RESTING MEMBRANE POTENTIALS

A Self-Instructional Package

by Howard Kutchai
Department of Physiology
University of Virginia

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INTRODUCTION

Your major goal in this package is to learn how the ionic permeability properties of the plasma membranes of cells, especially nerve and muscle cells, leads to a resting state in which the cytosol is electrically polarized (negative) with respect to the extracellular fluid. This steady-state electrical potential (voltage) difference across the cell membrane is known as the resting membrane potential. After completing this package you will be able to make fairly accurate predictions of the resting membrane potential for a cell if you are given numerical values for the concentrations of the major ions (Na\(^+\), K\(^+\), Cl\(^-\)) in the cytosol and the extracellular fluid as well as the conductances of the plasma membrane to these ions. You will also be able to predict the changes that occur in the membrane potential when the conductances of the membrane to various ions or the concentrations of the ions in the cytosol or extracellular fluid change.

The presence of the resting membrane potential is required for the electrical excitability that characterizes nerve and muscle cells. The same ionic mechanisms that determine the resting potential play a role in the rapid changes in membrane potential that occur during the action potentials that allow intercellular communication in the nervous system and initiate the contraction of skeletal muscle cells.

OBJECTIVES

1. Be able to define and recognize examples of: resting membrane potential, action potential, hyperpolarization, depolarization, local response, threshold, propagated response, all-or-none response.

2. Be able to write down the approximate (± 20%) concentrations of Na\(^+\), K\(^+\), Cl\(^-\) in a skeletal muscle cell and in extracellular fluid and the resting membrane potential. Know that the net tendency of Na\(^+\) is to flow into the cell, the net tendency of K\(^+\) is to flow out of the cell, and that Cl\(^-\) is approximately in equilibrium across the membrane of the resting muscle cell.

3. Be able to recognize the following properties of the Na-K pump (Na,K-ATPase): a) Pumps Na\(^+\) out and K\(^+\) in; b) 3Na\(^+\) pumped out and 2K\(^+\) pumped in for each ATP hydrolyzed; c) transport stimulated by ATP; d) transport slowed by metabolic inhibitors.

4. Given a hypothetical concentration cell, with a membrane permeable to ions of positive or negative charge only, and given the composition of the solutions on either side of the membrane, you will be able to calculate the steady-state electrical potential difference across the membrane (both magnitude and direction).

5. Given the conductances of a particular membrane for all ions concerned and the concentrations of those ions on both sides of the membrane, you will use the Conductance Equation to compute the steady-state potential difference across the membrane (magnitude and direction).

6. Using the Conductance Equation, you will be able to predict the effect on the resting membrane potential of a significant change in the membrane's conductance to a particular ion or to a change in its intra- or extracellular concentration.
PRACTICE CYCLE #1

INPUT 1

The squid contains a giant axon (up to 500μm in diameter) that is very easy to penetrate with microelectrodes. Consider a squid giant axon removed from the animal and placed in a bath of solution similar in composition to the animal's coelomic fluid. If we have two microelectrodes (1 & 2) and the ability to record the potential difference between them we can do the following experiment. If we place both electrodes in the bath we observe no electrical potential (voltage) difference between them since the salt solution is an extremely good conductor. If we advance the microelectrode (#2) toward the giant axon, we can penetrate the cell membrane of the axon. At the moment penetration occurs, we observe a potential difference of about 70 mV between electrodes 1 and 2, electrode 2 being negative. This is the resting membrane potential of the cell \(E_m(\text{rest})\). If we then advance a third microelectrode (#3) into the cell, we observe that this electrode also becomes about 70 mV negative to electrode #1. There is no potential difference between electrodes 2 and 3 because the cytoplasm of the giant axon is a good conductor and in the steady-state there is no net current flow inside the axon.

We can now place another electrode near the cell membrane and electrode 2 for the purpose of passing current across the cell membrane. If we pass a pulse of current that causes depolarization of the membrane, this will diminish the magnitude of the resting membrane potential and will depolarize the cell at electrode #2. No change will be observed in the membrane potential at electrode #3 unless electrode #3 is within a few mm of electrode #2. A pulse of current that hyperpolarizes the membrane will transiently increase the magnitude of \(E_m\) at electrode #2. Again, no change is seen at electrode #3 unless it is quite close to the site of current passage.
PRACTICE 1
In the membrane potential recording given below identify $E_m$(rest), depolarization, hyperpolarization.

FEEDBACK 1
Did you say $E_m$(rest) a,c, e, g, i?
hyperpolarization b, d?
depolarization f, h ?

Good! Sometimes the words hyperpolarization and depolarization cause confusion. If the membrane potential goes from -70 to -60 mV this is called depolarization because it lessens the potential difference or polarity across the cell membrane (in spite of the fact that -60 is a larger number than -70). Likewise if the potential goes from -70 to -80 mV the polarity across the membrane has increased, hence we call this hyperpolarization.

PRACTICE CYCLE #2

INPUT 2
To the same experimental set-up we used above let us add another electrode (#4) that penetrates the cell membrane only about 1 mm from electrode #2.

