

# PRINCIPLES OF NEURAL SCIENCE

THIRD EDITION

Edited by

ERIC R. KANDEL  
JAMES H. SCHWARTZ  
THOMAS M. JESSELL

Center for Neurobiology and Behavior  
College of Physicians & Surgeons of Columbia University  
and  
The Howard Hughes Medical Institute



APPLETON & LANGE  
Norwalk, Connecticut

John Koester

# Membrane Potential

## Membrane Potential Results from the Separation of Charge Across the Cell Membrane

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**T**he flow of information within and between neurons is conveyed by electrical and chemical signals. Transient electrical signals are particularly important for transferring information rapidly and over long distances. These electrical signals—receptor potentials, synaptic potentials, and action potentials—are all produced by temporary changes in the current flow into and out of the cell that drives the electrical potential across the cell membrane away from its resting value.

Current flow into and out of the cell is controlled by ion channels embedded in the cell membrane. There are two types of ion channels in membrane—gated and nongated. Nongated channels are always open and are not influenced significantly by extrinsic factors. They are primarily important in maintaining the resting membrane potential—the electrical potential across the membrane in the absence of signaling activity. Gated channels, in contrast, can open and close. Most gated channels are closed when the membrane is at rest, and their probability of opening is greatly enhanced by the three influences that we considered in the last chapter—change in membrane potential, ligand binding, or stretch of the membrane.

An analysis of the mechanisms underlying the resting membrane potential is a first step toward understanding how transient electrical signals are generated. Therefore, in this chapter we shall first discuss how the nongated ion channels establish the resting potential and how the flux of ions through gated channels generates the action potential. We shall then illustrate how the channels, along with other components important for nerve cell signaling, can be represented by an electrical equivalent circuit. The circuit approach is commonly used in neurobiology because it provides a complete quantitative description of the electrical signaling properties of the neuron. An understanding of this equivalent circuit model provides basic insights into the principles of signaling in excitable cells and serves as an essential foundation for interpreting all clin-

ical tests of the electrical function of nerve and muscle. The equivalent circuit approach is extended in Chapter 7 to describe how the passive, nonchanging electrical properties of the neuron influence the active signals—action potentials, synaptic potentials, and receptor potentials. The gating mechanisms of ion channels that mediate these three types of signals are then described in Chapters 8–11 and 23, respectively.

### Membrane Potential Results from the Separation of Charge Across the Cell Membrane

Every neuron has a separation of electrical charge across its cell membrane consisting of a thin cloud of positive and negative ions spread over the inner and outer surfaces of the membrane (Figure 6–1). A nerve cell at rest has an excess of positive charges on the outside of the membrane and an excess of negative charges on the inside. This separation of charge is maintained because the lipid bilayer acts as a barrier to the diffusion of ions, as explained in Chapter 5. The charge separation gives rise to an electrical potential difference across the membrane. The potential difference, or voltage, is called the *resting membrane potential*. It is directly proportional to the charge separation across the membrane. In most neurons the resting membrane potential ranges from about 60 mV to 70 mV. All electrical signaling results from brief changes away from the resting membrane potential (Box 6–1).

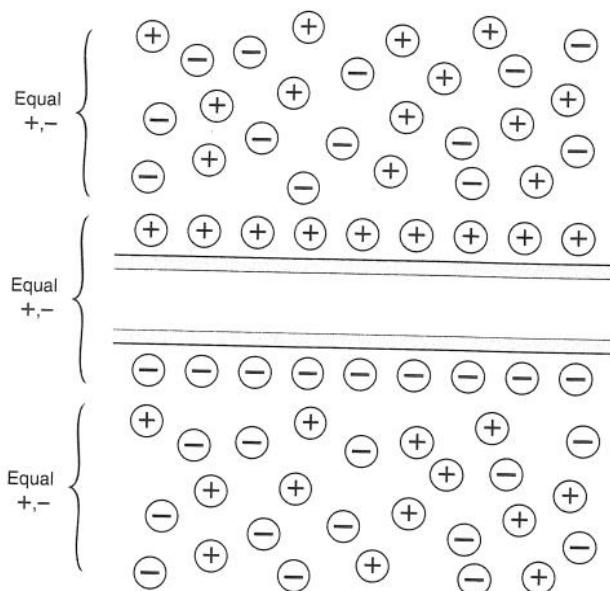
The term resting membrane potential applies only to the potential across the membrane when the cell is at rest. The more general term *membrane potential* refers to the electrical potential difference across the membrane at any moment in time—at rest or during signaling. By convention, the potential outside the cell is arbitrarily defined as zero, so membrane potential ( $V_m$ ) is defined as

$$V_m = V_{in} - V_{out}$$

where  $V_{in}$  is the potential on the inside of the cell and  $V_{out}$  the potential on the outside. According to this convention the resting potential ( $V_R$ ) is negative

$$V_R = -60 \text{ to } -70 \text{ mV.}$$

In an ionic solution electrical current is carried by ions—both anions and cations. By convention, the direction of current flow is defined as the direction of *net* movement of *positive* charge. Thus, in an ionic solution cations move in the same direction as the current, and anions move in the opposite direction. The charge separation across the membrane is disturbed whenever there is a net flux of ions into or out of the cell, thus altering the polarization of the membrane. A reduction of the charge separation is called *depolarization*; an increase in charge separation is called *hyperpolarization* (see Box 6–1). Passive depolarizing or hyperpolarizing responses of the membrane potential to current flow are called *electrotropic potentials*. Hyperpolarizing responses are purely passive. Small depolarizations are also passive. However, at a critical level of depolarization, called the *threshold*,



**FIGURE 6–1**

The membrane potential results from a separation of positive and negative charges across the cell membrane. The excess of positive charges outside and negative charges inside the membrane of a nerve cell at rest represents a small fraction of the total number of ions inside and outside the cell.

the cell responds actively with an all-or-none *action potential* (Box 6–1).

We shall begin our examination of the membrane potential by analyzing how the passive flux of individual ion species through nongated membrane channels generates the resting potential. We shall then be able to understand how the selective gating of different types of ion channels generates the action potential, as well as the receptor and synaptic potentials.

### The Resting Membrane Potential Is Determined by the Relative Abundance of Different Types of Nongated Ion Channels

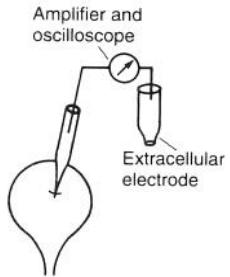
No single ion species is distributed equally on the two sides of a nerve cell membrane. Of the four most abundant types of ions found on either side of the cell membrane,  $\text{Na}^+$  and  $\text{Cl}^-$  are more concentrated outside the cell, and  $\text{K}^+$  and organic anions ( $\text{A}^-$ ) are more concentrated inside. The organic anions are primarily organic acids and proteins. The distribution of these ions inside and outside the membrane of the giant axon of the squid, which is a popular experimental preparation for neurophysiology, is shown in Table 6–1. In vertebrate nerve cells the absolute values of the concentration of various ions in nerve cells are two- to threefold lower, but the concentration gradients are about the same.

The unequal distribution of ions raises two important questions. First, how do these ionic gradients contribute

### Recording the Membrane Potential

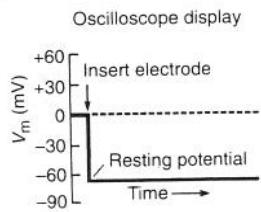
Reliable techniques for intracellular recordings were developed in the late 1940s. These allowed measurement across the membrane of both the resting and the action potentials. To measure the resting potential, an intracellular electrode is inserted into the nerve cell. The electrode is a glass pipette drawn out to a tip about  $0.5\text{ }\mu\text{m}$  in diameter and filled with a concentrated salt solution (usually 3 M KCl). The pipette acts as a salt bridge, providing an electrical connection between the cytoplasm and a metal electrode that is connected to the electronic apparatus. A second salt bridge of the same ionic composition, connected to a metal electrode, is used as the extracellular electrode. The two metal electrodes inserted into the back ends of the two salt bridges are connected to a voltage amplifier, which in turn is connected to an oscilloscope that displays the amplitude of the membrane potential as the vertical deflection of a spot of light on the screen.

**FIGURE 6–2A**



When both electrodes are outside the cell, no electrical potential difference is recorded; but as soon as one electrode is inserted into the cell, the oscilloscope displays a steady deflection of about  $-65\text{ mV}$ , the resting membrane potential.

