4

THE ORIGIN OF BIOPOTENTIALS

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This chapter deals with the genesis of various bioelectric signals that are recorded routinely in modern clinical practice. Given adequate monitoring equipment, many forms of bioelectric phenomena can be recorded with relative ease. These phenomena include the electrocardiogram (ECG), electroencephalogram (EEG), electroneurogram (ENG), electromyogram (EMG), and electroretinogram (ERG).

Engineers generally have a good physical insight into the nature of electromagnetic fields produced by bioelectric sources, and, because of their comprehensive understanding of the physical problem, they may contribute to the solution of biological problems.

This chapter begins by introducing bioelectric phenomena at the cellular level. It proceeds to discuss volume-conductor potential distributions of simple bioelectric sources, and gradually more anatomically complex ones. The volume-conductor electric field problem provides the link (mapping) between microscopic electrical activity generated within the bioelectric source, the flow of action current through the conducting medium, and the macroscopic potential distribution produced at the surface of the body. We continue with a discussion of the functional organization of the peripheral nervous system (outside the brain and spinal cord), which leads to a discussion of the ENG and EMG. Finally, other bioelectric sources (and associated field potentials) are discussed including the active heart (ECG), retina (ERG), and brain (EEG).

4.1 ELECTRICAL ACTIVITY OF EXCITABLE CELLS

Bioelectric potentials are produced as a result of electrochemical activity of a certain class of cells, known as excitable cells, that are components of nervous, muscular, or glandular tissue. Electrically they exhibit a resting potential and, when appropriately stimulated, an action potential, as the following paragraphs explain.

THE RESTING STATE

The individual excitable cell maintains a steady electrical potential difference between its internal and external environments. This resting potential of the
internal medium lies in the range $-40$ to $-90$ mV, relative to the external medium.

Figure 4.1(a) shows how the resting potential is usually measured. A micromanipulator advances a microelectrode (see Section 5.8) close to the surface of an excitable cell and then, by small movements, pushes it through the cell membrane. For the membrane to seal properly around the penetrating tip, the diameter of the tip must be small relative to the size of the cell in which it is placed. Figure 4.1(b) shows a typical electrical recording from a single nerve fiber, including the dc offset potential (resting potential) that occurs upon penetration of the membrane. It also shows the transient disturbance of membrane potential (the action potential) when an adequate stimulus is given.

The cell membrane is a very thin ($7$ to $15$ nm) lipoprotein complex that is essentially impermeable to intracellular protein and other organic anions ($A^-$). The membrane in the resting state is only slightly permeable to $Na^+$ and rather...
freely permeable to $K^+$ and $Cl^-$. The permeability of the resting membrane to potassium ion ($P_K$) is approximately 50 to 100 times larger than its permeability to sodium ion ($P_{Na}$).

Typically, the $K^+$ concentration of the internal medium (cytosol) is 140 mmol/liter, whereas that of the external (bathing) medium is 2.5 mmol/liter. The concentration difference creates a diffusion gradient that is directed outward across the membrane. The movement of the $K^+$ along this diffusion gradient (while the nondiffusible anion component stays within the cell) is in such a direction as to make the interior of the cell more negative relative to the external medium (that is, positive charge is removed from the interior). Consequently, a transmembrane potential difference is established. Electrically the membrane can be described as a leaky capacitor, since structurally it is comprised of a thin dielectric material (the lipoprotein complex) that acts as a charge separator, and yet it has transmembrane ion channels (pores) of different types, some of which allow a leakage flow of ions across the membrane at rest. The electric field supported by the membrane capacitor at rest is directed inward from positive to negative across the membrane. It tends to inhibit the outward flow of positively charged ions (such as $K^+$), as well as the inward flow of negatively charged ions (such as $Cl^-$). Thus the diffusional and electrical forces acting across the membrane are opposed to one another, and a balance is ultimately achieved. The membrane potential at which such an equilibrium occurs (considering $K^+$ to be the main ionic species involved in the resting state; that is, $P_K \gg P_{Na}$) is called the equilibrium potential for the $K^+$ ($E_K$). It is measured in volts and is calculated from the Nernst equation,

$$E_K = \frac{RT}{nF} \ln \left( \frac{[K]_o}{[K]_i} \right) = 0.0615 \log_{10} \left( \frac{[K]_o}{[K]_i} \right) \quad (V)$$

at 37 °C (body temperature). Here $n$ is the valence of the $K^+$, $[K]_i$ and $[K]_o$ are the intracellular and extracellular concentrations of $K^+$ in moles per liter, respectively, $R$ is the universal gas constant (Appendix), $T$ is absolute temperature in K, and $F$ is the Faraday constant (Appendix). Equation (4.1) provides a reasonably good approximation to the potential of the resting membrane, which indicates that the resting membrane is effectively a potassium membrane. A more accurate expression for the membrane equilibrium potential $E$, which accounts for the influence of other ionic species in the internal and external media was first developed by Goldman (1943) and later modified by Hodgkin and Katz (1949), who assumed a constant electric field across the membrane:

$$E = \frac{RT}{F} \ln \left\{ \frac{P_K[K]_o + P_{Na}[Na]_o + P_{Cl}[Cl]_o}{P_K[K]_i + P_{Na}[Na]_i + P_{Cl}[Cl]_o} \right\} \quad (4.2)$$

Here $E$ is the equilibrium transmembrane (resting) potential when net current through the membrane is zero and $P_M$ is the permeability coefficient of the
membrane for a particular ionic species M. It is called the Goldman–Hodgkin–Katz (GHK) formulation.

**EXAMPLE 4.1** For frog skeletal muscle, typical values for the intracellular and extracellular concentrations of the major ion species (in millimoles per liter) are as follows.

<table>
<thead>
<tr>
<th>Species</th>
<th>Intracellular</th>
<th>Extracellular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺</td>
<td>12</td>
<td>145</td>
</tr>
<tr>
<td>K⁺</td>
<td>155</td>
<td>4</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>4</td>
<td>120</td>
</tr>
</tbody>
</table>

Assuming room temperature (20°C) and typical values of permeability coefficient for frog skeletal muscle ($P_{Na} = 2 \times 10^{-8} \text{ cm/s}$, $P_{K} = 2 \times 10^{-6} \text{ cm/s}$, and $P_{Cl} = 4 \times 10^{-6} \text{ cm/s}$), calculate the equilibrium resting potential for this membrane, using the Goldman equation.

**ANSWER** From (4.2),

$$E = 0.0581 \log_{10} \left( \frac{P_{K}(4) + P_{Na}(145) + P_{Cl}(4)}{P_{K}(155) + P_{Na}(12) + P_{Cl}(120)} \right)$$

$$= 0.0581 \log_{10} \left( \frac{26.9 \times 10^{-6}}{790.24 \times 10^{-6}} \right) = -85.3 \text{ mV}$$

which is close to typical measured values for the resting membrane potential in frog skeletal muscle.

Maintaining the steady-state ionic imbalance between the internal and external media of the cell requires continuous active transport of ionic species against their electrochemical gradients. The active transport mechanism is located within the membrane and is referred to as the sodium–potassium pump. It actively transports Na⁺ out of the cell and K⁺ into the cell in the ratio 3Na⁺ : 2K⁺. The associated pump current $i_{NaK}$ is a net outward current that tends to increase the negativity of the intracellular potential. Energy for the pump is provided by a common source of cellular energy, adenosine triphosphate (ATP) produced by mitochondria in the cell.

Thus the factors influencing the flow of ions across the membrane are (1) diffusion gradients, (2) the inwardly directed electric field, (3) membrane structure (availability of pores), and (4) active transport of ions against an established electrochemical gradient. The charge separated by the cell membrane and the structure of this membrane ($P_{K}, P_{Na}, P_{Cl}$) account for the resting potential. K⁺ diffuses outwardly according to its concentration gradient, whereas the nondiffusible organic anion component remains within the cell, creating a potential difference across the membrane. Electroneutrality is maintained within the bulk internal and external media, but due to the membrane capacitance, there
is a monolayer of cations distributed on the outer membrane surface and a monolayer of anions along the inner surface. The number of ions responsible for the membrane potential, however, is very small relative to the total number present in the bulk media. The Na\(^+\) influx does not compensate for the K\(^+\) efflux because, in the resting state, \(P_{Na} \ll P_{K}\). Chloride ion diffuses inward down its concentration gradient, but its movement is balanced by the electrical gradient.

**EXAMPLE 4.2** The giant axon of the squid is frequently used in electrophysiological investigations because of its size. Typically it has a diameter of 1000 \(\mu\)m, a membrane thickness of 7.5 nm, a specific membrane capacity of 1 \(\mu\)F/cm\(^2\), and a resting transmembrane potential \(v_m\) of 70 mV. Assume a uniform field within the membrane and calculate the magnitude and direction of the electric field intensity \(E\) within the membrane.

**ANSWER** The membrane is quite thin, serves as a charge separator, and can be represented by a parallel-plate capacitor with \(E\) directed inward.

\[
E = \frac{v_m}{d} = \frac{70 \times 10^{-3}}{7.5 \times 10^{-9}} = 9.33 \times 10^6 \text{ V/m}
\]

**THE ACTIVE STATE**

Another property of an excitable cell is its ability to conduct an action potential [Figure 4.1(b)] when adequately stimulated. An *adequate stimulus* is one that brings about the depolarization of a cell membrane that is sufficient to exceed its threshold potential and thereby elicit an all-or-none action potential (brief transient disturbance of the membrane potential), which travels in an unattenuated fashion and at a constant conduction velocity along the membrane. Because of the steady resting potential, the cell membrane is said to be *polarized*. A lessening of the magnitude of this polarization is called *depolarization*, whereas an increase in magnitude is referred to as *hyperpolarization*. The all-or-none property of the action potential means that the membrane potential goes through a very characteristic cycle: a change in potential from the resting level of a certain amount for a fixed duration of time. For a nerve fiber, \(\Delta v \approx 120 \text{ mV}\) and the duration is approximately 1 ms. Further increases in intensity or duration of stimulus beyond that required for exceeding the threshold level produce only the same result.

The origin of the action potential lies in the voltage- and time-dependent nature of the membrane permeabilities (or equivalently, in electrical terms, membrane conductivities) to specific ions, notably Na\(^+\) and K\(^+\). As the *transmembrane potential* \((v_m)\) is depolarized, the membrane permeability to sodium \(P_{Na}\) (or, equivalently, the conductance of the membrane to sodium \(g_{Na}\)) is significantly increased. As a result, Na\(^+\) rushes into the internal medium of the cell, bringing about further depolarization, which in turn brings about a further increase in \(g_{Na}\) (i.e., \(g_{Na}\) is dependent on transmembrane potential). If the membrane potential threshold is exceeded, this process is self-regenerative.
and leads to runaway depolarization. Under these conditions, \( v_m \) tends to approach the equilibrium Nernst potential of sodium, \( E_{Na} \), which has a value of about +60 mV.

However, \( v_m \) never achieves this level because of two factors: (1) \( g_{Na} \) is not only voltage dependent but also time dependent, and (as shown in Figure 4.2) it is relatively short-lived compared with the action potential. (2) There is a delayed increase in \( g_K \) that acts as a hyperpolarizing influence, tending to restore \( v_m \) to resting levels (Figure 4.2). As \( v_m \) ultimately returns to the resting level, \( g_K \) is still elevated with respect to its resting value and returns slowly along an exponential time course. Since \( K^+ \) continue to leave the cell during this time, the membrane hyperpolarizes and an undershoot is produced in the transmembrane potential waveform (\( v_m \)).

The calculated \( g_{Na} \) and \( g_K \) waveforms of Figure 4.2 are based on voltage-clamp data from squid axon. In voltage-clamp experiments, transmembrane potential \( v_m \) is held at prescribed levels via a negative-feedback control circuit.
Membrane currents in response to step changes in $v_m$ are studied in order to determine the voltage- and time-dependent nature of $g_{Na}$ and $g_K$.

Figure 4.3 shows a network equivalent circuit describing the electrical behavior of a small unit area of membrane. The entire nerve axon membrane can be characterized in a distributed fashion by utilizing an iterative structure of this same basic form.

**EXAMPLE 4.3**

Suppose that the electrical properties of an elongated excitable cell of cylindrical geometry (such as a nerve or skeletal muscle fiber) can be modeled fairly accurately with a distributed parameter “cable” model such as that of Figure 4.3. What should the temporal-membrane potential response to brief square pulses of stimulating current look like at some fixed distance from a particular stimulating electrode? As the separation distance between the particular stimulating electrode and the exploring micropipette is progressively increased, in what manner should the amplitude of the subthreshold response change?

**ANSWER**

Figure 4.3 shows that each section of the distributed parameter model forms an $R–C$ low-pass filter. Multiple sections form multiple low-pass
filters. Thus the response due to the stimulating square-wave pulse is progressively smoothed and attenuated as the separation distance increases.

When an excitable membrane produces an action potential in response to an adequate stimulus, the ability of the membrane to respond to a second stimulus of any sort is markedly altered. During the initial portion of the action potential, the membrane cannot respond to any stimulus, no matter how intense. This interval is referred to as the absolute refractory period. It is followed by the relative refractory period, wherein an action potential can be elicited by an intense superthreshold stimulus (Figure 4.2). The existence of the refractory period produces an upper limit to the frequency at which an excitable cell may be repetitively discharged. For example, if a nerve axon has an absolute refractory period of 1 ms, it has an upper limit of repetitive discharge of less than 1000 impulses/s.

For an action potential propagating along a single unmyelinated nerve fiber, the region of the fiber undergoing a transition into the active state (the active region) at an instant of time is usually small relative to the length of the fiber. Figure 4.4(a) shows schematically the charge distribution along the fiber

![Figure 4.4](image-url)
in the vicinity of the active region. Note that the direction of propagation of the action potential (considered frozen in time) is to the left, and the membrane lying ahead of the active region is polarized, as in the resting state. A reversal of polarity is shown within the active region because of depolarization of the membrane to positive values of potential. The membrane lying behind the active zone is repolarized membrane.

From the indicated charge distribution, solenoidal (closed-path) current flows in the pattern shown in Figure 4.4(a). In the region ahead of the active zone, the ohmic potential drop across the membrane caused by this solenoidal current flowing outward through the membrane is of such a polarity as to reduce the magnitude of $v_m$, i.e., depolarize the membrane. When $v_m$ is depolarized to the threshold level (about 20 mV more positive than the resting potential), this region becomes activated as well. The same current pattern flowing behind the active region is ineffective in re-exciting the membrane, which is in the refractory state. The nature of this process is therefore self-excitatory, each new increment of membrane being brought to the threshold level by lines of current from the active source region. The membrane stays in the active state for only a brief period of time and ultimately repolarizes completely. In this way, the action potential propagates down the length of the fiber in an unattenuated fashion, the signal being built up at each point along the way.

