INTRODUCTION TO SYNAPTIC CIRCUITS

GORDON M. SHEPHERD

Synapses are contacts that enable neurons to interact. Through these interactions they form the circuits that mediate the specific functional operations of different brain regions. The subject of synaptic organization is concerned with the principles underlying these circuits.

Synaptic organization differs from other fields of study in several ways. First, it is a multidisciplinary subject, requiring the integration of results from experimental work in molecular neurobiology, neuroanatomy, neurophysiology, neurochemistry, neuropharmacology, developmental neurobiology, and behavioral neuroscience. It is a multi-level subject, beginning (from the bottom up) with the properties of ions, transmitter molecules, and individual receptor and channel proteins and building up through individual synapses, synaptic patterns, dendritic trees, and whole neurons to the multi-neuronal circuits that are characteristic of each brain region. Finally, it is a field with a theoretical foundation, building and testing its experimentally derived results within a framework of theoretical studies in biophysics, neuronal modeling, computational neuroscience, and neural networks.

Studies of synaptic organization have been pursued vigorously for half a century, with increasing intensity. The co-authors of this book have been leaders in this effort. Each chapter lays out the synaptic organization of a specific brain region—in its full multidisciplinary, multilevel, and theoretical dimensions.

In this chapter, we introduce some of the basic principles that are common to the different regions. We show that it is possible to identify fundamental types of synaptic circuits at successive levels of organization. These types are called basic, or canonical, circuits. Like the Bohr atom in physics or gene families in molecular biology, canonical circuits are a conceptual tool for organizing the great varieties of circuits present in the nervous system. In parallel, we describe the canonical operations that the circuits perform. This provides a conceptual framework for understanding the adaptations of these operations that are unique to each of the regions considered in subsequent chapters.

It is a common lament in neuroscience that there is a lack of basic principles for understanding the vast amount of information about the brain that is accumulating. One
of the main aims of this book is to show that this lament ignores the progress that is being made in understanding synaptic organization, which is leading to a quiet revolution in our understanding of the neural basis of behavior.

THE TRIAD OF NEURONAL ELEMENTS

Figure 1.1 illustrates that the brain consists of many local regions, or centers, and of the many pathways between them. At each center, the input fibers make synapses onto the cell body (soma) and/or the branched processes (dendrites) emanating from the cell body of the nerve cells contained therein. Some of these neurons send out a long axon...
that, in turn, carries the signals to other centers; these are termed principal, relay, or projection neurons. Other cells are concerned only with local processing within the center; these are termed intrinsic neurons, local neurons, or interneurons. An example of this latter type is shown in the cerebral cortex in Fig. 1.1. The distinction between a principal and an intrinsic neuron cannot be rigid, because principal neurons also take part in local interactions. It is nonetheless a useful way of characterizing nerve cells, which is used throughout this book.

The principal and intrinsic neurons, together with the incoming input fibers, are the three types of neuronal constituents common to most regions of the brain. We refer to them as a triad of neuronal elements. The relations among the three elements vary in different regions of the brain, and these variations underlie the specific functional operations of each region.

THE SYNAPSE AS THE BASIC UNIT OF NEURAL CIRCUIT ORGANIZATION

Interactions among the triad of neuronal elements are mediated by the junctions termed synapses. It follows that the synapse is the elementary structural and functional unit for the construction of neural circuits. Traditionally, most concepts of neural organization have assumed that a synapse is a simple connection that can impose either excitation or inhibition on a receptive neuron. Much experimental evidence indicates that this assumption needs to be replaced by an appreciation of the complexity of this functional unit.

Figure 1.2 summarizes the current view of the synapse. Most synapses involve the apposition of the plasma membranes of two neurons to form a punctate junction, also termed an active zone. The junction has an orientation, thus defining the presynaptic process and the postsynaptic process. At a chemical synapse such as that depicted in Fig. 1.2, the presynaptic process liberates a transmitter substance that acts on the postsynaptic process. From an operational point of view, a synapse converts a presynaptic electrical signal into a chemical signal and back into a postsynaptic electrical signal. In the language of the electrical engineer, such an element is a nonreciprocal two-port (Koch and Poggio, 1987).

THE SYNAPSE AS A MULTIFUNCTIONAL MULTITEMPORAL UNIT

The mechanism of a synapse involves a series of steps, which are summarized in Fig. 1.2 (see Chap. 2) (for a comprehensive review, see Cowan et al., 2001). These include (1) depolarization of the presynaptic membrane; (2) influx of Ca$^{2+}$ ions into the presynaptic terminal; (3–5) a series of steps leading to fusion of a synaptic vesicle with the plasma membrane; (6) release of a packet (quantum) of transmitter molecules; (7) diffusion of the transmitter molecules across the narrow synaptic cleft separating the presynaptic and postsynaptic processes; and (9) action of the transmitter molecules on receptor molecules in the postsynaptic membrane, (10) leading in some cases to direct gating of the conductance at an ionotropic receptor. This changes the membrane potential (11) and hence the excitability of the postsynaptic process. A depolarizing change increases the excitability; this is called an excitatory postsynaptic potential.
(EPSP). A hyperpolarizing change decreases the excitability; this is called an inhibitory postsynaptic potential (IPSP). The mechanisms mediated by ionotropic receptors are concerned with rapid (1–20 msec) transmission of information, as in rapid sensory perception, reflexes, and voluntary movements (such as those used to type this text and you are using to read it).
Chapter 1. Introduction to Synaptic Circuits

The transmitter molecule may also activate a metabotropic receptor \((10a)\) linked to a second-messenger pathway that modulates a membrane conductance or has other metabolic effects \((11a\) and 12\). The presynaptic process is itself a possible target, either of the transmitter acting on autoreceptors \((8a)\) or of diffusible second messengers such as nitric oxide, produced by nitric oxide synthase (NOS) in the postsynaptic process, which can modulate transmitter release in an activity-dependent manner (also called retrograde messengers). The synapse can thus be regarded not only as a one-way relay but also as a more complicated bidirectional junction \((Jessell and Kandel, 1993)\). Although presynaptic-to-postsynaptic activation can be fast, retrograde messengers typically act more slowly.

Activation of second messengers can have short- as well as long-lasting metabolic effects that lead to changes in synaptic efficacy. Of these, long-term potentiation (LTP) and long-term depression (LTD) are the most prominent. They are discussed in the following chapters as prime candidates for "activity-dependent" mechanisms that may underlie learning and memory. Also of interest are short-term facilitation and depression, which may occur over shorter periods of 10–100 msec \((Markram and Tsodyks, 1996; Abbott et al, 1997; for a review, see Koch, 1997)\).

Many cellular mechanisms impinge on synaptic transmission over longer time periods. These include steps involved in axonal and dendritic transport, storage of transmitters and peptides, corelease of peptides, and direct modulation of transmitter responses (see Neuromodulation in Fig. 1.2). These effects are slow (seconds to minutes) or very slow (hours and longer); the slowest processes merge with mechanisms of development, ageing, and hormonal effects.

From these properties one can appreciate that the synapse is admirably suited to be a unit for building circuits. The multiple steps of its mechanism confer a considerable flexibility of function by means of different transmitters and modulators, different types of receptors, and different second-messenger systems linked to the different kinds of machinery in the cell: electrical, mechanical, metabolic, and genetic. This means that several mechanisms, with different time courses, can exist at the same synapse, conferring on the individual synapse the ability to coordinate rapid activity with the slower changes that maintain the behavioral stability of the organism over time. It is a multi-functional, multitemporal junctional unit.

TYPES OF SYNAPSES

In view of this tremendous potential for functional diversity, it is remarkable that synapses throughout the nervous system show such a high degree of morphological uniformity. Synapses in the brain tend to fall into two groups (see Fig. 1.3A): those with asymmetrical densification of their presynaptic and postsynaptic membranes and those with symmetrical densification. Gray (1959) termed these type 1 and type 2, respectively. Depending on the histological fixatives used, type 1 is usually associated with small, round, clear synaptic vesicles, and in a number of cases has been implicated in excitatory actions. By contrast, type 2 is usually associated with small, clear, flattened or pleomorphic vesicles and is implicated in inhibitory synaptic actions.

Many examples of these types of synapses are identified throughout this book. There are well recognized exceptions to these structure–function relations—for example, inhibitory actions by synapses that do not have type 2 morphology (cf. cerebellar basket
The Synaptic Organization of the Brain

B. Levels of Brain Organization

A. Types of Synapses

- presynaptic processes
- postsynaptic process
  - asymmetric
  - symmetric

**type 1** (excitatory)
**type 2** (inhibitory)

B. Multiple levels of organization. This book focuses on the levels from synapses to local circuits as a basis for understanding the expression of molecules and ions in an integrative context and for understanding the circuit basis of behavioral systems.

LEVELS OF ORGANIZATION OF SYNAPTIC CIRCUITS

It might seem that one could simply connect neurons together by means of synapses and make networks that mediate behavior, but this is not the way nature does it. A general principle of biology is that any given behavior of an organism depends on a hierarchy of levels of organization, with spatial and temporal scales spanning many orders of magnitude. This is nowhere more apparent than in the construction of the brain. As applied to synaptic circuits, it means, as already indicated, that one needs to identify the main levels of organization to provide a framework for understanding the principles underlying their construction and function.

The analysis of local regions over the past two decades has led to the recognition of several important levels of circuit organization (Fig. 1.3B). The most fundamental level...
Chapter I. Introduction to Synaptic Circuits

is the information carried in the genes, which, interacting with the cellular environment, read out the basic protein molecular components of the cells in different regions. These molecular components are organized into organelles of the cell. For circuit formation, as we have seen, the most critical organelle is the synapse.

Synaptic organization begins at the next level, with the organization of multiple gene products into the synapse. The most local patterns of synaptic connection and interaction, involving small clusters of synapses, are termed microcircuits (Shepherd, 1978). The smallest microcircuits have extents measured in microns; their fastest speed of operation is measured in milliseconds. Microcircuits are grouped to form dendritic subunits (Rall, 1977; Shepherd, 1972b; Koch et al., 1982). The dendritic trees of individual neurons are a rich integrative substrate (Rall, 1977; Llinás, 1988). The entire neuron, containing its several dendritic and axonal subunits, is the next level of complexity. Interactions between neurons within a region form local circuits (Rakic, 1976); these perform the operations characteristic of a particular region. Above this level are the interregional pathways, columns, laminae, and topographical maps, involving multiple regions in different parts of the brain, that form the systems that mediate specific types of behavior.

