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Equilibrium theory in 2D Riemann manifold for heterogeneous biomembranes with arbitrary variational modes

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Abstract

Based on the first and second gradient operators and their integral theorems in 2D Riemann manifold, the equilibrium differential equations and geometrically constraint equations for heterogeneous biomembranes with arbitrary variation modes are developed. Through the combination of these equations, the equilibrium theory for heterogeneous biomembranes is established in 2D Riemann manifold. From the equilibrium theory, various interesting information is revealed: Different from homogeneous biomembranes, heterogeneous one posses new equations within the membrane's tangential planes, i.e. the in-plane equilibrium differential equations, the in-plane boundary conditions and the in-plane geometrically constraint equations. Different from the equilibrium theory in Euclidean space, the one in 2D Riemann manifold displays strict constraints between the physical coefficients and characteristic geometric parameters of biomembranes.

MSC: 20F65; 62P35; 70G45; 74L15

Keywords: Heterogeneous biomembranes; Differential operators; Equilibrium differential equations; Geometrically constraint equation; Arbitrary variational mode

1. Introduction

This paper deals with the equilibrium theory for heterogeneous biomembranes with arbitrary variational mode. As far as the equilibrium of biomembranes is concerned, variational principles [1–4] are used to derive the equilibrium differential equations and boundary conditions. During the variational process, how to select the variational modes is a core problem. Theoretically, the most general mode for the variation of the location (i.e. the virtual displacement vector $\boldsymbol{V}$) at a point on a biomembrane should be taken as (see Fig. 1):

$$\boldsymbol{V} = \boldsymbol{v} + \psi \boldsymbol{n}. \tag{1}$$

Here $\boldsymbol{v}$ is the tangential displacement vector and $\psi \boldsymbol{n}$ is the normal one with $\boldsymbol{n}$ the unit outward normal vector of the biomembrane. In the past, most researches mainly deal with the normal deformation mode. Recently, both normal and tangential deformation modes (i.e. arbitrary variational modes) have drawn the attentions of researchers [5,6].

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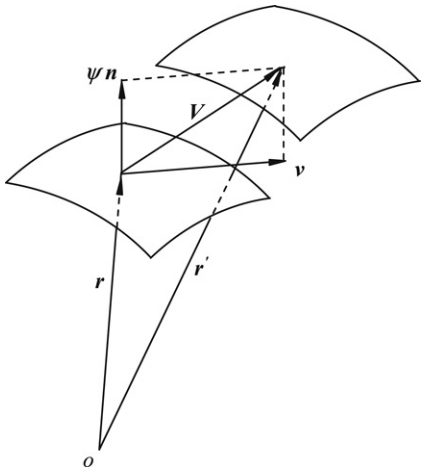

Fig. 1. A schematic diagram for the arbitrary deformation mode in a biomembrane.

This paper will concentrate on heterogeneous biomembranes with arbitrary variational modes. This topic is worth to be explored systematically because of the following reasons: First, practical biomembranes are usually heterogeneous. For example, cell membranes consist of various constituents such as lipid molecules, proteins and enzymes, etc. Interactions among them may cause the aggregations of constituents and lead to domains with certain biological functions. Second, the roles played by tangential deformation mode may be more important in heterogeneous biomembranes than in homogeneous one. In fact, the theory for heterogeneous biomembranes with tangential deformation mode included may bring about new information. In short, the theory for heterogeneous biomembranes may have its own characteristics and should be investigated independently.

The equilibrium theory in this paper will be specially expressed through differential operators. The reason is as follows. Once the tangential deformation mode is introduced, the theoretical system may become much more complicated. To simplify the theory and make the theory more understandable to researchers, a simple and convenient mathematical frame is necessary. This may be realized through differential operators. Recently, new gradient operator is defined from the studies on biomembranes and a series of integral theorems in 2D Riemann manifold are proved [7–9]. These mathematical results in turn may provide powerful tools to the explorations of heterogeneous biomembranes either with normal deformation mode [10] or with arbitrary one.

This paper includes four parts. First, a few differential operators are introduced. Second, these operators and their integral theorems are applied to heterogeneous biomembranes to derive the equilibrium equations and geometrically constraint equations. To one's surprise, new equations, including the equilibrium differential equations, boundary conditions and geometrically constraint equations within the tangential plane of a biomembrane are revealed. Third, the potential importance and possible applications of the in-plane equations are predicted. Fourth, two appendixes in which all the variational quantities are expressed through differential operators are presented.

2. Brief summary of a few differential operators

In physics and mechanics, gradient is an important concept. A gradient is physically a "force" that drives various dynamics in macro or micro scales. Without pressure gradient, deformation gradient, temperature gradient and electromagnetic gradient, there would be no fluid dynamics, solid mechanics, thermal dynamics and electromagnetism. In differential geometry, there is the conventional 2D gradient operator ∇ defined on a curved surface:

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

Recently, another 2D gradient operator $\overline{\nabla}$ is derived during the study on biomembranes [7–9]:

$$\overline{\nabla} = \hat{L}^{ij}\boldsymbol{g}_i \frac{\partial}{\partial u^j} \quad (i, j = 1, 2). \tag{3}$$

In Eqs. (2) and (3), u^i is the Gauss parameter coordinate. $\boldsymbol{g}_i$ is the covariant base vector. g^{ij} is the contravariant component of the first fundamental tensor $\boldsymbol{G}$. $\hat{L}^{ij}$ is the contravariant component of the tensor $\hat{\boldsymbol{L}} = K\boldsymbol{L}^{-1}$ with K the Gauss curvature and $\boldsymbol{L}$ the second fundamental tensor. ∇ and $\overline{\nabla}$ are termed "the first and second gradient operators" respectively, because they are dominated by the first and second fundamental tensors respectively [8,9]. Different from ∇, $\overline{\nabla}$ is strongly affected by the bending extent of the curved space.

