SYMPOSIUM 7: Remodeling the Membrane

936-Symp
Sculpting Cellular Membranes from Inside or Outside
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The shape of cellular membranes can be induced by in situ transmembrane proteins as well as by peripheral proteins. Membrane sculpting is a dynamic process and few, if any, experimental methods can capture it. However, molecular dynamics simulations can reveal the process in atomic detail as local membrane bending, once the protein components are in place, occurs within microseconds or faster. Two cases will be discussed.
Purple bacteria develop pseudo-organelles made of photosynthetic membranes that are spherically shaped (diameter 70 nm) in some species while they are flat in other species. The main molecular component of the membranes are transmembrane proteins, namely light-harvesting protein LH1 complexed with reaction centers and light-harvesting protein LH2. Simulations in combination with crystallography, electron microscopy, atomic force microscopy and spectroscopy provide a close-up view of membrane sculpting by these photosynthetic transmembrane proteins while also offering an explanation of the geometrical and physical principles at work.
The sculpting strategy of N-BAR and F-BAR domains, which have been observed in vitro to form tubular membranes from vesicles, has also been revealed in simulations. A combination of coarse-grained and all-atom molecular dynamics simulations demonstrated that these peripheral proteins, in forming regular lattices as observed by electron microscopy, bend flat membranes into tubes which remain stable even after the proteins are removed. The simulations also revealed that certain protein-lipid interactions are responsible for membrane bending. While the highly regular BAR domain latices seen under in vitro conditions are likely artifactual, the simulations suggest that the proteins work in localized teams in vivo as well.
Membrane sculpting poses a fascinating conceptual challenge to biophysicists as an explanation of the process needs to link physical properties at a wide range of time and length scales.

937-Symp
Contributions of Cryoem to Visualize Membrane Curvature Generation - Mechanisms and Implications
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938-Symp
Protein-Mediated Induction of Membrane Curvature
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The control of membrane curvature plays an important role in a number of membrane remodeling events. Recent evidence suggests that these processes are mediated by proteins which can sense or induce membrane curvature. Membrane curvature-inducing proteins can alter the shape of membranes and they typically have the ability to convert liposomes into small and highly curved vesicles or narrow membrane tubules. In order to understand the mechanism of membrane curvature induction, we have studied the membrane interaction of the N-BAR proteins (endophilin and amphiphysin) and EHD2. According to crystal structures, the N-BAR proteins have a bent helical structure with a curvature complementary to that of the highly curved membrane structures they induce. Using site-directed spin labeling and electron paramagnetic resonance, we found that this structure is maintained upon membrane interaction. The degree to which this structure interacts with the membrane, however, depends significantly upon the bilayer geometry and lipid composition. We also found that amphipathic helices are suspended on the convex side of the BAR domain and that these helices directly interact with the membrane where they are likely to promote membrane curvature by acting as molecular wedges. The ability of amphipathic helices to induce membrane curvature is further supported by our finding that α-synuclein, which can form an extended helical structure, readily cause tubulation and/or vesiculation under the appropriate lipid conditions. Structural and mechanistic studies describing how membrane interaction causes conformational changes in the aforementioned proteins and how these changes, in turn, affect membrane structure will be presented.

939-Symp
Simple Cell, Complex Envelope: Modeling the Heterogeneous Membranes of E.coli
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Gram-negative bacteria such as E.coli are typically regarded as ''simple'' model organisms, yet their cell envelopes are surprisingly complex. The cells of these bacteria are protected by two membranes; the inner and outer membrane, which differ in their overall composition, and which are separated by the periplasmic space. The proteins residing within these membranes perform a variety of functions including roles in controlling the influx/efflux of solutes, protein transport, catalysis, adhesion and recognition processes.
Recent experimental and theoretical studies have revealed that contrary to the traditional view of the cell membrane as a passive bystander in membrane protein function, it plays a key role in protein folding, assembly, and function. To study the influence of the bacterial membrane on the dynamics of the embedded proteins, we have performed multi-scale molecular dynamics simulations of a range of E.coli proteins in membrane models of increasing complexity. In particular, our aim has been to capture the details of lipid composition within E.coli membranes. For example, we have modeled the outer membrane as an asymmetric bilayer containing an asymmetric distribution of lipopolysaccharide (LPS) and heterogeneous phospholipid mixtures. By extending the simulation timescales out to hundreds of nanoseconds (in all-atom models) or to microseconds (in coarse-grained models), we are gaining important new insights into the influence of "realistic" membrane environments on the structure and dynamics of membrane proteins.

SYMPOSIUM 8: Systems Biology-Control of Cellular Behaviors, Including Gradients and Feedback

940-Symp
Pili Expression in Uropathgenic E. coli: Stochastic Switching and Epigenetic Control
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The Pap phase variation system controls expression switching of the bacterial pili that mediate adhesion to epithelial cells in the urinary tract. Such pili have been implicated in causing a large percentage of urinary tract infections. Piliation is controlled by a stochastic genetic switch that exhibits a number of important regulatory aspects including binding of proteins to multiple DNA sites, DNA methylation, modulation of protein-DNA interactions by co-factors, feedback-repression, and the modulation of switch frequency by environmental inputs. We present a detailed stochastic model of the pap switch that captures these relevant interactions. We then develop a new computational methodology for solving the corresponding Chemical Master Equation and use it to compute the probability of rare switching events. Quantitative analyses made possible by these methods enable us to elucidate the role of stochasticity and epigenetics in pili expression.

941-Symp
Homeostatic Regulation of the Unfolded Protein Response
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The unfolded protein response (UPR) is an intracellular signaling pathway that maintains proper function of the endoplasmic reticulum (ER), counteracting variable stresses that impair folding of proteins entering the secretory pathway. In that capacity, the UPR is at the center of many normal physiological responses and pathologies. In this study, we quantitatively interrogate the homeostatic capacity of the UPR. Moving between a predictive computational model and quantitative dynamic measurements, we establish how the ER chaperone BiP modulates the core ER stress sensor Ire1's activation and deactivation dynamics. Specifically, we demonstrate the ability of BiP binding to Ire1 and its dissociation in an ER stress-dependent manner to buffer the system against mild stresses. Furthermore, we show that BiP binding accelerates Ire1 deactivation when stress is removed. Therefore, BiP binding to Ire1 fine-tunes the dynamic behavior of the UPR by modulating its sensitivity and shutoff kinetics. The interaction between Ire1 and BiP to accomplish such intricate dynamic control may be a general paradigm for other systems in which proper signal sensing and amplification through oligomer formation and disassembly must be finely regulated. More generally, we discuss how dynamic measurements are key to uncovering the elaborate control strategies of homeostatic cellular networks.

942-Symp
Signaling Gradients in Embryos'
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Signaling gradients in developing embryos: experiments and theory.