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Spike propagation in dendrites with stochastic ion channels

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Abstract We investigate the effects of the stochastic nature of ion channels on the faithfulness, precision and reproducibility of electrical signal transmission in weakly active, dendritic membrane under in vitro conditions. The properties of forward and backpropagating action potentials (BPAPs) in the dendritic tree of pyramidal cells are the subject of intense empirical work and theoretical speculation (Larkum et al., 1999; Zhu, 2000; Larkum et al., 2001; Larkum and Zhu, 2002; Schaefer et al., 2003; Williams, 2004; Waters et al., 2005). We numerically simulate the effects of stochastic ion channels on the forward and backward propagation of dendritic spikes in Monte-Carlo simulations on a reconstructed layer 5 pyramidal neuron. We report that in most instances there is little variation in timing or amplitude for a single BPAP, while variable backpropagation can occur for trains of action potentials. Additionally, we find that the generation and forward propagation of dendritic Ca^{2+} spikes are susceptible to channel variability. This indicates limitations on computations that depend on the precise timing of Ca^{2+} spikes.

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Abbreviations: BAC: Backpropagation activated Ca^{2+} spike; AP: Action potential; BPAP: Backpropagating action potential; ISI: Interstimulus interval; **rp:** Reference point

1. Introduction

The effects of stochastic ion channel transitions in the central nervous system are not well understood (White et al., 2000; van Rossum et al., 2003; Diba et al., 2004; Jacobson et al., 2005). Whereas the effects of ion channels on membrane properties are often studied in the macroscopic limit of large membranes, the thermal environment of the brain leads to temperature-dependent, random (stochastic) changes in the configuration of individual channels (Hille, 2001). As a first order approximation, the variance of voltage noise from stochastic channels is proportional to N, the number of channels, and Z^2, the square effective impedance (DeFelice, 1981; Manwani and Koch, 1999). From the viewpoint of voltage-gating, this means that when Z is small, channel stochasticity effects are negligible. At the cell body of pyramidal neurons (in culture and in vitro), channel stochasticity leads to sub-millivolt fluctuations in the subthreshold membrane potential (Diba et al., 2004; Jacobson et al., 2005). What are the effects of stochasticity on suprathreshold behavior?

In the axon initial segment (or spike initiation zone at the first node of Ranvier), the density of Na^+ channels is quite large, estimated at around $1500/\mu m^2$ (Mainen and Sejnowski, 1998). Schneidman et al. (1998) showed numerically that for large impedance axonal patches, the spike firing time can jitter significantly in response to sustained,

suprathreshold input (several-to-tens of milliseconds) as was found experimentally in slice preparation by Mainen and Sejnowski (1995). Indeed, only a small number of channels need to open near threshold in order to generate a spike. Others have proposed that channel stochasticity places constraints on axonal diameter to limit spontaneous generation of action potentials (APs) (Horikawa, 1991; Faisal and Laughlin, 2002).

The faithful propagation of spiking events is important for effective transmission and computation of neural information. Modeling studies of axonal propagation have failed to find significant effects from noisy channels except in very thin, high impedance axons (<0.1 μm diameter; Horikawa, 1991; Kuriscak et al., 2002). The sharply rising foot of the AP recruits ion channels synchronously and, thus, the firing of the AP is temporally faithful. Under physiological conditions (axonal diameter $\sim$1 μm; Mainen and Sejnowski, 1998), axonal propagation of APs occurs with microsecond precision (Kuriscak et al., 2002). However, channel stochasticity may be of more relevance for propagation past a branch point or during neuromodulation (Horikawa, 1993; Debanne, 2004).

In the present study we ask: what limits does the intrinsic stochasticity of ionic channels place on signal transmission along weakly excitable dendrites, where the membrane conductance can be small, and the impedance therefore large (Manwani and Koch, 1999)? In particular, how are the timing and amplitude of backpropagating action potentials (BPAPs) affected by variability in channel opening and closing? We address this question using Monte-Carlo simulations in a reconstructed layer 5 neuron (Steinmetz et al., 2000). We replace all the deterministic channels in the model of Schaefer et al. (2003) with their corresponding stochastic versions (DeFelice, 1981; Johnston and Wu, 1995; Steinmetz et al., 2000). By using a random number generator to determine state transitions in each compartment, we explore the effects of stochastic channels on spike accuracy and variability for both backpropagation of Na^+ spikes under in vitro conditions, as well as the initiation and forward propagation of Ca^{2+} spikes. Our work extends the studies of Mainen and Sejnowski (1995) and Schneidman et al. (1998), which focused on reliability and precision of spike initiation of Na^+ spikes, rather than on their propagation.

