they are much less efficient than ion channels in mediating ion fluxes.

John D. Koester
Bruce P. Bean

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9

Membrane Potential and the Passive Electrical Properties of the Neuron

Information is carried within neurons and from neurons to their target cells by electrical and chemical signals. Transient electrical signals are particularly important for carrying time-sensitive information rapidly and over long distances. These transient electrical signals—receptor potentials, synaptic potentials, and action potentials—are all produced by temporary changes in the electric current into and out of the cell, changes that drive the electrical potential across the cell membrane away from its resting value. This current represents the flow of negative and positive ions through ion channels in the cell membrane.

Two types of ion channels—resting and gated—have distinctive roles in neuronal signaling. Resting channels are primarily important in maintaining the resting membrane potential, the electrical potential across the membrane in the absence of signaling. Some types of resting channels are constitutively open and are not gated by changes in membrane voltage; other types are gated by changes in voltage but are also open at the negative resting potential of neurons. Most voltage-gated channels, in contrast, are closed when the membrane is at rest and require membrane depolarization to open.

In this and the next several chapters, we consider how transient electrical signals are generated in the neuron. We begin by discussing how particular ion channels establish and maintain the membrane potential when the membrane is at rest and briefly describe the mechanism by which the resting potential can be perturbed, giving rise to transient electrical signals

such as the action potential. We then consider how the passive electrical properties of neurons—their resistive and capacitive characteristics—contribute to the integration and local propagation of synaptic and receptor potentials within the neuron. In Chapter 10 we examine the detailed mechanisms by which voltage-gated Na^+, K^+, and Ca^{2+} channels generate the action potential, the electrical signal conveyed along the axon. Synaptic potentials are considered in Chapters 11 to 14, and receptor potentials are discussed in Part IV in connection with the actions of sensory receptors.

The Resting Membrane Potential Results From the Separation of Charge Across the Cell Membrane

The neuron's cell membrane has thin clouds of positive and negative ions spread over its inner and outer surfaces. At rest, the extracellular surface of the membrane has an excess of positive charge and the cytoplasmic surface an excess of negative charge (Figure 9–1). This separation of charge is maintained because the lipid bilayer of the membrane is a barrier to the diffusion of ions (Chapter 8). The charge separation gives rise to the *membrane potential* (V_m), a difference of electrical potential, or voltage, across the membrane 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.

The membrane potential of a cell at rest, the *resting membrane potential* (V_r), is equal to V_{in} since by convention the potential outside the cell is defined as zero. Its usual range is –60 mV to –70 mV. All electrical signaling involves brief changes away from the resting membrane potential caused by electric currents across the cell membrane.

The electric current is carried by ions, both positive (cations) and negative (anions). The direction of current is conventionally defined as the direction of *net movement of positive charge.* Thus, in an ionic solution, cations move in the direction of the electric current and anions move in the opposite direction. In the nerve cell at rest, there is no net charge movement across the membrane. When there is a net flow of cations or anions into or out of the cell, the charge separation across the resting membrane is disturbed, altering the electrical potential of the membrane. A reduction or reversal of charge separation, leading to a less negative membrane potential, is called *depolarization.* An increase in charge separation, leading to a more negative membrane potential, is called *hyperpolarization.*

Changes in membrane potential that do not lead to the opening of gated ion channels are passive responses of the membrane and are called *electrotonic potentials.* Hyperpolarizing responses are almost always passive, as are small depolarizations. However, when depolarization approaches a critical level, or threshold, the cell responds actively with the opening of voltage-gated ion channels, which produces an all-or-none *action potential* (Box 9–1).

