A few questions on the content of the previous lecture

slido

A neuron receives input through its..., and sends output through its...

ⓘ Start presenting to display the poll results on this slide.

The...myelinate the axons of neurons in the CNS, while...myelinate the axons of neurons in the peripheral nervous system.

ⓘ Start presenting to display the poll results on this slide.

slido

Genetic information encoded in the DNA in a cell's nucleus is transmitted to different parts of the cell, outside the nucleus, by...

ⓘ Start presenting to display the poll results on this slide.

Any questions/remarks before we begin today's lecture?

Neural Signaling 1

Dr. Lavinia Carmen Uscătescu

October 30th 2023

What you can gain from this lecture

- Knowledge about the mechanisms of ion flow across the neuronal membrane
- Essential vocabulary to describe the electrical activity of neurons
- Notable historical discoveries that contributed to our understanding of ion transport across the neuronal membrane
- Knowledge about how electrical activity is propagated in neurons

Outline

1. Resting membrane potential

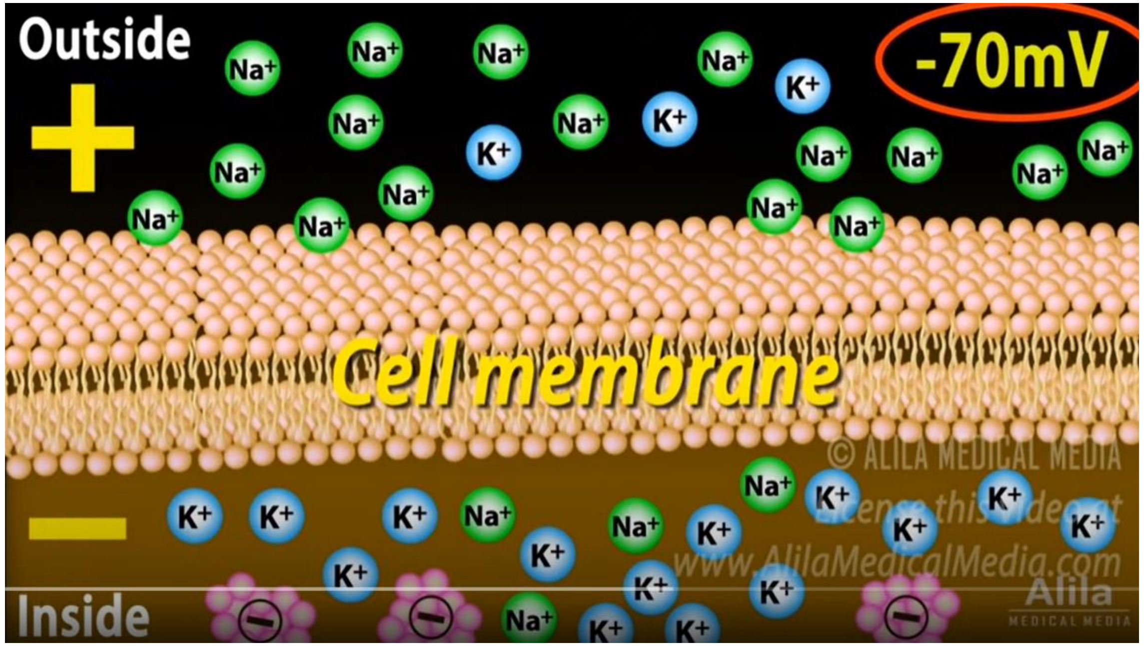
- Na^+ and K^+ ions
- Na^+/K^+-ATPase pump

2. Postsynaptic potential
3. Action potential

Resting membrane potential

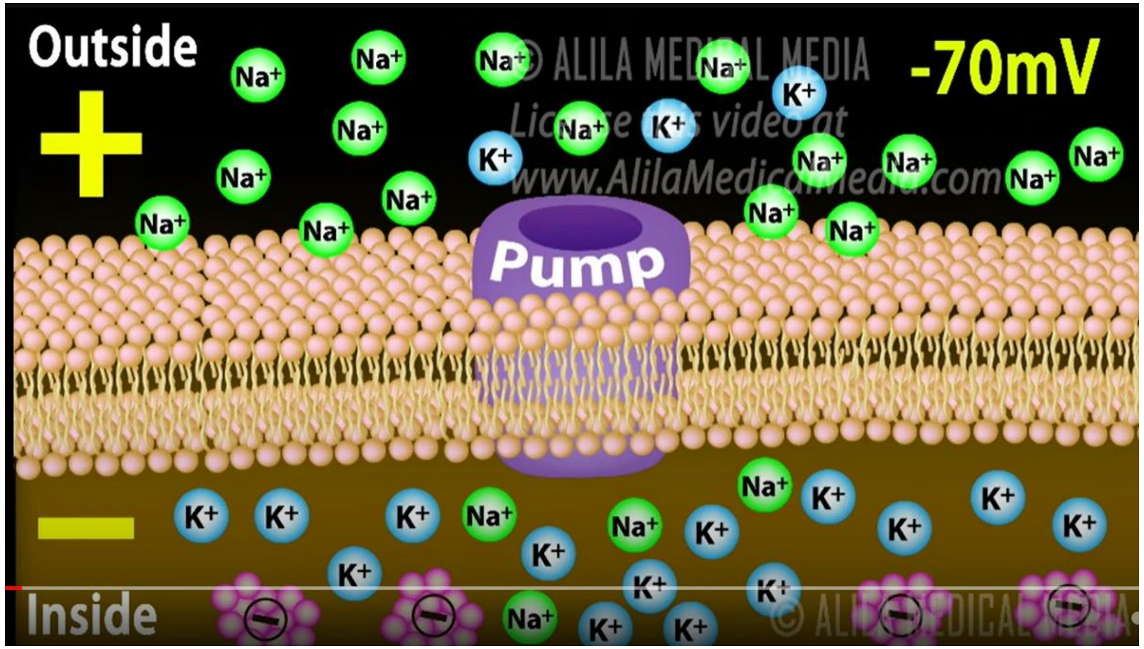
Let’s first set the stage for today’s lecture

Membrane Potential, Equilibrium Potential, Resting Potential



https://www.youtube.com/watch?v=MplWXZTOk6o

Action Potential in Neurons



https://www.youtube.com/watch?v=iBDXOt_uHTQ

Neuronal communication = an **electrochemical** event

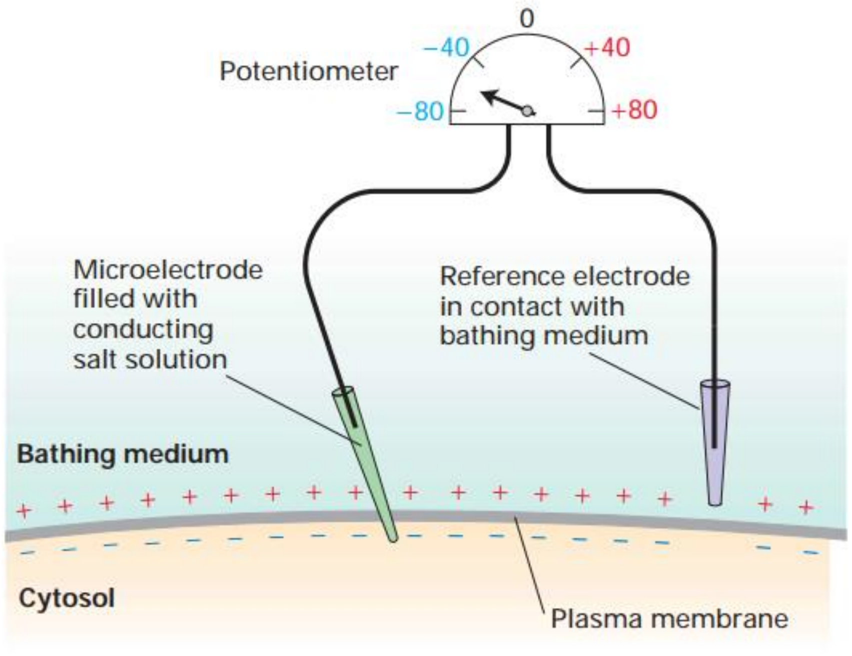
The **movement of the action potential** down the axon = **electrical** → the focus of today's lecture

The **movement of the neurotransmitters** across the synaptic space = **chemical** → the focus of our next lecture

*Note however that **most, but not all synapses are chemical**; **some are electrical**. These are faster than the chemical ones and occur when two neurons communicate via **gap junctions**.*

If you need a refresher on what the components of an atom are and how this relates to the electrical charge of an ion, please watch the following video: https://www.youtube.com/watch?v=fN8kH9Vvqo0

How is voltage across the neuronal membrane measured?



▲ **EXPERIMENTAL FIGURE 7-14 The electric potential across the plasma membrane of living cells can be measured.** A microelectrode, constructed by filling a glass tube of extremely small diameter with a conducting fluid such as a KCl solution, is inserted into a cell in such a way that the surface membrane seals itself around the tip of the electrode. A reference electrode is placed in the bathing medium. A potentiometer connecting the two electrodes registers the potential, in this case −60 mV. A potential difference is registered only when the microelectrode is inserted into the cell; no potential is registered if the microelectrode is in the bathing fluid.

Lodish et al., (2008), pg. 262

voltage or **potential difference** is the **difference** in **electric potential** between two points (e.g., between the inside and the outside of a cell membrane)

V or volt

unit of measure for voltage

mV = 10^{-6} V

K potassium

Na sodium

Cl chloride

KCl potassium chloride

these are electrolytes

electrolyte

substance that conducts electric current as a result of a dissociation into positively and negatively charged particles called **ions**

ion

molecule with an electrical charge

cation

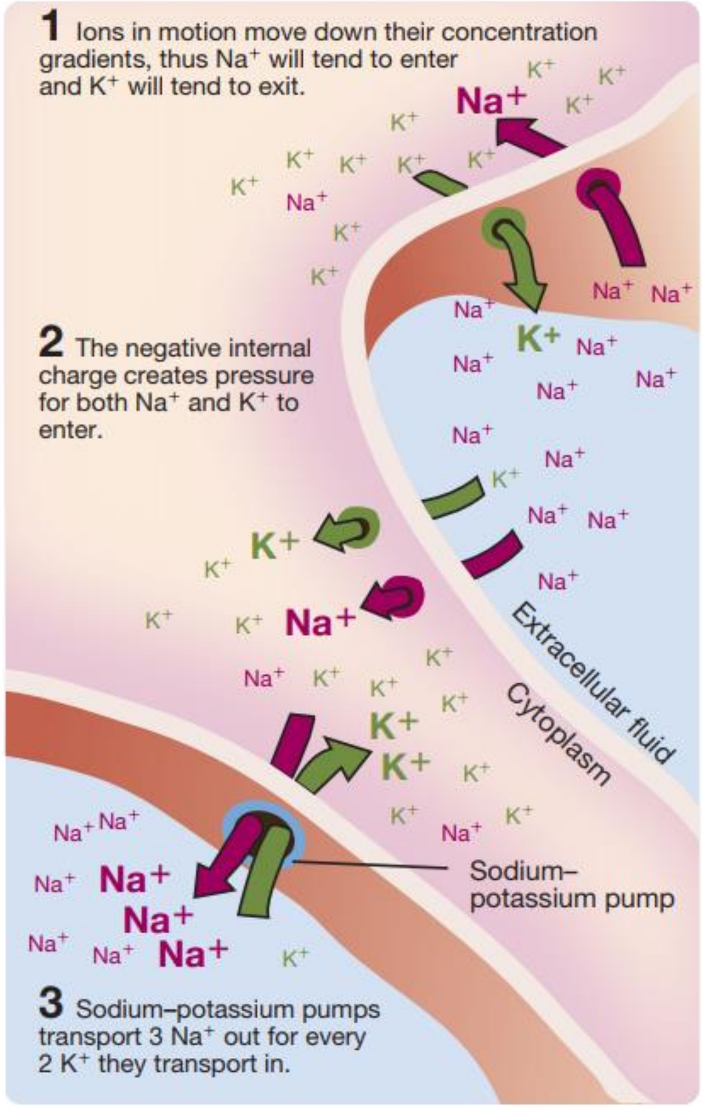
positively charged ion

anion

negatively charged ion

Movement of **Na⁺** and **K⁺** ions across the resting neuron membrane

Figure 4.1 Three factors that influence the distribution of Na^+ and K^+ ions across neural membranes, illustrated in a resting neuron.



Pinel & Barnes, (2021), p. 100

In **resting neurons**, there are **more Na^+ ions outside the cell** than inside and **more K^+ ions inside** than outside. Also, the inside of a resting neuron is more negative than the outside of the cell, at **-70 mV**.

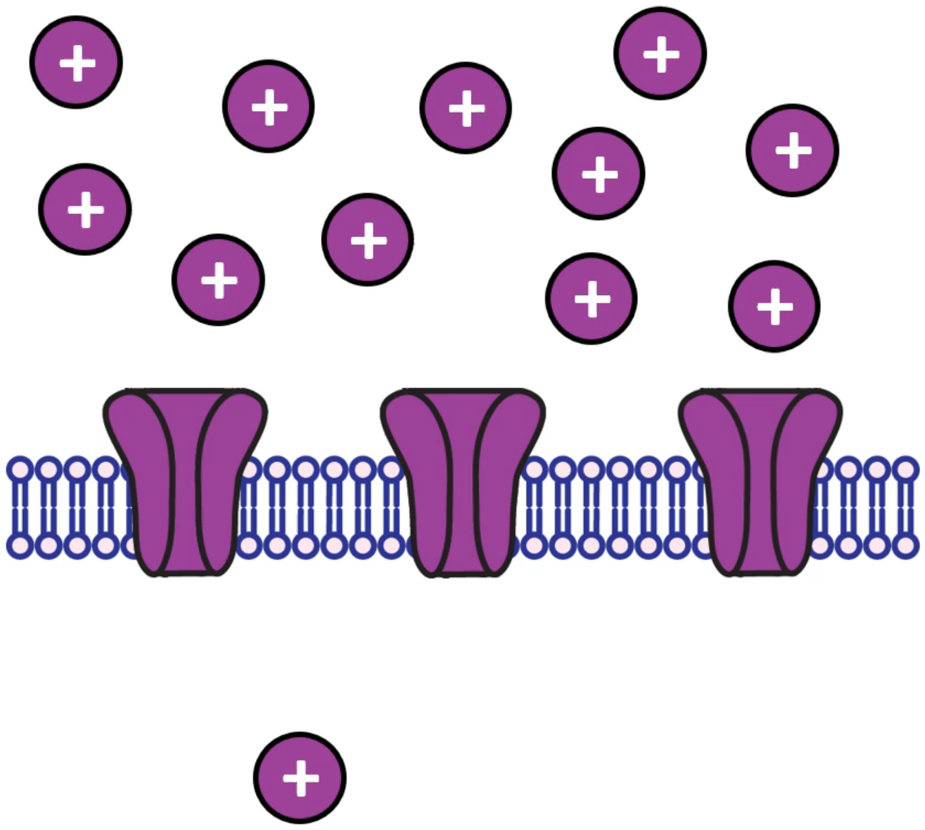
The Na^+ ions are under pressure to enter the cell, for two reasons:

(1) => ions have a tendency to become equally distributed by moving down their **concentration gradients** (i.e., from high to low concentration)

