Gen Phys

Excitable Cells Resting Properties

Introduction

Cell membranes are **lipid bilayers** and are **impermeable to ions**. Ions, even as small as they are, require **channels** to let them through because they cause a charge. Thus, ions flow only when the normally impermeable membrane becomes permeable because of channels. Channels can be always open (**leak**), they can be opened by binding a receptor (**ligand-gated**), or they can be opened by voltage changes (**voltage-gated**).

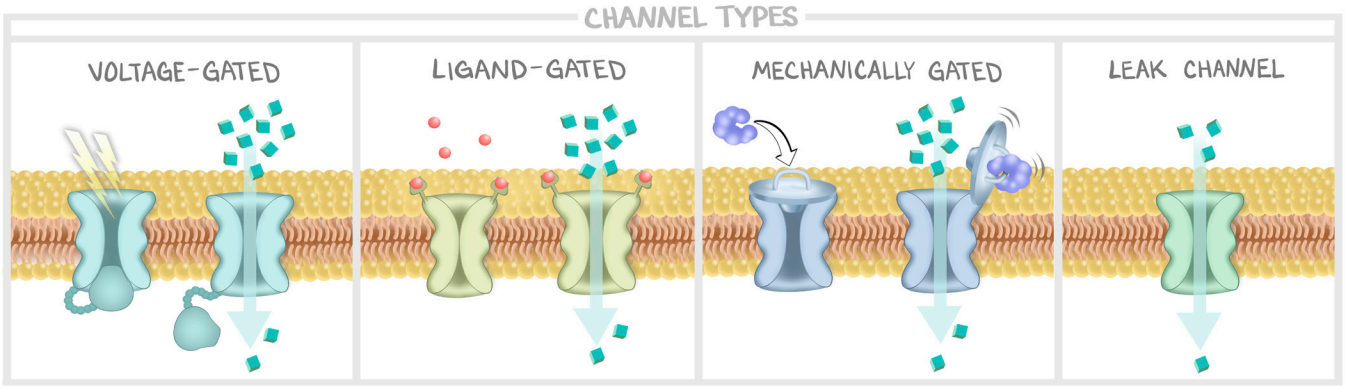

Figure 6.1: Types of Channels

Image of the different types of channels. All channels allow molecules (usually ions) through the cell membrane. Some are activated by voltage, some by ligands, some mechanically, and others are the always open leak channels.

The forces that drive the ion in a certain direction are both **chemical** (the concentration gradient) and **electrical** (ions carry charge). The electrical force that balances the chemical force is called the **equilibrium potential**, calculated by the Nernst equation, and so also referred to as the **Nernst potential.** When a cell membrane becomes permeable to an ion, the ion will move down its concentration gradient. To compensate for that change in chemical force, the membrane potential, the voltage across the membrane will change, bringing the cell closer to that ion's **Nernst potential**.

