# Chapter 1

# The Membrane Equation

Any physical or biophysical mechanism instantiating an information processing system that needs to survive in the real world must obey several constraints: (i) it must operate at high speeds, (ii) it must have a rich repertoire of computational primitives, with the ability to implement a variety of linear and nonlinear operations, and (iii) it must interface with the physical world—in the sense of being able to accurately represent sensory input pattern and translate the result of the computations into action, i.e. motor output.

The membrane potential is the one physical variable within the nervous system that fulfills these three requirements: it can vary rapidly over large distances (e.g. an action potential changes the potential by 100 mV within 1 msec, propagating up to a centimeter or more down an axon within that time) and the membrane potential controls a vast number of nonlinear gates—ionic channels—that provide a very rich substrate for implementing nonlinear operations. These channels transduce visual, tactile, auditory, and olfactory stimuli into changes of the membrane potential and such voltage changes back into the release of neurotransmitter or the contraction of muscles.

This is not to deny that ionic fluxes or chemical interactions of various substances with each other are not crucial to the working of the brain. They are, and we will study some of these mechanisms in chapter 11. Yet the membrane potential is the incisive variable that serves as primary vehicle for the neuronal operations underlying rapid computations—at the fraction of a second time scale—in the brain.

We will introduce the reader in a very gentle manner to the electrical properties of nerve cells by starting off with the very simplest of all neuronal models, consisting of nothing more than a resistance and a capacitance (a so-called *RC circuit*). Yet endowed with synaptic input, this model can already implement a critical nonlinear operation, *divisive normalization* and *gain control*.

## 1.1 The Structure of the Passive Neuronal Membrane

As starting point, we choose a so-called *point* representation of a neuron. Here, the spatial dependency of the neuron is reduced to a single point or compartment; such an approximation

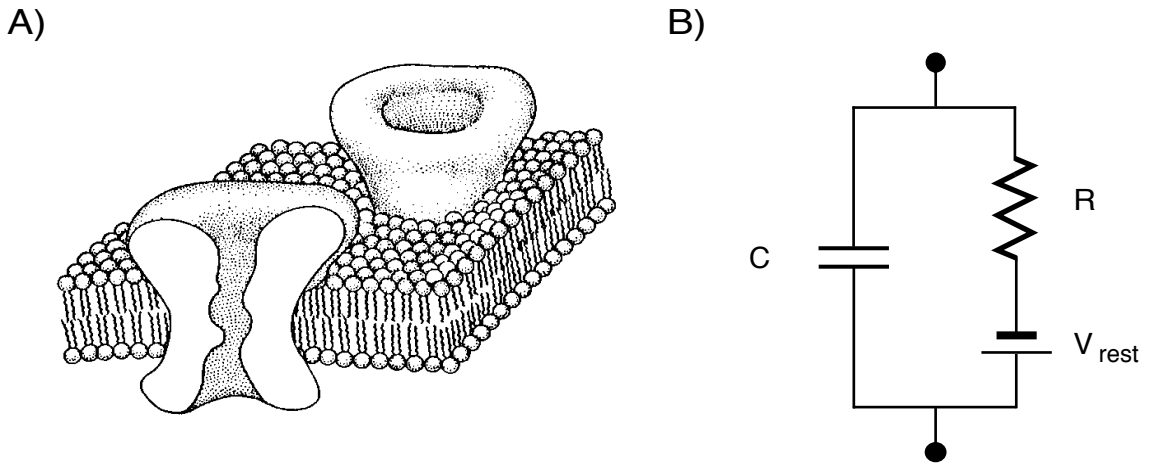


Figure 1.1: NATURE OF THE PASSIVE NEURONAL MEMBRANE
**(A)** Schematic representation of a small patch of membrane of the types enclosing all biological cells. The 30-50$\AA$ thin bilayer of lipids isolates the extra- from the intra-cellular side. From an electrical point of view, the resultant separation of charge across the membrane acts akin to a capacitance. Proteins inserted into the membrane, here ionic channels, provide a conduit through the membrane. From Hille (1992). **(B)** The associated lumped electrical circuit for this patch, consisting of a capacitance and a resistance in series with a battery. The resistance mimics the behavior of voltage-independent ionic channels inserted throughout the membrane and the battery accounts for the cell's resting potential, $V_{rest}$.

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would be valid, for instance, if we are investigating a small, spherical cell without a significant dendritic tree.

### 1.1.1 The Resting Potential

The first thing we notice once we managed to penetrate into this cell with a wire from which we can record (termed an intracellular *microelectrode*) is the existence of an electrical potential across this membrane. Such experiments, carried out in the late 1930's by Cole and Curtis (1936) in Woods Hole, Massachusetts and by Hodgkin and Huxley (1939) on the other side of the Atlantic, demonstrated that almost always, the membrane potential, defined as the difference between the intracellular and the extracellular potential, or

$$V_m(t) = V_i(t) - V_e(t)\,, \tag{1.1}$$

is negative. Here $t$ stands for time. In particular, at rest, all cells, whether neurons, glia or muscle cells, have a negative resting potential, symbolized throughout the book as $V_{rest}$. Depending on circumstances it can be as high as -30 mV or as low as -90 mV. Note that when we say the cell is at "rest", it is actually in a state of dynamic equilibrium; ionic currents are flowing across the membrane, but they balance each other, in such a manner

that the net current flowing across the membrane is zero. Maintaining this equilibrium is a major power expenditure for the nervous system. Half of the metabolic energy consumed by a mammalian brain has been estimated to be due to the membrane-bound pumps that are responsible for the upkeep of the underlying ionic gradients (Ames, 1997).

