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Molecular Dynamics Study of Nanobio Membranes

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Abstract: Living cells have lipid bilayer membranes in liquid phase. The detail structure of nanobio membrane in biological cell membranes is illustrated here and the interfaces included in this structure are introduced. Molecular models of lipid bilayers have ignored the interface of two monolayers of nanobio membranes in detail by now, however in this paper a new physical model is proposed based on variation of surface tension in the interface of two monolayers of membrane. Experimental results have shown that some peptides and proteins like antimicrobial peptides and cytotoxins are able to change the shape of-or in some cases to destroy-the bilayer membrane during insertion to external monolayer. All interfaces in nanobio membrane are liquid/liquid type. Since in liquid/liquid interfaces the normal and tangential pressure components are very different near the interface, the usual Molecular Dynamics Simulation ensembles aren't suitable for this case. In this study appropriate ensembles to simulate liquid/liquid interfaces are presented with special focus on proper ones for surface tension analysis.

Key words: Nanobio membrane, interface, molecular dynamics, pressure, cytotoxin

INTRODUCTION

Living cells have lipid bilayer membranes in liquid phase. The structure of this bilayer is based on properties of phospholipids. Each phospholipid has a hydrophilic head and a hydrophobic tail. Lipid bilayers are composed of two monolayers, each monolayer is a line of phospholipids. The hydrophilic heads of outer monolayer are oriented to water solutions outside the cell and those of inner monolayer to water solutions inside the cell. The hydrophobic tails of all phospholipids are oriented to the inner side of bilayer. The average thickness of this bilayer is about 5 nm, so it well falls in the category of nanobio membranes. The most important function of lipid nanobio membrane is to preserve the inner parts of the cell. (Lodish *et al*., 2000).

Experimental results have shown that some antimicrobial peptides (Brogden, 2005) and cytotoxins are able to deform -or in some cases to destroy-the nanobio membrane. The insertion of these peptides and proteins to the outer monolayer of the lipid bilayer changes the form of the nanobio membrane. Sometimes this changes lead to death of the cell. One of the most interesting cytotoxins are Cobra venom cytotoxins (cardiotoxins) that are small basic proteins (60-62 amino acid residues, 4 disulfide bridges) belonging to the large family of three-fingered toxins (Shanmugam *et al*., 2008). One simulated cytotoxin is shown in Fig. 1.

The mechanism of this process has been studied experimentally by different methods such as NMR (Dubovskii *et al*., 2005) and fluorescence (Feofanov *et al*., 2005). Thus, it has been shown that cytotoxins are able to bind both to multilamelar liposomes and to lipid monolayers (Dubovskii *et al*., 2005; Perlmutter and Sachs, 2009). It has been shown also that the strength of the interaction depended on both: the nature of toxin and lipid. The mechanism of the changes is not clear. The chemical bonds are so stable that there is no probability of occurring any chemical process in this interaction. So, there should be a physical model to illustrate what happens (Maftouni *et al*., 2007; Maftouni *et al*., 2009a, b).

In the case of cytotoxins it is necessary to know the mechanism of this interaction to find proper solutions to preserve cells from death (Hereman *et al*., 2007). Until now, some different models are proposed to illustrate this phenomenon. Usually molecular simulation methods like Monte Carlo and Molecular Dynamics Simulation (Efremov *et al*., 2002; Mashl *et al*., 2001) are used to simulate the proposed models and to check the compatibility of the models with experimental observations.

In this study a new physical model is innovated based on variation of surface tension in the interface of two monolayers of membrane during interaction with cytotoxin.

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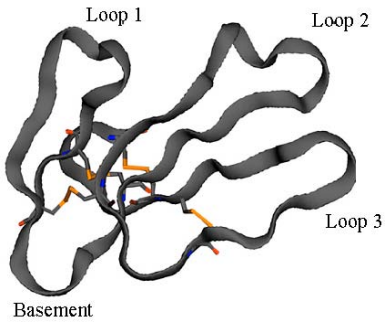

Fig. 1: A modeled cytotoxin

Since in liquid/liquid interfaces the normal and tangential pressure components are very different near the interface, the usual Molecular Dynamics Simulation ensembles aren't suitable for this case. In this study appropriate ensembles to simulate liquid/liquid interfaces are presented.

METHODS

All interfaces in nanobio membrane are liquid/liquid type. A model POPC nanomembrane which we have simulated is shown in the Fig. 2.

As it is observable in the Fig. 2 the interfaces in nano-bilayer in biological cell membranes aren't so exact. The interface in this problem is an approximated interpolated surface, which is mentioned as black lines. The upper and downer lines are the interfaces between nanobio membrane and both outer and inner water solutions. The middle black line indicates the interface between two monolayers of the nanobio membrane.

