Biophysics I (BPHS 4080)

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Website: http://www.yorku.ca/cberge/4080W2018.html

York University
Winter 2018
Lecture 28

Summary: HH Equations

$$\frac{1}{2\pi a(r_o + r_i)} \frac{\partial^2 V_m}{\partial z^2} = C_m \frac{\partial V_m}{\partial t} + G_K(V_m, t)(V_m - V_K)$$

$$+ G_{Na}(V_m, t)(V_m - V_{Na}) + G_L(V_m - V_L)$$

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

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

$$n(V_m, t) + \tau_n(V_m) \frac{dn(V_m, t)}{dt} = n_\infty(V_m)$$

$$m(V_m, t) + \tau_m(V_m) \frac{dm(V_m, t)}{dt} = m_\infty(V_m)$$

$$h(V_m, t) + \tau_h(V_m) \frac{dh(V_m, t)}{dt} = h_\infty(V_m)$$

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

$$x_\infty = \alpha_x / (\alpha_x + \beta_x) \text{ and } \tau_x = 1/(\alpha_x + \beta_x)$$

$$\alpha_m = \frac{-0.1(V_m + 35)}{e^{-0.1(V_m + 35)} - 1},$$

$$\beta_m = 4e^{-(V_m + 60)/18},$$

$$\alpha_h = 0.07e^{-0.05(V_m + 60)},$$

$$\beta_h = \frac{1}{1 + e^{-0.1(V_m + 30)}},$$

$$\alpha_n = \frac{-0.01(V_m + 50)}{e^{-0.1(V_m + 50)} - 1},$$

$$\beta_n = 0.125e^{-0.0125(V_m + 60)},$$

Question:
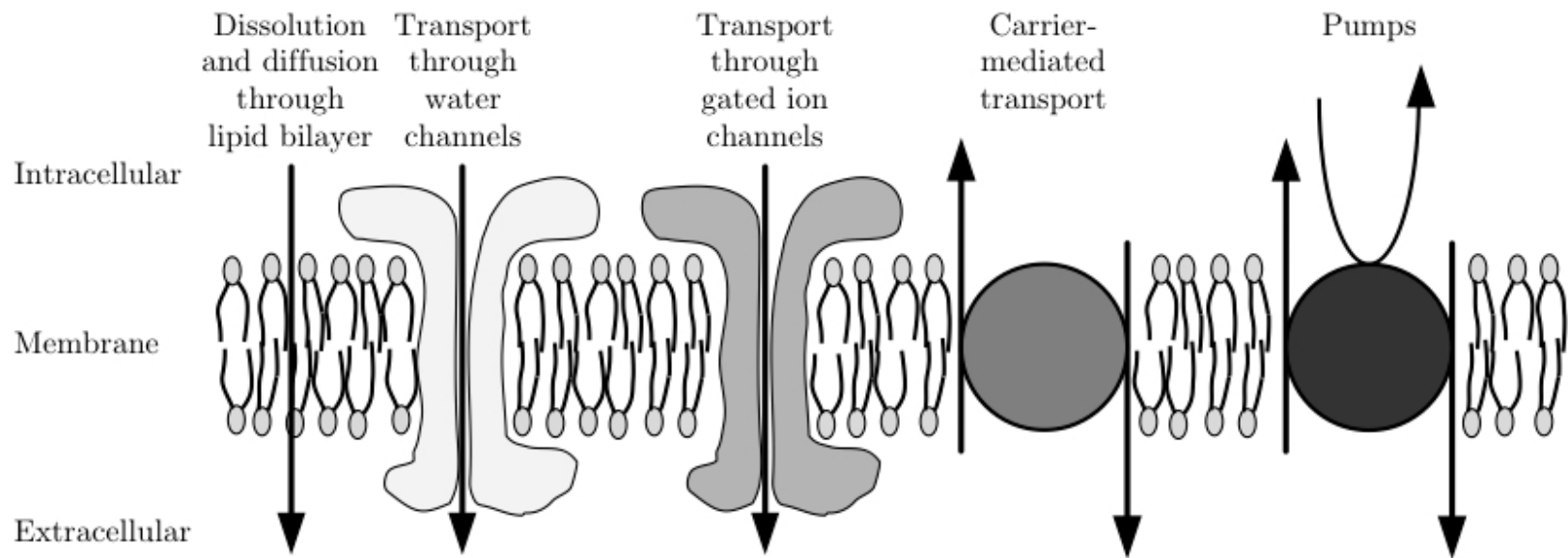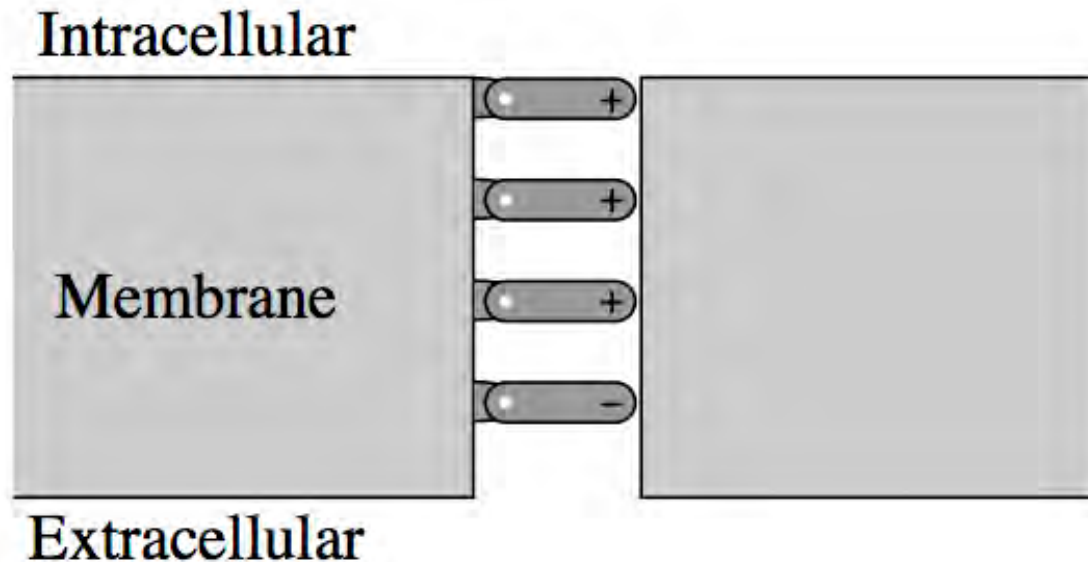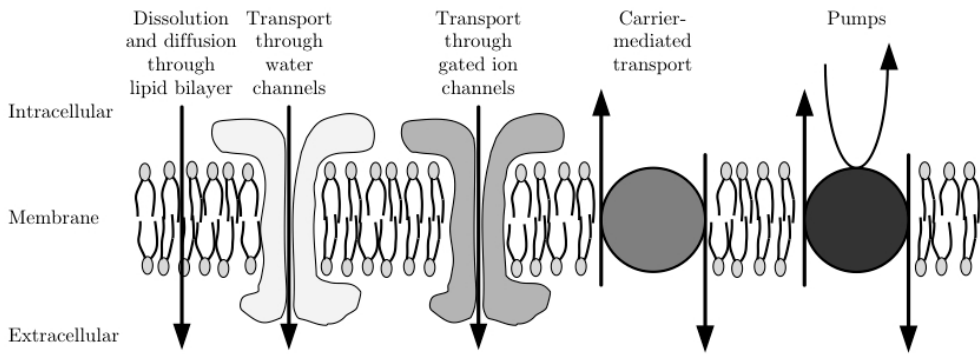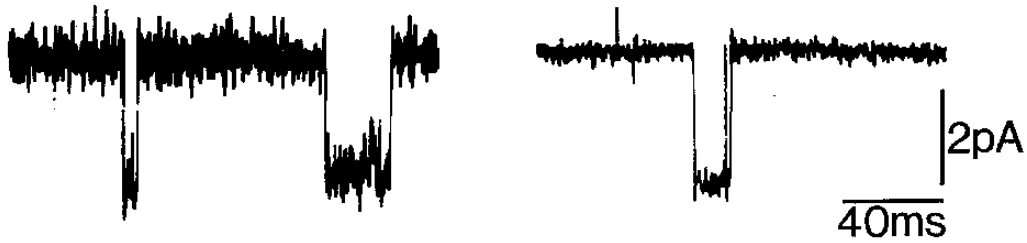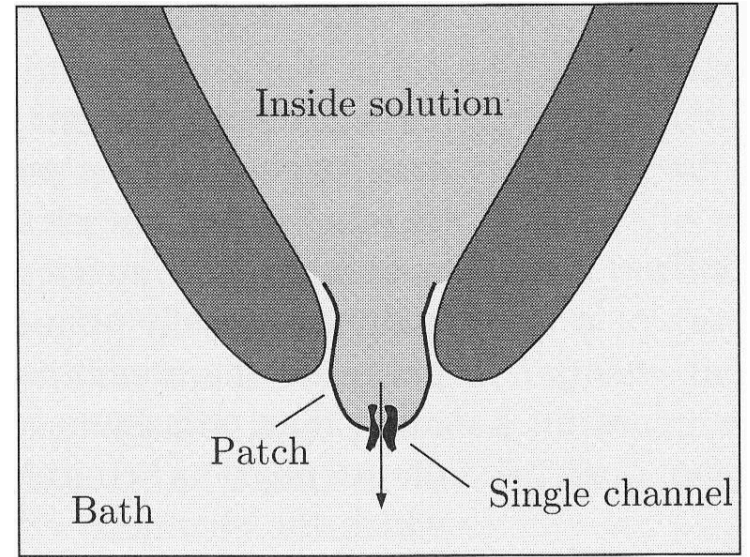So what do m, h, and n physically represent?