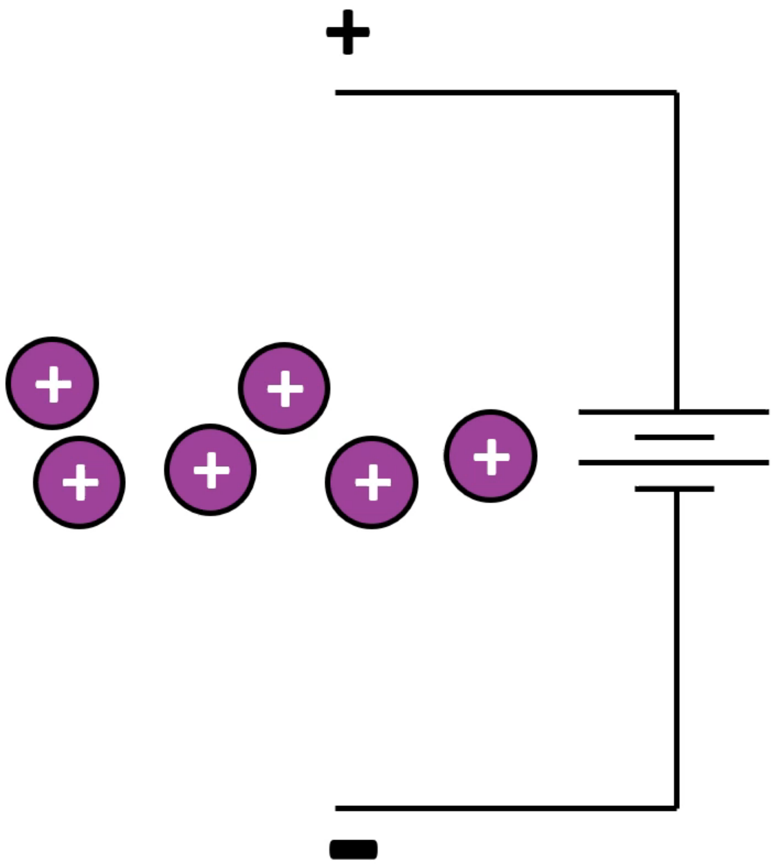
(2) **electrostatic pressure** => ions are attracted to an opposite charge

=> Na^+ ions (being positively charged) are attracted to the negative charge inside the cell

Concentration Gradient

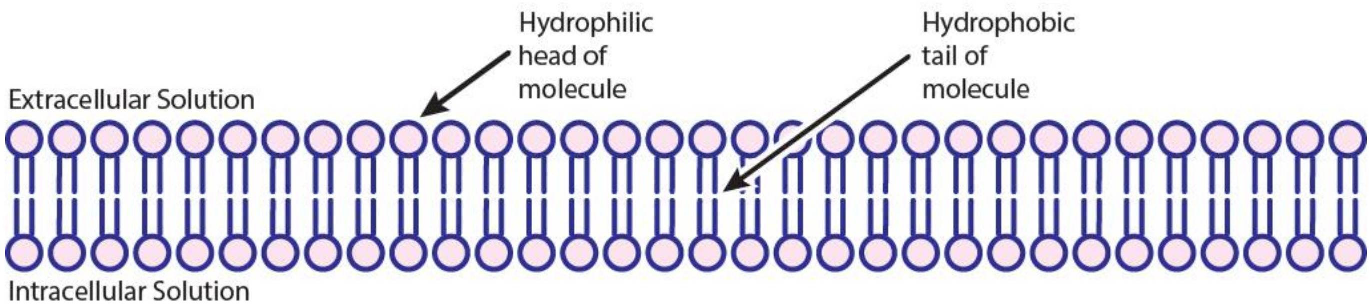


Electrical Gradient

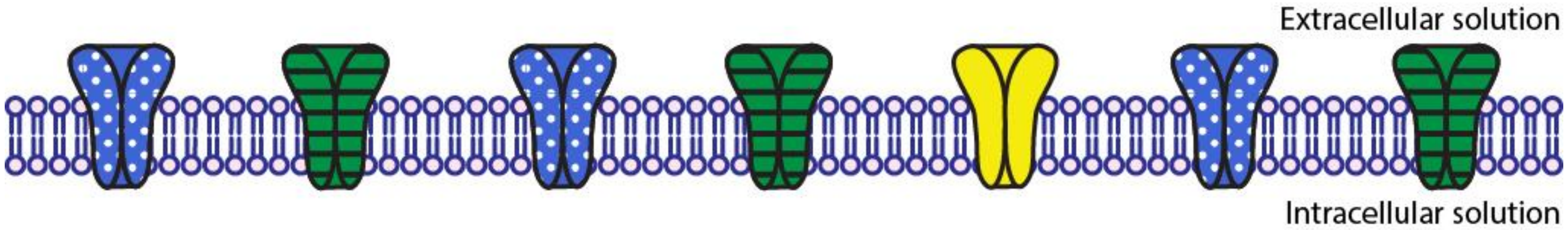


https://openbooks.lib.msu.edu/neuroscience/chapter/ion-movement/

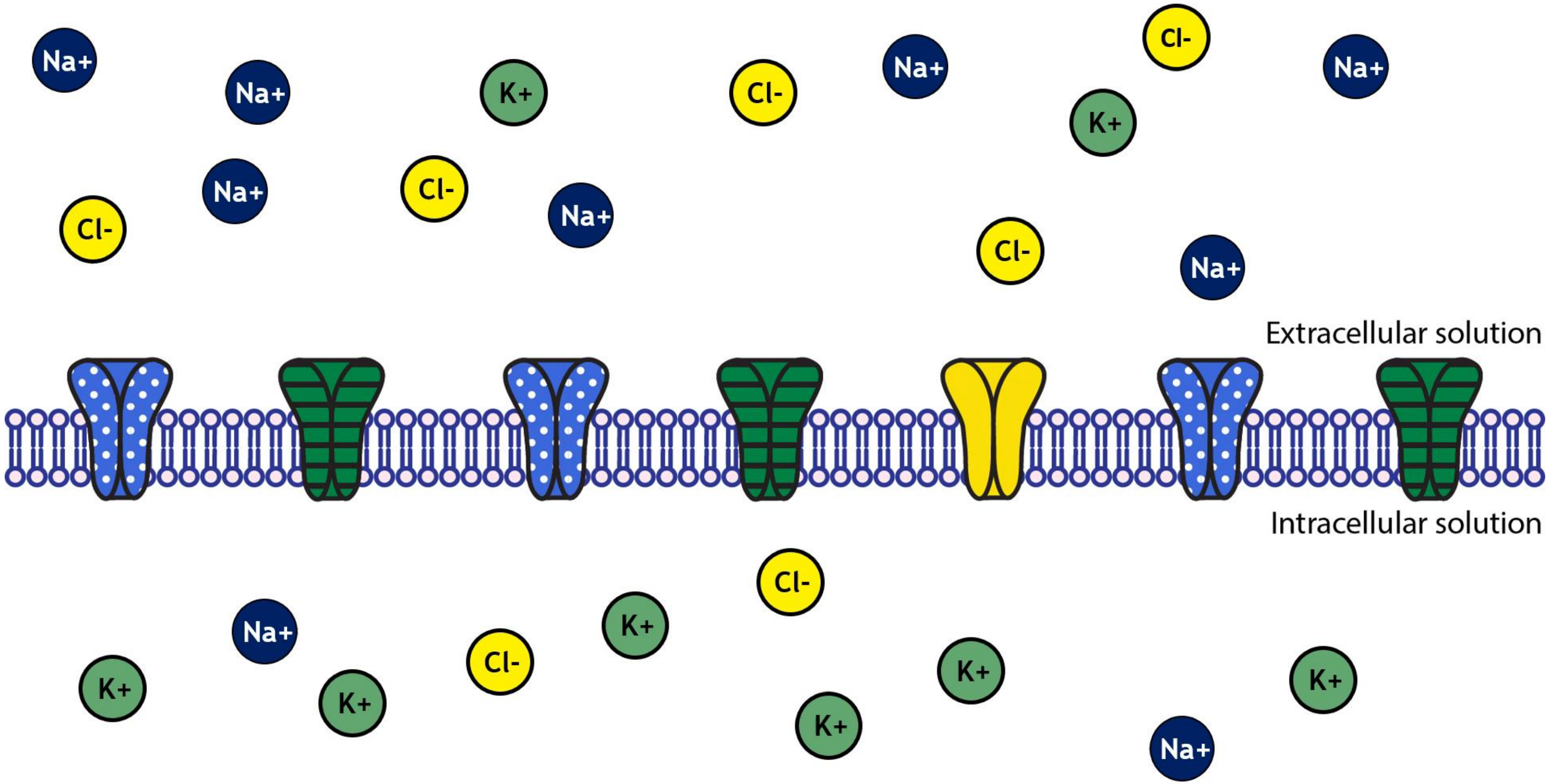
The cell membrane is **impermeable** to the passage of ions.



The cell membrane is lined with **ion channels** (i.e., proteins that span the width of the cell membrane). Ions can however move in and out of the cell only when the ion channels are **open**. Channels that open and close **spontaneously** are called **leak** or **non-gated channels**. Channels that open in response to a **change in membrane potential** are called **voltage-gated**.

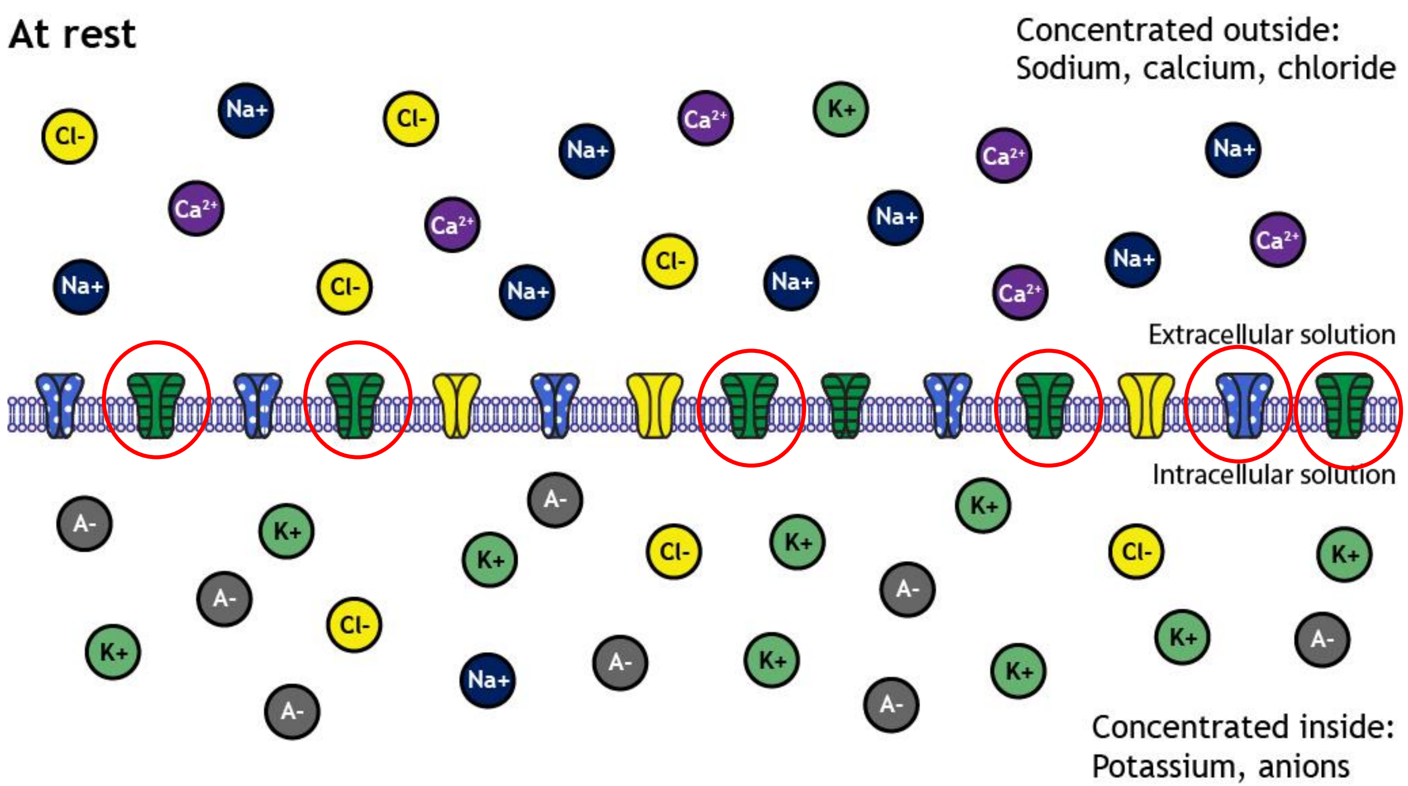


Images source: https://openbooks.lib.msu.edu/neuroscience/chapter/ion-movement/



https://openbooks.lib.msu.edu/neuroscience/chapter/ion-movement/

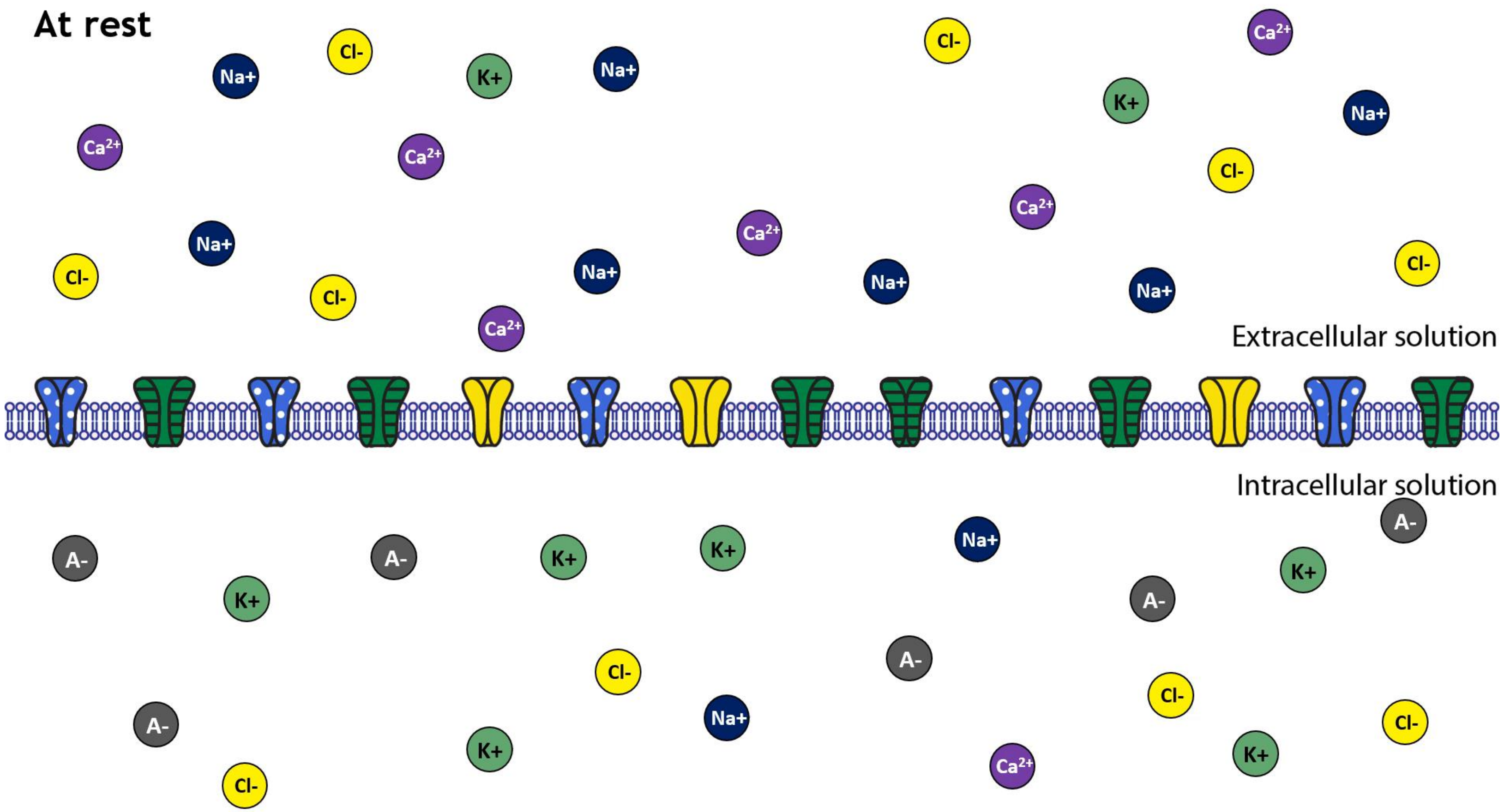
Resting membrane potential



At rest, the **inside** of the cell is **more negatively charged** (-70 mV) compared to the outside, due to the abundance of **anions**.

