Mathematical models of action potentials

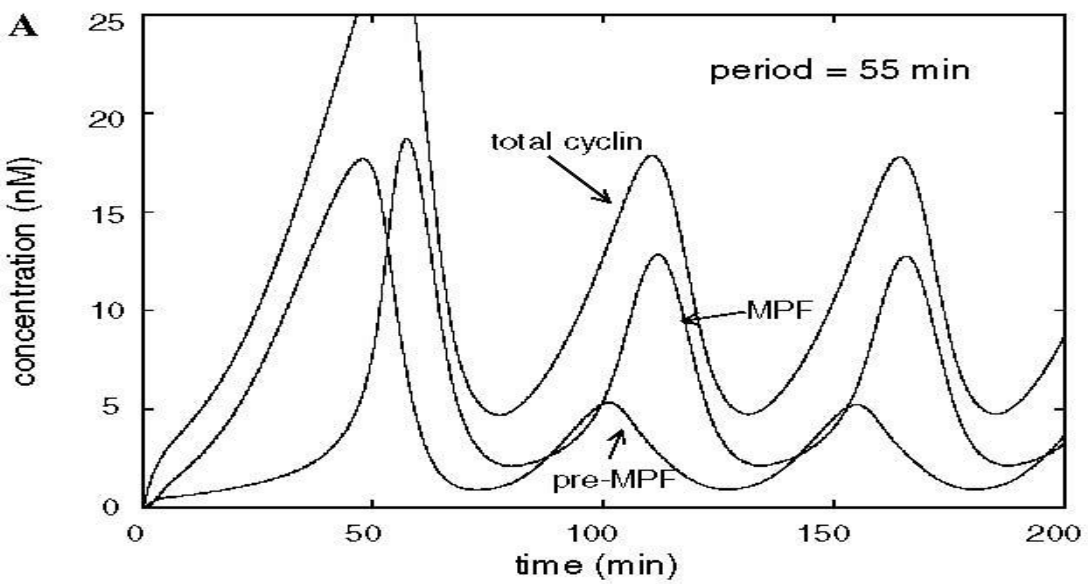
Part 1

Icahn School of Medicine at Mount Sinai

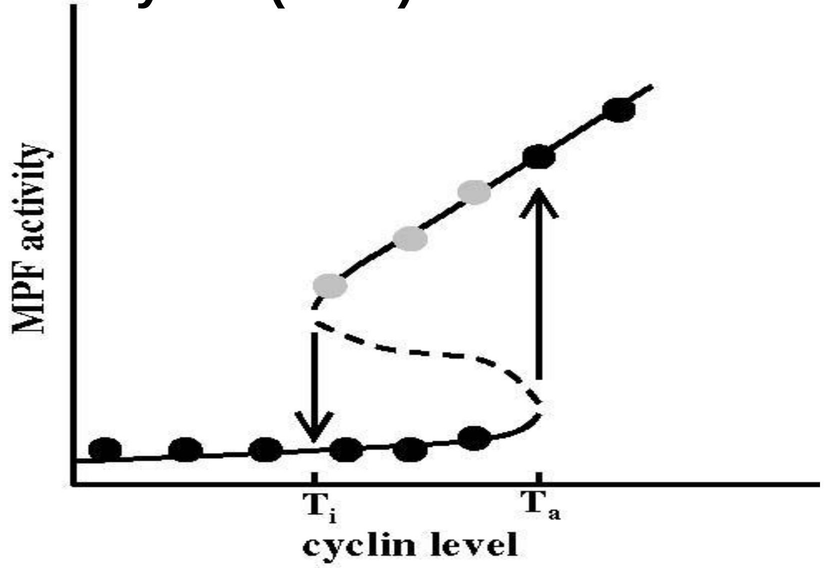
SBCNY

Relating to previous lectures

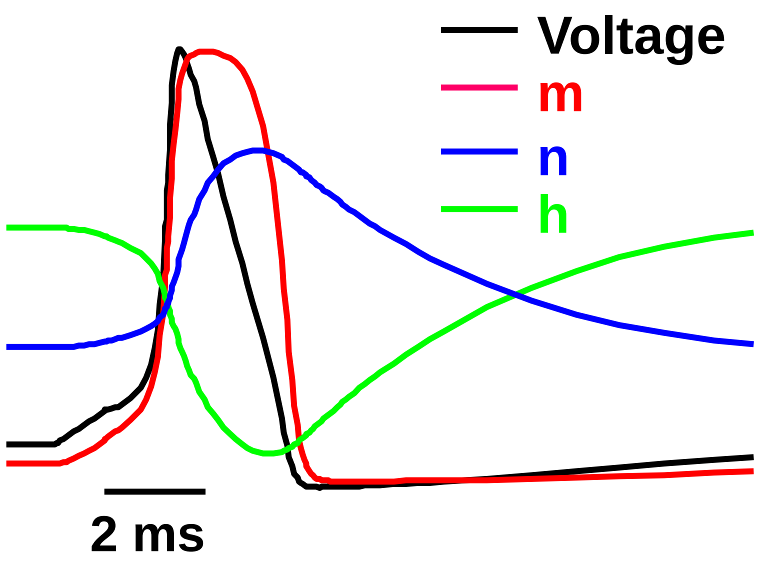
Cell cycle model

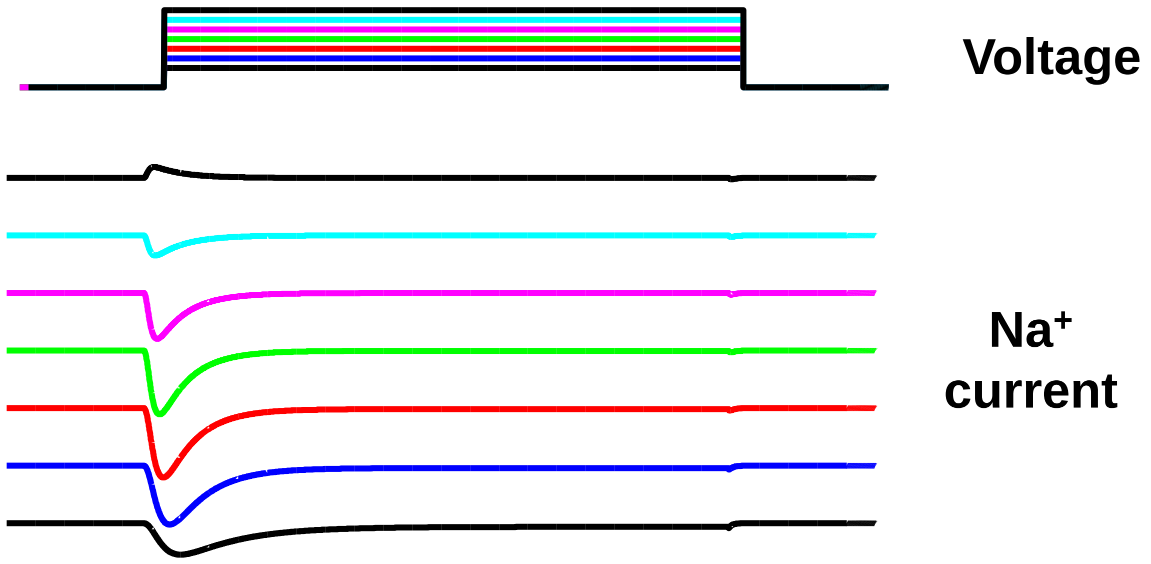


