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Computational Neuroscience

Theoretical Insights into Brain Function

EDITED BY
Paul Cisek
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John F. Kalaska

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VOLUME 165

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Preface

In recent years, computational approaches have become an increasingly prominent and influential part of neuroscience research. From the cellular mechanisms of synaptic transmission and the generation of action potentials, to interactions among networks of neurons, to the high-level processes of perception and memory, computational models provide new sources of insight into the complex machinery which underlies our behaviour. These models are not merely mathematical surrogates for experimental data. More importantly, they help us to clarify our understanding of a particular nervous system process or function, and to guide the design of our experiments by obliging us to express our hypotheses in a language of mathematical formalisms. A mathematical model is an explicit hypothesis, in which we must incorporate all of our beliefs and assumptions in a rigorous and coherent conceptual framework that is subject to falsification and modification. Furthermore, a successful computational model is a rich source of predictions for future experiments. Even a simplified computational model can offer insights that unify phenomena across different levels of analysis, linking cells to networks and networks to behaviour. Over the last few decades, more and more experimental data have been interpreted from computational perspectives, new courses and graduate programs have been developed to teach computational neuroscience methods and a multitude of interdisciplinary conferences and symposia have been organized to bring mathematical theorists and experimental neuroscientists together.

This book is the result of one such symposium, held at the Université de Montréal on May 8–9, 2006 (see: http://www.grsnc.umontreal.ca/XXVIIIs). It was organized by the Groupe de Recherche sur le Système Nerveux Central (GRSNC) as one of a series of annual international symposia held on a different topic each year. This was the first symposium in that annual series that focused on computational neuroscience, and it included presentations by some of the pioneers of computational neuroscience as well as prominent experimental neuroscientists whose research is increasingly integrated with computational modelling. The symposium was a resounding success, and it made clear to us that computational models have become a major and very exciting aspect of neuroscience research. Many of the participants at that meeting have contributed chapters to this book, including symposium speakers and poster presenters. In addition, we invited a number of other well-known computational neuroscientists, who could not participate in the symposium itself, to also submit chapters.

Of course, a collection of 34 chapters cannot cover more than a fraction of the vast range of computational approaches which exist. We have done our best to include work pertaining to a variety of neural systems, at many different levels of analysis, from the cellular to the behavioural, from approaches intimately tied with neural data to more abstract algorithms of machine learning. The result is a collection which includes models of signal transduction along dendrites, circuit models of visual processing, computational analyses of vestibular processing, theories of motor control and learning, machine algorithms for pattern recognition, as well as many other topics. We asked all of our contributors to address their chapters to a broad audience of neuroscientists, psychologists, and mathematicians, and to focus on the broad theoretical issues which tie these fields together.

The conference, and this book, would not have been possible without the generous support of the GRSNC, the Canadian Institute of Advanced Research (CIAR), Institute of Neuroscience, Mental Health and Addiction (INMHA) of the Canadian Institutes of Health Research (CIHR), the Fonds de la

Recherche en Santé Québec (FRSQ), and the Université de Montréal. We gratefully acknowledge these sponsors as well as our contributing authors who dedicated their time to present their perspectives on the computational principles which underlie our sensations, thoughts, and actions.

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CHAPTER 1

The neuronal transfer function: contributions from voltage- and time-dependent mechanisms

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Abstract: The discovery that an array of voltage- and time-dependent channels is present in both the dendrites and soma of neurons has led to a variety of models for single-neuron computation. Most of these models, however, are based on experimental techniques that use simplified inputs of either single synaptic events or brief current injections. In this study, we used a more complex time-varying input to mimic the continuous barrage of synaptic input that neurons are likely to receive in vivo. Using dual whole-cell recordings of CA1 pyramidal neurons, we injected long-duration white-noise current into the dendrites. The amplitude variance of this stimulus was adjusted to produce either low subthreshold or high suprathreshold fluctuations of the somatic membrane potential. Somatic action potentials were produced in the high variance input condition. Applying a rigorous system-identification approach, we discovered that the neuronal input/output function was extremely well described by a model containing a linear bandpass filter followed by a nonlinear static-gain. Using computer models, we found that a range of voltage-dependent channel properties can readily account for the experimentally observed filtering in the neuronal input/output function. In addition, the bandpass signal processing of the neuronal input/output function was determined by the time-dependence of the channels. A simple active channel, however, could not account for the experimentally observed change in gain. These results suggest that nonlinear voltage- and time-dependent channels contribute to the linear filtering of the neuronal input/output function and that channel kinetics shape temporal signal processing in dendrites.

