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Dendritic size and topology influence burst firing in pyramidal cells

Arjen van Ooyen, Ronald A. J. van Elburg

Abstract. Neurons have highly branched dendrites that form characteristic tree-like structures. The morphology of these dendritic arborizations is not fixed and can undergo significant alterations in many pathological conditions. However, little is known about the impact of morphological changes on neuronal activity. Using computational models of pyramidal cells, we study the influence of dendritic tree size and branching structure on burst firing. Burst firing is the generation of two or more action potentials in close succession, a form of neuronal activity that is critically involved in neuronal signaling and synaptic plasticity. We show that there is only a range of dendritic tree sizes that supports burst firing, and that this range is modulated by the branching structure of the tree. Shortening as well as lengthening the dendritic tree, or even just modifying the pattern in which the branches in the tree are connected, can shift the cell's firing pattern from bursting to tonic firing. The influence of dendritic morphology on burst firing is attributable to the effect that dendritic size and branching pattern have on the average spatial extent of the dendritic tree and the spatiotemporal dynamics of the dendritic membrane potential. Our results suggest that alterations in pyramidal cell morphology, such as those observed in Alzheimer's disease, mental retardation, epilepsy and chronic stress, can change neuronal burst firing and thus ultimately affect information processing and cognition.

Introduction

Neurons exhibit a wide range of intrinsic firing patterns (Connors and Gutnick 1990, Contreras 2004). A distinct firing pattern that is critically involved in neuronal signaling and synaptic plasticity is burst firing, the generation of clusters of spikes with short interspike intervals (Krahe and Gabbiani 2004). Bursts improve the signal-to-noise ratio (Eggermont and Smith 1996), are transmitted more reliably than isolated spikes (Swadlow and Gusev 2001), are more effective than single spikes in inducing synaptic long-term potentiation (LTP) (Yun et al 2002), and can even determine whether LTP or LTD (long-term depression) occurs (Birtoli and Ulrich 2004).

Two main classes of ionic mechanisms underlying intrinsic neuronal burst firing have been identified (Krahe and Gabbiani 2004). In so-called dendrite-independent mechanisms—responsible for bursting in thalamic relay neurons (McCormick and Huguenard 1992), for example—the fast, spike-generating conductances and the slow, burst-controlling conductances are co-localized in the soma. Conversely, in dendrite-dependent mechanisms—involved in pyramidal cell burst firing—these conductances are distributed across the soma and dendrites, with the interaction between somatic and dendritic conductances playing an essential role in burst generation. Dendritic voltage-gated Na^+ and K^+ channels, which promote propagation of action potentials from the soma into the dendrites, cause the dendrites to be depolarized when, at the end of a somatic spike, the soma is hyperpolarized, leading to a return current from dendrites to soma. The return current gives rise to a depolarizing afterpotential at the soma, which, if strong enough, produces another somatic spike (Williams and Stuart 1999, Wang 1999). This whole process was described by Wang (1999) as 'ping-pong' interaction between soma and dendrites.

Although ion channels play a central role in burst firing, dendritic morphology also appears to be an important modulating factor. In many cell types, including neocortical and hippocampal pyramidal cells (Mason and Larkman 1990, Chagnac-Amitai et al 1990, Bilkey and Schwartzkroin 1990), neuronal firing patterns and the occurrence of bursts are correlated with dendritic morphology. Results from modeling studies also suggest a relationship between dendritic morphology and firing pattern (Mainen and Sejnowski 1996, Sheasby and Fohlmeister 1999, Van Ooyen et al 2002, Krichmar et al 2002). However, these studies are mainly correlative, focus on morphologically very distinct cell classes, use only the physiologically less appropriate stimulation protocol of somatic current injection, and do not investigate the impact of topological structure of dendritic arborizations.

In this chapter, we summarize our study (Van Elburg and Van Ooyen 2010) in which we used computational models of neocortical pyramidal neurons to investigate the impact of a cell's dendritic morphology (both size and topological structure) on the ping-pong mechanism of burst firing, under either somatic current injection or synaptic stimulation of the apical dendritic tree.

Methods

Pyramidal cell

We used a morphologically and biophysically realistic model of a bursting layer 5 pyramidal cell (Mainen and Sejnowski 1996) implemented in NEURON (Hines and Carnevale 1997). The pyramidal cell was activated by either somatic or dendritic stimulation. For somatic stimulation, the cell was continuously stimulated with a fixed current injection of 0.2 nA. For dendritic stimulation, the cell was stimulated by synapses that were regularly distributed across the apical dendrite. Each synapse was randomly activated.

