864-Pos Board B664
Predicting Transmembrane Dimerization and the Interfaces in Thyroid-Stimulating Hormone Receptor (TSHR) Using Brownian Dynamics Stimulation
Rejwan Ali, Rauf Latif, Terry Davies, Mihaly Mezei.
The TSHR receptor, a member of the GPCR protein family, has not been fully modeled. Only the crystal structure of the ecto-domain has been reported. Experimental data with truncated TSHRs indicate that the trans-membrane region has a major role in dimerization/ multimirization of this receptor. Biophysical (FRET) and biochemical (co-immunoprecipitation) studies from our laboratory have established that the TSH receptor, similar to other GPCRs, has the propensity to form dimers and multimers both in native and non-native cells. Recent experimental studies also from this laboratory have further reported that dimerization interfaces can reside in the extracellular domain. In addition, the TSHR, bereft of the ectodomain, shows similar characteristics, indicating that the transmembrane domains of TSHR are also involved in dimerization, receptor stability and trafficking. As server-based predictions for possible dimerization interfaces, have large uncertainties and wide variances precluding any definitive conclusions, we have resorted to the more robust and refined algorithm of Brownian dynamics in predicting transmembrane dimerization, a standard and established technique in such biological phenomena. A recently developed variant of Brownian dynamics has become an important computational tool to predict dimerization/multimerization of transmembrane proteins.
The method is implemented in a program called Macrodox and involves complementing the Poisson-Boltzmann equation based calculation of the electrostatic interactions with the calculation of Van der Waals interactions. Furthermore, in this method the sampling efficiency is enhanced by restricting the protein movements within the membrane plane. Both translational ($0.101x10^{-01}$ Å ^{2}/ps) and rotational diffusion constants ($0.165x10^{-04}$ Å ^{2}/ps) and several other physical parameters (radius of gyration=18.17 Å) have been computed for each TSHR monomer. We will present the results for contact residues from the trajectory of simulations and abrogation of dimerization following mutation of critical contact residues.

865-Pos Board B665
Fd Bacteriophage Coat Protein Structure Prediction and Design for the Assembly of Hydroxyapatite Nanorods and Bone Tissue Regeneration
Moon Young, Liza Lee, Binrui Cao, Chuanbin Mao, Jeffrey J. Gray.
Bone tissue engineering seeks to develop viable substitutes that repair and maintain the function of human bone tissue. To fabricate a bone scaffold that mimics extracellular matrix, we have assembled hydroxyapatite (HAp) nanorods and HAp-binding fd bacteriophages selected from landscape phage libraries against HAp powder (biopanning). The phage peptides for the top six HAp-binding phages have been analyzed further with a computational biomolecular suite Rosetta to deduce high-resolution chemical interactions occurring at the peptide-HAp interface. To simulate the structural environment of coat proteins, we have adsorbed each peptide to HAp (100) monoclinic crystal while considering its helix tilt angle and c-terminus distance away from the mineral surface. The incorporation of geometrical constraints improves sampling of the predicted structures and scoring of the best binding coat peptide among the top six peptides. The predicted structure of the best binding peptide reveals possible key residues and local conformations that contribute to favorable HAp-phage interface energy, which is important in building a HAp nanorod scaffold for bone regeneration.

866-Pos Board B666
A modified Morse Potential for Coarse Grained Water-Alkane Interaction
See-Wing Chiu, Eric Jakobsson.
We have developed a coarse grained (CG) model based on the Morse potential with bulk densities, thermodynamical data and surface tensions as targets, for the molecules (n-alkanes and water) that are model components of phospholipid membranes [1]. In this work, a modified Morse potential was used to characterize the CG water-alkane and water-water interactions. The Morse parameters for the alkane-alkane interaction were taken from our previous work [1]. Alkane-water interfacial tensions, solvation free energies of water (alkanes) in alkanes (water) were used as targets for the parameterization. Correct interfacial tension is an essential ingredient in models of phospholipid mebranes since the driving force of self-assembly in aqueous amphiphilic enviornments is the segregation of hydrophic and hydrophobic regions. The so obtained CG force field parameters yields simulated thermodynamical data such as transfer free energies of water (alkane) from liquid water (alkane) to liquid alkane (water) in good agreement with the experimental data available in literature.
Reference:
[1] See-Wing Chiu, H. Larry Scott, and Eric Jakobsson. *J. Chem. Theo. Comput*. *6*, 851, **2010**.

