Several mathematical problems in elastic theory of biomembranes

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Outline

• Introduction
• Variational problems
• Problems on solutions
• Summary and perspectives
I. Introduction

--- Biological background
Human (normal): diameter 8μm, height 2 μm; **biconcave** discoid (why?)

No inner cellular organelles. Shapes are determined by membranes.
Cell membrane

Fluid mosaic model
[Singer & Nicolson (1972) Science]

Shape determined mainly by lipid bilayer.

Lipid bilayer in **liquid crystal** phase
Experiment: lipid vesicles opened by Talin

Experimental fact: The size of hole is enlarged with increasing the concentration of talin

[Saitoh et al. (1998) PNAS]
Two key problems we may deal with

- How to derive the equation(s) to describe the equilibrium configurations?
- Can we find the solutions to this (these) equation(s)? We may explain
  - Why do RBCs have biconcave discoid shapes?
  - Opening process of vesicles by talin
II. Variational problems
Curvatures of a surface

- Principal curvatures
  Rotate 2 normal plane, curvature radii of 2 curves varies.

\[ c_1 = -\frac{1}{\min\{R_1\}}, \quad c_2 = -\frac{1}{\max\{R_2\}} \]

- Mean and gaussian curvatures

\[ H = \frac{c_1 + c_2}{2}, \quad K = c_1 c_2 \]
A curve in a surface

- Geodesic curvature & normal curvature
  
  $k_g$: Curvature of $C'$ at $P$ (roughly)
  
  $k_g = \kappa n \cdot n'$  (exactly)

  $k_n$: Curvature of $C''$ at $P$ (roughly)
  
  $k_n = \kappa n \cdot N$  (exactly)

  Obviously, $k_g^2 + k_n^2 = \kappa^2$

- Geodesic torsion
  
  $\tau_g = -\dot{N} \cdot n'$

$t, n$: tangent and normal vectors of $C$

$N$: normal vector of surface

$n'$: normal vector of $C'$, such that

$\{t, n', N\}$ right-handed
Free energy

• Min $F \iff$ equilibrium shapes

Finding $\min F \iff$ Solving $\delta F=0$

Stable: $\delta^2 F>0$; unstable: $\delta^2 F<0$
The meaning of variation

\[ \delta F = F[M'] - F[M] \quad \text{for} \quad M' \rightarrow M \]

\(\delta F = 0 \Rightarrow \) Euler-Lagrange equation(s) describing equilibrium shapes
Variational problems on shapes in history

- **Fluid films**
  Viewed as a surface in mathematics

  # Soap films ---- minimal surfaces, Plateau (1803)

  \[ F = \lambda \int dA \quad \delta F = 0 \Rightarrow H = 0 \]

  # Soap bubble ---- sphere, Young (1805), Laplace (1806)

  \[ F = \lambda \int dA + \Delta p \int dV \]

  \[ \delta F = 0 \Rightarrow H = \Delta p / 2 \lambda \]

  "An embedded surface with constant mean curvature in \( E^3 \) must be a spherical surface"

  --- Alexandrov (1950s)
• Solid shells

# Possion (1821)

\[ F = \int H^2 \, dA \]

# Schadow (1922)

\[ \delta F = 0 \Rightarrow \nabla^2 H + 2H(H^2 - K) = 0 \]

Laplace operator

# Willmore (1982) problem of surfaces

Finding surfaces satisfying the above equation.
- Lipid bilayer (almost in-plane incompressible)

  # Spontaneous curvature energy, Helfrich (1973)

  \[ g = \frac{k_c}{2} (2H + c_0)^2 - k K \]

  spontaneous curvature

  Analogy

  Bending LC box \[ \Rightarrow \] Lipid bilayer

  # Shape equation of vesicles, Ou-Yang & Helfrich (1987)

  \[ F = \int g \, dA + \int \lambda \, dA + \Delta p \int dV \]

  \[ \delta F = 0 \Rightarrow \Delta p - 2 \lambda H + 2k_c \nabla^2 H + k_c (2H + c_0)(2H^2 - c_0 H - 2K) = 0 \]

  \[ k_c = 0 \Rightarrow \Delta p - 2 \lambda H = 0 \text{ (Young–Laplace equation)} \]

  \[ \Delta p = 0, \lambda = 0, c_0 = 0 \Rightarrow \nabla^2 H + 2H (H^2 - K) = 0 \text{ (Willmore surfaces)} \]
Calculus of variation with the moving frame method