These many interwoven levels of organization are a feature of the brain not shared by its artificial cousin, the digital computer, in which few intermediate modular structures exist between the individual transistor, on the one hand, and a functional system, such as a random-access memory chip, on the other.

An important aim of the study of synaptic organization is to identify the types of circuits and the functional operations that they perform at each of these organizational levels. In the rest of this chapter, we consider examples at each level. Subsequent chapters show how, in each region, the nervous system rings changes on these basic themes, with variations of circuits exquisitely adapted for the specific operations and computations carried out by that region on its particular input information.

THE SYNAPSE AS AN INTEGRATIVE MICRO-UNIT

In addition to its ability to mediate different specific functions, an important property of the synapse is its small size. The area of contact has a diameter of 0.5–2.0 \( \mu \text{m} \), and the presynaptic terminal (a varicosity or bouton) has a diameter that characteristically is only slightly larger. These small sizes mean that large numbers of synapses can be packed into the limited space available within the brain. For example, in the cat visual cortex (see Chap. 12), 1 mm\(^3\) of gray matter contains approximately 50,000 neurons, each of which gives rise on average to some 6,000 synapses, making a total of 300 million (300 \( \times \) 10\(^6\)) synapses (Beaulieu and Colonnier, 1983). It has been estimated that 84% of these are type 1 and 16% are type 2. If the cortical area of one hemisphere in the human is approximately 100,000 mm\(^2\), there must be on the order of 10 billion cells in the human cortex and 60 trillion (60 \( \times \) 10\(^12\)) synapses. In the cerebellum (see Chap 7), it has been estimated that the small granule cells number up to 100 billion, each making up to 100 synapses onto cerebellar nuclear and cortical cells.

Like the national debt, these numbers are so large that they lose meaning. The important point is that the number of synapses amplifies the number of neurons by several orders of magnitude, providing a rich substrate for the construction of microcircuits within the packed confines of the brain.
DEVELOPMENT OF SYNAPTIC CIRCUITS

In early development, an exuberance of synapses is generated throughout the nervous system; during this time synapses are very dynamic and appear and disappear relatively rapidly. When the animal reaches maturity, the final synaptic density may be reduced by as much as half (yet the size of the brain has expanded considerably) (Rakic et al., 1986). Studies of these kinds of mechanisms are extremely important for understanding the strategy of construction of synaptic circuits. Developmental mechanisms are a vast field of contemporary neuroscience (for a comprehensive review, see Sanes et al., 2000). Particular aspects of development are considered in this book as they relate to basic principles, but the primary focus will be the organization and functional operations of the mature nervous system.

SYNAPTIC MICROCIRCUITS

Excitation and inhibition by single synapses have little behavioral significance by themselves; it is the assembly of synapses into patterns of connectivity during development that produces functionally significant operations. The process can be likened to the assembly of transistors onto chips to form microcircuits in computers. By analogy, we refer to these most local synaptic patterns as neuronal microcircuits. Let us consider several basic (canonical) types.

ELECTRICAL COUPLING

The simplest type of microcircuit involves a connection between two or more presynaptic terminals by electrical (gap) junctions (Fig. 1.4A). Through these junctions the electrical current in one process is distributed to the other process(es) (see Chap. 2). This arrangement has several important functions in synaptic microcircuits.

Signal-to-Noise Enhancement. The distribution of current through the electrical synapse reduces the amount of current in the active process. This reduces the impact of random (noisy) activity in single processes while enhancing the impact of simultaneous (signal specific) activity in two or more processes (this mechanism is described in the retina, Chap. 6).

Synchronization. Activity in one process may tend to activate other processes at the same time, thus promoting synchronization of activity. This can occur in either pre- or postsynaptic locations (see inferior olive cells, Chap. 7).

Gating by Different Mechanisms. The conductivity of the electrical connection may be gated by different mechanisms, such as membrane depolarization or hyperpolarization, pH, metabolic products, neurotransmitters and neuropeptides (Chap. 2). This can occur in both directions, or in only one direction (rectification). Gap junctions are thus dynamic rather than static connection elements.

Exchange of Small Molecules. Gap junctions allow the free passage of small molecules, providing the means for mediating tissue homeostasis, cellular organization, cellular differentiation and other developmental processes.
Chapter 1. Introduction to Synaptic Circuits

SYNAPTIC DIVERGENCE

A fundamental and common pattern of synaptic organization is to have multiple outputs from a single source. In neural network terminology, this is called "fan-out." A common pattern consists of multiple branches of a single axon (Fig. 1.4B). Fan-out from a single axon may be considerable, as exemplified by the several thousand synapses made by a typical cortical cell mentioned earlier. Fan-out is essential if information carried in one cell in one region is to be combined with information from cells in other regions.

Fan-out may also occur from a single terminal. As indicated in Fig. 1.4C, a presynaptic terminal (a) has excitatory synapses onto postsynaptic dendrites (b–f). An action potential (ap) invading the presynaptic terminal can thus cause simultaneous EPSPs in many postsynaptic dendrites.

SYNAPTIC CONVERGENCE

Fig. 1.4. The simplest types of synaptic microcircuits. **Synaptic divergence.** A: Divergence by electrical interactions through gap junctions. In this example, an action potential (ap) invades terminal (a) to activate a synapse onto (b); the current spreads through the gap junction from terminal (a) into terminal (a') to activate (b) near-synchronously. B: Divergence through chemical synapses. Action potential invades terminals (a) and (a'), leading to activation of (b) and (b'). C: Action potential invades large terminal (a), which has synapses onto (b–f). **Synaptic convergence.** D: Multiple synapses from a single terminal converge onto a single postsynaptic process. E: Synaptic convergence of several axons (a–c) onto a single postsynaptic neuron (d). **F: Presynaptic inhibition** by axon b onto axon a, which is presynaptic to axon c. See text.

PRESYNAPTIC INHIBITION
The operational advantages of this arrangement are several:

**Amplification.** When there are multiple outputs from a single terminal, the activity in a single axon is amplified into activity in many postsynaptic neurons, conferring a high gain upon the system. This can be important in increasing the signal-to-noise ratio underlying signal detection.

**Synchronization.** Activation of multiple synapses from a single terminal occurs simultaneously. This retains the precise timing of the input and mediates synchronization of the postsynaptic responses. Synchronization underlies oscillatory activity, which is increasingly recognized as important for signal processing in the brain.

**Retention of Sign.** The synapses from a given terminal are likely to be release the same transmitter and, although not necessarily, have the same action on postsynaptic cells (e.g., excitation → excitation).

These factors may also apply to divergence from multiple terminals, although with more variation. Divergence from single terminals is found in many parts of the nervous system. A single mossy fiber terminal in the cerebellum, for example, may make synapses onto dendrites of as many as 100 or more granule cells (cf. Chap. 7). Single terminals with more modest divergence factors are made by sensory afferents in thalamic relay nuclei (see Chap. 8) and the substantia gelatinosa of the dorsal horn.

**Release Probabilities and Safety Factors.** Multiple outputs from a presynaptic terminal can be organized in an entirely different way, as is shown by the well-known example of the neuromuscular junction (NMJ) (see Fig. 1.4D). The NMJ also consists of a large presynaptic terminal with many release sites, but they are all made onto the same muscle fiber. It is known that of 1000 or so release sites, only 100–200 are actually activated by invasion of a single impulse into the presynaptic terminal. Thus, there is a probability of only 0.1–0.2 that a given site will release transmitter when depolarized by an impulse. The multiple release sites onto the same muscle fiber therefore raise the "safety factor" for synaptic transmission, ensuring that an action potential in the presynaptic nerve will always lead to a response in the muscle fiber. Multiple synapses by a presynaptic onto a postsynaptic process are also found between neurons; an example is discussed in the retina (see Chap. 6).

The release sites of the NMJ are equivalent to the active zones of central synapses, each with its own release probability. This implies that, in the example of Fig. 1.4C, presynaptic depolarization would cause some synapses to release transmitter (e.g., b, c) but not others (e.g., d). The divergent pattern thus has the advantages noted earlier but has the disadvantage of making each connection less reliable, dependent on probability of release and other modulatory factors (see Chap. 12).

**Silent Synapses.** The NMJ example illustrates that morphological studies can identify the pattern of synaptic connections, but their actual use is physiological and probabilistic (see Kom and Faber, 1987). The release probability can be up- or down-regulated by the amount and timing of presynaptic and postsynaptic activity, providing an effective mechanism for adjusting the effect that a synapse has on its postsynaptic target (Stevens and Wang, 1994; Abbott et al., 1997). Synapses that are not activated by a single action potential but depend on these multiple factors for activation are called silent synapses.
Chapter 1. Introduction to Synaptic Circuits

SYNAPTIC CONVERGENCE

The considerable divergence that characterizes the output of a single neuron is matched by the considerable convergence of many inputs onto a single neuron. In neural network terminology, this is called "fan-in." The essence of this convergence at the microcircuit level is depicted in Fig. 1.4E, where two terminals (a, b) make synapses onto a postsynaptic dendrite (d). These simple canonical convergence patterns have a number of important properties:

**Temporal Summation.** Let us consider first the case in which both terminals are excitatory. Spread of an impulse into terminal (a) sets up an EPSP; slightly later, spread of an impulse into terminal (b) sets up an EPSP that summates with that of (a). This is termed temporal summation. Note that although the impulses in (a) and (b) may be asynchronous, their EPSPs nonetheless can summate. For relatively fast EPSPs, the prolongation that makes temporal summation possible is due mainly to the membrane capacitance, which slows the dissipation of charge across the postsynaptic membrane (cf. Johnston and Wu, 1995; Shepherd, 2003a). For slower EPSPs, the time course is controlled by biochemical processes, such as second messengers.

**Quantal vs. Graded Actions.** When a single synapse releases a single vesicle, the action on a postsynaptic process is quantal in amplitude, that is, all-or-nothing. This is likely to be the case for the postsynaptic response of a dendritic spine receiving one synapse (see later). When multiple synapses are activated by different input fibers, summation in the dendritic branches and cell body of the postsynaptic cell is graded in amplitude with the numbers of input fibers and their release probabilities. Thus, synaptic actions are either quantal or graded, depending on the numbers of synapses involved and the spatial extents of the summating process.

