Elasticities and stabilities: lipid membranes vs cell membranes

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ABSTRACT

A cell membrane can be simply regarded as composite material consisting of lipid bilayer, membrane cytoskeleton beneath lipid bilayer, and proteins embedded in lipid bilayer and linked with membrane cytoskeleton if one only concerns its mechanical properties. In this Chapter, above all, the authors give a brief introduction to some important work on mechanical properties of lipid bilayers following Helfrich’s seminal work on spontaneous curvature energy of lipid bilayers. Next, the entropy of a polymer confined in a curved surface and the free energy of membrane cytoskeleton are obtained by scaling analysis. It is found that the free energy of cell membranes has the form of the in-plane strain energy plus Helfrich’s curvature energy. The equations to describe equilibrium shapes and in-plane strains of cell membranes by osmotic pressures are obtained by taking the first order variation of the total free energy containing the elastic free energy, the surface tension energy and the term induced by osmotic pressure. The stability of spherical cell membrane is discussed and the critical pressure is found to be much larger than that of spherical lipid bilayer without membrane cytoskeleton. Lastly, the authors try to extend the present static mechanical model of cell membranes to the cell structure dynamics by proposing a group of coupling equations involving tensegrity architecture of cytoskeleton, fluid dynamics of cytoplasm and elasticities of cell membranes.

INTRODUCTION

Cells are the basic elements of living organisms, such as plants and animals. Viewed from structure, an eukaryotic cell consists of cell membrane, cytoplasm, cytoskeleton, nucleus and so on. Cell membrane defines the boundary between the living cell and its environment, including extracellular matrix and liquid
surroundings. Cytoplasm is a kind of viscous fluid. Cytoskeleton is a three-dimensional structure composed of three classes of fibers [1]: microtubules (20 nm in diameter), elements built of polymers of the protein tubulin; microfilaments (7 nm in diameter), built of the protein actin; and intermediate filaments (10 nm in diameter), built of one or more rod-like protein subunits. Nucleus of the eukaryotic cell is enclosed by membrane.

Membranes consist of lipids, proteins and carbohydrates etc. Lipids and proteins are dominant components of membranes. One of the principal types of lipids in membranes is phospholipid. A phospholipid molecule has a polar hydrophilic head group and two hydrophobic hydrocarbon tails. In physical point of view, a lipid molecule can be simply regarded as an amphipathic rod. When a quantity of lipid molecules disperse in water, they will assemble themselves into a bilayer in which the hydrophilic heads shield the hydrophobic tails from the water surroundings because of the hydrophobic forces.

There are many simplified models for cell membranes in history [2]. Among them, the widely accepted one is the fluid mosaic model proposed by Singer and Nicolson in 1972 [3]. In their model, cell membrane is considered as a lipid bilayer where the lipid molecules can move freely in the membrane surface like fluid, while the proteins are embedded in the lipid bilayer. Some proteins are called integral membrane proteins because they traverse entirely in the lipid bilayer and play the role of information and matter communications with both the inside of the cell and its outer environment. The others are called peripheral membrane proteins because they are partially embedded in the bilayer and accomplish the other biological functions. Beneath the lipid membrane, the membrane cytoskeleton, a network of proteins, links with the proteins in lipid membrane.

The first step to study the elasticity of cell membrane is to study lipid bilayer. Usually, the thickness of lipid bilayer is about 4 nanometers which is much less than the scale of the whole lipid bilayer (about several micrometers). Therefore, it is reasonable to describe the lipid bilayer by a mathematical surface. In 1973, Helfrich [4] recognized that the lipid bilayer was just like a nematic liquid crystal at room temperature. Based on the elastic theory of liquid crystal [5], he proposed the curvature energy per unit area of the bilayer

\[ f_c = \left( k_c / 2 \right) \left( 2H + c_0 \right)^2, \]  

where \( k_c \) is an elastic constant; and \( H, c_0 \) are mean curvature and spontaneous curvature of the membrane surface, respectively. In this chapter, Gaussian curvature \( K \) is not written explicitly because only close bilayer is discussed in this chapter. We can safely ignore the thermodynamic fluctuation of the curved bilayer at the room temperature because of \( k_c \approx 10^{-19} J \gg k_B T \) [6, 7], where \( k_B \) is the Boltzmann factor and \( T \) the room temperature. Based on Helfrich’s curvature energy, we can express the free energy of a closed bilayer under the osmotic pressure \( \Delta p \) (the outer pressure minus the inner one) as:

\[ \mathcal{F}_H = \int (f_c + \mu) dA + \Delta p \int dV, \]
where \( dA \) is the area element and \( V \) the volume enclosed by the closed bilayer. \( \mu \) is the surface tension of the bilayer. Based on above free energy, many researchers studied the shapes of bilayers [8–10]. Especially, by taking the first order variation of above free energy and doing the complicated calculations of tensors, Ou-Yang et al. derived an equation to describe the equilibrium shape of the bilayer as [11, 12]:

\[
\Delta p - 2\mu H + k_c(2H + c_0)(2H^2 - c_0H - 2K) + k_c \nabla^2(2H) = 0. \tag{3}
\]

This equation is now called the shape equation of closed membranes or generalized Laplace equation. They also obtained that the threshold pressure for instability of spherical bilayer was \( \Delta p_c \sim k_c/R^3 \), where \( R \) being the radius of spherical bilayer.

Using the shape equation (3) of closed bilayers, Ou-Yang predicted that there was a lipid torus with the ratio of two radii being exactly \( \sqrt{2} \) [13]. His prediction was soon confirmed by the experiments [14–16]. Otherwise, researchers obtained an analytical solution to Eq. (3) which explained the classical problem [17]—the biconcave discoidal shape of normal red cells [18].

