CHAPTER

4

NEURONS

The basic *anatomical* unit in the nervous system is a specialized cell called the **neuron**. An artist's view of a typical neuron is shown in Figure 4.1. Many extensions of the single cell are long and filamentary; these structures are called **processes**. Every neuron plays several functional roles in a neural system:

1. Metabolic machinery within the cell provides a power source for information-processing functions. In addition, the cell enforces a certain unity for biochemical mechanisms throughout its extent.
2. A tree of processes called **dendrites** is covered with special structures called **synapses**, where junctions are formed with other neurons. These synaptic contacts are the primary information-processing elements in neural systems.
3. Processes act as wires, conveying information over a finite spatial extent. The resistance of fine dendrites allows the potential at their tips to be computed with only partial coupling to other computations in the tree.
4. Temporal integration of signals occurs over the short term through charge storage on the capacitance of the cell membrane, and over the longer term by means of internal second messengers and complex biochemical mechanisms.

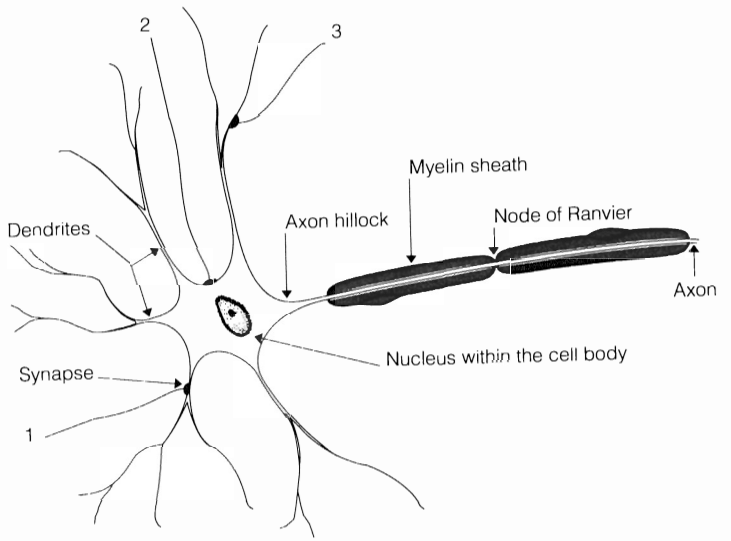

FIGURE 4.1 Conceptual structure of a classical neuron. Synaptic inputs are collected by the dendritic tree and are integrated on the capacitance of the cell body. When the potential at the axon hillock exceeds threshold, a nerve pulse is generated and is propagated down the axon. The capacitance of the axon to the extracellular fluid is reduced by the myelin sheath. Breaks in the sheath (nodes of Ranvier) allow periodic restoration of the pulse.

Axons (numbered 1, 2, and 3) from other neurons synapse onto their target neuron in different ways. Axon 1 synapses onto the trunk of a particular dendritic structure; axon 2 synapses onto the cell body; axon 3 synapses onto a more distal dendrite. (*Source:* Adapted from [Katz, 1966].)

5. Certain neurons are equipped with a long, specialized process called an **axon**. The axon is used for "digitizing" data for local transmission, and for transmitting data over long distances.

We shall first review the classical doctrine of how a neuron operates. We then shall be in a position to integrate several more recent findings, out of which a considerably richer and more complex picture emerges. The classical neuron is equipped with a tree of filamentary dendrites that aggregate synaptic *inputs* from other neurons. The input currents are integrated by the capacitance of the cell until a critical **threshold** potential is reached, at which point an *output* is generated in the form of a nerve pulse—the **action potential**. This output pulse propagates down the axon, which ends in a tree of synaptic contacts to the dendrites of other neurons.

The resistance of a nerve's cytoplasm is sufficiently high that signals cannot be transmitted more than about 1 millimeter before they are hopelessly spread out in time, and their information largely lost. For this reason, axons

are equipped with an active amplification mechanism that restores the nerve pulse as it propagates. In lower animals, such as the squid, this restoration is done continuously along the length of the axon. In higher animals, many axons are wrapped with a special insulating material called **myelin**, which reduces the capacitance between the cytoplasm and the extracellular fluid, and thereby increases the velocity at which signals propagate. The sheaths of these myelinated axons have gaps called **nodes of Ranvier** every few millimeters. These nodes act as repeater sites, where the signal is periodically restored. A single myelinated fiber can carry signals over a distance of 1 meter or more.

Even the most casual exploration of nervous tissue with an electrode reveals a host of signals encoded as trains of action potentials. For this reason, the mechanism of initiation of the nerve pulse, and of its restoration as it propagates down the axon, became the center of early physiological investigations. The first quantitative work was carried out by Hodgkin, Huxley, and Katz [Hodgkin et al., 1952a; Hodgkin et al., 1952b; Hodgkin et al., 1952c; Hodgkin et al., 1952d] on the giant axon of the squid—an unmyelinated structure nearly 1 millimeter in diameter. This classic investigation revealed the following fascinating story:

1. The cytoplasm in the cell's interior is normally **polarized**—charged to a potential of approximately −80 millivolts with respect to the extracellular fluid
2. This potential difference is supported across a **cell membrane** so thin that it can be resolved only by an electron microscope
3. If sufficient current is injected into the cytoplasm in the direction to depolarize the membrane to a threshold potential of approximately −40 millivolts, a nerve pulse is initiated
4. The pulse travels in both directions from the initiation point, and its shape rapidly becomes independent of the mechanism through which the initiation took place

What are the mechanisms by which the axon initiates and propagates the action potential? That question motivated a sustained investigation by many workers over more than 5 decades. In any great scientific detective story, the resolution of a mystery at one level sharpens the focus of the researchers, and creates pressing questions at the next level. In the following sections, we will trace the story of the axon clue by clue. In the process, we will see how the nerve membrane is constructed, and how the electrical mechanism embedded in that membrane is responsible for the active transmission of nerve pulses. Only after we understand the axon will we be in a position to investigate how information processing is done in the dendritic tree of the neuron. That story is still unfolding.

