1P043 Computational design of short peptide inhibitors of protein-protein interactions in intracellular signaling mediated by CRK-SH2

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CRK is a signal transducing adaptor protein, which mediates protein-protein interactions in signaling pathways. CRK has several protein-binding modules named SH2 and SH3 domains. Our goal is the design of high-affinity peptides binding to CRK SH2.

First, we developed original GPU docking program using MM potential energy and the generalized born (GB) solvent as scoring functions. After pose predictions, MM-PBSA rescoring were conducted. In rescoring, we compared several radii sets which determines the boundary between solute and solvent. Furthermore, we performed additional conformational search of peptides in the unbound states to take account of ligand’s reorganization effects. Our methods showed high performances in discrimination of known binding sequences.

1P044 Electrostatic similarities between protein and small molecules facilitate the rational design of protein-protein interaction inhibitors

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We have developed a method (Elekit) that measures the similarity of the electrostatic fields for the discovery of protein-protein interaction inhibitors. The electrostatic values are mapped onto a 3D grid surrounding the molecules. A bitmask is created such that only the grid points, representing the electrostatic field towards the receptor protein, are taken into account. The Spearman rank correlation coefficient between the SMPPII ligand and the known protein ligand is computed. Analysis of all available SMPPII structures indicates that SMPPII have similar electrostatic properties as the ligand proteins of the same receptor. Elekit can be used as a post-processing filter for docking and/or pharmacophore based SMPPII virtual screening experiments.

1P045 レプリカ置換法による生体分子に対する効率的な構造サンプリング

Efficient sampling for biomolecules by the replica-permutation method

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Efficient sampling in the conformational space is necessary to predict the native structures of proteins. The replica-exchange method (REM) is one of the most well-known methods among the generalized-ensemble algorithms which realize efficient sampling in the conformational space. We had recently proposed a better alternative to the REM, the replica-permutation method (RPM) [1], in which temperatures are permuted among more than two replicas. Furthermore, the Suwa-Todo algorithm is employed in RPM instead of the Metropolis algorithm.

We will show the results of RPM in our presentation. These results will be compared with those of REM to see sampling efficiency of RPM.

References

1P046 Metadynamics: Implementation in GENESIS Software Package and Demonstration of the Efficient Computational Simulations of Biomolecules

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Metadynamics (MTD) is an accelerated sampling algorithm aiming to maximize the output of molecular dynamics (MD) simulations. MTD, by design, is capable of the efficient simulation of biosystems with large energetic barriers and rough energy landscape within the limited time scale of MD simulations, and it is applicable to arbitrary large systems and complex phenomena (i.e. folding, binding, chemical reactions, etc.). Our implementation of MTD in GENESIS is focused toward scalability to utilize massively-parallel computers (i.e. “K computer”). The accuracy and efficiency is demonstrated with several simulations of biomolecules and compared with another established accelerated sampling method, replica-exchange MD (REMD).

1P047 Motion Treeを利用したcapping proteinの動的構造解析

Dynamical study of capping protein by Motion Tree

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Capping protein (CP) binds to the barbed end of an actin filament and inhibits the further polymerization. V-1 and CARMIL inhibit CP to bind the barbed end, but their inhibition mechanisms are quite different: V-1 sterically inhibits the CP binding to actin filament, and allosterically does CARMIL. In addition, CARMIL can uncap CP from actin filament or V-1. To elucidate the regulation mechanism of CARMIL, we conducted molecular dynamic simulation for the structures of free CP, CP/CARMIL and CP/V-1 complexes, and investigate the dynamic properties of CP. For the snapshot ensemble of CP, Motion Tree was applied and the distribution of rigid bodies was examined. We found the CARMIL binding suppresses large domain motions of CP.

1P048 MSESにより明らかになった蛋白質遭遇複合体構造アンサンブル

 Structural ensemble of protein encounter complex revealed by Multiscale Essential Sampling

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Many proteins perform their functions by specific complex formation. Paramagnetic relaxation enhancement (PRE) experiments indicate the existence of non-specific encounter complex preceding the formation of the specific complex. However, structural details of the encounter complex still remain unclear even after many experimental and computational studies. Here, we simulated the process of the complex formation between N-terminal domain of enzyme 1 (EIN) + HPr (PDB ID: 3EZB) by Multiscale Essential Sampling (MSES), which allows an enhanced sampling of solvated all-atom structures. The structural ensemble including the encounter complexes successfully reproduced the PRE data. Free energy landscape of the complex formation revealed the role of the encounter complexes.