RESEARCH ACTIVITIES

Division of Advanced Molecular Science

The division consists of two sections. In the first one, scientists of the first water are invited as "distinguished professors," and the environment, in which they can devote themselves to their own research, is provided. The research in this section should be the last word in the field of molecular science.

In the second section, we invite researchers in the universities performing unique researches in the field of molecular science as cross-appointment faculty members, and provide the research environment to enable research activity with advanced facilities in IMS.

Second-Generation Crystalline Sponges: Structural Analysis of Medium-Sized Pharmaceutical Compounds

Division of Advanced Molecular Science

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Education

1980	B.S. Chiba University
1982	M.S. Chiba University
1987	Ph.D. Tokyo Institute of Technology

Professional Employment

1982	Researcher, Sagami Chemical Research Center
1988	Assistant Professor to Associate Professor, Chiba University
1997	Associate Professor, Institute for Molecular Science
1999	Professor, Nagoya University
2002	Professor, The University of Tokyo
2018	Distinguished Professor, Institute for Molecular Science
2019	Distinguished Professor, The University of Tokyo

Awards

1994	Progress Award in Synthetic Organic Chemistry, Japan
2000	Division Award of Chemical Society of Japan (Organic Chemistry)
2001	Tokyo Techno Forum 21 Gold Medal
2001	Japan IBM Award
2003	Nagoya Silver Medal
2004	Izatt-Christensen Award
2006	G. W. Wheland Award (Chicago University Lectureship Award)
2010	The Reona Esaki Award
2010	The JSCC Award
2011	3M Lectureship Award (University of British Columbia)
2012	Thomson Reuters Research Front Award 2012
2013	The Chemical Society of Japan (CSJ) Award
2013	Arthur C. Cope Scholar Award (ACS National Award)
2013	Merck-Karl Pfister Visiting Professorship (MIT Lectureship Award)
2014	ISNSCE 2014 Nanoprize
2014	Medal with Purple Ribbon
2014	Fred Basolo Medal (Northwestern University)
2018	Wolf Prize in Chemistry
2019	The Imperial Prize and the Japan Academy Prize
2020	The 73rd Chunichi Cultural Award
2020	Clarivate Citation Laureates (Chemistry)
2020	"Major Results" of Nanotechnology Platform, MEXT
2022	Le Grand Prix 2022 de la Fondation de la Maison de la Chimie
2023	Asahi Prize2023
2023	2022 Natta Award (Politecnico di Milano)
2024	Van't Hoff Award
2025	International Honorary Member of American Academy of Arts & Sciences

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MASUDA, Michiko
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Keywords Self-Assembly, Nano-Space, Coordination Cages

The crystalline sponge (CS) method is a novel technique for X-ray diffraction analysis, in which a porous crystal absorbs and aligns target molecules, thereby eliminating the need for crystallization of the analyte. However, this approach faces significant challenges when analyzing large or highly polar molecules. We are developing a second-generation CS (2G-CS) method that employs coordination cages as CS, leveraging their exceptional guest-binding capability to overcome these limitations. This breakthrough method greatly expands the range of analyzable compounds, now including water-soluble molecules and large amphiphilic pharmaceutical compounds (MW > 1000). We anticipate this method will become a definitive technique for molecular structure determination in both academia and industry.

Selected Publications

- Y. Inokuma, S. Yoshioka, J. Ariyoshi, T. Arai, Y. Hitora, K. Takada, S. Matsunaga, K. Rissanen and M. Fujita, "X-Ray Analysis on the Nanogram to Microgram Scale Using Porous Complexes," *Nature* **495**, 461–466 (2013).
- M. Fujita, D. Oguro, M. Miyazawa, H. Oka, K. Yamaguchi and K. Ogura, "Self-Assembly of Ten Molecules into Nanometre-Sized Organic Host Frameworks," *Nature* **378**, 469–471 (1995).

1. Supramolecular Coordination Cages as Crystalline Sponges through a Symmetry Mismatch Strategy[1)]

The self-assembled octahedral M_6L_4 coordination cage **1** exhibits exceptional guest-binding abilities in solution. In the past thirty years, the rich host–guest chemistry of its host–guest complexes was thoroughly investigated and frequently elucidated through crystallographic studies. Motivated by these results, we aimed to convert this cage into a crystalline material that can enhance the current CS method.

Introducing large aromatic “sticker” anions **2** into the cage solution leads to the formation of high-quality crystals, driven by electrostatic interactions between the positively charged cage and the negatively charged anions. The symmetry mismatch between the T_d-symmetric cage and the D_{2h}-symmetric anions resulted in the production of crystals in a low-symmetry space group (P-1), preventing the disorder of guest molecules and leading to the formation of guest-accessible channels in the crystal.

This cage-immobilized crystals were examined for the CS method to determine the structure of guest molecules. Guest molecules can be introduced to the crystal either before or after the cage crystallization. Owing to the versatile molecular recognition with cage, analytes with molecular weights ranging from 200 to 1200 can be captured by the cage thus enabling their structural determination *via* X-ray diffraction analysis. Notably, various large amphiphilic molecules **3**–**6** with significant pharmaceutical interest were examined and successfully determined the molecular structures.

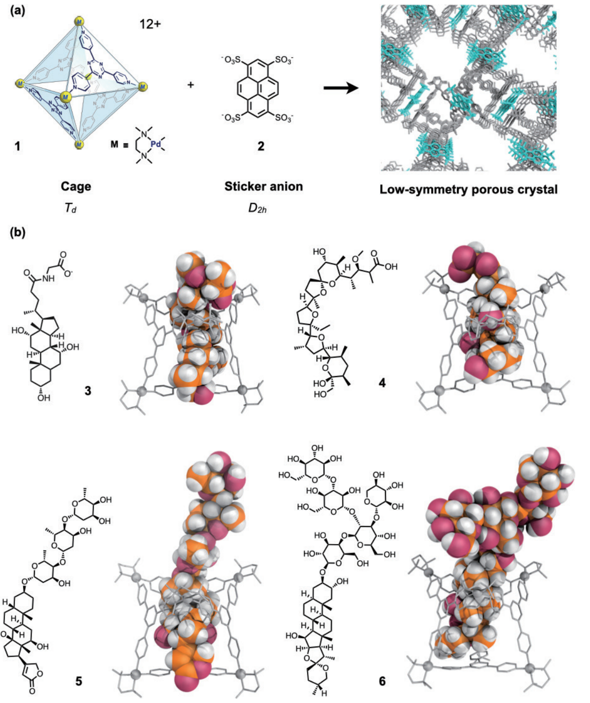

Figure 1. Coordination cages as crystalline sponges for structural analysis of medium-sized pharmaceutical compounds. (a) Symmetry-mismatched pair used for crystallization. (b) Crystal structures of amphiphilic molecules **3**–**6** encapsulated in cage-based crystals.

2. Host–Guest Chemistry in a Capillary Applied to the Facilitation of the Crystalline Sponge Method[2)]

Although conceptually elegant, the traditional CS method requires delicate handling and high experimental skill, limiting its broader applicability. Major challenges include handling trace amounts of analyte and simplifying the workflow.

