“The obvious is that which is never seen until someone expresses it simply.” — Christian Morgenstern
Ion Channels: Models of Gating

(Gillespie and Walker)

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Living organisms are full of sensors, some of which we are conscious of, others of which we are not.

- Obvious examples – touch, hearing, vision, taste, smell
- Less obvious – sharks and the ampullae of Lorenzini – electrical detection.
- Sensors from pH to temperature to sugar.
Cells divided into a number of membrane-bound compartments.
Concentrations in different compartments can be orders of magnitude different.
Proteins (ion channels, transporters) mediate these concentration gradients.
Membrane proteins central to huge range of processes – cell signaling, nerve impulses, nutrient transport, etc.

\[
Ca_{in}^{2+} \approx 10^{-4} \text{mM} \quad Ca_{out}^{2+} \approx 1 \text{mM} \\
K_{in}^{+} \approx 140 \text{mM} \quad K_{out}^{+} \approx 5 \text{mM}
\]
Crossing the Membrane

The diagram illustrates the processes of passive and active transport across the cell membrane. Passive transport includes:
- **Simple Diffusion**: Molecules move from an area of higher concentration to an area of lower concentration without the need for energy.
- **Channel-Mediated Transport**: Molecules use a channel protein to facilitate transport from one side of the membrane to the other.

Active transport includes:
- **Carrier-Mediated Transport**: Molecules are transported using carrier proteins that require energy to move against a concentration gradient.

The concentration gradient is depicted on the right side of the diagram, indicating the direction of transport.
Channels open in response to a variety of different stimuli.

Key mechanisms are voltage gating, ligand binding-induced gating and mechanical tension in the membrane.
Some famous examples of ion channels studied by structural biologists.

Nicotinic acetylcholine receptor

EM & X Ray structures

(Doyle et al.)

K Channel

(Unwin et al.)
The idea: grab a patch of membrane and apply a potential difference to measure the currents.

Fraction of time spent open depends upon magnitude of driving force.

(Sukharev et al.)

pA currents lasting several milliseconds.
Electrophysiology measurements (patch clamping) lead to current vs membrane tension. Measurements reveal five distinct conductance substates.

(Sukharev et al.)
Consequences of Ion Channel Gating: The Action Potential

(A) propagation

(B) instantaneous view at $t = 0$

Na⁺ channels closed inactivated open closed
axon plasma membrane

membrane

Figure 12-38 Essential Cell Biology, 2/e. ©2004 Garland Science
Ubiquitous Phenomenon of Mechanosensation

- The main point: mechanosensation is everywhere.
- Informational currency is electrical – detection is mechanical.
- Repetition of same motif – mechanical excitation results in transient flow of ions.

Touch sensation in worm

Mechanical response of hair cells

(Gillespie and Walker)
Mechanosensitive Channels as Osmotic Pressure Relief Valves

- **Hierarchy of mechanically-gated channels.**

- **Properties of channel have been investigated using electrophysiology.**

- **Gating tension of MscL serves to avoid membrane rupture.**

(Perozo and Rees)
More on Osmotic Shock

Figure 12.16  Essential Cell Biology, 2/e. (© 2004 Garland Science)
Description of biological structures can be undertaken from a variety of different perspectives. Two key ways of viewing structure are ribbon diagrams and all-atom descriptions.
Hypothesized structural pathway for opening the channel. Tilting of alpha helices and corresponding opening of the pore.

Key Question: How does mechanical tension couple to the conformational change?

What are the energetic consequences to the surrounding membrane as a result of channel opening?

(Sukharev et al.)
Hydrophobic tails and polar head groups.

Favorable for lipids to spontaneously assemble to form bilayers.

(Avanti Polar Lipids)
Membranes In Vivo

- Real biological membranes contain many different lipids & transmembrane proteins!

