Biophysics I (BPHS 3090)

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Website: http://www.yorku.ca/cberge/3090W2015.html

York University
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Lecture 30

Reference/Acknowledgement:
- TF Weiss (Cellular Biophysics)
- D Freeman

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?

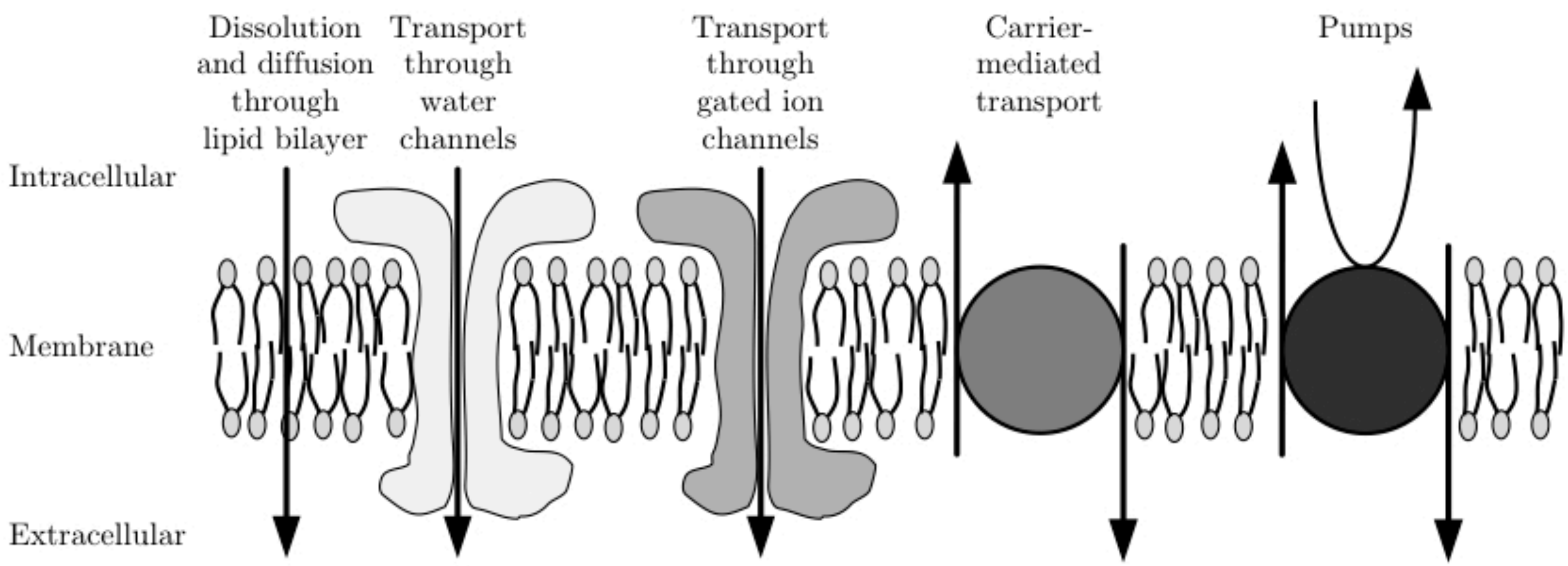


Figure 2.19

→ Notion of an *ion channel*

Macroscopic Ionic Currents: HH Methodology

Voltage clamp

'subtraction'

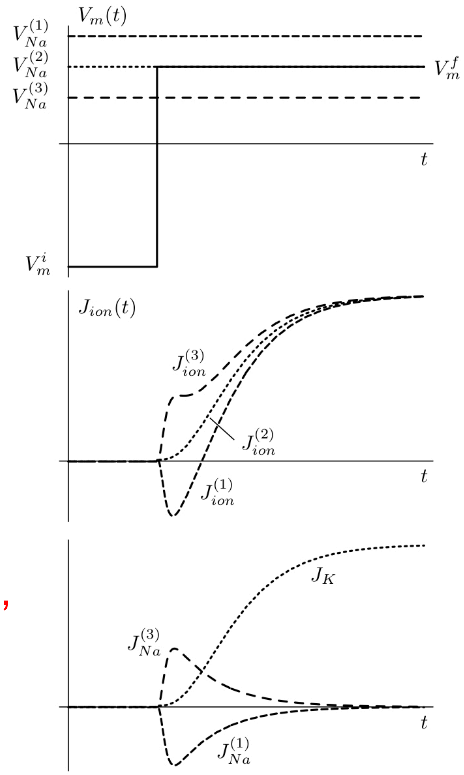


Figure 4.17

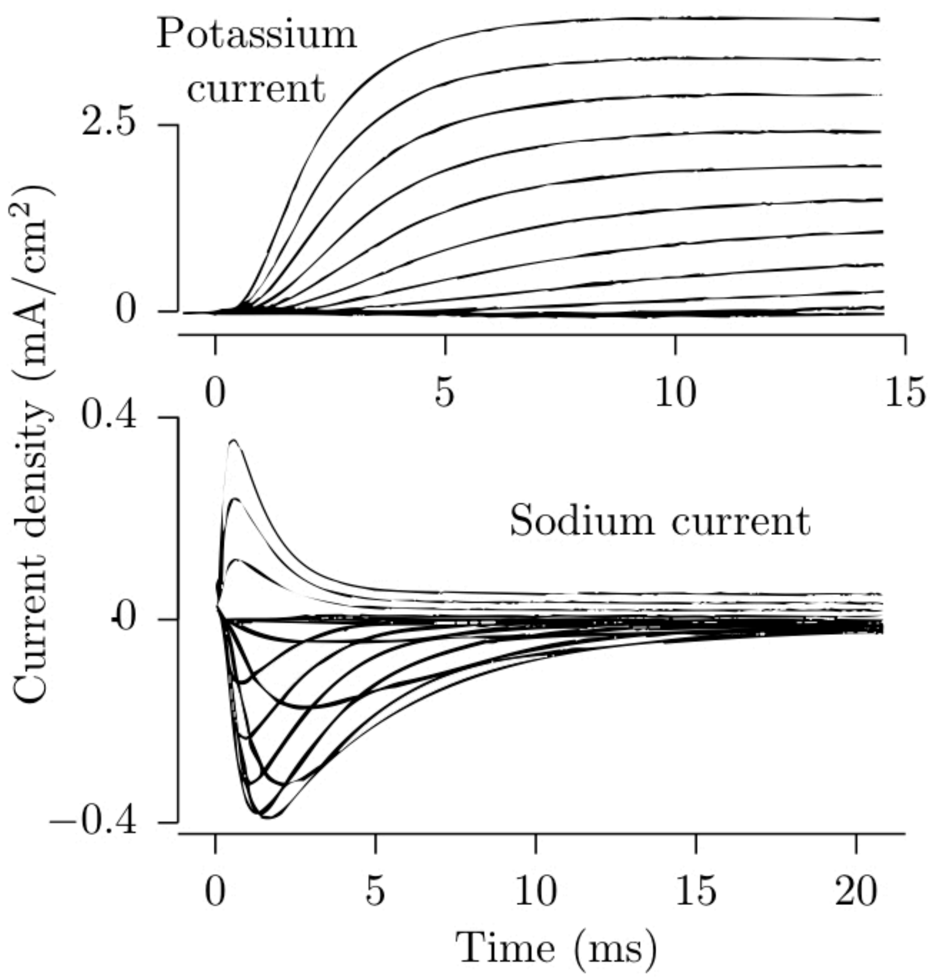


Figure 4.20

NOTE: Other methods besides subtraction (e.g., TTX to block Na^+ current, replace K^+ w/ Cs^+, etc...)

<u>Macroscopic Ionic Currents</u>: Selectivity

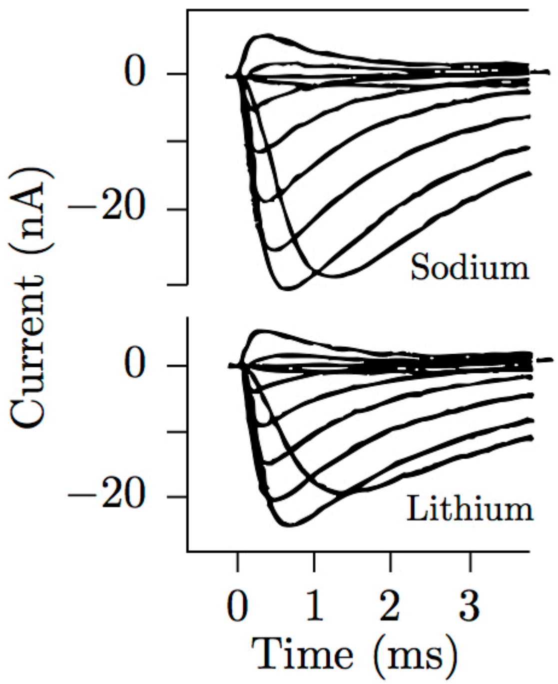


Figure 6.8

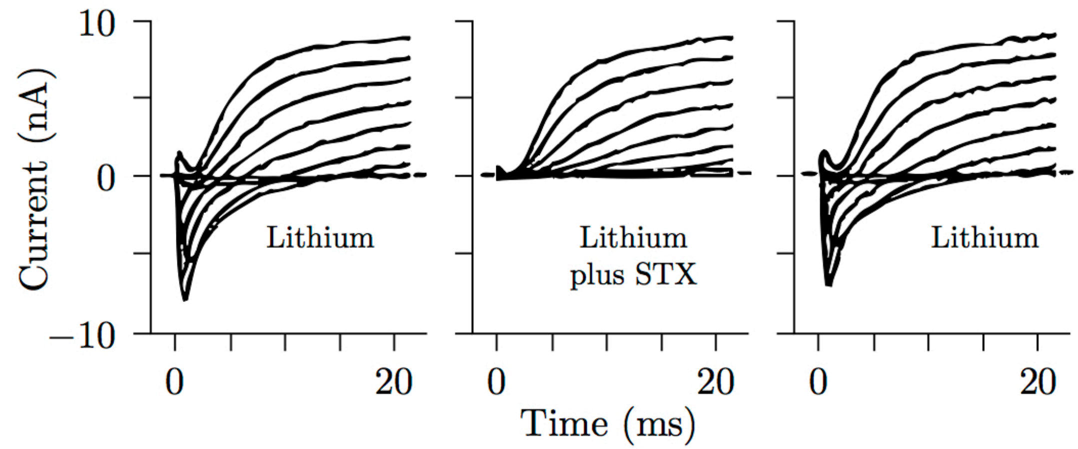


Figure 6.9

Table 6.1 (mod)

