underperform when trying to reproduce or predict particular phenomena under investigation. Furthermore, among individual myocytes there is significant phenotypic variability, which is dependent on factors such as source location in the heart and variation in expression levels of voltage-gated ion channels. In an attempt to overcome such model shortcomings, we present a genetic-algorithm based approach to tune maximal ionic conductances for cardiac myocyte models. Using stochastic pacing protocols to efficiently sample a cell's range of dynamic behavior, we show that such tuning can greatly improve model fidelity compared to the nominal model.

852-Pos Board B652
How do Sterols Determine the Antifungal Effect of Amphotericin B? free Energy of Binding Between the Drug and its Membrane Targets
Anna Neumann, Maciej Baginski, **Jacek Czub**.
Amphotericin B (AmB) is a well known polyene antibiotic used to treat systemic fungal infections. It is commonly accepted that the presence of sterols in the membrane is essential for the AmB biological activity, i.e, for the formation of transmembrane ion channels. The selective toxicity of AmB for fungal cells is attributed to the fact that it is more potent against fungal cell membranes containing ergosterol than against the mammalian membranes with cholesterol. According to the 'primary complex' hypothesis, AmB associates with sterols in a membrane to form binary complexes which may subsequently assemble into a barrel-stave channel. To elucidate the molecular nature of the AmB selectivity for ergosterol-containing membranes, in the present work, we tested this hypothesis at the microscopic level. Specifically, we used computational methods to study the formation of the putative AmB/sterol complexes in a lipid bilayer. The free energy profiles for the AmB-sterol association in phospholipid bilayers containing 30 mol % of sterols were calculated and thoroughly analyzed. The results obtained confirm the formation of specific AmB/ergosterol complexes and are used to determine the energetic and structural origin of the enhanced affinity of AmB for ergosterol than for cholesterol. The significance of this affinity difference for the mechanism of action of AmB is discussed. The data obtained allowed us also to suggest a possible origin of the increased selectivity of a novel class of less toxic AmB derivatives.

853-Pos Board B653
Structure Based Virtual Inhibitor Screening of Membrane Channel Proteins
Sören Wacker, Bert de Groot.
In the context of computer aided drug design we validated, optimized and applied methods for the estimation of absolute and relative biological activities of drug like molecules acting on membrane channel proteins. These proteins are important for many different physiological processes and therefore attractive targets for modern drug discovery. Structure Based Virtual Screening (SBVS) is an established technique in drug design, but it is still unclear whether standard SBVS approaches can be successfully applied to channel like proteins. Based on a library of 2675 compounds with known activity on the voltage gated potassium channel Kv1.2, the ability to identify active and inactive compounds of three different Structure Based Virtual Screening algorithms were evaluated. We found that the approaches cannot be applied to cavity like active sites without further ado. The algorithms were optimized and combined by consensus approaches. These approaches were applied to the clean-drug-like subset of the ZINC database and validated by electrophysiological experiments.

854-Pos Board B654
First Step Towards Glycan Modeling: Charmm-Gui Glycan Reader and Glycan Database
Sunhwan Jo, Kevin Song, Alexander D. MacKerell Jr., Wonpil Im.
Glycosylation is an important post-translational modification of proteins. Considerable efforts have been made to understand how glycosylation affects the structure, dynamics and function of proteins, yet, in general terms, it remains an unsolved questions due to the diversity and variability in the glycosylation. Primary sequences and the composition of glycans on a glycosylation site can be identified using mass spectrometry, and, although scarce, the number of glycoprotein structures in PDB is increasing. An aspect of structural glycobiology in which further advances need to be made is the ability to model reliable atomic structures of glycans and study their structure and dynamics in silico. Here we present a web-based toolset for glycan modeling, surface electrostatic potential visualization, and simulation input generation for various simulation packages. Based on a survey of all glycan structures available in PDB, a database will be also developed for glycan fragment structures that may be used to facilitate glycan modeling. The toolset and database will be freely available through the web-based CHARMM-GUI resource (www.charmm-gui.org).