**FIGURE 6–2B**

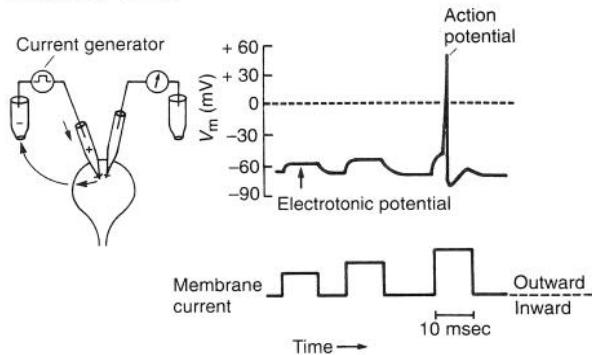


The membrane potential can be changed using a current generator connected to a second pair of electrodes—one intracellular and one extracellular. By making the intracellular current electrode positive with respect to the external electrode, the current generator delivers a pulse of current that depolarizes the cell. Current flows into the neuron from the intracellular electrode causing a net accumulation of

### BOX 6–1

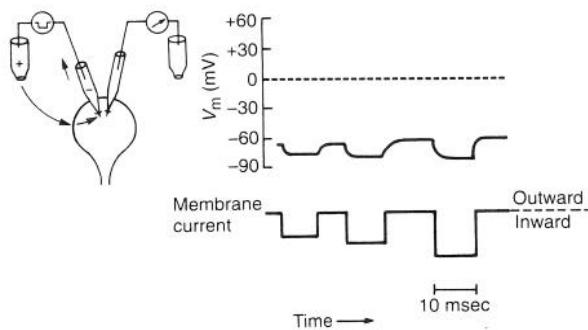
positive charge on the inside of the membrane; at the same time, net positive charge is withdrawn from the outside of the membrane by the extracellular electrode. The result is a progressive decrease in the normal separation of charge or *depolarization*.

**FIGURE 6–2C**



Reversing the direction of current flow—by making the intracellular electrode negative with respect to the extracellular electrode—makes the membrane potential more negative. This results in an increase in charge separation or *hyperpolarization*.

**FIGURE 6–2D**



The membrane can respond to current injections either passively or actively. The responses to hyperpolarization are purely passive (electrotonic). As the size of the current pulse increases, the hyperpolarization increases proportionately. Likewise, small depolarizing current pulses evoke purely electrotonic potentials, and the size of the potential change is proportional to the size of the current pulses. However, depolarizing current eventually drives the membrane potential to a critical level called the *threshold*, where an active response, the all-or-none *action potential*, is triggered (Figure 6–2C). The action potential differs from the electrotonic potential in magnitude, duration, and the way in which it is generated.

**TABLE 6-1.** Distribution of the Major Ions Across the Membrane of the Squid Giant Axon

Ion	Cytoplasm (mM)	Extracellular fluid (mM)	Nernst potential* (mV)
K <sup>+</sup>	400	20	-75
Na <sup>+</sup>	50	440	+55
Cl <sup>-</sup>	52	560	-60
A <sup>-</sup>	385	—	—

\*The membrane potential at which there is no net flux of an ion across the cell membrane.

to the resting membrane potential? Second, how are they maintained? What prevents the ionic gradients from being dissipated by passive diffusion of ions across the membrane through the passive (nongated) channels? These two questions are interrelated, and we shall answer them by considering two examples of membrane permeability: the resting membrane of glial cells, which is selectively permeable to only one species of ions, and the resting membrane of nerve cells, which is permeable to three species of ions. In this discussion we shall consider only the nongated ion channels, which are always open.

#### Nongated Channels in Glial Cells Are Selective Only for Potassium

A membrane's selectivity for permeant ions is determined by the relative proportions of various types of ion channels. The membranes of glial cells have nongated channels that for the most part are selectively permeable to K<sup>+</sup>, and thus are almost exclusively permeable to K<sup>+</sup> ions when the cell is at rest. A glial cell has a high concentration of K<sup>+</sup> and organic anions on the inside and a high concentration of Na<sup>+</sup> and Cl<sup>-</sup> on the outside. Assume that initially there is no potential difference across the membrane. Since the glial cell membrane is selectively permeable to K<sup>+</sup>, the K<sup>+</sup> diffuses down its concentration gradient out of the cell, leaving nonpermeant anions behind (Figure 6-3).<sup>1</sup> The result is a surplus of cations outside the cell and a surplus of anions inside the cell. The electrostatic attraction between the excess cations on the outside of the membrane and the excess anions on the inner surface generates a thin cloud of positive charges on the exterior surface of the membrane and an equal density of negative charge on the interior surface (Figure 6-1).

The diffusion of K<sup>+</sup> out of the cell is self-limiting. The buildup of positive charge outside the cell and negative charge inside impedes the efflux of K<sup>+</sup> by electrostatic repulsion and attraction. Thus, two opposing forces act on each K<sup>+</sup> ion, one chemical and the other electrical. The

<sup>1</sup>If there is no electrical potential difference across the membrane, the permeability of the membrane to an ion ( $P_i$ ) is defined as the net flux ( $I_i$ ) of that ion divided by the product of the concentration difference of that ion across the membrane ( $\Delta C_i$ ) times the membrane area ( $A$ ):

$$P_i = I_i / (\Delta C_i A)$$

driving force of the chemical concentration gradient tends to drive K<sup>+</sup> out of the cell through the K<sup>+</sup> channels. As the outside of the cell membrane becomes positive relative to the inside, the electrostatic force due to the charge separation results in an *electrical potential difference* that tends to push K<sup>+</sup> back into the cell. The difference in electrical potential across the membrane increases as the diffusion of K<sup>+</sup> continues to increase the separation of charge. It continues to increase until it reaches a value that has an effect on K<sup>+</sup> equal and opposite to the effect of the concentration gradient. At this value of membrane potential, which in most glial cells is about -75 mV, the K<sup>+</sup> concentrations inside and outside the cell are in equilibrium. In a cell permeable only to K<sup>+</sup> ions the resting membrane potential is therefore the K<sup>+</sup> *equilibrium potential*.

In a cell that has only K<sup>+</sup> channels in its membrane, no metabolic energy is required to maintain the ionic concentration gradients shown in Table 6-1. The membrane potential automatically settles at the K<sup>+</sup> equilibrium potential. The gradients for other ions are not important, because these ions cannot pass through the membrane. Thus, once the ionic gradients are established, they will persist indefinitely with no expenditure of metabolic energy.

The membrane potential at which K<sup>+</sup> ions are in equilibrium across the membrane can be calculated from an equation derived in 1888 from basic thermodynamic principles by the German physical chemist Walter Nernst:

$$E_K = \frac{RT}{ZF} \ln \frac{[K^+]_o}{[K^+]_i} \quad \text{Nernst Equation}$$

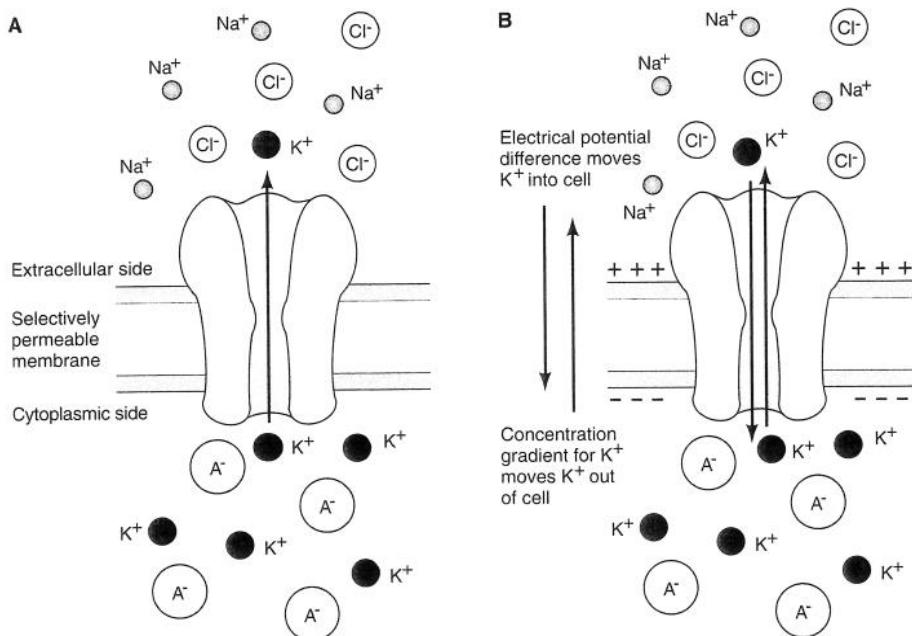
where  $E_K$  is the value of membrane potential at which K<sup>+</sup> is in equilibrium (the K<sup>+</sup> *Nernst potential*),  $R$  is the gas constant,  $T$  the temperature in degrees Kelvin,  $Z$  the valence of K<sup>+</sup>,  $F$  the Faraday constant, and  $[K^+]_o$  and  $[K^+]_i$  the concentrations of K<sup>+</sup> on the outside and inside of the cell. To be precise, chemical activities should be used rather than concentrations. For K<sup>+</sup>,  $Z = +1$ , and at 25°C  $RT/ZF$  is 26 mV. The constant for converting from natural logarithms to base 10 logarithms is 2.3. Substituting the values of K<sup>+</sup> concentration given in Table 6-1, we have

$$E_K = 26 \text{ mV} \times 2.3 \log_{10} \frac{20}{400} = -75 \text{ mV}$$

The Nernst equation can be used to find the equilibrium potential of any ion that is present on both sides of a membrane permeable to that ion. The Na<sup>+</sup>, K<sup>+</sup>, and Cl<sup>-</sup> Nernst potentials for the distributions of ions across the squid axon are given in Table 6-1.

