AT REST, A NEURON HAS A STEADY ELECTRICAL POTENTIAL across its plasma membrane, the inside being negative with respect to the outside. In relation to the extracellular fluid, the neuron has a high intracellular potassium concentration and low intracellular concentrations of sodium and chloride, so that potassium tends to diffuse out of the cell and sodium and chloride tend to diffuse in. The tendency for potassium and chloride to diffuse down their concentration gradients is opposed by the membrane potential. In a model cell permeable only to potassium and chloride, the concentration gradients and the membrane potential can be balanced exactly so that there is no net flux of either ion across the membrane. The membrane potential is then equal to the equilibrium potential for both potassium and chloride.

In the model cell, changing the extracellular potassium concentration changes the potassium equilibrium potential, and hence the membrane potential. In contrast, changing the extracellular chloride concentration eventually leads to a change in intracellular chloride. As a result the chloride equilibrium potential and the membrane potential are unchanged.

Real cells are also permeable to sodium. At rest, sodium ions constantly move into the cell, reducing the internal negativity of the membrane. As a result, potassium, being no longer in equilibrium, leaks out. If there were no compensation, these fluxes would lead to changes in the internal concentrations of sodium and potassium. However, the concentrations are maintained by the sodium-potassium exchange pump, which transports sodium out and potassium in across the cell membrane in a ratio of 3 sodium to 2 potassium. The resting membrane potential depends on the potassium equilibrium potential, the sodium equilibrium potential, the relative permeabilities of the cell membrane to the two ions, and the pump ratio. At the resting potential, the passive fluxes of sodium and potassium are exactly matched by the rates at which they are transported in the opposite direction. Because the sodium-potassium exchange pump transports more positive ions outward than inward across the membrane, it makes a direct contribution of several millivolts to the membrane potential.

The chloride equilibrium potential may be positive or negative with respect to the resting membrane potential, depending on chloride transport processes. Although the chloride distribution plays little role in determining the resting membrane potential, a substantial chloride permeability is important in some cells for electrical stability.
Electrical signals are generated in nerve cells and muscle fibers primarily by changes in permeability of the cell membrane to ions such as sodium and potassium. Increases in permeability allow ions to move inward or outward across the cell membrane down their electrochemical gradients. As we discussed in Chapter 2, permeability increases are due to activation of ion channels. Ions moving through the open channels change the charge on the cell membrane, and hence change the membrane potential. In order to understand how signals are generated, it is necessary to understand the nature of the standing ionic gradients across the cell membrane, and how these influence the resting membrane potential.

**A MODEL CELL**

It is useful to begin with the model cell shown in Figure 5.1. This cell contains potassium, sodium, chloride, and a large anion species, and it is bathed in a solution of sodium and potassium chloride. Other ions present in real cells, such as calcium or magnesium, are ignored for the moment, as their direct contributions to the resting membrane potential are negligible. The extracellular and intracellular ion concentrations in the model cell are similar to those found in frogs. In birds and mammals, ion concentrations are somewhat higher; in marine invertebrates such as the squid, very much higher (see Table 5.1). The model cell membrane is permeable to potassium and chloride, but not to sodium or to the internal anion. There are three major requirements for such a cell to remain in a stable condition:

1. The intracellular and extracellular solutions must each be electrically neutral. For example, a solution of chloride ions alone cannot exist; their charges must be balanced by an equal number of positive charges on cations such as sodium or potassium (otherwise electrical repulsion would literally blow the solution apart).

2. The cell must be in osmotic balance. If not, water will enter or leave the cell, causing it to swell or shrink, until osmotic balance is achieved. Osmotic balance is achieved when the total concentration of solute particles inside the cell is equal to that on the outside.

3. There must be no net movement of any particular ion into or out of the cell.

**Ionic Equilibrium**

How are the concentrations of the permeant ions maintained in the model cell, and what electrical potential is developed across the cell membrane? Figure 5.1 shows that the two ions are distributed in reverse ratio: Potassium is more concentrated on the inside of the cell, chloride on the outside. Imagine first that the membrane is permeable only to potassium; the question that arises immediately is why potassium ions do not diffuse out of the cell until the concentrations on either side of the cell membrane are equal. The answer is that they cannot because as they diffuse outward, positive charges accumulate on

**FIGURE 5.1 Ion Distributions in a Model Cell.** The cell membrane is impermeable to Na⁺ and to the internal anion (A⁻), and permeable to K⁺ and Cl⁻. The concentration gradient for K⁺ tends to drive it out of the cell (black arrow); the potential gradient tends to attract K⁺ into the cell (red arrow). In a cell at rest the two forces are exactly in balance. Concentration and electrical gradients for Cl⁻ are in the reverse directions. Ion concentrations are expressed in millimolar (mM).
the outer surface of the membrane and an excess of negative charges is left on the inner surface. As a result, a difference in potential develops across the membrane, the inside being negative with respect to the outside. The electrical gradient slows the efflux of positively charged potassium ions, and when the potential becomes sufficiently large, further net efflux of potassium is stopped. This is the potassium equilibrium potential \( E_K \). At \( E_K \) the effects of the concentration gradient and the potential gradient on ion flux through the membrane balance one another exactly. Individual potassium ions still enter and leave the cell, but no net movement occurs. The potassium ion is in equilibrium.

