The Origin of the Resting Membrane Potential

3.1

Learning Objectives

- Write the Nernst equation for any given ion
- Define equilibrium potential
- Be able to calculate the equilibrium potential for any ion
- Recognize the proper form of the Goldman–Hodgkin–Katz equation
- Explain why in the Goldman–Hodgkin–Katz equation the anion concentration in one compartment appears on the opposite side of the argument from the cation concentration in the same compartment
- Define and distinguish between slope conductance and chord conductance
- Write the chord conductance equation
- Explain what happens to membrane potential when the conductance to a particular ion changes

INTRODUCTION

In Chapter 2.6, we analyzed the energetics of membrane transport across resting cardiac muscle cells that have a membrane potential of about -80 mV, negative inside. At rest, the concentration gradient favored Na^+ and Ca^{2+} entry into the cell and K^+ exit. These gradients produced slow leaks of ions that were continually balanced by active transport mechanisms such as the Na,K-ATPase and Na–Ca exchanger so that the ionic composition of the cytosol stayed constant.

The resting membrane potential is extremely important because, first, all cells have a membrane potential (but not the same value!), and modulation of the membrane potential is associated with modulation of cellular activity. Certain cells of the body, called **excitable cells**, can use rapid changes in their membrane potential as a signal. These cells include nerve cells and muscle cells.

Now we ask the question, where did the resting membrane potential come from? To answer this question, we will consider hypothetical membranes. These membranes are not like any biological membrane, but we consider them because they will clarify how the resting membrane potential comes to be what it is. Here we will use concepts of potential and capacitance already covered in Chapter 1.3, and the concept of the electrochemical potential discussed in Chapter 1.7.

THE EQUILIBRIUM POTENTIAL ARISES FROM THE BALANCE BETWEEN ELECTRICAL FORCE AND DIFFUSION

First we consider a **hypothetical membrane that is permeable only to Na^+ ions**. Suppose that $[Na^+]_o$, the outside or extracellular sodium concentration, is 145×10^{-3} M, and $[Na^+]_i = 12 \times 10^{-3}$ M. And suppose that initially there is no membrane potential. What happens? As shown in Figure 3.1.1, the diffusion gradient for Na^+ favors Na^+ entry into the cell, and the initial Na^+ influx carries a charge that builds up on the inside of the cell. This produces a potential (recall that separation of charge produces a potential) across the membrane that impedes further Na^+ ion movement because the positive charges repel the positively charged Na^+ ion. The potential that develops is related to the electric force that now works against further Na^+ movement. Eventually the electric force will get so large that the diffusive flow will be exactly counterbalanced, and net flow will stop. This will occur at the **Na equilibrium potential**. We can calculate what that potential should be in two ways: first by looking at Fick's law and second by analyzing the energetics. We get the same answer either way. The situation for the development of the Na^+ equilibrium potential is shown in Figure 3.1.1.

Fick's law with an electrical force is given as

[3.1.1] $$J_s = -D\frac{\partial C}{\partial x} - \frac{D}{RT}Cz\Im\frac{\partial \psi}{\partial x}$$

This is Eqn [1.7.19]. Here J_s is the solute flux, in this case the flux of Na^+, D is the diffusion coefficient, C is the concentration of Na^+, R is the gas constant, T is the absolute temperature, z is the charge on the ion ($+1$ for Na^+), and $\Im$ is the faraday, the number of coulombs per mole. At equilibrium, $J_s = 0$, and we equate the diffusive force and the electrical force:

[3.1.2] $$\frac{RT}{C}\frac{\partial C}{\partial x} = -z\Im\frac{\partial \psi}{\partial x}$$

Integrating both sides from outside to inside of the membrane, we get

[3.1.3]
$$\int_o^i \frac{RT}{C}\frac{\partial C}{\partial x}\,dx = \int_o^i -z\Im\frac{\partial \psi}{\partial x}\,dx$$
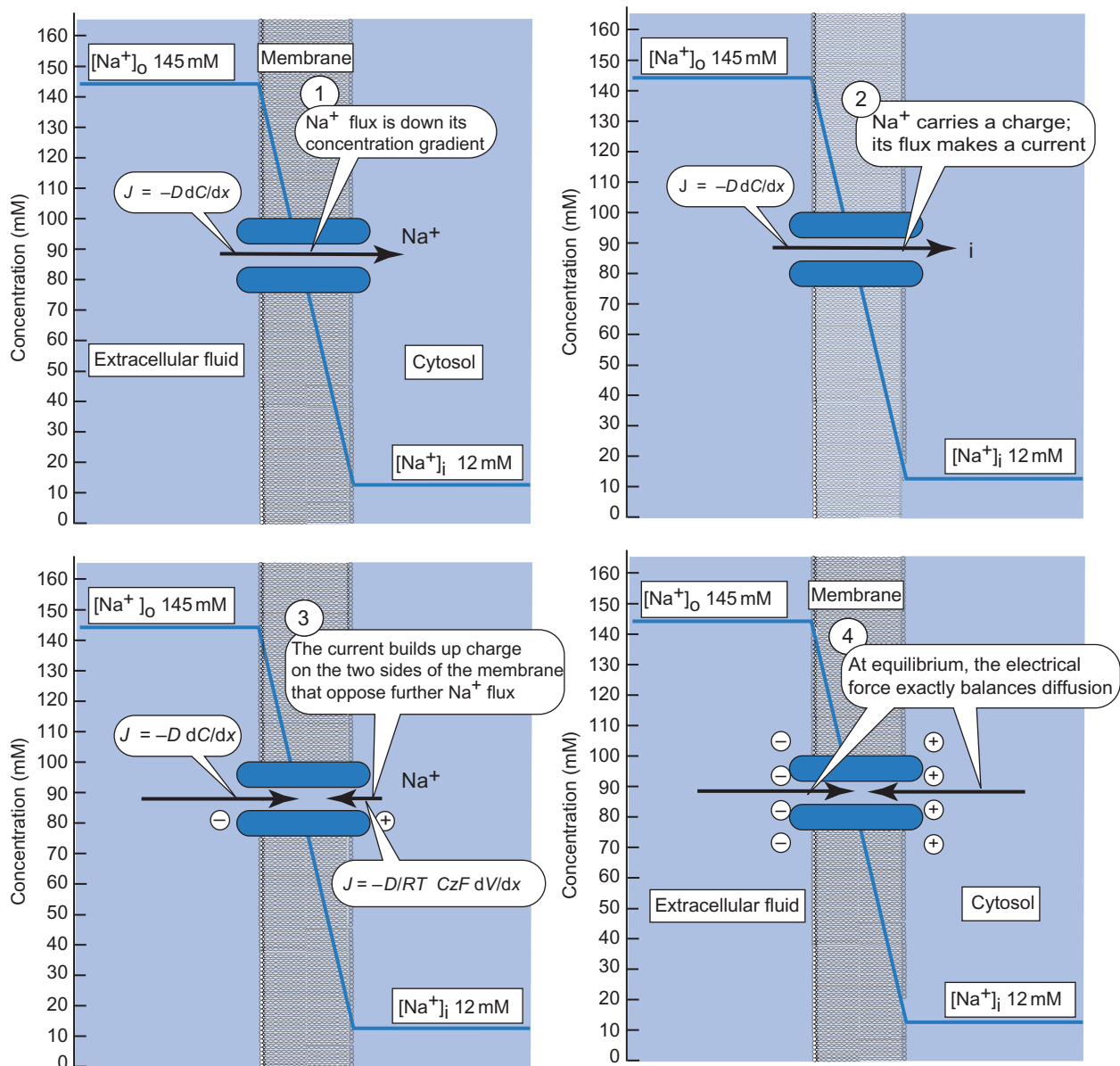
$$RT \ln\frac{C_i}{C_o} = z\Im(\psi_o - \psi_i)$$

