1

BIOLOGICAL NEURAL NETWORKS

1.1 Neuron Physiology

The **neuron** (Greek: nerve cell) is the fundamental unit of the nervous system, particularly the brain [1, 2, 3]. Considering its microscopic size, it is an amazingly complex biochemical and electrical signal processing factory. From a classical viewpoint, the neuron is a simple processing unit that receives and combines signals from many other neurons through filamentary input paths, the **dendrites** (Greek: treelings) (Figure 1-1).

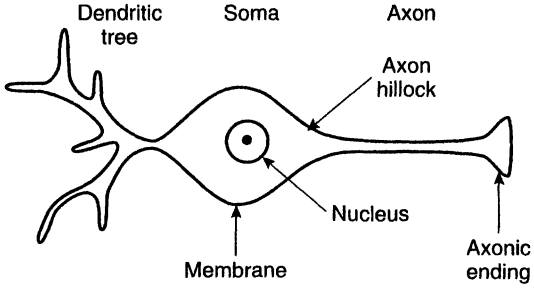

Figure 1-1 Representation of a neuron.

Dendrites are bunched into highly complex "dendritic trees," which have an enormous total surface area. Dendritic trees are connected with the main body of the nerve cell, the **soma** (Greek: body). The soma has a pyramidal or cylindrical shape. The outer boundary of the cell is the **membrane**. The interior of the cell is filled with the **intracellular fluid**, and outside the cell is the **extracellular fluid**. The neuron's membrane

and the substances inside and outside the neuron play an important role in its operation and survival. When excited above a certain level, the **threshold**, the neuron *fires*; that is, it transmits an electrical signal, the **action potential**, along a single path called the **axon**.* The axon meets the soma at the **axon hillock**. The axon ends in a tree of filamentary paths called the **axonic endings** that are connected with dendrites of other neurons. The connection (or junction) between a neuron's axon and another neuron's dendrite is called a **synapse** (Greek: contact). A synapse consists of the **presynaptic terminal**, the **cleft** or the synaptic junction, and the **postsynaptic terminal** (Figure 1-2).

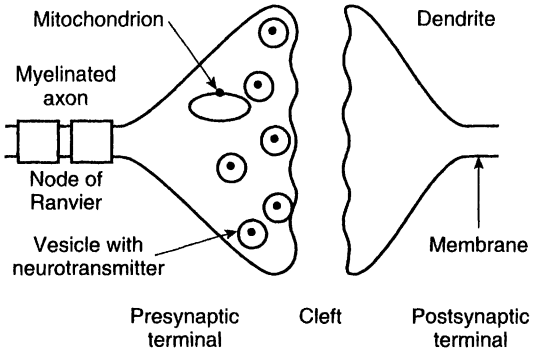

Figure 1-2 Synapse in detail.

A single neuron may have 1000 to 10,000 synapses and may be connected with some 1000 neurons. Not all synapses are excited at the same time, however. Because a received sensory pattern via the synapses probably excites a relatively small percentage of sites, an almost endless number of patterns can be presented at the neuron without saturating the neuron's capacity. When the action potential reaches the axonic ending, *chemical messengers*, known as **neurotransmitters**, are released. The neurotransmitters are stored in tiny spherical structures called **vesicles** (see Figure 1-2) and are responsible for the effective communication of information between neurons.

When a neurotransmitter is released, it drifts across the synaptic junction or cleft and initiates the **depolarization** of the postsynaptic membrane; in other words, the ion distribution at the surface of the membrane changes, and thus the voltage across the membrane of the receiving neuron, the **postsynaptic potential**, changes. The stronger the junction, the

* In some neurons, a *collateral axon* may grow from the main axon.

more neurotransmitter reaches the postsynaptic membrane. Known neurotransmitters include synapsin 1, synaptophysin, calelectrin, mediatophore, and synuclein. Depending on the type of neurotransmitter, the postsynaptic potential is either **excitatory** (more positive) or **inhibitory** (more negative).

Decoding at the synapse is accomplished by **temporal** summation (Figure 1-3) and **spatial** summation [4]. In temporal summation each potential of an impulse (consider signals in the form of a train of impulses) adds to the sum of the potentials of the previous impulses. The total sum is the result of impulses and their amplitude. Spatial summation reflects the integration of excitations or inhibitions by all neurons at the target neuron. The total potential charge from temporal and spatial (**spatiotemporal**) summations is encoded as a nerve impulse transmitted to other cells. The impulses received by the synapses of a neuron are further integrated over a short time as the charge is stored in the cell membrane. This membrane acts first as a capacitor and later as an internal second messenger when complex biochemical mechanisms take place.

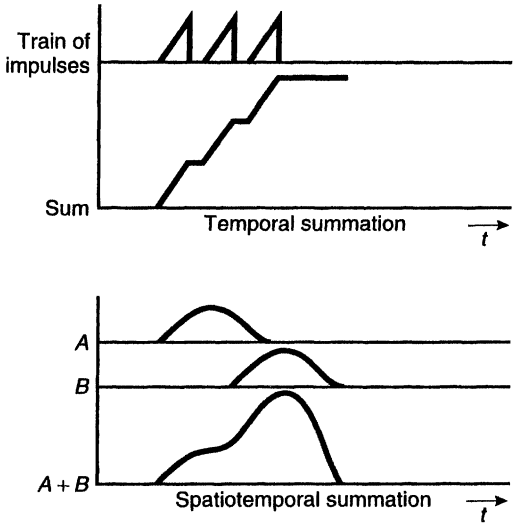

Figure 1-3 Temporal and spatiotemporal summation.

All integrated signals are combined at the soma, and if the amplitude of the combined signal reaches the threshold of the neuron, a "firing" process is activated and an output signal is produced. This signal, either a single pulse or a sequence of pulses at a particular rate, is transmitted along the cell's axon to the axonic endings.

1.1.1 The Soma

The *soma* operates like a highly complex biological, chemical, and electrical plant. The membrane of the cell encloses the cytoplasm. Looking under a microscope, one recognizes the nucleus, the Golgi apparatus, the vacuole, the endoplasmic reticulum with ribosomes, the mitochondria, and the centrosome. The endoplasmic reticulum with ribosomes forms a series of canals and is the chemical plant of the cell. Enzymes in this structure convert glucose to glycogen, which is stored in the canals. When energy is needed, the glycogen is converted back to glucose, thereby releasing energy. The mitochondria are the power plants of the cell. When oxygen and nutrients enter this organelle, an enzyme causes a chemical reaction to manufacture adenosine triphosphate (ATP) from adenosine diphosphate (ADP). Upon formation, ATP [5] is used for synthesizing chemical compounds, such as DNA, in the cell's **ribosomes**. It is also believed that ATP is responsible for, or contributes to, the action potential. When ATP is used, it converts to ADP, which returns to mitochondria for reactivation to ATP by the use of oxygen. The product of the reaction, carbon dioxide (CO_2), diffuses out of the cell, finds its way into the blood vessels, and is eliminated by the lungs. The detailed chemistry in the mitochondria is described by the Krebs cycle and can be found in biochemistry and physiology textbooks.

For the study of the action potential, it is important to understand the electrical charge distribution around the membrane—that is, the ionic concentrations and the potentials inside and outside the cell. The electrical charge distribution in the squid cell,* for example, is listed in Table 1-1. In comparing the ionic concentration of potassium and sodium, notice that there is a strong imbalance between the exterior and interior of the cell. The interior is rich in potassium, whereas the exterior is rich in sodium. The potential difference, due to ionic concentration imbalance at either side of the membrane, is expressed in terms of the internal and external ionic concentration (N_{in}, N_{ext}), the ionic charge, q, and absolute temperature, T:

$$V_t = \frac{kT}{q}\frac{N_{in}}{N_{ext}}, \tag{1.1}$$

where k is Boltzmann's constant, 1.38×10^{-23} joules/K, and $q = 6.09 \times 10^{-19}$ coulombs.

* Squid cells have been extensively used in experiments because of their relatively large cell size.

Table 1-1. Electrical Charge Distribution in the Squid Cell

Ion Type	*Ionic Concentration Inside Cell (mM/L)*	*Ionic Concentration Outside Cell (mM/L)*	*Reversal Potential (mV)*
Potassium	155	4	−92
Sodium	12	145	+55
Chloride	5	105	−65

1.1.2 Cell Membrane Structure

The skin of the nerve cell is the **membrane**. The basic building blocks of the nerve membrane are long **phospholipid** molecules. At one end of a phospholipid molecule is a **hydrophobic** (Greek: water repellent) hydrocarbon chain; at the other end is a **hydrophilic** (Greek: water friendly) **polar head group**. Similarly, the long molecule of common soap has a hydrophobic end and a hydrophilic end. Because of this structure of the soap molecule, oil-based substances can be removed with soap and water during wash. Now, consider many phospholipid molecules such that they form a two-dimensional matrix layer with the hydrocarbon (hydrophobic) chains all at the same surface. The membrane consists of two such layers. The layers are placed atop each other with the hydrocarbon surfaces face to face. Thus, this bilayer membrane has the (hydrophilic) polar head-groups at both surfaces. Proteins are also in the membrane structure (Figure 1-4).

