Chapter 5

Electrotonic Filtering

INTRODUCTION

Chapters 2 and 4 dealt with patterns of current flow in neurons without considering the sources of the currents. This and the following several chapters will discuss synapses as a source of currents that flow into and out of neurons. Most neurons receive thousands, or even tens of thousands, of synapses. It will ultimately be necessary to think about how all of these currents interact. However, it will be easiest to start by looking at currents that are generated by a single synapse positioned somewhere on the surface of the neuron. Let's begin by looking at how synaptic currents can be incorporated into cable models of neurons. The fundamental work in this area was done by Wilfrid Rall at the National Institutes of Health. Segev et al. (1994) have prepared a compendium of Rall's papers.

SYNAPTIC CURRENTS IN LINEAR CABLES

To get a feel for how synapses interact with the passive electrotonic structure of a neuron, let's think about a chemical synapse situated at position, x, on a cable with constant diameter, d, length, l, and uniform biophysical parameters, r_m, c_m and r_a (Fig. 5-1A). The synapse generates a synaptic current, $I_{syn}(x,t)$, that flows through the membrane. This is a *postsynaptic current* (PSC). The current passing through the resistance of

the membrane produces a change in membrane potential that is called a postsynaptic potential (PSP). Depending on the properties of the synapse, the effect of its activation will be to depolarize the cylinder and move its membrane towards zero, or to hyperpolarize the cylinder and move its membrane away from zero (Fig. 5-1B). The current is called an *excitatory postsynaptic current* (EPSC) in the first case and an *inhibitory postsynaptic current* (IPSC) in the second. The resulting PSPs are an *excitatory postsynaptic potential* (EPSP) or an *inhibitory postsynaptic potential* (IPSP), respectively. The problem is: given the electrotonic structure of the cylinder and the properties of the PSC, predict the resulting PSP.

We can approach the problem by thinking of the cable as a "system" or "black box" which is specified by its input-output relationships (Fig. 5-1C). Imagine some input -- the synaptic current, $I(X,T)$, in this case -- is provided to the system. (Note that we have switched to normalized coordinates, $X = x/\lambda$, $T = t/\tau$). It produces an output from the system or box in the form of a voltage transient, $V(0,T)$, that is recorded by an electrode at the origin of the coordinate system (corresponding to the soma of the cell). The problem stated in mathematical terms is to predict $V(0,T)$ given $I(X,T)$. We think of the system as a filter (or mathematical operator) that transforms the input into the output. Predicting the voltage transient involves two different steps: first, characterize the synaptic current and, second, characterize the input-output relationship of the system.

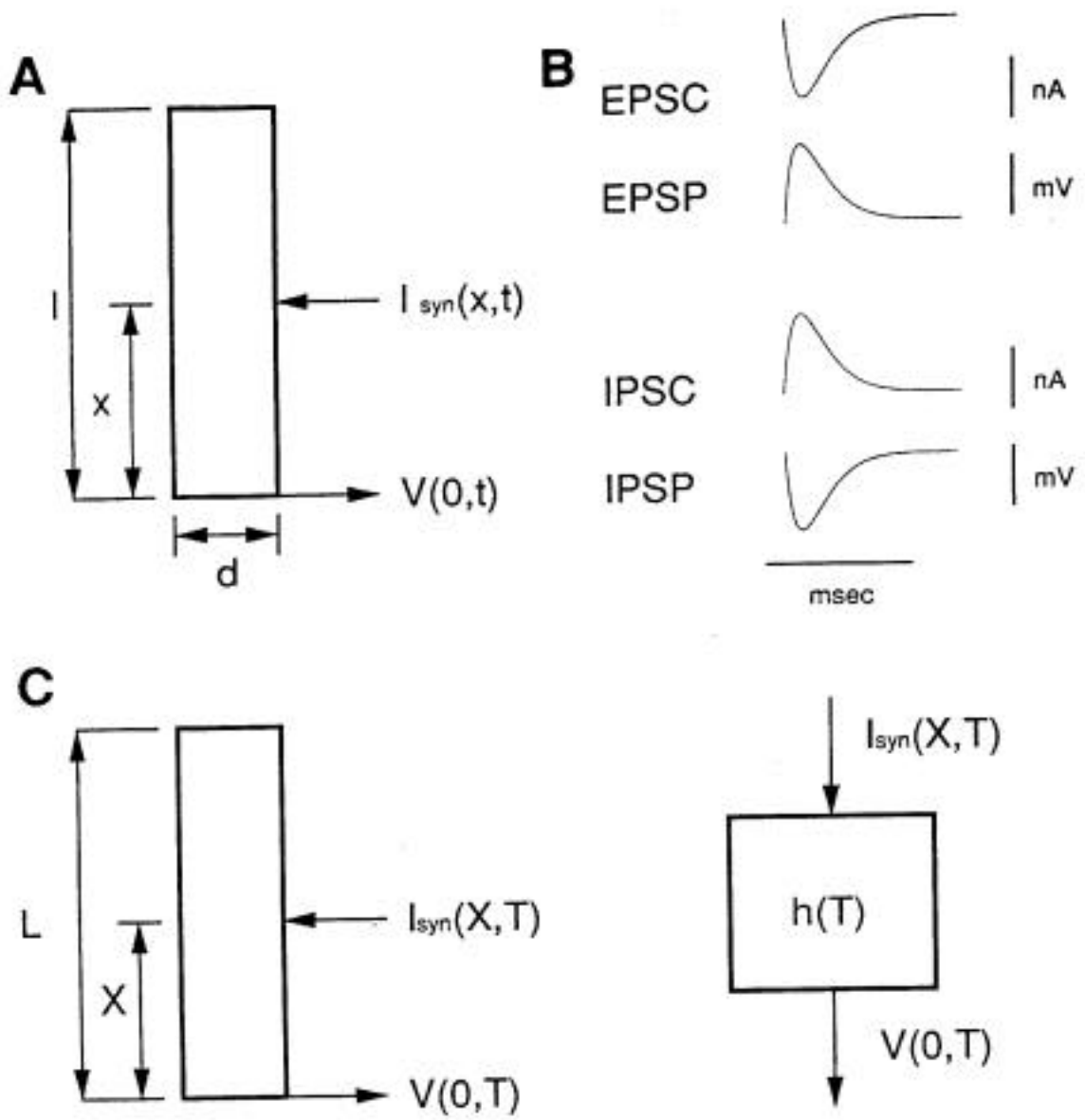

Figure 5-1. Synapse on a linear cable. A. A synaptic current, Isyn(x,t), is situated at a distance, x, from the recording site at the origin. V(0,t) is the membrane potential recorded at the origin. The cable has a diameter, d, and a length, l. B. An excitatory postsynaptic current (EPSC) produces an excitatory postsynaptic potential (EPSP). An inhibitory postsynaptic current (IPSC) produces an inhibitory postsynaptic potential (IPSP). C. The cable shown in A is transformed to electrotonic coordinates. X is electrotonic distance and L is electrotonic length. The sketch to the right symbolizes the cable as a "black box" which is represented by the function, h(T).

Characterizing synaptic currents

Even the small currents generated by active synapses can be measured reliably with the amplifiers and oscilloscopes available for electrophysiology experiments. The instruments are used in two different ways or modes. The experiments discussed in Chapter 2 all involved injecting a known current into a cell and measuring the resulting voltage transient. This is called *current clamp mode* because the injected current is being controlled or "clamped" to some specific value. When the goal is to measure the current resulting from either synaptic activity or the activity of voltage-gated channels, the experiment is carried out in *voltage-clamp mode*. The voltage is clamped, or controlled, in this case. Voltage clamp allows the investigator to measure currents produced in the cell so the properties of an individual current -- generated, for example, by synaptic activity -- can be analyzed quantitatively.

Such studies are based on the properties of an equivalent circuit that represents the membrane of the cell (Fig. 5-2). The concept of an equivalent circuit was introduced in Chapter 3 and Kirchoff's law was used to write the relationship between currents flowing through the cell membrane. If a synaptic current, I_{syn}, is added, Kirchoff's law becomes

(5-1) $$I_C + I_R + I_{syn} = 0 \quad .$$

Using the relationships for the capacitive current, I_c, and resistive current, I_R, of the membrane (Equations 2-13 and 2-14) we have

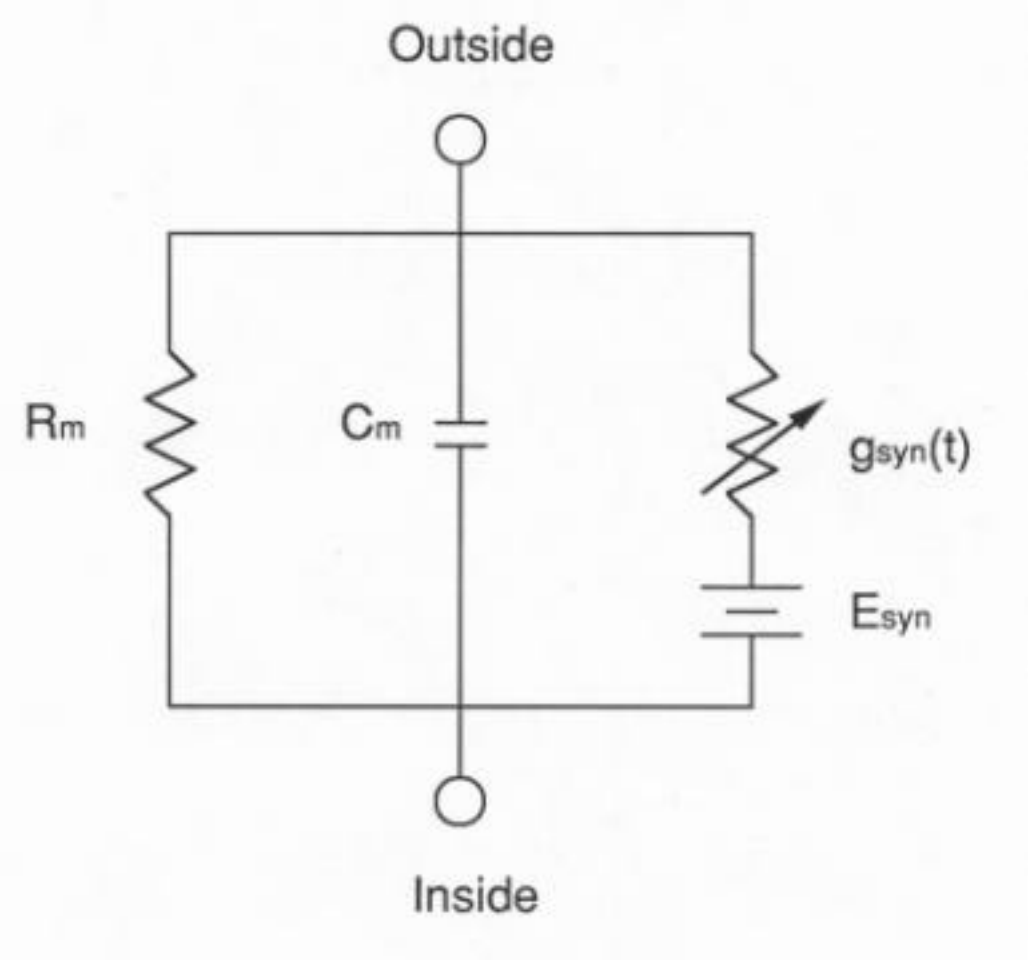

Figure 4-2. Equivalent circuit including a synapse. A chemical synapse is represented as a variable conductance, gsyn(t) in series with a battery, Esyn. The membrane resistance, Rm, and capacitance, Cm, are arranged in parallel, as they were in Chapters 2 and 3.

