7

Membrane Potential

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INFORMATION IS CARRIED WITHIN and between neurons by electrical and chemical signals. Transient electrical signals are particularly important for carrying time-sensitive 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 drive the electrical potential across the cell membrane away from its resting value.

This current flow is controlled by ion channels in the cell membrane. We can distinguish two types of ion channels—resting and gated—by their distinctive roles in neuronal signaling. Resting channels normally are open and are not influenced significantly by extrinsic factors, such as the potential across the membrane. They are primarily important in maintaining the resting membrane potential, the electrical potential across the membrane in the absence of signaling. Most gated channels, in contrast, are closed when the membrane is at rest. Their probability of opening is regulated by the three factors we considered in the last chapter: changes in membrane potential, ligand binding, or membrane stretch.

In this and succeeding chapters we consider how transient electrical signals are generated in the neuron. We begin by discussing how resting ion channels establish and maintain the resting potential. We also briefly describe the mechanism by which the resting potential can be perturbed, giving rise to transient electrical signals such as the action potential. In Chapter 8 we shall consider how the passive properties of neurons—their resistive and capacitive characteristics—contribute to local signaling within the neuron. In Chapter 9 we shall examine how voltage-gated Na^+, K^+, and Ca^{2+} channels generate the action potential, the electrical signal conveyed along the axon. Synaptic and receptor potentials are considered in Chapters 10,11,12,13 in the context of synaptic signaling between neurons.

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

Every neuron has a separation of charges across its cell membrane consisting of a thin cloud of positive and negative ions spread over the inner and outer surfaces of the cell membrane (Figure 7-1). At rest a nerve cell 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 of the membrane blocks the diffusion of ions, as explained in Chapter 6. The charge separation gives rise to a difference of electrical potential, or voltage, across the membrane called the *membrane potential.* The 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.

The membrane potential of a cell at rest is called the *resting membrane potential.* Since, by convention, the potential outside the cell is defined as zero, the resting potential (V_r) is equal to V_{in}. Its usual range in neurons is -60 mV to -70 mV. All electrical signaling involves brief changes from the resting membrane potential due to alterations in the flow of electrical current across the cell membrane resulting from the opening and closing of ion channels.

The electric current that flows into and out of the cell is carried by ions, both positively charged (cations) and negatively charged (anions). The direction of current flow 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, anions in the opposite direction. Whenever 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 polarization of the membrane. A reduction 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 called *electrotonic potentials* and are said to be passive responsives of the membrane. Hyperpolarizing responses are almost always passive, as are small depolarizations. However, when depolarization approaches a critical level, called the *threshold*, the cell responds actively with the opening of voltage-gated ion channels, which at threshold produces an all-or-none *action potential* (Box 7-1).

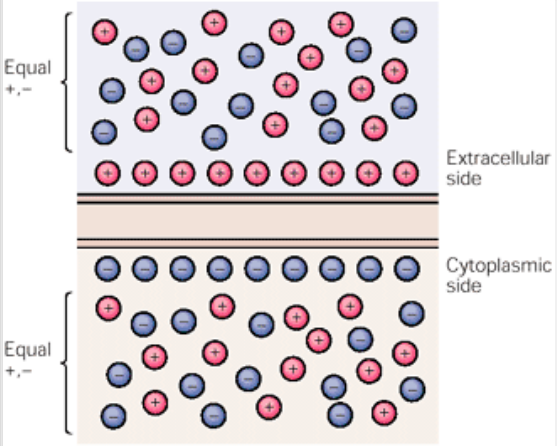

Figure 7-1 The membrane potential results from a separation of positive and negative charges across the cell membrane. The excess of positive charges (**red circles**) outside the membrane and negative charges (**blue circles**) inside the membrane of a nerve cell at rest represents a small fraction of the total number of ions inside and outside cell.

We begin examining the membrane potential by analyzing how the passive flux of individual ion species through resting 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 Resting Ion Channels

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 more concentrated outside the cell, and K^+ and organic anions (A^-) are more concentrated inside. The organic anions are primarily amino acids and proteins. Table 7-1 shows the distribution of these ions inside and outside one particularly well-studied nerve cell process, the giant axon of the squid, whose blood has a salt concentration similar to sea water. Although the absolute values of the ionic concentrations for vertebrate nerve cells are two- to threefold lower than those for the squid giant axon, the concentration *gradients* (the ratio of the external ion concentration to internal ion concentration) are about the same.

The unequal distribution of ions raises several important questions. How do ionic gradients contribute to the resting membrane potential? How are they maintained? What prevents the ionic gradients from dissipating by diffusion of ions across the membrane through

P.127

P.128

the passive (resting) channels? These questions are interrelated, and we shall answer them by considering two examples of membrane permeability: the resting membrane of glial cells, which is permeable to only one species of ions, and the resting membrane of nerve cells, which is permeable to three. For the purposes of this discussion we shall consider only the resting ion channels, which are always open.

Box 7-1 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 and the action potentials and make use of glass micropipettes filled with a concentrated salt solution that serve as electrodes. These microelectrodes 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 tip diameter of a microelectrode is very small (<1 μM), it can be inserted into a cell with relatively little damage to the cell membrane.

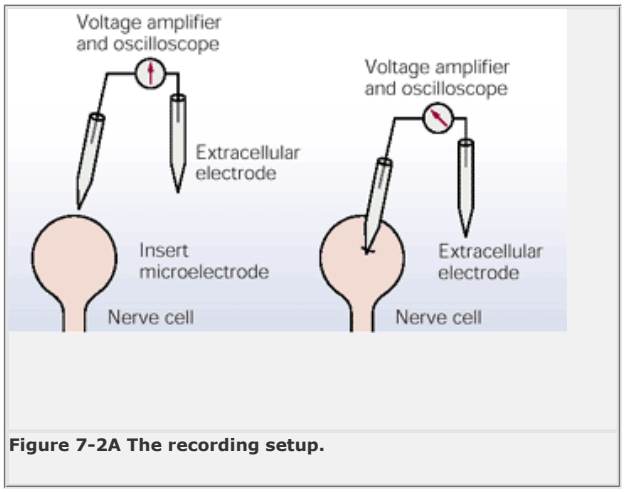

Figure 7-2A The recording setup.

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 around -65 mV.

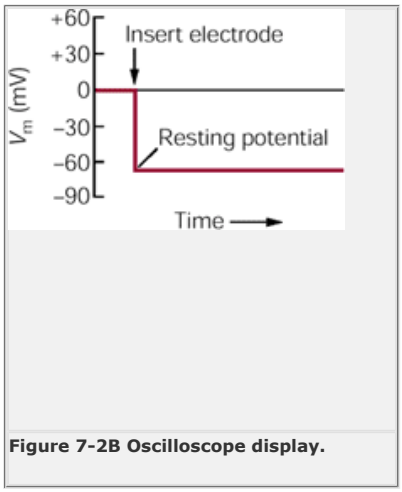

Figure 7-2B Oscilloscope display.

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 generator will cause current 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 progressive *decrease* in the normal separation of charge is called *depolarization.*

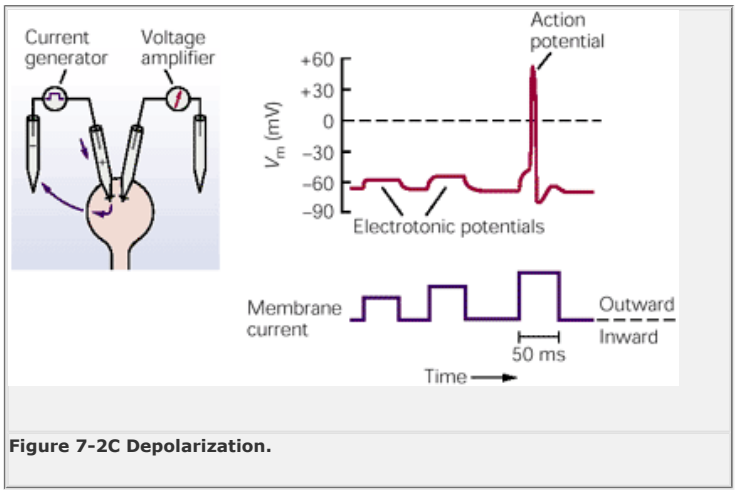

Figure 7-2C Depolarization.

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, 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 not only in the way in which it is generated but also in magnitude and duration.

Reversing the direction of current flow—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.*

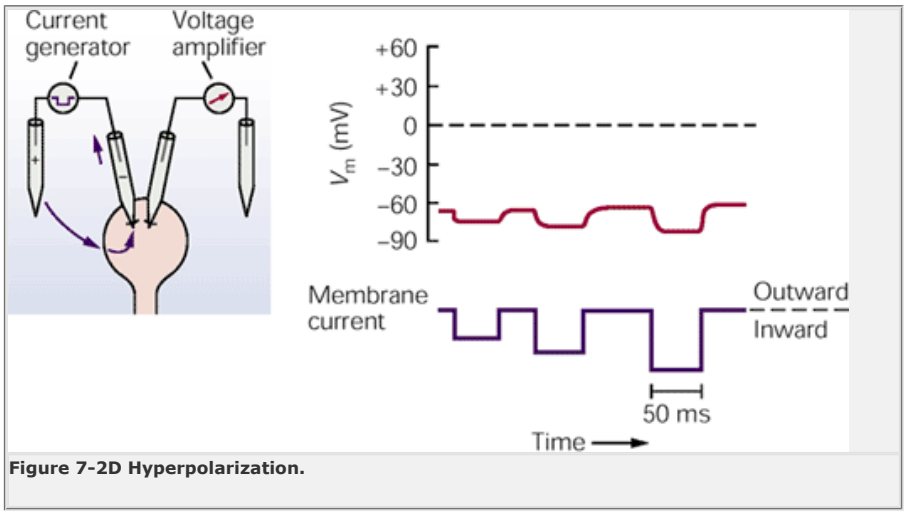

Figure 7-2D Hyperpolarization.

The responses of the cell to hyperpolarization are usually purely electrotonic—as the size of the current pulse increases, the hyperpolarization increases proportionately. Hyperpolarization does not trigger an active response in the cell.

Table 7-1 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	——	

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

Resting Channels in Glial Cells Are Selective for Potassium Only

A membrane's overall selectivity for individual ion species is determined by the relative proportions of the various types of ion channels in the cell that are open. The simplest case is that of the glial cell, which has a resting potential of about -75 mV. Here, the vast majority of resting channels in the membrane are permeable only to K^+. As a result, the glial cell membrane at rest is almost exclusively permeable to K^+ ions. A glial cell has a high concentration of K^+ and negatively charged organic anions on the inside and a high concentration of Na^+ and Cl^- on the outside.

How do these ionic gradients generate the membrane potential of the glial cell? Because K^+ ions are present at a high concentration inside the cell and glial cells are selectively permeable to them, K^+ ions tend to diffuse from inside to outside the cell, down their chemical concentration gradient. As a result, the outside of the membrane accumulates a positive charge (due to the slight excess of K^+) and the inside a negative charge (because of the deficit of K^+ and the resulting slight excess of anions). Since 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 (see Figure 7-1).

The diffusion of K^+ out of the cell is self-limiting. The separation of charge resulting from the diffusion of K^+ gives rise to an electrical potential difference:

positive outside, negative inside. The more K^+ continues to flow, the more charge will be separated and the greater will be the potential difference. Since K^+ is positively charged, this potential difference tends to oppose the further efflux of K^+. Thus, ions are subject to two forces driving them across the membrane: (1) a *chemical driving force* that depends on the concentration gradient across the membrane and (2) an *electrical driving force* that depends on the electrical potential difference across the membrane. Once K^+ diffusion has proceeded to a certain point, a potential develops across the membrane at which the electrical force driving K^+ into the cell exactly balances the chemical force driving K^+ ions out of the cell. 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 potassium equilibrium potential, E_K (Figure 7-3). In a cell permeable only to K^+ ions, E_K determines the resting membrane potential, which in most glial cells is about -75 mV.

