Lecture 8. Bio-membranes

Zhanchun Tu (涂展春)

Department of Physics, BNU

Email: tuzc@bnu.edu.cn

Homepage: www.tuzc.org
Main contents

• Introduction
• Mathematical and physical preliminary
• Lipid membrane
• Cell membrane
• Summary and perspectives
§8.1 Introduction
Size and morphology of cells

- **Size:** several to tens of μm
- **Various shapes**

(a) 5 cells of *E. coli* bacteria
(b) 2 cells of yeast
(c) Human red blood cell
(d) Human white blood cell
(e) Human sperm cell
(f) Human epidermal (skin) cell
(g) Human striated muscle cell (myofibril)
(h) Human nerve cell

Why various shapes?
Animal cell

The shapes of most of animal cells are determined by cytoskeleton.
Red blood cell

No inner cellular organelles. Shape is determined by membrane.

Human (normal): diameter 8μm, height 2 μm; biconcave discoid (why?)
Cell membrane

Fluid mosaic model
[Singer & Nicolson 1972]

Shape determined mainly by lipid bilayers.
• Timeline: cell-membrane bilayers

- Lipid structures

- **micelle**
- **bilayer**
- **vesicle**

Liquid crystal phase. Cannot endure shear strain!
• Cell membrane is usually in liquid crystal phase

Liquid crystal phase is a **necessary condition** for cell as an **open system**

Solid shell $\implies$ cell is dead

Isotropic fluid $\implies$ no difference between inner and outside of cells in equilibrium

$\implies$ cell cannot exist as an basic unit for life

Cancer might be related to the transition from LC to isotropic fluid
Some problems we may deal with

- How to describe shapes mathematically?
- **Does there exist a universal equation to govern the shapes?**
- Why is human normal RBC a biconcave discoid?
- **What is the mechanical function of membrane skeleton?**
- To what extent membrane proteins will influence the shapes of membranes?
§8.2
Mathematical & physical preliminary
Curvature and torsion of a curve

- Curvature and torsion

Each 3 points determine a curvature circle

\[ \kappa(2) = \frac{1}{r} \]

\[ \tau(2) = \frac{\theta_{\text{plane } O123 \land \text{plane } O'234}}{s_{23}} \]

- Tangent, normal, and binormal vector

\( t \): tangent vector

\( n \): normal vector, point to \( O \)

\( b \): binormal vector, \( b \perp t, b \perp n \)

\( t, n, b \) right-handed

1,2,3,4 close to each other
• **Two examples**

\[ \kappa = \frac{1}{R}, \quad \tau = 0 \]

![Diagram of two examples](image)

• **Frenet formula**

$s$: arc length parameter

Each $s$ corresponds a point in the curve

Different $t$, $n$, $b$ at different points

Different $\kappa$ and $\tau$ at different points

\[
\begin{bmatrix}
\dot{t} \\
\dot{n} \\
\dot{b}
\end{bmatrix} =
\begin{bmatrix}
0 & \kappa & 0 \\
-\kappa & 0 & \tau \\
0 & -\tau & 0
\end{bmatrix}
\begin{bmatrix}
t \\
n \\
b
\end{bmatrix}
\]

\[
\kappa = \frac{R}{R^2 + (h/2\pi)^2}
\]

\[
\tau = -\frac{h/2\pi}{R^2 + (h/2\pi)^2}
\]
A curve in a surface

- **Geodesic curvature & normal curvatures**

  \[ \kappa_g : \text{Curvature of } C' \text{ at } P \text{ (roughly)} \]
  \[ \kappa_g = \kappa \mathbf{n} \cdot \mathbf{n}' \quad \text{(exactly)} \]

  \[ \kappa_n : \text{Curvature of } C'' \text{ at } P \text{ (roughly)} \]
  \[ \kappa_n = \kappa \mathbf{n} \cdot \mathbf{N} \quad \text{(exactly)} \]

  Obviously, \[ \kappa_g^2 + \kappa_n^2 = \kappa^2 \]

