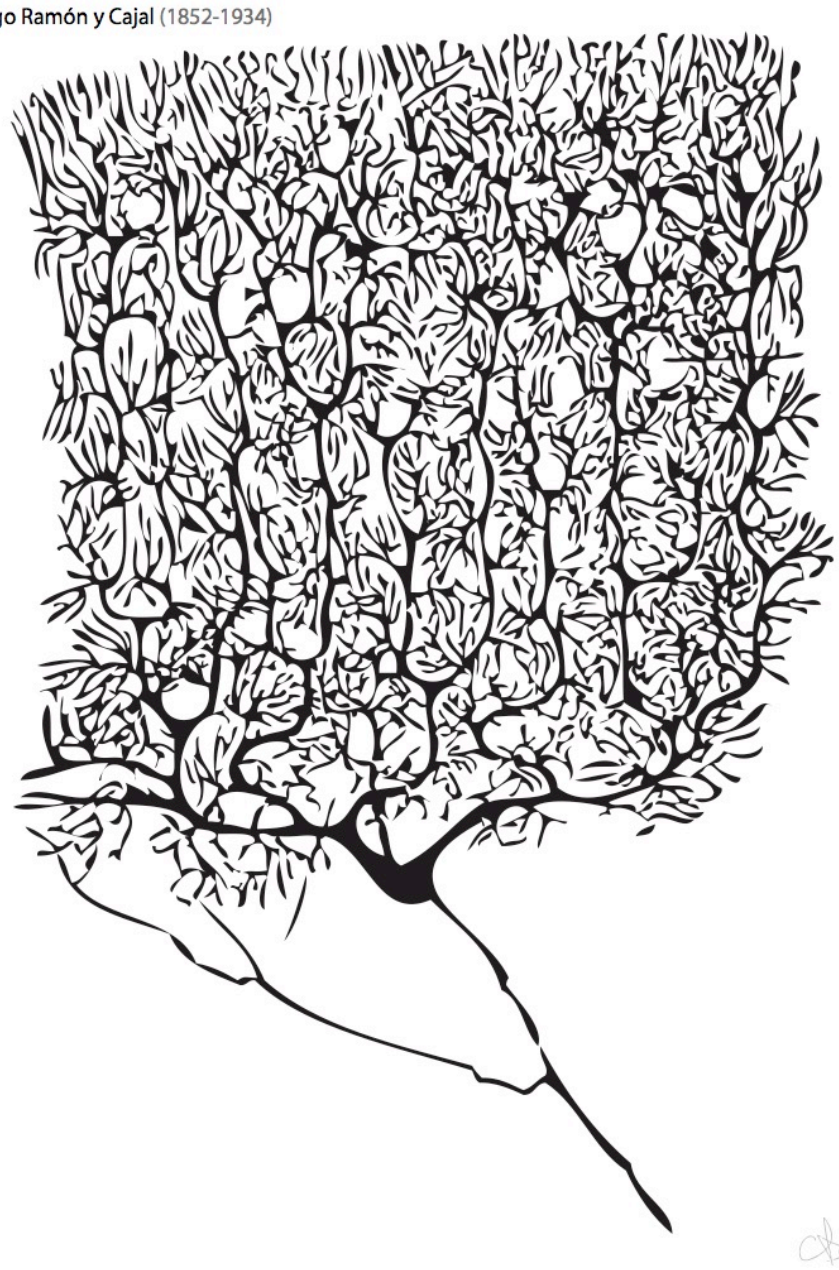
Cellular Electrodynamics



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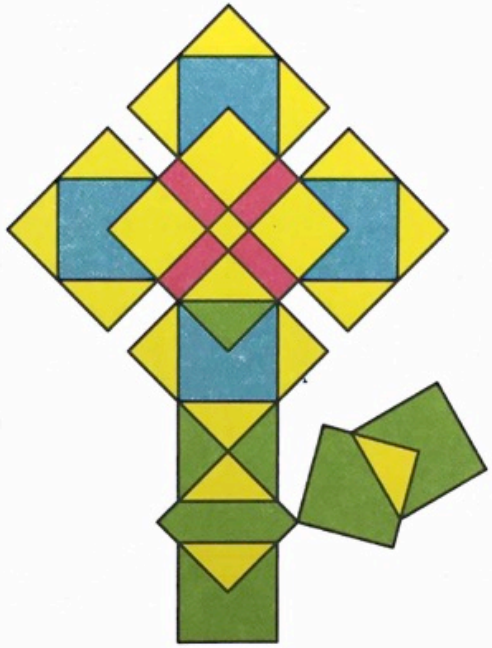
Website:
http://www.yorku.ca/cberge/4080W2020.html

York University
Winter 2020
BPHS 4080 Lecture 14

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

221. Shapes in a Flower



Which shapes can be found most frequently in the flower: squares or triangles (or is there an equal number of both)?

Triangles | Squares | Equal

York University BPHS 4080 (Winter 2020)

Project Overview

As per the course syllabus, there are two parts of the "project" component of BPHS 4080. For both (described in detail below), students will self-form into pairs (and different pairs for each of the two components). For each part, everything will be done together (e.g., there will be one report per group to hand in) and one grade will be assigned to everyone in the group for that part. Each student is expected to contribute equally.

1 Hodgkin–Huxley Simulations

1.1 Timeline

- 3/6 – Proposals due by 4:00 PM (soft copy okay; lateness penalty applies)
- 3/30 – In-class presentations (including a hard copies of your slides)

2 "Journal Club"

2.1 Timeline

- 3/13 – Deadline for getting a paper approved by the course instructor
- 4/2 – In-class "journal club" presentations
- 4/2 – Report due (but you can turn it in by 4/8 without penalty)

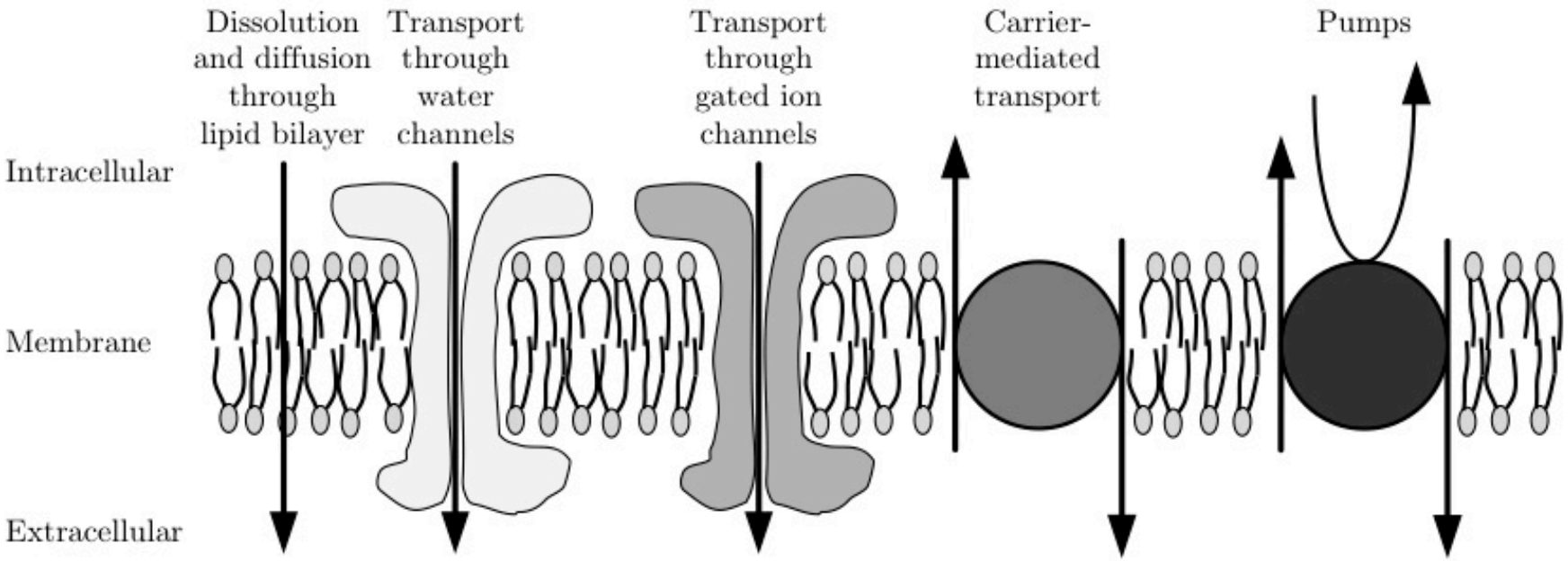

Dissolution and diffusion through lipid bilayer
Transport through water channels
Transport through gated ion channels
Carrier-mediated transport
Pumps
Intracellular
Membrane
Extracellular