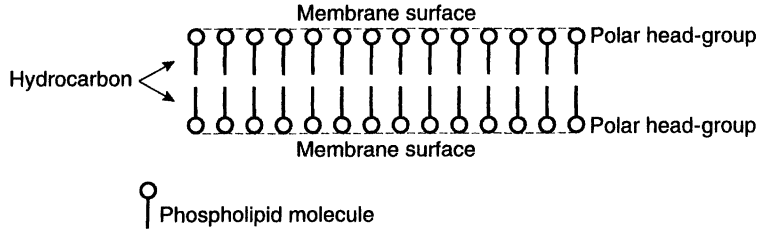

Figure 1-4 Membrane structure cross section.

1.1.3 Proteins: The Cell's Signature

Proteins are essential components of a cell [6]. They are long polymers composed of some 20 types of **amino acids** that form chains of about 300 in a specific sequence. Hence, the potential number of different proteins is enormous. Each sequence constitutes a specific code that characterizes

a protein and distinguishes it from any other. This code is referred to as a **gene**. Genes contain the amino acid deoxyribonucleic acid (DNA). In the 1950s, Crick and Watson proved that DNA consists of two long spiral strands of polymerized sugar forming a double helix. The two strands are held together between a pyrine and a pyrimidine base by hydrogen bonds. These bonds project inward from two chains containing alternate links of deoxyribose and phosphate. Thus, the two strands are interlocked. Proteins are arranged in a definite configuration, believed to be different for every organism, that determines that cell's functionality. Think of it as the *signature* of the cell. This signature determines every physiological and mental* characteristic of the cell.

When a protein is formed, certain amino acid links are weaker than others, thus deforming (or forming) the protein geometry. Protein geometry plays an important role in the recognition process. Proteins of a certain geometry recognize other proteins with matching geometry and combine to give enzymes with interesting properties. Thus, *the shape of a protein constitutes the protein's program to perform a particular function.* Certain proteins are not programmed. Fortunately, this lack of programmability of proteins may be an advantage in gene engineering whereby links may be manipulated to produce *artificially programmed* proteins that perform a desired function. This concept is used in biocomputing research (see Section 1.1.11).

Protein is continuously manufactured by the cell for its growth, function, and maintenance. The protein factory of the cell is the endoplasmic reticulum with ribosomes. The DNA molecule forms various types of ribonucleic acid (RNA), such as messenger RNA (mRNA) and soluble or transfer RNA (tRNA); each has a different role. For instance, the mRNA carries the genetic code to the endoplasmic reticulum, and the soluble RNA finds the proper amino acids and brings them to this site. Each form of tRNA is a specific carrier for each of the 20 known amino acids. Arginine, for example, is transported by the tRNA specialized to transport arginine; leucine is transported by the specific tRNA for leucine, and so on. Once an amino acid is delivered, the tRNA goes back for more. As each type of amino acid is delivered at the site, a remarkable creation begins. The ribosomes move along the mRNA, *read* the code, and, according to this code, synthesize from the received amino acids a polypeptide chain [7]. From this chain a "cloning process" takes place whereby exact replicas of the protein molecules are produced. Thus, we may conclude that genes

* Here the word *mental* should be considered within the framework of this text, without any intention of raising philosophical or religious eyebrows.

constitute the permanent memory of the cell, which is carried from parent to children cells. This process is a submicroscopic, highly complex, and precisely timed biochemical factory, the details of which are beyond our present understanding. How does the RNA know what to do, when to do it, and how? Where is the knowledge of processing and formation stored? Is it a probabilistic or accidental phenomenon, or is there something beyond our understanding? Obviously, this process cannot be random or accidental because it is reproducible, predictable, and under nature's control.

1.1.4 Membrane Proteins

Proteins manufactured in the soma are either free to move within the cell by diffusion or are firmly embedded in the lipid layers of the membrane. Proteins embedded in the membrane are called **intrinsic**. Intrinsic proteins are not uniformly distributed over the membrane surface. Membrane proteins are essential for many aspects of neuron functions and are classified as **pump, channel, receptor, enzyme,** and **structural** proteins.

Pump proteins move particular ions from one side of the membrane to the other, thus altering the ion concentrations. The pumps are highly important in the functioning and survival of the cell; see Section 1.1.6 for more detail.

Channel proteins provide pathways through which specific ions can diffuse at command, thus helping to cancel the ion buildup of the pumps. The opening of the sodium channel is from 0.4 to 0.6 nm. Channels open at different times, stay open for different time intervals, and allow different types of ions (sodium, potassium, or calcium) to pass. Two fundamental properties of channels are selectivity and gating. The channels are selective to sodium or potassium. When these channels open, sodium or potassium diffuses through them. Some selective channels may pass seven sodium ions for every 100 potassium ions. Some channels are nonselective; they allow about 85 sodium ions for every 100 potassium. These channels are known as *acetylcholine activated channels*. Water (H_2O) in the channel also seems to be important in ion selection. Potassium channels contain less water and have a smaller opening than sodium channels. The density of channels in the membrane is reported to be from zero to 10,000 per square micrometer.

The gating mechanism of a channel may be voltage activated (i.e., it opens and closes in response to a voltage difference across the membrane) or chemically activated (i.e., it opens and closes in the presence of certain neurotransmitters). Chemically activated channels are named after the chemical that activates them: the GABA-activated channel, for instance,

is so named because it activates gamma-aminobutyric acid (GABA). Axons have mostly electrically activated channels, whereas the postsynaptic membrane has mostly chemically activated channels.

Receptor proteins provide selective binding sites to neurotransmitters.

Enzymes are placed in or at the membrane to facilitate chemical reactions at the membrane surface. The enzyme adenylate cyclase is an important protein that regulates the intracellular substance cyclic adenosine monophosphate.

Structural proteins are responsible for maintaining the cellular structure and interconnecting cells.

Moreover, other proteins at the membrane carry different essential nervous-system functions, many of which are not yet well understood. It is believed that some proteins may have more than one function in the neuron.

1.1.5 Membrane Strength

Despite the complex structure of the neuron's membrane, it is only 5 to 50 angstroms (50 to 500 nm) thick. One would think that such a thin membrane would be highly unstable and would collapse easily, yet it is so stable that it can withstand electrical fields across it that can easily exceed 100 mV to 100 kV/cm without damage. Interestingly, this voltage difference is in the neighborhood of the breakdown voltage of the SiO_2 layer in metal oxide semiconductor (MOS) transistors. This remarkable stability of the membrane is attributed to the extremely strong binding forces created by the interaction of the aqueous solution with charges in the hydrophilic polar head-group of the lipid molecules at either side of the membrane.

1.1.6 The Sodium Pump: A Pump of Life?

According to nature's laws, when an ionic concentration difference is formed, an electric field that causes diffusion in a direction that balances out the ionic concentration difference is created. Despite nature, a substantial ionic concentration difference and an electric field across the cell membrane are well sustained. This irregularity puzzled scientists who tried to explain this nature-defying mechanism. The only logical explanation is the presence of a mechanism at the membrane that counteracts nature's diffusion process.

Imagine a pumping mechanism embedded in the cell membrane that keeps sodium ions outside and potassium ions inside the cell [8]. If this

mechanism pumps sodium out faster than nature diffuses sodium into the cell, then a sodium imbalance is created; in other words, the mechanism is direction-selective ion pumping. Direction-selective pumps explain how a nonequilibrium condition—and, hence, the electrical potential difference across the membrane, known as the **resting potential**—is sustained. Such a pump should not be thought of as a single device in the cell's membrane but, instead, as many submicroscopic ion-pumping mechanisms embedded in and distributed over the molecular structure of the membrane. It has been found, however, that pump distribution in the cell's membrane is not uniform. Most neurons have approximately 100 to 200 sodium pumps per square micrometer of membrane surface; some parts of the cell membrane have 10 times more than that, others have less.

The sodium-potassium adenosine triphosphate pump or, briefly, the **sodium pump**, consists of intrinsic proteins. It is slightly larger than the membrane thickness and has a molecular weight of 275,000 daltons. Each sodium pump expends the energy stored in the phosphate bond of the ATP to exchange three sodium ions from inside the cell for two potassium ions from outside the cell. The rate at which this ion exchange takes place depends on the needs and conditions of the cell. It has been calculated that at a maximum rate, each pump can transport 200 sodium ions and 130 potassium ions per second.

1.1.7 Cell Resting Potential

One can simulate the membrane with an equivalent circuit in terms of the conductance (or resistance) of the membrane for each ion and the potential difference each ion generates across the membrane. From simple circuit analysis at equilibrium with V_0 for the resting potential we obtain

$$I = 0 = (V_{\mathrm{K}} - V_0)G_K + (V_{\mathrm{Na}} - V_0)G_{\mathrm{Na}} + (V_{\mathrm{Cl}} - V_0)G_{\mathrm{Cl}}, \quad (1.2)$$

where G_{K}, G_{Na}, G_{Cl} are the conductances $(1/R)$ of the membrane for potassium (K), sodium (Na), and chloride (Cl), respectively, and V_{K}, V_{Na}, and V_{Cl} are the potential differences across the membrane due to K, Na, and Cl, respectively. The chloride current is comparatively small and can be neglected, and the membrane conductance for potassium is about 20 times larger than the sodium conductance. Thus, the resting potential V_0 is approximately

$$V_0 = \frac{V_{\mathrm{K}}G_{\mathrm{K}} + V_{\mathrm{Na}}G_{\mathrm{Na}}}{G_{\mathrm{K}} + G_{\mathrm{Na}}} \approx V_{\mathrm{K}} + \frac{V_{\mathrm{Na}}}{21}. \quad (1.3)$$

The cell rests at a negative potential because its membrane is selectively permeable to potassium. This resting potential, depending on conditions and the type of cell, is about -65 to -85 mV.