We addressed these by employing glass capillaries—a convenient tool for transferring, mixing, and storing micro-volumes of liquid. Our optimized protocol involves simply dipping the capillary into a series of bench-stable standard solutions. This process yields sponge crystals encapsulating the target molecule. The resulting in-capillary crystals are comparable in quality to those grown in flasks and can be directly analyzed within the capillary using standard laboratory X-ray diffractometers.

This miniaturized approach reduces the required sample amount from milligrams to micrograms and shortens the analysis time from weeks to days. As a result, the CS method is transformed from a specialized technique into a simple, broadly applicable tool suitable for any chemical laboratory, enabling on-site molecular detection and promoting broader adoption in both academia and industry.

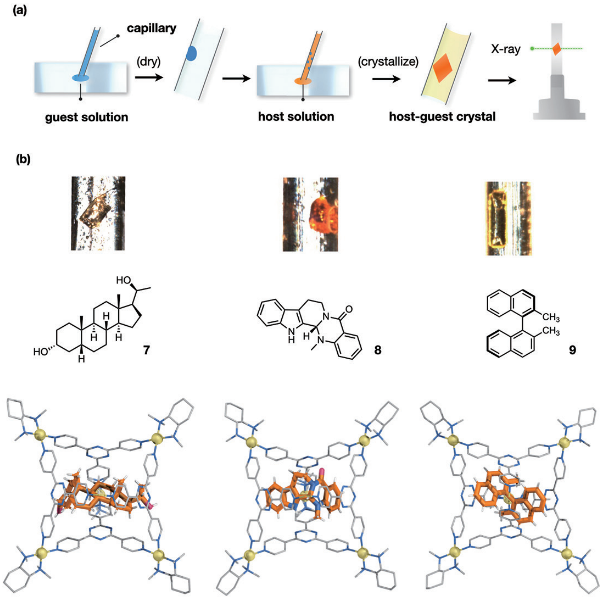

Figure 2. Highly practical CS analysis using glass capillaries. (a) Schematic illustration of the in-capillary workflow. (b) Photographs of guest-encapsulated crystals in capillaries, chemical structures, and X-ray structures of molecules **7**–**9**.

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1) W. He, Y. Yu, K. Iizuka, H. Takezawa and M. Fujita, *Nat. Chem.* **17**, 1–10 (2025).

2) W. He, H. Takezawa, R. Yakushiji, S. Yoshida, S. Sato and M. Fujita, *Angew. Chem., Int. Ed.* **64**, e202501025 (2025).

Exploring Novel Physical Properties by Multi-Dimensional Spectroscopy

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Education

1988	B.S. Tohoku University
1990	M.S. Tohoku University
1991	Ph.D. Tohoku University

Professional Employment

1991	JSPS Postdoctoral Fellow, Tohoku University
1993	Research Associate, Kobe University
1993	Research Associate, Institute for Molecular Science
1998	Associate Professor, Kobe University
2002	Associate Professor, Institute for Molecular Science
2013	Professor, Osaka University
2020	Professor (Cross Appointment), Institute for Molecular Science

Awards

2001	Young Incentive Award, Japanese Society for Synchrotron Radiation Research
2008	The Commendation for Science and Technology by MEXT, Japan Science and Technology Prize (Research Field)
2008	Morita Memorial Prize

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Keywords Condensed Matter, Electronic Structure, Synchrotron Radiation

Physical and chemical properties of solids, such as conductivity, magnetism, superconductivity, and chemical reactions, originate from microscopic electronic structure, lattice/molecular vibrations, and molecular movements based on quantum mechanics in materials and their interactions. By revealing the microscopic states and their evolution, we can learn about the origin of physical and chemical properties and hidden functionalities. Also, the microscopic information is helpful for the creation of novel functional properties. To visualize hidden microscopic information, we develop novel spectroscopic techniques using synchrotron radiation, high brilliant electron beams, and other so-called quantum beams. We have started a novel electron spectroscopy technique, Spin-Resolved resonant Electron-Energy-Loss Spectroscopy (SR-rEELS), with bulk-sensitive primary energies of 0.3–1.5 keV. At present, we combine it with a time- and angle-resolved technique, shown in Figure 1, to simultaneously observe both the changing electronic structure and collective excitations and the lattice and magnetic structure relaxation. Based on the obtained information on electronic structures, we aim to develop novel physical properties of new materials.

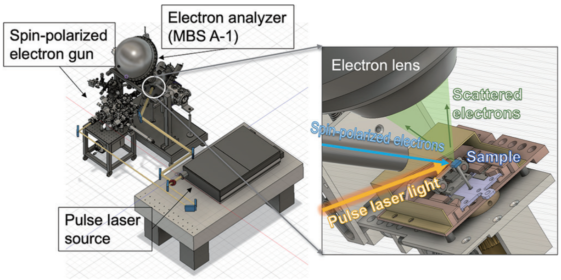

Figure 1. Time-, Spin-, and Angle-Resolved resonant Electron-Energy-Loss Spectroscopy (tSAR-rEELS) apparatus, which our group is now developing. The apparatus comprises a high-brilliant spin-polarized electron gun, a photoelectron spectrometer, and a femtosecond pulse laser with an optical parametric amplifier.

Selected Publications

- T. Nakamura, H. Sugihara, Y. Chen, R. Yukawa, Y. Ohtsubo, K. Tanaka, M. Kitamura, H. Kumigashira and S. Kimura, "Two-Dimensional Heavy Fermion in Monoatomic-Layer Kondo Lattice $YbCu_2$," *Nat. Commun.* **14**, 7850 (7 pages) (2023).
- Y. Ohtsubo, T. Nakaya, T. Nakamura, P. Le Fèrve, F. Bertran, F. Iga and S. Kimura, "Breakdown of Bulk-Projected Isotropy in Surface Electronic States of Topological Kondo Insulator SmB_6(001)," *Nat. Commun.* **13**, 5600 (7 pages) (2022).
- S. Kimura, T. Kawabata, H. Matsumoto, Y. Ohta, A. Yoshizumi, Y. Yoshida, T. Yamashita, H. Watanabe, Y. Ohtsubo, N. Yamamoto and X. Jin, "Bulk-Sensitive Spin-Resolved Resonant Electron Energy-Loss Spectroscopy (SR-rEELS): Observation of Element- and Spin-Selective Bulk Plasmons," *Rev. Sci. Instrum.* **92**, 093103 (8 pages) (2021).
- K. Hagiwara, Y. Ohtsubo, M. Matsunami, S. Ideta, K. Tanaka, H. Miyazaki, J. E. Rault, P. Le Fèvre, F. Bertran, A. Taleb-Ibrahimi, R. Yukawa, M. Kobayashi, K. Horiba, H. Kumigashira, K. Sumida, T. Okuda, F. Iga and S. Kimura, "Surface Kondo Effect and Non-Trivial Metallic State of the Kondo Insulator YbB_{12}," *Nat. Commun.* **7**, 12690 (7 pages) (2016).