Figure 2.19

Review: Membrane as a circuit

Model of Steady-State Electrodiffusion through Membranes

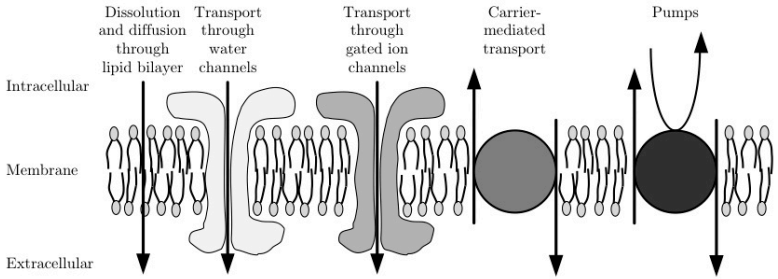
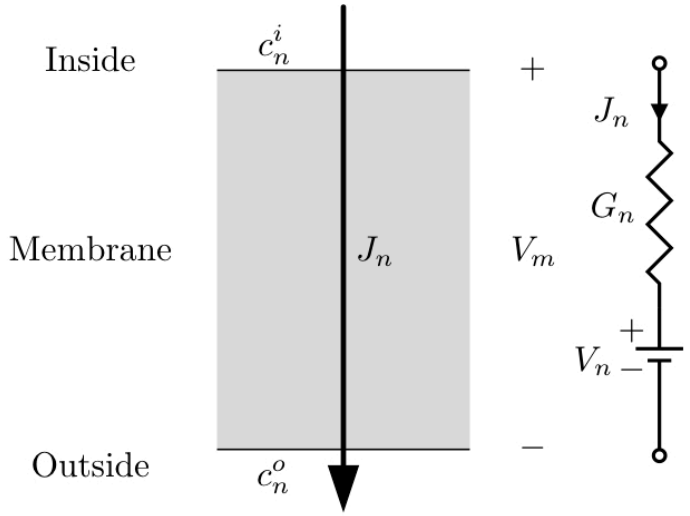


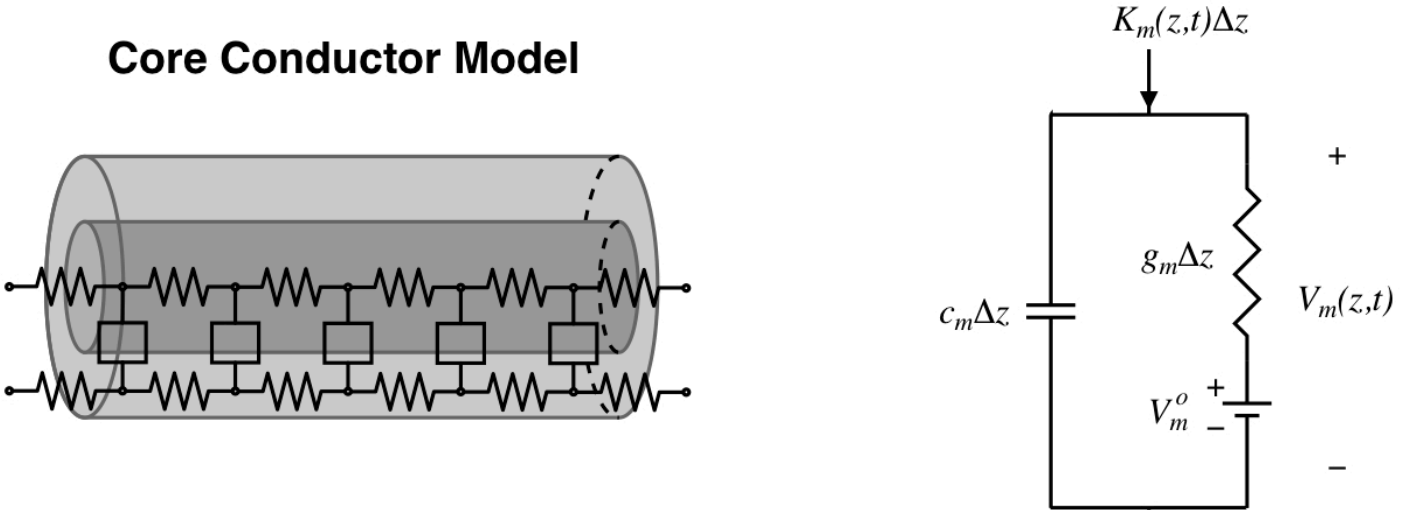
Figure 2.19



$$\text{Nernst Equilibrium Potential } V_n = \frac{RT}{z_n F} \ln \frac{c_n^o}{c_n^i}$$

$$\text{Electrical Conductivity } G_n = \frac{1}{\int_o^d \frac{dx}{u_n z_n^2 F^2 c_n(x)}} \geq 0$$

Review: Cell as a “leaky submarine cable”



Let $V_m = v_m + V_m^o$:

$$v_m + \tau_M \frac{\partial v_m}{\partial t} - \lambda_C^2 \frac{\partial^2 v_m}{\partial z^2} = r_o \lambda_C^2 K_e \quad \text{(Cable Equation)}$$

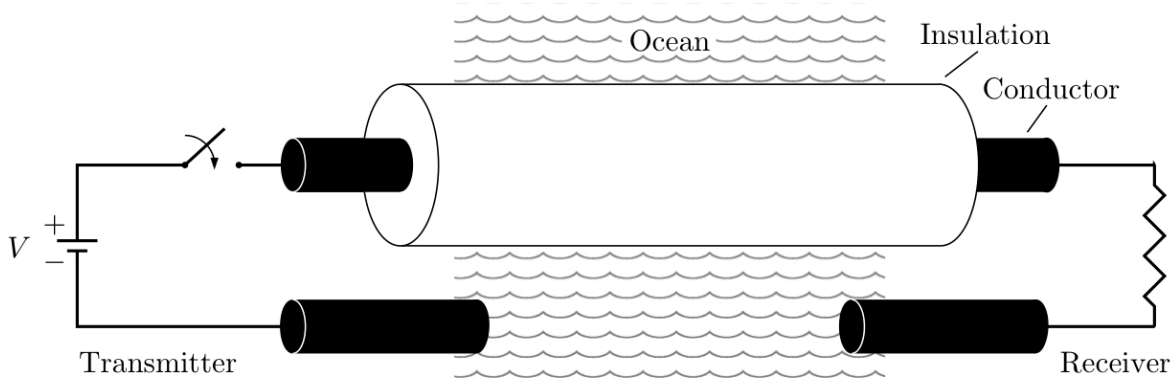
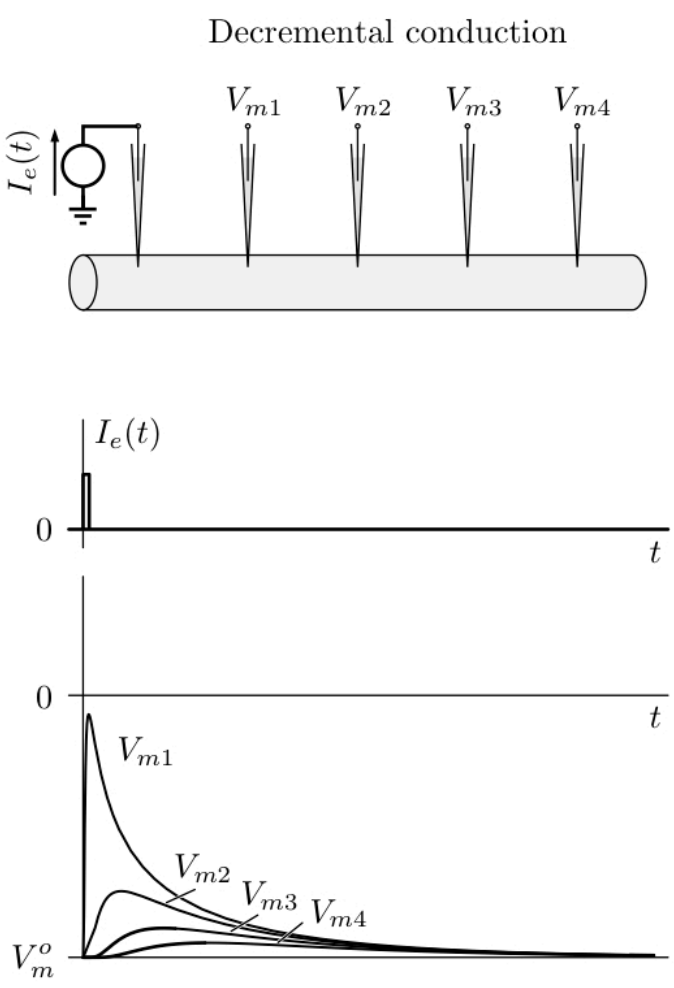
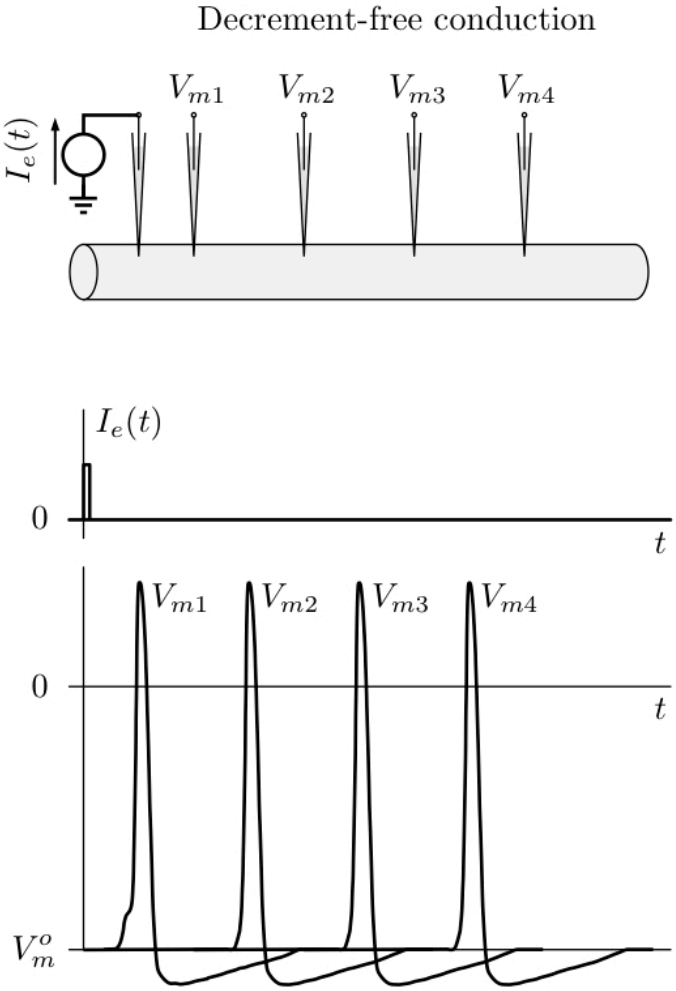


