reality. The dielectric constant is expected to vary depending on the local electrostatic environments and the structural constraints imposed on the system. In this study, we calculated the local dielectric environments of protein-water systems by employing the theoretical framework proposed by Guest et al. (PCCP, 2011) where the dipole-dipole correlations are properly taken into account. We used long molecular dynamics simulation trajectories of the three systems (solvated myosin, solvated actin, and F_o in the solvated lipid bilayer systems) to evaluate the dipole-dipole correlations. From the local dielectric constant map, we found that the regions around the flexible loops tend to exhibit a large dielectric constant. The regions with a large dielectric constant are supposed to respond well to the approaching charges of the binding partner and stabilize the electrostatic self-energy of the charges. Similarly, we will discuss the ion translocation path in F_o portion of ATP synthase in terms of the local dielectric constant map. We also point out a technical problem that calculated dielectric constants sometimes become too large or even negative, and discuss a possible solution to this problem.

1PT170 シグナル伝達に関する PDZ ドメインの分子動力学データに対する時系列解析

The time series analysis of molecular dynamics data about PDZ domain in synapse

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The functions of a protein are supposed to have relation to its structures. We study the relationship between its functions and movement from data of molecular dynamics(MD) simulation. We analyse the protein called the PDZ domain. For human being, we can find them in a synapse of the nervous system. In particular, these proteins exist mainly in postsynaptic cells as domains of receptors. They play an important role in signaling in the nervous systems[1]. We chose one of the PDZ, and its PDB code is 1BE9. It is the third domain of PSD-95, where PSD-95 is a receptor which is in the center of the postsynaptic cell. For the signaling, the clustering of domain is essential, and is caused by interaction with other proteins. Here, we pay our attention to the mechanism of signaling. It is shown that it has a path within the domain and signals are transduced along this path[2]. We study its motion with wavelet transform and canonical correlation analysis. First, by wavelet transform, we can find the time-dependent spectra and find which parts of the secondary structure move with large amplitude. Second, in order to find whether we can see the flow of thermal energy along this path at room temperature, we compare the correlations between amino acids by canonical correlations analysis.

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[3]A.Dyle,et al.1996.Cell,85,1067-1076

1PT171 粗視化シミュレーションによる 3 ドメインタンパク質 suf1 のコ・トランスレーショナルフォールディングの研究

Co-translation folding of a three-domain protein suf1 studied by coarse-grained molecular simulations

Tomohiro Tanaka, Naoto Hori, Syoji Takada (*Dept. of Biophys., Kyoto Univ.*)

Proteins are synthesized linearly from N-terminus in ribosome and gradually extruded from it. The native interactions of extruded polypeptide chain may be initiated before the protein synthesis is completed. Protein folding which proceeds during the synthesis is termed co-translational folding. Because total conformation space of a polypeptide chain under translation is smaller than that of the full-length polypeptide chain of the protein, co-translational folding could be facilitated kinetically. In addition, the rate of translation is not uniform, but is affected by tRNAs abundance. Recently, it was found that the correct folding of suf1, a three-domain protein, is maintained by the particular use of rare codons. When the rare codons were replaced with codons by synonymous mutations, successful folding yield substantially decreased. However, the detailed mechanism of this phenomenon is unclear. To understand the mechanism, we developed a coarse-grained (CG) model and simulated suf1 co-translational folding as well as post-translational folding as a control. The CG model is a mixture of Go like atomic interaction based CG (AICG) model and generic hydrophobic interactions which makes correct folding and misfolding possible. Via comprehensive simulations, we address the difference between co- and post-translational folding.

1PT172 粗視化シミュレーションによるサテライトタバコモザイクウイルスの安定性とダイナミクス

Stability and dynamics of satellite tobacco mosaic viruses studied by coarse-grained simulations

Koji Ono, Naoto Hori, Shoji Takada (*Dept of Biophys, Kyoto Univ*)

Satellite tobacco mosaic virus (STMV) is one of the smallest (about 170 angstrom diameter) and icosahedral virus ($T = 1$). The virus consists of 60 copies of single proteins to make a icosahedral capsid and a 1058-base RNA genome. The existence and importance of the viral genome for its stability have been acknowledged. Recently, STMV was analyzed by an all-atom MD simulation. The research indicated that their RNA is important to stable their capsid structure. All-atom simulation is, however, limited of the system size and the time scale. To overcome them, we used coarse-grained simulation (CafeMol developed by Our lab) to simulate STMV virus for longer time than all-atom MD could do. In this simulation, each amino acid is represented as a CG bead and interactions are modeled with structure-based potential. We first carried out simulation of STMV without their RNA in various environments to investigate the STMV particle stability and dynamics. For example at low ion strength or high temperature, how the virus is deformed has been studied. We discuss importance of the RNA genome for the stability of this virus.

