REVIEW

Challenges in the theoretical investigations of lipid membrane configurations*

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We report some key results in the theoretical investigations of configurations of lipid membranes and present several challenges in this field, which involve (i) the exact solutions to the shape equation of lipid vesicles, (ii) the exact solutions to the governing equations of open lipid membranes, (iii) the neck condition of two-phase vesicles in the budding state, (iv) the nonlocal theory of membrane elasticity, and (v) the relationship between the symmetry and the magnitude of the free energy.

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1. Introduction

Biological membranes are the basic elements of cells and cellular organelles. A membrane consists of a lipid bilayer mosaicked with a variety of proteins. As model systems, lipid bilayer membranes are the leading research objects in the field of membrane biophysics.[1] Due to the large aspect ratio between the lateral dimension and the thickness as well as the small compressibility, a lipid membrane is usually regarded as an incompressible elastic thin film in mechanics and a smooth surface in mathematics when we study its large scale behaviors. The geometry of the surface can be determined by its mean curvature and Gaussian curvature, while the equilibrium configuration of a membrane corresponds to the local minimum of the free energy. The bending energy contributes most to the free energy, which usually takes Helfrich's form[2]

$$f_{\mathrm{H}} = \frac{k_{\mathrm{c}}}{2}(2H + c_0)^2 + \bar{k}K, \tag{1}$$

where k_{c} and $\bar{k}$ are two bending rigidities, k_{c} should be positive while $\bar{k}$ can be negative or positive for lipid membranes, H and K represent the local mean curvature and the Gaussian curvature of the membrane surface, respectively, and c_0 is called the spontaneous curvature which reflects the asymmetry of the lipid distribution or other chemical or physical factors between the two leaves of lipid bilayers. Since the spontaneous curvature model can also be obtained from the symmetric argument for 2-dimensional (2D) isotropic elastic entities, it is of generic significance not only for lipid membranes, but also for other membranes consisting of 2D isotropic materials such as carbon nanotubes and graphene.[3]

Based on Helfrich's spontaneous curvature model, the equilibrium configurations of lipid vesicles have been intensively investigated in the past forty years.[4–8] Instead of fully presenting the previous theoretical advances in this field, we will propose five challenges according to these theoretical advances and the author's personal views in this review. We will briefly mention some theoretical advances when interpreting these challenges. The rest of this review is organized as follows. In Section 2, we present the shape equation to describe the equilibrium configurations of lipid vesicles. Then we show some analytic solutions and their corresponding configurations including a sphere, torus, biconcave discoid, and so on. It is a big challenge to find other solutions to the shape equation. In Section 3, we present the governing equations to describe the equilibrium configurations of the open lipid membranes and verify a theorem of non-existence. Here two challenges are respectively related to the minimal surfaces with a boundary curve and neck condition of two-phase vesicles in the budding state. In Section 4, we discuss the nonlocal theory of membrane elasticity, which is beyond Helfrich's model. We can still derive a governing equation to describe the configurations of vesicles. It is a big challenge to seek possible analytic solutions to the governing equation. In Section 5, we investigate the relationship between the symmetry and the magnitude of the free energy and show the conditions with which the higher symmetric configurations correspond to the lower free energy within the framework of Helfrich's model. In the last section, we summarize the challenges and call on physicists and mathematicians to overcome these challenges.

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2. Solutions to the shape equation of lipid vesicles

Here we will discuss the configurations of lipid vesicles composed of uniformly distributed lipids.

2.1. Shape equation

Since experiments have revealed that the area of a lipid membrane is almost incompressible and the membrane is impermeable for solutions at both sides of the membrane, the equilibrium configuration of a lipid vesicle is expected to correspond to the local minimal of the extended Helfrich free energy

$$F_{\rm H} = \int \left[\frac{k_{\rm c}}{2}(2H + c_0)^2 + \bar{k}K\right] {\rm d}A + \lambda A + pV, \tag{2}$$

where the integral is taken over the whole membrane surface of the vesicle, A and V represent the total area of the membrane surface and the volume enclosed in the vesicle, respectively. The λ and p are two Lagrange multipliers which constrain constants A and V when the vesicle takes various possible configurations. They can be physically understood as the apparent surface tension and the osmotic pressure (pressure difference between the outside and the inside) of the lipid vesicle, respectively.

Minimizing the free energy in the configuration space corresponds to a variational problem. The first order variation of the free energy (2) leads to the shape equation[9,10] of the vesicle, which reads

$$\tilde{p} - 2\tilde{\lambda}H + (2H + c_0)(2H^2 - c_0 H - 2K) + \nabla^2(2H) = 0, \tag{3}$$

with reduced parameters $\tilde{p} = p/k_{\rm c}$ and $\tilde{\lambda} = \lambda/k_{\rm c}$. In physics, this formula represents the force balance along the normal direction of the membrane surface.

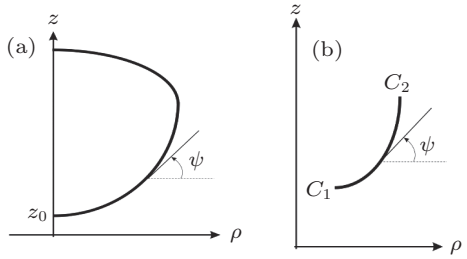


Fig. 1. Generation curves for (a) an axisymmetric vesicle and (b) an open membrane.

