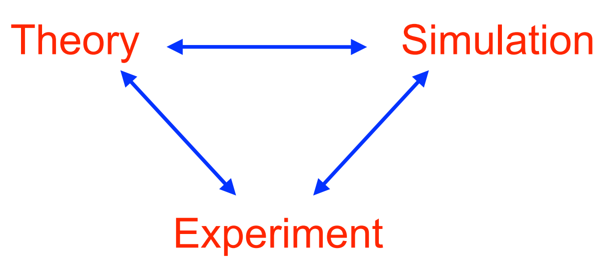
Cellular Electrophysiology

Part 1: Resting and Action Potentials

Cardiac Electrophysiology



Scale

- The membrane: structure, channels and gates
- The cell: resting potential, whole cell currents, cardiac cell types
- The tissue: myocardial structure, propagation
- The heart: conduction system, extracellular electrograms
- ECG and the volume conductor: the heart in the thorax

Membrane Composition

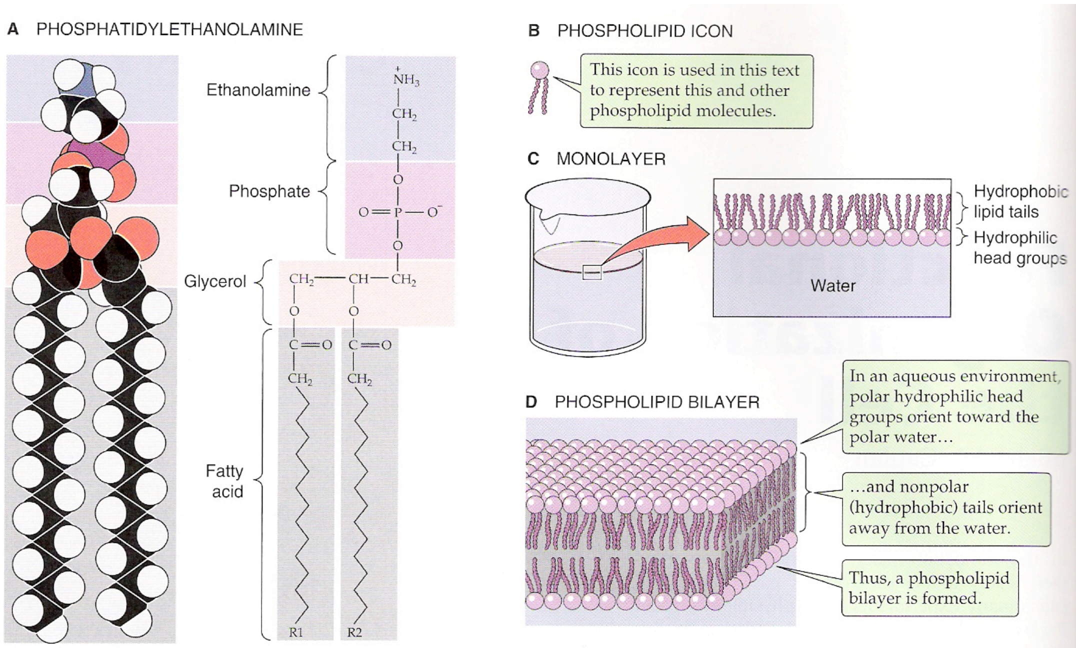
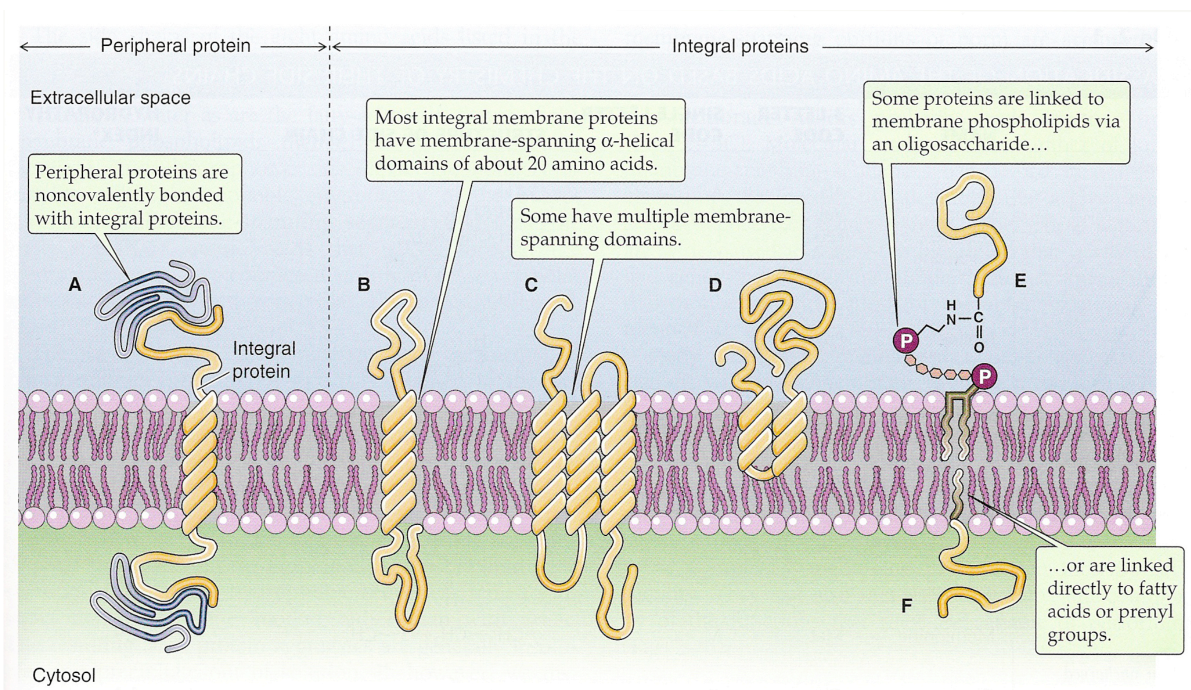


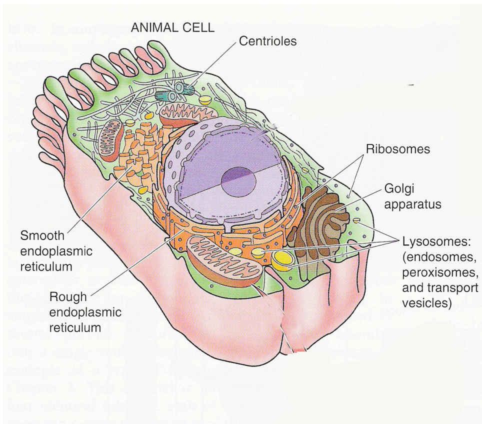
FIGURE 2–1. Phospholipids.