- **Geodesic torsion**

  \[ \tau_g = -\dot{\mathbf{N}} \cdot \mathbf{n}' \]

\[ t, \mathbf{n} : \text{tangent and normal vectors of } C \]
\[ \mathbf{N} : \text{normal vector of surface} \]
\[ \mathbf{n}' : \text{normal vector of } C' \text{, such that} \]
\[ \{t, \mathbf{n}', \mathbf{N}\} \text{ right-handed} \]
• Two examples

\[ \kappa = \frac{R}{R^2 + (h/2\pi)^2}, \quad \tau = -\frac{h/2\pi}{R^2 + (h/2\pi)^2} \]

\[ \kappa_g = 0, \quad \kappa_n = -\frac{R}{R^2 + (h/2\pi)^2} \]

\[ \tau_g = \frac{h/2\pi}{R^2 + (h/2\pi)^2} \]

\[ \kappa = \frac{1}{R \sin \theta}, \quad \tau = 0 \]

\[ \kappa_g = \frac{\cot \theta}{R}, \quad \kappa_n = -\frac{1}{R} \]

\[ \tau_g = 0 \]
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**

  \[ H = \frac{c_1 + c_2}{2}, \quad K = c_1 c_2 \]
• Two examples

\[ c_1 = -\frac{1}{R}, \quad c_2 = 0 \]

\[ H = \frac{c_1 + c_2}{2} = -\frac{1}{2R}, \quad K = c_1 \cdot c_2 = 0 \]

\[ c_1 = c_2 = -\frac{1}{R} \]

\[ H = \frac{c_1 + c_2}{2} = -\frac{1}{R}, \quad K = c_1 \cdot c_2 = \frac{1}{R^2} \]
Topological invariant of closed surface

- Gauss-Bonnet formula

\[ \iint K \, dA = 4\pi (1 - g) \]

\[ g = 0 \Rightarrow \iint K \, dA = 4\pi \]
\[ g = 1 \Rightarrow \iint K \, dA = 0 \]
\[ g = 2 \Rightarrow \iint K \, dA = -4\pi \]
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

\[ \delta F = F[S'] - F[S] \]

\( \delta F = 0 \Rightarrow \) Euler-Lagrange equation(s) describing equilibrium shapes

Euler-Lagrange equation(s) \( \Leftrightarrow \) force balance equation(s)
Variational problems on shapes in history

• Fluid films

Viewed as a surface in mathematics

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

\[ F = \lambda \int dA \]

\[ \delta F = 0 \Rightarrow H = 0 \]
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)

\[ \Delta p = p_{out} - p_{in} \]

Sphere \( \frac{1}{R} = -\frac{\Delta p}{2 \lambda} \)

Cylinder \( \frac{1}{R} = -\frac{\Delta p}{\lambda} \)
• 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)

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

  spontaneous curvature

  Bending LC box \[ \Rightarrow \] Lipid bilayer

  Analogy

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

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

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

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

  \[ \Delta p = 0, \lambda = 0, c_0 = 0 \Rightarrow \nabla^2 H + 2H (H^2 - K) = 0 \quad \text{(Willmore surfaces)} \]
Puzzle from the shape of RBC

• Sandwich model (Fung & Tong, 1968)

To obtain the shape of biconcave discoid, they should assume the thickness of the membrane is nonuniform in μm scale.

Pinder's experiment (1972): the nonuniform thickness exists only in molecular (nm) scale. The thickness is uniform in large scale of μm.

• Nonuniform charge model (Lopez, 1968)

Nonuniform charge distribution results in the shape of biconcave discoid.

Experiment by Greet & Baker (1970): NO
• Incompressible shell model (Canham, 1970)

Given the area and volume of membrane, the biconcave discoid minimizes the curvature energy

\[ \int H^2 dA \]

Helfrich & Deuling (1975): the dumbbell-like shape can have the same curvature energy as the biconcave disk. But dumbbell-like shape has never observed in the experiment.
• Spontaneous curvature model (Helfrich, 1973)

Given the area and volume of membrane, the biconcave discoid minimizes the spontaneous curvature energy: 
\[ \int (2H + c_0)^2 dA \]

\[ c_0 < 0 \Rightarrow \text{biconcave discoid is energetically favorable} \]

Can we give an analytic result from the shape equation?

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

----Soft-incompressible fluid film

  can endure bending but not static shear.

  May be asymmetric in inner side and outer one.
Lipid vesicles

- Spherical vesicles

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

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

\[ H = -\frac{1}{R}, \quad K = \frac{1}{R^2} \]

\( f(R) \)  
\( \Delta p < 0, c_0 < 0 \)  
\( \Delta p < 0, c_0 > 0 \)  
\( \Delta p > 0, c_0 > 0 \)