Consider an axisymmetric vesicle generated by the planar curve shown in Fig. 1(a). The ψ is the angle between the tangent of the generation curve and the horizontal plane, with which the shape equation (3) can be transformed into[11,12]

$$\tilde{p} + \tilde{\lambda}h + (c_0 - h)\left(\frac{h^2}{2} + \frac{c_0 h}{2} - 2K\right)$$

$$- \frac{\cos\psi}{\rho}(\rho\cos\psi h')' = 0, \tag{4}$$

where $h \equiv \sin\psi/\rho + (\sin\psi)'$ and $K = \sin\psi(\sin\psi)'/\rho$. The $'$ represents the derivative with respect to ρ. The shape equation (4) of the axisymmetric vesicle is a third-order differential equation. Zheng and Liu[13] found the first integral η_0 for this equation and then transformed it into a second-order differential equation

$$\cos\psi h' + (h - c_0)\sin\psi\psi' - \tilde{\lambda}\tan\psi + \frac{2\eta_0 - \tilde{p}\rho^2}{2\rho\cos\psi} - \frac{\tan\psi}{2}(h - c_0)^2 = 0. \tag{5}$$

It is found that the present shape equation of the axisymmetric vesicle degenerates into the form derived by Seifert *et al.*[14] when $\eta_0 = 0$ in Eq. (5), which holds for vesicles with spherical topology free from singular points.[15]

2.2. Typical solutions

Up to date, we have found several analytic solutions to shape equations (3) or (5). They correspond to surfaces of constant mean curvature (including spherical, cylinder, and unduloid), torus, biconcave discoid, unduloid-like surfaces, cylinder-like surfaces, and so on.[6,16–23] Among them, only the sphere, torus, and biconcave discoid are closed configurations which can be sketched as follows.

Firstly, let us consider a spherical surface with radius R, then $H = -1/R$ and $K = 1/R^2$. Substituting them into Eq. (3), we derive

$$\tilde{p}R^2 + 2\tilde{\lambda}R - c_0(2 - c_0 R) = 0. \tag{6}$$

Under proper conditions, the parameters c_0, $\tilde{p}$, and $\tilde{\lambda}$ take proper values, then the solution to the above equation exists.

Secondly, the torus shown in Fig. 2 is a revolution surface generated by a circle with radius r rotating around an axis in the same plane of the circle. The revolving radius R should be larger than r. The generation curve can be expressed as[6,24]

$$\sin\psi = (\rho/r) - (R/r). \tag{7}$$

Substituting it into Eq. (5), we arrive at $R/r = \sqrt{2}$, $2\tilde{\lambda}r = c_0(4 - c_0 r)$, $\tilde{p}r^2 = -2c_0$, and $\eta_0 = -1/r \neq 0$.

Thirdly, for $0 < c_0\rho_{\rm B} < {\rm e}$, the parameter equation

$$\begin{cases} \sin\psi = c_0\rho\ln(\rho/\rho_{\rm B}), \\ z = z_0 + \int_0^\rho \tan\psi d\rho \end{cases} \tag{8}$$

corresponds to the planar curve shown in Fig. 2. Substituting it into Eq. (5), we have $\tilde{p} = 0$, $\tilde{\lambda} = 0$, and $\eta_0 = -2c_0 \neq 0$. That is, a biconcave discoid generated by revolving this planar curve around the z axis can satisfy the shape equation of vesicles. This result can give a good explanation for the shape of human red blood cells under normal physiological conditions.[25,26]

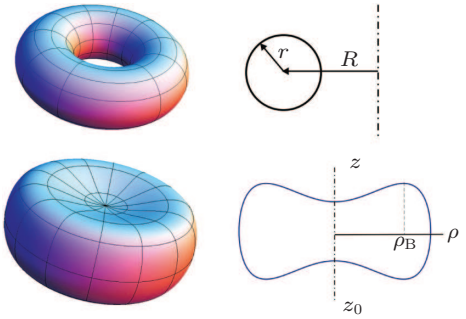


Fig. 2. (color online) Torus and biconcave discoid as well as their generation curves.

It is necessary to point out that the inverted catenoid[27] is also a closed surface satisfying the shape equation. However, the poles of this surface contact tightly with each other, which is not permitted by real physical systems.

2.3. Challenge

Can we find some other analytic solutions to shape equations (3) or (5) which represent closed vesicles without self-contact? Under certain conditions, equation (5) can be extremely simplified. Considering $h = \sin\psi/\rho + (\sin\psi)'$, we chose a new variable

$$\xi = \frac{\sin\psi}{\rho} + \frac{\mathrm{d}(\sin\psi)}{\mathrm{d}\rho} - c_0, \tag{9}$$

then equation (5) can be expressed in a very concise form

$$\frac{\mathrm{d}}{\mathrm{d}\rho}\left(\frac{\cos\psi}{\xi}\right) + \frac{\tan\psi}{2} = 0 \tag{10}$$

when $\tilde{\lambda}$, $\tilde{p}$, and η_0 are vanishing. It might be much easier to find solutions to Eqs. (9) and (10). However, it is still a challenge to find the solutions to these equations.

On the other hand, we need to consider other probabilities if all our efforts are in vain. Among closed non-intersect surfaces, probably only a sphere, torus, and biconcave discoid can satisfy the shape equation and be expressed as the elementary functions. It is also valuable to make this negative proposition verifiable or falsifiable.

3. Solutions to the governing equations of open lipid membranes

Here we will discuss configurations of open lipid membranes composed of uniformly distributed lipids.

3.1. Governing equations

As shown in Fig. 3, a lipid membrane with a free edge can be expressed as an open smooth surface with a boundary curve C in geometry. Because the freely exposed edge is energetically unfavorable, we assign the line tension (energy cost per unit length) to be $\gamma > 0$. Then the free energy to minimize can be expressed as

$$F_O = \int \left[\frac{k_c}{2}(2H + c_0)^2 + \bar{k}K\right] \mathrm{d}A + \lambda A + \gamma L, \tag{11}$$

where L is the total length of the free edge.

