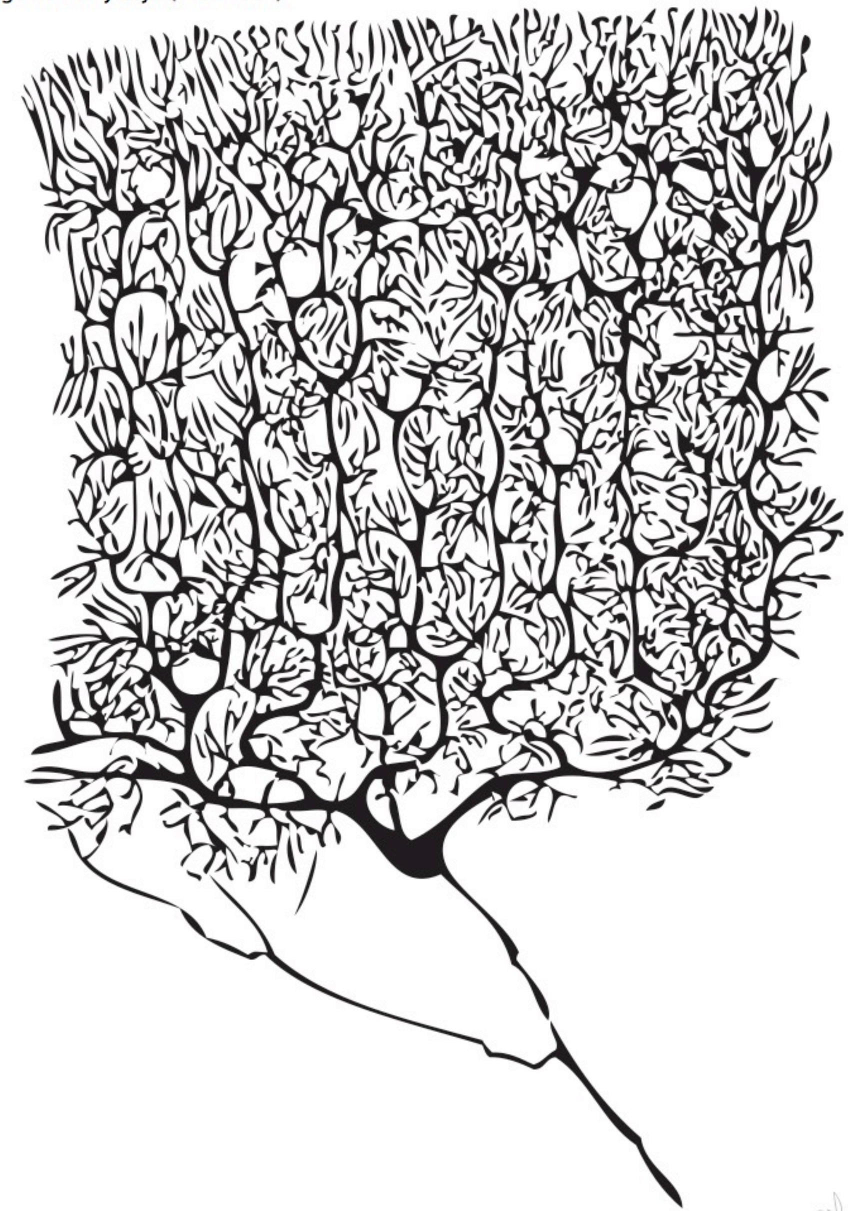
Cellular Electrodynamics

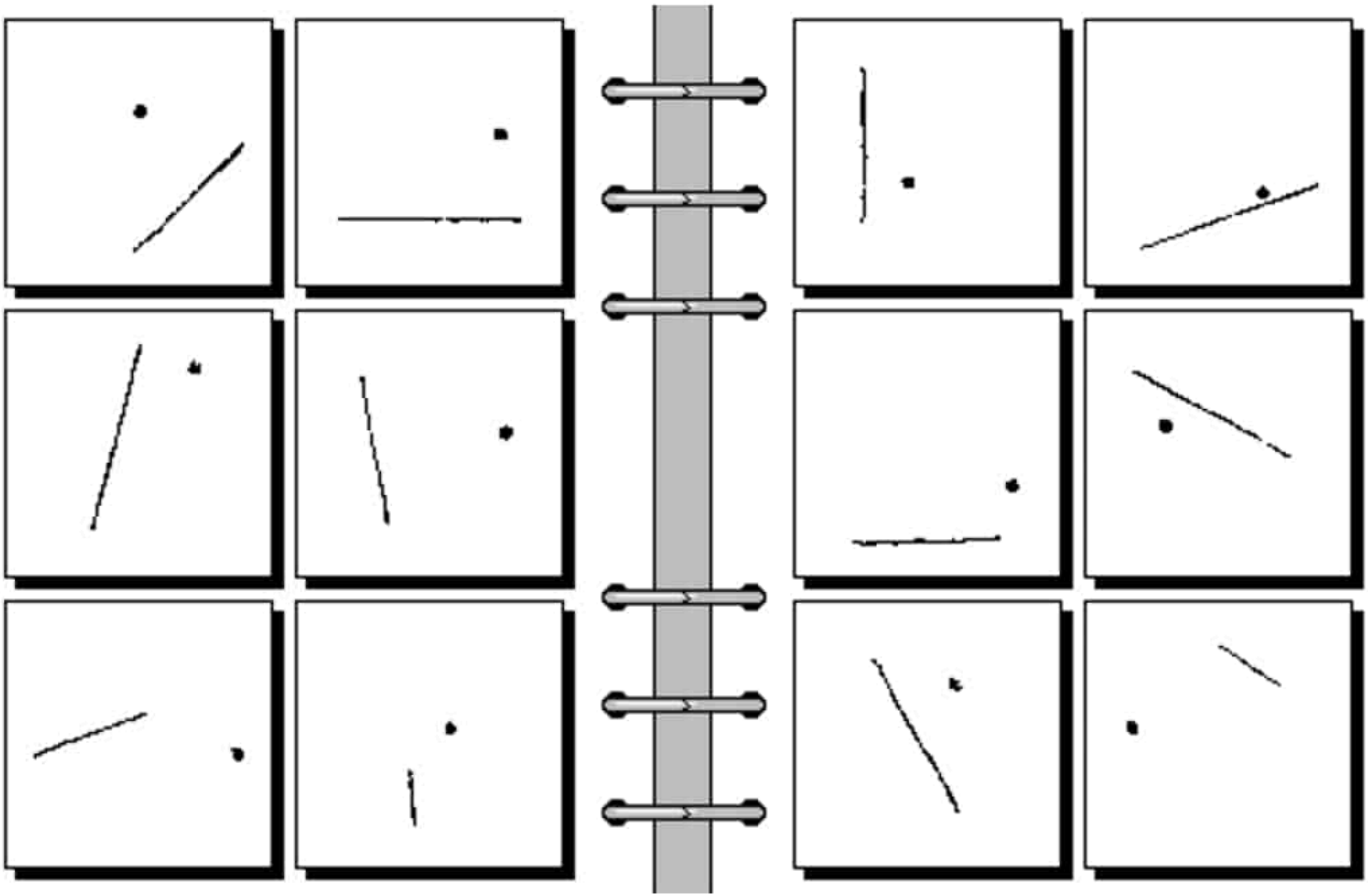


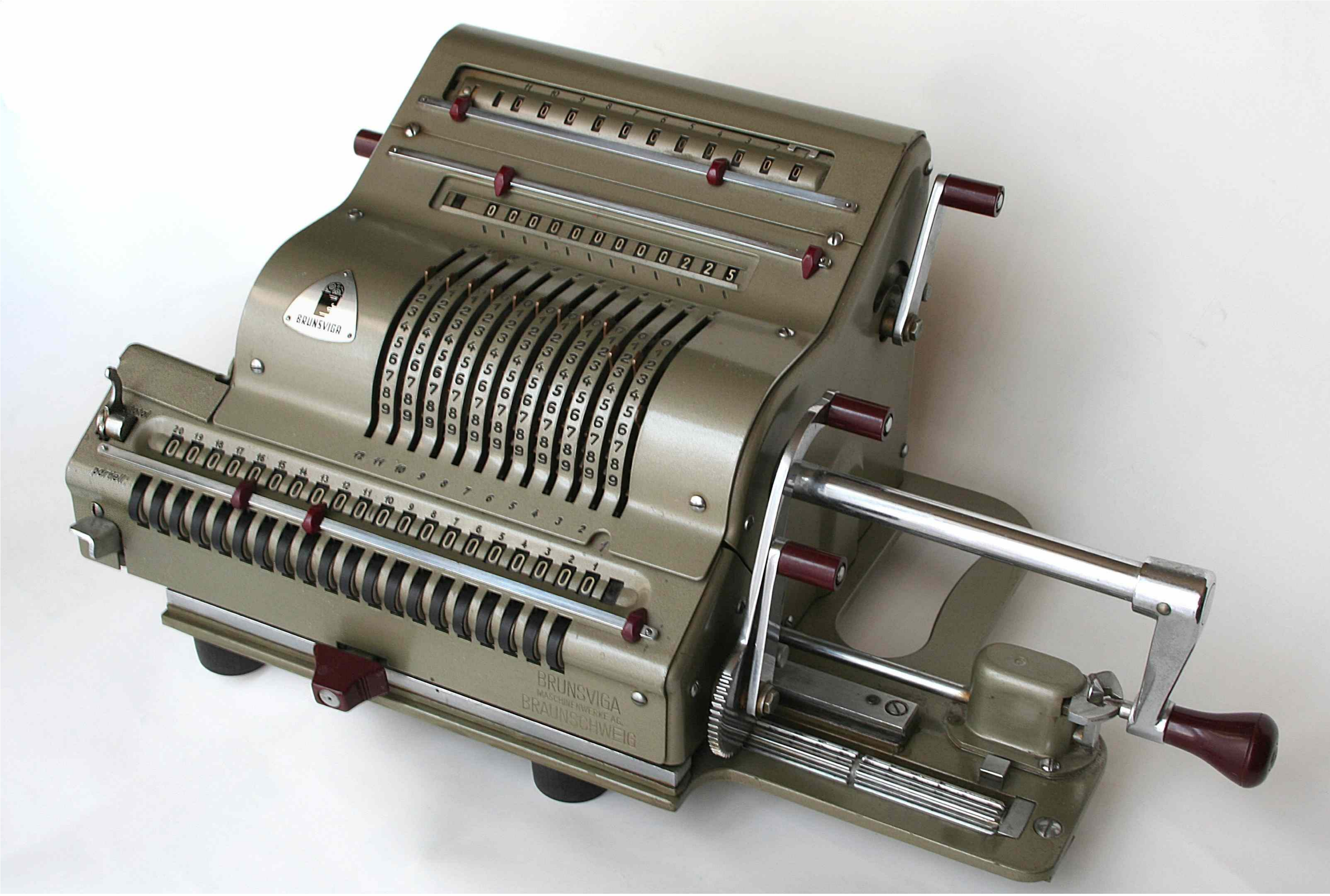
Instructor:
Prof. Christopher Bergevin (cberge@yorku.ca)