The conditions for potassium to be in equilibrium across the cell membrane are the same as those described in Chapter 2 for maintaining zero net flux through an individual channel in a membrane patch. There, a concentration gradient was balanced by a potential applied to the patch pipette. The important difference here is that the ion flux itself produces the required transmembrane potential. In other words, equilibrium in the model cell is automatic and inevitable. Recall from Chapter 2 that the potassium equilibrium potential is given by the Nernst equation:

\[
E_K = \frac{RT}{2F} \ln \left( \frac{[K]_o}{[K]_i} \right) = 58 \log \left( \frac{[K]_o}{[K]_i} \right)
\]

where \([K]_o\) and \([K]_i\) are the external and internal potassium ion concentrations. For the cell shown in Figure 5.1, \( E_K \) is 58 log (1/30) = –85 mV.

Suppose now that, in addition to potassium channels, the membrane has chloride channels. Because for an anion \( z = -1 \), the equilibrium potential for chloride is:

\[
E_{Cl^-} = -58 \log \left( \frac{[Cl^-]_o}{[Cl^-]_i} \right)
\]

or (from the properties of logarithmic ratios):

\[
E_{Cl^-} = 58 \log \left( \frac{[Cl^-]_i}{[Cl^-]_o} \right)
\]

In our model cell, the chloride concentration ratio is again 1:30, and \( E_{Cl^-} \) is also –85 mV. As with potassium, the membrane potential of –85 mV balances exactly the tendency for chloride to move down its concentration gradient, in this case into the cell.

In summary, the tendency for potassium ions to leave the cell and for chloride ions to diffuse inward are both opposed by the membrane potential. Because the concentration ratios for the two ions are of exactly the same magnitude (1:30), their equilibrium potentials are exactly the same. Since potassium and chloride are the only two ions that can move across the membrane and both are in equilibrium at –85 mV, the model cell can exist indefinitely without net gain or loss of ions.

**Electrical Neutrality**

The charge separation across the membrane of our model cell, produced by outward movement of potassium and inward movement of chloride, means that there is an excess of anions inside the cell and of cations outside. This appears to violate the principle of electrical neutrality that we started with, but in fact does not. Potassium ions diffusing outward collect an excess cations against the outer membrane surface, leaving excess anions closely attracted to the inner surface. Both the potassium ions and the counterions they leave behind are, in effect, removed from the intracellular bulk solution, leaving it neutral. Similarly, chloride ions diffusing inward add to the collection of excess anions on the inner surface and leave counterions in the outer charged layer, so that the extracellular solution remains neutral as well. The outer layer of cations and inner layer of anions, of equal and opposite charge, are not in free solution, but are held to the membrane surface by mutual attraction.

Thus, the membrane acts as a capacitor, separating and storing charge.

This does not mean that any given anion or cation is locked in position against the membrane. Ions in the charged layer interchange freely with those in the bulk solution.
The point is that although the identities of the ions in the layer are constantly changing, their total number remains constant, and the bulk solution remains neutral.

Another question we might ask about charge separation is whether the number of ions accumulated in the charged layer represents a significant fraction of the total number of ions in the cell. The answer is that it does not. If we consider our cell to have a radius of 25 \( \mu \)m, then at a concentration of 120 mM there are roughly \( 4 \times 10^{12} \) cations and an equal number of anions in the cytoplasm. At a membrane potential of \(-85\) mV, the amount of charge separated by the membrane is about \( 5 \times 10^{11} \) univalent ions/cm\(^2\) (Chapter 7). Our cell has a surface area of about \( 8 \times 10^{-5} \) cm\(^2\), so there are approximately \( 4 \times 10^7 \) negative ions collected at the inner surface of the membrane, or \( 1/100,000 \) the number in free solution. Thus, the movements of potassium and chloride ions required to establish the membrane potential have no significant effect on intracellular ion concentrations.

