6 Impulses in Nerve and Muscle Cells

A nerve cell conducts an electrochemical impulse because of changes that take place in the cell membrane. These allow movement of ions through the membrane, setting up currents that flow through the membrane and along the cell. Similar impulses travel along muscle cells before they contract. This chapter reviews the basic properties of electric fields and currents that are needed to understand the propagation of the nerve- or muscle-cell impulse.

Section 6.1 introduces the physiology of nerve conduction. The next eight sections develop the electrostatics and the physics of current flow needed to understand how the action potential propagates along the cell.

The next sections deal with the charge distribution on a resting cell membrane (Sect. 6.10) and the cable model of the axon (Sect. 6.11). If the membrane properties do not change as the voltage across the membrane changes, this leads to electrotonus or passive spread (Sect. 6.12). If the membrane properties do change, a signal can propagate without change of shape. Section 6.13 tells how Hodgkin and Huxley developed equations to describe the membrane changes, and Sects. 6.14 and 6.15 apply their results to the propagation of a nerve impulse. The chapter to this point forms an integrated story of conduction in an unmyelinated axon.

Propagation in a myelinated axon is described in Sect. 6.16. Section 6.17 examines the capacitance of a bilayer membrane that has layers with different properties. Section 6.18 shows how minor alterations in the membrane properties can transform the Hodgkin–Huxley model to one that displays repetitive electrical activity.

Section 6.19 illustrates how tabulated solutions to the electrical capacitance of conductors in different geometries can be used to solve diffusion problems with similar geometric configurations.

6.1 Physiology of Nerve and Muscle Cells

A nerve[1] consists of many parallel, independent signal paths, each of which is a nerve cell or fiber. Each cell has an input end (*dendrites*), a *cell body*, a long conducting portion or *axon*, and an output end. The axon portion of the cell can transmit a nerve pulse in either direction. The ends give the cell its unidirectional character. The input end can be a transducer (stretch receptor, temperature receptor, etc.) or a junction (*synapse*) with another cell. A threshold mechanism is built into the input end; when an input signal exceeding a certain level is received, the nerve fires an *impulse* or *action potential* of fixed size and duration that travels down the axon. There may be several inputs that can either aid or inhibit each other, depending on the nature of the synapses.

Muscle cells are also long and cylindrical. An electrical impulse travels along a muscle cell to initiate its contraction. This chapter concentrates on the propagation of the action potential in a nerve cell, but the discussion can be regarded as a model for what happens in muscle cells as well.

The axon transmits the impulse without change of shape. The axon can be more than a meter in length, extending from the brain to a synapse low in the spinal cord or from the spinal cord to a finger or toe. Bundles of axons constitute a nerve. The output end branches out in fine nerve endings, which appear to be separated by a gap from the next nerve or muscle cell that they drive.

The long cylindrical axon has properties that are in some ways similar to those of an electric cable. Its diameter may range from less than one micron (1 μm) to as much as 1 mm

[1] A good discussion of the properties of nerves and the Hodgkin–Huxley experiments is found in Katz (1966). More modern descriptions of nerves and nerve conduction are found in many books, such as Patton et al. (1989) or Nicholls et al. (2011).

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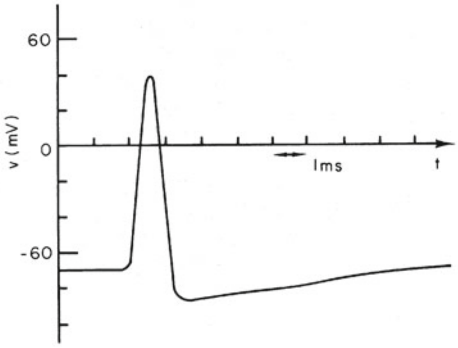

Fig. 6.1 A typical nerve impulse or action potential, plotted as a function of time

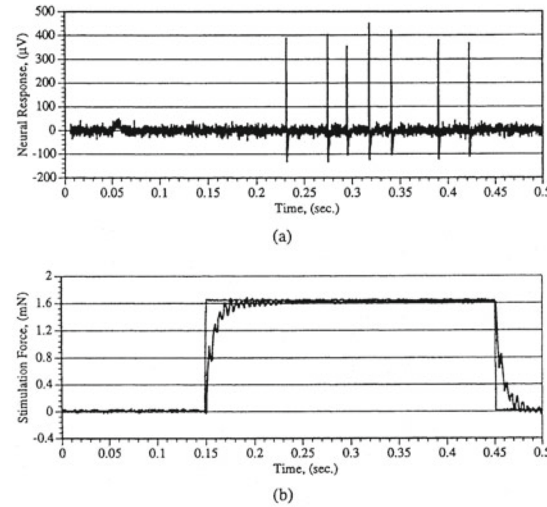

Fig. 6.2 The response of a mechanical receptor in the cornea to an applied force. **a** The impulses recorded on the surface of the nerve bundle. **b** The applied force. Impulses occur while the force is applied. (Source: Kane et al. 1995) © 1995 IEEE. Reprinted by permission

for the giant axon of a squid; in humans the upper limit is about 20 μm. Pulses travel along it with speeds ranging from 0.6 to 100 m s^{-1}, depending, among other things, on the diameter of the axon. The axon core may be surrounded by either a membrane (for an *unmyelinated* fiber) or a much thicker sheath of fatty material (*myelin*) that is wound on like tape. A myelinated fiber has its sheath interrupted at intervals and replaced by a short segment of membrane similar to that on an unmyelinated fiber. These interruptions are called *nodes of Ranvier*. A typical human nerve might contain twice as many unmyelinated fibers as myelinated. We will see in Sect. 6.16 that the myelin gives a faster impulse conduction speed for a given axon radius. Myelinated fibers conduct information where speed is important, such as motor information; unmyelinated fibers conduct information such as temperature, for which speed is not important. A typical unmyelinated axon might have a radius of 0.7 μm with a membrane thickness of 5–10 nm. Myelinated fibers have a radius of up to 10 μm, with nodes spaced every 1–2 mm. We will find later that the spacing of the nodes is about 140 times the inner radius of the fiber, a fact that is quite important in the relationship between conduction speed and fiber radius.

A microelectrode inserted inside a resting axon records an electrical potential that is about 70 mV less than outside the cell. (We will define electrical potential difference in Sect. 6.4.) A nerve impulse or action potential or spike in an unmyelinated axon is shown as a function of time in Fig. 6.1. As the impulse passes by the electrode, the potential rises in a millisecond or less to about +40 mV. The potential then falls to about −90 mV and then recovers slowly to its resting value of −70 mV. The membrane is said to *depolarize* and then *repolarize*.

The history of recording the action potential has been described by Geddes (2000). The propagation speed of the action potential was first measured by Helmholtz around 1850. The measurement technology steadily improved, culminating in the use of a microelectrode inserted by Hodgkin and Huxley (1939) into the cut end of the giant axon of the squid to record the action potential directly.

The information sent along a nerve fiber is coded in the repetition rate of these pulses, all of which are the same shape. Figure 6.2 shows the response of a low-threshold mechanoreceptor in the cornea to a mechanical stimulus. The heavy curve in the bottom panel shows the applied force, and the upper panel shows the impulses.

Comparison of the *intracellular fluid* or *axoplasm* with the *extracellular* fluid surrounding each axon shows an excess of potassium and a deficit of sodium and chloride ions within the cell, as shown in Fig. 6.3. The regenerative action

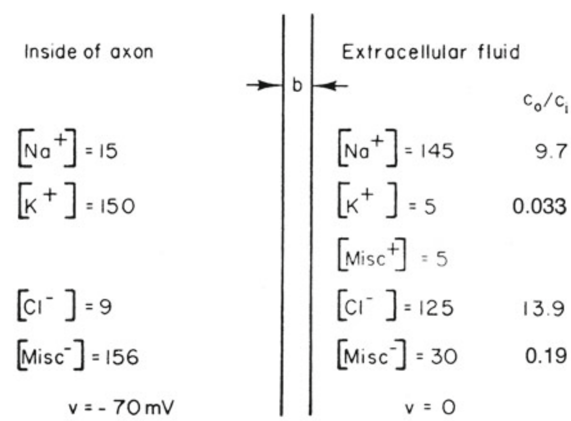

Fig. 6.3 Ion concentrations in a typical mammalian nerve and in the extracellular fluid surrounding the nerve. Concentrations are in mmol l^{-1}; c_o/c_i is the concentration ratio. The membrane thickness is b

that produces the sudden changes of membrane potential is caused by changing permeability of the membrane to ions—primarily sodium and potassium—as discussed in Sects. 6.13 and 6.14. On the molecular level these permeability changes are due to the opening and closing of selected *ion channels*, discussed in more detail in Chap. 9.

The axon can be removed from the rest of the cell and it will still conduct nerve impulses. The speed and shape of the action potential depend on the membrane and the concentration of ions inside and outside the cell. The axoplasm has been squeezed out of squid giant axons and replaced by an electrolyte solution without altering appreciably the propagation of the impulses—for a while, until the ion concentrations change significantly. The axoplasm does contain chemicals essential to the long-term metabolic requirements of the cell and to maintaining the ion concentrations.

At the end of a nerve cell the signal passes to another nerve cell or to a muscle cell across a *synapse* or junction. A few synapses in mammals are electrical; most are chemical (Nolte 2002, p. 193; Hall 2011, Chap. 45). In electrical synapses, channels connect the interior of one cell with the next. In the chemical case a neurotransmitter chemical is secreted by the first cell. It crosses the synaptic cleft (about 50 nm) and activates or inhibits the next cell.

At the neuromuscular junction the transmitter is *acetylcholine* (ACh). ACh increases the permeability of nearby muscle to sodium, which then enters and depolarizes the muscle membrane. The process is quantized.[2] Packets of acetylcholine of definite size are liberated (Katz 1966, Chap. 9; Patton et al. 1989, Chap. 6).

There are a number of neurotransmitters in the central nervous system. *Glutamate* is a common excitatory neurotransmitter in the central nervous system. It increases the membrane permeability to sodium ions, which enhances depolarization. *Glycine*, on the other hand, is an inhibitory neurotransmitter. It causes the interior potential to become more negative (hyperpolarized) and firing is inhibited. A number of other chemical mediators such as norepinephrine, epinephrine, dopamine, serotonin, histamine, aspartate, and gamma-aminobutyric acid, are also found in the nervous system (Hall 2011, Chap. 45).

If the potential becomes high enough (that is, more positive or less negative), the regenerative action of the membrane takes over, and the cell initiates an impulse. If the input end of the cell acts as a transducer, the interior potential rises when the cell is stimulated. If the input is from another nerve, the signal may cause the potential to increase by a subthreshold amount so that two or more stimuli must be received simultaneously to cause firing, or it may decrease the potential and inhibit stimulation by another nerve at the synapse.

[2] See Prob. 3 in Appendix J.

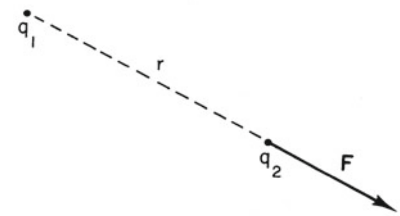

Fig. 6.4 Force **F** is exerted by charge q_1 on charge q_2. It points along a line between them. An equal and opposite force $-\mathbf{F}$ is exerted by q_2 on q_1

This makes possible the logic network that comprises the central nervous system.

6.2 Coulomb's Law, Superposition, and the Electric Field

Coulomb's law relates the electrical force between two charged objects. If two objects have electrical charge q_1 and q_2, respectively, and are separated by a distance r, then there is a force between them, the magnitude of which is given by

$$|\mathbf{F}| = \left(\frac{1}{4\pi\epsilon_0}\right)\frac{q_1 q_2}{r^2}. \tag{6.1}$$

When the charge is measured in coulombs (C), F in newtons (N), and r in meters (m), the constant has the value

$$\frac{1}{4\pi\epsilon_0} \approx 9 \times 10^9 \text{ N m}^2 \text{ C}^{-2} \tag{6.2}$$

to an accuracy of 0.1 %. The direction of the force is along the line between the two charges as shown in Fig. 6.4. If the charges are both positive or both negative, the force is repulsive, which is consistent with assigning a positive sign to **F**. If one is positive and the other negative, then the force is attractive, and **F** is assigned a minus sign. Force **F** is exerted by charge q_1 on charge q_2. The force exerted by q_2 on q_1 has the same magnitude but points in the opposite direction. The forces on both charges act to separate them if they have the same sign and to attract them if the signs are opposite.

If two or more charges exert a force on the particular charge being considered, the total force is found by applying Coulomb's law to each charge (paired with the one on which we want to find the force) and adding the vector forces that are so calculated. An example of this is shown in Fig. 6.5. Charges q_1, q_2, and q_3 are $+1.0 \times 10^{-6}$, -2.0×10^{-6}, and $+3.0 \times 10^{-6}$ C, respectively. The magnitude of the force that q_1 exerts on q_3 is

$$F_{1\text{ on }3} = \frac{(9 \times 10^9)(1 \times 10^{-6})(3 \times 10^{-6})}{(2 \times 10^{-2})^2} = 67.5 \text{ N}.$$

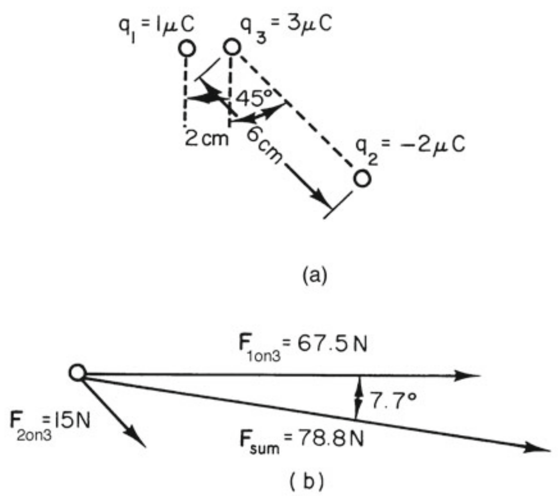

Fig. 6.5 An example of applying Coulomb's law and adding forces on q_3 due to charges q_1 and q_2. **a** The arrangement of charges. **b** The forces on q_3

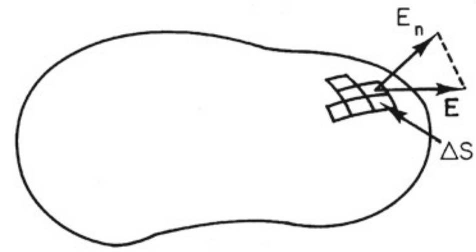

Fig. 6.6 Calculating the integral of the normal component of **E** through a surface

Similarly, the force exerted by q_2 on q_3 is

$$F_{2\text{ on }3} = \frac{(9\times 10^9)(-2\times 10^{-6})(3\times 10^{-6})}{(6\times 10^{-2})^2} = -15\text{ N}.$$

The minus sign means that the force is attractive, that is, toward q_2. The two forces are shown in Fig. 6.5b, along with their vector sum. The sum can be found by components as in Chap. 1. The result is 78.8 N at an angle of 7.7° clockwise from the direction of $\mathbf{F}_{1\text{ on }3}$.

If a collection of charges causes a force to act on some other charge (a *test charge*) located somewhere in space, we say that the collection of charges produces an *electric field* at that point in space. One can think, for example, of charge q_1 producing an electric field vector, of magnitude

$$|\mathbf{E}_1| = \frac{1}{4\pi\epsilon_0}\frac{q_1}{r^2} \tag{6.3}$$

pointing radially away from q_1 (if q_1 is positive) or radially toward q_1 (if q_1 is negative). The force on test charge q_2 placed at the observing point is then

$$\mathbf{F} = q_2\mathbf{E}_1. \tag{6.4}$$

6.3 Gauss's Law

It is possible to derive a theorem about the electric field from a collection of charges, known as *Gauss's law*. Rather than derive it from Coulomb's law, we will state it and show that Coulomb's law can be derived from it. Then we will consider some examples of its use.

Divide up *any* closed surface into elements of surface area, such as ΔS in Fig. 6.6. For each element ΔS, calculate the component of **E** normal to the surface, E_n, and multiply it by the magnitude of the surface area ΔS. Add these quantities for the entire closed surface, calling them positive if the normal component of **E** points outward and negative if **E** points inward. Gauss's law says that the resulting sum is equal to the total charge inside the surface, divided by ϵ_0. In symbols,[3]

$$\iint E_n\, dS = \frac{q}{\epsilon_0} = \frac{4\pi q}{4\pi\epsilon_0}. \tag{6.5}$$

This surface integral is exactly the same as the flux of the continuity equation, Eq. 4.4. It is in fact called the electric field flux.[4] The surface is called a *Gaussian surface*.

While Gauss's law is always *true*, it is not always *useful*. It is helpful only in cases where **E** is constant over the entire surface of integration, or when the surface can be divided into smaller surfaces, on each of which E_n can be argued to be constant or zero. One of the few cases in which Gauss's law is useful to calculate **E** is the case of a point charge, and another is related to the cell membrane. In each case, the symmetry of the problem allows the surface of integration to be specified so that E_n is either constant or zero.

The first example is a point charge in empty space. Since such a charge has no preferred orientation (it is a point), and since there is nothing else around to specify a preferred direction in space, the electric field must point radially toward or away from the charge and must depend only on distance from the charge. Therefore, if the Gaussian surface is a sphere centered on the charge, E_n is the same everywhere on the sphere.

[3] Some books use one integral sign in this equation and others use two. Strictly speaking the integral over a surface is a two-dimensional integral.

[4] Additional discussion and examples can be found in Schey (2004).

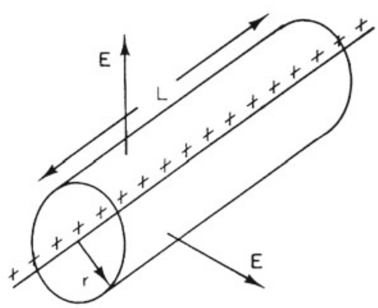

Fig. 6.7 Gauss's law is used to calculate the electric field from an infinite line of charge. The Gaussian surface is a segment of a cylinder concentric with the line of charge

It can be taken outside the integral in Eq. 6.5 to give

$$\iint E_n \, dS = E \iint dS.$$

The integral of dS over the entire surface of the sphere is just the surface area of the sphere, $4\pi r^2$ (see Appendix L). Gauss's law gives

$$4\pi r^2 E = \frac{q}{\epsilon_0}$$

or

$$E = \frac{q}{4\pi\epsilon_0 r^2}.$$

Gauss's law implies Coulomb's law for the case of a point charge.

If the charge in this problem is not a point charge, nothing changes in the argument as long as the charge distribution is spherically symmetric. The electric field at a distance r from the center of the distribution is the same as if all the charge within the sphere of radius r were located at the center of the sphere.

Next, consider a problem with cylindrical symmetry rather than spherical symmetry. An example is an infinitely long line of charge. For a segment of the line of charge of length L, the amount of charge is proportional to L, $q = \lambda L$, where λ is the linear charge density in units C m^{-1}. Symmetry shows that **E** must point radially outward (or inward) and be perpendicular to the line. Therefore if the Gaussian surface is a cylinder of length L and radius r, the axis of which is the line of charge, one can argue that on the end caps $E_n = 0$, while on the wraparound surface of the cylinder $E_n = |\mathbf{E}|$. This is shown in Fig. 6.7. The total integral is therefore the integral for the wraparound surface, which is $E \iint dS$. The surface area of the cylinder is its circumference $(2\pi r)$ times its length (L). Therefore Gauss's law becomes $2\pi r L \, E = \lambda L/\epsilon_0$, or

$$E = \frac{\lambda}{2\pi\epsilon_0 r}. \tag{6.6}$$

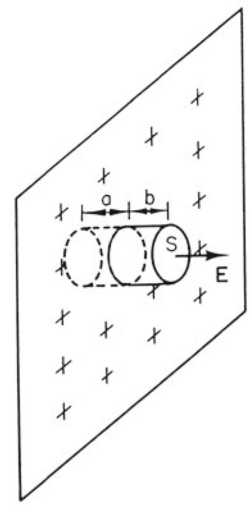

Fig. 6.8 A portion of an infinite sheet of charge and the appropriate Gaussian surface

Since the constant $1/4\pi\epsilon_0$ is so easily remembered, it is convenient to write this as

$$E = \frac{1}{4\pi\epsilon_0} \frac{2\lambda}{r}. \tag{6.7}$$

Consider next an infinite sheet of charge, with charge per unit area σ C m^{-2}. The symmetry of the situation requires that **E** be perpendicular to the sheet. To see why, suppose that **E** is not perpendicular to the sheet. I stand on the sheet looking in such a direction that **E** points diagonally off to my left. If I turn around in place, I see **E** pointing diagonally off to my right. Since the charge per unit area is constant and extends an infinite distance in every direction, the charge distribution looks exactly the same as it did before I turned around. The only way to resolve this contradiction (that **E** changed direction while the charge distribution did not change) is to have **E** perpendicular to the sheet.

The Gaussian surface can be a cylinder with end caps of area S and sides perpendicular to the sheet. Let the end caps be a distance a from the charge sheet on one side and b from the charge sheet on the other, as in Fig. 6.8. Since there is no component of **E** across the sides of the cylinder, changing b or a does not change the total flux through the surface. Since the charge inside the volume does not change, E must be independent of distance from the sheet of charge. (This is true only because the charge sheet is infinite.) By symmetry, the flux through each end cap is the same, as may be seen from the cross section of the surface in Fig. 6.9. The total flux is therefore $2ES$, while the charge within the volume is σS. Therefore, Gauss's law gives

$$E = \frac{\sigma}{2\epsilon_0} = \frac{1}{4\pi\epsilon_0} 2\pi\sigma. \tag{6.8}$$

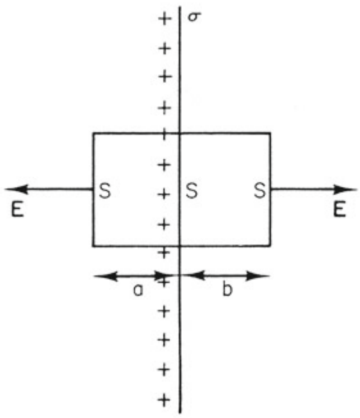

Fig. 6.9 A side view of the Gaussian surface in Fig. 6.8

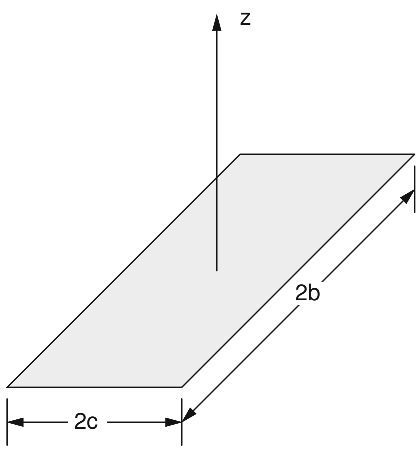

Fig. 6.10 A rectangular sheet of charge. The electric field along the z axis is shown in Fig. 6.11 for $2b = 200\,\text{m}$ and $2c = 2\,\text{m}$

There is, of course, something quite unreal about a sheet of charge extending to infinity. However, it is a good approximation for an observation point close to a finite sheet of charge. If the sheet is limited in extent and the observation point is far away, the distance to all parts of the sheet from the observation point is nearly the same, and the charge sheet may be regarded as a point charge. If one considers a rectangular sheet of charge lying in the xy plane of width $2c$ and length $2b$, as shown in Fig. 6.10, it is possible to calculate exactly the **E** field along the z axis. By symmetry, the field points along the z axis. The surface charge density is σ. The distance is $r = \left(x^2 + y^2 + z^2\right)^{1/2}$. The component of **E** parallel to the z axis is $E \cos\theta = Ez/r$. Therefore, if the charge in element of area $dx\,dy$ is $\sigma\,dx\,dy$, the field is

$$E = \frac{\sigma z}{4\pi\epsilon_0} \int_{-b}^{b} \int_{-c}^{c} (x^2 + y^2 + z^2)^{-3/2}\,dx dy. \tag{6.9}$$

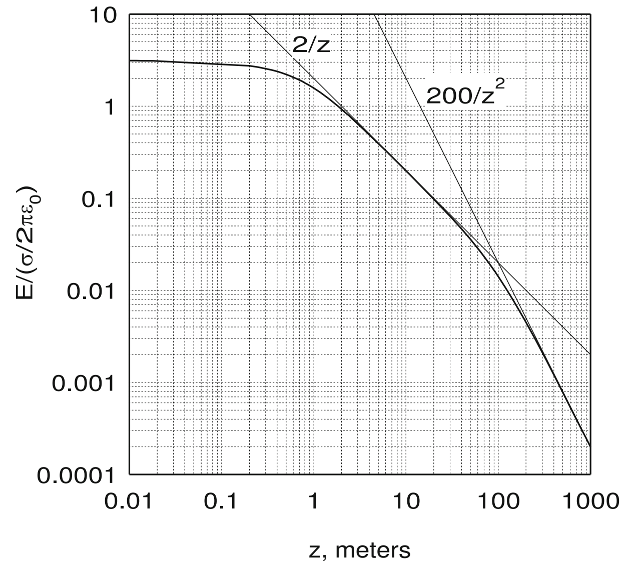

Fig. 6.11 A log-log plot of the electric field from a sheet of charge of width 2 m and length 200 m, measured along the perpendicular bisector of the sheet (Fig. 6.10). Much closer than 1 m, the field is constant. Around 10 m the field is proportional to $1/r$, the field from a line charge. Farther away than 100 m the field is proportional to $1/r^2$, the field from a point charge

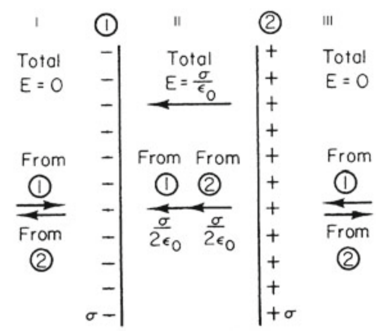

Fig. 6.12 The electric field due to two infinite sheets of charge of opposite sign

This integral can be evaluated (see Problem 7). The result is

$$E = \frac{4\sigma}{4\pi\epsilon_0} \tan^{-1}\left(\frac{bc}{z\sqrt{c^2 + b^2 + z^2}}\right). \tag{6.10}$$

This is plotted in Fig. 6.11 for $c = 1\,\text{m}$, $b = 100\,\text{m}$. Close to the sheet ($z \ll 1$) the field is constant, as it is for an infinite sheet of charge. Far away compared to 1 m but close compared to 100 m, the field is proportional to $1/r$ as with a line charge. Far away compared to 100 m, the field is proportional to $1/r^2$, as from a point charge.