1. Current- and Photo-Induced Phase Transition on Black Samarium Monosulfide[1,2]

A strongly correlated insulator, samarium mono-sulfide (SmS), is well-known to present a pressure-induced insulator-to-metal transition (IMT) with the color change from black to golden-yellow. Recently, it has also shown current-induced IMT (CIMT) with negative resistance. To clarify the origin of the CIMT of SmS and also the relation to the pressure-induced IMT, the electronic structure change has been investigated by optical reflectivity and angle-integrated photoelectron spectra by applying an electric current. At lower temperatures than about 100 K, where the nonlinear V–I curve has been observed, the carrier density rapidly increases, accompanied by decreasing relaxation time of carriers with increasing current. Then, the direct gap size increases, and the mean valence changes from Sm^{2+}-dominant SmS to the mixed-valent one with increasing current. These results suggest that the CIMT originates from increasing the Sm $4f$–$5d$ hybridization intensity induced by the applied current.

One scenario for the pressure-induced IMT of SmS is exciton condensations with decreasing energy gap by pressure. To investigate the role of the excitons, optical reflectivity, Sm $3d$ x-ray absorption spectroscopy (XAS), and x-ray diffraction (XRD) with the creation of excitons by photoexcitation (PE) are reported. In the pump–probe reflectivity measurement, following a huge reflectivity change of about 22%, three different relaxation times with a vibration component were observed. The fast component with the relaxation time (τ) of less than 1 ps is due to the excitation and relaxation of electrons into the conduction band, and the slowest one with $\tau >$ several 100 ps originates from the appearance of the photo-induced (PI) state. The components with $\tau \sim 10$ ps and vibration originate from the appearance of the PI state and the interference between the reflection lights at the sample surface and the boundary between the black-insulating and PI states, suggesting that the electronic structure of the PI phase is different from that of the black insulating state. XAS spectra indicate that the Sm mean valence is shifted from the Sm^{2+} dominant to the intermediate between Sm^{2+} and Sm^{3+} by PE, but did not change to that of the golden metallic phase across the IMT, consistent with the reflectivity data. The XRD result after PE shows that the PI state has much less lattice contraction than the golden metallic phase. These results suggest that the IMT cannot be achieved solely by creating excitons after PE but requires other effects, such as a lattice contraction. The photo-induced phase transition and the golden metallic phase are schematically explained in Figure 2.

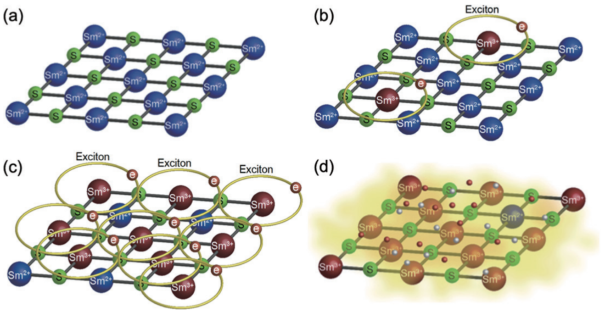

Figure 2. Schematic figure of the photo-induced phase transition along the excitonic instability picture. (a) The black insulating phase. (b) After the photoexcitation (PE) by several pulses irradiated to the sample, $4f$ electrons are excited and become excitons. The created excitons are isolated and localized at the original sites. The electronic structure and optical constants are slightly changed, but the lattice constant is identical before the PE. (c) After many laser pulses PE with a pile-up effect, many excitons are created but still isolated. The valence transition becomes visible by XAS because of many Sm^{3+} states. (d) The golden metallic phase, where excitons are condensed, and the state becomes metallic.

2. Light-Field-Driven Non-Ohmic Current Generation by an Intense THz Pulse in a Weyl Semimetal[3]

In recent years, coherent electrons driven by light fields have attracted significant interest in exploring novel material phases and functionalities. However, observing coherent light-field-driven electron dynamics in solids is challenging because the electrons are scattered within several tens of femtoseconds in ordinary materials, and the coherence between light and electrons is disturbed. This study presents the light-field-driven dynamics by applying a THz pulse (~1 ps) to the Weyl semimetal $\mathrm{Co_3Sn_2S_2}$, which has a relatively long coherent time to pico-seconds. As the electric-field intensity of the irradiating THz pulse was increased, the reflected/emitted THz wave changed from being similar to the incident THz wave to an asymmetric electric field. This asymmetric electric field emission suggests the generation of non-Ohmic direct current *via* coherent acceleration, and the fact that its intensity dependence is proportional to the square of the electric field suggests electronic excitation by the Landau–Zener transition, a characteristic of the light-field picture.

References

1) S. Kimura, H. Watanabe, S. Tatsukawa, T. Nakamura, K. Imura, H. S. Suzuki and N. K. Sato, *J. Phys. Soc. Jpn.* **93**, 013701 (5 pages) (2024). [Editors' Choice]
2) H. Watanabe, Y. Takeno, Y. Negoro, R. Ikeda, Y. Shibata, Y. Chen, T. Nakamura, K. Yamagami, Y. Hirata, Y. Zhang, R. Takahashi, H. Wadati, K. Tamasaku, K. Imura, H. S. Suzuki, N. K. Sato and S. Kimura, *Phys. Rev. B* **110**, 245133 (8 pages) (2024). [Editors' Suggestion]
3) R. Ikeda, H. Watanabe, J. H. Moon, M. H. Jung, K. Takasan and S. Kimura, *J. Phys. Soc. Jpn.* **93**, 053701 (5 pages) (2024).

Operando Molecular Science in Liquid–Solid Interfaces of Finite Thickness

Division of Advanced Molecular Science (Department of Materials Molecular Science, Electronic Structure)

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Education

1985	B.S. The University of Tokyo
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Professional Employment

1989	Assistant Professor, The University of Tokyo
1997	Associate Professor, The University of Tokyo
1999	Project Leader, Kanagawa Academy of Science and Technology
2004	Professor, Kobe University
2021	Professor (Cross Appointment), Institute for Molecular Science

Awards

2001	Young Scientist Award , Catalysis Society of Japan
2002	Nano-Probe Technology Award, Nano-Probe Technology Committee, JSPS
2003	Technical Award, Surface Science Society of Japan
2004	Yazaki Award, Yazaki Foundation
2019	Society Award, Japan Society of Vacuum and Surface Science

Member
Secretary
KURITA, Yoshiko

Keywords Reactions at Interfaces, Catalysis, Energy-Related Chemistry

We are proud of our internationally compatible studies of liquid–solid interfaces; photocatalysts for artificial photosynthesis, lubricants for smooth tribology, and ice in antifreeze liquids. Characterization with advanced AFM, time-resolved ATR-IR spectroscopy, soft X-ray absorption and microelectrode-based amperometry are being developed. We look forward to collaborating with researchers in academic and industrial organizations to unravel the science behind material conversion and energy dissipation at liquid–solid interfaces.

A new era of molecular science will be revealed at liquid–solid interfaces of finite thickness (Figure 1). The molecular interface is the site of reaction where molecules of interest collide or interact with other molecules. We need to observe individual molecules there. On the other hand, the molecular interface is connected to the liquid and solid. Materials and energy come from/to the two condensed phases, since functional interfaces are always open to the environment. Operando characterization is absolutely necessary to study the interface in its working state.

