General Mathematical Frame for Open or Closed Biomembranes: Stability Theory Based on Differential Operators

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Abstract. Based on a few differential operators and their integral theorems on curved surfaces, the second variations of the general potential functional and various geometric quantities defined on biomembranes are derived in this paper. Through the combination of the stably permissible condition and geometrically constraint equation, the differential-operator-based stability theory for open or closed biomembranes is established in 2D Riemann manifold. Application of the stability theory to vesicles not only shows its effectiveness, but also reveals the difference between stability theories in 2D Riemann manifold and that in Euclidean space.

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1. Introduction

In previous paper, a unified mathematical frame for the equilibrium theory of open or closed biomembranes is developed in 2D Riemann manifold (Y.J. Yin, J. Yin and D. Ni, 2005). In this paper, the general stability theory for biomembranes, also established in 2D Riemann manifold, will be focused.

In cell biology, a closed cell membrane may play an important role not only as a boundary to separate the inside of the cell from the external environment, but also as a machine to transit signals and exchange matters or energies between outside and inside environments (H. Lodish, et al., 1995). As for an open cell membrane, a pore in the membrane may be an important route for the drug delivery (T.M. Allen, 1996) and gene therapy (R.G. Crystal, 1995). To realize these biological functions, the stability of the cell membrane should be maintained. Hence to develop a general stability theory for biomembranes may be of biological importance.

As far as the general stability theory for biomembranes is concerned (Z.C. Ou-Yang and W. Helfrich, 1989, R. Capovilla, J. Guven and J.A. Santiago, 2003), the main obstacle may come from geometry. First, a biomembrane may be idealized as a 2D Riemann manifold or curved surface. Thus different from the stability theory for structures in Euclidean space, the one for biomembranes should be built in 2D Riemann space. To do so, systematic knowledge of differential geometry is indispensable. However, to know deeply differential geometry may not be an easy task. Second, in stability theory the second variations of the potential functional as well as some geometric quantities defined on biomembranes are very complicated, which makes the theory difficult to

understand and apply. Therefore, how to overcome the above obstacle and make the stability theory simple becomes an essential problem. Fortunately, this problem may be solved with the aid of a few differential operators defined on curved surface and their differential or integral theorems (Y.J. Yin et al., 2005, Y.J. Yin, 2005) proved in 2D Riemann manifold. This forms one objective of the paper.

Except for the mathematical obstacle above, another important problem is about the difference between the stability theories for structures in different geometric spaces. In Euclidian space a stable structure just needs to satisfy the stably permissible condition. However, in 2D Riemann space the universal “geometrically constraint equation” (GCE) (Y.J. Yin, J. Yin and D. Ni, 2005, Y.J. Yin and J. Yin, 2004) for biomembranes exists, which means that a practical biomembrane should meet not only the stably permissible condition, but also the GCE. Thus questions may be asked: What will happen if the GCE is introduced into the stability theory for biomembranes? Does the GCE cause any change in the stability theory? How can we understand these changes? To make clear the doubts forms another objective of the paper.

The paper includes five parts. In section 2, a few differential operators defined on curved surfaces and useful in the stability theory for biomembranes are briefly introduced. In section 3, the general frame of the differential-operator-based stably permissible condition for open or closed biomembranes is presented. In section 4, the GCE for open or closed biomembranes is briefly summarized and the consequence caused by the GCE is analyzed. Section 3 and section 4 together form the core of the stability theory. In

section 5, a simple application of the stability theory to vesicles is displayed and the characteristics of the stability theory in 2D Riemann manifold are disclosed. In appendixes A and B, derivations for the second variations of the potential functional and various geometric quantities are listed. All the second variations, especially those of the mean curvature and Gauss curvature, are expressed through differential operators.

2. Brief summary of a few differential operators

In differential geometry, there is the conventional 2D gradient operator ∇ defined on curved surfaces

$$\nabla = g_i g^{ij} \frac{\partial}{\partial u^j} \quad (i, j = 1, 2) \quad (1)$$

Recently, another 2D gradient operator $\bar{\nabla}$ is defined during the study on biomembranes (Y.J. Yin, J. Yin and D. Ni, 2005, Y.J. Yin et al., 2005, Y.J. Yin, 2005)

$$\bar{\nabla} = g_i \hat{L}^{ij} \frac{\partial}{\partial u^j} \quad (i, j = 1, 2) \quad (2)$$

In (1) and (2), u^i is the Gauss parameter coordinate. g_i is the covariant base vector. g^{ij} is the contravariant component of the first fundamental tensor G . $\hat{L}^{ij}$ is the contravariant component of the tensor $\hat{L} = KL^{-1}$ with K the Gauss

curvature and L the second fundamental tensor.