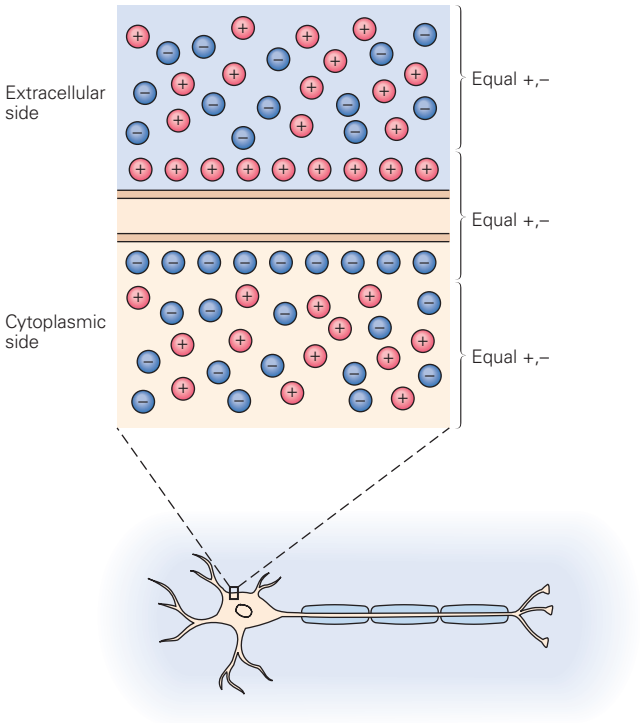

Figure 9–1 **The cell membrane potential results from the separation of net positive and net negative charges on either side of the membrane.** The excess of positive ions outside the membrane and negative ions inside the membrane represents a small fraction of the total number of ions inside and outside the cell at rest.

The Resting Membrane Potential Is Determined by Nongated and Gated Ion Channels

The resting membrane potential is the result of the passive flux of individual ion species through several classes of resting channels. Understanding how this passive ionic flux gives rise to the resting potential enables us to understand how the gating of different

Box 9–1 Recording the Membrane Potential

Reliable techniques for recording the electrical potential across cell membranes were developed in the late 1940s. These techniques allow accurate recordings of both the resting membrane potential and action potentials (Figure 9–2).

Glass micropipettes filled with a concentrated salt solution serve as electrodes and are placed on either side of the cell membrane. Wires inserted into the back ends of the pipettes are connected via an amplifier to an oscilloscope, which displays the amplitude of the membrane potential in volts. Because the diameter of such a *microelectrode* tip is minute (<1 μm), it can be inserted into a cell with relatively little damage to the cell membrane (Figure 9–2A).

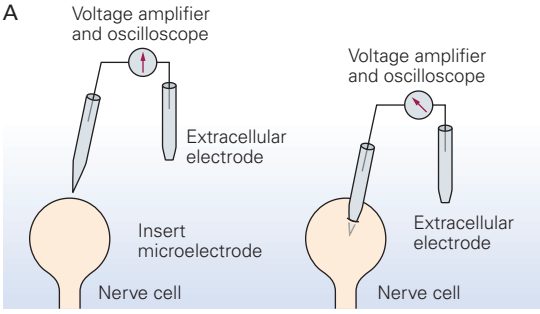

Figure 9–2A Recording setup.

When both electrodes are outside the cell, no electrical potential difference is recorded. But as soon as one microelectrode is inserted into the cell, the oscilloscope shows a steady voltage, the resting membrane potential. In most nerve cells at rest, the membrane potential is approximately −65 mV (Figure 9–2B).

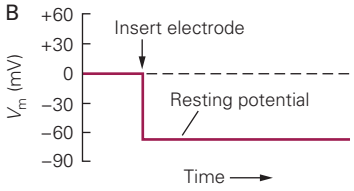

Figure 9–2B Oscilloscope display.

The membrane potential can be experimentally changed using a current generator connected to a second pair of electrodes—one intracellular and one extracellular. When the intracellular electrode is made positive with respect to the extracellular one, a pulse of positive current from the current generator causes positive charge to flow into the neuron from the intracellular electrode. This current returns to the extracellular electrode by flowing outward across the membrane.

As a result, the inside of the membrane becomes more positive while the outside of the membrane becomes more negative. This decrease in the separation of charge is called *depolarization*.

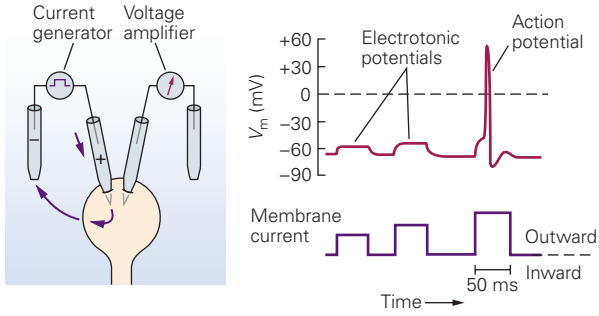

Figure 9–2C Depolarization.

Small depolarizing current pulses evoke purely electrotonic (passive) potentials in the cell—the size of the change in potential is proportional to the size of the current pulses. However, a sufficiently large depolarizing current triggers the opening of voltage-gated ion channels. The opening of these channels leads to the action potential, which differs from electrotonic potentials in the way in which it is generated as well as in magnitude and duration (Figure 9–2C).

