Voltage-Dependent Properties of Dendrites That Eliminate Location-Dependent Variability of Synaptic Input

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Cook, Erik P. and Daniel Johnston. Voltage-dependent properties of dendrites that eliminate location-dependent variability of synaptic input. *J. Neurophysiol.* 81: 535–543, 1999. We examined the hypothesis that voltage-dependent properties of dendrites allow for the accurate transfer of synaptic information to the soma independent of synapse location. This hypothesis is motivated by experimental evidence that dendrites contain a complex array of voltage-gated channels. How these channels affect synaptic integration is unknown. One hypothesized role for dendritic voltage-gated channels is to counteract passive cable properties, rendering all synapses electrotonically equidistant from the soma. With dendrites modeled as passive cables, the effect a synapse exerts at the soma depends on dendritic location (referred to as location-dependent variability of the synaptic input). In this theoretical study we used a simplified three-compartment model of a neuron to determine the dendritic voltage-dependent properties required for accurate transfer of synaptic information to the soma independent of synapse location. A dendrite that eliminates location-dependent variability requires three components: *1*) a steady-state, voltage-dependent inward current that together with the passive leak current provides a net outward current and a zero slope conductance at depolarized potentials, *2*) a fast, transient, inward current that compensates for dendritic membrane capacitance, and *3*) both α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid– and *N*-methyl-D-aspartate–like synaptic conductances that together permit synapses to behave as ideal current sources. These components are consistent with the known properties of dendrites. In addition, these results indicate that a dendrite designed to eliminate location-dependent variability also actively back-propagates somatic action potentials.

INTRODUCTION

Experimental evidence established that the dendrites of central neurons contain a complex array of voltage-gated channels (for reviews see Johnston et al. 1996; Stuart et al. 1997; Yuste and Tank 1996). How these channels affect neuronal processing of synaptic input is unknown. Many plausible hypotheses have been proposed regarding the role active dendrites play in synaptic integration (e.g., Bernander et al. 1994; Mel 1993; Shepherd and Brayton 1987; Softky 1994; for a review see Mel 1994). One of the earliest was the "boosting hypothesis," which proposed that dendritic voltage-gated channels counteract passive cable properties, rendering all synapses electrotonically equidistant from the soma (Andersen et al. 1980; De Schutter and Bower 1994; Jack et al. 1975; Miller et al. 1985; Schwindt and Crill 1995; Shepherd et al. 1985; see also De Schutter 1998). In this theoretical study we focus on this hypothesis by addressing the question: What voltage-dependent properties are necessary for a dendrite to implement the boosting hypothesis?

Rall (1959) modeled the passive electrical properties of dendrites with three cable parameters: axial resistance (R_i), membrane capacitance (C_m), and membrane conductance (G_m). With the passive model of dendrites the effect a synapse exerts at the soma depends on dendritic location. We refer to this as location-dependent variability of the synaptic input.

There are examples where synapse location may be an important component of the synaptic signal. For example, the large mossy fiber synaptic terminals on hippocampal CA3 cells may be positioned near the soma to strongly influence the somatic membrane potential. It is possible, however, that, for large populations of homogeneous synaptic inputs (e.g., Schaffer collateral inputs onto hippocampal CA1 cells), eliminating the distortion caused by location-dependent variability would be desirable. This would be particularly important if information storage at these synapses is represented by the strength of the synaptic contact and not synaptic location, as proposed by many theories of neural network function. The idea that location should not be part of the synaptic signal was the primary motivation for this study.

We previously demonstrated that voltage-dependent inward currents can minimize location-dependent variability in a reconstructed CA1 neuron (Cook and Johnston 1997). In this study, we build on those results by now determining the theoretical requirements for not just minimizing but eliminating this variability. Starting with a simplified three-compartment passive neuron model, we found that a dendrite that eliminated location-dependent variability required three components: *1*) a steady-state depolarization-activated inward current that together with the passive leak current produced an outward current with a zero slope conductance, *2*) a fast, transient, depolarization-activated inward current that compensated for dendritic capacitance, and *3*) both α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)- and *N*-methyl-D-aspartate (NMDA)-like synaptic conductances that together allowed synapses to behave as ideal current sources. In addition, we found that a dendrite designed to eliminate location-dependent variability also actively back-propagates somatic action potentials.

METHODS

The neurophysiological modeling program NEURON was used for all simulations (Hines 1993). Figure 1*A* illustrates the basic three-compartment model. The passive parameters were $G_m = 0.1\ \mu S/cm^2$ (equivalent

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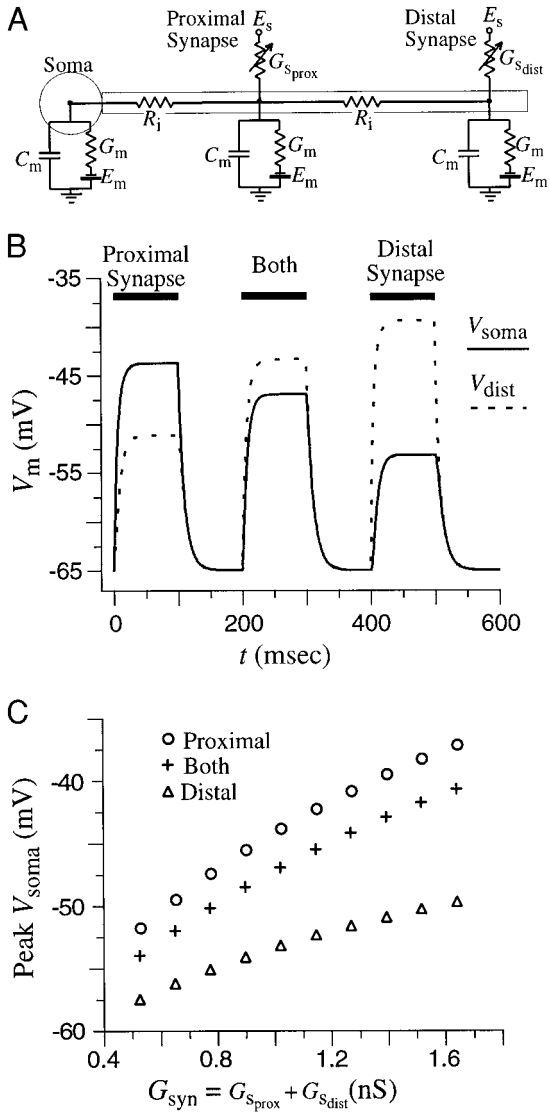

