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Signal Propagation in Oblique Dendrites of CA1 Pyramidal Cells

Michele Migliore^{1,2}, Michele Ferrante³, and Giorgio A. Ascoli^{3,4}

¹Department of Neurobiology, Yale University School of Medicine, New Haven, Connecticut

²Institute of Biophysics, National Research Council, Palermo, Italy

³Krasnow Institute for Advanced Study, George Mason University, Fairfax, Virginia

⁴Psychology Department, George Mason University, Fairfax, Virginia

Abstract

The electrophysiological properties of the oblique branches of CA1 pyramidal neurons are largely unknown and very difficult to investigate experimentally. These relatively thin dendrites make up the majority of the apical tree surface area and constitute the main target of Schaffer collateral axons from CA3. Their electrogenic properties might have an important role in defining the computational functions of CA1 neurons. It is thus important to determine if and to what extent the back- and forward propagation of action potentials (AP) in these dendrites could be modulated by local properties such as morphology or active conductances. In the first detailed study of signal propagation in the full extent of CA1 oblique dendrites, we used 27 reconstructed three-dimensional morphologies and different distributions of the A-type K^+ conductance (K_A), to investigate their electrophysiological properties by computational modeling. We found that the local K_A distribution had a major role in modulating action potential back propagation, whereas the forward propagation of dendritic spikes originating in the obliques was mainly affected by local morphological properties. In both cases, signal processing in any given oblique was effectively independent of the rest of the neuron and, by and large, of the distance from the soma. Moreover, the density of K_A in oblique dendrites affected spike conduction in the main shaft. Thus the anatomical variability of CA1 pyramidal cells and their local distribution of voltage-gated channels may suit a powerful functional compartmentalization of the apical tree.

INTRODUCTION

Pyramidal neurons in hippocampal area CA1 and neocortical layer V have many small oblique dendrites stemming out of the main apical trunk at different distances from the soma. The main apical trunk of CA1 pyramidal cells has been intensively investigated with respect to the distribution and kinetics of voltage-gated conductances (e.g., Bekkers 2000; Chen and Johnston 2004; Magee and Johnston 1995; Shao et al. 1999), electrogenic characteristics (e.g., Bernard and Johnston 2003; Gasparini et al. 2004; Golding et al. 2001; Kasuka et al. 2003), and synaptic properties (e.g., Frick et al. 2004; Otmakhova et al. 2002; Spruston et al. 1995; Zamanillo et al. 1999). In contrast, the experimental investigation of the biophysical properties of oblique dendrites is exceedingly difficult because of the technical unfeasibility of patching such fine branches in uncertain positions. Their possible functional roles thus remain largely unknown.

This is an important issue because in CA1 cells, oblique dendrites constitute the majority of the apical tree surface and represent the main site of excitatory synaptic target from CA3 Schaffer collaterals. A recent single-cell computational study showed that the CA1 pyramidal neuron's subthreshold integration of synaptic inputs can be characterized as a sum of nonlinear responses, each from an individual oblique dendrite (Poirazi et al. 2003a,b). Experimental investigations in cortical pyramidal cells confirmed that synchronous inputs are integrated sigmoidally within the same dendritic branch, but the summation becomes linear among inputs located on widely separate dendrites (Polsky et al. 2004). These data suggest that oblique dendrites constitute fairly independent input/output units that can be viewed as a separate computational layer from the soma and main trunk. Such views point to the need for a deeper understanding of suprathreshold signal propagation to and from the oblique trees as an essential step to characterize the computational power of CA1 pyramidal cells. This is especially important in light of the direct experimental evidence (from the main trunk) that spike back propagation can subserve Hebbian plasticity (Magee and Johnston 1997; Markram et al. 1997). If the invasion of oblique dendrites by antidromic spikes can be independently modulated, synapses on various trees could have different susceptibility to associative plasticity. Similarly, relative isolation of oblique trees from the rest of the neuron would enable local Hebbian plasticity mediated by dendritic spikes (e.g., Alkon 1999).

It is well established, with both models and experiments, that action potential (AP) propagation in the main trunk of pyramidal neurons can be regulated by active conductances (e.g., Hoffman et al. 1997; Johnston et al. 1999; Migliore et al. 1999) and local morphology (Schaefer et al. 2003; Vetter et al. 2001). However, a detailed picture of how APs propagate into/from the oblique dendrites is still missing. The major problem is that experimental data on CA1 oblique biophysics is limited to a few studies on the interaction of subthreshold inputs (Cash and Yuste 1999; Liu 2004) and imaging studies of Ca^{2+} concentration and dynamics (Frick et al. 2003; Nakamura et al. 2002). The local distribution of active channels is still largely unknown with the notable exception of the work by Frick et al. (2003), demonstrating the presence of a full set of active channels with a possible major role for the A-type K^+ conductance (K_A). Because this current is modulated by protein kinases (Johnston et al. 1999), and thus ultimately by local neuronal activity, signal propagation into/from oblique dendrites cannot be expected to follow along the same lines as in the trunk. It will depend on the interaction of factors that, in addition to the local K_A density, include distance from soma, local geometry at branch points, and dendritic AP initiation site. These issues have not, and cannot be, easily explored experimentally. In this paper, we use realistic computational models of CA1 pyramidal cells to determine how and to what extent the local K_A and morphological properties might regulate the backward and forward propagation of action potentials (APs) in the full length of the oblique branches (i.e., 600 μm from the soma).