Website:
http://www.yorku.ca/cberge/4080W2020.html

York University
Winter 2020
BPHS 4080 Lecture 16

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





https://de.wikipedia.org/wiki/Brunsviga_Maschinenwerke

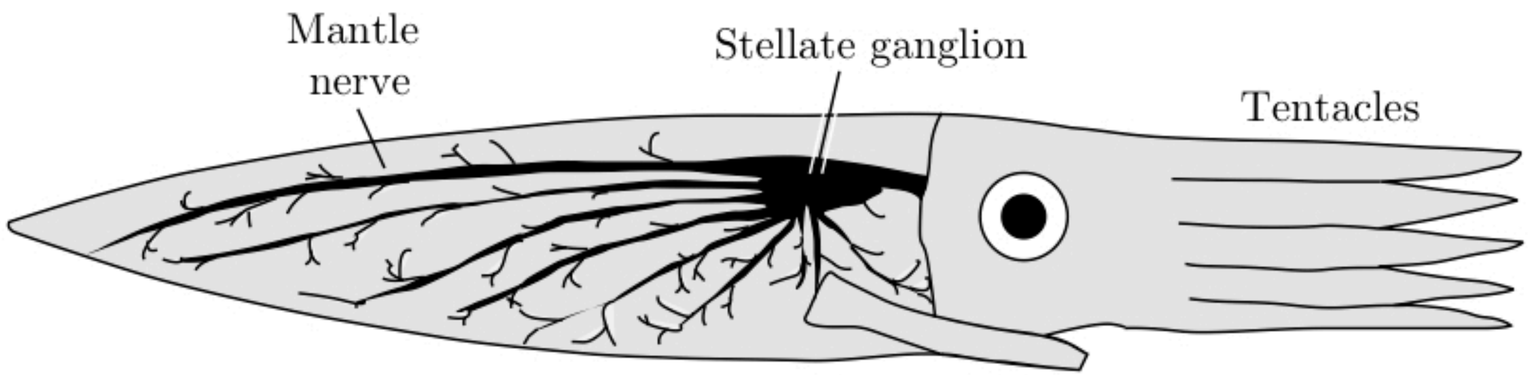


Figure 1.28

Some key observations...

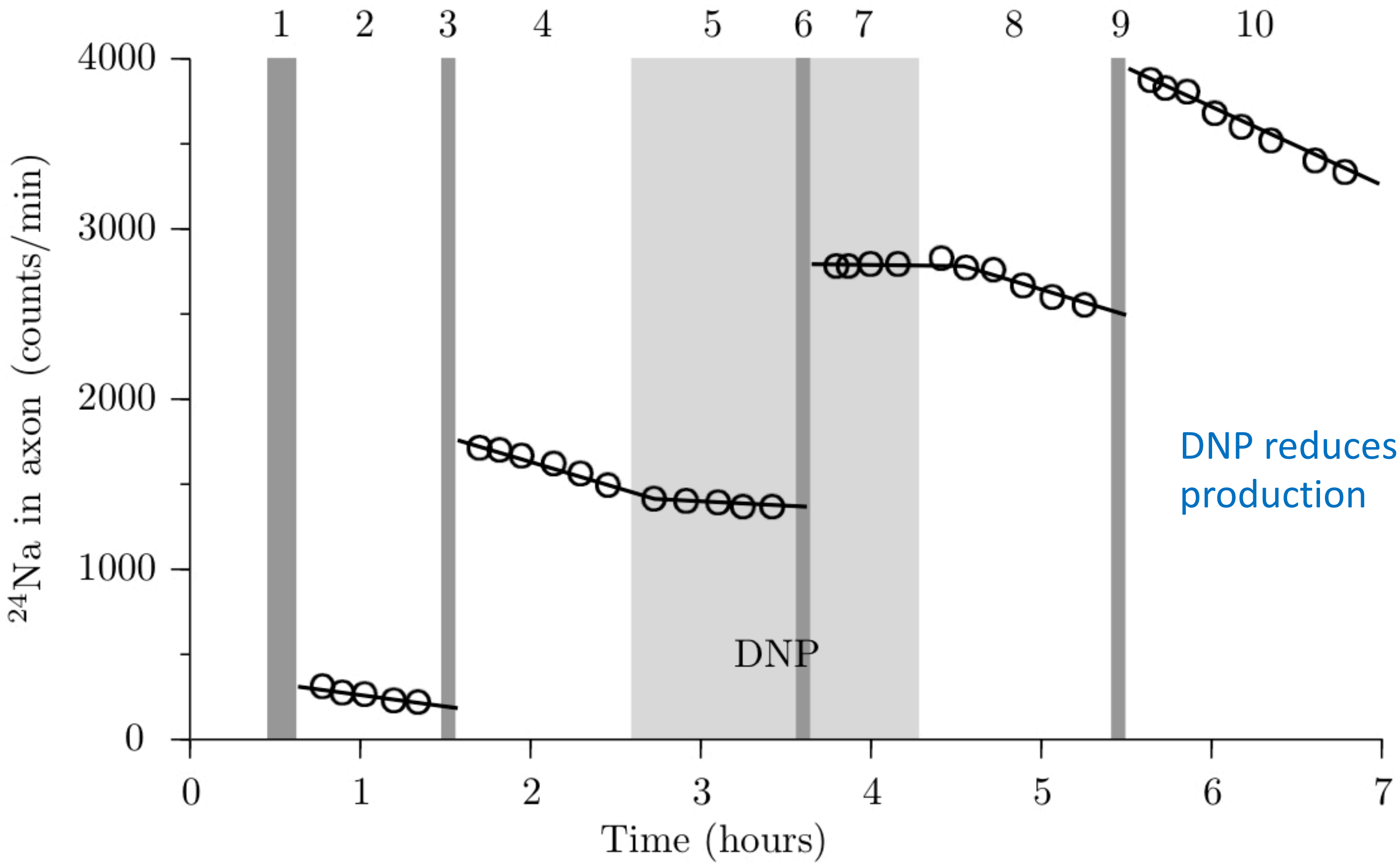


Figure 7.38

DNP reduces ATP production

Interrelationships between:
Na^+ flux, 'active' transport, & action potentials

→ Active transport not a priori required for AP generation

Some key observations...

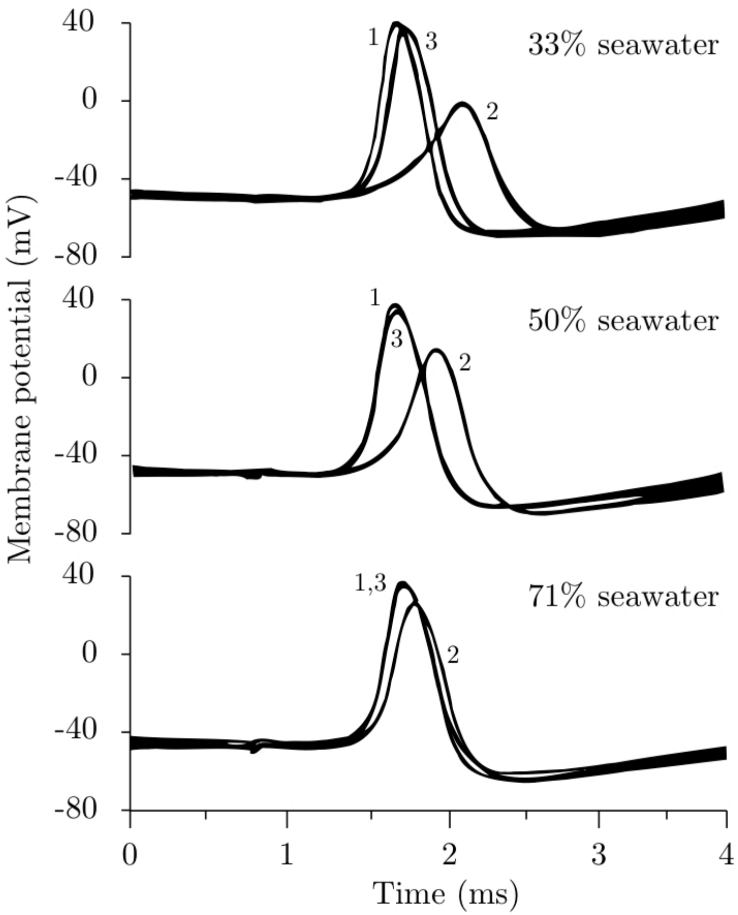


Figure 4.2

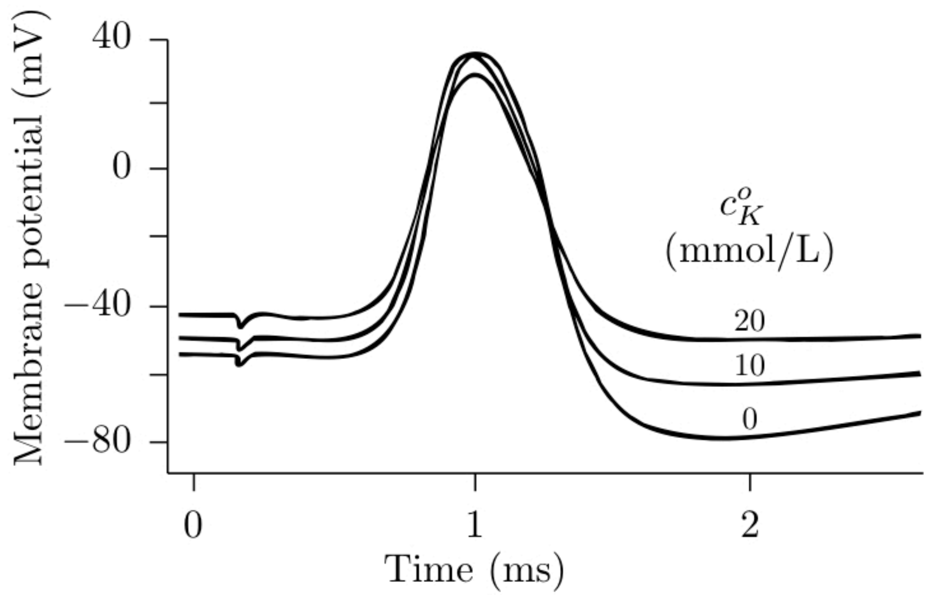


Figure 4.5

→ K^+ flux affects APs (*later on*)

→ Na^+ flux affects APs (*early on*)

