2016-Pos Board B786
Computational Analysis of the Interactions Between Carbon Nanotubes and Cell Membranes
Mickael G. Lelimousin, Mark SP Sansom.
University of Oxford, Oxford, United Kingdom.
Carbon nanotubes (CNTs) have potential benefits in medicine, e.g. as drug delivery vehicles. However, CNTs and related nanoparticles might be significantly toxic. Although it is well established that cells ingest CNTs, we still have a limited understanding of the interactions at a molecular level between CNTs and cell membranes. Rational CNT derivatizations may allow targeting specific receptors as well as better penetrating cells, while pristine CNTs have shown strong antibacterial activity. In many cases, mechanistic details of such experimental results remain unknown. Consequently, recent computational and theoretical studies have tried to model possible internalization mechanisms of functionalized nanoparticles into cells. Here, we report coarse-grained molecular dynamics simulations of pristine CNTs in interaction with a dipalmitoylphosphatidylcholine (DPPC) lipid bilayer. Both single- and multi-wall CNTs, of different lengths (from 2 to 10 nm) and diameters (from 1.5 to 5 nm), are investigated. We characterize the insertion mechanism of pristine CNTs into the cell membrane model. Strong perturbations of the membrane are observed, as assessed by important phase transitions in the lipid bilayer. Based on our simulations of pristine CNTs, we finally suggest a mechanism for their antibacterial activity. The overall results shed light on the action of CNTs in cellular environment, which will contribute to guide both prevention of health risks and development of therapeutic applications.

2017-Pos Board B787
Protonation and the Matrix Effect of Oleate Vesicles, a Coarse Grained Molecular Dynamics Study
Bram van Hoof, Albert J. Markvoort, Rutger A. van Santen,
Peter A.J. Hilbers.
Technische Universiteit Eindhoven, Eindhoven, Netherlands.
Oleate vesicles provide an intriguing system to study amphiphile aggregation. Their behavior has been studied extensively in literature, revealing several interesting properties. Particularly interesting is the so called ''matrix effect''; when vesicles are formed de novo, the process is slow and the size distribution is broad, whereas in presence of ''seed vesicles'' with a narrow size distribution, the formation speeds up and the size of new vesicles correlates with the seed vesicles' size. To explain this matrix effect, a ''replication by division mechanism'' has been proposed, where division occurs due to asymmetric growth of the membrane caused by the fast insertion of fatty acids into the outer leaflet. The resulting area imbalance between the two leaflets can only partially be restored by flip-flop to the inner leaflet. The remaining imbalance is relaxed by deformation of the vesicle, followed by fission, competing with vesicle growth to determine the resulting vesicle size. In growing oleate vesicles, the generation of a transmembrane pH gradient is reported in the literature, explained by a net inward flip-flop upon oleate adsorption to the outer leaflet. In agreement with the replication by division mechanism, we hypothesize that in the matrix experiments a built-up proton gradient across the membrane during growth, counteracts inward flip-flop and, therefore, directly promotes the division of the vesicles. Here, the role of protonation at the molecular level at each stage of the replication by division process is investigated using molecular dynamics, using a coarse grained model developed specifically for this purpose, employing the recently developed CUMULUS coarse graining method.

2018-Pos Board B788
CaM Induced Gating Mechanism of AQP0
Daniel M. Clemens, Juan A. Freites, Karinne L. Németh-Cahalan,
Douglas J. Tobias, James E. Hall.
UC Irvine, Irvine, CA, USA.
Aquaporin 0 (AQP0) is a water channel protein necessary for lens transparency. AQP0 water permeability is lower than that of other aquaporins, and is regulated by calcium through the action of calmodulin (CaM). NMR studies indicate that one CaM monomer interacts with the C-terminal α-helices of two adjacent AQP0 monomers residing in an AQP0 tetramer. Our goal is to determine the mechanism by which CaM gates AQP0 water permeability. We utilize molecular dynamics simulations of a model of the AQP0-CaM complex. Trajectories of AQP0 and the AQP0-CaM complex embedded in a POPC lipid bilayer show differences between the water occupancy of the AQP0 pore with and without bound CaM. The motion of tyrosine 149 (Y149), a residue residing in the 'phenolic barrier' of AQP0, is reduced in the AQP0-CaM complex. Hypotheses concerning the gating mechanism of AQP0 are tested utilizing the *Xenopus* oocyte-swelling assay. Specifically, Y149 mutants are tested for calcium regulation. Analysis of the interface between AQP0 and CaM shows a chain of interacting residues connecting the interface and Tyr149. Analysis of our simulations indicates that Tyr149 serves as the gate in the regulation of AQP0 water permeability by CaM. Under conditions of low CaM binding, Tyr149 moves dynamically into and out of the AQP0 pore with a low open (out-of-pore) probability. Upon CaM binding, the motion of Tyr149 is decreased and the open probability is reduced. These results reveal a novel gating mechanism in which the binding of a protein to AQP0 reduces the dynamics of pore lining residues, thereby reducing the open-probability of the pore.