METHODS

All simulations were implemented and run with the NEURON program (v5.7) (Hines and Carnevale 1997) using the variable time step feature. In most cases, simulations were carried out using the *ParallelContext*() feature of NEURON under MPI on a Beowulf cluster (34 processors) or a IBM Linux cluster (1024 processors). The model and simulation files are available for public download under the ModelDB section (Davison et al. 2004; Migliore et al. 2003) of the Senselab database (<http://senselab.yale.med.edu>).

To ensure a representative range of morphological properties, we used 27 three-dimensional (3D) reconstructions of rat CA1 neurons from four different laboratories, ages (from 6 wk- to 12 mo old), and preparation protocols. These included neurons from the studies of Amaral

(Ishizuka et al. 1995), Turner (Pyapali et al. 1998; edited as described in Donohue et al. 2002), Claiborne (Carnevale et al. 1997), and our own lab (Brown et al. 2005). Apical subtrees were defined as oblique if they stemmed from the main trunk and ended within stratum radiatum (i.e., failed to invade stratum lacunosum-moleculare). Operationally, we started from each terminal tip within stratum lacunosum-moleculare and marked as “nonoblique” its entire dendritic path to the soma. After repeating this operation for every terminal tip in stratum lacunosum-moleculare, all remaining subtrees were marked “oblique” (see Fig. 1A). The digital files of the 27 neuronal morphologies are available for public download (www.krasnow.gmu.edu/l-Neuron) (see Ascoli et al. 2001).

The stratum radiatum in our morphologies, and thus the maximal projection of the oblique branches, could extend up to $\sim 600 \mu\text{m}$ from the soma. This may seem at odds with a number of studies reporting a s. radiatum extension of $\sim 350 \mu\text{m}$. Most intracellular electrophysiology is carried out in young (~ 6 wk) rats. About 2/3 of our neurons are from the Amaral study, which uses 1- to 2-mo-old females. Our reconstructions instead include several neurons (from Turner, Claiborne, and our own lab) reconstructed from adult (6- to 12-mo old) male rats (Fig. 1). These neurons can be up to twice as big as the young neurons, consistent with the full body, brain, and hippocampus proportions of these animals. This could justify the larger range of stratum radiatum extensions for the neurons used in this work.

A second notable characteristic of the reconstructions used in this study is the wide range ($0.3\text{--}5 \mu\text{m}$) of initial diameters observed for the oblique branches, in apparent contrast with the tight range ($0.5\text{--}0.7 \mu\text{m}$) reported by a few studies (Bannister and Larkman 1995; Megias et al. 2001; Trommald et al. 1995). Although some of the thicker branches are in fact large subtrees originating from major bifurcation points (see the discussion of Fig. 8), the real range for the initial diameter of the oblique dendrites is still not definitively known. Light microscopy (used in the majority of the studies) does not have enough resolution power, whereas electron microscopy is not suitable for extensive sampling. We have thus chosen to include all of the obliques ($n = 664$) in our analyses, while verifying specific hypotheses in a subset with a tighter range of diameters (e.g., Fig. 6C).

The same standard, uniform, passive properties were used for all neurons ($\tau_m = 28 \text{ ms}$, $R_m = 28 \text{ k}\Omega \cdot \text{cm}^2$, $R_a = 150 \Omega \cdot \text{cm}$). The basic set of active dendritic properties included sodium, DR- and A-type potassium conductances (Na , K_{DR} , K_A , respectively), and I_h current. All channels kinetic and distribution, identical to those previously published, were based on the available experimental data for CA1m neurons (reviewed in Migliore and Shepherd 2002) and have been validated against several experimental findings (e.g., Migliore 2003; Migliore et al. 1999; Poolos et al. 2002; Watanabe et al. 2002) (all models are available on ModelDB). Briefly, the Na and K_{DR} were uniformly distributed over the entire (basal and apical) dendritic arborization (with peak conductance $g_{\text{Na}} = 0.25 \text{ nS}/\mu\text{m}^2$ and $g_{\text{KDR}} = 0.1 \text{ nS}/\mu\text{m}^2$). The K_A and I_h increased linearly with distance, d , from the soma, as $g_{K_A} = 0.3 \cdot (1 + d/100)$ and $g_h = 0.0005 \cdot (1 + 3d/100)$ (Hoffman et al. 1997; Magee 1998). Because not all morphologies included an axon, a synthetic axon ($100 \mu\text{m}$ long, $1 \mu\text{m}$ diam, $g_{\text{Na}} = 1.25 \text{ nS}/\mu\text{m}^2$, $g_{\text{KDR}} = 0.1 \text{ nS}/\mu\text{m}^2$, $g_{K_A} = 0.3 \text{ nS}/\mu\text{m}^2$) was included for consistency in all reconstructions and attached to the soma. In all cases, this resulted in the axonal initiation of APs for somatic current injections. With these passive and active properties in place, the input resistance (R_N) of the model neurons spanned a large range of values (Fig. 1B), consistent with in vitro slice recordings (e.g., Pyapali et al. 1998). As can be seen from Fig. 1B, the R_N values appear to fall within two loose categories (below and above $\sim 40 \text{ M}\Omega$). The 40- to 90-M Ω group corresponds to the Amaral cells (young animals). The lower resistance of the other cells (Claiborne, Turner, and our own) is in part explained by their larger size (and ultimately the age of the animal, as discussed in the preceding text). Other

reasons for such a discrepancy may include experimental details of the anatomical procedure, including rat strain, objective magnification, reconstruction software, etc., and have been recently discussed, specifically for CA1 pyramidal cells, in three independent modeling studies (Ambros-Ingerson and Holmes 2005; Scorcioni et al. 2004; Szilagy and De Schutter 2004).

