Molecular modeling of the pathways of vesicle–membrane interaction

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I. ELECTRONIC SUPPLEMENTARY INFORMATION (ESI): METHODS

Dissipative particle dynamics method

The dissipative particle dynamics (DPD) method[1,2] was proved to be especially useful in studying the mesoscale behaviors of lipid membranes. In the DPD method, the total force, $f_{i,}$ exerted on a bead i includes the conservative force (F_{ij}^{C}), dissipative force (F_{ij}^{D}), and random force (F_{ij}^{R}),

$$f_i = \sum_{j \neq i} (F_{ij}^{C} + F_{ij}^{D} + F_{ij}^{R}) \tag{1}$$

The conservative force between beads i and j is determined by

$$F_{ij}^{C} = a_{ij} \hat{\mathbf{r}}_{ij} \max\left\{1 - r_{ij} / r_c, 0\right\} \tag{2}$$

where a_{ij} is the maximum interaction strength, $\mathrm{r}_{ij}=\mathrm{r}_j-\mathrm{r}_i$ (r_i and r_j are the positions of beads i and j), $r_{ij}=|\mathrm{r}_{ij}|$, $\hat{\mathbf{r}}_{ij} = \mathrm{r}_{ij}/|\mathrm{r}_{ij}|$, and r_c is the interaction range.

In the model of lipids, the interaction representing the bond potential between neighboring beads was described by a harmonic spring force,

$$F_S = K_S (r_{ij} - r_{eq}) \hat{\boldsymbol{r}}_{ij} \tag{3}$$

where K_S is the spring constant and r_{eq} is the equilibrium bond length. The numerical values of K_S and r_{eq} used for our simulations are $128 k_{\mathrm{B}} T$ and $0.7 r_{\mathrm{c}}$, respectively, with k_B the Boltzmann constant. The force constraining the variation of bond angles, is given by

$$F_{\varphi} = -\nabla U_{\varphi} \quad \text{and} \quad U_{\phi} = K_{\phi}(1-\cos(\phi-\phi_0)) \tag{4}$$

where ϕ_0 is set to π and the bond bending force constant K_{ϕ} is set to 10.0. Although some atomistic details are sacrificed in this coarse-graining procedure, the essential thermodynamics of the system is reproduced by the simulation model and the parameter set.[1, 2, 3]

As usual, we have chosen the interaction cutoff r_c, the bead mass m, and the thermostat temperature k_BT to unity. To convert r_c to its realistic physical size, we used the formula proposed by Groot and Rabone,[4] r_c=3.107$(\rho N_m)^{1/3}$[$\mathring{A}$], with N_m the number of water beads and ρ the density (the number of DPD beads in a unit volume of r_c^3). In this work, we set N_m=3, ρ=3.0 and a water molecule having a volume of 30 cubic Angstroms, and accordingly, we obtain r_c=6.46 Angstroms. Hence, our simulation box of 80×80×50 corresponds to 51.7nm×51.7nm×32.3nm. Because the temperature control of the DPD thermostat is degraded for large time steps, we used a time step of 0.02, for which the Groot-Warren integrator has been shown to be as accurate as more complicated, self-consistent schemes, and for which the temperature drift is less than 1% for all our simulations. Besides, both dissipative and random force was shown to act as a thermostat that keeps the system's kinetic temperature at a constant average value.

N-varied DPD method

To simulate the interaction between cellular membrane and elastic vesicles, in this work, the N-varied DPD simulation method,[5,6] a particular variant of DPD method, was used to control the membrane tension. In this method the targeted membrane tension is controlled by adjusting the number of lipids per area (LNPA) in the membrane boundary region. The boundary region of the membrane, which surrounds the central square region of the membrane, plays a role as a reservoir of lipids.[6] The value of LNPA in the boundary region is kept to remain in a defined range

($\rho_{LNPA}^{min} < \rho_{LNPA} < \rho_{LNPA}^{max}$) by addition/deletion moves of lipid. In an addition move, new lipid molecules are inserted into the boundary region if the local area density is less than ρ_{LNPA}^{min}. Conversely, if the average area density of lipids in the boundary region exceeds ρ_{LNPA}^{max}, a few lipid molecules should be deleted randomly from the boundary region. Simultaneously, a corresponding number of water beads is randomly added or deleted to keep the whole density of the beads in the simulation box constant (3 beads per unit volume). In practice, we performed one addition/deletion move every 1500 time steps in order to leave enough time for the propagation of membrane tension.

