mean field measured by EEG and MEG, but in order to keep things simple, let us ignore the latter for the moment. The "mean field" measured outside the neurons in the extracellular space simply reflects the "average" behavior of large numbers of interacting neurons. The large degree of freedom—the essence of brain activity—is thus replaced by the "typical" average behavior. The exact nature of such cooperation is, of course, the million dollar question. Before attempting to address this complex question, let us begin with a single neuron.

Neurons Communicate with Spikes

Neurons share the same characteristics and have the same parts as other cells in the body, but they can pass messages to each other over long distances through their axonal processes. Like virtually any cell in the body, neurons have a high concentration of ions of potassium (K^+) and chloride (Cl^-) inside and keep the sodium (Na^+) and calcium (Ca^{2+}) ions outside. This arrangement produces a small battery that maintains a voltage difference of –60 millivolts relative to the world outside of the cell membrane. This ion separation is perhaps attributable to our single-cell ancestors and where they came from: the sea. Given the high concentration of Na^+ in seawater, keeping Na^+ outside the cell was a smart choice. However, when more developed organisms migrated to land, they had to carry the sea with them to maintain the same extracellular environment. For this purpose, the circulation of lymph and blood developed. All our cells are constantly bathed in water, more precisely, salt water. Each cell's membrane is perforated by myriads of small pores, appropriately called channels, through which ions can move in and out. Neurons can open and close these ion channels very quickly, thereby altering the flux of ions and, as a consequence, the voltage difference across the membrane. For example, the Na^+ channel opening initially occurs linearly with time, with a consequent linear decrease of the voltage difference between the inside and outside of the membrane: the neuron depolarizes. However, after some critical amount of Na^+ crosses the membrane, something entirely novel occurs. At this critical threshold, Na^+ influx will facilitate the opening of additional Na^+ channels, leading to an avalanche of Na^+ influx. This fast, strongly nonlinear event will depolarize the membrane so that the inside becomes positive by about 20 millivolts, as if the battery was reversed temporally. This fast depolarizing event is portrayed by the rising phase of the action potential (figure 4.3). At this voltage level, the process stops mostly due to another feature of the membrane, the voltage-dependent inactivation of Na^+ channels.

Pumping all the excess Na^+ out of the neuron is a lengthy process. To regain the resting voltage across the membrane more rapidly, neurons opted for another strategy: voltage dependence of K^+ channel activity. As the action potential reaches its peak, the voltage-dependent K^+ channels are activated and quickly repolarize the cell. This fast repolarization is the falling phase of the action potential (figure 4.3). Thus, the positive charge created by the influx of Na^+ is compensated for by the quick efflux of equal charges carried by K^+. This push-pull process, active during the action potential, takes about a millisecond (absolute refractoriness) and limits the maximum firing rate of the neuron. Because the action potential appeared as a