1.1.8 Action Potential: Cell Firing

In living organisms the electrical activity of a neuron is triggered by many mechanisms. For example, light triggers photoreceptors in the eye, mechanical deflection of hair triggers cells in the ear, chemical substances affect the responsivity of synapses or the ionic concentration inside and outside the cell, and voltage affects the firing process of the cell and the axon.

When the permeability of the membrane is locally disturbed by signals at one or more synapses, the pumping process at this location is disturbed. If the applied potential is more positive than the resting potential, in other words, if the applied signal is **excitatory**, then it *depolarizes* the membrane and the pumps stop functioning for the duration of the depolarization. Then, naturally, sodium rushes in through the sodium channels and potassium rushes out through the potassium channels of the depolarized part of the membrane in an attempt to balance the ionic concentration difference. Thus, the ionic concentrations across the membrane at the location of disturbance change and the potential difference collapses because it is not able to sustain the ionic concentration difference across the membrane at that location. If the "collapse" of potential is intense enough (i.e., if it exceeds certain characteristics that determine the cell's threshold), then the neighboring areas of the membrane are influenced and the depolarization starts traveling along the membrane; in other words, a wave of depolarization sweeps along the membrane that eventually reaches the axon hillock. At that point the depolarization wave, or the **action potential**, propagates along the axon down to the axonic endings (see Section 1.1.9).

If, on the other hand, the applied potential is more negative—that is, the disturbance is **inhibitory**—then the membrane is *hyperpolarized.* Hyperpolarization and depolarization may take place at the same time at two or more neighboring parts of a cell membrane. Obviously, hyperpolarization influencies depolarization of a membrane, and vice versa. Thus, it is believed that the resultant action potential is the algebraic sum of both hyperpolarization and depolarization activities provided that the net sum exceeds the threshold characteristics of the cell; the latter forms the basis of modeling artificial neurons.

1.1.9 The Axon: A Transmission Line

The axon is the neuron's transmission line. It transfers the excitation signal, or action potential, from the hillock down to the axonic endings. The axon exhibits certain fundamental differences in structure and properties from the dendrites. In the classical simplistic neuron, the axon is thought of as a tube filled with **axoplasm**, which is rich in potassium and poor in sodium. In addition, the axon consists of many microfilaments (thin fibers) called **neurofibrils** or **neurofilaments**. The branches of the dendrites cluster closer to the main body of the cell while the axon is longer and thinner than the dendritic branch, and it branches out at the end of the axon fiber. The membrane of the axon is specialized. At the terminal of the axon, the membrane is structured to release neurotransmitters, whereas the membrane of the dendrites is structured to receive neurotransmitters. The proteins in the axonic membrane are electrically activated, the proteins at the postsynaptic membrane are mostly chemically activated, and the soma membrane contains many kinds of proteins. The electrical resistance of the nerve's cytoplasm is so high (1000–10,000 ohms/cm) that it would dissipate the energy of the electrical signal, the action potential, within a few millimeters of travel. Thus, another paradox is presented: How can the axon sustain data transmission in the form of action potential over relatively long distances without severe signal attenuation?

The axon's structure is ingenious. It is equipped with a regeneration mechanism that restores the attenuated pulses as they propagate, a familiar practice to transmission systems engineers. The regeneration mechanism, depending on the type of neuron and species, may be continuous or repeated at fixed intervals, similar to the repeaters in transmission lines of communication systems. For example, in the squid's neuron the amplification mechanism is continuous along the axon (Figure 1-5a), whereas in higher animals it is repeated at fixed intervals (Figure 1-5b). In the latter case, the axon is covered with an insulating material called **myelin**. Myelin reduces membrane capacitance, thus increasing signal propagation speed, and amplifies signal strength. Amplification occurs as follows. Every few millimeters the continuous sheath of myelin is interrupted, forming gaps known as **nodes of Ranvier**. The gaps act as *repeaters* or regeneration sites where the signal is periodically restored. This amplification is so successful that myelinated axons can carry signals up to 1 m in length.

When depolarization exceeds the threshold of the cell, a nerve impulse starts at the origin of the axon, the axon hillock, and the voltage difference

across the axon membrane is locally lowered. Immediately ahead of the electrically altered region, channels in the membrane open and let sodium ions pour into the axon. Then the voltage across this membrane region is lowered, which causes more sodium channels to open just a little farther ahead. Thus, once the depolarization process of the axonic membrane is triggered, it becomes self-stimulated and continues until it reaches the axonic endings. The axonic membrane does not stay depolarized for long. As soon as the depolarization impulse is gone, in a matter of milliseconds the sodium channels close, known as **sodium inactivation**, and the pump mechanism restores the nonequilibrium state of the ion concentration of the membrane, starting from the origin of the axon. Thus, if an electrical probe is placed in the axon, one could detect a signal in the shape of a pulse propagating down the axon (Figure 1-5). For the squid axon, which is about 600 μm, the speed of the action potential is about 20 m/s (or approximately 70 km/h).

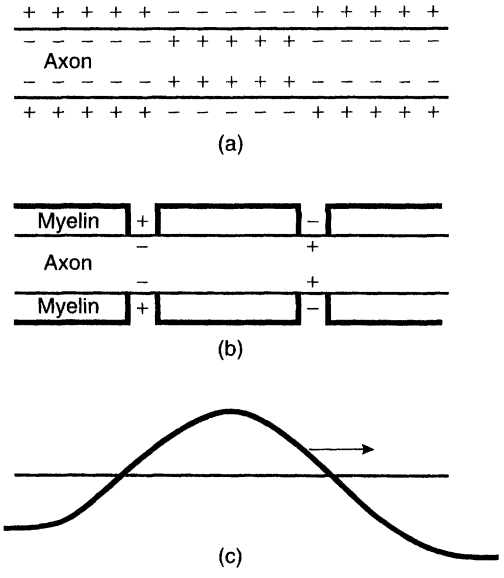

Figure 1-5 (a) Charge distribution in unmyelinated axon. (b) Charge distribution in myelinated axon. (c) Action potential.

1.1.10 The Synapse

The synapse is where two neurons connect. It consists of the flattened-tip, buttonlike terminal of an axonic ending, or **presynaptic terminal**, and the receptor part of another neuron, or **postsynaptic terminal**. The presynaptic

and postsynaptic terminals are separated by the **synaptic cleft**, which is about 200 nm thin. Within the presynaptic terminal are **mitochondria** and **vesicles**. The mitochondria produce chemical **neurotransmitters** and the vesicles store them (Figure 1-6). About 50 neurotransmitters have been identified so far.

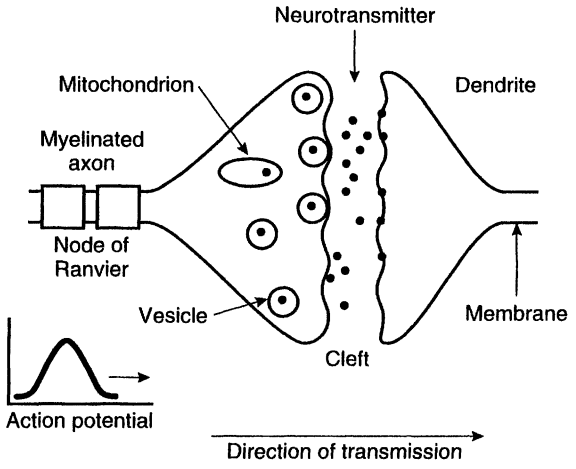

Figure 1-6 Synapsis in action.

The cleft is filled with extracellular material containing, for example, calcium ions. Calcium is extremely important for transmitting signals between neurons. When an action potential arrives at the presynaptic terminal, the electrical impulse opens voltage-activated calcium channels in the membrane. Through these channels calcium ions flow from the extracellular environment into the presynaptic terminal. The calcium ions attract the vesicles close to the presynaptic membrane and, in a synchronized manner, aid the fusion of the vesicles to the membrane. The vesicles then break up and "spray" the cleft space with the neurotransmitter. This fusion of vesicles and subsequent neurotransmitter release is called **exocytosis**. The time span of the calcium ions' inrush is quite brief and, once the ions accomplish their job, they are neutralized by an as yet indeterminate mechanism, so that the ion concentration in the presynaptic terminal returns to normal. The almost empty vesicles are reclaimed and quickly refilled with a new neurotransmitter. Every vesicle is filled with about 10,000 molecules of the same neurotransmitter. Some neurons may have only one type of neurotransmitter, whereas others, such as those in the brain, may have more than one.

When the cleft is sprayed with the neurotransmitter, postsynaptic membrane channels are chemically activated (i.e., they open) and pass the neu-

rotransmitter inside. These channels may be either sodium or chloride. At the other end of the channels, inside the neuron, is a concentration of receptor proteins that react with the incoming neurotransmitter. The reaction product may lower or raise the potential difference across the membrane, depending on which receptor matches with the received neurotransmitter and how well they match. It has been experimentally verified that, although the neurotransmitter may be the same (acetylcholine, serotonin, dopamine, GABA, histamine, etc.), depending on the type of synapse, the excitation, referred to as **neuronal modulation**, may be inhibitory or excitatory. For example, the intrinsic rhythm of the human heart is the result of neuronal modulation. Two types of neurons—*cholinergic* and *nonadrenergic*—are responsible for the heart's fast or slow beat. Cholinergic neurons connect to the vagus nerve and exhibit an inhibitory action when activated; nonadrenergic neurons, on the other hand, connect to the accelerator nerve and when activated exhibit an excitatory action. Either neuron type is activated by acetylcholine (ACh).