NERVE MEMBRANE

All electrical activity in a neuron takes place in the thin membrane that electrically separates the neuron's interior from the extracellular fluid. The nerve membrane is formed from phospholipid molecules arranged in a **bilayer** about

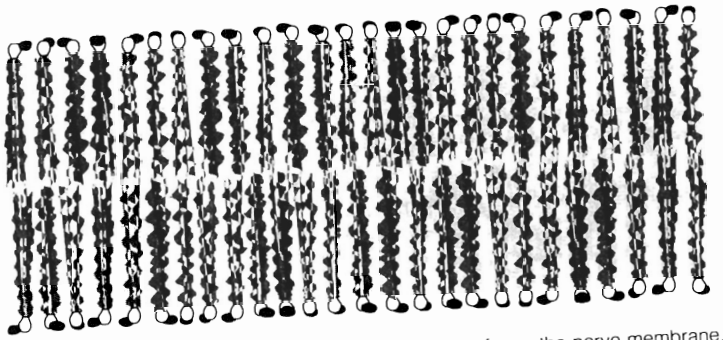

FIGURE 4.2 Cross-section of the bilayer structure that forms the nerve membrane. Individual lipid molecules have polar head-groups containing positive (white) and negative (black) charges. The hydrocarbon tails of the lipid molecules turn inward to avoid confronting the water (not shown). The energy of the electric dipole head-groups is much lower in the water surrounding the entire configuration than in hydrocarbon, which stabilizes the entire structure. The energy of an ion is much higher in the hydrocarbon membrane core, where the polarizability is low, than it is in the water, where the polarizability is high. The membrane thus forms an energy barrier to the passage of ions.

50 angstroms (5×10^{-9} meter) thick. The approximately 100-millivolt potential across the membrane creates an electric field of approximately 2×10^7 volts per meter—only 10 times less than the maximum field that can be supported reliably by the silicon dioxide insulator of a MOS transistor. How can so thin a structure be formed, and how can it be stable enough to support such large electrical gradients?

The structure of the bilayer is shown in Figure 4.2. The polar head-groups at one end of the lipid molecules bind to the aqueous solution, whereas the hydrocarbon chains on the other end of the molecules are hydrophobic. A highly stable structure is formed by two layers, oriented with hydrocarbon chains facing one another in the membrane's interior. The binding forces responsible for the great stability of the bilayer structure result from the interaction of water with charges in the polar head-group of each lipid molecule. The greedy oxygen atom in a water molecule forcibly removes an electron from each of its smaller hydrogen sidekicks. The oxygen end of the molecule thus becomes *negative*, and the hydrogen end is left *positive*. When another polar object is immersed in water, water molecules in its vicinity **polarize**—they orient such that the positive parts of the object are surrounded by negative ends of water molecules, and negative parts snuggle up to positive ends of other water molecules.[1] In such an arrangement, everyone is warm and happy—in technical terms, the energy of the system has been reduced.

In the bilayer, the hydrophilic polar head-groups of the lipid molecules face

[1] This use of the term *polarize* (from physics) should not be confused with the neurobiological usage, where the word means to charge the interior of a neuron to a negative potential. The only similarity between the two uses is that they both involve electrostatic potentials.

outward into the aqueous solution on either side, to which they are attracted by these electrostatic forces. Each head-group is an **electric dipole**, a positive and a negative charge separated by some distance. The energy of these charges in water is much lower than in the hydrocarbon phase, and results in the stability of the bilayer structure. The entire structure is a wonderful example of *self-assembly*. A tiny drop of lipid on the surface of a dish filled with water will spread out into a monolayer—the molecules immediately bury their head-groups in the water, leaving their hydrocarbon tails sticking straight up into the air. If we place a fine wire parallel to the surface and immerse it slowly through the monolayer into the water, the wire will carry the two halves of the monolayer with it. The exposed nonpolar hydrocarbon surfaces of the two halves join quickly to avoid confronting the hostile water molecules. We now have two monolayers back to back, forming the membrane structure shown in Figure 4.2. This monolayer technique is routinely used to create artificial bilayers in the laboratory.

Nature has evolved a great trick—the use of the electrical polarizability of water to attract charged sites on molecules. This technique is the ultimate basis of the three-dimensional conformation of most biologically important entities. It is the primary reason that the plan for building a three-dimensional organism can be embedded in a one-dimensional genetic code. Biological molecules fold into their stable conformations in reaction to the same hydrophobic and hydrophilic forces that organize the lipid bilayer. If there were to be a secret of life as we know it, this would be it.

In quantitative terms, we can estimate the energy of a single charge in water or hydrocarbon in the following way. The **permittivity** ϵ is a measure of the polarizability of a medium. The permittivity of free space is

$$\epsilon_0 = 8.85 \times 10^{-12} \frac{\text{coulombs per meter}^2}{\text{volts per meter}} \qquad \text{(farads per meter)}$$

The permittivity of water is about 80 times that of free space, whereas that of the hydrocarbon phase in the interior of the membrane is only about two times that of free space. The energy of a charged ion in either phase can be calculated by integrating the energy required to assemble the charge q in this position from a large number of infinitesimal charges at infinity. The potential for a given accumulated charge can be calculated by integration of Equation 2.1 (p. 13) with respect to r, from infinity to the **ionic radius** r_i. The result of this integration is

$$V = \frac{q}{r_i} \frac{1}{4\pi\epsilon}$$

The potential computed in this way also is the energy per unit charge required to add an infinitesimal charge dq to the total charge. The total energy W is given by

$$W = \frac{1}{4\pi\epsilon} \int_0^q \frac{q'}{r_i} dq' = \frac{q^2}{r_i} \frac{1}{8\pi\epsilon} \tag{4.1}$$

The energy of an ion such as sodium, which has a 1-angstrom radius in

water, is approximately 0.1 electron volts. In the interior of the bilayer, the energy is approximately 2.4 electron volts, which is approximately 100 kT. The difference between the two energies is an **energy barrier** that prevents ions in the aqueous phase from entering the membrane. The energy barrier is strictly the result of the difference between the polarizability of water and that of the hydrocarbon phase.

ELECTRICAL OPERATION

The energy barrier formed by the nerve membrane is so high that, at room temperature, vanishingly few ions are able to surmount it. For this reason, it is possible to treat the membrane as a perfect insulator. Any current flow through it will have to be mediated by some agent other than the bare ions in the aqueous solution on either side. It is by the manipulation of these agents that living systems achieve the gain in signal energy required for information processing. What kind of agents operate in the nerve membrane, and what operations do they perform?