When the membrane is at rest, **many K^+** leak ion channels are open. Other leak ion channels are also open, though **fewer** than those for potassium; permeability for chloride is ~ half that for potassium, and permeability for sodium is ~ 25 to 40 times less than that of potassium.

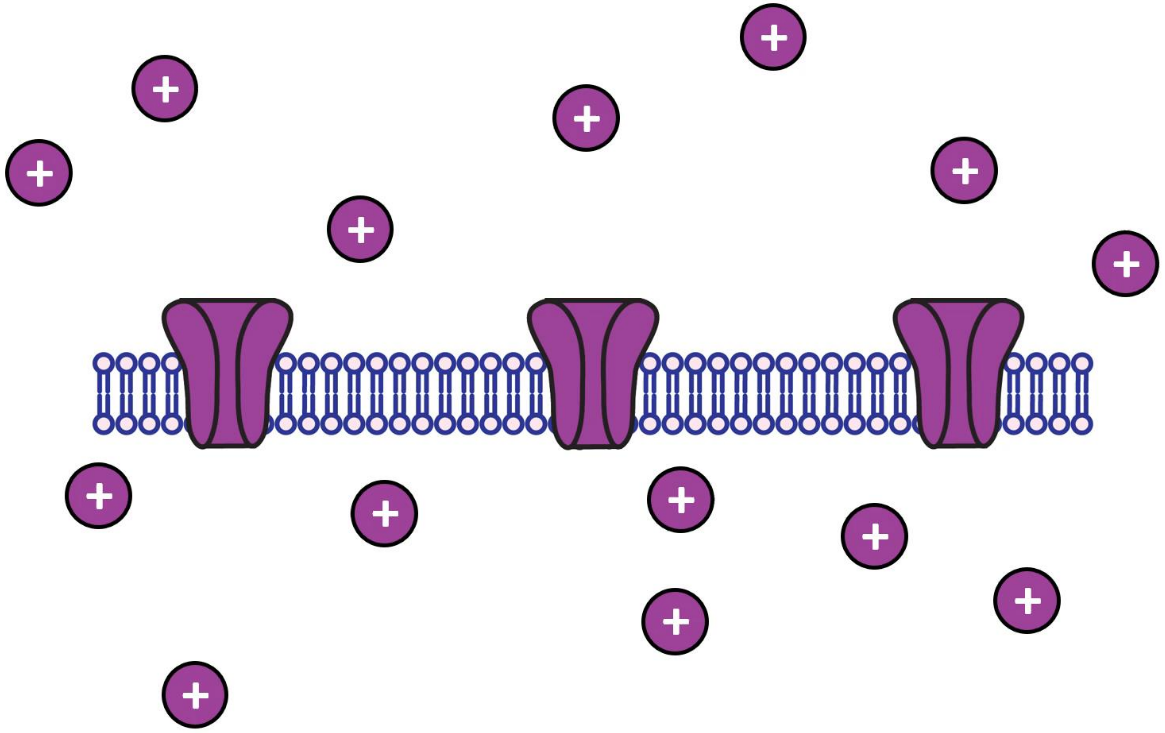
https://openbooks.lib.msu.edu/neuroscience/chapter/the-membrane-at-rest/



https://openbooks.lib.msu.edu/neuroscience/chapter/the-membrane-at-rest/

Due to many K^+ leak ion channels being open, there is an **efflux of potassium** from inside the cell. The **equilibrium potential** for potassium is -80 mV, so K^+ ions will move according to the electrochemical gradient towards this equilibrium.

The membrane resting potential remains nevertheless -70 mV due to other leak ion channels also being open (e.g., Cl^-)



https://openbooks.lib.msu.edu/neuroscience/chapter/ion-movement/

equilibrium

when the concentration and electrical gradients acting on the ion achieve balance

At equilibrium, ions still move across the membrane through open channels, but there is **no net movement** in either direction (i.e., an equal number of ions move into and out of the cell).

In the animation on the left, there are seven cations on either side of the membrane, before and after they move across the membrane.

How do we know all this?

J Physiol. 2012 Jun 1; 590(Pt 11): 2571–2575.
Published online 2012 May 31. doi: 10.1113/jphysiol.2012.230458

PMCID: PMC3424716
PMID: 22787170

A brief historical perspective: Hodgkin and Huxley

Christof J Schwiening

Working together in 1939, and again from 1946 to 1952, Alan Hodgkin and Andrew Huxley formed one of the most productive and influential collaborations in the history of physiology. Their work, both in the Physiological Laboratory in Cambridge and at the Laboratory of the Marine Biological Association in Plymouth, provided fundamental insights into nerve cell excitability. Their legacy is not only our understanding of how voltage-gated ion channels give rise to propagating action potentials, but also the very framework for studying and analysing ion channel kinetics. Their work won them a share of the 1963 Nobel Prize in Physiology or Medicine (Fig. 1) as well as laying the foundations for other Nobel Prize-winning work including that of Erwin Neher and Bert Sakmann 'for their discoveries concerning the function of single ion channels in cells' and Roderick MacKinnon 'for structural and mechanistic studies of ion channels'.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3424716/

Fig. 1. The cover of the 1963 Nobel Prize Programme

The dissection of the squid giant axon
https://vimeo.com/345423415

https://www.youtube.com/watch?v=k48jXzFGMc8

The squid giant axon can be **up to 1.5 mm in diameter** => easier to manipulate and visualize

Given this constant inflow and outflow of ions, how is the resting membrane potential maintained?

The Nobel Prize in Chemistry 1997

Paul D. Boyer
John E. Walker
Jens C. Skou

Share this

Jens C. Skou
Facts

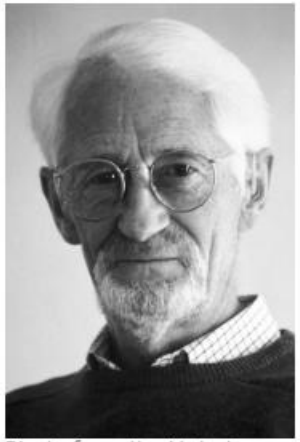


Photo from the Nobel Foundation archive.

Jens C. Skou
The Nobel Prize in Chemistry 1997

Born: 8 October 1918, Lemvig, Denmark

Died: 28 May 2018, Aarhus, Denmark

Affiliation at the time of the award: Aarhus University, Aarhus, Denmark

Prize motivation: “for the first discovery of an ion-transporting enzyme, Na+, K+ -ATPase”

Prize share: 1/2

Work

Many of the cell’s functions, such as those concerned with nerve impulses, muscular contractions and digestion, require that the concentration of potassium ions inside the cell is higher than outside it, whereas the concentration of sodium ions must be lower inside than outside. It takes a great deal of energy to bring this about. The energy is stored in a special substance, adenosine triphosphate (ATP). In 1957 Jens Christian Skou discovered an enzyme, Na+/K+-ATPase, that serves as a sort of biological pump to transport ions.

https://www.nobelprize.org/prizes/chemistry/1997/skou/facts/

Na+/K+-ATPase pump

(or simply, **sodium-potassium pump**)

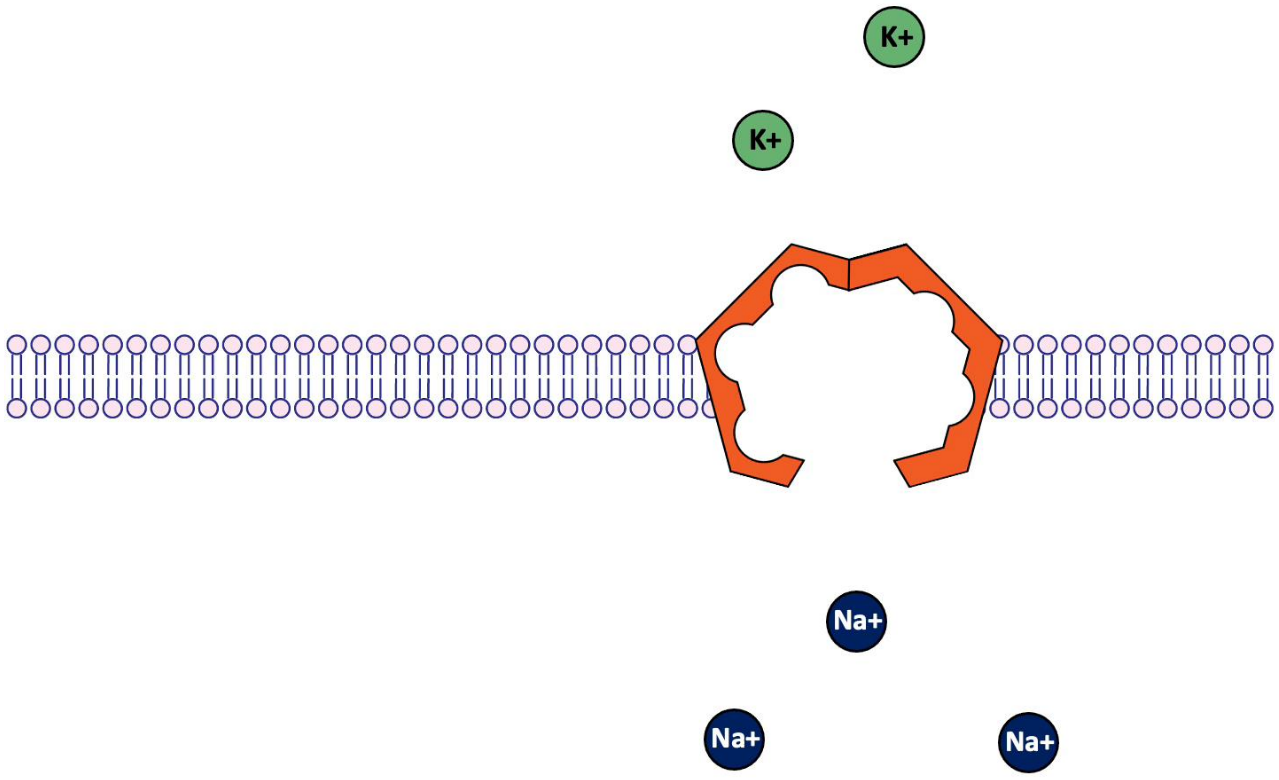
is an **enzyme** (an **electrogenic transmembrane ATPase**) found in the membrane of all animal cells

** remember ATP from our previous lecture: this was the molecule produced in the cell mitochondria to store the energy necessary to the cell*

ATPase

the **enzyme** that breaks down the ATP molecule to release the energy necessary for certain processes

The sodium-potassium pump allows **3 Na^+ ions to exit** the cell for every **2 K^+ ions that enter** the cell



https://openbooks.lib.msu.edu/neuroscience/chapter/the-membrane-at-rest/

Note that the ATPase enzyme breaks off one of the three phosphates of the ATP molecule into **ADP (Adenosine di-phosphate) + phosphate**. The energy holding that phosphate molecule is now released and available to do work for the cell.

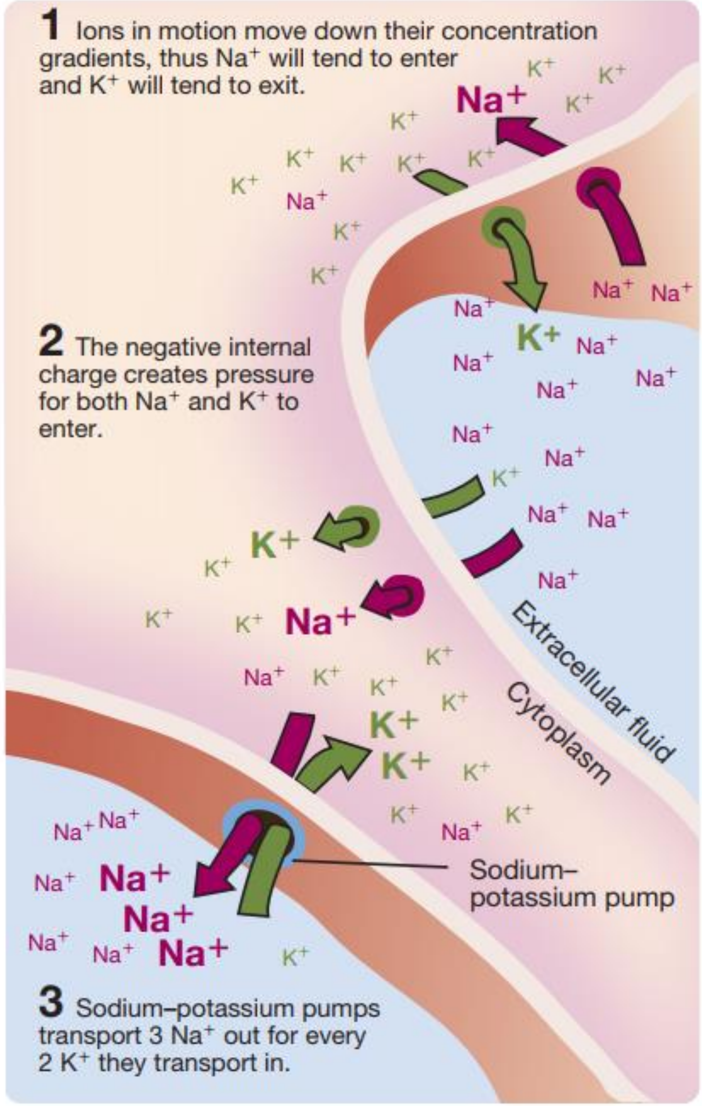
There are two steps to this process:

(1) ATP => ADP => conformational change of the pump; the intracellular side closes, and the extracellular side opens => 3 Na^+ ions leave the pump, while 2 extracellular K^+ ions enter;

(2) The attached phosphate molecule leaves => the pump opens toward the inside of the neuron => the K^+ ions leave, and the cycle begins again.

There are important **differences** between ion channels and ion pumps

Figure 4.1 Three factors that influence the distribution of Na^+ and K^+ ions across neural membranes, illustrated in a resting neuron.



Pinel & Barnes, (2021), p. 100

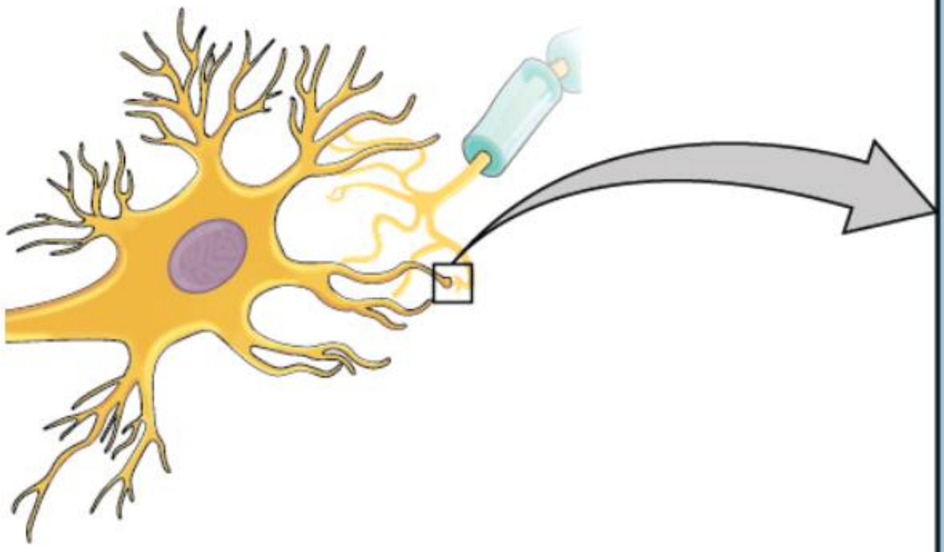
These ion pumps move ions **against** their electrical and chemical gradients.

