by binding to the pore of WD domain, a highly conserved region of Gro/TLE protein family. Reliable methods for predicting binding sites would allow a better understanding of protein selective recognition mechanisms. This, in turn, would help developments of new organism-specific medications. To the best of the author's knowledge, this is the first study that uses amino acid sequences to predict binding sites of eh1-like motifs to the WD domain. Three-dimensional models of known eh1-like motifs were generated. Their interactions with the WD domain were studied and optimized using Deep View program and the Swiss-Model server. Spatial distributions of binding sites, residue properties, and bonds' stabilities were used to devise a scoring function. The scoring function was employed to predict and evaluate putative binding sites of randomly generated eh1-like sequences. Bioinformatics database searches were used to check whether the scoring function consistently discriminated between viable and non-viable eh1 candidates and corresponding binding sites. The scoring function expressed well a general relationship between putative motifs' residue sequences and their binding sites with the WD domain. Although the function gave a few false positive findings, it reliably identified sequences that did not form stable bonds with the WD domain. The results of this study should lead to a better understanding of mechanisms of transcriptional regulation and selective protein recognition. The method presented may be used to predict binding sites of other regulatory motifs.

**3365-Pos Board B412**

**Genome-wide modeling and analysis of BAR Domains in *Arabidopsis thaliana.***

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The BAR (Bin-Amphiphysin-Rvs) Domain is a conserved dimerization protein domain which senses membrane curvature and binds to the lipid plasma membrane. The Amphiphysin protein family, which contain the BAR domain, are thought to be the modulators of the early phases of endocytosis and intracellular transport. It is theorized that this crescent shaped domain dimer show a preference for binding to highly curved, negatively charged membranes. It has been noted that in mammals and higher organisms, the BAR domain with an N-terminal amphipathic helix and BAR domain (N-BAR) can drive the membrane curvature both *in vivo* and *in vitro*. We have studied the BAR domain in the small flowering plant which is widely used as the model for plant biology, *Arabidopsis thaliana*, where its function remains largely unexplored. We have modeled all the BAR domains of *Arabidopsis thaliana* using an automated modeling pipeline with manual refinement methods and investigated their mechanism relative to other higher organisms. We have identified eight non-redundant domain sequences in *Arabidopsis thaliana*, which can be grouped into three different classes, based on their electrostatic profiles and domain architecture. We provide new insight into the features of plant BAR domains including distinct electrostatic profiles for domain sequences categorized within the same class and atypical electrostatic profiles showing a concentration of positively charged residues at both extremities of the structural fold. Our results are important in understanding the differences in signaling through BAR domains in plants and its implication in plant signaling and membrane trafficking.

**3366-Pos Board B413**

**Interactive Visualization of Protein Dynamics in Ribbon Mode**

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In recent years, experimental methods have uncovered more and more dynamic properties of molecular systems. Novel techniques for post-processing data from cryo-electron microscopy or small angle X-ray scattering nowadays routinely reveal conformational differences linked to functional states of a biological system. As opposed to molecular dynamics, these methods typically yield information about larger systems, which in effect makes an interactive visualization of the results challenging.

This poster presents an approach that computes a depiction in the more abstract ribbon or cartoon mode, which highlights the secondary structure information of a protein. To accomplish interactive frame rates, the algorithm offloads computational work from a PC's CPU to its graphical processing unit (GPU). This is achieved by separating two phases in the calculation of the geometry representing the protein. The first one involves creating a smooth curve along the protein's backbone, which requires global information and thus has to be computed by the CPU. In the second phase, vertices along that curve are moved to build the geometry for the molecule's depiction. Because local information is sufficient for that, this is handled exclusively by the GPU.

The speed-up factor achieved moves a range of large time-varying proteins into the category of those which can be depicted with interactive frame rates. For intermediate sized molecules, the speed-up results in an even smoother animation and an overall increase of the reactivity of the whole program. Especially simultaneously running processes, e.g. calculations for multi-scale modeling, can benefit from the additionally available CPU resources, too.

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**3367-Pos Board B414**

**Dynamics-based Alignment: A Novel Tool For Comparing Large-scale Movements In Proteins With Same Or Different Fold**

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The biological function of several proteins and enzymes is assisted by large scale conformational changes that are excited in thermal equilibrium. In terms of the traditional logical cascade, sequence -> structure -> function, it is expected that the functional movements of a protein are influenced by the structural architecture. Proteins with similar structures are known to sustain similar large-scale movements; yet it has recently emerged [Carnevale et al. JACS 2006, Capozzi et al. J_Proteome_Res 2007, Zen et al. Prot_Sci 2008] that similar functional movements are shared by proteins with different architecture or topology.

This observation parallels the known paradigm that (i) proteins with similar primary sequences usually attain a similar fold but also that (ii) the same fold is adopted by non-homologous proteins. The sophisticated interplay between sequence and structure has now been extensively characterized thanks to the availability of sequence and structural alignment methods. By analogy, the availability of quantitative methods for comparing the functional-oriented dynamics in proteins would allow to take to a new level the investigation of the structure/function relationship.

We report on a first attempt in this direction by discussing a pairwise alignment scheme that identifies groups of amino acids that undergo similar concerted movements in proteins. The alignment method is based on a coarse-grained elastic network model and requires as input the sole proteins' native structures. No prior detection of structure and sequence correspondence is used. The scheme is first used to perform a dynamics-based alignment (and grouping) of a data set of $>70$ representative enzymes covering the main functional and structural classes. Finally we discuss an application where the method is used to identify the putative nucleic-acid-binding regions of proteins having AXH-domains [de Chiara et al. Structure 2005].

**3368-Pos Board B415**

**Template-Based Modeling of Protein-Protein Interfaces**

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Modeling of protein binding sites is important for 3D prediction of protein complexes. Statistical analysis of target-template PSI-BLAST sequence alignments was performed for 329 two-chain target protein complexes selected from DOCKGROUND database. For 214 complexes (~65 %) the alignments contained all interface residues (full interface coverage or FIC alignments) for both complex monomers and 101 (~30 %) complexes had FIC alignments for one of the monomers. The FIC alignments were observed even in the case of poor alignments where only a small portion of the target sequence (as low as 40%) was aligned to template sequence with low alignment identity (40%) alignments, whereas for the low-identity alignments the situation is opposite. Homology models were built based on the FIC alignments with target sequence coverage $< 60$ %. The results showed that one third of the target sequences with such short FIC alignments produced models with interface RMSD (i-RMSD) $< 5$ Å, suitable for low-resolution ab initio docking. The proteins with i-RMSD $< 5$ Å had domain structure, whereas models with 5 Å $<$ i-RMSD $< 8$ Å (accuracy suitable for structure-alignment methods) were generated for single-domain proteins as well. The results provide guidelines for building 3D protein models for docking studies.

**3369-Pos Board B416**

**Homology Modeling and Molecular Dynamics Simulation Studies of the human resistin protein**

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Resistin is a member of a secretory protein family, known as resistin-like molecules (RELMs) which were exclusively found in mammalian genomes. Though human resistin molecule has high sequence similarity with mouse, its structural and physiological roles differ considerably from mouse and the

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.

**3370-Pos Board B417**

**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.

**3371-Pos Board B418**

**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.

**3372-Pos Board B419**

**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.

**3374-Pos Board B421**

**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