Mesoscale Simulation of Vesiculation of Lipid Droplets

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An implicit solvent coarse-grained (CG) lipid model using three beads to reflect the basically molecular structure of two-tailed lipid is developed. In this model, the nonbonded interaction employs a variant MIE potential and the bonded interaction utilizes a Harmonic potential form. The CG force field parameters are achieved by matching the structural and mechanical properties of dipalmitoylphosphatidylcholine (DPPC) bilayers. The model successfully reproduces the formation of lipid bilayer from a random initial state and the spontaneous vesiculation of lipid bilayer from a disk-like structure. After that, the model is used to systematically study the vesiculation processes of spherical and cylindrical lipid droplets. The results show that the present CG model can effectively simulate the formation and evolution of mesoscale complex vesicles.

Key words: Mesoscale simulation, Implicit solvent coarse-grained lipid model, Lipid droplet, Complex vesicle

I. INTRODUCTION

The amphiphilic phospholipids are major components of cell membranes or organelle membranes [1] and can self-assemble into various micelles such as spherical, worm-like, lamellar micelles, and vesicles. Lipid micellar structures have important applications in the field of drug carriers [2–4], synthetic templates [5, 6], and microreactors [7]. The micellar structures not only depend on the lipid properties, but also are influenced by the kinetics pathways. In previous simulation work, we studied the dependence of the micellar structures on the sizes and components of the lipid droplets [8, 9]. The formation processes of various lipid micelles from small lipid droplets were clearly shown, although the more complex micellar structures using larger lipid droplets are still unknown. In order to simulate the self-assembly process of lipids on larger time and space scales, a coarse-grained (CG) lipid model meanwhile containing the important molecular information is required.

Up to now, various CG models for lipids [10–13] have been developed to overcome the limitation of all-atom molecular simulations on time and space scales. Marrink et al. developed a popular explicit solvent CG model for lipids in which an approximate 4:1 mapping ratio was used and the parameters were achieved by fitting the thermodynamic and structural properties of lipids in experiments and atomistic simulations [13–15]. Orsi and co-workers developed a CG explicit solvent model for lipids by using the Lennard-Jones potential for the spherical units of the choline and phosphate groups and the Gay-Berne potential for soft uniaxial ellipsoids of the glycerol and hydrocarbon groups. In this model, each dimyristoylphosphatidylcholine (DMPC) was mapped into 10 sites, and each dioleoylphosphatidylcholine (DOPC) was represented by 12 beads [16, 17]. The model reproduced the elasticity, electrostatics and dynamics of a DMPC or DOPC bilayer quantitatively and was further modified by Lennard-Jones potentials [18, 19]. Recently, Shinoda and co-workers presented a new explicit solvent model with a mapping ratio of 3:1, where the force field parameters were extracted by combining the atomistic to CG mapping scheme via the inverse Boltzmann method and the simple functional forms to match the thermodynamic properties [20, 21]. Compared with the explicit solvent lipid models, the implicit solvent lipid models possess higher efficiency in computation. Considering the intramolecular structure, Wang et al. proposed an implicit solvent model with 16 CG beads for quantitative simulations of 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC) bilayers [22]. In their model, the bonded and nonbonded interactions together with the effective cohesion mimicking the hydrophobic effect were tuned by matching structural and mechanical properties of lipid bilayer using the iterative Boltzmann techniques. Curtis and Hall presented a DPPC bilayer model using LIME (lipid intermediate resolution...
model) force filed using hard-sphere and square-well potentials [23]. In their model, each DPPC molecule was mapped into 14 beads with two tails. As the degrees of coarse graining continued to increase, the five-bead model [24, 25] and three-bead model [26–28] were proposed, in which each lipid was coarse-grained into a linear structure neglecting major intramolecular structure of two hydrophobic tails for most of the phospholipid molecules. Therefore, it is still an open question: how to find an effective and simple CG model with the least beads meanwhile remaining two-tailed structure of lipid molecules and reproducing the properties of lipid bilayer.

