7 Neurons as Conductors of Electricity

ACTION POTENTIALS PROPAGATE ALONG AXONS by the longitudinal spread of current. As each region of the membrane generates an all-or-nothing impulse, it depolarizes and excites the adjacent, not yet active region. This depolarization gives rise to a new regenerative impulse. To understand impulse propagation, as well as synaptic transmission and integration, one has to know how electrical currents spread passively along a nerve.

As current spreads along a nerve axon or dendrite, it becomes attenuated with distance. This attenuation depends on a number of factors, principally the diameter and membrane properties of the fiber. Longitudinal current spreads farther along a fiber with large diameter and high membrane resistance. The electrical capacitance of the membrane influences the time course of the electrical signals and usually their spatial spread as well. To estimate how far a subthreshold potential change will spread, one needs to know the geometry and membrane characteristics of the neuron, and, in addition, the time course of the potential change.

The axons of many vertebrate nerve cells are covered by a high-resistance, low-capacitance myelin sheath. This sheath acts as an effective insulator and forces currents associated with the nerve impulse to flow through the membrane at intervals where the sheath is interrupted (nodes of Ranvier). The impulse jumps from one such node to the next, and thereby its conduction velocity is increased. Myelinated nerves occur in pathways in the nervous system where speed of conduction is important.

Electrical activity can also pass between neurons through specialized regions of close membrane apposition called gap junctions. Pathways for current flow in such regions are provided by intercellular channels called connexons.

PASSIVE ELECTRICAL PROPERTIES OF NERVE AND MUSCLE MEMBRANES

The permeability properties of nerve cell membranes and the way in which these properties produce regenerative electrical responses have been discussed in the preceding chapters. In this chapter we describe in more detail how currents spread along nerve fibers to produce local graded potentials.

The **passive electrical properties** of neurons, specifically the resistance and capacitance of the nerve cell membrane, and the resistance of the cytoplasm, play a major role in signaling. At sensory end organs they are the link between the stimulus and the production of impulses; along axons they allow the impulse to spread and propagate; at synapses they enable the postsynaptic neuron to add and subtract synaptic potentials that arise from numerous converging inputs—some close to the cell body, others on remote dendritic sites. To understand phenomena such as impulse initiation and propagation and interactions between synaptic inputs, it is necessary to know how electrical signals spread along nerve processes. The discussion that follows deals primarily with the spread of current along nerve fibers of uniform diameter—that is, along cylindrical conductors. Further, throughout the discussion we will assume that in the absence of regenerative action potentials the nerve fiber membranes are indeed passive—that is, that changes in potential below action potential threshold do not activate any voltage-sensitive channels that would change the membrane resistance. The concepts we develop are also applicable in principle to more complex structures, such as arborizations of axon terminals or branched dendritic trees with nonuniform electrical properties.[1,2] Such complex structures play an important role in nervous system function, but quantitative treatments of their electrical properties require more complicated analyses.

Nerve and Muscle Fibers as Cables

A cylindrical nerve fiber has the same formal components as an undersea cable—namely, a central or core conductor and an insulating sheath surrounded by a conducting medium. However, the two systems are quantitatively very dissimilar. In a cable, the core conductor is usually copper, which has a very high conductance, and the surrounding insulating sheath is neoprene, plastic, or some other material of very high resistance. In addition, the sheath is usually relatively thick, so it has a very low capacitance (Appendix A). Voltage applied to one end of such a cable will spread an immense distance because the resistance to longitudinal current flow along the copper conductor is relatively low and virtually no current is lost through the insulating sheath. In a nerve fiber, on the other hand, the core conductor is a salt solution similar in concentration to that bathing the nerve and (compared with copper) is a poor conductor. Furthermore, the plasma membrane of the fiber is a relatively poor insulator and, being thin, has a relatively high capacitance. A voltage signal applied to one end of a nerve fiber, then, will fail to spread very far for two reasons: (1) The core material has a low conductance; that is, the resistance to current flow down the fiber is high. (2) Current that starts off flowing down the axoplasm is lost progressively along the fiber by outward leakage through the poorly insulating plasma membrane.

The analysis of current flow in cables was developed by Lord Kelvin for application to transatlantic telephone transmission and refined by Oliver Heaviside in the late nineteenth century. Heaviside was the first to consider the effect of resistive leak through the insulation, equivalent to the membrane resistance in nerve, and made many other contributions to cable theory, including the concept of what he called impedance. Cable theory was first applied coherently to nerve fibers by Hodgkin and Rushton,[3] who used extracellular electrodes to measure the spread of applied current along lobster axons. Later, intracellular electrodes were used in a number of nerve and muscle fibers for similar studies.

Here we consider how the spread of current along a cylindrical axon is affected by the resistive properties of the membrane and of the axoplasm. The main requirement is that we keep in mind Ohm's law: A given amount of current, i, passed through a resistor, r, produces a voltage $v = ir$ (Appendix A). Later in this chapter we consider the additional effects of membrane capacitance on the magnitude and time course of the current spread.

[1]Rall, W. 1967. *J. Neurophysiol.* 30: 1138–1168.

[2]Lev-Tov, A., et al. 1983. *J. Neurophysiol.* 50: 399–412.

[3]Hodgkin, A. L., and Rushton, W. A. H. 1946. *Proc. R. Soc. Lond. B* 133: 444–479.

Flow of Current in a Cable

One way to gain an intuitive feeling about how current spreads in a cable is to think of the spread of heat along a metal rod surrounded by insulation and immersed in a conducting material (such as water). If one end of the rod is heated continuously, heat spreads along the rod and, as it spreads, is lost to the surrounding medium. At progressively greater distances from the heated end, the temperature becomes progressively lower; as the temperature decreases with distance, the rate at which heat is lost decreases as well. Assuming that the surrounding medium is a good heat conductor, the distance over which the heat spreads depends primarily on (1) the conductivity of the rod and (2) the effectiveness of the insulation in preventing heat loss.

Flow of electrical current in a cable can be described in similar terms. A voltage applied to one end of the cable causes current to flow along the core, some of which is lost to the surrounding medium through the insulation. At progressively greater distances from the end, less and less current remains. The distance along which the current spreads depends on the conductivity of the core and the effectiveness of the insulation in preventing current loss. Low-resistance insulation allows all the current to leak out before it can spread very far. A larger-resistance insulation allows the current to flow a greater distance along the core.

In an axon, current is carried by the flow of ions: If we inject current from a microelectrode into a nerve fiber (e.g., a lobster axon), as shown in Figure 7.1A, positive charges flowing into the axoplasm from the tip of the microelectrode repel other cations and attract anions. By far the most abundant small ion in the axoplasm is potassium, which therefore carries most of the current. The current flows longitudinally along the axon,

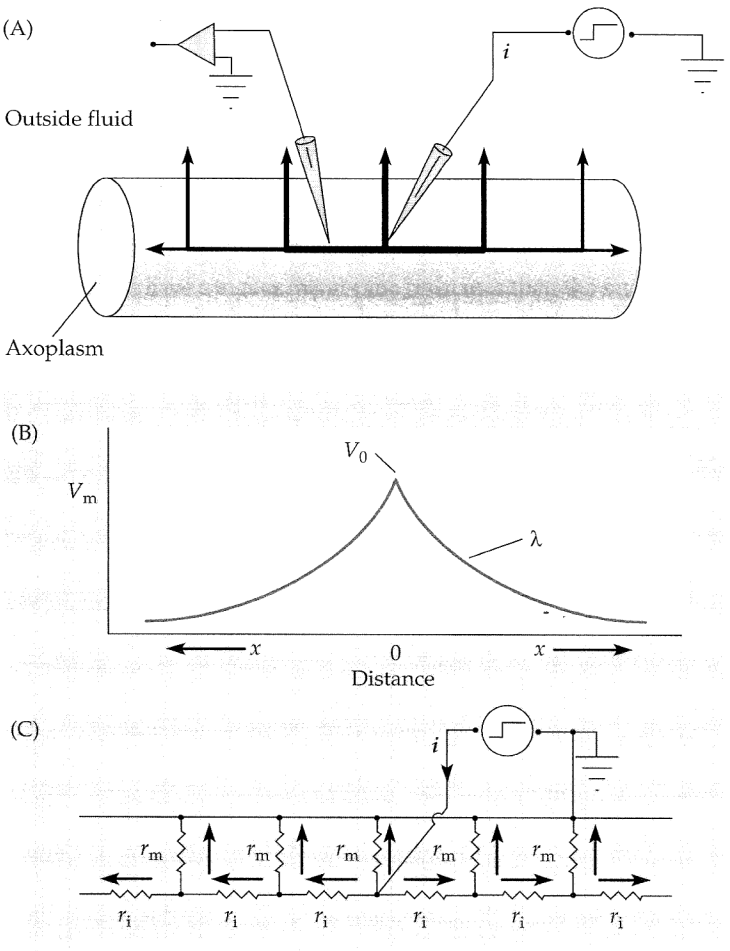


FIGURE 7.1 Pathways for Current Flow in an axon. (A) Current flow (i) across the membrane produced by a steady injection of current from a microelectrode. Thickness of the arrows indicates current density at various distances from the point of injection. The second electrode (left) records membrane potential at various distances from the current electrode. (B) Potential (V_m) measured along the axon as a function of distance (x) from the point of current injection. Decay of voltage is exponential, with a length constant λ. (C) Equivalent electrical circuit, assuming zero resistance in the external fluid and ignoring membrane capacitance. r_i = longitudinal resistance of axoplasm per unit length; r_m = membrane resistance of a unit length.

and as it spreads away from the electrode some is lost by ion movements through the membrane. The distance the potential spreads along the axon depends on the resistance of the cell membrane relative to that of the axoplasm. A low-resistance membrane with high ionic conductances allows current to leak out before it can spread very far; a larger-resistance membrane allows a greater portion of the current to spread laterally before escaping to the external solution.