Keywords: dendrite; integration; hippocampus; CA1; channel; system-identification; white noise

The neuronal input/output function

What are the rules that single neurons use to process synaptic input? Put another way, what is the neuronal input/output function? Revealing the answer to this question is central to the larger task of understanding information processing in the brain. The past two decades of research have significantly increased our knowledge of how neurons integrate synaptic input, including the finding that dendrites contain nonlinear voltage- and time-dependent mechanisms (for review, see Johnston et al., 1996). However, there is still no consensus on the precise structure of the rules for synaptic integration.

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Early theoretical models of neuronal computation described the neuronal input/output function as a static summation of the synaptic inputs (McCulloch and Pitts, 1943). Rall later proposed that cable theory could account for the passive electrotonic properties of dendritic processing (Rall, 1959). This passive theory of dendritic integration has been extremely useful because it encompasses both the spatial and temporal aspects of the neuronal input/output function using a single quantitative framework. For example, the passive model predicts that the temporal characteristics of dendrites are described by a lowpass filter with a cutoff frequency that is inversely related to the distance from the soma.

The recent discovery that dendrites contain a rich collection of time- and voltage-dependent channels has renewed and intensified the study of dendritic signal processing at the electrophysiological level (for reviews, see Hausser et al., 2000; Magee, 2000; Segev and London, 2000; Reyes, 2001; London and Hausser, 2005). The central goal of this effort has been to understand how these active mechanisms augment the passive properties of dendrites. These studies, however, have produced somewhat conflicting results as to whether dendrites integrate synaptic inputs in a linear or nonlinear fashion (Urban and Barrionuevo, 1998; Cash and Yuste, 1999; Nettleton and Spain, 2000; Larkum et al., 2001; Wei et al., 2001; Tamas et al., 2002; Williams and Stuart, 2002). The focus of past electrophysiological studies has also been to identify the conditions in which dendrites initiate action potentials (Stuart et al., 1997; Golding and Spruston, 1998; Larkum and Zhu, 2002; Ariav et al., 2003; Gasparini et al., 2004; Womack and Khodakhah, 2004), to understand how dendrites spatially and temporally integrate inputs (Magee, 1999; Polsky et al., 2004; Williams, 2004; Gasparini and Magee, 2006; Nevian et al., 2007), and to reveal the extent of local dendritic computation (Mel, 1993; Hausser and Mel, 2003; Williams and Stuart, 2003).

Although these past studies have shed light on many aspects of single-neuron computation, most studies have focused on quiescent neurons in vitro. A common experimental technique is to observe how dendrites process brief "single-shock" inputs, either a single EPSP or the equivalent dendritic current injection, applied with no background activity present (but see Larkum et al., 2001; Oviedo and Reyes, 2002; Ulrich, 2002; Oviedo and Reyes, 2005; Gasparini and Magee, 2006). Based on the average spike rate of central neurons, it is unlikely that dendrites receive single synaptic inputs in isolation. A more likely scenario is that dendrites receive constant time-varying excitatory and inhibitory synaptic input that together produces random fluctuations in the membrane potential (Ferster and Jagadeesh, 1992; Destexhe and Pare, 1999; Chance et al., 2002; Destexhe et al., 2003; Williams, 2004). The challenge is to incorporate this type of temporally varying input into our study of the neuronal input/output function. Fortunately, system-identification theory provides us with several useful tools for addressing this question.

Using a white-noise input to reveal the neuronal input/output function

The field of system-identification theory has developed rigorous methods for describing the input/output relationships of unknown systems (for reviews, see Marmarelis and Marmarelis, 1978; Sakai, 1992; Westwick and Kearney, 2003) and has been used to describe the relationship between external sensory inputs and neuronal responses in a variety of brain areas (for reviews, see Chichilnisky, 2001; Wu et al., 2006). A prominent tool in system-identification is the use of a "white-noise" stimulus to characterize the system. Such an input theoretically contains all temporal correlations and power at all frequencies. If the unknown system is linear, or slightly nonlinear, it is a straightforward process to extract a description of the system by correlating the output with the random input stimulus. If the unknown system is highly nonlinear, however, this approach is much more difficult.

