بسم الله الرحمن الرحيم

﴿ وَإِن تَتَوَلَّوْا يَسْتَبْدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَالَكُم ﴾

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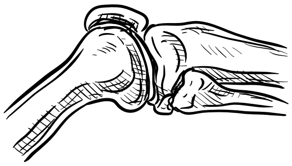

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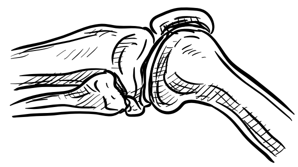

MID | Lecture 1

Action Potential

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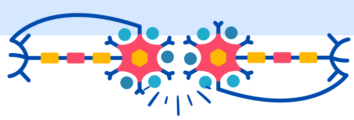

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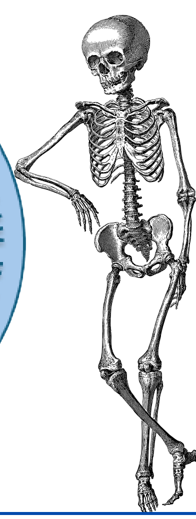
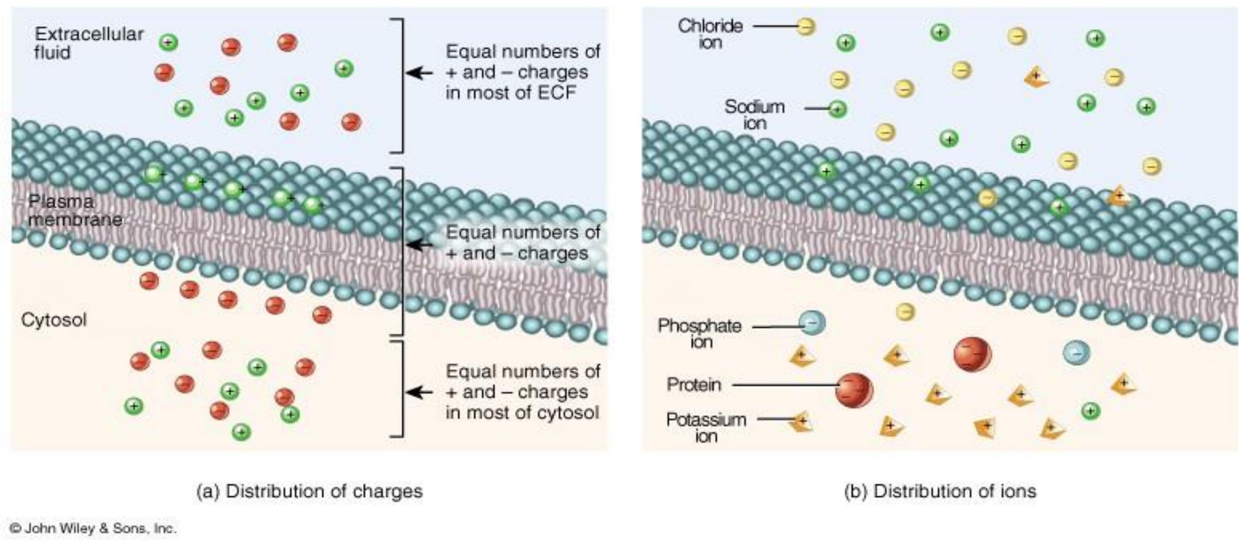


