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REstretto: An Efficient Protein-Ligand Docking Tool based on a Fragment Reuse Strategy

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Keywords: Protein-ligand docking, Fragment commonality, Software implementation

Virtual screening is a commonly used process to search for feasible drug candidates from a huge number of compounds during the early stages of drug design. As the compound database continues to expand to billions of entries or more, there remains an urgent used to accelerate the process of docking calculation. Reuse of calculation results is a possible way to accelerate the process.

In this study, we first propose novel virtual screening-oriented docking strategy by combining three factors, namely, compound decomposition, simplified fragment grid storing *k*-best scores, and flexibility consideration with pre-generated conformers. Candidate compounds contain many common fragments (chemical substructures). Thus, the calculation results of these common fragments can be reused among them.

As a proof-of-concept of the aforementioned strategies, we also conducted the development of REstretto, a tool that implements the three factors to enable the reuse of calculation results. We demonstrated that the speed and accuracy of REstretto were comparable to those of AutoDock Vina, a well-known free docking tool. The implementation of REstretto has much room for further performance improvement, and therefore, the results dhow the feasibility of the strategy.

The code is available under an MIT license at https://github.com/akiyamalab/restretto.

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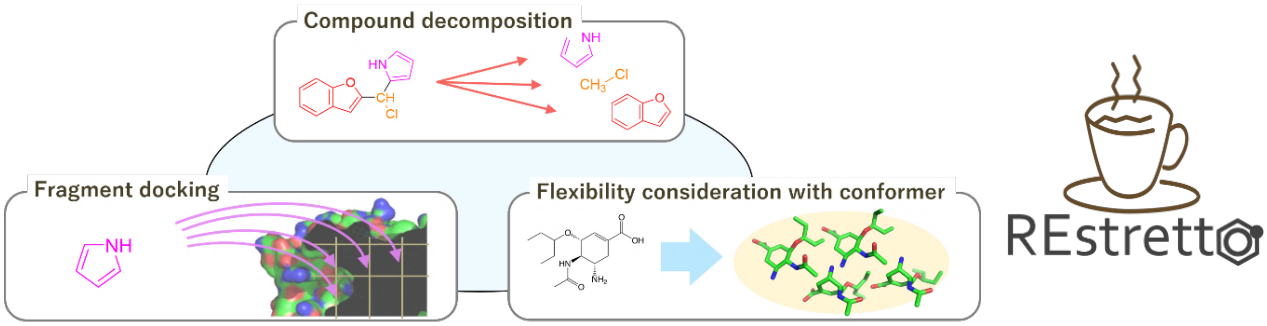

Binding specificity of phosphopeptide recognition domain analyzed by gREST simulation

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

Protein-protein interactions play an important role in intracellular signal transduction. Protein phosphorylation is common in modulating interacting partners to induce signals of interest. Thus, the binding specificity of phosphopeptide recognition domains is an important subject for understanding cellular function and for therapeutic purpose. Peptide array techniques and available three-dimensional structures of complexes provide a powerful means to determine the binding specificity of phosphopeptide recognition domains. However, the underlying recognition mechanisms remain elusive due to their dynamic and complex nature, making the development of reliable predictive models difficult. Here, we apply the generalized replica-exchange with solute tempering method, gREST [1] implemented in GENESIS [2], which is a generalization of REST/REST2 [3], to analyze the binding mechanism of phosphopeptides by Src homology 2 (SH2) domain. By selecting the phosphopeptide and the binding site residues as the solute region, the protein-peptide interactions are effectively weakened, and many of the 16 replicas showed the binding/unbinding events, which is not possible using conventional molecular dynamics simulations. Details of binding mechanism and possible determinants of specificity will be discussed.

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Dynamical interaction analysis of Remdesivir with SARS-CoV-2 RNA-dependent RNA polymerase by MD and FMO calculations

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Keywords: SARS-CoV-2, RNA dependent RNA polymerase (RdRp), Molecular Dynamics, Fragment Molecular Orbital Method (FMO)

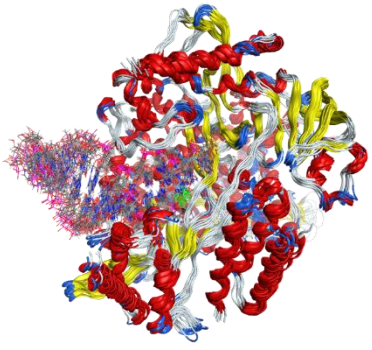
Remdesivir (Rem), one of the COVID-19 therapeutics, is incorporated into the RNA-dependent RNA polymerase (RdRp) of the SARS-CoV-2 virus in competition with Adenine and inhibits RNA elongation when located at the position -3 on the RNA recognized by RdRp. In this study, we aim to investigate the detailed molecular mechanism of Rem.