1PT173 エピレギュリン抗体の分子動力学シミュレーション

Molecular dynamics simulation of epiregulin and its antibody

Keiko Shinoda, Hideaki Fujitani (*Laboratory for Systems Biology and Medicine, Research Center for Advanced Science and Technology, University of Tokyo*)

We present a molecular dynamics study of protein target for cancer, epiregulin and its antibody. Epiregulin is a member of the epidermal growth factor family and stimulates EGFR-driven cancer cell growth such as pancreatic cancer. To investigate the structural stability and thermodynamic property of the epiregulin-antibody complex, we have performed 1- μ s molecular dynamics simulations and free energy calculations. In this meeting, we discuss the results of the simulations and compare with experimental results.

1PT174 Molecular Dynamics Simulation of Protein Using Robot Dynamics Algorithm

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In the simulation study of biophysical phenomena, the gap between the time scale of the simulation and that of the target process is a major bottleneck of Cartesian Molecular Dynamics (CMD). High frequency motions in proteins prohibit CMD from enlarging the simulation time step beyond 1.0-2.0 fs. To overcome this limitation, we adopted a strategy to consider the torsion angles as the only degrees of freedom (DOF) which enables us to employ a method developed originally in robotics, namely Articulated-Body Algorithm (ABA), which can solve the equations of motion of internal coordinates with the small computational cost that linearly depends on the number of DOF. The program of Molecular Dynamics in Torsion Angle space (TAMD) is equipped with an extended version of ABA, so-called Freed-end ABA developed by the authors. The program can treat the AMBER and ECEPP force field and with NVE and NVT ensembles. To evaluate our program, we compared the spectra of 20 distinct dipeptides calculated by TAMD to the results of the normal mode analysis in torsion angle space. From good agreements in this comparison, we confirmed that the program can give reasonable results. We also searched the maximum time step length to give reasonable energy conservation based on the simulations of three proteins, villin head piece subdomain, BPTI and ubiquitin. We concluded that time step 4.0 fs can be employed with the original force field, and 6.0 fs can be employed if we scale the torsion energy terms of the terminal chemical groups.

1PT175 4 量体型サルコシン酸化酵素の酵素-基質複合体の分子動力学解析 Analysis of enzyme-substrate complex of heterotetrameric sarcosine oxidase by molecular dynamic simulation

Akinori Hiroshima, Haruo Suzuki, Shigetaka Yoneda (*Grad. Sch. Sci., Kitasato Univ.*)

Heterotetramic sarcosine oxidase [SO, EC 1.5.3.1] catalyses the oxidative demethylation of sarcosine to generate glycine, hydrogen peroxide, and formaldehyde or 5,10-methylene-tetrahydrofolate, depending on the availability of tetrahydrofolate. SO was first purified from *Corynebacterium* sp. U-96 [SO-U96], and then from various sources. SO-U96 comprises four non-identical subunits (α , 110 kDa; β , 44 kDa; γ , 21 kDa; δ , 10 kDa) and one FAD, one FMN, and one NAD⁺. The 3D structure of the SO-U96-complex with dimethylglycine [DMG] has been determined from X-ray crystallography. The structural and biochemical analyses gave new insight into the cavity, conformational change, and channeling of oxygen, sarcosine, and products through the cavity. The authors performed the free energy perturbation molecular dynamics simulations in which the bound DMG was mutated by the coupling parameter approach into sarcosine, and analysed the simulated enzyme-substrate complex from the structural and energetic viewpoints. The mobility of substrate was also analyzed to examine the possibility of realistic simulations of channeling of substrate and products. The GROMACS program, the GROMOS 53a6 energy parameters, and the SPC water parameters, and the particle mesh Ewald method were used. The numbers of the atoms were from 130 000 to 160 000, depending on the number of the water molecules included in the simulations.

1PT176 アデニル酸キナーゼ反応機構に関する ONIOM 法による研究
Study on the reaction mechanism of adenylate kinase with ONIOM method

Kenshu Kamiya (*Department of Physics, School of Science, Kitasato university*)

Adenylate kinase catalyzes the reaction: ATP + AMP + Mg²⁺ → ADP + ADP + Mg²⁺. In order to elucidate the nature of the reaction, we have been studying the theoretical model using MM/QM. We constructed the complex structure of enzyme and substrates, ATP and AMP with Mg ion, based on the PDB data of complex with inhibitor. After the full optimization of the whole molecule in vacuo with MM, we put TIP3P water molecules around catalytic center Mg ion with spherical boundary condition, and harmonic constraint potentials on the surrounding atoms in the boundary region. Some model structures were sampled from 900 K MD simulation followed by structural energy minimizations. In order to obtain the reasonable initial model of the transition state, we performed the molecular mutation calculation from the reactant to the product. Further truncated models were used for the calculations with ONIOM method, the reactant, product, transition structures were optimized. In these calculations, small barrier (several kcal/mol) shown in the low level model (19/834 atoms in QM/MM, HF/6-31G(d):AMBER) vanishes with higher level, and the present highest model (89/764 atoms in QM/MM, B3LYP/6-31+G(d):AMBER, embed model) gives the reaction barrier of 19 kcal/mol, and 10 kcal/mol exothermicity. For further discussion, however, more qualitative consideration as well as free energies on the conformational effects of the surrounding atoms is necessary.