Figure 2.19

→ Notion of an _ion channel_

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

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

$$n(V_m, t) + \tau_n(V_m) \frac{dn(V_m, t)}{dt} = n_\infty(V_m)$$

Question:
So what do m, h, and n physically represent?

$$m(V_m, t) + \tau_m(V_m) \frac{dm(V_m, t)}{dt} = m_\infty(V_m)$$

$$h(V_m, t) + \tau_h(V_m) \frac{dh(V_m, t)}{dt} = h_\infty(V_m)$$

Intracellular

Membrane

Extracellular

Figure 2.19

2pA

40ms

Macroscopic
sodium current

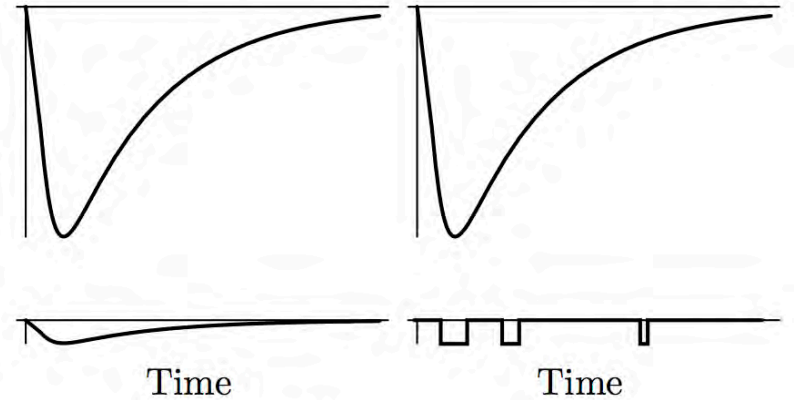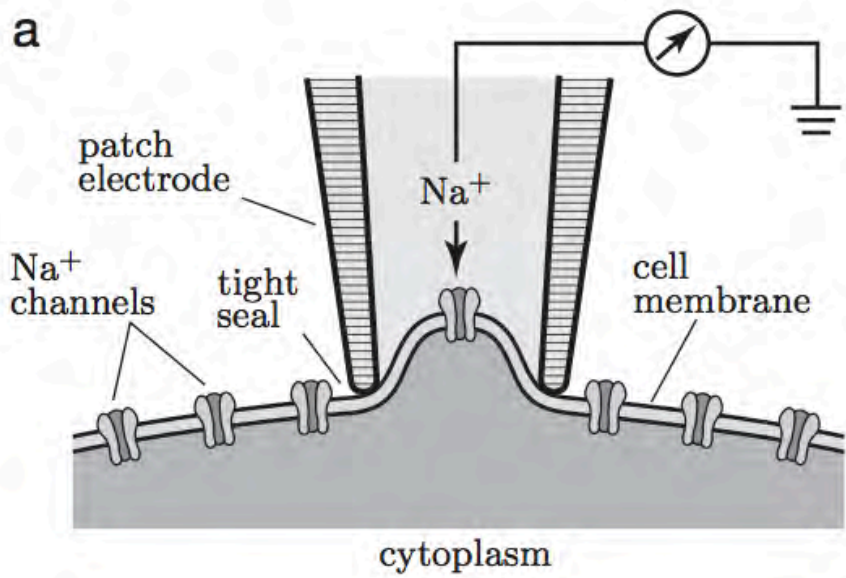Single-channel
sodium current
candidates

Time

Time

Figure 6.27

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- & macro-scopic descriptions requires a transition into the domain of probability & expectation values
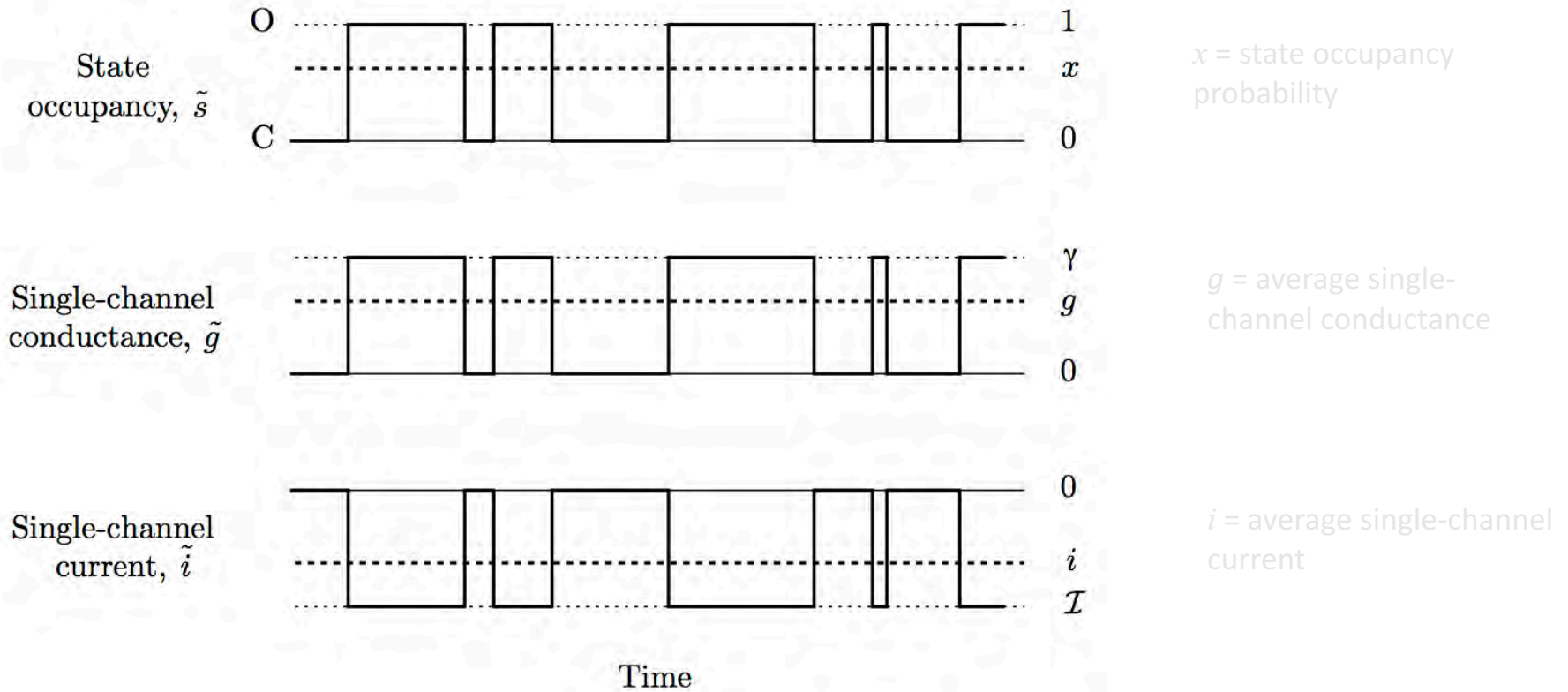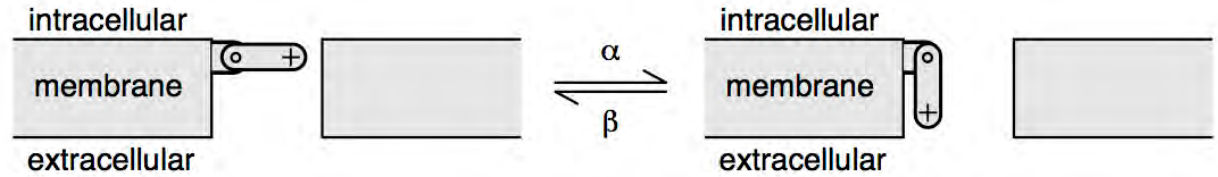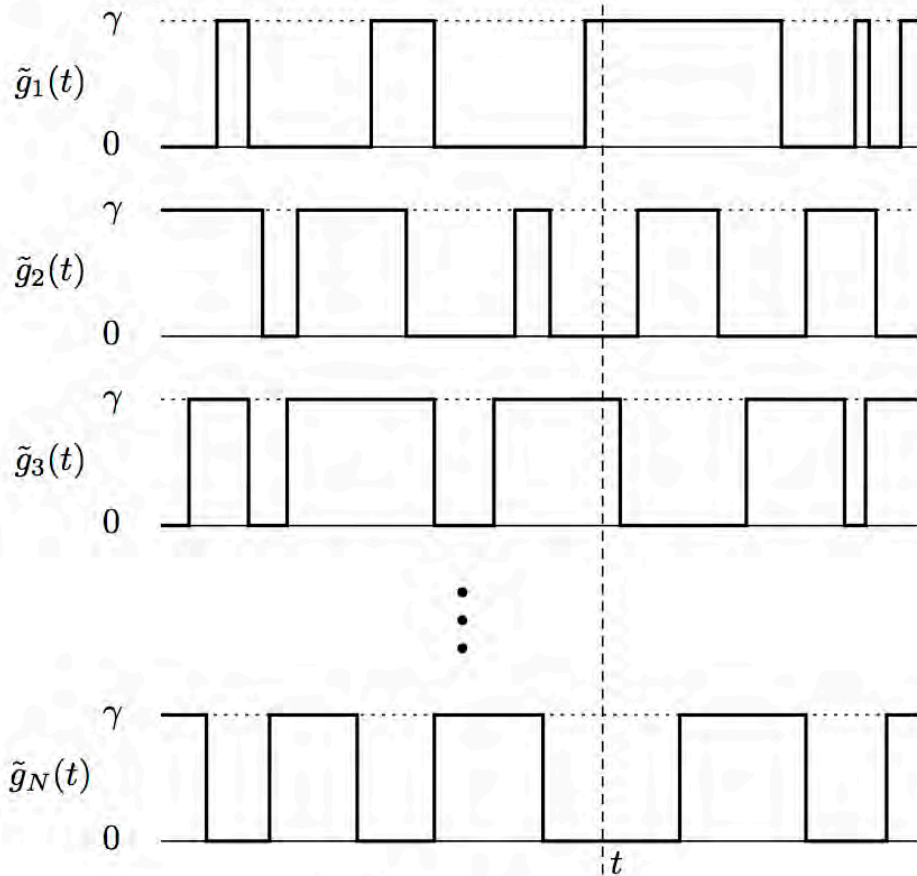

Figure 6.33 (mod)