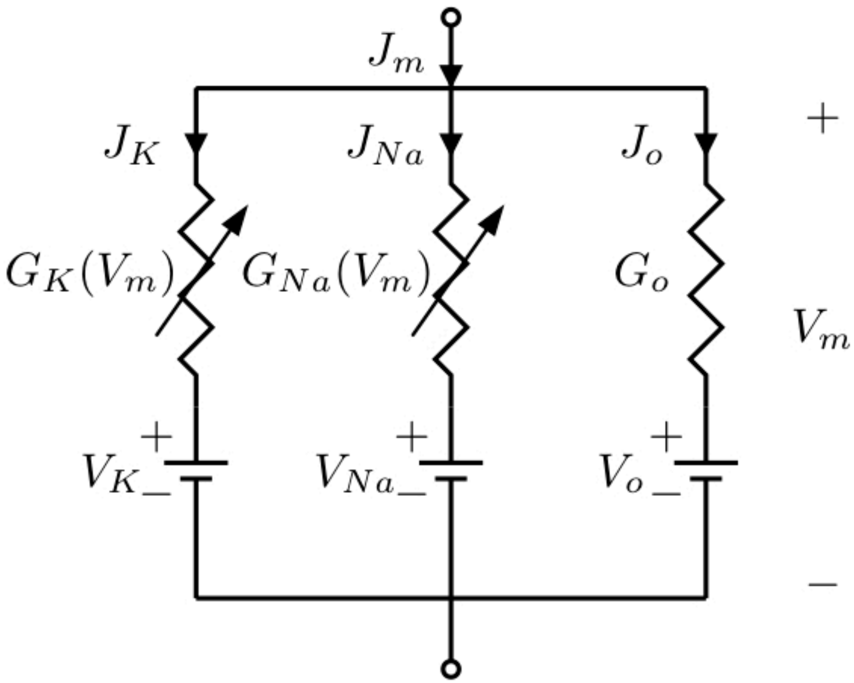
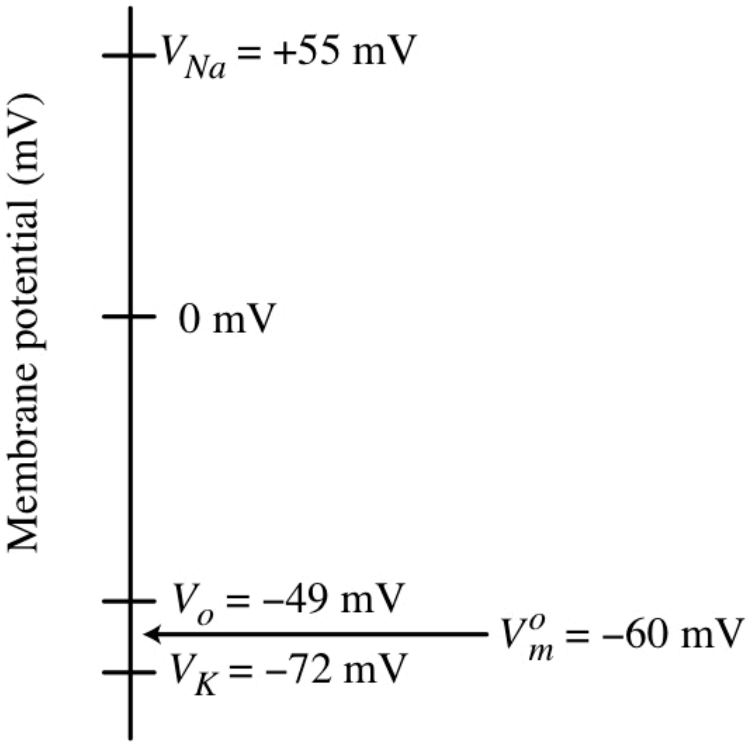


Figure 7.32



Idea 1 – Multiple permeant ions with different conductance (e.g., $G_k >> G_{Na}$)

Idea 2 – K+ and Na+ conductances can vary time

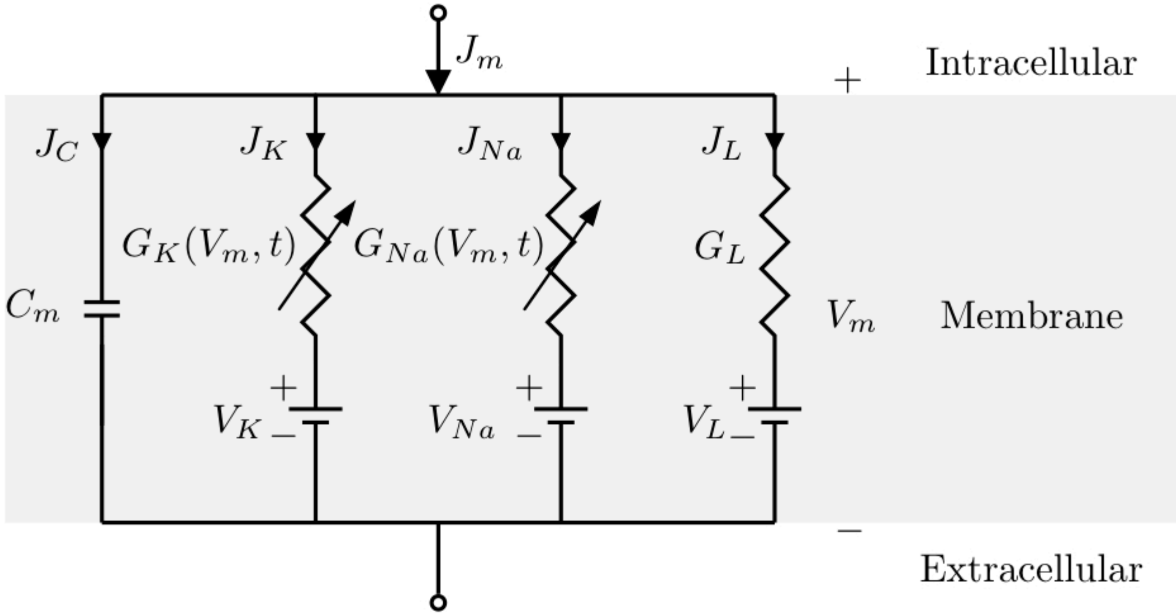


Figure 4.6

What are $G_K(V_m,t)$ and $G_{Na}(V_m,t)$?

→ Not easy to empirically distinguish, so new electrophysiological techniques were required

Space-Clamp

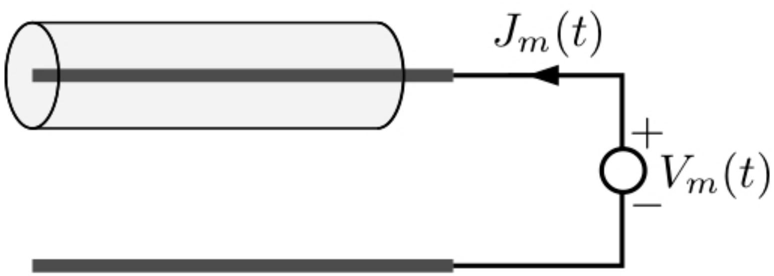


Figure 4.10

Kenneth Cole & George Marmont (1940s)

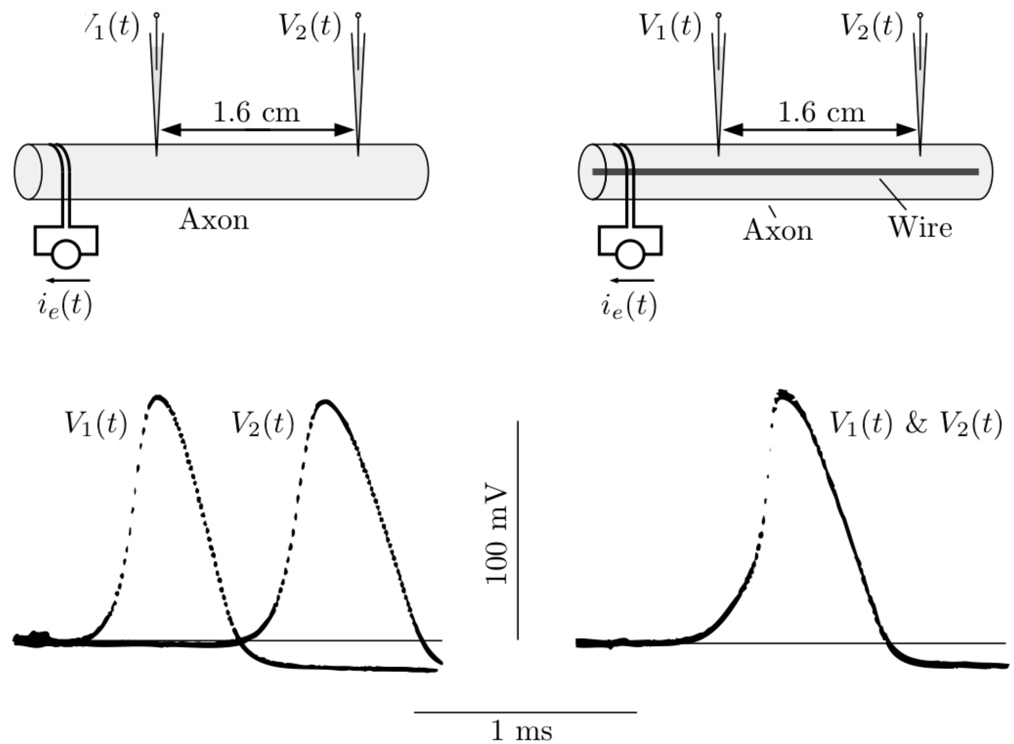


Figure 2.15

→ *Eliminates spatial dependence*

(i.e., make an electrically large cell a small one)

Conduction velocity

(Core-Conductor model)