Na$^+$ channel Frog node		K$^+$ channel Frog node	
Ion n	P_n/P_{Na^+}	Ion n	P_n/P_{K^+}
Na^+	1.0	Tl^+	2.3
Li^+	0.93	K^+	1.0
Tl^+	0.33	Rb^+	0.91
NH_4^+	0.16	NH_4^+	0.13
K^+	0.086	Cs^+	< 0.077
Rb^+	< 0.012	Li^+	< 0.018
Cs^+	< 0.013	Na^+	< 0.10

→ Ion channels ‘prefer’ certain ions, but are not necessarily exclusive

Microscopic Current Mechanism

Scaled version of macroscopic current?

Discrete on/off current?

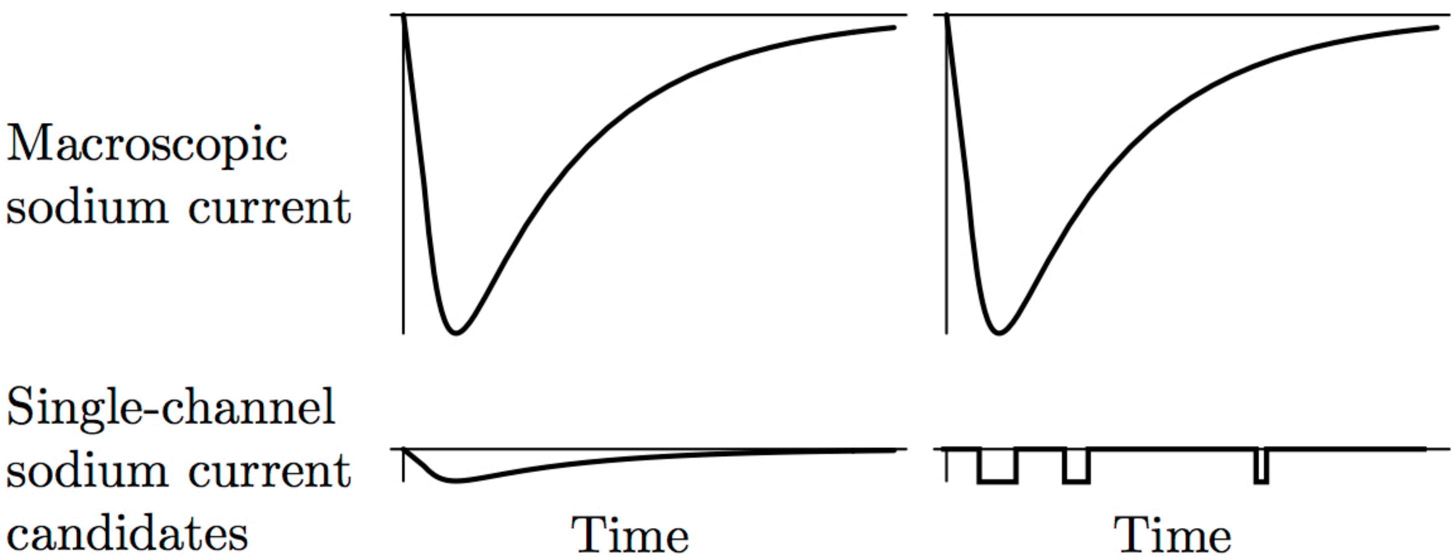
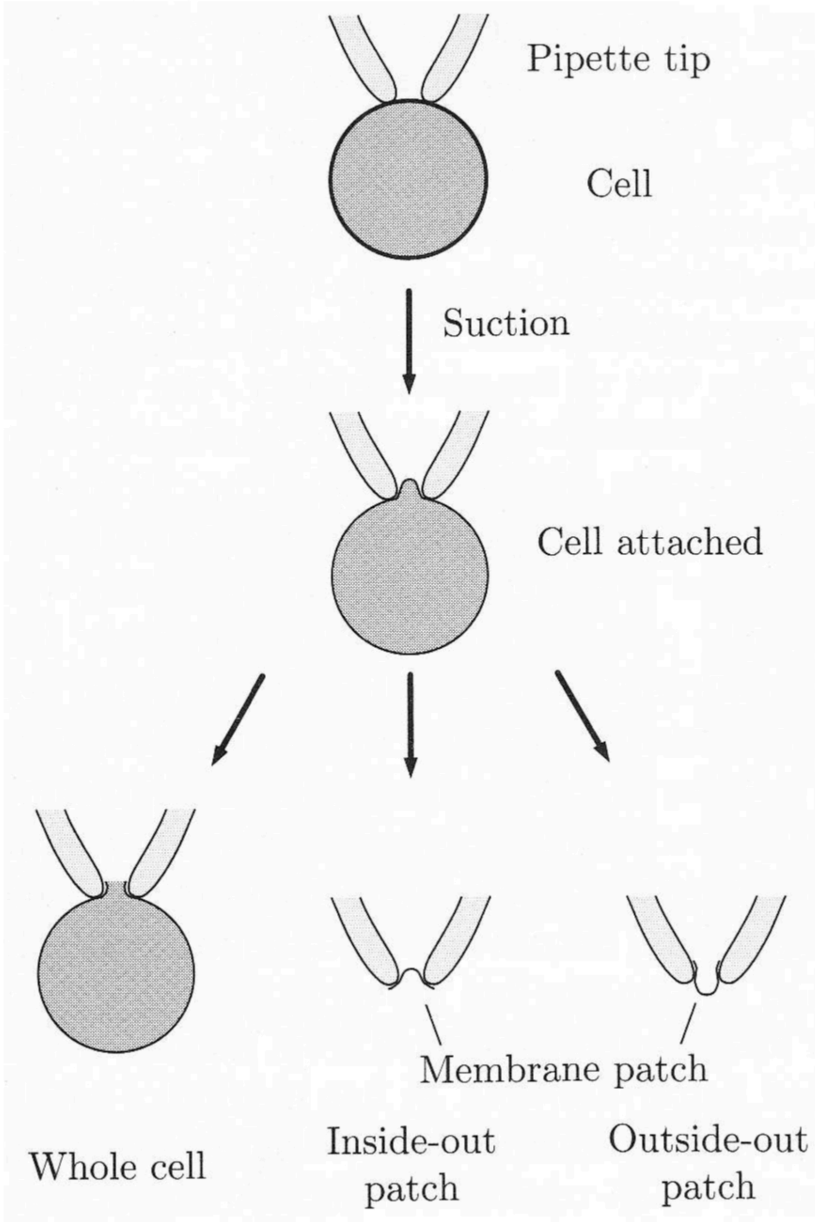


