Chapter 6
Temporal Interactions Between Postsynaptic Potentials

IDAN SEGEV

6.1 Introduction

The previous two chapters have introduced two of the essential ingredients for the description of neuronal behavior. Chapter 5 has discussed the passive propagation of synaptic inputs through the dendritic tree to the soma and the initial axon segment. Here, voltage-activated channels (Chapter 4) respond to produce the action potentials that are conducted along the axon, resulting in a release of neurotransmitters at the presynaptic terminals. The present chapter deals with the response of the postsynaptic region to this input — namely, with the development of the *postsynaptic potential* (PSP).

Synaptic inputs from different presynaptic sources converge onto the postsynaptic neuron; typically onto its soma-dendritic membrane surface. There these inputs interact with each other and are integrated before output is produced in the axon. The number of synaptic inputs, their characteristics, as well as their spatial and temporal distribution vary in different cell types and in the same cell under various conditions. Some neurons receive only a few synaptic inputs whereas a typical neuron in the mammalian central nervous system (CNS) may receive several thousands of such inputs. Nevertheless, the principles that govern the interactions among postsynaptic potentials both in time and in space is relatively well understood. In this chapter, we focus on the temporal aspect of this interaction.

Here we treat the events that take place locally, at the postsynaptic membrane. We

analyze the initiation of the postsynaptic potential following the opening of synaptic channels (i.e., a conductance change) induced by the release of the neurotransmitter from the presynaptic terminal. First, the basic (R-C) electrical model of a neuronal membrane is introduced. Then a synaptic branch is added to this analog circuit and the production of the PSP is discussed. The case of several inputs impinging on the same patch of membrane at different times is also considered. Finally, we use the GENESIS *Neuron* tutorial together with several suggested exercises in order to gain a better understanding of the significance of the temporal interaction between several excitatory and/or inhibitory synapses for the input-output function of neurons.

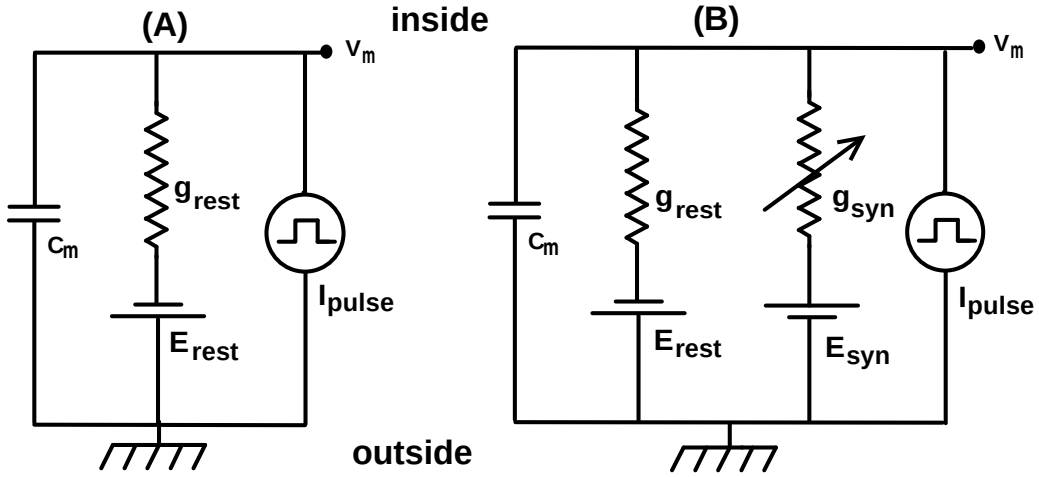

Figure 6.1 Equivalent circuits for electrical model of an isopotential nerve membrane. In (A), the passive (voltage- and time-independent) membrane elements are shown. The resting conductance g_{rest} represents the total conductance of all the transmembrane ion channels that are opened at the resting potential E_{rest}. The capacitance C_m represents the non-channel part of this membrane, and V_m is the voltage difference between the cell interior and the cell exterior. In (B), an additional conductive branch is added in parallel with the passive elements to represent the synaptic channels in the membrane. The total time-dependent conductance change induced by the activation of the synapse is denoted by g_{syn}; the associated reversal potential (the synaptic battery) is E_{syn}. I_{pulse} represents an externally applied current injection pulse.

6.2 Electrical Model of a Patch of Membrane

Figure 6.1 depicts the electrical circuit for a small isopotential patch of membrane that consists of two types of transmembrane channel. The passive channels are modeled by a constant (time- and voltage-independent) conductance (g_{rest}, in siemens = $1/\Omega$) in series with a fixed voltage source (E_{rest}, in volts) that designates the resting potential. The synaptic (chemically gated) channels are modeled by a separate conductive branch consisting of

a time-dependent conductance $g_{syn}(t)$ in series with a constant voltage source E_{syn}, the reversal potential of the synaptic current. In parallel with these conductive branches there is the capacitive branch C_m which models the dielectric properties of the lipid bilayer. Notice the correspondence between this figure and the "generic" neural compartment discussed in Chapter 2 and shown in Fig. 2.3. From this circuit, it is clear that the voltage difference V_m across the membrane depends on the values of the conductances and batteries involved in the circuit; V_m is expected to change when the values of the conductances g_{rest} and g_{syn} change. This is exactly what happens when a synapse is activated and the transmitter-gated channels are opened at the postsynaptic membrane. To clarify the principles that govern the voltage changes in the circuit of Fig. 6.1B, let us start with the simple case in which a constant current I_{pulse} is injected through an electrode across a patch of a membrane that consists of only passive channels. The corresponding model is depicted in Fig. 6.1A.