We investigated the effect of both dendritic size and dendritic topology on burst firing. The size of a dendritic tree is the total length of all its dendritic segments. The topology of a dendritic tree is the way in which the dendritic segments are connected to each other. For example, a tree with a given number of terminal segments can be connected in a fully asymmetrical (Fig. 4A) or a fully symmetrical way (Fig. 4B)

To investigate how the dendritic size of the pyramidal cell influences burst firing, we varied the total length of the cell's apical dendrite according to two methods. In the first method, we successively pruned terminal segments from the apical dendritic tree. Starting with the full pyramidal cell morphology, in each round of pruning we randomly removed a number of terminal segments from the apical dendritic tree. From the reduced dendritic tree, we again randomly cut terminal segments, and so on, until the whole apical dendrite was eliminated. This whole procedure of starting with the complete apical dendritic tree and sequentially stripping it of all its segments was repeated 20 times. The density of synapses was kept constant during pruning, so with dendritic stimulation pruning also changed the total input to the cell. With somatic simulation, the total input to the cell did not change when the apical dendrite was pruned.

In the second method, we kept the dendritic arborization intact and changed the size of the apical dendrite by multiplying the lengths of all its segments by the same factor. Thus, the

entire apical dendritic tree was compressed or expanded. For dendritic stimulation, we kept the total synaptic input to the cell constant by adapting the density of the synapses. So, both with somatic and dendritic stimulation, the total input to the cell did not change when the size of the apical dendrite was modified.

To examine the impact of the cell's dendritic branching structure on burst firing, we varied the topology of the apical dendritic tree by swapping branches within the tree. The apical dendritic trees that were generated in this way had exactly the same total dendritic length and other metrical properties such as total dendritic surface area and differed only in their topological structure. The total input to the cell, both with somatic and dendritic stimulation, did not change when the topological structure was altered.

Morphologically simplified cells

We also studied a set of morphologically simplified neurons, consisting of all the 23 topologically different trees with 8 terminal segments (two examples are shown in Fig. 4A, B), but with the same ion channel composition as in the full pyramidal cell model. All dendritic segments had the same length, so the tree topologies did not differ in total dendritic length. All terminal segments were given the same diameter (0.7 μm; Larkman 1991), while the diameters of intermediate segments were calculated using Rall's power law (Rall 1959), with a branch power of 1.5. This implied that asymmetrical topologies had a higher total dendritic surface area than symmetrical topologies. We therefore also considered the case in which all segments in the tree had the same diameter (3 μm) and all tree topologies thus had the same dendritic surface area. The neurons were continuously stimulated with a fixed current injection of 0.03 nA (0.1 nA for the non-Rall neurons) at the soma, or by uniformly distributed synapses across the dendritic tree.

To examine how the size of the dendritic tree influences firing pattern, we changed the total dendritic length of a given tree topology by multiplying the lengths of all its segments by the same factor. For dendritic stimulation, the total number of synapses on the tree was thereby kept constant. Thus, both with somatic and dendritic stimulation, the total input to the cell did not change when the size of the dendritic tree was modified.

Quantifying burst firing

Bursting is defined as the occurrence of two or more consecutive spikes with short interspike intervals followed by a relatively long interspike interval. To quantify bursting, we used the burst measure B developed in Van Elburg and Van Ooyen (2004). This measure is based

solely on spike times and detects the correlated occurrence of one or more short (intraburst) interspike intervals followed by a long (interburst) interspike interval. It quantifies the extent of bursting in the whole spike train; it does not try to identify individual bursts. The higher the ratio of inter- to intraburst interspike intervals, the stronger the bursting and the higher the value of B.

Input conductance and mean electrotonic path length

The input conductance of a pyramidal cell was determined by applying a subthreshold current injection at the soma. The ratio of the magnitude of the injected current to the resulting change in membrane potential at the soma is defined as the input conductance of the cell.

To quantify the electrotonic extent of a dendritic tree, we used the mean electrotonic path length (MEP) (Van Elburg and Van Ooyen 2010). For a given terminal segment, the electrotonic path length is the length (normalized to the electrotonic length constant) of the path from the tip of the segment to the soma. This electrotonic path length is determined for each terminal segment, and the sum of all electrotonic path lengths is divided by the total number of terminal segments to obtain the MEP of the dendritic tree.

Results

Employing a standard model of a bursting pyramidal cell (Mainen and Sejnowski 1996), we investigated how dendritic morphology influences burst firing by varying either the size or the topology of the apical dendrite. We also examined a set of morphologically simplified cells with systematic differences in dendritic topology.

Pyramidal cell

Dendritic size. To investigate how pyramidal cell size influences burst firing, we changed the total length of the apical dendrite according to two methods. In the first method, we successively pruned terminal branches off the apical dendrite. Both with somatic and with dendritic stimulation, the degree of bursting decreased as the dendritic tree became shorter (Fig. 1A). Reducing the size of the apical dendrite ultimately transformed the bursting pyramidal cell into a tonically firing cell. The removal of only a few small terminal segments could be enough to completely change the firing state of the cell (Fig. 1B). Because of the

random activation of synapses, the changes in the degree of bursting were more gradual with dendritic than with somatic stimulation.

In the second method, we kept the dendritic arborization intact and varied the size of the apical dendritic tree by multiplying the lengths of all its segments by the same factor. Both with somatic and with dendritic stimulation, and in line with the previous results, burst firing disappeared as the total dendritic length was decreased (Fig. 2A). Interestingly, the pyramidal cell also did not exhibit burst firing when the apical dendrite became too large. Only when the length of the apical dendrite remains within a certain range are bursts generated. Fig 2B shows the firing patterns of the pyramidal cell at increasing lengths of its apical dendrite.

