Neuro 80 Lecture 4 — September 16

Electrical basis of Neural Function

resting potential → action potential → synaptic potential

- Nernst Equation: impermeable anions and cation-selective channels
- Na^+ K^+ pump
- GHK equation

How does information flow?

- electrically
- chemically
- magnetically?

Luigi Galvani's Lab

Electricity in Nervous system vs wires

- Ions (cations: K^+, Na^+, Ca^{++}, anions: Cl^-) versus electrons
- Ionic current flows across membranes
- membrane potential = Δ inside and outside
- electrical principles same (Ohm's law, cable properties)

Cell membrane

outside - Extracellular matrix Na^+ heavy

phospholipid bilayer   } 6-8 nm

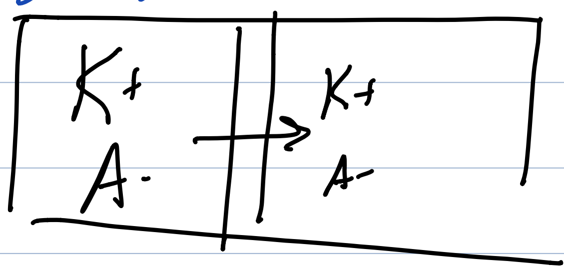
inside - Intracellular K^+ heavy

Sodium ions smaller than potassium ions,
so channels use size and charge selectivity

$K^+ > Na^+ > Ca^{2+} > Mg^{2+}$

- potassium ion selective channel allows K+ because of hydration shell
  - → sodium removing hydration shell is energetically unfavorable

Diffusion of ions across lipid bilayer



Electrical gradient ≡ membrane potential

- neurons and glia:
  1. anions (mostly large - proteins)
  2. cation channels open (leaky K+ channels)
- inside is positive, outside negative
- small amount of K+ moving → large effect on membrane potential

concentration change ~0.002%

- Assume concentration change = 0

Equilibrium reached when concentration gradient and electrical gradient are = and opposite

membrane potential

Lecture 4 - Electricity in the nervous system

Pre-class notes for September 16, 2019

Reading: *Neuroscience* by Purves et al. 6th edition, pages **33-37, 39-42**

The nervous system uses electric pulses to send fast (>100 meter/second) signals. While electronic devices generally rely on the movement of electrons through metal wires, and the movement of soluble ions across membranes creates electric signals in neurons, the basic electrical properties are the same.

Charge (Q) - fundamental quantity of electricity and a property of matter. A charge may be positive or negative. *Like charges repel while opposite charges attract*. An electron has an elementary charge of -1 and a proton has a charge of +1.

Electrical Potential Difference (V) - a difference in potential energy that exists when there is a separation of charges (an electrical gradient, see below). Measured in volts (V) and typical potentials in neurons are measured in millivolts (mV).

Ion - atoms or molecules with a net electric charge. When salts dissolve in water the ionic bond that holds the atoms together break leaving the ions soluble in water.

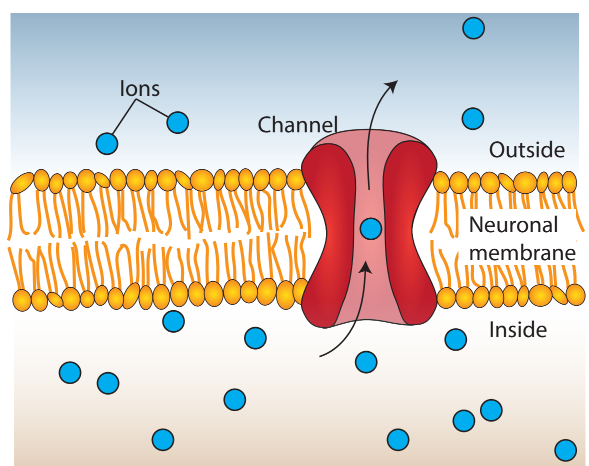
Anion - an ion with a net negative charge. Chloride (Cl^-) is the primary important anion for cellular physiology.

Cation - an ion with a net positive charge. Potassium (K^+), sodium (Na^+) and Calcium (Ca^{2+}) are the important cations for cellular physiology.

The differences in the net charge between the inside and outside of the neuron provide a source of potential energy, similar to that of a battery, that the neuron can quickly utilize for signaling. The selective permeability of the neuronal membrane is critical for establishing and maintaining the potential difference between the inside of the neuron and the surrounding fluid.

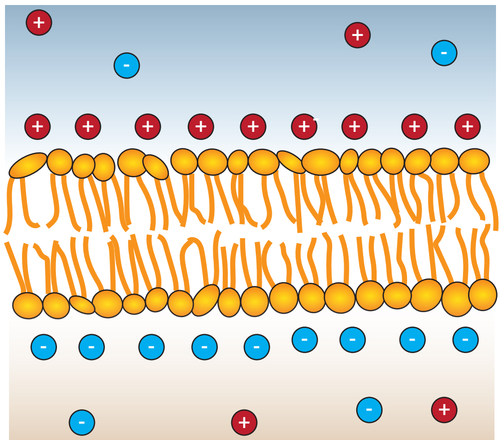
Membrane Potential - the electric potential difference across a cell's membrane with respect to the outside *extracellular* fluid.

Resting Potential or **Resting Membrane Potential** - the electric potential difference across a cell's membrane at rest (i.e. not during an action potential or a synaptic potential). A typical neuronal resting potential is about -65 mV, meaning that the inside is more negative than the extracellular fluid.



Phospholipid bilayer - major component of the cell's membrane with 2 layers of "water loving" *hydrophilic* heads and "water fearing" *hydrophobic* tails, arranged so the tails point towards each other. As the tails are *non polar* they form a barrier to most molecules, water soluble ions and even water itself.

Ion Selective Channels - channels or pores through the membrane, composed of proteins, that allow ions to pass through. Selectivity determined by pore size and charge. Many different types: Gated channels can be either open or closed by a variety of stimuli (e.g. voltage, neurotransmitter). Other channels that strongly contribute to the resting potential are open at rest and sometime known as "leak channels".

