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Introduction

ROMAIN BRETTE AND ALAIN DESTEXHE

Most of what we know about the biology of the brain has been obtained using a large variety of measurement techniques, from the intracellular electrode recordings used by Hodgkin and Huxley to understand the initiation of action potentials in squid axons to functional magnetic resonance imaging (fMRI), used to explore higher cognitive functions. To extract meaningful information from these measurements, one needs to relate them to neural activity, but this relationship is usually not trivial. For example, electroencephalograms (EEG) measure the summed electrical activity of many neurons, and relating the electrical signals of the electrodes to neural activity in specific brain areas requires a deep understanding of how these signals are formed. Therefore, the interpretation of measurements relies not only on an understanding of the physical measurement devices (what physical quantity is measured), but also on our current understanding of the brain (the relationship between the measured quantity and neural activity).

The biophysics of neurons is explained in great detail in a number of books. This book deals with the biophysical and mathematical principles of neural activity measurement, and provides models of experimental measures. We believe this should be useful for at least three broad categories of scientists: (1) neuroscientists who use these techniques in their own experimental protocols and need to interpret the results precisely, (2) computational neuroscientists who use the experimental results for their models, (3) scientists who want to develop new techniques or enhance existing techniques. Chapters in this book cover an exhaustive range of techniques used to measure neuronal activity, from intracellular recording to imaging techniques. Each chapter explains precisely what physical quantity the technique actually measures and how it relates quantitatively to neural activity.

In the remainder of this introduction, we will give a brief overview of neuronal biophysics, in relation with the different measurement techniques that are covered in this book. More detailed accounts can be found in several books (Tuckwell, 1988; Koch, 1999; Dayan and Abbott, 2001; Hille, 2001; Gerstner and Kistler, 2002).

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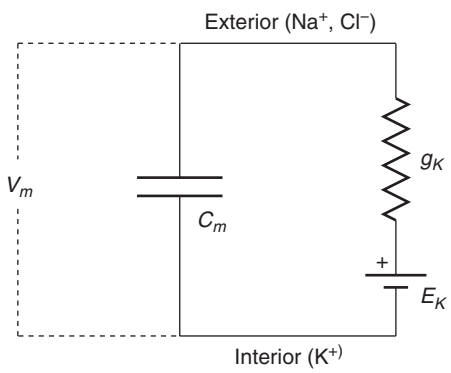

Figure 1.1 Equivalent electrical circuit of a patch of neuronal membrane: V is the membrane potential, g_K is the conductance of ionic channels permeable to K^+ ions, and E_K is the corresponding reversal potential.

The membrane of a neuron is a bipilid layer, which is an electrical insulator (see Figure 1.1). It separates the interior and the exterior of the cell, which contain ions in different proportions: sodium (Na^+) and chloride (Cl^-) ions outside the cell, potassium (K^+) ions inside the cell. These ions can enter or leave the cell through proteins in the membrane named *ionic channels*. An ionic channel forms a tiny hole in the membrane, that specific types of ions (e.g. K^+) can cross. At rest, the membrane is mostly permeable to K^+ (and a bit less to Na^+ and Cl^-). By diffusion, K^+ ions will tend to move from the interior of the cell, where the concentration is high, to the exterior of the cell, where it is lower. This phenomenon moves positive charges outside the cell, which creates an electrical field across the membrane. This field produces a movement of ions in the other direction (positive charges move to where there are fewer positive charges), and therefore an equilibrium is reached when the outward ion flux due to diffusion exactly matches the inward flux due to the electrical field. These are the basic principles of electrodiffusion. At equilibrium, there are more positive charges outside than inside the cell, and therefore the electrical potential is higher outside than inside. The *membrane potential* is defined as the difference $V_m = V_{in} - V_{out}$, and is thus negative at rest (typically around -70 mV): the membrane is *polarized*. The membrane potential at equilibrium for a given ionic channel is named the *equilibrium potential*, the *Nernst potential* or the *reversal potential*. The latter denomination means that the equilibrium potential is the membrane potential E at which the transmembrane current I changes sign: when $V_m = E_K$ no current passes through the channels (by definition), when $V_m > E_K$ positive charges exit the cell and therefore $I_K > 0$ (where the current is defined from inside to outside), and when $V_m < E_K$ positive charges enter the cell, $I_K < 0$.