Figure 3.8



Electrically inexcitable cell



Electrically excitable cell

- What (biophysically) distinguishes between these two?

→ Axon is **more** than just a "leaky submarine cable"

Looking Ahead....

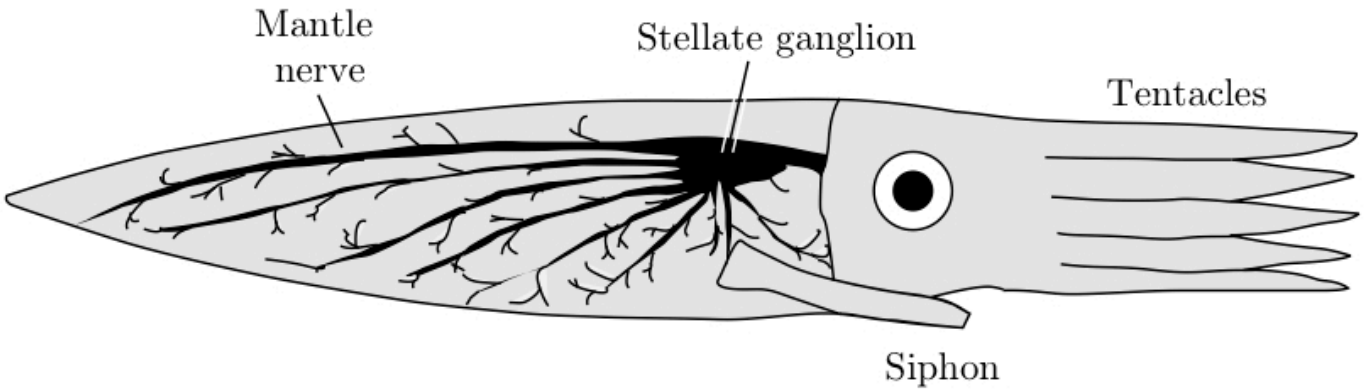
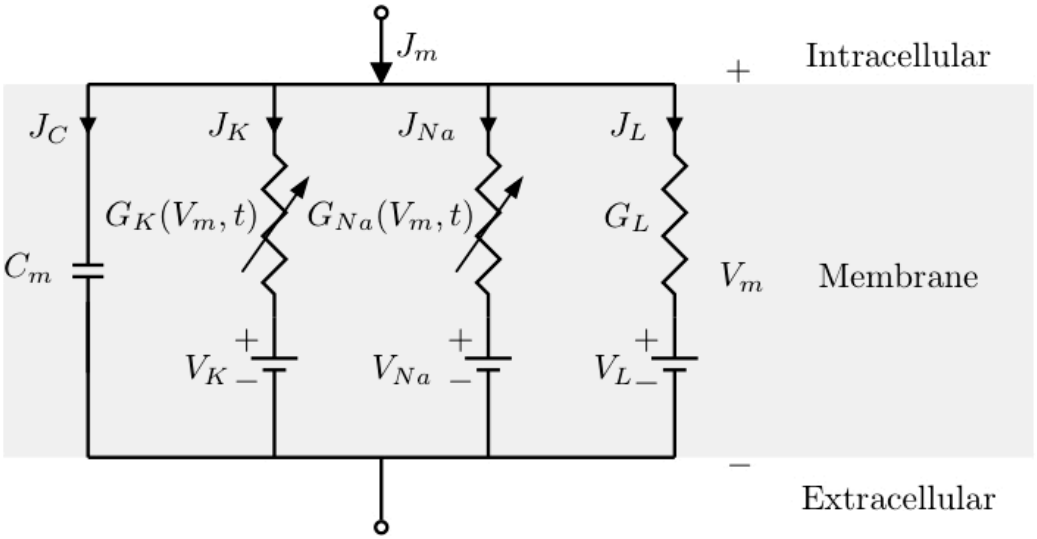


Figure 1.28

Hodgkin Huxley model

Variable Na+ and K+ conductances



The culmination of this effort was the systematic measurements and the theoretical formulations of Hodgkin and Huxley (Hodgkin et al., 1952; Hodgkin and Huxley, 1952a, 1952b, 1952c, 1952e), for which they were awarded the Nobel Prize in 1963. Their theory is one of the most successful mathematical theories in biology and greatly accelerated research in neurobiology. The theory explained the properties of the electrically excitable squid giant axon in terms of the measured relations of the membrane potential and the membrane current. The primitive entities of this theory were a set of hypothetical transmembrane ionic channels.

Hence, this research focused the attention of neurobiologists on the identification and elucidation of the properties of these ionic channels. Since the 1970s, electrophysiological techniques have been developed to record the ionic current through such isolated single channels, and molecular biological techniques have been developed to isolate the channel macromolecules.

→ Huge amount of scientific/biophysical “gravitas” here....

Weiss (v.2 ch.4)

Looking Ahead....

$$J_m = C_m \frac{\partial V_m}{\partial t} + G_K(V_m, t)\,(V_m - V_K) + G_{Na}(V_m, t)\,(V_m - V_{Na}) + G_L(V_m - V_L)$$

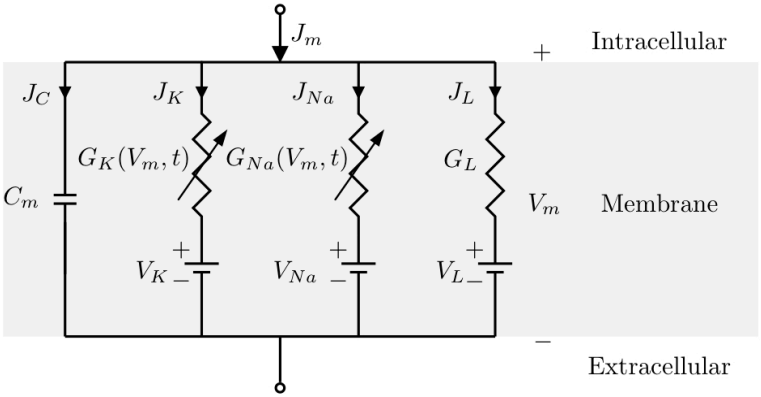


Figure 4.6

Nernst Potentials

$$V_{Na} = \frac{RT}{F} \log \frac{c_{Na}^o}{c_{Na}^i} \qquad V_K = \frac{RT}{F} \log \frac{c_K^o}{c_K^i}$$

