**Module 6 Review**

1. *What are the three main types of membrane potentials that neurons have and what are the features of each? Which of those involve a change in the membrane potential? Why are IPSPs, EPSPs, and receptor potentials called graded potentials (or electrotonic potentials)? How are graded potentials different from the action potential?*

The three main types of membrane potentials that neurons have/use are a) the resting membrane potential, b) the action potential (AP) and c) the graded/electrotonic potentials. The AP and graded/electrotonic potentials are the membrane potentials that involve rapid changes. The graded/electrotonic potentials include the postsynaptic IPSPs and EPSPs, the end plate potential and receptor potentials, which are called graded because their size (magnitude) and duration (time course) depend on how much synaptic signaling occurs. They can be small or large depending on how much synaptic or sensory signaling occurs. In contrast, the action potential is all-or-none. If threshold is reached, an AP will be generated and it doesn’t reflect how large the summed response was that produced it. Graded/electrotonic potentials are usually smaller than action potentials, and can be depolarizing (EPSPs/end plate potentials and receptor potentials) or hyperpolarizing (IPSPs).

1. *What are some important points to remember about ions and the resting membrane potential?*

* The overall/total bulk charges are the same outside and inside, the bulk charges are electrically neutral, they are isotonic & iso-osmotic (same number of solutes).
* When the resting membrane potential is established, it is an electric potential.
* The membrane potential occurs only very close to the membrane. Although the Na+/K+ pump is electrogenic (3 Na+ are pumped out for every 2 K+ pumped in), this contributes only a small amount (about -10 mV) to the resting membrane potential.
* The majority of the membrane potential is produced by the leak ion channels. The K+ leak channels are much more abundant (20-40 times more) than the leak Na+ channels, so there is a much greater net flow of K+ ions across the membrane to the outside, taking a positive charge to the outside of the membrane and leaving behind a negative charge inside.
* This is not an equilibrium system, it is at steady state; there is a constant flow (flux) of ions across the membrane, with a constant use of ATP to maintain the Na+ and K+ and other ion gradients.
* This is the membrane potential at rest. But neurons can activate and open gated ion channels to change the membrane potential. This is the basis of electrical signaling.

1. *Once the resting membrane potential is established in a neuron (and when that membrane potential changes), it provides a force that combines with the force of diffusion by the chemical gradient to influence the movement of ions. What is the electrochemical gradient on an ion? What is another name for the electrochemical gradient? Why is the electrochemical gradient different for every ion at every moment in the life of a neuron?*

The electrochemical gradient (also called the driving force) on an ion is determined by the chemical gradient for that ion and the membrane potential. Every ion has its own chemical gradient and charge. The chemical gradients are stable and do not change significantly when healthy neurons signal. However, the membrane potential can change, for example during the action potential or in graded potentials via synaptic transmission. Therefore, as the membrane potential changes it will directly impact the electrochemical gradient/driving force for that ion.

1. *Since we can convert the energy stored in the chemical gradient into an electric potential (the Nernst/Equilibrium potential or Ex), and we can measure the membrane potential (Vm) with an electrode, we can calculate the electrochemical gradient (Driving Force). The electrochemical gradient (Driving Force) equals \_\_\_. The Nernst potential doesn’t change in a healthy cell. Why? Therefore the driving force will change as the \_\_\_\_\_ changes.*

The electrochemical gradient (Driving Force) equals the membrane potential (Vm) minus the Nernst/Equilibrium potential (Ex). DF = Vm -Ex. All the active transporters work all the time to maintain the ion gradients, and they are not voltage dependent so Ex is constant. However, the membrane potential can change (for example during the action potential or synaptic graded-electrotonic potentials), and therefore the driving force will change as the membrane potential (Vm) changes. (Note that the electrochemical potential and the electrochemical gradient are two different terms that define different things. The electrochemical potential is the amount of energy stored in the ionic gradient (and is reflected in the Nernst/Equilibrium potential), while the electrochemical gradient is the difference between the membrane potential and the Nernst/Equilibrium potential.

What is the difference between the electrochemical potential (the Nernst potential) and the electrochemical driving force?

The electrochemical potential is the amount of electrical energy that is stored in an ion gradient. It only depends on the chemical/concentration gradient for an ion and its valence.

The electrochemical driving force is the difference between the membrane potential and the Nernst potential. It too depends on the chemical/concentration gradient for an ion and its valence. But importantly, it also depends on the membrane potential, and driving force changes as the membrane potential changes, for example when a neuron is active and signaling. The driving force is large if the membrane potential is very far from the Nernst potential, for example with Na+ at the resting membrane potential. The driving force is small if the membrane potential is close to the Nerst potential, for example with K+ at the resting membrane potential. The sign of the driving force tells us that if an ion channel was opened, which way a positive or negative ion (current) would flow (into or out of the cell). (See 8 below.)

