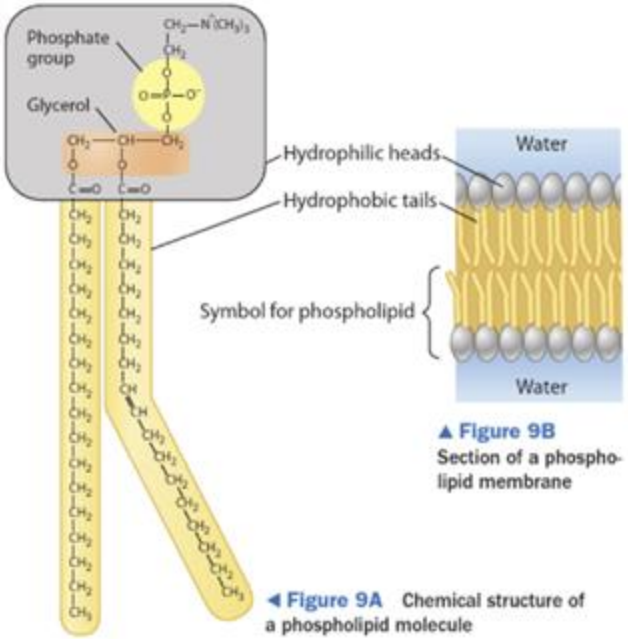
Summary- Week 2 Action Potentials

What are the cellular membranes made of?



▲ Figure 9B Section of a phospholipid membrane

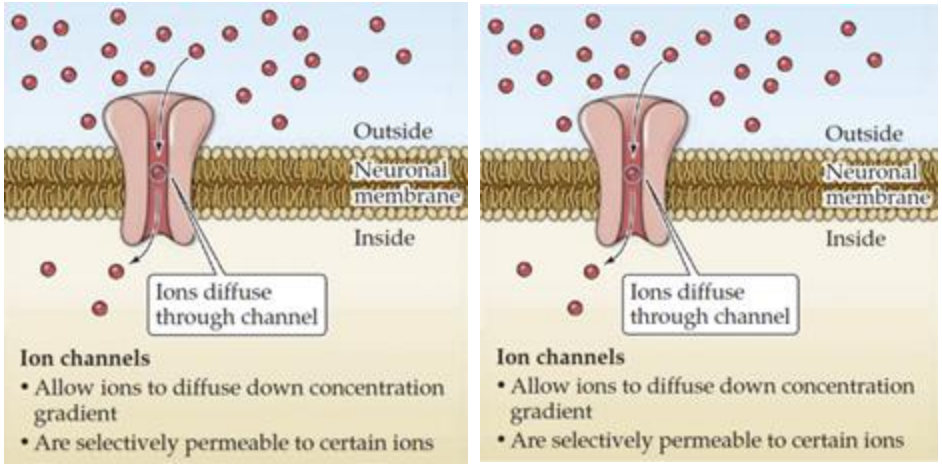
◀ Figure 9A Chemical structure of a phospholipid molecule

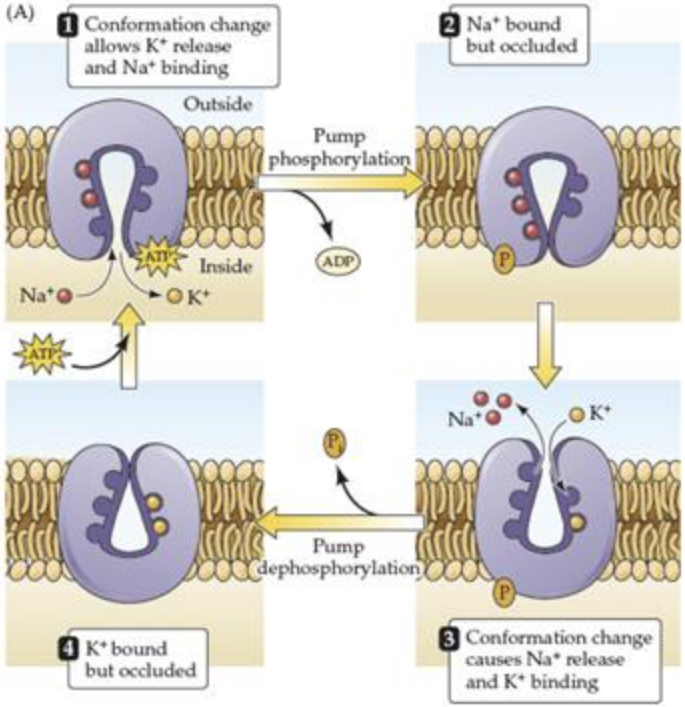
Phospholipids have a charged head group and a hydrophobic tail. For that reason, they assemble to form a bilayer in a watery environment/solution.

Phospholipids make up the celluar membrane. They prevent charged and polar molecules (like ions and water) to diffuse in and out of the cell.

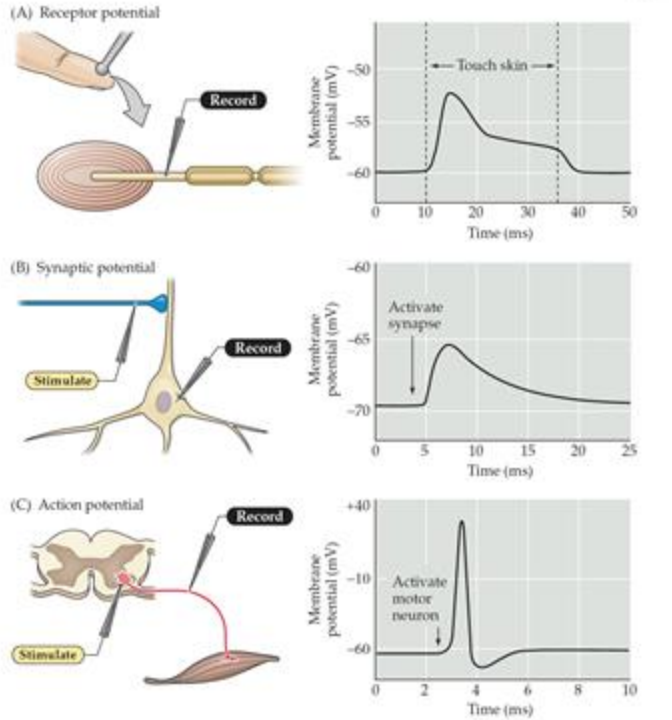
How can nutrients and charged molecules exit and enter the cell?

Explain how active transporters and ion channels work in maintaining ion homeostasis



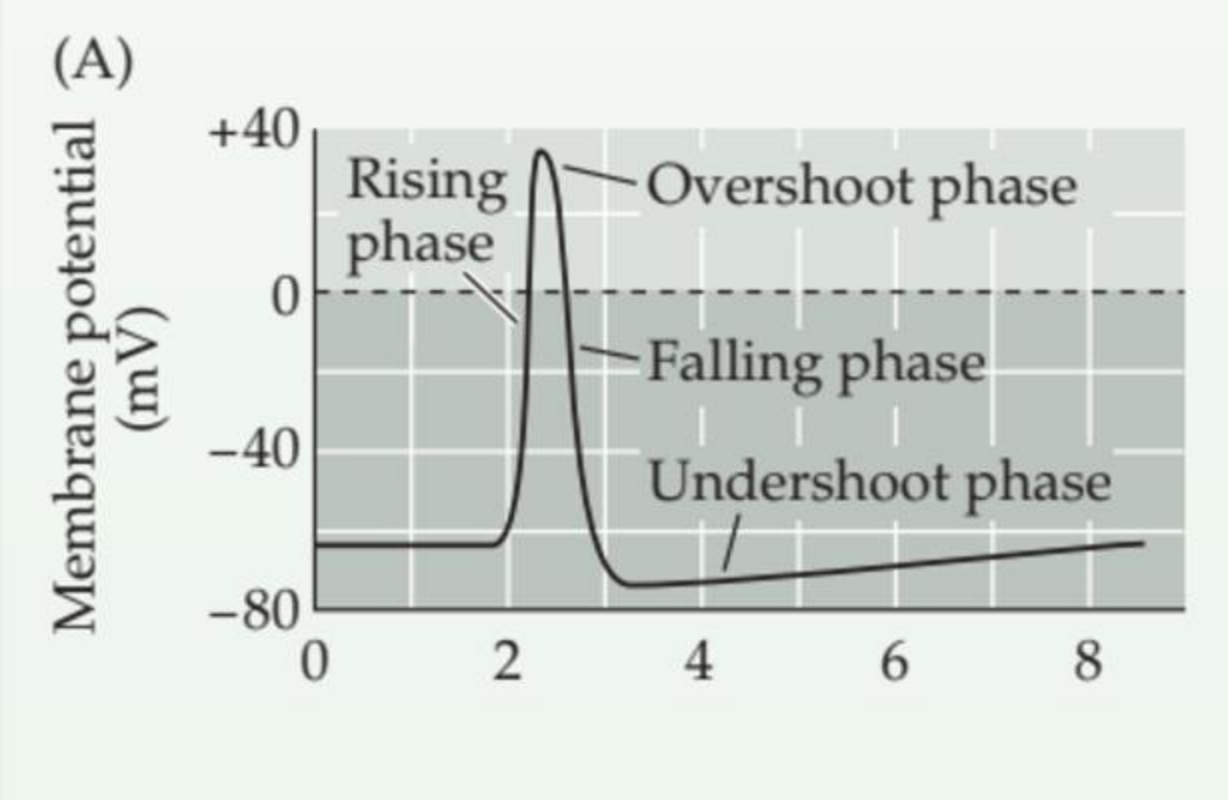


Compare the differences and magnitudes of the three types of potential - receptor, synaptic and action potential

