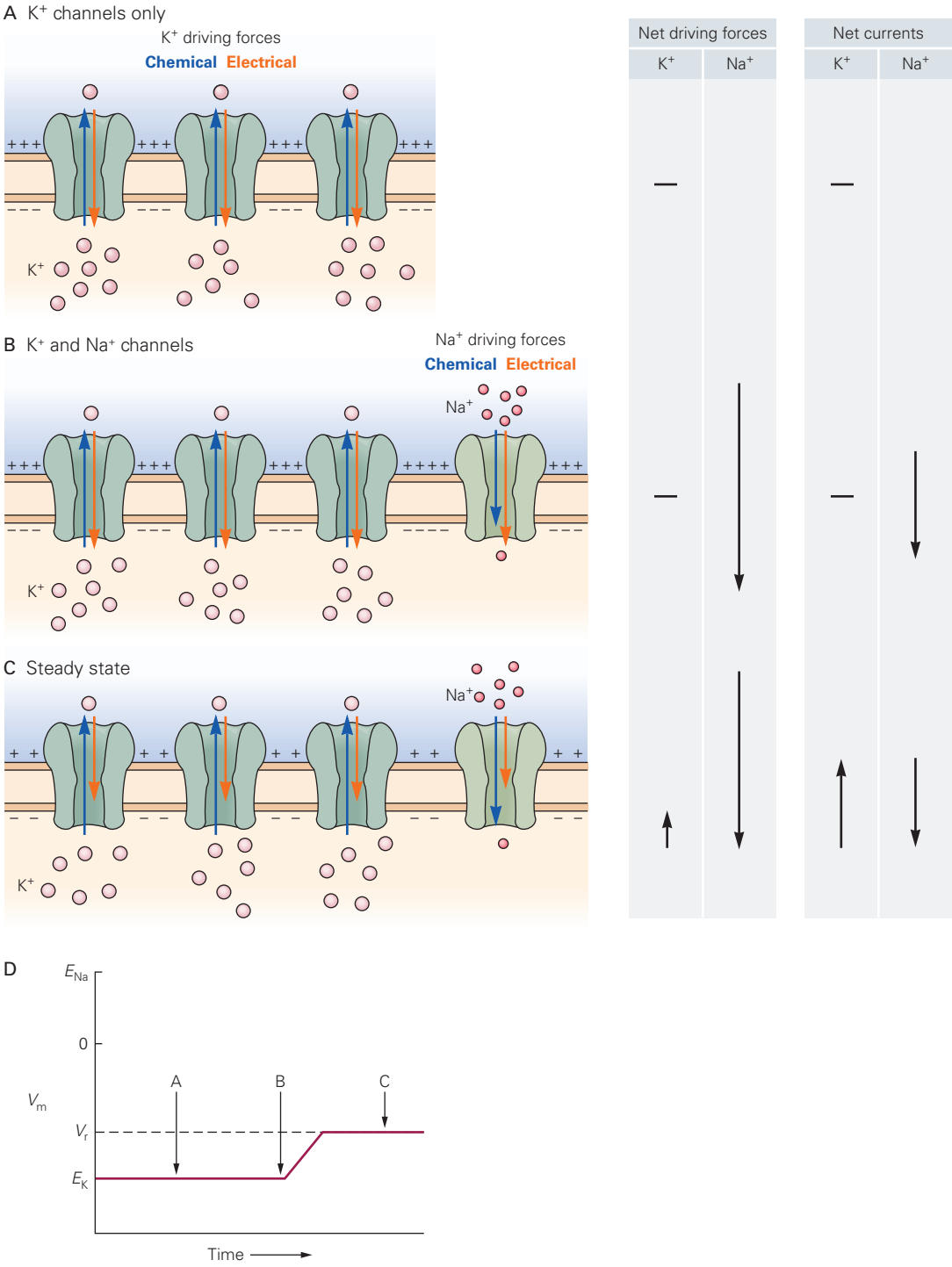

Figure 9–4 **The resting potential of a cell is determined by the proportions of different types of ion channels that are open, together with the value of their equilibrium potentials.** The channels in the figures represent the entire complement of K^+ or Na^+ channels in this hypothetical cell membrane. The lengths of the arrows within the channels represent the relative amplitudes of the electrical (**red**) and chemical (**blue**) driving forces acting on Na^+ or K^+. The lengths of the arrows in the diagram on the right denote the relative sizes of the net driving force (the sum of the electrical and chemical driving forces) for Na^+ and K^+ and the net ion currents. Three hypothetical situations are illustrated.

A. In a resting cell in which only K^+ channels are present, K^+ ions are in equilibrium and $V_m = E_K$.

B. Adding a few Na^+ channels to the resting membrane allows Na^+ ions to diffuse into the cell, and this influx begins to depolarize the membrane.

C. The resting potential settles at a new level (V_r), where the influx of Na^+ is balanced by the efflux of K^+. In this example, the aggregate conductance of the K^+ channels is much greater than that of the Na^+ channels because the K^+ channels are more numerous. As a result, a relatively small net driving force for K^+ drives a current equal and opposite to the Na^+ current driven by the much larger net driving force for Na^+. This is a steady-state condition, in which neither Na^+ nor K^+ is in equilibrium but the net flux of charge is null.