#### Nongated Channels in Nerve Cells Are Selective for Several Ion Species

In 1902 Julius Bernstein used the Nernst equation as the theoretical framework on which to develop the hypothesis that the resting potential of neurons is based on the selective permeability of the membrane to K<sup>+</sup>. Bernstein's idea

**FIGURE 6-3**

The flux of  $K^+$  across the membrane is determined by both the  $K^+$  concentration gradient and the electrical potential across the membrane.

**A.** In a cell permeable only to  $K^+$  the resting potential is generated by the efflux of  $K^+$  down its concentration gradient.

**B.** The continued efflux of  $K^+$  builds up an excess of positive charge on the outside of the cell and leaves behind on the inside an excess of negative charge. This buildup of charge acts to impede the further efflux of  $K^+$ , so that eventually an equilibrium is reached, at which the electrical and chemical driving forces are equal and opposite.

could not be tested quantitatively until the 1940s, when techniques for intracellular recording were developed. It then became possible to compare the measured resting membrane potential to the value of  $E_K$  predicted from the Nernst equation. The observed values of membrane potentials in neurons deviate from the theoretical curve for a Nernst potential for  $K^+$ , particularly at relatively low values of  $[K^+]_o$  (Figure 6-4). This suggests that neurons at rest have significant numbers of open channels that are selective to ions other than  $K^+$ . In contrast, the fit between theoretical and observed curves is much better for glial cells, with good agreement down to quite low values of  $[K^+]_o$ . Thus, glial cell membranes can be described to a first approximation as having only open  $K^+$  channels when the membrane potential is at its resting value.

Measurements of the resting membrane potential with intracellular electrodes and flux studies using radioactive tracers have verified that, unlike glial cells, nerve cells at rest are permeable to  $Na^+$  and  $Cl^-$  in addition to  $K^+$ . Of the most abundant ion species in nerve cells, only the large organic anions, such as amino acids and proteins, are nonpermeant. How can three concentration gradients (for  $Na^+$ ,  $K^+$ , and  $Cl^-$ ) be maintained across the cell membrane, and how do these three concentration gradients interact to determine the resting membrane potential?

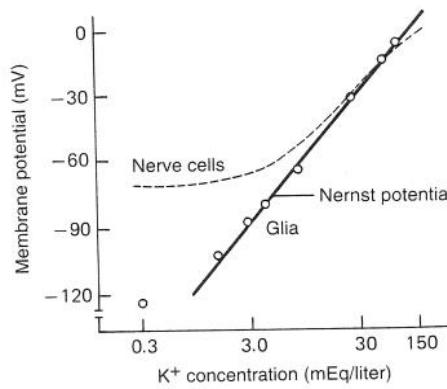
To answer these questions, it will be easiest to examine first only the diffusion of  $K^+$  and  $Na^+$ . Let us return to the simple example of a cell having only  $K^+$  channels, with unequal concentration gradients of  $K^+$ ,  $Na^+$ ,  $Cl^-$ , and  $A^-$  as shown in Table 6-1. Under these conditions the resting membrane potential,  $V_R$ , is determined solely by the  $K^+$  concentration gradient, so that  $V_R = E_K$ . Now consider what happens if a few  $Na^+$  channels are added to the membrane, making it slightly permeable to  $Na^+$ . Two forces act

on  $Na^+$  to drive it into the cell. First,  $Na^+$  is more concentrated outside than inside and therefore tends to flow into the cell down its concentration gradient. Second,  $Na^+$  is driven into the cell by the electrical potential difference across the membrane. The equilibrium potential for  $Na^+$ , calculated from the Nernst equation, is

$$E_{Na} = \frac{RT}{ZF} \ln \frac{[Na^+]_o}{[Na^+]_i}$$

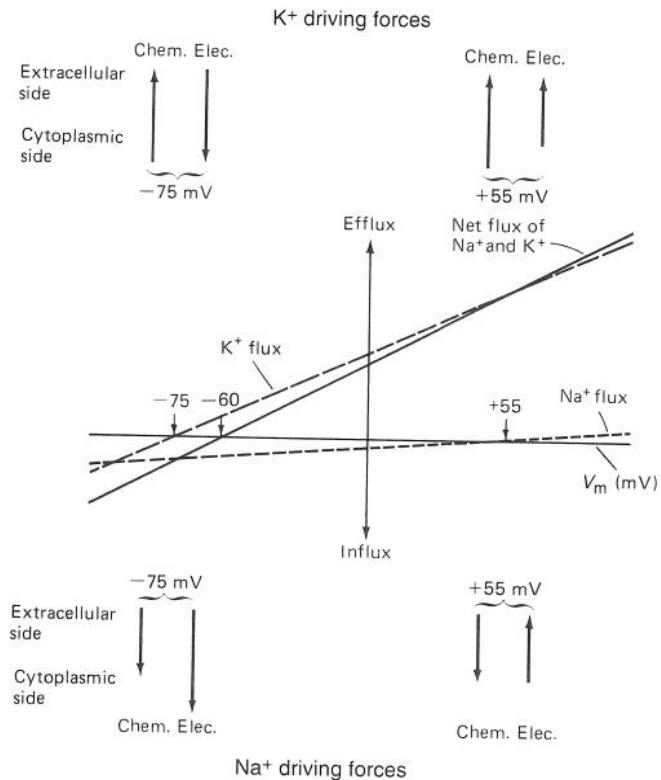
**FIGURE 6-4**

The relationship between membrane potential and external  $K^+$  concentration (log scale) in nerve cells and glia. The calculated Nernst potential for  $K^+$  (solid line) matches the observed membrane potential in glia (open circles) over a wide range of extracellular  $K^+$  concentration. In nerve cell membranes, however, the observed potential deviates from the theoretical curve at relatively low values of extracellular  $K^+$  (dashed line). (Adapted from Orkand, 1977.)



**FIGURE 6–5**

The resting potential of a cell with nongated  $\text{Na}^+$  and  $\text{K}^+$  channels is defined as the potential at which  $\text{K}^+$  efflux is balanced by  $\text{Na}^+$  influx. The direction and amplitude of the chemical and electrical driving forces acting on  $\text{Na}^+$  and  $\text{K}^+$  are shown for two different values of  $V_m$ . They result in the flux curves shown for each ion (broken lines) and the net flux curve for  $\text{Na}^+$  and  $\text{K}^+$  combined (solid line). The changes in driving force are the same for  $\text{Na}^+$  and  $\text{K}^+$  for a given change in  $V_m$ . The difference in the slopes of the  $\text{Na}^+$  and  $\text{K}^+$  flux curves reflects the fact that the resting membrane is more permeable to  $\text{K}^+$  than to  $\text{Na}^+$ . The shapes of the  $\text{Na}^+$  and  $\text{K}^+$  flux curves in the plot are simplified considerably. These curves become quite nonlinear as voltage-gated channels begin to open at values of  $V_m$  more positive than about  $-50$  mV, as described in Chapter 8.



For the value given in Table 6–1,

$$E_{\text{Na}} = 26 \text{ mV} \times 2.3 \log_{10} \frac{440}{50} = +55 \text{ mV.}$$

At a resting membrane potential of  $-75$  mV,  $\text{Na}^+$  will be  $130$  mV away from equilibrium, and a strong electrochemical force will drive  $\text{Na}^+$  through the open  $\text{Na}^+$  channels.

The influx of  $\text{Na}^+$  (driven by both the concentration and electrical gradients) depolarizes the cell, moving  $V_m$  toward  $E_{\text{Na}}$ . However, since many more  $\text{K}^+$  channels than  $\text{Na}^+$  channels are open in the resting membrane,  $V_m$  actually moves only slightly away from  $E_K$  and does not come close to approaching  $E_{\text{Na}}$ . For once  $V_m$  begins to diverge from  $E_K$ ,  $\text{K}^+$  flows out of the cell, tending to counteract the  $\text{Na}^+$  influx. The more  $V_m$  differs from  $E_K$ , the greater is the electrochemical force driving  $\text{K}^+$  out of the cell, and consequently the greater the  $\text{K}^+$  efflux. Eventually,  $V_m$  reaches a resting potential at which the outward movement of  $\text{K}^+$  just balances the inward movement of  $\text{Na}^+$ . This balance point ( $-60$  mV) is more positive than  $E_K$  ( $-75$  mV), but still far from  $E_{\text{Na}}$  ( $+55$  mV). Thus, if the resting membrane is only slightly permeable to  $\text{Na}^+$ ,  $V_R$  shifts slightly away from  $E_K$  toward  $E_{\text{Na}}$  (Figure 6–5).