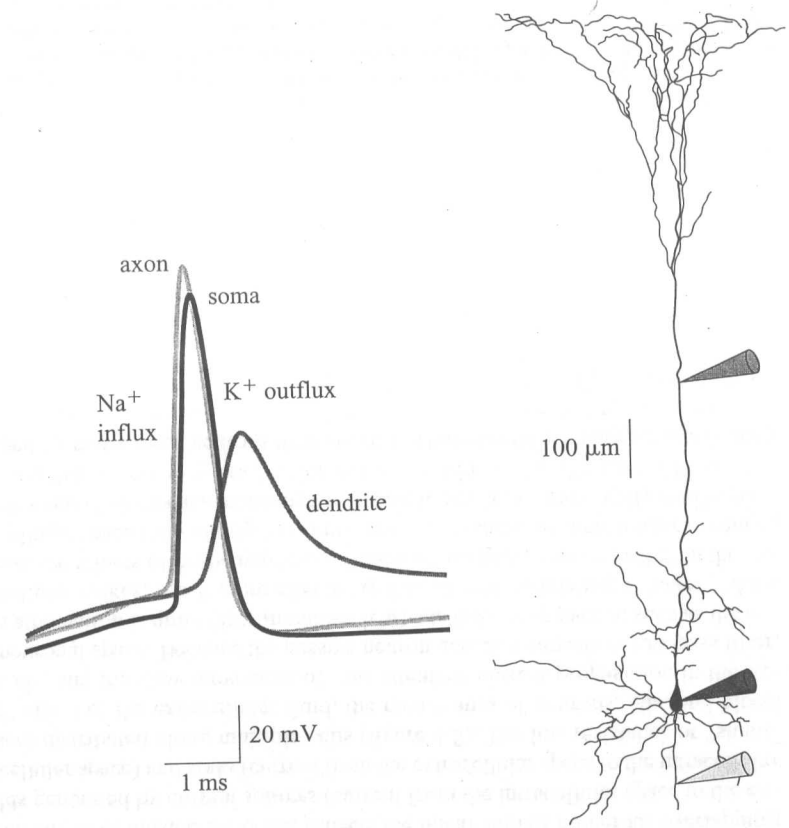

Figure 4.3. Fast action potentials propagate forward to the axon collaterals and backward to the dendrites: action potential waveforms (left) recorded with patch pipettes (described further below; see note 24) from the axon, soma, and dendrite in a layer 5 pyramidal neuron (right). Note delays and the different kinetics of Na^+ influx (rising phase of spike) and K^+ outflux (falling phase) and the associated different waveforms of the voltage traces. Reprinted, with permission, from Häusser et al. (2000).

short, large-amplitude event on the early chart recorders, investigators called the action potential a "spike." So when we refer to a spiking or firing neuron, what we really mean is that the neuron gives rise to action potentials.

In contrast to the megahertz speed of computers, the speed of spike transmission by neurons is limited to a maximum of a few hundred events per second. Nevertheless, once an action potential is initiated, it can propagate through the entire axon tree of the neuron and signal this event to all its downstream targets.[7]

7. Although failures may occasionally occur at junctions or in the terminals at higher frequencies, the current view is that the low-frequency action potential travels to all presynaptic boutons.

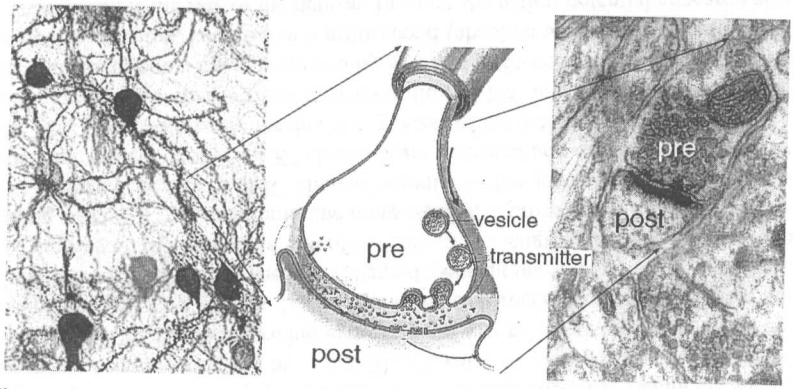

Figure 4.4. Neurons communicate mainly with chemical synapses. Left: Neural tissue with somata, dendrites, spines, and axons. Middle: An axon terminal (presynaptic, pre) in synaptic contact with a target (postsynaptic, post) neuron. Neurotransmitter is packaged into vesicles in the axon terminal. Upon arrival of an action potential and associated Ca^{2+} influx into the terminal, the vesicle empties its contents into the synaptic cleft, and the neurotransmitter binds onto its receptors in the postsynaptic membrane. Right: Electron microscopic picture of the synapse. Courtesy of T.F. Freund.

Again, compared to the traveling velocity of electricity in computer circuits, propagation of action potentials is quite sluggish at 0.5–50 meters per second, depending on the caliber and insulation type of the axon cable.[8] This slow transfer of neuronal information by the traveling action potentials is the most important limiting factor in the speed performance of neuronal networks.

Synaptic Potentials

Neurons are also good listeners, very much interested in what their upstream peers have to say. At the contact point of each axon terminal or "bouton," there is a thin physical gap between the membrane of the axon terminal and the membrane of the sensing neuron. This membrane–gap–membrane triad is called the synapse (figure 4.4). The presynaptic terminal is specialized to release a chemical substance, appropriately called a neurotransmitter, which then binds onto specialized receptors on the postsynaptic side. All cortical pyramidal cells release glutamate, which depolarizes and discharges the target neurons; therefore, glutamate is referred to as an excitatory neurotransmitter. In contrast, GABA typically hyperpolarizes the postsynaptic resting membrane, which is why GABA's effect is called inhibitory. Neurotransmitters exert their effect by binding to receptors that

8. The quantitative description of the events associated with the action potential, by Alan Lloyd Hodgkin and Andrew Fielding Huxley, remains among the most significant conceptual breakthroughs in neuroscience. Their success story is also a reminder of the power of long-term collaboration between people with different but overlapping expertise. For a quantitative description of the action potential, see Johnston and Wu (1994).

reside in the membrane of the postsynaptic neuron. When activated, the receptors facilitate or suppress the kinetic activity of the Na^+, K^+, Cl^-, and Ca^{2+} channels so that the membrane potential will deviate from the resting voltage (see figure 6.3).[9] To define these respective events more clearly, we distinguish excitatory postsynaptic potentials (EPSPs; or currents, EPSCs) from inhibitory postsynaptic potentials (IPSPs; or currents, IPSCs). Compared to the fast action potentials, membrane potential changes associated with EPSPs and IPSPs are several-fold smaller in amplitude. However, they last for tens of milliseconds. This latter property is critical for understanding the generation of EEG activity.

