What Brains are Made Of & What Makes them Electric

How Your Brain Works

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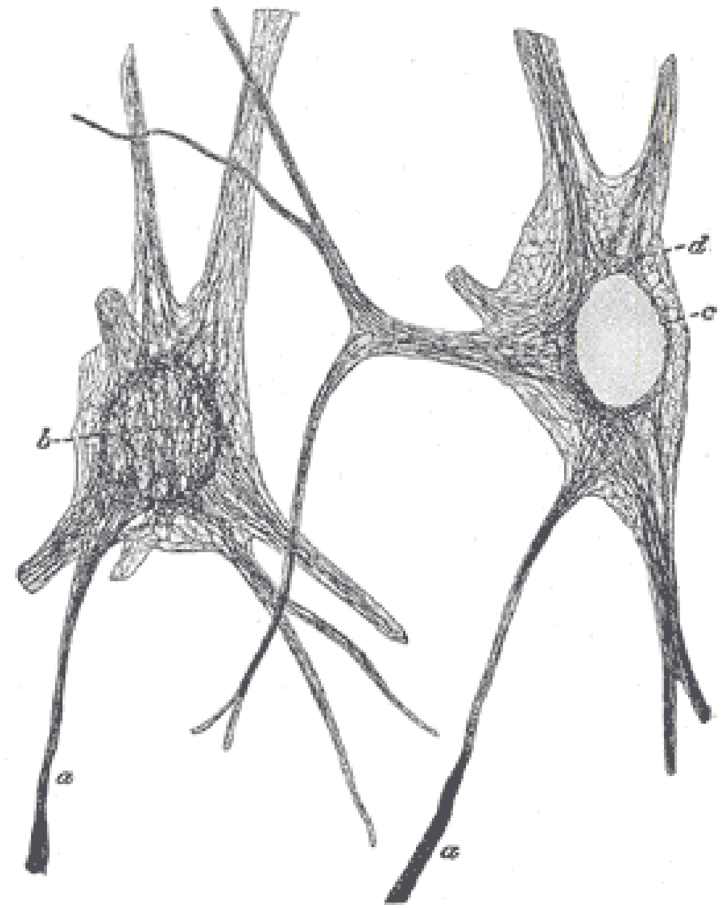
A Neuroscient's Favourite Atoms

There are well over 100 different types of atoms (chemical elements). Luckily, to understand how brains work we need to know only about a few of them, including:

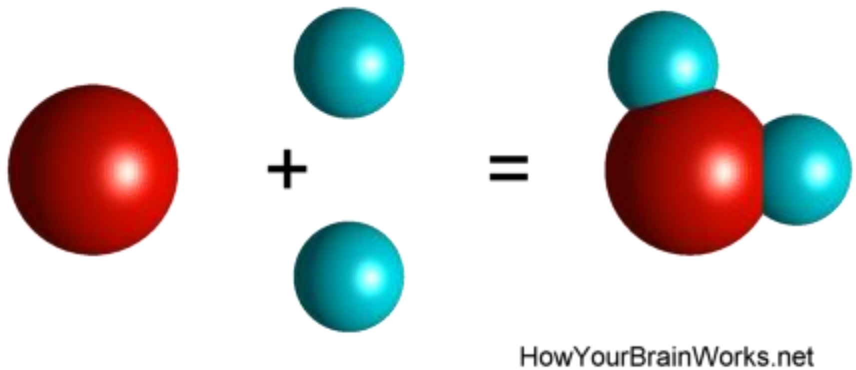
- Hydrogen (H)
- Oxygen (O)
- Carbon (C)
- Nitrogen (N)
- Phosphorus(P)
- Sodium (Na)
- Potassium (K)
- Calcium (Ca)
- Chlorine (Cl)
- Magnesium (Mg)

Recipe for Neurons

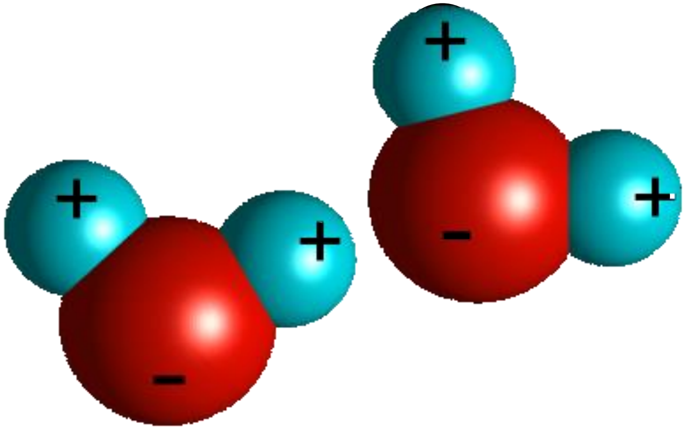
- *Ingredients:*
  - **Water** (H_2O)
  - **Salt** ($NaCl$)
  - **Fat** ($CH_3C_NH_NCOOH$)
  - **Protein** (lots of C and H, some O and N, and a tiny bit of S)



WATER (H_2O)

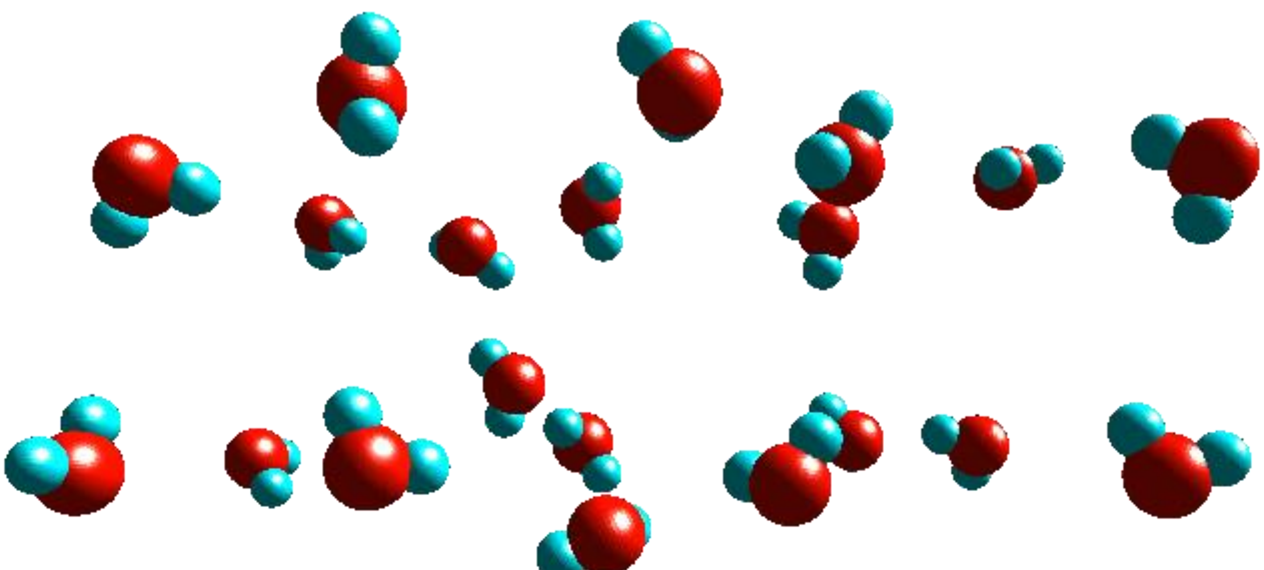


- Neurons are filled with *intracellular fluid* (*cytosol*, predominantly water) and are bathed in *extracellular fluid* (also predominantly water).

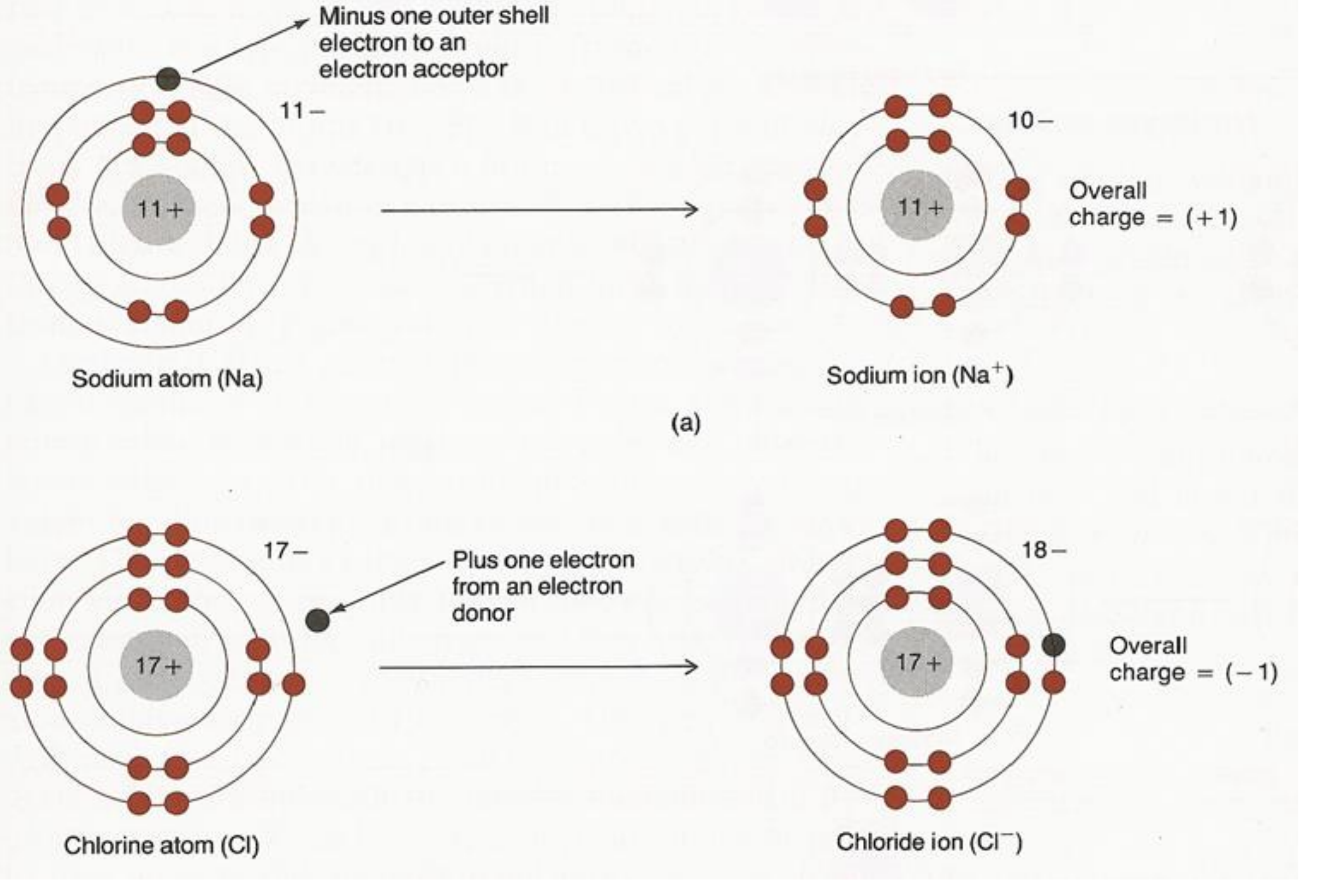


Water is a Polarized Molecule

Water molecules “stick together” due to electrostatic attraction and “hydrogen bonds”

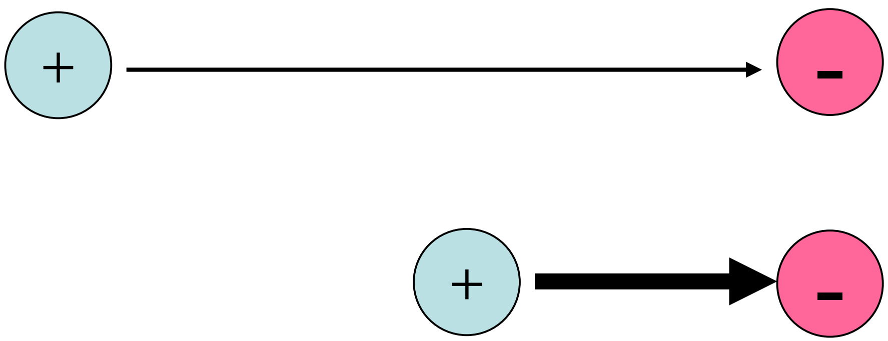


Salts form *Ions*



Electrostatic Forces

- **Coulomb's Law**: The electrostatic attraction (repulsion) between two opposite (identical) charges is inversely proportional to the square of the distance between them.