Now if we apply progressively stronger hyperpolarizing current pulses, we observe the following at electrodes #2, #3, and #4.
The extent of the hyperpolarizations observed at #2 is directly related to the strength of the current pulse applied there. At electrode #4 (1 mm away from the current passing electrode) we observe smaller hyperpolarizations. And at electrode #3, which is many mm away from the current passing electrode, we see nothing at all. Since the hyperpolarizing response to the current pulse is observed only near the site of current passage, it is called a local response. If electrode #4 were moved a bit further away from the site of current passage the responses would be still smaller. The magnitude of the local response declines exponentially with distance from the site of current passage.

![Graph showing voltage response vs. distance](image)

If we apply small depolarizing pulses of current, transient depolarizations of the membrane are observed. For small depolarizing currents, everything we have said above applies. In response to a larger depolarizing current, an action potential may be elicited.

**PRACTICE 2**

A microelectrode is placed in a muscle fiber and 1 mm away a current passing electrode is placed. Rather weak stimuli are administered as shown below.

![Diagram of membrane potential responses](image)

Draw in the response of the membrane potential to stimuli A, B, C, and D.

Which responses are local responses?________________________

Which are hyperpolarizations?_______________________________

Which are depolarizations?________________________________

**FEEDBACK 2**

Do you see why the responses go the direction they do? Note that response B is larger than A and response D is larger than C. Why is this? Since the recording electrode is a small distance (about 1 mm) from the point where current is passed, all of the
responses represent local responses. A and B are depolarizations, C and D are hyperpolarizations.

![Diagram of membrane potential](image)

**PRACTICE CYCLE #3**

**INPUT 3**

If small pulses of depolarizing current are applied to a nerve axon or muscle fiber, the local depolarizing responses described above occur. But if progressively larger depolarizing currents are applied a degree of depolarization is reached at which a different sort of response, the action potential occurs. The membrane potential at which the action potential occurs is called the **threshold** for the nerve or muscle fiber.

The action potential differs from the local response in that it is a much larger response (the polarity of the cell membrane actually reverses, the cytosol becoming positive with respect to the extracellular fluid) and an action potential is **propagated without decrement** down the length of the nerve or muscle fiber. "Without decrement" means that the height of the action potential remains the same as it travels along the fiber, rather than decaying exponentially with distance like the local response.

**PRACTICE 3**

![Diagram of squid axon and electrodes](image)

Progressively larger depolarizing current pulses are applied to a squid axon shown above. Transmembrane potentials are recorded at electrodes 1, 2, and 3. The membrane potential responses at electrodes 1, 2, and 3 are shown below.
Identify the local responses, action potentials, and the thresholds on each recording electrode tracing. Compare the sizes of local responses at electrodes 1, 2, 3. Why is this so? At what threshold transmembrane voltage is the action potential fired at each electrode?

**FEEDBACK 3**

Did you get these answers:
- a, b, g, h local responses (ie. subthreshold responses)
- c, e, i, k thresholds
- d, f, j, l, m, n action potentials

Did you say that the local responses at electrode 1 are larger than those at electrode 2 and that there are no local responses visible at electrode 3? Did you say that at all the electrodes the threshold for firing an action potential is the same, about -55 mV? Great.

The large depolarizing signals with arrows at the end (d, f, j, l, m, and n) in the last figure are action potentials. The action potentials are too large to fit on the figure. During an action potential in a squid giant axon the membrane potential reverses sign and reaches about +50 mV! If the stimulus is not strong enough for the membrane to reach threshold, no action potential will be fired. This is called a **subthreshold stimulus**. If the stimulus is strong enough to reach threshold an action potential will be fired. If a still stronger stimulus is administered, a **supra-threshold stimulus**, the action potential that results will be the same size and shape as one elicited by a threshold stimulus. A stimulus either fails to elicit an action potential (if it is subthreshold) or produces a full strength action potential (if it is threshold or supra-threshold). Thus the action potential is called an **"all-or-none" phenomenon**. In the next self-instructional package we will learn about what determines the size and shape of action potentials. The action potential is propagated down the fiber with unchanged size and shape. Hence the action potentials were recorded at electrode 3 even though electrode 3 is too far from the current electrode for any subthreshold response to occur at electrode 3.
The electrical polarization of the cell membrane that we call the resting potential is necessary for the action potential response. A nerve or muscle fiber can be depolarized by placing it in a solution containing high [K⁺]. Once the membrane potential becomes more depolarized than about -50 mV, an action potential can no longer be elicited even though the local response persists unimpaired. The point is that unless the cell membrane is sufficiently polarized it will not have the property of electrical excitability. The main purpose of this self-instructional package is to describe how the resting membrane potential comes to be.

The resting membrane potential, as we shall see, is the result of the fact that various ions (Na⁺ and K⁺ especially) are not in electrochemical equilibrium across the cell membrane. Typical values for the concentrations of Na⁺, K⁺, and Cl⁻ in the cell water of a muscle cell and in the extracellular fluid of a typical non-marine vertebrate (like you and me) is seen in the diagram below: The resting membrane potential is about 90 mV (inside negative relative to outside). That is $E_{in} - E_{out} = -90$ mV.