In this work, we propose an implicit solvent CG lipid model for simulating vesiculation of lipid droplets at mesoscale. The present model used three CG beads keeping the basic structure information of lipid molecule, i.e., one headgroup bead and two tail beads (see Fig.1). A set of simple potential functions are employed to match the properties of DPPC bilayers. Similar to the fitting technologies [22, 26–28], the force field parameters of the present model is achieved by fitting them with the structural and mechanical properties of DPPC bilayers such as the area per lipid, bending modulus, stretching modulus, and line tension. The dynamical behaviors of our CG model are proven to be consistent with the experimental and all-atomic simulation results. It is examined through simulating the formation of bilayer and vesicle. The influence of the initial state of lipid droplets on the formation of complex vesicle is further systematically studied via our model.

II. MODEL AND SIMULATIONS

A. CG lipid model

Based on the molecular structure of general lipid molecules (DPPC), each lipid molecule with one hydrophilic head and two hydrophobic tails is mapped into three CG beads (see Fig.1). The hydrophilic bead is labeled as “H” which represents choline and phosphate groups of a lipid molecule, and the two hydrophobic beads are marked as “T” which refers to the fat chain. In addition to reproducing bilayer properties, our model has more reasonable geometrical characteristic than that of the past linear CG models [24, 26, 27]. In the present model, the Hamiltonian consists of bonded and nonbonded interactions, i.e.

\[ U = U_{\text{bonded}} + U_{\text{angle}} + U_{\text{nonbonded}} \] (1)

\[ U_{\text{bonded}} \] is the bond stretching potential, \( U_{\text{angle}} \) is the angular bending potential, and \( U_{\text{nonbonded}} \) is the nonbonded potential for intermolecular interaction. The bonded stretching potential is represented with a harmonic potential:

\[ U_{\text{bonded}} = 0.5k_{\text{bonded}}(r - r_0)^2 \] (2)

where \( k_{\text{bonded}} \) is the force constant and \( r_0 \) is the equilibrium bonded length. The angular bending potential is described with a simple harmonic angular potential:

\[ U_{\text{angle}} = 0.5k_{\text{angle}}(\theta - \theta_0)^2 \] (3)

where \( k_{\text{angle}} \) is the force constant and \( \theta_0 \) is the equilibrium angle. In terms of the realistic size of a lipid molecule and Martini CG force field [14], the bond length and the bond force constant are empirically set as \( r_0 = 1 \text{ nm} \) and \( k_{\text{bond}} = 1 \text{ MJ/(mol-nm)}^2 \). Similarly, a small equilibrium angle (\( \theta_0 = 10^\circ \)) with the bending constant \( (k_{\text{angle}} = 20 \text{ kJ/(mol-rad)}^2) \) is empirically selected to stabilize the bilayer structure. After determining the intramolecular interaction, the self-assembly behavior of CG lipid model only depends on the nonbonded interaction.

In an implicit solvent lipid model, solvation effects of water are introduced into the nonbonded interaction \( U_{\text{nonbonded}} \) between CG lipid molecules. Meanwhile, considering the CG level of our model, the potential should be smooth enough (excess degree of freedom is averaged) to access a mesoscale level simulation. Previous studies on the implicit solvent lipid model has shown that the effective attractive potential between lipid tails is a crucial factor for reproducing the equilibrium structure of bilayers as well as the self-assembly properties [12, 13, 22–29]. The classical LJ potential only leads to solid membranes at low temperature and gas phases at high temperature, so a broad attractive interaction between tail beads is required to reproduce fluid characteristics of the bilayer membrane. In our model, the attractive potentials between lipid tails are also introduced. We divide the nonbonded interaction into two parts: the short-ranged interaction and the long-ranged interaction. The short-ranged interaction, which decays fast with the distance increasing, is used to mimic the excluded volume effect between CG beads. By contrast, the long-ranged interaction involves the effective potential of solvent effects, which is designed with a broad and slowly decaying shape. In order to
describe such a CG interaction in a flexible way, a variation form of MIE potential [30] is employed to describe an effective nonbonded interaction. For the two types of CG beads, the following potential combination is used:

\[
U_{\text{nonbonded}}^{\text{TT}} = \frac{\varepsilon}{6 - 0.5} \left[ 0.5 \left( \frac{r_m}{r} \right)^6 - 6 \left( \frac{r_m}{r} \right)^{0.5} \right] \tag{4}
\]