Proteins and the Membrane

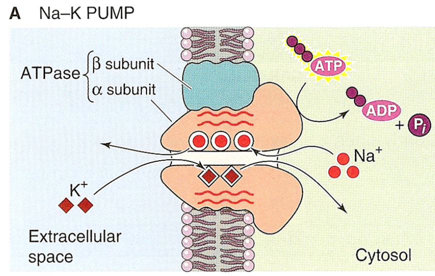


Membrane Functions

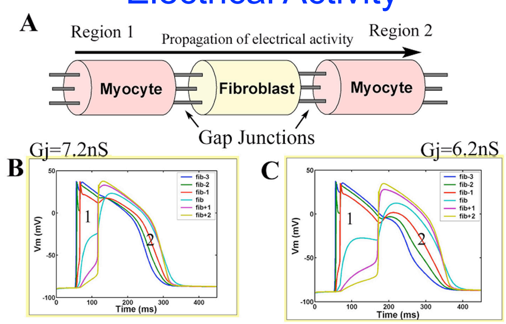
Compartmentalization



Control of solutes' movement



Electrical Activity



Theory ↔ Simulation

Experiment

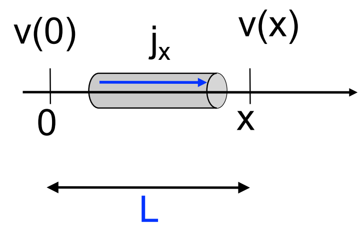
Background Physics

= Theory

Current and Ohm's Law

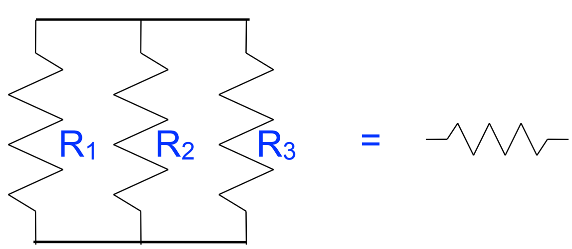
- Without potential difference there is no current!
- Without conductance, there is no current.
- Ohm's law:
  - linear relationship between current and voltage
  - not universal, especially not in living systems

$$I = \frac{1}{R}V = GV$$



Electricity Basics: Resistance

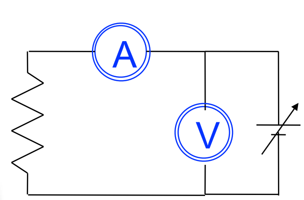
$R_{eq} = R_1 + R_2 + R_3$

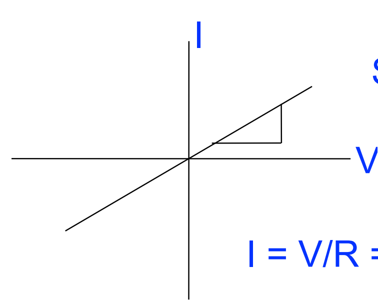


$1/R_{eq} = 1/R_1 + 1/R_2 + 1/R_3$

$G_{eq} = G_1 + G_2 + G_3$

I-V Curve



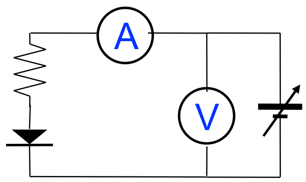


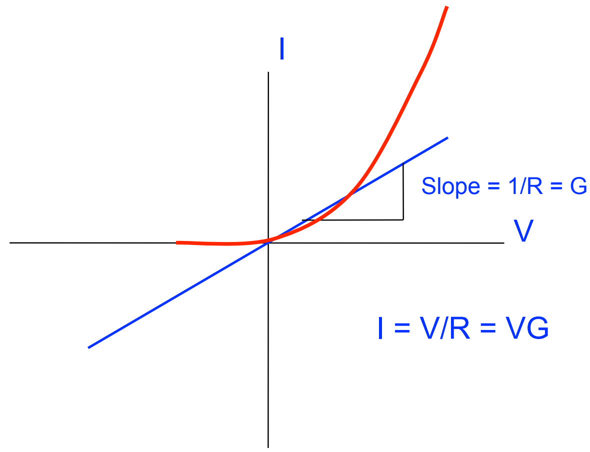
Slope = 1/R = G

I = V/R = VG

Electricity Basics: Rectification

I-V Curve





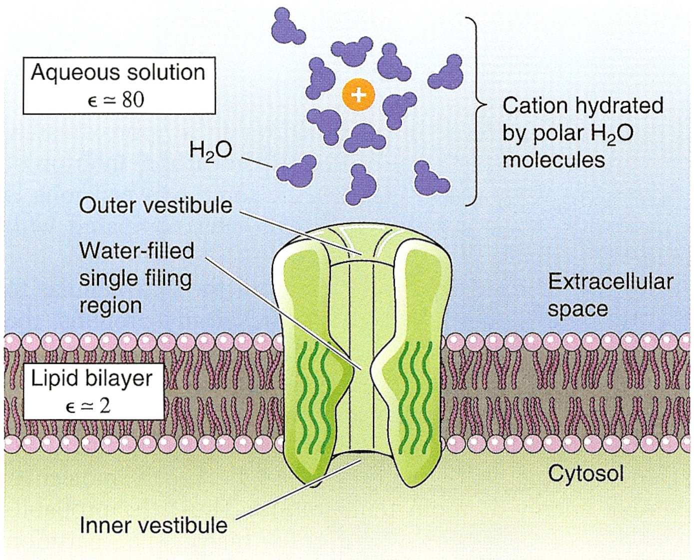
Equilibrium

$$\rightleftharpoons$$

Net Forces Equal Zero

No change over time

Ion Channel Permeability



An electron has a unitary charge of 1.6022×10^{-19} C

Cation+ has a charge of

$$q_o = z e_o$$

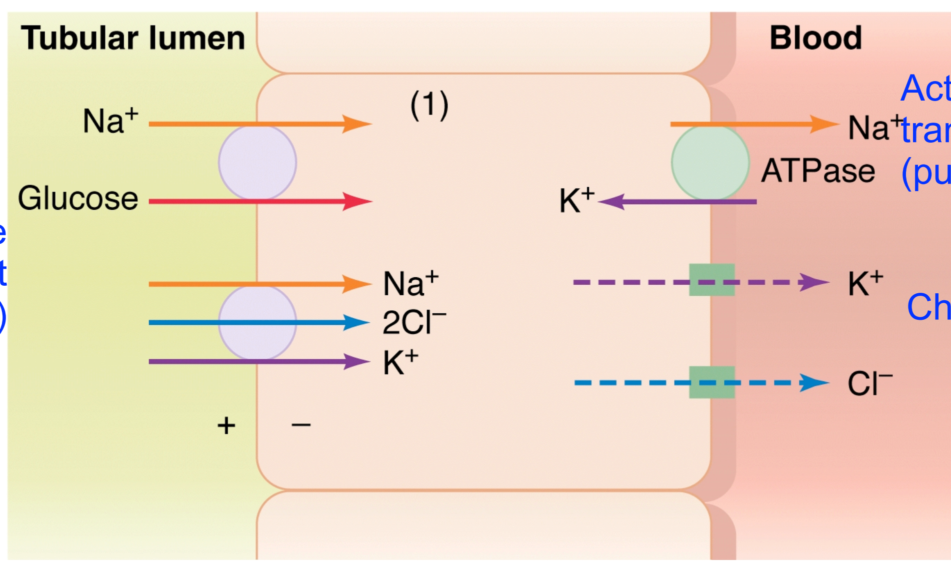
where z is the valence

The attractive force between ions is given by Coulombs law:

$$F = \frac{Z_1 \times Z_2}{\varepsilon r^2}$$

ε is the Dielectric constant, a parameter related to the properties of the material capable of separating charge

Ion Transport

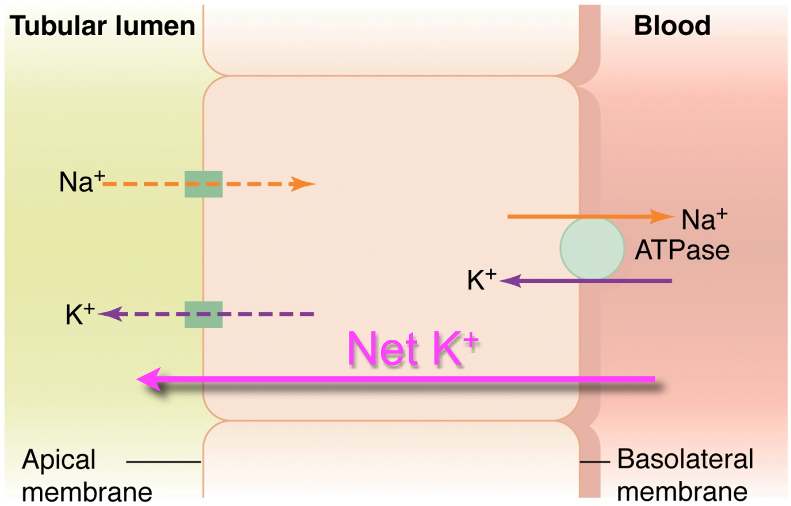


Passive cotransport (symporter)