D. Membrane voltage changes during the hypothetical situations illustrated in parts **A**, **B**, and **C**.

diffusion mechanisms discussed earlier. During periods of intense neuronal activity, the increased influx of Na^+ leads to an increase in Na^+-K^+ pump activity that generates a prolonged outward current, leading to a hyperpolarizing after-potential that can last for several minutes, until the normal Na^+ concentration is restored. The Na^+-K^+ pump is inhibited by ouabain or digitalis plant alkaloids, an action that is important in the treatment of heart failure.

The Na^+-K^+ pump is a member of a large family of pumps known as *P-type ATPases* (because the phosphoryl group of ATP is temporarily transferred to the pump). P-type ATPases include a *Ca^{2+} pump* that transports Ca^{2+} across cell membranes (Figure 9–5A). All cells normally maintain a very low cytoplasmic Ca^{2+} concentration, between 50 and 100 nM. This concentration is more than four orders of magnitude lower than the external concentration, which is approximately 2 mM in mammals. Calcium pumps in the plasma membrane transport Ca^{2+} out of the cell; other Ca^{2+} pumps located in internal membranes, such as the smooth endoplasmic reticulum, transport Ca^{2+} from the cytoplasm into these intracellular Ca^{2+} stores. Calcium pumps are thought to transport two Ca^{2+} ions for each ATP molecule that is hydrolyzed, with two protons transported in the opposite direction.

The Na^+-K^+ pump and Ca^{2+} pump have similar structures. They are formed from 110 kD α-subunits, whose large transmembrane domain contains 10 membrane-spanning α-helixes (Figure 9–5A). In the Na^+-K^+ pump, an α-subunit associates with an obligatory β-subunit that is required for proper assembly and membrane expression of the pump. In humans, four genes encode highly related Na^+-K^+ pump α-subunits (*ATP1A1*, *ATP1A2*, *ATP1A3*, *ATP1A4*). Mutations in *ATP1A2* result in familial hemiplegic migraine, a form

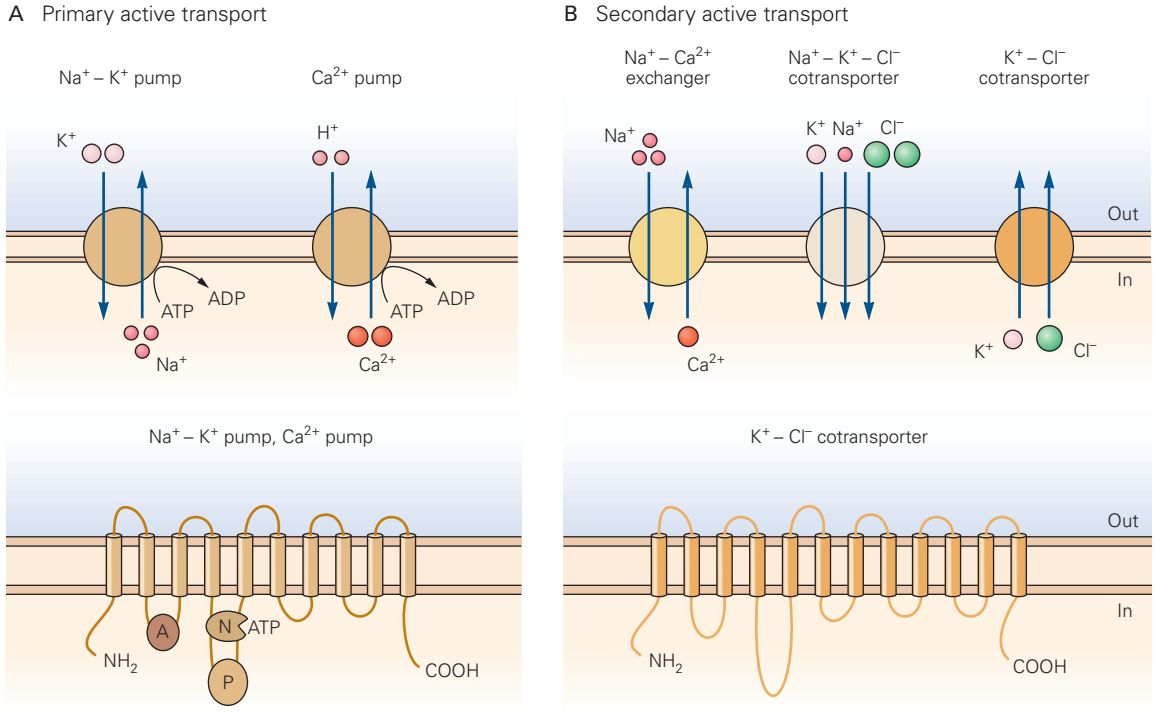

Figure 9–5 Pumps and transporters regulate the chemical concentration gradients of Na^+, K^+, Ca^{2+}, and Cl^- ions.

A. The Na-K^+ pump and Ca^{2+} pump are two examples of active transporters that use the energy of adenosine triphosphate (**ATP**) hydrolysis to transport ions against their concentration gradient. The α-subunit of a Na-K^+ pump or homologous Ca^{2+} pump (**below**) has 10 transmembrane segments, a cytoplasmic amino terminus, and a cytoplasmic carboxyl terminus. There are also cytoplasmic loops important for binding ATP (**N**), ATP hydrolysis and phosphorylation of the pump (**P**), and transducing phosphorylation to transport (**A**). The Na^+-K^+ pump also contains a smaller β-subunit with a single transmembrane domain plus a small accessory integral membrane protein **FXYD**, which modulates pump kinetics (not shown).