\[
U_{\text{nonbonded}}^{\text{HH-HT}} = \frac{0.4 \varepsilon}{6 - 0.5} \left( \frac{r_m}{r} \right)^6 \tag{5}
\]

where \( \varepsilon \) is the depth of the potential well and \( r_m \) is the distance of the minimal potential with zero force. The interaction between tails \( U_{\text{nonbonded}}^{\text{TT}} \) is described as an attractive broad potential to mimic solvent effect on the lipids as in Eq.(4), while the interaction between headgroups (or headgroups and tails) \( U_{\text{nonbonded}}^{\text{HH-HT}} \) is described as the repulsive potential with a reduced factor of 0.4 as in Eq.(5). Different from the original MIE potential, we choose \( r_m \) to substitute \( \sigma \) (the distance at which the potential is zero), because the value of \( r_m \) is a crucial parameter to determine the structure of bilayer. The advantage of the forms of Eq.(4) and Eq.(5) is that they are the functions of \( \varepsilon \) and \( r_m \) and more convenient to tune the properties of bilayer membrane.

To avoid the artifact at the cutoff position, the nonbonded potentials can be modified by a shift function that causes forces and their derivatives to be continuous at the cutoff radius. The shift function is applied to the force function (with the form identical to GROMACS) [31] and is given by

\[
S(r) = A(r - r_1)^2 + B(r - r_1)^3 \tag{6}
\]

\[
A = -\alpha \frac{(\alpha + 4) r_c - (\alpha + 1) r_1}{r_c^{\alpha+2} (r_c - r_1)^2} \tag{7}
\]

\[
B = \alpha \frac{(\alpha + 3) r_c - (\alpha + 1) r_1}{r_c^{\alpha+2} (r_c - r_1)^3} \tag{8}
\]

where \( r_1 \) is the start position of the shift function and \( r_c \) is the cutoff radius. The constants \( A \) and \( B \) follow from the conditions that the function should be smooth at \( r_1 \) and \( r_c \), \( \alpha \) is the power of the interaction (0.5 and 6 for attraction and repulsion in the present CG model, respectively). In the present CG model, \( r_c \) is set as 2.772 nm and the start position of \( r_1 \) is 2.25 nm. Compared with the standard LJ potential, the final potential has a broad and slowly decaying profile (see Fig.S1 in supplementary material 1).

B. Simulation parameters

The length unit is \( \sigma_0 = 1 \text{ nm} \), the mass unit is \( m_0 = 1 \text{ u} \) (1/12 of the mass of a \(^{12}\text{C} \) atom), and the energy unit is \( \varepsilon_0 = k_BT \approx 2.62 \text{ kJ/mol} \) at 315 K. Here, the beads of headgroup and tails have the same mass 245 u. The time step is set as 0.15 ps. For the implicit solvent simulations, we use stochastic dynamic with a leap-frog integration algorithm [32], where the friction constant is 0.5 ps. The simulations for the examination of the properties of fluid bilayer are implemented via GROMACS V4.0 [33] and the mesoscale simulations are carried out on personal supercomputers with Tesla C2050 GPUs using in-house software. Visualizations for the molecular conformation information are performed with VMD [34].

III. PROPERTIES OF THE FLUID MEMBRANE

The phase space of fluid lipid bilayers is explored by varying the parameter \( \varepsilon \) and \( r_m \), and then suitable parameters are determined by fitting the properties of fluid DPPC membrane. Finally, the dynamic properties of our bilayer model are examined.