1. *What does it mean that the membrane potential is “polarized” at rest? What do depolarization and hyperpolarization mean? How do neurons change their membrane potential? What changes do interneurons produce at the postsynaptic membrane and at the axon. What changes do sensory neurons produce?*

A membrane potential is called “polarized” at rest because there is a charge difference (electric potential) between the two sides of the membrane due to the different distribution of ions at the membrane surface. By convention, we consider the inside of the membrane relative to the outside (since the ground or reference electrode is usually placed outside of the cell.) Thus at rest the membrane potential is negative (about -67 mv) inside. When the membrane becomes less negative (more positive) then it is said to be depolarized. When the membrane is more negative (less positive) it is hyperpolarized. Depolarization or hyperpolarization is always described in reference to a starting point.

1. *What is current? Current can be positive or negative, explain.*

Current is the movement of charge across a certain point over time. For transmembrane currents, the movement of positive ions into the cell is called an inward current and has a negative sign. Movement of positive ions out of the cells is called an outward current and has a positive sign. (This is opposite for negative ions and we’ll discuss this in synaptic transmission.)

1. *Ion movement (current) across the membrane depends on two features. What are the two features that affect the movement of an ion across the membrane? Stated another way, ions will flow across the membrane (producing a current) only if there is an \_\_\_and \_\_\_ for that ion*.

Stated another way, ions will flow across the membrane (producing a current) only if there is an electrochemical gradient (Driving Force) and an open ion channel (conductance)\_for that ion.

1. *What are the driving forces (electrochemical gradients) for Na+ and K+ at the resting membrane potential (-67 mV), at 0 mV and at +40 mV. What does the sign on that electrochemical gradient mean?*

If the driving force is negative (for a positive ion) that will produce a negative current, and the ions will flow into the cell. If the driving force is positive (for a positive ion) that will produce a positive current and the ions will flow out of the cell. (This is different for negative ions such as Cl-.)

Definitions:

In [electrophysiological](https://www.physiologyweb.com/glossary/e/electrophysiology.html) convention, a negative [current](https://www.physiologyweb.com/glossary/c/current.html) value or downward deflection of a current trace is typically referred to as an inward current. A negative current value (i.e., inward current) can reflect either the movement of positive ions (cations) into the cell or negative ions (anions) out of the cell.

In [electrophysiological](https://www.physiologyweb.com/glossary/e/electrophysiology.html) convention, a positive [current](https://www.physiologyweb.com/glossary/c/current.html) value or upward deflection of the current trace is typically referred to as an outward current. A positive current value (i.e., outward current) can reflect either the movement of positive ions (cations) out of the cell or negative ions (anions) into the cell.

Here is a useful chart to determine the relationship among DF, direction and recorded current:



Negative Driving Force Positive Driving Force\_\_\_\_\_\_\_\_\_\_\_

Positive Ion Influx (in) Efflux (out)

(cation) (Record a negative current) (Record a positive current)

“inward current” “outward current”

Negative Ion Efflux (out) Influx (in)

(anion) (Record a negative current) (Record a positive current)

*although anions are moving out, it’s called an* *although anions are moving in, it’s called an* “inward current” “outward current”

1. *Ohm's law states that the current through a conductor between two points is directly proportional to the potential difference (V) across the two points. Voltage is an electromotive force that is able to drive current through/across a resistor. State Ohm’s Law in an equation.*

Ohm’s Law: V= i x R (V=iR) *Rearrange to state what current equals*. i= V/R. *How is the resistance/resistor and conductance/conductor related?* They are inversely proportional. Resistance= 1/conductance R=1/g or g=1/R

1. *In a typical R-C electrical circuit, how, and in which direction do electrons and current flow in the wire? What is each component of the R-C circuit in Ohm’s law?*

In a typical R-C electrical circuit, electrons flow from the negative side of the battery (anode) (where electrons are generated) to the positive side (cathode) (where electrons are consumed). By convention (thanks to Benjamin Franklin), however, the “current” is the movement of positive charges and flows from the positive electrode to the negative electrode, which is opposite of electron flow. The three components of Ohm’s law are current (i) which is the movement of electrons but defined as the movement of positive charges through the wire, resistance (R) which is produced by the presence of the resistor, and voltage (V) which is produced by the battery. Note that in a circuit, the wires are also conductors/resistors as well.