Another facet to the synapse's complexity is its **plasticity** [9]—its tendency to change its synaptic efficacy as a result of synaptic activity, strength, and frequency. Action potentials not only encode information; they also have metabolic aftereffects that alter network parameters over time.

Thus, each neuron is a sophisticated computer that continuously integrates up to 1000 synaptic inputs that do not add up in a simple linear manner.

1.1.11 The Synapse: A Biocomputer

Currently in computing research, a substantial effort to understand how nature computes is under way. The thinking here is entirely different from familiar binary computation. In pattern recognition, nature matches complete patterns in one simple step; in contrast, binary computers compare patterns bit by bit, which is an enormous expenditure of computing power and time. This thinking is based on the fact that proteins have characteristic shapes. When a neurotransmitter meets a receptor with the correct complementary shape, they form a specific messenger molecule (e.g., cyclic adenosine monophosphate, cAMP) similar to matching puzzle pieces.* This molecule is recognized by another readout enzyme that, in turn, triggers the membrane's depolarization process.

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* The cAMP messenger may also trigger events in the cytoskeleton, a network of microtubules and microfilaments (see Section 1.1.9).

Based on this operation of the synapse, a new technology has developed, **biocomputation** or **molecular computation**. Researchers in molecular engineering and computer architecture are looking for proteins and biocomputing structures to perform complicated computations in simple steps. (Other disciplines involved include gene and protein engineering, membrane engineering, polymer chemistry, and biochemistry.) This effort, though embryonic, has produced biosensors [10, 11, 12] that act as dedicated biocomputers to sense substances and their physical properties quickly and in minuscule quantities (glucose, oxygen, protein, etc.). For example, a fiber-optic biosensor is used to detect parts per billion of warfare agents, explosives, pathogens, and toxic materials [13] in a hazardous environment. In addition to biosensors, other molecular materials have been considered, such as rhodopsin—a purple, light-sensitive pigment in the eye responsible for vision (see Section 1.4)—as a fast optical switch in biochips and in processing synthetic aperture radar (SAR) signals [14].

1.1.12 Types of Synapses

One neuron can make many contacts with other neurons, thus forming a complicated network. The axonic endings of a neuron may contact another neuron to form a simple **excitatory** dendritic contact, an **inhibitory** dendritic contact, a direct contact with the trunk of a dendritic tree, a contact with the soma of a neuron, or even a contact with the axon itself. Moreover, some synapses—enabling synapses, modulating synapses, and inactive synapses—are more complicated (Figure 1-7). Some neurons feed back directly to themselves or indirectly via a third or fourth neuron. This diversity in synapse type is believed to control the operation and firing mechanism of the neuron; the function of each type, however, is not clearly understood in many neural networks.

1.1.13 The Developing Neuron: Forming Networks

How does an embryonic neuron (i.e., a neuron under development) know which neurons to contact so that a specific neural network can be formed? Developmental neuron research is addressing this question, and some evidence is available. In an embryonic neuron its axon is not fully developed and contacts with other neurons have not been fully formed. As the axon grows, however, the neuron recognizes the correct pathway using an ingenious mechanism that I call the **electrochemical seeking radar** (ECSR) to contact the target neuron. A radar transmits an electromagnetic wave,

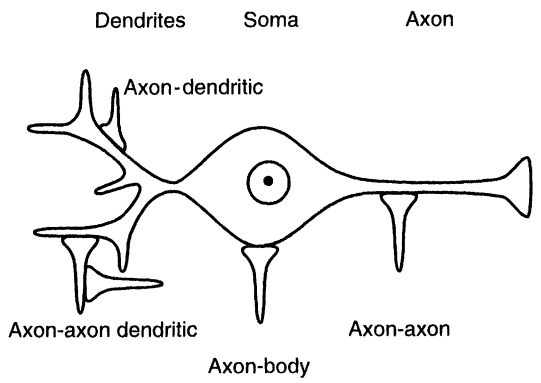

Figure 1-7 Types of synapses.

pauses briefly, receives the reflections of the transmitted wave, and analyzes the reflected signal, from which it identifies the location, movement pattern, and shape of the reflecting object. The *electrochemical seeking radar* is a strong hypothesis supported by scientific evidence as follows: A growing neuron seeks another neuron, the target neuron, by detecting specific cues left by it, similar to cues left in a trail and recognized by a hunting dog. In experiments with embryonic neuron growth in vitro, the addition of minute amounts of the cue, known as the **nerve-growth factor** (NGF) [15], everywhere in the culture resulted in a complete disorientation of the neuron's development and its growth in every possible direction (since the cues were present everywhere in the culture), resulting in a dense network of nerve fibers.

Moreover, it has been established that, during growth, the growing neuron fires periodically [16], and each firing is followed by a brief period of silence. Based on the ECSR hypothesis, the seeking neuron transmits a burst of a periodic signal, and the target neuron reacts to the received signal by releasing molecular cues. The latter cues are sensed by the growing neuron, decoded and recognized, and the neuron grows its axon a little toward it. This cycle repeats itself until the growing neuron eventually reaches its target neuron and makes one or more contacts with it. Thus, the growing neuron recognizes the correct target neuron from myriad other neurons with remarkable precision. From all the contacts made, those in which subsequent action potentials frequently appear increase their synaptic efficacy, whereas those in which the action potential is less frequent lose their strength. The ECSR hypothesis, however, has not yet been validated; the author encourages researchers to pursue this hypothesis.

1.1.14 Neuronal Specialization

All neurons are not the same, nor do they perform the same function. There are many categories of neurons with unique and highly specialized functions. Research has shown that some neurons have simple functions such as contracting or releasing a muscle, while other neurons control the excitatory or inhibitory behavior of other neurons. These neurons are known as **command cells**. It has been found that there are dual-action command neurons in a variety of animals. Command neurons may also remember a complete sequence of commands. Another type of neuron is the **neuroendocrine cell**. This neuron releases chemical substances called **hormones** in the bloodstream to be carried to remote sites. Such neurons form clusters called **bagcells**. Other types of neurons are specialized receptors (photonic, deflection, pressure, chemical, etc.). From an engineering point of view, the operation of some specialized neurons may be compared to a *communications network*, in which the bloodstream serves as the information highway with packets of information flowing in it. A protocol exists whereby a source receives acknowledgment that a chemical has reached its target via direct or indirect feedback mechanisms, causing the source to stop sending the chemical. In the next chapter some examples of biological neuronal networks with highly specialized neurons will be described. The purpose is to provide future direction and to support the argument that artificial neural networks could learn from the neuronal diversity in nature.

1.1.15 The Cell's Biological Memory

It is believed that a pattern is formed and stored when a group of events is associated in time (a belief shared by Aristotle). Patterns evoke other patterns. For instance, a friend's face can be linked with an event that took place at a different time. Thus, patterns are stored and linked with already stored ones. This type of memory is called **associative**. Experimental evidence [17] shows that the formation of memory involves molecular changes at the dendritic trees of neurons. Evidence suggests that each neuron can store thousands of patterns in the dendritic trees. The actual biochemical mechanism of storing and retrieving new information, however, has not been fully explored or understood.

There is no doubt that genes are memory banks of the cell that are preprogrammed permanently. But we don't know how, when, or with what these memory banks were programmed. It may be reasonable to assume

that, in addition, there are "unprogrammed" genes that can store new patterns on a more temporary basis because these patterns are induced to the cell by the synapses; this would explain the short-term memory, as opposed to the long-term or permanent memory, of a neural network [18]. If this assumption is true, then new patterns may be stored and may stay for some finite time, the length of which depends on how often the pattern appears or is evoked (i.e., refreshed) and on the type of compounds in its environment. If a pattern becomes inactive for some time, it may fade out. The assumption is based on evidence of molecular modification in the synaptic area [19]. When a phosphate group attaches to a protein, the protein's function is altered; this process is known as **phosphorilation**. Due to a recently discovered family of genes called **immediate early genes** (IEG), the protein may be activated rapidly by brief bursts of action potentials.

1.1.16 Weighting Factor

Recall that when a signal appears at a synapse, a charge is generated at the postsynaptic site. The magnitude of this charge depends on the strength of the incoming signal, which is weighted by a factor associated with this input. The **weighting factor** may not be constant over a long time. Ordinarily, potassium-ion flow is responsible for keeping the charge on a cell membrane well below the threshold potential. Moreover, the reduction of the potassium-ion flow is responsible for changing the weighting factors of electrical signals that can last for many days.

1.1.17 Factors Affecting Potassium-Ion Flow

Experiments have shown that a protein in the cytoplasm of rabbits and snails, kinasse (PKC), is calcium sensitive. When stimuli appear within a short period at the synapses, they cause changes in the calcium-ion concentration and in the diacylglycerol, another messenger. The PKC then moves from the cell cytoplasm to the cell membrane where it reduces the potassium-ion flow and thus alters the neuron's properties. In addition, another calcium-activated protein, CAM kinasse II, may also help reduce potassium-ion flow at the membrane.