Sible & Tyson (2007) *Methods* 41:238-247



Action potential model





Simulation of simplified experiment was critical for both model development and understanding

Outline: Part 1

Biology

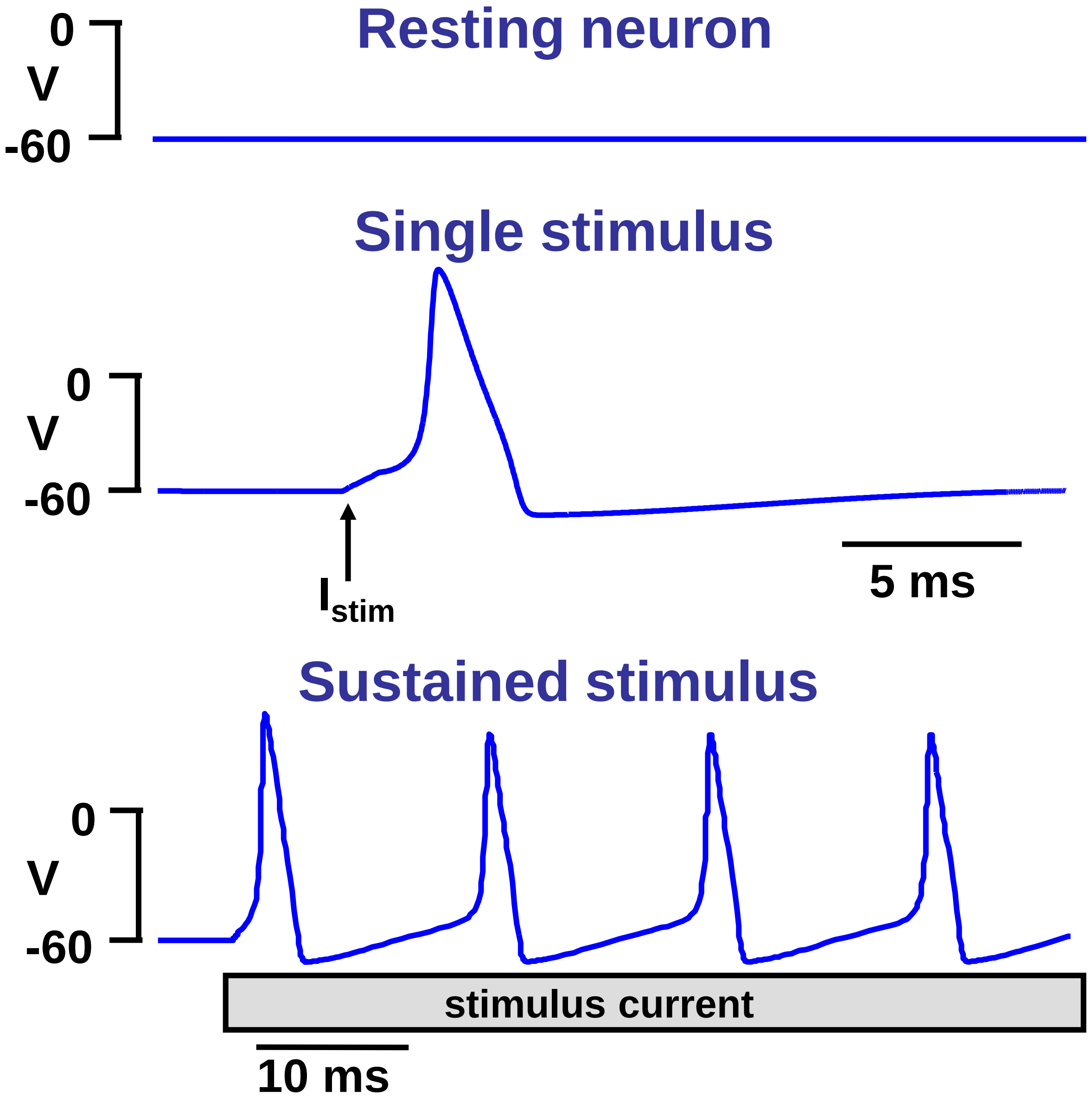
Interesting nonlinear behaviors of excitable cells