FIGURE 3.1.1 Generation of the Na equilibrium potential across a hypothetical membrane that is permeable only to Na. The $[Na]_o$ in this case is high, about 145 mM, whereas $[Na]_i$ is 12 mM. Thus the diffusion gradient favors Na^+ flux from the outside to the inside of the cell. Since Na^+ is electrically charged, flux of only Na^+ makes a current across the membrane that separates charges and thus produces an electrical potential. The electric field exerts forces on Na^+ that retards its movement. When the diffusive force exactly balances the electrical force, flux is zero and the potential is E_{Na}, the sodium equilibrium potential.

This gives the equilibrium membrane potential as

[3.1.4] $$\frac{RT}{z\Im} \ln \frac{C_i}{C_o} = (\psi_o - \psi_i)$$

It is usual for physiologists to take the outside solution as ground ($\psi_o = 0$) because it is potential *differences* that we are concerned with. Using this standard $\psi_o = 0$, we rewrite Eqn [3.1.4] as

[3.1.5] $$\frac{RT}{z\Im} \ln \frac{C_o}{C_i} = (\psi_i - \psi_o)$$

If you always put the outside ion in the numerator of the argument of the logarithm, then the sign of the membrane potential will be correct. This is a famous equation, the **Nernst equation**, named for Walther

Nernst (1864−1941), a physical chemist from Berlin, Germany. It calculates the potential at which net flux is zero, which occurs at equilibrium for the ion. **The membrane potential at which the diffusive force is exactly balanced by the electrical force is called the equilibrium potential for that ion**. For sodium, it is usually symbolized as E_{Na}.

The Nernst Equation can also be derived easily from considering the electrochemical potentials. At equilibrium we have

[3.1.6]
$$\Delta\mu = \mu_{Na_i} - \mu_{Na_o}$$
$$0 = \mu^o_{Na_i} + RT \ln[Na^+]_i + z\Im\psi_i - \mu^o_{Na_o}$$
$$- RT \ln[Na^+]_o - z\Im\psi_o$$

EXAMPLE 3.1.1 Calculate the Equilibrium Potential for Na⁺

Inserting values for $[Na^+]_i = 12 \times 10^{-3}$ M and $[Na^+]_o = 145 \times 10^{-3}$ M, into Eqn [3.1.5], we calculate

$$\psi_i - \psi_o = \frac{8.314\,J\,mol^{-1}\,K^{-1} \times 310\,K \times \ln\left(\dfrac{145 \times 10^{-3}\,M}{12 \times 10^{-3}\,M}\right)}{1 \times 9.649 \times 10^4\,C\,mol^{-1}} = 0.0666\,V$$

Note that the potential inside is positive, as it should be to impede further influx of a positive ion.

Canceling out the standard free energies, which are equal, we can arrange Eqn [3.1.6] to give

[3.1.7] $$\frac{RT}{z\mathfrak{I}}\ln\frac{[Na^+]_o}{[Na^+]_i} = (\psi_i - \psi_o)$$

The Nernst equation is often written with $\log_{10}$ instead of the natural logarithm. At $37°C = 310$ K, Eqn [3.1.7] can be written as

[3.1.8] $$0.0615\log\frac{[Na^+]_o}{[Na^+]_i} = (\psi_i - \psi_o)$$

where the log is now $\log_{10}$. The term 0.0615 is the evaluation of the expression $RT/z\mathfrak{I}$ and conversion of the natural log, ln, to $\log_{10}$. What this means is that every 10-fold gradient in concentration of a singly charged ion gives an equilibrium potential of 61.5 mV at $37°C$.

THE EQUILIBRIUM POTENTIAL FOR K⁺ IS NEGATIVE

Now we **suppose that the membrane is impermeable to Na⁺ and Cl⁻ ions but it is permeable only to K⁺**. The $[K^+]$ concentrations on the two sides of the membrane are those in a muscle cell, namely, $[K^+]_o = 4 \times 10^{-3}$ M and $[K^+]_i = 155 \times 10^{-3}$ M. Because of its concentration gradient, K⁺ will diffuse out of the cell, causing an outward current and accumulation of positive charges on the *outside* of the cell. The Nernst equation is

[3.1.9] $$\frac{RT}{z\mathfrak{I}}\ln\frac{[K^+]_o}{[K^+]_i} = (\psi_i - \psi_o)$$

The result of the calculation using $[K^+]_o = 4 \times 10^{-3}$ M and $[K^+]_i = 155 \times 10^{-3}$ M is **$E_K = -0.0977$ V** or **-97.7 mV**. Here the potential is strongly negative inside.

We can repeat this calculation for any ion to obtain its equilibrium potential. We must remember what goes into the equations, however. As an example, consider that **the membrane is not permeable to either K⁺ or Na⁺, but is freely permeable only to Cl⁻**. Suppose further that Cl⁻ is 100×10^{-3} M outside the cell and 5×10^{-3} M inside the cell. The Nernst equation for Cl is

[3.1.10] $$\frac{RT}{z\mathfrak{I}}\ln\frac{[Cl^-]_o}{[Cl^-]_i} = (\psi_i - \psi_o)$$

In this case, $z = -1$ because the Cl⁻ ion has a negative charge. This is equivalent to inverting the argument of the logarithm. Here we get $\psi_i - \psi_o = -0.0615\log(100/5) = -0.080$ V. Thus $E_{Cl} = -0.080$ V $= -80$ mV.

