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Chapter 12

Principles of Dendritic Integration

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Summary

The primary role of neurons is to integrate incoming information conveyed by synaptic input and convert it into an output, usually in the form of action potentials. This process is called synaptic integration. As the vast majority of synaptic input to neurons is made onto their dendrites, the morphology and membrane properties of dendrites play a critical role of this input-output transformation. In this chapter we discuss where action potentials are generated in neurons, as well as the various factors affecting how dendrites integrate synaptic potentials, highlighting the key role of dendritic excitability.

Introduction

Dendrites, as illustrated in previous chapters, are morphologically elaborate structures receiving thousands of presynaptic inputs. A quick glance at the morphology of various neurons (see Preface Figure 1) reveals their dramatic structural differences and hints at their functional

specialization. Indeed, the functional heterogeneity suggested by morphology is borne out by experimental analysis of different cell types. Functionally, dendrites are remarkably complex, with a wide variety of neurotransmitter receptors and voltage-activated channels distributed uniquely in different types of neurons. But what impact do these different properties have on dendritic function? And how is dendritic function enriched by the different distributions and properties of synapses and channels found in the dendrites? With the development of dendritic patch-clamp and imaging methods, significant progress toward answering these questions has been realized in recent years. Here we review various aspects of dendritic function, including principles that appear to hold for the majority of neurons studied, as well as examples of functional specialization in the dendrites of neurons in the mammalian CNS.

The action potential is the final output signal of most neurons

Most neurons communicate via action potentials – brief, all-or-none reversals of membrane potential polarity mediated by the opening of voltage-gated Na^+ (Na_v) and K^+ (K_v) channels. Though considerable debate exists regarding the details of information processing in neurons (Shadlen and Newsome 1994; Ferster and Spruston 1995; Shadlen and Newsome 1995; Softky 1995), the prevailing view is that in most neurons action potentials are used to produce a kind of digital code, with the state of the nervous system dictated by the rate and timing of action potentials across multiple, interconnected neural networks in the brain¹.

Most cells fire action potentials only when synaptic excitation sufficiently exceeds inhibition², allowing depolarization beyond the firing threshold. The simplest view of synaptic

¹ Some axons may also use a hybrid digital-analog code, in which synaptic potentials modulate action-potential mediated neurotransmitter release from the axon (Alle and Geiger 2006; Shu *et al.* 2006).

² There are some exceptions to this. Some neurons, like Purkinje cells in the cerebellum and dopaminergic cells in the substantia nigra, fire action potentials spontaneously, even when deprived of all synaptic inputs (Häusser *et al.* 2004). In such neurons, action potential firing is modulated primarily by inhibition, which reduces the firing rate and may synchronize firing across multiple neurons (Yung *et al.* 1991; Gao *et al.* 1996; Häusser and Clark 1997).

integration is that excitatory inputs sum, and if the resulting depolarization is large enough to reach threshold, an action potential is generated. In this simple model, inhibition opposes this depolarization, thus increasing the number of active excitatory inputs required to reach threshold. While this represents a vast over-simplification of how neurons integrate synaptic information, it serves as a useful starting point.

To influence action potential initiation, postsynaptic potentials (PSPs), both excitatory (EPSPs) and inhibitory (IPSPs), must spread from their site of generation to the action potential initiation zone. This propagation of synaptic potentials is affected by dendritic morphology and the passive cable properties of dendrites, as well as the voltage-gated conductances they contain. Furthermore, even in passive dendrites, excitatory and inhibitory potentials can sum nonlinearly, in a manner determined by their spatial and temporal relationship. Finally, the process of synaptic integration is influenced by ongoing action potential firing, which can shunt synaptic potentials and change the availability of voltage-gated conductances. All of these factors influence synaptic integration in complicated ways.

Action potentials are initiated in the axon

A central issue related to synaptic integration is to determine the final site of action potential initiation. Experiments dating back to the 1950's have addressed this question. Early microelectrode recordings from spinal motoneurons revealed that action potentials consisted of two components: an "initial segment spike" (IS spike) and a "somato-dendritic spike" (SD spike). The IS spike always preceded the SD spike, could be evoked in isolation by antidromic stimulation of the axon, and had a lower threshold than the SD spike (Coombs *et al.* 1957; Fatt 1957; Fuortes *et al.* 1957). These data were interpreted to suggest that the action potential begins

Other neurons, such as those in the supraoptic nucleus (Bourque and Renaud 1984), fire spontaneously in rhythmic bursts of action potentials. In these neurons, synaptic inputs can modulate the timing of these rhythmic oscillations.

as a low-threshold IS spike in the axon³, which subsequently triggers the SD spike in the soma and dendrites. This interpretation was later supported by simultaneous intracellular recording from the soma and dendrites of motoneurons *in vivo* (Terzuolo and Araki 1961).

In the years that followed these early experiments on motoneurons, a battery of experiments was performed on other types of neurons. Though some studies offered evidence that spikes can be generated in dendrites (see “Spikes can be generated in dendrites” below), a large body of evidence suggested that all-or-none action potentials are initiated in the axon of most neurons. Field potential recordings in the hippocampus indicated that action potentials were earliest and largest in the somatic and axonal fields (Jefferys 1979; Miyakawa and Kato 1986; Richardson *et al.* 1987), and comparison of somatic and dendritic microelectrode recordings suggested that the fast spikes mediated by Na_v channels are generated in the axons of hippocampal and neocortical pyramidal neurons and cerebellar Purkinje cells (Llinas and Sugimori 1980a; Benardo *et al.* 1982; Amitai *et al.* 1993).

Theoretical studies suggest that the threshold for action potential initiation may be lowest in the axon because of a 20-1000 fold higher density of Na_v channels in the axon relative to that found in the soma and dendrites (Dodge and Cooley 1973; Moore *et al.* 1983; Mainen *et al.* 1995; Rapp *et al.* 1996). Despite early experimental support for a high density of Na_v channels in axons (Conti *et al.* 1976; Sigworth 1980; Neumcke and Stämpfli 1982; Wollner and Catterall 1986), initial experimental estimates of Na_v channel density in the axon initial segment (AIS) using patch-clamp recording indicated it was similar to the soma in neocortical and hippocampal pyramidal neurons (Colbert and Johnston 1996; Colbert and Pan 2002). More recent work has challenged these earlier observations, and argues that the Na_v channel density in the AIS of

³ The IS spike was ascribed to the axon initial segment on the basis of its specialized structural features and proximity to the soma. It is worth noting, however, that these early studies provided no direct evidence against the possibility that the IS spike could be preceded by a spike in a more distal region of the axon, such as the first node of Ranvier.

neocortical pyramidal neurons is ~40 times that found at the soma, but is difficult to measure accurately using cell-attached or out-side out patch-clamp recording due to tight coupling of Na_v channels to the cytoskeleton (Kole *et al.* 2008). Work by others in a range of neuronal cell types has confirmed that the density of Na_v channels in the AIS is significantly higher than at the soma (Hu *et al.* 2009; Hu and Jonas 2014), although the magnitude of this difference is a matter of debate and likely to vary across different neuronal types (Schmidt-Hieber *et al.* 2008; Fleidervish *et al.* 2010). In addition to a higher Na_v channel density, other factors also contribute to a low-threshold for action potential initiation in the axon, including the low capacitance of small-diameter axons (Moore *et al.* 1983; Mainen *et al.* 1995; Baranauskas *et al.* 2013) and the hyperpolarized activation and inactivation voltage dependence of axonal Na_v channels compared to somatic Na_v channels (Rapp *et al.* 1996; Colbert and Pan 2002; Kole *et al.* 2008).

The most direct evidence that action potentials are generated in the axon comes from simultaneous somatic and axonal patch-pipette recordings, as well as optical imaging using voltage-sensitive dyes, which have demonstrated that the action potential occurs first in the axon and later in the soma in a number of neuronal types (Stuart and Häusser 1994; Stuart and Sakmann 1994; Colbert and Johnston 1996; Stuart *et al.* 1997a; Clark *et al.* 2005; Palmer and Stuart 2006; Kole *et al.* 2007; Shu *et al.* 2007; Schmidt-Hieber *et al.* 2008; Palmer *et al.* 2010; Hu and Jonas 2014), directly confirming axonal initiation of the action potential (Fig. 12.1A-C). Dopaminergic cells in the substantia nigra provide a particularly interesting demonstration of the axonal site of action potential initiation. In about half of these cells, the action potential occurs first at the dendritic recording site during double somatic-dendritic recording; in those cases, however, staining of the cells revealed that the axon emerged from a dendrite near the dendritic recording electrode, again indicating an axonal site of action potential initiation (Fig. 12.1D) (Häusser *et al.* 1995). Recent work in CA1 pyramidal cells has provided another example of this phenomenon, with a significant fraction of pyramidal neurons exhibiting an axon emerging from a dendrite (Thome *et al.* 2014).

Where exactly in the axon does the action potential initiate? In hippocampal neurons and Purkinje neurons, experiments using either local applications of TTX or cell-attached recordings initially suggested that the action potential is generated at the first node of Ranvier (Colbert and Johnston 1996). However, in neocortical layer 5 pyramidal neurons a variety of methods provide evidence that action potentials are initiated in the axon initial segment (Palmer and Stuart 2006; Kole *et al.* 2007; Shu *et al.* 2007). A range of more recent experiments in other neuronal cells types, including Purkinje cells, also indicate that the most likely site of action potential initiation is in the axon initial segment (Khaliq and Raman 2006; Schmidt-Hieber *et al.* 2008; Foust *et al.* 2010; Palmer *et al.* 2010; Hu and Jonas 2014).

In summary, the strong evidence in favor of the axon as the final site of action potential initiation, combined with the fact that the axon usually emerges from the soma, has had a powerful influence on the field of synaptic integration. From this perspective, it follows that the way neurons integrate their synaptic inputs should usually be analyzed from a somatocentric point of view (Häusser *et al.* 1995; Thome *et al.* 2014). This view is adopted as the default perspective for much of this chapter, while the role of active dendritic spikes is considered later⁴.

Summation and propagation of PSPs depend on dendritic cable properties

The resting potential (V_{rest}) of most neurons is more hyperpolarized than action potential threshold. Furthermore, unitary PSPs (mediated by one or more contacts between a single presynaptic axon and a postsynaptic dendrite) are usually too small to bridge the gap between the resting potential and action potential threshold. Multiple synaptic inputs must therefore sum to

⁴ The somato-centric view of synaptic integration, while well justified for most mammalian neurons, is not appropriate for most invertebrate neurons, because the soma is often electrotonically remote from both the dendrites and the axon.

produce action potential firing in most neurons⁵. This section considers the passive electrical structure of dendrites, and their effects on the integration of PSPs. Later we consider how dendritic voltage-activated channels further enrich synaptic integration.

Passive electrical properties of dendrites influence synaptic integration

As discussed above, action potentials are initiated in the axon of most neurons, which usually emerges from the soma. The ability of synaptic inputs to influence action potential generation therefore depends on their initial amplitude and the degree to which they attenuate as they propagate from the dendrites toward the soma and axon. Here, we summarize experimental data on the passive electrical structure of neurons, and illustrate, with examples, how synaptic integration is affected by these properties, the morphology of the cell, the location of a synapse, and the time course of the synaptic current.

Three passive electrical properties contribute to electrotonic structure of the dendritic tree: the specific membrane resistivity (R_m), the specific membrane capacitance (C_m), and the intracellular resistivity (R_i). High values of R_i and low values of R_m increase the attenuation of synaptic potentials as they propagate passively in dendrites. Attenuation is also greater for brief PSPs compared to more sustained changes in membrane potential (V_m) (Rall 1967; Jack *et al.* 1983; Spruston *et al.* 1994); this arises as a result of the membrane capacitance, which serves to filter transient changes in V_m . All of these effects are more pronounced for synapses that are located further from the site of action potential initiation.

Figure 12.2 illustrates the effects of R_m , R_i , and synapse location on synaptic integration. Panels A-C show the responses of a generic pyramidal neuron model to synaptic input in three

⁵ Exceptions to this include, for example, the spherical bushy cells of the ventral cochlear nucleus (Liberman 1991), neurons in the magnocellular nucleus of the trapezoid body (Borst *et al.* 1995), and ciliary ganglion neurons (Landmesser and Pilar 1972). In each of these cases a small number of presynaptic axons form a large, calyceal synapse capable of firing the postsynaptic neuron. Another exception is the climbing fiber input to the Purkinje cell, where a single presynaptic fiber reliably generates a stereotyped burst of spikes in the postsynaptic neuron (Llinas and Sugimori 1980a).

different locations. In the control case (Fig. 12.2, center column), moving the synapse from the soma (Fig. 12.2A, center) to a proximal dendrite (Fig. 12.2B, center) results in a smaller somatic EPSP because some of the synaptic charge deposited onto the dendrite capacitance is lost through the membrane resistance as it propagates toward the soma. This results in a nearly two-fold attenuation of the EPSP propagating from the dendrite to the soma in this example. Moving the synapse further out on the dendrite (Fig. 12.2C, center) increases the amplitude of the local synaptic potential in the dendrites, due to the higher input impedance and smaller local capacitance at this dendritic location compared to the soma, but it dramatically increases the dendro-somatic EPSP attenuation (nearly ten-fold attenuation). The result is a net reduction of the somatic EPSP amplitude by a factor of three compared to the somatic input shown in Figure 12.2A (center).

Reducing R_m by an order of magnitude has only a modest effect on the amplitude of the local synaptic potential, but has a much bigger effect on the amplitude of the somatic EPSP generated by dendritic synapses (Fig. 12.2, left column). For the most distal synaptic input, the EPSP attenuation (synapse to soma) for the low R_m value is almost 100 fold (Fig. 12.2C, left), resulting in a somatic EPSP about twenty times smaller than for the same synapse located at the soma. Such large values of dendro-somatic EPSP attenuation have been suggested from dendritic recordings and modeling of cortical and hippocampal pyramidal neurons, where the conductances open at the resting membrane potential has been shown to result in a leaky apical dendrite (Cauller and Connors 1992; Stuart and Spruston 1998; Golding *et al.* 2005; Krueppel *et al.* 2011). Direct measurement using simultaneous dendritic and somatic patch-clamp recordings has demonstrated EPSP attenuation of more than 40-fold from the dendrites to the soma of neocortical layer 5 pyramidal neurons (Williams and Stuart 2002; Nevian *et al.* 2007; Larkum *et al.* 2009). This remains an underestimate of the maximum EPSP attenuation, as direct recording from the smallest, most distal dendrites is not technically feasible.

The effect of reducing R_i by a factor of two is shown in the right column of Figure 12.2. For both dendritic synapse locations (Figs. 12.2B,C), this change in R_i results in a reduction of the

amplitude of the local dendritic EPSP that is greater than that produced by the ten-fold reduction in R_m . This relatively strong effect of R_i occurs because the voltage change during a brief synaptic current results from charging the membrane capacitance; reductions in R_i increase the radial flow of current away from the synapse, thus reducing the amount of charge deposited on the local capacitance. Because of this increase in radial current flow along the dendrite, however, the attenuation of the EPSP is reduced. The net effect of a change in R_i therefore is determined by the morphology- and location-dependent effects on local EPSP amplitude and dendro-somatic EPSP attenuation. For the intermediate synapse position shown in Figure 12.2B, these effects are about equal, so the change in R_i has only a small effect on the somatic EPSP amplitude. For the more distal synapse shown in Figure 12.2C, lowering R_i results in a decrease in the local EPSP amplitude but an increase in the amplitude of the somatic EPSP, due to reduced EPSP attenuation.

Experimental estimates of passive electrical properties

C_m has been widely regarded as a biological constant with a value of approximately $1 \mu\text{F}/\text{cm}^2$. Experimental analysis has provided confirmation of this value for a variety of neurons (Gentet *et al.* 2000). R_m has been measured for a large number of cell types, revealing a wide range of values for different neurons (see below). R_i in mammalian neurons has been estimated using a variety of methods, yielding values ranging from 70-500 Ωcm (Coombs *et al.* 1959; Rall 1959; Lux *et al.* 1970; Barrett and Crill 1974; Cauller and Connors 1992; Fromherz and Müller 1994; Major *et al.* 1994; Rapp *et al.* 1994; Thurbon *et al.* 1994; Bekkers and Stevens 1996; Meyer *et al.* 1997; Thurbon *et al.* 1998). Simultaneous somatic and dendritic patch-pipette recordings have been used to determine voltage attenuation along the apical dendrites of layer 5 pyramidal neurons (Stuart and Spruston 1998), CA1 pyramidal neurons (Golding *et al.* 2005), and the primary dendrites of cerebellar Purkinje neurons (Roth and Häusser 2001). Modeling of these data has indicated a value for R_i of 70-220 Ωcm . These experiments provide the most reliable available estimates of R_i , as the filtering of transient voltage changes by the dendrites, on

which these estimates are based, is very sensitive to R_i . Nevertheless, the range of estimates of R_i using this method remains large and it is unclear whether this represents true cell-to-cell variability in this property. In addition, the possibility that R_i might vary in different dendritic domains of the same cell should not be ruled out.

