Biophysics I (BPHS 3090)

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Website: http://www.yorku.ca/cberge/3090W2015.html
Figure 12.14: (Schematic; optical micrograph.) (a) A small patch of membrane containing only a single voltage-gated sodium channel (or a few) is electrically isolated from the rest of the cell by a patch electrode. The current entering the cell through these channels is recorded by a monitor connected to the patch electrode. (b) Patch-clamp manipulation of a single, live photoreceptor cell from the retina of a salamander. The cell is secured by partially sucking it into a glass micropipette (bottom), while the patch-clamp electrode (upper left) is sealed against a small patch of the cell’s plasma membrane. [Digital image kindly supplied by T. D. Lamb; see Lamb et al., 1986.]
**Model:** Voltage-Gated Two-State Molecular Gate

*Note:* The interplay between micro- & macroscopic descriptions requires a transition into the domain of probability & expectation values.

- **State occupancy, \( \tilde{s} \)**
  - \( C \rightarrow O \rightarrow 1 \times \rightarrow 0 \)

- **Single-channel conductance, \( \tilde{g} \)**
  - \( 0 \rightarrow g \rightarrow 0 \)

- **Single-channel current, \( \tilde{i} \)**
  - \( 0 \rightarrow i \rightarrow 0 \)

- \( x = \text{state occupancy probability} \)
- \( g = \text{average single-channel conductance} \)
- \( i = \text{average single-channel current} \)

*Figure 6.33 (mod)*
Microscopic model (+ law of large numbers) gives rise to macroscopic behavior

Question(s): How big must $N$ be? How “local” does it need to be (i.e., as a channel density)?
Model: Voltage-Gated Two-State Molecular Gate *(Expected Values)*

Assume $N$ channels per unit area, of which $n(t)$ are open.

\[
\frac{dn(t)}{dt} = \alpha(N - n(t)) - \beta n(t)
\]

\[
n(t) = n_\infty + (n(0) - n_\infty) e^{-t/\tau_x}; \quad n_\infty = \frac{\alpha}{\alpha + \beta} N, \quad \tau_x = \frac{1}{\alpha + \beta}
\]

First-order kinetics(!!)

Assume $N$ is large.

\[
x(t) = \text{probability gate is open} \approx \frac{n(t)}{N}
\]

\[
x(t) = x_\infty + (x(0) - x_\infty) e^{-t/\tau_x}; \quad x_\infty = \frac{\alpha}{\alpha + \beta}, \quad \tau_x = \frac{1}{\alpha + \beta}
\]
Model: Voltage-Gated Two-State Molecular Gate

The potential energy of an ion channel includes mechanical, chemical, and electrical contributions, each of which can be different in different conformations. Electrical potential energy depends on both the distribution of charge in the gate and on transmembrane potential. Therefore, $E_B$, $E_O$, and $E_C$ depend on $V_m$.

First-order kinetics variables

$$\frac{dx}{dt} = \alpha x (1 - x) - \beta x x$$

$\rightarrow$ Potential modifies energy configuration

$$\alpha = Ae^{(E_C - E_B)/kT}$$

$$\beta = Ae^{(E_O - E_B)/kT}$$
Ex. 

\[ E_B = \frac{1}{2} QV_B \; ; \; E_C = \frac{1}{2} QV_m \; ; \; E_O = -\frac{1}{2} QV_m \]

\[ \alpha = A e^{\frac{1}{2}Q(V_m-V_B)/kT} \; ; \; \beta = A e^{-\frac{1}{2}Q(V_m+V_B)/kT} \]

\[ x_\infty = \frac{\alpha}{\alpha + \beta} = \frac{1}{1 + \beta/\alpha} = \frac{1}{1 + e^{-QV_m/kT}} \]

\[ \tau_x = \frac{1}{\alpha + \beta} = \frac{1}{A(e^{\frac{1}{2}Q(V_m-V_B)/kT} + e^{-\frac{1}{2}Q(V_m+V_B)/kT})} \]

\[ = \frac{1}{Ae^{-\frac{1}{2}QV_B/kT}(e^{\frac{1}{2}QV_m/kT} + e^{-\frac{1}{2}QV_m/kT})} \]
Separating Out the Gating Current