6.2.1 Voltage Response of Passive Membrane to a Current Pulse

When the membrane patch does not contain synaptic channels (or when all the synaptic channels are closed, i.e., $g_{syn} = 0$), the circuit in Fig. 6.1B collapses into a simple R-C circuit (Fig. 6.1A). The value of g_{rest} is then the input conductance (1/input resistance) of this membrane patch (hereafter designated as the "compartment"). As previously noted, E_{rest} is the resting potential of this compartment (it is the reversal potential of the ions that flow through the passive channels). The value of E_{rest} is described by the classical equation of Goldman (see, for example, Jack et al. 1975). The Goldman equation shows that when different ion species (e.g., K^+, Na^+, Ca^{+2}, Cl^-) flow through transmembrane channels, the equilibrium potential (the resting potential) is determined by the relative permeability to the different ions and by their gradients across the membrane. As seen by the polarity of E_{rest}, the resting potential in nerve cells is negative; namely, the interior of nerve cells is more negative than the exterior.

The membrane capacitance C_m represents the effect of the lipids of the membrane; they are poor conductors and are able to store charges (ions) on either side of the membrane. The membrane resistance (also, in the isopotential case, the input resistance) is $R_m = 1/g_{rest}$.

When no current is injected into the compartment (and, therefore, the net current across the membrane is zero), the membrane voltage V_m remains at the resting potential. However, when a current pulse I_{pulse} is injected between the two sides of the membrane, the voltage across the membrane changes. The charging of the membrane capacitance by injection currents may be represented by an equation analogous to Eq. 4.1, which we used for the Hodgkin-Huxley model. According to Kirchoff's current law, the net current leaving the compartment (the algebraic sum of the capacitive current flow $I_C = C_m dV_m/dt$ which charges the membrane capacitance and the ionic current I_{rest} that flows across the membrane through the resting channels) should equal the injected current I_{pulse}. Hence,

$$I_C + I_{rest} = I_{pulse}. \tag{6.1}$$

Note that, as we have done in Chapters 4 and 5, we are using the "physiologists' convention" in which the ionic channel current (I_{rest}) is considered to be positive when positive charge flows *out* of the compartment. For this reason, I_{rest} and the inward current I_{pulse} appear on opposite sides of the equation. By analogy with Eq. 4.3, the ionic current at rest I_{rest} is $g_{rest}(V_m - E_{rest})$. Equation 6.1 then becomes

$$C_m \frac{dV_m}{dt} + g_{rest}(V_m - E_{rest}) = I_{pulse}. \tag{6.2}$$

For simplicity, from now on we will set E_{rest} to zero, as we have done in the previous two chapters. This way, all voltage displacements and batteries are measured with respect to the resting potential. Equation 6.2 is now

$$C_m \frac{dV_m}{dt} + g_{rest} V_m = I_{pulse}. \tag{6.3}$$

If we assume that the current injection pulse begins at time $t = 0$, when $V_m(0) = 0$, we may solve Eq. 6.3 by separating variables and obtain:

$$V_m(t) = \frac{I_{pulse}}{g_{rest}}(1 - e^{-g_{rest}t/C_m}) \tag{6.4}$$

or:

$$V_m(t) = I_{pulse} R_m (1 - e^{-t/\tau_m}). \tag{6.5}$$

In Eq. 6.5, we have defined the *membrane time constant* to be $\tau_m = C_m/g_{rest} = R_m C_m$. For an isolated isopotential compartment, the input resistance (Sec. 5.4.4) is equal to the membrane resistance R_m. As noted in Chapter 5, this is given by the specific resistance of the membrane R_M divided by the surface area A of the compartment. Because nerve cells vary in size and in the specific properties of the membrane, the value of R_m also varies in different cell types and may range from less than 1 $M\Omega$ to several hundred $M\Omega$ ($M = 10^6$). However, from the definitions of C_M and R_M (Eqs. 5.4 and 5.5), we can write $\tau_m = R_m C_m = R_M C_M$ (Eq. 5.8). Thus, although the input resistance and membrane capacitance individually vary with the cell area, the time constant is independent of area. Hence, the time constant of nerve cells does not depend on the dimensions of the cell but only on the properties of its membrane. As also mentioned in Chapter 5, C_M is close to 1 $\mu F/cm^2$ in most biological membranes. However, as the value of R_M varies among different cell types (the density of channels that are opened at rest varies) the time constant of these cells is different and may range from under 1 *msec* to several hundred milliseconds.

When calculating values of τ_m, it is important to be consistent in one's choice of units. In the SI (MKS) system of units, resistance and capacitance are measured, respectively, in

ohms and farads, and R_mC_m has units of seconds. However, it is often more convenient to use "physiological units" in which resistance is measured in $K\Omega$ (kilohms) and capacitance is measured in μF. The corresponding units for R_M and C_M would then be $K\Omega \cdot cm^2$ and $\mu F/cm^2$, meaning that τ_m will be expressed in milliseconds. We use these units in this chapter, and in the *Neuron* tutorial. The relationship between SI and physiological units is discussed in more detail in Chapter 13, and summarized in Table 13.1. As discussed below and in Chapter 5, the time constant and the input resistance have important consequences for the electrical behavior of nerve cells and many electrophysiological experiments are aimed at estimating their values for the cell under study.

Observing Eq. 6.5, one sees that during the application of a positive current pulse to the interior of the cell the membrane potential increases (depolarizes) exponentially from the resting potential (0) toward the maximal (steady-state) value $I_{pulse}R_m$. This is shown in Fig. 6.2. The rise is governed by the single time constant τ_m, which is equal to the time at which the voltage rises to 63% $(1-e^{-1})$ of its maximal (steady-state) value. The steady-state value is reached when the current is injected for an infinitely long duration (i.e., when $t \to \infty$). Then, the capacitive (time-dependent) current is zero and the membrane current is solely a resistive (ohmic) current. In the other extreme, when the duration of the pulse is very short, most of the injected current flows through the capacitance. In this case, the voltage response is almost independent of the input resistance of the cell, since very little current flows through g_{rest}. The latter statement can be proven by expanding Eq. 6.5 in a Taylor's series near $t = 0$, neglecting nonlinear terms in t.