(5-2) $$C\frac{dV}{dT} + \frac{V}{R} + I_{syn} = 0 \quad .$$

This equation highlights the problem posed by experimental attempts to measure the synaptic currents. The current flowing through the active synapses causes a change in the membrane potential, $V(X,T)$, but both the capacitive and resistive currents depend upon $V(X,T)$. The currents interact

with each other and confound attempts to measure one current in isolation from the others.

A way around this is to keep the membrane potential constant using special *voltage-clamp* circuits that are incorporated into all modern intracellular recording amplifiers. The experimenter then chooses a *holding potential* for the membrane and the amplfier maintains the membrane at the specified voltage. The capacitive current depends upon the time derivative of the voltage and becomes zero if the voltage is held constant. In practice, it is often difficult to hold the voltage absolutely constant if there is a rapid and large voltage fluctuation (such as that produced by an action potential). The voltage transient produces an artifactual capacitive transient, but there are technical ways to minimize the difficulty. The resistive current also depends upon the membrane voltage, but becomes a constant if the membrane voltage is held constant. It can then be subtracted from the measured current. The practical details of carrying out voltage clamp measurements are discussed in a variety of textbooks and manuals (e.g. Dempster, 1993).

The effect of voltage-clamping the cell's membrane is that Equation (5-2) is simplified because the capacitive current becomes zero and the resistive current is a constant. The synaptic current is the only time-varying current that remains. EPSCs are normally currents that flow from the extracellular space into the cell and are shown by convention as down-going currents in experimental traces. IPSCs are normally currents that flow out of the cell into the extracellular space and are shown as up-going traces. We will see later in this chapter that the direction of current flow

actually depends upon the value of the membrane potential at the time the synapse is active.

Figure 5-3 shows examples of EPSCs and IPSCs recorded from several different types of cells. PSCs are clearly not all the same. They have waveforms (Fig. 5-4) that vary in amplitude and shape due to factors discussed below. However, they generally rise to some maximal value referred to as the *amplitude* of the wave form. PSCs typically have amplitudes on the order of 10^{-12} amperes or picoamps (pAs). The time required for the current to reach its maximal value after its onset also varies. This is the *time-to-peak* or *rise time*. PSCs have rise times that vary from 10s or 100s of μsec to msec, depending on the type of synapse creating the current. Obtaining an accurate value for a rise time can be problematic because a PSC usually does not deviate sharply from the baseline of the recording, making it difficult to accurately identify the onset of the current. Rise times are, therefore, often reported as 10 % - 90 % or 20 %-80 % rise times. These are obtained by finding the maximal value of the waveform and then measuring the times at which the waveform reaches 10% and 90 % or 20 % and 80 % of its maximal value. Since PSCs vary in width, the half widths of the waveforms are often measured. The half width of a waveform is its width measured at its half-maximal value. Narrow waveforms have short halfwidths; broad waveforms have long halfwidths. Finally, the falling phase of the waveform can be described by one or more time constants. They are obtained by measuring the amplitude of the waveform at a series of times during its falling phase. The time constants are obtained from this plot in a way analogous to the analysis described in Chapter 4 for membrane and equalizing time constants.

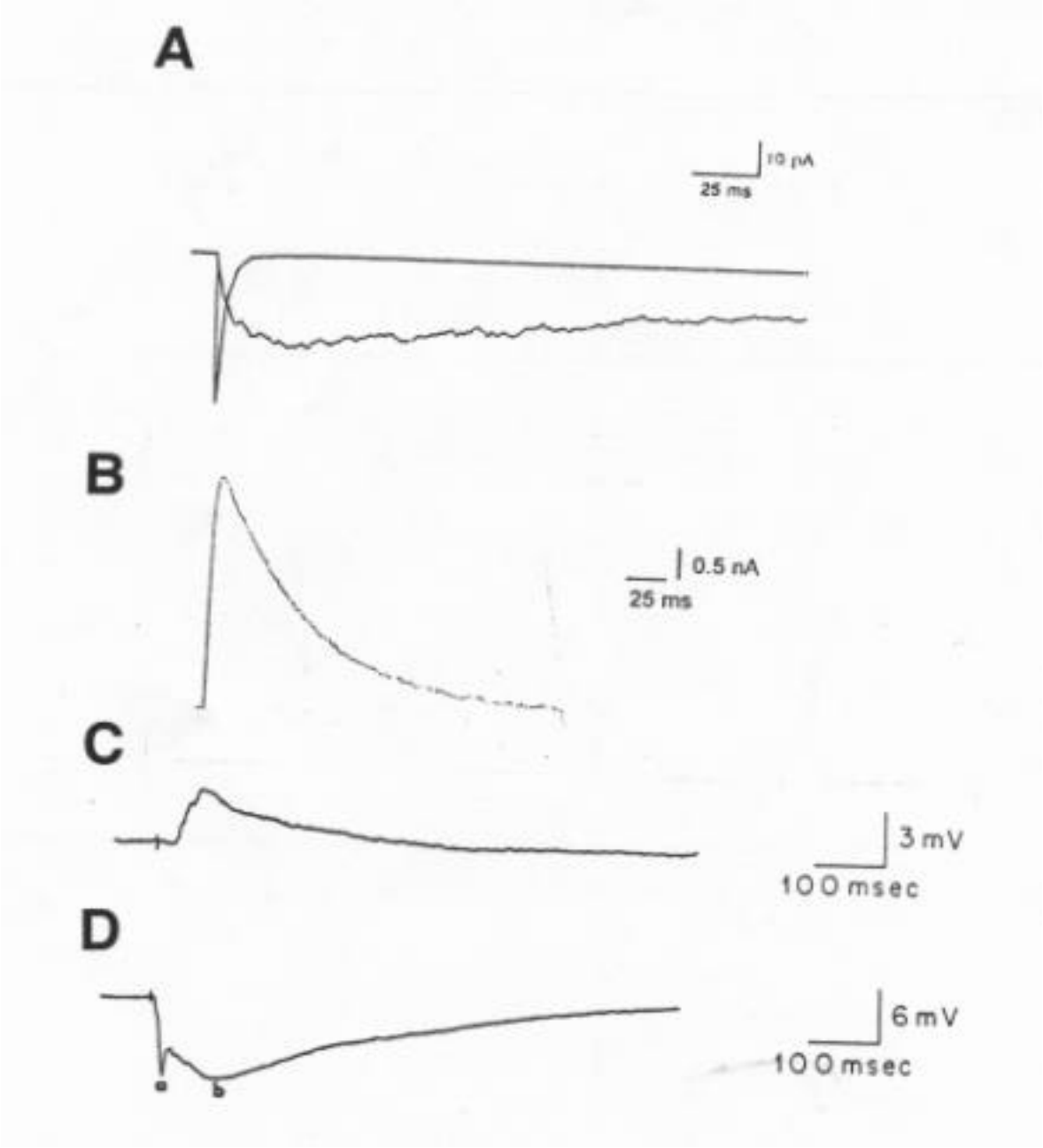

Figure 5-3. Examples of postsynaptic currents and potentials. A. Excitatory postsynaptic currents from rat hippocampal cells. Two superimposed traces show a fast and a slow current. From Spruston et al. (1995). B. Inhibitory postsynaptic current from a rat CA1 hippocampal pyramidal cell. From (Roepstorff and Lambert, 1994). C. Excitatory postsynaptic potential from a pyramidal cell in turtle visusal cortex. D. Inhibitory postsynaptic potential with fast (a) and slow (b) components from a pyramidal cell in turtle visual cortex.

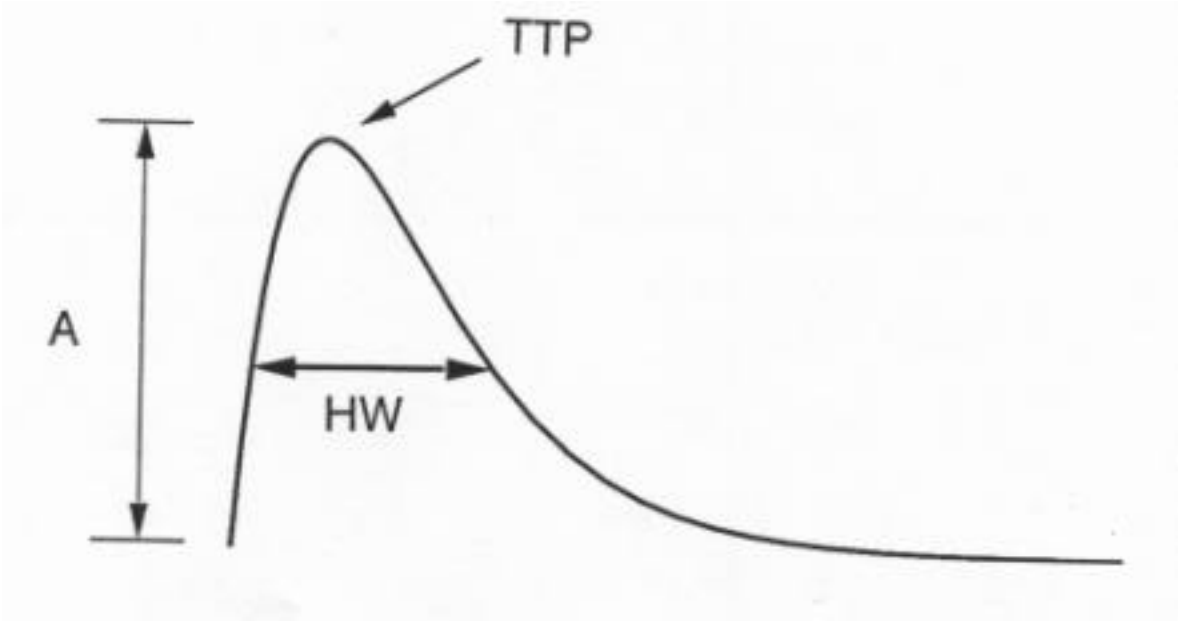

Figure 5-4. Parameters of postsynaptic currents and potentials. The trace is a postsynaptic current or potential. The amplitude (A) is measured from the base line to the maximum point on the trace. The halfwidth (HW) is the width of the trace measured at 50 % of its amplitude. The time-to-peak (TTP) is the time required for the trace to reach its maximal amplitude.