1.1.18 Firing, in a Nutshell

In conclusion, when the potassium-ion flow decreases at the membrane, particular input signals trigger impulses more readily. When the stimuli are intense enough so that the potential difference across the membrane

exceeds the threshold level, the sodium pump starts collapsing across the membrane and the potential difference moves toward the axon, where it propagates toward the axonic endings. Thus, the cell has fired. Since some of the synaptic inputs are contributing to and some are inhibiting the firing, and since the stimuli occur not simultaneously but within a time window, it is easy to think of a situation where the cell fires and then, shortly thereafter, the inhibitory stimuli appear for a short period and briefly reverse the firing process. If the contributing stimuli are still persistent, the action potential may result in some kind of temporary oscillation. In a neuronal system the inhibitory inputs may also come from other neurons. The firing of neurons thus activated reflects the distribution within each neuron and within each neuronal system of those sites that have conditioned excitability.

1.2 Neuronal Diversity

In the real world of neural networks, the neurons do not all perform exactly the same function or in exactly the same way (see Section 1.1.14). In fact, the functions of sensory neurons (compare optical and auditory sensors) and neural networks (compare visual and auditory neural networks) are quite diverse. This diversity adds to the complexity of the neural network. Whereas all neurons contain the same set of genes, individual neurons activate only a small subset of them; selective gene activation has been found in different neurons. Nevertheless, all neural networks exhibit certain properties, namely:

1. Many parallel connections exist between many neurons.
2. Many of the parallel connections provide feedback mechanisms to other neurons and to themselves.
3. Some neurons may excite other neurons while inhibiting the operation of still others.
4. Some parts of the network may be prewired, whereas other parts may be evolving or under development.
5. The output is not necessarily yes–no or (10), that is, of a binary nature.
6. Neural networks are asynchronous in operation.
7. Neural networks have a gross and slow synchronizing mechanism, as slow as the heartbeat, that supports their vital functions.

8. Neural networks execute a program that is fully distributed and not sequentially executed.
9. Neural networks do not have a central processor, but processing is distributed.

Biological neural networks are characterized by a hierarchical architecture. Lower-level networks preprocess raw information and pass their outcome to higher levels for higher-level processing.

The incredible functionality and the ability to process vast amounts of information have puzzled many from antiquity to modern times. Plato (427–347 B.C.), Aristotle (384–322 B.C.), Ramon y Cajal, Colgi, others in the nineteenth century, and many thousands in the twentieth century have searched for an answer. The following fundamental questions are often asked:

- How is the human neural network, the brain, designed?
- How does the brain process information?
- With what "algorithms" and "arithmetic" does the brain "calculate"?
- How can the brain imagine?
- How can the brain invent?
- What is "thought"?
- What are "feelings"?

From extensive research in biology, biochemistry, brain anatomy, behavioral and cognitive sciences, psychology, and other fields, we know that biological neural networks have the ability to learn from new information, to classify, store, recall, cross-reference, interpolate and extrapolate, to adapt network parameters, and to perform network maintenance. Research continues on all fronts.

Under certain circumstances, memories are brought back so strongly that we can almost "feel"; these *virtual senses* become mental reality for a short time. A few years ago during an operation on a human brain, part of the brain was electrically stimulated. After recovery, the patient told the doctors that during the operation he vividly remembered some pleasant events from the past; in fact, he almost relived these events. The doctors attributed this experience to the stimulation of the brain, which brought back memories so intensively that pleasure centers may have been activated, thus emulating the feeling of reality.

In summary, during the learning phases (i.e., input via senses), patterns are formed, stored, and associated (and experience is gained). Memories are linked and associated ("associative memories"). When a pattern is invoked, it triggers (recalls) other patterns, which then trigger others, so that a cascade of memories (recalled patterns) occurs.

1.3 Specifications of the Brain

Researchers estimate that there are 100 billion neurons in the human cerebral cortex. Each neuron may have as many as 1000 dendrites and, hence, 100,000 billion synapses (Table 1-2). Since each neuron can fire about 100 times per second, the brain can thus possibly execute 10,000 trillion synaptic activities per second. This number is even more impressive when we

Table 1-2. Data Sheet of Human Cortical Tissue (numbers are approximate)

Number of neurons	100 billion
Number of synapses/neuron	1000
Total number of synapses	100,000 billion
Operations/s/neuron	100
Total number of operations	10,000 trillion/s
Neuronal density	40,000/mm^3
Human brain volume	300 cm^3
Human brain weight	1.5 kg
Dendritic length of a neuron	1 cm
Duration of action potential	3 ms
Firing length of an axon	10 cm
Velocity of axon potential	3000 cm/s (108 km/h)
Resting potential across membrane	65 to −85 mV
Resistance of neuron's cytoplasm	1 k to 10 kΩ
Sodium pump size	6 to 8 nm
Sodium pump density	200/μm^2
Membrane thickness	5 to 50 Å
Membrane's breakdown voltage	10,000 V/cm
SiO_2 breakdown voltage	10,000 V/cm
Power dissipation per neuron	25×10^{-10} W
Power dissipation per binary act	3×10^{-3} erg

realize that the human brain weighs about 3 lb and occupies about 300 cm^3 (about a third of a liter). If we formed a 1-mm-thick layer with the brain, its dimensions would be about 0.6 m by 0.5 m. A fast supercomputer like the Cray C90 with 16 processors can execute at peak theoretical speed about 16 gigaflops (i.e., about 10^9 floating-point operations per second) and the Thinking Machines CM-2, with 16,384 processors, has a peak theoretical speed of 35 gigaflops [20, 21], not even close to the biological computer, the brain. Does this mean that there is no hope to emulate certain functions with an artificial neural computer? On the contrary, with the evolution of technology, certain human functions, such as vision (scene recognition and interpretation), speech (recognition and generation), logical interpretation of situations, and motion control, can possibly be emulated in the near future. Many are either deployed or in experimental stages. This belief is based on many factors: modern technology and materials that lend themselves to integration on the same substrate of optical and electronic components with switching characteristics on the order of terahertz [22] (1000 billion), materials and transistor structures with integration of more than several million transistors per square centimeter, integrated amplifiers with excellent characteristics, circuitry that consumes extremely low power, and materials such as amorphous crystals with new compound crystalline structures and molecular processors integrated on films (**biochips**) that may revolutionize the electronics and computer industry in the future.

1.4 The Eye's Neural Network

The eye is the visual window of the brain. It is an optical instrument marvel and an amazing bioelectrochemical computer. Light enters the eye and focuses on the **retina** [23, 24, 25] (Figure 1-8), and an amazing process then begins. The optical structure of the eye is similar to a fully automatic camera that has a lens focusing on a photographic film. The camera's lens, diaphragm, and film directly correspond to the eye's lens, iris, and retina.

1.4.1 Retina Structure

The retina consists of a dense matrix of photoreceptors of which there are two distinct types, according to their shape: **rods** and **cones**. From electron microphotographs, we can see that the rods are tubular and larger than the cones. The function of the rods and cones is highly specialized in

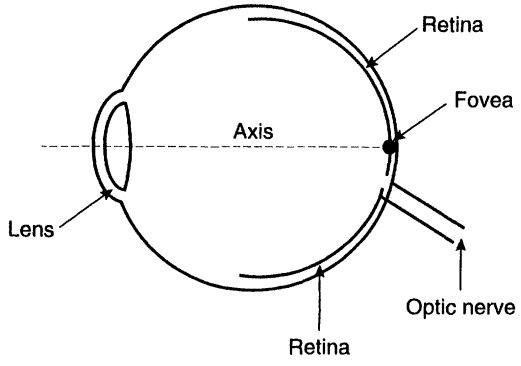

Figure 1-8 Simplified cross section of the eye.

responsiveness and sensitivity. Rods are about 100 times more sensitive to light than cones, but cones are about four times faster in response to light than rods. Rod cells form black-and-white images in dim light, and cones mediate color vision [26, 27]. Rods are activated by very few **photons** and thus mediate vision in dim light; cones sense color, are richer in spatial and temporal detail, and need many photons to be activated. Consequently, cones mediate color vision in ordinary light. As a result, we can see colors better in daylight than in dim light.

There is a high concentration of cones in the **fovea**, that part of the retina on the visual axis of the lens, and it is thus the area of highest resolution. The fovea, only 1.5 mm in diameter, contains about 2000 cones. Away from the fovea the concentration of cones decreases and the concentration of rods increases. The most sensitive light receptors are 20 degrees from the fovea. The total of rods and cones is estimated to be 130 million, about six percent of which are cones.

Photoreceptors (rods or cones) convert light to electrical signals. These signals are preprocessed by other retinal neurons that extract high-level information from the image on the retina. This information is transmitted to the brain by the **optic nerve** for further processing.

1.4.2 Rods and Cones

Conversion from light energy to electrochemical energy in the photoreceptors is a highly complex, perplexing process. Rods are narrow tubes that consist of an orderly pile of approximately 2000 microminiature disks placed flat, one on top of the other (Figure 1-9). This pile is covered by a separate surface membrane. The disks and outer membrane are made

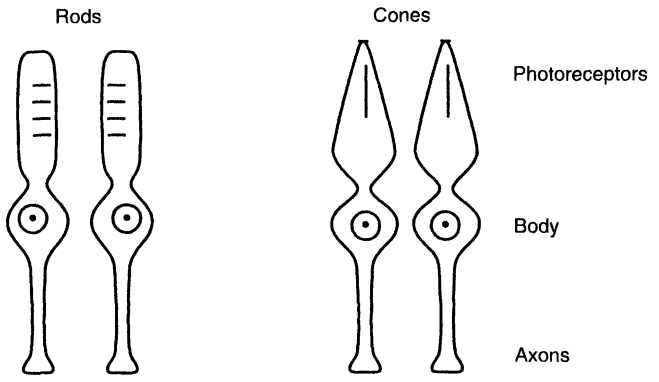

Figure 1-9 Rods and cones.

of the same type of bilayer membrane; the outer membrane, however, has a different protein consistency and response to the reception of light than does the disk membrane. The disk membrane contains most of the protein molecules that absorb light and initiate the excitation response. The outer membrane responds to a chemical signal with an electrical one.