**PRACTICE 4**

Which, if any, of these ions is in equilibrium across the cell membrane? (1) Use your knowledge from the package on Ionic Equilibria to calculate what the transmembrane potential would have to be in order for each ion to be in equilibrium (determine the magnitude and direction of the membrane voltage). (2) Are there any of the ions in electrochemical equilibrium when the transmembrane potential, $E_{in} - E_{out}$, is -90 mV? Which ion is closest to equilibrium? Which ion is farthest from equilibrium? (3) In which direction will Na⁺, K⁺, and Cl⁻ tend to flow spontaneously when the resting membrane potential is -90 mV?

**FEEDBACK 4**

1) Since we want to know what the transmembrane potential would have to be for each ion to be in equilibrium, the relevant relation is (you guessed it) the Nernst Equation.

$$E_{in} - E_{out} = (60 \text{ mV}/z) \log (C_{out}/C_{in})$$

Did you get the following equilibrium potentials for each ion?

$E_{Na} = +64.8$ mV  \hspace{1cm}  $E_{K} = -92.6$ mV  \hspace{1cm}  $E_{Cl} = -92.1$ mV

Good! What these numbers mean is as follows. If the membrane potential $(E_{in} - E_{out})$ were $+64.8$ mV, then Na⁺ would be in equilibrium (the concentration force for Na⁺ to enter the cell would just be counterbalanced by the electrical force causing Na⁺ to leave the cell). If the membrane potential were $-92.6$ mV, then K⁺ would be in equilibrium. If the membrane potential were $-92.1$ mV, then Cl⁻ would be in equilibrium.
2) Which ions are in equilibrium? Did you say that none of the ions is in equilibrium? Good! This is because an ion is in equilibrium only when the transmembrane potential difference is precisely equal to the equilibrium potential for that ion. The membrane potential is -90 mV. This is not equal to the equilibrium potential of any of the three ions. Which ion is closest to equilibrium? The answer is Cl\(^-\) because of the three ions its equilibrium potential is closest to the membrane potential. Cl\(^-\) can be said to be only 2.1 mV "out of equilibrium". Which ion is farthest from equilibrium? Did you say Na\(^+\)? Fine! Note that for Na\(^+\), both the electrical force and the concentration force tend to cause Na\(^+\) to enter the cell. There is thus no possibility for Na\(^+\) to be in equilibrium under these conditions. The difference between the equilibrium potential for Na\(^+\) and the actual membrane potential is 154.8 mV. This large difference is a measure of how far removed the Na\(^+\) distribution is from equilibrium.

3) In which direction will the ions tend to flow? Did you say that Na\(^+\) and Cl\(^-\) will tend to flow into the cell and K\(^+\) will flow out of the cell? If so, I'm impressed! We just noted that for Na\(^+\) both the electrical and concentration forces tend to cause Na\(^+\) to enter the cell, thus it will tend to flow in this direction. For both Cl\(^-\) and K\(^+\) the electrical force and the concentration force are oppositely directed. The concentration force tends to make K\(^+\) leave the cell, but the electrical force tends to cause it to enter. If the membrane potential were -92.6 mV, these two tendencies would be equal in magnitude. Since the electrical force is not -92.6, but only -90 mV, this force is somewhat lacking in strength relative to the concentration force. Since the concentration force is a bit larger, there is a net tendency for K\(^+\) to leave the cell. For Cl\(^-\) the concentration force tends to cause it to enter the cell, but the electrical force tends to make it leave the cell. If the membrane potential were -92.1 mV, Cl\(^-\) would be in equilibrium. Since \(E_m\) is only -90 mV, the concentration force is slightly larger, so Cl\(^-\) has a net tendency to enter the cell.

PRACTICE CYCLE #5

INPUT 5

We have just seen that there is a net tendency for Na\(^+\) to flow into the cell and for K\(^+\) to flow out of the cell. Studies with radioactive isotopes of K\(^+\) and Na\(^+\) have shown that the cell membrane is permeable to both of these ions, so we know that Na\(^+\) will flow into the cell and K\(^+\) will flow out of the cell. The only way, then, for the state of disequilibrium which exists with respect to Na\(^+\) and K\(^+\) to be maintained is for the cell to extrude Na\(^+\) as rapidly as it enters and to take K\(^+\) back up as rapidly as it leaves. As we learned in the package on Ionic Equilibria, to cause ions to flow against their gradient of electrochemical potential requires that work be done.

Cells do in fact do work to extrude Na\(^+\) and do accumulate K\(^+\). When cells are treated with metabolic poisons, so that their ability to do work is compromised, the cells lose K\(^+\) and take up Na\(^+\). When the poison is removed (provided the cells are not too severely damaged), K\(^+\) is accumulated and Na\(^+\) is extruded until the normal concentration differences are re-established. The agency responsible for extruding Na\(^+\) and accumulating K\(^+\) is known as the sodium pump. The sodium pump is a membrane protein called the Na,K-activated ATPase or the Na,K-ATPase. The Na,K-ATPase is a protein of molecular weight about 170,000 that consists of 2 or 3 different subunits. It binds Na\(^+\) at the inner surface of the plasma membrane and K\(^+\) at the outer surface of the plasma membrane and utilizes some of the energy of the high energy terminal phosphate bond of ATP to force Na\(^+\) out of the cell against its electrochemical potential gradient and to
force K$^+$ into the cell against its electrochemical potential gradient. The molecular mechanism by which the Na$^+$, K$^+$-activated ATPase "does its thing" is currently a subject of intense investigation.