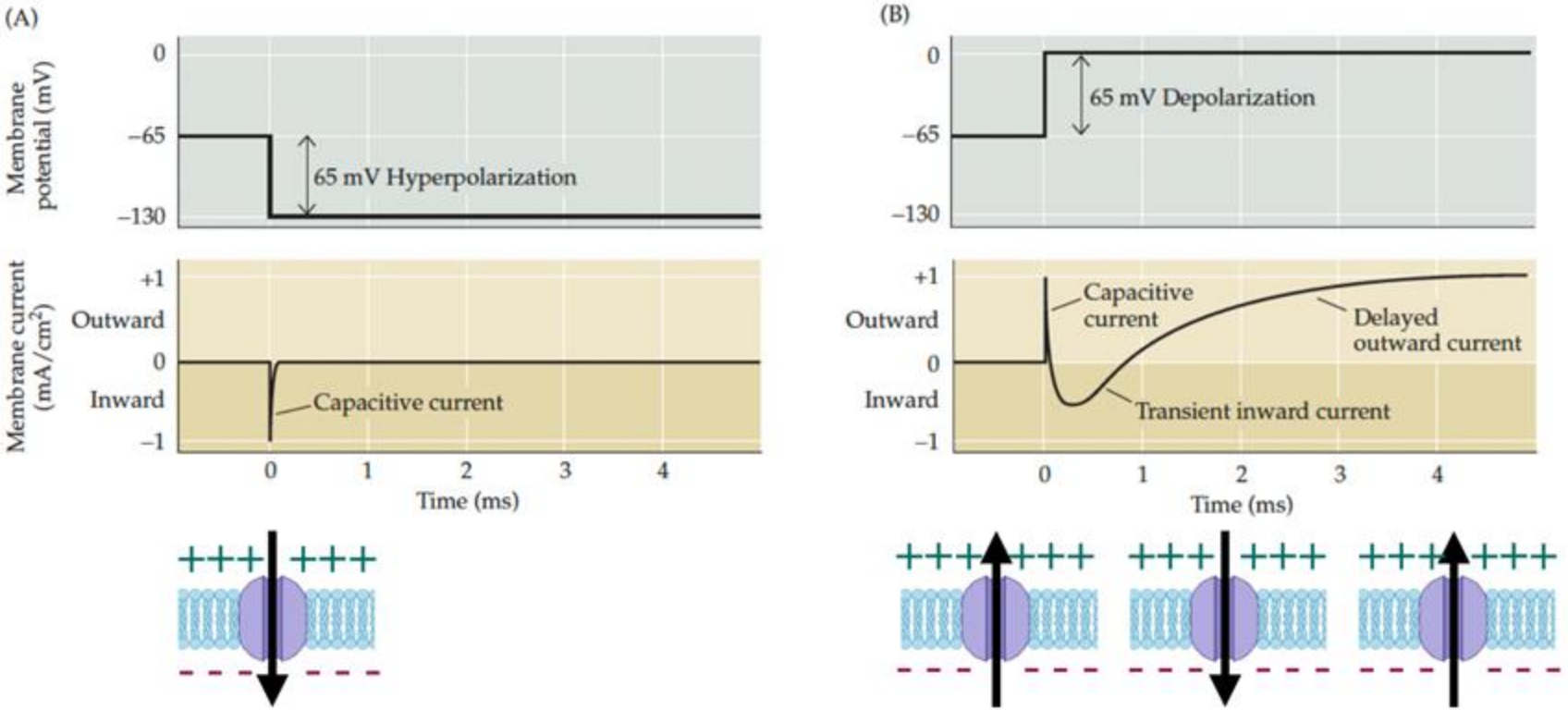


While synaptic (stimulation via other neuronal endings) and receptor potentials (triggered by external sensations like touch) cause a slight depolarization of the membrane. But this is only a fraction of what an action potential can do.