A. Phase diagram of fluid membrane and tensionless area per lipid

In our model, three phase states can be observed by varying \( \varepsilon \) and \( r_m \): a fluid bilayer, a solid bilayer and a gas phase. The equilibrium structures starting from a preassembled bilayer of 512 lipids were simulated in a cubic box with a side length of 12.9 nm under zero lateral tension. Figure 2(a) shows the diagram of equilibrium phase with different \( \varepsilon \) and \( r_m \). It indicates that...
present model can obtain the fluid bilayer in a broadened parameter region. To avoid artificial stabilization of the bilayer, a simulation from a random initial state under NVT ensemble was conducted. 512 lipids were randomly put into a constant cubic box with a length of 12.9 nm, and a bilayer formed spontaneously. The self-assembly process included the rapid local clustering of lipids, slow coarsening and the final merging to form a continuous lipid bilayer (see Fig.S2 in supplementary material), which is consistent with MARTINI model [14, 15]. The formation of a fluid bilayer took approximate 0.02 CPU hours (Intel Xeon E5405 2.00 GHz). In Wang’s model [22], a random solution of 288 POPC lipids self-assembling into a bilayer took approximate 0.02 CPU hours (Intel Xeon E5405 2.00 GHz). Discontinuous molecular dynamics simulating a membrane from a random solution composed of 256 DPPC molecules required 3.8 CPU hours (Intel Xeon E5520 2.27 GHz) [23]. The computational efficiency of our model with less CG beads is higher than the latest models [22], and it is approximately 5–6 orders of magnitude compared with all-atom simulation.

The area per lipid is one of the important quantities for fitting the force field parameters. To match the value of the area per lipid with suitable $\varepsilon$ and $r_m$, we chose the maximal value of $\varepsilon$ in the fluid phase space for a $r_m$ (see Fig.2(a)). A fluid bilayer with 4096 lipids was used to measure the area per lipid at an equilibrium state under tensionless condition (the simulation time is 1.4 $\mu$s). Figure 2(b) shows that the area per lipid becomes larger by increasing $r_m$ ($r_m$ is the equilibrium distance between the hydrophobic tail beads). When $r_m$ changes from 1.18 nm to 1.22 nm, the average values of the area per lipid increase from 0.594 nm$^2$ to 0.725 nm$^2$, which is in the range of the common phospholipid molecules from 0.54 nm$^2$ to 0.725 nm$^2$ in experiments [35]. This verifies that the present model can reproduce the area per lipid of the fluid. In particular, when $r_m$=1.20 nm and $\varepsilon$=2.10$k_BT$, the equilibrium area per lipid for DPPC at 315 K is 0.648 nm$^2$, close to MARTINI model 0.64 nm$^2$ at 323 K [14] and the experimental estimation of 0.64 nm$^2$ [36]. In order to match the mechanical properties of the fluid DPPC bilayer, $r_m$ and $\varepsilon$ are set as 1.20 nm and 2.10$k_BT$ respectively.

**B. Modulus and line tension**

The mechanical properties of the bilayer membrane, such as bending modulus, stretching modulus, and line tension, are crucial factors to testify the reliability of the coarse-grained model.

The bending modulus $\kappa$ represents the resistance of the membrane against bending force in a direction perpendicular to the membrane surface. A popular measurement method is utilized to calculate the membrane undulation spectrum which is independent of the model. The elastic energy of a deformed membrane, in the absence of external perturbation, is given by

$$ E = \frac{1}{2} \int_A \text{d}r \left( \Sigma \left| \nabla h_r \right|^2 + \kappa \left| \nabla^2 h_r \right|^2 \right) $$

(9)

where $\Sigma$ is the lateral tension, $A$ is the projected area of the membrane, $h_r$ describes the height of the membrane relative to a reference plane. After expanding $h_r$ in Fourier modes according to Eq.(10) and Eq.(11), and inserting the results into Eq.(9), the power spectrum of modes [27, 37] is shown in Eq.(12).

$$ h_r = \sum_q h_q e^{i\mathbf{q}\cdot\mathbf{r}} $$

(10)

$$ \mathbf{q} = \frac{2\pi}{L}(n_x\mathbf{i} + n_y\mathbf{j}) $$

(11)

$$ \langle |h_q|^2 \rangle = \frac{k_BT}{L^2(\kappa q^2 + \Sigma q^2)} $$

(12)

where $q$ is the magnitude of the vector $\mathbf{q}$, $L$ is the side length of the square membrane, and the $\Sigma q^2$ term vanishes under zero lateral tension. As the tension on the bilayer area is sensitive, the simulation box size should be as large as possible. In this work, we chose 4608 lipids in an ensemble of constant zero tension. In order to avoid the deviations at large $q$, we fitted $L^2\langle |h_q|^2 \rangle|q|^4$ for low $q$ with the functional [38]

$$ L^2\langle |h_q|^2 \rangle|q|^4 = \frac{k_BT}{\kappa} + c_1 q^{c_2/2} $$

(13)

where $c_1 q^{c_2/2}$ term ($c_2$=2) corresponds to a prominent contribution [39]. Figure 3 shows the fitting result $\kappa$=4.35$\times$10$^{-20}$ J with $c_2$=2.1, which is in agreement with the experimental estimate of 5.0$\times$10$^{-20}$ J [40].