As a final example, consider two infinite sheets of charge, one with density $-\sigma$ and the other with density $+\sigma$, as shown in Fig. 6.12. This can be solved by using the result for a single

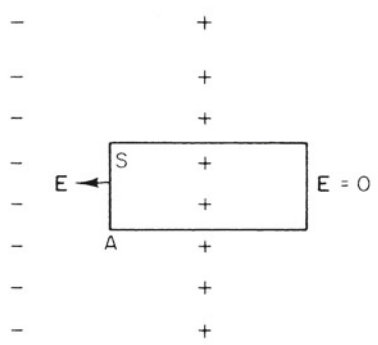

Fig. 6.13 A Gaussian surface to determine the electric field between two sheets of charge

sheet of charge, Eq. 6.8, and the principle of superposition. Consider first the region I of Fig. 6.12. There, the negative charge will give an **E** field that has magnitude $\sigma/2\epsilon_0$ and points toward the right, while the positive sheet of charge will give an **E** field of $\sigma/2\epsilon_0$ pointing to the left. The total **E** field in region I is zero. A similar argument can be made in region III with the field of the negative charge pointing left and that of the positive charge pointing to the right. Again the sum is zero. In region II, however, the two **E** fields point in the same direction, and the total field is

$$E = \frac{\sigma}{\epsilon_0} = \frac{1}{4\pi\epsilon_0} 4\pi\sigma. \qquad (6.11)$$

Notice the factor of 2 difference between Eqs. 6.8 and 6.11. Another way to explain the difference is that there is no **E** in region III, so that a Gaussian surface can be constructed as shown in Fig. 6.13. Then the flux is zero through every surface except cap A. The charge within the volume is σS, while the flux through cap A is ES. Therefore, $E = \sigma/\epsilon_0$.

Within a cell membrane of 6 nm thickness surrounding a cell of radius 5 µm or 5 000 nm, the electric field can be calculated by making the approximation that the sheets of charge are infinite. Suppose that the electric field within the membrane is 1.17×10^7 N C^{-1}. (We will learn how to determine this value later.) From Eq. 6.11 the charge density is

$$\sigma = \frac{E}{4\pi(1/4\pi\epsilon_0)} = \frac{1.17 \times 10^7}{4\pi(9 \times 10^9)} = 1.03 \times 10^{-4} \text{ C m}^{-2}.$$

This tells us something about the makeup of the cell. The membrane is in contact with atoms, each of which has a diameter of about 10^{-10} m. Therefore there are approximately 10^{20} atoms (in water molecules, as ions, etc.) in contact with 1 m^2 of the membrane surface. Suppose that the excess charge that causes the electric field in the membrane resides in these atoms and that each atom is either neutral or a monovalent ion. The number of atoms in the square meter which are charged is

$$\frac{1.03 \times 10^{-4} \text{ C m}^{-2}}{1.6 \times 10^{-19} \text{ C atom}^{-1}} = 6.4 \times 10^{14} \text{ atoms m}^{-2}.$$

The fraction of atoms that are charged is $(6.4 \times 10^{14})/(10^{20}) = 6.4 \times 10^{-6}$. Roughly 1 in every 10^5 atoms in contact with the membrane carries an unneutralized charge. (This result is modified by partial neutralization of this external charge by charge movement within the membrane. See Eq. 6.35 and the footnote on p. 157.)

6.4 Potential Difference

It is often convenient to talk about the *electrical potential difference*, or *voltage difference,* instead of the electric field. The potential is related to the difference in energy of a charge when it is at different points in space. Suppose that an electric field **E** of magnitude E_x points along the x axis. A positive charge is located at point A. A force $\mathbf{F}_{\text{ext}}$ must be applied to the charge by something besides the electric field, or else the charge will be accelerated to the right by the force qE_x. The charge can be moved slowly to the right at a constant speed so that its kinetic energy remains fixed, if the external force is always to the left and its magnitude is adjusted so that $F_{\text{ext}} = -qE_x$.

This situation is shown in Fig. 6.14. The external force does work on the charge. One can either say that the total work done on the charge by both forces is equal to zero, or one can ignore the work done by the electric force and invent the idea of potential energy—energy of position—due to the electric field. The increase in potential energy[5] as the charge moves a distance dx is

$$dU = F_{\text{ext}}\, dx = -qE_x\, dx.$$

If E_x varies with position, the total change in potential energy when the particle is moved without acceleration from A to B is given by

$$\Delta U = U(B) - U(A) = -q \int_A^B E_x(x)\, dx. \qquad (6.12)$$

For example, in a constant electric field of 1.4×10^7 N C^{-1}, a particle with charge $q = 1.6 \times 10^{-19}$ C experiences an electric force equal to 2.24×10^{-12} N. If it is moved 5 nm along the x axis, the electric force does 1.12×10^{-20} J of work on it, increasing its kinetic energy. To prevent this

[5] In earlier chapters the potential energy was called E_p, and the total energy was called U. For the next few pages U will be used for potential energy, to avoid confusion with a component of the electric field.

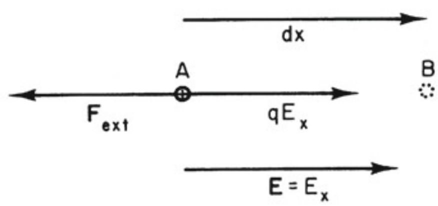

Fig. 6.14 A charge q is moved from A to B, a distance dx in the x direction. External force $\mathbf{F}_{\text{ext}}$ keeps the charge from being accelerated

increase in kinetic energy, F_{ext} must be applied. The external force does work -1.12×10^{-20} J. We can either say that the total work done by both forces is zero or we can ignore the electrical force and say that the external force changed the potential energy of the particle by -1.12×10^{-20} J as the particle moved from A to B.

If the displacement of the particle is perpendicular to the direction of the electric field, it is also perpendicular to the direction of $\mathbf{F}_{\text{ext}}$. Therefore neither force does work on the particle and the potential energy is unchanged. This fact can be used to prove (Serway and Jewett 2013, p. 567) that in three dimensions,

$$\Delta U = U(B) - U(A) \tag{6.13}$$
$$= -q\left(\int_A^B E_x\,dx + \int_A^B E_y\,dy + \int_A^B E_z\,dz\right).$$

Using the notation of a "dot" or scalar product of two vectors (Sect. 1.9), this can also be written as a line integral along any path from A to B:

$$\Delta U = -q \int_A^B \mathbf{E} \cdot d\mathbf{r}. \tag{6.14}$$

It is easier to evaluate the integral along some paths than along others.

The potential energy difference is measured in joules. It is always proportional to the charge of the particle that is moved in the electric field. It is convenient to define the *potential difference* Δv to be the potential energy difference per unit charge. When the energy difference is in joules and the charge is in coulombs, the ratio is J C^{-1}, which is called a volt (V):

$$\Delta v \quad (\text{V}) = \frac{\Delta U \quad (\text{J})}{q \quad (\text{C})}. \tag{6.15}$$

To move a charge of +3 C from point A to point B where the potential is 5 V higher requires that 15 J of work be done on the charge. If the charge is then allowed to move back to point A under the influence of only the electric field, its kinetic energy increases by 15 J as the potential energy decreases by the same amount.

This definition of potential, when combined with the definition of potential energy, Eq. 6.12, gives

$$\Delta v = -\int_A^B E_x\,dx$$

or

$$E_x = -\frac{\partial v}{\partial x}. \tag{6.16a}$$

That is, the component of the electric field in any direction is the negative of the rate of change of potential in that direction. The units of $\mathbf{E}$ were seen earlier to be N C^{-1} (from $\mathbf{F} = q\mathbf{E}$). Equation 6.16 shows that the units of $\mathbf{E}$ are also V m^{-1}. In three dimensions this relationship becomes

$$\mathbf{E} = -\operatorname{grad} v = -\nabla v, \tag{6.16b}$$

where grad is the gradient operation defined in Eq. 4.19.

Notice that only differences in potential energy and differences in potential (or colloquially, differences in voltage) are meaningful. We can speak of the potential at a point only if we have previously agreed that the potential at some other point will be called zero. Then we are really speaking of the difference of potential between the reference point and the point in question.

In many cases, it is customary to define the potential to be zero at infinity. Then the potential at point B is

$$v(B) = -\int_\infty^B E_x\,dx.$$

If you try to apply this equation to the infinite line and sheet of charge, you will discover that it does not work. The reason is that you cannot get infinitely far away from a charge distribution that extends to infinity.

6.5 Conductors

In some substances, such as metals or liquids containing ions, electric charges are free to move. When all motion of these charges has ceased and static equilibrium exists, there is no net charge within the conductor. To see why there is not, consider a small volume within the conductor. If there were an electric field within that region, the charges there would experience an electric force. Since they are free to move, this force would accelerate them. This force will vanish only when the electric field within the conductor is zero. Therefore, in the static case the electric field within a conductor is zero. Now apply Gauss's law to a small volume within the conductor. Since the electric field in the conductor is zero everywhere, the flux through the Gaussian surface is zero, and the net charge within the volume is zero.

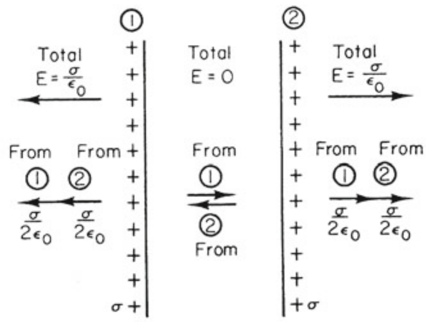

Fig. 6.15 The electric field in and around an infinite plane conductor carrying a charge on each surface

At the surface of the conductor, there may well be charge that gives rise to electric fields outside the conductor. Consider, for example, an infinite sheet of metal that has positive charge on it. The positive charge will distribute itself as shown in Fig. 6.15, and either superposition or Gauss's law may be used to show that the electric field outside the conductor is σ/ϵ_0.

Because the electric field is zero throughout a conductor in equilibrium, no work is required to move a charge from one point to another. All parts of the conductor are at the same potential. This statement is true only if the charges are not moving. We will see later that if they are (that is, if a current is flowing), then the electric field in the conductor is not zero and the potential in the conductor is not the same everywhere.

6.6 Capacitance

Suppose that two conductors are fixed in space, with charge $+Q$ on one and $-Q$ on the other. The potential difference v between the conductors is proportional to Q. The proportionality constant depends on the geometrical arrangement of the conductors. When the proportionality is written as

$$Q = Cv \tag{6.17}$$

the proportionality constant C is called the *capacitance*. The units of capacitance are C V^{-1} or farads (F).

As an example of capacitance, consider two parallel conducting plates side by side. Let the area of each be S and the separation be b. The charge layers of Fig. 6.13 might be charge on the inner surface of each conductor. The total charge on each plate has magnitude σS. The electric field between the plates is σ/ϵ_0 and the potential difference is $v = Eb = \sigma b/\epsilon_0$. (Note that the potential difference is proportional to the charge per unit area.) The capacitance is

$$C = \frac{Q}{v} = \frac{\sigma S \epsilon_0}{\sigma b} = \frac{\epsilon_0 S}{b}. \tag{6.18}$$

If the plates are separated further with a fixed charge on them, the potential difference increases and the capacitance is decreased. Increasing the area and charge of the plates with fixed σ and fixed b increases Q and C but not v.

6.7 Dielectrics

Charges rearrange themselves so that there is no static electric field within a conductor. In a dielectric, charges are not free to move far enough to completely cancel the effect of any external electric field, but they can move far enough to cause a partial cancellation.[6]

The partial neutralization of the external electric field can be understood from the following model. Consider a dielectric in the absence of external fields. The electron distribution of each atom is centered on the nucleus so that there is no electric field (at least when we average over a region containing many atoms). This is shown schematically in Fig. 6.16a, in which each + sign represents a nucleus and each circle represents a distribution of negative charge in an atom. Figure 6.16b shows some external charges producing an electric field. If the dielectric is introduced in the space where this electric field exists, the negative electron clouds are shifted with respect to the nuclei, as shown in Fig. 6.16b. The result is a polarization electric field $\mathbf{E}_p$, which is in the opposite direction to the external electric field. The total field within the dielectric is the vector sum of these two fields:[7]

$$\mathbf{E}_{\text{tot}} = \mathbf{E}_{\text{ext}} + \mathbf{E}_p. \tag{6.19}$$

In simple materials all three vectors are parallel and E_p is proportional to E_{tot}. Then we can define the *electric susceptibility* χ by the equation

$$E_p = -\chi E_{\text{tot}}.$$

This can be combined with the previous equation to get

$$E_p = -\frac{\chi}{1+\chi} E_{\text{ext}}.$$

[6] In some materials an electric field applied along one direction can cause charge displacement in a different direction. This book deals only with cases in which the induced electric field is parallel to the applied electric field.

[7] In most textbooks, it is customary to define the polarization by $\mathbf{P} = -\mathbf{E}_p$ or $\mathbf{P} = -\epsilon_0 \mathbf{E}_p$. We have not done that in order to make the phenomenon easier to understand.

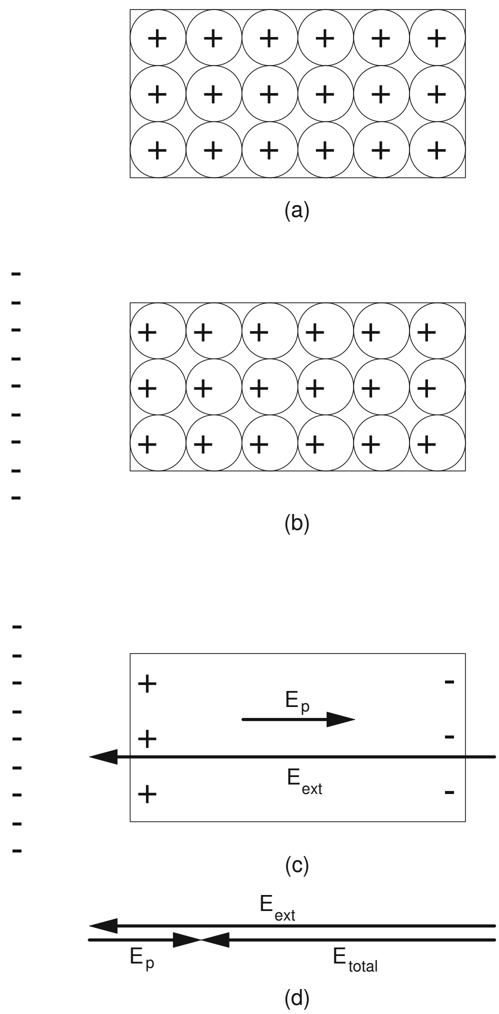

Fig. 6.16 The polarization of a dielectric by an external electric field. **a** Atoms in the absence of an external field. **b** An external electric field causes a shift of each electron cloud relative to the positively charged nucleus. **c** There is a net buildup of positive charge at the left edge of the dielectric and of negative charge at the right edge. **d** The total electric field within the dielectric is the sum of the external electric field and the polarization electric field induced in the dielectric

The polarization electric field is thus proportional to both the total electric field (proportionality constant $-\chi$) and the external field [proportionality constant $-\chi/(1+\chi)$]. The former relationship is more fundamental, since the field displacing charges in one atom is the total field, due to both external charges and to the charges in neighboring atoms.

The total field within the dielectric is

$$E_{\text{tot}} = E_{\text{ext}} - \frac{\chi}{1+\chi} E_{\text{ext}} = \frac{1}{1+\chi} E_{\text{ext}} = \frac{1}{\kappa} E_{\text{ext}}. \quad (6.20)$$

The factor $\kappa = 1 + \chi$ is called the *dielectric constant* of the dielectric. The electric field within the dielectric is reduced by the factor $1/\kappa$ from that which would exist without

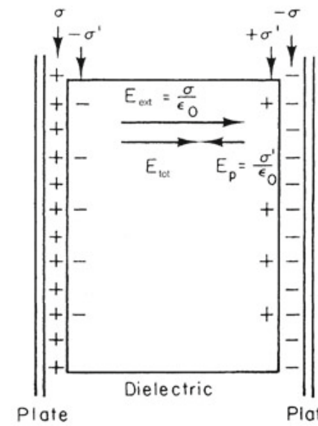

Fig. 6.17 The polarization electric field reduces the electric field between the plates. The conducting plates could be extracellular and intracellular fluid, and the dielectric could be the cell membrane

the dielectric. The dielectric constant for typical nerve membranes[8] is about 7. The dielectric constant of water is quite high (around 80) because the water molecules can easily reorient their charged ends.

The relationship between the applied field, the polarization field, and the total field can be seen in the following example. The electric field between two parallel sheets of charge of density $+\sigma$ and $-\sigma$ per unit area has magnitude $E_{\text{ext}} = \sigma/\epsilon_0$. If there is dielectric between them (such as a cell membrane) and if the polarization in the dielectric is uniform, then there is effectively a charge $\pm\sigma'$ induced on the surface of the dielectric that partially neutralizes the external charges. This is shown in Fig. 6.17. The total electric field within the membrane is $E_{\text{tot}} = \left|\mathbf{E}_{\text{ext}} + \mathbf{E}_p\right| = \sigma/\epsilon_0 - \sigma'/\epsilon_0 = \sigma_{\text{net}}/\epsilon_0 = E_{\text{ext}}/\kappa$.

To recapitulate, in Fig. 6.17 E_{ext} is σ/ϵ_0 and depends on the external charge distribution; the potential difference between the plates depends on the total field, and its magnitude is E_{tot} times the plate separation.

It is customary to refer to two different kinds of charge. The *free charge* is the charge that we bring into a region. We have some control over it. The *bound charge* is the charge induced in the dielectric by the movement or distortion of atoms and molecules in the dielectric in response to the free charge that has been introduced. Gauss's law can be written either in terms of the total charge (free plus bound)

$$\iint E_n \, dS = \frac{q_{\text{tot}}}{\epsilon_0} = \frac{q_{\text{free}} + q_{\text{bound}}}{\epsilon_0} \quad (6.21a)$$

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[8] This value is high compared to the dielectric constant for a pure lipid, which is between 2 and 3. See the discussion in Sect. 6.17.

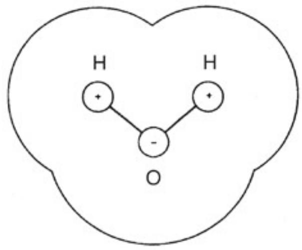


Fig. 6.18 A schematic diagram of a water molecule. The hydrogen nuclei are 96.5 pm from the oxygen nucleus; the included angle is about 104°. The radius of each hydrogen atom is about 120 pm; the radius of the oxygen atom is about 140 pm. The water molecule has a permanent electric dipole moment because the oxygen atom carries a partial negative charge and each hydrogen atom carries a partial positive charge

or in terms only of the free charge

$$\iint \kappa E_n \, dS = \frac{q_{\text{free}}}{\epsilon_0}. \tag{6.21b}$$

The dielectric constant is placed inside the integral sign because the Gaussian surface could pass through materials with different values of the dielectric constant.

As another example of the effect of a dielectric, consider a spherical ion of radius a in which all the charge resides on the surface. In a vacuum, the potential at distance r is $v = q/4\pi\epsilon_0 r$, so on the surface of the ion, the potential is $q/4\pi\epsilon_0 a$. The work required to bring to the surface an additional charge dq is $dW = v dq = q dq/4\pi\epsilon_0 a$. The total work required to place charge Q on the ion is therefore

$$W = \int dW = \frac{1}{4\pi\epsilon_0 a}\int_0^Q q\, dq = \frac{\frac{1}{2}Q^2}{4\pi\epsilon_0 a}.$$

If the sphere is immersed in a uniform dielectric the total electric field and therefore the potential is reduced by a factor κ. The energy required to assemble the ion is then

$$W = \frac{\frac{1}{2}Q^2}{4\pi\epsilon_0 \, \kappa \, a}. \tag{6.22}$$

This is called the *Born charging energy*. For an ion of radius 0.2 nm (200 pm) and $Q = 1.6 \times 10^{-19}$ C, the Born charging energy in a vacuum is 5.8×10^{-19} J ion^{-1}. Multiplying by Avogadro's number gives 3.5×10^5 J mol^{-1}. Often in problems involving charges of a few times the electronic charge, it is convenient to use the energy unit electron volt: 1 eV$= 1.6 \times 10^{-19}$ J. For this problem, the Born charging energy is 3.6 eV ion^{-1}.

If the ion is in a dielectric with $\kappa = 2$ (a lipid, for example), the Born charging energy is reduced to 1.8 eV ion^{-1}. Water has a very high dielectric constant (about 80) because the water molecules look roughly like that in Fig. 6.18, and the molecules can easily align with an applied electric field. The same ion in water has a Born charging energy of 0.045 eV. At room temperature, the Boltzmann factor for the energy required to create the ion in vacuum is 3.32×10^{-61}. In a lipid, it is 5.76×10^{-31}, and in water, it is 0.175. This explains why it is easy to form ionic solutions in water but not in lipids.

6.8 Current and Ohm's Law

In the electrostatic case, there are no moving charges and no electric field within a conductor. When a current flows in a conductor, charges are moving and there is an electric field.

The electric current i in a wire is the amount of charge per unit time passing a point on the wire. If the amount of charge in time dt is dQ, the current is

$$i = \frac{dQ}{dt}. \tag{6.23}$$

The units of the current are C s^{-1} or amperes (A) (sometimes called amps). The current density j (or j_Q in the notation of Chap. 5) is the current per unit area, i/S. The units are C m^{-2} s^{-1} or A m^{-2}. In an extended medium, the current density is a vector $\mathbf{j}$ at each point in the medium. The direction of $\mathbf{j}$ is the direction charge is moving at that point.

If there is no electric field in the conductor, there is no average motion of the charges. (There will be random thermal motion, but it will be equally likely in every direction. This random motion of charges is one cause of "noise" in electrical circuits.) To have a current there must be an electrical field in the conductor; this means that there will be a potential difference between two points in the conductor. If there is no potential difference between two points in the conductor, there is no current. For the simple conductor of Fig. 6.19, the current is found to be proportional to the voltage difference between the ends of the conductor. The current is shown flowing from B to A. When $v(B)$ is greater than $v(A)$, v is positive and the current is positive. When v is negative, the current is in the other direction and is also negative.

For the wire of Fig. 6.19, the relationship between current and voltage difference is linear. In that case, we can write *Ohm's law*:

$$i = \frac{1}{R}v = Gv \tag{6.24a}$$

or

$$v = iR. \tag{6.24b}$$

R is called the *resistance* of the conductor. Since the current is measured in amps and the voltage in volts, its units are V A^{-1} or ohms (Ω). The reciprocal of the resistance is the *conductance* G. Its units are Ω^{-1} or siemens (S).