The Effect of Extracellular Potassium and Chloride on Membrane Potential

In neurons, and in many other cells, the resting membrane potential is sensitive to changes in extracellular potassium concentration but is relatively unaffected by changes in extracellular chloride. To understand how this comes about it is useful to consider the consequences of such changes in the model cell. We will assume throughout this discussion that the volume of the extracellular fluid is infinitely large. Thus, movements of ions and water into or out of the cell have no significant effect on extracellular concentrations. Figure 5.2A shows the changes in intracellular composition and membrane potential that result from increasing extracellular potassium from 3 to 6 mM. This is done by replacing 3 mM NaCl with 3 mM KCl, thereby keeping the osmolarity unchanged, with a total

![Figure 5.2](image)

**FIGURE 5.2** Effects of Changing Extracellular Ion Composition on intracellular ion concentrations and on membrane potential. (A) Extracellular K\(^+\) concentration is doubled and, to keep osmolarity constant, Na\(^+\) concentration is reduced. (B) Half the extracellular Cl\(^-\) is replaced by an impermeant anion, A\(^-\). Ion concentrations are in millimolar (mM), and extracellular volumes are assumed to be very large with respect to cell volumes, so fluxes into and out of the cell do not change extracellular concentrations.
solute concentration of 240 mM. The increase in extracellular potassium reduces the concentration gradient for outward potassium movement, while initially leaving the electrical gradient unchanged. As a result there will be a net inward movement of potassium ions. As positive charges accumulate on its inner surface, the membrane is depolarized. This, in turn, means that chloride ions are no longer in equilibrium, and they move into the cell as well. Potassium and chloride entry continues until a new equilibrium is established, with both ions at a new concentration ratio consistent with the new membrane potential, in this example −68 mV.

Potassium and chloride entry is accompanied by the entry of water to maintain osmotic balance, resulting in a slight increase in cell volume. When the new equilibrium is reached, intracellular potassium has increased in concentration from 90 to 91 mM, intracellular chloride has increased in concentration from 4 to 7.9 mM, and the cell volume has increased by 3.5%.

At first glance it seems that more chloride than potassium has entered the cell, but think what the concentrations would be if the cell did not increase in volume: The concentrations of both ions would be greater than the indicated values by 3.5%. Thus, the intracellular chloride concentration would be about 8.2 mM (instead of 7.9 mM), and intracellular potassium would be about 94.2 mM, both 4.2 mM higher than in the original solution. In other words, we can think first of potassium and chloride entering in equal quantities (except for the trivial difference required to change the charge on the membrane), and then of water following to achieve the final concentrations shown in the figure.

Similar considerations apply to changes in extracellular chloride concentration, but with a marked difference: When the new steady state is finally reached, the membrane potential is essentially unchanged. The consequences of a 50% reduction in extracellular chloride concentration are shown in Figure 5.2B, in which 60 mM of chloride in the solution bathing the cell is replaced by an impermeant anion. Chloride leaves the cell, depolarizing the membrane toward the new chloride equilibrium potential (~68 mV). Potassium, being no longer in equilibrium, leaves as well. As in the previous example, potassium and chloride leave the cell in equal quantities (accompanied by water). Because the intracellular concentration of potassium is high, the fractional change in concentration produced by the efflux is relatively small. However, the efflux of chloride causes a sizable fractional change in the intracellular chloride concentration, and hence in the chloride equilibrium potential. As chloride continues to leave the cell, the equilibrium potential returns toward its original value. The process continues until the chloride and potassium equilibrium potentials are again equal and the membrane potential is restored.

**MEMBRANE POTENTIALS IN SQUID AXONS**

The idea that the resting membrane potential is the result of an unequal distribution of potassium ions between the extracellular and intracellular fluids was first proposed by Bernstein in 1902. He could not test this hypothesis directly, however, because there was no satisfactory way of measuring membrane potential. It is now possible to measure membrane potential accurately, and to see whether changes in external and internal potassium concentrations produce the potential changes predicted by the Nernst relation.

The first such experiments were done on giant axons that innervate the mantle of the squid. The axons are up to 1 mm in diameter, and their large size permits the insertion of recording electrodes into their cytoplasm to measure transmembrane potential directly (Figure 5.3A). Further, they are remarkably resilient and continue to function even when their axoplasm has been squeezed out with a rubber roller and replaced with an internal perfusate (Figure 5.3B and C). Thus, their internal, as well as external, ion composition can be controlled. A. L. Hodgkin, who together with A. F. Huxley initiated many experiments on squid axon (for which they later received the Nobel prize), has said, ³°It is arguable that the introduction of the squid giant nerve fiber by J. Z. Young in 1936 did more for axonology than any other single advance during the last forty years. Indeed a distinguished neurophysiologist remarked recently at a congress dinner (not, I thought, with the utmost tact), "It's the squid that really ought to be given the Nobel Prize."
FIGURE 5.3 Recording from a Squid Axon. (A) Isolated giant axon of the squid, with axial recording electrode inside. (B) Extrusion of axoplasm from the axon, which is then cannulated and perfused internally. (C) Comparison of records before (intact) and after perfusion shows that the resting and action potentials are unaffected by removal of the axoplasm. (A from Hodgkin and Keynes, 1956; B and C after Baker, Hodgkin, and Shaw, 1962.)