**Synaptic Summation Is Fundamentally Nonlinear:** Although it might appear that temporal summation involves simple linear addition of PSPs, in general this is not the case. This is because PSPs are generated by changes in membrane conductance to specific ions and not by current injection (see Chap. 2). The conductances act to shunt, or short-circuit, each other, so that the combined amplitude of a PSP is less than the sum of its parts. As first emphasized by Wilfrid Rall, this means that synaptic summation is essentially a nonlinear process (Rall, 1964, 1977; Johnston and Wu, 1995; Shepherd, 2003b).

**Types of Excitatory–Inhibitory Interactions.** Synaptic convergence also involves summation of excitatory and inhibitory PSPs. This process lies at the heart of the integrative mechanisms of neurons. Consider, for example, in Fig. 1.4E, that (b) is inhibitory. Activation sets up an IPSP, which opposes the EPSP set up by (a) and repolarizes the membrane toward the reversal potential for the inhibitory conductance (see Chap. 2). If the reversal potential is near the resting membrane potential, this is called silent, or shunting, inhibition. If it is more polarized, it gives rise to hyperpolarizing inhibition. Obviously, integration of excitatory and inhibitory synaptic responses can be highly nonlinear and complex, even without the added complication of active membrane properties (Rall, 1964; Koch et al., 1983; Koch, 1997).
Spatial Summation. It remains to note that inputs are characteristically distributed over the entire dendritic surface of a neuron [see (c) in Fig. 1.4E]. This means that, in addition to temporal summation, there is spatial summation of responses arising in different parts of a dendrite, as well as different parts of the whole dendritic tree. Spatial summation allows for combining many inputs into one integrated postsynaptic response. The separation of PSPs reduces the nonlinear interactions between synaptic conductances, making the summation more linear. However, it also increases the possibilities for local active mechanisms and the generation of nonlinear sequences of activation from one site to the next within the dendritic tree.

PRESYNAPTIC INHIBITION

This is a final type of simple synaptic combination involving a special type of convergence. In this arrangement (see Fig. 1.4F), a presynaptic terminal (a) is itself postsynaptic to another terminal (b). The presynaptic action may involve a conventional type of IPSP produced by (b) in the presynaptic terminal (a). Alternatively, there may be a maintained depolarization of the presynaptic terminal, reducing the amplitude of an invading impulse and with it the amount of transmitter released from the terminal. The essential operating characteristic of this microcircuit is that the effect of an input (a) on a cell (c) can be reduced or abolished (by b) without there being any direct action of (b) on the cell (c) itself. Control of the input (a) to the dendrite or cell body can thus be much more specific.

Presynaptic control may be exerted by either axon terminals or presynaptic dendrites. Note that the effect is presynaptic only with regard to the response of the postsynaptic cell. From the point of view of the presynaptic terminal, the effect is postsynaptic. There are many situations in the nervous system, involving multiple synapses between axonal and/or dendritic processes, in which sequences of pre- and postsynaptic effects can occur (see Chaps. 3, 5, 6, 8, on the spinal cord, olfactory bulb, retina, and thalamus).

INHIBITORY OPERATIONS

The patterns of synaptic connections considered thus far mediate elementary excitatory and inhibitory operations. Let us next consider canonical arrangements that carry out operations for specific information processing functions through inhibitory interneurons.

Feedforward Inhibition. Sensory processing commonly involves an inhibitory "shaping" of excitatory events. An important mechanism for producing this is by a pattern of synaptic connections that mediates feedforward inhibition. The most common type involves excitatory input to both a principal neuron and an inhibitory interneuron, so that the activated interneuron "feeds forward" inhibition onto the principal neuron (Fig. 1.5A, left). A special variation of this type of arrangement (Fig. 1.5A, right) consists of an afferent terminal (a) which makes synapses onto the dendrites of both a relay neuron (b) and an interneuron (c). The dendrites of both neurons respond by generating EPSPs. However, the interneuron also has inhibitory dendrodendritic synapses onto the relay neuron; the EPSP activates these synapses, producing an inhibition of the relay neuron. The extra synapse in this pathway helps to delay the inhibitory input, so that the combined effect in (b) is an excitatory–inhibitory sequence.
Chapter I. Introduction to Synaptic Circuits

A. FEEDFORWARD INHIBITION

B. RECURRENT INHIBITION

C. RECURRENT AND LATERAL INHIBITION

Fig. 1.5. Microcircuits that mediate different types of postsynaptic inhibition. A: Feedforward inhibition: on the left, through an interneuronal axon, on the right, through an interneuronal dendrite. B: Recurrent inhibition, in which a relay neuron (a) is both presynaptic and postsynaptic to the dendrite (d) of an inhibitory interneuron (b). This microcircuit mediates both recurrent and lateral inhibition, through the series of steps indicated by 1–6. C: Comparison between lateral inhibition mediated by axon collateral and interneurons and by dendrodendritic connections. See text.

This type of sequence is found in the thalamus (see Chap. 8) and many sensory pathways. By restricting the excitation of relay neurons to the onset of an excitatory input, it serves to enhance the sensitivity to changing stimulation, and thus performs a kind of temporal differentiation on changing sensory states (Koch, 1985). By means of spread of postsynaptic responses through dendritic trees, it may also contribute to the enhancement of spatial contrast through lateral inhibition (see later).
Note that the microcircuits in Fig. 1.5A are built of all three elementary patterns discussed earlier and depicted in Fig. 1.4. Thus, they combine divergence from terminal (a) with convergence of (a) and (c) onto (b) and presynaptic control by (a) of (c).

**Recurrent Inhibition.** A common type of operation in the nervous system is one in which the excitation of a neuron leads to inhibition of that neuron and/or of neighboring neurons. This is called feedback or recurrent inhibition. It can be mediated by several types of circuit, the most local of which involves reciprocal dendrodendritic synapses.

This mechanism has been worked out at the synaptic level in the olfactory bulb (see Chap. 5) and is illustrated in Fig. 1.5B. The output neurons of the olfactory bulb are mitral and tufted cells (a). They are activated by EPSPs, which spread through a primary dendrite (1) to the cell body (2) to set up an impulse that propagates into the axon (3). The impulse also backspreads into secondary dendrites (4), where it activates output synapses that are excitatory to spines of granule cell dendrites (5). The EPSP in the spine then activates a reciprocal inhibitory synapse back into the mitral cell dendrite (6); the IPSP spreads through the neuron to inhibit further impulse output.

Reciprocal synapses thus form an effective microcircuit module carrying out an elementary computation—in this case, recurrent inhibitory feedback of an activated neuron. Reciprocal synapses are found in a number of regions of the nervous system; in addition to the olfactory bulb, they include the dorsal horn of the spinal cord, retina (see Chap. 6), thalamus (see Chap. 8), and suprachiasmatic nucleus. There also is evidence for feedback from dendrites onto axon terminals in the cerebral cortex (Zilberter, 2000). Their presence in the different nuclei of the thalamus means that they play a role in the thalamocortical circuits that control cortical operations (cf. Chap. 8).

**Lateral Inhibition.** In addition to recurrent inhibition, the same microcircuit may mediate lateral inhibition. In Fig. 1.5B, the EPSP in the granule cell spine spreads through the dendritic branch to other spines, activating inhibitory output onto neighboring, less active, mitral cells. The more common implementation is through axon collaterals of an output neuron that feed back onto an interneuron, which inhibits other output neurons through its axonal connections. This was first described in the spinal cord, where it was named Renshaw inhibition, after its discoverer (see Chap. 3).

The two neural substrates for lateral inhibition are compared in Fig. 1.5C in relation to the axon hillock of the output cell. Dendrodendritic inhibition is activated by the backspreading action potential from the axon hillock. It is therefore “prehillock” in location (Fig. 1.5C, right). The pathway is local, limited to the dendritic tree of that neuron and its interconnections with local subunits of the interneuronal dendrites. By contrast, Renshaw inhibition is due to the forward-propagating action potential from the axon hillock and is therefore “trans-hillock” in nature (Fig. 1.5C, left). The pathway consists of the global output of the axon collaterals of the output neuron and the axonal branches of the activated interneurons.

Lateral inhibition is a fundamental mechanism of neural processing. We will see numerous examples of how it is implemented in virtually every region of the brain.
Chapter 1. Introduction to Synaptic Circuits

DENDRITIC INTEGRATION AND DENDRITIC SUBUNITS

We now move to the next higher level of organization, of dendritic trees. Understanding of the functional properties of dendritic trees began with the pioneering studies of Wilfrid Rall (Rall, 1957; 1959a,b; Segev et al., 1995). Neuronal dendrites are characteristically highly branched, which obviously increases the surface area for receiving synaptic inputs. Despite this wide distribution of synapses on the dendrites, it is common practice in neuroanatomical textbooks, and it is the common assumption underlying the vast majority of neural network simulations, to consider nerve cells to be single-node, linear integration devices, in which the effects of dendritic morphology and synaptic patterns on the functions of individual cells are totally neglected.

In fact, the patterns of dendritic branching impose critical geometrical constraints on the integration of activity in different branches. The rules for integration were developed in a comprehensive theoretical framework by Wilfrid Rall (summarized in Segev et al., 1995) which applies to the analysis of dendritic properties in all the chapters of this book. The geometry of the branches and the sites of specific inputs combine with the electrotonic properties to ensure that parts of a dendritic tree can function semi-independently of one another. If one adds the fact that voltage-gated channels can confer excitable properties onto local dendritic regions, it is clear that the dendrites, far from being functionally trivial appendages of a cell body, are the substrate for generating a rich repertoire of computation that contributes critically to the overall input-output functions of the neuron. It is thus evident that single-node network models ignore several levels of dendritic organization responsible for much of the computational complexity of the real nervous system.

Four factors—dendritic branching architecture, synaptic placement, and passive and active membrane properties—must be taken into account in assessing the nature of the integrative activity of dendrites. Characterization of the electrotonic spread of potentials is difficult because of the complex branching patterns of many dendrites. An introduction to one-dimensional passive cable theory is provided in several accounts (Rall, 1977; Johnston and Wu, 1995; Segev, 1995; Shepherd, 2003a). The ways that active conductances can contribute to dendritic activity are considered in Chap. 2.

The functional role of dendritic activity in information processing within synaptic circuits is a common theme running through the accounts of most of the cells in the brain regions considered in this book. Here we provide a brief introduction to the nature of dendritic integration and the ways that functional compartments are created at several levels of dendritic organization. Although dendritic branching patterns seem infinitely variable, canonical operations can be seen to apply across most of these patterns.