∇ and $\overline{\nabla}$ are two vector differential operators. The inner dot product operations between them will lead to four scalar differential operators, i.e. $\nabla\cdot\nabla$, $\nabla\cdot\overline{\nabla}$, $\overline{\nabla}\cdot\nabla$ and $\overline{\nabla}\cdot\overline{\nabla}$. Two of them have been proved playing important roles in biomembranes: One is the classical Laplace–Beltrami operator ∇^2 and another is the new one $\overline{\nabla}^2$ [7,11]. Their analytical structures are as follows:

$$\nabla^2 = \frac{1}{\sqrt{g}}\frac{\partial}{\partial u^i}\left(\sqrt{g}g^{ij}\frac{\partial}{\partial u^j}\right) \tag{4}$$

$$\overline{\nabla}^2 = \frac{1}{\sqrt{g}}\frac{\partial}{\partial u^i}\left(\sqrt{g}\hat{L}^{ij}\frac{\partial}{\partial u^j}\right). \tag{5}$$

From differential geometry, we know that the first divergence of a vector $\boldsymbol{a} = a^i\boldsymbol{g}_i$ defined on the curved surface is calculated by $\nabla\cdot\boldsymbol{a} = \frac{1}{\sqrt{g}}\frac{\partial(\sqrt{g}a^i)}{\partial u^i}$. Let $\boldsymbol{a} = \nabla$ and $a^i = g^{ij}\frac{\partial}{\partial u^j}$, one has the formulation $\nabla\cdot\nabla = \frac{1}{\sqrt{g}}\frac{\partial}{\partial u^i}\left(\sqrt{g}g^{ij}\frac{\partial}{\partial u^j}\right) = \nabla^2$, which is exactly Eq. (4). Similarly, let $\boldsymbol{a} = \overline{\nabla}$ and $a^i = \hat{L}^{ij}\frac{\partial}{\partial u^j}$, one has $\nabla\cdot\overline{\nabla} = \frac{1}{\sqrt{g}}\frac{\partial}{\partial u^i}\left(\sqrt{g}\hat{L}^{ij}\frac{\partial}{\partial u^j}\right) = \overline{\nabla}^2$, which is exactly Eq. (5).

Various integral theorems based on the vector operator $\overline{\nabla}$ and the scalar one $\overline{\nabla}^2$ have been proved in Refs. [8,9]. In the following sections, these differential operators and integral theorems will be used to establish the equilibrium theory for heterogeneous biomembranes with arbitrary variational modes, and reveal the new equations in the tangential planes of heterogeneous biomembranes.

3. Equilibrium differential equations

3.1. Equilibrium differential equations for open biomembranes

An open biomembrane may be geometrically regarded as a curved surface A with a boundary curve C (Fig. 2). The general free energy density of such a heterogeneous biomembrane may be the function of the mean curvature H, the Gauss curvature K and the membrane density ρ as well, i.e. $\phi = \phi(H, K, \rho)$. The surface energy density is $\lambda = \lambda(u^i)$ and the edge energy density is $\gamma = \gamma(u^i)$. The total potential functional of the open heterogeneous biomembrane is given by the sum of the free energy, surface energy and edge energy:

$$F = \iint_A \phi(H, K, \rho)\mathrm{d}A + \iint_A \lambda\mathrm{d}A + \oint_C \gamma\mathrm{d}s. \tag{6}$$

Suppose that a virtual displacement vector $\boldsymbol{V}$ expressed in Eq. (1) takes place at every point of the surface. The equilibrium differential equation and boundary conditions may be derived through minimizing the total potential functional F:

$$\delta^{(1)}F = 0. \tag{7}$$

With the aid of the differential operators ∇, $\overline{\nabla}$, ∇^2, $\overline{\nabla}^2$ and their integral theorems, $\delta^{(1)}F$ may be simply formulated as (Appendix A):

$$\begin{aligned}\delta^{(1)}F = {} & \iint_A (\nabla\cdot\boldsymbol{U} + f)\psi\mathrm{d}A + \oint_C \left(\frac{1}{2}\phi_{,H} + \kappa_n\phi_{,K}\right)\boldsymbol{m}\cdot\nabla\psi\mathrm{d}s - \oint_C \left[\boldsymbol{m}\cdot\boldsymbol{U} + \kappa_n\gamma + \frac{\mathrm{d}(\tau_g\phi_{,K})}{\mathrm{d}s}\right]\psi\mathrm{d}s \\ & + \iint_A (\rho\nabla\phi_{,\rho} - \nabla\lambda)\cdot\boldsymbol{v}\mathrm{d}A + \oint_C \left[(\phi + \lambda - \phi_{,\rho}\rho - \kappa_g\gamma)\boldsymbol{m} - \frac{\mathrm{d}\gamma}{\mathrm{d}s}\boldsymbol{t}\right]\cdot\boldsymbol{v}\mathrm{d}s\end{aligned} \tag{8}$$

where

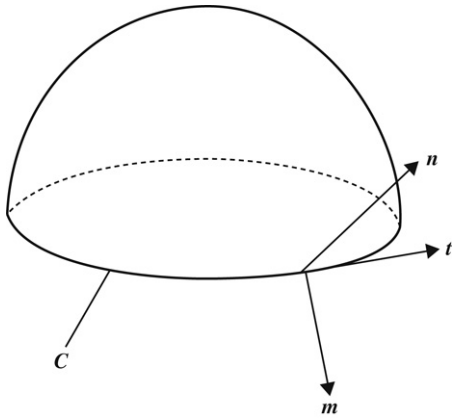

Fig. 2. A curved surface with boundary C. $\boldsymbol{n}$ is the unit normal of the surface. $\boldsymbol{t}$ is the unit tangent to the positive direction of the curve C. $\boldsymbol{m} = \boldsymbol{t} \times \boldsymbol{n}$ is the unit vector on the tangent plane and normal to the curve C.