Most neurons in invertebrates are unmyelinated, but most vertebrate neurons are myelinated. That is, the axon is insulated by a sheath of myelin, a lipoprotein complex formed from successive wrappings of the axon by a special support cell found along nerve fibers. In peripheral nerves—those that lie outside the central nervous system (CNS)—this support cell is known as a Schwann cell. In myelinated CNS neurons, this function is served by a special glial cell known as an oligodendroglialcyte. The myelin sheath is interrupted at regular intervals (1 to 2 mm, depending on the species) by nodes of Ranvier; a single Schwann cell thus provides the insulating myelin sheath covering of the axon between two successive nodes of Ranvier [Figure 4.4(b)]. The tightly wrapped membranes of the Schwann cell closely adhere to the axon membrane and increase its thickness by a factor of 100. This substantially decreases the capacitance of the modified membrane and increases the transverse impedance to current flow in the internodal region of the fiber. Sodium ion channels are distributed in a nonuniform manner in myelinated fibers, being densely clustered at the nodes of Ranvier and very sparsely distributed in the internodal region. Multiple types of potassium channels (fast-gated, slow-gated) are distributed in the paranodal regions lying adjacent to each node of Ranvier. These channels are distributed to a lesser extent throughout the remainder of the internodal region in both amphibian and mammalian species.

Once the myelinated nerve fiber is activated, conduction proceeds through a process of local circuit current flow, much as in the case of the unmyelinated nerve fiber described earlier [Figure 4.4(a)]. There are differences, however, in that the sources for action current flow are localized at the nodes of Ranvier and are therefore not uniformly distributed along the axonal membrane, as in
the case of the unmyelinated fiber. Myelination of the internode reduces leakage currents, decreases membrane capacitance, and improves the transmission properties of the cable-like myelinated fiber. Local circuit currents emanating from an active node have an exponentially diminishing magnitude over an axial distance spanning several internodal lengths. Accordingly, they contribute to a drop in nodal potential as current passes outward through a given inactive nodal membrane [Figure 4.4(b)].

Thus myelinated nerve fiber conduction proceeds via rapid, sequential activation of the nodes of Ranvier, and local circuit current provides the underlying mechanism for bringing the nodal membrane voltage to threshold. This process is frequently called *saltatory conduction* (from the Latin *saltare*, “to leap or dance”), because action potentials appear to leap from node to node. For an axon of a given diameter, myelination improves the conduction rate by a factor of approximately 20. By reason of its structure, the myelinated nerve fiber represents a more complicated bioelectric action current source than the unmyelinated nerve fiber. Mathematical modeling studies of conduction in both unmyelinated and myelinated nerve fibers have appeared in the literature (Moore *et al.*, 1978; Waxman and Brill, 1978; Halter and Clark, 1991; Moffit *et al.*, 2004).

### 4.2 Volume-Conductor Fields

A fundamental problem in electrophysiology is that of the single active cell immersed in a volume conductor (a salt solution simulating the composition of body fluids). A study of this simple problem lends considerable insight into other, more complex volume-conductor-field problems, including the ENG, EMG, and ECG.

The problem consists of two parts: (1) the bioelectric source and (2) its bathing medium or electrical load. The bioelectric source is the active cell, which behaves electrically as a constant-current source, delivering its solenoidal activation current to the resistive bathing medium over a large range of loading conditions. We consider the single active unmyelinated nerve fiber (bioelectric source) bathed by a volume conductor (specific resistivity $\rho$) whose dimensions are large relative to the spatial extent of the electric field surrounding the nerve fiber (infinite volume conductor). The lines of solenoidal current flow emanating from the active fiber into the bathing medium and returning to the fiber are indicated schematically in Figure 4.4(a). This pattern of current flow is consistent with the charge distribution shown in Figure 4.4(a).

We assume that the action potential travels down the fiber at a constant conduction velocity. Hence, the temporal waveform $v_m(t)$ can be converted easily to a spatial distribution $v_m(z)$, where $z$ is the axial distance along the fiber. For a simple monophasic action potential, the associated potential waveform at the outer surface of the membrane is (1) triphasic in nature,
(2) of greater spatial extent than the action potential, and (3) much smaller in peak-to-peak magnitude. The magnitude of the field potential in a large bathing medium falls off exponentially with increasing radial distance from the active fiber (potential zero within fifteen fiber radii). Field potential magnitude at the fiber surface depends on the amount of active cell membrane surface area (bioelectric source) contributing to the signal and is usually on the order of tens of microvolts (µV).

Changes in the properties of the volume conductor can also have an effect on the field potential magnitude. If its specific resistivity (ρ) is increased, the magnitude of the field potential measured at the outer membrane surface increases, as it would if the volume conductor is made smaller. In each case, the extracellular load resistance to current flow from the constant action current generator (membrane) is greater. From Ohm’s law, potential is increased [by changing material properties of volume conductor (ρ) or its dimensions].

If instead, we consider the source to be an active nerve trunk with its thousands of component nerve fibers simultaneously activated, the extracellular field potential recorded in an infinite homogeneous bathing medium can appear quite similar to the triphasic response of the single fiber [Figure 4.5(b)].

![Figure 4.5](image)

**Figure 4.5** Extracellular field potentials (average of 128 responses) were recorded at the surface of an active (1 mm-diameter) frog sciatic nerve in an extensive volume conductor. The potential was recorded with (a) both motor and sensory components excited (Sm+Ss), (b) only motor nerve components excited (Sm), and (c) only sensory nerve components excited (Ss).
Here, the extracellular field potential is formed from the superimposed electric fields of individual active fibers within the nerve trunk. The extracellular potential recorded at a field point in the volume conductor is triphasic, low-microvolt range in amplitude, and it diminishes in amplitude and high-frequency content as field point is moved to larger radial distances from the surface of the trunk. The frog sciatic nerve utilized in this experiment is a rather complex bioelectric source, consisting of large diameter motor fibers running from the spinal cord to the leg muscles, as well as large and small sensory fibers running from sensory receptors in the leg and skin to the spinal cord. In Figure 4.5(a), the entire nerve trunk (containing both motor and sensory fibers of different diameters) was simultaneously excited by a brief suprathreshold electric stimulus.

It is possible, however, to excite the motor and sensory components of the trunk separately by isolating the nerve trunk in the vicinity of the spinal cord. Here the nerve trunk divides into a sensory branch (the dorsal root) and a motor branch (the ventral root). The results of separate motor and sensory stimulation are shown in Figure 4.5(b) and (c). Stimulation of the many large-diameter motor fibers in the trunk provides the largest extracellular response (largest active membrane surface area), whereas stimulation of the sensory root excites at least two groups of sensory fibers—a group of larger, fast conducting fibers (group I) and a group of smaller, slower fibers (group II). Observing the extracellular waveform produced by combined stimulation [Figure 4.5(a)], we can see the approximate superposition of motor and sensory responses.

The volume-conductor load of the active nerve trunk can also be altered and made more complicated. A relatively simple variation is to increase the $\rho$ of the bathing medium or decrease the radial extent of the volume conductor, or both. These alterations produce larger extracellular potentials due to the constant nature of the bioelectric current source. Ultimately, the volume-conductor load can consist of a nonhomogeneous multilayered conducting medium containing skeletal muscle, blood vessels and bone (leg or arm).
Current flow patterns are altered in this case due to regional differences in specific resistivity (e.g., bone and blood) and skeletal muscle fiber orientation. Skeletal muscle constitutes an anisotropic conducting medium (specific resistivity different in each coordinate direction) and exhibits preferential conduction in the direction of fiber orientation. Regardless, homogeneous volume-conductor models using bulk anisotropic properties of the passive conducting medium can serve as useful approximations to the field potential distribution in such media, lending insight into the interpretation of recorded waveforms.

The foregoing discussion may be considered an explanation of the electrogenesis of the ENG, which is commonly recorded from the surface of an arm, a leg, or the face. The concepts introduced here apply directly to the interpretation of many bioelectric phenomena including those associated with the nervous system (e.g., evoked potential recordings from fiber tracts in the spinal cord and sensory centers in the brain), as well as active skeletal muscle (EMG), cardiac muscle (ECG), and smooth muscle (EGG).

### 4.3 FUNCTIONAL ORGANIZATION OF THE PERIPHERAL NERVOUS SYSTEM

#### THE REFLEX ARC

The spinal nervous system is functionally organized on the basis of what is commonly called the reflex arc [Figure 4.6(a)]. The components of this arc are as follows:

1. A **sense organ**, consisting of many individual sense receptors that respond preferentially to an environmental stimulus of a particular kind, such as pressure, temperature, touch, or pain.
2. A **sensory nerve**, containing many individual nerve fibers that perform the task of transmitting information (encoded in the form of action potential frequency) from a peripheral sense receptor to other cells lying within the central system (brain and spinal cord).
3. The **CNS**, which in this case serves as a central integrating station. Here information is evaluated, and, if warranted, a “motor” decision is implemented. That is, action potentials are initiated in motor-nerve fibers associated with the motor-nerve trunk.
4. A **motor nerve**, serving as a communication link between the CNS and peripheral muscle.
5. The **effector organ**, which consists, in this case, of skeletal muscle fibers that contract (shorten) in response to the driving stimuli (action potentials) conducted by motor-nerve fibers.

The simplest example of the behavior of the reflex arc is the knee-jerk reflex, in which the patellar tendon below the knee is given a slight tap that stretches...
specialized length receptors, called muscle spindles, within the muscle and subsequently excites them. This excitation results in action potentials that propagate along the sensory nerve that enters the spinal cord and communicates with CNS cells, specifically motoneurons. The resultant motor activity reflexly brings about contraction of the muscle that was initially stimulated, and the shortening muscle jerks the limb, producing the well-known knee-jerk response. Note that the initial stimulus to the muscle was a stretch, whereas the response was a contraction of the muscle. This simple reflex arc has many of the features of a negative-feedback loop, in which the control variable is muscle length [Figure 4.6(b)]. The CNS acts as the controller, the muscle spindle as a feedback length sensor, and the muscle–limb system as the process to be controlled.

JUNCTIONAL TRANSMISSION

Within the reflex arc there are intercommunicating links between neurons (neuro–neuro junctions) called synapses, as well as communicating links between neurons and muscle fibers called neuromuscular junctions. These occur at small, specialized regions of the muscle fiber referred to as an end-plate regions. The junctional transmission process in each of these cases is electrochemical in nature. There is a prejunctional fiber involved in the
neuromuscular junction that, when depolarized, releases a neurotransmitter substance acetylcholine (ACh), which diffuses across a very small fluid-filled gap region approximately 20 nm in thickness. The fluid filling the gap is assumed to be ordinary interstitial body fluid. Once ACh reaches the postjunctional membrane, it combines with a membrane receptor complex that activates an ion channel, which leads to a relatively brief transient depolarization of the postjunctional membrane and subsequently to the initiation of an action potential that propagates away from the junctional region. The electrochemical transmission process at the junction involves a time delay on the order of 0.5 to 1.0 ms. More detailed descriptions of interneuronal and neuromuscular transmission are available in general physiology texts (e.g., Levitan and Kaczmarek, 2002).

Another time delay associated with the neuromuscular system is the delay between electrical activation of the musculature and the onset of mechanical contraction. This delay, which is referred to as excitation–contraction time, is a property of the muscle itself. When the muscle is repeatedly stimulated, the mechanical response summates. At high stimulation rates, the mechanical responses fuse into one continuous contraction called a tetanus (or tetanic contraction).

### 4.4 THE ELECTRONEUROGRAM

Conduction velocity in a peripheral nerve is measured by stimulating a motor nerve at two points a known distance apart along its course. Subtraction of the shorter latency from the longer latency (Figure 4.7) gives the conduction time

![Figure 4.7](image_url)

**Figure 4.7** Measurement of neural conduction velocity via measurement of latency of evoked electrical response in muscle. The nerve was stimulated at two different sites a known distance $D$ apart.
along the segment of nerve between the stimulating electrodes. Knowing the separation distance, we can determine the conduction velocity of the nerve, which has potential clinical value since, e.g., conduction velocity in a regenerating nerve fiber is slowed following nerve injury (Sinkjaer et al., 2006). Skeletal muscle fibers (70 μm diameter) are much larger than myelinated nerve fibers (2 to 20 μm); hence the amplitude of field potentials recorded from active nerve trunks are much smaller than field potentials recorded from groups of active muscle fibers (larger active membrane surface area). Such potentials can be recorded with either concentric needle electrodes or surface electrodes (Chap. 5). Nerve field potentials can also be evoked by applying stimuli to “mixed” nerves that contain both motor and sensory components (such as the ulnar nerve of the arm), in which case the resultant field potentials are derived from both types of active fibers. However, field potentials can also be elicited from purely sensory nerves (e.g., the sural nerve in the leg) or from sensory components of a mixed nerve, wherein stimulation is applied in a manner that does not excite the motor components of the nerve. In general, the study of evoked field potentials from sensory nerves has been shown to be of considerable value in diagnosing peripheral nerve disorders.

Although measurements of conduction velocity and latency are most useful in the assessment of peripheral nerve function, the characteristics of the field potentials evoked in muscle, as stimulated by its active motor nerve, are also important. When considering evoked muscle potentials, the duration of the response is frequently of interest, since slowed conduction in a few motor nerve fibers may lead to late activation of a portion of the muscle. The integrated field potential thus recorded may appear prolonged and polyphasic. If the component motor fibers of the muscle have a uniform conduction velocity, there will be a superposition of the recorded field potentials resulting in a larger amplitude, shorter duration triphasic response. Slowed conduction in some of the motor fibers may lead to partial fractionation of the integrated field potential waveform with a decrease in its magnitude and a broadening of its duration.

**FIELD POTENTIALS OF SENSORY NERVES**

Extracellular field responses from sensory nerves can be easily measured from the median or ulnar nerves of the arm by using ring-stimulating electrodes applied to the fingers (Figure 4.8). Recording at two sites a known distance apart along the course of the nerve enables one to compute the conduction velocity of the sensory nerve. In the case of the ulnar nerve (roughly, it supplies the third and fourth fingers), evoked neural potentials can be recorded from different sites along the course of the nerve as high as the armpit. In the case of the median nerve (roughly, it supplies the index and the second fingers), field potentials can be recorded from the nerve at and above the elbow.