The equilibrium potential for any ion X can be calculated from an equation derived in 1888 from basic 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 $[X]_i$ are the concentrations of the ion outside and inside of the cell. (To be precise, chemical activities should be used rather than concentrations.)

Since RT/F is 25 mV at 25°C (room temperature), and the constant for converting from natural logarithms

P.129

to base 10 logarithms is 2.3, the Nernst equation can also be written as:

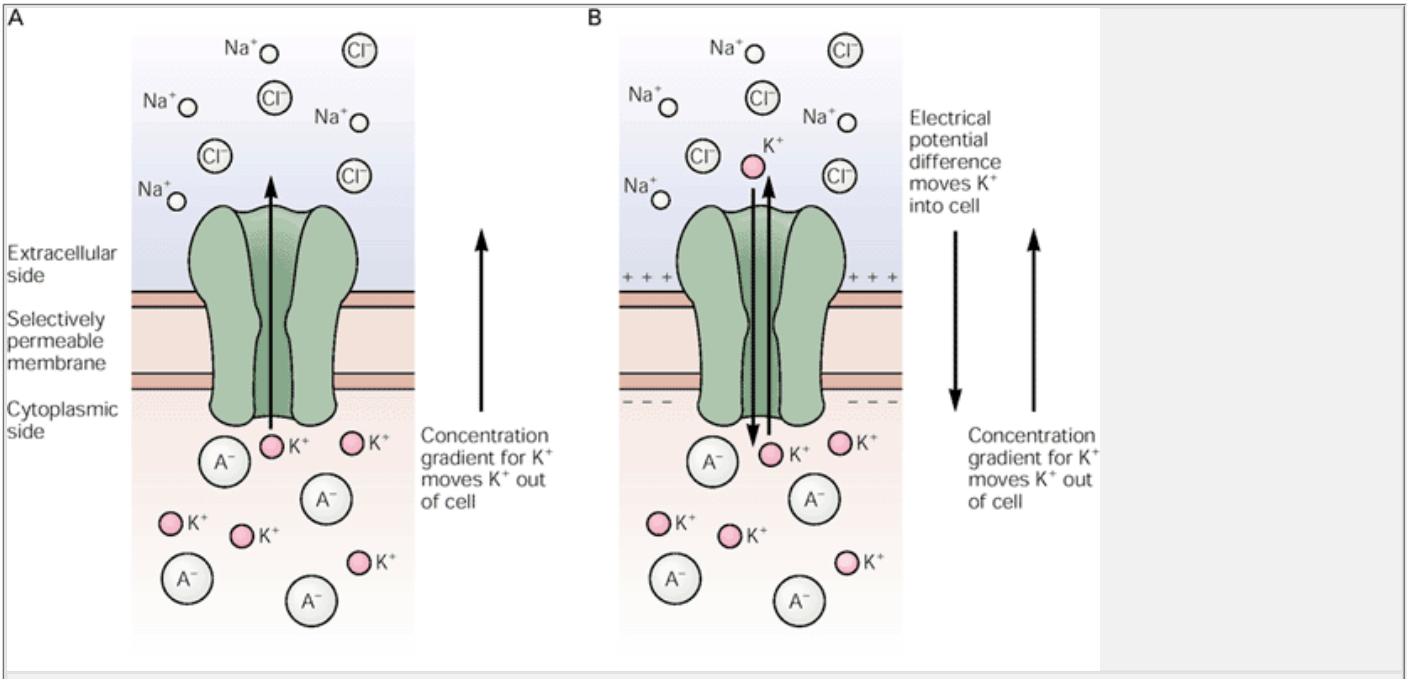

Figure 7-3 The flux of K^+ across the membrane is determined by both the K^+ concentration gradient and the electrical potential across the membrane.

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

$$E_X = \frac{58 \text{ mV}}{z} \log \frac{[X_o]}{[X_i]}.$$

Thus, for K^+, since $z = +1$ and given the concentrations inside and outside the squid axon in Table 7-1:

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

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 Na^+, K^+, and Cl^- equilibrium potentials for the distributions of ions across the squid axon are given in Table 7-1.

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

Resting Channels in Nerve Cells Are Selective for Several Ion Species

Measurements of the resting membrane potential with intracellular electrodes and flux studies using radioactive tracers show that, 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^-)—negatively charged proteins and amino acids—are unable to permeate the cell membrane. How can the concentration gradients for the three permeant ions (Na^+, K^+, and Cl^-) be 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 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 concentration gradients for K^+, Na^+, Cl^-, and A^- as shown in Table 7-1. Under these conditions the resting membrane potential, V_r, is determined solely by the K^+ concentration gradient and will be equal to E_k (-75 mV) (Figure 7-4A).

Now consider what happens if a few resting 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 it tends to flow into the cell down its chemical concentration gradient. Second, Na^+ is driven into the cell by the negative electrical potential difference across the membrane (Figure 7-4B). The influx of positive charge (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.

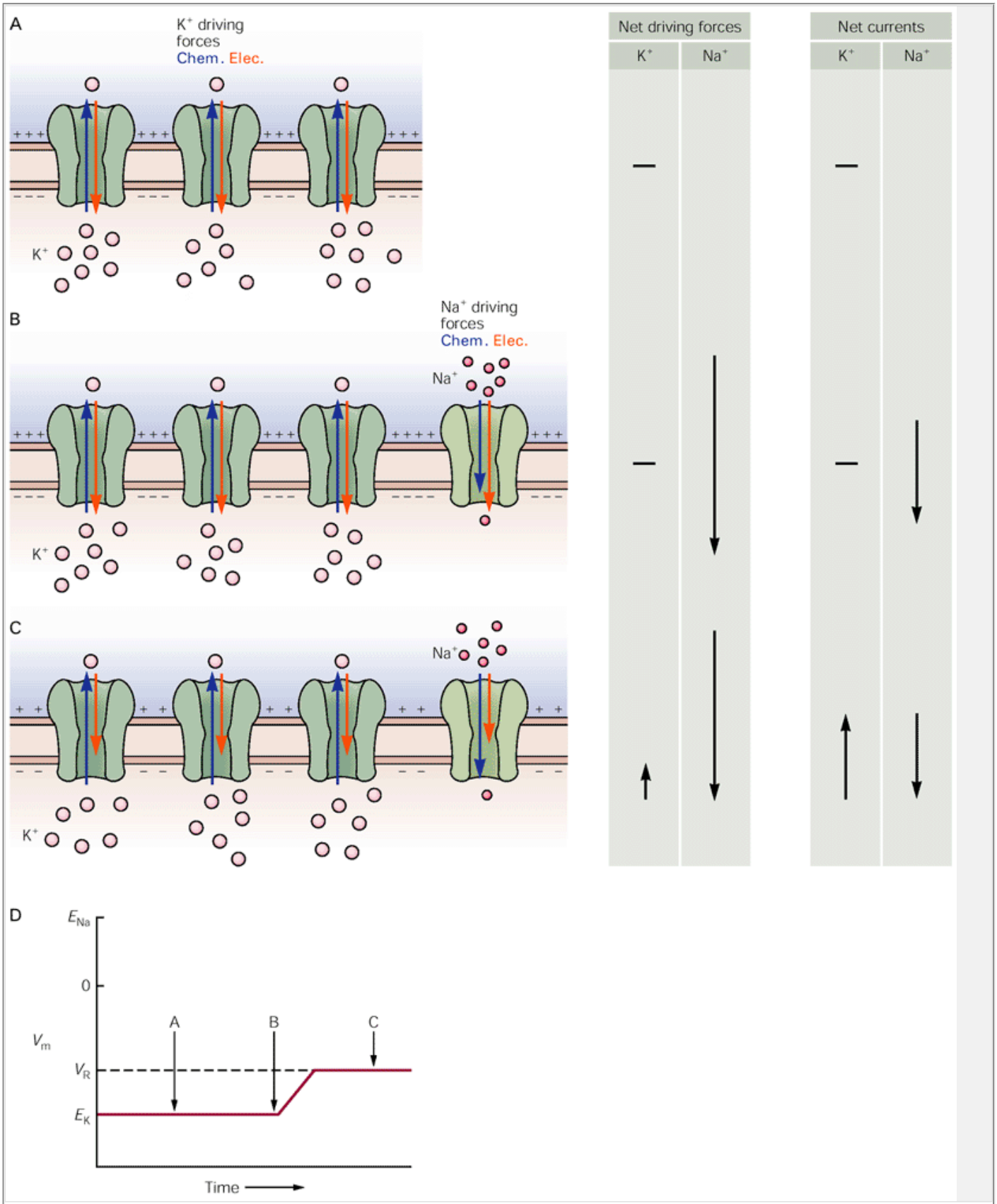

Figure 7-4 The resting potential of a cell is determined by the relative proportion of different types of ion channels that are open, together with the value of their equilibrium (Nernst) potentials. In this simplified diagram the channels shown represent the entire complement of K^+ or Na^+ channels in the 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^+ and K^+. The lengths of the arrows on the **right** denote the net driving force on a particular ion (that is, the sum of the electrical and chemical driving forces) and the relative sizes of the different net ion fluxes. Three hypothetical situations are illustrated.

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

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

C. The resting potential settles at a new resting potential, which is the value of V_m where $/_{Na} = -/_K$. 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^+ ions drives a current equal and opposite to the Na^+ current driven by the much larger net driving force for Na^+ ions. This is a steady-state condition, in which neither Na^+ nor K^+ is in equilibrium but the net flux of charge is null.

D. Illustration of membrane voltage changes during the hypothetical situations considered in **A, B, and C**.

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 negative electrical force driving K^+ into the cell means that there will be a net efflux of K^+ out of the cell, tending to counteract the Na^+ influx. The more the membrane potential is depolarized and moves away from the K^+ equilibrium potential, the greater is the electrochemical force driving K^+ out of the cell and consequently the greater is the K^+ efflux. Eventually, the membrane potential reaches a new resting potential at which the outward movement of K^+ just balances the inward movement of Na^+ (Figure 7-4C). This balance point (usually -60 mV) is far from the Na^+ equilibrium potential (+55 mV) and is only slightly more positive than the equilibrium potential for K^+ (-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 driving force and the chemical driving force due to the concentration gradient) and the conductance of the membrane to the ion:

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

A cell has relatively few resting Na^+ channels so at rest the conductance to 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, since there are many resting K^+ channels, the membrane conductance of K^+ is relatively large. As a result, the small net outward force acting on K^+ at the resting membrane potential is enough to produce a K^+ efflux equal to the Na^+ influx.

Passive Flux of Sodium and Potassium Is Balanced by Active Pumping of the Ions

For a cell to have a steady resting membrane potential the charge separation across the membrane must be maintained constant over time. That is, 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. As we have seen, the passive movement of K^+ out of the cell through resting channels balances the passive movement of Na^+ into the cell. However, these steady ion leaks 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 Na^+-K^+ pump, which moves Na^+ and K^+ *against* their net electrochemical gradients: it extrudes Na^+ from the cell while taking in K^+. The pump therefore requires energy to run. The energy comes from the 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.

The Na^+-K^+ pump is a large membrane-spanning protein with catalytic binding sites for Na^+, K^+, and ATP. The sites for Na^+ and ATP are located on its intracellular surface and the sites for K^+ on its extracellular surface. With each cycle the pump hydrolyzes one molecule of ATP. It then uses this energy to extrude three Na^+ ions 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 outward flux of positive charge tends to hyperpolarize the membrane to a somewhat more negative potential than would be achieved by the simple passive-diffusion mechanisms discussed above.