Active transport (pump)

Channels

Ion Transport



Forces

Diffusive Force

$$J = -D\nabla c \qquad \frac{\partial c}{\partial t} = D\nabla^2 c$$

Chemical Potential

$$\mu = \mu_0 + RT\ln(c)$$

Electrical Force

$$F_e = k_e \frac{q_1 q_2}{r^2}$$

Electrical Potential

$$\phi = zF\Phi$$

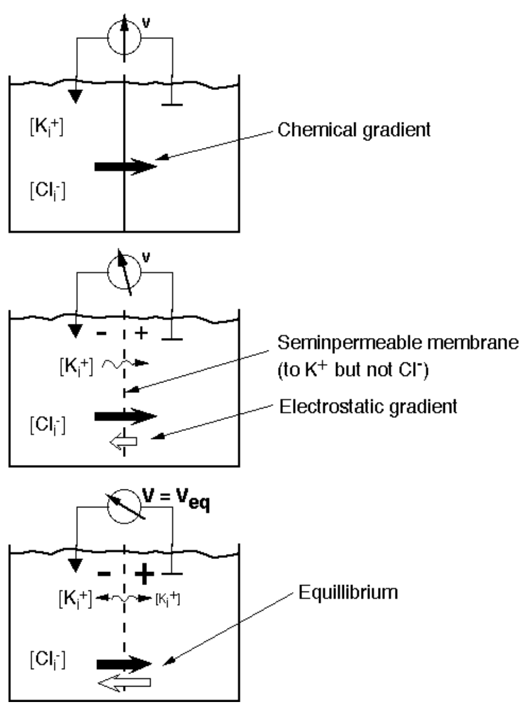
Resting Potential

Equilibrium Potential

a) Membrane is impermeable

b) Membrane becomes permeable to potassium only (semipermeable)

c) Equilibrium established when electrostatic and chemical gradients balance.



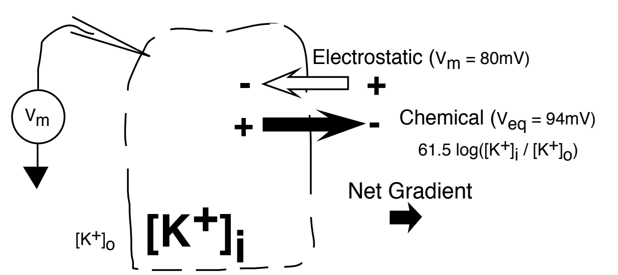
Example Nernst Potentials

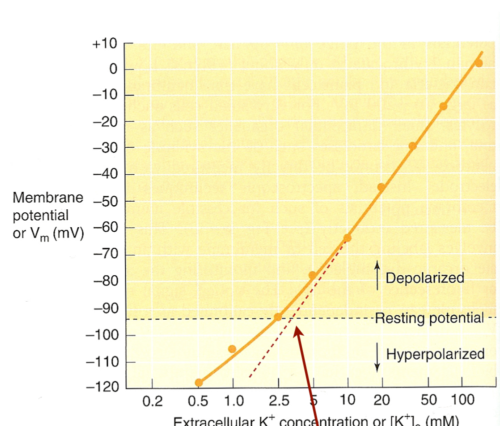
$$E = \frac{25}{z} \log_e \frac{[X]_1}{[X]_2}$$

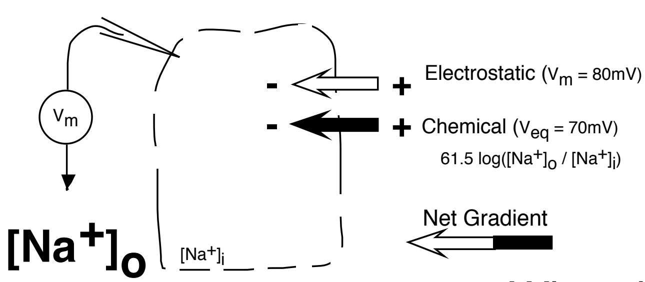
$$E = \frac{58}{z} \log_{10} \frac{[X]_1}{[X]_2}$$

	Ion	External	Internal	Nernst Potential (mV)
Frog muscle	K	2.25	124	-101
	Na	109	10.4	+59
	Cl	77.5	1.5	-99
Squid axon	K	20	400	-75
	Na	440	50	+55
	Cl	560	108	-41

Resting Potential







K+ Nernst Potential

What determines resting potential?

Cellular Electrophysiology
Bioengineering 6000 CV Physiology

Resting Potential

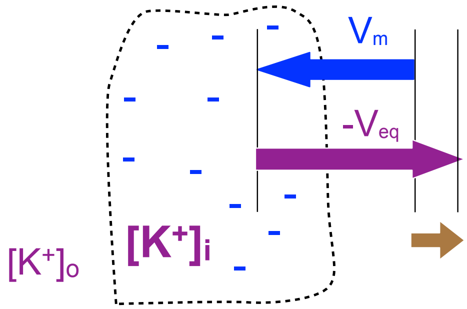
- All ions contribute
- Goldman-Hodgkin-Katz Equation

$$E_m = \frac{RT}{F} ln \left(\frac{\sum_i^N P_{M_i^+}[M_i^+]_{out} + \sum_i^N P_{A_i^+}[A_i^+]_{in}}{\sum_i^N P_{M_i^+}[M_i^+]_{in} + \sum_i^N P_{A_i^+}[A_i^+]_{out}} \right)$$

Cardiac Action Potentials

Driving Force

Sign convention is inside relative to outside.



V_m = -80 mV (electrical)

V_{eq} = -94 mV (chemical)

$V_D = V_m - V_{eq}$ = 14 mV (net)

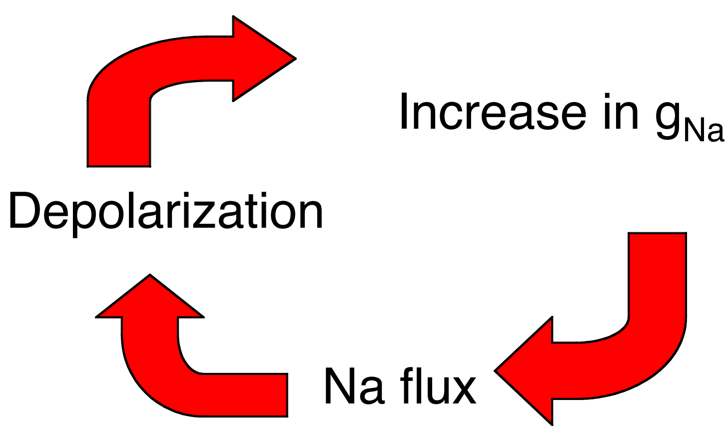
Driving Force $= V_m - V_{eq}$ is the potential available to drive ions across the membrane.