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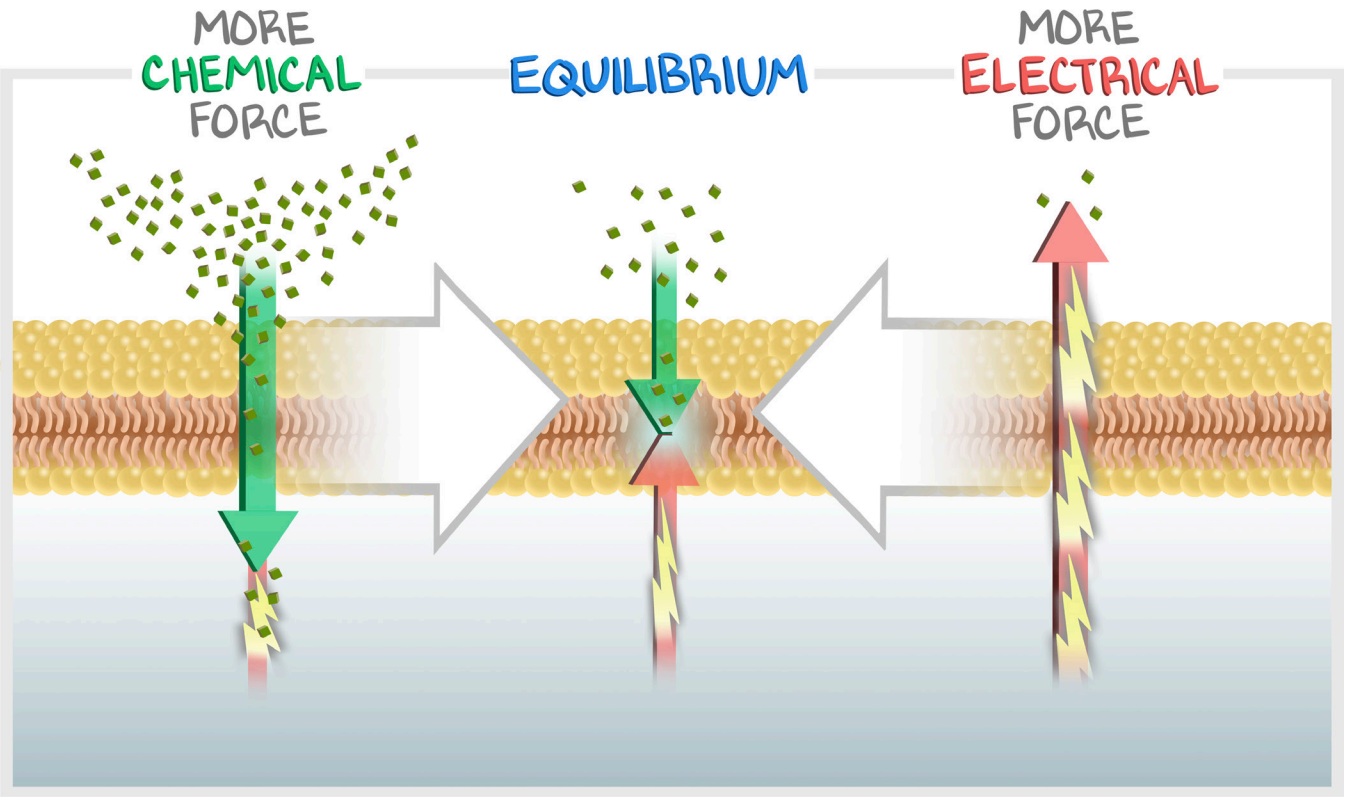

Figure 6.2: Chemical and Electrical Forces

The concentration gradient establishes a chemical force. We scientists can inflict a voltage such that the electrical force will balance the flow of ions or even reverse the flow of ions. When a cell membrane becomes permeable to an ion, the ion will move down its concentration gradient. To balance the chemical force, the membrane voltage will shift towards that ion's equilibrium potential.

For example, let's look at the two most important ions: potassium and sodium. The Nernst potential for potassium (K^+) is -95. If the cell became permeable to K^+, and K^+ only, and infinitely permeable to K^+, the cell potential would go to -95. The Nernst potential for sodium (Na^+) is +65. If the cell became permeable to Na^+, and Na^+ only, and infinitely permeable to Na^+, the cell's membrane potential would go to +65. There are other ions that matter, such as chloride and calcium, but the major players will be K^+ and Na^+.

Membrane conductance is how permeable the membrane is to an ion. Permeability and conductance are going to be used interchangeably in this lesson. Membrane conductance is a product of the number of channels, how many are open, and how well those channels conduct that ion.

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Membrane Conductance = Number of Channels × % Open × Channel Conductance

The more the open channels and the better those channels allow that one ion to move down its concentration gradient, the higher the membrane conductance. The higher the membrane conductance, the faster those ions will move and the faster the cell membrane will approach that ion's Nernst potential. A membrane with a **higher conductance approaches the Nernst potential faster.**

Establishing a Resting Membrane Potential

In real life an excitable cell has a **constant resting membrane potential**. That is, the voltage is always about the same until ions start moving. For the examples used in this lesson, we are going to use a resting membrane potential of -70. We want to see how that is created.

First, all cells have the **Na^+/K^+-ATPase**, which uses the energy from the hydrolysis of ATP to move sodium (Na^+) against its concentration gradient and potassium (K^+) against its concentration gradient. **3 Na^+** pumped out, and **2 K^+** pumped in. Without even engaging Nernst potentials, that takes 3 plus-charges and pushes them outside the cell, and lets only 2 plus-charges in. With more plus moved out than plus moved in, the cell becomes **more negative** just on this pump alone.