A particularly critical factor affecting PSP summation is the membrane time constant (τ_m), which is given by the product of R_m and C_m . For any change in membrane potential, the slowest component of voltage decay is determined by τ_m . Thus, τ_m defines the time window over which synaptic potentials can sum; for presynaptic inputs separated by more than two to three τ_m , temporal summation becomes diminishingly small.

The membrane time constant can be estimated directly from the slowest exponential component in a multi-exponential fit of the voltage relaxation following current injection. τ_m has now been estimated for several cell types, revealing a tremendous range in the resting membrane properties of different types of neurons. Given that C_m is likely to be a biological constant, variations in τ_m presumably reflect variation in R_m due to differences in the types and densities of ion channels open in the membrane at the resting potential. Hippocampal CA3 pyramidal neurons have among the slowest τ_m values measured – about 70 ms in brain slices at physiological temperatures (Spruston and Johnston 1992). Even within the hippocampus, τ_m for other cell types differs from this value; in CA1 pyramidal neurons, τ_m is less than half this value – about 30 ms in slices (Spruston and Johnston 1992). The fastest τ_m values recorded so far are from octopus cells in the ventral cochlear nucleus (Golding *et al.* 1999a). Patch-pipette recordings from these cells in slices reveal τ_m values of about 0.2 ms. Based on τ_m alone, it can be inferred that in principle CA3 pyramidal neurons will be able to integrate synaptic inputs over a time window about 350-fold longer than in cochlear octopus cells. Differences such as these are certain to be functionally important. For example, cochlear octopus cells *in vivo* phase lock their firing to sound tones of up to 1 kHz (Smith *et al.* 1993). This kind of precise temporal coding would be difficult or impossible to achieve in a neuron with a long membrane time constant.

Resting membrane properties

Theoretically, τ_m is a purely passive measure, determined only by the membrane capacitance and voltage-independent leak conductances of a neuron. In cells where this assumption has been tested, however, it has proven to be an oversimplification, as measured values of τ_m are voltage dependent and influenced by blockers of voltage-dependent conductances. For example, block of hyperpolarization-activated conductance (I_h) and inward-rectifying K^+ channels (with CsCl) results in an approximately 50% increase in the apparent τ_m in CA3 and CA1 pyramidal neurons (Spruston and Johnston 1992), a two-fold increase in τ_m in neocortical pyramidal neurons (Stuart and Spruston 1998), and a twenty fold increase in τ_m in cochlear octopus cells (Golding *et al.* 1999a). Similarly, even small changes in V_m near V_{rest} have been shown to significantly affect estimates of τ_m and input resistance (R_N) (for example: Spruston and Johnston 1992; Waters and Helmchen 2006). These findings suggest that the so-called “passive” membrane properties of most neurons might be more aptly referred to as “resting” membrane properties, since they are actually determined in large part by voltage-dependent channels that are open at V_{rest} . The situation is further complicated by the fact that the resting membrane properties of many neurons are unlikely to be uniform. Experimental evidence indicates that many conductances are distributed non-uniformly along dendrites. In neocortical and hippocampal pyramidal neurons, conductances that are open at the resting potential, including I_h and others, are present at higher densities in the distal regions of the apical dendrite (Magee 1998; Stuart and Spruston 1998; Williams and Stuart 2000b; Berger *et al.* 2001; Lörincz *et al.* 2002). The net effect of the additional leak in the distal apical dendrites is to increase the electrical isolation of distal synapses (Stuart and Spruston 1998; Golding *et al.* 2005).

Synaptic conductances that are on at rest will also lower the effective τ_m by lowering the effective R_m (Bernander *et al.* 1991; Rapp *et al.* 1992; Rudolph and Destexhe 2003). In many brain areas, such as the cerebellar cortex, neurons providing the synaptic input are spontaneously active, thus generating a tonic synaptic conductance that significantly shortens the effective τ_m (Häusser and Clark 1997). The same is also true in the neocortex, where a reduction of ongoing

synaptic activity by local application of TTX has been shown to increase τ_m and input resistance (R_N) substantially, suggesting that synaptic activity reduces both R_N and τ_m (Paré *et al.* 1998; Destexhe and Paré 1999). Other work indicates that synaptic activity associated with active network states produces only small changes in R_N and τ_m , in part due to voltage-gated channels, which serve to oppose the decrease in R_m introduced by synaptic activity (Waters and Helmchen 2006). Earlier estimates of larger changes in τ_m and R_N may also be influenced by higher firing rates, as action potentials can shunt PSPs (Häusser *et al.* 2001). Thus, the effects of background synaptic activity on the effective R_N and τ_m , and hence the time window for temporal summation, depends on the rate, number, and conductance of activated synapses, as well as active responses produced by synaptic input.

Spatial and temporal integration

R_m , C_m and R_i are not the only factors that influence summation of synaptic potentials and their propagation to the action potential initiation zone. The structure of the dendritic tree and the position of synapses on dendrites influence synaptic summation in many ways. To illustrate this, Figure 12.3A shows a simulation of two synapses on a simple isopotential neuron with no dendritic tree. In this system individual EPSPs decay according to τ_m , and summation is dependent on the timing of the two inputs relative to the membrane time constant. In the simulation shown in Figure 12.3A, τ_m is 20 ms, and the EPSPs sum to a peak depolarization 1.37 times the individual EPSP amplitude when the two inputs are separated by 20 ms. The dashed line shows the subtraction of the first response alone from the paired response. Note that the peak of this subtracted EPSP is slightly smaller than that of the first EPSP (Fig. 12.3A). This occurs because the depolarization associated with the first EPSP produces a slight reduction in driving force for the synaptic current when the second input is activated. Next consider two synapses on a similar soma, but with the addition of apical and basal dendrites (Fig. 12.3B). The synaptic conductances have been scaled up so that the peak of the first EPSP at the soma is the same as in the cell with no dendrites (6 mV in both cases). Note, however, that the EPSPs now rise and

decay more quickly, so less summation occurs (Fig. 12.3B; 1.27 times the single EPSP; i.e., less summation than the simulation with no dendrites). This is because only the *final* decay of the EPSP is determined by τ_m ; the early decay of the EPSP is accelerated in this case due to redistribution of charge into the dendrites (see Chapter 15; Rall 1967; Koch *et al.* 1996; Geiger *et al.* 1997; Häusser and Clark 1997). Now consider moving the synapses from the soma to the apical dendrite (Fig. 12.3C). Again the synaptic conductances have been increased in amplitude so that each input produces a 6 mV EPSP at the soma. The time course of these EPSPs at the soma is slowed, due to the filtering properties of the dendritic membrane between the synapse and the soma (Fig. 12.3C; dashed lines are the simulation from B, for comparison). As a result, more temporal summation occurs (Fig. 12.3C; 1.40 times the single EPSP). Finally, consider the effect of moving the two synapses to different dendrites. In this case, summation at the soma is maximized (Fig. 12.3D; 1.55 times the single EPSP). This occurs for two reasons: first, the decay of the first EPSP (apical synapse) is slowed because of its greater electrotonic distance from the soma; second, the effect of the first EPSP on the driving force of the second synapse is small, because of the greater electrotonic separation of the two synapses. These simulations illustrate three important points regarding summation in passive neurons: (1) the presence of dendrites accelerates the EPSP decay near the synapse, (2) cable filtering of dendritic EPSPs slows their time course as measured at the soma, thus increasing temporal summation at the soma, and (3) sublinear summation is expected for synapses located electrotonically close together, but is minimal for electrotonically distant inputs⁶.

Normalization of temporal summation

An intriguing possibility is that non-uniform channel distributions may equalize temporal summation along the length of the dendrite. As illustrated in Figure 12.3, uniform passive membrane properties predict that distal inputs will summate to a greater extent in the soma

⁶ An elegant example of this is found in the medial superior olive (MSO). In this auditory nucleus, binaural processing is optimized by inputs from each side of the brain contacting separate dendrites of MSO neurons in order to minimize nonlinear summation of signals arriving from each ear (Agmon-Snir *et al.* 1998).

because they are broader there than more proximally generated EPSPs. An increased density of I_h in the apical dendrite may compensate for this location specific dependence of temporal summation (Magee 1999; Williams and Stuart 2000b; Berger *et al.* 2001; Williams and Stuart 2003b; Day *et al.* 2005). However, I_h is capable of normalizing temporal summation even in neurons that lack a strong somato-dendritic I_h gradient (Bullis *et al.* 2006; Angelo *et al.* 2007). Other voltage-gated conductances, including various subtypes of dendritic K_v channels, have also been suggested as contributing to the location independence of temporal summation over a broad range of frequencies (Desjardins *et al.* 2003; Williams and Stuart 2003b). Accordingly, modulation of these conductances can influence the extent to which temporal summation is normalized for dendritic location (Takigawa and Alzheimer 2003; Chen and Johnston 2005; Day *et al.* 2005).

Excitation-inhibition interactions in dendrites

Inhibition is another central factor limiting the way excitatory synaptic inputs summate in space and time during synaptic integration. Inhibitory inputs do not simply counter the depolarizing effects of excitation; they are also critical determinants of spike timing. Inhibition can synchronize spiking in a population of neurons, as cells receiving common inhibitory input can stop spiking and subsequently return to threshold at the same time (Cobb *et al.* 1995). Inhibition also influences spike timing by limiting the time window for temporal summation of excitatory inputs. Many neural circuits include feed-forward inhibition, which can limit the duration of excitatory inputs to less than a few milliseconds, thus requiring temporally coincident excitatory inputs to trigger action potential firing (Pouille and Scanziani 2001; Mittmann *et al.* 2005). Similarly, feedback inhibition does not prevent spiking at the onset of an excitatory stimulus, but can limit the duration of spiking in response to a sustained excitatory stimulus. In the hippocampus, different types of inhibitory interneurons provide feedback inhibition to different dendritic domains with different temporal dynamics (Müller and Remy 2013). The functional implications of this differential dendritic targeting are not understood, but these

processes influence dendritic computation in many brain regions, thus highlighting the need to further explore how dendrites influence the integration of excitatory and inhibitory synaptic inputs.

The principles governing dendritic integration of EPSPs apply similarly to IPSPs. The time course of an IPSP at the soma is slowed if the inhibitory synapse is located on the dendrites. In addition, depolarization induced by EPSPs, or hyperpolarization by other IPSPs, will affect the driving force for the inhibitory synaptic current more for synapses that are located close together. The latter point is particularly important for IPSPs, as the reversal potential at many inhibitory synapses is close to the resting membrane potential (most notably GABA_A and glycinergic synapses, which activate Cl⁻ channels). Hence, very small changes in V_m can have relatively large effects on the inhibitory synaptic current. This effect of inhibition can be considerable, even when IPSPs generate no change in membrane potential on their own. Figure 12.4A shows the result of activating two excitatory synapses on the soma, either with (solid line) or without (broken line) prior activation of an inhibitory synapse. In these simulations, inhibition is simulated with a reversal potential equal to the resting potential, and hence alone it generates no change in membrane potential. Nevertheless, inhibition results in a 35% reduction of the first EPSP, and about a 13% reduction of the second EPSP (Fig. 12.4A). The relative ineffectiveness of the inhibition on the second EPSP occurs because the inhibitory synaptic conductance is largely over by the time the second EPSP arrives. This result demonstrates that inhibition is most effective during the inhibitory synaptic conductance change itself. The special case where inhibition occurs without a change in membrane potential is a good illustration of the concept of “shunting inhibition,” which describes the ability of inhibition to be effective even when it produces little or no change in membrane potential on its own, because the effect of the inhibitory conductance change is similar to a transient reduction in R_m , which “shunts” the EPSP without an obvious change in membrane potential. Shunting occurs because the depolarization associated with the EPSP increases the driving force for outward current at the inhibitory synapse (Fig. 12.4A, bottom trace).

The ability of an inhibitory synapse to shunt current from excitatory synapses depends on the spatial arrangement of the two inputs (Fig. 12.4B-D). Inhibition placed at the soma has a similar effect on EPSPs arriving from all dendritic locations, whereas inhibition located on particular dendrites can be specific for particular inputs. Figure 12.4B illustrates that somatic inhibition reduces EPSPs originating on different dendrites to similar extents. In fact, somatic inhibition in this case has a slightly more pronounced effect for dendritic excitation than somatic excitation (compare Figs. 12.4A,B). When the inhibitory synapse is moved onto a dendrite, the EPSP generated on the same dendrite is preferentially inhibited, leaving the peak of the other EPSP relatively unaffected (Fig. 12.4C). In passive neurons, or when dendritic non-linearities are not engaged, dendritic inhibition is most effective at limiting somatic EPSPs if the inhibitory synapse is located “on path” between the excitatory synapse and the soma. “Off path” inhibition is only effective if both the excitatory and inhibitory synapses are located near the end of a dendrite; in this case “off path” can be almost as effective as the “on path” inhibition (Fig. 12.4D; this effect is also illustrated nicely in figure 7.36 of Jack *et al.* 1983). As shown in Figure 12.4D, however, distal dendritic inhibition is only effective for excitatory synapses on the same dendritic branch as the inhibitory synapses, and relatively ineffective if located on a different branch.

The location-dependent effects of dendritic inhibition have been explored systematically in a model of a CA1 pyramidal neuron (Hao *et al.* 2009). This work revealed that inhibition on the apical trunk most effectively shunted (reduced) EPSPs generated at the same dendritic location or more distally; inhibition of the apical dendritic trunk was progressively less effective for excitatory synapses located at increasingly proximal dendritic locations. Furthermore, the effect of dendritic inhibition on apical oblique branches was largely restricted to excitatory synapses on the same branch, with the same location-dependent rules described above for the apical trunk (Hao *et al.* 2009).

An interesting example where distal dendritic inhibition may be important has been noted in the CA1 region, where inhibitory interneurons with somata in stratum oriens extend axons to stratum lacunosum-moleculare (thus named O-LM cells) and impinge on the most distal

dendrites of CA1 pyramidal neurons (Sik *et al.* 1995). With this arrangement, inhibition could selectively limit the depolarization from the perforant path, which has excitatory synapses on the distal dendrites of CA1 cells. A similar arrangement exists in neocortical pyramidal neurons, where the apical tuft is selectively inhibited by Martinotti cells (Silberberg and Markram 2007). The effects of O-LM and Martinotti cells is complicated, however, by the fact that they may also inhibit other interneuron subtypes, leading to disinhibition (Leao *et al.* 2012; Müller and Remy 2013; Pfeffer *et al.* 2013).

The effects of inhibition discussed above provide the basis for understanding the integration of excitatory and inhibitory synaptic inputs in passive dendritic trees or in the subthreshold regime of active dendrites. However, as discussed below and in Chapter 15, the situation is quite different when one considers the effects of inhibition on the initiation and propagation of spikes in active dendrites.

Compensating for dendritic attenuation

The elaborate interactions that occur between excitatory and inhibitory synapses in the dendritic tree indicate that the process of synaptic integration is complex. Ultimately, however, synaptic activation must lead to action potential firing in the soma and axon. One prediction of the this somato-centric view of the neuron is that the ability of a synapse to contribute to action potential initiation will be diminished for synapses located further from the soma. As discussed above, synaptic potentials generated in distal dendrites may attenuate over 100-fold by the time they reach the soma⁷, suggesting that such synapses will be less efficacious (in terms of somatic or axonal depolarization) than more proximal synapses. Two important factors mitigate this seemingly extreme disparity between proximal and distal synapses. First, attenuation of synaptic charge is much less than the attenuation of fast synaptic voltage changes. Second, at least some synapses may scale their conductance to compensate for dendritic distance.

⁷ The long electrotonic location of most synapses from the soma in many neurons also contributes to serious errors associated with the estimation of synaptic conductances and kinetics using somatic voltage clamp (Spruston *et al.* 1993; Williams and Mitchell 2008).

EPSP attenuation and temporal filtering depends not only on the distance of the synapse from the soma, but also on the EPSP time course, with faster EPSPs attenuated and filtered more than slower EPSPs. By contrast, attenuation of synaptic charge depends only on distance from the soma and not on the time course of the charge entry at the synapse (Jack *et al.* 1983). In addition, the same factors that increase voltage attenuation along small-diameter dendrites (high axial resistance and input impedance) also increase the magnitude of the local synaptic potential (Rall and Rinzel 1973; Rinzel and Rall 1974). This was illustrated in Figure 12.2 (center column), as moving the synapse further from the soma reduced the somatic EPSP, but also increased the local EPSP at the synapse. This increase in local EPSP, which is dependent on dendritic morphology (Jaffe and Carnevale 1999), can result in a significant reduction of the driving force for synaptic charge entry and thereby further decrease somatic EPSP amplitude. On the other hand, it can also result in increased current through NMDA receptors, as a result of greater relief of voltage-dependent Mg^{2+} block particularly at the ends of small diameter dendrites where input impedance is high (Branco and Hausser 2011). Similar effects can be seen in dendritic spines due to the spine neck resistance (Gulledge *et al.* 2012; Harnett *et al.* 2012), which can reduce the location dependence of EPSP amplitude at the site of synaptic input (Gulledge *et al.* 2012).