Until now, we have analyzed the development of membrane voltage while the current injection is still on. Suppose that the current pulse lasts for a duration of $t = t_{pulse}$; what happens at $t > t_{pulse}$? Now the external current source terminates and, therefore, the net current through the membrane is zero. In this case, the charge on the membrane capacitance dissipates by flowing through the resting ionic channels and

$$C_m \frac{dV_m}{dt} + g_{rest}V_m = 0; t \geq t_{pulse}. \tag{6.6}$$

The solution is

$$V_m(t) = V_m(t_{pulse})e^{-(t-t_{pulse})/\tau_m}; t \geq t_{pulse}. \tag{6.7}$$

Thus, following the termination of the current pulse, the voltage decays (repolarizes) exponentially from the maximal value $V_m(t_{pulse})$, obtained at the end of the rectangular current pulse, toward the resting level. It decays with the same time constant (τ_m) as it rises during the current pulse. If you wish, you may use the *Cable* tutorial from Chapter 5, or the *Neuron* tutorial which we use in this chapter to verify that the results are as shown in Fig. 6.2.

Before leaving this section, let us briefly mention the implications of τ_m and R_m for the integrative capabilities of nerve cells. As demonstrated in Fig. 6.2, the time constant

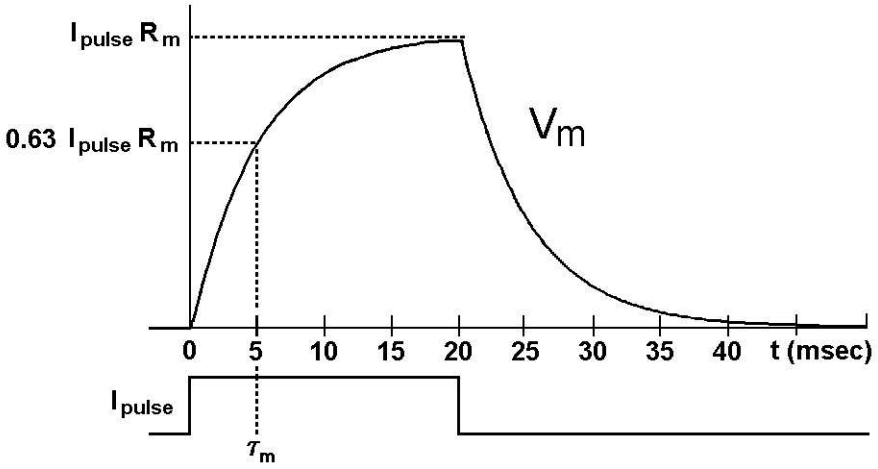

Figure 6.2 The response of the passive circuit in Fig. 6.1 to a positive rectangular current pulse. The current I_{pulse} is given for a duration of 20 *msec* (bottom trace) and the resultant voltage V_m across the membrane is shown above. The input resistance of the cell is denoted by R_m $(= 1/g_{rest})$. The time constant $(\tau_m = R_m C_m)$ of this cell was set to 5 *msec*. Hence, V_m approaches the maximal (steady-state) value $I_{pulse}R_m$. As expected from Eq. 6.5, V_m reaches $(1 - 1/e)$, or 63% of its maximal value at $t = \tau_m$. This time constant also governs the exponential decay of V_m at the end of the current application. Then, $V_m = V_0 e^{-(t-t_{pulse})/\tau_m}$, where V_0 is the maximal voltage reached at $t = t_{pulse} = 20$ *msec*.

(Eqs. 6.5 and 6.8) implies that the buildup of voltage at the postsynaptic membrane as a response to an input takes time, and that when the input ends the membrane "remembers" the effect of the input for some time (for several units of the time constant) until the decaying voltage approaches the resting potential. Hence, a cell with a long time constant (say, 30 *msec*) will sum successive inputs that arrive every 5 *msec* (for example) better than a cell with a shorter time constant (say, 5 *msec*). The voltage change will remain for a longer duration in the cell with the longer τ_m following an input. The other parameter, the input resistance R_m, implies that for a given (long-lasting) input, the cell with the larger R_m value will produce a larger voltage displacement (Fig. 6.2 and Eq. 6.5). Hence, a more powerful input will be required for a similar displacement of V_m in cells with a small R_m value. These important consequences of τ_m and R_m for synaptic integration in nerve cells can be explored using the *Neuron* tutorial.

Finally, it is worth recalling from Chapter 2 that the "membrane model" of Figs. 6.1A and 6.1B serves as a basis for many models that are concerned with the electrical activity of nerve cells. Any additional type of channels (e.g., voltage-gated channels) that may be present in the modeled patch of membrane can be represented by an additional (voltage-dependent) resistive branch and an associated battery, both in parallel to the circuit of Fig. 6.1B. Furthermore, a distributed (non-isopotential) system, such as the dendritic tree

or the axon can, in principle, be constructed from a set of such patches of isopotential membrane compartments that are connected to each other through the cytoplasmic (axial) resistance, as we have done in Chapter 5. This is indeed the common approach used to model the spread of potentials along the detailed structure of dendritic and axonal trees (Segev et al. 1989).

6.3 Response to Activation of Synaptic Channels

In the case of the classical *fast synapse*, the release of neurotransmitter from the presynaptic terminal directly results in the opening of chemically gated ion channels at the postsynaptic membrane. Thus, the input induced by the synapse is primarily expressed as a *local conductance change* at the membrane situated just opposite to the presynaptic release site. Subsequently, specific ions can flow through these channels to produce the synaptic current (I_{syn}) that gives rise to the postsynaptic potential. A concise review of other types of synapses may be found in McCormick (1990).

It is important to note that although both the synaptic input and an electrode which injects a current pulse (as in the case analyzed above) result in the flow of ions across the membrane, the two types of inputs differ in a significant way. Although the electrode does not change the properties of the membrane (provided that the membrane is not injured by the electrode), the synaptic input, due to its inherent characteristics, changes the membrane properties of the postsynaptic cell; it opens new channels there. In the case of an electrode, the current is produced by an external source (the electrode), whereas in the case of a synapse the current source is part of the neuronal system (the ion gradients across the membrane and the transmembrane synaptic channels). As shown below, the difference between these two type of inputs is manifested in the behavior of the corresponding membrane voltage.