Might be related to endocytosis
• Torus [Ou-Yang (1990) PRA]

\[
\begin{align*}
&\{(r + \rho \cos \varphi) \cos \theta, (r + \rho \cos \varphi) \sin \theta, \rho \sin \varphi\} \\
&2H = -\frac{r + 2\rho \cos \varphi}{\rho (r + \rho \cos \varphi)}; \quad K = \frac{\cos \varphi}{\rho (r + \rho \cos \varphi)}
\end{align*}
\]

\[
\begin{align*}
&2k_c / \nu^2 + k_c (c_0^2 \rho^2 - 1) + 2(\Delta p \rho + \lambda) \rho^2 \\
&+ \frac{4k_c c_0^2 \rho^2 - 4k_c c_0 \rho + 8\lambda \rho^2 + 6\Delta p \rho^3}{\nu} \cos \varphi \\
&+ \frac{5k_c c_0^2 \rho^2 - 8k_c c_0 \rho + 10\lambda \rho^2 + 6\Delta p \rho^3}{\nu^2} \cos^2 \varphi \\
&+ \frac{2k_c c_0^2 \rho^2 - 4k_c c_0 \rho + 4\lambda \rho^2 + 2\Delta p \rho^3}{\nu^3} \cos^3 \varphi = 0
\end{align*}
\]

The coefficients of \(\{1, \cos \varphi, \cos^2 \varphi, \cos^3 \varphi\}\) should vanish!

\[
\begin{align*}
&\nu = \sqrt{2} \\
&\Delta p = -\frac{2k_c c_0}{\rho^2}, \lambda = k_c c_0 \left(\frac{2}{\rho} - \frac{c_0}{2}\right)
\end{align*}
\]

[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 \( \Psi = \sin \psi \)

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

[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-OY (1993) PRE]
Lipid membranes with free edges

- **Experiment:** Opening process of lipid vesicles by Talin

[Saitoh *et al.* (1998) *PNAS*]
• Previous theories
  – Derived from axisymmetric variation
    • [Jülicher -Lipowsky (1993) PRL]

    Confine the variational problem in a subspace. Unreasonable results exist.

  – General case
    • [Capovilla-Guven-Santiago (2002) PRE]
      Governing equations of edges are not expressed in the explicit forms of curvature and torsion.

    • [Tu-OuYang (2003) PRE]
      Overcome the above shortages.
Main results in [Tu-OuYang (2003) PRE]

Free energy per area

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

Total free energy

\[ F = \int G \, dA + \gamma \oint ds \]

\[ \delta F = 0 \Rightarrow \text{shape equation} + \text{boundary conditions} \]
Shape equation: force balance in the normal direction

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

Boundary conditions (curve C satisfies...)

\[ k_c (2H + c_0) - \bar{k} k_n = 0 \]

Force balance equation of points in the edge along normal direction

\[ 2k_c \frac{\partial H}{\partial b} + \gamma k_n - \bar{k} \tau_g = 0 \]

Moment balance equation of points in the edge around \( t \)

\[ G + \gamma k_g = 0 \]

Force balance equation of points in the edge along \( b \)
Axisymmetric analytic solutions

Center of torus

Axisymmetric numerical solutions

Cup-like open membrane

Solid squares: experiment data [Saitoh etal. (1998) PNAS]
§8.4 Cell membrane

----It is beyond the lipid bilayer.

How can we model it?
Composite membrane model
[Sackmann (2002)]

- Cell membrane = bilayer + membrane skeleton

<table>
<thead>
<tr>
<th></th>
<th>shear</th>
<th>bending</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilayer</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>MSK</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>CM</td>
<td>YES</td>
<td>YES</td>
</tr>
</tbody>
</table>

Diagram: Inside of cell membrane
Outside of cell membrane

- Lipid
- Bulk protein
- Protein filament
• Basic assumptions

  1. CM: “smooth” surface
  2. Polymer in MSK: almost same chain length
  3. CM: in-plane isotropic, i.e. lipid crystal phase
  4. Chain length << curvature radius of CM
  5. Small deformations
  6. Free energy per area: analytical function
  7. Invariance of free energy: Strain tensor (+) (-)
• Energy density (energy per area)

Assumption 1-4 => \[ G = G(2H, K, 2J, Q) \]

\[ 2J = \text{Tr} \begin{pmatrix} \epsilon_{11} & \epsilon_{12} \\ \epsilon_{12} & \epsilon_{22} \end{pmatrix}, \quad Q = \text{det} \begin{pmatrix} \epsilon_{11} & \epsilon_{12} \\ \epsilon_{12} & \epsilon_{22} \end{pmatrix} \]

Assumption 5-7 => up to the second order terms

\[ G = \frac{k_c}{2} (2H + c_0)^2 - \tilde{k} K + \frac{(k_d/2)(2J)^2 - \tilde{k} Q + \lambda}{\text{Contribution from LB}} \quad \text{Bending energy} \]

\[ \text{Contribution from MSK} \quad \text{Compress and shear energy} \]
Shape equation & in-plane strain equation