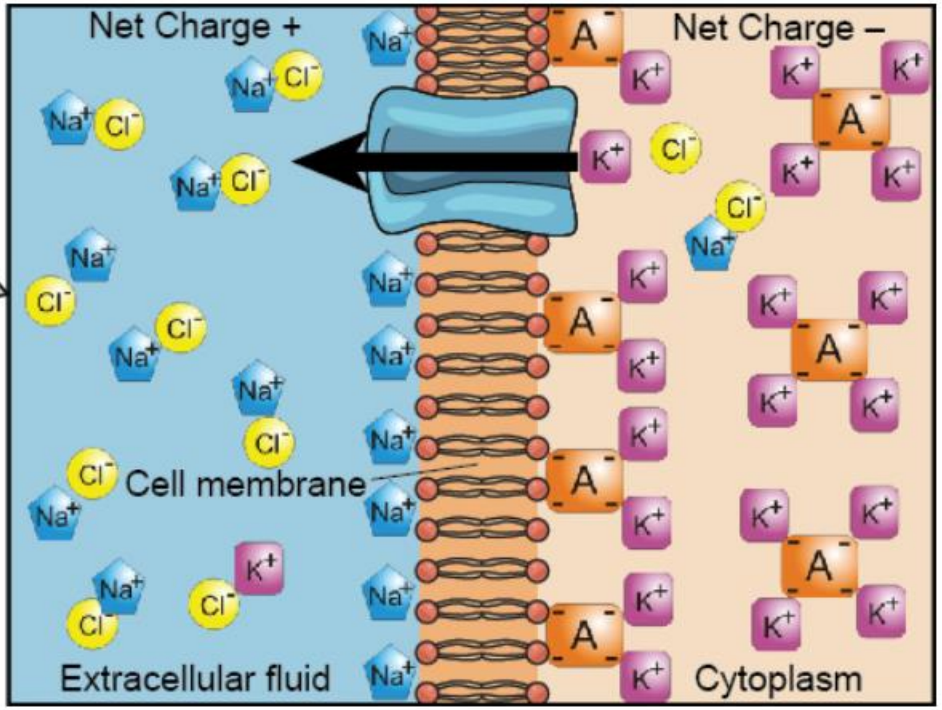
Each time a pump moves an ion or group of ions across the membrane *(active transport),* it must undergo a series of conformational changes

=> ions flow 100 to 100,000 times slower than through ion channels

=> energy consuming process

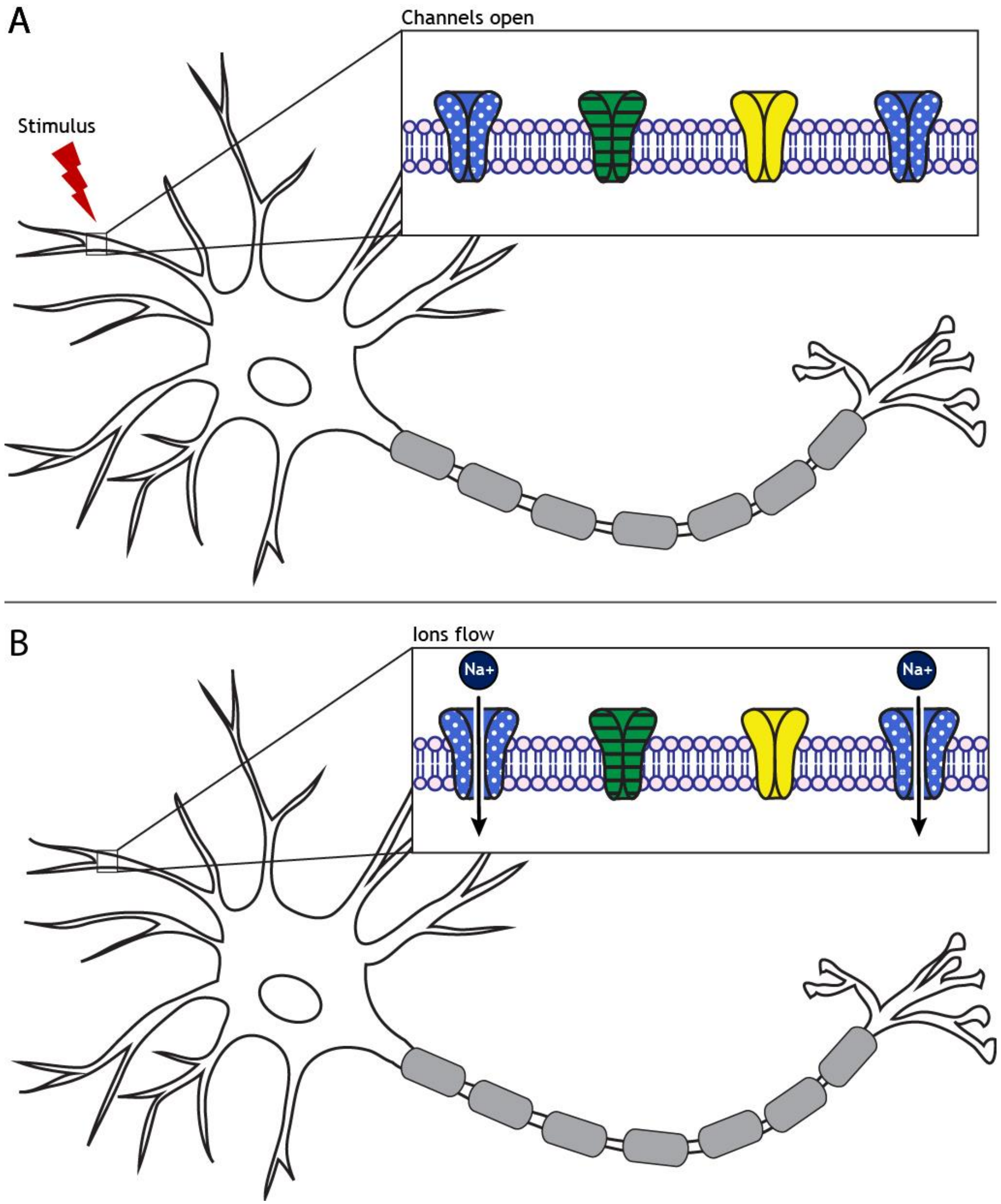
Postsynaptic potential





Spielman et al., (2020), p. 81

Remember that at rest, the net electrical **charge inside the cell is negative**, while the net electrical **charge outside the cell is positive**. Also, Na^+ is more concentrated outside the cell, while K^+ is more concentrated inside the cell. Remember also that a neuron's **resting membrane potential** is around **-70 mV**.



https://openbooks.lib.msu.edu/neuroscience/back-matter/images-of-animations/

Remember that a neuron receives input through its **dendrites**. Once the dendrites are stimulated (e.g., by the presence of neurotransmitters), the ion channels are open and ions start to flow across the cell membrane.

A **postsynaptic potential** is thus created, which reflects the shift in the membrane potential away from its resting state (i.e., moving away from -70 mV).

hyperpolarization

an increase in the membrane potential (i.e., it becomes more negative)

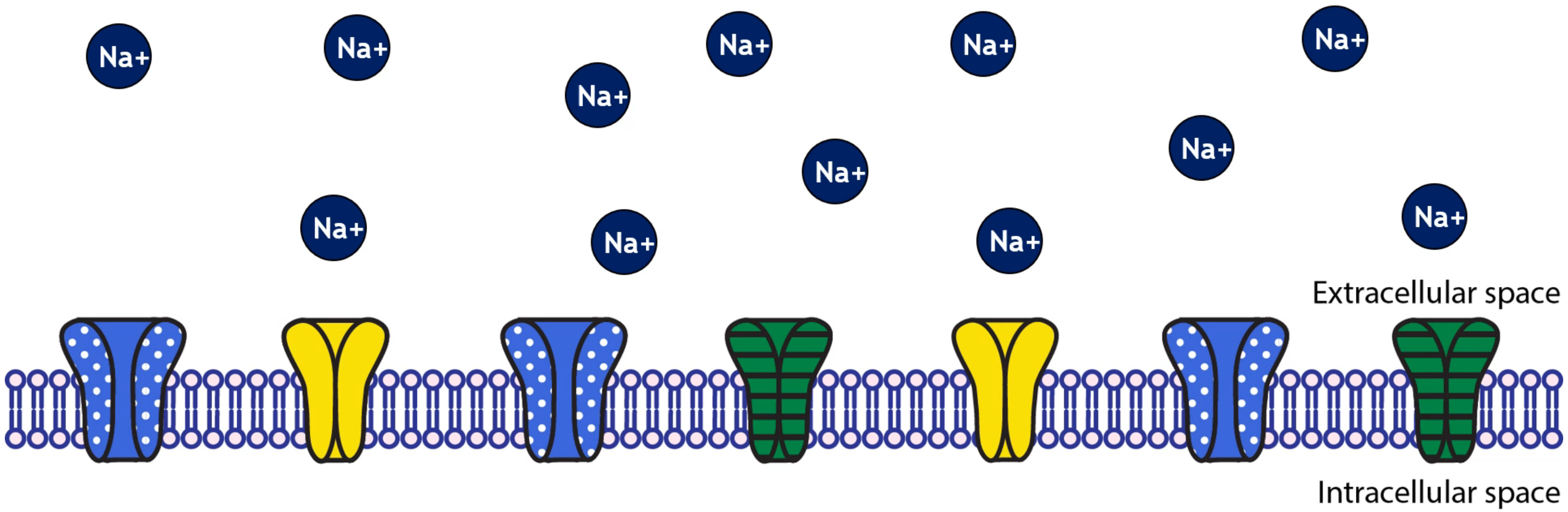
e.g., from -70 to -72 mV

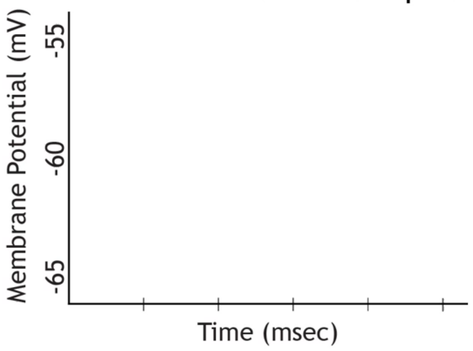
depolarization

a decrease in the membrane potential (i.e., it becomes more positive)

e.g., from -70 to -67 mV

Excitatory postsynaptic potential (**EPSP**)





Equilibrium potential of sodium: +60 mV

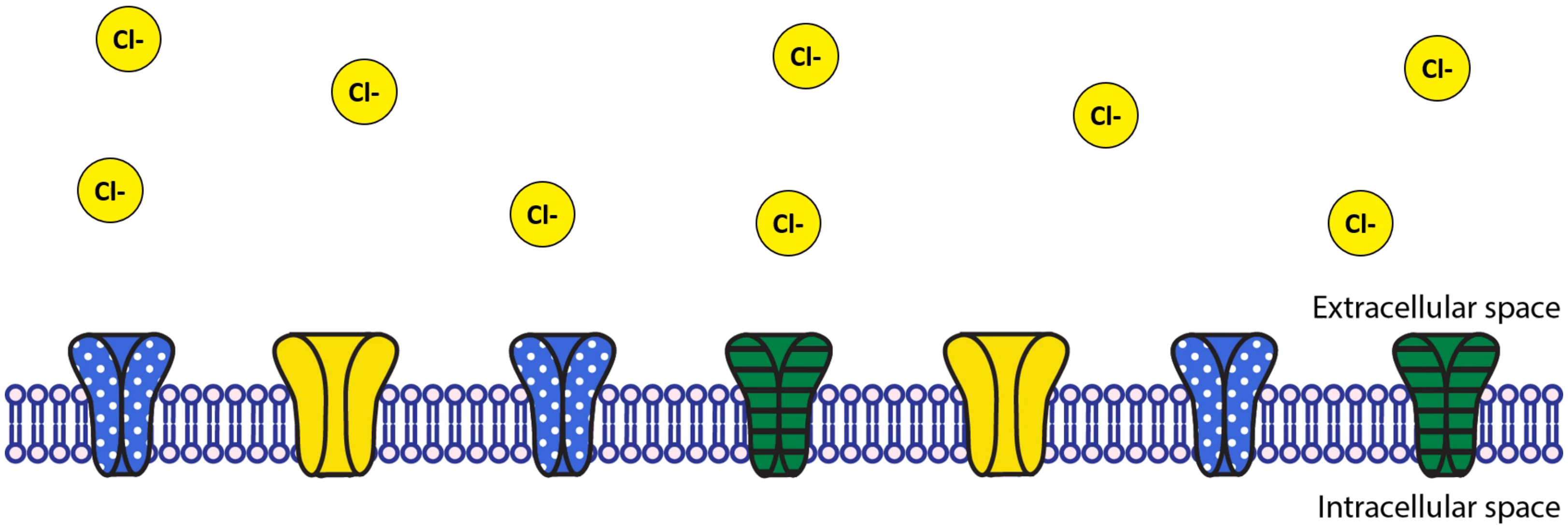
An EPSP occurs when the **sodium ion channels open** in response to a stimulus => **Na⁺ rushes into** the cell => the membrane potential becomes more positive (i.e., **depolarization**).

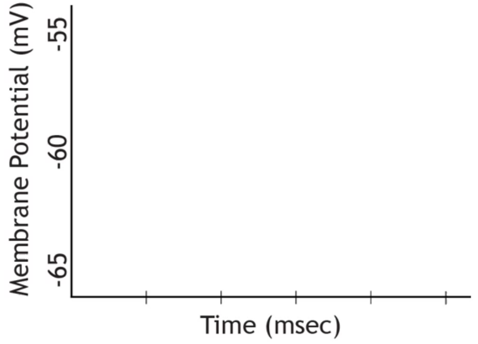
Depolarizing the membrane increases the likelihood for an **action potential** to be fired => this ion flow is **excitatory**.

https://openbooks.lib.msu.edu/neuroscience/chapter/postsynaptic-potentials/

The **threshold of excitation** (also **threshold potential**) = how depolarized a membrane must become in order for an action potential to be fired (most often around -65 mV).

Inhibitory postsynaptic potential (**IPSP**)





Equilibrium potential of chloride: -65 mV

https://openbooks.lib.msu.edu/neuroscience/chapter/postsynaptic-potentials/

An IPSP occurs when the **chloride ion channels open** in response to a stimulus => **Cl^- rushes into** the cell => the membrane potential becomes more negative (i.e., **hyperpolarization**).

Hyperpolarizing the membrane decreases the likelihood for an **action potential** to be fired => this ion flow is **inhibitory**.

All PSPs (both excitatory and inhibitory) are **graded potentials**; the amplitudes of PSPs are directly proportional to the intensity of the signals that elicit them: weak signals elicit small PSPs, and strong signals elicit large ones.

PSPs **travel quickly** (almost instantaneously) from their sites of generation (on the dendrites or cell body), but **do not travel far** (usually no more than a couple of millimetres). Furthermore, their transmission is **decremental** (i.e., it decreases in amplitude) as they travel.