DENDRITIC COMPUTATION

In assessing the nature of dendritic integration, it is increasingly fashionable to use computational metaphors. Although this obscures many functional roles of dendrites that are not strictly "computational" (e.g., mechanisms involved in development, maturation, activity-dependent changes, etc.), it has the advantage of providing a specific framework within which the capacity of dendrites to carry out well-characterized types of operations can be assessed.
The importance of the sites and types of synaptic inputs on a dendritic branch can be illustrated by using the paradigm of logic operations. In the diagram of Fig. 1.6A, alternating excitatory and inhibitory synapses are arranged along a dendritic branch. Given the nonlinear interactions between these synapses, as discussed earlier, an inhibitory synapse \((i_1, i_2, i_3)\) with a synaptic reversal potential close to the resting potential of the cell ("shunting" or "silent" synapse, see Chap. 2) can effectively oppose an excitatory synapse \((e_1-e_3)\).

Fig. 1.6. Arrangements of synapses that could subserve logic operations. A: A single dendrite receives excitatory \((e_1-e_3)\) and inhibitory \((i_1-i_3)\) synapses. An inhibitory input can effectively veto only more distal excitatory responses; this approximates an AND-NOT logic operation, e.g., \([e_2 \text{ AND NOT } i_1 \text{ or } i_2]\). B: Branching dendritic tree with arrangements of excitatory and inhibitory synapses. As in A, inhibitory inputs effectively veto only the excitatory response more distal to it, e.g., \([e_5 \text{ AND NOT } i_5 \text{ AND NOT } i_7]\). C: Branching dendritic tree with excitatory synapses on spines and inhibitory synapses either on spine necks or on dendritic branches. Different types of logic operations arising out of these arrangements are indicated. In all cases (A–C), inhibition is of the shunting type. See text. [A, B adapted from Koch, 1983; C based on Shepherd and Brayton, 1987.]
("veto") the ability of a membrane potential change generated by any more distal excitatory synapse to spread to the soma and generate impulses there. By contrast, an inhibitory synapse has little effect in vetoing the voltage change initiated by more proximal excitatory synapses. This operation is an analog form of a digital AND-NOT gate (e and not more proximal i) and has been postulated to be a mechanism underlying various computations, such as direction selectivity in retinal ganglion cells.

This type of synaptic arrangement can also be found in more localized parts of dendritic trees. Figure 1.6B depicts a case in which a dendrite has numerous distal branches, each with an excitatory and an inhibitory synapse. The same "on-path" rule still applies: an inhibitory synapse effectively vetoes a more distal excitatory synapse on the same branch but has little effect in opposing excitatory responses originating anywhere else in the dendritic tree, which are effectively sited more proximally to the soma. Thus, the combination of dendritic morphology in conjunction with synaptic placement enables the cell to "synthesize" analog versions of logical, boolean operations.

In summary, local dendrites can be considered canonical structures that apply across most types of dendritic branching. In addition, logic operations can be considered canonical operations, in terms of basic properties of coincidence detection and excitatory-inhibitory interactions, that also apply across most types.

DENDRITIC SPINE UNITS

The smallest compartment, structurally and functionally, within a dendritic tree is the dendritic spine, a small (1–2 \( \mu \text{m} \)), thornlike protuberance. It is already evident from Fig. 1.5 that spines are an important component in many kinds of microcircuits. An electron micrograph of a spine in the cerebral cortex is shown in Fig. 1.7. Spines are extremely numerous on many kinds of dendrites; in fact, they account for the majority of postsynaptic sites in the vertebrate brain. They are especially prominent in the cerebellar cortex (see Chap. 7), basal ganglia (see Chap. 9), and cerebral cortex (see Chaps. 10–12). Within the cerebral cortex, about 79% of all excitatory synapses are made onto spines and the rest are made directly onto dendritic branches, whereas 31% of all inhibitory synapses are made onto spines. A spine with an inhibitory synapse always carries an excitatory synapse as well (Beaulieu and Colonnier, 1983). Given the dominance of excitatory synapses, about 15% of all dendritic spines carry both excitatory and inhibitory synaptic profiles.

On dendrites of cortical pyramidal cells, spine densities may reach several spines per micrometer of dendritic length. Because spines are characteristically located on dendrites at some distance from the cell body, experimental evidence regarding their physiological properties is still difficult to obtain. However, their obvious importance has stimulated considerable interest (Shepherd, 1996; Harris, 1999; Yuste and Majewska, 2001; Nimchinsky et al., 2002; Segal, 2002). It is now possible to obtain direct structural, molecular, and functional data on spine properties. Subsequent chapters will give abundant testimony to this new work.

**Specific Information Processing.** To illustrate the potential importance of spines for information processing in synaptic circuits, the paradigm of logic operations is useful. The diagram in Fig. 1.6C represents a dendritic tree with its distal branches covered by spines. Assume that there are patches of active membrane in the distal dendrites and
Fig. 1.7. The fine structure of a dendritic spine. This electron micrograph shows (bottom) a longitudinally cut dendrite from which arises a spine (s). The spine is approximately 1.5 \( \mu m \) in length and 0.1 \( \mu m \) at its narrowest width. At its head it receives a synapse, which has the round vesicles and asymmetrical density characteristic of Gray's type 1. In the neck and head are small clumps of ribosomes; in the dendrite are longitudinally cut microtubules. [From Feldman, 1984.]

that these give rise to a regenerative membrane event if there is sufficient depolarization by an excitatory synaptic response (Miller et al., 1985; Perkel and Perkel, 1985; Shepherd et al., 1985). One possible arrangement is that the impulse would fire if any one of several spines in a cluster should receive an excitatory input; this would be equivalent to an OR gate in the logic paradigm. Alternatively, two simultaneous inputs might be required; this would constitute an AND gate. Finally, one might have AND-NOT gates. Depending on the placement of the inhibition, the gate might be localized to an individual spine, or it might involve a dendritic branch containing a cluster of spines. These possibilities can all be traced in the diagram of Fig. 1.6C. Experimental studies suggest that these simple combinations of excitatory and inhibitory interactions do occur in natural activity, and computer simulations have shown that the logic operations arise readily out of these arrangements (Shepherd and Brayton, 1987; Shepherd et al., 1989).
Chapter 1. Introduction to Synaptic Circuits

These studies indicate that interactions in the smallest compartments of the nervous system—terminal dendritic branches and dendritic spines—may be capable of powerful and precise types of information processing. A further interest is that, through sequential activation of active sites along branches within the dendritic tree, synaptic responses initiated in the most distal parts of the tree nonetheless can exert precise control over the generation of impulses in the cell body and initial axonal segment.

In summary, the spine may be considered as a canonical unit for synaptic reception and in some cases synaptic output as well. It does not have a single function, however; rather, it appears to be a unit with multiple canonical functions (Shepherd, 1996). Some of those functions are summarized in Table 1.1. They are described in detail in subsequent chapters.

Associative Learning. In recent years considerable attention has been focused on the possibility that LTP of cortical neurons may underly learning and memory (reviewed in Nicoll and Malenka, 1995). This involves a long-term (hours to weeks) increase in synaptic efficiency in response to a presynaptic input volley. There is growing evidence of anatomical, biochemical, and physiological changes in dendritic spines of these cells during LTP. It has been shown, for example, that sufficient depolarization of a spine increases calcium ion ($Ca^{2+}$) conductance; the calcium ions are then available to bring about biochemical and structural changes in the spine that could function in the storage of information (see Fig. 1.2; these mechanisms are discussed in detail in Chap. 1). To the extent that these changes involve activation thresholds and nonlinear properties, they can be incorporated into the logic paradigm of spine interactions illustrated in Fig. 1.6C.

DENDRITIC BRANCH SUBUNITS

Functional compartments can be created in dendritic trees in various ways. The interactions between excitatory and inhibitory synaptic responses described earlier define relatively small functional subunits. By contrast, larger functional compartments are built into the branching structure of dendrites during development.

The mitral cell of the olfactory bulb provides a clear example of this level of organization. As shown in Fig. 1.8A (left), each mitral cell has a primary dendrite, divided into two subunits: a terminal tuft (T) and a primary dendritic shaft ($I^\circ$). The function of the terminal tuft is to receive the sensory input through the olfactory nerves and process the responses through dendrodendritic interactions (see inset). The function of the primary dendritic shaft is to pass on this integrated response to the cell body. The third dendritic subunit in this cell consists of the secondary ($2^\circ$) dendrites, which take part in dendrodendritic interactions with the granule cells and thereby control the output from the cell body (these have been described above; see Fig. 1.5B). Thus, the mitral cell dendritic tree is fractionated into three large subunits, each with a distinct function that is carried out semi-independently of the others (see Chap. 5 for further details).

Another example of dendritic compartmentalization is provided by the starburst amacrine cell of the retina. This cell (see Fig. 1.8B) has a widely radiating dendritic tree. Like olfactory granule cells; amacrine cells lack axons; the distal dendritic branches are the sites of synaptic output, whereas synaptic inputs are present both
Table 1.1. Functions That Have Been Ascribed to Spines