In cones, the membrane consists of one continuous and elaborately folded sheet that serves as both the photosensitive membrane, similar to the disks of a rod, and the surface membrane. The human retina has three kinds of cones. Each contains a pigment that absorbs strongly in the short (blue), middle (green), or long (red) wavelength of the visible spectrum. This difference in color absorption of the three cone pigments provides the basis for color vision. Color television capitalizes on this fact, and the sensation of many colors is created by synthesis of these three fundamental colors.

1.4.3 From Photons to Electrons: A Photochemical Chain Reaction

Proteins are key ingredients for the response of rods and cones. In the absence of light, there is high concentration of cyclic guanosine monophosphate (cGMP), a chemical transmitter that binds to the pores of the surface membrane and keeps them open, allowing sodium to enter. To maintain the ionic equilibrium, the membrane continually pumps the sodium ions out. Rods contain the reddish protein **rhodopsin*** in disks that absorb photons singly and contribute to the initial response of a chain of events that un-

* Rhodopsin turns the retina or salt ponds purple. It may play a key role in tomorrow's biochips and biocomputers (see Section 1.1.11).

derlies vision. Rhodopsin has two components, **11-*cis*-retinal** and **opsin**. An organic molecule derived from vitamin A, 11-*cis*-retinal, (11-*cis*) is isomerized when light falls on it (i.e., it changes shape but retains the same number of atoms). Opsin is a protein that can act as an enzyme in the presence of the isomerized 11-*cis*. When light falls on a rod, it is absorbed by its rhodopsin in a disk, and the 11-*cis* is isomerized. The isomerized 11-*cis* triggers the enzymatic activity of the opsin. Then the active opsin catalytically activates many molecules of the protein **transducin** [28]. The activated transducin molecules in turn activate the enzyme **phosphodiesterase**, which cleaves cGMP by inserting a water molecule into it. This process is known as **hydrolysis**. Each enzyme molecule can cleave several thousand cGMPs, which now are not capable of keeping the membrane pores open. Thus, many pores close and the concentration of cGMP drops, reducing the permeability of the membrane and thus the influx of sodium. This causes the negative polarization of the cell interior to increase—the cell is **hyperpolarized**—and the generated action potential to travel down to the axonic endings. Thus, this chemical reaction behaves like a **chemical photomultiplier**. Subsequent to this a restoration process begins: the cGMP is restored and attached to the membrane pores, which reopen, and the transducin and rhodopsin are deactivated so that the cycle may repeat.

Each rod contains about 100 million rhodopsin molecules. One photon is capable of activating one rhodopsin molecule, which eventually triggers an action potential. Obviously, the more photons absorbed, the stronger the action potential. Because of their photomultiplier effect, rods are so sensitive to light that under normal conditions the human eye can see a lighted candle at a distance of 27 km [29]. The light energy reaching the photoreceptors is integrated in the first 0.1 s and not thereafter [30]. That is, a light stimulus lasting 0.01 s has the same effect with a stimulus that lasts 0.0001 s but is 100 times stronger. On the other hand, if it has the same strength, then the faster stimulus will be noticed less. This temporal response of the rods and cones explains how magicians can deceive the human eye by acting fast, how we can see the movement of a clock's second hand but not its hour hand, and how we perceive continuous motion in cinematography and television.

1.4.4 Organization and Communication of the Retina Neural Network

The complex structure of the retina consists of cells arranged in layers of differently specialized neurons with numerous interconnections between

them. The eye's rods and cones convert photonic signals into electrochemical ones, as described earlier. Other neurons in the retina are the **bipolar**, the **horizontal**, the **amacrine**, and the **ganglions** (Figure 1-10).

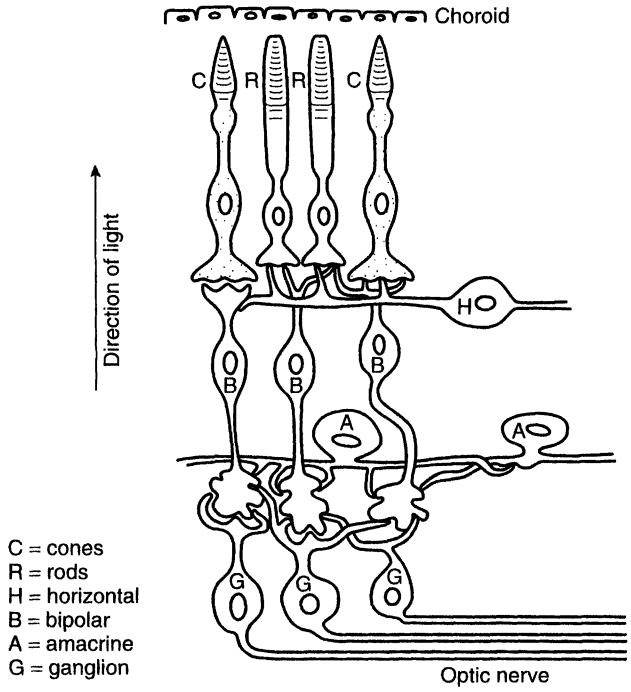

Figure 1-10 Neurons in the retina.

Rods and cones synapse with bipolar neurons, which in turn synapse with ganglion neurons. The axons of the ganglions form the **optic nerve**. Although there are 120 million rods and 7 million cones, there are only 1 million ganglions and optic-nerve fibers. In the central fovea region there is a one-to-one connection between cones, bipolars, and ganglions, whereas in other regions of the retina many rods and cones synapse with one bipolar. The one-to-one connection explains the superb resolution of the fine features of a scene.

Horizontal neurons connect rods and cones with bipolars. They are inhibitory in function and provide feedback from one receptor to another, adjusting their response so that the retina can deal with the dynamic range of light intensities that far exceed the dynamic range of individual neurons. Remarkably, vision responds to both sunlight and starlight, a range of 10 billion.

The ganglion neurons have special functions. They are "wired" with other neurons such that different ganglions convey different elemental features from a scene. Direction-selective ganglions transmit a maximum signal when movement is in a preferred direction, no signal when movement is opposite to the preferred direction, and a weak signal if the direction is in between.

Amacrine neurons are inhibitory, connect bipolars with ganglions, and regulate ganglion behavior with transient response to stimulation by light. When light strikes photoreceptors, the amacrine cells fire a burst of action potential, but they cease firing under continued light stimulation. In certain species amacrine-to-amacrine chains contribute to the more complex data processing operations in the retina. The four best-known amacrine neurons are **cholinergic** or **acetylcholine** (their name comes from their chemical neurotransmitter), **AII**, **dopaminergic**, and **indoleamine accumulating**.

Cholinergic neurons are numerous, and their branching dendrites form an almost uninterrupted mesh, particularly in the peripheral retina. They excite certain ganglions, among them the direction-selective ones. AII amacrine neurons are small, their dendrites are sparser but numerous, and they cover the entire surface of the retina. They connect rod-activated bipolars with ganglions to function under both bright- and dim-light conditions, and they transmit a transient response to ganglions, sharpening their response to light changes. The flow of information here is from rod to bipolar to AII to ganglion. Dopaminergic neurons are very sparse, with longer dendrites that form a loose mesh. These neurons synapse only with other amacrine neurons. Although their exact function is not known, it is possible that they calculate the average activity of other amacrine neurons over the entire retina, thus making second-order adjustments to transient light and light intensity responses. Indoleamine-accumulating neurons are part of the dense plexus lining the inner part of the inner synaptic layer. These neurons make a characteristic synapse, called a **reciprocal** synapse, from dendrite to dendrite, that allows for information flow from one amacrine to another in either direction. Their function is not well understood.

1.4.5 Image Preprocessing in the Retina

Let us recapture the information processing that takes place in retinal neurons. When the photoreceptors are excited, their information is transmitted to one or more bipolars and to horizontal neurons. The horizontals receive signals from a group of photoreceptors and, depending on received signal strength and their functionality, make adjustments to the responsivity of

the bipolars. The bipolars receive signals from one or more photoreceptors and from the horizontal neurons. When all conditions are satisfied, based on their functionality, they transmit their signal to one or more ganglions and to the amacrine neurons. The ganglions receive signals from one or more bipolars and from the amacrine neurons, and if all conditions are met, they transmit their electrical signal down their axons, which make up the optic nerve (Figure 1-11).

Thus, an amazing preprocessing of the image takes place right at the retina level where "prewired" neural networks recognize bits of information, or elemental features, and generate signals. The results of this "preprocessed picture" are then transmitted via the optic nerve to the inner brain where they are further processed [31, 32].