Reversing the direction of current—making the intracellular electrode negative with respect to the extracellular electrode—makes the membrane potential more negative. This increase in charge separation is called *hyperpolarization*.

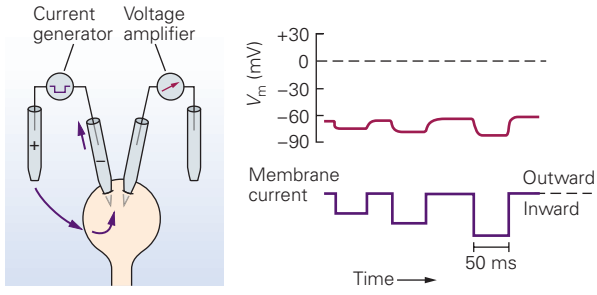

Figure 9–2D Hyperpolarization.

Hyperpolarization does not trigger an active response in the cell. The responses of the cell to hyperpolarization are usually purely electrotonic. As the size of the current pulse increases, the hyperpolarization increases proportionately (Figure 9–2D).

Table 9–1 Distribution of the Major Ions Across a Neuronal Membrane at Rest: The Giant Axon of the Squid

Species of ion	Concentration in cytoplasm (mM)	Concentration in extracellular fluid (mM)	Equilibrium potential[1] (mV)
K^+	400	20	–75
Na^+	50	440	+55
Cl^-	52	560	–60
A^- (organic anions)	385	None	None

[1]The membrane potential at which there is no net flux of the ion species across the cell membrane.

types of ion channels generates the action potential, as well as the receptor and synaptic potentials.

No single ion species is distributed equally on the two sides of a nerve cell membrane. Of the four most abundant ions found on either side of the cell membrane, Na^+ and Cl^- are concentrated outside the cell and K^+ and A^- (organic anions, primarily amino acids and proteins) inside. Table 9–1 shows the distribution of these ions inside and outside of one particularly well-studied nerve cell process, the giant axon of the squid, whose extracellular fluid has a salt concentration similar to that of seawater. Although the absolute values of the ionic concentrations for vertebrate nerve cells are two- to three-fold lower than those for the squid giant axon, the *concentration gradients* (the ratio of the external to internal ion concentration) are similar.

The unequal distribution of ions raises several important questions. How do ionic gradients contribute to the resting membrane potential? What prevents the ionic gradients from dissipating by diffusion of ions across the membrane through the resting channels? These questions are interrelated, and we shall answer them by considering two examples of membrane permeability: the resting membranes of glial cells, which are permeable to only one species of ion, and the resting membranes of nerve cells, which are permeable to three. For the purposes of this discussion, we shall only consider the resting channels that are not gated by voltage and thus are always open.

Open Channels in Glial Cells Are Permeable to Potassium Only

The permeability of a cell membrane to a particular ion species is determined by the relative proportions of the various types of ion channels that are open. The simplest case is that of the glial cell, which has a resting potential of approximately –75 mV. Like most cells, a glial cell has high concentrations of K^+ and A^- on the inside and high concentrations of Na^+ and Cl^- on the outside. However, most resting channels in the membrane are permeable only to K^+.

Because K^+ ions are present at a high concentration inside the cell, they tend to diffuse across the membrane from the inside to the outside of the cell down their chemical concentration gradient. As a result, the outside of the membrane accumulates a net positive charge (caused by the slight excess of K^+) and the inside a net negative charge (because of the deficit of K^+ and the resulting slight excess of anions). Because opposite charges attract each other, the excess positive charges on the outside and the excess negative charges on the inside collect locally on either surface of the membrane (Figure 9–1).

The flux of K^+ out of the cell is self-limiting. The efflux of K^+ gives rise to an electrical potential difference—positive outside, negative inside. The greater the flow of K^+, the more charge is separated and the greater is the potential difference. Because K^+ is positive, the negative potential inside the cell tends to oppose the further efflux of K^+. Thus, K^+ ions are subject to two forces driving them across the membrane: (1) a *chemical driving force,* a function of the concentration gradient across the membrane, and (2) an *electrical driving force,* a function of the electrical potential difference across the membrane.

Once K^+ diffusion has proceeded to a certain point, the electrical driving force on K^+ exactly balances the chemical driving force. That is, the outward movement of K^+ (driven by its concentration gradient) is equal to the inward movement of K^+ (driven by the electrical potential difference across the membrane). This potential is called the K^+ *equilibrium potential*, E_K (Figure 9–3). In a cell permeable only to K^+ ions, E_K determines the resting membrane potential, which in most glial cells is approximately –75 mV.