Extracellular Currents

For the transmembrane potential to change in a given neuron, there must be a transmembrane current, that is, a flow of ions across the membrane. Opening of membrane channels (or, more precisely, an increase in their open state probability) allows transmembrane ion movement and is the source of ion flow in the extracellular space. The local field potential (i.e., local mean field), recorded at any given site in or outside the brain, reflects the linear sum of numerous overlapping fields generated by current *sources* (current from the intracellular space to the extracellular space) and *sinks* (current from the extracellular space to the intracellular space) distributed along multiple cells (figure 4.5). The low resistance or "shunting" effect of the extracellular fluid, the membranes of neurons, glia, and blood vessels, and the slow movement of ions attenuate current propagation in the extraneuronal space. Because the passive neuron acts as a capacitive low-pass filter, this attenuation is quite discriminative: it affects fast-rising events, such as the extracellular spikes, much more effectively than slowly undulating voltages.[10] As a result, the effects of postsynaptic potentials can propagate much farther in the extracellular space than can spikes. Furthermore, because of their longer duration, EPSPs and IPSPs have a much higher chance to occur in a temporally overlapping manner than do the very brief action potentials. Finally, EPSPs and IPSPs are displayed by many more neurons than are spikes because only a very small minority of neurons reach the spike threshold at any instant in time. For these reasons, the contribution of action potentials to the local field and especially to the scalp EEG is negligible.[11]

Excitatory currents, involving Na^+ or Ca^{2+} ions, flow inwardly at an excitatory synapse (i.e., from the activated postsynaptic site to the other parts of the cell) and outwardly away from it. The passive outward current far away from the synapse is referred to as a return current from the intracellular milieu to the extracellular

9. Besides the major neurotransmitters glutamate and GABA, several other subcortical neurotransmitters are known (see Johnston and Wu, 1994; see also Cycle 7).

10. A low-pass filter offers easy passage to low-frequency signals and difficult passage to high-frequency signals because the capacitor's impedance decreases with increasing frequency.

11. This is not necessarily the case under epileptic conditions, when neurons can synchronize within the duration of action potentials. The synchronously discharging neurons create local fields, known as compound or "population" spikes.

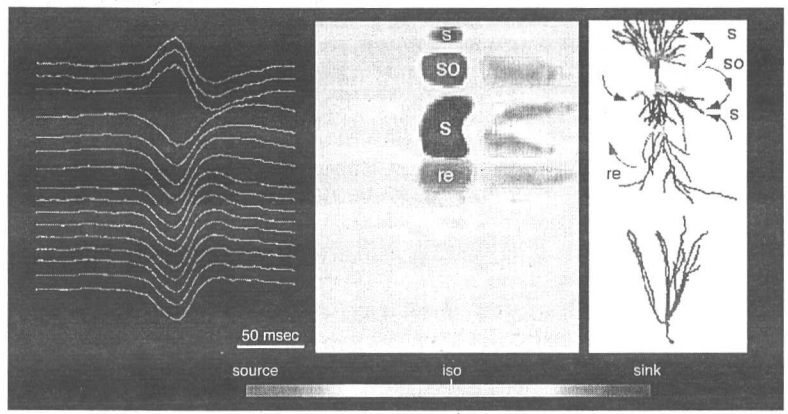

Figure 4.5. Generation of extracellular field potentials. Left: Spontaneously occurring field potential (sharp wave) recorded simultaneously in various layers of the hippocampus (CA1–dentate gyrus axis). The traces represent averages of 40 events. Middle: Current-source density map, constructed from the field potentials. Interpretation of the current sinks (s) and sources (so) is on the basis of anatomical connectivity, representing different domains of parallel-organized pyramidal cells and granule cells. Active currents are indicated on the right, and passive return (re) currents on the left, of the pyramidal neuron. The sinks in the dendritic layers are caused primarily by excitation from the upstream CA3 pyramidal cells, whereas the source around the soma reflects mainly inhibition, mediated by basket interneurons. Iso, isoelectric (neutral) state.