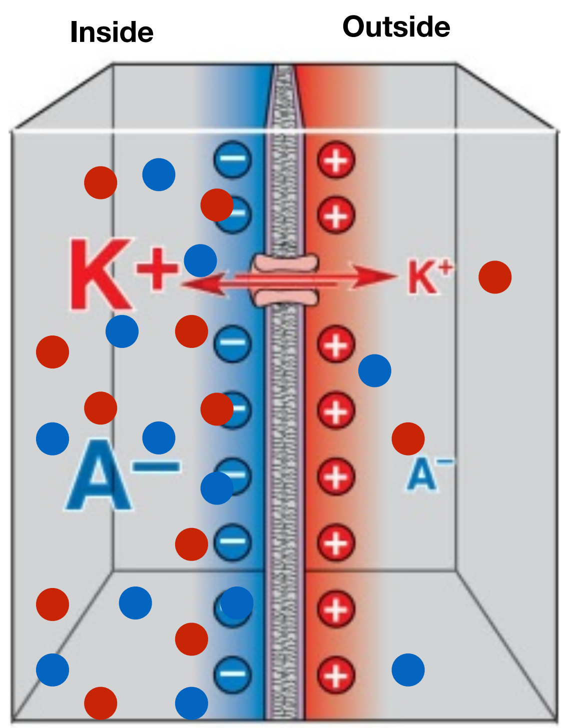


Current (I) - the movement of electrical charge, represented by the symbol "I" and measured in units called *amperes* (Amps).

Capacitor - an insulator (i.e. cell membrane), separating two conducting materials, that can store charge. In neurons, *capacitance* determines how quickly the membrane potential can respond to changes in current.

Diffusion - passive movement of particles; no energy required. Particles move "down a gradient" from high concentration to low concentration through random, thermal movement.

Two different forces or gradients act on ions, the **electrical gradient** - a difference in charge (across a membrane) and the **chemical gradient** - a difference in concentration of ions or molecules (*molarity*) (n*ote:* does not have to be continuous, can be across a membrane*).* When these gradients/forces are balanced it is called **equilibrium**, or when a system has stabilized and all competing forces are balanced.



If a lipid bilayer separates two compartments with 10 times (10X) concentration of a salt (K^+ and a generic anion "A^-"), initially there will be no potential, as there are equal positive and negative charges on each side. Opening or the insertion of K^+ ion selective channels, will initially cause K^+ ions to flow down the concentration gradient, giving the inside (or the side with the greater concentration) a net negative charge and the outside a net positive charge. Eventually however the K^+ exiting due to the concentration gradient is counterbalanced by K^+ attracted to the inside and repulsed by the outside because of the increasing electrical gradient (inside is negative; outside is positive).

A minuscule amount of K^+ moving causes a huge effect on the membrane potential. Translation of 25 million K^+ ions out of a 30µm diameter cell will bring the membrane potential to -80 mV (this is a typical potential for cells such as glia, that are only permeable to K^+). Though this seems like a large number, there are typically over 1 trillion K^+ ions inside a cell, thus the movement of less than 0.002% of the ions can lead to large changes in potential. Thus while scientist discuss the "flow" of ions, this movement is small and *total concentrations remain constant*.

Learning Objectives: (By the <u>end</u> of Lecture 4 you should be able answer the following)

1. Contrast ways electricity in the nervous system differs from electricity in wires.
2. What is a lipid bilayer composed of and how are these molecules arranged? Why, in the absence of channels, is it so impermeable to ions?
3. What are ion selective channels, and briefly describe what they do and what causes their selectivity?
4. If a membrane of a cell is permeable to all ions, is there a point when net ion flow across the membrane finally stops? Why or why not (in 2 sentences or less)?
5. Diagram how a cell membrane is like a capacitor.
6. How does ion selectivity in membrane channels give rise to a non-zero membrane potential?

MCB/Neuro 80 - Neurobiology of Behavior

Today's Topic:

Electrical Basis of Neural Function

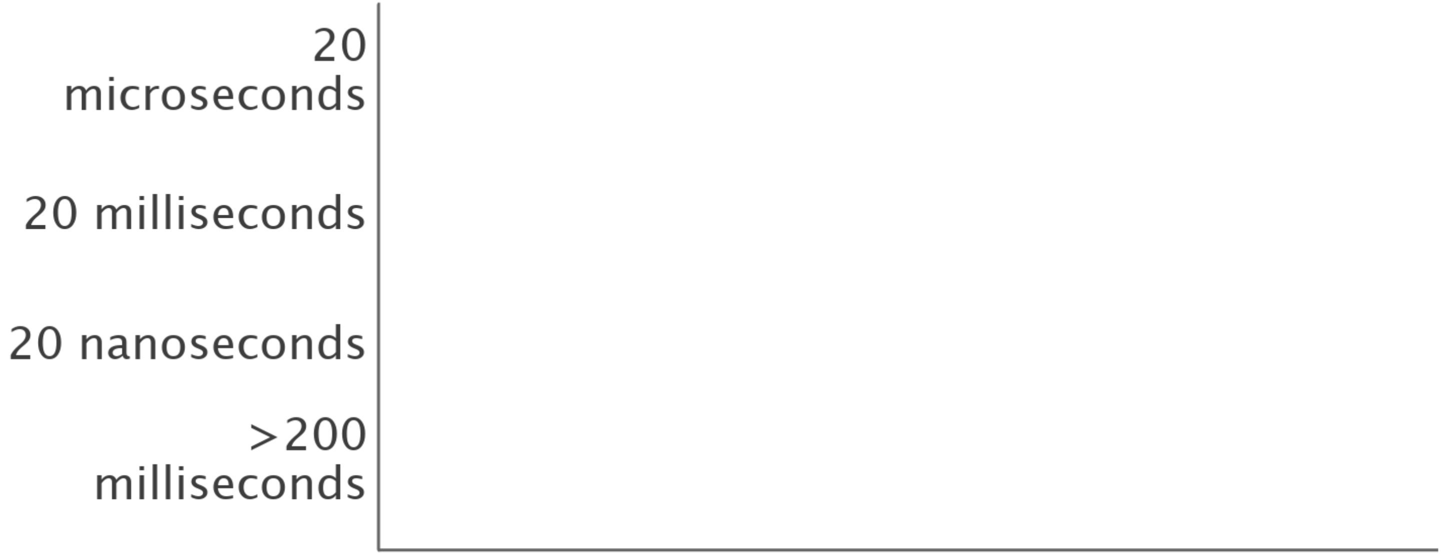
Lecture 4

Optional reading: Purves et al., *Neuroscience* 6th pages: 33-37, 39-42

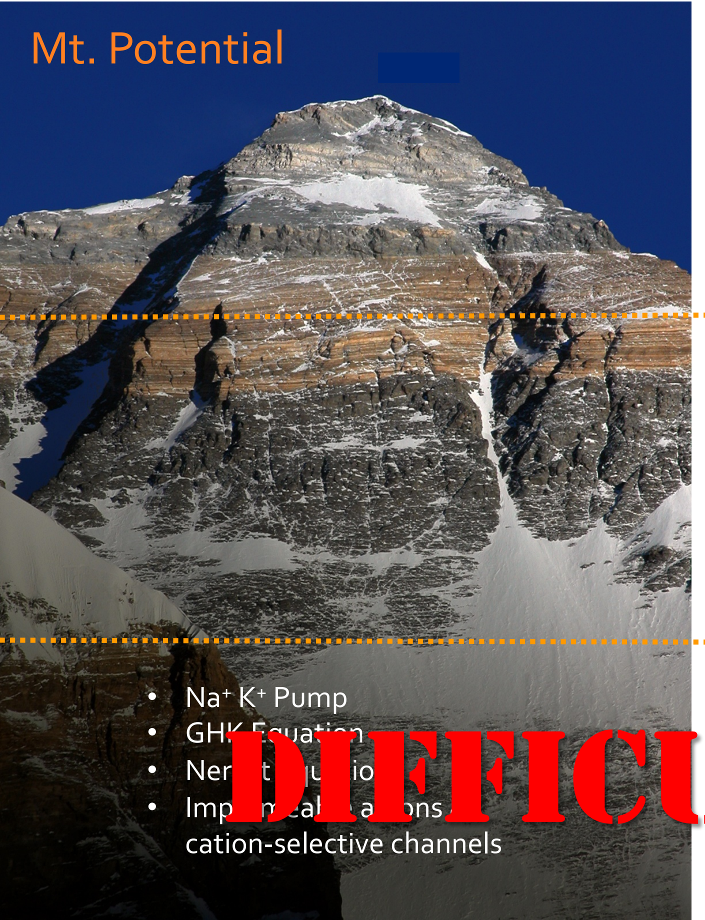
Lecture notes, review questions, office hour times available at:

https://canvas.harvard.edu/courses/59120

What is the time latency between hitting a tendon and getting a muscle contraction?



Mt. Potential



Synaptic Potential

Action Potential

- Na^+ K^+ Pump
- GHK Equation
- Nernst Equation
- Impermeable anions / cation-selective channels

Resting Potential

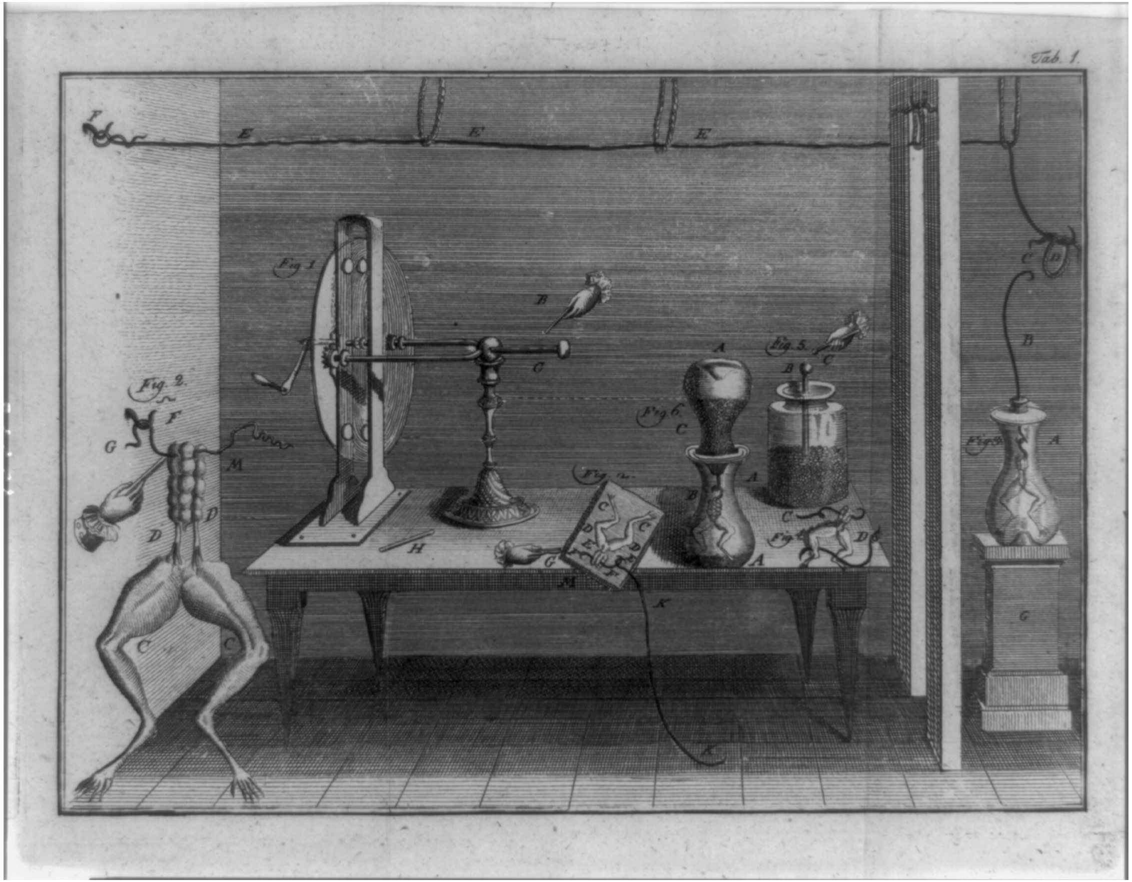
DIFFICULT STUFF!

How does information flow in the nervous system?