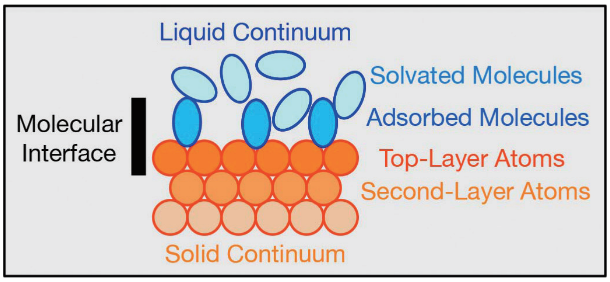

Figure 1. Liquid–Solid Interface of Finite Thickness.

Selected Publications

- Y.-H. Chew, N. Saijo, Y. Kumabe, T. Tachikawa and H. Onishi, “Unravelling the Influence of Major Seawater Salt Ions on the Photogenerated Charge Carriers in a Sr-Doped NaTaO$_3$ Photocatalyst *via* ATR-FTIR,” *J. Phys. Chem. C* **129**, 3531–3538 (2025).
- M. Yanagi, J. Casanova-Cháfer, T. Hara, Y.-H. Chew, T. Yoshida, H. Onishi, C. Bittencourt and N. Ichikuni, “Calcination-Driven Co^{4+} Incorporation in Hydrothermally Synthesized NaTaO$_3$,” *Chem. Lett.* **54**, upaf053 (2025).
- R. Yanagisawa, T. Ueda, K. Nakamoto, Z. Lu, H. Onishi and T. Minato, “The Iinterface between Ice and Alcohols Analyzed by Atomic Force Microscopy,” *J. Chem. Phys.* **161**, 024702 (2024).
- Z. Fu, T. Hirai and H. Onishi, “Long-Life Electrons in Metal-Doped Alkali-Metal Tantalate Photocatalysts Excited under Water,” *J. Phys. Chem. C* **125**, 26398–26405 (2021).
- T. Kosaka, Y. Teduka, T. Ogura, Y. Zhou, T. Hisatomi, H. Nishiyama, K. Domen, Y. Takahashi and H. Onishi, “Transient Kinetics of O$_2$ Evolution in Photocatalytic Water-Splitting Reaction,” *ACS Catal.* **10**, 13159–13164 (2020).
- S. Moriguchi, T. Tsujimoto, A. Sasahara, R. Kokawa and H. Onishi, “Nanometer-Scale Distribution of Lubricant Modifier on Iron Films: A Frequency-Modulation Atomic Force Microscopy Study Combined with Friction Test,” *ACS Omega* **4**, 17593–17599 (2019).

1. Atomic Force Microscopy (AFM) in Sub-Zero Antifreeze Liquid

Ice in nature is surrounded by liquid most of the time, and therefore it is key to understand how ice and liquid interact. Atomic force microscopy is widely used for topographic imaging and force sensing at liquid–solid interfaces. Operation in antifreeze liquids has been examined at temperatures below the freezing point of water, although most AFM research in liquid is conducted in water at room temperatures. In our recent study,1) the topographic imaging in the amplitude-modulation mode and force curves in the contact mode were examined on ice films under antifreeze liquid, using a Dimension XR Icon Nano Electrochemical microscope (Bruker).

In the present study,2) a Shimadzu microscope (SPM-8100FM) capable of imaging and force spectroscopy in the frequency-modulation mode was utilized for probing graphite in 1-octanol ($C_8H_{17}OH$) liquid at temperatures as low as −15 °C. The topography of octanol molecules adsorbed on graphite was resolved, and octanol molecules in the liquid phase exhibited flat layers over graphite as evidenced in force spectroscopy. These results underlined the viability of frequency-modulation atomic force microscopy (FM-AFM) in sub-zero temperature liquids.

The resonance oscillation of the cantilever was mechanically excited with a piezo-actuator. In octanol liquid at RT, the resonant frequency of the cantilevers (f_0) was 100–140 kHz, with the quality factor of resonance ranging from 2 to 4. The oscillation amplitude was regulated at a preset amplitude in topographic imaging. When a conservative force was applied to the tip, the resonance frequency of the cantilever oscillation shifted accordingly. The topography of the object was traced by regulating the frequency shift (Δf) at a predefined setpoint. Figure 2 illustrates the topographic images observed at 27 and −11 °C.

In the images, linear stripes were recognized with trenches between the stripes. The edges of the stripes were presented brighter than the middle. This appearance is consistent to what proposed in earlier studies; the alcohol molecules are paired *via* hydrogen bonding when adsorbed on graphite, and the paired molecules exhibit stripes that are epitaxial to the graphite lattice.

To visualize the local density distribution of octanol liquid, the resonantly oscillating cantilever was scanned vertically from the bulk octanol to the graphite surface. During one such vertical scan, the frequency shift was recorded as a function of vertical coordinate, thereby obtaining one Δf–distance curve. Upon reaching a predetermined Δf threshold, signifying tip-to-solid contact, the cantilever was retracted into octanol by 4–5 nm. Subsequent to this retraction, the cantilever was shifted in the horizontal direction, and an additional vertical scan was conducted. A total of 1024 vertical scans were systematically acquired to construct a Δf map on a plane perpendicular to the graphite surface.

Figure 3 shows two Δf maps observed at 27 °C and −6 °C. The maps are associated with the distribution of the octanol-induced force on the AFM tip apex. Bright color in the Δf maps represent positive frequency shift. The brightest region at the bottom of each map represents the boundary between the liquid and solid. The repulsive force on the tip exhibited a rapid increase when the tip penetrated deeper into this region, signifying tip-to-solid contact. Hence, the envelope of the brightest region delineates the topography of the physisorbed octanol monolayer on graphite.

The frequency shift exhibited an uneven distribution in the proximity of the surface. Alternating dark and bright layers appeared in the maps, suggesting that the surface was covered by five or six liquid octanol layers. The vertical distance between the layers was 0.5 and 0.6 nm at 27 °C and −6 °C, respectively. The octanol liquid layers were suggested to be separated by this distance. The liquid-induced force pushing or pulling the tip apex is contingent on the local liquid density, though force–density relation is not straightforward. Subsequent examination of continuous scanning within a temperature range of −14 °C to 30 °C revealed no substantial structural variation, despite the lowest temperature was close to the freezing point of octanol.

Part of this research was supported by the Advanced Materials Research Infrastructure Project of the Ministry of Education, Culture, Sports, Science and Technology of Japan (JPMXP1224MS0005) and conducted at the Institute for Molecular Science, National Institutes of Natural Sciences. Financial support by JSPS KAKENHI (grant number 23H05448) is acknowledged.

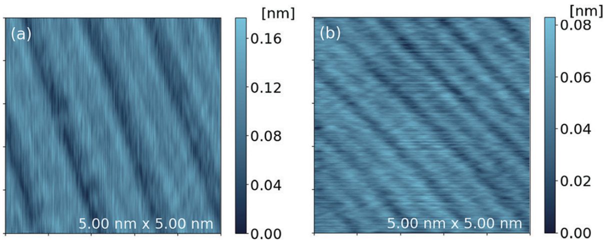

Figure 2. Topographic images of 1-octanol physisorbed on graphite captured at (a) 27 and (b) −11 °C.