Recently, Tu and Ou-Yang have proposed a mathematical scheme to discuss the elasticities and stabilities of cell membranes with membrane cytoskeleton and found that the membrane cytoskeleton enhances the stabilities of cell membranes [19]. But they have omitted the effect of in-plane modes of membranes on the stabilities. In this chapter, we will first retrospect to elasticities and stabilities of lipid bilayers following Helfrich’s seminal work on spontaneous curvature energy of lipid bilayers. Next, we will fully discuss the entropic elasticity of membrane cytoskeleton, as well as the elasticities and stabilities of cell membranes with membrane cytoskeleton. Last, we will expatiate on how to construct the framework of cell structure dynamics involving tensegrity architecture of cell cytoskeleton, fluid dynamics of cytoplasm and elasticities of cell membranes (with membrane cytoskeleton).

**LIPID MEMBRANE**

In this section, we will recur to some main results on elasticities and stabilities of lipid bilayers by adopting the mathematical scheme proposed in Ref. [19–21].

We use a smooth and closed surface \( M \) in 3-dimensional Euclid space \( \mathbb{E}^3 \) to represent a membrane. As shown in Fig. 1 we can construct a right-hand orthonormal system \( \{e_1, e_2, e_3\} \) at any point \( r \) in the surface and call \( \{r; e_1, e_2, e_3\} \) a moving frame. The differential of the frame is denoted by

\[
\begin{align*}
\,d\!r &= \omega_1 e_1 + \omega_2 e_2, \\
\,d\!e_i &= \omega_{ij} e_j \quad (i = 1, 2, 3),
\end{align*}
\]

where \( \omega_1, \omega_2 \) and \( \omega_{ij} = -\omega_{ji} \) \( (i, j = 1, 2, 3) \) are 1-forms. The structure equations of the surface are

\[
d\omega_1 = \omega_{12} \wedge \omega_2; \tag{5}
\]
\[ d\omega_2 = \omega_{21} \wedge \omega_1; \quad (6) \]
\[ \omega_{13} = a\omega_1 + b\omega_2, \quad \omega_{23} = b\omega_1 + c\omega_2; \quad (7) \]
\[ d\omega_{ij} = \omega_{ik} \wedge \omega_{kj} \quad (i, j = 1, 2, 3). \quad (8) \]

Readers should notice that the operator “\(d\)” is an exterior differential operator [19] in this chapter. The area element, mean curvature and Gaussian curvature are respectively expressed as [22]:

\[ dA = \omega_1 \wedge \omega_2, \quad (9) \]
\[ H = (a + c)/2, \quad (10) \]
\[ K = ac - b^2. \quad (11) \]

![Figure 1: Smooth and orientable surface](image)

If \(M\) undergoes an infinitesimal deformation such that every point \(\mathbf{r}\) of \(M\) has a displacement \(\delta\mathbf{r}\), we obtain a new surface \(M' = \{\mathbf{r}'|\mathbf{r}' = \mathbf{r} + \delta\mathbf{r}\}\). \(\delta\mathbf{r}\) is called the variation of surface \(M\) and can be expressed as

\[ \delta\mathbf{r} = \delta_1\mathbf{r} + \delta_2\mathbf{r} + \delta_3\mathbf{r}; \quad (12) \]
\[ \delta_i\mathbf{e}_i = \Omega_{i1}\mathbf{e}_1 + \Omega_{i2}\mathbf{e}_2 + \Omega_{i3}\mathbf{e}_3, \quad (i = 1, 2, 3), \quad (13) \]

where the repeated subindexes do not represent Einstein summation. Due to the deformation of \(M\), \(\mathbf{e}_1, \mathbf{e}_2, \mathbf{e}_3\) also change. We denote the change as

\[ \delta_i\mathbf{e}_i = \Omega_{i1}\mathbf{e}_1 + \Omega_{i2}\mathbf{e}_2 + \Omega_{i3}\mathbf{e}_3, \quad \Omega_{i1} = -\Omega_{1i}. \quad (14) \]

Using the commutativity between \(\delta_i \quad (i = 1, 2, 3)\) and \(d\), we obtain the fundamentally variational identities of the move frame [19]:

\[ \delta_1\omega_1 = d\Omega_1 - \omega_2\Omega_{121}, \quad (15) \]
\[ \delta_1 \omega_2 = \Omega_1 \omega_{12} - \omega_1 \Omega_{112}, \quad (16) \]
\[ \Omega_{113} = a \Omega_1, \quad \Omega_{123} = b \Omega_1; \quad (17) \]
\[ \delta_2 \omega_1 = \Omega_2 \omega_{21} - \omega_2 \Omega_{221}, \quad (18) \]
\[ \delta_2 \omega_2 = d \Omega_2 - \omega_1 \Omega_{212}, \quad (19) \]
\[ \Omega_{213} = b \Omega_2, \quad \Omega_{223} = c \Omega_2; \quad (20) \]
\[ \delta_3 \omega_1 = \Omega_3 \omega_{31} - \omega_2 \Omega_{321}, \quad (21) \]
\[ \delta_3 \omega_2 = \Omega_3 \omega_{32} - \omega_1 \Omega_{312}, \quad (22) \]
\[ d \Omega_3 = \Omega_{313} \omega_1 + \Omega_{323} \omega_2; \quad (23) \]
\[ \delta_i \omega_{ij} = d \Omega_{lij} + \Omega_{lik} \omega_{kj} - \omega_{ik} \Omega_{lkj}. \quad (24) \]

Now we can take the first order variation of functional \( \mathcal{F}_H \) by considering above variational identities \((15)–(24)\) and Stokes theorem. It is not hard to obtain \([19]\):
\[ \delta \mathcal{F}_H = \int [\Delta p - 2\mu H + k_c (2H + c_0) (2H^2 - c_0 H - 2K)] + k_c \nabla^2 (2H) \Omega_3 dA. \quad (25) \]

Thus the Euler-Lagrange equation corresponding to the functional \( \mathcal{F}_H \) reduces to equation \((3)\) because \( \Omega_3 \) is an arbitrary function. Equation \((3)\) describes the equilibrium shapes of lipid membranes.

