theoretical approach for describing the electronic structure of heterostructures under applied bias.2) It has been shown that change in the electronic properties of heterostructures by an applied bias strongly depends on the atomic scale details of the interfacial region. We further extend the developed approach to address photoexcited systems under an applied bias.

References

1) K. Iida, M. Noda and K. Nobusada, *J. Phys. Chem. C*, in press.
2) K. Iida, M. Noda and K. Nobusada, *J. Chem. Phys.* **146**, 084706 (10 pages) (2017).

Theory and Computation of Reactions and Properties in Solutions and Liquids

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

ISHIDA, Tateki
Assistant Professor

We are interested in the projects both on ultrafast photoinduced electron energy transfer in the excited state in solution and on ionic liquids (ILs). The project on photoinduced electron energy transfer processes in the excited state in solution is aimed at the development of a theoretical method to study electron energy transfer. Also, ILs' projects are focused on the investigation of dynamical properties on ionic liquids including temperature effects and the unique dissolution process of cellulose polysaccharides using molecular dynamics simulation technique.

1. The Theoretical Investigation of Photoinduced Electron Energy Transfer Processes in the Excited State in Solution1)

We have developed a procedure for investigating the time-dependent evolution of the electronic structure of a solute molecule in solution, coupling an electronic structure theory with solvent motion. It is shown that the coupling between solvation processes and a fast intramolecular electron energy transfer is likely to play an important role in the emergence of photoinduced unique functionalities in biochemical and metal complex systems.

2. Investigations of Ionic Liquids1–2) with Molecular Dynamics Simulation

We focus on the dynamical properties on ionic liquids (ILs). With molecular dynamics simulation procedure, it have been reported that ILs show unique collective dynamics. In addition, we have investigated interesting dynamical heterogeneity in ILs at room temperature. Also, we have studied the solvation mechanism of cellulose polymer in ILs.

References

1) T. Ishida, *AIP Conf. Proc.* **1642**, pp. 518–521 (2015).
2) T. Ishida, in preparation.

Visiting Professors

Visiting Professor

NAKANO, Masayoshi *(from Osaka University)*

Theoretical Study on Photofunctionalities of Open-Shell Molecular Systems

Recently, the unique electronic structures and highly efficient functionalities in open-shell singlet molecules have attracted much attention both theoretically and experimentally. First, we have clarified the open-shell character dependences of the second hyperpolarizability γ for rectangular-shaped tetraradicaloid models, such as diradical dimers, using numerically exact solutions of the extended Hubbard model. The system shows two kinds of enhancements of the γ components, γ_{intra} and γ_{inter} (caused, respectively, by intra- and intermolecular diradical interactions): (i) a system with a large y_{intra} (y_{inter}) (> ~0.4) exhibits the enhancement of a single component of γ, γ_{inter} (γ_{intra}), at the intermediate y_{inter} (y_{intra}) region (~0.3–0.4), and (ii) the system exhibits a further enhancement of both components of γ (γ_{intra} and γ_{inter}) at the region where $y_{\text{intra}} \sim y_{\text{inter}}$ with small values ($\leq$ ~0.3). The obtained relationships are verified by using ab initio quantum chemical calculations of the realistic tertraradical models of a 4,4'-bis(1,2,3,5-dithiazdiazolyl) (BDTDA) dimer and a disilene dimer. Second, we have investigated the y–γ correlation of a new class of open-shell NLO molecules, alkaline earth metal inverse sandwich complexes, and found that the y value can be controlled by the metal species (Ca, Mg) and ring ligands (cyclopentadienyl, cyclooctatetraene). A combination of higher period alkaline earth metal and larger organic antiaromatic ($4n\pi$) ring is found to enhance the γ due to the intermediate diradical character and large effective diradical distance.

Visiting Associate Professor

NAKAYAMA, Akira *(from Hokkaido University)*

First-Principles Simulations of the Molecular Process at the Interface of Liquid/Metal-Oxide

A detailed understanding of the interface between liquid and metal-oxide is fundamental due to its relevance to the broad range of physicochemical phenomena and technological applications. To provide insight into microscopic structures and dynamics at the interface, we perform the first-principles molecular dynamics simulations and unveil the intricate molecular process occurring at the liquid/metal-oxide interface. In this year, we have focused on the catalytic reactions at the water/CeO_2 and methanol/CeO_2 interfaces and investigated the role of acid-base and redox sites over CeO_2. In particular, we have worked on the following topics: (1) Structure and dynamical properties of water molecules at the water/CeO_2 interface. (2) Substrate-specific adsorption of 2-cyanopyridine and hydration reaction over CeO_2. (3) Formation of a strong base site by hybridization of 2-cyanopyridine and CeO_2. (4) The reaction mechanism for the direct synthesis of dimethyl carbonate from methanol and CO_2 over CeO_2.

Visiting Associate Professor

KIM, Kang *(from Osaka University)*

Theoretical and Computational Research for Complex Fluids and Soft Matters

We are working on theoretical and simulation approaches to reveal various dynamical processes in complex fluids and soft matters. Recent topics frequently occurred in my research are multiple time and length scales in disordered and glassy systems. In particular, we have revealed the spatio-temporal structures of dynamic heterogeneities using molecular dynamics simulations. It is demonstrated that those spatially heterogeneous dynamics are closely relevant with the anomalous rheological behaviors including the violation of Stokes-Einstein relation. Furthermore, we have developed a supercooled liquid model, for which we can systematically control the manner of structural relaxation widely ranging from silica-like to metallic-like glasses.