Some progresses in shape problems following the Helfrich model are reported. Based on
the Helfrich model, we have predicted not only the exact solution for discoidal shape of
red blood cells but also a special kind of toroidal vesicle with the ratio of two generation
radii being $\sqrt{2}$. The Helfrich model can also be extended to investigate the complex
structures in other soft matters such as the formation of focal conic domains in smectic
liquid crystal, the tube-to-sphere transition in peptide nanostructures, and icosahedral
configuration of small virus capsids.

Keywords: Fluid membrane; Helfrich model; application.

PACS numbers: 87.10.-e, 87.16.D-

1. Introduction

The study of shapes of structures stemmed from real bio- and abiotic-materials in
nature gives rise to many nice theories in sciences. The observation of law of constant
angle of crystal planes by Stensen\textsuperscript{1} leads to the Wulff construction\textsuperscript{2} for determining
the equilibrium shape of a crystal with fixed volume inside a separate phase. The
beautiful shapes of soap films observed by Plateau\textsuperscript{3} emerge a “golden age” in the
The investigation on the rise of a liquid in a capillary tube generates Young–Laplace theory on a surface of constant mean curvature. We can only observe spherical soap bubbles because “an embedded surface with constant mean curvature in 3-dimensional (3D) Euclidian space must be a spherical surface”. The bending energy density of a solid shell is taken as the square of the mean curvature, which leads to the Willmore surfaces. However, a long-standing problem in physiology why the red blood cells in human bodies are always in a biconcave discoidal shape has puzzled researchers for more than 100 years. It is Helfrich who pointed the right direction by recognizing that the membrane is in a liquid crystal state. Based on the elastic theory of liquid crystal, he achieved the curvature energy of a lipid bilayer membrane, which leads to a shape equation of lipid vesicles. This equation is called the generalized Young–Laplace equation, and the Helfrich theory is regarded as the renewal of the Poisson’s elastic shell theory. In this review, we will report some progresses of our study following the Helfrich model for 25 years. Based on the Helfrich theory, we can predict not only the exact solution for biconcave discoidal shape of red blood cells but also a special kind of toroidal vesicle with the ratio of two generation radii being $\sqrt{2}$. Especially, the Helfrich model was successfully extended to investigate the complex structures in other soft matters such as the formation of focal conic domains in smectic liquid crystal, the tube-to-sphere transition in peptide nanostructures, and icosahedral configurations of small virus capsids.

2. Helfrich Model and the Shape Equation

Human red blood cells in mature stage have no internal organelles. Thus the physical property of membranes uniquely determines the shape of red blood cells. Normal human red cells at rest are typically of biconcave discoidal shape. Many theoretical models are proposed to explain this fancy configuration. Most of them are unsuccessful because they have not recognized the correct physical state — liquid crystal state of cell membranes. It is the first time that Helfrich recognized cell membranes in the liquid crystal state. By analogy with a bended nematic crystal box shown in Fig. 1, he argued that the curvature energy density of the lipid bilayer membrane could be expressed as:

$$g = \frac{k_c}{2}(2H + c_0)^2 + \bar{k}K,$$

Fig. 1. Analogy: bended liquid crystal box and lipid bilayer membrane.
where \( k_c \) and \( \bar{k} \) are two bending moduli. The measured value of \( k_c \) is about \( 10^{-19} \) J by micropipette. \( H \) and \( K \) are the local mean curvature and Gaussian curvature of the membrane surface, respectively. The parameter \( c_0 \) is called spontaneous curvature which reflects the asymmetry between two leaves of the membrane.