Similarly, we can obtain the second order variation of functional \( \mathcal{F}_H \):
\[ \delta^2 \mathcal{F}_H = \int \Omega_3 \nabla^2 \Omega_3 \left[ k_c (14H^2 + 2Hc_0 - 4K - c_0^2/2) - \mu \right] dA + k_c \int (\nabla^2 \Omega_3)^2 dA \]
\[ + \int k_c (2H + c_0) \left[ \nabla (2H \Omega_3) \cdot \nabla \Omega_3 - 2 \nabla \Omega_3 \cdot \nabla \Omega_3 - 4 \nabla^3 \Omega_3 \cdot \nabla \Omega_3 \right] dA \]
\[ + \int \Omega_3 [k_c (16H^4 - 20H^2 K + 4K^2 + Kc_0^2) + 2K \mu - 2H \Delta p] dA. \quad (26) \]

The detailed expressions of operators \( \nabla, \tilde{\nabla}, \nabla^2, \nabla \cdot \nabla, \nabla \cdot \tilde{\nabla} \) in above equation can be found in Appendix D of Ref. \([19]\).

Now, we discuss mechanical stability of spherical lipid membrane with radius \( R \). In this case, we have \( H = -1/R \) and \( K = 1/R^2 \). Substituting them into equation \((3)\), we arrive at
\[ \Delta p R^2 + 2 \mu R - k_c c_0 (2 - c_0 R) = 0. \quad (27) \]

Using \( r = R (\sin \theta \cos \phi, \sin \theta \sin \phi, \cos \theta) \) to represent the point in the spherical membrane, we have \( \nabla = -(1/R) \nabla, \nabla \cdot \nabla = -(1/R) \nabla^2 \) and \( \nabla^2 = \frac{1}{R^2 \sin^2 \theta} \frac{\partial^2}{\partial \phi^2} \) Under the condition \((27)\), equation \((26)\) is transformed into
\[ \delta^2 \mathcal{F}_H = (2c_0 k_c/R + \Delta p R) \int_0^\pi \sin \theta d\theta \int_0^{2\pi} d\phi \Omega_3^2. \]
\[
+ (k_c c_0 R + 2k_c + \Delta p R^3 / 2) \int_0^\pi \sin \theta d\theta \int_0^{2\pi} d\phi \Omega_3 \nabla^2 \Omega_3
+ k_c R^2 \int_0^\pi \sin \theta d\theta \int_0^{2\pi} d\phi (\nabla^2 \Omega_3)^2.
\] (28)

Expand \( \Omega_3 \) by the spherical harmonic functions [23]:
\[
\Omega_3 = \sum_{l=0}^{\infty} \sum_{m=-l}^{l} a_{lm} Y_{lm}(\theta, \phi), \quad a_{lm}^* = (-1)^m a_{l,-m}.
\] (29)

If considering \( \nabla^2 Y_{lm} = -l(l+1)Y_{lm}/R^2 \) and \( \int_0^\pi \sin \theta d\theta \int_0^{2\pi} d\phi Y^*_{lm} Y_{l'm'} = \delta_{mm'} \delta_{ll'} \), we transform equation (28) into
\[
\delta^2 F_H = (R/2) \sum_{l,m} |a_{lm}|^2 \{l(l+1) - 2\} \{2k_c / R^3 [l(l+1) - c_0 R] - \Delta p \}.
\] (30)

Obviously, \( \delta^2 F_H \) is a positive definite form if \( \Delta p < p_l \equiv (2k_c / R^3) [l(l+1) - c_0 R] \) \( (l = 2, 3, \cdots) \). Therefore, we can take the critical pressure as
\[
\Delta p_c = \min \{p_l\} = p_2 = (2k_c / R^3)(6 - c_0 R).
\] (31)

If \( \Delta p > \Delta p_c \), the spherical bilayer will be instable and inclined to transform into the biconcave discoid shape.

In this section, we have discussed the elasticity of and stability of lipid bilayer under the pressure. But lipid bilayer is oversimplified model of cell membrane which contains the membrane cytoskeleton. That is, for cell membrane, we must take into account the contribution of membrane cytoskeleton.

**MEMBRANE CYTOSKELETON**

In this section, we will discuss the contribution of membrane cytoskeleton to the free energy of cell membrane. The membrane cytoskeleton is cross-linking chain-like protein structure which can be thought of as a polymer membrane. Now we will derive its free energy by analogy with the polymer membrane [24].

