

INFLUENCE OF ASYMMETRIC ATTENUATION OF SINGLE AND PAIRED DENDRITIC INPUTS ON SUMMATION OF SYNAPTIC POTENTIALS AND INITIATION OF ACTION POTENTIALS

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Abstract—Previous studies revealed mechanisms of dendritic inputs leading to action potential initiation at the axon initial segment and backpropagation into the dendritic tree. This interest has recently expanded toward the communication between different parts of the dendritic tree which could preprocess information before reaching the soma. This study tested for effects of asymmetric voltage attenuation between different sites in the dendritic tree on summation of synaptic inputs and action potential initiation using the NEURON simulation environment. Passive responses due to the electrical equivalent circuit of the three-dimensional neuron architecture with leak channels were examined first, followed by the responses after adding voltage-gated channels and finally synaptic noise. Asymmetric attenuation of voltage, which is a function of asymmetric input resistance, was seen between all pairs of dendritic sites but the transfer voltages (voltage recorded at the opposite site from stimulation among a pair of dendritic sites) were equal and also summed linearly with local voltage responses during simultaneous stimulation of both sites. In neurons with voltage-gated channels, we reproduced the observations where a brief stimulus to the proximal ascending dendritic branch of a pyramidal cell triggers a local action potential but a long stimulus triggers a somal action potential. Combined stimulation of a pair of sites in this proximal dendrite did not alter this pattern. The attraction of the action potential onset toward the soma with a long stimulus in the absence of noise was due to the higher density of voltage-gated sodium channels at the axon initial segment. This attraction was, however, negligible at the most remote distal dendritic sites and was replaced by an effect due to high input resistance. Action potential onset occurred at the dendritic site of higher input resistance among a pair of remote dendritic sites, irrespective of which of these two sites received the synaptic input. Exploration of the parameter space showed how the gradient of voltage-gated channel densities and input resistances along a dendrite could draw the action potential onset away from the stimulation site. The attraction of action potential onset toward the higher density of voltage-gated channels in the soma during stimulation of the proximal dendrite was, however, reduced after the addition of synaptic noise. © 2012 IBRO. Published by Elsevier Ltd. All rights reserved.

INTRODUCTION

It is generally understood that the phenomenal capabilities of neural networks derive from the connectivity among neurons forming a network and from the firing properties of these neurons (Büschges et al., 2011; Fortier et al., 2005; Getting, 1989; Marder, 1998). Each neuron can be viewed as a biological device that sums excitatory and inhibitory synaptic inputs leading to an axon hillock action potential when the sum crosses its threshold. More recently, other more complex properties than simply summation of synaptic inputs have been shown to play a role (Fiala and Harris, 1999; Magee, 2008; Mel, 2008; Nusser, 2008; Rabinowitch et al., 2008; Spruston et al., 2008). For example, the intrinsic firing properties of a neuron, whether adapting non-adapting or bursting, is influenced by the complexity of arborization in the dendritic tree (Mainen and Sejnowski, 1996). Furthermore, the responses to paired stimuli can reflect simple linear summation or supralinear summation depending on whether they are delivered to separate dendritic branches or to the same branch (Polsky et al., 2004; Spruston and Kath, 2004). These responses are further influenced by the level of synaptic noise such that subthreshold membrane fluctuations can nevertheless trigger an action potential (Priebe and Ferster, 2008).

These more complex properties of dendritic trees have led researchers to suggest a framework for dendritic processing of information that is similar to that of neural networks (Branco and Häusser, 2010; Spruston et al., 2008). That is, for neural networks formed of point neurons lacking dendrites (Segev and London, 2000) there is summation of synaptic inputs to determine whether an action potential will be generated in order to transmit information further along the network. By viewing separate dendritic branches as presynaptic neurons and dendritic branch points as postsynaptic neurons, it has been proposed that very complex processing normally attributed to a network of neurons could be performed within a single dendritic tree (Branco et al., 2010; Spruston and Kath, 2004). Thus the number of neurons forming a neural network for information processing (Munro et al., 1994) may be substantially smaller than expected because of complex processing within single neurons (Fortier et al., 2005).

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Consequently, there is considerable interest in revealing principles of signal processing by dendritic trees (Stuart et al., 2007). The present study focuses on the impact of asymmetric voltage attenuation which is a function of asymmetrical input resistance along the dendritic tree. It has been observed repeatedly, that orthodromic voltage attenuation from dendrites to soma is much greater than antidromic voltage attenuation from soma to dendrites (Briska et al., 2003; Ledergerber and Larkum, 2010; Mel, 1994; Rabinowitch et al., 2008; Segev and London, 1999; Segev and London, 2000). It is not fully known how this asymmetric voltage attenuation would impact processing within the dendritic tree. Recent studies have shown that the higher input resistances in more distal parts of the dendritic tree lead to stronger activation of NMDA receptors enabling the neuron to distinguish between opposite directions of input activation along the dendritic tree (Branco et al., 2010; Branco and Häusser, 2011). Summation within the dendritic tree can derive from a large number of presynaptic inputs but the basic principles could be described by the interaction between two dendritic inputs. Studies of dendritic processing are technically difficult and are consequently limited to larger dendrites that are more proximal to the soma. As done in other studies (Mainen and Sejnowski, 1996; Spruston and Kath, 2004), a mechanistic modeling approach was used to circumvent this technical limitation and provide a glimpse into processing of information within the dendritic tree. The model used in the present study incorporated features of progressively increasing complexity so that it would be possible to isolate the contributions of passive electrotonic conduction, active membrane properties and synaptic noise. Since there is an asymmetric attenuation of voltage along the dendritic tree, it was hypothesized that the summation of synaptic potentials would be differentially affected by downstream (toward soma) or upstream (away from soma) synaptic sites. However, a synaptic current of fixed amplitude delivered to either one of a pair of dendritic sites always transferred the same voltage response to the opposite site of the pair. The site of action potential onset was, however, affected by the asymmetric input resistance along the dendritic tree.