$$r_i = \frac{\rho_i}{\pi a^2} \qquad \nu = \sqrt{\frac{K_m a}{2\rho_i}}$$

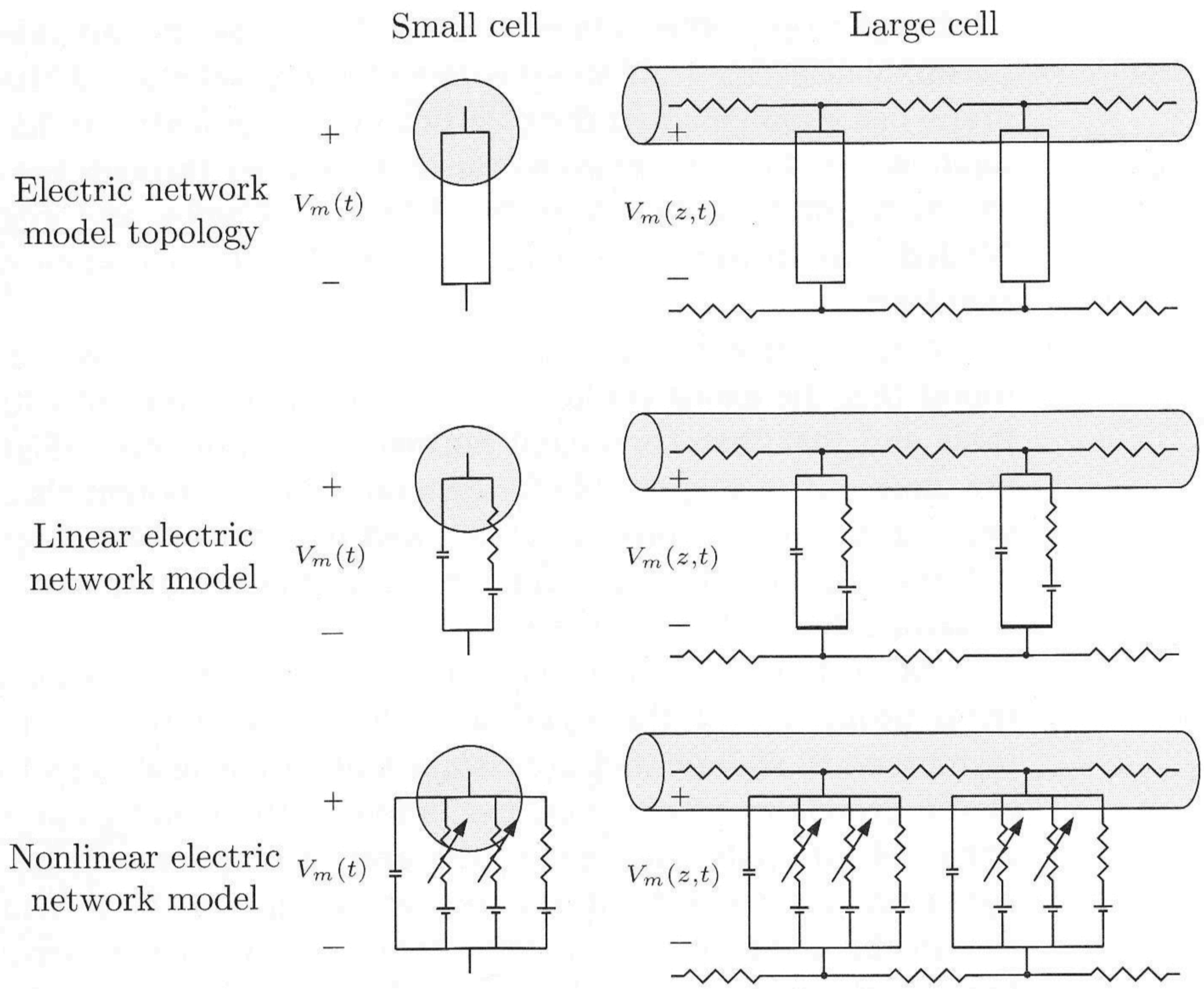
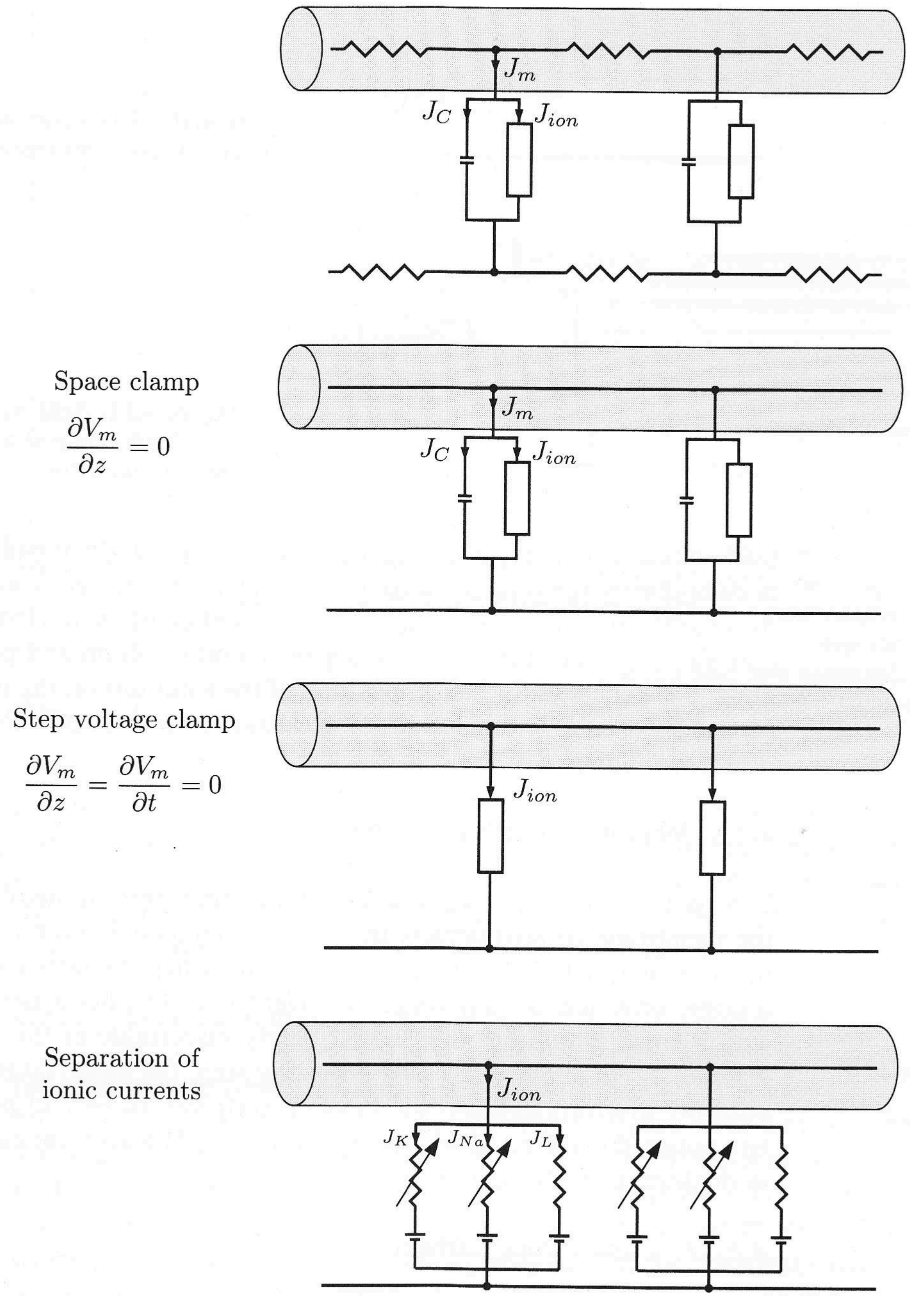


Figure 1.32

→ Electrically 'small' cell can still fire action potentials

Voltage-Clamp



Separating Ionic Currents

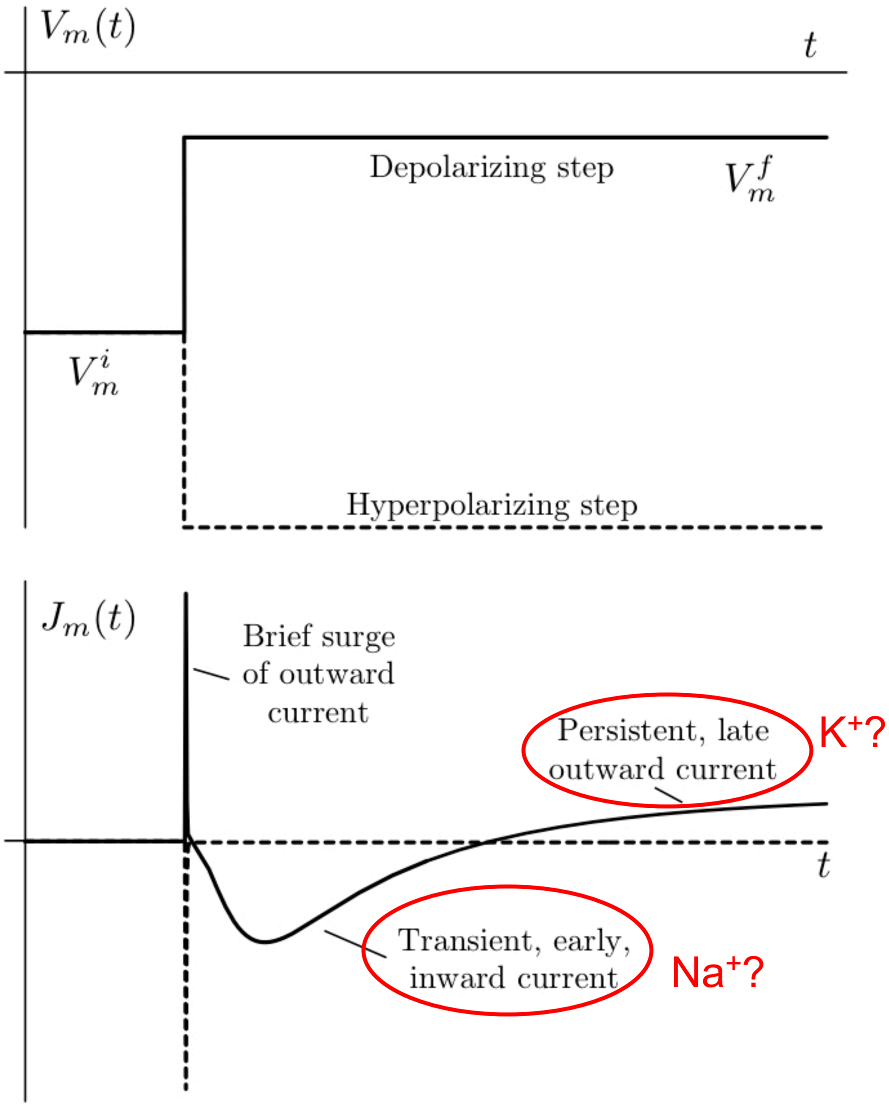


Figure 4.12

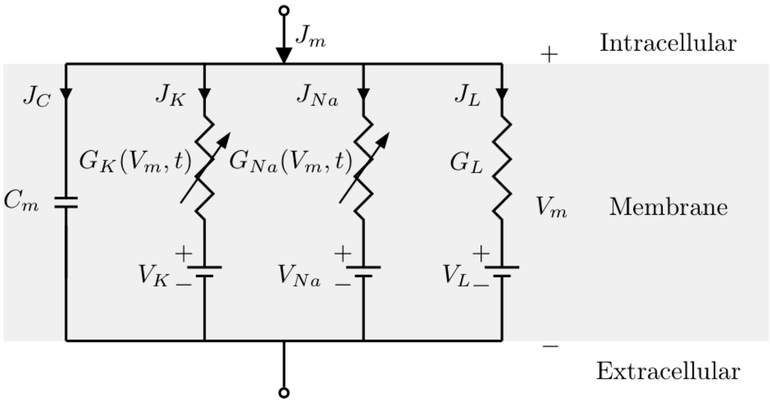


Figure 4.6

Capacitive Current

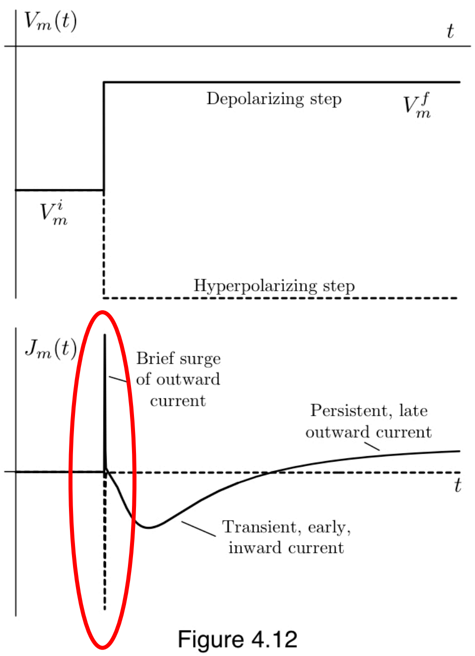
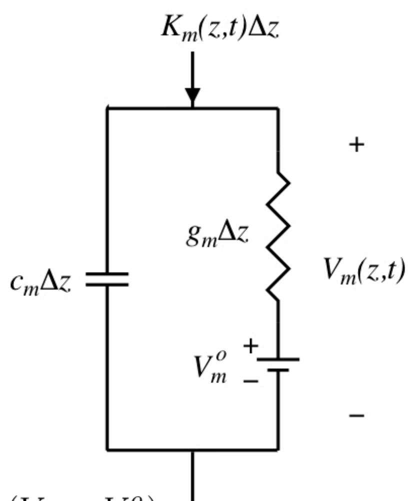