Action potential and NMJ

Gradient across the membrane



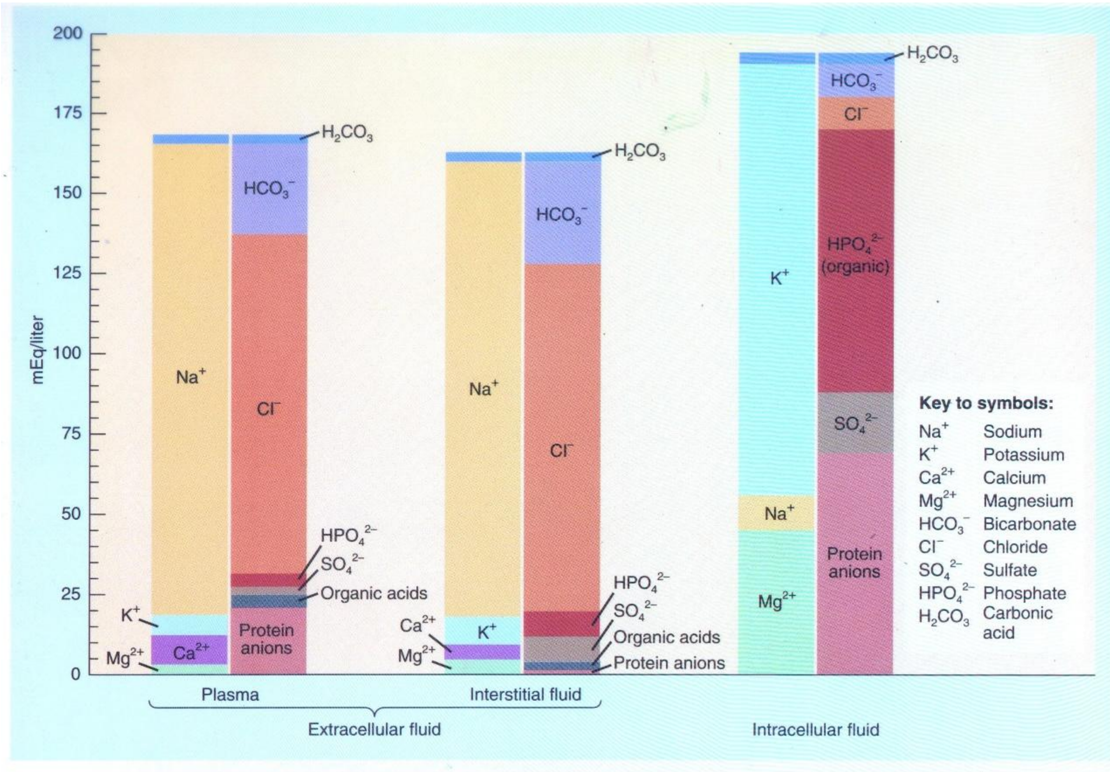
The selective permeability of the plasma membrane allows a living cell to maintain different concentrations of certain substances on either side of the plasma membrane as it is composed of a phospholipid bilayer that acts as a boundary between the extracellular and intracellular compartments, it also serves an important role in the communication between the two compartments.

The plasma membrane also creates a difference in the distribution of positively and negatively charged ions between the two sides of the plasma membrane.

Apart from the sides of the membrane there is an **equal distribution** of ions between the extracellular and intracellular compartments, what differs between the two is:

- **Sodium cations and chloride anions** are the most abundant ions **extracellularly**.
- **Potassium cations and phosphate anions** are the most abundant ions **intracellularly**, also the **large negatively charged proteins** contribute to the charge distribution.

Typically **(near the sides of the membrane)**, the inner surface of the plasma membrane is more negatively charged, and the outer surface is more positively charged. This charge difference is termed the **membrane potential**.



Comparison of Electrolyte and Protein Anion Concentrations in the Body Fluid Compartments, Fig# 27.4

This table summarizes the components of the extra- and intracellular compartments, there are some ions that are not mentioned above as they don't play a major role as potassium, sodium, chloride ..... etc.

As the membrane is composed of lipids, it can't permit the movement of any substances across it unless it is lipophilic; as the ions are hydrophilic, they require a transmembrane protein (channel) that they can move through.

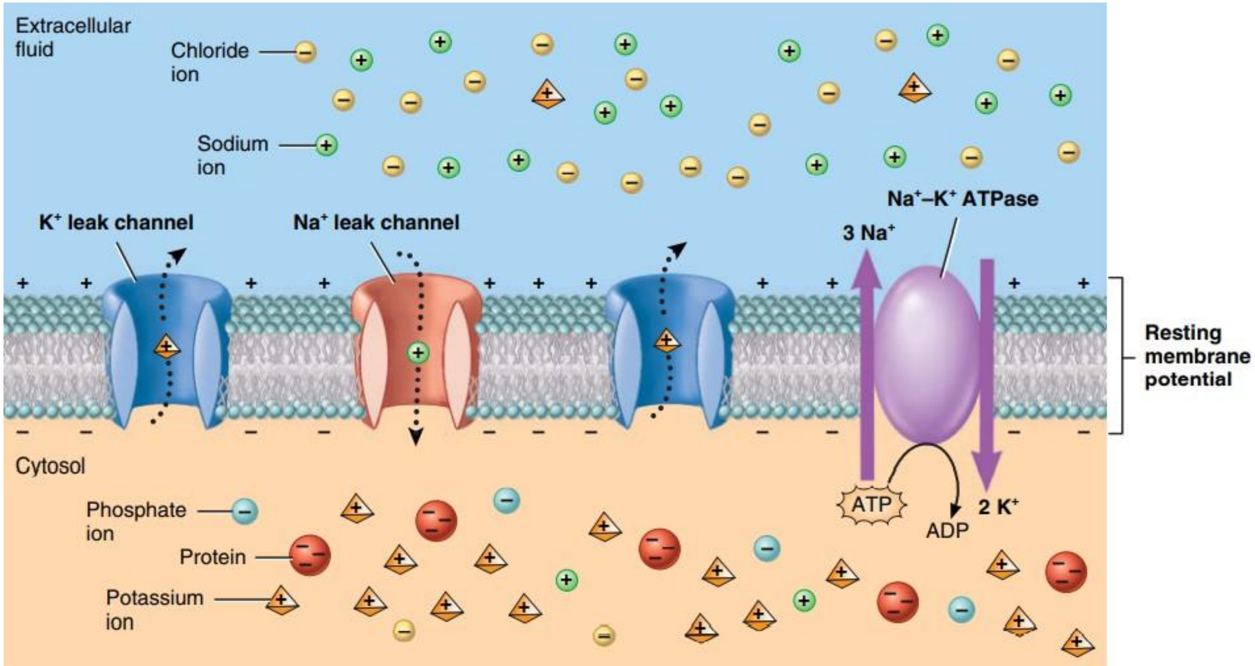
Ion	Extracellular Concentration*	Intracellular Concentration*	Relative Permeability
Na^+	150	15	1
K^+	5	150	25–30
A^-	0	65	0

