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ABSTRACTS

Artificial force induced reaction method: A computational approach for exploring chemical reactions based on quantum chemical calculations

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ABSTRACT

The motion of atoms during a chemical reaction, called reaction path hereafter, can in principle be elucidated by repeatedly performing quantum chemical calculations at all energetically feasible atomic configurations. However, the number of possible arrangements involved in a reaction path can be huge. Previous studies have thus relied on assumptions, i.e., human inputs, concerning the atomic configurations along the targeted reaction path.

The human inputs may bias the results. To avoid that, we have developed an automated reaction path search method called artificial force induced reaction (AFIR) [1]. AFIR explores possible reaction paths automatically by inducing geometrical transformations in a molecule systematically using a virtual force. Combining it with a chemical kinetics method called rate constant matrix contraction (RCMC), on-the-fly kinetics simulation can be performed (FIG. 1).

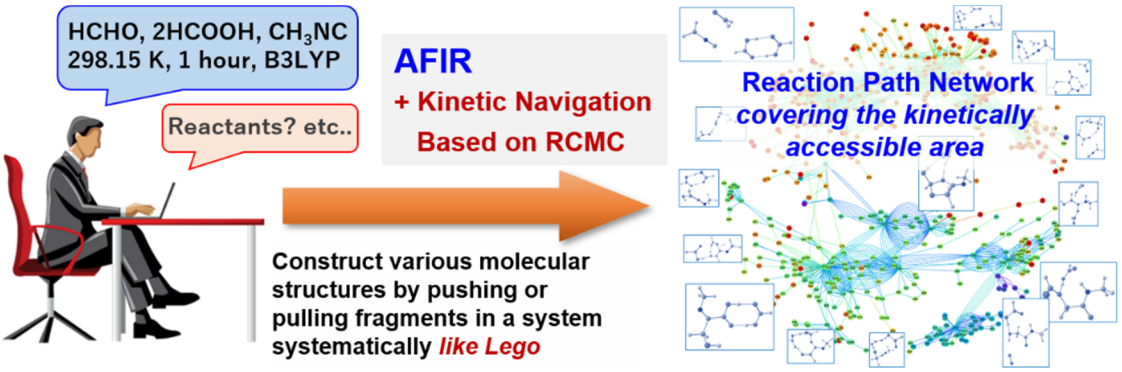

FIG 1. A schematic illustrating on-the-fly kinetics simulation by AFIR and RCMC. Based on the input, i.e., reactants, reaction temperature, reaction time, and computational level, AFIR finds many reaction paths. RCMC identifies the most feasible reaction path from the resultant network.

Recently, we proposed a concept, quantum chemistry-aided retrosynthetic analysis (QCaRA). QCaRA predicts reaction paths affording a given product by an inverse reaction path search from the product toward various reactant candidates using AFIR. In a proof-of-concept study, we set difluoroglycine as the synthetic target. Then, a new synthetic route of producing a difluoroglycine derivative was proposed as the reverse process of one of the obtained reaction paths [2]. Further generalization of the algorithm to perform QCaRA to predict multistep reactions [3] and a new design strategy of transition metal catalysis [4] will also be presented.

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Machine Learning for Heterogeneous Catalyst Design and Discovery

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ABSTRACT

Molecular/materials informatics has become a central paradigm in molecular and materials science thanks to the enormous potential it holds to revolutionize the design of functional molecules/materials. However, although we have already seen proof-of-concept examples that artificial intelligence (AI) can reduce the time and costs involved and also can find new compounds, most of them have only been tested on benchmark problems and no fundamentally-new molecules/materials or synthetic-transformations have been found. This is primarily due to lack of data and that machine learning (ML), the main player in this campaign, is highly focused on optimization rather than finding novel compounds and phenomena (extrapolation).

Establishing "Catalysis Informatics" is even more challenging.[1] Although it is highly related to materials informatics and chemoinformatics, it is distinguished by the fact that catalysis is a time-dependent dynamic event controlled by the structures and chemical nature of catalytically active sites. In particular, heterogeneous catalysis is still a largely empirical science due to the complexity of the surface chemistry involved. This situation causes lack of data as the computational costs to obtain accurate theoretical models for such complex heterogeneous catalysis are currently prohibitively high and high-throughput experimental methods, which have been applied successfully to relevant fields, have not been explored fully at the current time. In this regard, building ML models that effectively find novel catalysts within diverse chemical space from "real world" experimental catalysis data (not from well-behaved computational data) is highly desirable.