We take de Gennes’ convention [25] in this section: the entropy \( S \) is a dimensionless quantity and Boltzmann factor \( k_B \) is implicated in temperature \( T \). If we regard the protein in membrane cytoskeleton as Gaussian chains [34], its root of mean square end-to-end distance is \( R_0 \sim \sqrt{N b_0} \), where \( b_0 \) is the segment length of protein and \( N \gg 1 \) is the number of segments. Assume that the principal radii of the membrane are much larger than \( R_0 \). If we denote the in-plane strain tensor by \( \epsilon \) which is assumed to be a small quantity, the entropy of the protein chain must be the function of \( 2HR_0, KR_0^2, 2J \) and \( Q \) because entropy is a dimensionless invariable under the transformation of coordinates, where \( H, K, J = \text{tr} \epsilon \) and \( Q = \text{tr} \epsilon \) are the mean curvature, the Gaussian curvature, the trace of strain tensor and the determinant of strain tensor, respectively. Thus
we can expand it as 
\[ S \sim A_1(2HR_0) + A_2(2HR_0)^2 + A_3KR_0^2 + B_2(2J)^2 + B_3Q \] 
up to the second order terms, where \( A_1, A_2, A_3, B_2, B_3 \) are constants. There is no first order term of \( 2J \) in the expression of the entropy because we expect that \( -\epsilon \) plays the same role as \( \epsilon \) in the entropy. It is useful to write the entropy in another equivalent form \( S \sim A_2R_0^2(2H + c_0)^2 + A_3R_0^2K + B_2(2J)^2 + B_3Q \), where \( c_0 \) is a constant called spontaneous curvature and we expect \(|c_0R_0| \ll 1\). Consequently, the elastic free energy per area of a membrane consisting of protein chains has the following form

\[
f = -(Mh)TS = \frac{k_d}{2}((2J)^2 - \nu Q) + \frac{k_d}{2}(2H + c_0)^2 - \bar{k}'K, \tag{32}
\]

where \( h \) is thickness of the membrane, \( M \) the number of protein chains per volume, and \( k_d, \nu, k', \bar{k}' \) are unknown universal constants. Here we neglect the entanglement of proteins. We will show \( k_d = 4MhT \) and \( \nu = 1 \) as follows.

Let us consider an ideal case–the planar membrane with the homogenous in-plane strains. In this case, \( H, K \) and \( c_0 \) are vanishing for planar membrane with symmetry between its two sides. On the one hand, equation (32) is simplified as

\[
f = \frac{k_d}{2}((2J)^2 - \nu Q). \tag{33}
\]

For homogenous stain \( \epsilon \), we can express it by its components \( \epsilon_{11}, \epsilon_{22} \) and \( \epsilon_{12} = \epsilon_{21} = 0 \) in some orthonormal coordinate system so that \( 2J = \epsilon_{11} + \epsilon_{22} \) and \( Q = \epsilon_{11}\epsilon_{22} \).

On the other hand, this structure can be compared with the structure of rubber. In terms of the elasticity theory of rubber [26], the deformation energy of a planar rubber per area can be expressed as \( f_r = (MhT/2)[\lambda_1^2 + \lambda_2^2 + 1/\lambda_1^2\lambda_2^2 - 3] \), where \( \lambda_1 = 1 + \epsilon_{11} \) and \( \lambda_2 = 1 + \epsilon_{22} \) are extensions. For small strains, it is expanded to the lowest order terms as \( f_r \sim 2MhT(\epsilon_{11}^2 + \epsilon_{11}\epsilon_{22} + \epsilon_{22}^2) = 2MhT[(2J)^2 - Q] \). Thus we can obtain \( k_d = 4MhT \) and \( \nu = 1 \) by comparing it with equation (33).

In this section we do not discuss the mechanical property of membrane cytoskeleton alone. We will discuss it with the cell membrane in the next section.

**CELL MEMBRANE WITH MEMBRANE CYTOSKELETON**

The free energy of cell membrane with membrane cytoskeleton is taken as the sum of the free energies of lipid bilayer and membrane cytoskeleton. Thus we write the free energy of cell membrane under the osmotic pressure \( \Delta p \) as:

\[
\mathcal{F} = \int \left( \frac{k_d}{2} \right) ((2J)^2 - Q) dA + \int (k_{c'}/2)(2H + \bar{c}_0)^2 + \mu \] + \Delta p \int dV, \tag{34}
\]

where \( k_c = k_c + k', \bar{c}_0 = k_c c_0 / k_c \), and the term related to the Gaussian curvature disappears because its integration \( \int K dA \) is an unimportant constant so that it is omitted.
Before taking the first order variation of the free energy \(F\), we must introduce the strain analysis expressed by the notation of differential forms [19].

If a point \(r_0\) in a surface undergoing a displacement \(u\) to arrive at point \(r\), we have \(du = dr - dr_0\) and naturally \(\delta u = \delta dr (i = 1, 2, 3)\).

If denote \(dr = \omega_1 e_1 + \omega_2 e_2\) and \(du = U_1 \omega_1 U_2 \omega_2\) with \(|U_1| \ll 1, |U_2| \ll 1\), we can define the in-plane strains [27]:

\[
\begin{align*}
\varepsilon_{11} & = \left[ \frac{du \cdot e_1}{|dr_0|} \right]_{\omega_2 = 0} \approx U_1 \cdot e_1, \quad (35) \\
\varepsilon_{22} & = \left[ \frac{du \cdot e_2}{|dr_0|} \right]_{\omega_1 = 0} \approx U_2 \cdot e_2, \quad (36) \\
\varepsilon_{12} & = \frac{1}{2} \left[ \left( \frac{du \cdot e_2}{|dr_0|} \right)_{\omega_2 = 0} + \left( \frac{du \cdot e_1}{|dr_0|} \right)_{\omega_1 = 0} \right] \approx \frac{1}{2} (U_1 \cdot e_2 + U_2 \cdot e_1). \quad (37)
\end{align*}
\]