*Concentration expressed in millimoles per liter, mM

The movement of these ions across the membrane depends on three factors:

1. **Concentration gradient**
    - The concentration gradient of the sodium ions favors their movement from the extra- to the intracellular compartment and vice versa for the potassium ions.
2. **Electrical gradient (charge)**
    - Anions movement is restricted. The negatively charged proteins can never leave the cells.
3. **Plasma membrane permeability**
    - The membrane permeability for potassium ions is 25-30 times more than the permeability for sodium ions, notice that the anions have a near 0 permeability and are concentrated intracellularly.

Resting membrane potential



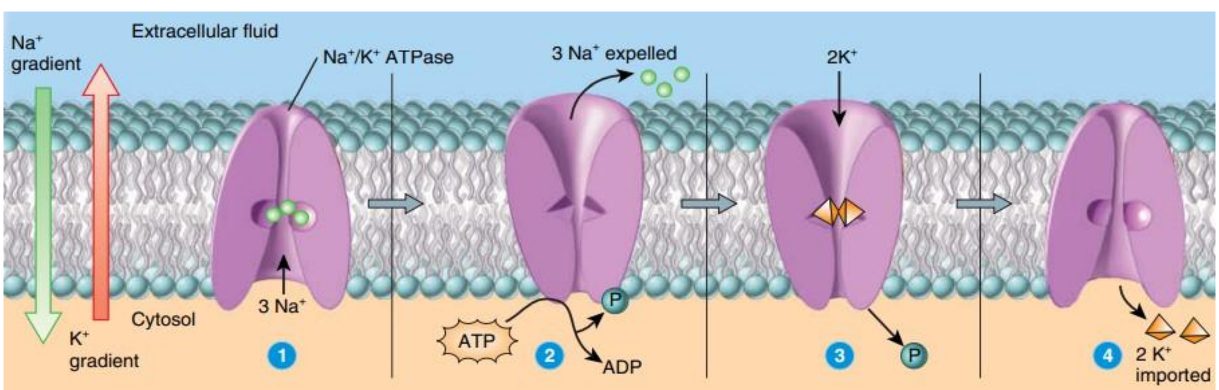
A separation of positive and negative electrical charges is a form of potential energy, which is measured in volts or millivolts.

The greater the difference in charge across the membrane, the larger the membrane potential (voltage).

The buildup of charge occurs only very close to the membrane. The cytosol or extracellular fluid elsewhere in the cell contains equal numbers of positive and negative charges and is electrically neutral.

The resting membrane potential arises from three major factors:

1. **Unequal distribution of ions in the ECF and cytosol**.
   - Extracellular fluid is rich in Na+ and Cl−. In cytosol, however, the main cation is K+, and the two dominant anions are phosphates attached to molecules, such as ATP, and amino acids in proteins.
   - Because the plasma membrane typically has more K+ leaky channels than Na+ leaky channels, the number of K+ that diffuse down their concentration gradient out of the cell into the ECF is greater than the number of Na+ that diffuse down their concentration gradient from the ECF into the cell.
   - As more and more positive K+ exit, the inside of the membrane becomes increasingly negative, and the outside of the membrane becomes increasingly positive.
2. **Inability of most anions to leave the cell**.
   - Most anions inside the cell are not free to leave. They cannot follow the K+ out of the cell because they are attached to non- diffusible molecules such as ATP and large proteins, thus they contribute to the negativity of the resting potential.
3. **Electrogenic nature of the Na+–K+ ATPases**.



   - Na+–K+ ATPases (sodium–potassium pumps) help maintain the resting membrane potential by pumping out Na+ as fast as it leaks in. At the same time, the Na+–K+ ATPases bring in K+. However, K+ eventually leak back out of the cell as they move down their concentration gradient.

- Na+–K+ ATPase pump needs ATP as it moves each of the sodium and potassium against their concentration gradient, it contributes to the negativity of the resting membrane potential (i.e. the pump is **electrogenic**) as it expels 3 sodium ions outside the cell while bringing only 2 potassium ions to the inside of the cell. **More '+' out.**

The resting membrane potential is called "resting" as it is independent of a stimulus, all the cells in our body have a resting membrane potential with a specific value depending on the type of the cell. It could be -90, -70 ... etc.