space. Inhibitory loop currents, involving Cl^- or K^+ ions, flow in the opposite direction. Viewed from the perspective of the extracellular space, membrane areas where current flows into or out of the cells are termed sinks or sources, respectively. The current flowing across the external resistance of the extraneuronal space sums with the loop currents of neighboring neurons to constitute the local mean field or local field potential (figure 4.5). In short, extracellular fields arise because the slow EPSPs and IPSPs allow for the temporal summation of currents of relatively synchronously activated neurons.[12]

Depending on the size and placement of the extracellular electrode, the volume of neurons that contributes to the measured signal varies substantially. With very fine electrodes, the local field potentials reflect the synaptic activity of tens to perhaps thousands of nearby neurons only. Local field potentials are thus the electric fields that reflect a weighted average of input signals on the dendrites and cell bodies of neurons in the vicinity of the electrode. If the electrode is small

12. This "classical" description of the origin of extracellular fields must be supplemented by the recent findings about the active properties of neurons (see Cycle 8; Llinás, 1988). Subthreshold oscillations, afterpotentials, Ca^{2+} spikes, and other intrinsic events also produce relatively long-lasting transmembrane events. The contribution of these nonsynaptic events to the local field potential can often be more important than the contribution of synaptic events (Buzsáki et al., 2003b).

enough and placed close to the cell bodies of neurons, extracellular spikes can also be recorded. Therefore, in such a small volume of neuronal tissue, one often finds a statistical relationship between local field potentials, reflecting mostly input signals (EPSPs and IPSPs), and the spike outputs of neurons. The reliability of such relationship, however, progressively decreases with increasing the electrode size, by lumping together electric fields from increasingly larger numbers of neurons. This is why the scalp EEG, a spatially smoothed version of the local field potential at numerous contiguous sites, has a relatively poor relationship with spiking activity of individual neurons.

In architecturally regular regions of the brain, such as the neocortex, the locations of the extracellular currents reflect the geometry of the inputs. Using several microelectrodes with regular distance from each other, one can calculate the density of the local currents from the simultaneously measured voltages, provided that information is available about the conductance of the tissue. Consider a distant current source relative to three equally spaced recording sites. Each electrode will measure some contribution of the field (due to the passive return currents that pass through the extracellular space) from the distant source. The voltage *difference* between two adjacent electrodes can determine the voltage gradient, that is, how fast the field attenuates with distance from the current source. Because the source is outside the area covered by the electrodes, the voltage gradient will be the same between electrodes 1 and 2 and between electrodes 2 and 3. Taking the difference between the voltage gradients, we get a value of zero, an indication that the measured field did not arise from local activity but was volume-conducted from elsewhere. In contrast, if the three electrodes span across a synchronously active afferent pathway, the voltage gradients will be unequal and their difference will be large, indicating the local origin of the current. By placing more microelectrodes closer to each other, we can more precisely determine the maximum current density and therefore the exact location of the maximum current flow.[13]

Unfortunately, from measuring the local current density alone, we have no way of telling whether, for example, an outward current close to the cell body layer is due to active inhibitory synaptic currents or if it reflects the passive return loop current of active excitatory currents produced in the dendrites. Without additional information that can clarify the nature of the current flow, the anatomical

13. Current density is is the current entering a volume of extracellular space, divided by the volume. The current flow between two sites (e.g., between recording electrodes 1 and 2 and between electrodes 2 and 3 in the example) can be calculated from the voltage difference and resistance using Ohm's law. The difference between these currents (i.e., the spatial derivative) is the current density. More precisely, the current density is a vector, reflecting the rate of current flow in a given direction through the unit surface or volume (measured in amperes per square meter for a surface and amperes per cubic meter for a volume). Current density depends on both the electric field strength and the conductivity (σ) of the brain. The conductance is a factor of both conductivity and the shape of volume. Conductivity is inversely proportional to resistivity. The average resistivity of white matter is ~ 700 Ω. cm, and that of gray matter is ~ 300 Ω.cm. The proportion of fibers therefore significantly affects tissue resistivity. For a thorough theoretical discussion of the current density method, I recommend Mitzdorf (1985) and Nicholson and Freeman (1975).

source remains ambiguous. The missing information may be obtained by simultaneous intracellular recording from representative neurons that are part of the population responsible for the generation of the local current. Alternatively, one can record extracellularly from identified pyramidal cells and interneurons and use the indirect spike-field correlations to determine whether, for example, a local current is an active, hyperpolarizing current or a passive, return current from a more distant depolarizing event. Taking these extra steps is worthwhile. The reward one obtains by pinning down the currents is crucial information about the anatomical source of the input to those same neurons whose output (i.e., spiking) activity is simultaneously monitored. Once information about both the input and output of a small collection of neurons working together becomes available, one may begin to understand the transformation rules governing their cooperative action. This approach is the next best thing to the ideal condition when all inputs (synapses) and the output of each cell could be monitored simultaneously and continuously.[14]