One goal for this chapter is to understand factors leading to variations in PSCs and how their properties affect the integrative properties of the neurons. All that is required for the moment, however, is a way of describing a PSC by an analytic expression that can predict its interaction with the electrical properties of the neuron. Two such expressions are widely used (Fig. 5-5). The first is to represent PSCs as *alpha functions* of the form

(5-3) $$I_{syn}(t) = I_{\max} \alpha t e^{-\alpha t}$$

where $I_{\max}$ is the maximal value of the current. To understand alpha functions, notice first that Equation (5-3) reduces to the simple linear

equation, $I_{syn}(t) = \alpha t$, for small values of t because the exponential term is then approximately $e^0 = 1$. The alpha factor determines the initial rise of the waveform. A small value of alpha produces a slowly rising synaptic current; a large value produces a rapidly rising synaptic current. The alpha factor also determines the time-to-peak of the synaptic current. To see this, recall that an extreme value of a function occurs when its first derivative equals zero. We can calculate the time at which Equation (5-3) reaches its maximum value by finding the first derivative of $I_{syn}(t)$ and setting it equal to zero

(5-4) $$\frac{dI_{syn}(t)}{dt} = I_{\max}\left[\alpha t\frac{d}{dt}e^{-\alpha t} + e^{-\alpha t}\frac{d}{dt}\alpha t\right] = I_{\max}\left[-\alpha^2 te^{-\alpha t} + \alpha e^{-\alpha t}\right] = I_{\max}\alpha e^{-\alpha t}[-\alpha t + 1] = 0$$

and

(5-5) $$\alpha t = 1 \quad .$$

Thus, the time-to-peak of the alpha function is equal to α^{-1}. Finally, notice that alpha also is a time constant that determines the time course of the falling phase of the synaptic current. Alpha functions closely resemble the waveforms of many PSCs, and a specific PSC can be represented by choosing the correct value of α^{-1}.

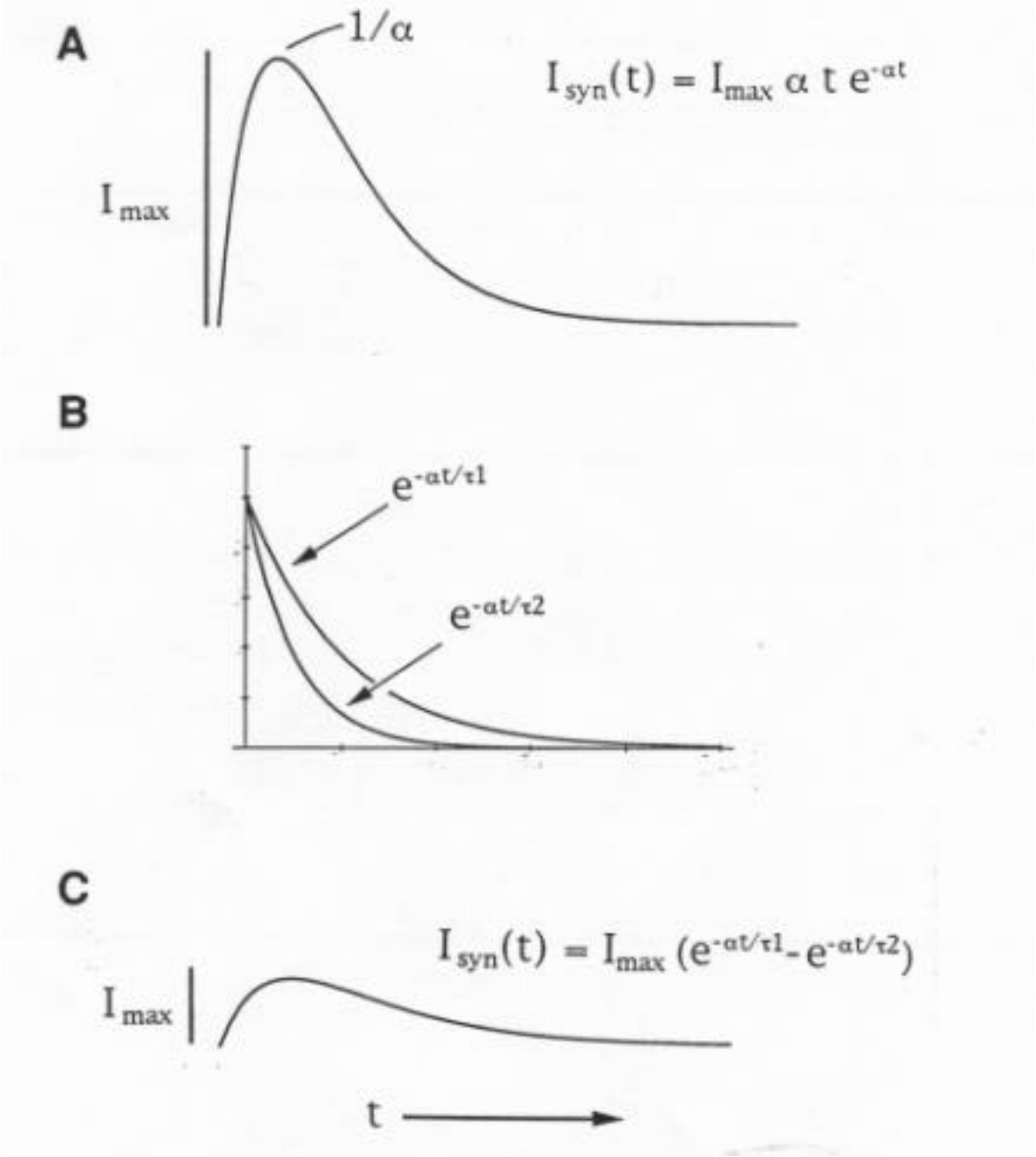

Figure 5-5. Alpha and dual exponential functions. A. An alpha function. B. Two exponential functions with different time constants. C. The dual exponential function obtained by subtracting one exponential from the other. Imax is the maximal amplitude of the synaptic current. α is the parameter of the alpha function. The two τs are the time contants of the exponential functions.

The drawback to representing synaptic currents by alpha functions is that the choice of alpha specifies three features of the waveform that might actually require independent values. Since many PSCs have falling-phase time constants that are independent of their times-to-peak, not all synaptic currents can be represented as alpha functions. A more flexible choice is to represent synaptic currents as a *difference of two exponential functions*

(5-6) $$I_{syn}(t) = I_{\max}\left[e^{-t/\tau_1} - e^{-t/\tau_2}\right] \quad .$$

You should find the first derivative of Equation (5-6) and show that the time-to-peak of a dual exponential function depends on both τ_1 and τ_2. Dual exponential functions, thus, provide two different parameters that can be chosen independently of each other and can accurately represent a wider range of PSCs.

Now we have a way of representing synaptic currents and the next step is to find a way to represent the properties of the system, or neuron.

Impulse response functions The key to describing the input-output relationships of neurons represented by cables is that the cable equation describes a linear system. We have already used this property to our advantage in Chapter 2 to construct general solutions to the cable equation, and we use it now to describe the response of a cable to a synaptic current by viewing the synaptic currents as a series of simpler currents. Suppose we approximate the synaptic current as a series of square current

pulses of varying amplitudes (Fig. 5-6A). Since the system is linear, the response of the cable to the series of pulses will equal the sum of its responses to each individual pulse. The difficult problem of calculating the response of the cable to a time-varying current is reduced to the problem of calculating its response to a square current pulse. There are obvious errors in approximating the synaptic current as a series of square current pulses if the individual pulses are wide. The best approximation will be obtained by making the individual current pulses as narrow as possible and ultimately using the rules of calculus to take a limit as the width of the pulse approaches zero. It is natural, then, to define the response of the system to a current pulse that occurs in an infinitely small time period.