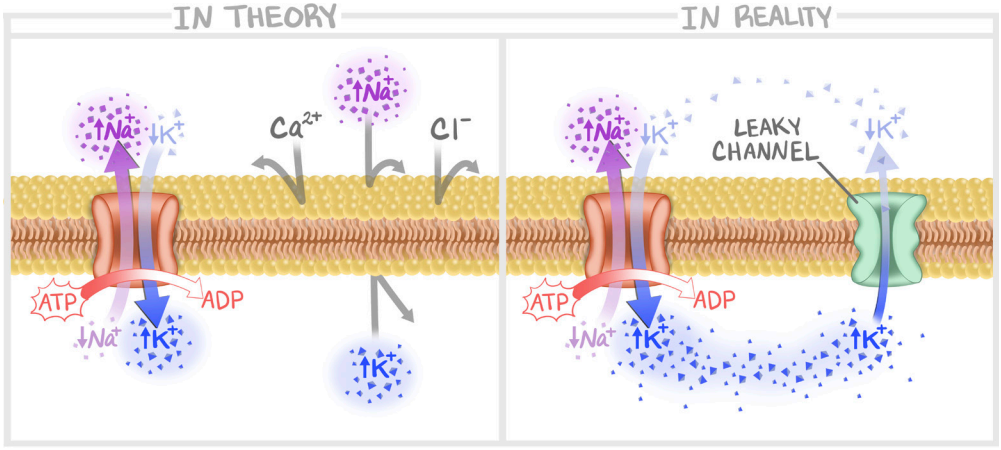

Figure 6.3: The resting membrane potential, Na^+/K^+-ATPase, leak channels

The plasma membrane is impermeable to all ions. At rest, an excitable cell uses ATP to pump 3 Na^+ out of the cell, and pump 2 K^+ into the cell, against their concentration gradients. Low conductance potassium leak channels. This alleviates the potassium concentration gradient. Because potassium ions are flowing down their concentration gradient, the membrane potential heads towards the Nernst potential for K^+, -95 mV.

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With that concentration gradient established, Na^+ wants to get into the cell and K^+ wants out. **At rest**, the cell membrane is **mostly impermeable to everything.** The trick is that, at rest, the membrane has **potassium leak channels.** Leak channels are few in number and have poor channel conductance to potassium so that they do not permit a rush of potassium. Since the **membrane conductance to potassium is low**, but the membrane conductance to all other ions is nonexistent, the cell approaches—but slowly—the Nernst potential for potassium. These potassium leak channels allow K to flow down the concentration gradient and exit the cell.

Because the Nernst potential for K is -95, the resting membrane potential heads in that direction.

If there were only leak channels, meaning the cell were permeable only to potassium, and only when at rest, the membrane potential would be the Nernst potential for K^+. But the Na^+/K^+-ATPase brings K^+ into the cell while leak channels let it out, and other ions matter, too. But things like chloride (Cl^-), sodium (Na^+), and calcium (Ca^{++}) have such low membrane conductance at rest, that they don't impact the resting membrane potential substantially. In real cells, not the theoretical model we've proposed with total impermeability except through potassium channels, the resting membrane potential is actually around -70 mV. Accept this as truth. Which excitable cell has a different resting potential value is of no consequence—the resting membrane potential is very negative because excitable cells at rest have potassium leak channels.

Polarization

When a cell's membrane becomes more positive, it's said to **depolarize**. To depolarize means "to undo the polarity" or reverse the negative charge. The cell's membrane becomes more positive. Becomes more positive means, "moves towards sodium's Nernst." Calcium is also a depolarizing signal because calcium has a Nernst potential above threshold. You should think of depolarization as "*goes towards sodium's Nernst*."