A membrane is thought of as a 2D smooth surface in 3D Euclidean space because its thickness is much smaller than its lateral dimension. The configuration of a vesicle is determined by minimizing the Helfrich curvature energy under the constraints of constant surface area and constant volume enclosed by the vesicle. In other words, we need to calculate the variation of the functional

\[
F_H = \oint g \, dA + \lambda A + pV, \tag{2}
\]

where \( g \) is the density of Helfrich curvature energy in Eq. (1). The symbols \( A \) and \( V \) represent the total area of the membrane surface and the volume enclosed in the vesicle, respectively. \( \lambda \) and \( p \) are two Lagrange multipliers which can be regarded as the apparent surface tension and osmotic pressure of the lipid vesicle. The general Euler–Lagrange equation corresponding to functional (2) reads\(^{11,12}\)

\[
\tilde{p} - 2\bar{\lambda}H + (2H + c_0)(2H^2 - c_0H - 2K) + \nabla^2(2H) = 0, \tag{3}
\]

with reduced osmotic pressure \( \tilde{p} \equiv p/k_c \) and reduced surface tension \( \bar{\lambda} \equiv \lambda/k_c \). \( \nabla^2 \) is the Laplace operator on 2D surface. This equation is called the shape equation of lipid vesicles.

An axisymmetric vesicle can be represented by its contour line which can be parameterized as function \( \psi = \psi(\rho) \) where \( \rho \) represents the rotation radius of some point in the contour line while \( \psi \) is the tangent angle of the contour line at that point. In this representation, shape equation (3) can be further transformed into\(^18\):

\[
\tilde{p} + \bar{\lambda}H + (c_0 - H) \left( \frac{H^2}{2} + \frac{c_0 H}{2} - 2K \right) - \frac{\cos \psi}{\rho} (\rho \cos \psi H')' = 0, \tag{4}
\]

where \( H \equiv \sin \psi/\rho + (\sin \psi)' \) and \( K = \sin \psi(\sin \psi)'/\rho \). The “prime” represents the derivative with respect to \( \rho \). This equation is integrable and may be transformed into a second-order differential equation\(^19\)

\[
\cos \psi H' + (H - c_0) \sin \psi \psi' - \bar{\lambda} \tan \psi + \frac{\eta_0/\rho - \bar{p} \rho/2}{\cos \psi} - \frac{\tan \psi}{2} (H - c_0)^2 = 0 \tag{5}
\]

with the first integral \( \eta_0 \).

3. Analytical Solutions to the Shape Equation

It is found that sphere, torus, and biconcave discoid shown in Fig. 2 are closed configurations satisfying the shape equation (3) or its equivalent form (5).

Firstly, a spherical surface with radius \( R \) can satisfy the shape equation (3) when

\[
\tilde{p} R^2 + 2\bar{\lambda}R - c_0(2 - c_0R) = 0. \tag{6}
\]
Fig. 2. (Color online) Analytical solutions to the shape equation: (a) sphere; (b) torus; (c) biconcave discoid.

Secondly, a torus 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

\[
\sin \psi = \frac{\rho}{r} - \frac{R}{r}.
\]  (7)

Substituting it into Eq. (5), one can arrive at \( R/r = \sqrt{2} \), \( 2\lambda r = c_0(4 - c_0r) \), \( \bar{p}r^2 = -2c_0 \) and \( \eta_0 = -1/r \neq 0 \). That is, there exists a lipid torus with the ratio of its two generation radii being \( \sqrt{2} \), which was confirmed by the experiment.\(^{21}\)

Thirdly, for \( 0 < c_0\rho_B < e \), the parameter equation

\[
\sin \psi = -c_0\rho \ln(\rho/\rho_B)
\]  (8)

corresponds to a biconcave discoidal shape. Substituting it into Eq. (5), we have \( \bar{p} = 0 \), \( \bar{\lambda} = 0 \), and \( \eta_0 = -2c_0 \neq 0 \). This result can give a good explanation to the shape of human red blood cells under normal physiological conditions.\(^{22,23}\) An interesting fact is that the red blood cells seem to take the golden section. In terms of the surface area \( A \) of red blood cells, we can obtain the reduced radius \( R_0 = \sqrt{\frac{A}{4\pi}} \).