$$f = (2H^2 - K)\phi_{,H} + 2HK\phi_{,K} - 2H(\lambda + \phi - \rho\phi_{,\rho}) \tag{9}$$

$$\phi_{,H} = \partial\phi/\partial H, \quad \phi_{,K} = \partial\phi/\partial K, \quad \phi_{,\rho} = \partial\phi/\partial\rho \tag{10}$$

$$\kappa_n = \frac{\mathrm{d}\boldsymbol{t}}{\mathrm{d}s} \cdot \boldsymbol{n}, \quad \kappa_g = -\frac{\mathrm{d}\boldsymbol{t}}{\mathrm{d}s} \cdot \boldsymbol{m}, \quad \tau_g = \frac{\mathrm{d}\boldsymbol{n}}{\mathrm{d}s} \cdot \boldsymbol{m}, \quad \boldsymbol{U} = \nabla\phi_{,H}/2 + \overline{\nabla}\phi_{,K}. \tag{11}$$

Here κ_n, κ_g and τ_g are respectively the normal curvature, geodesic curvature and geodesic torsion on curve C. $\boldsymbol{U}$ is an in-plane vector. Definitions of the unit vectors $\boldsymbol{t}$ and $\boldsymbol{m}$ on the boundary curve C are shown in Fig. 2. $\delta^{(1)}F$ in Eq. (8) includes two portions. One is the out-plane portion relevant to the normal displacement ψ. Another is the in-plane portion corresponds to the tangential displacement $\boldsymbol{v}$. The out-plane portion is the same as the first variation of the potential function for open biomembranes with normal variational mode [10], but the in-plane one is new.

For arbitrary normal displacement ψ and gradient $\nabla\psi$, $\delta^{(1)}F = 0$ will lead to:

$$\nabla \cdot \boldsymbol{U} + f = 0 \tag{12}$$

$$\left(\frac{1}{2}\phi_{,H} + \kappa_n\phi_{,K}\right)\Big|_C = 0 \tag{13}$$

$$\left[\boldsymbol{m} \cdot \boldsymbol{U} + \kappa_n\gamma + \frac{\mathrm{d}(\tau_g\phi_{,K})}{\mathrm{d}s}\right]\Big|_C = 0. \tag{14}$$

Eq. (12) is the equilibrium differential equation along the normal direction $\boldsymbol{n}$. This is a scalar differential equation with rank two, and two boundary conditions (i.e. Eqs. (13) and (14)) are necessary to determine its solutions. Eq. (13) means the equilibrium of bending moments along the direction $\boldsymbol{t}$ on curve C. Eq. (14) means the equilibrium of shearing forces along the direction $\boldsymbol{n}$ on curve C. Because Eqs. (12)–(14) depict the equilibrium outside the tangential plane of the biomembrane, they may be termed respectively the "out-plane equilibrium differential equation" and the "out-plane boundary conditions". Eqs. (12)–(14) are completely the same as these for open biomembranes with just normal variational mode [10].

For arbitrary tangential displacement vector $\boldsymbol{v}$, $\delta^{(1)}F = 0$ will assure:

$$\rho\nabla\phi_{,\rho} - \nabla\lambda = \boldsymbol{0} \tag{15}$$

$$\left[\left(\phi + \lambda - \rho\phi_{,\rho} + \kappa_g\gamma\right)\boldsymbol{m} - \frac{\mathrm{d}\gamma}{\mathrm{d}s}\boldsymbol{t}\right]\Big|_C = \boldsymbol{0}. \tag{16}$$

Eq. (15) is the equilibrium differential equation within the tangential plane of the biomembrane. This is a vector differential equation with rank one, and a vector boundary condition (i.e. Eq. (16)) is needed to determine its solutions. Because Eqs. (15) and (16) depict the equilibrium inside the tangential plane of the biomembrane, they may be termed respectively the "in-plane equilibrium differential equation" and the "in-plane boundary conditions".

Because of $\boldsymbol{m} \perp \boldsymbol{t}$, Eq. (16) may be further divided into two scalar equations:

$$(\phi + \lambda - \rho\phi_{,\rho} + \kappa_g\gamma)|_C = 0 \tag{16′}$$

$$\left.\frac{\mathrm{d}\gamma}{\mathrm{d}s}\right|_C = 0 \quad \text{or} \quad \gamma|_C = \text{Const.} \tag{16″}$$

Eq. (16′) implies the equilibrium of tensile forces along the direction $\boldsymbol{m}$ on the boundary C. Eq. (16″) means that the shearing force $\frac{\mathrm{d}\gamma}{\mathrm{d}s}$ along the tangential direction $\boldsymbol{t}$ of the boundary C must be zero—i.e. whatever the shape of the boundary C may be, γ should always be a constant. This is a combined constraint to the line tension γ both from geometry and from physics. It is a geometric requirement, because it comes from the variational transformations along the curved surface. It is also a physical constraint, because any gradient of the line tension γ will break balance and enable the lipid molecules to migrate from one location to another along the boundary curve. Although this constraint is obtained in heterogeneous biomembranes, it is also valid for homogeneous one.