FIG. 1. Example of location-dependent variability in passive dendrites. *A*: 3-compartment model with passive dendrites and soma (see METHODS). The 2 synaptic input locations are shown. *B*: somatic (V_{soma}) and distal dendritic (V_{dist}) membrane potential in response to 3 different 100-ms, 1-nS synaptic inputs, each applied with a different spatial pattern (heavy bars). The 3 patterns of input were all input on the proximal dendrite compartment ($G_{s_{prox}} = 1$ and $G_{s_{dist}} = 0$ nS), input divided equally between the proximal and distal dendrites ($G_{s_{prox}} = G_{s_{dist}} = 0.5$ nS), or all input on the distal dendrite compartment ($G_{s_{prox}} = 0$ and $G_{s_{dist}} = 1$ nS). *C*: peak somatic potentials for a range of synaptic input strengths. Every input strength ($G_{syn} = G_{s_{prox}} + G_{s_{dist}}$) was applied in each of the 3 spatial input patterns. For every G_{syn}, the peak V_{soma} is dependent on the spatial pattern of input.

to $R_m = 10{,}000\ \Omega cm^2$), $C_m = 1\ \mu F/cm^2$, $R_i = 200\ \Omega cm$, and $E_m = -65$ mV. The soma compartment was $10 \times 10\ \mu m$ (length $\times$ width), and each of the two dendritic compartments were $300 \times 1\ \mu m$. Synapses were placed at the center of each dendritic compartment. Synaptic inputs were modeled as sustained conductance changes with a duration of 100 ms. The model for the NMDA-like voltage-dependence was that of Holmes and Levy (1990). The synaptic reversal potentials were $E_s = E_a = 0$ mV (AMPA-like) and $E_n = 10$ mV (NMDA-like) (MacDermott et al. 1986). For Fig. 7, the fast Na^+ ($\bar{g}_{Na} = 0.02\ S/cm^2$) and the delayed-rectifier K^+ ($\bar{g}_{KDR} = 0.04\ S/cm^2$) channel models were previously described by Cook and Johnston (1997). The voltage-dependent currents I_v and I_t are described in the APPENDIX. All simulations were run on a Silicon Graphics Onyx 2 system.

RESULTS

Location-dependent variability in passive dendrites

We first illustrated location-dependent variability by using the model in Fig. 1*A*. This model had a passive soma compartment and two passive dendritic compartments to which synaptic input was applied. Location-dependent variability was demonstrated by applying a sustained conductance synaptic input[1] to the dendrites in three different spatial arrangements: 1 nS on the proximal compartment only, 0.5 nS applied to both compartments, or 1 nS on the distal compartment only. In each case, the total strength of the synaptic input (G_{syn}) was the same, and only the spatial pattern was varied. In Fig. 1*B*, the somatic (V_{soma}) and distal dendritic dendritic (V_{dist}) potential is shown in response to each of these patterns of synaptic input. Each heavy bar represents the duration of the synaptic input (100 ms), with its location indicated. Although G_{syn} for each pattern was identical, the amount of somatic depolarization varied. A model that had no location-dependent variability would have produced the same response at the soma for each of the three input patterns.

Figure 1*C* illustrates location-dependent variability for a range of G_{syn} values. The peak somatic potential is plotted as a function of the total synaptic strength for each of the three input patterns. As predicted by passive cable theory, the proximal input is always more effective than either the distributed or distal input patterns. We now posed the following question. How might this variability be eliminated? In this case, the differences in the peak response among the three spatial patterns would be zero. Thus V_{soma} would only be a function of the total strength of the synaptic input.

Dendritic voltage-dependent conductances alone cannot eliminate location-dependent variability

We previously demonstrated that location-dependent variability can be reduced with dendritic voltage-dependent channels (Cook and Johnston 1997). Such a mechanism alone, however, cannot eliminate location-dependent variability. To understand this, one must examine the circuit of the passive model in Fig. 1. The basic problem faced by any mechanism attempting to eliminate location-dependent variability is that, as a synaptic conductance is activated, it alters the electrical circuit of the dendrites. Every different spatial pattern and strength of synaptic input results in a different dendritic circuit. As a result, there is no direct correspondence between the dendritic membrane potential and the strength of synaptic input. This makes it impossible for any voltage-dependent membrane conductance alone to eliminate location-dependent variability for all possible patterns of synaptic input.

The situation might be different, however, if synapses were approximated by ideal current sources rather than conductance changes. Ideal current sources have infinite input resistance and would not affect the dendritic circuit when activated. To test this, we replaced the synaptic conductances in our model with ideal current sources. Figure 2*A* illustrates synaptic inputs modeled as ideal current sources (I_s). The total input strength

[1] The sustained synaptic conductance was intended to represent the time-averaged effect from a train of EPSPs (Bernander et al. 1991).

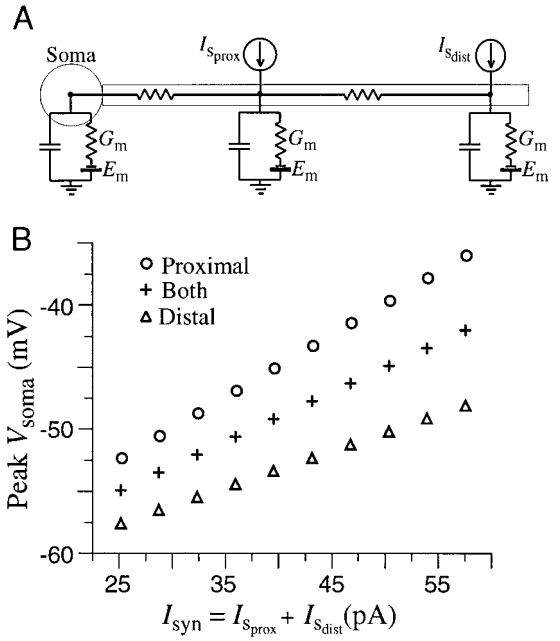

FIG. 2. Replacing synaptic conductances with ideal current sources. *A*: model with passive dendrites and ideal current sources as the synaptic input. *B*: peak V_{soma} in response to the 3 input patterns for a range of synaptic input strengths ($I_{syn} = I_{s_{prox}} + I_{s_{dist}}$). The spatial input patterns were the same as that in Fig. 1.

(I_{syn}) was varied to produce the same range of peak somatic depolarizations as in Fig. 1*C*. Peak somatic responses are shown in Fig. 2*B* with each value of I_{syn} applied in the three different spatial input patterns. Location-dependent variability is still present even with synapses modeled as ideal current sources, although the relationship between the somatic response and I_{syn} is now linear.

Adding a steady-state voltage-dependent current to the dendrites

With synapses modeled as ideal current sources, it now becomes possible to apply a simple approach to eliminate location-dependent variability. If a depolarizing-activated inward current that produced a negative-slope conductance equal to $-G_m$ were added to the dendrites, only a fixed amount of synaptic current would escape across the dendritic membrane as it traveled toward the soma. The amount of current escaping across the dendritic membrane would be independent of the dendritic membrane potential. The remaining synaptic current would reach the soma regardless of where it entered the dendrite.