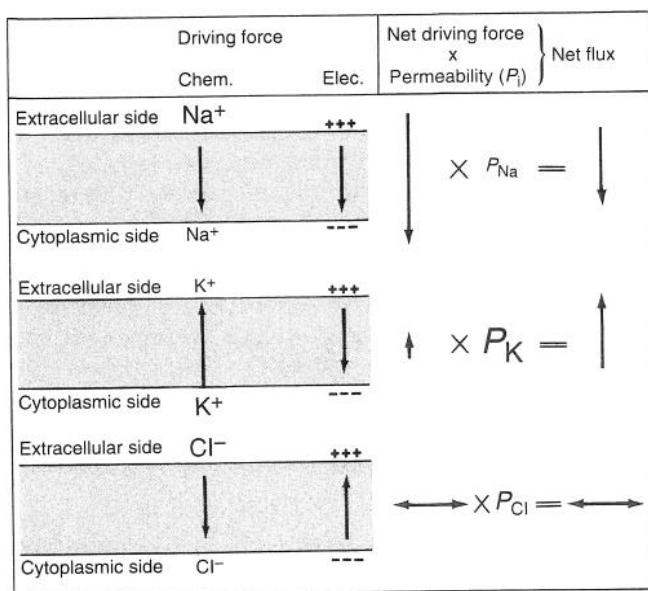
To understand how this balance point is determined, bear in mind that the flux of an ion across a cell membrane is the product of its electrochemical driving force times the permeability of the membrane to the ion. In a cell at rest ( $V_m = V_R$ ), relatively few  $\text{Na}^+$  channels are open, so the permeability to  $\text{Na}^+$  is quite low. As a result, the in-

flux of  $\text{Na}^+$  is small, despite the large chemical and electrical forces driving  $\text{Na}^+$  into the cell. The  $\text{K}^+$  concentration gradient driving  $\text{K}^+$  out is only slightly greater than the electrical force acting to hold it in. Nevertheless, because the membrane permeability to  $\text{K}^+$  is relatively large, the small net outward force acting on  $\text{K}^+$  is enough to produce a  $\text{K}^+$  efflux that balances the  $\text{Na}^+$  influx (Figure 6–6).

#### *The Passive Fluxes of Sodium and Potassium Through Nongated Channels Are Balanced by Active Pumping of Sodium and Potassium Ions*

For the cell to have a steady resting membrane potential, the charge separation across the membrane must be constant: The influx of positive charge must be balanced by the efflux of positive charge. If these fluxes were not equal, the charge separation across the membrane, and thus the membrane potential, would vary continually. Therefore, for the cell to achieve a resting state, the movement of  $\text{K}^+$  out of the cell must balance the movement of  $\text{Na}^+$  into the cell (Figure 6–5). Although these steady ion leaks cancel each other, they cannot be allowed to continue unopposed for any appreciable length of time. Otherwise,  $[\text{K}^+]_i$  would be depleted,  $[\text{Na}^+]_i$  would increase, and the ionic gradients would gradually run down, reducing the resting membrane potential.

Dissipation of ionic gradients is prevented by the  $\text{Na}^+-\text{K}^+$  pump, which extrudes  $\text{Na}^+$  from the cell while

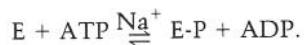
**FIGURE 6–6**

The fluxes for  $\text{Na}^+$ ,  $\text{K}^+$ , and  $\text{Cl}^-$  across the cell membrane are a result of their chemical and electrical driving forces and the permeability of the membrane. The fluxes shown here are for a cell with a membrane potential of  $-60 \text{ mV}$  and the ionic gradients shown in Table 6–1. (Horizontal arrows signify no net driving force or no net flux.)

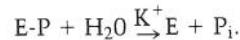
taking in  $\text{K}^+$  (Figure 6–7). Because the pump moves  $\text{Na}^+$  and  $\text{K}^+$  against their net electrochemical gradients, energy must be provided to drive these actively transported fluxes. The energy comes from the hydrolysis of ATP.

The  $\text{Na}^+-\text{K}^+$  pump is an integral membrane protein. It is a multimeric complex consisting of two different polypeptides: a transmembrane catalytic subunit ( $\alpha$ ) and a glycoprotein regulatory subunit ( $\beta$ ). The probable structure of the holoenzyme is  $\alpha_2\beta_2$  with a molecular weight of 270,000. The catalytic subunit has binding sites for  $\text{Na}^+$  and ATP on its intracellular surface and sites for  $\text{K}^+$  and ouabain, a poison that specifically and irreversibly inhibits the pump, on its extracellular surface. ATP transfers its terminal phosphate group to the catalytic subunit ( $\text{E}$ )

forming a covalent intermediate ( $\text{E}-\text{P}$ ) at a specific  $\beta$ -aspartic acid residue. This reaction depends on the presence of  $\text{Na}^+$  ions:



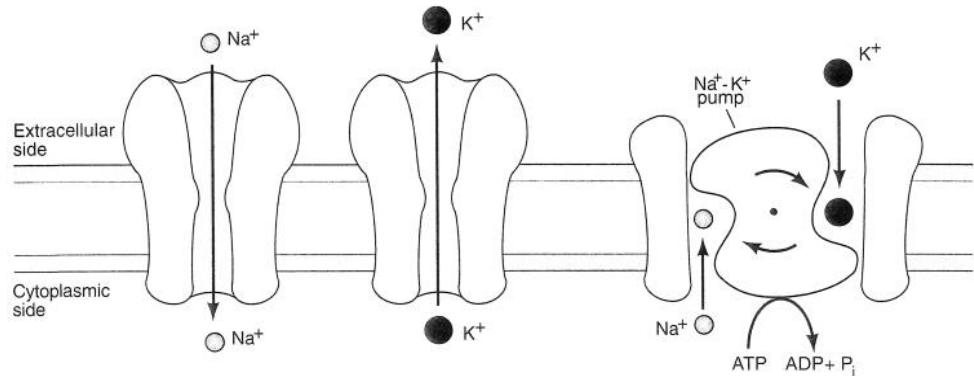
Protein phosphorylation changes the conformation of the complex, which leads to the removal of three  $\text{Na}^+$  ions from the inside of the cell to the outside in exchange for two extracellular  $\text{K}^+$  ions. The phosphorylated catalytic subunit is hydrolyzed in the presence of  $\text{K}^+$  ions:



Thus, the overall reaction results in the hydrolysis of ATP.

When the cell is at rest, the active fluxes (driven by the pump) and the passive fluxes (due to diffusion) are balanced for  $\text{Na}^+$  and  $\text{K}^+$ , so that the net flux of each of these two ions is zero. Thus, at the resting membrane potential the cell is not in equilibrium, but rather in a *steady state*: Metabolic energy must be used to maintain the ionic gradients across the membrane.

Because the pump extrudes three  $\text{Na}^+$  ions for every two  $\text{K}^+$  ions it brings in, it is said to be electrogenic. This net outward flux of positive charge tends to hyperpolarize the membrane. The greater the hyperpolarization, the greater the inward electrochemical force driving  $\text{Na}^+$  into the cell, and the smaller the force driving  $\text{K}^+$  out. Thus,  $\text{Na}^+$  current ( $I_{\text{Na}}$ ) and  $\text{K}^+$  current ( $I_{\text{K}}$ ) that result from passive diffusion are no longer in balance, and there is a net inward current through the nongated channels. The steady state for such a cell is achieved when a membrane potential is reached at which there is a net passive inward current through the ion channels that exactly counterbalances the active outward current driven by the pump. This balance occurs when three  $\text{Na}^+$  ions diffuse in for every two  $\text{K}^+$  ions that diffuse out. When this condition is met, the active and passive fluxes of  $\text{Na}^+$  are equal and opposite, as are the corresponding  $\text{K}^+$  fluxes, so the concentration gradients for  $\text{Na}^+$  and  $\text{K}^+$  remain constant. The resting potential for a cell with an electrogenic pump is typically a few millivolts more negative than would be expected from the purely passive diffusion of ions.

**FIGURE 6–7**

When the cell is at rest the passive fluxes of  $\text{Na}^+$  and  $\text{K}^+$  into and out of the cell are balanced by active transport driven in the opposite direction by the ATP-dependent  $\text{Na}^+-\text{K}^+$  pump.

### Chloride Ions Are Often Passively Distributed

In the discussion above we have ignored the contribution of  $\text{Cl}^-$  to the generation of the resting potential, even though all nerve cells have nongated  $\text{Cl}^-$  channels. Whether this simplification is valid for a particular type of cell depends on whether the cell membrane has a  $\text{Cl}^-$  pump. In cells without a  $\text{Cl}^-$  pump  $V_R$  is ultimately determined by  $\text{K}^+$  and  $\text{Na}^+$  fluxes, because their intracellular concentrations are fixed by the  $\text{Na}^+/\text{K}^+$  pump. The  $\text{Cl}^-$  concentration inside the cell is free to change, because it is acted on only by passive forces (electrical potential and concentration gradient). In a cell with no  $\text{Cl}^-$  pump, therefore,  $\text{Cl}^-$  ions must be in equilibrium across the membrane and the concentration ratio of intracellular and extracellular  $\text{Cl}^-$  settles at a value such that  $E_{\text{Cl}} = V_R$ .