We can do this by defining a pulse with an amplitude that approaches infinity as its width approaches zero. Such a pulse is represented mathematically by a *Dirac delta function*, δ(t), (Fig. 5-6B). (The Dirac delta function should not be confused with the Kronecker delta function introduced in Chapter 4.) You can think of the Dirac delta function as a square current pulse with infinitely small width and infinitely large amplitude. The response of the system to a Dirac delta function is a function, $h(t)$, called the *impulse response function* (Fig. 5-6C). Impulse response functions can be measured

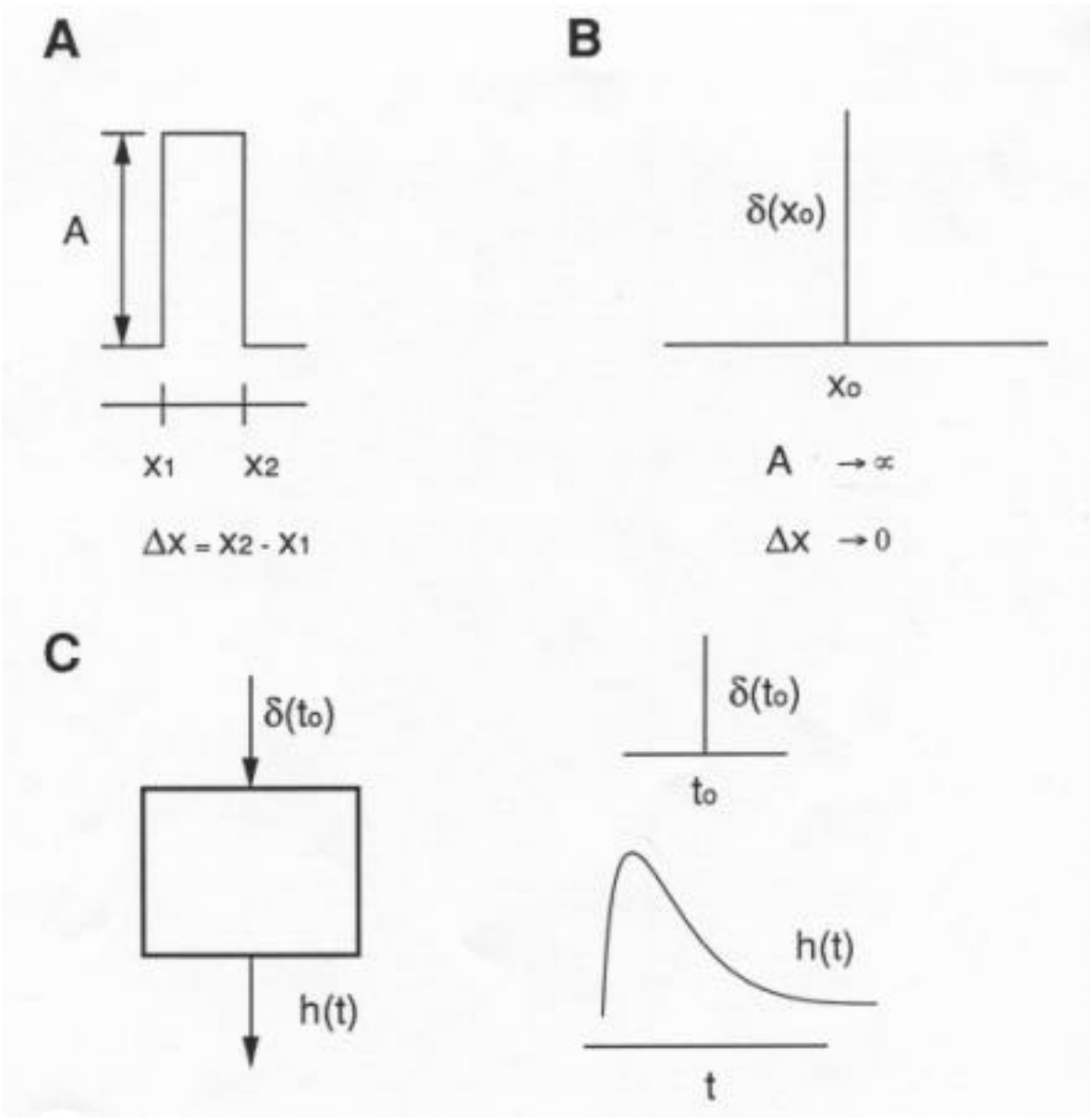

Figure 5-6. Delta and impulse response functions. A. A rectangular pulse with amplitude, A, and width Δx. B. A Dirac delta function, $\delta(xo)$, results from taking the limit as A approaches infinity and Δx approaches zero C. An impulse response function, h(t), results from using a delta function as an input to the system. The graphs to the right show the time courses of the delta function and the resulting impulse response function.

experimentally by measuring the voltage transient produced by a current pulse that is much smaller than the time constant of the system.

An important property of linear systems is that the response, $y(t)$, of the system to any time-varying input, $x(t)$, can be predicted by evaluating the *convolution integral*

(5-7) $$y(t) = \int_0^t h(u)x(t-u)du \quad .$$

The input function is said to be *convolved* with the impulse response function. Notice that the integration is carried out with respect to the *integration variable*, u, rather than time, t. The response of the cable to a synaptic current can be obtained by convolving the synaptic current with the impulse response function of the cable

(5-8) $$V(t) = \int_0^t h(u)I_{syn}(t-u)du \quad .$$

because the cable is a linear system.

To understand where the convolution integral comes from, let's do a thought experiment in which the membrane bounding an isopotential cylinder has no capacitance (Fig. 5-7A). The only current term in the membrane equation is then the resistive term, which is governed by Ohm's law. The voltage response to a very brief current pulse of duration, Δu_1, at time t_i is given by $V(t) = IR_N \Delta u_1$, where R_N is the input resistance of the cylinder and I is the current flowing through the membrane per unit time. Because the membrane is purely resistive, it has no history dependence or memory. If we take the limit as $\Delta u_1 \rightarrow 0$, we find that the response of the system to an infinitely short pulse at time, t_1, is $V(t) = IR_N \delta(t_1)$. If we subject the system to

a train of pulses with durations, Δu_1, Δu_2, ..., Δu_k at times u_i, u_2, ..., u_k, then the response of the system is

(5-9) $$V(t) = \sum_{i=1}^{k} IR_N \delta(u_i) \quad .$$

The situation changes when capacitance is put back into the system (Fig. 5-7B). We know from Equation (2-29), that the response of the system to a brief current pulse at time, t_o, is $V(t) = I(t_0)\Delta u R_N e^{-t/\tau m}$. We can find the response of the system at each of two pulses presented separately in the same way. Since the system is linear, the response to both pulses presented simultaneously will equal the sum of the individual responses. A technical problem, however, is that we need a way to express both pulses in the same time frame. We can do this by measuring time with the dummy variable, u. Then, the response of the system to an input of duration Δu at u is $I(u)\Delta u R_N e^{-u/\tau_m}$. If we express the input current in terms of the variable, u, as $I(t-u)$, the response of the system to inputs at times u_1, u_2, ..., $u_k = t$ will be given by

(5-10) $$V(t) = \sum_{i=1}^{k} R_N e^{-u_i/t\tau_m} I(t-u_i)\Delta u = \sum_{i=1}^{k} h(u_i) I(t-u_i)\Delta u \quad .$$

The convolution integral (Equation 5-8) results from taking the limit as $\Delta u \to 0$. It represents the synaptic current as an infinite number of infinitely short current pulses, and calculates the membrane voltage at time t by adding together the voltage transients resulting from all of the current pulses that occurred at time values $u \le t$. We can calculate the voltage transient produced in the cylinder by any synaptic current (as long as we can

represent it by an analytic function, like an alpha or dual exponential function) if we also have an analytic expression for the impulse response function of the cylinder.

We are almost ready to calculate the voltage transients produced by synaptic currents in cylinders, but it will be helpful to first digress and develop an additional mathematical tool.

Digression on Laplace transforms

Transforms are mathematical entities that change a function of one variable into a function of another variable. This is in contrast to operators, which change a function, but do not change its variable. The *Laplace transform* is a specific type of transform that changes a function from one independent variable (often time, t) to a new variable, s. The transform expresses the function in the *Laplace transform domain* rather than the *time domain*. The transform is defined by the following integral

(5-11) $$y(s) = \int_0^\infty e^{-st} Y(t) dt$$

where $Y(t)$ is some function of t and $y(s)$ is the *Laplace transform* of the function. The Laplace transform of $Y(t)$ is also written as $\mathrm{L}\{Y(t)\}=\bar{Y}(s)$.

Laplace transforms of many functions are available in mathematical tables, but let's look briefly at some simple examples. If $Y(t)=1$,

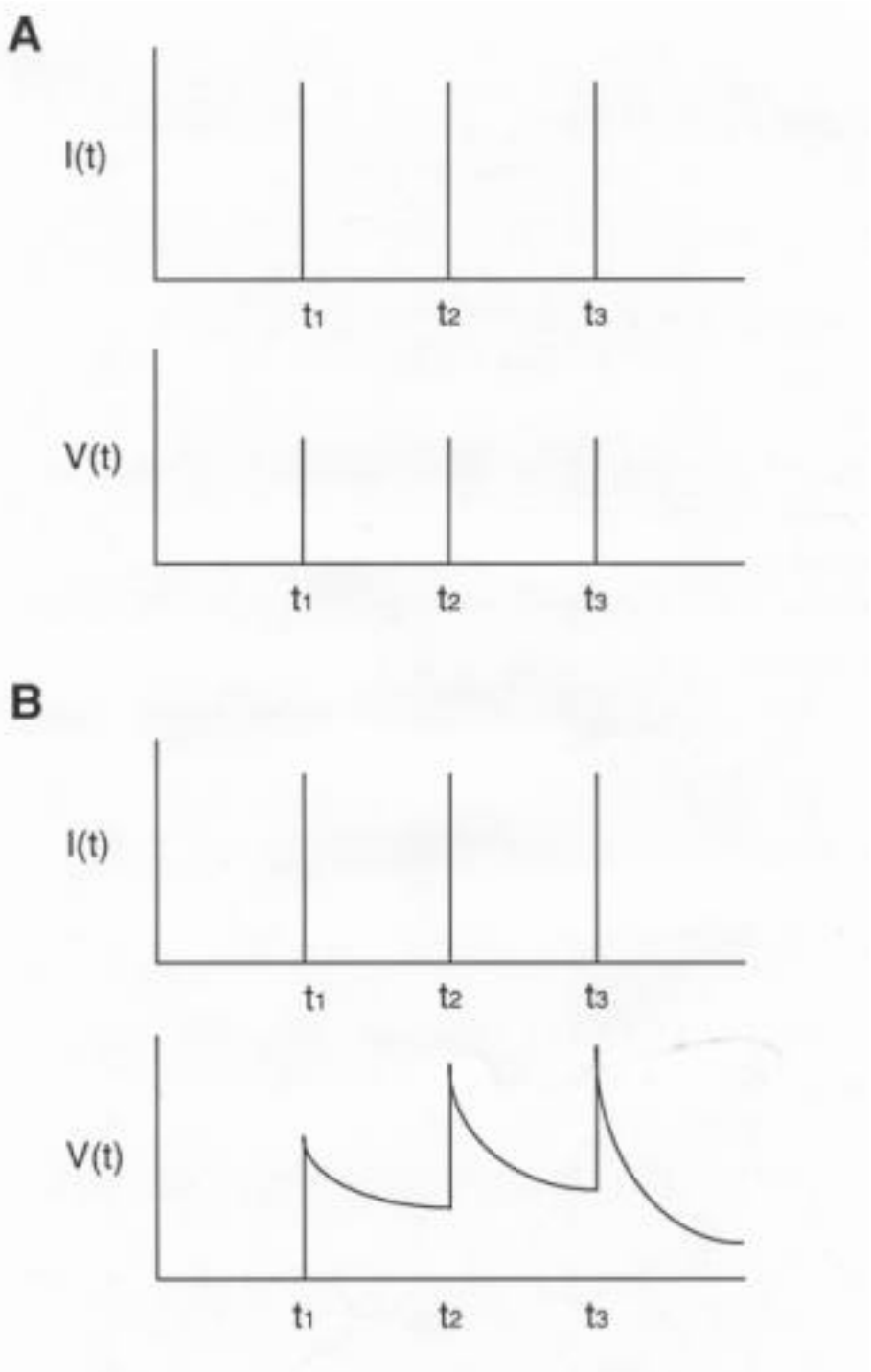

Figure 5-7. Response of a linear system to a sequence of delta function inputs. A. The top graph shows a series of delta function current inputs at a sequence of three times. The bottom graph shows the response of a linear system to these inputs as a function of time. Because the system has no capacitance, or memory. Each delta function input produces a delta function output. B. The top graph, again, shows a sequence of delta function inputs. In this case, the system includes a capacitor which gives the system a memory, so the response produced by each successive input sums with preceding responses.