To accomplish this, we added an instantaneous voltage-dependent conductance (G_v) to the dendritic membrane (Fig. 3*A*).[2] This current activated at -55 mV and produced a negative slope conductance equal to $-G_m$. The effect of G_v on the dendritic *I-V* relationship is shown in Fig. 3*B*. G_v produces an inward current (I_v) that counteracts the positive slope conductance of the leak current (I_m) to produce a net current ($I_m + I_v$) with a zero slope conductance. A zero slope conductance allows all synaptic current entering the dendrites (minus a fixed amount) to arrive at the soma. All depolarization activated inward currents (e.g., voltage-gated Na^+ and Ca^+ currents) produce negative slope conductance relationships.

Although in theory the addition of G_v should have eliminated location-dependent variability, it did not. Figure 3*C* illustrates V_{soma} in response to the three spatial synaptic input patterns. On obtaining a membrane potential of -55 mV, the zero slope conductance of $I_m + I_v$ introduced an infinite membrane time constant in the dendrites, and V_{soma} slowed considerably.[3] Note, however, that this occurs only in the depolarizing direction. When the synaptic current injection ends, the membrane rapidly hyperpolarizes with a time constant similar to the passive model in Fig. 1*B*. This is due to the constant outward current of $I_m + I_v$ rapidly charging the dendritic capacitance.

[2] G_v is similar to G_{boost} used in Cook and Johnston (1997).

[3] This results from the dendritic membrane having an equivalent infinite membrane resistance at potentials positive to -55 mV, requiring the dendritic capacitance to discharge through the soma.

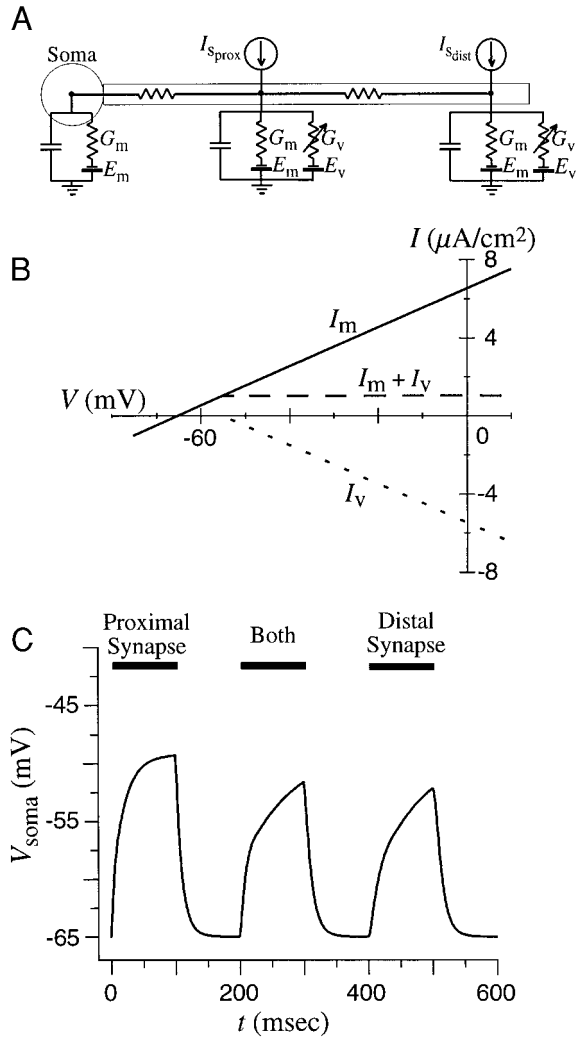

FIG. 3. Adding a steady-state voltage-dependent inward current (I_v) to the dendrites. *A*: model with the voltage-dependent conductance G_v added to the dendrites. *B*: *I-V* relationship of the dendritic membrane. On activation of I_v, the passive leak current (I_m) and I_v together produce a net outward current with a 0 slope conductance ($I_m + I_v$). *C*: V_{soma} in response to a 24.5-pA synaptic input current applied in the 3 spatial input patterns. The soma depolarizes excessively slow on activation of I_v. However, repolarization remains fast.