∇ and $\bar{\nabla}$ are two vector differential operators. The dot products between them will lead to three independent scalar differential operators, i.e. $\nabla \square \nabla$, $\nabla \square \bar{\nabla} = \bar{\nabla} \square \nabla$ and $\bar{\nabla} \square \bar{\nabla}$ (Y.J. Yin, 2005). Two of them have played important roles in the equilibrium theory for biomembranes: One is the classical Laplace-Beltrami operator ∇^2 and another is the new one $\bar{\nabla}^2$ (Y.J. Yin et al., 2005, H. Naito, M. Okuda and Z.C. OuYang, 1995). Their analytical structures are as follows:

$$\nabla^2 = \nabla \square \nabla = \frac{1}{\sqrt{g}} \frac{\partial}{\partial u^i} \left(\sqrt{g} g^{ij} \frac{\partial}{\partial u^j} \right) \quad (3)$$

$$\bar{\nabla}^2 = \bar{\nabla} \square \bar{\nabla} = \frac{1}{\sqrt{g}} \frac{\partial}{\partial u^i} \left(\sqrt{g} \hat{L}^{ij} \frac{\partial}{\partial u^j} \right) \quad (4)$$

Here g_{ij} is the covariant component of the first fundamental tensor G and $g = |g_{ij}|$ is the determinant.

Various integral theorems about $\bar{\nabla}$ and $\bar{\nabla}^2$ have been published (Y.J. Yin, 2005). In the following sections, these differential operators and their integral theorems will be used to establish and simplify the stability theory for biomembranes.

3. Stably permissible condition for open or closed biomembranes

An open biomembrane may be geometrically regarded as a curved surface A with a boundary curve C (Fig.1). The general potential functional F of the open biomembrane is given by:

$$F = \iint_A \phi(H, K) dA + \iint_A \lambda dA + \oint_C \gamma ds \quad (5)$$

Here we suppose the free energy density of biomembranes, *i.e.* $\phi(H, K)$, is just the function of the mean curvature H and Gauss curvature K of the membrane surface. The surface energy density λ remains constant and the edge energy density γ keeps unchanged along the boundary C of the membrane. Suppose an arbitrary virtual perturbation ψ takes place along the normal direction of the membrane's surface. The second variation $\delta^{(2)}F$ expressed by differential operators may be given by (Appendix A):

$$\begin{aligned} \delta^{(2)}F = & \frac{1}{2} \iint_A \left\{ \alpha_1 \psi^2 + \alpha_2 \psi \nabla^2 \psi + \alpha_3 \psi \bar{\nabla}^2 \psi + \alpha_4 \nabla \psi \square \nabla \psi + \alpha_5 \nabla \psi \square \bar{\nabla} \psi \right. \\ & \left. - \nabla \phi_{,K} \left[\nabla \psi \nabla^2 \psi - \nabla \nabla \psi \square \nabla \psi \right] + \left[(1/2) \nabla^2 \psi \partial / \partial H + \bar{\nabla}^2 \psi \partial / \partial K \right]^2 \phi \right\} dA \\ & + \frac{1}{2} \oint_C \left\{ \left[(2H \kappa_n - K) \psi^2 + \dot{\psi}^2 \right] \gamma + \left[\phi_{,K} \left(\nabla \psi \nabla^2 \psi - \nabla \nabla \psi \square \nabla \psi \right) + \psi^2 \nabla \phi \right] \cdot \mathbf{m} \right\} ds \end{aligned} \quad (6)$$

The symbols in (6) are formulated by:

$$\alpha_1 = \left[(2H^2 - K) \partial / \partial H + 2HK \partial / \partial K \right]^2 \phi - 2K \left[(H \partial / \partial H + K \partial / \partial K) \phi - (\phi + \lambda) \right] - \nabla^2 \phi,$$

$$\alpha_2 = \partial f / \partial H + 2(\phi + \lambda), \quad \alpha_3 = 2 \partial f / \partial K, \quad \alpha_4 = H(\phi_{,H} + 4H\phi_{,K}) + (\phi + \lambda),$$

$$\alpha_5 = -(\phi_{,H} + 2H\phi_{,K}), \quad \phi_{,H} = \partial \phi / \partial H, \quad \phi_{,K} = \partial \phi / \partial K, \quad \kappa_n = \mathbf{n} \cdot d\mathbf{t} / ds, \quad \dot{\psi} = d\psi / ds$$

$$f = \left[(2H^2 - K) \partial / \partial H + 2HK \partial / \partial K \right] \phi - 2H(\phi + \lambda)$$

Here κ_n is the normal curvature on curve C . $\mathbf{n}$ is the outward unit normal of the surface and $\mathbf{t}$ is the unit vector along the positive tangential direction of the boundary curve C . $\mathbf{m} = \mathbf{t} \times \mathbf{n}$ is the unit vector perpendicular to $\mathbf{t}$ and $\mathbf{n}$.