Usually differential equation and its boundary conditions have strict correspondence in Euclidean space. However, this strict correspondence seems to be relaxed in a 2D Riemann curved surface such as a biomembrane. For example, for a uniform biomembrane, Eq. (15) may vanish, but Eq. (16) may still exist and slightly change into:

$$\left[(\phi + \lambda + \kappa_g\gamma)\boldsymbol{m} - \frac{\mathrm{d}\gamma}{\mathrm{d}s}\boldsymbol{t}\right]\Big|_C = \boldsymbol{0}. \tag{16‴}$$

Thus even for uniform biomembrane, Eq. (16‴) has to be observed to keep the boundary equilibrium. Generally, the existence of Eq. (16‴) may not cause contradictions. On the contrary, it may be used to determine the location and shape of the boundary curve in a uniform biomembrane.

3.2. Equilibrium differential equations for closed biomembranes

The total potential functional F for a closed heterogeneous biomembrane is:

$$F = \oiint_A \phi(H, K, \rho)\mathrm{d}A + \iiint_V \Delta p \mathrm{d}V + \oiint_A \lambda \mathrm{d}A \tag{17}$$

where $\Delta p = p_{\text{out}} - p_{\text{in}}$ is the difference between the outer and inner pressures acted on the biomembrane. Similar to the previous section, $\delta^{(1)}F$ for closed biomembranes may be written as (Appendix A):

$$\delta^{(1)}F = \oiint_A [(\nabla \cdot \boldsymbol{U} + f_p)\psi + (\rho\nabla\phi_{,\rho} - \nabla\lambda)\cdot\boldsymbol{v}]\mathrm{d}A. \tag{18}$$

$\delta^{(1)}F = 0$ will lead to the out-plane equilibrium differential equation and the in-plane one for closed biomembranes:

$$\nabla \cdot \boldsymbol{U} + f_p = 0 \tag{19}$$

$$\rho\nabla\phi_{,\rho} - \nabla\lambda = \boldsymbol{0} \tag{20}$$

where

$$f_p = f + \Delta p. \tag{21}$$

Different from open biomembrane, the closed one has no boundary conditions.

4. Geometrically constraint equations

As mentioned above, geometrically a biomembrane may be treated as a 2D Riemann manifold or curved surface. Physically such a membrane is self-organized through complicated interactions between various long-chain molecules and solutions. Thus a biomembrane may not be formed freely and strict constraints should be observed. Except for such physical constraints as the equilibrium differential equations and boundary conditions above, geometrical one (e.g. the so-called "geometrically constraint equations (GCE)") [10,12] are also indispensable.

4.1. Out-plane GCE for open or closed biomembranes

The concept of GCE is first defined in lipid bilayer vesicles [12]. Recently, this concept is further developed in heterogeneous biomembranes just with normal variational mode [10]. Mathematically, the GCE is originated from the integral theorems for differential operators, the equilibrium differential equations and boundary conditions for biomembranes. Since the out-plane equilibrium equations and boundary conditions for heterogeneous biomembranes with arbitrary variational mode are the same as that for biomembranes with normal variational mode, the out-plane GCE is also the same [10]. In Ref. [10], the proof for the out-plane GCE comes from the generalized Green's theorems about ∇^2 and $\overline{\nabla}^2$ [9]. Here, a different proof is suggested. In differential geometry, there is the conventional divergence theorem about the first gradient operator ∇ and any vector $\overline{\boldsymbol{V}}$:

$$\iint_A \nabla \cdot \overline{\boldsymbol{V}} \mathrm{d}A = \oint_C \overline{\boldsymbol{V}} \cdot \boldsymbol{m} \mathrm{d}s - \iint_A 2H\overline{\boldsymbol{V}} \cdot \boldsymbol{n} \mathrm{d}A. \tag{22}$$

In Eq. (22) by letting $\overline{\boldsymbol{V}} = \boldsymbol{U}$ and using Eq. (12), Eq. (14) and $\boldsymbol{U} \cdot \boldsymbol{n} = 0$, one has the out-plane GCE for open biomembranes:

$$\iint_A f \mathrm{d}A = \oint_C \kappa_n \gamma \mathrm{d}s = \gamma \oint_C \kappa_n \mathrm{d}s. \tag{23}$$

For closed one it becomes:

$$\oiint_A f_p \mathrm{d}A = 0. \tag{24}$$

4.2. In-plane GCE for open or closed biomembranes

In differential geometry, there is the conventional gradient theorem about the first gradient operator ∇:

$$\iint_A \nabla\varphi \mathrm{d}A = \oint_C \varphi \boldsymbol{m} \mathrm{d}s - \iint_A 2H\varphi \boldsymbol{n} \mathrm{d}A. \tag{25}$$

By letting $\varphi = \lambda$ and $\varphi = \rho\phi_{,\rho}$ respectively and using Eqs. (15) and (16′), one gets the in-plane GCE for open biomembranes:

$$\iint_A \vec{\boldsymbol{f}}\, \mathrm{d}A = \oint_C (\phi + \kappa_g \gamma) \mathrm{d}\boldsymbol{s}. \tag{26}$$

For closed one, the line integral in the right-hand side of Eq. (26) vanishes and the in-plane GCE becomes:

$$\oiint_A \vec{\boldsymbol{f}}\, \mathrm{d}A = \boldsymbol{0}. \tag{27}$$

Here $\vec{\boldsymbol{f}}$ is a vector function formulated by:

$$\vec{\boldsymbol{f}} = (\nabla\rho)\phi_{,\rho} - 2H(\lambda - \rho\phi_{,\rho})\boldsymbol{n}. \tag{28}$$

5. Discussions

Because the out-plane equations above are the same as that for biomembranes with normal variational mode [10] and the in-plane one are seldom reported in the literatures, the latter will be focused below.