Figure 3.1.2 shows the concentration differences for Na⁺, K⁺, and Cl⁻ and the equilibrium potential for each of these ions. It is important to remember what the equilibrium potential is. It is the potential at which the electrical force exactly balances diffusion so that the net flux of the ion across the membrane is zero. Since there is no flux, there is no change in the concentrations on the two sides of the membrane and the ion is at equilibrium.

Such hypothetical membranes as the ones we have been considering that are permeable only to Na⁺, or only to K⁺ or only to Cl⁻ do not exist. Real membranes have some nonzero permeability to all of these ions. So what is the membrane potential across a membrane that is permeable to all three? The short answer is: it depends on how permeable the membrane is to each of the ions. What we need is some expression that tells us what the magnitude of the membrane potential will be, given the equilibrium potentials and the relative permeabilities of the ions.

INTEGRATION OF THE NERNST−PLANCK ELECTRODIFFUSION EQUATION GIVES THE GOLDMAN−HODGKIN−KATZ EQUATION

When there is a flux of solute, and the solute is charged, there is a current. The relationship between current density and flux is

[3.1.11] $$I_i = z\mathfrak{I}J_i$$

where the subscript i denotes the particular ion that is carrying the current. The total current is the sum of all the ionic currents. Now we substitute in for the flux using Eqn [3.1.1] to get

[3.1.12] $$I_i = z_i\mathfrak{I}J_i = -z_i\mathfrak{I}\left(D_i\frac{\partial C_i}{\partial x} + \frac{D_i}{RT}C_i z_i\mathfrak{I}\frac{\partial\psi}{\partial x}\right)$$

This is the **Nernst−Planck electrodiffusion equation**. We can obtain an expression for I_i by integrating this equation over the thickness of the membrane (from
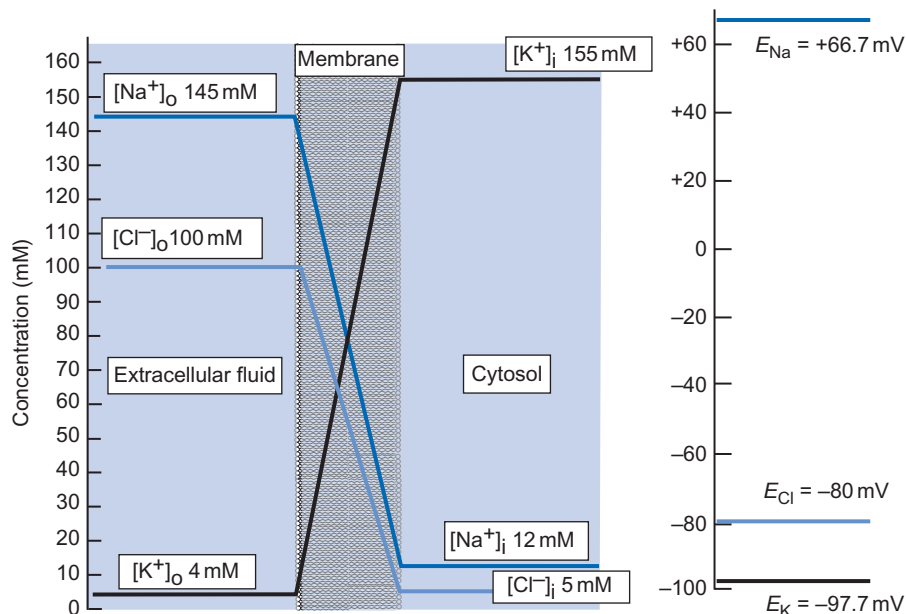
FIGURE 3.1.2 Equilibrium potentials for Na, K, and Cl in a muscle cell. A positive equilibrium potential is needed to prevent Na^+ ions from entering the cell from the extracellular fluid; a negative equilibrium potential is needed to prevent Cl^- ions from entering; a negative equilibrium potential is needed to prevent K^+ ions from exiting the cell. The solid lines represent ion concentrations.

$x = 0$ to δ, where δ is the thickness of the membrane), but this integration can be accomplished in closed form only if we assume that the potential gradient is linear. This is called the **constant field assumption**. The integration gives

$$[3.1.13] \qquad I_i = \frac{z_i^2 \mathfrak{S}^2 D_i}{RT\delta} E_m \left(\frac{C_i e^{(z_i \mathfrak{S} E_m / RT)} - C_o}{e^{(z_i \mathfrak{S} E_m / RT)} - 1} \right)$$

as detailed in Appendix 3.1.A1. This is often written in an alternate form by multiplying both numerator and denominator by $e^{(-Z\mathfrak{S}/RT)E_m}$:

$$[3.1.14] \quad I_{ion} = \frac{(D/\delta)[(z^2 \mathfrak{S}^2 / RT) E_m][C_i - C_o e^{(-z\mathfrak{S}/RT)E_m}]}{[1 - e^{(-z\mathfrak{S}/RT)E_m}]}$$

This is the **Goldman−Hodgkin−Katz (GHK) current equation**. It relates the current carried by each ion to its concentration on both sides of the membrane (C_i and C_o) and to the membrane potential, E_m. Now at steady-state resting membrane potential, the total current across the membrane must be zero, or otherwise E_m would be changing:

$$[3.1.15] \qquad I_{total} = I_{Na} + I_K + I_{Cl} = 0$$

By substituting in for the expression for I_{Na}, I_K, and I_{Cl}, we can derive an expression for E_m:

$$[3.1.16] \quad E_m = \frac{RT}{\mathfrak{S}} \ln \left[\frac{P_K[K^+]_o + P_{Na}[Na^+]_o + P_{Cl}[Cl^-]_i}{P_K[K^+]_i + P_{Na}[Na^+]_i + P_{Cl}[Cl^-]_o} \right]$$

This is the **GHK equation**. It describes the resting membrane potential when only Na^+, K^+, and Cl^- are permeant, but it can be expanded to include other ions. The inside concentration of Cl^- appears in the numerator with the outside concentrations of Na^+ and K^+ because z for Cl^- is -1.0 and z for Na^+ and K^+ is $+1.0$. Additional ions can be added to this equation if they contribute significantly to the currents across the membrane. This equation shows that the resting membrane potential results from the concentration-weighted permeabilities across the membrane because each permeability is multiplied by the concentration of the ion. Appendix 3.1.A1 presents a full derivation of this equation.