By using the variational method, the shape equation

$$(2H + c_0)(2H^2 - c_0 H - 2K) - 2\tilde{\lambda}H + \nabla^2(2H) = 0, \tag{12}$$

and three boundary conditions

$$\left[(2H + c_0) + \tilde{k}\kappa_n\right]_C = 0, \tag{13}$$

$$\left[-2\partial H/\partial \boldsymbol{b} + \tilde{\gamma}\kappa_n + \tilde{k}\dot{\tau}_g\right]_C = 0, \tag{14}$$

$$\left[(1/2)(2H + c_0)^2 + \tilde{k}K + \tilde{\lambda} + \tilde{\gamma}\kappa_g\right]_C = 0 \tag{15}$$

are derived.[28,29] Here $\tilde{k} \equiv \bar{k}/k_c$ and $\tilde{\gamma} \equiv \gamma/k_c$ are the reduced bending modulus and the reduced line tension, respectively, κ_n, κ_g, and τ_g are the normal curvature, the geodesic curvature, and the geodesic torsion of the boundary curve, respectively, and the $\cdot$ represents the derivative with respect to the arc length of the edge. Equation (12) expresses the normal force balance of the membrane, while equations (13)–(15) represent the force and the moment balances at each point in curve C.[30,31] Thus, in general, the above four equations are independent of each other and available for an open membrane with several edges.

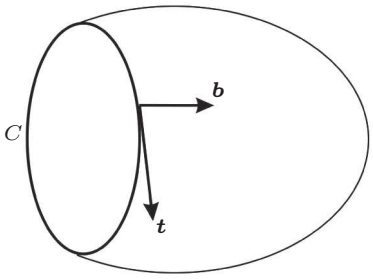


Fig. 3. An open smooth surface with boundary curve C. For a point in C, $\boldsymbol{t}$ and $\boldsymbol{b}$ are located in the tangent plane of the surface, respectively. The former is the tangent vector of C, while the latter is perpendicular to $\boldsymbol{t}$ and points to the side in which the surface is located.

An axisymmetric surface can be generated by a planar curve C_1C_2 revolving around an axis, as shown in Fig. (1b). Equations (12)–(15) can be simplified as[29,31]

$$(h - c_0)\left(\frac{h^2}{2} + \frac{c_0 h}{2} - 2K\right) - \tilde{\lambda}h + \frac{\cos\psi}{\rho}(\rho\cos\psi h')' = 0, \tag{16}$$

$$\left[h - c_0 + \tilde{k}\sin\psi/\rho\right]_C = 0, \tag{17}$$

$$\left[-\sigma\cos\psi h' + \tilde{\gamma}\sin\psi/\rho\right]_C = 0, \tag{18}$$

$$\left[\frac{1}{2}(h - c_0)^2 + \tilde{k}K + \tilde{\lambda} - \sigma\tilde{\gamma}\frac{\cos\psi}{\rho}\right]_C = 0, \tag{19}$$

where C represents the edge point C_1 or C_2, and $\sigma = 1$ (-1) if the tangent vector $\boldsymbol{t}$ of the boundary curve is parallel (antiparallel) to the rotation direction.

Similar to that in the above section, shape equation (16) is integrable, which can be reduced to a second-order differential equation

$$\cos\psi h' + (h-c_0)\sin\psi\psi' - \tilde{\lambda}\tan\psi + \frac{\eta_0}{\rho\cos\psi} - \frac{\tan\psi}{2}(h-c_0)^2 = 0 \quad (20)$$

with an integral constant η_0.[32] The configuration of an axisymmetric open lipid membrane should satisfy shape equation (20) and boundary conditions (17)–(19). In particular, the points in the boundary curve should satisfy not only the boundary conditions but also the shape equation (20) because they also locate in the surface. That is, equation (17)–(20) should be compatible with each other in the edge. Substituting Eqs. (17)–(19) into Eq. (20), we derive the compatibility condition[32]

$$\eta_0 = 0. \quad (21)$$

Under this condition, the shape equation is reduced to

$$\cos\psi h' + (h-c_0)\sin\psi\psi' - \tilde{\lambda}\tan\psi - \frac{\tan\psi}{2}(h-c_0)^2 = 0, \quad (22)$$

while the three boundary conditions are reduced to two equations, i.e., Eqs. (17) and (19).

3.2. Finding solutions: mission impossible

Now our task is to find analytic solutions that satisfy both the shape equation and the boundary conditions. An obvious but trivial one is a planar circular disk with radius R. In this case, equation (12)–(15) degenerate into

$$\tilde{\lambda}R + \tilde{\gamma} = 0. \quad (23)$$

Can we find nontrivial analytic solutions? We have found some analytic solutions that satisfy the shape equation (12), which include surfaces with constant mean curvature, biconcave discoid, torus, and invert catenoid. Can we find a closed curve on these surfaces that satisfies the boundary conditions (13)–(15)? We will prove the following theorem of nonexistence: for finite line tension, there is no open membrane that is a part of surfaces with constant (non-vanishing) mean curvature, biconcave discoid (valid for axisymmetric case), or Willmore surfaces (torus, invert catenoid). Several typical impossible open membranes with free edges are shown in Fig. 4.

The original version of this theorem was proposed in Refs. [7] and [23]. Here we refine the proof of this theorem and correct some flaws.

Firstly, it is easy to prove that there is no open membrane that is a part of a spherical vesicle or cylindrical surface. The details are neglected here, as they can be found in Ref. [7]. We emphasize that the key obstacle lies in boundary condition (14) which implies that the out-of-plane forces cannot balance in the edge.