For a closed biomembrane, the general potential functional is suggested as

$$F = \iiint_A \phi(H, K) dA + \iiint_A \lambda dA + \iiint_V \Delta p dV \quad (7)$$

where $\Delta p = p_{out} - p_{in}$ is the difference between the outer and inner pressures

acted on the biomembrane. The $\delta^{(2)}F$ for closed biomembranes may be obtained from (6) through vanishing the boundary integral, replacing f by $f_p = f + \Delta p$

and changing α_1 into $\alpha_1' = \alpha_1 - 2\Delta p H$:

$$\delta^{(2)}F = \frac{1}{2} \iint_A \left\{ \alpha_1' \psi^2 + \alpha_2 \psi \nabla^2 \psi + \alpha_3 \psi \bar{\nabla}^2 \psi + \alpha_4 \nabla \psi \square \nabla \psi + \alpha_5 \nabla \psi \square \bar{\nabla} \psi \right. \\ \left. - \nabla \phi_{,K} \left[\nabla \psi \nabla^2 \psi - \nabla \nabla \psi \square \nabla \psi \right] + \left[(1/2) \nabla^2 \psi \partial/\partial H + \bar{\nabla}^2 \psi \partial/\partial K \right]^2 \phi \right\} dA$$

(8)

For a stable biomembrane the second variations in (6) or (8) should be positive and definite for any perturbation mode ψ ($\psi \neq 0$), which leads to the stably permissible condition

$$\delta^{(2)}F > 0 \quad (9)$$

From (7) or (8), it's clearly shown that the differential operators ∇ , $\bar{\nabla}$, ∇^2 and $\bar{\nabla}^2$ play dominating roles in the stably permissible condition. Once their differential and integral calculus are known and the original equilibrium configuration of the biomembrane is given, the inequality (9) under arbitrary perturbation mode ψ can be judged without difficulty. Thus it is the differential operators that make the stably permissible condition both simple and understandable to researchers with knowledge in common differential and integral calculus.

Besides, the stably permissible condition in (7) or (8) quantitatively reveals all the factors that may affect the stability of a biomembrane: (a) the shape and size of the original equilibrium configuration of the biomembrane; (b) the distribution of the free energy density ϕ , with the physical parameters of the

membrane molecules included; (c) the surface energy density λ . Except for the above common factors, there are some special ones related to the topological structures of the biomembrane: For an open biomembrane there are the location, size and bending extent of the boundary curve C and the edge energy density γ , whereas for a closed biomembrane there is the pressure difference Δp .

4. Geometrically constraint equations for open or closed biomembranes

The GCE is first derived from closed vesicles (Y.J. Yin and J. Yin, 2004). Recently, the GCE is further extended to arbitrary biomembranes. For an open biomembrane with constant edge energy density γ , the GCE may be written as (Y.J. Yin, J. Yin and D. Ni, 2005)

$$\iint_A f dA = \oint_C \kappa_n \gamma ds = \gamma \oint_C \kappa_n ds \quad (10)$$

For a closed biomembrane the line integral in (10) vanishes and the f should be replaced by f_p :

$$\iint_A f_p dA = 0 \quad (11)$$

To understand the roles of the GCE in the stability theory, a few viewpoints will

be emphasized below.

First, the GCE is the inevitable outcome of curved surfaces and only exists in 2D Riemann manifolds. This viewpoint can be confirmed from two view angles. (a) On a developable curved surface such as a circular cylindrical one, (10) or (11) may occur. Nevertheless once the circular cylindrical surface is unfolded into a plane, (10) or (11) will disappear. (b) From the deriving procedure (Y.J. Yin, J. Yin and D. Ni, 2005), we can find that the GCE is mainly based on the integral theorems about the differential operators ∇ and $\bar{\nabla}$ or ∇^2 and $\bar{\nabla}^2$. Because these differential operators are defined on curved surfaces and their integral theorems are proved in 2D Riemann manifolds, we may conclude that the GCE mainly reflects the characteristics of the curved space occupied by the biomembrane and is universally valid. In another word, any biomembrane should observe the GCE without exceptions.