855-Pos Board B655
CHARMM-GUI: Brining Advanced Computational Techniques to Web Interface
Sunhwan Jo, **Wonpil Im**.
The CHARMM-GUI resource (www.charmm-gui.org) has been developed to provide a web-based graphical user interface to generate various input files and molecular systems to facilitate and standardize the usage of common and advanced simulation techniques in CHARMM. We have made significant efforts to implement basic and common molecular dynamics simulation techniques into web interface and the web interface has generated a multitude of positive feedback from our users. In this work, we describe our latest efforts to bringing more advanced molecular modeling and simulation techniques to the web interface, such as ligand binding free energy calculation, grand canonical Monte Carlo/Brownian dynamics, glycan reader and builder, electron microscopy density map fitting, protein-protein docking, and NMR structure calculation.

856-Pos Board B656
Web-Based Interface for Brownian Dynamics Simulation of Ion Channels and Its Application to Vdac
Kyu Il Lee, Sunhwan Jo, Huan Rui, Wonpil Im.
We have developed a web-based graphical user interface (GUI) for automated input/system generation of grand canonical Monte Carlo/Brownian dynamics (GCMC/BD) ion channel simulation in the CHARMM-GUI resource (www.charmm-gui.org/input/gcmcbd). The GCMC/BD GUI starts with reading a PDB structure and generates input files necessary for GCMC/BD simulations of ion channels in symmetric or asymmetric solutions at any transmembrane potential. The GCMC/BD GUI facilitates (1) an appropriate placement of membrane channels having various pore sizes and orientations in implicit membrane bathed in electrolyte solution, (2) calculation of ion accessible region and generation of a protein charge map, and (3) calculation of the steric and electrostatic potential maps. To illustrate its efficacy in preparing and simulating ion channels under various conditions, we used the GCMC/BD GUI to investigate ion transport through the voltage dependent anion channel (VDAC) which is the primary pathway for metabolites and electrolytes in the mitochondrial outer membrane. GCMC/BD simulations were performed for all twenty NMR structures of human VDAC isoform 1 (hVDAC1, PDB:2K4T) to examine the ion transport properties such as single-channel conductance and ion selectivity. Using the space-dependent diffusion constant from the molecular dynamics (MD) simulation, GCMC/BD simulation results show similar ion transport properties of hVDAC1s to those from the MD simulations. Also, the ion transport properties have been compared with experimental measurement and analyzed to emphasize the importance of electrostatic contribution from protein charges in determining the channel transport properties. Furthermore, GCMC/BD simulations of hVDAC1 mutants have been performed for detailed analysis on the variation of ion selectivity.

857-Pos Board B657
Efficiency of Replica Exchange Sampling in Protein Folding
Weihng Zhang, Jianhan Chen.
Replica exchange molecular dynamics (REX-MD) is a generalized ensemble method, which periodically exchanges replicas between neighbor temperature windows to help cross energy barriers in energy space, therefore enhancing the sampling efficiency. It has been shown to be very effective on simple two-state model systems. However, for more complicated processes such as protein folding, REMD has not been adequately tested. In particular, in simulations of proteins in the current physics-based force fields, different replicas often end up trapped in segregated regions of the phase space, which significantly reduces the sampling efficiency. Here we systematically investigate the efficiency of REX sampling using simplified, yet realistic, corse-grained protein models with various degree of frustration in the protein energy landscape. We also investigate the efficacy of using several previously proposed optimal setups, such as the highest temperature, in REXMD. At the end, we also propose a simple strategy to circumvent the phase space trapping by periodically forcing replicas to visit different temperature ranges.

