accessory secondary structures in some cases. We found that the atomic fluctuations of each of the beta-strands have a high correlation with its immediate beta-strand neighbour in the core. Compared to the beta strands, the alpha helices have less correlation with each other and almost none with the strands. We also defined rotation and translation vectors to decompose the type of movements to which the normal modes of these TIMs correspond. We relate differences in the mobility of the individual secondary structure elements to the differences in function and structure of the five different enzymes.

1168-Pos   Board B60
Comparing Normal Modes of Protein Structures using Webnm@ 2.0
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Normal modes analysis (NMA) has been shown to be an effective computational method to study the movements of proteins, especially at the domain level. WEBnm@ (http://apps.cbu.uib.no/webnma/home) is a web-tool which provides access to calculations of these modes on C-alpha atoms of protein structures and various analyses with output as images, plots or raw data points. We have improved the efficiency for input processing and have added new functionality that interprets the normal modes calculated. In the Single Analysis section, we have included an interactive visualisation of the lowest six mode vectors, the calculation of the correlation matrix based on all the modes vectors and the overlap analysis with another conformation of the same structure. The newest section, Comparative Analysis, calculates and compares the normal modes of a set of aligned protein structures, which is currently not available in any other tool. It includes comparative analyses such as fluctuations profiles, deformation energies and comparison of modes calculated on the input structures using the root mean square inner product (RMSIP) . For this part, more than one structure can be submitted along with a FASTA file of their alignment. In addition to the updates, we have also provided a SOAP web-service for a more programmable interface for both of these sections.

1169-Pos   Board B61
A Quantitative Measure of Protein Flexibility
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Protein flexibility plays an important role in the proper structure and function of proteins. It also dominate complex phenomenon such as protein-ligand interactions, protein-protein interactions. A quantitative measure of protein flexibility would be valuable in many applications such as docking and modeling problems. In this work we provide a quantitative measure of protein flexibility based on side-chain conformational analysis and hydropathy pattern for all possible tripeptide strings in the protein sequence. We used 5730 PDB structures culled by PISCES server based on sequence identity, resolution and R-factor. We used the chi-1-3CPD (chi-1 three (3) conformational propensity diversion) parameter defined as the standard deviation of RFs (relative frequencies) in 3 possible conformations of central residue in each tripeptide. Chi-1-3CPD = 0 means RFs in G+, G- and Trans are exactly equal. We used chi-1-3CPD index in sliding window method to get flexibility predicted values. Our analysis showed a strong correlation between chi-1-3CPD and backbone flexibility indicated by the B-factor. We then analyzed the hydropathy pattern from all possible tripeptides we have had used in these studies. Our findings illustrated, those tripeptides with non-homogeneous hydropathy pattern for all their three residues have small values of chi-1-3CPD. For instance, tripeptides with hydrophilic central residue and hydrophobic marginal residues had minimum chi-1-3CPDs value (less chi-1-3CPD means central residue has nearly equal propensity for three possible conformations and more like for conformational switching). It is suggested that the hydropathy pattern of residues play a major role in the flexibility of proteins. The knowledge-based flexibility prediction method presented here is a simple and non-expensive method comparable to previously sophisticated methods used for flexibility analysis of proteins.

1170-Pos   Board B62
Structural Dynamics Flexibility Informs Function and Evolution at a Proteome Scale
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Abstract: Protein structures are dynamic entities with a myriad of atomic fluctuations, side chain rotations, and collective domain movements. While the importance of these dynamics to proper functioning of some proteins is emerging, there is a lack of broad evidence for the critical role of protein dynamics in shaping the biological functions and protein evolution for a large number of

proteins in a proteome. To this aim, we develop novel dynamic flexibility index (*dfi*) to quantify the dynamic properties of individual residues in any protein using perturbation response scanning that couples elastic network models with linear response theory. Then, we use *dfi* to assess the importance of protein dynamics in over 100 human proteins. Our analyses involving functionally critical positions, disease-associated and benign population variations, and the rate of interspecific substitutions per residue produce concordant patterns and establish that the preservation of dynamic properties of residues in a protein structure are critical for maintaining the protein/biological function at a proteome scale. Therefore, structural dynamics needs to become a major component of the analysis of protein function and evolution.