In this context, our group has made a new ML approach which uses elemental features as the input representations rather than inputting the catalyst compositions directly.[2,3] Namely, in our proposed method, the elemental composition ratios are multiplied by elemental descriptors such as electronegativities, melting points, atomic radii, etc. which are unique for each element. For demonstration of our ML approach, literature data based on the oxidative coupling of methane (OCM) and water gas shift (WGS) reactions have been analyzed. Our ML approach, which considers elemental features as input representations rather than the catalyst compositions, was successfully applied, and new promising catalyst candidates for future research were proposed. Latest results on CO_2 hydrogenation will also be shown in the presentation.

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Modularly Designed Supramolecular Catalytic Assembly for the Strategic Enantioselective Borylation of Remote C–H Bonds

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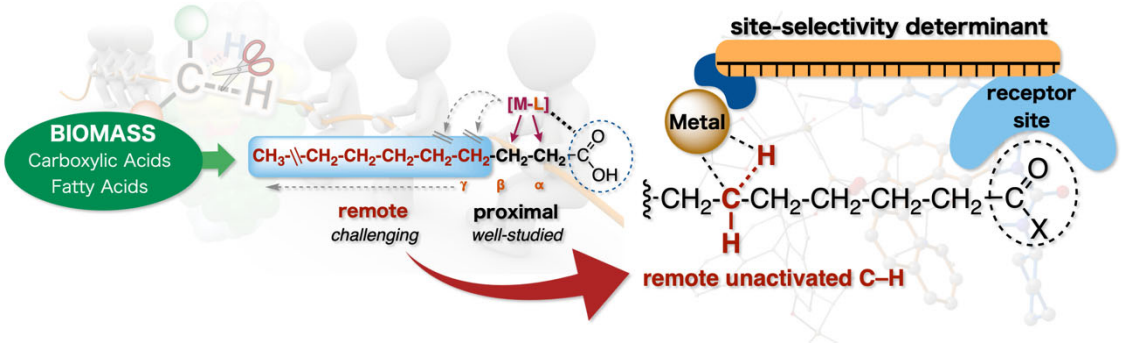
ABSTRACT

There exists in nature efficient catalytic systems that enable the challenging functionalization of ubiquitous C–H bonds in diverse substrate classes. Enzymatic assemblies have inspired the creation of wide-ranging synthetic supramolecular catalysts that mimic their proficient activities. Despite the conceptual advances of these synthetic biomimetic systems, the elaborate preparations and limited substrate compatibility limit their utilities in organic synthesis.

With our interest in the development of novel methodologies for the transformation of C–H bonds in readily available feedstock chemicals, we previously demonstrated the competent activation and subsequent asymmetric borylation of C(sp^3)–H bonds under Ir or Rh catalysts utilizing a chiral monophosphite ligand system allowing the preparation of biologically-active and synthetically useful organoboronates.[1,2] Our collaboration with ICReDD scientists has given us infinite opportunity to further extend the reactivity of our catalytic system. Thus, guided by calculation derived transition-state models, we recently succeeded in the asymmetric borylation of remote γ-C–H bonds in aliphatic carboxylic amides and esters using a chiral, modular Ir-monophosphite catalyst and a urea receptor ligand that recruits the substrate via noncovalent interactions – a direct functionalization realized using a modularly designed supramolecular catalytic assembly.[3] In this aspect, the overall efficiency relies on the crucial interactions between the catalytic system and the substrate within a reaction cavity or pocket that resembles the active site of natural enzymes. Inspired and goal-driven by these results, further collaboration and joint efforts has led us to the possibility of designing catalytic assemblies to target more distal C–H bonds in the aliphatic hydrocarbon chain of common and readily available chemical feedstocks including biomass resources allowing for a more sustainable and efficient organic synthesis.

In this presentation, the development of catalytic enantioselective borylation of C–H bonds will be described in the context of reaction discovery, design, and utility. Strategic convergence of experimental and theoretical studies will be outlined to emphasize our approach in targeting remote C–H bonds beyond the γ-position, further highlighting the need for the creation of methodologies that will allow challenging transformations.