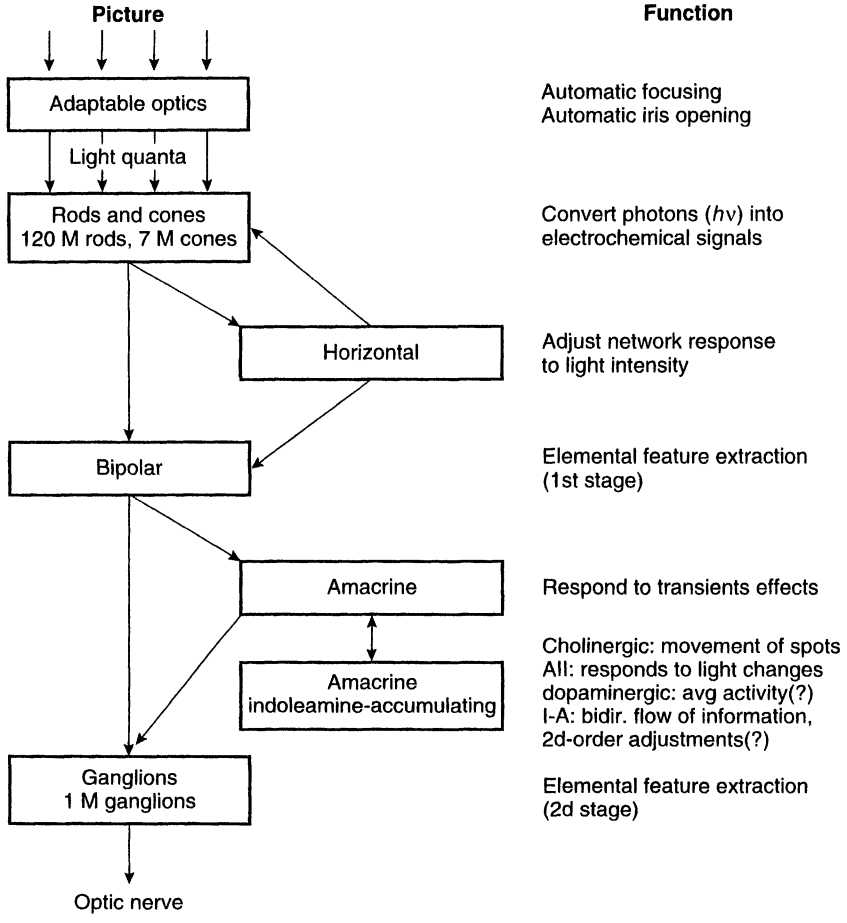

Figure 1-11 Signal processing in retinal neurons.

A substantial effort has been made to understand these elemental features. Experiments have shown that certain retinal neuron circuits respond to dots of light, yet others respond to lines, bands of light, corners, circles, and so on. Another group of retinal circuits responds to motion. Some respond to motion in one direction or another but not in both directions, or to a specific direction and not to any direction [33, 34, 35] and so on. Artificial neural networks mimic this process of feature extraction in handwritten numeric character [36] recognition, visual pattern recognition [37], and speech recognition [38].

1.4.6 Visual Pathways

Most of the optic-nerve fibers derived from the ganglions terminate in the **lateral geniculate nucleus** (LGN) in the brain (Figure 1-12).

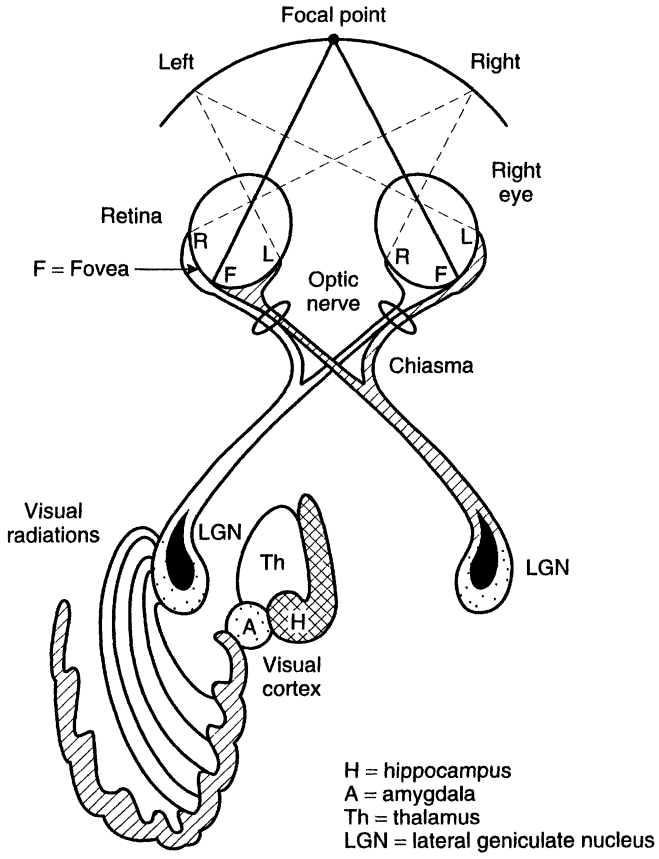

Figure 1-12 Neural net for vision.

The LGN neurons project their axons directly to the **primary visual cortex** via the **optic radiations** region [39, 40]. From there, after several synapses, the messages are sent to destinations adjacent to the cortical areas and other targets deep in the brain. One target area even projects back to the LGN, establishing a feedback path.

Each side of the brain has its own LGN and visual cortex. The optic nerve from the left eye and that from the right eye cross in front of the LGNs at the optic **chiasm**. At the chiasm, part of the left optic nerve is directed to the right side of the brain and the other part to the left side of the brain, and similarly for the right optic nerve. As a result of the optic chiasm, the LGN and the visual cortex on the left side are connected to the two left-half retinas of both eyes and are therefore concerned with the right half of the visual scene; the converse is true for the right LGN and visual cortex.

The pathways terminate in the brain's **limbic system**, which contains the **hippocampus** and the **amygdala**, which have important roles in the memory—in fact, they appear to be the crossroads of memories. Memories from the present and the past and from various sensory inputs meet and associate there, leading to the development of emotions and, perhaps, invention. The amygdala and the hippocampus seem to be coequal concerning memory, especially recognition.

The LGN contains two types of **opponent** neurons, **nonopponent** and **spectrally opponent**. Nonopponent neurons process light intensity information. Spectrally opponent neurons process color information.

The visual cortex registers a systematic map of the visual field so that each small region of the field activates a distinct cluster of neurons that is organized to respond to specific stimuli. There are four types of neurons here. **Simple** neurons respond to bars of light, dark bars or straight-line edges in certain orientations and in a particular part of the visual field. **Complex** neurons respond like simple neurons but independently of the position of lines in the visual field. They also respond to select directions of movement. **Hypercomplex** neurons respond to the stimuli of lines of certain length and orientation. **Superhypercomplex** neurons respond to edges of certain width that move across the visual field, and some respond to corners. The visual cortex is organized into columns where neurons in a given column have similar receptive fields. Thus, one column might respond to vertical lines, another to motion to the right, and so on.

The pathway extends into the **inferior temporal cortex**. Distinct cortical stations are connected in various sequences along the pathway. Neurons here respond to more complex shapes. Each neuron receives data from large segments of the visual world and responds to progressively more complex

physical properties such as size, shape, color, and texture until, in the final station, the neurons synthesize a complete representation of the object.

Thus, one concludes with a high degree of confidence that the visual system seems to have a pyramidal hierarchical structure whereby an elemental set of features is extracted first, and from this more complex patterns are extracted, and so on. They are then combined with color information, movement, and their direction and their relative spatial relationship and are finally stored and associated with other features.

1.5 Areas for Further Investigation

1. When the action potential arrives at the axonic ending, determine all mechanisms that dissipate the arriving electrical energy, as in transmission lines. [*Hint*: Some of the energy is dissipated to open the calcium channels, some to move the vesicles closer to the membrane, and some may aid in the production of more neurotransmitters.]

2. Does the axon conduct in one direction only? Is part of the signal used in a feedback mechanism either by back-propagation or by causing a back-propagating molecular reaction? [*Hint*: The hypothesis that a message is sent back to the soma and to the membrane proteins to adjust synaptic weights and threshold may corroborate with Hebbian "learning" and "programming" of the neuron (see also Section 2.4.7).]

3. (a) What are the selection criteria and selection mechanisms in neurons with more than one type of neurotransmitter? (b) Upon arrival of the action potential at the axonic endings, is one neurotransmitter released or are more released in a combination of different proportions? (c) Upon arrival of the action potential at the axonic ending, what determines which neurotransmitter will be released (if more than one) and in what proportions? [*Hint*: Although not experimentally established, let us take a closer look at these questions: The intensity of a stimulus as it arrives at the synapse is coded (in many neurons) in a train of impulses. The frequency of impulses varies from few to hundreds per second. In addition, the number of impulses in the train varies, but all have the same amplitude: the larger the stimulus, the faster the rate of impulses. It may be reasonable to assume that the frequency and amplitude of the arriving signal contribute to the selection of the neurotransmitter and/or the quantity to be released. One may thus test for a hypothesis that I call the "neurotransmitter reso-

nant or tuning fork." Think of the presynapsis as the receiving antenna and the neurotransmitters as tuning forks (or tuned oscillators), each tuned to a different frequency. Then, depending on the arriving frequency, one or more neurotransmitters will directly or indirectly be excited and at different proportions, depending on how close to the frequency they are tuned. In addition, the amplitude of the arriving signal may excite the tuning forks—the neurotransmitters—at different levels. Thus the arriving signal frequency and amplitude may provide answers to the stated questions. The assumption is in alignment with another experimental finding: a neuron that fires rapidly releases more neurotransmitter molecules than a neuron that fires less rapidly. The more neurotransmitter molecules, the more channels open at the postsynaptic membrane, and, therefore, the larger the postsynaptic potential is at the contact.]