1. *In the equivalent electrical circuit (EEC) of the neuron, describe what each biological component is in the circuit. Define conductance (g) (both descriptively and mathematically) for an ion to flow across the membrane. Starting with Ohm’s law, make the rearrangements and substitutions to get to current = driving force times open ion channels. What does it mean in the EEC that the batteries and resistors for each ion function in parallel? In the EEC, the R (1/g) is said to be variable. What does that mean?*

In the EEC of the neuron, current is the movement of ions, the wires are the intracellular and extracellular aqueous solutions, the battery (V) is the driving force (the membrane potential minus the Nernst/equilibrium potential), and the resistor (R) is the plasma membrane plus ion channels. We can also express R as conductance (g) where R = 1/g. (Conductance is the inverse of resistance.) For Ohm’s law i= V/R. Substitute V= DF and R = 1/g. Then i= DF x g and thus, current= driving force times open ion channels.

Resistance/conductance depends on how many ion channels are open. Each of the batteries and resistors function in parallel because ion transporters and channels function independently; ions must move through only one type of channel across the membrane. The R (or g) is variable because it can change depending on whether the ion channels are open or closed (gated ion channels require signals to be open).

1. *What is the purpose of current (ion flow) across the membrane? What do neurons use changes in membrane potential for? Neurons endogenously change the current flow across the membrane through the activation/opening of \_\_. When current flows across the membrane, how does that affect Vm?*

Neurons use ion movement across the membrane (the transmembrane current) to change their membrane potential, and neurons use changes in membrane potential to communicate. Neurons endogenously change the current flow across the membrane through the activation/opening of ion channels. Interneurons produce graded/electrotonic potential (called EPSPs and IPSPs) at synapses, which are small changes in the membrane potential used for short distance signaling. Sensory neurons produce receptor potentials at their sensory endings. These are usually larger changes in the membrane potential that are also for short distance signaling to the nearby axon. Neurons also produce action potentials, which are for long distance signaling along the axon.

1. *Describe the transmembrane current and cytoplasmic/axial current. What are the two forces on an ion?*

The transmembrane current is the movement of ions across the membrane and depends on the electrochemical gradient/driving force and conductance/open ion channel. The cytoplasmic/axial current depends on the chemical gradient and Coulomb force, and any resistance of the cytoplasm.

1. *For graded/electrotonic potentials, the membrane potential decreases (decays) as a function of time and distance away from where the transmembrane current is produced. Why?*

The membrane potential will decrease/decay with time and distance away from where the initial transmembrane current occurred that changed the membrane potential. (This decrease is also said to dissipate or spread.) This happens because ions move/diffuse in the cytoplasm and along the inside of the membrane. Ion movement is current. Ions move in solution (either within the cytoplasm, in the extracellular solution or across the membrane) because of the two forces on an ion: chemical diffusion and Coulomb forces. (The same forces that produce the driving force which affect an ions ability to move across the membrane, also affect the movement of those ions once they are in the cytoplasm or ECF.) As the ions move away from their source of entry, the ions will diffuse away from the membrane and into the cytoplasm or be transported back across the membrane, or leak across the membrane via channels. As the ions move away, the membrane potential will return to the RMP.

1. *Why do neurons need an “active” change in the membrane potential (the action potential) for long distance signaling? (What does the action potential overcome?)*

If there were only passive flow of current (and passive change in membrane potential) down the axon, the membrane depolarization would decrease/decay with distance and time, and return to resting potential before reaching the end of the axon. (Hence the signal from the postsynaptic cell would be very weak or nothing, and no or only a little communication would occur.) The action potential overcomes the issue of decay/decrease by providing a mechanism for regenerating a change in the membrane potential. The AP is regenerated without loss (without decrement) all the way to the end of the axon, the presynaptic region.