The concentrations of some of the major ions in squid blood and in the axoplasm of the squid nerves are given in Table 5.1 (several ions, such as magnesium and internal anions, are omitted). Experiments on isolated axons are usually done in seawater, with the ratio of intracellular to extracellular potassium concentrations 40:1. If the membrane potential ($V_m$) were equal to the potassium equilibrium potential, it would be $-93$ mV. In fact, the measured membrane potential is considerably less negative (about $-65$ to $-70$ mV). On the other hand, the membrane potential is more negative than the chloride equilibrium potential, which is about $-55$ mV.

Bernstein's hypothesis was tested by measuring the resting membrane potential and comparing it with the potassium equilibrium potential at various extracellular potassium concentrations. (As with our model cell, such changes would be expected to produce no significant change in internal potassium concentration.) From the Nernst equation
Table 5.1
Concentrations of ions inside and outside freshly isolated axons of squid

<table>
<thead>
<tr>
<th>Ion</th>
<th>Axoplasm (mM)</th>
<th>Blood (mM)</th>
<th>Seawater (mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium</td>
<td>400</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Sodium</td>
<td>50</td>
<td>440</td>
<td>460</td>
</tr>
<tr>
<td>Chloride</td>
<td>60</td>
<td>560</td>
<td>540</td>
</tr>
<tr>
<td>Calcium</td>
<td>0.1 μM*</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>


(Chapter 2), changing the concentration ratio by a factor of 10 should change the membrane potential by 58 mV at room temperature. The results of such an experiment on squid axon, in which the external potassium concentration was changed, are shown in Figure 5.4. The external concentration is plotted on a logarithmic scale on the abscissa and the membrane potential on the ordinate. The expected slope of 58 mV per 10-fold change in extracellular potassium concentration is realized only at relatively high concentrations (straight line), with the slope becoming less and less as external potassium is reduced. This result indicates that the potassium ion distribution is not the only factor contributing to the membrane potential.

The Effect of Sodium Permeability

From the experiments on squid axon we can conclude that the hypothesis made by Bernstein in 1902 is almost correct: The membrane potential is strongly but not exclusively dependent on the potassium concentration ratio. How do we account for the deviation from the Nernst relation shown in Figure 5.4? Simply by abandoning the notion that the membrane is impermeable to sodium. A real cell membrane has, in fact, a permeability to sodium that ranges between 1 and 10% of its permeability to potassium.

To consider the effect of sodium permeability, we begin with our model cell and, for the moment, ignore any movement of chloride ions. The membrane potential is at the potassium equilibrium potential, so there is no net movement of potassium across the membrane. If we now make the cell permeable to sodium, both the concentration gradi-

Figure 5.4 Membrane Potential versus External Potassium Concentration in squid axon, plotted on a semilogarithmic scale. The straight line is drawn with a slope of 58 mV per 10-fold change in extracellular potassium concentration, according to the Nernst equation. Because the membrane is also permeable to sodium, the points deviate from the straight line, especially at low potassium concentrations. (After Hodgkin and Keynes, 1955.)
ent and the membrane potential tend to drive sodium into the cell. As sodium ions enter, the accumulation of positive charge depolarizes the membrane. As a result, potassium is no longer in equilibrium and potassium ions leave the cell. As the depolarization progresses, the driving force for sodium influx decreases and that for potassium efflux increases. The process continues until the influx of sodium is exactly balanced by the efflux of potassium. At that point there is no further charge accumulation, and the membrane potential remains constant. In summary, the membrane potential lies between the potassium and sodium equilibrium potentials, and is the potential at which the sodium and potassium currents are exactly equal and opposite.

Chloride ions participate in the process as well, but as we have already seen, there is ultimately an adjustment in intracellular chloride concentration in the model cell so that the chloride equilibrium potential matches the new membrane potential. As the cation fluxes gradually reach a balance, the intracellular chloride concentration increases until there is no net chloride flux across the membrane.