B. The Na^+-Ca^{2+} exchanger uses the potential energy of the electrochemical gradient of Na^+ to transport Ca^{2+} out of a cell. The Na^+-Ca^{2+} exchanger contains nine transmembrane segments, two reentrant membrane loops important for ion transport, and a large cytoplasmic regulatory loop. Chloride ions are transported into the cell by the Na^+-K^+-Cl^- cotransporter and out of the cell by the K^+-Cl^- cotransporter. These transporters are members of a family of Cl^- transport proteins with 12 transmembrane segments (**below**).

of migraine associated with an aura and muscle weakness. Certain mutations in the neuron-specific *ATP1A3* isoform lead to rapid-onset dystonia parkinsonism, a movement disorder that first occurs in late adolescence or early adulthood. A different set of mutations lead to a distinct neurological disorder, alternating hemiplegia of childhood, a paralysis that affects one side of the body and develops in children under the age of 2.

Most neurons have relatively few Ca^{2+} pumps in the plasma membrane. Instead, Ca^{2+} is transported out of the cell primarily by the *Na^+-Ca^{2+} exchanger* (Figure 9–5B). This membrane protein is not an ATPase but a different type of molecule called a *cotransporter*. Cotransporters move one type of ion against its electrochemical gradient by using the energy stored in the electrochemical gradient of a second ion. (The CLC Cl^--H^+ cotransporter discussed in Chapter 8 is a type of exchanger.) In the case of the Na^+-Ca^{2+} exchanger, the electrochemical gradient of Na^+ drives the efflux of Ca^{2+}. The exchanger transports three or four Na^+ ions into the cell (down the electrochemical gradient for Na^+) for each Ca^{2+} ion it removes (against the electrochemical gradient of Ca^{2+}). Because Na^+ and Ca^{2+} are transported in opposite directions, the exchanger is termed an *antiporter.* Ultimately, it is the hydrolysis of ATP by the Na^+-K^+ pump that provides the energy (stored in the Na^+ gradient) to maintain the function of the Na^+-Ca^{2+} exchanger. For this reason, ion flux driven by cotransporters is often referred to as *secondary active transport*, to distinguish it from the *primary active transport* driven directly by ATPases.

Chloride Ions Are Also Actively Transported

So far, for simplicity, we have ignored the contribution of chloride (Cl^-) to the resting potential. However, in most nerve cells, the Cl^- gradient across the cell membrane is controlled by one or more active transport mechanisms so that E_{Cl} differs from V_r. As a result, the presence of open Cl^- channels will bias the membrane potential toward its Nernst potential. *Chloride transporters* typically use the energy stored in the gradients of other ions—they are cotransporters.

Cell membranes contain a number of different types of Cl^- cotransporters (Figure 9–5B). Some transporters increase intracellular Cl^- to levels greater than those that would be passively reached if the Cl^- Nernst potential was equal to the resting potential. In such cells, E_{Cl} is positive to V_r so that the opening of Cl^- channels depolarizes the membrane. An example of this type of transporter is the Na^+-K^+-Cl^- cotransporter. This protein transports two Cl^- ions into the cell together with one Na^+ and one K^+ ion. As a result, the transporter is electroneutral. The Na^+-K^+-Cl^- cotransporter differs from the Na^+-Ca^{2+} exchanger in that the former transports all three ions in the same direction—it is a *symporter.*

In most neurons, the Cl^- gradient is determined by cotransporters that move Cl^- out of the cell. This action lowers the intracellular concentration of Cl^- so that E_{Cl} is typically more negative than the resting potential. As a result, the opening of Cl^- channels leads to an influx of Cl^- that hyperpolarizes the membrane. The K^+-Cl^- cotransporter is an example of such a transport mechanism; it moves one K^+ ion out of the cell for each Cl^- ion it exports.

Interestingly, in early neuronal development, cells tend to express primarily the Na^+-K^+-Cl^- cotransporter. As a result, at this stage the neurotransmitter γ-aminobutyric acid (GABA), which activates ligand-gated Cl^- channels, typically has an excitatory (depolarizing) effect. As neurons develop, they begin to express the K^+-Cl^- cotransporter, such that in most mature neurons GABA typically hyperpolarizes the membrane and thus acts as an inhibitory neurotransmitter. In some pathological conditions in adults, such as certain types of epilepsy or chronic pain syndromes, the expression pattern of the Cl^- cotransporters may revert to that of the immature nervous system. This will lead to aberrant depolarizing responses to GABA that can produce abnormally high levels of excitation.

The Balance of Ion Fluxes in the Resting Membrane Is Abolished During the Action Potential

In the nerve cell at rest, the steady Na^+ influx is balanced by a steady K^+ efflux, so that the membrane potential is constant. This balance changes when the membrane is depolarized toward the threshold for an action potential. As the membrane potential approaches this threshold, voltage-gated Na^+ channels open rapidly. The resultant increase in membrane conductance to Na^+ causes the Na^+ influx to exceed the K^+ efflux once threshold is exceeded, creating a net influx of positive charge that causes further depolarization. The increase in depolarization causes still more voltage-gated Na^+ channels to open, resulting in a greater influx of Na^+, which accelerates the depolarization even further.