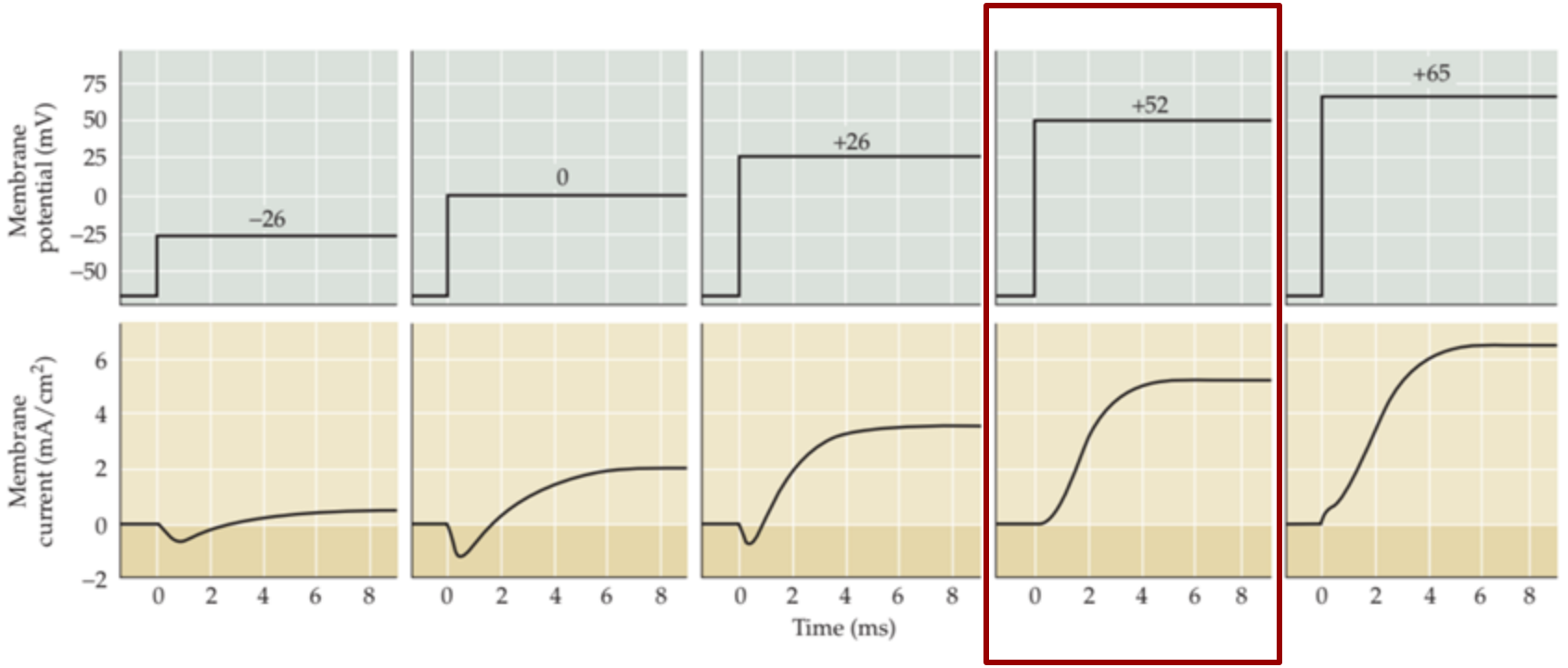
Phases of the action potential



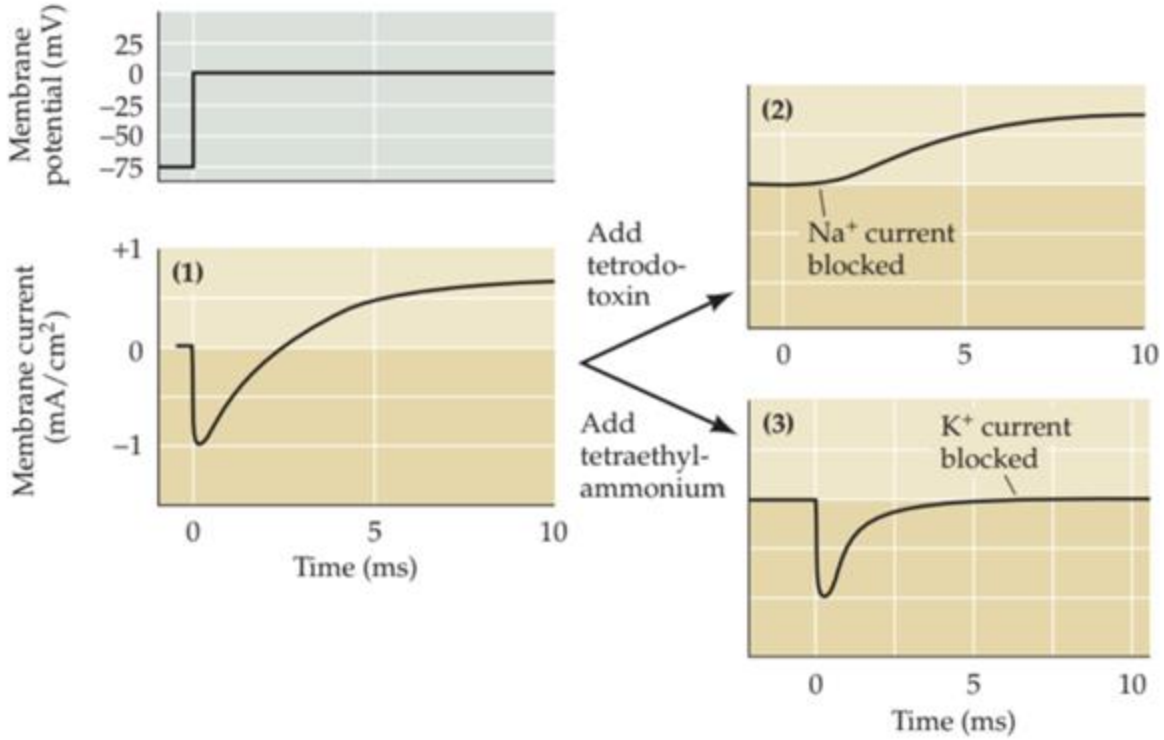
Membrane permeability of axons is voltage dependent



At the equilibrium potential of sodium, there is no inward current

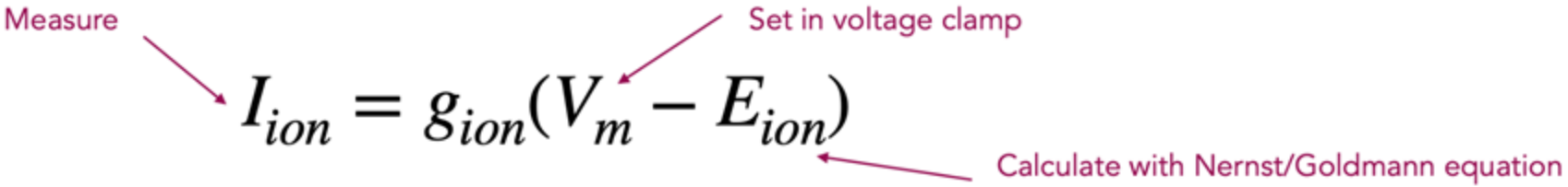


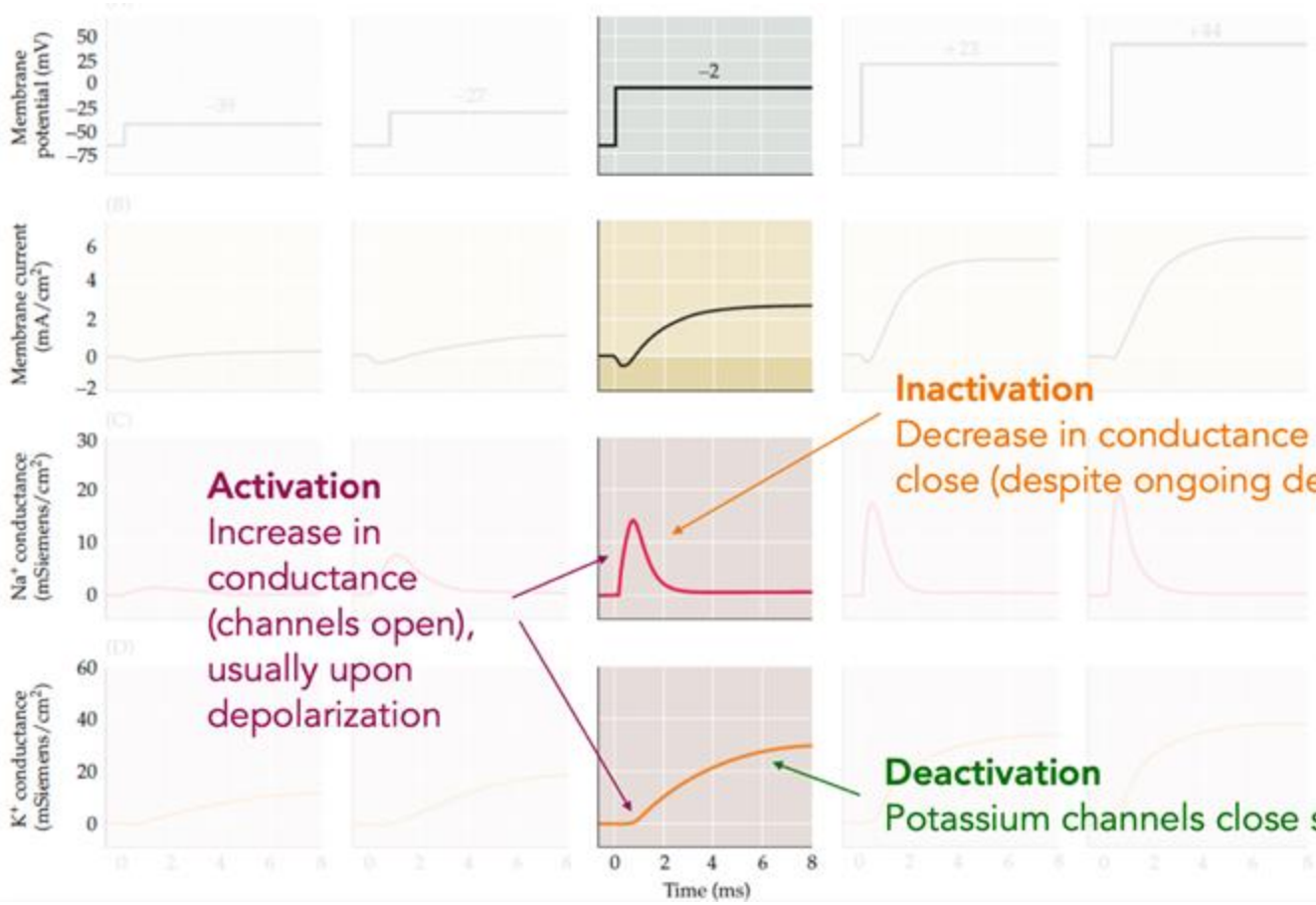
Sodium and potassium currents to understand action potentials