Simulations of liquid/liquid interfaces under a normal pressure Pn of 1 atm present a difficulty not encountered in liquid/vapor systems. In the latter, simulations are typically carried out at constant particle number, volume and energy (the NVE, or micro canonical, ensemble) with periodic boundary conditions. Because there is explicit vacuum, the density in the interfacial region can readily adjust to its equilibrium value. Consequently, a slab taken from a previous simulation of the bulk fluid provides an adequate initial condition. The dynamical equations for the micro canonical ensemble are also straight forward. Now consider an NVE simulation of the liquid/liquid interface. An initial condition comprised of two abutting slabs of bulk fluid would most likely relax to a system with Pn significantly different from 1 atm. In general, prior knowledge of the interfacial density profile or related quantities is required. Otherwise, the volume of the simulation cell must be adjusted manually during the equilibration until the normal pressure equals the desired

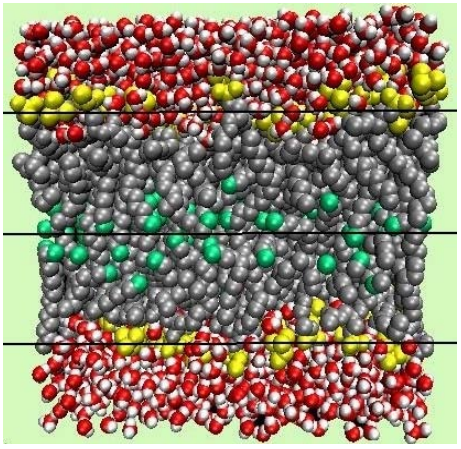

Fig. 2: POPC nanobio membrane simulated with VMD to use by GROMACS

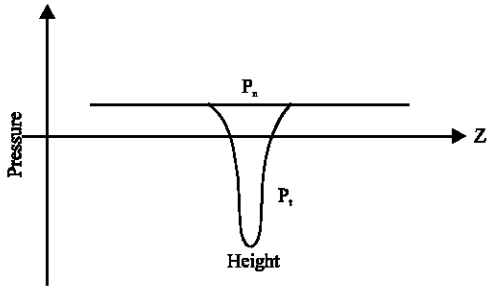

Fig. 3: A sketch of pressure profiles in the region of a planar interface between two liquids. Pn and Pt are the normal and tangential components of the pressure tensor, respectively

value or the densities far from the interface approach their bulk values. The natural approach is to allow volume or shape fluctuations by setting thermodynamic quantities such as the normal pressure, surface area or surface tension to appropriate target values. Figure 3 shows a sketch of pressure profiles in the region of a planar interface between two liquids. Pn and Pt are the normal and tangential components of the pressure tensor, respectively. (Zhang and Feller, 1995).

Including these situations there are four proper adiabatic ensembles, all with constant particle number to simulate liquid/liquid interfaces:

- constant normal pressure and surface area (NP_nAH);
- constant tangential pressure and length normal to the surface (NP_th_zH)
- constant volume and surface tension ($NV\gamma H$)
- constant normal pressure and surface tension ($NP_n\gamma H$)

The first law of thermodynamics is used for each ensemble and equations of motion are derived regarding to Anderson's pressure piston model (Andersen, 1980). The surface tension is defined as follows:

$$\gamma=\int_{-\infty}^{+\infty}[P_n-P_t(z)]dz$$

The Lagrangian is written for each ensemble and the Hamiltonian is derived from it. Proper Lagrangian for two ensembles which are required for modeling and simulation of nanobio membrane and to obtain surface tension are as follow:

Constant NP_nAH_{pn}:

$$L(r,h_z)=\sum_{i=1}^{N}\left[\frac{1}{2}m_i\dot{x}_i^2+\frac{1}{2}m_i\dot{y}_i^2+m_i(\dot{z}t-\frac{\dot{h}_z}{h_z}z_i)^2\right]-U(r)+\frac{1}{2}M_Z\dot{h}_z^2-P_{n0}\,h_x\,h_y\,h_z$$

where, m_i is the mass of the ith atom, U(r) is the interparticle potential energy and P_{n0} is the reference normal pressure. $h_x\,h_y\,h_z$ are dimensions of simulation box. A schematic of this ensemble is shown in Fig. 4.

Constant $NP_n\gamma H_{p\gamma}$:

$$L(r,h_x,h_y,h_z)=\sum_{i=1}^{N}\left[\begin{array}{l}\frac{1}{2}m_i(\dot{x}_i\frac{\dot{h}_x}{h_x}x_i)^2+\frac{1}{2}m_i(\dot{y}_i\frac{\dot{h}_y}{h_y}y_i)^2\\ \frac{1}{2}m_i(\dot{z}_i\frac{\dot{h}_z}{h_z}z_i)^2\end{array}\right]-U(r)$$

$$+\frac{1}{2}M_x\dot{h}_x^2+\frac{1}{2}M_y\dot{h}_y^2+\frac{1}{2}M_z\dot{h}_z^2-P_{no}h_xh_yh_z+\gamma_o\,h_x\,h_y$$

where, P_{n0} and γ_0 are the reference normal pressure and surface tension, respectively. The schematic of this ensemble is shown in Fig. 5.