(5-12) $$\mathrm{L}\{1\} = \int_0^\infty e^{-st}(1)dt = \frac{-1}{s}e^{-st}\Big|_0^\infty = 0 - \left(\frac{-1}{s}\right) = \frac{1}{s} \quad .$$

If $Y(t) = a$, where a is a constant, $y(s) = a/s$. A slightly more complicated function is $X(t) = e^{at}$, where a is a constant. The Laplace transform is

(5-13) $$\mathrm{L}\{e^{at}\} = \int_0^\infty e^{-st}(e^{at})dt = \int_0^\infty e^{-(s-a)t}\,dt = \frac{1}{s-a}$$

An important relationship is that the Laplace transform of the Dirac delta function is 1

(5-14) $$\mathrm{L}\{\delta(t)\} = \int_0^\infty e^{-st}\delta(t)\,dt = 1 \quad .$$

This reinforces the idea that the delta function is a unit input to a system. Finally, it is possible to show that the Laplace transform of the derivative $dY(t)/dt$ is

(5-15) $$\mathrm{L}\{dY(t)/dt\} = sy(s) - Y(0)$$

where $Y(0)$ is an initial value that is specified by the problem.

To see how Laplace transforms can be helpful, consider the simple ordinary differential equation $dV(t)/dt = -V(t)/\tau$ for the initial condition $V(0) = V_o$ at $t = 0$. Taking the Laplace transform of both sides of the equation

(5-16) $$\mathrm{L}\{\frac{dV(t)}{dt}\} = \mathrm{L}\{\frac{-V(t)}{\tau}\}$$

(5-17) $$sv(s) - V(0) = \frac{-v(s)}{\tau} \quad .$$

Rearranging this equation and solving it for $v(s)$

(5-18) $$v(s) = \frac{V_o}{s + 1/\tau} \quad .$$

It is necessary now to convert this equation from the Laplace transform domain back into the time domain. This involves using the *inverse Laplace transform* which is defined by

(5-19) $$\mathrm{L}^{-1}\{y(s)\} = Y(t) \quad .$$

In this case, it is clear from Equation (5-14) that the inverse Laplace transform of $1/(s-a)$ is the exponential function e^{at}. Thus,

(5-20) $$\mathrm{L}^{-1}\{v(s)\} = V_0 e^{-t/\tau} \quad .$$

Encouragingly, this is the same solution we obtained in Chapter 2.

PSPs in an isopotential cylinder

We are now in a position to find the impulse response function for an isopotential cable using Laplace transform methods. Knowing the impulse response function will allow us to calculate the waveform of PSPs produced

by known PSCs. It simplifies the algebra if we work in terms of normalized coordinates, X and T. The cable equation simplifies to

(5-21) $$\frac{dV(T)}{dT} + V(T) = 0 \quad .$$

in this case because the cable is isopotential and the spatial derivative vanishes. The two terms in the equation represent the resistive and capacitive currents through the cable's membrane. The problem is to calculate the response of the membrane to a depolarizing impulse current represented by $-\delta(T)I_o$, where, I_o, is the magnitude of the current per unit time. This adds a new term to the membrane current, so Equation (5-21) becomes

(5-22) $$\frac{dV(T)}{dT} + V(T) - \delta(T)I_o R_N = 0$$

where R_N is the total resistance of the cable. We transform this equation from the time domain to the Laplace transform domain by taking the Laplace transform of each term in the equation

(5-23) $$\mathrm{L}\{\frac{dV(T)}{dT}\} + \mathrm{L}\{V(T)\} + \mathrm{L}\{\delta(T)I_o R_N\} = 0$$

and

(5-24) $$sv(s) - V(0) + v(s) + I_o R_N = 0 \quad .$$

If we use $V(0) = 0$ at $T = 0$, it is easy to rearrange this equation and solve for $v(s)$

(5-25) $$v(s) = \frac{I_o R_N}{s+1}$$

We can then find $V(T)$ by taking the inverse Laplace transform of both sides of Equation (25) and using Equation (4-13)

(5-26) $$V(t) = \mathrm{L}^{-1}\{v(s)\} = \mathrm{L}^{-1}\{\frac{I_o R_N}{s+1}\} = I_o R_N e^{-T} = I_o R_N e^{-t/\tau_m}$$

Since $V(t)$ is the response of the system to a delta function input, it is by definition the impulse response function for the system. This calculation shows formally what we guessed should be the case: the impulse response function for the isopotential cylinder is $h(t) = R_N e^{-t/\tau}$.

We can now model an input PSC as an alpha or dual exponential function and calculate the waveform of the resulting PSP by convolving the input function, $I_{syn}(t)$, with the impulse response function, $h(t) = R_N e^{-t/\tau_m}$. We remember to put the history dependence of the membrane into the integral by using the integration variable, u:

(5-27) $$V(t) = \int_0^t R_N e^{-u/\tau_m} I_{syn}(t-u)du \quad .$$

Evaluation of the integral is not very difficult when either alpha or dual exponential functions are used as input functions. To get a general idea of how a synaptic current interacts with the passive membrane of the neuron,

let's model the synaptic current by the function $I_{syn}(t) = -I_{\max} e^{-t/\tau_{syn}}$. The minus sign indicates that the current is inwards and depolarizes the membrane. $I_{\max}$ is the amplitude per unit time of the current. This synaptic currrent turns on instantaneously (or at least very quickly relative to the membrane constant) and then decays exponentially with a time constant, τ_s. This is a reasonable approximation to a synaptic current because the time course by which ligand-gated receptors are activated is usually less than a millisecond, so a synaptic current rises almost instantaneously as compared to the membrane time constant (which is on the order of several milliseconds). We substitute the synaptic current and impulse response function into the convolution integral and do the calculation

(5-28a) $$V(t) = \int_0^t \left[R_N e^{-u/\tau_m} \right] \left[-I_{\max} e^{-(t-u)/\tau_{syn}} \right] du$$

(5-28b) $$= -I_{\max} R_N e^{-t/\tau_s} \int_0^t Exp\left[-\frac{\tau_s - \tau_m}{\tau_s \tau_m} u \right] du$$

(5-28c) $$= I_{\max} R_N e^{-t/\tau_s} \left[\frac{\tau_m \tau_s}{\tau_m - \tau_s} \right] Exp\left[-\frac{\tau_s - \tau_m}{\tau_s \tau_m} u \right] \Big|_0^t$$

(5-28d) $$= I_{\max} R_N e^{-t/\tau_s} \left[\frac{\tau_m \tau_s}{\tau_m - \tau_s} \right] Exp\left[-\frac{\tau_s - \tau_m}{\tau_s \tau_m} t \right] - 1$$

(5-28e) $$= I_{\max} R_N e^{-t/\tau_s} \left[\frac{\tau_m \tau_s}{\tau_m - \tau_s} \right] \left\{ e^{-t/\tau_m} e^{+t/\tau_s} - e^{-t/\tau_s} e^{+t/\tau_s} \right\}$$

(5-28f) $$V(t) = I_{\max} R_N \left[\frac{\tau_m \tau_s}{\tau_m - \tau_s} \right] \left[e^{-t/\tau_m} - e^{-t/\tau_s} \right]$$

Figure 5-8 shows plots of the PSC and the resulting PSP. Notice that the waveform of the voltage transient is significantly different from that of the synaptic current. Important features are that the sign of the PSP is opposite that of the PSC, the onset of the PSP is delayed relative to that of the PSC and the PSP has a much longer rise time than does the PSC. The second two effects are due to the membrane capacitance which appears in Equation (5-28f) through the time constant $\tau_m = R_m C_m$. The amplitude of the PSC and PSP are also different due to the input resistance factor in the impulse response function. The conclusion from this analysis is that the membrane of the cylinder transforms the waveform of the input current, changing its amplitude, delaying its onset and lengthening its rise time. This transformation is called *electrotonic filtering*.

PSPs in infinite and finite cables

A comparable approach can be used to determine the impulse response function for infinite and finite cables. The waveforms of PSPs in these cables can then be calculated by convolving the impulse response functions with an input function (Jack and Redman, 1971; Walmsley and Stuklis, 1989). The mathematics becomes more complex and we will omit the calculations, but interested readers are referred to Jack and Redman (1971). The principal conclusion is that the impulse response function and PSPs depend on the electrotonic distance of the input current from the recording

electrode in both cases and on the electrotonic length of a finite cable. For the infinite cable,

(5-29) $$h(t) = R_N \frac{1}{\sqrt{\pi T}} Exp\left[\frac{-X^2 - 4T^2}{4T}\right] \qquad T > 0.$$

An alpha function can be used to describe the synaptic current, and the voltage transients produced in a cable calculated by convolving the impulse response function in Equation (5-29) with the alpha function.