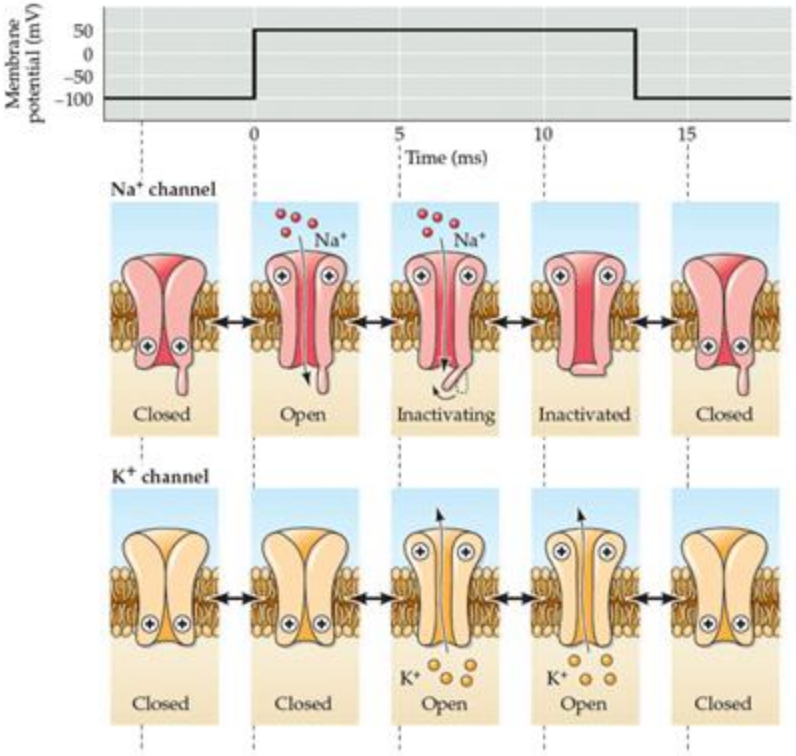
Hodgkin and Huxley modeled voltage dependent membrane conductance

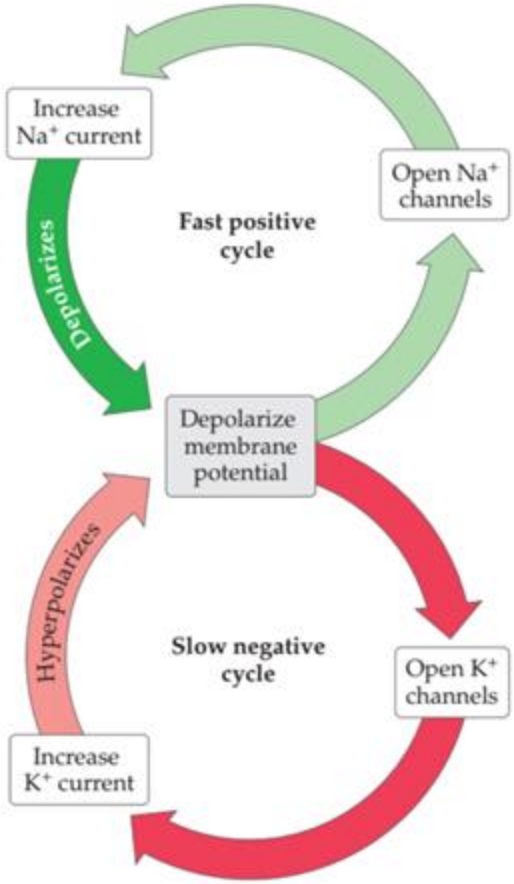
Ion currents change due to membrane conductance (g)



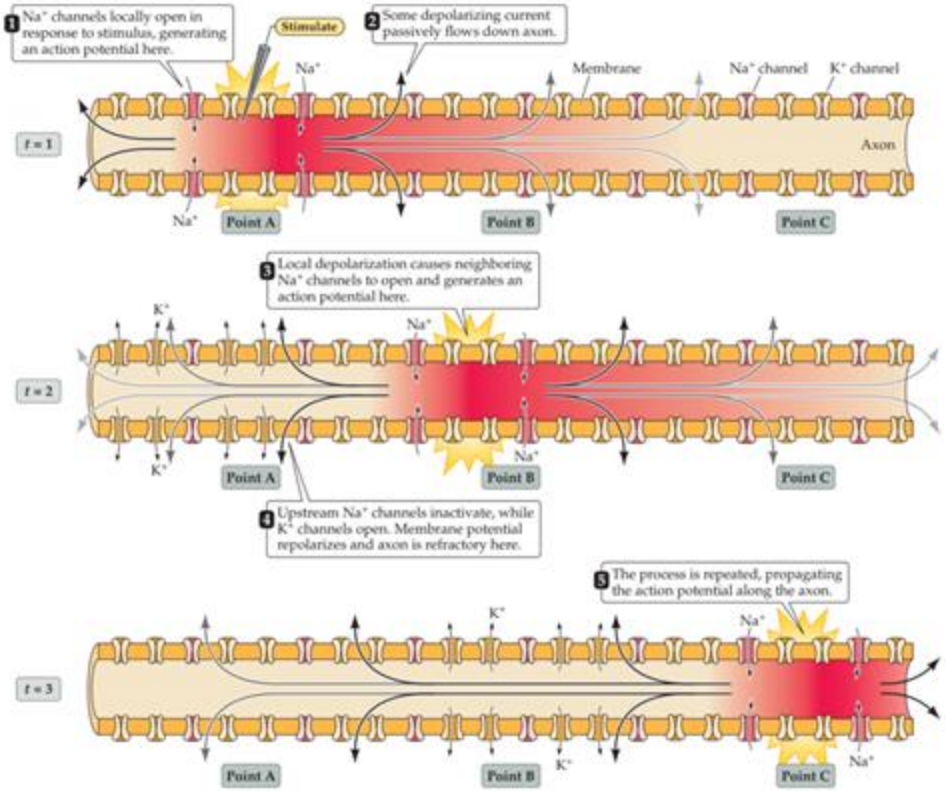

Membrane potential (mV)
50
25
0
−25
−50
−75
−2
Membrane current (mA/cm²)
6
4
2
0
−2
Na⁺ conductance (mSiemens/cm²)
30
20
10
0
K⁺ conductance (mSiemens/cm²)
60
40
20
0
0
2
4
6
8
Time (ms)
Activation
Increase in conductance (channels open), usually upon depolarization
Inactivation
Decrease in conductance - Sodium channels close (despite ongoing depolarization)
Deactivation
Potassium channels close slowly

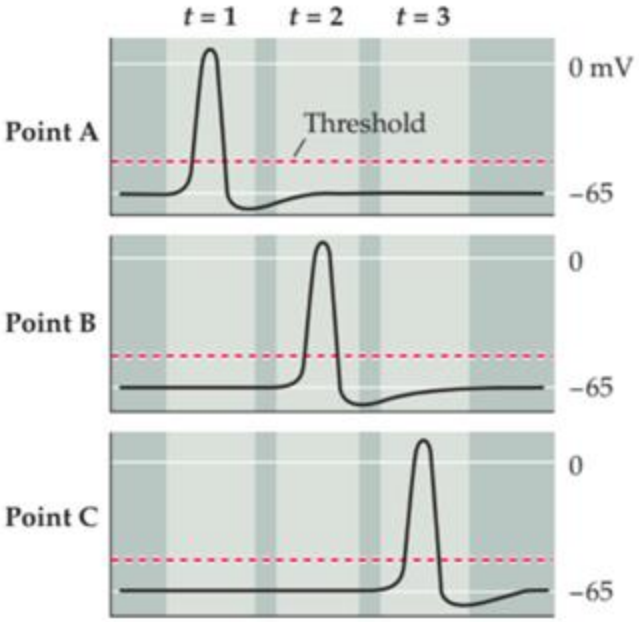
Feedback cycles during an action potential