5.1. Possible meanings and applications of the in-plane differential equations

Eq. (15) (or Eq. (20)) includes plentiful meanings: (a) There are two origins for the in-plane forces: One is the inhomogeneous density ρ, and another is the heterogeneous surface tension λ. Correspondingly there are two in-plane

forces: One equals to $\rho\nabla\phi_{,\rho}$, and another equals to $\nabla\lambda$. At equilibrium the two in-plane forces will be balanced and Eq. (15) (or Eq. (20)) will be satisfied. For heterogeneous biomembranes the existence of the in-plane forces and in-plane equilibrium differential equations implies that the interactions between constituents harden the membranes and enable them to resist in-plane tensile or shearing forces. (b) The surface tension λ and the density ρ strongly affect each other. This is true for cell membranes: The distribution of proteins on cell membranes may intensively change the surface tensions. In fact, interactions between proteins and lipid molecules vary the density distribution on biomembranes, which may in turn change the interactions between biomembranes and solutions and cause the redistribution of surface tensions. (c) For a uniform biomembrane such as lipid vesicles, one has $\rho = \text{Const.}$ and $\phi = \phi(H, K)$, and hence $\phi_{,\rho} = 0$ and $\nabla\phi_{,\rho} = 0$. This will assure, $\nabla\lambda = 0$ and $\lambda = \text{Const.}$ Thus for uniform biomembranes, both the in-plane forces and the in-plane equilibrium differential equations vanish. This implies that the fluidity of membranes makes them lose the ability to resist in-plane tensile or shearing forces.

Eq. (15) (or Eq. (20)) may be very useful. For given function $\phi = \phi(H, K, \rho)$ the in-plane equilibrium differential equations may quantitatively define the relation:

$$\rho = \rho(H, K, \lambda). \tag{29}$$

Eq. (29) may explain various interesting phenomena occurred on biomembranes. In the past years, experiments have shown that the aggregations and phase separations of constituents on biomembranes are always accompanied by the transitions in geometries and topologies [13]. Such phenomena may be well-annotated through Eq. (29). Since the density distribution and the bending extent of the biomembrane are coupled with each other, two conclusions may be drawn: On the one hand, certain curvature distribution will correspond to certain density distribution. On the other hand, the density redistribution will certainly cause the transition in shapes and topologies. This judgment qualitatively coincides with the phenomena observed in experiments [13].

The in-plane equilibrium differential equations may not be solved independently. To get the correct geometries and topologies of biomembranes, the out-plane equilibrium differential equation and the in-plane one should be combined together: The former mainly dominates the shapes of biomembranes, while the latter mainly controls the distributions of the heterogeneous constituents on biomembranes.

5.2. About the in-plane GCE

There are obvious differences between the in-plane GCE and the out-plane one: The former is a vector equation, while the latter is a scalar one. Even so as GCEs all the viewpoints about the out-plane GCE [10,12] are still valid for the in-plane one. Except for the common viewpoints in Refs. [10,12], there is a new one: i.e. the in-plane GCE clearly reflects the interactions between the heterogeneous matters distributed inside the biomembrane and the geometric space occupied by the biomembrane. To understand this judgment, the in-plane GCE for a homogeneous biomembrane may be taken as a contrast. On a homogeneous biomembrane the in-plane GCE (Eq. (26) or Eq. (27)) will become:

$$\iint_A (-2H\lambda)\boldsymbol{n}\mathrm{d}A = \oint_C (\phi + \kappa_g\gamma)\boldsymbol{m}\mathrm{d}s. \tag{30}$$

According to the analysis in Section 5.1, for uniform biomembrane there is $\lambda = \text{Const.}$ Then Eq. (30) may be rewritten as:

$$\iint_A 2H\boldsymbol{n}\mathrm{d}A = -\oint_C [(\phi + \kappa_g\gamma)/\lambda]\boldsymbol{m}\mathrm{d}s. \tag{31}$$

On the curve C there is also the boundary condition in Eq. (16′):

$$\left.\frac{(\phi + \kappa_g\gamma)}{\lambda}\right|_C = -1. \tag{32}$$

Thus Eq. (31) is equivalent to:

$$\iint_A 2H\boldsymbol{n}\mathrm{d}A = \oint_C \boldsymbol{m}\mathrm{d}s. \tag{33}$$

To one's surprise, Eq. (33) is exactly the conventional integral theorem about mean curvature H in differential geometry. This means that the in-plane GCE for uniform biomembranes is equivalent to the integral theorem. Hence

the in-plane GCE (Eqs. (26) or (27)) for heterogeneous biomembranes may be understood as the "weighted" integral theorem with the heterogeneity as the weight factors.

5.3. About the Riemann space viewpoint for biomembranes

This paper implies the Riemann space viewpoint: Not only biomembranes should be understood from the viewpoint of Riemann space, but also the theories (including the equilibrium theory) about biomembranes should be built on Riemann space instead of Euclidean space. This viewpoint may be essential for the following reasons:

First, as concrete examples of 2D Riemann manifolds, biomembranes should be interpreted from two sides: On the one hand they form 2D Riemann spaces. On the other hand they are formed in 2D Riemann spaces. In this sense we may say that biomembranes "chose" the 2D Riemann geometry and the most suitable geometry for biomembranes is the differential geometry.

