

Predicting spectral properties of polarity sensitive dyes with QM/MM simulation

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stacked layers of saturated long-chain ceramides, free fatty acids and cholesterol, but we know surprisingly little of the detailed molecular structure. It is believed to be formed through a reorganization of glycosylceramide-based bilayers with cubic-like symmetry into ceramide-based bilayers with stacked lamellar symmetry. The process is accompanied by deglycosylation of glycosylceramides and by gradual dehydration of the lipid complex, which eventually turns it into skin. We show that it is possible to model a simplified version of this formation process in molecular dynamics simulations, and in particular study the effects of deglycosylation and dehydration on bilayers of human skin glycosylceramides and ceramides, which fold in 3D space with cubic (gyroid) symmetry. Deglycosylation of glycosylceramides destabilizes the cubic lipid bilayer phase and triggers a cubic to lamellar transition. Furthermore, subsequent dehydration of the deglycosylated lamellar ceramide system closes remaining pores between adjacent lipid layers and locally induces a ceramide chain transformation from hairpin-like to splayed conformation. By employing electron microscopy simulation, it is possible to model expected cryo-EM micrographs from the simulations, and these agree surprisingly well with original cryo-EM imaging of stacked ceramide layers in the stratum corneum. This both provides insight into the formation of the skin barrier, and molecular models that could help us better understand the permeability of skin.

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Plant Polyphenols Induced the Polymorphic Phase Transition of Membrane Lipids

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Flavonoids are called "natural modifiers of biological reaction" due to their ability to change the response of the human body to allergens, viruses and oncogens. This is evidenced by their antioxidant, anti-inflammatory and antiparasitic and antibacterial properties. However, its use is limited by low relatively bioavailability. At the present time, the most perspective way to increase the bioavailability of polyphenols is used the complexes of modifiers with lipid vesicles. We had found that flavonoids (phloretin, butein, 4'-hydroxychalcone, naringenin, quercetin, myricetin, biochanin A, genistein, cardamonin, licochalcone A, liquiritigenin) are able to induce a polymorphic phase transition of DPPC. Large unilamellar liposomes were prepared by extrusion methods. The lipid:polyphenol ratio was equal to 3:1, 1:1, and 1:3. Visualization of the polyphenol-induced non-bilayer lipid structures enriched with polyphenols were processed by laser scanning confocal microscope, Olympus FV3000. Phloretin, cardamonin, biochanin A, genistein, quercetin and myricetin caused the appearance of needle-shaped spherical non-bilayer structures, while the addition of butein and naringenin in the liposomal suspension leads to the appearance of rod-like structures. The morphology of non-bilayer structures induced by polyphenols does not depend on the ratio of lipid:polyphenol. The addition of 4'-hydroxychalcone, liquiritigenin and licochalcone A to the liposome suspension did not induced a polymorphic phase transition of lipids. Our results indicated a dependence of the polyphenol ability to induce the formation of non-bilayer structures on the number of OH groups in the molecule. It is proposed to apply the methods of electron microscopy and small-angle X-ray scattering to study the thin structure of the polyphenol-induced non-bilayer lipid structures. The study was supported in part by RFS (#17-74-10137).

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Homeostatic Remodeling of Mammalian Membranes in Response to Dietary Lipid Perturbations is Essential for Cellular Fitness

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A major fraction of cellular bioactivity occurs at membranes, with the lipidic matrix constituting a functional, dynamic interface that actively regulates protein activity and cell physiology. Proper membrane functionality requires maintenance of a narrow range of physical properties under challenge from external inputs. The most prominent example of such maintenance is homeostatic adaptation of membrane properties to temperature variation, a fundamental and ubiquitous design feature in ectothermic organisms. However, such responsive membrane adaptation has not been widely investigated in homeotherms. Here, we report that challenging mammalian membrane homeostasis by dietary lipid inputs leads to robust lipidomic remodeling to maintain membrane physical properties. Specifically, supplementation with polyunsaturated fatty acids (PUFAs) leads to rapid and extensive incorporation of the exogenous fats into membrane lipids, inducing a reduction in membrane packing. These effects are rapidly compensated for by upregulation of saturated lipids and cholesterol, via activation of the mammalian sterol regulatory machinery, specifically SREBP pathway, resulting in recovery of membrane fluidity. Inhibition of membrane remodeling results in decreased cellular fitness when membrane homeostasis is challenged by dietary PUFAs.

