Dendrite-to-Soma Input/Output Function of Continuous Time-Varying Signals in Hippocampal CA1 Pyramidal Neurons

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Cook EP, Guest JA, Liang Y, Masse NY, Colbert CM. Dendrite-to-soma input/output function of continuous time-varying signals in hippocampal CA1 pyramidal neurons. J Neurophysiol 98: 2943–2955, 2007. First published September 19, 2007; doi:10.1152/jn.00414.2007. We examined how hippocampal CA1 neurons process complex time-varying inputs that dendrites are likely to receive in vivo. We propose a functional model of the dendrite-to-soma input/output relationship that combines temporal integration and static-gain control mechanisms. Using simultaneous dual whole cell recordings, we injected 50 s of subthreshold and suprathreshold zero-mean white-noise current into the primary dendritic trunk along the proximal 2/3 of stratum radiatum and measured the membrane potential at the soma. Applying a nonlinear system-identification analysis, we found that a cascade of temporal integration and static-gain terms fully accounted for the nonspiking input/output relationship between the dendrite and soma. The estimated filters contained a prominent band-pass region in the 1- to 10-Hz frequency range that remained constant as a function of stimulus variance. The gain of the dendrite-to-soma input/output function of continuous time-varying signals in hippocampal CA1 pyramidal neurons.

INTRODUCTION

Revealing the rules neurons use to process inputs is essential to understanding single-neuron computation. The discovery that dendrites contain a variety of voltage-gated channels (for review, see Johnston et al. 1996) has led to intensive investigations of dendritic computation (for reviews, see Haussler et al. 2000; London and Haussler 2005; Magee 2000; Migliore and Shepherd 2002; Reyes 2001; Segev and London 2000). Although our knowledge of the electrophysiological properties of dendrites has greatly advanced, previous studies have usually examined neuronal computation by studying how neurons process brief excitatory postsynaptic potentials (EPSPs) or current injections applied to the dendrites (but see Gasparini and Magee 2006; Larkum et al. 2001; Schwindt and Crill 1997; Turner et al. 1991; Williams and Stuart 2002). Although the precise nature of this computational change remains unclear, adaptation and regulation of neuronal gain has been shown to be a prominent component of many forms of neuronal processing (for reviews, see Davis and Bezprozvanny 2001; Salinas and Sejnowski 2001; Salinas and Thier 2000; Turnigiano and Nelson 2000). In addition, information theory dictates, and subsequent experiments have shown, that efficient representation of information requires the nervous system to adapt to the statistical properties of the signals being encoded (e.g., Atick 1992; Barlow 1961; Bialek and Rieke 1992; Fairhall et al. 2001; Hosoya et al. 2005). Therefore a second goal of our study was to determine whether intrinsic channel nonlinearities that modulate the input-output relationship of neurons depending on whether the input is strong enough to initiate dendritic action potentials (Ariav et al. 2003; Gasparini et al. 2004; Golding and Spruston 1998; Hausser and Mel 2003; Magee 1999; Mel 1993; Nakamura et al. 2007; Polsky et al. 2004; Schaeffer et al. 2003; Williams 2004).

Based on the average background-firing rate of most central neurons, it is unlikely that dendrites receive a “single shock” of only a few isolated EPSPs at any given time. A more realistic scenario is that across the many thousands of synaptic inputs, dendrites receive a constant barrage of excitatory and inhibitory activity that produces a complex time-varying input (Anderson et al. 2000; Borg-Graham et al. 1998; Destexhe and Pare 1999; Destexhe et al. 2003; Ferster and Jagadeesh 1992; Hirsch et al. 1998; Ho and Destexhe 2000). Therefore it is important that we also include this temporal component in our description of the dendrite-to-soma relationship. In this study, we apply system-identification analysis to reveal how the proximal apical dendrites of CA1 hippocampus neurons process a continuous time-varying input. Our first goal was to produce a model that accounted for the signal processing between the proximal apical dendrites and soma.

It has been proposed that dendrite computation includes nonlinearities that modulate the input-output relationship of neurons depending on whether the input is strong enough to initiate dendritic action potentials (Ariav et al. 2003; Gasparini et al. 2004; Golding and Spruston 1998; Hausser and Mel 2003; Kamondi et al. 1998; Karkum et al. 2001; Schwindt and Crill 1997; Turner et al. 1991; Williams and Stuart 2002). Although the precise nature of this computational change remains unclear, adaptation and regulation of neuronal gain has been shown to be a prominent component of many forms of neuronal processing (for reviews, see Davis and Bezprozvanny 2001; Salinas and Sejnowski 2001; Salinas and Thier 2000; Turrigiano and Nelson 2000). In addition, information theory dictates, and subsequent experiments have shown, that efficient representation of information requires the nervous system to adapt to the statistical properties of the signals being encoded (e.g., Atick 1992; Barlow 1961; Bialek and Rieke 1992; Fairhall et al. 2001; Hosoya et al. 2005). Therefore a second goal of our study was to determine whether intrinsic channel nonlinearities that modulate the input-output relationship of neurons depending on whether the input is strong enough to initiate dendritic action potentials (Ariav et al. 2003; Gasparini et al. 2004; Golding and Spruston 1998; Hausser and Mel 2003; Magee 1999; Mel 1993; Nakamura et al. 2007; Polsky et al. 2004; Schaeffer et al. 2003; Williams 2004).
mechanisms within single neurons contribute to these adaptive processing strategies.