Some synapses may also compensate for dendritic distance by scaling synaptic conductance. In CA1 pyramidal neurons, the Schaffer collateral inputs from CA3 are distributed over about two-thirds (several hundred microns) of the apical dendritic tree, but the average amplitude of somatically recorded EPSPs from these inputs does not vary with the distance of the activated synapses from the soma (Magee and Cook 2000). This “synaptic scaling” appears to be mediated by a population of synapses with higher AMPA receptor density at greater distances from the soma (Andrasfalvy and Magee 2001; Andrasfalvy *et al.* 2003; Smith *et al.* 2003). This distance-dependent increase of AMPA receptors does not continue into the apical tuft dendrites; however, the NMDA/AMPA receptor ratio is higher in tuft dendrites than in more proximal apical dendrites, suggesting another mechanism by which synaptic efficacy could be scaled in a distance-dependent manner (Bittner *et al.* 2012). In the basal dendrites of CA1 pyramidal

neurons, using immune-EM to compare the largest population of synapses at distal and proximal locations, the distal synapses had more AMPA receptors but fewer NMDA receptors (Menon *et al.* 2013).

Morphological and immunocytochemical analysis of synapses on spines in CA1 apical dendrites suggests that the largest synapses in CA1 correspond to “perforated” synapses, which have large, perforated postsynaptic densities and high AMPA receptor densities; these presumably powerful synapses are most abundant in the distal apical dendritic region innervated by Schaffer collaterals. This form of scaling does not appear to extend to the most distal apical dendrites, nor does it apply in the basal dendrites (Nicholson *et al.* 2006; Menon *et al.* 2013). Furthermore, synaptic scaling has not been observed in neocortical layer 5 pyramidal neurons (Williams and Stuart 2002; Nevian *et al.* 2007), suggesting that additional mechanisms must exist to allow distal dendritic synapses to contribute to somatic/axonal action potential generation (Williams and Stuart 2003a). Collectively, these results suggest that a variety of mechanisms may be used to regulate the distance-dependent effects of synaptic strength, and that these mechanisms may be differentially employed in different dendritic domains or in different cell types. These effects are further influenced by the effects of voltage-gated channels on synaptic integration, which may also be distance-dependent.

Dendritic voltage-gated channels contribute to synaptic integration

Although some evidence supports the view that synaptic potentials are summated linearly or slightly sublinearly (Burke 1967; Cash and Yuste 1999; London and Hausser 2005; Jia *et al.* 2010; Zhao *et al.* 2012; Longordo *et al.* 2013), dendrites are clearly not passive. Though theoretical analysis of the electrical properties of dendrites originally focused largely on passive cable properties⁸, the importance of active dendrites was considered extensively, and modeled as

⁸ The focus of dendritic cable theory on passive behavior was partially based on the fact that passive systems are more easily treated analytically, whereas simulation of active properties such as Hodgkin-Huxley Na⁺ and K⁺ channels requires numerical approaches. Numerical methods for simulating nonlinear conductances in complex dendritic geometries using compartmental models were introduced later by Rall (1964).

early as the late 1960s (Rall and Shepherd 1968; Miller *et al.* 1985; Perkel and Perkel 1985; Shepherd *et al.* 1985).

One of the biggest challenges facing neurophysiologists interested in dendritic function is to determine which types of voltage-gated channels are present in dendrites and how they influence the input-output computations that can be accomplished with synapses on dendrites. Two major obstacles stand in the way of tackling this challenge. First, the small size of dendrites makes them relatively difficult to probe experimentally. Even with the advent of methods for obtaining patch-clamp recordings from dendrites, the smallest dendrites are very difficult to patch and dendritic spines have not yet proven to be accessible to recording with electrodes. Advances in our understanding of voltage-gated channels in dendrites will therefore require a combination of approaches including dendritic patch-clamp recording, fluorescent imaging using ion- and voltage-sensitive dyes, immunocytochemical localization of channels, and genetic manipulation of channels to analyze their expression.

The second problem is that different types of neurons have different channel distributions, reflecting their different functional properties within specialized neural networks. There will be no substitute, therefore, for studying many different cell types using similar methodology and experimental design. Furthermore, these properties are likely to change during development, so each cell type will have to be studied at several development stages (i.e., from neonatal to old age), with special consideration paid to key developmental events affecting the system under study (e.g., eye opening for neurons of the visual system).

In addition to tackling these two challenges, an integrated view of each cell type will rely on understanding the interactions between the structure of the dendrites, the types of channels they contain, and the synaptic inputs they receive. Progress on all of these issues is reviewed in the following sections, culminating with a discussion of current answers to the question, “What are the functions of dendritic excitability?”

Spikes can be generated in dendrites

Although action potentials are usually generated preferentially at a low-threshold initiation zone in the axon, there is good evidence that regenerative events (“spikes”) can be generated in dendrites under some conditions. The first evidence for dendritic spike⁹ generation came from field potential recordings in the hippocampus, which indicated an electrogenic response in the apical dendrites of CA1 neurons that preceded the somatic/axonal population spike (Cragg and Hamlyn 1955; Andersen 1960; Fujita and Sakata 1962; Andersen *et al.* 1966; Herreras 1990). Around the same time, Eccles and colleagues reported that spikes could be generated in the dendrites of chromatolyzed motoneurons (Eccles *et al.* 1958) and Spencer and Kandel observed small, spike-like events in intracellular recordings from CA1 neurons *in vivo* (“fast prepotentials”), which they inferred were generated in the dendrites (Spencer and Kandel 1961)¹⁰. Similar events, termed “dendritic spikes”, were observed in recordings from neocortical neurons (Purpura 1967) and cerebellar Purkinje cells (Llinas *et al.* 1968; Llinas *et al.* 1969; Llinas and Nicholson 1971). Later, dendritic recordings from hippocampal and neocortical neurons in slices and *in vivo* supported the view that dendrites are capable of generating regenerative spikes mediated by Na_v and/or Ca_v channels (Wong *et al.* 1979; Turner *et al.* 1993; Schiller *et al.* 1997; Seamans *et al.* 1997; Stuart *et al.* 1997a; Golding and Spruston 1998; Kamondi *et al.* 1998). Early evidence for dendritic spikes has been reviewed elsewhere (Purpura 1967; Stuart *et al.* 1997a; Golding and Spruston 1998; Segev and Rall 1998; Johnston and Narayanan 2008). Here we consider some of the most recent findings.

Simultaneous somatic and dendritic patch-pipette recordings have provided direct demonstration of dendritic spike generation. In both layer 5 and hippocampal pyramidal neurons,

⁹ For convenience, we refer to regenerative events initiated in dendrites as “dendritic spikes.” This offers a semantic way of distinguishing dendritically initiated spikes from the all-or-none action potential initiated in the axon.

¹⁰ Whether these events truly represent dendritic spikes has been a subject of debate (Macvicar and Dudek 1981; Turner *et al.* 1993; Valiante *et al.* 1995; Nedergaard and Hounsgaard 1996; Epsztein *et al.* 2010). Nevertheless, direct evidence now supports the occurrence of dendritic spikes in CA1 neurons (see below).

dendritic spikes have been recorded either in the absence of somatic spikes or preceding them (Fig. 12.5A). In both of these cell types, the incidence of dendritic spikes is promoted by strong synaptic excitation (Wong *et al.* 1979; Schiller *et al.* 1997; Stuart *et al.* 1997a; Golding and Spruston 1998; Golding *et al.* 1999b; Sun *et al.* 2014); see also (Turner *et al.* 1989; Turner *et al.* 1991). Dendritic spikes preceding or uncoupled from somatic action potentials have also been observed in hippocampal CA3 and CA2 pyramidal neurons (Kim *et al.* 2012; Sun *et al.* 2014), neocortical pyramidal neurons in layer 6 (Ledergerber and Larkum 2010), cerebellar Purkinje cells (Rancz and Häusser 2006), hippocampal interneurons (Martina *et al.* 2000), olfactory mitral cells (Chen *et al.* 1997; Chen *et al.* 2002), and retinal ganglion cells (Velte and Masland 1999; Sivyer and Williams 2013).

Dendritically initiated spikes can be generated by activation of Na_v channels, voltage-gated Ca^{2+} (Ca_v) channels, or NMDA receptors, leading to sodium spikes (Fig. 12.5A), calcium spikes (Fig. 12.5A) and NMDA spikes (Fig. 12.5B-D). In Purkinje cells, because there are no Na_v channels or NMDA receptors in the dendrites, dendritic spikes are mediated solely by Ca_v channels, which is consistent with the broad width of these spikes (Llinas and Sugimori 1980a). In pyramidal cells, the situation is more complex, because Na_v , Ca_v , and NMDA receptor channels are all present in the dendrites. In hippocampal CA1 pyramidal neurons, brief dendritic current injections or uncaging of glutamate produces narrow dendritic spikes (width at half amplitude of a few milliseconds) that can be blocked by TTX, indicating that they are mediated primarily by Na_v channels (Golding and Spruston 1998; Gasparini *et al.* 2004; Gasparini and Magee 2006; Losonczy and Magee 2006; Kim *et al.* 2015). Longer current injections or glutamate uncaging produces broader dendritic spikes that are not blocked by TTX, but are sensitive to Ca_v channel blockers (Golding *et al.* 1999b; Wei *et al.* 2001). Dendritic spikes elicited by strong synaptic activation are difficult to study pharmacologically (because of presynaptic effects of Na_v and Ca_v channel blockers), but their widths vary considerably, depending on synaptic strength, location of the recording, and presumably the location of activated synapses (Golding *et al.* 1999a; Golding *et al.* 2002). This variability in the shape of

synaptically evoked dendritic spikes suggests that they are produced by variable contributions from Na_v , Ca_v and NMDA channels. Similar observations have been made in neocortical layer 5 pyramidal neurons, where additional evidence suggests that dendritic spikes in relatively proximal locations are mediated mostly by Na_v channels, while more distal dendritic spikes have a larger contribution from voltage-activated Ca_v channels (Schiller *et al.* 1997; Stuart *et al.* 1997a; Larkum *et al.* 1999b, 2001), although in prefrontal cortex it has been suggested that this situation is reversed (Seamans *et al.* 1997). Synaptic activation of basal and distal tuft dendrites in layer 5 pyramidal neurons and CA3 pyramidal neurons have also been shown to elicit NMDA spikes (Schiller *et al.* 2000; Larkum *et al.* 2009; Makara and Magee 2013). Voltage-dependent unblock of these channels by Mg^{2+} allows them to mediate regenerative events when present at sufficiently high densities (Rhodes 2006; Major *et al.* 2013). NMDA spikes differ fundamentally from spikes mediated by voltage-gated channels, because the requirement for glutamate binding dictates that they cannot actively spread beyond the region of synaptic activation.

Taken together, the evidence suggests that although the voltage threshold for action potential initiation is lowest in the axon, under some conditions, a higher threshold dendritic spike initiation zone may be activated first, resulting in a dendritic spike. Because the dendrites are weakly excitable compared to the axon, dendritic spikes can only occur if the local synaptic potential in dendrites is relatively large and fast. The initiation of dendritic spikes is facilitated by the high input impedance of small-diameter branches, which allows a relatively small number of co-activated synapses on the same branch to produce a large local EPSP, and thus evoke a dendritic spike (Losonczy and Magee 2006; Katz *et al.* 2009). When a dendritic spike is initiated, and the activated dendrite is sufficiently electrotonically isolated from the axon, voltage attenuation and delay causes the dendritic spike to fail to trigger a somatic action potential (Fig. 12.5A, 2nd from top) or to precede the somatic action potential with a long delay (Fig. 12.5A, 3rd from top), because the lower, axonal threshold is reached well after dendritic spike initiation. In other cases, dendritic spikes immediately precede and presumably help trigger action potential initiation (Fig. 12.5A, bottom). Whether a dendritic spike occurs or not, axonal action potentials

are followed by an action potential at the soma, which then backpropagates into the dendrites (Fig. 12.5B). Because dendritic spikes in pyramidal neurons only poorly invade the soma, and sometimes fail to trigger axonal action potentials, these dendritic spikes should be regarded as a form of active synaptic integration, where the final site of synaptic integration is in the axon. As discussed in more detail below, the ability of dendritic spikes to propagate to the soma and influence action potential firing in the axon is regulated by many factors.

Propagation of action potentials and dendritic spikes

Action potentials propagate through the dendritic tree in complex ways that are influenced by a variety of factors. Here we consider the effects of dendritic morphology, properties of dendritic voltage-gated channels and synaptic inhibition on the propagation of action potentials initiated in the axon and spikes generated in dendrites.

Action potential backpropagation

Following their initiation in the axon, action potentials propagate back into the soma and the dendritic tree. The invasion of the dendrites by so-called “backpropagating action potentials” or “bAPs” varies across different cell types. In most neurons where they have been studied, including neocortical and hippocampal pyramidal neurons, hippocampal granule cells and interneurons, dopaminergic and GABAergic neurons in substantia nigra, spinal motoneurons, and mitral cells of the olfactory bulb, action potentials propagate actively back into the dendrites. The amplitude of bAPs in these cell types generally diminishes as the action potential propagates away from the soma, but remains above that expected for passive spread of the action potential (Stuart and Sakmann 1994; Häusser *et al.* 1995; Spruston *et al.* 1995; Larkum *et al.* 1996; Bischofberger and Jonas 1997; Chen *et al.* 1997; Martina *et al.* 2000; Golding *et al.* 2001; Waters *et al.* 2003; Hu *et al.* 2010; Krueppel *et al.* 2011; Kim *et al.* 2012). In pyramidal neurons, bAPs invade not only the primary apical dendrite, but also radial oblique and basal dendrites (Frick *et al.* 2003; Nevian *et al.* 2007), but may decay to passive propagation in the apical tuft, at

least under some conditions (Golding *et al.* 2001; Larkum *et al.* 2001; Stuart and Häusser 2001; Bernard and Johnston 2003). Active backpropagation is supported by Na_v channels, which have been shown to be present in the dendrites of several types of neurons (Stuart and Sakmann 1994; Häusser *et al.* 1995; Magee and Johnston 1995; Bischofberger and Jonas 1997). In most neurons, however, backpropagation is decremental, presumably because the density of Na_v channels is too low to support non-decremental conduction.

There is some variation in dendritic Na_v channel densities between cells. Pyramidal neurons have a low (but relatively constant) density of Na_v channels along the main apical dendrite (Stuart and Sakmann 1994; Magee *et al.* 1995), while mitral cells in the olfactory bulb appear to have a higher density of dendritic Na_v channels and support more reliable backpropagation (Bischofberger and Jonas 1997). Cerebellar Purkinje cells, in contrast, have a very low density of Na_v channels in their dendrites, and do not support active action potential backpropagation (Llinas and Sugimori 1980a, b; Lasser-Ross and Ross 1992; Stuart and Häusser 1994). However, the correlation between dendritic Na_v channel density and backpropagation is not a strict one, as substantia nigra dopamine neurons have essentially non-decremental backpropagation, even though they have a lower apparent dendritic Na_v channel density than pyramidal cells (Häusser *et al.* 1995). Even within a class of neuron, cell-to-cell variation in action potential backpropagation can be considerable, as a result of the sensitivity of backpropagation to a variety of factors, including morphology, channel densities, and membrane potential (Golding *et al.* 2001; Larkum *et al.* 2001; Bernard and Johnston 2003; Schaefer *et al.* 2003). Backpropagation may also be regulated within a given cell, as a result of ongoing synaptic activity, neuromodulatory states or long-term, activity-dependent plasticity (Hoffman and Johnston 1999; Stuart and Häusser 2001; Frick *et al.* 2004).

Effects of morphology on action potential backpropagation

The morphology of the dendritic tree can affect action potential backpropagation in the same way as has been previously shown for propagation of action potentials in axons, where diameter,

tapering and branching are important determinants of action potential propagation (Goldstein and Rall 1974). Using simplified analytical solutions of action potential propagation, Goldstein and Rall demonstrated that branch points are particularly sensitive regions where action potentials can fail. They quantified branch point geometry using the geometric ratio (GR), defined as:

$$GR = \sum_j d_j^{3/2} / d_a^{3/2}$$

where d_a is the diameter of the cable along which an action potential is propagating (the “parent” branch), and d_j are the diameters of the branches the action potential propagates into (the “daughter” branches; Goldstein and Rall 1974). This geometric ratio defines the impedance mismatch between the parent and daughter dendrites (Fig. 12.6A). If one assumes that the membrane properties are uniform and the branch is not near a termination point of a cable, the geometric ratio predicts the behavior of the action potential as it propagates across the branch. If $GR=1$ (i.e., if the 3/2 power law is obeyed, and therefore the impedance is “matched”), the only effect on propagation is that the velocity decreases due to the smaller diameter of the distal branches. If $GR<1$, a favorable impedance mismatch holds, and action potentials propagate efficiently (i.e., with less decrement; Fig. 12.6A1), as in cables with a step decrease in diameter. If $GR>1$, the impedance mismatch is unfavorable, and action potentials propagate inefficiently (Fig. 12.6A2), as though they encounter a step increase in diameter, with propagation failing completely for sufficiently high values of GR. The critical value depends on the density and kinetics of the Na_v and K_v channels in the different branches, as well as the passive membrane properties R_m , R_i and C_m . Another way of expressing this is that the safety factor for action potential conduction decreases when an action potential propagates into branches that are just slightly smaller, the same size, or larger than the parent dendrite (Rall 1964).