Second, as the both sides of a coin, good physics and good geometry form the core of a good theory. To depict biomembranes properly, correct physics and suitable geometry should be combined organically. This regulation is observed in this equilibrium theory: The minimum energy principle comes from physics, while the differential operators and integral theorems origin from differential geometry. Perfect combinations between them make the equilibrium theory both simple and understandable.

Third, equilibrium theory in 2D Riemann space has its own characteristics and differences from that in Euclidean space. In Euclidean space, equilibrium theory only includes equilibrium differential equations and boundary conditions. In 2D Riemann space, equilibrium theory not only includes equilibrium differential equations and boundary conditions, but also consists of the GCEs. The former may theoretically define a solution space for equilibrium biomembranes. However, the latter may narrow this solution space—Once the GCEs are coupled, part of the solutions have to be cancelled out. Especially, the out-plane GCE may be the symbol for the equilibrium theory in 2D Riemann space—It only exists in 2D Riemann manifolds. It is the inevitable outcome of the integral theorems for differential operators in 2D Riemann space. Concretely speaking, it is the result of the divergence theorem for the gradient operator ∇ (or the Green theorems for the differential operators ∇^2 and $\overline{\nabla}^2$ [9,10]) on curved surfaces. In appearance the out-plane GCE is an integral equation, but in essence it is an algebraic one that defines a "parameter space" including all the physical coefficients (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 coefficients and the geometrical sizes of the biomembrane are not independent with each other. Here we see more clearly the differences between structures in Euclidean space and 2D Riemann manifold—In Euclidean space, physical coefficients are seldom related to geometrical ones. In short, the out-plane GCE mainly reflects the characteristics of the curved space occupied by the biomembrane.

6. Conclusions

This paper develops a unified mathematical frame for heterogeneous biomembranes with the aid of differential operators and their integral theorems on curved surface. The equilibrium differential equations, boundary conditions and geometrically constraint equations both in normal direction and within the tangential plane of the biomembranes are derived. From the mathematical frame, our knowledge about heterogeneous biomembranes with arbitrary deformation modes may be enriched, and the behaviors of heterogeneous biomembranes may be better understood. Besides, the differences between such soft matters as biomembrane in 2D Riemann space and structures in Euclidean space are annotated.

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Appendix A. The first variation of the potential functional

The first variation of the total potential functional F for open heterogeneous biomembranes in Eq. (6) can be expressed as:

$$\delta^{(1)}F = \iint_A (\phi_{,H}\delta^{(1)}H + \phi_{,K}\delta^{(1)}K + \phi_{,\rho}\delta^{(1)}\rho)\mathrm{d}A + \iint_A (\phi+\lambda)\delta^{(1)}\mathrm{d}A + \oint_C \gamma\delta^{(1)}\mathrm{d}s. \tag{A.1}$$

Substitution of $\delta^{(1)}\mathrm{d}s$, $\delta^{(1)}\mathrm{d}A$, $\delta^{(1)}H$, $\delta^{(1)}K$ and $\delta^{(1)}\rho$ in Appendix B into Eq. (A.1) will lead to:

$$\begin{aligned}\delta^{(1)}F = {} & \iint_A \left[\frac{1}{2}\phi_{,H}(\nabla^2\psi + 2\nabla H\cdot\boldsymbol{v}) + \phi_{,K}(\nabla^2\psi + \nabla K\cdot\boldsymbol{v}) - \rho\phi_{,\rho}\nabla\cdot\boldsymbol{v}\right]\mathrm{d}A \\ & + \iint_A [(\phi+\lambda)\nabla\cdot\boldsymbol{v} + f\psi]\mathrm{d}A - \oint_c \gamma(\kappa_n\psi - \kappa_g\boldsymbol{m}\cdot\boldsymbol{v})\mathrm{d}s.\end{aligned} \tag{A.2}$$

According to the integral theorems in Refs. [8,9], Eq. (A.2) may be further written as:

$$\begin{aligned}\delta^{(1)}F = {} & \iint_A \left(\frac{1}{2}\nabla^2\phi_{,H} + \overline{\nabla^2}\phi_{,K} + f\right)\psi\mathrm{d}A - \oint_C \left(\kappa_n\gamma + \frac{1}{2}\boldsymbol{m}\cdot\nabla\phi_{,H} + \boldsymbol{m}\cdot\overline{\nabla}\phi_{,K}\right)\psi\mathrm{d}s \\ & + \oint_c \left(\frac{1}{2}\phi_{,H}\boldsymbol{m}\cdot\nabla\psi + \phi_{,K}\boldsymbol{m}\cdot\overline{\nabla}\psi\right)\mathrm{d}s + \iint_A [\phi_{,H}\nabla H + \phi_{,K}\nabla K + \nabla(\rho\phi_{,\rho} - \phi - \lambda)]\cdot\boldsymbol{v}\mathrm{d}A \\ & + \oint_C \left[(\phi + \lambda - \phi_{,\rho}\rho + \kappa_g\gamma)\boldsymbol{m} - \frac{\mathrm{d}\gamma}{\mathrm{d}s}\boldsymbol{t}\right]\cdot\boldsymbol{v}\mathrm{d}s.\end{aligned} \tag{A.3}$$

On the boundary C the line integral term $\oint_C \phi_{,K}\boldsymbol{m}\cdot\overline{\nabla}\psi\mathrm{d}s$ needs to be specially treated. It is easy to get the relations $\boldsymbol{m}\cdot\hat{\boldsymbol{L}} = \kappa_n\boldsymbol{m} + \tau_g\boldsymbol{t}$ and $\boldsymbol{m}\cdot\overline{\nabla}\psi = \boldsymbol{m}\cdot\hat{\boldsymbol{L}}\cdot\nabla\psi = (\kappa_n\boldsymbol{m} + \tau_g\boldsymbol{t})\cdot\nabla\psi$. The line integral term may be rewritten as:

$$\oint_C \phi_{,K}\boldsymbol{m}\cdot\overline{\nabla}\psi\mathrm{d}s = \oint_C \kappa_n\phi_{,K}\boldsymbol{m}\cdot\nabla\mathrm{d}s - \oint_C \psi\mathrm{d}(\tau_g\phi_{,K}). \tag{A.4}$$