The equilibrium potential for any ion *X* can be calculated from an equation derived in 1888 from basic

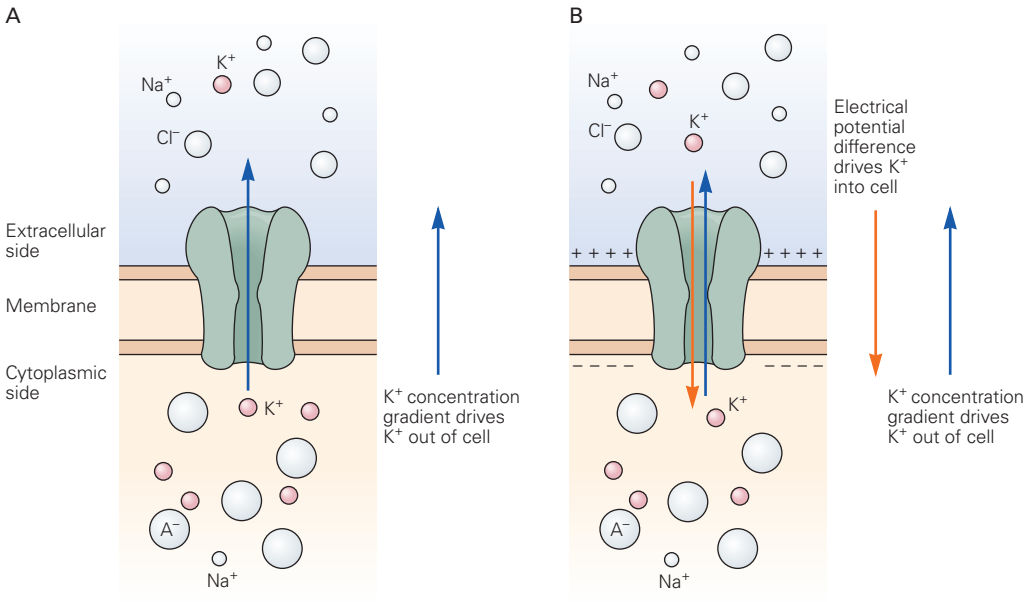

Figure 9–3 The flux of K^+ across a cell membrane is determined by both the K^+ concentration gradient and the membrane potential.

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 an excess of negative charge inside the cell. This buildup of charge leads to a potential difference across the membrane that impedes the further efflux of K^+, so eventually an equilibrium is reached: The electrical and chemical driving forces are equal and opposite, so as many K^+ ions move in as move out.

thermodynamic principles by the German physical chemist Walter Nernst:

$$E_x = \frac{RT}{zF} \ln \frac{[X]_o}{[X]_i}, \qquad \textbf{Nernst Equation}$$

where R is the gas constant, T the temperature (in degrees Kelvin), z the valence of the ion, F the Faraday constant, and $[X]_o$ and $[X]_i$ the concentrations of the ion outside and inside the cell. (To be precise, chemical activities rather than concentrations should be used.)

Since RT/F is 25 mV at 25°C (77°F, room temperature), and the constant for converting from natural logarithms to base 10 logarithms is 2.3, the Nernst equation can also be written as follows:

$$E_x = \frac{58\,\text{mV}}{z} \log \frac{[X]_o}{[X]_i}.$$

Thus, for K^+, since $z = +1$ and given the concentrations inside and outside the squid axon in Table 9–1:

$$E_K = \frac{58\,\text{mV}}{1} \log \frac{[20]}{[400]} = -75\,\text{mV}.$$

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 potential is sometimes called the *Nernst potential*). The equilibrium potentials for the distributions of Na^+, K^+, and Cl^- ions across the squid giant axon are given in Table 9–1.

In our discussion so far, we have treated the generation of the resting potential as a passive mechanism—the diffusion of ions down their chemical gradients—one that does not require the expenditure of energy by the cell. However, energy from hydrolysis of adenosine triphosphate (ATP) is required to set up the initial concentration gradients and to maintain them in neurons, as we shall see below.

Open Channels in Resting Nerve Cells Are Permeable to Three Ion Species

Unlike glial cells, nerve cells at rest are permeable to Na^+ and Cl^- ions in addition to K^+ ions. Of the abundant ion species in nerve cells, only the large organic anions (A^-) are unable to permeate the cell membrane. How are the concentration gradients for the three permeant ions (Na^+, K^+, and Cl^-) maintained across the membrane of a single cell, and how do these three

gradients interact to determine the cell's resting membrane potential?