SLOPE CONDUCTANCE AND CHORD CONDUCTANCE RELATE ION FLOWS TO THE NET DRIVING FORCE

The GHK current equation (Eqn [3.1.14]) describes the current carried by any given ion in terms of its concentration on both sides of the membrane and the membrane potential. If we assume that the permeability, D/δ, is constant, we can calculate the current carried by each ion as a function of the membrane potential. The currents carried by K^+ and Na^+ for a muscle cell containing 155 mM $[K^+]_i$ and 12 mM $[Na^+]_i$ and 4 mM $[K^+]_o$ and 145 mM $[Na^+]_o$ as predicted from the GHK current equation are shown in Figure 3.1.3. At the equilibrium potential for each ion, there is no current. This equilibrium potential is also called the **reversal potential**, because at this point the current changes from negative (positive charges enter the cell—by convention this is an **inward current**) to positive (positive charges exits the cell−this is an **outward current**).
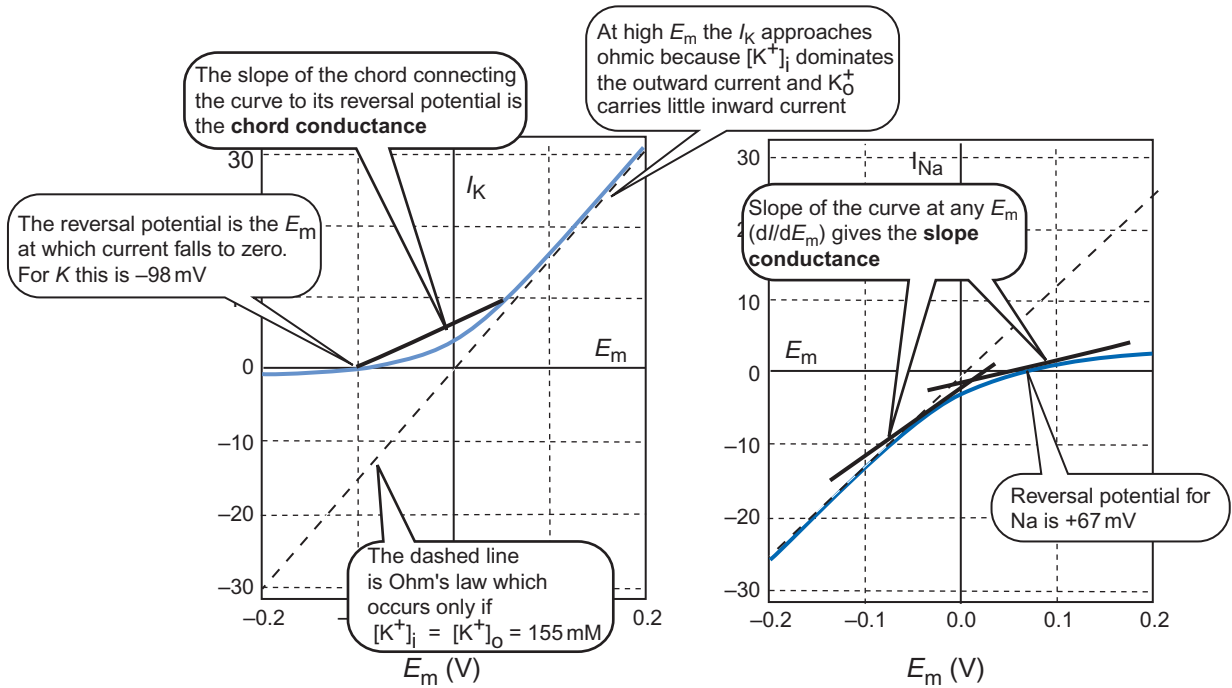
FIGURE 3.1.3 Currents carried by K^+ (left) and Na^+ (right) as predicted by the GHK current equation if the membrane was permeable only to K^+ (left) or to Na^+ (right).

The relationship between current and voltage can be described by a **conductance**. Ohm's law states

[3.1.17] $$I_i = \frac{E}{R_i} = g_i E$$

where E is the potential difference that drives current flow (NOT the electric field intensity!), R_i is the **resistance** to the ion i, and g_i is the **conductance**. Resistances have units of ohms. Conductances have units of ohm^{-1}, which is a **siemen**, equal to $1\ AV^{-1}$. According to Ohm's law, the conductance is defined for a line that passes through the origin. The origin is the point at which there is no net driving force for current flow. For ions that are not uniformly distributed across the membrane, however, the point of no net current flow occurs at the reversal potential. Thus we *define* a **chord conductance**:

[3.1.18] $$I_i = g_i(E_m - E_i)$$

where g_i is the chord conductance at E_m, E_m is the membrane potential at any point in the current–voltage curve, and E_i is the equilibrium potential = reversal potential for a single ion, i. This conductance is the slope of the chord joining the curve to its reversal potential, as shown in Figure 3.1.3. Thus the chord conductance is not constant but varies with membrane potential, E_m.

We can also define a **slope conductance** that relates I to E. This is obtained by differentiating Eqn [3.1.17]:

[3.1.19] $$g = \frac{dI_i}{dE_m}$$

Neither the slope conductance nor the chord conductance is a constant. Even for a straight cylindrical pore that is specific for some ion, the conductance varies with voltage because the current is carried only by one ion and its concentration is not the same on the two sides of the membrane.

THE CHORD CONDUCTANCE EQUATION RELATES MEMBRANE POTENTIAL TO ALL ION FLOWS

There are two ways to answer the problem of finding the resting membrane potential when the membrane is permeable to several ions. One way focuses on the permeabilities as we have already defined them, and a second focuses on the conductances, which are related, but not identical, to the permeabilities. We will use conductances here because it makes it easier to understand other electrical phenomena in cells. We begin with the fact that the total current at the resting membrane potential is zero. This is Eqn [3.1.15]:

[3.1.15] $$I_{total} = I_{Na} + I_K + I_{Cl} = 0$$

Substituting in from Eqn [3.1.18] for the individual currents, we get

[3.1.20] $I = g_{Na}(E_m - E_{Na}) + g_K(E_m - E_K) + g_{Cl}(E_m - E_{Cl})$

At rest, $I = 0$, and so we collect terms in E_m on the left-hand side to find

[3.1.21] $(g_{Na} + g_K + g_{Cl})E_m = g_{Na}E_{Na} + g_K E_K + g_{Cl}E_{Cl}$

Solving for E_m, we obtain

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

[3.1.22]

This is the **chord conductance equation**. What it says is that **the resting membrane potential is the conductance-weighted average of the equilibrium potentials** for the ions that have any conductance across the membrane. We can clearly enlarge Eqn [3.1.22] to include other ions such as Ca^{2+}.