Dendritic topology. To examine whether dendritic branching structure, or topology, could influence burst firing, we varied the topology of the apical dendritic tree by swapping branches within the tree. Thus, all the dendritic trees generated in this way had exactly the same metrical properties (total length, total surface area) and differed only in the way their branches were connected. Within this set, we found pyramidal cells that produced firing patterns ranging from tonic firing to strongly bursting (Fig. 3). Just remodeling the topology of the apical dendrite could completely change the firing state of the cell and turn a bursting cell into tonically firing cell or vice versa. Interestingly, dendritic topology not only affected whether a cell exhibited bursting or not (Fig. 3A-C versus Fig. 3D-F), but also influenced the fine structure or degree of bursting. The cell displayed in Fig. 3A generated (with somatic stimulation) two-spike bursts alternating with single spikes. The cells in Figs. 3B and 3C both produced a pattern of two-spike bursts, but the relative sizes of the interspike intervals between and within bursts were different. Although dendritic stimulation introduced irregularities in firing pattern because of the stochastic nature of the activation of synapses, somatic and dendritic stimulation yielded comparable results.

Morphologically simplified cells

Dendritic size and topology. To analyse more precisely the effect of dendritic morphology on burst firing, we also investigated (Van Elburg and Van Ooyen 2010) a set of 23 morphologically simplified neurons consisting of all the topologically different trees with 8 terminal segments (two examples are shown in Fig. 4A, B). The total length of a given tree topology was varied by changing the lengths of all the segments in the tree by the same factor. Under all conditions (somatic or dendritic simulation, trees with uniform segment diameters

or trees whose segments diameters obeyed Rall's power law), bursting occurred only for a certain range of tree sizes, as in the full pyramidal cell model. Interestingly, this range depended on the topology of the dendritic tree: trees with an asymmetric branching structure started bursting at a lower total dendritic length than trees with a symmetric branching structure, and also stopped bursting at a lower total dendritic length.

Also under all conditions, we found that both the onset and the cessation of bursting were strongly correlated, not to the input conductance, but to the mean electrotonic path length of the dendritic tree (see Methods), with burst firing occurring only within a certain range of path lengths. Burst firing occurred when the mean electrotonic path length was higher than a certain critical value. At the same total dendritic length, asymmetrical trees have a higher mean electrotonic path length than symmetrical trees, and consequently reached this critical value earlier than symmetrical trees as dendritic length was increased.

Importance of electrotonic distance and dendritic topology for burst firing. Why is mean electrotonic path length important for bursting? In the burst firing mechanism of pyramidal cells, a somatically generated action potential propagates into the dendritic tree and depolarizes the dendrites, creating a potential difference between distal dendrites and soma. This leads to a return current from dendrites to soma, which, if strong enough, produces another somatic spike ('ping-pong' mechanism; see also Introduction). The arrival of the backpropagating action potential in the dendritic tips marks the onset of the return currents. If these return currents reach the soma when the delayed-rectifier K^+ conductance is still high, it will be difficult for the soma to depolarize and produce a spike. Since the propagation velocity of voltages and currents is proportional to the electrotonic length constant (Koch 1999), the mean electronic path length is a measure for the average time it takes for a backpropagating action potential to travel to the dendritic tips (and for the return current to move to the soma). Thus, if the mean electronic path length is too small, the return current will arrive too early at the soma, when the delayed-rectifier K^+ conductance is still high, so that it cannot produce another spike—that is, no bursting. Furthermore, if the electrotonic distance between soma and distal dendrites is too small, the large conductive coupling will lead to currents that quickly annul membrane potential differences between soma and distal dendrites. This prohibits a strong and long-lasting differentiation in membrane potential between soma and distal dendrites, which is the generator of the return current.

However, if the electrotonic distance between soma and distal dendrites is too large, bursting will also not occur. Note that even in the absence of a return current, the cell will

generate a next spike as a result of the external (somatic or dendritic) stimulation. So, what the return current in fact does when it causes bursting is to advance the timing of the next spike. If the electronic distance is too large, the return current will arrive too late—that is, not before the external stimulation has already caused the cell to spike. Furthermore, if the electrotonic distance is too large, the potential gradient between distal dendrites and soma will become too shallow for a strong return current.

Importantly, the mean electrotonic path length depends also on the topology of the dendritic tree, which accounts for the influence of dendritic topology on burst firing. In asymmetrical trees, the terminal segments are on average further away from the soma than in symmetrical trees. Consequently, at the same dendritic size, asymmetrical trees have a higher mean electrotonic path length—as well as 'normal' mean path length—than symmetrical trees (both in trees with uniform segment diameters and in trees whose segments diameters obey Rall's power law). As a result, asymmetrical trees reach the critical values of mean electrotonic path length from where bursting starts, and from where it stops, at lower dendritic sizes than symmetrical trees. Fig. 4 illustrates the importance of electrotonic distance and the impact of topological structure on burst firing.

