incorporate long-range pairwise interactions between model states via mean-field-like approximations. We give the detailed formulation of the model, self-consistent approximations for treating long-range interactions, and algorithms for computing partition functions and marginal probabilities. We also outline the methods for the global optimization of model parameters as well as a Bayesian framework for parameter learning and selection of optimal alignments.

1P-010 ギャップジャンクションヘテロチャネル形成の適合性に関する構造的考察
Structural insight into docking compatibility of heterotypic gap junction channel

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One type of communication between cells is mediated via intercellular channels that cluster in specialized regions of the plasma membrane to form gap junctions consisting of connexins. Multiple connexins are coexpressed in a single cell type. Heterotypic gap junction channels show various properties by their combinations. We have determined the structure of human gap junction channel composed of connexin26 (Cx26) at 3.5 Å resolution. According to this structure, two connexons form a full gap junction channel by several interactions between each two extracellular loops.

In this research, docking selectivity for each pair of different connexons was inspected by homology modeling using the structure of Cx26 gap junction channel as the template. We selected 10 connexins of human origin as object of this experiment. In every combination of different connexons, E1 of one connexon binds to E1 of the other connexon with hydrogen bonds and doesn't have any steric hindrances as in Cx26 gap junction channel. In E2, however, replacement of the position 176th with His or Tyr seemed to cause the incompatibility with Lys or Arg at the position of 168th. This result is in good agreement with electrophysiological or cell biological experiments. These combinations would be unfavorable and fail to form a gap junction channel. Our study suggests that E2, especially 168th and 176th residues of Cx26, could have a key role in formation of "functional" intercellular channel.

1P-011 X線小角散乱法による CEL-III の多量体化機構及びその構造解析
ANALYSIS OF THE OLIGOMERIZATION MECHANISM AND STRUCTURE OF CEL-III BY SMALL-ANGLE X-RAY SCATTERING

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CEL-III is a Ca^{2+} -dependent, Gal/GalNAc-specific lectin purified from the sea cucumber *Cucumaria echinata*, which shows haemolytic activity by oligomerization on the cell surface. We found that the oligomerization of this protein can be induced not only in lipid membranes but also in solution under the appropriate conditions. CEL-III forms an oligomer in solution when complexed with lactose at high pH values and in the presence of high concentrations of salt. To elucidate the oligomeric structure and mechanism of oligomerization of CEL-III, small-angle x-ray scattering (SAXS) measurements were carried out. Previous report shows that the molecular weight of the oligomer is determined as 1019 k from its forward scattering value by SAXS which is much larger than that estimated using SDS-PAGE, 270 k. To elucidate the effects of detergents, we measured SAXS in the presence of detergents. The results showed that the oligomer dissociated into hexamer (290 k) and the radius of gyration of oligomer was 62 to 75 Å, which well agreed with the result of SDS-PAGE. Kratky plot of both profiles showed that the two peaks which are typical for oligomeric proteins, a-hemolysine, one of the pore forming proteins associates into heptamer on the cell surface. These results suggest that the oligomeric structure in the presence of the detergents is a minimum unit of hemolytic activity and oligomer without detergents consists of 4 oligomers with detergents by weak interactions.

1P-012 ヒト MTH1 活性部位の二つの Asp 残基のプロトネーション状態が異なる分子動力学シミュレーション
Molecular dynamics simulations of human MTH1 under different protonation states for two Asp residues in its active site