When a cell's membrane becomes more negative, it's said to **hyperpolarize**. To hyperpolarize means, "to gain more polarity" or to make larger the negative charge. The cell's membrane becomes even more negative. "Becomes more negative" means, "moves towards potassium's Nernst." Chloride is also a hyperpolarizing signal. You should think of hyperpolarizing as, "*goes towards potassium's Nernst.*"

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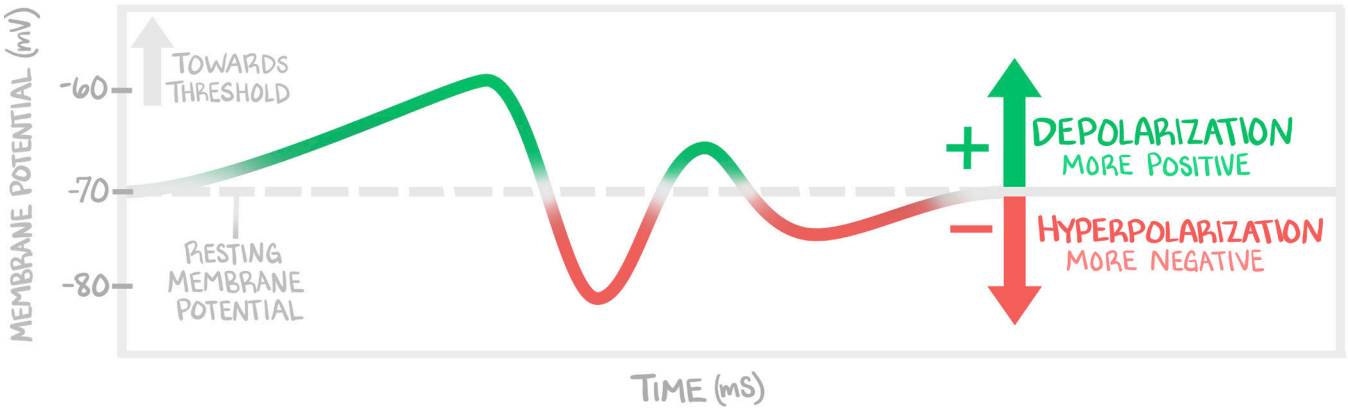

Figure 6.4: Hyperpolarization vs. Depolarization

If a channel opens and the cell becomes permeable to an ion, the ion will move down its concentration gradient. In doing so, it will move the local membrane potential closer to that ion's equilibrium potential, that ion's Nernst. What you should take away is that any stimulus that heads towards 0, that is, in a positive direction, is a depolarizing stimulus, and is probably Na^+ or Ca^{++}. Any stimulus that heads more negative from resting is a hyperpolarizing stimulus, and is probably K^+ or Cl^-. This is an obvious oversimplification, but it works.

Potassium and the Resting Membrane Potential

Because the resting membrane potential is dependent on potassium leak channels, and because potassium leak channels allow for movement of potassium based on the concentration gradients, alterations in the extracellular potassium can have an effect on that resting potential.

Hypokalemia (low circulating potassium) means there is less potassium outside the cell. This means the concentration gradient is greater, and so more potassium is pushed out of the cell. Think of it in two ways: first, by pushing more positive charges out of the cell, the cell becomes more negative. The second approach is more technical. Because the driving force for potassium is increased, the membrane conductance of potassium is higher (because the flux of potassium out increases), thereby driving the cell towards the Nernst potential for potassium. "*Drive towards Nernst potential of potassium*" and "*make more negative*" are the same thing—**hypokalemia hyperpolarizes the cell**.

Hyperkalemia decreases the chemical gradient, favoring potassium remaining in the cell. This means more positive charges stay in the cell, so the cell becomes more positive, called **depolarization**. Or, being technical, since the flow of potassium through leak channels is lower, the conductance through the membrane is lower, and the cell will not tend towards the K^+ Nernst potential.