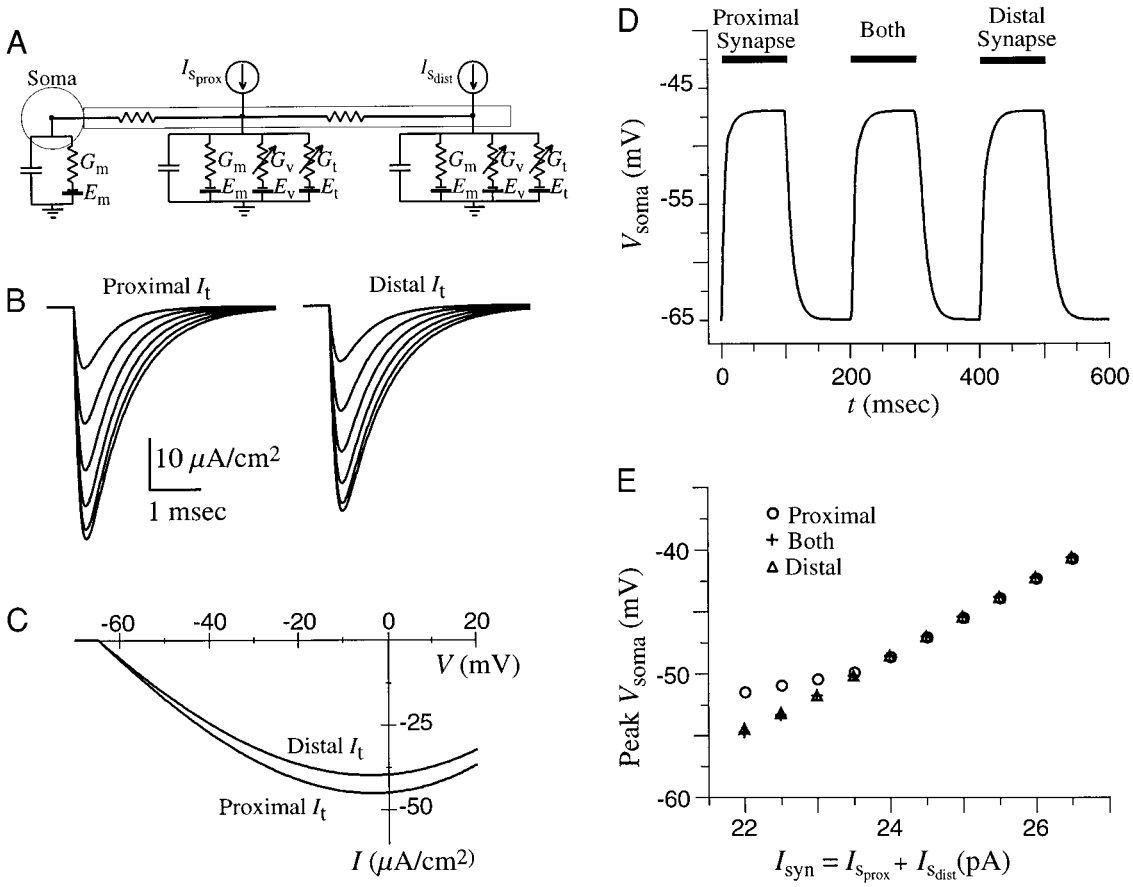

FIG. 4. Capacitive compensation with the fast, transient, voltage-dependent current (I_t). *A*: model with both G_v and G_t added to dendrites. *B*: I_t of the proximal and distal dendritic compartments in response to voltage-clamp steps from −55 to −5 mV. *C*: peak I_t as a function of membrane potential. *D*: V_{soma} in response to a 24.5-pA synaptic current applied in the 3 different spatial input patterns. Note the lack of location-dependent variability. *E*: peak V_{soma} for a range of synaptic input strengths. Location-dependent variability was eliminated on activation of G_v and G_t in the dendrites.

Capacitive compensation with a fast, transient, dendritic voltage-dependent conductance

The addition of G_v to the dendrites eliminated the location-dependent loss of synaptic current across the dendritic membrane yet introduced the undesirable infinite time constant. The capacitive current is $I_c = Cdv/dt$ and is outward with membrane depolarization. This suggests the need for a transient inward current to compensate for I_c. Such a current would "supercharge" the membrane, allowing rapid depolarization. An example of this occurs in voltage-clamp amplifiers that make use of capacitive compensation to allow fast changes in clamp potential.

A transient voltage-dependent conductance (G_t) was constructed with the activation, inactivation, and time constants of activation and inactivation as free parameters. We inserted G_t into the dendrites of the model, which also contained the steady-state conductance G_v (Fig. 4*A*). Numerical methods were used to find the set of parameters for G_t that best eliminated location-dependent variability and provided a fast response at the soma. The parameters for G_t were fitted for both dendritic compartments simultaneously. Details of the numerical methods are described in the APPENDIX.

After many iterations, the computer produced a model of G_t for each dendrite compartment that together with G_v eliminated location-dependent variability without compromising the speed of somatic depolarization. Voltage-clamp responses of the transient current (I_t) produced by G_t are shown in Fig. 4*B* for each dendritic compartment. The time constant of activation was found to be very fast, whereas the time constant of inactivation was much slower. The *I-V* relationship of the peak current is shown in Fig. 4*C*.

With G_t added to the dendritic membrane, the model eliminated location-dependent variability of the synaptic input and responded quickly in the depolarizing direction (Fig. 4*D*).[4] Figure 4*E* illustrates that location-dependent variability is eliminated for a range of synaptic input strengths (compare with Fig. 2*B*). The presence of location-dependent variability for values of peak V_{soma} less than −50 mV results from the lack of sufficient dendritic depolarization to activate G_v in both dendritic compartments.

A role for the NMDA voltage-dependent synaptic current

The dendritic model that eliminated location-dependent variability required synapses to behave as ideal current sources. When the current sources of the model in Fig. 4*A* were replaced with synaptic conductances, location-dependent vari-

[4] Because the computer did not use the first 25 ms of the response in fitting G_t (see APPENDIX), there is a small location-dependent variability in the rise-time of V_{soma}.

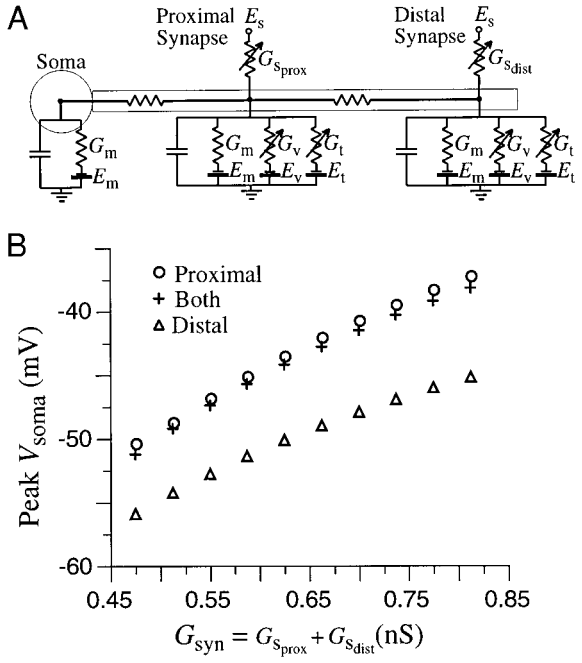

FIG. 5. Adding back synaptic conductances. *A*: model. *B*: peak V_{soma} for a range of synaptic input strengths. Location-dependent variability is again present in the model.

ability returned (Fig. 5). This increase in location-dependent variability came from two sources. First, the synaptic conductances added a positive slope conductance to the membrane. This upset the balance between G_m and G_v, resulting in a dendrite that no longer had a net zero slope conductance membrane. Second, the amount of synaptic current entering the dendrites is now affected by the dendritic membrane potential, which is determined by the spatial pattern of synaptic input.

It is possible to eliminate these two consequences of the synaptic input by adding a NMDA-like voltage-dependent synaptic conductance (G_n) to the model, as shown in Fig. 6*A*. The proper ratio of AMPA- (G_a) and NMDA-like conductance produced a synaptic current that behaves as an ideal current source over a limited range of dendritic membrane potentials. Figure 6*B* illustrates the *I-V* relationship of the AMPA- (I_a) and NMDA-like (I_n) currents for a ratio of G_n to G_a of 2.2. From approximately −50 to −30 mV, the net synaptic current ($I_a + I_n$) behaved as an ideal current source. The resulting synaptic current is voltage independent and thus does not affect the overall membrane *I-V* relationship.