Definitions of terms

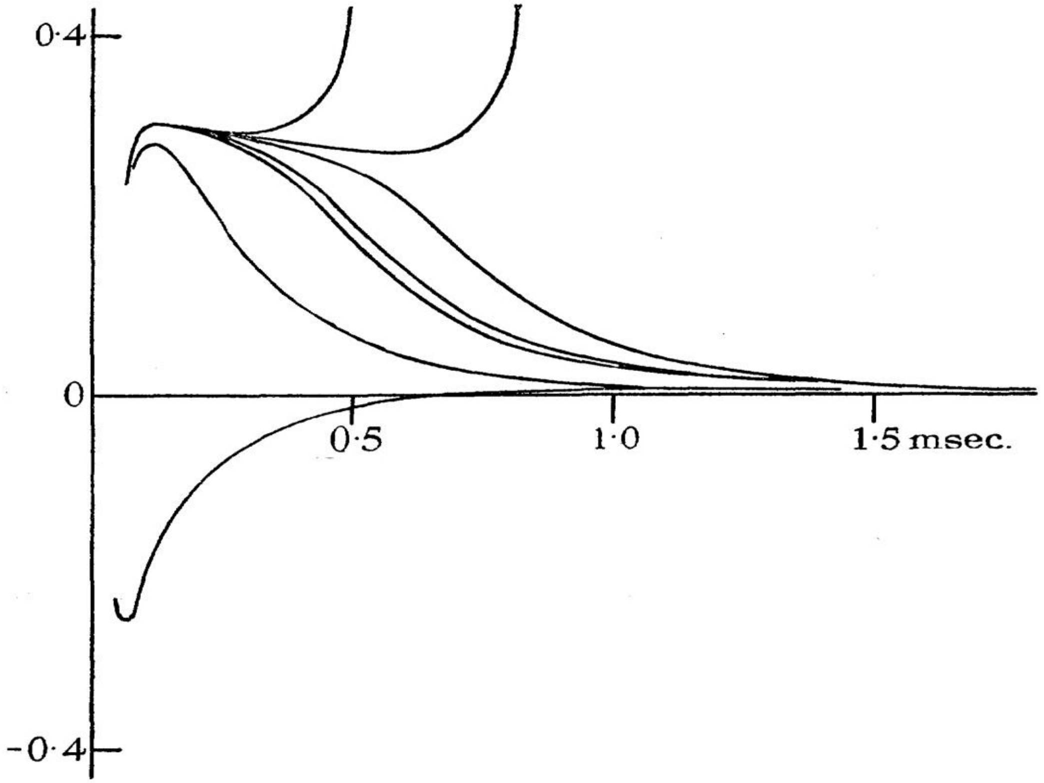
Electrochemical potential and driving force