Both the chord conductance equation and the GHK equation indicate that all permeant ions contribute to the resting membrane potential. Those ions with the largest conductances, or the largest permeabilities, are correspondingly greater determinants of the resting membrane potential.

THE CURRENT CONVENTION IS THAT AN OUTWARD CURRENT IS POSITIVE

As mentioned earlier, the reversal potential is the potential at which the current reverses direction: it changes from positive to negative. It is important here to remember the sign convention for these currents. First, **current is taken as the direction of positive charge flow**. Second, a **positive current is taken as an outward current**—it goes from the inside of the cell to the outside. Third, a **negative current is taken as an inward current**. This convention becomes apparent when we consider the individual ionic currents.

According to Eqn [3.1.18], the individual ionic currents are

$$I_{Na} = g_{Na}(E_m - E_{Na})$$

[3.1.23] $$I_K = g_K(E_m - E_K)$$

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

Recall that g stands for a conductance. **Conductances are always positive**.

We consider the example given above for the concentrations and equilibrium potentials. These values are recapitulated in Table 3.1.1.

Suppose that the resting membrane potential is -85 mV. The Na current could then be calculated as

TABLE 3.1.1 Concentrations of Ions and Their Equilibrium Potentials

n	[Ion]$_{out}$	[Ion]$_{in}$	E_i
Na^+	145×10^{-3} M	12×10^{-3} M	$+66.6$ mV
K^+	4×10^{-3} M	155×10^{-3} M	-97.7 mV
Cl^-	100×10^{-3} M	5×10^{-3} M	-80.0 mV

$$I_{Na} = g_{Na}(-85 \text{ mV} - 66.7 \text{ mV}) = -g_{Na} \times 151.7 \text{ mV}$$

Which way does the Na^+ ion go? Its concentration is higher outside the cell than inside. A potential of $+66.6$ mV *inside* would be necessary to stop the diffusive flow down its concentration gradient, but the resting membrane potential is -85 mV. Thus the negative membrane potential further drives Na^+ influx. Na^+ goes into the cell, but *the current is negative*, as indicated by the sign and the fact that g_{Na} is always positive. The current is negative because that is our convention for determining the direction of current. An inward current (flux of a positive ion) is a negative current. From Eqn [3.1.11], we see that the current is in the same direction as the flux:

[3.1.11] $$I_i = z_i \Im J_i$$

Thus inward Na flux is also a negative flux. The convention for positive flux is also from inside the cell to outside.

In the case of K^+, the current is given as

$$I_K = g_K(-85 \text{ mV} + 97.7 \text{ mV}) = g_{Na} \times 8.7 \text{ mV}$$

which is positive. It takes -97.7 mV to stop K^+ exit from the cell. The resting membrane potential of -85 mV is insufficient to stop K^+ exit, so at rest there is some outward I_K. Because it is an outward current, it is positive. The J_K is similarly positive.

In the case of Cl^-, the current is

$$I_{Cl} = g_{Cl}(-85 \text{ mV} + 80 \text{ mV}) = -g_{Cl} \times 5 \text{ mV}$$

So the current is negative. Here -80 mV is enough to stop Cl entry into the cell. This is the E_{Cl} and you can see that if the membrane potential was -80 mV, I_{Cl} would be zero. But the membrane potential is -85 mV, which is more negative than E_{Cl}; thus the negative inside potential forces Cl^- out of the cell. There is an outward flux of Cl^-, which is a positive flux. But the charge on Cl^-, $z_{Cl} = -1$ and so the current carried by Cl^- is opposite to its flux! (see Eqn [3.1.11]). The negative current is an inward current carried by the outward flux of Cl^-.