Figure 6.27

Patch Clamp



→ Refinement of voltage-clamp

Figure 6.1

Patch Clamp

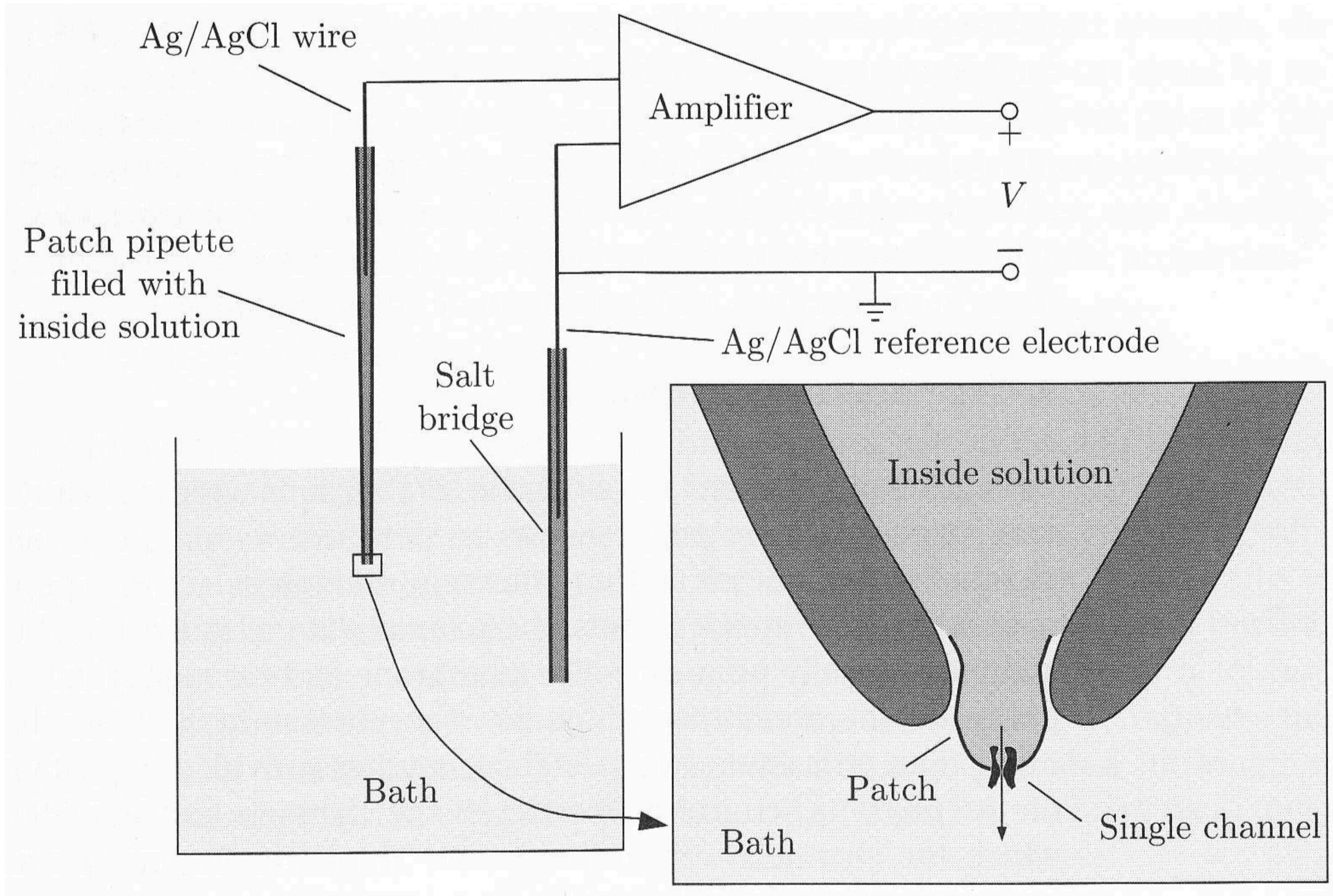
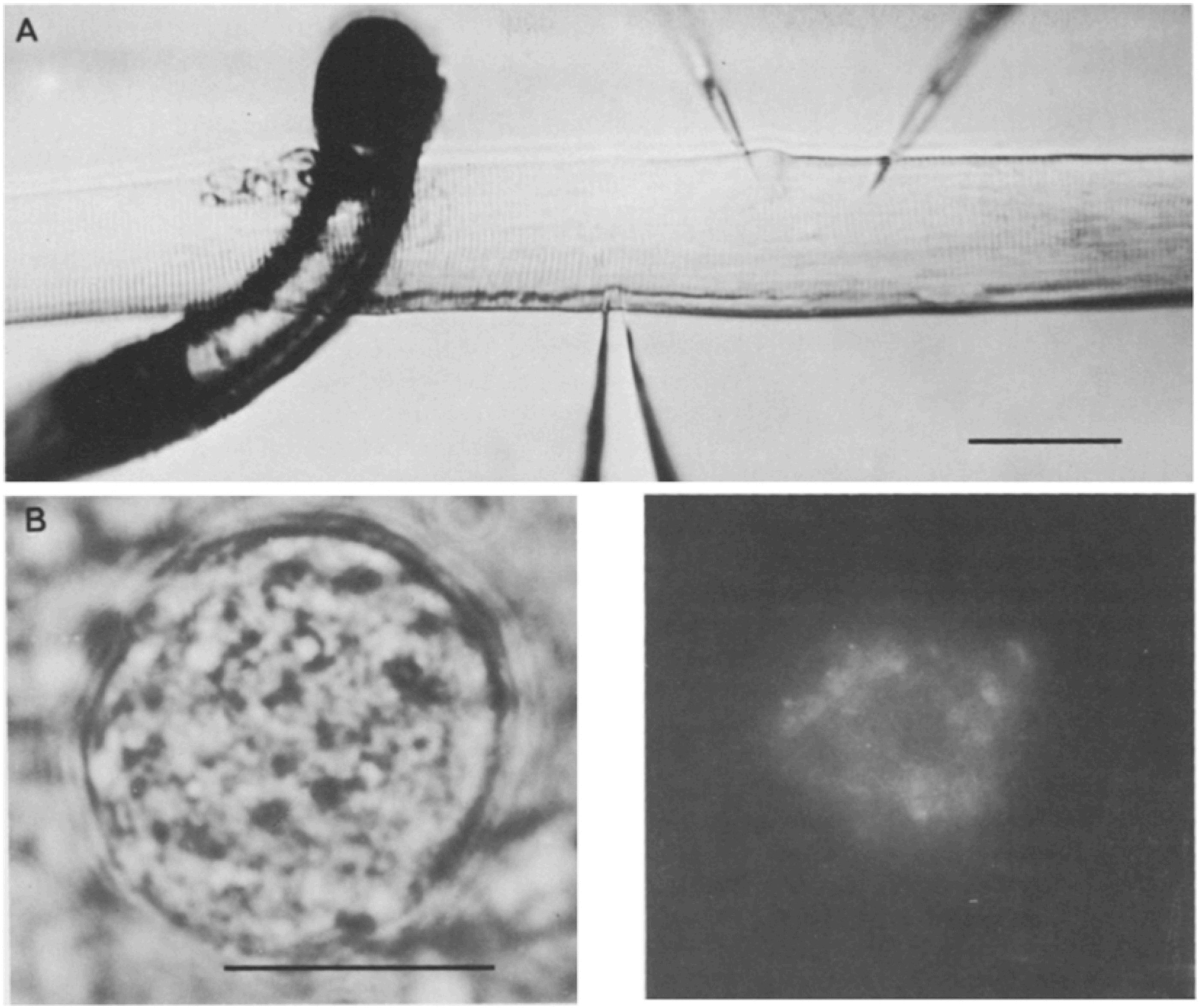


Figure 6.2

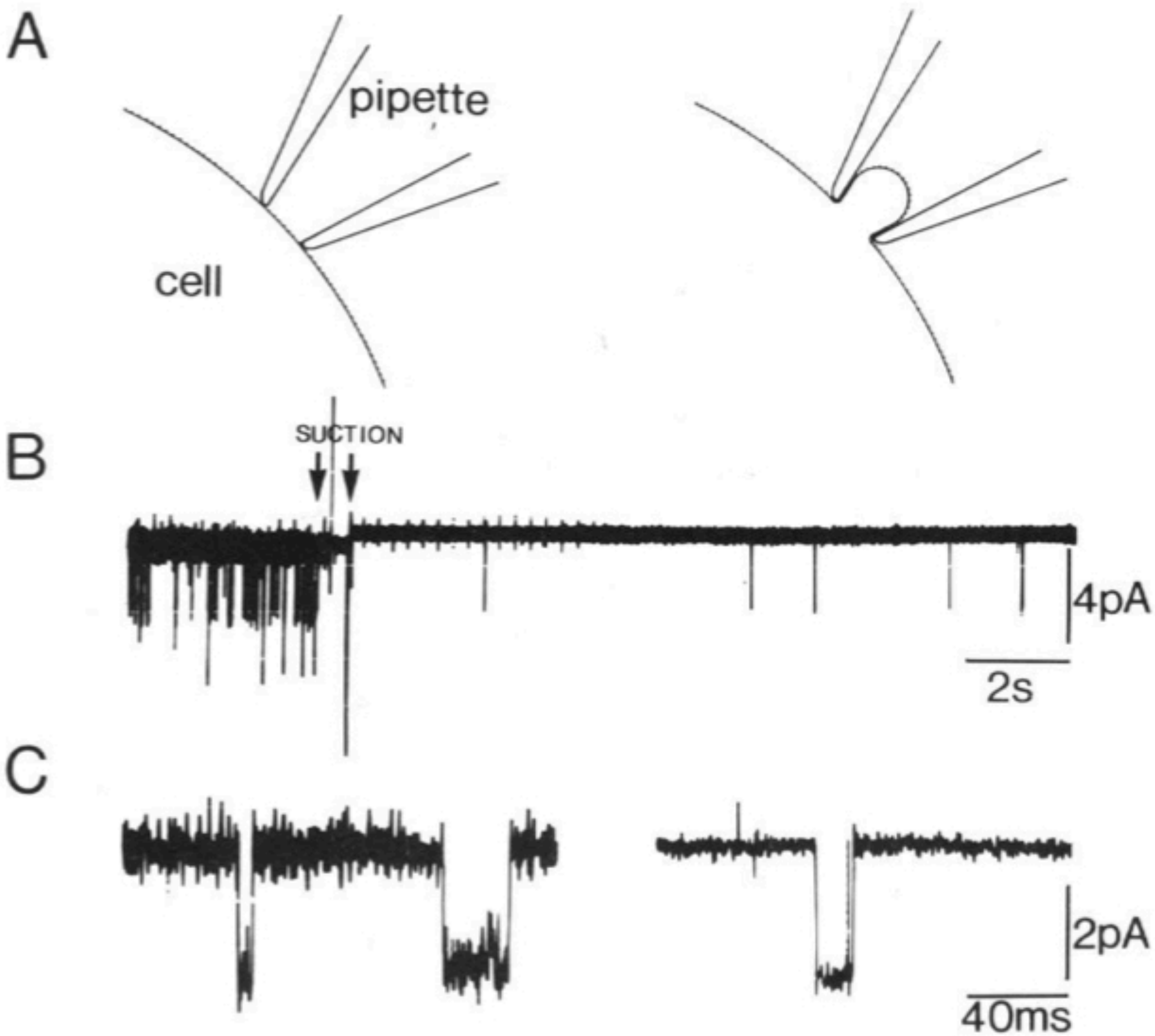
→ Goal is to isolate a single ion channel

Patch Clamp



Hamill et al. (1981)

Patch Clamp



→ Current through a single channel!