Our results suggest that the dendrite-to-soma input/output relationship is well described by a functional model containing a band-pass filter in the theta frequency range followed by an adapting nonlinear gain-control. In addition, we found that the voltage-dependent current, $I_d$, contributes to both the frequency response and the gain regulation of the input/output function. A previous abstract of this work has been presented in preliminary form (Cook et al. 2005).

**METHODS**

**Data collection**

Hippocampal slices (300 μm thick) were prepared from male Sprague-Dawley rats (140–197 g, age between 5 and 6 wk) using standard protocols approved by the University of Houston Animal Care and Use Committee (Colbert and Pan 2002). Individual CA1 neurons were visualized with differential interference contrast optics using infrared illumination. Dual simultaneous whole cell patch-clamp recordings were made using two Dagan BVC-700 amplifiers in “bridge” mode, and data were low-pass filtered at 2 kHz (using an external 8-pole Butterworth filter, Krohn-Hite) and acquired at 5 kHz. The normal external recording solution contained (in mM) 125 NaCl, 2.5 KCl, 1.25 NaH₂PO₄, 25 NaHCO₃, 2.0 CaCl₂, 1 MgCl₂, and 25 dextrose, bubbled with 95% O₂-5% CO₂ at −32°C (pH 7.4). The normal intrapipette solution consisted of (in mM) 140 KMeSO₄, 10 HEPES, 1 BAPTA, 0.28 CaCl₂, 4.0 Mg₂ATP, 0.3 Tris₂GTP, 14 phosphocreatine, and 4 NaCl (pH 7.25 with KOH).

Whole cell recording pipettes (somatic, ~8 MΩ; dendritic, ~10 MΩ), were pulled from borosilicate glass (Warner). The average capacitance of the dendritic electrodes was ~10 pF, measured by fitting a single exponential to a 600-pA current step filtered at 20 kHz and sampled at 50 kHz. Current steps were performed while the electrode was positioned in the bath at approximately the same depth as the target dendrite. Recordings were performed at 30–32°C.

**White-noise stimulus**

Fifty seconds of Gaussian distributed (0 mean) random current was injected with the dendritic electrode (Fig. 1A). The white-noise stimulus was generated using Matlab and played into the dendrite at 5 kHz. This stochastic signal is completely defined by its mean and variance. The average SD of the injected current ($I_d'$) was adjusted to be either low (0.3 ± 0.01 nA) or high (1.9 ± 0.3 nA), with the high value set for each neuron individually to just reach the threshold for action potential production. The same noise pattern was injected on every trial (i.e., only the amplitude was varied). Alternating sweeps of low- and high-input variance current were injected for as long as a stable recording configuration could be maintained.

**Data analysis**

All variability is reported as ± SE. Action potentials were identified in MATLAB, checked by eye, and removed by linearly interpolating the somatic voltage ($V_s$) from 1 ms before the action potential peak to either 5 or 10 ms after the peak (both time windows were used and produce equivalent results). Because of the low firing rate, action potentials constituted a very small proportion of the 50 s of data and our analysis produced the same qualitative results when action potentials were included. As our stimulus had a zero mean, our model of the input/output relationship was designed to reproduce the somatic voltage fluctuations around the resting membrane potential. Therefore after action potentials were removed, individual voltage traces were mean subtracted and linearly detrended to remove any slow DC drifts. These slow drifts were usually <1 mV over the 50 s of recording and were as likely to go up as to go down. Traces were then averaged for each input condition. Because the average spectrum of the somatic membrane potential showed very little power above 200 Hz, we digitally low-pass filtered our data at 250 Hz and then resampled at 500 Hz using the Digital Signal Processing Toolbox in MATLAB. This reduced our 50 s of recorded data to 25,000 data points.

We compensated for any filtering of the injected current ($I_d'$) by the dendritic electrode. From our measured dendrite electrode capacitance ($C_d$), we estimated the electrode’s capacitive current ($I_d'$) using

$$I_c = C_d \frac{dV_c}{dt}$$

where $V_c$ is the dendritic electrode potential measured at the amplifier.

The current injected into the dendrite follows as

$$I_d = I_i - I_c$$

where $I_i$ is the injected current measured at the amplifier. Our results, however, were qualitatively the same (i.e., the dendrite-to-soma input/output band-pass filter and gain characteristics did not change) whether or not we adjusted for the dendritic electrode’s capacitance. This method accounts for the effect that dendritic access resistance, $R_c$, has on the injected current. Because we were interested in how the signal ($I_d'$) was processed as it passed through the dendrite, it was not necessary to measure the dendritic potential, $V_c$, and thus compensation at the amplifier for $R_c$ was not required.

**LN model**

We described the dendrite-to-soma input/output relationship using an LN model (Fig. 2B). The LN stands for “linear/nonlinear” and the
model has the form of a cascade of a linear filter followed by a nonlinear static-gain function (Hunter and Korenberg 1986). The input to the LN model was the time-varying current injection and the output was the somatic membrane potential. The output of the model is expressed mathematically as

\[ V_S^\hat{} = H \ast I_d \]

where \( H \) is a linear filter, \( \ast \) is the convolution operator, \( G \) is a static-gain function, and \( V_S^\hat{} \) is the estimated somatic potential. \( G \) was defined as two quadratic functions

\[ G(F) = \begin{cases} aF + bF^2 & \text{for } F \geq 0 \\ aF + cF^2 & \text{for } F < 0 \end{cases} \]

At any time sample \( t \), Eq. 3 can be expanded to express the convolution of the linear filter and the dendritic current injection as

\[ V_S^\hat{} = G(h_1I_d(t) + h_2I_d(t-1) + \cdots + h_nI_d(t-n+1)) \]

where \( h_i \) are the coefficients of the linear filter \( H \) of length of \( n \). The length of the filter was chosen after preliminary data analysis demonstrated the impulse response function of the linear filter decayed to zero by 400 ms. The quadratic form of \( G \) was chosen after observing the data passed through the origin and was compressive as a function of positive and negative values of \( F \). Thus the LN model had 203 unknown parameters, 200 coefficients in \( H \), and 3 parameters in \( G \) that were optimized using the 25,000 data points. It should be noted, however, that the resulting filter was a smooth function that could have been described by only a few nonlinear parameters. Having 200 coefficients allowed the use of optimal linear estimation methods without a priori assumptions regarding the shape of the filters.

We optimized the LN model by minimizing the mean-squared error (MSE) between the model's output, \( V_S^\hat{} \), and the recorded somatic membrane potential \( V^S \) using a standard iterative procedure (Hunter and Korenberg 1986). At each iteration, the solution to the linear filter was solved first followed by optimizing the nonlinear gain-function. This procedure was iteratively repeated until the MSE was minimized. Solving for the linear filter was accomplished by expressing the convolution in Eq. 5 as an over-determined system of linear equations.
optimized, the inverse for parameters for the static gain function. This was accomplished by optimizing the coefficients of the linear filter. Equation 6 was solved using standard packages for multi-dimensional linear regression in Matlab.

In the second step of each iteration, we solved for the nonlinear processing terms such as temporal filtering and gain control. For our data, we found the MSE usually converged within 20 iterations. The model was optimized separately for the low- and high-variance input conditions.

RESULTS

We wanted to understand how neurons process continuous time-varying inputs. Single EPSPs or isolated brief current injections are not rich enough stimuli to reveal the complex temporal and statistical dependencies of the dendrite-to-soma input/output relationship. Therefore we applied a commonly used system-identification approach to describe neuronal processing of sensory information (for a review, see Wu et al. 2006). In this study, we directly injected randomly varying current into the dendrites to quantify the temporal and adaptive components of the dendrite-to-soma input/output function. Importantly, the stochastic nature of this type of stimulus permitted us to examine how neurons adapted to the changes in input statistics such as variance.

Simultaneous dual whole cell patch recordings were made along the main apical trunk of CA1 pyramidal neurons in slices (see Methods). Fifty seconds of zero-mean Gaussian distributed random current ($I_d$) was injected with the dendritic electrode and the resulting change in membrane potential ($V_S$) was measured with the somatic electrode (Fig. 1A). Electrode separation ranged from 55 to 210 μm (median: 145 μm, mean: 125 μm), which roughly corresponds to the proximal 2/3 of stratum radiatum (Ishizuka et al. 1995).

Our random stimulus was defined by two statistics: mean and variance. Although dendritic voltage-dependent channels are no doubt sensitive to the mean of an input, less is known about their sensitivity to fluctuations about the mean. To reveal how the statistics of these fluctuations affected dendritic signal processing, we kept the mean of the injected current at zero and changed the variance on alternate trials between low and high levels. An example recording in Fig. 1, B and C, illustrates 20 s of the dendritic current injection and the subsequent membrane potential at the soma. The low-variance input produced small voltage fluctuations at the soma, whereas the high-variance input produced large fluctuations that included an irregular train of action potentials. The average SD of the somatic membrane potential across our population of cells was 1.3 ± 0.1 and 5.8 ± 0.4 mV for the low- and high-variance inputs, respectively ($n = 15$).

Across all our neurons, average firing rates in the high-variance input condition ranged from 0.2 to 2.0 (mean: 0.9) spikes/s; these were similar to typical CA1 mean firing rates recorded in vivo (Markus et al. 1995). This suggests that the high-variance input produced overall levels of excitation that the dendrites might reasonably be expected to receive. It is important to emphasize, however, that we do not infer that our continuous-time white-noise current injection was identical to the in vivo synaptic input that CA1 pyramidal cells receive in any specific context.

The amplitude of the linear filter was normalized to insure any change in gain would be expressed by the static-gain function. For our data, we found the MSE usually converged within 20 iterations. The model was optimized separately for the low- and high-variance input conditions.

For example, when we compared the interspike interval distributions of our neurons to that of CA1 neurons recorded from behaving animals on a circular track [in vivo data kindly provided by J. Kneierim and D. Yoganarasimha (Yoganarasimha et al. 2006)], we found that on average the in vivo CA1 neurons were more likely to fire in high-frequency bursts. However, the spike statistics of the in vivo recordings were highly variable with long periods of low-frequency firing interspersed with more robust activity. From the in vivo recordings it was possible to identify 50-s epochs, during which the animal actively moved around the track, where the interspike interval distribution (Fig. 1D, - - -) was qualitatively similar to that of our in vitro recorded neurons (---). Thus our random current injection produced a firing pattern that mimicked in vivo activity under at least some conditions.

LN model captures the dendrite-to-soma input/output function

To describe the dendrite-to-soma signal processing, we functionally represented the neuron as a cascade of a linear filter followed by a nonlinear static-gain function as shown in Fig. 2B (Hunter and Kornenberg 1986; Kornenberg et al. 1988, 1989). This type of functional representation, referred to as a linear/nonlinear model, or LN model for short, has successfully been used to characterized visual processing in the retina (for reviews, see Chichilnisky 2001; Meister and Berry 1999; Wu et al. 2006) as well as the processing of current injected into the soma of neurons (Binder et al. 1999; Bryant and Segundo 1976; Poliakov et al. 1997; Slee et al. 2005).

The LN model is an ideal representation for the dendrite-to-soma input/output function because the linear filter and nonlinear static-gain function, respectively, separate the time-dependent dynamics from any amplitude nonlinearities. However, the most beneficial aspect of the LN model is that it is a functional representation that allows us to discuss the dendrite-to-soma relationship using well-defined signal-processing terms such as temporal filtering and gain control.

As we were primarily interested in understanding the dendrite-to-soma signal processing of the neuron, we did not try to account for the generation of action potentials, which were removed before analysis (see Methods). However, our results were qualitatively the same (i.e., the dendrite-to-soma input/ output filter and gain characteristics did not change) when action potentials were included in the analysis.

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We optimized the parameters of the LN model to best reproduce the somatic voltage ($V_S$) for both input-variance conditions separately (see Methods). Figure 2 provides an example of the optimized LN model to reproduce the dendrite-
to-soma input/output relationship of one of our neurons. A portion of the input current and the somatic membrane potential with action potentials removed are shown on an expanded 500-ms time scale in Fig. 2A (black traces). The red and blue traces in Fig. 2A are the LN model’s predicted output ($V^*$). As this example illustrates, the LN model’s predicted output closely matched the recorded somatic potential and only when the voltage scale is expanded by 10 times is any error noticeable (inset). Over the entire 500 s of recording for this particular neuron, the LN model produced a fit that accounted for 97 and 98% of the variance in the somatic membrane potential for the low- and high-variance input conditions, respectively.

The excellent fit demonstrates that the LN model fully captured the input/output function of the somatic voltage in response to a continuous-time random input applied to the dendrite. This result suggests the neuron was stationary (i.e., its properties did not change over the relatively long 50-s recording interval) with inward and outward voltage-gated currents acting in a balanced and predictable fashion. Furthermore, the neuron remained stationary even during the suprathreshold high-variance input condition when action potentials were produced by this cell at an average rate of 0.8 spike/s.

Figure 2, C and D, illustrates the components of the LN model that were fit to our example cell. For this neuron, the impulse response functions of the linear filters were biphasic (Fig. 2C) and exhibited band-pass characteristics in the 1- to 10-Hz theta range (inset shows the frequency response of the filters). An important observation is that unlike the static-gain function (see following text), the linear filters did not appreciably differ between the low- and high-variance input conditions.

Figure 2D shows the static-gain functions for our example neuron. In these plots, 0 mV corresponds to resting membrane potential. The role of the static-gain function is to transform the output of the linear filter, $F$, into the membrane potential at the soma, $V_s$. Importantly, the static-gain function allows nonlinearities in the amplitude response to be represented in the model. We modeled the static-gain function as a quadratic function of $F$ (see Eq. 4 in METHODS).

The nearly straight-line gain function corresponding to the low-variance input indicates that the neuron was linear for small subthreshold inputs. In contrast, the high-variance input exposed two prominent nonlinearities in the gain function. First, there was an overall reduction in gain as revealed by the reduced slope of the static-gain function at rest (0 mV). Second, there was a gentle compressive nonlinearity at hyperpolarized and depolarized potentials that further attenuated large fluctuations in the input. When the variance of the input increased, the gain of this cell was reduced by 14% at rest and by as much as 40% at depolarized potentials. Thus this neuron changed its gain, but not its temporal filtering characteristics, in response to changes in the variance of the input.

It is important to note that only active dendrites would be expected to exhibit band-pass filtering and nonlinear gain changes. To confirm this point and verify our analysis procedures, we injected the same Gaussian random current into the dendrite of a computer model of a passive neuron. Performing the same analysis produced an LN model with a low-pass filter that exhibited a monophasic impulse response function and a straight-line static-gain function (data not shown). Both the filter and the static-gain function remained the same when the input variance was changed between the low and high conditions.

**Summary results of the LN model**

We assessed how well the LN model described the input/output relationship of the neurons by comparing the recorded ($V_s^*$) with the predicted ($V^*_S$) somatic potential. Figure 3A shows the goodness-of-fit of the LN model for our two input conditions for all cells. Across our 15 dual recordings, we found that the LN model described the input/output function equally well for both input conditions (mean $R^2$ of the LN model fits was 0.97). The correlation of the goodness-of-fit between the low-
and high-variance input conditions in Fig. 3A is likely due to correlated experimental noise that varied between recording sessions. These results demonstrate that the LN model captured most of the input/output relationship from the dendrite to the soma for all of our cells.

We averaged the linear filters and static-gain functions for each input condition across our 15 neurons. We found that the average filters corresponding to the low- and high-variance input conditions were very similar (Fig. 3B). Thus changes in input variance did not produce systematic changes in the shape of the temporal filter. In contrast to the temporal filtering, however, the static-gain functions showed a systematic reduction in slope during the high-variance input condition (Fig. 3C).

The straight line for the average low-variance gain function indicates that the neurons processed small inputs linearly (blue). For the suprathreshold high-variance inputs (red), however, input/output relation exhibited nonlinear behavior with a reduction in gain (i.e., the slope of the static-gain function) at rest that increased for both depolarized, and to a lesser extent, hyperpolarized potentials. Figure 3C shows both static gain functions on the same graph to allow a direct comparison of the slopes.

**Adaptation to input variance around the resting membrane potential**

Gain control is a fundamental signal processing principle that is observed in many neuronal systems, especially those involved in sensory processing (for reviews, see Salinas and Sejnowski 2001; Salinas and Thier 2000). Both synaptic conductance changes (Chance et al. 2002; Holt and Koch 1997; Kerr and Capogna 2007; Mitchell and Silver 2003; Prescott and De Koninck 2003; Shu et al. 2003) and intrinsic properties of the neuron (Burdakov 2005; Sanchez-Vives et al. 2000) can regulate neuronal gain (Azouz 2005; Higgs et al. 2006; Kim and Rieke 2001). That the gain of the input/output function of our CA1 neurons was sensitive to the input variance delivered directly to the dendrites adds support to the idea that intrinsic nonlinearities, such as voltage- and time-dependent channels, may contribute to the activity-dependent regulation of gain.

Because the scales of the two static-gain functions in Fig. 3C were dramatically different, we re-analyzed the change in gain in another way that would not be biased by gain changes at the extremes of the measured voltages. We fit new static-gain functions over a small limited range of somatic membrane potentials around the resting membrane potential. Figure 4A shows the data from the example cell in Fig. 2 plotted on the same scale (data points corresponding to the high-variance input condition that fall outside this scale were not included in this analysis). Linear fits to each condition in Fig. 4A show a significant change in slope indicating the gain for the high-variance input was reduced over the same somatic potentials as the low-variance input ($P < 0.001$, bootstrap described in the following text).

Applying this analysis to all our cells, we confirmed the systematic reduction in gain that occurred when the variance of the input was increased. Figure 4B shows the distribution of the gain change for our population of cells and demonstrates a significant median 14.3 ± 2.2% (mean 13.7%) reduction in gain at rest ($P < 0.01$, 1 sided $t$-test).

We applied a bootstrap method to determine if the change in gain for each neuron was significant (Efron and Tibshirani 1993). The analysis in Fig. 4A was repeated 5,000 times for each cell using bootstrap sampling to estimate the variance in the slopes of the linear fits. In 13 of 15 cells, the change in slope (i.e., gain) was significant ($P < 0.01$, Fig. 4, B and C, open bars and symbols). Thus the dendrite-to-soma input/output function underwent a reduction change in gain when the variance of the input was increased.

As Fig. 4B illustrates, our cells did not always produce the same decrease in gain for the high-variance input. This was because the high-variance input current ($I_{h}$) was adjusted.
during each experiment to just produce action potentials and this threshold varied between cells. The advantage, however, of using different input variances between cells was that it allowed us to test if gain changed as a continuous function of input variance. As shown in Fig. 4C, we found that the reduction in gain was moderately correlated with the increase in input variance ($R^2 = 0.26$), suggesting that dendrites adjust their gain in a graded manner. Thus the dendrites performed a sophisticated form of gain control that was based on the variance of the input signal.

Although our white-noise current injection had a zero mean for both the low- and high-variance conditions, it was possible that the mean soma potential varied between the two conditions. Action potentials produced in the high-variance input may have elevated the somatic potential compared with the low-variance condition. To examine this, we calculated the average somatic potential for both input conditions. Our average potential difference ($V_s(\text{high-variance}) - V_s(\text{low-variance})$) was small and ranged from −4.5 to 1.6 mV (mean: −0.9 mV). Importantly, there was no relationship between the change in mean membrane potential at the soma and the change in gain ($R^2 = 0.05$). Nearly identical results were obtained when we compared the changes in mean potential after spikes were removed. Thus the average somatic potential was not likely a factor in our observed change in gain.

**Effects of dendritic location on filtering and gain**

The passive cable model of dendrites predicts increased filtering at more distal locations (Rall 1959). We wanted to know how the LN model varied between more proximal and more distal dendritic inputs. Figure 5 illustrates the average filter and gain function for our four most proximal (---) and four most distal recordings (−−−). For clarity, we show only the filter and gain corresponding to the high-variance input condition; however, the results for the low-variance input were similar. The proximal recordings where made between 50 and 60 μm from the soma while the distal where between 160 and 210 μm from the soma.

The average impulse-response function for our two groups (Fig. 5A) illustrates a large difference during the first 25 ms of the filter. For later portions of the impulse-response function, however, there is little difference in the shape of the two filters except that the duration of the negativity is slightly longer in the distal condition. The frequency response shows a slight increase in the attenuation at low (<1 Hz) and high (>20 Hz) frequencies for distal inputs. The average gain curves for our two populations are nearly identical with a slight decrease in gain at both hyperpolarized and depolarized potentials for the more distal input (Fig. 5B). These results suggest that the dendrites are likely contributing to some of the components of the LN model in a location-dependent manner; however, it is not known whether these differences are large enough to be functionally significant.

**Contribution of $I_h$ to the input/output function**

Our results thus far suggest that active channels are contributing to the neuron’s frequency response and gain control. To test this, we next blocked $I_h$, a prominent dendritic voltage-dependent current in CA1 neurons (Lorincz et al. 2002; Magee 1998). $I_h$ has been shown to contribute to the frequency response of cortical pyramidal cells (Ulrich 2002) and affect the nonlinear integrative properties of dendrites in CA1 pyramidal cells (Magee 1999). In addition, removing the contribution of $I_h$ from the neuron’s input/output function was an important test of the sensitivity of the LN model.

Figure 6A illustrates 500 ms of the input current ($I_d$, black traces, left) and somatic membrane potential ($V_s$, black traces, right) for a cell where we block $I_h$ by bath applying 20 μM Zd7288. Using the same analysis previously described, we fit the LN model to the data. The predicted somatic membrane potential is shown for both input conditions ($V_s$, red and blue in Fig. 6A). As was the case for experiments performed in normal external solution, the LN model fully captured the input/output response for this cell ($R^2 = 0.95$). The average goodness-of-fit for our five cells recorded in Zd7288 (Fig. 7A), however, was slightly lower than those recorded in normal solution.

Blocking the contribution of $I_h$ had a noticeable effect on the estimated filters and static-gain function (Fig. 6, B and C). Although the estimated filters were similar for both the low- and high-variance input conditions, neither exhibited the prominent biphasic impulse response function and had flat bandpass characteristics (inset). In contrast to the presence of $I_h$, the addition of Zd7288 produced an increase in the static-gain function at the resting membrane potential. Thus for this cell,
removing the contribution of $I_h$ appeared to have altered both the temporal filtering and gain control.

The average filters and static-gain functions for our population of neurons recorded in Zd7288 are shown in Fig. 7, B and C ($n = 5$). Blocking $I_h$ greatly attenuated the band-pass normally present in the 1- to 10-Hz range (Fig. 7B, inset) and altered the static-gain function corresponding to the high-variance input condition (Fig. 7C). Instead of a gain decrease, the lack of $I_h$ produced an average gain increase for the high-variance input condition.

To verify the effect of removing $I_h$ on gain control, we repeated the analysis in Fig. 4 by focusing on the gain change in the neighborhood of the somatic resting membrane potential. Figure 8A shows that eliminating $I_h$ produced an average gain increase (median: 26%, mean: 28%, $P < 0.01$, t-test) compared with cells with $I_h$ present ($\bigcirc$ data are re-plotted from Fig. 4). Unlike the normal condition, there was no systematic relationship between this increase in gain and the increase in input variance (Fig. 8B, $\bigcirc$).

For the data in Fig. 8, there are two possible interpretations regarding the role $I_h$ has on the input/output gain. First, it is possible that $I_h$ alone underlies the decrease in gain with increased input-variance that was observed in the normal condition (see Fig. 8B, $\bigcirc$ re-plotted from Fig. 4). Another possibility, however, is that Zd7288 upset the balance of inward and outward currents, which reduced the stationarity in the dendrite-to-soma input/output function. This second hypothesis is supported by the reduced goodness-of-fit that occurred when $I_h$ was blocked (compare Figs. 3A and 7A).

Unfortunately, the low number of cells recorded in Zd7288 makes it difficult to fully distinguish between these two possibilities. Nevertheless, these results suggest $I_h$ plays a prominent role, either by itself or through its interaction with other voltage-dependent channels, in shaping the input/output function of a neuron by contributing to both the frequency response and regulation of the input/output gain.

**DISCUSSION**

We demonstrate a model for quantifying the temporal processing and regulation of gain in the dendrite-to-soma input/output relationship. Applying a well-established systems-identification approach allowed us to precisely describe how CA1 neurons process arbitrary time-varying inputs by separating the temporal processing from the static-gain control. Changing the variance of the random input allowed us to characterize the input/output function from the proximal apical dendritic trunk to the soma under sub and suprathreshold (i.e., spiking) input conditions. Our results suggest that the gain of the input/output function of a neuron by contributing to both the frequency response and regulation of the input/output gain.

**FIG. 6.** Example cell with $I_h$ blocked by the application of Zd7288. A: example of 500 ms of the injected current and recorded somatic potential (black) in the presence of 20 μM Zd7288. The predicted somatic membrane potential is shown for the low (blue)- and high (red)-variance input conditions. B and C: estimated filters (B) and gain functions (C) for this cell in the presence of Zd7288 for the low (blue)- and high (red)-variance inputs.

**FIG. 7.** Blocking $I_h$ eliminates the band-pass properties of the filters and gain adaptation. A: goodness-of-fit of the LN model for neurons recorded in the presence of 20 μM Zd7288. The point marked $a$ corresponds to the example cell in Fig. 6. B and C: filters (B) and gain functions (C) corresponding to the low (blue)- and high (red)-variance input conditions averaged across 5 dual recordings in the presence of Zd7288. Error bars and shading are SE.
function is sensitive to the statistics of the input while maintaining constant band-pass filter characteristics. In addition, the voltage-dependent current $I_h$ is a prominent player in shaping both the frequency response and gain control of the input/output relationship.

There is a long history of using white-noise stimuli to quantitatively extract the transfer-function of physiological systems (for reviews, see Marmarelis and Marmarelis 1978; Sakai 1992; Westwick and Kearney 2003) and single neurons (e.g., Jahnsen and Karnup 1994; Moore and Christensen 1985; Wright et al. 1996). In addition to more closely mimicking the highly variable input dendrites are likely to receive in vivo, white-noise also has the advantage of containing all frequencies and temporal correlations. Thus it is a relatively “unbiased” stimulus that is suitable for extracting the input/output properties of the system under study. Although Ulrich (2002) used a sinusoidal “chirp” stimulus to characterize the linear portion of the dendrite-to-soma transfer-function in cortical neurons, to our knowledge a full white-noise characterization has never been applied to the dendrite-to-soma input/output function.

The significance of our observations is supported by the fact that the LN model was able to account for >97% of the variance in the somatic potential in responses to the random current injected at the dendrite. Thus the LN model represents a full description of the neuronal input/output relationship over a wide range of input amplitudes. The excellent fit was not due to over-fitting as the number of data points far exceeded the number of free parameters in the LN model (see METHODS). Given the extreme nonlinearities of voltage-dependent channels, it was surprising to find that a simple functional model captured the input/output function even under large suprathreshold input conditions that produced robust spiking activity.

It should be emphasized that our experiments do not distinguish between the respective contributions of the soma and dendrites to the input/output function. Based on the high density of $I_h$ and other channels in the dendrites of neurons (e.g., Lorincz et al. 2002;Magee 1998) and an abundance of electrophysiological data showing that these channels are activated by subthreshold synaptic input (e.g., Magee 1998; Magee and Johnston 1995; Williams and Stuart 2000), it is likely that active voltage-dependent dendritic currents play some role in shaping the input/output relationship of the neuron. However, future experiments will be required to fully quantify the extent to which the dendrites contribute to the filtering and gain control of continuous time-varying input signals.

**Theta-frequency band-pass of the dendrite-to-soma linear filter**

It is notable that the dendrite-to-soma input/output relationship contained a prominent band-pass in the theta frequency range. Specific cognitive and behavioral states are correlated with theta oscillations in the neuronal activity of the hippocampus. These oscillations occur during active exploration of the environment, during REM sleep and may underlie memory related processes (for reviews, see Buzsaki 2002; Lengyel et al. 2005).

It has been proposed that there is a link between the electrical properties of single neurons and network oscillations in the brain (for review, see Hutcheon and Yarom 2000). Using single-electrode recordings at the soma, studies have demonstrated a band-pass frequency response in variety of central and peripheral neurons (Erchova et al. 2004; Hutcheon et al. 1996; Leung and Yu 1998). In the context of network oscillations, this band-pass feature of the membrane potential is usually referred to as resonance. Importantly, these studies demonstrate that the voltage and time-dependent properties of membrane conductances account for a neuron’s resonance. Thus in addition to its role in neuronal oscillations, our results and those of Ulrich (2002) suggest that the resonance of a neuron, as revealed by the dendrite-to-soma linear filter of the LN model, fundamentally affects how dendritic inputs are processed.

The band-pass filtering observed in our experiments agrees with a study on neocortical pyramidal dendrites by Ulrich (2002). The main difference between our approaches is that the sinusoid input used by Ulrich contains strong temporal correlations compared with the flat autocorrelation function of our random stimulus. Although our stimuli were substantially different and the linear filtering and nonlinear gain control were not separated in Ulrich’s study, his results also suggest the dendrite-to-soma input/output function of pyramidal neurons contains a prominent band-pass in the theta frequency range.

Ulrich also found that the dendritic band-pass filtering remained relatively constant under sub and super-threshold inputs that varied in amplitude by ∼20%. We found a similar constancy of filtering using a much larger range of input amplitudes. Thus the constant band-pass filtering may be a...
general feature of dendritic processing used by pyramidal neurons throughout the brain.

**Gain control in neural systems**

As predicted by information theory, adaptation to the input statistics is a prominent feature of sensory processing at the network and systems level (e.g., Atick 1992; Barlow 1961; Bialek and Rieke 1992; Hosoya et al. 2005; Van Wezel and Britten 2002). For example, there is ample evidence that neuronal responses in the visual system adapt to the variance (also referred to as contrast) of the visual input (e.g., Albrecht et al. 1984; Baccus and Meister 2002; Fairhall et al. 2001; Kim and Rieke 2001; e.g., Maffei et al. 1973; Movshon and Lennie 1979). These mechanisms are generally thought to contribute to the efficient representation of information in the face of changing input statistics. Gain modulation at the circuit level has also been shown to occur throughout the nervous system in a variety of other information processing contexts such as attention (McAdams and Maunsell 1999; Reynolds et al. 2000; Treue and Martinez Trujillo 1999), input normalization (Carandini and Heeger 1994), and gain fields (Salinas and Abbott 1997). It was recently reported that attentional gain changes did not alter the linear transfer function of visual cortical neurons (Cook and Maunsell 2004), which agrees with our current observations that changes in gain occurred with no systematic changes in the temporal filtering of the dendrite-to-soma input/output function.

At first glance, a median 14% reduction in gain of the dendrite-to-soma transfer function observed in our experiments may seem small compared with the relatively large increase in input variance. In vivo studies, however, have shown that small modulations in neuronal activity are correlated with significant changes in behavior. For example, in vivo electrophysiology in non-human primates has demonstrated that attentional state can greatly affect behavioral performance in a visual task while modulating neuronal activity by relatively small amounts of 10–20% (Cook and Maunsell 2002b). In other non-human primate in vivo studies, the correlation between the behavioral choice an animal makes in a task and the corresponding change in neuronal activity is governed by small changes in spike rates of <10% (Britten et al. 1996; Cook and Maunsell 2002a; Dodd et al. 2001; Purushothaman and Bradley 2005; Uka and DeAngelis 2004). Although we do not know the behavioral significance of small modulations in CA1 pyramidal neuron activity, the evidence from in vivo electrophysiology studies suggest even small modulatory effects may carry important behavioral consequences.

Several studies have observed regulation of neuronal gain of signals injected directly into the soma of neurons. These results have suggested that regulation of neuronal gain is due to intrinsic channel mechanisms (Sanchez-Vives et al. 2000), changes in background synaptic activity (Chance et al. 2002; Kerr and Capogna 2007; Mitchell and Silver 2003; Prescott and De Koninck 2003; Rauch et al. 2003; Shu et al. 2003), or an interaction of synaptic input and intrinsic voltage- and time-dependent channel properties (Azouz 2005; Higgs et al. 2006; Kim and Rieke 2001). A recent computer modeling study suggests \( I_h \) may contribute to the neuronal gain when combined with other voltage-dependent channels (Burdakov 2005). An intriguing possibility is that control of gain may be possible through diffused modulatory inputs that regulate dendritic plasticity (Magee and Johnston 2005). We should note, however, that our observed gain change is opposite in sign to that recently proposed by Larkum and colleagues (2004), raising the possibility of multiple gain control mechanisms in dendrites of different classes of neurons.

That changing the variance of the input produced a gain change with no change in the filter properties of the input/output function is somewhat surprising given that our high-variance input was large enough to produce action potentials. This is because mechanisms that could potentially modify gain, such as the opening of dendritic voltage-gated conductances, would also be expected to change the temporal filtering properties of the dendrite. Neuronal mechanisms that provide multiplicative changes in gain with no change in the temporal properties have not been easy to resolve and represent an active area of neuroscience investigation (Salinas and Thier 2000).

**Functional implications of the LN model**

Investigators have been applying system identification methods to characterize the input/output relationship of neuronal systems for many years (e.g., Jones and Palmer 1987; Marmarelis and Marmarelis 1978). Because the LN model separates the temporal and amplitude dependent processing, this functional description provides a satisfying and intuitive picture of input/output function. Describing neuronal processing in precise terms such as filtering and gain control is a distinct advantage because it allows us to draw on the wealth of expertise in the signal processing and information sciences.

Our results suggest that CA1 neurons integrate time-varying inputs in a linear to sublinear fashion that is dependent on the statistics of the input. There are several points to consider when comparing our results with other studies of dendritic integration. First, nonlinear systems often exhibit linear behavior over small input perturbations. Thus dendritic summation may appear linear when explored with small subthreshold EPSPs, or in the case of our study, the low-variance input. A second consideration is that we bypassed the synaptic machinery by using dendritic current injection. Synaptic conductances have nonlinearities that arise from both the reduction in driving force and the voltage dependence of the \( N\)-methyl-d-aspartate (NMDA) synaptic conductance.

The third, and potentially most important consideration when comparing the difference between various studies is the state of voltage- and time-dependent channels in the neuron when the synaptic input arrives. Previous studies of dendritic integration usually invoked EPSPs in neurons at rest with no background activity (but see Gasparini and Magee 2006; Larkum et al. 2001; Oviedo and Reyes 2002, 2005). As both depolarization and hyperpolarization produces changes in the activation state of voltage and time-dependent conductances in the dendrite, it is likely that our continuous time-varying input produced a state change in the neuron compared with a quiescent cell at rest. Given that a typical CA1 cell receives thousands of synaptic connections, it is highly unlikely that a neuron is ever in such a quiescent state in vivo.

Several recent studies by Gasparini and colleagues have shown that action potentials initiated in the dendrites produce a supralinear, or expansive nonlinear, effect on synaptic sum-
mation (Gasparini and Magee 2006; Gasparini et al. 2004). Because of the random nature of our continuous stimulus, we were unable to clearly determine if our action potentials were initiated in the dendrites during the high-variance input. However, the effect of the high-variance input was the introduction of a compressive nonlinearity, which is opposite to that observed by Gasparini et al. The differences in our results could be explained by the fact their synaptic input was applied to quiescent neurons at rest compared with our continuous-time input. It is also possible that our high-variance input, although strong enough to produce action potentials, was too weak to initiate dendritic action potentials. Another important difference is that our dendritic input was relatively proximal (within the proximal 2/3 of the apical trunk) compared with Gasparini et al. Distal dendrites may be much more active and the effects of very distal inputs on the LN model is the topic for a future study.

That our LN model accounted for much of the input/output function suggests the signal propagation from the proximal apical dendrites to the soma may be highly reliable. A major focus of neuroscience centers on the question of why central neurons produce highly variable patterns of action potentials when recorded in vivo (for review, see Stein et al. 2005). However, single neurons can produce very reliable timing of action potentials in response to fluctuating somatic current injections (Mainen and Sejnowski 1995). Although our experiments did not include enough repeated stimulus presentations to quantitatively assess the reliability of our soma-to-dendrite transfer function, a casual observation of our data suggests there was very little variation of the somatic membrane potential from one repeat to the next. Thus it is possible that signals arriving on the main apical trunk of the dendrites are passed on to the soma with little additive noise.

**Contribution of I \(_h\) to the input/output function**

Although many voltage-dependent conductances play a role in shaping the input/output properties of neurons, our results suggest that I \(_h\) may have a primary role in determining the band-pass filter characteristics. Ulrich (2002) also reported that I \(_h\) contributes to the band-pass properties in cortical pyramidal neurons while also showing that changes in the DC level of the input altered the linear filtering. It remains to be determined how the DC level of our noise input would affect the components of the LN model.

The precise role of I \(_h\) on gain regulation is difficult to reveal because of the contribution of other voltage-dependent currents at depolarized potentials. I \(_h\) is clearly a prominent player in the regulation of gain and removing this voltage-dependent current caused the input/output function to go from an average decrease to an average increase in gain with increased input variance (Fig. 8). This suggests a dampening, or shunting, role of I \(_h\) in the regulation of the input/output function. That the LN model predicted slightly less of the somatic voltage potential suggests the removal of I \(_h\) pushed the input/output relationship of the neuron toward a more nonlinear regime that is less stationary and thus less amenable to a description by a simple functional model.

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