6.3.1 The Postsynaptic Current

In Fig. 6.1B, the opening of synaptic channels in an isopotential patch of membrane is modeled by a time-dependent conductance change ($g_{syn}(t)$). This conductance lies in series with a battery (E_{syn}, the synaptic reversal potential or the synaptic battery) that drives the ions involved in the synaptic process. Note that here we assume that the synaptic channels are time-dependent but voltage-independent. This is true for many types of synaptic channels but not for all (e.g., the NMDA receptor, which is modeled in Chapter 19). According to Ohm's current law, the synaptic current through the right-most branch in Fig. 6.1B is,

$$I_{syn}(t) = g_{syn}(t)(V_m - E_{syn}), \tag{6.8}$$

where g_{syn} is the synaptic conductance in siemens. V_m, the voltage across the membrane and E_{syn}, the synaptic battery, are both measured relative to the resting potential (which was set to zero in the present chapter).

When only the synapse is active (without an external current source) V_m is the postsynaptic potential that arises from the activation of the synaptic channels. As can be seen from the circuit in Fig. 6.1B, an increase in g_{syn} causes V_m to move closer to E_{syn}. Therefore, the direction of the change in V_m depends on the sign of the difference $(V_m - E_{syn})$. If E_{syn} is more positive than V_m then an increase in g_{syn} causes V_m to be more positive — a depolarization. If $V_m > E_{syn}$, the activation of the synapse hyperpolarizes the cell. Note also that when $V_m = E_{syn}$, the activation of the synapse does not produce synaptic current (Eq. 6.8) and thus the voltage across the membrane does not change when such a synapse is activated (a *silent synapse*). However, the activation of such a synapse causes an increase in the input conductance (a decrease in the input resistance) of the postsynaptic cell since it does open new channels there. As a result, the voltage response of such a shunted cell to *other* inputs (either from an electrode or from another synapse) will decrease relative to the case where the silent synapse is not active. This *inhibitory* effect is further discussed below.

6.3.2 The Postsynaptic Potential

As in the case with a current that is injected into a cell through an electrode, the displacement of the voltage at the post synaptic membrane that results from opening synaptic channels depends on the magnitude and shape of the synaptic current, as well as on the passive electrical properties of the postsynaptic cell. Hence, the voltage (the PSP) that is developed in the circuit of Fig. 6.1B due to the activation of the synaptic input depends both on the characteristics of the synaptic branch (on g_{syn} and E_{syn}) as well as on the passive (g_{rest} and C_m) elements. Again, when no external current is injected into the cell model of Fig. 6.1B, the net current across the membrane is zero. This time it is the sum of the capacitive current I_C, the ionic current that flows through the resting channels I_{rest} and the synaptic current (I_{syn}),

$$I_C + I_{rest} + I_{syn} = 0 \tag{6.9}$$

or:

$$C_m \frac{dV_m}{dt} + g_{rest} V_m + g_{syn}(t)(V_m - E_{syn}) = 0. \tag{6.10}$$

The solution, $V_m(t)$, describes the buildup of voltage while the synaptic channels are opened (i.e., when $g_{syn} > 0$). For the special case where the synaptic conductance change is a rectangular pulse with an amplitude of g_{syn} and a duration of t_{syn}, the solution, obtained as before by separating variables and integrating, can be written explicitly,

$$V_m(t) = \frac{g_{syn}}{g_{syn}+g_{rest}} E_{syn}(1-e^{-t(g_{syn}+g_{rest})/C_m}), \text{ for } 0 \le t \le t_{syn}. \quad (6.11)$$

This equation connects the conductance change induced by the neurotransmitter (g_{syn}) and the transient PSP induced at the postsynaptic membrane. The steady-state solution, obtained when the synaptic channels are opened for an infinitely long duration ($t_{syn} \to \infty$) is

$$V_m = \frac{g_{syn}}{g_{syn}+g_{rest}} E_{syn} = \frac{1}{1+g_{rest}/g_{syn}} E_{syn}. \quad (6.12)$$

Equations 6.11 and 6.12 are strictly applicable only to step-conductance changes. Nevertheless, they provide several important general insights into the functional consequences of synaptic mechanisms. One is that, unless $E_{syn} = 0$ (a silent synapse) the PSP is always smaller (in absolute value) than E_{syn} (Eq. 6.12). Only when $g_{syn} \gg g_{rest}$ (the total conductance of the synaptic channels is much larger than that of the resting channels) does V_m approach E_{syn}. Secondly, one can see that V_m is a nonlinear (sublinear) function of g_{syn}. For example, Eq. 6.12 tells us that if $g_{syn} = g_{rest}$, then $V_m = E_{syn}/2$. Assuming that $E_{syn} = 90\ mV$, the steady-state value of the PSP is 45 mV for this particular example. Multiplying g_{syn} by a factor of two (so that $g_{syn} = 2g_{rest}$) produces a steady depolarization of 60 mV rather than 90 mV, as expected in a linear case. This nonlinearity implies also that successive synaptic inputs (unlike current inputs) will not sum linearly with each other. We examine this nonlinearity in more detail below.

The third point to note from Eq. 6.11 is that, as with a current step (Eq. 6.4), for the case of a rectangular g_{syn} the PSP increases exponentially as long as the synaptic input is present. However, these two cases are markedly different, because in the case of the synaptic input the time constant depends on g_{syn} as well as on g_{rest}. The time constant $C_m/(g_{syn}+g_{rest})$ in Eq. 6.11 is briefer than the resting time constant $\tau_m = C_m/g_{rest}$. Hence, when the synaptic channels are opened, $V_m(t)$ builds up faster than in the resting conditions. The larger g_{syn} is, the faster $V_m(t)$ develops towards its maximal value.

At the end of the synaptic action (for $t > t_{syn}$), when the synaptic channels are closed again ($g_{syn} = 0$), the membrane conductance returns to its passive (resting) value. During this time interval the synaptic potential decays towards the resting value with the passive time constant τ_m, as in the case of the current input (Eq. 6.7). Thus, unlike the case of a constant current input of Fig. 6.2, in the case of a synaptic input the PSP rises faster than it decays.