One difficulty of describing the input/output function of a single neuron is that we lack precise statistical descriptions of the inputs neurons receive over time. Given that a typical pyramidal neuron has over ten thousand synaptic contacts, one might reasonably estimate that an input arrives on the dendrites every millisecond or less, producing membrane fluctuations that are constantly varying

in time. Thus, using a white-noise input has two advantages: (1) it affords the use of quantitative methods for identifying the dendrite input/output function and (2) it may represent a stimulus that is statistically closer to the type of input dendrites receive in vivo.

We applied a system-identification approach to reveal the input/output function of hippocampal CA1 pyramidal neurons in vitro (Fig. 1). We used standard techniques to perform dual whole-cell patch clamp recordings in brain slices (Colbert and Pan, 2002). More specifically, we injected 50 s of white-noise current (I_d) into the dendrites with one electrode and measured the membrane potential at the soma (V_s) with a second electrode. The amplitude distribution of the injected current was Gaussian with zero mean. Electrode separation ranged from 125 to 210 μm with the dendrite electrode placed on the main proximal apical dendritic branch. Figure 1 illustrates a short segment of the white-noise stimulus and the corresponding somatic membrane potentials.

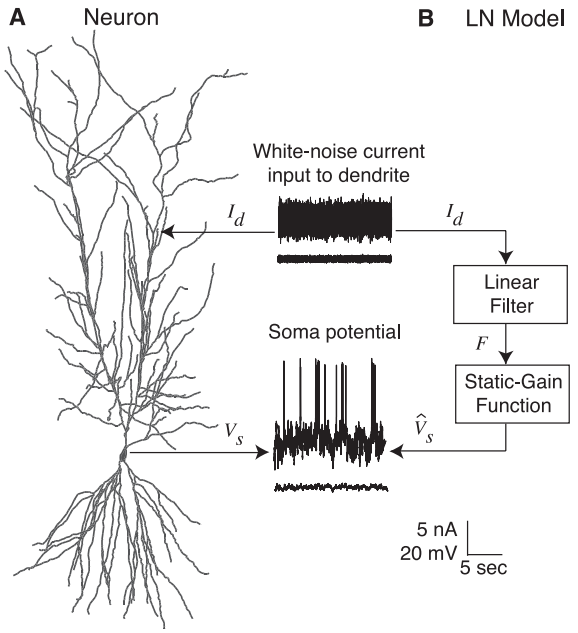

Fig. 1. Using a system-identification approach to characterize the dendrite-to-soma input/output function. (A) Fifty seconds of zero-mean Gaussian distributed random current (I_d) was injected into the proximal apical dendrites of CA1 pyramidal neurons and the membrane potential (V_s) was recorded at the soma. The variance of the injected current was switched between low (bottom traces) and high (top traces) on alternate trials. Action potentials were produced with the high-variance input. (B) An LN model was fit to the somatic potential. The input to the model was the injected current and the output of the model was the predicted soma potential ($\hat{V}_S$). The LN model was composed of a linear filter that was convolved with the input current followed by a static-gain function. The output of the linear filter, F (arbitrary units), was scaled by the static-gain function to produce the predicted somatic potential. The static-gain function was modeled as a quadratic function of F.

To examine how the input/output function changed with different input conditions, we alternately changed the variance of the input current between low and high values. The low-variance input produced small subthreshold fluctuations in the somatic membrane potential. In contrast, the high-variance input produced large fluctuations that caused the neurons to fire action potentials with an average rate of 0.9 spikes/s. This rate of firing was chosen because it is similar to the average firing rate of CA1 hippocampal neurons in vivo (Markus et al., 1995; Yoganarasimha et al., 2006). Thus, we examined the dendrite-to-soma input/output function under physiologically reasonable subthreshold and suprathreshold operating regimes.