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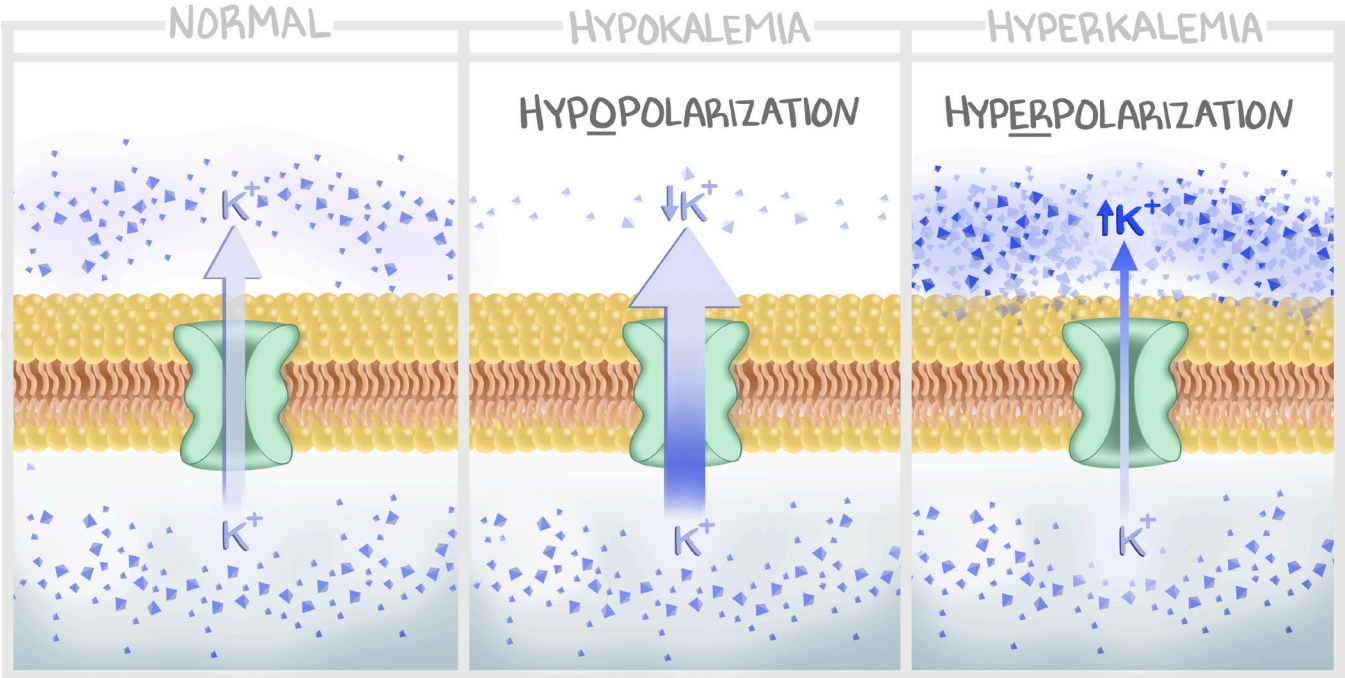

Figure 6.5: Serum Potassium Does Change Excitability

Normal potassium results in a normal leak, and a normal concentration gradient establishes a normal resting membrane potential. Hypokalemia means reduced serum concentration of potassium, so favors the concentration gradient that moves potassium out of the cell. The more potassium flowing, the closer to the Nernst it goes, the more hyperpolarized the cell. Hyperkalemia means increased serum potassium, so the concentration gradient is weaker for potassium to exit the cell, meaning there is less movement of potassium ions, and so the cell membrane goes away from the potassium equilibrium potential, more depolarized than normal, leading to ectopy and erroneous activation of cells.

Because the resting membrane is **not permeable** to Na^+, Ca^{++}, or Cl^-, these ions do not significantly alter the resting membrane potential. Only **extracellular potassium** changes have meaningful impact on excitable cells, such as cardiac myocytes. This is also why small variations in the potassium can be fatal—the normal serum potassium is 3.5-5.0, with lethal concentrations at 7.0.

Subthreshold Stimulus

If a stimulus is applied to an excitable cell, the cell will **depolarize**. That happens because the membrane becomes more permeable to Na^+. But if insufficient depolarization is made, if the mild depolarization was **below the threshold** potential, nothing else will happen. As the Na^+ is brought in (the depolarizing stimulus bringing the cell towards Na^+'s Nernst potential), a bunch of positive charges enter

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the cell. Those plus charges meet some potassium, which also has plus charges. The plus charges don't like each other, and so try to run away from each other. Sodium is careening down its concentration gradient, so the only direction Na^+ is moving is into the cell. Because of the potassium leak channels, K^+ has a way out. So the plus ions that leave the cell are K^+. That is, the inward flow of Na^+ will provide an electrical force to increase the driving force through the potassium leak channels, balancing the membrane potential towards resting potential. Then the Na^+/K^+-ATPase gets the sodium back out of the cell and the potassium back in, reestablishing resting potentials.