Chloride Ions May Be Passively Distributed

So far we have ignored the contribution of chloride (Cl^-) to the resting potential, even though many nerve cells have Cl^- channels that are open in the resting membrane. This simplification is valid for nerve cells that do not have a mechanism for active transport of Cl^- against an electrochemical gradient. In these cells the resting potential is ultimately determined by K^+ and Na^+ fluxes because the intracellular concentrations of $K^+$and Na^+ are fixed by active transport (the Na^+-K^+ pump), whereas the Cl^- concentration inside the cell is affected only by passive forces (electrical potential and concentration gradient). Therefore, the movement of Cl^- ions tends toward equilibrium across the membrane, so that E_{Cl} is equal to the resting potential, V_r, and there is no net Cl^- flux at rest.

In many nerve cells the Cl^- gradient is controlled by an integral membrane protein called a Cl^- transporter. Like the Na^+-K^+ pump it catalyzes the movement of ions across the membrane against an electrochemical gradient without forming a continuous pore. Unlike the Na^+-K^+ pump, the transport process does not require the hydrolysis of ATP. Although no chemical bond energy is utilized in the transport process, the Cl^- transporter can move Cl^- against its electrochemical gradient by utilizing the energy stored in a preexisting ionic concentration gradient for a different type of ion—a process known as *secondary active transport.* For example, one type of Cl^- transporter couples the outward movement of one Cl^- ion to the outward movement of one K^+ ion. Since the electrochemical gradient for K^+ is outward, the energetically favorable outward K^+ flux is able to drive the energetically unfavorable outward Cl^- flux. As a result, the outside-to-inside ratio of Cl^- is greater than would result from passive diffusion alone. The effect of increasing the Cl^- gradient is to make the equilibrium potential for Cl^- ions more negative than the resting membrane potential overall. (Remember, the valence (z) of Cl^- is -1.)

The Balance of Ion Fluxes That Gives Rise to the Resting Membrane Potential 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, however, when the membrane is depolarized past the threshold for generating an action potential. Once the membrane potential reaches this threshold, voltage-gated Na^+ channels open rapidly. The resultant increase in membrane permeability to Na^+ causes the Na^+ influx to exceed the K^+ efflux, 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 toward the Na^+ equilibrium potential of +55 mV:

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

However, the membrane potential never quite reaches that point because K^+ efflux continues throughout the depolarization. A slight influx of Cl^- into the cell also counteracts the depolarizing tendency of the Na^+ influx. Nevertheless, so many voltage-gated Na^+ channels open during the rising phase of the action potential that the cell's permeability to Na^+ is much greater than to 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 membrane potential would remain at this large positive value near the Na^+ equilibrium potential indefinitely but for two processes that repolarize the membrane, thus terminating the action potential. First, as the depolarization continues, the population of voltage-gated Na^+ channels gradually closes by the process of inactivation (see Chapters 6 and 9). Second, opening of the voltage-gated K^+ channels causes the K^+ efflux to gradually increase. The increase in K^+ permeability is slower than the increase in Na^+ permeability because of the slower rate of opening of the voltage-gated K^+ channels. The delayed increase in K^+ efflux combines with a decrease in Na^+ influx to produce a net efflux of positive charge from the cell, which continues until the cell has repolarized to its resting membrane potential.

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

Although Na^+ and K^+ fluxes set the value of the resting potential, V_m is not equal to either E_K or E_{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 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. In terms of electrical current flow, the membrane's conductance (1/resistance) provides a convenient measure of how readily the ion crosses the membrane. Another convenient measure is the permeability (P) of the membrane to that ion in units of velocity, cm/s. This measure is similar to that of a diffusion constant, which measures the rate of solute movement in solution. The dependence of membrane potential on ionic permeability and concentration is given quantitatively 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

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 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

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

Alan Hodgkin and Bernard Katz used the Goldman equation to analyze changes in membrane potential. They first measured the variation in membrane potential of a squid giant axon while systematically changing 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, however, the variation of V_m with external ionic concentrations was fit best if a quite different set of permeability ratios were assumed:[1]

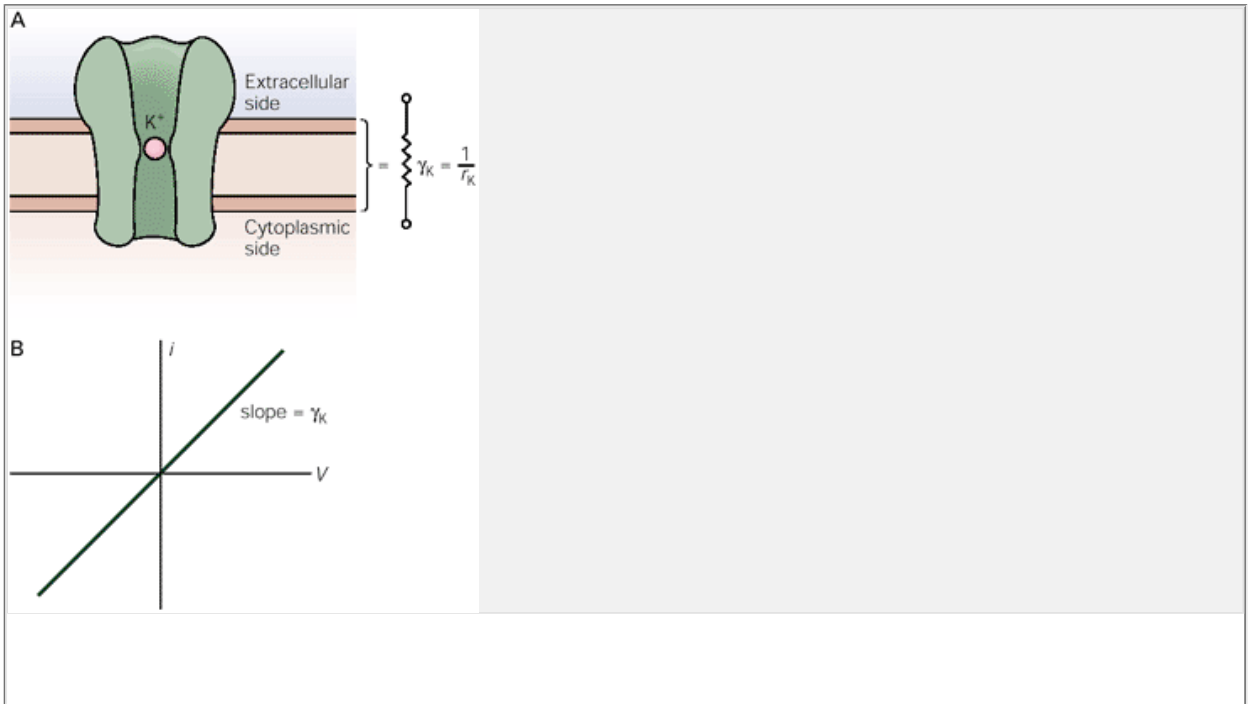

Figure 7-5 Electrical properties of a single K^+ channel.

A. A single K^+ channel can be represented as a conductor or resistor (conductance, γ, is the inverse of resistance, r).

B. The current-voltage relation for a single K^+ channel in the absence of a concentration gradient. The slope of the relation is equal to γ_K.

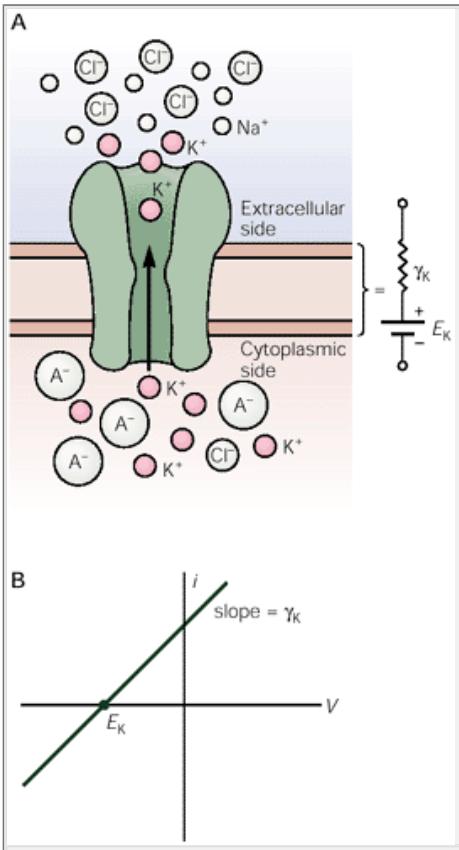

Figure 7-6 Chemical and electrical forces contribute to current flow.

A. A concentration gradient for K^+ 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 this circuit the battery is in series with a conductor, γ_K, representing the conductance of a channel that is selectively permeable to K^+ ions.

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

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

For these values of permeabilities 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}, the Nernst potential for Na^+.

P.134

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

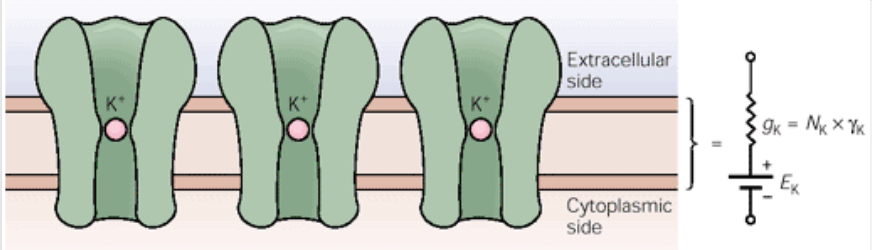

Figure 7-7 All of the passive K^+ channels in a nerve cell membrane can be lumped into a single equivalent electrical structure comprising a battery (E_K) in series with a conductor (g_K). The conductance is $g_K = N_K \times \gamma_K$, where N_K is the number of passive K^+ channels and γ_K is the conductance of a single K^+ channel.

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

The Goldman equation is limited because it cannot be used to determine how rapidly the membrane potential changes in response to a change in permeability. Moreover, it is inconvenient for determining the magnitude of the individual Na^+, K^+, and Cl^- currents. This information can be obtained with a simple mathematical model derived from electrical circuits. Within 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 or resistors (representing the ion channels), batteries (representing the concentration gradients of relevant ions), and capacitors (the ability of the membrane to store charge). Equivalent circuits provide us with 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 a circuit is to relate the membrane's discrete physical properties to its electrical properties. (A review of elementary circuit theory in Appendix A may be helpful before proceeding to the discussion that follows.)

Each Ion Channel Acts as a Conductor and Battery in Parallel

As described in Chapter 6, the lipid bilayer of the membrane is a poor conductor of ionic current because it is not permeable to ions. 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} cm^2. If the membrane were composed solely of lipid bilayer, its electrical conductance would be only about 1 pS. In reality, however, the membrane contains thousands of resting ion channels through which ions constantly diffuse, so that the actual conductance of the membrane at rest is about 40,000 pS or 40×10^{-9} S, ie, 40,000 times greater than it would be if no ion channels were present.

In an equivalent circuit each K^+ channel can be represented as a resistor or conductor of ionic current with a single-channel conductance of γ_K (remember, conductance = 1/resistance) (Figure 7-5). If there were no K^+ concentration gradient, the current through the K^+ channel would be given by Ohm's law: $i_K = \gamma_K \times V_m$. Since there is normally a K^+ concentration gradient, there will be a chemical force driving K^+ across the membrane. In the equivalent circuit this chemical force is represented by a battery, whose electromotive force is given by the Nernst potential for K^+, E_K (Figure 7-6). (A source of electrical potential is called an *electromotive force* and an electromotive force generated by a difference in chemical potentials is called a *battery*.)