1. *The Ag-AgCl electrode can be used to measure the membrane potential and also to change the membrane potential. a) Describe the Ag/AgCl electrode. b) Explain the reactions at the electrode. How can an electrode transform electrons (in a wire) into ions (in solution) and ions in solution into electrons in a wire. c) How can the Ag/AgCl electrode be used to both measure and change the membrane potential. d) Explain the current clamp mode and the voltage clamp mode and why they are useful.*
2. From Wikipedia: “Today, most microelectrodes used for intracellular recording are glass micropipettes, with a tip diameter of < 1 um. The micropipettes are filled with a solution that has a similar ionic composition to the intracellular fluid of the cell. A chlorided silver wire [which forms an AgCl salt precipitate on the wire] inserted into the pipet connects the electrolyte electrically to the amplifier and signal processing circuit. The voltage measured by the electrode is compared to the voltage of a reference electrode, usually a silver chloride-coated silver wire in contact with the extracellular fluid around the cell.”
3. The Ag/AgCl electrode functions through a reversible reaction: Ag + Cl- <-> AgCl + e-, where Ag is solid silver (metal), AgCl is the salt (but note that AgCl salt is a precipitate since it has low solubility) and e- is an electron. When the membrane potential becomes more negative, Cl- ions inside the electrode are repelled by the membrane potential, move toward the silver wire where they react with the Ag metal to produce AgCl and an electron (e-) is released which flows through the wires to the voltmeter. When compared with the reference electrode, is recorded as a membrane hyperpolarization. When the membrane potential becomes more positive, Cl- ions move away from the electrode (since they are attracted toward the more positive membrane potential), and a Cl- ion is released from the AgCl at the electrode and hence an electron flows to the electrode where it is consumed. When compared with the reference electrode, it is recorded as a membrane depolarization.

c) Using a two electrode system (with each electrode having its own reference/ground electrode), the measuring electrode will measure the membrane potential (how many electrons are flowing out of or into the silver wire) while the stimulating (injecting) electrode will generate or consume electrons that will change the membrane potential. Each electrode is attached to a voltmeter/potentiometer and can be controlled separately or the two systems can be connected in the case of the voltage clamp.

d) From Wikipedia:

The two electrode **voltage clamp** is an experimental method used by electrophysiologists to measure the ion currents through the membranes of excitable cells, such as neurons, while holding the membrane voltage at a set level. The voltage clamp technique allows an experimenter to "clamp" the cell potential at a chosen value. This makes it possible to measure how much ionic current crosses a cell's membrane at any given voltage. This is important because many of the ion channels in the membrane of a neuron are voltage-gated ion channels (including those involved in the action potential which we’ll learn about in the next Module), which open only when the membrane voltage is within a certain range. A basic voltage clamp will iteratively measure the membrane potential, and then change the membrane potential (voltage) to a desired value by adding/injecting the necessary current. This "clamps" the cell membrane at a desired constant voltage, allowing the voltage clamp to record what currents are delivered. Because the currents applied to the cell must be equal to (and opposite in charge to) the current going across the cell membrane at the set voltage, the recorded currents indicate how the cell reacts to changes in membrane potential. Cell membranes of excitable cells contain many different kinds of ion channels, some of which are voltage-gated. The voltage clamp allows the membrane voltage to be manipulated independently of the ionic currents, allowing the current–voltage relationships of membrane channels to be studied.

An analogy is the thermostat, heater and air conditioner in your home. In winter, when the temperature decreases (detected by the thermostat which is analogous to the measuring electrode), the gas heater will turn on for some interval, the temperature will increase and eventually reach the desired temperature detected by the thermostat and turn off. The gas heater is injecting heat, which is analogous to the injection of say positive current. You know how long/hard the heater worked when you get your gas bill at the end of the month, which is analogous to how much positive current the stimulating electrode need to inject to keep the potential clamped. On the opposite side, in summer when the temperature increases, detected by the thermostat, the air conditioner will turn on for some interval, the temperature will decrease and eventually reach the desired temperature and turn off. The AC is injecting cold air, which is analogous to say negative current. You know how long/hard the AC worked when you get your electric bill at the end of the month, which is analogous to how much negative current the stimulating electrode needed to inject to keep the membrane potential clamped. Note that the thermostat needed to be connected to the heater or AC.

The two electrode **current clamp** technique records the membrane potential by injecting current into a cell through the stimulating electrode. Unlike in the voltage clamp mode, where the membrane potential is held at a level determined by the experimenter, in "current clamp" mode the membrane potential is free to vary, and the amplifier records whatever voltage the cell generates on its own or as a result of stimulation. This technique is used to study how a cell responds when electric current enters a cell; this is important for instance for understanding how neurons respond to neurotransmitters that act by opening membrane ion channels. Most current-clamp amplifiers provide little or no amplification of the voltage changes recorded from the cell. The "amplifier" is actually an electrometer, sometimes referred to as a "unity gain amplifier"; its main purpose is to reduce the electrical load on the small signals (in the mV range) produced by cells so that they can be accurately recorded by low-impedance electronics. The amplifier increases the current behind the signal while decreasing the resistance over which that current passes. Note that the recording and stimulating electrodes don’t need to be connected in this system and work independently.

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**Lecture Notes/ Study Guide**