Second, in appearance the GCE is an integral equation, but in essence it is an algebraic one that gives the relation between the physical parameters (such as Δp , λ , γ and membrane rigidities) and the geometrical ones (such as the characteristic sizes) of the biomembrane. This implies that the physical properties and the geometrical ones of the biomembrane are not independent with each other, which clearly reveals the differences between structures in Euclidean space and 2D Riemann manifold. In Euclidean space, physical parameters are seldom related to geometrical ones. However, in 2D Riemann manifold, physical parameters are closely connected with the properties of the geometric space.

Third, the GCE is not only part of the equilibrium theory, but also part of the

stability theory for biomembranes. Just the equilibrium differential equation (Y.J. Yin, J. Yin and D. Ni, 2005) for biomembranes may define a solution space inside which equilibrium configurations of biomembranes may be theoretically realized. However, once the GCE is combined with the equilibrium differential equation, this solution space may be narrowed — part of the solutions may not satisfy the GCE and have to be cancelled out (Y.J. Yin, J. Yin and D. Ni, 2005). Similarly, just the stably permissible condition in (9) may define a parameter space inside which the stability of biomembranes may be theoretically kept. Nevertheless, once the GCE is combined with the stably permissible condition, the parameter space may be cut down — part of the parameter space may not satisfy the GCE and have to be discarded. This judgment will be proved through an example in the following section. In short, in the stability theory for biomembranes the stably permissible condition in inequality (9) and the GCE in (10) or (11) should be satisfied simultaneously, and any practical biomembrane should be both a stably permissible one and a geometrically permissible one.

5. Applications of the stability theory to vesicles

To further display the characteristics of the stability theory in 2D Riemann manifold and reveal its difference from the stability theory in Euclidean space, lipid bilayer vesicle will be studied below.

5.1 General stability analysis of closed vesicles

Lipid bilayer vesicles are a special kind of biomembranes with uniform distribution of molecules. For closed vesicles the free energy density is usually

taken as (W. Helfrich, 1973)

$$\phi(H, K) = \frac{1}{2}k_c(2H + c_0)^2 + k_G K \quad (12)$$

where k_c , k_G and c_0 are respectively the elastic modulus and the spontaneous curvature. In differential geometry there is the Gauss-Bonnet theorem for a closed surface, i.e. $\iint_A K dA = \text{Const.}$. Thus the corresponding variation meets $\delta \iint_A K dA = 0$ and the variational terms associated with k_G can be cancelled out. From (8), (12) and inequality (9) the differential-operator-based stably permissible condition for closed vesicles may be given by

$$\begin{aligned} \delta^{(2)}F = \frac{1}{2}k_c \iint_A \left\{ \left[4(2H^2 - K)^2 - K(4H^2 - c_0^2) + (2/k_c)(\lambda K - \Delta p H) \right. \right. \\ \left. \left. + 2\nabla[(H\nabla H - \bar{\nabla}H)]\right] \psi^2 + \left[2(5H^2 - 2K) - c_0^2/2 - \lambda/k_c \right] \psi \nabla^2 \psi \right. \\ \left. - 2(2H + c_0)\psi \bar{\nabla}^2 \psi + (\nabla^2 \psi)^2 \right\} dA \\ > 0 \end{aligned} \quad (13)$$

According to (10) the GCE for closed vesicles may be written as

$$\iint_A \left[c_0^2 H + 2c_0 K - 4H(H^2 - K) + (1/k_c)(2\lambda H - \Delta p) \right] dA = 0 \quad (14)$$

5.2 Stability analysis of circular cylindrical vesicles

Here the circular cylindrical vesicle with radius R will be taken as an

example for the stability analysis. We have

$$H = -\frac{1}{2R}, \quad K = 0 \quad (15)$$

In this simple case the GCE in (14) may be changed into

$$(c_0 R)^2 + 2(\Delta \bar{p} + \bar{\lambda}) - 1 = 0 \quad (16)$$

Here $\Delta \bar{p} = \Delta p R^3 / k_c$ is the dimensionless pressure difference and $\bar{\lambda} = \lambda R^2 / k_c$ ($\bar{\lambda} > 0$) is the dimensionless density of surface energy. A real c_0 in (16) will give out the geometrically permissible condition for circular cylindrical vesicles

$$2\Delta \bar{p} + 2\bar{\lambda} \leq 1 \quad (17)$$

The perturbation mode ψ in the cross-section and along the normal direction of the circular cylindrical vesicle is usually chosen as (Z.C. Ou-Yang and W. Helfrich, 1989)

$$\psi = \sum_m a_m e^{im\theta}, \quad 0 \leq \theta \leq 2\pi \quad (18)$$

By combining (13), (16), (18) and canceling out the parameter c_0 , one has

$$\delta^{(2)}F = \frac{\pi k_c}{R^3} \sum_m |a_m|^2 (m^2 - 1)(m^2 - 1 - \Delta\bar{p}) > 0 \quad (19)$$

At the lowest order of the perturbation mode (*i.e.* $m=2$), the dimensionless stably permissible condition of circular cylindrical vesicles may be obtained from (19)

$$\Delta\bar{p} < 3 \quad (20)$$

The inequalities (19) and (20) form the stably and geometrically permissible parameter spaces for circular cylindrical vesicles (Fig.2).