What happens when several synapses, each with its own conductance change and battery, impinge on the same isopotential patch of postsynaptic membrane? The resulting equation is similar to Eq. 6.10, with the additional synaptic currents added to the sum,

$$C_m \frac{dV_m}{dt} + g_{rest} V_m + g_{syn}^{(1)}(t)(V_m - E_{syn}^{(1)}) + g_{syn}^{(2)}(t)(V_m - E_{syn}^{(2)}) + \ldots = 0. \tag{6.13}$$

Now, each synaptic input may have a different reversal potential ($E_{syn}^{(1)}$, $E_{syn}^{(2)}$, ...) and a different corresponding conductance change ($g_{syn}^{(1)}$, $g_{syn}^{(2)}$, ...) which may be activated at different times (Δt_1, Δt_2, etc.), respectively. Depending on the sign of the difference, $V_m - E_{syn}$, some synapses may contribute depolarizing currents, whereas others may contribute hyperpolarizing currents. The PSP in this case is the (nonlinear) sum of the effects of all the synaptic inputs. The general solution to Eq. 6.13 for the case where all g_{syn}s are rectangular is an extension of Eq. 6.11,

$$V_m(t) = \frac{g_{syn}^{(1)} E_{syn}^{(1)} + g_{syn}^{(2)} E_{syn}^{(2)} + \ldots}{g_{total}} (1 - e^{-g_{total} t / C_m}). \tag{6.14}$$

Here, g_{total} is the sum of all the conductances at that patch of membrane, namely,

$$g_{total} = g_{rest} + g_{syn}^{(1)} + g_{syn}^{(2)} + \ldots. \tag{6.15}$$

Note that when $E_{syn} = 0$ (i.e., a silent synapse) it contributes to the sum in the denominator but not to the numerator. Thus, such a synapse acts to reduce $V_m(t)$ and is, therefore, called an *inhibitory synapse* (see Sec. 6.4).

6.3.3 Smooth Synaptic Conductance Change: The "Alpha Function"

The synaptic conductance change is better described by a smooth function rather than by a rectangular pulse, as treated above. It is convenient to use an analytical expression to approximate the smooth shape of the experimentally observed synaptic conductance change. A fairly good approximation may be obtained by an analytical function that was first used for this purpose by Rall (1967) and later by Jack et al. (1975) and is referred to as an *alpha function*,

$$g_{syn}(t) = g_{max} \frac{t}{t_p} e^{(1 - t/t_p)}. \tag{6.16}$$

This function increases rapidly to a maximum of g_{max} at $t = t_p$. Following its peak, $g_{syn}(t)$ decreases more slowly to zero, as was shown to be the case in the previous chapter. Note that in Eq. 6.16, $g_{syn}(t)$ is determined by two independent parameters g_{max} and t_p. A "slow synapse" (a synapse whose channels kinetics are slow) will be modeled by a relatively large t_p. A powerful synapse (a synapse that opens many channels and produces a significant conductance change) will obtain a large g_{max} value.

The GENESIS simulator uses a slightly more general form, the dual exponential function, to describe $g_{syn}(t)$,

$$g_{syn}(t) = \frac{Ag_{max}}{\tau_1 - \tau_2}(e^{-t/\tau_1} - e^{-t/\tau_2}), \text{ for } \tau_1 > \tau_2, \tag{6.17}$$

where A is a normalization constant chosen so that g_{syn} reaches a maximum value of g_{max}. When $\tau_1 = \tau_2 = t_p$, this is equivalent to the alpha function form of Eq. 6.16. When the synaptic conductance change is modeled by either Eq. 6.16 or 6.17, there is no explicit solution to Eq. 6.10 and the numerical techniques discussed in Chapters 2 and 20 must be employed.

Figure 6.3 shows the response of the cell model in Fig. 6.1B to the activation of a train of four identical excitatory synaptic inputs at 2 *msec* intervals. The conductance, shown in the lower plot, is of the form given by Eq. 6.16. Here, the rise time of the synaptic conductance is brief, $t_p = 0.2$ *msec*, whereas the membrane time constant is relatively long, $\tau_m = 5$ *msec*. The resulting postsynaptic potential (upper plot) illustrates an important aspect of the temporal behavior that was discussed in the previous chapter (Sec. 5.4.3) and which we will explore with the *Neuron* tutorial. As shown in the dashed curve, the much longer membrane time constant causes the PSP due to a single synaptic input to persist much longer than the conductance change. This results in a *temporal summation* of the series of inputs to produce the larger PSP shown in the solid curve.

6.4 A Remark on Synaptic Excitation and Inhibition

As explained below, it is functionally reasonable to define a synapse as being excitatory or inhibitory with respect to the value of the threshold for action potential firing V_{th}. Hence, a synapse that increases the conductance and whose reversal potential is more positive than V_{th} will tend to excite the cell (since it can, provided that g_{syn} is sufficiently large, produce a PSP that is more depolarizing than V_{th}). Thus, the corresponding potential is called an EPSP (*excitatory postsynaptic potential*). A synapse that produces a conductance increase and whose reversal potential is more negative than V_{th} will tend to inhibit the cell from firing. The corresponding potential is called an IPSP (*inhibitory postsynaptic potential*).

Using this operative definition, a synapse with $E_{syn} \leq 0$ (the synaptic battery is more negative than the resting potential) is, clearly, an inhibitory synapse. The activation of such a synapse will both shunt and hyperpolarize the cell. As already discussed, a synapse will only increase the conductance (without changing the voltage) when $E_{syn} = 0$. In both cases the synapse acts to reduce the effect of the EPSPs produced by excitatory inputs that impinge on the cell, thus making the firing of an action potential less likely.