Similar considerations are expected to hold for action potentials propagating in dendritic trees. Because the safety factor for propagation of action potentials in dendrites is low to begin with (recall that backpropagation is decremental in pyramidal neurons), unfavorable impedance mismatches at branch points may result in failure of bAPs or dendritic spikes. Indeed, changes in

the shape of bAPs in hippocampal dendrites have been observed (Spruston *et al.* 1995), which resemble the shape of action potentials propagating close to failure in axons (Lüscher *et al.* 1994). Furthermore, as discussed earlier in the chapter, different neuronal types show very different degrees of backpropagation (Stuart *et al.* 1997b), which may be related to the striking differences in dendritic geometry shown by different cell types. To investigate the contribution of dendritic geometry, one study (Vetter *et al.* 2001) performed simulations in which the same complement of active and passive properties was inserted into detailed reconstructions of a large variety of cell types, thus isolating morphology as the only variable. Interestingly, the pattern of backpropagation in the different geometries matched the experimental findings, with substantia nigra dopamine neurons showing the least attenuation and Purkinje cells the most.

Morphological analysis of the dendritic trees revealed that backpropagation was strongly correlated with the way in which membrane area was distributed in the dendritic tree, a function of both the number of branch points and the geometric ratio at individual branch points. This study (Vetter *et al.* 2001) also demonstrated that in very elaborate morphologies, such as Purkinje cells, backpropagation is insensitive to the Na_v channel density over the physiological range, in contrast to pyramidal cells, where modulation of Na_v or K_v channel density can produce a wide range of dendritic action potential amplitudes.

Other studies have demonstrated that even within a given class of neuron, variations in dendritic geometry can affect action potential backpropagation. For example, in CA1 pyramidal neurons, bAPs in distal dendrites are either relatively large (strong backpropagation) or small (weak backpropagation). The absence of intermediate amplitudes suggests that backpropagation can fail at a critical point in the dendritic tree, about 300 μm from the soma (Golding *et al.* 2001). Modeling studies indicate that failure of action potential backpropagation is sensitive not only to Na_v and K_v channel density, but also to the number of dendritic branches in this region (Golding *et al.* 2001). Similarly, in cortical layer 5 pyramidal neurons, the ability of somatic action potentials to influence the distal dendrites is variable and has been shown to be sensitive to the number of oblique dendrites branching from the main apical dendrite (Larkum *et al.* 2001;

Schaefer *et al.* 2003). One view is that depending on whether oblique branches are strongly or weakly excitable and whether or not they are excited or inhibited by synaptic input, they may either facilitate or limit action potential backpropagation (Fig. 12.6A3).

Together, these studies indicate that dendritic morphology, and in particular the branching pattern, is a major determinant of how dendrites will behave functionally, confirming a prediction made by Rall in the mid-1960s (Rall 1964).

Effects of dendritic voltage-gated channels on action potential backpropagation

Non-uniform distributions of channels, as well as changes in the activation patterns of channels with activity, add a further layer of complexity to our understanding of action potential propagation in dendrites. For example, regional Na_v channel inactivation or non-uniform distributions of dendritic K_v channels can have significant effects on propagation. Hoffman and colleagues have shown that the density of A-type K_v channels in the apical dendrites of CA1 neurons increases as a function of distance from the soma; furthermore, A-type K_v channels in these cells have a lower activation voltage in the distal dendrites than in the soma and proximal dendrites (Hoffman *et al.* 1997). This channel distribution appears to contribute to a number of physiological features of CA1 neurons, including the relatively high threshold for dendritic spike initiation, and the decremental nature of action potential backpropagation (Hoffman *et al.* 1997; Frick *et al.* 2003).

Action potentials backpropagating into CA1 dendrites undergo marked amplitude attenuation during repetitive activity (Andreasen and Lambert 1995b; Callaway and Ross 1995; Spruston *et al.* 1995; Golding *et al.* 2001). A similar form of activity-dependent action potential backpropagation occurs in the distal regions of the apical dendrites of neocortical pyramidal neurons (Stuart *et al.* 1997a). This property of action potential backpropagation appears to be largely attributable to the inactivation properties of dendritic Na_v channels (Fig. 12.7A,B). Na^+ currents in cell-attached patches from CA1 pyramidal neurons undergo a form of inactivation that develops rapidly but recovers slowly (Colbert *et al.* 1997; Jung *et al.* 1997; Mickus *et al.*

1999). This prolonged inactivation is particularly pronounced in patches from the apical dendrite. As each action potential invades the dendrites, it leaves a fraction of Na_v channels in a long-lived inactivated state, effectively reducing the density of available Na_v channels to support backpropagation of action potentials arriving even several hundred milliseconds later. Because the safety factor for action potential backpropagation is low (Vetter *et al.* 2001), owing to the relatively low Na_v channel density, high A-type K_v channel density, and extensive branching of CA1 dendrites, inactivation of even a small number of Na_v channels can significantly affect action potential backpropagation. In this way, prolonged inactivation of dendritic Na_v channels reduces action potential backpropagation, and causes an activity-dependent decline in action potential amplitude at a given dendritic recording site. This inactivation, together with unfavorable branching geometry, may also contribute to failure of bAPs to invade some dendritic branches in CA1 neurons (Spruston *et al.* 1995).

The amplitude of bAPs is affected by other factors as well during repetitive spiking. For example, natural spike trains propagate most reliably into dendrites during periods of high-frequency activity. This frequency-dependent amplification depends on temporal summation of bAPs and activation of distal dendritic Na_v channels (Williams and Stuart 2000a). These effects are mimicked by depolarization and reversed by hyperpolarization, indicating that synaptic activity will also affect action potential backpropagation.

Effects of synaptic excitation and inhibition on action potential backpropagation

Synaptic excitation and inhibition is another important factor that has been shown to influence action potential backpropagation. In both CA1 and layer 5 pyramidal neurons, synaptic depolarization of the dendrites has been shown to facilitate the invasion of the apical dendrites by bAPs (Hoffman *et al.* 1997; Stuart and Häusser 2001; Watanabe *et al.* 2002), while synaptic activation of GABAergic inhibitory conductances in the dendrites limits action potential backpropagation (Tsubokawa and Ross 1996; Perez-Garci *et al.* 2006). Similarly, in olfactory mitral cells, inhibition limits the spread of action potentials along the lateral dendrites (Lowe

2002; Xiong and Chen 2002). The details of synaptic control of bAPs are likely to be complex. For example, in addition to simply inhibiting dendritic excitability, hyperpolarization associated with inhibition could, if appropriately targeted and timed, increase the recovery of dendritic Na_v channels from the slow inactivated state, thus increasing the amplitude of bAPs (Spruston *et al.* 1995; Colbert *et al.* 1997; Jung *et al.* 1997). On the other hand, hyperpolarization could decrease excitability by removing inactivation of A-type K_v channels (Hoffman *et al.* 1997). Thus, the effects of hyperpolarization may be complex, and dependent on the prior firing history of the neuron.

Dendritic spike propagation

In some neurons, such as mitral cells of the olfactory bulb (Chen *et al.* 1997; Djurisic *et al.* 2004; Urban and Castro 2005) and hippocampal CA2 pyramidal neurons (Sun *et al.* 2014), dendritic spike propagation is reliable and robustly triggers an action potential in the axon. In other neurons, however, such as the widely studied hippocampal CA1 pyramidal neurons, neocortical layer 5 pyramidal neurons, and cerebellar Purkinje neurons, the propagation of dendritic spikes is unreliable. Several observations suggest that dendritic sodium and calcium spikes propagate poorly in these neurons. First, the amplitude of dendritic sodium and calcium spikes is smaller than the somatically recorded action potential, even when the dendritic spike occurs first. Second, dendritic spikes are sometimes observed in isolation of somatic action potentials in both hippocampal and neocortical pyramidal neurons (Fig. 12.5A; Stuart *et al.* 1997a; Golding and Spruston 1998; Golding *et al.* 2002). Third, imaging studies show that Ca^{2+} signals associated with distal calcium spikes can remain localized to their site of origin in pyramidal cells and Purkinje cells, with little or no calcium signal spreading to the soma (Miyakawa *et al.* 1992; Eilers *et al.* 1995; Hartell 1996; Schiller *et al.* 1997; Schiller *et al.* 2000; Wei *et al.* 2001; Ariav *et al.* 2003; Polsky *et al.* 2004). Fourth, small (<20 mV), spike-like events have been recorded in CA1 pyramidal neuron somata in response to synaptic stimulation. These events, which are observed frequently during perisomatic application of TTX to eliminate axonal

action potential firing, correspond to much larger spikes recorded simultaneously in the dendrites (Wong and Stewart 1992; Golding *et al.* 2002; Jarsky *et al.* 2005). A similar observation has been made in retinal ganglion cells (Oesch *et al.* 2005). Fifth, local uncaging of glutamate on pyramidal neuron dendrites produces dendritic spikes, as well as nonlinear increases in dendritic calcium and somatic dV/dt , even in the absence of somatic action potentials (Wei *et al.* 2001; Ariav *et al.* 2003; Gasparini and Magee 2006; Losonczy and Magee 2006). Finally, triple recordings from the axon, soma, and apical dendrite of the same neocortical pyramidal neuron indicate that the axonal action potential always precedes the somatic action potential, even when the dendritic spike precedes the somatic action potential (Fig. 12.5B; Stuart *et al.* 1997a). These observations suggest that dendritic spikes do not propagate reliably to the soma and axon of neocortical and hippocampal pyramidal neurons. As a consequence, the dendritic spike-mediated depolarization that reaches the soma is sometimes small. In some cases the somatic depolarization due to the EPSP and dendritic spike together are large enough to initiate an axonal action potential, whereas in other cases, the EPSP and dendritic spike together produce a subthreshold depolarization in the soma and axon, resulting in an isolated dendritic spike (Fig. 12.5A).

Even though dendritic calcium spikes are typically broader than dendritic sodium spikes, they can also fail as they propagate toward the soma in pyramidal neurons (Schiller *et al.* 1997; Golding *et al.* 2002). In fact, calcium spikes are rarely observed in somatic recordings, but they can influence action potential initiation by promoting action potential bursting (Schiller *et al.* 1997; Golding *et al.* 1999b; Larkum *et al.* 1999b; Williams and Stuart 1999), as originally described in cerebellar Purkinje cells (Llinas and Nicholson 1971; Llinas and Sugimori 1980a).

Whether or not dendritic spikes propagate successfully to the soma depends on a number of factors, including dendritic geometry, channel densities, and the spatial and temporal profile of synaptic excitation and inhibition (Segev and Rall 1998). Dendritic excitability is also affected by previous activity and neuromodulation, thus making the process of dendritic spike initiation and propagation just as complex as action potential backpropagation.

The morphology of the dendritic tree clearly plays an important role in determining this behavior. Small-diameter dendritic branches have higher input impedance than large-diameter branches and may therefore be depolarized to threshold for a dendritic spike by relatively small synaptic conductances (Losonczy and Magee 2006; Nicholson *et al.* 2006; Katz *et al.* 2009). However, the fact that dendritic spike propagation is generally unreliable in pyramidal neurons is also likely to be largely attributable to dendritic geometry, particularly at branch points. As discussed above, spike propagation through branch points depends on geometric ratio of the parent and daughter dendrite diameters (Goldstein and Rall 1974; Jack *et al.* 1983). Spikes that begin in small dendritic branches will have a tendency to fail as they propagate into larger branches (Fig. 12.6B1). Dendritic spikes must frequently traverse such a geometric arrangement as they propagate toward the soma in neurons such as pyramidal cells and Purkinje cells. By contrast, bAPs tend to propagate from large branches into smaller ones (Fig. 12.6A1). Thus, the geometry of the dendritic tree is even less favorable for forward propagation than for backpropagation.

The reason that dendritic spikes tend to fail as they propagate from small (high impedance) to large (low impedance) dendrites is that more current is required to depolarize the larger branch to threshold. Even if a spike begins in a relatively large dendritic branch, it will tend to fail when it must charge two dendrites of similar diameter at a branch point (Fig. 12.6B2). Thus, the propagation of dendritic spikes will be greatly influenced by the synaptic activation of neighboring dendritic branches. Consider, for example, a branch point with one large parent dendrite giving rise to two smaller daughter branches. If a spike initiates in one of the daughter branches, it will tend to fail as it propagates into the larger parent dendrite (Fig. 12.6B1). If the spike originates in both daughter branches, however, forward propagation will be more effective, because there is a larger current source to depolarize the parent dendrite (not illustrated). This mechanism has been suggested to lead to reliable propagation of dendritic spikes in layer 5 pyramidal neurons and hippocampal CA2 pyramidal neurons, where spikes in multiple apical branches can converge at a proximal branch point (Larkum *et al.* 2009; Piskorowski and

Chevaleyre 2011; Sun *et al.* 2014). Even if the spike is restricted to one of the daughter branches, synaptic depolarization of the other daughter branch and/or the parent branch will also increase the likelihood of successful forward propagation; synaptic inhibition, on the other hand, would have the opposite effect (Jarsky *et al.* 2005).

The effect of radial oblique branches on dendritic spike propagation in pyramidal neurons depends on the origin of the spike and the excitability of the oblique branches. For spikes propagating down the main apical dendrite, oblique branches can act to reduce or facilitate forward propagation of the spike, depending on whether the oblique branch is strongly excitable or weakly excitable (Fig. 12.6B3). Synaptic excitation of the oblique branch would tend to favor propagation, while inhibition would reduce the forward propagating spike. On the other hand, dendritic spikes beginning in oblique branches will tend to fail as they propagate into the large-diameter main apical dendrite (not shown, but similar to Fig. 12.6B1).

Though dendritic geometry may be partly responsible for the poor forward propagation of dendritic spikes, including the occurrence of isolated dendritic spikes (Schiller *et al.* 1997; Stuart *et al.* 1997a; Golding and Spruston 1998), other factors are likely to be important as well. For example, action potential backpropagation may limit the propagation of subsequent dendritic spikes to the soma of CA1 neurons (Golding and Spruston 1998; Remy *et al.* 2009), due to inactivation of dendritic Na_v channels (Fig. 12.7C). Non-uniform K_v channel distribution may be another important factor. Although the distribution of dendritic A-type K_v channels (Hoffman *et al.* 1997) probably has the reverse gradient required to explain the poor forward propagation of dendritic spikes, other K_v channels may also be distributed non-uniformly (e.g. Andreassen and Lambert 1995a). The distributions and effects of a variety of K_v channel subtypes still need further investigation. Interestingly, mitral cells appear to display much better forward propagation than pyramidal cells (Chen *et al.* 1997) under similar experimental conditions, presumably due to the uniform, and unbranching nature of the main apical dendrite in these neurons.

A question of significant importance is whether the propagation of action potentials (backpropagation) and dendritic spikes (forward propagation) *in vivo* is similar to the situation studied *in vitro*. Although this question cannot yet be clearly answered, some evidence is beginning to emerge. This subject is considered in detail in Chapter 13. Here, it should be noted that all of the factors discussed here are subject to modulation by activity, neurotransmitters, and various kinds of plasticity (Tsubokawa and Ross 1997; Colbert and Johnston 1998; Hoffman and Johnston 1999; Williams 2004; Magee and Johnston 2005; Johnston and Narayanan 2008; Losonczy *et al.* 2008; Makara and Magee 2013). Even dendritic structure is not static (see Chapter 19), indicating that the effects of morphological changes on action potential and dendritic spike propagation must be considered.

Effects of inhibition on dendritic spikes

Synaptic inhibition has been shown to influence dendritic sodium and calcium spikes. In both hippocampal CA3 and neocortical layer 5 pyramidal neurons, early work showed that inhibition can prevent, delay, or shorten dendritic spikes, depending on its timing and strength (Kim *et al.* 1995; Miles *et al.* 1996; Larkum *et al.* 1999b). In hippocampal neurons, the effects of inhibition on spike firing depend on the location of the inhibitory input. Dendritic inputs inhibit dendritic spikes, whereas perisomatic inhibition suppresses repetitive discharge of somatic action potentials (Miles *et al.* 1996). Computational modeling suggests the location of dendritic inhibition determines whether it affects dendritic spike initiation or spike amplitude (Jadi *et al.* 2011). However, experimental work indicates that dendritic inhibition may primarily affect dendritic spike initiation and that the effects of dendritic inhibition can be overcome by activity-dependent increases in dendritic branch excitability (Lovett-Barron *et al.* 2012; Müller *et al.* 2012). In layer 5 pyramidal neurons, distal dendritic inhibition has been shown to inhibit calcium spikes not only through hyperpolarization and shunting, but also by GABA_B receptor-mediated inhibition of dendritic Ca_v channels (Perez-Garci *et al.* 2006; Murayama *et al.* 2009; Breton and Stuart 2012; Palmer *et al.* 2012). The effects of inhibition on dendritically generated spikes have

also been explored in mitral cells of the olfactory bulb, where perisomatic inhibition can prevent dendritic sodium spikes from invading the soma and axon (Chen *et al.* 1997).