PSPs are summated:

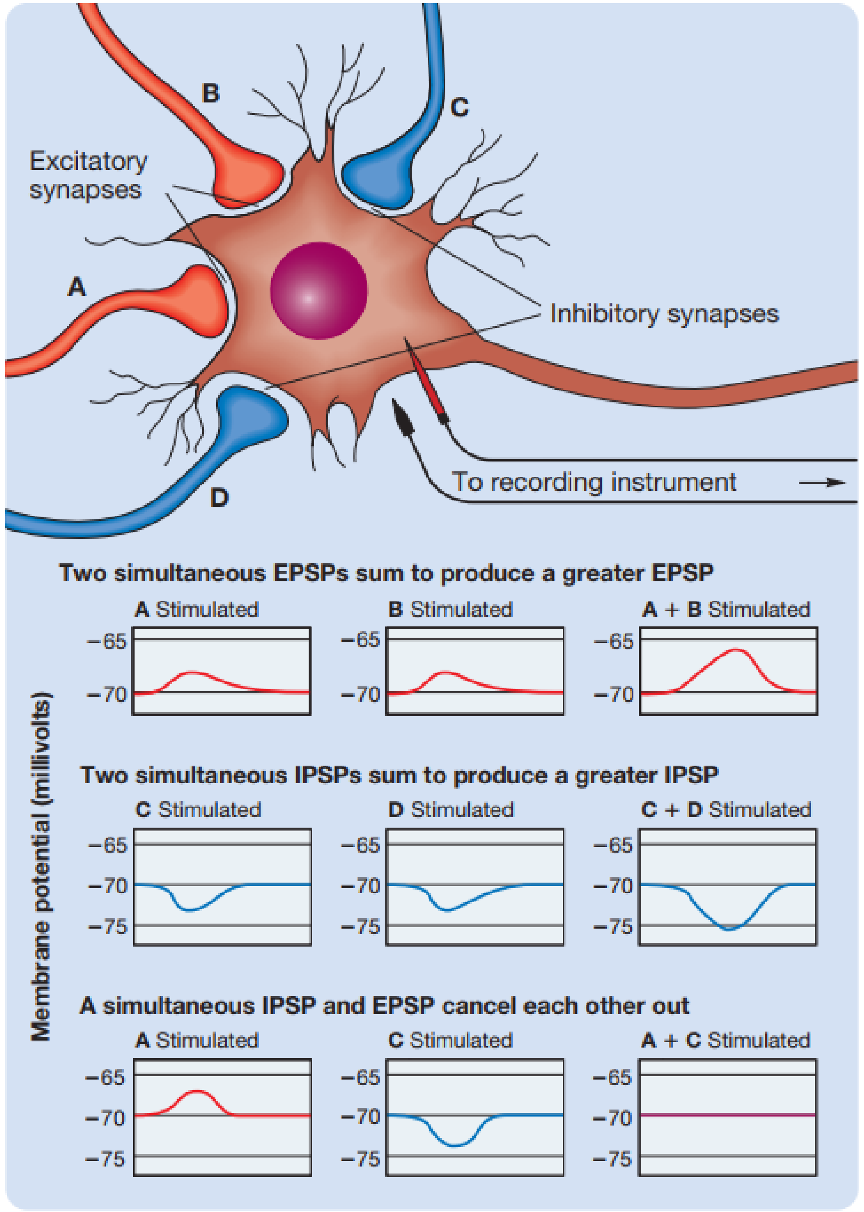
(1) **temporal** summation = one presynaptic input stimulates a postsynaptic neuron multiple times in a row;

(2) **spatial** summation = multiple presynaptic inputs each stimulate the postsynaptic neuron at the same time.

Both result in a **shift of a higher magnitude** in the membrane potential than if only one input occurred.

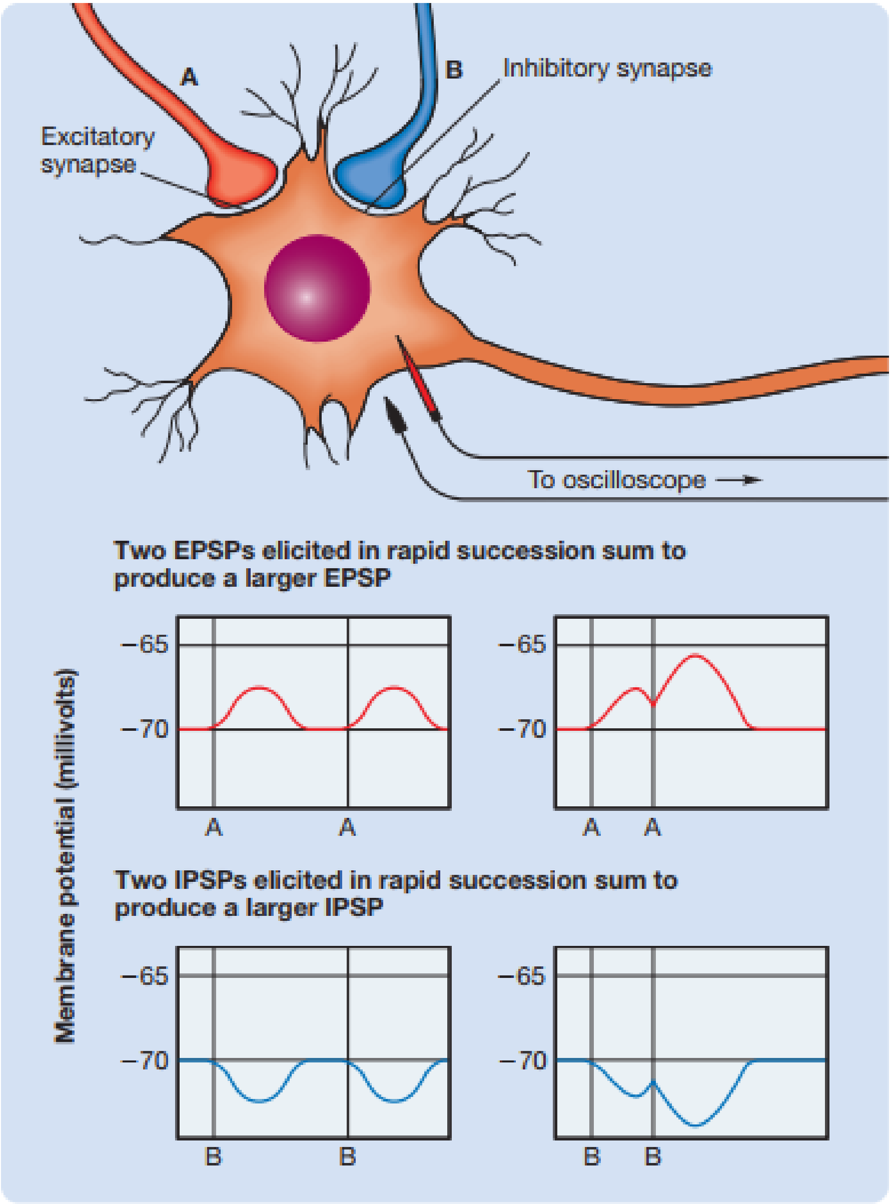
EPSPs and IPSPs ca be summated => depending on the strength of the inhibitory input: (1) either a weaker depolarization compared to a single excitatory stimulus, or (2) no depolarization at all.

Figure 4.3 The three possible combinations of spatial summation.



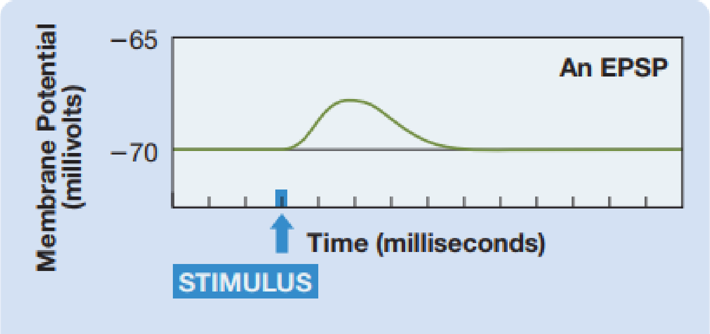
Pinel & Barnes, (2021), p. 102

Figure 4.4 The two possible combinations of temporal summation.

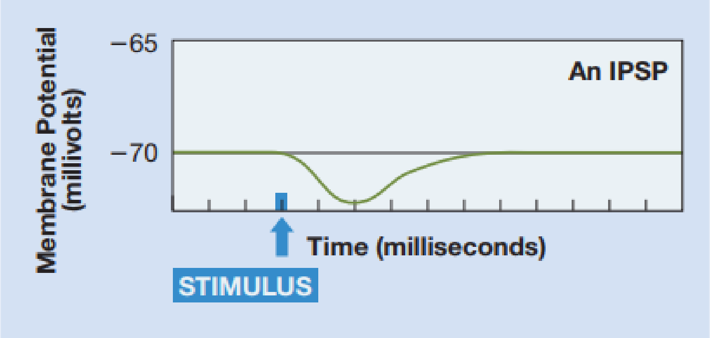


Pinel & Barnes, (2021), p. 103

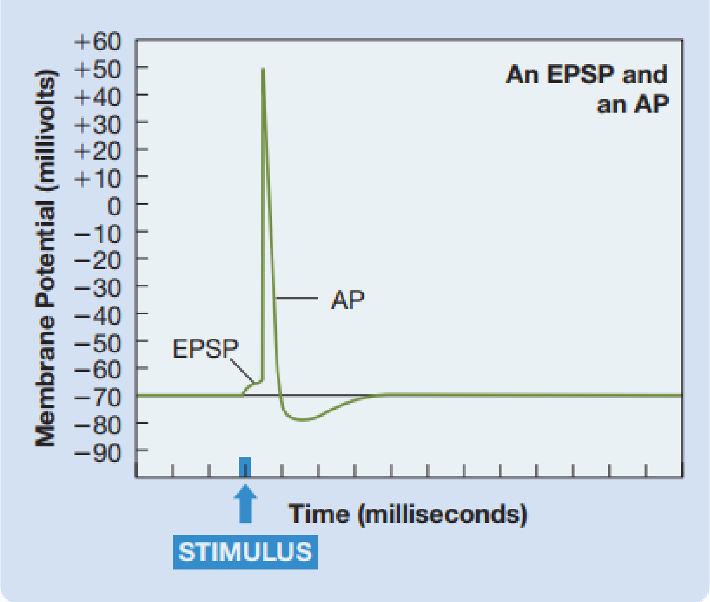
Action potential



EPSP => membrane **depolarization** (less negative)



IPSP => membrane **hyperpolarization** (more negative)



EPSP reaches the **threshold potential** => an **action potential (AP)** is initiated

Importantly

AP are not graded; they either occur or not (*all-or-none responses*)

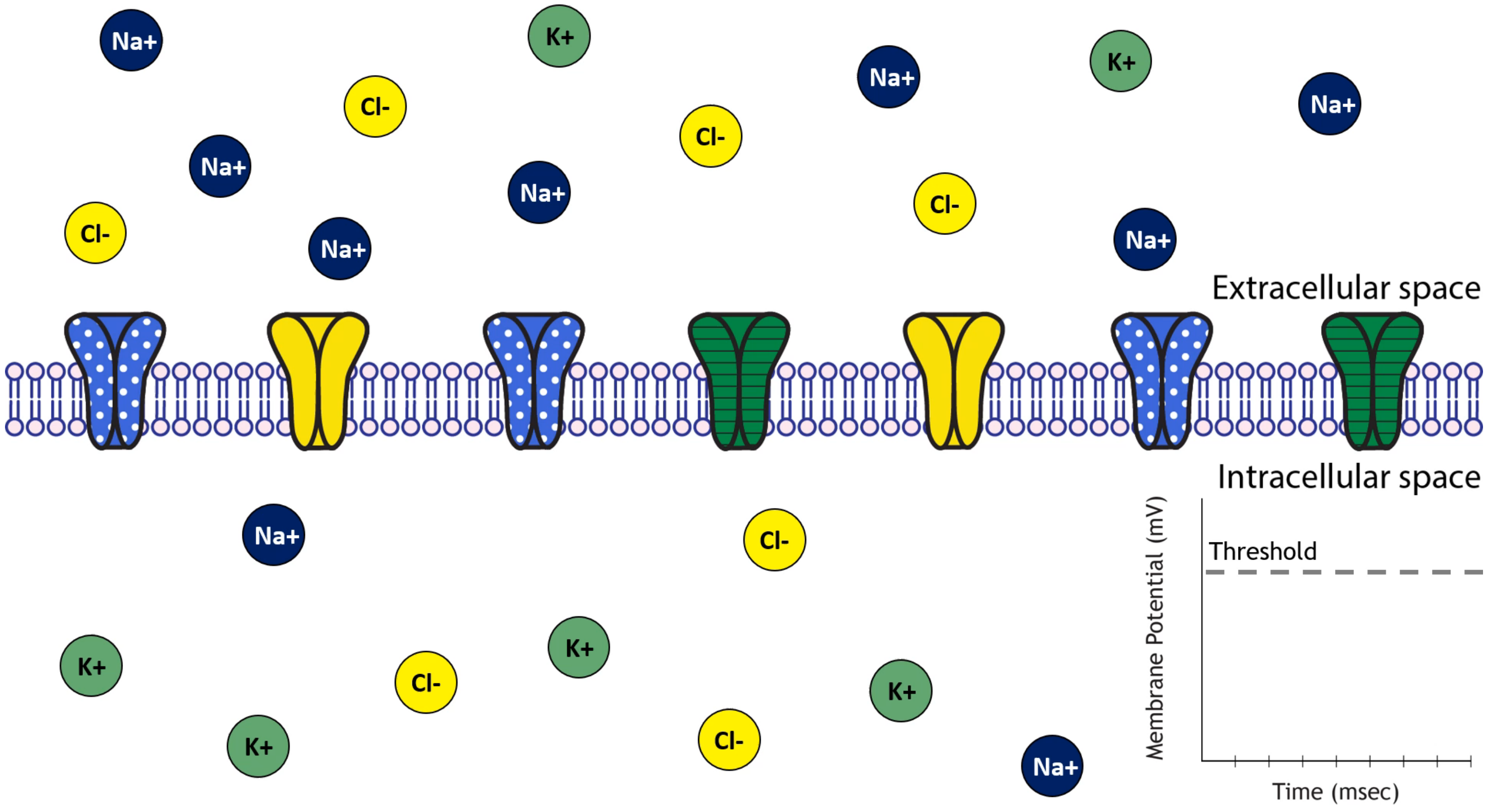
The magnitude of APs is **not related to stimulus intensity**

Very brief ~ 1 ms

Massive reversal of the membrane potential from ~ -70 to ~ +50 mV

Pinel & Barnes, (2021), p. 101

Voltage-gated ion channels

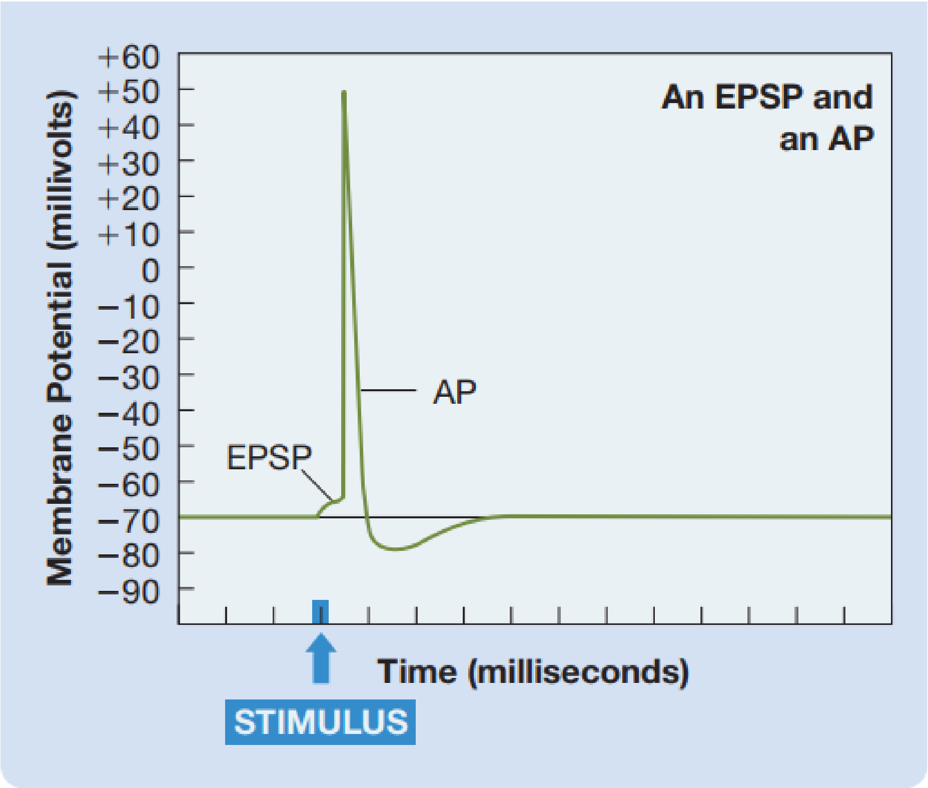


They require a **change in membrane potential** in order to open and allow the flow of ions across the membrane. This change in membrane potential must reach the **threshold potential**.