Another important modulus of the membrane, the stretching modulus, describes the resistance against the stretching force. Under tensionless condition, the stretching modulus $\kappa_{str}$ can be calculated via the thermal fluctuation of the membrane area:

$$ \kappa_{str} = \frac{k_BT \langle A \rangle}{\langle A^2 \rangle - \langle A \rangle^2} $$

(14)
where $A$ is the projected area of membrane under constant zero tension. We obtained $\kappa_{str}=157.5$ mN/m from the projected area fluctuation after 1.4 $\mu$s equilibration. The stretching modulus measured in our model is smaller than the experimental value for DPPC [37], which is reported to be $\kappa_{str}=231\pm20$ mN/m.

The line tension (edge energy) opposes the creation of the pore and stabilizes the neat bilayer, which can be calculated by the critical tension for a pore stabilizing inside a membrane [14, 41, 42] or by the stress-strain relation of a bilayer [26, 27, 43]. In this work, we employ a simple method which is similar to the work reported by Wang et al. [22]. Firstly, an equilibrium bilayer of 4608 lipids prepared in a periodic box under constant zero tension. Then, the $y$-direction of the periodic box increases, and the membrane re-equilibrates in NVT ensemble (after 1.5 $\mu$s). Finally, two stable open edges were observed (see Fig.4). The line tension along the $x$-direction is half of the force exerted on the two open edges. Therefore, the simple formula for the line tension can be written as

$$\gamma = -\frac{1}{2} \langle \sigma_{xx} \rangle L_y L_z$$

(15)

where $\sigma_{xx}$ is the $xx$-component of the stress tensor, and $L_y$ and $L_z$ are the lengths of the simulation periodic box in $y$- and $z$-direction, respectively. The value measured in our model is $\gamma=7.2$ pN, which is in the range of experimental results of 6.5–30 pN for phosphatidylcholine bilayer membranes [22, 44–47].

### C. Dynamic simulation and lateral diffusion

The dynamical behaviors of the formation of vesicle should be examined in addition to determining the static structure properties of the DPPC fluid bilayer in our model ($r_m=1.20$ nm and $\varepsilon=2.106qT$). According to the critical packing parameter theory [48], DPPC molecules favor to aggregate into vesicle or flexible bilayer, whose packing parameter equals 0.7 as reported in experiment [49]. When the number of DPPC molecules of a disk-like bilayer is above the critical value of 1553, the vesiculation trend is so strong that any initial lamella will spontaneously curve into a vesicle [8]. Here, a disk-like bilayer consisting of 2048 DPPC molecules was preassembled, and then equilibrated in NVT ensemble.

Figure 5 shows the structural evolution from a disk to a unilamellar vesicle (ULV). The large disk bilayer has to bend in order to reduce the rim energy (see Fig.5 from 0 ns to 322.5 ns) until a cup-like micelle forms at 481.5 ns. The cup-like micelles is an intermediate structure, which closes up and becomes a vesicle ultimately at 648 ns. The simulation result is in agreement with the prediction of both the critical packing parameter theory and the previous work. It indicates that our model can reproduce the self-assembly of DPPC molecules.

A fluid lipid bilayer generally has a larger lateral diffusion constant than a gel phase membrane. The in-plane lateral diffusion of lipids is calculated to measure the dynamics properties of lipid molecules in the present bilayer model. According to Einstein relation [50], the coefficient of lateral diffusion is calculated as follows:

$$4D_{lat} t = \langle |r(t+\tau) - r(\tau)|^2 \rangle$$

(16)

where $D_{lat}$ is the diffusion constant, $\langle |r(t+\tau) - r(\tau)|^2 \rangle$ is the mean square displacement (MSD) of the center of mass at time $t$ averaging all starting time $t_0$. The MSD is calculated by a DPPC bilayer of 2048 lipids in NVT ensemble with periodic boundary conditions.