858-Pos Board B658
Wavelet Transform Method to Characterize Dendrites in Digital Images of Brain Tissue
Frank Jones, Luis Cruz.
The effects of normal (non-disease) aging in the brain can be characterized by impairments in memory and executive function. These impairments usually start developing in healthy people in their early twenties and progressing linearly until old age. This is usually labeled as the ''normal'' effects of age. The precise nature of these effects in the brain, however, are not known. Extensive studies have shown that neurons are not lost with age, in contrast with other neurodegenerative diseases such as Alzheimer's disease. In a previous joint

computational and anatomical study, it was found that neurons in aged brains suffered from a loss of organization when compared with young subjects. This meant that neurons that are typically organized in anatomical structures known as microcolumns, would lose their columnar organization due to random small displacements of their positions. The current hypothesis is that the dendrites that surround and in a way support the neurons suffer atrophy with age. In this work we present a method to assess this atrophy from digital immunostained photomicrographs of brain tissue samples. By applying a wavelet transforms to digital images of brain tissue we characterize the widths and separation of bundles of dendrites. By correlating these quantities with age, we determine if they contribute to the anatomical changes found in neurons and cognitive impairment. A correlation between results from our wavelet transform method and the more time-consuming acquisition of data by measuring by hand will be presented as a validation of our method. By exploiting the parallel nature of image analysis, an NVIDIA CUDA implementation of our wavelet transform will be presented in which hardware acceleration increases execution by up to ten orders of magnitude.

859-Pos Board B659
Cell Morphology Linked to Substrate Stiffness - A Possible Solution to Determine the Cell Modulus
Li Yang, Yanzi Yangben, Martin Chiang.
A mathematical model, based on thermodynamics, was developed to demonstrate how substrate stiffness influences cell morphology. The mechanism by which substrate stiffness is translated into cell morphological changes is described. The hypothesis in the model is that the morphology of a cell adhering to a substrate is characterized by the competition between strain energies (in the cell and substrate) and interfacial energy (work of adhesion at the cell periphery), and that the final configuration of the cell morphology is determined by the minimum of the total free energy of the cell/substrate system. Thus, the cell changes into its energetically favorable shape by the assembling/disassembling of focal adhesions distributed around the cell periphery. By using this model, reported experimental observations on cell morphological changes can be better understood with a theoretical basis. In addition, these observations can be more accurately correlated with the variation of substrate stiffness. This study indicates that the activity of the adherent cell is dependent not only on the substrate stiffness but also is correlated with the relative stiffness between the cell and substrate. More importantly, guided by the suggestion from the mathematical model, we have experimentally demonstrated that cell modulus can be estimated based on the substrate stiffness corresponding to the change of trend in morphological stability.

860-Pos Board B660
Linear-Scaling Soft Core Scheme for Alchemical Free Energy Calculations
Floris P. Buelens, Daniel Seeliger, Bert L. de Groot, Helmut Grubmueller.
Alchemical free energy calculations hold the promise of unrivalled quantitative accuracy in the computational study of molecular recognition and related biochemical processes. Although noteworthy successes have been reported, there remains significant room for improvement in algorithm design and sampling methods.
We here present an alternative formulation of a soft-core nonbonded potential, designed to be suitable for linear mixing of potential functions. The use of soft-core potentials is essential when considering thermodynamic cycles involving the insertion / removal of atoms from the surroundings. Existing formulations resolve the numerical instabilities that normally accompany linear mixing, but render the mixing of potential functions a non-linear function of the coupling parameter (lambda). Our formulation permits linear mixing while avoiding the numerical instability normally associated with simple scaling of the Lennard-Jones and Coulomb potentials. We demonstrate the advantages of linear mixing with reference to optimisation of free energy estimation, and of protocol design from the perspective of phase space overlap. We assess the performance of protocols based on the linear scaling soft-core potential as applied to the calculation of relative binding free energies for a complex biomolecular system, consisting of a zinc finger protein and a series of bound DNA oligonucleotides.