Input Resistance and Length Constant

In Figure 7.1A the relative amounts of current flowing across the membrane at various distances from the current electrode are indicated roughly by the thickness of the arrows. The potential change produced across the membrane at any given distance is proportional to the current flow across the membrane at that point, in accordance with Ohm's law. Two questions arise from an experiment of this kind: (1) For a given amount of current injected into the pipette, how much voltage change will be produced at the electrode? (2) How far will this voltage change spread along the fiber? These questions can be answered by measuring the potential change with a second micropipette, which we can insert at various positions along the fiber, as indicated in Figure 7.1A. The results of such measurements are shown in Figure 7.1B. The current produces a change in potential that is greatest at the point of injection and falls off with distance on either side.

The decrease in potential with distance from the current electrode is exponential, so the potential (V_x) at any distance x on either side is given by

$$V_x = V_0 e^{-x/\lambda}$$

The peak potential change, V_0, is proportional to the size of the injected current. The constant of proportionality is known as the **input resistance** of the fiber, r_{input}. It is the average resistance presented by the fiber to the flow of current through the axoplasm and surface membrane to the extracellular solution. Thus, if the amount of current injected is i, then

$$V_0 = ir_{input}$$

The **length constant** of the fiber, λ, is the distance over which the potential falls to $1/e$ (37%) of its maximum value. The two parameters r_{input} and λ define how much depolarization is produced by a given amount of current, and how far that depolarization spreads along the fiber.

Membrane Resistance and Longitudinal Resistance

We can think of a cable as a series of resistive elements, r_m and r_i, connected in a chain (Figure 7.1C). The circuit is obtained by imagining that the axon is cut along its length into a series of short cylinders. The membrane resistance, r_m, represents the resistance across the cylinder wall; the longitudinal resistance, r_i, represents the internal resistance along the axoplasm from the midpoint of one cylinder to the midpoint of the next. Because nerves in a recording chamber are normally bathed in a large volume of fluid, the *extracellular* longitudinal resistance along the cylinders is represented as zero. This approximation is not always adequate in the central nervous system, where nerve axons, dendrites, and glial cells (Chapter 8) are closely packed, and pathways for extracellular current flow thereby are restricted. For our experiment, however, the assumption is valid and serves the purpose of keeping the algebra as simple as possible. Any length could be selected for the cylinders themselves; however, by convention, the resistances r_m and r_i are specified for a 1 cm length of axon. The membrane resistance, r_m, has the dimensions ohms × centimeters (Ωcm). The dimensions may seem strange until one realizes that membrane resistance *decreases* as the fiber length increases (more channels are available for current to leak through the membrane). Thus, the resistance in ohms of a given length of axon membrane is the resistance of a 1 cm length (r_m, in Ωcm) divided by the length (in cm). The dimensions of r_i are ohms per centimeter (Ω/cm), as expected.

Calculating Membrane Resistance and Internal Resistance

The length constant of the fiber depends on both r_m and r_i:

$$\lambda = \left(\frac{r_m}{r_i}\right)^{1/2}$$

This expression has the dimensions of centimeters as required, and it fulfills the intuitive expectation that the distance over which the potential change spreads should increase with increasing membrane resistance (which prevents loss of current across the membrane) and decrease with increasing internal resistance (which resists current flow along the core of the fiber).

Similarly, the input resistance depends on both parameters:

$$r_{input} = 0.5(r_m r_i)^{1/2}$$

Again the expression has the required dimensions (ohms), and tells us that the input resistance increases with both membrane resistance and internal resistance. The factor 0.5 arises because the axon extends in both directions from the point of current injection; each half has an input resistance equal to $(r_m r_i)^{1/2}$.

Knowing these relations, we can determine the resistive properties of the membrane and axoplasm from experiments such as that shown in Figure 7.1. After we have measured r_{input} and λ experimentally, it is a simple matter to rearrange the equations to calculate r_m and r_i:

$$r_m = 2r_{input}\lambda$$

$$r_i = \frac{2r_{input}}{\lambda}$$

Specific Resistance

The calculated values of r_m and r_i specify the resistive characteristics of a cylindrical segment of the axon 1 cm in length. They do not, however, provide precise information about the resistive properties of the membrane itself, or of the axoplasmic material, because these depend on the size of the fiber. All else being equal, a 1 cm length of small fiber should have a higher membrane resistance than the same length of larger fiber, simply because the smaller fiber has less membrane surface. On the other hand, the smaller fiber might contain a much higher density of ion channels and thereby have about the same resistance per unit length.

To compare one *membrane* to another we need to know the specific resistance (R_m) of each, which is the resistance of 1 cm^2 of membrane and has the units Ωcm^2. A 1 cm length of axon of radius a has an area of $2\pi a$ cm^2. Its membrane resistance (r_m) is obtained by dividing R_m by the membrane area: $r_m = R_m/2\pi a$. Turning the equation around, we get

$$R_m = 2\pi a r_m$$

R_m is important because it is independent of geometry and therefore enables us to compare the membrane of one cell with that of another of quite different size or shape.

In most neurons, R_m is determined primarily by the resting permeabilities to potassium and chloride (Chapter 5); these vary considerably from one cell to the next. The average value for R_m reported by Hodgkin and Rushton for lobster axons was about 2000 Ωcm^2; in other preparations, measurements range from less than 1000 Ωcm^2 for membranes with a large number of channels through which ions can leak to more than 50,000 Ωcm^2 for membranes with relatively few such channels.

The specific resistance (R_i) of the axoplasm is the internal longitudinal resistance of a 1 cm length of axon 1 cm^2 in cross-sectional area. It is also independent of geometry and is a measure of how freely ions migrate through the intracellular space. To calculate R_i from r_i for a cylindrical axon, recall that the resistance along the core of a cylinder decreases as the cross-sectional area increases. Therefore, the resistance of a 1 cm length of

axon (r_i) is obtained by dividing R_i by the cross-sectional area of the axon: $r_i = R_i/\pi a^2$. Again we can turn the equation around, to get

$$R_i = r_i \pi a^2$$

R_i has the dimensions Ωcm. In squid nerve, it has a value of about 30 Ωcm at 20°C, or about 10^7 times that of copper. This value is expected from the ionic composition of squid axoplasm.[3] In mammals, where the ion concentration in the cytoplasm is lower, the specific resistance is higher, about 125 Ωcm at 37°C; in frogs, with still lower ion concentration, the specific resistance is about 250 Ωcm at 20°C.

The Effect of Diameter on Cable Characteristics

Given a specific resistance, R_i, for the axoplasm and a specific membrane resistance, R_m, how are the cable parameters r_{input} and λ influenced by fiber diameter? The answer can be obtained from the relations presented in the preceding paragraphs. Beginning with input resistance, we know that $r_{input} = 0.5(r_m r_i)^{1/2}$ and that $r_m = R_m/2\pi a$ and $r_i = R_i/\pi a^2$. Putting these relations together, we get

$$r_{input} = 0.5\left(\frac{R_m R_i}{2\pi^2 a^3}\right)^{1/2}$$

Thus, as the fiber radius (a) increases, the input resistance decreases, varying inversely with the 3/2 power of the radius.

Using the same approach, we find the length constant:

$$\lambda = \left(\frac{aR_m}{2R_i}\right)^{1/2}$$

Other properties being equal, λ increases with the square root of the fiber radius. We can use this relation to compare various fibers, assuming in each case that the specific membrane resistance is 2000 Ωcm^2: A squid axon of 1 mm diameter with a specific internal resistance of 30 Ωcm would have a length constant of almost 13 mm. Because of its smaller diameter and larger specific internal resistance, a 50 μm diameter frog muscle fiber would have a length constant of only 1.4 mm, and a 1 μm diameter mammalian nerve fiber a length constant of 0.3 mm.

In summary, the cable parameters r_{input} and λ determine the size of a signal generated in a nerve process, and how far the signal will spread. For example, other properties being equal, an excitatory synaptic potential (Chapter 9) will be larger in a small dendritic process (larger r_{input}) than in a large one. On the other hand, in the larger dendrite the potential will spread farther toward the cell body (larger λ). However, r_{input} and λ depend not only on fiber size but also on the resistive properties of the cytoplasm and plasma membrane. It is reasonably safe to assume that the specific resistance of the cytoplasm is the same in all cells in any animal class. Guesses about specific membrane resistance are much less certain; values may vary between one cell and the next by a factor of 50 or more.

Membrane Capacitance

In addition to allowing the passage of ionic currents, the cell membrane accumulates ionic charges on its inner and outer surfaces (Chapter 5). Electrically, the charge separation means that the membrane has the properties of a capacitor. In general, a capacitor consists of two conducting sheets, called plates, separated by a layer of insulating material; in manufactured capacitors the conductors are usually metallic foil, and the insulator is mica or a plastic such as Mylar. In the case of a nerve cell the conductors are the two layers of fluid that lie against either side of the membrane, and the insulating material is the membrane itself. When a capacitor is charged by connecting a battery to the two plates, it accumulates an excess of positive charges on one plate, leaving an equal excess of negative charges on the other. Its capacitance (C) is defined by how much charge (Q) it will accumulate for each volt of potential (V) applied to it; specifically, $C = Q/V$. C has the units coulombs per volt, or farads (F). The closer together the plates are, the greater their

ability to separate and store charge. Because the cell membrane is only about 5 nm thick, it is capable of storing a relatively large amount of charge. Typically nerve cell membranes have a capacitance on the order of 1 $\mu F/cm^2$ (1 $\mu F = 10^{-6}$ F). Turning the equation around, the charge stored in a capacitor is given by $Q = CV$. Thus, if a cell has a resting potential of –80 mV, the amount of excess negative charge at the inner surface of the membrane will be $(1 \times 10^{-6}) \times (80 \times 10^{-3}) = 8 \times 10^{-8}$ coulombs/cm^2, which is equivalent to 5×10^{11} univalent ions (0.8 pmol) for each square centimeter of membrane.

The current flowing into or out of a capacitor can be deduced from the relation between charge and voltage, and remembering that current (i, in amperes) is the rate of change of charge with time, that is: amperes = coulombs/s. Thus, since $Q = C/V$, we can write

$$i = \frac{dQ}{dt} = C\frac{dV}{dt}$$

The rate of change of the voltage on the capacitor is directly proportional to the current flow. If the current i is constant, then the voltage will change at a constant rate $dV/dt = i/C$.