Using \(\delta dr = \delta dr\) and the definitions of strains (35 – 37), we can obtain the leading terms of variational relations:

\[
\begin{align*}
\delta_1 \varepsilon_{11} \omega_1 \wedge \omega_2 & = \delta_1 \omega_1 \wedge \omega_2, \quad (38) \\
\delta_1 \varepsilon_{12} \omega_1 \wedge \omega_2 & = \frac{1}{2} [\omega_1 \wedge \delta_1 \omega_1 + \delta_1 \omega_2 \wedge \omega_2], \quad (39) \\
\delta_1 \varepsilon_{22} \omega_1 \wedge \omega_2 & = \omega_1 \wedge \delta_1 \omega_2. \quad (40)
\end{align*}
\]

From equations (15) – (24) and (38) – (40), we have [19]:

\[
\begin{align*}
\delta_1 F & = \int k_d [-d(2J) \wedge \omega_2 - \frac{\varepsilon_{11} \omega_2 - \varepsilon_{12} \omega_1}{2} \cdot d(\varepsilon_{12} \omega_1 + \varepsilon_{22} \omega_2)] d\Omega, \quad (41) \\
\delta_2 F & = \int k_d [d(2J) \wedge \omega_1 - \frac{\varepsilon_{12} \omega_2 - \varepsilon_{22} \omega_1}{2} \cdot d(\varepsilon_{11} \omega_1 + \varepsilon_{12} \omega_2)] d\Omega, \quad (42) \\
\delta_3 F & = \int [\kappa_c (2H + \bar{c}_0) (2H^2 - \bar{c}_0 H - 2K) + \bar{k}c \nabla^2 (2H) \\
& \quad + \Delta p - 2H (\mu + k_d J) - \frac{k_d}{2} (a \varepsilon_1 + b \varepsilon_{12} + c \varepsilon_{22}) d\Omega dA]. \quad (43)
\end{align*}
\]

Thus the Euler-Lagrange equations corresponding to the functional (34) are

\[
\begin{align*}
k_d [-d(2J) \wedge \omega_2 - \frac{1}{2} (\varepsilon_{11} \omega_2 - \varepsilon_{12} \omega_1) + \frac{1}{2} d(\varepsilon_{12} \omega_1 + \varepsilon_{22} \omega_2)] & = 0, \quad (44) \\
k_d [d(2J) \wedge \omega_1 - \frac{1}{2} (\varepsilon_{12} \omega_2 - \varepsilon_{22} \omega_1) - \frac{1}{2} d(\varepsilon_{11} \omega_1 + \varepsilon_{12} \omega_2)] & = 0, \quad (45) \\
\Delta p - 2H (\mu + k_d J) + \bar{k}_c (2H + \bar{c}_0) (2H^2 - \bar{c}_0 H - 2K) + \bar{k}_c \nabla^2 (2H) \\
& - \frac{k_d}{2} (a \varepsilon_1 + b \varepsilon_{12} + c \varepsilon_{22}) & = 0. \quad (46)
\end{align*}
\]

Equations (44) and (45) are called the in-plane strain equations because they describe the in-plane strains of cell membrane under the pressure \(\Delta p\). Equation
where equations (41)–(43) and (47). Eventually, we arrive at (38)–(40), we can calculate $d^2\mathcal{F}$ of exterior differential and Hodge star $\ast$. Here we also consider the contribution of in-plane modes. Due to the notation in-plane strains whose radius satisfies equation (47) for simplicity.

(34). Additionally, we only consider the spherical membrane with uniform in-plane strains over equation (46) degenerates into shape equation (3) of closed lipid bilayers. Generally speaking, it is difficult to find the analytical solutions to equations (44)–(46). But we can verify that $\epsilon_{11} = \epsilon_{22} = \bar{\epsilon}$ (a constant), $\epsilon_{12} = 0$ can satisfy (44)–(46) for a spherical membrane with radius $R$ if the following equation is valid:

$$\Delta p R^2 + (2\mu + 3k_d\bar{\epsilon})R + \bar{k}_c\bar{c}_0(\bar{c}_0 R - 2) = 0. \quad (47)$$

Now we discuss the effect of membrane cytoskeleton on the stability of cell membrane. That is, we will calculate the second order variation of functional $\mathcal{F}$. Additionally, we only consider the spherical membrane with uniform in-plane strains whose radius satisfies equation (47) for simplicity.

In Ref. [19], only the term $\delta_3^2\mathcal{F}$ related to the out-plane mode is calculated. Here we also consider the contribution of in-plane modes. Due to the notation of exterior differential and Hodge star $\ast$, $\Omega_1$ and $\Omega_2$ can be expressed as $\Omega_1 = \omega_1 + \Omega_2\omega_2 = d\Omega + \ast d\chi$ by two scalar functions $\Omega$ and $\chi$. Using equations (41)–(44) and (33)–(36), we can calculate $\delta_1^2\mathcal{F}$, $\delta_2^2\mathcal{F}$, $\delta_3^2\mathcal{F}$, $\delta_1\delta_2\mathcal{F}$, $\delta_1\delta_3\mathcal{F}$, and $\delta_2\delta_3\mathcal{F}$ from equations (31)–(34) and (37). Eventually, we arrive at

$$\delta^2\mathcal{F} = \delta_1^2\mathcal{F} + \delta_2^2\mathcal{F} + \delta_3^2\mathcal{F} + 2\delta_1\delta_2\mathcal{F} + 2\delta_1\delta_3\mathcal{F} + 2\delta_2\delta_3\mathcal{F} \equiv G_1 + G_2, \quad (48)$$