<table>
<thead>
<tr>
<th>Function</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site of synaptic connection</td>
<td>Receives synaptic input</td>
</tr>
<tr>
<td>Site of excitatory synaptic input</td>
<td>Site of inhibitory synaptic input (axon initial segment)</td>
</tr>
<tr>
<td>The spine only connects</td>
<td></td>
</tr>
<tr>
<td>Developmental synaptic target</td>
<td>Increases dendritic surface area</td>
</tr>
<tr>
<td>Makes synaptic connections tighter</td>
<td></td>
</tr>
<tr>
<td>Critical for development of synaptic connections</td>
<td></td>
</tr>
<tr>
<td>Matching of pre- and postsynaptic elements</td>
<td></td>
</tr>
<tr>
<td>Local dendritic input-output unit</td>
<td>Mediates prolonged synaptic output</td>
</tr>
<tr>
<td>Serves as dendrodendritic input-output unit</td>
<td></td>
</tr>
<tr>
<td>Passive synaptic potential modification</td>
<td></td>
</tr>
<tr>
<td>Spine: dendrite impedance matching</td>
<td></td>
</tr>
<tr>
<td>Synaptic potential attenuation</td>
<td></td>
</tr>
<tr>
<td>Constant current device</td>
<td></td>
</tr>
<tr>
<td>Large amplitude, rapid local responses (EPSP amplification)</td>
<td></td>
</tr>
<tr>
<td>Unit for synaptic plasticity</td>
<td></td>
</tr>
<tr>
<td>Spine stem modulates synaptic spread into dendrite</td>
<td></td>
</tr>
<tr>
<td>Spine stem involved in memory (EPSP amplitude modulation)</td>
<td>Site of LTP/LTD</td>
</tr>
<tr>
<td>Rapid mechanical changes: do spines twitch?</td>
<td></td>
</tr>
<tr>
<td>Active synaptic boosting unit</td>
<td></td>
</tr>
<tr>
<td>Site of local impulse amplification</td>
<td></td>
</tr>
<tr>
<td>Site of pseudosalvatory conduction</td>
<td></td>
</tr>
<tr>
<td>Information processing unit</td>
<td></td>
</tr>
<tr>
<td>Thresholding operational unit</td>
<td></td>
</tr>
<tr>
<td>Active logic gate: specific information processing in distal dendrites</td>
<td></td>
</tr>
<tr>
<td>Temporal processing unit</td>
<td></td>
</tr>
<tr>
<td>Acts as coincidence detector</td>
<td></td>
</tr>
<tr>
<td>Biochemical compartment</td>
<td></td>
</tr>
<tr>
<td>Absorbs nutrients</td>
<td></td>
</tr>
<tr>
<td>Provides for biochemical isolation related to single synapse</td>
<td></td>
</tr>
<tr>
<td>Site of local protein synthesis (polyribosomes)</td>
<td></td>
</tr>
<tr>
<td>Site of local Ca(^{2+}) increase</td>
<td></td>
</tr>
<tr>
<td>Neuroprotection: isolates the dendrite from toxic Ca(^{2+}) levels</td>
<td></td>
</tr>
<tr>
<td>Membrane surface shape properties</td>
<td></td>
</tr>
<tr>
<td>Target for electrophoretic membrane migration</td>
<td></td>
</tr>
<tr>
<td>Increases dendritic membrane capacitance</td>
<td></td>
</tr>
<tr>
<td>Shortest wire in the nervous system</td>
<td></td>
</tr>
<tr>
<td>Increases intersynaptic distance</td>
<td></td>
</tr>
</tbody>
</table>

For references, see text. EPSP, excitatory postsynaptic potential; LTP, long-term potentiation; LTD, long-term depression.

Source: Shepherd, 1996, with permission.
Fig. 1.8. Organization of subunits within dendritic trees. A: Mitral cell of the olfactory bulb, showing division of the dendritic tree into three main subunits. Abbreviations: aff., afferent; t, dendritic tuft; 1°, 2°, primary and secondary dendrites. Synaptic microcircuits are indicated in insets. B: Starburst amacrine cell in the retina, showing division of dendritic tree into functional subunits, as exemplified by a–c. Microcircuits are indicated in the insets. [A after Shepherd, 1979; B based in part on Koch, 1982.]

This information can be combined with other information to begin to give an integrated understanding of this particular type of microcircuit. The starburst cells synthesize and release acetylcholine (ACh), providing excitatory input to direction-selective ganglion cells. Pharmacological evidence suggests that the most common inhibitory neurotransmitter, gamma-aminobutyric acid (GABA), provides the inhibitory input in the cell’s null direction. Thus, an excitatory bipolar cell input to the amacrine cell could, in conjunction with GABAergic input from inhibitory bipolar or inhibitory cells, function as an AND-NOT gate, in analogy with the corresponding arrangement illustrated in Fig. 1.6B. Paradoxically, starburst amacrine cells also appear to synthesize, store, and release GABA (see Chap. 6). Until recently, such a colocalization of two fast-acting neurotransmitters was thought not to exist. Its presence obviously increases the opportunities for more complex synaptic interactions at the local level. We discuss retinal circuits for movement detection further later.
A BIOPHYSICS OF COMPUTATION

We have seen that a neuron generally contains several levels of organization within it, starting with the synapse as the basic functional unit. The different patterns of synapses, coupled with passive and active membrane properties and the geometry of the dendrites, provide a rich substrate for carrying out neuronal computations. The time scale of these computations varies greatly, from the fraction of a millisecond required for inhibition to suppress EPSPs in dendritic spines to many hundreds of milliseconds or seconds in the case of the slowly acting effects of neuropeptides on the electrical properties of neurons.

A description of the way that different types of membrane conductances, each with a characteristic distribution in the cell body and dendrite, combine to control the flow of information through the neuron is given in Chap. 2. Table 1.2 provides a brief compendium of some elementary synaptic circuits and biophysical mechanisms relevant for carrying out specific computations in the nervous system. In addition to their interest for neuroscience, these operations are of considerable potential relevance in computer science, where work on the "physics of computation" attempts to characterize the physical mechanisms that can be exploited to perform elementary information processing operations in artificial neural systems (Mead and Conway, 1980). These mechanisms constrain in turn the types of operations that can be exploited for computing. It has been suggested that a "biophysics of computation" is needed for understanding the roles of membranes, synapses, neurons, and synaptic circuits in information processing in biological systems, to bridge the gap between computational theories and neurobiological data (Koch, 1999; Shepherd, 1990). This knowledge will also enable us to understand the fundamental limitations in terms of noise, accuracy, and irreversibility on neuronal information processing.

The vast majority of neural network simulations—in particular, connectionist models—consider individual nerve cells to be single-node, linear integration devices. They thus neglect the effect of dendritic, synaptic, and intrinsic membrane properties on the function of individual cells. An important goal of the study of synaptic organization is therefore to identify the specific operations, such as those summarized in Table 1.2, that arise from these properties and incorporate them into more realistic network simulations of specific brain regions.

THE NEURON AS AN INTEGRATIVE UNIT

How are these different levels of dendritic functional units coordinated with the soma and initial segment of the axon to enable neurons to function as complex integrative units? The answer to this question requires an understanding of how synaptic activity in the dendrites is related to action potential generation in the axon hillock and initial axonal segment. These points are amplified in Chap. 2 and in subsequent chapters for specific neuronal types.

ACTION POTENTIAL INITIATION

The modern view of how a neuron generates an action potential arose in the 1950s, when the first intracellular recordings from spinal motoneurons showed that EPSPs in
### Table 1.2. Some Neuronal Operations and Their Underlying Biophysical Mechanisms

<table>
<thead>
<tr>
<th>Biophysical Mechanism</th>
<th>Neuronal Operation</th>
<th>Example of Computation</th>
<th>Time Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Action potential initiation</td>
<td>Threshold, one-hit analog-to-digital converter</td>
<td></td>
<td>0.5–5 msec</td>
</tr>
<tr>
<td>Action potentials in dendritic spines</td>
<td>Binary OR, AND, AND-NOT gate</td>
<td>$a$</td>
<td>0.1–5 msec</td>
</tr>
<tr>
<td>Nonlinear interaction between excitatory and inhibitory synapses</td>
<td>Analog AND-NOT veto operation</td>
<td>Retinal directional selectivity$^b$</td>
<td>2–20 msec</td>
</tr>
<tr>
<td>Spine–triadic synaptic circuit</td>
<td>Temporal differentiation high-pass filter</td>
<td>Contrast gain control in the LGN$^c$</td>
<td>1–5 msec</td>
</tr>
<tr>
<td>Reciprocal synapses</td>
<td>Negative feedback</td>
<td>Lateral inhibition in olfactory bulb$^d$</td>
<td>1–5 msec</td>
</tr>
<tr>
<td>Low-threshold calcium current ($I_T$)</td>
<td>Triggers oscillations</td>
<td>Gating of sensory information in thalamic cells$^e$</td>
<td>5–15 Hz</td>
</tr>
<tr>
<td>NMDA receptor current ($I_A$)</td>
<td>AND-NOT gate</td>
<td>Associative LTP$^f$</td>
<td>0.1–0.5 sec</td>
</tr>
<tr>
<td>Regulation of potassium currents ($I_M, I_{AHP}$) via neurotransmitter</td>
<td>Temporal delay</td>
<td>Escape reflex circuit in Tritonia$^g$</td>
<td>10–400 msec</td>
</tr>
<tr>
<td></td>
<td>Gain control</td>
<td>Spike frequency accommodation in sympathetic ganglion$^h$</td>
<td>0.1–2 sec</td>
</tr>
<tr>
<td></td>
<td></td>
<td>and hippocampal pyramidal cells$^i$</td>
<td></td>
</tr>
<tr>
<td>Long-distance action of neurotransmitters</td>
<td>Routing and addressing</td>
<td></td>
<td>1–100 sec</td>
</tr>
</tbody>
</table>

Note: The time scales are only approximate. LGN, lateral geniculate nucleus; LTP, long-term potentiation; NMDA, N-methyl-D-aspartate.

Sources: Includes the chapter in which the mechanism is discussed and the original reference.

$^a$ Chap. 1; see also Shepherd and Brayton, 1987.

$^b$ Chap. 1; see also Koch et al., 1982, 1983.

$^c$ Chap. 8; see also Koch, 1985.

$^d$ Chap. 5; see also Rall and Shepherd, 1968.

$^e$ Chaps. 2 and 8; see also Jahnsen and Llinás, 1984a,b.

$^f$ Chap. 2; Jahr and Stevens, 1986.

$^g$ See Getting, 1983.

$^h$ Chap. 3; see also Adams et al., 1986.

$^i$ Chap. 11; see also Madison and Nicoll, 1982.


The dendrites spread through the soma to initiate the action potential in the axon hillock-initial segment. These early studies are reviewed elsewhere (Shepherd, 2003b). The problem has been re-investigated thoroughly since the introduction of the multiple patch recording method by Stuart and Sakmann in 1993. The classical concept holds for low-to-medium levels of synaptic input, but there can be a shift to dendritic sites of action...
potential initiation with medium to high levels of input. We discuss two examples in relation to Fig. 1.9.

*Cortical Pyramidal Neurons.* In pyramidal cells of the hippocampus and neocortex, the action potential in response to synaptic excitation in the dendrites arises in the initial axonal segment and propagates both down the axon and back into the soma.