Protein Structure Prediction

1171-Pos   Board B63
De Novo Protein Structure Determination from Incomplete Experimental Data
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The problem of theoretical *de novo* protein structure prediction has been already investigated for a few decades. Throughout those years numerous different algorithms have been proposed to solve this problem. The most successful ones are capable of predicting the structure for small-size globular proteins (up to 80 amino acids). Recent years have also witnessed improvement in experimental structure determination methods, which became throughput and highly automated. Several steps however still have to be done manually. Combination of *de novo* prediction methods with fragmentary experimental data can be used to alleviate some of these bottlenecks.
In our work we combined one of the most successful approaches for protein structure modeling: fragment recombination (ROSETTA method[1]) into a single protocol that employs fragmentary NMR data: Chemical Shifts, J-couplings as well as TEDOR and VEANS obtained in Solid State NMR experiments. The protocol, managed by BioShell[2,3] software is very general and can utilize a wide variety of other than NMR types of data. The experimental restraints are applied on various stages of the procedure: to derive distance restraints, to select matching protein fragments from a structural database, to guide the conformational search and finally to score the obtained models. Our results show that in several cases it is possible to calculate a high-resolution protein structure without long-range experimental restraints i.e. solely from local backbone information. Moreover, the use of high-resolution lattice model greatly improves computational efficiency of the whole protocol.
References
1. R. Das and D. Baker, *Ann. Rev. Biochem.* **77**, 363-382 (2008).
2. D. Gront and A. Kolinski, *Bioinformatics* **22**, 621-622 (2006).
3. D. Gront and A. Kolinski, *Bioinformatics* **24**, 584-585 (2008).

1172-Pos   Board B64
Large Scale Structure Sampling for Protein Fold Prediction using the Generalized Simulated Annealing
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Proteins are the building blocks of cells and the executioners of nearly all cellular functions. Their structure is of paramount importance to understand their dynamics and function, as well as the interactions with other molecules.
In this work, we apply the Generalized Simulated Annealing (GSA) to guide the exploration of the energy hyper surface of the protein folding process, looking for the global minimum and, hence, the native fold of the protein. The GSA is a stochastic search algorithm employed in energy minimization and used in global optimization problems, such as gravity models, fitting of numerical data and conformation optimization of small molecules. Our software applies the analytical inverse of the probability distribution from GSA, a new method to apply rotations to the phi and psi angles of the peptide bonds and side chains, faster connection with NAMD for potential energy calculation and the possibility of parallel execution, granting a new take on ab-initio protein structure prediction. The new design also allows for an easier inclusion of knowledge derived potentials, based on experimentally determined protein structures.
We present results for the 14 amino acid protein mastoparan-X. The chain folds with RMSD of 3,0 angstroms after 500.000 GSA steps. Currently, for this

system, the software calculates 5 million GSA steps in under 6 hours using 4 processors in one node.

Predicted structures can be refined with molecular dynamics simulations and used to study proteins whose conformation can not be determined with experimental methods. These structures can be used in protein engineering, drug development and biotechnological research.

1173-Pos   Board B65
Novel Physics-Based Protein Structure Refinement Method
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Refinement of low-resolution protein structures is still a major problem despite the advancements in structure prediction and refinement methods. We have recently developed a new approach, which mimics the mechanism of chaperones that rehabilitate misfolded proteins by causing them to unfold, and then giving them a new chance to refold. The target protein is unfolded by selectively pulling different ends, using geometric based simulation techniques, FRODA (1), and then refolded by the zipping and assembly method (ZAM) (2-3). During these steps, the unfolded trajectories are used to identify conserved backbone dihedral angles and hydrophobic-hydrophobic contacts, and then this acquired information is used as energetic restraints to enforce contacts and dihedral angles during refolding, through 10ns of replica-exchange molecular dynamics using the AMBER force field with implicit solvation. We have tested this refinement method on CASP9 and CASP10 targets, and observed that usually misfolded parts of the chain unfold first and most importantly refolds to produce a better refined structure.

1. de Graff, Adam M.R.; Shannon, Gareth; Farrell Daniel W.; Williams, Philip M.; Thorpe, M.F. Biophys J. (2011) 101(3):736-744
2. Ozkan, SB; Wu, GA; Chodera, JD; Dill, KA Proc. Natl Acad. Sci USA (2007) 104:11987-11992.
3. Glembo, TJ and Ozkan SB, Biophys. J. (2011) 98:1046-1054