The equilibrium potential of each ion alone is calculated through the Nernst equation, the equillibrium potential of K+ is around -90 to -94 mV while the equillibrium potential for Na+ is around +60 to +65 mV, the resting membrane potential is calculated through the Goldman-Hodgkin-Katz equation as it takes into consideration all the ions that contribute to the resting potential, notice that the value of the resting membrane potential is around -70 mV. This value is close to the equillibrium potential of K+ as it has the highest permeability through the plasma membrane.

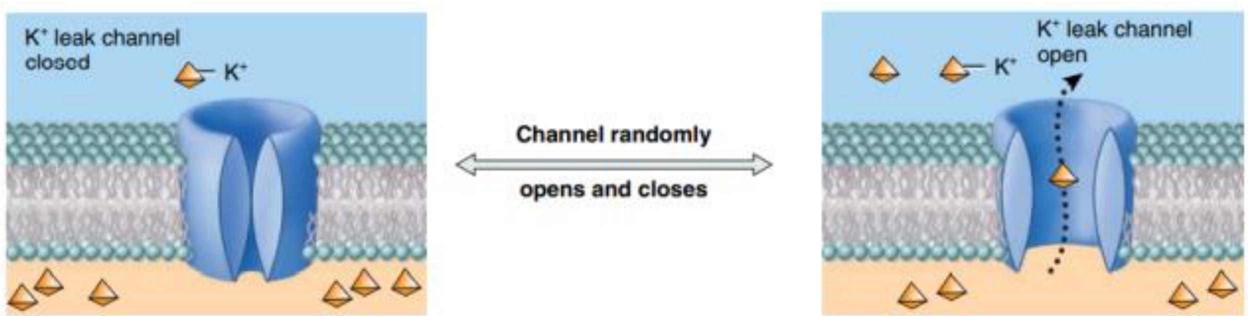
Excitable cells

- **Neurons and muscle fibers** are considered excitable cells because they exhibit electrical excitability, the ability to respond to certain stimuli by producing electrical signals (action potential).
- These cells generate rapidly changing electrochemical impulses at their membranes, and these impulses are used to transmit signals along their membranes.
- A stimulus could be transmitted from an efferent neuron to a muscle fiber in the form of action potential moving along the membrane of the neuron, once the stimulus reaches a muscle fiber it generates an action potential around the membrane of that fiber causing the contraction of the muscle.

Ion channels in excitable cells

The electrical signals produced by neurons and muscle fibers rely on four types of ion channels: leak channels, ligand-gated channels, mechanically gated channels, and voltage-gated channels:

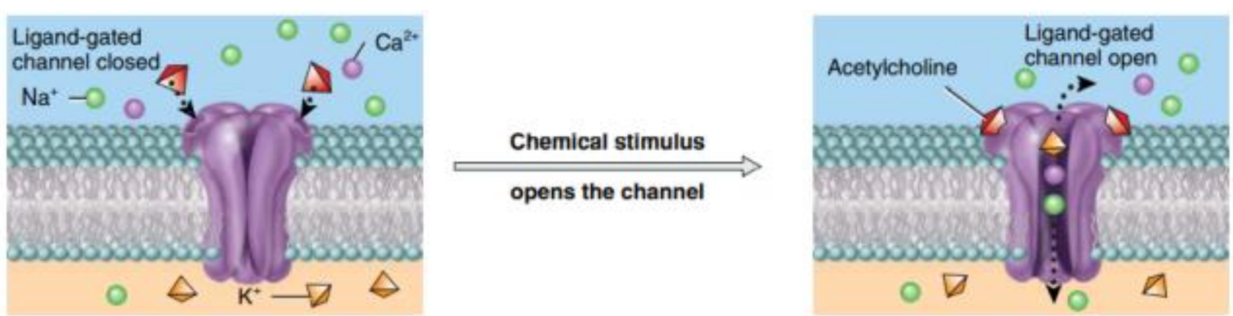
A) Leak channels:



(a) Leak channel

These channels depend on concentration gradients of ions and help in maintaining the resting potential of the cell membrane; they do not need a stimulus to be functional.

