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An important step toward protein structure prediction is to develop the efficient method to select good models from candidate model structures. For that purpose, various types of 3D1D methods have been developed and successfully applied in CASP tests. We here report a new method of model selection based on the use of the context-specific (CS) structure-profile table. At each residue of the model, the local structure is classified into 24 classes and the protein structure is represented by a string of 24 alphabets, which we call the model structure (MS) string. Around each residue, 9-residue-length fragments are selected from the library of non-redundant protein structures by consulting the sequence profile table generated by PSI-BLAST. Then, by counting the probability of appearance of 24 alphabets among the selected fragments, the CS structure profile is generated. The CS score of the model structure is evaluated by applying the CS structure profile to the MS string. As a benchmark test, all server models of CASP8 were sorted with this CS score, and it was shown that models with high CS score are often near enough to the experimentally observed structures. This method can correctly distinguish two targets, T0498 and T0499 in CASP8, which have high sequence identity but different fold. By selecting 400 models generated by the Langevin MD simulation [T. N. Sasaki, et al. BBRC (2008)], the method predicted better results than servers for some free-model (FM) targets in CASP8.

3P-014 フラグメントアセンブリによる大規模蛋白質構造リファインメント

Large scale protein structure refinement by fragment assembly

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Much progress has been made in predicting the three-dimensional structures of proteins. So far, the most successful prediction methods have been template based modeling, which heavily relies on known templates. It is reported that the fraction of sequence for which comparative models can be obtained automatically is ~60%.[1] Thus, if we were able to generate high accuracy models by homology modeling technique, we would obtain millions of protein structures. However, in cases of low homology or where templates require substantial editing, it has been challenging to refine structures better than the closest template. Here, we describe our new method of the refinement procedure from templates that require substantial editing.

Our strategy of refinement procedure is use of the tool which is often used in De Novo protein structure prediction: fragment assembly method. There are two key features in our new approach. The first is the fragment collection, in which fragment candidates for all possible short segments of the chain are extracted from PDB by a structural alignment of the template, not sequence alignment. The second is incorporating a relaxation step after insertion of fragment structure in order to reflect flexibility of a protein chain. Detailed results and discussion will be given in the presentation.

[1] Pieper,U., Eswar,N., Eramian,D.et al. (2006) Nucleic Acids Res., 34, D291–D295.

3P-015 “ゴーストウォーター”を含む全原子モデルによるタンパク質構造予測

Protein structure prediction by the all atom model that includes “ghost water”

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Methods for de novo protein folding and tertiary structure prediction require accurate energy functions based on physical interactions. For rapid energy calculation, implicit solvent models are useful and widely used. In all these models, there are several energy term: such as van der Waals interactions, hydrophobic interaction, hydrogen bonding, and so on. Among them, one of the most important term is the hydrogen bonding. This is because (1) free energy differences of native and denatured state are almost equal to a few hydrogen bonding energy. (2) it is reported that almost all donor/acceptor atoms in proteins satisfy hydrogen bonding if both intra-peptide and peptide-water hydrogen bonding are considered. Thus, it would be meaningful to develop an implicit solvent model that directly takes into account of the hydrogen bonding satisfaction rule.

In this presentation, we will introduce our new implicit solvent all atom model, and report its structure prediction benchmark tests. Our model is based on charmm19 and Lazaridis & Karpul implicit solvent model. The novelty of our model is hydrogen bonding energy term. In order to directly take into account of the hydrogen bonding satisfaction into the model, we introduce virtual water molecules, called “ghost water”. Ghost water molecules are always attached to donor/acceptor atoms of a protein and contribute stabilization by forming hydrogen bonding. But if any other protein atoms occupy the space of ghost water, ghost water disappears breaking the hydrogen bonding.

3P-016 マウスプリオンタンパク質ミュータントの線維形成

Fibril formation of mouse prion mutants

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We analyzed the influence of mutation on the conformational stability of the S2 region of mouse prion protein (PrP^C) with varying pHs. Recombinant full-length prion protein (23-231) has as follows: indicated that N96C, D143C, and T189C are localized in a Cu²⁺-binding region, Helix1 and Helix2, respectively; Y161C, D176S, D177N are around the salt bridge linked to the S2 region; G57C is the around base octapeptide repeats domain that have Cu²⁺-binding site. Circular dichroism spectra of D177N mutant showed the conformational instability caused by the disappearance of salt bridge (H176-R163) leading to S2 region. For the fibril formation, mutants were gently rotated for 3 days at room temperature in 2 M GdnHCl/50 mM Tris-HCl pH 7.5 or 4.0. After rotation, mutants were further incubated with 10 μM Thioflavine T for 30 s and then the increase of fluorescence intensity was measured. Fibril formation was also examined using atomic force microscopy (AFM). Fluorescent assay and AFM indicated the fibril formation of D177N. Pyrazolone derivatives, which have been reported as antiprion compounds (*J. Med. Chem.*, 2007, 50, 5053-5056), were tested for anti fibril formation. The increase of fluorescence intensity using Thioflavine T in rotated D177N was inhibited by these derivatives to some extent. These results suggest that the conformational stability of salt bridge may play important role in suppression of prion disease.

3P-017 アミノ酸対形成傾向がβシート中でのストランド配置順に与える効果

Effect of amino acid pairing propensity on β-strand order in the β-sheets

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The prediction accuracy of secondary structures has already reached 75%, and the packing prediction method of these secondary structures has been developed. In this packing process, β-sheet formation is one of the most important steps. In this study, the statistical scores were computed from the frequency of the inter-strand amino acid residue pairs based on experimental protein structure data, taking the existence of hydrogen bond formation into account. These scores showed that residues on a strand tend to avoid inconvenient residues on the other strand as partners (negative selection) rather than to select convenient residues (positive selection). Prediction accuracy for strand order in the β-sheets using residue pairing propensity and number of H-bonds were 78% and 38% for 3- and 4- strand sheets, respectively. Analysis of mis-predicted results showed that when the strand order was predicted to be interchanged between neighboring strands, directions of these strands tend to be opposite to the actual directions. This means that some β-sheets consists of some of β-strand blocks and our method can detect some of these blocks but have not enough power for rebuilding the combination of strands blocks.

3P-018 網羅的比較シミュレーションシステムの開発

Development of an exhaustive comparative simulation system

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Structural bioinformatics, which study the relationships between the tertiary structures of biological macromolecules and their primary sequences and biological functions, have greatly contributed to the advances in biology. One major approach taken by the researchers in this field is to exhaustively compare the tertiary structures in PDB to find out some rules. By analogy, exhaustive comparison of molecular dynamics (MD) simulation data should provide a new insight into the mechanisms of the functions of the biological macromolecules, because the MD simulation can add information about dynamics to the static structural data. Although it has been unfeasible to perform MD simulations for all the PDB entries, it will become feasible with the next-generation supercomputer. Therefore, we are now developing a system that manages exhaustive comparative simulations. The system is composed of three parts: (1) Database part that downloads PDB files, extracts primary sequences and missing-residue and ligand information from the files, and registers the information, (2) Modeling part that generates initial structures and adds hydrogen atoms considering protonation states of titratable groups, and (3) Simulation part that performs energy minimizations, places water molecules around the structures and conducts MD simulations. Here, we report the results obtained by applying this system to sets of protein pairs that have similar primary sequences but have different tertiary