Figure 6*C* illustrates somatic (V_{soma}) and distal dendritic (V_{dist}) potentials in response to the three spatial patterns of synaptic input. Compared with Fig. 1*B*, location-dependent variability was effectively eliminated for the somatic responses. Figure 6*D* illustrates the lack of location-dependent

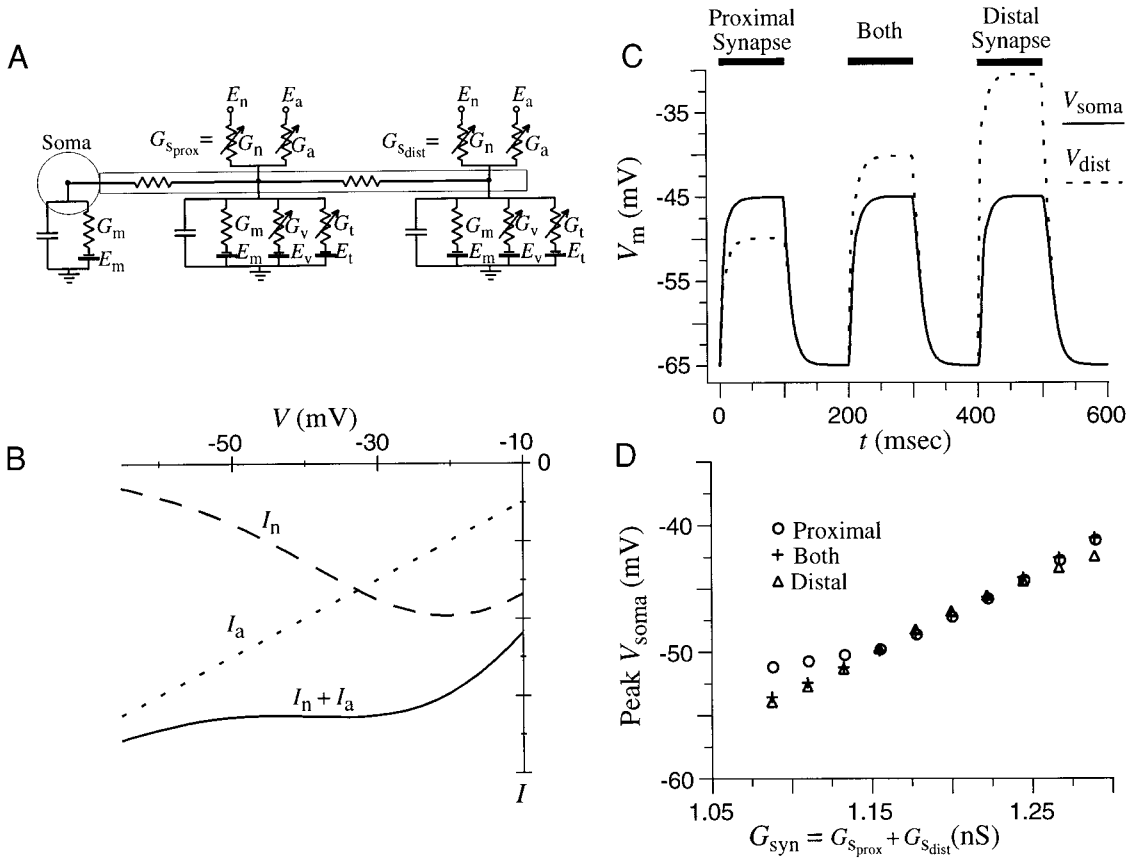

FIG. 6. *N*-methyl-D-aspartate (NMDA)–like voltage-dependence allows synapses to approximate ideal current sources. *A*: model with synapses containing α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)– (G_a) and NMDA-like (G_n) conductances. $G_n/G_a = 2.2$. *B*: *I-V* relationship of the NMDA- (I_n) and AMPA-like (I_a) current. The net synaptic current ($I_n + I_a$) exhibits a region of zero slope conductance. *C*: V_{soma} and V_{dist} (distal dendritic potential) in response to a total synaptic input of 1.23 nS ($G_n + G_a$) applied in the 3 different spatial input patterns. *D*: location-dependent variability is eliminated for a range of input strengths (where $G_s = G_n + G_a$).

variability over a range of G_{syn} (compare with Fig. 1*C*). As the total synaptic conductance is increased beyond 1.25 nS, the dendritic potential exceeds the range in which the synaptic conductances behave as ideal current sources, and location-dependent variability returns.

Back-propagation of dendritic action potentials

One consequence of active dendrites that eliminate location-dependent variability is their ability to back-propagate somatic action potentials. Figure 7 illustrates the propagation of an action potential initiated in the soma for passive (Fig. 1*A*) and active dendrites (Fig. 4*A*). For these simulations, fast Na^+ and delayed-rectifier K^+ currents were added to the soma only. The action potential was initiated with a short (20 ms) current injection to the soma. Although we did not explicitly develop the model of active dendrites to back-propagate action potentials, it is a natural consequence of the capacitive compensation produced by G_t.

DISCUSSION

By using a simplified model we determined the voltage-dependent properties required by dendrites to rapidly and accurately communicate the strength of their synaptic inputs to the soma. This model eliminated location-dependent variability and, as an indirect result, produced back-propagating dendritic action potentials. To accurately convey synaptic strength, dendrites have to overcome passive cable properties. To do this, dendrites require three principle voltage-dependent mechanisms: *1*) a steady-state voltage-dependent inward current that results in a net outward current with a zero slope conductance. This net outward current allowed the dendrites to quickly repolarize back to the resting membrane potential. *2*) A fast, transient, voltage-dependent inward current that compensated for the membrane capacitance. *3*) Both AMPA- and NMDA-like synaptic conductances that together allow the synaptic input to behave as an ideal current source. All three mechanisms are consistent with known dendritic physiology. With the exception of the NMDA-like voltage-dependent synaptic conductance, we did not attempt to model specific channel types. In our model, it is assumed that G_v and G_t represent the net interaction of many types of voltage-gated channels.

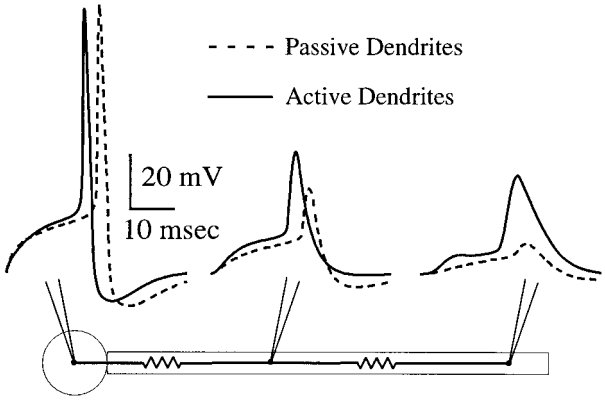

FIG. 7. Back-propagation of dendritic action potentials. Fast Na^+ and delayed-rectifier K^+ conductances were added to the soma of the passive (Fig. 1*A*) and active (Fig. 4*A*) dendrites. An action potential was elicited with a 20-ms, 25-pA current pulse to the soma. The responses from the soma, proximal, and distal dendrites are shown.