The origin of $V_{rest}$ lies in the differential distribution of ions across the membrane, which we do not further describe here (see section 4.4 and Hille, 1992). $V_{rest}$ need not necessarily be fixed; indeed, we will discuss in chapter **??** conditions under which a network of cortical cells can dynamically adjust the resting potential.

### 1.1.2 The Membrane Capacity

What is the nature of the membrane separating the intra- from the extra-cellular cytoplasm (Fig. 1.1)? The two basic constitutive elements of biological membranes, whether from the nervous system or from non-neuronal tissues such as muscle or red blood cells, whether prokaryotic or eukaryotic, are *proteins* and *lipids* (Gennis, 1989).

The backbone of the membrane is made of two layers of phospholipid molecules, with their polar heads facing the intracellular cytoplasm and the extracellular space, thereby separating the internal and external conducting solutions by an 30-50 $\mathring{A}$ thin insulating layer. We know that whenever a thin insulator is keeping charge apart it will act like a *capacitance*. The capacitance $C$ is a measure of how much charge $Q$ needs to be distributed across the membrane in order for a certain potential $V_m$ to build up. Or, conversely, the membrane potential $V_m$ allows the capacitance to build up a charge $Q$ on both sides of the membrane, with

$$Q = CV_m \,. \tag{1.2}$$

In membrane biophysics, the capacitance is usually specified in terms of the *specific membrane capacitance* $C_m$, in units of microFarad per $cm^2$ of membrane area. The actual value of $C$ can be obtained by multiplying $C_m$ by the total membrane area. The thickness and dielectric constant of the bilipid layer determines the numerical value of $C_m$. For the simplest type of capacitance formed by two parallel plates, $C_m$ scales inversely with the thickness separating the charges (the thinner the distance between the two plates, the stronger the mutual attraction of the charges across the insulating material). As discussed in Appendix A, the specific capacitance per unit area of biological membranes is between 0.7 and 1 $\mu F/cm^2$. For the sake of convenience, we adopt the latter, simple to remember, value. This implies that a spherical cell of 5 $\mu$m radius with a resting potential of -70 mV stores about -0.22·$10^{-8}$ Coulomb of charge just below the membrane and an equal but opposite amount of charge outside.

When the voltage across the capacitance changes, a current will flow. This *capacitive current* that moves on or off the capacitance is obtained by differentiating eq. 1.2 with respect to time (remember that current is the amount of charge flowing per time),

$$I_C = C\frac{dV_m(t)}{dt} \,. \tag{1.3}$$

For a fixed current, the existence of the membrane capacitance imposes a constraint on how rapidly $V_m$ can change in response to this current; the larger the capacitance, the slower the resultant voltage change.

It is important to realize that there is never any actual movement of charge across the insulating membrane. When the voltage changes with time, the charge changes and a current will flow, in accordance with eq. 1.3, but never directly across the capacitance. The charge merely redistributes itself across the two sides by way of the rest of the circuit.

Can any current flow directly across the bilipid layers? As detailed in Appendix A, the extremely high resistivity of the lipids prevents passages of any significant amount of charge across the membrane. Indeed, the specific resistivity of the membrane is approximately one billion times higher than that of the intracellular cytoplasm. Thus, from an electrical point of view, the properties of the membrane can be satisfactorily described by a sole element: a capacitance.

### 1.1.3 The Membrane Resistance

With no other components around, life would indeed be dull. What endows a large collection of squishy cells with the ability to move and to think are the all important *proteins* embedded within the membrane. Indeed, they frequently penetrate the membrane, allowing ions to pass from one side to the other (Fig. 1.1). Protein molecules, making up anywhere from 20 to 80% (dry weight) of the membrane, subserve an enormous range of specific cellular functions, including ionic channels, enzymes, pumps, and receptors. They act as doors or gates in the lipid barrier through which particular information or substances can be transferred from one side to the other. As we shall see later on, a great variety of such "gates" exists, with different keys to open them. For now, we are interested in those membrane proteins that act as ionic *channels* or *pores*, enabling ions to travel from one side of the membrane to the other. We will discuss the molecular nature of these channels in more detail in chapter **??**.

For now, we will summarily describe the current flow through these channels by a simple linear resistance $R$. Since we also have to account for the resting potential of the cell, the simplest electrical description of a small piece of membrane includes three elements, $C, R$ and $V_{rest}$ (Fig. 1.1). Such a circuit describes a *passive* membrane in contrast to *quasi-active* and *active* membranes, that contain, respectively, linear, inductance-like and nonlinear voltage-dependent membrane components. For obvious reasons, it is also sometimes known as a *RC circuit*. Fortuitously, the membranes of quite a few cells can be mimicked by such RC circuits, as least under some limited conditions.

The membrane resistance is usually specified in terms of the *specific membrane resistance* $R_m$, expressed in terms of resistance times unit area (in units of $\Omega cm^2$). $R$ is obtained by dividing $R_m$ by the area of the membrane being considered. The inverse of $R_m$ is known as the passive conductance per unit area of dendritic membrane or, for short, as the *leak conductance* $G_m = 1/R_m$ and is measured in units of Siemens per $cm^2$, abbreviated as $S/cm^2$.