![Diagram of a Pyramidal cell](image)

**A. Pyramidal cell**

![Diagram of a Mitral cell](image)

**B. Mitral cell**

Fig. 1.9. Sites within the neuron for action potential initiation. A: Pyramidal cell in the rat cerebral cortex. [From Stuart et al., 1997.] B: Mitral cell in the rat olfactory bulb. [From Chen et al., 1997.] See text.
dendrites (Fig. 1.9A). Action potential initiation and forward propagation in the axon of course are supported by high densities of sodium (Na) channels in the initial segment and nodes of Ranvier, respectively. By contrast, the soma-dendrites have a low density of Na channels, which are not sufficient to generate action potentials directly in response to the relatively low amplitudes of dendritic EPSPs but can be activated by the large-amplitude depolarizations of backpropagating action potentials. In general, EPSPs in the distal dendrites by themselves give rise to slow low-amplitude regenerative "spikes" that forward propagate only under special conditions; this is explained further in Chaps. 11 and 12.

The back propagating action potentials are believed to have several possible roles in the integrative activity of cortical pyramidal neurons (reviewed in Stuart et al., 1999; Spruston et al., 2000). (1) They may function as "hot spots" to boost EPSPs in spreading from distal dendrites to the soma and axon hillock. (2) They may serve as sites of local integration and thresholding operations at dendritic branch points. (3) Their activity may contribute to synaptic plasticity and memory mechanisms. (4) Finally, they appear to boost the backspreading impulse so that it may send a more global retrograde signal to the entire dendritic tree that an impulse output has occurred. These and other possibilities are discussed in the appropriate chapters of this book; see especially Chap. 8 (cerebellum), Chap. 11 (hippocampus), and Chap. 12 (neocortex).

Mitral Cells. As described earlier, the sensory-evoked EPSP in the distal dendritic tuft spreads through the primary dendrite and soma to the axon hillock to initiate the action potential, which both propagates into the axon and spreads back into the soma and dendrites. Double-patch recordings have confirmed this classic model with weak synaptic excitation (Fig. 1.9B, 17 μA). However, with stronger excitation, the site of initiation shifts to the distal dendritic region, and a full action potential propagates through the primary dendrite to the soma and out the axon (Fig. 1.9B, 33 μA). An action potential in the soma has been shown experimentally under direct observation to propagate actively through the secondary dendrites. These experiments, together with computer simulations, are discussed further in Chap. 5.

As discussed earlier in this chapter, the backpropagating action potential in the secondary dendrites of mitral cells is believed to mediate several specific functions: recurrent inhibition of the activated mitral cell, lateral inhibition of neighboring mitral cells; and oscillatory firing of the mitral cell population. The functions associated with the backpropagating action potential in the primary dendrite, analogous to the apical dendrite of cortical pyramidal neurons, are less well understood. These questions are discussed further in Chap. 5.

The Concept of the Canonical Neuron. From these experiments on cortical pyramidal neurons and mitral cells, it is clear that the central neurons are much more complex integrative units than is usually realized. A key question that follows is: How much of this complexity is necessary to build realistic neuronal and network models in order to simulate brain functions?

The pyramidal neuron of the cerebral cortex is a prime example of this problem. Clearly, an understanding of the functional organization of this type of neuron is critical for an understanding of cognitive functions. Pyramidal neurons are the principal
neurons in all three basic types of cortex: olfactory (see Chap. 10), hippocampal (see Chap. 11), and neocortex (see Chap. 12). Although they vary in size and shape, one can identify a "canonical" pyramidal neuron in the same way that one identifies a gene family by certain shared characteristics. What we particularly need to know is: What is the minimum architecture necessary to capture the integrative structure of the pyramidal neuron?

An approach to this answer is illustrated by the reduced representation in Fig. 1.10, left. It consists of (1) division of the dendritic tree into apical and basal parts, (2) dendritic spines on both apical and basal dendrites, and (3) different excitatory and inhibitory synaptic inputs to different levels of the apical and basal dendritic trees. A final feature (4) (not shown) is a long axon that gives off axon collaterals that makes synapses on targets within the neighborhood of the cell and at different distances from the cell.

This canonical cell can be converted into a canonical model by representing it as a series of compartments, as shown in Fig. 1.10, right. Each compartment can be seen to form a local subunit that can play a critical role in information processing within the neuron by virtue of its unique combination of synaptic inputs, passive properties, active properties, and relation to other subunits. Thus, the spines (A1, A2) represent principal sites of excitatory inputs; their interactions may generate specific local information processing and local activity-dependent changes, as discussed earlier. The activity spreading in dendritic branches (B, C) is summed at a branch point (D), which acts as a local decision point for passing activity toward the soma. Whether this ac-

![Fig. 1.10. Left: Canonical representation of a cortical pyramidal neuron. Right: Further abstraction of a cortical pyramidal neuron as a branching system of integrative units. See text. [Modified from Shepherd, 1994.]]
tivity spreads effectively to the soma depends on modulatory gating by both excitatory and inhibitory inputs along the apical shaft (D). There is a further stage of summation between the activities spreading to the soma from the apical (D) and basal (E) dendrites. Finally, there are direct inputs to the soma, many of them inhibitory, which provide for global integration and modulation of the neuronal output, in contrast to the local activities taking place within each dendritic branch and field. When the impulse is initiated in the axon hillock, in addition to propagating along the axon, it back-propagates into the dendrites, thus sending a global signal that an output has occurred to the local subunits, modulating the excitability of the dendrites in relation to further synaptic inputs and perhaps triggering dendritic outputs onto those input terminals.

In summary, a logical parsing of the canonical structure indicates a sequence of functional operations, proceeding from the local to the global, which is likely to underlie the roles of pyramidal neurons in cortical functions. The diagram indicates the minimal structure necessary to capture the essential functional organization of the pyramidal neuron. Just as the classical Bohr atom gave a working representation of the essentials of atomic structure, so does the canonical neuron give a working representation of the essentials of neuronal structure. The canonical neuron becomes the basis for construction of canonical circuits (see later).

LOCAL CIRCUITS

No matter how complicated a single neuron may be, it cannot play a role in the processing of information without interacting with other neurons. The circuits that mediate interactions between neurons within a region are called local, or intrinsic, circuits. They include all of the levels of organization we have considered previously, plus the longer-distance connections made by axons and axon collaterals within a given brain region. In turning our attention to these more extensive circuits, we continue to distinguish between simple excitatory and inhibitory synaptic actions. Although the types of neurons and their circuits appear to be distinctive for each region, we will see that the operations they carry out can be grouped into several basic types.

EXCITATORY OPERATIONS

Excitatory local circuits can be grouped into two main types: feedforward excitation in input pathways and feedback excitation between output cells. We will discuss these operations with particular reference to the organization of the cerebral cortex.

In many regions of the nervous system, the input fibers (arising from output cells in other regions) are excitatory. Thus, nearly all of the long-range projections to, from, and within the cerebral cortex are excitatory, as are the projections to and from the specific thalamic nuclei. The rules of connectivity for the targets of these excitatory inputs vary, however, in different regions.

We begin by noting that in many regions there are inputs that connect directly to the output neurons of that region. The target may be the distal or proximal dendrites of a cortical pyramidal neurons (Fig. 1.10). Other cells in which synaptic excitation of distal dendrites is important are mitral cells (see Chap. 5) and cerebellar Purkinje cells (see Chap. 7). The incoming fibers converge and diverge according to the canonical arrangements described in Fig. 1.4.
Feedforward Excitation. A common pattern of excitatory input is that input fibers connect to excitatory interneurons, which provide circuits for feedforward excitation. In the cerebellar cortex, for example, mossy fibers make excitatory synapses onto granule cells, which then make excitatory connections onto the Purkinje cell dendrites. The advantage of this arrangement is that it gives the opportunity for additional patterns of convergence and divergence (Fig. 1.11A). These complex patterns through granule cells are in parallel with the direct access of excitatory climbing fiber inputs to the Purkinje cells.

![Diagram of excitatory local circuits in different brain regions.](image)

**Fig. 1.11.** Excitatory local circuits in different brain regions. A–C: Excitatory feedforward circuits. A: Cerebellum. Mossy fibers (mf) have excitatory (e) connections onto granule cells (GC) whose parallel fibers (pf) excite Purkinje cells (PC). B: Dentate-CA3 region of hippocampus. Perforant pathway axons from entorhinal cortex (EC) excite dentate granule cells (DGC) whose mossy fibers (mf) excite pyramidal cells (PC). C: Neocortex. Thalamocortical cells (TC) excite stellate cells (SC) whose axons excite pyramidal cells (PC). D–E: Mixed excitatory feedforward and feedback connections. D: Dorsal cortex of reptiles and olfactory cortex of mammals. Lateral olfactory tract (LOT) axons excite pyramidal cells (PC) whose axon collaterals feedback excitation onto the same and neighboring pyramidal cells. E: Hippocampal complex. Mossy fibers (see B) from dentate granule cells (DGC) excite CA3 pyramidal cells (PC) whose axon collaterals feedback excitation onto the same PCs and feedforward excitation on CA1 PCs. See text and relevant chapters.
In the hippocampus, there is a feedforward excitatory pathway from the dentate granule cells through relatively short mossy fibers to the CA3 hippocampal pyramidal cells (Fig. 1.11B; see Chap. 11).

In the cerebral cortex, excitatory interneurons in input pathways are exemplified by the spiny stellate cells of laminar IV, found in sensory areas and association areas of granular cortex. As shown in Fig. 1.11C, this provides for an intracortical feedforward excitatory relay from the afferents onto the output neurons. As in the cerebellum, this can be regarded as a staging step in the processing of afferent information and presenting it to the cortex, by convergence–divergence patterns of connections (cf. Fig. 1.4). In addition to such serial excitatory sequences, there are parallel input pathways, including direct afferent inputs to the pyramidal neurons, which contribute to the abstraction of receptive field properties. Inhibitory interactions also contribute very importantly to these properties (see later).

In summary, feedforward excitation is built into local circuits by expansion of canonical arrangements of convergent, divergent, and multiple synaptic connections. The resulting control of different inputs in exciting their target neurons gives a range of safety factors for inputs in activating their targets. This varies from high safety factors through multiple synapses onto the same target (climbing fibers onto cerebellar Purkinje cells; see Chap. 7) to low safety factors through massive divergence–convergence (cerebellar parallel fibers (see Chap. 7), Ia inputs to motoneurons (see Chap. 3), striatal inputs (see Chap. 9), etc.).

Feedback Excitation. Within a region, there are mechanisms that provide for re-excitation of activated neurons. The simplest type of re-excitation is implemented by the action of a released excitatory neurotransmitter onto the releasing process. This action on autoreceptors (Fig. 1.2, 9a) is found in many synaptic circuits. It has the advantage of being very localized in its action.