SYNAPTIC CURRENTS IN COMPARTMENTAL MODELS

Calculating PSPs produced by synaptic currents becomes more cumbersome in complicated cases and is generally impractical for branched cables. It is generally best in these cases to rely upon compartmental models of neurons to study electrotonic filtering. Including synaptic currents in compartmental models is a relatively simple matter that involves adding an additional limb to the equivalent circuit for each compartment that receives a synaptic input. Figure 5-10A is the equivalent circuit for an isopotential compartment that contains a synapse. As before, the membrane is represented by a resistor, with conductance g_l, and a capacitor in parallel. The resting membrane potential is represented by a battery with a reversal potential of V_r. The synapse is represented by a variable resistor (shown by a resistor symbol with an arrow through it) in series with a battery. The resistor (or conductor) is variable because the pore in the receptor-channel complex will be closed in the absence of transmitter and

will result in an infinite resistance. As transmitter binds to the receptor, the channel opens, ions

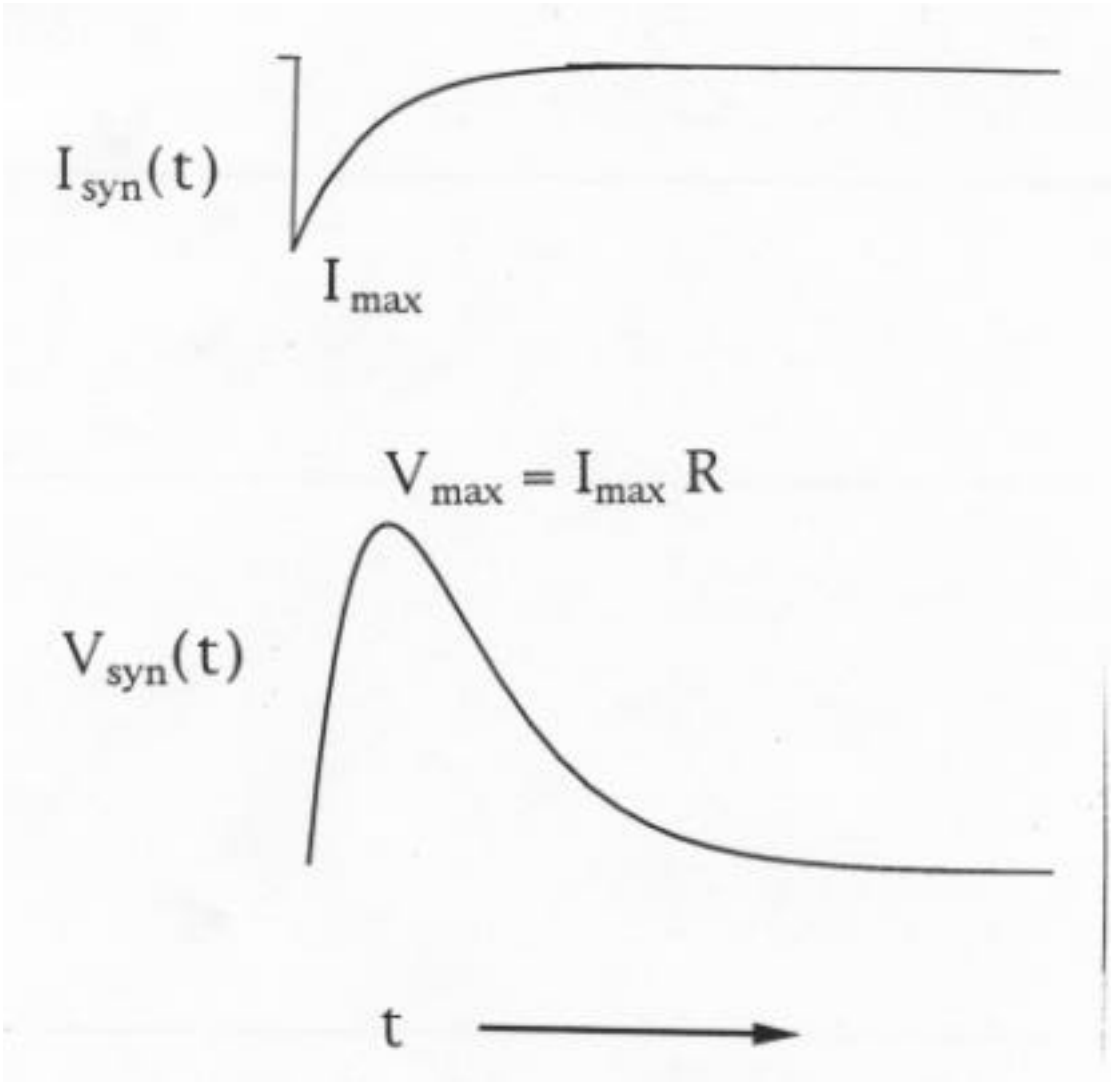

Figure 5-8. Electrotonic filtering. The top trace is an EPSC resulting from activation of a synapse on an isopotential compartment. The bottom trace is the EPSP obtained by convolving the input current with the impulse response function for an RC circuit.

begin to flux through the channel and the resistance decreases. This synaptic current can be represented by the product of two factors:

(5-30) $$I_{syn}(t) = g_{syn}(t)\left[V(t) - V_{syn}\right] .$$

The first factor is the *synaptic conductance,* $g_{syn}(t) = \bar{g}g(t)$. It is the product of a *maximal conductance*, $\bar{g}$, which is the conductance when all of the receptors in the membrane are open and a function, $g(t)$, that specifies the time course of the synaptic conductances. It gives the fraction of channels that are open at time, t. Like synaptic currents and potentials, $g(t)$ can be represented as an alpha function or a difference of two exponentials. Since the compartment is isopotential, all of the individual channels in the compartment's membrane can be lumped together. The second factor is a *driving potential*, $V(t) - V_{syn}$, where $V(t)$ is the membrane potential of the compartment and V_{syn} is the Nernst potential for the receptor. The membrane equation (Equation 4 – 2) for the compartment is now

(5-31) $$C\frac{dV}{dt} + \frac{[V - V_r]}{R} + g_{syn}[V - V_{syn}] = 0.$$

The value of V_{syn} depends upon the ion (or ions) that flux through the channel. Excitatory synapses typically flux several ionic species and have reversal potentials near 0 mV. Inhibitory synapses typically flux chloride or potassium ions and have reversal potentials on the order of - 70 to - 90 mV. The reversal potential is not really a constant in that it depends upon the local concentrations of ions inside and outside of the cell, and can actually change with synaptic activity.

The nature of the reversal potential can be appreciated by making a plot of the synaptic current as a function of membrane potential (Fig. 5-9B).

Notice that the synaptic current, $I_{syn} = g_{syn}\left[V - V_{syn}\right]$, is zero when the membrane potential is held at V_{syn}. A plot of the amplitude of the resulting PSP as a function of holding potntial is a straight line that passes through the reversal potential on the voltage axis. The sign of the current (negative for an inward current and positive for an outward curent) changes or reverses as the membrane potential is changed. An important consequence is that representing a synapse as a current, as we did at the start of the chapter, introduces errors in many cases. If the synaptic current is active long enough to produce a change in membrane potential, then the magnitude of the driving force will change so the amount of current that can flow through the synapse changes with time.

The conductance change that results from activating a synapse is typically on the order of 5 nS. If the synapse uses an excitatory transmitter substance and has a reversal potential of 0 mV, and if the membrane has a resting membrane potential of - 50 mV, the maximal synaptic current would be

(5-32) (5 nS) (-50 mV - 0 mV) = - 25 pA .

If the neuron has a total input resistance of 100 MΩ, the synaptic potential would have an amplitude of roughly 0.25 mV. (Remember that a negative synaptic current produces a depolarizing synaptic potential.)

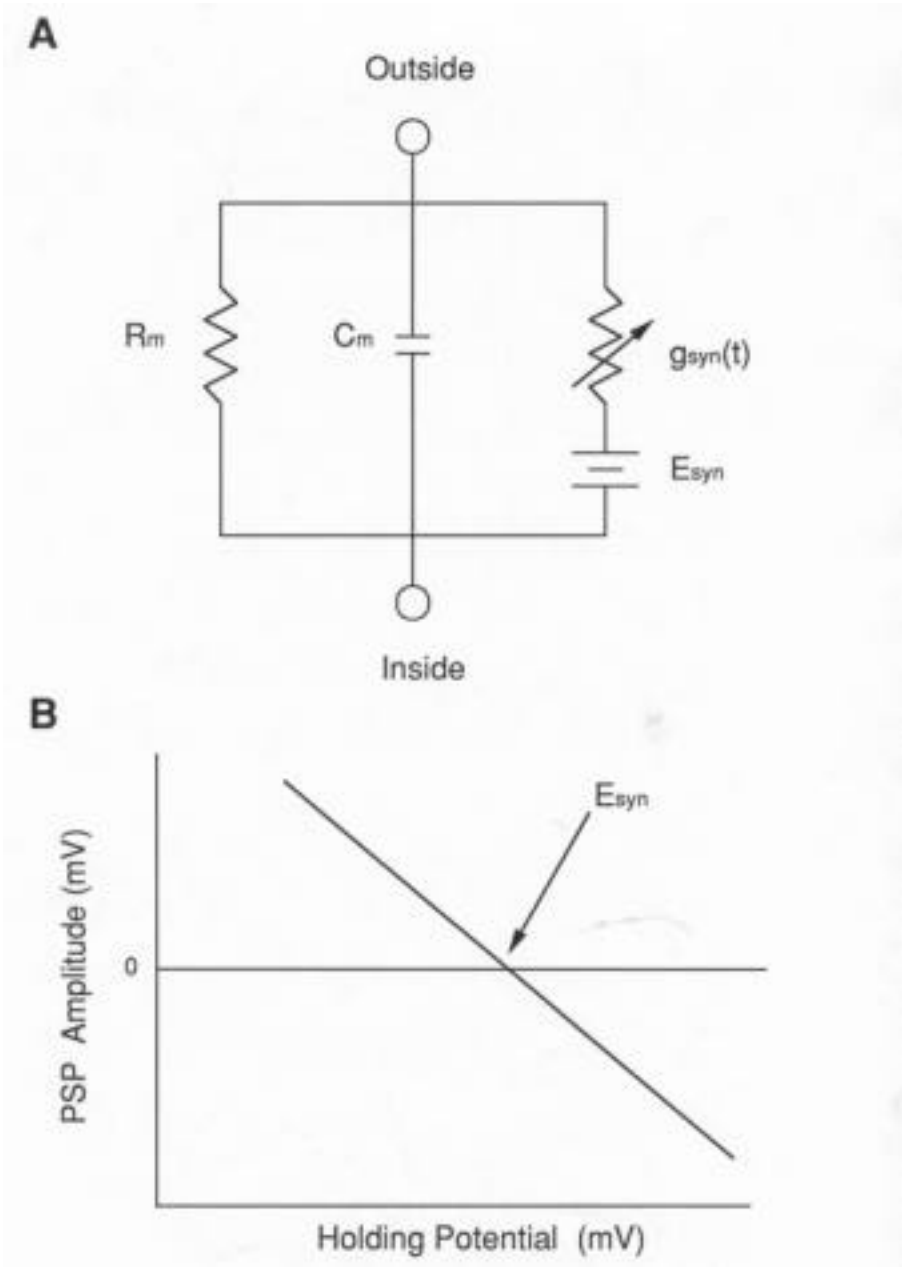

Figure 4-9. Equivalent circuit for a chemical synapse. A. The synapse is represented as a variable conductance in series with a battery. B. Amplitude of the PSP produced by activation of the synapse as a function of the membrane holding potential. The battery produces a linear amplitude-voltage curve that crosses zero at the synaptic reversal potential.