While the effects of dendritic inhibition were discussed above for passive dendrites (or in active dendrites below threshold for engaging nonlinearities), the effects of dendritic inhibition can be quite different in active dendrites. When an active dendritic “hot spot” exists – either because of clustered excitatory synaptic input or clustered Na_v or Ca_v channels – dendritic inhibition more effectively prevents dendritic spike generation if it is distal to the hot spot than if it is proximal to the hotspot (Gidon and Segev 2012). This effect, which is described in more detail in Chapter 15, results largely from the greater shunting effect of a given inhibitory conductance, relative to the local input conductance, for distal versus proximal inhibition. However, just as inhibition proximal to the soma more effectively shunts somatic EPSPs in passive dendrites, once a spike is generated at a dendritic hotspot, proximal inhibition more effectively reduces the propagation of the spike toward the soma (Gidon and Segev 2012).

What are the functions of dendritic excitability?

Backpropagating action potentials and dendritic spikes can serve a number of functions. One immediate effect is elevation of intra-dendritic Ca^{2+} concentration, via activation of Ca_v channels and removal of Mg^{2+} block at glutamate-bound NMDA receptors (Chapter 8). This can in turn result in release of neurotransmitters or other substances from dendrites (Chapter 21) or induction of synaptic plasticity (Chapter 18). Another important function of dendritic excitability is to change the way synaptic inputs affect dendritic membrane potential, thus affecting the way that synaptic inputs lead to action potential initiation. This aspect of dendritic excitability is discussed in detail below.

Subthreshold amplification of EPSPs by Na_v and Ca_v channels and NMDA receptors

Depending on the types, densities, and distributions of channels in dendrites, PSPs may be amplified and shaped in subtle ways by voltage-gated conductances. For example, Na_v and/or

Ca_v channels and NMDA receptors can amplify EPSPs without generating a spike. One of the first indications that voltage-gated conductances may amplify EPSPs in this manner was the observation that a marked increase in the amplitude and integral of EPSPs was observed when pyramidal neurons were held at depolarized potentials (Masukawa and Prince 1984; Stafstrom *et al.* 1985; Thomson *et al.* 1988; Deisz *et al.* 1991). A similar voltage-dependent amplification was observed in response to brief somatic current injections used to mimic EPSPs (Deisz *et al.* 1991). Stuart and Sakmann extended this idea by comparing the voltage dependence of EPSPs and EPSP-like depolarization evoked by injecting current in the shape of an excitatory postsynaptic current (EPSC) through a dendritic recording electrode (Stuart and Sakmann 1995). They found that the voltage-dependent amplification of both real and “simulated” EPSPs was blocked by application of TTX. Because the activation of Na_v channels occurred in a voltage range below threshold for action potential initiation, and because the effect of TTX on the EPSP integral was larger than on the peak, the amplification was interpreted to be due to activation of a non-inactivating, or persistent, Na_v conductance. Furthermore, because the amplification of EPSPs was greatest in the soma, and indeed the axon, and selectively blocked by local application of TTX to the soma and axon, it appears that this form of amplification occurs primarily due to activation of persistent Na^+ current in the axon (Stuart and Sakmann 1995). In CA1 pyramidal neurons distally generated EPSPs can be amplified by perisomatic persistent Na^+ current (Andreasen and Lambert 1999), and other experiments also indicate that persistent Na^+ current is generated primarily in the axon (Astman *et al.* 2006).

Interestingly, inhibitory synaptic potentials (IPSPs) can also be modulated by axonal persistent Na^+ current in a complementary manner (Stuart 1999). IPSPs turn off the persistent Na^+ current, producing a net outward current, which increases the amplitude and duration of IPSPs. At the soma and axon this increases the ability of inhibition to block action potential generation (Stuart 1999), whereas in the dendrites it could enhance the ability of synaptic inhibition to block dendritic spike generation and propagation. The same mechanism that allows

persistent Na^+ current to amplify IPSPs also causes it to enhance the AHP, thus affecting spike rate and timing (Vervaeke *et al.* 2006).

The voltage-dependent boosting effects described above were generated primarily by axosomatic channels. However, the dendrites of mammalian neurons are richly endowed with voltage-gated channels that also can contribute to boosting effects, particularly for larger and more prolonged synaptic inputs. In the hippocampus, dendritic patch-clamp recordings from CA1 neurons have shown directly that Na_v and Ca_v channels can be activated by EPSPs (Magee *et al.* 1995). Furthermore, blockers of Na_v and low-threshold Ca_v channels have been shown to reduce the amplitude and duration of EPSPs measured at the soma in CA1 and CA3 pyramidal neurons (Lipowsky *et al.* 1996; Gillessen and Alzheimer 1997; Urban *et al.* 1998). However, the most powerful contribution to dendritic nonlinearities triggered by synaptic input is via the NMDA receptor channels which are found at most excitatory synapses. The regenerative nature of NMDA current, caused by the voltage-dependent Mg^{2+} block of the channel and the consequent region of negative slope of the I-V relationship, can lead to a number of different effects, depending on the level of depolarization (Schiller and Schiller 2001; Poirazi *et al.* 2003a; Major *et al.* 2013). A mild depolarization can lead to graded inward current, causing boosting of EPSPs; more depolarization can lead to bistability of membrane potential; and strong depolarization can lead to full-blown spikes with a distinct threshold, which have been termed 'NMDA spikes' (Schiller *et al.* 2000; Major *et al.* 2013). Two-photon glutamate uncaging experiments have allowed the contribution of different voltage-gated channels to subthreshold dendritic amplification of EPSPs to be evaluated on a quantitative level in cortical pyramidal cells (Gasparini and Magee 2006; Losonczy and Magee 2006; Branco and Hausser 2010, 2011). This work has shown that while blockers of voltage-gated Na_v and Ca_v channels can reduce amplification of EPSPs, blocking NMDA receptors can entirely abolish amplification. This indicates that the NMDA receptor channel nonlinearity is both necessary and sufficient to trigger regenerative boosting of EPSPs, with the other channel types adding additional regenerative inward current. The recruitment of the NMDA receptor nonlinearity depends critically on the

temporal and spatial properties of the synaptic inputs: when synaptic input arrives asynchronously or is highly distributed in space, then integration is linear; it is only when input is near-synchronous and clustered that strong nonlinearities are recruited (Gasparini and Magee 2006). Interestingly, applying the same input at different locations along the same dendrite changes the steepness of the resulting non-linear input-output curve, which in turn depends on NMDA receptor activation (Branco and Hausser 2011). This suggests that the degree to which dendritic voltage-gated channels amplify EPSPs depends on the location of the activated synapses, with distal inputs exhibiting a higher gain for amplification than proximal inputs. Ironically, these differences in active properties are a consequence of the passive electrotonic structure of the dendrite, with the passive impedance gradient along the dendrite 'helping' to recruit active nonlinearities for inputs made towards the end of a dendrite (Branco and Hausser 2010, 2011).

Subthreshold attenuation by K_v channels

The effects of K_v channel activation on EPSPs must also be considered. Support for activation of voltage-gated K_v channels in response to subthreshold EPSPs comes from a variety of experiments. Block of K_v channels with 4-AP increases dendritic EPSP amplitude in hippocampal pyramidal neurons (Hoffman *et al.* 1997) and can convert sub-linear summation to supra-linear summation in hippocampal pyramidal neurons (Cash and Yuste 1998, 1999). Other experiments indicate that the effects of dendritic voltage-gated channels depend on the timing of summated EPSPs (Margulis and Tang 1998): when two inputs were activated at an interval of less than 10 ms, the second input was amplified by a TTX-sensitive conductance. At slightly longer intervals (15-100 ms) the second input was depressed by a K_v conductance. Experiments using stimulation of perforant path (PP) and mossy fiber (MF) inputs at different time intervals support a similar conclusion regarding K_v channel activation in CA3 neurons (Urban and Barrionuevo 1998). In these experiments, activation of MF synapses shunted perforant path EPSPs when MF stimulation preceded PP stimulation by less than 20 ms. This effect was voltage

dependent, and blocked by intracellular 4-AP, suggesting that the depolarization by the MF EPSP activates A-type K_v channels, which then shunts the PP EPSP propagating from the distal dendrites.

The current view in hippocampal pyramidal neurons is that the effect of activation of Na_v and Ca_v channels by subthreshold EPSPs are dampened by activation of K_v channels, particularly the A-type K_v channel, which is present at high density in CA1 apical dendrites (Hoffman *et al.* 1997). However, the generation of dendritic sodium spikes in CA1 neurons suggests that dendritic Na_v channel activation can tip this balance, particularly during synchronous synaptic excitation (Golding and Spruston 1998; Ariav *et al.* 2003; Gasparini and Magee 2006; Losonczy and Magee 2006).

EPSP shunting by backpropagating action potentials

The bAP can also interact with synaptic potentials. The conductances necessary to generate the action potential are large, and therefore generate a substantial drop in apparent membrane resistance, which is localized largely to the axon and soma. This shunt effectively shortens the membrane time constant in these regions, draining charge from the membrane capacitance. In this way, action potentials can reduce the amplitude of EPSPs and IPSPs, thus providing a mechanism for terminating ongoing synaptic integration. In neocortical layer 5 pyramidal cells, somatic EPSPs generated by basal synaptic inputs can be attenuated by up to 80% by a single action potential (Häusser *et al.* 2001). The degree to which action potentials shunt synaptic potentials depends not only on the magnitude of the local conductances activated by the action potential, but also on the location and kinetics of the synaptic conductance. As a consequence, synaptic potentials generated by synaptic conductance changes with a slow time course (e.g., those mediated by NMDA receptors) are less sensitive to shunting by relatively brief action potentials. In addition, more distal inputs are shunted less, as they are further away from the conductance change generated during the action potential, and shunting of dendritic synaptic

events locally is small due to the relatively low density of dendritic conductances activated during action potential backpropagation (Häusser *et al.* 2001).

Dendritic spikes and synaptic integration

The possibility that dendrites might generate spikes has presented a conundrum for understanding synaptic integration: if spikes can be generated in dendrites, the integrative power of the dendritic tree would appear to be minimized, because many of the spatial and temporal interactions involving excitation and inhibition (discussed in the preceding section) would be negated by the generation of a dendritic spike in response to a small number of excitatory inputs. A possible solution to this puzzle was presented as early as 1959, when Lorente de Nó suggested that decremental conduction of dendritic spikes might play an important role in dendritic integration in the central nervous system (Lorente De No and Condouris 1959). In the scenario he envisioned, spikes could be generated in dendrites, but would not propagate reliably to the soma. The effect of dendritic spikes would therefore be to increase the depolarization associated with some synaptic inputs, but would not necessarily trigger an action potential. Jack, Noble and Tsien (1983) also pointed out that an obvious possible function of this kind of restricted dendritic spike would be to amplify synaptic potentials, thus increasing the likelihood that a combination of synapses that evoke a dendritic spike will eventually result in an output from the neuron via generation of an action potential in the axon. As discussed above, there is now good experimental evidence in support of this idea (Schiller *et al.* 1997; Stuart *et al.* 1997a; Andreasen and Lambert 1998; Golding and Spruston 1998; Larkum *et al.* 1999b; Ariav *et al.* 2003; Polsky *et al.* 2004; Gasparini and Magee 2006; Losonczy and Magee 2006; Katz *et al.* 2009). In some cases the additional somatic depolarization associated with the dendritic spike brings the membrane potential above threshold for a somatic/axonal action potential.

One prominent view of the pyramidal neuron is that individual dendritic branches may operate as computational subunits, each of which is capable of generating dendritic spikes. Whether or not these spikes result in action potential firing depends on integration of these

subunit responses to determine if a somatic/axonal action potential will be generated. This idea was first advanced on theoretical grounds (Archie and Mel 2000; Poirazi *et al.* 2003a), but now has considerable experimental support (see Chapter 16). Dendritic spikes can be triggered by clustered or distributed inputs to a single dendritic branch, but the same number of inputs distributed multiple branches are less effective (Ariav *et al.* 2003; Polsky *et al.* 2004; Gasparini and Magee 2006; Losonczy and Magee 2006; Larkum and Nevian 2008; Branco and Häusser 2010; DeBello *et al.* 2014) (Fig. 12.8A-D). This view has led to the idea that the pyramidal neuron can be treated as a two-layer network with integration by individual branches serving as one layer and integration of multiple branch responses serving as a second layer (Häusser and Mel 2003; Poirazi *et al.* 2003b; Katz *et al.* 2009; Jadi *et al.* 2014). This idea could be extended to treat the pyramidal neuron as a multi-layer network, for example with integration by the apical tuft, apical oblique, and basal dendritic branches acting as intermediate layers in this scheme (Spruston and Kath 2004; London and Häusser 2005; Larkum *et al.* 2009) (Fig. 12.8E). Whether this notion accurately captures the computational function of neurons remains to be determined, but there is certainly good evidence that synaptic inputs targeting different dendritic compartments can be integrated in interesting ways. For example, in CA1 pyramidal neurons, activation of the perforant-path inputs, which target the distal apical tuft exclusively, can lead to dendritic spikes whose propagation to the soma and axon is facilitated by activation of Schaffer collateral inputs targeting more proximal apical dendrites (Jarsky *et al.* 2005) (Fig. 12.9A-C).

Action potential bursting and dendritic excitability

Another way that dendritic excitability can contribute to synaptic integration is by promoting action potential burst firing. Dendritic calcium spikes activated by strong synaptic excitation can lead to burst firing in hippocampal and neocortical pyramidal neurons (Schwartzkroin and Slawsky 1977; Wong and Stewart 1992; Schiller *et al.* 1997; Stuart *et al.* 1997a; Golding *et al.* 1999b), thalamo-cortical relay cells (Destexhe *et al.* 1998), cerebellar Purkinje cells (Llinas and Sugimori 1980a; Llinas 1988), and neocortical interneurons (Goldberg *et al.* 2004). The reason

for this is simply that propagation to the soma of the more prolonged inward current generated during dendritic calcium spikes can trigger multiple action potentials in the axon and soma. In addition, however, modeling studies have suggested that the backpropagation of action potentials from the soma into the dendrites can promote bursting in neurons with excitable dendritic trees (Pinsky and Rinzel 1994; Mainen and Sejnowski 1996).

Backpropagating action potentials can contribute to bursting in multiple ways. First, the bAP can generate current that flows back to the soma to contribute to an afterdepolarization (ADP), which can promote bursting (Lemon and Turner 2000). In neocortical layer 5 pyramidal neurons, such a mechanism depends on the recruitment of dendritic Ca_v channels by bAPs (Williams and Stuart 1999). In CA1 pyramidal neurons, bursting via this mechanism is limited by A-type and D-type K_v channels in the apical dendrites, as the ADP and bursting are increased following block of these channels (Magee and Carruth 1999; Metz *et al.* 2007).

A second mechanism by which bAPs can promote bursting is by triggering calcium spikes in the dendrites, as first suggested in early models of CA3 pyramidal neurons (Traub *et al.* 1991; Traub *et al.* 1994). In layer 5 pyramidal neurons, high frequency action potential firing alone can trigger dendritic calcium spikes in both apical and basal dendrites (Larkum *et al.* 1999a; Kampa and Stuart 2006). bAPs can also facilitate the initiation of distal dendritic calcium spikes by synaptic input, resulting in bursts of action potentials at the soma (Larkum *et al.* 1999b, 2001; Stuart and Häusser 2001; Larkum *et al.* 2004) (Fig. 12.9D-H). This interaction between bAPs and dendritic calcium spikes can greatly increase the impact of distal synaptic excitation during ongoing network activity (Williams 2005) and can also contribute to synaptic plasticity, as dendritic calcium spikes very effectively relieve Mg^{2+} block of dendritic NMDA receptors (Kampa *et al.* 2006; Letzkus *et al.* 2006).

Concluding remarks

While it has been clear since the end of the 19th century that dendrites come in all shapes and sizes (see Chapter 1), research has shown that this diversity in structure is also associated with

diversity in the active and passive membrane properties. Voltage-gated channels are found in the dendrites of all neurons examined to date, with cell-specific differences in the types, properties and distributions of these channels (Chapter 9). Furthermore, passive membrane properties differ between neuronal types, and even at different locations within single neurons. Together, these differences impart richness to synaptic integration that was unimaginable in the 1950s, when dendrites were regarded by some as more of a nuisance than an asset (see Chapter 14).

The circumstances under which synaptic activation of dendritic voltage-gated channels causes a departure from the passive behavior of dendrites and thus helps define the input-output relation of neurons remains a matter of intense study, especially *in vivo* (see Chapter 13). Strong evidence indicates that bAPs and dendritically initiated spikes occur in many cell types, where they may mediate functions such as dendritic neurotransmitter release (Chapter 21) and induction of synaptic plasticity (Chapter 18), as well as having a direct influence over the process of synaptic integration, which is ultimately responsible for action potential generation in the axon. Generalization about the function of dendritic excitability across cell types is made difficult by the wide range of behaviors observed in different neurons. This diversity reflects complexity in the mosaic of active channels and the variety of dendritic morphologies, which is likely related to the different functional roles of individual neurons in their respective networks. Only by studying this diversity and its consequences can we better understand the way in which individual neurons are tuned to perform their particular computational tasks.