Power Supply

Before there is gain, there must be a power supply. The most basic charge-transfer agents in all nerve membranes are the metabolically driven **pumps** that actively expel sodium ions from the cytoplasm and concomitantly import potassium ions from the extracellular fluid. As a result of this pumping process, the cytoplasm is enriched in potassium and depleted of sodium, whereas the converse is true of the seawater outside the cell. The concentrations of relevant ions inside and outside a nerve cell are shown in Table 4.1 [Katz, 1966 (p. 43)].

A concentration gradient of any charged particles can be used to power electrical activity. Suppose, for the moment, that the membrane is permeable to only one type of ion—potassium, for example. Due to the gradient in density, ions will diffuse out of the cell, causing a net negative charge to accumulate inside the cell. This negative charge will accumulate on the capacitance of the cell membrane, causing a negative potential in the cytoplasm relative to the

TABLE 4.1 Typical concentrations of ions inside neural processes and in the extracellular fluid. (*Source:* Adapted from [Katz, 1966].)

	Concentration (mM/l)		Reversal potential
Ion*	Inside	Outside	(mV)
K^+	400	10	−92
Na^+	50	460	55
Cl^-	40	540	−65

* K^+: potassium; Na^+: sodium; Cl^-: chlorine.

extracellular fluid. This situation is an exact analog to the one that created the exponential density gradient in the atmosphere in Chapter 2. The diffusion of ions outward will be exactly counterbalanced by the drift inward when the voltage across the membrane reaches the value V_r such that the relation of Equation 2.15 (p. 25) is satisfied:

$$V_r = -\frac{kT}{q} \ln \frac{N_{\text{in}}}{N_{\text{ex}}} \tag{4.2}$$

Here N_{ex} is the ion density in the extracellular fluid, and N_{in} is the density in the cytoplasm. All voltages are referred to the extracellular fluid. If we artificially raise the potential inside the cell above (more positive than) V_r, we will cause a positive current to flow outward. If we reduce the potential inside the cell below (more negative than) V_r, we will cause a positive current to flow inward. For this reason, V_r is called the **reversal potential** for the ion at the ionic concentration ratio given in Equation 4.2. The reversal potentials for the three ionic species also are given in Table 4.1. In operational terms, we can think of the sodium reversal potential as the positive power-supply rail for the nerve, and the potassium reversal potential as the negative rail.

We should note that the concentrations shown in Table 4.1 are for the giant axon of the squid; they vary considerably among species, and even among cell types in a given organism. There is recent evidence that different regions of the same neuron may have different ionic concentrations to achieve different synaptic behavior at different but electrically related points.

Equivalent Circuit

A schematic diagram that summarizes the contribution of the three ionic

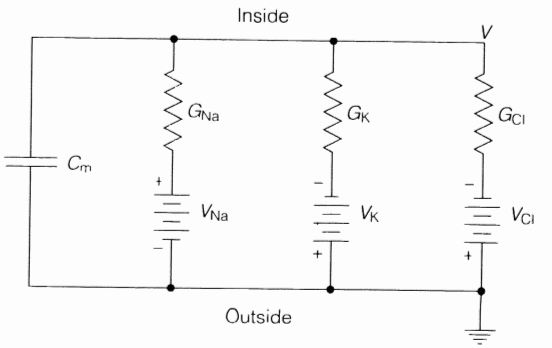

FIGURE 4.3 Equivalent circuit of a patch of nerve membrane. The batteries represent the reversal potentials for particular ions; the conductances represent the membrane permeability for the same ion. The membrane capacitance is shown as a lumped capacitor.

gradients to the membrane current is shown in Figure 4.3. From it, we can visualize the operation of the membrane over a wide range of conditions. In this diagram, the Vs are the reversal potentials of the ions, and the Gs are the conductances of the membrane for the flow of these ions. Using Figure 4.3, we can compute the membrane current I for any given cytoplasmic potential V, and for any values of ionic conductances:

$$I = (V_K - V)G_K + (V_{Na} - V)G_{Na} + (V_{Cl} - V)G_{Cl} \tag{4.3}$$

Any net current will charge or discharge the capacitance of the membrane until the current is reduced to zero. Hodgkin et al. [Hodgkin et al., 1952b] found that, under normal conditions, the chloride current can be neglected. Making this assumption, we can solve Equation 4.3 for the voltage V_0 at which the current is zero:

$$V_0 = \frac{V_K G_K + V_{Na} G_{Na}}{G_K + G_{Na}}$$

V_0 is called the **resting potential** of the cytoplasm, because it is the potential at which the cell will come to rest if left electrically undisturbed. In a typical neuron, G_K is approximately 20 times G_{Na}. Using that value, and the concentrations given in Table 4.1, V_0 is -85 millivolts. The resting potential can vary considerably from one set of experimental conditions to another.

We have come to a solution of the first riddle in the axon story: A neuron at rest is **polarized** to a negative potential because its membrane is selectively permeable to potassium. A nerve pulse is a transient excursion of the cytoplasmic potential in a positive direction; it is an example of an **excitatory** signal because it **depolarizes** the membrane. If the membrane is charged more negatively than its resting voltage, it is said to be **hyperpolarized**, in which case the signal is **inhibitory**.

We achieve electrical activity in a patch of nerve membrane by making one or more of the ionic conductances dependent on some **control quantity**. That quantity can be the voltage (as in the axon), the concentration of a chemical substance (as in chemical synapses), the intensity of light (as in photoreceptors), or the degree of mechanical deflection (as in the hair cells in the ear). We will first see how these conductances are responsible for the generation and propagation of the action potential in an axon. In later sections, we will consider other ways that the potential inside the neuron is manipulated by the nervous system to accomplish information-processing tasks.

THE ACTION POTENTIAL

We have seen that the membrane potential can be manipulated by any agent that selectively increases the permeability of the membrane to one ionic species. How can agents of this kind be employed to initiate and propagate an action potential?