In general, the results obtained with dendritic stimulation are comparable to those produced with somatic stimulation (Figs. 1-3). In the ping-pong mechanism of burst firing, the sequence and timing of events start when a somatic action potential propagates into the dendritic tree. How this action potential is generated in the first place, by current injection into the soma or as a result of summation of dendritic synaptic inputs, appears not to be crucial.

Discussion

Burst firing is critically involved in synaptic plasticity and neuronal signaling, and it is therefore important to know what factors might affect bursting. We showed that either shortening or lengthening the apical dendrite tree beyond a certain range can transform a bursting pyramidal cell into a tonically firing cell. Remarkably, altering only the topology of the dendritic tree, whereby the total length of the tree remains unchanged, can likewise shift the firing pattern from bursting to non-bursting or vice versa. Moreover, both dendritic size and dendritic topology not only influence whether a cell is bursting or not, but also affect the number of spikes per burst and the interspike intervals between and within bursts.

The influence of dendritic morphology on burst firing is attributable to the effect dendritic length and dendritic topology have, not on input conductance, but on the spatial

extent of the dendritic tree, as measured by the mean electrotonic path length between soma and distal dendrites. For the spatiotemporal dynamics of dendritic membrane potential to generate burst firing, this electrotonic distance should be neither too small nor too large. Because the degree of symmetry of the dendritic tree also determines mean electrotonic path length, with asymmetrical trees having larger mean path lengths than symmetrical trees, dendritic topology as well as dendritic size affects the occurrence of burst firing.

In Mainen and Sejnowski's (1996) two-compartment model for explaining the role of dendritic morphology in shaping firing pattern, the spatial dimension of morphology was completely reduced away. Although the model is able to reproduce a wide range of firing patterns, it does not capture the essential influence of dendritic morphology on burst firing, for which, as we have shown here, the spatial extent of the dendritic tree and the resulting spatiotemporal dynamics of the dendritic membrane potential are important.

Our results are in accord with empirical observations suggesting that pyramidal cells should have reached a minimal size to be capable of burst firing. In weakly electric fish, the tendency of pyramidal cells to fire bursts is positively correlated with the size of the cell's apical dendritic tree (Bastian and Nguyenkim 2001). In rat prefrontal cortex (Yang et al 1996) and visual cortex (Mason and Larkman 1990), the classes of pyramidal cells that exhibit burst firing have a greater total dendritic length than the other classes.

In addition, the developmental time course of bursting shows similarities with that of dendritic morphology. In rat sensorimotor cortex, the proportion of bursting pyramidal cells progressively increases from postnatal day 7 onwards, while at the same time the dendritic arborizations become more complex (Franceschetti et al 1998). In pyramidal cells from rat prefrontal cortex, the total lengths of apical and basal dendrites increase dramatically between postnatal days 3 and 21, with neurons capable of burst firing appearing only from postnatal day 18 onwards (Zhang 2004, Dégenètais et al 2002).

Dendritic morphology can undergo significant alterations in many pathological conditions, including chronic stress (Sousa et al 2000, Radley et al 2004, Cook and Wellman 2004, Magariños et al 1996), epilepsy (Teskey et al 2006), hypoxic ischemia (Ruan et al 2006), Alzheimer (Yamada et al 1988, Moolman et al 2004), and disorders associated with mental retardation (Kaufman and Moser 2000). Functional consequences of these morphological changes are usually interpreted in terms of loss or formation of synaptic connections as a result of a diminished or expanded postsynaptic surface area. Our modeling results indicate that alterations in dendritic morphology can directly modify neuronal firing, irrespective of changes in total synaptic input.

Chronic stress, as well as daily administration of corticosterone, induces extensive regression of pyramidal apical dendrites in hippocampus (Sousa et al 2000, Magariños et al 1996, Woolley et al 1990) and prefrontal cortex (Radley et al 2004, Cook and Wellman 2004). As a result of a decrease in the number and length of terminal branches, the total apical dendritic length can reduce by as much as 32% (Cook and Wellman 2004). Similarly large alterations have been observed in response to mild, short-term stress (Brown et al 2005). Our results predict that stress and the accompanying reduction in apical dendritic length could turn a bursting neuron into a non-bursting one. Indeed, Okuhara and Beck (1998) found that two weeks of high corticosterone treatment caused a decrease in the relative number of intrinsically bursting CA3 pyramidal cells. Since burst firing of CA3 pyramidal cells is critically involved in LTP (Bains et al 1999), this could have profound functional consequences for hippocampal information processing (Pavlides et al 2002).

With regard to epilepsy, a significant decrease in total dendritic length and number of branches has been found in pyramidal cells following neocortical kindling (Teskey et al 2006). In line with our results, Valentine et al (2004) reported that cells recorded from the primary auditory cortex of kindled cats showed a reduction in the amount of burst firing and a decrease in the number of spikes per burst.