where

$$G_1 = \int \Omega_3^2 \left\{ 3k_d/R^2 + (2\bar{k}_c\bar{c}_0/R^3) + \Delta p/R \right\} dA$$

$$+ \int \Omega_3 \nabla^2\Omega_3 \left\{ \bar{k}_c\bar{c}_0/R + 2\bar{k}_c/R^2 + \Delta p R/2 \right\} dA + \int \bar{k}_c(\nabla^2\Omega_3)^2 dA$$

$$+ \frac{3k_d}{R} \int \Omega_3 \nabla^2\Omega dA + k_d \int (\nabla^2\Omega)^2 dA + \frac{k_d}{2R^2} \int \Omega \nabla^2\Omega dA, \quad (49)$$

$$G_2 = \frac{k_d}{4} \int (\nabla^2\chi)^2 dA + \frac{k_d}{2R^2} \int \chi \nabla^2\chi dA. \quad (50)$$
If we take $\kappa = \bar{k}_c/2$, $K = 3k_d/2$, $\mu = k_d/2$, $w = \Omega_3$ and $\Psi = \Omega$ in equations (6) and (7) of Zhang et al.'s paper [28], then $G_1$ and $G_2$ correspond to $F_1[w, \Psi]$ and $F_2[\chi]$ in that paper under the conditions of $\Delta p = 0$ and $\delta_0 = R = 2$. Obviously, there is no coupling between modes $\{\chi\}$ and $\{\Omega, \Omega_3\}$; but there is coupling between in-plane mode $\{\Omega\}$ and out-of-plane mode $\{\Omega_3\}$. We will show that in-plane modes have quantitative effect on the stability of the cell membrane although they can not qualitatively modify the results of Ref. [19].

Because $G_2$ is obviously positive definite, we merely need to discuss $G_1$, $\Omega_3$ and $\Psi$ in the expression of $G_1$ can be expanded by spherical harmonic functions [23] as $\Omega_3 = \sum_{l=0}^{\infty} \sum_{m=-l}^{l} a_{lm} Y_{lm}(\theta, \phi)$ and $\Psi = \sum_{l=0}^{\infty} \sum_{m=-l}^{l} b_{lm} Y_{lm}(\theta, \phi)$ with $a_{lm} = (-1)^m a_{l,-m}$ and $b_{lm} = (-1)^m b_{l,-m}$. It follows that

$$G_1 = \sum_{l=0}^{\infty} \sum_{m=0}^{l} 2|a_{lm}|^2 \left\{ 3k_d + [l(l+1) - 2](l(l+1)\bar{k}_c/R^2 - \bar{k}_c - \delta_0/R - \Delta p R/2) \right\}$$

$$- \sum_{l=0}^{\infty} \sum_{m=0}^{l} \frac{3k_d}{R} l(l+1)(a_{lm}^* b_{lm} + a_{lm} b_{lm}^*)$$

$$+ \sum_{l=0}^{\infty} \sum_{m=0}^{l} \frac{k_d}{R} \left[ 2l^2(l+1)^2 - l(l+1) \right] |b_{lm}|^2.$$

We find that if $\Delta p < p_1 = \frac{3k_d}{2l(l+1)-1} + \frac{2k_c[l(l+1)-\delta_0 R]}{R^2} \quad (l = 2, 3, \cdots)$, then $G_1$ is positive definite, i.e., the membrane is stable. We must take the minimum of $p_1$ to obtain the critical pressure:

$$\Delta p_c = \min\{p_1\} = \left\{ \begin{array}{ll}
\frac{3k_d}{2R} + \frac{2k_c[l(l+1)-\delta_0 R]}{R^2} & < \frac{\bar{k}_c[23-2\delta_0 R]}{R^2}, \quad (3k_d R^2 < 121\bar{k}_c) \\
2\sqrt{\frac{3k_d R^2}{\bar{k}_c}} + \frac{\bar{k}_c}{R^2} (1-2\delta_0 R) & (3k_d R^2 > 121\bar{k}_c)
\end{array} \right.$$

But if we do not consider the in-plane mode $\{\Omega\}$, we will obtain the critical pressure [19]:

$$\Delta p_c = \left\{ \begin{array}{ll}
\frac{3k_d}{2R} + \frac{2k_c(6-\delta_0 R)}{R^2} & < \frac{2k_c (10-\delta_0 R)}{R^2}, \quad (3k_d R^2 < 16\bar{k}_c) \\
\frac{4k_c R^2}{\bar{k}_c} + \frac{2\bar{k}_c}{R^2} (2-\delta_0 R) & (3k_d R^2 > 16\bar{k}_c)
\end{array} \right.$$

Comparing equation (52) with (53), we find that in-plane modes have quantitative effect on the stability of the cell membrane although they can not qualitatively modify the result without considering them.

On the one hand, equation (52) includes the classical results for stability of elastic shells. For classic shell, the critical pressure for spherical shell is $\Delta p_c \sim Yh^2/R^2$ [29,30], where $Y$ is the Young’s modulus of the shell. If taking $\delta_0 = 0$, $k_d \sim Yh$, $\bar{k}_c \sim Yh^3$ and $R \gg h$, our equation (52) also gives $\Delta p_c \sim Yh^2/R^2$. On the other hand, equation (52) includes the critical pressure for stability of lipid membranes. For spherical lipid membranes, the critical pressure is $\Delta p_c \sim \bar{k}_c/R^3$ [11], which is the natural result of equation (52) only if let $k_d = 0$ in it. Otherwise, if we take the typical parameters of cell membranes
as $k_c \sim 20k_BT$ [6, 7], $k_d \sim 2.4\mu N/m$ [31], $h \sim 4\text{nm}$, $R \sim 1\mu m$, $c_0R \sim 1$, we obtain $\Delta p_c \sim 2\text{ Pa}$ from equation (52), which is much larger than $\Delta p_c \sim 0.2\text{ Pa}$ without considering $k_d$ induced by membrane cytoskeleton. This result reveals that membrane cytoskeleton greatly enhances the mechanical stabilities of cell membranes, at least for spherical shape.