Long pulses cause muscle contractions, limb movement, and undesired signals (*artifacts*). These are avoided by positioning the limb in a comfortable, relaxed posture and applying a brief, intense stimulus (square pulse of approximately 100 V amplitude with a duration of 100 to 300 μs). Such a
stimulus excites the large, rapidly conducting sensory nerve fibers but not small pain fibers or surrounding muscle. To minimize artifacts caused by stimuli, we use a stimulus isolation unit (isolation transformer, diode-bridge circuit, optical coupler, and so on) to isolate the bipolar stimulating electrodes from ground. A patient ground is placed at the wrist between the stimulating and recording electrodes to provide a ground point for the passive electric field coupling from the stimulating electrodes. The skin should be abraded under both the stimulating and recording electrodes (Section 5.5) to reduce skin resistance and ensure good contact.

Clinically, field potentials are recorded using high-gain, high-input-impedance differential preamplifiers with good common-mode rejection capability and low inherent amplifier noise (Section 6.5). Figure 4.8 shows that the measured ENGs are on the order of 10 μV, and power-line interference is sometimes a problem even with good amplifier common-mode properties. The input leads should be properly twisted together and shielded. In addition, if warranted, the subject could be placed in an adequately shielded room or cage.

A further step we can use to enhance the signal-to-noise ratio in the presence of random noise (for the most part generated by the amplifier) is to use a signal averager (Section 6.8).

**MOTOR-NERVE CONDUCTION VELOCITY**

*In vivo* measurement of the conduction velocity of a motor nerve may be obtained as shown in Figure 4.7. For example, the peroneal nerve of the left leg may be stimulated first behind the knee and second behind the ankle. A
muscular response is obtained from the side of the foot, using surface or needle electrodes.

**REFLEXLY EVOKED FIELD POTENTIALS**

When a peripheral nerve is stimulated and an evoked field potential is recorded in the muscle it supplies, it is sometimes possible to record a second potential that occurs later than the initial response. As the neural stimulus site is brought progressively closer to the muscle, the latency of the first response decreases, whereas the latency of the second response is increased. This behavior of the second response indicates that to activate the muscle, the stimulus must travel along the nerve toward the central nervous system (proximally) for some distance before ultimately traveling in the opposite direction (distally). The latency of the second response is such that the activity could have traveled proximally along sensory nerves as far as the spinal cord to elicit a spinal reflex.

If the posterior tibial nerve in the leg is stimulated, a late potential can be evoked from the triceps sural muscle (Figure 4.9). This long latency response has a low threshold and appears at stimulus intensities that are well below the levels required to elicit the conventional (short-latency) M wave. This long-latency potential—known as the H wave—was discovered by Hoffman (Figure 4.9). Its latency indicates that it is a spinal reflex. It is, in fact, the electrical homolog of the simple “ankle-jerk” reflex.

Thus, when a mixed peripheral nerve such as the posterior tibial nerve is stimulated by a stimulus of low intensity, only fibers of large diameter are stimulated because they have the lowest threshold. These large fibers are sensory.

![Figure 4.9 The H reflex](image)

The four traces show potentials evoked by stimulation of the medial popliteal nerve with pulses of increasing magnitude (the stimulus artifact increases with stimulus magnitude). The later potential or H wave is a low-threshold response, maximally evoked by a stimulus too weak to evoke the muscular response (M wave). As the M wave increases in magnitude, the H wave diminishes. (From J. A. R. Lenman and A. E. Ritchie, *Clinical Electromyography*, 2nd ed., Philadelphia: Lippincott, 1977; reproduced by permission of the authors.)
fibers from muscle spindles that conduct toward the CNS and ultimately connect with motor fibers in the spinal cord via a single synapse. The motoneurons discharge and produce a response in the gastrocnemius muscle of the leg (the H wave). With a stimulus of medium intensity, smaller motor fibers in the mixed nerve are stimulated in addition to the sensory fibers, producing a direct, short-latency muscle response, the M wave (Figure 4.9). With still stronger stimuli, impulses conducted centrally along the motor fibers may interfere with the production of the H wave (these excited motor fibers are in their refractory period) so that only an M wave is produced (Figure 4.9). The amplitude of the H response depends on the number of motoneurons discharged. Its amplitude is also somewhat variable as a result of fluctuating background neural conditions within the spinal cord. These neural disturbances are provided by the activity of other spinal and higher center neurons impinging on the motoneuron(s) involved in the reflex.

4.5 THE ELECTROMYOGRAM

Skeletal muscle is organized functionally on the basis of the motor unit (see Figure 4.10), which consists of a single motor nerve fiber and the bundle of

![Diagram of a single motor unit (SMU) (Figure 4.10)](image)

Figure 4.10  Diagram of a single motor unit (SMU), which consists of a single motoneuron and the group of skeletal muscle fibers that it innervates. Length transducers [muscle spindles, Figure 4.6(a)] in the muscle activate sensory nerve fibers whose cell bodies are located in the dorsal root ganglion. These bipolar neurons send axonal projections to the spinal cord that divide into a descending and an ascending branch. The descending branch enters into a simple reflex arc with the motor neuron, whereas the ascending branch conveys information regarding current muscle length to higher centers in the CNS via ascending nerve fiber tracts in the spinal cord and brain stem. These ascending pathways are discussed in Section 4.8.
muscle fibers to which it is attached. The motor unit is the smallest unit that can be activated by a volitional effort, in which case all constituent muscle fibers are activated synchronously. The component fibers of the motor unit extend lengthwise in loose bundles along the muscle. In cross section, however, the fibers of a given motor unit are interspersed with fibers of other motor units. Thus, the active muscle fibers of the single motor unit (SMU) constitute a distributed bioelectric source located in a volume conductor that consists of all other fibers within the muscle (active and inactive), blood vessels and connective tissue. The evoked field potential from the active fibers of an SMU has a triphasic form of brief duration (3 to 15 ms) and an amplitude of 20 to 2000 μV, depending on the size of the motor unit. The frequency of discharge usually varies from 6 to 30 per second (De Luca, 2006).

One of the disadvantages of recording the EMG by using the convenient surface electrodes is that they can be used only with superficial muscles and are sensitive to electrical activity over too wide an area. Various types of monopolar, bipolar, and multipolar insertion-type electrodes are commonly used in electromyography for recording from deep muscles and from SMUs. These types of electrodes generally record local activity from small regions within the muscle in which they are inserted. Often a simple fine-tipped monopolar needle electrode can be used to record SMU field potentials even during powerful voluntary contractions. Bipolar recordings are also employed. Various types of electrodes are discussed in Chapter 5.

Figure 4.11 shows motor unit potentials from the normal dorsal interosseus muscle under graded levels of contraction. At high levels of effort, many superimposed motor unit responses give rise to a complicated response (the interference pattern) in which individual units can no longer be distinguished. In interpreting Figure 4.11, note that when a muscle contracts progressively under volition, active motor units increase their rate of firing and new (previously inactive) motor units are also recruited.

The shape of SMU potentials is considerably modified by disease. In peripheral neuropathies, partial denervation of the muscle frequently occurs and is followed by regeneration. Regenerating nerve fibers conduct more slowly than healthy axons. In addition, in many forms of peripheral neuropathy, the excitability of the neurons is changed and there is widespread slowing of nerve conduction. One effect of this is that neural impulses are more difficult to initiate and take longer in transit to the muscle, generally causing scatter or desynchronization in the EMG pattern.

A number of mathematical modeling studies of single-fiber and multiple-fiber (single motor unit) action potentials have appeared in the literature (Nandedkar et al., 1985; Ganapathy et al., 1987), as well as detailed volume-conductor-based simulations of surface EMG signals (Duchêne and Hogrel, 2000; Farina et al., 2004). Signal processing methods have been
employed in the analysis of surface EMGs and SMU signals (Reucher et al., 1987; Farina et al., 2003), as have automatic techniques for the detection, decomposition, and analysis of EMG signals (Mambrito and De Luca, 1984; Stashuk 2001).
ANATOMY AND FUNCTION OF THE HEART

The heart serves as a four-chambered pump for the circulatory system (Figure 4.12). Its main pumping function is supplied by the ventricles. The atria are merely antechambers to store blood during the time the ventricles are pumping. The resting or filling phase of the heart cycle is referred to as diastole, whereas the contractile or pumping phase is called systole. The smooth, rhythmic contraction of the atria and ventricles has an underlying electrical precursor in the form of a well-coordinated series of electrical events that takes place within the heart. That this set of electrical events is intrinsic to the heart itself is well demonstrated when the heart (particularly that of cold-blooded vertebrates such as the frog or turtle) is removed from the body and placed in a nutrient medium (such as glucose-Ringer solution). The heart continues to beat rhythmically for many hours. Thus, the coordinated contraction of the atria and ventricles is set up by a specific pattern of electrical activation in the musculature of these structures. In humans, these electrical activation patterns in the walls of the atria and ventricles are initiated by a coordinated series of events within the specialized conduction system of the heart (Figure 4.12).

In relation to the heart as a whole, the specialized conduction system is very small and constitutes only a minute portion of the total mass of the heart. The wall of the left ventricle (Figure 4.12) is 2.5 to 3.0 times as thick as the right ventricular wall, and the intraventricular septum is nearly as thick as the left ventricular wall. Thus, the major portion of the muscle mass of the ventricles consists of the free walls of the right and left ventricles and the septum. Considering the heart as a bioelectric source, the source strength at each instant can be expected to be directly related to the active muscle mass at that moment (i.e., to the number of active myocardial cells). Hence, the active free walls of the atria and ventricles and the interventricular septum can be considered the major action current sources responsible for the production of external field potentials recorded from the heart (e.g., recorded within the thoracic volume-conductor medium or at the surface of the body).

ELECTRICAL BEHAVIOR OF CARDIAC CELLS

The heart comprises several different types of tissues (SA and AV nodal tissue; atrial, Purkinje, and ventricular tissue). Representative cells of each type of tissue differ anatomically to a considerable degree. They are all electrically excitable, and each type of cell exhibits its own characteristic action potential (Figure 4.13).

THE VENTRICULAR CELL

The ventricular myocardium is composed of millions of individual cardiac cells (15 × 15 × 150 μm long). Figure 4.14 is a drawing of a small section of cardiac muscle as seen under light microscopy. The individual cells are relatively long.
and thin, and although they run generally parallel to one another, there is considerable branching and interconnecting (anastomosing). The cells are surrounded by a plasma membrane that makes end-to-end contact with adjacent cells at a dense structure known as the **intercalated disk**.
Each fiber contains many contractile myofibrils that follow the axis of the cell from one end (intercalated disk) to the other. These myofibrils constitute the “contractile machinery” of the fiber. The component cells of cardiac tissue are in intimate contact at the intercalated disks, both electrically and mechanically, so the heart muscle functions as a unit (a functional syncytium).

Prior to excitation, the typical ventricular cell has a resting potential of approximately $-85\text{ mV}$. The initial rapid depolarization phase has a rate of rise that is usually greater than 150 V/s. This phase is followed by an initial rapid repolarization that leads to a maintaineddepolarizing plateau region lasting approximately 200 to 300 ms. A final repolarization phase restores membrane potential to the resting level and is maintained for the remainder of the cardiac cycle.

Figure 4.13 Represente the electric activity from various regions of the heart
The bottom trace is a scalar ECG, which has a typical QRS amplitude of 1 to 3 mV. (Copyright © 1969 CIBA Pharmaceutical Company, Division of CIBA-GEIGY Corp. Reproduced, with permission, from The Ciba Collection of Medical Illustrations, Frank H. Netter, M.D. All rights reserved.)

(Figure 4.14). Each fiber contains many contractile myofibrils that follow the axis of the cell from one end (intercalated disk) to the other. These myofibrils constitute the “contractile machinery” of the fiber. The component cells of cardiac tissue are in intimate contact at the intercalated disks, both electrically and mechanically, so the heart muscle functions as a unit (a functional syncytium).

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Figure 4.14 The cellular architecture of myocardial fibers
Note the centroid nuclei and transverse intercalated disks between cells.
cycle. The duration of the action potential waveform is collectively referred to as electrical systole; the resting phase is referred to as electrical diastole.

Most models of membrane excitability that have been used in cardiac electrophysiology are of the Hodgkin–Huxley (HH) type (Hodgkin and Huxley, 1952). The HH formalism was first applied to Purkinje fibers of the specialized conduction system by Noble (1962). This model was later extensively revised by McAllister et al. (1975), and variations have been used in simulations of the electrophysiological responses of ventricular (Beeler and Reuter, 1977) and SA pacemaker cells (Yanagihara et al., 1980). These models however, were based on multicellular voltage clamp data that was approximate and contained experimental error. The discovery of (1) enzymatic dispersion techniques suitable for the production of isolated cardiac cells and (2) patch clamp electrode techniques made quantitative whole-cell voltage clamping of individual cells possible (early 1980s). Current–voltage characteristics of different types of ion channels could now be measured accurately and by the 1990s several good mathematical models of different cardiac cell types were available. Importantly, these models contained descriptions for ion pumps (e.g., Na\(^+\)/K\(^+\) ATPase, Ca\(^{2+}\) ATPase) and exchangers (e.g., Na\(^{+}\)–Ca\(^{2+}\), Na\(^{+}\)–H\(^+\) exchangers), as well as, better fluid compartment models describing ionic content of the internal medium, the sarcoplasmic reticulum (SR), and extracellular restricted diffusion spaces in the intra- and extracellular media. The seminal model initiating these extensive changes in cardiac cell modeling was the Purkinje fiber model developed by DiFrancesco and Noble (1985). It still utilized some ion channel data derived from multicellular voltage clamp experiments, but nevertheless pointed the way to the development of modern day cardiac cell models for all cell types: SA node (Wilders et al., 1991; Demir et al., 1994); atrial cell (Nygren et al., 1998); ventricular cell (Luo and Rudy, 1994; Puglisi and Bers, 2001).