- **Moving frame method** [Chern, Lectures On Differential Geometry]

  # Orthogonal moving frame

  \[
  e_i \cdot e_j = \delta_{ij}, \quad (i, j = 1, 2, 3)
  \]

  \[
  \{ P; e_1, e_2, e_3 \}
  \]

  # Differential of frame

  \[
  dr = \lim_{P \rightarrow P'} PP' = \omega_1 e_1 + \omega_2 e_2
  \]

  \[
  de_i = \omega_{ij} e_j; \quad \omega_{ij} = -\omega_{ji}, \quad (i = 1, 2, 3)
  \]

  \[
  \omega_1 \wedge \omega_2 \text{ is the area element } dA
  \]
# Structure equations of the surface

\[
d\mathbf{r} = 0 \quad \& \quad d\mathbf{e}_i = 0
\]

\[
d\omega_1 = \omega_{12} \wedge \omega_2;
\]

\[
d\omega_2 = \omega_{21} \wedge \omega_1;
\]

\[
\omega_1 \wedge \omega_{13} + \omega_2 \wedge \omega_{23} = 0;
\]

\[
d\omega_{ij} = \omega_{ik} \wedge \omega_{kj} \quad (i, j = 1, 2, 3)
\]

\[
\omega_1 \wedge \omega_{13} + \omega_2 \wedge \omega_{23} = 0 (Cartan)
\]

\[
\Rightarrow \omega_{13} = a\omega_1 + b\omega_2, \omega_{23} = b\omega_1 + c\omega_2
\]

Curvature matrix

\[
\begin{pmatrix}
a & b \\
b & c
\end{pmatrix}
\]

\[
\text{Mean curvature: } H = (a + c)/2
\]

\[
\text{Gaussian curvature: } K = ac - b^2
\]
• Hodge star * operator

\[ *f = f\omega_1 \wedge \omega_2; \]
\[ *\omega_1 = \omega_2, *\omega_2 = -\omega_1; \]

**Definition**

\[ \text{define } \nabla^2 f : d * df = \nabla^2 f\omega_1 \wedge \omega_2 \]

\[ \text{Laplace operator (of the first kind)} \]

**The second Green identity:** for functions \( f \) and \( h \) defined on the surface \( M \)

\[ \int_M (f d * dh - hd * df) = \int_{\partial M} (f * dh - h * df) \]

\[ \int_M (f \nabla^2 h - h \nabla^2 f) dA = \int_{\partial M} \left( f \frac{\partial h}{\partial n} - h \frac{\partial f}{\partial n} \right) ds \]

[Westenholz, *Differential Forms in Mathematical Physics*]
Modified Hodge star * operator

Define $\tilde{*}$:

$\tilde{*} \omega_{13} = \omega_{23}, \tilde{*} \omega_{23} = -\omega_{13}$

Define $\tilde{d}$:

$\tilde{d} f = f_1 \omega_{13} + f_2 \omega_{23}$ if $df = f_1 \omega_1 + f_2 \omega_2$

Two identities (similar to Green 2nd identity): for functions $f$ and $h$ defined on the surface $M$

$$\int_M (f \tilde{d} \tilde{*} \tilde{d} h - h \tilde{d} \tilde{*} \tilde{d} f) = \int_{\partial M} (f \tilde{*} \tilde{d} h - h \tilde{*} \tilde{d} f)$$

$$\int_M f \tilde{d} \tilde{*} \tilde{d} h - h \tilde{d} \tilde{*} \tilde{d} f = \int_{\partial M} f \tilde{*} \tilde{d} h - h \tilde{*} \tilde{d} f$$

Here we can define the Laplace operators of the second and third kinds

Define $\nabla \cdot \tilde{\nabla}$:

$$d \tilde{*} \tilde{d} f = \nabla \cdot \tilde{\nabla} f \omega_1 \wedge \omega_2$$

Define $\nabla \cdot \tilde{\nabla}$:

$$d \ast \tilde{d} f = \nabla \cdot \tilde{\nabla} \omega_1 \wedge \omega_2$$
- **Calculus of variation**