These results reveal a mammalian mechanism for homeostatic membrane remodeling - analogous to homeoviscous adaptation in poikilotherms - wherein cells remodel their membrane lipidomes in response to dietary lipid inputs in order to maintain functional membrane phenotypes.

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Predicting Spectral Properties of Polarity Sensitive Dyes with QM/MM Simulation

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Polarity sensitive, lipophilic dyes such as Laurdan report lipid packing in biomembranes, as the emission spectrum is red shifted in more polar environments. In simple membranes, the dye is more accessible to solvent in more disordered membranes, and the spectral shift is well-explained by dipolar relaxation of the solvent. However, in more complex systems other factors may contribute, especially hydrogen bonding between the environment and the chromophore. An approach has been developed in which the local environment is first sampled by classical molecular dynamics simulation of the dye in different environments, followed by prediction of the absorption spectrum by numerical quantum mechanics. Simulation results are presented for an optimized model of Laurdan and C-Laurdan for use with the CHARMM family of forcefields in a variety of membrane environments. Several different quantum methods are compared, including time-dependent density functional theory and GW-BSE.

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Humectants' Influence on the Nanostructure and Thermotropic Behavior of Fully Hydrated Phospholipids

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Humectants are hygroscopic substances used to retain moisture in many personal care products, particularly in phospholipid-based skin creams and haircare products. Here we studied the effect of humectants on the thermotropic behavior and nanostructure of fully hydrated 1, 2-dipalmitoyl-sn-glycero-3-phosphocholine, DPPC, from 25 to 50 °C. Three humectants have been investigated: betaine, sarcosine and acetamide monoethanolamine, AMEA. Small angle X-ray scattering, SAXS, differential scanning calorimetry, DSC, and isothermal calorimetry, ITC, have been applied. The general trend is that all humectants induce an increase in both the pre-transition temperature (gel to ripple phase) and the main transition temperature (ripple to fluid phase). At lower concentrations of humectant (0.05-0.4 M), however, we observed a lowering in the pre-transition temperature. Deduced electron density profiles of the gel phase of DPPC display for all three humectants similar effects: the membrane thickness marginally increases with increasing concentration of humectant, and concomitantly the interstitial water layer decreases significantly. This suggests that the membrane becomes more rigid upon addition of humectants leading to a reduced inter-membrane repulsion (reduction of the Helfrich undulation force). Furthermore, DSC results reveal strong enthalpy variations compared to DPPC in pure water. Complementing ITC measurements on the solution/dissolution enthalpy of the humectants confirmed that changes in the lipid/water partition coefficient across the main transition are responsible for an overall increase of the enthalpy in the presence of AMEA and leads to a decrease with sarcosine. Betaine instead has no great influence on the main transition enthalpy. In conclusion, by combining SAXS, DSC and ITC (i) nanostructural changes in the DPPC bilayer as well as (ii) different lipid/water partitioning behavior of the humectants can be unraveled.

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Dumbbell-Shaped Janus Dendrimersomes Exhibit Lamellar to Sponge Phase Transitions

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Self-assembling amphiphilic Janus dendrimers, composed of hydrophobic and hydrophilic branches, are promising models for understanding the complexity of biological membranes. Modeling the transitions of membrane shapes from lamellar to non-lamellar is particularly desirable as these transitions play essential roles in key cellular processes, such as membrane fusion and fission, and occur in response to external stimuli, including drug treatment and heat. We previously reported that mixtures of novel hydrogenated, fluorinated, and hybrid Janus dendrimers self-assemble into dumbbell-shaped structures. Here, we show that these structures undergo a thermally induced lamellar-to-sponge transition. The sponge phase (L_3) is characterized as an isotropic multi-connected 3D bilayer that forms when the surfactant monolayer of a bilayer exhibits a spontaneous curvature toward the bulk solvent. We used