The Constant Field Equation

To determine the exact membrane potential in our model cell we have to consider the individual ion currents across the membrane. The inward sodium current \( i_{Na} \) depends on the driving force for sodium \( (V_m - E_{Na}) \) (Chapter 2), and on the membrane conductance for sodium \( (g_{Na}) \). The conductance depends on the average number of sodium channels that are open in the resting membrane: The more open channels, the greater the conductance. So the sodium current is:

\[
i_{Na} = g_{Na}(V_m - E_{Na})
\]

This is also true for potassium and chloride:

\[
i_K = g_K(V_m - E_K)
\]

\[
i_{Cl} = g_{Cl}(V_m - E_{Cl})
\]

If we assume that chloride is in equilibrium, so that \( i_{Cl} = 0 \), then for the membrane potential to remain constant, the potassium and sodium currents must be equal and opposite:

\[
g_K(V_m - E_K) = -g_{Na}(V_m - E_{Na})
\]

It is useful to examine this relation in more detail. Suppose \( g_K \) is much larger than \( g_{Na} \). Then, if the currents are to be equal, the driving force for potassium efflux must be much smaller than that for sodium entry. In other words, the membrane potential must be much closer to \( E_K \) than to \( E_{Na} \). Conversely, if \( g_{Na} \) is relatively large, the membrane potential will be closer to \( E_{Na} \).

By rearranging the equation we arrive at an expression for the membrane potential:

\[
V_m = \frac{g_K E_K + g_{Na} E_{Na}}{g_K + g_{Na}}
\]

If, for some reason, chloride is not at equilibrium, then chloride currents across the membrane must be considered as well, and the equation becomes slightly more complicated:

\[
V_m = \frac{g_K E_K + g_{Na} E_{Na} + g_{Cl} E_{Cl}}{g_K + g_{Na} + g_{Cl}}
\]

These ideas were developed originally by Goldman,\(^4\) and independently by Hodgkin and Katz.\(^5\) However, instead of considering equilibrium potentials and conductances, they derived an equation for membrane potential in terms of ion concentrations outside the cell \( ([K]_o, [Na]_o, [Cl]_o) \) and inside the cell \( ([K], [Na], [Cl]) \), and membrane permeability to each ion \( (p_K, p_{Na}, \text{and } p_{Cl}) \):

\[
V_m = 58 \log \frac{p_K [K]_o + p_{Na} [Na]_o + p_{Cl} [Cl]_o}{p_K [K]_i + p_{Na} [Na]_i + p_{Cl} [Cl]_i}
\]

---


As before, if chloride is in equilibrium, the chloride terms disappear. This equation is sometimes called the GHK equation after its originators and is known also as the constant field equation because one of the assumptions made in arriving at the expression was that the voltage gradient (or "field") across the membrane is uniform. It is entirely analogous to the conductance equation and makes the same predictions: When the permeability to potassium is very high relative to the sodium and chloride permeabilities, the sodium and chloride terms become negligible and the membrane potential approaches the equilibrium potential for potassium: \( V_m = 58 \log ([K]_o/[K]_i) \). Increasing sodium permeability causes the membrane potential to move toward the sodium equilibrium potential.

The constant field equation provides us with a useful general principle to remember. The membrane potential depends on the relative conductances (or permeabilities) of the membrane to the major ions, and on the equilibrium potentials for those ions. In real cells the resting permeabilities to potassium and chloride are relatively high, so the resting membrane potential is close to the potassium and chloride equilibrium potentials. When sodium permeability is increased, as during an action potential (Chapter 6) or an excitatory postsynaptic potential (Chapter 9), the membrane potential moves toward the sodium equilibrium potential.

**The Resting Membrane Potential**

As useful as the constant field equation is, it does not provide us with an accurate description of the resting membrane potential. This is because the requirement for zero net current across the membrane is not, in itself, adequate. Our third requirement for the cell to remain in a stable condition—namely, that each individual ionic current must be zero—is not satisfied. As a result, the cell will gradually fill up with sodium and chloride and lose potassium. In real cells, intracellular sodium and potassium concentrations are kept constant by sodium–potassium ATPase (Chapter 4). To counteract the constant influx of sodium and the efflux of potassium, the pump transports a matching amount of each ion in the opposite direction (Figure 5.5). Thus, metabolic energy is used to maintain the cell in a steady state.