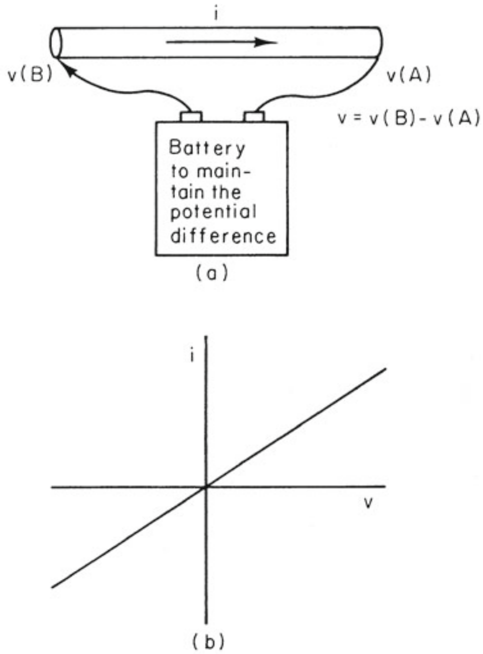


Fig. 6.19 A current flows in the wire as long as the battery or some other device maintains a potential difference between two points on the wire. The potential difference means that there is an electric field within the wire. If the wire obeys Ohm's law, the current is proportional to the potential difference

Ohm's law is not universal. It describes only certain types of conductors. Figure 6.20 shows the current–voltage characteristics of several devices that have nonlinear behavior and that make modern electronic circuits possible (Horowitz and Hill 2015). They are shown here not for their own sake, but to emphasize the limited validity of Ohm's law. The nerve cell membrane is not linear.

It is possible to write Ohm's law in another form. Placing two identical wires in parallel in the circuit of Fig. 6.19 would cause twice as much current to flow (assuming that the battery maintains the voltage difference at the original level). The current density j remains constant as the cross-sectional area of the wire is changed, when the wire length and voltage difference are held fixed. Similarly, to maintain the same current through a single wire twice as long requires a voltage difference twice as great. Therefore, it is voltage per unit length that determines the current. In this spirit, Ohm's law can be written as

$$j = \frac{i}{S} = \frac{v(B) - v(A)}{SR}.$$

If L is the length of the wire and x the position along it, this can be written as

$$j_x = -\frac{L}{SR}\frac{v(x=L) - v(x=0)}{L} = -\frac{L}{SR}\frac{\partial v}{\partial x}, \quad (6.25a)$$

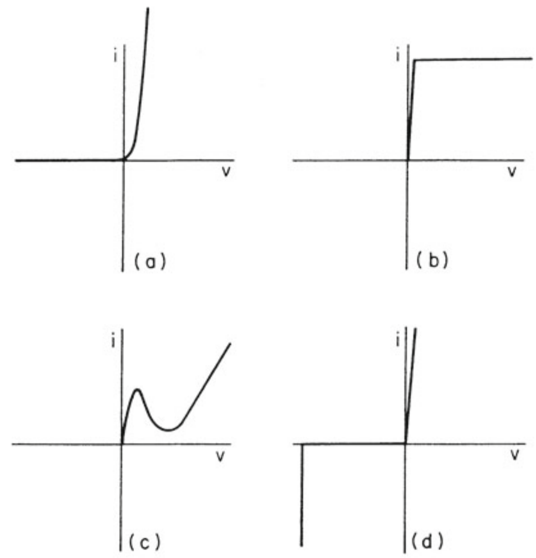


Fig. 6.20 Current–voltage relationships for some nonlinear devices used in electronic circuits. **a** Diode. **b** Transistor. **c** Tunnel diode. **d** Zener diode

$$j_x = -\sigma \frac{\partial v}{\partial x}. \quad (6.25b)$$

In three dimensions this alternative statement of Ohm's law becomes

$$\mathbf{j} = \sigma \mathbf{E}. \quad (6.26)$$

The σ in this equation[9] is the electrical conductivity, measured in (A m^{-2})/(V m^{-1}) or S m^{-1}. Its reciprocal is the resistivity of the material, ρ. The units of resistivity are Ω m. For a cylindrical conductor, the resistivity and the resistance are related by

$$\frac{1}{\rho} = \frac{L}{SR}$$

or

$$R = \rho \frac{L}{S}. \quad (6.27)$$

This shows that making the conductor longer increases its resistance, while increasing the cross-sectional area lowers the resistance.

Suppose that an electric field acts on a charge moving in a medium that obeys Ohm's law. The electric field does work on the charge, but the energy is continually transferred to the medium by collisions between the charge and other particles

[9] Note that σ has now been used for two things in this chapter: surface charge per unit area and conductivity. This notation is standard in the literature. You can tell from the context which is meant. Similarly, the symbol ρ is used for charge per unit volume and for resistivity (and for mass density in other chapters). These double usages are found frequently in the literature.

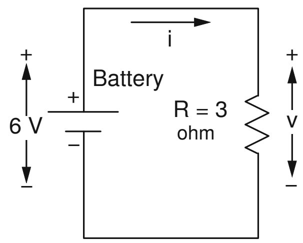


Fig. 6.21 A resistor connected to a battery

in the medium. If a charge Q moves to a lower potential, all the energy it gained is transferred to heat. The rate of energy dissipation is the *power*

$$P = vi. \tag{6.28}$$

The units of power are J s^{-1} or watts (W). For a material that obeys Ohm's law, Eq. 6.28 can be combined with Ohm's law to give

$$P = i^2 R \tag{6.29}$$

or

$$P = \frac{v^2}{R}. \tag{6.30}$$

This type of energy loss has clinical significance. If a patient contacts a source of very high voltage such as an 11,000-V power line, the strong electric fields will cause current to flow throughout the patient's body or limb, because $\mathbf{j} = \sigma \mathbf{E}$. The resistive heating can be enough to boil water within the tissues. If the limb is x rayed, the steam bubbles will look very much like the bubbles that appear in *clostridium* (gas gangrene) infections; if the x ray is deferred a few days, it will be impossible to tell from the x ray whether the bubbles are due to the electrical injury or subsequent infection.

6.9 The Application of Ohm's Law to Simple Circuits

The ultimate goal of this chapter is to apply Ohm's law to the axon. Before doing that, however, it is worthwhile to see how it can be applied to some simpler circuits in which the current and voltage are not changing with time.

The simplest circuit is a resistance R connected across a battery, as shown in Fig. 6.21. The battery voltage of 6 V is the potential difference across the resistor. If the resistance is 3 Ω, the current is $i = v/R = 6/3 = 2$ A. The rate of heat production in the resistor is $P = vi = (6)(2) = 12$ W. This could also have been calculated from $P = v^2/R = 36/3$, or $P = i^2 R = (4)(3)$. A current of 2 A means that every second 2 C of charge leave the positive terminal of the battery and flow through the resistor. When the charge arrives at the other end of the resistor, it has lost 12 J of energy to heat. The 2 C then travel through the battery back to the positive terminal, gaining 12 J from a chemical reaction within the battery.

This example has been stated as though the positive charge moves. In a metallic conductor negative charges (electrons) move from the negative terminal of the battery through the resistor to the positive terminal. In salt water and most body fluids, both positive and negative ions move. From a macroscopic point of view, we cannot tell the difference between the transport of a charge $-q$ from point A to point B, and the transport of a charge $+q$ from point B to point A. Both processes make the total charge at B less positive and the total charge at A more positive by an amount q.

Two fundamental principles used in this discussion have not been explicitly stated. The first is the *conservation of electric charge*: all charge that leaves the battery passes through the resistor. The second is the *conservation of energy*: a charge that starts at some point in the circuit and comes back to its starting point has neither lost nor gained energy. (The energy gained by a charge in the battery is equal to the energy lost by it in passing through the resistor.) These principles become less obvious and more useful in a circuit that is more complicated than the one considered above. They are known as *Kirchhoff's laws*.

In a more complicated circuit, Kirchhoff's first law (conservation of charge) takes the following form. Any junction where the current can flow in different paths is called a *node*. The algebraic sum of all the currents into a node is zero. (By algebraic sum we mean that currents into the node are positive, while currents leaving the node are negative, or vice versa.) This ensures that no charge will accumulate at the node.[10]

As an example of Kirchhoff's first law, consider the node in Fig. 6.22. Conservation of charge requires that $2+3+i = 0$ or $i = -5$ A. (In this case positive currents flow into the node; the negative current means that 5 A is flowing out of the node as current i.)

Kirchhoff's second law was used implicitly in the example above to say that the voltage across the resistor is 6 V. In general, Kirchhoff's second law says that if one goes around any closed path in a complicated circuit, the total voltage change is zero.

[10] More generally, the node could represent a conductor, such as the plate of a capacitor, on which charge can accumulate. In that case the charge Q changes with time:

$$\frac{dQ}{dt} = \sum (\text{all currents into the node}).$$

This statement is quite similar to the continuity equation of Sect. 4.1.

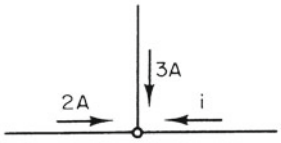


Fig. 6.22 Conservation of charge means that current i is -5 A

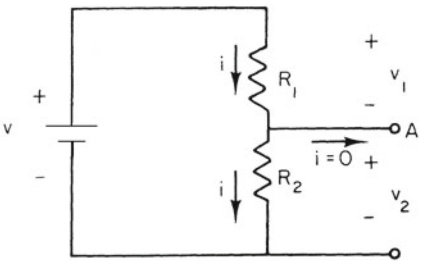


Fig. 6.23 A more complicated circuit, sometimes called a voltage divider

Kirchhoff's laws can be applied to show that the total resistance of a set of resistors in series is

$$R = R_1 + R_2 + R_3 + \cdots .$$

This follows from the definition of resistance, the fact that the same current flows in each resistor, and the total potential difference across the set of resistors is the sum of the potential difference across each one. Kirchhoff's laws can also be used to show that for a collection of resistors in parallel, the total resistance is given by

$$\frac{1}{R} = \frac{1}{R_1} + \frac{1}{R_2} + \frac{1}{R_3} + \cdots ,$$

(see Problem 24).

Consider a more complicated example in which two resistors are connected across a battery. The battery voltage is v, and the resistances are R_1 and R_2, as shown in Fig. 6.23. If no current flows out lead A, then conservation of charge requires that the same current i flows in each resistor. The sum of the voltages v_1 and v_2 is v. Therefore, $i = v_1/R_1 = v_2/R_2$ and $v = v_1 + v_2 = iR_1 + iR_2 = i(R_1 + R_2)$. The voltage across R_2 is iR_2 or

$$v_2 = \frac{R_2}{R_1 + R_2} v. \tag{6.31}$$

6.10 Charge Distribution in the Resting Nerve Cell

The axon consists of an ionic intracellular fluid and an ionic extracellular fluid, separated by a membrane. The intracellular and extracellular media are electrical conductors. When

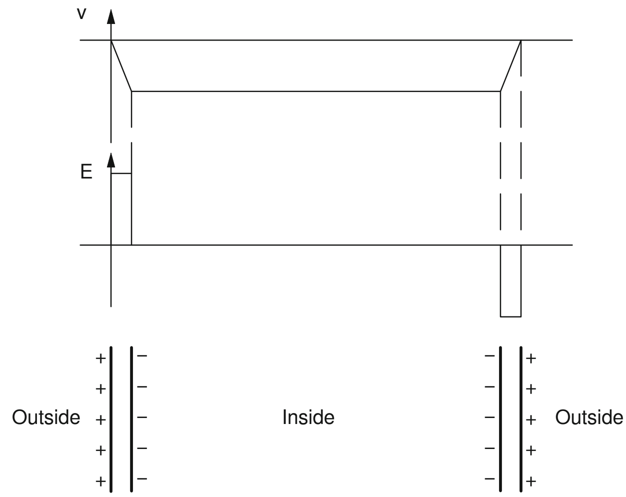


Fig. 6.24 The potential, electric field, and charge at different points on the diameter of a resting nerve cell. Portions of the cell membrane on opposite sides of the cell are shown. Outside the cell on the left the potential and electric field are zero. As one moves to the right into the cell, the electric field in the membrane causes the potential to decrease to -70 mV. Within the cell the field is zero and the potential is constant. Moving out through the right-hand wall the potential rises to zero because of the electric field within the membrane

the cell is in equilibrium there is no current and no electric field in these regions. There will be a field and currents when an impulse is traveling along the axon.

Because the electric field in the resting cell is zero, there is no net charge in the fluid. Positive ions are neutralized by negative ions everywhere except at the membrane. A layer of charge on each surface generates an electric field within the membrane and a potential difference across it.

Measurements with a microelectrode show that the potential within the cell is about 70 mV less than outside. If the potential outside is taken to be zero, then the interior resting potential is -70 mV. Figure 6.24 shows a slice across the cell, showing the membrane on opposite sides of the cell and the charges and electric field. If the potential drops 70 mV as one enters the cell on the left, if the membrane thickness is 6 nm, and if the electric field within the membrane is assumed to be constant, then

$$E = -\frac{dv}{dx} = -\frac{-70 \times 10^{-3}\ \text{V}}{6 \times 10^{-9}\ \text{m}} = 1.17 \times 10^{7}\ \text{V m}^{-1}. \tag{6.32}$$

This is how the value of E was determined for use on p. 147.

Except for the layers of charge on the inside and outside of the membrane, which are shown in Fig. 6.24 and which give rise to the electric field and potential difference, the extracellular and intracellular fluids are electrically neutral. However, the ion concentrations are quite different in each (Fig. 6.3). There is an excess of sodium ions outside and an excess of potassium ions inside.

It is possible to see which concentrations (if any) are consistent with the hypothesis that the ions can pass freely through the membrane. If a species is in equilibrium, the concentration ratio c_i/c_o across the membrane is given by a Boltzmann factor or the Nernst equation (see Chap. 3). The potential energy of the ion is zev, where z is the valence of the ion, e the electronic charge (1.6×10^{-19} C), and v the potential in volts. Using subscripts i and o to represent inside and outside the cell, we have

$$\frac{c_i}{c_o} = \frac{e^{-zev_i/k_B T}}{e^{-zev_o/k_B T}} = e^{-ze(v_i - v_o)/k_B T}. \tag{6.33}$$

Here k_B is Boltzmann's constant, 1.38×10^{-23} J K^{-1}. For a situation in which $T = 310$ K and $v_i - v_o = -70 \times 10^{-3}$ V, c_i/c_o is 13.7 for univalent positive ions and $1/13.7 = 0.073$ for negative ions. The ratios in Fig. 6.3 are 0.103 for sodium, 30 for potassium, and 0.071 for chloride. The chloride concentration ratio is consistent with equilibrium, while the sodium concentration ratio is much too small (too few sodium ions inside) and the potassium concentration ratio is too large (too many potassium ions inside). A potential of -90 mV would bring the potassium concentration ratio into equilibrium, but then chloride would not be in equilibrium and sodium would be even farther from equilibrium. In fact, tracer studies show that potassium leaks out slowly and sodium leaks in slowly. The resting membrane is not completely impermeable to these ions (Hodgkin 1964, Chap. 6; Laüger 1991). To maintain the ion concentrations a membrane protein called the sodium–potassium pump uses metabolic energy to pump potassium into the cell and sodium out. The usual ratio of sodium to potassium ions in this active transport is 3 sodium to 2 potassium ions (Patton et al. 1989, Vol. 1, p. 27).

The intracellular and extracellular fluids can be modeled as two conductors separated by a fairly good insulator. The conductors have a capacitance between them. We can estimate this capacitance in two ways. We can either regard the membrane as a plane insulator sandwiched between plane conducting plates (as if the membrane had been laid out flat as in Fig. 6.25), or we can treat it as a dielectric between concentric cylindrical conductors. The text will use the first approximation, while the second will be left to a problem. Suppose that two parallel plates have area S and charge $\pm Q$, respectively, then the charge density on each is $\sigma = \pm Q/S$. Equation 6.11 gives the electric field without a dielectric between the conductors: $E_{\text{ext}} = \sigma/\epsilon_0 = Q/\epsilon_0 S$.

With the dielectric of dielectric constant κ, the field is reduced to $E = E_{\text{ext}}/\kappa = \sigma/\kappa\epsilon_0 = Q/\kappa\epsilon_0 S$ as was seen in Eq. 6.20. The magnitude of the potential difference is E times the plate separation b: $v = Eb = Qb/\kappa\epsilon_0 S$. The capacitance is $C = Q/v$:

$$C = \frac{Q\kappa\epsilon_0 S}{Qb} = \frac{\kappa\epsilon_0 S}{b}. \tag{6.34}$$

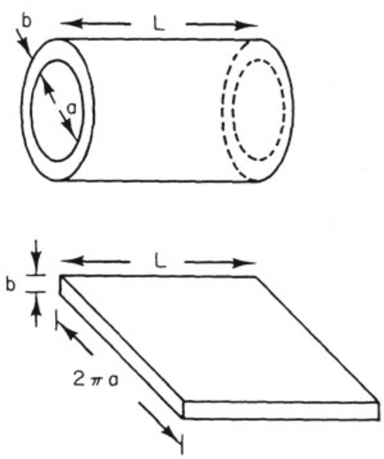


Fig. 6.25 A portion of a cell membrane of length L, in its original configuration and laid out flat. The membrane thickness is b and the radius of the axon is a. The plane approximation is used to calculate both the capacitance and resistance of the membrane

The charge density on the surface of the membrane is obtained from $\sigma = Q/S = Cv/S = \kappa\epsilon_0 v/b$.

Measurements of the dielectric constant κ for axon membrane show it to be about 7. Using values of -70 mV for v and 6 nm for b, the capacitance per unit area of membrane can be calculated, as can σ:

$$\frac{C}{S} = \frac{(7)(8.85 \times 10^{-12})}{6 \times 10^{-9}} = 0.01 \text{ F m}^{-2} = 1\ \mu\text{F cm}^{-2},$$

$$\sigma = (0.01)(70 \times 10^{-3}) = 7 \times 10^{-4} \text{ C m}^{-2}. \tag{6.35}$$

This value for the surface charge density is larger by a factor of 7 than that calculated in Sect. 6.3. The reduction of the electric field by polarization of the dielectric has been taken into account in the present calculation. A larger external charge is required to give the same field within the dielectric.

The value of b for myelinated fibers is much greater, typically 2000 nm instead of 6 nm. This reduces the capacitance per unit area by a factor of 300.

6.11 The Cable Model for an Axon

We now consider the rather complicated flow of charge in the interior of an axon, through the membrane, and in the conducting medium outside the cell during departures from rest. We will model the axon by electric conductors that obey Ohm's law inside and outside the cell and a membrane that has capacitance and also conducts current. We will apply

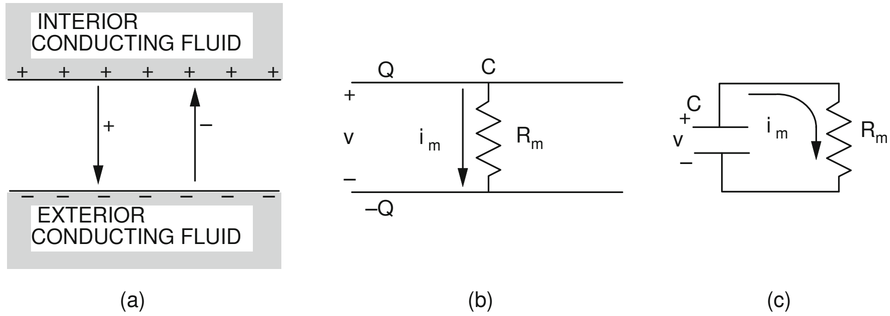


Fig. 6.26 Leakage currents through the membrane. **a** The flow of positive and negative ions. **b** The membrane capacitance is represented by the parallel plates and the leakage resistance by a single resistor. **c** The capacitance and resistance are usually drawn like this

Kirchhoff's laws—conservation of energy and charge—to a small segment of the axon. The result will be a differential equation that is independent of any particular model for the cell membrane. This is called the *cable model* for an axon. We will then apply the cable model in two cases. The first case is when the voltage change does not alter the properties of the membrane. The second case is a voltage change that changes the ionic permeability of the membrane, thereby generating a nerve impulse.

Consider the small segment of membrane shown in Fig. 6.26a. For the moment we ignore the resting potential on the membrane. We will see later that accounting for the resting potential requires only a small change to the model. The upper capacitor plate, corresponding to the inside of the membrane, carries a charge Q. The lower capacitor plate (the outside of the membrane) has charge $-Q$. The charge on the membrane is related to the potential difference across the membrane by the membrane capacitance C_m: $Q = C_m v$. Figure 6.26a shows positive ions on the inside and negative ions on the outside of the membrane. (In a resting nerve cell, there is negative charge on the inside of the membrane, Q is negative, $-Q$ is positive, and $v < 0$.)

If the resistance between the plates of a capacitor is infinite, no current flows, and the charge on the capacitor plates remains constant. However, a membrane is not a perfect insulator; if it were, there would be no nerve conduction. Some current flows through the membrane. We call this current i_m and *define* outward current to be positive, as in Fig. 6.26b.

Imagine for now that there is no current along the axon. In that case i_m discharges the membrane capacitance, and the charge and potential difference fall to zero as charge flows through the resistor. When i_m is positive, Q and v decrease with time:

$$-i_m = \frac{dQ}{dt} = C_m \frac{dv}{dt}. \tag{6.36}$$

Let us explore the behavior of this isolated segment of axon a bit further. For now we think of the total leakage current as being through a single effective resistance R_m. This is shown in Fig. 6.26b. It is customary to draw the resistance separately, as in Fig. 6.26c. The current is then $i_m = v/R_m$ and $C_m(dv/dt) = -i_m = -v/R_m$,

$$\frac{dv}{dt} = -\frac{1}{R_m C_m} v. \tag{6.37}$$

This is the familiar equation for exponential decay of the voltage (see Chap. 2). If the initial voltage at $t = 0$ is v_0, the solution is

$$v(t) = v_0 e^{-t/\tau}, \tag{6.38}$$

where the time constant τ is given by

$$\tau = R_m C_m. \tag{6.39}$$

Referring to Fig. 6.25, we saw that if we have a section of membrane of area S and thickness b the capacitance is given by Eq. 6.34. For a conductor of the same dimensions we saw [Eq. 6.27] that the resistance is $R_m = \rho_m b/S$, so the time constant is

$$\tau = R_m C_m = \frac{\rho_m b}{S} \frac{\kappa \epsilon_0 S}{b} = \kappa \epsilon_0 \rho_m. \tag{6.40}$$

We have the remarkable result that the time constant is independent of both the area and thickness of the membrane. Doubling the area S doubles the amount of charge that must leak off, but it also doubles the membrane current. Doubling b doubles the resistance, but it also makes the membrane capacitance half as large. In each case the factors S and b cancel in the expression for the time constant.

If a very thin lipid membrane is produced artificially, it is found to have a very high resistivity—about 10^{13} Ω m (Scott 1975, p. 493). Certain proteins added to the lipid material reduce the resistivity by several orders of magnitude. For natural nerve membrane the resistivity is about

$$\rho_m = 1.6 \times 10^7 \ \Omega \text{ m}. \tag{6.41}$$

This is the effective resistivity for resting membrane, taking into account all of the ion currents. If ρ_m had this constant value the time constant would be $\tau = \kappa \epsilon_0 \rho_m =$

Table 6.1 Properties of a typical unmyelinated nerve

a	Axon radius	5×10^{-6} m
b	Membrane thickness	6×10^{-9} m
ρ_i	Resistivity of axoplasm	$0.5\ \Omega$ m
$r_i = \rho_i/\pi a^2$	Resistance per unit length inside axon	$6.4 \times 10^{9}\ \Omega\ \mathrm{m}^{-1}$
κ	Dielectric constant of membrane	7[a]
ρ_m	Resistivity of membrane	$16 \times 10^{6}\ \Omega$ m
$\kappa\rho_m$		$112 \times 10^{6}\ \Omega$ m
$c_m = \kappa\epsilon_0/b$	Membrane capacitance per unit area	$10^{-2}\ \mathrm{F\ m}^{-2}$
$2\pi\kappa\epsilon_0 a/b$	Membrane capacitance per unit length of axon	$3 \times 10^{-7}\ \mathrm{F\ m}^{-1}$
$g_m = 1/\rho_m b$	Conductance per unit area of membrane	$10\ \mathrm{S\ m}^{-2}$
$1/g_m$	Reciprocal of conductance per unit area	$0.1\ \Omega\ \mathrm{m}^2$
$2\pi a/\rho_m b$	Membrane conductance per unit length of axon	$3.2 \times 10^{-4}\ \mathrm{S\ m}^{-1}$
v_r	Resting potential inside axon	-70 mV
$E = v_r/b$	Electric field in membrane	$1.2 \times 10^{7}\ \mathrm{V\ m}^{-1}$
$\kappa\epsilon_0 v_r/b$	Charge per unit area on membrane surface	$7 \times 10^{-4}\ \mathrm{C\ m}^{-2}$
	Net number of univalent ions per unit area	$4.4 \times 10^{15}\ \mathrm{m}^{-2}$
	Net number of univalent ions per unit length	$6.6 \times 10^{7}\ \mathrm{m}^{-1}$

[a]See Sect. 6.17 for a discussion of the dielectric constant.

$(7)(8.85 \times 10^{-12})(1.6 \times 10^{7}) = 1 \times 10^{-3}$ s. (Actually, the resistivity changes drastically as the potential across the membrane changes during the propagation of a nerve impulse.) Since we observe a potential difference across the membrane, there must be a mechanism for renewing the charge on the membrane surface.

