Abstract

Lipid bilayers are essential components of cell membranes because they serve as semi-permeable barriers between the extracellular and intracellular environments. Fluid (L_α), ripple (P_β), and gel (L_β) are the three primary phases of lipid membranes. The functionality of the cell membrane is active at its fluid phase and at a full hydration level. A co-existence in the gel and the fluid phases in membranes results in the creation of grain boundary defects and helps in a drug release. Water molecules near membranes regulate various properties of the cell such as transport, raft formation, molecular recognition, signal transduction and so on. Such water have different characteristics than bulk water (BW). Thus understanding the role of water on the membrane phase transitions is crucial to control the function of membrane under physiological and low temperature conditions. Although water dynamics and thermodynamics around membranes have been found to be correlated with the phase transition, the underlying mechanism of the correlation is not explored and not characterized. The current thesis provides evidences of emergence of dynamical heterogeneity in interface water (IW) near membranes at three phases using all-atom molecular dynamics simulations. The correlation between the structure and dynamics of the IW and membranes are quantified across fluid to ripple to gel phase transitions.

To understand whether the regional coupling of lipid and water dynamics is significant enough to capture any perturbation in fluid membrane, we identify IW near a fluid membrane composed of 1,2-dimyristoyl-sn-glycero-3-phosphorylcholine (DMPC) lipids. IW residing within a distance of ± 0.35 nm of the locations of the most probable density of CO/PO/Glyc. heads of DMPC molecules are referred to as IW-CO^d/PO^d/$Glyc^d$. All IW molecules manifest signatures of dynamical heterogeneity at room temperature due to regional confinement and exhibit multiple structural relaxation time-scales. Both fast and slow relaxation time scales of the IW^d are correlated to the respective time scales of the closest lipid moieties. These analyses imply that the spatially resolved interface water dynamics can act as a sensitive reflector of regional membrane dynamics occurring at sub ps to hundreds of ps time scales and thus will be able to capture any alterations in membrane structure and function in future. Since membranes are active at a fully hydrated state and the cells die upon dehydration, understanding biological cell membranes under anhydrous conditions is of tremendous importance. We find that the bilayer undergoes from a disordered state to a ordered state upon dehydration with a drastic slow-down in the relaxation times of the IW originated from dynamical heterogeneity. The diffusion constants and the structural relaxation times of the IW obey the Stokes-Einstein (SE) relation for the bilayer fluid phase which changes to a fractional SE-like relation at the onset of bilayer ordering. Thus, our analysis provides the mechanistic insights of dehydration induced bilayer ordering. To understand the structural changes of the IW due to bilayer phase transitions, we perform a $\sim 11.55\mu$s long all-atom molecular dynamics simulation at the gel, ripple and the fluid phases of the bilayers. The first and second peak heights of the radial distribution functions (RDF) of the BW increase monotonically with a decrease in temperature, signifying the presence of enhanced tetrahedrality at the lowest temperature which is below the homogeneous ice nucleation temperature accessing the "no man's land". Similar behaviour is observed for the IW near fluid and gel phases but not for the ripple phase, probably due to the curvature induced in the ripple phase. Changes in locations of the first and the second hydration shells show two crossovers near fluid to ripple and ripple to gel phase transitions. The angular distribution functions of the IW near the fluid bilayers exhibit peaks corresponding to a distorted tetrahedral arrangement similar to the high-density liquid (HDL) phase due to the presence of interstitials. This changes to tetrahedral

arrangement for the IW near the gel bilayer, indicating the presence of low-density liquid (LDL) like phases. As temperature reduces, membrane phase transitions are associated with a drastic slow down in structural relaxation times of the interface water (IW) and the lipids originated from dynamical heterogeneity. Diffusion constants of the IW undergo dynamic crossovers at both fluid-to-ripple-to-gel phase transitions with the highest activation energy near the gel phase leading to a stronger correlation of the IW dynamics with the gel membrane due to larger number of hydrogen bonds. Similar to the BW, Stoke Einstein (SE) relations are conserved for the IW near all three phases of membranes for the time scales derived from the diffusion exponents and the non-Gaussian parameters, indicating that these time scales are coupled with the diffusion even at lower temperatures. However, the SE relationship breaks for the time scales calculated from the self intermediate scattering functions. The behavioural differences in these different time scales upon supercooling are found to be universal irrespective of the nature of the water and other glass forming liquids. The spatial correlation length scale of the heterogeneous local dynamics of the IW are captured from the data collapse of block size dependent Binder cumulant which is a scaling function of only the underlying correlation length. The dynamical length of the IW is found to have inverse power law dependence on temperature for the fluid phase. The dependence becomes very weak for the gel phase unlike glass forming liquids. Interestingly, the dynamical length scale of the IW near the ripple phase is temperature independent and thus, can capture to the domain size of the ripple signifying a possibility of probing the heterogeneity length scale of a bio-membrane from its curvature induced domain size. The length scale is monotonically dependent on the first peak of the radial distribution function of the IW near all phases this suggests that the heterogeneity length scale is structure dominated. Our analyses, for the first time, estimate the coupling between the spatio-temporal scales of the IW and membranes across phase transitions. The structural relaxations of the IW follow an activated dynamical scaling with the heterogeneity length scale only for the gel phase which is similar to that predicted from the random first order transition theory. However, the drastic growths in the heterogeneity length scale across phase transitions are not accompanied by similar growth in the heterogeneity time scales. This is because, the growing structural relaxation time scales of the IW are dominated by the supercooling whereas the growing length scales are dictated by the membrane phase transitions.

In summary, the thesis sheds light on how the structure and dynamics of lipids and IW are correlated across a wide range of temperature and hydration numbers relevant for physiological and extreme conditions. Our findings suggest that hydration water dynamics can sensitively reflect localized membrane movements and thus can be an alternate tool to probe any perturbations in membranes. These can help to understand drug delivery mechanisms and mimic cryo preservation procedures for use in biomedical applications in the future.