This regenerative, positive feedback cycle develops explosively, driving the membrane potential rapidly toward the Na^+ equilibrium potential of +55 mV:

$$E_{Na} = \frac{RT}{F} \ln \frac{[Na]_o}{[Na]_i} = 58 \text{ mV} \times \log \frac{[440]}{[50]} = +55 \text{ mV}.$$

However, the membrane potential never quite reaches E_{Na} because K^+ efflux continues throughout the depolarization. A slight influx of Cl^- into the cell also counteracts the depolarizing effect of the Na^+ influx. Nevertheless, so many voltage-gated Na^+ channels open during the rising phase of the action potential that the cell membrane's Na^+ conductance is much greater than the conductance of either Cl^- or K^+. Thus, at the peak of the action potential, the membrane potential approaches the Na^+ equilibrium potential, just as at rest (when permeability to K^+ is predominant), the membrane potential tends to approach the K^+ equilibrium potential.

The Contributions of Different Ions to the Resting Membrane Potential Can Be Quantified by the Goldman Equation

Although K^+, Na^+, and Cl^- fluxes set the value of the resting potential, V_m is not equal to E_K, E_{Na}, or E_{Cl} but lies at some intermediate value. As a general rule, when V_m is determined by two or more species of ions, the contribution of one species is determined not only by the concentrations of the ion inside and outside the cell but also by the ease with which the ion crosses the membrane.

One convenient measure of how readily the ion crosses the membrane is the *permeability* (P) of the membrane to that ion, which has units of velocity (cm/s). This measure is similar to that of a diffusion constant, which determines the rate of solute movement in solution driven by a local concentration gradient. The dependence of membrane potential on ionic permeability and concentration is given by the Goldman equation:

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

Goldman Equation

This equation applies only when V_m is not changing. It states that the greater the concentration of an ion species and the greater its membrane permeability, the greater is its contribution to determining the membrane potential. In the limit, when permeability to one ion is exceptionally high, the Goldman equation reduces to the Nernst equation for that ion. For example, if $P_K >> P_{Cl}$ or P_{Na}, as in glial cells, the equation becomes as follows:

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

Alan Hodgkin and Bernard Katz used the Goldman equation to analyze changes in membrane potential in the squid giant axon. They measured the variations in membrane potential in response to systematic changes in the extracellular concentrations of Na^+, Cl^-, and K^+. They found that if V_m is measured shortly after the extracellular concentration is changed (before the internal ionic concentrations are altered), $[K^+]_o$ has a strong effect on the resting potential, $[Cl^-]_o$ has a moderate effect, and $[Na^+]_o$ has little effect. The data for the membrane at rest could be fit accurately by the Goldman equation using the following permeability ratios:

$$P_K : P_{Na} : P_{Cl} = 1.0 : 0.04 : 0.45.$$

At the peak of the action potential, there is an instant in time when V_m is not changing and the Goldman equation is applicable. At that point, the variation of V_m with external ionic concentrations is fit best if a quite different set of permeability ratios is assumed:

$$P_K : P_{Na} : P_{Cl} = 1.0 : 20 : 0.45.$$

For these values of permeability, the Goldman equation approaches the Nernst equation for Na^+:

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

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}. However, the finite permeability of the membrane to K^+ and Cl^- results in K^+ efflux and Cl^- influx that partially counterbalance Na^+ influx, thereby preventing V_m from quite reaching E_{Na}.

The Functional Properties of the Neuron Can Be Represented as an Electrical Equivalent Circuit

The utility of the Goldman equation is limited because it cannot be used to determine how membrane potential changes with time or distance within a neuron in response to a local change in permeability. It is also inconvenient for determining the magnitude of the individual Na^+, K^+, and Cl^- currents. This information can be obtained using a simple mathematical model derived from electric circuit theory. The model, called an *equivalent circuit*, represents all of the important electrical properties of the neuron by a circuit consisting of conductors or resistors, batteries, and capacitors. Equivalent circuits provide us with an intuitive understanding as well as a quantitative description of

how current caused by the movement of ions generates electrical signals in nerve cells.

The first step in developing an equivalent circuit is to relate the membrane's discrete physical properties to its electrical properties. The lipid bilayer endows the membrane with electrical *capacitance*, the ability of an electrical nonconductor (insulator) to separate electrical charges on either side of it. The nonconducting phospholipid bilayer of the membrane separates the cytoplasm and extracellular fluid, both of which are highly conductive environments. The separation of charges on the inside and outside surfaces of the cell membrane (the capacitor) gives rise to the electrical potential difference across the membrane. The electrical potential difference or voltage across a capacitor is

$$V = Q/C,$$

where Q is the net excess positive or negative charge on each side of the capacitor and C is the capacitance.