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Novel quantum chemical approach to chemical reactions: reduced-dimensionality reaction space and natural reaction orbital

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ABSTRACT

ICReDD promotes fusion research to accelerate the development of useful chemical reactions through "*Chemical Reaction Design and Discovery (CReDD)*" by integrating computational science, information science, and experimental science. As a quantum chemical computation team, our group is working on elucidating the mechanism of complex chemical reactions in collaboration with experimental and information science groups by applying the artificial force induced reaction (AFIR) method, an automated reaction path search method, which is a fundamental technology of ICReDD. We are also developing new methodologies for chemical reaction analysis based on quantum chemistry. In this talk, I will introduce the reaction space projector (ReSPer) method [1] and natural reaction orbital (NRO) concept [2] as newly developed methods for chemical reaction analysis in our group.

In the quantum chemical approach, the mechanism of a chemical reaction is investigated based on the intrinsic reaction coordinate (IRC) defined on the potential energy surface (PES). The AFIR method allows us to construct a global reaction route map containing multiple IRCs, while the on-the-fly molecular dynamics method, which is based on electronic structure calculations to determine the forces acting on atoms, generate classical trajectories with unrestricted motion on the full-dimensional PES. We have developed a method to visualize the reaction route map in a low-dimensional space by introducing inter-structure distances for structure pairs, and named it ReSPer. It is also possible to project dynamical trajectories onto the reaction space defined based on the reaction route map, which is expected to serve as a general method for analyzing chemical reaction mechanisms and dynamics.

Electronic degrees of freedom dominate the potential energy surface that determines reaction paths and dynamical trajectories, and it is no exaggeration to say that the elucidation of chemical reaction mechanisms is only complete when we understand the movement of electrons associated with changes in molecular structure. The NRO method elucidates the electron motion associated with the movement of nuclear coordinates by pairs of occupied and virtual orbitals, and can extract regions along the reaction path where the electron motion is more pronounced. In this talk, I will demonstrate the usefulness of NRO analysis by applying it to several reactions.

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Negative Charge delivery in ice at 10 K: the role of surface OH radicals

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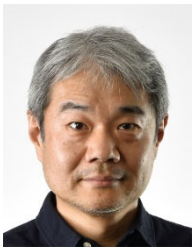

ABSTRACT

Since the study by von Grotthuss at the beginning of the 1800s, ice has been widely accepted to carry a positive current by the transfer of excess protons via H_3O^+, similar to a "p-type" semiconductor. Although the proton transfer is still a matter of controversy at low temperatures and is therefore addressed both experimentally and theoretically, this phenomenon can be well described by the Grotthuss mechanism. In contrast, although "proton-hole transfer (PHT)" has been theoretically proposed as a possible mechanism for delivering negative charges in water and ice, no clear evidence for the occurrence of this mechanism has been provided. Consequently, the concept of negative current conductivity by the PHT has remained to be confirmed experimentally for a hundred years.

Recently, we observed experimentally a negative constant current through ice at 10 K when OH radicals coexist with electrons on the ice surface [1]. From quantum chemical calculations and the experiments using the combination of photostimulated desorption and resonance-enhanced multi photoionization methods [2], the surface OH radicals were monitored with and without electrons [3], we conclude that once OH adsorbate captures an electron on the surface, the surface OH^- anions trigger the flow of negative current in ice by the sequential PHT in ice. The OH^- on the surface reproduces H_2O after proton abstraction from neighbouring H_2O. Negative current conductivity was found to be preserved even at temperatures below 50 K, where a positive current by the well-known Grotthuss mechanism is highly suppressed. The negative charge delivery by the PHT was also confirmed in other hydrogen-bonding systems like SH_2 and NH_3 solids.

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Transient Charging and Charge Carrier Trapping in Semiconductor Nanocrystals

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ABSTRACT

The size- and composition-dependent tunable bandgap or emission color of cadmium chalcogenide quantum dots and hybrid halide perovskite nanocrystals are fascinating inventions in nanoscience and nanotechnology.[1,2] The tunable optical and electronic properties accompanied these tiny crystals to various disciplines of basic research,[1,3] making them promising for brilliantly luminescent displays, high-efficiency photovoltaics, and sophisticated quantum computers. However, photo-generated carriers in these tiny crystals show stochastically fluctuating carrier/exciton recombination rates, rendering these semiconductors intermittent or blinking light emitters at the single particle levels.[4-9]

Conversely, interparticle states and carrier traps enable delayed emission in closely packed states, extending the photoluminescence lifetime to the microsecond scale. For single quantum dots, the blinking time fluctuates on a wide time scale – from microseconds to minutes, preventing the applications of these nanomaterials to on-demand light sources. The size, ligands, surface morphologies, chemical compositions, the nature and density of defects, the intensity and energy of incident light, and band-edge states affect the exciton, carrier, and intermittency stabilities/durations. Although the relations of blinking to the intensity and energy of incident light and the nature and density of defects are widely appreciated since 1995,[3] the development of non-blinking quantum dots or nanocrystals is challenging even today.