The sodium pump is stimulated by elevated internal sodium concentrations, by elevated external K$^+$ concentrations, and requires internal ATP. The pump has a stoichiometry of 3 Na$^+$ pumped out and 2 K$^+$ pumped in for each ATP split. The Na$^+$, K$^+$-ATPase is specifically inhibited by the drugs known as cardiac glycosides (or digitalis alkaloids). In addition any inhibition of a cell's ability to make ATP may result in inhibition of the sodium pump.

**PRACTICE 5**

We have suspended a frog sartorius muscle in a bath of 20$^\circ$C oxygenated solution. After 30 min. we change the bath solution for one which is identical except that it contains no oxygen (it has been equilibrated with pure nitrogen gas). We leave the muscle for 60 min. in the N$_2$-equilibrated solution and then change back to an oxygenated solution. Draw a graph showing the intracellular concentrations of Na$^+$ and K$^+$ during the whole time course of this experiment.

**FEEDBACK 5**

Did you draw something like this?

The point here is that when N$_2$-equilibrated buffer is added the muscle cannot maintain its intracellular level of ATP. Thus the rate of ion pumping by the Na$^+$, K$^+$-activated ATPase slows down to the point that Na$^+$ enters the cell faster than it can be pumped out and K$^+$ leaves the cell faster than it can be pumped back in. Thus the intracellular level of K$^+$ falls, while the level of Na$^+$ rises. Upon restoration of the oxygen-equilibrated medium, oxidative metabolism resumes, the ATP levels are restored to normal, and the Na$^+$, K$^+$-activated ATPase goes to work to restore the normal intracellular levels of Na$^+$ and K$^+$. 

![Graph showing intracellular Na$^+$ and K$^+$ concentrations during the experiment.](image-url)
PRACTICE CYCLE #6

INPUT 6

Do you recall that at the beginning of this package we mentioned that the resting membrane potential of nerve and muscle cells is caused by the ion gradients which exist across them. The fact is that the energy inherent in an ion gradient can be used to create an electrical potential difference across a membrane. To see how this can come about, let's first consider a rather simple model situation called a concentration cell.

Consider the situation above. The membrane separating chamber A from chamber B is permeable to cations, but not to anions. Thus the membrane will allow $K^+$ to pass, but not $Cl^-$. Initially $K^+$ will begin to diffuse from A to B because of the "concentration force". Since $Cl^-$ cannot cross the membrane, net positive charge crosses the membrane from A to B, so that a transmembrane voltage builds up with side A negative and side B positive. Note that this "electrical force" on $K^+$ is in the opposite direction to the "concentration force" on $K^+$. Ultimately $K^+$ will come into equilibrium when this "electrical force" just balances the "concentration force". The Principle of Electroneutrality requires that only a very small number of $K^+$ ions can flow across the membrane, since $Cl^-$ cannot accompany $K^+$. Such a small amount of $K^+$ will flow that the final concentrations of $K^+$ in A and B will not be measurably different from those shown in the diagram. What then will be the equilibrium transmembrane electrical potential difference in this system? Since $K^+$ comes to equilibrium the Nernst Equation is valid and

$$E_A - E_B = (60 \text{ mV/z}) \log \left( \frac{C_B}{C_A} \right)$$

$$= 60 \text{ mV} \log \left( \frac{0.1}{1} \right) = 60 \text{ mV} \log \left( \frac{1}{10} \right) = -60 \text{ mV} \log 10 = -60 \text{ mV}$$

So the transmembrane voltage difference at equilibrium will be -60 mV (side A negative with respect to side B).

The situation we have considered shows a transmembrane concentration difference of an ion can serve as a battery to generate a transmembrane voltage equal to the equilibrium potential for that ion. This situation shown in the previous figure, where the membrane is permeable to only one ionic species, is called a concentration cell.

PRACTICE 6

In the concentration cell diagrammed below the membrane separating chamber A from chamber B is permeable to anions, but not to cations.

![Diagram of concentration cell with chambers A and B, showing 1 M KCl in A and 0.1 M KCl in B.](image-url)
At equilibrium what will be the concentrations of Na\(^+\) and Cl\(^-\) in A and B and what will be the transmembrane electrical potential difference? Which side is negative?

**FEEDBACK 6**

Did you say the equilibrium concentrations of Na\(^+\) and Cl\(^-\) will be those shown in the diagram above? Good! That is because the Principle of Electroneutrality allows only a tiny amount of Cl\(^-\) to flow in the absence of accompanying Na\(^+\) (Na\(^+\) cannot flow because the membrane will not allow it to pass).

Did you say that the equilibrium transmembrane potential will be \(E_A - E_B = -18\) mV (side A is negative since \(E_A - E_B\) is a negative number)? Double good! Since equilibrium is reached we can use the Nernst Equation:

\[
E_A - E_B = (60\text{ mV}/z) \log \left(\frac{C_B}{C_A}\right)
\]

\[
= (60\text{ mV}/-1) \log \left(\frac{0.1}{0.05}\right)
\]

\[
= -60\text{ mV} \log 2 = -60\text{ mV} (0.3) = -18\text{ mV}
\]

You could have also found out that side A must be negative by noting that the "concentration force" tends to make Cl\(^-\) flow from B to A, so that in order to balance this the "electrical force" must cause Cl\(^-\) to flow from A to B. If side A is negative relative to side B, Cl\(^-\) will be repelled from A toward B as required.

