Sensory and Motor

Class 2

Announcements

- Remember to find a partner and submit a topic with your group!
- Bring a Calculator!
- Be cognizant of quiz dates, presentation dates, and test dates.

Goals for class today

- Learn how cells (not just neurons) set a resting membrane potential.
- Introduction to ion channels
- The action potential

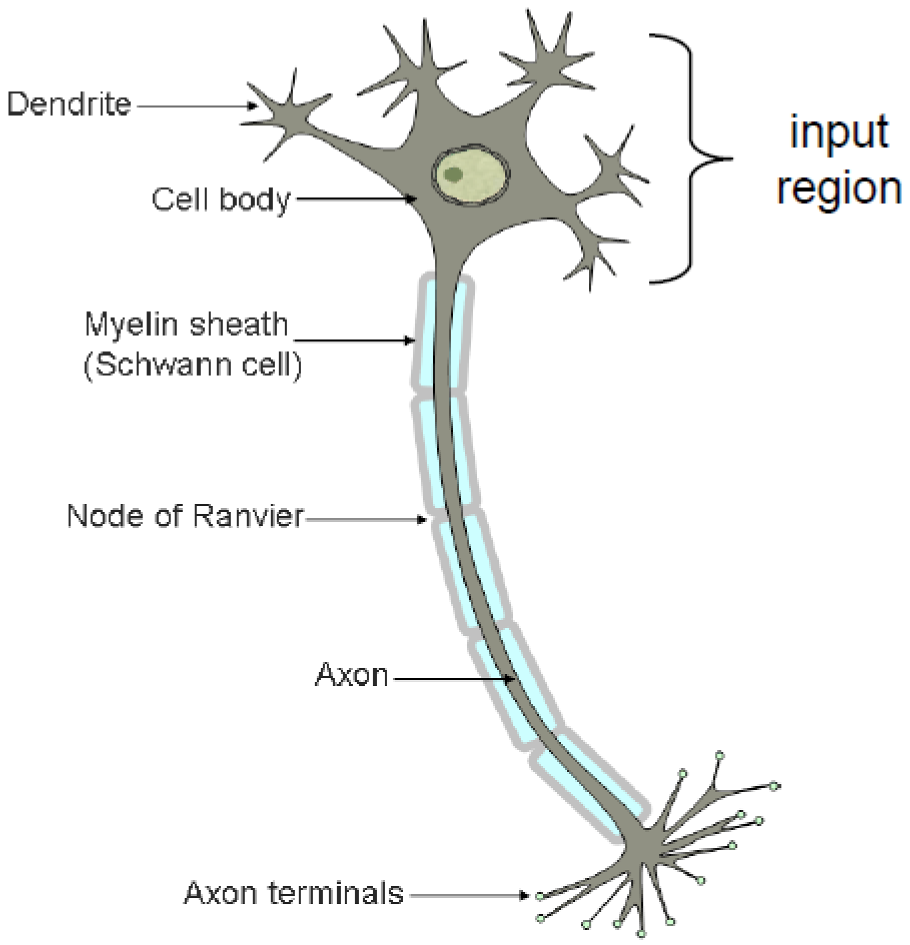
The neuron – a specialized cell type that can signal over long distances

There are 3 main <u>regions of the neuron</u>:

Dendrites

Cell body (or soma)

Axon



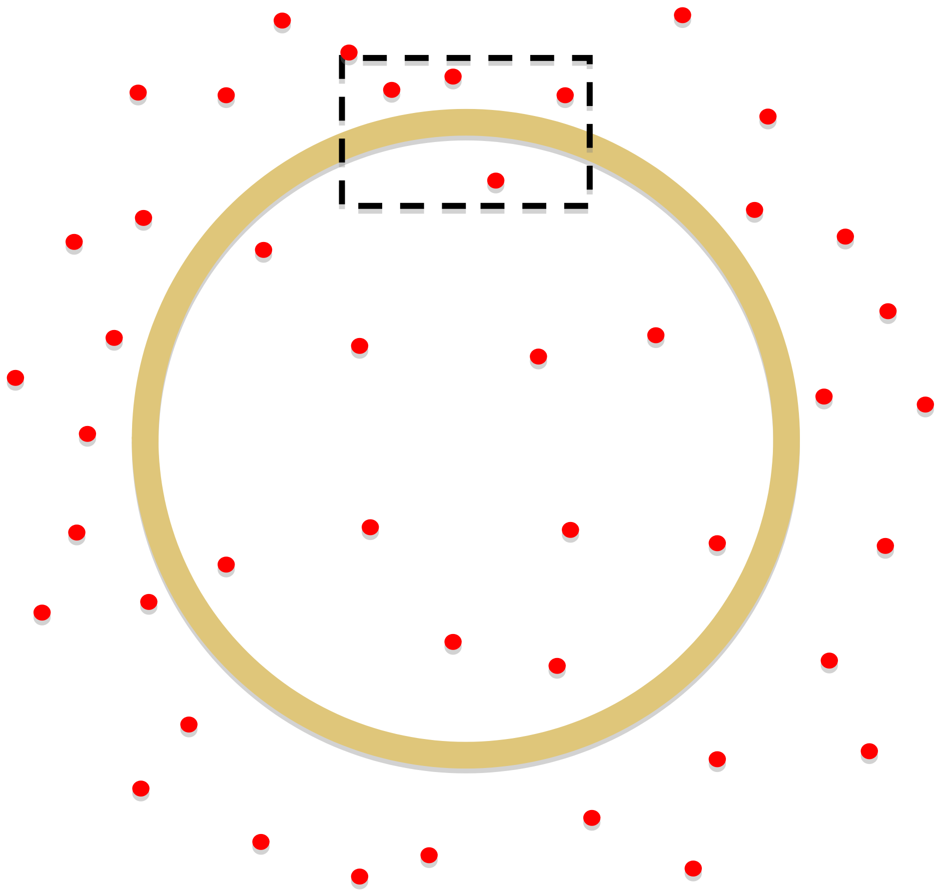
http://scienceblogs.com/neurotopia/2006/07/stem_cells_for_spinal_cord_inj.php

<u>Terminology</u>
axon
dendrite

Understanding what dictates the membrane potential across a biological membrane is one of the most fundamental concepts in neuroscience!!

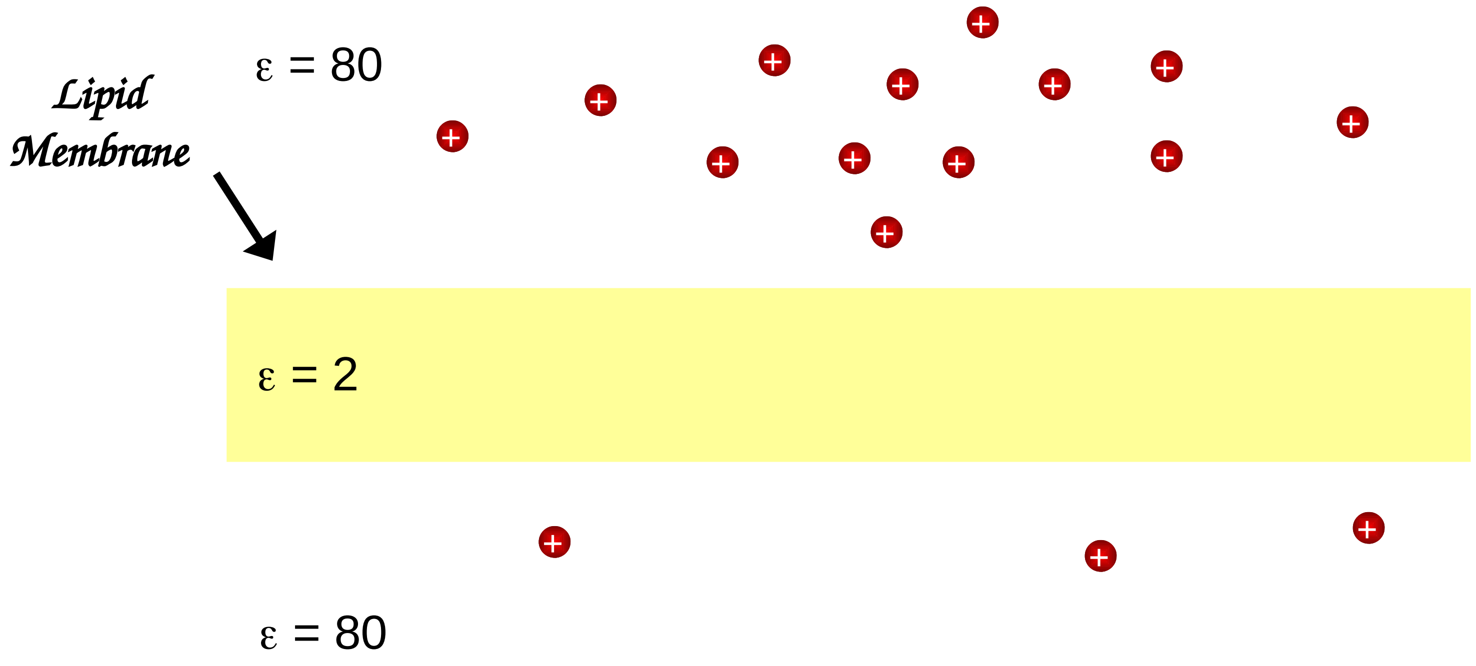
Biological Cell Membrane

Conceptual Model



Biological Cell Membrane

Conceptual Model



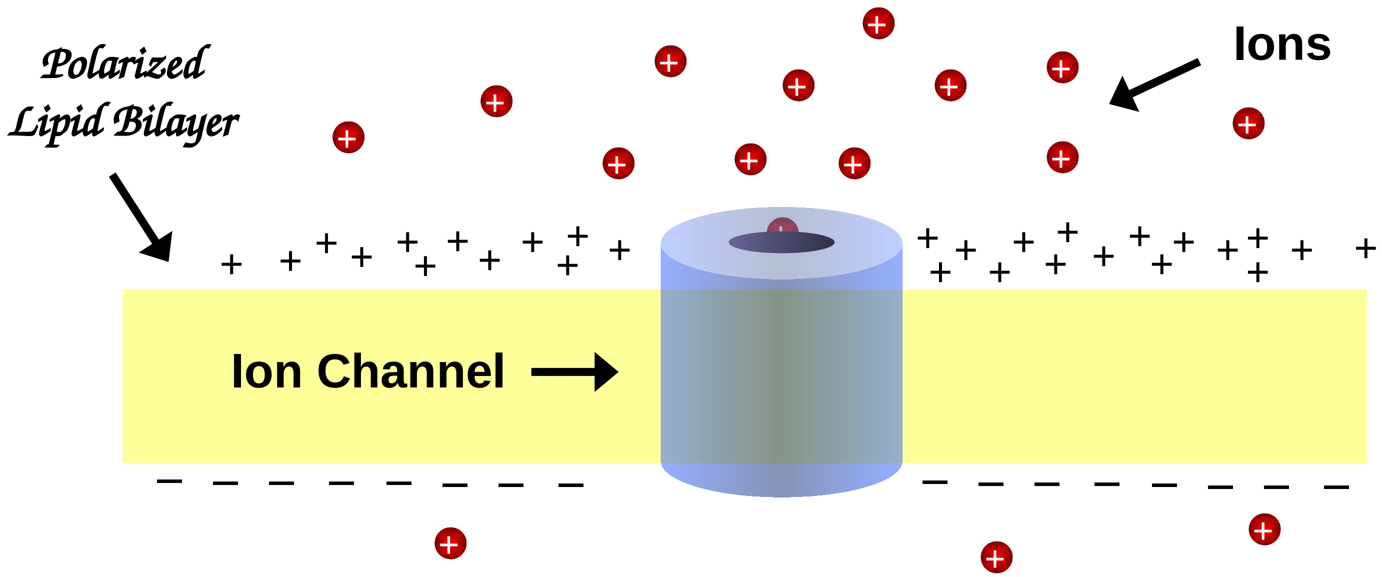
The lipid bilayer of biological membranes are oily barriers that cannot solvate ions (i.e., the dielectric constant of the membrane is very low)

Thus, the lipid bilayer represents an insurmountable energy barrier for ions
How do cell membranes lower this energy barrier?

Permittivity (dielectric constant) is a material property that affects the Coulomb force between two point charges in the material.

Biological Cell Membrane

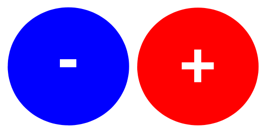
Conceptual Model



Ion channels are membrane-spanning proteins containing aqueous pores that reduce the lipid bilayer energy barrier by providing an alternate pathway for ions to cross the membrane. Thus, ion channels are catalytic membrane proteins.

Attraction between two opposite charges

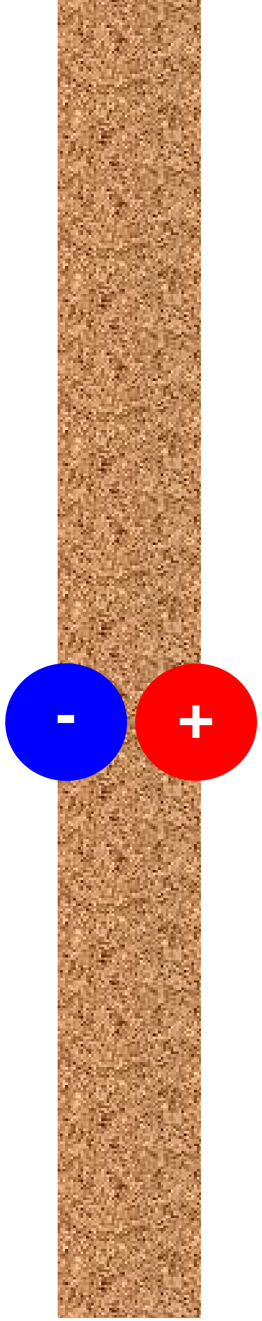
Attraction between two opposite charges



Low Energy

(charges cannot do work)

Charges separated by an insulator



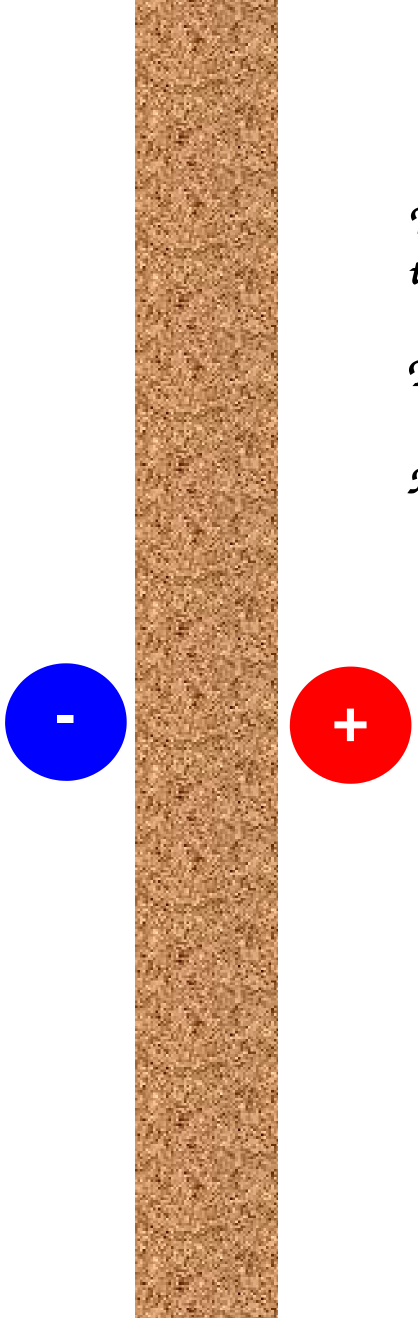
Work was done to separate the charges. Now there is a voltage across the insulator.*

The insulator is "energized"

How is this done in biological cell membranes?

** 1 Volt = 1 Joule / 1 Coulomb*

Charges separated by an insulator



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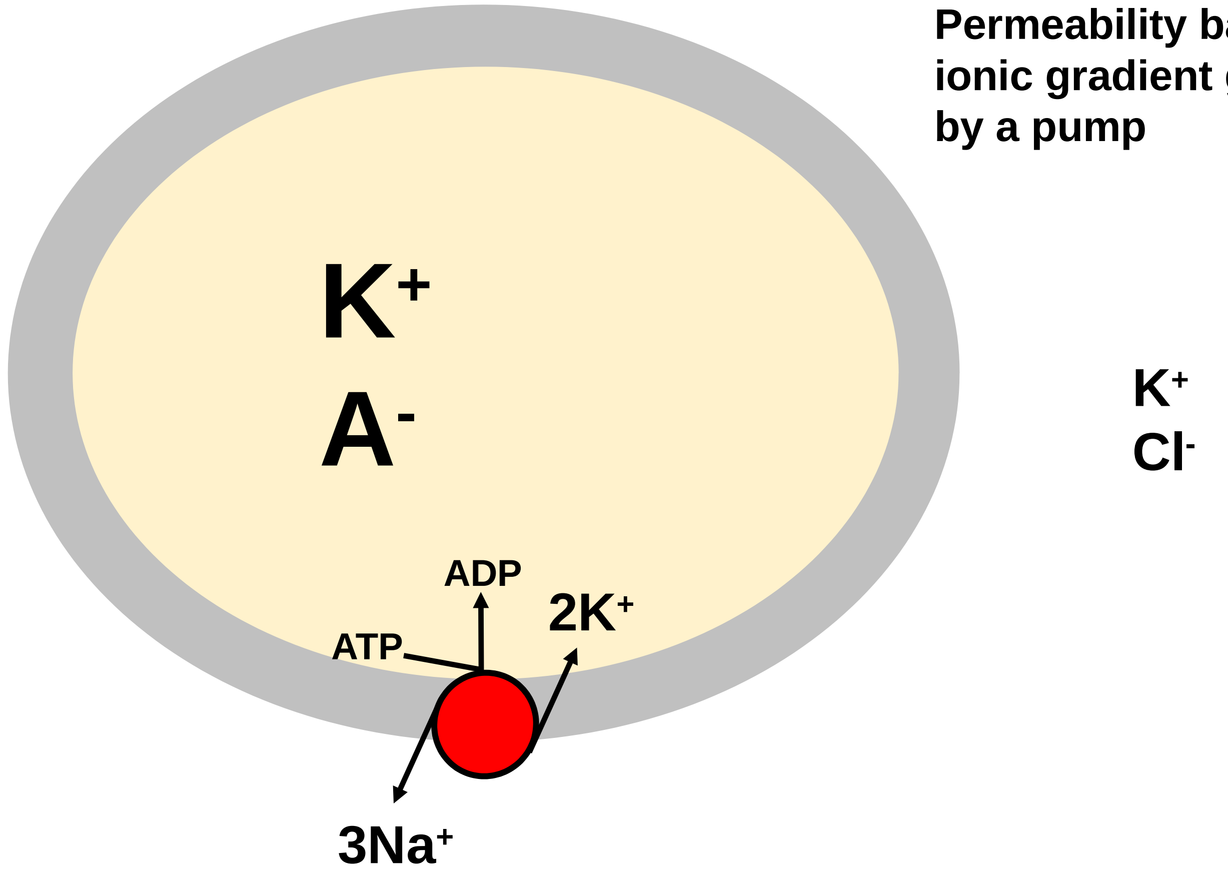
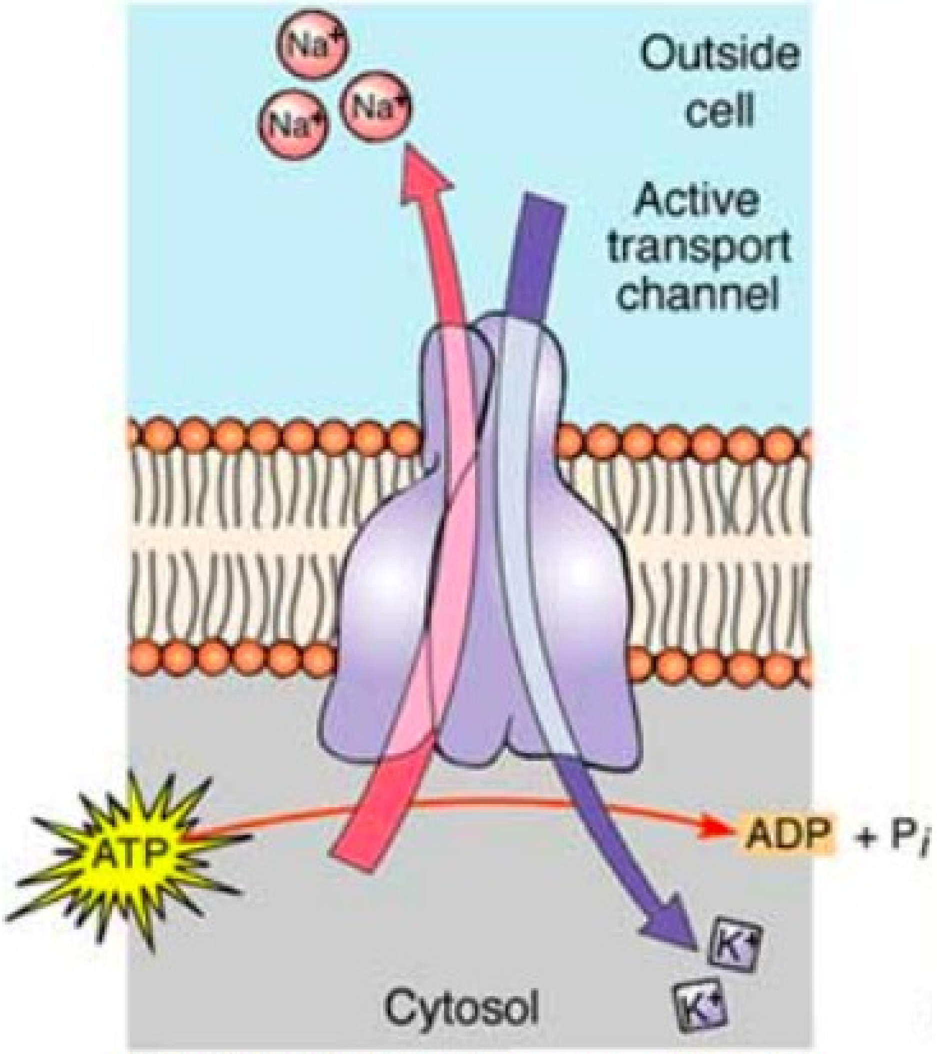
Generation of the Membrane Potential (V_m)

Permeability barrier and ionic gradient generated by a pump



Na+/K^+ pump



http://163.16.28.248/bio/activelearner/05/ch5c4.html
Thomson Learning, Inc.

The sodium-potassium pump uses ATP to actively exchange extracellular K+ for intracellular Na+. (aka "Na-K ATPase")

3 Na+ ions are removed for every 2 K+ ions that are pumped into the cell.

This requires an enormous amount of energy in the brain (70% of all ATP-->ADP).

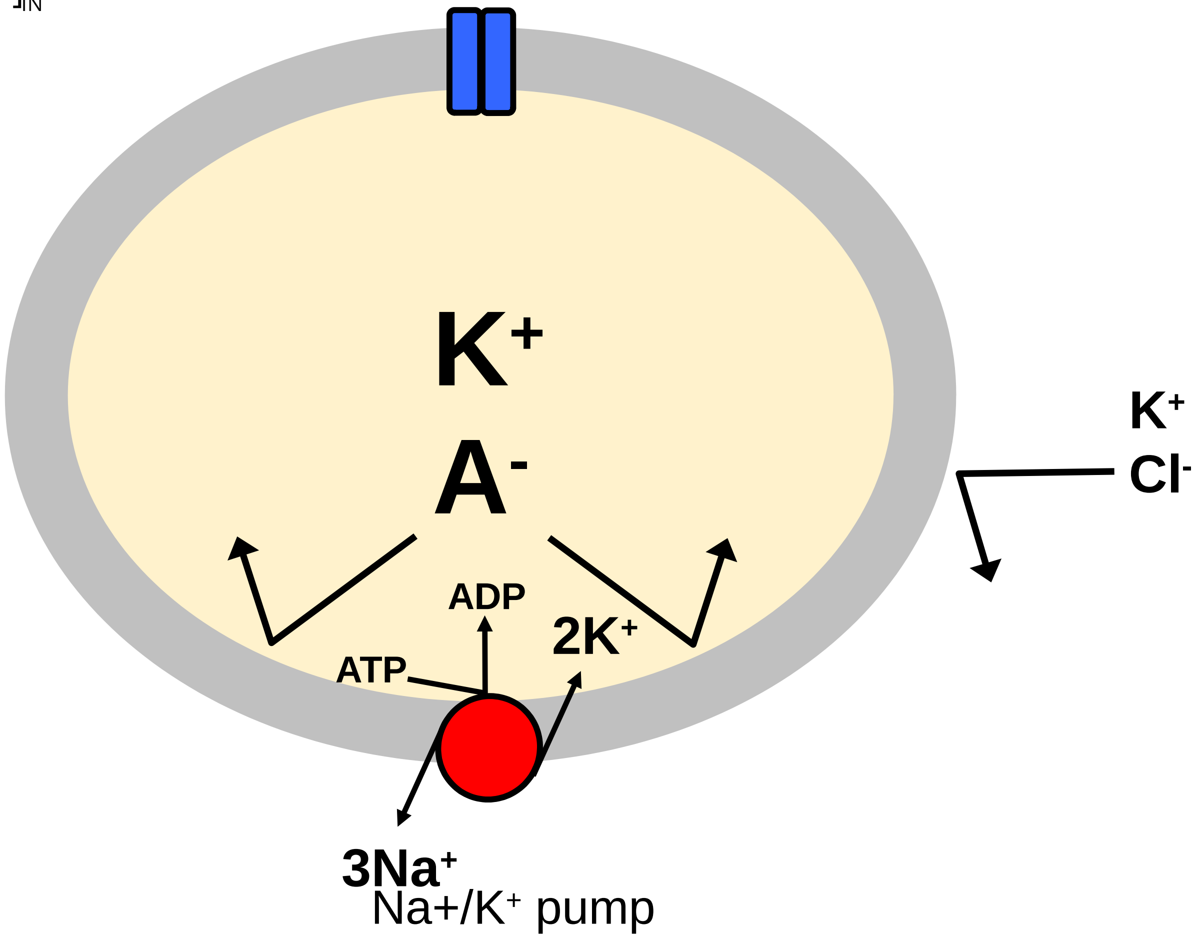
The pump is "electrogenic" - helping contribute to Vm (net 1+ out)

If the Na+/K+ pump stops working, a neuron slowly loses its concentration gradient, membrane potential, and dies.