Conduction of action potentials

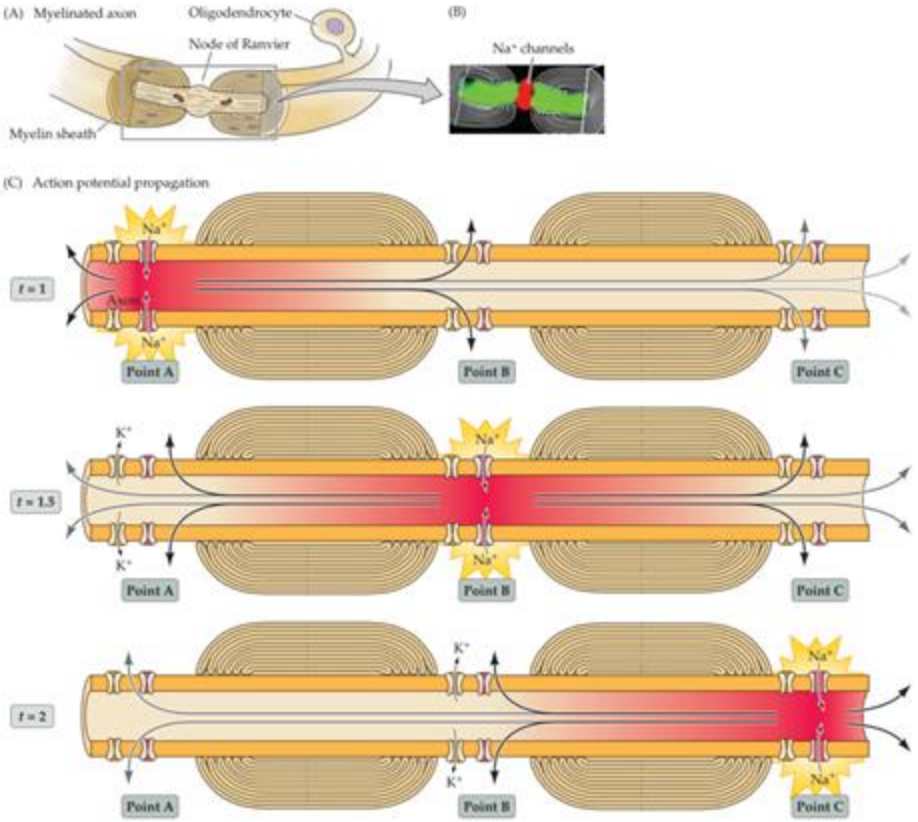




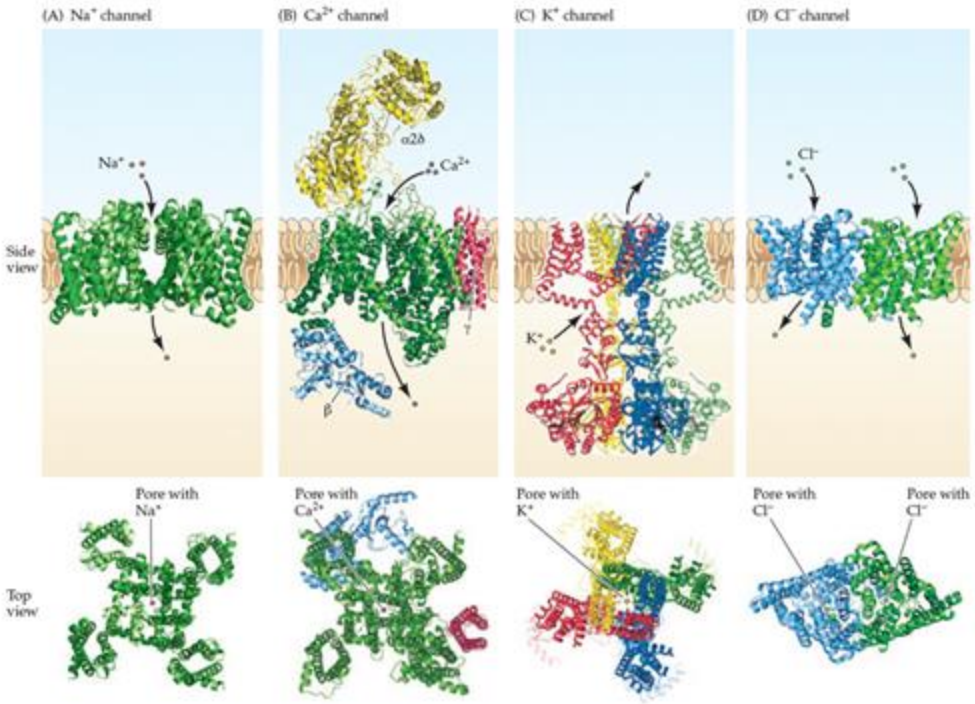
Why does the action potential not travel backwards?

How does action potential propagate fast?

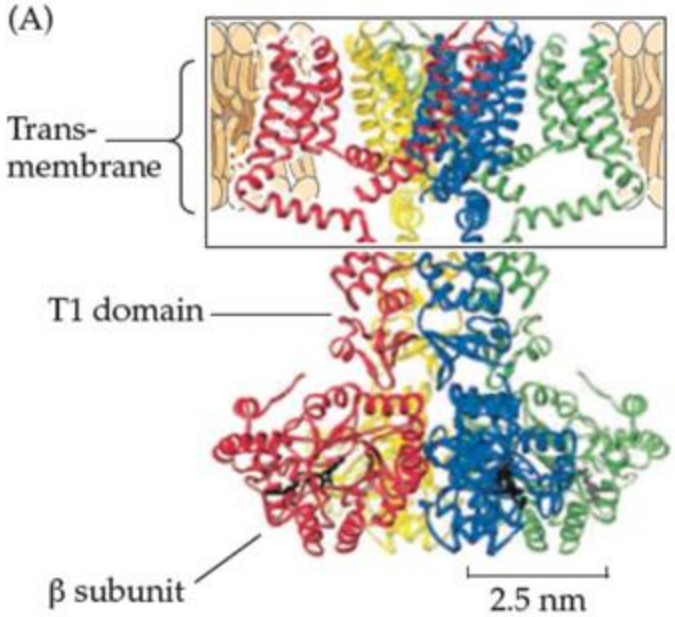
Myelin and saltatory propagation

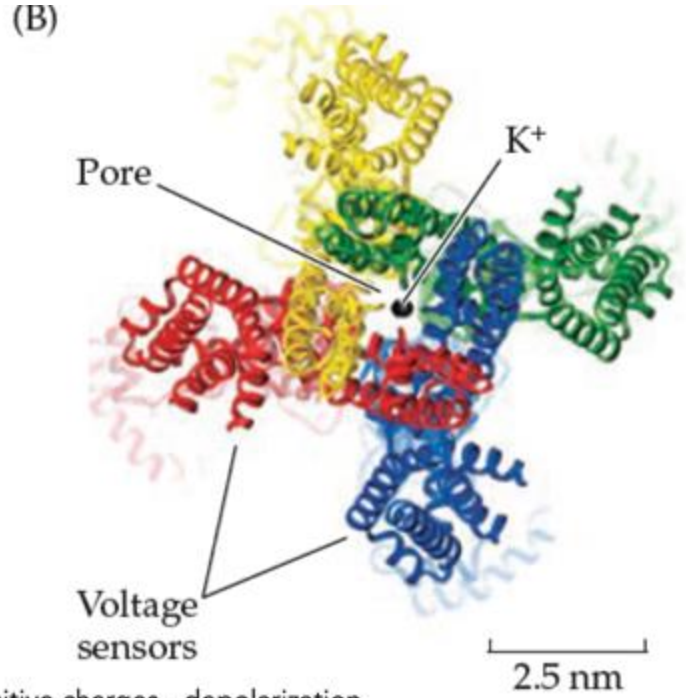


Different types of voltage gated ion channels are present in the nervous system



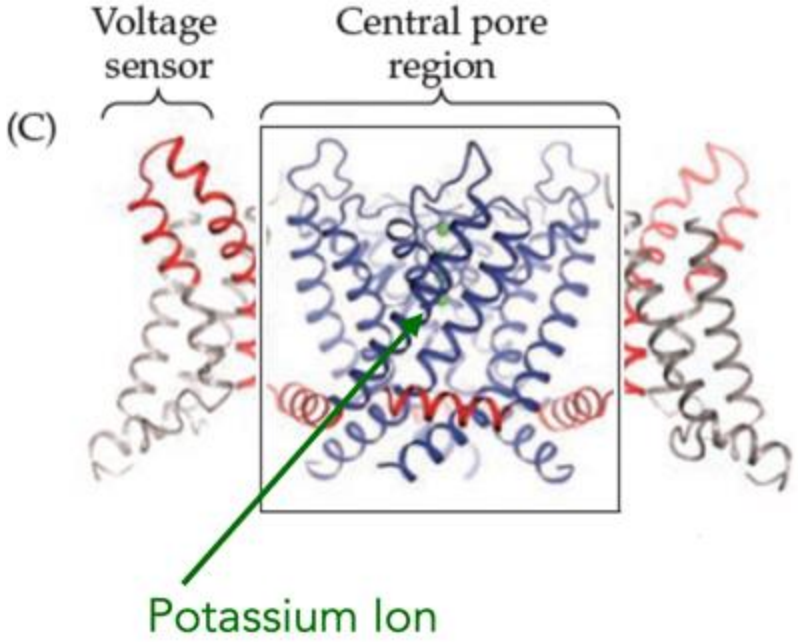
Structure of a voltage gated ion channel

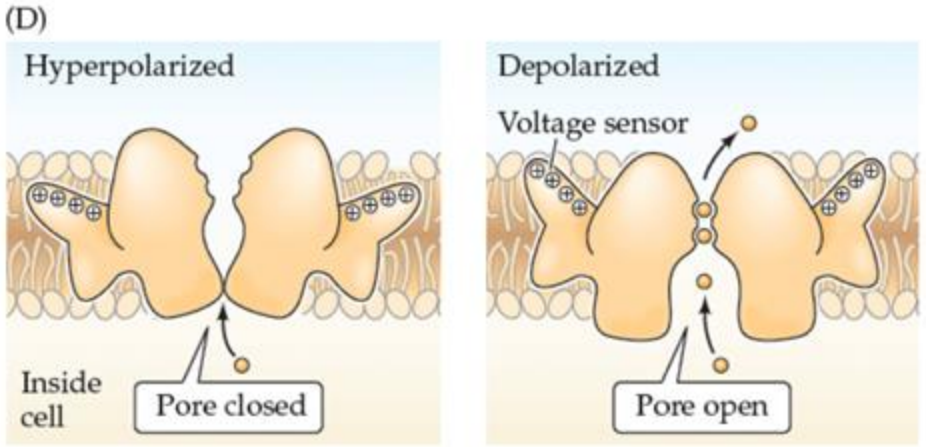




Positive charges - depolarization induces movement and pulls on the pore

How do voltage gated ion channels function?





