Behavioral Neuroscience A
4: Signal Transmission

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https://youtu.be/LyMPlT2JRp4

Lecture Video at above link.

Today’s aim

How is information communicated between neural cells?

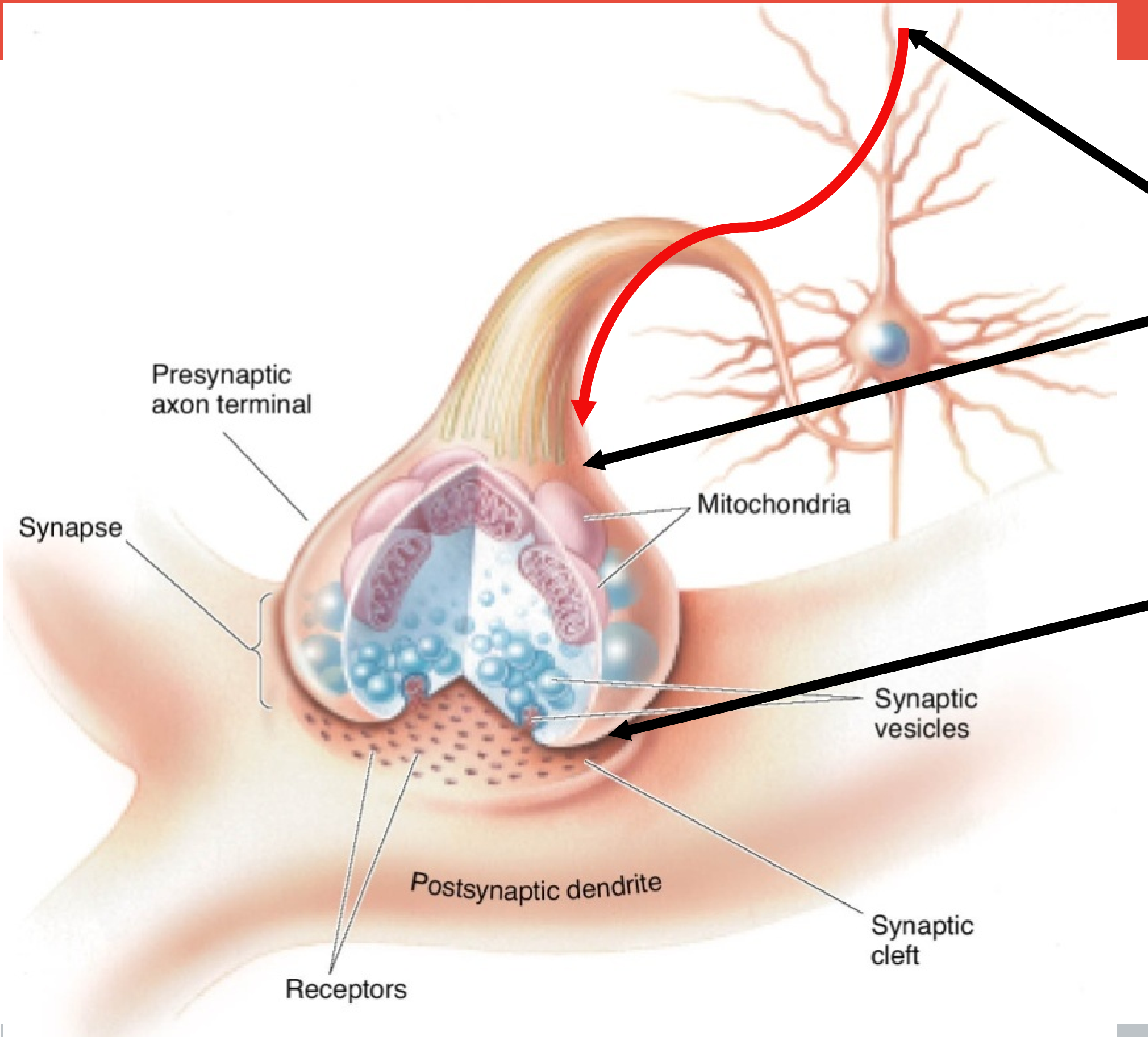
→ Learn how signals are conducted electrically

Two main concepts today:

1) Resting membrane potential

2) Action potential

Overview of Today’s Contents



Electrical signal transmission along neurite (today)

Chemical signal transmission across synapse (next week)

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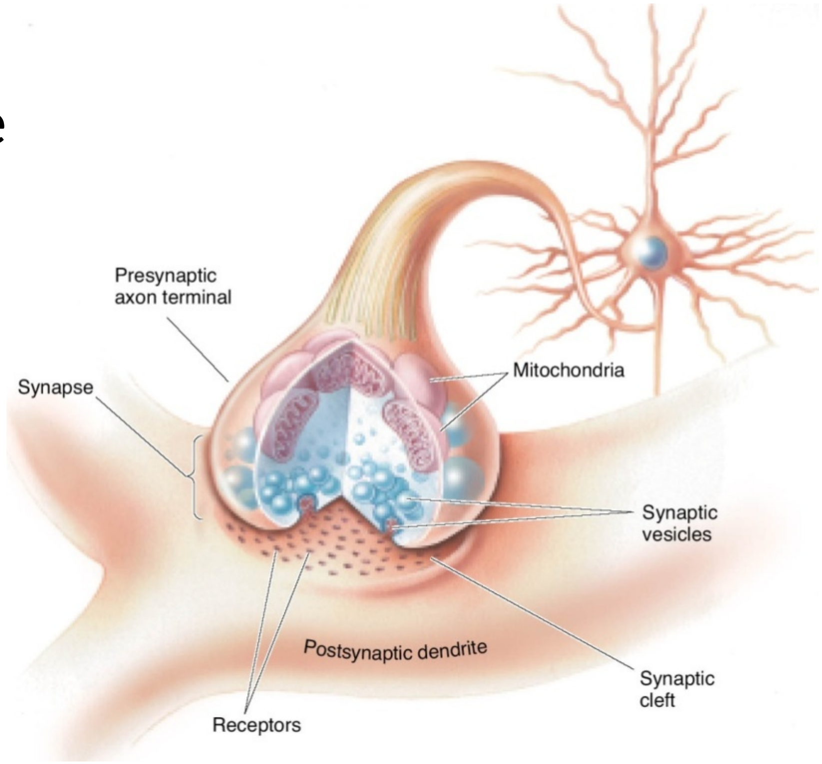
Today's contents

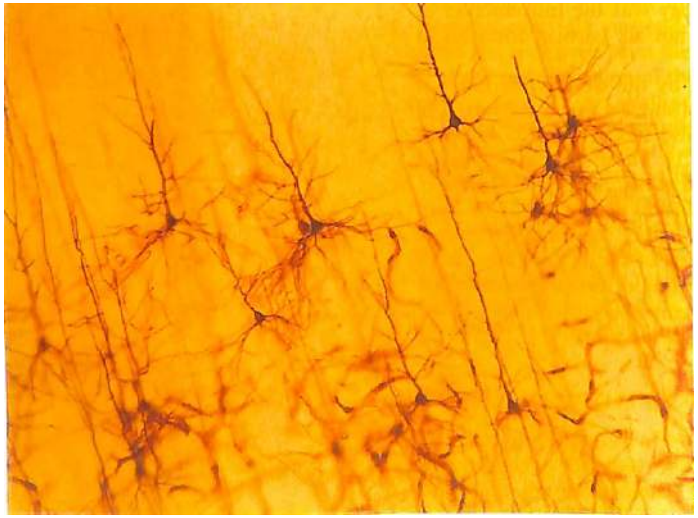
<u>Neural information processing</u>

1) The resting membrane potential
    - The cell membrane
    - Diffusion and electrical force
    - The equilibrium potential
    - Different ion concentrations inside and outside the cell

2) The action potential
    - Time-course of membrane potential change
    - Voltage gated channels
    - Channel toxins
    - Conduction
    - Optogenetics



Neurons ↔ Phone wire



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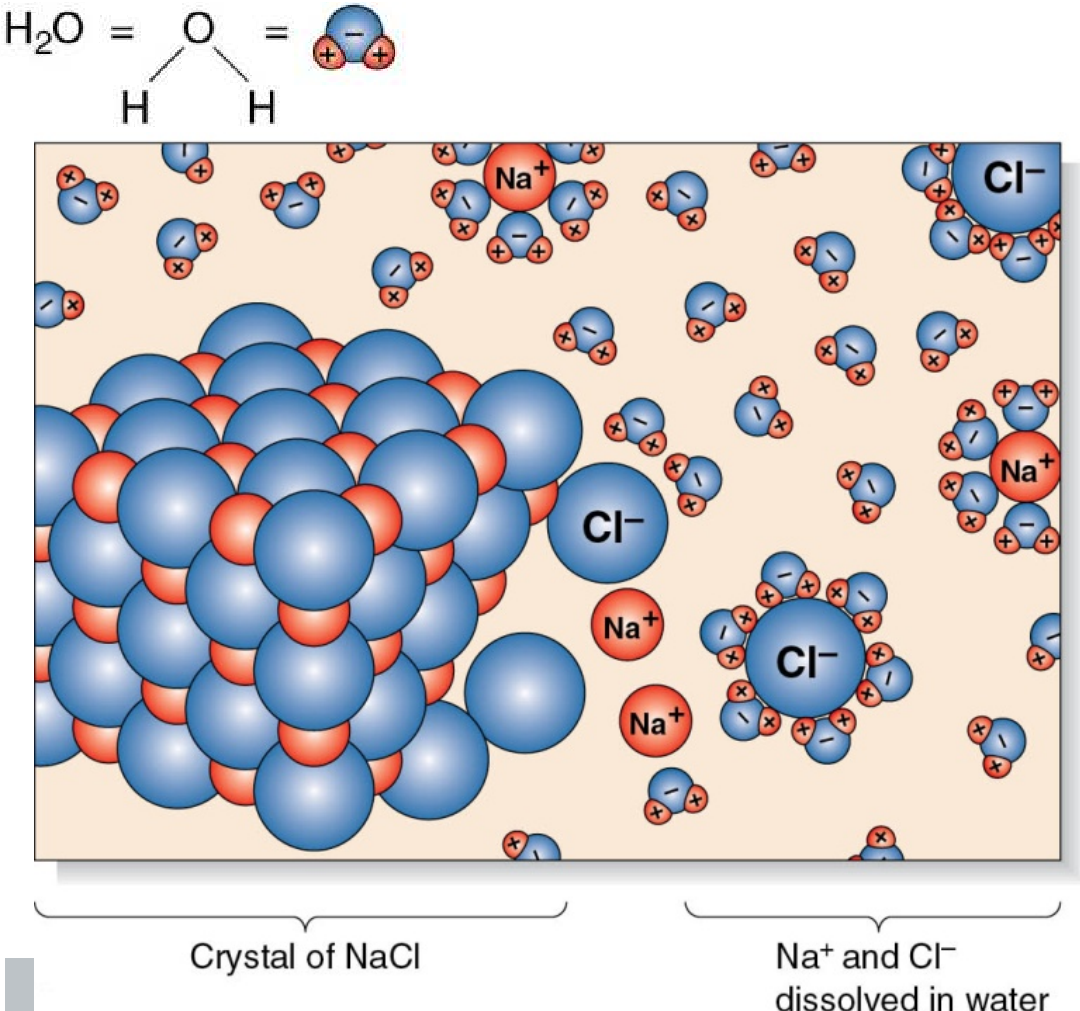
Neurons		Phone wire
Ions in intra/extra-cellular cell “soup”	<u>Medium</u>	electrons in copper line
slow (e.g., 10 m/s)	<u>Speed</u>	fast (c/2 ≈ 150,000,000 m/s)
leaky	<u>Quality</u>	well insulated

Part 1: (Resting) Membrane Potential

Inside and outside neurons

Main component of intracellular and extracellular fluid is water.
Salts like NaCl are dissolved in it due to the electrical polarity of H_2O.



Ions important for neural function:

Na^+ : sodium (natrium)

Cl^- : chloride

K^+ : potassium (kalium)

Ca^{2+}: calcium

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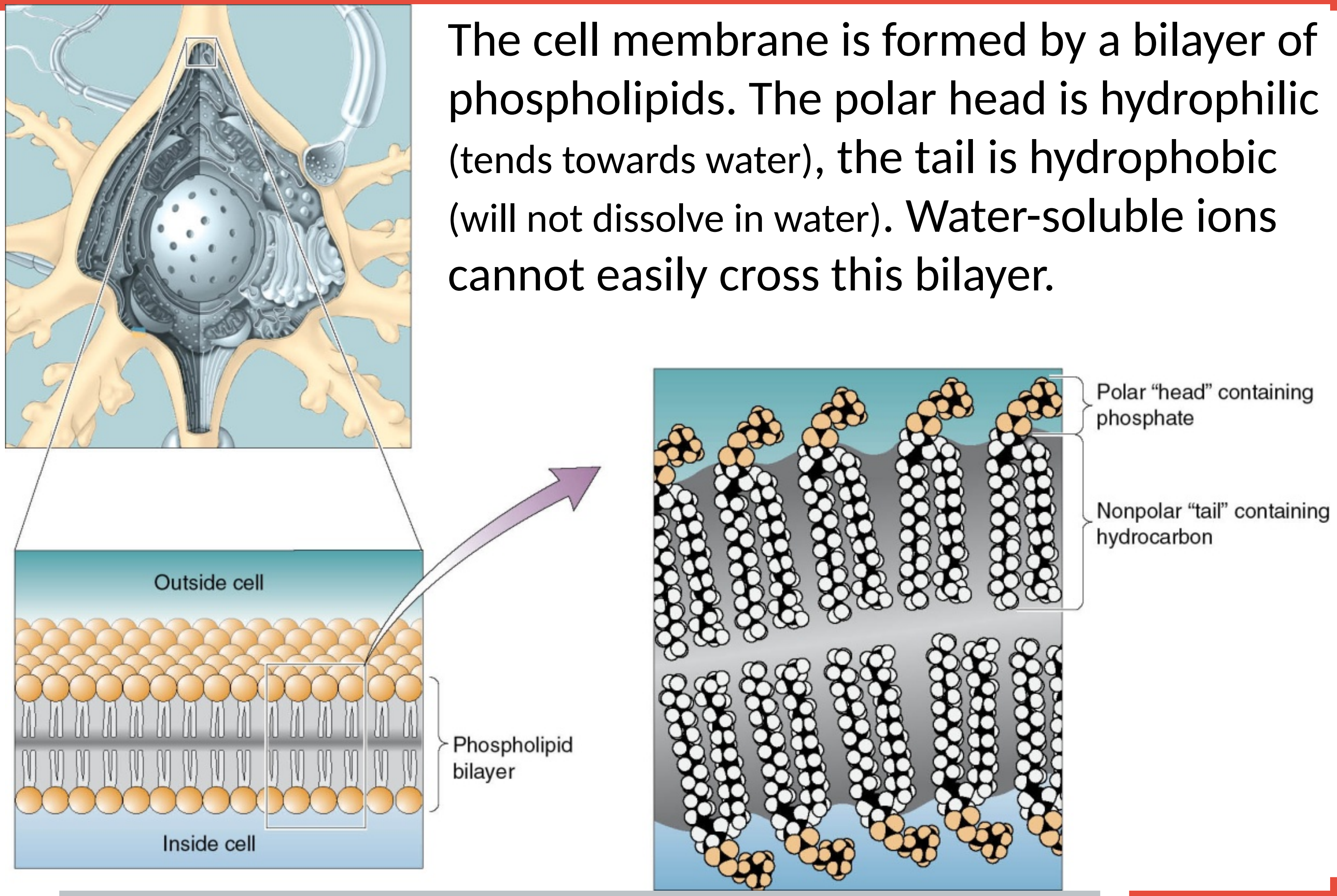
Cell membrane (skin)

The cell membrane is formed by a bilayer of phospholipids. The polar head is hydrophilic (tends towards water), the tail is hydrophobic (will not dissolve in water). Water-soluble ions cannot easily cross this bilayer.