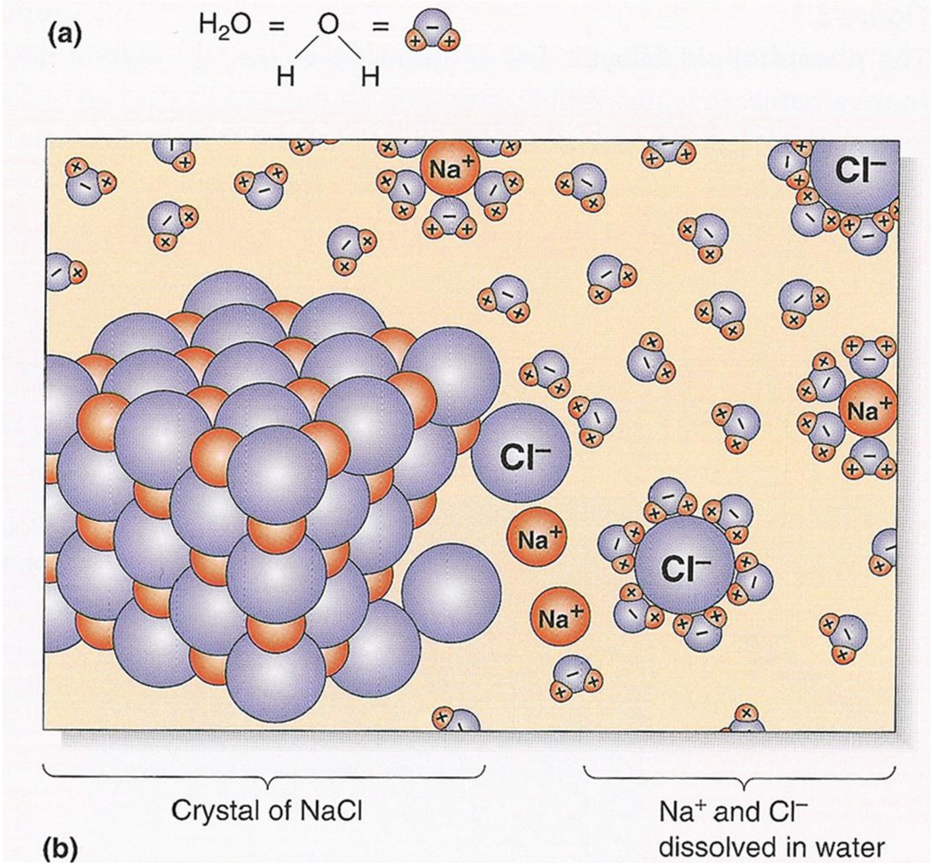


$$F = \frac{q_1 \cdot q_2}{4 \cdot \pi \cdot \varepsilon_0 \cdot r^2}$$

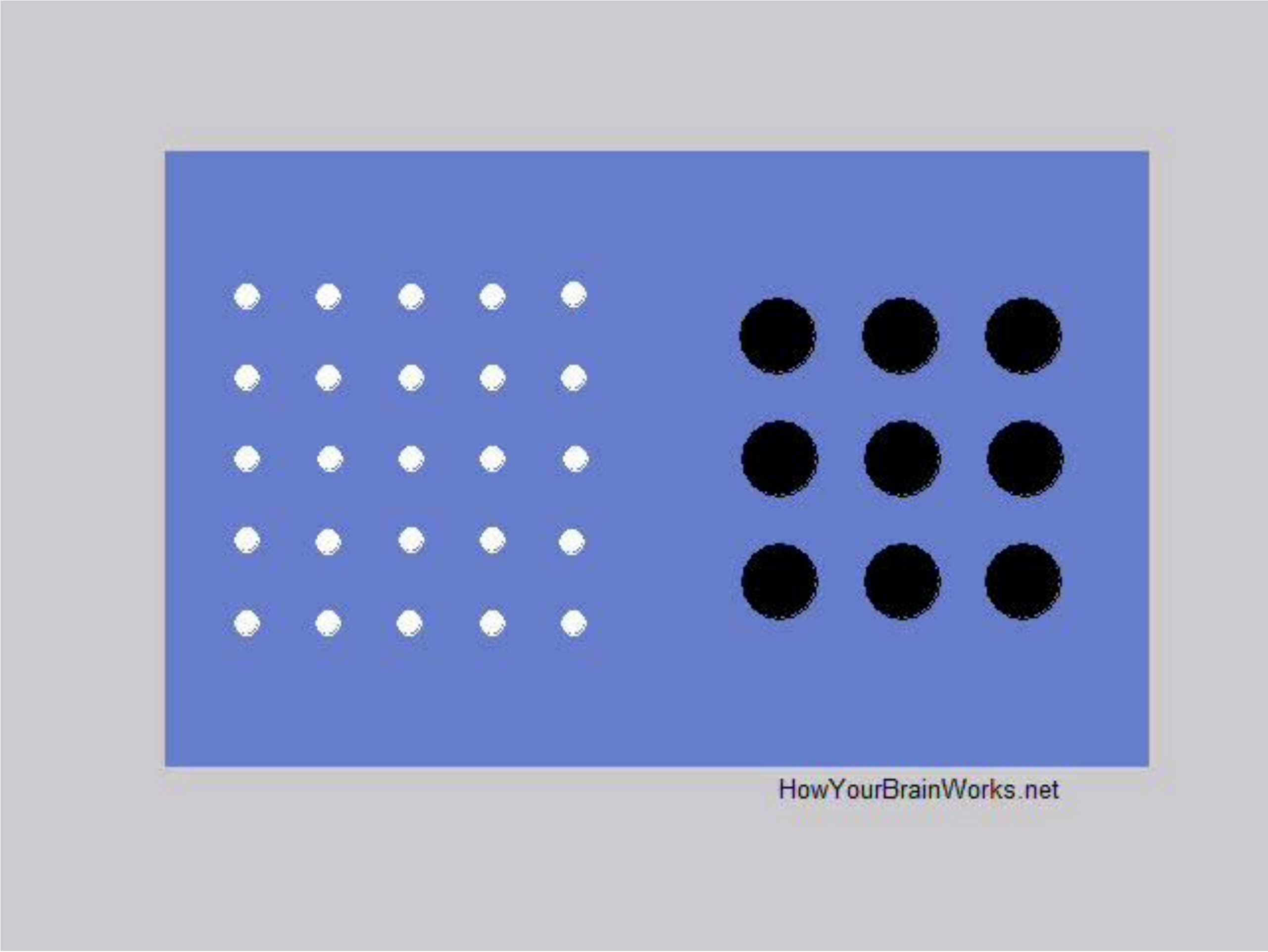
- Half the distance → four times the force.
- Large distance → very small force.
- Zero distance → infinite force.

Salt in Solution

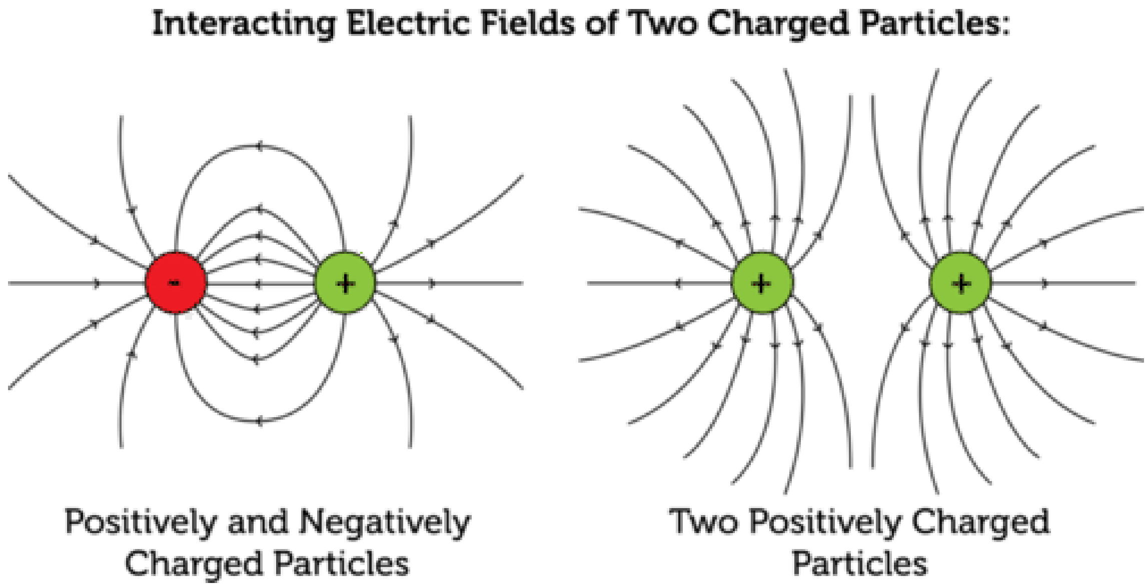
When dissolved in water, salts dissociate into electrically charged *ions* which can move freely in the solution.



Diffusion



Electric Fields and Forces



- Electric charges create an ***electric field*** around them. The fields act on other charges, causing the attraction or repulsion we saw in Coulomb’s law earlier.

Electric Potentials (Voltages)

- A charged particle sitting in an electric field has ***potential energy*** because the force generated by the field can accelerate the particle.
- A ***voltage*** effectively measures how much energy would be either needed or released to move a unit of positive charge through an electric field from one given point to another. [By definition: Volt = Newton (force) times meter (distance) divided by Coulomb (amount of charge)]
- Clearly, the larger the electric fields between the two points, the larger the Voltage.

Electric Currents

- Whenever charged particles move, we can speak of ***electric currents***.
- The unit of current (Amperes) simply measures how much "*net positive*" charge moved through some given area in a given amount of time.
- "Net" here means that if the same amount of negative and positive charge moves together, the total current would be zero.
- If negative charges move from A to B then we would speak of an electric current from B to A.
- In your brain, electric currents are generated by moving ions.

Electric Resistance and Conductance

- If electrical currents can flow easily, the resistance *R* is said to be low. If they can't, the resistance is high.
- Numerically: Current = Voltage / Resistance
  $I=V/R$ ("Ohm's Law")
- Conductance = 1 / Resistance.
- Insulators have (close to) infinite resistance, so the current that can flow through them is zero (or negligibly small)

Ions of Importance in Neuroscience:

- *Cations:*
  - Sodium: Na^+
  - Potassium: K^+
  - Calcium: Ca^{++}
- *Anions:*
  - Chloride: Cl^-
  - Organic Anions

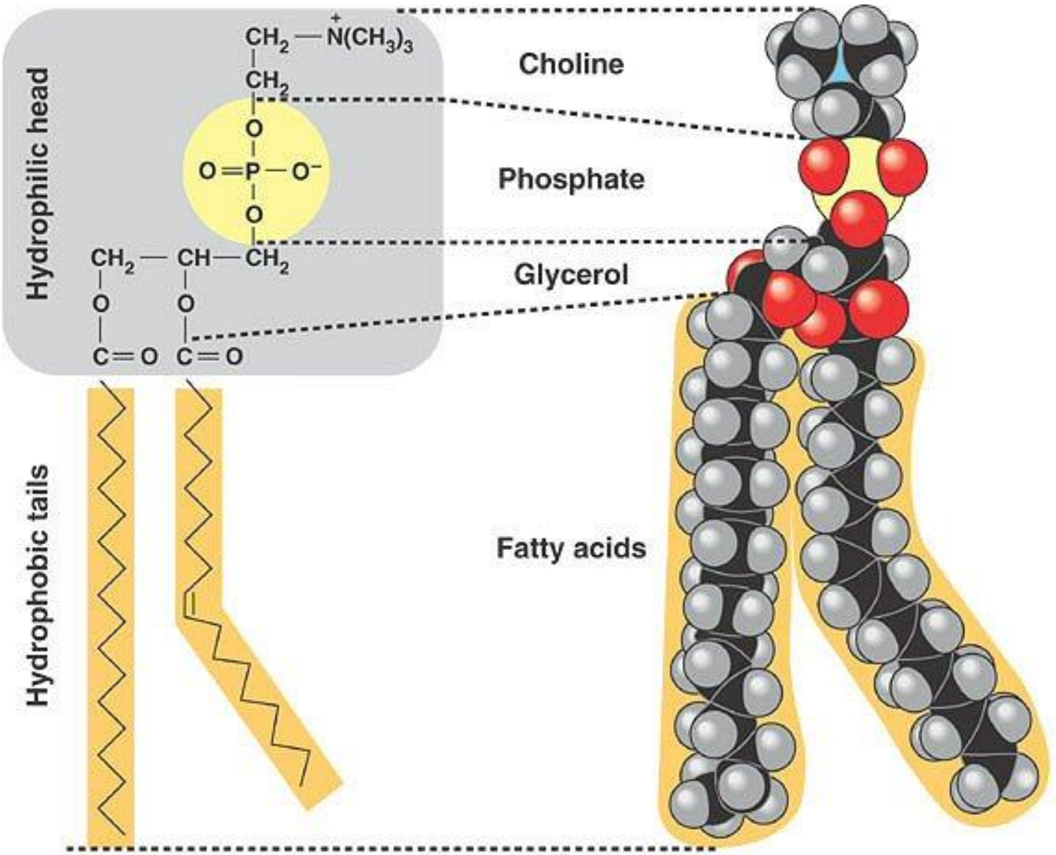
- In Greek, "ana" is "up" and "kata" is "down". Cation is "the down-going", Anion is "the up going").
- If you kind of think of it to be "the normal default" of charges to be positive and to flow "downhill" then you can remember that positive charges will flow "towards the cathode" ("the down path").

Important take-home message

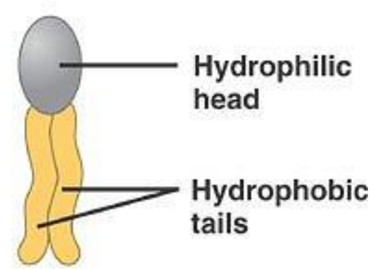
- Because nerve cells are both filled with, and surrounded by “salty water” with lot’s of Brownian motion and diffusion pushing charged ions this way and that, on, there are lots of tiny random electrical currents all the time.
- But on average there is as much chance of a charge being pushed left as of it being pushed right, the average net current is going to be very close to zero pretty much all the time (unless the movement of ions can be “organized” somehow).