Membrane resistance = R_m is the resistance of the membrane through a specific channel for a specific ion.

$$I = \frac{V_m - V_{eq}}{R_m}$$

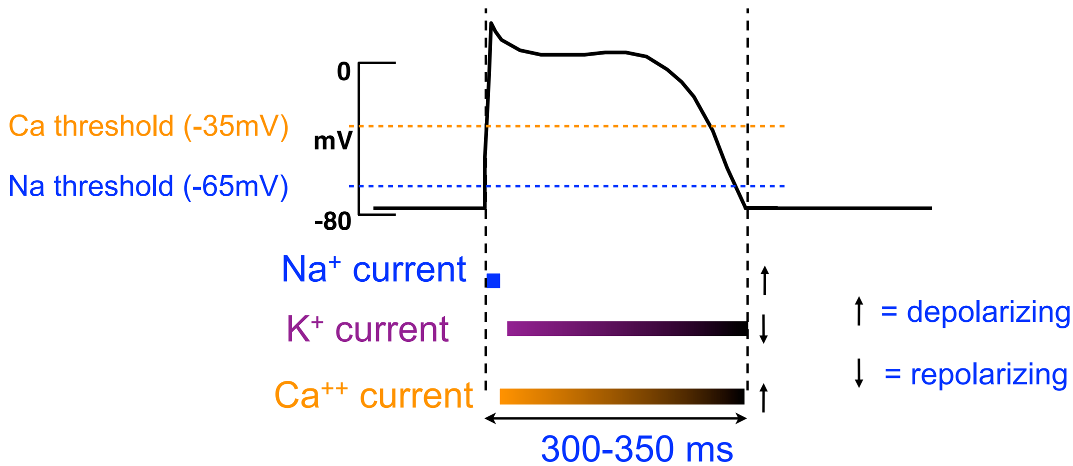
Ohm's Law: links these parameters and describes the membrane current.

Action Potentials-Positive Feedback

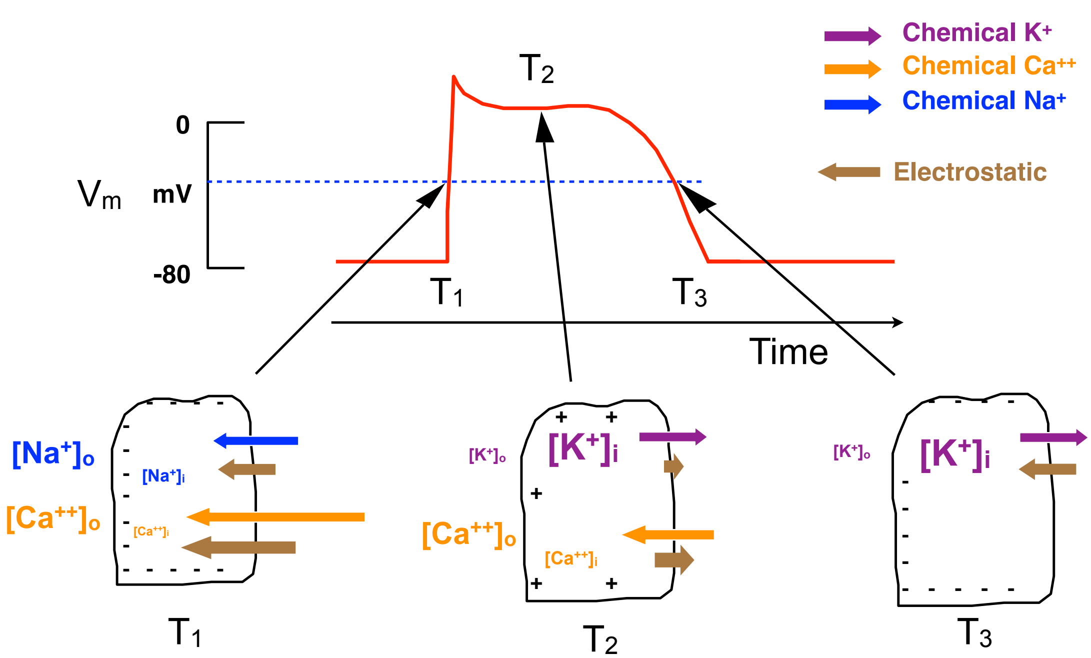


- What starts the positive feedback?
- What stops the positive feedback?

Cardiac Action Potential



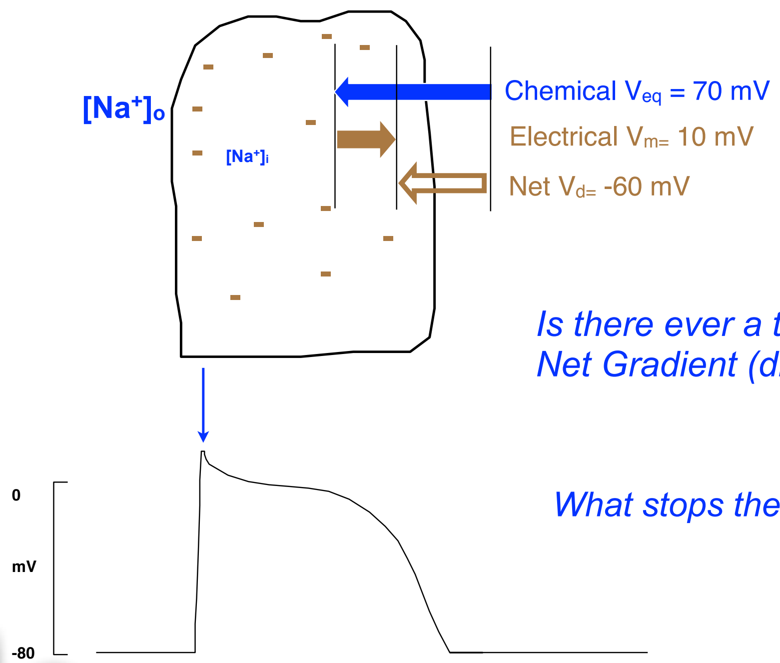
Cardiac Cell Currents



Note: Only includes relevant currents, i.e., for which G > 0

Driving Force: Sodium

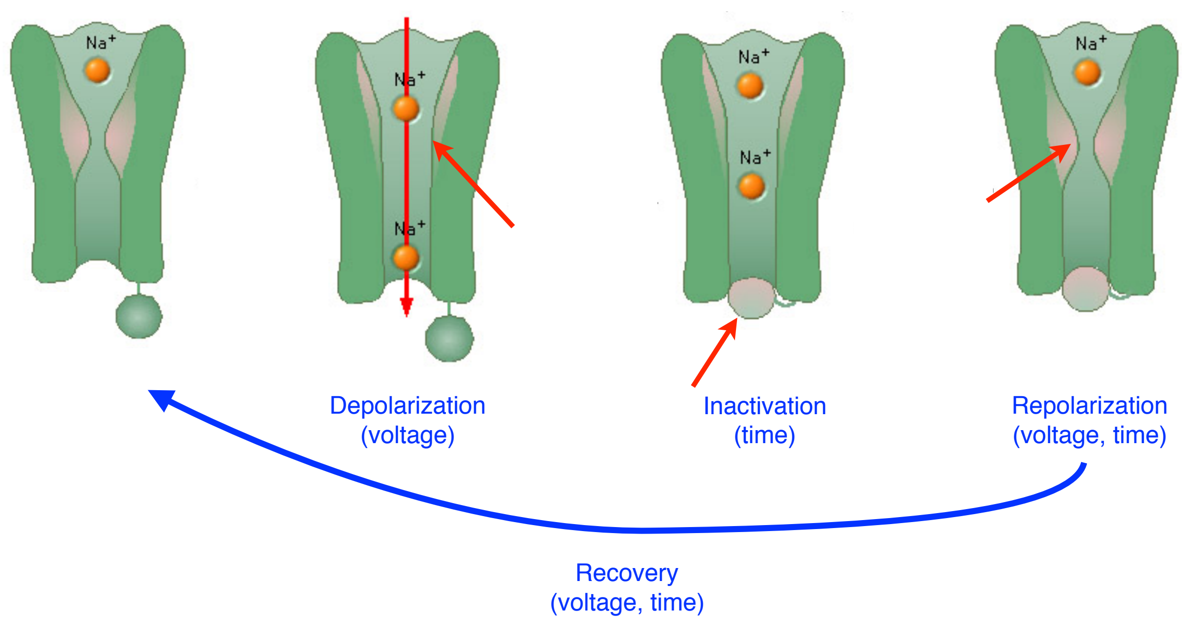
At AP peak:



Is there ever a time when the Net Gradient (driving force) = 0?