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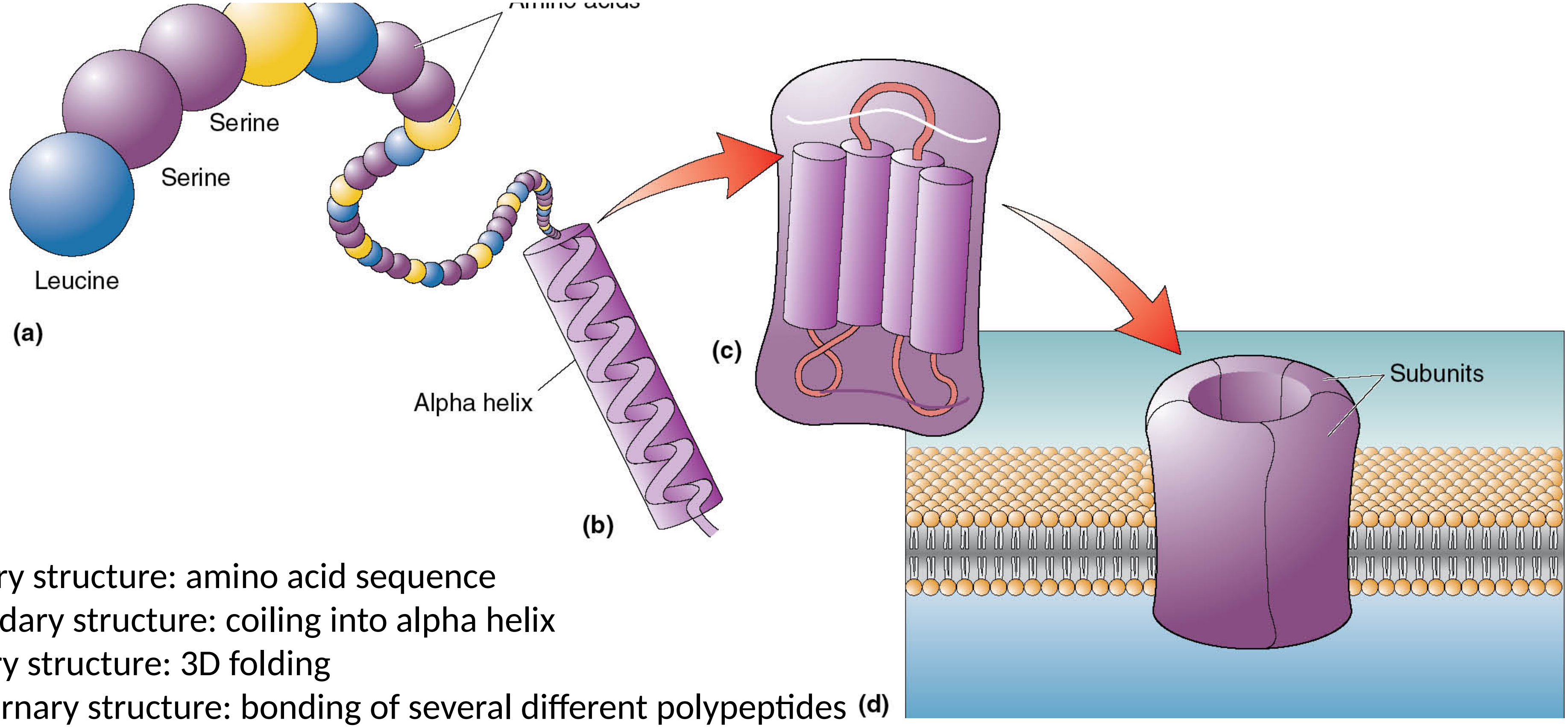
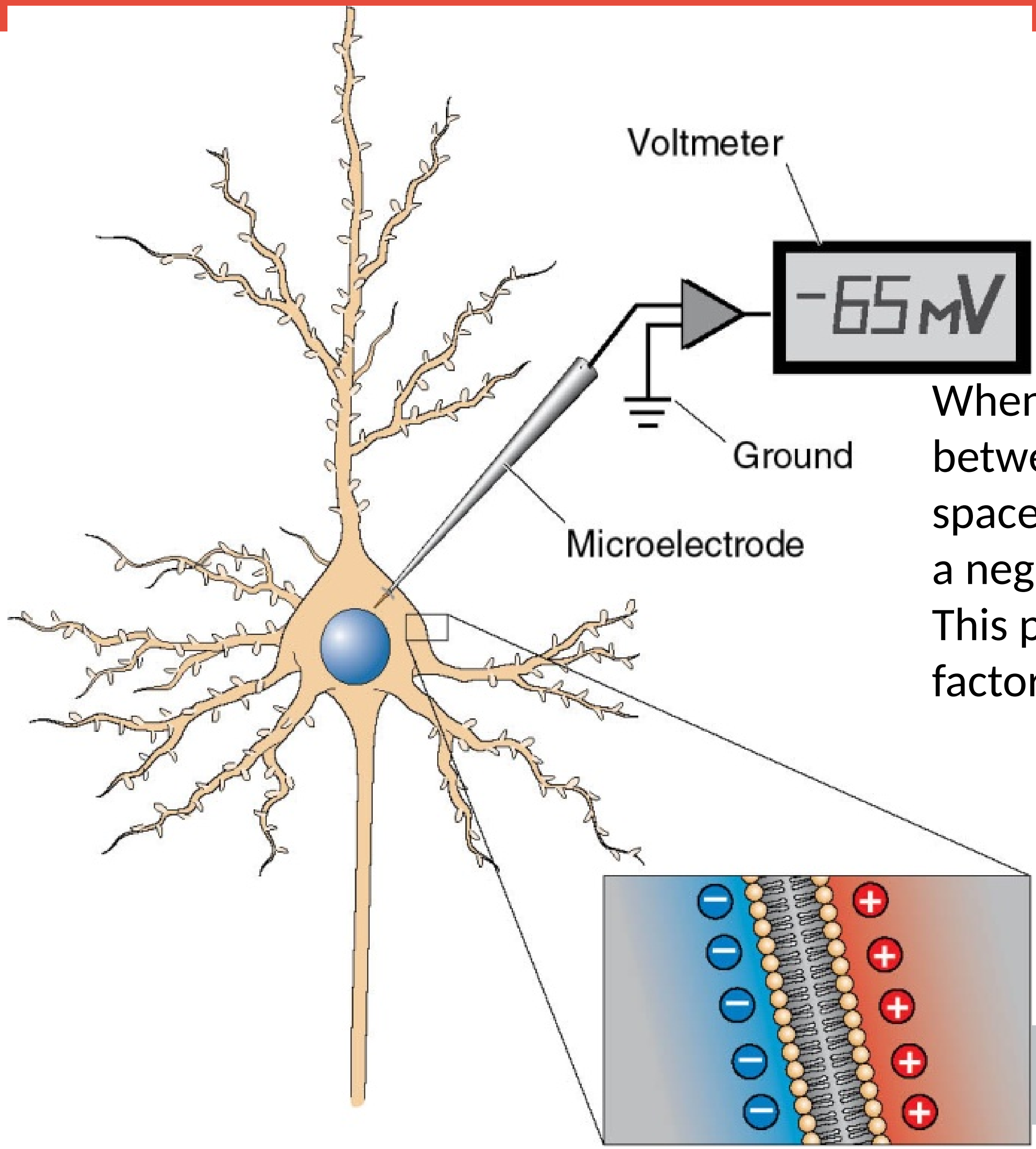
Ion chanels (tunnels through the skin)

Embedded into the cell membrane are membrane proteins (consisting of amino acids). Some of them function as ion channels that let ions pass the cell membrane.



a) Primary structure: amino acid sequence
b) Secondary structure: coiling into alpha helix
c) Tertiary structure: 3D folding
d) Quaternary structure: bonding of several different polypeptides

Membrane Potential (Voltage)



When we measure the voltage between intra- and extracellular space of neurons, we see that there is a negative resting potential (~65 mV). This potential arises because of two factors:

1) Diffusion of ions
2) Electrical force

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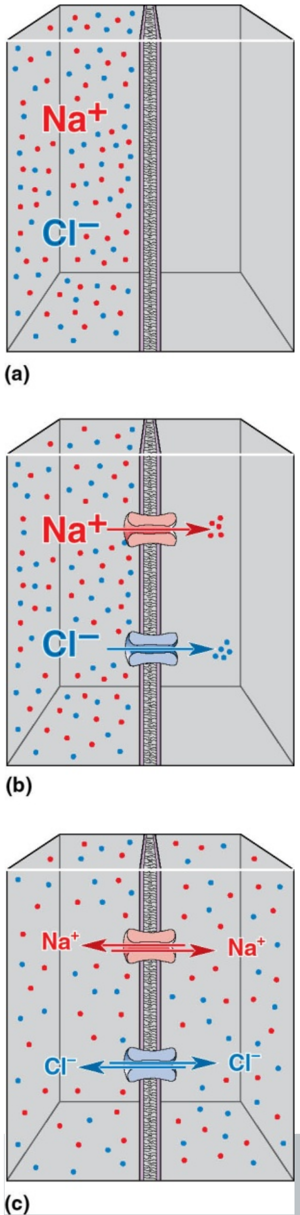
Cause 1: Ion Diffusion



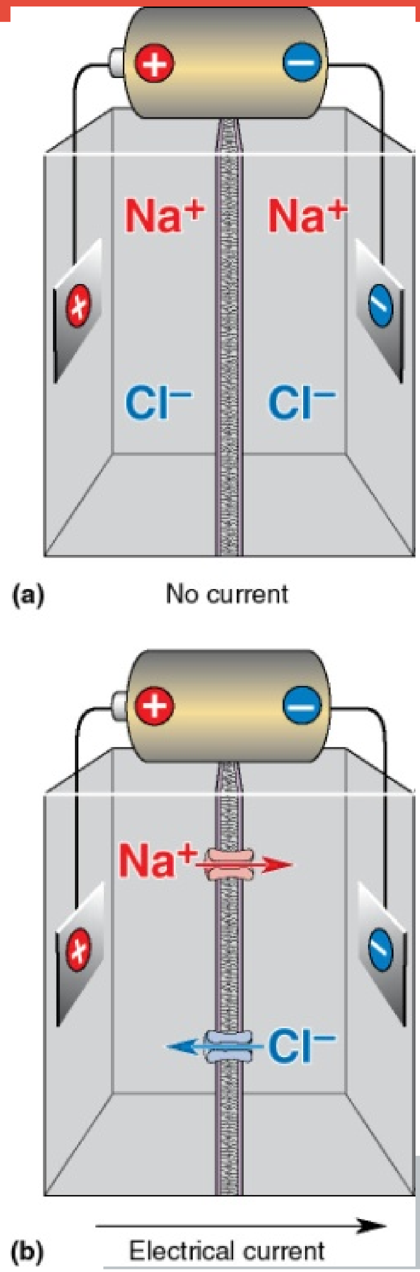
1) **Diffusion** through the membrane

No transmembrane flow of ions is possible when there are no pores/channels in the membrane.

Channels (leakage channels) allow for transmembrane flow -> ions will flow down the concentration gradient.

Ions free to diffuse will compensate the concentration gradient.

Cause 2: Electrical Force



2) Electrical force

Membrane is impermeable-> no ion flow possible -> no electrical current.

If the membrane is permeable, ions will flow towards the pole with opposite charge.

(anions[-] flow to anode [+], cations[+] flow to cathode[-])

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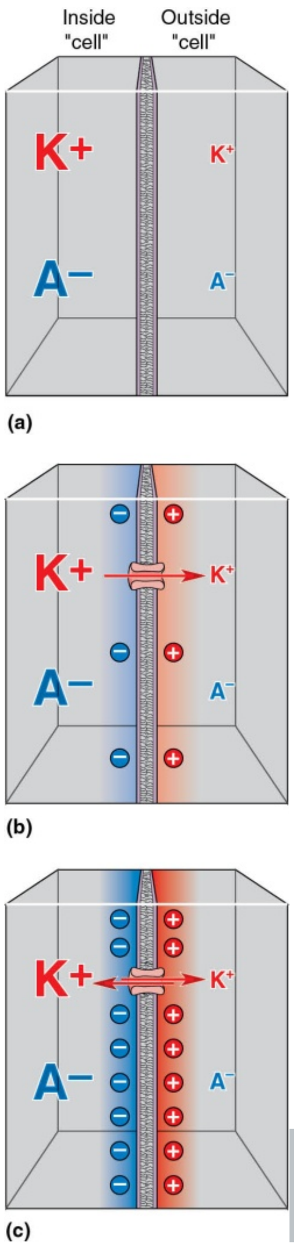
Potassium (K+) ion balance



K^+ and anions A^-

K^+ and anions A^- (mainly amino acids and proteins) have higher concentration inside the cell.

Selective channels (potassium channels, also leakage channels) let K^+ ions pass the membrane, but not A^- (which is left inside the cell).

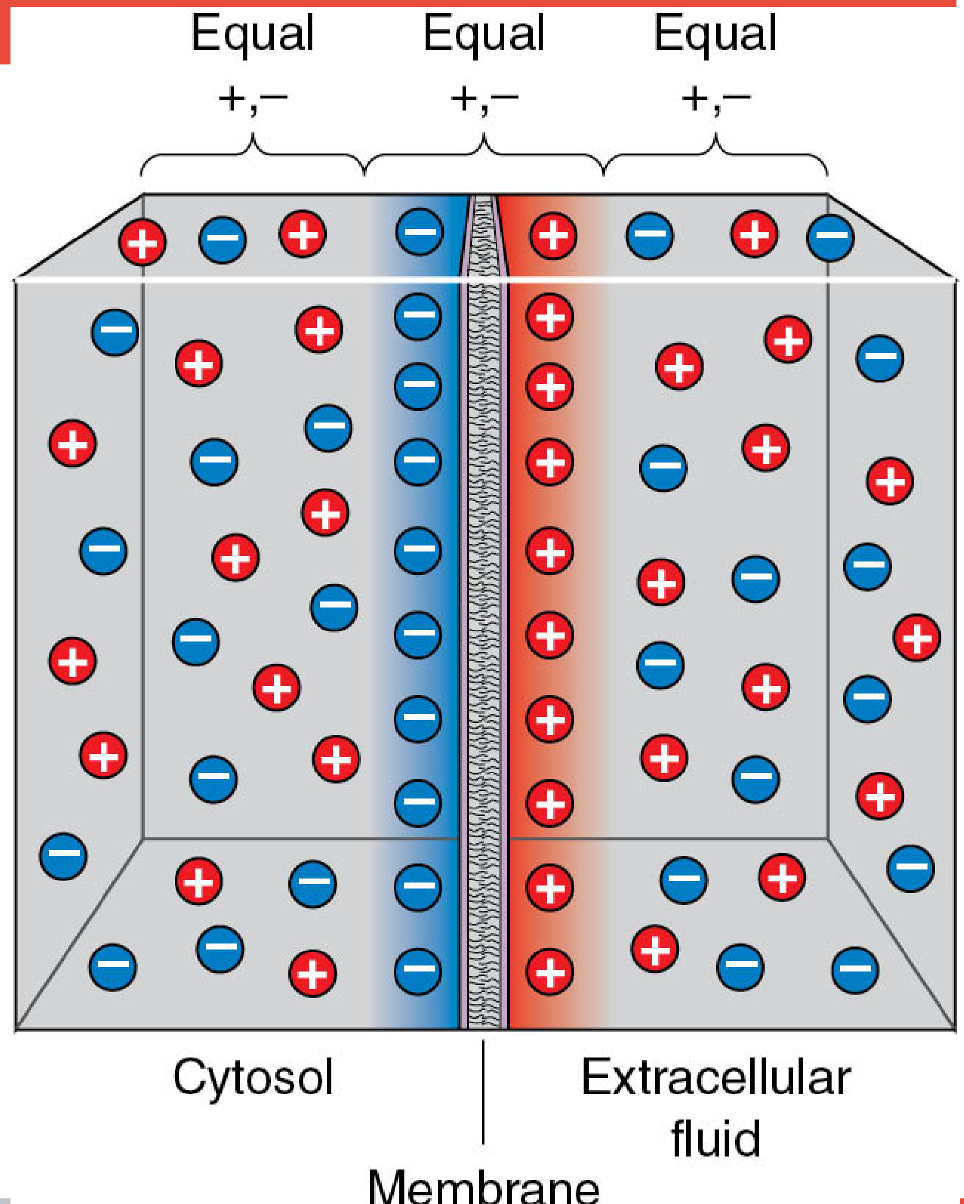
This leads to an equilibrium between diffusion and electric force: diffusion forces the K^+ ions outside, but the increasing electrical negativity draws K^+ ions back inside.

→ equilibrium potential: -80mV

Membrane Potential

The surplus of positive and negative ions attract each other electrically across the membrane.

Most of the intra- and extracellular fluid is electrically neutral.



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Sodium (Na+) ion balance

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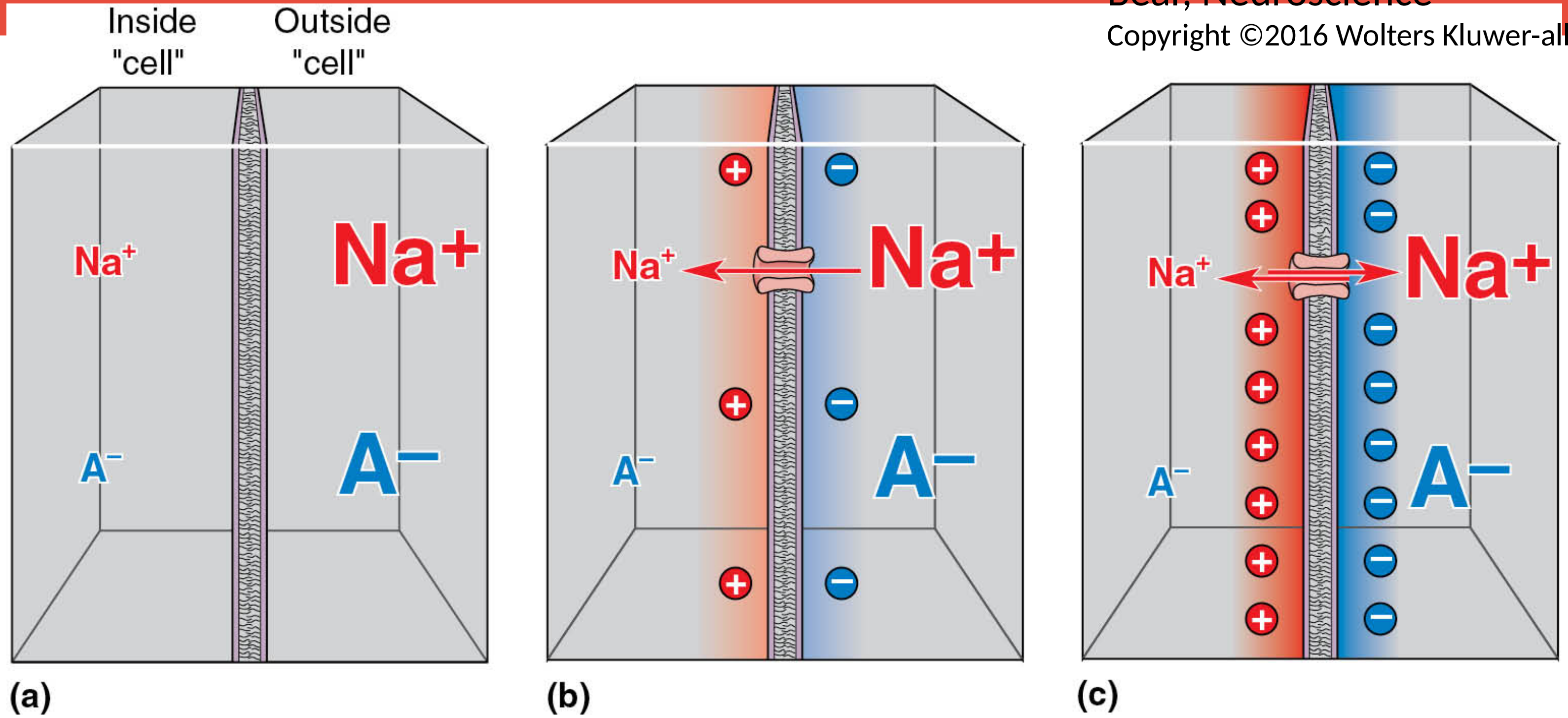


