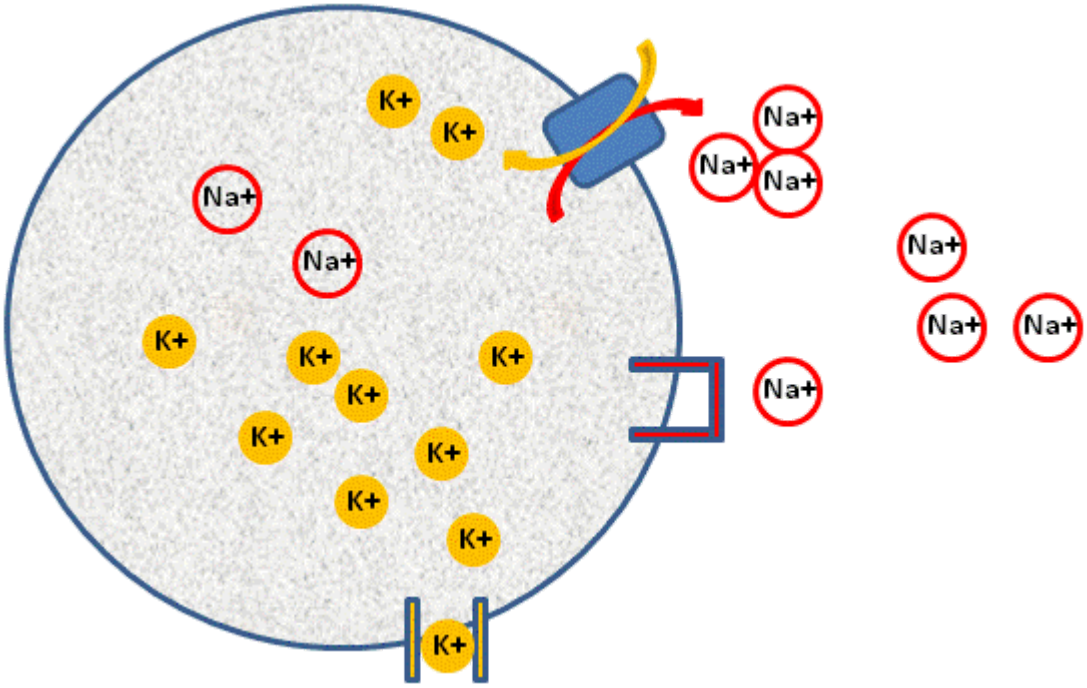
5.3.2

Membrane Potentials

In the cell, we use the same principles as the two-chamber analogy, except that we initially use energy and work, to separate the ions from each other (think of our balloon and hair experiment described above). As mentioned above, this work is primarily accomplished by the Na^+/K^+ ATPase pump. This pump moves three Na^+ ions out of the cell and two K^+ ions into the cell for every ATP (energy) molecule hydrolyzed (see figure below).



Resting Membrane Potential. *Image created at BYU-Idaho by JH, 2013.*

Diagram of a cell establishing a resting membrane potential. Shown are representations of a K^+ channel that allows for the movement of K^+ out of the cell, a closed Na^+ channel that prevents movement of Na^+ into the cell, and a Na^+/K^+ ATPase pump that moves three Na^+ ions out of the cell and two K^+ ions into the cell for every ATP molecule hydrolyzed. ATP hydrolysis is not shown.

This pump is found in every cell in the body. It creates a concentration gradient for both K^+ and Na^+. It causes a much higher concentration of K^+ to exist inside the cell and a much higher concentration of Na^+ to exist outside the cell. This results in a very large concentration gradient for K^+ to leave the cell and a very large concentration gradient for Na^+ to come into the cell. While the cell membrane expresses Na^+ channels, they remain

closed under normal ‘resting’ conditions and prevent Na^+ from diffusing into the cell. The cell membrane also expresses K^+ leak channels (no gate to regulate K^+ permeability) that allow K^+ ions to leave the cell. As a result of these differences, the membrane is 50–100 times more permeable to K^+ than Na^+ under resting conditions.