Figure 6.34

→ 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)?
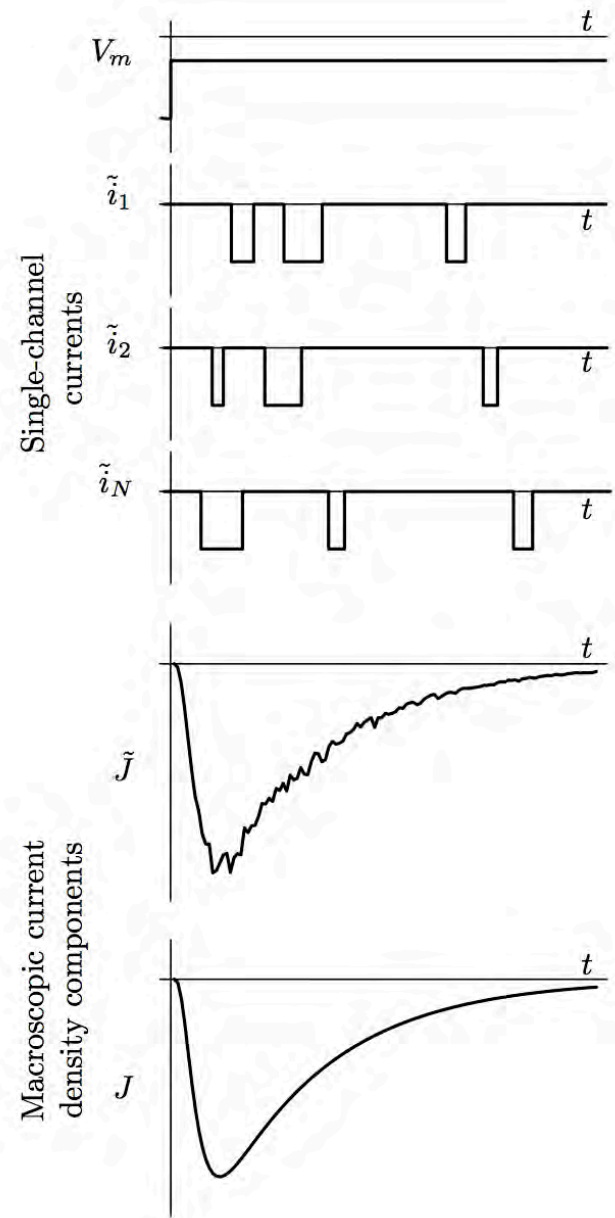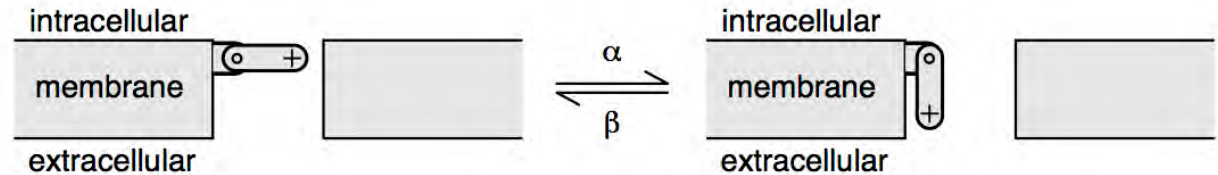

Figure 6.50 (mod)

Model: Voltage-Gated Two-State Molecular Gate *(Expected Values)*

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

$n(t)$ is average # of open channels

$$\frac{dn(t)}{dt} = \alpha(\mathcal{N} - n(t)) - \beta n(t)$$

$$n(t) = n_\infty + (n(0) - n_\infty)\, e^{-t/\tau_x}\; ;\qquad n_\infty = \frac{\alpha}{\alpha + \beta}\,\mathcal{N}\,,\quad \tau_x = \frac{1}{\alpha + \beta}$$
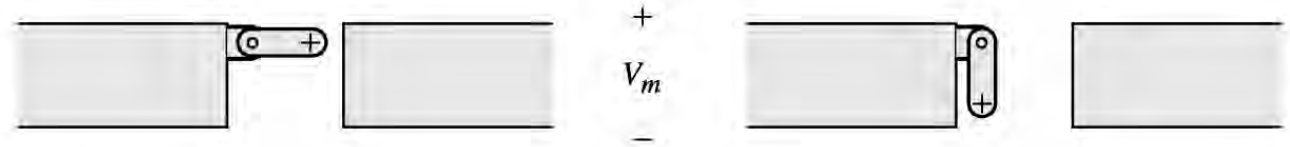
First-order kinetics(!!)

Assume $\mathcal{N}$ is large.

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

$$x(t) = x_\infty + (x(0) - x_\infty)\, e^{-t/\tau_x}\; ;\qquad x_\infty = \frac{\alpha}{\alpha + \beta}\,,\quad \tau_x = \frac{1}{\alpha + \beta}$$

# 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

$$\frac{dx}{dt} = \alpha_x(1-x) - \beta_x x$$

Voltage
Gating
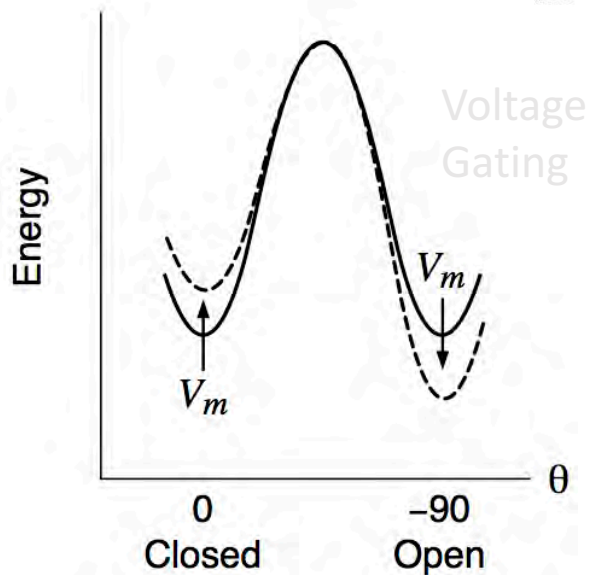
→ Potential modifies energy configuration
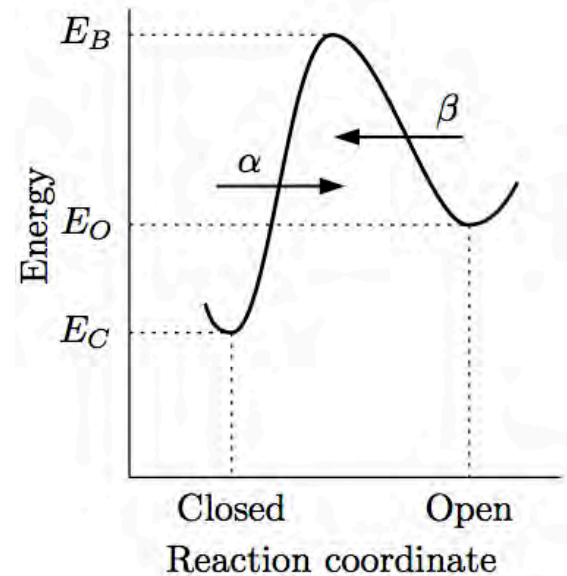
$$\alpha = Ae^{(E_C - E_B)/kT}$$

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

<u>Ex.</u>

$$E_B = \frac{1}{2}QV_B \; ; \quad E_C = \frac{1}{2}QV_m \; ; \quad E_O = -\frac{1}{2}QV_m$$
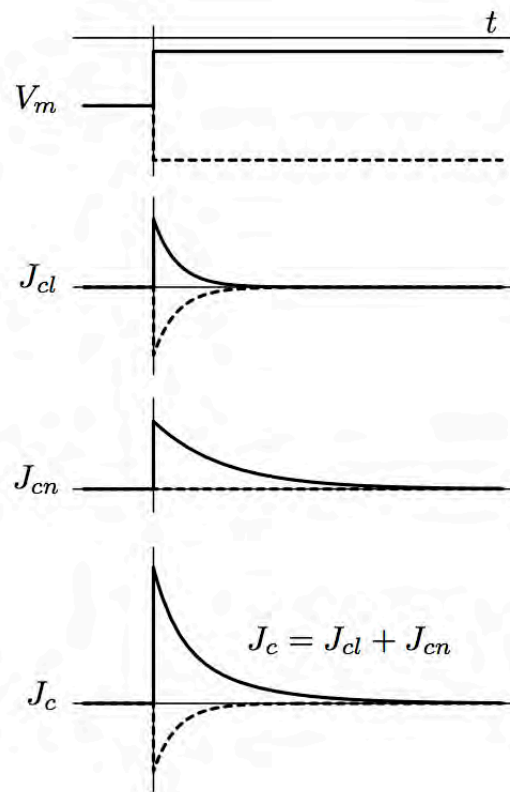
$$\alpha = A\, e^{\frac{1}{2}Q(V_m - V_B)/kT} \; ; \quad \beta = A\, e^{-\frac{1}{2}Q(V_m + V_B)/kT}$$

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

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

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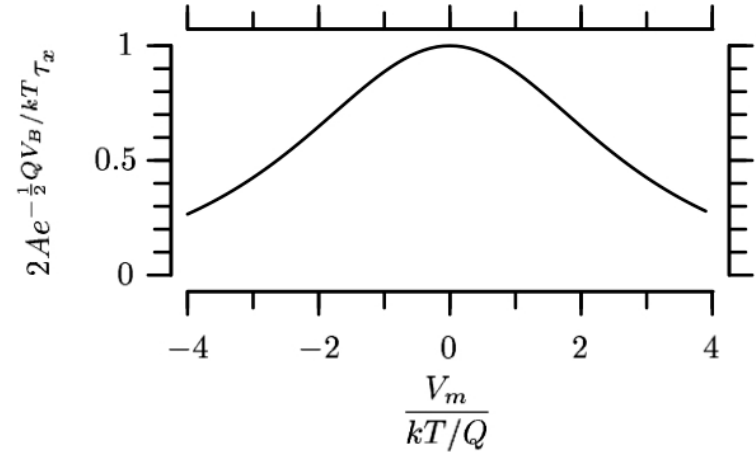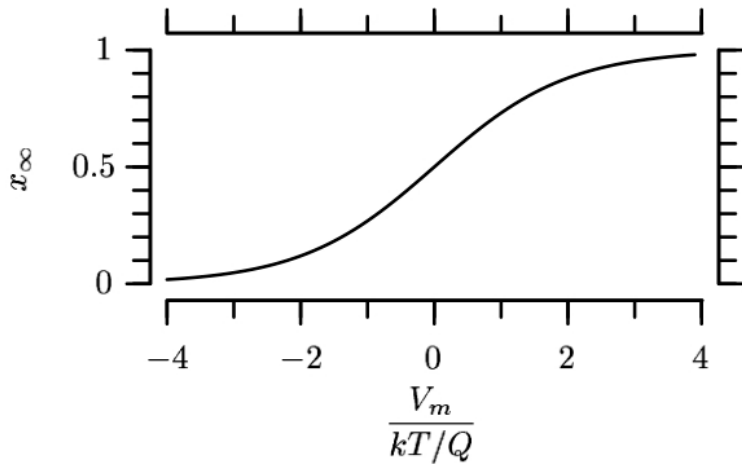
Separating Out the Gating Current