Capacitance is measured in units of farads (F), and charge is measured in coulombs (where 96,500 coulombs of a univalent ion is equivalent to 1 mole of that ion). A charge separation of 1 coulomb across a capacitor of 1 F produces a potential difference of 1 volt. A typical value of membrane capacitance for a nerve cell is approximately 1 μF per cm^2 of membrane area. Very few charges are required to produce a significant potential difference across such a capacitance. For example, the excess of positive and negative charges separated by the membrane of a spherical cell body with a diameter of 50 μm and a resting potential of −60 mV is 29×10^6 ions. Although this number may seem large, it represents only a tiny fraction (1/200,000) of the total number of positive or negative charges in solution within the cytoplasm. The bulk of the cytoplasm and the bulk of the extracellular fluid are electroneutral.

The membrane is a *leaky capacitor* because it is studded with ion channels that can conduct charge. Ion channels endow the membrane with conductance and with the ability to generate an electrical potential difference. The lipid bilayer itself has effectively zero conductance or infinite resistance. However, because ion channels are highly conductive, they provide pathways of finite electrical resistance for ions to cross the membrane. Because neurons contain many types of channels selective for different ions, we must consider each class of ion channel separately.

In an equivalent circuit we can represent each K^+ channel as a resistor or conductor of ionic current with a single-channel conductance γ_K (remember, conductance = 1/resistance) (Figure 9–6A). If there were no K^+ concentration gradient, the current through a single K^+ channel would be given by Ohm's law: $i_K = \gamma_K \times V_m$. However, normally there is a K^+ concentration gradient, and thus also a chemical force driving K^+ across the membrane, represented in the equivalent circuit by a battery. (A source of electrical potential is called an *electromotive force* [EMF], and an electromotive force generated by a difference in chemical potentials is called a battery.) The electromotive force of this battery is given by E_K, the Nernst potential for K^+ (Figure 9–6).

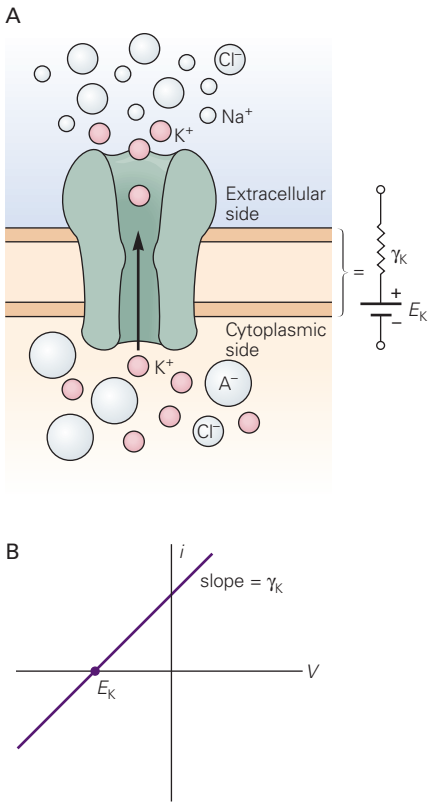

Figure 9–6 Chemical and electrical forces contribute to current through an ion channel.

A. A concentration gradient for K^+ gives rise to an electromotive force, which has a value equal to E_K, the Nernst potential for K^+. This can be represented by a battery. In this circuit, the battery E_K is in series with the conductor γ_K, representing the conductance of the K^+ channel.

B. The current-voltage relation for a K^+ channel in the presence of both electrical and chemical driving forces. The membrane potential at which the current is zero is equal to the K^+ Nernst potential.

In the absence of voltage across the membrane, the normal K^+ concentration gradient causes an outward K^+ current. According to our convention for current, an outward movement of positive charge across the membrane corresponds to a positive current. According to the Nernst equation, when the concentration gradient for a positively charged ion, such as K^+, is directed

outward (ie, the K^+ concentration inside the cell is higher than outside), the equilibrium potential for that ion is negative. Thus, the K^+ current that flows solely because of its concentration gradient is given by $i_K = -\gamma_K \times E_K$ (the negative sign is required because a negative equilibrium potential produces a positive current at 0 mV).

Finally, for a real neuron that has both a membrane potential and a K^+ concentration gradient, the net K^+ current is given by the sum of the currents caused by the electrical and chemical driving forces:

$$i_K = (\gamma_K \times V_m) - (\gamma_K \times E_K) = \gamma_K \times (V_m - E_K). \quad \textbf{(9–1)}$$

The factor $(V_m - E_K)$ is called the *electrochemical driving force.* It determines the direction of ionic current and (along with the conductance) its magnitude. This equation is a modified form of Ohm's law that takes into account the fact that ionic current through a membrane is determined not only by the voltage across the membrane but also by the ionic concentration gradients.

A cell membrane has many resting K^+ channels, all of which can be combined into a single equivalent circuit element consisting of a conductor in series with a battery. In this equivalent circuit, the total conductance of all the K^+ channels (g_K), ie, the K^+ conductance of the cell membrane in its resting state, is equal to the number of resting K^+ channels (N_K) multiplied by the conductance of an individual K^+ channel (γ_K):

$$g_K = N_K \times \gamma_K.$$

Because the battery in this equivalent circuit depends solely on the concentration gradient for K^+ and is independent of the number of K^+ channels, its value is the equilibrium potential for K^+, E_K.

Like the population of resting K^+ channels, all the resting Na^+ channels can be represented by a single conductor in series with a single battery, as can the resting Cl^- channels. Because the K^+, Na^+, and Cl^- channels account for the bulk of the passive ionic current through the membrane in the cell at rest, we can calculate the resting potential by incorporating these three pathways into a simple equivalent circuit of a neuron (Figure 9–7).