Functional Magnetic Resonance Imaging

Currently, the best-known noninvasive procedure for the functional investigation of the human brain is magnetic resonance imaging (MRI). The method is based on the detection and analysis of magnetic resonance energy from specific points in a volume of tissue. The MRI technique provides far better images than those the traditional X-ray and other scanning technologies. Hydrogen atoms of water represent tiny magnetic dipoles, which can align in an orderly way when placed inside of a very strong magnetic field. In practice, a short pulse of RF energy perturbs these tiny magnets from their preferred alignment. As they subsequently return to their original position, they give off small amounts of energy that can be detected and amplified with a "receiver coil" placed directly around the head. The injection of electromagnetic energy into a single plane is used to produce a slice through the brain volume. To produce consecutive brain slices, the head is advanced in small increments. Because gray matter and white matter contain different amounts of water, this difference generates a contrast between the surface of the neocortex and the underlying white matter and other areas of the brain that can be used to provide a detailed image of the brain. However, while the MRI method offers exquisite details about the structure of the brain, it does not tell us anything about neuronal activity.

As previously mentioned, active neurons consume a lot of energy, and in areas

14. Spike occurrences of in the vicinity of the cell body of the neurons reliably reflect their output messages. Unfortunately, no reliable methods exist to monitor all individual inputs to a single neuron simultaneously. Inputs can be estimated only by recording the local field potentials that reflect the spatially averaged activity of many neurons and inferring indirectly the mean input. Another, equally difficult approach is to monitor the spike output of the afferent neurons to the chosen recipient neuron and infer the input configurations from their spiking.

with high neuronal activity this results in a large difference between the concentration of the oxygenated hemoglobin in the arterial blood and the deoxygenated hemoglobin in the venous outflow. These local magnetic-field inhomogeneities can be assessed by the BOLD (blood-oxygenation-level–dependent) method. Functional MRI (fMRI), which uses the BOLD method, can measure neuronal activity indirectly.[15] Because of the unprecedented details of localized changes in the brain in response to various challenges and perturbations, the fMRI method has become the leading tool in cognitive science research. Nevertheless, as with any technique, fMRI has its limitations. The first limitation has to do with the general statement that "fMRI measures neuronal activity." Neuronal activity has numerous components, including intrinsic oscillations, EPSPs, IPSPs both in principal cells and in inhibitory interneurons, action potential generation and propagation along the axon, and release, binding, reuptake, and reprocessing of the released neurotransmitter. Which of these processes, alone or in combination, are responsible for the changes in BOLD has yet to be worked out. Without such crucial information, it is not possible to conclude whether an increase in BOLD results from increased firing of principal cells or interneurons or increased release of neurotransmitter from afferents whose cell bodies are outside the area with increased BOLD signal.

The second problem arises from the neurophysiological observations that numerous brain operations are brought about by changing the firing patterns of neurons without any change in the rate of postsynaptic potentials or alteration of neuronal firing rates (I provide some examples in Cycles 8, 9, and 12). For example, recognition or recall of the correct and incorrect information may use different sets of neurons but engages those neurons with the same magnitude of activity. Thus, fundamentally different cognitive operations in the same structures can be generated with the same amount of energy, with no expected change in BOLD. This reverse engineering problem is, of course, identical to that of the EEG and MEG. Thus, with the exception of significantly improved spatial resolution, one cannot expect more from fMRI than from EEG measurements.

The third technical drawback of fMRI is its slow temporal resolution. Not only is the blood-flow response delayed about half a second after neuronal activation, but also the second-scale temporal resolution of the BOLD imaging method is excessively long for assessing spatiotemporal evolution of neuronal activity across brain domains. As discussed in Cycle 2, activity can get from any structure to just about any other structure in the brain by crossing just five to six synapses within a second. Even if only a few areas show increased BOLD activity, we have no knowledge about the temporal sequence of their activation, a critical issue for

15. During the late 1980s, Seiji Ogawa, then at Bell Labs in Murray Hill, New Jersey, noted that cortical blood vessels became more visible as blood oxygen was lowered. From these initial observations, he concluded that the local magnetic field inhomogeneities can be used to assess neuronal activity, and termed his invention the blood-oxygenation-level–dependent (BOLD) method (Ogawa et al., 1990). For a brief discussion on the complex origin of BOLD, I suggest Logothetis (2003), Logothetis et al. (2001), and Raichle (2003).