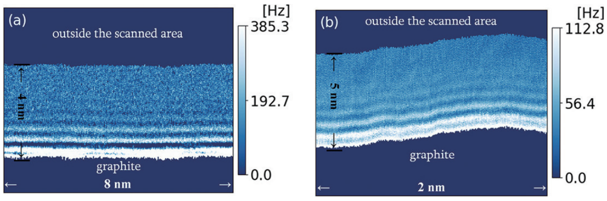

Figure 3. 1-Octanol liquid over a graphite wafer at (a) 27 and (b) −6 °C. The frequency-shift of the cantilever resonance oscillation (Δf) was mapped on a plane that was perpendicular to the wafer. A large (or small) positive frequency-shift is depicted using a bright (or dark) color.

References

1) R. Yanagisawa, T. Ueda, K. Nakamoto, Z. Lu, H. Onishi and T. Minato, *J. Chem. Phys.* **161**, 024702 (2024).

2) Z. Lu, R. Yanagisawa, S. Moriguchi, T. Ueda, K. Nakamoto, T. Minato and H. Onishi, *Jpn. J. Appl. Phys.* **64**, 05SP05 (2025).

Engineering of PET Hydrolase for Plastic Recycling and Environmental Remediation, and Engineering of Plastic Binding Domains for Detection and Quantification of Particles

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Education

2009	B.S. The University of Tokyo
2014	Ph.D. The University of Tokyo

Professional Employment

1995	Postdoctoral Fellow, The University of Tokyo
2015	Assistant Professor, Okazaki Institute for Integrative Bioscience
2018	Assistant Professor, Institute for Molecular Science
2020	Tenure-track Associate Professor, Shizuoka University
2022	Associate Professor (Cross Appointment), Institute for Molecular Science
2025	Professor, Shizuoka University
2025	Professor (Cross Appointment), Institute for Molecular Science

Awards

2015	HAMMON President Choice
2019	ATI Research Encouragement Award
2019	Early Career Award in Biophysics
2021	8th Biophysics and Physicobiology Editors' Choice Award
2024	Early Career Award in Glycoscience

Member
Secretary
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KAWAGUCHI, Ritsuko

Keywords Solid–Liquid Interfacial Reaction, Protein-Engineering, Single-Molecule Observation

Plastic is an indispensable material in our daily lives. It is used in a wide variety of products because it is low-cost, mass-producible, and easy to mold and process. However, due to its convenience, the amounts of plastic used and disposed are increasing every year, raising concerns about its environmental impact and sustainability. Therefore, there is a need to develop efficient and environmentally friendly recycling methods, as well as simple and rapid methods to detect plastics that have leaked into the environment.

We are attempting to obtain more active mutants by exhaustively mutating amino acid residues on the enzyme surface and screening their activity using a dispensing robot. We are also attempting to create plastic adsorption domains by modifying the amino acids constituting the adsorption surface of the carbohydrate binding domain and using a phage display method.

These studies will promote the recycling of used plastics by enzymatic degradation and promote more sustainable use of plastics. In addition, by creating a protein that detects and stains plastics, we will contribute to the protection of the natural environment by monitoring the small plastics runoff into the environment (Figure 1).

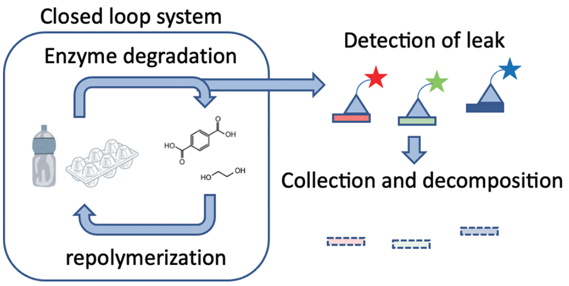

Figure 1. Scheme of plastic recycling and detection system.

Selected Publications

- T. Matsuzaki, T. Saeki, F. Yamazaki, N. Koyama, T. Okubo, D. Hombe, Y. Ogura, Y. Hashino, R. Tatsumi-Koga, N. Koga, R. Iino and A. Nakamura, "Development and Production of Moderate-Thermophilic PET Hydrolase for PET Bottle and Fiber Recycling," *ACS Sustainable Chem. Eng.* **13**, 10404–10417 (2025).
- Y. Ogura, Y. Hashino and A. Nakamura, "Direct Screening of PET Hydrolase Activity in Culture Medium Based on Turbidity Reduction," *ACS Omega* **9**, 34151–34160 (2024).
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1. Development and Production of Moderate-Thermophilic PET Hydrolase for PET Bottle and Fiber Recycling

We developed a highly efficient PET hydrolase variant, PET2-21M, that functions under moderate temperature conditions and enables practical enzymatic recycling of PET bottles and blended fibers.[1)] PET recycling is an urgent challenge, since mechanical methods usually yield downgraded materials and chemical recycling requires harsh reagents and conditions. Enzymatic approaches offer a sustainable alternative, but natural PET hydrolases typically show low activity at moderate temperatures, limiting their industrial applicability. We aimed to engineer a robust enzyme with high catalytic efficiency, thermostability, and broad substrate scope.

We started from our previously optimized variant, PET2-7M, and introduced additional beneficial mutations using random mutagenesis, rational design, and structural insights. We identified seven novel mutations that enhanced activity, and we further modified surface charges to improve PET binding. Inspired by structural features of HotPETase, we redesigned the substrate-binding cleft. By combining these improvements, we created PET2-14M-6Hot, and then advanced it to PET2-21M with 21 total mutations. These changes substantially increased enzyme activity and maintained stability around 60 °C, in contrast to many existing hydrolases that require higher temperatures.

We demonstrated significant performance gains with PET2-21M. Compared to the original PET2, our variant produced about 30 times more soluble degradation products. At 60 °C, in the presence of 20 g/L PET powder, PET2-21M depolymerized 95% of the substrate within 24 hours, surpassing LCC-ICCG, which required 72 °C to reach a comparable result. Even with reduced enzyme loading, PET2-21M remained highly efficient: at 2.5 mg/L, it maintained nearly half of its maximum activity, about twice that of LCC-ICCG under the same conditions. At 40 g/L PET, we achieved almost 80% conversion with 10 mg/L enzyme, and 44% with 5 mg/L, both outperforming the benchmark.

We also validated our variants on PET fibers and blended textiles. PET2-14M-6Hot produced 75.7 mM degradation products from pure PET fibers at 60 °C, exceeding the 70 °C performance of LCC-ICCG. For PET/cotton blends, we measured 62.8 mM compared to 46.7 mM for the comparator. For PET/PU blends at 50 °C, our enzyme generated 19.2 mM, more than double the 8.2 mM obtained with LCC-ICCG. These findings show that our engineered enzymes are effective not only for bottles but also for complex textile waste streams.