This current convention and the convention that membrane potential is defined as $E_m = \psi_i - \psi_o$ are true conventions in that the opposite conventions do not violate any physical law. These conventions are equivalent to the orientation of the x-axis perpendicular to the surface of the cell membrane. The convention is that $x = 0$ is on the inside of the cell and $x = \delta$, where δ is the thickness of the membrane, is on the outside surface. Figure 3.1.4 illustrates this convention and what it means for the gradients in C and ψ.
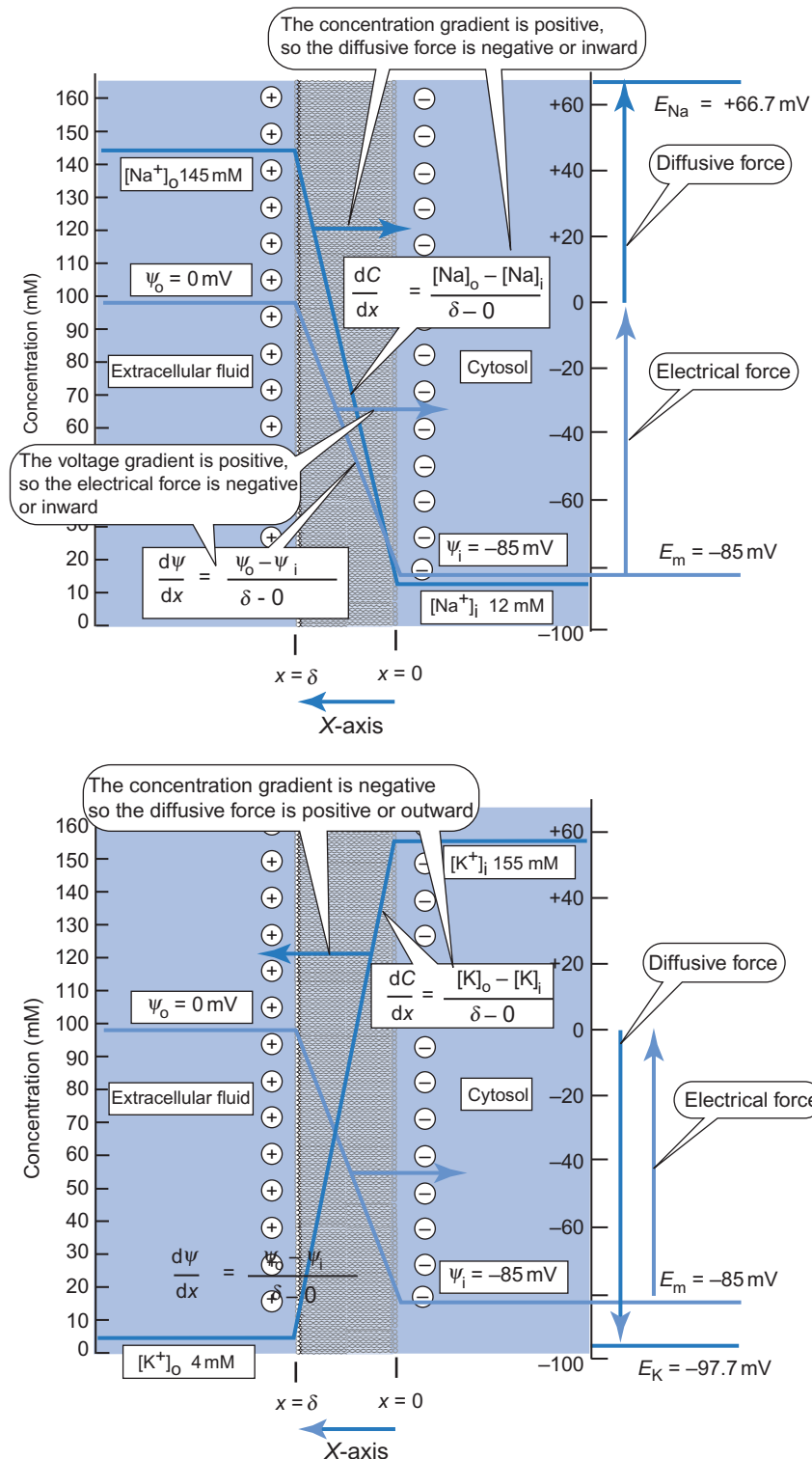
FIGURE 3.1.4 Cartoon of the concentration and voltage gradients and their resulting parts of the ion flux. Top, situation with Na^+ ions. The $[Na^+]_o$ is about 145 mM, whereas the $[Na^+]_i$ is about 12 mM. Thus the concentration gradient is positive (it slopes up with x; the direction of the x-axis is from inside to outside of the cell as indicated at the bottom of the figure). Fick's law gives the diffusive flux as being proportional to the negative of the gradient. Thus the diffusive force favors a negative flux, which is directed inward. The outside potential, ψ_o, is taken as zero. At rest, ψ_i is about -85 mV. Thus the voltage gradient is also positive. The flux produced by the electrical force is also proportional to the negative of the electrical gradient. Thus the positive voltage gradient produces a negative flux, which is inward. Thus for Na^+, both the diffusive force and electrical force produce an inward flux and an inward current. The bottom panel illustrates the situation with K^+ ions. $[K^+]_o$ is just 4 mM and $[K^+]_i = 155$ mM, so the concentration gradient is negative. Thus the diffusive force is positive or directed outward. The negative electrical potential inside makes a positive electrical potential gradient, which favors a negative K^+ movement, or an inward current and flux. Thus here the diffusive force and the electrical force oppose each other, but their magnitudes are not equal. Another way of looking at the equilibrium potential is that it is the magnitude of the diffusive force expressed in electrical terms. The net effect on movement is obtained by subtracting the two forces.

SUMMARY

Separation of charges produces an electric field defined as the force experienced by a test positive unit charge. The field at any point is also characterized by a potential, defined as the work necessary to move a positive unit test charge from infinite separation to that point. The potential surrounding positive charge is positive, and that surrounding negative charge is negative. Thus the separation of charges across a membrane produces a potential difference between the two sides of the membrane.

Ions move in response to concentration differences and in response to electrical forces. If a membrane is permeable only to a single ion, and the concentration of the ion is different on the two sides of the membrane, then the ion will diffuse from its high concentration toward its low concentration. Since it is charged, the ion movement makes a current and there is a separation of charge. This separation of charge produces an electrical force that opposes further diffusion. The electric field is the force per unit test charge, and this is the negative spatial derivative of the potential. The membrane potential at which diffusion is exactly balanced by the electrical forces is called the equilibrium potential. It can be calculated by using the Nernst equation:

$$\frac{RT}{z\Im}\ln\frac{C_o}{C_i} = (\psi_i - \psi_o)$$

The equilibrium potentials for K^+, Na^+, and Cl^- depend on their concentrations on both sides of the membrane and they are typically different from each other. In the Nernst equation, put the outside concentration in the numerator to agree with the sign convention.

Real membranes are permeable to a variety of ions, but with different permeabilities. The permeability can be expressed either as a permeability relating flux to driving force in concentration units or as conductance relating current to driving force in voltage units. The resting membrane potential occurs at a net zero membrane current. This occurs at a membrane potential that is the conductance-weighted average of the equilibrium potentials, as described by the chord conductance equation:

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

Thus the resting membrane potential is closest to the equilibrium potential of the ion with the highest conductance. The resting membrane potential also can be expressed in terms of the permeabilities: it depends on the concentration-weighted permeabilities as expressed in the GHK equation.

Membrane potential is defined as $E_m = \psi_i - \psi_o$. An outward flow of positive ions is taken as a positive current. The current for any ion is given as

$$I_i = g_i(E_m - E_i)$$

where g_i is the conductance to the particular ion, in siemens. This is a chord conductance which is distinguished from a slope conductance. Here E_i is the equilibrium potential for the ion in question. Conductances are always positive. A negative current means that the current is directed inward.

REVIEW QUESTIONS

1. What is the current of an ion at its equilibrium potential? What would the current look like as a function of membrane potential if the ion had the same concentration on both sides of the membrane?
2. If the conductance of the membrane to K^+ was increased, what would happen to the equilibrium potential for K^+ (E_K)? What would happen to E_m?
3. Why is Cl_o in the denominator of the GHK equation when Na_o and K_o are in the numerator?
4. What potential is calculated by the Nernst equation?
5. What potential is calculated by the GHK equation?
6. What is a siemen?
7. What is meant by an inward current? Outward current? What sign does an inward current have? If Cl^- exits the cell, does it make a positive or negative current?