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

Combine w/ Core-Conductor & Cable models

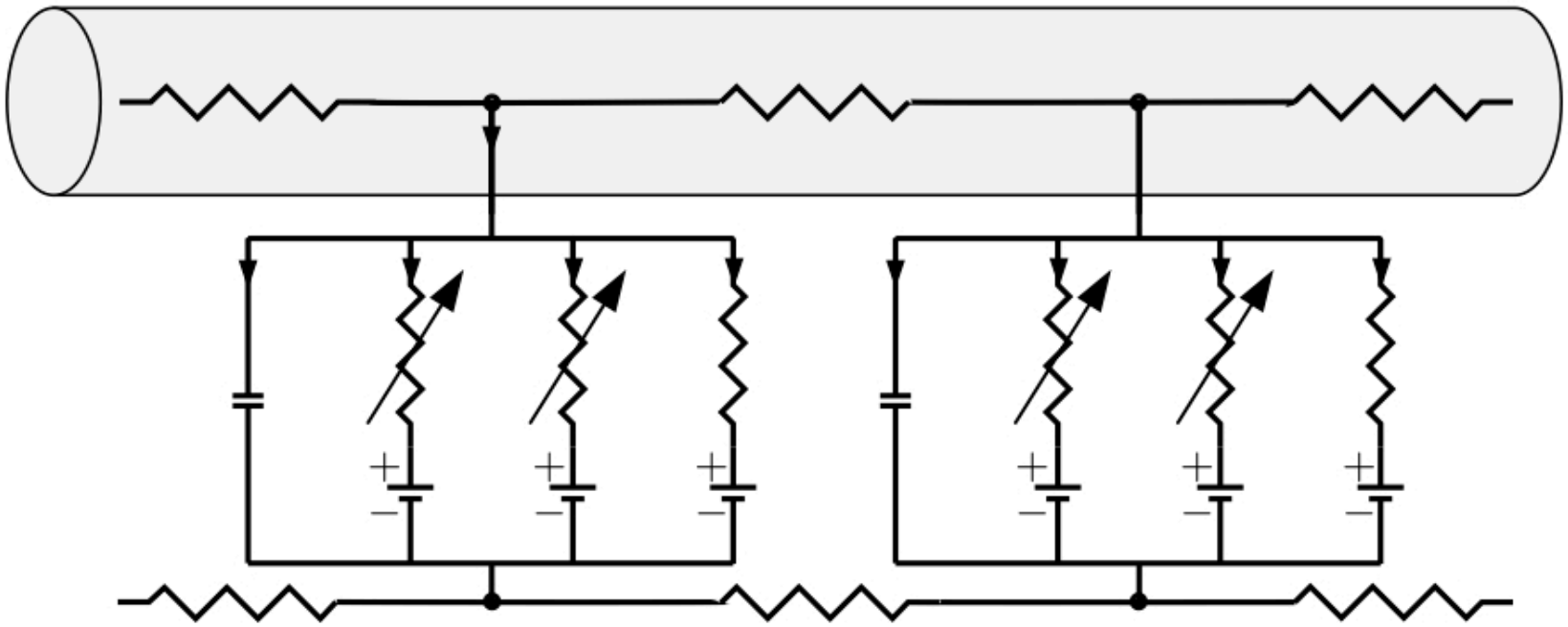


Figure 4.7

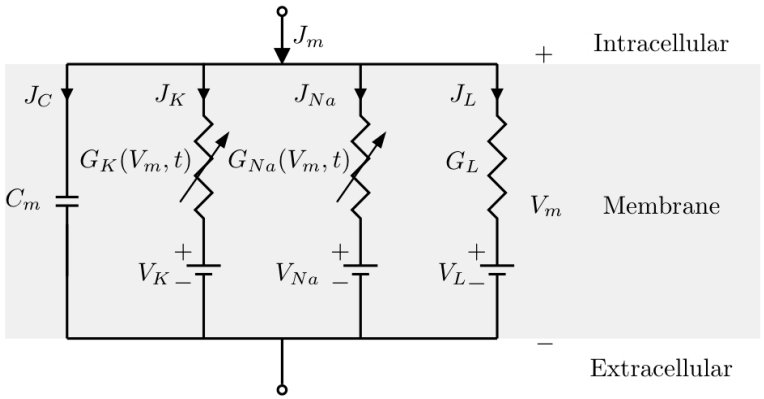


Figure 4.6

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

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

This gets to the heart of the Hodgkin-Huxley model as we'll see.....

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

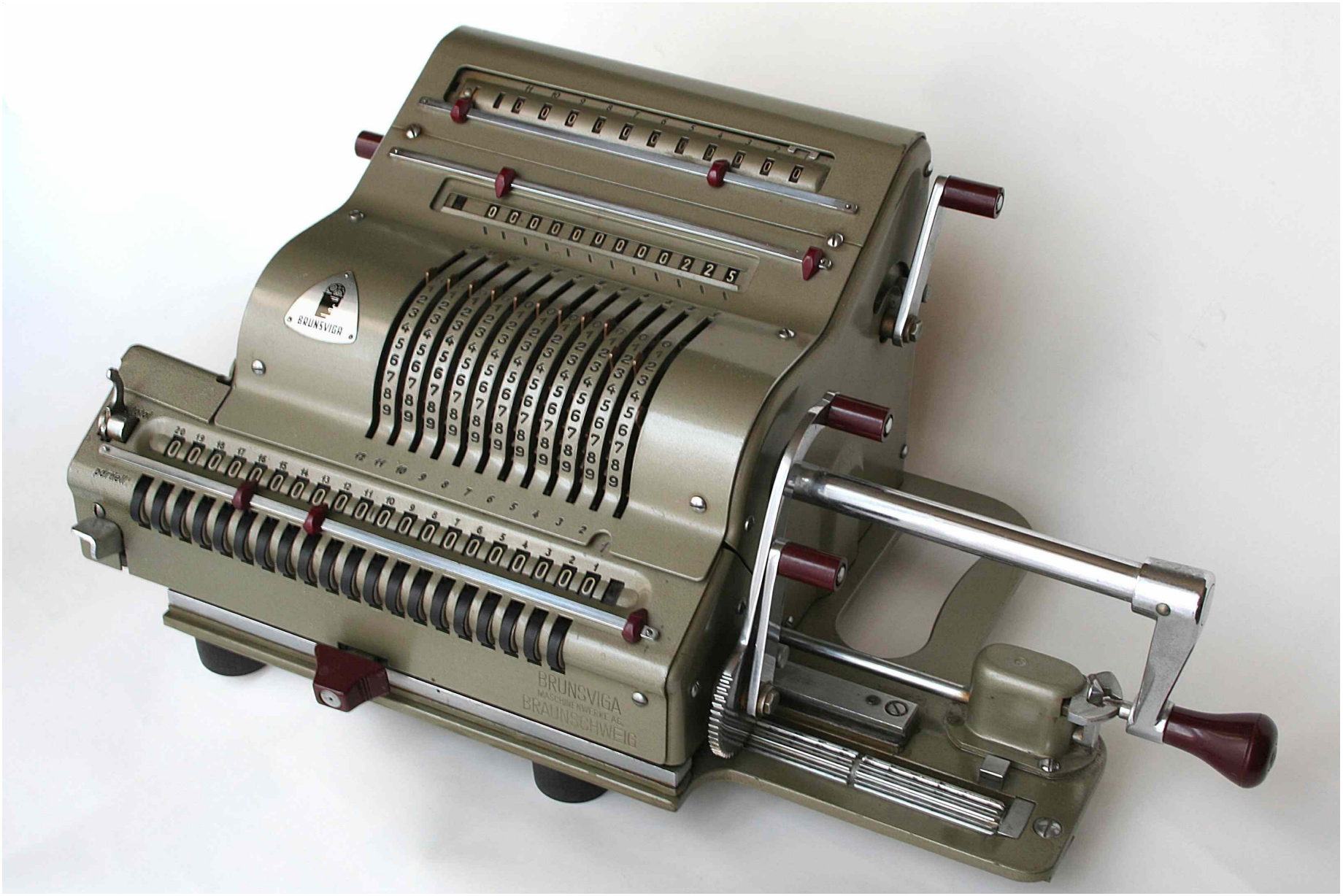
$$G_{Na}(V_m,t) = \overline{G}_{Na} m^3(V_m,t) h(V_m,t)$$

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

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

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

Finally there was the difficulty of computing the action potentials from the equations which we had developed. We had settled all the equations and constants by March 1951 and hoped to get these solved on the Cambridge University computer. However, before anything could be done we learnt that the computer would be off the air for 6 months or so while it underwent a major modification. Andrew Huxley got us out of that difficulty by solving the differential equations numerically using a hand-operated Brunsviga. The propagated action potential took about three weeks to complete and must have been an enormous labour for Andrew. But it was exciting to see it come out with the right shape and velocity and we began to feel that we had not wasted the many months that we had spent in analysing records.
—Hodgkin, 1977



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

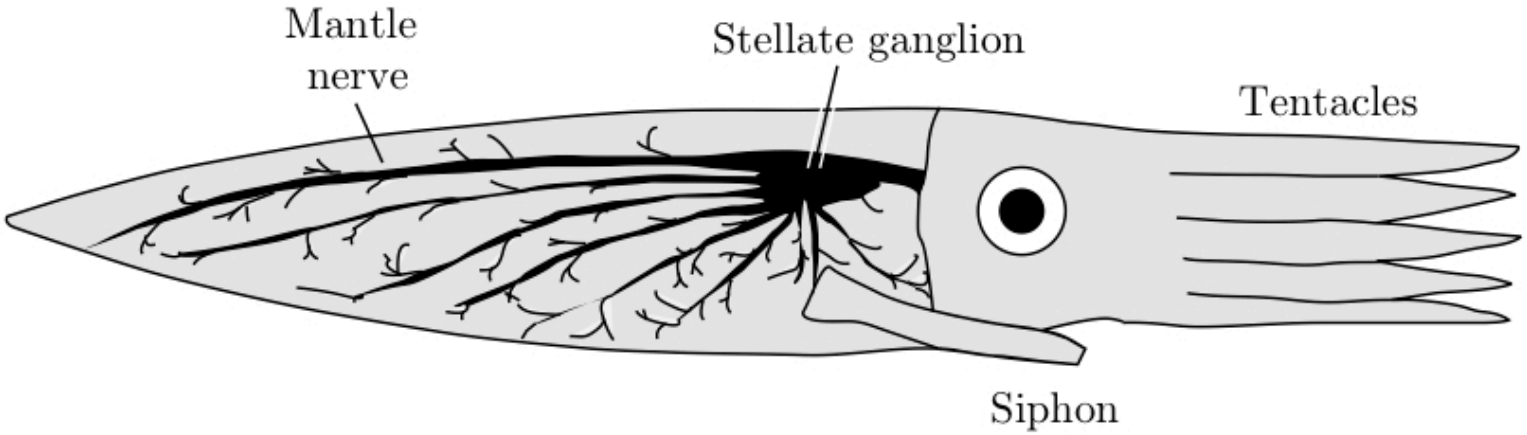


Figure 1.28

Some key observations...