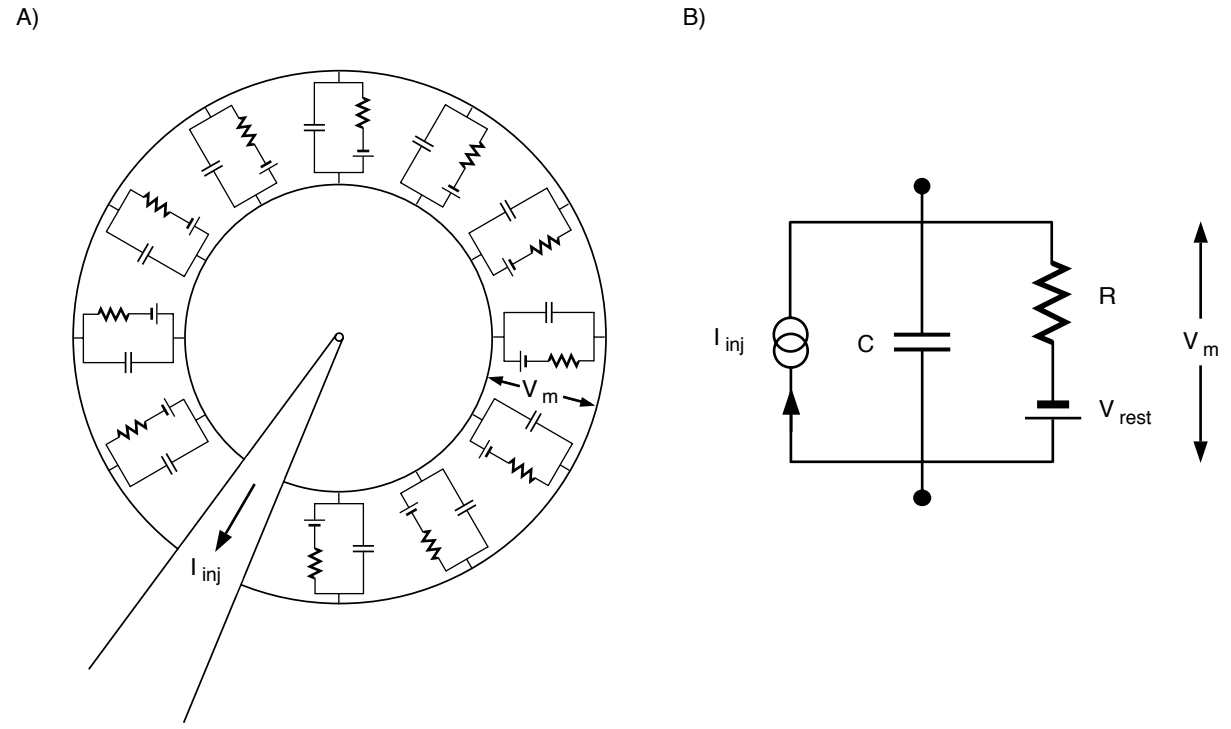


Figure 1.2: The Electrical Structure of a Small, Passive Neuron
**(A)** The equivalent, electrical model of a spherical cell with passive membrane. An intracellular electrode delivers current to the cell. By convention, an outward current is positive; thus, the arrow. We assume that the dimensions of the cell are small enough so that spatial variations in the membrane potential can be neglected. **(B)** Under these conditions, the cell can be reduced to a single *RC* compartment in series with an ideal current source $I_{inj}$.

## 1.2 A Simple RC Circuit

Let us now carry out a virtual electrophysiological experiment. Assume that we have identified a small spherical neuron of diameter $d$ and have managed to insert a small electrode into the cell without breaking it up. Under the conditions of our experiments, we have reasons to believe that its membrane acts passive. We would like to know what happens if we inject current $I_{inj}(t)$ through the microelectrode directly into the cell. This electrode can be thought of as an ideal *current source* (in contrast to an ideal voltage source, such as a battery).

How can we describe the dynamics of the membrane potential $V_m(t)$ in response to this current? The cell membrane can be conceptualized as being made up out of many small RC circuits (Fig. 1.2A). Because the dimensions of the cell are so small, the electrical potential across the membrane is everywhere the same and we can neglect any spatial dependencies; physiologists will say the cell is *isopotential*. This implies that the electrical behavior of the cell can be adequately described by a single RC compartment with a current source

(Fig. 1.2B). The net resistance $R$ is determined by the specific membrane resistance $R_m$ divided by the total membrane area $\pi d^2$ (since the current can flow out through any one part of the membrane) while the total capacitance $C$ is given by $C_m$ times the membrane area.

It is straightforward to describe the dynamics of this circuit by applying *Kirchhoff's current law* that states that the sum of all currents flowing into or out of any electrical node must be zero (the current can't disappear, it has to go somewhere). The current across the capacitance is given by expression 1.3. The current through the resistance is given by *Ohm's law*,

$$I_R = \frac{V_m - V_{rest}}{R}\,. \tag{1.4}$$

Note that the potential across the resistance is not equal to $V_m$, but to the difference between the membrane potential and the fictive battery, $V_{rest}$, that accounts for the resting potential. Due to current the conservation of current the capacitive and resistive currents must be equal to the external one, or

$$C\frac{dV_m(t)}{dt} + \frac{V_m(t) - V_{rest}}{R} = I_{inj}(t)\,. \tag{1.5}$$

With $\tau = RC$, with units of $\Omega F = sec$, we can rewrite this as

$$\tau\frac{dV_m(t)}{dt} = -V_m(t) + V_{rest} + RI_{inj}(t)\,. \tag{1.6}$$

A minor, but important, detail is the sign of the external current (after all, we could have replaced $+I_{inj}$ by $-I_{inj}$ in the above equation). By convention, an outward current, that is charge flowing from inside the neuron to the outside, is represented as a positive current. An outward going current that is delivered through an intracellular electrode will make the inside of the cell more positive, the physiologist says that the cell is *depolarized*. Conversely, an inward directed current supplied by the same electrode, plotted by convention in the negative direction, will make the inside more negative, that is *hyperpolarize*, the cell. If the current is not applied from an external source but is generated by a membrane conductance, the situation is different (see chapter **??**).