Subthreshold stimuli are **graded,** which means they are NOT all-or-nothing—the degree of depolarization is proportional to the magnitude of the stimulus. These stimuli degrade over distance and time. They can also be summative if done temporally close to another one, and they add to each other. But if a threshold is not reached, they will always return to the resting potential.

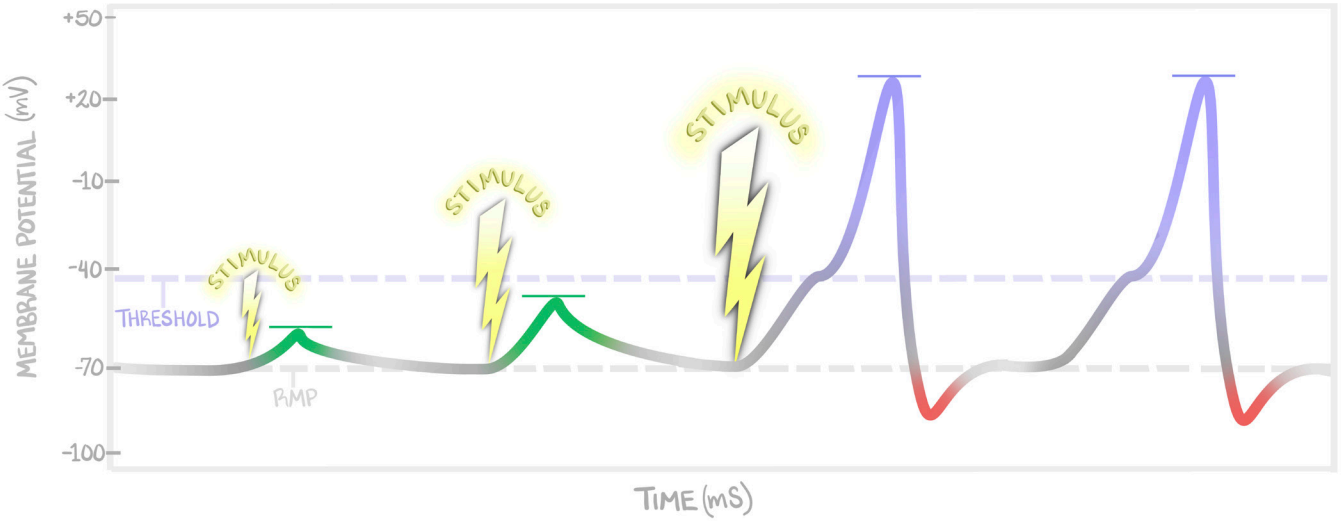

Figure 6.6: Subthreshold and Threshold Stimuli

There are two types electrical signals: graded (subthreshold) and action potential. Both spread over time and distance, but the graded signals fade as they travel, whereas the action potentials are regenerated. Graded signals often are insufficient to induce the action potential, but multiple subthreshold stimuli can summate to reach the threshold potential. Once threshold is reached, it is an all-or-nothing response. If threshold is not reached, it is graded, decaying in distance and time.

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Threshold Stimulus

If enough depolarization occurs to an excitable cell, it will cross the **threshold potential**. The threshold potential is a local phenomenon whereby the voltage change caused by **non-voltage-gated channels** depolarize the cell sufficiently to a point where specialized **voltage-gated Na^+ channels open**. The threshold potential is the membrane voltage at which voltage-gate Na^+ channels open. If the threshold is reached, all local channels open. If it is not reached, none of the local channels opens. Voltage-gated sodium channels possess two gates—an activation and inactivation gate. At rest, the activation gate is closed and the inactivation gate is open. When threshold is crossed, the **activation gate** undergoes a conformational change and the channel opens. But on a membrane, it isn't one channel that opens. Once the threshold is met, all of the channels open. This massively shifts the membrane conductance of ions and changes the cell membrane's potential drastically.

When threshold is reached, what happens after is all-or-none. It will be the action potential for that cell. The action potential looks different from cell type to cell type, but is reliably constant within a cell type, and this is the topic of the next lesson. Subthreshold stimuli can be combined, and they decay gradually back to baseline. Once any stimulus (one large one or many subthresholds added together) cross threshold—it is an action potential.