VENTRICULAR ACTIVATION

Investigators have conducted studies of ventricular activation on experimental animals using multiple “plunge-type” electrodes inserted into many sites in the heart (Spach et al., 1972) (see Figure 4.15). The time of arrival of electrical activation is noted, and isochronous (synchronously excited) excitation surfaces can be mapped. Figure 4.15 shows a plot of isochronous lines of activation for the perfused heart of a human who died from a noncardiac condition. Note that activation first takes place on the septal surface of the left ventricle (5 ms into the QRS complex) and that the activity spreads with increasing time in a direction from left to right across the septum. At 20 ms, several regions of the right and left ventricles are simultaneously active. As time increases, excitation spreads and tends to become more confluent. For example, at 30 ms a nearly closed activation surface is seen. Excitation then proceeds in a relatively uniform fashion in an epicardial (outside the heart) direction. The apex of the heart is activated roughly in the period 30 to 40 ms, along with other sites on the right and left ventricular walls where “breakthrough” of activation has occurred. From both Figure 4.15 and data taken in other planes, we can see that the posterior-basal region of the heart is the last region activated.
The isochronous electromotive surface propagates through the myocardium in an outward direction from the endocardium (the inside of the heart). The seat of this electromotive surface is, of course, the individual cardiac cell. In a localized region of the heart, however, many of these cells are active simultaneously because of the high degree of electrical interaction between cells. The anatomical substrate for this electrical interaction is the high degree of branching of individual cardiac cells and the low resistance of the intercalated disks at the junctions between cells (Barr et al., 1965).

**Figure 4.15 Isochronous lines of ventricular activation of the human heart**


The isochronous electromotive surface propagates through the myocardium in an outward direction from the endocardium (the inside of the heart). The seat of this electromotive surface is, of course, the individual cardiac cell. In a localized region of the heart, however, many of these cells are active simultaneously because of the high degree of electrical interaction between cells. The anatomical substrate for this electrical interaction is the high degree of branching of individual cardiac cells and the low resistance of the intercalated disks at the junctions between cells (Barr et al., 1965).

**BODY-SURFACE POTENTIALS**

The preceding section dealt with the sequence of events involved in electrical activation of the ventricle. This activation sequence leads to the production of closed-line action currents that flow in the thoracic volume conductor (considered a purely passive medium containing no electric sources or sinks). Potentials measured at the outer surface of this medium—that is, on the body surface—are referred to as electrocardiograms (ECGs).

In the electrocardiographic problem, the heart is viewed as an electrical equivalent generator. A common assumption is that, at each instant of time in the sequence of ventricular activation, the electrical activity of the heart can be represented by a net equivalent current dipole located at a point that we call
the electrical center of the heart. This center is assumed to lie within the anatomical boundaries of the heart. The magnitude and orientation of the net equivalent dipole can change with time.

Figure 4.15 shows that several regions of both ventricles may be active simultaneously. Considering time frozen, we represent the electrical activity of each active region as a local current dipole and calculate a net equivalent dipole from this distribution at the electrical center. In the next instant, new areas can activate, others de-activate, and local current strengths change according to the active muscle mass. We calculate another net dipole equivalent at the electrical center and proceed. This approach can be applied to the analysis since the volume-conductor-field problem has been shown to be quasistatic (Plonsey, 1969). The thoracic medium can be considered the resistive load of this equivalent cardiac generator. With cardiac activity, a field potential distribution is set up in the thoracic volume conductor where the magnitude of potential decreases with increasing distance from the source. Ohmic potential drops can be measured between surface points (e.g., between points A and B in Figure 4.16) or between a single surface point and an assigned reference point. The general volume-conductor problem is illustrated in a highly schematic fashion in Figure 4.16 in terms of current source and lumped resistive load.

A scalar “lead” gives the magnitude of a single body-surface potential difference plotted versus time. Figure 4.13 (bottom) shows a typical scalar electrocardiographic lead, where the significant features of the waveform are the (1) individual waves (P, Q, R, S, and T), (2) wave durations, and (3) specific time intervals (e.g., the P–R, S–T, and Q–T intervals). This figure also shows the temporal relationship between single transmembrane cellular activities in

![Figure 4.16 The electrocardiographic problem](image)

Points A and B are arbitrary observation points on the torso, \( R_{AB} \) is the resistance between them, and \( R_{T1}, R_{T2} \) are lumped thoracic medium resistances. The bipolar ECG scalar lead voltage \( \Phi_{AB} = \Phi_A - \Phi_B \), where these voltages are both measured with respect to an indifferent reference potential.
various regions of the heart (atria, ventricles, and specialized conduction system) and this typical ECG waveform.

Clearly the P wave is produced by atrial depolarization, the QRS complex primarily by ventricular depolarization, and the T wave by ventricular repolarization. The manifestations of atrial repolarization are normally masked by the QRS complex. The P–R and S–T intervals are normally at zero potential, the P–R interval being caused mainly by conduction delay in the AV node. The S–T segment is related to the average duration of the plateau regions of individual ventricular cells. A small additional wave, called the U wave, is sometimes recorded temporally after the T wave. It is not always present and is believed to be the result of slow repolarization of ventricular papillary muscles.

Section 6.2 describes the 12 standard leads that constitute a diagnostic ECG, so they will not be considered further here.

NORMAL AND ABNORMAL CARDIAC RHYTHMS

Each beat of the normal human heart originates in the SA node. The normal heart rate is approximately 70 beats per minute (bpm). The rate is slowed (bradycardia) during sleep and is accelerated (tachycardia) by emotion, exercise, fever, and many other stimuli. Detailed aspects of the control that the nervous system has over heart rate are beyond the scope of this book; the reader interested in further discussion is referred to Rowell (1993). Because many parts of the heart possess an inherent rhythmicity (e.g., nodal tissue, Purkinje fibers of the specialized conduction system, and atrial tissues), any part under abnormal conditions can become the dominant cardiac pacemaker. This can happen when the activity of the SA node is depressed, when the bundle of His is interrupted or damaged, or when an abnormal (ectopic) focus or site in the atria or in specialized conduction-system tissue in the ventricles discharges at a rate faster than the SA node.

When the bundle of His is interrupted completely, the ventricles beat at their own slow inherent rate (the idioventricular rhythm). The atria continue to beat independently at the normal sinus rate, and complete or third-degree block is said to occur [Figure 4.17(a)]. The idioventricular rate in human beings is approximately 30 to 45 bpm.

When the His bundle is not completely interrupted, incomplete heart block is present. In the case of first-degree heart block, all atrial impulses reach the ventricles, but the P–R interval is abnormally prolonged because of an increase in transmission time through the affected region [Figure 4.17(b)]. In the case of second-degree heart block, not all atrial impulses are conducted to the ventricles. There may be, for example, one ventricular beat every second or third atrial beat (2:1 block, 3:1 block, and so on).

In another form of incomplete heart block involving the AV node, the P–R interval progressively lengthens until the atrial impulse fails to conduct to the ventricle (Wenckebach phenomenon). The first conducted beat after the pause (or dropped beat) has a shorter P–R interval (sometimes of normal length) than any subsequent P–R interval. Then the process of the lengthening of the P–R interval begins anew, progressing over several cardiac cycles until another
beat is dropped. The electrocardiographic sequence starting with the ventricular pause and ending with the next blocked atrial beat constitutes a Wenckebach period. The ratio of the number of P waves to QRS complexes determines the block (for example, 6:5 or 5:4 Wenckebach periods).

When one branch of the bundle of His is interrupted, causing right- or left-bundle-branch block, excitation proceeds normally down the intact bundle and then sweeps back through the musculature to activate the ventricle on the blocked side. The ventricular rate is normal, but the QRS complexes are prolonged and deformed.

**ARRHYTHMIAS**

A portion of the myocardium (or the AV node or specialized conduction system) sometimes becomes “irritable” and discharges independently. This site is then referred to as an ectopic focus. If the focus discharges only once, the result is a beat that occurs before the next expected normal beat, and the

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**Figure 4.17  Atrioventricular block**  (a) Complete heart block. Cells in the AV node are dead and activity cannot pass from atria to ventricles. Atria and ventricles beat independently, ventricles being driven by an ectopic (other-than-normal) pacemaker. (b) AV block wherein the node is diseased (examples include rheumatic heart disease and viral infections of the heart). Although each wave from the atria reaches the ventricles, the AV nodal delay is greatly increased. This is first-degree heart block. (Adapted from Brendan Phibbs, The Human Heart, 3rd ed., St. Louis: The C.V. Mosby Company, 1975.)
cardiac rhythm is therefore transiently interrupted. (With respect to atrial, nodal, or ventricular ectopic beat, see Figure 4.18.) If the focus discharges repetitively at a rate that exceeds that of the SA node, it produces rapid regular tachycardia. [With respect to atrial, nodal, or ventricular paroxysmal tachycardia or atrial flutter, see Figure 4.19(a) and (b).] A rapidly and irregularly discharging focus or, more likely, a group of foci in the atria or ventricles may

Figure 4.18  Normal ECG followed by an ectopic beat  An irritable focus, or ectopic pacemaker, within the ventricle or specialized conduction system may discharge, producing an extra beat, or extrasystole, that interrupts the normal rhythm. This extrasystole is also referred to as a premature ventricular contraction (PVC). (Adapted from Brendan Phibbs, The Human Heart, 3rd ed., St. Louis: The C.V. Mosby Company, 1975.)

Figure 4.19  (a) Paroxysmal tachycardia. An ectopic focus may repetitively discharge at a rapid regular rate for minutes, hours, or even days. (b) Atrial flutter. The atria begin a very rapid, perfectly regular “flapping” movement, beating at rates of 200 to 300 bpm. (Adapted from Brendan Phibbs, The Human Heart, 3rd ed., St. Louis: The C.V. Mosby Company, 1975.)
be the underlying mechanism responsible for atrial or ventricular fibrillation [Figure 4.20(a) and (b)].

EXAMPLE 4.4 Premature ventricular contractions can be identified because (1) they arrive early, (2) the following beat occurs at the normal time, because it is generated by the SA node, and (3) the QRS width is greater than the normal 80 ms. Describe a software algorithm to detect and count PVCs by using all these criteria.

ANSWER There will be slight variations in width and R–R interval of QRS complexes. A PVC is wide. Use unfiltered ECG to determine average width (\( AW = \text{average of 10} \)). The algorithm should test that width \( W_t > 1.3AW_{t-1} \). Use narrowband filter plus threshold to determine time of each R wave. Determine average R–R interval (\( AR = \text{average of 10} \)). A PVC occurs early. The algorithm should test that the \( R–R_{t-1} \) interval < 0.8 \( AR–R_{t-2} \). A PVC is followed by a compensatory pause. The algorithm should test that \( R–R_{t-1} + R–R_t \) is approximately \( 2(AR–R_{t-2}) \). All three tests should be positive to yield a PVC.

Rhythm disturbances can arise from sources other than ectopic foci or competing pacemakers. A feasible alternative is a circus re-excitation or
re-entrant mechanism (Allessie et al., 1973). This concept assumes a region of depressed conductivity within the atrium, Purkinje system, or ventricle. It is therefore ischemic (deficient in its blood supply) relative to surrounding normal tissue. This brings about pronounced electrophysiological changes in the ischemic zone and a decreased velocity of conduction (see Figure 4.21).

Propagation in this area is slow enough to permit other areas to recover from initial excitation and be re-entered by the slowly emerging impulse. The re-entrant impulse may in turn re-excite the area of slow conduction to complete a circus-movement loop. Intermittent establishment of a re-entrant circuit would result in occasional ectopic beats (extrasystoles), and continuous propagation of impulses in the established circuit would underlie an episode of tachyarrhythmia.

**ALTERATION OF POTENTIAL WAVEFORMS IN ISCHEMIA**

Of particular interest in Figure 4.21 is the change in the intracellular and extracellular potential waveforms in ischemia. Note particularly that in late ischemia (ischemia that occurs several minutes after induced coronary occlusion), there are decreases in the magnitudes of the resting potential, the velocity of the upstroke, and the height and duration of the action potential. (A decrease in upstroke velocity is indicative of a lowered velocity of conduction of the action-potential wave front through this ischemic region.) The slope of the potential during the plateau phase of the action potential is also altered in ischemia (increased). These changes in the action-potential...
waveform bring about changes in the extracellular field potentials produced by individual cardiac cells. The action current contributions of normal and ischemic cells superimpose in the linear volume-conductor medium to bring about altered forms of the ventricular portion of the ECG (QRS complex, S–T segment, and T wave, as shown in Figures 4.13 and 4.21).

Occlusion of the blood supply to a given myocardial region brings about relatively rapid electrolytic adjustments in the affected region. Specifically, there is a loss of K\(^+\) and an uptake of Na\(^+\) within the ischemic cell. Ca\(^{2+}\) and H\(^+\) also accumulate within the cell, and water shifts inward as well. These ionic shifts produce membrane depolarization and are indicative of the depressed activity of the Na\(^+\)–K\(^+\) pump, which is metabolically dependent. Changes in the cell resting potential and the action potential waveform in ischemia are simply external manifestations of the underlying electrochemical changes brought about by an inadequate oxygen (blood) supply.

### 4.7 THE ELECTRORETINOGRAM

**ANATOMY OF VISION**

The normal eye is an approximately spherical organ about 24 mm in diameter (Figure 4.22). The retina, located at the back of the eye, is the sensory portion of the eye.

![Eye Diagram](image)

**Figure 4.22** The transparent contact lens contains one electrode, shown here on horizontal section of the right eye. Reference electrode is placed on the right temple.
The light-transmitting parts of the eye are the cornea, anterior chamber, lens, and vitreous chamber, named in the order in which these structures are traversed by light. A transparent fluid, the aqueous humor, is found in the anterior chamber. The vitreous chamber is filled by a transparent gel, the vitreous body. The aqueous humor provides a nutrient transport medium, but it is also of further optical significance. It is normally maintained at a pressure (20 to 25 mm Hg) that is adequate to inflate the eye against its resistive outer coats (the sclera and choroid). This makes possible the precise geometrical configuration of the retina and the optical pathway that is necessary to ensure formation of a clear visual image. In addition, the aqueous humor is the essential link between the circulatory system and the lens and cornea, which themselves lack blood vessels. To satisfy the respiratory and nutritive requirements of these two structures, there is a continual movement of fluid and solute material between the aqueous humor and contiguous blood vessels. Interference with this flow, in pathological conditions, not only leads to damage of the lens and cornea but may also result in the development of pressures within the eye that are high enough to injure the retina. Glaucoma is the term applied to this high-pressure condition.