In Alzheimer's disease, various aberrations in dendritic morphology have been observed—including a reduction in total dendritic length and number of dendritic branches (Yamada et al 1988, Moolman et al 2004) and alterations in the pattern of dendritic arborization (Arendt et al 1997)—which may contribute to the abnormal neurophysiological properties of Alzheimer pyramidal cells (Stern et al 2004). The anomalies in morphology could influence the cells' ability to produce burst, and, because of the role of burst firing in LTP and LTD (Yun et al 2002, Birtoli and Ulrich 2004), ultimately affect cognition. In disorders related with mental retardation, the observed alterations in dendritic length and pattern of dendritic branching (Kaufman and Moser 2000), e.g., changes in the degree of symmetry of the apical dendrite (Belichenko et al 1994), may likewise be hypothesized to contribute to impaired cognition.

In conclusion, our results show that alterations in either the size or the topology of dendritic arborizations, such as those observed in many pathological conditions, could have a marked impact on pyramidal cell burst firing and, because of the critical role of bursting in neuronal signaling and synaptic plasticity, ultimately affect cognition.

Outlook

One way to test experimentally the importance of mean electrotonic path length for burst firing is to study whether the occurrence of bursting in a large set of electrophysiologically similar pyramidal cells correlates with the mean electrotonic path length (or alternatively, 'normal' path length) of their apical dendrites. Direct experimental testing of the influence of dendritic morphology on burst firing could be done by physically manipulating the shape or size of the dendritic tree, e.g., by using techniques developed by Bekkers and Häusser (2007). In line with our results, they showed that dendrotomy of the apical dendrite abolished bursting in layer 5 pyramidal cells.

Since firing patterns characteristic of different classes of neurons may in part be determined by total dendritic length, we expect on the basis of our results that a neuron may try to keep its dendritic size within a restricted range in order to maintain functional performance. Indeed, Samsonovich and Ascoli (2006) have shown that total dendritic size appears to be under intrinsic homeostatic control. Statistically analyzing a large collection of pyramidal cells, they found that, for a given morphological class and anatomical location, fluctuations in dendritic size in one part of a cell tend to be counterbalanced by changes in other parts of the same cell so that the total dendritic size of each cell is conserved. We predict that dendritic topology may similarly be protected from large variations. In fact, there could be a trade-off between dendritic size and dendritic topology. In a set of bursting pyramidal cells, we expect that apical dendritic trees with a lower degree of symmetry are shorter in terms of total dendritic length or have thicker dendrites to reduce electrotonic length than those with a higher degree of symmetry.

We investigated the impact of dendritic morphology on the ping-pong mechanism of burst firing (Williams and Stuart 1999, Wang 1999) in pyramidal cells. Future computational studies could also examine the role of morphology in other mechanisms of burst firing (McCormick and Huguenard 1992).