The relations between current and voltage in circuits with resistors and capacitors in parallel are illustrated in Figure 7.2. When a rectangular current pulse of amplitude i is applied to a resistor (R), this produces a voltage pulse across the resistor of amplitude $V = iR$ (Figure 7.2A). If the same pulse is applied to a capacitor (C), the voltage on the capacitor builds up at a rate $dV/dt = i/C$ (Figure 7.2B). When the two elements R and C are combined in parallel (Figure 7.2C), all of the initial current goes to charge the capacitor at a rate of i/C; however, as soon as voltage starts to develop across the capacitor, current is driven through the resistor as well. As the voltage increases further, more current is diverted

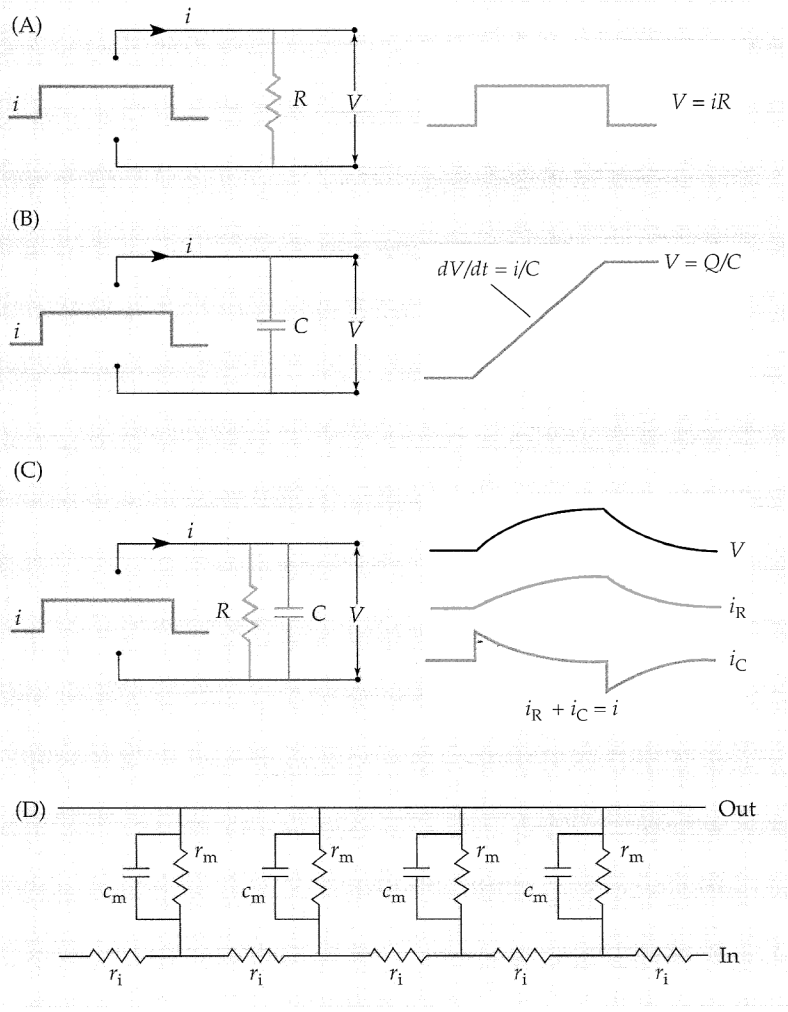


FIGURE 7.2 Effect of Capacitance on Time Course of potentials. (A) Potential (V) produced by a rectangular pulse of current (i) in a purely resistive network. Voltage is proportional to, and has the same time course as, the applied current. (B) In a purely capacitative network the *rate of change* of voltage is proportional to the applied current. (C) In a combined *RC* network the initial surge of current is into the capacitor (i_C); by the end of the pulse all of the current flows through the resistor (i_R). Voltage rises to the final value iR exponentially with time constant $\tau = RC$. After termination of the current pulse, the capacitance discharges through the resistance with the same time constant and i_C and i_R are equal and opposite. (D) Electrical model of a cable as in Figure 7.1C, but with membrane capacitance per unit length (c_m) added.

through the resistor, and the rate at which the capacitor charges is decreased. Eventually all of the applied current flows through the resistor, producing a potential $V = iR$, and the capacitor is fully charged to the same potential. When the pulse is terminated, the charge stored in the capacitor leaks away through the resistor and the voltage returns to zero.

Time Constant

The rise and fall of the potential in Figure 7.2C are described by exponential functions. The rising phase during the pulse is described by

$$V = iR(1 - e^{-t/\tau})$$

where t is the time from the beginning of the pulse. It turns out that the exponential time constant, τ, is given by the product of the resistance and capacitance in the circuit: $\tau = RC$. It is the time for the potential to rise to a fraction $(1 - 1/e$, or 63%) of its final value. The fall in voltage is again exponential, with the same time constant. Just as the voltage rises and falls exponentially, so must the resistive current, i_R. On the rising phase, then, the resistive current starts at zero and rises exponentially toward its final value i. Conversely, the capacitative current, i_C, starts at i and falls with the same time constant. After termination of the pulse, because external current is no longer being applied, the only current flowing across the resistor is that flowing out of the capacitor. Consequently, the resistive and capacitative currents must be equal and opposite as shown.

The circuit just described, with a resistor and capacitor in parallel, can be used to represent a spherical nerve cell with an axon and dendrites so small that they make only negligible contributions to the electrical properties of the cell. In the equivalent circuit for an axon or muscle fiber, however, the membrane capacitance, like the resistance, is distributed along the length of the fiber, as shown in Figure 7.2D. The membrane capacitance per unit length, c_m (in μF/cm), is related to the specific capacitance per unit area, C_m (in μF/cm^2), by the expression $c_m = 2\pi a C_m$, where a is the fiber radius.

Box 7.1 Electrotonic Potentials and the Membrane Time Constant

The electrotonic potentials shown in Figure 7.3, recorded at various distances along an axon from the point of current injection, do not rise and fall exponentially. Instead their waveforms are described by complicated functions of both time and distance. The potentials rise more rapidly than exponentials near the current electrode and more slowly farther away. Consequently, the membrane time constant, $\tau = R_m C_m$, cannot be obtained simply by measuring the time for an electrotonic potential to rise to 63% of its final value, as with an exponential voltage change. At the point of current injection, the potential rises to 84% of its maximum amplitude in one time constant. At a distance of one length constant from the point of current injection the potential does reach 63% of its final value in one time constant, but two length constants away it reaches only 37% of its final value in the same time. How, then, does one measure τ in a cable? To do this, it is necessary to know the separation between the current-passing and voltage-recording electrodes as a fraction of the length constant, λ. We can then consult a table of values to find out how far the electrotonic potential will rise in one time constant at that particular electrode separation. An abbreviated version of such a table is presented here. The numbers give the amplitude (V_τ) reached by an electrotonic potential at one time constant after the onset of the current pulse, for various electrode separations (d). The amplitudes are expressed as a fraction of the final steady-state amplitude (V_∞) and the distance between the electrodes as fractions or multiples of one length constant (λ).

Amplitude Reached by an Electrotonic Potential in One Time Constant

Separation (d/λ)	0	0.2	0.4	0.6	0.8	1.0	1.5	2.0
Amplitude (V_τ/V_∞)	0.84	0.81	0.77	0.73	0.68	0.63	0.50	0.37

Source: Calculated from Hodgkin and Rushton, 1946.

The membrane time constant of a spherical cell or of a fiber ($\tau_m = R_m C_m$) is independent of cell or fiber size. This is because an increase in radius (and hence in membrane surface area) causes not only an increase in capacitance, but also a corresponding decrease in resistance, so the product remains constant. Because C_m has been found to be approximately the same (1 μF/cm^2) for all nerve and muscle membranes, τ provides a convenient measure for the specific membrane resistance of a cell. The time constant is the third parameter specifying the behavior of an axon, the other two being the input resistance and the length constant. Time constants in nerve and muscle cells typically range from 1 to 20 ms.

Capacitance in a Cable

How does the time constant affect current flow in a cable? As with the simple *RC* circuit (see Figure 7.2C), the rise and fall of the potential change produced by a rectangular current pulse are slowed by the presence of the capacitance. The effects are more complicated, however, because current no longer flows into a single capacitor; instead each segment of the circuit with its capacitative and resistive elements interacts with the others. Because of this interaction, the rising and falling phases of the potential changes are not exponential, and the growth and decline of the potentials become increasingly prolonged as records are made farther and farther from the point of current injection (Figure 7.3). Because the rate of rise depends on the distance between the recording electrode and the point of current injection, the membrane time constant cannot be obtained by measuring the time to rise to 63% of its final value, except in the unique case when the separation is one length constant (Box 7.1).

Again, the effect of membrane capacitance can be explained in terms of ion movements. When positive current is injected into the axon, intracellular ions (mostly potassium) on the inside spread longitudinally along the fiber. Some ions accumulate to change the charge on the membrane capacitance, and some flow out through the membrane resistance. (Negatively charged chloride ions are, at the same time, moving in the opposite direction.) Eventually the membrane potential reaches a new steady state with the distributed capacitances fully charged to their new potential and a steady ionic current through the membrane. The time required to reach the steady state is determined by the membrane time constant.

A further consequence of the membrane capacitance is that brief signals do not spread as far as signals of long duration. For sufficiently long pulses, when the potential can reach a steady state, the capacitance is fully charged and the spatial distribution of the potential is determined by the resistances of the membrane and cytoplasm; that is, $V_x = V_0 e^{-x/\lambda}$, as described earlier. However, for brief events, such as synaptic potentials, the current flow giving rise to the signal may end before the membrane capacitances become fully charged. This has the effect of reducing the spread of the potential along the fiber. In other words, for brief signals the effective length constant is less than for those of longer duration. In addition, such signals are distorted as they spread along the fiber, the peaks becoming more rounded and occurring progressively later with increasing distance.