How do active transporters and ion channels work to move charged molecules inside the cell?

Active transporters move ions into or out of the cell against their concentration gradient using cellular energy. Ion channels are selectively permeable to certain ions and allow ions to cross the membrane in the direction of their concentration gradients.

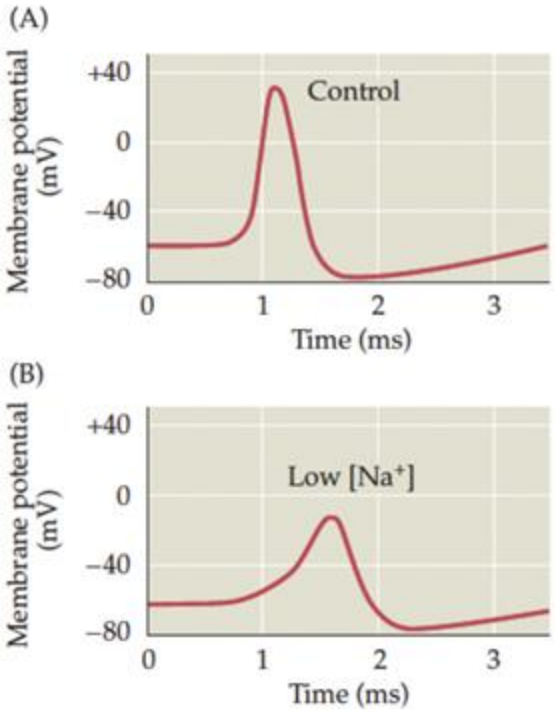
If a cell membrane is only permeable for K+ and has a higher concentration inside of the cell than outside, what would be the direction of the diffusion gradient?

The diffusion gradient would drive K^+ ions out of the cell.

Explanation:

- **Potassium ions naturally move from areas of higher concentration to areas of lower concentration to equalize their distribution. Since there is more K^+ inside the cell, the diffusion gradient pushes K^+ ions outward.**

What happens to the action potential when extracellular Na is removed?



Membrane potential (+58mV) is most similar to Na+ potential. This led Hodgkin and Katz to hypothesize that transient influx of Na+ is what causes the action potential. So they removed extracellular Na+ and indeed saw that this reduces both frequency of firing and amplitude of action potentials.

Does removing extracellular Na+ change the resting membrane potential and what does this imply?

It does not, as seen in experiments of Hodkin and Katz. This implies that the membrane is only slightly permeable to Na+ in resting state, but very permeable during the generation of action potentials.

When the K+ ions start leaving the cell, what pushes them back inward and prevents leakage until a proper chemical equilibrium?

The K+ ions will go down the concentration gradient. But they won't completely equalize in concentrations - so something is preventing complete chemical equilibrium - which is the electrical repellence of like charges. This is what we call an electrochemical equilibrium - balance between the push to go down the concentration gradient, and the repelling force that pushes the ions back.

What does the Nernst equation predict?

It predicts when an electrochemical equilibrium will be reached for any given ion, not taking into account the complexity of specific permeabilities.

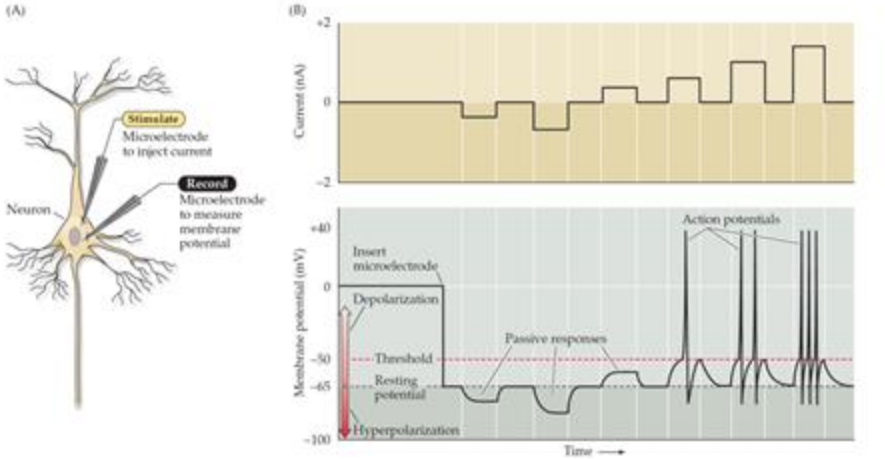
When the K+ ions leave the inside of the cell, why does the inside of the cell become more negatively charged?

Because K+ is inside the cell bound to ANIONS (negatively charged ions), so when K+ leaves the cell, it leaves more negativity behind. The channels are only permeable to K+, not its related anions.

A current that depolarizes the membrane can trigger an action potential. Will a stronger current provide a higher amplitude action potential?

No, it will provide multiple electrical spikes, which means that the stimulus strength is encoded in the spike frequency, not it's amplitude, which remains constant.

How will the cell membrane potential respond if a hyperpolarizing current is provided to the cell?



The membrane potential will dip, but very passively, only to the degree of the provided current. Magic happens when you provide depolarizing current to a certain threshold - triggering large impulses that propagate across even very long axons

If the intracellular concentration of K+ is 155mM and the extracellular concentration of K+ is 4mM, what would be the Nernst potential for this membrane at 37 degrees?

$$E_X = \frac{RT}{zF} ln(\frac{[]_{out}}{[]_{in}})$$

Ratio of K outside/K inside = 4/155 = 0.0258

E(K)= 61.5/+1 log10(0.0258)
= -97mV.

Simplified equation for 37 degrees:

$$E_X = \frac{61.5}{z} log_{10}(\frac{[]_{out}}{[]_{in}})$$

According to the Goldmann equation, which ions are crucial to determine the membrane potential?

The Goldmann equation is essentially Nernst equation that also takes into account permeabilities of different ions.

$$V_m = 58 \log \frac{P_K[K]_{out} + P_{Na}[Na]_{out} + P_{Cl}[Cl]_{in}}{P_K[K]_{in} + P_{Na}[Na]_{in} + P_{Cl}[Cl]_{out}}$$

Note that for Cl in and out are flipped in the equation. Why?

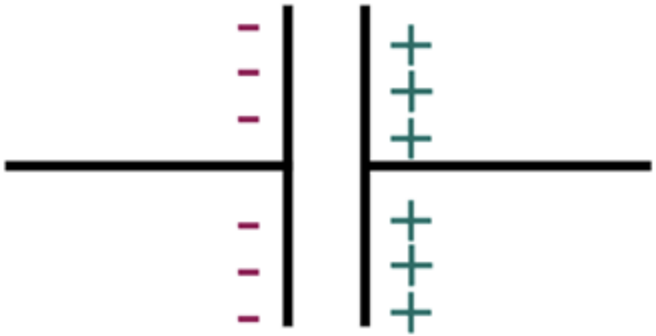
Because Cl is negatively charged, unlike the other two ions.

In generation of action potentials, which channels become transiently permeable and which ion enters the cell?