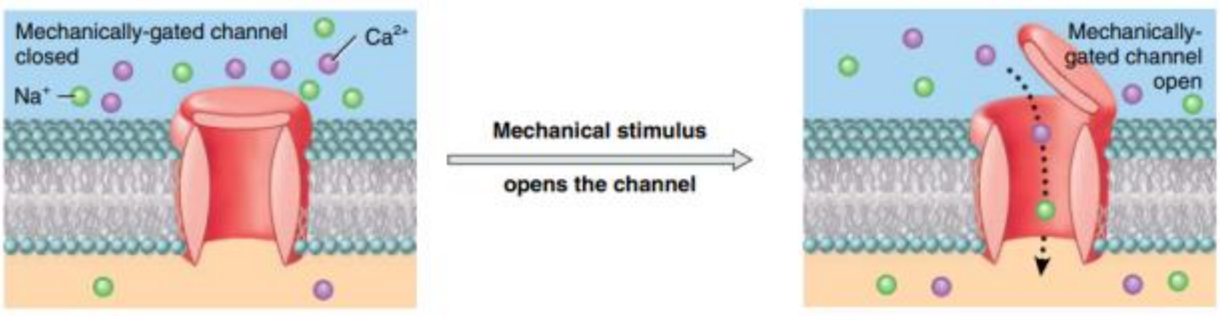
B) Ligand-gated channels:



(b) Ligand-gated channel

These channels are activated by binding a ligand (such as a neurotransmitter), causing a conformational change in the receptor and allowing the respective ion to move inside or outside the cell.

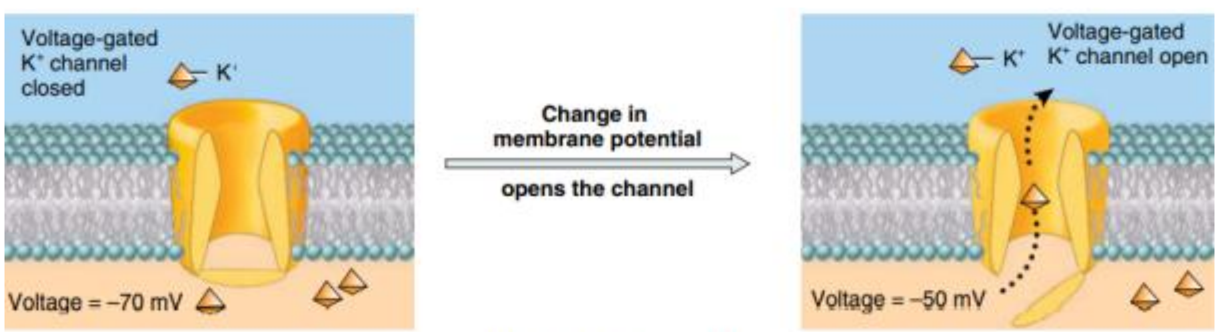
C)Mechanically gated channels:



(c) Mechanically-gated channel

They are similar to ligand-gated channels but are sensitive to mechanical forces instead of ligands. Mechanical forces can have many shapes, such as pressure or stretching, also causing a conformational change.

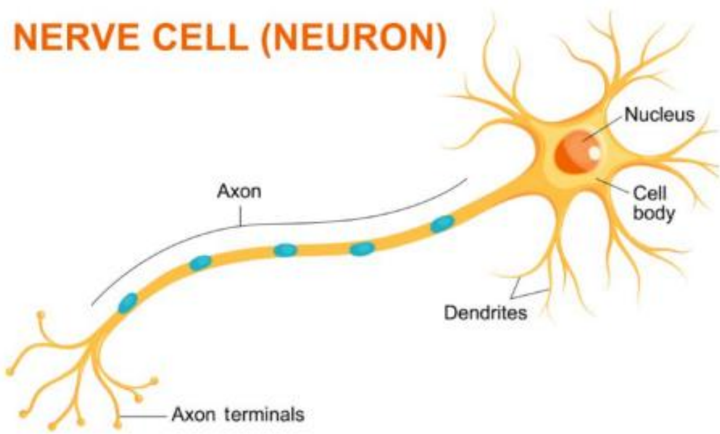
D)Voltage-gated channels (most important in this context):



(d) Voltage-gated channel

They also need a stimulus to become active; the stimulus is voltage difference across the membrane. Different voltage-gated channels have different activation voltages as will be explained in the next pages. These channels are very important because they control the action potential initiation and termination.

Excitable cells

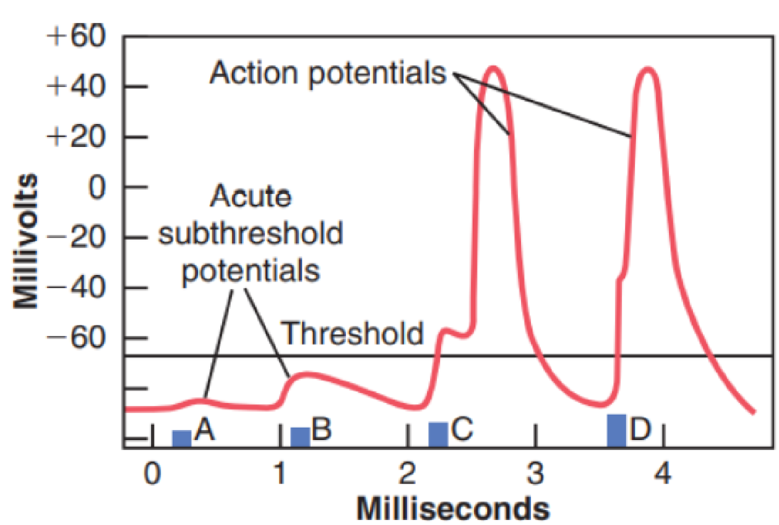


Excitable cells communicate together using 2 types of electrical signals:

1) Graded potentials: used for short distances only.
2) Action potentials: allow for long-distance communications.

