Computational and experimental studies of hot spots in the c-Myb–KIX interaction

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Keywords: Protein–protein interaction, Hot spot, Peptide

Protein-protein interactions (PPIs) play key roles in biological functions. Since undesired PPIs can cause serious diseases, inhibiting the PPIs is a promising strategy for therapeutics. However, developing inhibitors targeting PPIs is challenging due to their large and flat interfaces. A key challenge in solving this problem is to identify energetically favorable residues in PPIs, called “hot spots” [1].

The KIX domain of the CREB-binding protein interacts with many transcription factors, including c-Myb, and is implicated in serious diseases [2]. Thus, inhibitors of the c-Myb–KIX interaction is potentially useful as antitumor agents. Here, we computationally and experimentally investigated hot spots in the binding of KIX to c-Myb. To identify the hot spots, we used various computational tools including AlphaFold 2. Then, we experimentally searched for the host spots on KIX using an alanine scanning mutagenesis for 21 residues at the c-Myb binding interface of KIX. The changes in the stability and c-Myb binding affinity of the 21 mutants of KIX were examined by circular dichroism and isothermal titration calorimetry, respectively. We found that three KIX mutants reduced the c-Myb binding affinity by more than 2 kcal/mol, indicating that these residues are the hot spots for c-Myb binding of KIX.

Comparison of the computational alanine scanning mutagenesis with the experimental results showed that the mCSM program [3] outperformed other computational methods in predicting the hot spots of KIX. In addition, we propose a method to find hot spots using the pLDDT scores predicted by AlphaFold 2, which was the second best method for predicting the host spots of KIX. These results may be useful in computationally identifying hot spots in PPIs.

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Upgrade of AI-AAM and its application to lead-to-lead and peptide downsizing scaffold hopping

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Keywords: AI Drug Discovery, LBDD, de novo design, PPIs, AI-AAM

The failure rate in drug discovery and development after *in vivo* and *vitro* testing is higher than 90% [1]. To minimize the rate, we developed a scaffold hopping methodology called Artificial Intelligence-Amino Acid Mapping (AI-AAM) to obtain hit compounds from a known hit ligand maintaining the binding affinities to its target protein [2]. Since it was highly essential to use the descriptors that could represent binding affinities for the purposes, we designed a molecular simulation-based descriptor, Amino Acid Mapping (AAM), assuming protein–ligand binding could be described as the set of interactions between amino acids and the ligand. As an extension of the previous work, we upgraded AI-AAM to automatically find and design a lead compound from a known lead ligand and a hit compound from a bioactive peptide (Fig. 1). Here, we provide a brief description of the content of each work (see our posters for the detail).

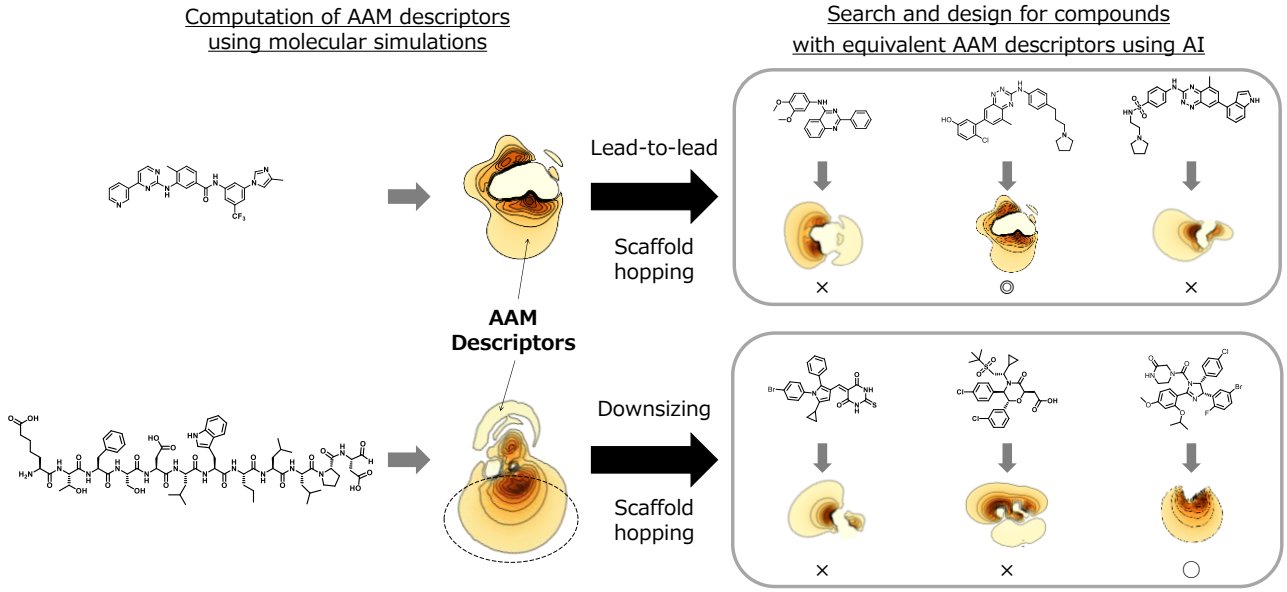

Fig. 1 Overview of AI-AAM

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Molecular design method using a reversible tree representation of chemical compounds and deep reinforcement learning

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Keywords: deep learning, reinforcement learning, drug design

Automatic design of molecules with specific chemical and biochemical properties is an important process in material informatics and computational drug discovery. In this study, we designed a novel coarse-grained tree representation of molecules (“RJT”) for the aforementioned purposes, which is reversely convertible to the original molecule without external information. By leveraging this representation, we further formulated the molecular design and optimization problem as a tree-structure construction using deep reinforcement learning (“RJT-RL”). In this method, all the intermediate states of reinforcement learning and the final structures are convertible to valid molecules, which could efficiently guide the optimization process in simple benchmark tasks. We further examined the multi-objective optimization and fine-tuning of the reinforcement learning models using RJT-RL, demonstrating the applicability of our method to more realistic tasks in drug discovery.

Improvement 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.

We developed a VAFM with remote machine operation interface on the VR system to manipulate a dispensing machine that emulates a real AFM, with hand movements and to observe the movements. We also improved the system for obtaining more detailed hand information and for modifying the virtual cantilever movements on the VAFM with machine learning techniques to increase the speed and accuracy of the movements.

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Experimental Investigation of Extended Nucleic Acid Generation Circuits for DNA-based Signal Transduction

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Keywords: DNA generation circuit, DNA-based computing, molecular robotics

We had previously proposed various types of extension for a DNA generation circuit that generate single-stranded DNA molecules as signals at a physiological temperature in response to nucleic acid inputs [1]. For the purpose of nucleic acid testing and construction of synthetic signal transduction systems for DNA-based computing and molecular robotics, its modular architecture allowing modulation of signal generation performance via design and combination of template DNA strands is promising [2-4]. In the present study, we experimentally investigated the DNA generation circuit in terms of the input nucleic acid forms and fluorophore-modified DNA probes. In addition, application of the DNA generation circuit within a tiny solution environment towards digital bioassay and connection to the other DNA-based computing reaction for achieving more intelligent functions of DNA-based artificial molecular systems will be discussed.

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