867-Pos Board B667
A novel Brownian-Dynamics Algorithm for the Simulation of Ion Conduction Through Membrane Pores
Claudio Berti, Dirk Gillespie, Bob Eisenberg, Simone Furini, Claudio Fiegna.
Brownian-Dynamics (BD) is a powerful approach for the simulation of ion conduction through membrane pores. BD simulations are much less computational demanding than molecular dynamics simulations, thus allowing the analysis on the microsecond time-scale. Furthermore, compared to other simplified approaches like Poisson-Nernst-Planck that use point-charge ions, BD preserves the discrete nature of the ionic particles, which is particularly important in narrow pores. For these reasons, BD simulations have been widely used to analyze conduction in membrane proteins or carbon nanotubes, obtaining good agreement with experimental data.
Published implementations of BD suffer from severe shortcomings, both in terms of accuracy and efficiency. Electrostatic forces due to source and induced (polarization) charges are usually computed in advance, and then tabulated for fast recovery during the numerical integration of the BD equations. Simulation accuracy requires dense grids and this results in low efficiency. In order to improve the state of the art in this field, we have implemented BD code using the Induced Charge Computation (ICC) algorithm to solve the Poisson equation in discrete-charges systems. The accuracy and speed of ICC allows run-time solution of the Poisson equation during simulation. It does not need lookup tables. We compared our new implementation with a standard algorithm, based on tabulation of the electrostatic potential, using as a benchmark a toy-model of a pore with cylindrical profile. Our algorithm provides a considerable increase of efficiency at given accuracy, and a significant increase of accuracy at given computation time. We expect further improvements, in both accuracy and performance, when simulating pores with more irregular profiles, as required for the analysis of real membrane proteins.

868-Pos Board B668
Tracking Single Particles and Elongated Filaments with Nanometer Precision
Felix Ruhnow, David Zwicker, Stefan Diez.
Recent developments in image processing have greatly advanced our understanding of biomolecular processes in vitro and in vivo. In particular, using Gaussian models to fit the intensity profiles of nanometer-sized objects have enabled their two-dimensional localization with a precision in the one-nanometer range. Here, we present a novel algorithm to precisely localize curved filaments whose structures are characterized by subresolution diameters and micrometer lengths. Utilizing surface-immobilized microtubules, fluorescently labeled with rhodamine, we demonstrate positional precisions of about 1 nm when determining the filament centerline and about 9 nm when localizing the filament tips. Combined with state-of-the-art single particle tracking we apply the algorithm (i) to motor-proteins stepping on immobilized microtubules, (ii) to depolymerizing microtubules, and (iii) to microtubules gliding over motor-coated surfaces.

869-Pos Board B669
Fast and Efficient Calculations of Binding Affinities for C8-Substituted GTP Analogues to the FtsZ Protein
Jozef Hritz, Tilman Läppchen, Chris Oostenbrink.
The FtsZ protein plays a central role in bacterial cell division. Several C8-substituted GTP analogs are known to inhibit the polymerization of FtsZ proteins by competing with the natural ligand, GTP, at the same binding site. C8-substituted nucleotides exhibit high energy barriers between the anti and syn conformations of the base and therefore represent challenging targets for free energy calculations due to sampling limitations of conformational space. We tackled this problem and found a highly efficient way for calculating the relative free energies of FtsZ-bound and free nucleotide in explicit water solvent using one-step (OS) and enhanced sampling OS (ES-OS) perturbation methods. The calculated values of the relative binding affinities agree well with the available experimental data.
The main contribution to the calculated binding affinities arises from conformational restriction of the ligands. It is known that in water the dihedral angle distributions around the glycosidic bond for these compounds is highly variable and depend on physico-chemical properties of the C8 substituent. However, when bound to the FtsZ protein, only negligible influences on the dihedral angle distributions are seen and all angles reside in the narrow region of for the compounds investigated here. The corresponding ensemble averaged 3J(C4,H1′) coupling constants were calculated to be 2.95+-0.1Hz and the conformational selection of the GTP analogues upon binding was quantified from the