Figure 4.12



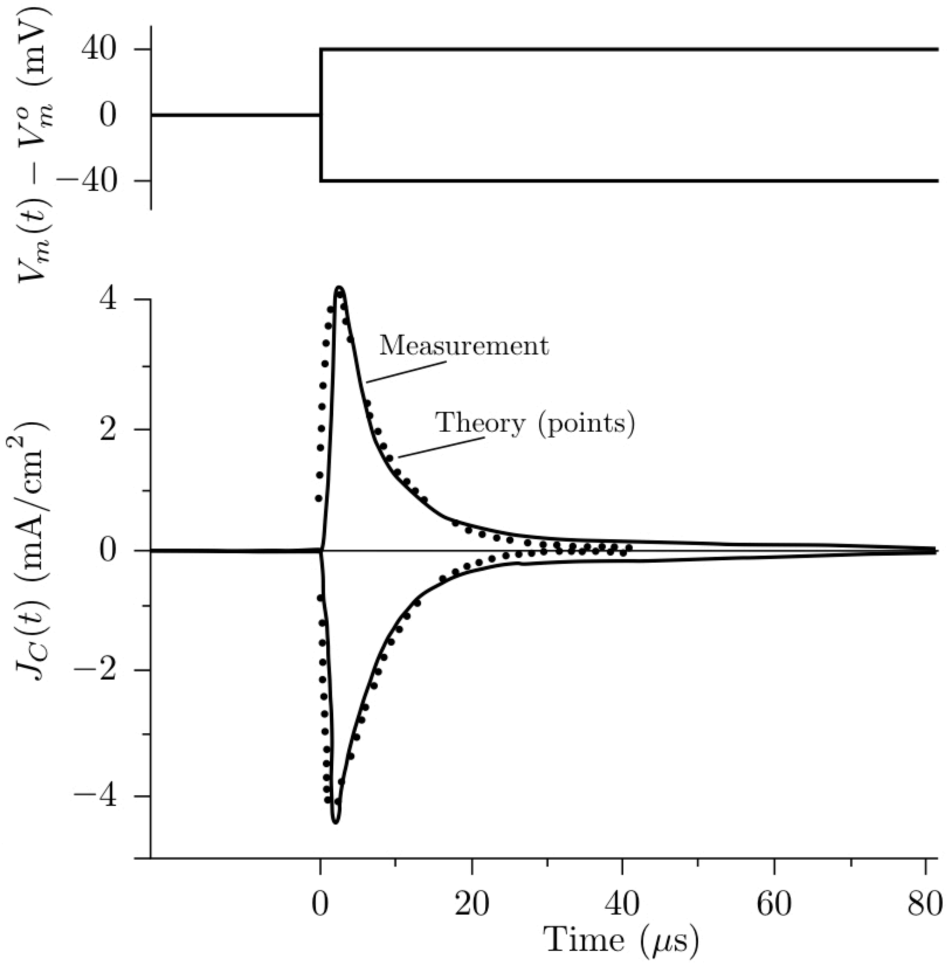


Figure 4.13

$$i_e(t) = AJ_m = AC_m \frac{dV_m}{dt} + AG_m(V_m - V_m^o)$$

$$\frac{AC_m}{AG_m}\frac{dV_m}{dt} + V_m = V_m^o + \frac{i_e(t)}{AG_m}$$

But what of the other ionic currents?

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

→ What are $G_K(V_m,t)$ and $G_{Na}(V_m,t)$?

$$V_{Na} = \frac{RT}{F} \log \frac{c^o_{Na}}{c^i_{Na}}$$

→ Separating ionic currents by subtraction
(assumes J_K unaffected by changes in [Na⁺])

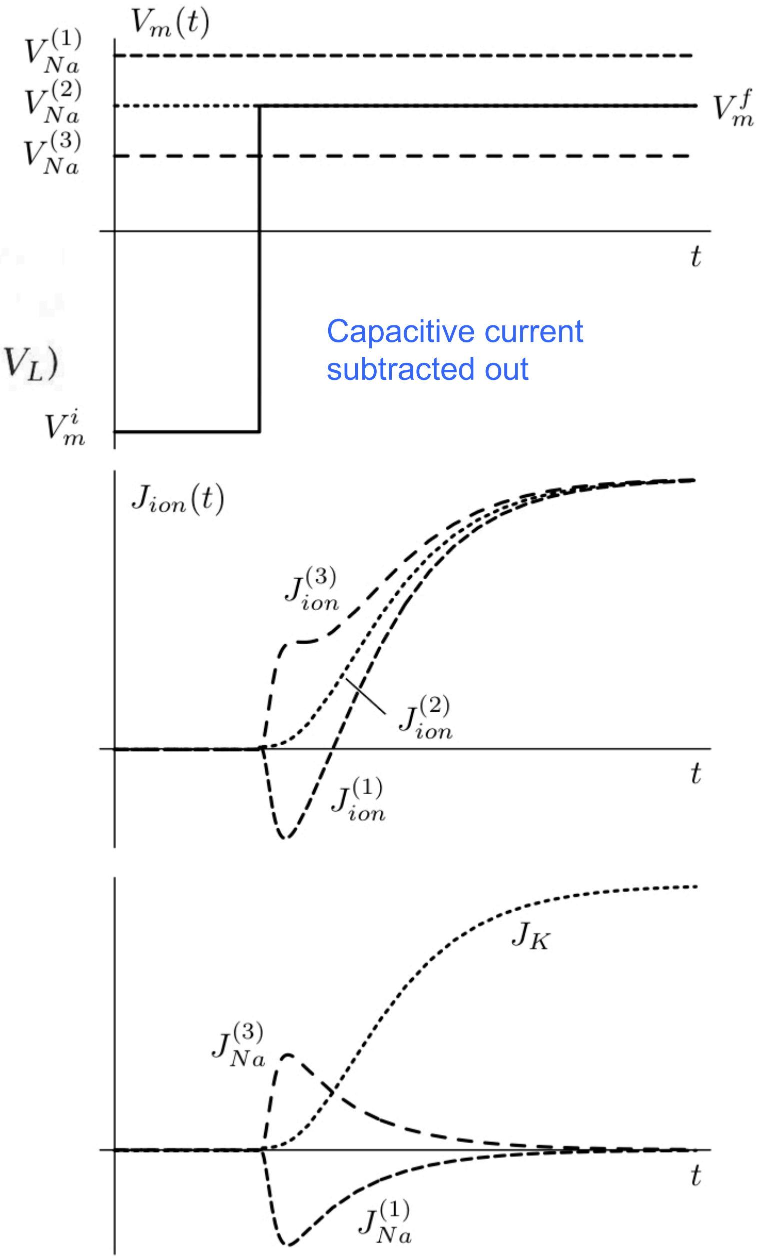


Figure 4.17

Reversal Potential?

