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Posters

Protein Structure Prediction & Drug Design

3140-Pos Board B1
Integrative Structure Determination of the Components of the Nuclear Pore Complex by X-Ray Crystallography, Small Angle X-Ray Scattering, Electron Microscopy, NMR, and Comparative Modeling
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The Nuclear Pore Complex (NPC, ~50 MDa) is the sole passageway for the transport of macromolecules across the nuclear envelope. The NPC plays a key role in numerous critical cellular processes such as transcription, and many of its components are implicated in human diseases such as cancer. Previous work (ref 1, 2) defined the relative positions of its 456 constituent proteins (nucleoporin or Nups), based on spatial restraints derived from biophysical, electron microscopy, and proteomic data. Further elucidation of the evolutionary origin, transport mechanism, and assembly of the NPC will require higher resolution information. As part of an effort to improve upon the resolution and accuracy of the NPC structure, we set out to determine the atomic structures of the NPC components. Because it proved difficult to determine the atomic structures of whole Nups by X-ray crystallography alone, we are relying on multiple datasets that are combined computationally by our Integrative Modeling Platform (IMP) package (http://salilab.org/imp). In particular, we developed an integrative modeling approach that benefits from crystallographic structures of fragments of the protein or its homologs, Solution Small Angle X-ray Scattering (SAXS) profiles of the protein and its fragments (ref 3), NMR, and negative stain Electron Microscopy (EM) micrographs of the protein. Each dataset is converted into a set of spatial restraints on the protein structure, followed by finding a model that satisfies the restraints as well as possible using a Monte Carlo / molecular dynamics optimization procedure. The approach will be illustrated by its application to yeast Nup133.
1. Alber et al., Nature 450, 683-694 (2007).
2. Alber et al., Nature 450, 695-701 (2007).
3. Förster et al., J Mol Biol 382 (4), 1089-1106 (2008).

3141-Pos Board B2
A Next Step in Protein Secondary Structure Prediction
Hui Liu[1], Yaohang Li[2], Ionel Rata[1], **Eric Jakobsson**[1].
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We report on a new methodology for protein secondary structure prediction based on: step 1) constructing a new scoring function by taking short and long distance triplet residues interactions into consideration, 2) generating reference states from protein database with high similarity, and 3) using a genetic algorithm to refine the predictions from the consensus templates of existing secondary structure prediction methods to utilize both near and intermediate distance context. In most targets we tested, we found that our method at worst performs essentially as well as the best of the other constituent methods and at best performs much better. At the submission time of this abstract we believe that the performance limitations are lack of code optimization to fully utilize more compute power and do more exhaustive context dependent probability matrix for scoring. Our ultimate goal is to combine new improved secondary structure prediction methodology with improved loop protein structure prediction from our team (Rata et al, J Phys Chem B, 2010; Li et al, BMC Structural Biol. 2010; Li et al, JCIM, 2011) to enable improved tertiary structure prediction. Supported by NSF grant 1066471 to Li and NSF grant 489521 to Jakobsson.

3142-Pos Board B3
AWSEM-MD: Coarse-Grained Protein Structure Prediction using Physical Potentials and Bioinformatically Based Local Structure Biasing
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A coarse grained protein model was used for structure prediction. Prediction results are presented for varying degrees of local structure biasing based on a simple sequence alignment procedure to proteins with known structure. The local structure biasing is complemented by several physically motivated interactions. Pairwise direct contact and many body burial and water/protein mediated interactions were optimized using energy landscape theory. Alpha helical and beta strand hydrogen bonding potentials were parameterized using bioinformatic surveys. All of these potentials and several others, collectively known as the Associative memory Water mediated Structure and Energy Model (AWSEM), were recently integrated with LAMMPS, a popular open source molecular dynamics simulation package.

3143-Pos Board B4
Insights on the Evolutionary Conservation of Mating-Type HMG Domains are Revealed using Multiple Homology Models
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MATα1 works in coordination with MCM1 and other transcriptional regulatory proteins (ie. STE11) to activate transcription of α-specific genes and ultimately determine yeast cells mating type. Although structural knowledge exist for MCM1, MATα2 and MATa1, for MATα1 and all other mating-type homologues of MATα1, they are non-existent. Recent studies have suggested that the highly conserved alpha-domain of MATα1 belongs to the HMG family of DNA binding proteins. Analysis of 27 HMG domain structures in the Protein Data Bank allowed us to make theoretical predictions on the structure of the HMG domain of MATα1. A highly conserved α-helix required for DNA binding in all HMG domains and shares 50% homology to the structure of Lef-1/DNA. A base specific interaction using a conserved arginine is not seen in current HMG structures determined to date but is predicted in our models. Ultimately we hope that the model structures will yield further insight on the evolution of the HMG and the α-domain. Attempts to determine the structure of MATα_HMG domain by X-ray crystallography are currently being pursued and will also be discussed.

3144-Pos Board B5
Refinement and Quality Assessment of Predicted Protein Structures
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In recent years in silico protein structure prediction reached a level where a variety of servers can generate large pools of near-native structures. However, the identification and further refinement of the best structures from the pool of decoys continue to remain problematic. To address these issues we have developed the MUFOLD-MD server that uses the Rosetta software for structure refinement and a molecular dynamics (MD) based ranking (MDR) method for structure selection. The refinement of the selected structures is done by employing Rosetta's relax mode, subject to certain constraints. MDR selects the best structures by testing their relative stability against gradual heating during all atom MD simulations. The MUFOLD-MD server uses three sequential steps consisting of, i.e., structure: 1) generation, 2) refinement and 3) selection. 1) By using sequence-profile alignment (e.g., PSI-BLAST) and profile-profile alignment (e.g., HHSearch) methods, the query sequence is classified as either ''hard'' or ''easy'' target. For hard targets, models are generated using the Rosetta 3.2 software (ab initio method) and then ranked by using their Rosetta energy score. For easy targets, models are generated with the Multi-Dimensional Scaling (MDS) method and then ranked using the OPUS_Ca scoring function. 2) The structures (subject to certain constraints) are refined by employing the ''relax'' mode of Rosetta 3.2. 3) The MDR method is used to select the top 5 structures as the output of the server. Our MUFOLD-MD server was tested in both CASP8 and CASP9 competitions. Based on the official CAP8 results, MUFOLD-MD was ranked as number one server in the Free Modeling category.

3145-Pos Board B6
Physics Based Protein Structure Refinement
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Accurate protein structure predictions are important for a number of purposes ranging from computational drug design, understanding experimental data and designing new experiments, to the emerging technique of de novo phasing in crystallography. The process of protein structure refinement occurs at the end of the structure prediction pipeline. The goal is to take an approximately correct starting model and further refine the details to produce a more accurate prediction. We have developed a physics-based approach to refinement that combines Hamiltonian exchange molecular dynamics with bioinformatics-derived restraints. The use of restraints dramatically reduces the volume of phase space that must be sampled and makes the procedure practical on small to medium