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Abbreviations used in this chapter

4-AP	4-amino pyridine
AIS	axon initial segment
AMPA	alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
bAP	backpropagating action potential
CA1	cornu ammonis (Ammon's horn), subregion 1
C_m	specific membrane capacitance
CNS	central nervous system
d	diameter
EPSC	excitatory postsynaptic current
EPSP	excitatory postsynaptic potential
E_{rev}	reversal potential
GABA	γ -amino-butyric acid
GABA _A	GABA receptor, type A
GR	geometric ratio
g_{syn}	synaptic conductance
I_{dend}	dendritic membrane current
IPSP	inhibitory postsynaptic potential
l	length
L	electrotonic length
MF	mossy fiber
mV	millivolts
ms	milliseconds
O-LM	oriens lacunosum-moleculare
PSP	postsynaptic potential
PP	perforant path
R_i	intracellular resistivity
R_m	specific membrane resistivity

R_N	input resistance
TTX	tetrodotoxin
V_{com}	command potential
V_{dend}	dendritic membrane potential
V_m	membrane potential
V_{rest}	resting potential
V_{soma}	somatic membrane potential
V_{syn}	synaptic membrane potential
X	electrotonic distance
τ_{decay}	time constant of decaying exponential
τ_m	membrane time constant
τ_{rise}	time constant of rising exponential

Figure legends

Figure 12.1. Axonal initiation of action potentials (APs). **A.** Biocytin filled layer 5 neuron with the soma, axon initial segment (AIS) and an axon bleb indicated. **B.** APs evoked by somatic current injection and recorded at the soma (black) and the AIS or an axon bleb (red) 38 μm (top) and 620 μm (bottom) from the axon hillock. $t = 0$ marks time of onset of the somatic AP. **C.** Plot of AP latency relative to the soma (black) for axonal APs recorded from the AIS (gray circles, $n = 45$) or axon blebs (open circles, $n = 22$) versus recording distance from the axon hillock. Minimum onset latency occurs $\sim 38 \mu\text{m}$ from the axon hillock, indicating the site of AP initiation in the AIS. **D.** Simultaneous dendritic (blue) and somatic (green) recordings (top) from two different substantia nigra dopamine neurons (bottom) during AP generation. The axon originates from a dendrite 215 μm from the soma in the neuron on the left, and at the soma in the neuron on the right. APs are observed first at the recording site closest to the site of axon origin, indicating that they are initiated in the axon of these neurons.

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Figure 12.2. Effects of R_i and R_m on EPSP attenuation. A single excitatory synaptic conductance (g_{syn}) was simulated either at the soma, a mid-apical dendrite, or a distal apical dendrite. Membrane potential at the soma (V_{soma}) and the synapse (V_{syn}) is shown. The center columns illustrate the simulations under control conditions; the left column represents a lower R_m case; the right column represents a lower R_i case. See text for discussion of simulation results.

Simulation methods. All simulations were performed using NEURON (Hines and Carnevale 1997). The parameters used in the model were: soma, $l = 20 \mu\text{m}$, $d = 20 \mu\text{m}$; main apical dendrite, $l = 350 \mu\text{m}$, $d = 2.94 \mu\text{m}$; distal apical and basal dendrites, $l = 250 \mu\text{m}$, $d = 1.5 \mu\text{m}$; $C_m = 1.0 \mu\text{F}/\text{cm}^2$; control $R_m = 20,000 \Omega\text{cm}^2$; control $R_i = 150 \Omega\text{cm}$. R_m was halved and C_m doubled to account for spines throughout. Using these parameters, the electrotonic lengths (L) of the apical and basal dendrites are 1.0 and 0.5, respectively. The cell had a resting potential (V_{rest}) of -60 mV. Synapses were placed either at the soma (A), 300 μm from the soma on the main apical dendrite (B, electrotonic distance $X = 0.43$), or 550 μm from the soma on a distal apical dendrite (C, apical $X = 0.9$). Synapses were modeled as conductance changes ($g_{syn} = 6.38 \mu\text{S}$) with a rising exponential (τ_{rise}) of 0.2 ms and a decaying exponential (τ_{decay}) of 2.0 ms and a reversal potential (E_{rev}) of 0 mV.

Figure 12.3. Dendrite structure and synapse location influence EPSP summation. In each panel, the simulation is represented by a schematic diagram with excitatory synapses positioned as shown. In each case the solid line is the simulation of somatic membrane potential following activation of the two excitatory synapses with a 20 ms delay between them. Numbers by each pair of traces represent the ratio of the peak amplitudes of the second EPSP relative to the first. **A.** Temporal summation in a simple model consisting of only a soma. The dashed line is the subtracted difference between the response to activation of both synapses and just the first (see text). **B.** Addition of dendrites to the model accelerates the decay of the somatic EPSPs, reducing temporal summation. The dashed line represents the response shown in A. **C.** Moving the synapses from the soma to the dendrites slows the somatic EPSP, increasing temporal summation. The dashed line represents the response shown in B. **D.** Separating the synapses onto different dendrites maximizes summation (see text). The dashed line represents the response shown in C.

Simulation methods. All simulations use the same model described in Figure 12.2, except for the isolated soma model. In each case two identical synapses were activated, with a delay of

20 ms. Synapses were located at the soma (A, B), 300 μm from the soma on the main apical dendrite (C, $X = 0.43$), 550 μm from the soma on a distal apical dendrite (D, $X = 0.9$), or 200 μm from the soma on a basal dendrite (D, $X = 0.4$). Synaptic conductances were chosen to yield EPSPs of 6 mV in the soma (A, $g_{syn} = 1.34 \mu\text{S}$ each; B, $g_{syn} = 6.38 \mu\text{S}$ each; C, $g_{syn} = 13.25 \mu\text{S}$ each; D, apical $g_{syn} = 66.6 \mu\text{S}$, basal $g_{syn} = 16.38 \mu\text{S}$).

Figure 12.4. The spatial relationship between inhibition and excitation influences dendritic integration. In each panel, the simulation is represented by a schematic diagram with excitatory and inhibitory synapses positioned as shown. The inhibitory synapse (Δ , i) is activated 5 ms before the excitatory synapse (\blacktriangle , e) and has $E_{rev} = V_{rest}$, resulting in no hyperpolarization by activation of the inhibitory synapse at rest. Numbers by each pair of traces represent the peak of the EPSP with inhibition (solid lines) relative to the EPSP without inhibition (dashed lines). **A.** Two excitatory synapses on the soma are activated (with a 20 ms delay between them, arrowheads indicate timing) either with inhibition or without inhibition. The lower traces show the time course of the inhibitory synaptic conductance (thick line, peak = 50 nS) and current (thin line, peak = 109 pA). **B.** Separate responses to activation of the excitatory synapse on the apical dendrite (top traces) or basal dendrite (bottom traces) with and without somatic inhibition. **C.** Responses to activation of the same synapses as in B with and without apical dendritic inhibition. **D.** Responses to activation of the same excitatory synapses as in B and C with and without distal apical inhibition. The trace with long-dashed trace indicates simultaneous activation of the excitatory synapse and inhibition on a different branch (peak = 0.88 of control at top and 1.0 at bottom, obscured by the solid line response). Arrowheads indicate the timing of synaptic activation in B–D.

Simulation methods. All as described in Figures 12.2 and 12.3, including placement and conductance of excitatory synapses for corresponding schematic diagrams. Inhibitory synapses were placed either at the soma (A, B), 300 μm from the soma on the main apical dendrite (C, $X =$

0.43), or at the end of a distal apical dendrite (D, $X = 1.0$). Inhibitory synapses were modeled with the following parameters: $\tau_{rise} = 2$ ms; $\tau_{decay} = 20$ ms; $g_{syn} = 50$ μ S; $E_{rev} = V_{rest} = -60$ mV.

Figure 12.5. Dendritic spikes and their relation to axonal action potential initiation. **A.** Somatic (green traces) and dendritic (blue traces; 440 μ m from the soma) recording from a neocortical layer 5 pyramidal neuron during synaptic stimulation in layer 2/3. All recordings from the same cell at similar stimulation intensity. Top: Subthreshold somatic and dendritic EPSPs. Second from the top: Initiation of a dendritic sodium spike in the absence of somatic action potentials. Second from the bottom: Initiation of a dendritic sodium spike in relative isolation from somatic action potentials which occur in a burst due to generation of a dendritic calcium spike. Bottom: Initiation of a dendritic spike just prior to a somatic action potential. **B.** Layer 5 pyramidal neuron with dendritic recording pipettes at two locations in the apical tuft (red, 875 μ m from the soma; blue, 715 μ m from the soma). An extracellular stimulation electrode (black) was positioned ~ 100 μ m distal to the distal recording pipette. **C.** Responses to graded increase in extracellular stimulation (from 4 to 9 μ A) recorded at both locations. **D.** Distal tuft dendritic recording from a different pyramidal neuron (807 μ m from the soma) in control (red) and after addition of 50 μ M AP5 (black). **E.** Somatic (green traces), dendritic (blue traces; 300 μ m from the soma) and axonal (red traces; 20 μ m from the soma) recording from a neocortical layer 5 pyramidal neuron during synaptic stimulation in layer 2/3. All recordings from the same cell. Left: Synaptic stimulation in layer 2/3 at threshold for somatic action potential initiation. Right: High intensity synaptic stimulation, which initiated a dendritic spike prior to the somatic action potential.

Part A adapted from Action potential initiation and propagation in rat neocortical pyramidal neurons, Greg Stuart, Jackie Schiller, Bert Sakmann, *The Journal of Physiology*, 505(3), pp. 617–32, Figure 11b and c, Copyright 1997, John Wiley and Sons. Parts B–D adapted from Matthew E. Larkum, Thomas Nevian, Maya Sandler, Alon Polsky, and Jackie Schiller, *Synaptic*

integration in tuft dendrites of layer 5 pyramidal neurons: a new unifying principle, *Science*, 325(5941) pp. 756–760, doi: 10.1126/science.1171958 (c) 2009, The American Association for the Advancement of Science. Reprinted with permission from AAAS. Part E adapted from Action potential initiation and propagation in rat neocortical pyramidal neurons, Greg Stuart, Jackie Schiller, Bert Sakmann, *The Journal of Physiology*, 505(3), pp. 617–32, Figure 11b and c, Copyright 1997, John Wiley and Sons.

Figure 12.6. Effects of dendritic branching on spike propagation. **A.** Action potential backpropagation from a large parent dendrite (black dot) into two smaller daughter dendrites is efficient when $GR \leq 1$ (case A1; see text). Backpropagation is inefficient when the daughter dendrites are large, such that $GR > 1$ (case A2). Backpropagation past oblique branches (case A3) is dependent (denoted by ?) on the geometry and excitability of the oblique branch. If the branch is long and/or relatively inexcitable, it draws current away from the large dendrite, thus reducing backpropagation. If the branch is short and/or relatively excitable, the spike in the oblique branch can return current back to the main dendrite, thus increasing backpropagation. This latter effect is facilitated by synaptic depolarization of the oblique branch. **B.** Dendritic spikes propagating from a small dendrite (black dot) into a larger one will have a tendency to fail. The smaller black dot indicates that less current is needed to produce a spike in a small-diameter dendrite (case B1). The lower input impedance of the larger branch will cause the membrane potential to drop (possibly below threshold for a spike) at the branch point. Even if a dendritic spike starts in a larger dendrite (case B2), it will tend to fail at branch points, as it is difficult for the current from one branch to bring both branches to threshold for a spike. For both of these cases, dendritic spike propagation will be more efficient if either or both of the downstream branches are depolarized by synaptic input. Propagation of dendritic spikes along a large apical dendrite will be influenced by oblique branches in a way that depends (?) on the excitability of the oblique branch (case B3). Long and/or inexcitable oblique branches will promote propagation failure,

whereas shorter and/or more excitable branches will provide return current and promote successful propagation.

Figure 12.7. Effects of prolonged Na⁺ channel inactivation on bAPs and dendritic spikes in CA1 pyramidal neurons. **A.** A train of action potentials evoked by somatic current injection (300 pA) and recorded simultaneously in the soma (green traces) and apical dendrite (blue traces, 200 μm from the soma). Repetitive action potential firing results in an activity-dependent decline in the amplitude of bAPs (see Spruston et al. 1995b). **B.** Dendritic Na⁺ currents recorded in a cell-attached patch on an apical dendrite 203 μm from the soma. Brief depolarization (2 ms, 70 mV) via a command potential (V_{com} , relative to V_{rest}) delivered to the patch pipette evoked TTX-sensitive inward currents that accumulated in an inactivated state during the train, due to slow recovery from inactivation. A test pulse 500 ms after the train shows only 38% recovery from inactivation. Adapted from Jung et al. 1997. **C.** A depolarizing prepulse in a somatic recording (green traces) evokes four action potentials, which backpropagate into the dendrites, exhibiting activity-dependent amplitude attenuation in a simultaneous dendritic recording (blue traces, 267 μm from the soma). This prepulse of bAPs (left) suppressed dendritic spike initiation in response to synaptic stimulation in stratum radiatum when evoked less than 500 ms after the prepulse (right). Adapted from Golding and Spruston 1998.

Part A is unpublished data collected as part of Golding et al., *Journal of Neuroscience*, 1999. Part B is adapted from Jung et al., 1997. Adapted from *Neuron*, 21(5), Nace L Golding and Nelson Spruston, Dendritic sodium spikes are variable triggers of axonal action potentials in hippocampal CA1 pyramidal neurons, pp.1189–1200, Copyright 1998, Elsevier. With permission from Elsevier.

Figure 12.8. Dendritic spikes in individual dendritic branches suggest a multi-layer model of dendritic integration.

A. Somatic voltage recordings in response to uncaging glutamate at a progressively increasing number of locations for distributed (red) and clustered (green) configuration with a 0.1 ms interval. The lower traces represent the corresponding temporal derivatives. Dashed lines across the temporal derivatives indicate the subthreshold dV/dt levels. **B.** Image of the apical dendritic region of a CA1 pyramidal neuron showing positions of the seven spines on a radial oblique branch for clustered (green dots) and distributed (red dots) experimental arrangements.

Associated numbers indicate the temporal sequence of distributed locations during uncaging with a 0.1 ms interval. **C.** Plot showing measured versus expected amplitudes of glutamate-evoked potentials for the clustered and distributed recordings shown in A and B. **D.** Schematic representation of the main finding of Polsky *et al.* (2004): Two multi-synaptic inputs onto a single dendritic branch exhibit supra-linear summation of somatic EPSPs (top). Inputs onto separate branches exhibit roughly linear summation (bottom). **E.** Reconstructed layer 5 pyramidal neuron (left) and an abstracted three-layer network model (right; based on Häusser and Mel 2003). Red branches represent the distal apical inputs; light blue branches represent the perisomatic inputs. Together, these inputs constitute the first layer of the network model, each performing supra-linear summation of the type shown in A (indicated by small circles with sigmoids). The outputs of this first layer feed into two integration zones: one near the perisomatic branches (e.g. soma, dark blue) and one near the distal apical branches (e.g. apical spike initiation zone, purple). These integration zones constitute the second layer of the network model (large circles with sigmoids). The third layer (not shown) is the action potential initiation zone in the axon. Grey circles indicate connections between layers.

Parts A-C adapted from Losonczy *et al.* 2006. Parts D and E adapted with permission from Macmillan Publishers Ltd: Nature Neuroscience, 7(6), Nelson Spruston and William L Kath, Dendritic arithmetic, pp.567–569, 2004, Nature Publishing Group.

Figure 12.9. Gating of dendritic spike propagation by synaptic depolarization. **A.** Color map of peak depolarization and voltage versus time plots at three dendritic locations for activation of 10% of perforant path (PP) synapses (one trial) in a CA1 pyramidal neuron model with weak dendritic excitability. **B.** Response of the same model to activation of 3% of Schafer collateral (SC) synapses in the upper apical dendrites. **C.** Response of the same model to coincident activation of 10% PP and 3% SC synapses leading to AP output. Adapted from Jarsky *et al.* 2005. **D.** Reconstruction of a biocytin-filled pyramidal neuron, with the recording pipette positions shown symbolically (770 μm from soma in red, 400 μm from soma in blue and one at the soma in grey). Cortical layers are indicated on the left. Scale bar, 200 μm . **E.** EPSP-like current injection of (I_{stim} , 0.3 nA peak) at the distal pipette (red trace, bottom) produced a subthreshold somatic voltage response (V_m) of only 1.4 mV. Color indicates the corresponding electrode in the diagram. **F.** Threshold current injection at the soma (I_{stim}) evoked an action potential that was reduced in amplitude but increased in width in the dendrite. **G.** The combination of the injections of current used in E and F separated by an interval of 5 ms (Δt) evoked a burst of action potentials. Scale bars in C also apply to B and D. **H.** A similar dendritic calcium spike could be evoked by a larger (1.2 nA) current injection alone at the distal dendritic electrode.