EXPERIMENTAL PROCEDURES

The NEURON simulation software (Carnevale and Hines, 2006) was used to reproduce the morphology and electrical properties of neurons. The uppercase word NEURON refers to the simulation software while the lowercase word neuron refers to the biological cell. The neuron morphologies included a thalamic interneuron reproduced from a previous study (Briska et al., 2003) and a pyramidal neuron (49-L5pyr-na) obtained from neuromorpho.org which is a centrally curated inventory of digitally reconstructed neurons. The three-dimensional structure of each neuron was represented in a standardized SWC file format (Cannon et al., 1998) which can be loaded into NEURON for display. The thalamic interneuron was composed of 670 segments and the pyramidal neuron was composed of 523 segments whose size and location were defined for three-dimensional space.

The passive electrical properties of all neurons included a specific membrane capacitance of $1 \mu\text{f}/\text{cm}^2$, a cytoplasmic resistivity of $70 \Omega \text{ cm}$ and a specific leak conductance of $16 \mu\text{S}/\text{cm}^2$ for the thalamic interneuron and $50 \mu\text{S}/\text{cm}^2$ for the pyramidal neuron. The resting membrane potential was set at -70 mV . The input resistance of a neuron segment was obtained by dividing the steady-state membrane voltage by the depolarizing current step amplitude while the membrane time constant was recorded as the time required for the voltage to reach $1 - 1/e$ of its steady-state value.

Active electrophysiological properties simulating the voltage-gated channels responsible for the action potential were then added to the pyramidal neuron. These channels were modeled according to the Hodgkin–Huxley convention in order to predict the sodium and potassium currents associated with an action potential threshold of about -55 mV . The sodium and potassium voltage-gated channels used were from model 3808 in the database available at senselab.med.yale.edu/ModelDB. The density of voltage-gated channels was adjusted according to published data (Lorincz and Nusser, 2010; Migliore and Shepherd, 2002; Nevian et al., 2007; Schmidt-Hieber and Bischofberger, 2010) in order to reproduce the typical spiking behavior of a pyramidal neuron (Larkum et al., 2001) where brief dendritic inputs produce local action potentials but long ones trigger action potentials near the axon hillock. The density of voltage-gated channels at the axon hillock drops about 40-fold toward the main ascending branch of the pyramidal neuron (Lorincz and Nusser, 2010; Migliore and Shepherd, 2002; Nevian et al., 2007; Schmidt-Hieber and Bischofberger, 2010). This voltage-gated channel density was modeled as an exponential drop with distance from the axon hillock using the equation $G(d) = m + (mre^{-d/k})$, where G is the maximum conductance representing the voltage-gated channel density for a section at a distance d microns from the axon hillock, m is the minimum conductance allowed for any section, $r = 40$ is the 40-fold drop for sections away from the axon hillock, $e = 2.7183$ is Euler's constant, and $k = 130$ is a constant for the rate of exponential drop. For sodium voltage-gated channels $m = 0.012 \text{ S}/\text{cm}^2$ and for potassium voltage-gated channels $m = 0.004 \text{ S}/\text{cm}^2$. Besides this exponential drop in voltage-gated channels to reproduce the firing behavior of pyramidal neurons, other distributions of voltage-gated channels were simulated in order to tease out the contribution of voltage-gated channel density to the pyramidal neuron responses reported in the results. These are described where appropriate in the results.

Synaptic conductance noise was also added to the neurons using a model of fluctuating synaptic conductances that produces synaptic background activity similar to in vivo measurements (Rudolph and Destexhe, 2005). This implementation of synaptic noise was obtained from the NEURON model 64259 in the senselab database. Independent synaptic conductance noise was added to each section of a neuron in order to reflect random synaptic inputs throughout a neuron.

All inputs were delivered as current clamp stimuli to different locations in a neuron. Normal stimulation of a neuron is usually through excitatory synapses where channel opening leads to an inward current that depolarizes the cell. The synaptic current at any point along the dendritic tree would depend on the density of these channels and the ion electrical gradient across the membrane. These properties could vary greatly to produce different synaptic currents or they could be adjusted toward optimal levels by homeostatic mechanisms to produce comparable synaptic currents. Precise details are lacking. As a starting point, therefore, we chose to examine the effects of fixed inward currents on the electrical behavior of dendrites. The passive properties of neurons were tested with rectangular current pulses whereas the active properties were tested with stimuli delivered as double exponentials ($f(t) = (1 - e^{-t/\tau_1})e^{-t/\tau_2}$, where $\tau_2 = 4\tau_1$) to reproduce the shapes of synaptic

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