Action potentials in squid giant axon

They exhibit unusual nonlinear behavior



Sharp response threshold



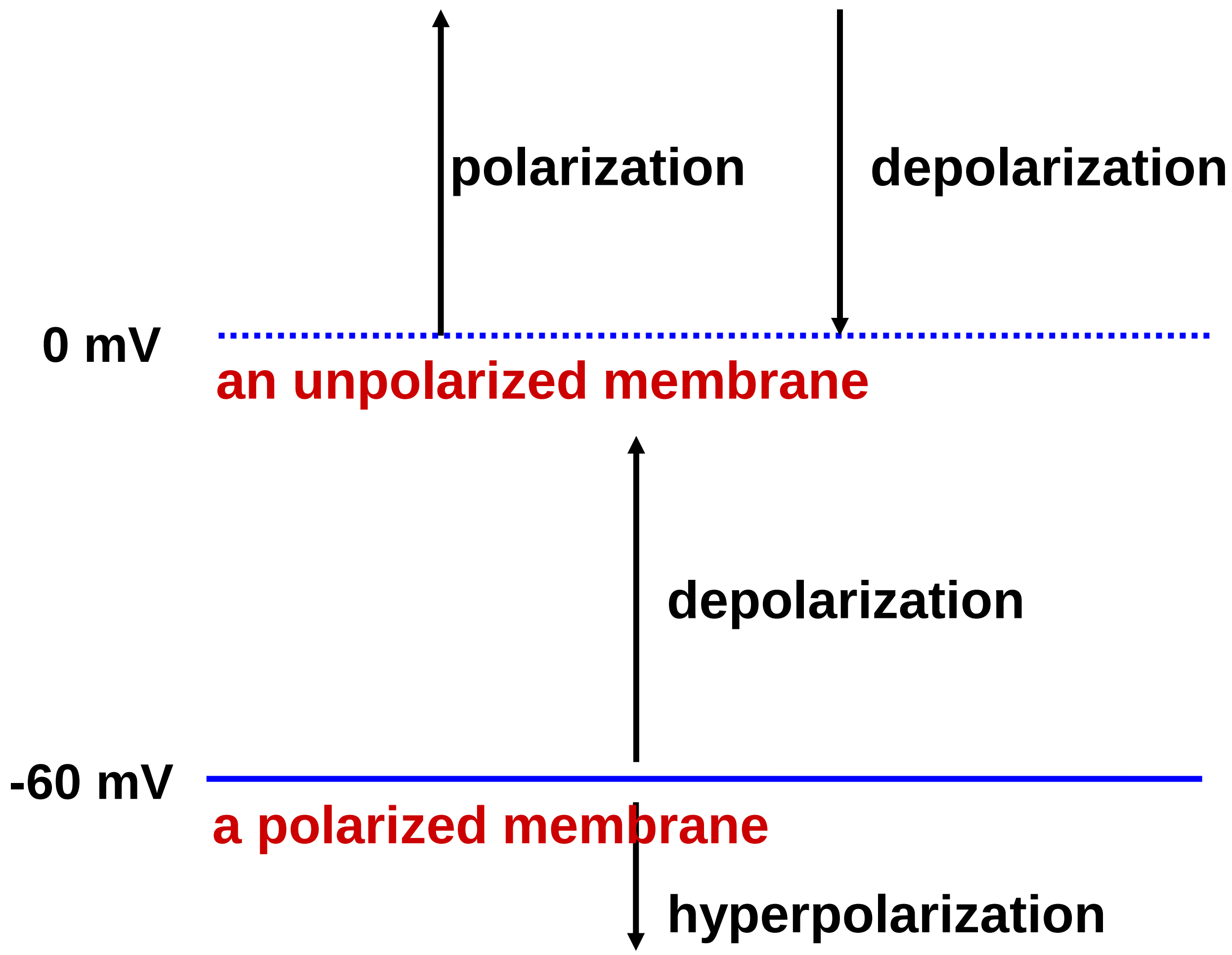
Hodgkin (1938), *Proc. Roy. Soc. B* 126:87-121.

How can we account for this behavior quantitatively?