It is inevitable in the implicit solvent models that a few molecules can fly out of bilayer under the ther-
nal fluctuation. It affects the measurement of the lateral diffusion constant of lipids. Cooke and Deserno checked the suitability of Eq.(16) for implicit solvent models, and concluded that the diffusion coefficient can be measured directly via Eq.(16) without significant influence from lipids flying out of the bilayer [27]. Here, we calculate the diffusion constant in 10 ns averaged by five different time periods under two conditions: removing the stray lipids and including all lipids. The coefficients are 4.0 $\times$ 10$^{-6}$ and 4.1 $\times$ 10$^{-6}$ cm$^2$/s, respectively. The values are approximately equal, which is in agreement with the conclusion of Cooke and Deserno, i.e., the reabsorption of the bilayer and the periodic condition weakens the effect of free diffusion in the gas phase. Then, the lateral diffusion constant is fitted from 1 $\mu$s to 4 $\mu$s for a long time by using Eq.(16) directly and equals 3.925 $\times$ 10$^{-6}$ cm$^2$/s (see Fig.S3 in supplementary material), which is faster by 2 orders of magnitude compared with experimental value of 5$\times$10$^{-8}$ cm$^2$/s at 314 K [51], due to the reduced degrees of freedom in the CG model.

For comparison, the LJ time scale in our model $\tau=\sigma_0(\mu_0/\epsilon_0)^{1/2}=0.62$ ps is calculated, and the lateral diffusion constant can convert to 6.33$\times$10$^{-4}$ $\sigma_0^2/\tau$, which is less than the value of 0.01$\sigma_0^2/\tau$ measured in the Cooke-Deserno model [27], because the CG lipids of our model have two tails which diffuse slower than the linear structure in the Cooke-Deserno model. Compared with the Cooke-Deserno model, the radius distribution profiles of tail beads in our model are more consistent with that in all atomic model [52] (see Fig.S4 in supplementary material). Because the most of biological membrane lipids are two-tailed phospholipids, the present model can better reflect the real structure of most lipids. Based on critical packing theory [48], single-tailed lipids favor to form spherical and rod-like micelles, and two-tailed lipids tend to form bilayers or vesicles, so the present model is consistent with the theory for studying the self-assembly of phospholipids. In addition, the two-tailed model is necessary for studying membrane fusion, because the spaying of lipid tails is essential to form a stalk which is an important intermediate in the fusion process [53].

IV. THE VESICULATION OF LIPID DROPLETS

We investigated the vesiculation of spherical and cylindrical lipid droplets at mesoscale using the present model. The formation of vesicle could be affected by the kinetic pathway, and the initial structure plays a critical role in determining intermediate shape formed in evolution process. Our study is based on currently developed experimental techniques via micro-fluid devices or microsprayer, i.e., ejecting or spraying lipid droplets with different structures. By changing the shapes of the lipid droplets, such as sphere and cylinder with different length-diameters, one can manipulate the structure of vesicle.

First, we selected a large spherical droplet as an initial state. Then multimellar vesicle (MLV) is observed, and the number of layers increases with increasing the size of the spherical droplets. Figure 6 shows the dynamic pathway for the droplet consisting of 1$\times$10$^4$ lipids. During the early period of evolution, the hydrophilic and hydrophobic beads hurriedly separated due to the repulsive interaction between them. The lipids flipped and rearranged quickly in the local region avoiding contacts between the hydrophobic tails and water molecules. Then, a rough layer structure began to appear and the multilayer formed due to the repulsion between the hydrophilic head groups. At 0.09 $\mu$s, an onion-like double-layered vesicle with an internal spherical micelle was observed. As the simulation carried on, the spherical micelle gradually disappeared. At 0.15 $\mu$s, the onion-like vesicle of two bilayers took shape. However, the onion-like vesicle was not of equilibrium state. The lipids slowly diffused from the inner bilayer to the outer bilayer. After dozens of microseconds, when the number of inner vesicle decreased to 500, the small inner vesicle merged into the large outer bilayer and the large outer vesicle became larger. Finally, a ULV formed (the changes of the density distributions of one hydrophobic tail in the process are shown in supplementary material). Unlike the generic vesicle formation, the formation process of ULV includes the aggregation of amphiphilic molecules and the rearrangement of solvophobic and solvophilic parts. Here, the lipid molecules suffer in situ micellization, hence the molecular aggregation disappears, and the rearrangement processes quickly end. An aging process exists in the transformation from MVL to ULV, which will be conducted in our future work.

