Free Energy Analysis of Vesicle-to-Bicelle Transformation – Supplementary Information –

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1 Derivation of Eqs. (8) and (9)

To derive Eqs.(8) and (9), we consider the volume of a (hemi)spherical slice with a constant thickness of *t*. The volume, V_C , is assumed to be constant during the operation to open the vesicle using a conical bias potential. Using $\rho(\theta)$, which is the outer radius of the spherical volume, V_C is calculated by integration of a volume element in spherical coordinates;

$$V_C = \int_0^{2\pi} d\psi \int_{\theta}^{\pi} d\phi \int_{\rho(\theta)-t}^{\rho(\theta)} dr r^2 \sin\phi$$

= $\frac{2}{3}\pi \left\{ \rho(\theta)^3 - (\rho(\theta) - t)^3 \right\} (1 + \cos\theta)$ (S1)

Thus, Eq.(9) was derived. Without a conical bias potential, i.e., $\theta = 0$, V_C is simply

$$V_C = \frac{4}{3}\pi \left\{ \rho(0)^3 - (\rho(0) - t)^3 \right\},$$
(S2)

and $\rho(0)$ is the outer radius of the closed spherical slice (the hydrophobic core of the closed vesicle).

Now we consider the center of mass (COM) of the (hemi)spherical slice to obtain $Z_C(\theta)$. The *z* value of an arbitrary point in the (hemi)spherical slice is written by using spherical coordinates as;

$$z = Z_C(\theta) + r\cos\phi \tag{S3}$$

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Assuming a homogeneous density over the (hemi)spherical slice, we can write the COM of the hemispherical slice,

Ż, as

$$\bar{Z} = \frac{\int_{0}^{2\pi} d\Psi \int_{\theta}^{\pi} d\phi \int_{\rho(\theta)-t}^{\rho(\theta)} drr^{2} \sin\phi(Z_{C}(\theta) + r\cos\phi)}{\int_{0}^{2\pi} d\Psi \int_{\theta}^{\pi} d\phi \int_{\rho(\theta)-t}^{\rho(\theta)} drr^{2} \sin\phi} \\
= \frac{\int_{0}^{2\pi} d\Psi \int_{\theta}^{\pi} d\phi \int_{\rho(\theta)-t}^{\rho(\theta)} drr^{2} \sin\phi(Z_{C}(\theta) + r\cos\phi)}{V_{C}} \\
= Z_{C}(\theta) + \frac{\pi}{4V_{C}} (\cos^{2}\theta - 1) \left\{ \rho(\theta)^{4} - (\rho(\theta) - t)^{4} \right\}.$$
(S4)

Since the COM is constrained to the origin, $\overline{Z} = 0$. Thus, we obtain

$$Z_{C}(\theta) = -\frac{\pi}{4V_{C}}(\cos^{2}\theta - 1)\left\{\rho(\theta)^{4} - (\rho(\theta) - t)^{4}\right\}$$
$$= \frac{\pi}{4V_{C}}\sin^{2}\theta\left\{\rho(\theta)^{4} - (\rho(\theta) - t)^{4}\right\}$$
(S5)

Thus, we obtain Eq. (8).

2 Free energy computation

To demonstrate here that the choice of force constant of the bias wall potential does not affect the computed free energy, we plot in Figure S1 the pore formation free energy in the flat membrane using cylinder bias potential. When we use the softer wall potential, we have a larger difference of the actual pore size of lipid membrane \mathcal{R} from the radius of cylinder potential \mathcal{R} . $\mathcal{R} - \mathcal{R}$ was about 0.1 nm for $k = 100 \text{ kcal/mol/Å}^3$ though it was about 0.02 nm for $k = 1000 \text{ kcal/mol/Å}^3$. As seen from Fig 1, the free energy cost calculated for the pore formation is identical regardless of the force constant used.

On the other hand, we usually simulate the flat membrane system in a 3-dimensional periodic boundary condition. Since we simulate the tension-free membrane using the NPT ensemble, by opening the pore in the flat membrane, the simulation box should be expanded laterally. At the same time, the simulation box should shrink in the normal direction of membrane to maintain the hydrostatic pressure. Because the membrane thickness is not largely changed due



Figure S1 Comparative plots of pore formation free energy in the flat DMPC membrane using two different force constants for the cylindrical bias wall potential.

to this box deformation, the inter-bilayer distance, *i.e.*, the thickness of water slab between membranes, is shortened during the pore opening operation. Figure S2 compares the pore formation free energies of the flat DMPC membrane using two different water contents. For the lower water content, which corresponds to the saturated water content in multi-stacking membrane, the free energy curve deviates from the linear slope. This suggests that the calculated free energy involves additional contribution other than the line tension term. Actually, with this water content, the distance of the neighboring periodic images of membrane is too short to ignore the energy contribution from the direct interaction. Of course, by using a thick enough water slab as shown in Fig. 3 (a), the energy contribution between the bilayers become negligible.

It may be valuable to give comments on the previous reports of the pore formation free energy in the planar membranes.^{1–4} Wang and Frenkel studied the pore formation free energy of the membrane under tension using the umbrella sampling technique.¹ The advantage of this method is that no assumption is needed for the shape of the pore in the membrane. The line tension was successfully evaluated by a fitting of the free energy curve that was obtained for a system described by an implicit-solvent simple model. However, the estimation of the pore size seems to be highly sensitive to the definition of the pore and may be more difficult to be used for a finer grained (e.g., all-atom)



Figure S2 Comparative plots of pore formation free energy in the flat DMPC membrane with two different water contents.



Figure S3 Snapshots of flat DMPC membranes with two different water contents when the pore radius of 4 nm. Left panel: the system is composed of 1152 DMPC and 33057 water CG particles, and right panel: 1152 DMPC and 10215 water CG particles. Blue line denotes the simulation box. Small red dots are water particles.

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model. The free energy method proposed by the group of den Otter and Briels is the thermodynamic integration, which is the same as the present study. The major difference is the choice of the reaction coordinate to control the pore size. Using the reaction coordinate defined in Ref. [2-4], one can measure the negative mean force (negative gradient of the free energy) as growing the pore size, though it was not detected in the actual calculation of the model membranes. Our method, in contrast, measures the mean force to the cylindrical repulsive wall, assuming the positive free energy gradient (the pore growth in the membrane always costs the free energy), which is true for the membrane under zero tension. However, the simple choice of the bias potential is useful to evaluate the line tension accurately and can easily be extended for the conical bias potential to evaluate the pore formation free energy of the closed vesicle as shown in the present paper.

References

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