Interaction parameters

In order to reproduce the structure and thermodynamic behavior of the pure system of DMPC bilayer,[3] the interaction parameters between beads of the same type were set to $a_{WW} = a_{HH} = 25$ and $a_{TT} = 15$, and those between the different types of beads were $a_{TW} = 80$, $a_{HT} = 50$, and $a_{HW} = 25$. Note that in DPD simulation method, all interactions are repulsive. If an interaction parameter in our simulation system is larger than 25 (the water-water interaction), the corresponding interaction can be effectively regarded as repulsive. On the other hand, if the interaction parameter is smaller than 25, the corresponding interaction is effectively attractive.

Except the ligand-receptor interaction, interaction parameters associated with receptors (R) were set to the same as those for lipids in the membrane, and those for ligands (L) were set to the same as lipids in the vesicles. To represent the ligand-receptor interaction, the head groups of ligands in vesicles (L_H) show a strong attraction with that of the membrane receptors (R_H), and the interaction parameter $a_{L_H R_H}$ can be varied to represent different strengths of vesicle-membrane adhesion. In addition, the interaction between hydrophobic tail of lipids in vesicle (V_T) and that of lipids in membrane, a_{TV_T}, can also be varied to represent qualitatively the attractive ($a_{TV_T} = 15$) or effectively repulsive ($a_{TV_T} = 80$) interaction, which is caused by the

molecular difference between membrane lipids and vesicle lipids. In Table S1 we list all interaction parameters used in this work.

Table S1 Interaction parameters used in our simulation.

	W	H	T	R_H	R_T	V_H	V_T	L_H	L_T
W	25	25	80	25	80	15	80	15	80
H	25	25	50	25	50	25	50	25	50
T	80	50	15	50	15	80	15-80	80	15-80
R_H	25	25	50	25	50	25	50	0.0-4.0	50
R_T	80	50	15	50	15	80	15-80	80	15-80
V_H	15	25	80	25	80	35	80	35	80
V_T	80	50	15-80	50	15-80	80	25	80	25
L_H	15	25	80	0.0-4.0	80	35	80	35	80
L_T	80	50	15-80	50	15-80	80	25	80	25

II. ESI: FIGURES AND DISCUSSION

Effects of the simulation box size

In order to study effects of the simulation box size (finite size effects), we also simulated a soft vesicle adsorbing on a smaller lipid membrane (60×60), and compared its endocytosis process with that adsorbed on the larger membrane (80×80) studied in the text. Note that except the membrane size, other parameters were set to the same for the two cases. Both typical snapshots and time evolution of wrapping extent and that of ellipsoidal parameter are given in Fig. S1.

In general, for the two cases the membrane-vesicle interaction achieves nearly the same trend for vesicle endocytosis (see Fig. S1). However, a detailed analysis of Fig. S1 shows that there exists a subtle difference between the two cases. According to the time evolution of wrapping percentage (Fig. S1B), the vesicle seems to be wrapped more efficiently by the larger membrane. Besides, both typical snapshots (Fig. S1A)

and time evolution of ellipsoidal parameter (Fig. S1C) also confirm this trend. This observation can be ascribed to the fact that the small size of membrane patch not only constrains the membrane fluctuation, and but also increase effectively the energy cost to bend the membrane. Therefore, we infer that in real cellular systems, a less negative membrane tension may be sufficient for the endocytosis of vesicles because the larger membrane size and much longer endocytic time are available.