K$^+$– selective pore:

Diffusional work = $RT \ln \frac{[K^+]_{OUT}}{[K^+]_{IN}}$

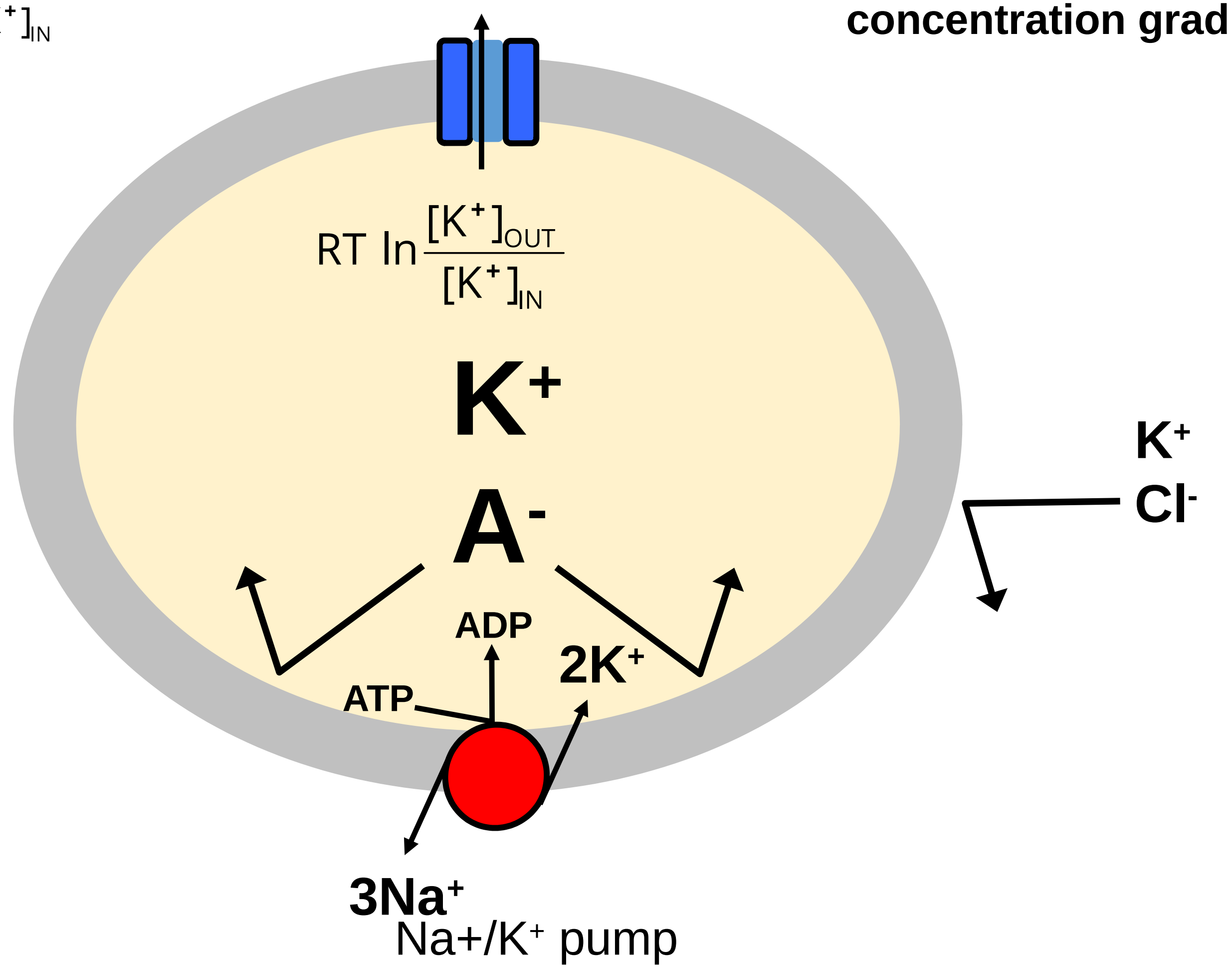
Membrane is doped with a K$^+$ –selective ion channel



K^+– selective pore:

$$\text{Diffusional work} = RT \ln \frac{[K^+]_{OUT}}{[K^+]_{IN}}$$

Once the K^+ –selective ion channel opens, K^+ starts diffusing down the concentration gradient

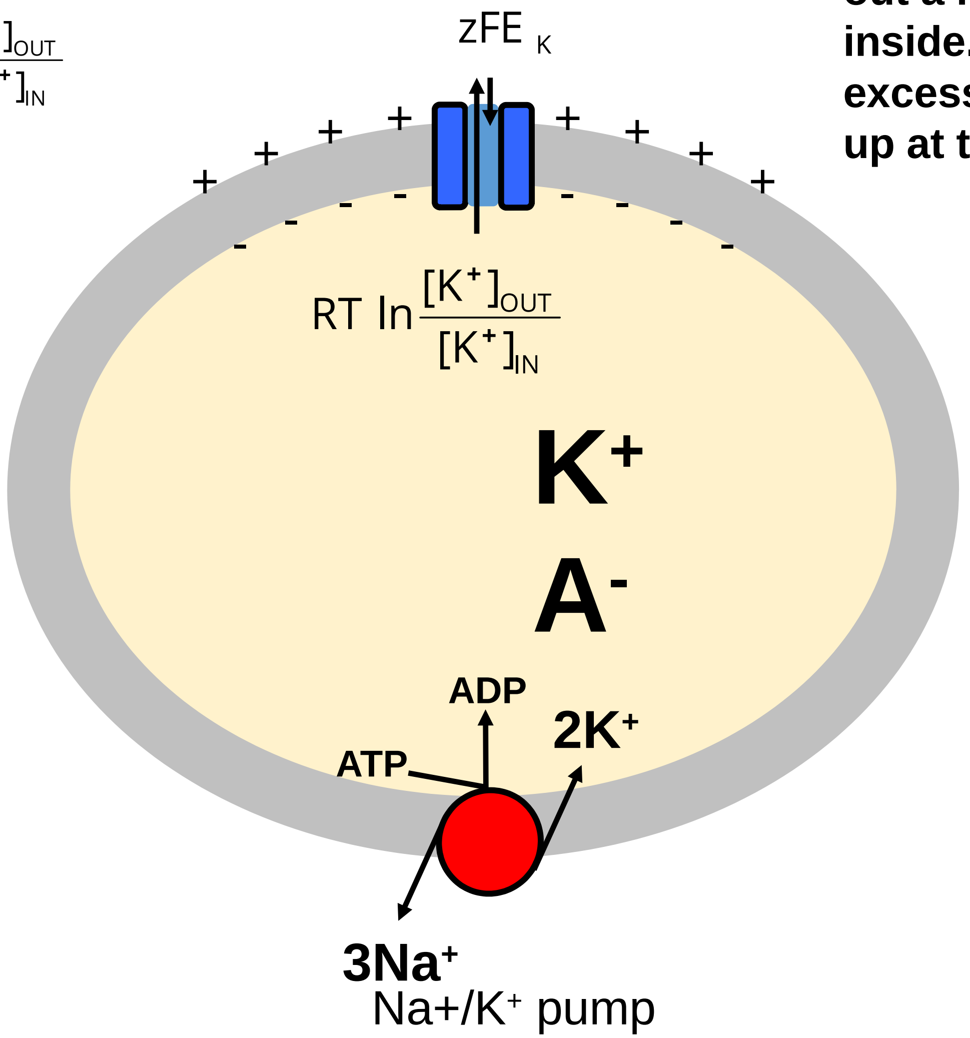


K^+– selective pore:

Diffusional work = $RT \ln \frac{[K^+]_{OUT}}{[K^+]_{IN}}$

Electrical work = zFE_K

For every K^+ that moves out a negative ion is left inside. As a result an excess of charge builds up at the membrane



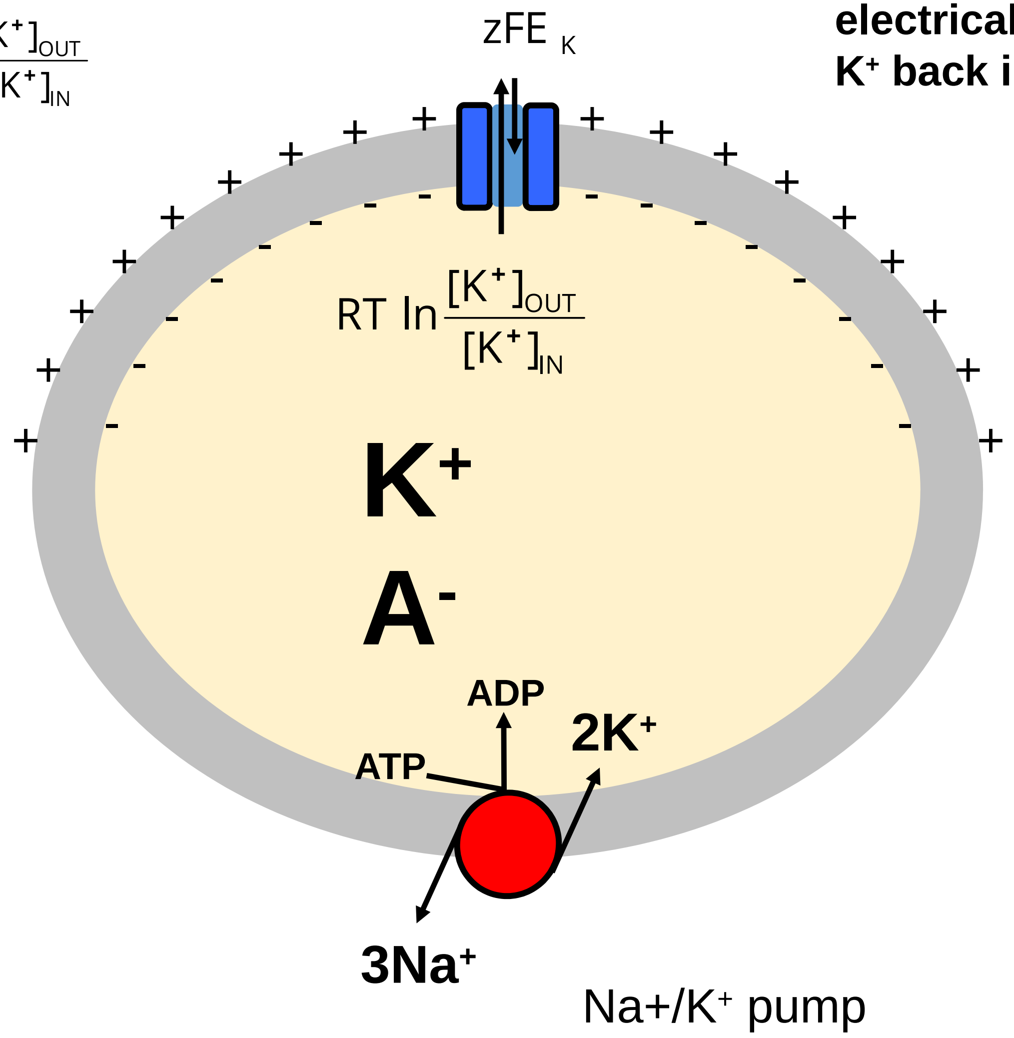
K^+
Cl^-

K⁺– selective pore:

Diffusional work = $RT \ln \frac{[K^+]_{OUT}}{[K^+]_{IN}}$

Electrical work = zFE_K

The separation of charge at the membrane generates an electrical force that pushes K^+ back in



K^+
Cl^-

K^+– selective pore:

Diffusional work = $RT \ln \frac{[K^+]_{OUT}}{[K^+]_{IN}}$

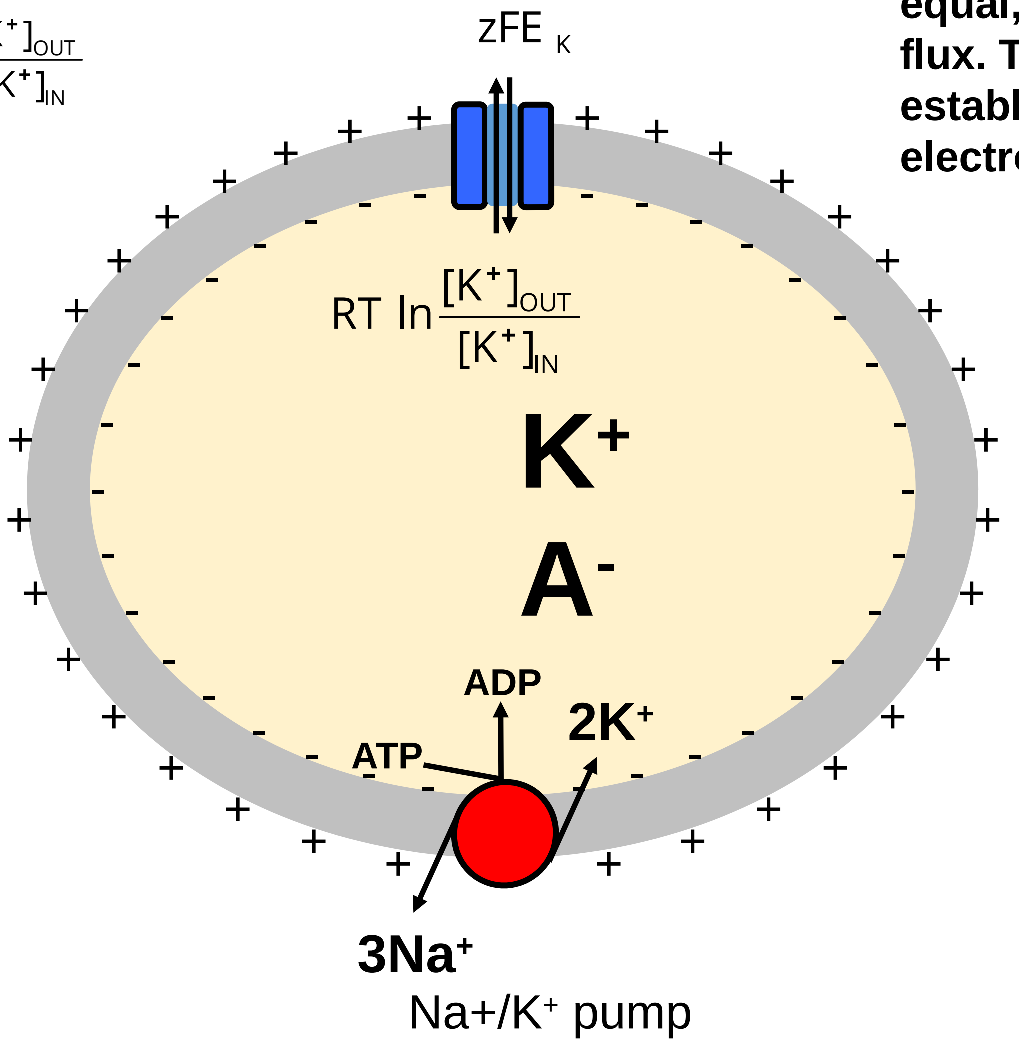
Electrical work = zFE_K

Equilibrium:

$$zFE_K = RT \ln \frac{[K^+]_{OUT}}{[K^+]_{IN}}$$

$$E_K = \frac{RT}{zF} \ln \frac{[K^+]_{OUT}}{[K^+]_{IN}}$$

The Nernst Eq.



When the electrical and diffusional forces are equal, there is not net K^+ flux. This equilibrium establishes the electrochemical potential

Calculating Equilibrium Potentials

If a cell membrane is *preferentially* permeable to ion *X*, the Equilibrium Potential of ion *X* approximates V_m, and is calculated by applying the *Nernst Equation*:

$$E_X = \frac{RT}{zF} \ln \frac{[X]_{OUT}}{[X]_{IN}}$$

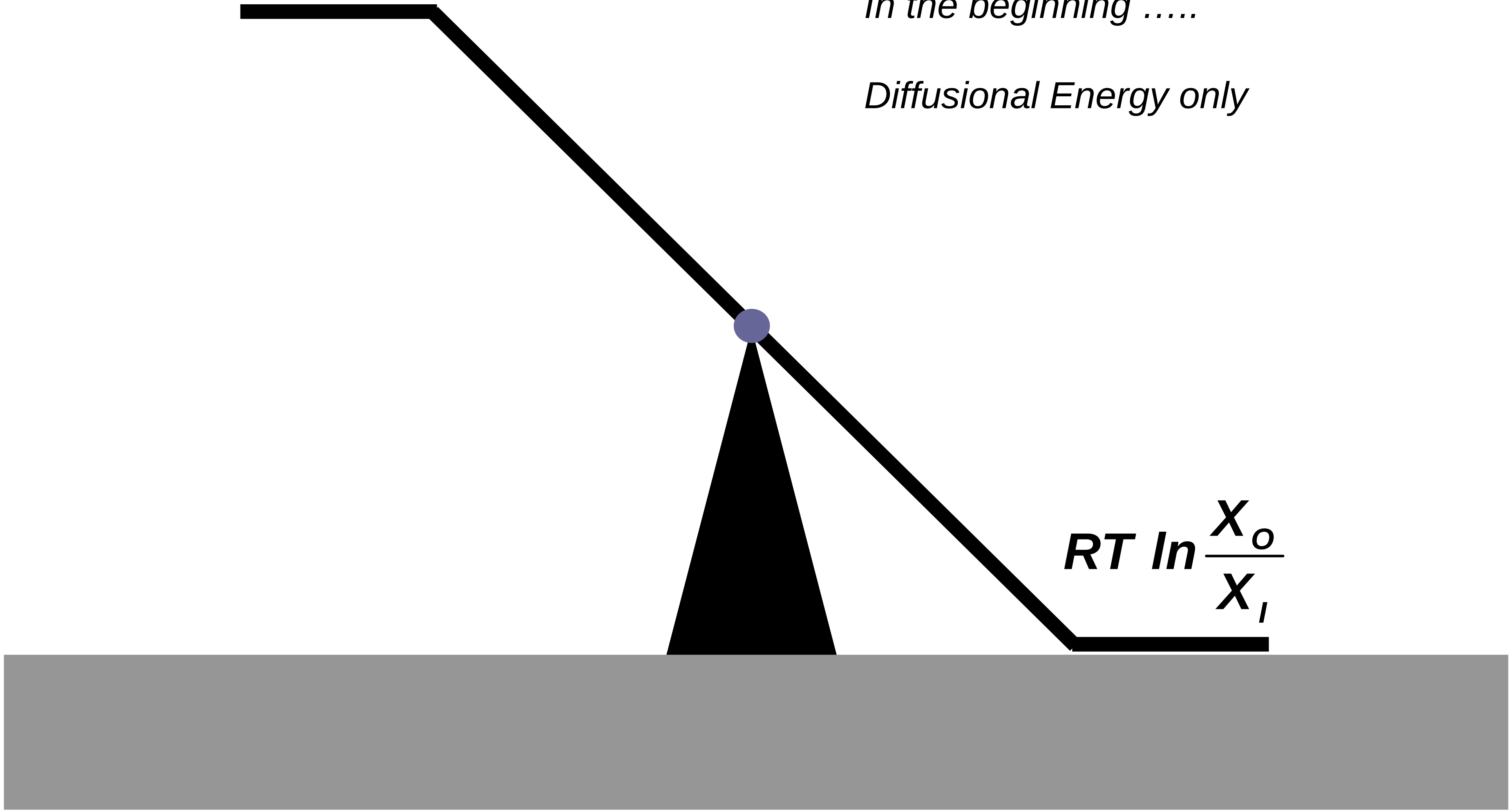
R = gas constant
T = abs. temperature
F = Faraday constant
z = valence of ion

$$E_X = 2.303 \frac{RT}{zF} \log_{10} \frac{[X]_{OUT}}{[X]_{IN}} = 58 \log_{10} \frac{[X]_{OUT}}{[X]_{IN}} \quad \text{at } 22\ {}^{0}\text{C}$$

$$E_X = 62 \log_{10} \frac{[X]_{OUT}}{[X]_{IN}} \quad \text{at } 37\ {}^{0}\text{C}$$

In the beginning …..

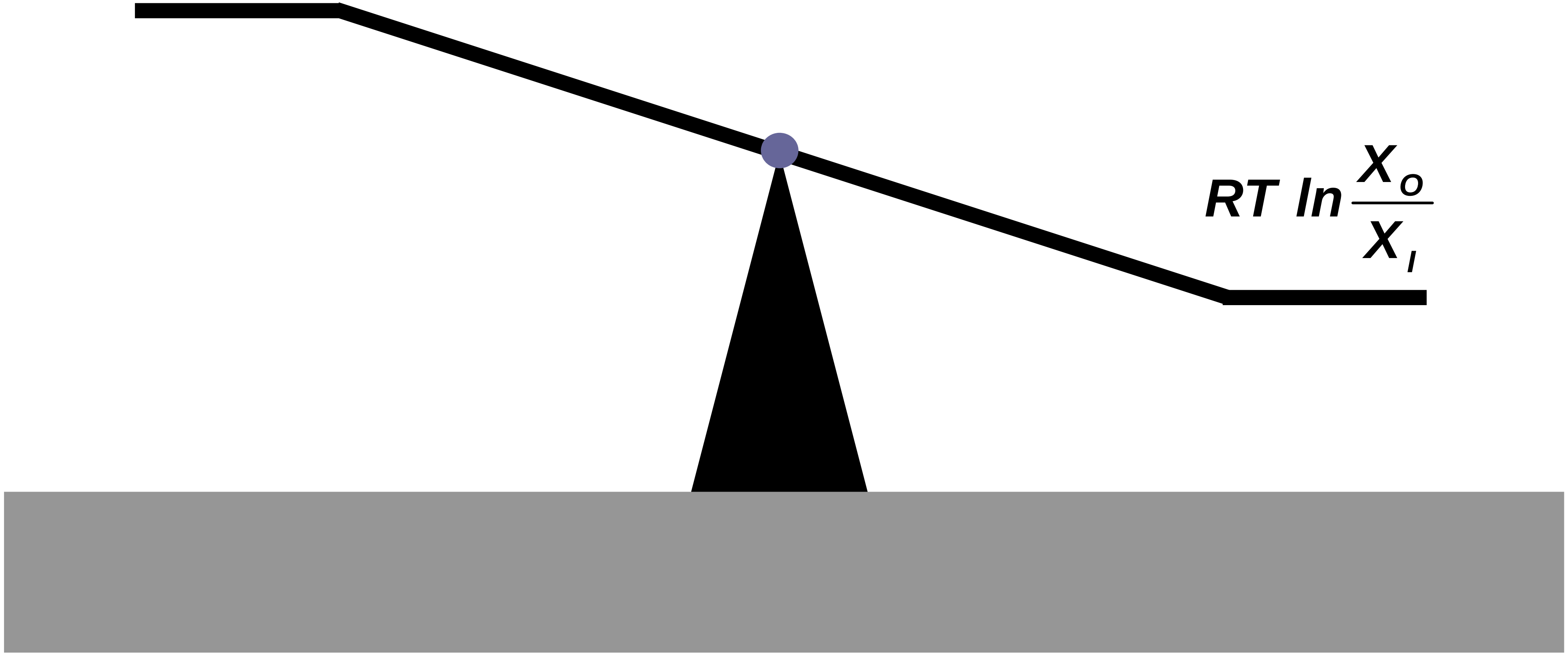
Diffusional Energy only



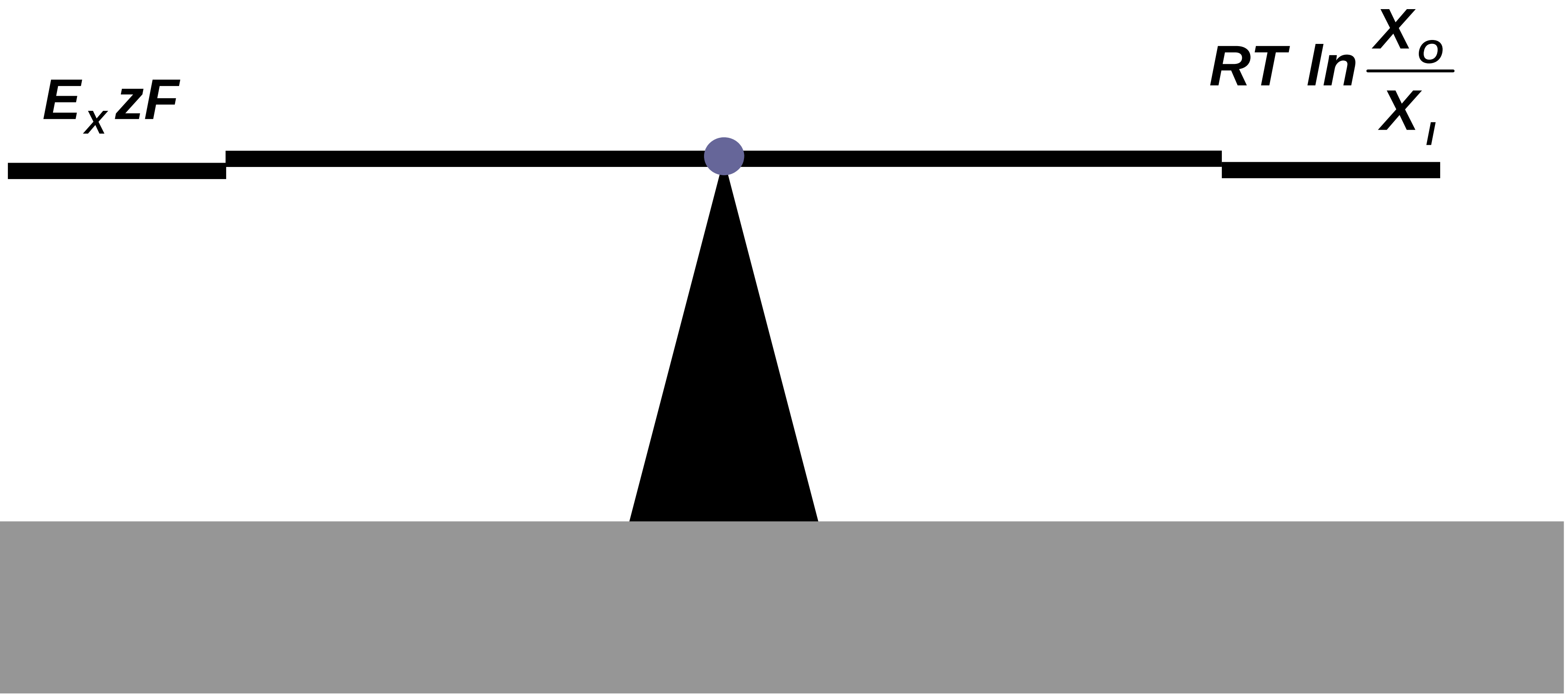
Using the diffusional energy, ions flow down the concentration gradient through ion-selective channels and the separation of charge across the membrane begins. Thus, electrical energy starts to counteract the diffusional energy

Separation of charge

$E_X zF$



When the tendency of ions to flow down the concentration gradient (diffusional energy) is exactly balanced by the tendency of ions to flow back under the influence of an electrical potential (electrical energy), the system has reach an electrochemical equilibrium



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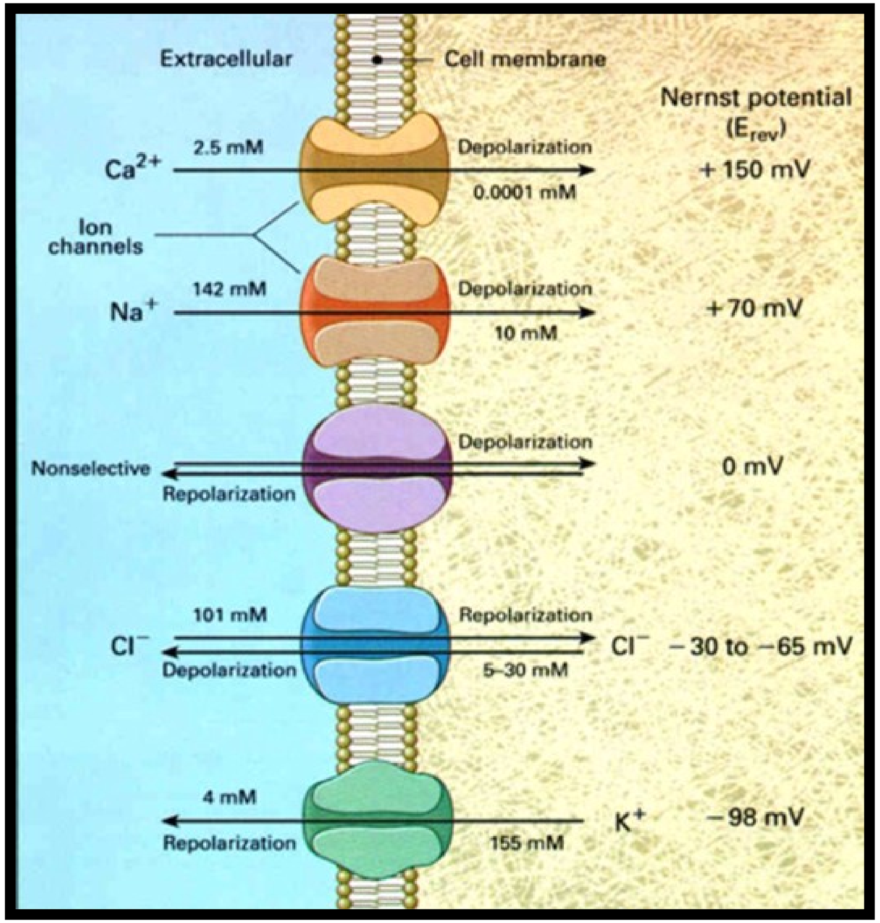
$$E_X = 62 \log_{10} \frac{[X]_{OUT}}{[X]_{IN}} \quad \text{at } 37\ ^0C$$

Applications of the Nernst Equation

if only one ion-selective channel is open at a given time, the Nernst Equation can calculate the V_m of a cell



Sodium:

$$E_{Na} = 58\,[\log\,(142 / 10)] = +66\ mV$$

Potassium:

$$E_K = 58\,[\log\,(4 / 155)] = -91\ mV$$

Chloride:

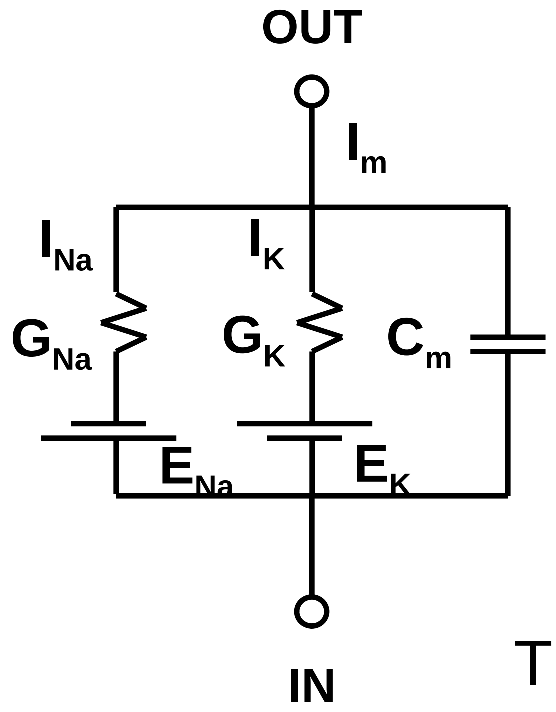
$$E_{Cl} = 58\,[\log\,(30 / 101)] = -30\ mV$$