This presentation highlights synthesis, quantum confinement, bandgap engineering, and optical properties of selected semiconductor quantum dots with special references to the origins of long photoluminescence lifetimes,[10-12] and intermittent emission[5-8,13] and suggests methods to cosset the blinking by carrier de-trapping, electron transfer, or defect passivation.

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Acceleration of Designing Chemical Reactions by Contextual Multi-armed Bandit Algorithm

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ABSTRACT

Most typical machine learning approaches for chemical reactions is perhaps first to map the desired quantities such as reaction yield, enantioselectivity etc measured for many systems with different catalysts, substituents, and experimental conditions for a reaction to be explored to a certain feature space, and then to infer which feature(s) are most relevant to the desired quantities, which may help to design a desired reaction system with high yield and/or high enantioselectivity. However, this approach requires a huge set of reaction data *a priori*, which includes lots of undesired reactions of low performance to reveal the important features.

Reinforcement learning, utilized in the Monte Carlo tree search in alpha-GO, does not necessarily require any set of data *a priori*, and is rather aimed at providing an experimentation protocol on how to choose next experiment (that may have different catalyst, different substituents and forth) in order to discover the desired reaction system(s) with as fewer experiments as possible, with guaranteeing the accuracy of the prediction.

In this talk, we present our recent study on designing chemical reactions in which contextual multi-arm Bandits algorithm[1,2] in reinforcement learning is introduced to choose a catalyst to yield high enantioselectivity for an asymmetric hydroalkoxylation reaction. Here, as a proof-of-concept of our algorithm, we used 38 reaction data associated with enantioselectivity and more than 500 dimensional molecular features extracted by ISIDA descriptor, with the knowledge of the most desired reaction[3]. We show how one can accelerate to discover the most desired reaction before being performed all experiments.

This is a joint collaboration with List group (Dr. Tsuji) and Varnek group (Dr. Sidorov) in ICReDD.

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Approaches to Construction of Chemical Reaction Image Diagnosis System Using Machine Learning

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ABSTRACT

Appearance information such as color and shape are usually used to distinguish compounds. When confirming the progress of chemical reactions, there are many opportunities to judge the appearance of compounds. However, precision in judging the reaction yield varies significantly depending on experimental skills and knowledge level. By making machine learning models[1] using well-defined images of compounds, we expected that anyone can easily perform the diagnosis of reaction yields with high reproducibility, instead of using unclear parameters based on empirical results.

In this presentation, I would like to talk about the construction of an imaging diagnosis system using machine learning models, collaborating with Prof. Takikawa's group (ICReDD). In order to conduct image diagnosis of reaction yields, it is necessary to discriminate quantitatively compound ratios before and after the reaction. The effective collection of images in appropriate formats for machine learning is also an important factor. We proposed to use commercially available sugar (sucrose) and table salt (NaCl: sodium chloride) to create a large number of datasets with desired mixing ratios (wt%) (**Fig. 1a**). To ensure higher diagnostic accuracy, we attempted to normalize the imaging capture settings. After optimization of the amount and shape of the mixture samples, image diagnosis systems embedded with the pre-trained model (using 500 images) were constructed. A third person uploads an image prepared with any mixing ratio to the diagnostic imaging system, and the predicted values are displayed on the system within a few minutes (**Fig. 1b**). It is also available to provide observed-predicted plots, MAE, RMSE, and R2 values as evaluation indicators (**Fig. 1c**). Furthermore, we can predict with high accuracy the mixture sample ratio of α-glycine and γ-glycine, which have different crystal polymorphs[2].