Equation of motion: The equations of motion consistent with the ensembles just defined are different. For the micro canonical, these are simply Newton's equations. For the others, the constraint conditions are applied using the extended system approach (Martyna *et al*., 1996). This method introduces additional degrees of freedom (often referred to as 'pistons') that couple dynamically to the rest of the system, thereby imposing the constraint (e.g., Pn = 1 atm) on average; it is to be distinguished from constraint dynamics (Feller *et al*., 1995), where the constraint is rigorously satisfied at each time step of the simulation.

Various extended system algorithms have been proposed for performing constant pressure molecular dynamics computer simulations for a homogeneous molecular system. Two of them have been widely used. The first, proposed by Andersen (Martyna *et al*., 1996) and later generalized to the constant pressure tensor by Parrinello and Rahman (Parrinello and Rahman, 1981) and Nose and Klein (1983), describes the piston with second order differential equations.

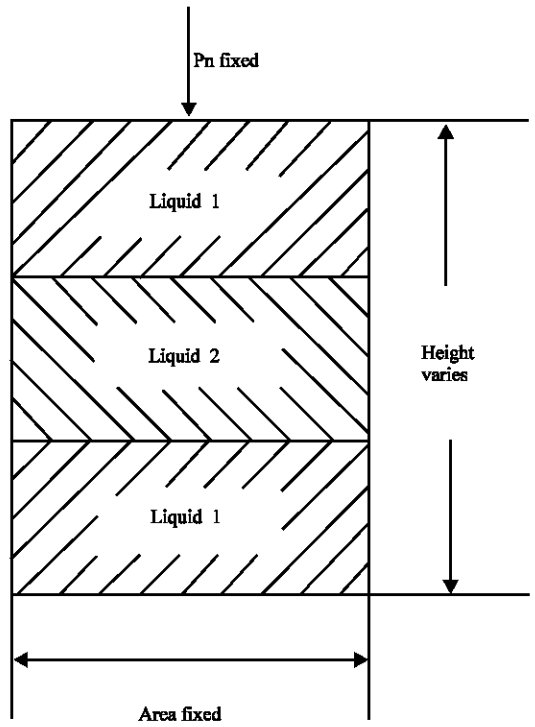

Fig. 4: Schematic of Constant NP_nAH_{pn} ensemble

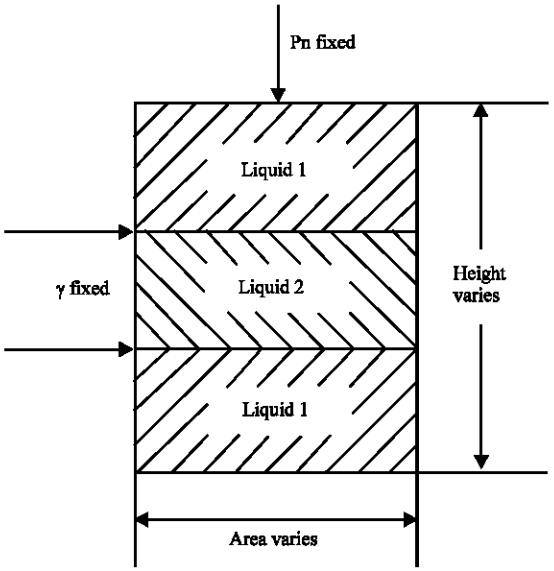

Fig. 5: Schematic of constant $NP_n\gamma H_{p\gamma}$ ensemble

The second is the weak coupling algorithm of Berendsen and co-workers (Berendsen *et al*., 1984) in which the equations of motion for the pressure pistons are first order diffusive like.

Regarding to Hamiltonian Mechanics the equations of motion are derived for each ensemble and then all properties could be calculated. Now simulation of interaction of cytotoxin with nanobio membrane using these ensembles clears the relation between variation of surface tension in interfaces of nanobio membrane and different position of cytotoxin during process. This leads to find a criterion for nanobio membrane deformation and rupture.

CONCLUSION

To exact analyze of nanobio lipid bilayer membrane it is necessary to know the properties at the interface between two monolayers. Simulating this liquid/liquid type interface needs special ensembles. Two of the proper ensembles are useful for cell membrane simulation: constant normal pressure and surface area (NP_nAH); and constant normal pressure and surface tension ($NP_n\gamma H$). The purposed model relates the variation of surface tension to deformation of cell membrane. This new model is appropriate to study the interaction of cytotoxin and nanobio lipid membrane.

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