Resting Membrane Potential

Remember that the Na^+/K^+ ATPase pump transports 3 Na^+ ions out and only 2 K^+ ions into the cell every cycle. This means that over time the outside of the cell will become more positively charged because more positive ions are being pumped out of the cell than into the cell. Additionally, due to the K^+ leak channels expressed on the cell membrane, K^+ will start to diffuse out of the cell going down its concentration gradient. As K^+ leaves the cell, it will leave behind negative charges, just like what happened when the K^+ diffused to side A in our two-chamber analogy illustrated above. Inside the cell however, most of the negative charge comes from negatively charged proteins. The result of this K^+ diffusion is the same as the analogy: the inside of the cell will start to become negative with respect to outside of the membrane. As more K^+ diffuses out of the cell, the inside of the cell becomes more negative. When the membrane reaches a state of equilibrium (i.e. the chemical gradient driving K^+ out of the cell equals the electrical gradient forcing K^+ to remain in the cell), the difference in charge between the intra- and extracellular environments is called the **resting membrane potential (or voltage)**. We can actually measure the negative charge inside the cell and express this measurement in millivolts (mv). It is critical that you understand this concept. Remember that the resting membrane potential is dependent on the 3 things described above: 1) The work of the Na^+/K^+ ATPase pump; 2) the diffusion of K^+ out of the cell via K^+ leak channels; and 3) the negatively charged proteins that remain in the cell.

Membrane Potentials and Excitable Tissues

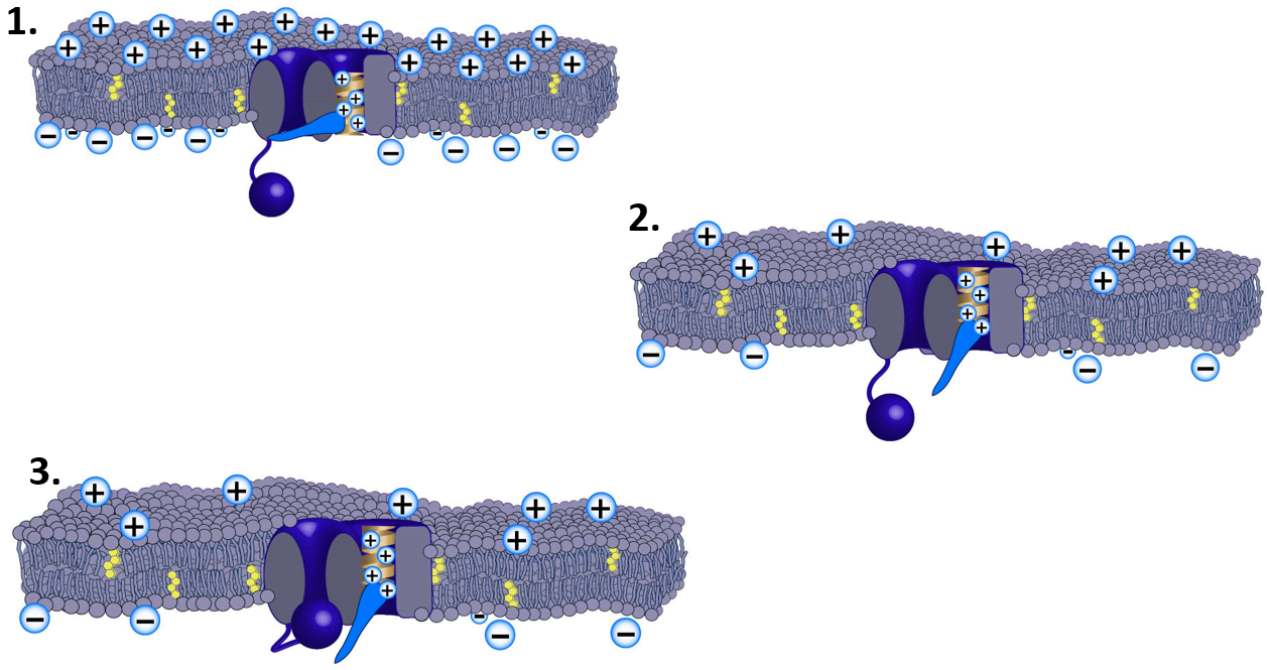
So what? Who cares if the inside of cells are negative? You may know that a battery, like the one that powers your phone, is nothing more than a separation of electrons. When you connect the ends of a battery with a wire, those electrons flow through them and can do work, like light your screen. How do you measure how strong a battery is? It’s voltage! In the same way, when our cells separate charge across the membrane, they create a voltage, or potential energy that can be used to do work. While all cells have a resting membrane potential, they are not the same for all cells. For example, the resting membrane potential for a neuron is -70mv while that of a red blood cell is only -10mv.This brings up an important concept: some cells are *excitable*, meaning they can be stimulated to experience a very predictable and rapid change in membrane potential. These are called action potentials and will be discussed later. Excitable cells include neurons, skeletal and cardiac muscle cells. Excitable cells have resting membrane potentials that range from -50mv to -85mv, while *non-excitable* cells have potentials ranging from -5mv to -10mv. Non-excitable cells do not experience action potentials and include blood cells and epithelial cells.