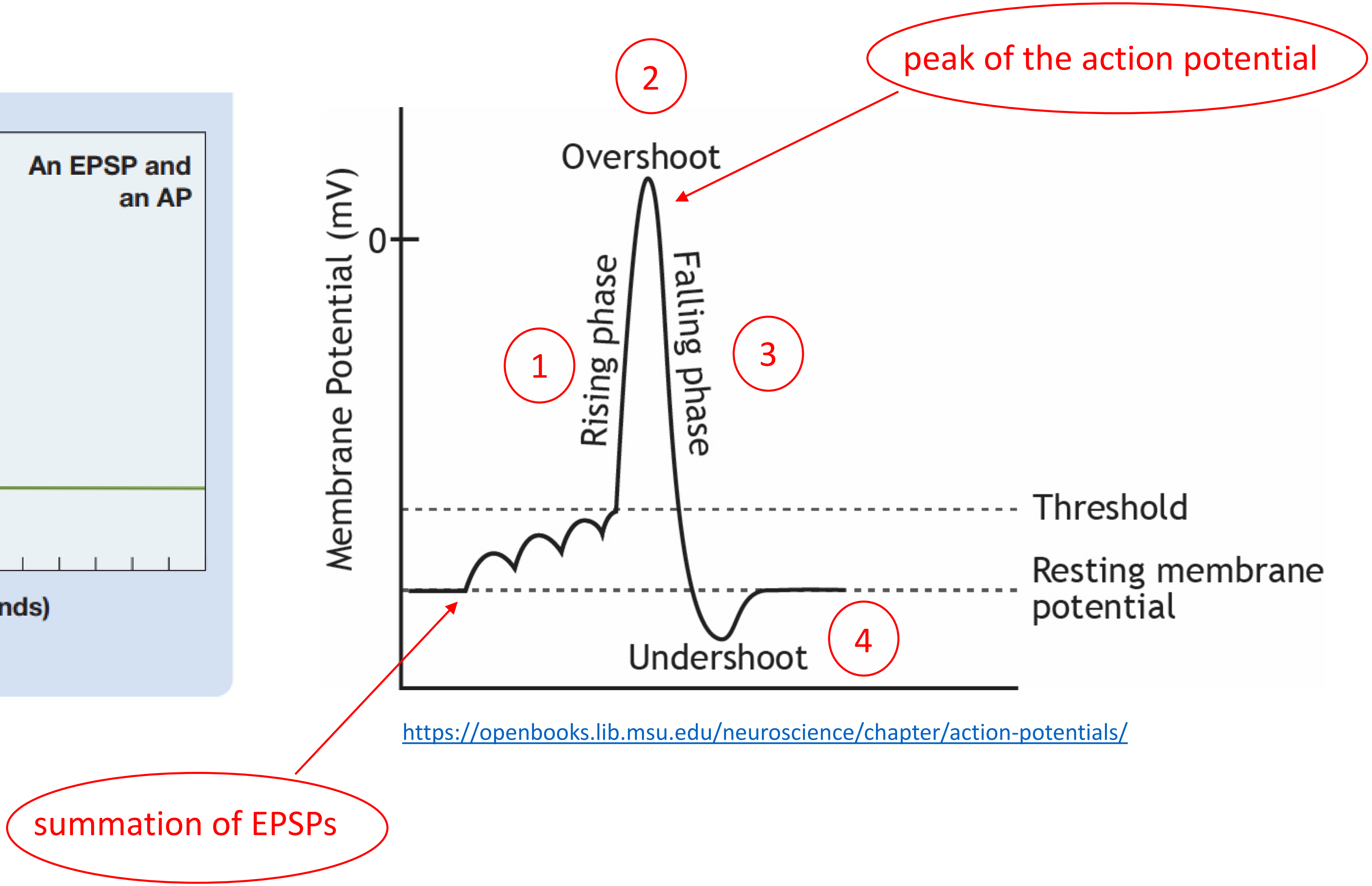
The activity of voltage-gated ion channels determine the phases of the AP.

https://openbooks.lib.msu.edu/neuroscience/chapter/action-potentials/

Phases of the AP

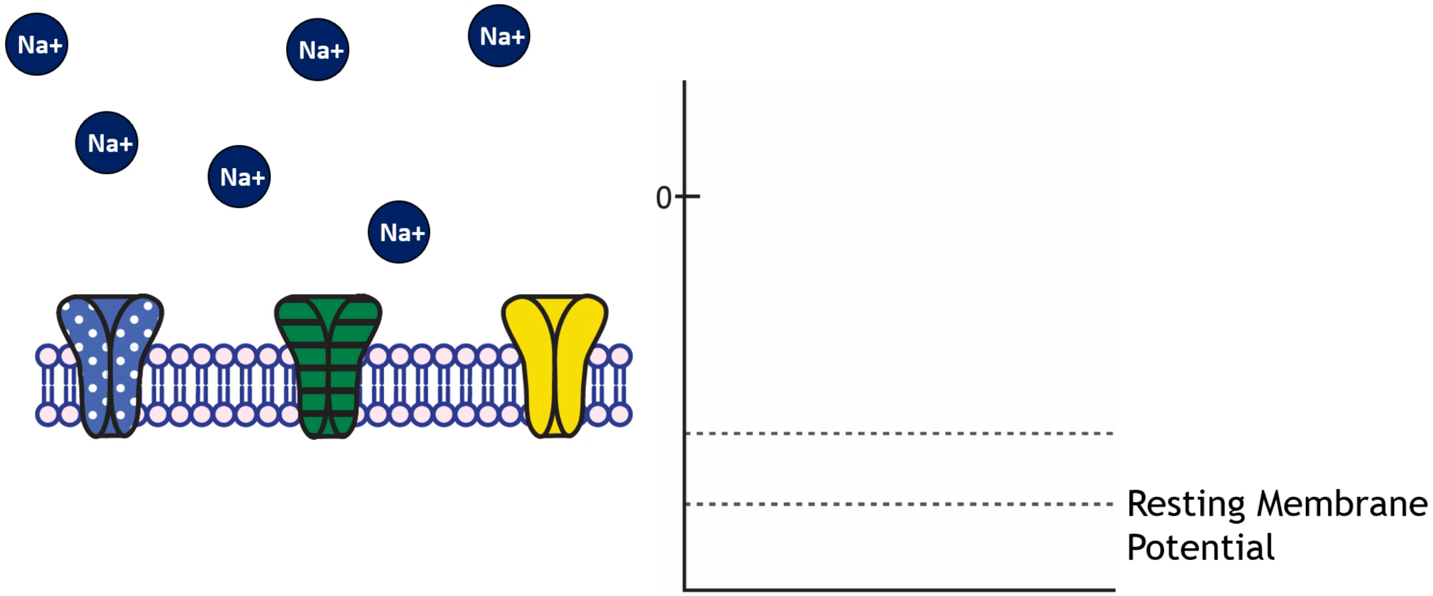


Pinel & Barnes, (2021), p. 101



https://openbooks.lib.msu.edu/neuroscience/chapter/action-potentials/

The rising phase



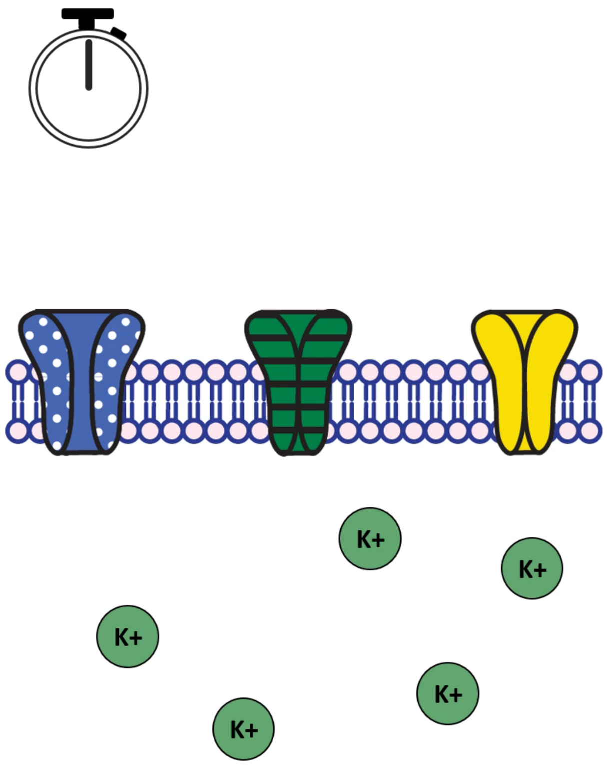
EPSPs summate until the membrane reaches the **threshold potential**.

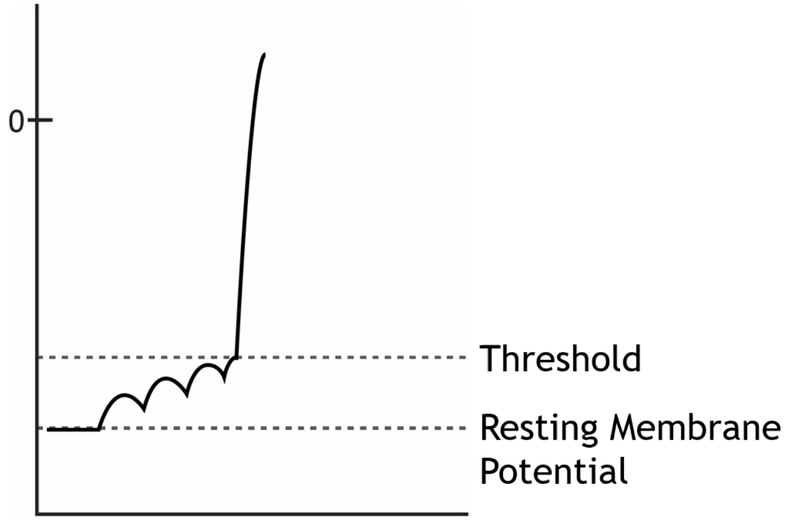
This causes the **voltage-gated Na^+ ion channels** to **open** and allow Na^+ ions into the cell.

This influx of Na^+ ions causes a **large depolarization** of the membrane (i.e., the **rising phase**).

https://openbooks.lib.msu.edu/neuroscience/chapter/action-potentials/

The falling phase



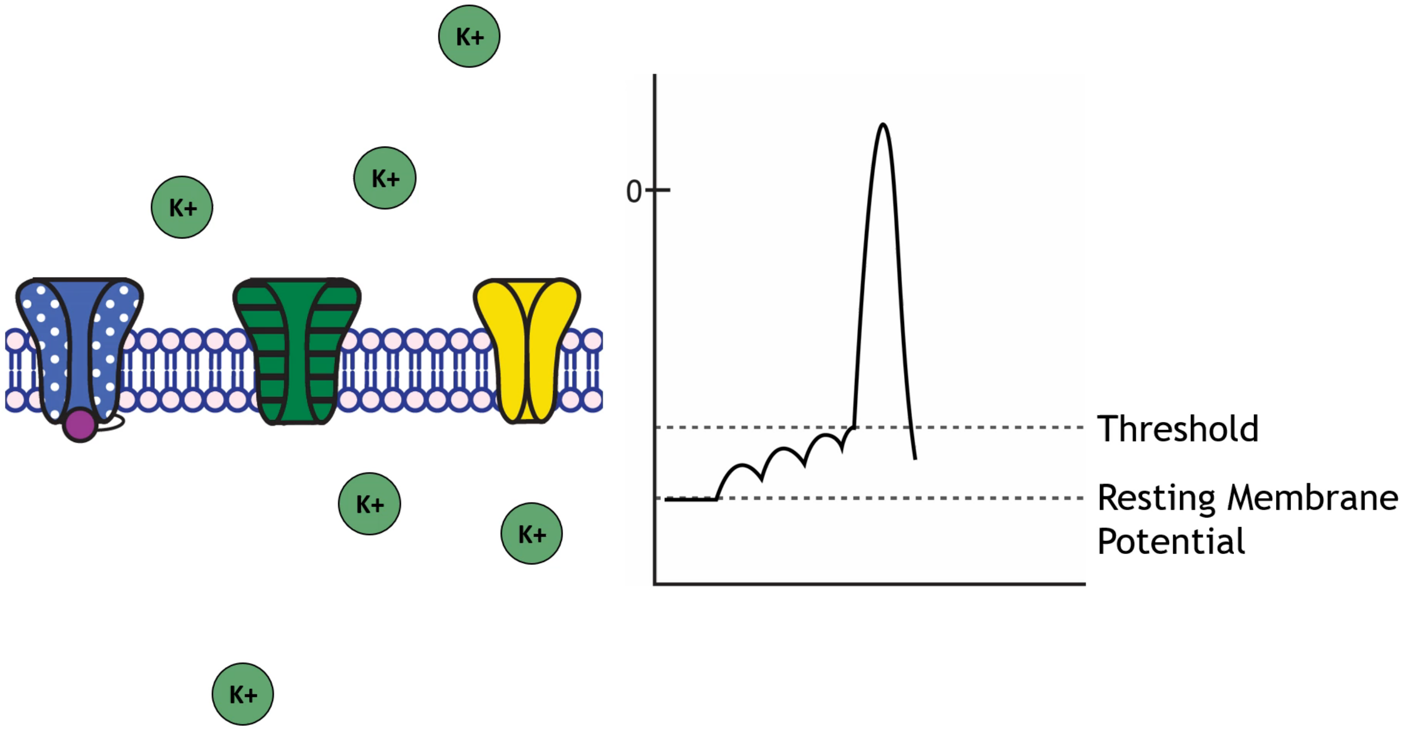


Approximately **1 ms after** the rising phase, **voltage-gated Na^+** ion channels become **inactivated**, and **voltage-gated K^+** ion channels now **open**. This allows K^+ ions to exit the cell.