FAT

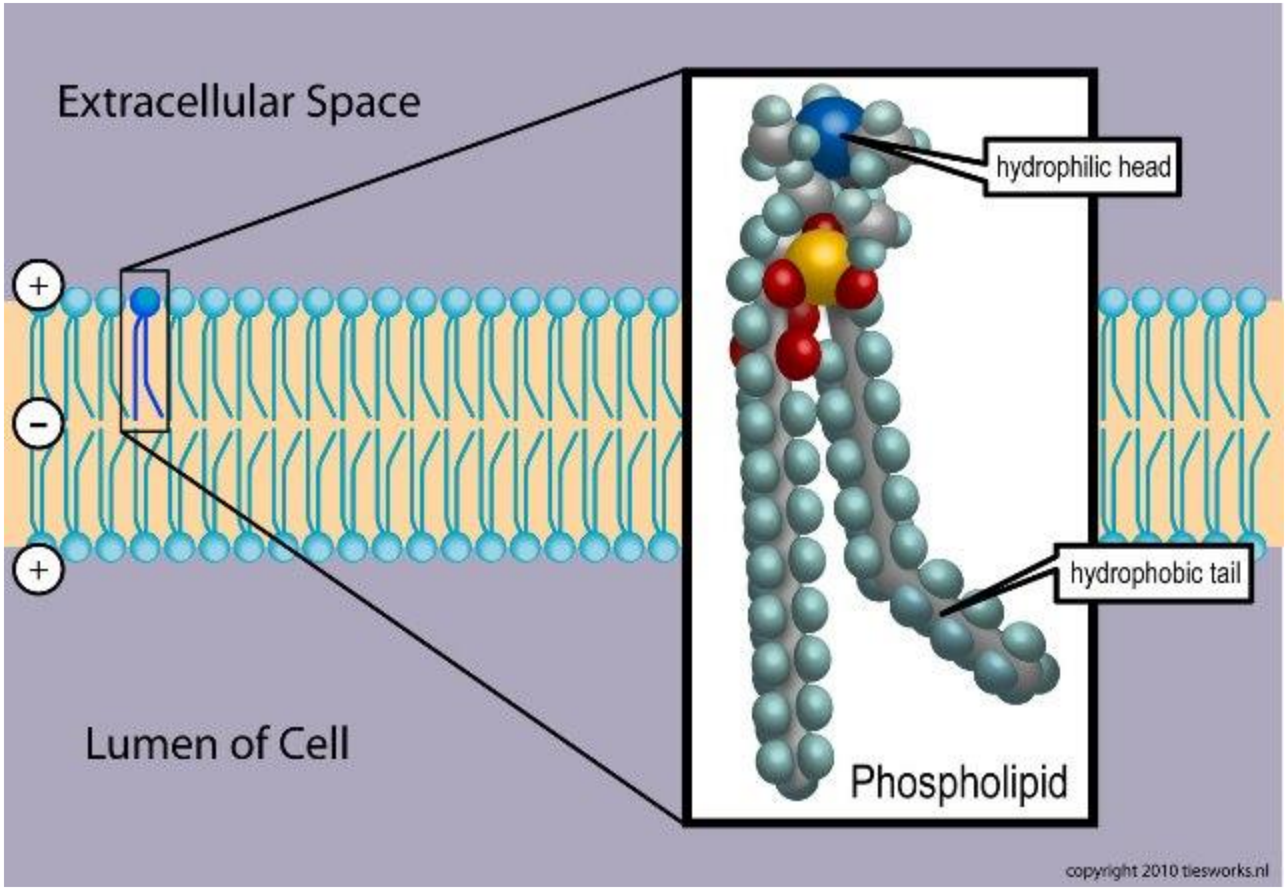
$(CH_3\text{-}(CH_2)_N\text{-}COOH)$



Cell membranes are made of fat (Phospholipids)



Phospholipid Bilayers



- Cell membranes are water-impermeable sheets of phospholipids

Cell Membranes and Electrical Currents

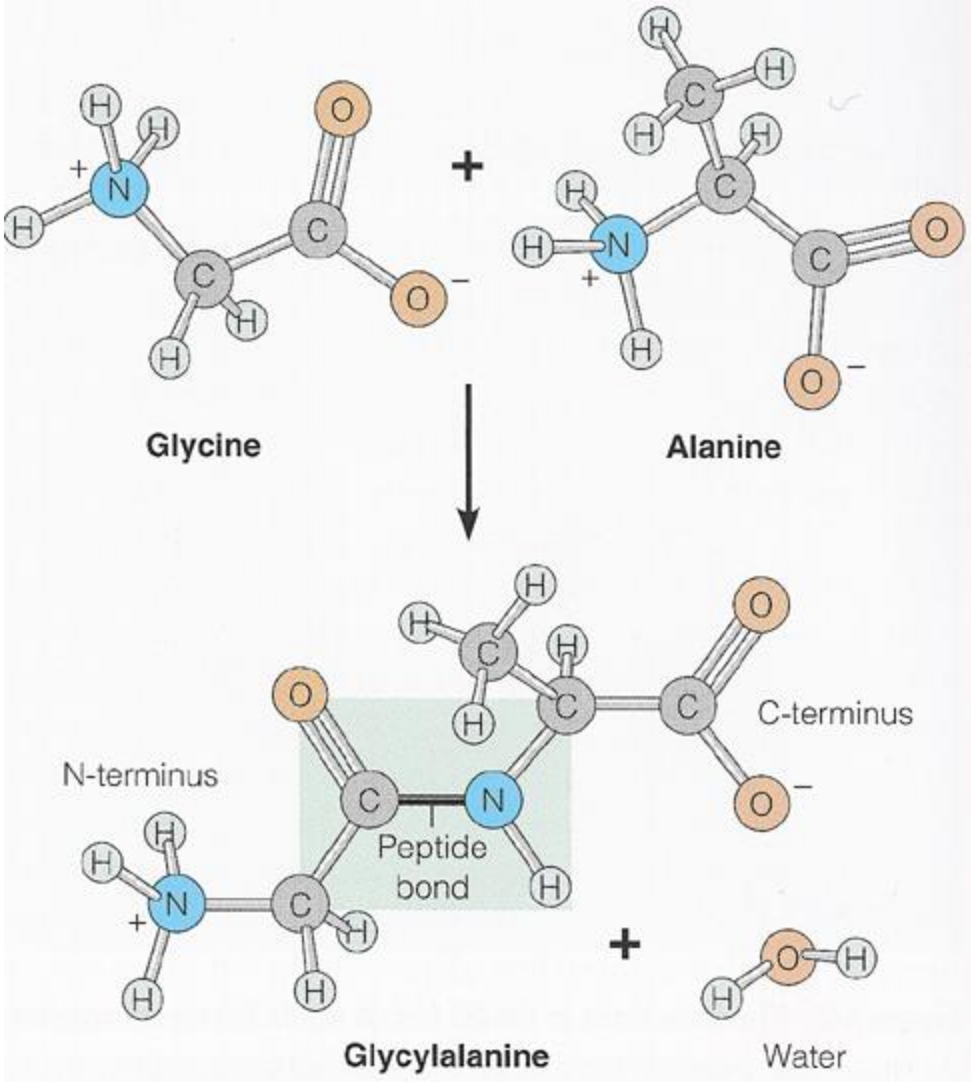
- The movement of electrically charged *ions* that are dissolved in water is the basis of *electrical currents* in and around nerve cells.

- The fatty cell membrane (phospholipid) is impermeable to ions. Electric currents therefore can flow along membranes easily, but through membranes only where there are pores (“channels”) in the membrane.

Protein

- Proteins are chains of amino acids.
- All proteins are made from only 20 different amino acids.
- Amino acids come in fat soluble (lipophilic), water soluble (hydrophilic), as well as charged and uncharged varieties.
- You don’t have to remember the names of all 20 amino acids but you should have heard of them so you can recognize them.

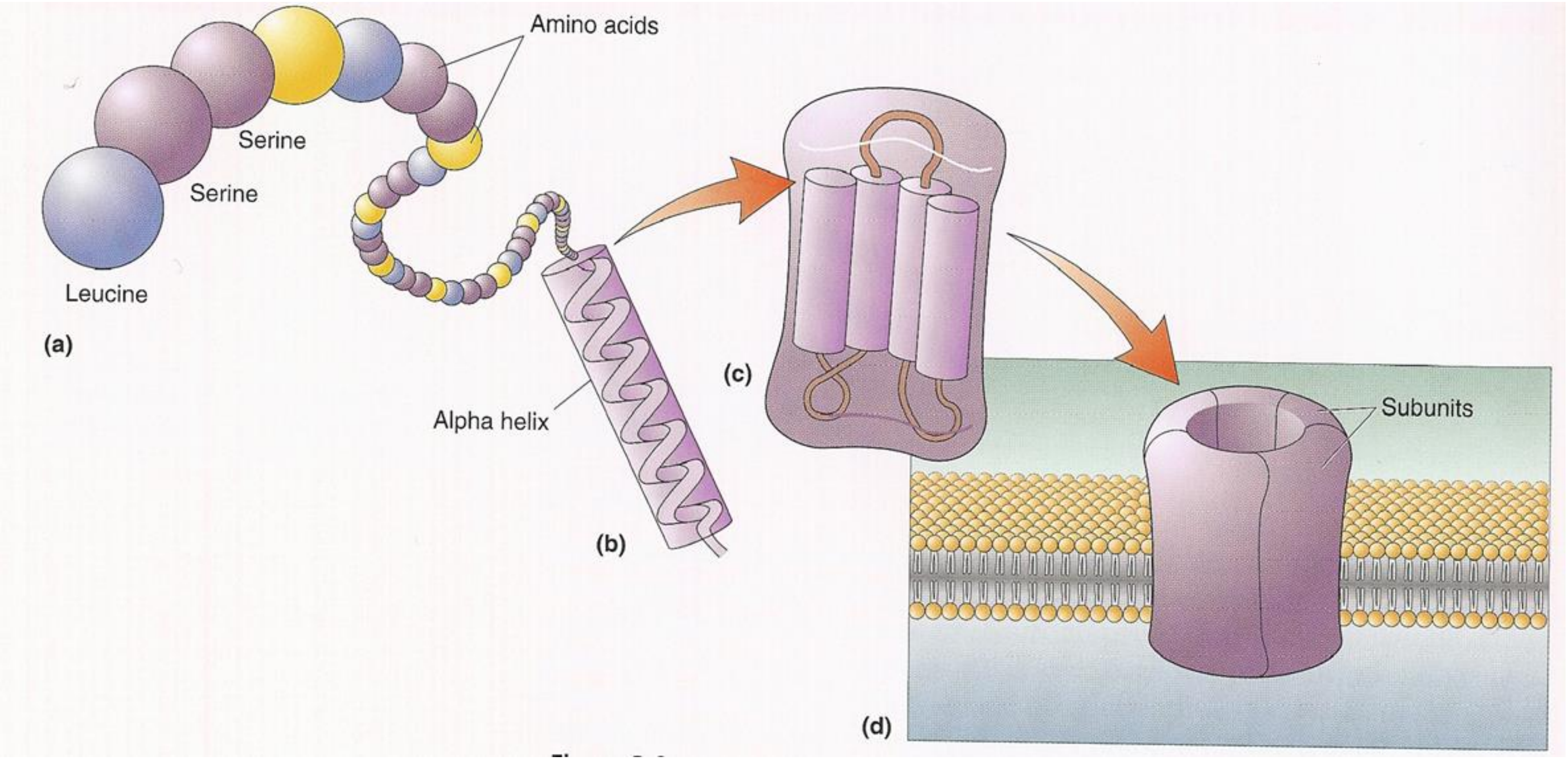
Hydrophobic	**Hydrophilic**	**Charged**
Glycine	Serine	Aspartate
Alanine	Threonine	Glutamate
Valine	Cysteine	
Leucine	Tyrosine	Lysine
Isoleucine	Asparagine	Arginine
Methionine	Glutamine	Histidine
Phenylalanine		
Tryptophan		
Proline		



Peptide Bonds

- bind amino acids together to form "peptides" (short chains) or proteins (long chains)