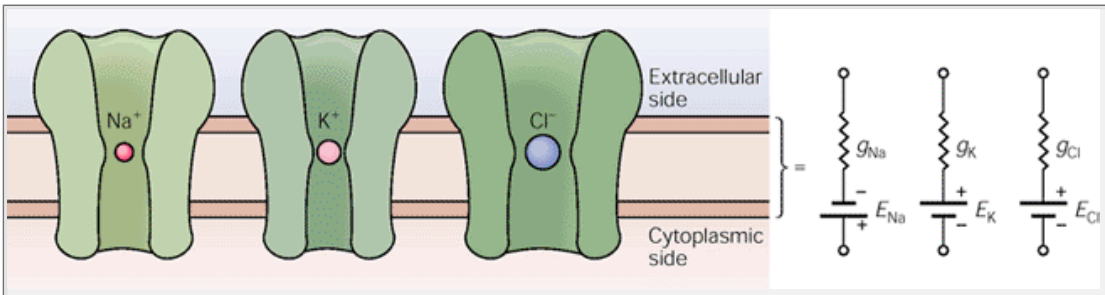

Figure 7-8 Each population of ion channels selective for Na^+, K^+, or Cl^- can be represented by a battery in series with a conductor. Note the directions of poles of batteries, indicating a negative electromotive force for K^+ and Cl^- and a positive one for Na^+.

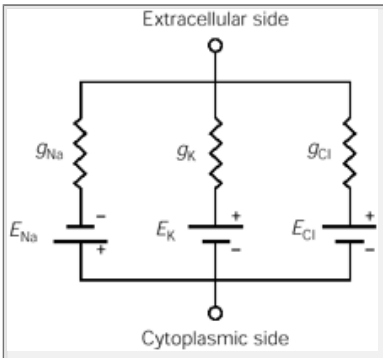

Figure 7-9 The passive current flow in a neuron can be modeled using an electrical equivalent circuit. The circuit includes elements representing the ion-selective membrane channels and the short-circuit pathways provided by the cytoplasm and extracellular fluid.

In the absence of voltage across the membrane the normal K^+ concentration gradient will cause an outward K^+ current flow. According to our conventions for electrical current flow an outward movement of positive charge corresponds to a positive electric current. From the Nernst equation, we also saw that when the concentration gradient for a positively charged ion, such as K^+, is directed outward (ie, there is a higher K^+ concentration inside than outside the cell), 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).

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

$$i_K = (\gamma_K \times V_m) - (\gamma_K \times E_K) = \gamma_K \times (V_m - E_K).$$

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

So far we have used two terms to indicate the ability of ions to cross membranes: permeability and conductance. Although they are related, we should be careful not to confuse them. The *permeability* of a membrane to an ion is an intrinsic property of the membrane that is a measure of the ease with which the ion passes through the membrane (in units of cm/s). Permeability depends only on the types and numbers of ion channels present in the membrane. *Conductance*, on the other hand, measures the ability of the membrane (or channel) to carry electrical current (in units of 1/ohms). Since current is carried by ions, the conductance of a membrane will depend not only on the properties of the membrane but also on the concentration of ions in solution. A membrane can have a very high permeability to K^+ ions, but if there is no K^+ in solution there can be no K^+ current flow and so the conductance of the membrane will be zero. In practice, permeability is used in the Goldman equation whereas conductance is used in electrical measurements and equivalent circuits.

A cell membrane has many resting K^+ channels, all of which can be combined into a single equivalent circuit consisting of a conductor in series with a battery (Figure 7-7). 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 N of resting K^+ channels multiplied by the conductance of an individual K^+ channel (γ_K):

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

Since 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 (Figure 7-7).

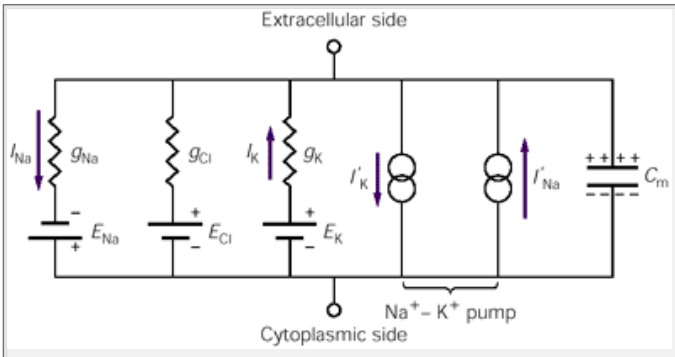

Figure 7-10 Under steady state conditions the passive Na^- and K^+ currents are balanced by active Na^+ and K^+ fluxes (I'_{Na} and I'_K) driven by the Na^+-K^+ pump. The lipid bilayer endows the membrane with electrical capacitance (C_m). Note I'_{Na} is 50% greater than I_K (and therefore INa is 50% greater than IK) since the Na^+-K^- pump transports three Na^+ ions out for every two K^+ ions it transports into the cell.

Box 7-2 Using the Equivalent Circuit Model to Calculate Resting Membrane Potential

The equivalent circuit model of the resting membrane can be used to calculate the resting potential. To simplify the calculation we shall initially ignore Cl^- channels and begin with just two types of passive channels, K^+ and Na^+, as illustrated in Figure 7-11. Moreover, we ignore the electrogenic influence of the Na^+-K^+ pump because it is small. Because we will consider only steady-state conditions, where V_m is not changing, we can also ignore membrane capacitance. (Membrane capacitance and its delaying effect on changes in V_m are discussed in Chapter 8.) Because there are more passive channels for K^+ than for Na^+, the membrane conductance for current flow carried by K^+ is much greater than that for Na^+. In the equivalent circuit in Figure 7-11, g_K is 20 times higher than g_{Na} (10×10^{-6} S compared to 0.5×10^{-6} S). Given these values and the values of E_K and E_{Na}, the membrane potential, V_m, is calculated 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_{Na} is equal and opposite to I_K:

$$-I_{Na} = I_K$$

or

$$I_{Na} + I_K = 0 \qquad \textbf{(7-1)}$$

We can easily calculate I_{Na} and I_K in two steps. First, we add up the separate potential differences across the Na^+ and K^+ branches of the circuit. Going from the inside to the outside across the Na^+ branch, the total potential difference is the sum of the potential differences across E_{Na} and across g_{Na}:*

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

Similarly, for the K^+ conductance branch

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

Next, we rearrange and solve for I:

$$I_{Na} = g_{Na} \times (V_m - E_{Na}) \qquad \textbf{(7-2a)}$$
$$I_K = g_K \times (V_m - E_K) \qquad \textbf{(7-2b)}$$

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. 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).

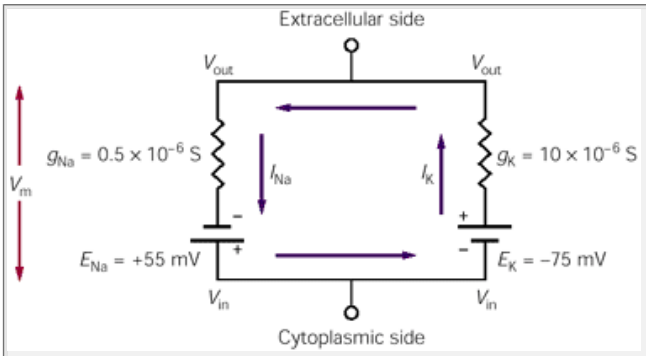

Figure 7-11 This electrical equivalent circuit omits the Cl^- pathway and Na^+-K^+ pump for simplicity in calculating the resting membrane potential.

In Equation 7-1 we saw that $I_{Na} + I_K = 0$. If we now substitute Equations 7-2a and 7-2b for I_{Na} and I_K in Equation 7-1, multiply through, and rearrange, we obtain the following expression:

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

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

$$V_m = \frac{(E_{Na} \times g_{Na}) + (E_K \times g_K)}{g_{Na} + g_K}. \qquad (7\text{-}3)$$

From this equation, using the values in our equivalent circuit (Figure 7-11), we calculate V_m = -69 mV.

Equation 7-3 states that V_m will approach the value of the ionic battery that is associated with the greater conductance. This principle can be illustrated by considering what happens during the action potential. At the peak of the action potential g_K is essentially unchanged from its resting value, 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 example shown in Figure 7-11 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 7-3 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, since g_{Na} is now 25-fold greater than g_K, the Na^+ battery becomes much more important than the K^+ battery in determining V_m.

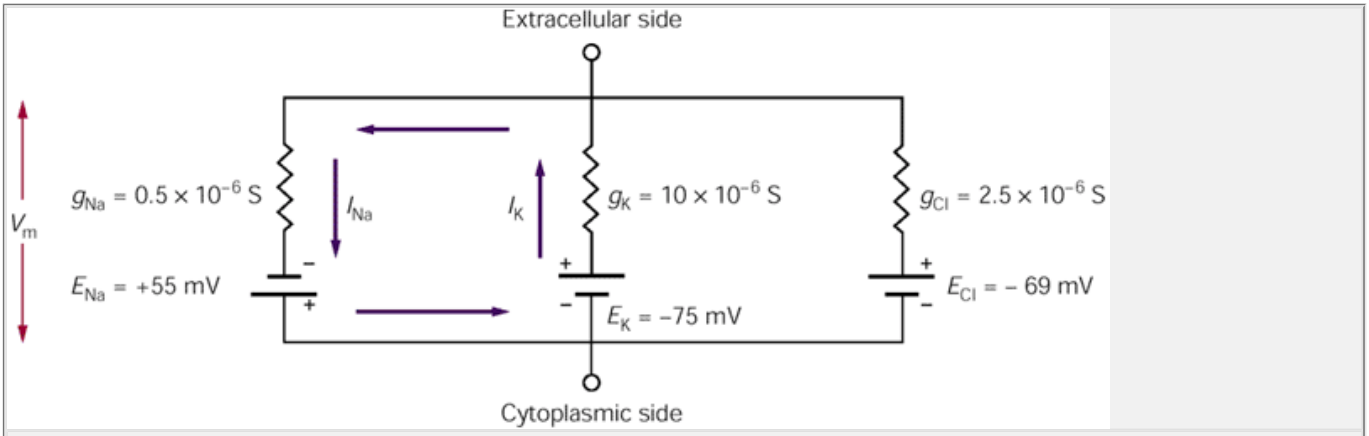

Figure 7-12 This electrical equivalent circuit includes the Cl^- pathway. However, no current flows through the Cl^- channels in this example because V_m is at the Cl^- equilibrium (Nernst) potential.

The real resting membrane has open channels not only for Na^+ and K^+, but also for Cl^-. One can derive a more general equation for V_m, following the steps outlined above, from an equivalent circuit that includes a conductance pathway for Cl^- with its associated Nernst battery (Figure 7-12):

$$V_m = \frac{(E_{Na} \times g_{Na}) + (E_K \times g_K) + (E_{Cl} \times g_{Cl})}{g_{Na} + g_K + g_{Cl}}. \qquad (7\text{-}4)$$

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 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 for Na^+ and K^+ only (Figure 7-11) and for all three ions (Figure 7-12). 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. In the circuit in Figure 7-12, 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 we include g_{Cl} and E_{Cl} from Figure 7-12 in the calculation of V_m, the calculated value of V_m does not differ from that for Figure 7-11. On the other hand, if Cl^- were not passively distributed but actively transported out of the cell, then E_{Cl} would be more negative than -69 mV. Adding the Cl^- pathway to the calculation would then shift V_m to a slightly more negative value.

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_l and replacing the battery for each conductance channel with a single battery whose value, E_l, is that predicted by Equation 7-4 (Figure 7-13). This simplification will prove useful when we consider the effects of gated channels in later chapters.