Figure 6.20

Two components (why?)
- Linear
- Nonlinear

V_m

J_{cl}

J_{cn}

$J_c = J_{cl} + J_{cn}$

J_c

t
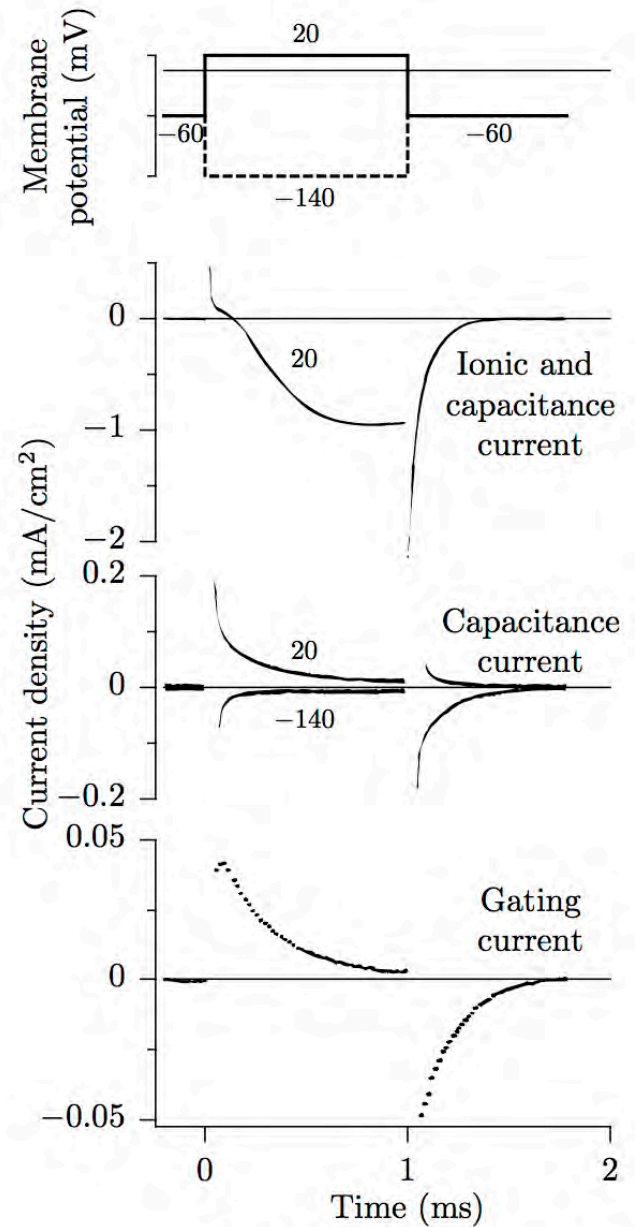
Figure 6.21

Separating Out the Gating Current
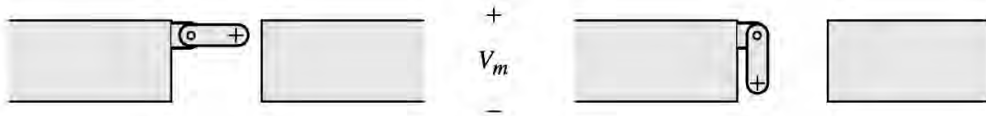
→ Sign of gating current can inform about structure/charge distribution of the channel
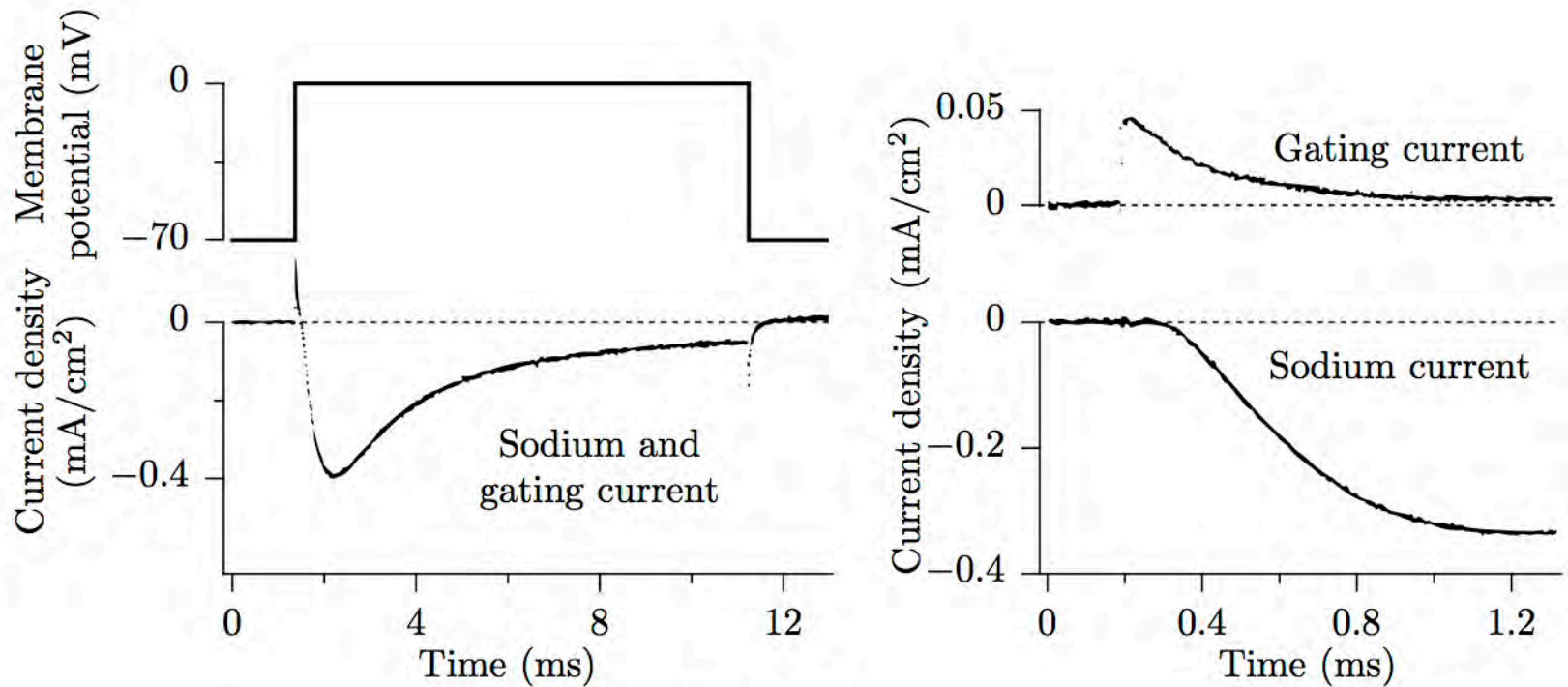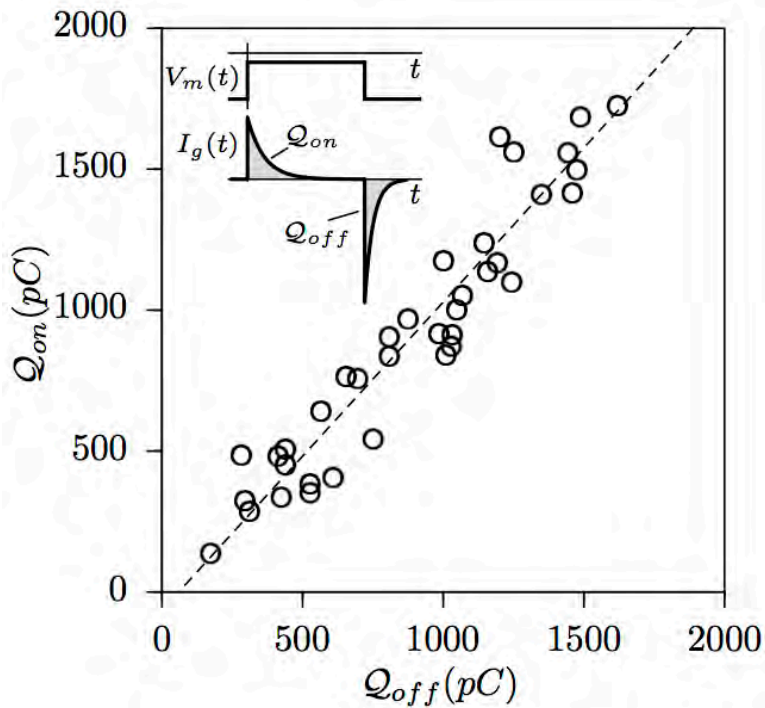
Figure 6.22

Figure 6.24

Figure 6.25

Reversibility

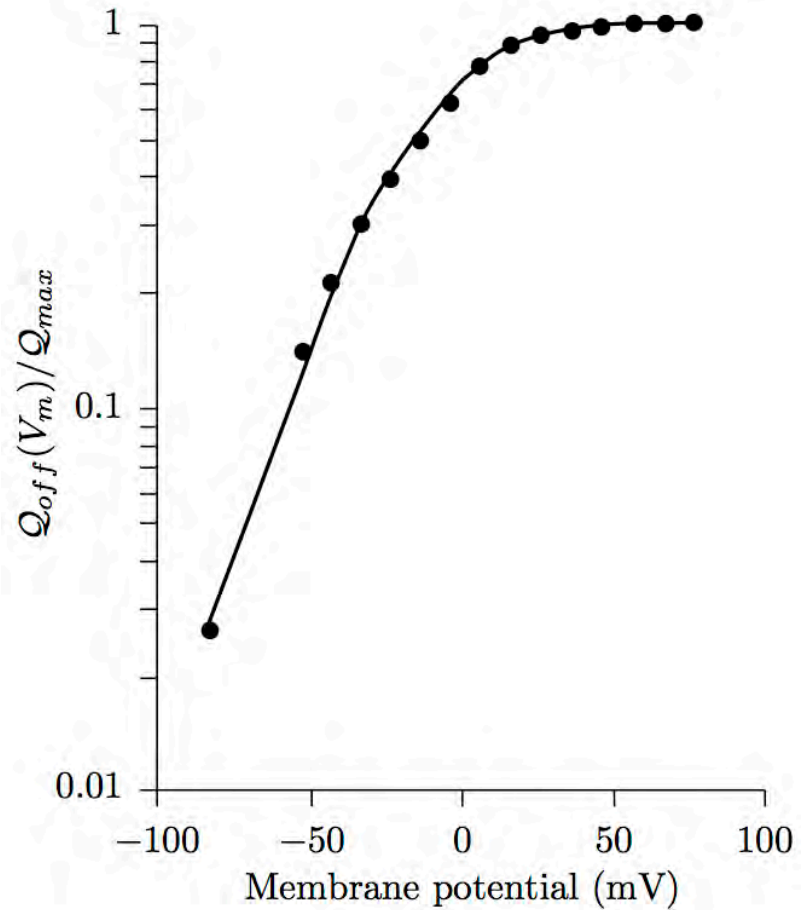(i.e., $Q_{on} = Q_{off}$ implies charge is conserved)