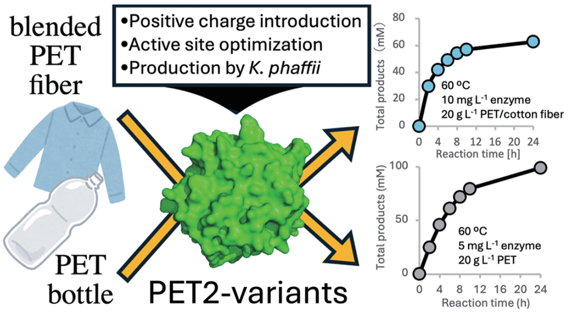

Figure 2. Scheme of PET fiber degrading enzyme development.

To ensure industrial scalability, we expressed our variants in the yeast *Komagataella phaffii*. We obtained high yields, with PET2-14M-6Hot reaching nearly 700 mg/L secretion. We also observed limited glycosylation, simplifying purification and downstream processing. These results confirm that our engineered enzymes can be produced in large amounts in microbial hosts suitable for industrial application.

In summary, we achieved a major advance in enzymatic PET recycling by creating PET hydrolases that combine high activity at moderate conditions with effectiveness on bottles and blended fibers. Our enzymes reduce energy demands, increase efficiency, and can be manufactured at scale. We believe this work provides a strong foundation for future development of cost-effective, environmentally friendly plastic recycling systems that align with circular economy goals.

2. Artificial Evolution of Carbohydrate Binding Domain to PET Binding Domain

To develop a method for detection of plastics using plastic binding proteins, we developed PET binding protein using saturation mutagenesis and M13 phage display. We have already developed 2 generations of mutants which reduced the binding affinity to chitin and cellulose. Thus, we also checked the binding properties of the mutants against PET powder.

The binding affinities of six 2nd generation mutants (LWL to WVF) and one 1st generation mutant (4M) were compared with that of the template protein from *Pyrococcus furiosus* (WT). LWL showed 2.5 times higher binding amount (0.10 nmol) and similar dissociation constant (3.1 mg/mL) than WT (0.041 nmol and 3.2 mg/mL). We started to determine the binding and dissociation rate constants of LWL mutant and WT by single molecule observation for revealing the improved parameter of LWL mutant.

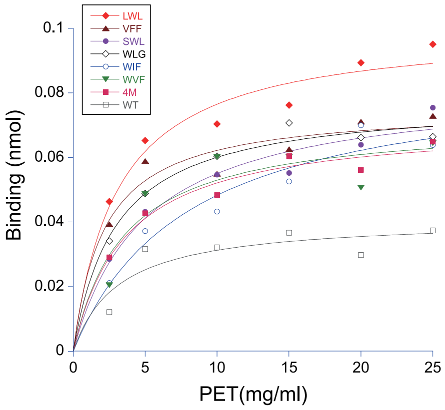

Figure 3. Binding measurement of 2nd generation of mutants against PET powder.

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Molecular Science of Bio-Metal Dynamics: Understanding and Regulation of Metals in the Cells

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Professional Employment

2003	Junior Research Associate, RIKEN
2006	IMS Fellow, Institute for Molecular Science
2007	JSPS Postdoctoral Fellow
2010	Research Assistant Professor, Okazaki Institute for Integrative Bioscience
2013	Assistant Professor, University of Hyogo
2022	Associate Professor, Nagasaki University
2024	Associate Professor (Cross Appointment), Institute for Molecular Science
2025	Professor, Osaka Metropolitan University
2025	Professor (Cross Appointment), Institute for Molecular Science
2025	Visiting Professor, Nagasaki University

Awards

2010	Yamamura Fellow, Fumi Yamamura Memorial Foundation for Female Natural Scientists, Chuo Mitsui Trust and Banking
2012	Shiseido Female Researcher Science Grant, SHISEIDO Company, Limited
2018	Excellent Research Award, The Japanese BioIron Society

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MURAKI, Megumi
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Keywords Cellular Iron Dynamics via Protein Interactions, Live Cell Imaging for Trace Metals by Soft X-Ray

Metals play important roles in sustaining life. Cells are mainly composed of water, proteins, and lipids, but they also contain small amounts of metals that help maintain health by being acquired from food. Those metals have been known for many years to be used as active centers of enzymes that carry out functions essential to sustaining life, *e.g.* transport and storage of oxygen, energy production, gene synthesis. However, the series of molecular mechanisms underlying metal dynamics in the body (absorption, sensing, transport, storage, and excretion of metals) and selectivity for individual metals to maintain the metal homeostasis remain unknown (Figure 1). We focus on "iron," which is the most important metal among the essential metals for sustaining life of living things, and various proteins that play a role in the selective absorption, sensing, and intracellular transport of iron in food. We are not only elucidating the structure of related proteins but also exploring their relationship with their functions in human cells.

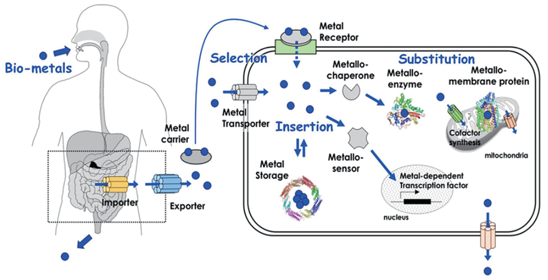

Figure 1. Our aim is to understand the uptake, trafficking, and regulation of "bio-metals" through the relay of protein–protein interactions.

Selected Publications

- M. Ganasen, H. Togashi, H. Takeda, H. Asakura, T. Tosha, K. Yamashita, K. Hirata, Y. Nariai, T. Urano, X. Yuan, I. Hamza, A. G. Mauk, Y. Shiro, H. Sugimoto and H. Sawai, "Structural Basis for Promotion of Duodenal Iron Absorption by Enteric Ferric Reductase with Ascorbate," *Commun. Biol.* **1**, 120 (2018). DOI: 10.1038/s42003-018-0121-8
- G. S. A. Wright, A. Saeki, T. Hikima, Y. Nishizono, T. Hisano, M. Kamaya, K. Nukina, H. Nishitani, H. Nakamura, M. Yamamoto, S. V. Antonyuk, S. Samar Hasnain, Y. Shiro and H. Sawai, "Architecture of the Complete Oxygen-Sensing FixL-FixJ Two-Component Signal Transduction System," *Sci. Signaling* **11**, eaaq0825 (2018). DOI: 10.1126/scisignal.aaq0825
- M. Nishinaga, H. Sugimoto, Y. Nishitani, S. Nagai, S. Nagatoishi, N. Muraki, T. Tosha, K. Tsumoto, S. Aono, Y. Shiro and H. Sawai, "Heme Controls the Structural Rearrangement of Its Sensor Protein Mediating the Hemolytic Bacterial Survival," *Commun. Biol.* **4**, 467 (2021). DOI: 10.1038/s42003-021-01987-5
- H. Sawai, "Molecular Science of Biological Iron: Dynamics and Regulation of Iron Ions and Heme Iron," *Artif. Blood* **33**, 55–63 (2025).