Due to the existence of the battery, $V_{rest}$, the electrical diagram in Fig. 1.2B does **not**, formally speaking, constitute a *passive* circuit, since its current-voltage relationship is not restricted to the first and third quadrants of the I-V plane. This implies that power is needed to maintain this I-V relationship, ultimately supplied by the differential distributions of ions across the membrane. Because the I-V relationship has a non-zero, positive derivative for every value of $V_m$, it is known as an *incrementally passive* device. This point is not without interest, since it relates to the stability of circuits built using such components (Wyatt, 1982). We here do not take a purist point of view and will continue to refer to a membrane whose equivalent circuit diagram is similar to that of Figs. 1.1B and 1.2B as passive.

Equation 1.6 is known as the *membrane equation* and constitutes a first-order, ordinary differential equation. With the proper initial conditions, it specifies an unique voltage trajectory. Let us assume that the membrane potential starts off at $V_m(t = 0) = V_{rest}$. We

can replace this into eq. 1.6 and see that in the absence of any input ($I_{inj}$=0) this yields $dV_m/dt$=0, *i.e.* once at $V_{rest}$, the system will remain at $V_{rest}$ in the absence of any input. This makes perfect sense. So now let us switch on, at $t = 0$, a step of current of amplitude $I_0$. We should remember from the theory of ordinary differential equations that the most general form of the solution of eq. 1.6 can be expressed as

$$V_m(t) = v_0 e^{-t/\tau} + v_1 \,, \tag{1.7}$$

where $v_0$ and $v_1$ depend on the initial conditions. Replacing this into eq. 1.6 and canceling identical variables on both sides leaves us with

$$v_1 = V_{rest} + RI_{inj} \,. \tag{1.8}$$

We obtain the value of $v_0$ by imposing the initial condition $V_m(t = 0) = v_0 + v_1 = V_{rest}$. Defining the steady-state potential in response to the current as $V_\infty = RI_{inj}$, we have solved for the dynamics of $V_m$ for this cell

$$V_m(t) = V_\infty(1 - e^{-t/\tau}) + V_{rest} \,. \tag{1.9}$$

This equation tells us that the time course of the deviation of the membrane potential from its resting state, *i.e.* $V_m(t) - V_{rest}$, is an exponential function in time, with a time constant equal to $\tau$. Even though the current changed instantaneously from zero to $I_0$, the membrane potential can't follow but plays catch up (this is graphically demonstrated in Fig. 1.3). How slowly $V_m$ can change is determined by the product of the membrane resistance and capacitance; the larger the capacitance, the larger the current that goes towards charging up $C$. Note that $\tau$ is independent of the size of the cell:

$$\tau = RC = R_m C_m \,. \tag{1.10}$$

As we will discuss in considerable detail in later chapters, passive time constants range from 1-2 msec in neurons that are specialized in processing high-fidelity temporal information to 100 msec or longer for cortical neurons recorded under slice conditions. A typical range for $\tau$ recorded from cortical pyramidal cells in the living animal[1] is between 10 and 20 msec.

Remember the origin of the membrane capacitance in the molecular dimensions of the bilipid membrane. A thicker membrane would lead to a smaller value for $C_m$ and faster temporal responses[2].

The final voltage level in response to the current step is $V_\infty = RI_0$ (from Ohm's law). If $I_0 > 0$, the cell will depolarize (*i.e.* $V_\infty > V_{rest}$), while for $I_0 < 0$, the converse occurs. The

[1]This is called *in vivo*. Such experiments need to be distinguished from the cases in which a very thin slice is taken from an animal's brain, placed in a dish and perfused with a nutrient solution. This would be termed an *in vitro* experiment.

[2]As an aside to the neuromorphic engineers among us designing analog integrated electronic circuits, $C_m$=1 $\mu F/cm^2$ is about 20 times higher than the specific capacitance obtained by sandwiching a thin layer of silicon dioxide between two layers of poly silicon (using a standard 2.0 or 1.2 $\mu$ m CMOS process (Mead, 1989).

resistance $R$ is also termed the *input resistance* of the cell; the larger $R$, the larger the voltage change in response to a fixed current. The input resistance at the cell bodies of neurons, obtained by dividing the steady-state voltage change by the current causing it, ranges from a few $M\Omega$ for the very large motoneurons in the spinal cord to hundreds of $M\Omega$ for cortical spiny stellate cells or cerebellar granule cells.