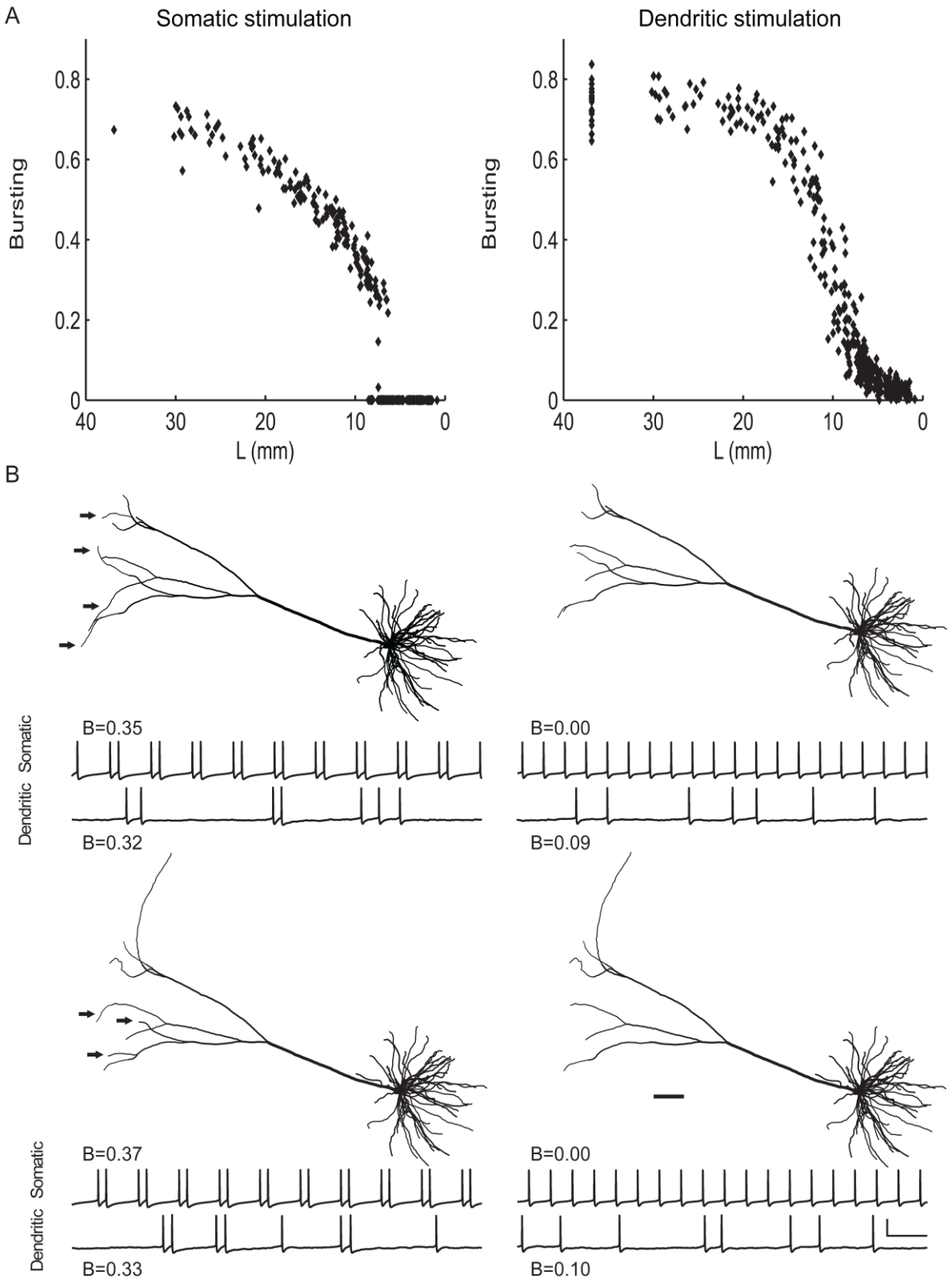

Figure 1. Both with somatic and with dendritic stimulation, pyramidal cell burst firing decreased as the apical dendrite became shorter. **A,** The degree of bursting, as measured by the burst measure *B*, against the total length of the apical dendritic tree. The total length of the

apical dendritic tree was gradually reduced by successively removing terminal segments. Results are shown of 20 times starting with the complete apical dendritic tree and randomly removing terminal segments until the whole tree was eliminated. The complete apical dendritic tree had a total length of 36865 μm. **B,** Examples from the experiment in A showing that the removal of only a few small terminal segments from the apical dendritic tree could change the firing state of the cell. Morphology of pruned pyramidal cells, and voltage traces for both somatic and dendritic stimulation. *Left,* Bursting cells (*Top*, 9772 μm; *Bottom*, 8925 μm). *Right*, Non-bursting cells (*Top*, 8184 μm; *Bottom*, 6927 μm). Scale bar: 100 ms, 50 mV. Scale bar (anatomy): 100 μm. Arrows in the bursting cells indicate the branches that were shorter or absent in the non-bursting cells. (Reproduced from Van Elburg and Van Ooyen 2010)

