10月28日（木）

Zoom ブレイクアウトルーム

口頭発表５

＜口頭発表５＞『計算化学（分子計算）／計算化学（分子認識）／分子ロボティクス』
座長：佐藤 佑介（東北大学）、高岡 雄司（ダッソー・システムズ㈱）

05-01 Hiroki Ozono (Kagoshima University)
"Visualization of the interfacial electrostatic complementarity: A method for analysis of protein-protein interaction based on fragment molecular orbital method"

05-02 Suyong Re (National Institutes of Biomedical Innovation, Health and Nutrition)
"gREST prediction of substrate bindings to stereoselective enzymes"

05-03 Ikuo Kurisaki (Kobe Univ., Grad. Sch. Sys. Inform.)
"Prediction of Disassembly Pathway of Multimeric Protein Complex by Hybrid Monte Carlo Simulations"

05-04 Ken Komiya (Japan Agency for Marine-Earth Science and Technology)
"Investigation of the optimal arrangement of state sequences for efficient operation of a DNA state machine"

05-05 Gregory Gutmann (Tokyo Institute of Technology)
"Toward Hands-on Molecular Design and Testing Enabled by Interactive VR Simulation"

05-06 Hirotaka Kondo (Kansai University, Organization for Research and Development of Innovative Science and Technology)
"Development of a prototype VR AFM manipulation system emulated by a dispensing machine"

05-1

Visualization of the interfacial electrostatic complementarity: A method for analysis of protein-protein interaction based on fragment molecular orbital method

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Keywords: Electrostatic complementarity, Protein–Protein interaction, Fragment molecular orbital method, PAICS

Protein–protein interactions (PPIs) are extensively investigated due to their important roles in numerous biological processes, resulting in that PPIs are now spotlighted as a new target of drug discovery. Additionally, a detailed understanding of PPIs is essential for the design of antibodies used for various research purposes and/or therapeutic applications based on their high affinity and target specificity. Therefore, the importance of computational approaches to provide physicochemical insight into PPIs has increased. To accurately evaluate the charge transfer and polarization caused by the protein–protein bindings, quantum chemical approaches are desired.

Very recently, we developed a method for analyzing the PPI based on the *ab initio* fragment molecular orbital (FMO) method [1,2], which is called visualization of the interfacial electrostatic complementarity (VIINEC). In this method, electrostatic interaction at the protein–protein interface can be visually analyzed using the electron density (EDN) and electrostatic potential (ESP) obtained from the FMO calculation of the complex. VIINEC was implemented in PAICS (one of the FMO program packages) [3,4], and several calculations showed that VIINEC quantitatively evaluates the electronic induced fit due to the complex formation by comparison with the ESPs calculated in the isolate condition. The degree of the contribution of each amino acid to the electrostatic complementarity between the proteins was also quantitatively calculated. In addition, a part of the mechanism of the specificity of the target recognition of anti-bodies could be addressed.

Here we report the methodological aspects of VIINEC and illustrative calculations for the complexes of programmed cell death-1 (PD-1) with its ligand or anti-bodies targeting PD-1, which demonstrates the potential of VIINEC in life-science researches.

[1] T. Ishikawa, A novel method for analysis of the electrostatic complementarity of protein-protein interaction based on fragment molecular orbital method, Chem. Phys. Lett., 761 (2020) 138103.
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05-2

gREST prediction of substrate bindings to stereoselective enzymes

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Keywords: Protein-ligand binding, Molecular dynamics simulation, generalized replica-exchange with solute tempering

Molecular Dynamics (MD) simulations are increasingly used to predict protein-ligand bindings. Advances in enhanced sampling algorithms enable us to perform ms-scale simulations, rapidly raising the predictive power. Here, we apply the generalized replica-exchange with solute tempering method, gREST [1], which is a generalization of REST/REST2 [2], for the prediction of substrate bindings of stereoselective enzymes, Fsa2 and Phm7 [3]. Two enzymes catalyze [4+2] cycloadditions to form enantiomeric products. The gREST simulations extensively sampled possible binding poses otherwise elusive in conventional simulations, predicted the binding models consistent with the site-directed mutagenesis experiment. Intriguingly, the substrate bound to each of enzymes exhibits largely different flexibility, suggesting the distinctive mechanism behind these stereoselective reactions.

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05-3

Prediction of Disassembly Pathway of Multimeric Protein Complex by Hybrid Monte Carlo Simulations

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Keywords: Molecular Recognition, Molecular Dynamics, Mass Spectrometry, Hybrid Monte Carlo

Physicochemical characterization of multimeric biomacromolecule assembly and disassembly processes is a milestone for understanding biological phenomena at the molecular level. Mass spectroscopy (MS) and structural bioinformatics (SB) techniques have become feasible to identify subcomplexes involved in such processes [1,2]. This kind of information can be an initial and critical step toward calculations of free energy profiles of the processes, although the atomistic information that MS and SB studies give is not satisfactory for the purpose.