Hamill et al. (1981)

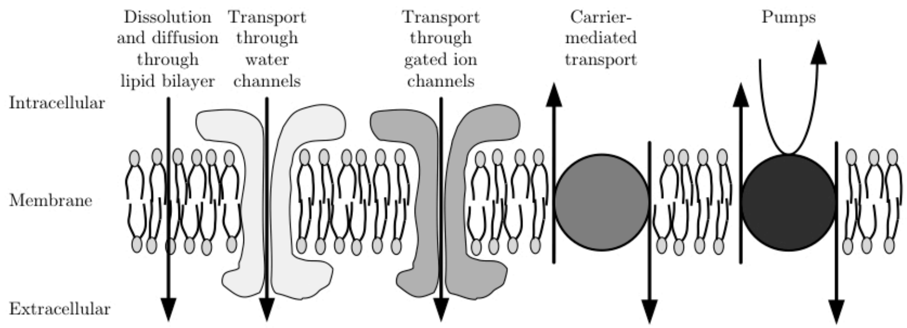
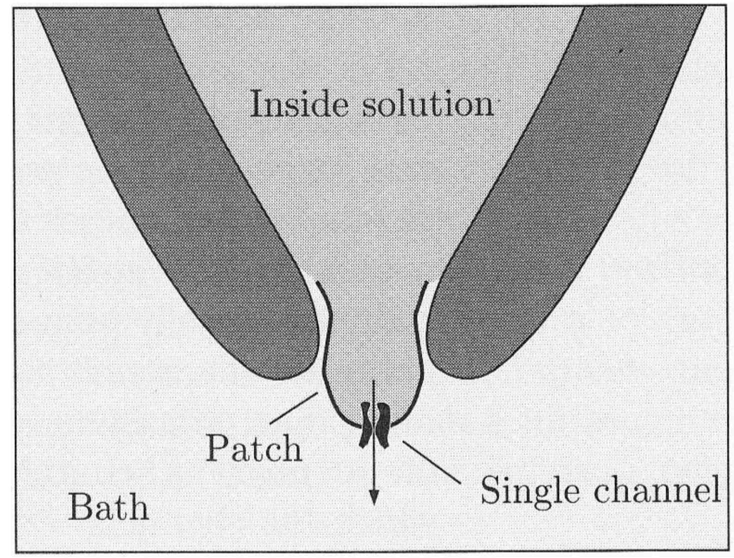


Figure 2.19



→Single ion channel current appears ‘gated’ (i.e., on/off)

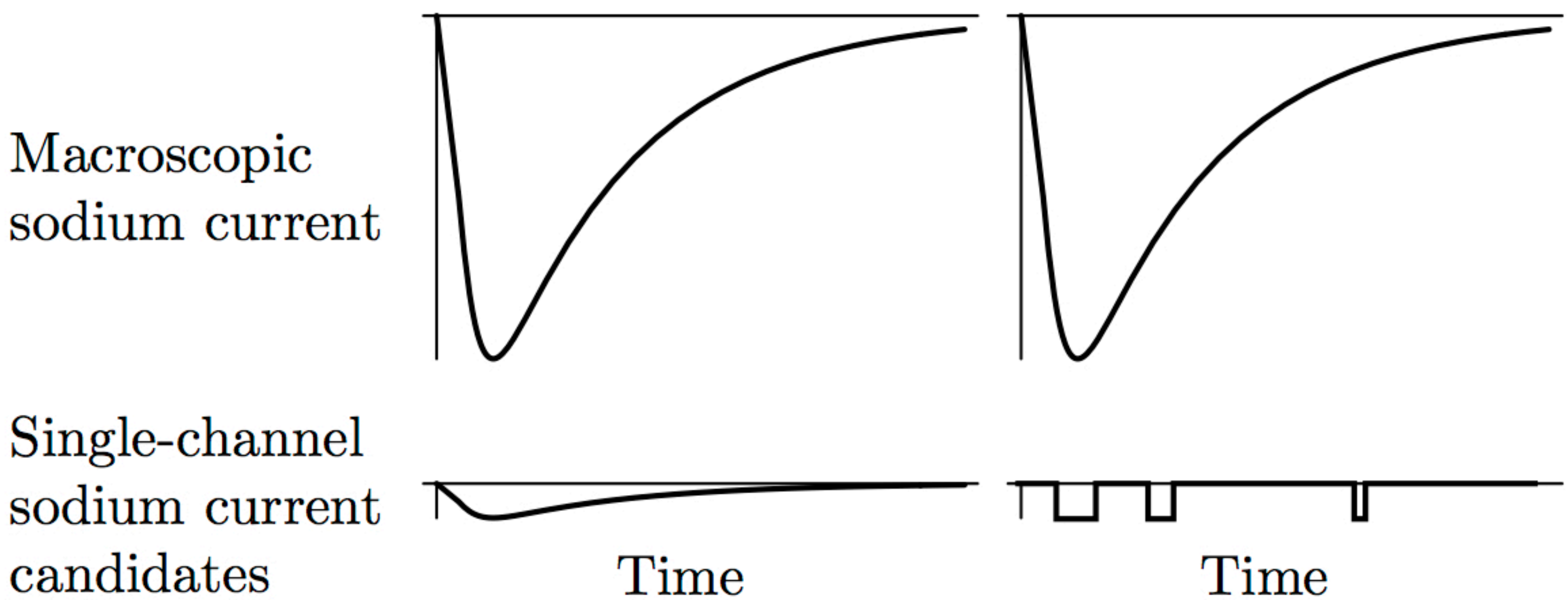

Macroscopic
sodium current
Single-channel
sodium current
candidates
Time
Time

Figure 6.27

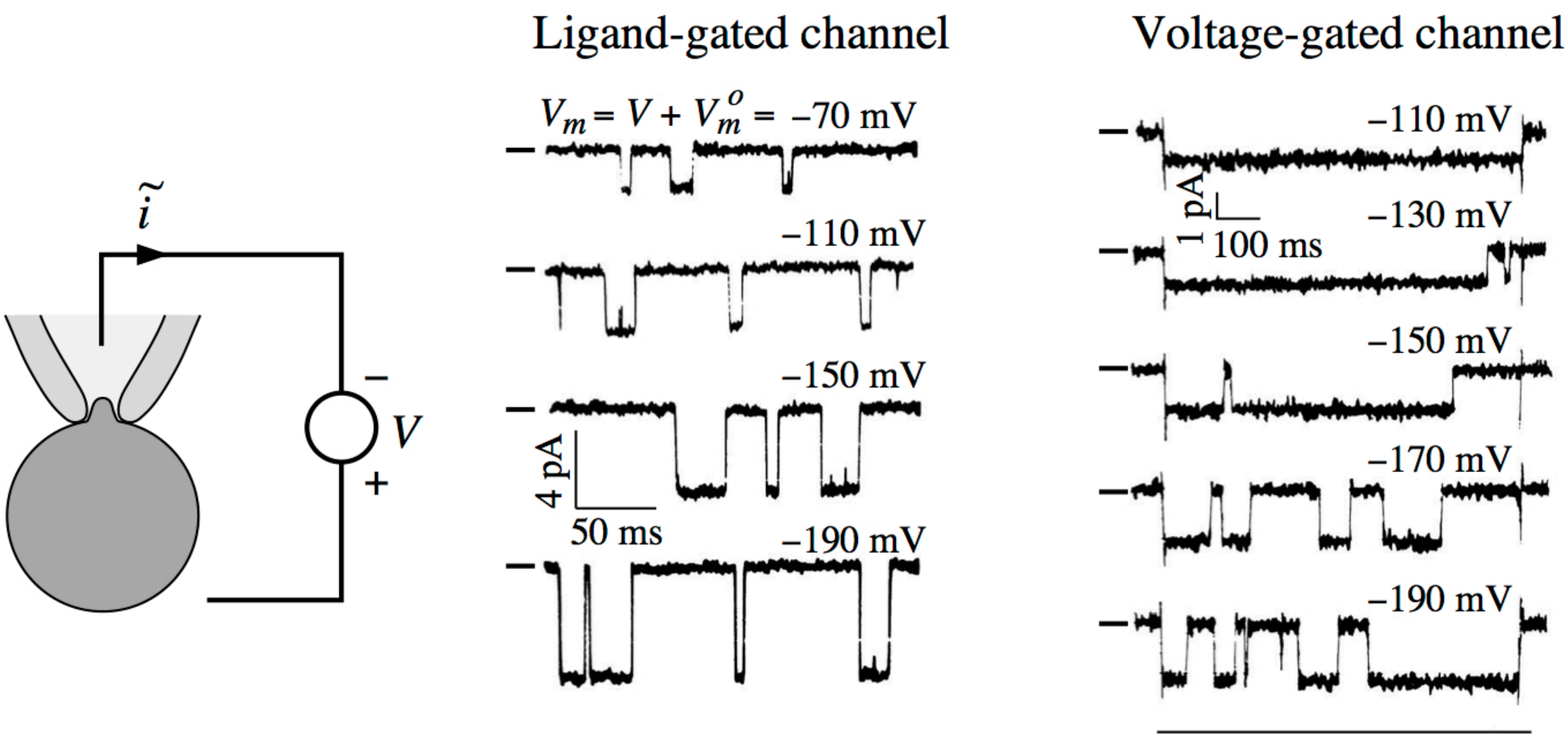


Figure 6.28

- Random nature of channels
- Voltage-gated channels more likely to be open when magnitude of potential increased
- Note change in current (both cases) with respect to holding potential