POSITION DEPENDENCE VS. PASSIVE NORMALIZATION

Cable and compartmental models allow us to make predictions about how synaptic currents interact with the passive electrotonic structure of virtually any neuron. These interactions can become complicated and will be discussed in detail in several chapters later in the book. However, a relatively simple question is how the position of a single synapse on the dendrites or soma of a neuron influences the shape of the PSP or PSC at the soma of the neuron. Plots of the voltage transients as a function of the electrotonic distance between the synaptic input and the recording electrode for a finite cable (Fig. 5-10) demonstrate that the amplitude of the resulting PSP decreases as a function of electrotonic distance while the rise time and half width become longer (Walmsley and Stuklis, 1989). Rall carried out a detailed analysis of the effect of synaptic position on PSP waveforms in a series of papers (Rall, 1964; 1967a,b; 1970). He found systematic changes in the PSP waveforms for synapses located in different compartments of a model neuron (Fig. 5-11A). He referred to the *amplitude*, *time-to-peak* and the *half width* of a PSP as its *shape indices* and found that the basic features of PSP waveforms for a given cell could be summarized in *shape index plots*. One plot involves plotting the amplitude of individual PSPs as a function of their rise times. The other involves plotting rise times as a function of half widths. PSPs obtained from several individual neurons can be combined in a single plot if their shape indices are first normalized by dividing the rise times and half widths for PSPs from each individual cell by the membrane time constant of that cell. A plot of halfwidth vs. time-to-peak for EPSPs simulated in a compartmental model shows that halfwidth

and time-to-peak are positively correlated while amplitude and time-to-peak are negatively correlated (Fig. 5-11B). Theoretical analysis of electrotonic filtering of synaptic currents by both linear systems and compartmental

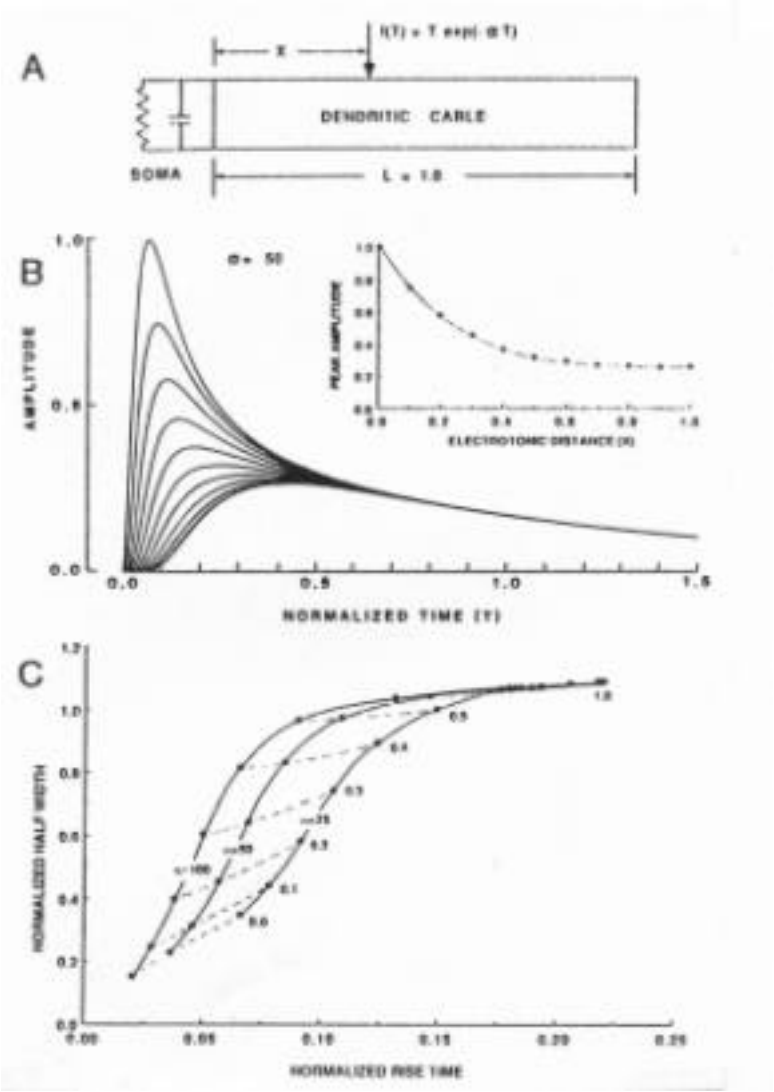

Figure 5-10. Calculated PSPs for a finite cable. A. A cable model with electrotonic length, L = 1.0. A synaptic current is activated at electrotonic distance, X, from the soma. The synaptic current is modeled as an alpha function. B. The main graph shows the time courses of EPSPs as a function of the electrotonic distance of the synapse from the soma. The amplitudes of the EPSPs have been normalized to 1.0. The inset graph plots the normalized amplitude of the EPSPs as a function of electrotonic distance. C. Plots of half width as a function of rise time for a series of values of alpha. Both half width and rise time are in normalized time, T. From Walmsley and Stuklis (1989).

modeling methods, thus, lead to the important concept that the shapes and amplitudes of PSPs depend upon the electronic structure of the neuron and the position of the synapse upon it.

Experimental tests of these theoretical predictions require the activation of synapses situated at known distances from a recording electrode. One approach is to use cell cultures in which individual neurons

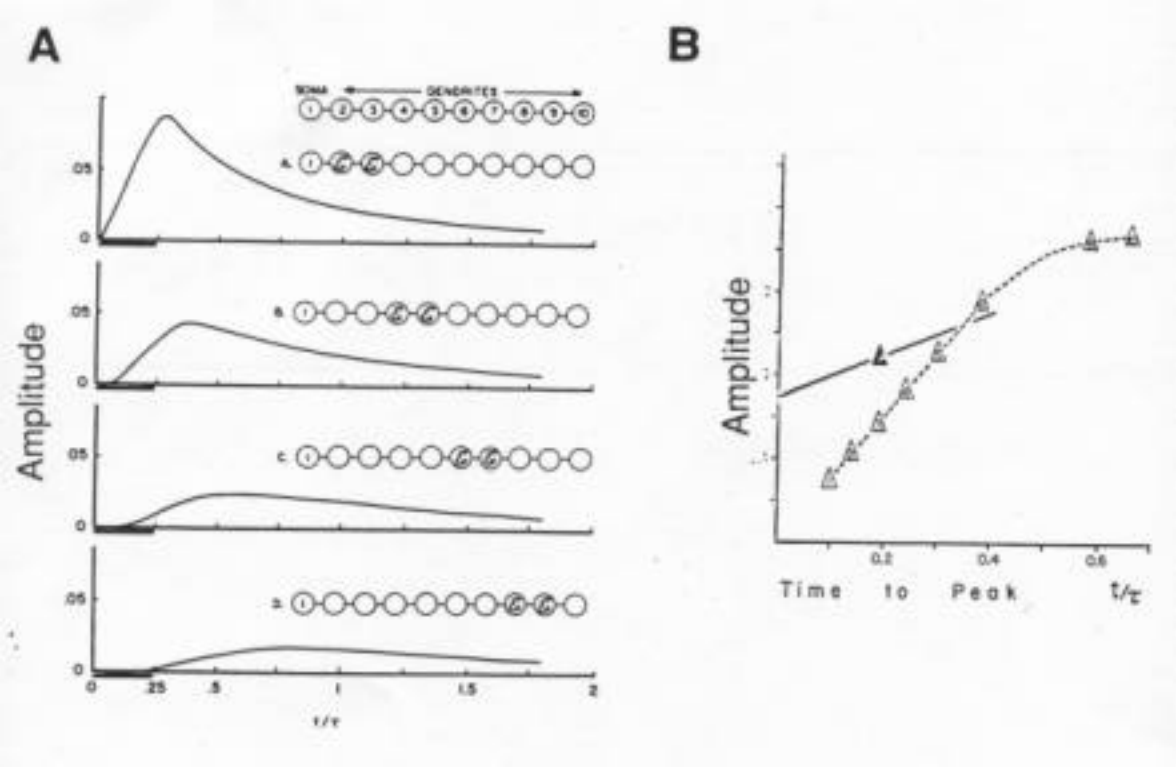

Figure 5-11. Shape index plots. A. EPSPs produced in a compartmental model. The model consists of a linear sequence of 10 compartments. Synapses were activated in two adjacent compartments. The traces shows the EPSPs produced by synapses situated at a series of different compartments. The amplitudes of the EPSPs have been normalized. B. Plot of half width as a function of rise time for the EPSPs shown in A. Both parameters are expressed in normalized time, T. From Rall et al. (1967).

are visualized while recordings are made from specified points on the neuron's surface. Bekkers and Stevens (1990) carried out such an

experiment using CA1 and CA3 pyramidal cells from neonatal rats (Fig. 5-12). They prepared cultures in which cell density was sufficiently low that the dendritic fields of individual neurons could be traced. They used whole-cell patch methods to record EPSCs from the somata of neurons (Bekkers and Stevens, 1989). Synapses were activated by using a small pipette containing hyperosmotic solutions. The mechanism by which hyperosmotic solutions cause the release of neurotransmitter from axonal terminals is not certain, but it is known that local application of such solutions elicit PSCs at restricted foci on dendrites (Bekkers and Stevens, 1989). The preparation could be used to record at the soma currents produced at known positions on the dendritic tree. The synaptic currents varied in amplitude but, on average, conformed to the predictions of linear cable theory. EPSCs elicited at the soma had larger mean amplitudes than those elicited at dendritic sites, and EPSCs elicited 90 μm from the soma were larger than those elicited at 170 μm from the soma. EPSCs elicited at distal sites also had longer rise times and longer halfwidths than those elicited at proximal sites.