CELL STRUCTURE DYNAMICS

In above discussions, we only consider the static elasticities of cell membranes. However, it is more important to understand the dynamics of cells. At least, we much cover the dynamic behavior of cell membrane, cytoplasm, cytoskeleton and nucleus. In this section, we will propose a framework of cell structure dynamics involving tensegrity architecture of cytoskeleton, fluid dynamics of cytoplasm and elasticities of cell membranes with membrane cytoskeleton. We make a model of a cell as follows.

(i) Nucleus. The nucleus is thought of as a small rigid sphere in the middle of cell because it is a relative stiff membrane. Its inner structure is neglected.

(ii) The tensegrity architecture of cytoskeleton [32, 33]. Cytoskeleton is a cross-linked structure comprised of microfilaments, microtubles and intermediate filaments. Microfilaments are better at resisting tension while microtubules at withstanding compression. Intermediate filaments also resist tension, but only for significant strains of cells. Thus the cytoskeleton is an integral system consists of continuum tension elements (microfilaments) and discrete compression elements (microtubules) prestressed by osmotic pressure acting on the cell membranes and adhesions of other cell or extracellular matrix. The total free energy of cytoskeleton might be written as $F_{csk} = F_{ten} + F_{com}$, where $F_{ten}$ is free energy contributed by tension elements and $F_{com}$ comes from compression elements. $F_{ten}$ can be written as the production of tension and total length of tension elements for large strains because the tension is continuously transferred and the entropic elasticity is not important. Its form for small strains must refer to the entropic elasticity of biopolymers [34]. $F_{com}$ depends on the stresses and strains in each compression elements. In fact, $F_{csk}$ depends implicitly on the relative positions of junction points between cytoskeleton and cell membrane. The equilibrium conditions of force can be expressed as

$$f_i = \partial F_{csk}/\partial r_i$$

if we omit the inertial term of cytoskeleton. Here $\{R_i\}$ and $\{f_i\}$ represent the positions of junction points between cytoskeleton and cell membrane, and the forces at that junction points induced by cell membrane, respectively.

(iii) Cytoplasm and the liquid surroundings of the cell. Cytoplasm and the liquid surroundings of the cell are regarded as incompressible viscous fluid. The dynamics might be describe by Navier-Stokes equation [35]:

$$\frac{\partial \mathbf{v}}{\partial t} + (\mathbf{v} \cdot \nabla)\mathbf{v} = -\nabla p/\rho + (\eta/\rho)\nabla \cdot \nabla \mathbf{v},$$

$$\nabla \cdot \mathbf{v} = 0,$$
where $v$, $\rho$, $p$ and $\eta$ are the velocity vector, density, pressure and dynamic viscosity of fluid, respectively. The components of viscosity stress tensor $\tau$ has the form

$$\tau_{ij} = \eta \left( \frac{\partial v_i}{\partial x_j} + \frac{\partial v_j}{\partial x_i} \right), (i, j = 1, 2, 3), \quad (57)$$

where $v_1$, $v_2$, and $v_3$ are, respectively, three components of velocity in three Cartesian coordinates $x_1$, $x_2$, and $x_3$.

(iv) The coupling between cell membrane and cytoskeleton, cytoplasm as well as liquid surroundings. The equilibrium equations of cell membrane under the interaction of cytoskeleton, cytoplasm and liquid surroundings can be expressed as

$$\frac{k_d}{2} \left[ (\epsilon_{22} - \epsilon_{11}) \frac{\partial \sqrt{g_{22}}}{\partial u^1} - \sqrt{g_{22}} \frac{\partial}{\partial u^1} (2\epsilon_{11} + \epsilon_{22}) - \sqrt{g_{11}} \frac{\partial \epsilon_{12}}{\partial u^2} - 2\epsilon_{12} \frac{\partial \sqrt{g_{11}}}{\partial u^2} \right]$$

$$= e_1 \cdot \Delta \tau \cdot e_3 + \sum_i f_i \cdot e_1 \delta(r - r_i), \quad (58)$$

$$\frac{k_d}{2} \left[ (\epsilon_{11} - \epsilon_{22}) \frac{\partial \sqrt{g_{11}}}{\partial u^2} - \sqrt{g_{11}} \frac{\partial}{\partial u^2} (\epsilon_{11} + 2\epsilon_{22}) - \sqrt{g_{22}} \frac{\partial \epsilon_{12}}{\partial u^1} - 2\epsilon_{12} \frac{\partial \sqrt{g_{22}}}{\partial u^1} \right]$$

$$= e_2 \cdot \Delta \tau \cdot e_3 + \sum_i f_i \cdot e_2 \delta(r - r_i), \quad (59)$$

$$\Delta p - 2(\mu + k_d J) H + \bar{k}_c (2H + \bar{e}_0)(2H^2 - \bar{e}_0 H - 2K) + \bar{k}_c \nabla^2 (2H)$$

$$- \frac{k_d}{2} [a \epsilon_{11} + 2b \epsilon_{12} + c \epsilon_{22}] = e_3 \cdot \Delta \tau \cdot e_3 + \sum_i f_i \cdot e_3 \delta(r - r_i), \quad (60)$$

where $\Delta$ represent the outer quantity minus the inner one. In above three equations, we omit the inertial term of cell membrane because it is expected to be much smaller than the viscosity force. Moreover, these equations are valid only for small in-plane deformations of cell membranes. If we only considering lipid membrane, these equations are degenerated to the key equations in Ref. [36].