(Primitive) Ion Channel Model

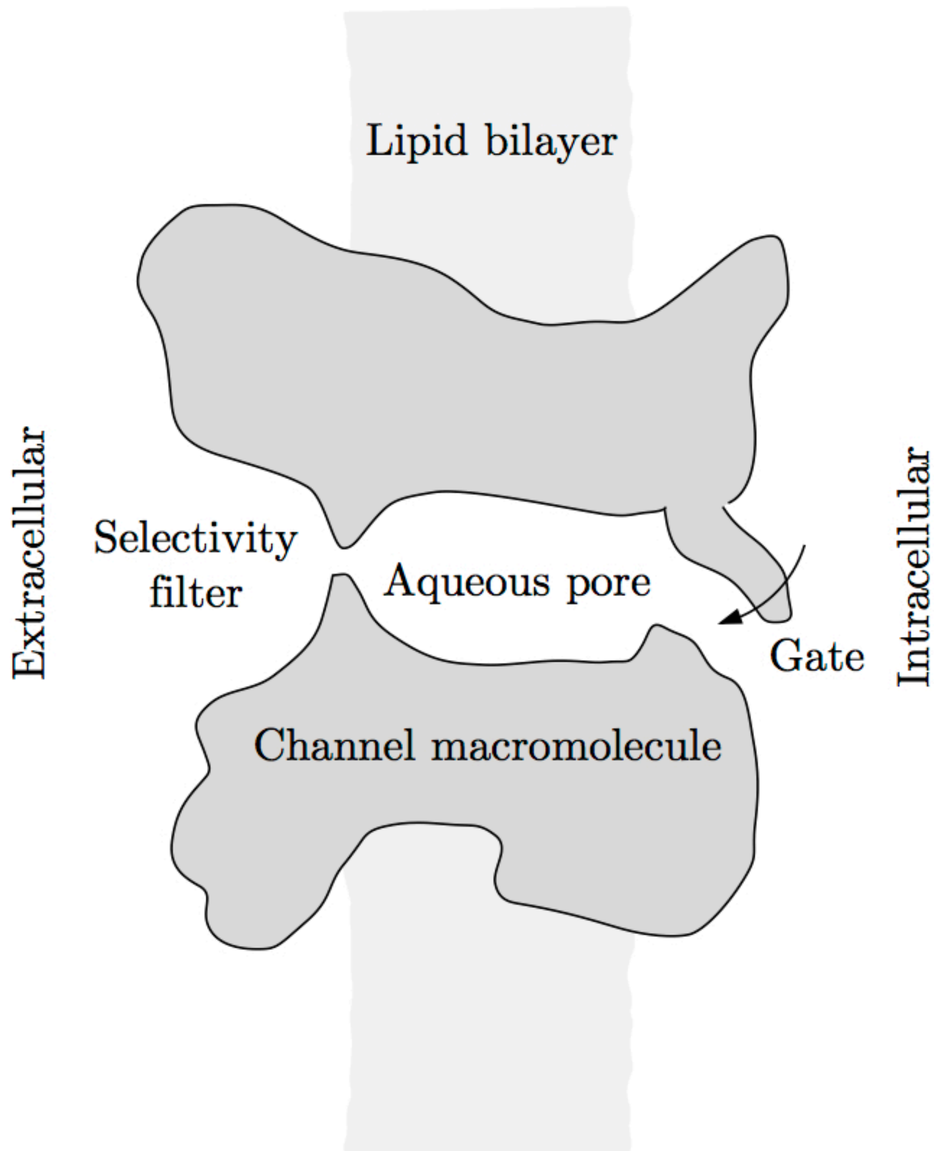


Figure 6.3

Current types:
1. Ionic
2. Gating/capacitive

Current types

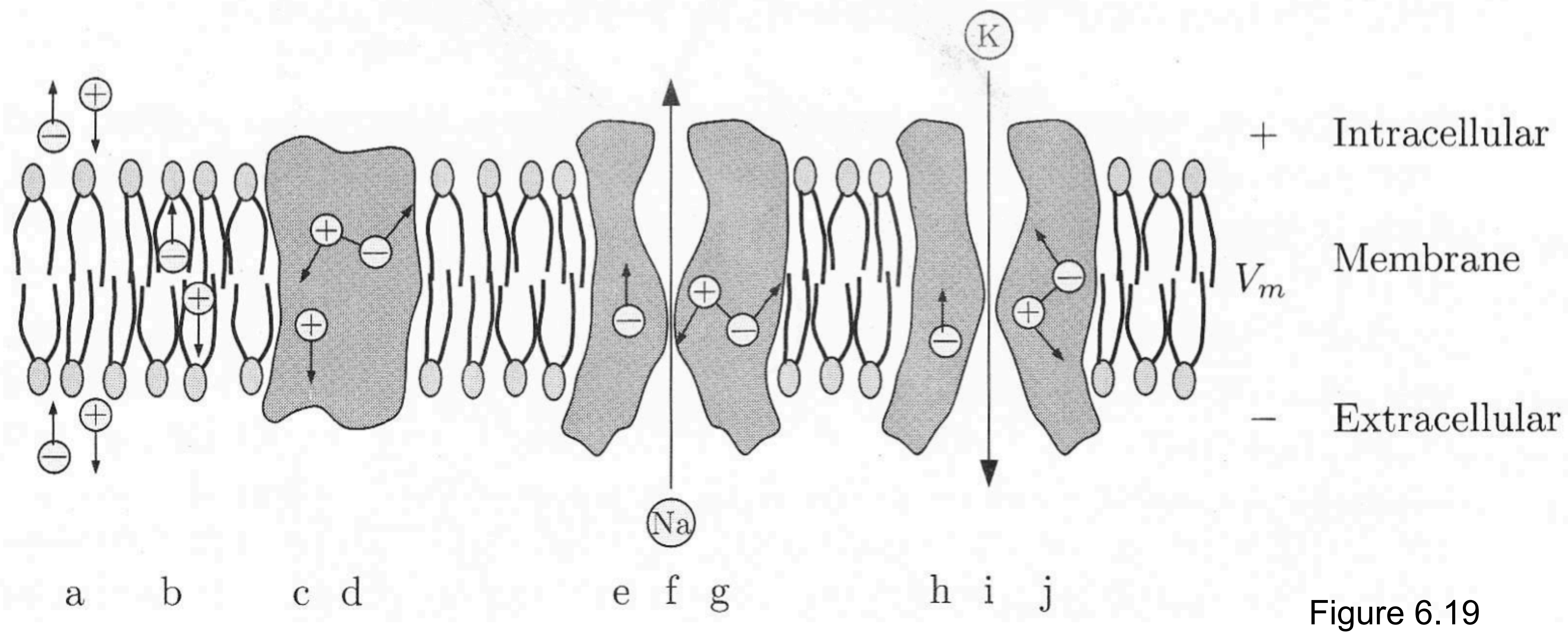


Figure 6.19

- f, i – Ionic currents (due to charge "flow" across membrane)
- a-e, g, h, j – Capacitive currents (due to charge "displacement" or redistribution along/inside membrane)

Gating current

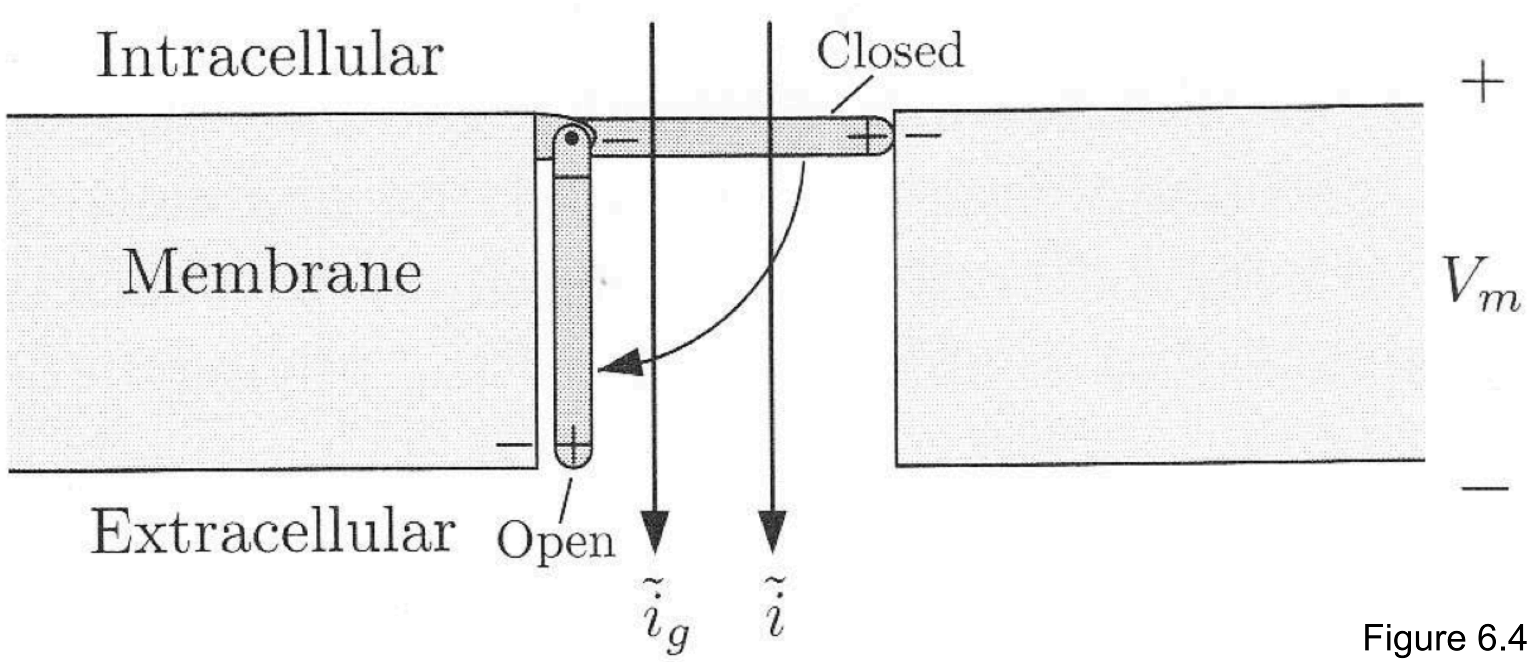
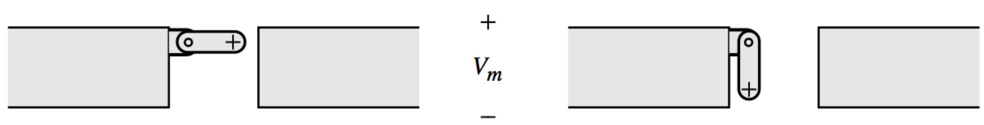