1. Development of Intracellular Fe Imaging in Living Cells Using Soft X-Ray Microscopy

The eminent physician of ancient Greece, Hippocrates, is reputed to have stated that “iron acts as a medicine,” thereby underscoring the maintenance of metal homeostasis within the human body, as well as the pathological consequences arising from altered metal quantities and distributions, which remain enigmatic to this day. Therefore, the regulatory mechanisms of metals in the body and the factors of diseases related to altered metal concentrations are not yet fully understood. In response to these issues, our group, together with Dr. Iwayama’s group at UVSOR, has started to develop new techniques to visualize metals in living cells by chemical species using soft X-rays from this year. Dr. Iwayama has developed the “contact-type soft X-ray microscope”1) for biological samples. This technique allows the measurement of transmitted X-ray images of biological samples at the K- or L-edge energies of metal elements. Biological samples are placed on a Ce:YAG scintillator and covered with a Si_3N_4 membrane. The transmitted X-ray image is converted into a visible-light image by the scintillator and then captured by a CMOS camera. By changing the photon energies, we can obtain photon-energy dependence of transmitted images. From the Lambert-Beer’s law, we can obtain a XANES spectrum for each pixel of the image. The experiment was performed on the beamline BL4B at UVSOR.

Our group is conducting research on iron in living organisms. Iron is an essential metal for all living organisms because of its unique chemical properties that control physiological functions essential for life.2) Conversely, iron within cells is predominantly found in the reduced form of iron ions (Fe^{2+}). However, in a cellular environment where oxygen is present, excess iron can promote reactions that generate hydroxyl radicals, the most potent reactive oxygen species. Oxidized iron ions (Fe^{3+}) have extremely low water solubility and low toxicity.3) However, in a reducing intracellular environment, they are easily converted to Fe^{2+}, indicating that the accumulation of Fe^{3+} can also be a factor in non-alcoholic steatohepatitis, multi-organ dysfunction due to iron overload (hereditary hemochromatosis) and neurodegenerative diseases. Therefore, the technique that can distinguish between Fe^{2+} and Fe^{3+} in living cells and tissues and simultaneously observe their distribution and local concentrations would be useful, but such technology has not yet been developed. First, we tried to observe intracellular iron levels in MDCK cells. However, due to the low iron concentration, we were unable to obtain soft X-ray transmission images with sufficient intensity for analysis. Therefore, in this study, we attempted iron imaging using red blood cells, which have the highest iron content in the body, as a model cell. We succeeded in observing the localized distribution of Fe^{2+} and Fe^{3+} in red blood cells isolated from preserved bovine blood (Figure 2). Moving forward, we will develop a comprehensive library of XANES spectra of hemoglobin to visualize the distribution of iron in hemoglobin based on their states, such as oxygen-bound or met form. We will also conduct similar iron imaging studies in cells with high iron content, such as liver cells.

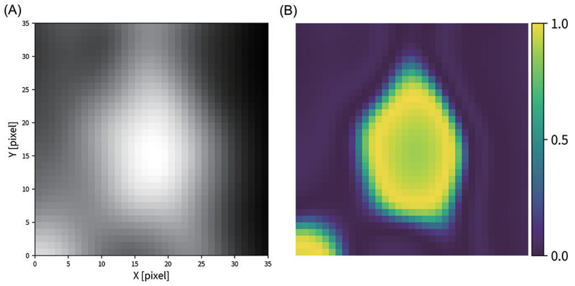

Figure 2. Fe imaging results of a single red blood cell from bovine blood. (A) XANES image of the cell detected at 700 eV. (B) Maps of spectral features calculated from the XANES spectra at each pixel position. This map shows that the Fe^{2+} species are located in the yellowish area.

In addition to developing this new technology, our group has been engaged in research for a few years on the interactions of proteins involved in the absorption, concentration sensing, transport, and storage of iron in cells. We also investigated the maturation process of iron-binding proteins using intracellular iron delivery chaperones.4) This year, we initiated research endeavors aimed at identifying novel genes (proteins) that are influenced by fluctuations in intracellular metal levels. This objective will be achieved by CRISPR screening in cases where intracellular metal levels are high.

Our research has begun to focus on establishing a framework for the future, in which diseases stemming from disruptions in metal homeostasis can be identified at an early stage. This objective will be pursued by leveraging the application of soft X-ray spectroscopy, a technique employed in materials science, to develop novel methodologies within the realm of life sciences (Figure 3).

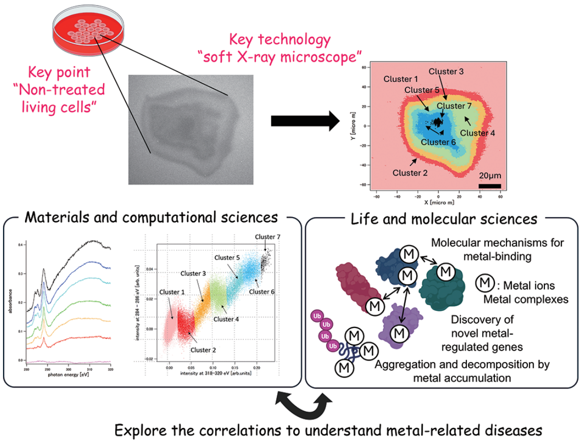

Figure 3. Concept diagram of this study.

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Integration of Quantum Chemistry and Machine Learning for a Deeper Understanding and Rational Design of Functional Materials

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Education

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2008	Ph.D. Keio University

Professional Employment

2009	Research Associate (fixed term/research incentive), Keio University
2011	Fukui fellow, Kyoto University
2015	Assistant Professor, Kindai university
2015	Japan Science and Technology Agency (JST) PRESTO Researcher
2017	Associate Professor, Nara Institute of Science and Technology
2020	Associate Professor, Keio University
2024	Associate Professor (Cross Appointment), Institute for Molecular Science
2025	Professor, Keio University
2025	Professor (Cross Appointment), Institute for Molecular Science

Awards

2017	11th PCCP Prize
2019	12th Young Scientist Award of the Japan Society for Molecular Science
2021	The Chemical Society of Japan Award for Outstanding Young Women Chemists for 2021
2021	MEXT National Institute of Science and Technology Policy (NISTEP), NISTEP Selection (The Researchers with Nice Step) 2021

Member
Secretary
CHIBA, Fumika

Keywords Materials Informatics, Lanthanide, Computational Chemistry

We develop computational methods, apply them to elucidate mechanisms, and design materials using data science techniques such as machine learning (ML). Currently, our research focuses on the following subjects:

(1) Lanthanide Photofunctional Materials

Lanthanide (Ln) luminescence, originating from 4f–4f transitions, has been applied in various optical materials. While the 4f–4f emission wavelengths of Ln complexes are almost independent of the surroundings, the emission intensities are heavily influenced, making the design of appropriate ligand crucial. To get deeper insights into Ln luminescence, we proposed the energy shift method, which has contributed to the understanding and design of various Ln materials and has also been applied to non-Ln systems. However, it could not handle 4f–5d and charge transfer excited states, which are particularly important for cerium and europium complexes. To address this limitation, we are developing an updated method. In addition, we have constructed a database of cerium complexes containing 1.7k geometries and electronic properties. We plan to make this database public and further develop it into a platform for optical function prediction *via* ML.