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Human MTH1 hydrolyzes oxidized purine nucleotide triphosphate molecules such as 8-oxo-dGTP and 2-OH-dATP. Mechanisms by which MTH1 distinguishes damaged purine nucleotides from the others are not fully elucidated. In the crystal structures of 8-oxo-dGMP-bound MTH1, two aspartate residues, Asp119 and Asp120, were in the vicinity of the guanine base of the ligand, although the oxidized location was on the opposite side of the base. Because hydrogen bonds are critical in understanding specific interactions, we studied the influence of the protonation states of the two residues on MTH1-ligand interactions, using molecular dynamics (MD) simulations. A 50 ns MD run was

carried out using AMBER 8 for each combination of four protonation states and with or without a bound 8-oxo-dGMP molecule. 2–50ns of each trajectory was divided into eight 6ns segments and structures were averaged over every time segments, yielding 64 structures. The structures were subject to cluster analysis, using C- α RMSD as a distance measure. As a result, it was found that the structures could be roughly divided into two classes, i.e., ligand-bound and ligand-unbound structures. Generally, the ligand-bound structures have more inflated binding-pocket, produced by outward shifts of three adjacent loops. An example of exception was the ligand-unbound and both deprotonated structure, which adopted a conformation similar to that of ligand-bound and singly protonated structures.

1P-013 複数のサポートベクタマシンの組み合わせによるタンパク質局所構造予測法の開発

Development of protein local structure prediction method based on combination of multiple support vector machines

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Recently, many researches about residual local structures in protein unfolding state and statistical analyses of protein structure database to find structural motif of proteins suggest that many parts of proteins are to some extent restricted by local amino acid sequences. It is very useful to obtain such local structural tendencies from their sequences for *de novo* protein structure prediction and understanding of protein folding mechanism.

We have developed a novel method for protein local structure prediction from sequence information based on combination of multiple support vector machines (SVMs). Prediction procedure is as follows: First, PSI-BLAST (Altschul 1997) is applied to query sequence with up to five iterations to make position specific scoring matrix (PSSM). PSIPRED secondary structure prediction (McGuffin 2000) is also applied and scores for secondary structure types (helix / strand / others) are obtained for each residue. Then PSSM and PSIPRED scores are divided into fragments with overlap. These fragments are submitted to multiple support vector machines. Each SVM predicts whether end-to-end distance of the input fragment is longer than the assigned distance or not, and outputs a decision value for the prediction. Finally, probability density function of end-to-end distance of the fragment is estimated as the distribution of end-to-end distances of fragments in a database of known structures which have similar decision value pattern. We applied our method to a set of fold representatives of SCOP 1.73 (Murzin 1995) and validated its effectiveness.

1P-014 アミノ酸側鎖のペプチド立体構造に及ぼす影響

The side chain effects on the conformation of the peptides

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Protein is a sequence of amino acids. To elucidate the interaction between amino acids is important as the first step to clear the principle of protein folding. The energy expressions in classical molecular dynamics simulation are limited since it use predefined potential energy function to calculate energy and forces of the system. On the other hand, the energy calculated by *ab initio* molecular orbital theory which treats the electronic structure of the system is more accurate than the one calculated by using classical force field. In this point of view, we applied multicanonical *ab initio* molecular dynamics simulation to tetrapeptide, Ace-Ala-X-Ala-Nme (X=Ala, Gly, Ser). Quantum chemical calculations were performed at the HF/6-31G** level of theory. We will report the results, the comparison with that from AMBER ff99SB simulation and the influence of side chain for the conformation of peptides.

1P-015 バイオロジカルユニットを考慮したリガンド結合タンパク質データベースの構築

Development of protein-ligand complex's database considering biological units

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It is pointed out that ligand binding sites sometimes exist not only in the pocket of a protein domain but also between the surfaces of two or more protein domains. When we analyze ligand binding to proteins, we need to take into account quaternary structure biological unit, the state of the proteins within the living organisms. So, we develop a database of protein-ligand complex considering biological units of proteins. We target ligands which are mainly low molecular, not all the HETATMs. We do not target DNA, RNA, proteins and low molecular ions. The initial dataset of ligand binding conformations is obtained from four databases, PDBbind, BindingDB, Protein Ligand Database and AffinDB. All the possible conformations are subjected to a clustering procedure based on the sequence identity between clusters to remove redundancy. At last, the most representative conformation from each cluster is selected and is manually checked