2. Methods

The reconstructed cell shown in Fig. 1A, obtained from layer 5 of rat somatosensory cortex, is used for all simulations (courtesy of Schaefer et al. (2003)). In preliminary studies with other models (including a single cable with only Hodgkin and Huxley (1952) channels), we obtained qualitatively similar results. The model contains stochastic versions of a fast Na^+ channel, a transient, and a high-voltage activated Ca^{2+} channel, a delayed-rectifier, an A-type, a Ca^{2+}-dependent, and a muscarinic K^+ channel. All model parameters follow the example of Schaefer et al. (2003) and are based on the kinetic models of Mainen and Sejnowski (1996). Conductances at the soma are (in pS/μm^2): $g^{soma}{}_{Na} = 54$, $g^{soma}{}_{Kv} = 600$, $g^{soma}{}_{Km} = 0.2$, $g^{soma}{}_{K(Ca)} = 6.5$, $g^{soma}{}_{A} = 600$, $g^{soma}{}_{Ca} = 3$; and in the dendrites: $g^{dend}{}_{Na} = 27$, $g^{dend}{}_{Kv} = 30$, $g^{dend}{}_{Km} = 0.1$, $g^{dend}{}_{K(Ca)} = 3.25$, $g^{dend}{}_{A} = 300$, $g^{dend}{}_{Ca} = 1.5$. The single channel conductances are (in pS): $\gamma_{Na} = 20$, $\gamma_{Kv} = 15$, $\gamma_{Km} = 40$, $\gamma_{K(Ca)} = 180$, $\gamma_{A} = 10$, $\gamma_{Ca} = 20$, based on published results (Kang et al., 1996; Mainen and Sejnowski, 1998; Hille, 2001). The Ca^{2+} hotspot from Schaefer et al. (2003), with $g_{Ca} = 4.5$ pS/μm^2, $g_T = 5$ pS/μm^2 and $\gamma_T = 8$ pS, is included only when studying Ca^{2+} spike generation for Fig. 3. This allows us to investigate a wide range of Na^+ channel densities without the proliferation of dendritic Ca^{2+} spikes. All other model details adhere to those found in Schaefer et al. (2003). 30 trials are performed at each setting. The Monte-Carlo methods are based on the algorithm of Steinmetz et al. (2000), using the NEURON simulation environment (Hines and Carnevale, 1997); the code can be found online at http://osiris.rutgers.edu/~diba/Sbpap_code.zip. Briefly, a Markov model of channel states is assumed (DeFelice, 1981; Hille, 2001). The number of channels in each gating state is tracked for each compartment. At a fixed time step of 6.25 μs, the number of channels making a transition between each state is determined using a pseudo-random binomial deviate, driven by a random number generator (Press, 1992). The probabilities for the transitions are obtained from the deterministic rates (Hodgkin and Huxley, 1952; Hille, 2001). Similar Monte-Carlo algorithms have been used elsewhere (Skaugen and Walloe, 1979; Chow and White, 1996; Schneidman et al., 1998).

3. Results

3.1. Fine-tuning Leads to Variability in BPAP Amplitude

In our stochastic simulations of reconstructed neurons, as well as of simple branching cables (not shown), the extent of backpropagation falls into one of two stereotypical categories: robust excitable backpropagation, or weak, decremental invasion of the dendrites. Increasing some parameters, such as Na^+ channel density, increases the effectiveness of backpropagation. Other factors hinder backpropagation; these include increases in K^+ and leak channel density, increases in membrane capacitance, and impedance mismatches at branch points. By varying Na^+ channel density alone, we show in Fig. 1 that: (1) If the density of Na^+ channels is large enough in the dendrites, relative to these