This outflow of cations drives the membrane potential back towards its resting potential (i.e., **repolarization**).

https://openbooks.lib.msu.edu/neuroscience/chapter/action-potentials/

Undershoot

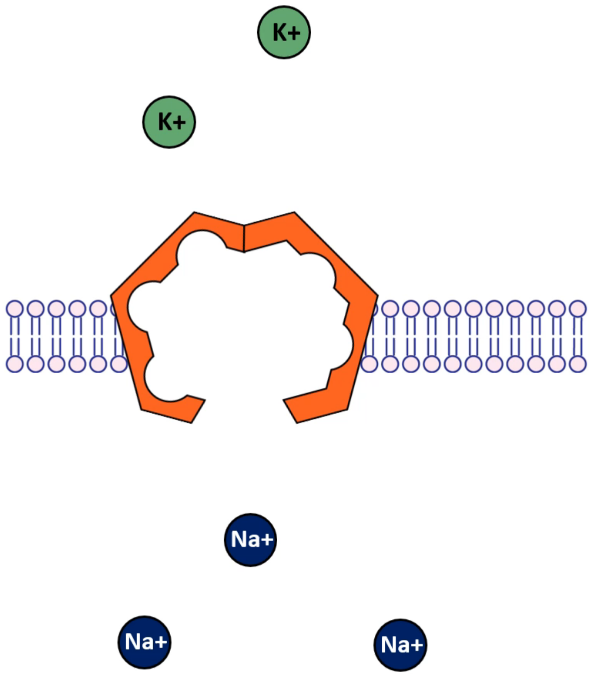


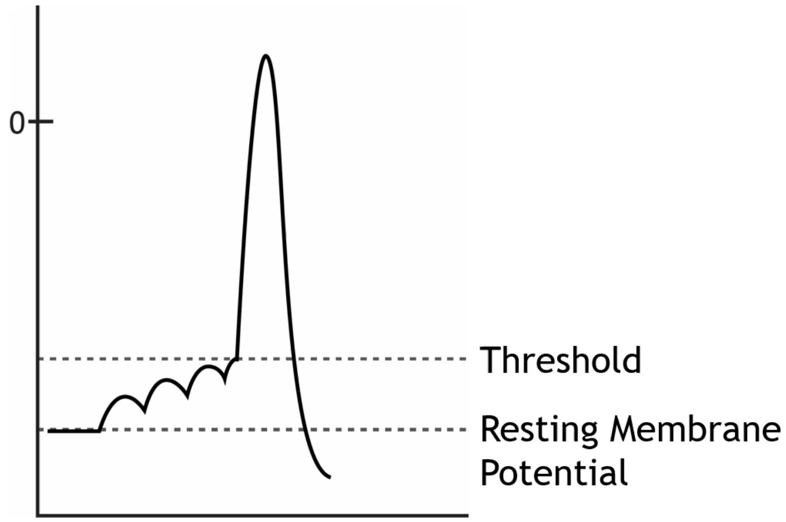
As the membrane potential reverts to its resting potential, voltage-gated Na+ ion channels switch from being inactivated to being **closed**.

Voltage-gated K^+ ion channels remain open for a little while longer, enough to cause a **further hyperpolarization** of the membrane, below the resting potential and towards the **equilibrium potential of potassium** of -80 mV.

https://openbooks.lib.msu.edu/neuroscience/chapter/action-potentials/

Return to rest



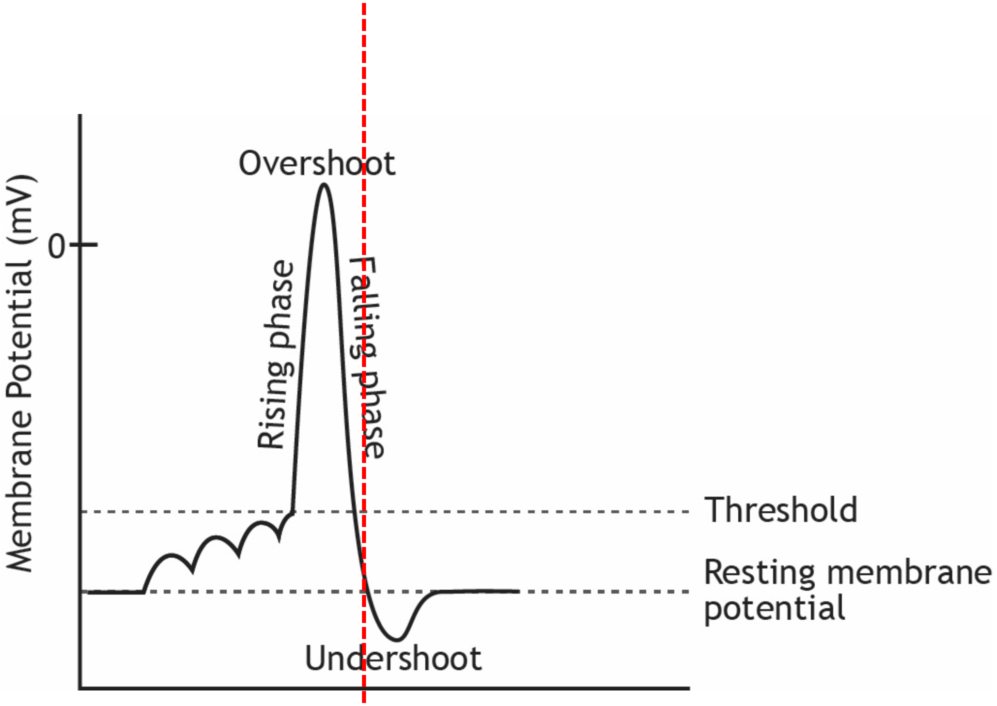


Once the voltage-gated channels close, the **sodium-potassium pumps** reestablish the proper ionic concentrations needed for the electrochemical gradients.

This action along with **open leak ion channels** in the membrane will return the cell to its **resting membrane potential**, ready to fire another action potential.

https://openbooks.lib.msu.edu/neuroscience/chapter/action-potentials/

The refractory period



absolute refractory period

due to **inactivated Na⁺** channels

no new AP can be initiated

relative refractory period

due to continued outward **diffusion of K⁺**

a new AP can be initiated given a strong enough EPSP (and a **stronger stimulus**)

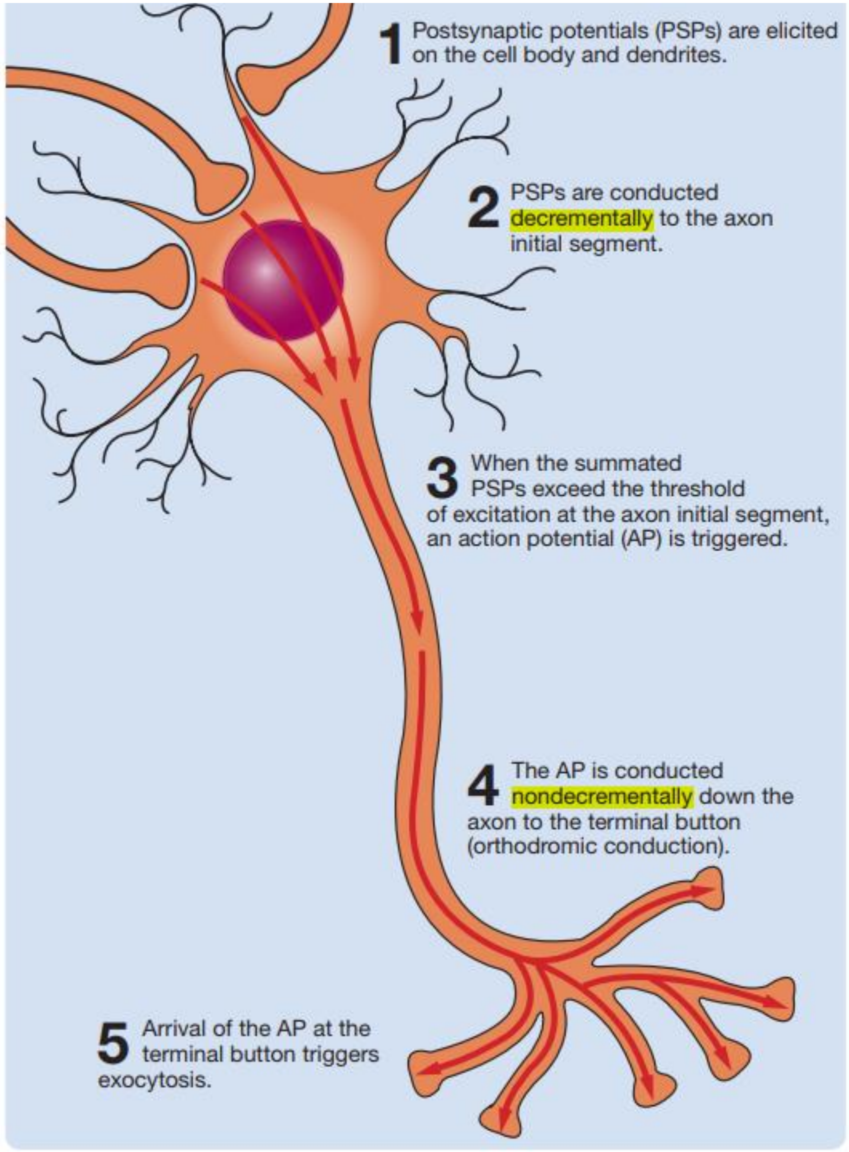
During the **falling phase**, the AP leaves the voltage-gated Na^+ ion channels inactivated and the voltage-gated K^+ ion channels activated for a brief time. These transitory changes make it harder for the axon to produce subsequent APs during this interval. This is called the **refractory period**.

This limits the number of APs that a neuron can produce per unit time. Different types of neurons have different **maximum rates of action potential firing** due to different types and densities of ion channels.

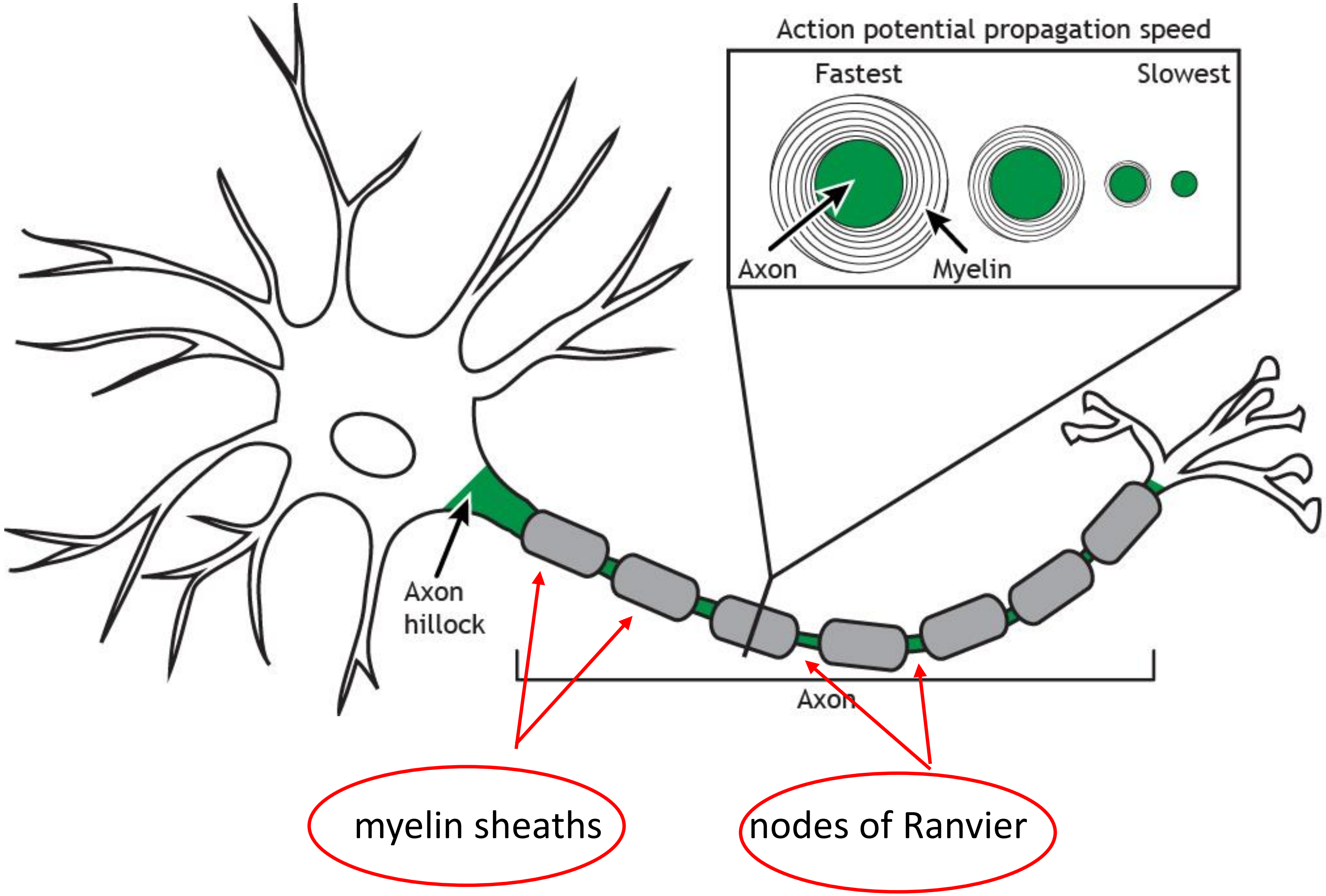
The refractoriness of the membrane explains why APs do not propagate back toward the point of their initiation as they travel along an axon.

AP propagation along the axon

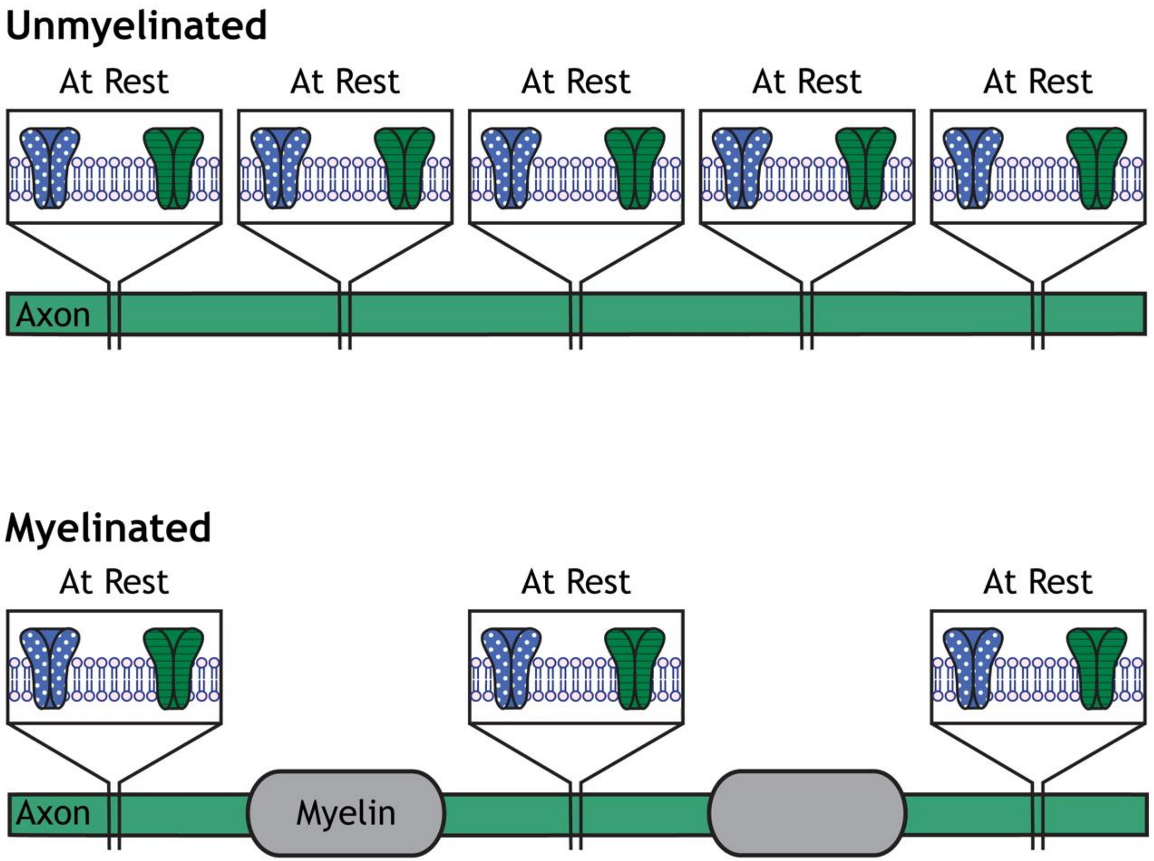
Figure 4.6 The usual direction of signals conducted through a multipolar neuron (i.e., orthodromic conduction).



Pinel & Barnes, (2021), p. 106



https://openbooks.lib.msu.edu/neuroscience/chapter/action-potentials/



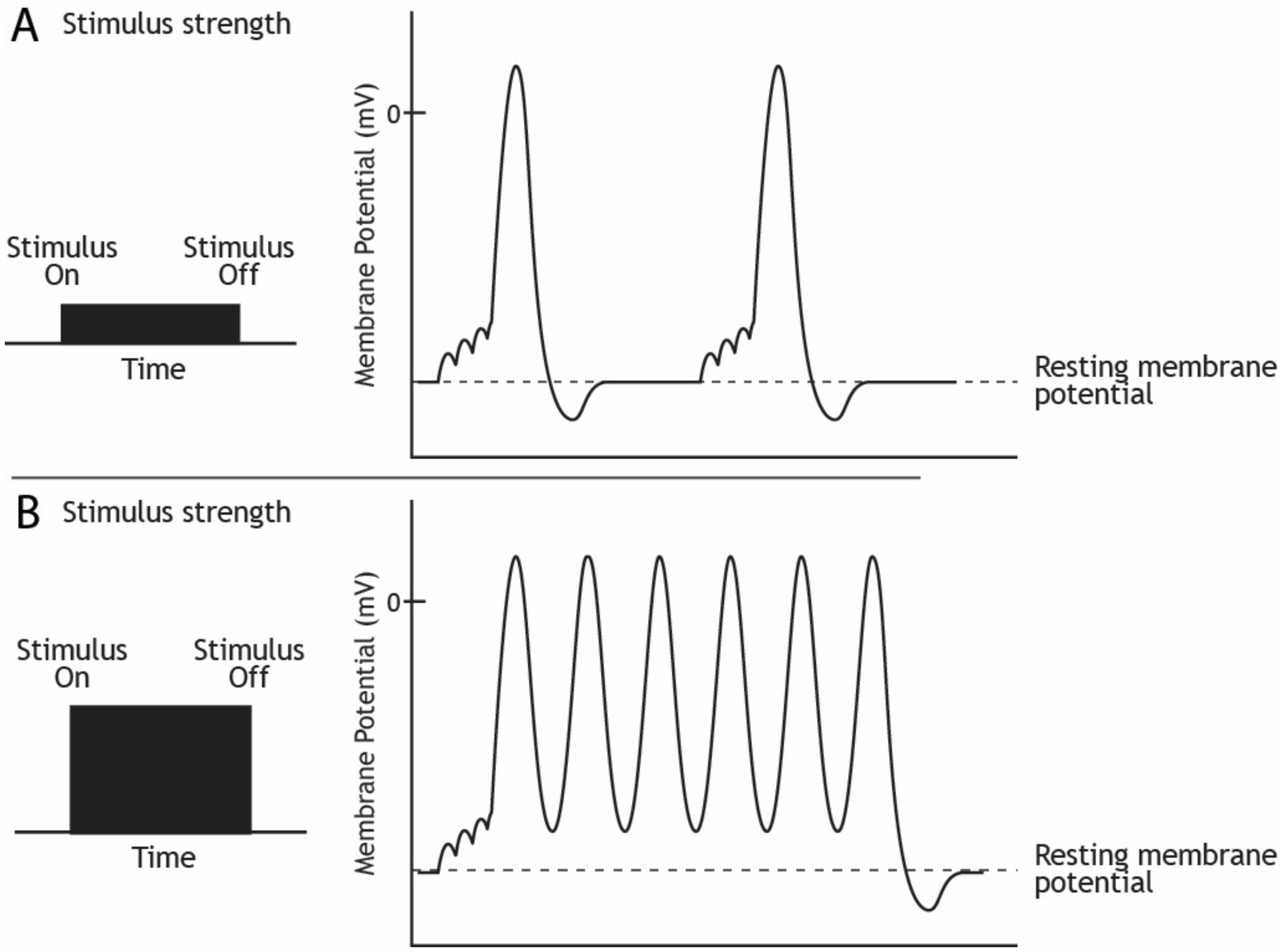
https://openbooks.lib.msu.edu/neuroscience/chapter/action-potentials/

The **speed** of AP propagation depends on myelination and axon diameter.

Propagation is faster along myelinated axons and along axons with a larger diameter. In myelinated axons, the AP "jumps" from one node of Ranvier to the next (i.e., **saltatory conduction**).

The **direction** of APs is down along the axon, towards the axon terminals.

The **frequency** of an AP informs the neuron about the strength of the stimulus.



https://openbooks.lib.msu.edu/neuroscience/chapter/action-potentials/

Stimulus strength determines the **frequency** of a neuron's **firing rate**.

We can listen to the firing rate of a neuron (e.g., in the primary visual cortex, in this video from Hubel and Wiesel's experiments)

https://www.youtube.com/watch?v=8VdFf3egwfg

Further reading

The Nobel Prize in Physiology or Medicine 1963

Sir John Eccles
Alan Hodgkin
Andrew Huxley

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The Nobel Prize in Physiology or Medicine 1963

Photo from the Nobel Foundation archive.

Sir John Carew Eccles

Prize share: 1/3

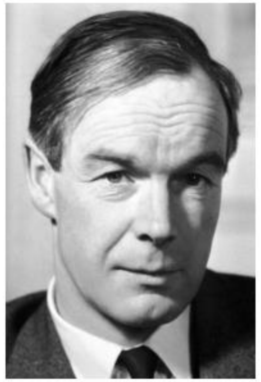

Photo from the Nobel Foundation archive.

Alan Lloyd Hodgkin

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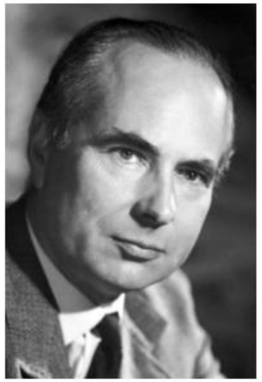

Photo from the Nobel Foundation archive.

Andrew Fielding Huxley

Prize share: 1/3

The Nobel Prize in Physiology or Medicine 1963 was awarded jointly to Sir John Carew Eccles, Alan Lloyd Hodgkin and Andrew Fielding Huxley "for their discoveries concerning the ionic mechanisms involved in excitation and inhibition in the peripheral and central portions of the nerve cell membrane"

https://www.nobelprize.org/prizes/medicine/1963/summary/

The Nobel Prize in Chemistry 2003

Peter Agre
Roderick MacKinnon

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Roderick MacKinnon Facts

Photo from the Nobel Foundation archive.

Roderick MacKinnon
The Nobel Prize in Chemistry 2003

Born: 19 February 1956, Burlington, MA, USA

Affiliation at the time of the award: Rockefeller University, New York, NY, USA; Howard Hughes Medical Institute, USA

Prize motivation: “for structural and mechanistic studies of ion channels”

Prize share: 1/2

Life

Roderick MacKinnon was born in Burlington, Massachusetts. As an adult, he studied not far from Massachusetts' capital, Boston. He first studied biochemistry at Brandeis University and then earned a medical degree from Tufts University in 1982. After a few years working as a doctor, MacKinnon returned to Brandeis University as a researcher at age 30. He later moved to Harvard University in 1989 and then to Rockefeller University, New York, in 1996, where he conducted the research that led to his Nobel Prize. MacKinnon is married to Alice Lee, an organic chemist.

https://www.nobelprize.org/prizes/chemistry/2003/mackinnon/facts/

The Nobel Prize in Physiology or Medicine 1991

Erwin Neher
Bert Sakmann

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The Nobel Prize in Physiology or Medicine 1991

Photo from the Nobel Foundation archive.
Erwin Neher
Prize share: 1/2

Photo from the Nobel Foundation archive.
Bert Sakmann
Prize share: 1/2

The Nobel Prize in Physiology or Medicine 1991 was awarded jointly to Erwin Neher and Bert Sakmann "for their discoveries concerning the function of single ion channels in cells"

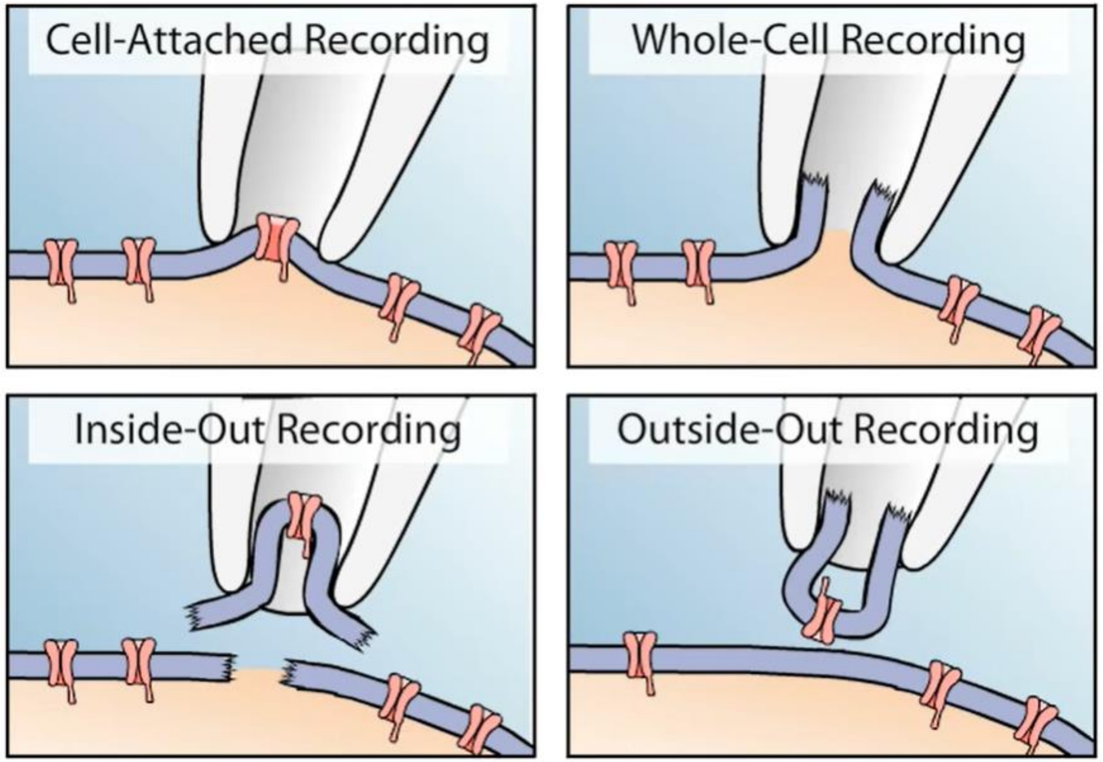
https://www.nobelprize.org/prizes/medicine/1991/summary/

> Pflugers Arch. 1981 Aug;391(2):85-100. doi: 10.1007/BF00656997.

Improved patch-clamp techniques for high-resolution current recording from cells and cell-free membrane patches

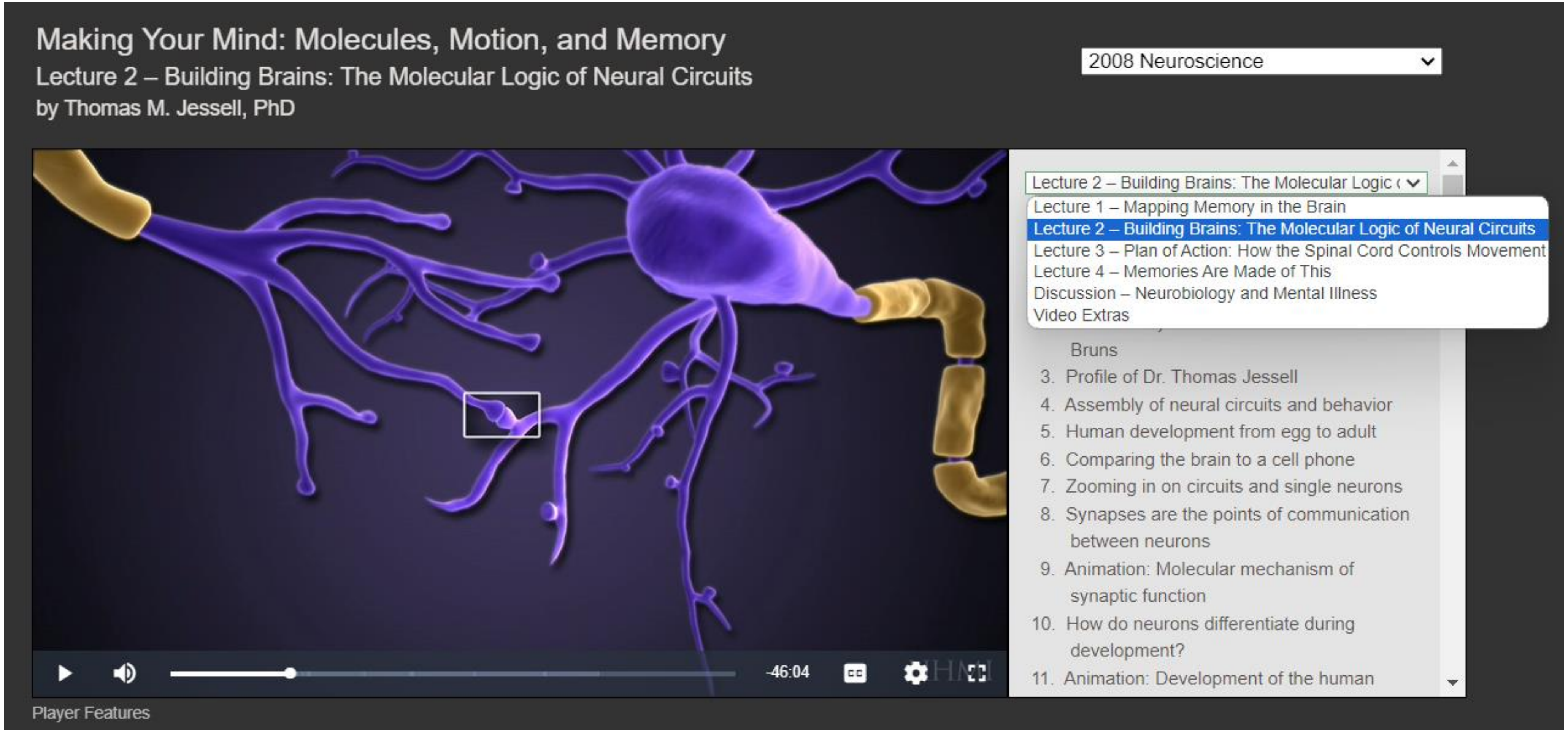
https://pubmed.ncbi.nlm.nih.gov/6270629/

O P Hamill, A Marty, E Neher, B Sakmann, F J Sigworth



https://www.youtube.com/watch?v=mVbkSD5FHOw

Additional resources



Thomas Jessel's recorded lectures: https://tinyurl.com/379svn2j

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CONTENTS

FOUNDATIONS OF NEUROSCIENCE

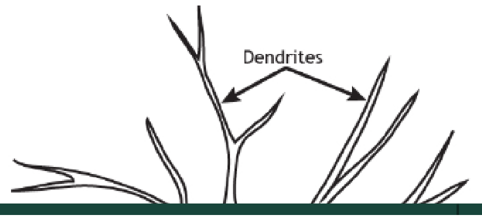
1.

THE NEURON

Neurons are the basic units of the brain. Their main function is to send electrical signals over short and long distances in the body, and they are electrically and chemically excitable. The function of the neuron is dependent on the structure of the neuron. The typical neuron consists of the dendrites, cell body, axon (including the axon hillock), and presynaptic terminal.

Resources

- Key Takeaways
- Test Yourself
- Video Lecture



Excellent open access chapters with illustrations and animations from Michigan State University
https://openbooks.lib.msu.edu/neuroscience/chapter/the-neuron/