In nerve cells that do have a  $\text{Cl}^-$  pump the active transport is directed outward, so that  $[\text{Cl}^-]_o/[\text{Cl}^-]_i$  is greater than the ratio that would result from passive diffusion alone. The effect of increasing the  $\text{Cl}^-$  gradient is to make  $E_{\text{Cl}}$  more negative than  $V_m$ . This difference between  $E_{\text{Cl}}$  and  $V_R$  results in a steady inward leak of  $\text{Cl}^-$  that is balanced by active extrusion of  $\text{Cl}^-$  by the  $\text{Cl}^-$  pump.

### The Action Potential Is Generated by the Sequential Opening of Voltage-Gated Channels Selective for Sodium and Potassium

In the nerve cell at rest, the steady  $\text{Na}^+$  influx through nongated channels is balanced by a steady  $\text{K}^+$  efflux, so that the membrane potential is constant. This steady-state balance changes, however, when the cell is depolarized sufficiently to trigger an action potential. A transient depolarizing potential, such as an excitatory synaptic potential, causes some voltage-gated  $\text{Na}^+$  channels to open, and the resultant increase in membrane  $\text{Na}^+$  permeability allows  $\text{Na}^+$  influx to outstrip the  $\text{K}^+$  efflux. Thus, a net influx of positive charge flows through the membrane, and positive charges accumulate inside the cell, causing further depolarization. The increase in depolarization causes more voltage-gated  $\text{Na}^+$  channels to open, resulting in a greater influx of positive charge, which accelerates the depolarization still further.

This regenerative, positive feedback cycle develops explosively, driving the membrane potential toward the  $\text{Na}^+$  equilibrium potential of +55 mV. Because  $\text{K}^+$  efflux continues through the  $\text{K}^+$  channels, the membrane potential at the peak of the action potential never actually reaches  $E_{\text{Na}}$ . A slight diffusion of  $\text{Cl}^-$  into the cell also counteracts the depolarizing tendency of the  $\text{Na}^+$  influx. Nevertheless, so many voltage-gated  $\text{Na}^+$  channels open during the rising phase of the action potential that the permeability to  $\text{Na}^+$  is much greater than that to  $\text{Cl}^-$  or  $\text{K}^+$ . To a first approximation, the membrane potential approaches  $E_{\text{Na}}$  at the peak of the action potential, just as it approaches  $E_K$  at rest, when the  $\text{K}^+$  permeability is predominant.

The membrane potential would remain at this large positive value indefinitely but for two processes that re-

polarize the membrane, terminating the action potential. First, as the depolarization continues, it slowly turns off, or *inactivates*, the voltage-gated  $\text{Na}^+$  channels. That is, the  $\text{Na}^+$  channels have two types of gating mechanisms: activation, which rapidly opens the channel in response to depolarization, and inactivation, which slowly closes the channel if the depolarization is maintained. The second repolarizing process results from the delayed opening of voltage-gated  $\text{K}^+$  channels. As  $\text{K}^+$  channels begin to open,  $\text{K}^+$  efflux increases. The delayed increase in  $\text{K}^+$  efflux combines with a decrease in  $\text{Na}^+$  influx to produce a net efflux of positive charge from the cell, which continues until the cell has repolarized to its resting value of  $V_R$ .

### The Resting and Action Potentials Can Be Quantified by the Goldman Equation

Although  $\text{Na}^+$  and  $\text{K}^+$  fluxes set the value of the resting potential,  $V_R$  is not equal to either  $E_K$  or  $E_{\text{Na}}$ , but lies between them. As a general rule, when  $V_m$  is determined by two or more species of ions, the influence of each species is determined both by its concentrations inside and outside the cell and by the permeability of the membrane to that ion. This relationship is given quantitatively by the *Goldman equation*<sup>2</sup>:

$$V_m = \frac{RT}{F} \ln \frac{P_K[\text{K}^+]_o + P_{\text{Na}}[\text{Na}^+]_o + P_{\text{Cl}}[\text{Cl}^-]_i}{P_K[\text{K}^+]_i + P_{\text{Na}}[\text{Na}^+]_i + P_{\text{Cl}}[\text{Cl}^-]_o} \quad \text{Goldman Equation}$$

This equation applies only when  $V_m$  is not changing. It states that the greater the concentration of a particular ion species and the greater its membrane permeability, the greater its role in determining the membrane potential. In the limiting case, when permeability to one ion is exceptionally high, the Goldman equation reduces to the Nernst equation for that ion. For example, if  $P_K \gg P_{\text{Cl}}, P_{\text{Na}}$ , as in glial cells, the equation becomes

$$V_m \approx \frac{RT}{F} \ln \frac{[\text{K}^+]_o}{[\text{K}^+]_i}.$$

In 1949 Alan Hodgkin and Bernard Katz first applied the Goldman equation systematically to changes in membrane potential evoked by altering external ion concentrations in the squid giant axon. They measured the variation of  $V_R$  while changing extracellular concentrations of  $\text{Na}^+$ ,  $\text{Cl}^-$ , and  $\text{K}^+$ . Their results showed that if  $V_R$  is measured shortly after the concentration change, before the internal ionic concentrations are altered,  $[\text{K}^+]_o$  has a strong effect

<sup>2</sup>There are three basic steps in the derivation of this equation:

- Express the flux ( $J$ ) of each species of ion ( $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Cl}^-$ ) across the membrane as a function of  $V_m$ , concentration, and membrane permeability:  $J_i = f(V_m, \text{conc}_i, P_i)$ .
- Convert these fluxes to membrane currents,  $I$  (e.g., an influx of  $\text{Na}^+$  or an efflux of  $\text{Cl}^-$  is an *inward* membrane current). Since  $V_m$  is constant, the charge separation across the membrane is not changing, so that  $I_{\text{Cl}} + I_{\text{Na}} + I_K = 0$ .
- Substitute the equations from step 1 into the equation in step 2, rearrange terms and solve for  $V_m$ .

on the resting potential,  $[Cl^-]_o$  has a moderate effect, and  $[Na^+]_o$  has little effect. Their data could be fit accurately to the Goldman equation by assuming the following permeability ratios for the membrane at rest:

$$P_K : P_{Na} : P_{Cl} = 1/0.04/0.45.$$

For the membrane at the peak of the action potential, however, the variation of  $V_m$  with external ionic concentrations could be fit best by assuming a quite different set of permeability ratios:

$$P_K : P_{Na} : P_{Cl} = 1/20/0.45.$$

For this set of permeabilities ( $P_{Na} \gg P_K, P_{Cl}$ ), the Goldman equation reduces to

$$V_m \approx \frac{RT}{F} \ln \frac{[Na^+]_o}{[Na^+]_i} = +55 \text{ mV}.$$

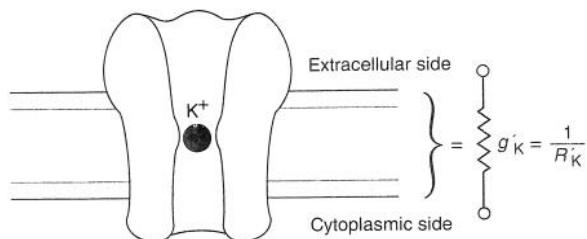
Thus, at the peak of the action potential, when the membrane is much more permeable to  $Na^+$  than to any other ion,  $V_m$  approaches  $E_{Na}$ , the Nernst potential for  $Na^+$ .

### The Neuron Can Be Represented by an Electrical Equivalent Circuit

A simple mathematical model derived from electrical circuits is helpful for describing the three critical features used by the nerve cell for electrical signaling—the ion channels, the concentration gradients of relevant ions, and the ability of the membrane to store charge. In this model, called an *equivalent circuit*, all of the important functional properties of the neuron are represented by an electrical circuit consisting only of conductors (resistors), batteries, and capacitors. This model provides an intuitive understanding as well as a quantitative description of how current flow due to the movement of ions generates signals in nerve cells. The first step in developing the model is to relate the discrete physical properties of the membrane to its electrical properties. A review of elementary circuit theory in Appendix A may be helpful before proceeding.

#### Each Ion Channel Acts as a Conductor and Battery

As described in Chapter 5, ions do not enter the lipid bilayer of the membrane; the bilayer is therefore a poor conductor of ionic current. Even a large potential difference will produce practically no current flow across a pure lipid bilayer. Consider the cell body of a typical spinal motor neuron, which has a membrane area of about  $10^{-4} \text{ cm}^2$ . If that membrane were composed solely of lipid bilayer, its electrical conductance would be only about 1 pS. But because thousands of nongated ion channels are embedded in the membrane, ions constantly diffuse across it, so that its actual resting conductance is about 40,000 times greater, or about 40 nS.



**FIGURE 6–8**

A single  $K^+$  channel can be represented by the electrical symbol for a conductor,  $g'_K$ .

