Response Properties and Synchronization of Rhythmically Firing Dendritic Neurons

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Goldberg, Joshua A., Chris A. Deister, and Charles J. Wilson. Response properties and synchronization of rhythmically firing dendritic neurons. J Neurophysiol 97: 208–219, 2007. First published September 6, 2006; doi:10.1152/jn.00810.2006. The responsiveness of rhythmically firing neurons to synaptic inputs is characterized by their phase-response curve (PRC), which relates how weak somatic perturbations affect the timing of the next action potential. The shape of the somatic PRC is an important determinant of collective network dynamics. Here we study theoretically and experimentally the impact of distally located synapses and dendritic nonlinearities on the synchronization properties of rhythmically firing neurons. By combining the theories of quasi-active cables and phase-coupled oscillators we derive an approximation for the dendritic responsiveness, captured by the neuron’s dendritic PRC (dPRC). This closed-form expression indicates that the dPRCs are linearly filtered versions of the somatic PRC and that the filter characteristics are determined by the passive and active properties of the dendrite. The passive properties induce leftward shifts in the dPRCs and attenuate them. Our analysis yields a single dimensionless parameter that classifies active dendritic conductances as either regenerative conductances that counter the passive properties by boosting the dPRCs or restorative conductances that high-pass filter the dPRCs. Thus dendritic properties can generate a qualitative difference between the somatic and dendritic PRCs. As a result collective dynamics can be qualitatively different depending on the location of the synapse, the neuronal firing rates, and the dendritic nonlinearities. Finally, we use dual whole cell recordings from the soma and apical dendrite of cortical pyramidal neurons to test these predictions and find that empirical dPRCs are shifted leftward, as predicted, but may also display high-pass characteristics resulting from the restorative dendritic HCN (h) current.

INTRODUCTION

Most studies of synaptic transmission are conducted in cells with no background synaptic input. In the brain, however, most cells fire continuously and synaptic inputs act to change the timing of the next action potential (AP), not to determine whether there will be a next AP (Reyes and Fetz 1993). Because it is difficult to measure the effect of a single stimulus in a cell receiving a noisy background of synaptic input, for many purposes we settle for quiescent neurons. To overcome this limitation, techniques developed for studying rhythmically firing neurons can be used. One such technique—the theory of phase-coupled oscillators—predicts that the propensity of a neuron to either advance or delay the next AP in response to a depolarizing perturbation is an important determinant of the collective dynamics of networks of such neurons. Neurons whose APs can only be advanced in response to depolarizing perturbations are said to display a type I response and tend to phase lock with delays if coupled by fast excitation (Hansel et al. 1995; van Vreeswijk et al. 1994). These phase delays may underlie the propagation of waves in networks of neurons coupled by fast excitation (Ermentrout and Kleinfeld 2001). Neurons whose APs can also be delayed in response to depolarizing perturbations are said to exhibit a type II response and tend to synchronize in-phase when coupled by fast excitation.

The response type of a rhythmically firing neuron is quantified using its phase-response curve (PRC), which measures the phase perturbation induced by a small and brief voltage perturbation, as a function of the timing (or phase) at which the perturbation is delivered along the trajectory of the neuronal oscillation. Because type I implies that APs are only advanced, the PRC of a type I neurons is nonnegative. This PRC is typically unimodal, attaining its minimum at the time of the AP (when the neuron is entirely nonresponsive to perturbations). The PRCs of neurons with type II responses decrease shortly after the AP, exhibiting a negative lobe followed by a positive one. PRCs have been measured experimentally for various neurons and both type I and type II neurons have been reported (Bennett and Wilson 1998; Galán et al. 2005; Keck et al. 2003; Netoff et al. 2005; Pinsker 1977; Reyes and Fetz 1993). In these experiments, the PRCs were determined by perturbing the voltage with somatic current injections. However, is there any guarantee that the somatic PRC reliably represents the responsiveness of the neuron to dendritic inputs that are located more distally? Could the dendritic PRC (dPRC) be of a different type than the somatic one, so that synaptic inputs have qualitatively different effects depending on their proximity to the soma? For computational simplicity, studies often assume that neurons are electrotonically compact. If the dPRC is qualitatively different from the somatic one, the validity of studies that neglect the dendritic location of synaptic inputs is compromised. To address this issue, Crook et al. (1998) studied a model neuron composed of a passive dendritic cable attached to a pace-making soma. Two such neurons were coupled reciprocally by way of a synapse that was located at the other end of the cable. The authors showed that the neurons alternated between in-phase and out-of-phase solutions as the length of the dendrite (cable) was increased.

We use the formalism of Crook et al. (1998) to derive a mathematical approximation for the dPRC given the structure of the somatic PRC and the properties of the dendrite. The approximation is found to be precise in the case of a passive...
dendrite. To extend this result to include active dendritic conductances, we follow Bressloff (1999) and treat nonlinear dendrites as a quasi-active medium (Koch 1984; Mauro et al. 1970). In this regime our approximation is found to still be good. The motivation for deriving this closed-form approximation is that it is expressed entirely in terms of properties of the postsynaptic neuron and is independent of the properties of the synaptic input per se. This approach enables us to study theoretically how the somatic PRC is transformed into the dPRC solely due to the impact of the passive and active properties of the dendrite. Moreover, we then test the theoretical predictions by recording simultaneously from the soma and dendrite of individual neurons using dual whole cell recordings in rat layer V pyramidal neurons. We demonstrate that the linear and nonlinear properties of dendrites can qualitatively alter the response properties and phase locking of a neuron when it is driven by dendritic synapses compared with when somatic ones drive it.

METHODS

The model

We consider a dendritic neuron composed of a semi-infinite cable of radius \( a \), representing the dendrite, and a somatic oscillator—that is, an isopotential sphere of radius \( A \)—lumped at one end. The location along the dendrite is represented by the variable \( x \), such that the location of the soma is at \( x = 0 \). The voltage (in millivolts) at location \( x \) and time \( t \) is denoted \( V(x,t) \). The cable is characterized by a time constant \( \tau \) (in milliseconds) and a space constant \( \lambda \) (in centimeters). In addition to its passive leak conductance, the dendrite expresses an active conductance that is characterized by a gating variable \( s(x,t) \), that has a monotonic voltage-dependent activation curve \( s^*(V) \) and a time constant \( \tau_s \). This, for simplicity, is assumed to be time independent. The density of the active conductance is assumed to be uniform along the cable. The equations for the cable are thus

\[
\begin{align*}
\frac{\partial}{\partial t} V(x,t) &= \lambda^2 \frac{\partial^2}{\partial x^2} V(x,t) - [V(x,t) - V_L] - \gamma_s s(x,t) [V(x,t) - V_L] \\
\tau_s \frac{\partial}{\partial t} s(x,t) &= s^*[V(x,t)] - s(x,t)
\end{align*}
\]

where \( V_L \) is the reversal potential of the leak conductance, \( V_s \) is the reversal potential of the active current and \( \gamma_s \) is the ratio of the active current’s maximal conductance to the leak conductance. Equation 1 has the following boundary conditions:

1) A sealed end at infinity

\[
\frac{\partial}{\partial x} V(x,t) = 0
\]

2) A Hodgkin–Huxley type oscillator at \( x = 0 \) (Crook et al. 1998)

\[
C \frac{\partial}{\partial t} V(0,t) = -g_L[V(0,t) - V_L] - g_{Na}m^2h[V(0,t) - V_{Na}] - g_{K}n^3[V(0,t) - V_K] \\
+ I_{app} + \kappa \frac{\partial}{\partial x} V(0,t) \quad \kappa = \frac{1}{R_c} \left( \frac{a}{2\lambda} \right)^2
\]

\[
\frac{d}{dt} X = \alpha_s[V(0,t)](1-X) - \beta_s[V(0,t)]X \quad X = m,n,h
\]

where \( m \) and \( n \) are the activation gates of sodium and delayed-rectifier potassium channels, respectively; \( h \) is the inactivation gate of sodium channel; \( g_L \) is the leak conductance (in mS/cm\(^2\)); \( g_{Na} \) and \( g_K \) are the maximal conductances; \( V_{Na} \) and \( V_K \) are the reversal potentials of the sodium and delayed-rectifier potassium currents, respectively; \( I_{app} \) is the injected current density (in \( \mu A/cm^2 \)) applied to the soma; \( C \) is the cell's capacitance (in \( \mu F/cm^2 \)); \( R_c \) is the cell’s resistance (in k\( \Omega \) cm); and \( \alpha_s(V) \) and \( \beta_s(V) \) are the forward and backward voltage-dependent rate functions of the \( X \)th gate, respectively.

Dendritic perturbation

The solution of Eqs. 1–3 is given by a set of periodic functions with period \( T \) for voltage and for all the gating variables [i.e., \( V_d(x,t) = V_d(x,t+T) \); \( s_d(x,t) = s_d(x,t+T) \); etc.]. The dendritic voltage oscillates around a resting potential \( V_R \) (i.e., the voltage to which the cable would relax if it were not driven by the somatic oscillator). We assume that the PRC of the somatodendritic system in response to perturbations at the soma is known (e.g., it can be measured experimentally) and is denoted \( Z \), and we want to calculate how the neuron’s phase is affected by a brief and spatially localized voltage perturbation to the dendrite. To do this we need to find the equations that govern how the system responds to a vanishingly small dendritic perturbation. Let us denote the solution for voltage of the perturbed cable as \( V_z(x,t) \), then we define \( U(x,t) \) as the difference between the perturbed and the periodic unperturbed solution, i.e., \( U(x,t) = V_z(x,t) - V_d(x,t) \). We can derive the approximate equations for \( U(x,t) \) by linearizing Eq. 1 in the vicinity of \( V_R \)

\[
\tau \frac{\partial}{\partial t} U(x,t) = \lambda^2 \frac{\partial^2}{\partial x^2} U(x,t) - \gamma_s U(x,t) - \gamma_s(V_R - V_s) \delta_s(x,t)
\]

\[
\tau_s \frac{\partial}{\partial t} \delta_s(x,t) = \frac{\partial}{\partial V} s^*(V_R) \delta V(x,t) - \delta_s(x,t)
\]

where \( \delta_s(x,t) \) is defined analogously to \( U(x,t) \) as \( \delta_s(x,t) = s_d(x,t) - s_d(x,t) \) and \( \gamma_R \) is equal to the total dendritic conductance at rest divided by the dendritic leak conductance \( \gamma_R = 1 + \gamma_s h^2(V_R) \). The boundary condition for \( U(x,t) \) at infinity remains a sealed end. In this approximation, the boundary condition at \( x = 0 \) is a killed end

\[
U(0,t) = 0
\]

These equations are linear and thus possess a Green’s function (or impulse response) that describes how a voltage perturbation at location \( y \) propagates to location \( x \). Solving the system’s Green’s functions, denoted \( G_{u}(x,y, t) \), yields

\[
G_{u}(x,y,t) = G(x-y,t) - G(x+y,t)
\]

resulting from the reflection induced by the killed end at \( x = 0 \). \( G(x,t) \) is given by

\[
G(x,t) = \frac{1}{2\pi} \int_{-\infty}^{\infty} dk \int_{-\infty}^{\infty} d\omega G(k,\omega) e^{i(kx + \omega t)}
\]

where

\[
G(k,\omega) = \frac{1/2\pi}{k^2 + \alpha(\omega) + i\beta(\omega)}
\]

\[
\alpha(\omega) = \gamma_s \left( 1 + \left( \omega/\omega_c \right)^2 \right)
\]

\[
\beta(\omega) = \omega \left( \tau - \frac{\mu \tau_s}{1 + (\omega/\omega_c)^2} \right)
\]

The parameter \( \mu \) in Eq. 8 is given by

\[
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\]
$$\mu = \gamma_s(V_s - V_c)$$

Note that in the case of a passive dendrite, $$\mu = \gamma_s = 0$$, which corresponds to $$\alpha(\omega) = 1$$ and $$\beta(\omega) = \omega \tau$$.

**Dendritic PRC**

Equipped with the solution $$U(x, t)$$ for the dendritic perturbation we can calculate the total contribution of this solution to the phase advancement of the somatic oscillator by integrating over time the product of the current injected by the cable and the somatic PRC and dividing by the specific capacitance (Crook et al. 1998; Kuramoto 1984)

$$\varphi = \frac{k}{C} \int_0^t \frac{dU}{dx}(0, t) dt$$

Using the Green’s function we can expand Eq. 10 as

$$\varphi = \frac{k}{C} \int_0^t \int_0^{\Delta V(y', t')} \int_0^t \frac{dG_s}{dy}(0, y', t - t') dt'$$

where $$\Delta V(y', t')$$ is formally some small dendritic voltage fluctuation. The dPRC is proportional to the functional derivative of $$\varphi$$ with respect to $$\Delta V(x_0, t)$$, yielding

$$\varphi(x_0, t) = \frac{d\varphi}{d\Delta V(x_0, t)} = \int_0^t \Delta V(x_0, t') dt'$$

$$K(x_0, t) = \frac{k \tau}{C} \frac{dG_s}{dx}(0, x_0, t) = \frac{k \tau}{C} \frac{d}{dx} \int_0^\infty \frac{d\omega}{2\pi} e^{-i\omega a (x_0, t')} \frac{d\sigma}{d\omega}$$

From here we see that the dPRC is a filtered version of the somatic PRC. The properties of the filter $$K(x_0, t)$$ are derived from the Green’s function of the linearized cable (Bressloff 1999). The final line in Eq. 12 is derived from Eqs. 6–8.

In contrast to the somatic PRC that is calculated in response to a perturbation that is assumed to be applied uniformly to its whole surface, the dPRC is calculated for a perturbation that is applied to an annulus of a vanishing width. As a result the dPRC is actually a density of the units of which are expressed as radians/(mV · cm). To calculate the phase perturbation resulting from an actual dendritic perturbation it is necessary to integrate this quantity over the length of the cable being perturbed (e.g., 0.1λ in the simulations).

**Numerical simulations**

We used one of two Hodgkin–Huxley type oscillators for the soma. The original Hodgkin–Huxley model, shifted by 65 mV (Hodgkin and Huxley 1952), was used as a realization of a Hodgkin class II oscillator (Hodgkin 1948) with a type II PRC. We used Traub’s model (as it appears in Ermentrout 1998) as a Hodgkin class I oscillator with a type I PRC (with two minor changes: $$g_L = 0.2 \text{ ms/cm}^2$$; $$g_Na = 80 \text{ mS/cm}^2$$). The soma was modeled as a single compartment whose voltage is denoted $$V$$, such that the last term in the current-balance equation in Eq. 3 was modeled as $$k(u_i - V)/\Delta x$$, where $$\Delta x = 0.1\lambda$$ is the spatial discretization of the cable and $$k = 0.025 \text{ ms/cm}$$. The cable was modeled as 51 compartments ($$u_1, u_2, \ldots, u_{51}$$) governed by the following equations

$$\tau \frac{du_i}{dt} = \frac{v^2}{\Delta x} (u_{i-1} - 2u_i + u_{i+1}) - (u_i - v) - \gamma s_i(u_i - V)$$

$$\tau \frac{du_i}{dt} = \frac{v^2}{\Delta x} (u_{i+1} - 2u_i + u_{i-1}) - (u_i - v) - \gamma s_i(u_i - V)$$

$$u_{51} = u_0$$

$$v = s(u)$$

$$s = s_i(u)$$

Using the Green’s function we can expand Eq. 10 as

$$\varphi = \frac{k}{C} \int_0^t \int_0^{\Delta V(y', t')} \int_0^t \frac{dG_s}{dy}(0, y', t - t') dt'$$

where $$\Delta V(y', t')$$ is formally some small dendritic voltage fluctuation. The dPRC is proportional to the functional derivative of $$\varphi$$ with respect to $$\Delta V(x_0, t)$$, yielding

$$\varphi(x_0, t) = \frac{d\varphi}{d\Delta V(x_0, t)} = \int_0^t \Delta V(x_0, t') dt'$$

$$K(x_0, t) = \frac{k \tau}{C} \frac{dG_s}{dx}(0, x_0, t) = \frac{k \tau}{C} \frac{d}{dx} \int_0^\infty \frac{d\omega}{2\pi} e^{-i\omega a (x_0, t')} \frac{d\sigma}{d\omega}$$

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**Electrophysiology and data analysis**

Sprague-Dawley rats of either sex aged 16–21 days, were deeply anesthetized with ketamine–xylazine and perfused through the heart with 10–20 ml of ice-cold modified artificial cerebrospinal fluid (ACSF), bubbled with 95% O2, 5% CO2, and contained (in mM): 2.5 KCl, 26 NaHCO3, 1.25 Na2HPO4, 0.5 CaCl2, 10 MgSO4, 230 sucrose, and 10 glucose. The brain was rapidly removed, blocked in the sagittal plane, and sectioned at a thickness of 300 μm. Slices were transferred to a holding chamber and submerged in ACSF, bubbled with 95% O2, 5% CO2, and contained (in mM): 2.5 KCl, 26 NaHCO3, 1.25 Na2HPO4, 2 CaCl2, 2 MgSO4, and 10 glucose.

For recording, slices were transferred to the recording chamber containing oxygenated ACSF at 32–35°C. A ×40 water-immersion objective (Axiioskop; Zeiss, Oberkochen, Germany) was used to examine the slice using infrared differential interference contrast video microscopy. Patch pipettes were prepared from thin-walled borosilicate glass (OD: 1.5 mm, ID: 1.17 mm) on a P-97 Flaming/Brown electrode puller (Sutter Instrument, Novato, CA) and were filled with a solution containing (in mM): 140.5 K-MeSO4, 7.5 NaCl, 0.01 phosphothreonine, 10 HEPES, 0.2 EGTA, 0.2 Na2GTP, and 2 Mg2+ATP. The pH and osmolarity of the intracellular solution were 7.3 (with KOH) and 275–300 mOsm/kg, respectively. The resistance of the filled pipettes ranged from 4 to 6 MΩ for somatic pipettes and 7 to 11 MΩ for dendritic pipettes and the junction potential was 7 mV (voltage traces are corrected for the junction potential). Recordings in the whole cell configuration were made using two Axopatch 200B amplifiers (Axon Instruments, Foster City, CA) in the fast current-clamp mode. Signals were digitized at 10 kHz and logged with pClamp 8.0.1 software (Axon Instruments).
of the oscillator was thus sampled randomly and uniformly. To guarantee weak perturbations, and to avoid inducing an AP with each pulse, we chose to use relatively weak perturbations: 50- or 100-pA pulses were delivered to the soma and 100- or 200-pA pulses were delivered dendritically. The scatterplot of phase perturbations was determined as depicted in Fig. 1B, where $\delta = 2 \pi \phi / T$ is the phase latency from the preceding AP to the perturbation and $\Delta T$ is the temporal latency from the preceding AP to the next one. $T$ was determined by averaging all the interspike intervals that preceded the perturbation in each trial. Because phase responses are periodic by definition, we used the method of Galán et al. (2005) to determine their structure. We fit to each scatterplot a periodic function composed of a DC term and two harmonics

$$\Delta \phi = a_0 + R, \cos(\phi - \varphi_1) + R, \cos^2(\phi - \varphi_2)$$

(14)

Use of more harmonics was attempted but suffered from overfitting and was abandoned. Position of the peak of this function was determined numerically. Even though in principle whether a response was type I or type II was related to the value of $R_1$, $R_1 \leq 1$ means that the amplitude of the fundamental mode is smaller than the amplitude of the DC term ($a_0 \geq 0$ in all cases observed), indicating the lack of a negative lobe, thereby corresponding to a type I response. Similarly, $R_1 > 1$ corresponded to a type II response. Low-pass filtering of $\Delta \phi$ reduces the value of $R_1$ as it attenuates the fundamental mode more than the DC mode. Conversely, high-pass filtering increases the value of $R_1$ because it attenuates the DC mode more than the fundamental mode. During the experiments, dendritic voltage slightly depolarized with time, but because our trials of somatic and dendritic perturbations were interspersed this could not have introduced any systematic error into the estimation of the empirical phase responses.

**RESULTS**

**The model**

We consider a model neuron composed of a rhythmically firing Hodgkin–Huxley-type somatic oscillator coupled to semi-infinite cylindrical cable (Fig. 1A). The soma is spherical with radius $A$; the radius of the dendrite is $a$. The equations for the somatic oscillator include a current-balance equation for voltage and the equations for the three standard gating variables: the $m$ gate for sodium activation, the $h$ gate for sodium inactivation, and the $n$ gate for the activation of the delayed rectifier potassium current. Our choice of the Hodgkin–Huxley formalism for the somatic oscillator (rather than using a detailed model including all known conductances for a particular neuron) stems from our focus on the impact of dendritic properties on PRCs and phase locking. We seek to use, on the one hand, a realistic spiking model for the soma, but at the same time use as simple and as generic a model as possible. Specifically, by using the Hodgkin–Huxley formalism we can generate somatic oscillators that exhibit either type I or type II PRCs. We begin our analysis by considering a passive cable whose time constant is $\tau$ (in milliseconds) and space constant is $\lambda$ (in centimeters). We will consider active conductances later. In this model the voltage in the dendrite oscillates around a resting potential. The dendritic oscillations are driven by the somatic oscillator and are attenuated versions of the somatic voltage trajectory. The soma is located at position $x = 0$ along the cable and we assume that an afferent synapse is positioned somewhere along the cable (at position $x = x_0$ in Fig. 1A).

Because the somatic voltage oscillates in time, with some period $T$, we can calculate the somatic PRC (Fig. 1B): a brief current injection, inducing a voltage perturbation of amplitude $\Delta V$, is delivered to the soma at latency $t_0$ from the previous AP (which in Fig. 1B occurs at time $0$), resulting in a slight change in the timing of the next AP, denoted $\Delta T$ (in the example in
Fig. 1B, the AP is advanced by the perturbation, so that $\Delta T > 0$). In model neurons, the phase deflection from brief, weak perturbations scales with the size of the perturbation. In this regime normalizing the PRC by the amplitude of the voltage perturbation yields a stimulus-size independent PRC (Fig. 1C). Thus the PRC at latency $t_0$, and denoted $Z(t_0)$, is defined as $(2\pi T) \times (\Delta T/\Delta V)$. In model neurons, whose differential equations are known, the PRCs can be calculated directly (without applying voltage perturbations) using the numerical adjoint method (solid line) (Ermentrout 2002; Ermentrout and Kopell 1991; Williams and Bowtell 1997).

The dendritic PRC is a shifted and filtered version of the somatic PRC

The dPRC at half a space constant from the soma ($x_0 = 0.5\lambda$) is shown in Fig. 1D. It is evident that the dPRC is shifted to the left relative to the somatic PRC (Fig. 1C). To understand the nature of the transformation from the somatic PRC to the dPRC we derived a closed-form approximation for the dPRC at any position $x = x_0$ along the cable (Eq. 12 in METHODS). This formula reveals that the dPRC is a filtered version of the somatic one. The kernel of the filter is (up to a scaling factor) the spatial derivative of the impulse response (or Green’s function) of the semi-infinite cable, estimated at the somatic end of the cable. This kernel describes the time evolution of the current injected by the dendrite into the soma that results from a brief and localized impulse delivered at some distance (e.g., $x_0 = \lambda$) along the dendrite (Fig. 1E). The filter peaks at some finite latency after the time of the impulse, which corresponds to the latency of the peak current injected into the soma as a result of this dendritic perturbation. In Fig. 1F we depict the dPRC at $x_0 = \lambda$, as calculated by our formula (“Theory,” solid line) and confirmed by the adjoint method (dashed line, indiscernible because of a negligible difference between the two estimates). Thus the displaced peak of the kernel induces the leftward shift in the dPRC relative to the somatic PRC arising from the time required for the dendritic perturbation to reach the soma and affect its phase (Pfeuty et al. 2005). As expected, the leftward shift at $x_0 = \lambda$ is larger than the shift at $x_0 = 0.5\lambda$.

In Fig. 1, G and H we depict the dendritic filter and the dPRC at $x_0 = 2\lambda$, respectively. The peak of the filter is shifted yet further to the right for this distal location and its amplitude is smaller and is more spread out. Both of these effects reflect the attenuation and dispersion of the perturbation. These properties of the propagation of the dendritic perturbation reflect the fact that the passive dendrite functions as a spatiotemporal low-pass filter. It is this property of the filter that causes the negative lobe present in the somatic PRC (Fig. 1C) to become progressively smaller in the dPRCs as one advances along the dendrite (compare Fig. 1, D, F, and H). At $x_0 = 2\lambda$ the region of dPRC immediately after the time of the AP is strictly positive, indicating a type I response. This implies that the proximal region of the dendrite exhibits a type II response, whereas the more distal region exhibits a type I response. The existence of a transition between response types as a function of the distance along the dendrite is essentially a corollary of a previous study that found a transition between in-phase and out-of-phase solutions in a coupled pair of soma-and-cable neurons as the cable is lengthened (Crook et al. 1998). In the following section we extend this result to show that locations of the transition points along the dendrite are under the control of the postsynaptic neuron’s firing rate.

Transition between type I and type II responses is controlled by firing rate

As demonstrated in Fig. 1, the transition from type II to type I occurs as a result of the low-pass filtering of the higher harmonic modes of the PRC waveform, thereby eradicating the negative lobe. Because the frequencies of these harmonics increase as the period of the oscillator is decreased, these modes should be more strongly attenuated by the dendritic low-pass filter when the period is shortened. This should lead to an eradication of a negative lobe and the type II response at a more proximal location (compare one space constant here to Fig. 1F). C: a pair of neurons symmetrically coupled by a fast, excitatory synapse located at $x_0 = \lambda$, display in-phase synchrony (parameters as in Fig. 1). D: when the firing rate is increased (parameters as in A and B) the neurons become antiphase to each other. Synaptic dynamics are described in METHODS. Gray shaded area depicts (qualitatively) the region of the dendrite where its dPRC is type I; the nonshaded area is where the dPRC is type II as is the somatic PRC.
rically by a fast excitatory synapse that was located at $x_0 = \lambda$. When the neurons’ period was $T = 14.4$ ms this synapse is located within the region of the type II response and the neurons consequently synchronized (Fig. 2C). However, when the period was reduced to $T = 9.3$ ms the neurons go into antiphase oscillations (Fig. 2D) as the region of type I response invades a more proximal region of the dendrite. Nevertheless at this firing rate somatic coupling led to in-phase oscillations (not shown). It should be noted that whether the pair synchronizes or not also depends on the waveform of the synaptic coupling, but we use sufficiently fast interactions so that the pair’s behavior can be predicted qualitatively from the neurons’ phase responses (Ermentrout and Kleinfeld 2001; Hansel et al. 1995; Kuramoto 1984). In light of these results it would be interesting to inquire about what happens when the neurons are coupled asymmetrically so that one neuron’s axon synapses onto the other’s type II response region, whereas the other neuron’s axon synapses onto the type I response region of the former. It can be shown that, whichever response type dominates the proximal region of the neuron (in our case it is type II) determines the nature of the solution of the pair of neurons (in our case in-phase synchrony). This is because the dPRC of the postsynaptic neuron with the more proximal synapse is larger and contributes more to determining the network solution than does the dPRC of the other neuron with the distal synapse. Therefore in general, the response type of the segment of the dendrite on which the more proximal synapse is located determines the pair’s configuration.

**The effect of active dendritic conductances on the PRCs and on phase locking**

Dendrites normally express a variety of active conductances. Several studies suggested that one such conductance, arising from the hyperpolarization-activated, cyclic nucleotide-gated cation (HCN) channel, promotes synchronization in a variety of neurons in response to dendritic inputs (Chan et al. 2004; Kole et al. 2006; Magee 1999; Williams and Stuart 2000). Because PRCs are defined as the phase response of the neuron to weak perturbations, the effect of the dendritic nonlinearities on such perturbations is small and can be described well by the linear approximation of these nonlinearities in the vicinity of the dendritic resting potential $V_R$ (Bressloff 1999). This linear approximation yields the quasi-active approximation of membrane nonlinearities (Koch 1984; Mauro et al. 1970), underlying phenomena such as noise amplification and resonances in the subthreshold voltage range (Hutcheon and Yarom 2000). In addition, this linear approximation is justified by the finding in cortical and hippocampal pyramidal neurons that dendritic processing of time-varying inputs can be described as a linear filter (Cook et al. 2005; Ulrich 2002). Thus we can extend our analysis to derive general results regarding the effect of dendritic nonlinearities on the response properties and synchronization of dendritic neurons.

**The quasi-active membrane approximation**

To study the effect of dendritic nonlinearities we added a single conductance to the semi-infinite cable. This active conductance is described by a gating variable $s$ that is characterized by a monotonic voltage-dependent activation curve $s^a(V)$ and a time constant $\tau_s$, which for simplicity is assumed to be voltage-independent. The reversal potential of its current is denoted, $V_s$. Including this current into the dendritic cable and linearizing it about the value of $V_R$, we find that we can still approximate the dPRC as filtered version of the somatic PRC. However, now the properties of the dendritic filter are altered by the presence of the active conductance (Bressloff 1999). The nonlinearity affects both the frequency spectrum and phase spectrum of the filter. These effects are controlled by a single dimensionless parameter $\mu = \gamma_s(V_R - V_s)(\partial s / \partial V)V_s^a(V_R)$, where $\gamma_s$ is the ratio of the maximal conductance of this current to the leak conductance of the dendrite, and the partial derivative conveys the slope of the activation curve at the resting potential of the dendrite.

What determines the sign of $\mu$? As is evident from its definition, $\mu$ is negative for two types of regenerative or amplifying (Hutcheon and Yarom 2000) currents: 1) currents, such as the persistent sodium current, that are activated at depolarized potentials (i.e., the partial derivative is positive) and have a depolarized reversal potential (relative to $V_R$); and 2) currents, such as the potassium inward rectifier (KIR) current, that are activated at hyperpolarized potentials and have a hyperpolarized reversal potential (Wilson 2005). Why these currents are called amplifying currents is evident from the frequency spectrum of the dendritic filter with these currents. As depicted in Fig. 3A (red), they lead to an amplified response in the low frequencies relative to the passive cable. $\mu$ is positive for two types of restorative or resonating (Hutcheon and Yarom 2000) currents: 1) currents, such as the HCN currents, that are activated by hyperpolarization and that have a depolarized reversal potential; and 2) currents, such as the delayed rectifier potassium current, that are activated at depolarized potentials and have a hyperpolarized reversal potential. Why these currents are called resonating is understood when considering the mildly band-pass structure of frequency response induced by these currents (blue), which can lead to resonance. This structure closely resembles the band-pass structure of the frequency response of dendrites of layer V cortical pyramidal cells, a structure that was shown to be sensitive to HCN channel blockers (Ulrich 2002).

These two classes of nonlinearities also result in different phase spectra (Fig. 3B). For regenerative currents the phase spectrum (red line) is more positive than the phase spectrum of passive dendritic filter (black). This implies that each one of the harmonic modes that makes up the somatic PRC will be shifted more to the left when generating the dPRC than in the case of the passive dendrite. Conversely, for restorative currents the phase spectrum of the filter (blue) is more negative than in the case of the passive filter, indicating less of a leftward shift of each of the modes relative to the passive cable.

**Effect of nonlinearities on type I somatic oscillators**

The frequency spectra of the linearized cable (Fig. 3A) indicate that the effects of regenerative currents (red) and restorative currents (blue) occur primarily at low firing rates. To study these effects we replaced our somatic oscillator with a different Hodgkin–Huxley-type oscillator that can attain low frequencies: the Traub model (Ermentrout 1998). In Fig. 3C we depict the somatic voltage trace of this neuron whose dendrite has a regenerative persistent sodium current in addition to a
We have assumed that the active conductances were mild compared with the leak conductance of the dendrite. However, when very strong nonlinearities are added to the dendrite they cause \( \gamma_R \), the conductance at rest (see METHODS), to increase. As depicted in Fig. 3H, this causes the phase spectra of the quasi-active cable to become smaller than in the passive case for both classes of nonlinearities (i.e., for both positive and negative values of \( \mu \)). This implies that each harmonic mode...
Dendritic HCN currents promote synchrony

To see an example of how a downward shift in the dPRC induced by restorative currents influences network dynamics, we simulated a pair of reciprocally coupled neurons with type I responses. First, the dPRC should be shifted to the left relative to the somatic PRC and, second, we should expect to find qualitative differences between somatic and dendritic PRCs. To test this we performed simultaneous whole cell recordings from the soma and the apical dendrite of layer V pyramidal neurons in slices from rat neocortex (Fig. 5A). Our sample was composed of six neurons. The distance of the dendritic recording from the soma ranged from 35 to 250 μm. We induced tonic firing at 9–16 spikes/s by injecting constant currents ranging from 200 to 550 pA into the soma. Brief, small depolarizing current pulses were injected into the soma or the dendrite to perturb the oscillation (Fig. 5B). By repeating this perturbation many times we uniformly sampled random phases φ of the oscillation and, using the method depicted in Fig. 1B, we generated a scatterplot of the phase perturbations resulting from these current perturbations (Fig. 5C). The empirical phase response, denoted Δφ and depicted by the solid lines, was estimated by fitting a periodic function composed of a DC term and two harmonics to the scatterplot (Eq. 14 in Methods). This recently described method has been shown to result in a robust and consistent estimate of the empirical phase response even for scatterplots that were considerably more variable than the present ones (Galán et al. 2005).

In all cases the peak of the empirical dendritic phase response was shifted to the left relative to the peak of the somatic one (Fig. 5D, P < 0.05, two-tailed Wilcoxon signed-ranks test). The average phase shift across the population was 0.39 radians. It may seem counterintuitive that with our relatively proximal dendritic recordings we should record such a measurable phase shift. However, this value is well predicted by the passive properties of the dendritic cable. For a purely sinusoidal somatic PRC the expected phase shift can be readily calculated assuming a passive cable, yielding

\[ \Delta \phi_{\text{passive}} = \frac{x_0}{\lambda} \sqrt{\frac{1 + (2nf_0)^2 - 1}{2}} \]

where \( f_0 \) is the mean firing frequency of the neuron. If we substitute into the above formula the empirical mean distance \( x_0 \) = 90 μm, the empirical mean firing frequency \( f_0 = 11 \) Hz, \( \lambda = 400 \) μm (Williams 2004), and choose \( \tau = 100 \) ms we arrive at a phase shift of 0.39 radians, as well, indicating that the measured shift in the dPRC is in agreement with the theory.

Whether a given empirical response \( \Delta \phi \) was type I or type II was determined by the value of the parameter \( R_1 \) (see Eq. 14 in Methods), which is the ratio of the amplitude of the fundamental mode of \( \Delta \phi \) to its DC mode. For purely positive type I responses \( R_1 < 1 \), whereas the presence of a negative lobe in the type II responses corresponds to \( R_1 > 1 \). Of the neurons we recorded the somatic phase response was type I in half of the cases and type II in the other half (Fig. 5E). In three cells the value of \( R_1 \) was smaller in the dendrite relative to the soma, consistent with a low-pass filtering operation, as shown in the
cell in Fig. 5C. However, in the remaining cells, there was an increase in the value of $R_1$. In two cases there was a change in the type or response observed in the dendrite relative to that observed in the soma (Fig. 5E). An example of a transition from a type I somatic response to a type II dendritic response is shown in Fig. 5F. Although the change seems modest, it does reflect the appearance of more incidents of delayed APs induced by perturbations that occur shortly after the previous AP.

**FIG. 5.** Comparison of empirical somatic and dendritic phase responses. A: infrared differential interference contrast image of dual whole cell recordings from the soma and apical dendrite of layer V pyramidal neurons in a sagittal slice of rat neocortex. B: simultaneous current-clamp recordings from soma (bottom) and dendrite (top) of the cell in response to a brief depolarizing pulse delivered to either the soma (left) or the dendrite (right). Expected time of the AP (see definition of $T$ in Methods) is marked by the vertical dashed line. Note that in both cases the depolarizing pulse delayed the next AP, representing a type II response. C: phase responses to somatic and dendritic perturbations. Scatterplots are the experimental points and solid line is the fit of a $2\pi$-periodic function, described by Eq. 14 in Methods. Both the somatic and dendritic phase responses, as determined by the fit, are type I responses, and the peak of the dendritic response is shifted 0.24 radians to the left. D: leftward shifts in peak phase of the dendritic response relative to the somatic response were observed in all cells recorded. $^*P < 0.05$. E: shifts in the value of $R_1$ from soma to dendrite. This index is the ratio of the amplitude of the fundamental mode to the DC mode of the phase response $\Delta \phi$. Shifts show no consistent result and indicate that there is heterogeneity in the response types of pyramidal neurons as well as in the relationship of the dendritic phase response to the somatic one. F: example of cell with a type II dendritic phase response and a type I somatic phase response.

**FIG. 6.** HCN currents promote type II phase responses in pyramidal neurons. A: example of cell in which both the somatic and dendritic phase responses are type II (example traces of delayed APs from this cell are shown in Fig. 5B). However, the negative lobe in the dendritic phase response is abolished after treatment with 50 $\mu$M ZD 7288, which blocks HCN channels. B: ZD 7288 abolishes the sag in the dendritic voltage trajectory in response to a 0.9-nA hyperpolarizing somatic pulse. C: example of type II somatic phase response that remains type II after treatment with ZD 7288.

Empirical type II responses are attributable to HCN currents

As we have seen from the modeling (Fig. 3G), the band-pass filtering characteristics of a dendrite that expresses restorative dendritic currents, such as the HCN current, can introduce a small negative lobe into the dPRC that is nevertheless sufficient to change the pattern of phase locking (Fig. 4D). Ulrich has shown by injecting chirp waveforms into the apical dendrites of layer V pyramidal neurons that the frequency response of these dendrites has a mild band-pass structure that peaks at 6 Hz. Moreover, he showed that this peak is abolished when treating the slice with the HCN channel blocker ZD 7288 (Ulrich 2002). It follows that if the HCN current is responsible for introducing a negative lobe in the dPRC, treatment with ZD 7288 should abolish or at least reduce the negative lobe in the phase response. Figure 6A depicts a cell that displays a type II response in both its somatic and its dendritic phase responses. Again, these negative lobes may seem small, but as can be seen in the traces in Fig. 5B that were taken from this cell, the APs of this neuron are truly delayed by somatic and dendritic perturbations that are delivered shortly after the previous AP. After treatment with 50 $\mu$M ZD 7288, which abolished the sag (Fig. 6B), the dendritic phase response became strictly positive (i.e., type I). We cannot rule out that the ZD 7288 treatment also altered the empirical somatic phase response. However, in two additional cells in which we measured only the somatic PRCs before and after ZD 7288 treatment, there was no change in the response type (e.g., Fig. 6C, both responses are type II). Nevertheless, in both cells, blocking the HCN current induced a decrease in the value of $R_1$ relative to control, indicating that this current increases the size of the fundamental mode relative to the DC mode of the PRC and thereby contributes to the

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propensity of layer V pyramidal cells to display negative lobes in their PRCs.

Discussion

We studied a model Hodgkin–Huxley-type somatic oscillator with a long dendrite and found that the phase responsiveness of the neuron to dendritic inputs can be qualitatively different from its response to somatic inputs. The qualitative difference comes about by altering the phase response type of the dendrite relative to the soma (from type I to type II or vice versa). The effect of the dendrite is derived from its linear response properties, which are captured by its frequency and phase spectra. These spectra relate how weak distal inputs are transformed into a current injected by the dendrite into the soma. They also define the filter that acts on the somatic PRC to produce the dPRC. We have described three different effects of this filtering operation. The first is shifting the dPRC leftward relative to the somatic PRC. The second effect—in the case of passive dendrites or dendrites with regenerative nonlinearities—is attenuation of high-frequency components of the PRC. This attenuation can abolish any negative lobe in the dPRC, thereby inducing a transition from a type II to a type I response. Finally, for resonating dendritic nonlinearities the filter preferentially attenuates low frequencies, which can potentially introduce a negative region into the dPRC, thereby inducing a transition from a type I to a type II response.

The theoretical justification for using the linear response properties of the dendrite to predict the dPRC, even for nonlinear dendrites, lies in the use of small perturbations to derive the phase responsiveness. Moreover, studies that used a systems-identification approach to characterize the dynamics of dendrites and axons found that they can be modeled as linear media over a broad range of physiological inputs (Cook et al. 2005; Ulrich 2002). By fitting optimal linear filters to predict the voltage fluctuations in these processes in response to chirps or broad-band noisy current injections, these studies demonstrated that the frequency spectrum of both processes has a weakly band pass structure. According to the theory of quasi-active cables, this structure is generated by the presence of restorative currents in the cable (Bressloff 1999; Hutcheon and Yarom 2000; Koch 1984; Mauro et al. 1970; Ulrich 2002). In the case of the dendrites of pyramidal cells it seems to arise from the restorative HCN current (Cook et al. 2005; Ulrich 2002).

Two major predictions arose from the model: 1) dPRCs should be shifted to the left relative to somatic PRC and 2) dPRCs can be qualitatively different from somatic PRCs. To test this we conducted dual whole cell configuration recordings from the soma and apical dendrites of the rat layer V pyramidal neurons. We found that dendritic phase responses are shifted leftward and found two examples out of the six neurons recorded in which the somatic phase response was of a type different from that of the dendritic phase response (Fig. 5E). The passive model of the dendrite made a strong prediction that the dPRC should be a low-pass filtered version of the somatic PRC. However, we found counterexamples of this in which it seemed that the dPRC underwent a high-pass filtering, which introduced negative lobes into the PRC (Fig. 5F). Because dendritic filters in some CA1 and cortical pyramidal neurons have a band-pass structure, apparently arising from the presence of HCN currents (Cook et al. 2005; Ulrich 2002), we predicted that blocking HCN currents should tend to reduce negative lobes and found this to be true (Fig. 6). Inclusion of restorative currents in the model dendrite elucidated how the dendritic filter acquires the band-pass structure.

In our simplified model of a dendritic nonlinearity in which the current is characterized by a reversal potential and a single gate with a monotonic activation curve, regenerative and restorative currents differ in the sign of a single dimensionless parameter $\mu$ (Eq. 9 in METHODS). This sign is determined by the product of 1) the sign of the difference between the reversal potential and the dendritic resting potential and 2) the sign of the derivative of the activation curve at the resting potential. This gives rise to four different configurations of activation curves and reversal potential as depicted in Fig. 3 of the review by Hutcheon and Yarom (2000). However, the sign of $\mu$ alone is not enough. To have a substantial effect on the filtering properties of the cable the absolute magnitude of $\mu$ must be on the order of unity (i.e., there must be some activation of the conductance at the resting membrane potential).

Even though our model for dendritic nonlinearities assumed voltage-dependent conductances, the formalism can be generalized to other nonlinearities, as well. For example, calcium-activated potassium currents acquire an effective voltage dependency from the voltage dependency of the calcium currents that activate it. If the calcium sources are high-voltage-activated calcium currents, the potassium current would be a restorative current (Koch 1984). More generally, the formalism by which we derive the frequency and phase spectra of the nonlinear cable can be extended to any form of nonlinearity by linearizing the active currents around the resting potential of the cable (Bressloff 1999). Having additional nonlinearities can lead, in principle, to a rich repertoire of spectra that include sharper resonances (Hutcheon and Yarom 2000) as well as multiple spectral peaks.

In their work on a pair of dendritic neurons symmetrically coupled by excitation, Crook et al. (1998) touched briefly on the issue of active dendritic conductances. They found that inward sodium and calcium currents generated larger phase shifts between the neurons, whereas the addition of strong calcium-activated afterhyperpolarizations currents promoted in-phase synchrony. Our study can shed light on these findings. The inward currents they used are of the regenerative sort. These endow the cable with a pronounced low-pass characteristic (Fig. 3A), which would tend to eradicate negative lobes in the PRC and promote type I responses. Neurons with this response phase lock with delays when coupled by fast excitation. Calcium-activated potassium currents are of the restorative type and would promote negative lobes and type II responses, which would lead to in-phase synchronization between neurons coupled by excitation. Our study is also consistent with a study of the effect of active conductances on the PRC of a quadratic integrate-and-fire neuron (Pfeuty et al. 2003). That study found that the persistent sodium current (which is a regenerative current) shifts the PRC to the left, whereas delayed-rectifier potassium current (a restorative current) shifted it to the right. We found that amplifying currents induce a stronger leftward shift, whereas the resonating currents induce a weaker leftward shift in the dPRC. If we subtract the leftward shift that is caused solely by passive dendritic delay (i.e., in the case of the passive cable), we too find that...
amplifying currents induce a relative leftward shift, whereas resonating currents induce a relative rightward shift.

Deactivation of dendritic HCN currents in response to excitatory synaptic inputs gives rise to an effective outward current in CA1 and layer V pyramidal neuron dendrites and is proposed to normalize somatic temporal integration, thereby enhancing synchronization (Magee 1999; Williams and Stuart 2000). Our study clarifies how this enhancement comes about. The effective outward current serves as a negative feedback to the depolarization and is precisely what underlies the resonating properties of this current and the band-pass structure of the effective dendritic filter (Fig. 3A, blue trace). These properties induce a negative region in the dPRC, which in the framework of the theory of weakly coupled oscillators are conducive to synchronization in the presence of fast excitatory synaptic input.

The finding that the dendrite can alter the phase response properties of the neuron should alert experimentalist and modelers alike. Experimentalists must realize that characterizing the phase response properties of the neurons using somatic perturbations may not reflect its response properties to synaptic inputs that are located distally (Keck et al. 2003). When simulating large-scale networks, modelers often opt to represent each constituent neuron as a single-compartment—and thus numerically simpler—neuron. However, neglecting the filtering effect of the dendrite could lead to a wrong conclusion about the collective dynamics of dendritic networks. The most prominent effects of the dendrite are to delay and attenuate the synaptic input. We found that these two effects can be rescued in networks of single-compartment models, without much loss of computational efficiency, by using synaptic interactions whose temporal waveform is delayed and attenuated [e.g., using a synaptic conductance \( g(t) \) that rises like a large power of \( t \)].

**Functional implications**

The common definition of excitatory and inhibitory synapses is influenced by the integrate-and-fire view of neuronal integration. Because excitatory inputs depolarize the cell from its subthreshold resting potential toward AP threshold, causing it to fire, excitatory synapses are defined as those that increase the probability of firing. Conversely, inhibitory synapses decrease this probability (Johnston and Wu 1995). As we have seen, in the case of rhythmically firing neurons that are certain to fire, synaptic inputs are better thought of as either advancing or delaying the next AP, depending on the time of delivery of the input along the trajectory of the neuronal oscillation. Furthermore, this characterization also depends on the location of the synapse on the dendritic tree (Crook et al. 1998). For example, for a neuron with a type I somatic oscillator, fast inhibitory synapses would be synchronizing only if they were located proximally, whereas fast excitatory synapses would be synchronizing only if they were located distally. Such a spatial segregation between inhibitory and excitatory synapses was previously described in CA1 pyramidal neurons (Megias et al. 2001). One well-known advantage of proximal inhibition is its ability to shunt distal excitatory inputs (Shepherd 2004). For neurons that display a type I somatic response, an alternative function of proximal inhibition versus distal excitation is to optimize the synchronization of the postsynaptic neuron to its afferent inputs. Our work demonstrates that the postsynaptic neuron can dynamically control whether a given synapse is synchronizing simply by changing its firing rate. This property could possibly serve as a mechanism for subsets of neurons to form synchronous cell assemblies simply by covarying their mean rates relative to the rest of the population. Additionally, selective dendritic expression of active conductances can enable the postsynaptic neuron to determine how it interacts with incoming synaptic inputs to blend into the collective network dynamics.

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