5.3 Discussions on the parameter spaces for circular cylindrical vesicles

The application above not only shows the convenience of the stability theory, but also discloses the characteristics of the stability theory in 2D Riemann manifold. On the $\bar{\lambda} \sim \Delta\bar{p}$ plane in Fig.2, the stably permissible parameter space and geometrically permissible parameter space for circular cylindrical vesicles are presented together. The district under the horizontal line is the stably permissible space and the region beneath the oblique line is the geometrically permissible space. In the past the opinion that a stable structure in Euclidean space certainly exists has been widely recognized. This may not be true for a structure in 2D Riemann manifold. In Fig.2, the geometrically permissible space is smaller than the stably permissible one. This means that a stably permissible vesicle may not be a geometrically permissible one or even may not exist. This simple result clearly reveals the differences between the stability theories in Euclidean space and Riemann space.

6. Conclusions

Although the differential geometry involved in the stability theory for biomembranes is complicated, the general formulations of the second variations of the total potential functional and various geometric quantities such as the mean curvatures and Gauss curvature can still be expressed concisely with the aid of the differential operators. Researchers who have knowledge in common differential and integral calculus are able to understand easily the stability theory here. Under the mathematical frame developed in this paper, the stability characteristics of biomembranes with arbitrary shapes and topologies may be explored without difficulty. Besides, for any stable biomembrane the stably permissible condition and geometrically permissible condition should be met at the same time.

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Appendix A: Second variation of the potential functional

From (5), the second variation $\delta^{(2)}F$ for open biomembranes is given by:

$$\begin{aligned}\delta^{(2)}F &= \delta^{(2)} \iint_A \phi dA + \iint_A \lambda \delta^{(2)} dA + \int_C \gamma \delta^{(2)} ds \\ &= \iint_A \delta^{(2)} \phi dA + \iint_A \delta^{(1)} \phi \delta^{(1)} dA + \iint_A (\phi + \lambda) \delta^{(2)} dA + \int_C \gamma \delta^{(2)} ds\end{aligned}\tag{A-1}$$

According to the rules for the variations of multivariable functions, the variations of the free energy function ϕ are defined as

$$\delta^{(1)}\phi = \left(\delta^{(1)}H \partial/\partial H + \delta^{(1)}K \partial/\partial K \right) \phi \quad (\text{A-2})$$

$$\delta^{(2)}\phi = \left(\delta^{(2)}H \partial/\partial H + \delta^{(2)}K \partial/\partial K \right) \phi + \frac{1}{2} \left(\delta^{(1)}H \partial/\partial H + \delta^{(1)}K \partial/\partial K \right)^2 \phi \quad (\text{A-3})$$

Substitution of (A-2) and (A-3) into (A-1), one can get

$$\begin{aligned} \delta^{(2)}F = & \iint_A \left\{ \frac{1}{2} \left[\phi_{,HH} \left(\delta^{(1)}H \right)^2 + 2\phi_{,HK} \delta^{(1)}H \delta^{(1)}K + \phi_{,KK} \left(\delta^{(1)}K \right)^2 \right] + \phi_{,H} \delta^{(2)}H + \phi_{,K} \delta^{(2)}K \right\} dA \\ & + \iint_A \left(\phi_{,H} \delta^{(1)}H + \phi_{,K} \delta^{(1)}K \right) \delta^{(1)}dA + \iint_A (\phi + \lambda) \delta^{(2)}dA + \oint_C \gamma \delta^{(2)}ds \end{aligned} \quad (\text{A-4})$$

Here $\phi_{,HH} = \partial^2\phi/\partial^2H$, $\phi_{,HK} = \partial^2\phi/\partial H\partial K$ and $\phi_{,KK} = \partial^2\phi/\partial^2K$. The first variations $\delta^{(1)}dA$, $\delta^{(1)}H$ and $\delta^{(1)}K$, based on differential operators, can be cited from Refs.(Y.J. Yin, J. Yin and D. Ni, 2005, Z.C. Ou-Yang and W. Helfrich, 1989, Y.J. Yin et al., 2005):