1174-Pos   Board B66
New Methods to Improve Protein Structure Prediction and Refinement
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We have developed and combined several novel methods to improve protein structure prediction from the amino acid sequence, and the structural refinement of protein models. One of the most promising developments in protein structure prediction are many-body potentials that take into account dense packing, and cooperativity of interactions in protein cores. We developed a method that uses whole protein information filtered through machine learners to score protein models based on their likeness to native structures. Testing on CASP 9 targets showed that our method is superior to the common DFIRE and its derivatives as well as to the current version of RWPlus, both of which are considered a standard in the field. By combing statistical contact potentials with entropies from the elastic network models of proteins we can compute free energy and improve coarse-grained modeling of protein structure and dynamics. The consideration of protein flexibility and its fluctuational dynamics improves protein structure prediction, and leads to a better refinement of computational models of proteins. We proposed a novel protein structural refinement procedure based on Anisotropic Network Model (ANM) of protein fluctuational dynamics and Go-like model of energy score. The starting structures were models from past CASP experiments. We changed positions of C-alpha atoms using ANM, creating a new set of 250 structures from the initial model, and computed energies of these structures using Go-like energy score. The top 5 coarse-grained structures were fully rebuilt with BBQ and Scrwl4. To remove bond stretches and the excluded volume clashes, short Molecular Mechanics simulations (up to 10,000 steps) were performed with OPLS-AA force field and implicit solvent GBSA-OBC. The whole structural refinement process was performed iteratively leading to the improvement of average RMSD from 3.8A to 2.6A in 50 iterations.

1175-Pos   Board B67
Absolute Quality Assessment of Protein Models
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Modeling methods increasingly attempt to close the gap between the number of known protein-coding sequences to that of structurally resolved proteins, but

the results of these methods have been of mixed success. Adequate models can be built for proteins with high sequence similarity to a structurally resolved protein and occasionally modeling even succeeds in the absence of a good template, but currently no method exists to reliably rate the quality of the models. Many protein structure prediction methods rate protein models using an established scoring function by comparing the energies of an ensemble of structures and choosing the lowest energy members of said ensemble as the prediction. The acceptance of theoretical protein models is limited in the life-sciences, as currently no method exists to rate the quality of a protein model a-priori, i.e. from the model alone.
Here we investigate an approach to provide an a-priori estimator of the quality of a protein model using a free-energy scoring function[1], without comparing it to a competing ensemble. We devised a N-dimensional statistical test based on the per-residue energies of amino acids in a set of high-resolution experimental structures. The quality of the protein structures can be assessed by comparison against these statistics. We were able to discriminate the low quality models for 93% of the 160 proteins tested, which is increased further to 99%, when excluding proteins, which bind cofactors or DNA; interactions not considered by the energy model or the training set. In combination with bioinformatics based methods that exclude proteins that are not covered by the scoring function, this measure for quality assessment of protein models may help increase the acceptance of qualified theoretical protein models in the life-sciences.
[1] Verma, A.,Wenzel, W. (2009). A Free-Energy Approach for All-Atom Protein Simulation. Biophys.J 96,3483-3494.

1176-Pos   Board B68
MQAPmulti2 and MQAPsingle2:Toward the Estimation of Model Quality When Not Only Many Models are Available
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We propose two new methods for the estimation of the quality of protein models. MQAPmulti2 performs well when scoring hundreds of alternative models, but also it can be applied when only a few models (~20) are available. We optimized MQAPmulti (developed earlier by Pawlowski and Bujnicki) to perform better when less than hundreds models are available.
The MQAPmulti2 prediction is based on three components: 1) TrueMQAP_-component - scoring is based on statistical and agreement potentials; 2) CLUST_component, which clusters models on the base of GDT_TS and SQ_score (our modification of Q-score that works by estimating the structural relatedness between two protein structures based on comparison of intramolecular distances); 3) CORR_component, a correlation based method that combines predictions of the TrueMQAP_componet with pair-wise models comparisons measured by GDT_TS and SQ_score. Finally, all of these components are used to predict the global quality of a model. To do so, on the base of the number of input models, the program chooses one of 3 regression models that describe the relationship between initial parameters and the global quality. These three regression models were created for following numbers of input models: 20, 150, 300 or more.
MQAPsingle2, that is a variant of the MQAPmulti2 program, that operates as a quasi-single model MQAP. This method applies MQAPmulti2 algorithm, however a model to be scored is not compared to the input models, but to models generated by GeneSilico fold prediction metaserver.
MQAPmulti2 was trained and tested for *CASP7th, 8th and 9th* models dataset by using 10-fold cross validation procedure. The value of Pearson's correlation coefficient between MQAPmulti2 global score and the GDT_TS is 0.712, 0.819 and 0.917 for cases of 20, 150 and 300 or more available input models, respectively.

1177-Pos   Board B69
Modeling Temperature-Dependent Ion Channel Protein Structural Changes with Rosetta
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Temperature-sensing ion channels are thought to adopt different conformations at varying temperatures, driven by a significant difference in free energy between the closed and open states. In support of this notion, we previously observed with site-directed fluorescence recordings that pore region undergoes substantial structural rearrangements during the heat activation of TRPV1 channels. Temperature-driven structural changes have also been suggested in other protein regions and channel types. To reveal such structural changes, we are exploring the Rosetta modeling method to predict channel protein structural differences at two different temperatures.