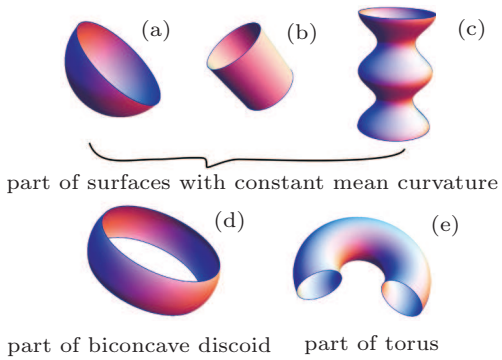


Fig. 4. (color online) Schematics of several impossible open membranes with free edges: parts of (a) sphere, (b) cylinder, (c) unduloid, (d) biconcave discoid, and (e) torus.

Secondly, we derive the second compatibility condition rather than Eq. (21). Let us consider the scaling transformation $\boldsymbol{r} \to (1+\varepsilon)\boldsymbol{r}$, where vector $\boldsymbol{r}$ represents the position of each point in the membrane and ε is a small parameter.[7,30,32] Under this transformation, we have $A \to (1+\varepsilon)^2 A$, $L \to (1+\varepsilon)L$, $H \to (1+\varepsilon)^{-1}H$, and $K \to (1+\varepsilon)^{-2}K$. Thus the free energy (11) is transformed into $F_O(\varepsilon)$. The equilibrium configuration should satisfy $\partial F_O/\partial\varepsilon = 0$, from which we obtain the second compatibility condition

$$2c_0\int H\mathrm{d}A + (2\tilde{\lambda} + c_0^2)A + \tilde{\gamma}L = 0. \quad (24)$$

Thirdly, we prove that there is no open membrane being a part of a curved surface with non-vanishing constant mean curvature. From shape equation (12), we derive $H = -c_0/2 \neq 0$ and $\tilde{\lambda} = 0$ in this case, which contradict the compatibility condition (24) for $\gamma \neq 0$.

Fourthly, we prove that there is no axisymmetric open membrane that is part of a biconcave discodal surface generated by a planar curve expressed by $\sin\psi = c_0\rho\ln(\rho/\rho_B)$. Substituting this equation into shape equation (20), we obtain $\tilde{\lambda} = 0$ and $\eta_0 = -2c_0 \neq 0$ which contradicts the compatibility condition (21).

Finally, we consider the Willmore surface[33] which satisfies the special form of Eq. (12) with vanishing $\tilde{\lambda}$ and c_0. Thus the compatibility condition (24) cannot be satisfied when $\tilde{\lambda} = 0$ and $c_0 = 0$ because $\tilde{\gamma}L > 0$. That is, there is no open membrane that is a part of the Willmore surface which includes a torus and inverted catenoid.

Up to now, we have proven the theorem of non-existence, which implies that it is hopeless to find analytic solutions to the shape equation and the boundary conditions of open lipid membranes. Thus numerical simulations[32,34] are highly appreciated.

3.3. Challenges

Now we will discuss how we can further develop the above results on open lipid membranes.

3.3.1. Minimal surface with boundary curve

Carefully analyzing the above theorem and its proof, we find that the minimal surface ($H = 0$) is not touched. In fact, when $c_0 = 0$, $H = 0$ with non-vanishing $\tilde{\lambda}$ can also satisfy the shape equation (12). Additionally, provided that $\tilde{\lambda} < 0$, the minimal surface is consistent with compatibility condition (24).

On the one hand, if $\tilde{k}$ is vanishing, boundary condition (13) holds naturally. Boundary condition (14) suggests $\kappa_n = 0$. Further, boundary condition (15) requires $\kappa_g = -\tilde{\lambda}/\tilde{\gamma} =$ constant.

On the other hand, if $\tilde{k} \neq 0$, boundary condition (13) gives $\kappa_n = 0$. Then boundary condition (14) suggests $\tau_g =$ constant. Since the classical differential geometry tells us $K = -\tau_g^2$ when $\kappa_n = 0$, boundary condition (15) still requires $\kappa_g =$ constant.

In short, the big challenge is whether we can find a closed curve with vanishing normal curvature and constant geodesic curvature on some minimal surfaces except the planar circular disk.

3.3.2. Neck condition of two-phase vesicles in the budding state

The governing equations of open lipid membranes can be extended to a lipid vesicle with two phases separated by a boundary curve C as shown in Fig. 5.

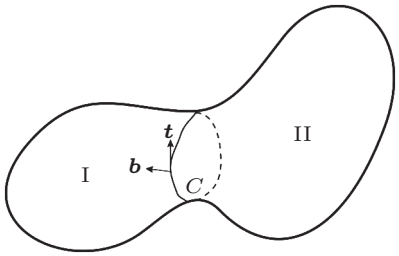


Fig. 5. A vesicle with two phases (I and II) separated by curve C. Here $\boldsymbol{t}$ and $\boldsymbol{b}$ are located in the tangent plane of the surface, the former is the tangent vector of C, while the latter is perpendicular to $\boldsymbol{t}$ and points to the side of phase I.

The free energy of the two-phase vesicle can be expressed as

$$\begin{aligned} F_T = & \int_I \left[\frac{k_c^I}{2}(2H + c_0^I)^2 + \bar{k}^I K\right] dA \\ & + \int_{II} \left[\frac{k_c^{II}}{2}(2H + c_0^{II})^2 + \bar{k}^{II} K\right] dA \\ & + \lambda^I A^I + \lambda^{II} A^{II} + pV + \gamma L, \end{aligned} \tag{25}$$

where the superscripts indicate the mechanical parameters for each phase, for example, c_0^I and c_0^{II} are the spontaneous curvatures for phases I and II, respectively.