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

\[ \delta F = 0 \quad \text{(Remark: only consider closed cell membrane)} \]

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

\[ + 2H(\tilde{k} - k_d)(2J) - \tilde{k} \, \mathcal{R} : \nabla \mathbf{u} = 0 \]

\[ (\tilde{k} - 2k_d) \nabla (2J) - \tilde{k} (\mathbf{\Box} \mathbf{u} + K \tilde{\mathbf{u}} + \nabla u_3) = 0 \]


Especially, if \( k_d = \tilde{k} = 0 \), the above two equations degenerate into

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

shape equation of lipid vesicles.
Spherical cell membrane and its stability

Homogenous in-plane strain \( \epsilon_{11} = \epsilon_{22} = \epsilon, \epsilon_{12} = 0 \)

\[
\Delta \cdot pR^2 + 2(\lambda + 2k_d \epsilon - \tilde{k} \epsilon)R + k_c c_0 (c_0 R - 2) = 0
\]

Stable \( \Leftrightarrow \delta^2 F > 0 \Leftrightarrow \Delta p < p_l \equiv \frac{2\tilde{k}(2k_d - \tilde{k})}{k_d l(l+1) - \tilde{k}}R + \frac{2k_c}{R^3}[l(l+1) - c_0 R], (l > 1) \)

Critical osmotic pressure \( p_c = \min\{p_l\} \)

\[
p_c = \frac{2k_c(6 - c_0 R)}{R^3} \quad \text{when} \quad \tilde{k} = 0 \quad [\text{return to the result of lipid vesicle, OuYang- Helfrich (1987) PRL}]
\]

\[
p_c = \frac{4\sqrt{(\tilde{k}/k_d)(2k_d - \tilde{k})}k_c}{R^2} \quad \text{when} \quad \frac{\tilde{k}k_d(2k_d - \tilde{k})R^2}{k_c(6k_d - \tilde{k})^2} > 1
\]
Typical parameters for cell membranes

\[ \tilde{k} \approx k_d \approx 4.8 \, \mu \text{N/m} \quad [\text{Lenormand et al. (2001) Biophys. J}] \]

\[ k_c \approx 10^{-19} \, \text{J} \quad [\text{Duwe et al. (1990) J. Phys. Fr.}] \]

\[ R \approx 5 \, \mu \text{m} \]

\[ \frac{\tilde{k} k_d (2 k_d - \tilde{k}) R^2}{k_c (6 k_d - \tilde{k})^2} > 1 \Rightarrow p_c = \frac{4 \sqrt{(\tilde{k} / k_d)(2 k_d - \tilde{k})} k_c}{R^2} \approx 0.1 \, \text{Pa} \]

If no MSK, i.e., lipid vesicle, \[ \tilde{k} = 0 \Rightarrow p_c = \frac{2 k_c (6 - c_0 R)}{R^3} \approx 0.008 \, \text{Pa} \]

Reveals a mechanical function of MSK: highly enhances stability of CM
§8.6 Summary and perspectives
Summary

- Mathematical description of shape of membranes.
- Physical meaning of variation; History of variational problem in shapes.
- Helfrich spontaneous curvature model.
- Lipid vesicles and lipid membrane with free edges.
- Composite membrane model for cell membrane.
Cell membrane consists of many different kinds of lipid molecules which usually form micro-domains as shown in left Fig at physiological temperature. Each domain contains one or several kinds of lipid molecules.

Lipid rafts

– Special domains

– depleted in unsaturated phospholipids

– enriched in cholesterol, sphingolipids and lipid-anchored proteins

Cholesterol/unsaturated phospholipid/sphingolipid bilayer

$l_o$: liquid-ordered phase

$l_c$: liquid-disordered phase

Morphology of model membrane with raft and non-raft domains

Red: liquid-disordered phase
“non-raft” domain

Blue: liquid-ordered phase
“raft” domain


We need to develop a new theory to explain various shapes of vesicles.
Ion-channel open probability as a function of pipette pressure (↔ surface tension) for mechanosensitive channels in lipids with different tail lengths

Insertion of various molecules can alter the protein-membrane interaction:
(1) Asymmetrical insertion of lysolipids produces a torque on the protein.
(2) Introduction of toxins can alter the boundary conditions between the protein and the surrounding lipids.
(3) Small rigid molecules can stiffen the membrane. [Phillips (2009) Nature]
Structure and energy at the protein–lipid interface

Challenge: extending Helfrich's model to include the protein-lipid interactions
Further reading


- 谢毓章, 刘寄星, 欧阳钟灿, 生物膜泡曲面弹性理论 (上海科学技术出版社 2003)