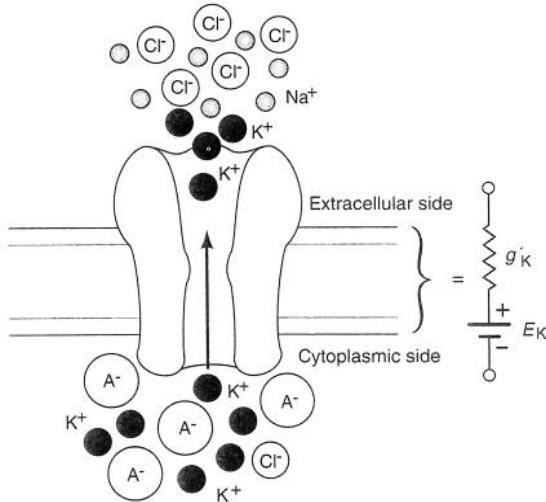
In the equivalent circuit model each  $K^+$  channel can be represented by the symbol for a conductor [Figure 6–8]. An ion going through an ion channel is likely to interact with the walls of the channel, as explained in Chapter 5. For this reason the conductance of the lumen of the channel is less than that of an equivalent volume of extracellular fluid. The conductance of a single channel (e.g.,  $g'_K$ ) is typically used in describing channel properties because it provides a direct measure of how efficiently the channel can conduct ions. But since conductance is inversely proportional to resistance, the resistance of the channel to current flow provides an equally valid description of this property:

$$g'_K = 1/R'_K.$$

Each open ion channel also contributes to the generation of an electrical potential difference across the membrane. For example,  $K^+$ , which is present at a higher concentration inside the cell, tends to diffuse out of the resting cell through nongated channels selective for  $K^+$ . This diffusion leads to a net separation of charge across the

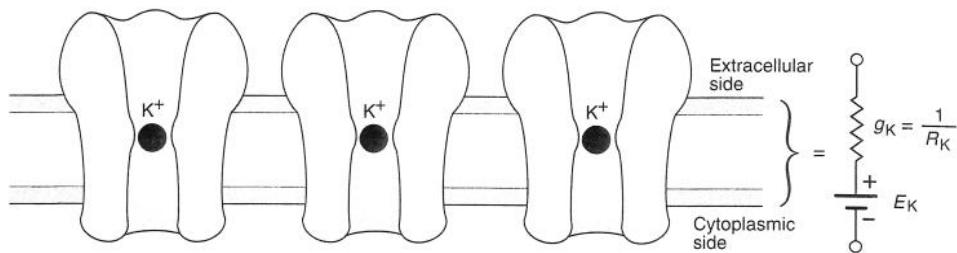
**FIGURE 6–9**

A channel selectively permeable to  $K^+$  ions gives rise to an electromotive force with a value equal to the  $K^+$  Nernst potential. This can be represented by a battery,  $E_K$ , in series with a conductor,  $g'_K$ .



**FIGURE 6–10**

All of the passive K<sup>+</sup> channels in a nerve membrane can be lumped into a single equivalent electrical structure: a battery ( $E_K$ ) in series with a conductor,  $g_K$ ;  $g_K = N_K \times g'_K$ , where  $N$  is the number of passive K<sup>+</sup> channels and  $g'_K$  is the conductance of a single K<sup>+</sup> channel.



membrane—positive charges accumulate on the outside, leaving an excess of negative charges on the inside—resulting in an electrical potential difference. A source of electrical potential is called an electromotive force. An electromotive force generated by a difference in chemical potentials is called a battery. We may therefore represent the electrical potential generated across each K<sup>+</sup> channel as a battery in series with the conductance of the channel (Figure 6–9). The potential generated by this battery is equal to  $E_K$ , which is typically about –75 mV.

All of the passive K<sup>+</sup> channels in the membrane can be combined into a single equivalent structure, consisting of a conductor in series with a battery (Figure 6–10).<sup>3</sup> The value of the K<sup>+</sup> conductance in this equivalent structure is determined by the fact that the total K<sup>+</sup> conductance ( $g_K$ ) of the cell membrane in its resting state is equal to the number of passive K<sup>+</sup> channels ( $N_K$ ) multiplied by the conductance of an individual K<sup>+</sup> channel ( $g'_K$ ):

$$g_K = N_K \times g'_K.$$

The value of the battery for this circuit equivalent of all the passive K<sup>+</sup> channels is determined by the concentration gradient for K<sup>+</sup> and is independent of the number of K<sup>+</sup> channels. Therefore its value is simply  $E_K$ .

#### *An Equivalent Circuit Model of the Membrane Includes Batteries, Conductors, a Capacitor, and a Current Generator*

As we have seen, the entire population of passive K<sup>+</sup> channels can be represented by a single conductor in series with a single battery. By analogy, all the passive Cl<sup>–</sup> channels can be represented by a similar combination, as can the passive Na<sup>+</sup> channels (Figure 6–11). These three types

<sup>3</sup>Although the membrane conductance to K<sup>+</sup> is related to the permeability of the membrane to K<sup>+</sup>, the two terms are not interchangeable. Permeability is determined by the state of the membrane, but conductance depends on both the state of the membrane and the concentration of surrounding ions. Consider a limiting case in which K<sup>+</sup> concentration is very low on both sides of the membrane. Even if a large number of open K<sup>+</sup> channels were present,  $g_K$  would be low because relatively few K<sup>+</sup> ions would be available to carry current across the membrane in response to a potential difference. At the same time, K<sup>+</sup> permeability would be quite high, since it depends only on how many K<sup>+</sup> channels are open. Under most physiological conditions, however, a membrane with high K<sup>+</sup> permeability also has a high K<sup>+</sup> conductance.

of channels account for the bulk of the passive ionic pathways through the membrane in the cell at rest.<sup>4</sup>

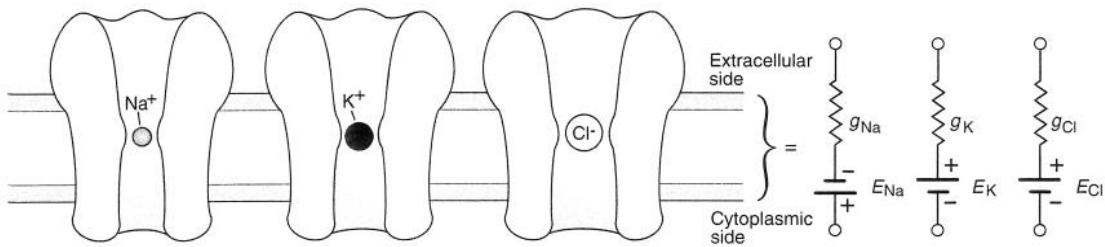
We can incorporate these electrical representations of the total population of passive Na<sup>+</sup>, K<sup>+</sup>, and Cl<sup>–</sup> channels into a simple equivalent circuit of a neuron to calculate the membrane potential. To construct this circuit we need only connect the elements representing each type of channel at their two ends by elements representing the extracellular fluid and cytoplasm. (These channels are, of course, in parallel with the conductance of the lipid bilayer. But, because the conductance of the bilayer is so much lower than that of the ion channel pathways, virtually all transmembrane current flows through the channels, and the negligible conductance of the bilayer can be ignored.) The extracellular fluid and cytoplasm are both excellent conductors because they have relatively large cross-sectional areas and many ions available to carry charge. The extracellular fluid and the cytoplasm can each be approximated by a short circuit—a conductor with zero resistance (Figure 6–12). The relationship between the electrical properties of the circuit in Figure 6–12 and membrane potential can be described by the following general equation (see the appendix at the end of this chapter for the derivation of this equation):

$$V_m = \frac{g_K \times E_K + g_{Cl} \times E_{Cl} + g_{Na} \times E_{Na}}{g_K + g_{Cl} + g_{Na}}.$$

In this equation the membrane potential is a weighted sum of the different ionic batteries, with each battery weighted according to the value of its membrane conductance. Note the similarity between this equation and the Goldman equation: Both equations state that  $V_m$  is determined by the ions with the greatest conductance or permeability.

The circuit model can be made more complete by adding a current generator. As described above, steady fluxes of Na<sup>+</sup> and K<sup>+</sup> ions through the passive membrane channel are exactly counterbalanced by active ion fluxes driven by the Na<sup>+</sup>–K<sup>+</sup> pump, which extrudes Na<sup>+</sup> ions and pumps in K<sup>+</sup> ions. This ATP-dependent Na<sup>+</sup>–K<sup>+</sup> pump, which keeps the ionic batteries charged, can be added to the

<sup>4</sup>Although there is good evidence that the membrane has separate gated channels for Na<sup>+</sup>, K<sup>+</sup>, Cl<sup>–</sup>, and Ca<sup>2+</sup>, it is not clear whether the different ion species have separate nongated channels or whether they all share a common (leakage) pathway. For convenience, we shall assume separate nongated channels.

**FIGURE 6-11**

Each population of ion channels selective for  $\text{Na}^+$ ,  $\text{K}^+$ , or  $\text{Cl}^-$  can be represented by a battery in series with a conductor.

equivalent circuit in the form of a current generator (Figure 6-13).

In addition to electromotive force and conductance, the third important passive electrical property of the neuron is capacitance. In general, an electrical capacitor is defined as two conducting materials separated by an insulating material. For the neuron the conducting materials are the cytoplasm and the extracellular fluid, the insulating material is the cell membrane, specifically the lipid bilayer. Because the bilayer is penetrated by ion channels, the membrane acts as a leaky capacitor. Nevertheless, since the density of ion channels is low, the capacitor portion of the membrane occupies at least 100 times the area of all the ion channels combined. Membrane capacitance is included in the equivalent circuit in Figure 6-13.