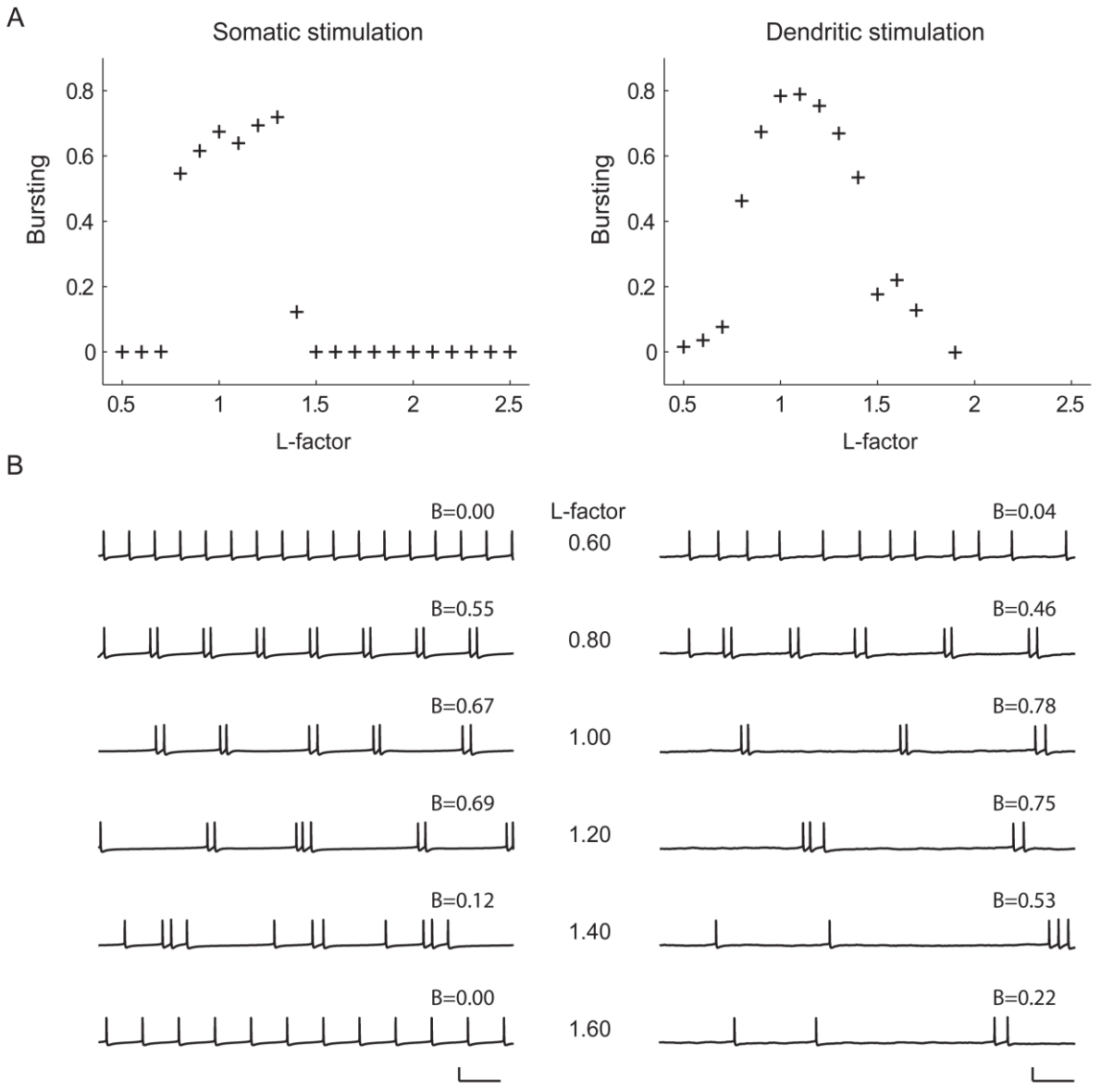

Figure 2. Both with somatic and with dendritic stimulation, pyramidal cell burst firing disappeared when the apical dendrite became either too large or too small. We varied the size of the apical dendrite by scaling the entire apical dendrite, thus keeping the dendritic arborization intact. **A,** The degree of bursting against the factor by which the length of all the apical dendritic segments was multiplied. **B,** Voltage traces obtained for different sizes of the apical dendrite. *Left*, somatic stimulation. *Right*, dendritic stimulation. Scale bars: 100 ms, 50 mV. (Reproduced from Van Elburg and Van Ooyen 2010)

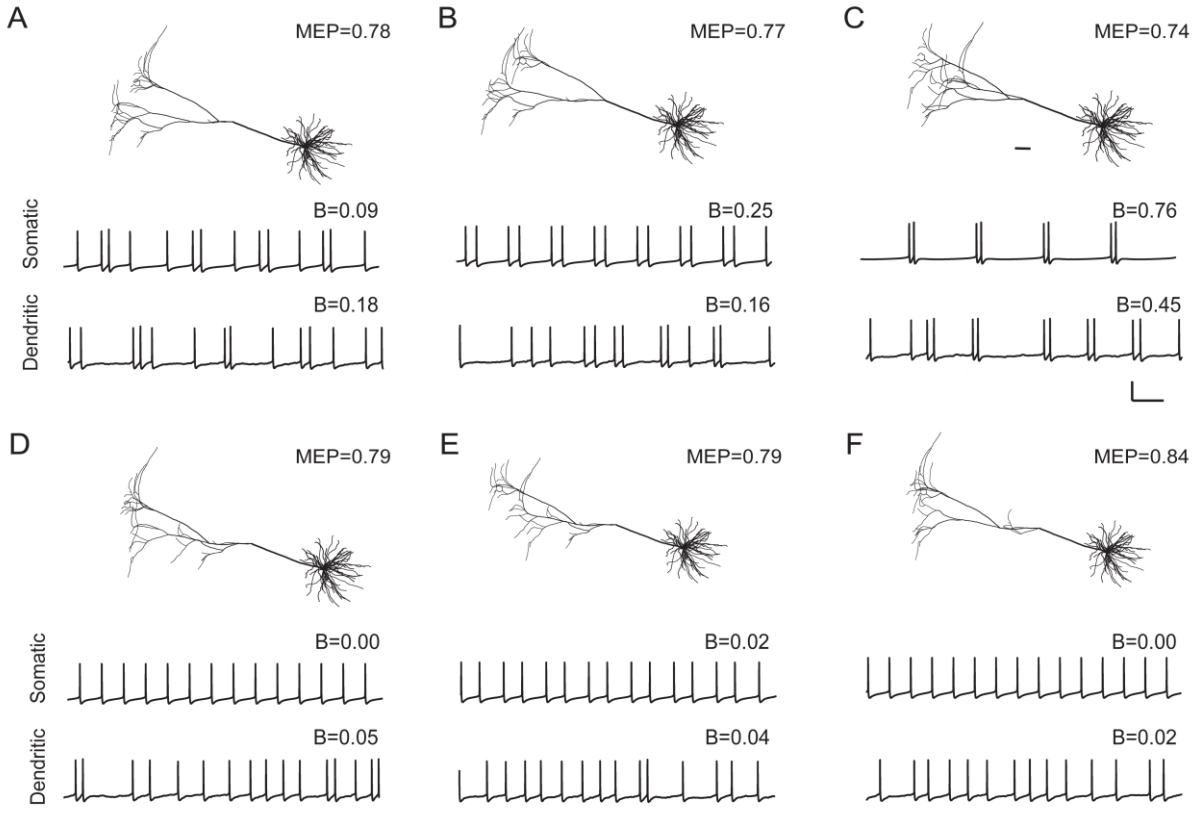

Figure 3. Both with somatic and with dendritic stimulation, dendritic topology affected pyramidal cell burst firing. We varied the topology of the apical dendritic tree by swapping branches within the tree. Thus, all the pyramidal cells shown had exactly the same total dendritic length and dendritic surface area and differed only in the topology of their apical dendrite (basal dendrites were the same). Voltage traces for three bursting cells (A-C), and three non-bursting cells (D-F). Scale bar: 100 ms, 50 mV. Scale bar (anatomy): 100 μm. MEP values indicate the mean electrotonic path length of the apical dendritic tree. (Reproduced from Van Elburg and Van Ooyen 2010)

