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Molecular dynamics simulations of lipid membranes with lateral force: Rupture and dynamic properties

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ABSTRACT

Membranes' response to lateral tension, and eventual rupture, remains poorly understood. In this study, pure dipalmitoylphosphatidylcholine (DPPC) lipid bilayers, under tension/pressure, were studied using molecular dynamics (MD) simulations. The irreversible membrane breakdown is demonstrated to depend on the amplitude of lateral tension, loading rate, and the size of the bilayer. In all of our simulations, −200 bar lateral pressure was found to be enough to rupture lipid membrane regardless of the loading rate or the membrane size. Loading rate and membrane size had a significant impact on rupture. A variety of dynamic properties of lipid molecules, probability distribution of area per lipid particularly, have been determined, and found to be fundamental for describing membrane behavior in detail, thus providing the quantitative description for the requirement of membrane rupture.

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1. Introduction

Membranes are essential to all living organisms. Mechanical forces act on organisms in a variety of ways. Cells have different mechanisms to respond to mechanical stimuli and convert mechanical signals into electrical or chemical signals, which plays a mechanotransduction role in a number of physiological activities such as cell growth, signal transduction, and transport [1,2]. Lateral membrane tension, caused by mechanical forces, may change the state (open/closed) of membrane channels [3]. Mechanical forces have also an important effect on membrane permeability [4,5]. Both lateral diffusion of lipids [6,7] and the formation of lipid rafts [8] rely, to some extent, on membrane tension. Knowing how lipid membranes respond to changes in lateral tension is crucial to understanding cellular functions. Rupture is an extreme response and may occur due to influence of tension or weakening of a membrane due to detergent as in bacterial disinfectants. Generally, rupture occurs when a membrane reaches its critical lateral tension [9].

The effect of mechanical stress on membranes has been studied extensively by experiments, see e.g. Ref. [10]. For example, the effect of force on sheared endothelial cells [6,7,11] as well as hair cells [12,13] has been studied. Membrane rupture is generally considered to occur at tensions from 1 to 25 mN/m [14]. When fluid membrane vesicles were subjected to a steady ramp of micropipette suction, it was found that the rupture strongly depended on the loading rate [14–16]: At high loading rates (up to 10 mN/m/s), the critical tension was 3–5 times larger than that at low loading rates (1–2 mN/m/s). Lipid composition has been considered to determine rupture strength [4]. Although such experimental techniques have shed considerable light on the properties of membranes, the presence of disorder in these systems greatly limits the nature of the structural data which can be obtained experimentally. The process of rupture is rather fast and involves subtle changes at the molecular level. It is difficult to study the molecular level mechanisms by experimental techniques.

Computational methods offer an alternative approach and MD simulations have been used to study water pore formation and membrane rupture. For example, in previous MD simulation of a pure DPPC bilayer [9], application of a large mechanical pressure of −200 bar led to pore formation (a water channel) and irreversible rupture. Membrane rupture has also been observed in simulations of different mixed bilayers of phosphatidylethanolamine and $C_{12}E_6$, which tried to determine the rupture properties of mixed bilayers of lipid and nonionic surfactant, and explain why dividing cells were more at risk than static cells [17].

Further MD simulations of pure DPPC bilayers showed that water pores, i.e., water channels, could be stabilized under low tension, but became unstable and caused membrane rupture when tension reached about 38 mN/m [18]. Self-organization of a stable pore structure (a sufficient number of water molecules in the hydrophobic region) in lipid bilayer has also been studied via MD simulations of a pure DPPC bilayer

Abbreviations: DPPC, dipalmitoylphosphatidylcholine; MD, molecular dynamics; DOPC, dioleoyl-phosphatidylcholine; VMD, Visual Molecular Dynamics; SPC, simple point charge; LINCS, linear constraint solver; PME, particle-mesh Ewald; PDF, probability density function; CDF, cumulative distribution function

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[19]. The results demonstrated that the probability of stable pore formation depends on the number of water molecules in the hydrophobic region when no external force was applied. The presence of small nanoparticles in lipid bilayers was demonstrated to decrease the membrane rupture tension by enhancing the probability of water penetration [20]. Nevertheless, the previous systems focused mostly on the phenomenon of how external stimuli caused water pore formation or membrane rupture, and thus the lack of membrane dynamic properties in atomistic details caused the loss of critical quantitative description in the membrane rupture essence. To quantify the effects of membrane tension on lipid structure and dynamics, Muddana et al. performed MD simulations of DiI-labeled DPPC lipid bilayers under lateral tension [21]. The study provided insights into the relationship between tension and lipid dynamics, nevertheless, none information about membrane rupture has been described. In addition, coarse-grained simulations of pure DPPC bilayers under membrane tension have been conducted in both gel and liquid phases [22]. The latest simulations also shed light on the effect of membrane tension on the physical properties of pure DOPC lipid bilayers [23] but the tension was far from the lysis tension of a pure DOPC bilayer, which resulted in no pore formation observed in this study. To the best of our knowledge, dynamical properties of lipid bilayers under different lateral tensions or pressures, particularly during rupture, such as lipid area distribution, lipid ordering and tilting, have not yet been investigated in detail.