Figure 6.4

- Component (i_g) of the capacitive current
- Due to channel (molecule with non-uniform charge distribution) moving open/closed

Separating Out the Gating Current



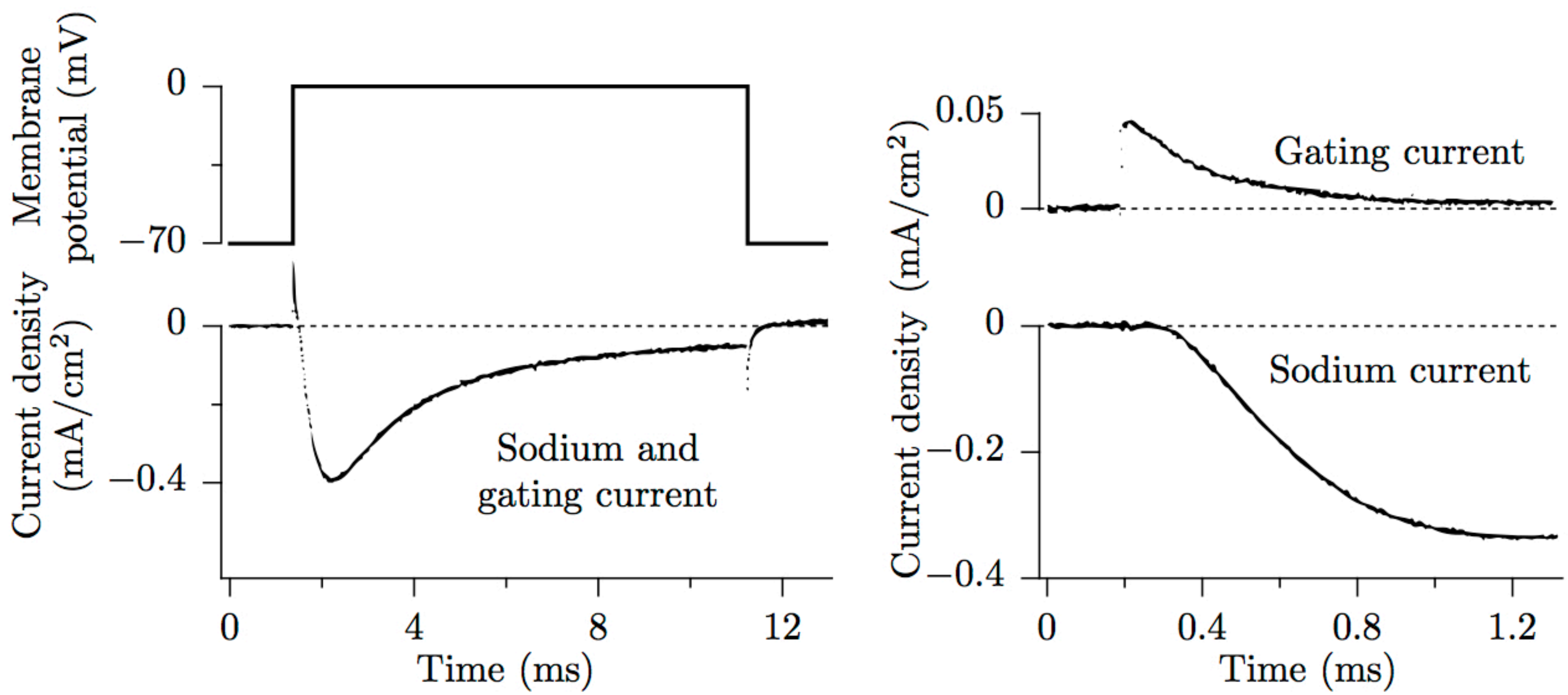


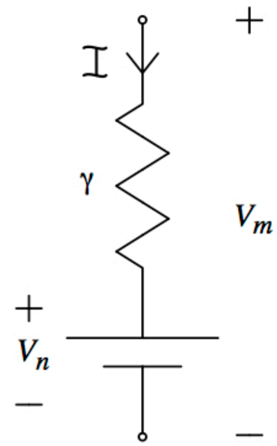
Figure 6.22

Ion Channel Model: Two Parts

1. Two-state gate model of kinetics

2. Passive electrodiffusive model of permeation

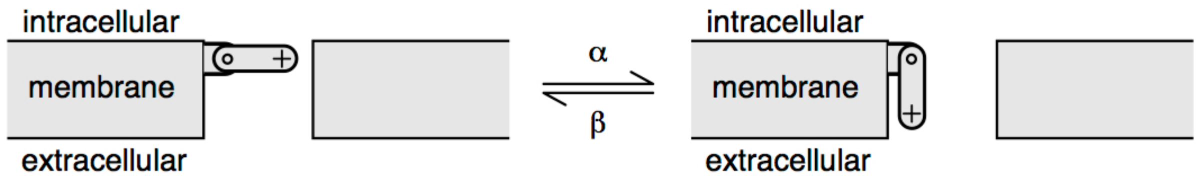
γ = single open-channel conductance



→ For a gate that is either closed or open, conductance is equal to $[0, \gamma]$ respectively

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



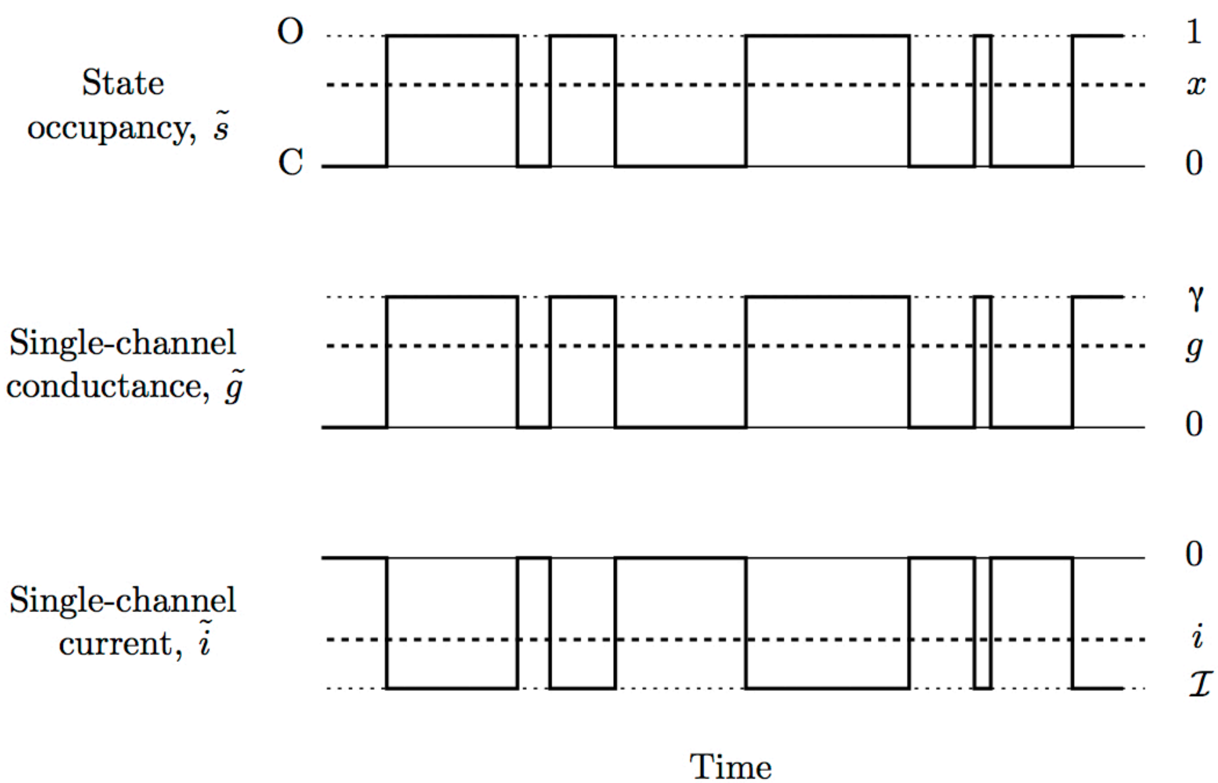


Figure 6.33 (mod)