**PRACTICE CYCLE #7**

**INPUT 7**

We can see from the example of the concentration cell, that if the plasma membrane of a cell were permeable to only one ion, then the concentration difference of that ion across the membrane would cause the transmembrane voltage to be equal to the equilibrium potential for that ion. The problem is that the plasma membrane is permeable to many ions. The answer to the quandary we have posed is that the steady-state membrane potential will be a weighted average of the equilibrium potentials of all the ions for which there is a gradient and to which the membrane is permeable. The more permeable the membrane to a given ion, the more that ion contributes to the weighted average.

To see how this result comes about consider a plasma membrane that is somewhat permeable to Na\(^+\), K\(^+\), and Cl\(^-\). The resting membrane potential is equal to \(E_m\). If \(E_m\) were equal to the equilibrium potential for a particular ion, say K\(^+\), there would be no net force on K\(^+\) and K\(^+\) would not flow in a net sense across the membrane. The further \(E_m\) is from the equilibrium potential for K\(^+\) (\(E_K\)), the larger net force on K\(^+\). **Thus the difference between \(E_m\) and \(E_K\) can represent the net driving force for K\(^+\) to cross the membrane.** The net flow of K\(^+\) will be proportional to \(E_m - E_K\) and the proportionality factor is called the membrane conductance for K\(^+\) (\(g_K\)). Thus the net potassium current (\(I_K\)) is \(g_K (E_m - E_K)\) (the driving force for K\(^+\)):

\[
I_K = g_K (E_m - E_K)
\]

I think you can see that we can write similar equations for the net currents \(I_{Na}\) and \(I_{Cl}\) of Na\(^+\) and Cl\(^-\), respectively:  \(I_{Na} = g_{Na} (E_m - E_{Na})\) and \(I_{Cl} = g_{Cl} (E_m - E_{Cl})\)

Now when the membrane potential of the cell (\(E_m\)) has reached a steady state (this means \(E_m\) is constant in time), there must be no net ionic current across the plasma membrane. If there were
net current then the value of $E_m$ would be changing. Since there is no net current in the steady-state this must mean the sum of the individual ionic currents ($I_K + I_{Na} + I_{Cl}$) must be zero. Thus

$$I_K + I_{Na} + I_{Cl} = 0,$$

so that

$$g_K (E_m - E_K) + g_{Na} (E_m - E_{Na}) + g_{Cl} (E_m - E_{Cl}) = 0$$

**PRACTICE 7**

Do some algebra and solve the last expression for $E_m$.

**FEEDBACK 7**

Did you get

$$E_m = \frac{g_K}{g_K + g_{Na} + g_{Cl}} E_K + \frac{g_{Na}}{g_K + g_{Na} + g_{Cl}} E_{Na} + \frac{g_{Cl}}{g_K + g_{Na} + g_{Cl}} E_{Cl}$$

Fine. We can simplify this a little by realizing that the denominator in each term is just the sum of the membrane to all ions being considered and call it $\Sigma g_i$ so that

$$E_m = \frac{g_K}{\Sigma g_i} E_K + \frac{g_{Na}}{\Sigma g_i} E_{Na} + \frac{g_{Cl}}{\Sigma g_i} E_{Cl}$$

As we mentioned in the input section, the steady-state or resting value of $E_m$ is a weighted average of the equilibrium potentials of the various ions. You can now see that the weighting factor for each ion is just the fraction that the conductance of that ion makes up of the total membrane conductance. Note that if the membrane were permeable to only one ion, then the fraction that all other ions contributed to the total conductance would be zero and we would have a simple concentration cell again. The equation you derived above is called the **Conductance Equation** and it is very useful for predicting the steady-state $E_m$ (or resting potential) of a cell.

**PRACTICE CYCLE #8**

**INPUT 8**

Let’s see how the Conductance Equation works. Consider the muscle cell we spoke of earlier.

<table>
<thead>
<tr>
<th>Ion</th>
<th>Cytosol (mM)</th>
<th>Extracellular Fluid (mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na$^+$</td>
<td>10</td>
<td>120</td>
</tr>
<tr>
<td>K$^+$</td>
<td>140</td>
<td>4</td>
</tr>
<tr>
<td>Cl$^-$</td>
<td>3.5</td>
<td>120</td>
</tr>
</tbody>
</table>

We calculated earlier the equilibrium potentials for the various ions and obtained:

$$E_K = -92.6 \text{ mV} \quad E_{Na} = +64.8 \text{ mV} \quad E_{Cl} = -92.1 \text{ mV}$$

The values of the conductances of K$^+$, Na$^+$, and Cl$^-$ in skeletal muscle vary somewhat with the organism from which the muscle is obtained, the particular muscle studied, and the conditions of measurement. Typical values for the ratio of $g_K : g_{Na} : g_{Cl}$ for vertebrate **skeletal muscle** are $1: 0.02 : 3$. Note that the chloride conductance is the largest of all.
PRACTICE 8
Use the Conductance Equation to predict the resting membrane potential of a skeletal muscle cell whose relative conductances and equilibrium potentials are given immediately above.