There is also an equilibrium potential for Na^+: +62 mV

because a) Na^+ concentration is higher outside the cell
b) Na^+ channels let Na^+ ions pass (A^- stay outside)
c) equilibrium between diffusion and electrical force

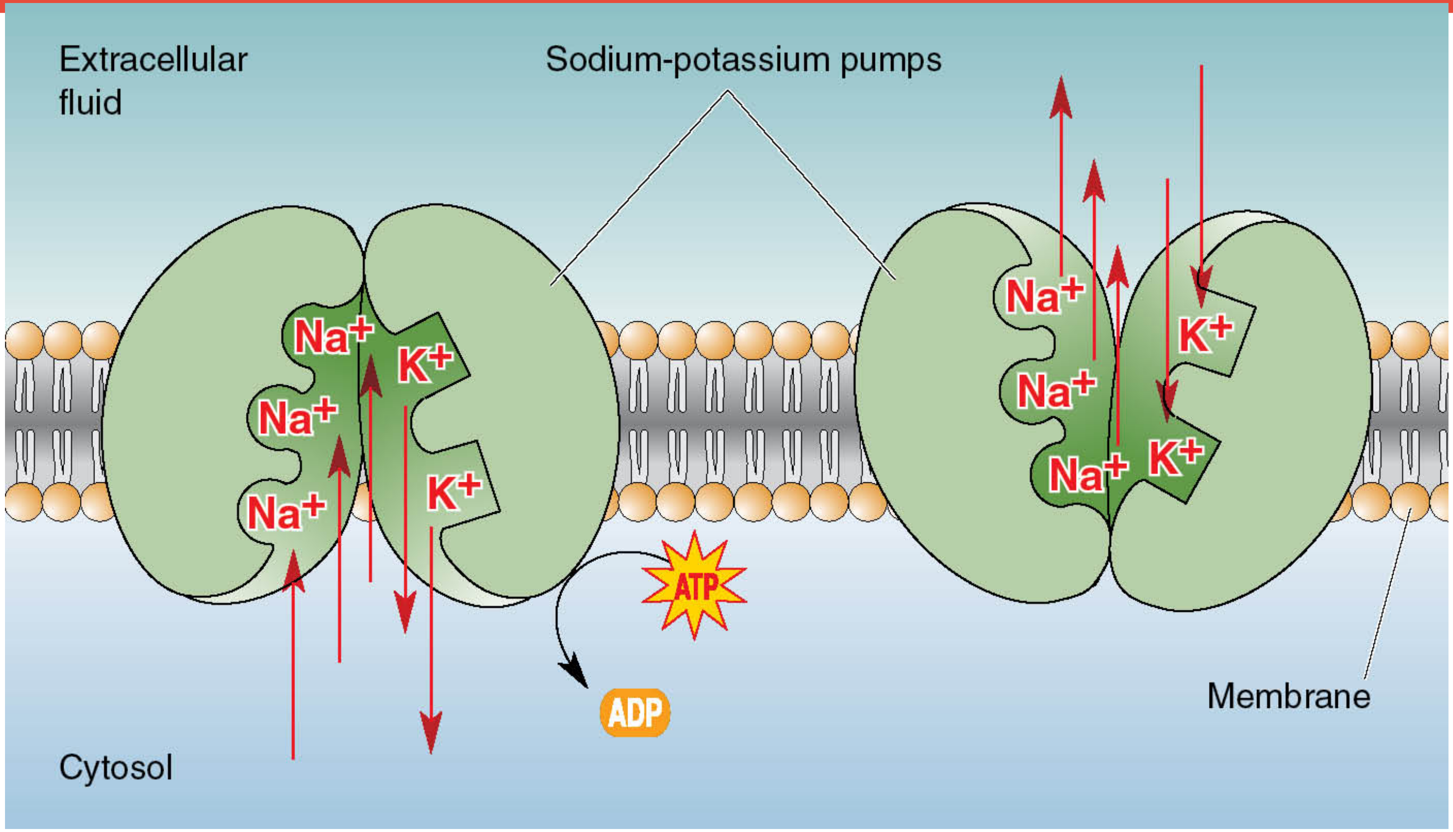
Resting Membrane Potential

Ion	Concentration Outside [mM]	Concentration Inside [mM]	Ratio Out:In	Equilibrium Potential
K^+	5	100	1:20	-80 mV
Na^+	150	15	10:1	+62 mV
Ca^{2+}	2	0.0002	10000:1	+123 mV
Cl^-	150	13	11.5:1	**-65 mV**

mM: millimolar: 6.02×10^{20} molecules / liter
Ca^{2+} is in particular important at the synapse (more next week)

Different ions have different equilibrium potentials.
The resulting resting membrane potential is around -65 mV
(mainly driven by Na^+ and K^+ equilibrium potentials).

Why more Na+ outside and K+ inside? → "ion pump"



The upkeep of concentration gradients requires active transport of ions across the membrane: The sodium-potassium ATPase transports Na^+ out, K^+ in and breaks down ATP (adenosine triphosphate) for energy.

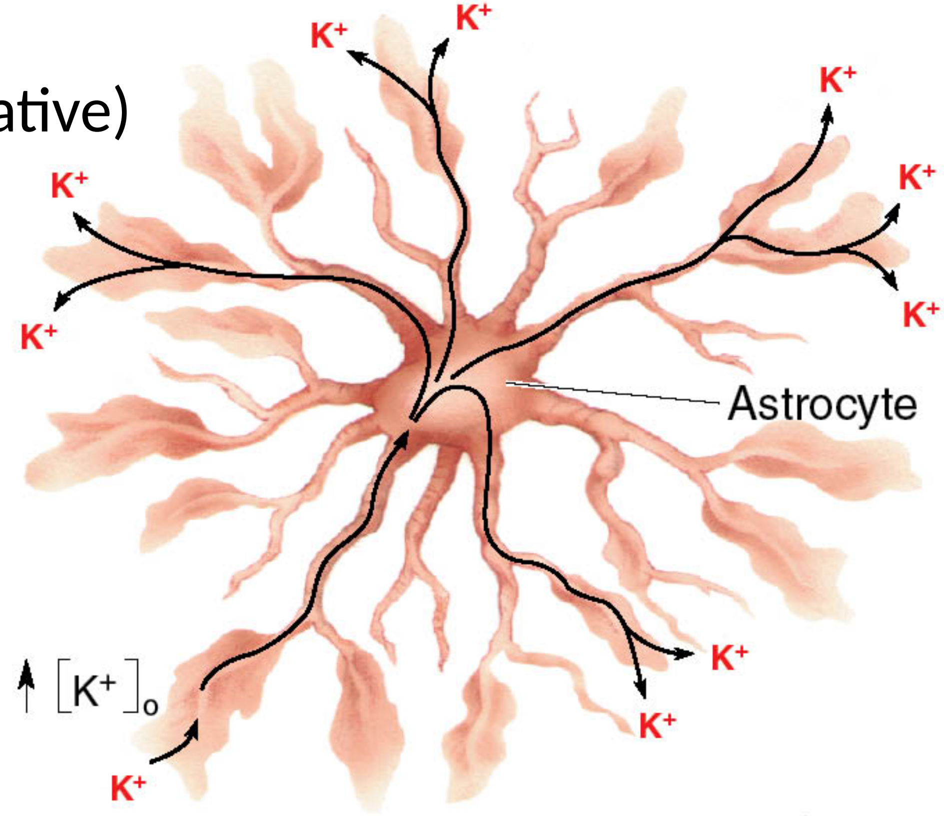
Astrocytes (Glial Cells) do it too…

Astrocytes, a form of glial cells, possess potassium channels.

When extracellular K^+ concentration increases, K^+ ions enter astrocytes through K^+ channels.

This will depolarize (make less negative) the astrocyte's membrane.

This in turn will drive K^+ ions into the cell, dissipate them in the astrocyte and finally drive the K^+ ions out where K^+ concentration is low.



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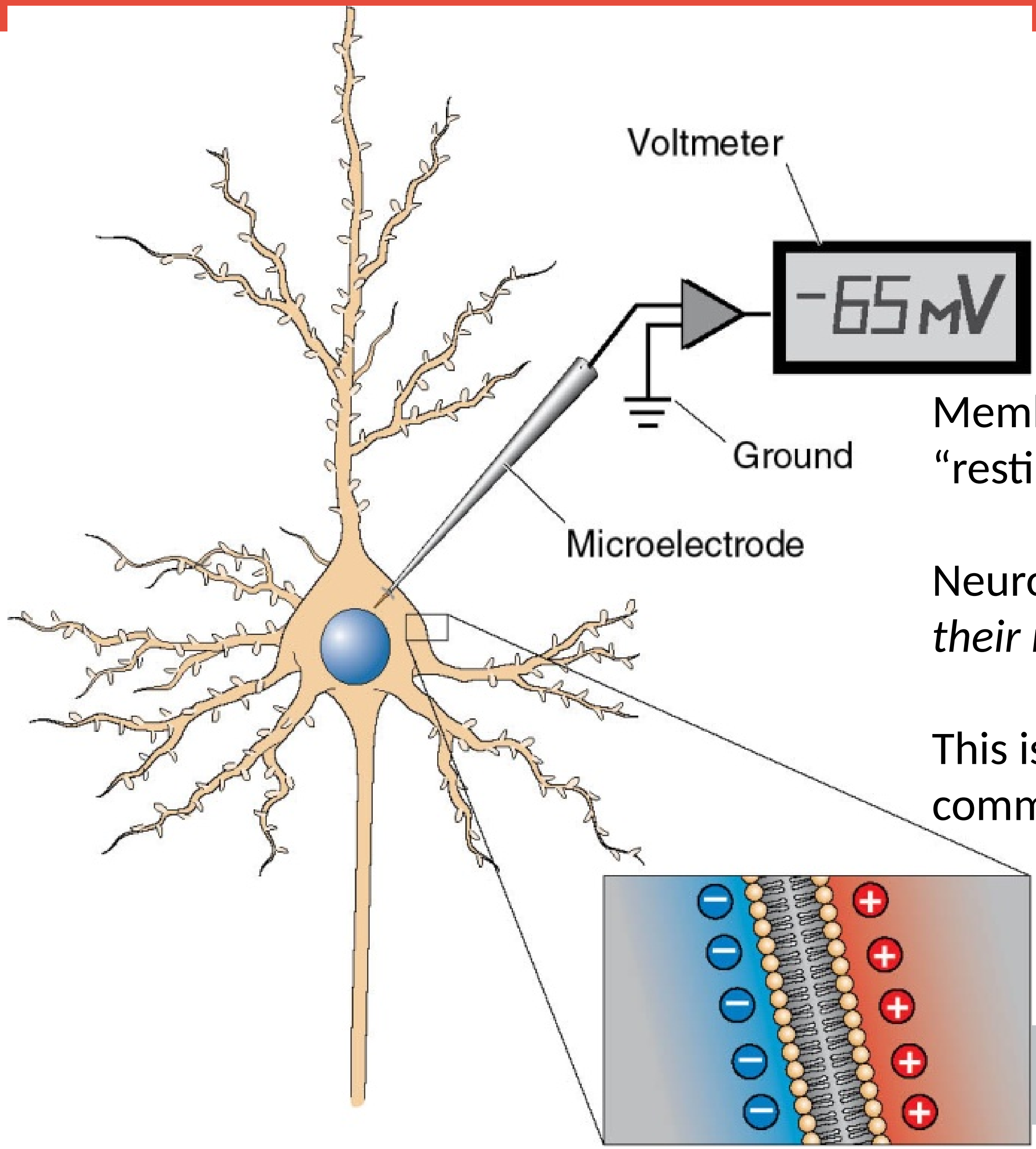
Video (Crayfish and Membrane Potential)

Part 2: Action Potentials

Membrane Potential *Changes*



Membrane potential is not always “resting”.

Neurons communicate by *changing their membrane potential*.

This is the “signal” neurons use to communicate with one another.

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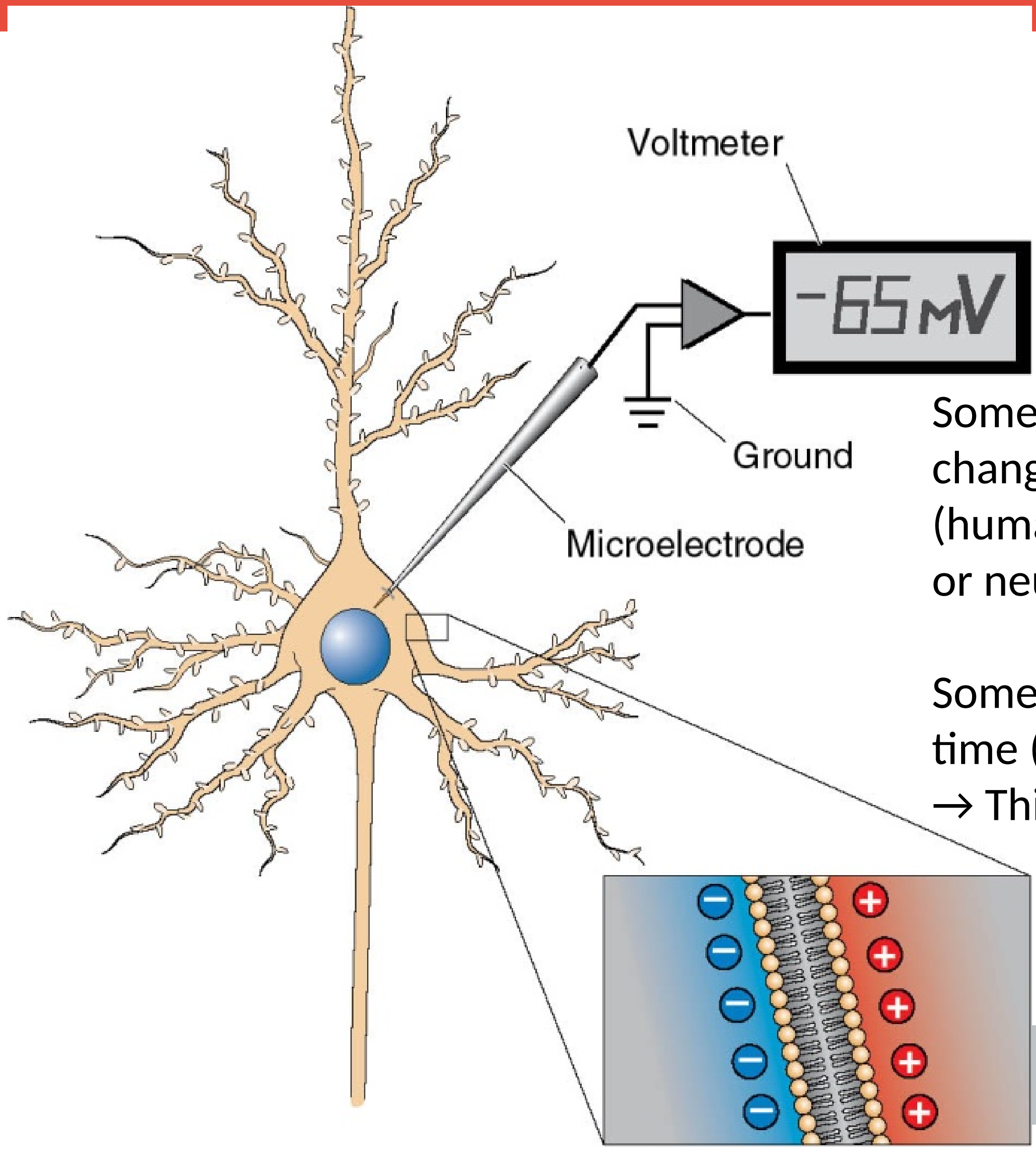
Membrane Potential *Changes*



Sometimes, membrane potential changes just a little bit at a time (human retinal photoreceptor cells, or neural cells in nematodes).

