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