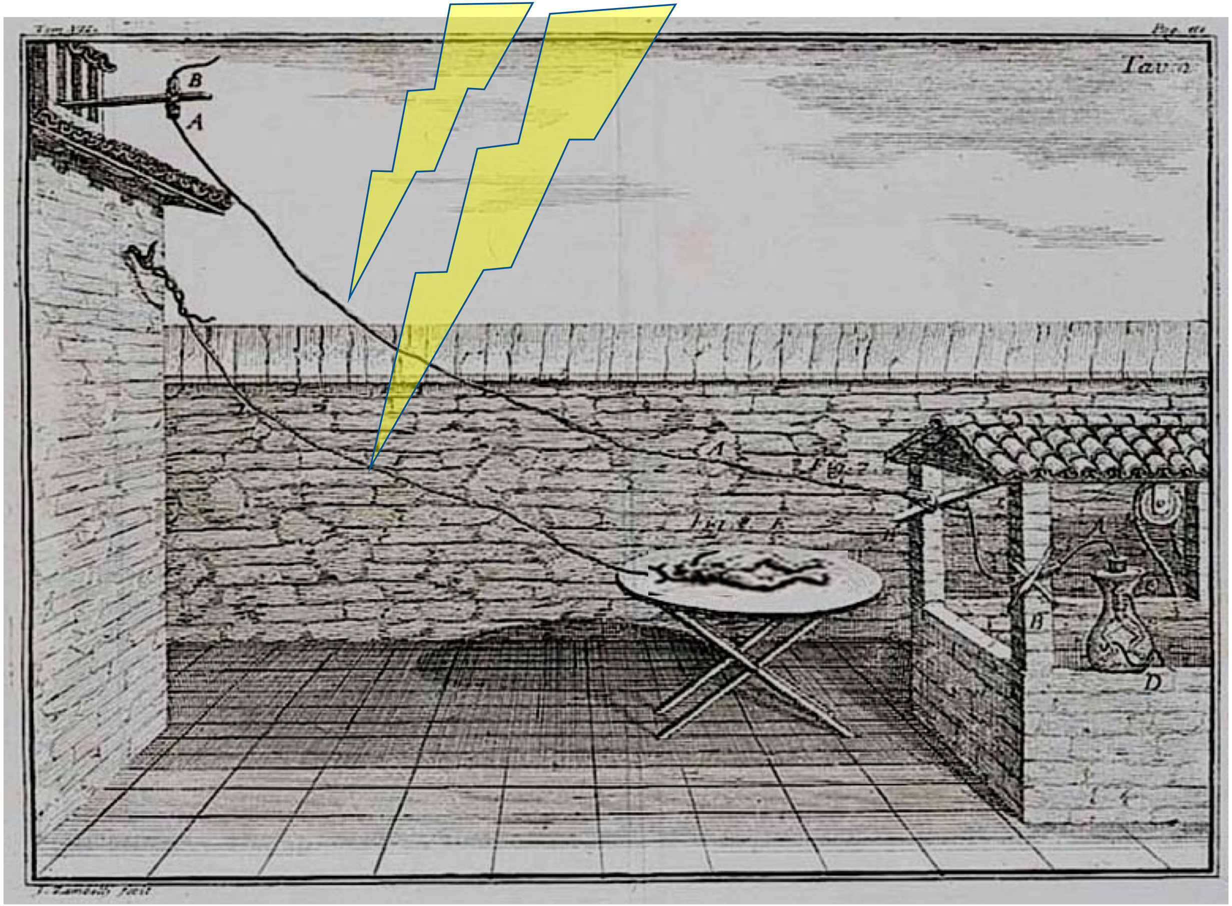
- Electricity (mainly)
- Field of study: "electrophysiology"
- Galvani was (likely) the first electrophysiologist

Luigi Galvani (1737-1798)

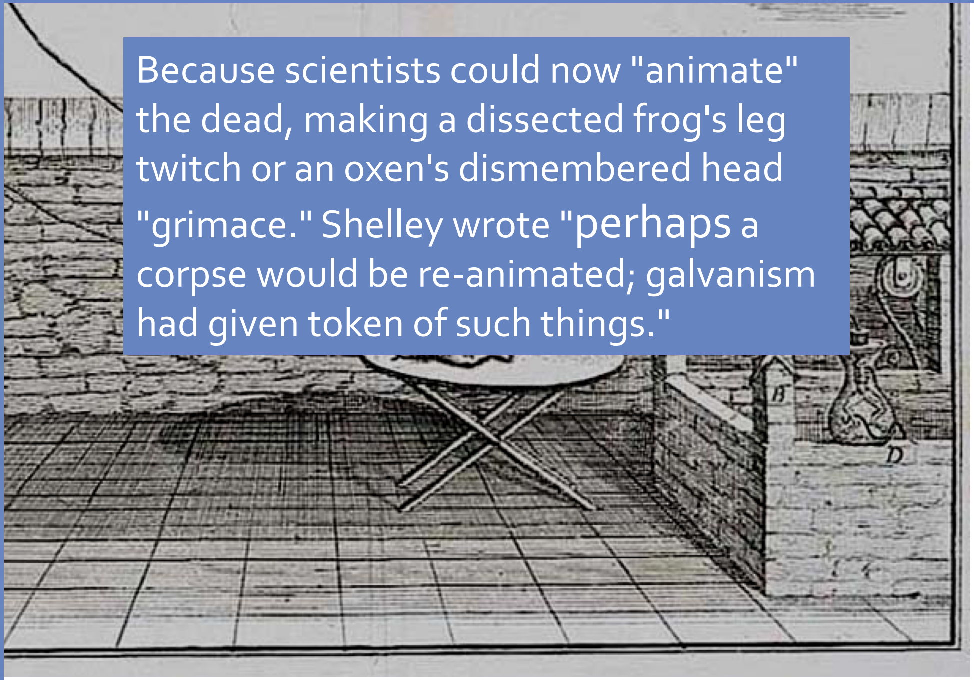
Luigi Galvani's Lab



Abhandlung uber die Krafte der thiereschen Elektrizitat auf die Bewegung der Muskeln / Luigi Galvani. Eine Uebersetztung, Prag. : J.G. Calve, 1793.


B
A
B
D

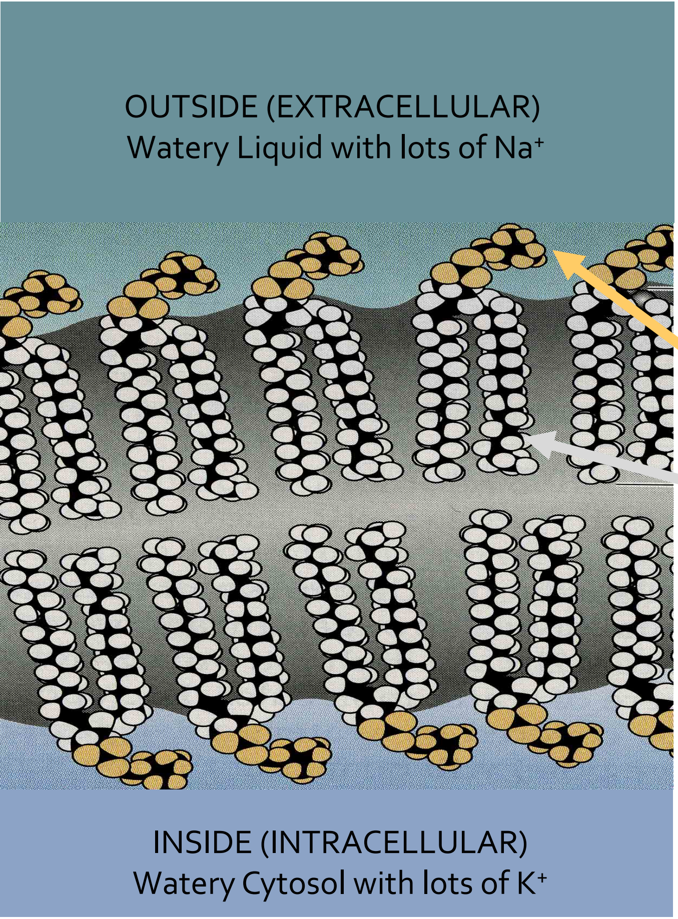
Mary Shelley ~40 years later wrote
Frankenstein; or, The Modern Prometheus
London, 1831



