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).

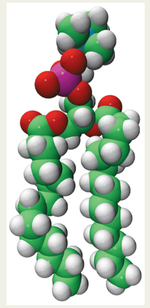

Fig.1 DMPC

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

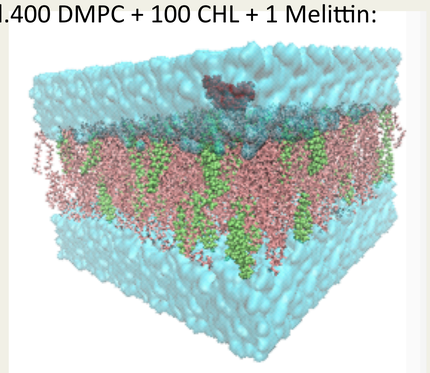

Fig.2 Simulation system

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

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

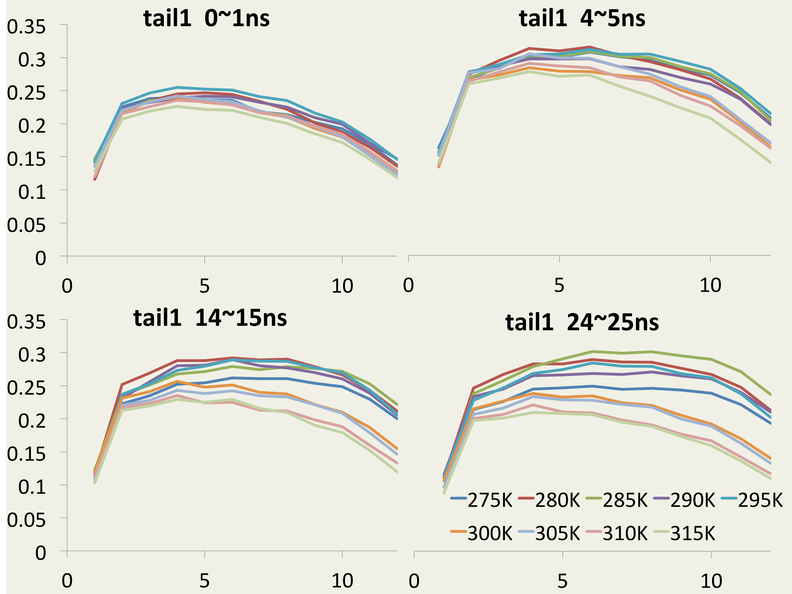

Fig.3 Order Parameter

In Fig.3, with the simulation time expanding, the order parameter curves of the first tail of DMPC with different temperatures are divided into two groups. One group of systems 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.

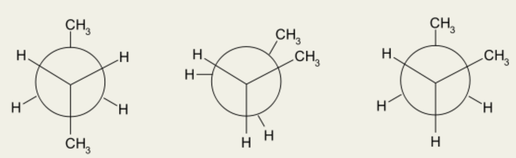

Fig.4 Trans and gauche rotamer of butane

Fig.4 shows the trans(left) and gauche(right) rotamers of butane. The two methyl groups can be in an anti-bonding relationship, or offset at sixty degree dihedral angles.

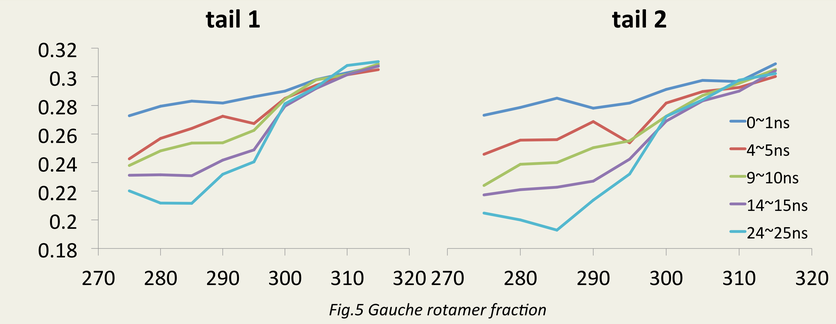

Fig.5 Gauche rotamer fraction

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 expanded. Therefore, we expanded all of our systems to 50ns and more work is still needed.

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.

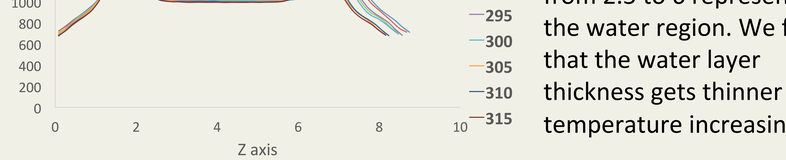

Fig.6 System density measurement

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. Area per lipid

Use ‘g_energy’ command in GROMACS and select to record x and y in each system. Then plot area per lipid (x × y/lipid number) versus time figure.

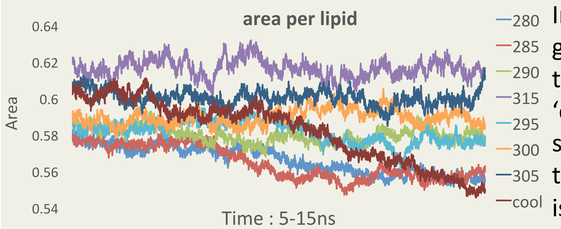

Fig.7 Area per lipid – change of box size

In Fig.7, the area per lipid generally increases with the temperature. The ‘cool’ curve represents system cooling from 310K to 280K at constant rate. It is obvious that the systems with temperatures lower than or equal to 300K are almost converged while systems with higher temperatures are still dropping down significantly, which means we need to expand our simulations longer as well.

Acknowledgments

Support from City University of Hong Kong, Oak Ridge National Laboratory, Joint Institute for Computational Sciences and University of Tennessee are gratefully acknowledged. We also thank Dr Jun Fan in City University of Hong Kong for her instruction.