In order to have a more complete and accurate description of the resting membrane potential, we must consider both the passive ion fluxes and the activity of the pump. Again, we first consider the currents carried by passive fluxes of sodium and potassium across the membrane:

\[
    i_{Na} = g_{Na}(V_m - E_{Na})
\]

\[
    i_K = g_K(V_m - E_K)
\]

We no longer assume that the sodium and potassium currents are equal and opposite, but if we know how they are related we can, as before, obtain an equation for the membrane potential in terms of the sodium and potassium equilibrium potentials and their relative conductances. This is where the pump comes in. Because it keeps intracellular sodium and potassium concentrations constant by transporting the ions in the ratio of 3 Na to 2K (Chapter 4), it follows that the passive ion fluxes must be in the same ratio: \( i_{Na}/i_K \) =

![FIGURE 5.5 Passive Ion Fluxes and Pumps in a Steady State. Net passive ion movements across the membrane are indicated by dashed arrows, transport systems by solid arrows and circles. Lengths of arrows indicate the relative magnitudes of net ion movements. Total flux is zero for each ion. For example, the net inward leak of Na\(^+\) is equal to the rate of outward transport. Na\(^+\)/K\(^+\) transport is coupled with a ratio of 3:2. In any particular cell, Cl\(^-\) transport may be outward (as shown) or inward.](image-url)
3/2. So we can write

$$i_{Na}^{+} = \frac{g_{Na}(V_m - E_{Na})}{g_{K}(V_m - E_{K})} = -1.5$$

The ratio is negative because the sodium and potassium currents are flowing in opposite directions. By rearranging, we get

$$V_m = \frac{1.5g_{K}E_{K} + g_{Na}E_{Na}}{1.5g_{K} + g_{Na}}$$

This equation is similar to the expression derived previously for the model cell, and it makes the same kinds of predictions. The membrane potential depends on the relative magnitudes of $g_{K}$ and $g_{Na}$. The difference is that the potassium term is multiplied by a factor of 1.5. Because of this factor, the membrane potential is closer to $E_{K}$ than would otherwise be the case. Thus, the driving force for sodium entry is increased, and that for potassium efflux is reduced. As a result the Na/K passive fluxes are in a ratio of 3:2 rather than 1:1.

In summary, the real cell differs from the model cell in that the resting membrane potential is the potential at which the passive influx of sodium is 1.5 times the passive efflux of potassium, rather than the potential at which the two fluxes are equal and opposite. The passive inward and outward currents are determined by the equilibrium potentials and conductances for the two ions; the required ratio of 3:2 is determined by the transport characteristics of the pump.

The problem of finding an expression for the resting membrane potential of real cells, taking into account the transport activity, was first considered by Mullins and Noda, who used intracellular microelectrodes to study the effects of ionic changes on membrane potential in muscle. Like Goldman and Hodgkin and Katz, they derived an expression for membrane potential in terms of permeabilities and concentrations. The result is equivalent to the equation we have just derived using conductances and equilibrium potentials:

$$V_m = 58 \log \frac{P_{K}[K]_o + P_{Na}[Na]_o}{P_{K}[K]_i + P_{Na}[Na]_i}$$

where $r$ is the absolute value of the transport ratio (3:2). The equation provides an accurate description of the resting membrane potential, provided all the other permeant ions (e.g., chloride) are in a steady state.

Chloride Distribution

How do these considerations apply to chloride? As for all other ions, there must be no net chloride current across the resting membrane. As already discussed (see Figure 5.2B), chloride is able to reach equilibrium simply by an appropriate adjustment in internal concentration, without affecting the steady-state membrane potential. In many cells, however, there are transport systems for chloride as well (Chapter 4). In squid axon and in muscle, chloride is transported actively into the cells; in many nerve cells active transport is outward (see Figure 5.5). The effect of inward transport is to add an increment to the equilibrium concentration such that there is an outward leak of chloride equal to the rate of transport in the opposite direction. Outward transport has the reverse effect.

An Electrical Model of the Membrane

For those attuned to electrical diagrams, these considerations are summarized in Figure 5.6. $E_{Na}$, $E_{K}$, and $E_{Cl}$ are represented by batteries, and the conductance pathways for sodium, potassium, and chloride by resistors. Passive ion currents through the resistors are equal and opposite to the corresponding currents generated by the pumps, so that the net current across the membrane for each ion is zero.
Predicted Values of Membrane Potential

How do these considerations explain the relation between potassium concentration and membrane potential shown in Figure 5.4? The answer becomes evident if we use real numbers in the equations. In squid axon, the permeability constants for sodium and potassium are roughly in the ratio 0.04:1.0.5 We can use these relative values, together with the ion concentrations given in Table 5.1, to calculate the resting membrane potential in seawater:

$$V_m = 58 \log \frac{(1.5)(10) + (0.04)(460)}{(1.5)(400) + (0.04)(50)} = -73 \text{ mV}$$