FEEDBACK 8
Did you obtain $E_m = -91.4\text{mV}$ (inside negative)? Good! Here's how I did it:

$$
E_m = \frac{g_K}{\sum g_i} E_K + \frac{g_{Na}}{\sum g_i} E_{Na} + \frac{g_{Cl}}{\sum g_i} E_{Cl}
$$

If we say that the sum of the conductances is $1 + 0.02 + 3 = 4.02$

$$
E_m = \frac{1}{4.02} (-92.6) + \frac{0.02}{4.02} (+64.8) + \frac{3}{4.02} (-92.1) = -91.4\text{mV}
$$

This is very close to the -90 mV we said was typical for skeletal muscle with those given ion concentrations. The Conductance Equation really does work to give a fairly good estimate of the resting membrane potential.

PRACTICE CYCLE #9

INPUT 9
We have seen that Cl\(^-\) is close to being in equilibrium across the plasma membrane of a typical skeletal muscle cell; that is to say that its equilibrium potential is quite close to the actual membrane potential. In some (but not all) excitable tissues the distribution of Cl\(^-\) between the extracellular fluid and the cytoplasmic fluid approaches electrochemical equilibrium. When this is true:

$$
I_{Cl} = g_{Cl} (E_m - E_{Cl}) = 0
$$

The major ion currents that remain are K\(^+\) and Na\(^+\)

$$
I_K = g_K (E_m - E_K) \quad \text{and} \quad I_{Na} = g_{Na} (E_m - E_{Na})
$$

In the steady-state the sum of the ion currents must be zero, so

$$
g_K (E_m - E_K) + g_{Na} (E_m - E_{Na}) \cong 0
$$

I have used the "approximately equal to" sign ($\cong$) because we know there is a small Cl\(^-\) current.

Multiplying through in the above equation and solving for $E_m$ we obtain

$$
E_m = \frac{g_K}{g_K + g_{Na}} E_K + \frac{g_{Na}}{g_K + g_{Na}} E_{Na}
$$

This is of the same form as the previously derived Conductance Equation, but with the Cl\(^-\) term omitted. We will call this the **Short Conductance Equation**. The Short Conductance Equation illustrates how the resting membrane potential of some cells is determined chiefly by the interplay between $g_K$ and $g_{Na}$ and it is useful for rapid computation of the approximate value of the membrane potentials of many cell types.
**PRACTICE 9**

Smooth muscle is characterized by a relative sodium conductance that is higher than that of other muscle types. This results in the resting membrane potential of smooth muscle being relatively low (typically it is -50 to -70 mV). The $g_{Na}$ of dog tracheal muscle has been determined to be 25% of $g_K$. Chloride ion is in equilibrium between the extracellular fluid and the cells of this tissue. Use the Short Conductance Equation to predict the resting membrane potential. Assume that the intra- and extracellular ion concentrations are the same as those in Practice Cycle 8.

**FEEDBACK 9**

Did you calculate that the resting membrane potential in this tracheal muscle is about -61.1 mV? Good! Here's how:

$$E_m = \frac{g_K}{g_K + g_{Na}} E_K + \frac{g_{Na}}{g_K + g_{Na}} E_{Na}$$

$$E_m = \frac{1}{1 + 0.25} (-92.6) + \frac{0.25}{1 + 0.25} (+64.8) = -61.1 \text{mV}$$

Typical values of the resting membrane potential measured in this tissue with a microelectrode are about -60mV. This illustrates that, when Cl$^-$ is in equilibrium, the resting membrane potential is determined by the ratio between the conductances of K$^+$ and Na$^+$. In such cases, the Short Conductance Equation applies at the resting potential. When $E_m$ is removed from the resting potential, chloride is no longer in equilibrium and must be taken into account. When $E_m$ is removed from the equilibrium potential for Cl$^-$, as it is during an action potential, chloride current will cause a restoring force attempting to return the value of $E_m$ to the original resting potential (the Cl$^-$ equilibrium potential).

**PRACTICE CYCLE #10**

**INPUT 10**

We have seen that different values for $g_K$, $g_{Na}$, and $g_{Cl}$ in different excitable tissues result in different values for the resting membrane potential. In tissues in which Cl$^-$ is in equilibrium, the relationship between $g_K$ and $g_{Na}$ determines the resting membrane potential. If either of these conductances were altered, for example by a drug, the resting membrane potential would change. Since each of the ions present exerts a "force" to bring the resting membrane potential toward its equilibrium potential, changing the equilibrium potential of a particular ion will also alter the membrane potential. This is especially true in the case of K$^+$ which, because of its large conductance, is often the dominant ion in determining the resting membrane potential. Altering the concentration of an ion in the extracellular fluid or in the cytoplasm will change its equilibrium potential.

**PRACTICE 10**

In cardiac muscle the distribution of K$^+$ and Na$^+$ is similar to that in skeletal muscle. Cl$^-$ is very close to electrochemical equilibrium and $g_{Cl}$ (unlike the case in skeletal muscle) is quite small.

```
<table>
<thead>
<tr>
<th>Ion</th>
<th>Cytosol (mM)</th>
<th>Extracellular Fluid (mM)</th>
<th>Equilibrium Potential (mV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>K$^+$</td>
<td>140</td>
<td>4</td>
<td>-92.6</td>
</tr>
<tr>
<td>Na$^+$</td>
<td>10</td>
<td>120</td>
<td>+64.8</td>
</tr>
</tbody>
</table>
```
1) What is the normal resting membrane potential of a cardiac ventricular cell for which \( g_{Na}/g_K = 0.05/1 \)?

