# Action Potentials

## Membrane Potentials and Excitable Tissues

Why does it matter that cells have a negative interior? Think of a battery. A battery works by separating charges, creating a flow of electrons through a circuit to power devices like your phone. Similarly, when cells separate charges across their membranes, they generate a voltage, or potential energy, that can perform work. Although all cells have a resting membrane potential, the magnitude and function of this potential differ depending on the cell type. For instance, a neuron typically has a resting potential of -70 mV, while a red blood cell's resting potential is closer to -10 mV. This brings us to an important distinction: **some cells are excitable, meaning they can undergo rapid and predictable changes in membrane potential.** These changes, known as **action potentials**, are critical for functions like nerve signaling and muscle contraction. Excitable cells, such as neurons, skeletal muscle cells, and cardiac muscle cells, have resting membrane potentials ranging from -50 mV to -85 mV. In contrast, non-excitable cells, such as blood cells and epithelial cells, have much smaller potentials, typically ranging from -5 mV to -10 mV. Non-excitable cells do not generate action potentials.

#### Introduction to Action Potentials

You might wonder, “What exactly is an action potential?” Before exploring that concept, it’s important to revisit the role of membrane transport proteins.

Cell membranes, composed of phospholipid bilayers, are virtually impermeable to ions and polar molecules. To overcome this, cells rely on specialized membrane transport proteins embedded within the membrane. These include channels (gated or leak) and carrier proteins, which facilitate the movement of hydrophilic compounds across the membrane.

Most channel proteins are highly specific, allowing only certain ions to pass through. Some channels, like **leak channels**, are always open, enabling a steady flow of ions. Others, like **gated channels**, are typically closed and open only in response to specific stimuli. The stimuli that open gated channels can vary:

1. **Voltage-gated channels** respond to changes in membrane potential.
2. **Mechanically gated channels** open in response to physical forces like pressure or stretch.
3. **Chemically gated (ligand-gated) channels** open when a specific chemical signal binds to them.

K⁺ can cross the membrane through leak channels or gated channels. Na⁺, on the other hand, has limited movement due to the scarcity of Na⁺ leak channels (approximately 1 Na⁺ leak channel for every 100 K⁺ leak channels) and the fact that most Na⁺ gated channels remain closed under resting conditions. Despite having a strong concentration gradient pushing Na⁺ into the cell, it cannot enter because these channels are shut.

**Activation of Voltage-Gated Channels** How, then, do gated ion channels open in excitable cells? The answer lies in the structure and flexibility of proteins. Proteins are dynamic molecules with shapes determined by the arrangement of their amino acids. These shapes can change in response to environmental cues, allowing the protein to transition from a closed state to an open state, permitting ion flow. Consider, for example, the following hypothetical voltage-gated ion channel.

Image by JS S25

In the cartoon above, the voltage-gated ion channel actually has two gates depicted as a lever, which we will call the activation gate, and a ball, which we will call the inactivation gate. The lever, or activation gate, is connected to a helix or “spring” called the S4 subunit that “pulls” the lever to an open position. Under normal resting conditions, this does not happen because the spring also has a net positive charge (notice the “+” symbols on the S4 segment) which is repelled by the positive charges collecting on the outer membrane. At the same time, the positive charges of the spring are attracted to the negative charges collecting on the inner membrane. Thus, the activation gate remains in its closed conformation. If, however, we were able to change the charges, even slightly, on the membrane, then we could affect the conformation of the protein allowing the activation gate to open. In the membrane cartoon above labeled #2, the charge was altered so that the inside suddenly became less negative and the outside less positive, notice that the spring could now move towards the outer side of the membrane and “pull” open the activation gate (lever). Once open, sodium ions which are specific to this channel can freely diffuse down their concentration gradients. However, the ball, or inactivation gate, also has charges on it that are attracted to complimentary charges in the mouth of the channel (not shown in the image). A few milliseconds after the activation gate (lever) opens, the inactivation gate (ball) closes the channel (see number 3 in the image above). The purpose of this inactivation gate is to regulate the amount of ions diffusing into the cell. Na+ moves in through the channel for a brief moment before the inactivation gate closes. Believe it or not, that brief moment of Na+ passing through the membrane is the basis of excitability. Does it appear clear now as to why these channels are called voltage-gated? It should make sense that changes in membrane voltage induce changes in protein channel shape which open and close the gate portions of the protein.