We believe that the three voltage-mechanisms proposed comprise the only way to eliminate location-dependent variability in a passive dendrite. In this way, the amount of somatic depolarization is only a function of the strength of the synaptic input. The exact spatial pattern of synaptic input does not affect the somatic response. It has been suggested that synaptic conductances may increase with distance from the soma (Brown et al. 1990; Pettit and Augustine 1997). This approach could theoretically reduce location-dependent variability but not eliminate it. Even if individual synapses were scaled in strength to provide the same effect at the soma, different spatial patterns of synaptic input would still produce different electrical circuits in the dendrites.

The dendritic voltage-dependent mechanisms proposed in this model produce a zero slope conductance with a net outward current ($I_m + I_v$ in Fig. 3). This net outward current is important for providing stability and may also suggest why dendrites exhibit passive properties at resting membrane potentials. If the dendritic membrane produced a zero slope conductance with a net inward current instead of a net outward current, the dendrites would be unstable and rapidly depolarize. This zero slope conductance relationship would not be required for all depolarized potentials, as modeled in Fig. 3*B*. Only in its operating voltage range would a region of dendrite require the zero slope conductance. It should also be noted that the linear relationship between somatic depolarization and synaptic input strength seen with our model is not essential for eliminating location-dependent variability.

Our use of voltage-dependent channels to counter the effects of membrane capacitance and membrane leak is analogous in concept to the use of active feedback processes for transmission in telecommunications cables (Black 1983). Furthermore, Bell (1992) demonstrated that voltage-dependent conductances can self organize based on a learning rule that flattens the voltage curvature of the membrane, thereby faithfully reproducing a previously presented voltage signal. Although we addressed a different dendritic function, our study produced a similar model with the important difference of a net outward current across the dendritic membrane.

In our previous study we demonstrated that realistic voltage-gated inward currents could provide the negative-slope conductance necessary to reduce location-dependent variability in a fully reconstructed CA1 neuron (Cook and Johnston 1997). However, we could not eliminate location-dependent variability. A major limitation of the previous model was that the membrane time constant of the dendrites became very large, making the model unresponsive. Using a more tractable neuron model in this study allowed us to explore the dendritic mechanisms that eliminate location-dependent variability and maintain rapid responses at the soma.

We propose that voltage-dependent currents found in dendrites together provide the equivalent functions of G_v and G_t. Estimates from dendritic patch recordings suggested a small bias of outward over inward current (Magee et al. 1998). Our model is in agreement with these experimental results. It has not been shown, however, whether dendritic voltage-dependent channels produce a net steady-state zero slope conductance *I-V* relationship at depolarized potentials.

Dendrites contain many voltage-gated channels with fast

transient properties (e.g., I_{Na} and I_A) that together could produce the equivalent effect of G_t. A dendrite using these currents to reduce capacitance loading would naturally backpropagate somatic action potentials. It has been shown that the composition of dendritic voltage-dependent channels varies with distance from the soma (Hoffman et al. 1997; Magee 1998; Magee and Johnston 1995). This does not necessarily indicate that different regions of the dendrites play different roles in processing synaptic inputs. Because the activation curves of voltage-gated channels are nonlinear, regions of dendrites that operate under different voltage ranges would require different combinations of channels to provide the same function. Indeed, distal dendrites experience increased depolarization during synaptic input (Cook and Johnston 1997). To reflect this, G_t differed slightly between the proximal and distal dendritic compartments of our model.

It is generally assumed that the primary role of NMDA-receptor–mediated synaptic currents is to induce plasticity. It has been shown, however, that NMDA currents boost synaptic input in a voltage-dependent manner (Jones and Baughman 1988; Thomson et al. 1988) and may endow certain computational properties to the dendrites (e.g., Mel 1992). Experimental findings from both spinal cord neurons (Westbrook and Mayer 1984) and retinal ganglion cells (Diamond and Copenhagen 1995; Mittman et al. 1990) demonstrate that NMDA and non-NMDA currents can together allow synaptic inputs to behave as ideal current sources. These results support our use of NMDA current in eliminating location-dependent variability. As there is no evidence of plasticity in retinal ganglion cells, this suggests that the voltage dependence of the NMDA receptor may play a major role in synaptic integration. Additionally, it was recently demonstrated that NMDA currents provide the voltage dependence necessary to allow linear summation of excitatory postsynaptic potentials (EPSPs) activated at different dendritic locations in cultured neurons (Cash and Yuste 1998). The authors also found a delicate balance among several different voltage-dependent channel types, demonstrating the possibility that dendrites may be capable of precise regulation of channel densities required to produce a zero slope conductance.

Assumptions of the model

In addition to the primary assumption that the effects of G_v and G_t can be reproduced by the proper mix of real voltage-gated channels, several other important assumptions require discussion.

The first concerns the effects a more realistic synaptic input may have on the ability of the model to eliminate location-dependent variability. A sustained synaptic conductance was used to simplify evaluation of location-dependent variability and has been shown to have the same time-averaged effect on a passive membrane as that of a train of synaptic inputs modeled with alpha-functions (Bernander et al. 1991). Hence the model was not intended to reduce variability from a single EPSP. In addition, the model was designed to integrate the synaptic input with a 10-ms time constant. As capacitive current is proportional to the derivative of the membrane potential, fast fluctuations in dendritic V_m would require increased compensating current. The magnitude of I_t fit by the computer is ~5–10 times less than the measured Na^+ current density in hippocampal dendrites (Magee and Johnston 1995).[5] This suggests that the model could have been designed with a faster integration time while maintaining a reasonable transient current density. Also, we did not model the kinetics of the NMDA conductance. How this might affect the balance between the AMPA- and NMDA-like slope conductances in our model was not determined. Finally, we did not include spines, which could play a significant role in determining the membrane potential synaptic conductances experience when activated.

A second major assumption is that the model would extend to a more realistic morphology. A two-compartment dendrite was employed to simplify the numerical derivation of the voltage-dependent current I_t. The mechanisms proposed to eliminate location-dependent variability are strictly local. As long as each small region of dendritic membrane maintains a zero slope conductance while compensating for capacitance, morphology would not affect the dendrite's ability to eliminate location-dependent variability. This does imply, however, that the entire dendritic tree must be depolarized enough to activate the required voltage-dependent currents. In light of the estimated synaptic background activity that central neurons receive (Bernander et al. 1991), it is quite possible that dendrites exist in a constant state of depolarization. As most physiology data come from slice preparations, where cells receive almost no background activity, little is known about the normal operating range of dendrites.