2) A patient with renal disease has a plasma of \([K^+] = 7\text{mM}\). What will be the resting membrane potential of the ventricular cells in the heart of this patient?

**FEEDBACK 10**

Did you compute -85 mV for the normal resting potential and -71.2 mV in the patient with high plasma \([K^+]\)? Fine! Here is how I did it:

1) \( g_{Na}/g_K = 0.05/1 \) leads to \( g_{Na}/(g_{Na}+g_K) = 0.048 \) and \( g_K/(g_{Na}+g_K) = 0.952 \)

The Short Conductance Equation may be applied since \( Cl^- \) is very close to equilibrium and \( g_{Cl} \) is quite small: \( E_m = (0.952)(-92.6) + (0.048)(+64.8) = -85 \text{ mV} \)

This is actually quite close to values measured with microelectrodes in myocardial ventricular cells.

2) In the patient with elevated plasma potassium, the equilibrium potential for \( K^+ \) will be altered: \( E_K = 60 \text{ mV} \log (7/140) = -60 \text{ mV} \log (20) = -78.1 \text{ mV} \). Using the Short Conductance Equation to compute the resting potential, we obtain:

\[
E_m = (0.952)(-78.1) + (0.048)(+64.8) = -71.2 \text{ mV}
\]

A resting membrane potential this low will cause the contractions of the heart to be weaker than normal and the heart will be much more susceptible than the normal heart to developing arrhythmias. If the plasma potassium level should rise a bit higher, the myocardial cells would depolarize still further, and the patient's life would be in grave danger.

**SUMMARY**

The aim of this self-instructional package is to show that the resting membrane potential of an excitable cell is due to the interplay of the electrochemical gradients of the various ions. Each ion exerts "force" that tends to bring the resting membrane potential toward the equilibrium potential for that ion. The greater the conductance of an ion, the greater its power to influence the membrane potential of the cell. The Conductance Equation shows that the resting membrane potential is a weighted average of the equilibrium potentials of the ions involved, with the weighting factor for each ion being the ratio of its conductance to the total ionic conductance. In different cell types the relative conductances and intracellular concentrations of ions vary and the resting membrane potential varies accordingly. In the next package we will consider the ionic mechanism of the action potential. We will see that the action potential is caused by rapid changes in the membrane conductances to various ions. First the conductance to \( Na^+ \) increases explosively, driving the membrane potential toward the \( Na^+ \) equilibrium potential (+64.8 mV). Then the \( Na^+ \) conductance decreases toward resting levels and the \( K^+ \) conductance increases. This causes the membrane potential to return toward the \( K^+ \) equilibrium potential (-92.6 mV). When the conductances of \( Na^+ \) and \( K^+ \) have returned to the resting values, the resting membrane potential is re-established.
POST TEST

1. Two microelectrodes are placed in a squid giant axon 1 mm apart. Current pulses are passed at electrode A to perturb the membrane potential and the resultant voltage changes at A and B are monitored. The tracings below show records of membrane potential (voltage) versus time at A and B.

```
A 1 2 3 4 5 6
B 7 8 9 10 11 12
```

Record all the numbers that represent:
- a) Resting potential.
- b) Action potential.
- c) Hyperpolarization.
- d) Depolarization.
- e) Local response.
- f) Threshold.
- g) Propagated response.

2. Fill in the appropriate ion concentrations (approximate + 20%) for the cellular and extracellular compartments of human skeletal muscle.

<table>
<thead>
<tr>
<th>Cytosol (mM)</th>
<th>Extracellular fluid (mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺</td>
<td></td>
</tr>
<tr>
<td>K⁺</td>
<td></td>
</tr>
<tr>
<td>Cl⁻</td>
<td></td>
</tr>
</tbody>
</table>

3. Check those of the following that are properties of the Na-K-ATPase.
   - _____ exchanges Na⁺ and K⁺ one for one.
   - _____ not affected by cellular level of ATP.
   - _____ affected by cellular level of leucine.
   - _____ stimulated by intracellular K⁺ and extracellular Na⁺.
   - _____ stimulated by extracellular K⁺ and intracellular Na⁺.
   - _____ requires intracellular ATP.
   - _____ not affected by cyanide and dinitrophenol.
   - _____ inhibited by cyanide and dinitrophenol.
   - _____ exchanges 3Na⁺ for 2K⁺.
   - _____ exchanges 2Na⁺ for 3K⁺.
   - _____ pumps Na⁺ in and K⁺ out of the cell.
_____ pumps Na\(^+\) out and K\(^+\) into the cell.

4. The membrane in the diagram below is permeable to Cl\(^-\) but not to K\(^+\). What will be the steady-state electrical potential across this membrane? Which side will be positive with respect to the other?