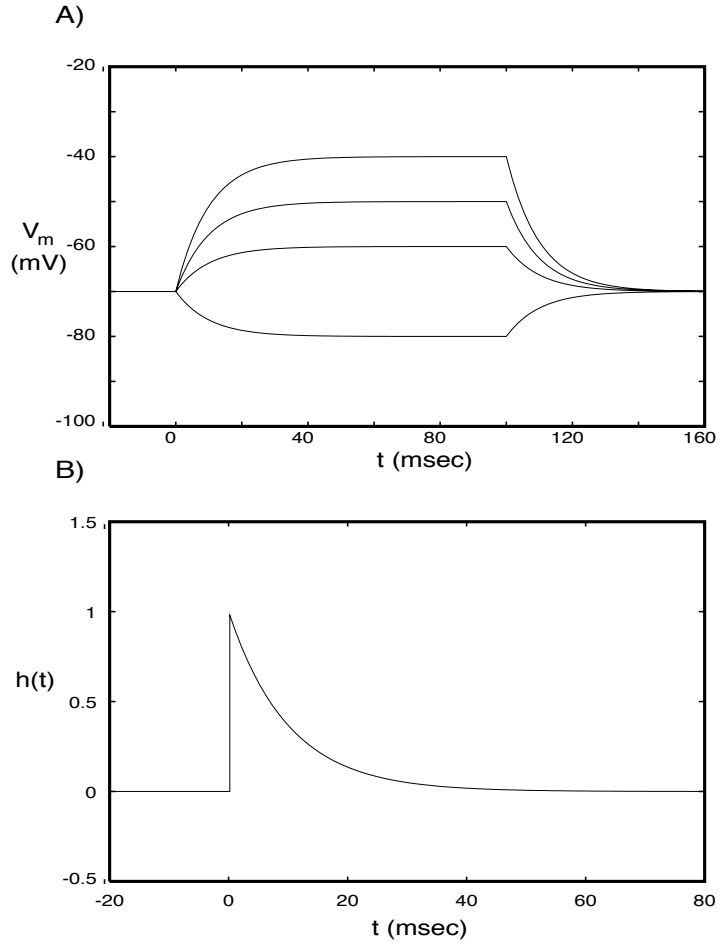


Figure 1.3: The Behavior of a RC Circuit

**(A)** The evolution of the membrane potential $V_m(t)$ in the single RC compartment of Fig. 1.2B when a current step of different amplitudes $I_0$ (see eq. 1.9) is switched on at $t$=0 and turned off at 100 msec. Initially, the membrane potential is at $V_{rest}$=-70 mV. We here assume $R$=100 M$\Omega$, C=100 pF, $\tau$=10 msec and four different current amplitudes $I_0$=-0.1, 0.1, 0.2 and 0.3 nA. **(B)** The normalized *Impulse Response* or *Green's* function (eq. 1.17) associated with the RC circuit of Fig. 1.2B. The voltage $V_m(t)$ in response to any current input $I_{inj}(t)$ can be obtained by convolving this function with the input.

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What happens if, after the membrane potential reaches its steady-state value $V_\infty$, the current is switched off at time $t_{off}$? An analysis similar to the above shows that the membrane

potential returns to $V_{rest}$ with an exponential time course; that is

$$V_m(t) = V_\infty e^{-(t-t_{off})/\tau} + V_{rest}\,, \tag{1.11}$$

for $t \geq t_{off}$ (this can be confirmed by placing this solution into eq. 1.6; see also Fig. 1.3A).

Now that we know the evolution of the membrane potential for a current step, we would like to know the solution in the general case of some time-dependent current input $I_{inj}(t)$. Are we condemned to explicitly solve eq. 1.6 for every new function $I_{inj}(t)$ that we use? Fortunately not; because the RC circuit we've been treating here is a shift-invariant, linear system, we can do much better.

## 1.3 RC Circuits as Linear Systems

*Linearity* is an important property of certain systems that allows us—in combination with shift-invariance— to completely characterize their behavior to *any* input in terms of the system's *Impulse response* or *Green's function* (named after a British mathematician living at the beginning of the nineteens century). Since the issue of linear and non-linear systems runs like a thread through this monograph, we urge the reader who has forgotten these concepts to quickly skim through Appendix B, summarizing the most relevant points.

### 1.3.1 Filtering by RC Circuits

Let us compute the voltage response of the RC circuit of Fig. 1.2B in response to an impulse of current $\delta(t)$. We will simplify matters by only considering the deviation of the membrane potential from its resting state $V_{rest}$. Here and throughout the book, we use the symbol $V(t) = V_m(t) - V_{rest}$ when we are dealing with the potential relative to rest and reserve $V_m(t)$ for the absolute potential. This transforms eq. 1.6 into

$$\tau \frac{dV(t)}{dt} = -V(t) + R\delta(t)\,. \tag{1.12}$$

We can transform this equation into Fourier space, where $\tilde{V}(f)$ corresponds to the Fourier transform of the change in membrane potential (for a definition, see Appendix B). Remembering that the $d\cdot/dt$ term metamorphoses into $i2\pi f$, where $i^2$=-1, we have

$$\tilde{V}(f) = \frac{R}{1 + i2\pi f\tau}\,. \tag{1.13}$$

A simple way to conceptualize this is to think of the input as a sinusoidal current of frequency $f$: $I_{inj}(t) = \sin(2\pi ft)$. Since the system is linear, the system responds by a sinusoidal change of potential at the same frequency $f$, but of different amplitude and shifted in time: $V(t) = \tilde{A}(f)\sin(2\pi ft + \tilde{\phi}(f))$. The amplitude of the voltage response at this frequency, termed $\tilde{A}(f)$, is given by

$$|\tilde{A}(f)| = \frac{R}{\sqrt{1 + (2\pi f\tau)^2}}\,, \tag{1.14}$$

and its phase

$$\tilde{\phi}(f) = -\arctan(2\pi f\tau)\,. \tag{1.15}$$

In the general case of an arbitrary input current, one can define the complex function $\tilde{A}(f)$ as the ratio of the Fourier transform of the voltage transform to the Fourier transform of the injected current:

$$\tilde{A}(f) = \frac{\tilde{V}(f)}{\tilde{I}_{inj}(f)}\,. \tag{1.16}$$

$\tilde{A}(f)$ is usually referred to as the *input impedance* of the system. Its value for a sustained or d.c. current input, $\tilde{A}(f=0)$=R, is known as the *input resistance* and is a real number. It is standard engineering practice to refer to the inverse of the input impedance as the *input admittance* and to the inverse of the input resistance as the *input conductance* (in units of *Siemens*).

