Molecular Insights into the Gel to Liquid-Crystalline Phase Transition of Phospholipid Bilayers

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Statement of Purpose: The lipid bilayer with embedded proteins surrounds cells and organelles as a barrier and serves as the site of many activities such as protein synthesis, sodium ion pumping and hormone reception. Many nanoparticles are engineered to either be targeted to the cell surface or to overcome the membrane barrier in order to perform therapeutic functions.[1] In addition to its roles as a gatekeeper and a reaction site, the lipid bilayer is also the essential structure of liposomes, artificially-prepared spherical vesicles for administration of nutrients and pharmaceutical drugs.[1] It is recognized that the phase of the lipid can significantly alter multiple characteristics of lipid bilayer such as its selective permeability, signal transduction, and mechanical properties, thereby affecting the functionality of biomaterials and the efficacy of drug delivery. Hence, it is fundamentally important to understand the structure and dynamics of lipid bilayers in different phases. For this purpose, molecular dynamics (MD) simulations can provide detailed information at the atomic level. In the present study we conducted MD simulations on hydrated 1,2-Dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) and 1,2-Dimyristoyl-sn-glycero-3-phosphocholine (DMPC) at various temperatures that span both the gel and liquid-crystalline states. The structural characteristics (e.g., tail alignment, area per lipid headgroup, bilayer thickness) of the lipid bilayer were investigated and an attempt was made to predict the gel to liquid-crystalline phase transition temperautre (T_m).

Simulation Methods: The lipid bilayer containing 128 DPPC (T_m=314 K) or DMPC (T_m=297 K) lipids (64 per leaflet) was generated by CHARMM-GUI[2] with a hydration level of 40 water molecules (TIP3P) per lipid. The aqueous DPPC and DMPC systems were equilibrated for 50 ns with the isothermal-isobaric ensemble at 370 K and 350 K, respectively. After the equilibration, the systems underwent a stepwise cooling of 10 K every 5 ns until 260 K for DPPC/water and 240 K for DMPC/water. Other simulation parameters were the same as those reported in the previous study[3] except that a time step of 1 fs was used in the stepwise cooling simulations. All the simulations were performed using NAMD (v2.9) with the CHARMM36 force field[4].

Results: The deuterium order parameters (S_{CD}) for the two acyl chains (*sn*-1 and *sn*-2) of lipid were calculated from the long-time average of the correlation function describing the reorientation of the C-D vector, providing a measure of the alignment of the phospholipid tails in the bilayer. The $|S_{CD}|$ profile of the *sn*-2 chain of DPPC is shown in Figure 1 (a) as an example. The chain is observed to be more ordered in the region nearest the headgroup, where $|S_{CD}|$ is highest (except for C2), with the order decreasing with increasing distance from the headgroup. The alignment of lipid tails can determine the phase of the bilayer. In other words, the order parameter is significantly higher in the gel phase than in the liquid-crystalline phase (see Figure 1 (b)). It can be observed that the variation of $|S_{CD}|$ with temperature follows a lognormal distribution between 370 K (>T_m) and 260 K (<T_m). The $|S_{CD}|$ changes continuously over this temperature range which brackets the experimentally determined gel to liquid-crystalline phase transition temperature. This study determined the T_m as the temperature corresponding to the inflection point of the best-fit curve (the solid line in Figure 1 (b)). The predicted T_m is 291.8±2.2 K for DPPC, which is lower than the experimental value. The discrepancy is likely due to the ultrafast cooling rate in the simulation compared to that in thermal analysis (1 K/min). The $|S_{CD}|$ profiles for the *sn*-1 chain of DPPC as well as chains of DMPC showed qualitatively the same trends as those in Figure 1.

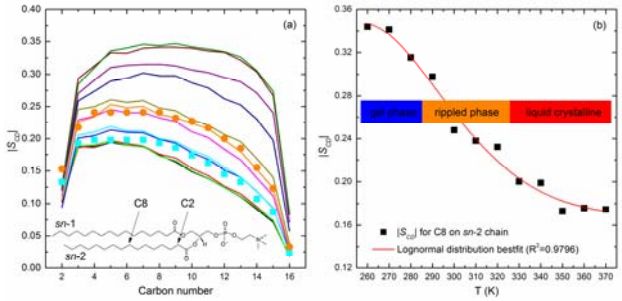

Figure 1. (a) The $|S_{CD}|$ profile for the *sn*-2 chain of DPPC at various temperatures (a) (lines: 260 to 370 K from top to bottom; squares: NMR results at 330 K[5]; circles: NMR results at 314 K[5]) and (b) the $|S_{CD}|$ for C8 on the *sn*-2 chain as a function of temperature

Conclusions: This study serves two main purposes: 1) to investigate the structural characteristics of phospholipid bilayers in gel and liquid-crystalline phases and 2) to explore the feasibility of predicting the gel to liquid-crystalline phase transition temperature by molecular simulation. It was found that $|S_{CD}|$ experienced a continuous decrease when transitioning from the gel to liquid-crystalline. The MD simulation technique underestimated the experimentally determined T_m, likely due to differences in cooling rate, which can be explored in future studies. The evaluation of the effect of biomaterials on the phase transition characteristics of lipid bilayer is suggested as a next step.

References:

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