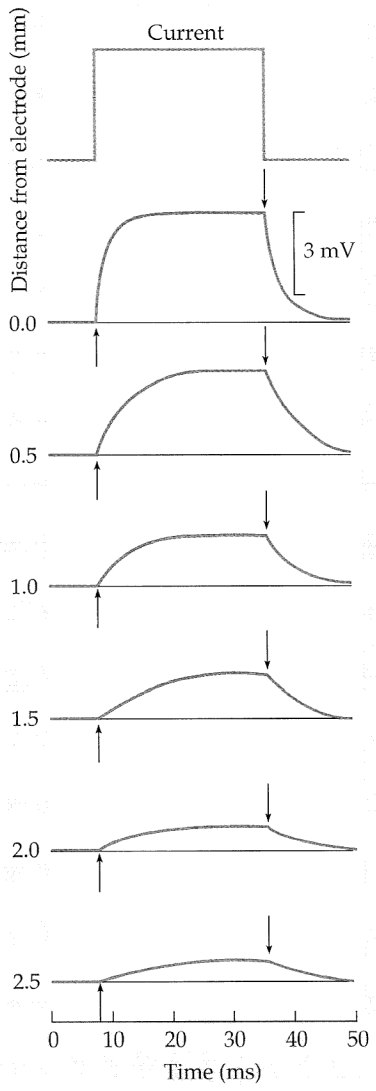


FIGURE 7.3 Spread of Potential along a lobster axon, recorded with a surface electrode. A rectangular current pulse is applied at 0 mm, producing an electrotonic potential. With increasing distance from the site of current injection, the rise time of the potential change is slowed and the height of the plateau attenuated. (After Hodgkin and Rushton, 1946.)

PROPAGATION OF ACTION POTENTIALS

Action potential propagation along a nerve fiber depends on the passive spread of current ahead of the active region to depolarize the next segment of membrane to threshold. To illustrate the nature of the current flow involved in impulse generation and propagation, we can imagine the action potential frozen at an instant in time and plot its spatial distribution along the axon as shown in Figure 7.4. The distance occupied depends on its duration and conduction velocity. For example, if the action potential duration is 2 ms and it is conducted at 10 m/s (10 mm/ms), then the potential will be spread over a 20 mm length of axon (almost an inch). Near the leading edge of the action potential, where the membrane potential has reached threshold, there is a rapid influx of sodium ions along their electrochemical gradient, depolarizing the cell membrane. Just as when current is injected through a microelectrode, the inward current spreads longitudinally in the fiber away from the active region. Ahead of the active region this current depolarizes a new seg-

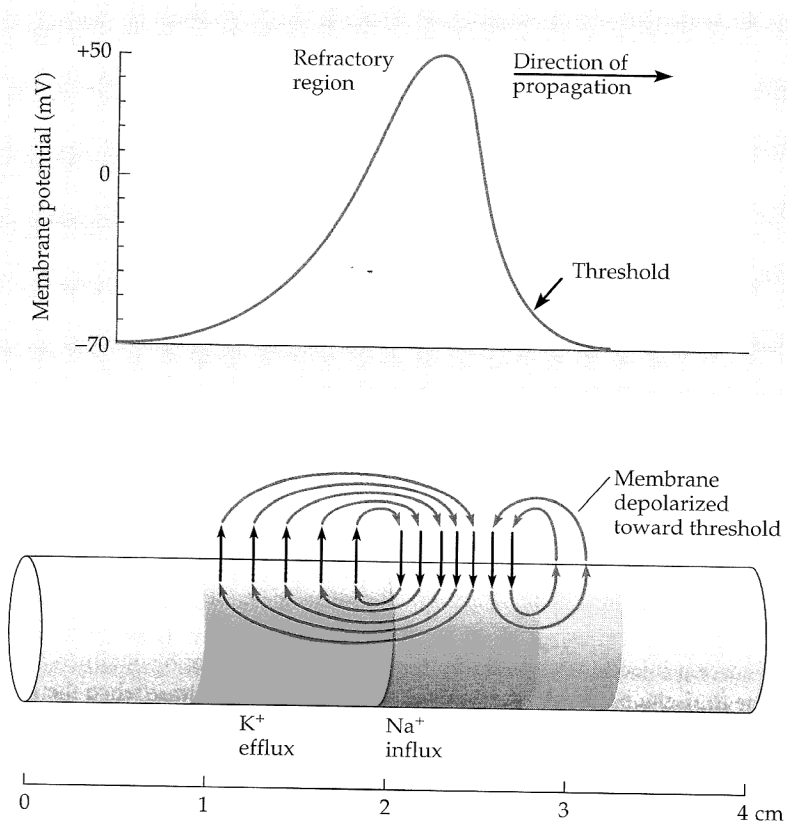


FIGURE 7.4 Current Flow during an Action Potential at an instant in time. Rapid depolarization during the rising phase of the action potential is due to the influx of positively charged sodium ions. The positive current spreads ahead of the impulse to depolarize the adjacent segment of membrane toward threshold. Repolarization on the falling phase is due to the efflux of potassium ions.

ment of membrane toward threshold. Behind the peak of the action potential the potassium conductance is high and current flows out through potassium channels, restoring the membrane potential toward its resting level.

Normally, impulses arise at one end of an axon and travel to the other. However, there is no inherent directionality to propagation. Impulses produced at a neuromuscular junction in the middle of a muscle fiber travel away from the junction in both directions toward the tendons. Except in unusual circumstances, however, an action potential, once initiated, cannot double back on itself, reversing its direction of propagation. This is because of the refractory period. In the refractory region, indicated in Figure 7.4, the sodium conductance is largely inactivated and the potassium conductance is high, so a backward-conducting regenerative response cannot occur. As the action potential leaves the region, the membrane potential returns to its resting value, sodium channel inactivation is removed, potassium conductance returns to normal, and excitability recovers.

Conduction Velocity

The conduction velocity of the action potential depends on how quickly and how far ahead of the active region the membrane capacitance is discharged to threshold by the spread of positive charge. This, in turn, depends on the amount of current generated in the active region and on the cable properties of the fiber. If the membrane time constant, $\tau_m = R_m C_m$, is small, the membrane will depolarize to threshold quickly, speeding conduction. If the length constant, $\lambda = (r_m/r_i)^{1/2}$, is large, the depolarizing current will spread a correspondingly large distance ahead of the active region, and the conduction velocity will be high.

How do these factors relate to fiber size? As already noted, the time constant is independent of size. The length constant, on the other hand, increases with the square root of the fiber diameter. Large fibers, then, conduct more rapidly than small fibers. A more detailed theoretical approach indicates that in unmyelinated fibers, such as squid axons, the velocity of propagation should vary directly with the square root of the fiber diameter.[4]

[4]Hodgkin, A. L. 1954. *J. Physiol.* 125: 221–224.

Myelinated Nerves and Saltatory Conduction

In the vertebrate nervous system the larger nerve fibers are myelinated. Myelin is formed in the periphery by Schwann cells and in the CNS by oligodendrocytes (Chapter 8). The cells wrap themselves tightly around axons, and with each wrap the cytoplasm between the membrane pair is squeezed out so that the result is a spiral of tightly packed membranes (Chapter 8). The number of wrappings (lamellae) ranges from a low of between 10 and 20 to a maximum of about 160.[5] A wrapping of 160 lamellae means that there are 320 membranes in series between the plasma membrane of the axon and the extracellular fluid. Thus, the effective membrane resistance is increased by a factor of 320, and the membrane capacitance is reduced to the same extent. In terms of dimensions, myelin usually occupies 20 to 40% of the overall diameter of the fiber. The myelin sheath is interrupted periodically by nodes of Ranvier, exposing patches of axonal membrane. The internodal distance is usually about 100 times the external diameter of the fiber, and it ranges from 200 μm to 2 mm.

The effect of the myelin sheath is to restrict membrane current flow largely to the node because ions cannot flow easily into or out of the high-resistance internodal region and the internodal capacitative currents are very small as well. As a result, excitation jumps from node to node, thereby greatly increasing the conduction velocity. Such impulse propagation is called **saltatory conduction** (from the Latin *saltare*, "to jump, leap, or dance"). Saltatory conduction does not mean that the action potential occurs in only one node at time. While excitation is jumping from one node to the next on the leading edge of the action potential, many nodes behind are still active. Myelinated axons not only conduct more rapidly than unmyelinated ones but also are capable of firing at higher frequencies for more prolonged periods of time. These capabilities may be related to an additional consequence of myelination—namely, that during impulse propagation fewer sodium and potassium ions enter and leave the axon because regenerative activity is restricted to the nodes. Consequently, less metabolic energy is required by the nerve cell to maintain the appropriate intracellular ion concentrations.

Experiments that demonstrated saltatory conduction were first made in 1941 by Tasaki[6] and later by Huxley and Stampfli,[7] who recorded current flow at nodes and internodes. Such an experiment on a single myelinated axon is illustrated in Figure 7.5. The nerve is placed in three saline pools, the central pool being narrow and separated from the others by air gaps of very high resistance. Electrically, the pools are connected by the external recording circuitry as shown, so that during impulse propagation currents that would otherwise be interrupted by the air gap flow instead into or out of the central pool through the resistor (R). The voltage drop across the resistor provides a measure of the magnitude and direction of the currents.

In the first experiment (Figure 7.5A) the central pool contains a node of Ranvier. Upon stimulation of the nerve, current first flows outward through the node and back toward the region of oncoming excitation (upward deflection) as the node is depolarized to threshold. This is followed by inward current at the node (downward deflection) when threshold is reached and an action potential is generated. When the central pool contains an internode (Figure 7.5B), there is no inward current, but only two small peaks of capacitative and resistive current flowing from the central pool toward the regions of excitation as the impulse first approaches in compartment 1 and then travels onward in compartment 3. Experiments such as this confirmed that there is no inward current, and hence no regenerative activity, in the internodal region.

Sophisticated techniques for recording saltatory conduction in undissected mammalian axons in situ have been developed by Bostock and Sears.[8] With such techniques it is possible to measure both inward currents at the nodes and longitudinal internodal currents and thereby to estimate accurately the positions of the nodes and distances between them.