Note the following differential relations:

$$\nabla(\rho\phi_{,\rho}) = \rho(\nabla\phi_{,\rho}) + \phi_{,\rho}\nabla\rho \tag{A.5}$$

$$\nabla\phi = \phi_{,H}\nabla H + \phi_{,K}\nabla K + \phi_{,\rho}\nabla\rho. \tag{A.6}$$

Eqs. (A.3)–(A.6) will lead to Eq. (8).

The first variation of the total potential functional F for closed biomembranes in Eq. (17) can be expressed as:

$$\delta^{(1)}F = \oiint_A (\phi_{,H}\delta^{(1)}H + \phi_{,K}\delta^{(1)}K + \phi_{,\rho}\delta^{(1)}\rho)\mathrm{d}A + \oiint_A (\phi+\lambda)\delta^{(1)}\mathrm{d}A + \iiint_V \Delta p\delta^{(1)}\mathrm{d}V \tag{A.7}$$

Substituting $\delta^{(1)}\mathrm{d}A$, $\delta^{(1)}\mathrm{d}V$, $\delta^{(1)}H$, $\delta^{(1)}K$ and $\delta^{(1)}\rho$ in Appendix B into Eq. (A.7) one obtains:

$$\delta^{(1)}F = \oiint_A \left(\frac{1}{2}\nabla^2\phi_{,H} + \overline{\nabla^2}\phi_{,K} + f_p\right)\psi\mathrm{d}A + \oiint [\phi_{,H}\nabla H + \phi_{,K}\nabla K + \nabla(\rho\phi_{,\rho} - \phi - \lambda)]\cdot\boldsymbol{v}\mathrm{d}A. \tag{A.8}$$

From Eqs. (A.5), (A.6) and (A.8), Eq. (18) can be derived.

Appendix B. The first variations of relevant geometric quantities

In this appendix the variations of the line element $\mathrm{d}s$, the area element $\mathrm{d}A$, the volume element $\mathrm{d}V$, the mean curvature H, the Gauss curvature K and the density ρ will be derived. Although these variations have been studied in the past, this appendix will express them by differential operators under arbitrary variational mode.

Suppose the surface A with position vector $\boldsymbol{r}$ takes place an arbitrary infinitesimal virtual displacement vector $\delta\boldsymbol{r} = \boldsymbol{V}$ and deforms to a new surface A' with position vector $\boldsymbol{r}'$. Then one has (see Fig. 1):

$$\delta\boldsymbol{r} = \boldsymbol{r}' - \boldsymbol{r} = \boldsymbol{V} = \boldsymbol{v} + \psi\boldsymbol{n}. \tag{B.1}$$

According to the Weingarten formula, the first variation of the covariant base vectors is:

$$\delta^{(1)}\boldsymbol{g}_i = \delta\boldsymbol{r}_{,i} = (\nabla_i v_j - \psi L_{ij})\boldsymbol{g}^j + (v^j L_{ij} + \psi_{,i})\boldsymbol{n}. \tag{B.2}$$

Here $\nabla_i v_j = (v_j)_{,i} - v_k \Gamma^k_{ij}$ is the covariant derivative of v_j. The first variation of g_{ij} is given by:

$$\delta^{(1)} g_{ij} = \delta^{(1)}(\boldsymbol{g}_i \cdot \boldsymbol{g}_j) = \delta^{(1)}\boldsymbol{g}_i \cdot \boldsymbol{g}_j + \boldsymbol{g}_i \cdot \delta^{(1)}\boldsymbol{g}_j = 2(\nabla_i v_j - \psi L_{ij}). \tag{B.3}$$

From Eq. (B.3), the first variations of g and $\sqrt{g}$ may be ascertained:

$$\delta^{(1)} g = 2g(\nabla \cdot \boldsymbol{v} - 2H\psi) \tag{B.4}$$

$$\delta^{(1)}\sqrt{g} = \frac{\delta^{(1)} g}{2\sqrt{g}} = \sqrt{g}(\nabla \cdot \boldsymbol{v} - 2H\psi). \tag{B.5}$$

With the aid of Eqs. (B.2) and (B.3) and the relations $g^{ij} = \boldsymbol{g}^i \boldsymbol{g}^j$ and $g_k = g_{kl}\boldsymbol{g}^l$, the first variation of g^{ij} is formulated by:

$$\delta^{(1)} g^{ij} = -2g^{im} g^{jn} \nabla_m v_n + 2\psi(2Hg^{ij} - \hat{L}^{ij}). \tag{B.6}$$

The length of the line element $\mathrm{d}s$ is defined as:

$$(\mathrm{d}s)^2 = \mathrm{d}\boldsymbol{r} \cdot \mathrm{d}\boldsymbol{r} = g_{ij}\mathrm{d}u^i \mathrm{d}u^j. \tag{B.7}$$

Take the first variation at both sides:

$$2\mathrm{d}s(\delta^{(1)}\mathrm{d}s) = (\delta^{(1)} g_{ij})\mathrm{d}u^i \mathrm{d}u^j = 2\mathrm{d}\boldsymbol{r} \cdot (\nabla \boldsymbol{v} - \psi \boldsymbol{L}) \cdot \mathrm{d}\boldsymbol{r}. \tag{B.8}$$