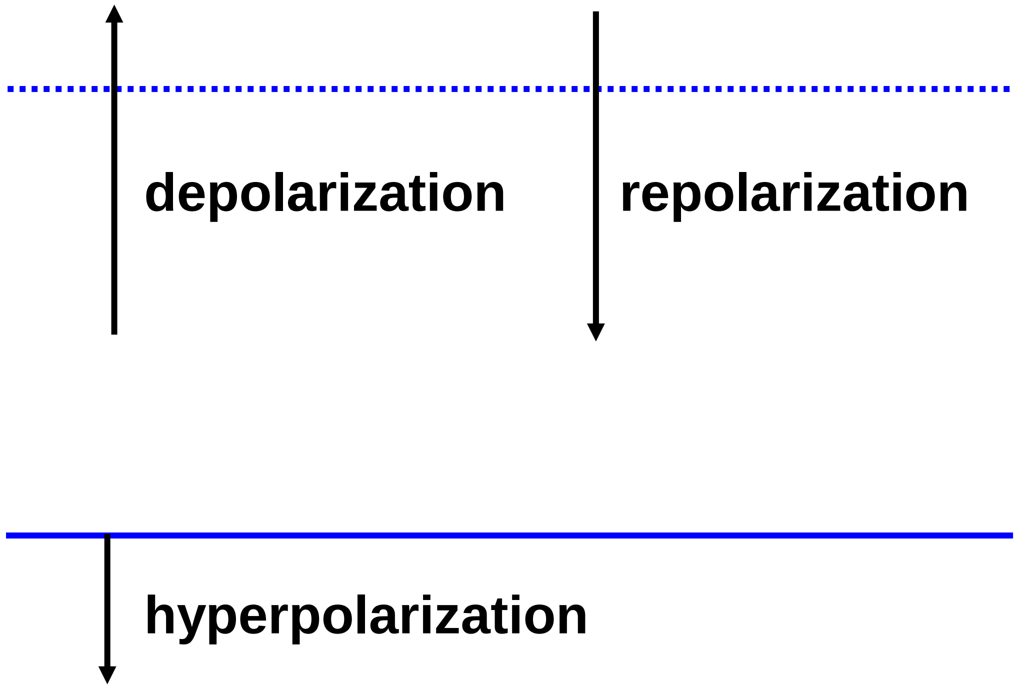
Important definition of terms

Depolarization, repolarization, and hyperpolarization

Technically correct

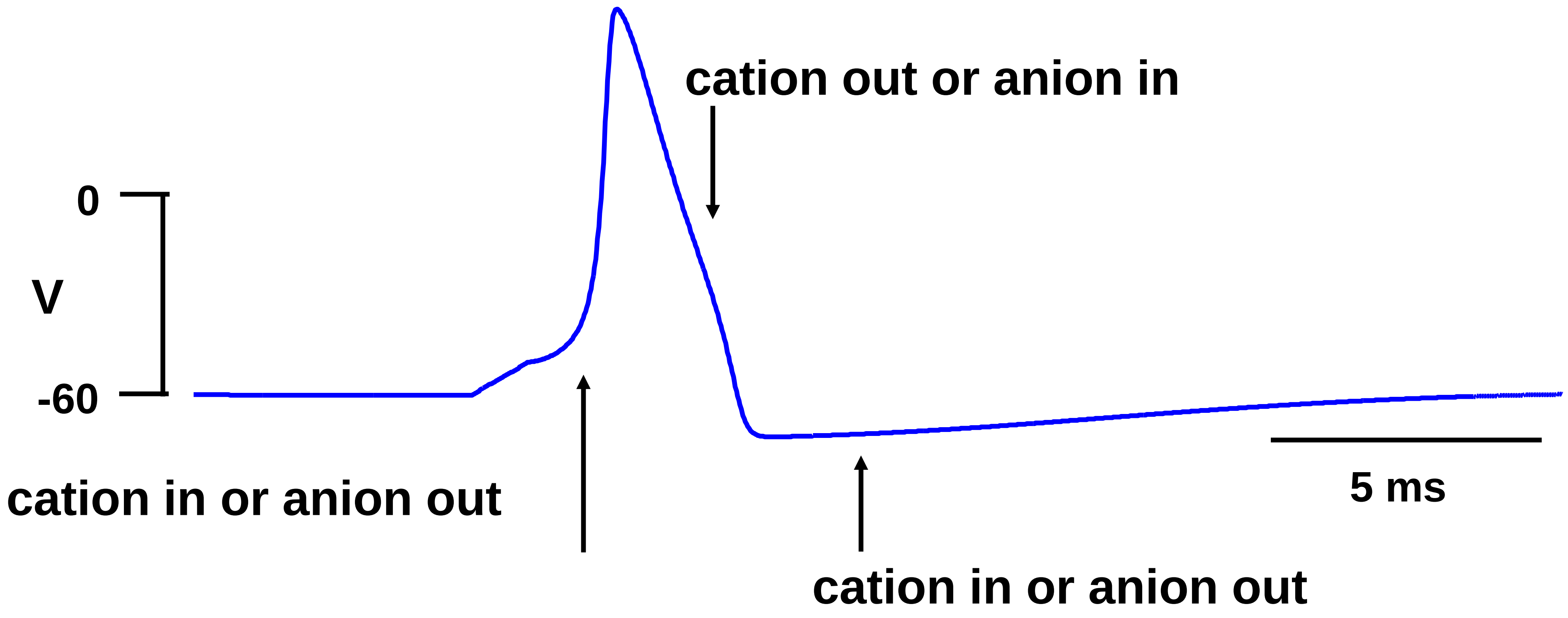


Colloquial



Voltage changes result from ion movements

Cations flowing in depolarize the membrane
Cations flowing out repolarize/hyperpolarize the membrane



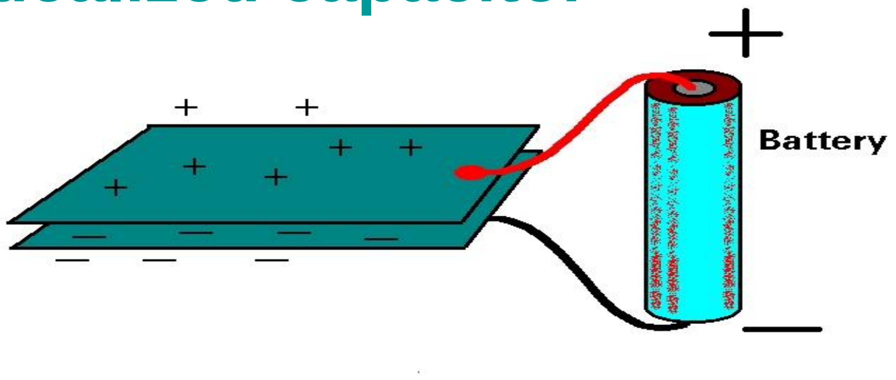
Two questions:

(1) How to describe depolarization/repolarization quantitatively?
(2) Which ions are the most likely candidates?