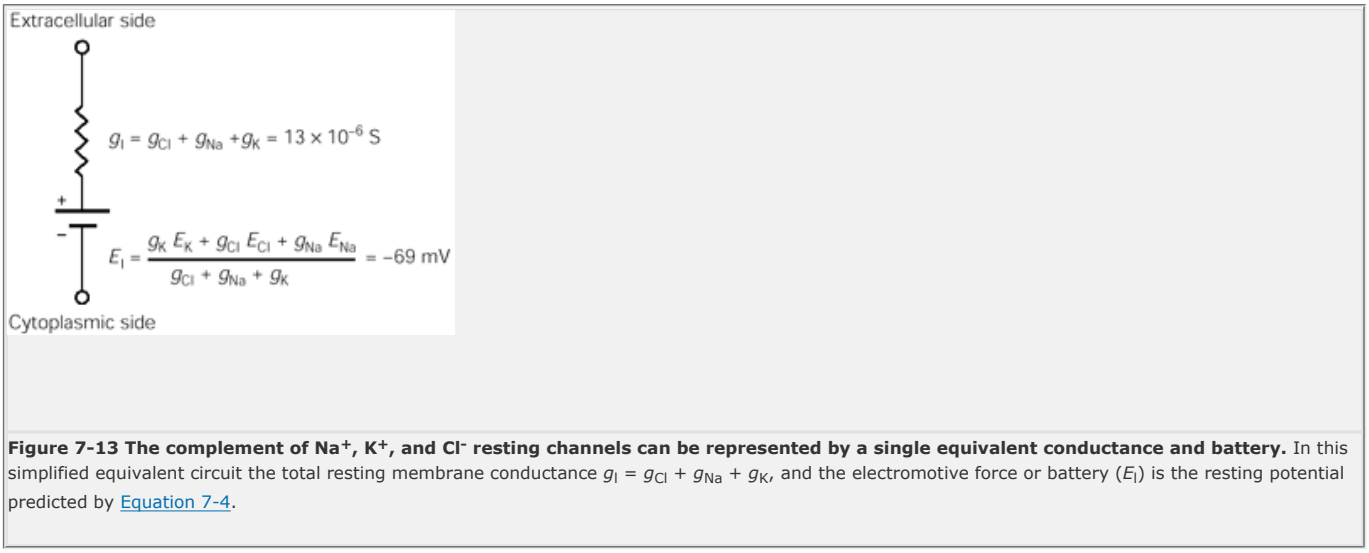

Figure 7-13 The complement of Na^+, K^+, and Cl^- resting channels can be represented by a single equivalent conductance and battery. In this simplified equivalent circuit the total resting membrane conductance $g_l = g_{Cl} + g_{Na} + g_K$, and the electromotive force or battery (E_l) is the resting potential predicted by Equation 7-4.

P.136

P.137

P.138

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

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 (Figure 7-8). Since 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 channels into a simple equivalent circuit of a neuron.

To construct this circuit we need only 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 excellent conductors because they have relatively large cross-sectional areas and many ions available to carry charge. Both can be approximated by a *short circuit*— a conductor with zero resistance (Figure 7-9).

The equivalent circuit of the neuron can be made more accurate by adding a current generator. As described earlier in this chapter, steady fluxes of Na^+ and K^+ ions through the passive membrane channels are exactly counterbalanced by 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, can be added to the equivalent circuit in the form of a current generator (Figure 7-10).

Finally, we can complete the equivalent circuit of the neuron by incorporating its *capacitance*, the third important passive electrical property of the neuron. Capacitance is the property of an electric nonconductor (insulator) that permits the storage of charge when opposite surfaces of the nonconductor are maintained at a difference of potential. For the neuron, the nonconductor (or capacitor) is the cell membrane, which separates the cytoplasm and extracellular fluid, both of which are highly conductive environments. Strictly speaking, the membrane is a leaky capacitor because it is penetrated by ion channels. However, since the density of the ion channels is low, the insulating portion of the membrane—the lipid bilayer—occupies at least 100 times the area of all the ion channels combined. Membrane capacitance is included in the equivalent circuit in Figure 7-10.

The electrical potential difference across a capacitor, V, is expressed as:

$$V = Q/C,$$

where Q is the excess of positive or negative charges on each side of the capacitor and C is the capacitance. Capacitance is measured in units of farads, F, where a charge separation of 1 coulomb across a 1 farad capacitor produces a 1 volt potential difference.

A typical value of membrane capacitance for a nerve cell is about 1 $\mu F/cm^2$ of membrane area. 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 use of the equivalent circuit model of the neuron to analyze neuronal properties quantitatively is illustrated in Box 7-2.

An Overall View

The lipid bilayer, which is virtually impermeant to ions, is an insulator separating two conducting solutions, the cytoplasm and the extracellular fluid. Ions can cross the lipid bilayer only by passing through ion channels in the cell membrane. When the cell is at rest, the 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 in nerve cells is determined primarily by resting channels selective for K^+, Cl^-, and Na^+. In general, the membrane potential will be closest to the equilibrium (Nernst) potential of the ion (or ions) with the greatest membrane permeability. The permeability for an ion species is proportional to the number of open channels that allow passage of that ion.

At rest, the membrane potential is close to the Nernst potential for K^+, the ion to which the membrane is most permeable. The membrane is also somewhat permeable to Na^+, however, and therefore an influx of Na^+ drives the membrane potential slightly positive to the K^+ Nernst potential. At this potential the electrical and chemical driving forces acting on K^+ are no longer in balance, so K^+ diffuses out of the cell. These two passive fluxes are each counterbalanced by active fluxes driven by the Na^+-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 inside and outside the cell. Under most physiological conditions the bulk concentrations of Na^+, K^+, and Cl^- inside and outside the cell are constant. During signaling the changes in membrane potential

P.139

(action potentials, synaptic potentials, and receptor potentials) are caused by substantial changes in the membrane's relative 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, cause changes in the net charge separation across the membrane.

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[1]At the peak of the action potential threr is an instant in time when V_m is not changing and the Goldman equation is applicable.

*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 with their positive poles toward the inside of the membrane (eg, E_{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 K^+ battery.

8

Local Signaling: Passive Electrical Properties of the Neuron

John Koester

Steven A. Siegelbaum

WHILE ALL CELLS OF THE body have a membrane potential, only neurons (and muscle cells) generate electrical signals that can be conducted rapidly over long distances. In the last chapter we saw how these electrical signals are generated by the flux of ions across the cell membrane through specialized ion channels, and how to calculate the expected membrane potential for any set of ionic concentration gradients and membrane permeabilities using the Goldman equation.

This description does not, however, provide any information about *changes* in the membrane potential in response to a stimulus, since the Goldman equation applies only to the steady state when the voltage does not change. During signaling, when the neuron generates action potentials, synaptic potentials, or sensory generator potentials in response to a stimulus, the membrane voltage changes constantly. What determines the rate of change in potential? Will a brief synaptic current always produce a similar potential change, regardless of the size of the postsynaptic cell? What determines whether a stimulus will or will not produce an action potential?

Here we consider how a neuron's passive electrical properties and geometry, which are relatively constant, affect the cell's electrical signaling. In the next chapter we shall consider how the properties of the ion channels that generate the active ionic currents also help determine changes in membrane potential.

Neurons have three passive electrical properties that are important to electrical signaling: the resting membrane resistance, the membrane capacitance, and the intracellular axial resistance along axons and dendrites. Because these elements provide the return pathway to complete the electrical circuit when active currents flow into or out of the cell, they determine the time course and amplitude of the synaptic potential change generated by the synaptic current. They also determine whether a synaptic potential generated in a dendrite will result in a suprathreshold depolarization at the trigger zone on the axon hillock. Still further, the passive properties influence the speed at which an action potential is conducted.

Input Resistance Determines the Magnitude of Passive Changes in Membrane Potential

The difference between the effects of passive and active properties of neurons can be demonstrated by injecting

current pulses into the cell body (see Box 7-1). Injecting a negative charge through an electrode increases the charge separation across the membrane, making the membrane potential more negative, or hyperpolarized. The larger the negative current, the greater is the hyperpolarization. In most neurons there is a linear relation between the size of the negative current and the steady-state hyperpolarization (Figure 8-1). The relation between current and voltage defines a resistance, R_{in}, the neuron's *input resistance.*

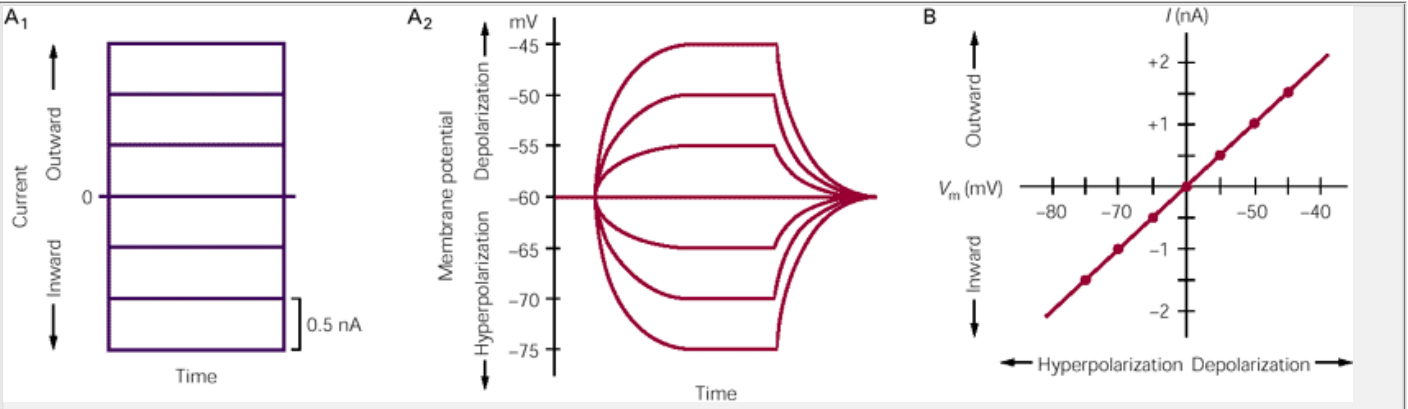

Figure 8-1 Current-voltage relationships. By passing subthreshold, graded, inward and outward current pulses into a cell, one can determine the relationship between current injected into the cell and the resulting changes in membrane potential, V_m.

A. Increases in outward or inward current pulses (**A**$_1$) produce proportional and symmetrical changes in V_m (**A**$_2$). Note that the potential changes more slowly than the step current pulses.

B. An *I-V* curve is obtained by plotting the steady state voltage against the injected current. The slope of the *I-V* curve defines the input resistance of the neuron. The *I-V* curve shown here is linear; V_m changes by 10 mV for every 1 nA change in current, yielding a resistance of 10 mV/1 nA, or 10 × 10^6 ω (10 Mω).

Likewise, when a positive charge is injected into the cell, producing depolarization, the neuron behaves as a simple resistor, but only over a limited voltage range. A large enough positive current will produce a depolarization that exceeds threshold, at which point the neuron generates an action potential. When this happens the neuron no longer behaves as a simple resistor because of the special properties of its voltage-gated channels considered in Chapter 9. Still, much of a neuron's behavior in the hyperpolarizing and subthreshold depolarizing range of voltages can be explained by simple equivalent circuits made up of resistors, capacitors, and batteries.