Sometimes it will change a *lot* at a time (like sending a "pulse").
→ This is **action potential**

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“Action” Potential

Information (e.g., sound hits our ear) is transmitted along neurons by changes of the neurons’ membrane potential, so called **action potentials** or **spikes**. The rate of action potentials can carry information (e.g. sound intensity)

Action potentials can be observed with intra- or extracellular recordings

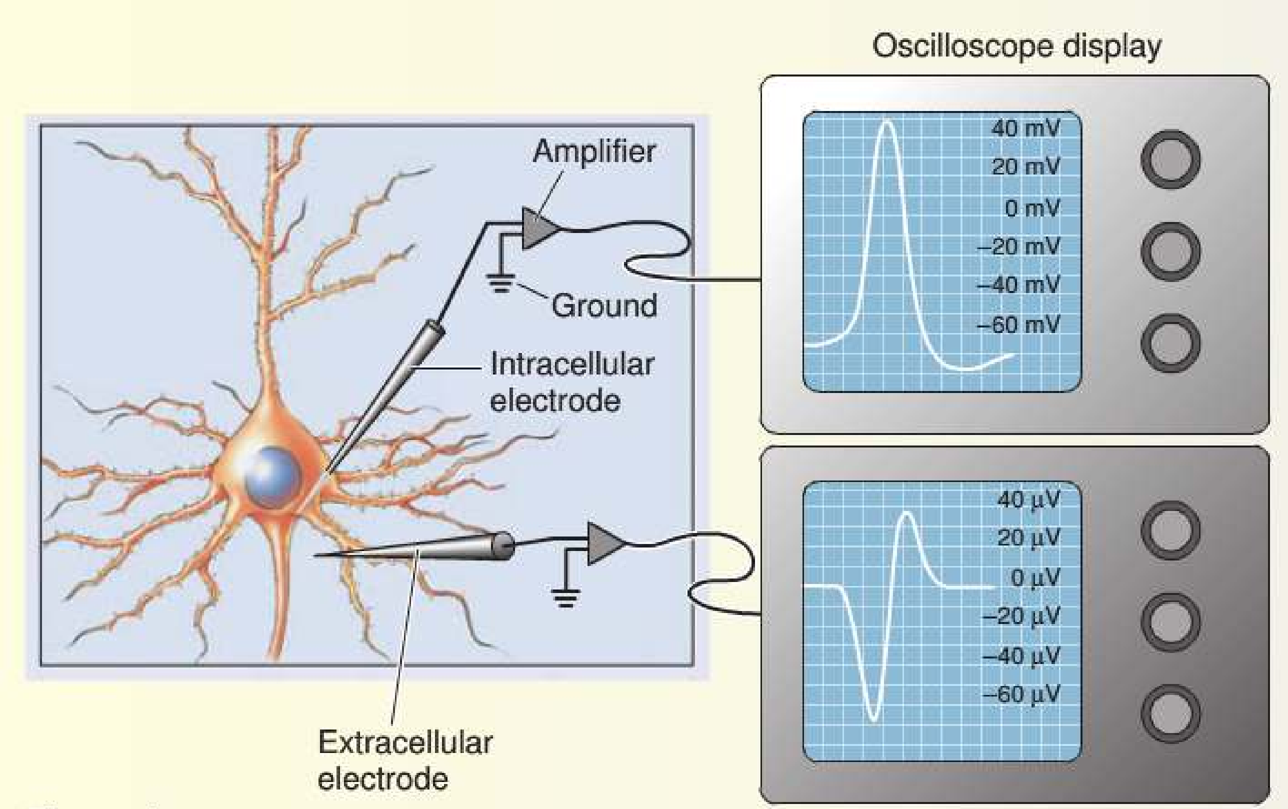
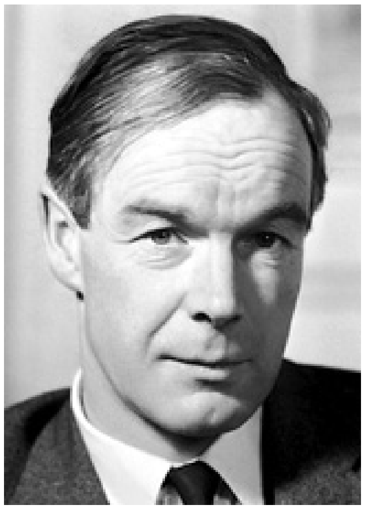
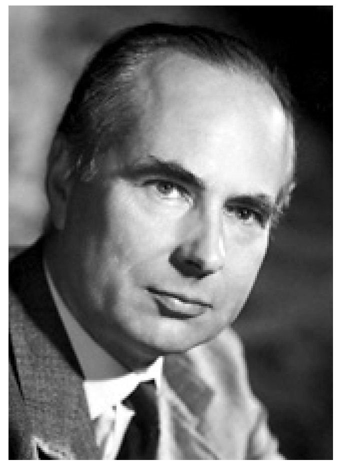


Figure A

Nobel Prize (1963)

Alan Hodgkin & Andrew Huxley





They characterized the action potential by recordings from the squid giant axon which is about 0.5-1mm in diameter and triggers a muscle to expel water from the siphon to escape (50-100 times wider than mammalian neurons and unmyelinated).

For an interview:
http://www.bbc.co.uk/archive/scientists/10607.shtml

Nobel Prize (1963)

J. Physiol. (1952) 116, 424–448

MEASUREMENT OF CURRENT-VOLTAGE RELATIONS N
THE MEMBRANE OF THE GIANT AXON OF *LOLIGC*

By A. HODGKIN, A HUXLEY and B. KATZ

From he Lab atory of the Mar Biological ssociation, Plymouth,
ysiological Labc ry, Univer ty of Cambridge

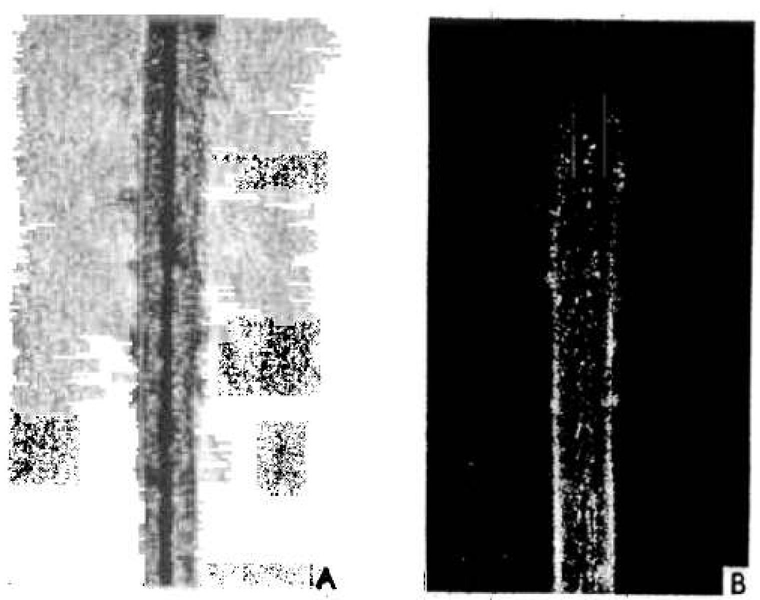
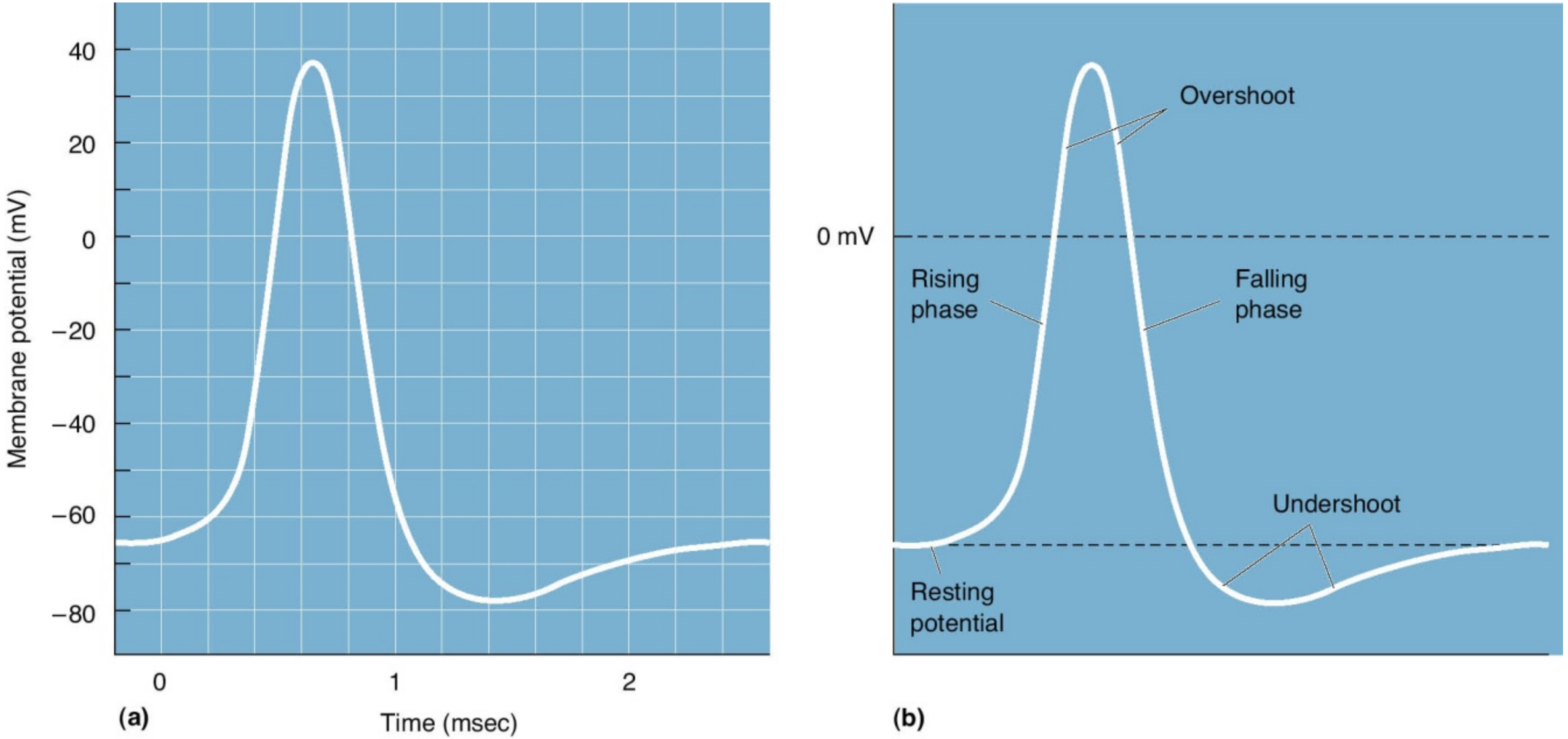


Fig. 5. Photomicrographs of giant axon and internal electrode. A, transmitted light; B, dark ground. The axon diameter was about 600 μ. The glass rod supporting the wires is not clearly seen.

Shape of Action Potential (“Spike”)

Shape of the action potential (change of membrane potential)



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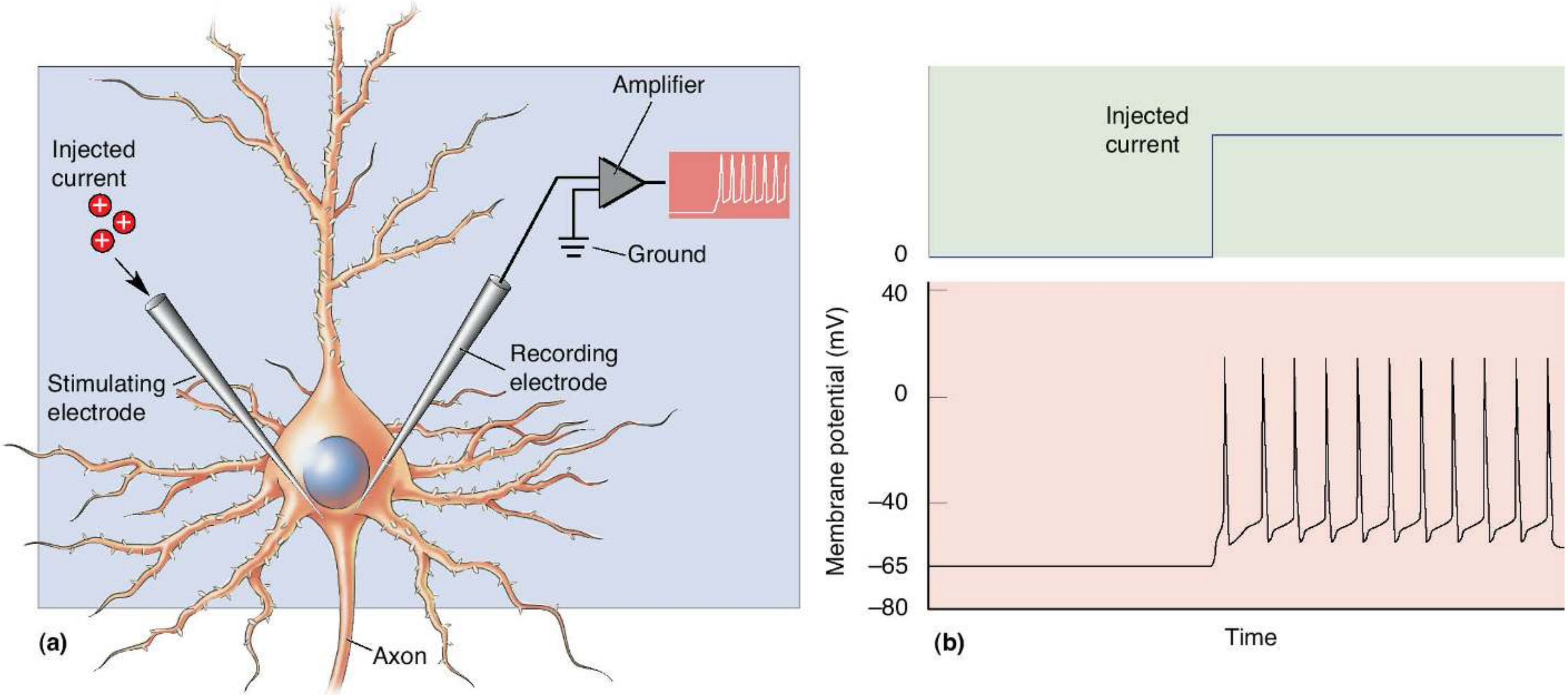
Artificially Induce Action Potentials

Injection of current leads to a depolarization (becoming more positive) of the membrane potential. If large enough, action potentials will occur (b, lower graph).



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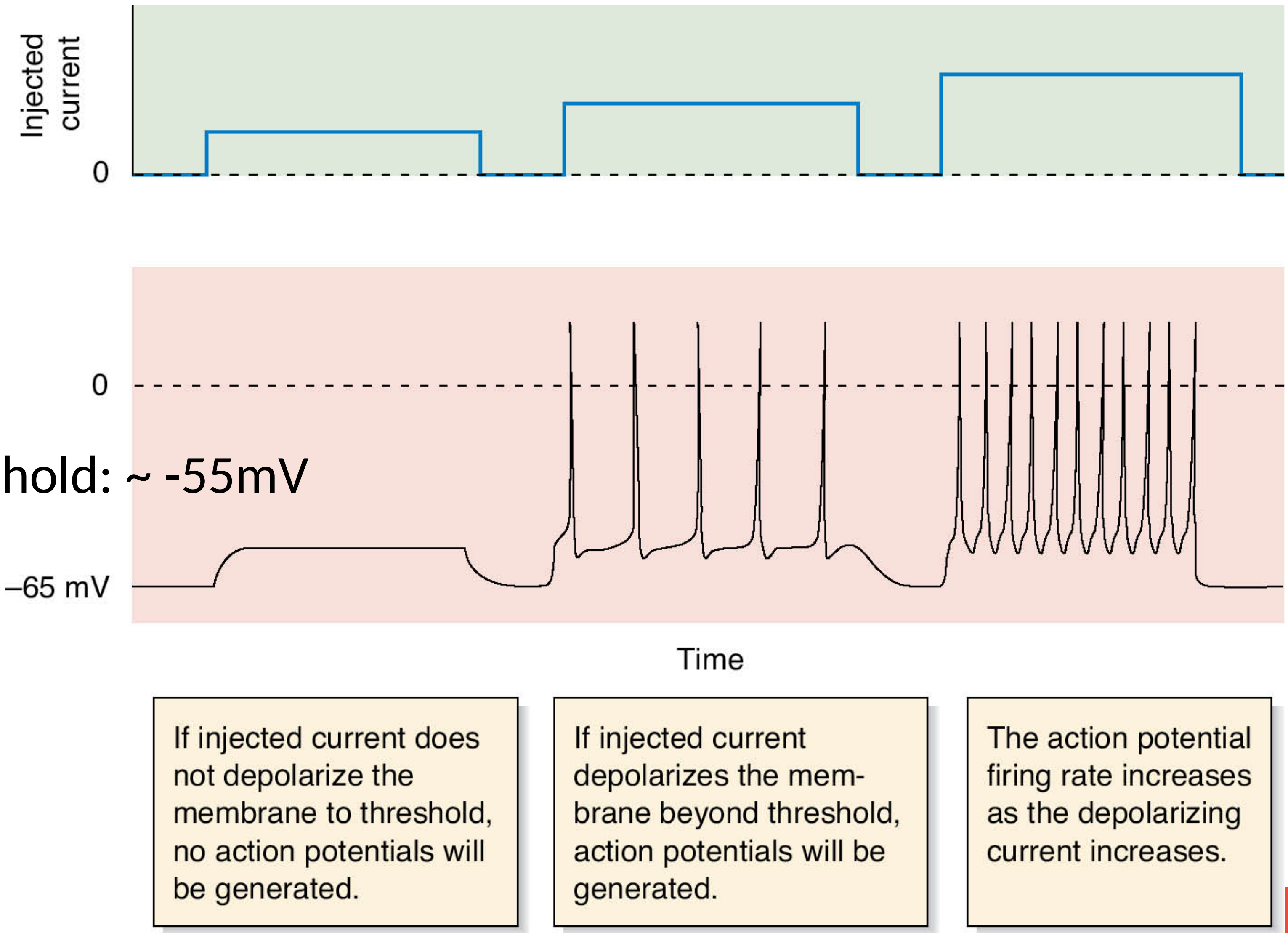
“Threshold” to cause AP