Note that, according to the preceding definition, a synapse may be inhibitory but still produce depolarization. This is true for the case when $0 < E_{syn} < V_{th}$. However, note

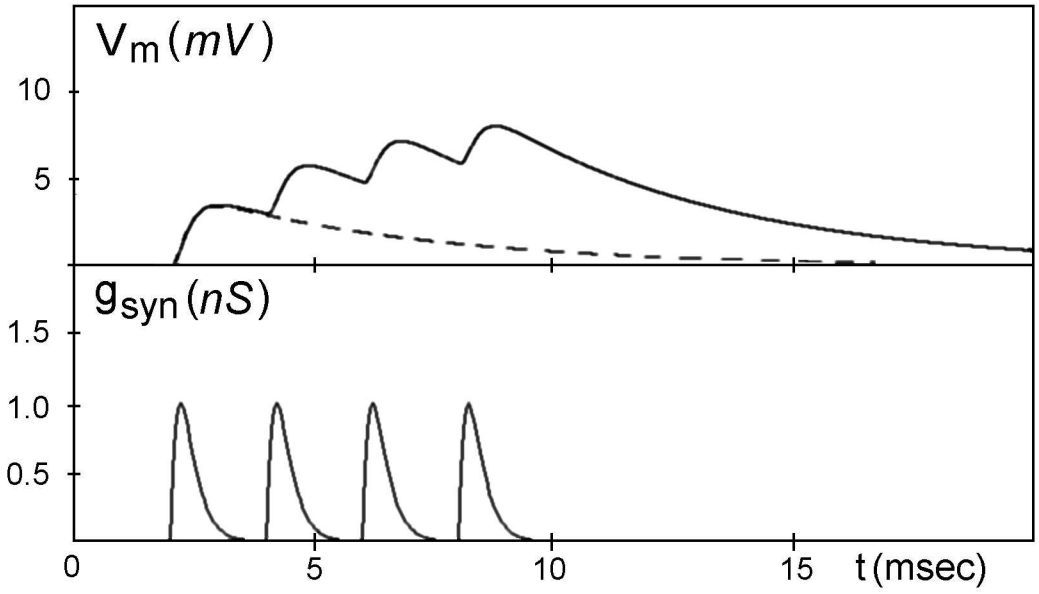

Figure 6.3 The response of the cell model in Fig. 6.1B to the activation of a train of four identical excitatory synaptic inputs at 2 *msec* intervals. The conductance, shown in the lower plot, is in the form of an alpha function. Each of these inputs has a peak value (g_{max}) of 1 *nS* and a time-to-peak (t_p) of 0.2 *msec*; the associated synaptic battery (E_{syn}) is 50 *mV* above the resting potential. The upper plot shows the potential change (the PSP) for a single synaptic input (dashed curve) and for the series of four inputs (solid curve). As a result of the larger membrane time constant (here, as in Fig. 6.2, $\tau_m = 5$ *msec*), the PSP persists much longer than the conductance change associated with the synaptic input. This allows a temporal summation of the inputs to produce a larger PSP than would be produced by an individual input.

from Eq. 6.12 that the activation of such a synapse cannot, in principle, reach the threshold for action potential firing. It can be shown that, in general, the facilitative effect of such a subthreshold depolarization is less significant than the inhibitory effect (on excitatory inputs) of the accompanied shunt induced by this synapse. Thus, it is still justified to call such a synapse inhibitory; the corresponding potential is sometimes called a depolarizing IPSP (Segev and Parnas 1983).

6.5 GENESIS Experiments with PSPs

We can study the effects of various synaptic inputs by using the GENESIS *Neuron* tutorial, which was briefly discussed in Chapter 3. This tutorial lets us perform experiments on a simple neuron model consisting of a soma and two dendrite compartments. The soma has Hodgkin-Huxley voltage-activated channels like the ones we used in the *Squid* simulation, and the dendrite compartments have both excitatory and inhibitory synaptically activated

channels that respond to spikes applied at the synapses.

To start the tutorial, change to the *Scripts/neuron* directory and give the command "`genesis Neuron`." Once the graphs and "control panel" appear on the screen, click the left mouse button on the box labeled `HELP` and spend a few minutes exploring the topics on the help menu, starting with `Using Help`. When you are ready to begin, set the soma injection current to zero in the `Soma Inj` dialog box. (Don't forget to hit "Return" after changing the value in a dialog box.) As we will be providing synaptic input to dendrite compartment #1, it would be a good idea to examine the default values of the parameters used for this compartment and the two channels that it contains. Click on `Dendrite 1` under the `Cell Parameters` heading. After reviewing the parameters used to model the compartment, click on `Exc. Ch.` at the top in order to bring up a secondary menu showing the parameters for the excitatory channel. This should reveal that the ionic equilibrium potential has been set to -10 *mV*. In this simulation, E_{rest} has been set to -70 *mV* rather than 0, as we have done so far in this chapter. Thus, $E_{syn} = -10$ *mV* corresponds to a value 60 *mV* above the resting value of V_m. This potential is typical of that for a depolarizing channel that allows both Na^+ and K^+ ions to pass. Although this channel is called the "Dendrite 1 Excitatory Channel", the name is due to the default value used for E_{syn}. By setting this to a value less than E_{rest} we could turn it into a hyperpolarizing inhibitory channel.

The default value of g_{max} (given in *mS*) corresponds to a value of 0.1 *nS*, or 0.1×10^{-9} siemens. This value is typical for a single synaptic input. The channel model used in GENESIS simulations is of the dual exponential form given in Eq. 6.17. As the two time constants τ_1 and τ_2 are each 3 *msec*, this corresponds to an alpha function (Eq. 6.16) with $t_p = 3$ *msec*. For now, we will use the default values of these parameters, so click on `DONE` to put this window away.

Clicking on `Inh. Ch.` in the `Dendrite 1` parameter window brings up a similar window for the channel that is nominally the inhibitory channel. The equilibrium potential has been set to -80 *mV*, which is the value used for potassium ions in our model. The maximum channel conductance and the time constants are the same as those used for the "excitatory" channel. Click on `DONE` in both windows to put them away. The default parameters for the `Dendrite 2` compartment and its channels are the same as those for `Dendrite 1`.