2. Material and methods

All MD simulations were performed with Gromacs v4.5.1 [24]. Visual Molecular Dynamics (VMD) [25] was used for all visualizations. For initial configurations, a DPPC lipid membrane from a previous 100 ns simulation was used[1] [26,27]. Two membrane sizes were used in the production simulations: A 128 DPPC system with 3655 water molecules and a larger bilayer of 512 DPPCs and 14620 water molecules which was constructed from the 128 DPPC systems. Force-field parameters for DPPC were taken from a previous developed lipid.itp file [28][2] and partial charges from the underlying model description [29]. For water, the simple point charge (SPC) model [30] was employed. All bonds were constrained to their equilibrium lengths with the linear constraint solver (LINCS) algorithm [31]. Periodic boundary conditions were applied. Lennard–Jones interactions and the real space part of electrostatic interactions were cut off at 1.0 nm. The particle-mesh Ewald (PME) method [32] was used to compute electrostatic interactions, since it has been shown that proper treatment of electrostatics is crucial in biomembrane systems [26,27,33,34]. For energy minimization, the steepest descent algorithm was used. All production MD simulations were done in the constant particle, pressure and temperature (NPT) ensemble with the V-rescale thermostat [35] at 323 K; the V-rescale thermostat has been shown to work very well in systems containing water and interfaces [33]. Surface tension was kept constant using the semi-isotropic Parrinello–Rahman pressure coupling algorithm [36,37] with the pressure set to 1 bar. The time step was set to 2.0 fs. Although the 128 DPPC systems were pre-equilibrated for 100 ns, both bilayers (128 and 512 lipids) were further equilibrated in the NPT ensemble for 100 ns. To ensure that equilibrium had been reached, we compared the area per lipid, order parameters, electrostatic potential, and the radial distribution functions to previous studies [26,27] and found full agreement.

To study the membranes' resistances to lateral tension and compression, we applied 1 bar, −50 bar, −100 bar, −200 bar, and 200 bar lateral pressure to the equilibrated 128 DPPC systems. A pressure of 1 bar was always applied in the normal direction. The corresponding surface tensions are 0 mN/m (1 bar), 17.93 mN/m (−50 bar), 30.79 mN/m (−100 bar), 44.78 mN/m (−200 bar), and −116.18 mN/m (200 bar). A pressure with positive value indicates compression while negative pressure means tension. In all former simulations, to our knowledge, tension was applied instantaneously [9,17,18,21–23]. We applied two different protocols: 1) high loading rate: −200 bar pressure was applied to the tension free membrane instantaneously and 2) low loading rate: −50 bar pressure was first applied for 10 ns. Then the pressure was changed to −100 bar for another 10 ns, and finally −200 bar pressure was applied. To gain insight into possible system size dependence, the same instantaneous lateral pressure of −200 bar was applied on both 128 DPPC and the larger 512 DPPC systems. Previous MD simulations have focused on the dependence of rupture at a specific lateral tension or lipid composition [9,17,18], or the lipid dynamic properties corresponding to several constant membrane tensions below rupture tension [21–23]. All production simulations lasted for 250 ns unless the membrane ruptured earlier. In all the figures, time 0 ns always corresponds to the beginning of the production simulation after which either the high or low loading protocol was applied.

The systems are labeled as follows: Normal Pressure (NP) for the pressure of 1 bar (reference system), T50 for −50 bar pressure, T100 for −100 bar pressure, LT200 for −200 bar pressure with low loading rate, HT200 for −200 bar pressure with high loading rate, BT200 for −200 bar pressure applied on 512 DPPC systems with high loading rate, and P200 for 200 bar pressure.

3. Results

3.1. Threshold of lateral tension for membrane rupture

The application of −200 bar lateral pressure always led to a rupture independent of the loading rate and membrane size. This is in agreement with previous simulations [9]. In the HT200 system, rupture occurred after about 6 ns, but it took about 35 ns for the BT200 system. The LT200 system remained intact for 50.2 ns after −200 bar pressure was reached, and after which it ruptured. In contrast, the T100 system remained stable for the full simulation time of 250 ns. Particularly, under lateral pressure loading of 200 bar, buckling of lipid bilayer was observed. The P200 system experienced a slight buckling deflection when lateral pressure was applied and remained stable through the whole simulation.

3.2. Membrane dimensions

One of the main bilayer characteristics is the average area per lipid molecule <A> (Fig. 1). As expected from 200 ns of pre-equilibration, the tensionless membrane was well equilibrated with $<A> = 0.656 \pm 0.010$ nm^2. This is in agreement with experiments and earlier MD studies [27,38,39]. As lateral tension increased, <A> increased noticeably. For T50, $<A> = 0.740 \pm 0.010$ nm^2, about 13% larger than the NP system, and for T100, $<A> = 0.867 \pm 0.010$ nm^2, about 32% increase. Finally, for LT200, $<A> = 1.178 \pm 0.020$ nm^2 before rupture, almost 80% larger than the reference system. For HT200, <A> remained at 1.199 ± 0.050 nm^2 only for 7 ns, followed by a rupture. In the BT200 system, $<A> = 1.226 \pm 0.050$ nm^2 for 45 ns followed by a rupture. Applying compression, P200, yielded $<A> = 0.441 \pm 0.001$ nm^2, which is 32.8% smaller than the reference value. The lipid membranes exposed to −200 bar lateral pressure had a transient state with area per lipid of ~1.2 nm^2 before rupture.

We also calculated the thickness of the bilayer defined as the average distance of P–P atoms in the lipid head groups (Fig. 2). For the NP system, we obtained 2.80 ± 0.05 nm. T50 gave 2.41 ± 0.05 nm, T100 1.97 ± 0.05 nm, LT200 before rupture 1.25 ± 0.05 nm, and P200 4.52 ± 0.05. When −200 bar pressure was applied, the thickness always remained at about 1.25 nm before rupture. HT200 stayed at 1.25 nm for only 3.5 ns, and then dropped to 1.0 nm abruptly within

[1] The topology file was available at http://www.softsimu.org/downloads/dppc-128-100.pdb.
[2] The force-field file was available at http://moose.bio.ucalgary.ca/files/lipid.itp.

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