The input resistance of the cell determines how much the cell will depolarize in response to a steady current. The magnitude of the depolarization, δV, is given by Ohm's law:

$$\Delta V = I \times R_{in}.$$

Thus, of two neurons receiving identical synaptic current inputs, the cell with the higher input resistance will show a greater change in membrane voltage. For an idealized spherical neuron with no processes, the input resistance depends on both the density of the resting ion channels in the membrane (that is, the number of channels per unit area of membrane) and the size of the cell. The larger the neuron, the greater will be its membrane surface area and the lower the input resistance, since there will be more resting channels to conduct ions.

To compare the membrane properties of neurons of differing sizes, electrophysiologists often use the resistance of a unit area of membrane, the *specific membrane resistance,* R_m, measured in units of ωcm^2. The specific membrane resistance depends only on the density of the resting ion channels (the number of channels per square centimeter) and their conductance.

To obtain the total input resistance of the cell we *divide* the specific membrane resistance by the membrane area of the cell because the greater the area of a cell, the lower its resistance. For the spherical neuron we obtain

$$R_{in} = R_m/4\pi a^2,$$

where *a* is the radius of the neuron. Thus, for a spherical cell the input resistance is inversely proportional to the square of the radius. For a real neuron with extensive dendrites and axons, the input resistance also depends

P.142

on the membrane resistance of its processes as well as on the intracellular cytoplasmic resistance between the cell body and those processes (discussed below).

Membrane Capacitance Prolongs the Time Course of Electrical Signals

In Figure 8-1 the magnitude of the steady state changes in the cell's voltage in response to subthreshold current resembles the behavior of a simple resistor, but the *time course* of the changes does not. A true resistor responds to a step change in current with a similar step change in voltage, but the cell in Figure 8-1 shows a voltage response that rises and decays more slowly than the step change in current. This property of the membrane is due to its *capacitance.*

To understand how the capacitance slows down the voltage response we need to recall that the voltage across a capacitor is proportional to the charge stored on the capacitor:

$$V = Q/C,$$

where Q is the charge in coulombs and C is the capacitance in farads. To alter the voltage, charge must either be added or removed from the capacitor:

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

The change in charge (δQ) is the result of the flow of current across the capacitor (I_c). Since current is the flow of charge per unit time (I_c = δQ/δt), we can calculate the change in voltage across a capacitor as a function of current and the time that the current flows (δt):

$$\Delta V = I_c \cdot \Delta t/C. \qquad \textbf{(8-1)}$$

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

Capacitance is directly proportional to the area of the plates of the capacitor. The larger the area of a capacitor, the more charge it will store for a given potential difference. The value of the capacitance also depends on the insulation medium and the distance between the two plates of the capacitor. Since all biological membranes are composed of lipid bilayers with similar insulating properties that provide a similar separation between the two plates (4 nm), the specific capacitance per unit area of all biological membranes, C_m, has the same value, approximately 1 μF/cm^2 of membrane. The total input capacitance of a spherical cell, C_{in}, is therefore given by the capacitance per unit area multiplied by the area of the cell:

$$C_{in} = C_m(4\pi a^2).$$

Because capacitance increases with the size of the cell, more charge, and therefore current, is required to produce the same change in membrane potential in a larger neuron than in a smaller one.

According to Equation 8-1 the voltage across a capacitor continues to increase with time as long as a current pulse is applied. But in neurons the voltage levels off after some time (Figure 8-1) because the membrane of a neuron acts as a resistor (owing to its ion-conducting channels) and a capacitor (owing to the phospholipid bilayer) in parallel.

In the equivalent circuit developed in Chapter 7 to model current flow in the neuron, we placed the resistance and capacitance in parallel, since current crossing the membrane can flow either through ion channels (the resistive pathway) or across the capacitor (Figure 8-2). The resistive current carried by ions flowing across the membrane through ion channels—for example, Na^+ ions moving through Na^+ channels from outside to inside the cell—is called the *ionic membrane current.* The current carried by ions that change the net charge stored on the membrane is called the *capacitive membrane current.* An outward capacitive current, for example, adds positive charges to the inside of the membrane and removes

P.143

an equal number of positive charges from the outside of the membrane. The total current crossing the membrane, I_m, is given by the sum of the ionic current (I_i) and the capacitive current:

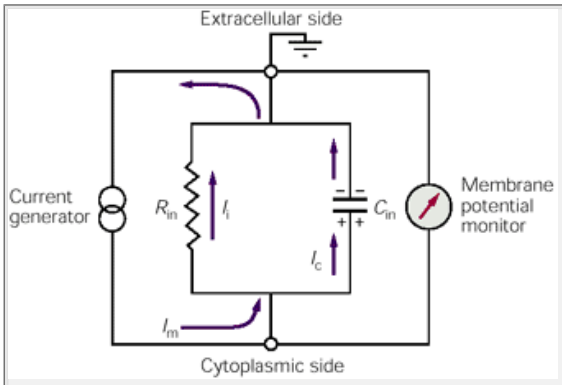

Figure 8-2 A simplified electrical equivalent circuit is used to examine the effects of membrane capacitance (C_{in}) on the rate of change of membrane potential in response to current flow. All resting ion channels are lumped into a single element (R_{in}). Batteries representing the electromotive forces generated by ion diffusion are not included because they affect only the absolute value of membrane potential, not the rate of change. This equivalent circuit represents the experimental setup shown in Box 7-1 (Figure 7-2C), in which pairs of electrodes are connected to the current generator and the membrane potential monitor.

$$I_m = I_i + I_c. \qquad \textbf{(8-2)}$$

The capacitance of the membrane has the effect of reducing the rate at which the membrane potential changes in response to a current pulse. If the membrane had only resistive properties, a step pulse of outward current passed across it would change the membrane potential instantaneously. On the other hand, if the membrane had only capacitive properties, the membrane potential would change linearly with time in response to the same step pulse 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 relation between V_m and time reflects a purely capacitive element, whereas the final slope and amplitude reflect a purely resistive element (Figure 8-3).

It is now easy to explain why a step change in current produces the slowly rising voltage waveform seen in Figure 8-3. Since the resistance and capacitance of the membrane are in parallel, the voltage across each element must always be the same and equal to the membrane potential. Assume that the membrane potential starts off at 0 mV and that at time t = 0 a depolarizing current step is applied from a current generator with magnitude I_m. Initially the voltage across the resistor and capacitor are both equal to 0 mV. Since the ionic current through the resistor is given by Ohm's law (I_i = V/R in), initially no current will flow through the resistor

(since V starts off at 0 mV) and all the current will flow through the capacitor (ie, $I_c = I_m$). As a result of the large initial capacitive current, the potential across the capacitor, and hence the membrane potential, will rapidly become more positive.

As V_m increases, the voltage difference across the membrane begins to drive current across the membrane resistance. As the voltage across the membrane becomes more positive, more current flows through the resistor and less flows across the capacitor, since I_c plus I_i is constant (and equal to I_m). As a result, the membrane potential begins to rise more slowly. Eventually, the membrane potential reaches a value where all the membrane current flows through the resistor ($I_i = I_m$). From Ohm's law this voltage is given by $V_m = I_m \cdot R_{in}$. At this point the capacitative current is zero and, following Equation 8-1, the membrane potential no longer changes. Once the step of current is turned off, the total membrane current I_m equals zero, so that the positive ionic current flowing through the resistor must flow back into the cell as an equal and opposite capacitive current, ie, $I_i = -I_c$. With no applied current, the charge on the capacitor dissipates by flowing in a loop around the circuit through the resistive pathway, and the membrane potential returns to zero.

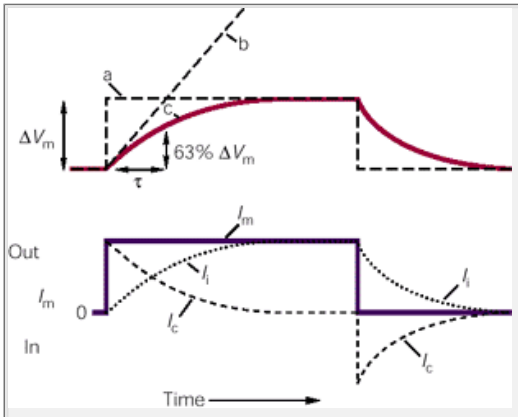

Figure 8-3 The rate of change in the membrane potential is slowed by the membrane capacitance. The response of the membrane potential (δV_m) to a step current pulse is shown in the **upper plot.** The actual shape of the response (**red line c**) combines the properties of a purely resistive element (**dashed line a**) and a purely capacitive element (**dashed line b**). The **lower plot** shows the total membrane current (I_m) and its ionic (I_i) and capacitive (I_c) components ($I_m = I_i = I_c$) in relation to the current pulse. The time taken to reach 63% of the final voltage defines the membrane time constant, τ. The time constants of different neurons typically range from 20 to 50 ms.

The rising phase of the potential change can be described by the following equation:

$$\Delta V_m(t) = I_m R_{in}(1 - e^{-t/\tau}), \qquad \textbf{(8-3)}$$

where e, which has a value of around 2.72, is the base of the system of natural logarithms, and τ is the *membrane time constant*, the product of the input resistance and capacitance of the membrane (R_{in} C_{in}). The time constant can be measured experimentally (Figure 8-3). It is the time it takes the membrane potential to rise to (1 - 1/e), about 63% of its steady state value. We shall return to the time constant when we consider the temporal summation of synaptic inputs in a cell in Chapter 12.

Membrane and Axoplasmic 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. Because the neuron's soma can be approximated

as a simple sphere, the effect of distance on the propagation of a signal does not matter. However, in electrical signaling along dendrites, axons, and muscle fibers, a subthreshold voltage signal decreases in amplitude with distance from its site of initiation. To understand how this attenuation occurs we will again have need of an equivalent circuit, one that shows how the geometry of a neuron influences the distribution of current flow.

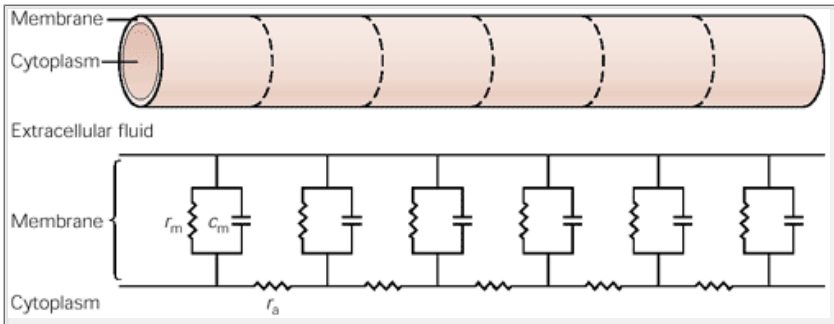

Figure 8-4 A neuronal process can be represented by an electrical equivalent circuit. The process is divided into unit lengths. Each unit length of the process is a circuit with its own membrane resistance (r_m) and capacitance (c_m). All the circuits are connected by resistors (r_a), which represent the axial resistance of segments of cytoplasm, and a short circuit, which represents the extracellular fluid.

Synaptic potentials that originate in dendrites are conducted along the dendrite toward the cell body and the trigger zone. The cytoplasmic core of a dendrite offers significant resistance to the longitudinal flow of current, because it has a relatively small cross-sectional area, and ions flowing down the dendrite collide with other molecules. The greater the length of the cytoplasmic core, the greater the resistance, since the ions experience more collisions the further they travel. Conversely, the larger the diameter of the cytoplasmic core, the lower will be the resistance in a given length, since the number of charge carriers at any cross section of dendrite increases with the diameter of the core.

To represent the incremental increase in resistance along the length of the dendritic core, the dendrite can be divided into unit lengths, each of which is a circuit with its own measurable membrane resistance and capacitance as well as an axial resistance within the cytoplasmic core. Because of its large volume, the extracellular fluid has only negligible resistance and therefore can be ignored. The equivalent circuit for this simplified model is shown in Figure 8-4.