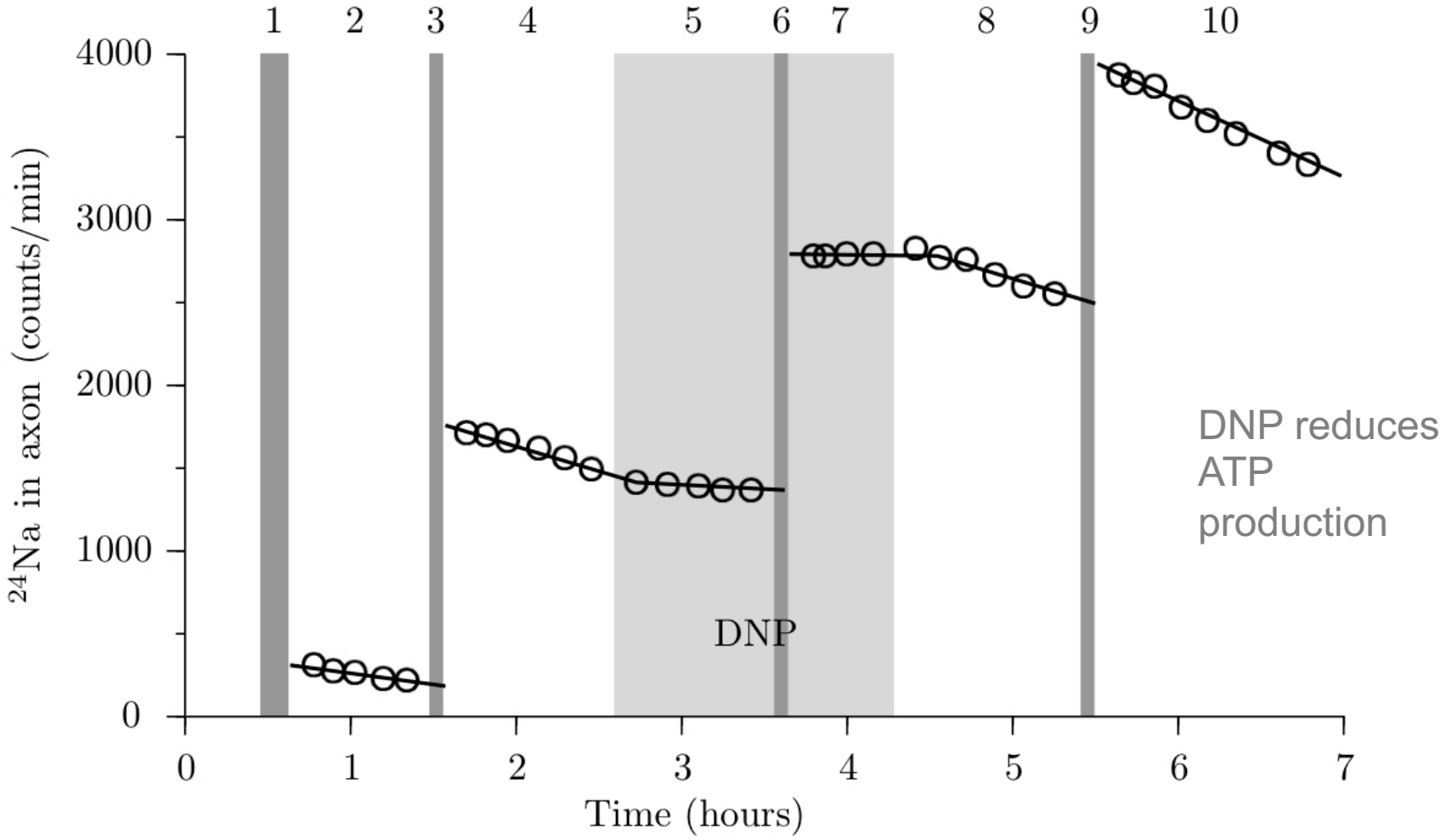


Figure 7.38

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

→ Active transport not a priori required for AP generation

Some key observations...

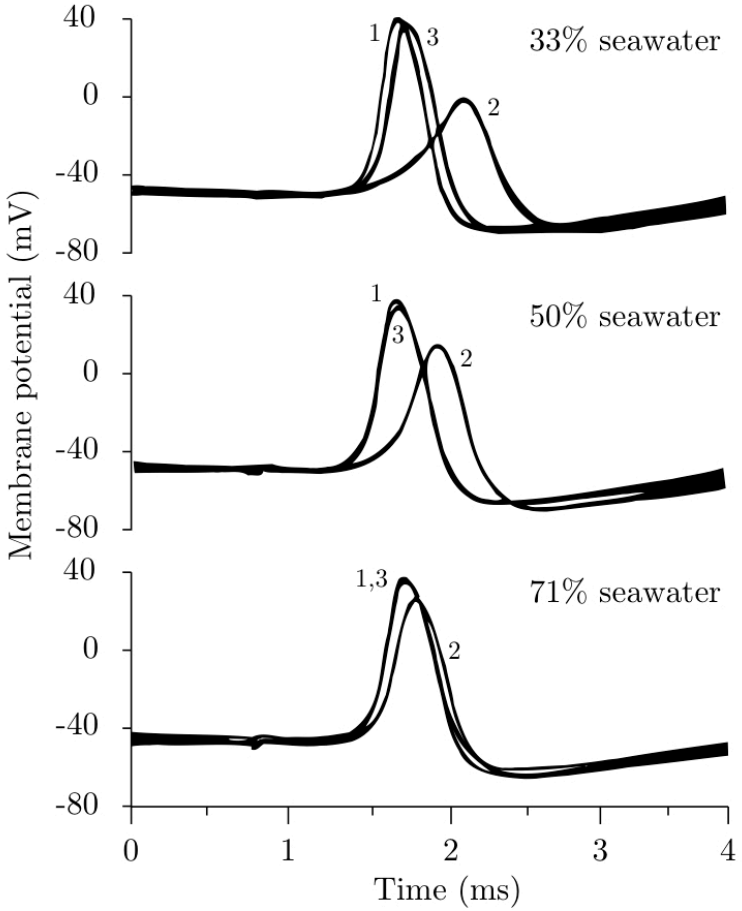


Figure 4.2

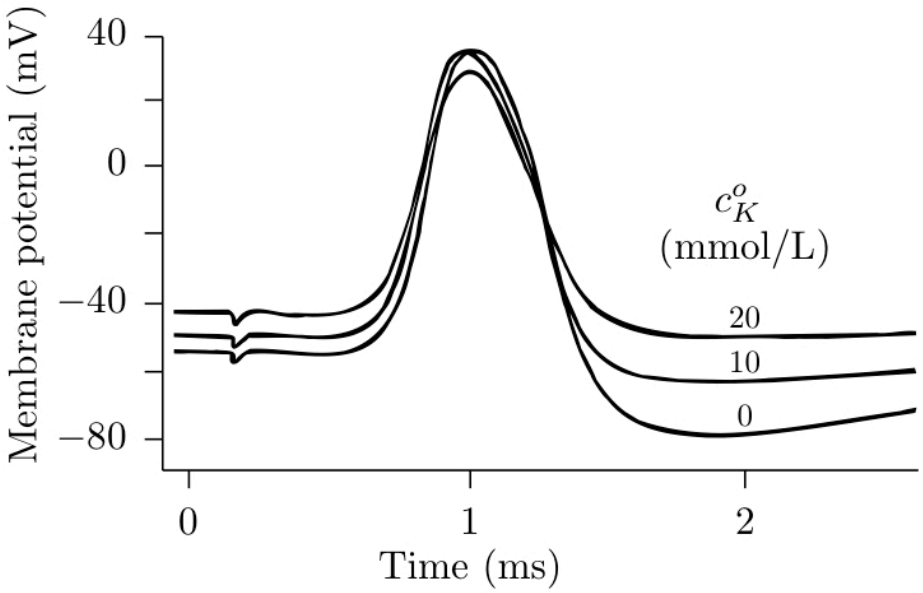


Figure 4.5

→ Na⁺ flux affects APs (*early on*)

→ K⁺ flux affects APs (*later on*)