<table>
<thead>
<tr>
<th>Purple Membrane</th>
<th>Human</th>
</tr>
</thead>
<tbody>
<tr>
<td>M_L/M_P</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>3-4</td>
</tr>
</tbody>
</table>

Biophysics Group UIUC

Figure 10-1. Molecular Biology of the Cell, 4th Edition.
Gating tension depends upon the length of the lipid tails.

Free energy cost associated with mismatch between thickness of protein and lipids.
The Membrane Free Energy

- The idea: solve boundary problem for protein embedded in membrane (Huang, Andersen and others).
- We use elasticity theory and can thereby compute the energy as function of protein shape.

**Bending:**

\[ E = \int_M d^2 \sigma \left( \frac{1}{2} K_C [S - C_0]^2 + K_G G \right) \]
The Membrane Free Energy: Part 2

Tension (in plane Stretch):

\[ E = \int_{\mathcal{M}} d^2 \sigma \, \alpha \]

Stretch (out of plane):

\[ E = \int_{\mathcal{M}} d^2 \sigma \, \frac{1}{2} K_A \left( \frac{u}{a} \right)^2 \]
Protein Boundary Value Problem

- Minimize free energy – Euler-Lagrange equations for midplane position \((h)\) and thickness \((2u)\).

- Solve equations, match BC’s, & compute deformation energy

\[
\left[ K_B \nabla^4 - \alpha \nabla^2 + \frac{K_A}{a^2} \right] u = 0 \quad \left[ K_B \nabla^2 - \alpha \right] h = 0
\]
Dissecting the Free Energy

**Applied Tension**

\[ G_A = -\alpha A \]

**Hydrophobic mismatch**

\[ G_u = \frac{1}{2} K_{ef} f U^2 C \]

**Midplane Bending**

\[ G_H = \frac{1}{2} \sqrt{\alpha K_B H} \]

**Spontaneous Curvature**

\[ G_{C_0} = K_B (C_0 H' + \bar{C}_0 U') C \]

**Conclusion:** Competition between terms with different radial character! Line Tension & Applied Tension
Dissecting the Free Energy: Hydrophobic Mismatch

Hydrophobic mismatch

\[ G_u = \frac{1}{2} K_{\text{eff}} U^2 C \]

- Can tune the hydrophobic mismatch two ways: change the lipids or mutate the protein.
Elastic deformation of the membrane is induced by channel.

Thicknness mismatch leads to a line tension which works against applied tension.

Effective potential analogous to a nucleation problem.

**Effective potential for channel radius**

\[ G_M = f2\pi R - \alpha \pi R^2 \]

- \( f = \) line tension
- \( \alpha = \) applied tension

\( f > 0 \)
Critical tension depends upon lipid length.

Curvature inducing lipids can change the sign of the effective line tension – stabilizing open state.

Amino acid substitutions that tune the hydrophobic width of the channel alter gating tension in a systematic fashion.
The Curious Case of Voltage Gating

- The idea: ion channels (such as for K) are gated by voltage.
- Structural biologists have made huge progress, but their successes have left a wake of paradoxes.
- RP opinion: careless in treatment of membrane! Membrane mechanics distinguishes them.

(Mackinnon et al.)
Flirting with a Simple Model of Voltage Gating

- Same logic – write free energy which reflects response of channel AND surrounding membrane.

\[ G_{\text{membrane}}[h(x)] = \frac{K_b}{2} \int \frac{h''^2}{(1 + h'^2)^3} \, dx + \alpha \int (\sqrt{1 + h'^2} - 1) \]

How gating depends upon voltage, tension (!), lipid character, etc… Testable – SMB bring it on! Two models have different consequences.
Collective response of multiple detectors driving multiple channels.
Richness of Dynamics: Adaptation

- **Hair cells exhibit nonlinear response** – they adapt to stimulus.
- **Relevant molecular participants are as yet unknown.**

(Sukharev et al.)

(Muller and Littlewood-Ev

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(A) 

(B)