Folding of Protein Chains

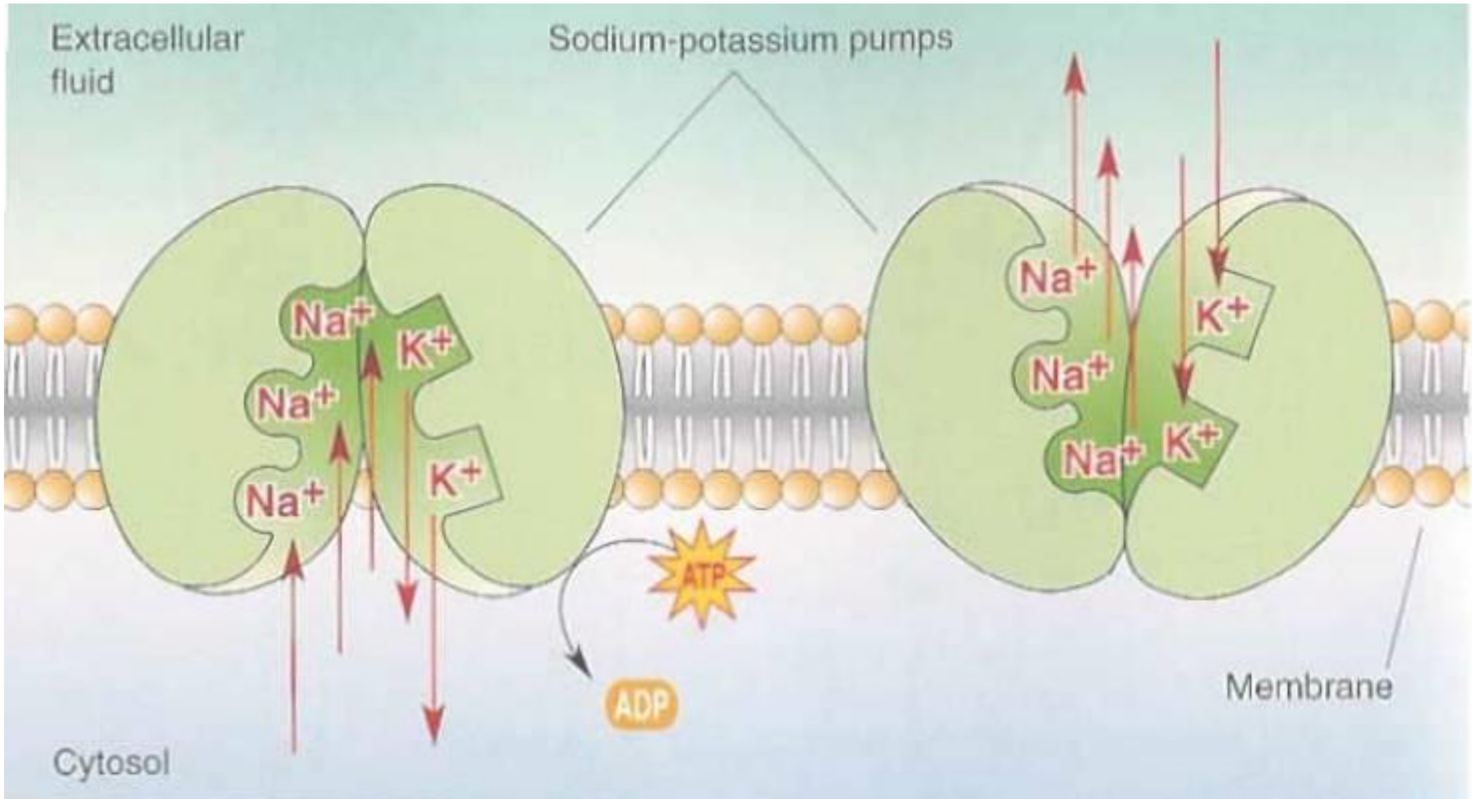


Proteins "fold" to form useful building blocks,
like trans-membrane channels, enzymes, or structural proteins

Important Proteins

- Enzymes: *catalyze* (i.e. facilitate) all sorts of biochemical reactions within the cell
- Trans-membrane channels: regulate the movement of ions and other substances through the cell membrane
- Receptors: sense the presence or absence of certain substances in the fluids outside the cell membrane
- Structural proteins: act like scaffolding and determine the cells shape.

The Sodium-Potassium Pump



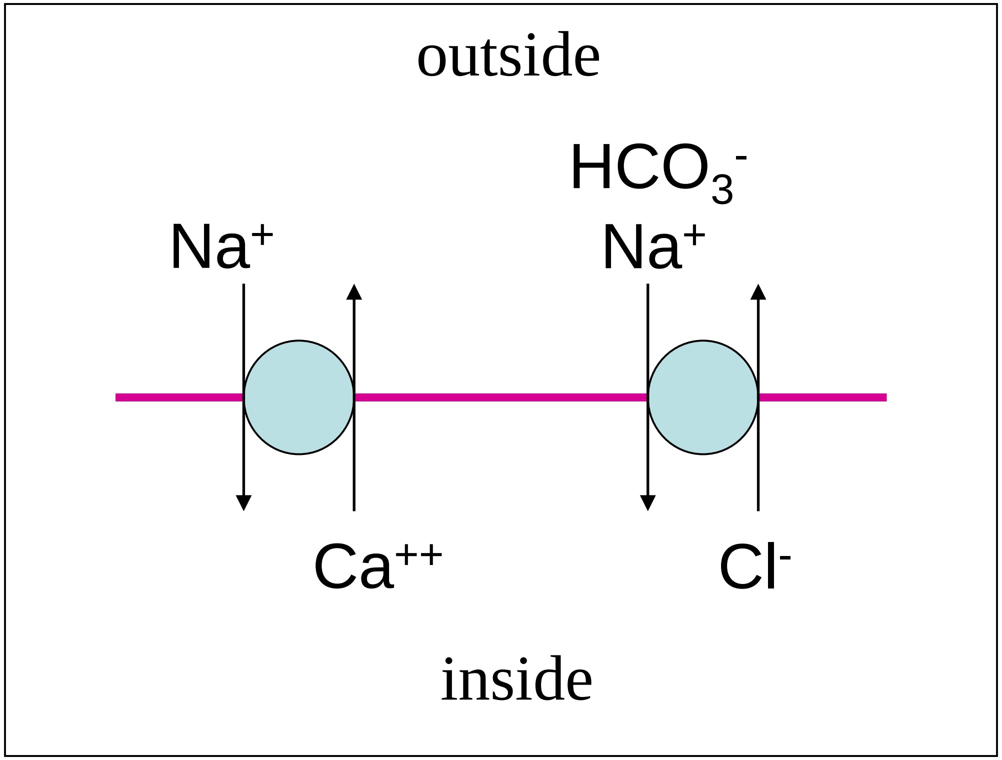
- The Na/K pump actively transports Na^+ out of the cell and K^+ into the cell
- It requires energy (provided by ATP)

Other Ion Pumps and Exchangers

- The Na^+/K^+ pump is only one of several ion pumps
- Some ion pumps are powered by concentration gradients, rather than ATP hydrolysis. These are called ion *exchangers*. Examples are shown here:

Na^+ - Ca^{++} exchanger

Bicarbonate - Cl^- exchanger



Ionic Concentrations

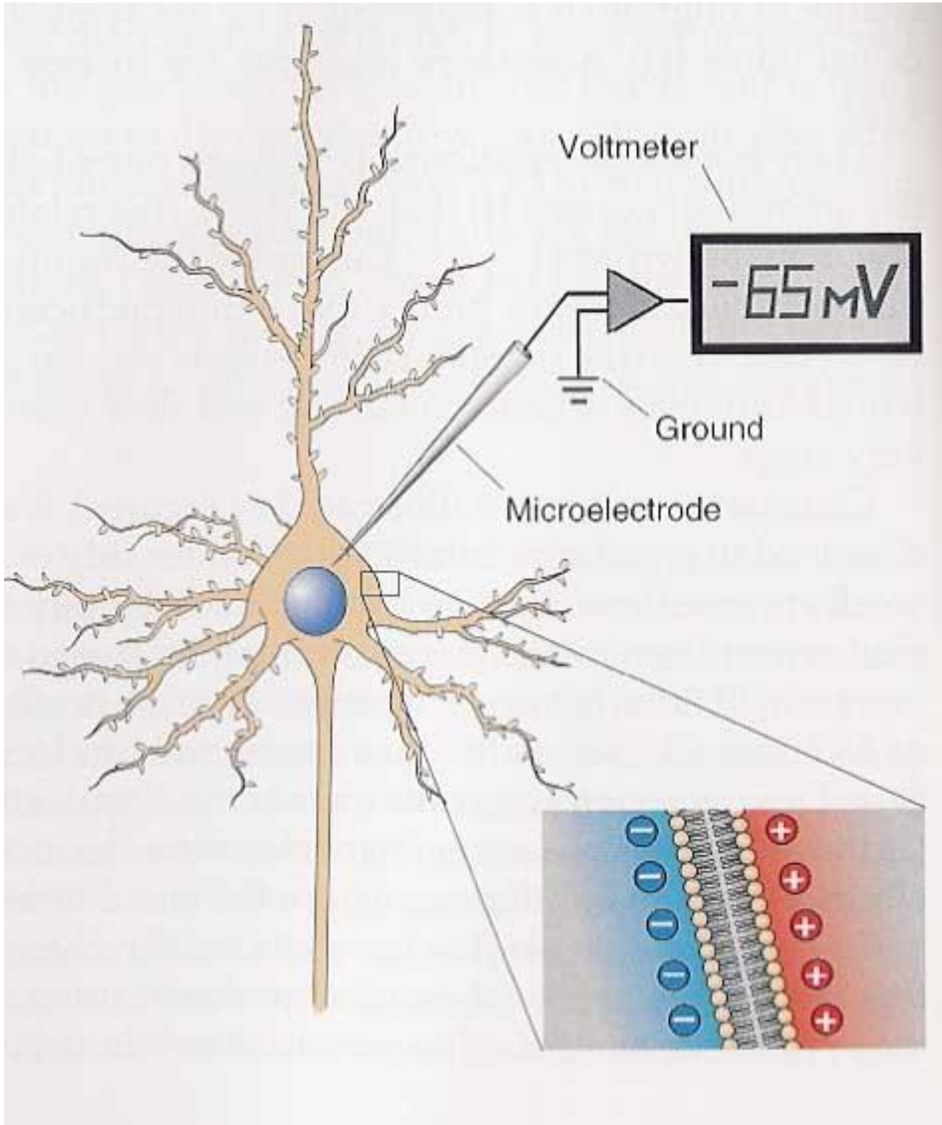
Ion	***Conc. In (mM)***	***Conc. Out (mM)***
Na+	18	150
Cl-	7	120
Ca++	0.00001	1.2
K+	135	5
organic anions	74	13

- Approximate intracellular and extracellular concentrations of a number of important ion species for a “typical mammalian neuron”. (You don’t have to remember them)

Remember This!

- **Na^+** and **Cl^-** concentrations are **higher outside** the neuron than inside.
- **K^+** and **A^-** concentration are **higher inside** than outside.
- Neurons keep **intracellular Ca^{++}** concentrations **very low**.
- Neurons are in **electrochemical equilibrium**