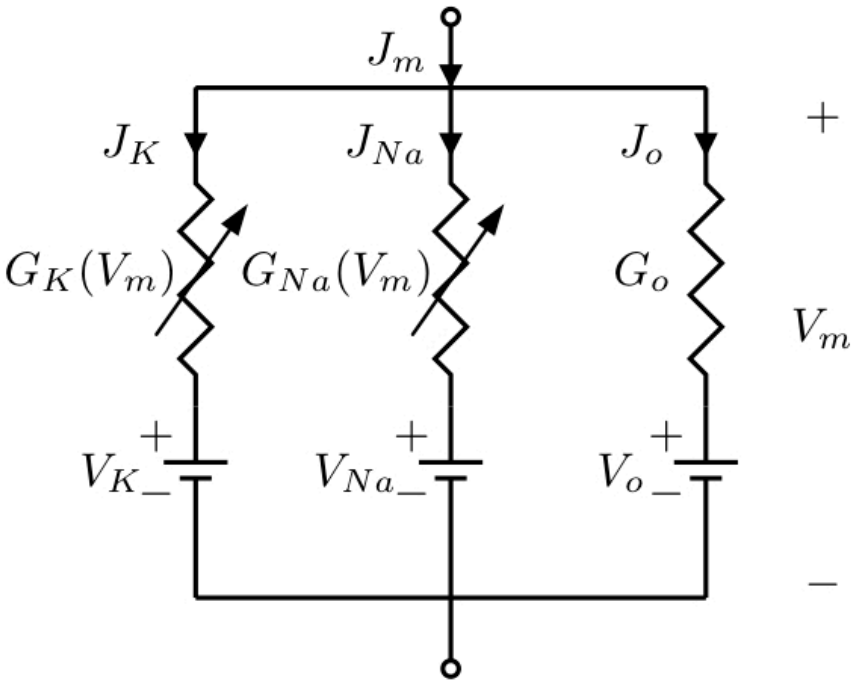
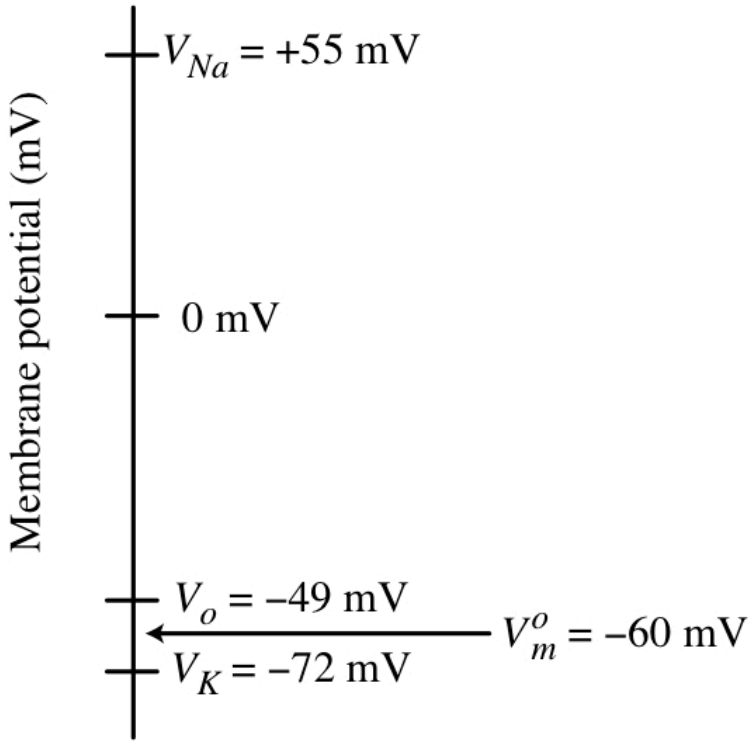


Figure 7.32



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

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

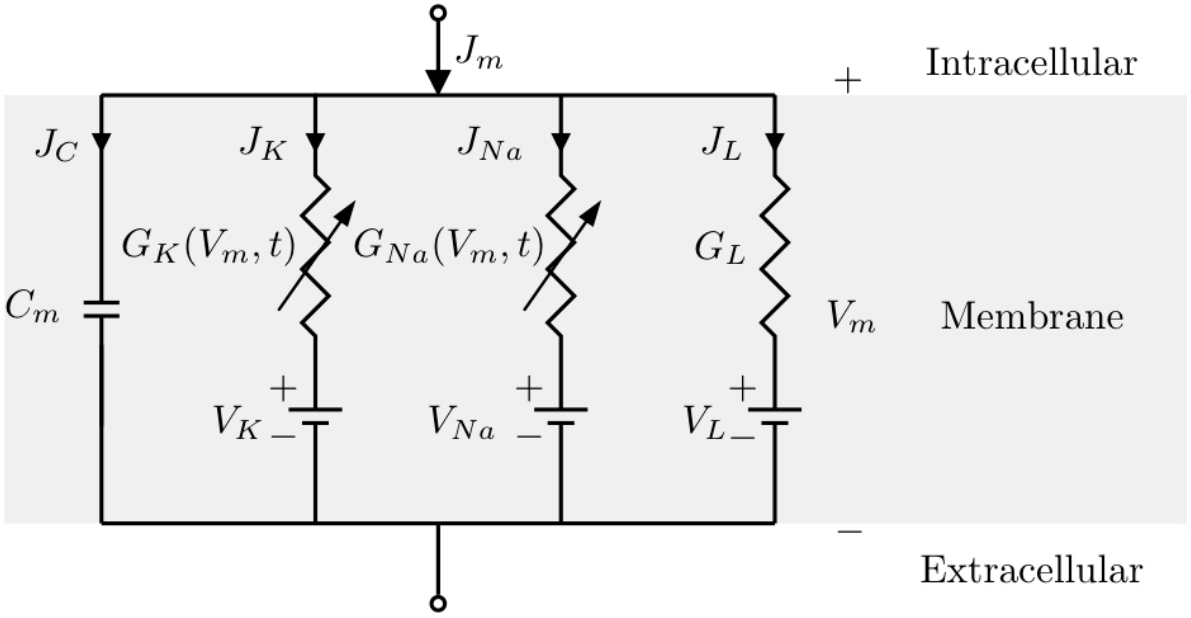


Figure 4.6

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

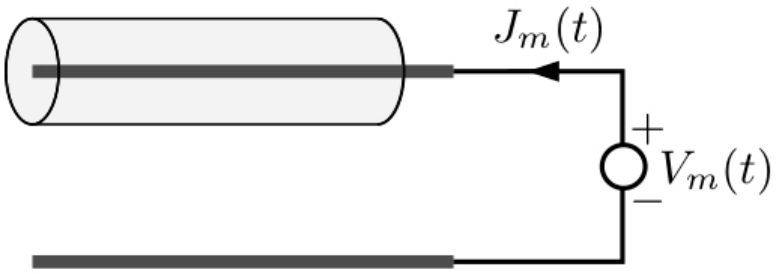
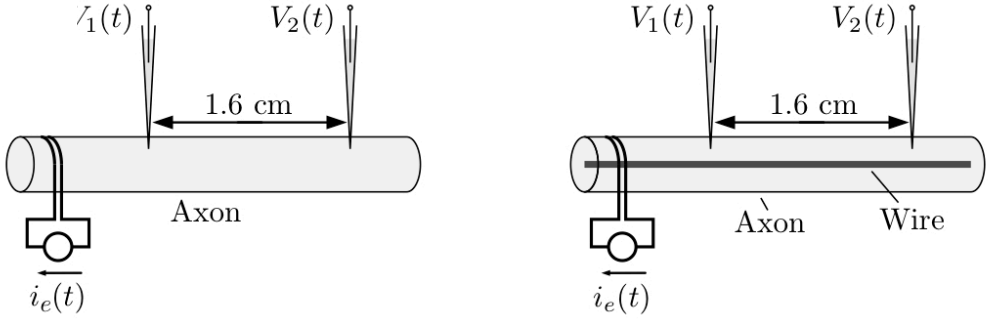


Figure 4.10

Kenneth Cole & George Marmont (1940s)



→ *Eliminates spatial dependence*
(i.e., make an electrically large cell a small one)

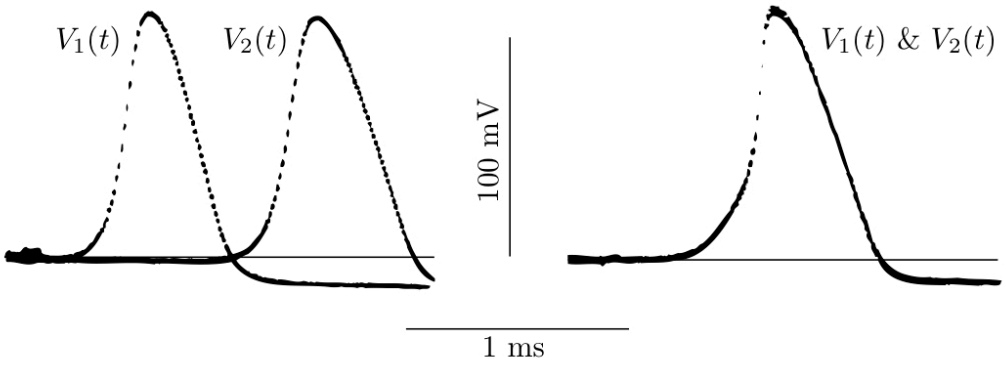


Figure 2.15

Conduction velocity
(Core-Conductor model)