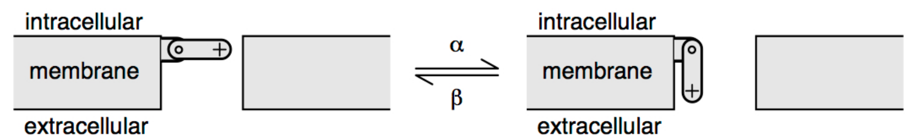
x = state occupancy probability

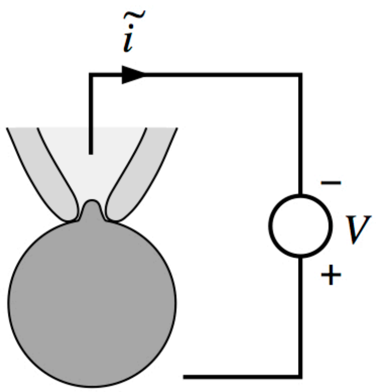
g = average single-channel conductance

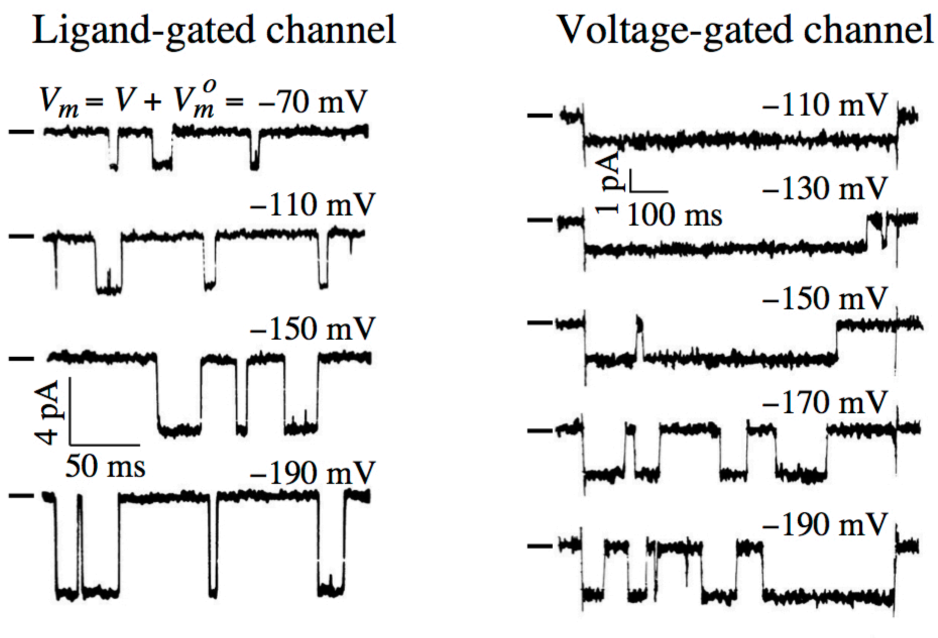
i = average single-channel current

→ Note stochastic nature for an individual channel

<u>Model</u>: Voltage-Gated Two-State Molecular Gate (*Stochasticity*)



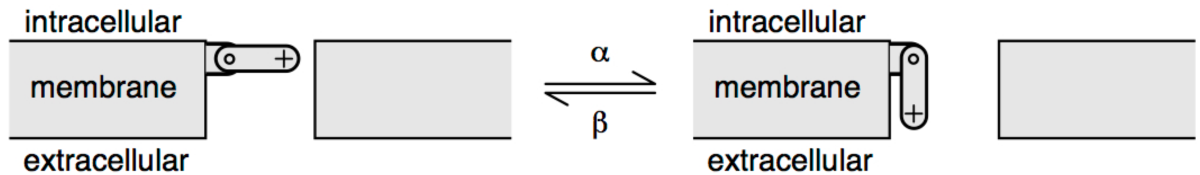




Why would the state of an individual channel be "stochastic" (i.e., randomly fluctuating)?

→ Molecular size + thermodynamics

<u>Model</u>: Voltage-Gated Two-State Molecular Gate (*Expected Values*)



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

$n(t)$ is <u>average #</u> of open channels

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

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

Assume $\mathcal{N}$ is large.

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

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

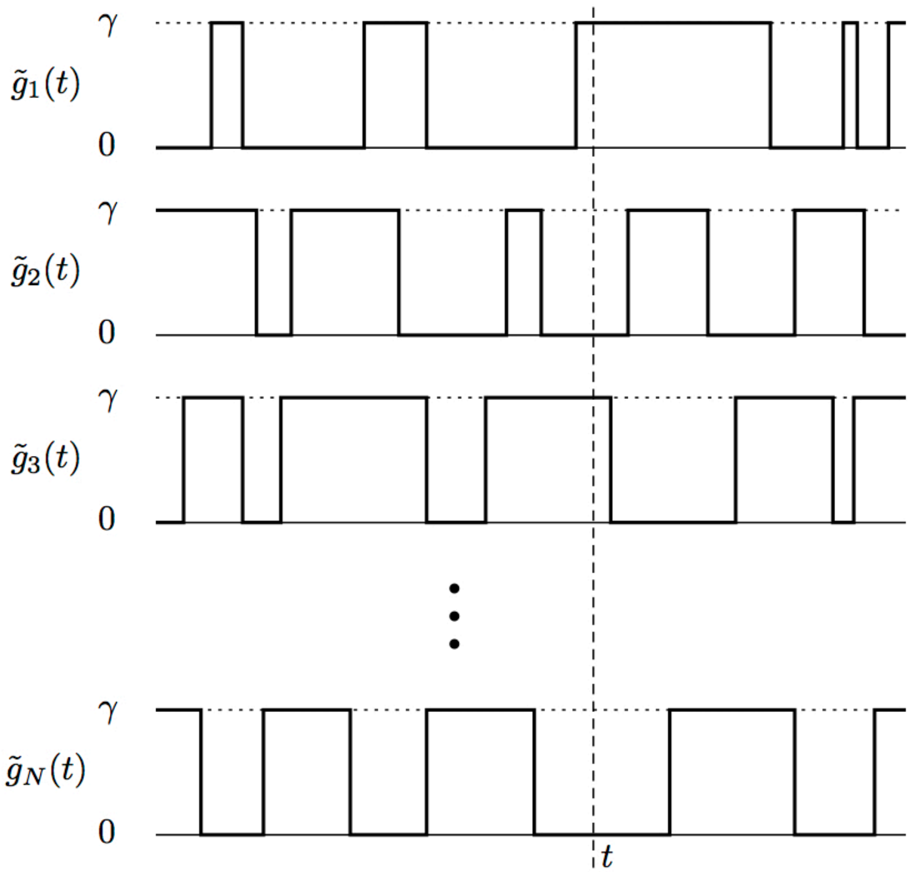


Figure 6.34

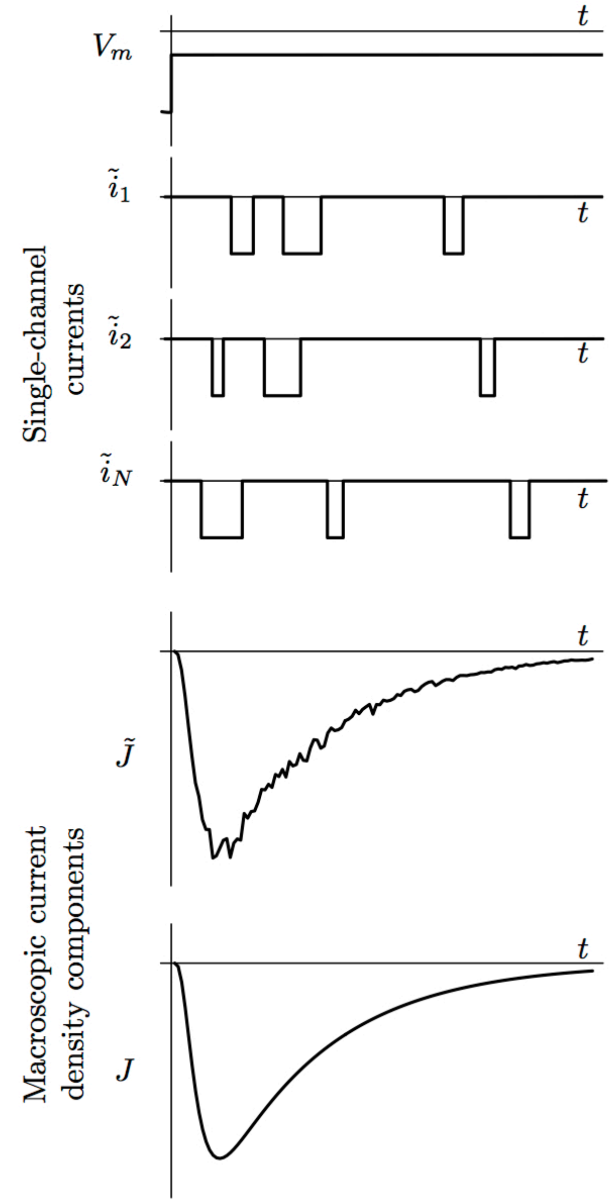


Figure 6.50 (mod)