Parts A-C adapted with permission from Macmillan Publishers Ltd: Nature Neuroscience, 8(12), Tim Jarsky, Alex Roxin, William L Kath, and Nelson Spruston, Conditional dendritic spike propagation following distal synaptic activation of hippocampal CA1 pyramidal neurons, pp. 1667–1676, 2005, Nature Publishing Group. Parts D-H adapted from Larkum *et al.*, Nature, 1999.

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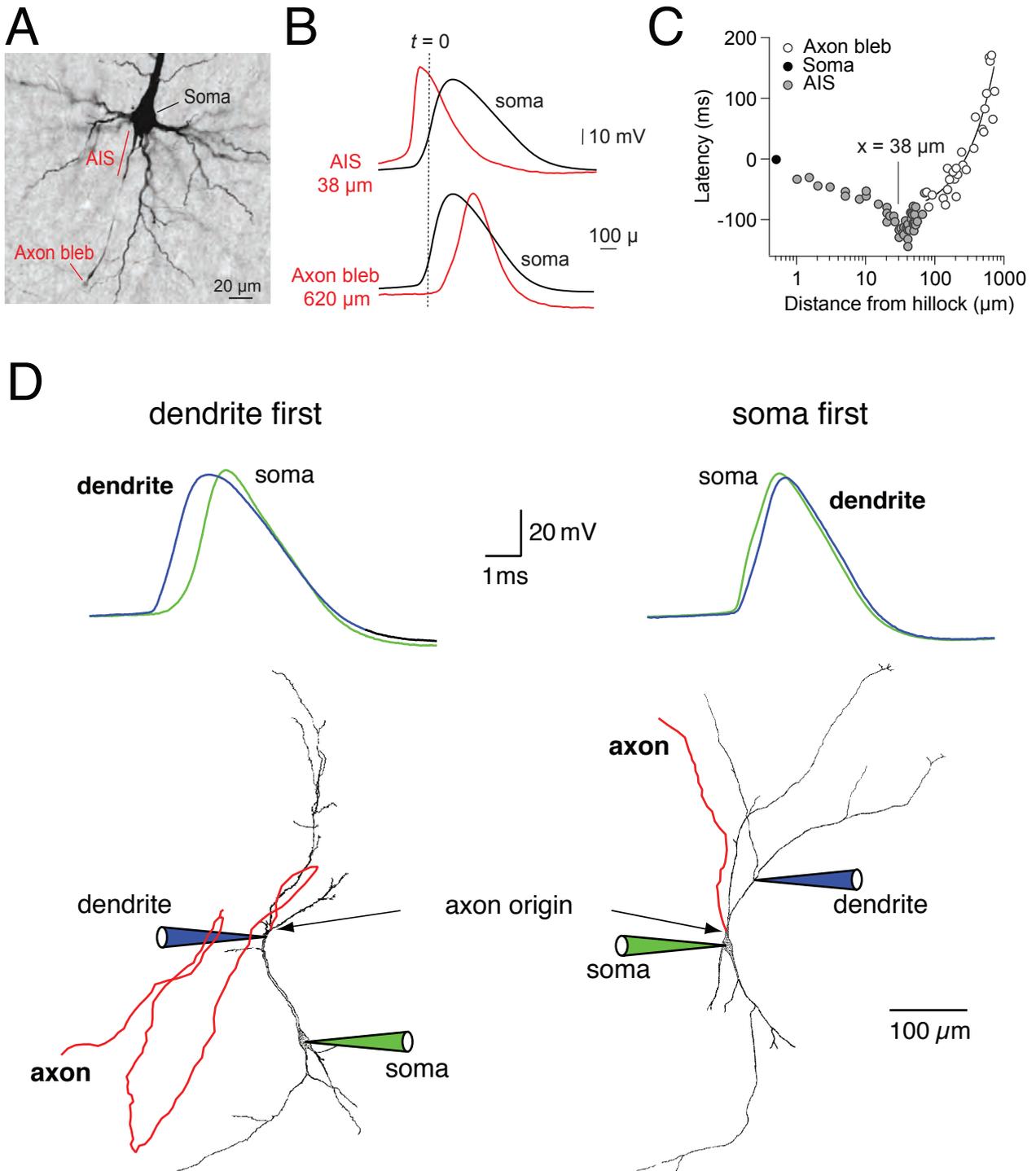