In considering the neural organization of the retina, we need examine only five types of nerve cells: photoreceptors and bipolar, horizontal, amacrine, and ganglion cells. The ganglion cells, the axons of which produce the nerve fibers sweeping across the inner retinal surface to be collected at the optic disk (and which form the greater bulk of the nerve fibers of the optic nerve), are substantially fewer in number than the photoreceptors. There is a convergence in the neural pathways of the retina as a whole. [That is, many photoreceptors terminate on each bipolar cell (n:1), and many bipolar cells, in turn, terminate on a single ganglion cell.] The degree of convergence varies considerably, being greater in the peripheral parts of the retina and minimal at the fovea (Figure 4.22). That is, the neural chain from photoreceptor to ganglion cell is 1:1 in the foveal region.] The synaptic interconnections between photoreceptors and bipolar cells and between bipolar cells and ganglion cells occur in two well-defined regions. The external plexiform layer is the region of contact between photoreceptor and bipolar cells, and the internal plexiform layer is the region of contact between bipolar and ganglion cells.

Lateral connections are also found in both layers. For example, horizontal cells interconnect rods and cones (defined below) at the level of the external plexiform layer, and amacrine cells provide a second horizontal network at the level of the inner plexiform layer. The retina may thus be considered functionally organized into two parts: an outer sensory layer containing the photoelectric sensors (photoreceptors) and an inner layer responsible for organizing and relaying electrical impulses generated in the photoreceptor layer to the brain.

Two types of photoreceptors occur in the human retina: rods (the agents of vision in dim light) and cones (the mediators of color vision in brighter light). Both rods and cones are differentiated into outer and inner segments. The inner segments are the major sites of metabolism and contain all the synaptic
terminals. Outer segments—typically cylindrical and thin in rods and stout and conical in cones—are sites of visual excitation. The first stage in the transduction of light to neural messages is the absorption of photons by photopigments localized in the outer segments of the retina’s photoreceptors. The photopigment localized in the compact membrane infolding of the rod’s external segment is rhodopsin. It is easily isolated and has been extensively studied. Cones in human beings contain one of three photopigments and have photospectral absorption characteristics that differ from one another, and from the rod pigment rhodopsin. Cone pigments have proved very difficult to isolate in humans and other vertebrates, and hence their spectral characteristics have usually had to be measured by indirect means (e.g., reflection densitometry). Each cone pigment responds to a range of light wavelengths, but with maximal light absorption in the red, green, or blue regions of wavelength, respectively. Photopigments are embedded in the specialized membranes of the outer segments of the photoreceptors, and they are photolabile; that is, events initiated by light absorption result eventually in breakdown or “bleaching” of the photopigment.

For example, the photopigment in rods is rhodopsin (Rh), and it is comprised of two parts: a protein called opsin and retinal, a light-sensitive chromophore derived from vitamin A. In the absence of light, retinal is in its 11-cis form and is bound to opsin. With absorption of a photon, retinal straightens out to assume its all-trans form and dissociates. This process initiates a cascade of intramolecular reactions that brings about a conformational change in rhodopsin (now called activated rhodopsin Rh*). Rh* in turn activates a G-protein coupled signal transduction cascade which targets closing of Na⁺ channels on the external segment membrane. An important second messenger mediating this channel closing is cyclic guanosine 3,5-cyclic monophosphate (GMP). Turning off the Na⁺ current that flows during the dark hyperpolarizes the cell membrane and reduces the release of neurotransmitter to downstream neurons in the visual pathway. Rhodopsin kinase and arrestin inactivate Rh* resetting the signal transduction pathway.

Details of the phototransduction process are beyond the scope of this book, but most physiology texts cover this subject intensively. Both intracellular and extracellular potential recordings have been made from isolated photoreceptors, as well as whole-cell voltage clamp recordings that provide quantitative descriptions of some of the membranes currents involved, e.g., Yagi and Macleish (1994).

**ELECTROPHYSIOLOGY OF THE EYE**

When the retina is stimulated with a brief flash of light, a characteristic temporal sequence of changes in potential can be recorded between an exploring electrode—placed either on the inner surface of the retina or on the cornea—and an indifferent electrode placed elsewhere on the body (usually the temple, forehead, or earlobe). These potential changes are collectively known as the electroretinogram (ERG), and they are clinically
recorded with the aid of an Ag/AgCl electrode embedded in a special contact lens used as the exploring electrode. The saline-filled contact lens is in good contact with the cornea, which is very thin and in intimate contact with the aqueous humor and passive fluid medium of the inner eye. The contact lens is usually well tolerated by the subject and permits long examinations without discomfort. By considering the eye as a fluid-filled sphere and the retina as a thin sheetlike bioelectric source attached to the posterior pole of the sphere (Figure 4.22), we can easily visualize the volume-conductor problem in electroretinography.

Figure 4.23 shows a typical vertebrate ERG waveform in response to a 2 s light flash. The four most commonly identified components of the ERG waveform (the a, b, c, and d waves) are common to most vertebrates, including humans. The first part of the response to a brief light flash is the early-receptor potential (ERP) generated by the initial light-induced changes in the photopigment molecules. It appears almost instantaneously with the onset of the light stimulus. The second component, with a latency of 1 to 5 ms, is the late-receptor potential (LRP), which has been found to be maximal near the synaptic endings of the photoreceptors and therefore reflects the outputs of the receptors. Normally the ERP and LRP sum to form the leading edge of the a wave. The b wave is generated by activity of the bipolar and ganglion cells of the inner layers of the retina. This is best seen in laboratory experiments under conditions where the retinal artery supplying the inner layers of the retina is occluded, and the b wave is abolished. This experimental technique is useful since in the absence of the b wave, the entire time course of the early photoreceptor response (ERP + LRP) can be studied. The ERP is linear with light intensity; the LRP is already markedly nonlinear, varying approximately logarithmically with intensity. The c wave is not generated by the retina itself, but rather by the pigment epithelial layer in which the tips of the external segments are embedded. This is shown experimentally by chemically ablating the pigment epithelium or using an isolated retina preparation. The d wave is the off-response of the retina to the light stimulus.
SPATIAL PROPERTIES OF THE ERG

It is possible to record ERGs from localized areas of the retina in addition to the classical response that we have described in previous sections. [This conventional response is usually elicited from the dark-adapted eye via a brief light flash (flash ERG)]. In laboratory experiments on frog, the sum of the ERGs produced by several retinal regions is equal to the single ERG produced when all these regions are stimulated simultaneously.

Linear superposition of ERG responses has likewise been confirmed in humans. In applying localized light stimuli to portions of the human retina, precautions should be taken to prevent light scattered within the eye from stimulating a much larger area of retina than is intended. Thus relatively high steady background illumination is supplied that illuminates most of the retina, and a localized stimulus is superimposed. The background illumination light causes the retina to adapt and renders it much less sensitive to light scattered from the stimulus region. In general, relatively high-background and low-stimulus intensities are preferred, making these locally generated ERG potentials low in amplitude and detectable with only average response calculations involving large numbers of responses. Without these special precautions, the resultant ERG represents the overall retinal response to light stimulation. Little is known about the actual nature of the light input to a particular retinal locus in the photoreceptive layer.

Despite the anatomical complexities of the retina, the problems of obtaining good records from untrained subjects, and the need for employing averaging techniques in obtaining spatially localized ERGs, the ERG has potential importance in assessing functional retinal behavior. It serves as an objective record of retinal function, is not dependent on the function of the optic nerve or the optic pathways, and is minimally affected by clouding of the optic pathway.

THE ELECTRO-OCULOGRAM (EOG)

In addition to the transient potential recorded as the ERG, there is a steady corneal–retinal potential. This steady dipole may be used to measure eye position by placing surface electrodes to the left and right of the eye (e.g., on the nose and the temple). When the gaze is straight ahead, the steady dipole is symmetrically placed between the two electrodes, and the EOG output is zero. When the gaze is shifted to the left, the positive cornea becomes closer to the left electrode, which becomes more positive. There is an almost linear relationship between horizontal angle of gaze and EOG output up to approximately $\pm 30^\circ$ of arc. Electrodes may also be placed above and below the eye to record vertical eye movements.

The EOG, unlike other bipotentials, requires a dc amplifier. The signal is in the microvolt range, so recessed Ag/AgCl electrodes are required to prevent drift. It is necessary to abrade the skin to short out changes in the potential that exists between the inside and the outside of the skin. A noise is present that is
compounded of effects from EEG, EMG, and the recording equipment; it is equivalent to approximately 1° of eye movement. Thus EOG data suffer from a lack of accuracy at the extremes. Specifically eye movements of less than 1° or 2° are difficult to record, whereas large eye movements (for example, greater than 30° of arc) do not produce bioelectric amplitudes that are strictly proportional to eye position. For an analysis of the accuracy and precision of electro-oculographic recordings, consult North (1965).

The EOG is frequently the method of choice for recording eye movements in sleep and dream research, in recording eye movements from infants and children, and in evaluating reading ability and visual fatigue. For a practical clinical EOG setup, see Niedermeyer and Lopes Da Silva (1999).

4.8 THE ELECTROENCEPHALOGRAM

The background electrical activity of the brain in unanesthetized animals was described qualitatively in the nineteenth century, but it was first analyzed in a systematic manner by the German psychiatrist Hans Berger, who introduced the term electroencephalogram (EEG) to denote the potential fluctuations recorded from the brain. Conventionally, the electrical activity of the brain is recorded with three types of electrodes—scalp, cortical, and depth electrodes. When electrodes are placed on the exposed surface (cortex) of the brain, the recording is called an electrocorticogram (ECoG). Thin insulated needle electrodes of various designs may also be advanced into the neural tissue of the brain, in which case the recording is referred to as a depth recording. (There is surprisingly little damage to the brain tissue when electrodes of appropriate size are employed.) Whether obtained from the scalp, cortex, or depths of the brain, the recorded fluctuating potentials represent a superposition of the field potentials produced by a variety of active neuronal current generators within the volume-conductor medium. Unlike the relatively simple bioelectric source considered in Section 4.2 (the nerve trunk with its enclosed bundles of circular cylindrical nerve axons), the sources generating these field potentials are aggregates of neuronal elements with complex interconnections. The neuronal elements mentioned previously are the dendrites, cell bodies (somata), and axons of nerve cells. Moreover, the architecture of the neuronal brain tissue is not uniform from one location to another in the brain. Therefore, prior to undertaking any detailed study of electroencephalography, we first discuss necessary background information regarding (1) the gross anatomy and function of the brain, (2) the ultrastructure of the cerebral cortex, (3) the field potentials of single neurons leading to an interpretation of extracellular potentials recorded in the cerebral cortex, and (4) typical clinical EEG waveforms recorded via scalp electrodes. We shall then focus on the general volume-conductor problem in electroencephalography and briefly discuss abnormal EEG waveforms (Sherman and Walterspacher, 2006).
INTRODUCTION TO THE ANATOMY AND FUNCTION OF THE BRAIN

The central nervous system (CNS) consists of the spinal cord lying within the bony vertebral column and its continuation, the brain, lying within the skull [Figure 4.24]. The brain is the greatly modified and enlarged portion of the CNS, surrounded by three protective membranes (the meninges) and enclosed within the cranial cavity of the skull. The spinal cord is likewise surrounded by downward continuations of the meninges, and it is encased within the protective bony vertebral column. Both brain and spinal cord are bathed in a special extracellular fluid called cerebral spinal fluid (CSF).

Division of the brain into three main parts—cerebrum, brainstem, and cerebellum—provides a useful basis for the study of brain localization and function (Figure 4.24). The brainstem (medulla, pons, midbrain, diencephalon) is the oldest part of the brain. It is actually a short extension of the spinal cord and

![Figure 4.24](image_url)

**Figure 4.24** Anatomical relationship of brainstem structures [medulla oblongata, pons, midbrain, and diencephalon (thalamus and hypothalamus)] to the cerebrum and cerebellum. General anatomic directions of orientation in the nervous system are superimposed on the diagrams. Here the terms rostral (toward head), caudal (toward tail), dorsal (back), and ventral (front) are associated with the brainstem; remaining terms are associated with the cerebrum. The terms medial and lateral imply nearness and remoteness, respectively, to or from the central midline axis of the brain. Symbols: T (thalamus), HT (hypothalamus), MB (midbrain), SC (spinal cord), P pituitary gland). (Adapted from John H. Martin, *Neuroanatomy: Text and Atlas*, 2nd ed., 1996, pp 14–15, with permission of Appleton and Lange, a Simon and Schuster Company.)
serves three major functions: (1) a connecting link between the cerebral cortex, spinal cord, and cerebellum; (2) an integrative center for several visceral functions (e.g., control of blood pressure and ventilation); and (3) an integration center for various motor reflexes. The diencephalon is the most superior portion of the brainstem; its chief component and largest structure is the thalamus. The thalamus serves as a major relay station and integration center for all of the general and special sensory systems, sending information to their respective cortical reception areas. It serves as the gateway to the cerebrum. Another major component of the diencephalon is the hypothalamus, which integrates functions of the autonomic nervous system and along with the pituitary gland, regulates functions of the thyroid, adrenal, and reproductive glands. The cerebellum is a coordinator in the voluntary (somatic) muscle system and acts in conjunction with the brainstem and cerebral cortex to maintain balance and provide harmonious muscle movements. The larger cerebrum occupies a special dominant position in the central nervous system, and conscious functions of the nervous system are localized within this structure.

Within the CNS there are ascending (sensory) nerve tracts that run from the spinal cord or brain stem to various areas of the brain, conveying information regarding changes in the external environment of the body that are reported by various peripheral biological sensors. There are a variety of such sensors, including the general sensors of temperature, pain, fine touch, pressure, as well as the special senses of vision, audition, equilibrium, taste, and olfaction. Figure 4.25 shows the basic plan associated with the general sense pathways from the periphery (e.g., skin, muscles) to the cortex. A three-neuron chain is involved in conveying information to the cortex where the primary neuron has its cell body in a ganglion outside the CNS and makes synaptic contact with a secondary neuron whose cell body is located in a nucleus within

![Figure 4.25](image)

**Figure 4.25** A simplified diagram of the CNS showing a typical general sense pathway from the periphery (neuron 1) to the brain (neuron 3). Note that the axon of the secondary neuron (neuron 2) in the pathway decussates (crosses) to the opposite side of the cord. Descending (motor) pathways are also crossed (see text).
either the spinal cord [e.g., the dorsal horn or the brain stem (Figure 4.25)]. Note from Figure 4.25 that the axon of the secondary neuron crosses (decussates) to the other side of the cord and joins a nerve fiber tract bound for the thalamus. The tertiary neuron in the pathway is located in a thalamic nucleus, and its axon travels in the thalamocortical radiations to the postcentral gyrus, which is located just posterior to the central sulcus [Figure 4.24 (inset)]. Thus, the postcentral gyrus is the cortical projection area for the general senses.