Current injection -> Depolarization

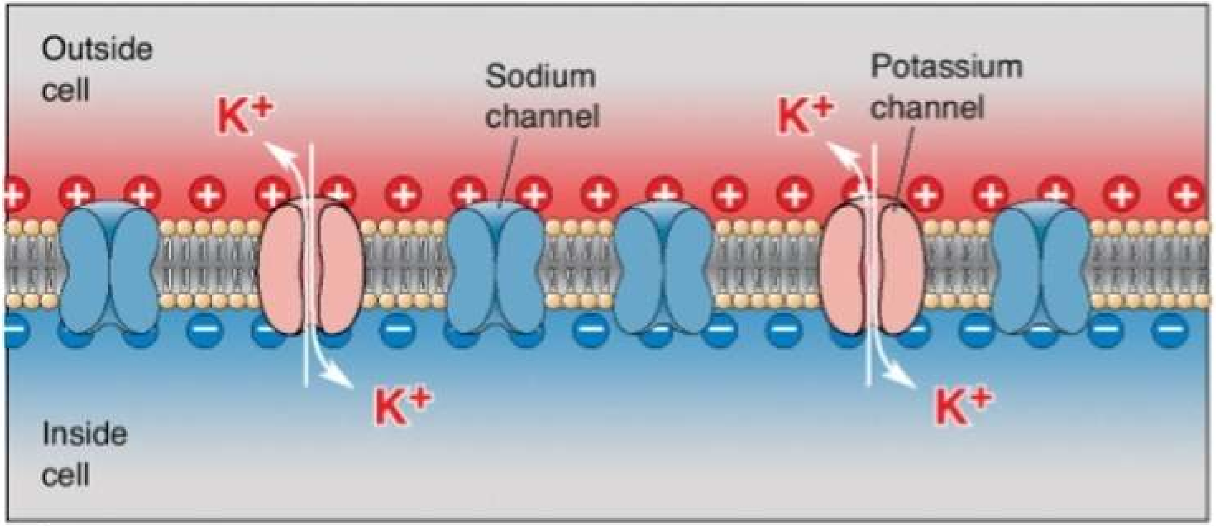


Threshold: ~ -55mV

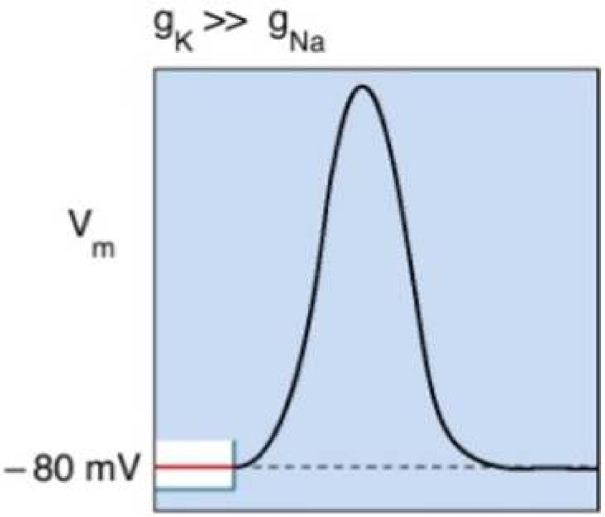
Phases of AP 1: Resting Potential

<u>Resting potential</u>
(the action potential curve is idealized in this graph)

g_K, g_{Na}: conductance
$g_K >> g_{Na}$ means that the membrane is more permeable for K^+ than Na^+



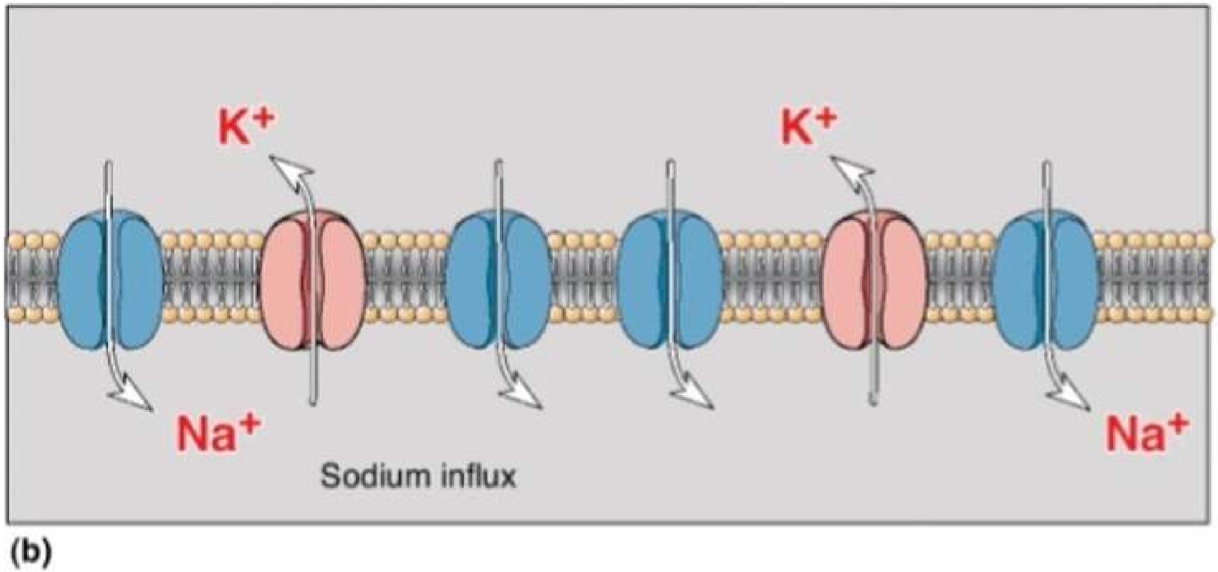
(a)

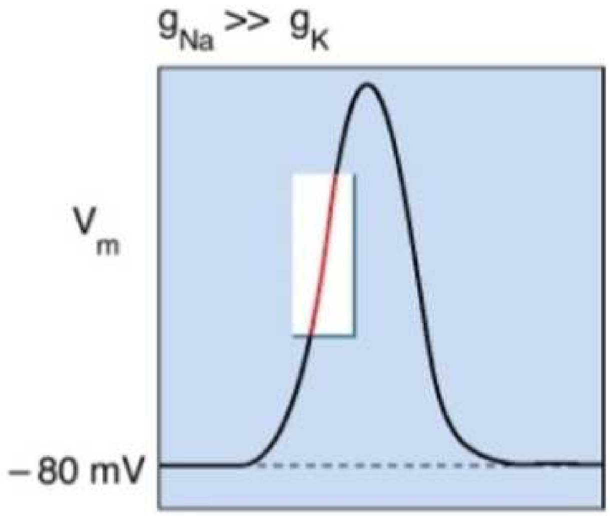


Phases of AP 2: Rising

<u>Rising phase</u>

Depolarization above threshold will cause the voltage-gated sodium channels to allow for Na^+ influx.

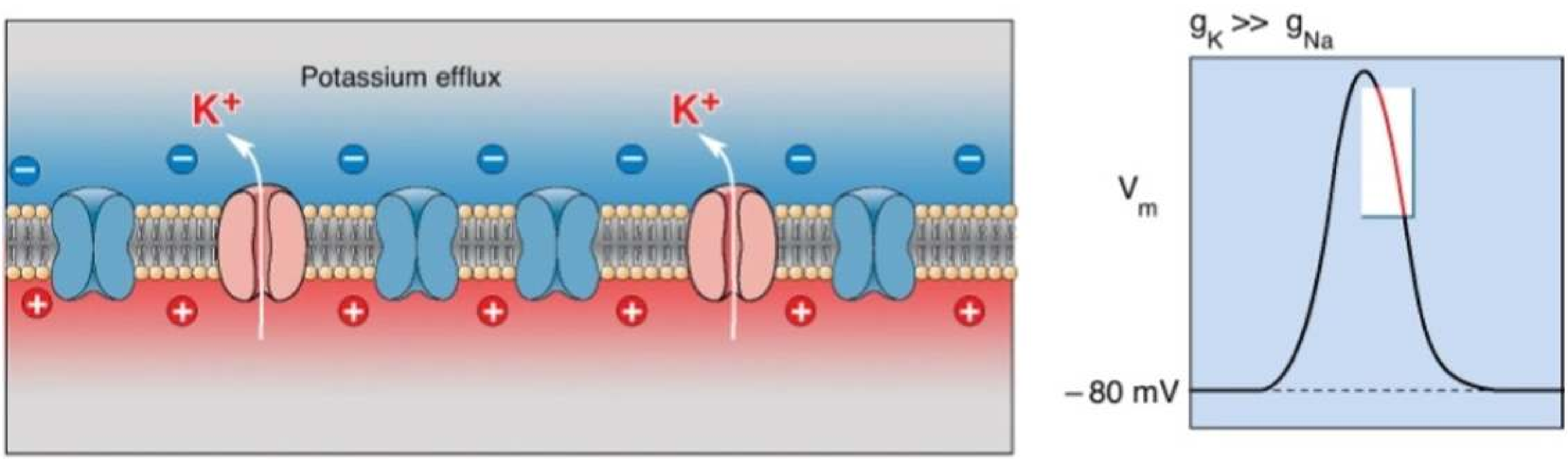




Phases of AP 3: Falling

<u>Falling phase</u>

Voltage-gated Na^+ channels will close quickly (1ms).
Potassium flows out to reach equilibrium.
Additional voltage-gated K^+ channels open up.



(c)

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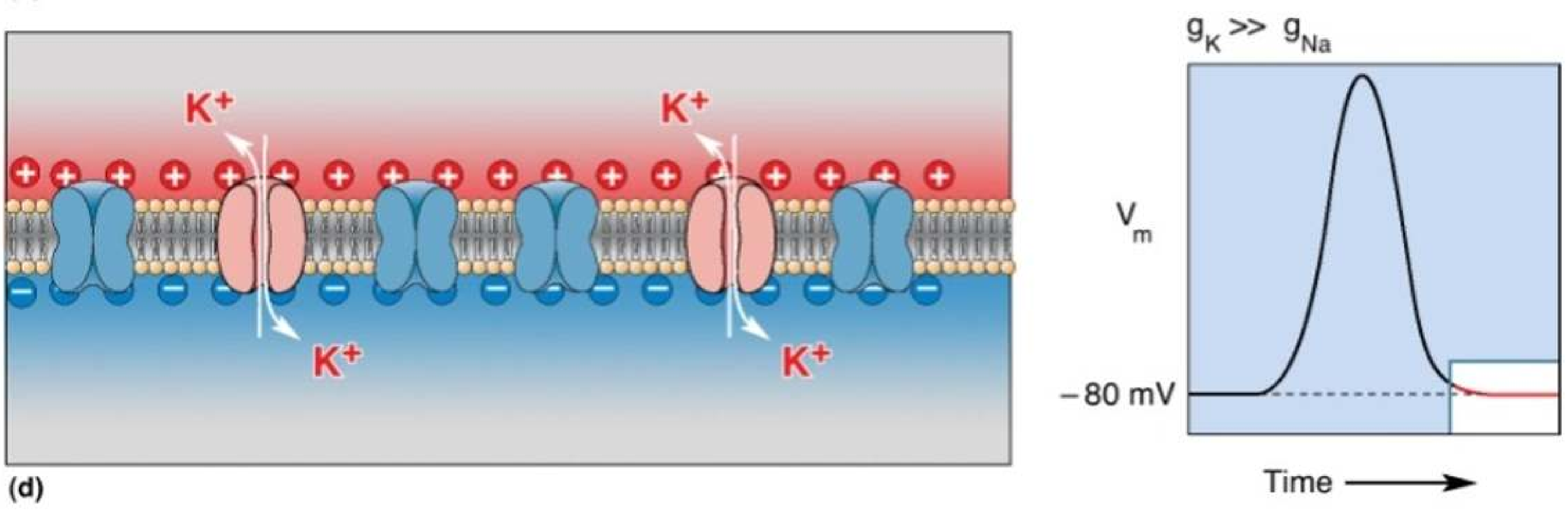
Phases of AP 4: Back to Resting

<u>Resting potential</u>:

After the action potential, the membrane potential will return to rest.



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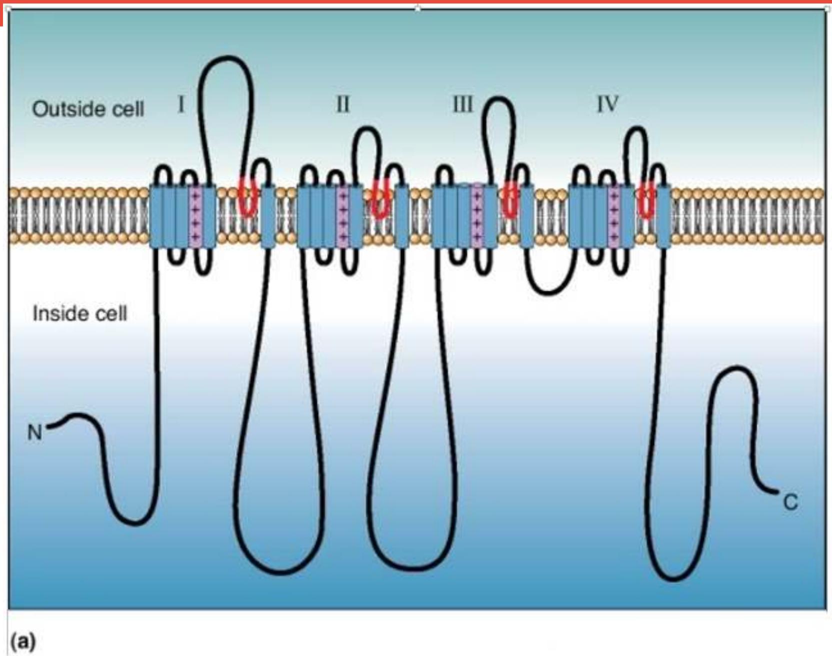
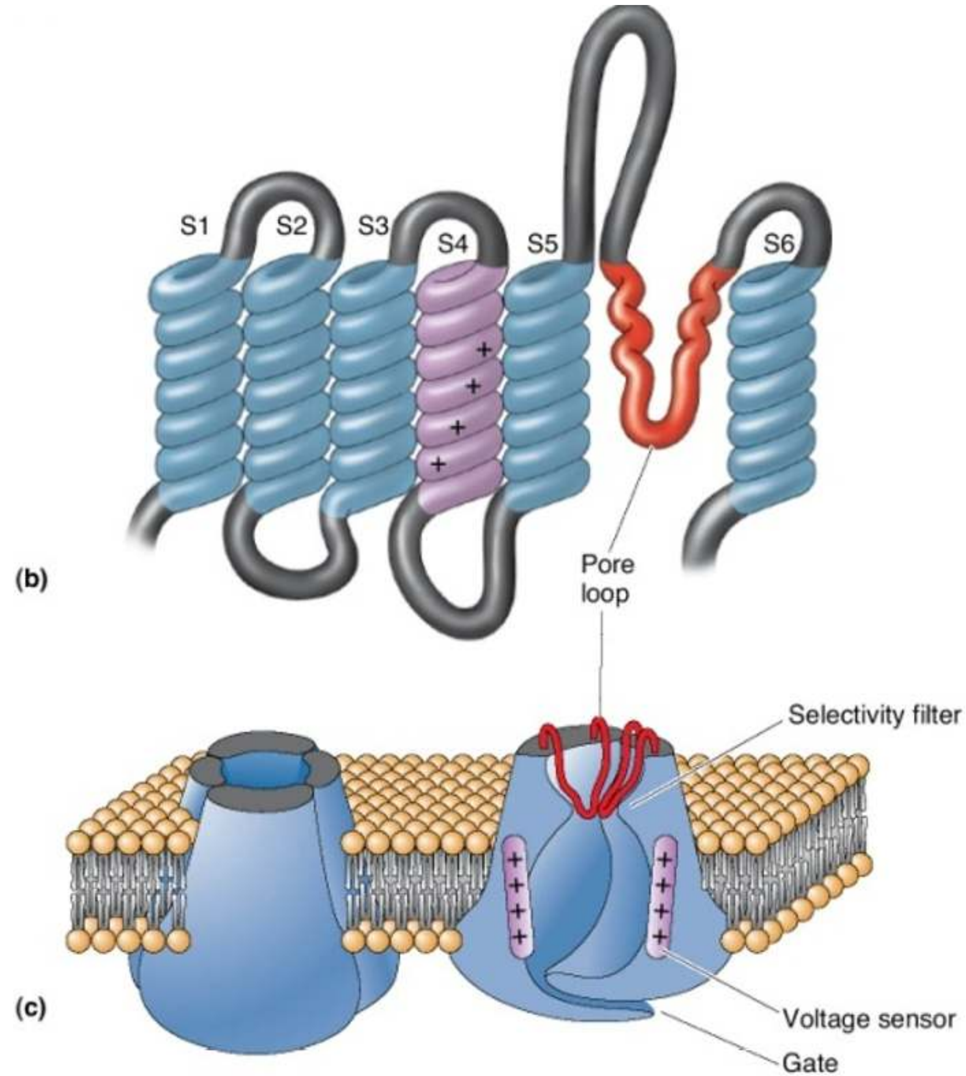
How does AP work: Na+ feedback loop



The voltage-gate Na^+ channel consists of four domains (I-IV, a), each with six transmembrane alpha helices (S1-S6, b). The channel is highly selective for Na^+ ions.



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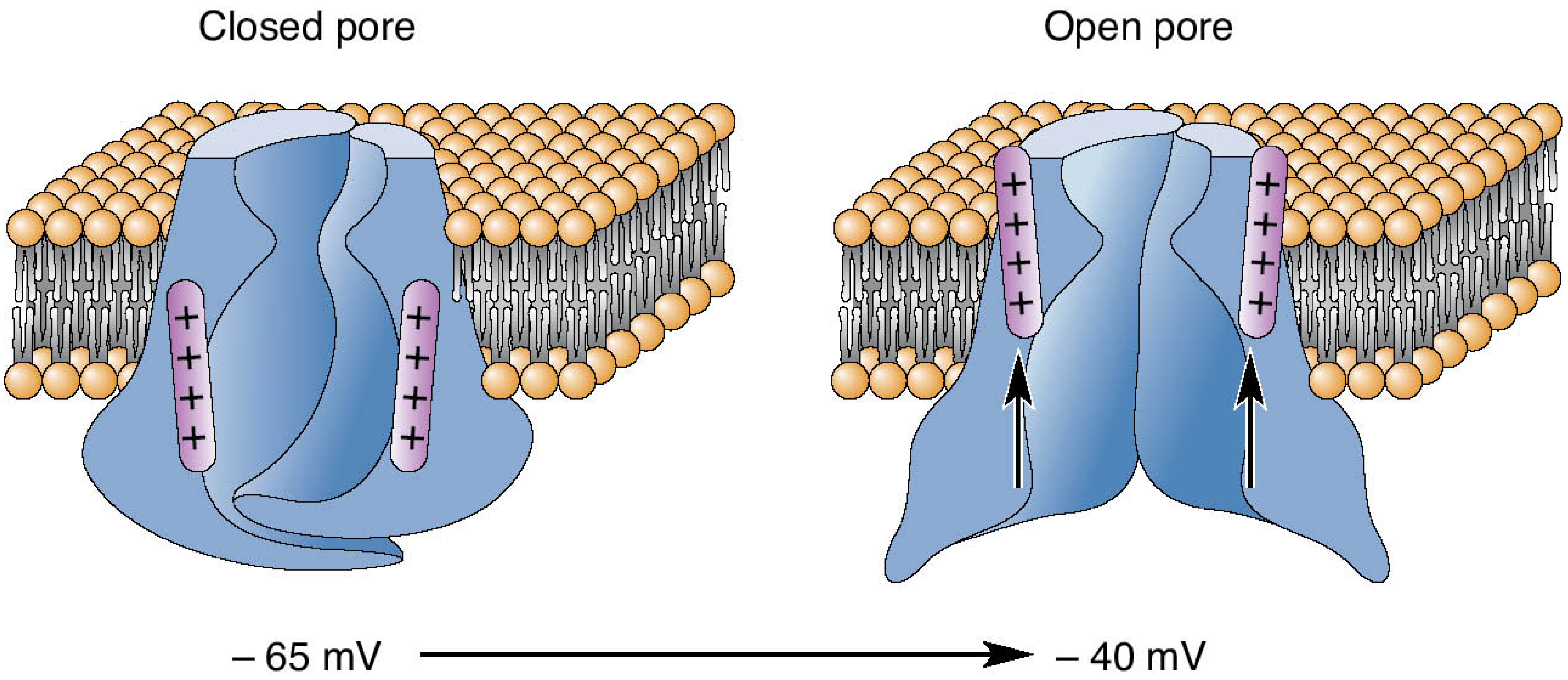
“Voltage Gated” Channel

A portion of the voltage-gate Na^+ channel (++++) in S4 responds to depolarization of the membrane with conformation changes (closed->open).