Figure 12.1

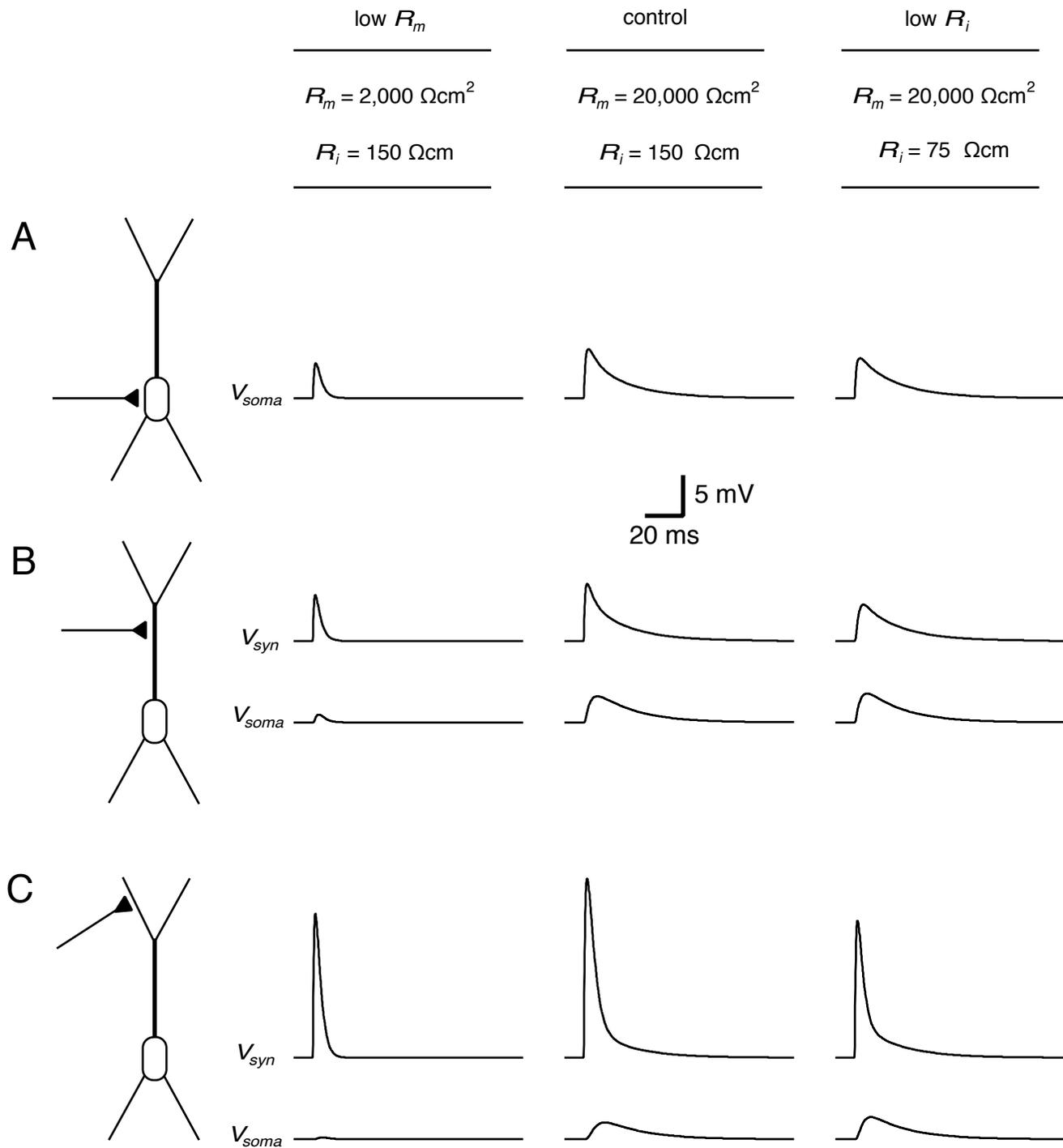


Figure 12.2

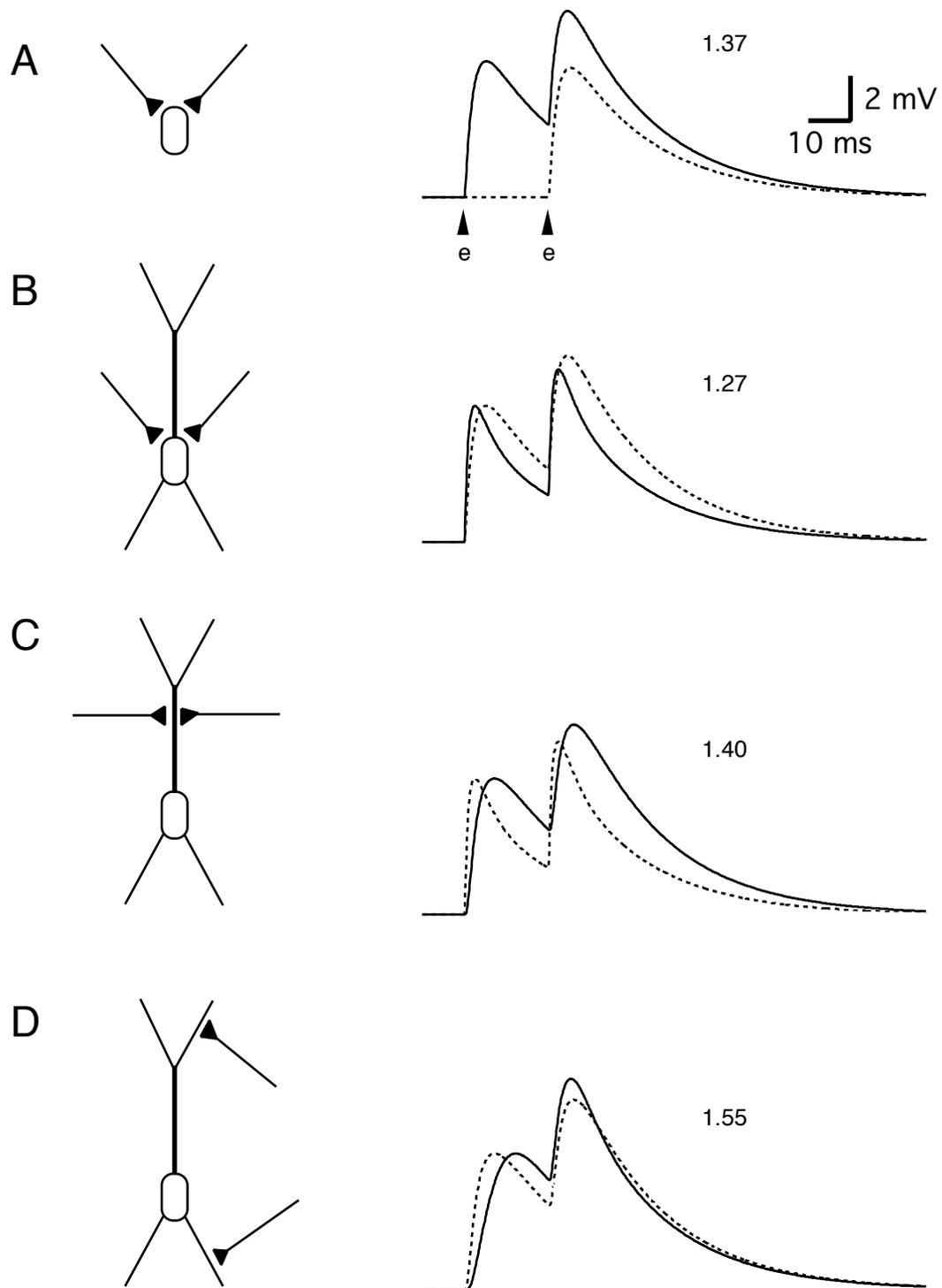


Figure 12.3

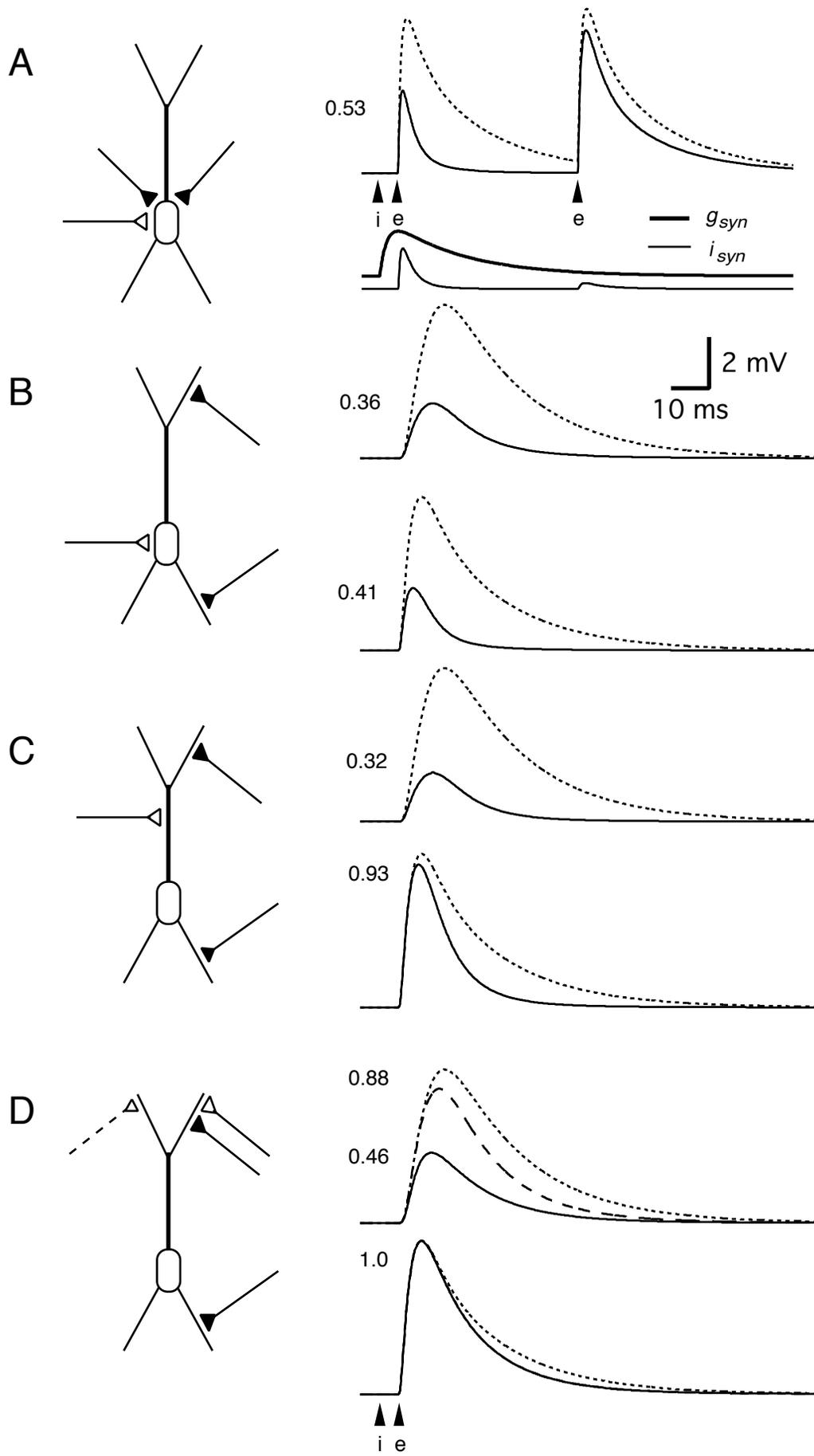


Figure 12.4

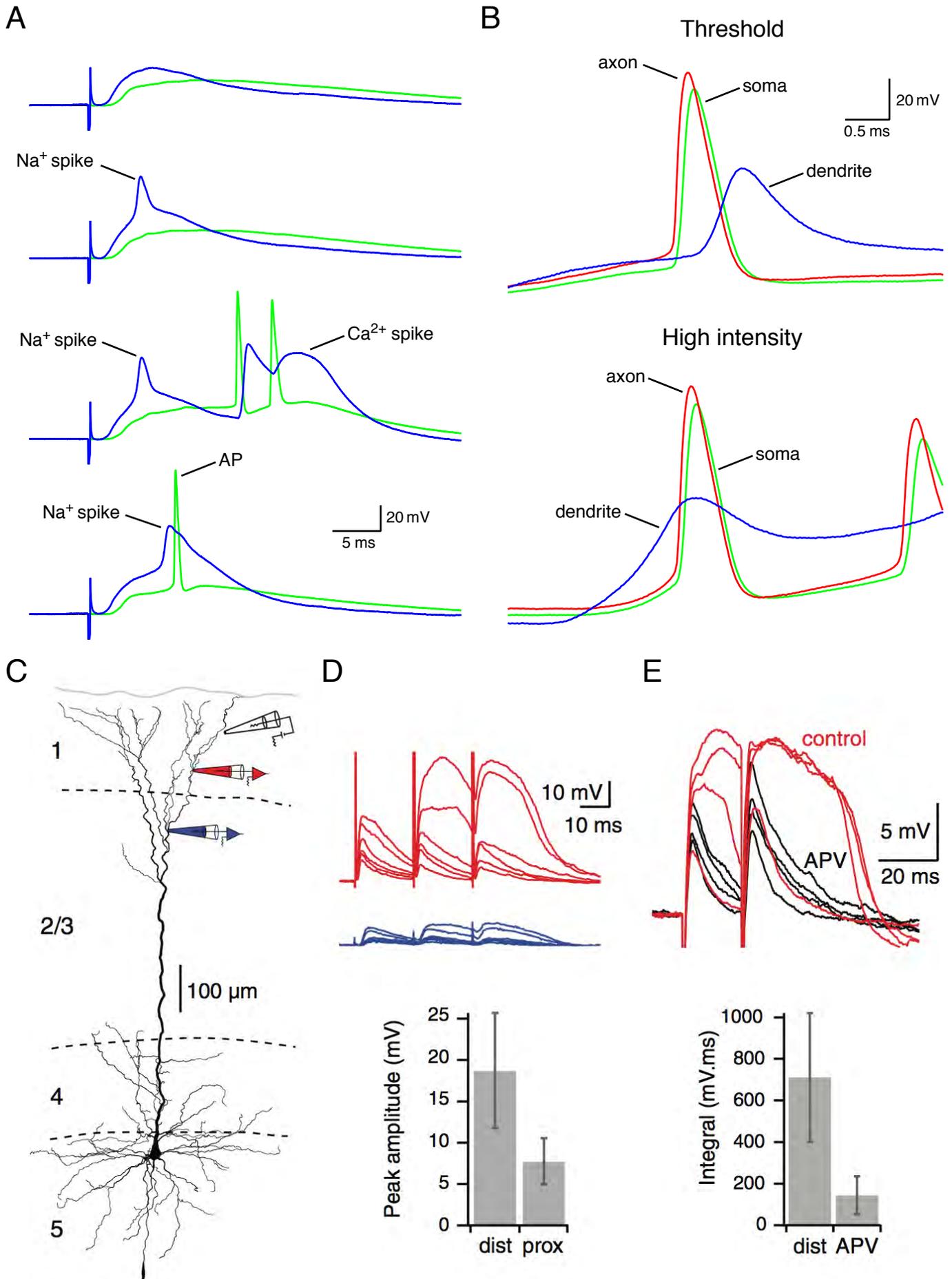


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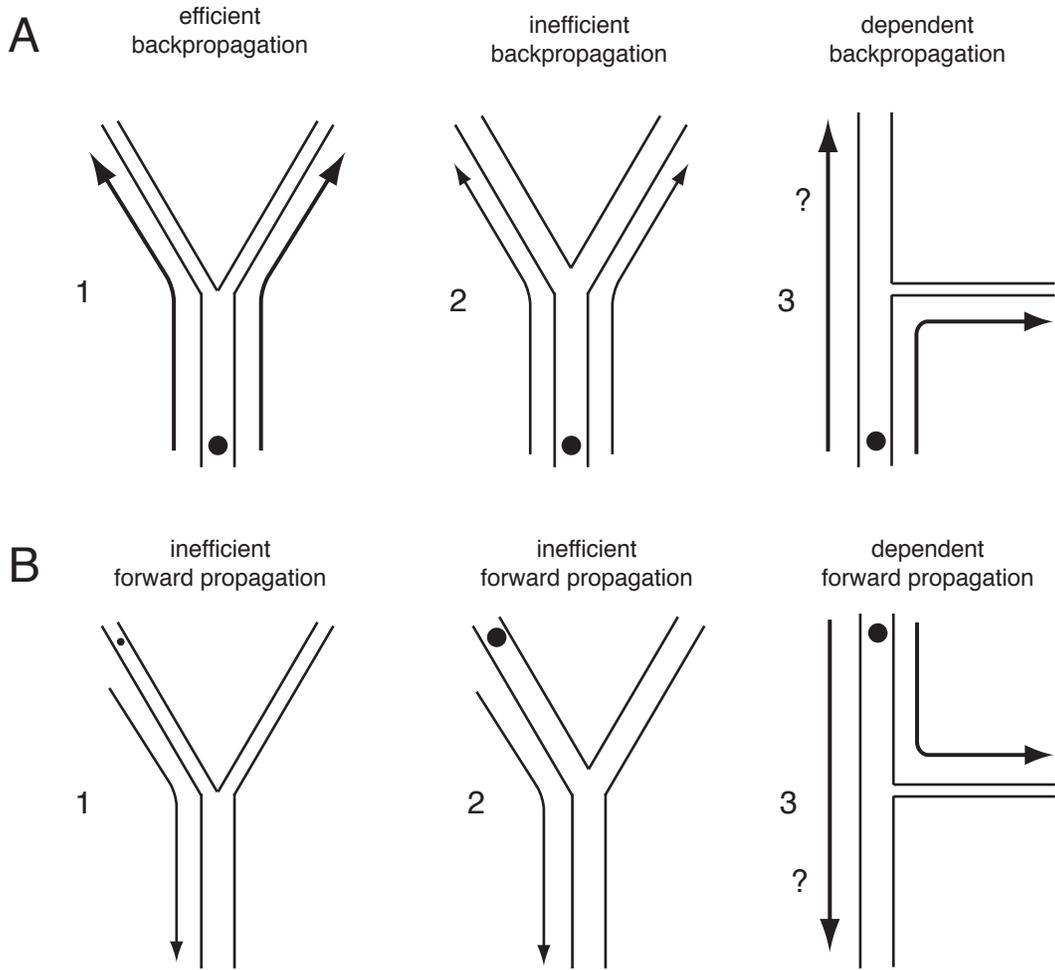


Figure 12.6

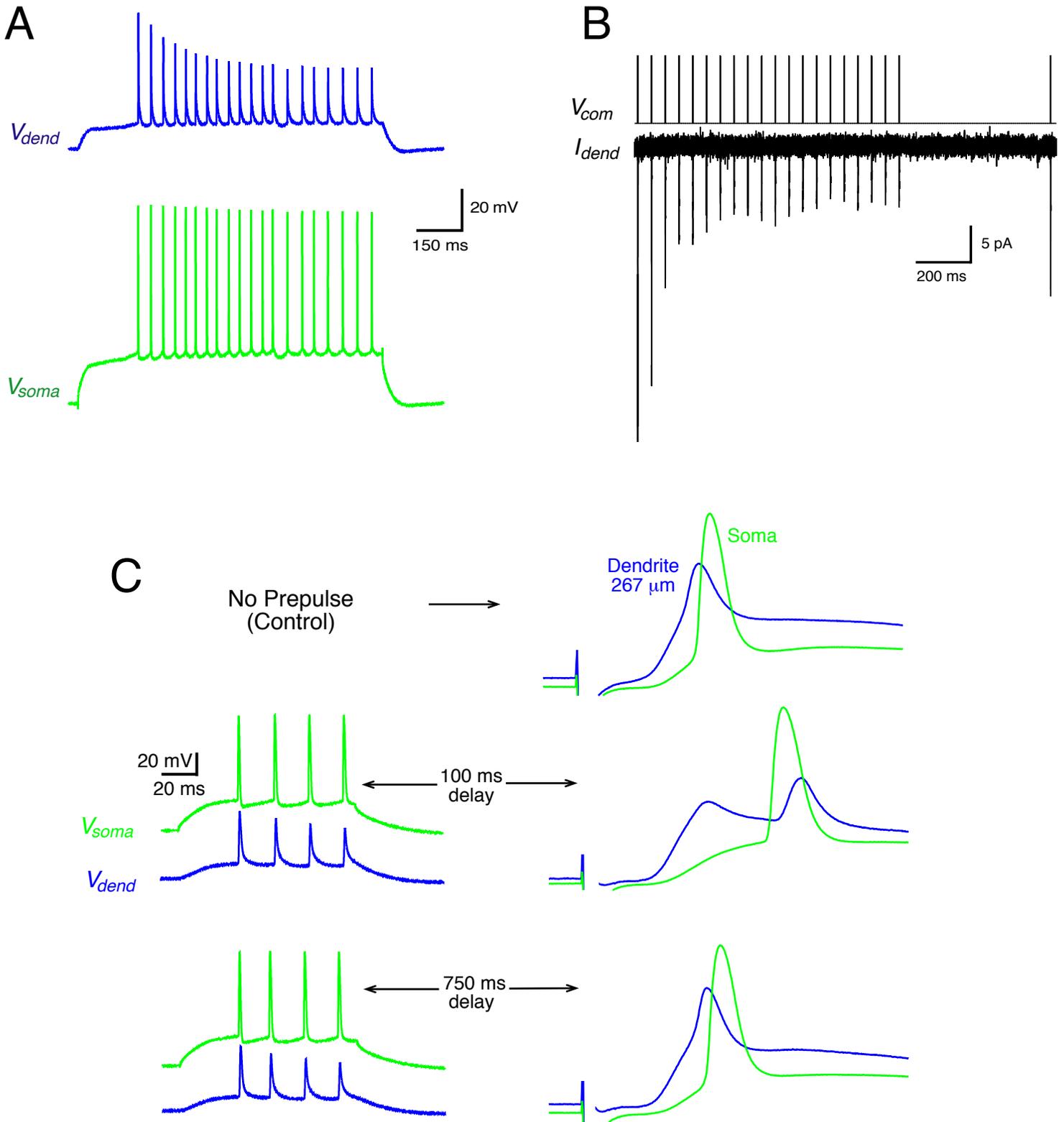


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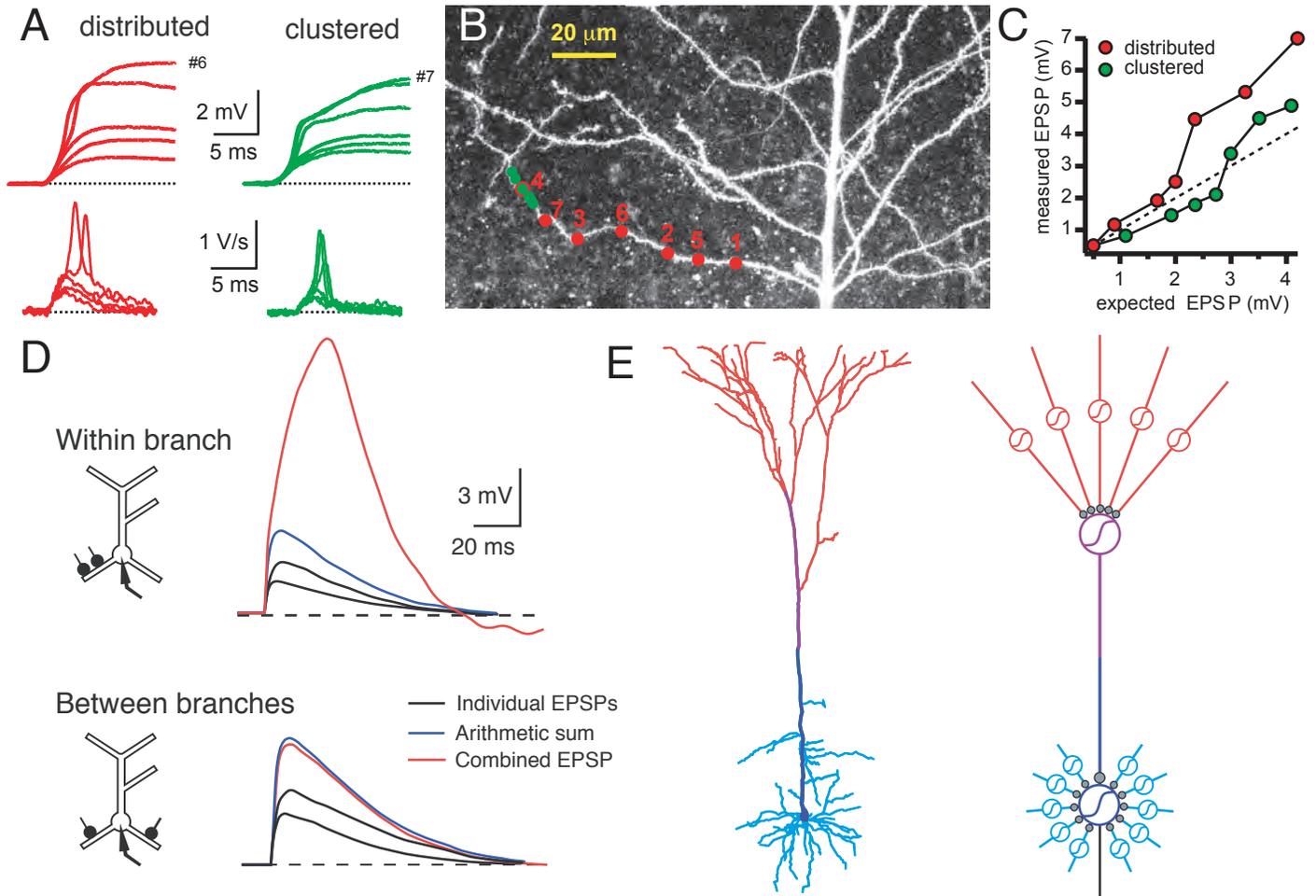


Figure 12.8

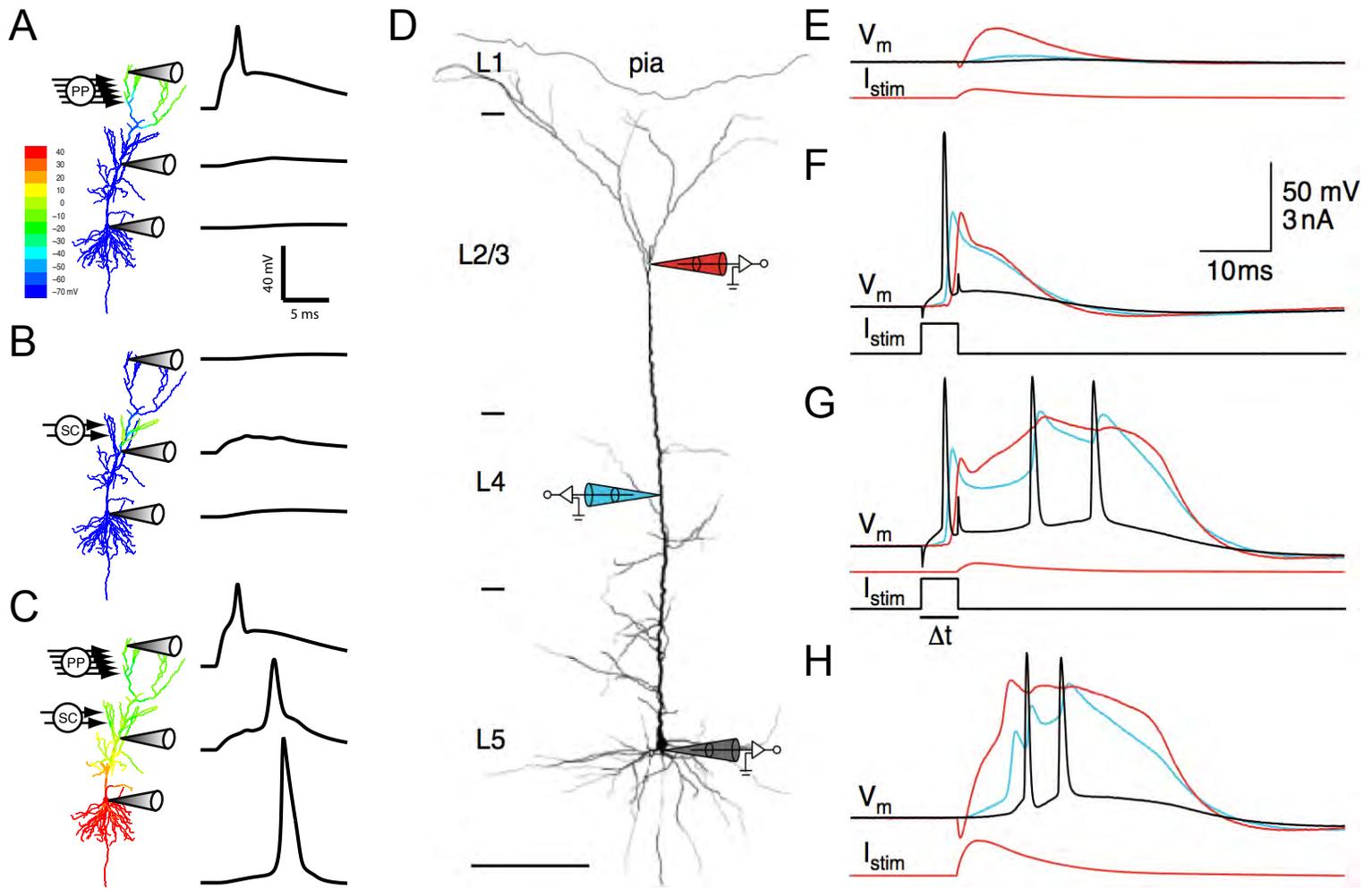


Figure 12.9