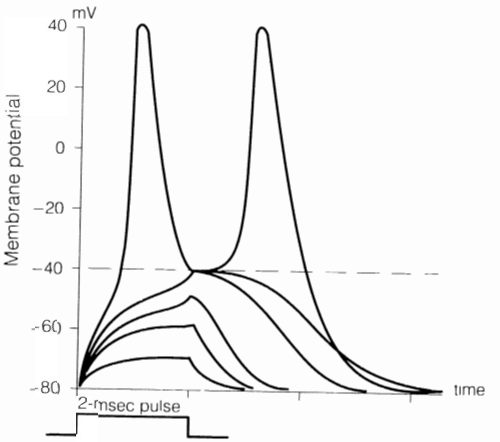

FIGURE 4.4 Response of the axon to stimulation by 2-millisecond current pulses of increasing magnitude When the pulse drives the potential of the cytoplasm higher than -40 millivolts relative to the extracellular fluid, an action potential is generated. Once this action potential is triggered, it acquires a constant shape, independent of the circumstances under which it originated. Marginal cases result in either a delayed action potential or a delayed falling transient, as shown by the rightmost two curves. (*Source:* Adapted from [Katz, 1966])

Initiation of the Action Potential

If we inject small pulses of current into the cytoplasm, the potential will respond as shown in Figure 4.4. For current levels that depolarize the membrane less than approximately 20 millivolts from its resting state, the potential shows a somewhat sluggish response that saturates after a few milliseconds. This type of response is characteristic of any circuit consisting of a capacitance in parallel with a conductance, as we will discuss in Chapter 8. In the case of the axon, the capacitance is that of the membrane, and the conductance is due to the potassium permeability. At higher current levels, we observe an exponential increase in the cell potential, culminating in the explosive generation of an action potential. If we terminate the current pulse before the potential has reached approximately -40 millivolts, the membrane recovers, and no pulse is generated. Once the potential is more positive than approximately -40 millivolts, however, a pulse is generated even if the driving current is terminated. That potential is therefore a **threshold**, beyond which a self-reinforcing reaction is underway, and no recovery is possible.

All the information we have presented so far was known by 1950. The key question was, *what mechanism was responsible for the self-reinforcing reaction*? That question was unraveled by the detective work for which Hodgkin and Huxley received the Nobel Prize in 1963. The giant axon of the squid is large enough

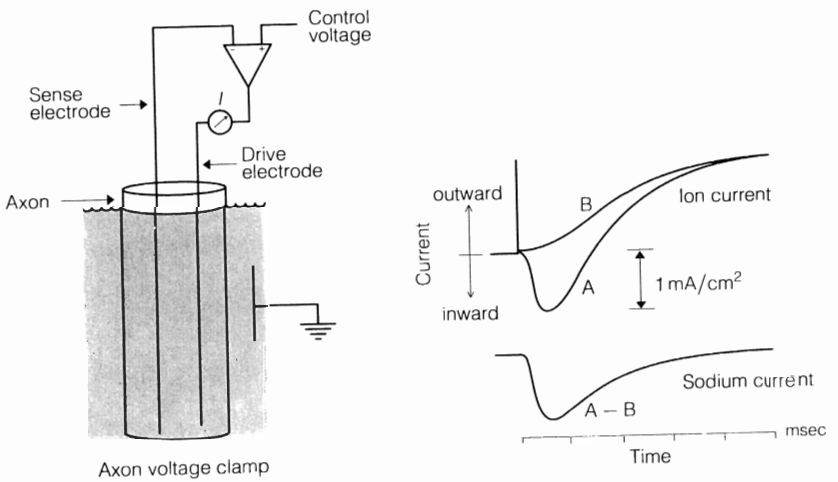

FIGURE 4.5 Schematic of the arrangement used by Hodgkin, Huxley, and Katz to measure the current through the membrane of a squid axon under conditions where the membrane potential was controlled precisely. The sense electrode assumes the potential of the cytoplasm. The amplifier generates a current *I* proportional to the difference between the actual potential and the desired potential. This current is in the direction to move the actual potential toward the desired value. The current is sensed by an oscilloscope, shown as a meter on the diagram; the extracellular fluid is ground for the entire arrangement. (*Source:* [Hodgkin et al., 1952a].)

The waveforms shown are a simplification of records taken, using this apparatus, for a step increase in membrane potential. The initial transient is the current required to charge the membrane capacitance. Curve A is the total current as a function of time. Curve B is the potassium current alone. The difference, A – B, is thus attributed to the sodium current, which rises to a maximum and then decays.

that an insulating rod carrying two independent electrodes can be placed inside it. Hodgkin and Huxley used the voltage-clamp arrangement shown in Figure 4.5.

When a voltage step from approximately −60 millivolts to near 0 millivolts was applied to the membrane, the current waveform labeled A in Figure 4.5 was observed. A transient *inward* current was followed by a sustained *outward* current. From Figure 4.3, we can see that there is only one source of inward-directed current—the sodium gradient. To check this conjecture, Hodgkin and Huxley replaced most of the sodium ions in the extracellular fluid with choline—large organic ions that cannot pass through the membrane. In this way, the researchers could approximately equalize the sodium concentration on the two sides of the membrane, thereby reducing the sodium reversal potential to zero and eliminating the sodium current at this voltage. Hodgkin and Huxley attributed the resulting current waveform (labeled B in Figure 4.5) to potassium. The difference between the two waveforms had to be the sodium current under normal conditions, as shown in the bottom trace in Figure 4.5.

In response to a depolarization of the membrane, there is a transient increase in the sodium conductance, followed by a delayed but prolonged increase in the potassium conductance. The currents through these conductances, acting on the capacitance of the membrane, create the action potential. Although this picture explains the qualitative shape of the action potential once the pulse is triggered, it tells us nothing about the mechanism that leads to the threshold, and to the all-or-nothing response. To understand that behavior, we must know how the conductances depend on the membrane potential.