To answer these questions, it is 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 concentration gradients for K^+, Na^+, Cl^-, and A^- as shown in Table 9–1. Under these conditions, the resting membrane potential V_r is determined solely by the K^+ concentration gradient and is equal to E_K (–75 mV) (Figure 9–4A).

Now consider what happens if a few resting Na^+ channels are added to the membrane, making it slightly permeable to Na^+. Two forces drive Na^+ into the cell: Na^+ tends to flow into the cell down its chemical concentration gradient, and it is driven into the cell by the negative electrical potential difference across the membrane (Figure 9–4B). The influx of Na^+ depolarizes the cell, but only slightly from the K^+ equilibrium potential (–75 mV). The new membrane potential does not come close to the Na^+ equilibrium potential of +55 mV because there are many more resting K^+ channels than Na^+ channels in the membrane.

As soon as the membrane potential begins to depolarize from the value of the K^+ equilibrium potential, K^+ flux is no longer in equilibrium across the membrane. The reduction in the electrical force driving K^+ into the cell means that there is now a net flow of K^+ out of the cell, tending to counteract the Na^+ influx. The more the membrane potential is depolarized and driven away from the K^+ equilibrium potential, the greater is the net electrochemical force driving K^+ out of the cell and consequently the greater the net K^+ efflux. Eventually the membrane potential reaches a new resting level at which the increased outward movement of K^+ just balances the inward movement of Na^+ (Figure 9–4C). This balance point (usually approximately –65 mV) is far from the Na^+ equilibrium potential (+55 mV) and is only slightly more positive than the K^+ equilibrium potential (–75 mV).

To understand how this balance point is determined, bear in mind that the magnitude of the flux of an ion across a cell membrane is the product of its *electrochemical driving force* (the sum of the electrical and chemical driving forces) and the conductance of the membrane to the ion:

$$\text{ion flux} = (\text{electrical driving force} + \text{chemical driving force}) \times \text{membrane conductance}.$$

In a resting nerve cell, relatively few Na^+ channels are open, so the membrane conductance of Na^+ is quite low. Thus, despite the large chemical and electrical forces driving Na^+ into the cell, the influx of Na^+ is small. In contrast, many K^+ channels are open in the membrane of a resting cell so that the membrane conductance of K^+ is relatively large. Because of the high conductance of K^+ relative to Na^+ in the cell at rest, the small net outward force acting on K^+ is enough to produce a K^+ efflux equal to the Na^+ influx.

The Electrochemical Gradients of Sodium, Potassium, and Calcium Are Established by Active Transport of the Ions

As we have seen, the passive movement of K^+ out of the resting cell through open channels balances the passive movement of Na^+ into the cell. However, this steady leakage of ions cannot be allowed to continue unopposed for any appreciable length of time because the Na^+ and K^+ gradients would eventually run down, reducing the resting membrane potential.

Dissipation of ionic gradients is prevented by the sodium-potassium pump (*Na^+-K^+ pump*), which moves Na^+ and K^+ *against* their electrochemical gradients: It extrudes Na^+ from the cell while taking in K^+. The pump therefore requires energy, and the energy comes from hydrolysis of ATP. Thus, at the resting membrane potential, the cell is not in equilibrium but rather in a *steady state*: There is a continuous passive influx of Na^+ and efflux of K^+ through resting channels that is exactly counterbalanced by the Na^+-K^+ pump.

As we saw in the previous chapter, pumps are similar to ion channels in that they catalyze the movement of ions across cell membranes. However, they differ in two important respects. First, whereas ion channels are passive conduits that allow ions to move down their electrochemical gradient, pumps require a source of chemical energy to transport ions against their electrochemical gradient. Second, ion transport is much faster in channels: Ions typically flow through channels at a rate of 10^7 to 10^8 per second, whereas pumps operate at speeds more than 10,000 times slower.