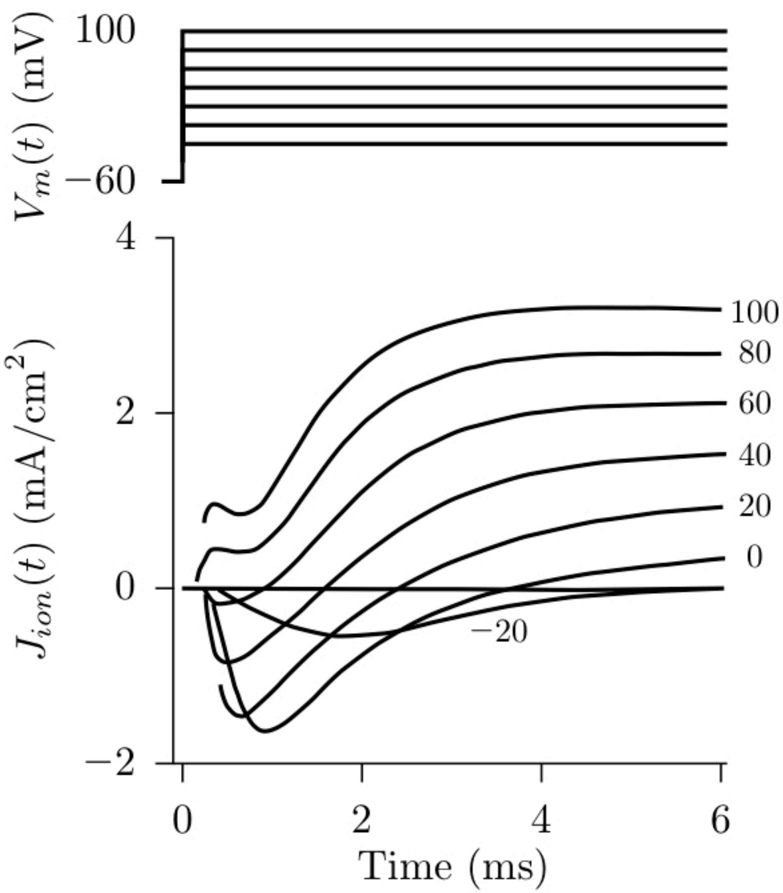


Figure 4.14

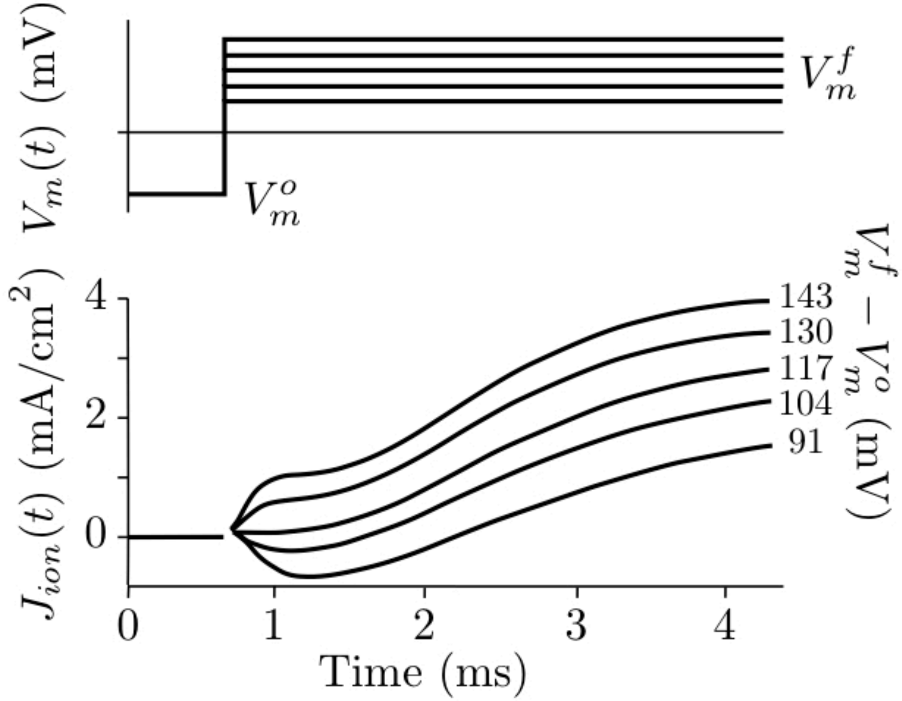
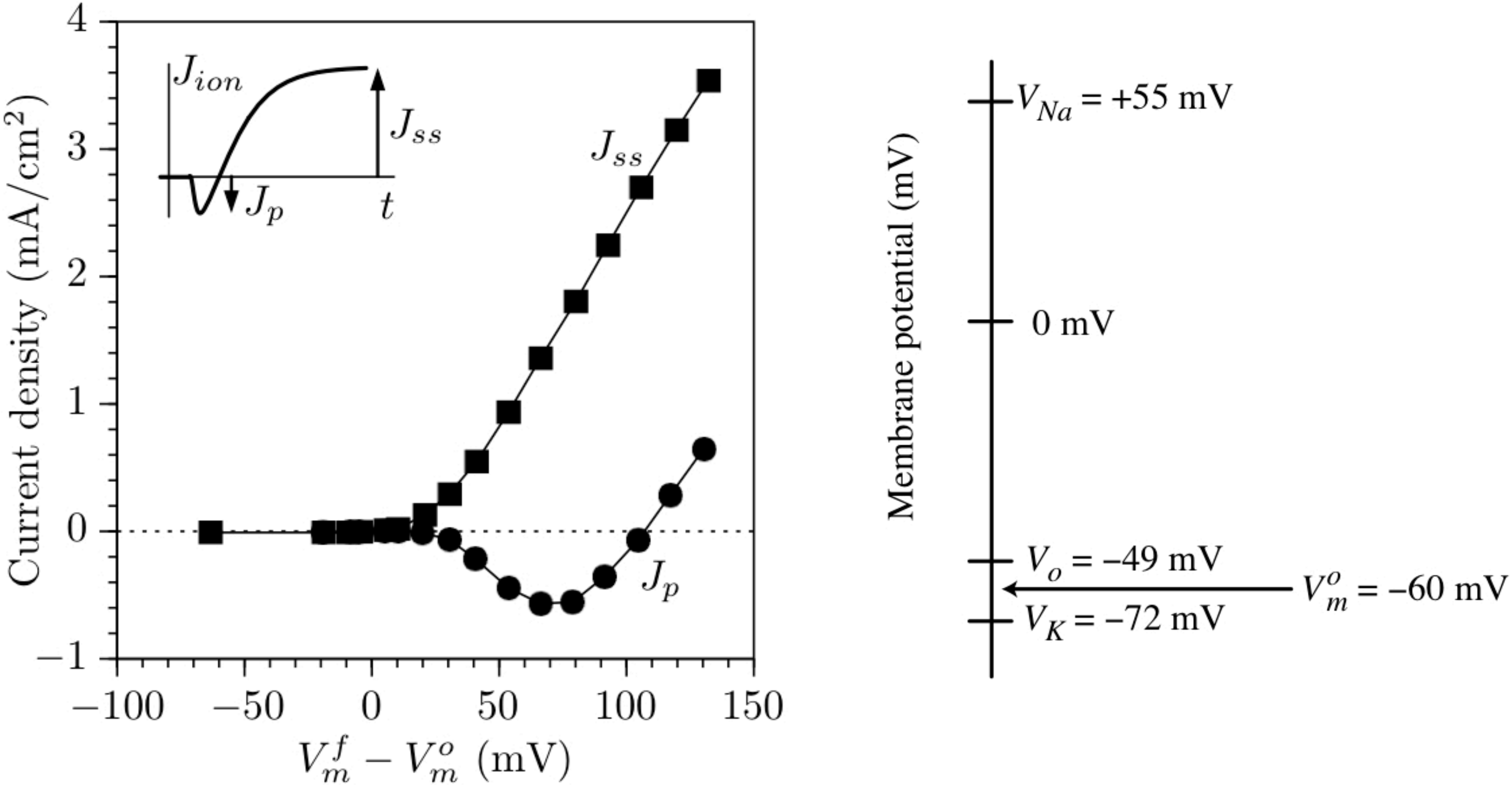


Figure 4.15

→ Close to Na^+ Nernst potential!



4
3
2
1
0
−1
Current density (mA/cm²)
J_{ion}
J_{ss}
J_p
t
J_{ss}
J_p
−100
−50
0
50
100
150
$V_m^f - V_m^o$ (mV)
Membrane potential (mV)
V_{Na} = +55 mV
0 mV
V_o = –49 mV
V_m^o = –60 mV
V_K = –72 mV

Figure 4.16

Separating Ionic Currents

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

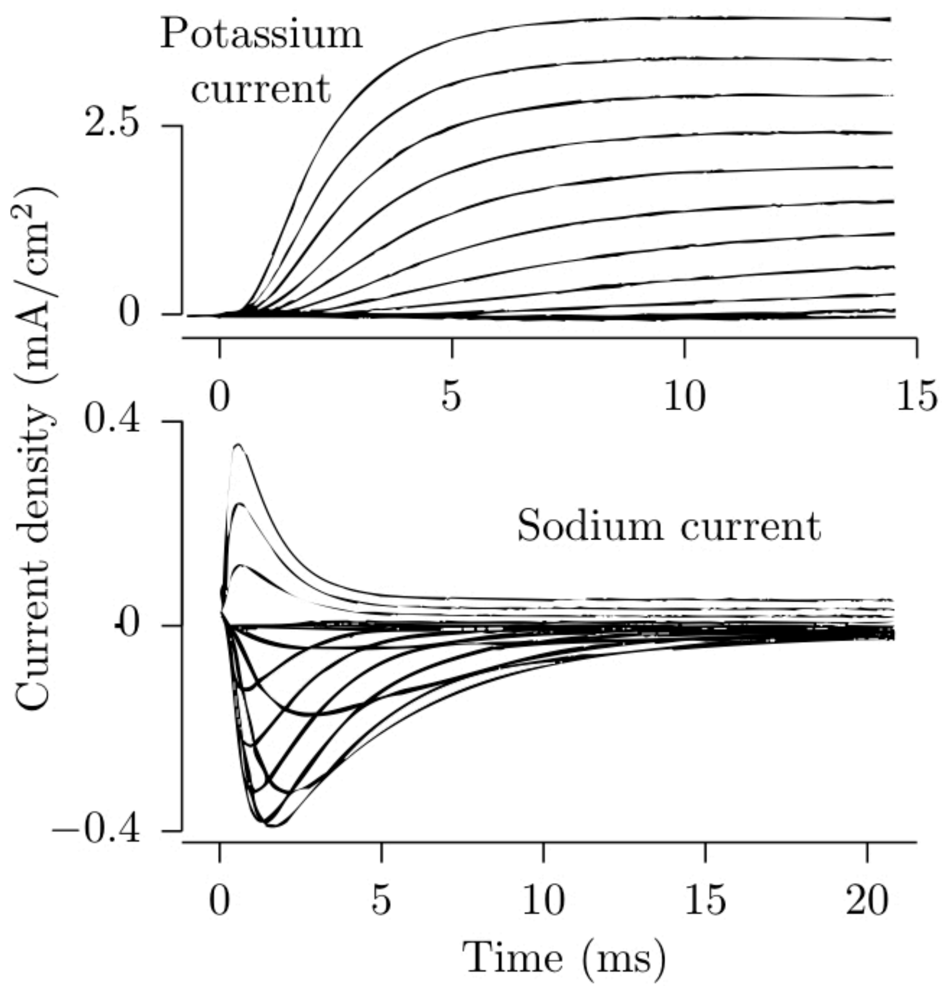


Figure 4.20

→ K^+ simply turns on
(with a bit of a slow start)

→ Na^+ more complex
(early 'activation', followed by 'inactivation)

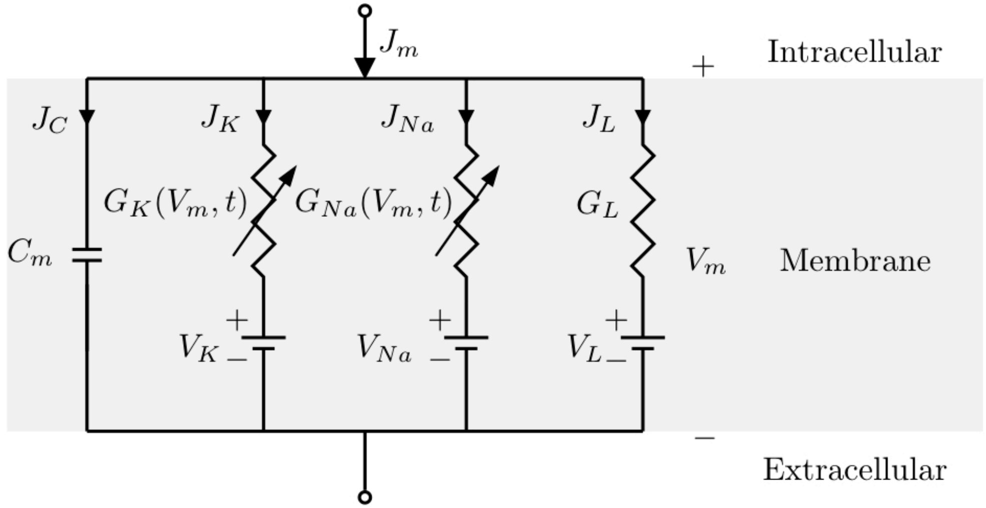


Figure 4.6

What are $G_K(V_m,t)$ and $G_{Na}(V_m,t)$?

→ Physiological data suggests Na^+ *activates* and then *inactivates* while K^+ simply *activates* (based upon V_m)

Model for $G_K(V_m,t)$ and $G_{Na}(V_m,t)$?