Voltage Dependence of the Conductances

By carrying out similar experiments at several depolarizing potentials, Hodgkin and Huxley gathered data on the time course of the two currents as a function of the membrane potential. From these data, they reconstructed the time dependence of the sodium and potassium *conductances* for different membrane potentials. Plots of the peak sodium conductance and the sustained potassium conductance as functions of the membrane potential are plotted in Figure 4.6. At low current levels, both conductances are exponential functions of the membrane potential, increasing by a factor of e for every approximately 4-millivolt increase in voltage. At higher current levels, both curves saturate—altogether reminiscent of the dependence of transistor current on gate voltage shown in Figure 3.7 (p. 38). The quantitative difference between the transistor current and the nerve current is that the latter has an exponential characteristic that is six

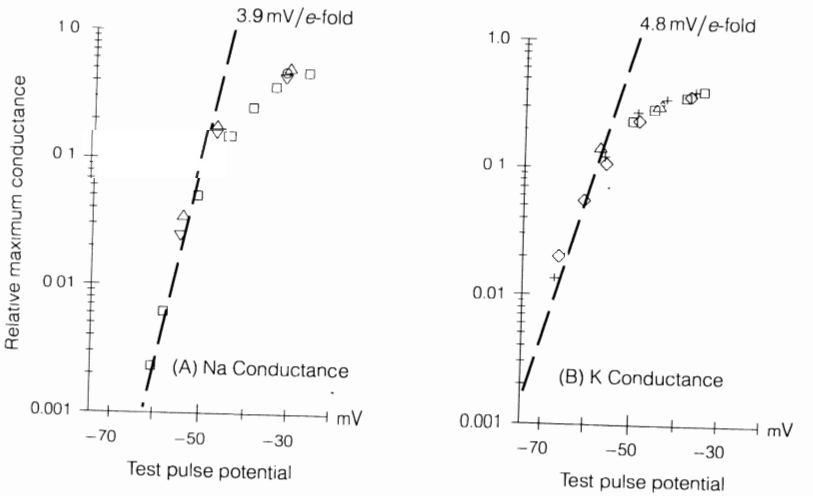

FIGURE 4.6 Exponential current–voltage characteristic of voltage-dependent channels. At high voltages, the fraction of channels that are open approaches unity, causing a saturation of the curves. (*Source:* [Hodgkin et al., 1952b, p. 464].)

times steeper than that of the former! It is this exponentially increasing current that gives the axon membrane the gain required to produce the self-reinforcing reaction leading to the all-or-nothing response.

Although Hodgkin and Huxley did not address the mechanism by which this remarkable exponential dependence comes about, their findings did allow them to reconstruct the initiation and propagation of the action potential. The summary in their 1952 paper is still the best short description of the phenomenon extant:

> *When the membrane potential is suddenly reduced (depolarization), the initial pulse of current through the capacity of the membrane is followed by large currents carried by ions (chiefly sodium and potassium), moving down their own electrochemical gradients. The current carried by sodium ions rises rapidly to a peak and then decays to a low value; that carried by potassium ions rises much more slowly along an S-shaped curve, reaching a plateau which is maintained with little change until the membrane potential is restored to its resting value.*
>
> *These two components of the membrane current are enough to account qualitatively for the propagation of an action potential, the sequence of events at each point on the nerve fibre being as follows: (1) Current from a neighbouring active region depolarizes the membrane by spread along the cable structure of the fibre ('local circuits'). (2) As a result of this depolarization, sodium current is allowed to flow. Since the external sodium concentration is several times greater than the internal, this current is directed inwards and depolarizes the membrane still further, until the membrane potential reverses its sign and approaches the value at which sodium ions are in equilibrium. (3) As a delayed result of the depolarization, the potassium current increases and the ability of the membrane to pass sodium current decreases. Since the internal potassium concentration is greater than the external, the potassium current is directed outwards. When it exceeds the sodium current, it repolarizes the membrane, raising the membrane potential to the neighbourhood of the resting potential, at which potassium ions inside and outside the fibre are near to equilibrium.* [Hodgkin et al., 1952b, p. 470]

IONIC CHANNELS

The question of electrical activity in the axon has been sharpened still further—*what is the mechanism by which the membrane conductance achieves its remarkable exponential dependence?* To find the answer, we need to take a close look at the sodium current.

Channel Conductance

A close look at the sodium current, finally captured in 1986 by Keller [Keller et al., 1986] and his coworkers, is shown in Figure 4.7. The ion-specific conductance changes in discrete steps; the height of each step is approximately linear

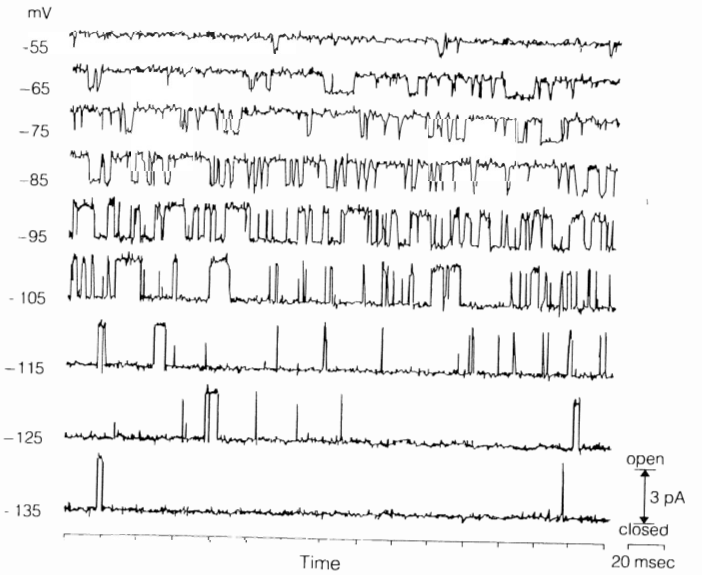

FIGURE 4.7 Current through nerve membrane as a function of time, for several membrane voltages. Upward steps are due to formation of sodium channels, downward steps are due to the channels' disappearance. The height of a single step is the current in a single channel, which increases approximately linearly with applied voltage, measured with respect to the sodium resting potential

Several charges are pulled through the membrane when a channel is formed; hence, the average number of channels penetrating the membrane decreases exponentially with applied voltage (*Source:* Adapted from [Keller et al., 1986].)

in the membrane potential relative to the reversal potential of the ion. At low currents, the number of steps and the width of each step are both exponential functions of the membrane potential. At any given voltage, the steps are all the same height. This remarkable finding suggests that each step is the result of an atomic action on the part of a single molecular entity. The molecular entities responsible for selective permeability of nerve membranes to specific ions are aggregates called **channels**. The channels responsible for propagating the nerve pulse in an axon are *voltage-controlled.*

Because the detailed structure has not been worked out for either the sodium or the potassium channels, we will exercise a bit of artistic license to visualize how one of these channels might operate. The result of this creative endeavor is shown in Figure 4.8.