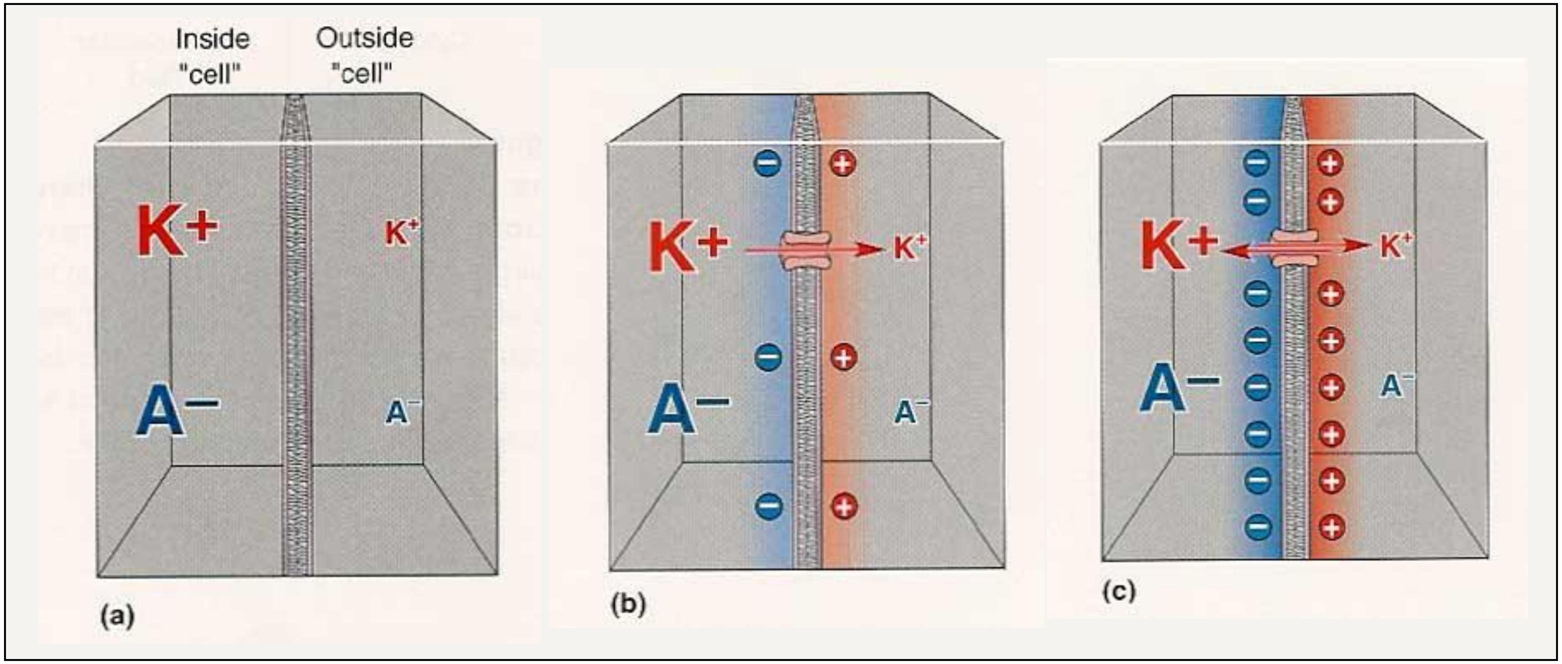
Resting Membrane Potentials



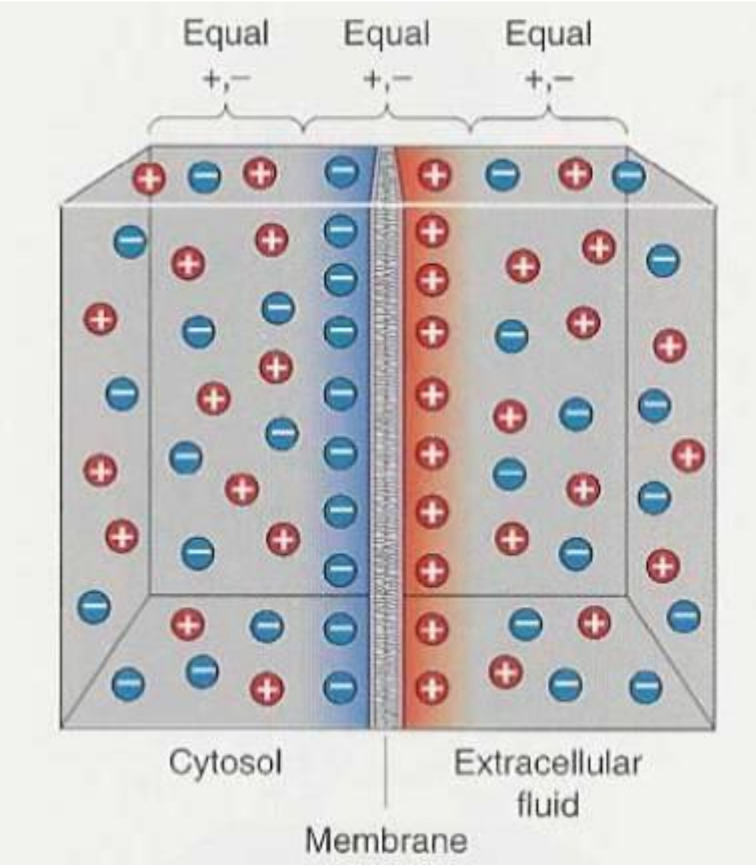
- All cells (not just neurons) display an electrical potential across their cell membranes.
- At rest, neurons display a ‘resting membrane potential’ of around -70 mV.
- Given that the membrane is only 10 nanometers (billionths of a meter) thick, the electric field strength in the membrane is ca 7 million volts / meter !

Electrochemical Equilibrium

- Ions diffuse through selective channels in a membrane.
- Their partners of opposite charge are left behind.
- An electrical gradient is set up across the membrane.
- Further diffusion is opposed by the electrical gradient.



Gradients, Concentrations and Charge



- Electrostatic forces are strong.
- Hence, a redistribution of a modest number of ions can give rise to sizeable potentials (voltages).
- The amount of charge (number of ions) that needs to be moved to set up a particular voltage depends on the *membrane capacitance.* C=Q/V => V=Q/C.
- Electrochemical equilibrium is reached after only tiny changes in relative ion concentrations.

The Nernst Equation

Predicts "equilibrium potential" (i.e. voltage large enough to stop net charge movement by diffusion)

$$E = \frac{RT}{Fz} \ln\left(\frac{C_{out}}{C_{in}}\right)$$

$$E_K = 58 \cdot \log_{10}\left(\frac{[K^+]_{out}}{[K^+]_{in}}\right)$$

$$\Rightarrow E_K \approx -83mV$$

$$E_{Na} \approx +53mV$$

- E : Voltage (mV)
- R : Gas Constant
- T : Temperature (°K)
- F : Faraday's Constant
- z : Number of Elementary Charges on each Ion
- C_{in}, C_{out}, $[]_{in}$, $[]_{out}$: Concentrations inside or outside the cell (mM)

The Goldman Equation

$$V_m = 58 \cdot \log_{10}\left(\frac{P_K[K^+]_{out} + P_{Na}[Na^+]_{out} + P_{Cl}[Cl^-]_{in}}{P_K[K^+]_{in} + P_{Na}[Na^+]_{in} + P_{Cl}[Cl^-]_{out}} \right)$$

An extension of the Nernst Equation, which considers several Ion species, and “weights” the contribution of each ion by it’s respective *permeability (P)*

(Note: whether the internal concentration appears in the numerator or the denominator depends on the sign of the charge of the ion)

Important take-home message

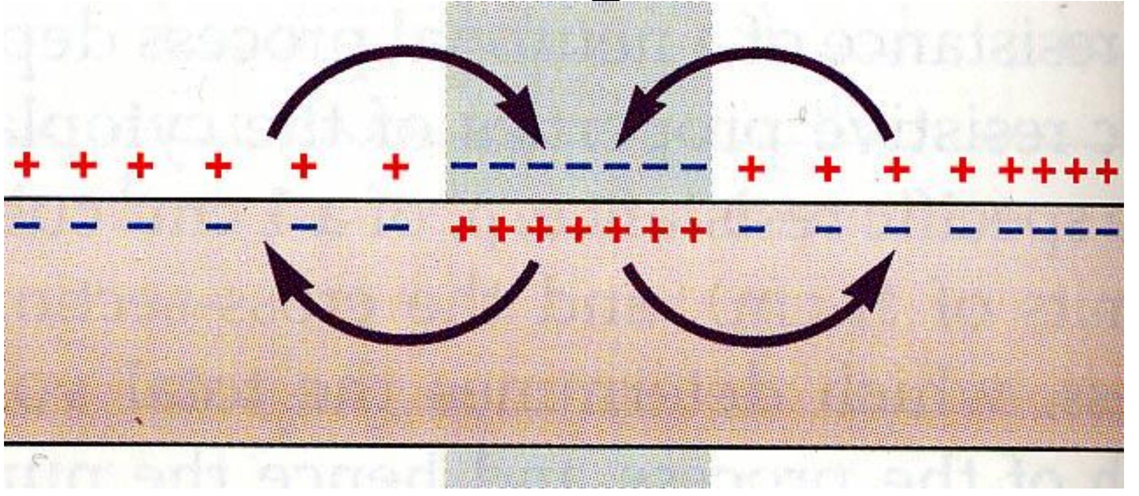
- Nerve cells are said to be in "***electro-chemical equilibrium***": electrostatic forces may push charged ions one way, diffusion down a concentration gradient may push them the other way.
- The voltage at which there is no net charge movement is called the ***equilibrium potential.*** It can be calculated with the Nernst (or Goldman) equation. (You will not be expected to remember these equations or to apply them for this course, but you should have heard of them).

Let’s take a short break

From Resting Potentials to Electrical Signals

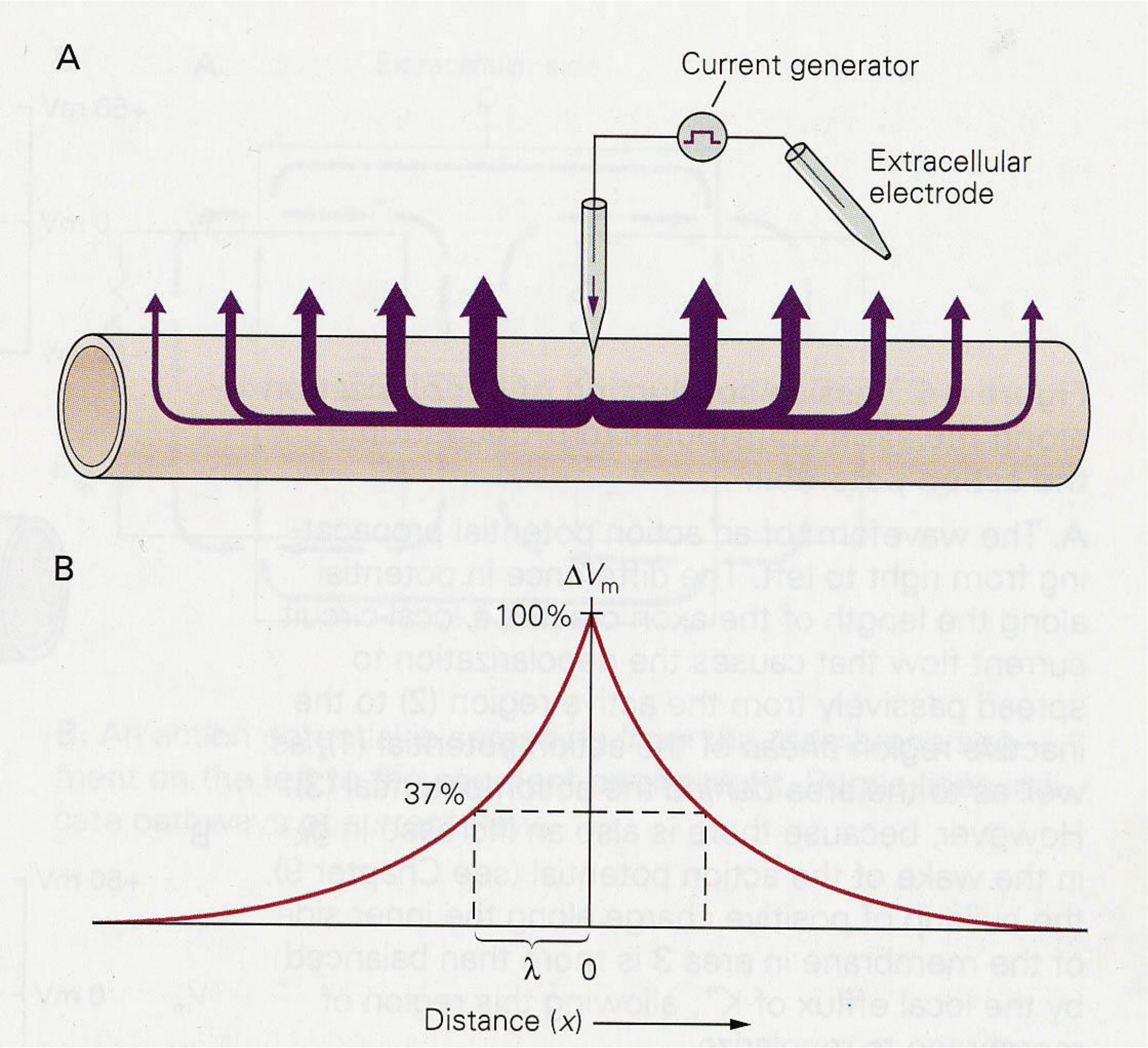
- In addition to the resting (K^+ leakage) channels, neurons can have a large variety of ***gated ion channels*** which will open transiently in the presence of certain stimuli or chemical signals. These gated channels may be permeable to Na^+, Cl^- or Ca^{++}.
- When these gated channels open, the voltage across the membrane will change to reflect the new permeabilities as predicted by the Goldman equation.
- The ***presence of physical or chemical signals which are capable of opening the gated channels is thus "encoded" as a change in membrane potential***.

Passive Propagation of Electrical Signals



- Ions flow easily along, but not across membrane. (Membrane ***resistance*** is much higher, than that of intracellular and extracellular fluid).
- To change the potential on a distant patch of membrane, enough ***current*** has to flow to discharge the membrane ***capacitance*** at that point.