Because the densities of K_A and I_h in the oblique dendrites, in the distal apical dendrites, and in the basal trees have not yet been characterized experimentally, we implemented three alternative types of distributions, schematically reported in Table 1. In the “linear increase” type (LI), we assumed that the experimental findings regarding the distribution of active conductances in the main apical trunk were representative of the whole dendritic arborization. Accordingly, in this case, K_A and I_h were linearly increased everywhere, including oblique, basal, and distal apical dendrites. In the “constant” distribution type (C1), we assumed no information beyond that obtained directly from dendritic patch-clamp recordings (Hoffmann et al. 1997; Magee 1998). The K_A and I_h linearly increased in the main trunk 350 μm from soma and were assumed to remain constant in the rest of the dendrites at the same value of the closest location in this range. In particular, each oblique subtree had constant K_A and I_h at the value of the point of attachment on the main trunk; distal apical dendrites (all the subtrees of the main trunk beyond 350 μm) had constant active current distributions at the value of the main trunk at 350 μm ; and basal dendrites had constant values equal to the somatic densities. Finally, the type C3 had the same distributions as C1 with the exception of the K_A values in the oblique. Following the indirect experimental suggestion that the density of these channels could be higher in the obliques than in the trunk (Frick et al. 2003), in this case, K_A was increased threefold in each oblique with respect to its value at the point of attachment in the main trunk. Little differences were observed in the input resistance of any given neuron using the three kinds of distribution (data not shown).

It should be noted that a number of additional mechanisms reported for CA1 pyramidal cells were not included in the model. Many of them, such as additional K^+ conductances, persistent Na^+ current, Ca^{2+} -dependent currents, but also activity-dependent changes in channel density or kinetic, nonuniform distribution of various Ca^{2+} currents, and intracellular Ca^{2+} dynamics, may modulate the signal propagation process (Golding et al. 1999; Lazarewicz et al. 2002; Magee and Carruth 1999). This is precisely why we did not include them in the model at this stage. In fact, we were interested in studying signal propagation to and from the oblique branches in CA1 neurons, a process that is exceedingly difficult to study experimentally and for the underlying mechanisms of which very little empirical evidence is available. For these reasons, we included only the main conductances involved in action potential generation and regulation (Na , K_{DR} , and K_A), and in subthreshold signal modulation (I_h). Such choice implies that these simulations can provide little definitive evidence of how spike initiation in oblique dendrites might occur and restricts the main object of this study to propagation, rather than initiation, of action potentials. It would be interesting to include additional cell properties in future studies to investigate how and to what extent they affect the basic findings reported in this paper.

Oblique stimulation was implemented with a double exponential time course (using the *Exp2Syn* built-in function of NEURON) with 1 and 5 ms for the rise and decay time, respectively, and a reversal potential of 0 mV. These values are consistent with experimental findings (Andrasfalvy and Magee 2001), and no qualitative differences were observed using different values in preliminary test simulations. The peak conductance was adjusted for each oblique compartment as the minimum value sufficient to elicit a local spike within the same oblique tree. The resulting means $\pm$ SD for the LI, C1, and C3 distribution types were (all in nS) 4.35 ± 2.76 , 5.01 ± 4.69 , and 10.15 ± 8.89 , respectively. In a set of simulations, a

dendritic spike was elicited in each of the oblique compartments while injecting a subthreshold steady depolarizing current in the main trunk at the point of attachment of the oblique tree. Trunk current injection values started from 0.01 nA and were increased by 0.01 nA at each iteration of the simulation. Membrane voltage was monitored both in the main trunk and in the soma, and the local spike was elicited in the oblique tree after stabilization of the somatic voltage. In particular, the local spike was elicited after 200 ms from the beginning of the depolarizing current step in the trunk (this delay was found to be long enough to allow for both decay of transients and steady-state conditions for all the currents). The iteration stopped either when a spike was detected in the soma in response to oblique stimulation or when a spike was elicited in the trunk by the current injection (i.e., the injected current was no longer subthreshold).

RESULTS

The CA1 pyramidal cell computational model was constructed and validated based on 3D anatomical reconstructions and available experimental data on the dendritic distribution of active and passive properties, as detailed in METHODS. Because the majority of experimental recordings from CA1 pyramidal cell dendrites are collected from the main trunk (Fig. 1A: black portion of the apical tree within $\sim 350 \mu\text{m}$ from the soma), three alternative distributions of conductance densities were employed in all simulations for the rest of the dendrites, LI, C1, and C3 (see Table 1 and METHODS for details). In all cases, the neurons exhibited a plausible range of input resistances (Fig. 1B shows the values for the LI model).

We first investigated the factors controlling AP invasion of obliques. The simulation protocol to study AP back-propagation was to elicit a single somatic spike with a short (2 ms) current pulse in the soma of each neuron and record the peak amplitude of the AP during somatofugal propagation along the main trunk and each of the oblique subtrees (Fig. 2A). The values of the current pulses for the LI, C1, and C3 distributions were 0.93 ± 0.76 , 0.85 ± 0.74 , and 0.86 ± 0.77 nA, respectively. The distribution of the average peak depolarization of the obliques (Fig. 2B) suggests that back propagation depends on the local K_A distribution and tends to be all-or-none. Back propagation does not depend, in contrast, on the local morphological properties, such as the ratio between the initial oblique diameter and the diameter of the trunk at the point of attachment (Fig. 2C) or the oblique surface area (Fig. 2D). Note that, in most cases (e.g., Fig. 2A), the spike amplitude increases on invasion of a small oblique dendrite attached to a large main branch as would be expected for reasons of alterations in the surface-to-volume ratio. Figure 2C, in contrast, shows that the *average* over the peak values of the membrane voltage reached throughout an oblique (plotted for all distances from the soma and trunk depolarizations) does not depend on the diameter ratio.

