vivo. Our technology shows promise as a tool for cancer diagnosis or image-guided surgery, and the demonstration of cargo delivery into tumors may lead to a new generation of targeted chemotherapeutic delivery.

472-Pos Board B227

Modeling Membrane Proteins with Slim, a New Implciit Membrane Model

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Computer simulations of proteins acting in biological membranes remain a very challenging task, due to the complexity and size of such systems. Depending upon the specific question to be addressed, implicit membrane models offer a computational less expensive alternative, that can help to shed light on the atomistic mechanisms that govern the function of such proteins. We have developed a new implicit membrane model, called SLIM, by combining the advantages from two other established models [1, 2]. Our model is based on the generalized Born formalism [3], with an efficient and accurate generalized Born implementation for aqueous solutions [4]. We demonstrate that Monte Carlo simulations of well characterized proteins like Melittin or the transmembrane domain of the M2-protein reliably reproduce position and orientation of these proteins in agreement with other experimental or computational studies. The addition of this model to the SIMONA software package [5] will provide the community a useful tool for Monte Carlo studies of membrane peptides and proteins.

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473-Pos Board B228

Membrane Fusion Peptide-Membrane Interactions: Comparing Simulations to Experimental Depth Measurements

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Enveloped viruses infect cells via a process of membrane fusion. The insertion of portions of the viral fusion protein into target membrane is critical to this process, and mutations that impair viral entry also appear to affect the depth or extent of peptide insertion. We have performed simulations of influenza and other class I fusion peptides interacting with lipid bilayers under conditions modeled closely on spectropic experiments on insertion depth. The simulations suggest substantial insertional variability, reflective of a flexible or dynamic process. Because peptide-membrane insertion simulations converge slowly, we have also explored a number of analytic techniques to improve sampling and convergence. Here, we explore ways in which both simple multi-scaling techniques and post-hoc analysis of many unbiased atomistic simulations can improve convergence and sampling.

474-Pos Board B229

Bending Modulus Dictates GUV Response to Stress

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We investigated the dynamic response of membranes with different bending moduli to stress, which phase diagrams for vesicles conformations at equilibrium cannot predict. We used melittin to systematically modify the bending modulus of 1,2-Dioleoyl-sn-glycero-3-phosphocholine (DOPC) phospholipid membrane. The bending moduli of DOPC giant unilamellar vesicles (GUVs) at different peptide-to-lipid (P/L) ratios were estimated with contour fluctuation analysis, for which we developed an edge finding algorithm for fluorescence images. We saw that the bending modulus decreased with increasing P/L before pore formation, but the trend was reversed after pore formation. When GUVs of different bending moduli were subjected to similar stress, the morphology distributions of large numbers of vesicles at equilibrium were different. The difference reflects the greater volume loss of vesicles with lower bending modulus, for which higher tension can build up in the membrane when vesicles deform under stress. Beyond a threshold tension, vesicles form transient pores through which contents can flow out to release the tension.

475-Pos Board B230

Investigation of the Mechanism of Antimicrobial Lipopeptides using Coarse-Grained Molecular Dynamics Simulations

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Antimicrobial lipopeptides (AMLPs) are a series of acylated cationic peptides with broad-spectrum antimicrobial activity and low hemolytic activity. We used microsecond-scale coarse-grained molecular dynamics simulations with the MARTINI force field to understand AMLPs' modes of action. Previous free energy calculation quantified the binding affinity and selectivity of a single AMLP to different membrane. Our data showed that the acyl chain of C16-KGGK, one of the AMLPs, is mainly responsible for its affinity to membrane while the peptide portion determines the selectivity towards different membrane lipid composition. Here we extend our free energy calculation to a micelle of C16-KGGK, which resembles the aggregated structure of C16-KGGK in solution. With the state-of-the-art umbrella-sampling/hamiltonian-exchange methods, we estimate the binding free energy of C16-KGGK micelle to different types of membrane. Our results provide biophysical insights into the mechanism of lipopeptides' antimicrobial action.

476-Pos Board B231

Modelling the Interactions of Equinatoxin II with Micelles

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Equinatoxin II (EqtII) is a 179-residue toxin from the venom of the sea anemone Actinia equina. EqtII is a member of the actinoporin family of proteins, which have potent lytic activity towards membranes containing sphingomyelin (SM). To gain insight into the atomic-level details governing SM selectivity, a series of all-atom molecular dynamics simulations were performed to model the binding of EqtII to micelles of n-dodecylphosphocholine (DPC) and DPC/SM. These models are in good agreement with concurrent high-resolution solution NMR studies and prior data that suggests membrane binding is dependent on a conserved cluster of aromatic amino acids. From this groundwork study, further simulations will be performed to investigate EqtII oligomerisation and membrane insertion to determine the mechanism of pore formation.

477-Pos Board B232

Ca^{2+} Influx and Tyr Kinases Trigger Bordetella Cyaa Endocytosis. Cell Physiology and Expression of the CD11B/CD18 Integrin, Major Determinants of the Entry Route

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Humans infected with *Bordetella pertussis*, the whooping cough bacterium, show evidences of impaired host defenses. This pathogenic bacterium produces a unique adenylate cyclase toxin (ACT) which enters human phagocytes and catalyzes the unregulated formation of cAMP, hampering important bactericidal functions of these immune cells that eventually cause cell death by apoptosis and/or necrosis. Additionally, ACT permeabilizes cells through pore formation in the target cell membrane. Recently, we demonstrated that ACT is internalised into macrophages together with other membrane components, such as the integrin CD11b/CD18 (CR3), its receptor in these immune cells, and GM1. The goal of this study was to determine whether ACT uptake is restricted to receptor-bearing macrophages or on the contrary may also take place into cells devoid of receptor and gain more insights on the signalling involved. Here, we show that ACT is rapidly eliminated from the cell membrane of either CR3-positive as negative cells, though through different entry routes, which depend in part, on the target cell physiology and characteristics. ACT-induced Ca^{2+} influx and activation of non-receptor Tyr kinases into the target cell appears to be common master denominators in the different endocytic strategies activated by this toxin. Very importantly, we show that, upon incubation with ACT, target cells are capable of repairing the cell membrane, which suggests the mounting of an anti-toxin cell repair-response, very likely involving the toxin elimination from the cell surface.

478-Pos Board B233

Tethering Dimers of Voltage Sensor Toxins can Selectively Amplify their Affinity for Kv Channels

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Potent and selective modulators are needed to elucidate the individual roles of ion channel subtypes in physiological systems. Many cystine knot peptides