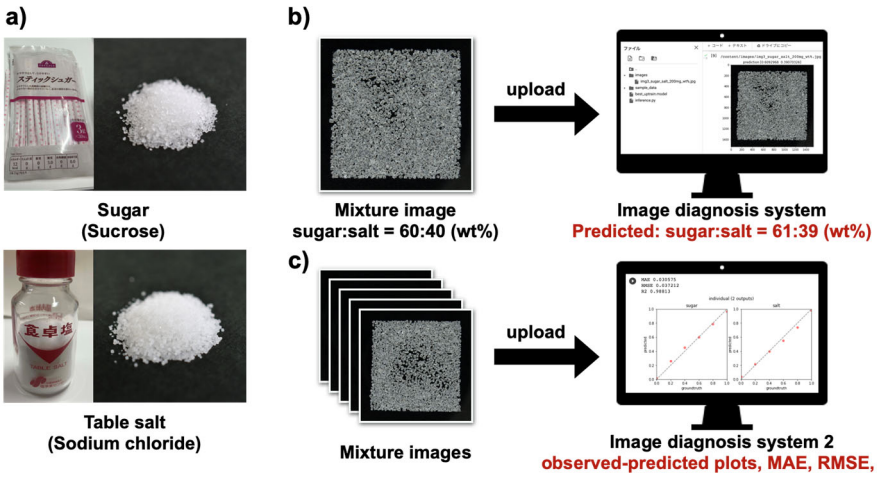

Fig. 1 Quantitative image diagnostic system using sugar and salt. **(a)** Commercial sugar and salt. **(b)** Simple image diagnosis system. **(c)** Image diagnosis system capable of exporting accuracy evaluation indicators.

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Data Representations for Deep Learning and Chemistry-Related Applications

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ABSTRACT

The ultimate goal of modern drug discovery is to find the target molecules with desired chemical properties, while the potential chemical space of drug-like compounds is 10^{23}–10^{60}.

Visual graph query composition can assist modern drug discovery. Instead of exploratory searching given a subgraph query in graph databases and showing matched graphs, we prefer to use generative models to grow novel molecules on the given subgraph. In the applications of drug discovery, such a subgraph query is usually called a scaffold (i.e., privileged or bioactive scaffold), and performs as a core structure in the molecule to preserve the preferable bioactivity properties. The generated novel molecular graphs are supergraphs of the scaffold thus being guaranteed to contain the scaffold to reveal the chemical properties. Fixing the scaffold usually dramatically reduces the search space of the desired drug thus saving experts' time and cost.

Due to surprising success of deep neural network (DNN) models these days, two categories of representations used in DNN-based models emerge in the drug discovery domain. (1) simplified molecular input line entry system (SMILES) strings representation. Several early works were proposed to learn the SMILES grammar using RNN architectures and then generate corresponding SMILES strings from the trained models. These methods have limitations to learning the unrelated grammar and thus have low chemical validity from generated SMILES. A recent trend is (2) undirected labeled graph representation. It is more natural to learn the original graph structure by using graph neural networks (GNNs). This representation can easily achieve higher chemical validity. In our work, we adopt the graph-based representation along with GNN models as our generative models. GNN models are employed during the visual graph query composition process to generate completed candidates.

In this talk, we present our recent study[1] on a GNN-based molecular graph generation system, to allow users to edit the intermediate graph candidates during the molecule design process in multiple steps, utilizing the edit operation to predict the user's real intention to improve effectiveness. We design an interactive substructure-by-substructure adopt process to verify this idea. This process guarantees the involvement of user decisions to interact with a generative user-centered AI system, which differentiates our work from previous studies that generate graphs in a single run. We test our system using a real-world molecular dataset containing nearly one million graphs to show the performance.

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Mechanochemical Organic Synthesis: A Revolution Platform

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ABSTRACT

Mechanochemical reactions have recently attracted attention as a new platform for the development of environmentally friendly organic reactions, as they can significantly reduce the usage of organic solvents and reduce the reaction times. Furthermore, by exploiting the unique environment of mechanochemical reactions, new reactions that cannot be found in solvents are expected to develop. It is expected that many organic chemists will make use of mechanochemical reactions in the future. The limited number of reactions tend to be used more frequently than others in the synthesis of organic compounds. It thus would be useful to focus on the most widely used reactions. The Suzuki-Miyaura and Hartwig-Buchwald couplings are extremely important reactions, representing 32% of those used in drug discovery. However, under mechanochemical conditions, catalyst deactivation and poor reactivity with solid substrates has been a problem. We found that the addition of 1,5-COD and heating conditions dramatically improve the efficiency of these cross-coupling reactions of solid substrates.[1-4] Grignard reaction is one of the fundamental and most widely used organic reactions developed by Victor Grignard 120 years ago. To conduct this reaction mechanochemically, we thoroughly investigated the reaction conditions and achieved almost the same reactivity as the Grignard reagent synthesized in solution under ball mill conditions.[5] We also developed mechano-redox reactions that mimics the photoredox reaction, which has attracted much attention recently, using piezoelectric materials.[6,7] Mechanochemical polymer functionalization will also be presented.[8]

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Imaging the mechano-chemical feedbacks in biological patterning