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

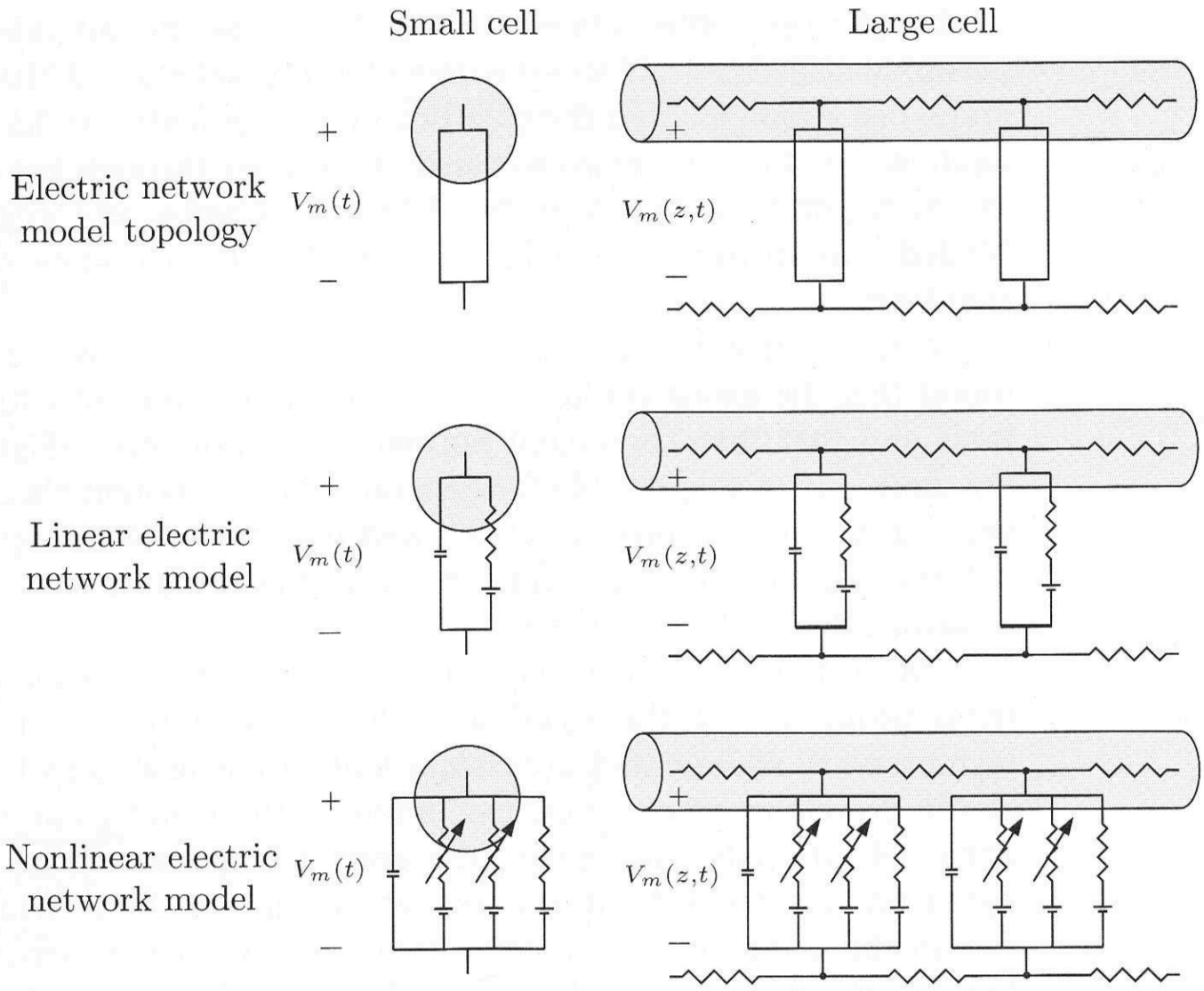
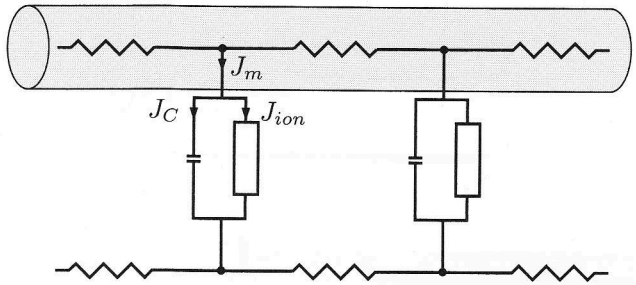


Figure 1.32

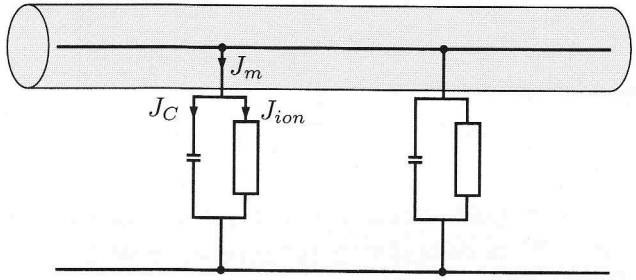
→ Electrically 'small' cell can still fire action potentials