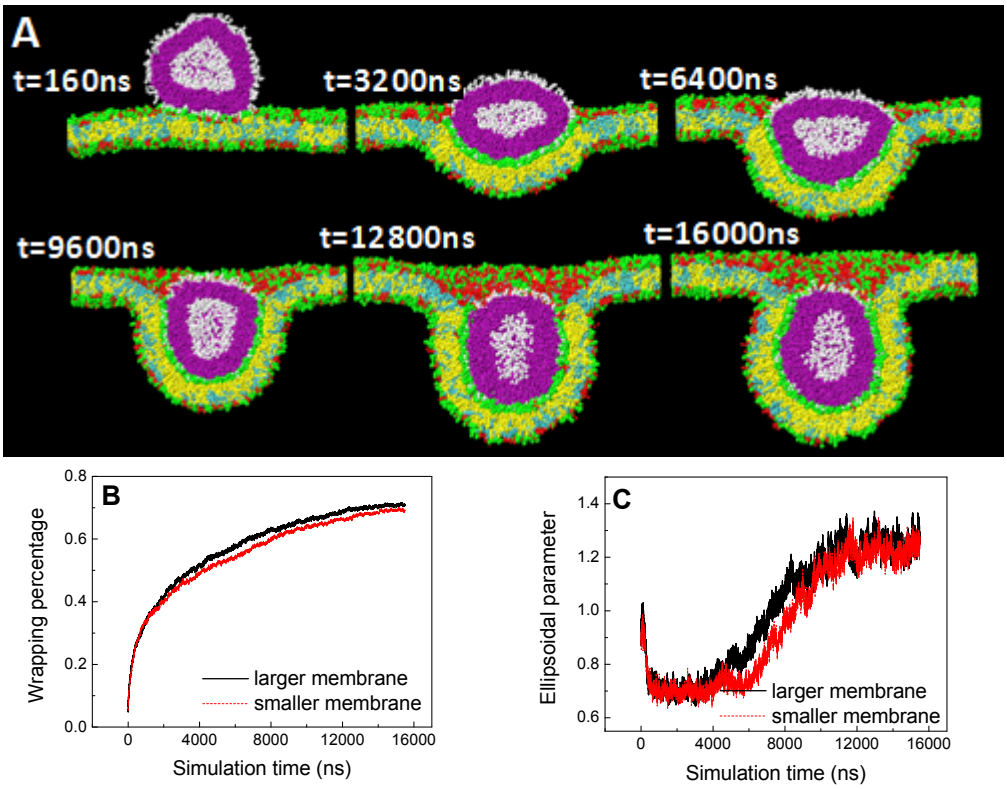

Fig. S1 Time sequence of snapshots for a typical process of receptor-mediated endocytosis of a vesicle adhering on a smaller membrane (60×60) (A), and corresponding evolution of the wrapping percentage (B) and that of the ellipsoidal parameter (C). In B and C, the evolution of wrapping percentage and ellipsoidal parameter of the vesicle adhering on a larger membrane (80×80) is also given for comparison. In this figure the receptor density is set to 50% under the condition of $a_{L_H R_H}$ =4.0 and ρ_{LNPA}=1.68. Color code for the snapshots is the same as in Fig. 1A of the text.

Effects of line tension

It is noteworthy that the line tension between vesicle and planar membrane plays an important role in the vesicle-membrane interaction. Especially it dominates the self-adjustment of the vesicle shape during vesicle endocytosis processes. In vesicle endocytosis and rupture processes, there exists a one-dimensional contact line at the boundary of three phases (water phase, vesicle phase, and planar membrane phase), as shown in Fig. S2. As the vesicle wrapping proceeds, undoubtedly, the length of the contact line first increases before half the vesicle is wrapped by the membrane, after which the length gradually decreases (Fig. S2).

Note that line tension is usually defined as the force operating in the three-phase contact line, or alternatively, as the free energy per unit length of the contact line. Therefore, qualitatively, the sign of line tension is first negative, and then gradually turns to be positive.

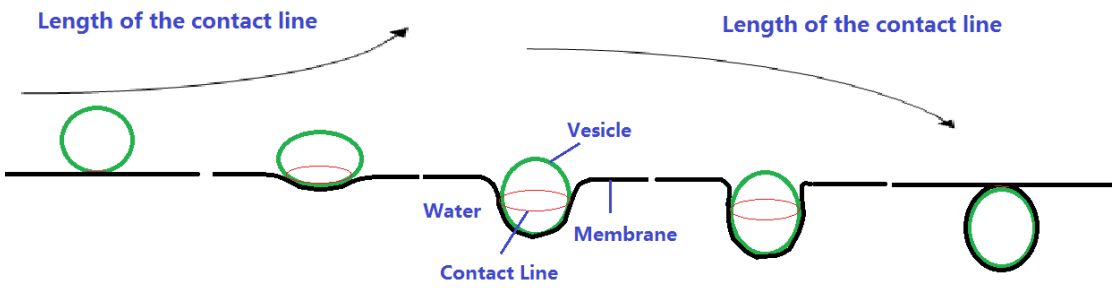

Fig. S2 Schematic representation of the evolution of contact line as the vesicle endocytosis proceeds.

References

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