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
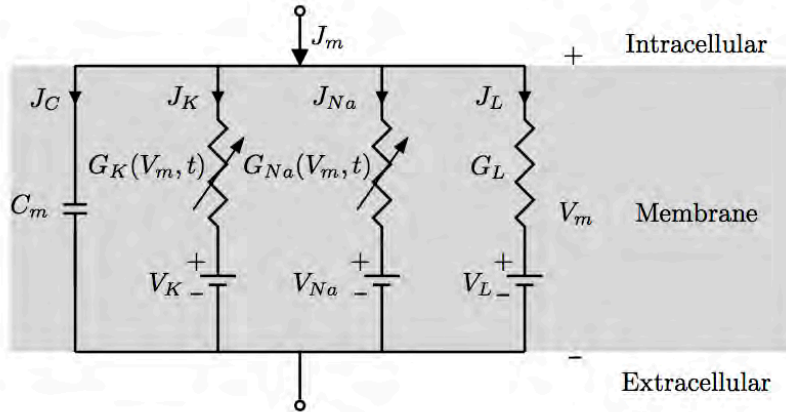
Intracellular

J_m

J_C J_K J_{Na} J_L

C_m $G_K(V_m, t)$ $G_{Na}(V_m, t)$ G_L

V_m Membrane

V_K V_{Na} V_L

Extracellular

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

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

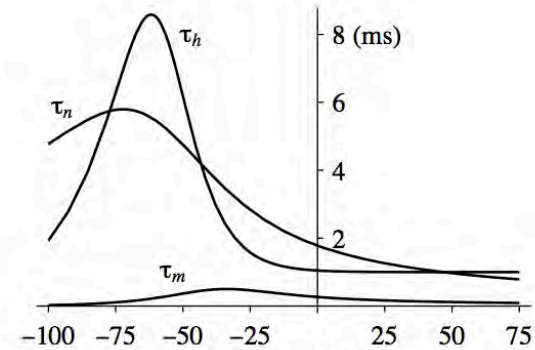$$n(V_m, t) + \tau_n(V_m)\frac{dn(V_m, t)}{dt} = n_\infty(V_m)$$

$$m(V_m, t) + \tau_m(V_m)\frac{dm(V_m, t)}{dt} = m_\infty(V_m)$$

$$h(V_m, t) + \tau_h(V_m)\frac{dh(V_m, t)}{dt} = h_\infty(V_m)$$

$\overline{G}_{Na} = 120$, $\overline{G}_K = 36$, and $G_L = 0.3$ mS/cm^2;

$c_{Na}^o = 491$, $c_{Na}^i = 50$, $c_K^o = 20.11$ $c_K^i = 400$ mmol/L;

$C_m = 1$ μF/cm^2; $V_L = -49$ mV; temperature is 6.3°C.

τ_h 8 (ms)
τ_n 6
4
2
τ_m
−100 −75 −50 −25   25 50 75

0.5 (ms)
0.4
0.3
τ_m 0.2
0.1
−100 −75 −50 −25   25 50 75

h_∞ 1
0.8
0.6
m_∞ 0.4
n_∞ 0.2
−100 −75 −50 −25   25 50 75
V_m (mV)
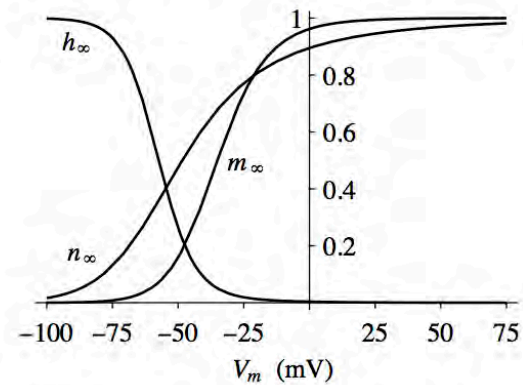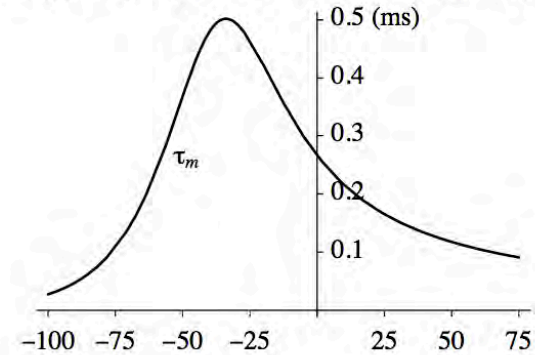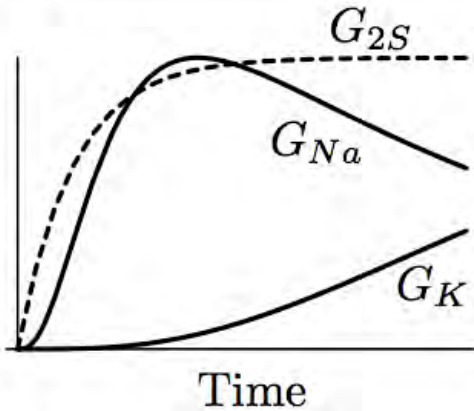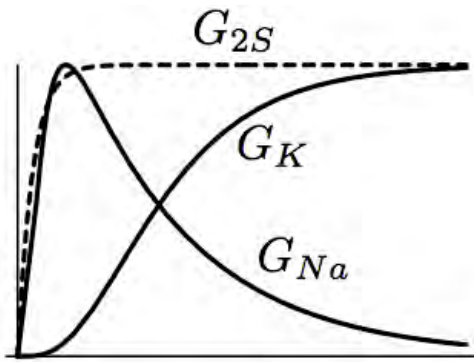
Figure 6.53

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

$$x_\infty = \alpha_x / (\alpha_x + \beta_x) \text{ and } \tau_x = 1/(\alpha_x + \beta_x)$$
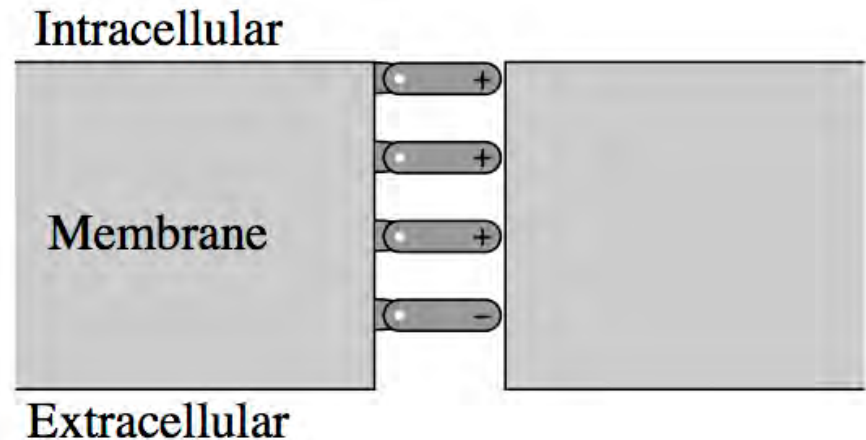
First-order, reversible reaction

$$R \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} P$$
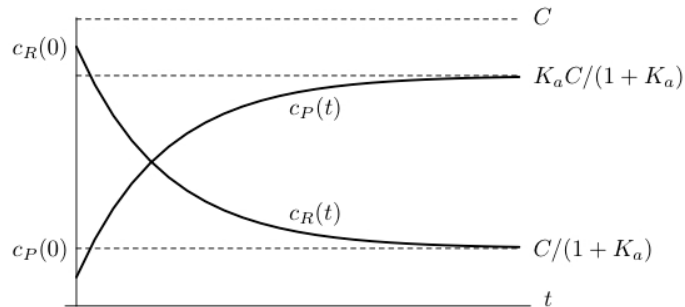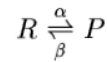
$$\tau = \frac{1}{\alpha + \beta}$$

→ Single two-state model too 'simple'

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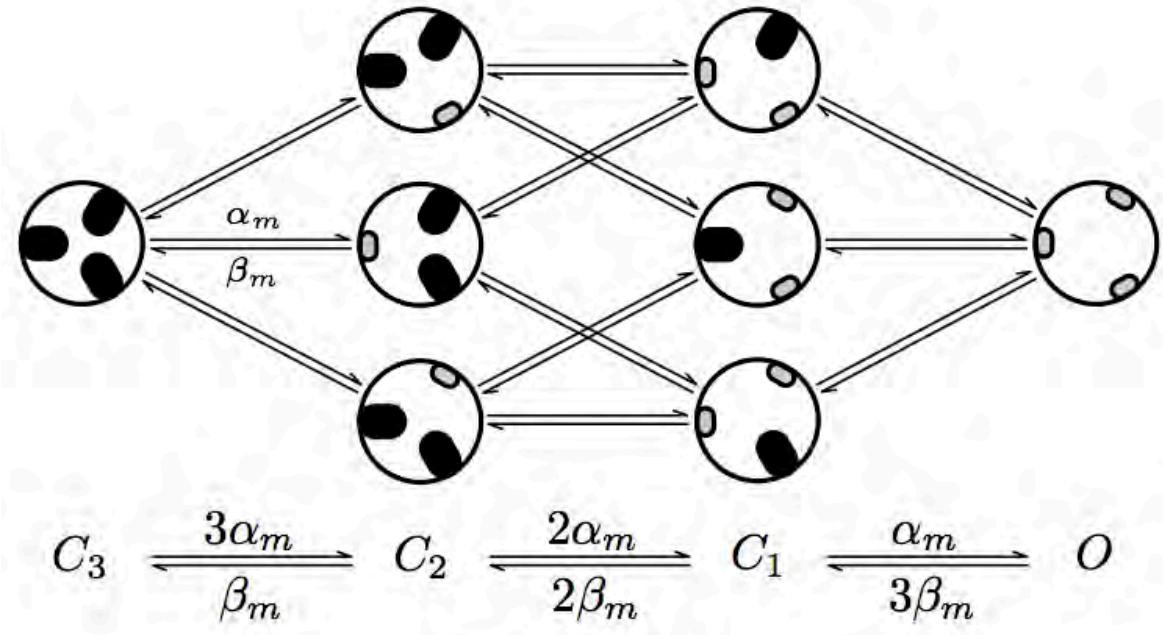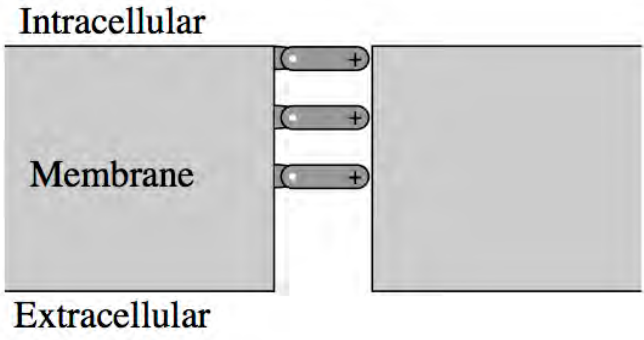
$$G_{Na}(V_m, t) = \overline{G}_{Na} m^3(V_m, t) h(V_m, t)$$