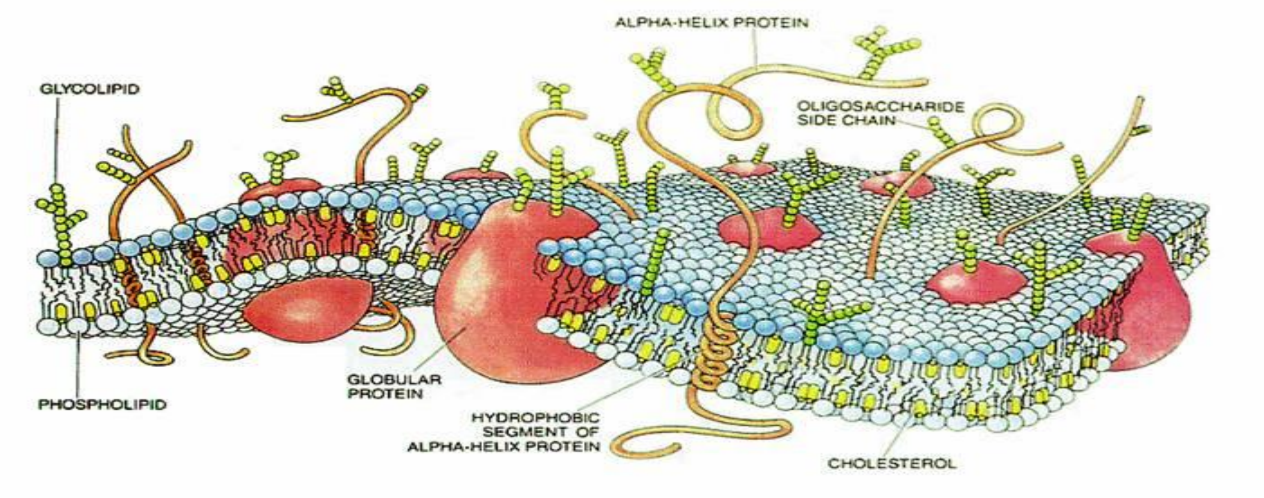
The cell membrane is a capacitor

Idealized capacitor

$$C\frac{dV}{dt} = I$$



Cell membrane

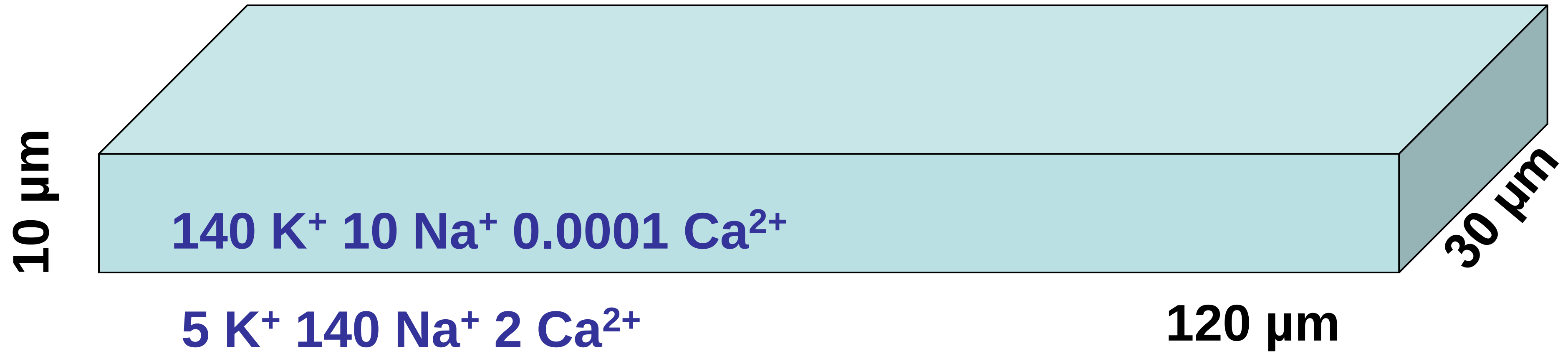


This is where we get our differential equation for membrane voltage

$$C_m\frac{dV}{dt} = -I_{ion}$$

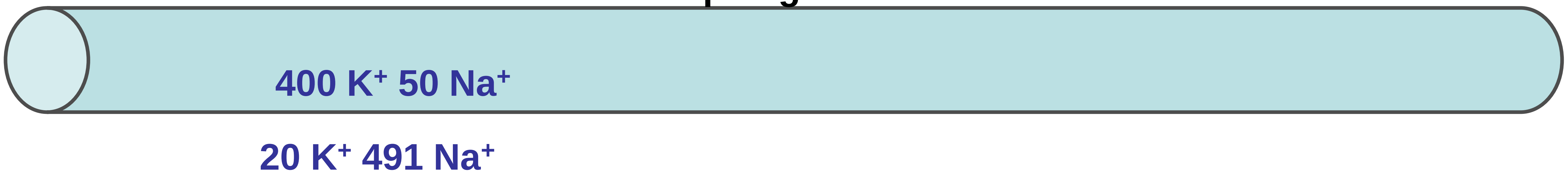
Ionic concentrations in cells

Mammalian ventricular myocyte



(concentrations in mM)