Exceptions to these general observations are apparent in Fig. 2, C and D, with groups of large peaks corresponding to C3 distribution ($\blacktriangle$) and, conversely, sporadic low values in the C1 distribution ($\circ$). These outliers do not correlate with the age of the animal, as the proportion between the number of points from 6-wk-old and that of 6- to 12-mo-old rats is roughly constant for the values >55 and <55 mV in both the C1 (473 vs. 113 and 59 vs. 18, respectively) and C3 simulations (99 vs. 23 and 434 vs. 108, respectively). However, the exceptions are significantly separated with respect to their path distance from the soma in both the C1 ($194.5 \pm 99.0 \mu\text{m}$ for values >55 mV and $382.6 \pm 105.2 \mu\text{m}$ for values <55 mV, $P < 0.0001$, 2-tailed unpaired t -test) and C3 cases ($69.4 \pm 22.6 \mu\text{m}$ for values >55 mV and $249.2 \pm 102.5 \mu\text{m}$ for values <55 mV, $P < 0.0001$), suggesting a clear interaction between these variables.

The local K_A distribution is thus a major mechanism for the regulation of antidromic AP propagation in the obliques. As shown in Fig. 3A, the average peak depolarization could be strongly reduced for any oblique at any distance from soma, except for the very proximal ones ($<100\ \mu\text{m}$), which have a less effective K_A , as experimentally found (Hoffman et al. 1997) for the apical trunk (in principle, different results could be obtained for proximal obliques by using for them a “distal” K_A kinetic). If the invasion of different oblique trees by back-propagating spikes could be independently and differentially modulated within the same neuron, it might underlie a powerful computational property of CA1 pyramidal cells. This is, in fact, what our model suggests, and a typical example is reported in Fig. 3, B and C, showing a simulation for an individual neuron with a C1 distribution (Fig. 3B) and a simulation of the same neuron in which $\approx 30\%$ of the obliques were assigned a C3 distribution (Fig. 3C). With only few exception at both of the extremes of path distance from the soma, the back propagating AP fully invades only the C1 obliques and is strongly and specifically attenuated in the C3 subtrees.

It could be expected that a background excitatory synaptic activity in a given oblique could improve AP back propagation in that subtree, especially in the presence of a particularly high density of K_A channels, such as our C3 distribution. We tested this hypothesis in several cases, and a typical result (for *neuron C81462*) is shown in Fig. 3D. Depolarizing current steps were applied to an oblique compartment, at $\approx 210\ \mu\text{m}$ from soma and $\approx 70\ \mu\text{m}$ from the branch point with the main trunk to obtain a local (subthreshold) depolarization of either 4 or 8 mV, before eliciting a somatic AP. A rather small improvement of the back propagation was observed with a 4-mV depolarization, whereas a dendritic spike was generated with an 8-mV depolarization. This result suggests that a rather strong excitatory background synaptic activity would be needed to overcome the shunting effect of K_A .

Interestingly, the specific K_A distribution in the obliques could also affect AP back propagation in the trunk. Figure 4A shows, for all neurons, the AP peak in the trunk as a function of the distance from soma using two different oblique K_A distributions (C1 and C3). Although the K_A density in the trunk is the same in both cases, the peak AP amplitude decreases much faster with the distance from soma using the higher K_A density (C3) in the obliques. We further investigated additional oblique properties that could be relevant to the modulation of AP back propagation in the trunk. Because of its kinetic properties and the steep linear increase of channel density with distance from soma, I_h could play an important role because it is experimentally known to affect resting potential and input resistance (Magee 1998). In a representative neuron (*C81462*), the peak I_h conductance was set to zero in the obliques at the beginning of a simulation. Depending on the K_A distribution (C1 or C3), the I_h block in the obliques resulted in a $\approx 5\text{--}15\%$ increase of R_N and a $\approx 1\text{--}2\text{ mV}$ somatic hyperpolarization. While no significant effects were observed with a C3 K_A distribution (Fig. 4B, compare open and gray triangles), a branch failure in AP back propagation was noticed with a C1 K_A distribution after a distal ($\approx 350\ \mu\text{m}$) major bifurcation (Fig. 4B, compare black and gray circles). Little differences were detected in the trunk peak AP amplitude between young and adult animals (Fig. 4, C and D).

We next studied the factors controlling orthodromic AP propagation from the obliques. In this case, the protocol to investigate signal forward propagation was to elicit a dendritic spike in each compartment of each oblique with a single, suprathreshold, synaptic input (Fig. 5A), recording the peak depolarization reached in all compartments of the neuron. Typically, the locally initiated spike did not propagate to other oblique trees (Fig. 5A, ○). The average peak AP amplitude in the stimulated oblique depended on the local K_A distribution (Fig. 5B), and the AP almost never propagated to the trunk (Fig. 5C; the threshold for spike initiation in the trunk is $\sim 25\text{ mV}$). In principle, this phenomenon could depend on the form of stimulation used to evoke spikes, i.e., short current injection, while

synaptic events with slower kinetics (e.g., *N*-methyl-D-aspartate receptor activation) might travel with higher efficacy toward the soma and presumably even amplify dendritic spikes occurring in these and neighboring dendrites. To test this hypothesis, we simulated the effect of kinetic parameters of the stimulus used to evoke spikes in the oblique dendrites on forward propagation. We found that neither increasing the decay time constant from 5 to 20 ms nor additionally increasing the rise time constant from 1 to 5 ms noticeably changed the manifold amplitude decrease as the signal enters the main trunk (not shown). Instead we found that a paramount role in hindering orthodromic spike propagation out of the obliques is played by the local morphological properties and in particular by their small diameter with respect to the main trunk.