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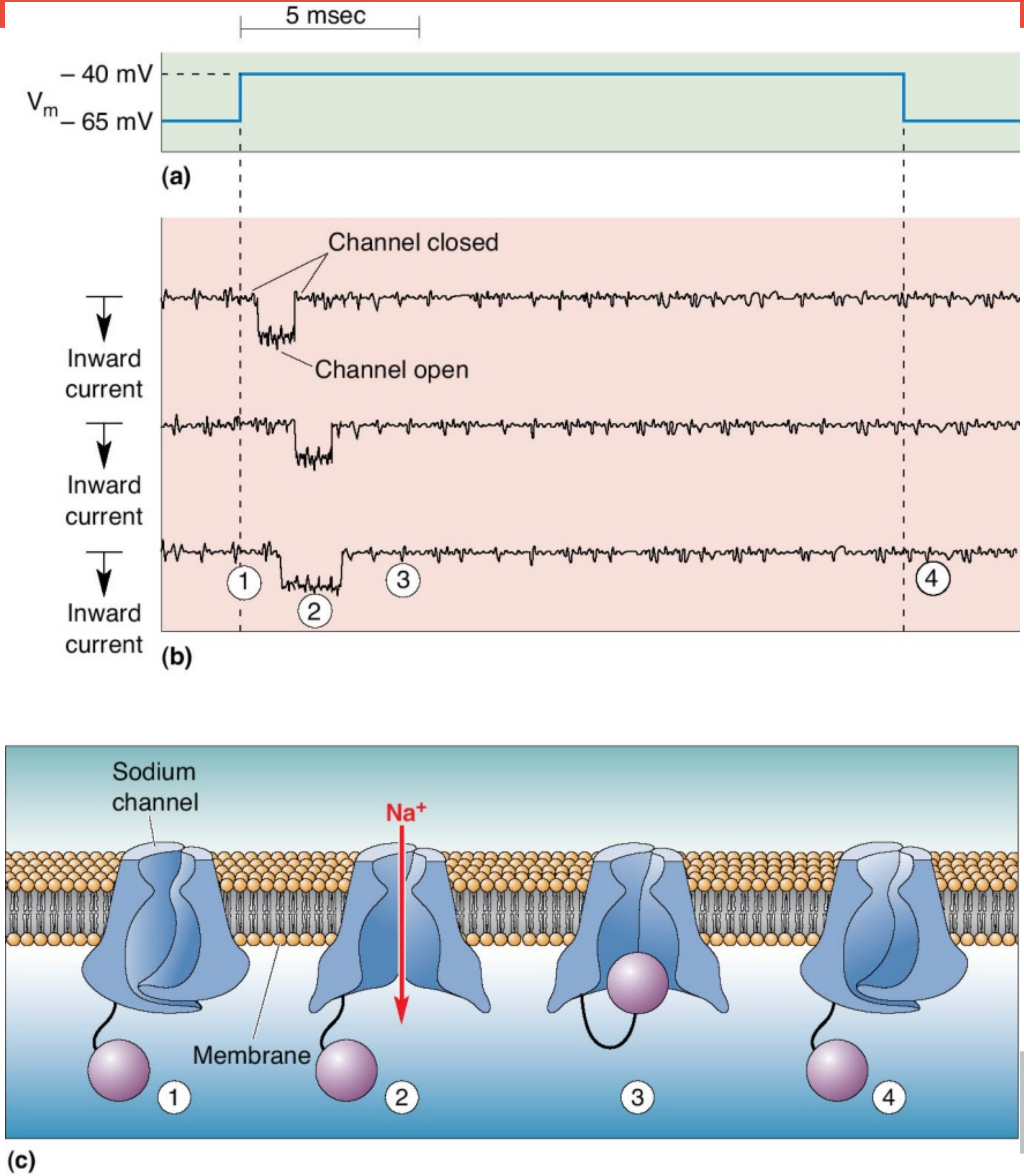
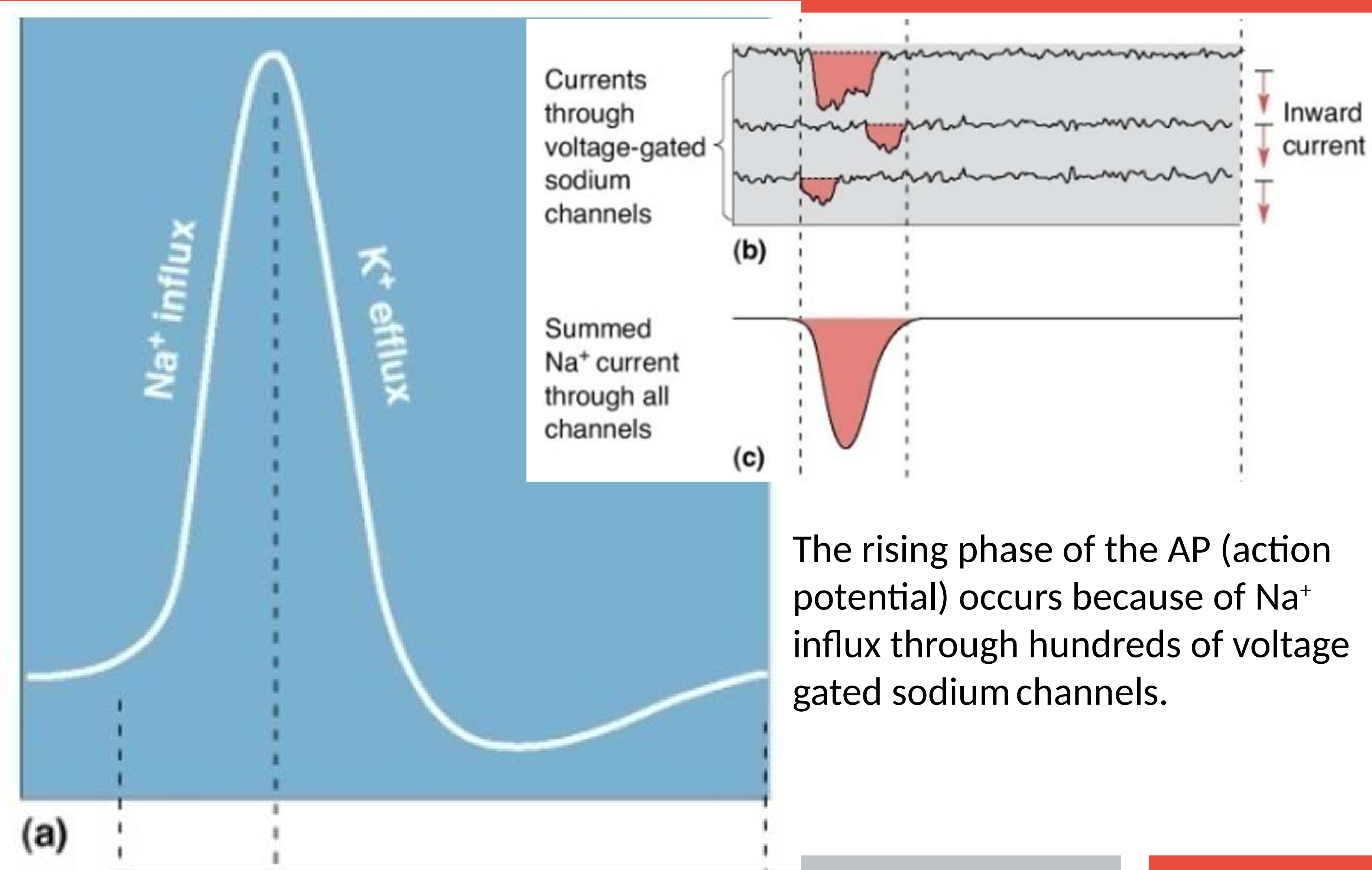
Voltage-gated Na+ Channel



1) Resting state
2) Channel opens during depolarization
3) Inactivation gate closes the gate (after 1ms)
4) Deinactivation after repolarization

AP: A little more complex...



The rising phase of the AP (action potential) occurs because of Na^+ influx through hundreds of voltage gated sodium channels.

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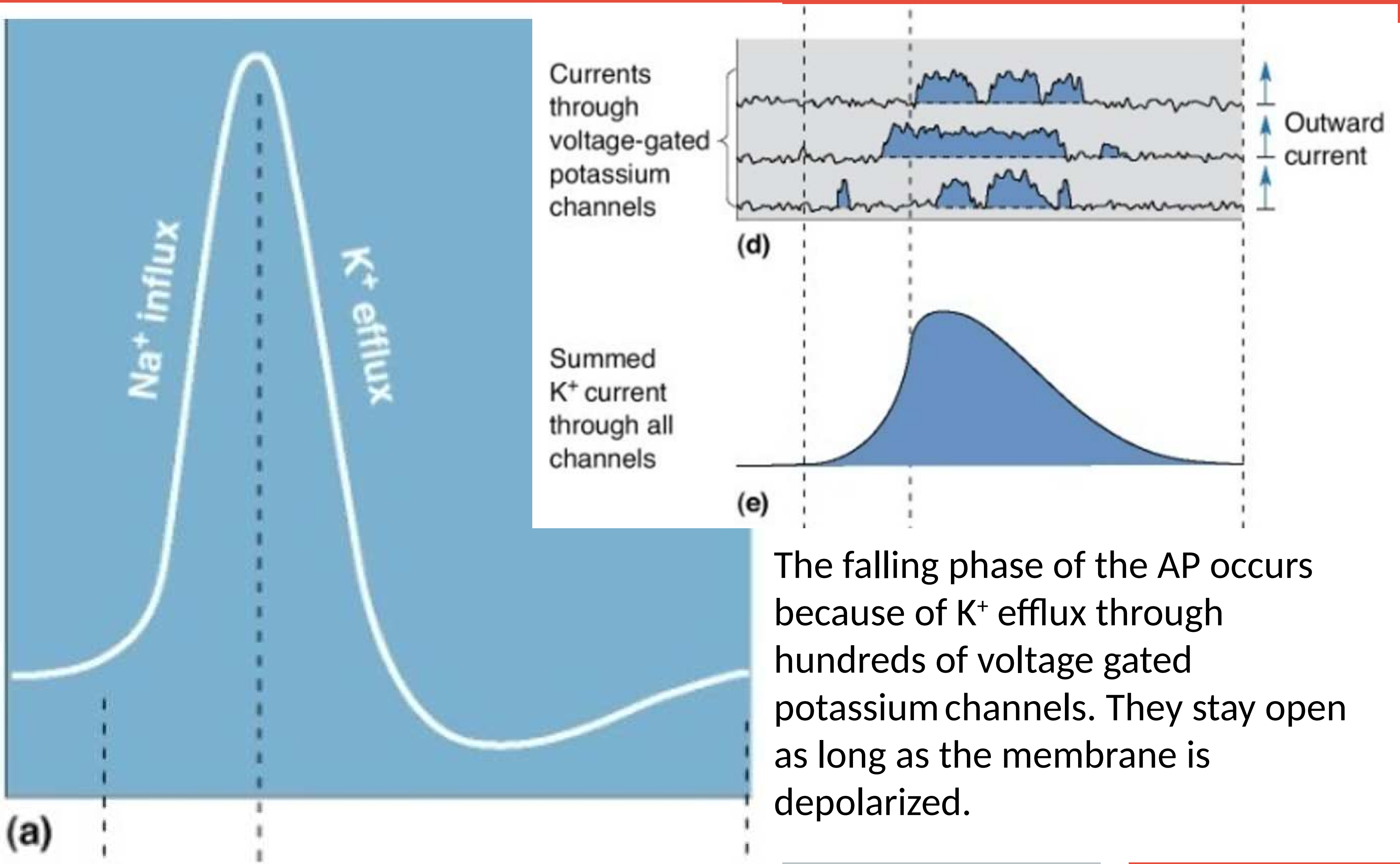
AP: A little more complex…



The falling phase of the AP occurs because of K^+ efflux through hundreds of voltage gated potassium channels. They stay open as long as the membrane is depolarized.

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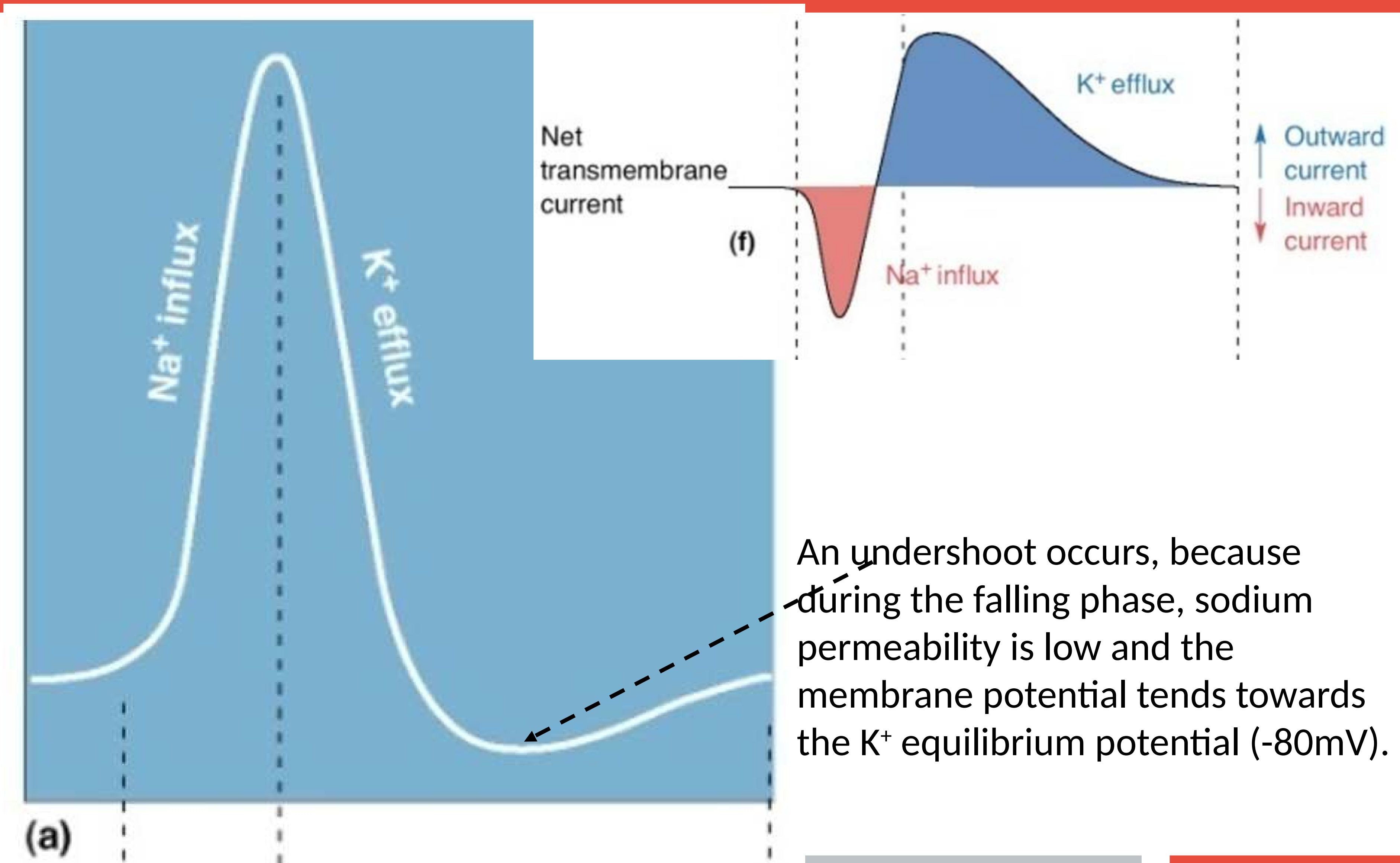
AP: A little more complex...



An undershoot occurs, because during the falling phase, sodium permeability is low and the membrane potential tends towards the K^+ equilibrium potential (-80mV).

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Poisons affecting membrane potential

What poisons do you know that affect electrical transmission in the nervous system?