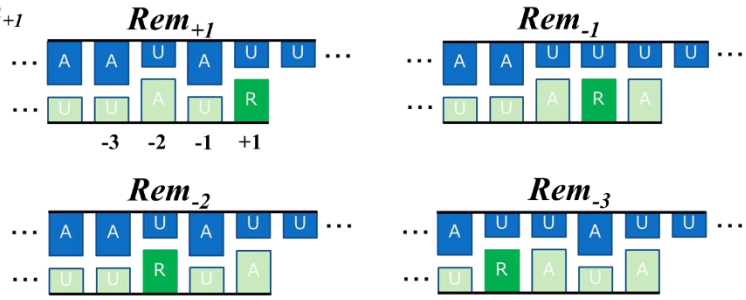
Based on the cryo-EM structure of the RdRp-RNA-Rem complex (PDBID:7BV2), seven structures were generated: five structures in which bases at the positions +1 to -3 of the elongated strand in the RNA duplex were replaced with Rem/Adenine (Rem_{+1} ～Rem_{-3}, and A_{-3}), a structure in which a cyano group was deleted from Rem in Rem_{-3} (Rem'_{-3}), and a structure in which Lys593 in Rem_{-3} was mutated to Ala ($Rem[K593A]_{-3}$). Then molecular dynamics (MD) calculations using the Amber20 program were performed for 50 ns for each structure. Finally, fragment molecular orbital (FMO) calculations were performed on a total of 70 structures extracted from the MD trajectories using the ABINIT-MP program on the supercomputer Fugaku (hp220143) to analyze the molecular interactions around Rem.

The inter-fragment interaction energy (IFIE) between the complementary strands in the RNA duplex was examined for Rem_{+1} to Rem_{-3}, and it was confirmed that the hydrogen bonds of base pairs from the position +1 to -2 were disrupted only when Rem was located at the position -3. In the interaction between Rem at the -3 position and the surrounding residues, the cyano group of Rem acquired a cation-π interaction with the Lys593. Therefore, we compared the average distance between Rem/Adenine at the -3 position and the Lys593, and found that Rem maintained an interaction with the Lys593 at a distance 0.7 Å shorter than that of Adenine. We compared the IFIE between Rem/Adenine at the -3 position and the Lys593, and found that Rem interacted with the Lys593 about 16.8 kcal/mol more stable than Adenine. The structure of RNA duplex was maintained in Rem'_{-3} and $Rem[K593A]_{-3}$.

These results suggest that Rem affects downstream RNA structure by interacting with the Lys593 at position -3, thereby inhibiting RNA elongation.

Structures after MD calculation of *Rem_{+1}*





Analysis of interaction energies for SMAD4 variants by computational science

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Keywords: SMAD4, Fragment Molecular Orbital Method, protein-protein interaction, mutation

TGF-β (Transforming Growth Factor β) is involved in numerous biological processes, including regulation of cell proliferation, differentiation, migration and apoptosis [1]. SMAD4 (Small Mothers Against Decapentaplegic 4) mediates this TGF-β signaling, and genetic mutations in SMAD4 have been associated with many cancers, including pancreatic cancer [2]. We have previously performed interaction analysis of SMAD4 mutants using the fragment molecular orbital (FMO) method [3-4]. In this research, we analyzed the mutations reported subsequently with the addition of pair interaction decomposition analysis (PIEDA) [5].

The crystal structure used in the calculations was obtained from the Protein Data Bank (PDB) as a wild-type homotrimer (PDBID: 1dd1) [6]. Mutations reported to be pathogenic and likely pathogenic in ClinVar were introduced the wild-type structure, followed by structure preparation and optimization by MOE. FMO calculations were performed on these structures and compared before and after mutation introduction using IFIE and PIEDA. ABINIT-MP was used for FMO calculations, and FMO2-MP2/6-31G* was used as the calculation level.