Calcium:

$$E_{Ca} = 29\,[\log\,(2.5 / 0.0001)] = +127\ mV$$

Calculating the Membrane Potential

a more realistic scenario- Multiple ions involved



Three-branch Model

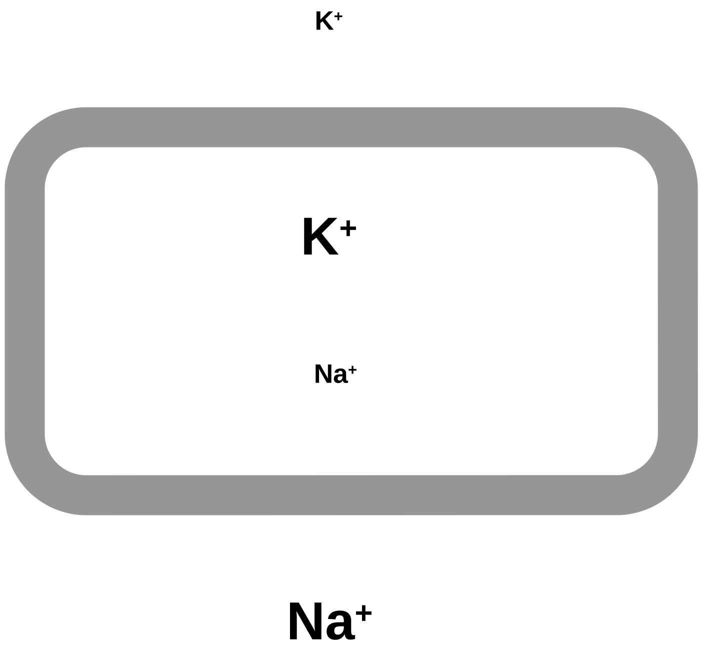
Steady-state: $I_m = I_{Na} + I_K = 0$. Then, applying Ohm's Law it is easy to show that:

$$V_m = E_{Na}\,(G_{Na}/G_m) + E_K\,(G_K/G_m)$$

where the total conductance is

$$G_m = G_{Na} + G_K$$

Thus, V_m is the *weighted average* of the E_X

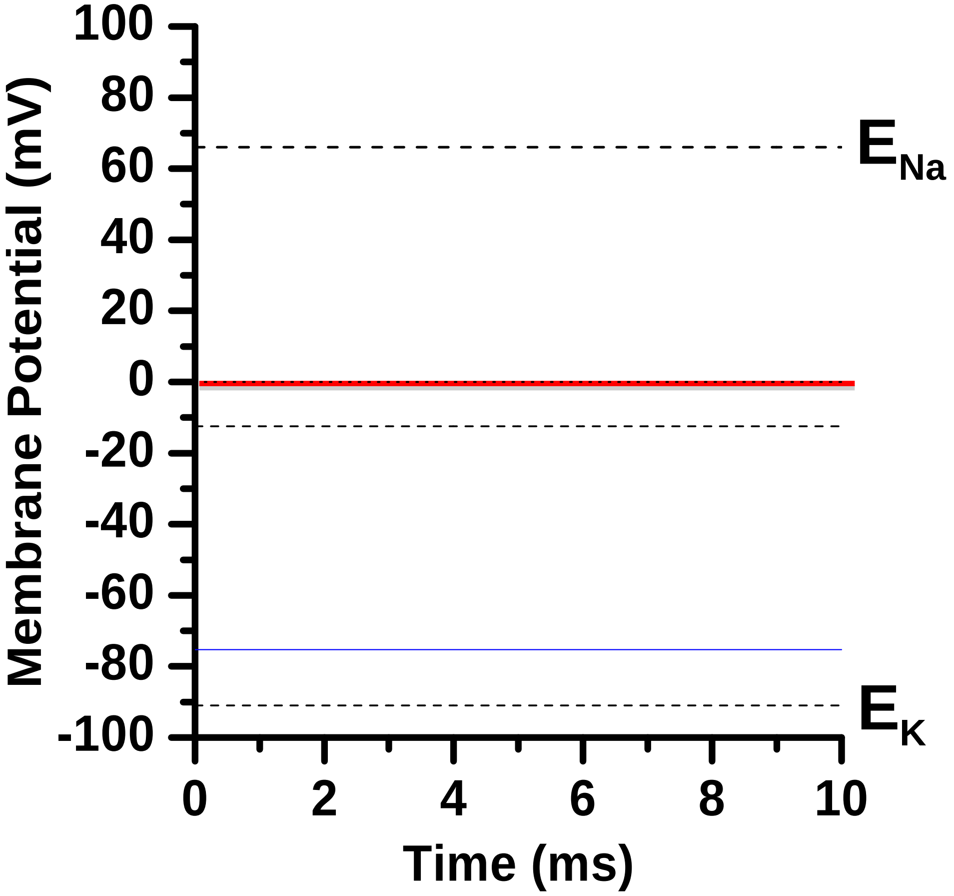


No ion channels

$$V_m = E_{Na}\,(G_{Na}/G_m) + E_K\,(G_K/G_m)$$

$$G_{Na}/G_m = 0 \quad G_K/G_m = 0$$

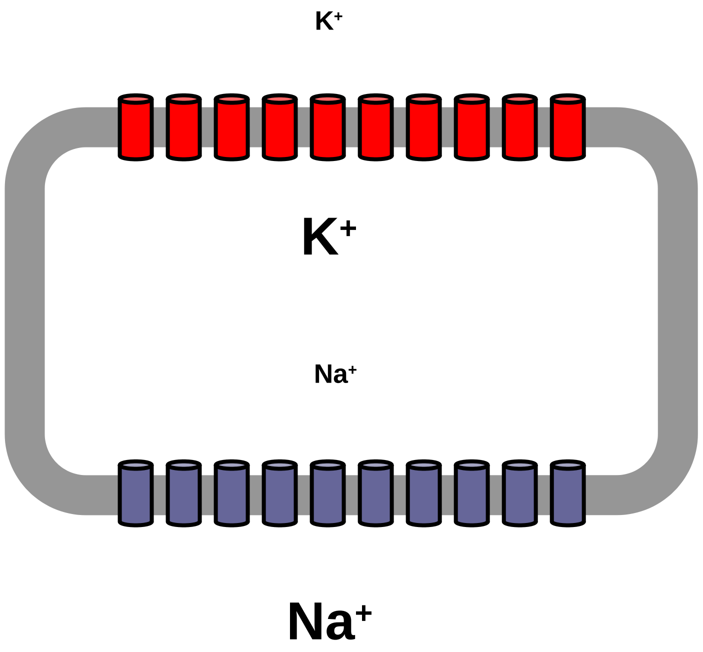
$$V_m = 0 \text{ mV}$$



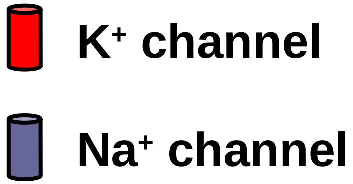
$$V_m = E_{Na}\,(G_{Na}/G_m) + E_K\,(G_K/G_m)$$

$$G_{Na}/G_m = 0 \quad G_K/G_m = 0$$

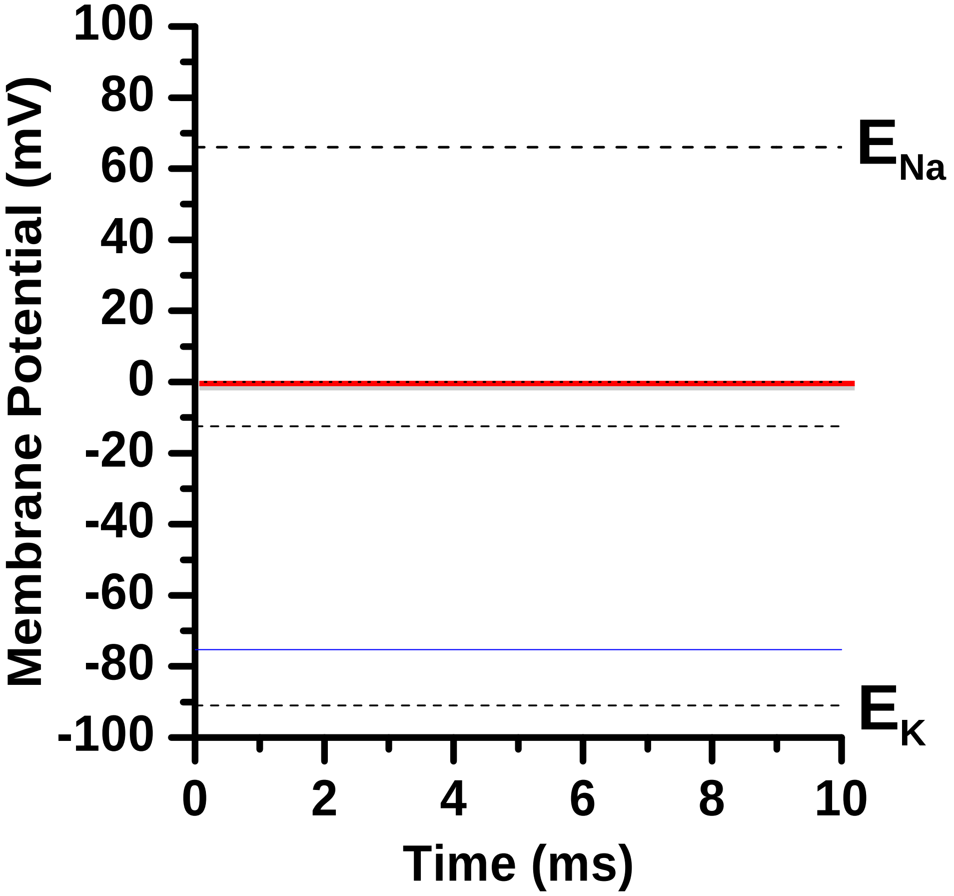
$$V_m = 0 \text{ mV}$$

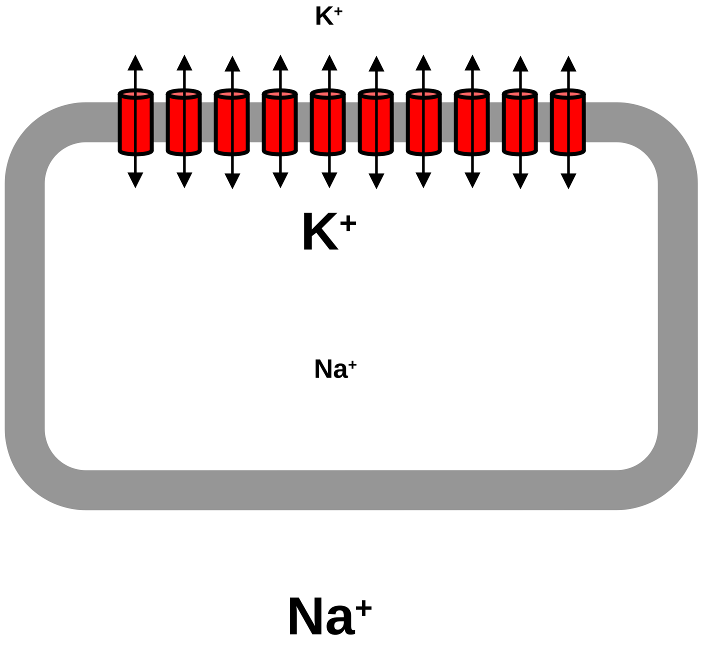


ion channels are closed



G_X α # open channels





K^+ channels are open

K^+ channel

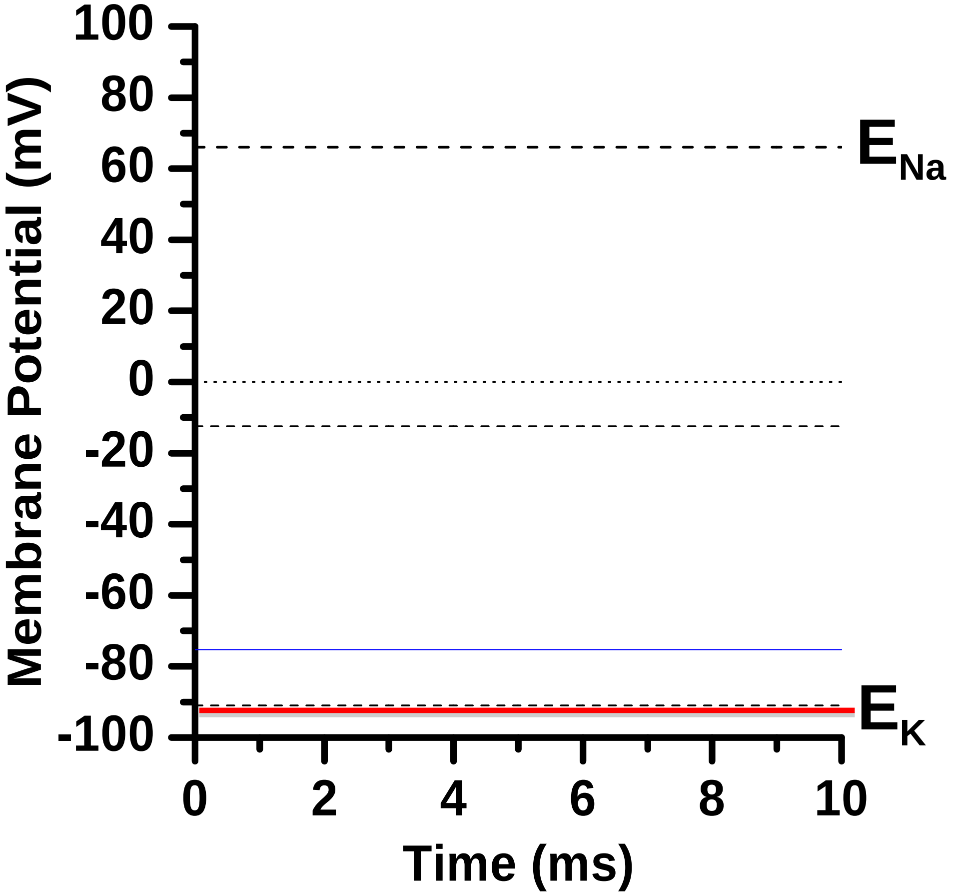
Na^+ channel

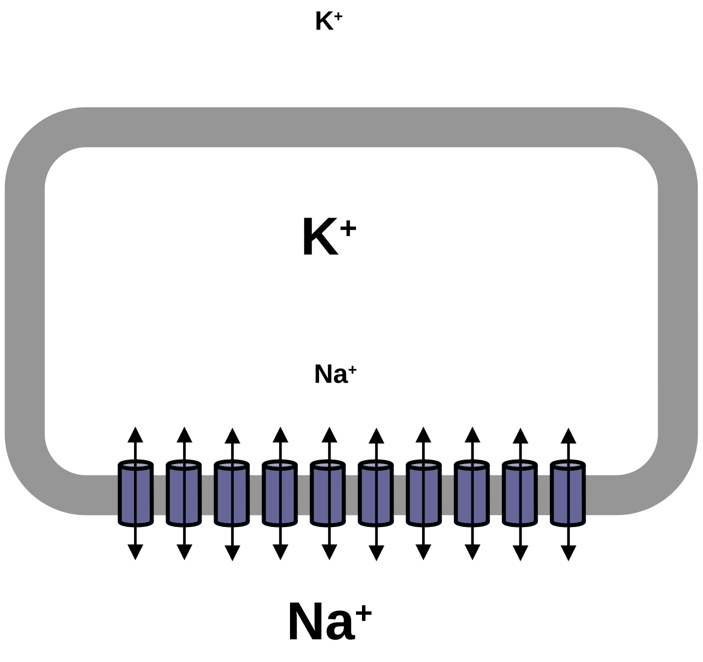
G_X α # open channels

$$V_m = E_{Na}\,(G_{Na}/G_m) + E_K\,(G_K/G_m)$$

$$G_{Na}/G_m = 0 \qquad G_K/G_m = 1$$

$$V_m = (+66)(0) + (-91)(1) = -91 \text{ mV}$$





Na⁺ channels are open

K⁺ channel

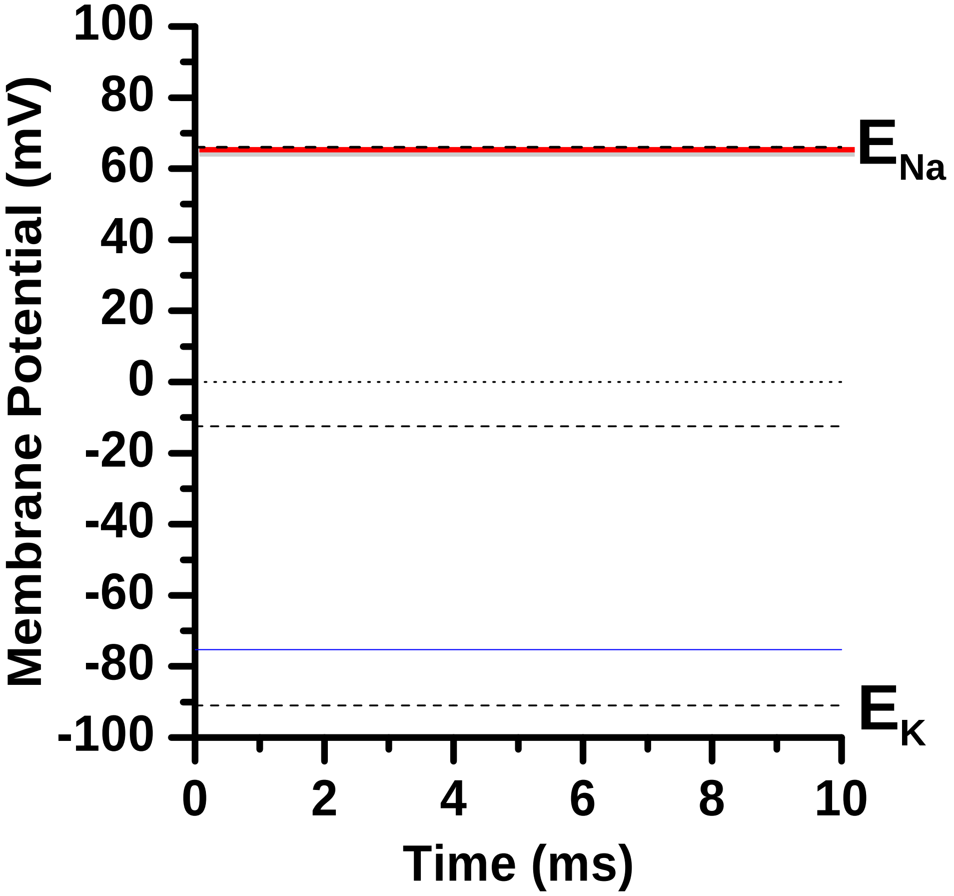
Na⁺ channel

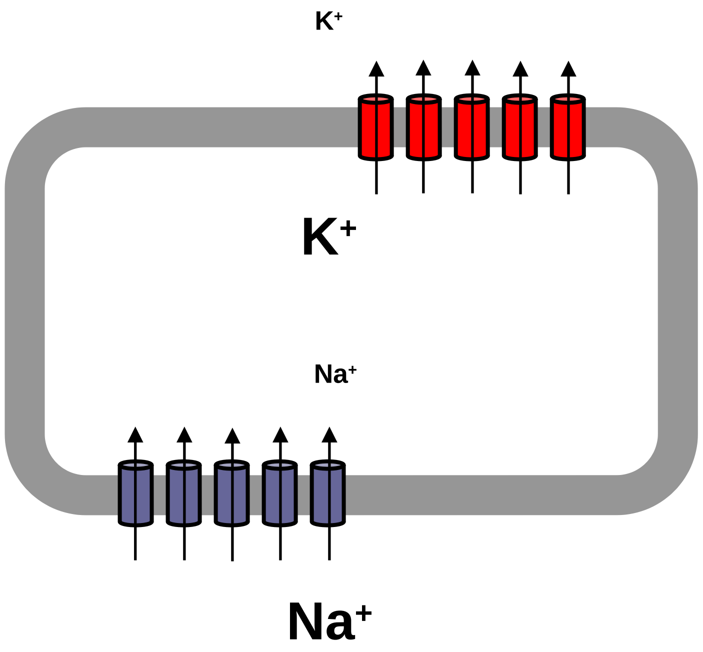
$G_X \alpha$ # open channels

$$V_m = E_{Na}\,(G_{Na}/G_m) + E_K\,(G_K/G_m)$$

$$G_{Na}/G_m = 1 \qquad G_K/G_m = 0$$

$$V_m = (+66)(1) + (-91)(0) = +66\text{ mV}$$





Na^+ & K^+ channels are open

K^+ channel

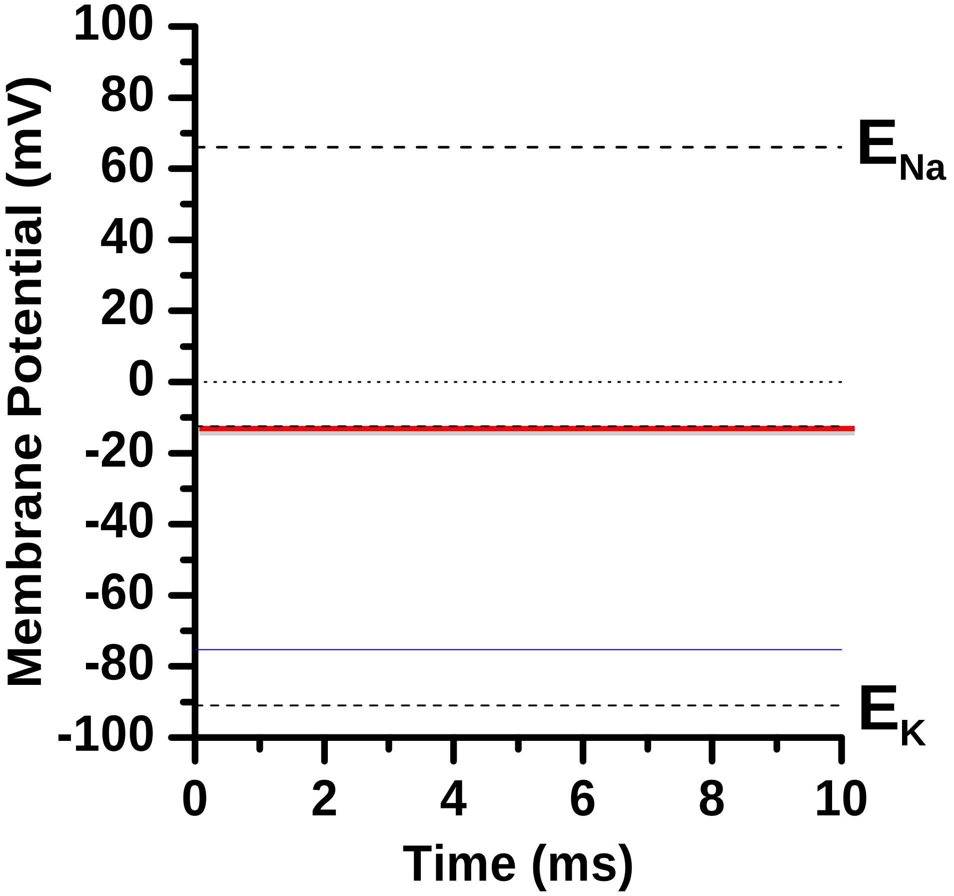
Na^+ channel

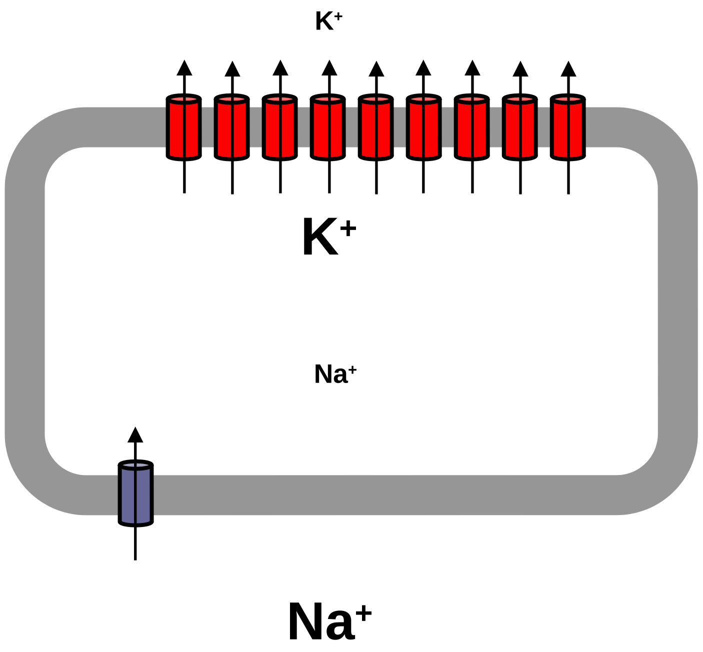
G_X α # open channels

$$V_m = E_{Na}\,(G_{Na}/G_m) + E_K\,(G_K/G_m)$$

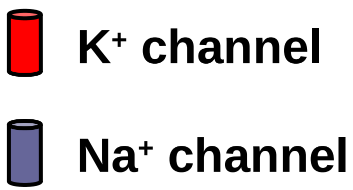
$$G_{Na}/G_m = 0.5 \qquad G_K/G_m = 0.5$$

$$V_m = (E_{Na} + E_K)\,/\,2 = -12.5\ \text{mV}$$





Na⁺ & K⁺ channels are open

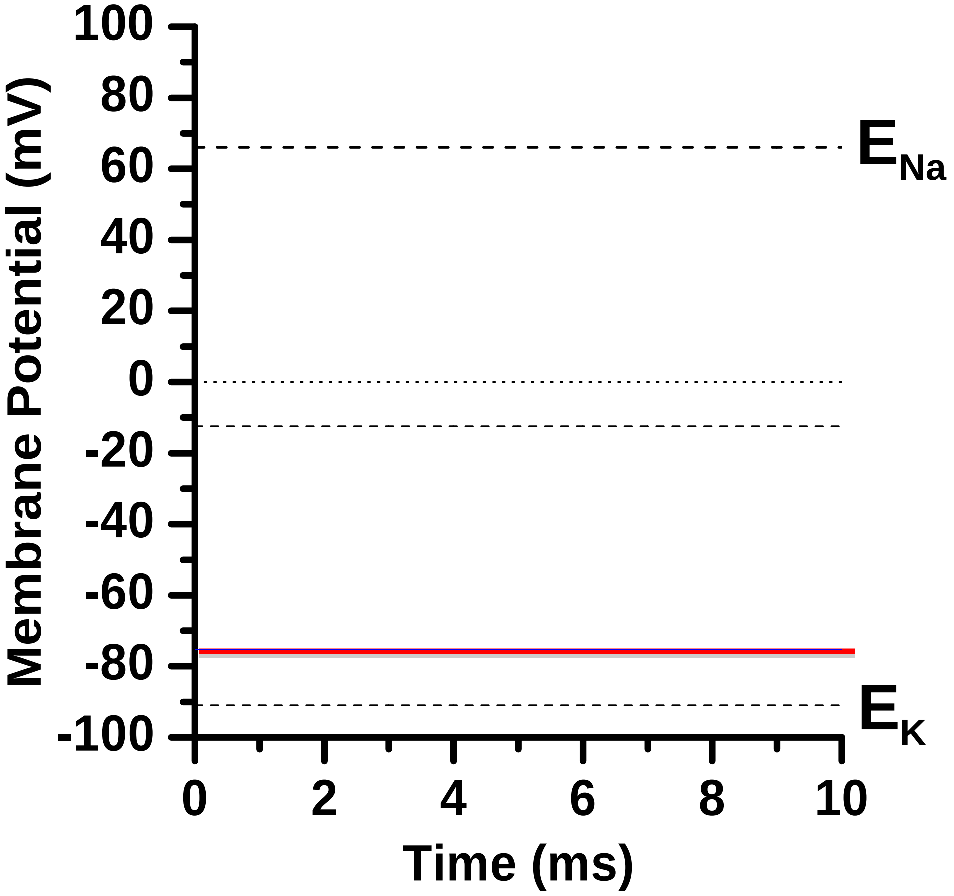


G_X α # open channels

$$V_m = E_{Na}\,(G_{Na}/G_m) + E_K\,(G_K/G_m)$$

$$G_{Na}/G_m = 0.1 \qquad G_K/G_m = 0.9$$

$$V_m = (+66)(0.1) + (-91)(0.9) = -75.3\ \text{mV}$$



Calculating the Membrane Potential
another method

The Goldman-Hodgkin-Katz (GHK) Equation

$$V_m = 62 \log_{10}\left(\frac{P_{Na}[\mathrm{Na}^+]_{\mathrm{OUT}} + P_K[\mathrm{K}^+]_{\mathrm{OUT}}}{P_{Na}[\mathrm{Na}^+]_{\mathrm{IN}} + P_K[\mathrm{K}^+]_{\mathrm{IN}}} \right)$$

P_X = relative permeability = P_x / P_K

The Goldman-Hodgkin-Katz Equation

$$V_m = \frac{RT}{F} * \ln \left(\frac{P_{Na+}[Na+]_{out} + P_{K+}[K+]_{out} + P_{Cl-}[Cl-]_{in}}{P_{Na+}[Na+]_{in} + P_{K+}[K+]_{in} + P_{Cl-}[Cl-]_{out}} \right)$$

Please note the solid line

Where:

Vm = membrane potential at steady state
P = permeability

R = gas constant = 8.314 J/Kmol
T = absolute temperature in kelvin = °C + 273
z = valence of the ion
F = Faraday constant = 96,485 C/mol

$\frac{RT}{F}$ at 37 °C = 0.0267 V = 26.7 mV

Permeability

Can be thought of as the number of open ion channels.