If current is injected into the dendrite at one point, how will the membrane potential change with distance along the dendrite? For simplicity, consider the variation of membrane potential with distance after a constant-amplitude current pulse has been on for some time ($t >>> \tau$). Under these conditions the membrane potential will have reached a steady value, so capacitive current will be zero. When $I_c = 0$, all of the membrane current is ionic ($I_m = I_i$). The variation of the potential with distance thus depends solely on the relative values of the *membrane resistance*, r_m (units of ωcm), and the *axial resistance*, r_a (units of ω/cm), per unit length of dendrite.

The injected current flows out through several parallel pathways across successive membrane cylinders along the length of the process (Figure 8-5). Each of these current pathways is made up of two resistive components in series: the total axial resistance, r_x, and the membrane resistance, r_m, of the unit membrane cylinder. For each outflow pathway the total axial resistance is the resistance between the site of current injection and the site of the outflow pathway. Since resistors in series are added, $r_x = r_a x$, where x is the distance along the dendrite from the site of current injection. The membrane resistance, r_m, has the same value at each outflow pathway along the cell process.

More current flows across a membrane cylinder near the site of injection than at more distant regions because current always tends to follow the path of least resistance, and the total axial resistance, r_x, increases with distance from the site of injection (Figure 8-5). Because $V_m = I_m r_m$, the change in membrane potential produced by the current across a membrane cylinder at position x, $\delta V_m(x)$, becomes smaller with distance down the dendrite away from the current electrode. This decay with distance is exponential (Figure 8-5) and expressed by

$$\Delta V(x) = \Delta V_0 e^{-x/\lambda},$$

where λ is the membrane *length constant, x* is the distance from the site of current injection, and δV_0 is the change in membrane potential produced by the current flow at the site of injection ($x = 0$). The length constant λ is defined as the distance along the dendrite to the site where δV_m has decayed to $1/e$, or 37% of its initial value (Figure 8-5), and it is determined as follows:

$$\lambda = \sqrt{(r_m/r_a)}.$$

The better the insulation of the membrane (that is, the greater r_m) and the better the conducting properties of the inner core (the lower r_a), the greater the length constant of the dendrite. That is, current is able to spread

P.145

farther along the inner conductive core of the dendrite before leaking across the membrane.

To consider how neuronal geometry affects signaling, it will be helpful first to consider how the diameter of a process affects r_m and r_a. Both r_m and r_a are measures of resistance that apply to a 1 cm segment of an individual neuronal process with a certain radius α. The axial resistance of a neuronal process depends on the intrinsic resistive properties of the cytoplasm, expressed as the specific resistance, r, of a 1 cm^3 cube of cytoplasm (in units of ωcm), and the cross-sectional area of the process, which determines the total volume in a unit length of the process and hence the number of charge carriers. Thus, r_a is given by

$$r_a = \rho/\pi a^2, \qquad \textbf{(8-4)}$$

and r_a has the required units of ω/cm. The diameter of the process also affects r_m since the total number of channels in a unit length of membrane is directly proportional to both the channel density (number of channels per unit area) and the membrane area. Since r_m is inversely related to the total number of channels in a unit length of membrane and the area in a unit length of cylinder depends on the circumference, r_m is given by

$$r_m = R_m/2\pi a, \qquad \textbf{(8-5)}$$

where R_m is the specific resistance of a unit area of membrane (units of ωcm^2) and r_m has the units of ωcm.

Neuronal processes vary greatly in diameter, from as much as 1 mm for the giant axon of the squid down to 1 μm for fine dendritic branches in the mammalian brain. These variations in diameter control the efficiency of neuronal signaling because the diameter determines the length constant. For processes with similar intrinsic properties (that is with similar values of R_m and ρ), the larger the diameter of the process (dendrite or axon), the longer the length constant, because r_m/r_a is directly related to the radius (Equations 8-4 and 8-5). Thus, the length constant is expressed in terms of the intrinsic (size invariant) properties R_m and ρ as follows:

$$\lambda = \sqrt{\frac{R_m}{\rho} \cdot \frac{a}{2}}.$$

That is, the length constant is proportional to the square root of the radius (or diameter) of a process. Thus, thicker axons and dendrites will have longer length constants than do narrower processes and hence will transmit electrotonic signals for greater distances. Typical values for neuronal length constants range from 0.1 to 1.0 mm.

The length constant is a measure of the efficiency of the passive spread of voltage changes along the neuron, or *electrotonic conduction.* The efficiency of electrotonic conduction has two important effects on neuronal function. First, it influences *spatial summation*, the process by which synaptic potentials generated in different regions of the neuron are added together at the trigger zone, the decision-making component of the neuron (see Chapter 12).

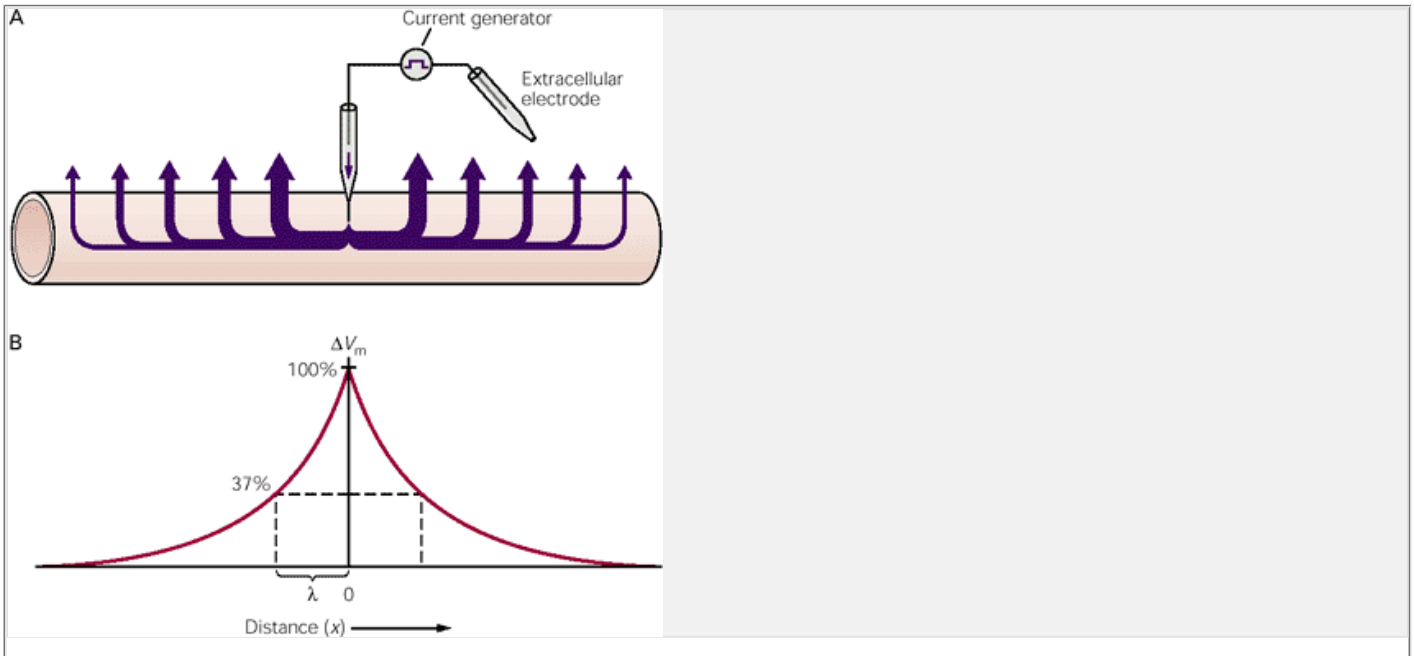

Figure 8-5 The voltage response in a passive neuronal process decays with distance due to electronic conduction. Current injected into a neuronal process by a microelectrode follows the path of least resistance to the return electrode in the extracellular fluid (**A**). The thickness of the arrows represents membrane current density at any point along the process. Under these conditions the change in V_m decays exponentially with distance from the site of current injection (**B**). The distance at which δV_m has decayed to 37% of its value at the point of current injection defines the length constant, λ.

Second, electrotonic conduction is a factor in the *propagation* of the action potential. Once the membrane at any point along an axon has been depolarized beyond threshold, an action potential is generated in that region in response to the opening of voltage-gated Na^+ channels (see Chapter 9). This local depolarization spreads electrotonically down the axon, causing the adjacent region of the membrane to reach the threshold for generating an action potential (Figure 8-6). Thus the depolarization spreads along the length of the axon by "local-circuit" current flow resulting from the potential difference between active and inactive regions of the axon membrane. In cells with longer length constants the local-circuit current has a greater spread and therefore the action potential propagates more rapidly.

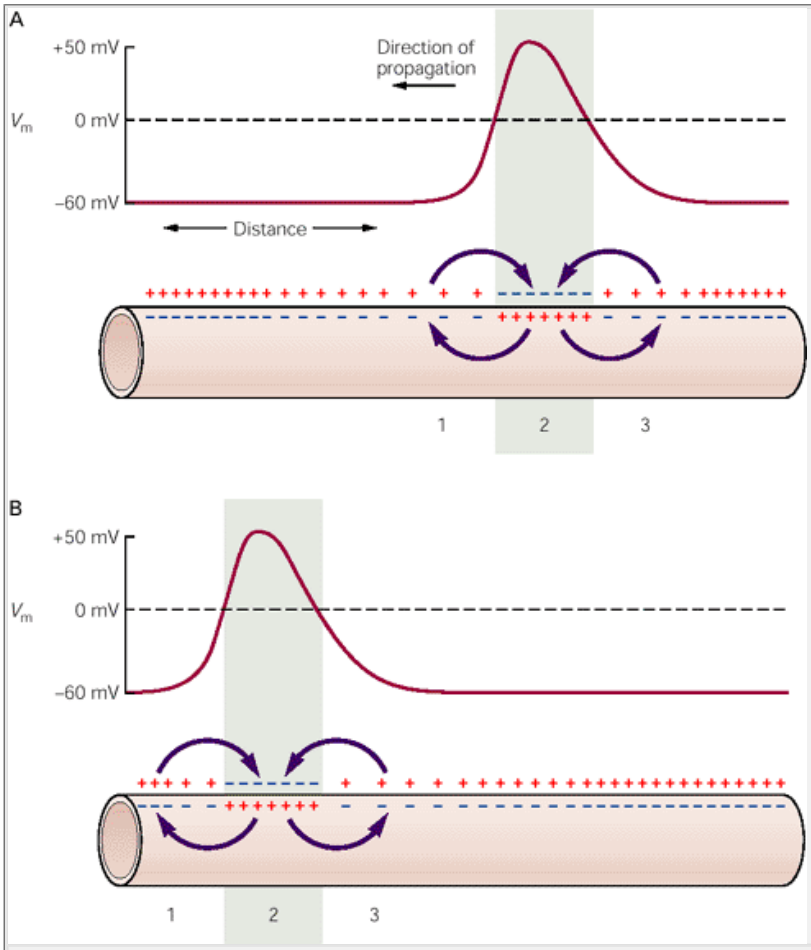

Figure 8-6 Passive conduction of depolarization along the axon contributes to propagation of the action potential.

A. The waveform of an action potential propagating from right to left. The difference in potential along the length of the axon creates a local-circuit current flow that causes the depolarization to spread passively from the active region (**2**) to the inactive region *ahead* of the action potential (**1**), as well as to the area *behind* the action potential (**3**). However, because there is also an increase in g_K in the wake of the action potential (see Chapter 9), the buildup of positive charge along the inner side of the membrane in area **3** is more than balanced by the local efflux of K^+, allowing this region of membrane to repolarize.