To complete this circuit, we first connect the elements representing each type of channel at their two ends with elements representing the extracellular fluid and cytoplasm. The extracellular fluid and cytoplasm are both good conductors (compared with the membrane) because they have relatively large cross-sectional areas and many ions available to carry charge. In a small region of a neuron, the extracellular and cytoplasmic resistances can be approximated by a *short circuit*—a conductor with zero resistance. The membrane capacitance (C_m) is determined by the insulating properties of the lipid bilayer and its area.

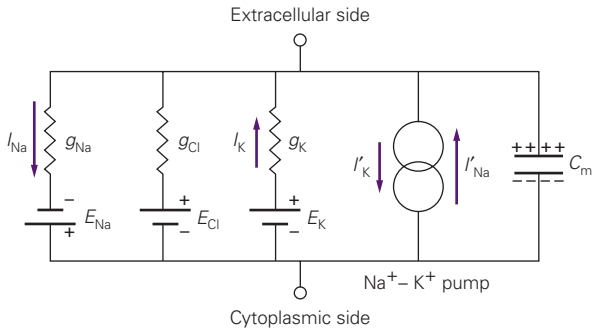

Figure 9–7 An equivalent circuit of passive and active current in a resting neuron. The total K^+ conductance represented by the symbol g_K is the product of $\gamma_K \times N$, the total number of open K^+ channels in the resting membrane. The total conductances for Na^+ and Cl^- channels are determined in a similar fashion. Under steady-state conditions, the passive Na^+ and K^+ currents are balanced by active Na^+ and K^+ fluxes (I'_{Na} and I'_K) driven by the Na-K^+ pump. The active Na^+ flux (I'_{Na}) is 50% greater than the active K^+ flux (I'_K) because the Na^+-K^+ pump transports three Na^+ ions out for every two K^+ ions it transports into the cell. As a result, for the cell to remain in a steady state, I_{Na} must be 50% greater than I_K (arrow size is proportional to current magnitude). There is no current through the Cl^- channels because in this example V_m is at E_{Cl}, the Cl^- equilibrium potential.

Finally, the equivalent circuit can be made complete by incorporating the active ion fluxes driven by the Na^+-K^+ pump, which extrudes three Na^+ ions from the cell for every two K^+ ions it pumps in. This electrogenic ATP-dependent pump, which keeps the ionic batteries charged, is represented in the equivalent circuit by the symbol for a current generator (Figure 9–7). The use of the equivalent circuit to analyze neuronal properties quantitatively is illustrated in Box 9–2, where the equivalent circuit is used to calculate the resting potential.

The Passive Electrical Properties of the Neuron Affect Electrical Signaling

Once an electrical signal is generated in part of a neuron, for example in response to a synaptic input on a branch of a dendrite, it is integrated with the other inputs to the neuron and then propagated to the axon initial segment, the site of action potential generation. When synaptic potentials, receptor potentials, or action potentials are generated in a neuron, the membrane potential changes rapidly.

Box 9–2 Using the Equivalent Circuit Model to Calculate Resting Membrane Potential

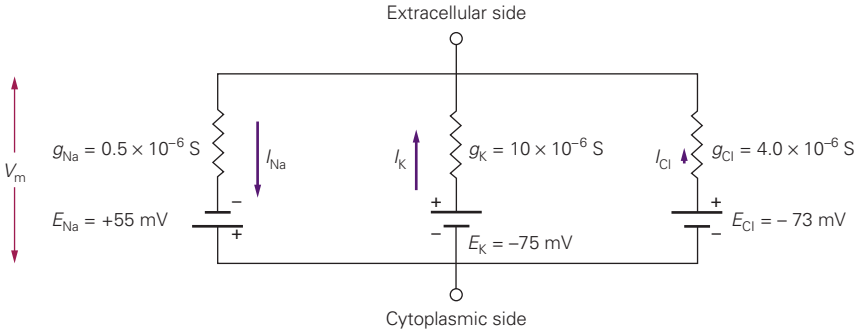

Figure 9–8 The electrical equivalent circuit used to calculate the resting membrane potential. In this example, it is assumed that the Cl^- cotransporter maintains intracellular Cl^- at a relatively low value. As a result, the Cl^- equilibrium potential is more negative than the resting potential.

An equivalent circuit model of the resting membrane can be used to calculate the resting potential (Figure 9–8). To simplify the calculation, we ignore the electrogenic influence of the Na^+-K^+ pump because it is small. We also ignore membrane capacitance because V_m is unchanging, so the charge on the capacitance is also not changing.

Because there are more resting channels for K^+ than for Na^+, the membrane conductance for K^+ is much greater than that for Na^+. In the equivalent circuit in Figure 9–8, g_K (10×10^{-6} S) is 20 times higher than g_{Na} (0.5×10^{-6} S). For most nerve cells, the value of g_{Cl} ranges from one-fourth to one-half of g_K. In this example, g_{Cl} equals 4.0×10^{-6} S. Given these values and the values of E_K, $E_{Cl,}$ and E_{Na}, we can calculate V_m as follows.