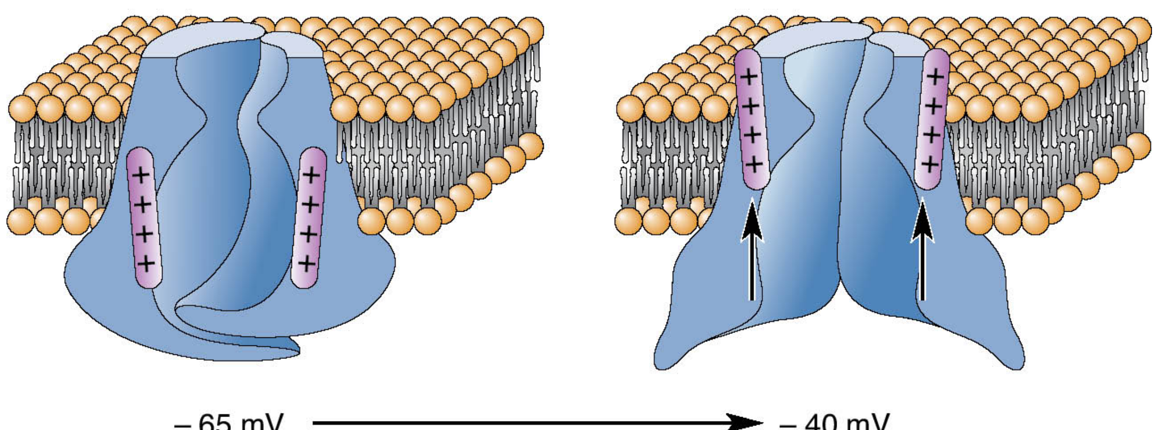
Fugu!

Fugu are Tetraodontidae, their toxin is called Tetrodotoxin (TTX).

Why Fugu is Dangerous: Stops AP

Toshio Narahashi

Tetradotoxin (TTX) “plugs” the sodium-channels from outside, thus preventing action potentials.



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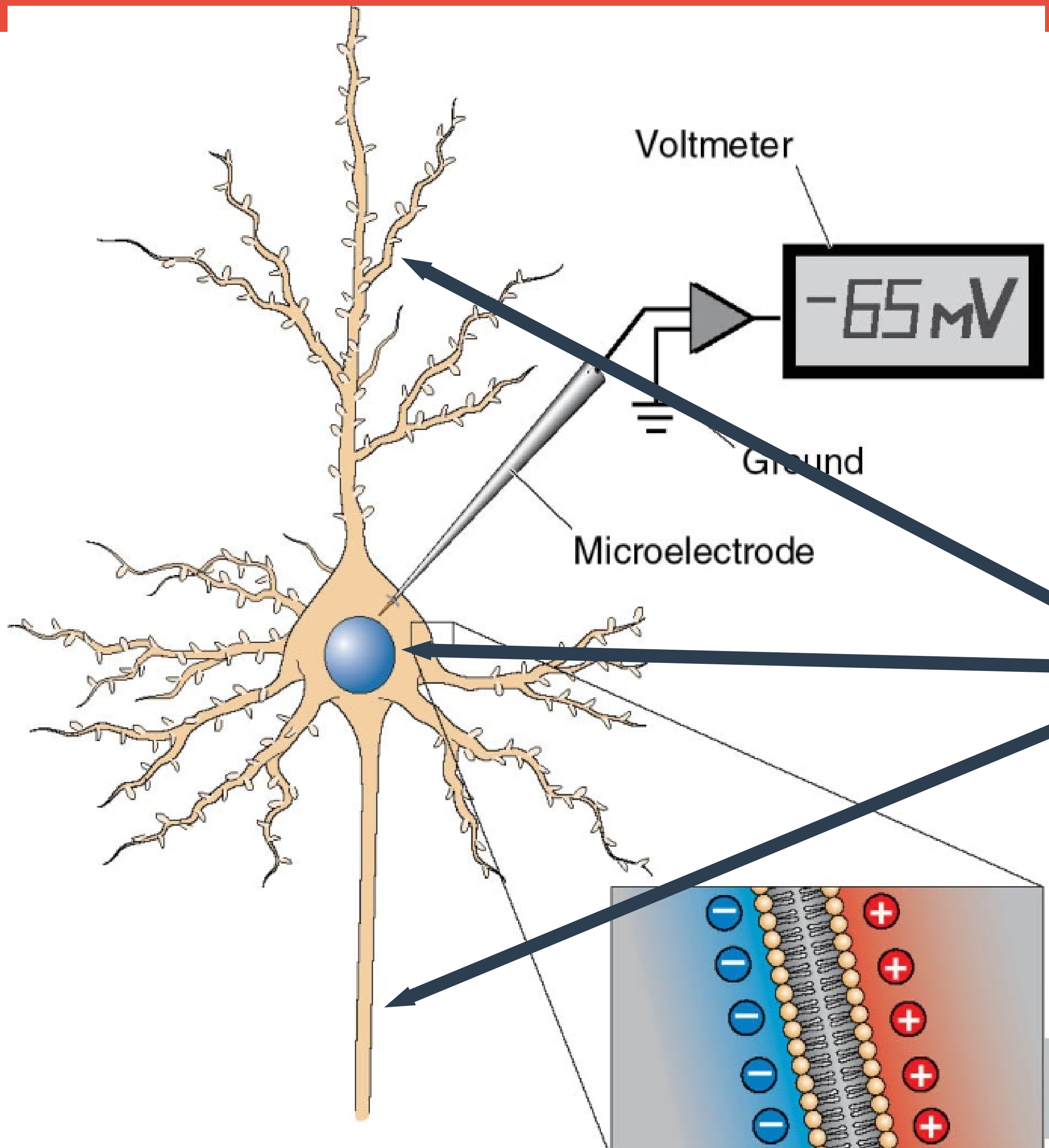
Part 3: AP along axon

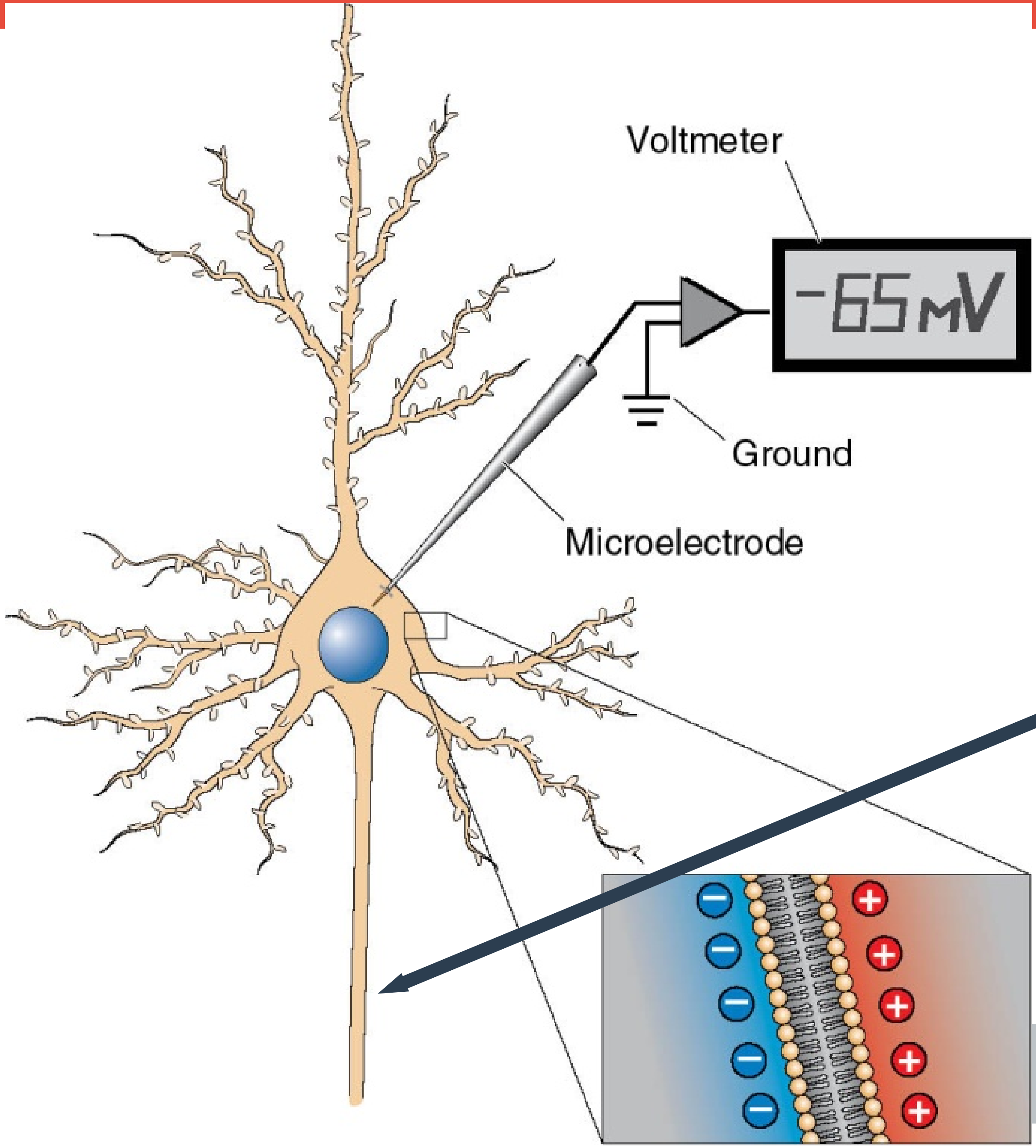
AP does not just happen in the “body”



Everywhere in the cell has a membrane potential

-Dendrites
-Cell Body (soma)
-Axon

AP does not just happen in the "body"



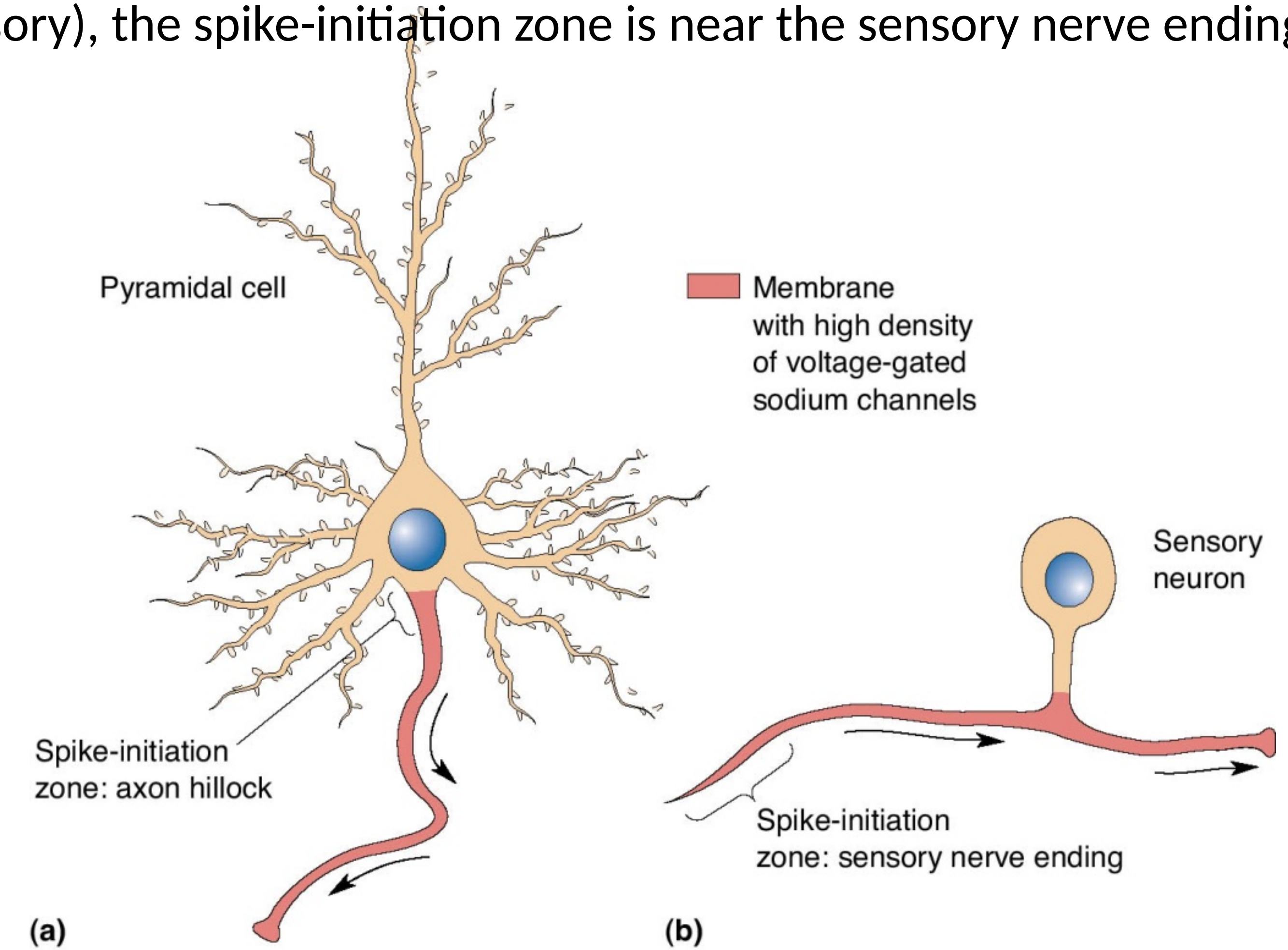
Everywhere in the cell has a membrane potential

-Dendrites
-Cell Body (soma)
-Axon

Remember: Axon sends signal to other brain cells!

Action Potential (Spike) initiation

Spike initiation mainly occurs in axons (from the axon hillock), because the other zones have only few voltage-gated sodium channels. In sensory neurons (e.g., somatosensory), the spike-initiation zone is near the sensory nerve ending.



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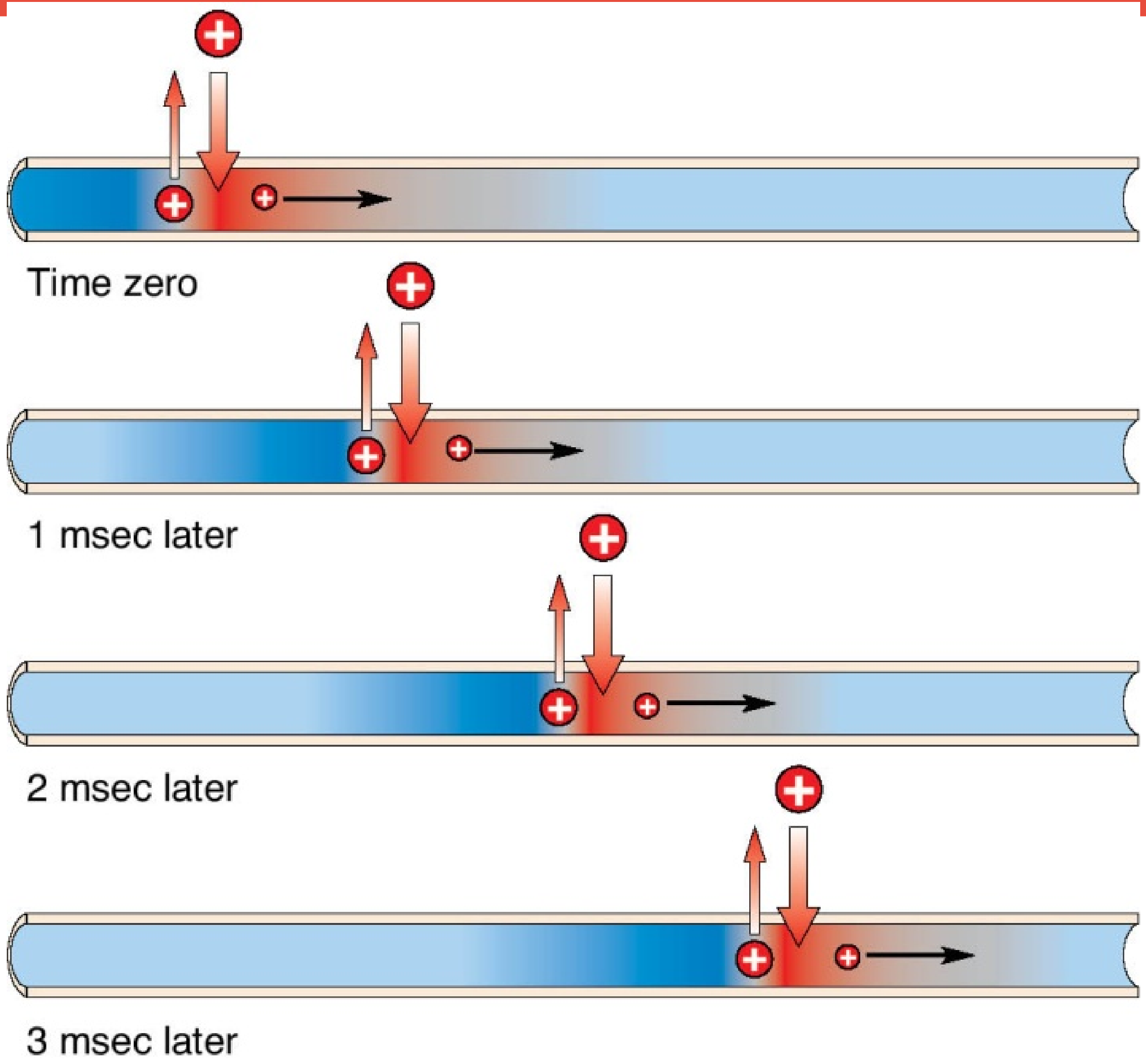
Action Potential Conduction

Action Potential doesn't happen "all at once"

Usually AP starts at the beginning of the axon (a special area called "axon hillock" where there are *extra* Na+ channels)