Does this definition of $\tilde{A}$ make sense? Let us look at two extreme cases. If we subject the system to a sustained current injection, the change in voltage in response to a sustained input current $I$ is proportional to $R$, Ohm's law. Conversely, what happens if we use a sinusoidal that has a very high frequency $f$? The amplitude of the voltage change becomes less and less since at high frequencies, as the capacitance essentially acts like a short-circuit. In the limit of $f \to \infty$, the impedance goes to zero.

For intermediate values of $f$, the amplitude smoothly interpolates between $R$ and 0. In other words, our circuit acts like a *low-pass* filter, preferentially responding to slower changing inputs and severely attenuating faster ones: $|\tilde{A}(f)|$ is a strictly monotonic decreasing function of the frequency $f$.

Experimentally, the impedance can be obtained by injecting a sinusoidal current of frequency $f$ and measuring the induced voltage at the same frequency. The ratio of the voltage to the current corresponds to $|\tilde{A}(f)|$. The use of impedances to describe the electrical behavior of neurons and, in particular, of muscle cells, has a long tradition going back to the 1930's (Cole and Curtis, 1936; Falk and Fatt, 1964; Cole, 1972).

The result of such a procedure, carried out in a regular firing cell in a slice taken from the visual cortex of the guinea pig is shown in Fig. 1.4. Carandini and his colleagues (1996) injected either sinusoidal currents or a noise stimulus into these cells and recorded the resultant somatic membrane potential (in the presence of spikes). Given their very fast time scale, somatic action potentials do not contribute appreciably to the total power of the voltage signal. Indeed, when stimulating with a sine wave at frequency $f$, the power of the voltage response at all higher frequencies was only 3.8% (median) of the power of the fundamental $f$. This implies that when judged by the membrane potential and not by the firing rate, and only considering input and output at the soma, at least some cortical cells can be quite well approximated by a linear filter (Carandini *et al.*, 1996).

This is surprising, given the presence of numerous voltage-dependent conductances at the soma and in the dendritic tree. It is, however, not uncommon in neurobiology to find that despite of—or, possible because of—a host of concatenated nonlinearities, the overall system behaves quite linearly (see section 21.1.3). Sometimes one has the distinct impression that