![Diagram of membrane with A and B compartments]

5. The following data pertains to a particular muscle cell and its plasma membrane.

<table>
<thead>
<tr>
<th>Ionic Species</th>
<th>Intracellular Concentration (mM)</th>
<th>Extracellular Concentration (mM)</th>
<th>Relative resting membrane conductance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na(^+)</td>
<td>12</td>
<td>120</td>
<td>0.05</td>
</tr>
<tr>
<td>K(^+)</td>
<td>120</td>
<td>4</td>
<td>0.5</td>
</tr>
<tr>
<td>Cl(^-)</td>
<td>4</td>
<td>120</td>
<td>0.45</td>
</tr>
</tbody>
</table>

Use the Conductance Equation to estimate the steady-state resting membrane potential of this cell. Is the cytosol negative or positive with respect to the extracellular fluid?

6. A cardiac muscle cell has the ionic distribution shown and ion conductances shown below

<table>
<thead>
<tr>
<th>Ionic Species</th>
<th>Intracellular Concentration (mM)</th>
<th>Extracellular Concentration (mM)</th>
<th>Relative resting membrane conductance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na(^+)</td>
<td>12</td>
<td>120</td>
<td>0.088</td>
</tr>
<tr>
<td>K(^+)</td>
<td>120</td>
<td>4</td>
<td>0.878</td>
</tr>
<tr>
<td>Cl(^-)</td>
<td>4</td>
<td>120</td>
<td>0.035</td>
</tr>
</tbody>
</table>

Note that the chloride conductance of cardiac muscle cells is much smaller than that of skeletal muscle (see problem 5. Since the Cl\(^-\) is not far removed from equilibrium and since the \(g_{Cl}\) is rather small, we may not be greatly in error if we ignore Cl\(^-\). Calculate the resting membrane potential of this cardiac

(a) Using the full Conductance Equation

(b) Using the Short Conductance Equation (ignoring Cl\(^-\))

(c) How large an error is caused by ignoring Cl\(^-\)?

7. The concentration of K\(^+\) in the extracellular fluid surrounding the cell in problem 6 is increased to 8 mM. Calculate (a) the K\(^+\) equilibrium potential and (b) the resting membrane potential.
ANSWERS TO POST TEST

1. Record all the numbers that represent:
   a) Resting potential: 1, 3, 7, 10
   b) Action potential: 6, 12
   c) Hyperpolarization: 2, 8
   d) Depolarization: 4, 9
   e) Local response: 2, 4, 8, 9
   f) Threshold: 5, 11
   g) Propagated response: 6, 12

2. Fill in the appropriate ion concentrations (approximate + 20%) for the cellular and extracellular compartments of a human muscle.

<table>
<thead>
<tr>
<th></th>
<th>Cytosol (mM)</th>
<th>Extracellular fluid (mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺</td>
<td>10</td>
<td>120</td>
</tr>
<tr>
<td>K⁺</td>
<td>140</td>
<td>4</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>3.5</td>
<td>120</td>
</tr>
</tbody>
</table>

3. Check those of the following that are properties of the Na-K-ATPase.

- Exchanges Na⁺ and K⁺ one for one.
- Not affected by cellular level of ATP.
- Affected by cellular level of leucine.
- Stimulated by intracellular K⁺ and extracellular Na⁺.
- Stimulated by extracellular K⁺ and intracellular Na⁺.
- Requires intracellular ATP.
- Not affected by cyanide and dinitrophenol.
- Inhibited by cyanide and dinitrophenol.
- Exchanges 3Na⁺ for 2K⁺.
- Exchanges 2Na⁺ for 3K⁺.
- Pumps Na⁺ in and K⁺ out of the cell.
- Pumps Na⁺ out and K⁺ into the cell.

4. \[ \Delta E = E_A - E_B = (60 \text{ mV}/z) \log \left(\frac{C_{i_i}}{C_{i_A}}\right) \]
   \[ = (60 \text{mV}/-1) \log(0.1/1) = +60 \text{mV} \]

5. First use the Nernst Equation to compute the equilibrium potentials:
   \[ E_{Na} = +60 \text{ mV} \] (inside cytosol relative to extracellular fluid)
   \[ E_K = -88.6 \text{ mV} \]
   \[ E_{Cl} = -88.6 \text{ mV} \]
   Then use the Conductance Equation to calculate \( E_m \):
   \[ E_m = \frac{g_K}{\sum g_i}E_K + \frac{g_{Na}}{\sum g_i}E_{Na} + \frac{g_{Cl}}{\sum g_i}E_{Cl} \]
   \[ E_m = 0.5E_K + 0.05E_{Na} + 0.45E_{Cl} = -81.2 \text{mV} \] (inside negative relative to outside)
6. The equilibrium potentials are the same as in the previous problem.

   a) Using the Conductance Equation, we obtain

   \[ E_m = (0.877)(-88.6 \text{ mV}) + (0.088)(+60 \text{ mV}) + (0.035)(-88.6 \text{ mV}) = -75.5 \text{ mV} \]

   b) When we use the Short Conductance Equation and omit Cl⁻, then the relative conductances of K⁺ and Na⁺ must add up to 1.0, so that

   \[ E_m = (0.909)(-88.6 \text{ mV}) + (0.091)(+60 \text{ mV}) = -75.1 \text{ mV} \]

   c) Error = 0.4 mV

7. a) \( E_K = 60 \text{ mV log}(8/120) = -60 \text{ mV log}(15) = -70.6 \text{ mV} \)

   b) \( E_m = (0.909)(-70.6 \text{ mV}) + (0.091)(+60 \text{ mV}) = -58.7 \text{ mV} \)