861-Pos Board B661
Optimized Image Charges for Reaction Field Calculations
Wei Song, Yuchun Lin, Andrij Baumketner, Wei Cai, Donald J. Jacobs.
We extend our previous image charge solvation model [1] based on a discontinuous dielectric model where a boundary separates a cavity filled with explicit solvent and outside there is a continuum dielectric medium. Inside the cavity, the dielectric constant $\epsilon_{in} = 1$. Outside the cavity, ϵ_{out} is often set to 80. Although the discontinuity from 1 to 80 at the cavity interface creates unnecessarily large artifacts [2], this model provides accurate simulations by using a buffer region containing imaged water. The purpose of this study is to use a different set of image charges to reflect a continuously changing dielectric profile at the boundary that will minimize the buffer layer volume, and to better reproduce the electrostatic force field associated with the actual dielectric properties of the model solvent. We optimize the image charges by solving an inverse problem using a least squares error method to determine the best match between the reaction fields calculated by the image charge solvation model to that obtained from a molecular dynamics (MD) simulation of a large periodic system. We perform an iterative calculation that self-consistently determines the dielectric constant for the continuum dielectric medium as the optimal placement and values for the image charges are constructed. This method is general, and it can be applied to any type of mixed solvent, including ionic solutions. With the optimal image charges parameterized, MD simulations can be performed on a solute molecule of interest that is solvated by explicit solvent within the cavity without invoking periodic boundaries. This work is supported by NIH 1R01 GM083600-04.
[1] Y. Lin, et. al., J. Chem. Phys., **131**(15): 154103 (2009).
[2] P. Qin, et. al., Comm. Comp. Phys., **6**, 955-977 (2009).

862-Pos Board B662
Molecular-Mechanical Model of Kinetochore-Microtubule Interactions Identifies Flexibility of the Kinetochore Mesh as a Key Determinant of Errorless Bi-Orientation
Fazly Ataullakhanov, **Anatoly Zaytsev**, Julie Welburn, Iain Cheeseman, Ekaterina Grishchuk.
The accuracy of chromosome segregation relies on the remarkable ability of mitotic kinetochores to bi-orient, whereby sister kinetochores form microtubule attachments to opposing spindle poles. Since the probability of forming erroneous attachments vastly exceeds the chance of attaching correctly, several mechanisms have been proposed to explain how kinetochores avoid and resolve these errors. Here, we use quantitative molecular-mechanical modeling of the kinetochore-microtubule interface to evaluate these factors and determine their respective roles. Our analysis defines several key features that ensure expedient error correction. First, geometric constraints, wich bias orientation of paired sister kinetochores such that they preferentially face opposite poles, contribute to proper attachments, but they are not sufficient to provide error-free segregation. Second, two aspects of Aurora B kinase-dependent regulation play significant and distinct roles in establishing and maintaining correct microtubule-attachments: 1) Its ability to promote the rapid turnover of all kinetochore-microtubule attachments, not just those that are inappropriately attached, and 2) phosphor-regulation of microtubule affinity of spatially-distributed factors in a manner that depends on inter-kinetochore tension. However, a combination of geometric constraints and the error-resolving activities of Aurora B are not sufficient for a fully robust error correction. To solve this problem we hypothesize that the individual microtubule binding sites behave semi-autonomously such that intra-kinetochore tension arises locally in a flexible kinetochore meshwork. Indeed, when such a meshwork is added to the model, kinetochore bi-orientation and expedient error correction occur in a highly reproducible, deterministic way over a significant range of system parameters and even when cells are challenged by error-inducing treatments. Our work has generated the first comprehensive quantitative model to explain spatiotemporal self-organization during chromosome segregation and has provided a solid molecular-mechanical basis for the error correction mechanism.

863-Pos Board B663
MMC: A Monte Carlo and Analysis Program
Mihaly Mezei.
The poster describes the program MMC that performs Monte Carlo simulations on a molecular assembly in the canonical, isothermal-isobaric and grand-canonical ensembles. Both all-atom and continuum treatment of the solvent environment is available; solvents can also be limited to a primary hydration shell that adjusts to the solute's shape. A variety of free-energy methodologies are implemented, including polynomial thermodynamic integration and adaptive umbrella sampling. The forcefields implemented include Charmm, Amber and Gromos/Gromacs. Extensive consistency checks and a large test suite are employed to keep the code as bug-free as possible.
The analysis options include determination of generic solvent sites, cavity and invagination detection, energy partitioning, and a wide range of analyses under the Proximity Criterion.
The Proximity Criterion partitions the space around the solute bases on bisectors or radical planes and for each region calculates, among others, radial distribution functions, coordination numbers, angular distributions and energy distributions. The analysis options can use as input simulation trajectories, besides those in MMC's own format, trajectories in Charmm or Amber formats as well.