  # Variation of the frame

\[ \delta \mathbf{r} \equiv \mathbf{v} = \Omega_{,j} \mathbf{e}_j \]

\[ \delta \mathbf{e}_i = \Omega_{,ij} \mathbf{e}_j, \quad (i = 1, 2, 3) \]

# Fundamental equations in the variational theory of surface

\[ \delta \omega_1 = d\mathbf{v} \cdot \mathbf{e}_1 - \omega_2 \Omega_{21} \]

\[ \delta \omega_2 = d\mathbf{v} \cdot \mathbf{e}_2 - \omega_1 \Omega_{12} \]

\[ \Omega_{13} = \Omega_{3,1} + a \Omega_1 + b \Omega_2 \]

\[ \Omega_{23} = \Omega_{3,2} + b \Omega_1 + c \Omega_2 \]

\[ \delta \omega_{ij} = d\Omega_{ij} + \Omega_{il} \omega_{lj} - \omega_{il} \Omega_{lj} \]

• General variational problem on 2D surface

Variation of area element and curvatures

\[ \delta dA = (\text{div} \, \mathbf{v} - 2H \Omega_3) \, dA \]

\[ \delta (2H) = [\nabla^2 + (4H^2 - 2K)] \Omega_3 + \nabla (2H) \cdot \mathbf{v} \]

\[ \delta K = \nabla \cdot \tilde{\nabla} \Omega_3 + 2KH \Omega_3 + \nabla K \cdot \mathbf{v} \]

Variational problem on a closed surface

Free energy functional

\[ \mathcal{F} = \int_M \mathcal{E}(2H[\mathbf{r}], K[\mathbf{r}]) \, dA + \Delta p \int_V dV \]

Euler-Lagrange equation (be also called shape equation)

\[ \left( \nabla^2 + 4H^2 - 2K \right) \frac{\partial}{\partial (2H)} \left( \nabla \cdot \tilde{\nabla} + 2KH \right) \frac{\partial}{\partial K} - 2H \right] \mathcal{E} + \Delta p = 0 \]

For lipid vesicles

\[ \mathcal{E} = \frac{k_c}{2} (2H + c_0)^2 + \tilde{k}K + \lambda \]

OuYang-Helfrich equation
# Variational problem on an open surface

Free energy functional

\[ \mathcal{F} = \int_M \mathcal{E}(2H[r], K[r]) \, dA + \int_C \Gamma(k_n, k_g) \, ds \]

Euler-Lagrange equation (be also called shape equation)

\[
\left( \nabla^2 + 4H^2 - 2K \right) \frac{\partial \mathcal{E}}{\partial (2H)} + \left( \nabla \cdot \tilde{\nabla} + 2KH \right) \frac{\partial \mathcal{E}}{\partial K} - 2H \mathcal{E} = 0
\]

Boundary conditions

\[
\begin{align*}
\mathbf{e}_2 \cdot \nabla \left[ \frac{\partial \mathcal{E}}{\partial (2H)} \right] + \mathbf{e}_2 \cdot \tilde{\nabla} \left( \frac{\partial \mathcal{E}}{\partial K} \right) - \frac{d}{ds} \left( \tau_g \frac{\partial \mathcal{E}}{\partial K} \right) + \frac{d^2}{ds^2} \left( \frac{\partial \Gamma}{\partial k_n} \right) + \left. \frac{\partial \Gamma}{\partial k_n} (k_n^2 - \tau_g^2) \right|_C &= 0, \\
\left. - \frac{\partial \mathcal{E}}{\partial (2H)} - k_n \frac{\partial \mathcal{E}}{\partial K} + \frac{\partial \Gamma}{\partial k_n} k_n - \frac{\partial \Gamma}{\partial k_n} k_g \right|_C &= 0, \\
\frac{d^2}{ds^2} \left( \frac{\partial \Gamma}{\partial k_g} \right) + K \frac{\partial \Gamma}{\partial k_g} - k_g \left( \Gamma - \frac{\partial \Gamma}{\partial k_g} k_g \right) + 2(k_n - H)k_g \frac{\partial \Gamma}{\partial k_n} &= 0, \\
-\tau_g \frac{d}{ds} \left( \frac{\partial \Gamma}{\partial k_n} \right) - \frac{d}{ds} \left( \tau_g \frac{\partial \Gamma}{\partial k_n} \right) - \mathcal{E} \bigg|_C &= 0.
\end{align*}
\]
For open lipid membranes with free edges