**Movement of Ions Through Protein Channels** When an ion channel opens, even for less than half a millisecond, its effect on the cell depends on the type of ion involved and the direction it moves. For example, potassium ions (K⁺) are more concentrated inside the cell, so they naturally diffuse outward, toward the extracellular space, following their concentration gradient. Since K⁺ carries a positive charge, this outward movement causes the cell to lose positive charges, making the inside of the cell more negative. But if K⁺ is already in steady state equilibrium, why does its movement change just by opening more channels? The equilibrium of K⁺ depends on the membrane's permeability, which is determined by how many channels are open. Opening additional voltage-gated K⁺ channels allow more K⁺ to diffuse out than just through the existing leak channels. This increased diffusion continues until a new balance is reached between the chemical gradient driving K⁺ out and the electrical gradient pulling it back in. This process ultimately makes the cell's interior even more negative.

Chloride ions (Cl⁻) can also make the cell more negative. Cl⁻ is more concentrated outside the cell, so when Cl⁻ channels open, making the cell more permeable to Cl-, these negatively charged ions diffuse into the cell, further lowering its internal charge. The opposite effect occurs with sodium (Na⁺) and calcium (Ca²⁺) ions. Both are positively charged and more concentrated outside the cell. When channels for these ions open, they diffuse into the cell, making the interior more positive.

Let’s cover some new terminology. Because we are dealing with charge differences and electrical currents (flow of ions), we use some unique terms to describe certain states of the membrane. At rest, the membrane is in a **polarized** state, polarized means there is a separation of charge across the membrane due to different ion concentrations on either side of the membrane (see table above). This polarized state is referred to as the **resting membrane potential (RMP)**. Already emphasized, the inside of the cell membrane will be negative in relation to the outside of the membrane. We can show this graphically by plotting membrane potential in millivolts (mV) on the y-axis and time in milliseconds (msec) on the x-axis (see figure below).

Image by JS S25

Any change in the membrane potential toward zero mV is termed a **depolarization** since the membrane is becoming less charged (i.e. there is less charge separation across the membrane). Any change in the membrane potential that moves back toward the resting potential is called a **repolarization**. And finally, any further decrease (more negative) in membrane potential below resting membrane potential is termed **hyperpolarization**. Note the prefixes of these terms as their meanings explain what is happening to the membrane potential in reference to the resting membrane potential. Opening channels for Na+ or Ca++ would cause a depolarization, while opening channels for K+ or Cl- would cause a repolarization or even a hyperpolarization.

Up to this point, we have explored how voltage-gated channels open and close in response to changes in voltage, but a major question remains: why does the voltage change in the first place? Left undisturbed, cells would maintain their polarized resting state indefinitely. To alter the voltage and initiate electrical changes, we rely on one or both of the other types of ion channels: the **ligand-gated channel**, also known as a chemically gated channel and/or the **mechanically gated channel**. Ligand-gated channels respond to specific chemical signals, such as neurotransmitters. When a chemical binds to these channels, they open, allowing ions such as Na⁺, K⁺, or Cl⁻ to move across the membrane. Mechanically gated channels open in response to pressures and forces working on the cell membrane. Opening of a ligand or mechanically gated channel causes small, localized changes in the membrane potential called **graded potentials**. In the picture just above, we see a depolarizing graded potential on the left and a hyperpolarizing graded potential on the right.

**Graded Potentials: Localized Electrical Changes**Graded potentials are small, transient changes in the membrane potential that are directly proportional to the strength of the stimulus. For instance, a strong chemical stimulus may induce a 10 mV depolarization, while a weaker chemical stimulus might only result in a 5 mV change. These changes occur in a limited region of the membrane, earning them the name **local potentials**. Graded potentials are characterized by two important features:

1. **Magnitude varies with stimulus strength:** The stronger the stimulus, the greater the depolarization or hyperpolarization.
2. **Ability to summate:** When graded potentials occur close together in time or space, they can combine (summation) to produce a larger overall effect. This summation is key for triggering action potentials.