An important type is excitatory feedback through synaptic connections from an output neuron onto itself and/or neighboring output neurons. This has the advantage of extending the possibilities for more complex information processing. Also called recurrent excitation, or simply re-excitation, it is rarely fed back through an excitatory interneuron. An obvious reason is that this would create a loop for amplifying positive feedback that would lead to powerful and widespread excessive excitation and seizure activity. Thus feedback excitation is usually mediated only by direct connections of the dendrites and/or recurrent collaterals onto other principal neurons.

Clear examples of re-excitation through axon collaterals are found in the vertebrate cerebral cortex. The simplest case is olfactory cortex, where the pyramidal neurons give off recurrent collaterals that feed back excitation onto the dendrites of nearby pyramidal neurons (Fig. 1.11D; see Chap. 10). Similar evidence for direct feedback excitation has been obtained in reptilian dorsal general cortex (Fig. 1.11D), which is regarded as a model for the evolutionary precursor of mammalian neocortex (Kriegstein and Connors, 1986), indicating that this has been a fundamental property in the evolution of the cerebral cortex. Another example is the Schaffer collateral system of the hippocampus, in which recurrent collaterals from pyramidal neurons of CA3 make excitatory connections onto the dendrites of pyramidal neurons in CA3 and CAI (see Fig. 1.11E; see Chap. 11). In the neocortex itself, pyramidal neurons have well-
developed recurrent axon collateral systems, and there has long been evidence for excitatory actions attributable to them. In addition to this intraregional excitatory feedback, there is a massive interregional feedback system originating among the pyramidal cells in the lower layers of cortex which projects back to those specific thalamic nuclei that provide the input to the cortex (see later and Chap. 12). Reciprocal excitatory connections between cortical areas are described in Chap. 12.

The significance of the local feedback connections is that activated pyramidal neurons can respond to an initial excitatory input with subsequent waves of re-excitation. Through this means, a subset of activated pyramidal neurons imposes a subsequent pattern of activation onto an overlapping subset of pyramidal neurons in the same region. It is believed that this is a powerful mechanism for achieving combinatorial patterns of activation reflecting both the pattern of the input signal and the experience-dependent patterns stored within the distributed connections of the local circuits of the region in question (see Haberly, 1985; Granger et al., 1988; Wilson and Bower, 1988; Douglas et al., 1995).

In summary, feedback excitatory connections constitute a canonical circuit element that is fundamental to combinatorial information processing within and between cortical regions.

**INHIBITORY OPERATIONS**

As is already clear, inhibitory circuits play large roles in determining the types of operations generated within a region. This was supported by early studies showing that if synaptically mediated inhibition is blocked pharmacologically, cells lose most of their distinguishing features; an example is the loss of orientation and directional sensitivity of visual cortical neurons (see Chap. 12).

A wide range of types of inhibitory actions in local neural circuits is suggested by a veritable explosion of different types of inhibitory neurons shown by recent experimental studies. For example, over two dozen types of inhibitory interneurons have been identified in the hippocampus on the basis of dendritic morphology and axonal connection patterns (see Chap. 11). Similarly, the retina is well known for the dozens of different types of amacrine cells, most of which are presumably inhibitory in their actions (see Chap. 6).

How do we see order in this diversity? The answer lies in the canonical approach, with a focus not so much on types of neurons but rather on types of local circuits. The basis for this is the expectation that there is a limited family of different types of inhibitory operations implemented by the circuit connections of different types of neurons in different brain regions.

We examine here four examples of inhibitory local circuits that perform distinct canonical functions. Our aim, first, is to show how inhibitory circuits can give rise to specific functions. A second aim is to consider these circuits within a comparative framework. This will allow us to see that each circuit employs an inhibitory neuron in a slightly different way. This enables different operations to be generated by relatively fine tuning of the connections of a generic inhibitory interneuron, in a manner analogous to the way that G protein-coupled receptors, all with the same basic seven-transmembrane domain architecture, are fine tuned by specific residue substitutions to respond to different neurotransmitter ligands.
Chapter 1. Introduction to Synaptic Circuits

Rhythmic Generation. Rhythmic activity is fundamental to the activity of the nervous system. It can be generated by two main mechanisms: intrinsic membrane properties and synaptic circuits.

Intrinsic membrane properties were first found in pacemaker neurons in central pattern generator circuits controlling breathing, walking, and other highly stereotyped behaviors in invertebrates. Since the early 1980s, research carried out on brain slices has shown that many types of neurons in the vertebrate central nervous system possess complex and highly nonlinear ionic conductances that endow these cells with the ability to respond to inputs with oscillations at various frequencies (Llinas, 1988). Thus, intrinsic oscillatory neurons may be far more common in the central nervous system than previously thought, enhancing the computational power of the system. An introduction to these ionic conductances is provided in Chap. 2, and examples are described throughout this book for virtually every brain region.

Rhythmic activity can also be a property of local circuit interactions. A common model, shown in Fig. 1.12A, consists of output neurons (b) connected through axon collaterals to inhibitory neurons (i), which in turn connect back into the output neurons. When an input (a) activates the output neurons, they begin to generate impulses, which leads to activation of the interneurons. This activation leads to feedback inhibition of the output neurons, which now can no longer respond to the input and thus also deprives the interneurons of their source of activation; they are, in a sense, presynaptically inhibited by themselves. Both populations, therefore, are silent until the IPSPs in the output neurons wear off and the cycle is ready to be repeated. The degree of synchronization of a region will obviously depend on the extensiveness of the connections. The circuit could thus be laid down during development by a simple rule for the interneurons to make extensive random connections on the output cell populations.

Rhythmic activity can also be generated by dendrodendritic microcircuits, as discussed above (see Fig. 1.5B and Chap. 5). Although the neural elements are different, the principles underlying the interactions are similar. This illustrates an important concept, that similar functions can be mediated by different neural substrates. Conversely, similar substrates can mediate different functions, by specific adaptations of general mechanisms.

In summary, three canonical mechanisms (membrane channels, circuits involving axon collaterals, and circuits involving dendritic interactions) can generate the same canonical operation: oscillatory activity. Conversely, each of these canonical mechanisms can potentially be refined to generate different oscillatory frequencies. This illustrates a recurrent theme in synaptic organization—that the same substrate can generate different functions and that different substrates can generate the same function. These are neural examples of general phenomena in biological organization. They reflect the ability of organisms to respond to adaptive pressures in multiple ways that ensure the survival of the organism.

Directional Selectivity. A second type of local circuit in which an inhibitory interneuron plays an essential role is in direction selectivity. The best known model is the retina, where ganglion cells in most vertebrate species show selective activation by stimuli moving in one direction. The proposed model is shown schematically in Fig. 1.12B. The essential element is an inhibitory interneuron whose connections are made in one
A. RHYTHM GENERATION

B. DIRECTION SELECTIVITY

C. SPATIAL CONTRAST

D. TEMPORAL CONTRAST
direction, opposite to the preferred direction. This means that stimuli moving in that direction (called the “null” direction) activate the inhibitory connections in that direction, so that cells farther along cannot respond. In the opposite, preferred, direction, by contrast, the cells are free to respond.

Several types of circuit connections might mediate this selectivity. In the retina, the most likely involves connections onto the dendrites and somata of ganglion cells (dashed line in Fig. 1.12B). The starburst amacrine cell has been proposed to play this role. The organization of this cell was discussed earlier (see Fig. 1.8B). These cells synthesize, store, and release the two most common fast-acting excitatory (ACh) and inhibitory (GABA) neurotransmitters, suggesting that one and the same cell could potentially act as both an excitatory and an inhibitory circuit element.

Directionally selective cells are also found in visual cortex, where this property is mediated by a combination of excitatory inputs and inhibitory interneurons (Ferster and Koch, 1987), whose connections are mainly onto cell bodies and proximal dendrites (solid line in Fig. 1.12E). This site is less selective but might be easier to target during development. Blocking the action of the inhibitory cells by an appropriate chemical substance leads to the almost total loss of direction selectivity (Sillito et al., 1980).

In summary, we again see that the same canonical function—directional selectivity—can be implemented by circuits with the same operational characteristics but different neuronal substrates.

**Spatial Contrast.** These concepts are further exemplified by the role of inhibitory circuits in mediating enhancement of spatial contrast, a common property of receptive field organization in many sensory systems. This property is illustrated in Fig. 1.12C, where there is strong stimulation of input (a1) and all elements to the left in the diagram (not shown) and weaker stimulation of input (a2) and elements lying to the right. The responses of b1 and b2 would start out being proportional; however, the stronger inhibition by b1 and i1 suppresses b2 more than the suppression of b1 by b2 and i2, thereby enhancing the difference in firing rates of b1 and b2. This effect falls off the farther away the elements are from the border, thereby enhancing the contrast between strong and weak stimulation at the border.

This is the basis for the classic description of Mach bands in the visual system, as first demonstrated in the *Limulus* eye (see Ratliff, 1965). It has turned out that the circuit for mediating this effect in *Limulus* appears to involve dendrodendritic connections without intervention of an inhibitory interneuron (Fahrenbach, 1985). In mammalian sensory systems, however, it characteristically involves inhibitory interneurons. An example is indicated in Fig. 1.12C, in which spatial contrast is mediated by a canon-
ical circuit involving axon collaterals and inhibitory interneurons. It can also be mediated by the canonical dendrodendritic pathway through an interneuron, as described in Fig. 1.5.

In summary, the spatial organization of receptive fields can be implemented by several types of canonical circuits: the resulting receptive fields can subserve processing of information in different modalities.

Temporal Contrast. Just as there is enhancement of spatial contrast between the activities of populations of cells, so is there enhancement of temporal contrast between successive activity states. This can also be mediated by intrinsic membrane properties or circuit properties. Membrane mechanisms are described in Chap. 2. Circuit mechanisms commonly involve the sequential action of synaptic excitation followed by inhibition. An example is illustrated in Fig. 1.12D as it might apply to the thalamic triad, in which excitation of an output neuron is followed by feedforward inhibition. As shown, this converts a step increase in activity in the input to a brief spike burst in the output. As for spatial contrast enhancement, the nervous system cares more about changes in stimulus conditions than in the steady state conditions. In summary, local inhibitory circuits are critical elements in extraction of changes in activity in both the spatial and temporal domains.