A more detailed analysis is shown in Fig. 6, for the subsets of obliques originating from three regions of the apical trunk at different distances from the soma (0–50, 200–250, and 350–400 μm). The ratio between the peak depolarization in the oblique and that which reached in the trunk at the branch point (Fig. 6A) was low (indicating good propagation) for stimulation sites close to the branch point. However, in all regions, this peak ratio increased with distance at a rate determined by the ratio between the oblique diameter and the trunk diameter at the branch point, as shown in the representative cases highlighted in different colors. Proximal obliques, however, typically showed a “plateau” for the peak ratio, whereas in more distal branches the peak ratio keeps increasing with the distance from the branch point. This mechanism could be explained with the different density of K_A in the two regions. For an AP generated in an oblique, the peak amplitude and the amount of depolarization reaching the trunk is determined by the local K_A . When an AP is generated in a proximal oblique, the relatively low K_A results in a larger depolarization of the entire oblique and a few millivolts of trunk depolarization. Because of the sealed end effect, for stimulations far from the branch point, the peak depolarization in the oblique is independent of the exact stimulation position. In these cases, the trunk reaches the same peak depolarization because of the relatively good propagation of the signal within the oblique. This causes a plateau in the peak ratio. For increasingly more distal trees, however, the AP propagation inside any given oblique becomes more and more hindered by the higher K_A , and only a very small depolarization is observed in the trunk. The local depolarization still has sealed end effects, but the trunk depolarization drops (to $\ll 1$ mV) because of the poor orthodromic signal propagation. This causes a steep increase of peak ratio with the distance from the branch point, an effect that is also amplified by the inverse relationship between the oblique and the trunk depolarization ($\text{PeakRatio} = \text{Obl}_{\text{depol}}/\text{Trunk}_{\text{depol}}$).

Diameter ratio and distance of the stimulation site from the branch point are then major factors in determining how much membrane depolarization reaches the trunk as a consequence of an oblique AP. As shown in Fig. 6B, for stimulations beyond 100 μm from the branch point, the dendritic depolarization could undergo a >20 -fold reduction during its forward propagation with much more moderate attenuation for more proximal stimulations (Fig. 6B, blue areas for distance <50 μm). In general, the reduction in dendritic depolarization was essentially independent of oblique diameter less than ~ 1 μm , but larger obliques showed a better propagation, indicated by lower peak ratios (Fig. 6B, blue and green areas for diameter more than ~ 1 μm). To illustrate the role played by different diameter ratios between the oblique and the trunk, we selected only obliques with a 0.3- to 0.4- μm diameter and plotted the peak ratio as a function of distance from the branch point and the $D_{\text{obl}}/D_{\text{trunk}}$ ratio (Fig. 6C). The peak ratios decrease with increasing diameter ratios, even for relatively thin obliques, suggesting that the impedance mismatch at the branch point is a significant factor hindering the forward AP propagation out of the dendrites.

The majority of oblique trees failed to propagate their locally generated spikes to the trunk (see Fig. 5C). However, concurrent synaptic activity in the rest of the neuron could improve

the yield of transmission of a local dendritic spike to the soma. To investigate how much concurrent activity in the neuron could be needed for an AP generated in a given oblique to elicit a somatic spike, we modeled the overall activity in the rest of the apical tree with a steady depolarizing current injection into the branch point between the trunk and the oblique stem. The following protocol was then used for each compartment of each oblique to determine the minimum trunk current injection needed to obtain a somatic spike (Fig. 7A). A subthreshold current step was injected at the branch point; after obtaining a stable membrane potential, a spike was elicited in the oblique. If the spike failed to reach the soma, the current injected into the trunk was increased (in steps of 0.01 nA) and the process repeated (see METHODS for details). This protocol classified oblique trees in three categories: those for which a somatic spike could be elicited by suprathreshold stimulation of at least one oblique location without additional current in the trunk (*always*), those for which a somatic spike could be elicited only in the presence of additional subthreshold stimulation of the trunk (*sometimes*), and those for which a somatic spike could not be elicited with any additional subthreshold stimulation of the trunk (*never*).

The relative proportion of the three categories of oblique trees with a type LI distribution changed regularly with the distance from the soma (Fig. 7B, *top*). In particular, always and never trees tended to predominate near and far from the soma, respectively, while the proportion of sometimes obliques was approximately constant and spanned the whole range of distances between 50 and 450 μm from the soma. In addition, the amount of current injected in the trunk to allow transmission of the spikes from the sometimes trees showed no significant dependence on the distance from the soma (Fig. 7C, LI, $R^2 < 0.01$, $P > 0.6$). The never and always categories completely disappeared using K_A distributions C1 and C3, respectively (Fig. 7B, *middle* and *bottom*), suggesting an interesting role for local K_A to gate the propagation of APs out of an oblique. Although Ca^{2+} -dependent potassium conductances are not included in our model, recent work attributes a specific role for SK-type (in addition to A-type) K^+ channels in regulating spike initiation and conduction between branches of pyramidal cell dendrites (Cai et al. 2004). Our results specifically confirm and highlight the role of K_A in determining spike properties with respect to conduction past branch points.