APPENDIX 3.1.A1 DERIVATION OF THE GHK EQUATION

The flux of an ion through a water-filled channel should be given by the generalized Fick's law given by Eqn [3.1.1]:

[3.1.A1.1] $$J_s = -D\frac{\partial C}{\partial x} - \frac{D}{RT}Cz\Im\frac{\partial \psi}{\partial x}$$

The flux can be obtained by integrating this equation. To begin, we multiply both sides of the equation by an integrating factor, ρ, and we choose ρ so that the right-hand side of the equation becomes an exact differential:

[3.1.A1.2] $$J_s\rho = -D\left[\rho\frac{\partial C}{\partial x} - \frac{Cz\Im\rho}{RT}\frac{\partial \psi}{\partial x}\right]$$

We choose ρ so that the terms in brackets are an exact differential. Thus we want

[3.1.A1.3] $$\rho\frac{\partial C}{\partial x} + \frac{Cz\Im\rho}{RT}\frac{\partial \psi}{\partial x} = \frac{d(\rho C)}{dx} = \rho\frac{\partial C}{\partial x} + C\frac{\partial \rho}{\partial x}$$

From comparing the extreme left of Eqn [3.1.A1.3] to the extreme right, we see that the condition that multiplication by ρ transforms the equation into an exact differential is met if

[3.1.A1.4] $$\frac{\partial \rho}{\partial x} = \frac{z\Im\rho}{RT}\frac{\partial \psi}{\partial x}$$

We rearrange this to get

[3.1.A1.5]
$$\frac{\partial \rho}{\rho} = \frac{z\Im}{RT}\partial\psi$$

A solution to Eqn [3.1.A1.5] is

[3.1.A1.6]
$$\rho = e^{(z\Im/RT)\psi}$$

We may insert this result back into Eqn [3.1.A1.2] to obtain

[3.1.A1.7]
$$J_s e^{(z\Im/RT)\psi} = -D\frac{d(Ce^{(z\Im/RT)\psi})}{dx}$$

which may be rewritten as

[3.1.A1.8]
$$J_s e^{(z\Im/RT)\psi}dx = -Dd(Ce^{(z\Im/RT)\psi})$$

The flux can be obtained by integrating this equation from $x = 0$ (one side of the membrane) to $x = \delta$, the other side of the membrane for a membrane with thickness δ:

[3.1.A1.9]
$$\int_0^\delta J_s e^{(z\Im/RT)\psi}dx = -D\int_0^\delta d(Ce^{(z\Im/RT)\psi})$$

In this case, we limit ourselves to the steady-state condition. In this case, J_s does not vary with distance across the membrane; it is constant. Therefore J_s may be removed from the integral and we get

[3.1.A1.10]
$$J_s = \frac{-D\int_0^\delta d(Ce^{(z\Im/RT)\psi})}{\int_0^\delta e^{(z\Im/RT)\psi}dx}$$

The numerator in this equation is the integral of an exact differential and can be immediately evaluated between the boundaries. This gives

[3.1.A1.11]
$$J_s = \frac{-D[C(\delta)e^{(z\Im/RT)\psi(\delta)} - C(0)e^{(z\Im/RT)\psi(0)}]}{\int_0^\delta e^{(z\Im/RT)\psi}dx}$$

The denominator in this equation can be evaluated only if $\psi(x)$ is known. However, generally $\psi(x)$ is unknown. We can integrate the denominator if we assume that ψ is a linear function of x. This is true if the electric field between $x = 0$ and δ is constant. Recall that the electric field intensity is the negative derivative of the potential. For this reason, the assumption of a linear potential gradient is called the **constant field** assumption. If the potential is linear, then we can write

[3.1.A1.12]
$$\psi = \psi(0) + \frac{\psi(0) - \psi(\delta)}{0 - \delta}x$$

The situation of $C(0)$, $C(\delta)$, $\psi(0)$, and $\psi(\delta)$ is illustrated in Figure 3.1.A1.1. The difference in potential across the membrane, $\psi(0) - \psi(\delta)$, is the the membrane potential E_m. Here $\psi(0)$ is the inside potential and $\psi(\delta)$ is the outside potential. Thus Eqn [3.1.A1.12] becomes

[3.1.A1.13]
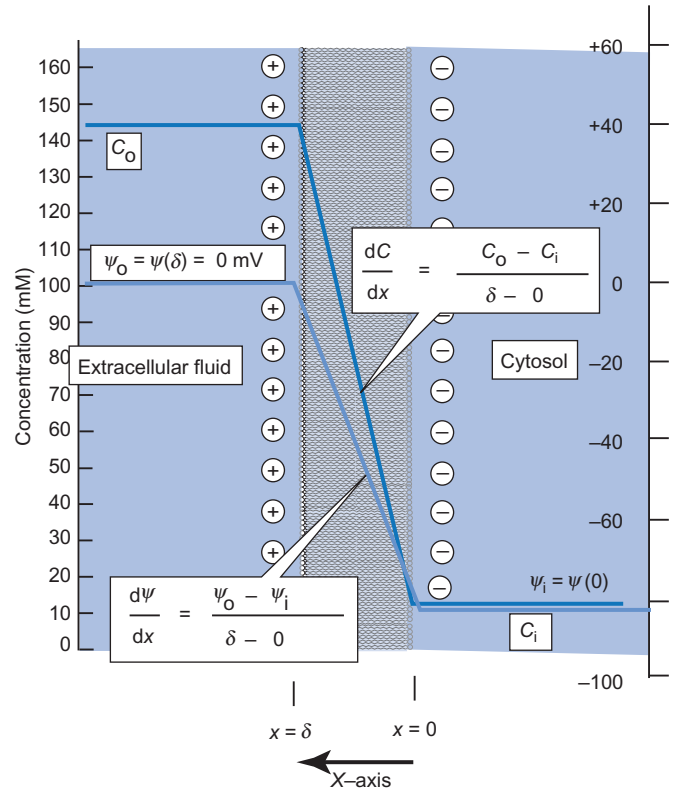$$\psi = \psi(0) + \frac{E_m}{\delta}x$$

FIGURE 3.1.A1.1 Concentration and potential profile across the membrane along with the convention for the location of the X-axis.

