Oral Presentation 7

日時：2020 年 10 月 30 日 13:00-14:30
チャンネル：1

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『新型コロナ等ウィルス対策/計算化学(分子認識)』
Drug Discovery/Clinical application (Focused on COVID-19)

座長：片倉 晋一 （慶應義塾大学）
Shinichi Katakura (Keio University)
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Kaori Fukuzawa (Hoshi University)
広川 貴次 （産業技術総合研究所）
Takatsugu Hirokawa (AIST)

O1-08
"Interaction analyses between SARS-CoV-2 main protease and inhibitor N3 by using fragment molecular orbital method and molecular dynamics simulation"
Ryo Hatada
(Department of Chemistry & Research Center for Smart Molecules, Faculty of Science, Rikkyo University)

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"Interaction analyses on SARS-CoV-2 spike proteins by using fragment molecular orbital method"
Kazuki Akisawa
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O1-10
"Predicting inhibitors for SARS-CoV-2 RNA- dependent RNA polymerase using machine learning"
Nazim Medzhidov
(Elix, Inc.)

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"Theoretical insights into the molecular mechanism of NA-I117V-Mediated Oseltamivir Resistance in H5N1 Avian Influenza Virus"
Mohini Yadav
(Department of Engineering, Chiba Institute of Technology)

O1-08

Interaction analyses between SARS-CoV-2 main protease and inhibitor N3 by using fragment molecular orbital method and molecular dynamics simulation

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Keywords: SARS-CoV2, Fragment molecular orbital (FMO) method, Molecular dynamics

Many research groups have engaged a variety of investigations against the worldwide issue of SARS-CoV-2. Here, we have performed a combination approach of fragment molecular orbital (FMO) calculation and molecular dynamics (MD) simulation to analyze the interactions between the SARS-CoV-2 Main protease (Mpro) and the N3 inhibitor in a statistical manner.

Prior to the MD-assisted investigation, a detailed analysis with inter-fragment interaction energy (IFIE) was performed for the crystal structure (PDB ID: 6LU7) [1] of complex between Mpro and N3 inhibitor, based on the FMO-MP2(PR)/6-31G* calculation by using ABINIT-MP [2,3]. Using AMBER [4], MD simulations for 100 ns were then performed from the 6LU7 initial structure, and a total of 100 structures were extracted from the trajectory. These sampled structures were subjected to a series of FMO calculations, and statistical evaluation of IFIEs was made.

Through these studies, several amino acid residues such as His163 and Glu166 was identified to be important in interacting with N3 with hydrogen bond. Interestingly, the structural fluctuation via MD sampling could alter the relative importance among the residues. We will report on the details of these results on the presentation day.

[Acknowledgment] The present work was supported by MEXT as a social and scientific priority issue #6 to be tackled by using post-K computer (FS2020), AMED-BINDS (JP20am0101113), and Rikkyo SFR. MD simulations were performed using TSUBAME 3.0 (BINDS quota) at the Tokyo Institute of Technology. For FMO calculations, computational resources of FX-100 at Nagoya University, RIKEN R-CCS Fugaku (priority trial use against coronavirus) and Oakforest-PACS (hp200146 quota) at JCAHPC were used.

[1] Jin, Z., *et al.*, Structure of Mpro from SARS-CoV-2 and Discovery of Its Inhibitors. *Nature*, 582 (7811): 289-293, **2020**.
[2] Tanaka, S., *et al.*, Electron-Correlated Fragment-Molecular-Orbital Calculations for Biomolecular and Nano Systems. *Phys. Chem. Chem. Phys.*,16 (22): 10310–10344, 2014.
[3] Hatada, R., *et al.*, Fragment Molecular Orbital Based Interaction Analyses on COVID-19 Main Protease − Inhibitor N3 Complex (PDB ID: 6LU7). *J. Chem. Inf. Model.*, 60 (7): 3593–3602, 2020.
[4] <https://ambermd.org/>.

O1-09

Interaction analyses on SARS-CoV-2 spike proteins by using fragment molecular orbital method

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Keywords: SARS-CoV2, Spike protein, Fragment molecular orbital (FMO) method, MP4(SDQ)

It is well known that the spike protein of SARS-CoV-2 commits the infection to human cells. Thus, considerable efforts in worldwide have been conducted to understand the natures of this protein build with 3 chains (a total of 3.3 thousand amino acid residues). Here, we have performed highly correlated FMO (fragment molecular orbital) calculations with ABINIT-MP [1]. The calculated systems were the spike protein of both closed (PDB ID: 6VXX) and open (PDB ID: 6VYB) structures and also a couple of RBD (receptor binding domain) complexes with human ACE2 (angiotensin-converting enzyme 2) (PDB ID: 6M0J) and B38 antibody (PDB ID: 7BZ5).

The structures of 6VXX and 6VYB were prepared with a homology modeling and relaxed by an MD (molecular dynamics) annealing using AMBER [2]. The structure preparations for 6M0J and 7BZ5 were rather simply done with MOE [5]. The level of FMO calculations were MP2, MP3 [2], and MP4(SDQ) [3], and a scaling for correlation energy such as MP2.5 was adopted to improve accuracy. The basis sets were 6-31G* and cc-pVDZ. A series of IFIE (inter-fragment interaction energy) analyses were then made for these systems.

It was found that the inter-chain stabilization energies (A-B, B-C and C-A) of the open structure (6VYB) were sizably different from those of the closed structure (6VXX). In particular, the stabilization energy of RBD in chain B of 6VYB is remarkably decreased relative to that of 6VXX. The importance of charged residues in chain interactions was illuminated as well.