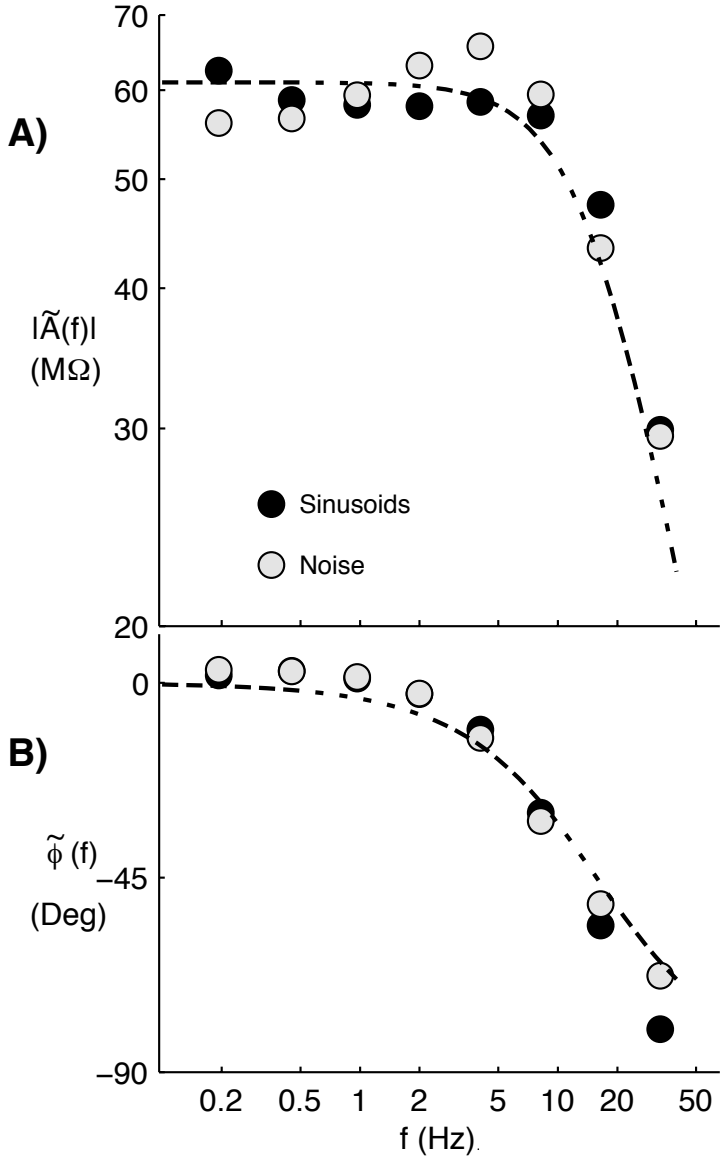


Figure 1.4: Cortical Cells Behave Like a RC Circuit

When either noise or sinusoidal currents are injected into the cell body of regular firing cells in guinea pig visual cortex, the membrane potential can be adequately modeled as resulting from convolving the current input by a low-pass filter of the sort described in eqs. 1.14 and 1.15 (here with $R$=58.3 MΩ and $\tau$ = 9.3 msec; $V_{rest}$=-70.7 mV; Carandini *et al.*, 1996). **(A)** The amplitude of the filter and **(B)** its phase. The noise current curve reveals a shallow peak at around 8 Hz. We conclude that from the point of view of somatic input-output, these cells can be reasonably well described by a single RC compartment. The responses were obtained by computing the first harmonic of the membrane potential response and dividing by the current. The power of the first harmonic was between 9 and 141 times the power of the higher harmonics. From Carandini *et al.*, 1996.

evolution wanted to come up with some overall linear mechanism, despite all the existing nonlinearities.

We will study later on how adding a simple, absolute voltage threshold to the RC compartment that gives rise to an output spike accounts surprisingly well for the spiking behavior of such cells. This simplest model of a spiking neuron, known as a *leaky integrate-and-fire* unit, is so important that it deserves its own detailed treatment in chapter 14.

We can recover the Green's function $h(t)$ of the RC compartment by applying the inverse Fourier transform to eq 1.13, resulting in

$$h(t) = \frac{1}{C} e^{-t/\tau}, \tag{1.17}$$

for $t \geq 0$ and 0 for negative times (the units of the Green's function are $\Omega$/sec). Conceptually, the extent of this filter, that is the temporal duration over which this filter is significantly different from zero, indicates to what extent the distant past influences the present behavior of the system. For a decaying exponential as in a RC circuit, an event that happened three time constants ago (at $t$ = -3$\tau$) will have roughly 1/20-th the effect of something that just occurred (Fig. 1.3B). This is expected in a circuit that implements a low-pass operation. Input is integrated in time, with long ago events having exponentially less impact that more recent ones.

## 1.4 Synaptic Input

So far, we have not considered how the output of one neuron provides input to the next one. Fast, one-way communication among neurons occurs at specialized contact zones, termed *synapses*. Synapses are the elementary structural and functional units for the construction of neuronal circuits. Conventional point-to-point synaptic interactions come in two different flavors: *electrical synapses*—also referred to as *gap junctions*—and the much more common *chemical synapses*. At about 1 billion chemical synapses per cubic millimeter of cortical grey matter, there are lots of synapses in the nervous system (on the order of $10^{15}$ for a human brain). In order to give the reader an appreciation of this, Fig. 1.5 is a photomicrograph of a small patch of the monkey retina at the electron-microscopic level, with a large number of synapses visible. Synapses are very complex pieces of machinery that can keep track of their history of usage over considerable time-scales. In this chapter, we introduce fast, voltage-independent chemical synapses from the point of view of the postsynaptic cell, deferring a more detailed account of synaptic biophysics, as well as voltage-dependent synapses and electrical synapses, to chapter 4, and an account of their adapting and plastic properties to chapter 13.

Upon activation of a fast, chemical synapse, one can observe a rapid and transient change in the *postsynaptic* potential. Here, postsynaptic simple means that we are observing this signal on the "far" or "output" side of the synapse; the "input" part of a synapse is referred to as the *presynaptic* terminal. When the synapse is an excitatory one, the membrane potential rapidly depolarizes, returning more slowly to its resting state: an *excitatory postsynaptic*

