ABSTRACT

Title of Dissertation: PHOSPHOLIPID BEHAVIOR AND DYNAMICS IN CURVED BIOLOGICAL MEMBRANES

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Curvature in biological membranes defines the morphology of cells and organelles and serves key roles in maintaining a variety of cellular functions, enabling trafficking, recruiting and localizing shape-responsive proteins. For example, the bacterial protein SpoVM is a small amphipathic alpha-helical protein that localizes to the outer surface of a forespore, the only convex surface in the mother bacteria. Understanding several of these membrane curvature dependent events rely on a thorough understanding of the properties, energetics, and interactions of the constituent lipid molecules in presence of curvatures.

In this dissertation, we have used molecular dynamics (MD) simulations to explore how the curvature of the lipid bilayer (LBL), a simplified mimic of the cell membrane, affects the packing fraction and diffusivity of lipid molecules in the LBL, energetics of lipid flip flop in the LBL, and lipid desorption from the LBLs. We have

also investigated the interaction between LBLs and a small bacterial protein, SpoVM, which was previously shown to preferentially embed in positively curved membranes. Our work started with simulating convex surface, represented by the nanoparticle supported lipid bilayers (NPSLBLs) in MD. We first quantified the self-assembly, structure, and properties of a NPSLBL with a diameter of 20 nm and showed how the type of the nanoparticle (NP) affects the properties of the NPSLBLs. Second, we studied the energetics of lipid flip flop and desorption from LBLs for the cases of planar substrate supported lipid bilayer (PSSLBL) and NPSLBL. Finally, we investigated the energetics of SpoVM desorption from the PSSLBL and the NPSLBL providing clues to the fundamental driving forces dictating the curvature sensing of SpoVM.

In Chapter 1, we discuss the motivation, methods, biological relevance, and the overall structure of this thesis. In Chapter 2, the structure and properties of a pre-assembled NPSLBL were studied. In Chapter 3, we report the MD simulation results on the structure and properties, such as diffusivity, of the lipid molecules within the LBLs of the NPSLBLs formed through the self-assembly route. We compare our findings with that of unsupported lipid bilayer nanovesicles (NVs). Our results show that the structure of the NPSLBLs, although affected by the type of the NPs, is still similar with the free NV consisting of identical number and species of lipid. On the other hand, the properties such as the diffusivity of the lipid molecules within the LBL are significantly different between the cases of NPSLBL and the free vesicle. Results are provided for different combinations of the lipid molecules and the NP

materials. The findings described in Chapters 2 and 3 will be eventually useful in long-term for designing new generation of NPSLBLs as drug carrier. In Chapter 4, we focus on the lipid flip-flop and desorption from the LBLs for NPSLBLs and PSSLBLs. We investigated the energetics of a lipid molecule traversing through the lipid bilayer (from inner-to-outer and outer-to-inner leaflet) as a function of the position of the hydrophilic head group of the lipid within the LBL. We obtained the potential of mean force (PMF) by using umbrella sampling. Most importantly, we observed little effect of the curvature in the variation of the lipid flip-flop PMF, establishing that the energetics of lipid migration within the supported bilayer, which implies that energy changes associated with bilayer fluctuations, is independent of the shape of the supported bilayer. The conclusion is supported by the reported experimental results. Next, in Chapter 5, MD simulations are carried out to reveal the energetics of a single SpoVM protein undergoing desorption from LBLs of NPSLBLs and PSSLBLs. The free energy comprises of five different contributions: 1) the free energy change for deforming the protein in the bilayer with respect to the conformation of the protein in the membrane, 2) the free energy change for reorienting the protein in the bilayer about the first Euler angle with the conformation of the protein restrained, 3) the free energy change for reorienting the protein in the bilayer about the second Euler angle with the conformation and the first Euler angle restrained, 4) the free energy change for changing the position of the center of the protein from the membrane to the bulk water with conformation and both Euler angles restrained, and 5) the free energy change for deformation of the protein in the bulk water with respect to the conformation of the protein in the membrane. Through

these simulations, we confirmed that SpoVM prefers NPSLBLs rather than PSSLBLs, indicating by a lower free energy change. Additionally, we revealed that the SpoVM membrane sensing is based on the interplay between the packing of the hydrophilic head groups of the lipids and the packing of the acyl chains of the lipids. Our findings reported in Chapter 5 might be helpful in the development of diagnosis and treatment of diseases associated with protein mislocalization.