(2) Transition Metal Catalysts

Transition metal (TM) complexes play a crucial role in organic synthesis, catalyzing a wide variety of chemical reactions. The catalytic abilities of TM complexes can be finely tuned by manipulating ligand-induced electronic and steric effects, which are key to controlling the reactivity and selectivity of specific reactions. In recent years, however, chemical products are being produced in smaller quantities and with greater variety, reducing the time available to study the synthesis conditions for each product. To address this challenge, we are constructing a database of TM complexes with various organophosphorus ligands, ranging from monodentate to multidentate skeletons. For descriptors applicable to different skeletons, we propose using the reaction energies of elementary reactions, such as oxidative addition and transmetallation. Our goal is to accelerate catalyst design by developing an ML model where our descriptors serve as explanatory variables and experimental catalytic activity results are used as objective variables.

Selected Publications

- S. Gocho, H. Nakamura, Q. Gao, T. Kobayashi, T. Inagaki and *M. Hatanaka, "Excited State Calculations Using Variational Quantum Eigensolver with Spin-Restricted Ansätze and Automatically-Adjusted Constraints," *npj Comput. Mater.* **9**, 13 (2023).
- X.-F. Wei, T. Wakaki, T. Itoh, H.-L. Li, T. Yoshimura, A. Miyazaki, K. Oisaki, *M. Hatanaka, *Y. Shimizu and *M. Kanai, "Catalytic Regio- and Enantioselective Proton Migration from Skipped Enynes to Allenes," *Chem* **5**, 585 (2019).
- *M. Hatanaka, Y. Hirai, Y. Kitagawa, T. Nakanishi, *Y. Hasegawa and *K. Morokuma, "Organic Linkers Control the Thermosensitivity of the Emission Intensities from Tb(III) and Eu(III) in a Chameleon Polymer," *Chem. Sci.* **8**, 423 (2017).

1. Ion Energy Shift (IES) Method for Exploring the Reaction Coordinate of Nonradiative Decay from Highly Excited State of Lanthanide Complexes

The exploration of minimum energy crossing points (MEXs) between potential energy surfaces (PESs) is essential for deepening our understanding of nonradiative decay mechanisms and plays a key role in the design of photofunctional materials. However, in lanthanide (Ln^{3+}) complexes, the presence of open-shell 4f electrons leads to quasi-degenerate electronic states, making MEX searches particularly challenging. To address this, the energy shift (ES) method has been used, in which the PES of a 4f–4f excited state is approximated by vertically shifting the ground-state PES by the corresponding 4f–4f excitation energy. This approach eliminates the need for explicit treatment of $4f^N$ electrons, enabling the use of large-core relativistic effective core potential (RECP) and conventional DFT methods to compute relevant states and locate key MEXs. While the ES method has greatly contributed to understanding and designing materials based on 4f–4f luminescence, it cannot be applied to 4f–5d or charge-transfer excited states (*i.e.*, $4f^{N-1}X$ states). To overcome this limitation, we proposed a new approximation, the ion energy shift (IES) method, which described the $4f^{N-1}X$ excited state using the large-core RECP for Ln^{4+} and shifted its PES to match the target excitation energy. The validity of the IES method was demonstrated by comparing its results with those of the multistate second-order perturbation theory (MSCASPT2). We applied it to elucidate the origin of the different excited-state lifetimes of hydrated Ce^{3+} complexes with and without coordination of a carboxylate ligand.

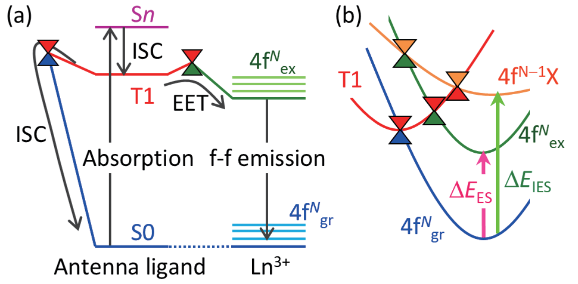

Figure 1. The Jablonski diagram of Ln^{3+} complex (a) and Schematic illustration of the ES and IES methods (b). The PES of the $4f^N$ excited states is described by shifting that of the ground state with the energy shift value of ΔE_{ES}. The PES of the $4f^{N-1}X$ excited state, in which $4f^{N-1}$ electrons were included in the large-core RECP for Ln^{4+}, is shifted to reproduce its excitation energy (ΔE_{IES}).

2. Database of Cerium Complexes for Excited State Analysis and Data-Driven Ligand Design

Since the early 2010s, the concept of data-driven materials discovery, commonly referred to as materials informatics, has gained significant traction. In response, a variety of databases compiling quantum mechanical (QM) calculations of materials have been developed. Large-scale QM datasets for molecules have also been constructed; however, due to the extreme diversity of chemical space, the field remains in a developing stage with respect to data diversity and extensibility. In particular, Ln complexes, which have broad industrial applications, pose challenges for establishing design guidelines because of their distinct structures, bonding characteristics, and physical properties. There is thus an urgent need for a database that captures the structural and electronic diversity of Ln complexes. To address this, we constructed a database of experimentally reported Ln complexes, including their optimized geometries and ground- and excited-state properties computed using DFT and TDDFT methods. In this initial study, we focus on Ce^{3+} complexes, which have recently attracted attention as photocatalysts. We collected 1635 Ce^{3+} complexes from the Cambridge Structural Database and identified key substructures that enhance excitation energy and oscillator strength by building machine learning models.

3. Mechanistic Study of C-Glycosylation Catalyzed by GgCGT Enzyme

C-glycosyltransferases have garnered attention owing to their ability to synthesize C-glycosides with high conversion and selectivity in one-pot reactions. Their potential in rational enzyme engineering makes them valuable for the synthesis of diverse C-glycosides. However, the detailed reaction mechanism remains unclear. To address this, we investigated the C-glycosylation of a polyphenol (phloretin) catalyzed by the glycosyltransferase GgCGT in the presence of the coenzyme UDP-glucose. Using the DFT calculations on a cluster model, we identified the most favorable pathway for C-glycosylation. The reaction proceeds *via* an initial proton transfer from phloretin to UDP-glucose, followed by the nucleophilic attack of phloretin on the glucose moiety and subsequent dissociation of UDP in an S_N2-like manner. The S_N2 step yields non-aromatic intermediate, which can be rapidly converted to C-glycoside even without an enzymatic environment. The key residue that facilitates the rate-determining S_N2 step is His-27, which stabilizes phloretin *via* hydrogen bonding. Additionally, to clarify why alternative products such as O-glycosides are not formed, we also investigated the O-glycosylation pathway. Our calculations revealed that O-glycosylation was promoted by proton transfer from UDP-glucose, like C-glycosylation, but was suppressed by structural fixation due to hydrogen bonding among phloretin, glucose, and GgCGT.

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3) R. Somaki, T. Inagaki and M. Hatanaka, *Mol. Inf.* **44**, e202400041 (2025).
4) H. Yamada, S. Takasuka, S. Oikawa, Y. Harashima, T. Takayama, A. Nag, A. Wakiuchi, T. Ando, T. Sugawara, M. Hatanaka, T. Miyao, T. Matsubara, Y. Ohnishi, H. Ajiro and M. Fujii, *ACS Appl. Eng. Mater.* **3**, 2402–2415 (2025).