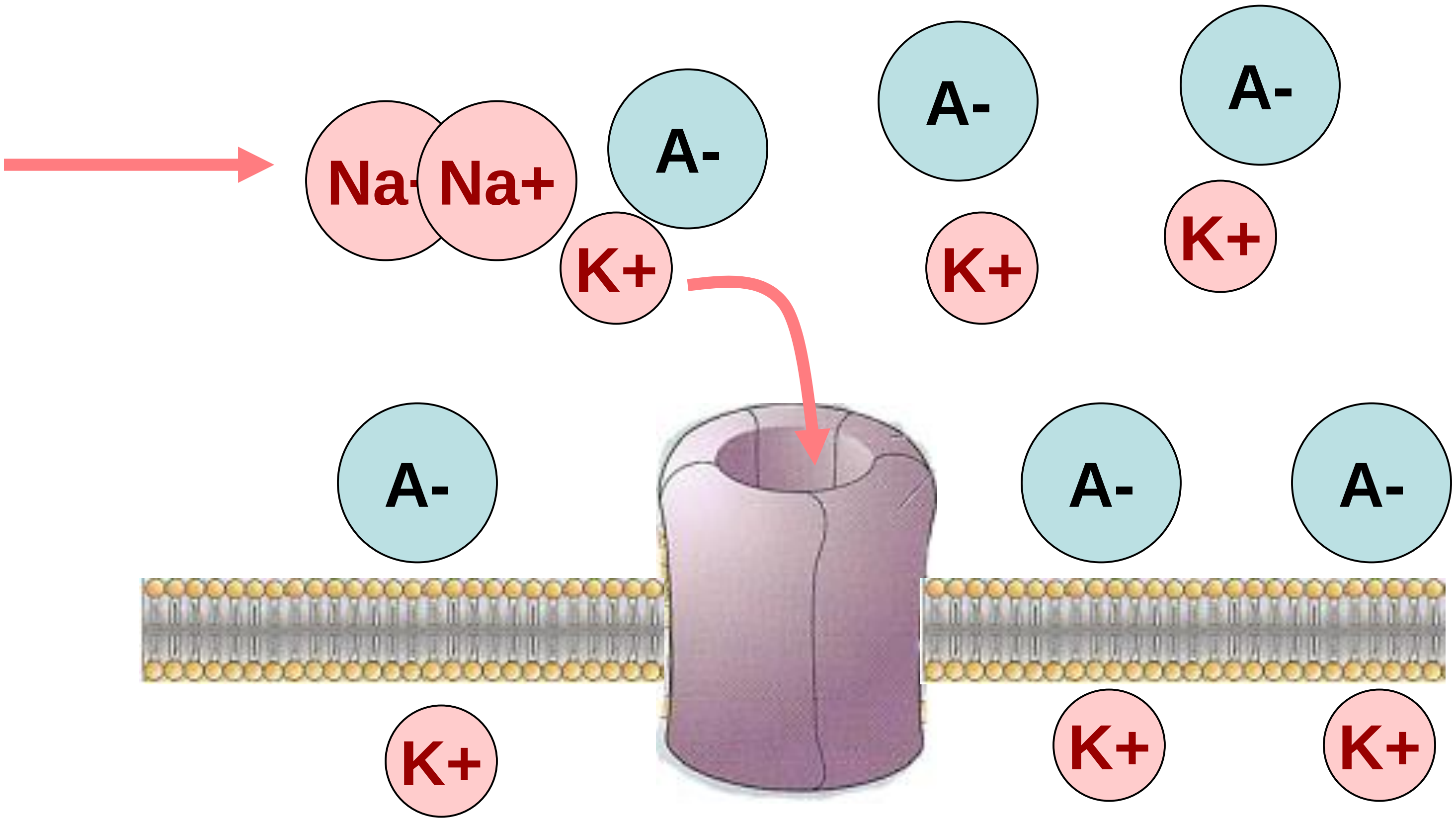
Limitations of Passive, Graded Signals



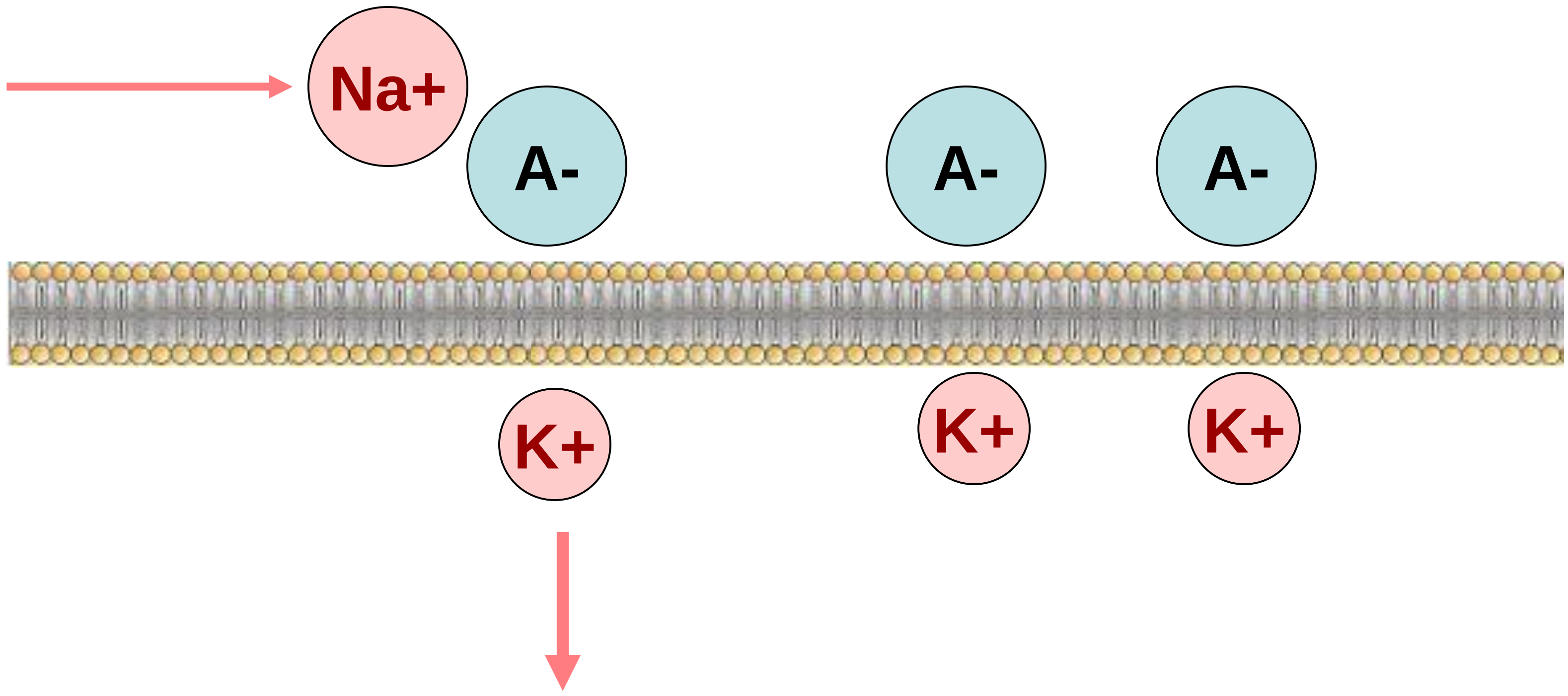
Some of the current does leak through the membrane.

Consequently passively conducted signals ***decay*** after relatively short distances (***small space constant***).

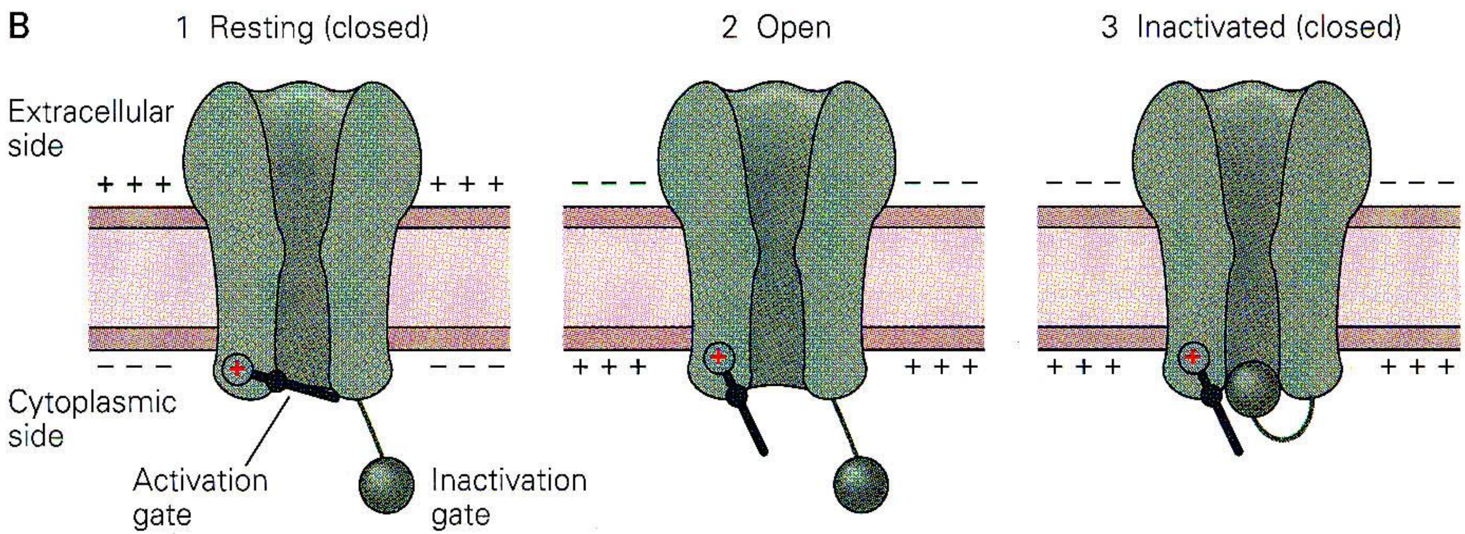
Leakage



Capacitative Leakage



The Voltage Gated Na+ Channel



Normally closed when the membrane is at rest.
Opens briefly (ca 0.5 ms) when the membrane depolarises to a certain ***threshold***.
Once open, rapidly closes again and remains ***inactivated*** (*"**refractory**")* for another 0.5 ms or so.

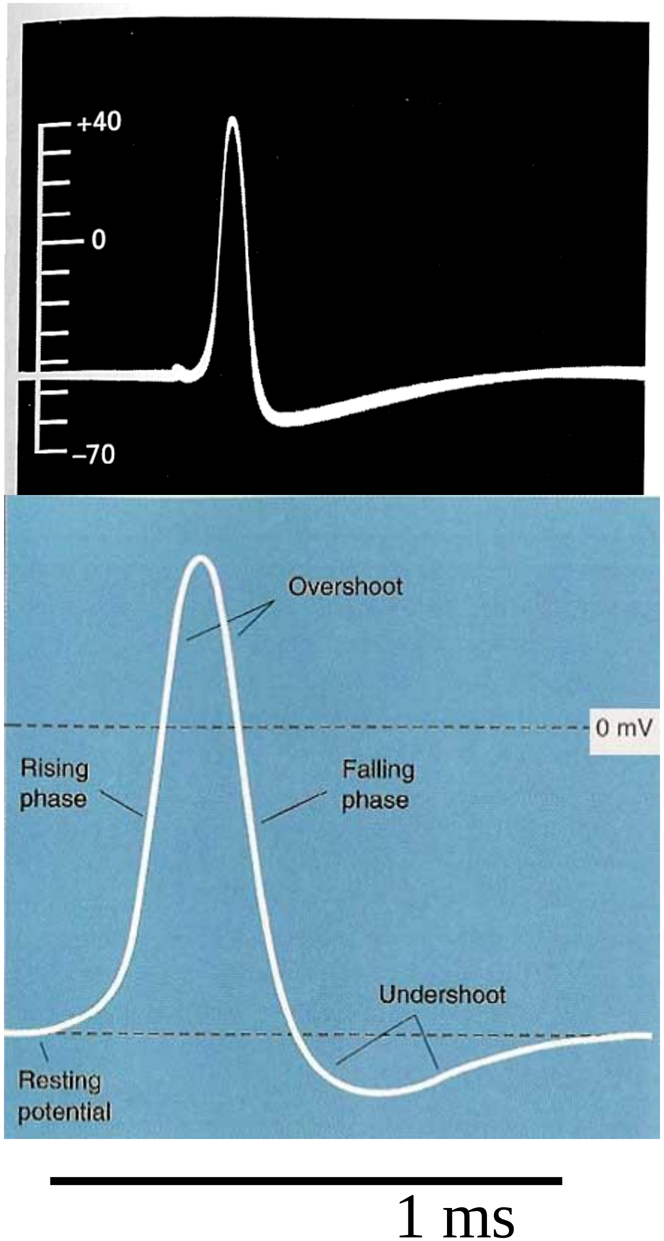
Action Potentials as Positive Feedback Processes

- Depolarisation to ***threshold*** opens a few Na^+ channels, which allows further Na^+ influx, causing further depolarisation, which spreads passively down the axon allowing further Na^+ channels to open.
- This ***positive feedback*** process continues until all voltage gated Na^+ channels in the local patch of membrane have been through the open state and are inactivated (refractory).

Consequences of Positive Feedback

- Advantage: the feedback current injection allows action potentials to travel along axons for considerable distances without loss of signal. (Fresh Na+ currents make up for leakage).
- Disadvantage: action potentials are “all or nothing”. They cannot transmit information by their amplitude, so graded voltage signals are no longer possible. Hence “spike codes” have to employ other coding strategies, relying purely on the rate or timing of action potentials.