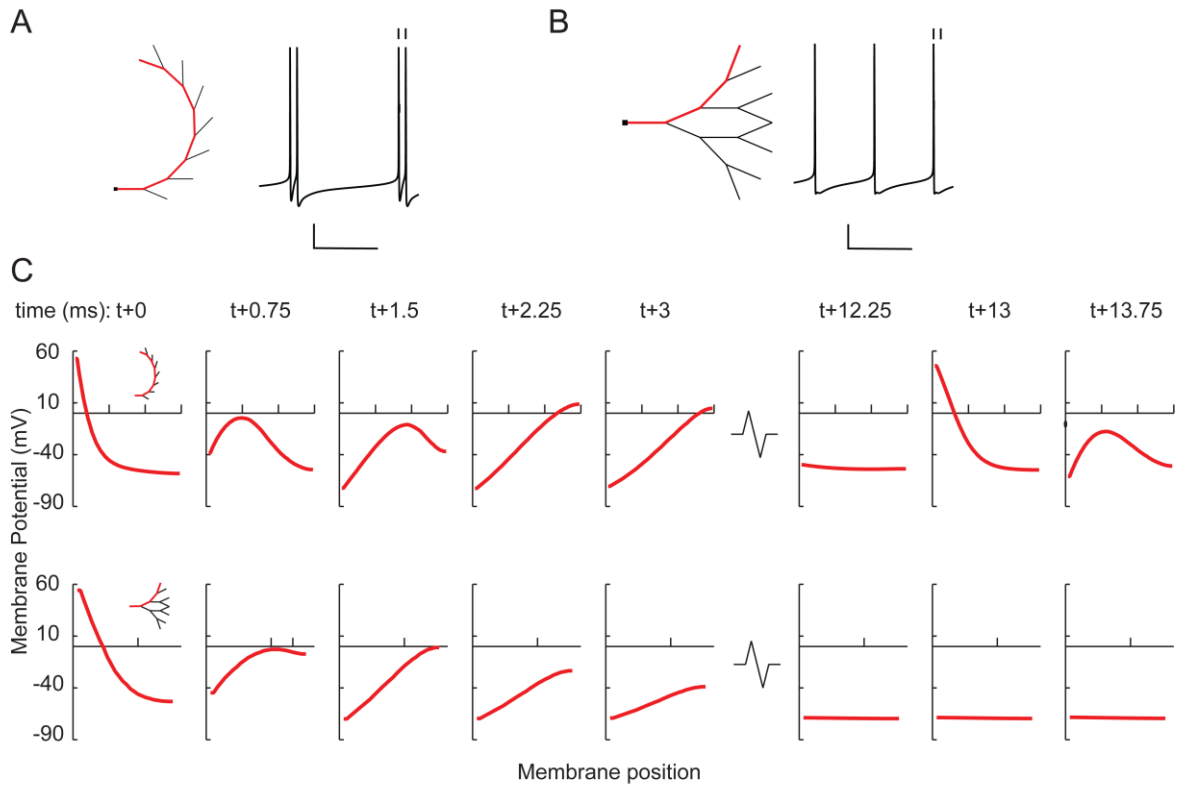

Figure 4. The importance of electrotonic distance for burst firing and the impact of dendritic topology illustrated with a fully asymmetrical and a fully symmetrical tree. **A, B,** At this dendritic size, the asymmetrical tree (**A**) generated bursts, whereas the symmetrical tree (**B**) produced single spikes. The segment diameters in the trees obeyed Rall's power law, and both trees had the same total dendritic length (1600 μm). The cell was stimulated at the soma. Scale bars: 100 ms, 20 mV. The ticks on top of the action potentials in A and B indicate the spikes that are shown at t + 0 and t + 13 in panel C. **C,** The membrane potential evolution over time in the asymmetrical tree (*top row*) and the symmetrical tree (*bottom row*) along the dendritic paths indicated in A and B. Time is relative to the first spike (at 0 ms), and membrane position on the x-axis runs from soma to the tip of the terminal segment. Because the distance between soma and terminal segment is smaller in the symmetrical than in the asymmetrical tree, the membrane potential evolution in the symmetrical tree had less spatial differentiation, the membrane potential reached a lower value at the distal end, and the distal membrane potential started decreasing earlier in time so that the return current from dendrites to soma reached the soma at a time when the delayed-rectifier K^+ channels were still open, preventing the generation of a second spike. (Reproduced from Van Elburg and Van Ooyen 2010)

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