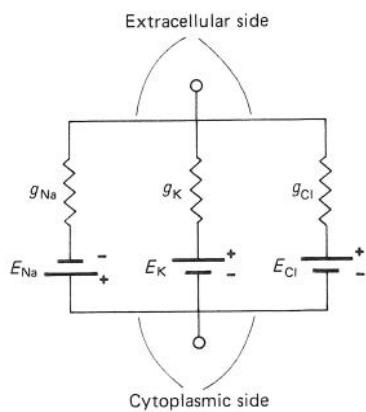
The fundamental property of a capacitor is the ability to store charges of opposite sign on its two surfaces. The excess of positive and negative charge stored on either side of a capacitor gives rise to an electrical potential difference, as expressed in the following equation:

$$V = \frac{Q}{C}$$

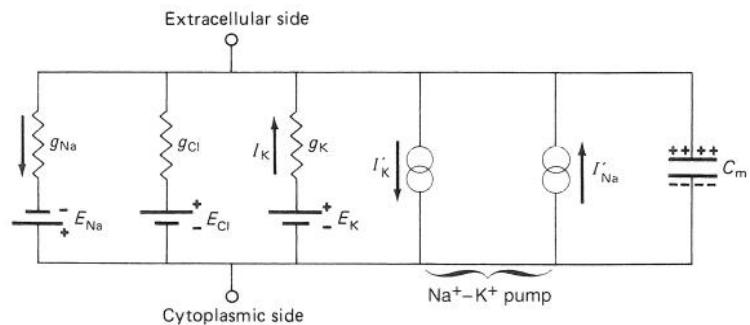
where  $V$  is the potential difference between the two sides,  $Q$  is the excess of positive or negative charges on either side of the capacitor, and  $C$  is the capacitance.

**FIGURE 6-12**

The current flow in a neuron can be modeled by an electrical equivalent circuit that includes elements representing the ion-selective membrane channels and the short-circuit pathways provided by the cytoplasm and extracellular fluid.

**FIGURE 6-13**

This electrical equivalent circuit of a neuron at rest includes the most abundant types of ion channels in parallel. Under steady-state conditions,  $\text{Na}^+$  and  $\text{K}^+$  currents resulting from passive diffusion through membrane channels are balanced by active  $\text{Na}^+$  and  $\text{K}^+$  fluxes ( $I'_{\text{Na}}$  and  $I'_{\text{K}}$ ) driven by the  $\text{Na}^+-\text{K}^+$  pump. The lipid bilayer endows the membrane with electrical capacitance ( $C_m$ ).



depolarize it from  $-60$  to  $+50$  mV. The influx of this number of  $\text{Na}^+$  ions produces only a 0.012% change in internal  $\text{Na}^+$  concentration from its typical value of 12 mM.

### An Overall View

The membrane at rest is a leaky capacitor. The lipid bilayer, which is virtually impermeant to ions, is an insulator separating two conductors, the cytoplasm and the extracellular fluid. Nevertheless, ions leak across the lipid bilayer through the ion channels. When the cell is at rest, these passive ionic fluxes into and out of the cell are balanced, so that the charge separation across the membrane remains constant and the membrane potential remains at its resting value.

The value of the resting membrane potential is determined primarily by nongated channels selective for  $\text{K}^+$ ,  $\text{Cl}^-$ , and  $\text{Na}^+$ . In general, the membrane potential will be closest to the Nernst potential of the ion or ions with the greatest membrane conductance. The conductance for an ion species is proportional to the number of open channels permeable to that ion.

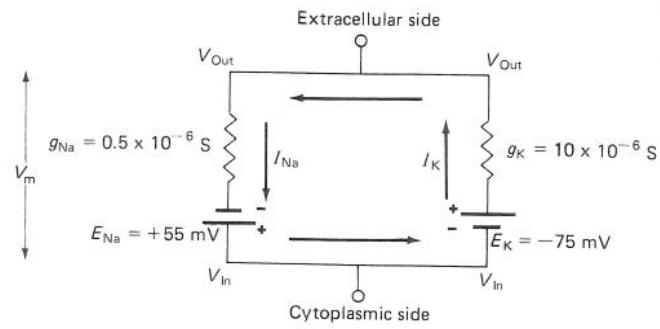
At rest, the membrane potential is close to the Nernst potential for  $\text{K}^+$ , the ion to which the membrane is most permeable. However, the membrane is also somewhat permeable to  $\text{Na}^+$ , and an influx of  $\text{Na}^+$  drives the membrane potential slightly positive to the  $\text{K}^+$  Nernst potential. At this potential the electrical and chemical driving forces acting on  $\text{K}^+$  are no longer in balance, so  $\text{K}^+$  diffuses out of the cell. These two passive fluxes are each balanced by active fluxes driven by the  $\text{Na}^+-\text{K}^+$  pump.

Chloride is actively pumped out of some, but not all, cells. When it is not, it is passively distributed so as to be at equilibrium. Under most physiological conditions the bulk concentrations of  $\text{Na}^+$ ,  $\text{K}^+$ , and  $\text{Cl}^-$  inside and outside the cell are constant. The changes in membrane potential that occur during signaling (action potentials, synaptic potentials, and receptor potentials) are caused by the substantial changes in the relative membrane permeabilities to these three ions, not by changes in the bulk concentrations of ions, which are negligible. These changes in permeability, caused by the opening of gated ion channels, in turn cause changes in the net charge separation across the membrane.

### Postscript

#### *Calculation of Membrane Potential from the Equivalent Circuit Model of the Neuron*

We shall illustrate with a simple example how the equivalent circuit of the neuron may be used to analyze neuronal properties quantitatively. The equivalent circuit model of the resting membrane will be used to calculate the resting potential. To simplify calculation of the membrane potential, we shall initially ignore  $\text{Cl}^-$  channels and begin with just two types of passive channels,  $\text{K}^+$  and  $\text{Na}^+$ , as illustrated in Figure 6–14. Because there are more passive channels for  $\text{K}^+$  than for  $\text{Na}^+$ , the membrane conduc-



**FIGURE 6–14**

This electrical equivalent circuit for calculating resting membrane potential omits the  $\text{Cl}^-$  pathway for simplicity.

tance for current flow carried by  $\text{K}^+$  is much greater than that for  $\text{Na}^+$ . In Figure 6–14,  $g_K$  is 20 times higher than  $g_{\text{Na}}$  ( $10 \times 10^{-6}$  S compared to  $0.5 \times 10^{-6}$  S). Given these values and the values of  $E_K$  and  $E_{\text{Na}}$ , we can calculate the membrane potential  $V_m$  as follows.

Since  $V_m$  is constant in the resting state, the net current must be zero, otherwise the separation of positive and negative charges across the membrane would change, causing  $V_m$  to change. Therefore,  $I_{\text{Na}}$  is equal and opposite to  $I_K$ :<sup>5</sup>

$$I_{\text{Na}} = -I_K \quad (6-1)$$

or

$$I_{\text{Na}} + I_K = 0.$$

We can easily calculate  $I_{\text{Na}}$  and  $I_K$  in two steps. First, we add up the separate potential differences across the  $\text{Na}^+$  and  $\text{K}^+$  branches of the circuit. As one goes from inside to outside across the  $\text{Na}^+$  branch, the total potential difference is the sum of the potential differences across  $E_{\text{Na}}$  and across  $g_{\text{Na}}$ :<sup>6</sup>

$$V_m = E_{\text{Na}} + I_{\text{Na}}/g_{\text{Na}}.$$

Similarly, for the  $\text{K}^+$  conductance branch

$$V_m = E_K + I_K/g_K.$$

Next, we rearrange and solve for  $I$ :

$$I_{\text{Na}} = g_{\text{Na}} \times (V_m - E_{\text{Na}}). \quad (6-2a)$$

$$I_K = g_K \times (V_m - E_K). \quad (6-2b)$$

As these equations illustrate, the ionic current through each conductance branch is equal to the conductance of that branch multiplied by the net electrical driving force.

<sup>5</sup>This equality is true only if one makes the simplifying assumption that the  $\text{Na}^+-\text{K}^+$  pump is electroneutral.

<sup>6</sup>Because we have defined  $V_m$  as  $V_{\text{in}} - V_{\text{out}}$ , the following convention must be used for these equations. Outward current (in this case  $I_K$ ) is positive and inward current ( $I_{\text{Na}}$ ) is negative. Batteries with their positive poles toward the inside of the membrane (e.g.,  $E_{\text{Na}}$ ) are given positive values in the equations. The reverse is true for batteries that have their negative poles toward the inside, such as the  $\text{K}^+$  battery.

For example, the conductance for the  $K^+$  branch is proportional to the number of open  $K^+$  channels, and the driving force is equal to the difference between  $V_m$  and  $E_K$ . If  $V_m$  is more positive than  $E_K$  ( $-75$  mV), the driving force is positive (outward); if  $V_m$  is more negative than  $E_K$ , the driving force is negative (inward).