Conduction Velocity in Myelinated Fibers

Conduction velocities of myelinated fibers vary from a few meters per second to more than 100 m/s. The world speed record is held by myelinated axons of the shrimp, which conduct at speeds in excess of 200 m/s (447 miles/h).[9] In the vertebrate nervous system, peripheral nerves have been classified into groups according to conduction velocity[10] and function

[5]Arbuthnott, E. R., Boyd, I. A., and Kalu, K. U. 1980. *J. Physiol.* 308: 125–157.

[6]Tasaki, I. 1959. In *Handbook of Physiology*, Section 1, Vol. 1, Chapter 3. American Physiological Society, Bethesda, MD, pp. 75–121.

[7]Huxley, A. F., and Stampfli, R. 1949. *J. Physiol.* 108: 315–339.

[8]Bostock, H., and Sears, T. A. 1978. *J. Physiol.* 280: 273–301.

[9]Xu, K., and Terakawa, S. 1999. *J. Exp. Biol.* 202: 1979–1989.

[10]Gasser, H. S., and Erlanger, J. 1927. *Am. J. Physiol.* 80: 522–547.

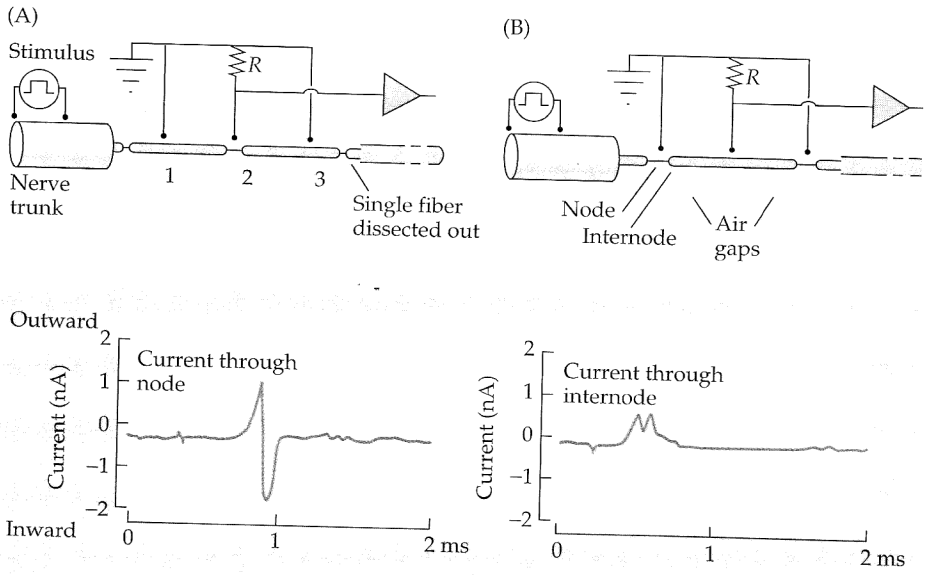


FIGURE 7.5 Current Flow through a Myelinated Axon. A single myelinated axon passes through two air gaps that create three compartments not linked by extracellular fluid. During the propagated action potential, currents into and out of the center compartment (2) flow through the resistor (*R*); the voltage drop across the resistor provides a measure of the current. (A) A node of Ranvier is in compartment 2. Initially, as the action potential approaches and the node is being depolarized, current flows through the resistor from compartment 2 to compartment 1 (upward deflection); when threshold is reached at the node, a large inward flux follows and the current is reversed. (B) An internode is in the center compartment and there is only outward current flow from the compartment, with no inward current, as the action potential first approaches and then leaves the internodal segment. (After Tasaki, 1959.)

(Box 7.2). Theoretical calculations suggest that in myelinated fibers, conduction velocity should be proportional to the diameter of the fiber.[11] Boyd and his colleagues have shown that in mammals, large myelinated fibers (greater than 11 μm in diameter) have a conduction velocity in meters per second that is equal to approximately six times their outside diameter in micrometers; for smaller fibers the constant of proportionality is about 4.5.[12]

One theoretical point of interest is the best thickness for the myelin sheath for optimal conduction velocity, given a particular outer diameter. Obviously the increase in membrane resistance in the myelinated region will be greater with a thick sheath than with a thin one. On the other hand, as the myelin thickness increases, the cross-sectional area of the axoplasm must decrease, thereby increasing internal longitudinal resistance. The first effect would be expected to increase conduction velocity, the second to decrease it. It turns out that the optimal compromise between these opposing effects is achieved when the axon diameter is about 0.7 times the overall fiber diameter. As already noted, the observed ratio in mammalian peripheral nerve ranges between 0.6 and 0.8.

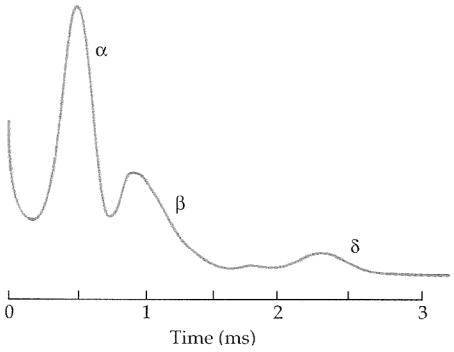
The calculated optimum internodal length for conduction is also approximately that found in reality—namely, about 100 times the external fiber diameter. Greater internodal distances would allow the excitation to spread farther, tending to increase conduction velocity. On the other hand, as the internodal distance increases, current flow from one node to the next decreases because of the greater longitudinal resistance. As a result, the nodal depolarization produced by activity in a preceding node would be smaller and rise more slowly, tending to decrease conduction velocity. Because of these opposing factors, modest variations in internodal length have little effect on conduction velocity. With a very large internodal distance, of course, depolarization from activity in a preceding node would no longer reach threshold, and conduction would be blocked.

[11]Rushton, W. A. H. 1951. *J. Physiol.* 115: 101–122.

[12]Arbuthnott, E. R., Boyd, I. A., and Kalu, K. U. 1980. *J. Physiol.* 308: 125–157.

Box 7.2 Classification of Nerve Fibers in Vertebrates

If we stimulate a peripheral nerve electrically at one end and record from it some distance away, the resulting record has a series of peaks. The peaks occur because of the dispersion of nerve impulses that travel at different velocities and therefore arrive at the recording electrode at different times after the stimulus. For example, a record taken from a rat sciatic nerve with 50 mm between the stimulating and recording electrodes might look like the figure shown here (the rapid deflection at the beginning is an artifact due to current spread from the stimulating electrode).



Vertebrate nerve fibers were classified into groups on the basis of differences in conduction velocity, combined with differences in function. Unfortunately, two such classifications developed simultaneously. In the first system, group A refers to myelinated fibers in peripheral nerve; in mammals, these conduct at velocities ranging from 5 to 120 m/s. Group A fibers were further subdivided according to conduction velocity into α (80–120 m/s), β (30–80 m/s), and δ (5–30 m/s). These conduction velocity peaks are indicated in the record shown here. Group B consists of myelinated fibers in the autonomic nervous system, which have conduction velocities in the lower part of the A-fiber range. Group C contains unmyelinated fibers, which conduct very slowly (less than 2 m/s). The term "γ fibers" is reserved for motor nerves supplying muscle spindles (Chapter 17), which have conduction velocities that span the β and lower part of the α range.

The second nomenclature applies to sensory fibers arising in muscle: Group I, corresponding to Aα; Group II (Aβ); Group III (Aδ). Group I afferent fibers were further classified into two separate groups depending on whether they conveyed information from muscle spindles (Ia) or from sensory receptors in tendons (Ib).

Distribution of Channels in Myelinated Fibers

In myelinated fibers, voltage-sensitive sodium channels are highly concentrated in the nodes of Ranvier, with potassium channels more concentrated under the paranodal sheath.[13] The properties of the axon membrane in the paranodal region normally covered by myelin were first examined by Ritchie and his colleagues.[14] To do this, the myelin was loosened by enzyme treatment or osmotic shock. Voltage clamp studies were then made of currents in the region of the node and compared with those obtained before the treatment. Such experiments showed that in rabbit nerve, nodes of Ranvier normally display only inward sodium current upon excitation. Repolarization occurs not through an increase in potassium conductance (as in other cells considered so far) but instead by rapid sodium inactivation and current flow through a relatively large resting conductance. When the axon membrane adjacent to the nodes (the paranodal region) was exposed, excitation then produced a delayed outward potassium current, with no increase in inward current, indicating that the newly exposed membrane contained delayed rectifier channels but not sodium channels. Later immunocytochemical studies confirmed that in rat myelinated nerve, voltage-sensitive potassium channels were confined to the paranodal region (Figure 7.6A).[15,16] It is interesting that the nodal regions of *Xenopus* axons contain *sodium-activated* potassium channels.[17] Such channels might be activated by sodium influx during the rising phase of the action potential and thereby speed repolarization.

Channels in Demyelinated Axons

Mammalian axons that have been demyelinated chronically by exposure to diphtheria toxin can develop continuous conduction through a demyelinated region,[7] implying that

[13] Vabnick, I., and Shrager, P. 1998. *J. Neurobiol.* 37: 80–96.

[14] Chiu, S. Y., and Ritchie, J. M. 1981. *J. Physiol.* 313: 415–437.

[15] Wang, H., et al. 1993. *Nature* 365: 75–79.

[16] Rasband, M. N., et al. 1998. *J. Neurosci.* 18: 36–47.

[17] Koh, D. S., Jonas, P., and Vogel, W. 1994. *J. Physiol.* 479(Pt.2): 183–197.