Thus the transmembrane current I has the sign of $V_m - E_K$. A linear approximation yields $I = g_K(V_m - E_K)$. The parameter g has the dimensions of a conductance and is therefore called the *channel conductance*. It is the inverse of a resistance: $g = 1/R$. Electrically, this is equivalent to a resistor in series with a battery (see Figure 1.1). If we assume that all points inside the cell have the same potential, and in the same way that the potential outside the cell is constant, then the membrane is equivalent to a capacitor, representing the bilipid layer, in parallel with a resistor in series with a battery, representing the ionic channels. Using Kirchhoff's law, we can describe the temporal evolution of the membrane potential with the following *membrane equation*:

$$C\frac{dV_m}{dt} + g_K(V_m - E_K) = 0$$

where the first term is the capacitive current, and the second term is the ionic channel current. This equation is often rewritten as follows:

$$\tau\frac{dV_m}{dt} + V_m - E_K = 0$$

where $\tau = C/g_K$ is the membrane time constant. To these currents, we should add many others: currents from synapses and from the dendritic tree, and currents through other types of ionic channels. In particular, action potentials are produced by currents through voltage-dependent ionic channels, i.e. channels with a conductance that depends on the membrane potential. We also assumed that ionic channels were permeable to a single type of ion (here K^+), while in reality they are permeable to several types. These finer aspects are described in more detail in all the books mentioned above.

The membrane potential can be recorded by inserting an electrode in the cell (Figure 1.2). Electrodes for neural recording are described in Chapter 2, and intracellular recording is described in Chapter 3.

In our description of neuronal electricity above, we assumed that the potentials inside and outside the cell were spatially uniform. This is only true for a small patch of membrane or for the soma of the neuron. Along a dendrite, the potential can vary because such small processes have an electrical resistance in the longitudinal direction (quantified by the *intracellular resistivity*). This longitudinal current can be added to the membrane equation, defined at a specific point along the dendrite:

$$\tau\frac{\partial V_m(x,t)}{\partial t} + V_m(x,t) - E_K - \lambda^2\frac{\partial^2 V_m(x,t)}{\partial x^2} = 0$$

where $V_m(x,t)$ is the membrane potential at a specific point of the dendrite, and λ is the space or length constant, also called *electrotonic length*. The last term is