The resistance and capacitance of the portion of the axon membrane in Fig. 6.25 can be written in terms of the axon radius a and the length L of the segment by noting that $S = 2\pi a L$. Then one has

$$C_m = \frac{\kappa\epsilon_0 2\pi a L}{b}, \qquad R_m = \frac{\rho_m b}{2\pi a L}.$$

It is convenient to recall that $v = iR$ can be written as $i = Gv$ and introduce the conductance of the membrane segment

$$G_m = \frac{2\pi a L}{\rho_m b}. \tag{6.42}$$

Both the capacitance and the conductance are proportional to the area of the segment S. It is also convenient to introduce the lowercase symbols c_m and g_m to stand for the membrane capacitance and membrane conductance per unit area:

$$c_m = \frac{C_m}{S} = \frac{\kappa\epsilon_0}{b}, \tag{6.43}$$

$$g_m = \frac{G_m}{S} = \frac{1}{\rho_m b} = \frac{\sigma_m}{b}. \tag{6.44}$$

(Remember that $\sigma_m = 1/\rho_m$ is the electrical conductivity, the reciprocal of the resistivity. It is *not* the charge per unit area. σ is frequently used for both quantities in the literature.)

Both c_m and g_m depend on the membrane thickness as well as the dielectric constant and resistivity of the membrane. The units of c_m and g_m are, respectively, $\mathrm{F\ m}^{-2}$ and $\mathrm{S\ m}^{-2}$. Be careful: many sources give them per square centimeter instead of per square meter.

We can rewrite Eq. 6.36 in terms of the current density j_m, which is proportional to the capacitance per unit area, c_m:

$$-j_m = c_m \frac{dv}{dt}. \tag{6.45}$$

Table 6.1 shows typical values for these quantities and some to be discussed later for an unmyelinated axon.[11] These values should not be associated with a particular species. Parameters such as the resistance and capacitance per unit length of the axon are measured directly. Others, such as ρ_m, require an estimate of membrane thickness and are less well known

Now let us consider current that flows inside and outside the axon. Assume that the currents inside are longitudinal, that is, parallel to the axis of the axon. A discussion of departures from this assumption is found in Scott (1975, p. 492). With this assumption, the interior fluid can be regarded as a resistance of length L and radius a as shown in Fig. 6.27. The resistance of such a segment is $R_i = \rho_i L/S = \rho_i L/\pi a^2$. It is convenient to work with the resistance per unit length, r_i:

$$r_i = \frac{R_i}{L} = \frac{\rho_i}{\pi a^2} = \frac{1}{\pi a^2 \sigma_i}. \tag{6.46}$$

[11] Some insight into the magnitude of the charge on the membrane can be obtained from these numbers. The excess charge on the surface of the membrane is $7 \times 10^{-4}\ \mathrm{C\ m}^{-2}$ for the unmyelinated fiber. This corresponds to 4.4×10^{15} ions m^{-2}, if each ion has a charge of 1.6×10^{-19} C. Each atom or ion in contact with the membrane surface occupies an area of about $10^{-20}\ \mathrm{m}^2$; thus there are about 10^{20} atoms or ions in contact with a square meter of membrane surface. These may be neutral or positively or negatively charged. If charged, most are neutralized by the presence of a neighbor of opposite charge. The excess charge density that is required can be obtained if $4.4 \times 10^{15}/10^{20}$ or roughly one out of every 20,000 of the atoms in contact with the surface is ionized and not neutralized.

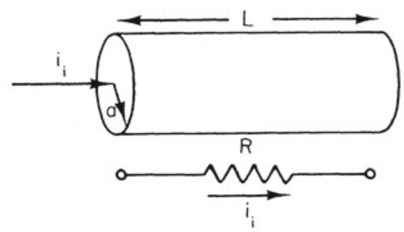


Fig. 6.27 Axoplasm of length L and radius a can be treated like a simple resistor

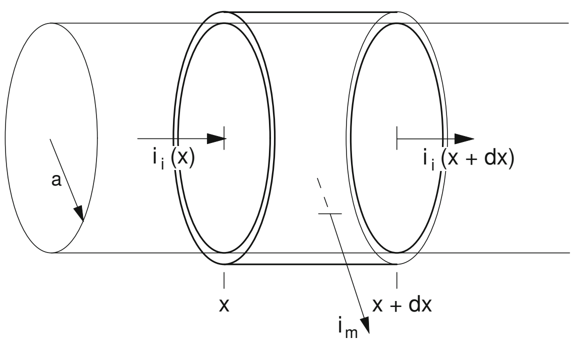


Fig. 6.28 The membrane surrounding a small portion of an axon is shown, along with the longitudinal currents in and out of the segment

The question of resistance of the extracellular fluid for currents outside the axon is more complicated. If the extracellular fluid were infinite in extent, the longitudinal resistance outside the cell would be very small (see Chap. 7). On the other hand, in a nerve or a muscle the axons or muscle cells are packed close together, there is not very much extracellular fluid, and the external resistance per unit length can be significant. There are some important effects that occur because of this. We will discuss them in Chap. 7.

Now we can consider the effect of both membrane and longitudinal currents. Figure 6.28 shows a small region of the axon between x and $x + dx$ and the surrounding membrane. Current i_i flows longitudinally along the axon on the inside. The current through the membrane is i_m. The potential difference across the membrane is $v = v_i - v_o$. In this section no attempt will be made to relate i_m or j_m to v. Charge Q resides on the inside surface of the membrane and can be either negative or positive. An equal and opposite charge $-Q$ resides on the outer surface of the membrane.

Because the capacitance can charge or discharge, Kirchhoff's law (conservation of charge) does not say that the sum of the currents is zero. Rather, it says that the net current into the volume of axoplasm between x and $x + dx$ changes the charge on the interior surface of the membrane:

$$i_i(x) - i_i(x + dx) - i_m = \frac{dQ}{dt} = C_m \frac{d(v_i - v_o)}{dt}. \quad (6.47a)$$

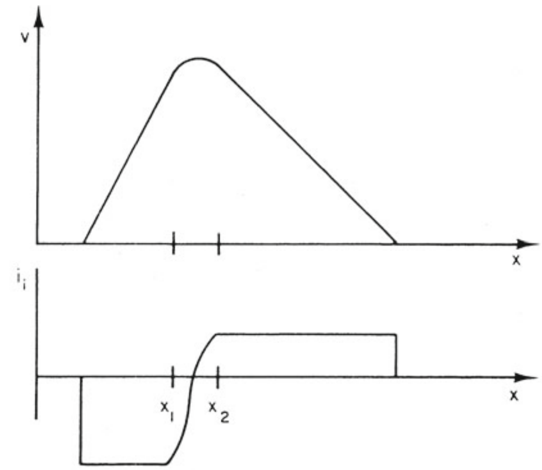


Fig. 6.29 A hypothetical plot of $v_i(x)$ and the longitudinal current i_i associated with it

When $i_i(x) = i_i(x + dx)$ this gives Eq. 6.36. The membrane current i_m represents an average value for the segment of membrane between x and $x + dx$. It is also a function of x.

We can define $di_i = i_i(x + dx) - i_i(x)$ as the increase in i_i along segment dx. Then we can rewrite Eq. 6.47a as

$$-di_i = C_m \frac{dv}{dt} + i_m. \quad (6.47b)$$

This is an important equation. It says that when the current flowing inside the axon decreases in a small distance dx, part of the current charges the capacitance of that segment of membrane, and the rest flows through the membrane.

Consider a small segment of axoplasm of length dx. The intracellular voltage at the left end is $v_i(x)$; at the right end it is $v_i(x + dx)$. The current along the segment is the voltage difference between the ends divided by the resistance of the segment. The resistance is $R_i = r_i\, dx$. Therefore the current is

$$i_i(x) = \frac{v_i(x) - v_i(x + dx)}{r_i\, dx} = -\frac{1}{r_i} \frac{dv_i}{dx}. \quad (6.48)$$

The voltage must change along the axon for a current to flow within it. The minus sign in Eq. 6.48 shows that a current flowing from left to right (in the $+x$ direction) requires a voltage that decreases from left to right, and vice versa. Figure 6.29 shows a hypothetical plot of $v_i(x)$ and the current which would accompany it. Notice that the current is flowing from the region of higher voltage to lower voltage–towards both ends from the region between x_1 and x_2. In that region either the charge on the membrane is changing or current is flowing through the membrane.

Consider again the cylindrical geometry shown in Fig. 6.28. The surface area of this portion of membrane is

$2\pi a\,dx$. Dividing each term of Eq. 6.47a by the area and remembering the definitions of j_m and c_m we obtain

$$c_m \frac{\partial v}{\partial t} = -j_m + \frac{1}{2\pi a}\left[\frac{i_i(x) - i_i(x+dx)}{dx}\right]. \tag{6.49}$$

It is necessary to use partial derivatives because the current and voltage depend on both x and t as an impulse travels down the nerve. As $dx \to 0$

$$\frac{i_i(x+dx) - i_i(x)}{dx} \to \frac{\partial i_i}{\partial x}.$$

This can be evaluated using the expression for Ohm's law in the axoplasm, Eq. 6.48:

$$\frac{\partial i_i}{\partial x} = -\frac{1}{r_i}\frac{\partial^2 v_i}{\partial x^2}. \tag{6.50}$$

When this is inserted in Eq. 6.49 the result is

$$c_m \frac{\partial (v_i - v_o)}{\partial t} = -j_m + \frac{1}{2\pi a\, r_i}\frac{\partial^2 v_i}{\partial x^2}. \tag{6.51}$$

In many cases the extracellular potential is small. In that case the voltage across the membrane, v, is approximately the same as the intracellular voltage, v_i, so we can rewrite Eq. 6.51 as

$$c_m \frac{\partial v}{\partial t} = -j_m + \frac{1}{2\pi a\, r_i}\frac{\partial^2 v}{\partial x^2}. \tag{6.52}$$

This rather formidable looking equation is called the *cable equation* or *telegrapher's equation*. It was once familiar to physicists and electrical engineers as the equation for a long cable, such as a submarine cable, with capacitance and leakage resistance but negligible inductance (Jeffreys and Jeffreys 1956, p. 602). It has the form of Fick's second law of diffusion, Eq. 4.26, with the addition of the j_m term.

It is worth recalling the origin of each term and verifying that the units are consistent. The term on the left is the rate at which the membrane capacitance is gaining charge per unit area. Therefore all terms in the equation have the units of current per unit area. The first term on the right is the current per unit area through the membrane in the direction that discharges the membrane capacitance. The second term on the right gives the buildup of charge on this area of the membrane because of differences in current along the axon. If $v(x)$ were constant, there would be no current along the inside of the axon. If function $v(x)$ had constant slope, the current along the inside of the axon would be the same everywhere and there would be no charge buildup on the membrane. It is only because $v(x)$ changes slope that i_i is different at two neighboring points in the axon and charge can collect on the membrane.

Now, for the units. Since $i = C(dv/dt)$, the units of $c_m \partial v/\partial t$ are current per unit area. The j_m term is by definition current per unit area. Since r_i has the units of $\Omega\ \mathrm{m}^{-1}$, the term $2\pi a r_i$ has the units of Ω. When this is combined with $\partial^2 v/\partial x^2$, which has units $\mathrm{V\ m^{-2}}$, the result is $\mathrm{A\ m^{-2}}$ as required.

This is a very general equation stating Kirchhoff's laws for a segment of the axon. The only assumptions are that the currents depend only on time and position along the axon and that voltage changes on the outside of the axon can be neglected. Particular models for nerve conduction use different relations between j_m and $v(x,t)$.

6.12 Electrotonus or Passive Spread

The simplest membrane model is one that obeys Ohm's law. This approximation is valid if the voltage changes are small enough so that the membrane conductance does not change, or if something has been done to inactivate the normal changes of membrane conductance with voltage. It is also useful for myelinated nerves between the nodes of Ranvier. This is called *electrotonus* or *passive spread*.

In its quiescent state, the voltage all along the inside of the axon has the constant resting value v_r. Both $\partial v/\partial t$ and $\partial^2 v/\partial x^2$ are zero. Equation 6.52 can be satisfied only if $j_m = 0$. Although j_m is zero, it may be made up of several leakage components. In this section we simply assume that j_m is proportional to $v - v_r$:

$$j_m = g_m(v - v_r). \tag{6.53}$$

This simple model does predict that $j_m = 0$ when $v = v_r$. It also predicts that the current will be positive (outward) if $v > v_r$ and negative (inward) if $v < v_r$. It does not explain the propagation of an all-or-nothing nerve impulse. The conductance per unit area, g_m, is assumed to be independent of v and of the past history of the membrane. This is a good assumption only for very small voltage changes. With this assumption, Eq. 6.52 becomes

$$c_m \frac{\partial v}{\partial t} = -g_m(v - v_r) + \frac{1}{2\pi a\, r_i}\frac{\partial^2 v}{\partial x^2}. \tag{6.54}$$

This equation is usually written in a slightly different form by dividing through by g_m:

$$\frac{1}{2\pi a\, r_i g_m}\frac{\partial^2 v}{\partial x^2} - v - \frac{c_m}{g_m}\frac{\partial v}{\partial t} = -v_r.$$

It is also customary to make the assignments

$$\lambda^2 = \frac{1}{2\pi a\, r_i g_m},$$

$$\tau = \frac{c_m}{g_m},$$

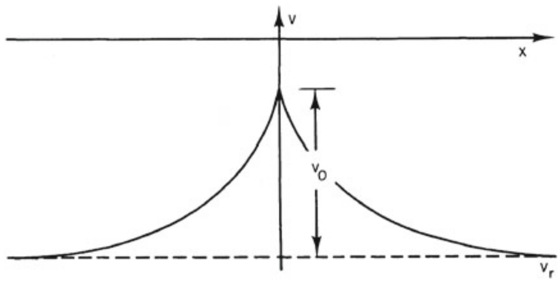


Fig. 6.30 The voltage distribution along an axon in electrotonus when the membrane capacitance is charged and the voltage is not changing with time

so that the equation becomes

$$\lambda^2 \frac{\partial^2 v}{\partial x^2} - v - \tau \frac{\partial v}{\partial t} = -v_r. \qquad (6.55)$$

In terms of the primary axon parameters, the parameters in Eq. 6.55 are

$$\lambda^2 = \frac{ab\rho_m}{2\rho_i}, \qquad (6.56)$$

$$\tau = \kappa \epsilon_0 \rho_m. \qquad (6.57)$$

The time constant was seen before in Eq. 6.40. Equation 6.55 has a steady-state solution $v = v_r$. If a new variable $v' = v - v_r$ is used, it becomes the homogeneous version of the same equation with a steady-state solution $v' = 0$.

For nerve conduction, the inhomogeneous equation with various exciting terms corresponding to physiological stimuli was discussed by Davis and Lorente de Nó (1947) and by Hodgkin and Rushton (1946). Their work is summarized by Plonsey (1969, p. 127).

Before considering general solutions to Eq. 6.55, consider some special cases. If $c_m = 0$, so that $\tau = 0$, or if enough time has elapsed so that the voltage is not changing with time and $\partial v/\partial t = 0$, the equation reduces to

$$\lambda^2 \frac{\partial^2 v}{\partial x^2} - v = -v_r.$$

You can verify by substitution that this has a solution

$$v - v_r = \begin{cases} v_0 e^{-x/\lambda}, & x > 0 \\ v_0 e^{x/\lambda}, & x < 0. \end{cases} \qquad (6.58)$$

If the voltage is held at a constant value $v = v_r + v_0$ at some point on the axon, the voltage will decay exponentially to v_r in both directions from that point. This is shown in Fig. 6.30.

Next suppose that $v(x, t)$ does not depend on x, so that there is no longitudinal current in the axon and $\partial^2 v/\partial x^2 = 0$. This can be accomplished experimentally by threading a wire axially along the axon, if the axon is fat enough. The equation reduces to

$$\tau \frac{\partial v}{\partial t} + v = v_r.$$

This is the familiar equation for exponential decay. If v were held at $v_0 + v_r$ and then the constraint were removed at $t = 0$, the voltage would decay exponentially back to v_r

$$v - v_r = v_0 e^{-t/\tau}.$$

This represents the discharge of the membrane capacitance through the membrane resistance.

The behavior of $v(x, t) - v_r$ at various times after an excitation is applied is shown in Fig. 6.31. The excitation is a constant current injected at $x = 0$ for all time $t > 0$. After a long time, the curve is identical to that in Fig. 6.30, as the membrane capacitance has fully charged. Only the membrane leakage current attenuates the signal. At earlier times the solution is not precisely exponential; the analytic solution involves error functions (Prob. 36). The change of voltage with time at fixed positions along the cable is also shown. Both the finite propagation time and the attenuation of the signal are evident.

6.13 The Hodgkin–Huxley Model for Membrane Current

If the voltage at some point along the axon changes by a few millivolts from the resting value, the voltage at other points

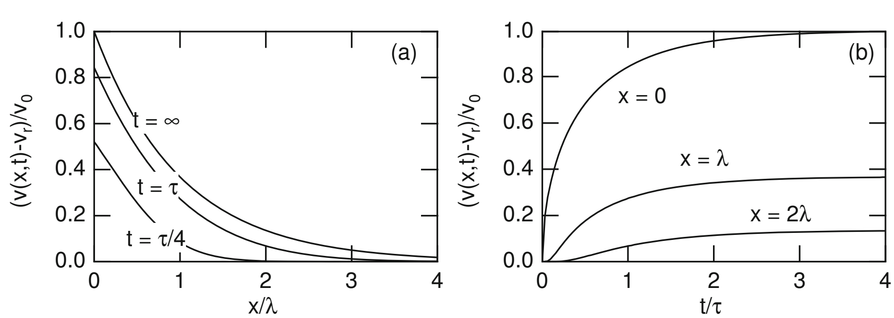


Fig. 6.31 Some representative solutions to the problem of electrotonus after the application of a constant current at $x = 0$. **a** The voltage along the axon at different times. **b** Voltage at a fixed point on the axon as a function of time

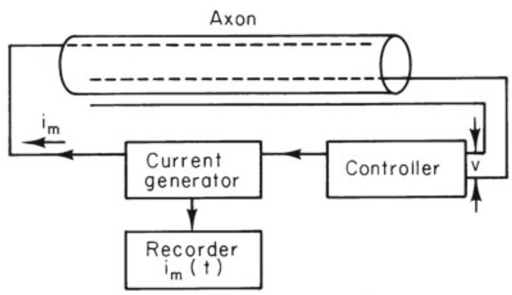


Fig. 6.32 Apparatus for voltage-clamp measurements

along the axon is described by electrotonus. However, if the inside voltage rises from the resting value by 20 mV or more, a completely different effect takes place. The potential rises rapidly to a positive value, then falls to about −80 mV, and finally returns to the resting value (Fig. 6.1). This behavior is attributable to a very nonlinear dependence of membrane current on transmembrane voltage.

Considerable work was done on nerve conduction in the late 1940s, culminating in a model that relates the propagation of the action potential to the changes in membrane permeability that accompany a change in voltage. The model (Hodgkin and Huxley 1952) does not explain why the membrane permeability changes; it relates the shape and conduction speed of the impulse to the observed changes in membrane permeability. Nor does it explain all the changes in current. (For example, the potassium current does fall eventually, and there are some properties of the sodium current that are not adequately described.) Nonetheless, the work was a triumph that led to the Nobel Prize for Alan Hodgkin and Andrew Huxley.

Most of the experiments that led to the Hodgkin–Huxley model were carried out using the giant axon of the squid. This is a single cell several centimeters long and up to 1 mm in diameter that can be dissected from the squid. The removal of axoplasm from the preparation and its replacement by electrolytes has shown that the critical phenomena all take place in the membrane. The important results are reviewed in many places (Katz 1966, Chaps. 5 and 6; Plonsey 1969, p. 127; Plonsey and Barr 2007, Chap. 4; Scott 1975, pp. 495–507).

6.13.1 Voltage Clamp Experiments

Voltage-clamp experiments were particularly illuminating. Two long wire electrodes were inserted in the axon and connected to the apparatus shown in Fig. 6.32. The resistance of the wires was so low that the potential at all points along the axon was the same at any instant of time. The potential depended only on time, and not on position. This is called a *space-clamped* experiment. One electrode, paired with an electrode in the surrounding medium, measured the voltage difference across the membrane. The other electrode was used to inject or remove whatever current was necessary to keep this voltage difference constant. Measurement of this current allowed calculation of the membrane conductance. This technique is called *voltage clamping*. The experiment described here was both voltage- and space-clamped.

When the membrane potential was raised abruptly from the resting value to a new value and held there, the resulting current was found to have three components:

1. A current, lasting a few microseconds, that changed the surface charge on the membrane.
2. A current flowing inward which lasted for 1 or 2 ms. Various experiments, such as replacing the sodium ions in the extracellular fluid with some other monovalent ion, showed that this was due to the inward flow of sodium ions. (Had the potential not been voltage-clamped by the electronic apparatus, this inrush of positive charge would have raised the potential still further.)
3. An outward current that rose in about 4 ms and remained steady for as long as the potential was clamped at this value. Tracer studies showed that this current was due to potassium ions. (Over a time scale of several tens of milliseconds, the potassium current, like the sodium current, does fall back to zero.)

The first current is the $c_m(\partial v/\partial t)$ term of Eq. 6.52; the second and third currents together constitute j_m. Because of the clamping wires, the $\partial^2 v/\partial x^2$ term is zero.

The next step is to develop a model that describes the major ionic constituents of the current. The sodium and potassium contributions to the current will be considered separately; all other contributions will be combined in a *leakage term*:

$$j_m = j_{Na} + j_K + j_L. \tag{6.59}$$

The leakage includes charge movement due to chloride ions and any other ions that can pass through the membrane.

Consider movement of sodium through the membrane. Similar considerations apply to potassium. The concentrations of sodium inside and out are $[\mathrm{Na}_i]$ and $[\mathrm{Na}_o]$. It will be seen later that the total number of ions moving through the membrane during a nerve pulse in a squid giant axon is too small to change the concentrations significantly. Therefore, the concentrations are fixed.

There would be no movement of sodium ions through the membrane, regardless of how permeable it is, when the concentrations and potential are related by the Boltzmann factor or Nernst equation (Eq. 6.33) with $v = v_i - v_o$:

$$\frac{[\mathrm{Na}_i]}{[\mathrm{Na}_o]} = e^{-ev/k_B T}.$$

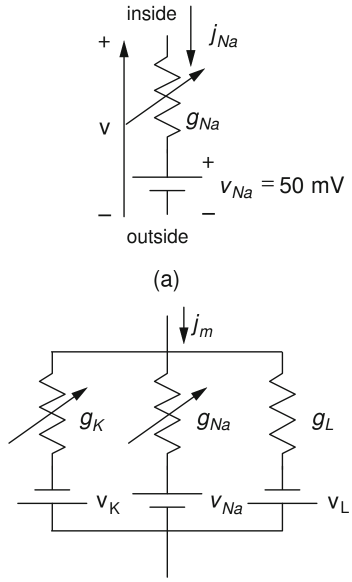


Fig. 6.33 Equivalent circuits for the membrane current. **a** The sodium current–voltage relationship of Eq. 6.61 is the same as that for a variable resistance in series with a battery at the sodium Nernst potential. **b** The total membrane current can be modeled with three such equivalent circuits. See the discussion of the sign of the potassium and leakage Nernst potentials in the text

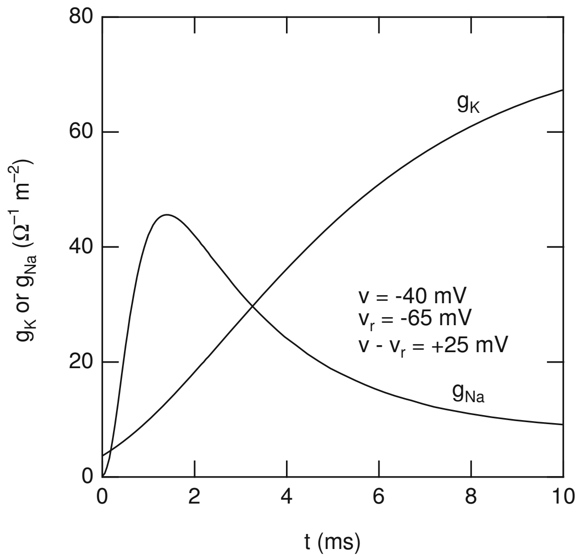


Fig. 6.34 The behavior of the sodium and potassium conductivities with time in a voltage-clamp experiment. At $t = 0$ the voltage was raised by 25 mV from the resting potential. The values are calculated from Eqs. 6.64–6.70 and are representative of the experimental data

For given concentrations, the sodium equilibrium or Nernst potential is

$$v_{Na} = \frac{k_B T}{e} \ln\left(\frac{[\mathrm{Na}_o]}{[\mathrm{Na}_i]}\right). \quad (6.60)$$

The sodium Nernst potential is usually about 50 mV. If $v = v_{Na}$ there is no current of sodium ions, regardless of the membrane permeability to sodium. If v is greater than v_{Na} (more positive), j_{Na} flows outward. If $v < v_{Na}$, the sodium current is inward. These currents can be described by

$$j_{Na} = g_{Na}(v - v_{Na}). \quad (6.61)$$

The coefficient g_{Na} is the sodium conductance per unit area. It is not constant but depends on the value of v and, in fact, on the past history of v. Defining the conductance this way makes the functional form of g_{Na} less complex; in particular, it does not have to change sign as v moves through v_{Na} and the sodium current reverses direction.