→ Microscopic model (+ law of large numbers) gives rise to macroscopic behavior

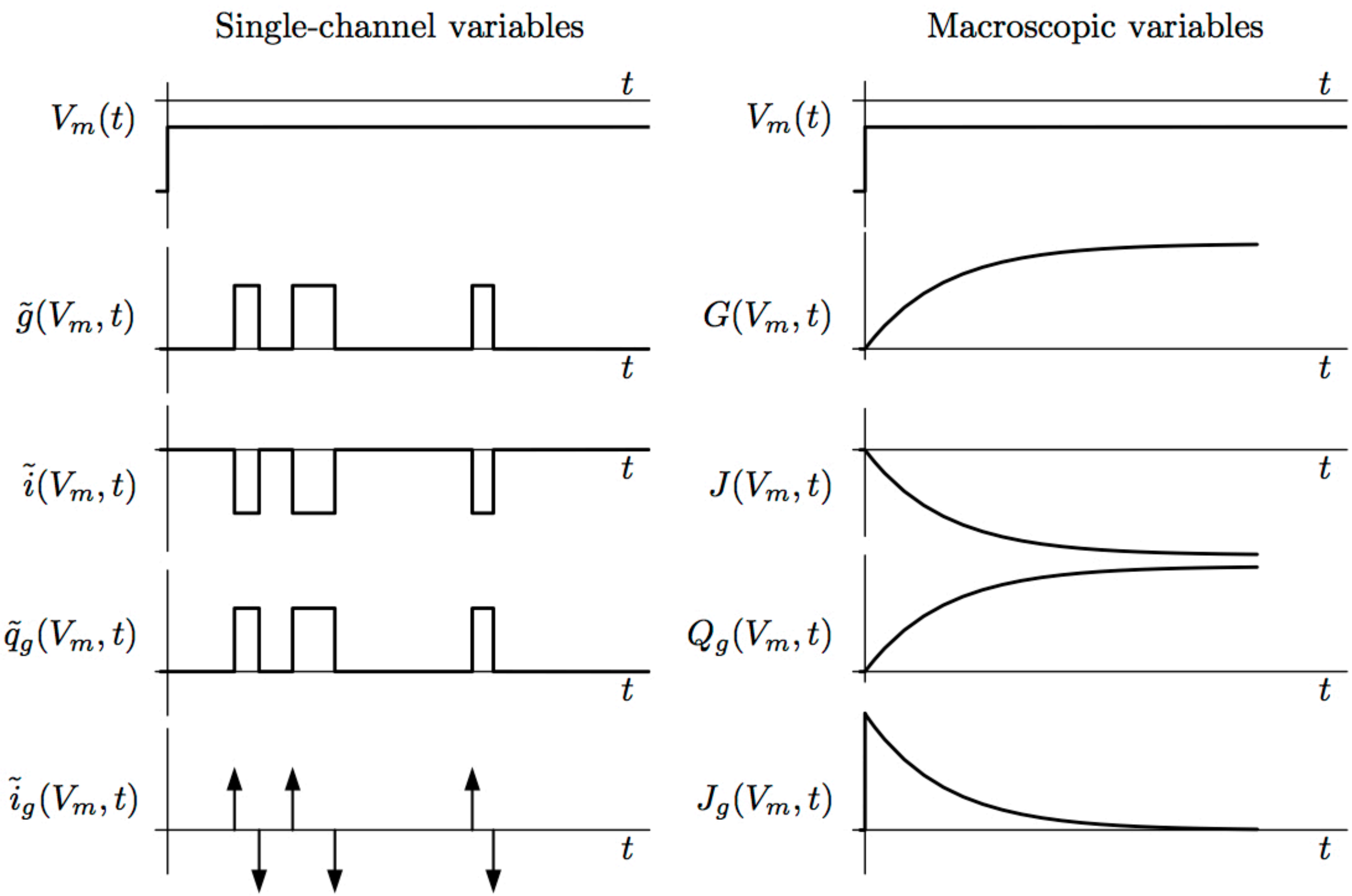


Figure 6.52

Biophysically, this figure encapsulates numerous key ideas....

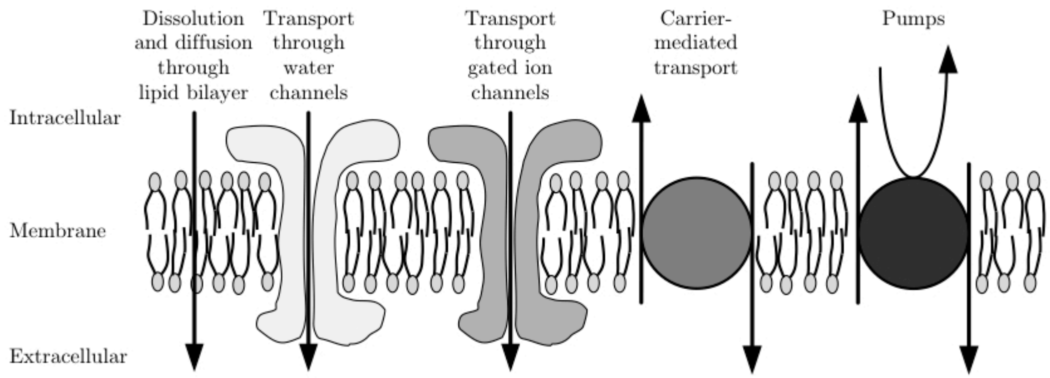


Figure 2.19

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

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

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

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

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

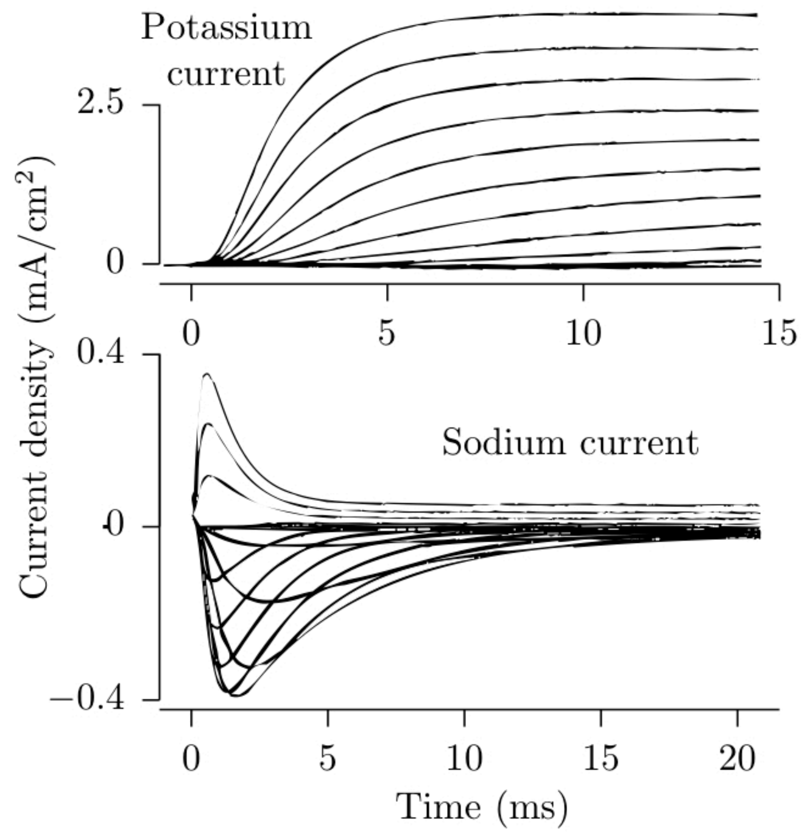
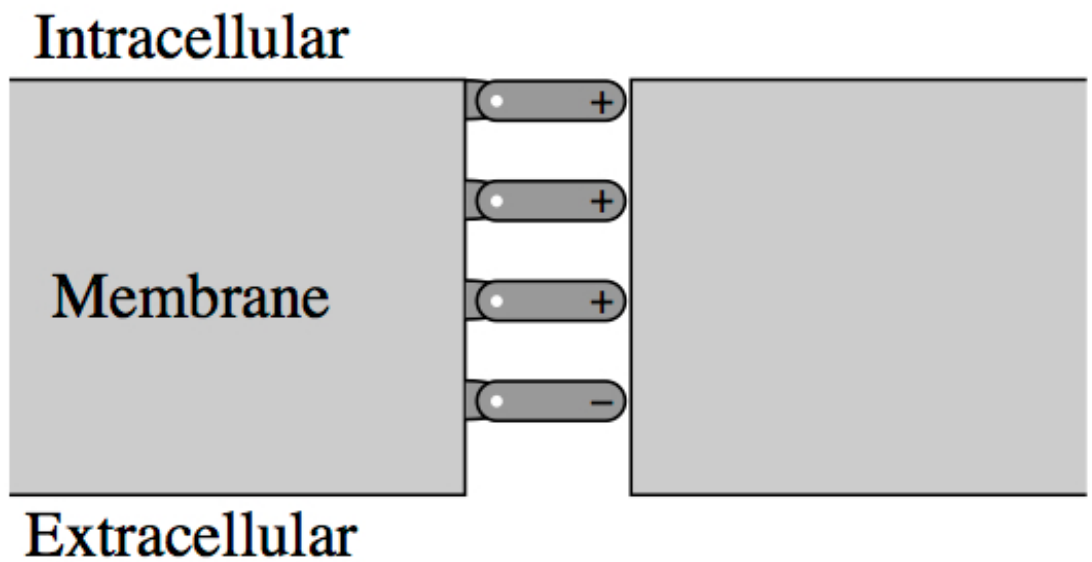


Figure 4.20



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