\[ \mathcal{E} = \frac{k_c}{2} (2H + c_0)^2 + \bar{k}K + \lambda \quad \Gamma = \gamma = \text{const.} \]

\[ \kappa_c (2H + c_0)(2H^2 - c_0H - 2K) - 2\lambda H + \kappa_c \nabla^2 (2H) = 0 \]

\[ \left[ \kappa_c (2H + c_0) + \bar{k}k_n \right]_C = 0 \]

\[ \left[ -2\kappa_c \frac{\partial H}{\partial e_2} + \gamma k_n + \bar{k} \frac{d\tau_g}{ds} \right]_C = 0 \]

\[ \left[ \frac{\kappa_c}{2} (2H + c_0)^2 + \bar{k}K + \lambda + \gamma k_g \right]_C = 0 \]

III. Problems on solutions
Analytic solutions (lipid vesicles)

- Shape equation

\[ \Delta p - 2\lambda H + k_c \nabla^2 (2H) + k_c (2H + c_0)(2H^2 - c_0 H - 2K) = 0 \]

Fourth order nonlinear PDE!

- Spherical vesicles

\[ \Delta p R^2 + (2\lambda + k_c c_0^2) R - 2k_c c_0 = 0 \]

\[ H = -\frac{1}{R}, \quad K = \frac{1}{R^2} \]
• Torus [Ou-Yang (1990) PRA]

\[
\{(r + \rho \cos \varphi) \cos \theta, (r + \rho \cos \varphi) \sin \theta, \rho \sin \varphi\}
\]

\[
2H = -\frac{r + 2\rho \cos \varphi}{\rho (r + \rho \cos \varphi)}; \quad K = \frac{\cos \varphi}{\rho (r + \rho \cos \varphi)}
\]

\[
\frac{r}{\rho} = \sqrt{2} \Rightarrow \frac{D}{d} = \sqrt{2} + 1 \approx 2.4
\]

[Mutz-Bensimon (1991) PRA]
● Axisymmetric surface and Biconcave discoid

\[ \Delta p - 2\lambda H + 2k_c \nabla^2 H + k_c (2H + c_0)(2H^2 - c_0H - 2K) = 0 \]

Axisymmetric \( \Psi = \sin \psi \)

\[
\frac{1}{2} \left( \frac{\rho \Psi'}{\rho} + c_0 \right) \left\{ \rho \left( \frac{\Psi'}{\rho} \right)' \right\}^2 - \frac{c_0 (\rho \Psi')'}{\rho} \} - \frac{\lambda (\rho \Psi')'}{k_c \rho} \\
+ \left\{ \rho \left( \frac{(\rho \Psi')'}{\rho} \right)' \right\} \frac{1 - \Psi^2}{\rho} - \left[ \frac{(\rho \Psi')'}{\rho} \right]' \Psi \Psi' + \frac{p}{k_c} = 0
\]

[Hu & Ou-Yang (1993) PRE]

For \( -e < c_0 \rho_B < 0 \)

\[
\begin{cases}
\sin \psi = c_0 \rho \ln(\rho / \rho_B) \\
z = z_0 + \int_0^\rho \tan \psi \, d\rho
\end{cases}
\]

describe a biconcave outline

[Naito,Okuda, Ou-Yang (1993) PRE]

[Evans&Fung (1972) Microvasc Res]
Solutions (open lipid membranes)

- Theorems of non-existence

Why non-existence? For a given surface $M$ satisfying SEq, we may not always find a curve $C$ satisfying BCs as the free edge.

Scaling analysis

\[
F = \int [(k_c/2)(2H)^2 + \bar{k}K]dA \\
+ 2k_c c_0 \int H dA + (\lambda + k_c c_0^2 / 2)A + \gamma L
\]

Under the scaling transformation $r \rightarrow \Lambda r$

\[
F(\Lambda) = \int [(k_c/2)(2H)^2 + \bar{k}K]dA \\
+ 2k_c c_0 \Lambda \int H dA + (\lambda + k_c c_0^2 / 2)\Lambda^2 A + \gamma \Lambda L
\]
Equilibrium configurations ⇔ $\delta F = 0 ⇔ \frac{\partial F}{\partial \Lambda} \bigg|_{\Lambda=1} = 0$

$$2c_0 \int H \, dA + (2\tilde{\lambda} + c_0^2) A + \tilde{\gamma} L = 0$$

with $\tilde{\lambda} = \frac{\lambda}{k_c}$, $\tilde{\gamma} = \frac{\gamma}{k_c}$