Usually, we can derive the matching conditions satisfied by curve C from the variation of the above free energy. But noticing that the physical meanings of Eqs. (13)–(15) are the force and the moment balances in the boundary, we can directly write the matching conditions as follows:[31]

$$\left[k_c^I(2H + c_0^I) - k_c^{II}(2H + c_0^{II}) + (\bar{k}^I - \bar{k}^{II})\kappa_n\right]_C = 0, \tag{26}$$

$$\left[\gamma\kappa_n + (\bar{k}^I - \bar{k}^{II})\dot{\tau}_g - 2(k_c^I - k_c^{II})\partial H/\partial \boldsymbol{b}\right]_C = 0, \tag{27}$$

$$\begin{aligned} & \left[\frac{k_c^I}{2}(2H + c_0^I)^2 - \frac{k_c^{II}}{2}(2H + c_0^{II})^2 \right. \\ & \left. + (\bar{k}^I - \bar{k}^{II})K + (\lambda^I - \lambda^{II}) + \gamma\kappa_g\right]_C = 0. \end{aligned} \tag{28}$$

We note that Das *et al.* also obtained an equivalent form of the above matching conditions in the axisymmetric case.[35]

Jülicher and Lipowsky investigated the budding of axisymmetric vesicles and found a limit shape which is the state of two vesicles connected by a small neck. They also derived the neck condition[5,36]

$$k_c^I M^I + k_c^{II} M^{II} = \frac{1}{2}\left[k_c^I c_0^I + k_c^{II} c_0^{II} + \gamma\right] \tag{29}$$

without considering the Gaussian bending terms. Here M^I and M^{II} correspond to $-H^I$ and $-H^{II}$ for the points nearby the neck in domains I and II, respectively. They also conjectured that this neck condition held for the asymmetric case and claimed the lack of a general proof to this conjecture.[1] It is not straightforward to drive the neck condition from the general matching conditions (26)–(28), which is a challenge to be solved in forthcoming years.

4. Nonlocal theory of membrane elasticity

There are two kinds of nonlocal theory of membrane elasticity. One is the area-difference elasticity, the other is the elasticity of membrane with nonlocal interactions between different points.

4.1. Area-difference elasticity

Since it is very difficult for lipid molecules to flip from one leaf to the other,[37] when the membrane is bent from the planar configuration, the area of per lipid molecule in one leaf should be larger than the equilibrium value while that in another leaf should be smaller than the equilibrium value. Considering the in-plane stretching or compression in each leaf, a nonlocal term $(k_r/2)(\int 2H dA)^2$ might be added to the free energy of membranes.[38,39] Here $k_r = k_a t^2/2A_0$ with k_a and t being the compression modulus and the thickness of the monolayer, respectively, and A_0 is the prescribed area of the membrane. Considering this term, we might express the free energy of the vesicle as

$$F_{AD} = \int \left[\frac{k_c}{2}(2H + c_0)^2 + \bar{k}K\right] dA$$

$$+\lambda A + pV + \frac{k_r}{2}\left(\int 2H\mathrm{d}A\right)^2. \quad (30)$$

Similarly, if the membrane is initially curved with (spontaneous) relative area difference a_0, the nonlocal term $(k_r/2)(\int 2H\mathrm{d}A + a_0)^2$ might be included in the free energy after the membrane is deformed.[40] Thus the free energy of the vesicle can be expressed as

$$F_{ADE} = \int\left[\frac{k_c}{2}(2H+c_0)^2 + \bar{k}K\right]\mathrm{d}A + \lambda A + pV + \frac{k_r}{2}\left(\int 2H\mathrm{d}A + a_0\right)^2. \quad (31)$$

In fact, if we make transformations $C_0 = c_0 + a_0 k_r/k_c$ and $\Lambda = \lambda + a_0^2 k_r/2A_0 - k_r a_c c_0 - k_r^2 a_0^2/2k_c$, the above free energy is transformed into the form of Eq. (30). Thus it is sufficient for us to consider the free energy (30). The budding transitions of axisymmetric fluid-bilayer vesicles have been fully investigated on the basis of area difference elasticity.[40] It is still necessary to discuss the general cases without the presumption of axisymmetry.

4.2. Membrane with nonlocal interactions

Some lipid molecules contain charged head groups, thus molecules in different regions of a membrane can interact with each other when two regions get close to each other. Intuitively, the free energy can be expressed as

$$F_{\mathrm{nint}} = \int\left[\frac{k_c}{2}(2H+c_0)^2 + \bar{k}K\right]\mathrm{d}A + \lambda A + pV + \varepsilon\int\mathrm{d}A\int\mathrm{d}A' U(|\boldsymbol{r}-\boldsymbol{r}'|), \quad (32)$$

where $\boldsymbol{r}$ and $\boldsymbol{r}'$ represent the position vectors of different points in the membrane surface, $\mathrm{d}A$ and $\mathrm{d}A'$ are the area elements corresponding to points $\boldsymbol{r}$ and $\boldsymbol{r}'$, respectively, H and K are the local mean curvature and the Gaussian curvature at point $\boldsymbol{r}$, respectively, and ε and U represent the energy scale and the function form of the nonlocal interactions, respectively.

Interestingly, we have proved that the Helfrich bending energy (1) with vanishing c_0 can be applicable to the bending of graphene.[3,41,42] If $U(|\boldsymbol{r}-\boldsymbol{r}'|)$ is the Van der Waals-like interaction, the relative large camber arch[43,44] in the edges of a bilayer graphene might be understood on the basis of free energy (32) without osmotic pressure.

4.3. Challenges

Now we will discuss how we can further develop the above two nonlocal theories.