Fitting the experimental shapes, we obtain \( c_0R = 1.618 \approx \frac{\sqrt{5} + 1}{2} \). It is still lack of a physical interpretation on this fancy fact.

4. Open Lipid Membranes

The observation\(^{24}\) of opening process of lipid vesicle by talin gives rise to the interest of studying the governing equations of lipid membranes with free exposed edges.\(^{25-29}\)

A lipid membrane with a free edge can be expressed as an open smooth surface with a boundary curve \( C \) in geometry. The free energy that we need to minimize may be expressed as

\[
F = \int g dA + \lambda A + \gamma L,
\]  (9)

where \( L \) and \( \gamma \) are the total length and the line tension of the free edge, respectively. By using the variational method, we can derive the shape equation\(^{27}\)

\[
(2H + c_0)(2H^2 - c_0H - 2K) - 2\lambda H + \nabla^2(2H) = 0,
\]  (10)
Study of Complex Shapes of Fluid Membranes

Fig. 3. (Color online) Impossible open membranes.

and three boundary conditions

\[(2H + c_0) + \tilde{k}\kappa_n][C = 0, \quad (11)
\]

\[-2\partial H/\partial b + \tilde{\gamma}\kappa_n + \tilde{k}\tau_g][C = 0, \quad (12)
\]

\[((1/2)(2H + c_0)^2 + \tilde{k}K + \tilde{\lambda} + \tilde{\gamma}\kappa_g)[C = 0, \quad (13)
\]

where \(\tilde{k} \equiv \bar{k}/k_c\) and \(\tilde{\gamma} \equiv \gamma/k_c\) are the reduced bending modulus, and reduced line tension, respectively. \(\kappa_n\), \(\kappa_g\), and \(\tau_g\) are the normal curvature, geodesic curvature, and geodesic torsion of the boundary curve, respectively. The “dot” represents the derivative with respect to the arc length of the edge. In general, the above four equations are independent of each other and available for an open membrane with several edges.

An obvious but trivial solution to the above equations is a planar circular disk with radius \(R\). In this case, Eqs. (10)–(13) degenerate into

\[\tilde{\lambda}R + \tilde{\gamma} = 0 \quad (14)
\]

when \(c_0 = 0\). We can also prove the following theorem of non-existence\(^{29,30}\): For finite line tension, there does NOT exist an open membrane being 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. 3. Therefore, it is almost hopeless to find analytic solutions to the shape equation and boundary conditions of open lipid membranes.

5. Focal Conic Domains in Smectic Liquid Crystal

Dupin cyclides are always formed when liquid crystal cools from isotropic (Iso) phase to Smectic A (SmA) phase,\(^{31}\) as shown in Fig. 4, this structure is called focal conic domains. It is a puzzle why the cyclides are preferred to other geometrical structures under the preservation of the interlayer spacing.\(^{32}\) The trick is that the relieved energy of the difference in Gibbs free energy of Iso-to-SmA transition must be balanced by the curvature elastic energy of SmA layers.\(^{33,34}\)
Let us consider the outward growth by adding a SmA layer of thickness $d$ on the top of the outermost equilibrium SmA nucleus. The corresponding net increase in the interfacial energy and bulk energy for the SmA domain can be expressed as:

$$\Delta F_A = \gamma \oint (-2dH_o + d^2K_o)\epsilon dA_o,$$

and

$$\Delta F_V = -g_0 \oint [d - d^2H_o + (1/3)d^3K_o]dA_o,$$

respectively, where $H_o$ and $K_o$ are the mean curvature and Gaussian curvature of the outer surface of the equilibrium SmA nucleus, respectively. $\epsilon$ represents the sign of $1 - 2dH_o + d^2K_o$. $\gamma$ is the SmA-Iso interfacial tension. $g_0$ is the difference in the Gibbs free energy densities between the Iso and SmA phases. In addition, the extra growth costs a curvature elastic energy