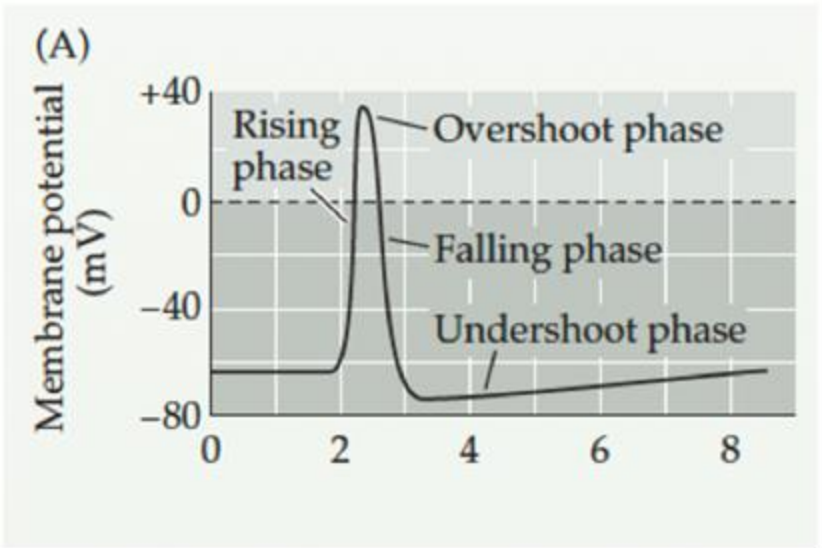
Na+ channels become transiently open, and Na+ (normally kept outside the cell) rushes inside and depolarizes the membrane.

In these ion exchanges, the cellular membrane plays the role of a ?

Capacitor - both inside and outside of the membrane are conductive, and the middle acts as an insulator due to the lipid composition.



List the steps that generate an action potential and the ionic conductance involved in the step.



Depolarization of membrane potential

Membrane potential reaching threshold

Influx of Na+ , Na+ channels open (Rising phase & overshoot phase)

Inactivation of Na+ channels (Falling Phase)

K+ efflux channels open (Falling phase)

K+ permeability is greater than resting membrane potential (Undershoot)

What is graded potential, and how is it different from action potentials?

How can action potentials travel long distances?

Action potential has a threshold and is generated by voltage gated ion channels. Graded potentials are generated by ligand gated ion channels. Action potential can travel long distances and would not lose its strength during transmission. Graded potential loses strength and can travel shorter distances. Graded potentials are additive but action potentials are not. Action potentials travel long distances by saltatory propagation and myelin sheath.

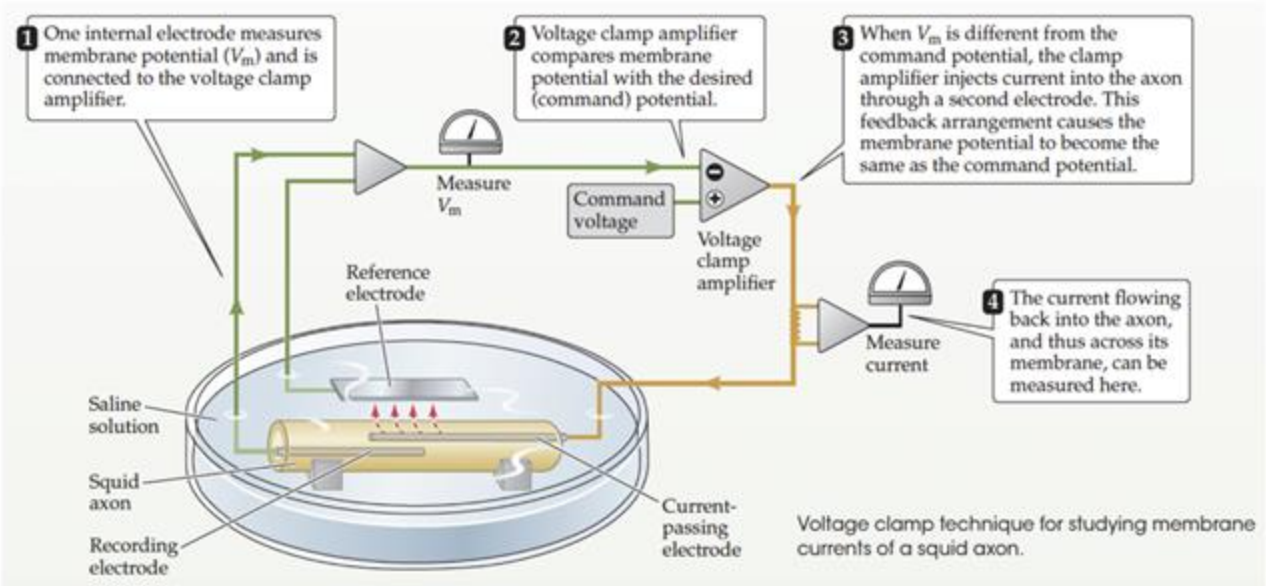
What is the difference between intracellular and extracellular recordings?

Intracellular recordings refer to recordings done from inside of the cell and extracellular recordings are recorded from the extracellular space.

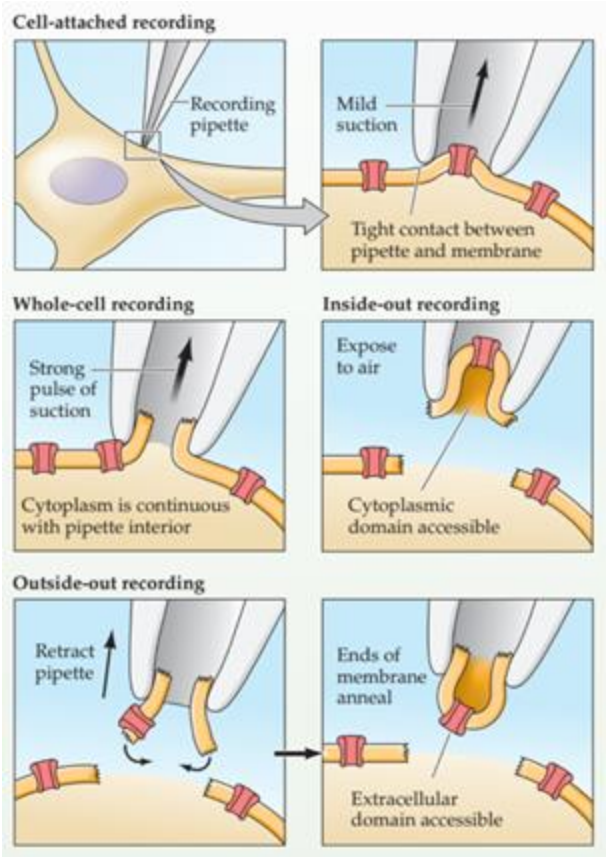
What are the voltage clamp and current clamp? What is the main difference between the two methods?

Voltage clamp controls the membrane potential at any level desired by the experimenter. It can indicate how membrane potential influences ion current flow across the membrane. In current clamp the current is controlled and the change in membrane potential is measured.

Explain the main principle for how the voltage clamp work. Why was the giant squid a useful model organism for the pioneering studies with this method?



What is a patch clamp, and what are the different ways of recording?



Technique capable of measuring the currents flowing through single channels. There are four configurations in patch clamp technique.

Cell attached recording- measuring all current flow when a single ion channel opens, allows experimental control of the membrane potential to characterize the voltage dependence of membrane currents

Whole cell recording- interior of the pipette becomes continuous with cell cytoplasm, measurement of currents from entire cell

Inside-out recording- makes it possible to change the medium to which the intracellular surface of the membrane is exposed, particularly for studying influence of intracellular molecules on ion channel function

Outside out recording- membrane patch produced has its extracellular surface exposed, optimal for studying how channel activity is influenced by extracellular chemical signals

What are the different types of gated channels?