The simulation findings were also analyzed as a function of the size of the oblique tree. The proportion of the always, sometimes, and never trees was rather independent of their surface area (Fig. 8A). However, the necessary amount of trunk current injection to allow spike transmission from the *sometimes* trees showed a sudden transition in the 450- to 500- μm^2 range (Fig. 8B). In particular, smaller trees ($<450 \mu\text{m}^2$, $n = 194$) required 0.15 ± 0.14 (SD) nA, whereas larger trees ($>450 \mu\text{m}^2$, $n = 81$) required 0.73 ± 0.25 nA ($P < 10^{-10}$, 2-tailed t -test). In contrast, the corresponding depolarization was basically independent of the tree surface area (Fig. 8B). These results did not depend on the kind of K_A distributions (not shown) but could be correlated with the average value of the obliques diameter, which displayed an abrupt and significant change around the same values of surface area (Fig. 8C, 450–500 μm^2). The diameter distribution of sometimes oblique trees revealed a clear bimodal distribution with a trough at $\sim 1 \mu\text{m}$ corresponding to the jump observed in Fig. 8C. Thus CA1 neurons have a considerable proportion of subtrees that, despite their large size, could be classified as oblique (because they are entirely confined within s. radiatum, see METHODS). These large oblique dendrites, which correspond to major bifurcations of the apical tree, required four times as much concurrent activity in the trunk than other oblique trees to propagate their spikes to the soma.

DISCUSSION

The functional role of oblique branches in pyramidal cells may be key to understanding computational processing in the principal neurons of the mammalian cortex (Poirazi et al.

2003a,b; Polsky et al. 2004; Schaefer et al. 2003). Morphological features specific of a given cellular class (Vetter et al. 2001) or different distributions of dendritic active channels (reviewed in Migliore and Shepherd 2002) could be expected to modulate bidirectional signal propagation between oblique dendrites and the rest of the cell. However, these mechanisms are impractical to explore experimentally, in particular far from branch points. A realistic computational model is thus a valuable alternative to investigate how the local oblique properties could affect signal propagation. In this work, we demonstrated that both back and forward propagation can be effectively and independently modulated in individual oblique branches of the same neuron. The distribution of K_A appears to be pivotal in gating back propagation (Fig. 3), whereas local morphology plays the lead role in regulating forward propagation (Fig. 6). Although this study mainly focused on the propagation of APs, these results must be considered in the context of previous work that dealt with spike initiation in cortical pyramidal cells (Andreasen and Lambert 1995, 1998; Golding et al. 1998; Spruston et al. 1995; Turner et al. 1991). Similarly, our findings are complementary to several key reports on the potential effects of a variable Na^+ spike threshold with distance (Bernard and Johnston 2003), and the importance of I_h in regulating dendritic excitability (Magee 1998; Migliore et al. 2004; Poolos et al. 2002).

The first important and novel result of this study is that spikes antidromically propagating from the soma, while attenuating continuously in the apical trunk, tend to invade oblique trees in an all-or-none fashion (Fig. 2). This observation can be explained on the basis of the experimental evidence suggesting that dendritic active channels support spike propagation at full amplitude in CA1 pyramidal cells (Frick et al. 2003). Let us assume, for example, that the initial part of an oblique, just after the branch point with the main trunk, reaches the threshold for spike generation. The local (distance-dependent) K_A conductance but also the oblique's morphology determine the overall possibility for a spike to propagate down the oblique. In most cases, obliques are relatively short and thin ($<150 \mu\text{m}$, $<0.5 \mu\text{m}$). This results in significant sealed end effects that increase the possibility of a full propagation. In longer or more distal obliques, the membrane potential will be dampened to a subthreshold value within a short distance from the branch point by the "shock adsorber" action of the K_A . These effects cause the overall "all-or-none" invasion observed in our model neurons (Fig. 2A). This phenomenon is essentially independent of local geometry, such as the diameter ratio between oblique stem and main trunk or oblique tree size. In contrast, the process is finely regulated by K_A . A local threefold increase of K_A , with respect to the levels observed in the main trunk, is sufficient to entirely isolate any given oblique from a back-propagating spike. This regulation holds on a tree-by-tree basis within the same neuron, such that the same somatic spike could reach some oblique trees and not others depending on their local concentration of K_A . Because the local dendritic activity of K_A can be quickly tuned by several enzymatic cascades (e.g., Alkon 1999; Johnston et al. 1999), such gating mechanism could enable a highly specific determination of which subtree can participate in back propagation-mediated Hebbian plasticity (Magee and Johnston 1997; Markram et al. 1997).

Other studies provided evidence for the important role of dendritic morphology in regulating the back propagation of spikes. In particular, the rate of increase in dendritic membrane area (which is related to the number of bifurcations) act together with dendritic voltage-gated channels to shape spike back propagation (Vetter et al. 2001; see also Stuart and Häusser 1994). Although the work by Vetter and colleagues largely involved the comparative analysis *among* cell classes, there is also evidence that individual neuronal differences within the same class affects firing patterns (Krichmar et al. 2002; Schaefer et al. 2003). Thus the conclusion that back propagation in individual oblique trees is mostly determined by the local density of K_A is just a first approximation of the complex interactions between morphology and biophysics.

The model also predicts that the distribution of K_A or I_h in the obliques can affect the propagation of antidromic spikes in the main trunk, although in opposite ways: an increase of I_h would facilitate AP back propagation, whereas an increase in K_A would reduce it, occluding the effect of I_h . This provides an intriguing explanation for the dichotomous AP back propagation occasionally observed in the apical tree (Golding et al. 2001). It should be stressed that the “shock absorber” property of K_A (Yuste 1997) and the facilitating effect of I_h cannot be directly characterized by experiments because dendritic recordings are currently limited to the main trunk, and pharmacological manipulations that selectively target many oblique dendrites at the same time have never been reported. Interestingly because the density of K_A increases with the distance from the soma (at least in the main apical trunk), its effect on spike back propagation indirectly correlates with the position of the oblique dendrite. In this sense, our results also provide an interesting explanation of the report of a different computational study (Schaefer et al. 2003), which found that proximal oblique dendrites might enhance back propagation by providing additional current, whereas more distal obliques will function as a current sink impairing back propagation.