Graded vs Action potential

At the dendrites/cells body, graded potentials form caused by channels such as mechanically or ligand-gated channels. These signals are carried to the axon hillock where they fire an action potential along the axon only if their sum reaches the threshold, which is the voltage needed to initiate an action potential. The action potential, as said before, is mediated by voltage gated channels to allow for long-distance communication, such as along axons.



As seen in the figure, there are 4 electrical signals (A → D).

It is clear that only C and D have achieved an action potential. This is because their graded potentials are greater than the threshold voltage (about -70 mV in the figure). Threshold values can differ between cells.

In contrast, A and B have failed to initiate an action potential because their graded potentials are subthreshold.

CHARACTERISTIC	GRADED POTENTIALS	ACTION POTENTIALS
Origin	Arise mainly in dendrites and cell body.	Arise at trigger zones and propagate along axon.
Types of channels	Ligand-gated or mechanically-gated ion channels.	Voltage-gated channels for Na^+ and K^+.
Conduction	Decremental (not propagated); permit communication over short distances.	Propagate and thus permit communication over longer distances.
Amplitude (size)	Depending on strength of stimulus, varies from less than 1 mV to more than 50 mV.	All or none; typically about 100 mV.
Duration	Typically longer, ranging from several milliseconds to several minutes.	Shorter, ranging from 0.5 to 2 msec.
Polarity	May be hyperpolarizing (inhibitory to generation of action potential) or depolarizing (excitatory to generation of action potential).	Always consist of depolarizing phase followed by repolarizing phase and return to resting membrane potential.
Refractory period	Not present; summation can occur.	Present; summation cannot occur.

This table summarizes some of the most important difference between the 2 types of potentials.

Graded potentials are either excitatory (positive; dome up) or inhibitory (negative; dome down). “Up” or “Down” is according to their graph shapes when plotting time against voltage. The nature of the signal depends on the type of ion gate opened.

A single graded potential doesn’t cause an action potential because it is usually of low magnitude.

Remember that graded potentials are summable, meaning that they can join on another increasing the effect. This is how graded potentials cause the initiation of an action potential.

They can cancel each other if they are opposite. Leading to a weaker effect.

Action potentials instead are not summable, and excessive stimulation changes the frequency of the action potential not its magnitude.

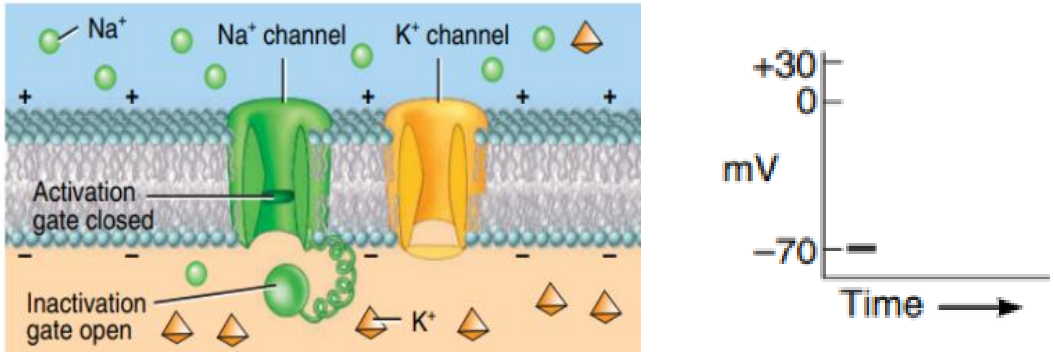
In summary, graded potentials serve as the starting point by which as cell is stimulated, and they are not enough unless their sum reaches a sufficient value, i.e. the threshold. After that action potential carries out the job!

Let us see the action potential in detail in the next pages:

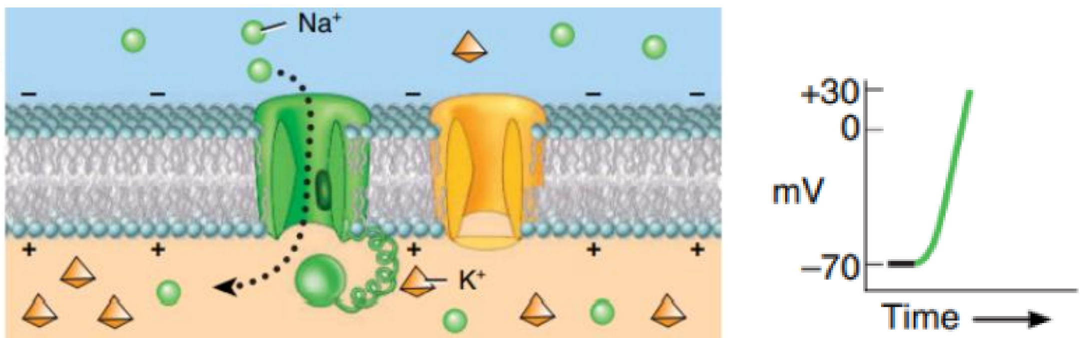
Action potential

It consists of many phases:

1. **Resting state:**
All voltage-gated Na^+ and K^+ channels are closed. The axon plasma membrane is at resting membrane potential: small buildup of negative charges along inside surface of membrane and an equal buildup of positive charges along outside surface of membrane.

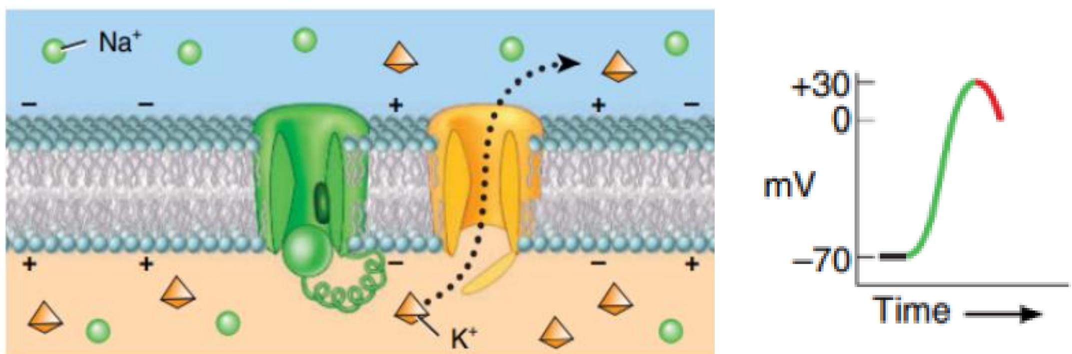


2. **Depolarizing phase:**
When membrane potential of axon reaches threshold, the Na^+ channel activation gates open. As Na^+ ions move through these channels into the neuron, a buildup of positive charges forms along inside surface of membrane and the membrane becomes depolarized.



3A **Repolarizing phase begins:**
Na+ channel inactivation gates close and K+ channels open.

The membrane starts to become repolarized as some K+ ions leave the neuron and a few negative charges begin to build up along the inside surface of the membrane.



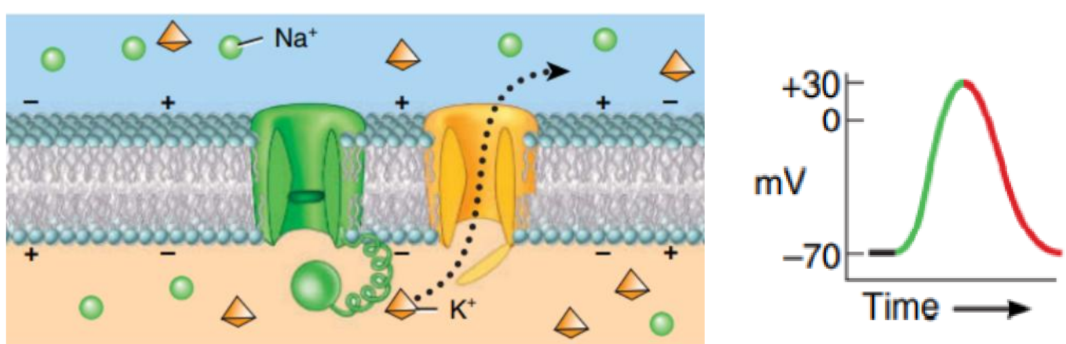
3B **Repolarization phase continues:**

K+ outflow continues.
As more K+ ions leave the neuron, more negative charges build up along inside surface of membrane.

K+ outflow eventually restores resting membrane potential.

Na+ channel activation gates close and inactivation gates open.

Return to resting state when K+ gates close.



Carefully look at the figures above with the explanation on the left. Also notice the phase of the graph on the right. Further details will be provided on the next page.

The Na^+ voltage-gated channel operates using a **positive feedback mechanism**, meaning that with each channel activated, more channels are activated, magnifying the effect and causing more sodium influx.

The Na^+ voltage-gated channel has **2 gates** – activation and inactivation.

For the channel to be open, both gates must be open:

During resting state: activation gate → closed; inactivation gate → open.

Both gates are open during depolarization (the channel is open).

During initial repolarization: activation gate → open; inactivation gate → closed.