6.5.1 Temporal Summation of Postsynaptic Potentials

We will start our investigation by applying a train of spike inputs to the excitatory channel of `Dendrite 1`. This should teach us several principles regarding the temporal summation of EPSPs. A single synaptic input is rarely sufficient to produce a very large effect in most neurons, so this simulation provides a simple way to scale the value of g_{max} without having to call up the sequence of menus needed to change g_{max}. The dialog box labeled `Dend #1 Exc. Wt.` contains the value of a synaptic weight to be used to scale the synaptic conductance. Thus, entering "10" is equivalent to providing simultaneous input to 10 identical

synapses, or to multiplying g_{max} for this channel by 10. The default value of 0 means that the channel is receiving no input. The toggle to the right of the dialog box can be used to switch the input between `Source A` and `Source B`.

For our experiment, set the weight for the `Dendrite 1` excitatory channel to 10 and leave the input set to `Source A`. We will use the default timings for the spike trains that come from `Source A`. Click on `STEP` and observe the three plots on the left. The upper plot shows (in red) that `Source A` is delivering a burst of spikes at 10 *msec* intervals. The plot below it shows the resulting channel conductance. Note the difference in the rise and fall times for the conductance. Can you explain these? The lower plot shows the rather small increase in the PSP associated with each spike. The plot to the right of this shows similar, but slightly attenuated, changes in the soma membrane potential.

Next, we would like to explore the effect of increasing the rate of input to this channel. This can be done by clicking on the `Inputs` button in the control panel. The menu that appears contains dialog boxes to set the delay before the onset of the burst of spikes, the width (duration) of the burst, and the interval between spikes. Change the spike interval for both `Source A` and `Source B` to 2 *msec*. In order to easily compare the results with the previous ones, click on the overlay toggle so that it reads `Overlay ON`, and then click on `RESET` and `STEP`.

As with Fig. 6.3, note the temporal summation of the consecutive increases of conductance in the plot of the channel conductance. These result in a buildup of the EPSP, as each increase is added to the previous one. Eventually, the potential becomes large enough to trigger action potentials in the soma. After the train of input spikes ends, the PSP decays to the point where no more action potentials are produced. If you look carefully, you may notice that the action potentials are a little higher in the plot of the soma membrane potential. This is because the PSP in the dendrite is propagated to the soma, where the voltage-activated channels cause the action potentials, and these are propagated back to the dendrite through the axial resistance. In the dendrite compartment, we are seeing a superposition of the PSP produced here and the action potential that is produced in the soma. If we were to look in a more distant dendrite section, the peaks would be much more attenuated.

To examine the effect of adding IPSPs to EPSPs, all we need do is to set the weight for the `Dendrite 1` inhibitory channel to 10, so that it will receive input from `Source B`. We previously set the `Source B` spike interval to 2 *msec*, and the default delay is 10 *msec* after the start of the spike train from `Source A`. After setting the weight, set the overlay toggle to `OFF`, click on `RESET` to clear the graphs, and click on `STEP` to run the simulation. You should see a result similar to that shown previously in Fig. 3.3. Shortly after the first action potential, we get a large buildup of conductance for the potassium channel. This decreases the net PSP in the soma to a value below that necessary for the production of further action potentials.

In Chapter 5, we studied the passive propagation and attenuation of pulses through a "cable" consisting of many compartments. Here, we can easily make a qualitative examina-

tion of the effect of spatially separating synaptic inputs by performing one more experiment on the model neuron. The simulation gives us the option of putting any number of passive "cable" compartments between the two dendrite compartments by entering a non-zero integer in the `Cable Compts.` dialog box. Set this value to 10 and switch the excitatory input to the `Dendrite 2` compartment using a weight of 100. Use the same input timing as in the previous experiment and compare the results with weights of 0 and 10 for the `Dendrite 1` inhibitory channel. Note how a comparatively small inhibitory input is able to inhibit the much larger excitatory input.

In order to see the channel conductances and the membrane potential in the `Dendrite 2` compartment, click on the `Plot Soma` toggle so that it reads `Plot Dend2`. Now, the lower right graph will plot the membrane potential for `Dendrite 2` instead of the soma. You should see very large EPSPs in `Dendrite 2`, with very attenuated soma action potentials superimposed. From the analysis of Chapter 5, you learned how to calculate this attenuation. Using the values of the parameters given for the dendrite compartments, can you verify that the attenuation is that which would be expected?

6.5.2 Nonlinear Summation of Postsynaptic Potentials

We can learn more about the principles underlying temporal summation of PSPs if we can find a way to eliminate the production of action potentials in the soma. This might be done by blocking the voltage-activated sodium channels in the soma, or by separating a section of dendrite from the soma. In our model, this could be accomplished by setting the maximum conductance of the soma sodium channel to zero, or by greatly increasing (decoupling) the axial resistance between the dendrite compartments and the soma. The latter method has the additional advantage that it reduces the conductance loading of the soma, with its smaller membrane resistance, so that we are left with an isolated section of dendrite and consequently may observe larger PSPs.

We will perform the rest of our experiments on the `Dendrite 2` compartment, isolating it from the rest of the cell. Call up the `Cell Parameters` window for `Dendrite 2` and increase the specific axial resistance R_A to 100 $K\Omega \cdot cm$. Note the effect on the value displayed for `Raxial` (R_a, in $K\Omega$). In order to analyze our results, we need to know the value of g_{rest} for this compartment. In the notation of this simulation, the input resistance (or membrane resistance) R_m in $K\Omega$ is `Rmem` and the specific membrane resistance R_M in $K\Omega cm^2$ is `RM`. You should verify that the values given in the dialog boxes for these two parameters lead to the result that $g_{rest} = 1.26\ nS$. After making this calculation, click on `DONE` to put the menu away. Click on the `Plot Soma` toggle so that it reads `Plot Dend2`, in order to plot the membrane potential for `Dendrite 2` in the lower right graph. Finally, set the overlay toggle to `OFF` and click on `RESET` to clear the graphs.

Let us start by demonstrating one of the important characteristics of synaptic inputs that was discussed above: the inherent nonlinearity in the generation and summation of PSPs.