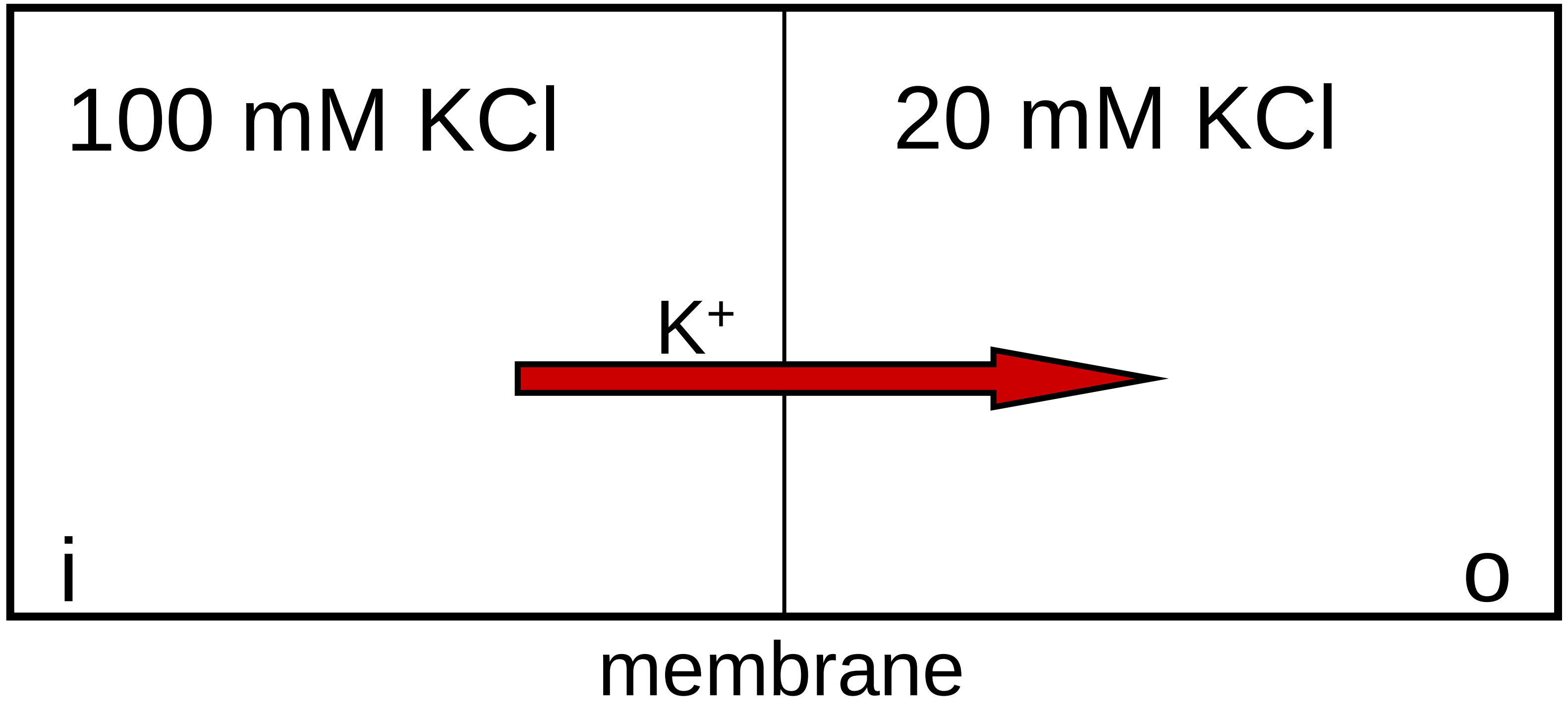
Squid giant axon



Thus, diffusion will drive Na^+ inward, K^+ outward

These movements will depolarize or hyperpolarize the membrane, respectively

Concentration Cell



Membrane permeable to K^+ but not to Cl^-

Qualitatively, what happens when [KCl] on left is increased?

1) K^+ ions flow from left to right.
2) Excess positive ions on right produce voltage difference
3) Voltage difference opposes left→right movement of K^+
4) Eventually, an equilibrium is reached.

How can we understand this more quantitatively?

Electrochemical potential

$$\mu = \mu^0 + RT \ln C + zFV$$

What is the significance of each term?

μ^0 **this is the "standard" electrochemical potential**

(same on both sides, can ignore)

$RT \ln C$ **this term describes diffusion: a higher concentration leads to a higher electrochemical potential**

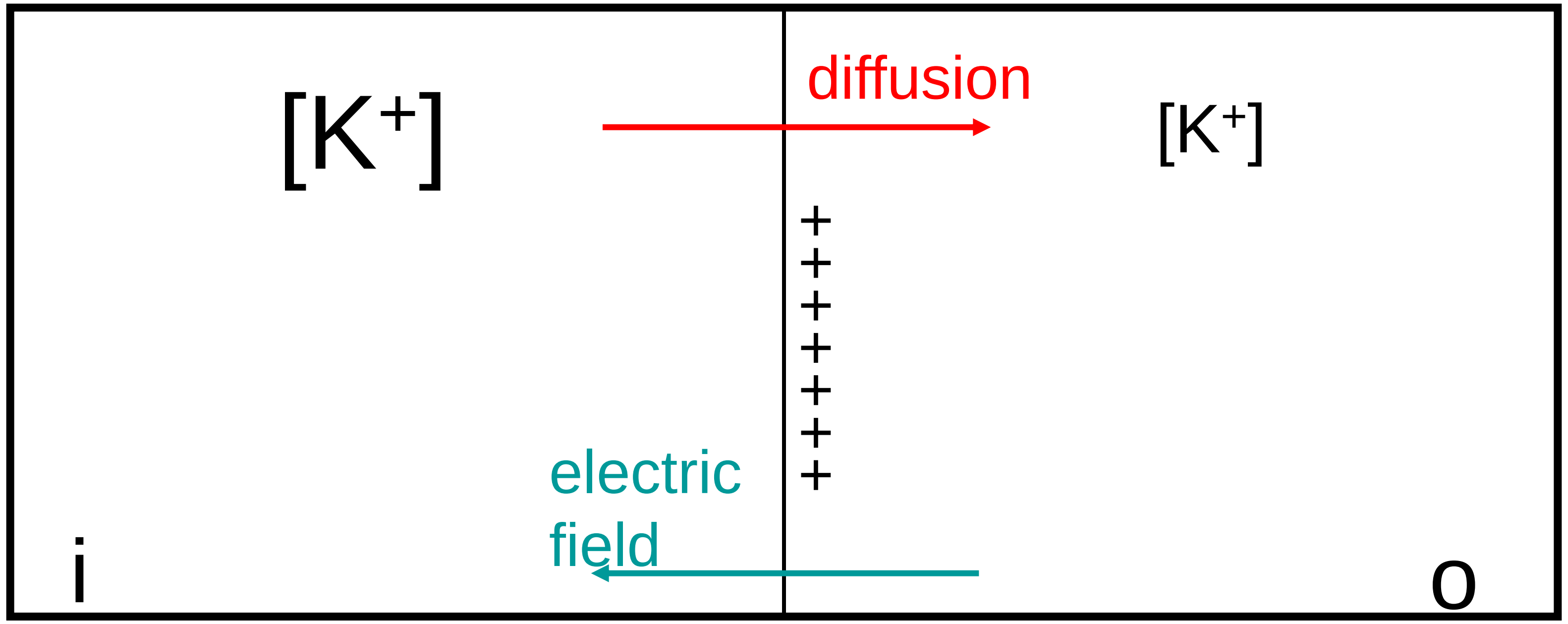
zFV **this term describes electrical effects: greater voltage means greater electrochemical potential, for positively charged species only (z > 0)**

Like a ball rolling down a hill, species want to move from higher to lower electrochemical potential

Units are J/mol

Energy, normalized by how much is present

Electrochemical potential



membrane

At equilibrium, $\mu_i = \mu_o$

$$RT \ln C_i + zFV_i = RT \ln C_o + zFV_o$$

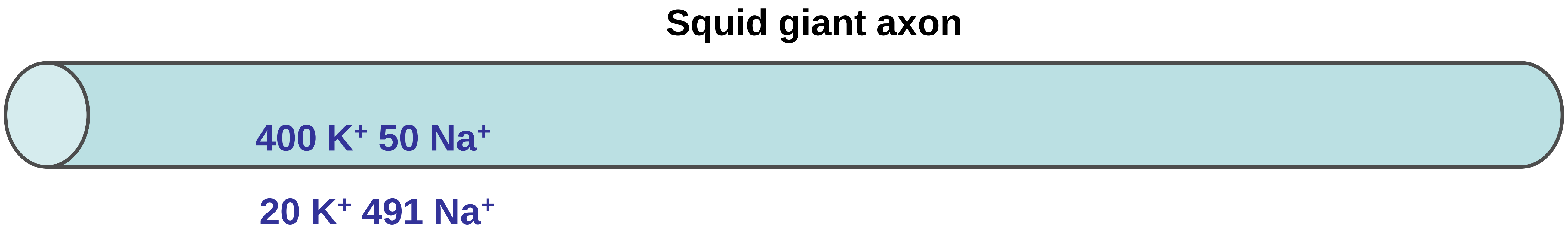
Then, rearranging terms:

$$zF(V_i - V_o) = RT(\ln C_o - \ln C_i)$$

$$V_i - V_o = \frac{RT}{zF} \ln \frac{C_o}{C_i}$$

This is definition of equilibrium or Nernst potential

So in the squid giant axon



Each ion associated with a Nernst potential

$$E_X = \frac{RT}{zF} \ln \frac{[X]_o}{[X]_i}$$

$E_K = -72\text{ mV}$ $E_{Na} = +55\text{ mV}$

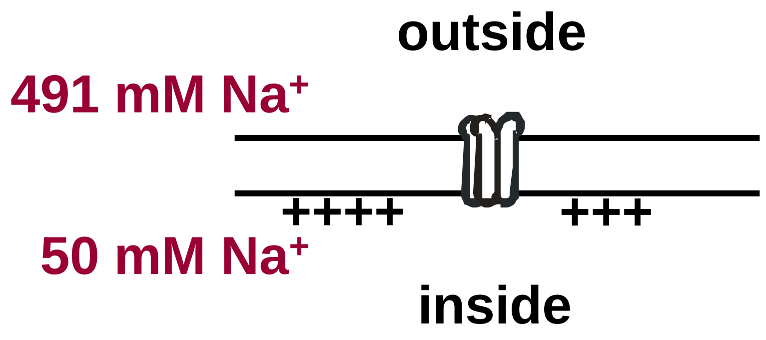
The distance away from the reversal potential, $V\text{-}E_X$ is the "driving force" for ion X.

This is basically converting electrochemical potential from units of J/mol to units of volts (J/C), i.e.

$$V - E_X = \frac{\Delta\mu_X}{F}$$

Driving force and ionic currents

Defined as: $V - E_{Na}$



If $V - E_{Na} > 0$, $\Delta\mu_{Na} > 0$, Na^+ moves out of the cell

If $V - E_{Na} < 0$, $\Delta\mu_{Na} < 0$, Na^+ moves into the cell

Ionic current, then, can be calculated as:

$$I_{Na} = g_{Na}(V - E_{Na})$$

Units:

- V, E_{Na}: mV
- I_{Na}: μA/cm^2 (μA/μF)
- g_{Na}: mS/cm^2 (mS/μF)

By convention, inward current is negative

In general, g_X can be dependent on both V and time

Summary

Neurons exhibit complex non-linear behavior that is challenging to describe mathematically.

Changes in membrane potential (voltage) result from ion movements across the cell membrane.

Electrochemical potentials determine which direction ions move, with the Nernst potential representing equilibrium.