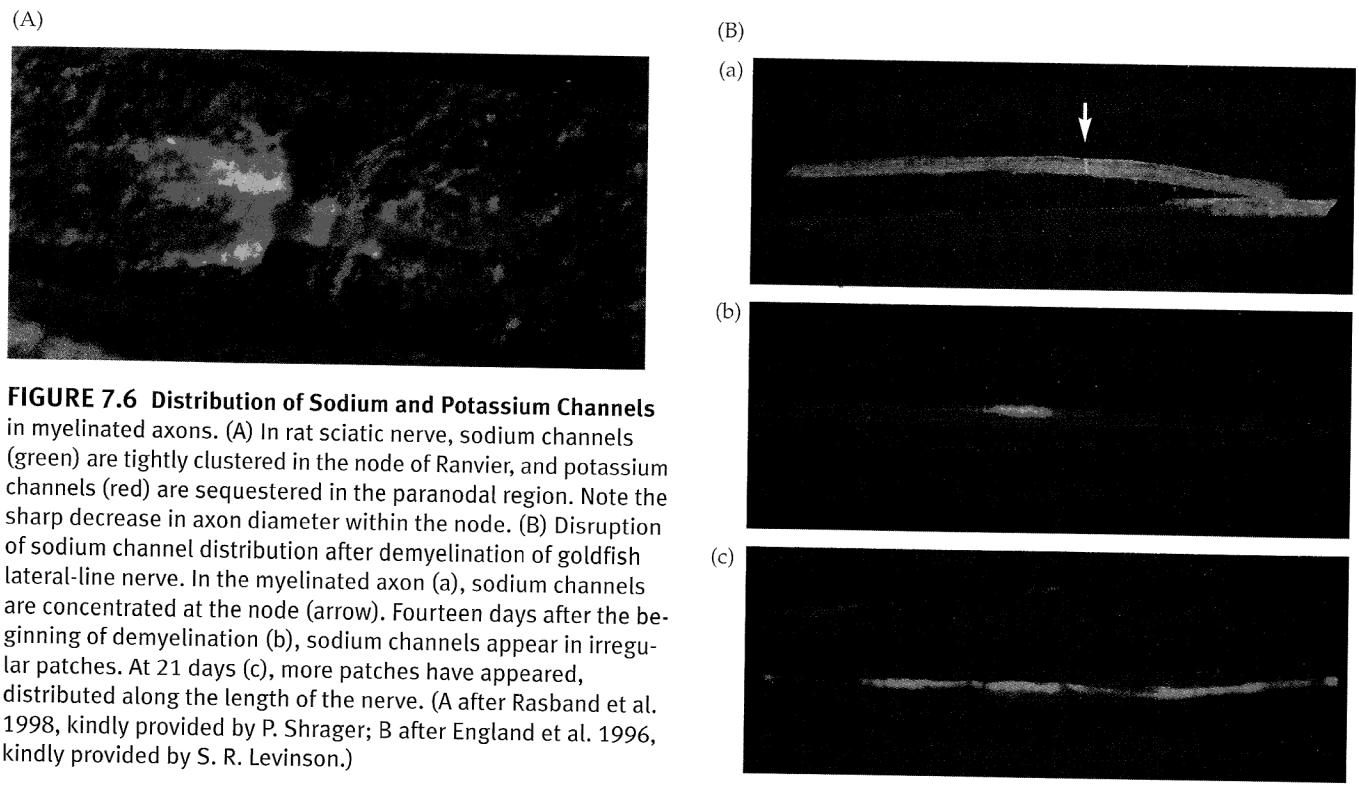


FIGURE 7.6 Distribution of Sodium and Potassium Channels in myelinated axons. (A) In rat sciatic nerve, sodium channels (green) are tightly clustered in the node of Ranvier, and potassium channels (red) are sequestered in the paranodal region. Note the sharp decrease in axon diameter within the node. (B) Disruption of sodium channel distribution after demyelination of goldfish lateral-line nerve. In the myelinated axon (a), sodium channels are concentrated at the node (arrow). Fourteen days after the beginning of demyelination (b), sodium channels appear in irregular patches. At 21 days (c), more patches have appeared, distributed along the length of the nerve. (A after Rasband et al. 1998, kindly provided by P. Shrager; B after England et al. 1996, kindly provided by S. R. Levinson.)

after demyelination, voltage-activated sodium channels appear in the exposed axon membrane. In other experiments, labeling of demyelinated nerves with antibodies to sodium channels shows that channels disappear from clusters in the former nodal regions and that new channels are distributed along previously myelinated regions (Figure 7.6B).[18] Voltage-activated potassium channels are redistributed as well.[14,19] Upon remyelination the normal clustering of sodium and potassium channels in newly formed nodes and paranodal regions is restored.

Geometry and Conduction Block

The simple uniform cable is an idealized structure resembling an unmyelinated axon, but not a neuron in its entirety, with its cell body, elaborate dendritic arborization, and numerous axonal branches. The complex geometry of the neuron provides many possibilities for block of action potential propagation. Specifically, propagation may fail wherever there is an abrupt expansion of membrane area. In such a situation the active membrane may not be able to provide enough current to depolarize the larger membrane area to threshold. For example, where an axon divides into two branches, the active segment of the single axon must contribute sufficient current to activate both branches. Under normal circumstances an impulse will usually be unimpeded, but after repeated firing, block may occur at the branch point. Other factors contribute to such block: In leech sensory cells, block can occur because of persistent hyperpolarization induced by increased electrogenic activity of the sodium pump (Chapter 15), and because of long-lasting increases in potassium permeability, both of which increase the amount of current required for depolarization to threshold.[20–22]

In myelinated peripheral nerve the safety factor for conduction is about 5; that is, the depolarization produced at a node by excitation of a preceding node is approximately five times larger than necessary to reach threshold. Again, this safety factor is reduced where branching occurs. Similarly, when the myelin sheath terminates—for example, near the end of a motor nerve—the current from the last node is then distributed over a large area

[18]England, J. D., Levinson, S. R., and Shrager, P. 1996. *Microsc. Res. Tech.* 34: 445–451.

[19]Bostock, H., Sears, T. A., and Sherratt, R. M. 1981. *J. Physiol.* 313: 301–315.

[20]Yau, K. W. 1976. *J. Physiol.* 263: 513–538.

[21]Gu, X. N., Macagno, E. R., and Muller, K. J. 1989. *J. Neurobiol.* 20: 422–434.

[22]Baccus, S. A. 1998. *Proc. Natl. Acad. Sci. USA* 95: 8345–8350.

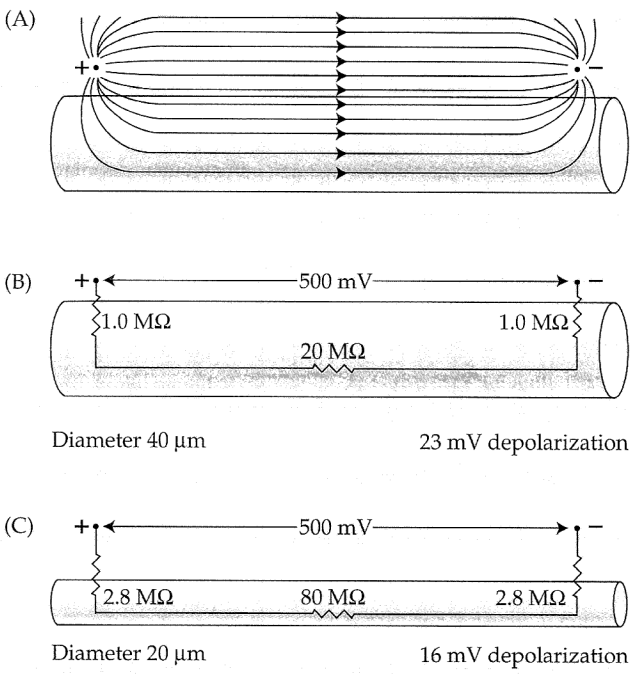
Box 7.3 Stimulating and Recording with External Electrodes

For much physiological work in the central and peripheral nervous systems, extracellular electrodes are used to stimulate or to record from axons of various diameters. When two extracellular electrodes are used to stimulate a nerve trunk (A in the figure), much of the current is diverted through the extracellular fluid; the remainder enters individual axons under the positive electrode, flows along the axoplasm, and exits under the negative electrode. Corresponding electrical circuits are shown in B and C. Current enters and leaves the axon through the input resistances, and between the regions of entry and exit it flows along an internal longitudinal resistance. Under the positive electrode there is a voltage drop across the membrane, producing a local hyperpolarization (the outside is made more positive). Current flow toward the negative electrode produces an additional voltage gradient along the core of the axon. Current leaving the axon under the negative electrode causes a local depolarization. These three voltage gradients must sum to equal the total voltage drop in the extracellular solution between the electrodes.

The voltage that must be applied to bring the membrane under the negative electrode to threshold depends on fiber diameter: Large fibers require less stimulating voltage than small fibers, because of geometrical factors. As fiber size increases, the internal longitudinal resistance (which varies inversely with the square of the diameter) decreases more rapidly than the input resistance (which varies inversely with the 3/2 power of the diameter). As a result, less of the applied voltage is dissipated along the core of the fiber, and a greater voltage drop is produced across the membrane. B and C illustrate this principle numerically. The diagrams represent the pathways for current flow through two unmyelinated fibers, between a pair of stimulating electrodes 2 cm apart. Plausible values for input resistances and longitudinal resistance for a 40 μm fiber are given in part B. A potential of 500 mV between the electrodes produces a depolarization of 23 mV. For a fiber with half the diameter (20 μm) (part C) the input resistances are increased by a factor of 2.8, the longitudinal resistance is increased by a factor of 4, and the depolarization is reduced to 16 mV.

Extracellular electrodes can also be used to record action potential activity in nerve trunks. This is possible because during action potential propagation, longitudinal currents in the surrounding extracellular fluid create potential gradients along the nerve fiber. Because of their larger membrane area and lower core resistance, larger fibers generate more current, and hence larger extracellular gradients, than smaller fibers. As a result, they produce larger signals at the recording electrodes.

The relation between size and threshold for stimulation by external electrodes is fortunate for physiological and clinical purposes. For example, threshold and conduction velocity can be tested in motor nerves, which are relatively large, without exciting pain fibers, which are very much smaller. Just as the largest fibers are the easiest to stimulate, they are often the most difficult to block—for example, by cooling or by local anesthetics. Again, this means that pain fibers can be blocked with anesthetic without interfering with conduction in larger sensory and motor fibers. But this relation between size and block of conduction does not always hold: Because of additional geometrical effects, block by localized pressure affects large axons first, then smaller axons as the pressure is increased.



of unmyelinated nerve terminal membrane and, as a consequence, provides less overall depolarization than would occur at a node. It is perhaps for this reason that the last few internodes before an unmyelinated terminal are shorter than normal: so that more nodes can contribute to depolarization of the terminal.[23]

[23] Quick, D. C., Kennedy, W. R., and Donaldson, L. 1979. *Neuroscience* 4: 1089–1096.