$$\Delta F_C = (k_1d/2) \oint (2H_o)^2dA_o + k_2d \oint K_o dA_o,$$

where $k_1$ and $k_2$ are two elastic constants of SmA layer. Totally, the net energy for the growth reads

$$\Delta F = - (g_0d^3/3) \oint K_o dA_o + d^2 \oint (g_0H_o + \gamma K_o)dA_o$$

$$+ d \oint (2k_1H_o^2 + k_2K_o - g_0 - 2\gamma H_o)dA_o.$$

The absolute minimum of $\Delta F$ must be located at $d = 0$, requiring that the terms of $d^2$ and $d$ in Eq. (18) are positive and zero, respectively. Thus we obtain the shape equation for the outermost layer of the SmA domain

$$\oint [2k_1H_o^2 + k_2K_o - g_0 - 2\gamma H_o]dA_o = 0,$$

and the stability condition

$$\oint (g_0H_o + \gamma K_o)dA_o > 0.$$
To achieve the shape equation of nucleus (i.e., the innermost layer of the SmA domain), we need to consider the surface energy of the inner and outer SmA-Iso interfaces:

\[ F_A = \gamma \oint [1 + (1 - 2DH + D^2K)\epsilon]dA, \tag{21} \]

the bulk free energy change due to the Iso-to-SmA transition:

\[ F_V = -g_0 \oint [D - D^2H + (1/3)D^3K]dA, \tag{22} \]

and the curvature elastic energy of the SmA domain:

\[ F_C = k_1 \oint \sqrt{H^2 - K} \ln \left( \frac{1 - DH + D\sqrt{H^2 - K}}{1 - DH - D\sqrt{H^2 - K}} \right) dA + (2k_1 + k_2)D \oint KdA, \tag{23} \]

where \( D \) is the thickness of the SmA domain while \( \epsilon \) represents the sign of \( 1 - 2DH + D^2K \). The variation of the total free energy \( F_A + F_V + F_C \) leads to the shape equation of SmA nucleus:

\[
(\nabla^2 H - \nabla^2) \frac{1}{\sqrt{H^2 - K}} \ln \left( \frac{1 - DH + D\sqrt{H^2 - K}}{1 - DH - D\sqrt{H^2 - K}} \right) \\
+ 2D[\nabla^2(H - DK) - \nabla^2(1 - DH)] \frac{1}{1 - DH + D^2K} \\
+ \frac{4D(H^2 - K)(2H - DK)}{1 - DH + D^2K} = \frac{2(2H - DK)(2\gamma - g_0D)}{k_1} = 0. \tag{24} \]

At the early stage of the growth of the SmA domain, \( D \) increases from zero to \( 2\gamma/g_0 \) with decreasing temperature at an optimum cooling rate where \( g_0 \) is temperature dependent. It is reasonable to set \( D = 2\gamma/g_0 \) at a constant temperature in the SmA phase. Since \( D \) is expected to be much smaller than the geometrical size of the nucleus, Eq. (24) is transformed into the Willmore equation:

\[ \nabla^2 H + 2H(H^2 - K) = 0. \tag{25} \]

Clifford torus has the lowest free energy among all genus-1 surfaces admitted by the above equation. In addition, it has been shown that a spherical SmA nucleus is unstable. Thus toroidal nuclei can be regarded as seeds of focal conic domains. Since the ratio of two generation radii of the torus should be \( R/r = \sqrt{2} \), the ratio of two generation radii of the focal conic domains should satisfy

\[ 2 \leq (R + r + D)/(r + D) \leq 1 + \sqrt{2}, \tag{26} \]

which is consistent with the experimental results.
6. Tube-to-Sphere Transition in Peptide Nanostructures

The above consideration can be extended to explain the tube-to-sphere transition in peptide nanostructures induced by concentrating solution only if we regard $g_0$ as the Gibbs free-energy density between the solution (S) and the aggregate (A) phase. The value of $g_0$ is positive and can be estimated with the ideal gas model:

$$g_0 = C_A k_B T \ln \left( \frac{C_A}{C_B} \right),$$

where $C_A$ and $C_S$ are the concentrations of dipeptide in the A and S phases, respectively. $k_B$ is the Boltzman constant, and $T$ is the temperature.