$$\delta^{(1)}dA = -2H\psi dA \quad (\text{A-5})$$

$$\delta^{(1)}H = \frac{1}{2}\nabla^2\psi + (2H^2 - K)\psi \quad (\text{A-6})$$

$$\delta^{(1)}K = \bar{\nabla}^2\psi + 2HK\psi \quad (\text{A-7})$$

The second variations $\delta^{(2)}ds$, $\delta^{(2)}dA$ and $\delta^{(2)}dV$ (Y.J. Yin, J. Yin and D. Ni, 2005, Z.C. Ou-Yang and W. Helfrich, 1989, Y.J. Yin et al., 2005) may be expressed by differential operators as follows

$$\delta^{(2)}ds = \frac{1}{2}\left[(2H\kappa_n - K)\psi^2 + \dot{\psi}^2\right]ds \quad (\text{A-8})$$

$$\delta^{(2)}dA = \left(\frac{1}{2}\nabla\psi\Box\nabla\psi + K\psi^2\right)dA \quad (\text{A-9})$$

$$\delta^{(2)}dV = -H\psi^2dA \quad (\text{A-10})$$

According to Appendix B, $\delta^{(2)}H$ and $\delta^{(2)}K$ may be formulated by:

$$\begin{aligned} \delta^{(2)}H = & (4H^2 - 3K)H\psi^2 + (2H\nabla^2\psi - \bar{\nabla}^2\psi)\psi + \frac{1}{2}\nabla H\Box(\psi^2) \\ & + \frac{1}{2}(H\nabla\psi - \bar{\nabla}\psi)\Box\nabla\psi \end{aligned} \quad (\text{A-11})$$

$$\begin{aligned}\delta^{(2)}K = & (4H^2 - K)K\psi^2 + (K\nabla^2\psi + 2H\bar{\nabla}^2\psi)\psi + \frac{1}{2}\nabla K\Box(\psi^2) \\ & + H(2H\nabla\psi - \bar{\nabla}\psi)\Box\nabla\psi + \frac{1}{2}\nabla\Box(\nabla\psi\nabla^2\psi - \nabla\nabla\psi\Box\nabla\psi)\end{aligned}\quad (\text{A-12})$$

To one's surprise, beautiful symmetry between the analytical structures of (A-11) and (A-12) exists. Substituting (A-5) ~ (A-12) into (A-4):

$$\begin{aligned}\delta^{(2)}F = & \frac{1}{2}\iint_A \left\{ \left[(2H^2 - K)^2\phi_{,HH} + 4(2H^2 - K)HK\phi_{,HK} + (2HK)^2\phi_{,KK} \right. \right. \\ & \left. \left. - 2K(H\phi_{,H} + K\phi_{,K} - \phi - \lambda) \right] \psi^2 \right. \\ & + \left[(2H^2 - K)\phi_{,HH} + 2HK\phi_{,HK} + 2(H\phi_{,H} + K\phi_{,K}) \right] \psi\nabla^2\psi \\ & + 2\left[(2H^2 - K)\phi_{,HK} + 2HK\phi_{,KK} - \phi_{,H} \right] \psi\bar{\nabla}^2\psi \\ & + \left[H(\phi_{,H} + 4H\phi_{,K}) + \phi + \lambda \right] \nabla\psi\Box\nabla\psi + \nabla\phi\Box(\psi^2) \\ & - (\phi_{,H} + 2H\phi_{,K})\bar{\nabla}\psi\Box\nabla\psi + \phi_{,K}\nabla\Box(\nabla\psi\nabla^2\psi - \nabla\nabla\psi\Box\nabla\psi) \\ & \left. + \frac{1}{4}\phi_{,HH}(\nabla^2\psi)^2 + \phi_{,HK}\nabla^2\psi\bar{\nabla}^2\psi + \phi_{,KK}(\bar{\nabla}^2\psi)^2 \right\} dA \\ & + \frac{1}{2}\oint_C [(2H\kappa_n - K)\psi^2 + \dot{\psi}^2] \gamma ds\end{aligned}\quad (\text{A-13})$$

According to the integral theorems (Y.J. Yin, 2005), a few terms in (A-13) may be further simplified:

$$\begin{aligned}\iint_A \nabla\phi\Box(\psi^2) dA &= \iint_A \left[\nabla\Box(\psi^2\nabla\phi) - \psi^2\nabla^2\phi \right] dA \\ &= \oint_C \psi^2\nabla\phi\Box m ds - \iint_A \psi^2\nabla^2\phi dA\end{aligned}\quad (\text{A-14})$$

$$\begin{aligned}
& \iint_A \phi_{,K} \nabla \left(\nabla \psi \nabla^2 \psi - \nabla \nabla \psi \square \nabla \psi \right) dA \\
&= \iint_A \left\{ \nabla \left[\phi_{,K} \left(\nabla \psi \nabla^2 \psi - \nabla \nabla \psi \square \nabla \psi \right) \right] - \nabla \phi_{,K} \left(\nabla \psi \nabla^2 \psi - \nabla \nabla \psi \square \nabla \psi \right) \right\} dA \\
&= \oint_C \phi_{,K} \left(\nabla \psi \nabla^2 \psi - \nabla \nabla \psi \square \nabla \psi \right) \square m ds - \iint_A \nabla \phi_{,K} \left(\nabla \psi \nabla^2 \psi - \nabla \nabla \psi \square \nabla \psi \right) dA
\end{aligned}$$