1. Use voltage-clamp to obtain suitable data

$$G_K(V_m,t) = \frac{J_K(V_m,t)}{V_m - V_K}$$

$$G_{Na}(V_m,t) = \frac{J_{Na}(V_m,t)}{V_m - V_{Na}}$$

2. Devise sufficient model to describe

→ First-order kinetics variables

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

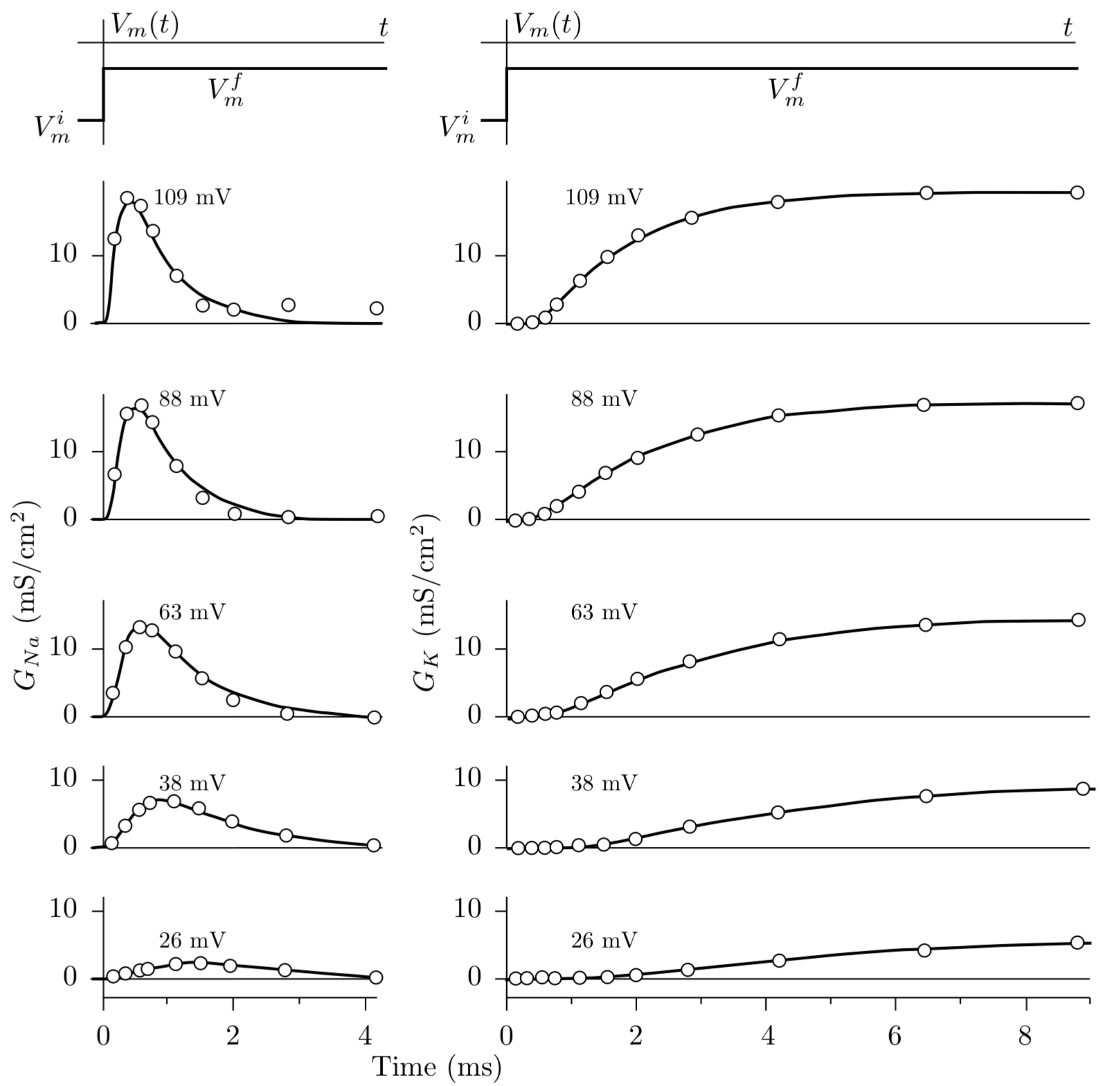


Figure 4.23

Review: First-Order Chemical Kinetics

First-order, reversible reaction

$$R \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} P$$

$$\frac{dc_R(t)}{dt} = \beta c_P(t) - \alpha c_R(t) \quad \text{AND} \quad \frac{dc_P(t)}{dt} = \alpha c_R(t) - \beta c_P(t)$$

Equilibrium:

$$\frac{dc_R(t)}{dt} = \frac{dc_P(t)}{dt} = 0 \quad \rightarrow \quad \beta c_P(\infty) = \alpha c_R(\infty)$$

$$\frac{c_P(\infty)}{c_R(\infty)} = \frac{\alpha}{\beta} = K_a \quad \left(\begin{array}{c}\text{association, equilibrium, affinity,}\\ \text{stability, binding, formation constant}\end{array}\right)$$

Kinetics: assume total amount of reactant and product is conserved

$$c_R(t) + c_P(t) = C$$

$$\frac{dc_R(t)}{dt} = \beta\Big(C - c_R(t)\Big) - \alpha c_R(t)$$

$$\frac{dc_R(t)}{dt} + (\alpha + \beta)c_R(t) = \beta C$$

Review: First-Order Chemical Kinetics

First-order, reversible reaction

$$R \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} P$$

First-order linear differential equation with constant coefficients

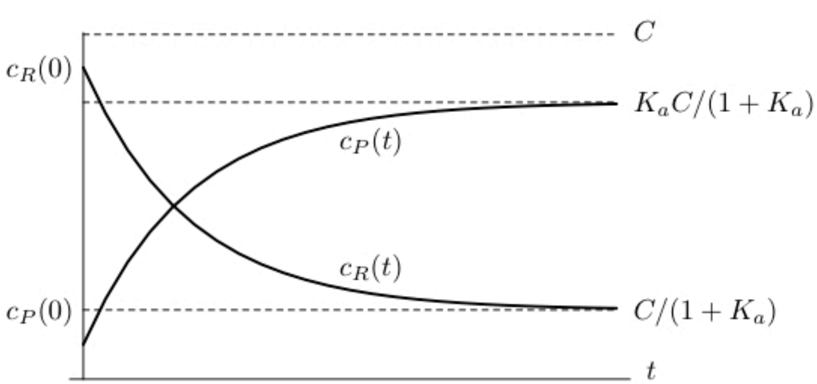
$$c_R(t) = c_R(\infty) - \Big(c_R(\infty) - c_R(0)\Big)\, e^{-t/\tau}, \text{ for } t > 0$$

$$c_R(\infty) = \frac{\beta}{\alpha+\beta} C = \frac{1}{1+K_a} C \quad \text{AND} \quad \tau = \frac{1}{\alpha+\beta}$$

$$c_P(t) = C - c_R(t)$$

First-order, reversible reaction

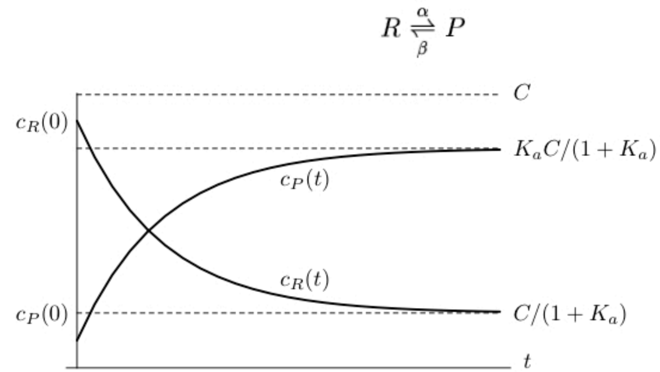
$$R \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} P$$



$\tau = \frac{1}{\alpha+\beta}$

HH: First-Order Kinetics

First-order, reversible reaction



$$\tau = \frac{1}{\alpha+\beta}$$

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

$$\tau_x \frac{dx}{dt} + x = x_\infty$$

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

functions of V_m only

$$x(t) = x_\infty - (x_\infty - x_o)e^{-t/\tau_x} \qquad t \geq 0$$

- Dynamics (i.e., depend. upon t) captured by chemical kinetics
- Voltage depend. (i.e., V_m) captured by how kinetic's parameters affected by membrane potential

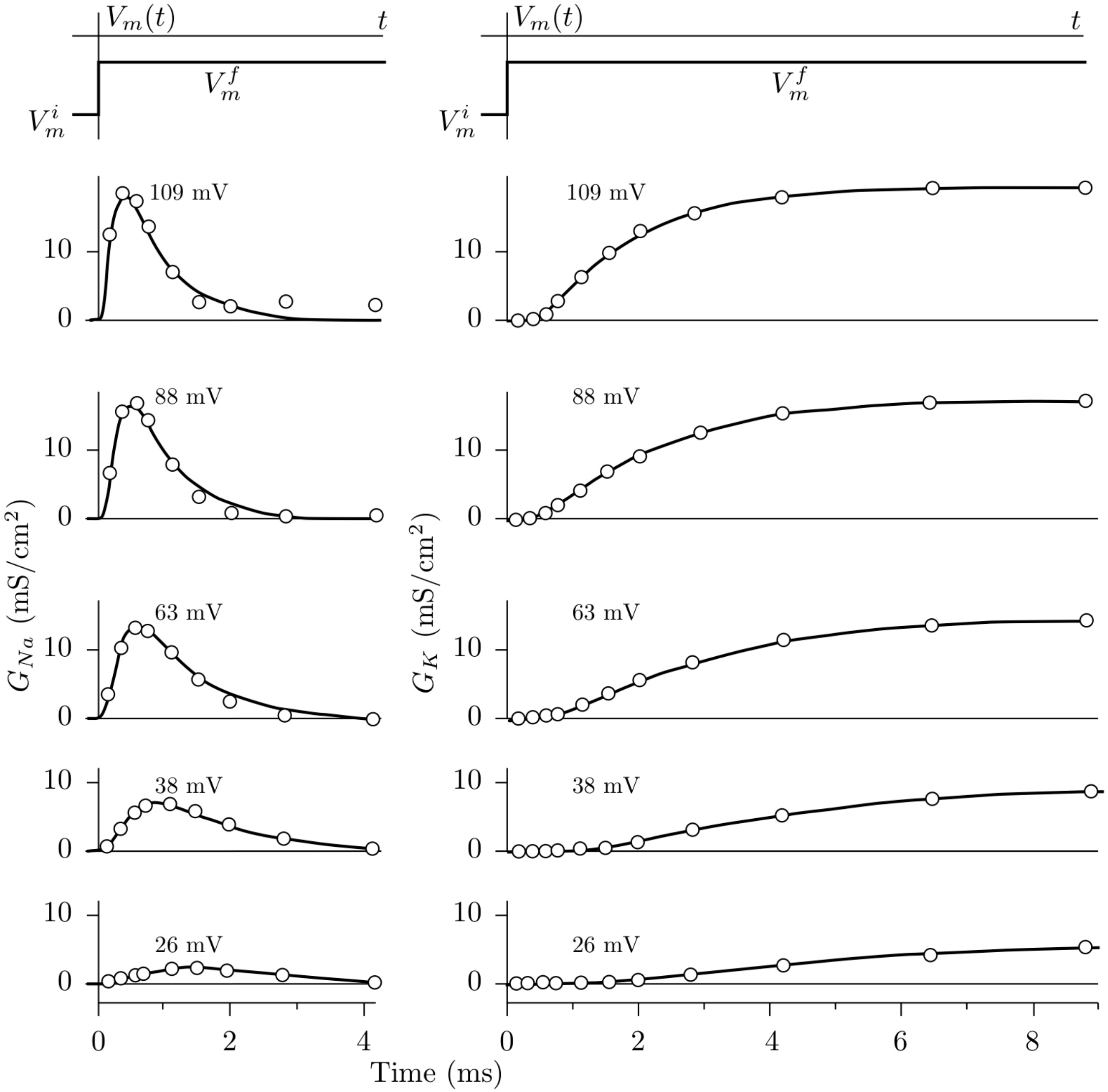


Figure 4.23

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

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

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

$$\tau_m = \frac{1}{\alpha_m + \beta_m}, \quad \text{and} \quad m_\infty = \frac{\alpha_m}{\alpha_m + \beta_m},$$

$$\tau_h = \frac{1}{\alpha_h + \beta_h}, \quad \text{and} \quad h_\infty = \frac{\alpha_h}{\alpha_h + \beta_h},$$

$$\tau_n = \frac{1}{\alpha_n + \beta_n}, \quad \text{and} \quad n_\infty = \frac{\alpha_n}{\alpha_n + \beta_n}.$$