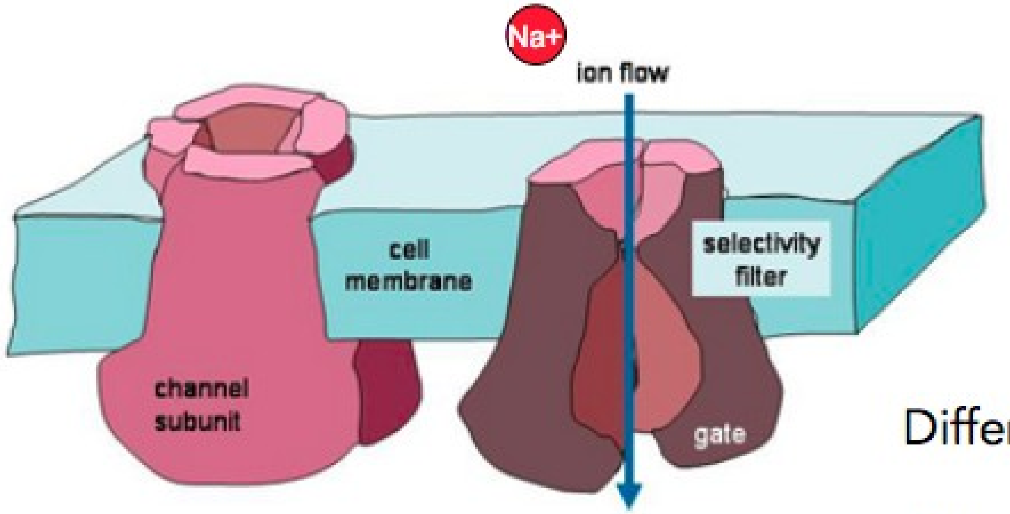
To simplify for GHK, P is usually written as a ratio, for example:

$$P_{Na+}:P_{K+}:P_{Cl-} = \sim 1:100:10$$

Now that we have learned how to measure the equilibrium potential (E) for individual ions and Vm when multiple ionic conductances are present we must learn about the proteins that make this possible:

Ion Channels

Charge moving over time = current



Difference in voltage is a potential

Movement of charge = current (I)
(eg. across voltage separation)

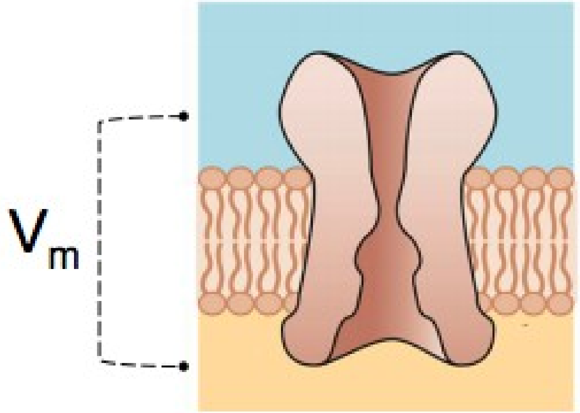
Current is abbreviated "I"
and is measured in amps

(Usually nA or pA for
neurons)

<u>Units</u>: Charge/time = current

Coulombs/sec = amperes

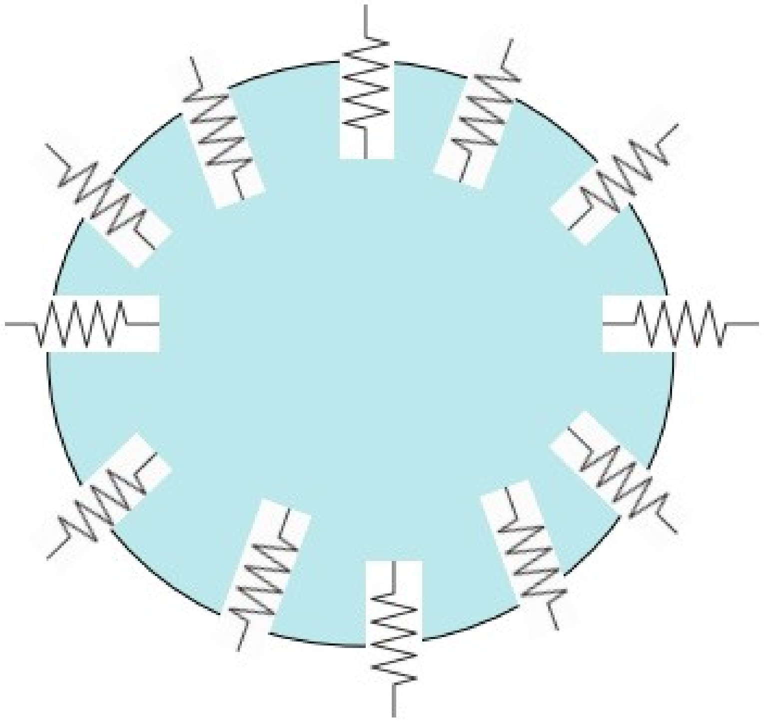
Think of a battery



Current follows the path of least resistance


Colourbox.com

In a three dimensional cell with many channels, many resistors combine to make up the overall "membrane resistance"



Because there is a simple way to relate voltage to current, neuronal recordings can easily monitor either

Voltage difference across the membrane

OR

Current flow across the membrane

$\Delta V = IR$

Voltage = Current x Resistance

How can we describe this process mathematically???

$$\Delta V = IR$$

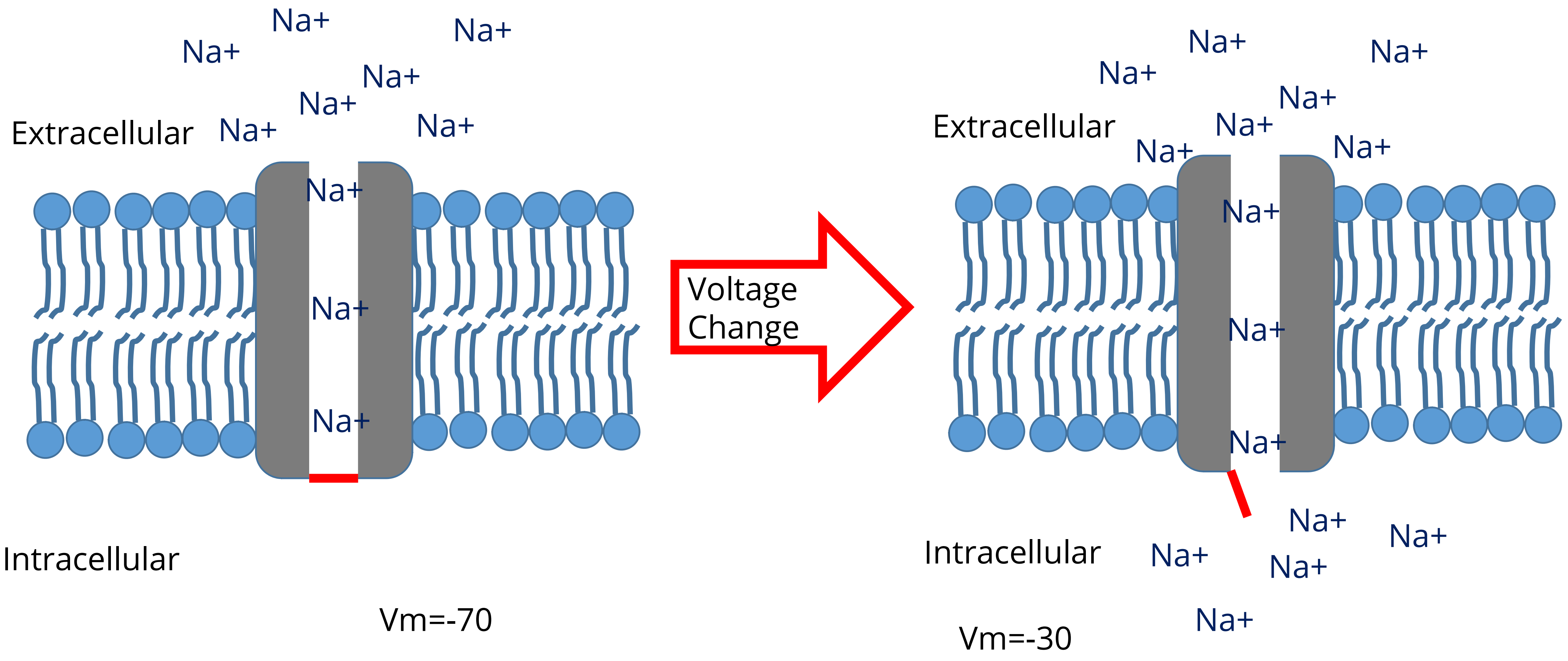
$$\Delta V = (V_m - E_{ion}) = \text{Driving Force}$$

Current in the form of moving ions (charged) through a resistor (permeation pore) across a voltage (Vm) is described by Ohm's Law.

V=IR R=1/G
R=Resistance
G=Conductance

- Not all channels are leak channels (always “open”)
- Some channels have GATES that keep them closed in the ABSENSE of a stimulus
- Three major groups of gated channels in neurons are 1)Voltage gated, 2) Ligand (chemically) gated, 3) and Mechanically gated ion channels

Voltage gated ion channels



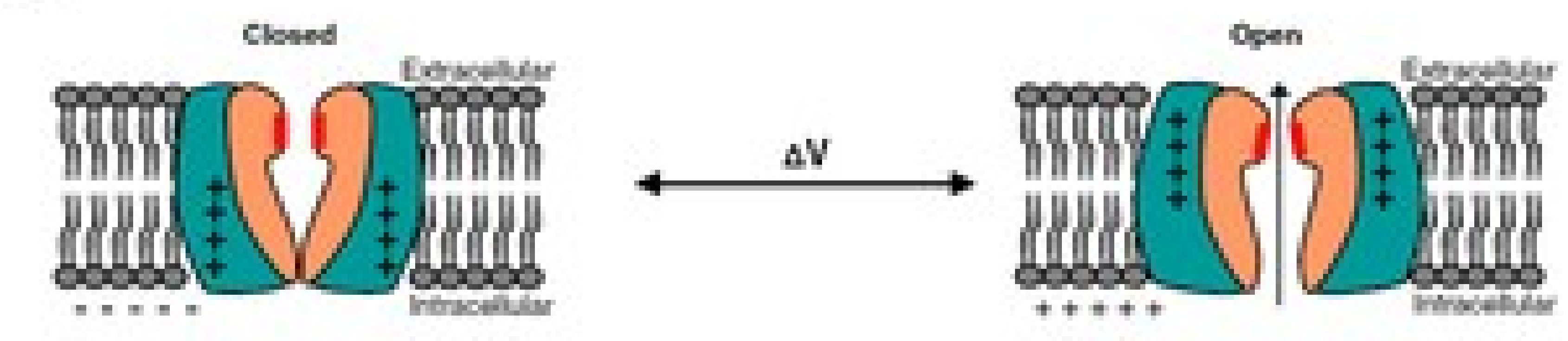
How do voltage gated channels gate??

Although this differs among different classes of voltage gated ion channels (K+, Na+, Ca2+), there are many more similarities.

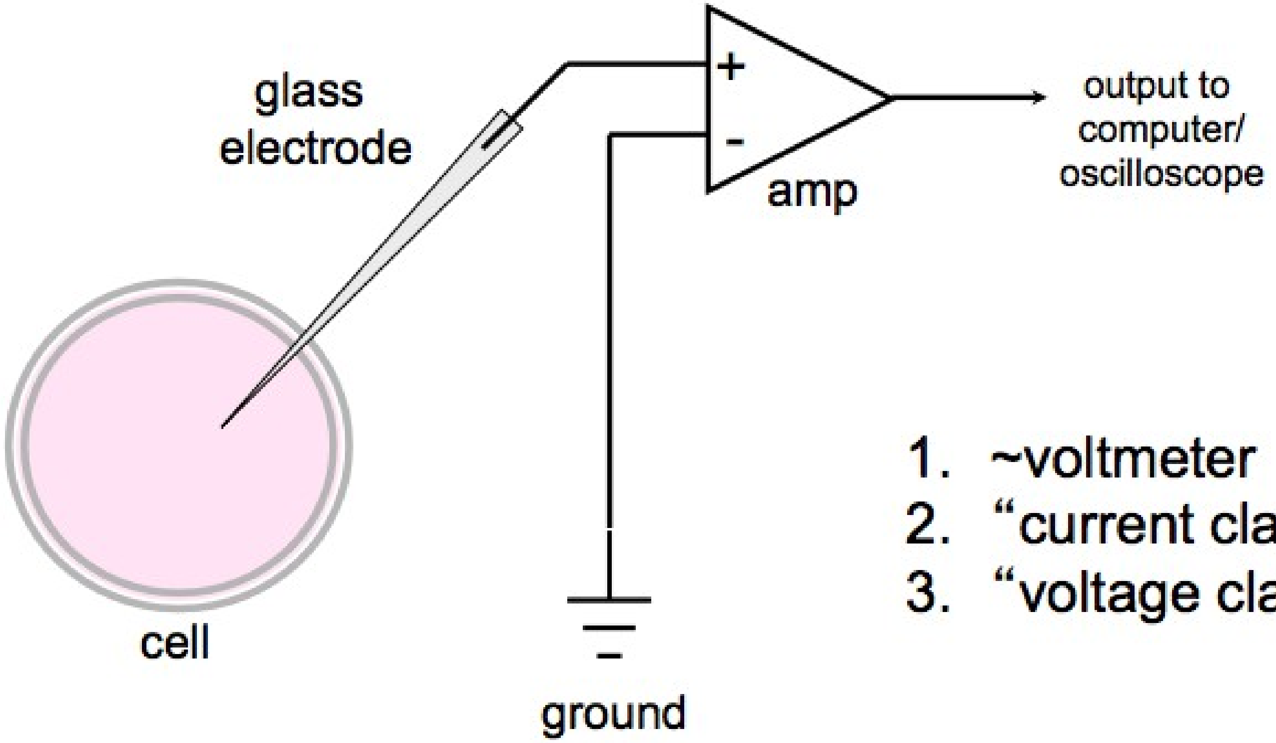
A change in voltage across a membrane moves parts of ion channels containing charged amino

- A net positive change on the inner leaflet of the plasma membrane induces an electrostatic repulsion of positively charged amino acids on the channel.

- This induces a conformational change of the tetramer that opens the “activation gate” and allows ions to flow.



Different methods for recording from cells

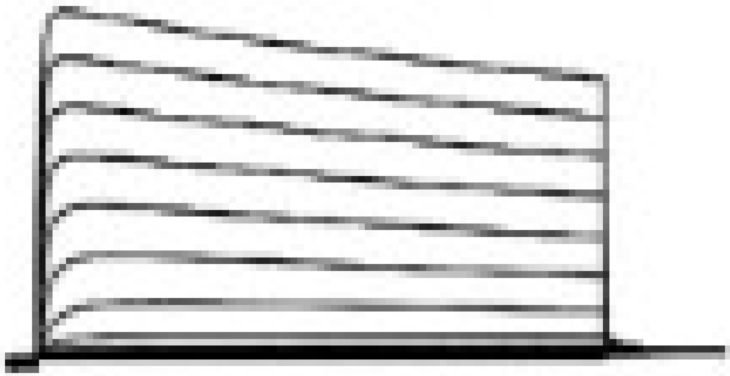


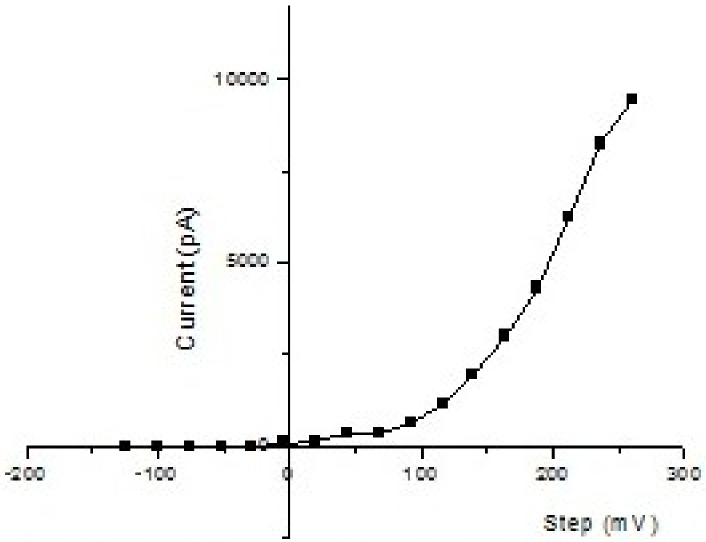
1. ~voltmeter
2. "current clamp" mode
3. "voltage clamp" mode

<u>*Terminology*</u>
current clamp
voltage clamp

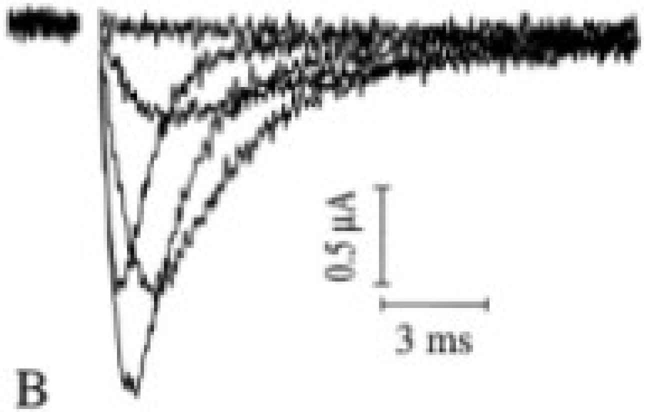
What do typical voltage gated Na+ (Nav) and K+ (Kv) currents look like at in voltage clamp?

- Kv





- Nav



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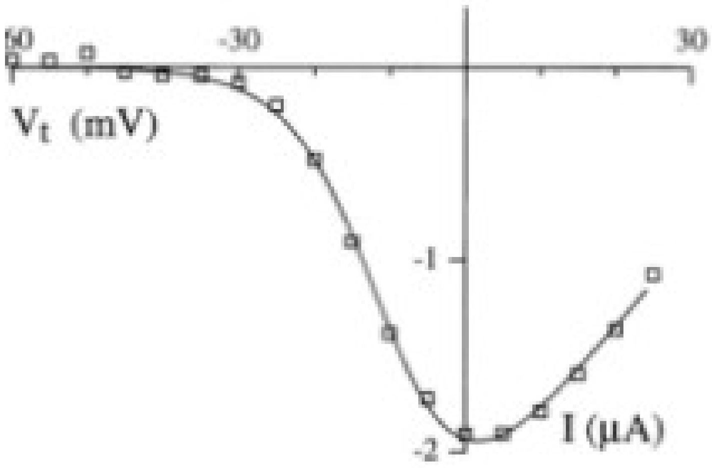
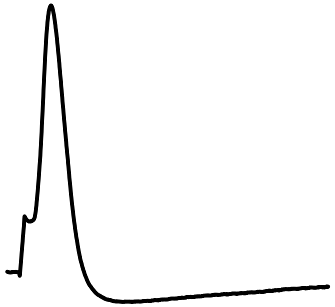
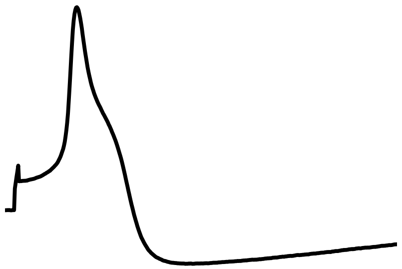


Lets take a break- 10 min

What do different action potentials look like in current clamp?

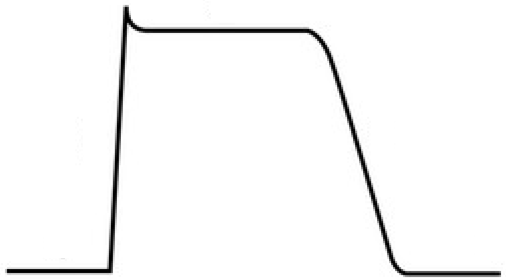
Spinal Cord – Dorsal Horn





Dorsal Root Ganglion

Squid Giant Axon

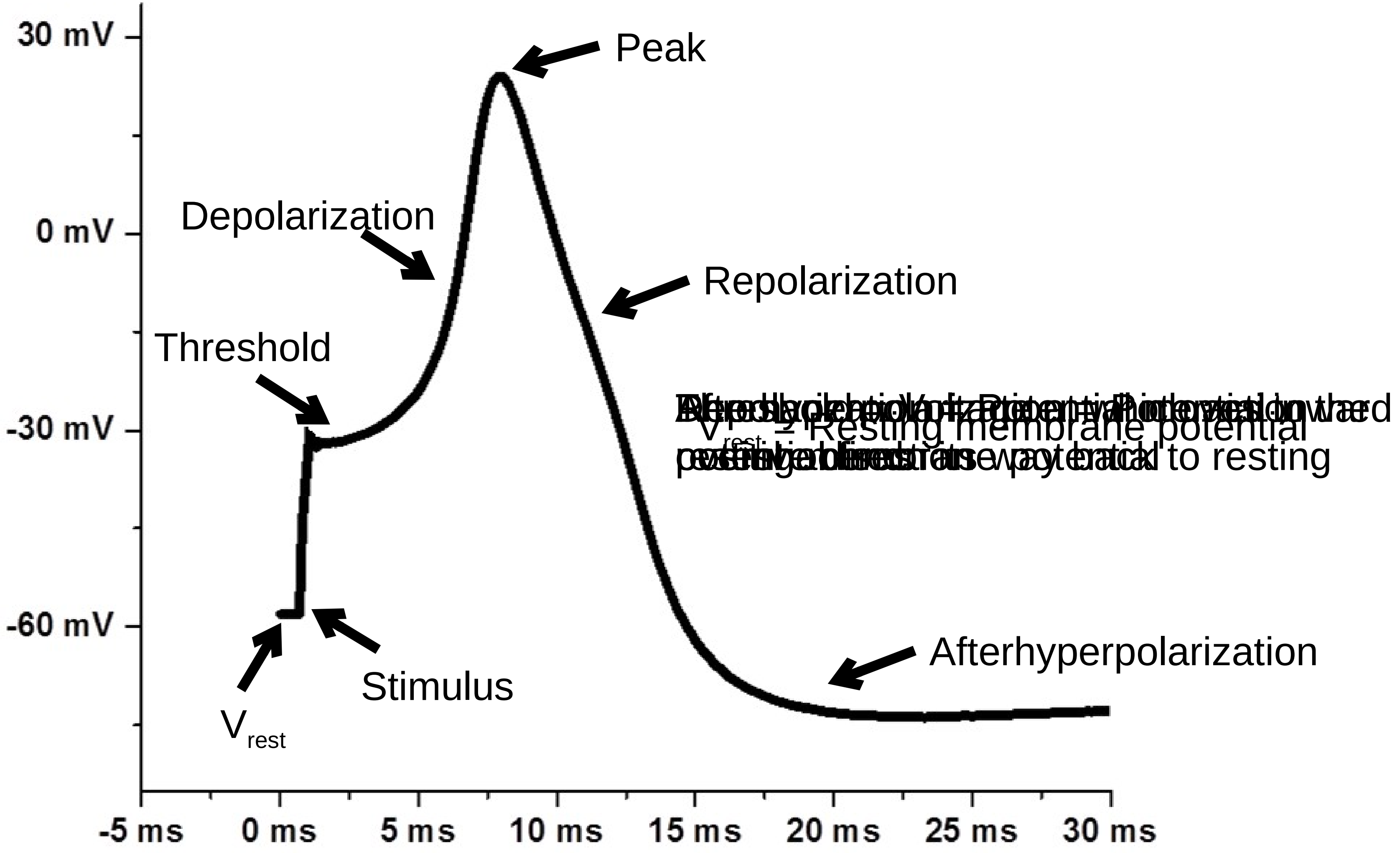


Cardiac Muscle

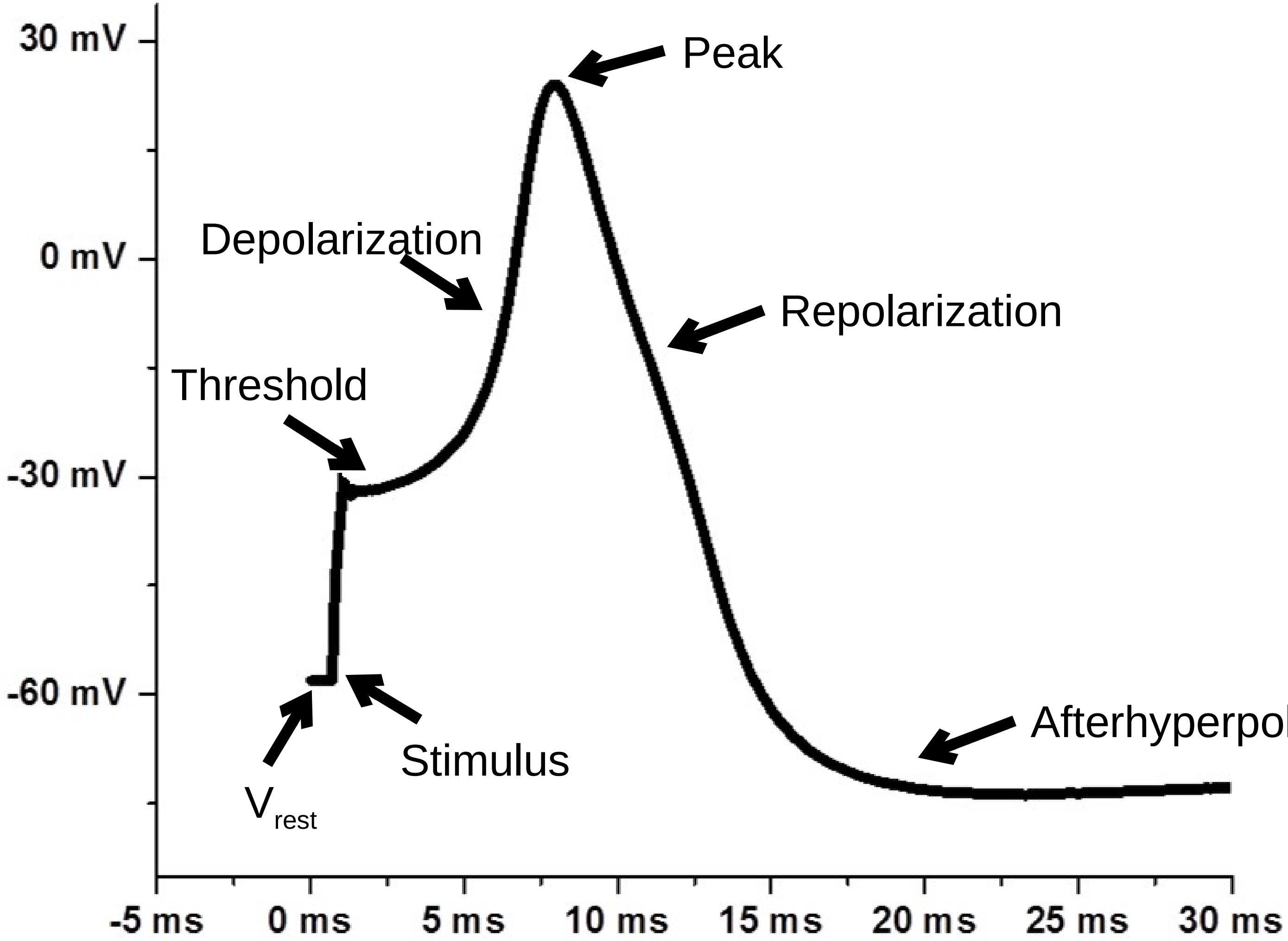
Skeletal Muscle

How do we use this information to understand the generation of Action Potentials in the nervous system?