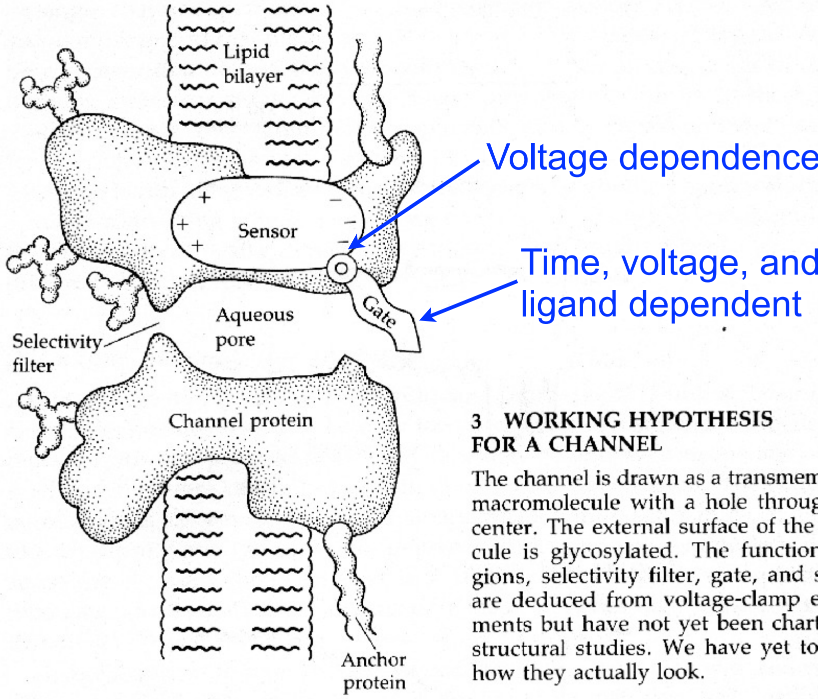
What stops the Na-current?

Sodium Channel Behavior



Note: voltage and time dependence

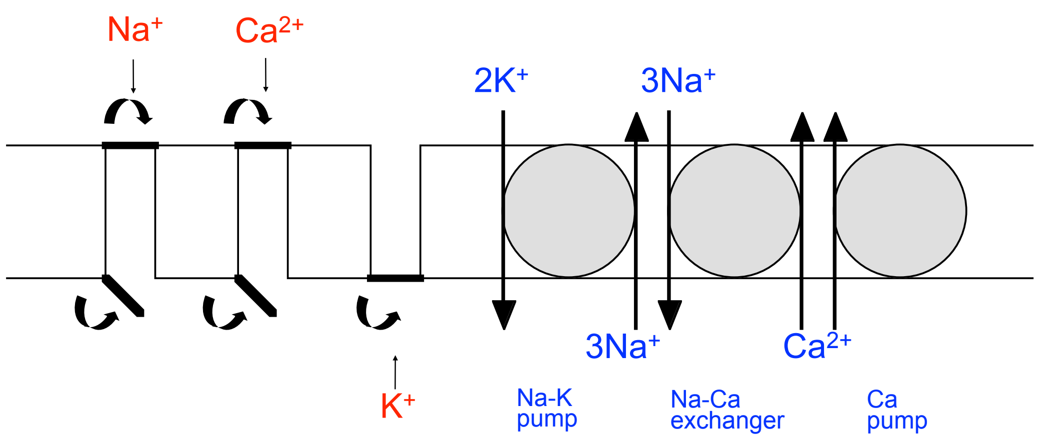
Summary: Membrane Channel



3 WORKING HYPOTHESIS FOR A CHANNEL

The channel is drawn as a transmembrane macromolecule with a hole through the center. The external surface of the molecule is glycosylated. The functional regions, selectivity filter, gate, and sensor are deduced from voltage-clamp experiments but have not yet been charted by structural studies. We have yet to learn how they actually look.

Cardiac Ion Currents



Ion channels

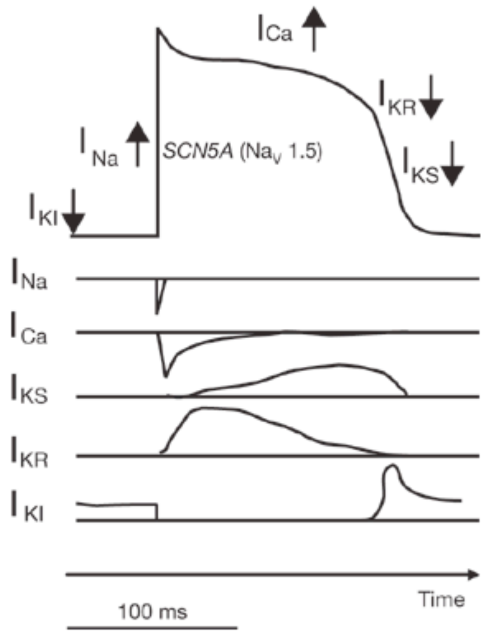
- Passive ion movement
- Driven by concentration and electrostatic gradients
- Channels are selective
- Gates control opening

Carrier mediated ion transport

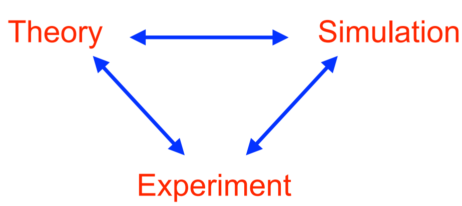
- Na-K and Ca pumps require ATP
- Capable of driving against concentration gradient
- Na-Ca exchange does not require ATP

Summary: Cardiac Action Potential

- Resting potential depends almost entirely on [K+].
- Na channels require time at potentials more negative than -65 mV in order to recovery. Without it, they will remain inactive.
- Slow (Ca++) channels have a threshold of -35 mV
- The plateau represents balance between Ca++ and K+ currents.
- Some cardiac cells depolarize spontaneously; most do not.



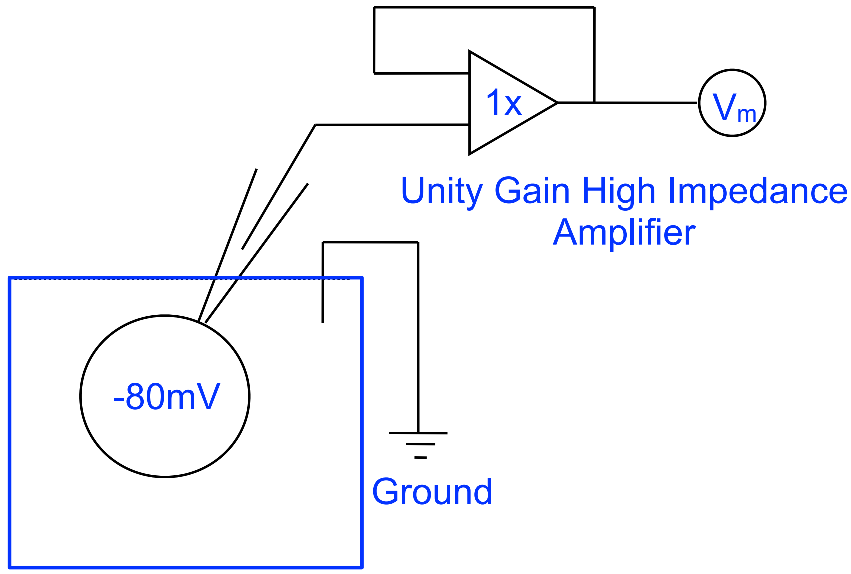
Nature Cell Biology **6**, 1039 - 1047 (2004)
Thomas J. Jentsch, Christian A. Hübner & Jens C. Fuhrmann