The calculated IFIEs of 6M0J and 7BZ5 suggested that the stabilization energy loss of RBD in chain B is partly compensated by the binding with ACE2 and B38 antibody. These results could be consistent with the fact that the open structure is responsible for the infection to human cell and the target of antibody. The details of these results will be reported on the day of the presentation.

[Acknowledgment] The present work was supported by Rikkyo SFR and AMED-BINDS (JP20am0101113). The world's largest scale higher-order correlated FMO calculations were carried out using the RIKEN R-CCS "Fugaku" (priority trial use against coronavirus) and the ITO System A (hp200147 quota) at the Kyushu University.

[1] Tanaka, S., et al., Electron-Correlated Fragment-Molecular-Orbital Calculations for Biomolecular and Nano Systems. Phys. Chem. Chem. Phys.,16 (22): 10310−10344, 2014.
[2] <https://ambermd.org>.
[3] Mochizuki, Y., et al., Large-Scale FMO-MP3 Calculations on the Surface Proteins of Influenza Virus, Hemagglutinin (HA) and Neuraminidase (NA). Chem. Phys. Lett. 2010, 493 (4), 346–352.
[4] Mochizuki, Y., et al., Higher-Order Correlated Calculations Based on Fragment Molecular Orbital Scheme. Theor. Chem. Acc. 2011, 130 (2), 515–530.
[5] < https://www.chemcomp.com/>.

O1-10

Predicting inhibitors for SARS-CoV-2 RNA-dependent RNA polymerase using machine learning

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Keywords: SARS-CoV-2, RdRp, Machine Learning

Global coronavirus disease pandemic (COVID-19) caused by newly identified SARS-CoV-2 coronavirus continues to claim the lives of thousands of people worldwide. The unavailability of specific medications to treat COVID-19 has led to drug repositioning efforts using various approaches, including computational analyses. Such analyses mostly rely on molecular docking and require the 3D structure of the target protein to be available. In this study, we utilized a set of machine learning algorithms and trained them on a dataset of RNA-dependent RNA polymerase (RdRp) inhibitors to run inference analyses on antiviral and anti-inflammatory drugs solely based on the ligand information. We also performed virtual screening analysis of the drug candidates predicted by machine learning models and docked them against the active site of SARS- CoV-2 RdRp, a key component of the virus replication machinery. Based on the ligand information of RdRp inhibitors, the machine learning models were able to identify candidates such as remdesivir and baloxavir marboxil, molecules with documented activity against RdRp of the novel coronavirus. Among the other identified drug candidates were beclabuvir, a non-nucleoside inhibitor of the hepatitis C virus (HCV) RdRp enzyme, and HCV protease inhibitors paritaprevir and faldaprevir. Further analysis of these candidates using molecular docking against the SARS-CoV-2 RdRp revealed low binding energies against the enzyme active site. Our approach also identified anti-inflammatory drugs lupeol, lifitegrast, antrafenine, betulinic acid, and ursolic acid to have potential activity against SARS-CoV-2 RdRp. We propose that the results of this study are considered for further validation as potential therapeutic options against COVID-19.

O1-11

Theoretical insights into the molecular mechanism of NA-I117V-Mediated Oseltamivir Resistance in H5N1 Avian Influenza Virus

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Keywords: Avian Influenza, Neuraminidase, H5N1, NA-I117V, Drug Resistance, Oseltamivir Resistance

Influenza is a contagious respiratory illness that infects the nose, throat, and lungs, causing mild to severe illness. Glycoproteins, hemagglutinin (HA) and neuraminidase (NA), of the influenza virus play essential roles in its replication process. HA binds to sialic acid (SA) at the end of a sugar chain present on the surface of a host cell, and then the virus is taken into the cell. NA on the virus surface plays a role of scissors to cleave the bond between SA and the sugar chain, which allows the daughter virus to liberate to begin infecting the surrounding cells.

Anti-influenza drugs that inhibit the interaction between NA and SA have been developed. Currently, four types of NA inhibitors (oseltamivir, zanamivir, peramivir, and laninamivir) have been used for the treatment of influenza in Japan. But resistance against available anti-influenza drugs is emerging rapidly. Hence, it's crucial to study the detailed mechanism of drug resistance to develop anti-influenza drugs which are less prone to resistance.

Most of the receptor mutations that lead to drug resistance occurs at its active site residues, since they are the key residues interacting with the drug. But residue 117 is not a part of active site of neuraminidase and still an Ile-to-Val substitution at position 117 (NA-I117V) causes a slight reduction in susceptibility to oseltamivir (OT) *in vitro* and dramatically *in vivo*.[1] However, the molecular mechanism of OT resistance caused by NA-I117V mutation is still not clear.

In this study, to clarify the binding affinities of SA and OT to the NA-I117V, we computed the corresponding binding free-energies using the molecular mechanics Poisson-Boltzmann surface area (MM-PBSA) method. We also computed the pairwise per-residue free energy decomposition calculation to clarify the molecular mechanism of OT resistance in NA-I117V mutant.

[1] Takano, R., Kiso, M., Igarashi, M., Le Q.M., Sekijima M., Ito, K., Takada, A., Kawaoka, Y., Molecular Mechanisms Underlying Oseltamivir Resistance Mediated by an I117V Substitution in the Neuraminidase of Subtype H5N1 Avian Influenza A viruses, *The Journal of Infectious Diseases,* 207:89-97, 2013.