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ABSTRACT

Cell polarity is necessary for diverse processes during development and prevents progression of cancer and ageing. A hallmark of polarized metazoan cells is the segregation of partitioning-defective (PAR) proteins into distinct compartments at the cell cortex. However, the design principle that governs local interactions among PAR proteins into global cellular patterning remains elusive. Using *Caenorhabditis elegans* zygotes as a model system, my group uncovered 1) the mechanisms underlying symmetry breaking by sperm-donated centrosome[1,2,3,6], and 2) how physical properties of the cell cortex ensures asymmetric segregation of PAR proteins[4]. Based on the core molecular players and interactions in zygotes, we re-constructed the pattern-forming circuits of PAR polarity network in apolar blastomeres[7] and non-metazoan yeast cells[5]. Our findings provide the simplest network that executes self-organizing polarization, which will permit synthetic control of the cell polarity program in living organisms.

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Structural bioinformatics studies of viral proteins

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ABSTRACT

Hemorrhagic fever viruses (HFVs), such as filovirus, arenavirus, nairovirus, are zoonotic pathogens that often cause severe, life-threatening disease in human. There are only a few approved therapeutics for these viral diseases. Although it has been reported that some antiviral drugs such as nucleotide analogues clinically used for other viral diseases may also be beneficial against these viruses, their efficacies have not been fully proven and concerns about adverse effects remain. Thus, the development of effective and safe therapeutics against hemorrhagic fever viruses is of crucial importance.

The present work was designed with two broad research objectives. Firstly, we aimed to computationally predict and experimentally evaluate the functionally relevant sites required for replication of hemorrhagic fever viruses, particularly the Ebola virus (EBOV). Secondly, as a complement to the previous objective, we focused on the design of small compounds that could target these functional regions of viral proteins.

In order to predict protein interaction sites on viral proteins, we analyzed 3D structures of viral proteins by using patch analysis. We found a novel hydrophobic patch on the surface of the EBOV VP35 protein and predicted that this patch is a functionally important site. Although the functionally important sites on viral proteins might be potential targets for antiviral drug discovery, most of these sites are likely to be engaged in protein-protein interactions (PPIs). Generally, targeting PPIs with small molecules is challenging, since protein–protein interfaces are relatively large, flat areas (1500–3000 $Å^2$). In this study, we explored the suitability of using small compounds to inhibit PPIs in viral proteins using several computational approaches. Druggable sites, or sites engaged in PPIs, on EBOV proteins were predicted using a combination of patch and cavity analyses. One site on VP35 was selected as a target for antiviral drug discovery. The other method, mixed solvent molecular dynamics simulation, confirmed the druggable site on VP35. We then performed *in silico* screening of 5,597 compounds from DrugBank, and the top-ranked compounds were selected for an *in vitro* assay. In this presentation, we will discuss the results obtained through our current analyses.

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Physics of gene regulation – Looking at genome from the viewpoint of soft matter physics and chemical reaction researches

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ABSTRACT

Recent development of experimental techniques, such as super-resolution microscopes and next generation sequencing techniques, has revealed highly organized structure of genome in the nucleus of eukaryotic cell. The structure and dynamics of genome is involved in the regulation of gene expression. For example, heterochromatin, which is highly condensed region of chromatin, coexists with euchromatin, which is relatively dilute region of chromatin[1]. Transcription, which is the first step of gene expression and is one of the important chemical reactions in life, is suppressed in heterochromain and is active in euchromatin. Enhancers, which are regulatory DNA sequences, are located at a few kb away from promoters of the target genes. Transcription machineries, such as RNA polymerase II, transcription factors, and mediators, form so-called transcriptional condensates by liquid-liquid phase separation and enhancers regulate the expression of target genes by localizing these genes at the proximity to the transcriptional condensates[2]. The structure and dynamics of genome as well as nuclear bodies, such as transcriptional condensates, can be treated by using an extension of soft matter physics. It is of interest to understand how gene expression is regulated by the structure and dynamics of genome as well as the interaction with other structures in nucleus, such as nuclear bodies and nuclear membranes, by combining the soft matter physics and the kinetics of biochemical reactions involved in gene expression.

In this talk, I will introduce our attempt to understand the mechanism of the assembly of paraspeckles[3-4] by the fusion research between (experimental) RNA molecular biology and (theoretical) soft matter physics, as an example of providing new understanding of biological systems by looking these systems from the viewpoint of soft matter physics and chemical reaction researches.

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