MD simulation of melittin in DMPC bilayer

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Background

Specific lipid-protein interactions involved in the anchoring and stabilization of membrane-bound proteins are of central importance in a large number of fundamental processes occurring at the surface of the cell. Melittin is a major protein component of the bee venom that has a pronounced effect on the lysis of the dimyristoylphosphatidylcholine (DMPC) bilayer membrane. It can increase membrane permeability by partial penetration of the bilayer.
Besides, a canal structure may be formed by the aggregation of four transbilayer melittin molecules. Aggregated melittin is involved in the solubilization of large lipid disks (leaving large holes in membrane).

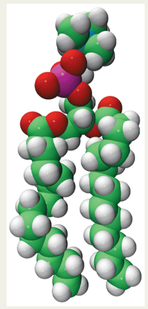

Fig.1 DMPC

Objective

To investigate the effect of melittin (a pore forming peptide) on the dynamics of lipid bilayer by Molecular Dynamics (MD) simulations and neutron experiments. The quasielastic neutron scattering (QENS)experiments are performed at ORNL. We are going to examine the effects of cholesterol and phase state (temperature) of the bilayer on the lipid-melittin interaction.

Experiments

I. Quasielastic neutron scattering (QENS) experiments

a. DMPC + Melittin
Melittin : DMPC = 1:500
b. DMPC + CHL + Melittin
CHL : DMPC = 1:4, Melittin : DMPC = 1:500

DMPC melting temperature is 297 K. The experiments are done for two temperatures 280 K for Gel phase and 310 K for liquid phase.

II. Simulation systems

a.500 DMPC:	275K, 280K, … , 315K
b.500 DMPC + 1 Melittin:	275K, 280K, … , 315K
c.400 DMPC + 100 CHL:	only 280K and 310K
d.400 DMPC + 100 CHL + 1 Melittin:	only 280K and 310K

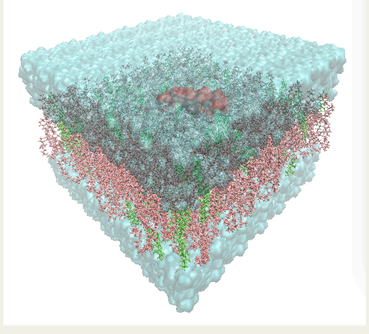

Fig.2 Simulation system

The temperature scan for DMPC only system and DMPC+Melittin system in a and b is for phase transition comparison. In this simulation, we want to observe the effects melittin and Cholesterol have on the dynamics of DMPC at both liquid and gel phases.

Results

I. Order Parameter

Lipid order parameters are a measure for the orientational mobility of the C–D bond and are defined as

$$S = \left\langle \frac{3\cos^2\Theta - 1}{2} \right\rangle$$

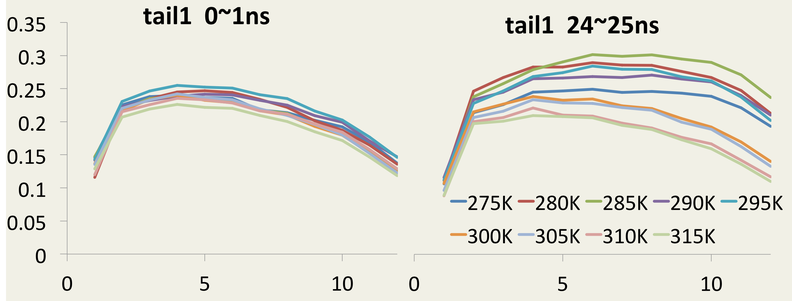

Fig.3 Order Parameter

In Fig.3, as the simulation goes on, the order parameter curves of the first tail of DMPC with different temperatures are divided into two groups. One group with temperature ranging from 275K to 295K has higher order parameter, which represents the gel phase that has higher order and less mobility. The other group from 300K to 315K stands for the liquid phase, which shows lower order parameter and higher flexibility. According to the experiment, the transition temperature of DMPC is 297K, which is in good accordance with our MD simulation results.

II. Gauche Structure Fraction

In stereochemistry, The term “gauche” refers to conformational isomers(conformers) where two vicinal groups are separated by a 60° torsion angle.