This equation can be multiplied by the membrane area to give a current–voltage relationship . Many authors draw a circuit diagram to represent the current flow through the membrane and along the axon. The sodium voltage–current relationship can be represented by a variable resistance corresponding to g_{Na} in series with a battery at the sodium Nernst potential, as shown in Fig. 6.33a.

An expression similar to Eq. 6.61 can be written for the potassium current density:

$$j_K = g_K(v - v_K). \quad (6.62)$$

The potassium Nernst potential is negative—about −77 mV—so the polarity of the potassium battery in Fig. 6.33b has been reversed. The leakage term will be considered later.

To summarize: v is the instantaneous voltage across the membrane. Both v_K and v_{Na} are constants depending on the relative ion concentrations inside and outside the cell and the temperature. The conductances per unit area depend on both the present value of v and its past history.

We can now describe the results of the voltage clamp experiments. The voltage in each experiment was changed from the resting value by an amount Δv. Therefore, $v - v_{Na}$ and $v - v_K$ had constant values after the change, and the changes in current density mirrored the changes in conductivity. Typical results for $\Delta v = 25$ mV and $T = 6\,°$C are shown in Figs. 6.34 and 6.35. [The method of distinguishing sodium from potassium current is described in the original papers, or in Hille (2001, p. 39).] For a voltage clamp experiment the current and conductance have the same time variation. The sodium conductance rises from nearly zero and then falls, while the potassium conductance rises more slowly from a small initial resting value. (The potassium current before the voltage clamp was applied was small, because the resting potential was close to the potassium Nernst potential.) Measurements for longer times

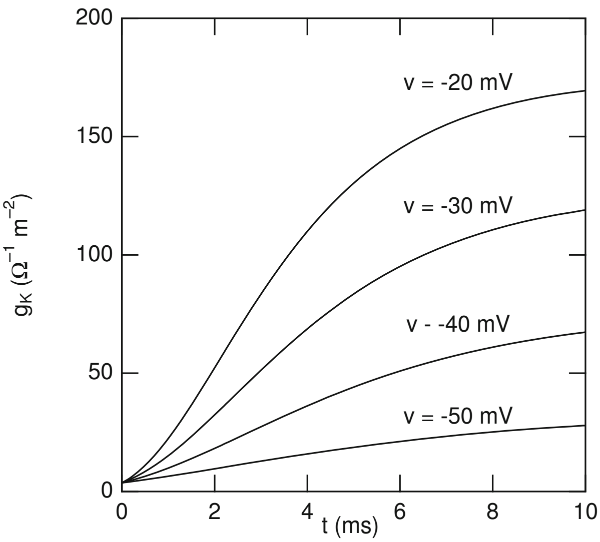


Fig. 6.35 The behavior of the potassium conductance for different values of the clamping voltage. These are representative curves calculated from Eqs. 6.64–6.66

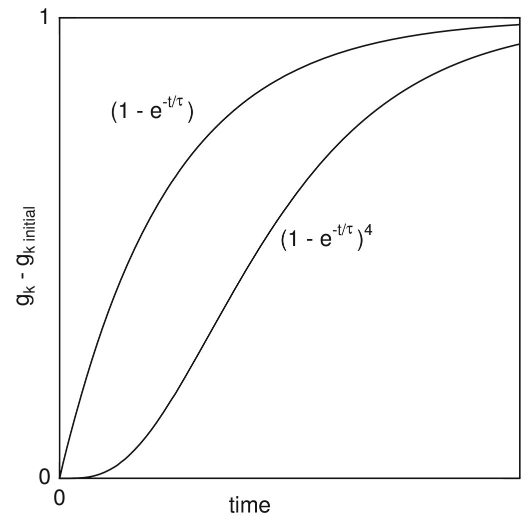


Fig. 6.36 A comparison of $(1 - e^{-t/\tau})$ with $(1 - e^{-t/\tau})^4$. The latter more closely approximates the shape of the potassium conductance in Fig. 6.34

show that the potassium conductivity rises to a constant value. Measurements for much longer times show that the potassium current falls after tens of milliseconds. For other values of Δv the conductance changes are different.

6.13.2 Potassium Conductance

Hodgkin and Huxley wanted a way to describe their extensive voltage-clamp data, similar to that in Figs. 6.34 and 6.35, with a small number of parameters. If we ignore the small nonzero value of the conductance before the clamp is applied, the potassium conductance curve of Fig. 6.34 is reminiscent of exponential behavior, such as $g_K(v,t) = g_K(v)(1-e^{-t/\tau(v)})$, with both $g_K(v)$ and $\tau(v)$ depending on the value of the voltage. A simple exponential is not a good fit. Figure 6.36 shows why. The curve $(1-e^{-t/\tau})$ starts with a linear portion and is then concave downward. The potassium conductance in Figs. 6.34 and 6.35 is initially concave upward. The curve $(1-e^{-t/\tau})^4$ in Fig. 6.36 more nearly has the shape of the conductance data. This suggests that we try to describe the conductance by

$$g_K(v,t) = g_{K\infty}\left[n_\infty(v)(1-e^{-t/\tau(v)})\right]^N. \qquad (6.63)$$

In this expression, $g_{K\infty}$ is the largest possible conductance per unit area. The value of $n_\infty(v)$ varies between 0 and 1 and determines the asymptotic value of the conductance change for a particular value of the voltage step. Hodgkin and Huxley found a good fit to their data with $N = 4$. If the initial value of the conductance were zero, our empirical fit to the potassium conductance data would be

$$g_K(v,t) = g_{K\infty}n^4(v,t), \qquad (6.64a)$$

$$n(v,t) = n_\infty(v)(1-e^{-t/\tau(v)}). \qquad (6.64b)$$

But the initial potassium conductance was not zero. How should this be handled? Hodgkin and Huxley assumed that n is a measure of some fundamental property of the potassium channels, and that the conductance is always described by Eq. 6.64a. When the clamp voltage changes, the subsequent change of n is described by an exponential decay with the appropriate values of $n_\infty(v)$ and $\tau(v)$. If the initial value of n is n_0, the expression for $n(v,t)$ after the voltage clamp change is

$$n(v,t) = n_\infty(v)\left[1 - \left(\frac{n_\infty(v) - n_0}{n_\infty(v)}\right)e^{-t/\tau(v)}\right]. \qquad (6.64c)$$

The function n is a solution to the differential equation

$$\frac{dn}{dt} = -\frac{n}{\tau} + \frac{n_\infty}{\tau}. \qquad (6.65a)$$

Hodgkin and Huxley wrote this instead in the form

$$\frac{dn}{dt} = \alpha_n(1-n) - \beta_n n. \qquad (6.65b)$$

The subscript n on α_n and β_n distinguishes them from similar parameters for the sodium conductance.

The dependence of α_n and β_n on voltage is quite pronounced. With v in mV and α_n and β_n in ms^{-1}, the equations used by Hodgkin and Huxley to describe their experimental values of α_n and β_n are

$$\alpha_n(v) = \frac{0.01\,[10 - (v - v_r)]}{\exp\left(\frac{10 - (v - v_r)}{10}\right) - 1},$$
$$\beta_n(v) = 0.125 \exp\left(\frac{-(v - v_r)}{80}\right). \tag{6.66}$$

The quantities α_n and β_n are rate constants in Eq. 6.65b. Like all chemical rate constants, they depend on temperature. The values above are correct when $T = 279$ K (6.3 °C). Hodgkin and Huxley assumed that the temperature dependence was described by a Q_{10} of 3. This means that the reaction rate increases by a factor of 3 for every 10 °C temperature rise. The rate at temperature T is obtained by multiplying rates obtained from Eq. 6.66 by

$$3^{(T-6.3)/10}. \tag{6.67}$$

For example, if the temperature is 18.5 °C, the rate must be multiplied by $3^{1.22} = 3.82$.

The variable n is often called the *potassium gate* or the *n gate*. It takes values between zero (a *closed* gate) and 1 (an *open* gate). The n gate is partially open at rest, making the resting membrane somewhat permeable to potassium. As v becomes more positive than the resting potential ("depolarizes"), the n gate opens further or "activates."

The behavior of α_n and β_n was determined from voltage-clamp experiments. In an actual nerve-conduction process, v is not clamped. Hodgkin and Huxley *assumed* that when v varies with time, the correct value of n can be obtained by integrating Eq. 6.65b. At each instant of time the values of α_n and β_n are those obtained from Eq. 6.66 for the voltage at that instant. This was a big assumption—but it worked. The value of $g_{K\infty}$ that they chose was 360 S m^{-2}.

6.13.3 Sodium Conductance

The sodium conductance was described by two parameters: one reproducing the rise and the other the decay of the conductance. The equation was

$$g_{Na} = g_{Na\infty} m^3 h.$$

The parameters m and h obeyed equations similar to that for n:

$$\frac{dm}{dt} = \alpha_m(1 - m) - \beta_m m, \tag{6.68}$$
$$\frac{dh}{dt} = \alpha_h(1 - h) - \beta_h h. \tag{6.69}$$

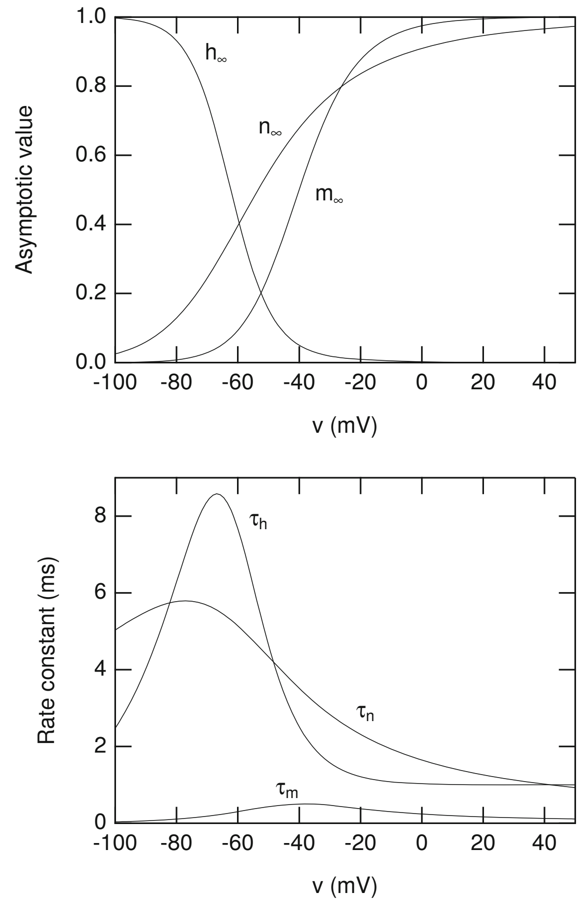


Fig. 6.37 Plots of the sodium and potassium conductance parameters versus the transmembrane potential

The v dependences were

$$\alpha_m = \frac{0.1[25 - (v - v_r)]}{\exp\left(\frac{25 - (v - v_r)}{10}\right) - 1},$$
$$\beta_m = 4 \exp\left(\frac{-(v - v_r)}{18}\right),$$
$$\alpha_h = 0.07 \exp\left(\frac{-(v - v_r)}{20}\right),$$
$$\beta_h = \frac{1}{\exp\left(\frac{30 - (v - v_r)}{10}\right) + 1}. \tag{6.70}$$

These values for α and β are also for a temperature of 6.3 °C. The temperature scaling of Eq. 6.67 must be used for other temperatures. The value of $g_{Na\infty}$ is 1200 S m^{-2}. Figure 6.37 plots the time constants and asymptotic values as a function of membrane potential. These are the parameters for the equations in the form of Eq. 6.65a rather than Eq. 6.65b.

The variable m (called the *sodium activation gate* or *m gate*) is nearly closed at rest, preventing the resting membrane from being permeable to sodium. As v is depolarized m opens, allowing sodium to rush in. The sodium ions carry positive charge, so this inward current causes v to depolarize further (if there is not a voltage clamp), causing m to increase even more. This positive feedback (see Chap. 10) is responsible for the rapid upstroke of the action potential. The inward sodium current ends when v approaches the sodium Nernst potential, about 50 mV.

Variable h (the *sodium inactivation gate* or *h gate*) is different than the n- and m gates because it is open at rest but closes upon depolarization. However, it is slow compared to the m gate (see Fig. 6.37), so during an action potential it does not fully close until after the m gate has opened completely. Once the action potential is finished and v has returned to the resting value, the slow h gate takes a few milliseconds to completely re-open. During this time, the membrane cannot generate another action potential (it is *refractory*) because the closed h gate suppresses the sodium current.

6.13.4 Leakage Current

All other contributions to the current (such as movement of chloride ions) were lumped in the leakage term $j_L = g_L(v - v_L)$. The empirical value for g_L is 3 S m^{-2}. The parameter v_L was adjusted to make the total membrane current equal zero when $v = v_r$. For example, with the data given, zero current is obtained with $v_r = -65$ mV and $v_L = v_r + 10.6 = -54.4$ mV. The three contributions to the membrane current can be thought of as the circuit shown in Fig. 6.33b.

The Hodgkin–Huxley parameters have been used for a wide variety of nerve and muscle systems, even though they were obtained from measurements of the squid axon. A number of other models have since been developed that incorporate the sodium–potassium pump, calcium, etc. They have also been developed for various muscle and cardiac cells (Demir et al. 1994; Luo and Rudy 1994; Wilders et al. 1991).

6.14 Voltage Changes in a Space-Clamped Axon

A space-clamped axon has an interior potential $v(t)$ which does not depend on x. If such an axon is stimulated, a voltage pulse is observed. The first test we can make of the Hodgkin–Huxley model is to see if the parameters from the voltage-clamp experiments can also explain this pulse. To do so, it is necessary to insert Eq. 6.59, with all the other equations that are necessary to use it, in Eq. 6.52. Life is made somewhat simpler by the fact that the spatial derivative in Eq. 6.52 vanishes when the wire is in the axon. The result is

$$c_m \frac{\partial v}{\partial t} = -g_{Na}(v - v_{Na}) - g_K(v - v_K) - g_L(v - v_L). \quad (6.71)$$

When $v = v_r$ the right-hand side of this equation is zero and v does not change. It is necessary to introduce a stimulus to cause the pulse. This has been done in the computer program of Fig. 6.38, which solves Eq. 6.71. This program is not the most efficient that can be used; it has been written for ease of understanding. A stimulus of 10^{-4} A cm^{-2} = 1 A m^{-2} is applied between 0.5 and 0.6 ms. This is an additional term in Eq. 6.71, so that in the program, Eq. 6.71 becomes

```
dvdt = (-jMemb + jStim)/Cmemb;
```

In this statement `dvdt` stands for $\partial v/\partial t$, `jMemb` stands for j_m, `Cmemb` for c_m, and `jStim` for the stimulus current. The equation is solved by repeated application of the approximation

```
v = v + dvdt * deltat;
```

which stands for

$$v(t + \Delta t) = v(t) + \left(\frac{\partial v}{\partial t}\right) \Delta t.$$

The program uses $\Delta t = 10^{-6}$ s. The present value of v is used to calculate the rate constants in procedure `Calcab`. These are then used to calculate the present value of each conductivity. The membrane current is then calculated, and the entire process is repeated for the next time step. The results are tabulated in Fig. 6.39 and plotted in Fig. 6.40.

One can see from the plot that j_m is proportional to $\partial v/\partial t$. Note that although g_{Na} is a smooth curve, j_{Na} has an extra wiggle near $t = 2$ ms, caused by the rapid decrease in the magnitude of $v - v_{Na}$ as the voltage approaches the sodium Nernst potential. The initial depolarization is due to an inrush of sodium ions. But there is still a considerable sodium current during the potassium current. The sodium and potassium currents are nearly balanced throughout most of the pulse. The pulse lasts about 2 ms.

If the temperature is raised, the pulse is much shorter. Figure 6.41 shows the impulse when the temperature is 18.5 °C, calculated by multiplying each of the α and β values by $3^{(18.5-6.3)/10} = 3.82$.

The potassium current is not actually needed to create a nerve impulse because of the leakage current (primarily chloride) and the fact that the sodium conductance decreases after the initial depolarization. The potassium current speeds up the repolarization process. It is easy to modify the program of Fig. 6.38 to show this.

```
//program HodgkinHuxley
//Calculates Hodgkin-Huxley
//space clamped axon at  6.3°C

#include <stdio.h>
#include <math.h>

const float
  deltat =   1e-6,//deltat for integration
  tPStep =   1e-4,//printthis often
  vRest  = -65e-3,//Resting Potential
  Cmemb  =  1e-6,//Membrane capacitance
  tMax   =   5e-3,//Time to quit
  vNa    = 50e-3,//Sodium Nernst pot.
  vK    =-77e-3;//Potassium Nernst pot.

double
  n, m, hh,
  an, am, ah,
  bn, bm, bh,
  dndt, dmdt, dhdt, dvdt,
  gK, gNa,
  jK, jNa, jL, jMemb,
  voltage, t,
  jStim,    //Stimulus current
  tPrint;   //Time interval to print

void Calcab (void)
/*   Calculates the alpha and betas for
n, m, h, using the Hodgkin-Huxley eqns.
The original eqns. were in mV and ms;
these are in volts and seconds  */
  {
  an = (10*(-1000*(voltage-vRest)+10))
       /(exp((-1000*(voltage-vRest)+10)
       /10)-1);
  am = (100*(-1000*(voltage-vRest)+25))
       /(exp((-1000*(voltage-vRest)+25)
       /10)-1);
  ah = 70*exp(-1000*(voltage-vRest)
       /20);
  bn = 125*exp(-1000*(voltage-vRest)
       /80);
  bm = 4000*exp(-1000*(voltage-vRest)
       /18);
  bh = 1000/(exp((-1000*(voltage-vRest)
       +30)/10)+1);
  }
void Calc_Init_Values(void) //Calculates
// initial values of n, m, hh
  {
  Calcab();
  n = an/(an+bn);
  m = am/(am+bm);
  hh = ah/(ah+bh);
  }

void Calc_Curr(void)
  // Calculate conductances in siemens
  //per sq cm and current densities
  {
  gK  = 36e-3*pow(n, 4);
  gNa = 120e-3*pow(m, 3)*hh;
  jK  = gK *(voltage-vK);
  jNa = gNa*(voltage-vNa);
  jL  = 3e-4*(voltage-vRest-10.6e-3);
  jMemb = jK+jNa+jL;
  }
main(void)
  {
  //Print Table Headings
  printf("time    v      jMemb     gNa
    jNa       gK       jK     jL\n");
  t = 0;
  voltage = vRest;
  tPrint = 0;
  Calc_Init_Values();
  while (t < tMax) //Step through times
    {
    Calc_Curr();//Calc. membrane
           // current from conductances
    if (t >= tPrint)  //Print at
           //certain times
      {
      printf("%4.1f %1s %5.1f %1s ",
1000*t, "", 1000*voltage, "");
      printf("%8.2e %1s %8.2e %1s
%8.2e", jMemb, "", gNa, "", jNa );
      printf("%1s %8.2e %1s %8.2e %1s
%8.2e\n","", gK, "",  jK,"",jL);
      tPrint = tPrint+tPStep;
      }    // end if

    if ((t >= 5e-4) && (t < 6e-4))
    //Stimulus current at beginning
      jStim = 1e-4;
    else
      jStim = 0;//End stimulus current
    dvdt = (-jMemb+jStim)/Cmemb;
    voltage = voltage+dvdt*deltat;
    Calcab();//Calc alpha, beta
    dndt = an*(1-n)-bn*n;
    dmdt = am*(1-m)-bm*m;
    dhdt = ah*(1-hh)-bh*hh;
    n  = n+dndt*deltat;
    m  = m+dmdt*deltat;
    hh = hh+dhdt*deltat;
    t  = t+deltat;
    }      //end while
  }        //end main
```

Fig. 6.38 The computer program used to calculate the response of a space-clamped axon to a stimulus. The results are shown in Figs. 6.39 and 6.40

6.15 Propagating Nerve Impulse

If the wire is not inserted along the axon, the voltage changes in the x direction. A strong enough stimulus at one point results in a pulse that travels along the axon without change of shape. The basic equation that describes it is again Eq. 6.52 with the spatial term and with the Hodgkin–Huxley model for the membrane current:

$$\frac{\partial v}{\partial t} = -\frac{j_m}{c_m} + \frac{1}{2\pi a\, r_i c_m}\frac{\partial^2 v}{\partial x^2},$$
$$j_m = g_{Na}(v - v_{Na}) + g_K(v - v_K) + g_L(v - v_L). \tag{6.72}$$

These can be solved numerically by setting up arrays for values of v, n, m, and h at closely spaced discrete values of x along the axon. If index i distinguishes different values of x, then the discrete equation is

```
dvdt[i]=-jMemb[i]/Cmemb
        +(1/(6.28*a*ri*Cmemb*dx*dx))
        *(v[i+1]-2*v[i]+v[i-1]).
```

Figure 6.42 shows each term in Eq. 6.72 multiplied through by c_m to have the dimensions of current per unit area. The term

$$c_m \frac{\partial v}{\partial t}$$

is the rate at which charge per unit area on the membrane must change in order to change the membrane potential at the rate $\partial v/\partial t$,

$$-j_m = -g_{Na}(v - v_{Na}) - g_K(v - v_K) - g_L(v - v_L)$$

is the rate of charge buildup because of current through the membrane, and

$$\frac{1}{2\pi a\, r_i}\frac{\partial^2 v}{\partial x^2}$$

is the rate of charge buildup on the inner surface of the membrane because the longitudinal current is not uniform.

time	v	jMemb	gNa	jNa	gK	jK	jL
ms	mV	A/sq m	S/sq m	A/sq m	S/sq m	A/sq m	A/sq m
0.0	-65.0	-3.24e-06	1.06e-01	-1.22e-02	3.67e+00	4.40e-02	-3.18e-02
0.2	-65.0	-2.90e-06	1.06e-01	-1.22e-02	3.67e+00	4.40e-02	-3.18e-02
0.4	-65.0	-2.68e-06	1.06e-01	-1.22e-02	3.67e+00	4.40e-02	-3.18e-02
0.6	-55.3	5.75e-02	1.99e-01	-2.09e-02	3.74e+00	8.11e-02	-2.71e-03
0.8	-55.9	5.17e-03	7.08e-01	-7.50e-02	4.02e+00	8.48e-02	-4.59e-03
1.0	-55.6	-3.69e-02	1.19e+00	-1.25e-01	4.31e+00	9.22e-02	-3.58e-03
1.2	-54.5	-7.33e-02	1.69e+00	-1.77e-01	4.62e+00	1.04e-01	-2.79e-04
1.4	-52.6	-1.24e-01	2.46e+00	-2.52e-01	5.01e+00	1.22e-01	5.49e-03
1.6	-49.2	-2.30e-01	4.02e+00	-3.99e-01	5.52e+00	1.54e-01	1.56e-02
1.8	-42.2	-5.34e-01	8.59e+00	-7.92e-01	6.34e+00	2.21e-01	3.67e-02
2.0	-22.3	-1.73e+00	3.14e+01	-2.27e+00	8.15e+00	4.45e-01	9.62e-02
2.2	28.7	-2.08e+00	1.83e+02	-3.89e+00	1.48e+01	1.56e+00	2.49e-01
2.4	38.7	2.13e-01	3.17e+02	-3.60e+00	3.06e+01	3.53e+00	2.79e-01
2.6	32.0	4.18e-01	2.98e+02	-5.35e+00	5.05e+01	5.51e+00	2.59e-01
2.8	22.7	5.00e-01	2.50e+02	-6.81e+00	7.10e+01	7.08e+00	2.31e-01
3.0	12.5	5.19e-01	2.04e+02	-7.67e+00	8.93e+01	7.99e+00	2.01e-01
3.2	2.2	5.06e-01	1.65e+02	-7.91e+00	1.04e+02	8.25e+00	1.70e-01
3.4	-7.7	4.80e-01	1.32e+02	-7.63e+00	1.15e+02	7.97e+00	1.40e-01
3.6	-17.1	4.56e-01	1.04e+02	-6.97e+00	1.22e+02	7.31e+00	1.12e-01
3.8	-26.0	4.43e-01	7.93e+01	-6.03e+00	1.25e+02	6.39e+00	8.52e-02
4.0	-35.0	4.63e-01	5.71e+01	-4.85e+00	1.25e+02	5.26e+00	5.82e-02
4.2	-45.0	5.54e-01	3.55e+01	-3.38e+00	1.22e+02	3.90e+00	2.81e-02
4.4	-57.5	6.86e-01	1.45e+01	-1.56e+00	1.16e+02	2.25e+00	-9.43e-03
4.6	-70.0	4.64e-01	1.98e+00	-2.37e-01	1.07e+02	7.47e-01	-4.68e-02
4.8	-75.2	1.04e-01	8.09e-02	-1.01e-02	9.64e+01	1.76e-01	-6.23e-02

Fig. 6.39 Results of the calculation for a space-clamped axon at 6.3 °C

6.16 Myelinated Fibers and Saltatory Conduction

We have so far been discussing fibers without the thick myelin sheath. Unmyelinated fibers constitute about two-thirds of the fibers in the human body. They usually have radii of 0.05–0.6 µm. The conduction speed in m s^{-1} is given approximately by $u \approx 1800\sqrt{a}$, where a is the axon radius in meters.[12] (Strictly speaking, in this formula a should be replaced by the outer radius $a + b$ including the membrane thickness, but for an unmyelinated fiber $b \ll a$.)