The Shape of Action Potentials

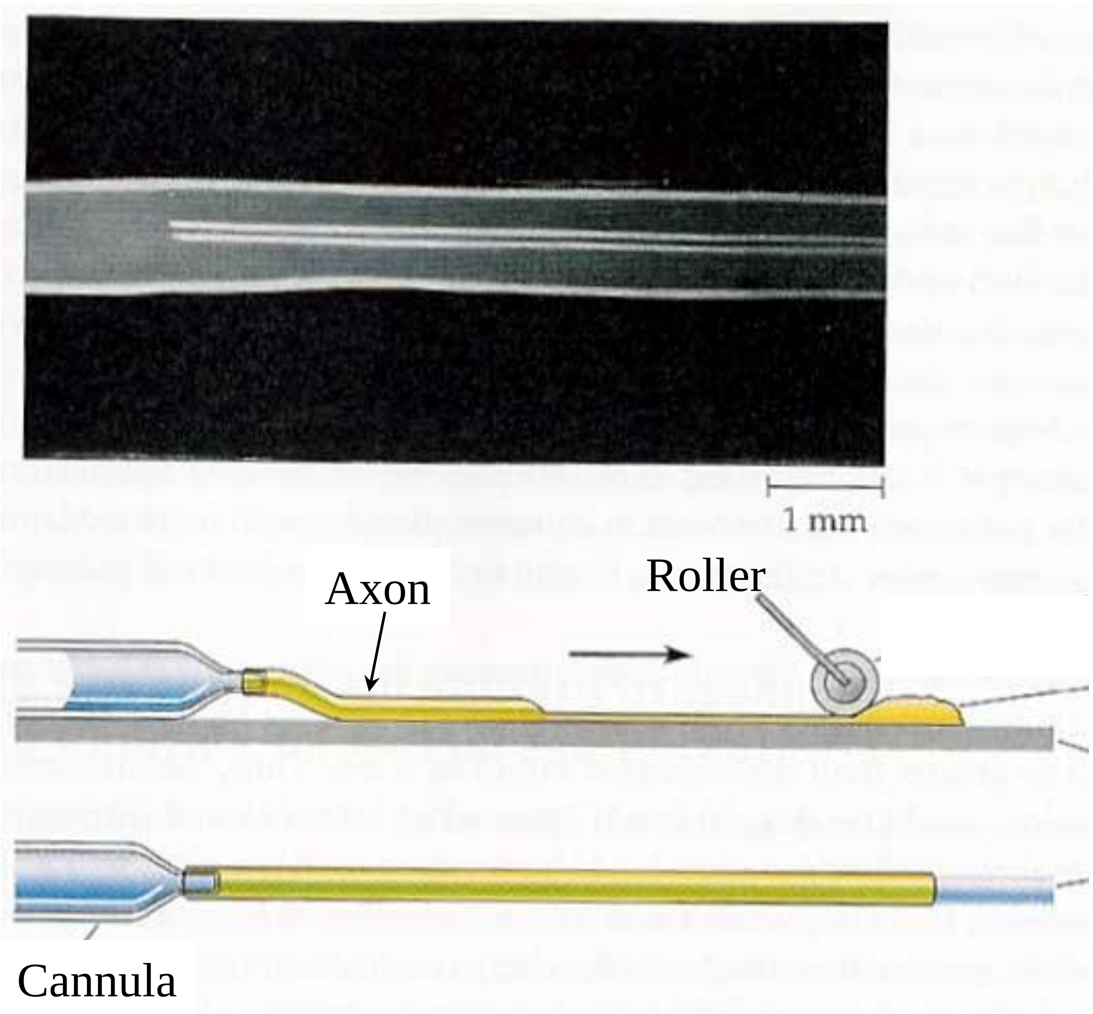


- The first published intracellular recording of an action potential, recorded by Hodgkin and Huxley in the giant axon of the squid.
- Note the overshoot: the peak of the action potential is *positive*. (E_{Na} is positive).
- The recording shows several other phases:
  - The stable resting potential
  - A rapid rising phase
  - A rapid falling phase
  - A prolonged **undershoot**

After-hyperpolarisation (or "Undershoot")

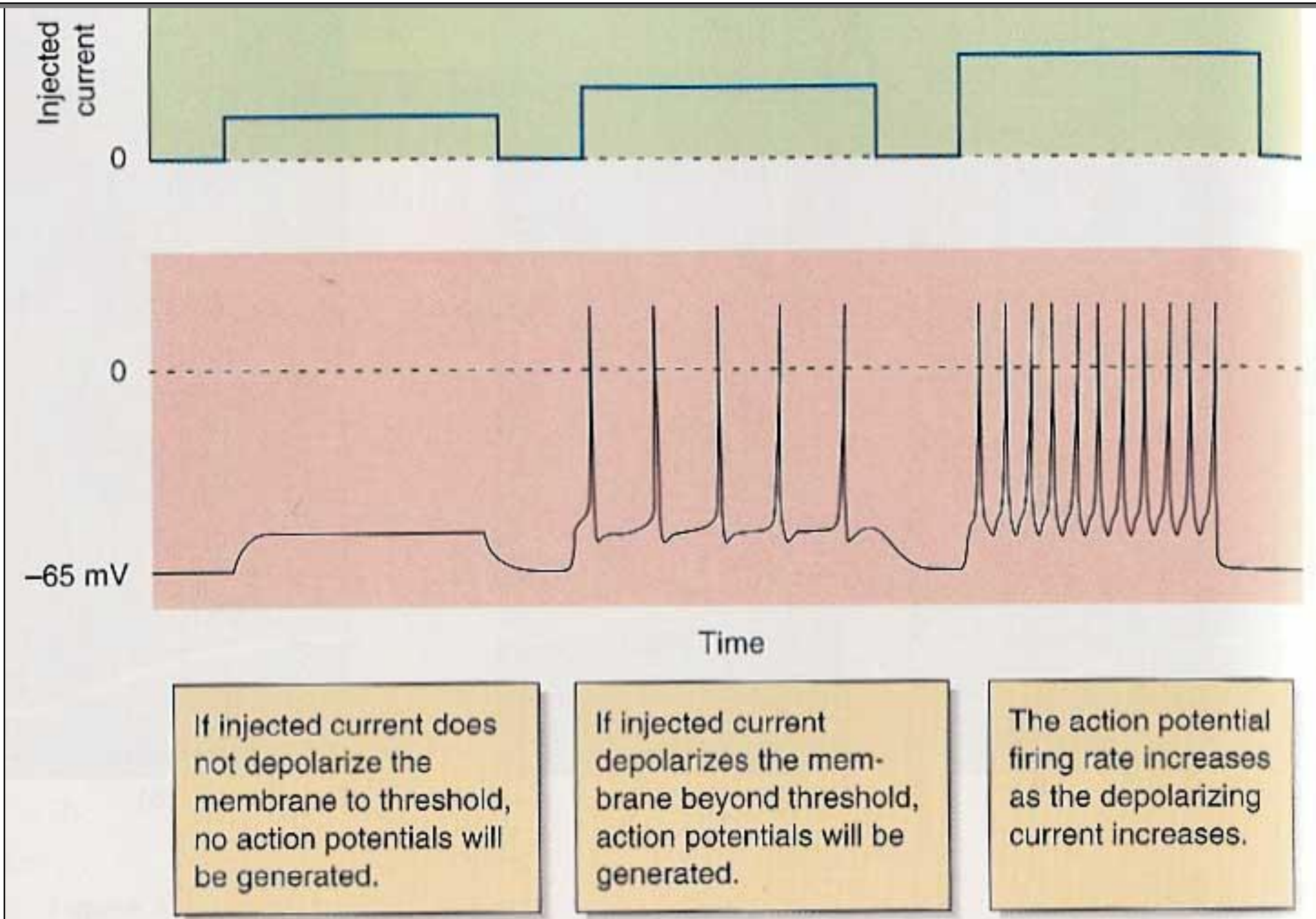
- In addition to Na^+ channels, many axons also contain voltage gated K^+ ("rapid rectifier") channels.
- K^+ rectifier channels are slower than Na^+ channels. They take longer to open, and stay open for longer.
- Their role is to speed up the re-polarisation of the membrane following the Na^+ action potential.

How Do We Know All This?



- Pioneering experiments by **Hodgkin & Huxley** were performed on giant axons of squid.
- These axons are large enough to allow axoplasm to be replaced by fluids of known ionic composition.

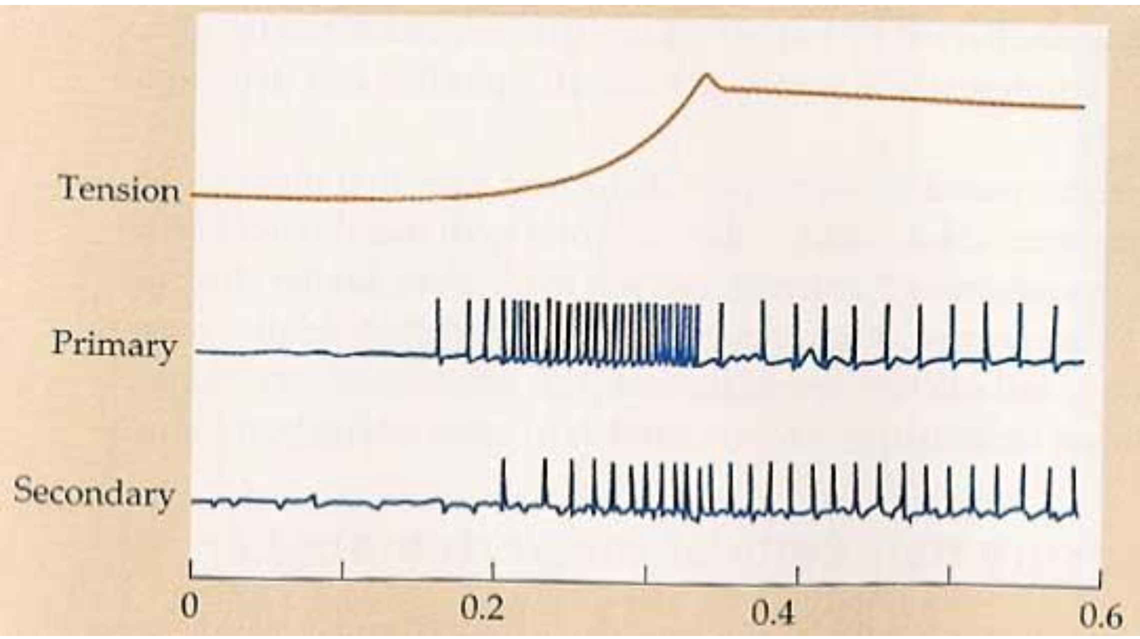
Another Look at AP Initiation: The Neuronal Threshold



Neurons “encode” injected currents as firing rates

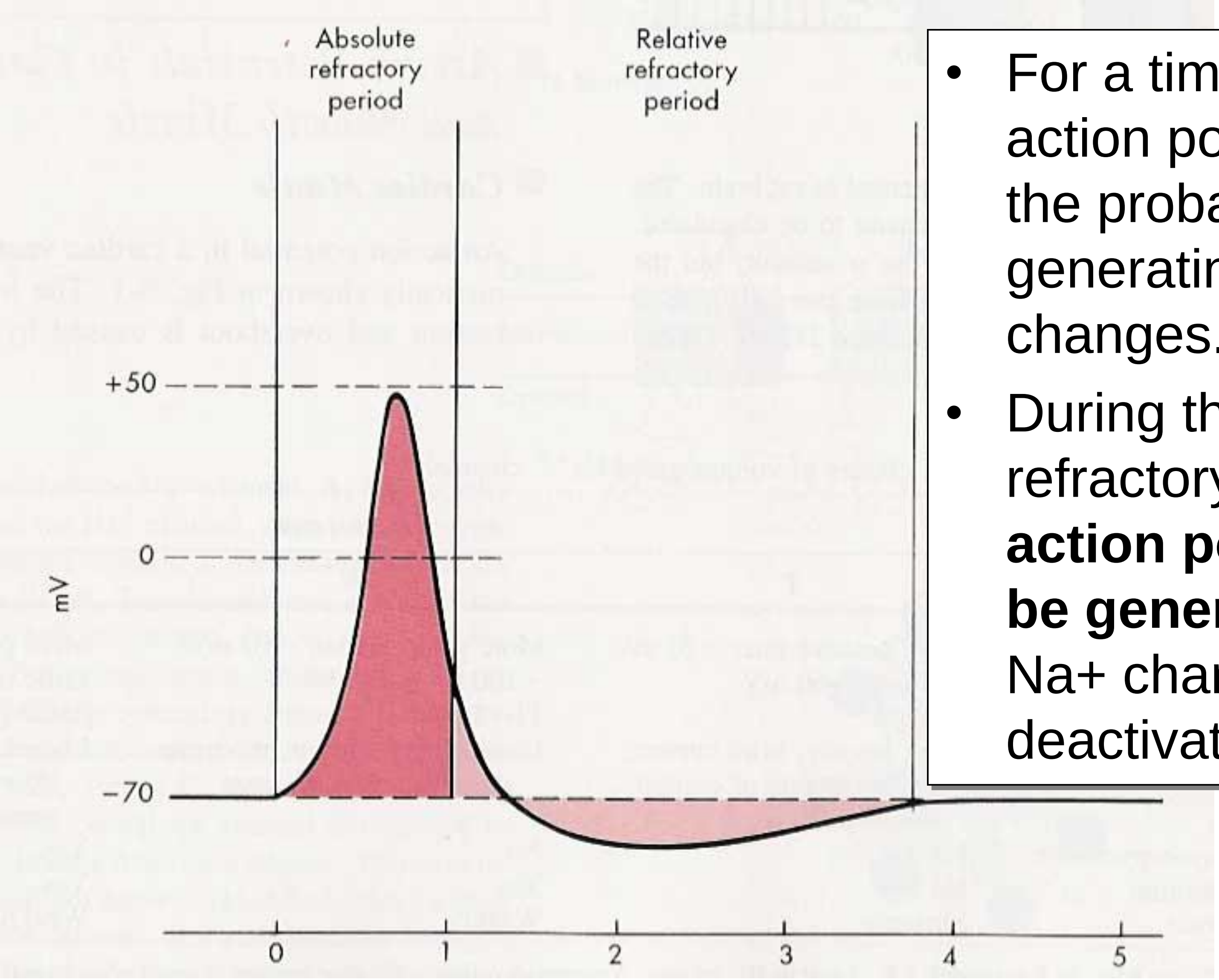
- Small, sub-threshold currents injected into a nerve cell don’t do anything, they just leak out again.
- Larger currents will trigger action potentials. The stronger the currents, the faster the action potential rate.
  => **“Rate Coding”**
- Reflect on why this is so. If you don’t understand this important principle, ask in the tutorials.