Imagine a molecule about 50 angstroms long, with two positive charges on one end of a long hydrocarbon backbone and two negative charges on the other. The backbone is sprinkled with occasional polar groups along its length. We suppose that, in their normal stable configuration (shown in the highly schematized

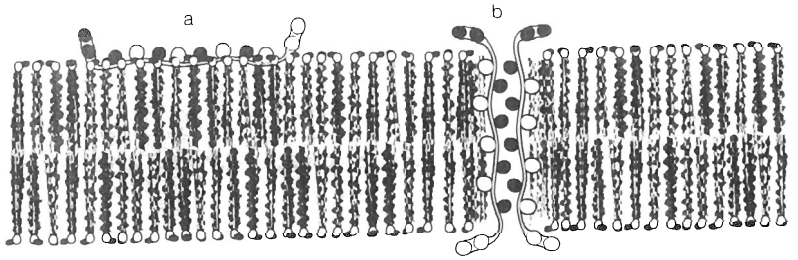

FIGURE 4.8 Cross-section of the bilayer structure of Figure 4.2 showing a conceptual model of how a voltage-controlled channel might operate. A triad of molecules can exist in two stable configurations (a) lying flat on one surface, or (b) penetrating the membrane. Each molecule of the triad has two positive (white) charges on one end, and two negative (black) charges at the other. Six charges are carried through the membrane when the triad switches from one configuration to the other. The energy of the penetrating configuration is dependent on the voltage across the membrane, whereas that of the flat configuration is not. The fraction of triads that are in the penetrating configuration thus will be exponentially dependent on the membrane voltage. The penetrating configuration provides a tortuous path lined with negative ions—the open channel—through which a small positive ion can pass.

rendition in Figure 4.8a), triads of these molecules are lying on one surface of the membrane in the form of a triangle, the positive end of one next to the negative end of its neighbor. The hydrocarbon backbones of all three are buried in the membrane to get away from the water. A single molecule would be capable of penetrating the membrane, placing the positively charged head-group on the opposite side of the membrane from the negatively charged tail-group.

The energy of such an isolated molecule in this new conformation would be much higher than that of the molecule in the original state, because the polar groups on the hydrocarbon backbone would be directly confronted with the low-permittivity membrane center. The triad of molecules could penetrate the membrane as a group, however, each one lowering the energy that the others must pay to get through the membrane. The symbiosis would allow each molecule to turn its backbone to the membrane's hydrocarbon interior and share polar groups with the other two in the triangular space between them. This configuration of our imaginary triad (shown in Figure 4.8b) would have six elementary positive charges on one side of the membrane, and six negative charges on the other. The transition from the surface configuration to the penetrating configuration would carry six charges from one side of the membrane to the other.

If it were indeed possible to construct a triad capable of this type of behavior, many of such triads would have been tried in the long course of evolution. Some, no doubt, would have a little space running down the center through which some enterprising ion might pass, in constant contact with a polar group from one molecule or another. In other words, the penetrating configuration of the triad might function as a *channel* for ionic flow through the membrane. If the

ion were too small, its energy in the center of the membrane would be too high, as per Equation 4.1. If the ion were too large, it could not fit through the space between polar groups. But an ion of just the right size might squeeze through, nicely shielded from the hostile hydrocarbon by the polar groups of the molecules in the triad. In this way, a particular molecule could form channels with a high degree of specificity for one ion.

The foregoing discussion is highly idealized, and in detail it is certainly not correct for any particular channel. It is, however, consistent in broad outline with the known properties of voltage-dependent channels. A detailed discussion of the known properties of channels can be found in Hille [Hille, 1984].

Voltage-Dependent Conductance

We can analyze the voltage dependence of the triads described in the previous section using a **two-state model**. Let us call the penetrating configuration the **open state,** and the surface configuration the **closed state**, of the triad. The two states have different energies; a transition from one state to the other will be associated with a **transition energy** E_t. The transition from the closed to the open state transports charges through the membrane, so the transition energy is voltage-dependent. The energy is lowered by the number of **gating charges** n transported through the membrane by the formation of the channel, times the potential V across the membrane:

$$E_t = E_0 - Vnq$$

where E_0 is the transition energy at zero membrane voltage.

Suppose there are N total triads associated with a particular membrane, and that, at a given time, N_c of them are closed and N_o of them are open. Recall the Boltzmann distribution of Chapter 2, from Equation 2.16 (p. 25) we know that

$$\frac{N_o}{N_c} = e^{-E_t/(kT)} \tag{4.4}$$

Because $N_o + N_c = N$, we can write Equation 4.4 in terms of the fraction $\theta = N_o/N$ of channels in the open state:

$$\frac{\theta}{1-\theta} = e^{-E_0/(kT)} e^{qnV/(kT)}$$

For θ much less than 1, the θ in the denominator will be negligible and the number of open channels will be an exponential function of the membrane voltage V. The average *conductance* of the membrane as a whole is the number of open channels multiplied by the conductance of each channel. For high values of V, θ will saturate at 1, all the channels will be open, and the conductance of the membrane will saturate, exactly as shown by the experimental data in Figure 4.6.

By this mechanism, the conductance for a given ion can be made to depend exponentially on the membrane potential. The dependence is very steep, because

a number of gating charges is involved in the reaction that opens the channel. For Figure 4.6, taken from the giant axon of the squid, there are approximately six gating charges involved. Recent work on the node of Ranvier of the frog suggests that two molecules form a channel in that system [DuBois et al., 1983]. The voltage dependence of Figure 4.7 gives approximately four gating charges. It thus seems that vertebrates employ a channel formed of two molecules, each carrying two charges through the membrane. If the charges in the reaction do not go all the way through the membrane, the energy they contribute is only a fraction of qV, and hence noninteger quantities often are observed.