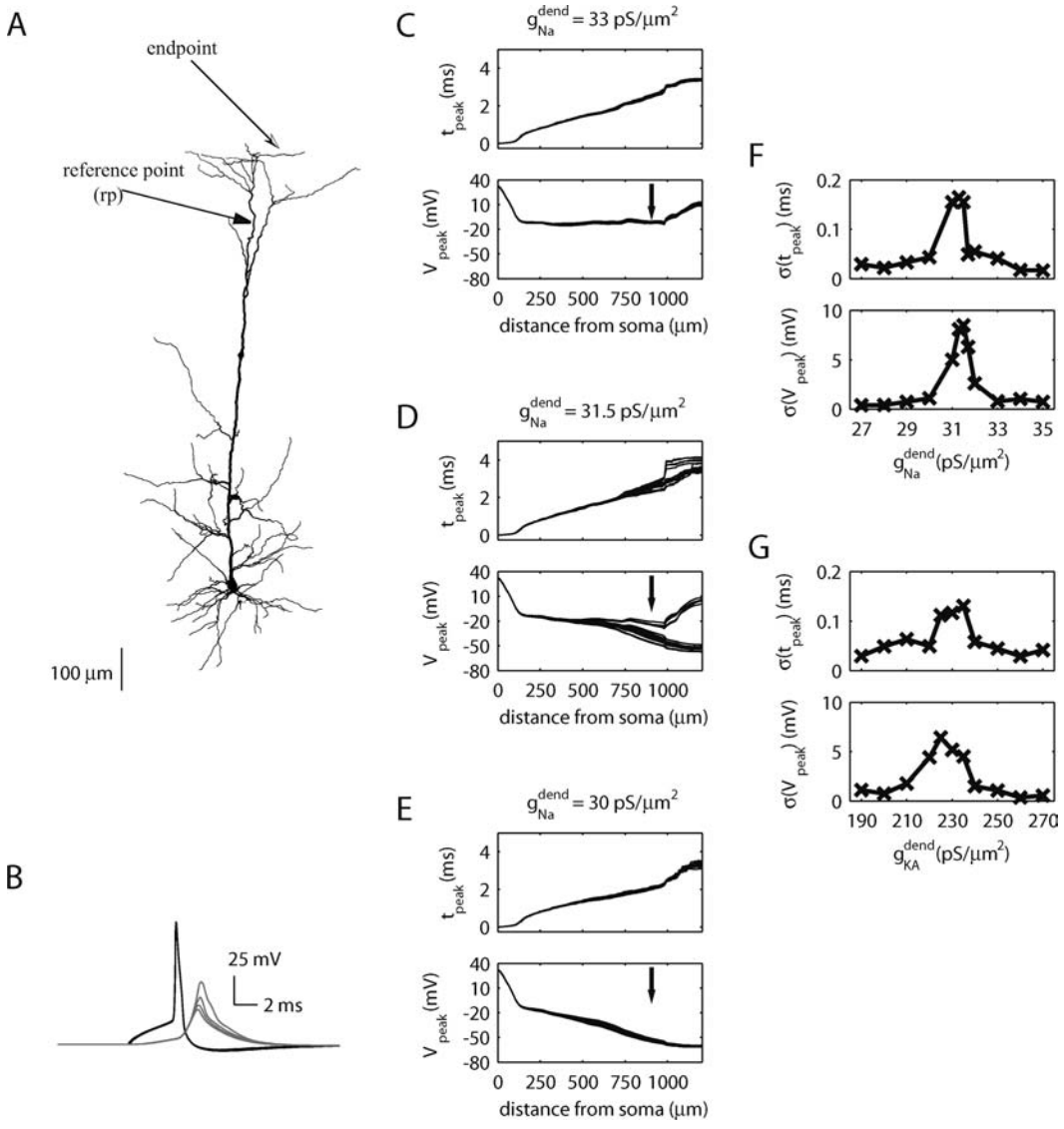

Figure 1. (A) Reconstructed cell used in all simulations, courtesy of Schaefer et al. (2003). To induce an action potential, a 2.0 nA amplitude, 5 ms long, depolarizing current step is injected into the soma. (B) Four superimposed traces are shown with the voltage trace from the soma in black and the reference point (**rp**) indicated in panel **A** in gray at $g^{dend}{}_{Na} = 31.5$, corresponding to panel D. At this setting of the Na^+ channel density, the largest stochasticity effects are seen. (C–E) Time-to-peak (t_{peak}) and voltage amplitude (V_{peak}) for the BPAP in 15 superimposed trials is shown as a function of distance from soma. Vertical arrows refer to point **rp** in **A**. (C) When the Na^+ conductance is large enough, robust backpropagation occurs at all dendritic branches and there is little trial to trial variability. (D) At a critical value of the Na^+ channel density, significant jitter in amplitude and timing of the BPAP occurs. Trial to trial variability can be discerned for distances greater than 600 μm from the soma. (E) Decreasing the Na^+ channel density further prevents active backpropagation into the dendrites; the BPAP amplitude decays with distance, with little variability in timing or amplitude. The standard deviation in the time and amplitude of the peak voltage are shown at **rp** in (F) as a function of the dendritic Na^+ channel density, and in **(G)** as a function of dendritic A-type K^+ conductance (30 trials at each setting). Variability is observed only in a limited range.

hindering factors, the AP backpropagates into all branches of the dendrites, effectively depolarizing these compartments. (2) If the Na^+ channel density is insufficient to overcome the hindering factors, then the amplitude of the BPAP decays with distance from the soma. Depending on the degree of branching and other parameters, this decay may start either from the soma or from further out on the dendrites (Vetter et al., 2001; Bernard and Johnston, 2003). (3) Stochasticity only becomes relevant when backpropagation falls in between these two limits: active versus passive propagation.

Figure 1 demonstrates the effect of dendritic Na^+ channel density on the reliability of backpropagation. The amplitude and time of peak voltage are plotted as a function of distance from the soma along the path to an endpoint along the apical dendrite (top arrow in Fig. 1A). In Fig. 1C, the density of Na^+ channels in the dendrites is $g^{dend}{}_{Na} = 33$ pS/μm^2, near phys-

iological values (Mainen and Sejnowski, 1998). Backpropagation is robust and the minimum depolarization is greater than −20 mV. Very little trial-to-trial variability is observed ($\sigma_V = 0.78$ mV, $\sigma_t = 0.010$ ms for V_{peak} at the reference point indicated in Fig. 1A (**rp** hereafter), 900 μm from the soma). In Fig. 1E, Na^+ channel density is reduced by about 10% to $g^{dend}{}_{Na} = 30$ pS/μm^2 and the backpropagation of the AP now becomes highly decremental ∼500 μm away from the soma (Fig. 1C, lower frame). In the distal branches, the peak voltage does not exceed −50 mV. Thus, decreasing the dendritic Na^+ channel density makes the backpropagation increasingly passive and dendritic BPAP invasion increasingly weak (see also Colbert et al., 1997; Migliore et al., 1999; Bernard and Johnston, 2003). In this regime, variability in the time and amplitude of the BPAP is also small ($\sigma_V = 1.11$ mV, $\sigma_t =$ 0.10 ms for V_{peak} at **rp**). In fact, noticeable amplitude variation occurs only when the Na^+ channel density falls between these two values: in Figs. 1B and D, $g^{dend}{}_{Na} = 31.5$ pS/μm^2. Here, on alternate trials, either weak or robust backpropagation can occur. In 10 out of the 15 trials shown, the BPAP fails to invade the most distal branches. Trial to trial variation in amplitude is consequently large ($\sigma_V = 8.47$ mV for V_{peak} at **rp**), illustrating a bifurcation point between robust and decremental backpropagation. The timing jitter also increases, but remains in the sub-millisecond range (with $\sigma_t = 0.22$ ms for V_{peak} at **rp**). This large variability in efficacy of backpropagation could have important consequences for coincidence detection and other phenomena that rely upon depolarization from BPAPs in distal dendritic branches. However physiologically plausible (Mainen and Sejnowski, 1998), the region in parameter space where this variability occurs is fairly small. This is confirmed by measuring the effect of dendritic Na^+ channel (Fig. 1F) and A-type K^+ channel (Fig. 1G) densities on the standard deviation of V_{peak} and t_{peak} at **rp**. Figure 1 therefore indicates that BPAP of single action potentials in weakly excitable dendrites is little affected by stochastic ionic channels under most circumstances.

3.2. Variability in backpropagating spike trains

It is natural to ask: if the biophysics of the neuron lies outside this limited region, can changes in the (in)activation of channels and their time constants bring the neuron into the stochastic regime? In Fig. 2 we explore two possibilities for such a scenario by looking at trains of APs propagating into the dendrites. Experimental results from hippocampal pyramidal cells in vitro and *in vivo* suggest that a BPAP following in the wake of a previous BPAP experiences stronger attenuation in amplitude (Spruston et al., 1995; Buzsaki et al., 1996). A possible mechanism for this phenomena is based on Na^+ channel inactivation (Colbert et al., 1997; Jung et al., 1997): The first BPAP elevates dendritic voltages, leading to inactivation of Na^+ channels, which can be slow to deinactivate. A closely following BPAP then experiences fewer available Na^+ channels for active propagation (Luscher et al., 1994; see also Hoffman et al., 1997). Such a situation is explored in Fig. 2A and 2B. Here, the parameters are similar to those in Fig. 1C, yielding robust backpropagation for the first spike, with little trial-to trial variability. A second 2.2 nA stimulus, 20 ms later, leads to another BPAP, which now becomes variable in amplitude ($\sigma_V = 6.96$ mV, $\sigma_t = 0.094$ ms for V_{peak} at **rp**). In 7 out of 30 trials, the second BPAP fails to invade the distal dendrites. Four overlapping trials are shown in Fig. 2A and the variability in timing and amplitude is shown in Fig. 2B for the second BPAP. In Fig. 2C, the observed variability at **rp** is plotted against the inter-stimulus interval (ISI). A specific range of ISIs leads to variable behavior. With small ISIs, the propagation to distal sites is fully passive (and therefore reliable) and for large ISIs, the propagation is fully active (and therefore reliable). Different values of $g^{dend}{}_{Na}$ likely produce noisy BPAPs at other intervals.

In layer 2/3 neocortical pyramidal cells, it has been demonstrated that unlike the scenario above, a BPAP can be boosted if it follows in the wake of a preceding BPAP (Waters et al., 2003). The biophysical mechanisms behind this phenomena are not yet well-understood. A possible mechanism is that in the dendrites of these neurons, K^+ channels that are inactivated by the first BPAP are slow to deinactivate, leading to a decreased shunt (Colbert et al., 1997; Johnston et al., 1999). This could then result in a boost for a subsequent BPAP. By removing inactivation from the Na^+ channels in the dendrites (and necessarily decreasing $g^{dend}{}_{Na}$ to 14 pS/μm^2) while increasing the lower limit of the K_A inactivation time constant to 16.5 ms (τ_l from Migliore et al. (1999)), we contrive a model for this scenario. Figure 2D illustrates variability in four trials with this model. The first BPAP amplitude decays with little variability in amplitude or timing. The second BPAP, however, "sees" less K^+ current and is actively propagated on 12 out of 30 trials ($V_{peak} > -40$ mV in the "end branch"), with a corresponding increase in variability (Fig. 2E; $\sigma_V = 21.8$ mV, $\sigma_t =$ 0.57 ms for V_{peak} at **rp**). Results are explored for other ISIs in Fig. 2F. These findings indicate that while the stochasticity of ion channels has little impact on the backpropagation of single APs, it may be of increasing importance for trains of APs. In particular, some ISIs can yield more noisy outcomes, depending on the properties and densities of the channel subtypes in the dendrites.

3.3. Variability in Dendritic Spike Generation

It has been shown that stochasticity of ionic channels can lead to variability in somatic spike generation (Schneidman et al., 1998; White et al., 1998; van Rossum et al., 2003). In some instances "suprathreshold" currents fail to generate spikes while in other instances, "subthreshold" stimuli lead

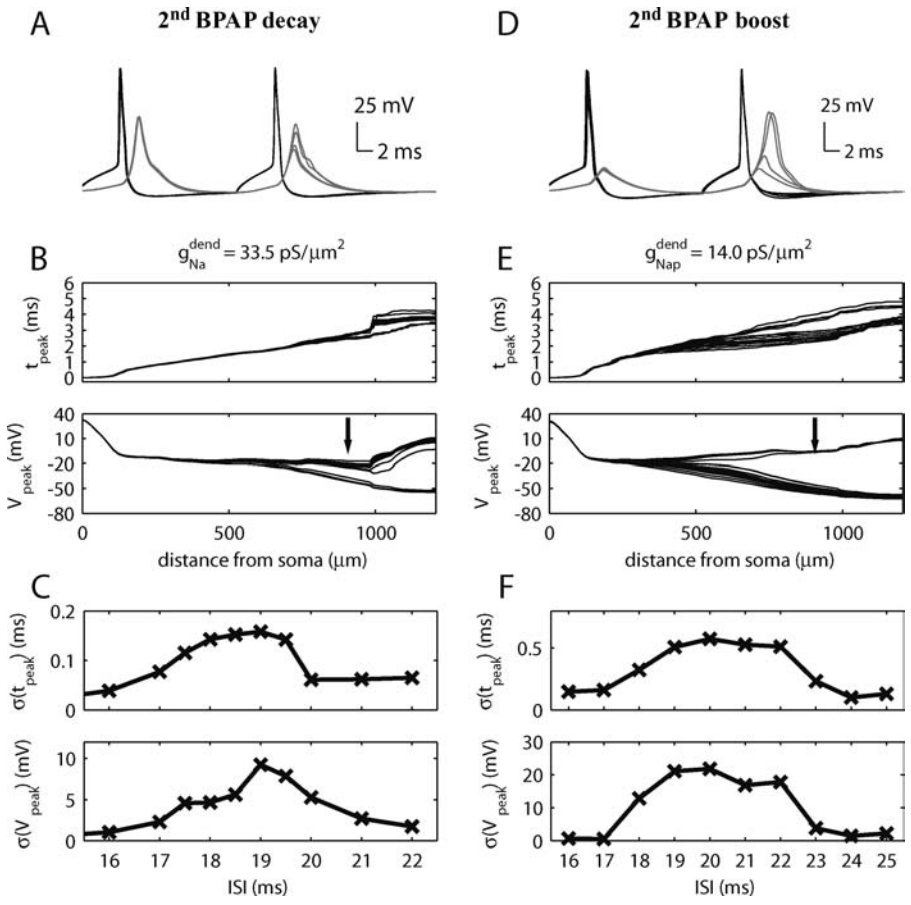

Figure 2. Trains of dendritic BPAPs can be vulnerable to channel stochasticity effects. (A) Two successive current steps are applied to the soma at a 20 ms interval, at a Na^+ channel density which produces robust backpropagation for a single AP. Four superimposed trials are shown, locked to the time of the second somatic AP. Somatic voltage is shown in black, and dendritic voltage for **rp** (see Fig. 1A) is shown in gray. Variability in amplitude can be observed for the second BPAP but not for the first BPAP. (B) Time-to-peak (t_{peak}) and voltage amplitude (V_{peak}) for the second BPAP in 15 superimposed trials is shown as a function of distance from soma. Point **rp** is indicated by an arrow. (C) Variability in t_{peak} and V_{peak} is explored for different values of the interstimulus interval (ISI). (D) Removing Na^+ channel inactivation in the dendrites and slowing K_A deinactivation (see text) yield increased backpropagation of the second spike. Four superimposed trials are shown. Large variability is evident for the second BPAP, which is more effective at depolarizing the dendritic branches. (E–F) As in panel **B–C**, but with these different settings.

to APs. Similar stochastic effects are evident in the generation of dendritic spikes. These can occur either through the injection of a large dendritic current, or through the coincidence method proposed by Larkum et al. (1999): if a BPAP coincides with a smaller dendritic EPSC, a dendritic Ca^{2+} spike can be generated, leading to a burst (typically triplet) of somatic action potentials. This spike triplet signifies "successful" detection of a coincidence.

Dendritic Ca^{2+} spikes have different dynamics than axonal Na^+ spikes. With the model developed by Schaefer et al. (2003) for backpropagation activated Ca^{2+} spike (BAC) firing, we can investigate potential variability due to stochastic ion channels in the above circumstances. We add hotspots of stochastic Ca^{2+} channels in the dendrites, as described by Schaefer et al. (2003). Direct injection of a synaptic 1.45 nA peak EPSC (Fig. 3A), or alternatively, a synaptic 0.40 nA peak EPSC timed to coincide with a BPAP (Fig. 3D), highlight a potential effect of stochastic Ca^{2+} channels in dendrites: channel noise creates a variable threshold for Ca^{2+} spike generation. For the dendritically initiated spikes, a spike doublet occurs at the soma in 21 out of 30 trials (Fig. 3A top), with a large standard deviation in the onset time ($\sigma = 3.9$ ms). Otherwise, no somatic spikes are seen (9 remaining trials; Fig. 3A bottom). In Fig. 3B, the number of trials (out of 30) showing dendritic spikes are plotted as a function of the peak EPSC. Variable behavior is observed between 1.375 and 1.475 nA. In general, the generation and forward propagation of dendritic spikes gives rise to a considerable amount of jitter in the timing of the resulting somatic AP. Fig. 3C demonstrates the standard deviation in the time of the somatic AP, as a function of the peak EPSC, which varies between 0.3 to 7.0 ms in the considered regime. Under the BAC coincidence detection paradigm, a spike triplet occurs at the soma in some of the trials (Fig. 3D

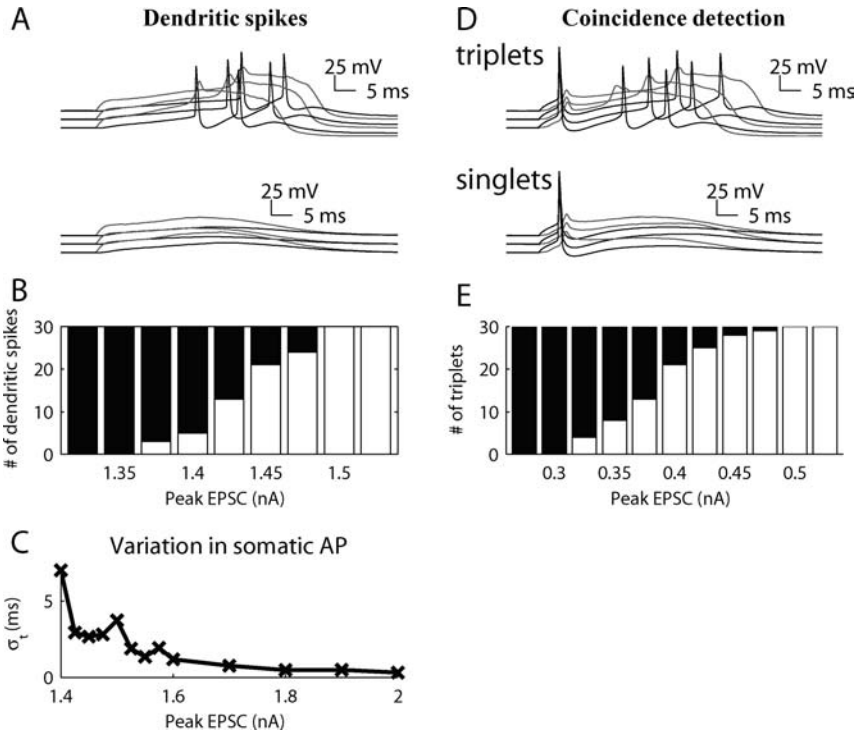

Figure 3. Stochasticity of Ca^{2+} spikes. Voltage traces are shown at the soma (black) and at the site of EPSC injection (gray), 750 μm away on the apical dendrite, as in (Schaefer et al., 2003). Calcium hotspots are added to allow for generation of dendritic Ca^{2+} spikes. Traces are vertically offset for visibility. (A) A direct 1.45 nA dendritic EPSC initiates Ca^{2+} spikes on some trials (upper frame; three superimposed trials), but not on others (lower frame; three superimposed trials). (B) The number of trials (shown in white, out of 30) in which a Ca^{2+} spikes is initiated at the dendrites, is shown as a function of the peak EPSC. (C) The timing of the resulting somatic AP can be variable, as demonstrated by plotting its standard deviation as a function of the peak EPSC amplitude. (D) When a somatic current injection is coupled with a 0.40 nA dendritic EPSC 2 ms later, somatic spike triplets occur in some trials (upper frame; three superimposed trials are shown). In other trials, only one spike occurs at the soma and the corresponding dendritic Ca^{2+} spike is dampened (lower frame; three superimposed "singlet" traces are shown). (E) The number of trials (out of 30) for which triplets occur is shown as a function of the peak EPSC amplitude.

top). The interspike interval between the 1st and 2nd spikes varies significantly at this setting (15–33 ms), though the standard deviation of the interval between the 2nd and 3rd spikes is minimal (0.13 ms). In the remaining trials, the dendritic Ca^{2+} spike fails, and only the original somatic AP (singlet) is visible (Fig. 3D bottom). Figure 3E shows the number of trials (out of 30) with spike triplets, as a function of the peak EPSC. The stochasticity of ionic channels renders dendritic spike generation unreliable for a range of EPSCs, either through local initiation, or through BAC firing.

4. Discussion

Our findings show that the backpropagation of isolated action potentials is robust to channel stochasticity effects, except in very limited regions of parameter space. Variability is observed only close to the boundary between two different outcomes: robust versus passive backpropagation, and near the threshold for dendritic Ca^{2+} spike generation. Changes in channel gating, for example, through neuromodulation or network activity, can, however, bring neuronal behavior into this regime. Other noise sources, in the form of channel or synaptic noise, may also enlarge the regime. Our study utilizes a sample model, but the results generalize to others models with opposing forces—in particular, the push-pull interplay between Na^+ (depolarizing) and K^+ (repolarizing) channels. We emphasize that previous studies showed that this interplay leads to sensitivity in the temporal precision of the initiation of an isolated spike (Mainen and Sejnowski, 1995; Schneidman et al., 1998), rather than its propagation after initiation.

Whereas nature can easily avoid noisy backpropagation for single APs by increasing or decreasing the presence of dendritic Na^+ and K^+ channels, more demanding conditions, such as bursts or trains of BPAPs can make stochasticity effects more consequential. The relevance of this possibility depends strongly on the nature of the backpropagation of AP trains for the neurons in question, presently a major topic of research (for a review see Waters et al., 2005); if trailing APs are strongly attenuated or boosted, depending on the ISI, then stochasticity likely follows for a critical range of ISIs. We studied scenarios under which robust backpropagation in the apical dendrite gave way to decremental propagation

into the distal dendrites. The stochasticity effects we report were restricted to the distal dendrites, and would not be observed with proximal recordings. The critical location for this change in propagation depends crucially on where and whether the shunting load imposed by dendritic branching (Vetter et al., 2001; Schaefer et al., 2003) alters the propagation of the BPAP from robust to decremental (Kim and Connors, 1993; Golding et al., 2001). The results presented here may also be relevant for trains of APs propagating past axonal branch points. Experiments have shown that trailing axonal APs can be lower in amplitude and are more vulnerable to propagation failure due to a variety of factors, including branch point impedance mismatches, and (in)activation of various channels (Debanne, 2004). Such factors increase the potential impact of channel stochasticity, akin to the situation in dendrites.

It is possible that synaptic background activity enhances or washes out the effects of stochastic channels. For example, up and down states, characterized by shifts of 10 to 20 mV in membrane potential that last for fractions of a second (Steriade et al., 1993; Destexhe et al., 2003), effectively change the parameter regime within which channels operate, with possibly significant effects on backpropagation (Waters and Helmchen, 2004; Waters et al., 2005). On the other hand, network high-conductance states may overwhelm the fluctuations in channel conductance studied here (Destexhe et al., 2003; Rudolph and Destexhe, 2003). Nevertheless, since active backpropagation arises from the activity of channels in the dendrites (Stuart et al., 1997), the stochasticity effects outlined here will remain important under any network model which allows BPAPs. The effects of synaptic activity will depend on the nature of the input, in particular, its amplitude and location on the dendritic tree, as well as its timing with respect to the BPAP. These present important topics for future exploration.

Finally, we have shown that processes which depend on the generation of dendritic Ca^{2+} spikes can exhibit variable behavior near threshold. Previous studies have largely focused on stochasticity near the Na^{+} spike threshold (Schneidman et al., 1998; White et al., 1998; van Rossum et al., 2003), but the kinetics of Ca^{2+} channels makes them a more variable trigger of spiking events. These results may be modified as the properties of Ca^{2+} are better understood (Jones, 2003), but are nevertheless consistent with experimental findings (Golding and Spruston, 1998), and place limitations on a neural code that relies on the precise timing of dendritic spikes (Larkum et al., 1999; Ariav et al., 2003; Schaefer et al., 2003; Williams, 2004).

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