Myelinated fibers are relatively large, with outer radii of 0.5–10 µm. They are wrapped with many layers of myelin between the nodes of Ranvier, as shown in Fig. 6.43. Typically, the outer radius is $a + b \approx 1.67a$ and the spacing between nodes is proportional to the outer diameter $D = 200(a + b) \approx 330a$ (See Prob. 69). These empirical proportionalities between node spacing and radius and between myelin thickness and radius will be very important to our understanding of the conduction speed. The conduction speed in a myelinated fiber is given approximately by $u \approx 12 \times 10^6(a + b) \approx 20 \times 10^6 a$. The conduction speeds of myelinated and unmyelinated fibers are compared in Fig. 6.44.

In the myelinated region the conduction of the nerve impulse can be modeled by electrotonus because the conductance of the myelin sheath is independent of voltage. At each node a regenerative Hodgkin–Huxley-type (HH-type) conductance change restores the shape of the pulse. Such conduction is called *saltatory conduction* because *saltare* is the Latin verb "to jump."

We saw that electrotonus is described by

$$\lambda^2 \frac{\partial^2 v}{\partial x^2} - v - \tau \frac{\partial v}{\partial t} = -v_r, \tag{6.73}$$

where the time constant is

$$\tau = \kappa \epsilon_0 \rho_m \tag{6.74}$$

and the space constant is

$$\lambda = \sqrt{\frac{ab\,\rho_m}{2\rho_i}}. \tag{6.75a}$$

The results of Problem 68 can be used to show that when the myelin thickness is appreciable compared to the inner axon radius, the space constant should be modified:

$$\lambda_{\text{thick}} = \sqrt{\frac{\ln(1 + b/a)\,\rho_m}{2\rho_i}}\,a. \tag{6.75b}$$

For a case in which $a = 5$ µm and $b = 3.3$ µm, the change is not very large. The thin membrane equation contains the quantity $ab = 17 \times 10^{-12}$ m^2 and the thick myelin equation contains $a^2 \ln(1 + b/a) = 12.8 \times 10^{-12}$ m^2.

We now want to understand the different dependence on radius of the conduction speed in the two kinds of fibers. We could do computer modeling for the unmyelinated fiber using Eq. 6.72 with axons of different radii, but this would not

[12] Values quoted in the literature range from $u = 1000\sqrt{a}$ (Plonsey and Barr 2007) to $u = 3000\sqrt{a}$ (Rushton 1951).

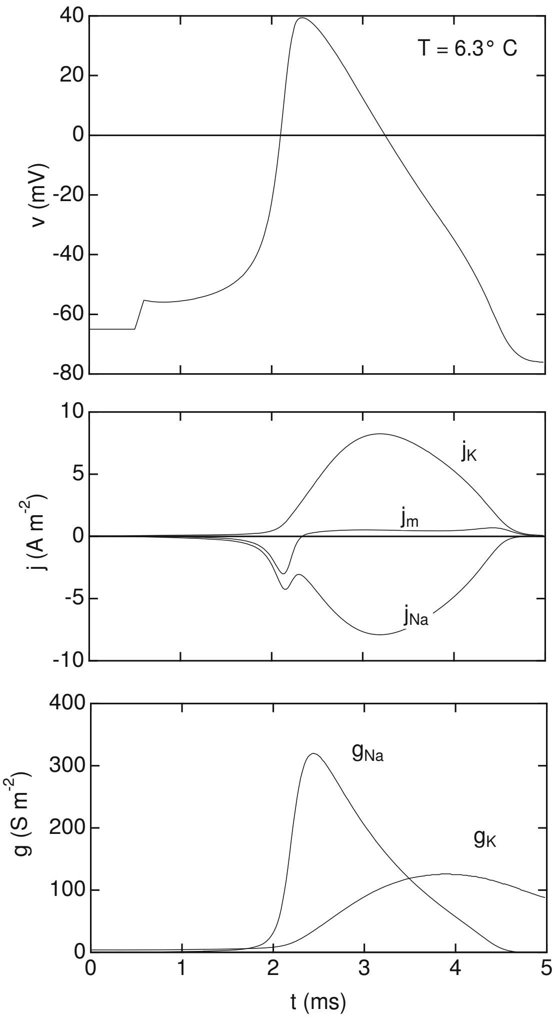


Fig. 6.40 A plot of the computation presented in Fig. 6.38 for a pulse in a space-clamped squid axon at $T = 6.3\,°\mathrm{C}$. The axon was stimulated at $t = 0.5$ ms for 0.1 ms

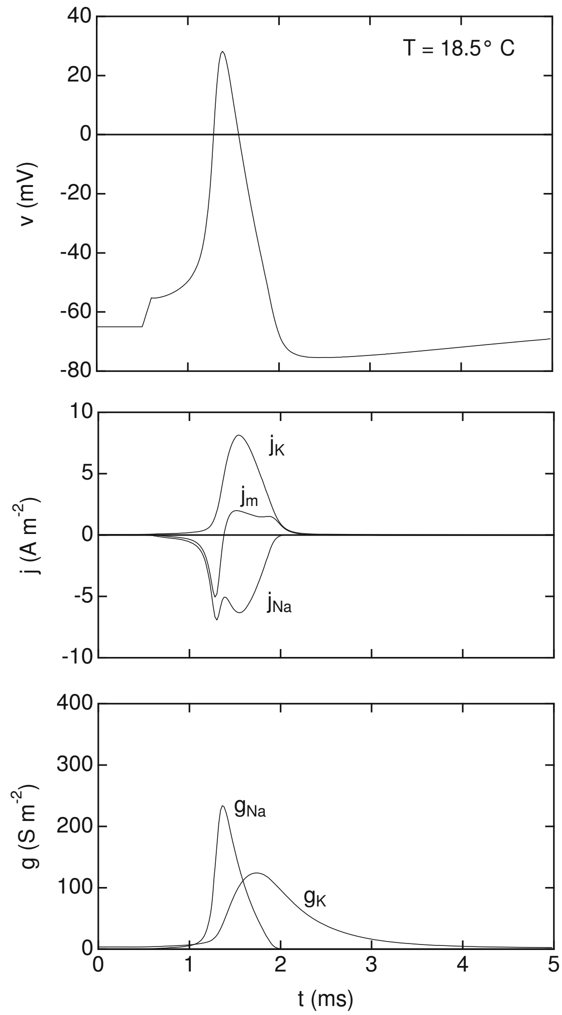


Fig. 6.41 A pulse in a space-clamped axon at 18.5 °C. The pulse lasts about 1 ms

provide an equation for $u(a)$. Rather than review the work that has been done (developing equations for the behavior of the foot of the action potential, for example), we will use a simple dimensional argument. This will not give an exact expression for $u(a)$, but it will indicate the functional form it must have.

In either the myelinated or the unmyelinated fiber the signal travels to neighboring regions by electrotonus, where it initiates HH-type membrane conductance changes. In the myelinated case the signal jumps from node to node; in the unmyelinated case the influence is on adjacent parts of the axon. When the neighboring region begins to depolarize, the HH change is much more rapid than that due to electrotonus. (Another way to say this is that during depolarization ρ_m and therefore τ become much smaller.) Therefore the conduction speed is limited by electrotonus. Regardless of the details of the calculation, the speed is proportional to the characteristic length in the problem divided by the characteristic time. For the unmyelinated case it is plausible to assume that the only characteristic length and time are λ and τ, so the speed is

$$u_{\text{unmyelinated}} \propto \frac{\lambda}{\tau} = \sqrt{\frac{b}{2\rho_i\,\rho_m}}\frac{1}{\kappa\epsilon_0}\sqrt{a}. \tag{6.76}$$

Since the membrane thickness for an unmyelinated fiber is always about 6 nm, this gives

$$u_{\text{unmyelinated}} \propto 270\sqrt{a} \tag{6.77}$$

as shown in Table 6.2.

For myelinated nerves the myelin thickness is $b \approx 0.67a$. This means that the space constant is proportional to a:

$$\lambda = \sqrt{\frac{ab\,\rho_m}{2\rho_i}} = \sqrt{\frac{0.67a^2\rho_m}{2\rho_i}} = a\sqrt{\frac{0.67\rho_m}{2\rho_i}} = 1750a. \tag{6.78}$$

Table 6.2 Properties of unmyelinated and myelinated axons of the same radius

Quantity	Unmyelinated	Myelinated
Axon inner radius a	5 μm	5 μm
Membrane thickness b'	6 nm	
Myelin thickness b		3.4 μm
$\kappa\epsilon_0$	6.20×10^{-11} s^{-1} Ω^{-1} m^{-1}	6.20×10^{-11} s^{-1} Ω^{-1} m^{-1}
Axoplasm resistivity ρ_i	1.1 Ω m	1.1 Ω m
Membrane (resting) or myelin resistivity ρ_m	10^7 Ω m	10^7 Ω m
Time constant $\tau = \kappa\epsilon_0\rho_m$	6.2×10^{-4} s	6.2×10^{-4} s
Space constant λ	$\lambda = \sqrt{\frac{ab\rho_m}{2\rho_i}} = 0.165\sqrt{a} = 370$ μm	$\lambda = \sqrt{\frac{ab\rho_m}{2\rho_i}} = \sqrt{\frac{0.67a^2\rho_m}{2\rho_i}} = a\sqrt{\frac{0.67\rho_m}{2\rho_i}} = 1750a = 8.8$ mm
Node spacing D		$D = 340a = 1.7$ mm
Conduction speed from model	$u_{\text{unmyelinated}} \propto \lambda/\tau \approx 270\sqrt{a}$	$u_{\text{myelinated}} \propto \lambda/\tau \approx 2.9 \times 10^6 a$ or $D/\tau = 0.55 \times 10^6 a$
Conduction speed, empirical	$u_{\text{unmyelinated}} \approx 1800\sqrt{a}$	$u_{\text{myelinated}} \approx 17 \times 10^6 a$
Ratio of empirical to model conduction speed	6.7	5.9 or 31
Space constant using thick membrane model		$\lambda = a\sqrt{\frac{\ln(1+b/a)\rho_m}{2\rho_i}} = a\sqrt{\frac{\ln(1.67)\rho_m}{2\rho_i}} = 1530a = 7.6$ mm

The spacing between the nodes, D, is about $340a$. There are two characteristic lengths for the myelinated case, both proportional to a because of the way the myelin is arranged. If we assume that the speed is proportional to D/τ, we obtain

$$u_{\text{myelinated}} \propto 0.55 \times 10^6 a. \tag{6.79}$$

If we assume that the speed is proportional to λ/τ, we obtain

$$u_{\text{myelinated}} \propto 2.9 \times 10^6 a. \tag{6.80}$$

Table 6.2 compares the space constants, time constants and conduction speeds for myelinated and unmyelinated fibers. The empirical expressions for the conduction speed are 7 or 8 times greater than what we estimate based on λ/τ. We might expect firing at the next node to occur when the signal has risen to about 10 % of its maximum value. This would reduce the time by about a factor of 10.

The internodal spacing is about 20 % of the space constant. Suppose that a constant current is injected at one node, as in Fig. 6.30. When the voltage has reached its full value at the next node it is given by

$$\frac{v}{v_0} = e^{-D/\lambda} = e^{-1.4/6.2} = 0.8.$$

If for some reason this node does not fire, the signal at the next node will be 0.64 of the original value, and so on. A local anesthetic such as procaine works by preventing permeability changes at the node. It is clear from this discussion that a nerve must be blocked over a distance of several nodes (a centimeter or more) in order for an anesthetic to be effective (Covino 1972).

6.17 Membrane Capacitance

The value of 7 for the dielectric constant, which has been used throughout this chapter, is considerably higher than the value 2.2, which is known for lipids. The inconsistency arises because part of the membrane is very easily polarized and effectively belongs to the conductor rather than to the dielectric; if the thickness of the lipid alone is considered in calculating the capacitance, then a value of 2.2 for κ is reasonable; if the entire membrane thickness is used, then the much higher dielectric constant for water and the polar groups within the membrane contributes, and $\kappa = 7$ is a reasonable value.

The easiest experiments to understand are those done with artificial bimolecular layers of lipid. The architecture of such a film is shown in Fig. 6.45. Each lipid molecule has a polar head and a hydrophobic tail. The molecules are arranged in a double layer with the heads in the aqueous solution. The dimensions in Fig. 6.45 are consistent with both measurements

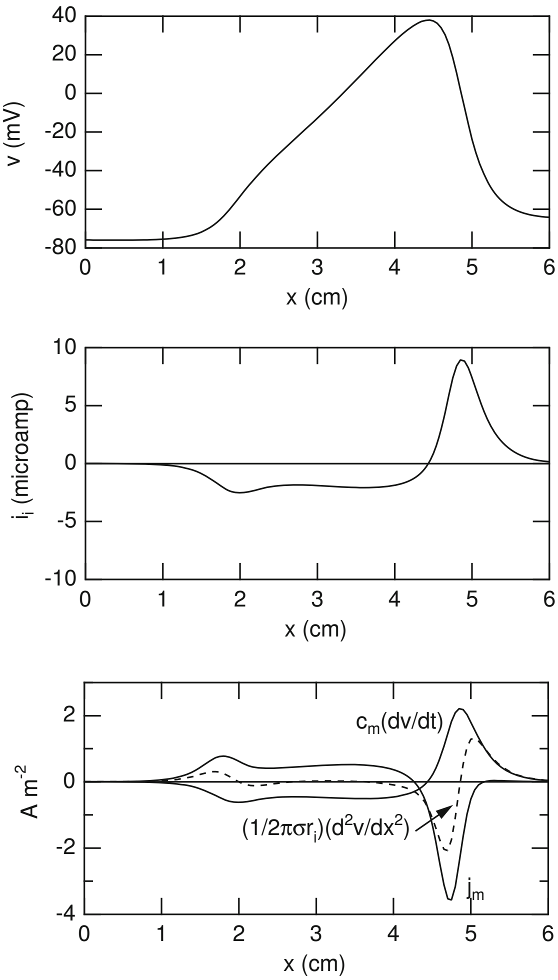


Fig. 6.42 A propagating pulse plotted against position along the axon at an instant of time. The middle graph shows the longitudinal current inside the axon. The bottom curve shows the current charging or discharging the membrane and the two terms comprising the right-hand side of Eq. 6.72

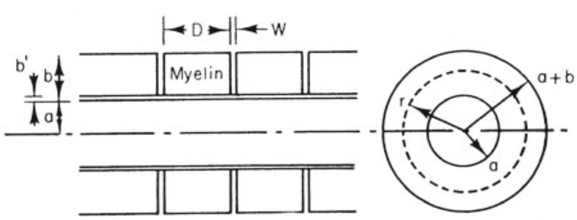


Fig. 6.43 The idealized structure of a myelinated fiber in longitudinal section and in cross section. The internodal spacing D is actually about 100 times the outer diameter of the axon

of the film thickness and with the known structure of the lipid molecules. Linear aliphatic hydrocarbons have a bulk dielectric constant of about 2. The polar heads have a much higher dielectric constant, probably about 50. Water has a dielectric constant of about 80.

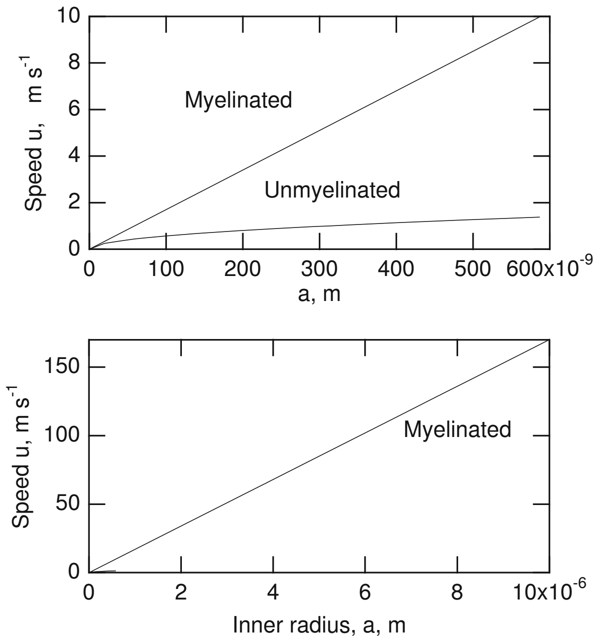


Fig. 6.44 The conduction speed versus the inner axon radius a for myelinated and unmyelinated fibers. Unmyelinated fibers with $a > 0.6\ \mu$m are not found in the body

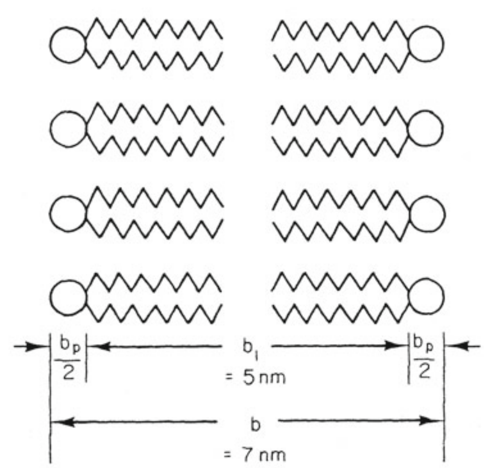


Fig. 6.45 Structure of a bimolecular lipid membrane

The capacitance per unit area of bimolecular lipid films is about 0.3×10^{-2} F m^{-2} (0.3 μF cm^{-2}). The simplest way to explain this value is to assume that the polar heads are part of the surrounding conductor. The capacitance per unit area is then

$$\frac{C}{S} = \frac{\kappa\epsilon_0}{b_1} = \frac{(2.2)(8.85 \times 10^{-12})}{5 \times 10^{-9}} = 0.4 \times 10^{-2}\ \mathrm{F\ m^{-2}}.$$

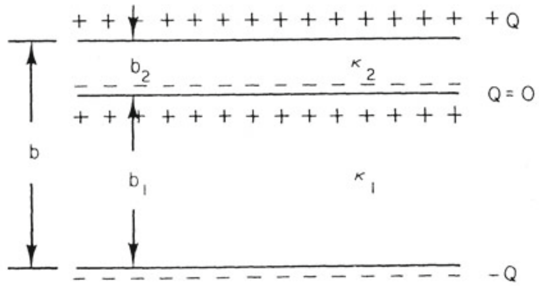


Fig. 6.46 A membrane composed of two phases. The ith phase has thickness b_i and dielectric constant κ_i. The total thickness is b and the effective dielectric constant is κ. The charges shown are external charge; polarization of the dielectric is not shown but determines the value of κ

A more sophisticated approach is to regard the membrane as made up of three layers: polar, lipid, polar. The same effect can be obtained by considering two layers with all the polar component lumped together, as in Fig. 6.46. Suppose that we put charge $+Q$ on one surface and $-Q$ on the other surface of the membrane. We put no charge on the interface between layers 1 and 2. The charge of zero on the interface can be thought of as a superposition of positive and negative charges as shown in Fig. 6.46. We are referring only to external charge which we place on the membrane; the charges induced by polarization of the dielectric are not shown. They are taken into account by the value of κ. The situation is that of two parallel-plate capacitors in series. Each layer has a capacitance C_i: $Q = C_i v_i = \kappa_i \epsilon_0 S v_i / b_i$. The total potential across the membrane is $v = v_1 + v_2 = Q/C$. The total capacitance is

$$C = \frac{Q}{v_1 + v_2} = \frac{Q}{Qb_1/\kappa_1\epsilon_0 S + Qb_2/\kappa_2\epsilon_0 S}$$
$$= \frac{1}{b_1/\kappa_1\epsilon_0 S + b_2/\kappa_2\epsilon_0 S}. \tag{6.81}$$

The effective dielectric constant is obtained by equating the total capacitance to $\kappa\epsilon_0 S/b$:

$$\kappa = \frac{b}{b_1/\kappa_1 + b_2/\kappa_2}. \tag{6.82}$$

Application of these equations to the bimolecular lipid membrane (with $\kappa_1 = 2.2$, $\kappa_2 = 50$, $b_1 = 5$ nm, $b_2 = 2$ nm) gives

$$\kappa = 3.0,$$
$$\frac{C}{S} = 0.38 \times 10^{-2}\ \mathrm{F\ m^{-2}}. \tag{6.83}$$

The capacitance per unit area is nearly that obtained by assuming the polar groups are perfect conductors.

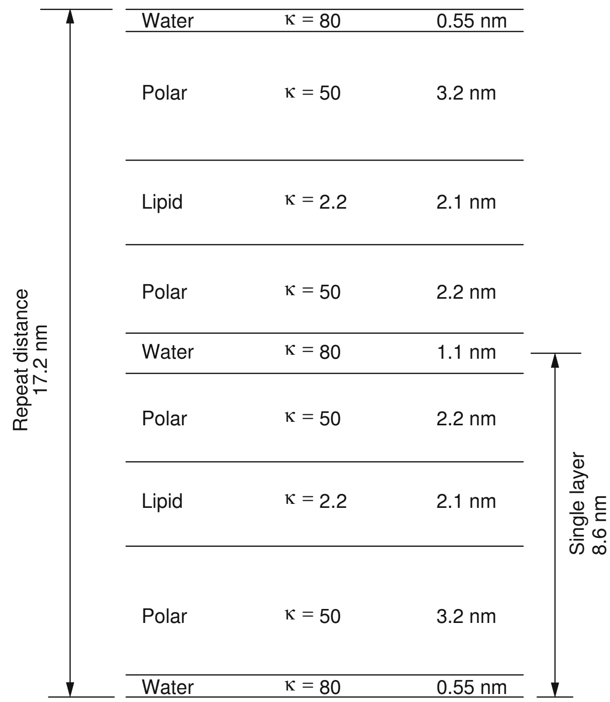


Fig. 6.47 The results of x-ray diffraction measurements of the structure of myelin surrounding frog sciatic nerve. Data are adapted from Worthington (1971, p. 35).

The myelin surrounding a nerve fiber consists of several layers wrapped tightly together. Each repeating layer is made up of two single layers back to back. The best data on the structure of these layers are from x-ray diffraction experiments. The layers repeat every 17 nm. One model for the structure within a repeat distance is shown in Fig. 6.47 (Worthington 1971, p. 35). A single layer of the myelin has a thickness of 8.55 nm. A surprising feature of this model is that the lipid layer is less than half the thickness of that in a bilayer lipid membrane. However, the measured capacitance of a nerve-cell membrane or myelin is greater than for the bilayer lipid membrane; if one is to keep the lipid value for κ, the membrane must be thinner. It is gratifying that the membrane thickness as measured by x-ray diffraction is consistent with the observed membrane capacitance.

To check the consistency, note that Eqs. 6.81 and 6.82 are easily extended to more than two phases. Use the following data:

	κ_i	b_i (nm)
Water	80	2.2
Lipid	2.2	4.2
Polar	50	10.8

With these values, the effective dielectric constant is

$$\kappa = \frac{17.2}{4.2/2.2 + 2.2/80 + 10.8/50} = 7.95.$$

If we assume that the membrane on an unmyelinated axon has the same structure as a half-unit of the myelin, then the thickness is 8.55 nm. With a dielectric constant of 7.95, the capacitance per unit area is calculated to be 0.82×10^{-2} F m^{-2}. The measured value is 1.0×10^{-2} F m^{-2}.

When one begins to look at the detailed structure of the membrane as we have done in this section, there is no justification for using the same membrane thickness b for the capacitance and the conductance of the membrane. The capacitance is determined primarily by the thickness of the lipid portion of the membrane; the conductance includes the effect of ions passing through the polar layers. The product, $\kappa\rho$, of the previous section is meaningful only for a membrane that is homogeneous and has the same thickness for both capacitive and conductive effects.

As long as the membrane structure is not being considered, it is safer to express such things as attenuation along the axon in terms of the directly measured parameters: length and time constants. Nonetheless, a preliminary formulation in terms of a homogeneous membrane model can be useful to start thinking about the problem.

6.18 Rhythmic Electrical Activity

Many cells exhibit rhythmic electrical activity. Various nerve transducers produce impulses with a rate of firing that depends on the input to which the transducer is sensitive. The beating of the heart is controlled by the *sinoatrial node* (SA node) that produces periodic pulses that travel throughout the heart muscle.

The mechanism for such repetitive activity is similar to what we have seen in the Hodgkin–Huxley model, though the details of the ionic conductance variations differ. The computer program of Fig. 6.38 can easily be modified to model rhythmic activity. Figure 6.48 shows a plot of the output of a modified program. The only modification was to make `jStim` be a constant leakage current of 0.2 A m^{-2} (0.2×10^{-4} A cm^{-2}). This provides the essential feature: a small inward current between beats that causes the potential inside the cell to increase slowly. When the voltage exceeds a certain threshold, the membrane channels open and the cell produces another impulse.