The Action Potential Waveform



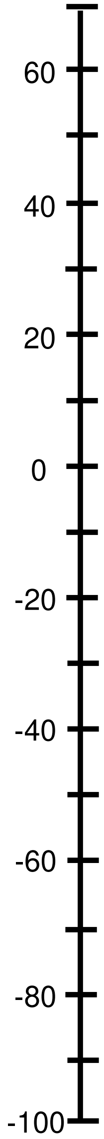
The Action Potential Waveform

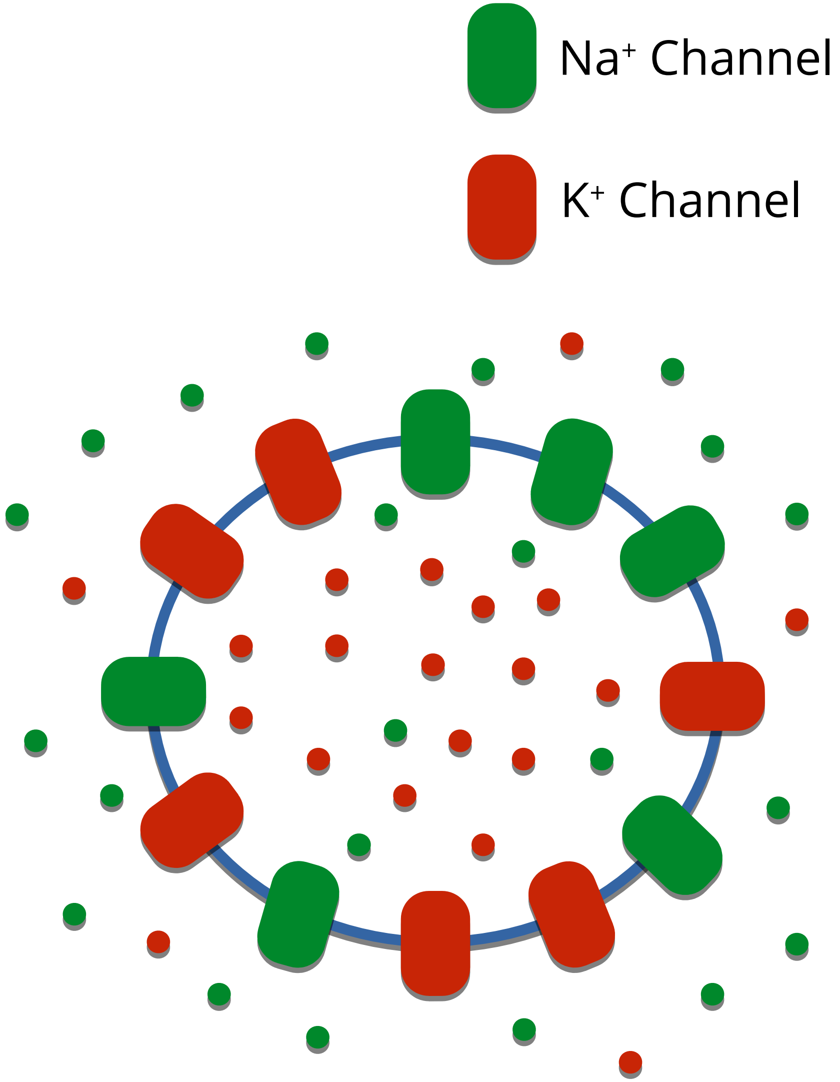


Defining terms

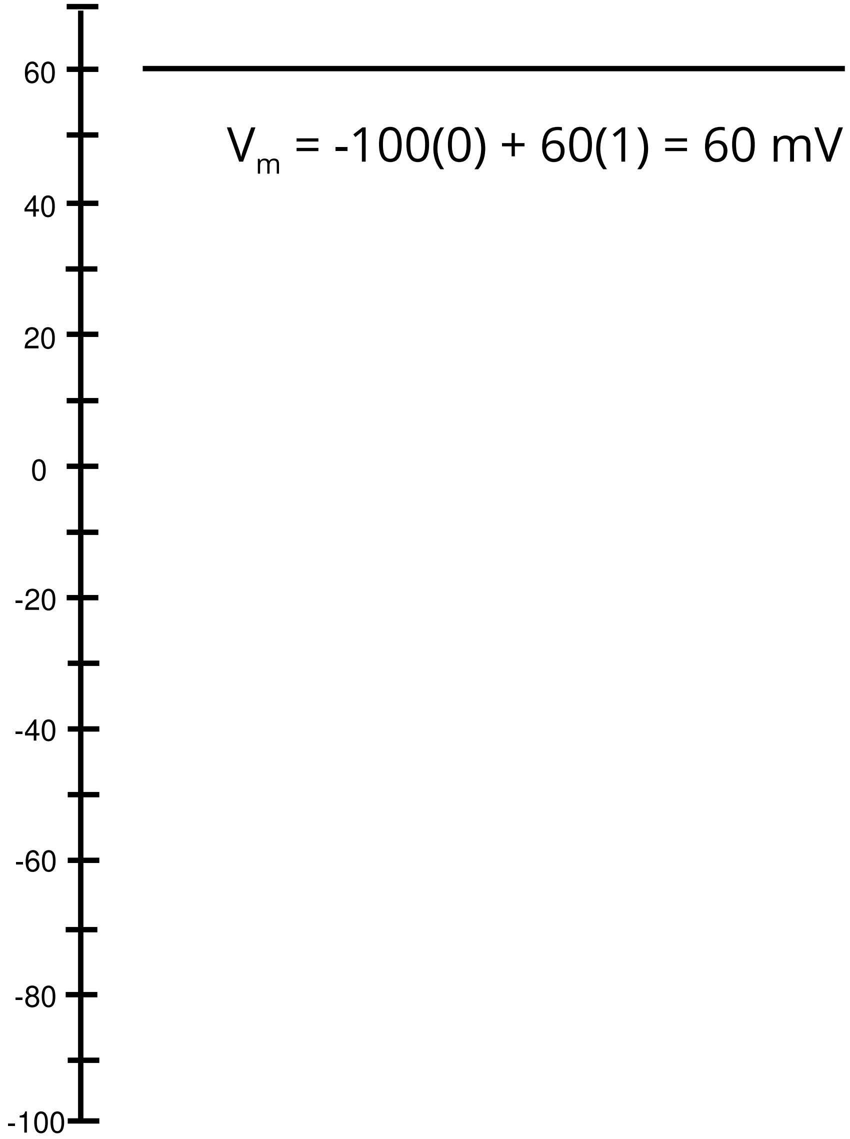
- Vrest = Resting membrane potential
- Threshold = Voltage at which action potential fires (point of no return)
- Depolarization = Potential moves in the positive direction
- Repolarization = Potential moves toward resting membrane potential
- Afterhyperpolarization = Potential overshoots on its way back to resting

Membrane Potential

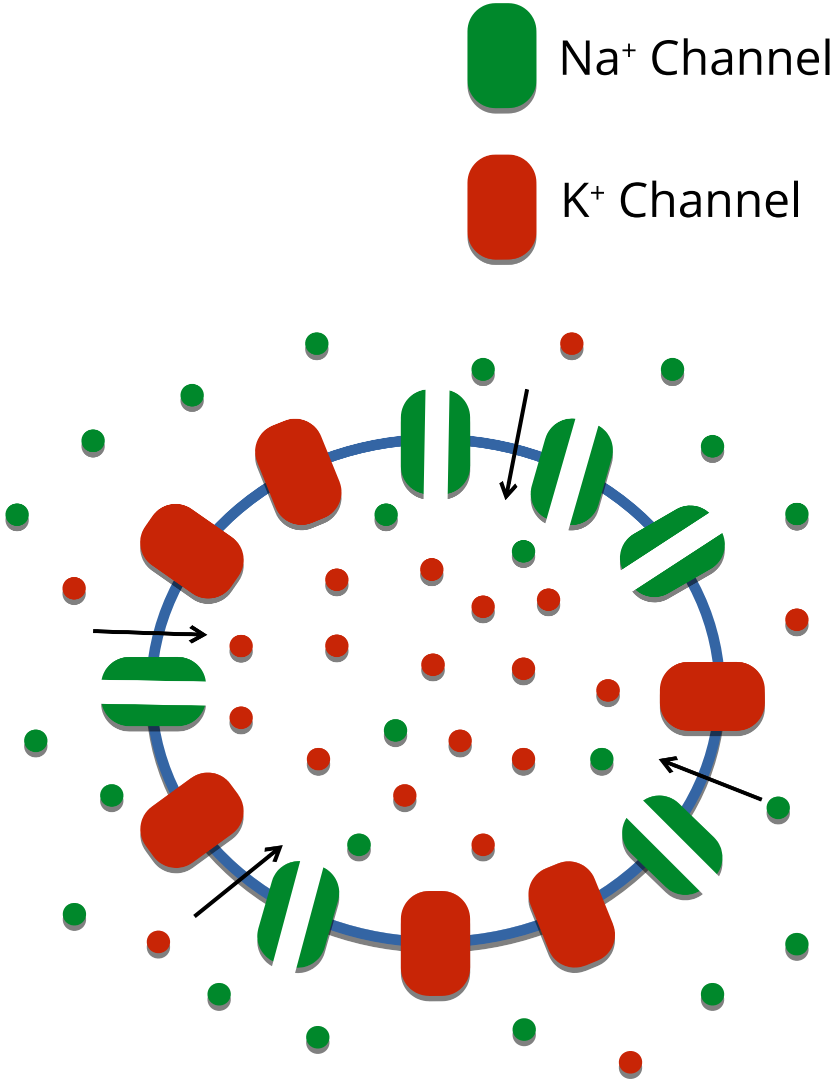




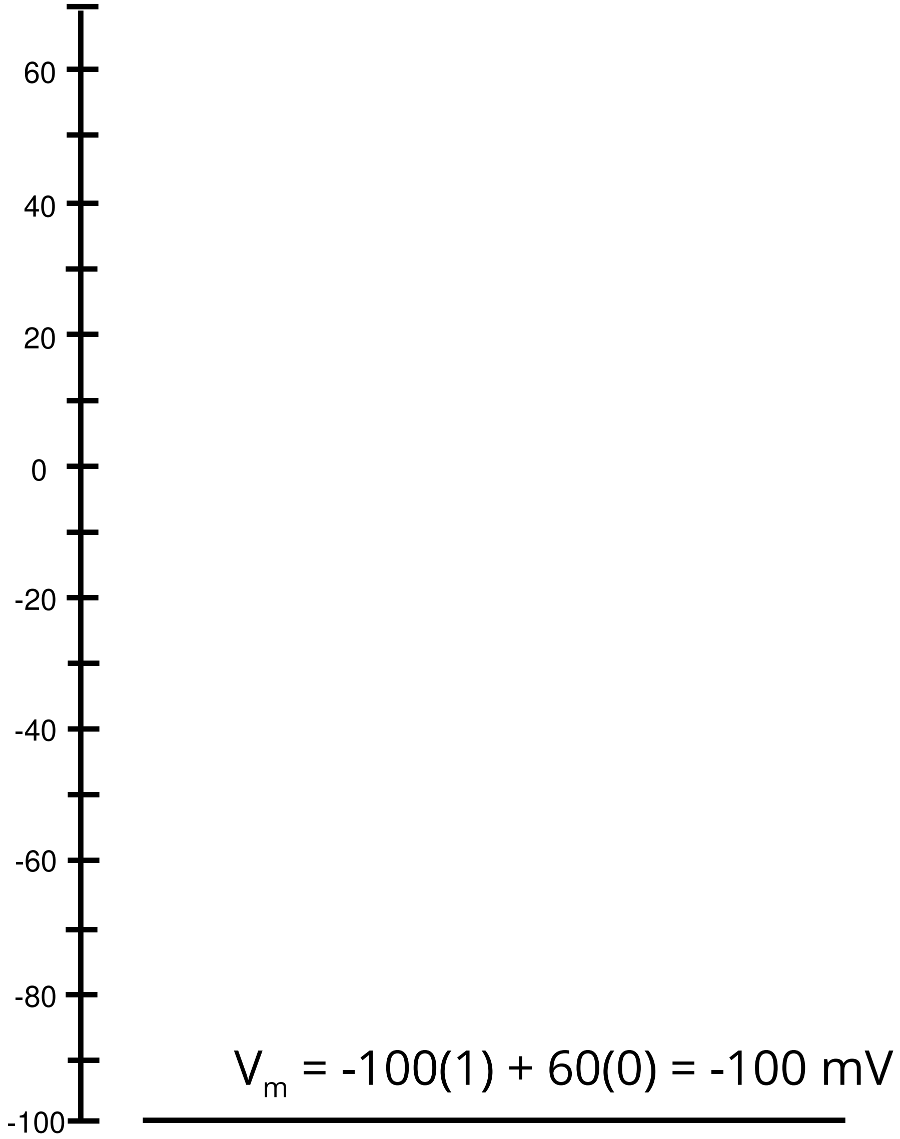
Membrane Potential

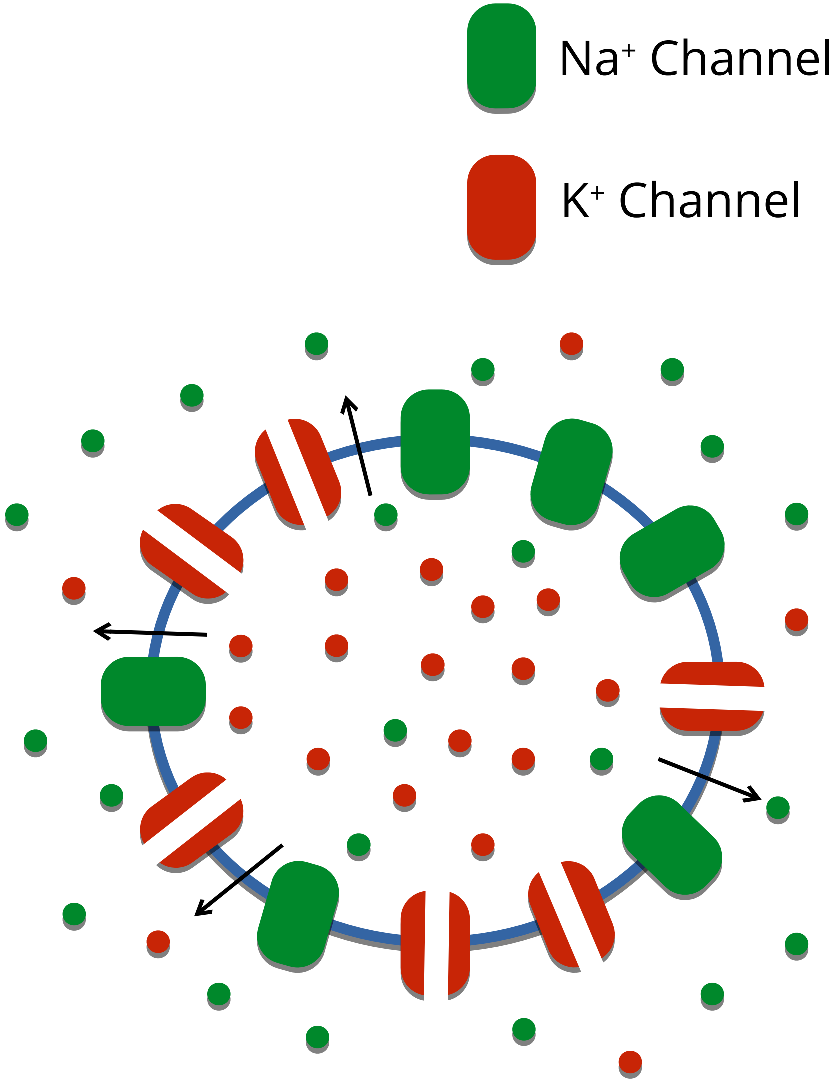


$V_m = -100(0) + 60(1) = 60$ mV

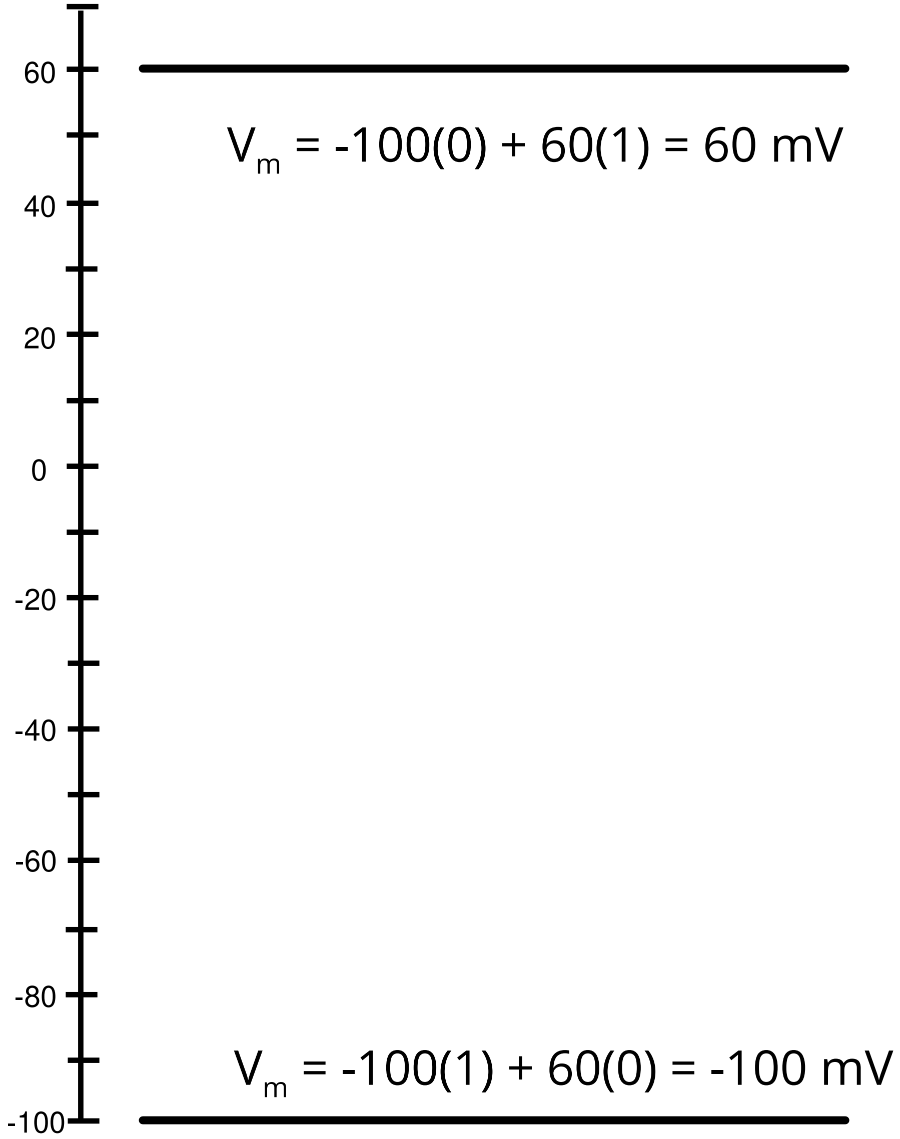


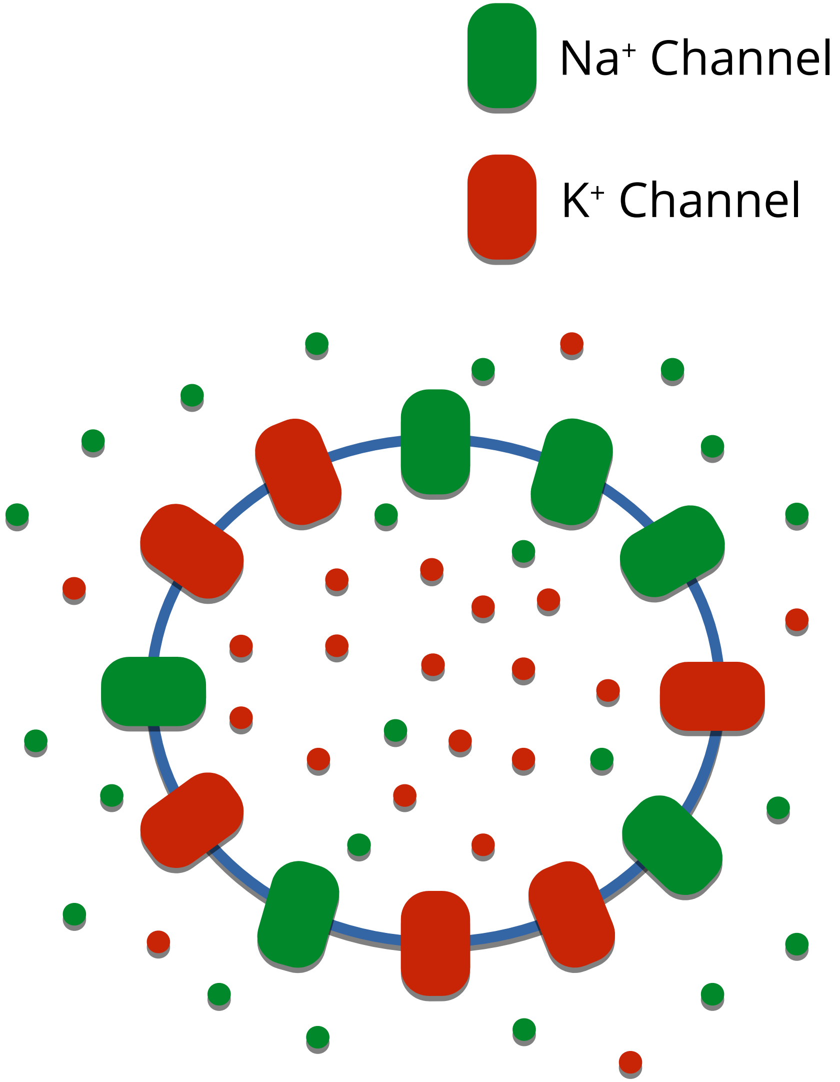
Membrane Potential



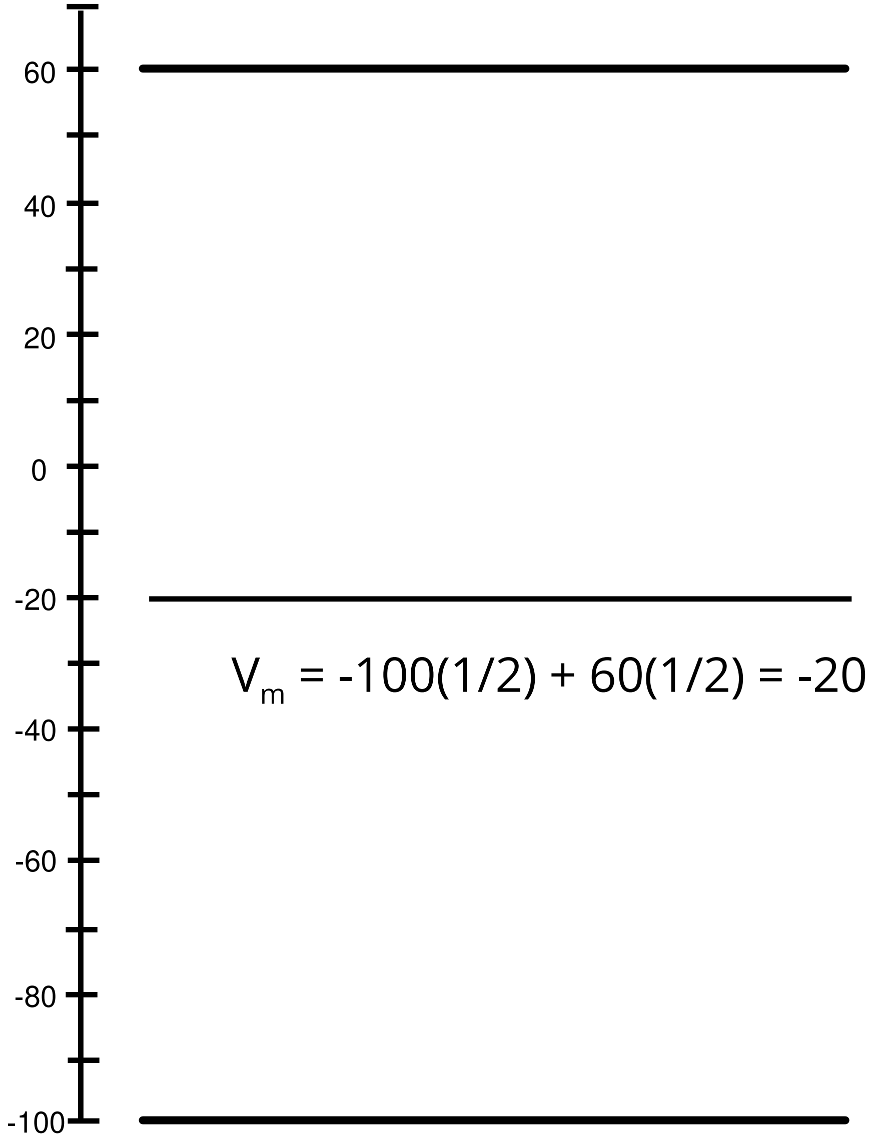


Membrane Potential

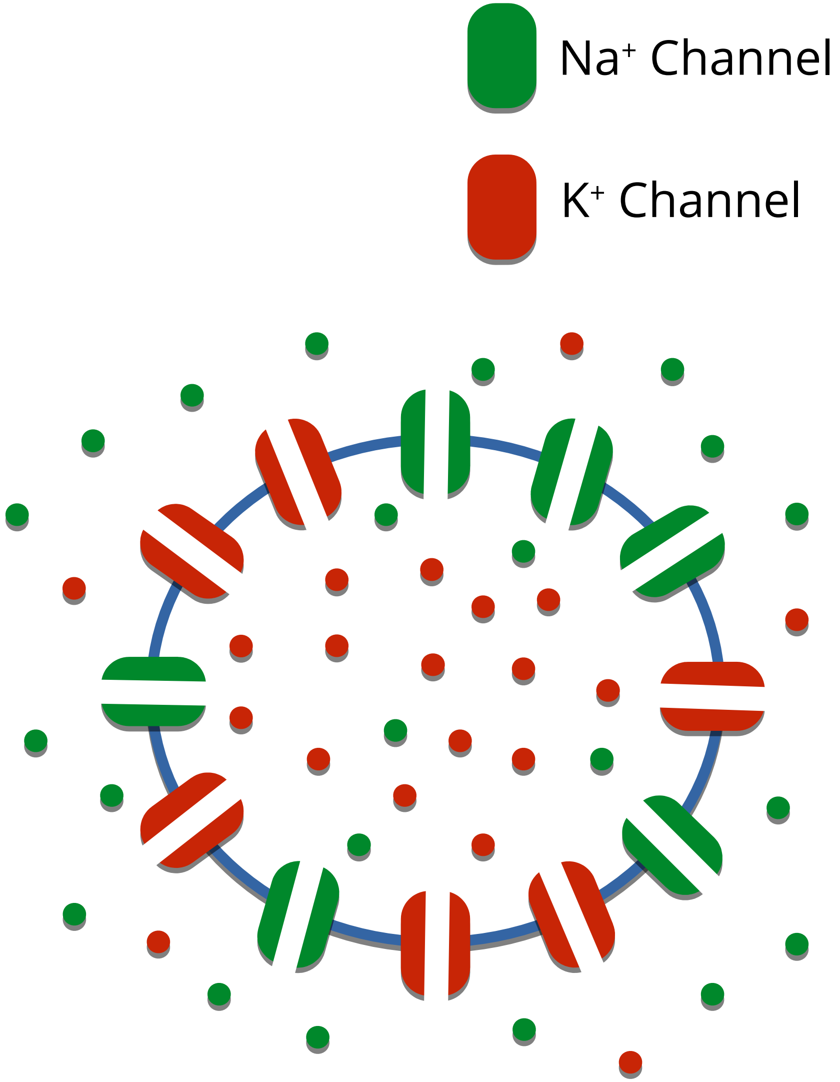




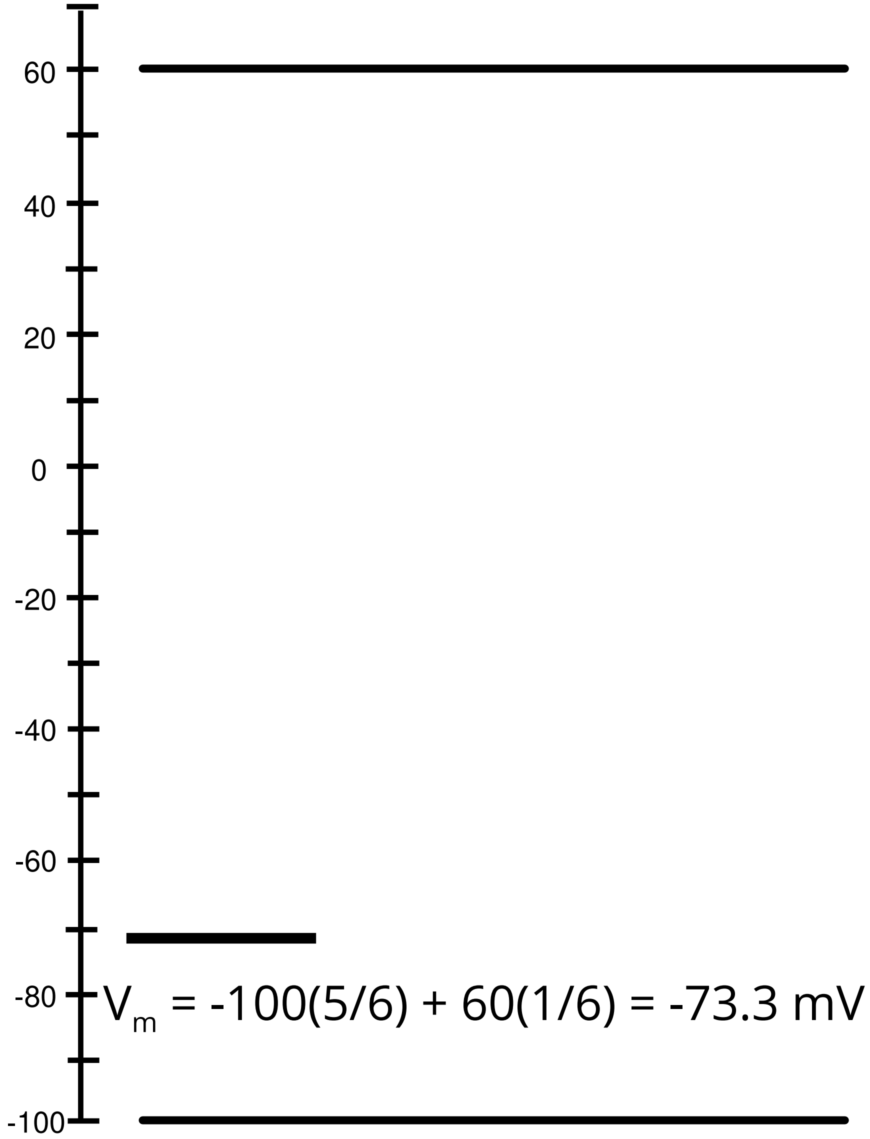
Membrane Potential



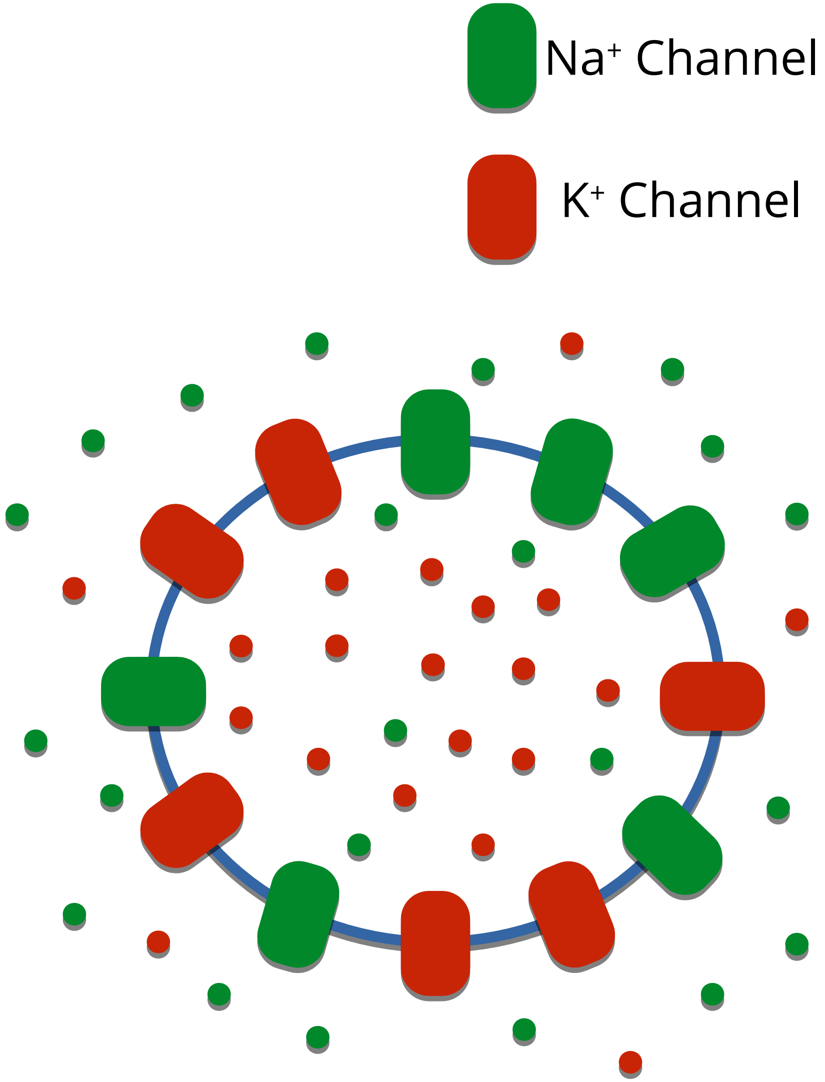
$V_m = -100(1/2) + 60(1/2) = -20$ mV



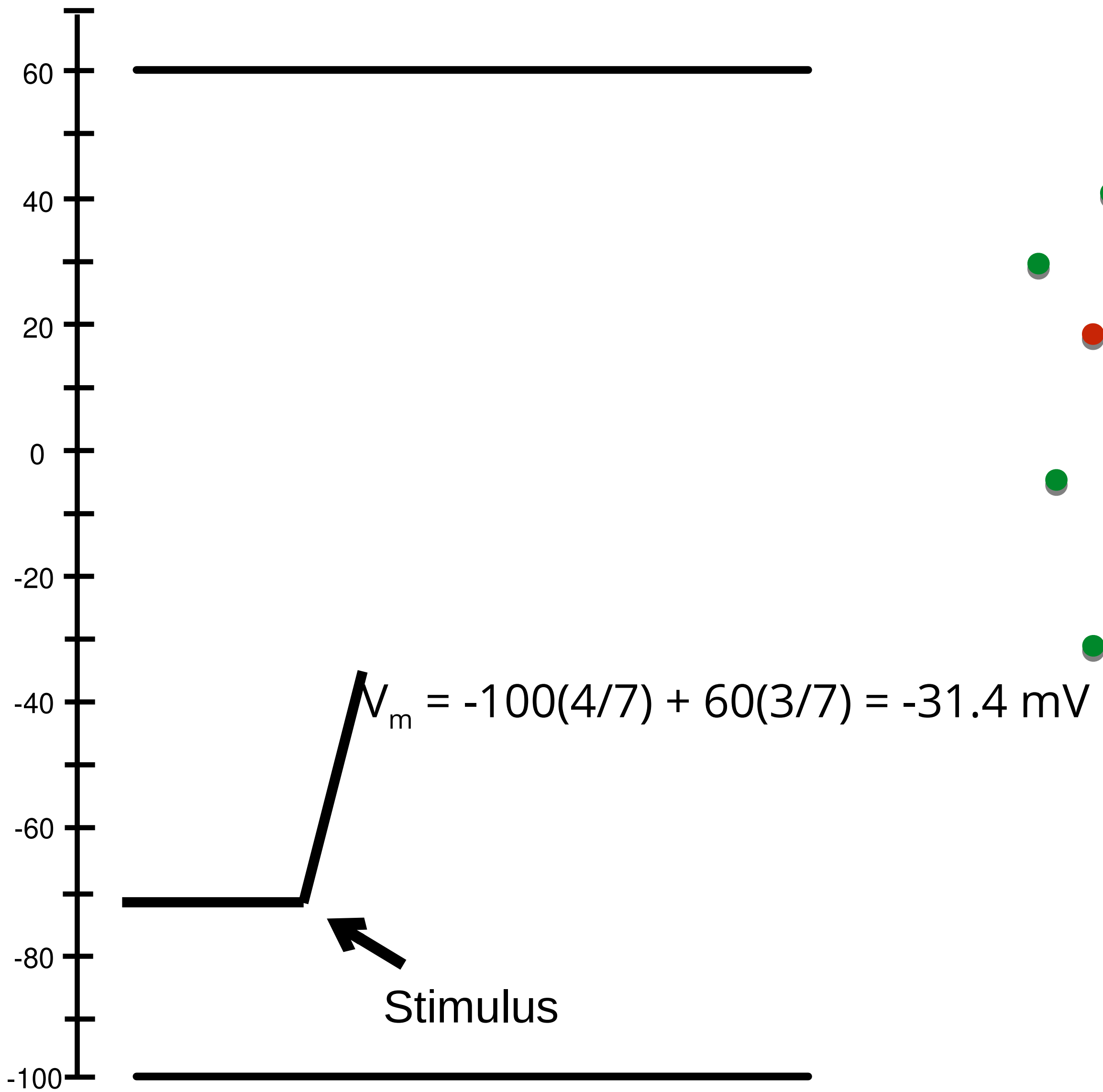
Resting



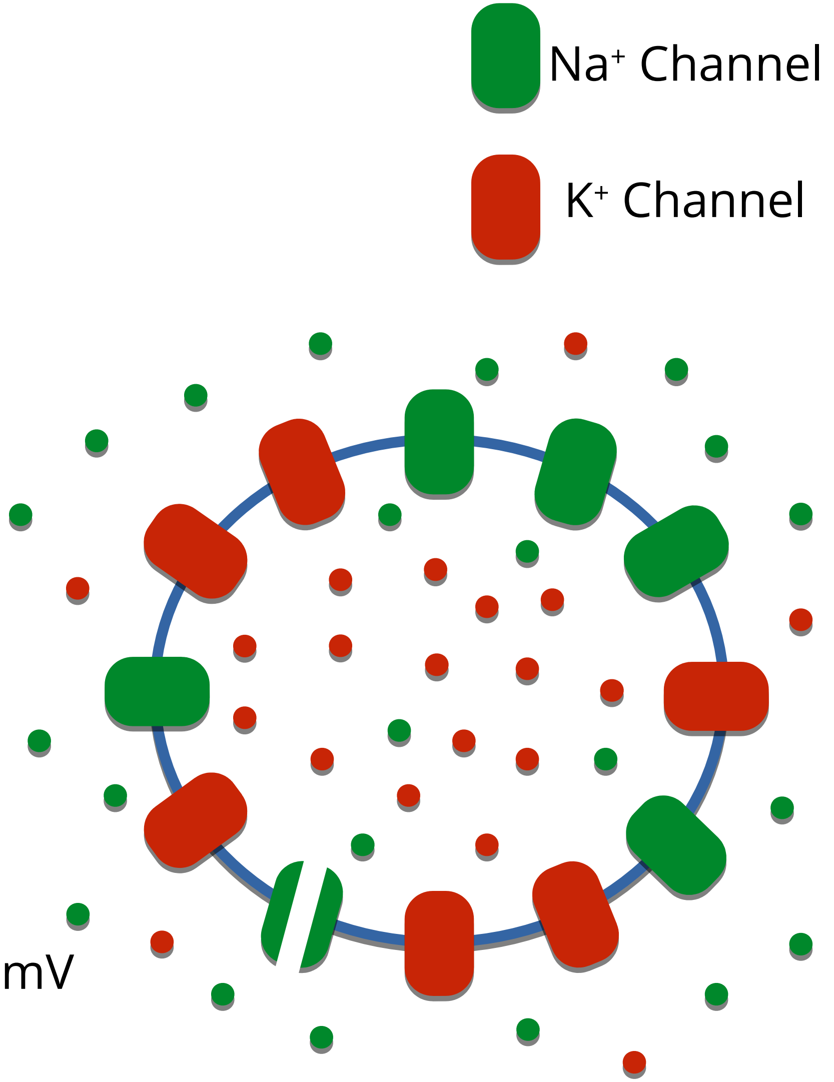
V_m = -100(5/6) + 60(1/6) = -73.3 mV



Threshold

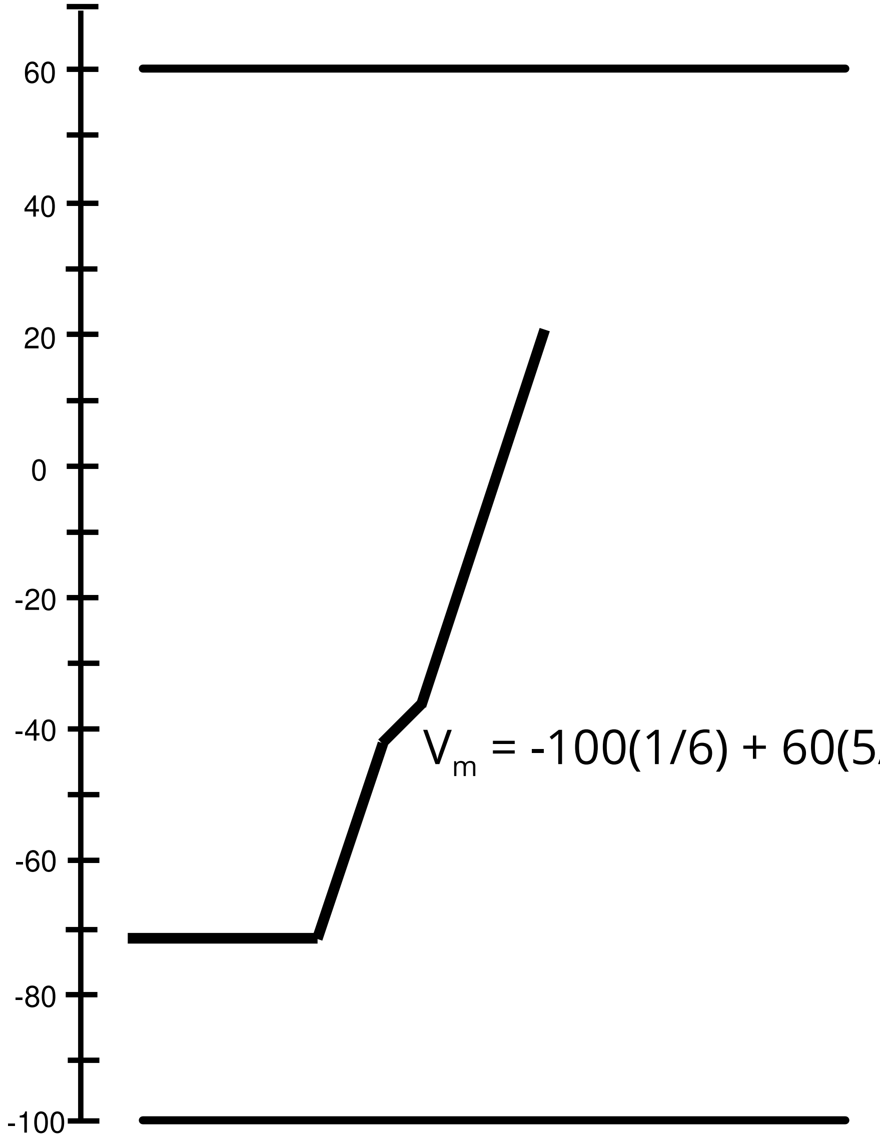


60
40
20
0
-20
-40
-60
-80
-100
$V_m = -100(4/7) + 60(3/7) = -31.4$ mV
Stimulus

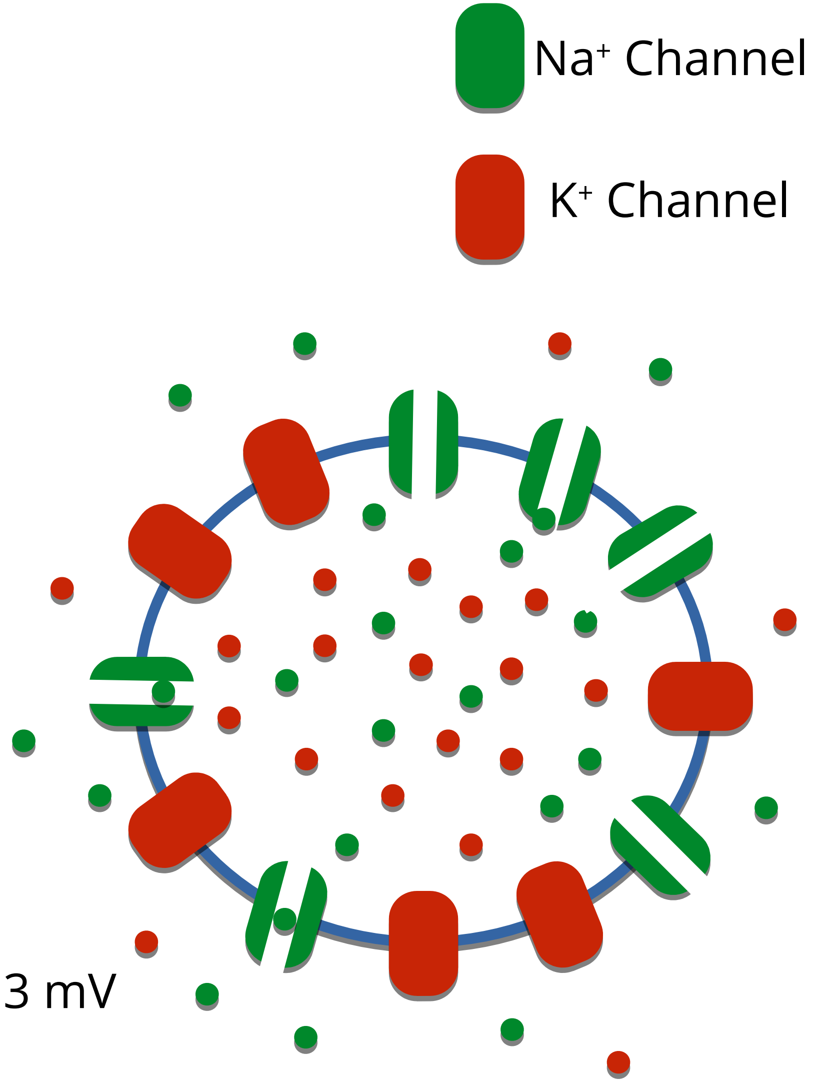


Na^+ Channel
K^+ Channel

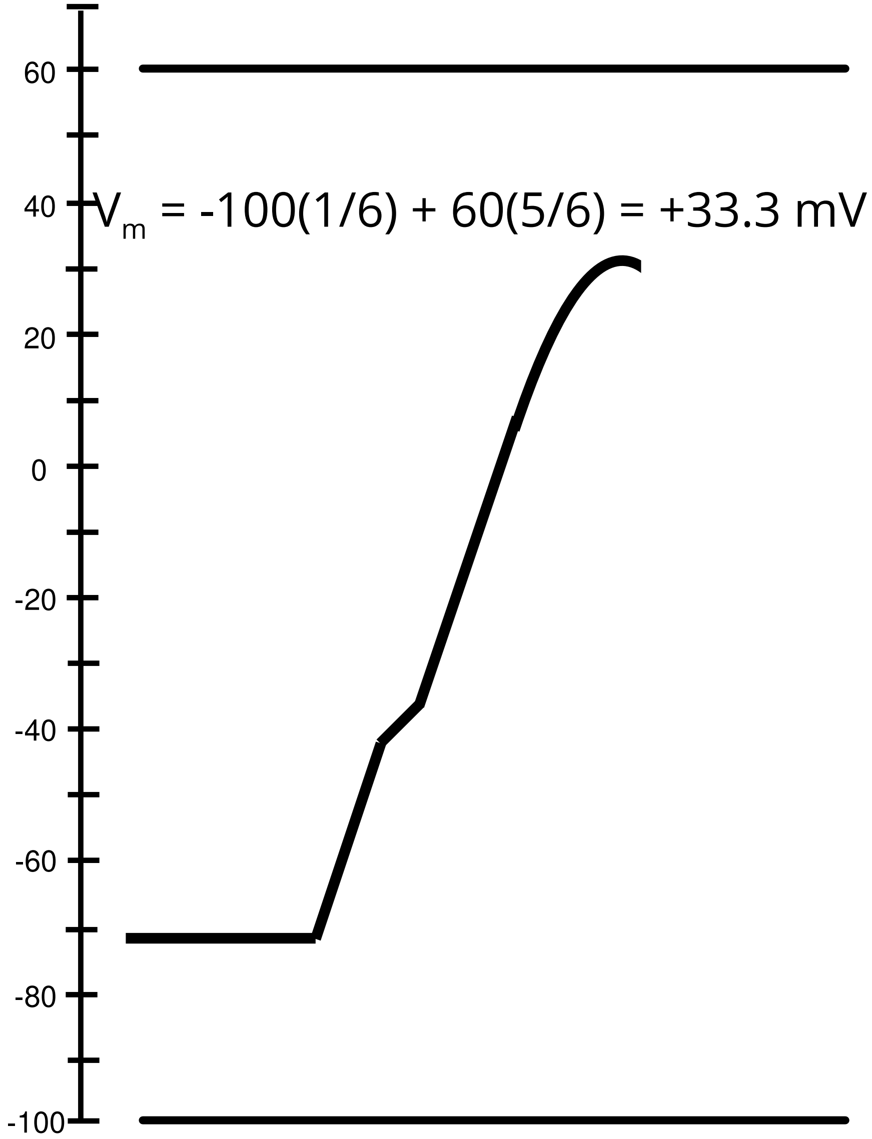
Depolarization



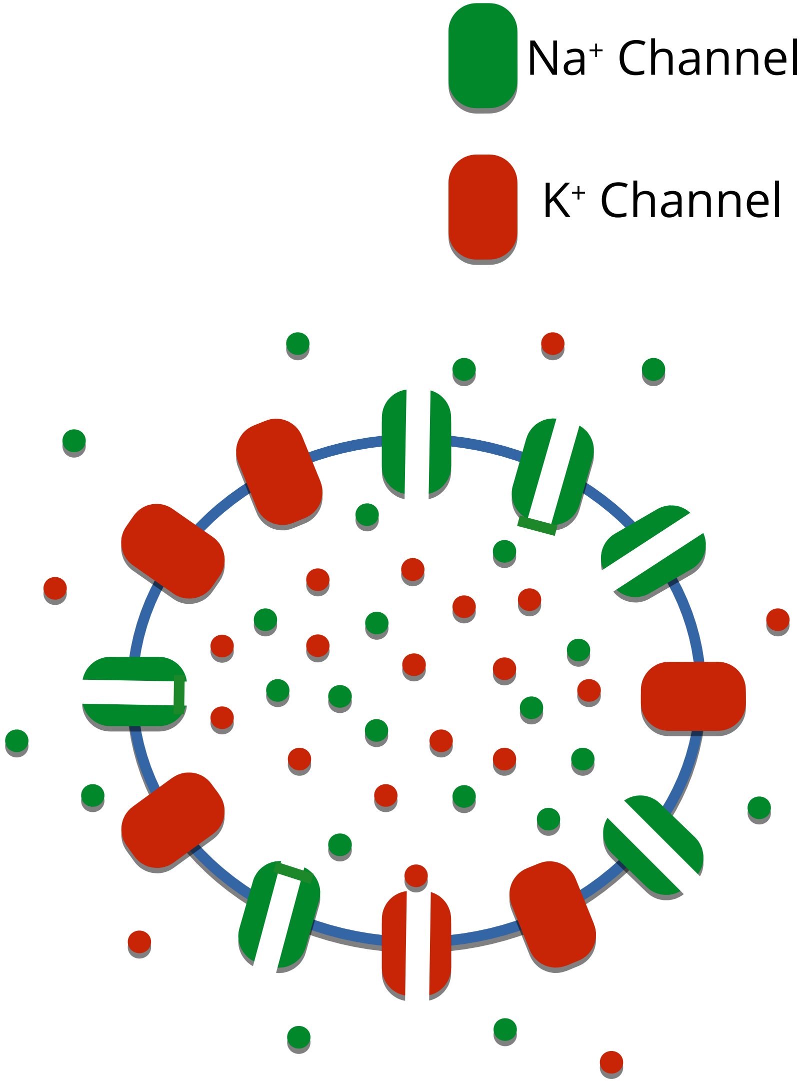
$V_m = -100(1/6) + 60(5/6) = +33.3$ mV



Peak

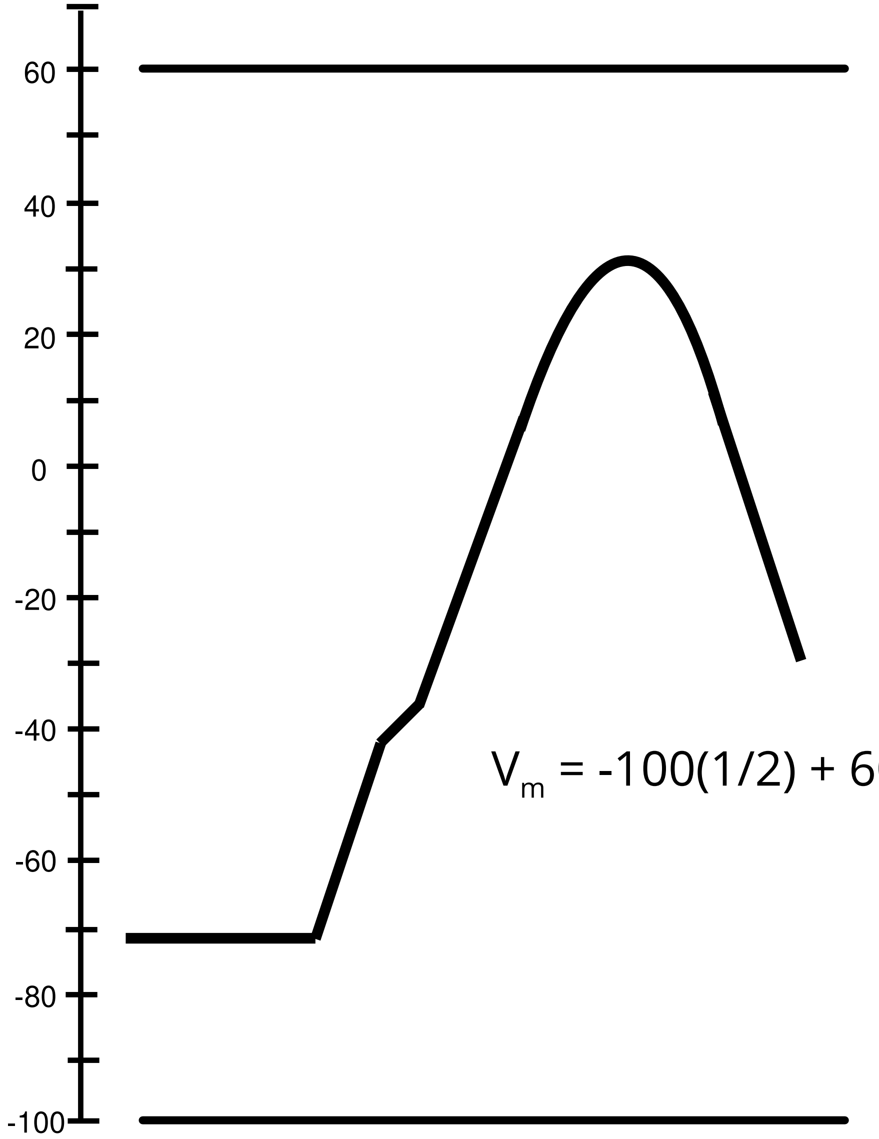


60
40
20
0
-20
-40
-60
-80
-100
V_m = -100(1/6) + 60(5/6) = +33.3 mV

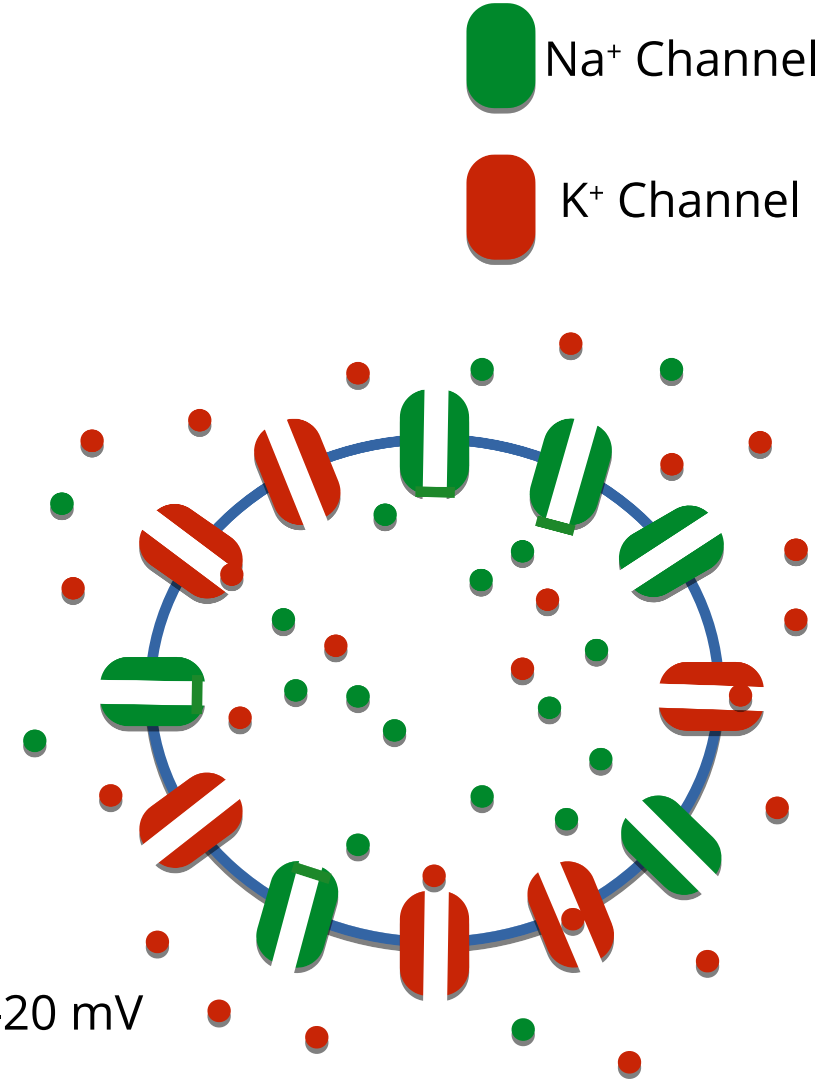


Na^+ Channel
K^+ Channel

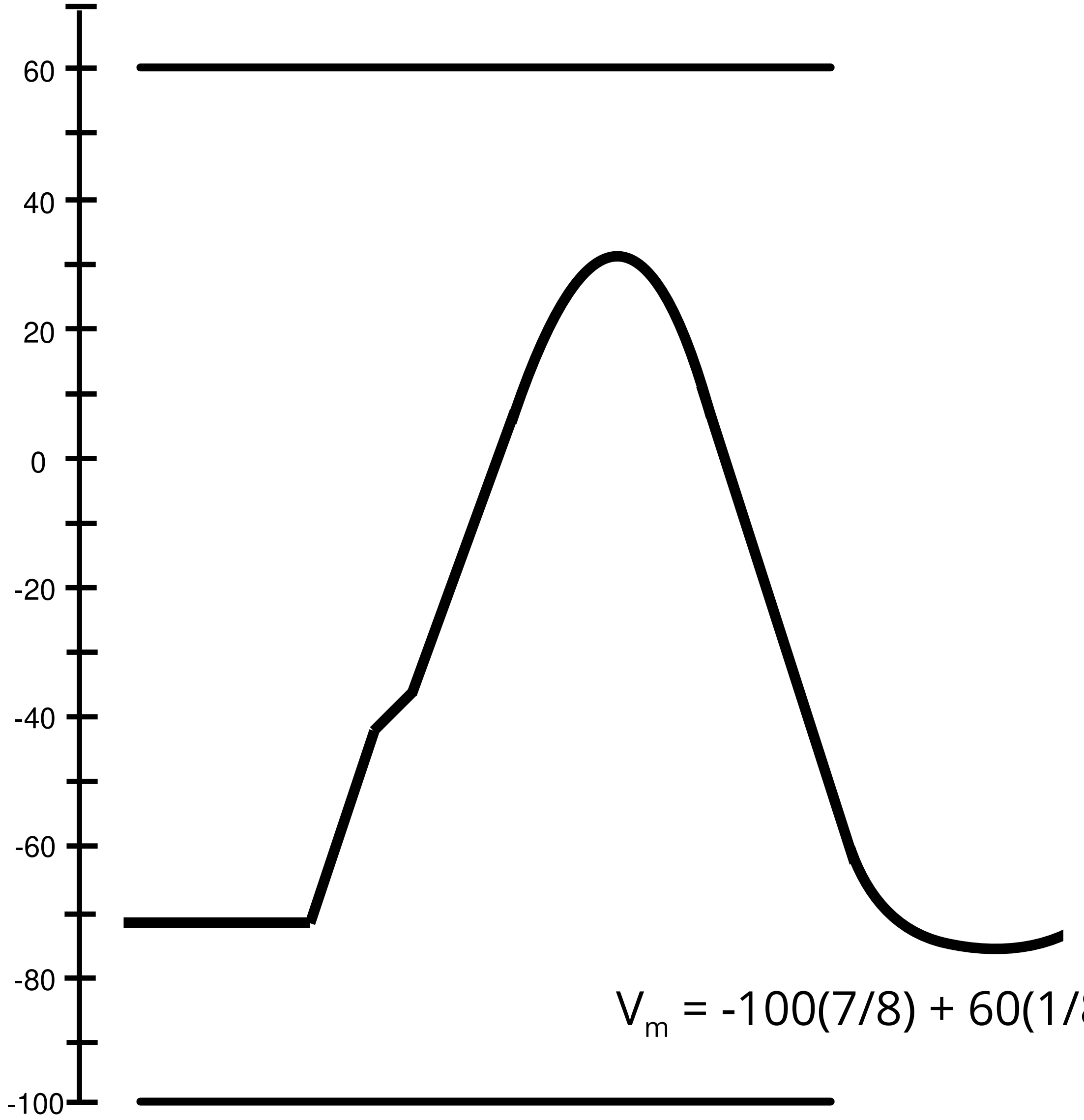
Repolarization

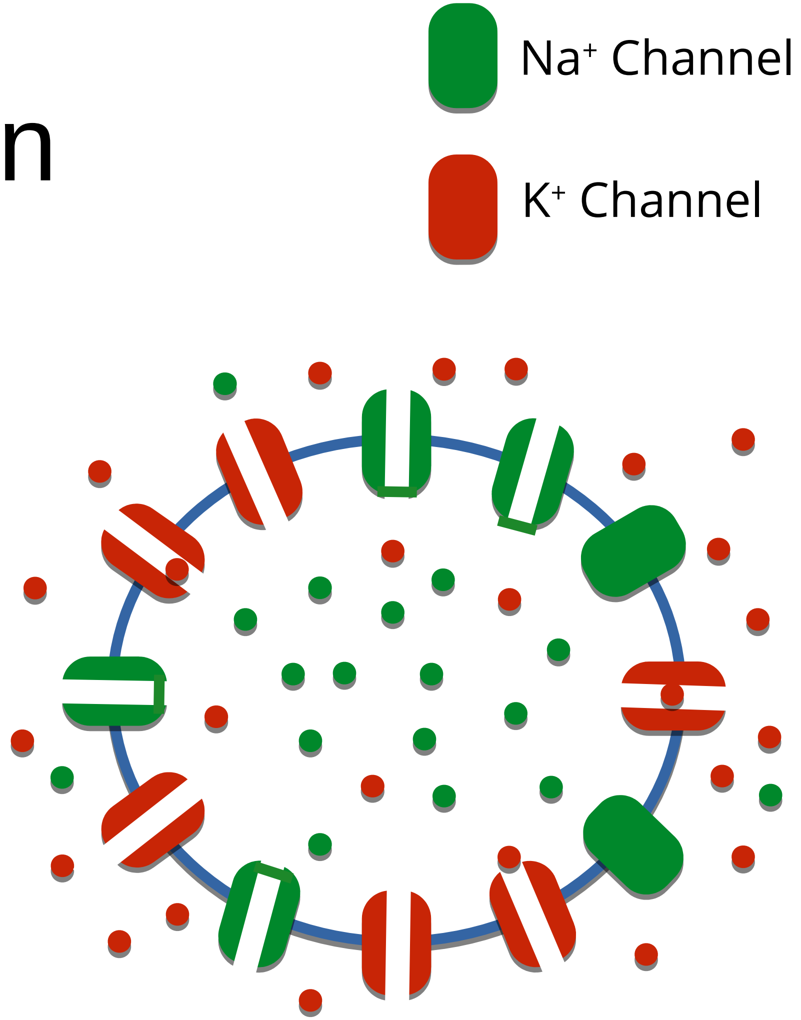


$V_m = -100(1/2) + 60(1/2) = -20 \text{ mV}$



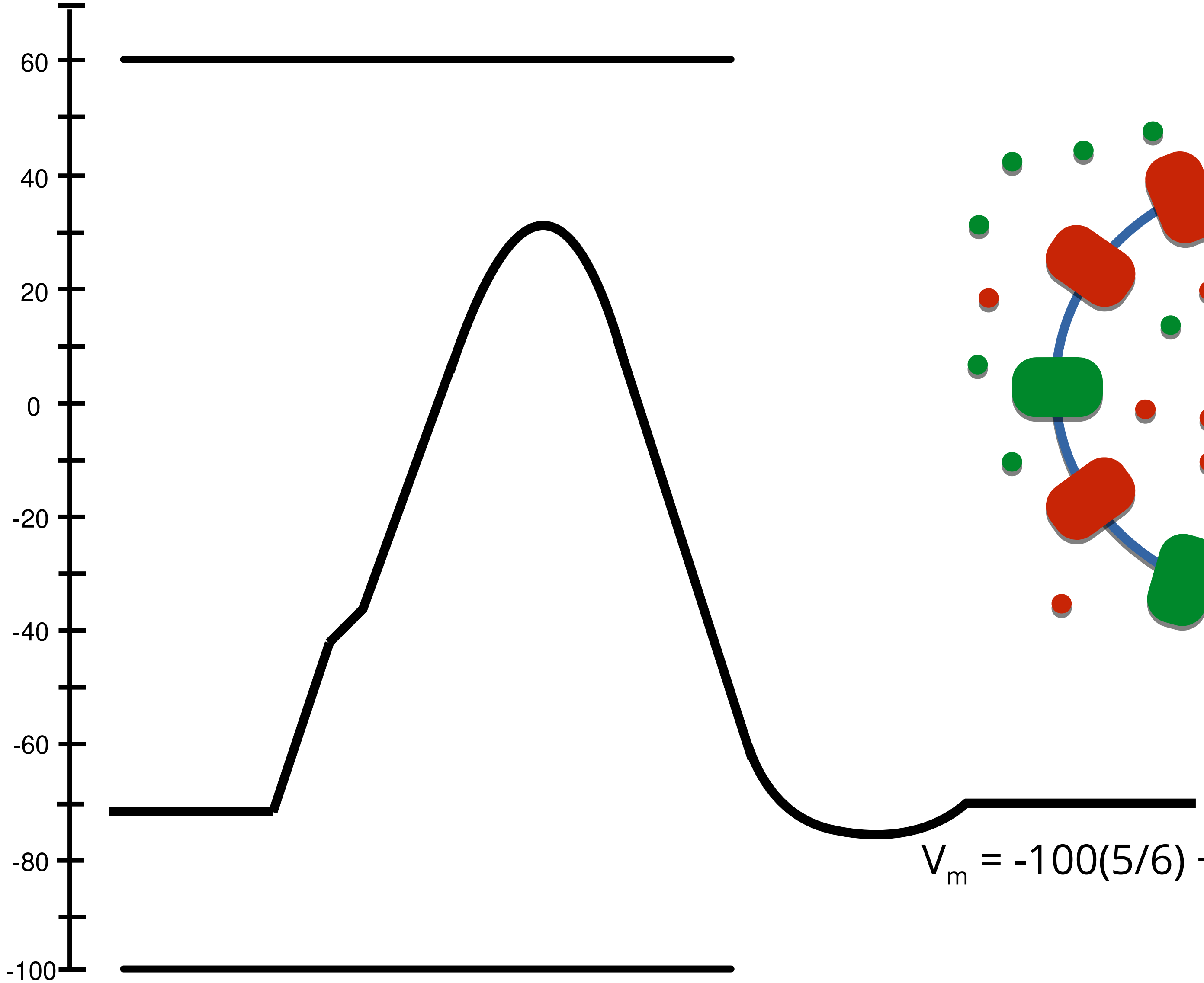
Afterhyperpolarization

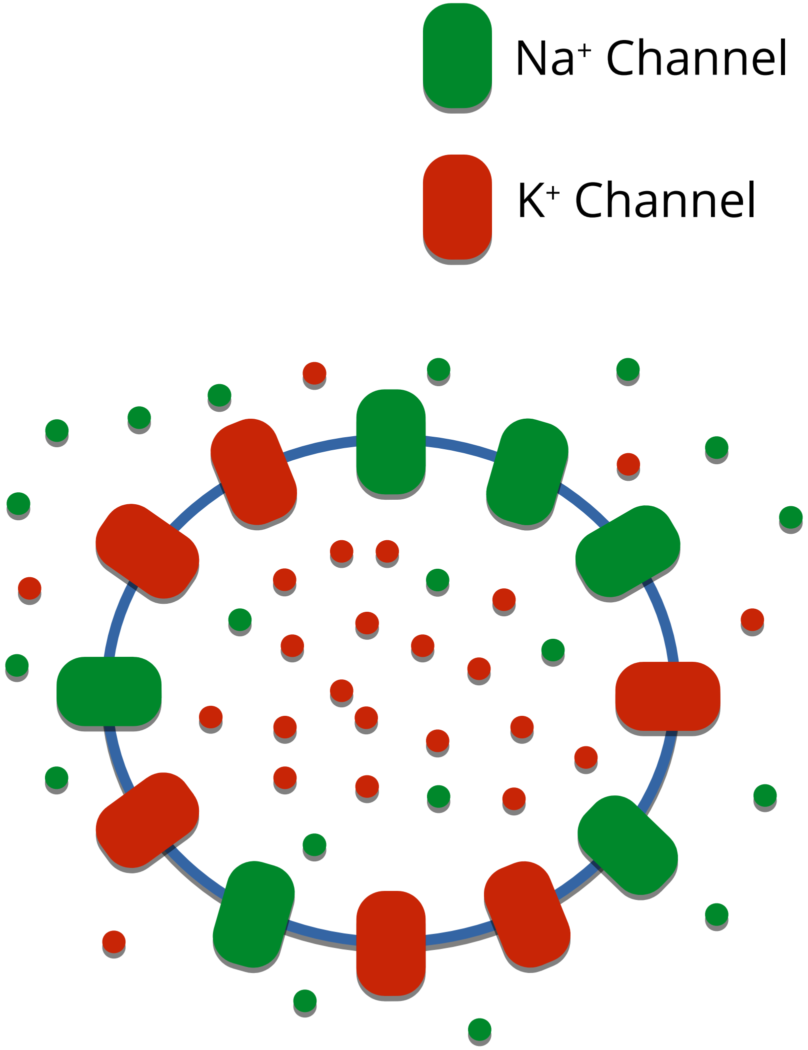




$$V_m = -100(7/8) + 60(1/8) = -80 \text{ mV}$$

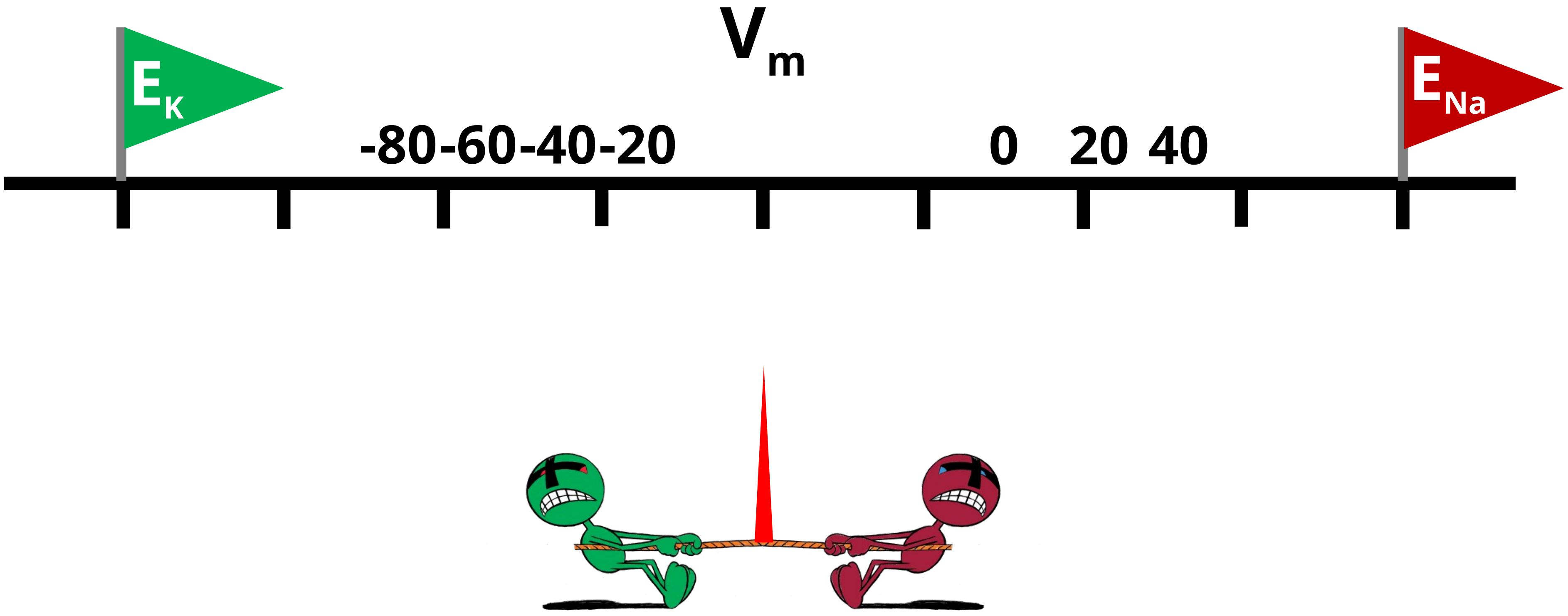
Return to Rest



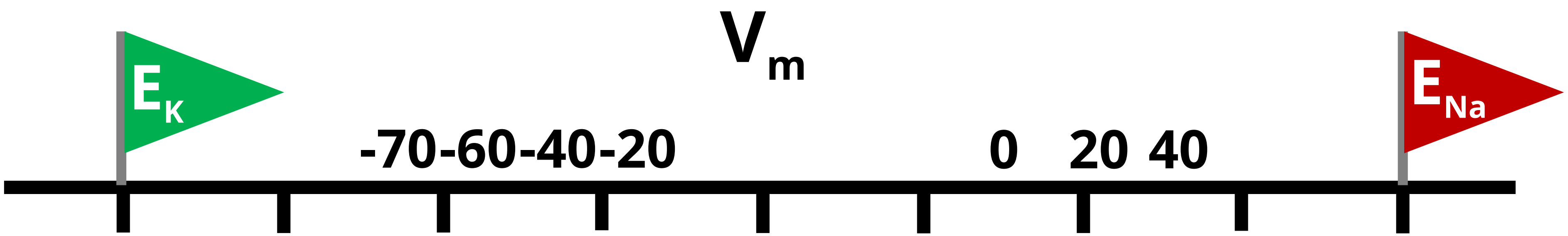


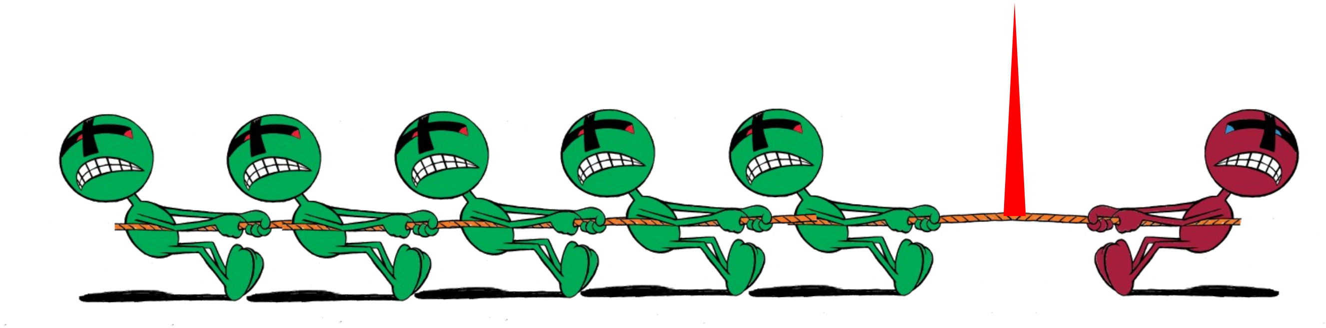
$V_m = -100(5/6) + 60(1/6) = -73.3$ mV

Conductance Tug-of-War Games



Conductance Tug-of-War Games

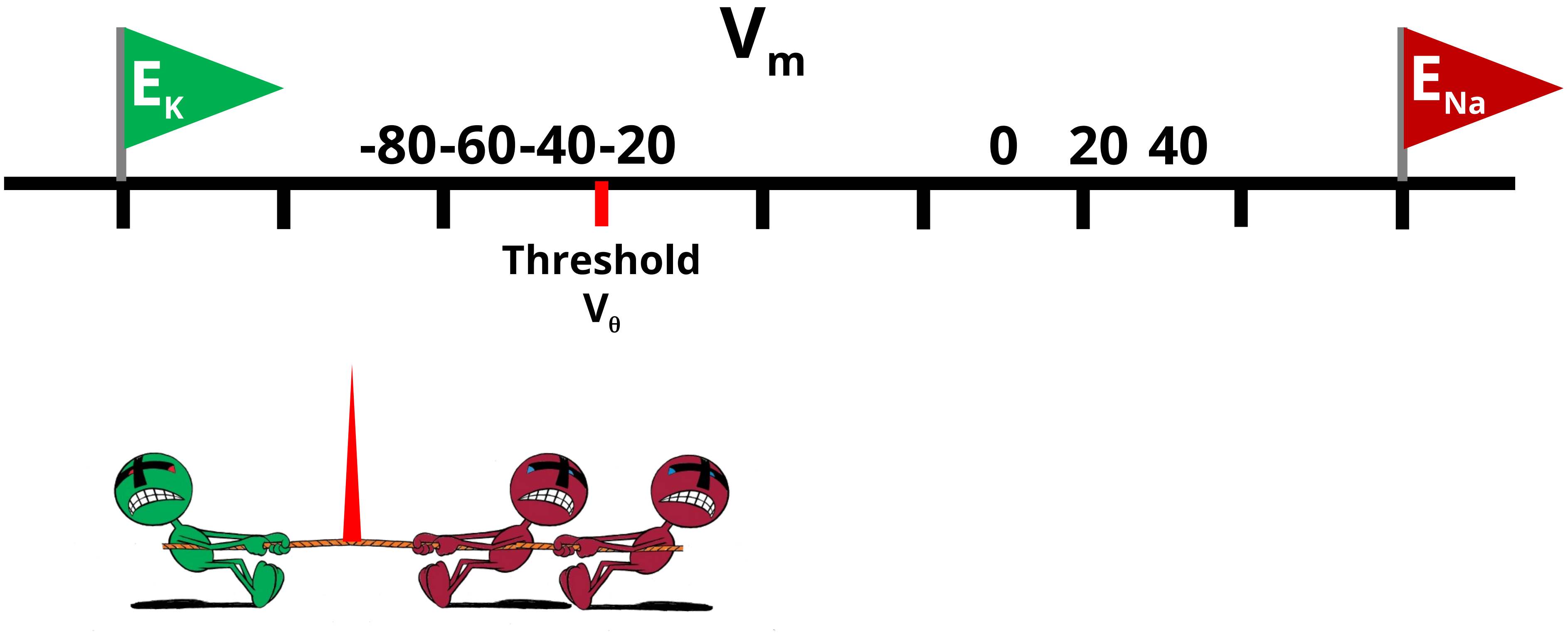




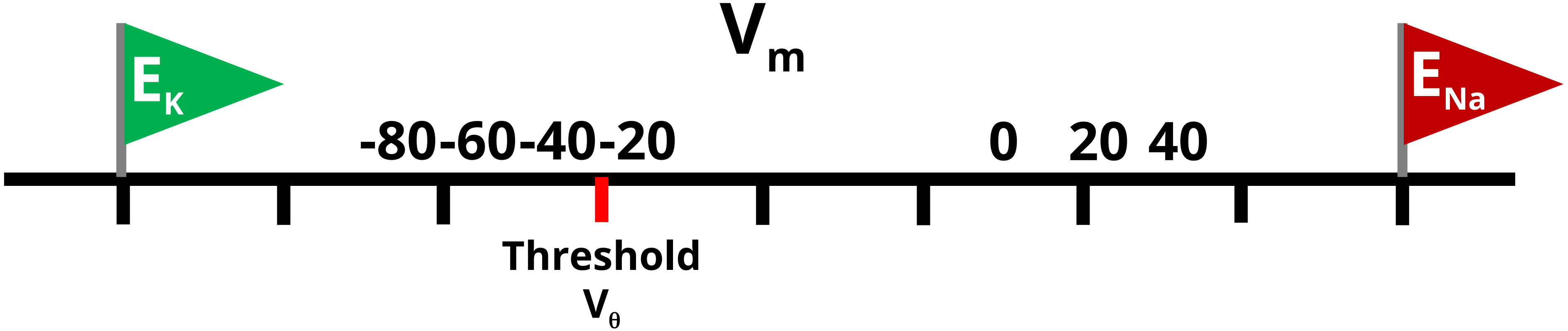
V_m = -100(5/6) + 60(1/6) = -73.3 mV

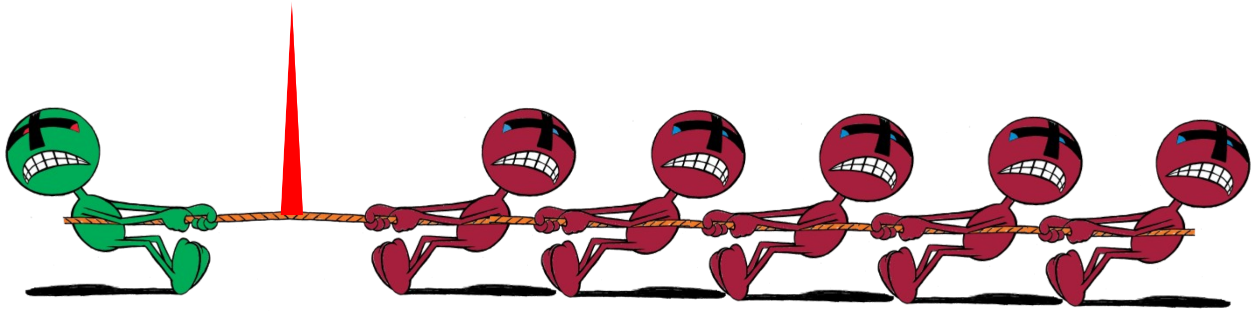
MC013

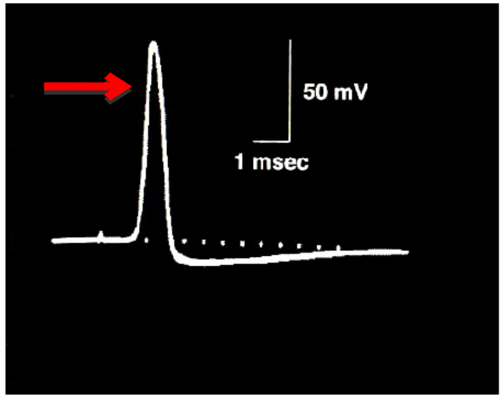
Conductance Tug-of-War Games



Conductance Tug-of-War Games

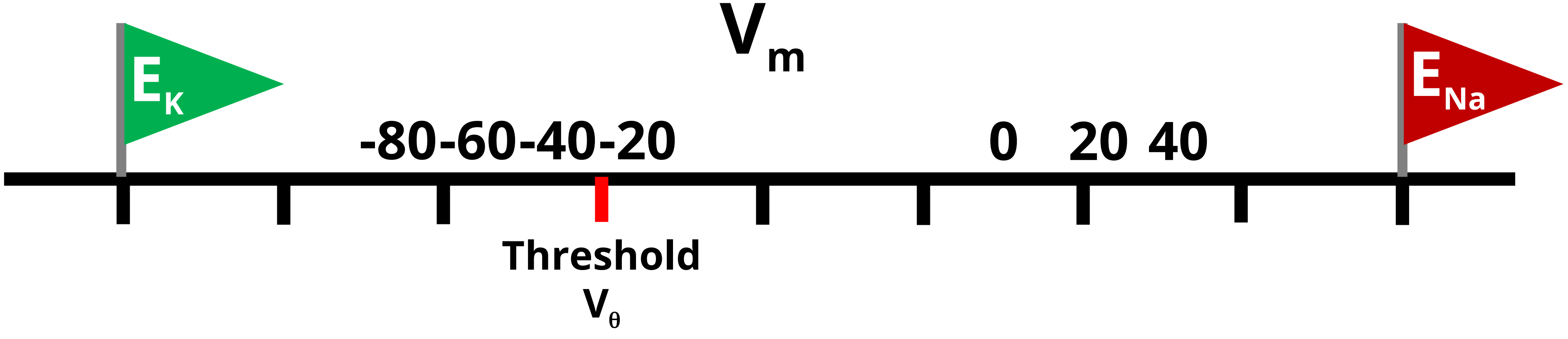


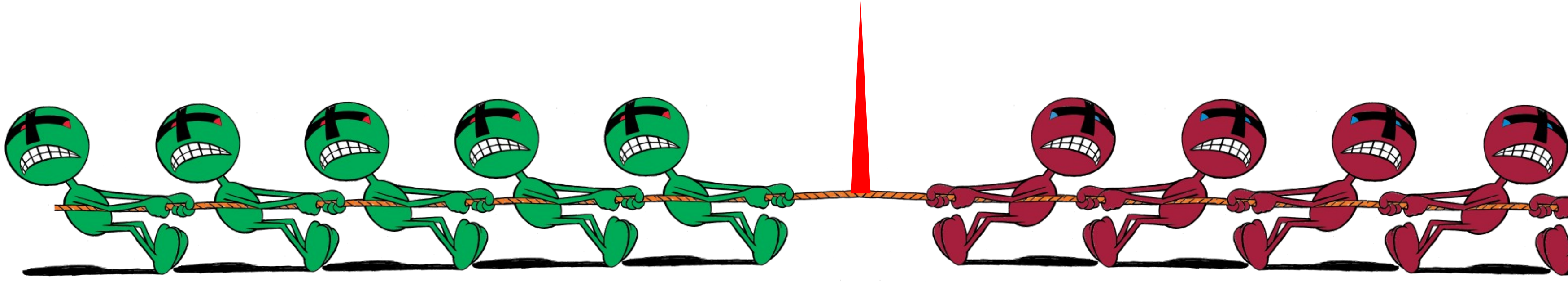


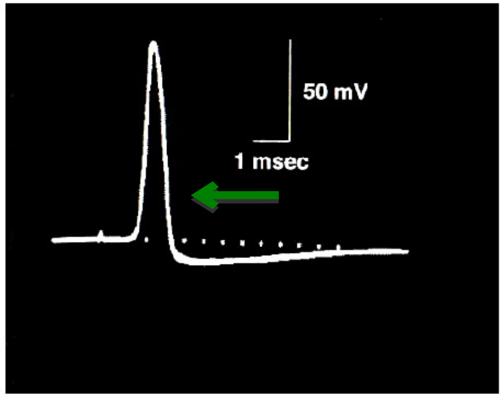


V_m = -100(1/6) + 60(5/6) = +33.3 mV

Conductance Tug-of-War Games

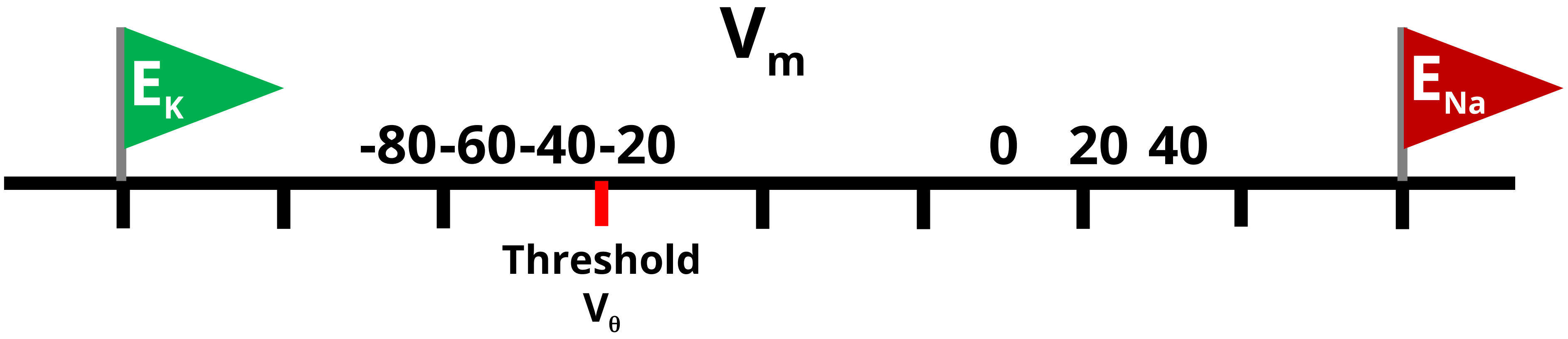


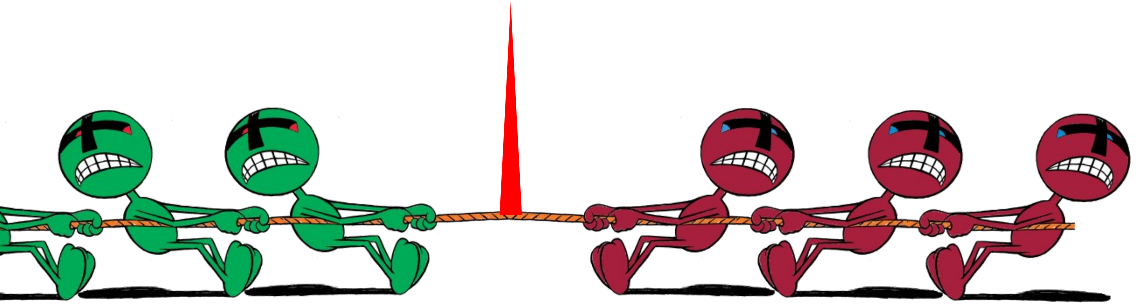


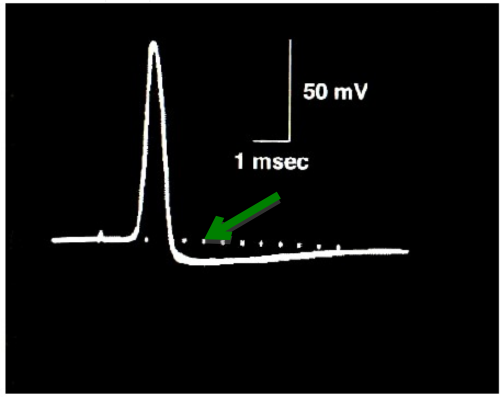


$V_m = -100(2/3) + 60(1/3) = -46.7$ mV MC©13

Conductance Tug-of-War Games

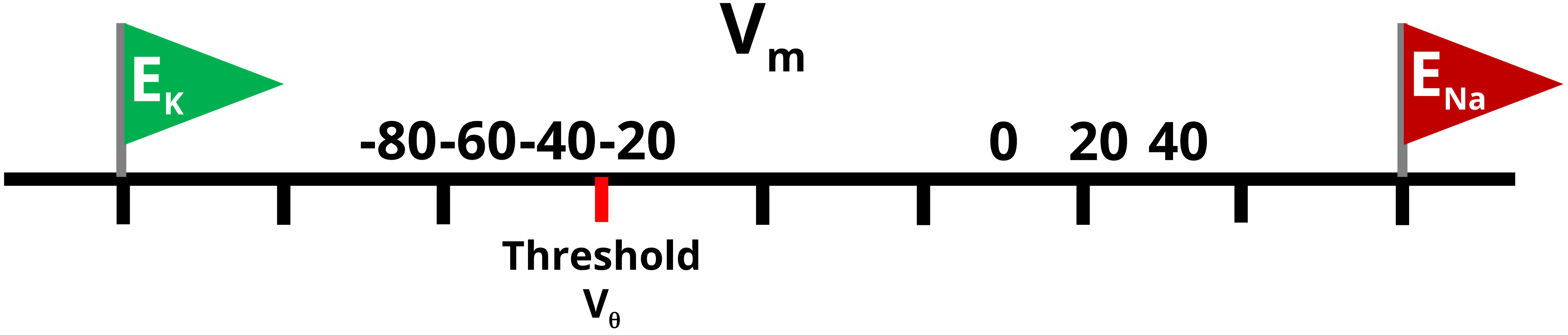


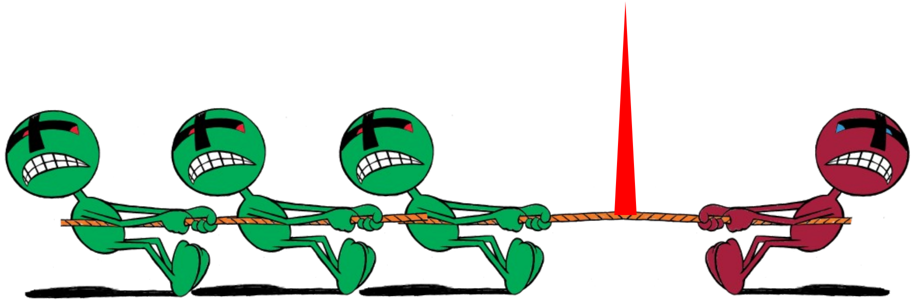


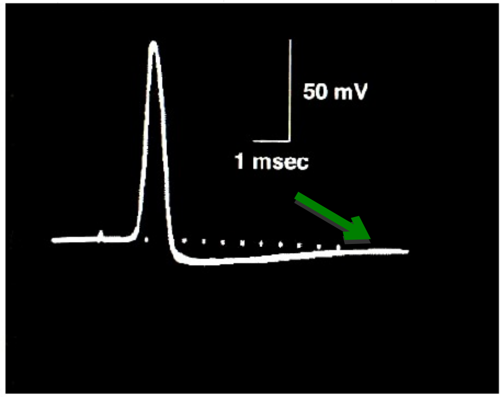


V_m = -100(6/6) + 60(0/6) = -100 mV

Conductance Tug-of-War Games