Intracellular

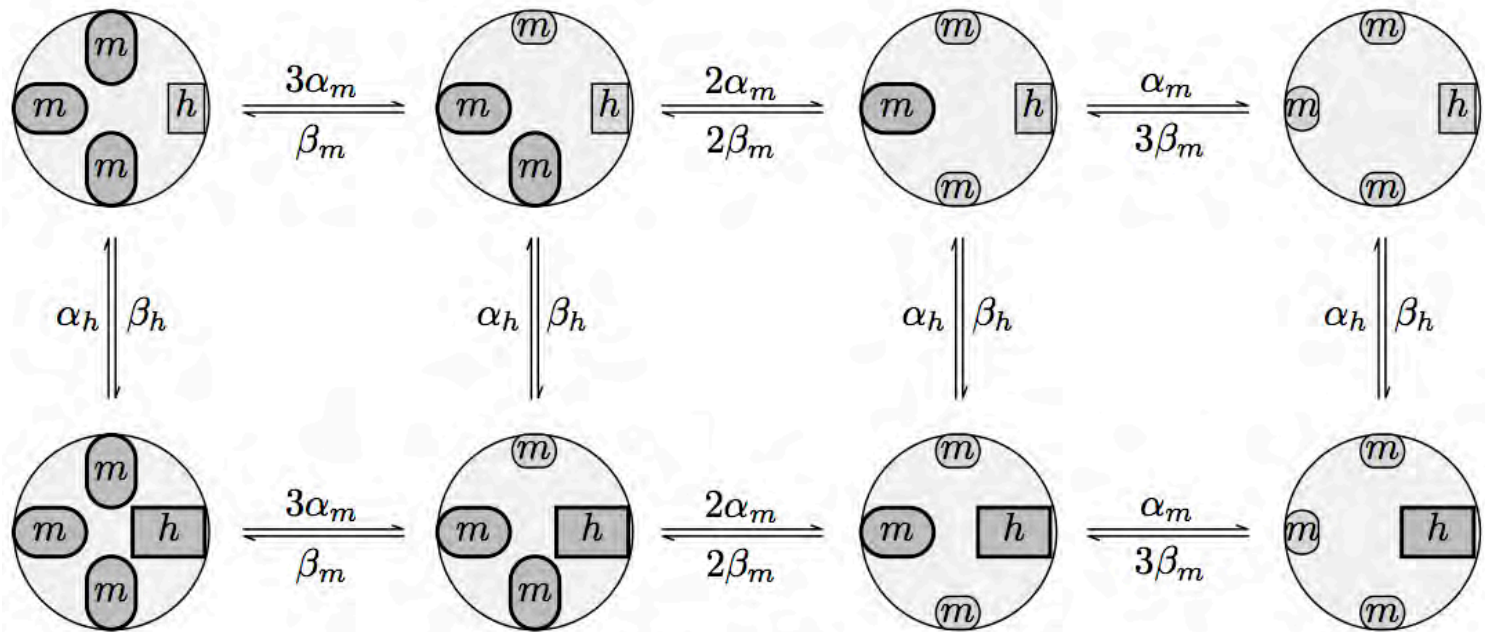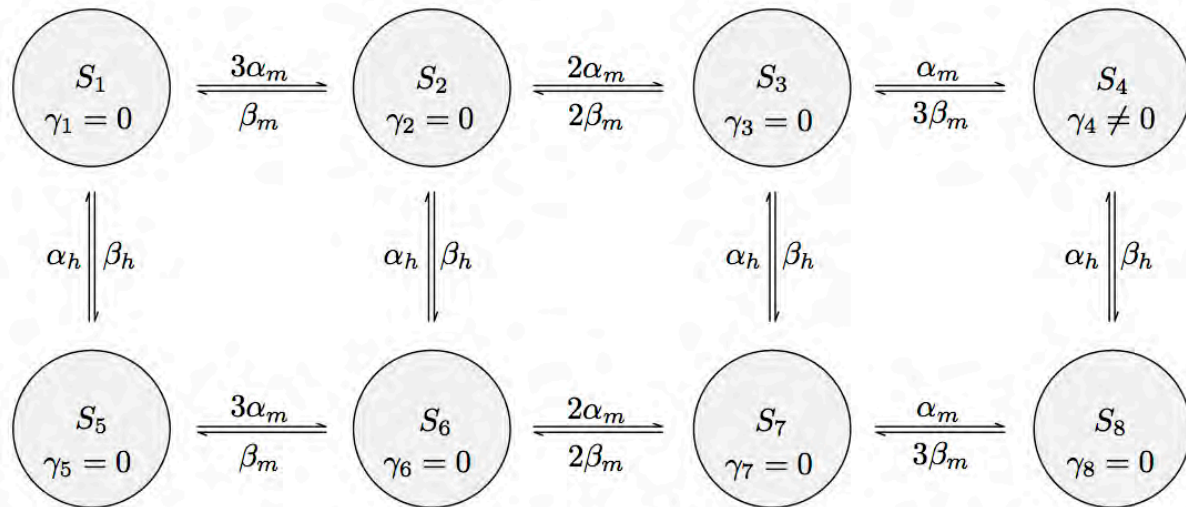Membrane

Extracellular

Figure 6.54
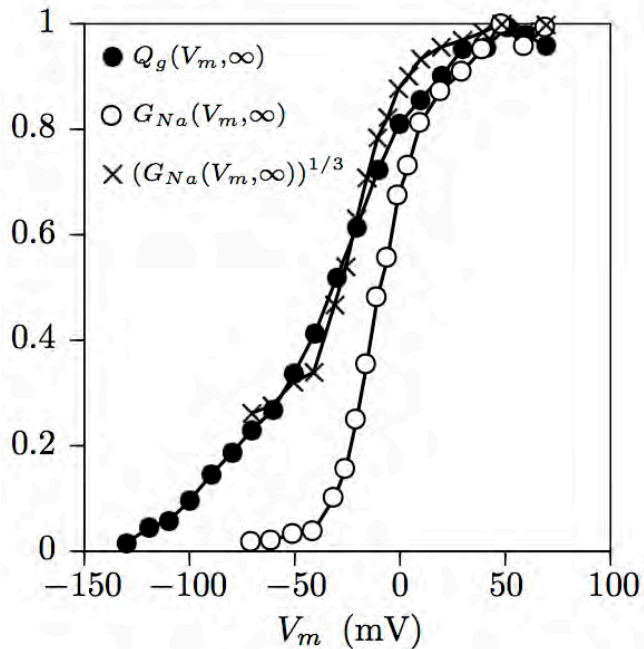
Figure 6.55

Figure 6.56

Figure 6.57

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...

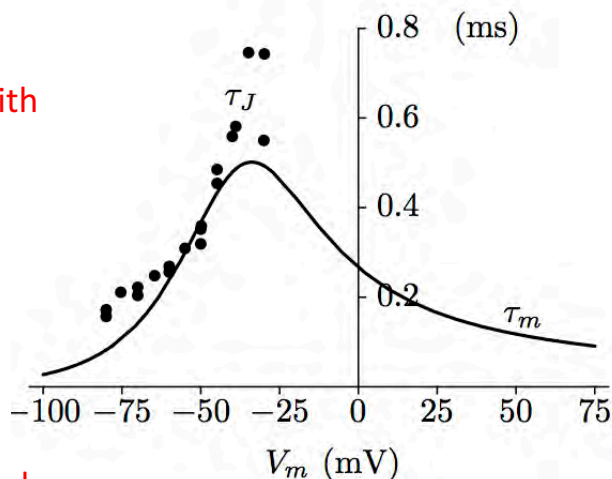... that are inconsistent with data ("tail currents")

Figure 6.59

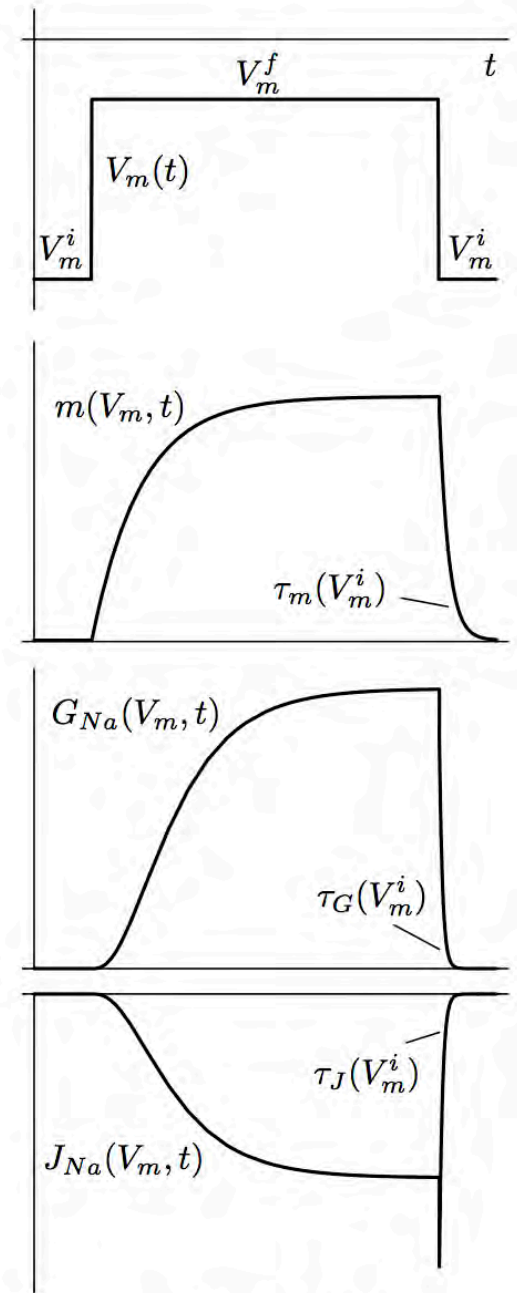→ Four independent two-state models still to simple. Multi-state channels?
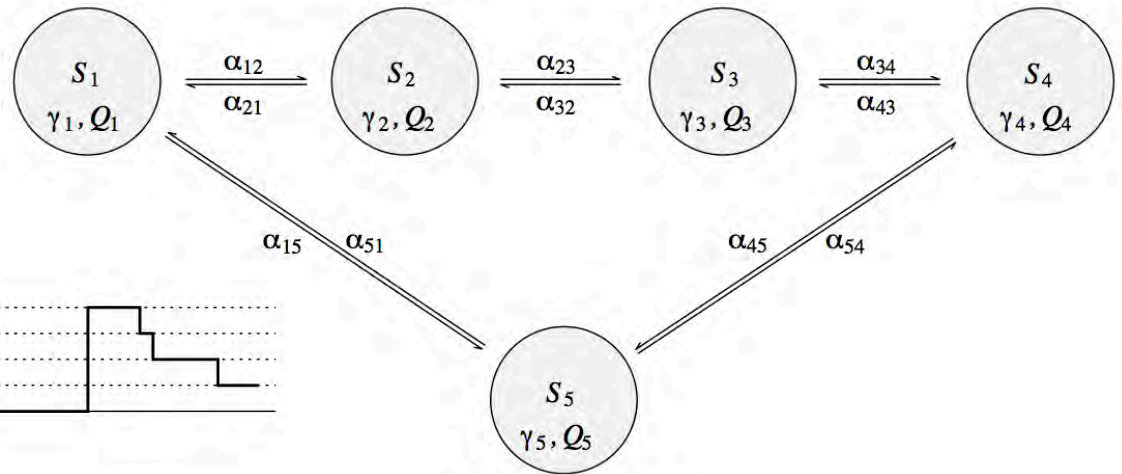