Equations (54)-(60) are highly nonlinear and coupling with each other so that they must be solved by numerical methods. The key point is to develop a arithmetic to dealing with the coupling boundary conditions (58)-(60).

**CONCLUSION**

In this chapter, we discuss elasticities and stabilities of lipid membranes and cell membranes. We obtain the equations to describe equilibrium shapes and strains of cell membranes by osmotic pressures. We find that the critical pressure for spherical cell membrane is much larger than that of spherical lipid bilayer without considering membrane cytoskeleton. We also try to construct a framework of cell structure dynamics involving tensegrity architecture of cytoskeleton, fluid dynamics of cytoplasm and elasticities of cell membranes with membrane cytoskeleton. It is an important direction to develop arithmetic to solve the coupling equations (54)-(60) in the future.
References

[1] Lodish, H. et al. Molecular Cell Biology; W. H. Freeman & Co.: New York, 1999; Chapter 1.

[2] Edidin, M. Nature Rev. Mol. Cell Bio. 2003, 4, 414-418.

[3] Singer, S. J.; Nicolson, G. L. Science 1972, 175, 720.

[4] Helfrich, W. Z. Naturforsch. C 1973, 28, 693-703.

[5] de Gennes, P. G. The Physics of Liquid Crystals; Clarendon Press: Oxford, 1975; 100-103.

[6] Duwe, H. P.; Kaes, J.; Sackmann, E. J. Phys. Fr. 1990, 51, 945-962.

[7] Mutz, M.; Helfrich, W. J. Phys. Fr. 1990, 51, 991-1002.

[8] Ou-Yang, Z. C.; Liu, J. X.; Xie, Y. Z. Geometric Methods in the Elastic Theory of Membranes in Liquid Cristal Phases; World Scientific: Singapore, 1999.

[9] Lipowsky, R. Nature 1991, 349, 475-481.

[10] Seifert, U. Adv. Phys. 1997, 46, 13-137.

[11] Ou-Yang, Z. C.; Helfrich, W. Phys. Rev. Lett. 1987, 59, 2486-2489.

[12] Ou-Yang, Z. C.; Helfrich, W. Phys. Rev. A 1989, 39, 5280-5288.

[13] Ou-Yang, Z. C. Phys. Rev. A 1990, 41, 4517-4520.

[14] Mutz, M.; Bensimon, D. Phys. Rev. A 1991, 43, 4525-4527.

[15] Lin, Z. et al. Langmuir 1994, 10, 1008-1011.

[16] Rudolph, A. S.; Ratna, B. R.; Kahn, B. Nature 1991, 352, 52-55.

[17] Feng, Y. Z. Bio-Mechanics; Science Press: Beijing, 1983.

[18] Naito, H.; Okuda, M.; Ou-Yang, Z. C. Phys. Rev. E 1993, 48, 2304-2307.

[19] Tu, Z. C.; Ou-Yang, Z. C. J. Phys. A: Math. Gen. 2004, 37, 11407C11429.

[20] Tu, Z. C.; Ou-Yang, Z. C. Phys. Rev. E 2003, 68, 61915.

[21] An, R.; Tu, Z. C. Preprint 2003. [math-ph/0307007]

[22] Chern, S. S.; Chen, W. H. Lectures on Differential Geometry; Peking University Press: Beijing, 2001; Chapter 6.

[23] Wang, Z. X.; Guo, D. R. Introduction to Special Function; Peking University Press: Beijing, 2000.
[24] Tu, Z. C.; Ge, L. Q.; Li, J. B.; Ou-Yang, Z. C. Prerint 2003, cond-mat/0312319.

[25] de Gennes, P. G. Scaling Concepts in Polymer Physics; Cornell University: New York, 1979.

[26] Treloar, L. R. G. The Physics of Rubber Elasticity; Clarendon Press: Oxford, 1975.

[27] Wu, J. K.; Wang, M. Z. Introduction to Elastic theory; Peking University Press: Beijing, 1981.

[28] Zhang, Z.; Davis, H. T.; Kroll, D. M. Phys. Rev. E 1993, 48, R651-R654.

[29] Pogorelov, A. V. Bendings of surfaces and stability of shells; Providence, R.I.: AMS, 1989.

[30] Landau, L. D.; Lifshitz, E. M. Theory of Elasticity; Butterworth-Heinemann: Oxford, 1997; 3rd edn.

[31] Lenormand, G. et al. Biophys. J. 2001, 81, 43-56.

[32] Ingber, D. E. J. Cell Sci. 2003, 116, 1157-1173.

[33] Stamenović, D.; Ingber, D. E. Biomechan. Model Mechanobiol. 2002, 1, 95-98.

[34] Dio, M.; Edwards, S. F. The Theory of Polymer Dynamics; Clarendon Press: Oxford, 1986.

[35] Landau, L. D.; Lifshitz, E. M. Fluid Mechanics; Butterworth-Heinemann: Oxford, 1998; Chapter 2.

[36] Komura, S.; Seki, K. Physica A 1993, 192, 27-46.