4.3.1. Shape equation and its solutions based on area-difference elasticity

According to the variational method developed in our previous work,[3,29,31] the shape equation of vesicles, which corresponds to the Euler–Lagrange equation of free energy (30), can be derived as

$$\tilde{p} - 2\quad \tilde{\lambda}H + (2H+c_0)(2H^2 - c_0H - 2K) + \nabla^2(2H) - 4\tilde{k}_r K\int H\mathrm{d}A = 0 \quad (33)$$

with reduced parameters $\tilde{p} = p/k_c$, $\tilde{\lambda} = \lambda/k_c$, and $\tilde{k}_r = k_r/k_c$. This is a fourth-order nonlinearly integro-differential equation, so it is hard to find exact solutions to this equation.

Obviously, a sphere is a solution to Eq. 33) which requires the radius R of the sphere satisfying

$$\tilde{p}R^2 - (2\tilde{\lambda} + 16\pi\tilde{k}_r)R - c_0(2 - c_0R) = 0. \quad (34)$$

Comparing this equation with Eq. (6), we find that the nonlocal term has effect on the surface tension.

To check the other axisymmetric solutions, we adopt the representation shown in Fig. 1. In this representation, $2H = -h = -[\sin\psi/\rho + (\sin\psi)']$, $K = \sin\psi(\sin\psi)'/\rho$, $\nabla^2(2H) = -(\rho\cos\psi h')'\cos\psi/\rho$, and $\mathrm{d}A = 2\pi|\sec\psi|\rho\mathrm{d}\rho$. Thus equation (33) is transformed into

$$\tilde{p} + \tilde{\lambda}h + (c_0 - h)\left(\frac{h^2}{2} + \frac{c_0h}{2} - 2K\right) - \frac{\cos\psi}{\rho}(\rho\cos\psi h')' + 4\pi\tilde{k}_r\left(\int h|\sec\psi|\rho\mathrm{d}\rho\right)K = 0. \quad (35)$$

It is necessary to note that the integral in the above equation is done on the minimal generation curve for the axisymmetric surface.

A torus can be generated by the planar curve expressed by Eq. (7). Substituting it into Eq. (35), we still derive $R/r = \sqrt{2}$, while $2\tilde{\lambda}r = c_0(4 - c_0r) - 16\sqrt{2}\pi^2\tilde{k}_r r$ and $\tilde{p}r^2 = 8\sqrt{2}\pi^2\tilde{k}_r r - 2c_0$. That is, the torus with ratio of two generation radii being $\sqrt{2}$ is also the solution to the shape equation of vesicles within the framework of area-difference elasticity.

Now we check the biconcave surface generated by planar curve $\sin\psi = \alpha\rho\ln(\rho/\rho_B)$. We find that equation (35) is satisfied when $\tilde{p} = 0$, $\tilde{\lambda} = (\alpha^2 - c_0^2)/2$, $\alpha = c_0 - \tilde{k}_r(4\pi|z_0| + \alpha A_0)$, where z_0 is the the coordinate of the pole shown in Fig. 2, and A_0 represents the total area of the membrane. That is, the biconcave surface generated by the planar curve is also the solution to the shape equation of vesicles within the framework of area-difference elasticity. Here the only difference is $\alpha \neq c_0$ when we consider the area-difference elasticity.

The above three examples imply that the shape equations of vesicles with and without consideration of the area-difference elasticity share the same forms of solutions. Now we will verify this proposition. Let us assume $c_0 = \bar{c}_0 - 2\tilde{k}_r\int H\mathrm{d}A$, then equation (33) is transformed into

$$\tilde{p} - 2\bar{\lambda}H + (2H+\bar{c}_0)(2H^2 - \bar{c}_0H - 2K) + \nabla^2(2H) = 0, \quad (36)$$

where $\bar{\lambda} = \tilde{\lambda} + (c_0^2 - \bar{c}_0^2)/2$. The above equation has the same form as Eq. (3), so the solutions to both equations have the

same forms. Therefore, the challenge here is the same as that in Subsection 2.3.

4.3.2. Shape equation and its solutions based on elasticity of membrane with nonlocal interactions

According to the variational method developed in our previous work,[3,29,31] the shape equation of vesicles which corresponds to the Euler–Lagrange equation of free energy (32) can be derived as

$$\tilde{p} - 2\tilde{\lambda}H + (2H + c_0)(2H^2 - c_0 H - 2K) + \nabla^2(2H) + 2\tilde{\varepsilon}\int (U_{\boldsymbol{n}} - 2HU)\mathrm{d}A' = 0, \tag{37}$$

where $\tilde{\varepsilon} \equiv \varepsilon/k_{\mathrm{c}}$, $U_{\boldsymbol{n}} = (\partial U/\partial R)\hat{R}\cdot\boldsymbol{n}$, $\boldsymbol{R} = \boldsymbol{r}' - \boldsymbol{r}$, $R = |\boldsymbol{R}|$, $\hat{R} = \boldsymbol{R}/R$, $U = U(R)$, $\mathrm{d}A'$ represents the area element at point $\boldsymbol{r}'$, and H, K, and $\boldsymbol{n}$ represent the mean curvature, the Gaussian curvature, and the normal vector of the membrane at point $\boldsymbol{r}$, respectively.

Since nonlocal term $\int(U_{\boldsymbol{n}} - 2HU)\mathrm{d}A'$ depends on vector $\boldsymbol{r}$ for a given function form of U, this term is equivalent to a nonuniform pressure applied on the membrane. The sphere is an obvious solution to Eq. (37) because nonlocal term $\int(U_{\boldsymbol{n}} - 2HU)\mathrm{d}A'$ gives a constant which corresponds to a uniform pressure. Thus equation (37) still reduces to the same form of Eq. (6), which determines the radius of the sphere. It is quite complicated to find the solutions corresponding to shapes other than a sphere, because the nonlocal term depends not only on the position of point in the membrane surface but also on the function form of U. In particular, presuming U to be of the Van der Waals-like form, can we find some solutions rather than the spherical one?