The exponential dependence of conductance on membrane potential is a result of the behavior of the *population of channels*, rather than of the conduction property of any given channel. A close look at the current in Figure 4.7 reveals a discrete increase in current as each channel opens, and an equal decrease as each channel closes. The size of an individual step is roughly linear in the difference between the membrane voltage and the reversal potential for the selected ion, indicating that an individual channel is **ohmic** (current proportional to voltage). The rate at which channels open increases, and the rate at which they close decreases, with voltage. Both dependencies are exponential, and can be seen clearly in Figure 4.7. The number of channels open at any time is a result of the balance of these two processes.[2]

The exponential current–voltage relation in the nerve is a result of the same physical laws responsible for the exponential transistor characteristic. There is an energy barrier between a state in which current can flow and one in which current cannot flow. The height of that barrier is dependent on a control voltage. The Boltzmann distribution determines the fraction of the total population that is in the conducting state. In the transistor, the electrons in the channel form the population in question, and these same electrons carry the current. In the nerve membrane, the channels form the population in question, and ions in the channels carry the current. In both cases, the number of individual charges in transit is exponential in the control voltage, and the transport of these charges results in a current that varies exponentially with the control voltage.

COMPUTATION

We have traced the ideas elucidated in one of the great endeavors in intellectual history; in the process, we have learned a great deal about the electrical machinery in the neuron. At one time, people might have supposed that understanding the action potential would be the key that would unlock a full

[2] This mechanism by which very steep exponentials can be created by a population of individual ohmic channels was first worked through quantitatively for the antibiotic alamethicin in artificial bilayer membranes [Eisenberg et al., 1973]. The technology for similar quantitative work for real nerve channels in natural membranes has become available only recently. A quantitative model of sodium channels from the node of Ranvier in the frog is given by DuBois and colleagues. [DuBois et al., 1983].

understanding of neural information processing in the brain. It is now clear that, although we have a good understanding of how the nervous system *transmits* information over large distances, this knowledge does not shed much light on how the information is *computed*. We have yet to find a single unifying principle in neural computation that shines with the same clarity as the axon story does; that work is ahead of us. The balance of this book describes one approach (of many) to a deeper understanding of the basic principles underlying neural computation. This quest will require the work of specialists in many fields over many years.

A few comments may serve to render our task a bit less daunting. Computation in neural systems uses the same kind of machinery that we have already encountered in the axon story. Once we can control the ionic conductances, we can manipulate the resting potential of the membrane. An increase in sodium conductance depolarizes the membrane, and is the action responsible for initiation of a nerve pulse. An increase in potassium conductance can hyperpolarize the membrane, and hence acts as an inhibitory influence.

If the chloride reversal potential is near the resting potential, as is often the case, an increase in chloride conductance will not have much effect on the potential of the membrane, but can decrease the effect of either a sodium or a potassium conductance by requiring more current for a given excursion in potential. This reduction in the sensitivity of the membrane by increasing its conductance to the resting potential is called **shunting inhibition**.

These and other methods of manipulating the membrane potential operate in the richly branched tree of dendrites to produce the complex interaction of electrical and chemical signals that is *neural computation*. Interactions in the dendritic tree can all work in a continuous analog fashion, as indicated by Equation 4.3. They neither require nerve pulses for their operation, nor necessarily result in the generation of a nerve pulse. In fact, the vast majority of computation in the nervous system is done with slowly varying analog potentials in the dendritic trees of neurons. These signals come about through the actions of synaptic contacts with other neurons. The result of the computation may or may not ever be converted into an action potential to be transmitted to the far reaches of the brain.

The synapses provide an entirely new class of function in dendritic computations. We can say that the synapse is to computation what the voltage-controlled channel is to communication. The story of the synapse is still being worked out, and the following section gives only the briefest account of this fascinating and rapidly evolving field.

SYNAPSES

We have seen how the *potential across a nerve membrane* can cause an *exponential change in current through the same membrane*. This action is appropriate for the propagation of an action potential, but is not sufficient for general compu-

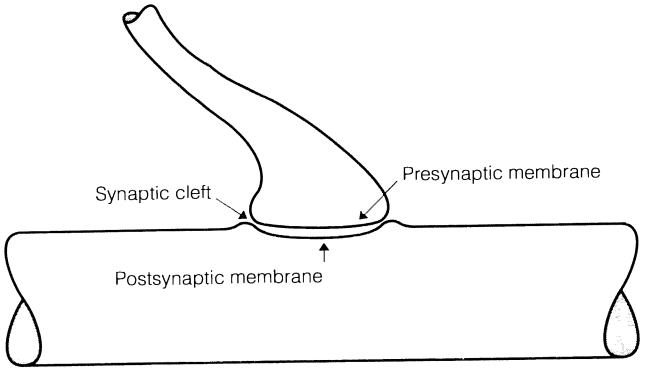

FIGURE 4.9 Simplified sketch of a synapse Depolarization of the presynaptic membrane results in neurotransmitter release. Neurotransmitter diffuses across the synaptic cleft, resulting in the opening of receptor channels in the postsynaptic membrane. Postsynaptic current flows from the cytoplasm to the extracellular fluid.

tation. What we need is the ability to control the *conductance through a second membrane*. The ability to control the current into or out of one electrical node by the potential on another node is the key ingredient that makes all information processing possible. This capability results in a natural *direction* in the flow of information; in neural systems, it is provided by *synapses*. These specialized structures are the central information-processing devices in neural systems.

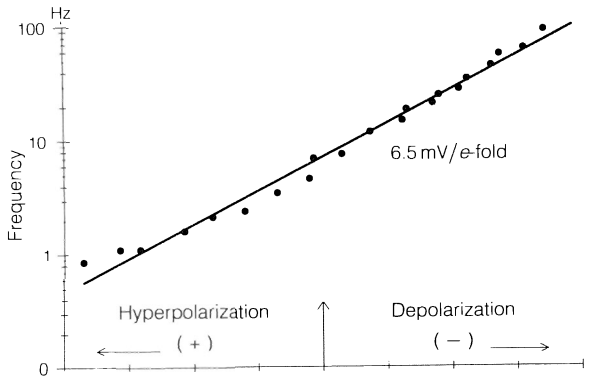

FIGURE 4.10 Exponential dependence of postsynaptic current on presynaptic membrane potential. The frequency of miniature end-plate potentials (plotted vertically) is a measure of current through the postsynaptic membrane. The current is extremely noisy, due to the quantal nature of neurotransmitter release. The solid line is an exponential fit to the experimental data (filled circles). (*Source:* Adapted from [Shepherd, 1979].)