Figure 6.58

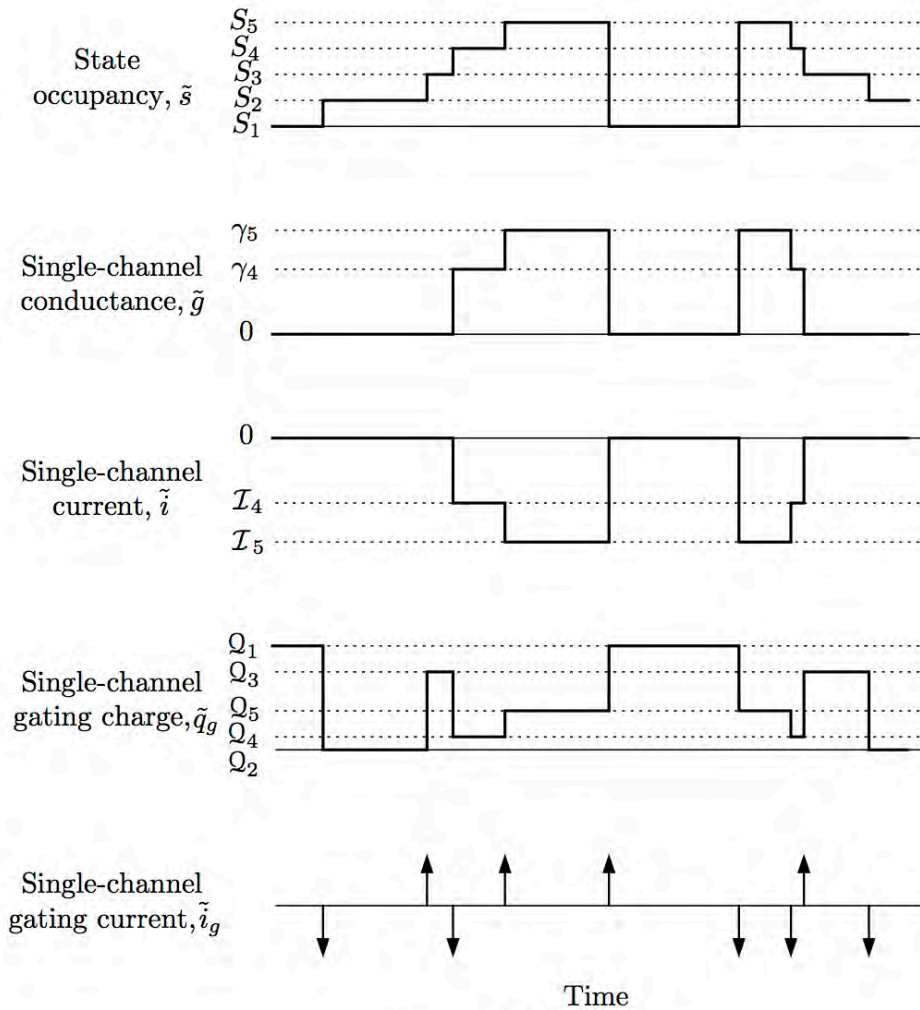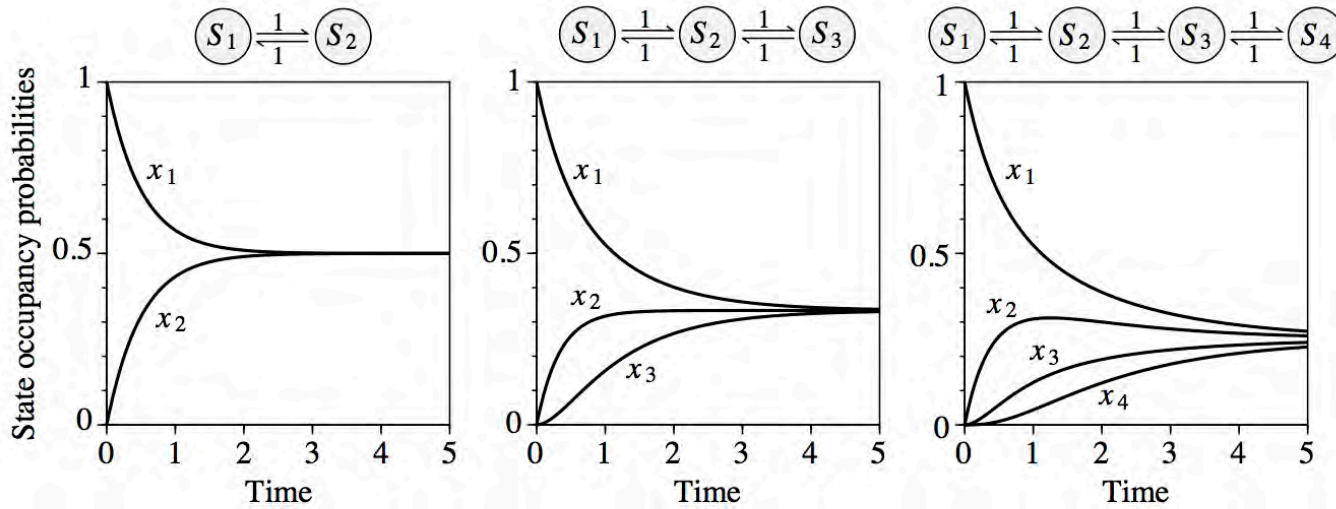# Multistate Channel Models
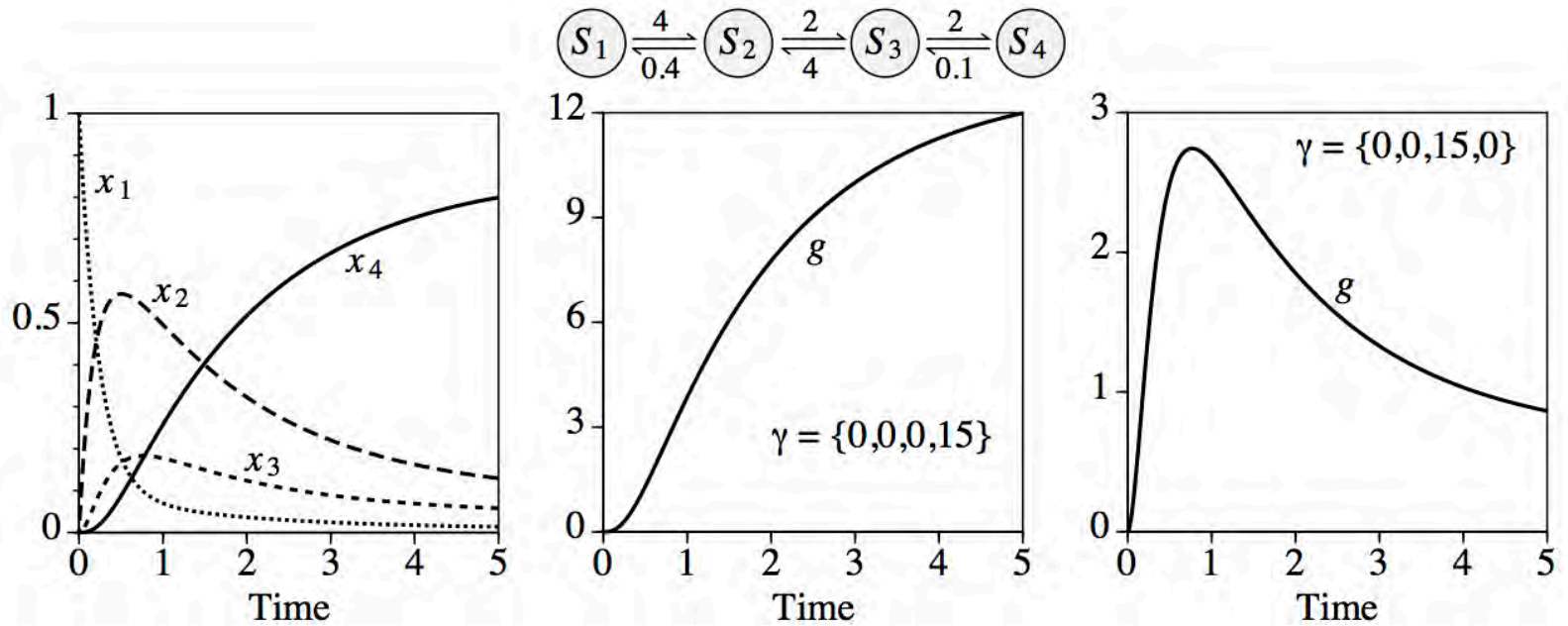