Finally, only a passive soma was used. For a soma that produces action potentials, the firing rate is determined by the current flowing into the soma from the dendrites (Bernander et al. 1994). This current is directly proportional to membrane potential for a passive soma. Action potentials produced in the soma would cause transient membrane potential fluctuations in the dendrites. Preliminary simulations suggest, however, that this would have little effect on the voltage-dependent mechanisms presented in our model.

Implications of active dendrites that eliminate location-dependent variability

This study is based on the idea that dendrites serve to provide the soma with an accurate measure of synaptic input strength. This reduction in dendritic distortion can theoretically lead to enhanced performance in associative neural networks that use synaptic efficacy as the locus of memory storage (Cook and Johnston 1997). We designed our model to eliminate location-dependent variability on a timescale of tens of milliseconds. It was proposed that neurons may integrate synaptic inputs on a much faster timescale (Softky and Koch 1993). Dendrites that provide the soma with an accurate millisecond-by-millisecond report of input magnitude would still function within the basic principles outlined in this study. To function on such a fast timescale, however, the voltage-dependent mechanisms that maintains zero slope conductance and capacitance compensation would be truly elegant works of electrical engineering.

Compared with the many roles proposed for active dendrites, the hypothesis that dendrites act as high-fidelity transducers of synaptic input to somatic depolarization may at first seem computationally trivial. As we attempted to demonstrate,

[5] Assuming a patch area of 1 μm^2.

dendrites that reduce location-dependent variability would require sophisticated mechanisms to maintain the correct balance of voltage- and time-dependent channels. How this regulation occurs is unknown. Recent studies have begun to explore the possibility that dendritic channels may self-organize in response to functional constraints (Bell 1993; Siegel et al. 1994; Turrigiano et al. 1998).

APPENDIX

Voltage-dependent currents

The voltage-dependent current I_v was modeled as

$$I_v = \begin{cases} G_v(V - E_v) & \text{if } V > E_v \\ 0 & \text{otherwise} \end{cases} \quad (A1)$$

where $E_v = -55$ mV.

The transient voltage-dependent current I_t was modeled as

$$I_t = \begin{cases} G_t(V - E_t) & \text{if } G_t > 0 \\ 0 & \text{otherwise} \end{cases} \quad (A2)$$

where $E_t = 50$ mV and G_t was a function of time and membrane potential. To reduce the number of free parameters fit by the computer, we used a simplified difference model to describe G_t.

$$G_t = m - h \quad (A3)$$

$$m = m_0 + (1 - e^{-dt/\tau_m})(m_\infty - m) \quad (A4)$$

$$h = h_0 + (1 - e^{-dt/\tau_h})(h_\infty - h) \quad (A5)$$

$$m_\infty = a_0 + a_1 V \quad (A6)$$

$$h_\infty = -m_\infty \quad (A7)$$

$$\tau_h = c_0 + c_1 V \quad (A8)$$

where τ_m, a_0, a_1, c_0, and c_1 were free parameters determined by the computer. In this model, m and h are state variables with first-order kinetics of τ_m and τ_h, respectively, and have linear dependence on membrane potential. Our rational for constructing such a simplified model of I_t was one of practical consideration. Using the standard Hodgken-Huxley formalism of multiplicative sigmoidal activation curves would have resulted in at least twice as many free parameters, which would have increased the difficulty of finding a good solution.

Numerical methods for finding I_t

The fast, transient, voltage-dependent current I_t was inserted into each dendritic compartment. A downhill simplex algorithm was then used to simultaneously find values for the five free parameters in each dendritic compartment [Nelder and Mead (1965) as reported by Press et al. 1986]. The criteria used to evaluate the numerical fits was the least-squared difference between the model in Fig. 4*A* and the model in Fig. 3*A*, which had C_m set to 0.01 μF/cm^2. The first 25 ms of the synaptic input was not used in the fitting procedure to help insure a good fit to the steady-state response. In this way, the parameters for I_t were derived that best compensated the dendritic capacitance. This fitting procedure was run 400 times, each with a different set of initial conditions. The parameters for I_t that best met the criteria were $\tau_m = 0.1$ ms (our minimum value allowed), $a_0 = 0.002696$, $a_1 = 2.09095 \times 10^{-5}$, $c_0 = 0.850899$, and $c_1 = 0.006226$ for the proximal dendritic compartment and $\tau_m = 0.1$ ms, $a_0 = 0.0005673$, $a_1 = 1.79591 \times 10^{-5}$, $c_0 = 0.926595$, and $c_1 = 0.006345$ for the distal dendritic compartment. Of the fits attempted, $\geq$50 produced qualitatively as good of performance as that shown in Fig. 4*E*, and of these, all produced fast transient inward currents. This would be expected for any capacitive compensation mechanism.

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REFERENCES

ANDERSEN, P., SILFVENIUS, H., SUNDBERG, S. H., AND SVEEN, O. A comparison of distal and proximal dendrite synapses on CA1 pyramids in guinea pig hippocampal slices in vitro. *J. Physiol. (Lond.)* 307: 273–299, 1980.

BELL, A. J. Self-organization in real neurons: anti-Hebb in channel space? In: *Neural Information Processing Systems 4*, edited by J. E. Moody, S. J. Hanson, and R. P. Lippmann. Morgan Kaufmann, 1992.

BELL, A. J. Self-organising ion channel densities: the rationale for 'anti-Hebb'. In: *Computation and Neural Systems*, edited by J. Bower and F. Eeckman. New York: Elsevier, 1993, vol. 2, p. 3–7.

BERNANDER, O., DOUGLAS, R. J., MARTIN, K.A.C., AND KOCH, C. Synaptic background activity influences spatiotemporal integration in single pyramidal cells. *Proc. Natl. Acad. Sci. USA* 88: 11569–11573, 1991.

BERNANDER, O., KOCH, C., AND DOUGLAS, R. J. Amplification and linearization of distal synaptic input to cortical pyramidal cells. *J. Neurophysiol.* 72: 2743–2753, 1994.

BLACK, R. M. *History of Electric Wires and Cables.* London: Peter Peregrinus Ltd., 1983.

BROWN, D. A., JACK, J.J.B., KULLMANN, D. M., LARKMAN, A. U., MAJOR, G., AND STRATFORD, K. J. Quantal analysis of excitatory synaptic mechanisms in the mammalian central nervous system. *Cold Spring Harbor Symp. Quant. Biol.* LV: 57–67, 1990.

CASH, S. AND YUSTE, R. Input summation by cultured pyramidal neurons is linear and position-independent. *J. Neurosci.* 18: 10–15, 1998.

COOK, E. P. AND JOHNSTON, D. Active dendrites reduce location-dependent variability of synaptic input trains. *J. Neurophysiol.* 78: 2116–2128, 1997.