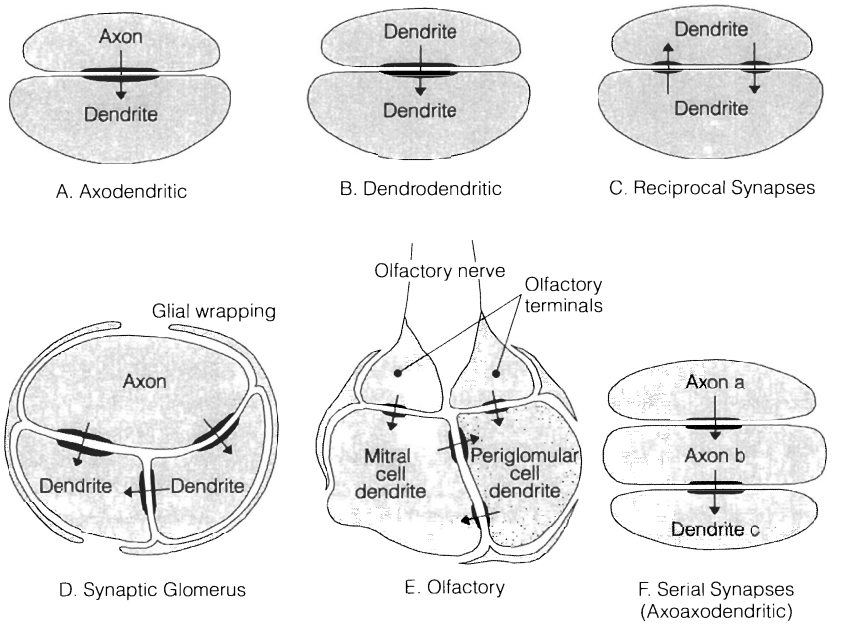

FIGURE 4.11 Examples of synaptic microcircuits by which neural processes interact Structures of this kind are found in many parts of the nervous system, indicating that much of the neural computation is local in nature. (*Source:* Adapted from [Shepherd, 1979].)

A drawing depicting a typical synaptic arrangement is shown in Figure 4.9. The function of a synapse is to control the conductance of the membrane separating the interior of the postsynaptic cell from the extracellular fluid. That conductance is controlled by the potential across the presynaptic membrane. The detailed mechanism by which synapses operate is extremely interesting, and will no doubt be the subject of study for many years. We will present here only the essential principles of synapse operation. There are several excellent reviews of the subject at various levels of detail [Shepherd, 1979].

Inside the presynaptic membrane is a high concentration of specific **neurotransmitter** molecules. When the presynaptic membrane is depolarized, calcium channels allow calcium ions (Ca^{2+}) to flow into the presynaptic cell from the synaptic cleft. The calcium ions activate the subcellular machinery that causes release of neurotransmitter molecules into the synaptic cleft, where these molecules diffuse to the postsynaptic membrane and initiate a chain of events that results in the opening of ion-specific channels. The quantity of neurotransmitter released, and therefore the change in conductance of the postsynaptic membrane, is an exponential function of the presynaptic potential, as shown in Figure 4.10.

If the channels opened by the neurotransmitter are specific for sodium, for example, a depolarization of the presynaptic membrane will result in a depolarization of the postsynaptic membrane, and the synapse is said to be **excitatory.** If the neurotransmitter leads to the opening of potassium-specific channels, the postsynaptic membrane will be hyperpolarized, and the synapse is said to be **inhibitory**. As we have noted previously, chloride channels can act to increase the conductance of the membrane without appreciable change in potential—synapses leading to this behavior are called **shunting**. Within these broad categories, many variations are possible. In addition, synapses are known that open channels for molecules other than sodium, potassium, or chloride. We shall not discuss any of these complexities here.

A single synapse is the neural counterpart of a transistor. The tip of every neural process ends in a synapse, and there are many synaptic contacts along the branches of the dendritic tree as well. As in electronic computational machinery, synapses occur not in isolation, but rather in *circuit arrangements.* Dendrites form a wide variety of synaptic connections with dendrites and axons of other neurons. The specialization of function of the many areas in the nervous system is largely a result of these synaptic circuit arrangements. Cross-sections through several representative synaptic structures are shown in Figure 4.11. Specific circuits for many parts of the brain are discussed in Gordon Shepherd's excellent book *The Synaptic Organization of the Brain* [Shepherd, 1979]. In addition, a lucid popular account has appeared in *Scientific American* [Shepherd, 1978]. Many of these arrangements have (not altogether by accident) parallels in circuits we will discuss in subsequent chapters.

REFERENCES

DuBois, J.M., Schneider, M.F., and Khodorov, B.I. Voltage dependence of intramembrane charge movement and conductance activation of batrachotoxin-modified sodium channels in frog node of Ranvier. *Journal of General Physiology,* 81:829, 1983.

Eisenberg, M., Hall, J.E., and Mead, C.A. The nature of the voltage-dependent conductance induced by alamethicin in black lipid membranes. *Journal of Membrane Biology,* 14:143, 1973.

Hille, B. *Ionic Channels of Excitable Membranes.* Sunderland, MA: Sinauer Associates, 1984.

Hodgkin, A.L., Huxley, A.F., and Katz, B. Measurement of current–voltage relations in the membrane of the giant axon of Loligo. *Journal of Physiology,* 116:424, 1952a.

Hodgkin, A.L. and Huxley, A.F. Current carried by sodium and potassium ions through the membrane of the giant axon of Loligo. *Journal of Physiology,* 116:449, 1952b.

Hodgkin, A.L. and Huxley, A.F. The components of membrane conductance in the giant axon of Loligo. *Journal of Physiology,* 116:473, 1952c.

Hodgkin, A.L. and Huxley, A.F. The dual effect of membrane potential on sodium conductance in the giant axon of Loligo. *Journal of Physiology,* 116:497, 1952d.

Katz, B. *Nerve, Muscle, and Synapse.* New York: McGraw-Hill, 1966.

Keller, B.U., Hartshorne, R.P., Talvenheimo, J.A., Catterall, W.A., and Montal, M. Sodium channels in planar lipid bilayers. *Journal of General Physiology.* 88:1, 1986.

Shepherd, G.M. Microcircuits in the nervous system. *Scientific American,* 238(2):93, February 1978.

Shepherd, G.M. *The Synaptic Organization of the Brain.* 2nd ed., New York: Oxford University Press, 1979.