Eqs. (B.3) and (B.8) may give:

$$\delta^{(1)}\mathrm{d}s = d(\boldsymbol{t} \cdot \boldsymbol{v}) + (\kappa_g \boldsymbol{m} \cdot \boldsymbol{v} - \kappa_n \psi)\mathrm{d}s. \tag{B.9}$$

The first variation of the area element $\mathrm{d}A$ is:

$$\delta^{(1)}\mathrm{d}A = \delta^{(1)}\left(\sqrt{g}\mathrm{d}u^1 \mathrm{d}u^2\right) = \delta^{(1)}\left(\sqrt{g}\right)\mathrm{d}u^1 \mathrm{d}u^2. \tag{B.10}$$

Substitution of Eq. (B.5) into Eq. (B.10) one obtains:

$$\delta^{(1)}\mathrm{d}A = (\nabla \cdot \boldsymbol{v} - 2H\psi)\mathrm{d}A. \tag{B.11}$$

With the aid of the definition of $\boldsymbol{n}$ and Eq. (B.5), $\delta^{(1)}\boldsymbol{n}$ may be determined:

$$\delta^{(1)}\boldsymbol{n} = -(\boldsymbol{L} \cdot \boldsymbol{v} + \nabla\psi). \tag{B.12}$$

The volume element is defined as $\mathrm{d}V = \frac{1}{3}\boldsymbol{r} \cdot \boldsymbol{n}\mathrm{d}A$. $\delta^{(1)}\mathrm{d}V$ is given by:

$$\delta^{(1)}\mathrm{d}V = \frac{1}{3}[(\delta\boldsymbol{r} \cdot \boldsymbol{n} + \boldsymbol{r} \cdot \delta^{(1)}\boldsymbol{n})\mathrm{d}A + \boldsymbol{r} \cdot \boldsymbol{n}\delta^{(1)}\mathrm{d}A]. \tag{B.13}$$

Combination of Eqs. (B.12) and (B.13) will assure:

$$\delta^{(1)}\mathrm{d}V = \left\{\frac{1}{3}\nabla \cdot [(\boldsymbol{r} \cdot \boldsymbol{n})\boldsymbol{v} - \psi\boldsymbol{r}] + \psi\right\}\mathrm{d}A. \tag{B.14}$$

From the definition of L_{ij}, the first variation $\delta^{(1)} L_{ij}$ is:

$$\begin{aligned}\delta^{(1)} L_{ij} &= \boldsymbol{n} \cdot \delta^{(1)}\boldsymbol{r}_{,ij} + \delta^{(1)}\boldsymbol{n} \cdot \boldsymbol{r}_{,ij} \\ &= \boldsymbol{n} \cdot \boldsymbol{v}_{,ij} - v^k L_{kl}\Gamma^l_{ij} + \nabla_i \psi_{,j} - (2HL_{ij} - Kg_{ij})\Psi \\ &= \boldsymbol{n} \cdot \nabla_i \boldsymbol{v}_{,j} + \nabla_i \Psi_{,j} - (2HL_{ij} - Kg_{ij})\Psi.\end{aligned} \tag{B.15}$$

Eqs. (B.2), (B.12) and (B.15) will lead to:

$$\delta^{(1)} L = L\overline{L}^{ij}\delta^{(1)} L_{ij} = g(\boldsymbol{n} \cdot \overline{\nabla}^2 \boldsymbol{v} + \overline{\nabla}^2\psi - 2HK\psi). \tag{B.16}$$

$\delta^{(1)}H$ is formulated by:

$$\delta^{(1)}H = \frac{1}{2}\delta^{(1)}(g^{ij}L_{ij}) = \frac{1}{2}(L_{ij}\delta^{(1)}g^{ij} + g^{ij}\delta^{(1)}L_{ij}). \tag{B.17}$$

Through substituting Eqs. (B.6) and (B.15) into Eq. (B.17) one has:

$$\delta^{(1)}H = \frac{1}{2}[\nabla^2\psi + 2(2H^2 - K)\psi + 2\nabla H \cdot \boldsymbol{v}]. \tag{B.18}$$

$\delta^{(1)}K$ may be written as:

$$\delta^{(1)}K = \delta^{(1)}\left(\frac{L}{g}\right) = \frac{1}{g}\delta^{(1)}L - \frac{L}{g^2}\delta^{(1)}g = \frac{1}{g}[\delta^{(1)}L - K\delta^{(1)}g]. \tag{B.19}$$

Combination of Eqs. (B.19), (B.4) and (B.16) will lead to:

$$\begin{aligned}\delta^{(1)}K &= \overline{\nabla}^2\psi + 2HK\psi + (\boldsymbol{n}\cdot\overline{\nabla}^2\boldsymbol{v} - 2K\nabla\cdot\boldsymbol{v}) \\ &= \overline{\nabla}^2\psi + 2HK\psi + \nabla K\cdot\boldsymbol{v}.\end{aligned} \tag{B.20}$$

Suppose that there are no diffusions of molecules on biomembranes during variational process. Then according to the mass conservation law, i.e. $\rho \mathrm{d}A = \text{Const.}$, one has:

$$\delta^{(1)}(\rho \mathrm{d}A) = (\delta^{(1)}\rho)\mathrm{d}A + \rho\delta^{(1)}\mathrm{d}A = 0. \tag{B.21}$$

Substitution of Eq. (B.11) into Eq. (B.21) will assure:

$$\delta^{(1)}\rho = -\rho(\nabla\cdot\boldsymbol{v} - 2H\psi). \tag{B.22}$$

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