Neural pathways for the special senses, particularly audition and vision, follow the same general ground plan; however, there are notable deviations from the scheme depicted in Figure 4.25. Usually, more than three neurons are involved in the pathway and not all of the “secondary neurons” decussate. Most of the neurons cross to the opposite (contralateral) side of the body, however a significant number ascend to the thalamus on the same (ipsilateral) side of the body. The auditory and visual pathways have their own special thalamic relay centers—the medial and lateral geniculate bodies, respectively, as well as their own cortical projection areas (Figure 4.24).

Likewise, within the CNS there are descending (motor) nerve tracts that originate in various brain structures such as the cerebrum and cerebellum (Figure 4.24) and terminate ultimately on motor neurons in the ventral horn of the spinal cord (Figure 4.10). These motoneurons, in turn, control the contractile activity of the skeletal musculature. For example, the corticospinal tract is a bundle of axons from the primary motor cortex [precentral gyrus, Figure 4.24 (inset)], which projects directly to motor neurons in the spinal cord. Since the ascending general sensory pathways are crossed, the descending corticospinal tracts each cross to the opposite side of the body prior to making synaptic contact with the spinal motor neurons.

Thus, two-way communication links exist between the brain and spinal cord that allow higher centers in the brain to control or modify the behavior of the elemental spinal reflex arc at a given spinal level. By means of these links, the brain is not only informed of a peripheral event but can also modify the response of the spinal reflex to that environmental stimulus. Information is transmitted to the brain by means of a frequency-modulated train of nerve impulses that, upon reaching specific areas of the brain, stimulates the activity of resident neurons. Similarly, the decision to implement a motor action in response to the initial stimulus is manifested in the electrical activity of cortical neurons in specific areas of the brain [e.g., precentral gyrus (primary motor cortex); premotor cortex in frontal lobe]. The pattern of activity is specific to the type of motor action to be taken.

Electrical activity in either ascending or descending nerve fiber tracts may be represented to a first approximation by an action current dipole oriented in the direction of propagation (bioelectric source model). One should be aware that the properties (e.g., size, bulk conductivity) of the volume-conductor medium can change along the length of a particular fiber tract between the spinal cord and the cortex, and the volume-conductor model adopted should be based on the particular measurement considered. The volume-conductor-field potential solutions can be used to both fit and interpret body surface
potential measurements obtained clinically. Recording field potentials non-invasively from the relatively small volume of active nerve trunks, invariably requires the use of cumulative signal averaging techniques. In Figure 4.8, the median nerve was stimulated and compound action potentials were recorded from the subject’s forearm. Although not shown in this figure, sensory fibers in the median nerve thus activated, initiate activity in the general sense pathways to the brain. Averaged field potential recordings can be taken at a variety of points along the ascending pathways [e.g., from spinal cord and brain stem tracts taking note of the crossed nature of the pathway, and finally at the cortex itself (postcentral gyrus)]. The field potentials associated with long nerve tracts depends to a large extent on (a) whether the tract is straight or bent and (b) the resistance (geometry and specific conductivity) of the surrounding volume-conductor media.

This important subject is discussed later; however, for the present, these different types of averaged field potentials are called collectively somato-sensory evoked potentials. The subject of nerve tracts has been discussed previously; however, the activity of both nuclei in the ascending pathway and clusters of cells in the cortex, depends not only on the ensemble of neurons there, but also on the geometry of the ensemble and the different types of synaptic connections involved.

Averaged sensory evoked potentials in response to brief auditory “clicks” or flashes of light are also routinely recorded as the auditory evoked response (AER) and the visual evoked response (VER), respectively (Jacobson, 1994; Heckenlively and Arden, 1991). Using an electromagnetic stimulating device held over the primary motor cortex (just anterior to the central sulcus), it is also possible to induce currents that activate the corticospinal tract, making possible the recording of averaged field potentials from the descending motor pathways (York, 1987; Geddes, 1987; Esselle and Stuchly, 1992). The same volume-conductor principles are applicable to the analysis of these different types of evoked potential recordings. The cerebrum is a paired structure, with right and left cerebral hemispheres, each relating to the opposite side of the body. That is, voluntary movements of the right hand are “willed” by the left cerebral hemisphere. The surface layer of the hemisphere is called the cortex; it receives sensory information from skin, eyes, ears, and other receptors located generally on the opposite side of the body. This information is compared with previous experience and produces movements in response to these stimuli.

Each hemisphere consists of several layers. The outer layer is a dense collection of nerve cells that appear gray in color when examined in a fresh state. It is consequently called gray matter. This outer layer, roughly 1 cm thick, is called the cerebral cortex. It has a highly convoluted surface consisting of gyri (ridges) and sulci (valleys), the deeper sulci being termed fissures. The deeper layers of the hemisphere (beneath the cortex) consist of myelinated axons (or white matter) and collections of cell bodies termed nuclei. Some of the integrative functions of the cerebrum can be localized within certain regions of the cortex; others are more diffusely distributed.
A major dividing landmark of the cerebral cortex is the lateral fissure (Figure 4.24), which runs on the lateral (side) surface of the brain from the open end in front, posteriorly and dorsally (backward and upward). The lateral fissure defines a side lobe of cortex inferior to (below) it that is called the temporal lobe [Figure 4.24 (inset)]. The superior (upper) part of this lobe contains the primary auditory cortex, which is the part of the cortex that receives auditory impulses via neural pathways leading from the auditory receptors in the inner ear.

The visual system is another example of the projection of the senses onto the cerebral cortex. The occipital lobe at the back of the head is the primary visual cortex. Light flashed into the eye evokes large electrical potentials from electrodes placed over this area of the cortex.

Another major landmark of the cerebral cortex is the central sulcus [Figure 4.24 (inset)]. However, it is not so prominent and unvarying an anatomical landmark as the lateral fissure. The central sulcus runs from the medial surface (surface along the midline of the brain) over the convexity of the hemisphere to the lateral fissure. It also represents the posterior border of the frontal lobe. The gyrus lying just anterior (forward) to the central sulcus is the precentral gyrus, which functions as the primary motor cortex. From this gyrus, nerve signals run down through the brainstem to the spinal cord for control of skeletal muscles via neural control of motoneurons in the ventral horn of the spinal cord (Figure 4.10). Lesions (destruction) of part of the precentral gyrus cause partial paralysis on the opposite side of the body.

Immediately posterior to the central sulcus [Fig. 24 (inset)] is the primary somatosensory cortex, the postcentral gyrus. This region receives impulses from all the general sense receptors from the skin (such as pressure, touch, and pain receptors). Each little area along this gyrus is related to a particular part of the body (for example, the legs on the medial end, the hand in the center, and the face on the end next to the lateral fissure). If a recording electrode is placed appropriately during a neurosurgical procedure, a cortical response can be evoked by tactile stimuli delivered to the contralateral (opposite) hand. Likewise, if a stimulus is applied through the same electrode, the subject reports a tingling sensation in the contralateral hand. Higher-order sensory discrimination, such as the ability to recognize a number drawn on the palm of the hand, is organized solely in the parietal lobe of which the postcentral gyrus is a part. Destruction of the parietal lobe results in a loss of this discriminative ability. For example, a subject may still know that he or she is being touched but cannot tell where or what is being drawn on the palm of the hand. The parietal lobe is also responsible for a person’s awareness of the general position of the body and its limbs in space.

ULTRASTRUCTURE OF THE CEREBRAL CORTEX

The functional part of the cerebrum is the cerebral cortex (bark, outer covering), a relatively thin layer of gray matter (1.5 to 4.0 mm in thickness) covering the outer surface of the cerebrum, including its intricate convolutions.
Because it is the most recent phylogenetic acquisition of the brain, the cerebral cortex has undergone a relatively greater development than other parts of the brain. The greatest advance in relative growth has been the neocortex, which is present on the superior and lateral aspects of the cerebral hemispheres. The distinctly different type of cortex located on the medial surface and base of the brain is known as the paleocortex. We shall use the term cortex in this chapter to refer specifically to the neocortex.

Cortical architectures in vertebrates share several common features: (1) stratified layers containing cell bodies and fiber bundles; (2) an outermost layer that lacks neurons (layer I); (3) at least one inner layer containing neurons that give rise to large dendrites, which rise vertically to layer I and travel in that layer forming multiple branches (arborization). The human cortex is generally arranged in six such cortical layers. The neurons are of two main types: pyramidal and nonpyramidal (many subtypes have been identified). There are also a large number of horizontally oriented layers of nerve fibers that extend between adjacent regions of the cortex, as well as vertically oriented bundles that extend from the cortex to more distant regions of the cortex or downward to the brainstem and spinal cord.

Figure 4.26 shows a schematic drawing of a typical cortical pyramidal cell. The bodies of this type of cell are commonly triangular in shape, with the base down and the apex directed toward the cortical surface. (Pyramidal

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**Figure 4.26** Electrogenesis of cortical field potentials for a net excitatory input to the apical dendritic tree of a typical pyramidal cell. For the case of a net inhibitory input, polarity is reversed and the apical region becomes a source (+). Current flow to and from active fluctuating synaptic knobs on the dendrites produces wavelike activity. (See text.)
cell bodies vary greatly in size, from axial dimensions of $15 \times 10 \, \mu m$ up to $120 \times 90 \, \mu m$ or more for the giant pyramids of the motor cortex, which are called Betz cells after their discoverer.) These cells usually consist of the following parts: (1) a long apical dendrite (up to 2 mm in length) that ascends from the apex of the cell body through the overlaying cellular layers, and which frequently reaches and branches terminally within the outermost layer of the cortex; (2) dense dendritic arborization occurring at the base of the pyramid-shaped cell (largely horizontally—basilar dendrites); and (3) a single pyramidal cell axon which can emerge from the inner surface of the cortex as projection fibers to other areas of the cortex, or to other structures (e.g., the thalamus, cerebellum, or spinal cord). Frequently these axons send recurrent collateral (feedback) branches back on the cellular regions from which they sprang. Axons of some pyramidal cells turn back toward the cortical surface (never leaving the gray matter) to end via their many branches on the dendrites of other cells.

Nonpyramidal cells of the neocortex differ remarkably from pyramidal cells. Their cell bodies are small, and dendrites spring from them in all directions to ramify in the immediate vicinity of the cell. The axon may arise from a large dendrite; it commonly divides repeatedly to terminate on the cell bodies and dendrites of immediately adjacent cells. The axons of other nonpyramidal cells may turn upward toward the cortical surface, or they may leave the motor cortex (though this is not common).

For a detailed exposition of the various cells, layers, cellular interconnections, inputs, and outputs of the neocortex, see Kandel et al. (1991).

**BIOELECTRIC POTENTIALS FROM THE BRAIN**

Unipolar recordings of the cortical surface potential relative to that of a remote reference potential may be viewed as a measurement of the integrated field potential at a boundary of a large volume conductor that contains an array of action current sources. Under normal conditions, action potentials conducted by axons in the cortical medium contribute very little to the integrated surface potential, since there are many axons in the cortex which run in many directions relative to the surface and which fire asynchronously. Consequently, their net spatial and temporal influence on the field potential at the surface is negligible. An exception occurs, of course, in the case of a response evoked by the simultaneous (synchronous) stimulation of a cortical input (e.g., direct electrical stimulation of thalamic nuclei or their afferent pathways, which project directly to the cortex via thalamocortical axons—the cortical input). These synchronous responses are called evoked potentials, and they are of relatively large amplitude. Synchronicity of the underlying fiber and cortical neuron activity is a major factor influencing surface potential magnitude. Unipolar field potentials recorded within the cortical layers have shown that the cortical surface potential is largely due to the net effect of local postsynaptic potentials of cortical cells (Figure 4.26). These may be of either sign (excitatory or inhibitory) and may occur directly underneath the electrode.
or at some distance from it. A potential change recorded at the surface is a measure of the net potential (current resistance $iR$) drop between the surface site and the distant reference electrode. It is obvious, however, that if all the cell bodies and dendrites of cortical cells were randomly arranged in the cortical medium, the net influence of synaptic currents would be zero. This would result in a “closed field” situation that produces relatively small far-field potentials (Lorente de No, 1947). Thus, any electrical change recorded at the surface must be due to the orderly and symmetric arrangement of some class of cells within the cortex.

Pyramidal cells of the cerebral cortex are oriented vertically, with their long apical dendrites running parallel to one another. Potential changes in one part of the cell relative to another part create “open” potential fields in which current may flow and potential differences can be measured at the cortical surface. Figure 4.26 illustrates this concept in diagrammatic fashion. Synaptic inputs to the apical dendritic tree cause depolarization of the dendritic membrane. As a result, subthreshold current flows in a closed path through the cytoplasmic core of the dendrites and cell body of the pyramidal cell, returning ultimately to the surface synaptic sites via the extracellular bathing medium. From the indicated direction of the lines of current flow, the extracellular medium about the soma behaves as a source (+), while the upper part of the apical dendritic tree behaves as a sink (−).

The influence of a particular dendritic postsynaptic potential (PSP) on the cortical surface recording depends on its sign [excitatory (−) or inhibitory (+)] and on its location relative to the measurement site. The effect of each PSP may be regarded as creating a radially oriented current dipole. Therefore, continuing synaptic input creates a series of potential dipoles and resulting current flows that are staggered but overlapped in space and time. Surface potentials of any form can be generated by one population of presynaptic fibers and the cells on which they terminate, depending on the proportion that are inhibitory or excitatory, the level of the postsynaptic cells in the cortex, and so forth.

Nonpyramidal cells in the neocortex, on the other hand, are unlikely to contribute substantially to surface records. Their spatially restricted dendritic trees are radially arranged around their cell bodies such that charge differences between the dendrites and the cell body produce fields of current flow that sum to zero when viewed from a relatively great distance on the cortical surface (closed-field situation).

Thus, to summarize, the apical dendrites of pyramidal cells constitute a meshwork of similarly oriented, densely packed units in the outer layers of the cortex. As multiple synaptic endings on the dendritic tree of each cell become active, current can flow in either direction between the dendritic process depending on whether the synapses are excitatory or inhibitory. The source–sink relationship between dendrite and cell is that of a constantly shifting current dipole, where variations in dipole orientation and strength produce wavelike fluctuations in the surface field potential (Figure 4.26). When the sum of dendritic activity is negative relative to the cell, the cell
is depolarized and quite excitable. When it is positive, the cell is hyperpolarized and less excitable.