B. A short time later the voltage waveform and the current distributions have shifted down the axon and the process is repeated.

Large Axons Are More Easily Excited Than Small Axons by Extracellular Current Stimuli

In examination of a neurological patient for diseases of peripheral nerves the nerve often is stimulated by passing current between a pair of extracellular electrodes placed over the nerve, and the population of resulting action potentials (the *compound action potential*) is recorded farther along the nerve by a second pair of voltage-recording electrodes. In this situation the total number of axons that generate action potentials varies with the amplitude of the current pulse.

To drive a cell to threshold, the current must pass through the cell membrane. In the vicinity of the positive electrode, current flows across the membrane into the axon. It then flows along the axoplasmic core, eventually flowing out through more distant regions of axonal membrane to the second (negative) electrode in the extracellular fluid. For any given axon, most of the stimulating current bypasses the fiber, moving instead through other axons or through the low-resistance pathway provided by the extracellular fluid. The axons into which current can enter most easily are the most excitable.

In general, axons with the largest diameter have the lowest threshold for extracellular current. The larger the diameter of the axon, the lower the axial resistance to the flow of longitudinal current because of the greater number of intracellular charge carriers (ions) per unit length of the axon. Therefore a greater fraction of total current enters the larger axon, so it is depolarized more efficiently than a smaller axon. For these reasons, larger axons are recruited at low values of current; smaller-diameter axons are recruited only at relatively greater current strengths.

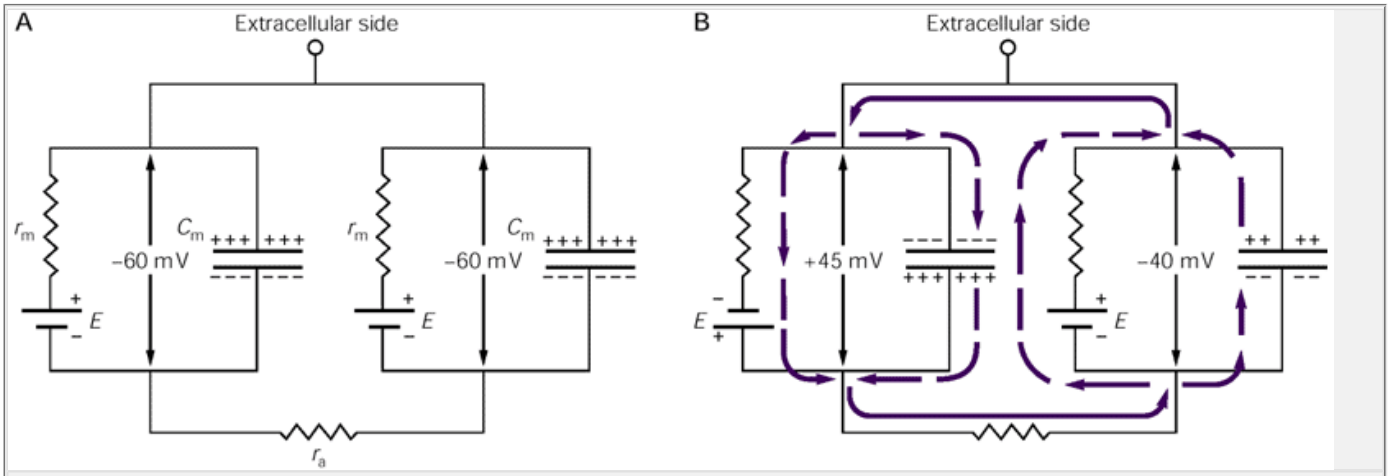

Figure 8-7 Axial resistance and membrane capacitance limit the rate of spread of depolarization during the action potential.

A. The electrical equivalent circuit represents two adjacent segments of the resting membrane of an axon connected by a segment of axoplasm (r_a).

B. An action potential is spreading from the membrane segment on the **left** to the segment on the **right.** Purple lines indicate pathways of current flow.

P.147

Passive Membrane Properties and Axon Diameter Affect the Velocity of Action Potential Propagation

The passive spread of depolarization during conduction of the action potential is not instantaneous. In fact, the electrotonic conduction is a rate-limiting factor in the propagation of the action potential. We can understand this limitation by considering a simplified equivalent circuit of two adjacent membrane segments connected by a segment of axoplasm (Figure 8-7). As described above, an action potential generated in one segment of membrane supplies depolarizing current to the adjacent membrane, causing it to depolarize gradually toward threshold. According to Ohm's law, the larger the axoplasmic resistance, the smaller the current flow around the loop ($I = V/R$) and the longer it takes to change the charge on the membrane of the adjacent segment.

Recall that since $\delta V = \delta Q/C$, the membrane potential changes slowly if the current is small because δQ changes slowly. Similarly, the larger the membrane capacitance, the more charge must be deposited on the membrane to change the potential across the membrane, so the current must flow for a longer time to produce a given depolarization. Therefore, the time it takes for depolarization to spread along the axon is determined by both the axial resistance, r_a, and the capacitance per unit length of the axon c_m (units F/cm). The rate of passive spread varies inversely with the product $r_a c_m$. If this product is reduced, the rate of passive spread increases and the action potential propagates faster.

Rapid propagation of the action potential is functionally important, and two distinct mechanisms have evolved to increase it. One adaptive strategy is to increase conduction velocity by increasing the diameter of the axon core. Because r_a decreases in proportion to the square of axon diameter, while c_m increases in direct proportion to diameter, the net effect of an increase in diameter is a decrease in $r_a c_m$. This adaptation has been carried to an extreme in the giant axon of the squid, which can reach a diameter of 1 mm. No larger axons have evolved, presumably because of the opposing need to keep neuronal size small so that many cells can be packed into a limited space.

A second mechanism for increasing conduction velocity is myelination of the axon, the wrapping of glial cell membranes around an axon (see Chapter 4). This process is functionally equivalent to increasing the thickness of the axonal membrane by as much as 100 times. Because the capacitance of a parallel-plate capacitor such as the membrane is inversely proportional to the thickness of the insulation material, myelination decreases c_m and thus $r_a c_m$. Myelination results in a proportionately much greater decrease in $r_a c_m$ than does the same increase in the diameter of the axon core. For this reason, conduction in myelinated axons is typically faster than in nonmyelinated axons of the same diameter.

P.148

In a neuron with a myelinated axon the action potential is triggered at the nonmyelinated segment of membrane at the axon hillock. The inward current that flows through this region of membrane is then available to discharge the capacitance of the myelinated axon ahead of it. Even though the thickness of myelin makes the capacitance of the axon quite small, the amount of current flowing down the core of the axon from the trigger zone is not enough to discharge the capacitance along the *entire* length of the myelinated axon.

To prevent the action potential from dying out, the myelin sheath is interrupted every 1-2 mm by bare patches of axon membrane about 2 μm in length, the nodes of Ranvier (see Chapter 4). Although the area of membrane at each node is quite small, the nodal membrane is rich in voltage-gated Na^+ channels and thus can generate an intense depolarizing inward Na^+ current in response to the passive spread of depolarization down the axon. These regularly distributed nodes thus boost the amplitude of the action potential periodically, preventing it from dying out.

The action potential, which spreads quite rapidly along the internode because of the low capacitance of the myelin sheath, slows down as it crosses the high-capacitance region of each bare node. Consequently, as the action potential moves down the axon it jumps quickly from node to node (Figure 8-8A). For this reason, the action potential in a myelinated axon is said to move by *saltatory conduction* (from the Latin *saltare*, to jump). Because ionic membrane current flows only at the nodes in myelinated fibers, saltatory conduction is also favorable from a metabolic standpoint. Less energy must be expended by the Na^+-K^+ pump in restoring the Na^+ and K^+ concentration gradients, which tend to run down as a result of action-potential activity.

Various diseases of the nervous system, such as multiple sclerosis and Guillain-Barre syndrome, cause demyelination (see Box 4-1). Because the lack of myelin slows down the conduction of the action potential, these diseases can have devastating effects on behavior (Chapter 35). As an action potential goes from a myelinated region to a bare stretch of axon, it encounters a region of relatively high c_m and low r_m. The inward current generated at the node just before the demyelinated segment may be too small to provide the capacitive current required to depolarize the demyelinated membrane to threshold. In addition, this local-circuit current does not spread as far as it normally would because it is flowing into a segment of axon that, because of its low r_m, has a short length constant (Figure 8-8B). These two factors can combine to slow, and in some cases actually block, the conduction of action potentials.

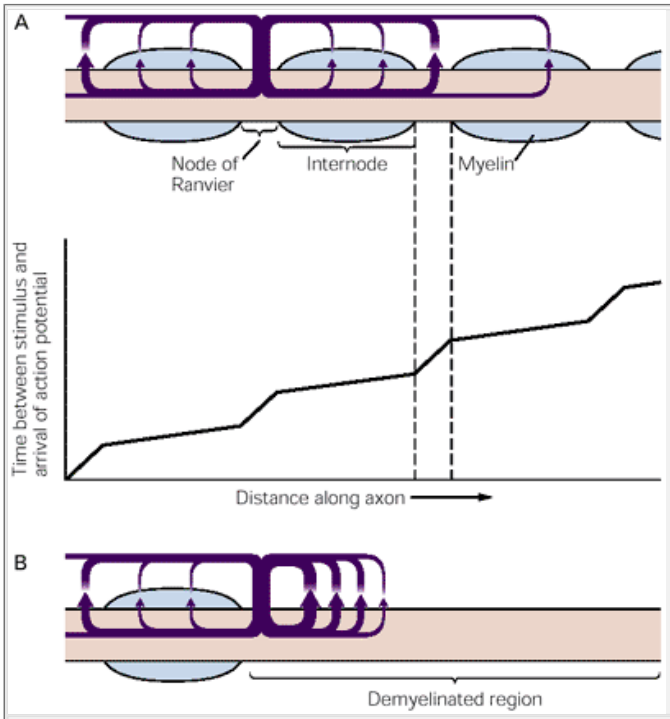

Figure 8-8 Action potentials in myelinated nerves are regenerated at the nodes of Ranvier.

A. In the axon capacitive and ionic membrane current densities (membrane current per unit area of membrane) are much higher at the nodes of Ranvier than in the internodal regions. The density of membrane current at any point along the axon is represented by the thickness of the **arrows**. Because of the higher capacitance of the axon membrane at the unmyelinated nodes, the action potential slows down as it approaches each node and thus appears to skip rapidly from node to node.

B. In regions of the axon that have lost their myelin, the spread of the action potential is slowed down or blocked. The local-circuit currents must charge a larger membrane capacitance and, because of the low r_m, they do not spread well down the axon.

An Overall View

Two competing needs determine the functional design of neurons. First, to maximize the computing power of the nervous system, neurons must be small so that large numbers of them can fit into the brain and spinal cord. Second, to maximize the ability of the animal to respond to changes in its environment, neurons must conduct signals rapidly. These two design objectives are constrained by the materials from which neurons are made.

Because the nerve cell membrane is very thin and is surrounded by a conducting medium, it has a very high capacitance, which slows down the conduction of voltage

signals. In addition, the currents that change the charge on the membrane capacitance must flow through a relatively poor conductor—a thin column of cytoplasm. The ion channels that give rise to the resting potential also degrade the signaling function of the neuron. They make the cell leaky and, together with the high membrane capacitance, they limit the distance that a signal can travel passively.

As we shall see in the next chapter, neurons use voltage-gated channels to compensate for these physical constraints when generating all-or-none action potentials, which are continually regenerated and conducted without attenuation. For pathways in which rapid signaling is particularly important, the conduction velocity of the action potential is enhanced either by myelination or by an increase in axon diameter, or by both.

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