This result can be substituted into the denominator of Eqn [3.1.A1.11] to give

$$\int_0^\delta e^{(z\Im/RT)\psi}dx = \int_0^\delta e^{(z\Im/RT)(\psi(0)-(E_m/\delta)x)}dx$$

$$= e^{(z\Im/RT)\psi(0)}\int_0^\delta e^{-(z\Im/RT)(E_m/\delta)x}dx$$

[3.1.A1.14]

Evaluation of the integral gives

[3.1.A1.15]
$$\frac{e^{(z\Im/RT)\psi(0)}}{-(z\Im/RT)(E_m/\delta)}(e^{-(z\Im/RT)E_m} - 1)$$

Inserting the result of Eqn [3.1.A1.15] back into Eqn [3.1.A1.11]

$$J_s = \frac{-D[C(\delta)e^{(z\Im/RT)\psi(\delta)} - C(0)e^{(z\Im/RT)\psi(0)}]}{(e^{(z\Im/RT)\psi(0)})/(-(z\Im/RT)(E_m/\delta))[e^{(z\Im/RT)E_m} - 1]}$$

[3.1.A1.16]

This can be simplified to

$$J_s = \frac{(D/\delta)[(z\Im/RT)E_m][C(\delta)e^{(z\Im/RT)\psi(\delta)} - C(0)e^{(z\Im/RT)\psi(0)}]e^{-(z\Im/RT)\psi(0)}}{[e^{-(z\Im/RT)E_m} - 1]}$$

[3.1.A1.17]

Multiplying through by the exponent in the numerator, and recalling that $E_m = \psi(0) - \psi(\delta)$, we convert Eqn [3.1.A1.17] into

[3.1.A1.18]
$$J_s = \frac{(D/\delta)[(z\Im/RT)E_m][C(\delta)e^{-(z\Im/RT)E_m} - C_0]}{[e^{-(z\Im/RT)E_m} - 1]}$$

This equation is typically rewritten by multiplying numerator and denominator by -1, with no change in meaning:

$$J_s = \frac{(D/\delta)[(z\mathfrak{S}/RT)E_m][C(0) - C(\delta)e^{-(z\mathfrak{S}/RT)E_m}]}{[1 - e^{-(z\mathfrak{S}/RT)E_m}]}$$

[3.1.A1.19]

This flux equation holds true for any ion including Na^+, K^+, and Cl^-. The current carried by each ion is given by Eqn [3.1.19] by multiplying the flux by $z\mathfrak{S}$. We identify $C(0)$ with the inside concentration of the ion, and $C(\delta)$ with the outside concentration, as described in Figure 3.1.A1.1 which of course are different for each of the ions. For each ion, we can write an equation for the current that has the form

$$I_{ion} = \frac{(D/\delta)[(z^2\mathfrak{S}^2/RT)E_m][C_i - C_o e^{-(z\mathfrak{S}/RT)E_m}]}{[1 - e^{-(z\mathfrak{S}/RT)E_m}]}$$

[3.1.A1.20]

Thus we can write

$$I_{Na} = \frac{(D/\delta)[(\mathfrak{S}^2/RT)E_m][[Na]_i - [Na]_o e^{-(\mathfrak{S}/RT)E_m}]}{[1 - e^{-(\mathfrak{S}/RT)E_m}]}$$

[3.1.A1.21]

[3.1.A1.22] $\quad I_K = \dfrac{(D/\delta)[(\mathfrak{S}^2/RT)E_m][[K]_i - [K]_o e^{-(\mathfrak{S}/RT)E_m}]}{[1 - e^{-(\mathfrak{S}/RT)E_m}]}$

$$I_{Cl} = \frac{(D/\delta)[(\mathfrak{S}^2/RT)E_m][[Cl]_{in} - [Cl]_{out} e^{(\mathfrak{S}/RT)E_m}]}{[1 - e^{(\mathfrak{S}/RT)E_m}]}$$

[3.1.A1.23]

Note that the exponent in the numerator and denominator of I_{Cl} is positive instead of negative! This is because the z term in the exponent in Eqn [3.1.A1.20] is -1 for Cl. The total current across the membrane is the sum of the currents carried by each ion. At steady state (the resting membrane potential), the current is zero. Thus we can write

[3.1.A1.24] $\quad\quad\quad I_{total} = I_{Na} + I_K + I_{Cl} = 0$

We now insert the expressions for each of the individual currents. Here, however, we make an additional substitution that the diffusion coefficient for each ion divided by the thickness of the membrane, D/δ, is equal to the permeability of the membrane to each ion. The result is

$$I_{total} = 0 = \frac{P_{Na}[(\mathfrak{S}^2/RT)E_m][[Na]_{in} - [Na]_{out}e^{-(\mathfrak{S}/RT)E_m}]}{[1 - e^{-(\mathfrak{S}/RT)E_m}]}$$

$$+ \frac{P_K[(\mathfrak{S}^2/RT)E_m][[K]_{in} - [K]_{out}e^{-(\mathfrak{S}/RT)E_m}]}{[1 - e^{-(\mathfrak{S}/RT)E_m}]}$$

$$+ \frac{P_{Cl}[(\mathfrak{S}^2/RT)E_m][[Cl]_{in} - [Cl]_{out}e^{(\mathfrak{S}/RT)E_m}]}{[1 - e^{(\mathfrak{S}/RT)E_m}]}$$

[3.1.A1.25]

Solving this equation, we find

$$0 = P_{Na}[[Na]_i - [Na]_o e^{-(\mathfrak{S}/RT)E_m}]$$

[3.1.A1.26] $\quad\quad + P_K[[K]_i - [K]_o e^{-(\mathfrak{S}/RT)E_m}]$

$$+ P_{Cl}[[Cl]_o - [Cl]_i e^{-(\mathfrak{S}/RT)E_m}]$$

where we have multiplied the numerator and denominator of the Chloride contribution to the current by exp $(-\mathfrak{S}/RT\, E_m)$ and rearranged the terms. Solving for E_m, we finally obtain

[3.1.A1.27] $\quad E_m = \dfrac{RT}{\mathfrak{S}} \ln \dfrac{[P_{Na}[Na]_o + P_K[K]_o + P_{Cl}[Cl]_i]}{[P_{Na}[Na]_i + P_K[K]_i + P_{Cl}[Cl]_o]}$

This is the GHK equation. It tells us that the resting membrane potential (at which point the net current across the membrane is zero) is determined by the concentrations of ions on both sides of the membrane and by their respective permeabilities. The ion with the largest permeability dominates the membrane potential by moving the potential closer to its equilibrium potential.