Figure 6.60

Figure 6.61

Figure 6.62

→ s-shape stems from "lag incurred by the state occupancy having to traverse earlier stages"
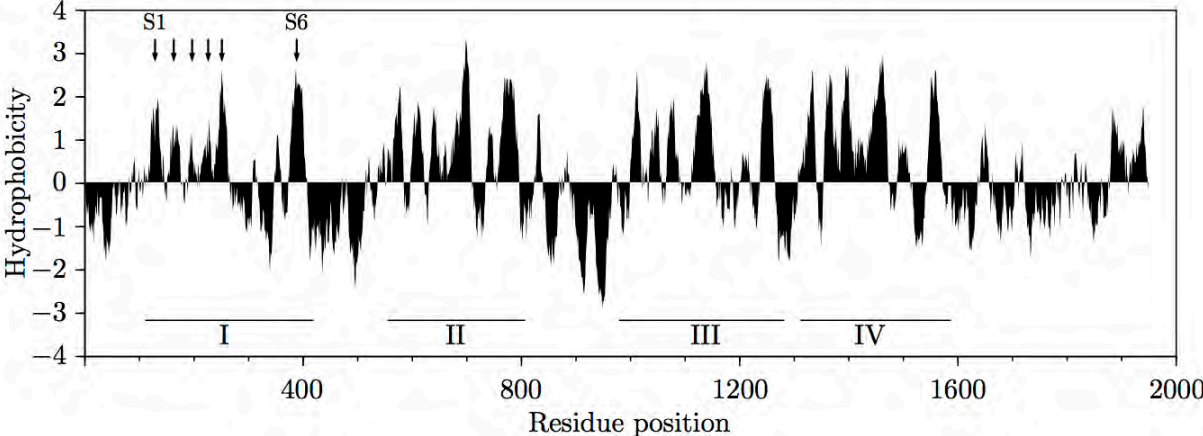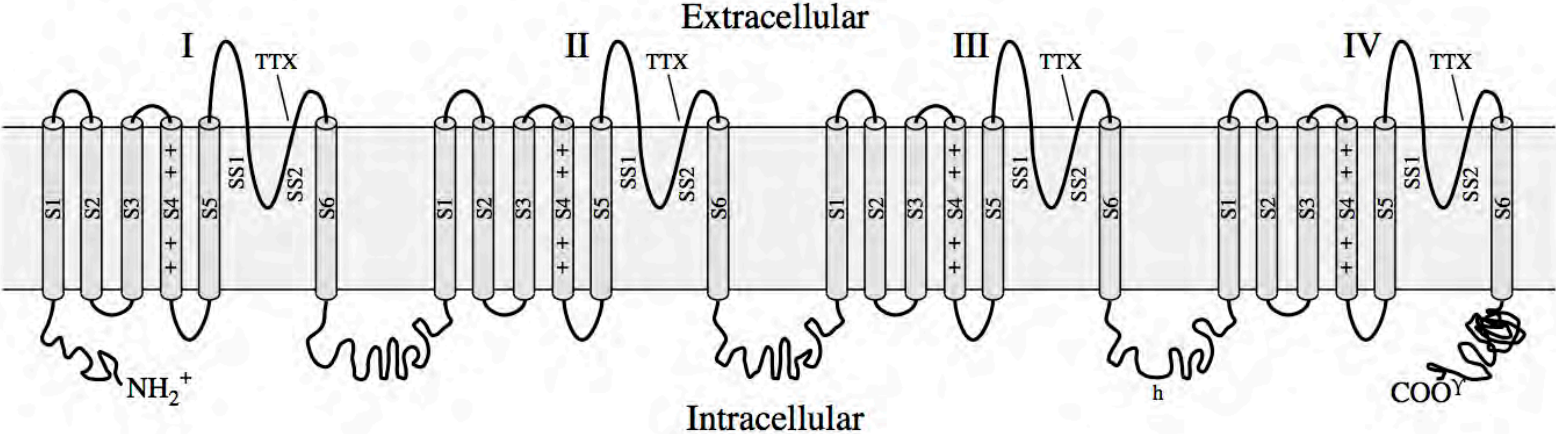
Molecular Underpinnings
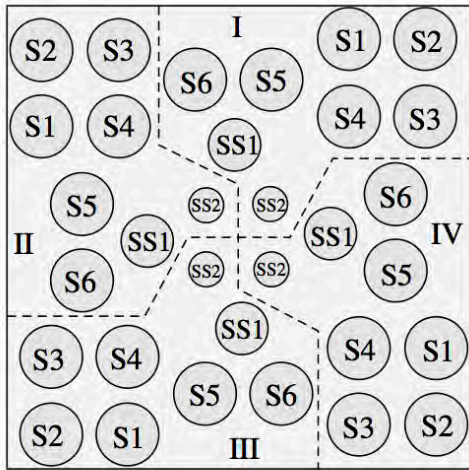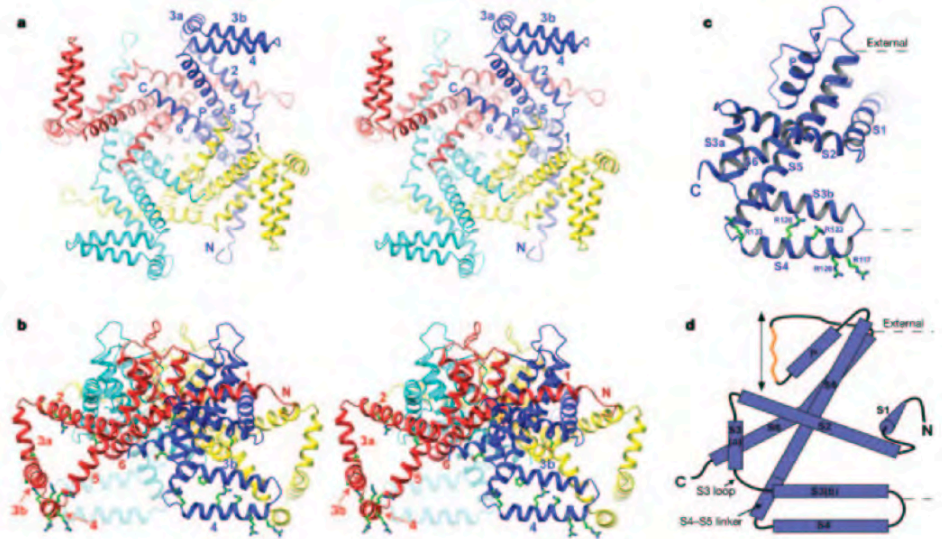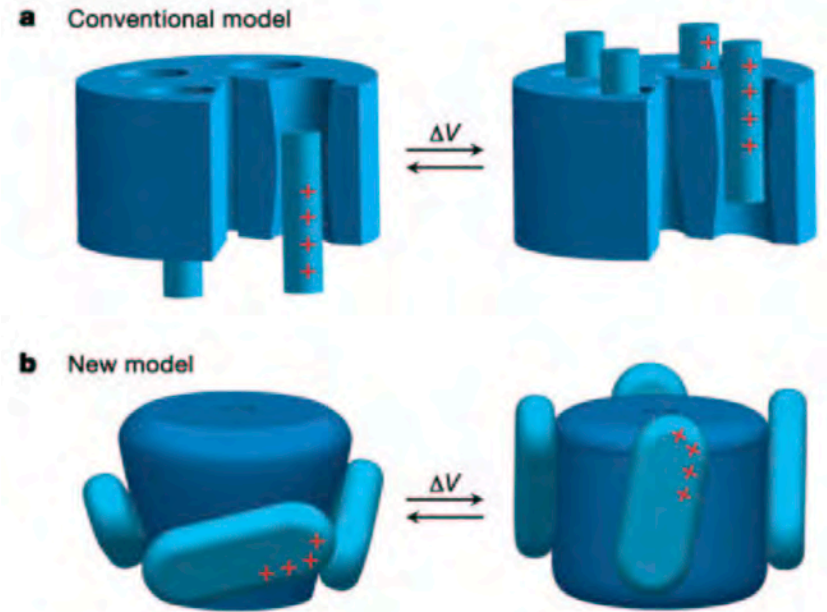

Figure 6.68

Figure 6.69

Figure 6.70

Y. Jiang, A. Lee, J. Chen, V. Ruta, M. Cadene, B. Chalt, and R. MacKinnon (2003),
Nature 423:33-41.

a Conventional model

b New model

Y. Jiang, A. Lee, J. Chen, V. Ruta, M. Cadene, B. Chalt, and R. MacKinnon (2003),
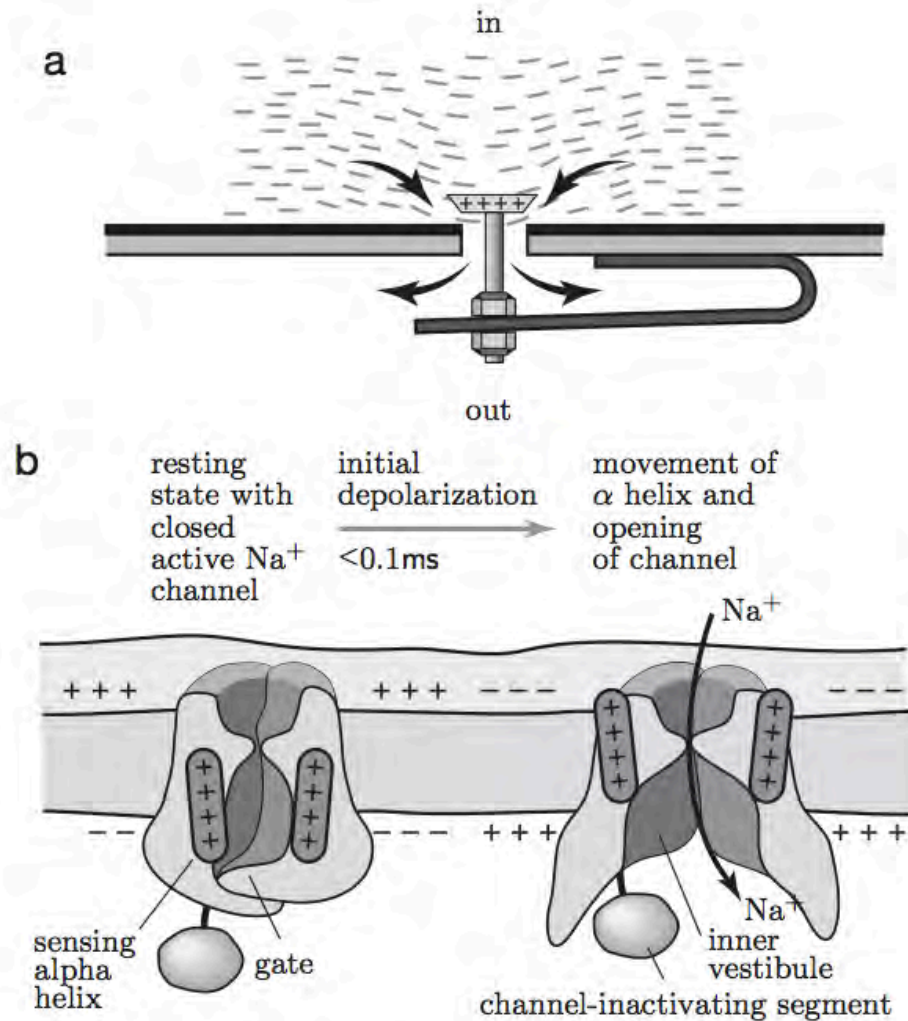Nature 423:33-41.

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 chanel itself is in its open conformation. [After Armstrong & Hille, 1998.]