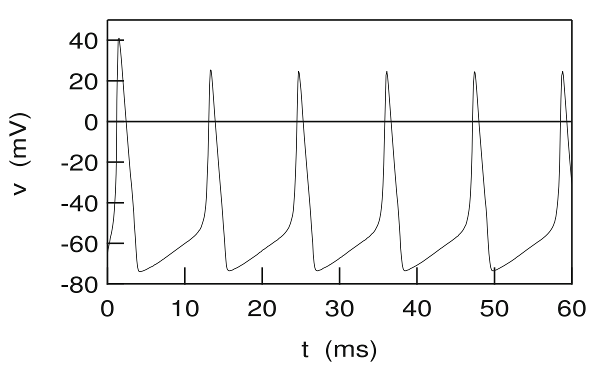


Fig. 6.48 By changing the leakage current, it is possible to make the Hodgkin–Huxley model display periodic electrical activity

While this simple change produces repetitive firing, and in fact the shape of the curve in Fig. 6.48 is very similar to that measured in the SA node, the details of ionic conduction are actually very different. The SA node contains no sodium channels. The rapid depolarization is due to an inward calcium current. There are a number of contributions to the current in the SA node, and detailed ionic models of them have been described (Demir et al. 1994; Noble 1989, 1995; Wilders et al. 1991).The slow leakage is a complicated combination of currents, the details of which are still not completely understood (Anumonwo and Jalife 1995; DiFrancesco et al. 1995).

6.19 The Relationship Between Capacitance, Resistance, and Diffusion

There is a fundamental relationship between the capacitance and resistance between two conductors in a homogeneous conducting dielectric. It is also possible to develop an analogy between capacitance and steady-state diffusion, so that known expressions for the capacitance of conductors in different geometries can be used to solve diffusion problems.

6.19.1 Capacitance and Resistance

Consider two conductors carrying equal and opposite charge and embedded in an insulating medium with dielectric constant κ. The potential difference between the conductors is Δv, and the magnitude of the charge on each is $Q = C\Delta v$. The electric field is $\mathbf{E}(x, y, z)$. In a vacuum Gauss's law applied to a surface surrounding the positively charged conductor gives $\iint \mathbf{E} \cdot d\mathbf{S} = Q/\epsilon_0$. Polarization in a dielectric surrounding the conductor reduces the electric field by a factor of κ. If $\mathbf{E}$ refers to the electric field in the dielectric and Q to the charge on the conductor, Gauss's law becomes

$$\iint \mathbf{E} \cdot d\mathbf{S} = Q/\kappa\epsilon_0. \tag{6.84}$$

For a given charge on the conductor, the presence of the dielectric reduces $\mathbf{E}$ and Δv by $1/\kappa$ and, therefore, increases the capacitance by κ.

Suppose that the dielectric is not a perfect insulator but obeys Ohm's law and has conductivity σ ($\mathbf{j} = \sigma\mathbf{E}$). If some process maintains the magnitude of the charge on each conductor at Q, the current leaving the positive conductor is

$$i = \iint \mathbf{j} \cdot d\mathbf{S} = \sigma \iint \mathbf{E} \cdot d\mathbf{S} = \sigma Q/\kappa\epsilon_0. \tag{6.85}$$

The resistance between the conductors is

$$R = \frac{\Delta v}{i} = \frac{Q/C}{\sigma Q/\kappa\epsilon_0} = \frac{\kappa\epsilon_0}{\sigma C}. \tag{6.86}$$

This inverse relationship between the resistance and capacitance is independent of the geometry of the conductors, as long as the dielectric constant and conductivity are uniform throughout the medium.

If the charge on the conductors is not replenished, it leaks off with a time constant $\tau = RC = \kappa\epsilon_0/\sigma$. We have seen this result earlier in several special cases; we now understand that it is quite general.

6.19.2 Capacitance and Diffusion

In Chap. 4, we saw that the transport equations for particles, heat, and electric charge all have the same form. We now develop an analogy between these transport equations and the equations for the electric field. The analogy is useful because it relates the diffusion of particles between different regions to the electrical capacitance between conductors with the same geometry; the electrical capacitance in many cases is worked out and available in tables.

Fick's first law of diffusion was developed in Chap. 4, Eq. 4.20:[13]

$$\mathbf{j}_s = -D\nabla c. \tag{6.87}$$

The relationship between fluence rate (particle current density) and particle flux (current) is

$$\iint \mathbf{j}_s \cdot d\mathbf{S} = i_s, \tag{6.88}$$

where i_s is the current of particles out of the volume enclosed by the surface. This equation is very similar to Gauss's law,

$$\iint_{\text{surface}} \mathbf{E} \cdot d\mathbf{S} = \frac{q}{\kappa\epsilon_0}, \tag{6.89}$$

where q is the electric charge. The electric potential and the electric field are related by the three-dimensional version of Eq. 6.16:

$$\mathbf{E} = -\nabla v. \tag{6.90}$$

[13] In this section, we will use c for concentration of solute particles and C for the electrical capacitance.

The similarity between Eqs. 6.90 and 4.20 and between 6.5 and 6.89 suggests that we make the substitutions

$$\begin{aligned} i_s &\longleftrightarrow \frac{q}{\kappa\epsilon_0}, \\ c &\longleftrightarrow \frac{v}{D}, \\ \mathbf{j}_s &\longleftrightarrow \mathbf{E}. \end{aligned} \tag{6.91}$$

For any electrostatic configuration in which there are two equipotential surfaces containing charge $+q$ and $-q$, there is an analogous diffusion problem in which there is a flow of particles from one surface to another, each surface having a constant concentration on it. In the electrical case, the charge and potential are related by the capacitance, which is a geometric property of the two equipotential surfaces: $q = C\Delta v$. An analogous statement can be made for diffusion between two surfaces of fixed concentration:

$$i_s = -\frac{C\,\Delta v}{\kappa\epsilon_0} = -\frac{C}{\kappa\epsilon_0} D\,\Delta c. \tag{6.92}$$

We can find the rate of flow of particles if we know the diffusion constant, the concentration difference, and the capacitance for the electrical problem with the same geometry. To see the utility of this method, we will consider some cases of increasing geometrical complexity.

As a first example, suppose that two concentric spheres have radii a and b. You can show (from the work in Problem 16, for example) that the capacitance of this configuration is

$$\frac{C}{\kappa\epsilon_0} = \frac{4\pi}{1/a - 1/b}. \tag{6.93}$$

As $b \to \infty$, this becomes

$$\frac{C}{\kappa\epsilon_0} = 4\pi a. \tag{6.94}$$

This can be applied to diffusion to or from a spherical cell of radius a. If the diffusion is outward, as of waste products, imagine that the outward flow rate is i_s and that the concentration difference between the cell surface and infinity is c_0. Then

$$i_s = -4\pi a\, D\, c_0. \tag{6.95}$$

If, on the other hand, the concentration infinitely far away is greater than that at the cell surface by an amount c_0, the number of particles in the cell will increase at a rate

$$i_s = +4\pi a\, D\, c_0. \tag{6.96}$$

These results were obtained directly in Chap. 4.

As another example, consider a circular disk of radius a with the other electrode infinitely far away. It is more difficult to calculate the capacitance in this case, but we can look it up (Smythe et al. 1957). It is $C/\kappa\epsilon_0 = 8a$. But this is the capacitance for the charge on *both sides* of the disk; the lines of **E** and **j** go off in both directions. We want only half of this, since we will use the result to calculate the end correction for a pore. (If we were concerned with diffusion to a disk-shaped cell, we would use the whole thing.) For the half-space

$$i_{s\ \text{half}} = -4Da\,\Delta c \tag{6.97}$$

is proportional to the radius of the disk, not its area.

Still another geometrical situation that may be of interest is the diffusion of particles from one sphere of radius a to another sphere of radius a, when the centers of the spheres are separated by a distance b.

The capacitance between two such spherical electrodes is (Smythe et al. 1957, pp. 5–14)

$$\frac{C}{\kappa\epsilon_0} = 2\pi a \sinh\beta\left(\frac{1}{\sinh\beta} + \frac{1}{\sinh 2\beta} + \frac{1}{\sinh 3\beta} + \cdots\right),$$

where $\cosh\beta = b/2a$. This formula is written in terms of the *hyperbolic functions*

$$\begin{aligned}\sinh\beta &= \tfrac{1}{2}\left(e^{\beta} - e^{-\beta}\right),\\ \cosh\beta &= \tfrac{1}{2}\left(e^{\beta} + e^{-\beta}\right).\end{aligned} \tag{6.98}$$

When the spheres are far apart $b/2a \to \infty$, and $\cosh\beta \approx \frac{1}{2}e^{\beta}$, $\sinh\beta \approx \frac{1}{2}e^{\beta}$. In that limit,

$$\begin{aligned}\frac{C}{\kappa\epsilon_0} &= 2\pi a\left(\tfrac{1}{2}e^{\beta}\right)\left(\frac{1}{\frac{1}{2}e^{\beta}} + \frac{1}{\frac{1}{2}e^{2\beta}} + \frac{1}{\frac{1}{2}e^{3\beta}} + \cdots\right)\\ &= 2\pi a e^{\beta}\left(e^{-\beta} + e^{-2\beta} + e^{-3\beta} + \cdots\right)\\ &= 2\pi a\left[1 + (a/b) + (a/b)^2 + \cdots\right].\end{aligned} \tag{6.99}$$

The diffusive flow between two spheres is therefore

$$i_s = -2\pi a\,D\,\Delta c \tag{6.100}$$

if they are sufficiently far apart. Note that this is just one-half of the flow from a sphere of radius a to a concentric sphere infinitely far away. The earlier results in this section show that the electrical resistance between two spherical electrodes sufficiently far apart is $1/2\pi\sigma a$.

Symbols Used in Chap. 6

Symbol	Use	Units	First used page
a	Distance	m	145
a	Axon inner radius	m	157
a	Radius of spherical ion or cell	m	173
a	Radius of disk	m	173
b, c	Distance	m	145
b	Membrane thickness	m	142
b	Myelin thickness	m	167
b'	Membrane thickness at node of Ranvier	m	168
b	Sphere radius	m	173
c	Concentration	m^{-3}	142
c_i, c_o	Ion concentrations	m^{-3}; mol l^{-1}	155
c_m	Membrane capacitance per unit area	F m^{-2}	157
e	Electronic charge	C	155
g_{Na}, g_K, g_m, g_L	Membrane conductance per unit area	S m^{-2}	157
$g_{Na\infty}, g_{K\infty}$	Asymptotic membrane conductance per unit area	S m^{-2}	163
h, h_∞	Parameters used to describe sodium conductance		164
i	Electric current	A	151
i_i	Currents along inside of axon	A	158
i_m	Current through a section of membrane	A	156
i_s	Solute current or flux	s^{-1}	173
$j, \mathbf{j}$	Current per unit area	A m^{-2}	151
j_m	Membrane current per unit area	A m^{-2}	157
j_{Na}, j_K, j_L	Membrane current per unit area for that species	A m^{-2}	161
k_B	Boltzmann's constant	J K^{-1}	155
m, m_∞	Parameters used to describe sodium conductance		164
n, n_∞	Parameters used to describe potassium conductance		163
$p, \mathbf{p}$	Dipole moment	C m	175
q	Electric charge	C	143
q_{bound}, q_{free}	Bound and free charge	C	150
$r, \mathbf{r}$	Distance	m	143
r_i	Resistance per unit length along inside of axon	$\Omega\ \text{m}^{-1}$	157
t	Time	s	142
u	Propagation velocity of a wave or signal	m s^{-1}	167
v	Potential difference	V	142
v	$v_i - v_o$	V	158
v_K, v_{Na}	Equilibrium (Nernst) potential for potassium, sodium	V	162
v_r	Resting membrane potential	V	159
x, y, z	Distance	m	146
z	Valence of ion		155
C	Capacitance	F	149

C_m	Membrane capacitance	F	156
D	Length of myelinated segment	m	167
D	Diffusion constant	$m^2\ s^{-1}$	173
$\mathbf{E}$, E_x, E_y, E_z	Electric field and components	$V\ m^{-1}$	144
E_p	Electric field due to polarization charge	$V\ m^{-1}$	149
E_e, E_{ext}	External electric field	$V\ m^{-1}$	149
$\mathbf{E}_{tot}$	Total electric field	$V\ m^{-1}$	149
$\mathbf{F}$	Force	N	143
$\mathbf{F}_{ext}$	External force	N	147
G	Conductance	Ω^{-1} or S	151
G_m	Conductance of a section of axon membrane	Ω^{-1} or S	157
L	Length of cylinder or axon segment	m	145
$[Na_i]$, $[Na_o]$	Sodium concentrations inside and outside an axon	m^{-3}	161
P	Power	W	153
Q	Electric charge	C	149
Q_{10}	Factor by which the rate of a chemical reaction increases with a temperature rise of 10 K		164
R	Resistance	Ω	151
R_i	Internal resistance along a segment of axon	Ω	157
R_m	Resistance across a segment of membrane	Ω	156
S, ΔS, dS	Surface area	m^2	144
T	Temperature	K	155
U	Potential energy	J	147
W	Work	J	151
α_m, β_m, α_n, β_n, α_h, β_h	Rate parameters for Hodgkin–Huxley model	s^{-1}	163
β	Dimensionless variable		174
ϵ_0	Electrical permittivity of free space	$N^{-1}\ m^{-2}\ C^2$	143
κ	Dielectric constant		150
λ	Charge per unit length	$C\ m^{-1}$	145
λ	Electrotonus spatial decay constant	m	159
ρ	Resistivity	Ω m	152
ρ_i	Resistivity of axoplasm	Ω m	157
ρ_m	Resistivity of membrane	Ω m	156
θ	Angle		146
σ	Charge per unit area	$C\ m^{-2}$	145
σ	Conductivity	$S\ m^{-1}$	152
χ	Electrical susceptibility		149
τ	Time constant	s	156
τ	Electrotonus time constant	s	160
τ_h, τ_m, τ_n	Time constants in Hodgkin-Huxley model	s	164

Problems

Section 6.1

Problem 1. Suppose that an action potential in a 1-μm diameter unmyelinated fiber has a speed of 1.3 $m\ s^{-1}$. Estimate how long it takes a signal to propagate from the brain to a finger. Repeat the calculation for a 10-μm diameter myelinated axon that has a conduction speed of 85 $m\ s^{-1}$. Speculate on the significance of these results for playing the piano.

Problem 2. The median nerve in your arm has a diameter of about 3 mm. If the nerve consists only of 1 μm-diameter unmyelinated axons, how many axons are in the nerve? (Ignore the volume occupied by extracellular space.) Repeat the calculation for 20 μm outer diameter myelinated axons. Repeat the calculation for 0.5 mm diameter unmyelinated axons (about the size of a squid axon). Speculate on why higher animals have myelinated axons instead of larger unmyelinated axons.

Section 6.2

Problem 3. Two equal and opposite charges $\pm q$ separated by a distance a form a dipole. The *dipole moment* $\mathbf{p}$ is a vector pointing in the direction from the negative charge to the positive charge of magnitude $p = qa$. In electrochemistry the dipole moment is often expressed in debyes: 1 debye (D) $= 10^{-18}$ electrostatic units (statcoulomb cm) (1 statcoulomb $= 3.3356 \times 10^{-10}$ C).

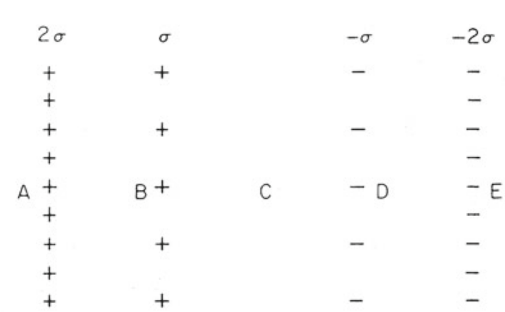
(a) Find the relationship between the debye and the SI unit for the dipole moment.

(b) Express the dipole moment of charges $\pm 1.6 \times 10^{-19}$ C separated by 2×10^{-10} m in debyes and in the appropriate SI unit.

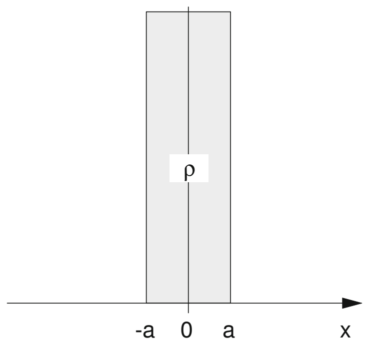
Problem 4. The electric field of a dipole can be calculated by assuming the positive charge q is at $z = a/2$ and the negative charge $-q$ is at $z = -a/2$ ($x = y = 0$). The electric field along the z axis is found by vector addition of the electric field from the individual charges using Eq. 6.3. Find an expression for the electric field. (Hint: $1/(1+x)^2$ is approximately equal to $1 - 2x$ for small x.) By what power of z does the electric field fall off?

Section 6.3

Problem 5. Use the principle of superposition to calculate the electric field in regions A, B, C, D, and E in the figure.



Problem 6. An infinite sheet of charge has a thickness $2a$ as shown. The charge density is ρ C m^{-3}. Find the electric field for all values of x.



Problem 7. Derive Eq. 6.10 from Eq. 6.9. At some point in your derivation you may need to use the substitution $u = y/\sqrt{c^2 + y^2 + z^2}$ and the integrals

$$\int \frac{dx}{(x^2 + a^2)^{3/2}} = \frac{x}{a^2\sqrt{x^2 + a^2}}$$

$$\int \frac{dx}{x^2 + a^2} = \frac{1}{a} \tan^{-1}\left(\frac{x}{a}\right).$$

Problem 8. Show that Eq. 6.10 reduces to Eq. 6.8 when $z \ll b, c$. Show that Eq. 6.10 is consistent with Coulomb's law when $z \gg b, c$.

Section 6.4

Problem 9. Show that N C^{-1} is equivalent to V m^{-1}.

Problem 10. Use Coulomb's law and $v = -\int_{\infty}^{x} E_x dx$ to determine the potential along the x axis due to a point charge. Assume that $v(x = \infty) = 0$. Because there is no preferred direction in space, the potential in any radial direction from the charge has the same form.

Problem 11. Try to apply the equation $v(r) = -\int_{\infty}^{r} E_r dr$ to the equation for the electric field of a line of charge, Eq. 6.7. Why does it not work?

Section 6.5

Problem 12. A person stands near a high-voltage power line. Assume for this problem that its voltage is not changing with time. Since much of a person's body is an ionic solution, treat the body as a conductor and the surrounding air as an insulator. In a static situation, what is the electric field inside the person's body caused by the power line? (Hint: Think before you calculate.)

Section 6.6

Problem 13. Two plane parallel conducting plates each have area S and are separated by a distance b. One carries a charge $+Q$; the other carries a charge $-Q$. Neglect edge effects.

(a) What is the charge per unit area on each plate? Where does it reside?
(b) What is the electric field between the plates?
(c) What is the capacitance?
(d) As the plate separation is increased what happens to E, v, and C?
(e) If a dielectric is inserted between the plates, what happens to E, v, and C? (See Sect. 6.7.)

Problem 14. It was shown in the text that the electric field from an infinitely long line of charge, of charge density λ C m^{-1}, is $E = \lambda/2\pi\epsilon_0 r$ at a distance r from the line.

(a) Show that if positive charge is distributed with density σ C m^{-2} on the surface of a cylinder of radius a, the electric field is

$$\begin{array}{ll} 0, & r < a \\ \sigma a/\epsilon_0 r, & r > a. \end{array}$$

(b) Find the potential difference between a point a distance a from the center of the cylinder and a point a distance d from the center of the cylinder ($d > a$).
(c) Is a or d at the higher potential?
(d) Suppose that another hollow cylinder of radius $d > a$ is placed concentric with the first. It has a charge $-\sigma'$ per unit area. How will its presence affect the potential difference calculated in part (b)?
(e) Calculate the capacitance between the two cylinders and show that it is $2\pi\epsilon_0 L/\ln(d/a)$, where L is the length of the cylinder.

Problem 15. Problem 14 showed that the capacitance of a pair of concentric cylinders, of radius a and d ($d > a$) is $2\pi\epsilon_0 L/\ln(d/a)$. Suppose now that $d = a + b$, where b is the thickness of the region separating the two cylinders. (It might, for example, be the thickness of the axon membrane.) Use the fact that $\ln(1+x) = x - x^2/2 + x^3/3 + \cdots$ to show that, for small b (that is, $b \ll a$), the formula for the capacitance becomes the same as that for a parallel-plate capacitor.

Problem 16. Find the capacitance of two concentric spherical conducting shells. The inner sphere has radius a and the outer sphere has radius b.

Section 6.7

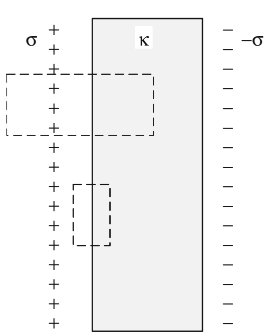
Problem 17. A parallel-plate capacitor has area S and plate separation b. The region between the plates is filled with dielectric of dielectric constant κ. The potential difference between the plates is v.

(a) What is the total electric field in the dielectric?
(b) What is the magnitude of the charge per unit area on the inner surface of the capacitor plates?
(c) What is the magnitude of the polarization charge on the surface of the dielectric?

Problem 18. For the unmyelinated axon of Table 6.1 and Fig. 6.3,
(a) How many sodium, potassium, and miscellaneous anions are there in a 1-mm segment?
(b) How many water molecules are there in a 1-mm segment?
(c) What is the charge per unit area on the inside of the membrane?
(d) What fraction of all the atoms and ions inside the segment are charged and not neutralized by neighboring ions of the opposite charge?

Problem 19. A nerve-cell membrane has a layer of positive charge on the outside and negative charge on the inside. These charged layers attract each other. The potential difference between them is $v = 70$ mV. Assuming a dielectric constant $\kappa = 5.7$ for the membrane, an axon radius of 5 µm, and a membrane thickness $b = 5$ nm, what is the force per unit area that the charges on one side of the membrane exert on the other? Express the answer in terms of b, v, and κ. (Hint: The force is calculated by multiplying the charge in a given layer by the electric field due to the charge in the other layer. Think carefully about factors of 2.)

Problem 20. The drawing represents two infinite plane sheets of charge with an infinite slab of dielectric filling part of the space between them. The dashed lines represent cross sections of two Gaussian surfaces. The sides are parallel to the electric field, and the ends are perpendicular to the electric field. Apply the second form of Gauss's law, Eq. 6.21b, to find the electric field within the dielectric using the upper Gaussian surface. Repeat using the lower Gaussian surface.



Section 6.8

Problem 21. This problem will give you some insight into the resistance of electrodes used in neurophysiology. Consider two concentric spherical electrodes. The region between them is filled with material of conductivity σ. The inner radius is a, the outer radius is b.
(a) Imagine that there is a total charge Q on the inner sphere. Find the electric field between the spheres in terms of the potential difference between them and their radii.
(b) The current density in the conducting material is given by $\mathbf{j} = \sigma \mathbf{E}$. Find the total current.
(c) Find the effective resistance, $R = v/i$. What is the resistance as $b \to \infty$? This is the resistance of a small spherical electrode in an infinite medium; infinite means the other electrode is "far away."

Problem 22. Patients undergoing electrosurgery sometimes suffer burns around the perimeter of the electrode. Wiley and Webster (1982) analyzed the potential produced by a circular disk electrode of radius a and potential v_0 in contact with a medium of conductivity σ. They found that the normal component of current density at the surface of the electrode is given by

$$j_n = \frac{2\sigma v_0}{\pi} \frac{1}{(a^2 - r^2)^{1/2}}, \qquad 0 < r < a.$$

(a) Calculate the total current I coming out of the electrode.
(b) Determine the resistance of the electrode.
(c) Plot j_n vs. r. Use the plot to explain why the patients suffer burns near the edge of the electrode.

Problem 23. The *Coulter counter* or resistive pulse technique is used to count and size particles in a wide variety of applications (Kubitschek 1969; DeBlois and Bean 1970), including the automated counting of blood cells. The cells being counted are assumed to be nonconducting and immersed in a conducting fluid. The fluid is made to flow through a narrow channel. When a suspended particle enters the channel there is a change in resistance. Assume a long channel of radius b with no end effects.
(a) What is the resistance of pure fluid of resistivity $\rho = 1/\sigma$ in a segment of channel of length $2a$?
(b) A cylindrical non-conducting cell of radius a and length $2a$ is in the channel. Its axis and the axis of the channel coincide. What is the resistance of a segment of channel of length $2a$? Ignore end effects.
(c) Show that the resistance change (the difference between these two reults) is proportional to the volume of the cell, $V = 2\pi a^3$, and inversely proportional to b^4.