DE SCHUTTER, E. Dendritic voltage and calcium-gated channels amplify the variability of post-synaptic responses in a Purkinje cell model. *J. Neurophysiol.* 80: 504–519, 1998.

DE SCHUTTER, E. AND BOWER, J. M. Simulated responses of cerebellar Purkinje cells are independent of the dendritic location of granule cell synaptic inputs. *Proc. Natl. Acad. Sci. USA* 91: 4736–4740, 1994.

DIAMOND, J. S. AND COPENHAGEN, D. R. The relationship between light-evoked synaptic excitation and spiking behavior of salamander retinal ganglion cells. *J. Physiol. (Lond.)* 487: 711–725, 1995.

HINES, M. NEURON—a program for simulation of nerve equations. In: *Neural Systems: Analysis and Modeling*, edited by F. Eeckman. Norwell, MA: Kluwer Academic, 1993, p. 127–136.

HOFFMAN, D. A., MAGEE, J. C., COLBERT, C. M., AND JOHNSTON, D. K^+ channel regulation of signal propagation in dendrites of hippocampal pyramidal neurons. *Nature* 387: 869–875, 1997.

HOLMES, W. R. AND LEVY, W. B. Insights into associative long-term potentiation from computational models of NMDA receptor-mediated calcium influx and intracellular calcium concentration changes. *J. Neurophysiol.* 63: 1148–1168, 1990.

JACK, J.J.B., NOBLE, D., AND TSIEN, R. W. In: *Electric Current Flow in Excitable Cells*. London: Oxford Univ. Press, 1975.

JOHNSTON, D., MAGEE, J. C., COLBERT, C. M., AND CHRISTIE, B. R. Active properties of neuronal dendrites. *Annu. Rev. Neurosci.* 19: 165–186, 1996.

JONES, K. A. AND BAUGHMAN, R. W. NMDA- and non-NMDA-receptor components of excitatory synaptic potentials recorded from cells in layer V of rat visual cortex. *J. Neurosci.* 8: 3522–3534, 1988.

MACDERMOTT, A. B., MAYER, M. L., WESTBROOK, G. L., SMITH, S. J., AND BARKER, J. L. NMDA-receptor activation increases cytoplasmic calcium concentrations in cultured spinal cord neurones. *Nature* 321: 519–522, 1986.

MAGEE, J. C. Dendritic hyperpolarization-activated currents modify the integrative properties of hippocampal CA1 pyramidal neurons. *J. Neurosci.* 18: 7613–7624, 1998.

MAGEE, J. C., HOFFMAN, D., COLBERT, C. M., AND JOHNSTON, D. Electrical and

calcium signaling in dendrites of hippocampal pyramidal neurons *Annu. Rev. Physiol.* 60: 327–346, 1998.

MAGEE, J. C. AND JOHNSTON, D. Characterization of single voltage-gated Na^+ and Ca^{2+} channels in apical dendrites of rat CA1 pyramidal neurons. *J. Physiol. (Lond.)* 487: 67–90, 1995.

MEL, B. NMDA-based pattern discrimination in a modeled cortical neuron. *Neural Comput.* 4: 502–517, 1992.

MEL, B. W. Synaptic integration in an excitable dendritic tree. *J. Neurophysiol.* 70: 1086–1101, 1993.

MEL, B. W. Information processing in dendritic trees. *Neural Comput.* 6: 1031–1085, 1994.

MILLER, J. P., RALL, W., AND RINZEL, J. Synaptic amplification by active membrane in dendritic spines. *Brain Res.* 325: 325–330, 1985.

MITTMAN, S., TAYLOR, W. R., AND COPENHAGEN, D. R. Concomitant activation of two types of glutamate receptor mediates excitation of salamander retinal ganglion cells. *J. Physiol. (Lond.)* 428: 175–197, 1990.

PETTIT, D. L. AND AUGUSTINE, G. L. Micromapping dendritic hotspots of glutamate receptors on hippocampal neurons. *Soc. Neurosci. Abstr.* 23: 1127, 1997.

PRESS, W. H., FLANNERY, B. P., TEUKOLSKY, S. A., AND VETTERLING, W. T. In: *Numerical Recipes: The Art of Scientific Computing*. Cambridge, UK: Cambridge Univ. Press, 1986, p. 305–309.

RALL, W. Branching dendritic trees and motoneuron membrane resistivity. *Exp. Neurol.* 1: 491–527, 1959.

SCHWINDT, P. C. AND CRILL, W. E. Amplification of synaptic current by persistent sodium conductance in apical dendrite of neocortical neurons. *J. Neurophysiol.* 74: 2220–2224, 1995.

SHEPHERD, G. M. AND BRAYTON, R. K. Logic operations are properties of computer-simulated interactions between excitable dendritic spines. *Neuroscience* 21: 151–165, 1987.

SHEPHERD, G. M., BRAYTON, R. K., MILLER, J. P., SEGEV, I., RINZEL, J., AND RALL, W. Signal enhancement in distal cortical dendrites by means of interactions between active dendritic spines. *Proc. Natl. Acad. Sci. USA* 82: 2192–2195, 1985.

SIEGEL, M., MARDER, E., AND ABBOTT, L. F. Activity-dependent current distributions in model neurons. *Proc. Natl. Acad. Sci. USA* 91: 11308–11312, 1994.

SOFTKY, W. Sub-millisecond coincidence detection in active dendritic trees. *Neuroscience* 58: 13–41, 1994.

SOFTKY, W. R. AND KOCH, C. The highly irregular firing of cortical cells is inconsistent with temporal integration of random EPSPs. *Neuroscience* 13: 334–350, 1993.

STUART, G., SPRUSTON, N., SAKMANN, B., AND HAUSSER, M. Action potential initiation and backpropagation in neurons of the mammalian CNS. *Trends Neurosci.* 20: 125–131, 1997.

THOMSON, A. M., GIRDLESTONE, D., AND WEST, D. C. Voltage-dependent currents proplongs single-axon postsynaptic potentials in layer III pyramidal neurons in rat neocortical slices. *J. Neurophysiol.* 60: 1896–1907, 1988.

TURRIGIANO, G. G., LESLIE, K. R., DESAI, N. S., RUTHERFORD, L. C., AND NELSON, S. B. Activity-dependent scaling of quantal amplitude in neocortical neurons. *Nature* 391: 892–896, 1998.

WESTBROOK, G. L. AND MAYER, M. L. Glutamate currents in mammalian spinal neurons: resolution of a paradox. *Brain Res.* 301: 375–379, 1984.

YUSTE, R. AND TANK, D. W. Dendritic integration in mammalian neurons, a century after Cajal. *Neuron* 16: 701–716, 1996.