[*Note that just before the resting potential is reached (≈ -55 mV), the inactivation gate is opened, and the Na^+ voltage-gated channel is now kept closed by the activation gate.* ***]***

The activation gate opens after the stimulus causes membrane voltage change, and doesn't close any time soon, instead **the inactivation gate closes the channel when the peak (overshoot) is reached and is opened when the resting potential is reestablished**. The activation gate is now responsible for keeping the channel closed.

Refractory period

Shortly after the action potential is initiated, the sodium channels become inactivated, and no amount of excitatory signal applied to these channels at this point will open the inactivation gates.

The period during which a second action potential cannot be elicited, even with a strong stimulus, is called the **absolute refractory period.**

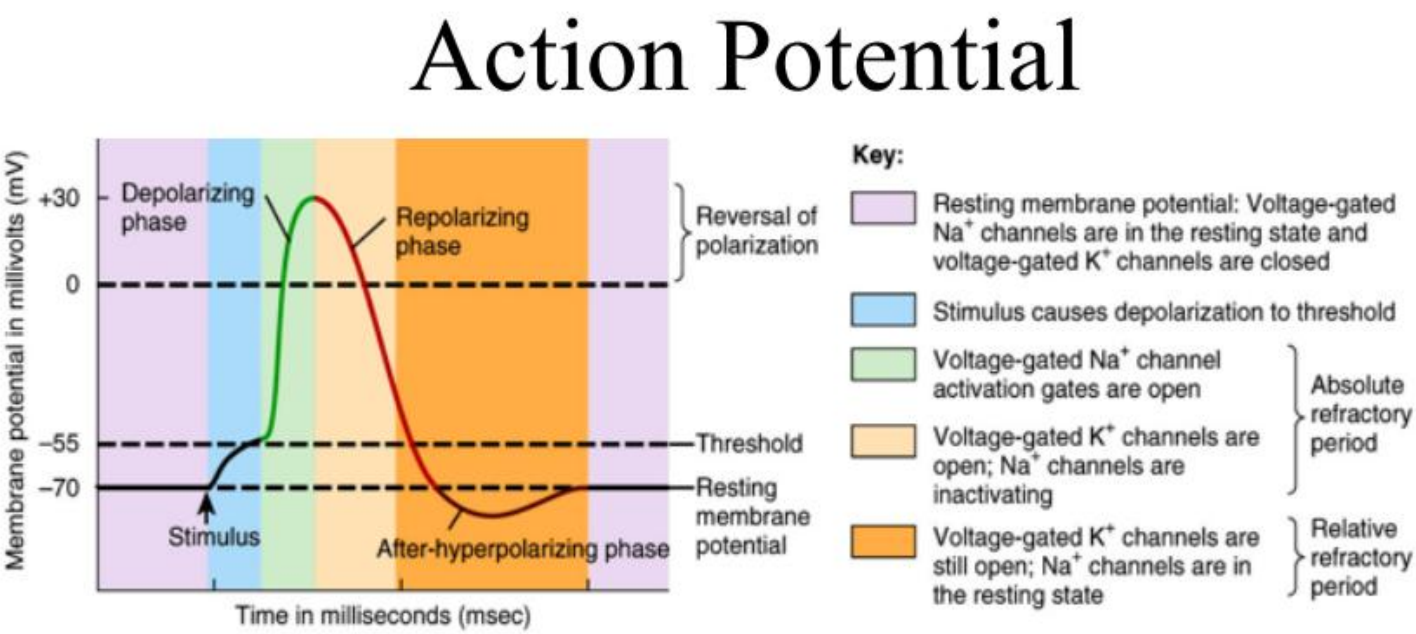
The only condition that will allow them to reopen is for the membrane potential to return to or near the original resting membrane potential level. Then, within another small fraction of a second, the inactivation gates of the channels open and a new action potential can be initiated.

At the end of the repolarization phase, excess K^+ efflux causes hyperpolarization. At this period, a normal stimulus would not cause any action potential because the gap between the current voltage and the threshold is larger than the normal, instead a stronger stimulus is needed. This period is referred to as the **relative refractory period.** Note that here the inactivation gate is open while the activation gate is closed.

Re-establishing membrane potential

Because Na+-K+ ATPase pump requires energy for operation, this “recharging” of the nerve fiber is an active metabolic process.

A special feature of this pump is that its degree of activity is strongly stimulated when excess sodium ions accumulate inside the cell membrane.



Look closely at the figure above, it illustrates the different phases of the action potential. Make sure to know what channels are responsible for each phase.

Additional Resources:

For further information about action potential, consider checking previous files that have been used during the general physiology course:

1. Dr. Khatatbeh Handout 😊
2. Comprehensive File 1 (pgs. 5 – 8)

رسالة من الفريق العلمي:

For any feedback, scan or click the code.

Versions	Page #	Before	After
V0 → V1	All (color code)	Black: Dr's explanation Blue: Slides	Black: Slides Blue: Dr's explanation
//	13	-	1. added "initial" to line 8 2. added the paragraph between [ ] 3. rephrased the last paragraph