1PT177 酵素の多機能性に関する解析
Analysis of enzyme promiscuity

Chioko Nagao, Kenji Mizuguchi (*NIBIO*)

For a long time, enzymes are believed to catalyze specific reactions with specific substrates. Specificity is essential for enzymes to work in the crowded environment of a cell. However, recent experimental studies have shown that many enzymes can catalyze more than one reaction or have broad substrates (i. e., enzyme promiscuity). It is becoming recognized that enzyme promiscuity is related to functional evolution, drug metabolism and protein engineering [1]. Although molecular mechanisms of promiscuity of each enzyme have been investigated, there have only been a few attempts to define the general properties that characterize promiscuous enzymes, and no comprehensive analysis using reaction constants have been made [2]. Moreover, a good measure for describing promiscuity has not been established.

In order to elucidate how widespread the substrates and reactions are that an enzyme can bind and catalyze, we performed a systematic analysis of the enzyme data in the BRENDA database [3]. The enzymes 1) for which UniProt ids were obtained from BRENDA or through PubMed ids and NCBI Entrez links, and 2) which have Michaelis constants or turnover numbers for at least ten different substrates were selected for the analysis. At the fourth level of Enzyme Commission Number and within an orthologous enzyme group, the relationships among sequence identities, reaction constants and substrate similarities are discussed.

1. Nat Biotechnol 2009;27:157. 2. Biochemistry 2008;47:157. Bioinformatics 2010;26:2012. 3. Nucleic Acids Res 2009;37:D588.

1PT178 Folding of topologically complex proteins by an atomic interaction based coarse grained model

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While fast folding of small proteins has been relatively well characterized by experiments and theories, much less is known for slow folding of larger proteins. Recent progress of experimental works on the folding of large proteins revealed a number of new features arising from the topological complexity, which poses new challenges to the current protein folding theories. Reasonably describing the folding of such topologically complex proteins needs more sophisticated theoretical models. In this presentation, we introduce a new model, i. e., AICG model, developed within the framework of the energy landscape theory. The features of this new model include: i) contact interactions are delicately weighted according to the atomic interactions via a multiscale protocol; ii) a realistically flexible energy function is used for the local interactions. We applied this model to a number of topologically complex proteins, including multi-domain proteins and knotted proteins, and it reproduced all the major features of folding revealed experimentally. Our results suggest that the structure-based model can capture the essential features of the folding of proteins with complex topologies after delicately weighting the contact interactions, and including realistic local flexibilities.

1PT179 多様な分子コンホメーションを取り得る溶質の小角 X 線散乱プロフィールの近似計算法

A new approximation method for estimating SAXS profiles of solutes with multiple molecular conformations

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Small-angle X-ray scattering (SAXS) has long been used as an important means for determining global-structure parameters of biopolymers in solution. It can be applied not only to natively globular proteins with a practically single global structure but also to natively unfolded proteins with many available conformations such as intrinsically disordered proteins (IDP). In the latter case, however, we need to evaluate a large number of SAXS profiles for averaging them, because the IDP consists of an ensemble with diverse conformations. The program CRYSOLE (Svergun, D. et al., *J Appl. Cryst.*, 1995) has been commonly used to calculate SAXS profiles of IDPs. We found that the calculated profiles contain a non-negligible amount of error caused by the approximation taken in estimating the contribution of protein hydration-layer. Though it is possible in principle to use the method combined with MD simulation (Seki, Y. et al., *Biophys. Chem.*, 2002) for removing the error, the computational cost would go impractically high for IDPs. We present here a new approximation method for estimating SAXS profiles applicable to solutes with multiple molecular conformations. Though the accuracy of this method is lower than that of the MD-combined method in the large-K region, it gives sufficient accuracy in small-K region with low computational cost. In the meeting, we will report on the detail of approximation and its applicable range of scattering angle.

1PT180 極低温電子顕微鏡による 26S プロテアソームの単粒子解析
Single particle analysis of 26S proteasome by cryo-electron microscopy

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The eukaryotic 26S proteasome functions to degrade a large fraction of intracellular proteins. The 26S proteasome is composed of at least 33 different subunits in 20S core particle (CP) and one or two 19S regulatory particles (RPs). Proteins destined for degradation are marked by poly-ubiquitin, a degradation signal that is recognized by the RPs. The proteolytic sites are sequestered inside the CP and are accessible only through a narrow channel. Thus the RP deconjugates ubiquitin chains, unfolds substrate proteins, and translocates them into the catalytic CP. The CP was amenable to structure determination by X-ray crystallography but the 26S holocomplex with 1 or 2 RPs has so far resisted all crystallization attempts. Here we optimized the single particle analysis methods by cryo-electron crystallography for the structural analysis of the 26S proteasome.