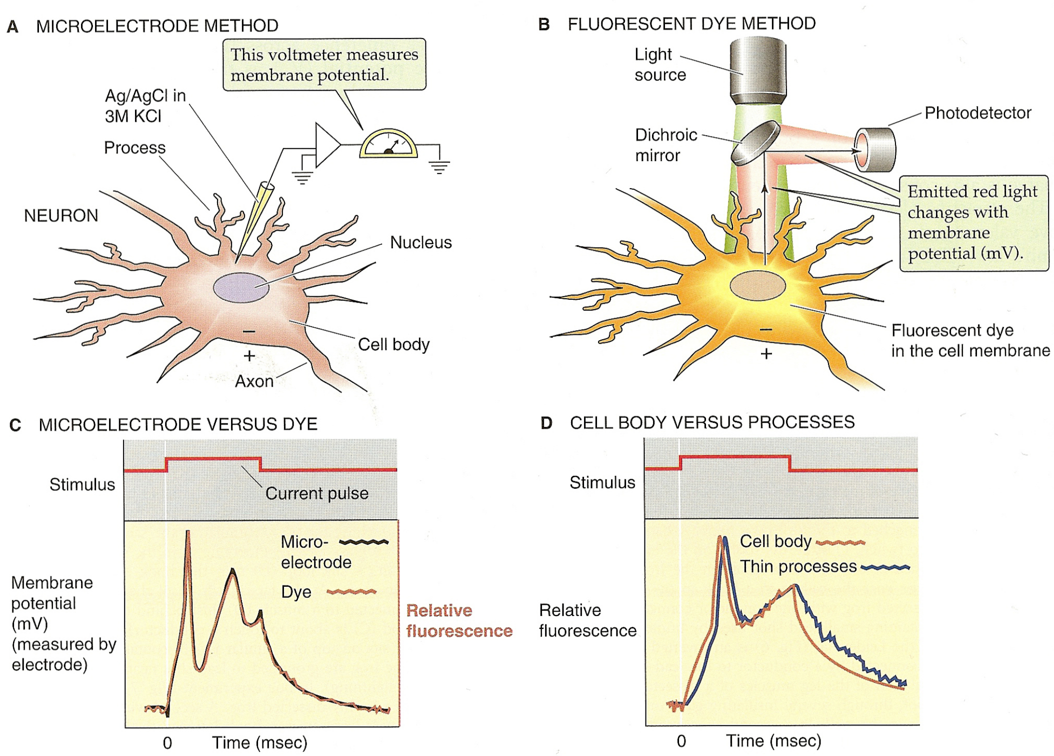
Measurement

= Experiment

Measuring Membrane Potential



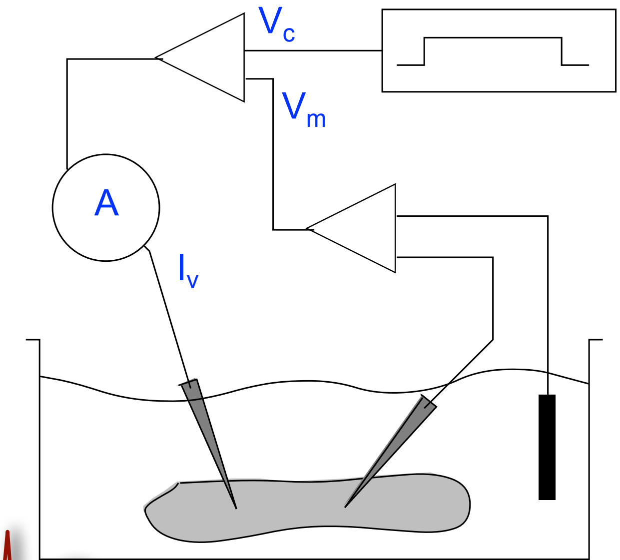
Optical Methods

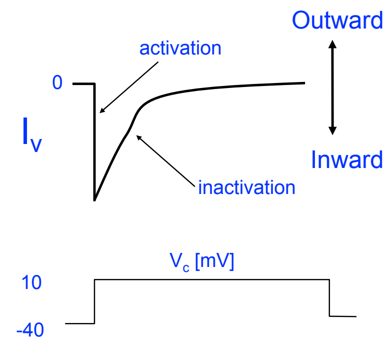


Whole Cell Currents (Voltage Clamp)

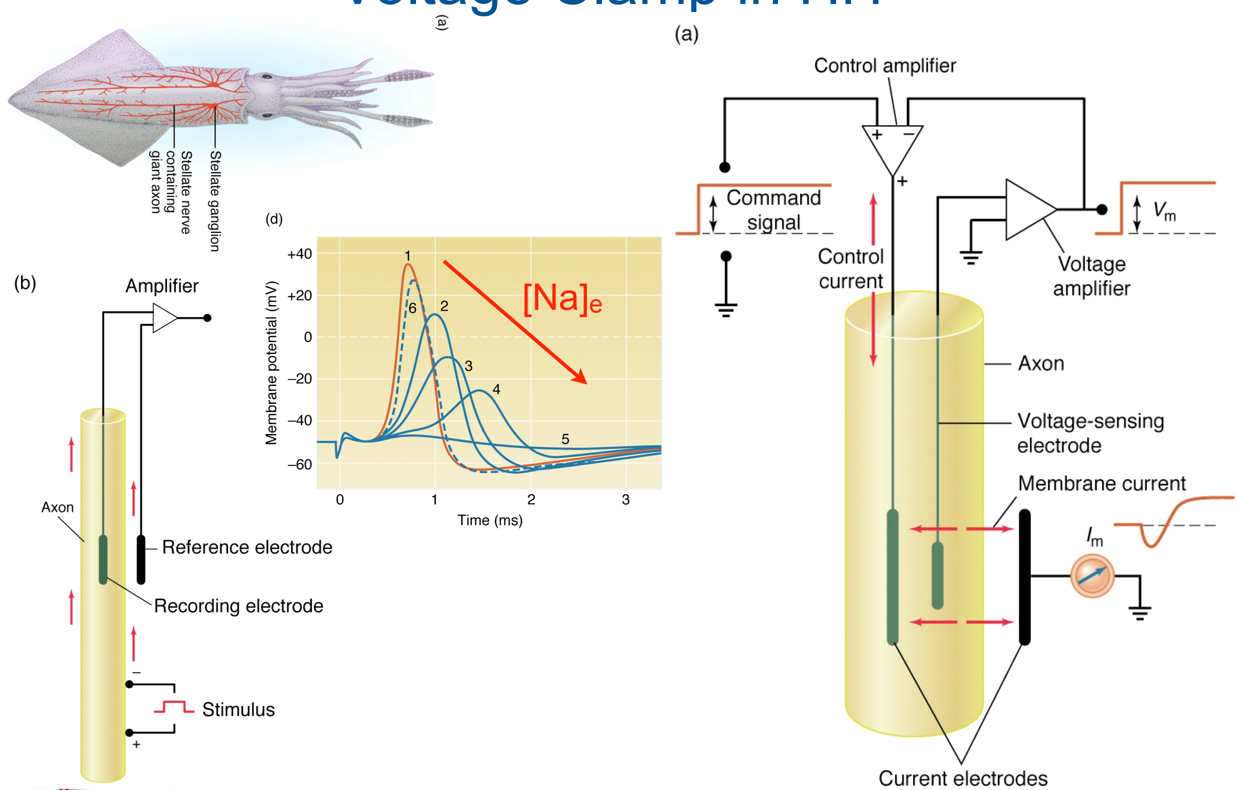
For each ion type:

$$i_K(V,t) = (V_m - E_K)g_K(V,t)$$



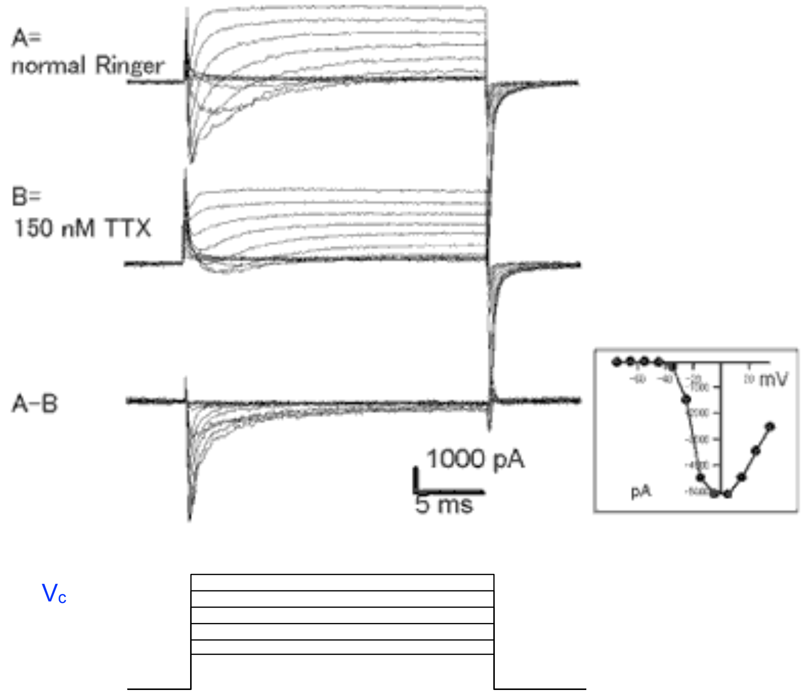


Voltage Clamp in HH

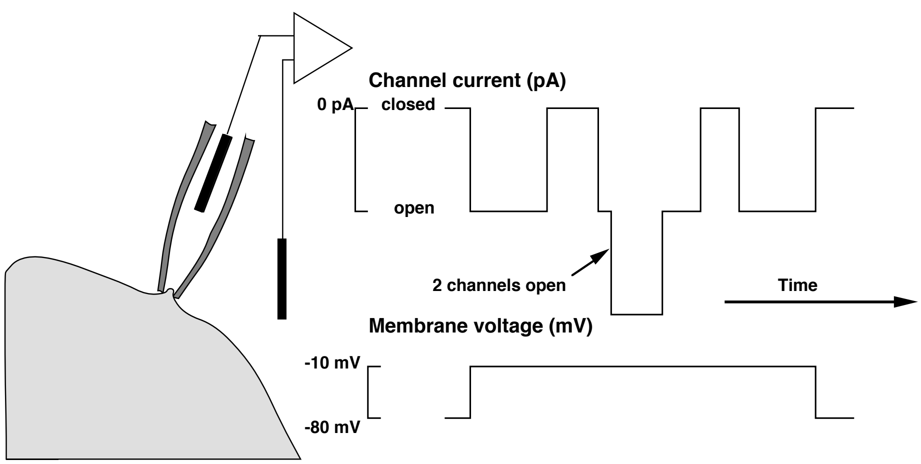


Voltage Clamp Results

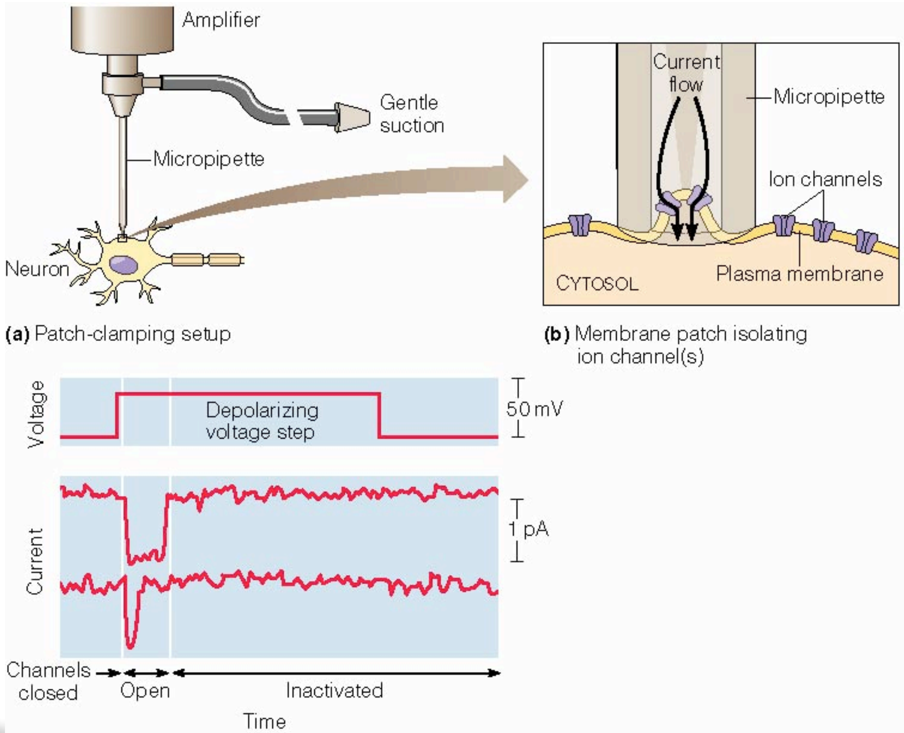
- Note use of Na Channel blocker to isolate Na current
- IV curve is nonlinear



