are coarse-grained. The peptide, which is described as a flexible bead model, is movable along the grid-points which are set surrounding the protein. An arbitrary state of the protein-peptide complex is subjected to Delaunay tessellation. Then, the fitness of a peptide-coordination to the protein is measured by a four-body statistical pseudo-potential. Through 1000 trials of a simple hill-climbing optimization, the best 15 peptide-coordinations with the 1st - 15th highest fitness values are selected as candidates for the correct coordination. Retrieving the available seventeen protein-peptide complexes from the Protein Databank, we carried out the blind docking test for each system. In most cases, our blind docking procedure predicted a nearly correct binding site and, in some cases, a nearly correct binding mode as well at low computational costs. For 15 out of the 17 cases investigated, the lowest values of RMSD ranged within 3.0 - 6.5 Å.

- 1P-236 MD シミュレーションとタンパク質のコンキャビティ形状比較を用いたバーチャルスクリーニング
Virtual screening to separate active ligands from decoys using MD simulation and concavity shape comparing

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Molecular docking screens of chemical databases are widely used for ligand discovery. To improve the performance, considering changes of a protein structure is important for some targets. Although several approaches have been reported, the methods retains room for improvement, and are computationally expensive.

We tested an alternative docking screen which uses MD simulations. MD simulations of a target protein without ligands were carried out, and then the concavity shapes of the protein were extracted from the MD trajectories. Screens were performed by comparing the concavity shapes and a query ligand shape. Shape similarity was represented by a similarity index (ex., 1 or 0). A docking score for the protein and the query ligand was defined as a sum of similarity indices along a MD trajectory. Preliminary study on a receptor protein proved our methods as effective as conventional docking softwares, DOCK or GLIDE. In this study, we evaluated our screening calculations for several target proteins, like nuclear hormone receptors, kinases, and serine proteases. These proteins, their active ligands, and the decoy molecules were chosen from a database DUD (directory of useful decoys). Parameters for the screening (conditions of MD simulations, thresholds for shape similarity index, etc.), the advantages and the drawbacks of the methods will be reported.

- 1P-237 アミノ酸配列からのタンパク質揺らぎ領域予測とタンパク質間相互作用への適用
Prediction of protein motion from amino acid sequence and its application to protein-protein interaction

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Structural flexibility is an important characteristic of proteins that is often related to their function. The movement of a polypeptide segment is theoretically classified into two forms: internal and external motion. The former is a deformation of the segment itself, but the latter involves only rotational and translational motions as a rigid body. Normal Mode Analysis (NMA) can derive these motions of two types, but its application remains limited because it requires complete structural information. In this work, we present a novel method for predicting two protein motions solely from amino acid sequence information. We prepared a dataset by calculating internal and external motions using NMA. First, we analyzed the relation between thermal motion as assessed using X-ray crystallographic B-factor and internal/external motion. As a result, the internal motion has different features from the B-factors. Next, we developed a prediction method based on the Random Forest algorithm. Our method exhibited moderate correlation with internal and external motion calculated using NMA, and higher prediction accuracy than naïve model. Finally, we observed significant overlap between predicted high internal motion region and observed conformational change when the proposed method was applied to a set of proteins that undergo large conformational change upon protein-protein interaction.

- 1P-238 構造生物学と計算機科学に基づいたタイトジャンクションを制御する化合物の探索
Search for compounds that modulate tight-junction activity: structural biology and computational approaches.

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[Introduction] In multi-cellular organisms, cell adhesion plays important roles in various cellular processes including morphogenesis, differentiation, and proliferation. Loss of adhesion machineries causes cancer and other diseases. Tight junction (TJ) functions as an epithelial barrier, which is comprised of claudins, occludin and PDZ domain proteins ZO1 - ZO3. Recently, Furuse's group showed that TJ is maintained by dynamic equilibrium between biogenesis and degradation (Iwamoto et al., J Cell Sci, 2009). They identified an E3 ubiquitin ligase LNX1p80, whose four PDZ domains serve as the binding sites for claudins, as the master molecule of TJ degradation. We hypothesize that TJ activity can be modulated by inhibiting interaction of claudins with either LNX1 or ZO1.

[RESULTS and DISCUSSION] We searched for compounds to bind ZO1-PDZ1 by either a biochemical method or a computational method. First, we performed PIP-strip assay for ZO1-PDZ1 and identified PtdIns(3,4,5)P3 and other PIPs serve as non-peptidic ligands for ZO1-PDZ1. NMR experiments confirmed that phytic acid (InsP6) also bound to ZO1-PDZ1. We further performed an *in silico* screening experiment against ZO1-PDZ1 with 600,000 compounds by using the program MOE. Many compounds harboring more than two carboxycyl / sulfonate groups were retrieved with high docking scores, which resemble to phytic acid in terms of multiple negative charges. These compounds are useful as novel chemical tools that modulate TJ biogenesis and degeneration, thereby controlling epithelial barrier functions.

- 1P-239 相互作用傾向値とホモログにおける既知相互作用部位の情報をを用いたドメイン間相互作用部位予測
Prediction of domain-domain interaction sites from interface propensity and known interface positions of homologs

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In both prokaryote and eukaryote genomes, the proportion of proteins composed of more than one structural domain is over two thirds. To elucidate the chemical function of these multi-domain proteins, the whole structures are very important. Improvements in techniques for 3D structure determination have gradually increased the number of multi-domain structures in the Protein Data Bank. However, only about one fourth of solved structures are classified into multi-domain and accurate prediction method for multi-domain structure is still needed. Docking of individual domains with guide information is effective in predicting the multi-domain structure. To obtain the guide information, we have developed a method for predicting domain-domain interface residues. In our method, whether a domain surface residue is a domain-domain interface residue or not is judged by two criteria. One criterion is that the value of a prediction score calculated from interface propensity, which means usage preference in domain-domain interfaces compared to the other part of domain surface, is higher than a certain threshold. To increase the specificity of prediction, we use two interface propensities, "core" and "peripheral", for the score calculation. Another criterion is that the position of the domain surface residue is same as a known domain-domain interface residue of homologs. At present, the accuracy of prediction by former criterion is lower than that of the latter criterion. We will discuss the accuracy of prediction using combined criteria.

- 1P-240 タンパク質間相互作用およびドメイン間相互作用ネットワークの構築と比較
Construction and comparison of PPI and DDI network

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Protein domains are considered to be structural units of protein, and most of Protein-Protein Interactions (PPIs) appear to be through protein domains. Because of great increase in number of PDB entries, it becomes possible to analyze PPI network using only the interactions observed in the structurally resolved protein complexes. Assigning protein domain information to each protein complex in this network, it is possible to determine which domain interacts, and introduce protein domains into the PPI network analysis. This study aimed to elucidate the relationships between PPI network and protein domains.

Previously, we constructed and analyzed two domain networks, named *domain-mediated PPI network* and *DDI network*, using iPFam database, where domain-domain interaction data derived from structurally resolved protein complexes are stored. However, iPFam is not updated recently, and the criterion for determining interacting residues in protein complexes is not revealed. Thus, we performed the similar analysis using 3did, which is another structure-based domain-domain interaction database. In addition, we analyzed the structural and functional characteristics of domains. As a result, the trends that functional domains and interaction domains are clearly separated are similar as a whole, but several differences are found in some domains. For example, although the total number of used complexes in the network with 3did is almost twice as many as iPFam, the number of used complexes including Ig domain in the 3did network is much less