(A-15)

By combining (A-13) ~ (A-15), one has (6).

Appendix B: Differential-operator-based second variations for mean curvature and Gauss curvature

If the second variations for the mean curvature H and the Gauss curvature K , i.e. $\delta^{(2)}H$ and $\delta^{(2)}K$, are not derived elaborately, the stability theory for biomembranes may become overcomplicated and inconvenient for applications. The objective of this appendix is to express the $\delta^{(2)}H$ and $\delta^{(2)}K$ by well-organized differential operators. The H and K are formulated by

$$H = \frac{1}{2} g^{ij} L_{ij}, \quad K = \frac{L}{g} \quad (\text{B-1})$$

Here $L = |L_{ij}|$ is the determinant and L_{ij} is the covariant component of the second fundamental tensor L . The second variations are

$$\delta^{(2)}H = \frac{1}{2} \left[g^{ij} \delta^{(2)}L_{ij} + L_{ij} \delta^{(2)}g^{ij} + \left(\delta^{(1)}g^{ij} \right) \left(\delta^{(1)}L_{ij} \right) \right] \quad (\text{B-2})$$

$$\delta^{(2)}K = K \left[\frac{\delta^{(2)}L}{L} - \frac{\delta^{(2)}g}{g} + \left(\frac{\delta^{(1)}g}{g} \right)^2 - \frac{\delta^{(1)}L}{L} \frac{\delta^{(1)}g}{g} \right] \quad (\text{B-3})$$

To get $\delta^{(2)}H$ in (B-2), the variations $\delta^{(2)}L_{ij}$, $\delta^{(2)}g^{ij}$, $\delta^{(1)}g^{ij}$ and $\delta^{(1)}L_{ij}$ are cited from Refs. (Y.J. Yin, J. Yin and D. Ni, 2005, Z.C. Ou-Yang and W. Helfrich, 1989, Y.J. Yin et al., 2005) and the terms in the right-hand side of (B-2) may be given by differential operators:

$$g^{ij} \delta^{(2)}L_{ij} = \nabla \psi \left[3H \nabla \psi - 2\bar{\nabla} \psi \right] + \frac{1}{2} \mathbf{G} : (\nabla \mathbf{L}) \nabla (\psi^2) \quad (\text{B-4})$$

$$L_{ij} \delta^{(2)}g^{ij} = 6H \left(4H^2 - 3K \right) \psi^2 - \nabla \psi \left[2H \nabla \psi - \bar{\nabla} \psi \right] \quad (\text{B-5})$$

$$\left(\delta^{(1)}g^{ij} \right) \left(\delta^{(1)}L_{ij} \right) = 2 \left(2H \nabla^2 \psi - \bar{\nabla}^2 \psi \right) \psi - 4H \left(4H^2 - 3K \right) \psi^2 \quad (\text{B-6})$$

To get $\delta^{(2)}K$ in (B-3), the variations $\delta^{(1)}g$, $\delta^{(1)}L$ and $\delta^{(2)}g$ are cited from Refs. (Y.J. Yin, J. Yin and D. Ni, 2005, Z.C. Ou-Yang and W. Helfrich, 1989, Y.J. Yin et al., 2005) and may be rewritten as follows by differential operators:

$$\delta^{(1)}g = -4Hg\psi \quad (\text{B-7})$$

$$\delta^{(1)}L = g \left(\bar{\nabla}^2 \psi - 2HK\psi \right) \quad (\text{B-8})$$

$$\delta^{(2)}g = g \left[2 \left(2H^2 + K \right) \psi^2 + \nabla \psi \square \nabla \psi \right] \quad (\text{B-9})$$