These findings for CA1 pyramidal cells are consistent with studies using compartmental models. Jaffe et al. (1999), for example, constructed a multi-compartmental model of a CA1 pyramidal cell. They then activated conductances of 500 pS or 1 nS - 5 nS in each of the compartments and recorded the amplitudes of the resulting PSPs in the soma compartment. They found that (Fig. 5-13) the amplitudes varied significantly as a function of the location of the synapse. The amplitudes of PSPs resulting from activation of 500 pS conductances along the large, primary dendrites of the cell decreased from about 0.35 mV to about 0.05 mV. There was, however, relatively little variation in the amplitudes of PSPs resulting from activation

of synapses along the secondary dendrites. Like the experimental studies, this analysis suggests that the effect of synapses in CA1 pyramidal cells shows a distinct position dependence: distal synapses produce small amplitude PSPs at the soma than do proximal synapses. Similar results were

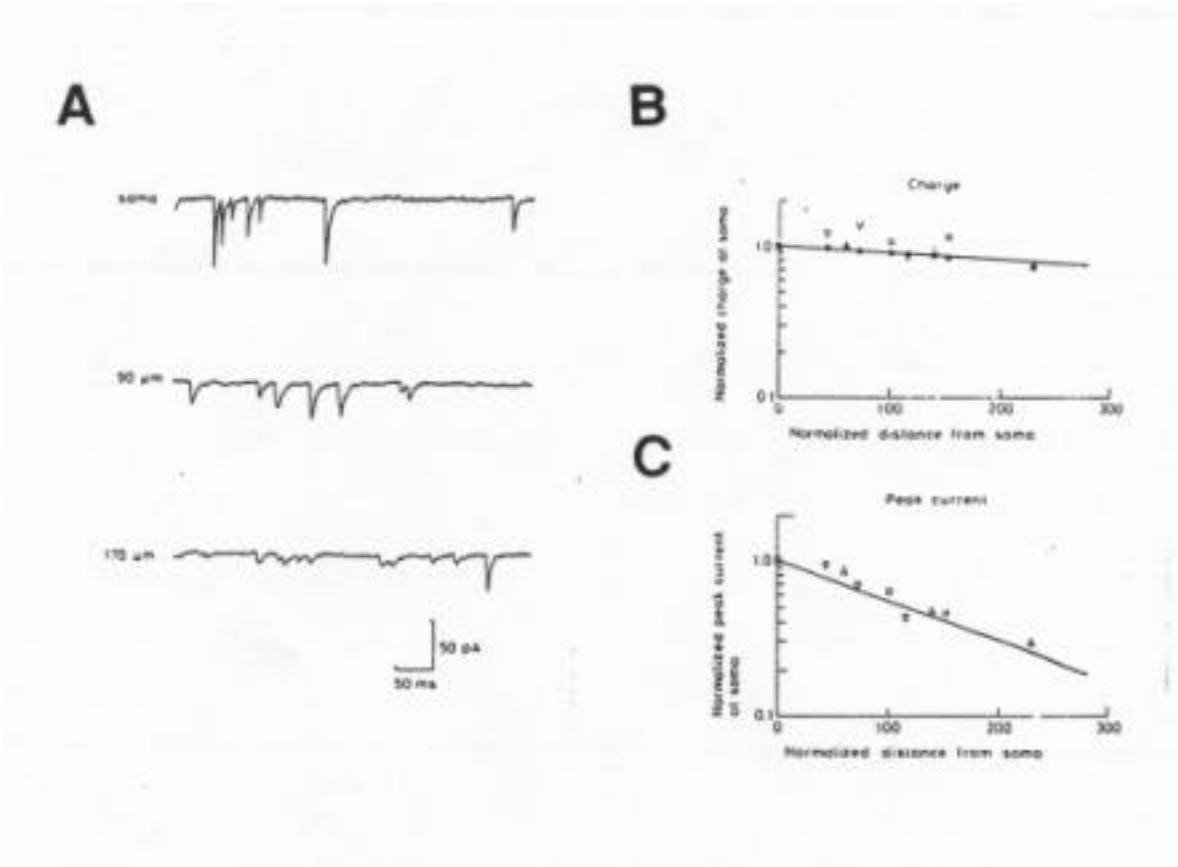

Figure 5-12. EPSCs in hippocampal pyramidal cells. A. EPSCs were recorded from the soma of a hippocampal neuron in culture while hyperosmotic solution was used to induce synaptic currents at the soma and at 90 µm and 170 µm distant from the soma. B. The normalized charge measured at the soma is plotted as a function of the distance of the active synapse from the soma. C. The normalized peak current is plotted as a function of distance from the soma. From Bekkers and Stevens (1990).

obtained with a model of neocortical pyramidal cells. However, models of a CA3 hippocampal pyramidal cell, a dentate gyrus pyramidal cell and hippocampal interneurons (Chitwood et al., 1999) yielded different results. PSP amplitude at the soma showed relatively little variation as a function of

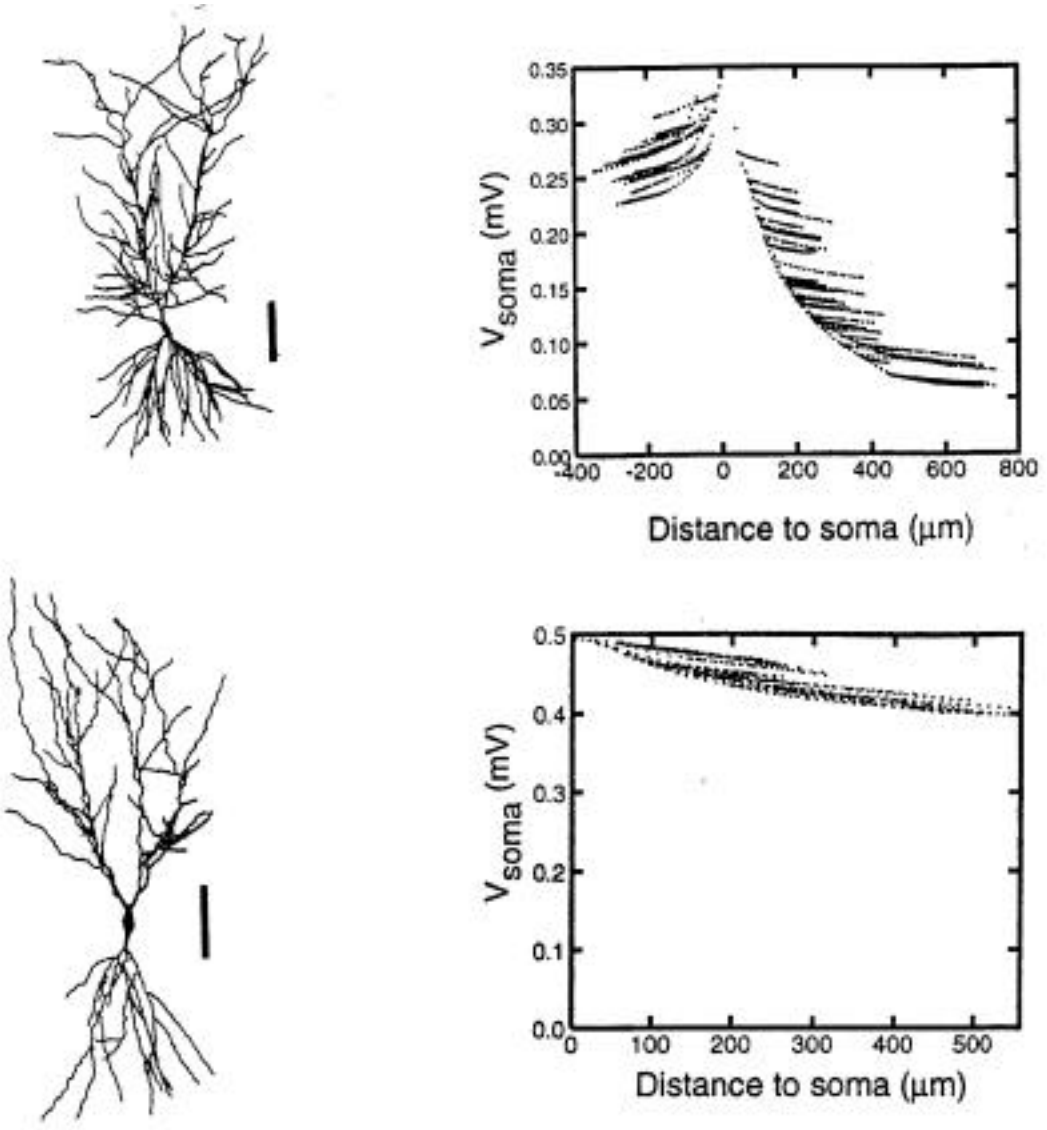

Figure 5-13. Position dependence and passive normalization. The efficiency of synapses placed at different points in the dendritic trees of CA1 pyramidal cells (top) and CA3 pyramidal cells (bottom) are shown. The anatomy of the two cells used to construct multicompartmental models is shown on the left. The plots on the right show the amplitudes of EPSPs recorded at the soma in the two types of cells plotted as functions of the distances of the synapses form the soma. Notice that the CA1 pyramidal cell shows a strong position dependence for synapses while the CA3 pyramidal cell shows a greater degress of passive normalization.

position. This independence of PSP amplitude on position can be called *passive normalization*. Whether the amplitudes of soma PSPs show position

dependence or passive normalization depends upon the geometry of the cell. Neurons, like CA1 or neocortical pyramidal cells, that have a long, relatively untapered aprical dendrite are well approximated as cables and show position dependence. However, neurons whose dendritic trees do not approximate cables and whose individual dendrites vary in diameter tend to show passive normalization.

One of the factors contributing to normalization is the local input resistance of the dendrites. Small diameter dendrites have relatively large input resistances (because input resistance inversely proportional to diameter). A given synaptic current, thus, produces a relatively large amplitude PSP as recorded at the dendrite. The amplitude of the PSP decreases along the length of the dendrite due to electrotonic filtering. However, the variation in the amplitude of the PSPs at their sites of origin tends to off set the effects of electrotonic filtering. The functional consequence of passive normalization is that synapses distributed over the surface of the neuron can have approximately the same probability of generating an action potential at the soma.