As a result of comparing the interaction energies for the Arg361 mutants, All five mutations reported in ClinVar were destabilized by loss of hydrogen bonding with Asp537 on adjacent strands, suggesting that they had a profound effect on trimerization. Structural comparison of mutations within the monomer revealed that Asp351His is destabilized by the loss of hydrogen bond with Arg361 and SH-O interaction with Cys363, which may affect the stability of the monomer.

This research was conducted within the activities of the FMO drug design consortium (FMODD); RIKEN R-CCS Fugaku was used for the FMO calculations (hp220143).

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Interaction analysis of 14-3-3 and p53 using fragment molecular orbital method

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Keywords: 14-3-3, p53, Fragment Molecular Orbital Method

14-3-3σ is associated with several types of cancer and down-regulates malignancy.[1]14-3-3σ is a positive regulator of p53, one of the tumor suppressor proteins, and protects p53 from proteosome degradation by MDM2 and increases transcriptional activity of p53. [2-3]

In this study, we performed interaction analysis of 14-3-3 and p53 complexes with stabilizing ligand by fragment molecular orbital (FMO) method to provide important information for the design of PPI stabilizers. 14-3-3σ is associated with several types of cancer and down-regulates malignancy.

The 22 crystal structures of structure of 14-3-3 and p53 complex with stabilizing ligand in the literature [4] were downloaded from Protein Data Bank (PDB). Structural preparation and optimizations were performed using MOE. We also prepared the complexes that was not registered in the PDB by MOE Dock. FMO calculations were performed for the structures and the inter-fragment interaction energies (IFIE) and pair interaction decomposition analysis (PIEDA) between each residue and inhibitor were calculated. ABINIT-MP was used for the FMO calculation, and MP2/6-31G* was used as the calculation level.

FMO calculations indicated that the amidine group, which is a common structure of ligand, has a large electrostatic interaction energy with residues in the 14-3-3 pocket. Structural analysis confirmed that the amidine group strongly interact with each other by forming salt bridges and hydrogen bonds. PIEDA also suggest that the structures with calculated the dispersion energies with CYS38 and the electrostatic interaction energies with ASP215 in 14-3-3 strongly interact with ligand. Therefore, it is considered that designing ligands to have these interactions will make them more stable stabilizers. In the interaction between 14-3-3 and p53, it was confirmed that the energy was significantly different by the conformational changes of charged amino acids such as LYS382 and ASP391 in p53.

This research was done in activities of the FMO drug design consortium (FMODD). For FMO calculations, RIKEN R-CCS Fugaku were used (hp210130, 220143 quota).

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Comparison of conformer models in PDB structure using Fragment Molecular Orbital Method

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Keywords: Protein Data Bank, Conformer, Fragment Molecular Orbital Method, Protein modeling

We are currently performing Fragment Molecular Orbital (FMO) Method [1] calculations on high-resolution crystal structure data registered in the PDB, and the problem of conformer model selection has arisen. When selecting conformers, modeling software usually reads the one with the highest occupancy as conformer A. However, we found that some structures registered in the PDB destabilize the energy of the calculation results when Conformer A is selected. Therefore, we performed FMO calculations on several high-resolution crystal structure data to identify differences in molecular stability between conformer combinations.

In this study, the high-resolution structure (PDB ID: 1W0N) [2] of the calcium-dependent carbohydrate-binding module (CBM36) was used to analyze the difference in molecular energy due to conformational selection.

The crystal structure of CBM36 was downloaded from Protein Data Bank (PDB), and four conformer combinations of Ile12 and Glu128 (A-A, A-B, B-A, and B-B) were prepared. Structural modifications and optimizations were performed using MOE2020 (CCG Inc.). FMO calculations were performed for the created structures and the inter-fragment interaction energies (IFIE) and the energy components by pair interaction energy decomposition analysis (PIEDA) [3] between Ile12 and Glu128 were calculated. ABINIT-MP was used as the FMO calculation, and FMO2-MP2/6-31G was used as the calculation level.

As a results of the FMO calculations, the interaction energies are very unstable in the structure between conformer A. This is because the closest atomic distance between conformer A is 2.0 Å. Comparing the Ile12-Glu128 interaction energies in the other three models showed that only conformer A-B are stabilized. Thus, it was found that the appropriate selection of conformers should be made when performing the calculations.

This research was done in activities of the FMO drug design consortium (FMODD). For FMO calculations, RIKEN R-CCS Fugaku was used (hp220143 quota).

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