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In Silico Modeling of Biologically Complex Membranes
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The detailed lipid organization of cellular membranes remains elusive. A typical plasma membrane contains hundreds of different lipid species that are actively regulated by the cell. Currently over 40,000 biologically relevant lipids have been identified and specific organisms often synthesize thousands of different lipid types. This is far greater diversity than is needed to maintain bilayer barrier properties and to solvate membrane proteins. Why do organisms go through the costly process of creating and maintaining such a large diversity of lipids? What is the individual role of these lipids, and how do they interact and organize in the membrane plane?
To start to address these questions we model biologically realistic membranes using coarse-grained Martini molecular dynamics simulations. We optimized and developed the Martini lipidome and systematically explored physiochemical properties of >100 different Martini lipid types. Bulk properties of each type (e.g. bilayer thickness, area per lipid, diffusion, order parameter and area compressibility) were analyzed and overall trends compared to experimental values. Biologically realistic idealized membrane compositions were constructed and simulated, such as in (Ingólfsson, et al. Lipid organization of the plasma membrane. JACS, 136:14554-14559, 2014). These large-scale simulations (~70 by 70 nm and multi microsecond long) are in terms of lipid composition by an order of magnitude the most complex simulations to date. They provide a high-resolution view of the lipid organization of biologically relevant membranes; revealing a complex global non-ideal lipid mixing of different species at different spatiotemporal scales. We analyze a variety of membrane physicochemical properties, including: lipid-lipid interactions, bilayer bulk material properties, domain formation and coupling between the bilayer leaflets, for a number of lipid mixtures and conditions.

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Vitamin E Promotes the Inverse Hexagonal Phase via a Novel Mechanism: Implications for Antioxidant Role
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Vitamin E (alpha-tocopherol) protects polyunsaturated membrane phospholipids from oxidation. How it accomplishes this task at relatively low concentrations is an ongoing area of investigation. An interesting property of alpha-tocopherol is that it promotes the inverse hexagonal (HII) phase in PE membranes. It has been well established that other compounds, such as dodecane and similar purely hydrophobic compounds, promote the HII phase by relieving extensive stress. We argue that alpha-tocopherol promotes the HII phase by a novel mechanism, by instead relieving compressive stress. With this new understanding, we examine the hypothesis that alpha-tocopherol will preferentially partition close to polyunsaturated lipids to maximize its effectiveness as an antioxidant.

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Anticancer Drug Colchicine Increases Disorder and Reduces Complexity in the Macrophage Membrane
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Macrophages are part of the immune system and play critical role in the host defense and tissue homeostasis ingesting a dead tissue and fighting invading pathogens. Exploring interactions of anticancer therapies with macrophages as part of innate immunity is important both for biomedical researches and applications and can help to combine various approaches with immunotherapy. In this study we evaluated the influence of anticancer drug colchicine on the disorder and complexity of the macrophage membrane from atomic force microscope (AFM) images. Fixed and dried mouse RAW 264.7 macrophage membranes were imaged with AFM operating in Peak Force mode. The disorder of the membrane was characterized by entropy and complexity - by fractal dimension. These parameters were calculated for a set of AFM images of untreated macrophages and macrophages pretreated with anticancer drug colchicine, using three different methods. Processing of AFM images and calculations were done with custom MATLAB code. We show that colchicine treatment yields entropy increase and therefore produces higher disorder of the macrophage membrane. Furthermore the membrane complexity is reduced demonstrating lower fractal dimension. In addition we studied also changes in the macrophage membrane disorder and complexity produced by microtubule stabilizing agent taxol, having opposite to the colchicine (inhibiting the microtubule polymerization) effect. These results demonstrate at the level of single cell that anticancer drug colchicine affects macrophage membrane structures producing more disordered state. Finally we discuss some possible consequences of this more disordered state on the macrophage activity.

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Hydration Mediated G-Protein-Coupled Receptor Activation
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G-protein-coupled receptors (GPCRs) comprise about 50% of the known drug targets and play crucial roles in numerous of physiological processes. Rhodopsin is a canonical GPCR, which upon photoactivation undergoes a series of conformational changes leading to a chemical equilibrium between closed inactive Meta-I and open active Meta-II states [1,2]. We hypothesize that activation of rhodopsin leads to an increase in hydrated protein volume in the active Meta-II state. Using UV-visible spectroscopy, we tested our hypothesis by evaluating how the Meta-I/Meta-II equilibrium and thermodynamic parameters are influenced by changing the membrane environment. We discovered a surprising bulk water influx (about 75 water molecules) during formation of the active protein. Moreover, our results with high molar mass osmolytes differ from previous osmotic stress studies with small osmolytes. We discovered that osmolytes of varying molar mass affect rhodopsin activation differently. Large osmolytes shift the equilibrium to the inactive Meta-I state, leading to efflux of water. By contrast, small osmolytes lead to an influx of water upon activation. We propose that small osmolytes affect rhodopsin activation similarly to the G-protein transducin, which stabilizes the active Meta-II state. Large osmolytes cannot gain access to the transducin binding site and exert osmotic stress on the protein. Our results are in agreement with molecular dynamics studies showing an influx of water during rhodopsin photoactivation [3]. Hence we propose that rapid high-fidelity signaling by rhodopsin involves cycling of water into and out of the protein core together with activation of transducin. Our studies give important insight in the role of water in activation of GPCRs like rhodopsin. [1] A.V. Struts et al. (2011) PNAS 108, 8263-8268. [2] A. V. Struts et al. (2015) Meth. Mol. Biol. 1271, 133-158. [3] N. Leioatts et al. (2013) Biochemistry 53, 376-385.

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Difffusion Dynamics of AChR Receptors on Live Muscle Cell Membrane
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The dynamic structure of a cell membrane allows it to become an effective platform for various biological functions, such as signal transduction, molecule transportation and endocytosis. We report here a single-molecular tracking experiment on a quantum-dot-labeled transmembrane protein, acetylcholine receptor (AChR), in cultured Xenopus muscle cells. We carried out a complete statistical analysis on a large set of AChR trajectories with more than 500 cells examined. Various drug treatments were used to perturb F-actin and scaffold proteins and examine their roles in regulating the motion of the AChRs. The diffusion dynamics of AChRs was characterized by three quantities: the mean-square displacement $\langle \Delta r2(\tau) \rangle$, the probability density function P(Dx) of instantaneous displacement $Dx(\tau)$ and the probability distribution $f(\delta)$ of instantaneous diffusion coefficient δ. After a careful analysis, we conclude that (1) AChRs show a hindered motion by the surrounding membrane molecules at short time and become diffusive at long time. (2) The mobile AChRs have a broad distribution in diffusion coefficient δ with a long exponential tail, which is universal and independent of different sample conditions. (3) The exponential distribution $f(\delta)$ leads to an exponential distribution P(Dx). Our measurements of membrane diffusion based on a large number of single molecular trajectories provide a complete statistical description of dynamic heterogeneity on live cell membrane. By combining all the experimental results available, we propose a dynamic picket-fence model of membrane organization involving slow active remodeling of the underlying cortical actin network to