Then the cylindrical structure as initial state is shown in Fig.7(a), where $R$ is the radius of the bottom sur-
The long cylindrical vesicle formed with a slightly expanded face of the cylinder and $H$ is the cylindrical height. By varying the value of $H/2R$, ULVs and MLVs were also observed in the early stages. When the value of $H/2R$ is close to 1, MLVs can be observed and the number of bilayers increases with the size of lipid droplets (see colored ranges in Fig.7(b)), which is similar to the self-assembly of the spherical droplets. As the droplet consists of $1 \times 10^4$ lipids, the DPPC molecules aggregated into ULVs when $H/2R<0.64$ or $H/2R>1$, and into MLVs when $0.64<H/2R<1$ (see Fig.7(b)). With the size of the droplet increasing, the number of bilayers in MVLs grew and the formation range of MLVs widened (see Fig.7(b)).

Take the system of $1 \times 10^4$ lipids as an example, when $H/2R=0.225$ and $H=10$ nm, the shape evolution starting from a flat cylinder is shown in Fig.8(a). Firstly, the lipid molecules of flat cylinder traveled in situ micellization, and the phase separation occurred between hydrophilic headgroups and hydrophobic tails. Then, a flat vesicle formed (see Fig.8(a), at 0.003 μs). The flat vesicle expanded and formed a biconcave vesicle ranging from 0.105 μs to 0.15 μs. As a metastable, the biconcave vesicle continued to expand, and then, an oblate vesicle was observed at 0.54 μs. As the oblate vesicle did not own enough stability, after a long structural optimization, a spherical vesicle finally formed (see Fig.8(a), at 4.95 μs). Figure 8(b) shows the dynamic pathway linking a long cylinder micelle with a spherical vesicle, where $H/2R=7.14$ and $H=100$ nm. At the early stage, the long cylindrical vesicle formed with a slightly expanded face of the cylinder and $H$ is the cylindrical height.
cylinder micelle is longer than the flat cylinder micelle due to the higher value of the cylindrical height. These two processes are similar and both demonstrate that the spherical vesicle is the equilibrium state regardless of whether it starts from flat or long cylindrical micelle. The result is consistent with the prediction of Helfrich theory of membrane elasticity, i.e., the spherical vesicle with the minimal energy is a stable shape in absence of osmotic pressure and surface tension (the detailed derivation is provided in supplementary material).

V. CONCLUSION

Finding a highly effective CG model for a fluid lipid membrane at mesoscale has always been an important task in the development of molecular simulation technology. In this work, we develop an implicit solvent CG lipid model which reflects the main structure of two-tailed lipids. The model employs a variation MIE potential which shows a broad tail attraction potential for the nonbonded interaction. Through scanning the phase diagram depending on the two critical parameters, this model shows a wide suitability in reproducing the properties of the fluid bilayer membrane. To match the area per lipid, bending modulus, stretching modulus and line tension of DPPC bilayer membrane, the precise parameters are achieved. Through examining the dynamic behavior of phospholipid self-assembly via our CG model, it is revealed that this new model not only reproduces the formation processes of bilayer/vesicle structures but also largely accelerates the processes. The speed-up factor is approximately 1–2 orders of magnitude compared with all atomic model. Furthermore, we use the implicit solvent CG model to study the vesiculation of spherical and cylindrical lipid droplets, and the MLVs and the ULVs are observed. It is shown that MLVs will slowly transform to ULVs and the formation of ULVs depends on the ratio of height to diameter of the cylindrical initial state. The new CG model can be used as a tool in the exploration of the formation and evolution of mesoscale complex vesicles.

Supplementary material: The verification of the CG model, the density distribution of one hydrophobic bead changes with time in the evolution process of MLVs, and the detailed derivation of Helfrich theory of membrane elasticity for oblate and prolate vesicle are given.

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