structural basis of this drastic functional diffrences are unknown The general objectives of our work are to address these issues and to progress towards a better understanding of the structural basis of resistin biology. Our primary focus is (i) to understand the similarities and differences between human and mouse resistin with respect to their structures and (ii) to infer, using computational approaches, putative functionally important residues. For that purpose we have applied known homology modelling approaches to build a comprehensive 3D model for human resistin using mouse crystallographic data as template. We further assessed the structural properties of this 3D model using molecular dynamics techniques. We importantly compared the properties of both mouse and human resistin structures. The structural status of conserved and non-conserved residues between mouse and human resistin were further investigated with particular emphasis on those residues involved in inter-chain contacts and those exposed on the surface. By identifying the few important residues from the above analysis, we further studied and compared the dynamic properties which provide important insights into structural and functional properties of resistin. Our work suggests that there are considerable differences in interchan interactions and contact surface area between human and mouse structures. Our work also suggests that considerable differences in N-terminal helical orientation in the human model.

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On Template Selection for Homology Modeling of G-Protein Coupled Receptors

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G-Protein Coupled Receptors (GPCRs) are a family of structurally similar integral membrane proteins that bind diverse ligands, from the size of a photon to small peptides. For several years the inactive conformation of Bos taurus rhodopsin has been the only GPCR crystal structure available at atomic resolution, thus serving as the most reliable template for homology modeling of other GPCRs. Over the past year, the atomic coordinates of several different new crystal structures of GPCRs (two of them encompassing some of the characteristic structural features that have often been attributed to GPCR activated states) have become available. Considering that acceptable models of the transmembrane (TM) regions of membrane proteins may be obtained for template sequence identities of 30% or higher, we investigated the extent to which current crystal structures of GPCRs are valuable templates for homology modeling of the TM regions of a dataset of non-redundant non-orphan non-olfactory Class A GPCRs from the human genome aligned using conserved functional residues in their TMs. While the recently solved crystal structures of beta-2 adrenergic receptor and mutant m23 beta-1 adrenergic receptor are calculated to be valuable templates for 16% and 18% of class A human GPCRs, respectively, our results indicate that the majority of GPCRs in the human genome needs better templates for their accurate homology modeling. Thus, our calculations point to specific GPCR targets whose crystal structures would be most beneficial to the majority of human GPCRs. Moreover, we suggest specific ways to improve GPCR modeling, including the use of hybrid templates.

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Protein Structure Prediction Without Optimizing Weighting Factors For Scoring Function

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Optimizing weighting factors for a linear combination of terms in a scoring function is a crucial step for success in developing a threading algorithm. Usually weighting factors are optimized to yield the highest success rate on a training dataset, and the determined constant values for the weighting factors are used for any target sequence. Here we explore completely different approaches to handle weighting factors for a scoring function of threading. Throughout this study we use a model system of gapless threading using a scoring function with two terms combined by a weighting factor, a main chain angle potential and a residue contact potential. We present three novel threading methods which circumvent training dataset-based weighting factor optimization. The basic idea of the three methods is to employ different weighting factor values and finally select a template structure for a target sequence by examining characteristics of the distribution of scores computed by using the different weighting factor values. Interestingly, the success rate of our approaches is comparable to the conventional threading method where the weighting factor is optimized based on a training dataset. Moreover, when the size of the training set available for the conventional threading method is small, our approach often performs better. In addition, we predict a target-specific weighting factor optimal for a target sequence by an artificial neural network from features of the target sequence. Finally, we show that our novel methods can be used to assess the confidence of prediction of a conventional threading with an optimized constant weighting factor by considering consensus prediction between them. Preliminary result of applying our approaches to docking is also presented.

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FRESS: an Efficient Monte Carlo Method for Biopolymer Structure Simulation

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An efficient exploration of the configuration space of a biopolymer is essential for its structure modeling and prediction. In this presentation, we report a new Monte Carlo method, Fragment Re-growth via Energy-guided Sequential Sampling (FRESS). We tested FRESS on hydrophobic-hydrophilic (HP) protein folding models in both two and three dimensions. For the benchmark sequences, FRESS not only found all the minimum energies obtained by previous studies with substantially less computation time, but also found new lower energies for all the three-dimensional HP models with sequence length longer than 80 residues. We also developed a new version of FRESS, mFRESS, whose performance will also be presented.

3373-Pos Board B420

Refinement Of Protein Model Structures In Explicit Solvent Using Biasing Potential Replica Exchange Simulations

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Comparative protein modeling of a target protein based on sequence similarity to a protein with known structure is widely used to provide structural models of proteins. Frequently, the quality of the target- template sequence alignment is non-uniform along the sequence: parts can be modeled with a high confidence, whereas other parts differ strongly from the template. In principle, molecular dynamics (MD) simulations can be used to refine protein model structures but it is limited by the currently accessible simulation time scales. We have used a recently developed biasing potential replica exchange (BP-Rex) MD method (Kannan, S. Zacharias, M. *Proteins* 2007, 66, 697-70) to refine homology modeled protein structure at atomic resolution including explicit solvent. In standard Rex-MD simulations several replicas of a system are run in parallel at different temperatures allowing exchanges at preset time intervals. In a BP-RexMD simulation replicas are controlled by various levels of a biasing potential to reduce the energy barriers associated with peptide backbone dihedral transitions. The method requires much fewer replicas for efficient sampling compared with standard temperature RexMD. It is also possible to focus the method to parts of a protein structure (segments of a model structure that may differ strongly from a template structure). Application to several protein structures indicates improved conformational sampling compared to conventional MD simulations. BP-RexMD simulations on several test cases starting from decoy structures deviating significantly from the native structure resulted in final structures in much closer agreement with experiment compared to conventional MD simulations.

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Protein Structure Refinement Using Physics-Based Models And Sampling

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Much progress has been made in predicting the three-dimensional structures of proteins from sequence alone. So far, the most successful prediction methods have been strongly bioinformatics-based, reliant on known templates or statistical features of solved protein structures. However, in cases of low homology or where templates require substantial editing, it has been challenging for bioinformatics methods to refine predictions better than the closest template [1]. Here, we discuss a strategy for refining structures generated by bioinformatics web servers using physics-based simulations, with an atomic physiochemical force field and canonical sampling at physiological temperature. Specifically, we use replica exchange molecular dynamics (REMD) simulations with an AMBER force field and implicit solvation model that we previously found to correctly stabilize short peptide [2] and small, single domain protein folds [3]. The present REMD simulations are seeded with different conformations, enabling simultaneous selection among and refinement of webserver structures. Periodic conformational clustering and re-seeding are also used to accelerate convergence. In addition, we narrow the sampling space by using restraints derived from the webserver structures to lock in common, high-confidence interactions, both in backbone secondary-structure preferences and in favorable hydrophobic interactions among side chains. These restraints are added in a manner congruent with hierarchical ''zipping'' folding behavior, where local structures form prior to global tertiary rearrangement. We demonstrate the success of the approach for a number of small proteins, and for several targets in