CONDUCTION IN DENDRITES

Apart from considerations of geometry, some regions of the neuron have a lower threshold for action potential initiation than others. This was first observed in spinal motoneurons by J. C. Eccles and his colleagues.[24] They found that upon depolarization action potentials were initiated first in the initial segment of the axon (between the cell body and the first internode) and then propagated both outward along the axon and back into the soma (cell body) and dendrites of the cell. At about the same time, Kuffler and Eyzaguirre found that depolarization of the dendrites in the crayfish stretch receptor initiated action potentials in or near the cell body, rather than in the dendrites themselves.[25] Observations of this kind led to the idea that dendrites were generally unexcitable and served only to transmit signals passively from dendritic synapses to the initial segment of the axon. This idea arose in spite of numerous observations to the contrary. For example, earlier extracellular recordings of electrical activity within the mammalian motor cortex by Li and Jasper gave clear indication of action potentials traveling upward along pyramidal cell dendrites from their cell bodies to the cortical surface, with a conduction velocity of about 3 m/s.[26]

Dendritic action potentials are now known to occur in a variety of neurons, mediated by regenerative sodium and calcium currents. Cerebellar Purkinje cells, in addition to producing sodium action potentials in their somatic regions, generate calcium action potentials in their dendrites.[27] As shown in Figure 7.7A, calcium action potentials generated in a dendrite spread effectively into the soma. Somatic action potentials, on the other hand, are not propagated into the dendrites, but spread passively a short distance into the dendritic tree.

Like Purkinje cells, cortical pyramidal cells exhibit sodium action potentials in their somatic regions, usually arising in the initial segment of the axon. In addition, regenerative calcium potentials are observed in the distal dendrite.[28,29] Responses of a pyramidal cell to depolarization of the distal dendrite by activation of excitatory synapses (Chapter 9) are shown in Figure 7.7B. Modest synaptic activation (part a of Figure 7.7B) produces dendritic depolarization that is attenuated as it spreads passively to the soma. The depolarization produces an action potential in the soma that spreads back into the dendrite. Stronger synaptic depolarization (part b of Figure 7.7B) results in direct activation of a dendritic calcium action potential that precedes the action potential generated in the soma.

Although there is now ample evidence of regenerative activity in dendrites, the general principle that the axon hillock is usually the most excitable region of the cell still holds.[30]

Propagation of electrical signals in a dendrite is clearly much more complex than in an axon. First of all, in the axon the assumption that subthreshold potential changes do not affect the passive membrane properties is more or less reasonable. Not so in dendrites, which are likely to contain a variety of voltage-dependent channels in addition to those associated with the action potential. Still more complexity is added by the coexistence of action potentials and synaptic potentials in the dendritic tree. For example, the safety factor for back-propagation of action potentials from the soma depends on the input resistance of the various branches; the input resistances, in turn, depend on the extent of activity at excitatory and inhibitory synapses. Thus, whether or not back-propagation occurs depends on synaptic activity.[31–33] At the same time, synaptic channels that are voltage-dependent will behave differently from one moment to the next, depending on whether back-propagation has occurred.[34] These factors add new dimensions to signal processing that are only beginning be understood.

PATHWAYS FOR CURRENT FLOW BETWEEN CELLS

In most circumstances electrical signals cannot pass directly from one cell to the next. Certain cells, however, are **electrically coupled**. The properties and functional role of electrical synapses are discussed in Chapter 9. Here we describe special intercellular structures that are required for electrical continuity between cells. The necessity for such specialized structures to mediate the spread of current from one cell to the next is shown in Box 7.4.

[24]Coombs, J. S., Eccles, J. C., and Fatt, P. 1955. *J. Physiol.* 130: 291–325.

[25]Kuffler, S. W., and Eyzaguirre, C. 1955. *J. Gen. Physiol.* 39: 87–119.

[26]Li, C-L., and Jasper, H. H. 1953. *J. Physiol.* 121: 117–140.

[27]Llinás, R., and Sugimori, M. 1980. *J. Physiol.* 305: 197–213.

[28]Stuart, G., Schiller, J., and Sakmann, B. 1997. *J. Physiol.* 505: 617–632.

[29]Svoboda, K., et al. 1999. *Nat. Neurosci.* 2: 65–73.

[30]Stuart, G., et al. 1997. *Trends Neurosci.* 20: 125–131.

[31]Tsubokawa, H., and Ross, W. N. 1996. *J. Neurophysiol.* 76: 2896–2906.

[32]Sandler, V. M., and Ross, W. N. 1999. *J. Neurophysiol.* 81: 216–224.

[33]Larkum, M. E., Zhu, J. J., and Sakmann, B. 1999. *Nature* 398: 338–341

[34]Markram, H., et al. 1997. *Science* 275: 213–215.

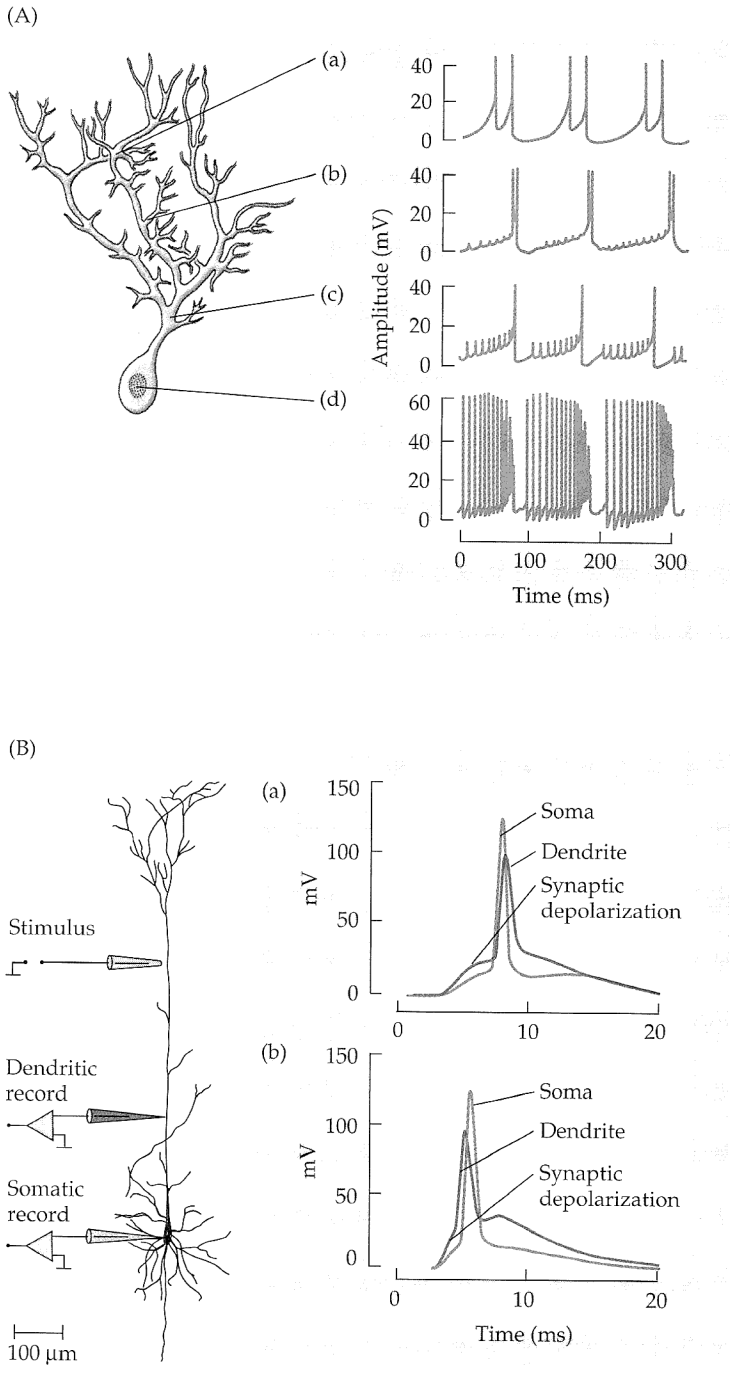


FIGURE 7.7 Spread of Action Potentials in Dendrites. (A) Records from a cerebellar Purkinje cell, obtained by impaling the cell at the indicated locations and passing a depolarizing current through the electrode. Near the end of the dendritic tree (a), depolarization produces long-duration calcium action potentials. In the cell soma (d), a steady depolarizing current produces high-frequency sodium action potentials, interrupted periodically by calcium action potentials. At intermediate locations (b and c), depolarization produces calcium action potentials in the dendrite. Accompanying sodium action potentials, generated in the soma, spread passively into the dendritic tree and die out after a short distance. (B) Conduction in a cortical pyramidal cell. The cortical cell dendrite is depolarized by activating distal excitatory synapses. (a) Moderate depolarization of the dendrite is attenuated as it spreads to the soma, where it initiates an action potential. The action potential then spreads back into the dendrite. (b) Larger depolarization produces a calcium action potential in the dendrite that precedes action potential initiation in the soma. (A from Llinás and Sugimori, 1980; B after Stuart, Schiller, and Sakmann, 1997.)

Structural Basis for Electrical Coupling: The Gap Junction

At sites of electrical coupling the intercellular current flows through **gap junctions**.[35] The gap junction is a region of close apposition of two cells characterized by aggregates of particles distributed in hexagonal arrays in each of the adjoining membranes (Figure 7.8). Each particle, called a **connexon**, is made up of six protein subunits arranged in a circle about 10 nm in diameter, with a 2 nm diameter central core.[36,37] Identical particles in the apposing cells are exactly paired to span the 2 or 3 nm gap in the region of contact. The core provides the pathway for the flow of small ions and molecules between cells. The conductance of an individual channel connecting adjacent cells (i.e., two connexons in series) is on the order of 100 pS.[38]

[35]Loewenstein, W. 1981. *Physiol. Rev.* 61: 829–913.

[36]Goodenough, D. A., Goliger, J. A., and Paul, D. 1996. *Annu. Rev. Biochem.* 65: 475–502.