Single Channel (Unitary) Currents

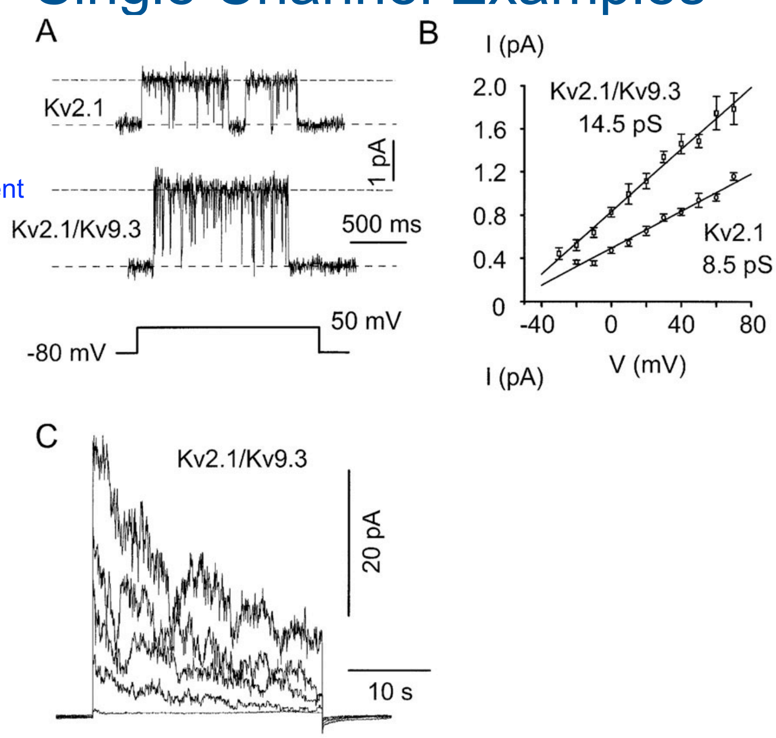


Membrane Patch Clamp



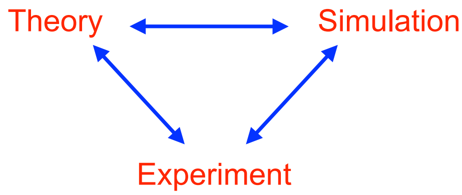
Single Channel Examples

Two different channels



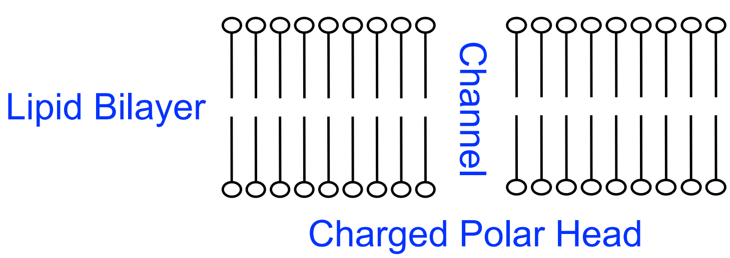
Current/ Voltage characteristic

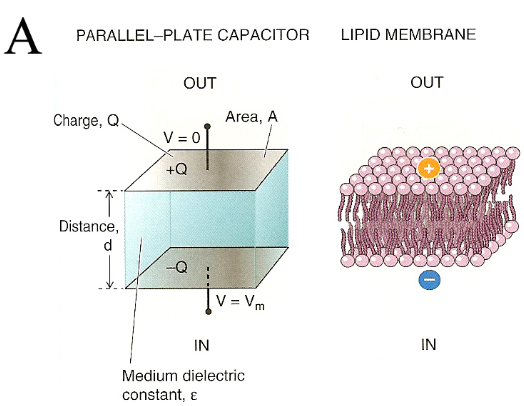
Current as function of voltage

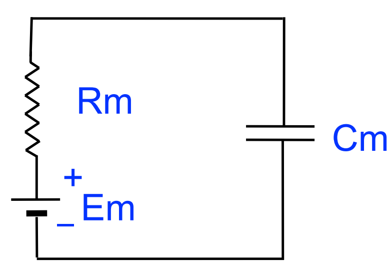


Simulations

Membrane Equivalent Circuit

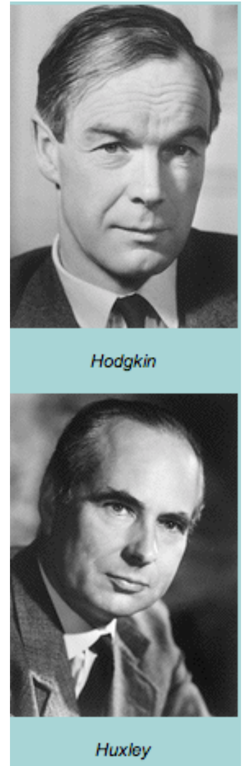




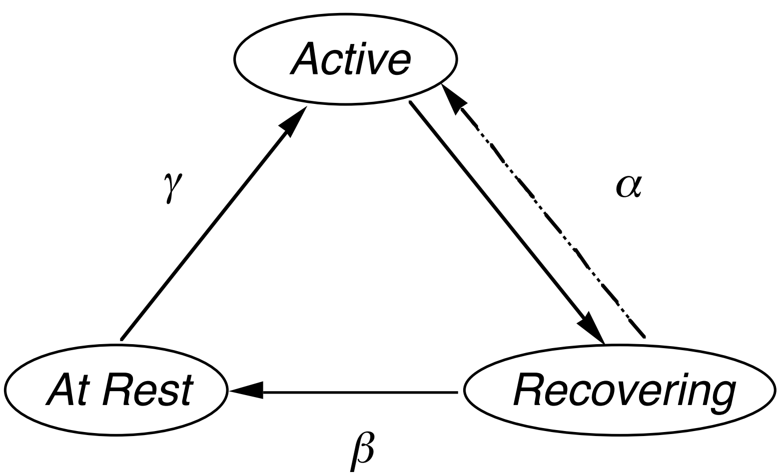


Hodgkin-Huxley Formalism

- Qualitative concepts
- Quantitative formulation and simulation (see next lecture)
- Sir Alan Hodgkin
  - 1914-1988
- Sir Andrew Huxley
  - 1917-2012
  - brother of Aldous Huxley
- Nobel Prize: 1963



Single Channel Model

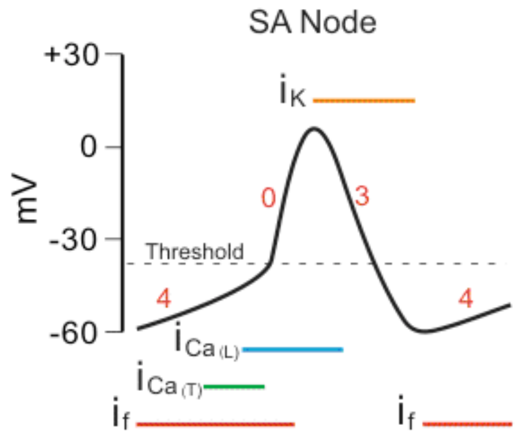


α, β, γ: state transition probabilities, (functions of v and t)

HH Derivation and Homework Assignment

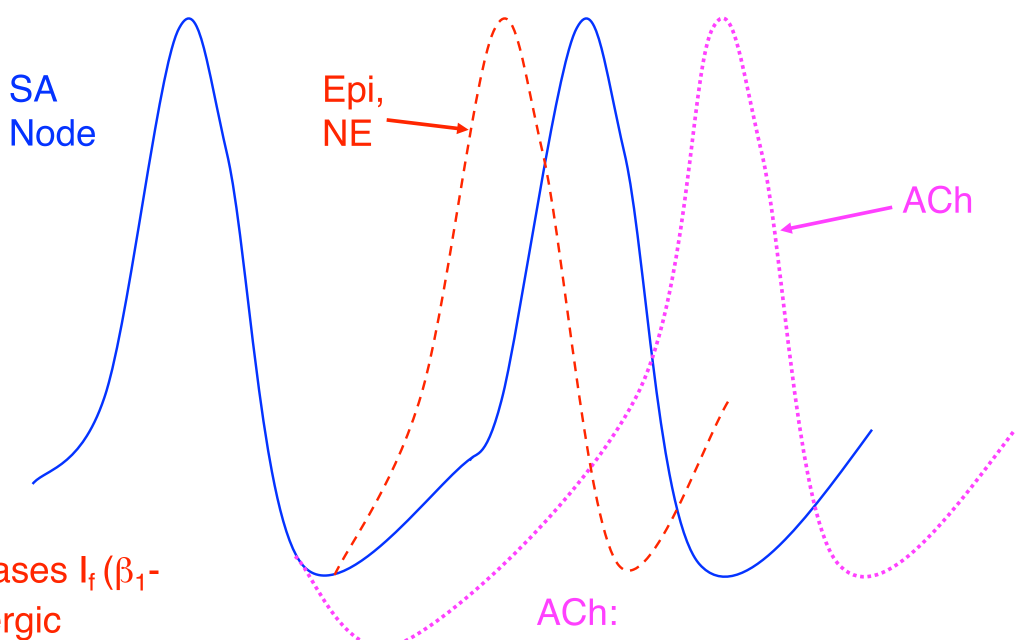
Control of Heart Rate - Pacemaking

Pacemaker Cells in the Heart



- Note difference in basic AP shape: why?
- Note unstable (depolarizing baseline): why?

Regulation of Heart Rate



Epi/NE;

- increases I_f (β_1-adrenergic receptor)

ACh:

- increases p_K
- reduces I_f

(muscarinic receptor)