2019-Pos Board B789
Pore Gating of K+ Channels Studied by Essential Dynamics Simulations using the Simplified Bacterial K+ Channel KcsA
Tobias Linder, Anna Stary-Weinzinger.
Institute of Pharmacology and Toxicology, University of Vienna, Vienna, Austria.
Voltage gated K+ channels open and close in response to voltage changes. While crystal structures capture a limited number of gating conformations (open, closed), the transition steps and mechanism are still unknown. A limited number of voltage gated potassium channels structures in either open or closed conformation have been crystallized. Since the bacterial K+ channel KcsA has been crystallized in open, intermediate (Cuello et al., 2010) and closed (Zhou et al., 2001) states, this channel offers an ideal model for pore gating simulations. Consequently, we applied essential dynamics simulations to study the gating pathway and energetics underlying pore gating. Essential dynamics simulations were performed at timescales ranging from 1 to 100 ns. Gating simulations were considered complete when the RMSD was below 1.5 Å to the target structure. This criterion was reached in most runs, however shorter simulation times usually resulted in lower RMSD values. In agreement with structural data (Cuello et al., 2010), all available KcsA transition structures (PDB identifier: 3fb5, 3fb6, 3f7y) were sampled with our essential dynamics protocol. Furthermore, molecular dynamics runs revealed that channel opening and closing sampled the same conformations along the transition pathway. Removal of pH-Sensor residues (H25, E120, R121, R122, H124) led to spontaneous channel openings on the nanosecond timescale. These unbiased opening simulations sampled the same conformations as our essential dynamics simulations, further supporting the validity of our method. Finally, umbrella sampling was used to estimate the energy profiles of the various gating states and the transition pathways of WT and mutant channels. As expected, the energy needed to open the channel is significantly decreased in the pH-Sensor deleted KcsA.

2020-Pos Board B790
Monte Carlo Loop Refinement of Trans-Membrane Domain of the Thyroid Stimulating Hormone Receptor
Rejwan Ali[1,2], Rauf Latif[1,3], Terry Davies[1,2], Mihaly Mezei[1].
[1]Mount Sinai School of Medicine, New York, NY, USA, [2]Thyroid Research Center, VA Hospital, Bronx, NY, USA, [3]Thyroid Research Center, VA, Bronx, NY, USA.
While the ectodomain structure of the Thyroid Stimulating Hormone Receptor (TSH-R) a GPCR, has been recently reported (Sanders, Chirgadze et al. 2007), for the transmembrane domain (TMD) only model structures exist. However, for virtual screen of small molecules targeting the TMD domain region reliable structure is a prerequisite. In this work we have used an ab initio method, that previously had reported to reproduce crystal structures within 2 Å RMSD, to model 3 extra-cellular and 3 intra-cellular TSHR-TMD loops (Cui, Mezei et al. 2008). The method employs Modeller (Sali and Blundell 1993) to generate an initial loop structure. This is followed by a Metropolis Monte Carlo run in the torsion angle space of the of loop regions at high temperature for extensive sampling of the conformation space. Selected conformations are subjected to simulated annealing and the final structure with the lowest energy is chosen as the loop structure.
The Charmm molecular mechanics force field is used for the VdW interactions between the protein atoms and for the torsion angles; water is represented by a sigmoidal distance dependent dielectric function and the Autodock desolvation term (Cui, Mezei et al. 2008). In addition, explicit hydrogen-bonding terms are used. We will present the computational and structural details of the methods used.

2021-Pos Board B791
Structure of the Antimicrobial Peptide HHC-36 and its Interaction with Model Cell Membranes
Mostafa NateghołEslam[1], Shaghayegh Vafaei[1], Matthew Nichols[2], Miljan Kuljanin[2], Masoud Jelokhani-Niaraki[2], Bruno Tomberli[3], Chris G. Gray[1].
[1]University of Guelph, Guelph, ON, Canada, [2]Wilfrid Laurier University, Waterloo, ON, Canada, [3]Brandon University, Brandon, MB, Canada.
HHC-36 is an antimicrobial peptide, designed through neural network algorithms. It has been tested in vivo and in vitro, and has proved to be strongly