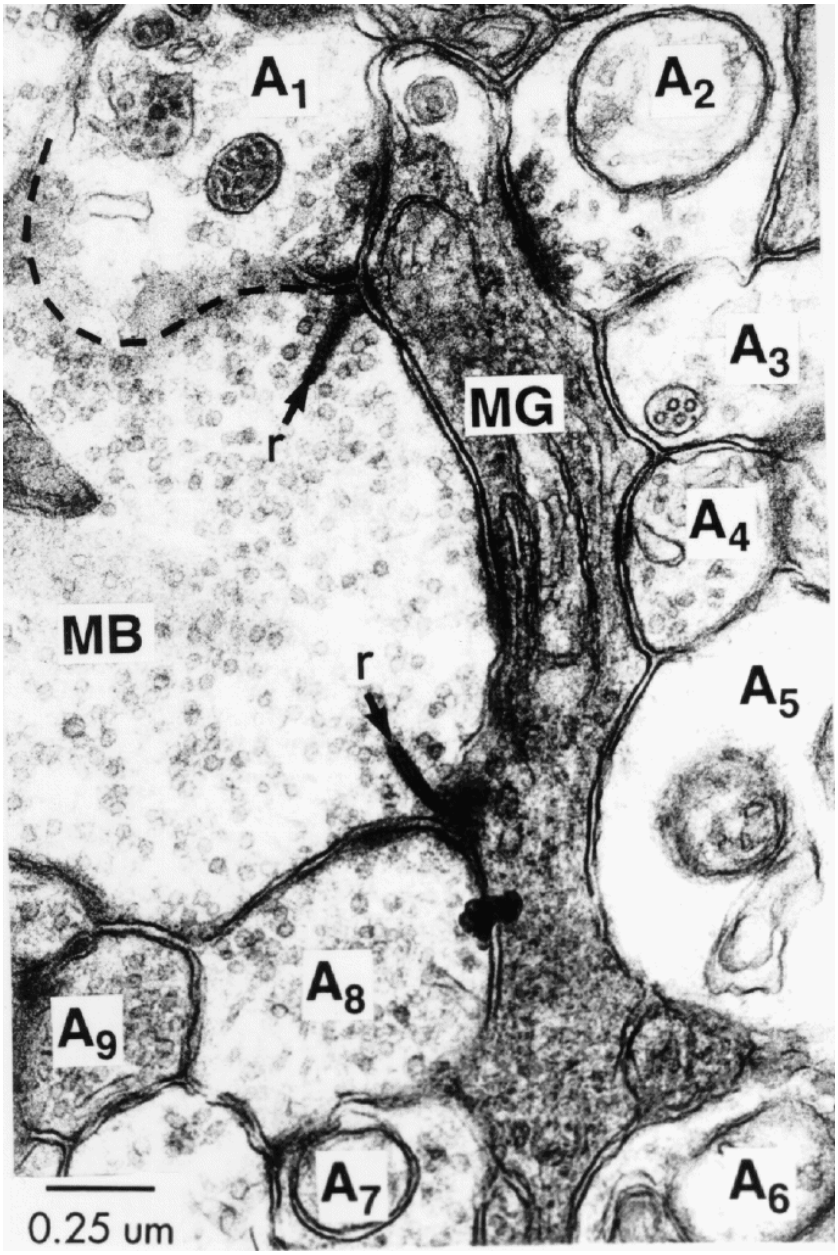


Figure 1.5: Synapses Among Retinal Neurons
Electronmicroscopic photograph of a few square micrometer of tissue in the central portion of the retina in the monkey. Here a midget bipolar cell (**MB**) makes two *ribbon synapses* onto a midget ganglion cell (**MG**). It is surrounded by nine processes belong to amacrine cells ($\mathbf{A}_1$ to $\mathbf{A}_9$). Some of these feed back onto the bipolar cell (e.g. $\mathbf{A}_8$), some feed forward onto the ganglion cell (e.g. $\mathbf{A}_1$), some do both and some also contact each other (e.g. $\mathbf{A}_2 \rightarrow \mathbf{A}_3$). Since neither the bipolar cell nor the amacrine cell processes have been shown to generate action potentials, these synapses are all of the analog variety, in distinction to synapses in the more central part of the nervous system that typically transform an action potential into a graded, postsynaptic signal. From Calkins and Sterling (1996).

*potential* (EPSP) has just occurred. Conversely, at an inhibitory synapse, the membrane will typically be transiently hyperpolarized, resulting in an *inhibitory postsynaptic potential* (or IPSP). These EPSPs and IPSPs are caused by so-called *excitatory* and *inhibitory postsynaptic currents*, EPSCs and IPSCs, triggered by the spiking activity in the presynaptic cell.

Fig. 1.6 illustrates some of the properties of a population of depolarizing synapses between the axons of granule cells, also called *mossy fibers*, and a CA3 hippocampal pyramidal cell[3]. The figure is taken from an experiment by Brown and Johnston (1983) that demonstrated for the first time how a synapse within the central nervous system could be voltage-clamped. The *voltage-clamp* technique was previously used on the very large synapse made between the axonal terminals of motoneurons and the muscle, the so-called *neuromuscular* junction (Katz, 1966; Johnston and Wu, 1994). It allows the experimentalist to stabilize the membrane potential (via a feedback loop) at some fixed value, irrespective of the currents that are flowing across the membrane in response to some stimulus. This allows the measurement of EPSCs at various fixed potentials (as in Fig. 1.6). The EPSC has its largest value at a holding potential of -65 mV, becoming progressively smaller and vanishing around about 0 mV. If the membrane potential is clamped to values more positive than zero, the EPSC reverse sign (Fig. 1.6A). When the relationship between the peak current and the holding potential is plotted (Fig. 1.6B), the data tend to fall on a straight line that goes through zero around -1.9 mV and that has a slope of 20.6 nS.

What we can infer from such a plot is that the postsynaptic event is caused by a temporary increase in the membrane conductance, here by a maximal increase of about 20 nS (due to simultaneous activation of numerous synapses) in series with a so-called *synaptic reversal battery*, $E_{syn}$=-1.9 mV (since the conductance change is specific for a particular class of ions). Spiking activity in the presynaptic cell triggers, through a complicated cascade of biophysical events (further discussed in Chapter 4), a conductance change in the membrane of the postsynaptic cell. Typically, the conductance $g_{syn}(t)$ transiently increases within less than a millisecond, before this increase subsides within 5 msec. The equivalent electrical circuit diagram of a synapse embedded into a patch of neuronal membrane is shown on the left side of Fig. 1.7. It is important to understand that from a biophysical, postsynaptic point of view, a synapse does not correspond to a fixed current source—in that case the slope of the I-V curve in Fig. 1.6 should have been zero—but to a genuine increase in the membrane conductance. As we will reemphasize throughout the book, this basic feature of the neuronal hardware has a number of important functional consequences.

Because of the existence of the synaptic battery, the *driving potential* across the synapse is the difference between $E_{syn}$ and the membrane potential. The postsynaptic current due to a single such synapse is given by Ohm's law:

$$I_{syn} = g_{syn}(t)(V_m(t) - E_{syn})\,. \tag{1.18}$$

Inserting this synapse into patch of a neuronal membrane (Fig. 1.7A) gives rise to the

[3]It should be pointed out that we are here looking at a population of synapses, made very close to the soma of the pyramidal cell, thereby minimizing space-clamp problems.