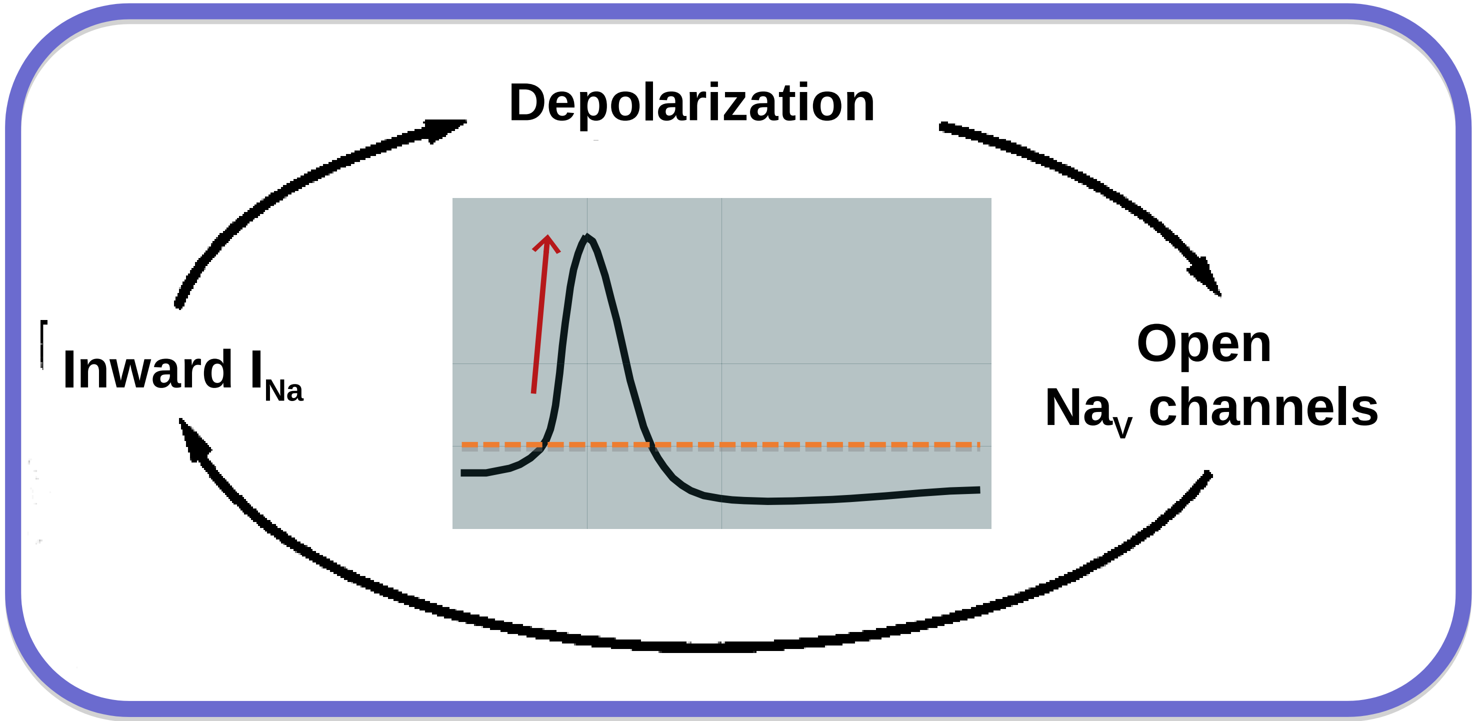


$V_m = -100(5/6) + 60(1/6) = -73.3\text{ mV}$

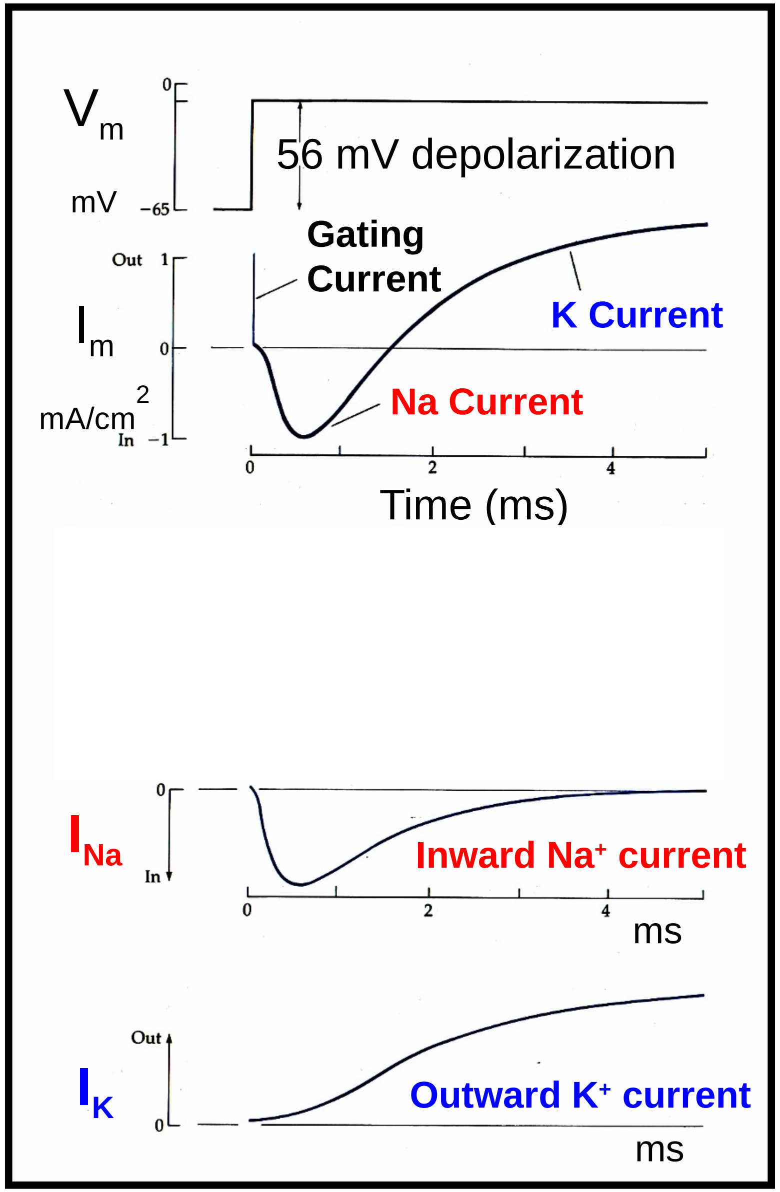
MC©13

The positive feedback loop of the action potential

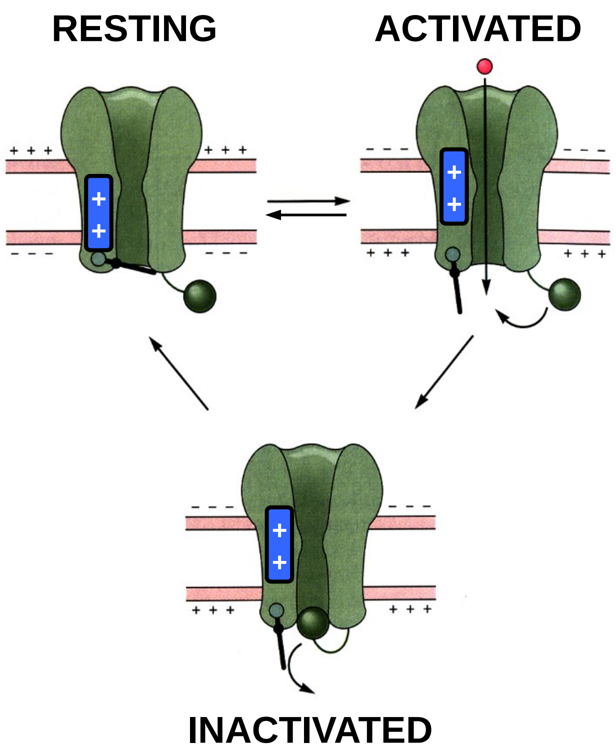
(regenerative property of the AP)



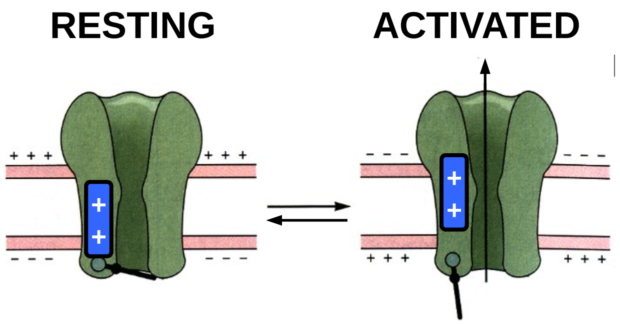
The Voltage-Clamp Perspective of the AP



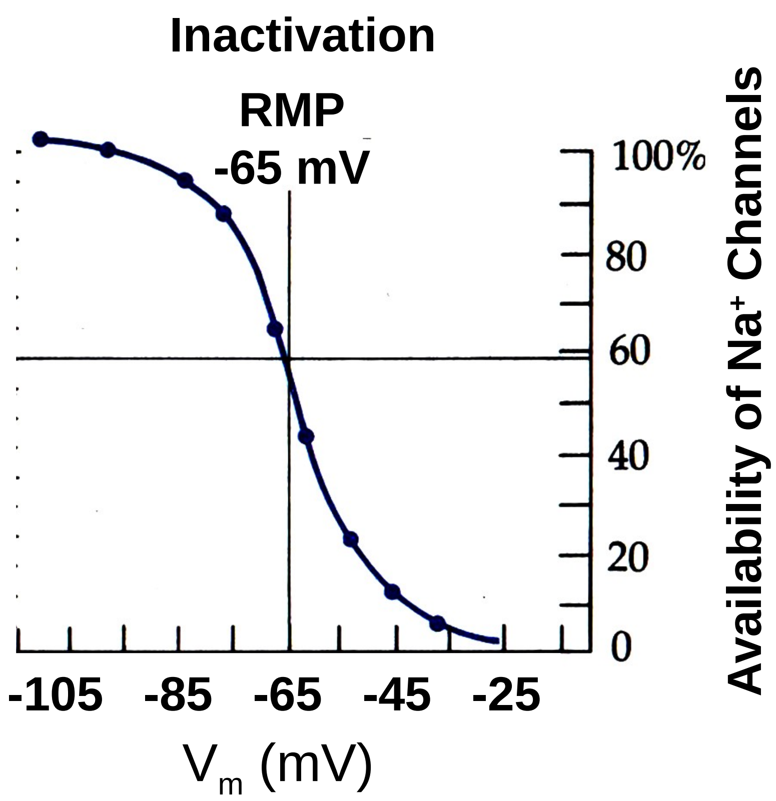
Na_V Channel

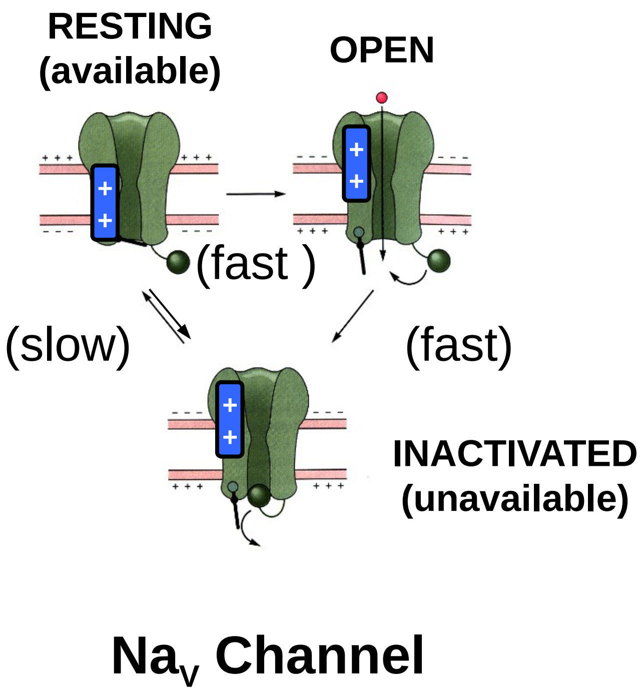


K_V Channel



Voltage-dependent Inactivation of Na^+ Channels



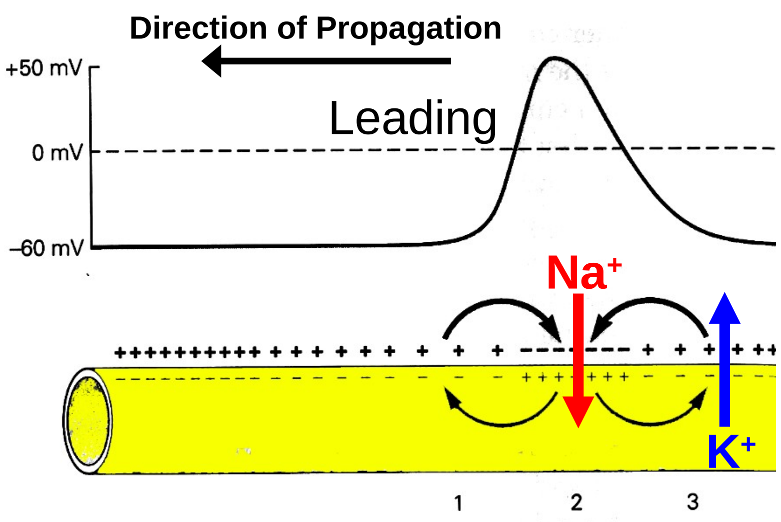


Na^+ channels can inactivate slowly without opening. Thus, a small sustained depolarization that does not reach threshold may be sufficient prevent AP firing. This may happen as a result of modest hyperkalemia (external K^+ is elevated)

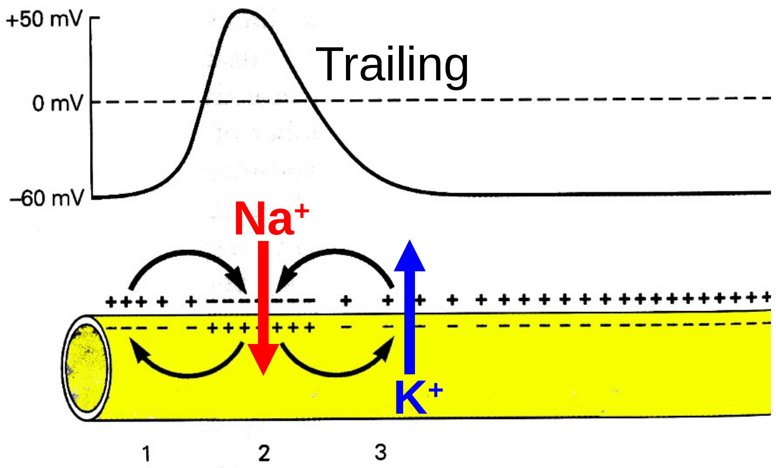
Active propagation in un-myelinated axons
Local Circuits

Active depolarization and repolarization at the leading and trailing edges of the AP, respectively

Unidirectional AP propagation

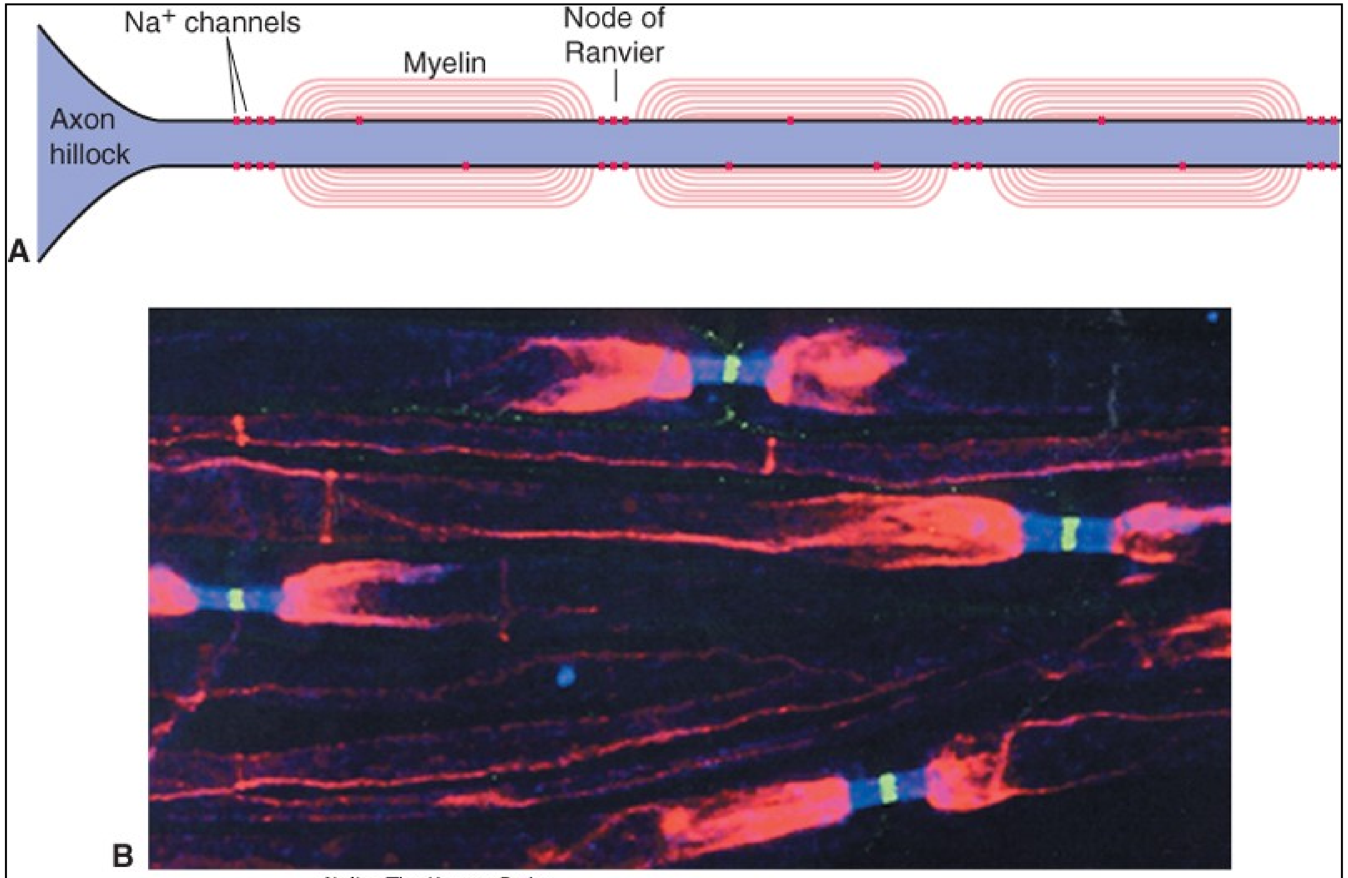


A short time later……..



Myelination

myelin sheaths at intervals of ~ 1 mm



Nolte: The Human Brain.
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Immunofluorescence: Node of Ranvier marker (blue); Na_V channels (green); K_V channels (red)