Two components (why?)
- Linear
- Nonlinear

\[ J_c = J_{cl} + J_{cn} \]

Figure 6.20

Figure 6.21
Separating Out the Gating Current

→ Sign of gating current can inform about structure/charge distribution of the channel

![Diagram showing membrane potential and current density](image)

**Figure 6.22**
Reversibility
(i.e., $Q_{on} = Q_{off}$ implies charge is conserved)

Saturation
(i.e., finite number of channels)

**Question:** If we know the single channel conductance, can we estimate the total # of contributing channels?
Hodgkin Huxley model

\[ G_K(V_m, t) = \overline{G}_K n^4(V_m, t) \]
\[ G_{Na}(V_m, t) = \overline{G}_{Na} m^3(V_m, t) h(V_m, t) \]

\[ n(V_m, t) + \tau_n(V_m) \frac{dn(V_m, t)}{dt} = n_\infty(V_m) \]
\[ m(V_m, t) + \tau_m(V_m) \frac{dm(V_m, t)}{dt} = m_\infty(V_m) \]
\[ h(V_m, t) + \tau_h(V_m) \frac{dh(V_m, t)}{dt} = h_\infty(V_m) \]

\( \overline{G}_{Na} = 120, \overline{G}_K = 36, \) and \( G_L = 0.3 \) mS/cm²;
\( c_{Na}^o = 491, c_{Na}^i = 50, c_K^o = 20.11 \) \( c_K^i = 400 \) mmol/L;
\( C_m = 1 \) \( \mu F/cm²; \) \( V_L = -49 \) mV; temperature is 6.3°C.
Two-state model → First-order kinetics

\[
\tau_x \frac{dx}{dt} + x = x_\infty \\
\frac{dx}{dt} = \alpha_x (1 - x) - \beta_x x
\]

\[x_\infty = \frac{\alpha_x}{(\alpha_x + \beta_x)} \text{ and } \tau_x = \frac{1}{(\alpha_x + \beta_x)}\]

First-order, reversible reaction

\[R \xrightarrow{\alpha \beta} P\]

\[c_B(0) \quad c_P(t) \quad K_a C/(1 + K_a)\]

\[c_P(0) \quad c_B(t) \quad C/(1 + K_a)\]

\[\tau = \frac{1}{\alpha + \beta}\]

→ Single two-state model too ‘simple’

\[
G_K(V_m, t) = \overline{G}_K n^4(V_m, t)
\]

\[
G_{Na}(V_m, t) = \overline{G}_{Na} m^3(V_m, t) h(V_m, t)
\]

Figure 6.53

Intracellular

Membrane

Extracellular
Figure 6.54
Figure 6.55

Figure 6.56
Conductance voltage-dependence consistent w/ HH if there are three independent activation gates (i.e., $m^3$)

HH predicts values for the various time constants...

... that are inconsistent with data ("tail currents")

→ Four independent two-state models still too simple. Multi-state channels?
Multistate Channel Models

Figure 6.60

Figure 6.61
s-shape stems from “lag incurred by the state occupancy having to traverse earlier stages”
Molecular Underpinnings
Figure 6.70


Conventional model

New model

Figure 12.16: (Schematic; sketch.) (a) Conceptual model of a voltage-gated ion channel. A spring normally holds a valve closed. An electric field pointing upward lifts the positively charged valve, letting water flow downward. (b) Sketch of the sodium channel. Left: In the resting state, positive charges in the channel protein's four “sensing” alpha helices are pulled downward, toward the negative cell interior. The sensing helices in turn pull the channel into its closed conformation. Right: Upon depolarization, the sensing helices are pulled upward. The channel now relaxes toward a new equilibrium, in which it spends most of its time in the open state. The lower blob depicts schematically the channel-inactivating segment. This attached object can move into the channel, blocking ion passage even though the channel itself is in its open conformation. [After Armstrong & Hille, 1998.]