Regarding signal forward propagation, we showed that local oblique spikes can seldom reach the soma (Fig. 5) without sustained activity in the rest of the neuron (Fig. 7), unless they initiate close to the branch point with the main trunk *and* in trees near the soma. The dramatic attenuation of oblique spikes during propagation into the main apical trunk depends on both the diameter ratio and the distance of the initiation site from the branch point (Fig. 6). Such effect represents one of the main findings of this work: in most cases, isolated spiking activity in an oblique tree has negligible effects on the rest of the neuron.

The amount of activity required in the rest of the tree for an oblique spike to reach the soma (~10 mV, Fig. 8B) corresponds approximately to the synchronous suprathreshold activation of two to three additional subtrees stemming from adjacent positions on the main trunk (~4 mV, Fig. 5C) or presumably many more in case of spatial and/or temporal separation. Oblique trees with larger surface area and stem diameter, corresponding to major apical bifurcations, need a substantial higher inward current in the trunk to reach the same depolarization and transmit the dendritic spike. Furthermore, a subset of oblique trees was incapable of transmitting a spike to the soma even in the presence of any additional (subthreshold) activity in the trunk. The proportion of these “mute” dendrites increased with the local K_A density and the distance from the soma but was independent of tree size. It is interesting to note that the LI model consistently behaved intermediately between the C1 and C3 models. Such a trend reflects the oblique’s density of K_A channels and not that of I_h (which is always greater in LI than in the C1/C3 models, see Table 1). This suggests a minor role of I_h in the suprathreshold phenomena examined in this work. Altogether, these results greatly expand on the recent experimental work on the propagation of locally initiated dendritic spikes in the main trunk of CA1 pyramidal cells (Gasparini et al. 2004).

The effective independence of oblique trees from each other, with respect to their spiking behavior, enables the independent implementation of “localized” Hebbian plasticity (Alkon 1999). A synapse may be strengthened when the presynaptic activity coincides not necessarily with the somatic spiking of the postsynaptic neuron but possibly just with a locally initiated oblique spike. Such form of synaptic plasticity could be ongoing continuously and in parallel in many oblique branches during “silent” periods (lack of somatic spiking activity) of a CA1 pyramidal cell.

In summary, signal propagation in CA1 pyramidal cells is shaped by the interaction of unique morphological and biophysical features. The dendritic distributions of all main active conductances are known to be qualitatively and quantitatively different in various neuronal classes (Migliore and Shepherd 2002). Earlier work showed that the dendritic morphology

of different classes can affect both back and forward propagation of action potentials and that different ratios of Na^+ and K^+ conductances can partially compensate for the morphological differences (Vetter et al. 2001). Here we demonstrate that signal propagation varies within the homogenous group of CA1 pyramidal cells and in fact within individual neurons.

The ability of specific morphological and biophysical parameters to isolate and independently modulate subcellular components of CA1 pyramidal neurons provides these cells with peculiar computational properties. At the level of synaptic integration, the computational power of the apical tree is enhanced by a “double-step” nonlinear process, in which individual oblique trees undergo parallel electrogenic threshold discriminations before the resulting signals, brought subthreshold into the main trunk, are integrated anew in the soma (Poirazi et al. 2003a,b). An even more important functional consequence of the oblique properties examined in this work, however, is the potential to independently modulate synaptic efficacies in every tree in parallel. In an insightful theoretical study, Poirazi and Mel (2001) analyzed the increased memory capacity of a neuronal architecture with independent nonlinear units. The present work suggests a physiologically plausible implementations of these mechanisms by means of the independent and parallel modulation of back and forward propagation in each oblique tree, based on developmental mechanisms (local morphological features) and dynamic rules (regulation of active conductances).

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FIG. 1.

Definition and basic properties of the CA1 pyramidal cell models. *A*: 2-dimensional projections of the digital morphological reconstructions of neurons *C91662* and *n400* (oblique trees are shown in gray). *B*: input resistance, R_N , of all the neurons used in the simulations (shown for the LI model); the vertical dotted line separates values for reconstructions of neurons from adult (*left*) and young (*right*) animals.

FIG. 2.

Depolarization of oblique branches caused by a back-propagating action potential (AP). *A*, left: schematic representation of the typical simulation setup: AP back propagation was studied by eliciting a somatic AP with a short somatic current pulse. The plot shows the peak AP amplitude along the trunk (closed symbols) and each oblique (open symbols) for neuron 5038804 (type LI). Inset: the somatic membrane potential. *B*: distribution of the average peak depolarization of each oblique branch, $\langle \text{peak}_{\text{obl}} \rangle$, using different K_A distributions. *C*: $\langle \text{peak}_{\text{obl}} \rangle$ as a function of the ratio between the diameter of the oblique and of the parent trunk at the branch point. *D*: $\langle \text{peak}_{\text{obl}} \rangle$ as a function of the oblique surface area. *B–D* show results for all neurons (open circles, type C1; closed triangles, type C3; the type LI yields similar, intermediate results, not shown for graphical clarity).

FIG. 3.

