Scien, 23,13-47, 2004). Usually the rate of this process is predicted using QSAR or other knowledge-based predictors (R Gozalbes, et al., Bioorganic & Med Chem,19, 2615-2624, 2011). However, this approach is not always accurate. Moreover, it does not provide the atomistic details of the process, and thus its prediction cannot be directly exploited to rationally design drugs with higher permeation rate. We developed a protocol for studying the permeation of small organic molecules (e.g. drugs) through lipid membranes by atomistic simulations. This protocol allows computing accurately the permeability coefficient, and provides a detailed atomistic picture of the process. The approach is based on an enhanced sampling technique, bias exchange metadynamics (S. Piana and A. Laio, J Phys Chem B, 111, 4553-4559, 2007), that allows deriving from atomistic simulations a multidimensional free energy landscape and an accurate kinetic model describing the transitions between the relevant metastable states of the system (F Marinelli, et al., Plos Comp Biol, 5, e1000452, 2009). As a benchmark, we applied this protocol on the permeation of ethanol through palmitoyloleoylphosphatidylcholine (POPC) membrane. We are applying the same procedure to study the permeation of two anti-HIV drugs where unbiased simulation of the permeation process is not possible.

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A New Monte Carlo Method for Exploring the Surface Area, Volume and Voids of Molecules in Protein Containing Lipid Bilayers with Atomistic Detail

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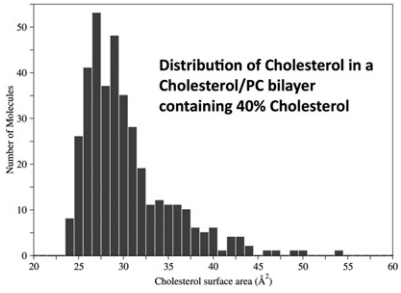
The distribution statistics of the surface area, volume and voids of biological molecules are important parameters to characterize the structures of lipid membranes in the field of atomistic MD simulations. Traditional surface area calculation methods are mostly based on various assumptions of the thickness of the membrane and the volumes of certain molecules. However, those methods usually lead to different surface area estimations and fail to estimate the voids. In the presence of protein, those methods are not applicable due to the presence of the conformal annular lipids surrounding the protein. We have therefore developed a new Monte Carlo method that is capable to calculate the distributions, averages and kinetics of surface area, volume and void space of the lipid or protein molecules in protein containing lipid bilayers obtained from MD simulations at the atomistic scale. We have successfully validated this method using an ordered hard-sphere test system. Results of the structural parameters of the annular lipids in close proximity to the embedded protein and the non-annular lipids using this new method will be presented.



3036-Pos Board B806

Extracting Kinetic Models from Single Molecule Experiments by Direct Inference

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The enterprise of kinetic model-building has been a key route to insight in biophysics. An explosive growth in single molecule experiments is yielding a wealth of information on time-ordered sequences of inter-conversion between conformational states. Current strategies for model building- Markov models - often start by picking a model topology, de-noise the data according to this topology and use the data to fit the rates of the model by maximum likelihood methods. This can bias the analysis and waste data by forcing it onto a particular model. Other methods, based on maximum entropy, do not waste data or bias the analysis though they only extract rate distributions from data not the entire kinetic model. We will discuss a method we are developing which, while based on maximum entropy, extracts the full model from single molecule time traces in an unbiased fashion. We do this by numerically extracting a quantity we call a memory kernel from data. The structure of the kernel tells us whether the data warrants a simple Markov model and, if so, towards which Markov model the data naturally tends towards within uncertainty bars and without wasting data. We apply this method to real single molecule data as well as simulated test cases.

3037-Pos Board B807

Modeling Fluorescence Observables, Particularly for FRET Experiments, using Markov Chain Analysis of Molecular Dynamics and Quantum Mechanics Simulations

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We present a new method for simulating fluorescence observables, particularly those related to bulk and single-molecule fluorescence-detected resonance energy transfer (FRET) experiments. In this method, a molecular dynamics (MD) simulation is used to sample configuration space and quantum mechanics (QM) calculations are used to estimate the electronic coupling between the donor and acceptor probes for snapshots along the MD trajectory. A Markov chain method is used to sample the resulting electronic coupling trajectory allowing accurate simulation of any desired fluorescence observables, such as FRET efficiency histograms or time-resolved donor fluorescence decays. The Markov chain results will be compared with the results of simple histogram and averaging schemes showing that the Markov chain is the only one that yields realistic results in well known examples such as the rapid diffusion limit. This combination of computational methods also avoids some pitfalls of traditional FRET analysis such as the kappa-squared and the ideal dipole approximations. Because the simulation results can be compared directly with experimental observables, this method may allow more detail to be derived from experiment than is traditionally possible.