Since the membrane potential is constant, there is no net current through the three sets of ion channels:

$$I_K + I_{Cl} + I_{Na} = 0. \qquad \textbf{(9–2)}$$

We can easily calculate each current in two steps. First, we add up the separate potential differences across each branch of the circuit. For example, in the K^+ branch, the total potential difference is the sum of the the battery E_K and the voltage drop across g_K given by Ohm's law ($V_m = I_K/g_K$):*

$$V_m = E_K + I_K/g_K$$

Similarly, for the Na^+ and Cl^- conductance branches:

$$V_m = E_{Cl} + I_{Cl}/g_{Cl}$$

$$V_m = E_{Na} + I_{Na}/g_{Na}$$

Next, we rearrange and solve for the ionic current I in each branch:

$$I_{Na} = g_{Na} \times (V_m - E_{Na}) \qquad \textbf{(9–3a)}$$

$$I_K = g_K \times (V_m - E_K) \qquad \textbf{(9–3b)}$$

$$I_{Cl} = g_{Cl} \times (V_m - E_{Cl}). \qquad \textbf{(9–3c)}$$

These equations are similar to Equation 9–1, in which the net current through a single ion channel is derived from the currents caused by the individual

*Because we have defined V_m as $V_{in} - V_{out}$, the following convention must be used for these equations. Outward current (in this case I_K) is positive and inward current is negative. Batteries whose positive pole is directed toward the inside of the membrane (eg, E_{Na}) are given positive values in the equations. The reverse is true for batteries whose negative pole is directed toward the inside, such as the K^+ battery.

What determines the rate of change in potential with time or distance? What determines whether a stimulus will or will not produce an action potential? Here we consider the neuron's passive electrical properties and geometry and how these relatively constant properties affect the cell's electrical signaling. The actions of the gated channels and the ionic currents that change the membrane potential are described in the next five chapters.

Neurons have three passive electrical properties that are important for electrical signaling. We have already described the resting membrane conductance or resistance ($g_r = 1/R_r$) and the membrane capacitance, C_m. A third important property that determines signal propagation along dendrites or axons is their intracellular axial resistance (r_a). Although the resistivity of cytoplasm is much lower than that of the membrane, the axial resistance along the entire length of an

driving forces. As these equations illustrate, the ionic current through each conductance branch is equal to the conductance of that branch multiplied by the net electrochemical driving force. Thus, for the K^+ current, the conductance 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 and the current is outward; if V_m is more negative than E_K, the driving force is negative and the current is inward.

Similar equations are used in a variety of contexts throughout this book to relate the magnitude of a particular ionic current to its membrane conductance and driving force.

As we saw in Equation 9–2, $I_{Na} + I_K + I_{Cl} = 0$. If we now substitute Equations 9–3a,b,c for I_{Na}, I_K, and I_{Cl} in Equation 9–2, multiply through, and rearrange, we obtain the following expression:

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

Solving for V_m, we obtain an equation for the resting membrane potential that is expressed in terms of membrane conductances g and batteries E:

$$V_m = \frac{(E_{Na} \times g_{Na}) + (E_K \times g_K) + (E_{Cl} \times g_{Cl})}{g_{Na} + g_K + g_{Cl}}. \qquad \textbf{(9–4)}$$

From this equation, using the values in our equivalent circuit (Figure 9–8), we calculate that $V_m = -70$ mV.

Equation 9–4 states that V_m approaches the value of the ionic batteries that have the greater conductance. This principle can be illustrated by considering what happens during the action potential. At the peak of the action potential, g_K and g_{Cl} are essentially unchanged from their resting values, but g_{Na} increases as much as 500-fold. This increase in g_{Na} is caused by the opening of voltage-gated Na^+ channels. In the equivalent circuit in Figure 9–8, a 500-fold increase would change g_{Na} from 0.5×10^{-6} S to 250×10^{-6} S.

If we substitute this new value of g_{Na} into Equation 9–4 and solve for V_m, we obtain +48 mV. 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 and 62.5-fold greater than g_{Cl}, so that the Na^+ battery becomes much more important than the K^+ and Cl^- batteries in determining V_m.

Equation 9–4 is similar to the Goldman equation in that the contribution to V_m of each ionic battery is weighted in proportion to the conductance 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 approaches the value of that ion's Nernst potential.

The equivalent circuit can be further simplified by lumping the conductance of all the resting channels that contribute to the resting potential into a single conductance, g_r, and replacing the battery for each conductance channel with a single battery E_r, whose value is given by Equation 9–4 (Figure 9–9). Here the subscript r stands for the resting channel pathway. Because the resting channels provide a pathway for the steady leakage of ions across the membrane, they are sometimes referred to as *leakage channels* (Chapter 10). This consolidation of resting pathways will prove useful when we consider the effects on membrane voltage of current through voltage-gated and ligand-gated channels in later chapters.