5. Relationship between symmetry and magnitude of free energy

Lipid vesicles in homogenous phase observed in experiments usually have higher degrees of symmetry such as spherical or axial symmetry.[45] In theoretical research, most vesicles are assumed to be axisymmetrical. Scientists seem to believe that the vesicles have lower free energy if they have higher degrees of symmetry under the same external conditions. To what extent is this insight true?

5.1. Symmetry and broken symmetry viewed from the free energy aspect

There exists some relationships between the symmetry and the free energy of a structure. Let us consider a classic example shown in Fig. 6. An external force f is applied along the axis of a long elastic rod. Assume the centerline of the rod is inextensible, so the only mode of deformation is the deflection of the rod. Assume that the centerline of the bent rod can be regarded as an arc of a circle with radius R. Note that this assumption is not accurate, but it can help us qualitatively and semi-quantitatively understand the main insights. The length of the rod is L, so the corresponding angle made by the arc can be expressed as $\theta = L/R$.

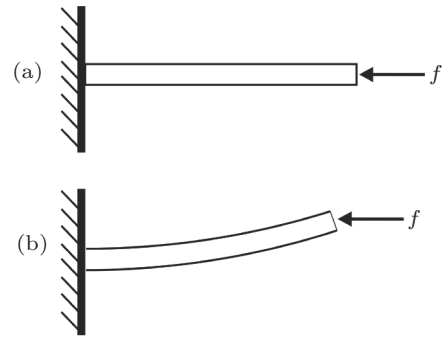


Fig. 6. Schematic diagrams of the broken symmetry of a rod: (a) straight conformation, (b) bent conformation.

The free energy of the system can be expressed as[46]

$$F_r = \frac{k_{\mathrm{b}}}{L}\frac{\theta^2}{2} - fL\left(1 - \frac{2}{\theta}\sin\frac{\theta}{2}\right), \tag{38}$$

where k_{b} is the bending rigidity of the rod. From $\partial F_r/\partial\theta = 0$, we have

$$\theta^3 + \bar{f}\left(\theta\cos\frac{\theta}{2} - 2\sin\frac{\theta}{2}\right) = 0, \tag{39}$$

where $\bar{f} \equiv fL^2/k_{\mathrm{b}}$ is the reduced force. We numerically solve the above equation, and find the bifurcate behavior of the solutions which is shown in Fig. 7. There is only one solution ($\theta^* = 0$, the solid line) when $\bar{f} < 12$ while two solutions ($\theta^* = 0$, the dashed line; $\theta^* > 0$, the solid line) when $\bar{f} > 12$.

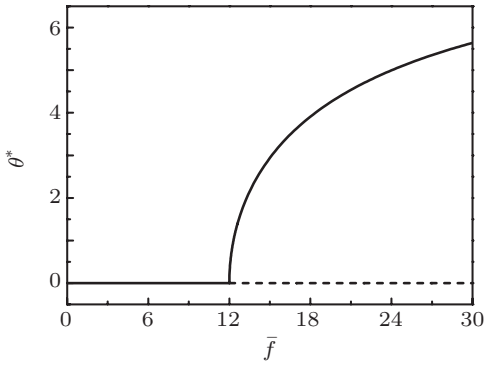


Fig. 7. Numerical solutions to Eq. (39) for various values of $\bar{f}$. There is only one solution ($\theta^* = 0$, the solid line) when $\bar{f} < 12$ while two solutions ($\theta^* = 0$, the dashed line; $\theta^* > 0$, the solid line) when $\bar{f} > 12$.

The solution $\theta^* = 0$ corresponds to the straight configuration, while $\theta^* > 0$ represents the bent configuration. Which one is favored by the lower free energy? In Fig. 8, we draw the typical diagrams of the relation between the reduced free energy $F_r L/k_{\mathrm{b}}$ and the angle θ for $\bar{f} < 12$ and $\bar{f} > 12$ respectively. We readily see that there is only one stationary point at $\theta^* = 0$ which makes $\mathrm{d}F_r/\mathrm{d}\theta = 0$ when $\bar{f} < 12$, and this point also makes the free energy take the minimum value. On the other hand, when $\bar{f} > 12$, there are two stationary points

which make $dF_r/d\theta = 0$. One point is located at $\theta^* = 0$ which corresponds to a local maximum of the free energy; the other point is located at $\theta^* > 0$ which corresponds to another local minimum of the free energy. In particular, the latter point is favored due to its lower free energy when $\bar{f} > 12$. Based on the above analysis, we find that the bent configuration (with lower symmetry) is favored in free energy for larger compression forces while the straight one (with higher symmetry) is favored for smaller compression forces. Of course, in the extreme case, the straight configuration (with higher symmetry) is always favored in free energy for stretching forces. Thus there is a certain relationship between the symmetry and the free energy under specific conditions.

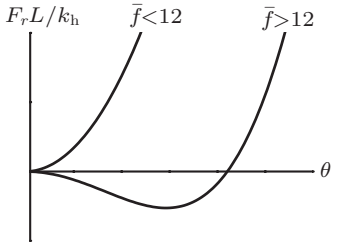


Fig. 8. Typical diagrams of the relationship between reduced free energy F_rL/k_b and angle θ.

5.2. Challenge—a conjecture

In fact, the experimental results[45] also reveal that there is a certain relationship between the symmetry and the free energy of a vesicle. Under a lower osmotic pressure, the biconcave discoidal vesicle is of axial symmetry. Under a higher osmotic pressure, the vesicle is transformed into triangle-like (C_3 symmetry) or even into other nonsymmetric shapes. Combining these experimental observations and the analysis on an elastic rod, we conjecture that for a given area, the vesicle topologically equivalent to sphere with higher symmetry corresponds to the lower Helfrich free energy (2) if the osmotic pressure is small enough.