Now we can see quantitatively why, when extracellular potassium is altered, the membrane potential fails to follow the Nernst potential for potassium, as shown in Figure 5.4. If, in the numerator of the equation, we look at the magnitude of the term involving extracellular potassium concentration (1.5 x 10 = 15) and the term that involves extracellular sodium concentration (0.04 x 460 = 18.4), we see that potassium contributes only about 45% to the total. Because of this, doubling the external potassium concentration does not double the numerator (as would happen in the Nernst equation), and as a consequence, the effect on the membrane potential of changing the extracellular potassium concentration is less than would be expected if potassium were the only permeant ion. When the external potassium concentration is raised to a high enough level (100 mM in Figure 5.4), the potassium term becomes sufficiently dominant for the relation to approach the theoretical limit of 58 mV per 10-fold change in concentration. This effect is enhanced by a factor discussed in Chapter 3: Many potassium channels are voltage-activated and open when the membrane is depolarized by increasing extracellular potassium. Because of the increased permeability to potassium, the relative contribution of sodium to the membrane potential is further reduced.

In general, nerve cells have resting potentials on the order of ~70 mV. In some cells, such as vertebrate skeletal muscle, the resting potential can be ~90 mV or larger, reflecting a low ratio of sodium permeability to potassium permeability. Glial cells in particular have a very low permeability to sodium, so that their resting potentials are nearly identical to the potassium equilibrium potential (Chapter 8). Other cells, such as leech ganglion cells and receptors in the retina, have relatively high membrane permeabilities to sodium and resting membrane potentials as small as ~40 mV.

Contribution of the Sodium–Potassium Pump to the Membrane Potential

The sodium–potassium transport system is electrogenic because each cycle of the pump results in the net outward transfer of one positive ion, thereby contributing to the excess negative charge on the inner face of the membrane. How large is this contribution? An easy way to find out is to calculate what the membrane potential would be if the pump were not electrogenic, or, in other words, if \( r = 1 \). Repeating the previous calculation with this condition yields the following:

---

**FIGURE 5.6 Electrical Model of the Steady-State Cell Membrane** shown in Figure 5.5. \( E_K \), \( E_{Na} \), and \( E_{Cl} \) are the Nernst potentials for the individual ions. The individual ion conductances are represented by resistors (having a resistance of \( 1/g \) for each ion). The individual ion currents (\( g_K \), \( g_{Na} \), and \( g_{Cl} \)) are equal and opposite to the currents (\( i_{Na}, i_{K}, \) and \( i_{Cl} \)) supplied by the sodium–potassium exchange pump (\( T_{Na-K} \)), and the chloride pump (\( T_{Cl} \)), so the net flux of each ion across the membrane is zero. The resulting membrane potential is \( V_m \).
\[ V_m = 58 \log \left( \frac{(1.0)(10) + (0.04)(460)}{(1.0)(400) + (0.04)(50)} \right) = -67 \text{ mV} \]

This is 6 mV less than the previous value, so the pump contributes –6 mV to the resting potential. In general, the size of the pump contribution depends on a number of factors, particularly the relative ion permeabilities. For a transport ratio of 3:2, the steady-state contribution to the resting membrane potential is limited to a maximum of about –11 mV.\(^\text{11}\) If the transport process is stopped, the electrogenic contribution disappears immediately, and the membrane potential then declines gradually as the cell gains sodium and loses potassium.\(^\text{11}\)

Ion Channels Associated with the Resting Potential

The resting permeabilities of membranes to sodium, potassium, and chloride have been determined in many nerve cells. It is a curious fact, however, that none of the channels underlying these resting permeabilities have been precisely identified in any specific cell. Candidates for potassium channels active in the resting membrane vary from one cell to the next. Among these are channels activated by intracellular cations: sodium-activated and calcium-activated potassium channels. In addition, many nerve cells have \("M\) potassium channels that are open at rest and closed by intracellular messengers (Chapter 16). Although it is unlikely that a large fraction of voltage-activated potassium channels ("delayed rectifier" and \("A\) channels) are open at rest, only 0.1 to 1% of the total number would be required to account for a substantial fraction of the resting conductance.\(^\text{12}\)

The specific sources of the resting sodium permeability of nerve cells are also uncertain. A part can be attributed to the movement of sodium through potassium channels, most of which have a sodium/potassium permeability ratio that ranges between 1% and 3%.\(^\text{13}\) In addition, both inward sodium and outward potassium fluxes may occur through cation channels that show little selectivity for potassium over sodium.\(^\text{14,15}\) An additional sodium influx is through sodium-dependent secondary active transport systems (Chapter 4). Finally, tetrodotoxin has been shown to block a small fraction of the resting sodium conductance, indicating a contribution by voltage-activated sodium channels.\(^\text{9}\)