Because scientists could now "animate" the dead, making a dissected frog's leg twitch or an oxen's dismembered head "grimace." Shelley wrote "perhaps a corpse would be re-animated; galvanism had given token of such things."

Electricity in nervous system vs. electricity in wires

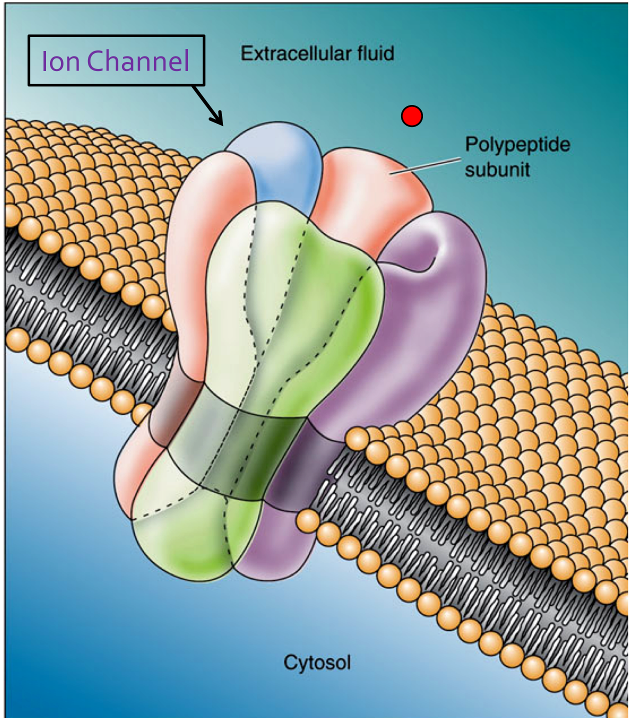
- Ions are atoms that are positively charged (cations: potassium =K^+, sodium=Na^+, calcium=Ca^{++} or negatively charged (anions: chloride=Cl^-) these are what moves around neurons (versus electrons in wires)
- The ionic current (net charge movement) flows mainly across membranes rather than the way electrons move along wire length. Inside of cell can become more negative or more positive
- These differences in the net charge between the inside and outside of the neuron are known as the *membrane potential* for which there is no analog in wires
- But the basic electrical principles are the same; notably Ohm's Law and Cable Properties (more on these later…)



Cell Membrane

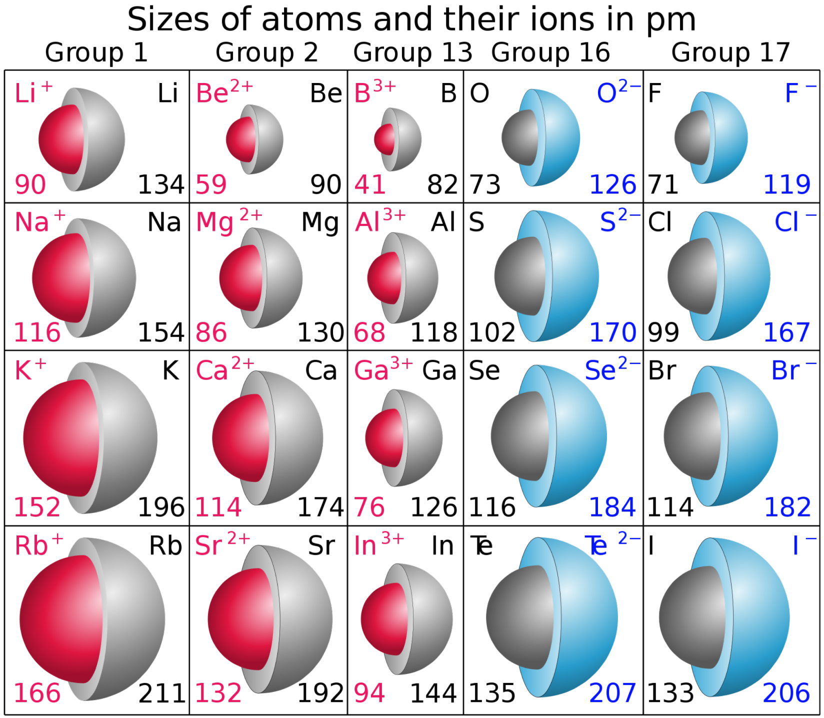
- Lipid bilayer- phospholipids
- Both a layer facing out and facing in (hence “bi”layer)
- Polar head phosphate containing (hydrophillic or “wettable”)
- Nonpolar (hydrophobic or “oily”) tail of hydrocarbon
- Bilayer is 6-8 nm thick
- (1000 nm = 1 mm = 0.001 mm)
- Impermeable to ions

Membrane potential is created in part by ion selective channels



- Protein “channels” have pores that ions can pass through.
- Amazing variety of types with different ion selectivities, some are “gated” (i.e., to open and close) by a range of stimuli.
- This week we mainly focus on channels that are not gated and are open when the neuron is at “rest”
- Ionic flux (movement) is mostly by passive diffusion a.k.a. Brownian motion (no added energy required)
- Up to 108 ions/second per channel!
- In most cases the channel pore for cations is lined with negatively charged amino acid groups that repulse anions and vice versa for anion channels.
- Ion “selectivity” for one cation over another (e.g., K+ vs. Na+) related to water molecules that stick to the ion in solution. Some ions shed their hydrated shell, others enter pores that can accommodate the shell (complicated)

Channel selectivity based on size and charge



Na+ channels:

Sodium ions are smaller than potassium ions, so these channels can use size and charge selectivity

Channel selectivity based on size and charge

K+ channels:

Even though a sodium ion plus its water hydration shell is smaller than a potassium ion plus its shell, the K+ selective channel allows potassium ions to pass through much more easily than sodium.

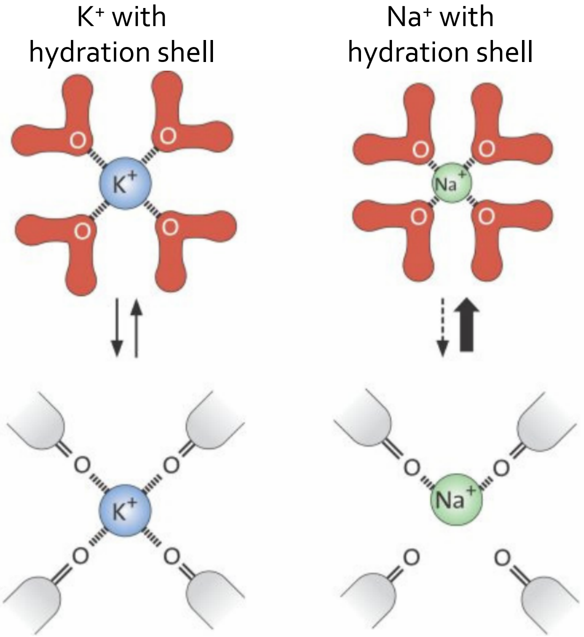
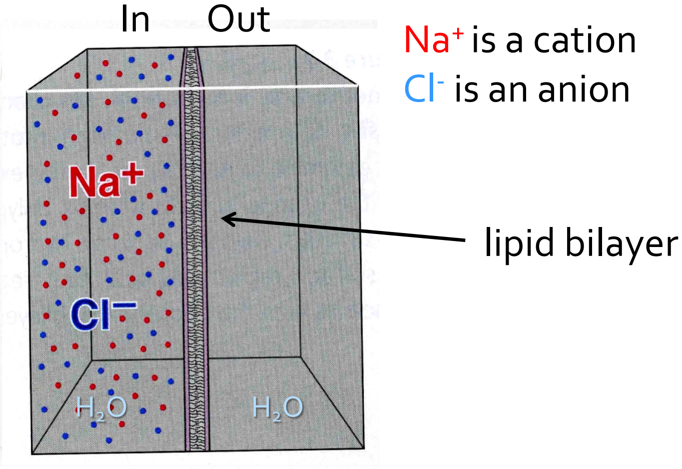


Fig. 4: Selectivity of a potassium channel

Shown are the ions K^+ and Na^+ with their respective hydration shells. The size of the shell is determined by the ions charge and radius (upper pictures). The filter of a potassium channel has the same radius as the hydration shell of K^+. Thus, switching from hydrated state to protein coordinated state is in equilibrium. Na^+ on the other hand has a smaller ion radius than K^+. It is not fully coordinated in by the carboxylic groups of the filter, thus the entering in the filter is energetically not favoured (picture is adapted from http://nobelprize.org/nobel_prizes/chemistry/laureates/2003/chempub4bhigh.jpg).

Diffusion of ions across lipid bilayer membrane

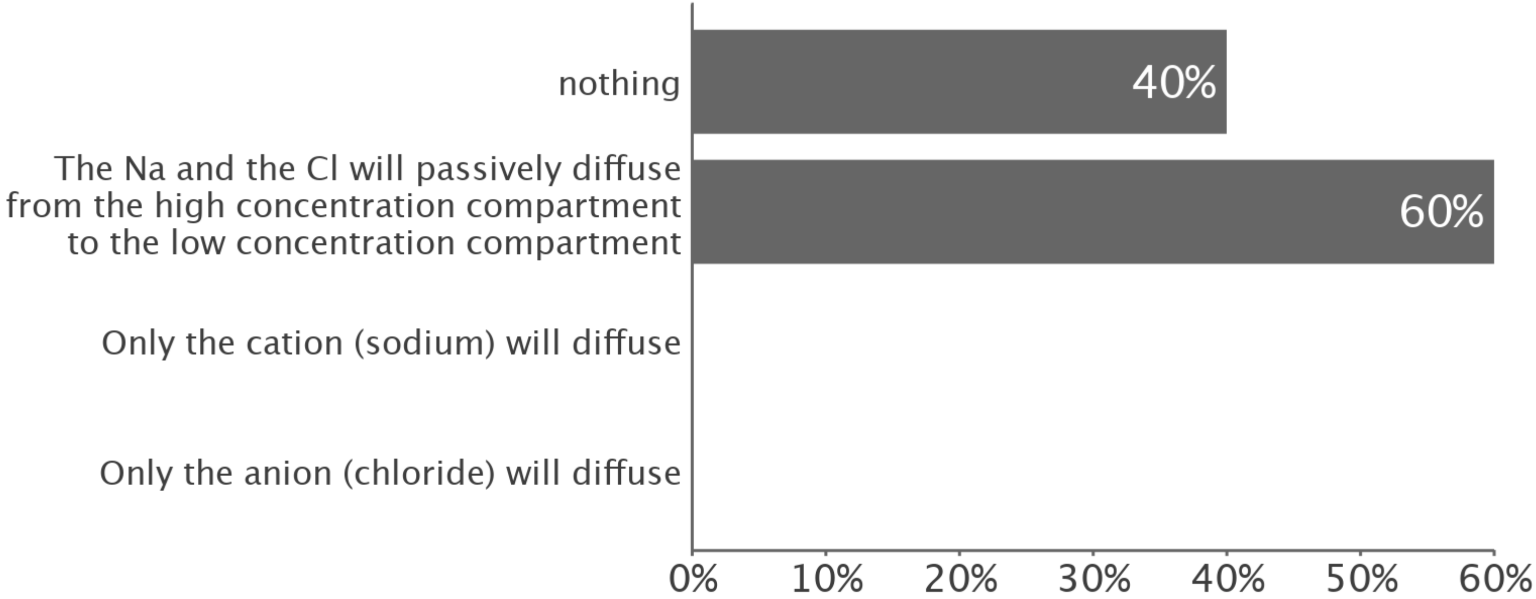
- What happens?:



Na^+ is a cation

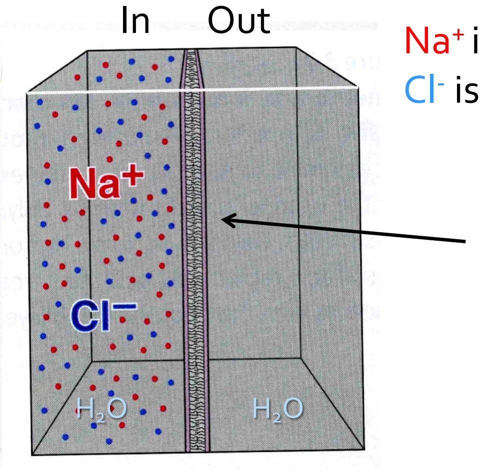
Cl^- is an anion

What happens when an NaCl salt solution is separated from a pure water filled compartment by a lipid bilayer?



Diffusion of ions across lipid bilayer membrane

- Passive flux across membrane only via permeable channels- so if no channels, no ion moves to other compartment



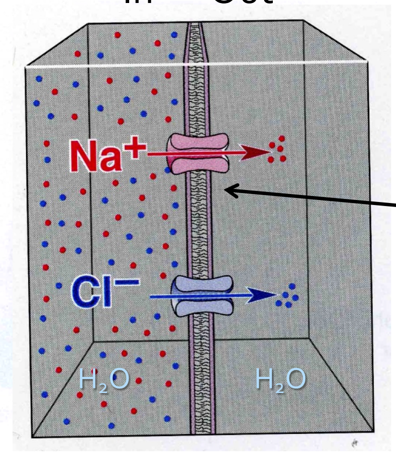
Na^+ is a cation

Cl^- is an anion

Diffusion of ions across lipid bilayer membrane

- Passive flux across membrane only via permeable channels - so if no channels, no ion moves to other compartment

In Out

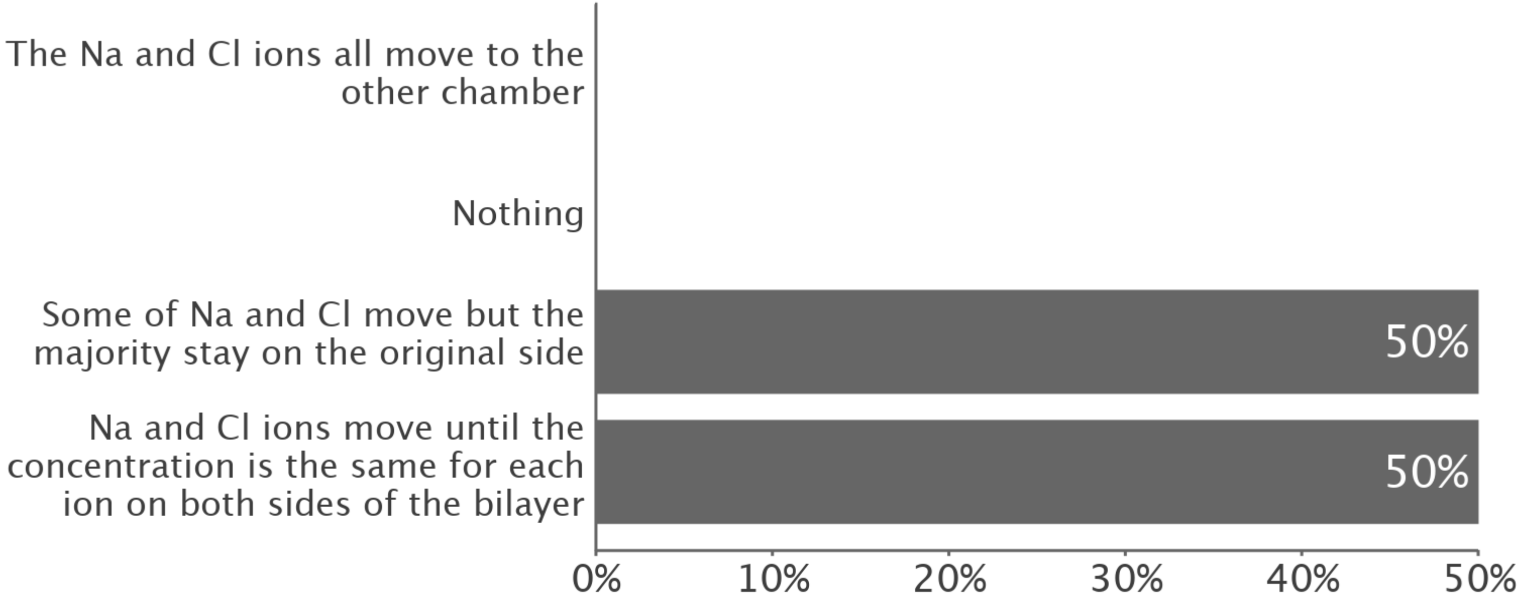


Na^+ is a cation
Cl^- is an anion

lipid bilayer

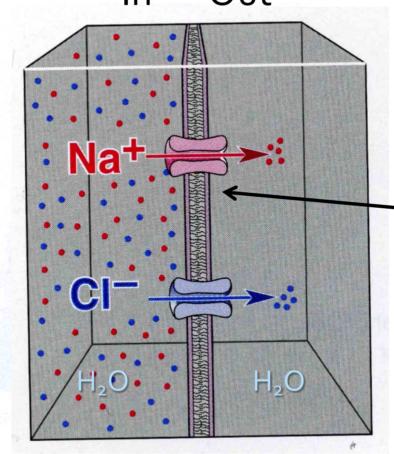
- If ion channels for cations and anions are present, then ions diffuse "down" their concentration gradients
- Then what?

If ion channels for cations and anions are present in the lipid bilayer then what happens??



Diffusion of ions across lipid bilayer membrane

- If ion channels for cations and anions are present, then ions diffuse "down" their concentration gradients



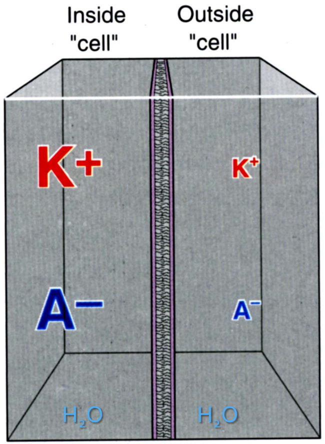
Na^+ is a cation
Cl^- is an anion

lipid bilayer

- Equilibrium reached when concentrations no longer change (Note: ions still moving - but equal flux in both directions)
- In this case the movements of + and – charges are balanced so that the final net charge is zero in both containers and therefore *the membrane potential*, *(a measure of difference in the net charges between the inside and out)* = 0 mV

Diffusion associated with an ion-selective channel can give rise to membrane potential

- In example shown on below, the solution has the same constituents both inside and outside but it is 20x more dilute outside.
- Q: What is membrane potential?

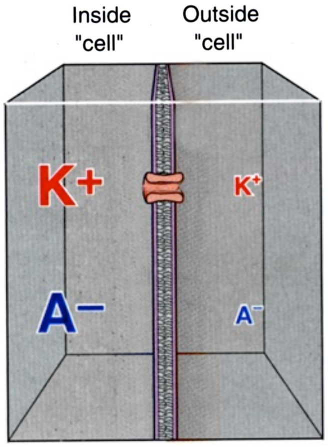


What is the membrane potential if a salt solution (KCl) is 20 times more concentrated on one side of a lipid bilayer than on the other side?

- A. Negative membrane potential on the side with the greater concentration of K
- B. 0 mV
- C. Positive membrane potential on the side with the greater concentration of K
- D. Can't be figured out without an electrode

Diffusion associated with an ion-selective channel can give rise to membrane potential

- In example shown on below, the solution has the same constituents both inside and outside but it is 20x more dilute outside.
- No net charge difference between the two sides (0 mV on each side) so still no membrane potential, however....



- If we add K+ selective channels (A- impermeant) then
- Q: What will happen?

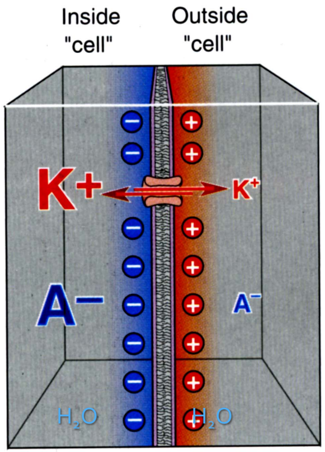
what happens if there are K selective channels in the lipid bilayer separating the 20X greater KCL concentration from the more dilute solution?

Nothing, because each side wants to remain electro-neutral

The K flows down its concentration gradient until it has the same concentration on both sides

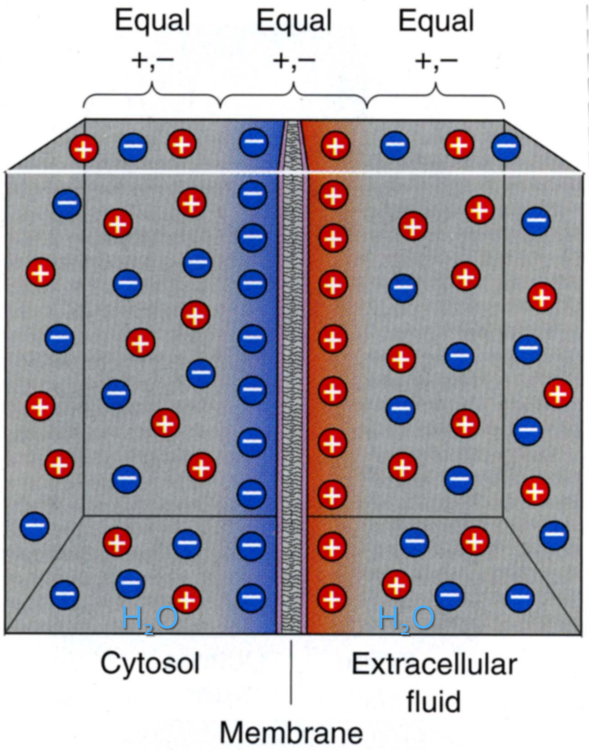
The K flows down its concentration gradient, but just just a little bit before it can't anymore

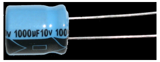
Diffusion associated with an ion-selective channel can give rise to membrane potential



- In example shown on the left the solution has the same constituents both inside and outside but it is 20x more dilute outside.
- No net charge difference between the two sides (zero on each side) so still no membrane potential, however….
- If we add K^+ selective channels (A^- impermeant) then: K^+ flows from inside to outside to flow down its concentration gradient and
- The inside gets a net negative charge and the outside gets a net positive charge
- Eventually however the K^+ exiting due to the concentration gradient is counterbalanced by K^+ attracted to the inside and repulsed by the outside because of the increasing electrical gradient (inside is negative; outside is positive)

The electrical gradient is the membrane potential



- In neurons and glia, impermeant anions in the cytosol (mainly big negatively charged proteins) plus a large number of cation channels open "at rest" (mainly K+ "leak" channels) lead to a potential difference across the membrane.
- Inside has net negative charge
- Outside has net positive charge
- Opposite charges attract so they line up on either side of the membrane which stores charge like an electrical capacitor 
- The bulk solution on both sides is electro-neutral
- To understand the exact value of the membrane potential we have to delve deeper…

A minuscule amount of K^+ moving causes a huge effect on the membrane potential

- Translocation of 25 million K^+ ions out of a 30 μm diameter cell will bring the membrane potential to its normal value of -80 mV ("millivolts") for cells only permeable to K^+ (glia).
- But the total # of K^+ ions inside a typical cell is over 1 trillion.
- So the K+ concentration changes less than 0.002%
- Therefore, one can assume that despite the movement of K^+ the intracellular K^+ never changes much and is a constant value

How do we calculate this potential?

- In the case we just went through (only potassium channels present) the resting potential is reached when there is no longer any net flow of K^+. That is when the forces pulling K^+ in and out are equal and the system has stabilized at equilibrium

"Equilibrium" for an ion is reached

when

its particular Concentration gradient

and the

cell's Electrical gradient

are

equal and *opposite*

What membrane potential is reached when a permeant ion is at equilibrium?

- If you know the internal and external concentrations of the ion that can move across the membrane, you can calculate what membrane potential at equilibrium
- This membrane potential arises from the balance of the two tendencies of the ion: (1) move to equalize the concentration, (2) move towards the opposite charge
- We will dive into all this on Wednesday

Learning Objectives

1. Contrast ways electricity in the nervous system differs from electricity in wires.

2. What is a lipid bilayer composed of and how are these molecules arranged? Why, in the absence of channels, is it so impermeable to ions?

3. What are ion selective channels, and briefly describe what they do and what causes their selectivity?

4. If a membrane of a cell is permeable to all ions, is there a point when net ion flow across the membrane finally stops? Why or why not (in 2 sentences or less)?
5. Diagram how a cell membrane is like a capacitor.

6. How does ion selectivity in membrane channels give rise to a non-zero membrane potential?