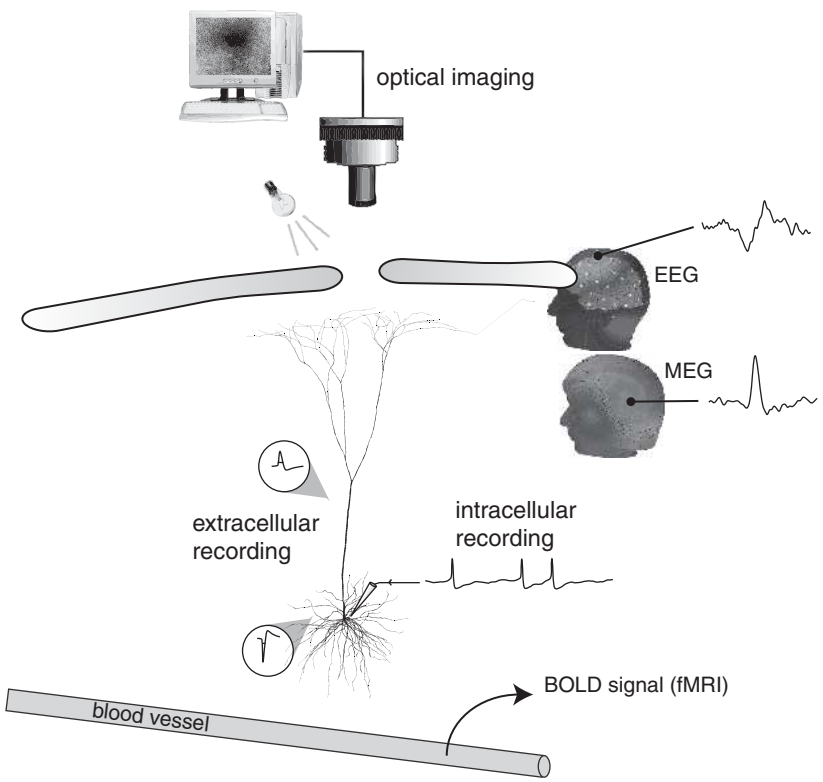

Figure 1.2 (See plate section for color version.) Correlates of neural activity and their measurement. A pyramidal cortical cell is displayed in the middle. Its membrane potential can be recorded with an intracellular electrode (*intracellular recording*, Chapter 3). Current flowing through the neuronal membrane creates extracellular potentials, which can be measured with an extracellular electrode (*extracellular recording*, Chapters 4 and 5). These potentials can also be measured with electrodes on the scalp (*EEG*, Chapters 6 and 7). Similarly, neural activity produces magnetic fields, measured with *MEG* (Chapters 6 and 7). Membrane potential can also be seen with a camera after opening the scalp and applying voltage-sensitive dyes onto the surface of the cortex (voltage-sensitive dye imaging, Chapter 9, an *optical imaging* technique). Calcium enters the cell when it spikes, which can also be recorded optically with a different technique (calcium imaging, Chapter 10). More indirectly, neural activity impacts metabolism, in particular the blood vessels, which produces signals that can be recorded with intrinsic signal optical imaging (Chapter 8, also an optical imaging method) and functional magnetic resonance imaging (*fMRI*, Chapter 11).

a diffusion term which represents the current escaping through the dendrite. By analogy with an electrical cable, this is called the *cable equation*.

Thus, there are currents flowing through the membrane across all of the surface of the cell: soma, dendrites and axon. These currents create electrical and magnetic

fields in the extracellular space, which derive from Maxwell's equations. These are treated in detail in Chapters 4–7. Therefore, an extracellular electrode (Figure 1.2) can record correlates of the electrical activity of a neuron, or of several neighboring neurons. These potentials tend to be small (typically less than a millivolt), because of the low resistance of the extracellular medium. The recorded extracellular potential is a complex function of electrical activity across the neuron, which is described in Chapter 4. Information about individual action potentials is typically extracted from the high-frequency band (>500 Hz) of the extracellular potentials. These signals may stem from a single neighboring neuron (single-unit recording) or more generally from an unknown number of neighboring neurons (multi-unit recording). The low-frequency part (<500 Hz) of the extracellular potentials is called the local field potential (LFP), and is described in Chapter 5.

Electrical potentials can also be recorded with electrodes at the surface of the scalp: this is the electroencephalogram (EEG), which is described in Chapters 6 and 7. Because EEG signals must propagate through various media, such as cerebrospinal fluid, dura mater, cranium, muscle and skin, they are much more filtered than LFPs. They also represent the activity of much larger neural populations. For this reason, a key issue in EEG recording is to relate the potentials measured at the scalp with their neuronal sources inside the brain. The same electrical activity also produces magnetic fields, which can be recorded with magnetoencephalographic (MEG) equipment, which raises similar issues (see Chapters 6 and 7).

Another way to measure the membrane potential is to apply a voltage-sensitive dye on the surface of the cortex. The dye molecules bind to the external surface of the membranes of all cells, and once excited with the appropriate wavelength, they emit an amount of light that depends on the membrane potential. This light can then be captured by a CCD camera (see Figure 1.2). This optical imaging technique, called voltage-sensitive dye imaging (VSDI), is described in Chapter 9. The relationship between the recorded signal and neural activity is complex, in particular because the dye penetrates several layers of the cortex and potentially because both glial and neuronal cells are dyed. Dyes are also used to image calcium concentration rather than membrane potential. Calcium is linked to many processes in all cells, in particular in neurons. For example, calcium enters the cell when an action potential is generated. The dynamics of calcium in a cell can be described by equations that are similar to the cable equation, and thus calcium signals can be related to neuronal activity, as is described in Chapter 10.

As we have seen, electrical activity in the cell relies on differences in the concentrations of various ionic species across the membrane. These differences are actively maintained by pumps, proteins which exchange Na^+ ions against K^+ ions. Because this exchange is against the diffusion flux, it consumes energy (in the form of ATP). Synaptic transmission is also a major source of energy consumption.

Thus, when a neuron fires, or when it receives synaptic currents, it consumes energy, that ultimately originates from the blood vessels (through glial cells). This results in metabolic correlates of neuronal activity that can be measured. For example, the light absorption properties of tissues change with metabolism (for example the volume of blood vessels changes with metabolism). These changes can be recorded optically with a CCD camera: this is *intrinsic signal optical recording*, and is described in Chapter 8. Finally, *functional magnetic resonance imaging* (fMRI), described in Chapter 11, measures changes in cerebral blood flow and oxygenation using the magnetic properties of hemoglobin. These two techniques measure changes in metabolism that are only indirectly related to neural activity, and the precise relationship between the measurements and neural activity is still a matter of investigation.