The LN model

Figure 1 illustrates our approach for describing the input/output function of the neuron using an LN model (Hunter and Korenberg, 1986). This is a functional model that provides an intuitive description of the system under study and has been particularly useful for capturing temporal processing in the retina in response to random visual inputs (for reviews, see Meister and Berry, 1999; Chichilnisky, 2001) and the processing of current injected at the soma of neurons (Bryant and Segundo, 1976; Poliakov et al., 1997; Binder et al., 1999; Slee et al., 2005). The LN model is a cascade of two processing stages: The first stage is a filter (the "L" stage) that linearly convolves the input current I_d. The output of the linear filter, F, is the input to the nonlinear second stage (the "N" stage) that converts the output of the linear filter into the predicted somatic potentials ($\hat{V}_S$). This second stage is static and can be viewed as capturing the gain of the system. The two stages of the LN model are represented

mathematically as

$$F = H^* I_d$$
$$\hat{V}_S = G(F) \quad (1)$$

where H is a linear filter, * the convolution operator, and G a quadratic static-gain function.

Having two stages of processing is an important aspect of the model because it allows us to separate temporal processing from gain control. The linear filter describes the temporal processing while the nonlinear static-gain captures amplitude-dependent changes in gain. Thus, this functional model permits us to describe the neuronal input/output function using quantitatively precise terms such as filtering and gain control. In contrast, highly detailed biophysical models of single neurons, with their large number of nonlinear free parameters, are less likely to provide such a functionally clear description of single-neuron computation.

It is important to note that we did not seek to describe the production of action potentials in the dendrite-to-soma input/output function. Action potentials are extremely nonlinear events and would not be captured by the LN model. We instead focused on explaining the subthreshold fluctuations of the somatic voltage potential. Thus, action potentials were removed from the somatic potential before the data were analyzed. This was accomplished by linearly interpolating the somatic potential from 1 ms before the occurrence of the action potential to either 5 or 10 ms after the action potential. Because action potentials make up a very small part of the 50 s of data (typically less than 2%), our results were not qualitatively affected when the spikes were left in place during the analysis.

The LN model accounts for the dendrite-to-soma input/output function

Using standard techniques, we fit the LN model to reproduce the recorded somatic potential in response to the injected dendritic current (Hunter and Korenberg, 1986). We wanted to know how the low and high variance input conditions affected the components of the LN model. Therefore, these conditions were fit separately. An example of the LN model's ability to account for the neuronal input/output function is shown in Fig. 2. For this neuron, the LN model's predicted somatic membrane voltage ($\hat{V}_S$, dashed line) almost perfectly overlapped the neuron's actual somatic potential (V_s, thick gray line) for both input conditions (Fig. 2A and B). The LN model was able to fully describe the somatic potentials in response to the random input current with very little error. Computing the Pearson's correlation coefficient over the entire 50 s of data, the LN model accounted for greater than 97% of the variance of this neuron's somatic potential.

Repeating this experiment in 11 CA1 neurons, the LN model accounted for practically all of the somatic membrane potential (average $R^2 > 0.97$). Both the low and high variance input conditions were captured equally well by the LN model. Thus, the LN model is a functional model that describes the neuronal input/output function over a range of input regimes from low-variance subthreshold to high-variance suprathreshold stimulation.

Gain but not filtering adapts to the input variance

The LN model's linear filters and nonlinear static-gain functions are shown for our example neuron in Fig. 2C and D. The impulse-response function of the linear filters (Fig. 2C) for both the low (solid line) and high (dashed line) variance inputs had pronounced negativities corresponding to a band-pass in the 1–10 Hz frequency range (inset). Although the two input conditions were significantly different, the filters for the low- and high-variance inputs were very similar. Across our population of neurons, we found no systematic change in the linear filters as the input variance was varied between low and high levels. Therefore, the temporal processing performed by CA1 pyramidal neurons on inputs arriving at the proximal apical dendrites does not change with the input variance.