Voltage gated- the opening is influenced by changes in the membrane potential

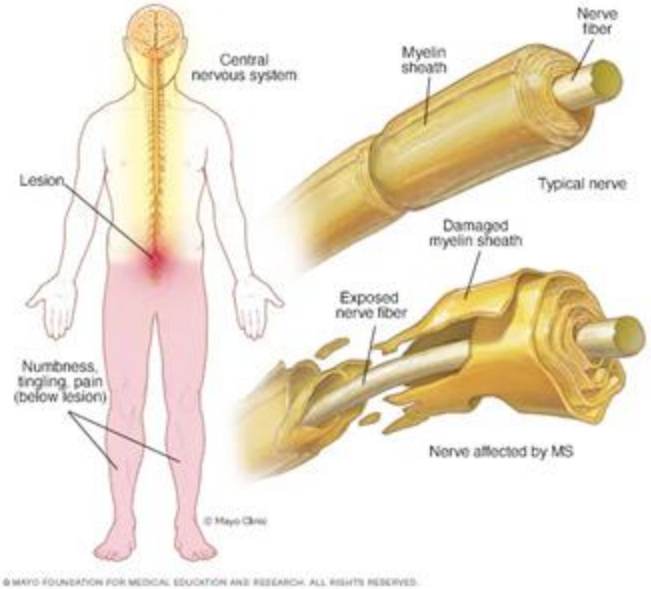
Ligand gated- respond to chemical signals (chemical messenger)

Thermosensitive – respond to temperature ranges, heat

Mechanosensitive- respond to mechanical distortion of the plasma membrane

Multiple sclerosis - causes and consequences

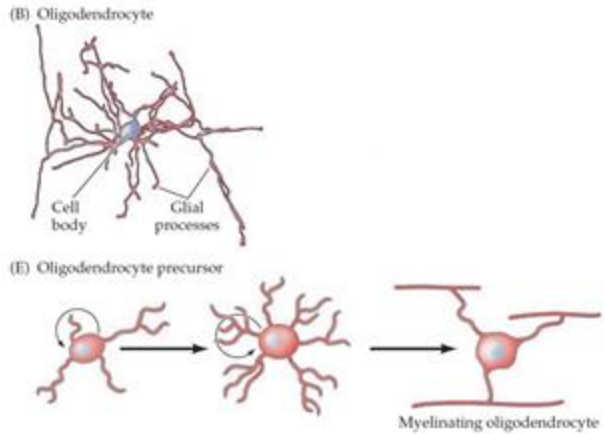
An autoimmune disease - the immune system is attacking the myelin sheath.



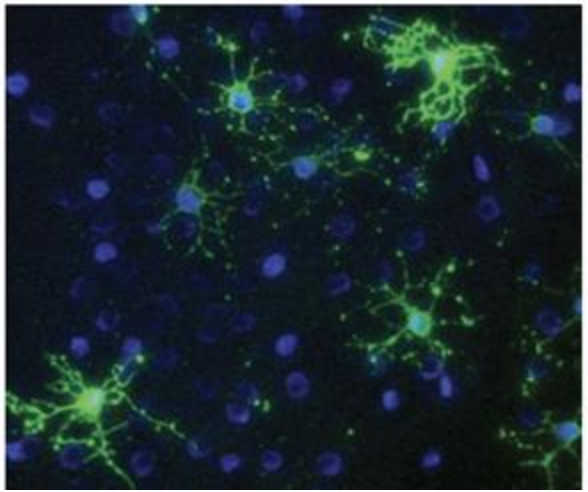
Loss of saltatory (fast, jumping) propagation of action potentials

Conducting signals now requires a lot of energy, making these neurons further vulnerable to stress and metabolic changes

Which cells produce the myelin sheath?



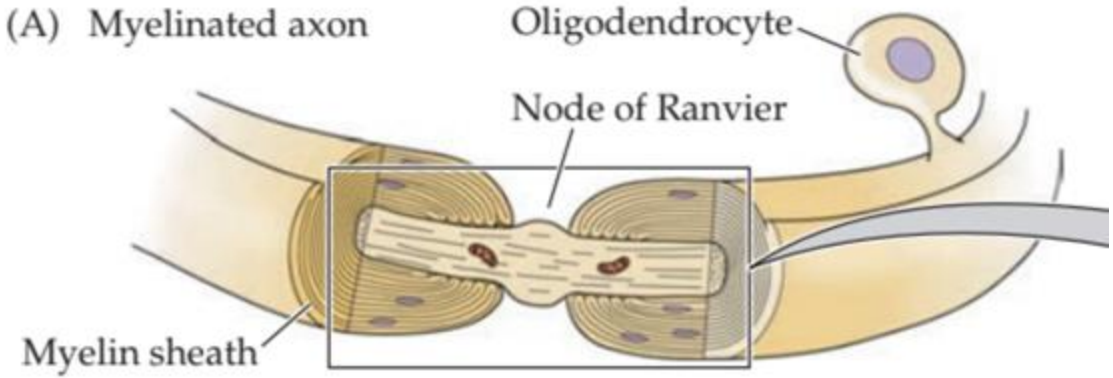
Oligodendrocytes, a type of glial cells in the CNS. A single oligodendrocyte can cover up to 40 axons.



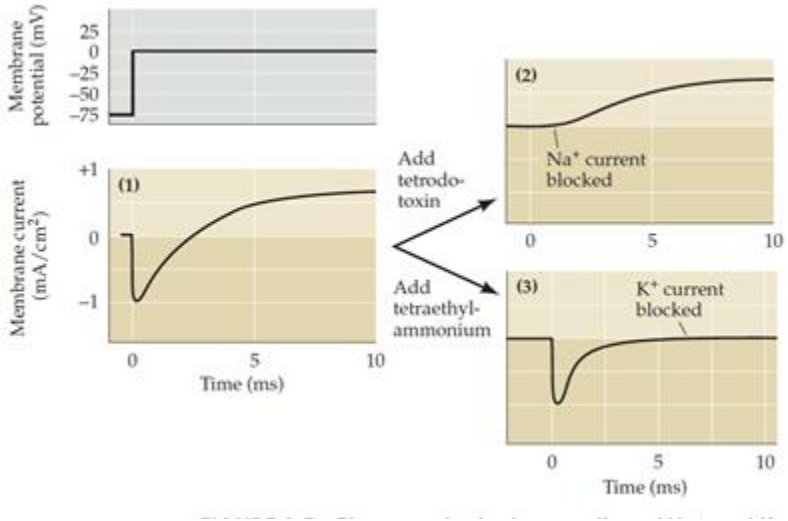
Here, oligodendrocytes are labeled with a specific antibody that targets their specific proteins, seen in green (from Purves, page 8, Fig. 1.5g)

What are the nodes of Ranvier, and what is their purpose?

Nodes of Ranvier is a part of the axon where action potentials are generated (there is a gap in the myelin wrapping).



What would happen to action potential propagation if voltage-gated sodium channels were blocked (e.g., by a toxin like tetrodotoxin)? How would this affect the nervous system function?



(1) shows the current that flows when the membrane potential of a squid axon is depolarized to 0 mV in control conditions. (2) Treatment with tetrodotoxin causes the early Na+ current to disappear but spares the late K+ current. (3) Addition of tetraethylammonium blocks the K+ current without affecting the Na+ current. (After Moore et al., 1967 and Armstrong and Binstock, 1965.)

This prevents the nervous system from carrying messages and thus muscles from contracting in response to nervous stimulation.
Some of the symptoms, if ingested: hypersalivation, sweating, headache, weakness, lethargy, incoordination, tremor, paralysis, bluish skin, loss of voice, difficulty swallowing, and seizures.

In epilepsy, neurons exhibit hyperexcitability and hypersynchrony, leading to excessive action potential firing. What changes in ion channel function or synaptic activity might explain this, and how could these changes disrupt the balance between excitation and inhibition in the brain?

Mutations in K+, Na+, Ca2+ channel genes can lead to epilepsy. For example mutations in Na+ channel genes (SCNA1, SCNA2) that can reduce the Na+ channel function, leading to impairment in the ability of inhibitory interneurons to fire action potentials. This can alter the balance between excitation and inhibition. Also slowing of Na+ channel inactivation can explain hyperexcitability.
Reduction of K+ current flow through mutated channels (mutations in KCNQ2, KCNQ3) probably explains neuronal hyperexcitability.

Discussion question: In neuroscience experiments, we often activate or silence particular groups of neurons to try to understand the consequences. Let's work out how this could be done genetically in simple organisms. (connecting the previous lectures, our knowledge of DNA regulatory regions, and what we now know about action potentials and how they affect activity).

First - we choose the neurons we want to manipulate - we could select them based on regulatory regions in DNA (like promoters and enhancers that are specific to them).

Then we choose a tool to, eg. activate them. Example would be Channelrodopsin2, which will activate neurons (depolarize them) when exposed to blue light.

Now we somehow just need to get this thing into the brain.

For this we chop up the sequence of the channelrodopsin2, put it in some kind of carrier (in this case we call it a vector), and find a suitable way this will integrate where we want. Sounds fancy, but is done very routinely in the lab using techniques such as molecular cloning cloning.

End result: you now can have a channel that will depolarize (Activate) specific neurons when exposed to blue light.

If these are neurons involved in aggression, you can shine blue light on the animal and make it aggressive instantly.

This video shows predatory behavior induced in the mouse exactly via the described method:

- Aggression neurons are targeted
- A light sensitive activation genetic tool is expressed in these neurons
- When light is shining - the mouse is in attack mode :)

https://www.youtube.com/watch?v=42bLSZnVf0g&ab_channel=NewScientist