The ideal measurement technique would be able to resolve the activity of single neurons (high spatial resolution), simultaneously in the whole brain (large spatial scale), at a submillisecond time scale (high temporal resolution). Currently,

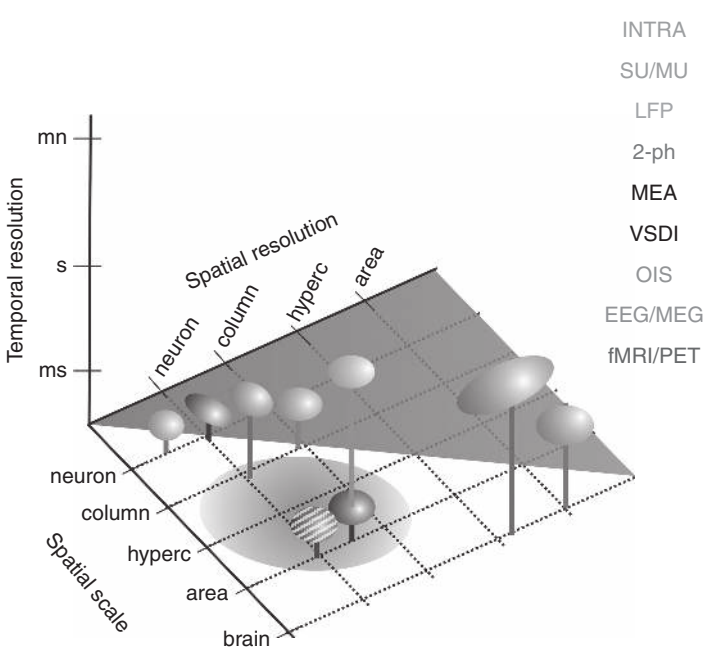

Figure 1.3 (See plate section, Plate 9.1, for color version.) Techniques classified according to their resolutions, both spatial and temporal, and their spatial scale (see figure 9.1). INTRA intracellular recording, SU/MU single-unit/multi-unit recording, LFP local field potential, 2-ph two-photon imaging, MEA multi-electrode array, VSDI voltage-sensitive dye imaging, OIS optical imaging of intrinsic signals, EEG/MEG electroencephalography/magnetoencephalography, fMRI/PET functional magnetic resonance imaging/positron emission tomography. The mesoscopic scale is represented by the oval shaded area. (Modified from Chemla and Chavane, 2010b).

no technique achieves all these goals simultaneously. Figure 1.3 summarizes the performance of the techniques described in this book along these three axes: each one has its advantages and limitations, and we hope that this book will be useful to compare and understand these techniques.

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2

Electrodes

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2.1 Introduction

Electrodes are the first technical interface in a system for recording bioelectrical potentials. The electrochemical and biological processes at the material–tissue interface determine the signal transfer properties and are of utmost importance for the long-term behavior of a chronic implant. Here, "electrode" is used for the whole device that consists of one or multiple active recording sites, a substrate that carries these active sites, as well as interconnections, wires, insulation layers and the connectors to the next stage of a complete recording system, whether it is wire bound or wireless. The application of the electrodes in fundamental neuroscience, diagnosis, therapy, or rehabilitation determines their target specifications. The most important factors are the application site, extracorporal device or implant, acute or chronic contact, size of the electrode (device) and the recording sites, number of active sites on a device, geometrical arrangement of electrodes and type of signal to be recorded. They influence the selection process of electrodes suitable for an envisioned application and help engineers as well as neuroscientists to choose the very best materials for the active sites, substrate and insulation and the most appropriate manufacturing technique. The properties of the recorded signals are also strongly related to this selection process since the tailoring of the transfer characteristics helps to pick up the "right" signal components and to ignore, neglect and reject the "wrong" electrical potentials that might be due to the body itself or the surrounding environment or interference caused by noise from the electrode sites and the amplifier of the recording system.

Bioelectrical potentials are generated from nerves and muscles all over the body to transmit information:

- from the central nervous system to peripheral actuators, like muscles and internal organs,