[37]Perkins, G., Goodenough, D., and Sosinsky, G. 1997. *Biophys. J.* 72: 533–544.

[38]Neyton, J., and Trautmann, A. 1985. *Nature* 317: 331–335.

Box 7.4 Current Flow between Cells

The figure shown here indicates pathways for current flow between the ends of two cylindrical neuronal processes, labeled "a" and "b" in the diagrams. In the first example (A), the ends are separated by a gap (as occurs, for example, at chemical synapses). Current passed into one of the processes (a) exits along the length of the process and out the end. How is the current flow distributed quantitatively? This can be determined by considering the resistances involved. The cylindrical conductor is a cable extending in one direction only. Its input resistance is:

$$r_{\text{input}} = \left(\frac{R_m R_i}{2\pi^2 a^3}\right)^{1/2}$$

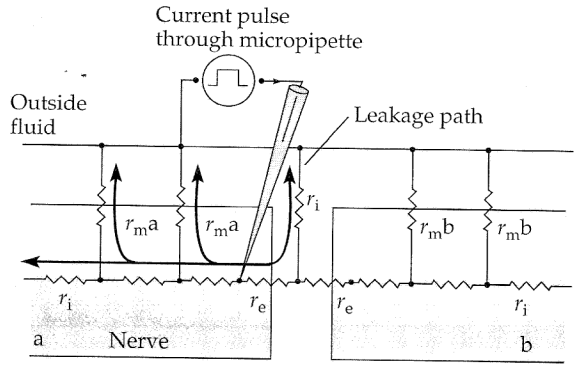
The resistance of the circular end is

$$r_e = \frac{R_m}{\pi a^2}$$

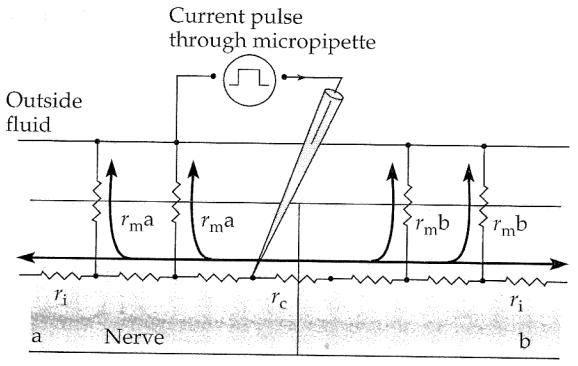
Suppose that for both cells $R_m = 2000\ \Omega\text{cm}^2$, $R_i = 100\ \Omega\text{cm}$, and $a = 10\ \mu\text{m}$ (all plausible values). Then r_{input} will be 3.2 MΩ, and r_e 637 MΩ. Because the end resistance is 200 times larger than the input resistance, only 0.5% of the current injected into the cylinder will flow outward through the end. Further, all of the current leaving the end will flow laterally out of the cleft, which has a low resistance, rather than entering the end of the second process (b).

What if we butt the two ends of the processes tightly together, as shown in B? The resistance to outward current flow along process a will be unchanged. The resistance to current flow into process b will be 1274 MΩ (r_c, the resistance of the two end membranes in series) plus 3.2 MΩ (the input resistance of process b). As a result, current flowing through the two ends and into process b is 0.025% of the total. Accordingly, an applied current of 10 nA would depolarize cell a by 31.7 mV, cell b by only about 79 μV. Clearly, significant coupling between the two processes requires not only that current be prevented from escaping the region of apposition, but also that the intercellular resistance be very much smaller than that normally found in membranes. Such low-resistance intercellular pathways are created by gap junctions (see text).

(A) Cells a and b separated by fluid-filled space



(B) Cells a and b apposed



A variety of connexon subunit proteins (**connexins**) have been isolated and sequenced, ranging in mass from 26 to 56 kDa.[36,39] Each is named according to its deduced mass—for example, connexin32 (32 kDa) is found in rat liver, connexin43 (43 kDa) in heart muscle, and so on. Hydropathy plots (Chapter 3) suggest that the connexins contain four membrane-spanning helices. Antibody-binding studies are consistent with this model and indicate that the amino terminus (and hence the carboxy terminus as well) resides in the cytoplasm. Only one, or perhaps a few, specific connexins form gap junctions in any given tissue, but functional intercellular coupling can occur between connexins of different types—for example, when message for connexin32 is injected into one cell and for connexin43 in the other.[40] Gap junctions can be formed artificially by the injection of mRNA coding for connexin into pairs of apposed *Xenopus* oocytes.[41] A major unsolved problem is how connexons in the juxtaposed cells align to make a channel without, at the same time, forming pores between the cytoplasm and the extracellular solution.

[39]Larsen, W. J., and Veenstra, R. D. 1998. In *Cell Physiology Source Book*, 2nd Ed. Academic Press, New York, pp. 467–480.

[40]Swensen, K. I., et al. 1989. *Cell* 57: 145–155.

[41]Werner, R., et al. 1985. *J. Membr. Biol.* 87: 253–268.

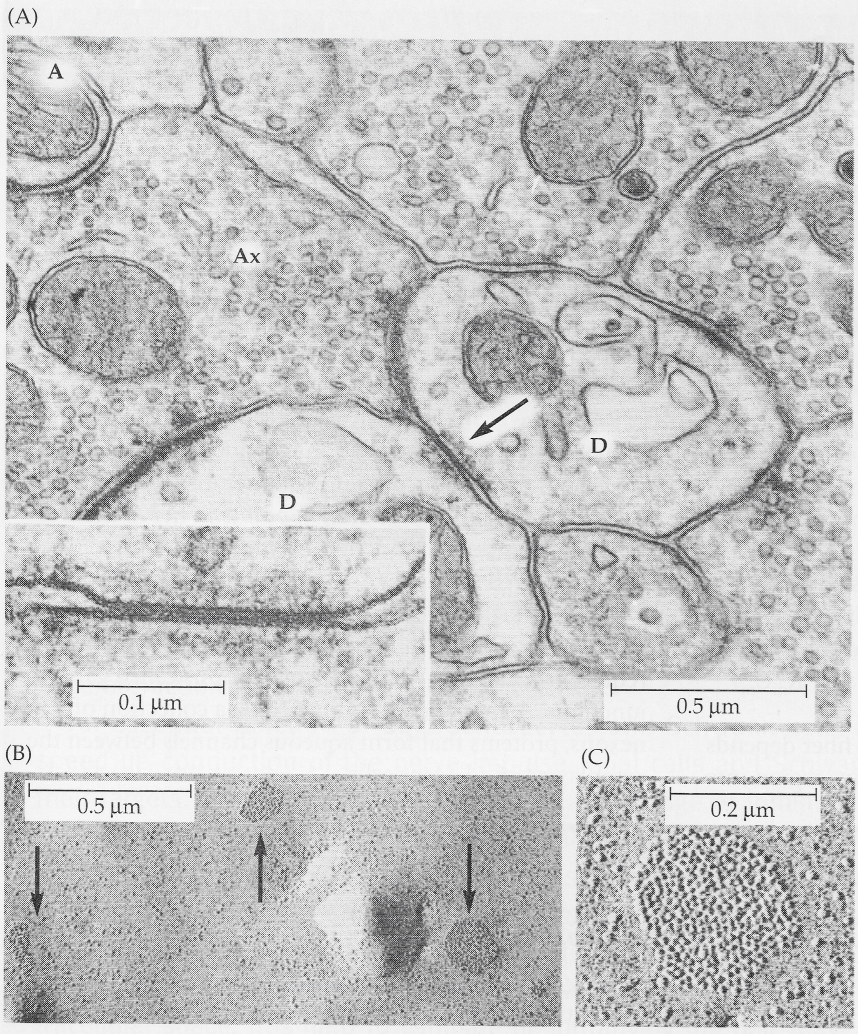


FIGURE 7.8 Gap Junctions between neurons. (A) Two dendrites (labeled D) in the inferior olivary nucleus of the cat are joined by a gap junction (arrow), shown at higher magnification in the inset. The usual space between the cells is almost obliterated in the contact area, which is traversed by cross-bridges. (B) Freeze-fracture through the presynaptic membrane of a nerve terminal that forms gap junctions with a neuron in the ciliary ganglion of a chicken. A broad area of the cytoplasmic fracture face is exposed, showing clusters of gap junction particles (arrows). (C) Higher magnification of one such cluster. Each particle in the cluster represents a single connexon. (D) Gap junction region, showing individual connexons bridging the gap between the lipid membranes of two apposed cells. (A from Sotelo, Llinás, and Baker, 1974; B and C from Cantino and Mugnani, 1975; D after Makowski et al., 1977.)

SUMMARY

■ The spread of local graded potentials in a neuron, and the propagation of action potentials along a nerve fiber, depend on the electrical properties of the cytoplasm and the cell membrane.

■ When a steady current is injected into a cylindrical fiber, the size of a local graded potential is determined by the input resistance of the fiber, r_{input}, and the distance over which it spreads is determined by the length constant of the fiber, λ.

■ The input resistance and length constant are determined, in turn, by the specific resistances of the cell membrane (R_m) and axoplasm (R_i), and by the fiber diameter.

■ Cell membranes, in addition to having a resistance, have a capacitance. The effect of the membrane capacitance, C_m, is to slow the rise and decay of signals. The magnitude of this effect is determined by the membrane time constant, $\tau = R_m C_m$.

■ Propagation of an action potential along a fiber depends on the passive spread of current from the active region into the next segment of membrane. The conduction velocity depends on the time constant and length constant of the membrane.

■ Large nerve fibers in vertebrates are wrapped in myelin sheaths formed by glial cells or Schwann cells. The myelin is interrupted by regularly spaced gaps, or nodes. During action potential propagation, excitation jumps from one node to the next (saltatory conduction).

■ Action potential propagation is influenced by geometrical factors that produce changes in membrane area: Propagation may be blocked at branch points in nerve terminal arborizations, and conduction may have a preferred direction in tapered dendrites.

■ Transfer of electrical signals from one cell to the next requires special low-resistance connections called gap junctions. A gap junction is formed by a collection of connexons, proteins that form aqueous channels between the cytoplasms of adjacent cells.

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