RESTING RHYTHMS OF THE BRAIN

Electric recordings from the exposed surface of the brain or from the outer surface of the head demonstrate continuous oscillating electric activity within the brain. Both the intensity and the patterns of this electric activity are determined to a great extent by the overall excitation of the brain resulting from functions in the brainstem reticular activating system (RAS). The undulations in the recorded electric potentials (Figure 4.27) are called brain waves, and the entire record is called an electroencephalogram (EEG).

![Brain waves diagram](image)

**Figure 4.27**  (a) Different types of normal EEG waves. (b) Replacement of alpha rhythm by an asynchronous discharge when patient opens eyes. (c) Representative abnormal EEG waveforms in different types of epilepsy. (From A. C. Guyton, *Structure and Function of the Nervous System*, 2nd ed., Philadelphia: W.B. Saunders, 1972; used with permission.)
The intensities of the brain waves on the surface of the brain (recorded relative to an indifferent electrode such as the earlobe) may be as large as 10 mV, whereas those recorded from the scalp have a smaller amplitude of approximately 100 μV. The frequencies of these brain waves range from 0.5 to 100 Hz, and their character is highly dependent on the degree of activity of the cerebral cortex. For example, the waves change markedly between states of wakefulness and sleep. Much of the time, the brain waves are irregular, and no general pattern can be observed. Yet at other times, distinct patterns do occur. Some of these are characteristic of specific abnormalities of the brain, such as epilepsy (discussed later). Others occur in normal persons and may be classified as belonging to one of four wave groups (alpha, beta, theta, and delta), which are shown in Figure 4.27(a).

Alpha waves are rhythmic waves occurring at a frequency between 8 and 13 Hz. They are found in EEGs of almost all normal persons when they are awake in a quiet, resting state of cerebration. These waves occur most intensely in the occipital region but can also be recorded, at times, from the parietal and frontal regions of the scalp. Their voltage is approximately 20 to 200 μV. When the subject is asleep, the alpha waves disappear completely. When the awake subject’s attention is directed to some specific type of mental activity, the alpha waves are replaced by asynchronous waves of higher frequency but lower amplitude. Figure 4.27(b) demonstrates the effect on the alpha waves of simply opening the eyes in bright light and then closing them again. Note that the visual sensations cause immediate cessation of the alpha waves; these are replaced by low-voltage, asynchronous waves.
EXAMPLE 4.5  Design a system that would provide nonvisual feedback to a subject who wished to maximize the amplitude of his EEG alpha waves. Explain its operation.

ANSWER  Three electrodes over the occipital lobe detect the 100 μV EEG and feed a differential amplifier with a gain of 10,000. A band-pass filter centered at 10 Hz selects the alpha waves, which are demodulated and filtered to yield a dc voltage proportional to amplitude. A voltage-to-frequency converter increases the frequency of an acoustic tone, and the subject attempts to maximize the frequency.

Beta waves normally occur in the frequency range of 14 to 30 Hz, and sometimes—particularly during intense mental activity—as high as 50 Hz. These are most frequently recorded from the parietal and frontal regions of the scalp. They can be divided into two major types: beta I and beta II. The beta I waves have a frequency about twice that of the alpha waves. They are affected by mental activity in much the same way as the alpha waves (they disappear and in their place appears an asynchronous, low-voltage wave). The beta II waves, on the other hand, appear during intense activation of the central nervous system and during tension. Thus one type of beta activity is elicited by mental activity, whereas the other is inhibited by it.

Theta waves have frequencies between 4 and 7 Hz. These occur mainly in the parietal and temporal regions in children, but they also occur during emotional stress in some adults, particularly during periods of disappointment and frustration. For example, they can often be brought about in the EEG of a frustrated person by allowing the person to enjoy some pleasant experience and then suddenly removing the element of pleasure. This causes approximately 20 s of theta waves.

Delta waves include all the waves in the EEG below 3.5 Hz. Sometimes these waves occur only once every 2 or 3 s. They occur in deep sleep, in infancy, and in serious organic brain disease. They can also be recorded from the brains of experimental animals that have had subcortical transections producing a functional separation of the cerebral cortex from the reticular activating system. Delta waves can thus occur solely within the cortex, independent of activities in lower regions of the brain.

A single cortical cell can give rise only to small extracellular current, so large numbers of neurons must be synchronously active to give rise to the potentials recorded from the cerebral surface. The individual waves of the EEG are of long duration (for example, 30 to 500 ms), and one might well ask how they are produced. They can be long-lasting depolarizations of the cell membranes (for example, of the apical dendrites of pyramidal cells) or a summation of a number of shorter responses. In any event, a sufficiently large number of neurons must discharge together to give rise to these cortical potentials. The term synchronization is used to describe the underlying process that acts to bring a group of neurons into unified action. Synaptic interconnections are generally thought to bring about synchronization, although extracellular field interaction between
**4.8 THE ELECTROENCEPHALOGRAM**

Cells has been proposed as a possible mechanism. Rhythmically firing neurons are very sensitive to voltage gradients in their surrounding medium.

Besides the synchronization required for each wave of resting EEG, the series of repeated waves suggests a rhythmic and a trigger or pacemaker process that initiates such rhythmic action. By means of knife cuts below the intact connective-tissue covering (meningeal layer or pia matter) of the brain, one may prepare chronic islands of cortex—with all neuronal connections cut, but with the blood supply via surface vessels intact. Only a low level of EEG activity remains in such islands. Though the isolated islands of cortex may not show spontaneous EEG activity, they still have the ability to respond rhythmically, which may be readily demonstrated by the rhythmic responses that are elicited by applying a single electrical stimulus. The inference is that various regions of the cortex, though capable of exhibiting rhythmic activity, require trigger inputs to excite rhythmicity. The RAS, mentioned earlier, appears to provide this pacemaker function.

**THE CLINICAL EEG**

The system most often used to place electrodes for monitoring the clinical EEG is the International Federation 10–20 system shown in Figure 4.28. This system uses certain anatomical landmarks to standardize placement of EEG electrodes. The representation of the EEG channels is referred to as a montage. In the bipolar montage, each channel measures the difference between two adjacent electrodes. In the referential montage, each channel

![Figure 4.28 The 10–20 electrode system](image-url) This system is recommended by the International Federation of EEG Societies. [From H. H. Jasper, “The ten–twenty electrode system of the International Federation in Electroencephalography and Clinical Neurophysiology.” *EEG Journal*, 1958, 10 (Appendix), 371–375.]
measures the difference between one electrode and a reference electrode, such as on the ear. In the average reference montage, each channel measures the difference between one electrode and the average of all other electrodes. In the Laplacian montage, each channel measures the difference between one electrode and a weighted average of the surrounding electrodes. The differential amplifier requires a separate ground electrode plus differential inputs to the electrode connections. The advantage of using a differential recording between closely spaced electrodes (between successive pairs in the standard system, for example) is cancellation of far-field activity common to both electrodes; one thereby obtains sharp localization of the response. Although the same electric events are recorded in each of the ways, they appear in a different format in each case. The potential changes that occur are amplified by high-gain, differential, capacitively coupled amplifiers. The output signals are recorded and displayed.

In the routine recording of clinical EEGs, the input electrodes are a problem. They must be small, they must be easily affixed to the scalp with minimal disturbance of the hair, they must cause no discomfort, and they must remain in place for extended periods of time. Technicians prepare the surface of the scalp, degrease the recording area by cleaning it with alcohol, apply a conducting paste, and glue nonpolarizable Ag/AgCl electrodes to the scalp with a glue (collodion) and hold them in place with rubber straps, or use a rubber cap that contains all electrodes.

The EEG is usually recorded with the subject awake but resting recumbent on a bed with eyes closed. With the patient relaxed in such a manner, artifacts from electrode-lead movement are significantly reduced, as are contaminating signals from the scalp. Muscle activity from the face, neck, ears, and so on is perhaps the most subtle contaminant of EEG records in the recording of both spontaneous ongoing activity in the brain and activity evoked by a sensory stimulus (evoked response). For example, the frequency spectrum of the field produced by mildly contracted facial muscles contains frequency components well within the nominal EEG range (0.5 to 100 Hz). After technicians have achieved resting, quiescent conditions in the normal adult subject, the subject’s scalp recordings show a dominant alpha rhythm in the parietal-occipital areas, whereas in the frontal areas, there is a low-amplitude, higher-frequency beta rhythm in addition to the alpha rhythm. In the normal subject there is symmetry between the recordings of the right and left hemispheres. There can be a wide range of EEG measurement artifacts.

In general there is a relationship between the degree of cerebral activity and the average frequency of the EEG rhythm: The frequency increases progressively with higher and higher degrees of activity. For example, delta waves are frequently found in stupor, surgical anesthesia, and sleep; theta waves in infants; alpha waves during relaxed states; and beta waves during intense mental activity. However, during periods of mental activity, the waves usually become asynchronous rather than synchronous, so that the magnitude of the summed surface potential recording decreases despite increased cortical activity.
SLEEP PATTERNS

When an individual in a relaxed, inattentive state becomes drowsy and falls asleep, the alpha rhythm is replaced by slower, larger waves (Figure 4.29). In deep sleep, very large, somewhat irregular delta waves are observed. Interdispersed with these waves—during moderately deep sleep—are bursts of alpha-like activity called sleep spindles. The alpha rhythm and the patterns of the drowsy and sleeping subject are synchronized, in contrast with the low-voltage desynchronized, irregular activity seen in the subject who is in an alert state.

The high-amplitude, slow waves seen in the EEG of a subject who is asleep are sometimes replaced by rapid, low-voltage irregular activity resembling that obtained in alert subjects. However, the sleep of a subject with this irregular pattern is not interrupted; in fact, the threshold for arousal by sensory stimuli is elevated. This condition has therefore come to be called paradoxical sleep. During paradoxical sleep, the subject exhibits rapid, roving eye movements. For this reason, it is also called rapid-eye-movement sleep, or REM sleep. Conversely, spindle or synchronized sleep is frequently called nonrapid-eye-movement (NREM), or slow-wave sleep. Human subjects aroused at a time when their EEG exhibits a paradoxical (REM) sleep pattern generally report

![Figure 4.29 The electroencephalographic changes that occur as a human subject goes to sleep](image)

The calibration marks on the right represent 50 μV. (From H. H. Jasper, “Electroencephalography.” In Epilepsy and Cerebral Localization, W. G. Penfield and T. C. Erickson (eds.). Springfield, IL: Charles C. Thomas, 1941.)
that they were dreaming, whereas individuals wakened from spindle sleep do not. This observation and other evidence indicate that REM sleep and dreaming are closely associated. It is interesting that during REM sleep, there is a marked reduction in muscle tone, despite the rapid eye movements.

**THE VOLUME-CONDUCTOR PROBLEM IN ELECTROENCEPHALOGRAPHY**

Geometrically speaking, the brain approximates a sphere surrounded by concentric shells that differ in impedance and comprise the meninges (connective tissue coverings of the brain), cerebral spinal fluid, skull, and scalp. This model is inaccurate to the extent that the brain is not really a true sphere, and its coverings are irregular in shape and thickness. Such irregularities are insignificant for the upper half of the brain, but complications are introduced by the marked departure of the lower parts of the brain from a spherical shape, as well as by variations in impedance produced by the openings (to the spinal column) through the base of the shell. Various cerebral structures differ somewhat in specific resistivity. Resistivity also varies in relation to the predominant direction of the fibers within the white matter. Thus the brain is neither a homogeneous nor an isotropic conducting medium.

In practice, neurological generators do not correspond precisely to simple, one-dimensional dipoles. Any source of activity large enough to manifest itself in the EEG constitutes at least a small area of the cortex containing synchronously active neurons. This source may be regarded as a three-dimensional sheet polarized across its thickness. If it is small enough, it may still be conveniently represented as an equivalent dipole per unit volume. A larger area of the cortex may be curved, or even convoluted, and the equivalent dipole then becomes a complex vector sum of the whole. When there are many widely scattered active-current generators, an infinite number of combinations may give rise to the same pattern of surface potentials.

Determining the equivalent dipole of cerebral activity is therefore of practical value only when EEG sources are highly “focal.” Fortunately, this condition occurs frequently in the brain’s response to sensory stimulation, as well as in pathological conditions. For example, Nunez (1981) considers in some depth the subject of the calculation of field potentials from equivalent current sources in inhomogeneous media. Particularly in Chapter of his book, Nunez provides an introduction to the equivalent source models that have been used in the field of theoretical electroencephalography to interpret scalp potentials. Examples of these models include the simple dipole at the center of a spherical conducting medium, the radially oriented dipole not at the center of a sphere (the radially oriented eccentric dipole), the freely oriented eccentric dipole in a sphere, the dipole in a three-concentric spherical shell model, and a dipole current source below a multilayered planar conducting medium.

Considerable interest has arisen in determining the location of intracerebral sources of the potentials that are measured on the scalp. In general, nonuniqueness of this inverse problem is well known in that different
configurations of sources can lead to the same surface distribution. The usual approach taken to obtaining an approximate solution to the inverse problem is as follows:

1. Assume a model (such as the eccentrically located dipole in a uniform, homogeneous spherical conducting medium. Assume that the electric field is quasistatic).

2. After obtaining a solution to the associated boundary-value problem (the forward problem), produce model-generated potential values at measurement points on the cortical surface.

3. Compare these theoretical potential values with particular discrete-time values of EEG waveforms measured at the same surface sites, and form a general least-squares reconstruction error function wherein the error is defined as the difference between predicted and measured potential at several selected cortical measurement sites.

4. Iteratively adjust the EEG dipolar source parameters at each discrete-time instant to obtain the best fit to sampled EEG waveforms in a least-squares sense. The optimal dipole location is assumed to be the dipole location obtained when the reconstruction error function is so minimized.

The influence of anisotropy on various EEG phenomena has been studied using models [Henderson et al. (1975); Cuffin (1991); Haueisen et al. (2002)]. These investigations, together with various in vivo studies, substantially agree that the presence of tissue anisotropy tends to attenuate and smear the pattern of scalp-recorded EEGs. However, this type of amplitude-related degradation apparently does not affect the model's ability to predict the locus of the EEG equivalent-dipole generator (although the dipole moment might be underestimated). This is important in the sense that one of the major objectives of electroencephalography is determination of source location—for localized or focal activity—because in case of evoked cortical potentials and deep-brain pathologies, this concept of an equivalent-dipole generator is of clinical value.