Willmore surfaces: $\nabla^2 H + 2H(H^2 - K) = 0$

that SEq with vanishing $c_0$, $\lambda$

The line tension always positive: $\gamma > 0$

Theorem 1: There is no open lipid membrane with free edge(s) being a part of a Willmore surface
# Axisymmetric open membranes

**SEq=>** \((h - c_0) \left( \frac{h^2}{2} + \frac{c_0 h}{2} - 2K \right) - \tilde{\lambda} h + \frac{\cos \psi}{\rho} (\rho \cos \psi h')' = 0\)

where \(h \equiv \sin \psi / \rho + (\sin \psi)'\) and \(K \equiv \sin \psi (\sin \psi)' / \rho\)

Integrable,

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

\[
\begin{aligned}
\left[ h - c_0 + \tilde{k} \sin \frac{\psi}{\rho} \right]_C &= 0 \\
\left[ -\sigma \cos \psi h' + \tilde{\gamma} \sin \psi / \rho \right]_C &= 0 \\
\left[ \tilde{k}^2 \left( \frac{\sin \psi}{\rho} \right)^2 + \tilde{k} K + \tilde{\lambda} - \sigma \tilde{\gamma} \frac{\cos \psi}{\rho} \right]_C &= 0
\end{aligned}
\]

where \(\tilde{k} = \bar{k} / k_c\)

The point at the free edge should satisfy the above four equation, thus we derive

**Condition of consistency:** \(\eta_0 = 0\)
Does there exist an axisymmetric open membrane being a part of a torus or a biconcave discoid?

**Generation curves:**

\[
\sin \psi = \alpha \rho + \sqrt{2}, \alpha \neq 0 \\
\eta_0 = -\alpha \neq 0
\]

\[
\sin \psi = c_0 \rho \ln \left(\rho / \rho_B\right), c_0 \neq 0 \\
\eta_0 = -2c_0 \neq 0
\]

Condition of consistency is violated! Thus we have

**Theorem 2.** There is no axisymmetric open membrane being a part of torus generated by a circle expressed by \( \sin \psi = \alpha \rho + \sqrt{2} \).

**Theorem 3.** There is no axisymmetric open membrane being a part of a biconcave discodal surface generated by a planar curve expressed by \( \sin \psi = c_0 \rho \ln \left(\rho / \rho_B\right) \).
• Axisymmetric numerical solutions

# Reduced SEq and BCs with the condition of consistency

SEq: \[
\cos \psi h' + (h - c_0) \sin \psi \psi' - \tilde{\lambda} \tan \psi - \frac{\tan \psi}{2} (h - c_0)^2 = 0
\]

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

2 BCs:

\[
\left[ \frac{\tilde{k}^2}{2} \left( \frac{\sin \psi}{\rho} \right)^2 + \tilde{k} K + \tilde{\lambda} - \sigma \tilde{\gamma} \frac{\cos \psi}{\rho} \right]_C = 0
\]

# Result from shoot method

Numerical results: solid, dash, dot lines

Experimental data: squares, circles, triangles

[Saitoh et al. (1998) PNAS]

Common parameters: \( \tilde{k} = -0.122, c_0 = 0.4 \mu m^{-1} \)
IV. Summary and perspectives
Summary

• Dealing with variational problems by using the moving frame method

• Shape equation of lipid vesicles and its three typical analytic solutions

• Shape equation and boundary conditions of open lipid membranes. Theorems of non-existence, condition of consistency, numerical solutions.
Perspectives

● Lipid domains

Cell membrane consists of many different kinds of lipid molecules which usually form micro-domains

Vesicles with different domains exhibit various shapes


We need to develop a new theory to explain various shapes of vesicles.
• Analytic solutions
  – Does there exist other analytic solutions to the shape equation of lipid vesicles?
  – Does there exist any analytic solutions to the shape equation and boundary conditions of open lipid membranes?

• Dynamics
  – Coupling with fluid, moving boundary.
  – Numerical simulations are required (phase field, immersed boundary, ?)
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