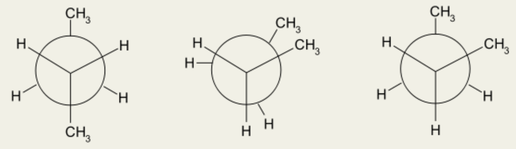

Fig.4 Trans and gauche rotamer of butane

Fig.4 shows the trans(left) and gauche(right) rotamers of butane.

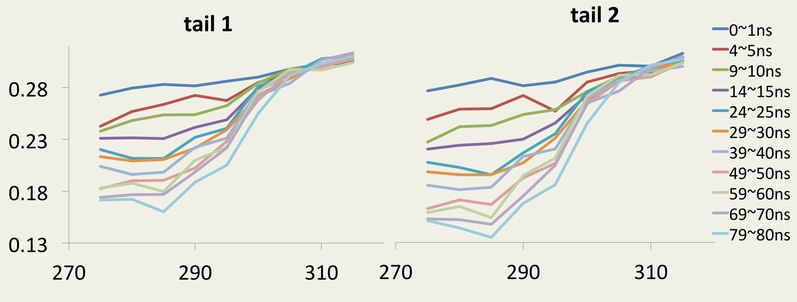

Fig.5 Gauche rotamer fraction

In general a gauche rotamer is less stable than an anti-rotamer. Hence in Fig.5, as the temperature increases, the gauche rotamer fraction increases as well. Besides, in lower temperature (275K~295K), or in gel phase, the gauche fraction is still dropping off, which means the systems are still not converged and the simulation needs to be extended.

III. System density measurement

The result reveals the change in density along the normal direction (z axis). By this type of analysis the location and thickness of different layers of component can be determined.

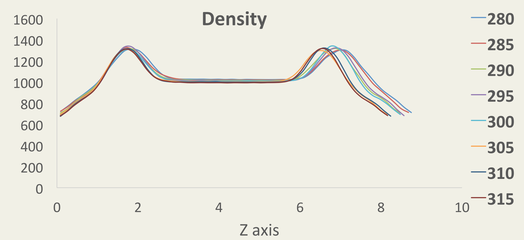

Fig.6 System density measurement

In Fig.6 the relative flat region with z coordinate from 2.5 to 6 represents the water region. We find that the water layer thickness gets thinner with temperature increasing.

IV. RMSF

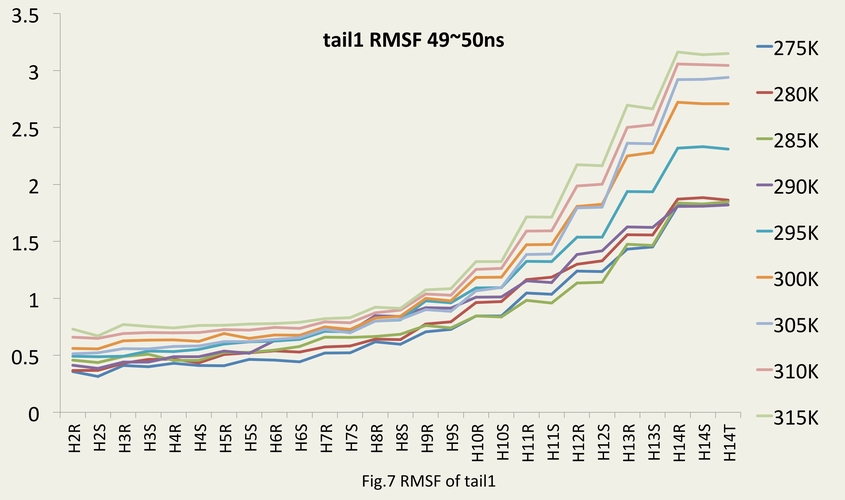

Fig.7 RMSF of tail1

In Fig.7 , RMSF stands for root mean square fluctuation, which can show the mobility of atoms. The RMSF of all the hydrogen atoms attached to the carbon in tail1 are calculated. From the head to the tail, RMSF significantly increases, which is consistent with the model experimentalists used. A big gap around 295K appears, which represents the phase transition.

Acknowledgments

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