REGIONAL CANONICAL CIRCUITS

How can one represent the different canonical excitatory and inhibitory local circuits, each with its underlying levels of canonical functional units, in a way that is not merely a catalog but gives insight into the functions of each region? A useful way to do this is by means of a basic (canonical) regional circuit, defined as a representation of the main patterns of synaptic connections and interactions most characteristic of a given region. Such a representation is useful in several ways: for identifying the principles of circuit organization of a region, for better understanding of relations between synaptic actions and dendritic properties, and for identifying the minimum of essential properties that must be included if a network simulation is to have validity as an accurate representation of that region.

RETINA AND OLFACTORY BULB

An advantage of thinking in this way about synaptic organization in terms of regional canonical circuits is that it provides a logical basis for comparing the functional organization of different brain regions. The olfactory bulb and retina provide useful examples. The similarities of their neural organization were already recognized by Cajal (1911). Their basic circuits were formulated independently by subsequent studies at the cellular level (Dowling, 1968; Shepherd, 1963, 1974) and are illustrated in Fig. 1.13. On the left is shown a basic circuit of the retina; on the right, the olfactory bulb. Despite the fact that these regions process entirely different sensory modalities, the basic circuits are similar in outline and in several details. In each case, there are parallel vertical pathways for straight-through transmission of information. In addition, there are horizontal connections, arranged in two main levels, for processing of information by lateral interactions. Within this framework are further similarities, such as recipro-
Fig. 1.13. Comparison between basic (canonical) circuits for the retina (A) and olfactory bulb (B). [From Shepherd, 1988]

cal synapses and interneurons that lack axons. All of these features are described in detail in Chaps. 5 and 6.

The purpose of such a comparison is not, of course, to suggest that the two regions are identical; rather, it is to be able to identify more clearly the principles that are common across regions, so that one can better analyze and understand the adaptations that make each region unique. Among the common principles are the notions that in each region there are three stages of information processing: an initial stage of input processing, a second stage of intrinsic operations within the synaptic circuits of the region, and a final stage of output control. These three levels can be seen most clearly in the basic circuits of tightly organized and highly laminar regions like the olfactory bulb and retina (see Fig. 1.12) but also are evident as we shall see in more spread-out regions like the cerebral cortex.

The regional canonical circuit thus provides a useful starting point for categorizing the organization of a region. In addition, it provides a rational framework for comparing the organization of disparate regions, a crucial step toward developing comprehensive theories of brain organization.

An objection to the idea of a regional basic circuit is that it does not adequately represent the rich diversity of neural elements and synaptic connections that can be found in most brain regions. However, the problem with this diversity is that it can obscure the crucial issue, of determining which properties are essential for which operations. This issue is critical, not only for experimentalists attempting to analyze these operations but also for theorists who seek to incorporate these essential properties into network simulations. The basic regional circuit can be expanded with subcircuits for specific functions as needed.
CEREBRAL CORTEX
The cerebral cortex presents perhaps the greatest challenge in elucidating principles of organization. How far can the canonical approach give insight into these principles?

Comparisons between the local circuits in the different types of cortex, as discussed earlier, give a different perspective on cortical organization from that derived from traditional views based on cortical cytoarchitectonics. From this new perspective, what is striking is the local circuit elements that are common to the different types.

We illustrate this comparative approach by considering three examples of basic circuits that have been proposed to account for experimental findings in cortical studies. First is dorsal turtle cortex. This relatively simple cortex in the reptilian forebrain is regarded as the evolutionary precursor of mammalian neocortex. A combined morphological and electrophysiological study (Kriegstein and Connors, 1986) led to the basic circuit shown in Fig. 1.14A. In this circuit, the afferent input (1, a, b) excites both pyramidal cells (P) and inhibitory interneurons (I). The I neuron feeds forward inhibition (2) to the P cells. The P cells feed back excitation (3) onto themselves and onto the I cells (4), which also receive other inhibitory modulation (5). The P cells send the output through their axons (6). The incorporation of many of the basic elements of excitatory and inhibitory local circuits that we have discussed earlier is obvious in the diagram.

An elaboration on this basic pattern to a sensory area of mammalian cortex is shown in Fig. 1.14B. This reflects the fact that mammalian cortex is characterized by six layers, involving superficial and deep populations of pyramidal cells (P 1, P 2) and stellate cells (S) in layer 4. In this cortex, afferent inputs (AFFd) excite pyramidal (P) cells (1,2) as well as inhibitory cells (i 1) (1). In addition, there is feedforward excitation (AFF3) through stellate cells (S), as described earlier (Fig. 1.11). The excited P cells have recurrent axon collaterals (rac) that recurrently and laterally excite the P cells (rac 1) as well as inhibitory cells (i 2) that provide for feedback and lateral inhibition. The balance of excitation and inhibition controls the output of the P cells (EFF 1,2). Note how the properties of the canonical pyramidal neuron depicted in Fig. 1.9 are incorporated into the basic circuit that contains it.

Close comparison of this circuit with dorsal cortex gives clues to the critical circuits added in the evolution from reptiles to mammals; these obviously include the extra layer of deep pyramidal cells (P 2), and the feedforward excitation through stellate cells (S). Other circuits can be added to the basic circuits to focus on more specific differences.

A third example is the canonical cortical circuit suggested by the studies of Douglas et al. (1989) (Fig. 1.14C). In their model the superficial population of excitatory pyramidal cells is represented by P2 and 3 (stellate cells in layer 4 (4) are also included) and deep cells in layers P5 and 6, and inhibitory cells by GABA cells. The excitatory and inhibitory interactions shown by their study are indicated by the diagram. The authors suggest that this set of connections and interactions may reflect a basic "canonical" circuit that can apply to all neocortex. The evidence for this is fully discussed in Chap. 12.

In order to compare this canonical circuit with the basic circuits of A and B, it is rearranged in the diagram to the right in (C) to conform more closely to the conventions used in the other diagrams. It can be seen that this brings out more clearly the basic similarities between the three basic circuits: the excitatory inputs to the P cells and inhibitory interneurons; the feedback and lateral excitatory actions of the P cell recur-
CEREBRAL CORTEX

The cerebral cortex presents perhaps the greatest challenge in elucidating principles of organization. How far can the canonical approach give insight into these principles?

Comparisons between the local circuits in the different types of cortex, as discussed earlier, give a different perspective on cortical organization from that derived from traditional views based on cortical cytoarchitectonics. From this new perspective, what is striking is the local circuit elements that are common to the different types.

We illustrate this comparative approach by considering three examples of basic circuits that have been proposed to account for experimental findings in cortical studies. First is dorsal turtle cortex. This relatively simple cortex in the reptilian forebrain is regarded as the evolutionary precursor of mammalian neocortex. A combined morphological and electrophysiological study (Kriegstein and Connors, 1986) led to the basic circuit shown in Fig. 1.14A. In this circuit, the afferent input (1, a, b) excites both pyramidal cells (P) and inhibitory interneurons (I). The I neuron feeds forward inhibition (2) to the P cells. The P cells feed back excitation (3) onto themselves and onto the I cells (4), which also receive other inhibitory modulation (5). The P cells send the output through their axons (6). The incorporation of many of the basic elements of excitatory and inhibitory local circuits that we have discussed earlier is obvious in the diagram.

An elaboration on this basic pattern to a sensory area of mammalian cortex is shown in Fig. 1.14B. This reflects the fact that mammalian cortex is characterized by six layers, involving superficial and deep populations of pyramidal cells (P 1, P 2) and stellate cells (S) in layer 4. In this cortex, afferent inputs (AFFd) excite pyramidal (P) cells (1,2) as well as inhibitory cells (I 1) (1). In addition, there is feedforward excitation (AFF3) through stellate cells (S), as described earlier (Fig. 1.11). The excited P cells have recurrent axon collaterals (rac) that recurrently and laterally excite the P cells (rac 1) as well as inhibitory cells (I 2) that provide for feedback and lateral inhibition. The balance of excitation and inhibition controls the output of the P cells (EFF 1,2). Note how the properties of the canonical pyramidal neuron depicted in Fig. 1.9 are incorporated into the basic circuit that contains it.

Close comparison of this circuit with dorsal cortex gives clues to the critical circuits added in the evolution from reptiles to mammals; these obviously include the extra layer of deep pyramidal cells (P 2), and the feedforward excitation through stellate cells (S). Other circuits can be added to the basic circuits to focus on more specific differences.

A third example is the canonical cortical circuit suggested by the studies of Douglas et al. (1989) (Fig. 1.14C). In their model the superficial population of excitatory pyramidal cells is represented by P2 and 3 (stellate cells in layer 4 (4) are also included) and deep cells in layers P5 and 6, and inhibitory cells by GABA cells. The excitatory and inhibitory interactions shown by their study are indicated by the diagram. The authors suggest that this set of connections and interactions may reflect a basic "canonical" circuit that can apply to all neocortex. The evidence for this is fully discussed in Chap. 12.

In order to compare this canonical circuit with the basic circuits of A and B, it is rearranged in the diagram to the right in (C) to conform more closely to the conventions used in the other diagrams. It can be seen that this brings out more clearly the basic similarities between the three basic circuits: the excitatory inputs to the P cells and inhibitory interneurons; the feedback and lateral excitatory actions of the P cell recur-
Building on the concept of the canonical neuron, we can thus designate a basic "cortical canonical circuit," which may be defined as the minimum architecture necessary for capturing the most essential cortical input-output operations.
The sets of local circuits depicted in Fig. 1.14 can be considered a superfamily unique to the vertebrate cerebral cortex, which is adapted and elaborated in the different types of cortex and the different cortical regions in order to carry out the set of operations characteristic of each (Shepherd, 1974; 1988). There is current debate about whether there is one basic cortical circuit or a diversity of circuits (Nelson, 2002). A full exposition of these basic circuits and their roles in different cortical functions is given in Chaps. 10–12.

In conclusion, the canonical circuit approach provides a useful first step for characterizing the essential organization of a brain region. As discussed above, for closer examination of a given region, one begins with the canonical circuit and introduces the particular adaptations and elaborations that underlie its unique properties. The canonical circuit is thus a flexible tool, not rigidly defined; the purpose is to represent the minimum of elements and connections that will capture the essence of the functional operations of a region. It provides the experimentalist and theorist a conceptual framework for integrating their analyses to give a more accurate representation and simulation of the functional operations of each region. Finally, it provides the reader of this book with a key to understanding and comparing the principles of synaptic organization across different brain regions.