Section 6.9

Problem 24. Derive the equation for the resistance of a set of resistors connected (a) in series and (b) in parallel.

Section 6.10

Problem 25. The resting concentration of calcium ions, [Ca^{++}], is about 1 mmol l^{-1} in the extracellular space but is very low (10^{-4} mmol l^{-1}) inside muscle cells. Determine the Nernst potential for calcium. Is calcium in equilibrium at a resting potential of -70 mV?

Problem 26. In our analysis of the electric field in the cell membrane, we assume the charge on the membrane can be represented as a continuous distribution of surface charge. For a 6-nm thick membrane this will be a good approximation if the number of discrete charges in a 6-nm square patch of membrane is large.

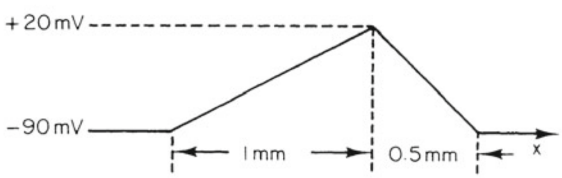
(a) Estimate how many discrete charged ions are present on a 6-nm square patch of membrane in a resting cell. Does the charge distribution appear to be continuous or discrete?

(b) Assume the ion has a diffusion constant in water of 10^{-9} m^2 s^{-1} and calculate the time required for the ion to diffuse 6 nm. If averaged over 1 ms, a time characteristic of neural activity, does the charge distribution appear continuous or discrete?

Section 6.11

Problem 27. The resistivity of the fluid within an axon is 0.5 Ω m. Calculate the resistance along an axon 5 mm long with a radius of 5 µm. Repeat for a radius of 500 µm.

Problem 28. The voltage along an axon is as shown at some instant of time. The axon radius is 10 µm; the resistivity of the axoplasm is 0.5 Ω m. What is the longitudinal current in the axon as a function of position?

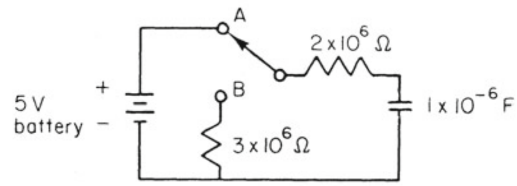


Problem 29. This problem is designed to show you how a capacitance, such as the cell membrane, charges and discharges. To begin, the switch has been in position B for a long time, so that there is no charge on the capacitor. At $t = 0$ the switch is put in position A. It is kept there for 20 s, then thrown back to position B.

(a) Write a differential equation for the voltage on the capacitor as a function of time when the switch is in position A and solve it.

(b) Repeat when the switch is in position B.

(c) Plot your results.



Problem 30. Sometimes an organ is lined with a single layer of flat cells. (One example is the lining of the *jejunum*, the upper portion of the small intestine.) Experimenters can then apply a time-varying voltage across the sheet of cells and measure the resulting current. The cells are packed so tightly together that one model for them is two layers of insulating membrane of dielectric constant κ and thickness b that behave like a capacitor, separated by intracellular fluid of thickness a and resistivity ρ. Find a differential equation or integral equation that relates the total voltage difference across the layer of cells $v(t)$ to the current per unit area through the layer, $j(t)$, in terms of κ, ρ, b, a.

Problem 31. The current that appears to go "into" a section of membrane is made up of two parts: that which charges the membrane capacitance and that which is a leakage current through the membrane: $i = v/R + C(dv/dt)$. Suppose that the total current is sinusoidal: $i = I_0 \cos \omega t$.

(a) Show that the voltage must be of the form $v = I_0 R' \cos \omega t + I_0 X \sin \omega t$ and that the differential equation is satisfied only if

$$R' = \frac{R}{1 + \omega^2 (RC)^2},$$

$$X = R \frac{\omega (RC)}{1 + \omega^2 (RC)^2}.$$

(b) What happens to R' and X as $\omega \to 0$? $\omega \to \infty$? For what value of ω is X a maximum? What is the corresponding value of R'? Plot these points.

(c) Your plot in part b should suggest that the locus of X vs R' is a semicircle, centered at $X = 0$, $R' = R/2$. Prove that this is so. [Remember that the equation of a circle is $(x - a)^2 + (y - b)^2 = r^2$.]

Section 6.12

Problem 32. Consider the myelinated and unmyelinated axons of Tables 6.1 and 6.2. Compare the decay distance for electrotonus in both cases. Neglect attenuation due to the leakage at the node of Ranvier.

Problem 33. Show by direct substitution that $v(x) = v_0 e^{-x/\lambda} + v_r$ satisfies the equation

$$\frac{d^2 v}{dx^2} = 2\pi a \, g_m r_i (v - v_r)$$

if v_r is constant.

Problem 34. In an electrotonus experiment a microelectrode is inserted in an axon at $x = 0$, and a constant current i_0 is injected. After the membrane capacitance has charged, the voltage outside is zero everywhere and the voltage inside is given by Eq. 6.58:

$$v - v_r = \begin{cases} v_0 e^{-x/\lambda}, & x > 0 \\ v_0 e^{x/\lambda}, & x < 0. \end{cases}$$

(a) Find $i_i(x)$ in terms of v_0, λ, and r_i.
(b) Find $j_m(x)$ in terms of g_m, v_0, and λ.
(c) Find the current i_0 injected at $x = 0$ in terms of v_0, λ, and r_i.
(d) Find the input resistance v_0/i_0.

Problem 35. The cable equation is $\lambda^2(\partial^2 v/\partial x^2) - v - \tau(\partial v/\partial t) = 0$. Let $v(x,t) = w(x,t)\exp(-t/\tau)$. Substitute this expression into the cable equation and determine a new differential equation for $w(x,t)$. You should find that $w(x,t)$ obeys the diffusion equation (Chap. 4). Find the diffusion constant in terms of the axon parameters and evaluate it for a typical case.

Problem 36. The voltage along an axon when a constant current is injected at $x = 0$ for all times $t > 0$ is given by Hodgkin and Rushton (1946)

$$v(x,t) - v_r = \begin{matrix} \frac{v_0}{2}\left\{ e^{-|x|/\lambda}\left[1 - \operatorname{erf}\left(\frac{|x|}{2\lambda}\sqrt{\frac{\tau}{t}} - \sqrt{\frac{t}{\tau}}\right)\right] \right. \\ \left. -e^{|x|/\lambda}\left[1 - \operatorname{erf}\left(\frac{|x|}{2\lambda}\sqrt{\frac{\tau}{t}} + \sqrt{\frac{t}{\tau}}\right)\right]\right\} \end{matrix}$$

where the error function erf(y) and its derivatives are

$$\operatorname{erf}(y) = \frac{2}{\sqrt{\pi}}\int_0^y e^{-z^2}dz$$
$$\frac{d}{dy}\operatorname{erf}(y) = \frac{2}{\sqrt{\pi}}e^{-y^2}.$$

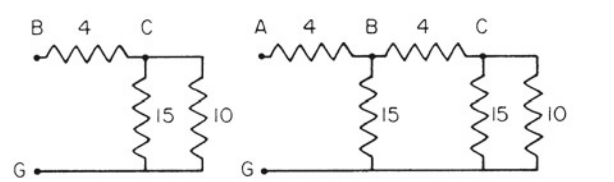
(a) Show that the expression for $v(x,t)$ obeys the cable equation, Eq. 6.55.
(b) Use $\operatorname{erf}(0) = 0$, $\operatorname{erf}(-\infty) = -1$, and $\operatorname{erf}(\infty) = 1$ to show that as $t \to \infty$, the expression for $v(x,t)$ approaches the solution in Eq. 6.58 and Fig. 6.30.
(c) Find a simple expression for $v(x,t)$ when $x = 0$. Use $\operatorname{erf}(1) = 0.843$ and $\operatorname{erf}(0.5) = 0.520$ to check that this expression is consistent with the plots in Fig. 6.31.

Problem 37. Consider a space-clamped axon with a membrane time constant τ. Initially ($t \le 0$), $v' = 0$. From $t = 0$ until a time $t = d$ a stimulus is applied to the membrane. Assume that when $v' < V'$ the membrane behaves passively (V' is called the threshold potential), and when $v' > V'$, an action potential will fire. v' obeys the equation $dv'/dt = -v'/\tau + s$.

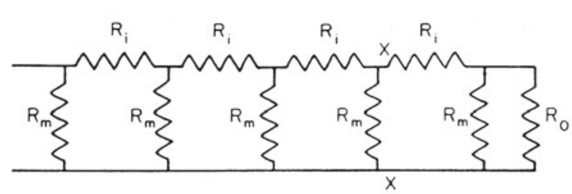
(a) Find v' for $0 < t < d$ and for $t > d$. Note that v' is maximum for $t = d$.
(b) Find an expression for $v(t = d)$, and then solve it for s.
(c) Plot s as a function of the pulse duration d. This plot is called the *strength–duration curve*.
(d) Find the value of s that corresponds to threshold stimulation for very long durations, in terms of V' and τ. This value of s is called the *rheobase* stimulus.
(e) Find the value of d corresponding to threshold stimulation using a stimulus strength of twice rheobase. This duration is called *chronaxie*.
(f) Find an expression for τ in terms of chronaxie. Measuring the strength–duration curve is one way to determine the membrane time constant.

Problem 38. An alternative model to the cable equation is an attenuating network of resistors and capacitors. This problem is designed to show you how a "ladder" of resistances can attenuate a signal.

(a) Show that the resistance between points B and G in the circuit on the left is 10 Ω.
(b) Show that the resistance between points A and G in the circuit on the right is also 10 Ω. What will be the result if an infinite number of ladder elements are added to the left of AG?
(c) Assume that v_C (measured with respect to point G) is 6 V. Calculate v_B and v_A. Note that the ratios are the same: $v_B/v_A = v_C/v_B$.



Problem 39. This is a more general version of the previous problem, which can be applied directly to electrotonus when capacitance is neglected. Consider the ladder shown, which represents an axon. R_0 is the effective resistance between the inside and outside of the axon to the right of the section under consideration. The axon has been divided into small slices; R_i is the resistance along the inside of the axon in the small slice, and R_m is the resistance across the membrane in the slice. The resistance outside the axon is neglected. Note that the resistance looking into the axon to the right of points XX is also R_0.



(a) Show that R_0 is given by a quadratic equation: $R_0^2 - R_i R_0 - R_i R_m = 0$ and that the solution is

$$R_0 = \frac{1}{2}\left[R_i + (R_i^2 + 4R_i R_m)^{1/2}\right].$$

(b) Show that the ratio of the voltage across one ladder rung to the voltage across the immediately preceding rung is

$$\frac{R_m R_0}{R_m R_0 + R_m R_i + R_i R_0}.$$

(c) Now assume that $R_i = r_i dx$ and $R_m = 1/(2\pi a g_m dx)$. Calculate R_0 and the voltage ratio. Show that the voltage ratio (as $dx \to 0$) is

$$\frac{1}{1 + (2\pi a r_i g_m)^{1/2} dx}.$$

(d) The preceding expression is of the form $1/(1+x)$. For sufficiently small x, this is approximately $1 - x$. Therefore, show that the voltage change from one rung to the next is $dv = -\left[(2\pi a\, r_i g_m)^{1/2} dx\right] v$ so that v obeys the differential equation

$$\frac{dv}{dx} = -(2\pi a r_i g_m)^{1/2} v.$$

Section 6.13

Problem 40. Use the Hodgkin–Huxley parameters to answer the following questions.
(a) When $v = v_r$, what are α_n and β_n?
(b) Show that $dn/dt = 0$ when $n = 0.318$. What is the resting value of g_K?
(c) At $t = 0$ the voltage is changed to -25 mV and held constant. Find the new values of α_n, β_n, n_∞, τ_n and the asymptotic value of g_K.
(d) Find an analytic solution for $n(t)$. Plot n and n^4 for $0 < t < 10$ ms.

Problem 41. Calculate the values of the gates m, n, and h for the resting membrane ($v = -65$ mV), using the Hodgkin and Huxley model. Recall that at rest, $m = m_\infty(v = -65\text{ mV})$, etc.

Problem 42. If α_n and β_n depend on temperature according to Eq. 6.67, how do n_∞ and τ_n depend on temperature?

Problem 43. Calculate the resting membrane conductance per unit area for the resting membrane, using the Hodgkin and Huxley model. Hint: $j_m = 0$ at rest. Let $v = v_r + dv$, where dv is small. Determine the steady-state j_m as a function of dv. To keep things simple, ignore any changes to m, n, and h resulting from dv.

Problem 44. In a voltage-clamp experiment, a wire of radius b is threaded along the interior of an axon of radius a. Assume the axoplasm displaced by the wire is pushed out the end so that the cross-sectional area of the axon containing the wire remains πa^2. The resistivities of wire and axoplasm are ρ_w and ρ_a. Find the wire radius needed so that voltage changes along the axon are reduced by a factor of 100 from what they would be without the wire. Ignore the electrode surface impedance.

Problem 45. A wire of resistivity $\rho_w = 1.6 \times 10^{-8}\ \Omega$ m and radius $w = 0.1$ mm is threaded along the exact center of an axon segment of radius $a = 1$ mm, length $L = 1$ cm, and resistivity $\rho_i = 0.5\ \Omega$ m. The axon membrane has conductance $g_m = 10$ S m^{-2}. Find numerical values for
(a) the resistance along the wire,
(b) the resistance of the axoplasm from the wire to the membrane, and
(c) the resistance of the membrane.

Problem 46. If the voltage across an axon membrane is changed by 25 mV as in Fig. 6.34, how long will it take for all the potassium to leak out if it continues to move at the constant rate at which it first leaks out? Use the asymptotic value for the potassium conductance from Fig. 6.34. Use Table 6.1, and Fig. 6.3 for any other values you need.

Section 6.14

Problem 47. Use the data of Fig. 6.40 to answer the following questions about a nerve impulse in a squid axon of radius $a = 0.1$ mm.
(a) Estimate the peak sodium ion flux (ions m^{-2} s^{-1}) and the total number of sodium ions per unit area that pass through the membrane in one pulse.
(b) By what fraction does the sodium concentration in the cell increase during one nerve pulse?
(c) Estimate the peak potassium flux and total potassium transport.

Problem 48. Show by direct substitution that Eq. 6.64c satisfies the equation $dn/dt = \alpha_n(1-n) - \beta_n n$ if α_n and β_n are functions of v, but not of time.

Problem 49. The Hodgkin–Huxley equation for the potassium parameter n is $dn/dt = \alpha_n(1-n) - \beta_n n$. What is the asymptotic value of n when $t \to \infty$?

Problem 50. For $t < 0$ a squid axon has a resting membrane potential of -65 mV. The sodium Nernst potential is $+50$ mV. The Hodgkin–Huxley parameters are $m = 0.05$, $h = 0.60$, and $g_{Na} = 1200$ S m^{-2}.
(a) What is j_{Na}?
(b) For $t > 0$ a voltage clamp is applied so that $v = -30$ mV. Suppose that $m = 0.72 - 0.67e^{-2.2t}$ and $h = 0.6e^{-0.63t}$ (where t is in milliseconds). What is the total charge transported across unit area of the membrane by sodium ions?

Problem 51. Consider a 1-mm long segment of a squid nerve axon, with a diameter of 1 mm.

(a) Let the intracellular sodium ion concentration be 15 mmol l^{-1}. Calculate the number of sodium ions in this segment of the axon.
(b) Use the plot of j_{Na} versus time in Fig. 6.41 to estimate the total number of sodium ions that enter the axon during the action potential (if you have to determine the area under the j_{Na} curve, just estimate it).
(c) Find the ratio of the number of sodium ions entering the axon in one action potential to the number present in the resting axon. Does a single action potential change the intracellular concentration of sodium ions significantly?
(d) What diameter axon is needed in order for the intracellular sodium ion concentration to change by 10 % during one action potential?

Problem 52. A stimulating current of 1 A m^{-2} is applied for 100 µs. How much does it change the potential across the membrane?

Problem 53. Using the resting value of j_K from Fig. 6.39, calculate how long it would take for the concentration of potassium inside an axon of radius 100 µm to decrease by 1 %.

Problem 54. Modify the program in Fig. 6.38 to calculate the values of m, h, and n as functions of time during an action potential. Plot $m(t)$, $h(t)$, $n(t)$, and $v(t)$.

Problem 55. Modify the program in Fig. 6.38 so it uses different stimulus strengths other than $j_{\text{stim}} = 1$ A m^{-2}. Find the minimum value of j_{stim} that results in an action potential. This value is known as the *threshold stimulus strength*.

Problem 56. Modify the program in Fig. 6.38 so it applies two stimulus pulses. The first is of strength $j_1 = 1$ A m^{-2}, duration 0.5 ms, and starts at $t_1 = 0$. The second is of strength j_2, duration 0.5 ms, and starts at time t_2. For a given t_2 value, determine the threshold stimulus strength j_2. Plot the threshold j_2 as a function of the interval $t_2 - t_1$, for 1 ms $< t_2 - t_1 <$ 10 ms. This plot is called a *strength–interval curve*. The increase of threshold j_2 for small intervals reflects the refractoriness of the membrane.

Problem 57. When a squid nerve axon is *hyperpolarized* by a stimulus (the transmembrane potential is more negative than resting potential) for a long time and then released, the transmembrane potential drifts back towards resting potential, overshoots v_r and becomes more positive than v_r, and eventually reaches threshold and fires an action potential. This process is called *anode-break excitation*: anode because the membrane is hyperpolarized, and break because the excitation does not occur until after the stimulus ends. Modify the program in Figure 6.38, so that the stimulus lasts 3 ms, and the stimulus strength is -0.15 A m^{-2}. Show that the program predicts anode break stimulation. Determine the mechanism responsible for anode break stimulation. Hint: pay particular attention of the sodium inactivation gate (the h gate). You may want to plot h versus time to see how it behaves.

Problem 58. Consider a space-clamped axon for which the resting potential is v_r. Assume that the membrane current density follows a very strange behavior:

$$j_m = \begin{cases} B(v - v_r)^2, & v > v_r \\ 0, & v < v_r. \end{cases}$$

(a) Write a differential equation for $v(t)$.
(b) What are the units of B?
(c) What sign would B have for depolarization to take place after a small positive change of v?
(d) Integrate the equation obtained in (a).

Problem 59. A comment was made in the text that the potassium current is not required to generate an action potential. Modify the program of Fig. 6.38 to eliminate the potassium current. (First make sure that you have an unmodified program that reproduces Fig. 6.39 correctly.) Comment on the shape of the resulting pulse. After the pulse there is a new value of the resting potential. Why? Is it significant?

Section 6.15

Problem 60. A pulse which propagates along the axon with speed u is of the form $v(x,t) = f(x - ut)$.
(a) Use the chain rule to show that this means

$$\frac{\partial v}{\partial t} = -u\frac{\partial v}{\partial x}, \qquad \frac{\partial^2 v}{\partial t^2} = u^2\frac{\partial^2 v}{\partial x^2}.$$

(b) Find an expression for the membrane current per unit area in terms of c_m, ρ_i, ρ_m, a, and the various partial derivatives of f with respect to x.

Problem 61. Consider an action potential propagating along an axon. The "foot" of the action potential is that part of the initial rise of the transmembrane potential that occurs before the sodium channels open. Starting from Eq. 6.72, set the j_m equal to zero and assume that the action potential propagates with a uniform speed u. As in Problem 60, replace the spatial derivatives with temporal derivatives and show that the transmembrane potential during the foot of the action potential rises exponentially. Find an expression for the time constant of this exponential rise in terms of r_i, c_m, a, and u.

Problem 62. An unmyelinated axon has the following properties: radius of 0.25 mm, membrane capacitance of 0.01 F m^{-2}, resistance per unit length along the axon of 2×10^6 Ω m^{-1}, and propagation velocity of 20 m s^{-1}. The propagating pulse passes an observer at $x = 0$. The peak of the pulse can be approximated by a parabola, $v(t) = 20(1 - 10t^2)$, where v is in millivolts and t is in milliseconds.
(a) Find the current along the axon at $x = 0$, $t = 0$.
(b) Find the membrane current per unit area j_m at $x = 0$, $t = 0$.

Problem 63. A space-clamped axon (v independent of distance along axon) has a pulse of the form

$$v(t) - v_r = \begin{cases} 0, & t < -t_1 \\ v_0\left[1 - (t/t_1)^2\right], & -t_1 < t < t_1 \\ 0, & t > t_1, \end{cases}$$

as shown in Problem 62. The axon has radius a, length L, resistivity ρ_i, and membrane capacitance c_m per unit area.

(a) What is the total change in charge on the membrane from $t = -t_1$ to $t = 0$?
(b) What is the total change in charge on the membrane from $t = -t_1$ to $t = +t_1$?
(c) What is $j_m(t)$?
(d) If j_m is given by $g_m(v - v_r)$, what is $g_m(t)$? Comment on its behavior.

Problem 64. Modify the program in Fig. 6.38 to include x-dependence as outlined in the text. Reproduce Fig. 6.42 and determine the propagation speed. Use $r_i = 19.89 \times 10^5\ \Omega\ \mathrm{m}^{-1}$ and $a = 0.238$ mm.

Section 6.16

Problem 65. Saltatory conduction is often described as the action potential jumping from node to node. In one sense this is correct: the nodes of Ranvier are active patches connected by passive myelinated segments. However, one should realize that the upstroke of the action potential is spread out over many nodes. Use Table 6.2, an action potential upstroke lasting 0.5 ms, and an outer diameter of 20 μm to estimate the number of nodes over which the action potential extends. If many nodes contribute simultaneously to the excitation, should propagation be considered continuous or discrete?

Problem 66. Consider a myelinated fiber in which the nodes of Ranvier are spaced every 2 mm. The resistance of the axoplasm per unit length is $r_i = 1.4 \times 10^{10}\ \Omega\ \mathrm{m}^{-1}$. The nodal capacitance is about 1.5×10^{-12} F.

(a) If the voltage difference between nodes is 10 mV, what is the current along the axon? Assume that the voltages are not changing with time, so that the membrane charge does not change. Also neglect leakage current through the membrane.
(b) If the nerve impulse rises from −70 mV to +30 mV in 0.5 ms, what is the average current required to charge the nodal capacitance?

Problem 67. A myelinated cylindrical axon has inner radius a and outer radius b. The potential inside is v. Outside it is 0. The myelin is too thick to be treated as a plane sheet of dielectric. Express all answers in terms of a, b, and v.

(a) Give an expression for E for $r < a$.
(b) Give an expression for E for $a < r < b$.
(c) Give an expression for E for $r > b$.
(d) Assuming $\kappa = 1$, what is the charge density on the inner surface? The outer surface?

Problem 68. Develop equations for the resistance and capacitance of a cylindrical membrane whose thickness is appreciable compared to its inner radius. Use Gauss's law for cylindrical symmetry to determine the electric field. Consider total charge Q distributed uniformly over the inner surface of a section of the membrane of length D and inner radius a. The membrane has dielectric constant κ.

(a) Any charge on the outer surface of the membrane has no effect on the calculation of the electric field between $r = a$ and $r = a + b$ as long as the charge is distributed uniformly on the outer cylindrical surface at $r = a + b$. Show that the electric field within the membrane is $E = \left(\frac{1}{4\pi\epsilon_0\kappa}\right) 2Q/Dr$.
(b) Show that the potential difference is $v = v(a) - v(a + b) = \frac{Q}{2\pi\epsilon_0\kappa D}\ln(1 + b/a)$, and that the capacitance is

$$C = \frac{2\pi\kappa\epsilon_0 D}{\ln(1 + b/a)} \quad \text{(cylinder)}.$$

(c) Now place a conducting medium with resistivity $\rho = 1/\sigma$ in the region of the membrane. Charge will move. It will be necessary to provide a battery to replenish it. Show that the resistance of the membrane segment of length D is given by $R = \frac{\rho}{2\pi D}\ln(1 + b/a)$, so that

$$\rho = \frac{2\pi R D}{\ln(1 + b/a)} \quad \text{(cylinder)}.$$

(d) Show that the resistivity of a plane resistor of cross sectional area $2\pi a D$ and thickness b is

$$\rho = \frac{2\pi R D}{b/a} \quad \text{(plane)},$$

and that the capacitance of this plane section of membrane is

$$C = \frac{2\pi\kappa\epsilon_0 D}{b/a} \quad \text{(plane)}.$$

(e) How large is this correction for a myelinated axon in which $b/a = 0.4$?

Problem 69. Suppose that the outer radius of a myelinated axon, $d = a + b$, is fixed. Determine the value of a that maximizes the length constant of the axon (Eq. 6.75b). Ignore the Nodes of Ranvier. Your result should be expressed as $a = \gamma d$, where γ is a dimensionless constant.

Problem 70. Use the empirical relationships between axon radius and conduction speed in Table 6.2 to determine the radius and speed at which the speed along a myelinated and unmyelinated fiber is equal. For radii less than this radius, is propagation faster in myelinated or unmyelinated fibers? For speeds greater than this speed, in what type of fibers is propagation fastest?

Section 6.18

Problem 71. Modify the computer program of Fig. 6.38 to have a constant value of `jStim` and run it.

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