The Na^+-K^+ pump is a large membrane-spanning protein with catalytic binding sites for Na^+ and ATP on its intracellular surface and for K^+ on its extracellular surface. With each cycle, the pump hydrolyzes one molecule of ATP. (Because the Na^+-K^+ pump hydrolyzes ATP, it is also referred to as the Na^+-K^+ ATPase.) It uses this energy of hydrolysis to extrude three Na^+ ions from the cell and bring in two K^+ ions. The unequal flux of Na^+ and K^+ ions causes the pump to generate a net outward ionic current. Thus, the pump is said to be *electrogenic.* This pump-driven efflux of positive charge tends to set the resting potential a few millivolts more negative than would be achieved by the passive

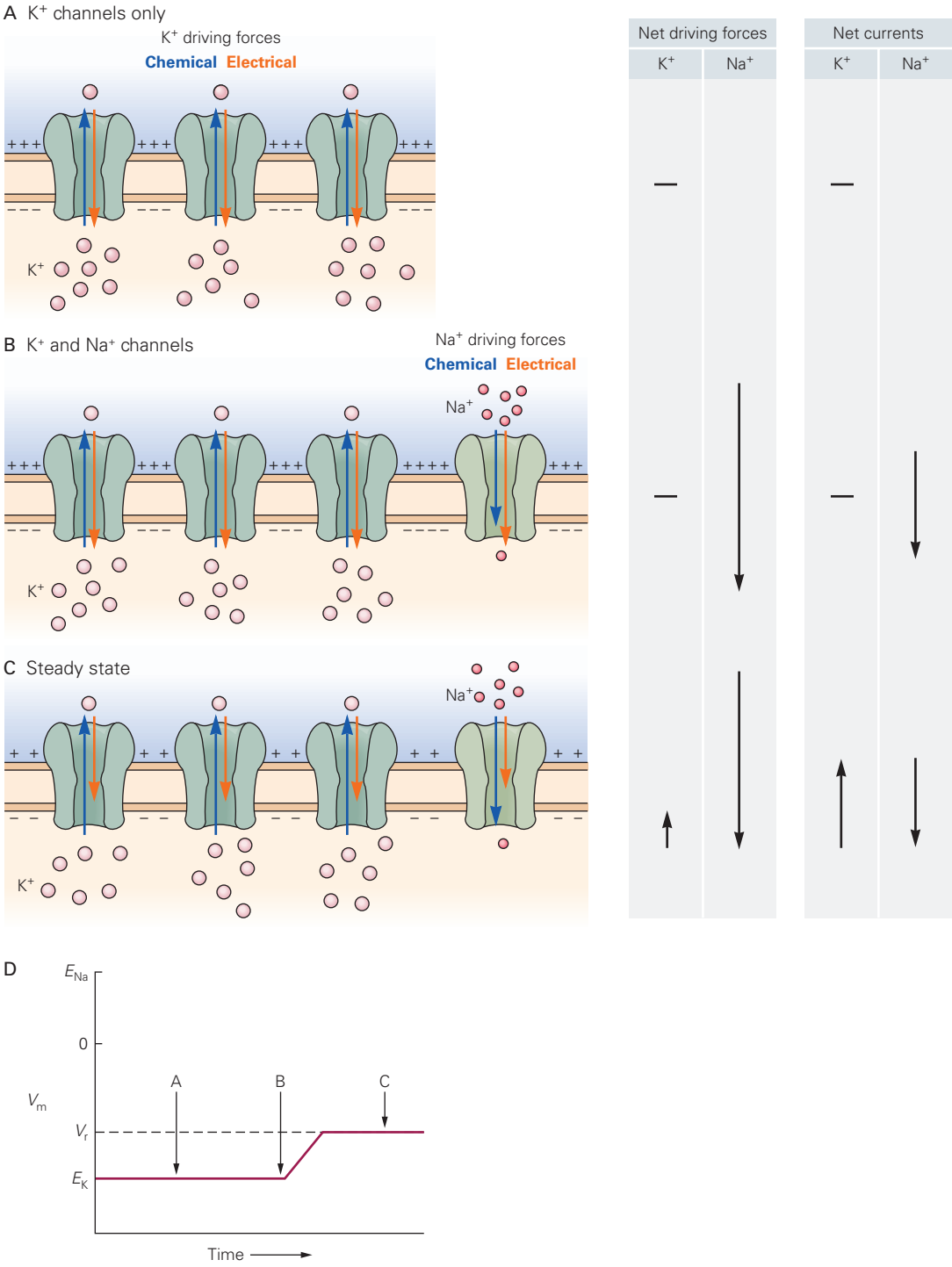

Figure 9–4 **The resting potential of a cell is determined by the proportions of different types of ion channels that are open, together with the value of their equilibrium potentials.** The channels in the figures represent the entire complement of K^+ or Na^+ channels in this hypothetical cell membrane. 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**.