Chloride channels of the CLC family (Chapter 3) are widely distributed in nerve and muscle. The presence of chloride channels is important in that they serve to stabilize the membrane potential (see the next section). The channels also interact with chloride transport systems to determine intracellular chloride concentrations.\(^\text{16,17}\) When CLC channel expression is low—for example, in embryonic neurons in the hippocampus—\(E_{Cl}\) is positive with respect to the resting membrane potential because of inward transport and accumulation of chloride in the cytoplasm. In adult neurons, the expression of CLC channels increases the chloride conductance of the membrane so that excess accumulation cannot occur, and \(E_{Cl}\) becomes equal to the membrane potential. In central nervous system neurons, chloride channels can account for as much as 10% of the resting membrane conductance.\(^\text{14}\)

CHANGES IN MEMBRANE POTENTIAL

It is important to keep in mind that the discussion of resting membrane potential is always in reference to steady-state conditions. For example, we have said that changing the extracellular chloride concentration has little effect on membrane potential because the intracellular chloride concentration accommodates to the change. This is true in the long run, but the intracellular adjustment takes time, and while it is occurring there will indeed be a transient effect.

The steady-state potential is the baseline upon which all changes in membrane potential are superimposed. How are such changes in potential produced? In general, transient changes, such as those that mediate signaling between cells in the nervous system, are the result of transient changes in membrane permeability. As we already know from

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the constant field equation, an increase in sodium permeability (or a decrease in potassium permeability) will move the membrane potential toward the sodium equilibrium potential, producing depolarization. Conversely, an increase in potassium permeability will produce hyperpolarization. Another ion of importance in signaling is calcium. Intracellular calcium concentration is very low (Chapter 4), and in most cells $E_C$ is greater than $+150 \text{ mV}$. Thus, an increase in calcium permeability results in calcium influx and depolarization.

The role of chloride permeability in the control of membrane potential is of particular interest. As we have noted, chloride makes little contribution to the resting membrane potential. Instead, intracellular chloride concentration adjusts to the potential and is modified by whatever chloride transport mechanisms are operating in the cell membrane. The effect of a transient increase in chloride permeability can be either hyperpolarizing or depolarizing, depending on whether the chloride equilibrium potential is negative or positive with respect to the resting potential. This, in turn, depends on whether intracellular chloride is depleted or concentrated by the transport system. In either case, the change in potential is usually relatively small. Even so, the increased chloride permeability can be important for the regulation of signaling because it tends to hold the membrane potential near the chloride equilibrium potential and thus attenuates changes in potential that are produced by other influences.

This stabilization of the membrane potential is important for controlling the excitability of many cells, such as skeletal muscle fibers, that have a relatively high chloride permeability at rest. In such cells a transient influx of positive ions causes less depolarization than would otherwise be the case because it is countered by an influx of chloride through already open channels. Chloride channel mutations that reduce chloride conductance are responsible for several muscle diseases. The diseased muscles are hyperexcitable (myotonic) because of a loss of the normal stabilizing influence of a high chloride conductance.\[19\,20\]

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**Summary**

- Nerve cells have a high intracellular concentration of potassium and low intracellular concentrations of sodium and chloride, so that potassium tends to diffuse out of the cell, and sodium and chloride tend to diffuse in. The tendency for potassium and chloride to diffuse down their concentration gradients is opposed by the electrical potential across the cell membrane.

- In a model cell permeable only to potassium and chloride, the concentration gradients can be balanced exactly by the membrane potential, so that there is no net flux of either ion across the membrane. The membrane potential is then equal to the equilibrium potential for both potassium and chloride.

- Changing the extracellular potassium concentration changes the potassium equilibrium potential, and hence the membrane potential. Changing the extracellular chloride concentration, on the other hand, leads ultimately to a change in intracellular chloride, so that the chloride equilibrium potential and the membrane potential differ from their original values only transiently.

- The plasma membranes of real cells are permeable to sodium, as well as to potassium and chloride. As a result, there is a constant passive influx of sodium into the cell, and an efflux of potassium. These fluxes are balanced exactly by active transport of the ions in the opposite directions, in the ratio of 3 sodium to 2 potassium. Under these circumstances, the membrane potential depends on the sodium equilibrium potential, the potassium equilibrium potential, the relative conductance of the membrane to the two ions, and the pump ratio.

- Because the sodium–potassium exchange pump transports more positive ions outward than inward across the membrane, it makes a direct contribution of several millivolts to the membrane potential.

- The chloride equilibrium potential may be positive or negative with respect to the resting membrane potential, depending on chloride transport processes. Although the chloride distribution plays little role in determining the resting membrane potential, a high chloride permeability is important for electrical stability.
SUGGESTED READING