In Equation 6–1 we saw that  $I_{Na} + I_K = 0$ . If we now substitute Equations 6–2a and 6–2b for  $I_{Na}$  and  $I_K$  in Equation 6–1, we obtain the following expression:

$$g_{Na} \times (V_m - E_{Na}) + g_K \times (V_m - E_K) = 0.$$

Multiplying through we see that

$$(V_m \times g_{Na} - E_{Na} \times g_{Na}) + (V_m \times g_K - E_K \times g_K) = 0.$$

This can now be rearranged to yield

$$V_m \times (g_{Na} + g_K) = (E_{Na} \times g_{Na}) + (E_K \times g_K).$$

Solving for  $V_m$ , we obtain an intuitively useful expression for the resting membrane potential:

$$V_m = \frac{(E_{Na} \times g_{Na}) + (E_K \times g_K)}{g_{Na} + g_K}. \quad (6-3)$$

This equation allows us to calculate  $V_m$  for the equivalent circuit. Using the circuit values of Figure 6–14, we can calculate  $V_m$  to be

$$\begin{aligned} V_m &= \frac{(+55 \times 10^{-3} \text{ V})(0.5 \times 10^{-6} \text{ S})}{0.5 \times 10^{-6} \text{ S} + 10 \times 10^{-6} \text{ S}} \\ &\quad + \frac{(-75 \times 10^{-3} \text{ V})(10 \times 10^{-6} \text{ S})}{0.5 \times 10^{-6} \text{ S} + 10 \times 10^{-6} \text{ S}} \\ &= \frac{-722.5 \times 10^{-9} \text{ V} \times \text{S}}{10.5 \times 10^{-6} \text{ S}} \\ &= -69 \text{ mV}. \end{aligned}$$

Equation 6–3 states that  $V_m$  will approach the value of the ionic battery that is associated with the greater conductance. This principle can be illustrated with another example as we consider what happens during the action potential. At the peak of the action potential, total membrane  $g_K$  is essentially unchanged from its resting value, but  $g_{Na}$  increases by as much as 500-fold. This increase in  $g_{Na}$  is caused by the opening of voltage-gated  $Na^+$  chan-

nels. In the example shown in Figure 6–14 a 500-fold increase would change  $g_{Na}$  from  $0.5 \times 10^{-6} \text{ S}$  to  $250 \times 10^{-6} \text{ S}$ . If we substitute this new value of  $g_{Na}$  into Equation 6–3 and solve for  $V_m$ , we obtain  $+50$  mV, a value much closer to  $E_{Na}$  than to  $E_K$ .  $V_m$  is closer to  $E_{Na}$  than to  $E_K$  at the peak of the action potential because  $g_{Na}$  is now 25-fold greater than  $g_K$ , so the  $Na^+$  battery becomes much more important than the  $K^+$  battery in determining  $V_m$ .

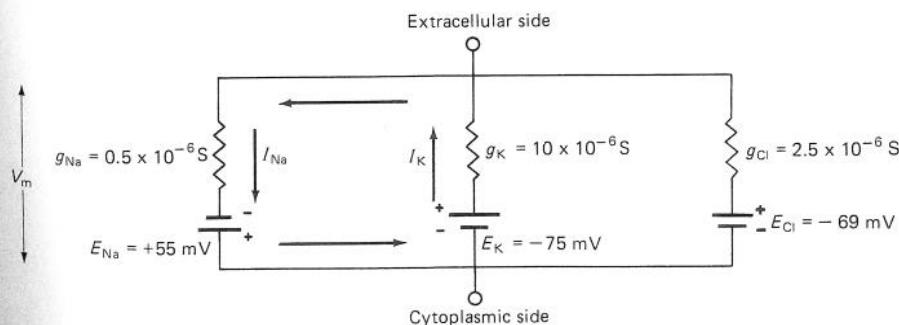
### The Equation for Membrane Potential Can Be Written in a More General Form

The resting membrane has open conductance channels not only for  $Na^+$  and  $K^+$ , but also for  $Cl^-$ . It is useful therefore to have a general equation to describe the resting potential as a function of all three permeant ions. If one constructs an equivalent circuit that includes a conductance pathway for  $Cl^-$  with its associated Nernst battery (Figure 6–8), one can derive a more general equation for  $V_m$  by following the same sequence of steps outlined above:

$$V_m = \frac{(E_K \times g_K) + (E_{Na} \times g_{Na}) + (E_{Cl} \times g_{Cl})}{g_K + g_{Na} + g_{Cl}}. \quad (6-4)$$

This equation is similar to the Goldman equation presented earlier in this chapter. As in the Goldman equation, the contribution to  $V_m$  of each ionic battery is weighted in proportion to the conductance (or permeability) of the membrane for that particular ion. In the limit, if the conductance for one ion is much greater than that for the other ions,  $V_m$  will approach the value of that ion's Nernst potential.

The contribution of  $Cl^-$  ions to the resting potential can now be determined by comparing  $V_m$  calculated for the circuits in Figures 6–14 and 6–15. For most nerve cells, the value of  $g_{Cl}$  ranges from one-fourth to one-half of  $g_K$ . In addition,  $E_{Cl}$  is typically quite close to  $E_K$ , but slightly less negative. For the example shown in Figure 6–15,  $Cl^-$  ions are passively distributed across the membrane, so that  $E_{Cl}$  is equal to the value of  $V_m$ , which is determined by  $Na^+$  and  $K^+$ . Note that if  $E_{Cl} = V_m$  ( $-69$  mV in this case), no net current flows through the  $Cl^-$  channels. If one includes  $g_{Cl}$  and  $E_{Cl}$  from Figure 6–15 in the calculation of  $V_m$  (i.e., Equation 6–4), the calculated value of  $V_m$  does not differ from that for Figure 6–14. On the other hand, if  $Cl^-$  were



**FIGURE 6–15**

The electrical equivalent circuit of a neuron in which  $Cl^-$  is passively distributed across the membrane. No current flows through the  $Cl^-$  channels in this example because  $V_m$  is at the  $Cl^-$  equilibrium (Nernst) potential.

not passively distributed but actively pumped out of the cell, then  $E_{\text{Cl}}$  would be more negative than  $-69$  mV. Adding the  $\text{Cl}^-$  pathway to the calculation would then shift  $V_m$  to a slightly more negative value.

### The Sodium-Potassium Pump Counteracts the Passive Fluxes of Sodium and Potassium

An important feature of the resting membrane is the steady leakage of  $\text{Na}^+$  into the cell and of  $\text{K}^+$  out of the cell, even when the cell is in its resting state. Referring back to the circuit in Figure 6–14, we can calculate these currents from Equations 6–2a and 6–2b:

$$\begin{aligned} I_{\text{Na}} &= g_{\text{Na}} \times (V_m - E_{\text{Na}}) \\ I_K &= g_K \times (V_m - E_K). \end{aligned}$$

Substituting the values from Figure 6–14 and the value of  $V_m$  calculated above yields

$$\begin{aligned} I_{\text{Na}} &= [0.5 \times 10^{-6} \text{ S}] \times [(-68.8 \times 10^{-3} \text{ V}) - (+55 \times 10^{-3} \text{ V})] \\ &= -62 \times 10^{-9} \text{ A} \\ I_K &= [10 \times 10^{-6} \text{ S}] \times [(-68.8 \times 10^{-3} \text{ V}) - (-75 \times 10^{-3} \text{ V})] \\ &= +62 \times 10^{-9} \text{ A}. \end{aligned}$$

These steady fluxes of  $\text{Na}^+$  and  $\text{K}^+$  ions through the passive membrane channels are exactly counterbalanced by active ion fluxes driven by the  $\text{Na}^+/\text{K}^+$  pump, as illustrated in Figure 6–13. To prevent the ionic batteries from running down, the  $\text{Na}^+/\text{K}^+$  pump continually extrudes  $\text{Na}^+$  ions and pumps in  $\text{K}^+$ , even when the cell is at rest. The actively driven  $\text{Na}^+$  current ( $I'_{\text{Na}}$ ) is equal and opposite to the passive  $\text{Na}^+$  current ( $I_{\text{Na}}$ ), and the actively driven  $\text{K}^+$  current ( $I'_K$ ) is equal and opposite to the passive  $\text{K}^+$  current ( $I_K$ ).

The equality between  $I_{\text{Na}}$  and  $I_K$  holds only for the simplified case in which the  $\text{Na}^+/\text{K}^+$  pump is electroneutral. If the pump is electrogenic—pumping three  $\text{Na}^+$  ions out for every two  $\text{K}^+$  ions that it pumps in—the membrane will be in a steady state when  $V_m = -70.8$  mV (for the example shown in Figure 6–13). Thus, the effect of the electrogenic pump is to generate a resting membrane po-

tential slightly more negative than the value that would result for passive diffusion alone. At this more negative potential

$$I_{\text{Na}}/I_K = I'_{\text{Na}}/I'_K = 3/2, I_{\text{Na}} = I'_{\text{Na}}, \text{ and } I_K = I'_K.$$

### Selected Readings

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