THE ABNORMAL EEG

One of the more important clinical uses of the EEG is in the diagnosis of different types of epilepsy and in the location of the focus in the brain causing the epilepsy. Epilepsy is characterized by uncontrolled excessive activity by either a part or all of the CNS. A person predisposed to epilepsy has attacks when the basal level of excitability of all or part of the nervous system rises above a certain critical threshold. However, as long as the degree of excitability is held below this threshold, no attack occurs.

There are two basic types of epilepsy, generalized epilepsy and partial epilepsy. Generalized epilepsy involves the entire brain at once, whereas partial epilepsy involves a portion of the brain—sometimes only a minute focal spot and at other times a fair amount of the brain. Generalized epilepsy is further divided into grand mal and petit mal epilepsy.
Grand mal epilepsy is characterized by extreme discharges of neurons originating in the brainstem portion of the RAS. These discharges then spread throughout the cortex, to the deeper parts of the brain, and even to the spinal cord to cause generalized tonic convulsions of the entire body. They are followed near the end of the attack by alternating muscular contractions, called clonic convulsions. The grand mal seizure lasts from a few seconds to as long as 3 to 4 min and is characterized by postseizure depression of the entire nervous system. The subject may remain in a stupor for 1 min to as long as a day or more after the attack is over.

The middle recording in Figure 4.27(c) shows a typical EEG during a grand mal attack. This response can be recorded from almost any region of the cortex. The recorded potential is of a high magnitude, and the response is synchronous, with the same periodicity as normal alpha waves. The same type of discharge occurs on both sides of the brain at the same time, indicating that the origin of the abnormality is in the lower centers of the brain that control the activity of the cerebral cortex, not in the cortex itself. Electrical recordings from the thalamus and reticular formation of experimental animals during an induced grand mal attack indicate typical high-voltage synchronous activity in these areas, similar to that recorded from the cerebral cortex. Experiments on animals have further shown that a grand mal attack is caused by intrinsic hyperexcitability of the neurons that make up the RAS structures or by some abnormality of the local neural pathways of this system.

Petit mal epilepsy is closely allied to grand mal epilepsy. It occurs in two forms, the myoclonic form and the absence form. In the myoclonic form, a burst of neuronal discharges, lasting a fraction of a second, occurs throughout the nervous system. These discharges are similar to those that occur at the beginning of a grand mal attack. The person exhibits a single violent muscular jerk involving arms or head. The entire process stops immediately, however, and the attack is over before the subject loses consciousness or stops what he or she is doing. This type of attack often becomes progressively more severe until the subject experiences a grand mal attack. Thus the myoclonic form of petit mal is similar to a grand mal attack, except that some form of inhibitory influence promptly stops it.

The absence type of petit mal epilepsy is characterized by 5 to 20 s of unconsciousness, during which the subject has several twitchlike contractions of the muscles, usually in the head region. There is a pronounced blinking of the eyes, followed by a return to consciousness and continuation of previous activities. This type of epilepsy is also closely allied to grand mal epilepsy. In rare instances, it can initiate a grand mal attack.

Figure 4.27(c) shows a typical spike-and-dome pattern that is recorded during the absence type of petit mal epilepsy. The spike portion of the record is almost identical to the spikes occurring in grand mal epilepsy, but the dome portion is distinctly different. The spike-and-dome pattern can be recorded over the entire cortex, illustrating again that the seizure originates in the RAS.

Partial epilepsy can involve almost any part of the brain, either localized regions of the cerebral cortex or deeper structures of both the cerebrum and
brainstem. Partial epilepsy almost always results from some organic lesion of the brain, such as a scar that pulls on the neuronal tissue, a tumor that compresses an area of the brain, or a destroyed region of the brain tissue. Lesions such as these can cause local neurons to fire very rapid discharges. When the rate exceeds approximately 1000/s, synchronous waves begin spreading over adjacent cortical regions. These waves presumably result from the activity of localized reverberating neuronal circuits that gradually recruit adjacent areas of the cortex into the “discharge,” or firing, zone. The process spreads to adjacent areas at rates as slow as a few millimeters per minute to as fast as several centimeters per minute. When such a wave of excitation spreads over the motor cortex, it causes a progressive “march” of muscular contractions throughout the opposite side of the body, beginning perhaps in the leg region and marching progressively upward to the head region, or at other times marching in the opposite direction. This is called Jacksonian epilepsy or Jacksonian march.

Another type of partial epilepsy is the so-called psychomotor seizure, which may cause (1) a short period of amnesia, (2) an attack of abnormal rage, (3) sudden anxiety or fear, (4) a moment of incoherent speech or mumbling, or (5) a motor act of rubbing the face with the hand, attacking someone, and so forth. Sometimes the person does not remember his or her activities during the attack; at other times the person is completely aware of, but unable to control, his or her behavior. The bottom tracing of Figure 4.27(c) represents a typical EEG during a psychomotor seizure showing a low-frequency rectangular-wave response with a frequency between 2 and 4 Hz with superimposed 14 Hz waves.

The EEG frequently can be used to locate tumors and also abnormal spiking waves originating in diseased brain tissue that might predispose to epileptic attacks. Once such a focal point is found, surgical excision of the focus often prevents future epileptic seizures.

The EEG is also used to monitor the depth of anesthesia.

The EEG is also used as a brain–computer interface to enable disabled persons to communicate with a computer.

4.9 THE MAGNETOENCEPHALOGRAM

Active bioelectric sources in the brain generate magnetic as well as electric fields. However, the magnitude of the magnetic field associated with active cortex is extremely low. For example, it is estimated that the magnetic field of the alpha wave is approximately 0.1 pT at a distance of 5 cm from the surface of the scalp. By way of comparison, this biomagnetic field associated with the magnetoencephalogram (MEG) is roughly one hundred million times weaker than the magnetic field of the earth (\(\sim 50 \mu T\)). Recent technological advances in the study of superconductivity have made measurement of these extremely low-strength magnetic fields possible. Specifically, the superconducting quantum interference device (SQUID) magnetometer, which is based on a
superconducting effect at liquid helium temperature, has sensitivity on the order of 0.01 pT. Background fields such as the earth’s magnetic field and urban magnetic noise fields (~10 to 100 nT) can be removed for all practical purposes by using a gradiometer technique.

Using the MEG offers a number of advantages: (1) The brain and overlying tissues can be characterized as a single medium having a constant magnetic permeability \( \mu \). Therefore, the magnetic field (unlike the electric field) is not influenced by the shell-like anisotropic inhomogeneities (meninges, fluid layers, skull, muscle layer, and scalp) surrounding the brain. (2) The measurement is indirect in that electrodes are not necessary to record the MEG. That is, the SQUID detector does not need to touch the scalp, because the magnetic field does not disappear in air.

The magnetic vector potential \( A \) has the same orientation as the equivalent current dipole representing an active region of the brain. For a derivation of the vector potential in terms of the volume current density \( J \), see Plonsey (1969). Because the magnetic field lies perpendicular to the vector potential, radially oriented current dipoles produce magnetic fields that are oriented tangentially to the sphere representing the head. Similarly, tangentially oriented brain dipoles produce radially oriented magnetic fields.

The local time dependence of biomagnetic fields can be recorded faithfully with SQUID detection systems, but in order to measure the field distribution over the surface of the scalp, measurements must be made at many locations. This is a time-consuming process. Superconducting quantum interference device (SQUID) magnetometer vendors have systems with well over 100 channels (Wiksow, 1995). Advances in material fabrication techniques in the field of superconductivity should yield smaller detector coils for better spatial resolution and, subsequently, more precise localization of intracerebral sources of activity.

**PROBLEMS**

4.1 What are the four main factors involved in the movement of ions across the cell membrane in the steady-state condition?

4.2 Assume that life on Mars requires an interior cell potential of +100 mV and that the extracellular concentrations of the three major species are as given in Example 4.1. Choose one species that has the permeability coefficient given, and assume the other two permeabilities are zero. Design the cell by calculating the intracellular concentration of the chosen species.

4.3 An excitable cell is impaled by a micropipette, and a second extracellular electrode is placed close by at the outer-membrane surface. Brief pulses of current are then passed between these electrodes, which may cause it to conduct an action potential. Explain how the polarity of the stimulating pair influences the membrane potential, and subsequently the activity, of the excitable cell.
4.4 Explain the subthreshold-membrane potential changes that would occur in the immediate vicinity of each of two extracellular stimulating electrodes placed at the outer-membrane surface of an excitable cell. (See Figure P4.1.) Assume that membrane potential is determined by impaling the cell with a micropipette at various points in the vicinity of the stimulating electrodes and recording the potential with respect to an indifferent extracellular electrode.

4.5 If a stimulus of adequate strength is supplied to the stimulating pair of Problem 4.4, an action potential is generated. Explain by means of the concept of “local-circuit” current flow how the action potential is able to propagate in an unattenuated fashion down the fiber and away from the site of stimulation.

4.6 If an elongated fiber is stimulated in the middle (as opposed to at either end), is an action potential propagated in both directions along the fiber? If so, would you expect any differences in the action-potential response measured at equal distances on either side of the stimulation site?

4.7 Define the following terms: (a) absolute refractory period, (b) relative refractory period, (c) compound nerve-action potential, (d) synapse, (e) neuromyo junction, (f) motor unit, (g) reflex arc.

4.8 An excised, active nerve trunk serves as a bioelectric source located on the axis of a circular cylindrical volume conductor. Field potentials are recorded at various radial distances from the nerve trunk from an appropriate electrode assembly connected to an amplifier. (a) Describe the behavior of the field potential with increasing radial distance from the nerve (angle and axial distance are fixed). (b) Describe the effect of increasing the specific resistivity $\rho$ of the bathing medium on the magnitude of the field potential, and explain how this change in $\rho$ might be accomplished experimentally. (c) In what manner would changing the radius of the surrounding volume-conductor affect the magnitude and waveshape of the extracellular field potential? (d) When can a volume conductor of finite dimensions be considered an essentially “infinite” volume conductor?

4.9 The experimental situation posed in Problem 4.8 is roughly analogous to the problem of recording either surface or intramuscular potentials from the arm of a human subject whose ulnar or median nerve has been stimulated (see Figure 4.8, for instance). Explain in terms of changes in specific resistivity and geometry why potential waveforms recorded at the wrist may differ considerably from those recorded at the level of the forearm (see Figure 4.8).

4.10 Define the M wave and the H reflex.

4.11 In many forms of peripheral neuropathies, the excitability of some neurons is changed, and their conduction velocities are consequently altered.
Describe the effect that this might have on an EMG recording and on muscular contraction.

4.12 A muscle is paralyzed if its neural connection to, or within, the CNS is interrupted. A disconnection at the level of the motor neuron is called a lower motoneuron lesion. A disconnection higher in the spinal cord or brain is called an upper motoneuron lesion. In both cases, the contractility of the peripheral skeletal muscle is initially preserved, but after a period of disuse, the muscle atrophies. (Atrophy, however, is much delayed in the case of an upper motoneuron lesion.) Consider Figure P4.2 to represent schematically a quadriplegic patient with paralyzed extremities as shown. Suggest a scheme for using the EMG from an auxiliary intact muscle (for example, the left trapezius muscle) to aid in the control of stimulation of the paralyzed limb. (The motor nerve supply to the trapezius muscle is assumed to lie above the site of spinal-cord lesion and is therefore under volitional control. Draw a block diagram of the suggested control system. Label the anatomical structures serving as the plant (or controlled system), the controller, the feedback pathway, the actuator, and so forth. [Hint: The EMG signal is usually amplified, rectified, and low-pass filtered before it is used to modulate a stimulator. For further interesting discussions of the work in this area, see Vodovnik et al. (1981).]

4.13 Conduct a search of the literature on the subject of the use of electromyography in the study of (a) the function of ocular muscles (the EMG yields valuable information regarding the synergistic action of the different ocular muscles, and it is of value in the interpretation of paralytic squint) and (b) myasthenia gravis and other disorders of neuromuscular transmission.

4.14 Define the following cardiac anatomical terms: (a) internodal tracts, (b) subendocardial layer, (c) intercalated disk, (d) bundle branches, (e) ventricular activation.

4.15 Draw a typical lead II electrocardiogram and label all waves (P, QRS, T) and intervals. Explain what is happening electrically within the heart during each wave or interval.
4.16 The electrical activity of the His bundle normally is not present in the typical ECG recorded at the body surface because of its relatively small tissue mass. However, clinical recordings of His bundle activity could be of considerable importance in the analysis of various disorders of the conduction system. The His bundle signal can be enhanced for such analyses by successively averaging the surface electrocardiogram, or—better yet—by using an invasive technique wherein a small bipolar electrode is introduced into the right atrial chamber via conventional techniques of cardiac catheterization. Conduct a search of the literature on the topics of noninvasive and invasive methods of recording His bundle activity as well as on the use of this signal in diagnosing various disorders of the conduction system.

4.17 Why is it necessary for the ventricular action potential to have a relatively long absolute refractory period?

4.18 Draw and label a block diagram of the retina considered as a photoelectric sensor. What is the output at the ganglion cell layer and at the photoreceptive layer?

4.19 Explain the components of the ERG in terms of retinal cell activity.

4.20 Discuss, in terms of volume-conductor theory, the production of an ERG signal at a point on the corneal surface of the eye when the retinal bioelectric source is considered an array of current dipole sources per unit volume. Consider the possibility of (experimentally) exciting each of the elements of retinal dipole array individually, one at a time, by applying a localized spot of light superimposed on a background illumination that partially adapts the retina. What special technical considerations are involved?

4.21 Discuss the use of the steady corneal-retinal potential of the eye to measure eye movements. How accurate is this technique? Discuss at least two applications of this method.

4.22 Explain the functional role played by the following CNS structures.
   a. The ascending pathways of the general sensory-nerve fibers and the descending pathways of the motor-nerve fibers
   b. The ascending reticular formation (RAS)
   c. The pre- and postcentral gyri
   d. The primary auditory and visual cortices
   e. The specific and nonspecific thalamic neural fibers to the cortex

4.23 Relate EEG-wave activity recorded at the surface of the cortex to the underlying activity of cortical neurons.

4.24 Discuss in general terms the design of a spectrum analyzer for automatic analysis of EEG waves.

4.25 How might volume-conductor theory aid in the analysis of evoked cortical potentials produced by specific repetitive stimuli (auditory, visual, etc.)?

4.26 Design the switches and resistor networks required, and show all connections between any four electrodes on the scalp (Fig. 4.28) and one differential amplifier, to record the EEG for each of the three types of electrode connections (monopolar, bipolar, and “average” potential recordings). See text associated with Figure 4.28.
REFERENCES