We can verify this conjecture for a nearly spherical vesicle with zero excess area and a small excess volume.[6] A spherical vesicle with radius R can be expressed in vector form $R\hat{R}$, where $\hat{R}$ represents the unit radial vector. The nearly spherical vesicle can be expressed as $\boldsymbol{r} = R[1 + \sum_{lm} a_{lm} Y_{lm}(\theta,\phi)]\hat{R}$ with $|a_{lm}| \ll 1$, where $Y_{lm}(\theta,\phi)$ is the spherical harmonics satisfying $Y_{00} = 1/\sqrt{4\pi}$ and $\nabla^2 Y_{lm} = -l(l+1)Y_{lm}$. Then the excess area up to the second-order term of a_{lm} can be expressed as

$$\begin{aligned} A_{\rm ex} &= A_{\rm vesicle} - A_{\rm sphere} \\ &= 4\sqrt{\pi}a_{00}R^2 + \frac{1}{2}\sum_{lm}[l(l+1)+2]|a_{lm}|^2R^2 = 0. \end{aligned} \quad (40)$$

Similarly, the excess volume can be expressed as

$$V_{\rm ex} = V_{\rm vesicle} - V_{\rm sphere} = 2\sqrt{\pi}a_{00}R^3 + R^3\sum_{lm}|a_{lm}|^2. \quad (41)$$

The bending energy can be expressed as

$$\begin{aligned} F_{\rm c} &= 2\pi k_{\rm c}(2-c_0R)^2 - 2k_{\rm c}\sqrt{\pi}a_{00}c_0R(2-c_0R) \\ &\quad + \frac{k_{\rm c}}{2}\sum_{lm}|a_{lm}|^2[l^2(l+1)^2 - l(l+1) \\ &\quad \times (2 + 2c_0R - c_0^2R^2/2) + c_0^2R^2]. \end{aligned} \quad (42)$$

Then the Helfrich free energy can be expressed as $F = F_{\rm c} + \lambda(4\pi R^2 + A_{ex}) + p(4\pi R^3/3 + V_{ex})$. When $|a_{lm}| \ll 1$, minimizing F with respect to a_{00}, we derive $\lambda = k_{\rm c}c_0(2-c_0R)/2R - pR/2$. Substituting it into the expression of F, we obtain

$$\begin{aligned} F &= F_{\rm sphere} + \frac{k_{\rm c}}{2}\sum_{lm}|a_{lm}|^2[l(l+1)-2] \\ &\quad \times [l(l+1) - c_0R - pR^3/2k_{\rm c}], \end{aligned} \quad (43)$$

where $F_{\rm sphere} = 4\pi k_{\rm c}(2-c_0R) - 2\pi pR^3/3$ is the free energy of the sphere.

The Y_{00} mode cannot be excited separately because of constraint (40). The Y_{1m} mode is trivial, which represents the small translation of the sphere. If $p < 2(6-c_0R)/R^3$, all the excited Y_{lm} modes make $F > F_{\rm sphere}$, i.e., increase the free energy. Thus the spherical shape (the higher symmetry) corresponds to lower free energy among all nearly spherical vesicles. However, it is a big challenge to generally prove this conjecture for a larger excess volume.

6. Conclusion

In the above discussion, we present some key results in the theoretical investigations on the configurations of lipid membranes. We also propose several challenges in this field, which are specifically highlighted again as follows.

Challenge 1 Can we find analytic solutions rather than sphere, torus, and biconcave discoid to the shape equation (3) or (5) which represents closed vesicles without self-contact? An alternative scheme is to find solutions to Eqs. (9) and (10) rather than the original shape equation. If all these efforts are in vain, can we verify among all closed non-intersect surfaces, there are only sphere, torus, and biconcave discoid that can satisfy the shape equation and be expressed as the elementary functions?

Challenge 2 Can we find a closed curve with vanishing normal curvature and constant geodesic curvature on some minimal surfaces except the planar circular disk? Or can we prove that the planar circular disk is the unique minimal surface with boundary curve which has vanishing normal curvature and constant geodesic curvature?

Challenge 3 Can we derive the neck condition (29) from the general matching conditions (26)–(28)?

Challenge 4 Can we find solutions rather than the spherical shapes to shape equation (37) on the basis of elasticity of membrane with nonlocal Van der Waals-like interactions?

Challenge 5 Can we prove the conjecture that among all vesicles topologically equivalent to sphere, the configuration with higher symmetry corresponds to lower Helfrich free energy (2) if the osmotic pressure is small enough?

Researchers have made fruitful progresses in the field of membrane biophysics since the 1970s. These achievements have also gained much recognition in the scientific community. In 2012, Helfrich was awarded the Charles Stark Draper Prize for the engineering development of the liquid crystal display utilized in billions of consumer and professional devices, and the Raymond and Beverly Sackler International Prize in Biophysics for his contributions to the biophysics of lipid bilayers and biological membranes. Jülicher was awarded the 2007 Raymond and Beverly Sackler International Prize in Biophysics for his seminal contributions to the field of the physics of non-equilibrium bio-cellular systems such as molecular motors, active membranes, filaments, and the cytoskeleton. With the increasing maturity of theoretical investigations on biological membranes, the remaining problems are even more difficult than before. Among them, we believe that the above five challenges are very significant for theoretical investigations on configurations of biological membranes and they are highly expected to be overcome through the collaborations between mathematicians and physicists in the forthcoming years.

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