We would like to apply a single spike input to the excitatory channel of `Dendrite 2`, using `Source A`. This may be accomplished by calling up the `Inputs` menu and setting the Source A spike interval to something large, say, 100 *msec*. Then set the `Dend #2 Exc. Wt.` dialog box value to 1, and the weights for the other three synapses to 0. Click on `STEP` to run the simulation. When it has finished, toggle to `Overlay ON`, click on `RESET`, and run the simulation again with a weight of 2. Note that this is equivalent to simultaneously activating 2 synapses, each having $g_{max} = 0.1\ nS$ or to activating a single synapse with $g_{max} = 0.2\ nS$. Repeat this experiment with weights of 10, 20, 100 and 200 and then estimate the peak values of the PSPs relative to the resting potential. In order to measure the heights of small PSPs, you can click on the `scale` button in the upper left corner of the graph. This will bring up a window with dialog boxes that can be used to set `ymin` and `ymax` to appropriate values.

From these experiments, you should conclude that the simultaneous inputs sum linearly for small values of g_{max}, but that the summation becomes increasingly nonlinear as g_{max} increases. We can understand this behavior from Eq. 6.11 and the discussion that follows it. If we approximate the alpha function conductance with a rectangular pulse having amplitude $g_{syn} = g_{max}$ and duration t_p, Eq. 6.11 tells us that the PSP will be roughly proportional to g_{syn} when $g_{syn} \ll g_{rest}$. When $g_{syn} \gg g_{rest}$, the amplitude of the PSP approaches E_{syn} and is independent of g_{syn}. This analysis is not exact, because we have neglected the details of the time dependence of the synaptic conductance. Nevertheless, you should be able to see rough agreement with the measurements that you have performed.

The effect of a "silent inhibition" on the EPSP may be examined using a similar procedure. Use Source B as an input to the `Dendrite 2` inhibitory synapse, setting the timing parameters for `Source B` to be the same as those for `Source A`. Set E_{syn} for this channel to be equal to E_{rest}, $-70\ mV$, and experiment with different magnitudes of the synaptic weights in order to make the effective value of g_{syn} much smaller or much larger than g_{rest}. What does Eq. 6.14 tell you about the circumstances in which the silent inhibition will have an effect upon the EPSP?

The exercises and projects listed at the end of this chapter suggest several other properties of summed synaptic inputs that you may explore with this simulation. You may also wish to design your own computer experiments in order to gain further insights into the local integration of synaptic inputs.

6.6 Concluding Remarks

We hope that you enjoyed the experiments with postsynaptic potentials and that they have helped to clarify some basic questions regarding synaptic summation and integration. One point to remember is that when membrane channels are the source for the production of voltage changes across the membrane, the reversal potential associated with these channels

is the maximal value that can be achieved using this mechanism. Hence, unless active electrogenic pumps are involved or current is injected from an external source (e.g., by an electrode), the membrane potential of the nerve cell can only vary among the ionic batteries involved (determined by the concentration gradients of the permeable ions across the membrane). In nerve cells the value of the ionic batteries is in the range of -30 *mV* up to 150 *mV* or so relative to the resting potential.

Secondly, synaptic inputs are inherently nonlinear inputs since the input itself (the conductance change) perturbs the system (the neuron's membrane). The nonlinearity is more apparent when the conductance change is significant (relative to the resting conductance). The nonlinearity is also marked when the membrane potential V_m is close to the reversal potential of the synaptic process (as is commonly the case with inhibitory synaptic inputs).

Finally, the fact that the neuron with its synaptic inputs is a nonlinear system has several important consequences for the information processing function of the cell. It can be shown that a rich repertoire of operations which could not be implemented in a linear system can be implemented in nonlinear systems such as real nerve cells. You may read more about this important issue in papers by Fatt and Katz (1953), Koch and Poggio (1987), Mel (1993), Rall (1964, 1967), Segev and Parnas (1983), and Segev (1992).

6.7 Exercises and Projects

Unless otherwise noted, perform these experiments on the Dendrite 2 compartment, using a large value of the axial resistance in order to isolate the compartment from the rest of the cell.

1. Find out how changes in the specific membrane resistance R_M in the Dendrite 1 compartment affect the amplitude and area of the EPSP. Check this once with the default value of t_p (3 *msec*) and then construct a faster synaptic input, say, $t_p = 0.3$ *msec*. Which one is more sensitive to changes in R_M? Explain your results.

2. For $g_{syn} \ll g_{rest}$, is the size of the PSP simply related to the size of the postsynaptic compartment? Is the value of t_p relevant in this case? Perform some experiments to investigate these effects and explain your results. Why is the dependence on t_p much less than in the case of the previous exercise? Suppose that g_{syn} is expressed in terms of a channel conductance density with units of mS/cm^2, so that g_{syn} scales with the area of the compartment. Would you then expect to see any dependence of the PSP on the size of the compartment?

3. Investigate the conditions under which a depolarizing IPSP can either facilitate or inhibit a simultaneous EPSP. To do this, set E_{syn} for the isolated "`Dendrite 2` inhibitory channel" to -65 *mV*, so that it is 5 *mV* above the resting potential. Use the

default values for the other channel parameters. Set the input timings for `Source A` and `Source B` so that they will each produce a single spike input at the same time. Experiment with both large and small magnitudes of the synaptic weights for the two channels in order to find out which values of g_{syn} will increase or decrease the PSP relative to the case when the inhibitory conductance is zero. Explain your results in terms of the equations given in this chapter.

4. How does the duration of the conductance change (the time-to-peak t_p) affect the amplitude of the PSP? Construct a plot of V_{peak} (measured relative to E_{rest}) vs. t_p and explain why your results are what one would expect.

5. Connectionist artificial neural networks often use a sigmoidal (S-shaped) curve to represent the input-output relation of an artificial "neuron." The input is an analog value representing the average rate of spikes that would be input to the neuron and the output represents the average firing rate of the neuron. Perform some experiments on this model neuron with the value of R_A and all other parameters restored to their default values. See if a plot of the firing frequency vs. input spike rate has roughly this shape (being zero for small inputs and saturating at a constant value for large inputs). Provide excitatory input to `Dendrite 1` with a synaptic weight of 12 and vary the spike interval for `Source A`.