Although brief and localized, graded potentials can have significant effects when they summate. For example, repeated depolarizing stimuli applied in rapid succession can add up to create a stronger depolarization. If this depolarization reaches a critical level, called the **threshold potential**, it triggers the opening of the voltage gated channels.

**Threshold Potential**

The threshold potential is the voltage level at which voltage-gated sodium (Na⁺) or calcium (Ca²⁺) channels open. This threshold is about -55 mV in most neurons. Once the membrane potential reaches this level, voltage-gated Na⁺ channels undergo a conformational change, opening their activation gates and allowing a rapid influx of Na⁺. This influx causes a dramatic depolarization, an event we refer to as the **action potential**. Without graded potentials, cells would lack the ability to reach this threshold potential, making action potentials impossible. Graded potentials act as the **triggers**, ensuring that neurons and muscle cells can respond to stimuli and carry out essential processes like nerve signaling and muscle contraction.

#### Action Potentials – The Spark of Excitable Tissues

An action potential is where things truly get exciting (pun intended). As previously stated, only excitable tissues, such as neurons and muscle cells, are capable of generating action potentials. At its core, an action potential is a rapid, dramatic depolarization of the membrane potential, followed by an equally rapid repolarization to the resting state. Unlike localized graded potentials, action potentials propagate along the entire cell membrane, making them the foundation for nerve signal transmission, muscle contraction, and sensory perception.

image by JS S25

Action potentials are initiated when depolarizing graded potentials raise the membrane potential to the threshold level. This triggers the activation of voltage-gated ion channels, most notably, voltage-gated Na⁺ channels. If the membrane potential fails to reach threshold, it is called a sub-threshold stimulus, and no action potential occurs.

However, once the threshold is reached, an action potential always occurs in its full form, regardless of whether the stimulus is barely sufficient or exceptionally strong. This is known as the "all-or-nothing principle": an action potential either happens completely or not at all. Furthermore, the magnitude of an action potential is consistent and cannot be summed or increased by multiple stimuli. In other words, one action potential is not stronger or bigger than another.

**The Process of an Action Potential**

image by JS S25

In a resting neuron, Na⁺ diffusion across the membrane is minimal, because of the scarcity of Na⁺ leak channels. However, when a sufficient graded potential depolarizes the membrane to threshold, voltage-gated Na⁺ channels undergo a conformational change, opening their activation gates. Because Na⁺ is highly concentrated outside the cell, its channels allow a rapid influx of Na⁺, further depolarizing the membrane. This positive feedback mechanism drives the membrane potential up to approximately +30 mV. During the rapid depolarization, the inactivation gates of the Na⁺ channels close, halting further Na⁺ entry. Interestingly, this dramatic depolarization requires only a tiny fraction of the total Na⁺ in the extracellular environment, just one in 100,000 Na⁺ ions need to enter the cell to cause a 100 mV change in potential. While Na⁺ channels inactivate, voltage-gated K⁺ channels, which are slower to open, begin to allow K⁺ ions to exit the cell. This outflow of K⁺, along with the continued activity of K⁺ leak channels, drives the repolarization of the membrane. In fact, the K⁺ efflux often overshoots, leading to **hyperpolarization**, a temporary state where the membrane potential becomes even more negative than the resting potential. Unlike Na⁺ channels, voltage-gated K⁺ channels close more slowly, contributing to this hyperpolarization.

Once these channels close, the membrane returns to its resting potential, primarily maintained by K⁺ leak channels. While the Na⁺/K⁺ ATPase pump gradually restores the ion gradients disrupted during the action potential, it’s worth noting that this pump is not immediately necessary. Neurons have enough ions in reserve to generate up to 10,000 action potentials without replenishment from the Na⁺/K⁺ ATPase pump. Action potentials are initiated and propagated by the sequential activation of thousands of voltage-gated sodium (Na⁺) and potassium (K⁺) channels along the neuron’s membrane. This process can be studied using a technique called **patch clamping**, which allows us to measure ion flow through individual channels. When a channel opens, it depolarizes the local membrane, triggering adjacent channels to open. However, in neurons that can extend up to a meter in length, waiting for each channel to activate sequentially can result in relatively slow signal transmission—about 35 mph. While this speed is sufficient for short distances, our nervous system requires faster signal transmission to ensure near-instantaneous reflexes.

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