The analysis in the previous section is still available for the growth of peptide nanostructures. The shape of the nanostructures should satisfy Eq. (19). For spherical structure, the radius should be

$$r_0 = \frac{(2k_1 + k_2)}{\sqrt{\gamma^2 + g_0(2k_1 + k_2) - \gamma}}.$$

For tube structure, the radius should be

$$\rho_0 = k_1 / \left[ \sqrt{\gamma^2 + g_0k_1} - \gamma \right].$$

Substituting the above two equations into Eq. (18), we can obtain the formation energies per unit area of a sphere layer and a tube layer, respectively. Comparing them we find the condition for transition from a tube to a spherical vesicle-like structure to be $g_0d > 3\gamma$. Finally, considering Eq. (27), we obtained the critical tube-to-sphere concentration:

$$CTSC = C_A e^{-3\gamma/C_A d k_B T}.$$

Beyond the CTSC, the tube will undergo the process shown in Fig. 5 and transform into a sphere vesicle.

![Fig. 5. Transition series from tube to necklace to sphere.](image)
7. Icosahedral Configurations of Virus Capsids

Small viruses in our planet prefer to the icosahedral configuration. This puzzle was recently solved by combining the Lenosky’s lattice model and Helfrich’s theory. Following Lenosky’s lattice model, Zhou and Ou-Yang derived the leading term of bending energy for polyhedral viral capsids in discrete level:

$$E_{bp} \simeq 2\sqrt{2\pi N_1 \tan(\pi/p)}\beta^2 k_c R/\sqrt{3a},$$

with

$$N_1 = \frac{2pq}{[4 - (p - 2)(q - 2)]}$$

and

$$\beta = \arccos[\cos(\pi/q)/\sin(\pi/p)],$$

where $p$ is the number of vertices or edges of each face while $q$ is the number of edges or faces at each cortex of each polyhedron. $a$ is the subunit spacing while $R \equiv \sqrt{A/4\pi}$ is the effective radius defined by the surface area $A$ of the viral capsid. According to Eq. (31), they found that the icosahedron is more stable among the five symmetric polyhedra shown in Fig. 6.

On the other hand, Lenosky’s lattice model in the continuum limit approaches to the Helfrich’s model without the spontaneous curvature. The bending energy of a spherical capsule can be expressed as:

$$E_{bs} = 4\pi k_c(1 + \nu)$$

with the Poisson ratio $\nu \approx 0.34$. Comparing this equation with Eq. (31), one can achieve the critical radius

$$R_c = \frac{(1 + \nu)a}{\beta^2 \sqrt{\frac{6\pi}{N_1 \tan(\pi/p)}}}.$$  

It is found that the icosahedral configuration ($p = 3$, $q = 5$, $N_1 = 30$ and $\beta = 20^\circ54'$) is more stable than a spherical configuration when $R < R_c \approx 6a$. In other words, the small virus prefers to the icosahedral configuration while the large virus prefers to the spherical configuration, which is consistent with experimental observations on small virus and huge virus.

8. Conclusion

In this review, we have only reported our work on the shape problems following the Helfrich model. Based on this model, we have predicted not only the exact solution for discoidal shapes of red blood cells but also a special kind of toroidal vesicle with
the ratio of two generation radii being $\sqrt{2}$. In addition, we investigate the complex structures in other soft matters such as the formation of focal conic domains in smectic liquid crystal, the tube-to-sphere transition in peptide nanostructures, and icosahedral configurations of virus capsids.

We are very regretted that many beautiful work following the Helfrich model by the other groups are not discussed. To learn them, we suggest the reader further read some comprehensive reviews.44–48

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