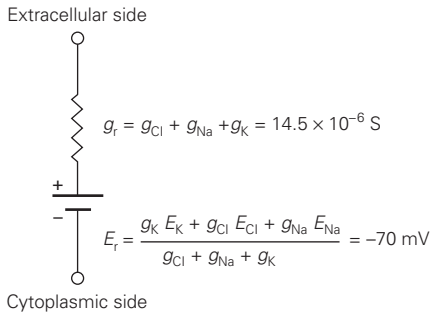

Figure 9–9 The Na^+, K^+, and Cl^- resting channels can be simplified to a single conductance and battery. For an equivalent circuit model of the resting membrane (eg, Figure 9–8), the total membrane conductance (g_r) is calculated from the sum of the Na^+, K^+, and Cl^- conductances, and the value of the resting potential battery (E_r) is calculated from Equation 9–4.

extended thin neuronal process can be considerable. Because these three elements provide the return pathway to complete the electrical circuit when active ionic currents flow into or out of the cell, they determine the time course of the change in synaptic potential generated by the synaptic current. They also determine whether a synaptic potential generated in a dendrite will depolarize the trigger zone at the axon initial segment enough to fire an action potential. Finally, the passive properties influence the speed at which an action potential is conducted.

Membrane Capacitance Slows the Time Course of Electrical Signals

The steady-state change in a neuron's voltage in response to subthreshold current resembles the behavior of a simple resistor, but the *time course* of the change

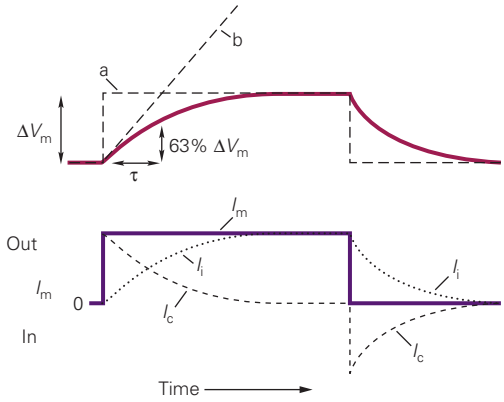

Figure 9–10 **The rate of change in the membrane potential is slowed by the membrane capacitance.** The **upper** plot shows the response of the membrane potential (ΔV_m) to a step current pulse (I_m). The shape of the actual voltage response (**red line**) combines the properties of a purely resistive element (**dashed line a**) and a purely capacitive element (**dashed line b**). The time taken to reach 63% of the final voltage defines the membrane time constant, τ. The **lower** plot shows the two elements of the total membrane current (I_m) during the current pulse: the ionic current (I_i) across the resistive elements of the membrane (ion channels) and the capacitive current (I_c).

does not. A true resistor responds to a step change in current with a similar step change in voltage, but the neuron's membrane potential rises and decays more slowly than the step change in current because of its *capacitance* (Figure 9–10).

To understand how the capacitance slows down the voltage response, recall that the voltage across a capacitor is proportional to the charge stored on the capacitor. To alter the voltage, charge Q must be added to or removed from the capacitor C:

$$\Delta V = \Delta Q/C.$$

To change the charge across the capacitor (the membrane lipid bilayer), there must be current across the capacitor (I_c). Since current is the flow of charge per unit time ($I_c = \Delta Q/\Delta t$), the change in voltage across a capacitor is a function of the magnitude and duration of the current:

$$\Delta V = I_c \cdot \Delta t/C.$$

Thus, the magnitude of the change in voltage across a capacitor in response to a current pulse depends on the duration of the current, because time is required to deposit and remove charge from the capacitor.

If the membrane had only resistive properties, a step pulse of outward current would change the membrane potential instantaneously. Conversely, if the membrane had only capacitive properties, the membrane potential would change linearly with time in response to the same step of current. Because the membrane has both capacitive and resistive properties in parallel, the actual change in membrane potential combines features of the two pure responses. The initial slope of the change reflects a purely capacitive element, whereas the final slope and amplitude reflect a purely resistive element (Figure 9–10, upper plot).

In the simple case of the spherical cell body of a neuron, the time course of the potential change is described by the following equation:

$$\Delta V_m\,(t) = I_m R_m (1 - e^{-t/\tau}),$$

where e is the base of the system of natural logarithms with a value of approximately 2.72, and τ is the *membrane time constant*, given by the product of the membrane resistance and capacitance ($R_m C_m$). The time constant can be measured experimentally as the time it takes the membrane potential to rise to $1 - 1/e$, or approximately 63% of its steady-state value (Figure 9–10, upper plot). Typical values of τ for neurons range from 20 to 50 ms. We shall return to the time constant in Chapter 13 where we consider the temporal summation of synaptic inputs in a cell.

Membrane and Cytoplasmic Resistance Affect the Efficiency of Signal Conduction

So far, we have considered the effects of the passive properties of neurons on signaling only within the cell body. Distance is not a factor in the propagation of a signal in the neuron's soma because the cell body can be approximated as a sphere whose membrane voltage is uniform. However, a subthreshold voltage signal traveling along extended structures (dendrites, axons, and muscle fibers) decreases in amplitude with distance from the site of initiation because some charge leaks out of the resting membrane conductance as it flows along the dendrite or axon. To show how this attenuation occurs, we will consider how the geometry of a neuron influences the distribution of current.

If current is injected into a dendrite at one point, how will the membrane potential change along its length? For simplicity, consider how membrane potential varies with distance after a constant-amplitude current pulse has been on for some time ($t >> \tau$). Under these conditions, the membrane capacitance is fully charged, so membrane potential reaches a steady value. The variation of the potential with distance depends on the fraction of charge that leaks out of the dendrite compared to the fraction that flows inside the dendrite towards the soma. Since charge flows along the path of least resistance, this depends on the relative values of the *membrane resistance* in a unit length of dendrite r_m