4. What is the role of the axonic neurofilaments, or neurofibrils, in the propagation of the signal from the soma and down the axon to the presynapsis of a neuron? [*Hint*: The axon consists of many filaments that are much smaller than existing probes. Electrical probes used in the lab have a diameter of 0.5 μm. A typical presynapsis is 0.1 to 5 μm. Due to technology limitations, however, it is almost impossible to single out and probe axonic filaments. Are the filaments part of the transmission mechanism, or do they serve as the mechanical structural skeleton of the axon only?]

5. Consider the hypothesis of the electrochemical seeking radar. When action potential is fired, identify the type of the neurotransmitter of a developing neuron and the type of molecular cues released by the target neuron. In addition, what is the time lapsed between the release of the neurotransmitter and the molecular cues? What happens if the molecular cues are altered? Does the developing neuron change path?

6. What happens to all the calcium that enters the presynaptic terminal during the firing process? Obviously it cannot stay there or else there would be an enormous accumulation of calcium over time. [*Hint*: It is reasonable to assume that there is a calcium pump mechanism at the presynaptic membrane, similar to the sodium pump. That is, there should be a protein with the assignment to capture calcium and abort it from the cell. Which protein is it? What are the dependencies of this protein? How is this protein manufactured? How is the operation of a neuron affected if there is some excess accumulation of calcium in the presynapsis due to malfunctioning of the hypothetical "calcium pump"?]

1.6 Review Questions

1.1. What is the basic building block of the nervous system?

1.2. What are the basic parts of a neuron?

1.3. What is the basic element of the membrane and how is the membrane constructed?

1.4. What is a synapse? Describe the three major parts of it.

1.5. Name two types of synapses.

1.6. When the action potential reaches the synaptic ending, what happens?

1.7. Briefly describe how the action potential is generated.

1.8. Name five membrane proteins.

1.9. Is it true that when the neuron is at rest the voltage across the membrane is zero?

1.10. When the neuron is at rest, what can you say about the concentration of sodium and potassium inside and outside the neuron?

1.11. Is it true that all neurons provide the same functionality?

1.12. Which neurons of the eye are responsible for vision in color and which for vision in gray?

1.13. What is the optic nerve?

1.14. Is it true that visual information is converted to bits (or pixels) that are transmitted from the eye to the brain, as in television? If not, then what happens?

1.15. Is it true that both rods and cones are equally sensitive to light? If not, which one is more sensitive?

1.16. Where in the retina are the cones in higher concentration?

1.17. If cones were not present in the retina, how would a color picture be perceived?

1.18. Name some of the neurons that make up the neural network of the retina.

1.19. What kind of signal preprocessing takes place at the retina?

1.20. How can the eye be adjusted to large differences in light intensity?

For answers, see page 185.

REFERENCES

[1] J. C. Eccles, *The Understanding of the Brain*, McGraw-Hill, New York, 1977.

[2] J. G. Nicholls, A. R. Martin, and B. G. Wallace, *From Neuron to Brain*, 3rd ed., Sinauer Associates, Inc., Publishers, Sunderland, Mass., 1992.

[3] J.-P. Changeux, "Chemical Signals in the Brain," *Sci. Am.*, vol. 269, no. 5, pp. 58–62, 1993.

[4] D. L. Alkon and H. Rasmussen, "A Spatial-Temporal Model of Cell Activation," *Science*, vol. 239, no. 4843, pp. 998–1005, 1988.

[5] P. C. Hinkle and R. E. McCarty, "How Cells Make ATP," *Sci. Am.*, vol. 238, no. 3, pp. 104–123, 1978.

[6] M. Karplus and J. A. McCammon, "The Dynamics of Proteins," *Sci. Am.*, vol. 254, no. 4, pp. 42–51, 1986.

[7] M. Radman and R. Wagner, "The High Fidelity of DNA Duplication," *Sci. Am.*, vol. 259, no. 2, pp. 40–46, 1988.

[8] R. D. Keynes, "Ion Channels in the Nerve-Cell Membrane," *Sci. Am.*, vol. 240, no. 3, pp. 126–136, 1979.

[9] G. E. Hinton, "How Neural Networks Learn from Experience," *Sci. Am.*, vol. 261, no. 9, pp. 144–151, 1992.

[10] M. Conrad, "The Lure of Molecular Computing," *IEEE Spectrum*, pp. 55–60, Oct. 1986.

[11] *Proc. of the Bioelectronic and Molecular Electronic Devices*, Tokyo, Nov. 1985.

[12] F. Carter, ed., *Molecular Electronic Devices*, M. Decker, New York, 1982.

[13] F. S. Ligler, *Fiber Optic Based Biosensor*, Report N92-22458, American Institute of Aeronautics and Astronautics, 1992.

[14] J. W. Yu et al., "Bacteriorhodopsin Film for Processing SAR Signals," *NASA Tech. Briefs*, p. 63, July 1992.

[15] R. Levi-Montalcini and P. Calissano, "The Nerve-Growth Factor," *Sci. Am.*, vol. 240, no. 6, pp. 68–77, 1979.

[16] C. J. Shatz, "The Developing Brain," *Sci. Am.*, vol. 261, no. 9, pp. 61–67, 1992.

[17] D. L. Alkon, "Memory Storage and Neural Systems," *Sci. Am.*, vol. 258, pp. 42–50, 1989.

[18] M. Mishkin and T. Appenzeller, "The Anatomy of Memory," *Sci. Am.*, vol. 256, no. 6, pp. 80–89, 1987.

[19] R. Kandell and R. D. Hawkins, "The Biological Individuality," *Sci. Am.*, vol. 261, no. 9, pp. 78–83, 1992.

[20] G. Cybenko and D. J. Kock, "Revolution or Evolution?" *IEEE Spectrum*, pp. 39–41, Sept. 1992.

[21] O. M. Lubeck et al., *The Performance Realities of Massively Parallel Processors: A Case Study*, Report LA-UR-92-1463, Los Alamos National Laboratory, June 19, 1992.

[22] *Future Electron Devices Jour.*, vol. 2, supplement, p. 53, 1992.

[23] A. I. Cohen, "The Retina and Optic Nerve," in *Adler's Physiology of the Eye: Clinical Applications*, 6th ed., E. Moses, ed., Mosby, St. Louis, 1975.

[24] T. L. Bennett, *Introduction to Physiological Psychology*, Brooks/Cole Publishing, Monterey, Calif., 1982.

[25] R. H. Masland, "The Functional Architecture of the Retina," *Sci. Am.*, vol. 255, no. 6, pp. 102–111, 1986.

[26] C. A. Podgham and J. E. Saunders, *The Perception of Light and Color*, Academic Press, New York, 1975.

[27] J. L. Schnapf and D. A. Baylor, "How Photoreceptor Cells Respond to Light," *Sci. Am.*, vol. 256, no. 4, pp. 40–47, 1987.

[28] L. Stryer, "Cyclic GMP Cascade of Vision," *Ann. Rev. Neurosci.*, vol. 9, pp. 87–119, 1986.

[29] M. H. Pirenne, "Absolute Visual Thresholds," *Jour. Physiol. (London)*, vol. 123, p. 409, 1953.

[30] S. Hecht et al., "Energy, Quanta and Vision," *Jour. Gen. Physiol.*, vol. 25, p. 819, 1942.

[31] T. Sato, T. Kawamura, and E. Iwai, "Responsiveness of Inferotemporal Single Units to Visual Pattern Stimuli in Monkeys Performing Discrimination," *Experimental Brain Res.*, vol. 38, no. 3, pp. 313–319, 1980.

[32] C. Bruce, R. Desimone, and C. G. Gross, "Visual Properties of Neurons in a Polysensory Area in Superior Temporal Sulcus of the Macaque," *Jour. Neurophysiol.*, vol. 46, no. 2, pp. 369–384, 1981.

[33] T. Poggio and Ch. Koch, "Synapses That Compute Motion," *Sci. Am.*, vol. 256, no. 5, pp. 46–52, 1987.

[34] S. V. Kartalopoulos, "Signal Processing and Implementation of Motion Detection Neurons in Optical Pathways," in Proceedings of Globecom'90 Conference, San Diego, Dec. 2–5, 1990.

[35] M. Bongard, *Pattern Recognition*, Spartan Books, New York, 1970.

[36] L. D. Jackel et al., "An Application of Neural Net Chips: Handwritten Digit Recognition," *Proc. ICNN*, San Diego, pp. II-107–II-115, 1988.

[37] K. Fukusima, "A Neural Network Model for Selective Attention in Visual Pattern Recognition," *Biol. Cybernetics*, vol. 55, no. 1, pp. 5–15, 1986.

[38] T. Matsuoka, H. Hamada, and R. Nakatsu, "Syllable Recognition Using Integrated Neural Networks," in Proceedings of IJCNN, Washington, D.C., pp. 251–258, June 18–23, 1989.

[39] H. J. A. Dartnall, ed., *Photochemistry of Vision*, Springer-Verlag, New York, 1972.

[40] H. Darson, ed., *The Eye*, 2d, Academic Press, New York, 1977.