You might be thinking, “So what is an action potential?” Before we can fully dive into this concept, we need to revisit the concept of membrane transport proteins. Remember, membranes are made up of phospholipid bilayers that are virtually impermeable to any ionic or polar compound. Membrane transport proteins like channels (gated or leak) and carrier proteins embedded in the membrane enable the movement of these hydrophilic compounds across the membrane. You may remember that most channel proteins are very specific and will only allow certain things to pass through; some channel proteins are open all the time (**leak channels**) and others are closed most of the time (**gated channels**). Gated channels can be opened by several different types of stimuli. If they open in response to changes in membrane potential, they are called **voltage-gated ion channels**. Those that open in response to mechanical stimulation are called **mechanical-gated ion channels**, and those that open in response to a chemical signal are called **chemically-gated**, or **ligand-gated ion channels**. K^+ can move across the membrane through K^+ leak channels or gated channels. Na^+ can also move across the membrane via Na^+ leak and gated channels, but in most cells there are small

numbers of Na^+ leak channels (~1 Na^+ leak channel per 100 K^+ leak channels) and high amounts of Na^+ gated channels. Under normal resting conditions, Na^+ has a very large concentration gradient to enter the cell, but it cannot enter because the gated channel proteins for sodium are closed. In fact, for most ions, their specific protein channel is closed most of the time.

Activation of Voltage Gated Channels

If most gated ion channels are closed, how then are they stimulated to open in excitable cells? Proteins have many possible shapes or *conformations* that are dictated by the way in which their amino acids are arranged. Consider, for example, the following hypothetical voltage-gated ion channel.



Closed Voltage-Gated Channel. *Image created at JS, 2015.*

Depiction of a voltage-gated channel. This depiction shows how charges on amino acids can be attracted to or repelled by the "membrane potential" and contribute to the open or closed conformation of the "gates." The light blue "lever" represents the "activation gate" and the dark blue ball represents the "inactivation gate."

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" that "pulls" the lever towards the outer membrane causing the gate to open. Under normal resting conditions, this does not happen because the spring also has a net positive charge (notice the "+" symbols on the spring) 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 second membrane cartoon above, the charge was altered so that the inside suddenly became less negative and the outside less positive, notice that the spring could now recoil more towards the outer side of the membrane and "pull" open the activation gate (lever). Once open, ions specific to this channel could 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. If the channel were permeable to Na^+, then Na^+ could move in through the channel for a brief moment before the inactivation gate closed. 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 <0.5 msec), the effect on the cell depends on the type of ion and the direction of diffusion. For example, since K^+ is high on the inside of the cell, the direction of movement, based on the concentration gradient, will be outward or towards the extracellular space. Since K^+ is a positively charged ion, moving more K^+ out will result in a loss of positive charges; hence, the cell will become even more negative. But wasn't K^+ already in equilibrium? Why would the movement of K^+ change if it was already in equilibrium by simply opening more channels? Well, the equilibrium of K^+ is based on the membrane permeability or the number of open channels. By opening voltage-gated K^+ channels, more K^+ will diffuse out of the cell than just the leak channels alone until a new electrical gradient is established to oppose the chemical gradient and a new equilibrium is established. Thus, the inside of the cell will become more negative because of the increased K^+ diffusion out of the cell.

Another ion that can cause the membrane potential to become more negative is the Cl^- ion. In contrast to K^+, the concentration of Cl^- is highest on the outside of the cell, so the opening of a Cl^- channel will allow Cl^- to diffuse into the cell, also making the cell more negative. The opposite is true for Na^+ and Ca^{++}, both of which are positive ions and have concentrations that are highest on the outside of the cell. Thus, opening channels for either Na^+ or Ca^{++} will result in the inside of the cell becoming more positive as these cations diffuse into the cell. The following table shows the relative ion concentrations (mEq/l) in the intra- and extracellular fluids.

Ion	Extracellular fluid	Intracellular fluid
Na^+	142	10
K^+	4	140
Ca^{++}	2.4	0.0001
Mg^{++}	1.2	58
Cl^-	103	4
HCO_3^-	28	10