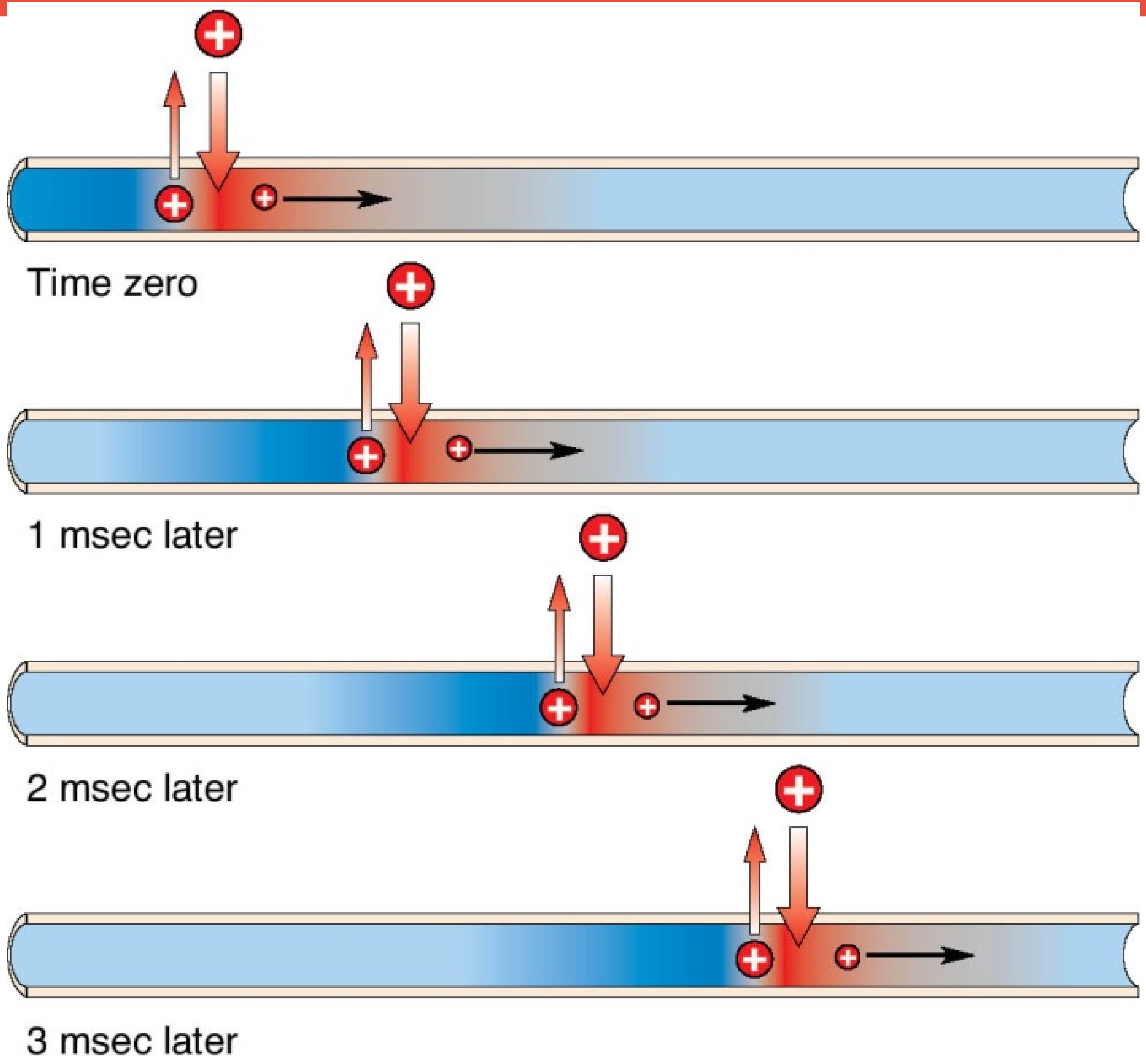
Then, it "travels down" the axon. Increase in voltage nearby → increase in current flowing into the region next to it → same as injecting current to that region!



Action Potential Conduction

Action potentials (APs) are usually conducted along one direction only, because the sodium channels behind the AP are refractory (they are still blocked by an inactivation gate).

The AP is always created anew and is thus conducted without decrement (like a repeater in a computer network).



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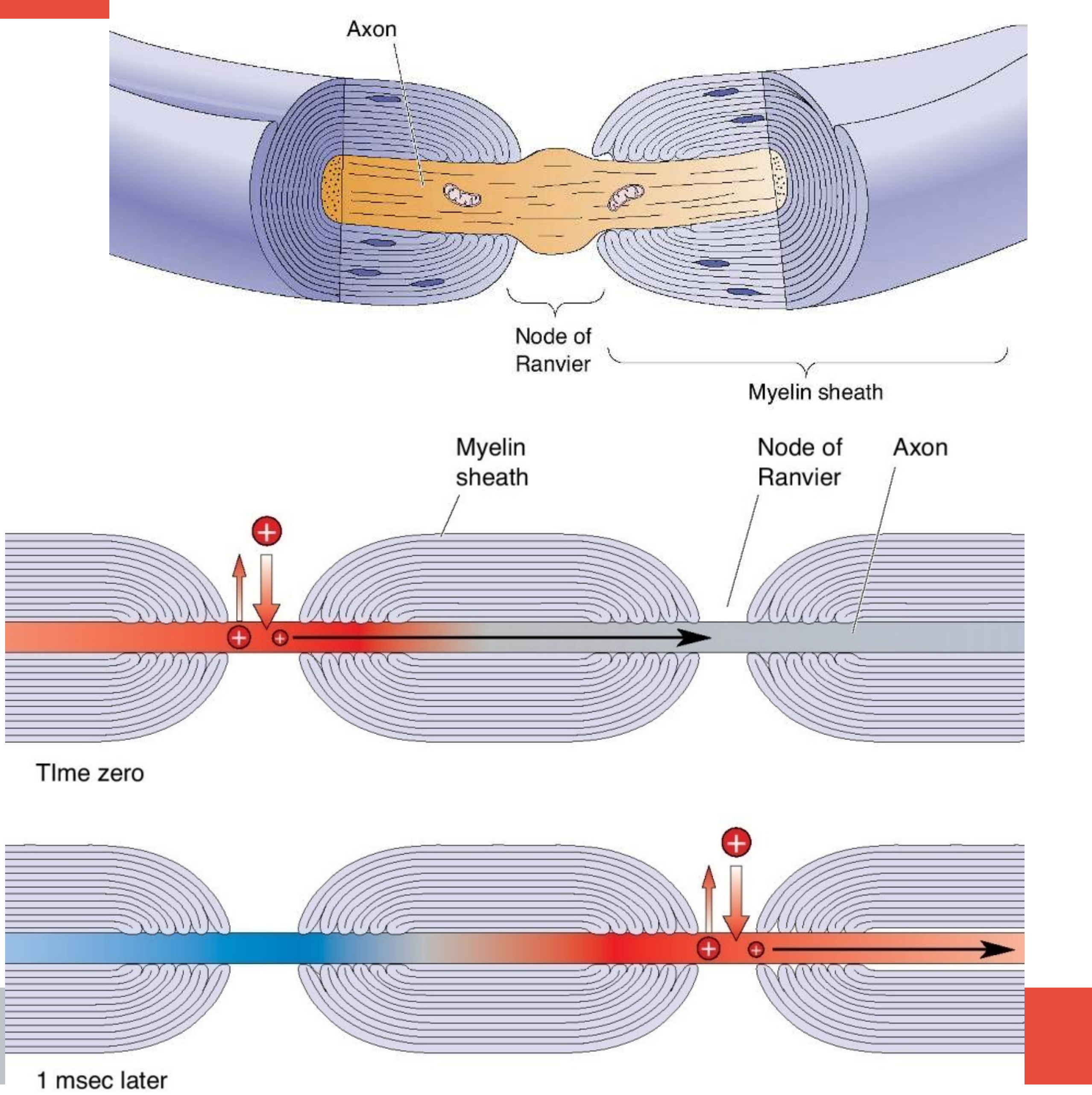
Saltatory Conduction

Vertebrate axons are often wrapped in myelin:

- It prevents leakage of ions and lets them move along the axon instead.
- It allows for saltatory conduction where APs only occur at interleaved nodes (nodes of Ranvier).

Both factors speed up conduction velocity.



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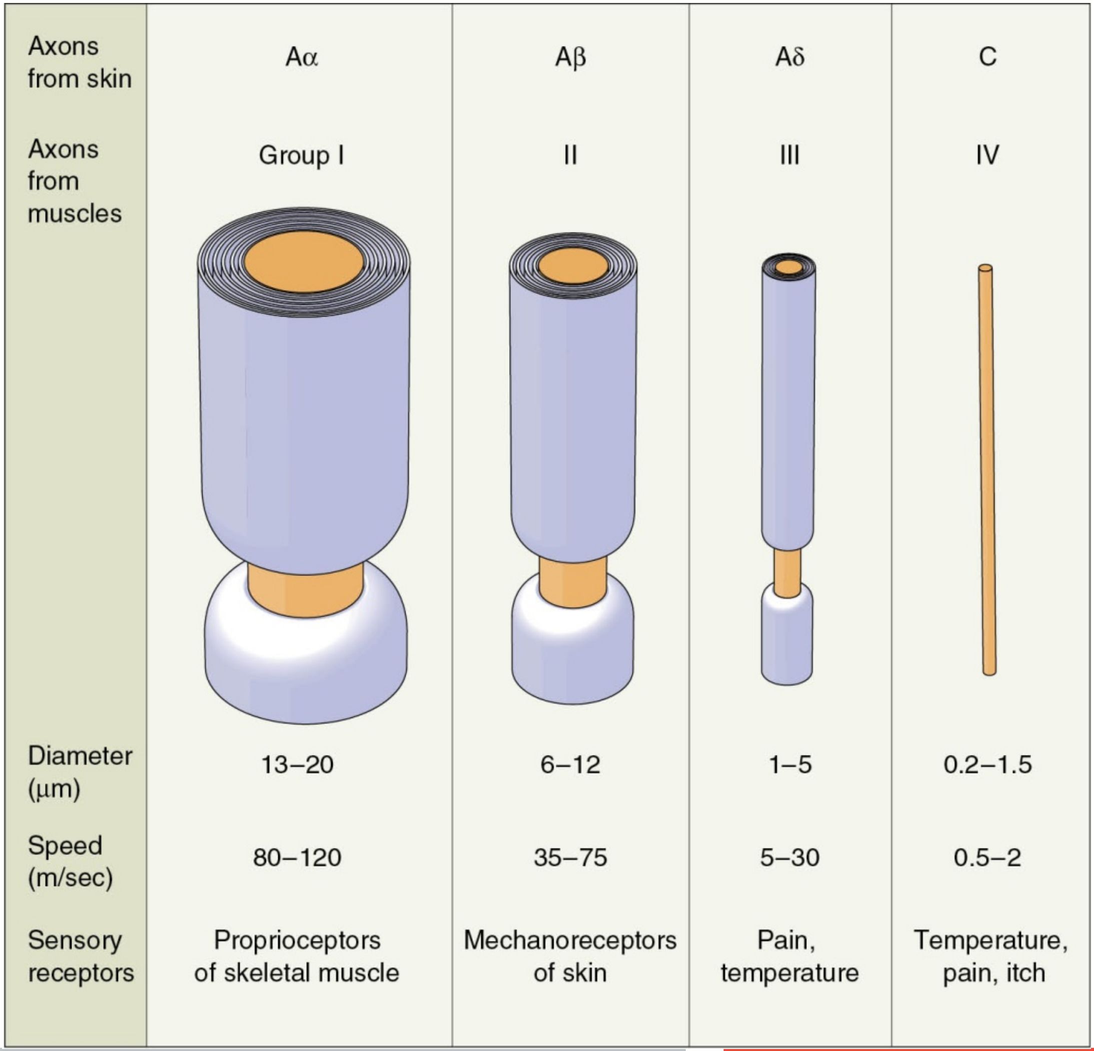
Speed of Transmission

Speed depends on the diameter of the nerve fiber and its coating with myelin (electrical insulation).

The squid giant axon has a diameter of about 500-1000 µm, no myelin sheath, and a conduction speed of about 25 m/s.



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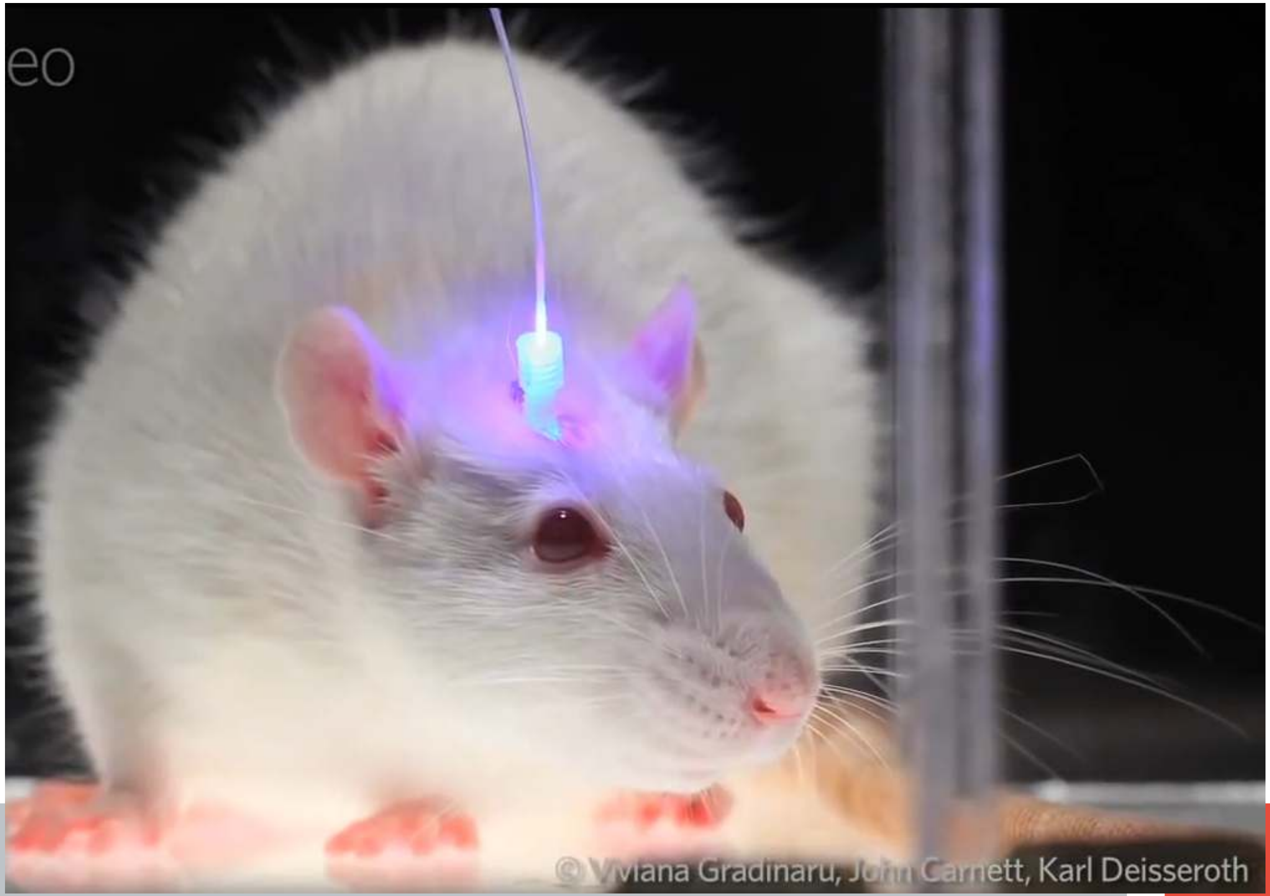
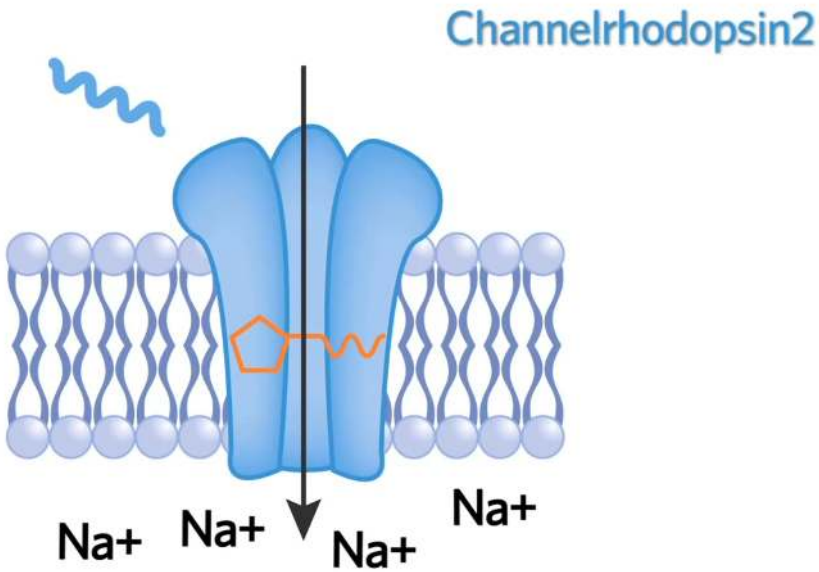
Other ways to artificially cause AP: Optogenetics

Neurons can be stimulated with injection of electrical current via electrodes, but a genetic method that can target specific cell types more selectively is optogenetics: genes (from algae or microbes) for light-activated ion channels are introduced into mammal neurons. These channels can be stimulated by shining light on them.

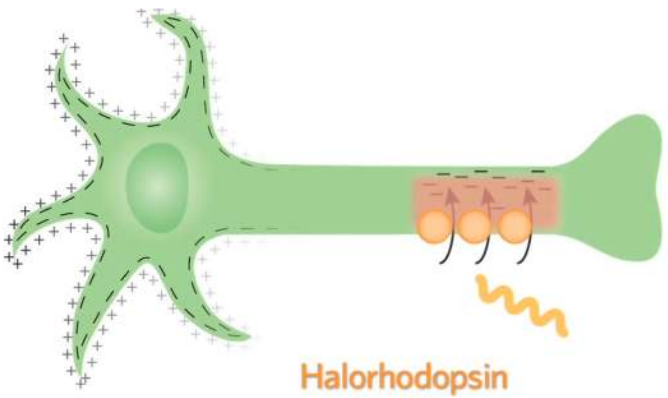


Optogenetics

<u>Channelrhodopsin2</u> from green algae responds to blue light by opening and letting Na^+ pass into the cell. This leads to depolarization and activation of the neuron.



<u>Halorhodopsin</u> from single-cell microbes responds to yellow light by opening and letting Cl^- pass into the cell. This leads to hyperpolarization and inhibition of the neuron.



Review of Today

For electrical signaling to occur in neurons, two concepts are essential:

1) The resting membrane potential
2) The action potential (AP)

Na^+ (sodium) and K^+ (potassium) ions are essential for these.

They can pass the cell membrane by passive (leakage) or voltage-gated channels.