To combine information derived from MS and SB studies with conventional free energy calculation protocols, we designed a new reaction pathway sampling method by employing a hybrid Monte Carlo/Molecular Dynamics (hMC/MD) scheme [3]. Rare events such as associative and dissociative molecular diffusions are accelerated in each MD phase by employing Steered MD (SMD) method. A reaction coordinate of the SMD simulation is randomly selected from the candidates of subunit pairs. Meanwhile, a configuration generated by enhanced sampling is rejected with a certain probability by Metropolis algorithm in MC phase to circumvent selection of subcomplex configurations anomalously deformed by the usage of the SMD simulations.

First, we applied it to simulating the disassembly process of serum amyloid P component (SAP) pentamer, a ring-shaped homomeric protein complex. The disassembly process we simulated is consistent with that of the earlier MS and SB studies for SAP subcomplex species. Furthermore, we observed a novel dissociation event, the ring-opening reaction of SAP pentamer, where one of the five subunit interaction interfaces is broken. This ring-open form emerges in advance to the other set of subcomplexes, the trimer plus dimer and tetramer plus monomer.

Next, employing free energy calculation combined with the hMC/MD reaction pathway trajectories, we obtained experimentally testable observations on (1) reaction time of the ring-opening reaction and (2) importance of Asp42 and Lys117 for stable formation of SAP oligomer.

We would also present the latest progress of the hMC/MD scheme, modifications to efficiently predict the disassembly process of heteromeric protein complexes.

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05-4

Investigation of the optimal arrangement of state sequences for efficient operation of a DNA state machine

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Keywords: DNA state machine, hairpin structure, statistical thermodynamic model

Whiplash PCR (WPCR) is a unique reaction system, which implements successive state transitions according to a computational program encoded by each DNA molecule, in the form of pairs of state sequences and intervening stopper sequences [1]. By iterating hairpin structure formation and DNA polymerase extension, WPCR allows the program-parallel computation to perform various types of information processing, including solution to a graph problem [2]. However, WPCR requires very high temperature conditions due to its characteristic reaction design utilizing the sub-stable hairpin formation. We formerly revealed that the competitive formation of the sub-stable hairpin structure as the target structure leads to the requirement of high temperature conditions [3, 4]. In this work, we investigated the effect of changing the arrangement and length of state sequences on the efficiency of the target hairpin structure formation. The present results would help to improve the design of WPCR, by reducing the problematic thermophilic property of the DNA state machine with the aid of statistical thermodynamic model simulation. In addition, we report a preliminary investigation of the proposed design via a biochemical experiment.

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05-5

Toward Hands-on Molecular Design and Testing Enabled by Interactive VR Simulation

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Keywords: Molecular Robotics, Interactive VR Simulation, Hands-on Molecular Design and Testing

Works in molecular and nanoscale research and engineering continue to be more common as the desire for better drugs, nanoscale machines, and materials are constant. However, the process of designing at the nano-scale is complicated by the fact that we cannot see or interact with target molecular objects directly due to their sizes. As a solution to this, we are proposing a method that will enable hands-on design and testing of nanoscale structures and systems. We are proposing an interactive VR simulation system that enables users to dive into the molecular world and interact with biomolecules at the nanoscale, as well as simulate with conventional MD equations. It is feasible that we could load atomic structures, probe their dynamics in VR, reposition them in solvent, simulate with conventional equations, and then probe the dynamics again to see the changes in the system. This would enable researchers to quickly set up experiments and obtain results in a hands-on manner, in contrast to time-consuming data entry, or relying on testing large sets of random initial conditions to find possible solutions.

By combining an interactive VR environment and molecular dynamics simulation, we believe our proposed work will be able to offer greater insight into the molecular world and enable a greater degree of control over the setup of virtual experiments, enabling users to analyze and understand the molecular world in greater detail as it floats in front of them in VR.

[1] Gregory Gutmann, Ryuzo Azuma, Akihiko Konagaya: A Virtual Reality Computational Platform Dedicated for the Emergence of Global Dynamics in a Massive Swarm of Objects, *J. of the Imaging Society of Japan*, **2018**, 57(6), 647-653.

05-6

Development of a Prototype VR AFM Manipulation System Emulated by a Dispensing Machine

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Keywords: Molecular Robotics, VR Simulation, Atomic Force Microscope, DNA origami

Molecular manipulation using a microscope probe tip is one of promising approaches to be applied not only for observation but also for selective molecular capture and microfabrication. In order to solve difficulties in operations of molecular manipulation using microscope imaging, we propose a VR system for interactive and intuitive molecular operations. The system consists of a virtual Atomic Force Microscope (VAFM) as a molecular-sized robot arm, virtual molecules, and a remote machine operation interface. Our virtual nano-mechanical DNA origami device (VDNA pliers) attached on the VAFM can bind a single target molecule selectively, so that it works as a gripper of the robot arm.

The remote machine operation interface enables us to manipulate a real experimental equipment from the VR system. Currently, we can intuitively manipulate virtual AFM, which is a dispensing machine that emulates a real AFM, with hand movements and observe the movement. This is a first step toward a nanoscale manipulator that can intuitively manipulate target molecules with DNA pliers attached to the end of an AFM cantilever operated from the VR system.

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