Selective control of antidromic AP invasion of an oblique branch. *A*: average peak depolarization of each oblique branch, $\langle \text{peak}_{\text{obl}} \rangle$, during the back propagation of a somatic AP using C1 and C3 distributions, as a function of the path distance between the oblique stem on the main trunk and the soma (each symbol represents 1 oblique). *B*: peak AP amplitude in neuron C81462 with a type C1 distribution as a function of distance from the soma (the 2 trunks correspond to a “main” bifurcation of the apical tree); Δ , trunk; $\bullet$, obliques. *C*: analogous simulation of the same neuron as in *B*, but with a type C3 distribution in $\approx 30\%$ of the obliques ($\circ$, oblique trees with a C3 distribution). *D*: effects of a local depolarization of 4 mV ($\circ$) or 8 mV ($\bullet$) on AP back propagation into an oblique with a C3 distribution; the arrow marks the location of a local depolarizing current step of 0.005 nA (4 mV) or 0.01 nA (8 mV); the neuron and channels distribution were the same as in *C*; for clarity, only the oblique used for the current injection and the apical trunk to which it is attached are shown.

FIG. 4.

A: peak AP amplitude in the trunk during back propagation as a function of distance from soma for C1 and C3 distributions. All neurons are included, and each symbol represents a different location along the apical trunks. *B:* peak AP amplitude in the trunk during back propagation as a function of distance from soma for *neuron C81462* using C1 (circles) and C3 (triangles) distributions with or without (gray symbols) I_h . *C* and *D:* average ($\pm$ SD) peak AP amplitude in the trunk during back propagation as a function of distance from soma (50- μ m bins) for neurons from young (*C*) or adult (*D*) animals using C1 (black bars) and C3 (gray bars) distributions.

FIG. 5.

Forward propagation of an AP elicited in an oblique. *A, left*: schematic representation of the typical simulation setup: forward propagation was studied by eliciting a single dendritic AP with a suprathreshold synaptic stimulation. The plot shows the peak AP amplitude along the trunk (●) and each oblique (○), for *neuron 5038804* (type LI). *Inset*: the dendritic membrane potential of a particular stimulation site (indicated marker, ~180 μm from soma). *B*: average peak depolarization of each oblique branch, $\langle \text{peak}_{\text{obl}} \rangle$, using different K_A distributions, as a function of the path distance between the oblique stem on the main trunk and the soma (each symbol represents 1 oblique). *C*: average peak amplitude reached in the main trunk at the branch point with the stimulated oblique tree.

FIG. 6.

The ratio between the peak membrane potential in the oblique and that reached in the trunk at the branch point following a dendritic AP, peak ratio, as a measure of forward propagation (data for LI distribution). *A*: peak ratio as a function of distance from the soma for obliques stemming out of the apical trunk at 0–50 μm (black symbols), 200–250 μm (white symbols), and 350–400 μm (gray symbols) from the soma; for clarity, 3rd-order branches are not shown. For each region, the compartments of 3 obliques from different neurons are highlighted in blue, red, and green for varying ratios between the diameter of the oblique and the diameter of the trunk at the branch point, $D_{\text{obl}}/D_{\text{trunk}}$ (reported in the *insets* above each region). *B*: peak ratio along all obliques compartments as a function of their diameter and distance from the branch point. *C*: peak ratio for obliques dendrites with

diameter $\sim 0.3\text{--}0.4\ \mu\text{m}$, as a function of $D_{\text{obl}}/D_{\text{trunk}}$ and distance from the branch point on the trunk.

FIG. 7.

Relative ability of oblique dendrites to transmit a local spike to the soma. **A**: schematic representation of a typical simulation setup: a single dendritic AP was elicited in the presence of a constant depolarizing current injection at the branch point in the trunk. **B**: proportion of oblique trees (total $n = 664$) for which a somatic spike could be elicited without additional stimulation of the trunk (always), those for which a somatic spike could be elicited only in the presence of additional subthreshold stimulation of the trunk (sometimes), and those for which a somatic spike could not be elicited with any additional subthreshold stimulation of the trunk (never). Results for the different K_A distributions types (LI, C1, and C3) are shown in different panels; sampling of 50 μm were used 500 μm , with oblique trees at 500 – 800 μm from soma ($n = 8$) grouped together. The total number of trees at each value is shown in the *top panel*. **C**: average ($\pm$ SD) value of the (subthreshold)

current injection in the trunk necessary to elicit a somatic spike during supra-threshold stimulation of an oblique tree in the sometimes group using different K_A distributions.

FIG. 8.

Influence of oblique tree surface area on the propagation of oblique spikes to the soma (data for LI distribution; qualitatively similar results were obtained for the C1 and C3 distributions). *A*: proportion of trees in the always, sometimes, and never categories as a function of the oblique surface area (numbers of trees at each abscissa value are reported on the top horizontal axis). *B*: average trunk current injection (blue, *left axis*) and resulting voltage depolarization (red, *right axis*) necessary to elicit a somatic spike during a local supra-threshold stimulation of sometimes oblique trees. Averages ($\pm$ SD) over all oblique trees of the mean values among all compartments of each tree are plotted. *C*: average diameter ($\pm$ SD) of the sometimes oblique trees as a function of their surface area. *D*: diameters distribution of the sometimes oblique trees.

TABLE 1

Schematic description of the distribution for the peak K_A and I_h conductances in the configurations explored in this work (LI, C1, and C3)

	K_A		I_h	
	Trunk	Oblique	Trunk	Oblique
LI	Linear increase (L.i.)	L.i.	L.i.	L.i.
C1	<350 μm : L.i. 350 μm : same value as 350 μm	Constant: same value as branchpoint	<350 μm : L.i. 350 μm : same value as 350 μm	Constant: same value as branchpoint
C3	Same as C1	Constant: 3 $\times$ the value at branchpoint	Same as C1	Same as C1