Voltage-Clamp



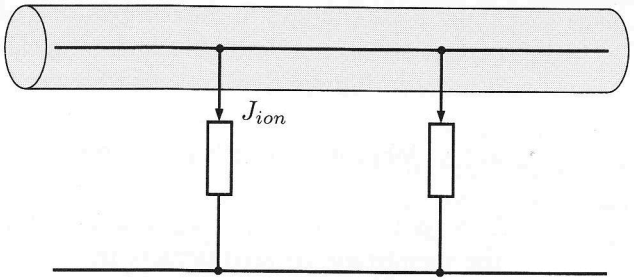
Space clamp

$$\frac{\partial V_m}{\partial z} = 0$$

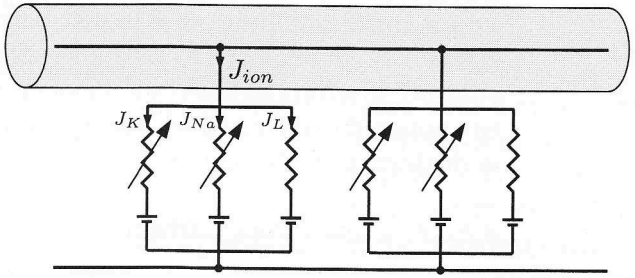


Step voltage clamp

$$\frac{\partial V_m}{\partial z} = \frac{\partial V_m}{\partial t} = 0$$



Separation of ionic currents



Separating Ionic Currents

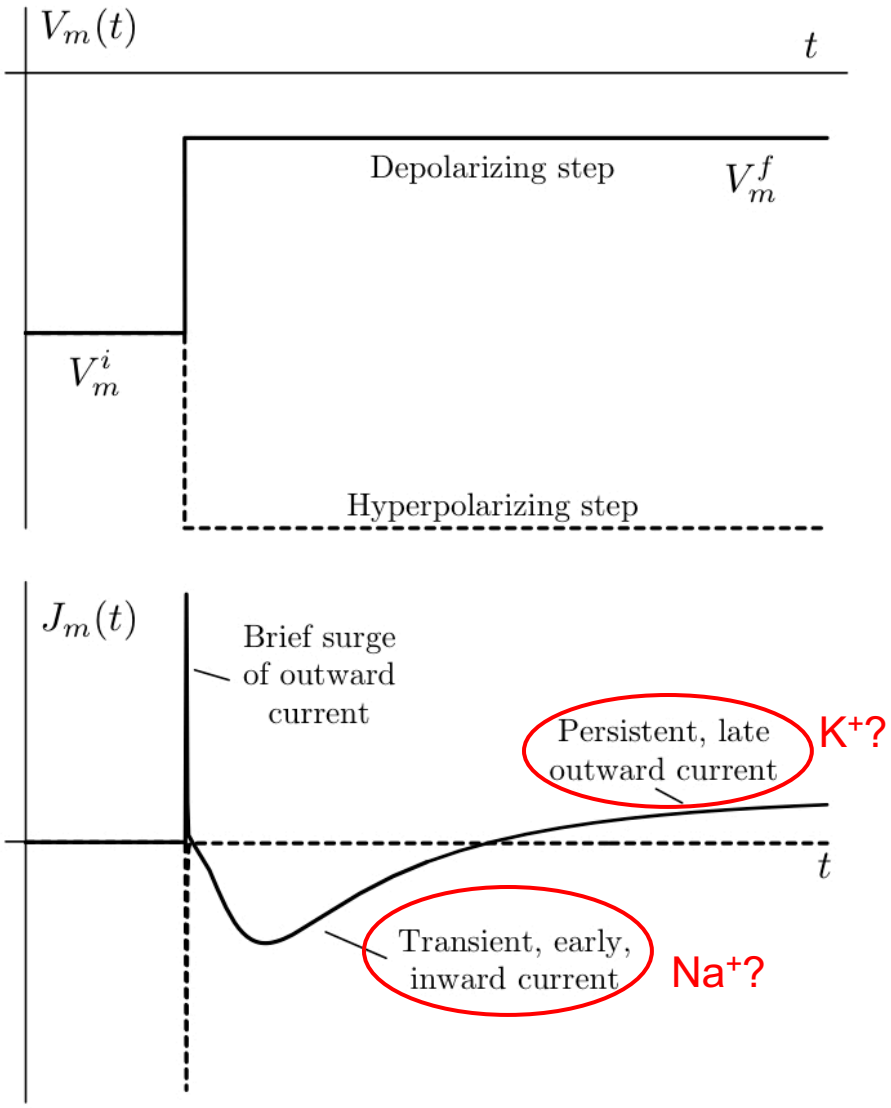


Figure 4.12

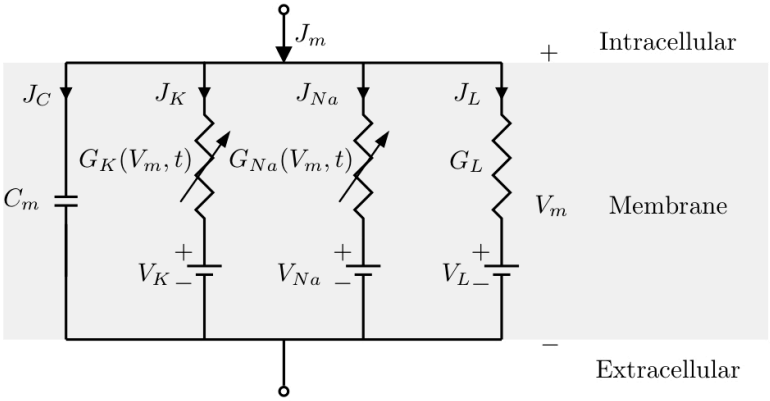


Figure 4.6

Capacitive Current

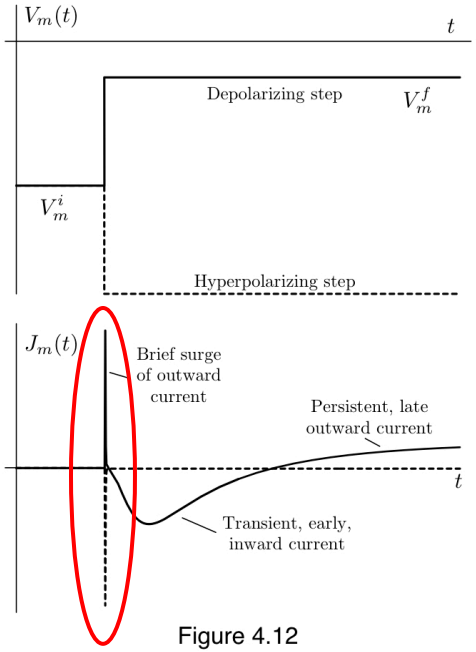
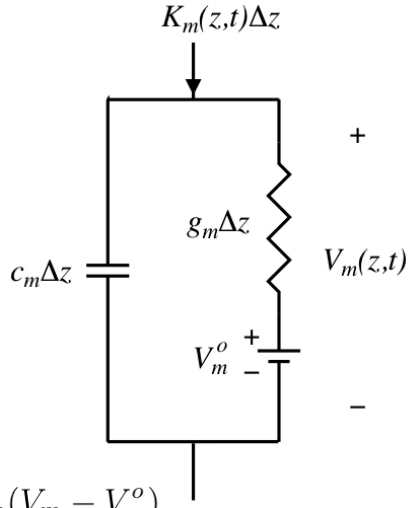


Figure 4.12



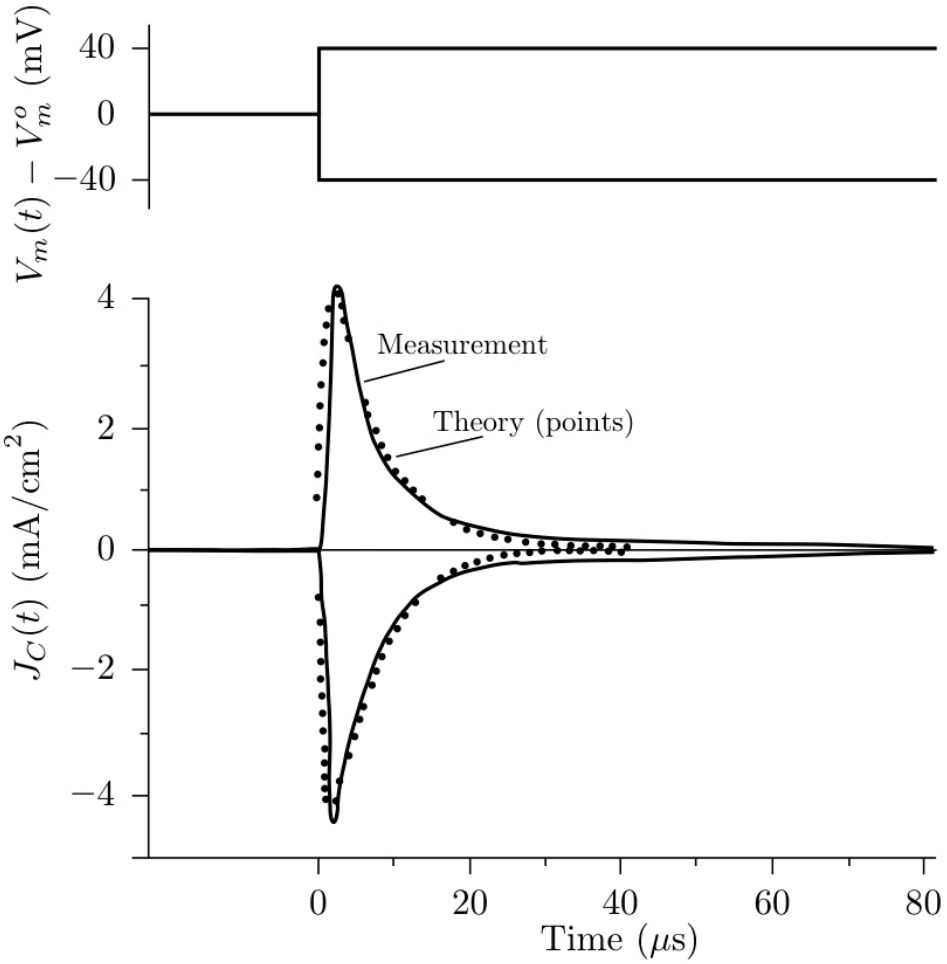


Figure 4.13

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

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

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^+])

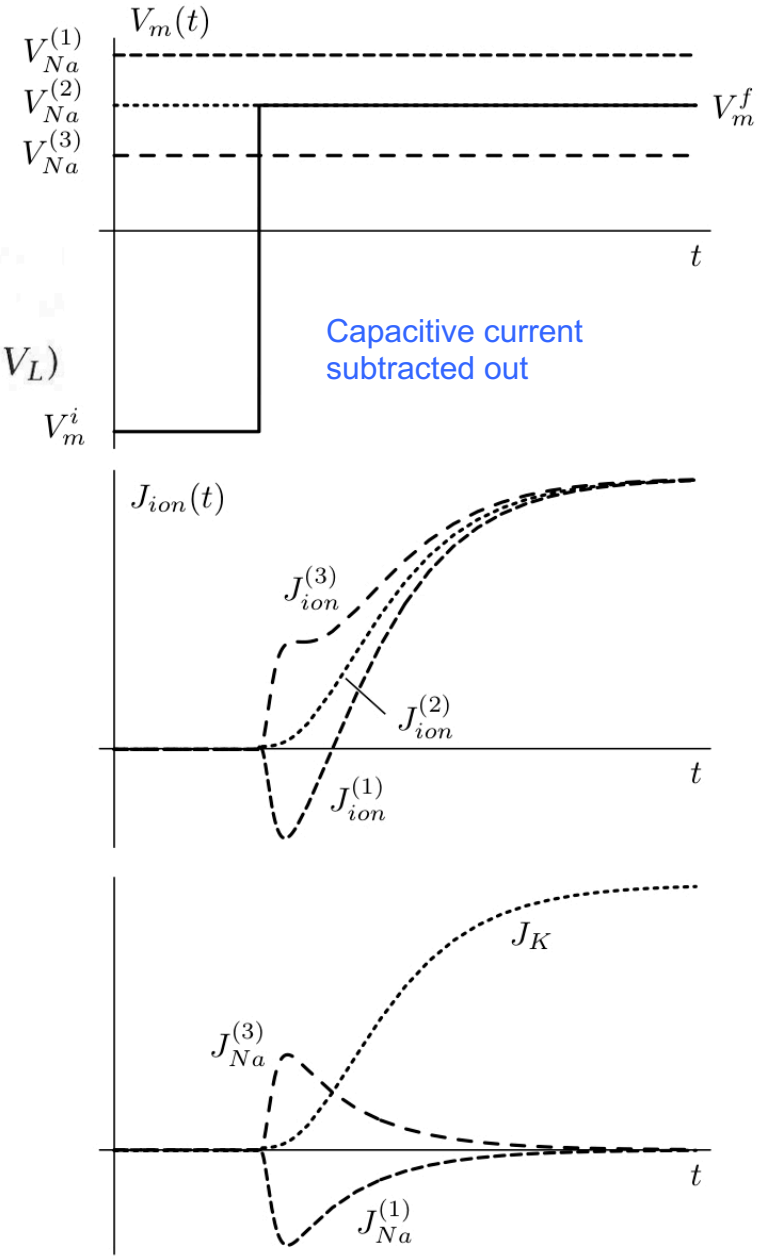


Figure 4.17