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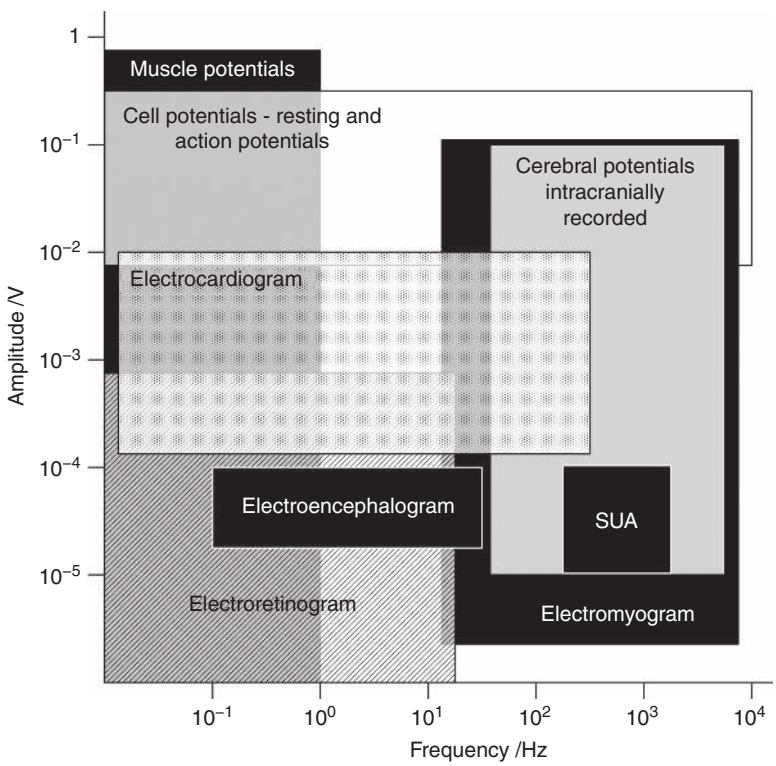

Figure 2.1 Amplitudes and frequency ranges of bioelectrical potentials in the human body. (Modified from Nagel, 2000.) SUA, single-unit activity.

- from natural sensors to the central nervous system to transfer versatile environmental modes into electrical signals as tactile sensors in the skin, the eye and the ear do, and
- within the central nervous system itself to process and compute the information in the brain.

Depending on the recording modality and the application, different amplitudes and frequency ranges will be obtained (Figure 2.1). Neural recordings in the central nervous system can be classified into (extracorporal) electroencephalograms (EEG), intracorporal electrocorticograms (ECoG) and intracortical/intracranial signals. All of these are extracellular recordings in which single-unit activity (SUA), multi-unit activity (MUA) and local field potentials (LFP) represent the spiking behavior of a single neuron, small ensembles of nerve cells and the slow potentials of local ensembles, respectively. Their amplitude is mostly in the upper microvolt range. However, the larger the electrode sites are the higher the amplitudes can be since more neurons contribute additively to the signal. In addition, strong bioelectrical

signals from the heart (ECG) and the skeletal muscles might be superimposed because of their larger amplitudes and might disturb the signal. Often, these potentials and signals occur as artifacts in the signal of interest and cannot be selectively filtered out since their frequency range is identical with that of the wanted signal. Therefore, the properties of the recording electrodes and the filter–amplifier system should match the particular properties of the wanted signal and thereby reject or suppress the components of the unwanted signals.

Neurological investigations use diagnosis methods that are mostly repetitive short-term examinations where recording electrodes are placed non-invasively on the surface of the skin for a very limited time. In therapy, rehabilitation and many fundamental neuroscientific research paradigms, however, electrodes are implanted for a subchronic (up to 30 days) or chronic (longer than 30 days) time period. In these cases, electrodes must provide a reliable interface to the neural target structure and the signal quality must not degrade over time. The long-term stability and functionality of the electrode site materials as well as insulation materials is of utmost importance to obtain reliable signals and to prevent any damage of the target tissue. Especially in recordings from neurons in the brain – the cortex as well as deep brain structures – relatively stiff electrodes have to interface with the delicate brain tissue, which is still a challenge in modern electrophysiology and neurotechnology.

If one summarizes the desired target specifications of neural recording electrodes, different aspects from medicine, material sciences, biomedical engineering and ergonomics are included (Loeb et al., 1995; Stieglitz, 2004; Williams, 2008):

- the material of the electrodes and coatings must not harm the surrounding tissue and must be tolerated by the body to reduce foreign body reactions,
- tailored and stable impedance at the phase boundary delivers a functional interface,
- tailored frequency characteristics are required to record wanted signals for the envisioned application,
- low noise (thermal as well as electrochemical) allows recording of signals with small amplitudes,
- low polarization at the phase boundary and low afterpotentials if recording is combined with electrical stimulation,
- integrated pre-amplifier to minimize interfering signals from the body and the environment.

If the electrode is part of a chronic implantable system, the following specifications have to be added to obtain a useful and safe system: