I-O Molecular Dynamics Simulations of Proteins

Molecular functions of proteins are investigated by molecular dynamics (MD) simulations. Using parallel computing, the present-day computer resources allow us to simulate a dynamical process of a protein system consisting of ~10^6 atoms over ~10^2 ns. The studies go one step further to develop the method of deriving biologically significant information from the MD trajectories. Here, we report a result of such simulation study. Each specific protein function requires its specific way of description. The following example is a problem of the stationary transport process of water through narrow channels formed by proteins and lipid molecules. The results of the analysis stress the importance of the single-file characteristics for the efficient transport.

I-O-1 Determinants of Water Permeability in Aquaporin Family: A Comparative Simulation Study

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Water permeation through the water channel, aquaporin (AQP), was studied by comparative molecular dynamics (MD) simulations of five members of the AQP family, AQP1, AQP4, AQPZ, GlpF, and AQP0, in the explicit membrane environment. Water permeability of the AQPs was determined from the MD trajectories in the form of the single-channel osmotic permeability pf using the linear response formula. Comparing the pf values of the five homologous proteins, we found several structural determinants of water permeability. First, the wider channel containing more water simply appeared to transport more water. Second, water permeability through the AQP channel is related to the frequency of the jumping motion determined by the free-energy barrier height for water to jump between two adjacent preferential hydrogen bonding sites. The third factor is the correlation in the motions of the channel waters. In the analysis of the newly developed pf matrix, we found that the water motion in AQPs was a perturbed single-file permeation, in which the two NPA motifs appear to interrupt the correlation in water motions, referring to the ideal single-file permeation in a carbon nanotube. This means that a smaller perturbation in the NPA region results in larger permeation. The importance of the single-file nature of water permeation was confirmed in MD simulations of three mutants of AQPZ mimicking AQP1.

I-P Bioinformatics Studies of Proteins

Database work on biological information, bioinformatics, is another important part of the theoretical studies of proteins. Molecular simulation focuses on each specific protein function. On the other hand, the database study treats the ensemble of proteins in the database. Here, we report two different types of bioinformatics study developing a new method. The first is about a method describing protein dynamics using the protein structure database and the elastic network model. This treats a problem of classical mechanics, or the separation of the internal and external degrees of freedom. The second is a method comparing two proteins using an analogy between dynamic programming and Ising model. Using the partition function of Ising model, we can further improve the conventional dynamic programming to detect remote homology in amino acid sequences.

I-P-1 Normal Mode Analysis Fixing the External Degrees of Freedom for Any Portion of a System

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Normal mode analysis, including the coarse-grained version of elastic network model, is most widely used to illustrate protein fluctuations. In the system with no external field, the external degrees of freedom are defined as the six normal modes with zero frequency. This definition is equivalent to those of the Eckart condition, or the Eckart frame. However, it has been recognized that the Eckart condition is not the best way to represent protein motions, but a relative motion to a certain fixed part of the protein gives a more transparent representation. We call it the fixed-domain frame. Here, we derived the formula converting the Hessian matrix, or the covariance matrix, defined in the Eckart frame into the one in the fixed-domain frame. This formula was derived by imposing fictitious external forces to the molecule so as to eliminate the external motions of the domain without affecting the internal degrees of freedom. The validity of the formula was confirmed by a comparison with the superposition of many snapshots obtained from a molecular dynamics simulation.

I-P-2 Probabilistic Alignment Detects Remote Homology in a Pair of Protein Sequences without Homologous Sequence Information

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Dynamic programming (DP) and its heuristic algorithms are the most fundamental methods for similarity searches of amino acid sequences. Their detection power has been improved by including supplemental information, such as homologous sequences in the profile method. Here, we describe a method, probabilistic alignment (PA) that gives improved detection power, but similarly to the original DP, uses only a pair of amino acid sequences. Receiver operating characteristic (ROC) analysis demonstrated that the PA method is far superior to BLAST, and that its sensitivity and selectivity approach to those of PSI-BLAST. Particularly for orphan proteins having few homologues in the database, PA exhibits much better performance than PSI-BLAST. Based on this observation, we applied the PA method to a homology search of two orphan proteins, Latexin and Resuscitation-promoting factor domain. Their molecular functions have been described based on structural similarities, but sequence homologues have not been identified by PSI-BLAST. PA successfully detected sequence homologues for the two proteins and confirmed that the observed structural similarities are the result of an evolutional relationship.