Action Potentials as a “Digital” Code



- An axon connected to a muscle stretch receptor signals the degree of stretch by the ***temporal pattern*** of action potentials
- Changes in stretch cause a change in the ***rate*** of action potentials.
- All the action potentials are roughly of the same height
- The action potentials are brief (ca 1 ms).

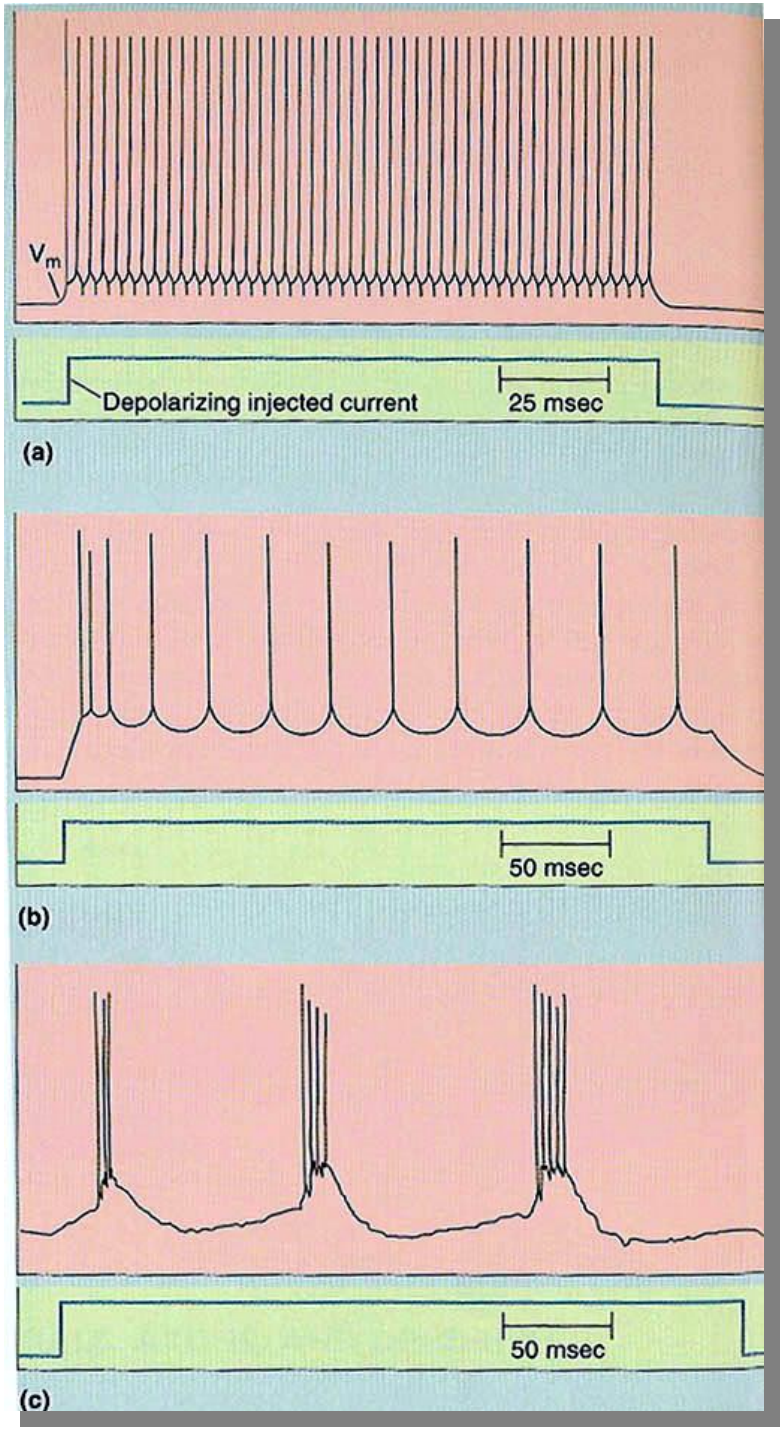
Refractory Period



- For a time after an action potential (AP), the probability of generating a second AP changes.
- During the **absolute** refractory period **no action potentials can be generated**, because Na+ channels are deactivated.

Refractory Periods and Firing Rates

- The absolute refractory period lasts ca 1 ms.
- Therefore, no neuron can fire at firing rates faster than ca 1000 Hz.
- Most neurons show some degree of adaptation, and rarely do neurons sustain firing rates of a few hundred Hz for any length of time.



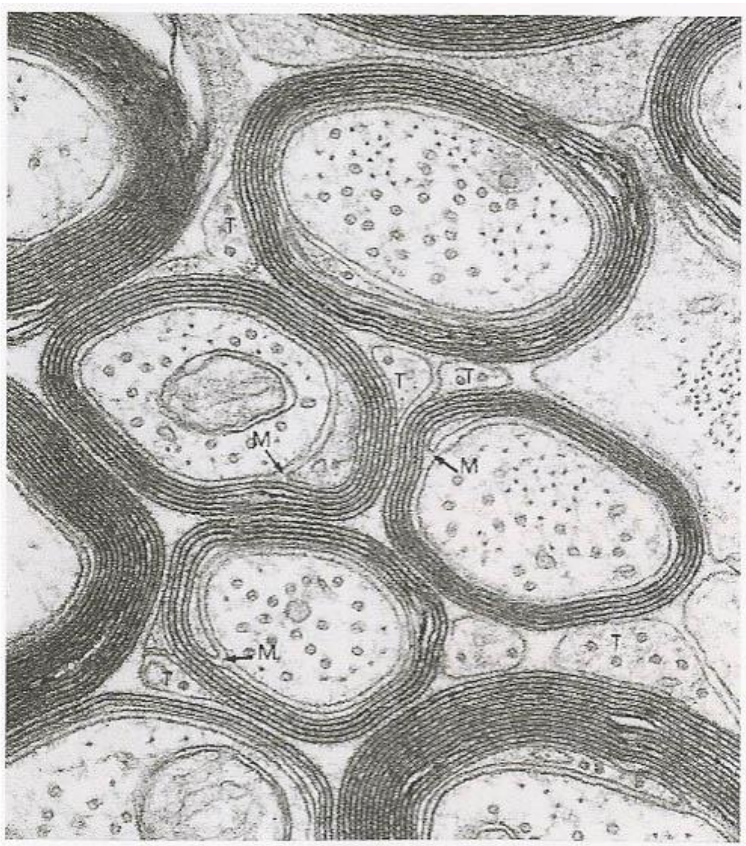
Firing Modes

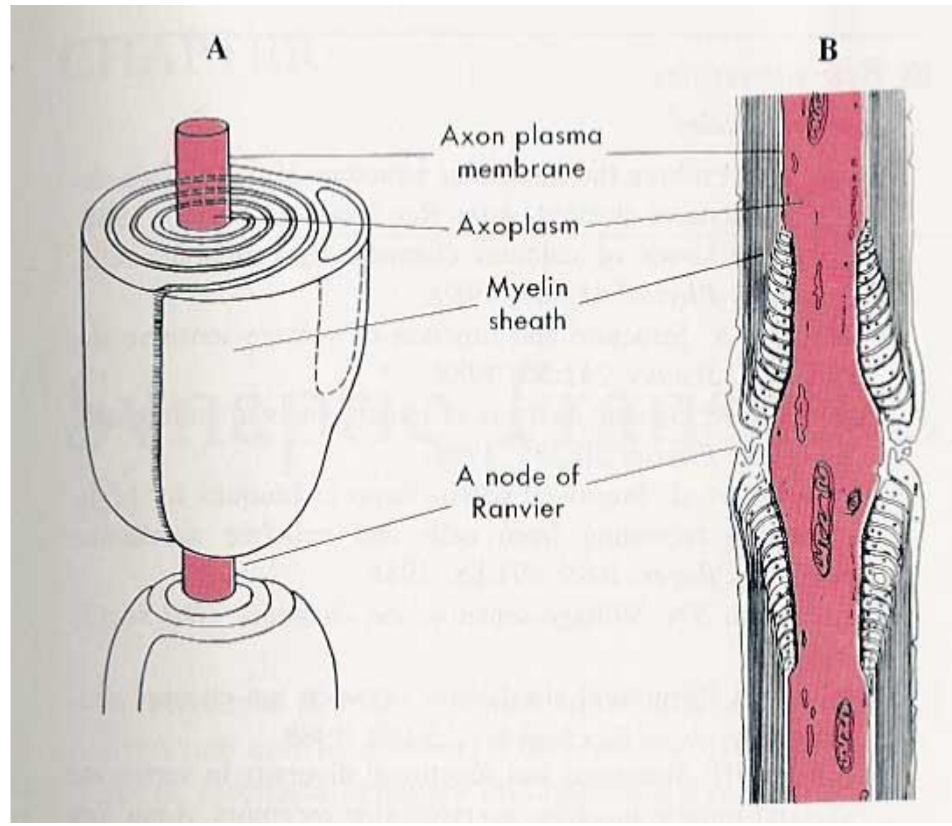
- ***Regular firing*** in response to a steady state current input is the exception in the brain.
- Most neurons show ***adaptation*** (decrease in firing rate). Some neurons fire ***bursts***.
- Some neurons may even change from regular to burst mode or vice versa depending on the animal's state of arousal or attention.
- Firing modes are due to the effect of other voltage gated channels.

Note that “rate coding” may be complicated

- Effects such as “refractory periods”, “adaptation”, and “active processes” such as bursting mean that the relationship between input current and output firing rate can differ from a simple, “linear” proportionality.

The Myelin Sheath



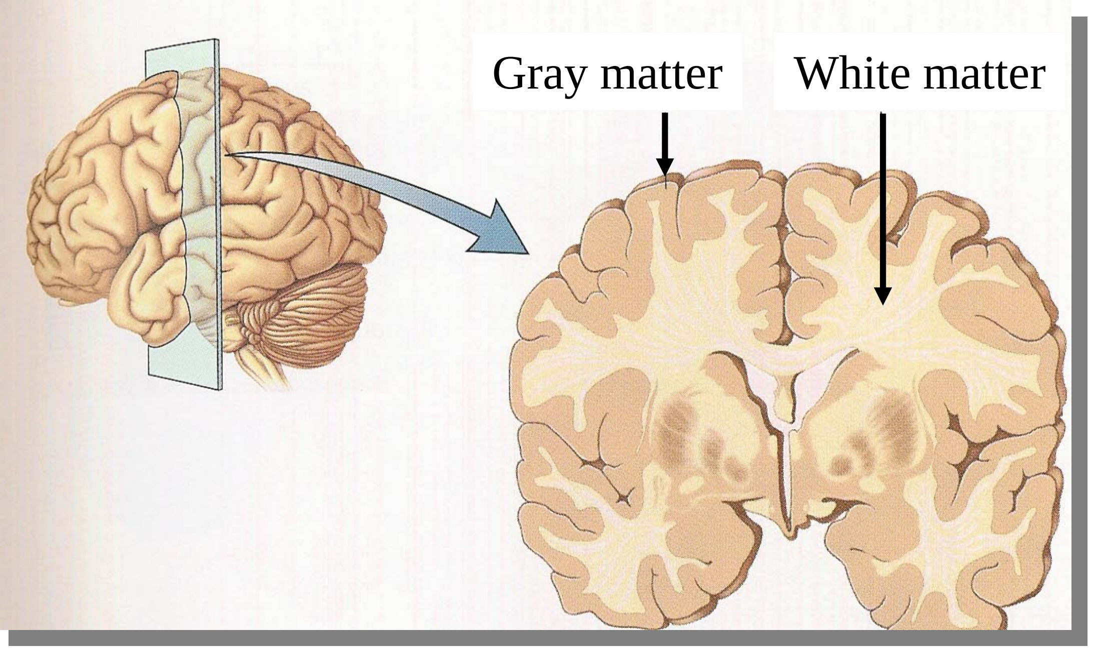


Myelin sheathes are specialised extensions of the cell membranes of certain glial cells (Schwann cells and oligodendrocytes), which tightly wrap around axons.

Demyelinating Diseases

- In certain diseases, such as ***Multiple Sclerosis***, the myelin sheath around axons becomes degraded.
- This will initially ***reduce conduction velocity,*** but as the disease progresses, ***action potential conduction*** will not only be slowed, but ***becomes unreliable*** and finally fails completely.
- This causes very serious problems, ranging from blurred vision and numbness to muscle weakness or even severe paralysis.

Myelin “Factoids”



- The brain’s “white matter” is white because of the high myelin content.
- The myelination of axons in the brain of human infants is not complete at birth (which partly explains their neurological immaturity).
- Myelin is an invention of vertebrate nervous systems (which is why even little squid need giant axons).

Summary

- Moving ions from dissolved salts carry electrical currents in neurons.
- Differences in ion concentrations between inside and outside of neurons can create voltages across the cell membrane. (“equilibrium potential”)
- Opening or closing chemically or mechanically gated ion channels in cell membranes changes the permeability which in turn changes the membrane voltage. This can encode information.
- Current leakage means that neurons cannot conduct electrical signals passively over distances greater than 1mm or so max.
- To send signals along potentially very long axons, nerve cells use action potentials (“nerve impulses”) which propagate through the help of voltage gated ion channels.
- Myelin sheaths on axons make action potential propagation faster and more reliable.