m – sodium activation

h – sodium inactivation

n – potassium activation

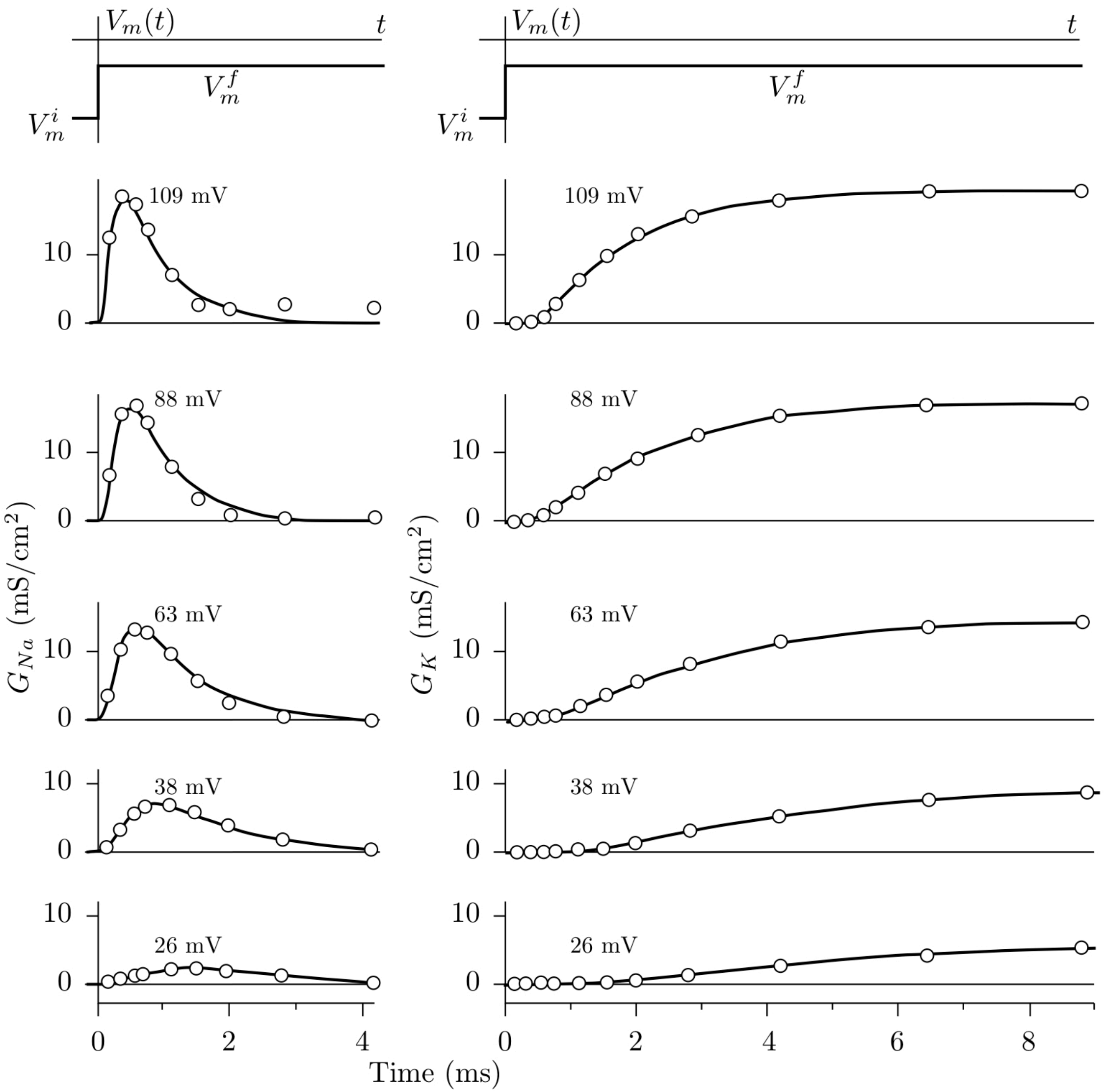


Figure 4.23

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

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

→ Functional form to best fit the data
(e.g., exponentiating yields sigmoids)

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

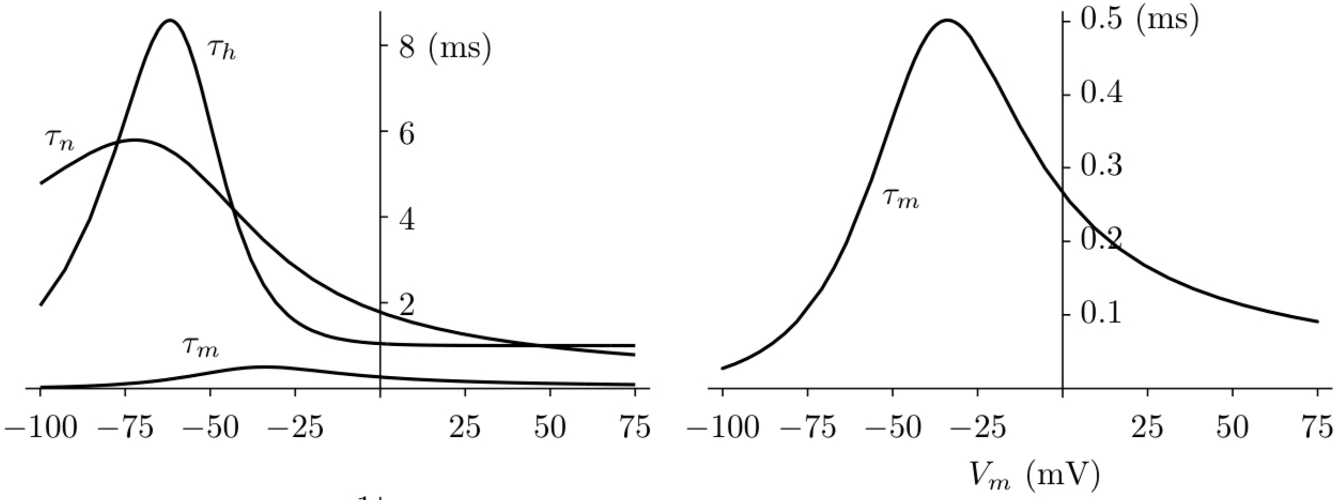
$$\beta_m = 4e^{-(V_m+60)/18},$$

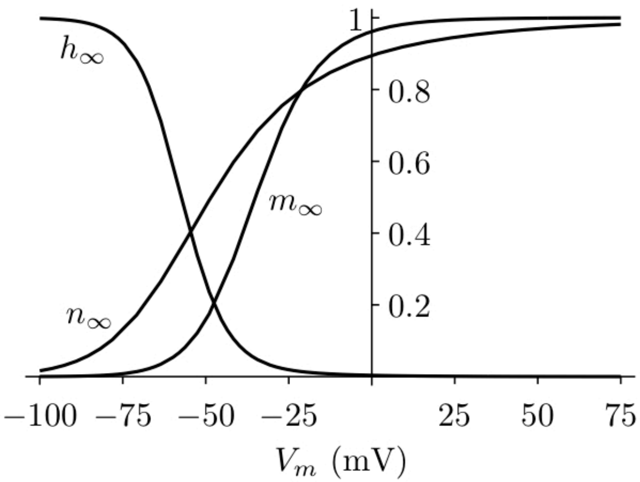
$$\alpha_h = 0.07e^{-0.05(V_m+60)},$$

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

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

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





→ Fast Na^+ activation

→ Slower Na^+ deactivation and K^+ activation

$\overline{G}_{Na} = 120$, $\overline{G}_K = 36$, and $G_L = 0.3$ mS/cm^2; $C_m = 1$ μF/cm^2; $c^o_{Na} = 491$, $c^i_{Na} = 50$, $c^o_K = 20.11$, $c^i_K = 400$ mmol/L; $V_L = -49$ mV; temperature is 6.3°C.

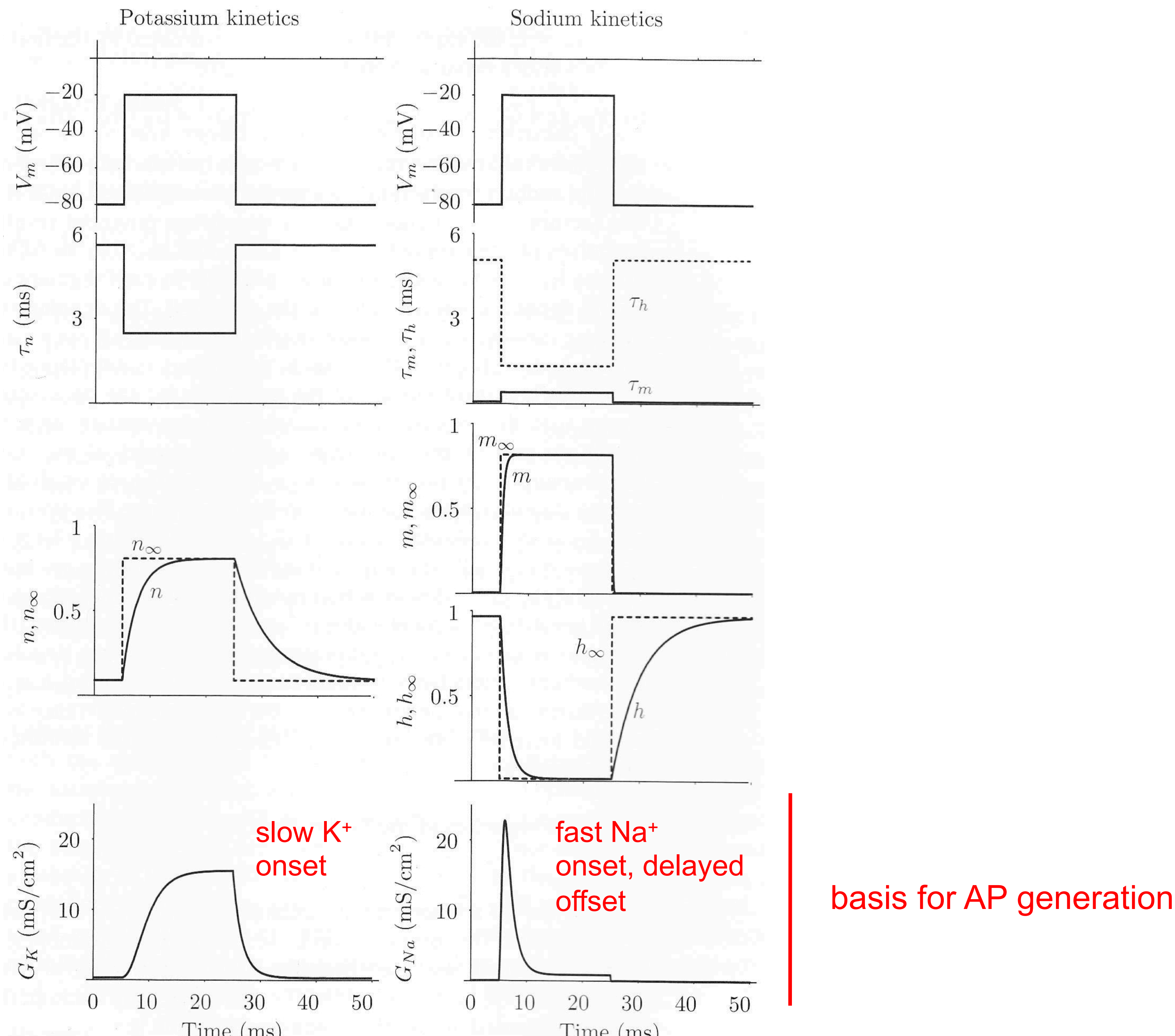

Potassium kinetics
Sodium kinetics
V_m (mV)
−20
−40
−60
−80
τ_n (ms)
6
3
τ_m, τ_h (ms)
τ_h
τ_m
m, m_∞
m_∞
m
1
0.5
n, n_∞
n_∞
n
h, h_∞
h_∞
h
G_K (mS/cm^2)
G_{Na} (mS/cm^2)
20
10
0
10
20
30
40
50
Time (ms)
slow K^+ onset
fast Na^+ onset, delayed offset
basis for AP generation

Figure 4.26