The second variation $\delta^{(2)}L$ can be expressed as:

$$\delta^{(2)}L = L \bar{L}^{ij} \delta^{(2)}L_{ij} + \delta^{(1)}L_{11} \delta^{(1)}L_{22} - \left(\delta^{(1)}L_{12} \right)^2 \quad (\text{B-10})$$

where $\bar{L}^{ij}$ is the contravariant component of the tensor $\bar{L} = L^{-1}$. The first term and the last two terms in the right-hand side of (B-10) should be invariants. After carefully investigation, these invariants are found to be of the forms:

$$\bar{L}^{ij} \delta^{(2)}L_{ij} = \nabla \psi \square \nabla \psi + \frac{1}{2} \hat{L} : (\nabla L) \square \nabla (\psi^2) \quad (\text{B-11})$$

$$\begin{aligned} & \delta^{(1)}L_{11} \delta^{(1)}L_{22} - \left(\delta^{(1)}L_{12} \right)^2 \\ &= KL\psi^2 - g \left(2H\bar{\nabla}^2 \psi - K\nabla^2 \psi \right) \psi + \nabla_1 \psi_{,1} \nabla_2 \psi_{,2} - \left(\nabla_1 \psi_{,2} \right)^2 \end{aligned} \quad (\text{B-12})$$

Here $\nabla_i \psi_{,j} = \frac{\partial^2 \psi}{\partial u^i \partial u^j} - \frac{\partial \psi}{\partial u^k} \Gamma_{ij}^k = \psi_{,ij} - \psi_{,k} \Gamma_{ij}^k$ is the covariant derivative of $\psi_{,j}$

and Γ_{ij}^k is the Christoffel symbol. Substitution of (B-11) and (B-12) into (B-10)

will give

$$\begin{aligned} \delta^{(2)}L = & L \left[K\psi^2 + \nabla\psi \square \nabla\psi + \frac{1}{2} \hat{\mathbf{L}} : (\nabla\mathbf{L}) \square \nabla(\psi^2) \right] - g \left(2H\bar{\nabla}^2\psi - K\nabla^2\psi \right) \\ & + \nabla_1\psi_{,1}\nabla_2\psi_{,2} - \left(\nabla_1\psi_{,2} \right)^2 \end{aligned} \quad (\text{B-13})$$

With all the variational terms known, the second variations $\delta^{(2)}H$ and $\delta^{(2)}K$ can be obtained as follows:

$$\begin{aligned} \delta^{(2)}H = & \left(4H^2 - 3K \right) H\psi^2 + \left(2H\nabla^2\psi - \bar{\nabla}^2\psi \right) \psi + \frac{1}{4} \mathbf{G} : (\nabla\mathbf{L}) \square \nabla(\psi^2) \\ & + \frac{1}{2} \left(H\nabla\psi - \bar{\nabla}\psi \right) \square \nabla\psi \end{aligned} \quad (\text{B-14})$$

$$\begin{aligned} \delta^{(2)}K = & \left(4H^2 - K \right) K\psi^2 + \left(K\nabla^2\psi + 2H\bar{\nabla}^2\psi \right) \psi + \frac{1}{2} \hat{\mathbf{L}} : (\nabla\mathbf{L}) \square \nabla(\psi^2) \\ & + \frac{1}{g} \left[\nabla_1\psi_{,1}\nabla_2\psi_{,2} - \left(\nabla_1\psi_{,2} \right)^2 \right] \end{aligned} \quad (\text{B-15})$$

From the characteristics of the differential operator and the fundamental tensors, one can prove the relations:

$$\mathbf{G} : (\nabla\mathbf{L}) = \nabla \square \mathbf{L} = 2 \left[\nabla H + \left(2H^2 - K \right) \mathbf{n} \right] \quad (\text{B-16})$$

$$\hat{\mathbf{L}} : (\nabla\mathbf{L}) = \bar{\nabla} \square \mathbf{L} = \nabla K + 2HK\mathbf{n} \quad (\text{B-17})$$

$$\begin{aligned} \frac{1}{g} \left[\nabla_1 \psi_{,1} \nabla_2 \psi_{,2} - (\nabla_1 \psi_{,2})^2 \right] &= \frac{1}{2} \left[(\nabla^2 \psi)^2 - (\nabla \nabla \psi) \square (\nabla \nabla \psi) \right] \\ &= \frac{1}{2} \left[\nabla \square (\nabla \psi \nabla^2 \psi - \nabla \nabla \psi \square \nabla \psi) + 2H (2H \nabla \psi - \bar{\nabla} \psi) \square \nabla \psi \right] \end{aligned} \quad (\text{B-18})$$

At last the final formulations of $\delta^{(2)}H$ and $\delta^{(2)}K$ in (A-11) and (A-12) can be ascertained through substituting (B-16) ~ (B-18) into (B-14) and (B-15).

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Fig.1. Schematic of the curved surface with unit vectors m , t and n at its boundary C

Fig.2. The geometrically and stably permissible parameter spaces for circular cylindrical vesicles

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