In contrast to the filtering properties of CA1 neurons, the static-gain function changed as a function of input variance. Figure 2D illustrates the static-gain function for both input conditions. In this plot, the resting membrane potential corresponds to 0 mV and the units for the output of the linear filter (F) are arbitrary. The static-gain function for the

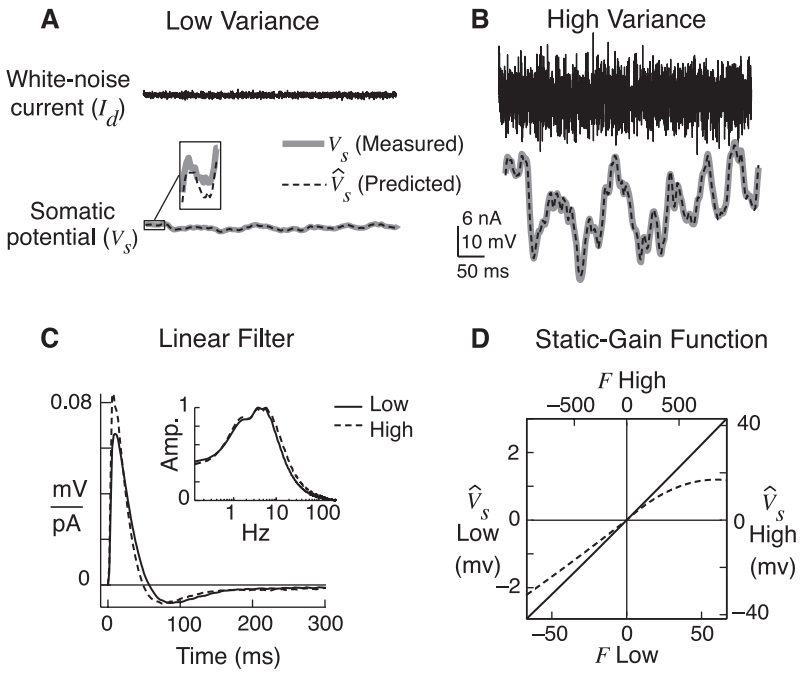

Fig. 2. The dendrite-to-soma input/output function of a CA1 neuron is well described by the LN model. (A) Example of 500 ms of the input current and somatic potential for the low-variance input. The predicted somatic membrane potential of the LN model ($\hat{V}_S$, dashed line) overlaps the recorded somatic potential (V_s, thick gray line). (B) Example of the LN model's fit to the high-variance input. Action potentials were removed from the recorded somatic potential before fitting the LN model to the data. (C) The impulse-response function of the linear filters for the optimized LN model corresponding to the low (solid line) and high (dashed line) variance inputs. Inset is the frequency response of the filters. (D) Static-gain function for the optimized LN model plotted for the low (solid line) and high (dashed line) variance inputs. The axes for the high variance input were appropriately scaled so that the slope of both static-gain functions could be compared.

low-variance input was a straight line indicating that the neuronal input/output function was linear. For the high-variance input, however, the static-gain function demonstrated two important nonlinearities. First, the static-gain function showed a compressive nonlinearity at depolarized potentials. Thus, at large depolarizing potentials, there was a reduction in the gain of the input/output relationship. Second, there was a general reduction in slope of the static-gain function for high-variance input compared with the low-variance slope, indicating an overall reduction in gain. Thus, for this neuron, increasing the variance of the input reduced the gain of the input/output function at rest that was further reduced for depolarizing potentials.

Across our population of 11 neurons, we found that increasing the variance of the input reduced the gain of CA1 neurons by an average of 16% at the resting membrane potential. This reduction in gain also increased with both hyperpolarized and depolarized potentials. Adapting to the variance of an input is an important form of gain control because it ensures that the input stays within the operating range of the neuron. Although a 16% reduction may seem small in comparison to the large change in the input-variance, there are many instances where small changes in neuronal activity are related to significant changes in behavior. For visual cortical neurons, it has been shown that small changes in spike activity ($<5\%$) are correlated with pronounced changes in perceptual abilities (Britten et al., 1996; Dodd et al., 2001; Cook and Maunsell, 2002; Uka and DeAngelis, 2004; Purushothaman and Bradley, 2005). Thus, even small modulations of neuronal activity can have large effects on behavior.

Voltage- and time-dependent properties that underlie neuronal bandpass filtering

The above experimental results suggest that the dendrite-to-soma input/output relationship is well described as a linear filter followed by an adapting static-gain function. We wanted to know the biophysical components that produce the filtering and gain control. To address this, we used the computer program NEURON (Hines and Carnevale, 1997) to simulate a multi-compartment "ball & stick" model neuron (Fig. 3A).

We applied the random stimulus that we used in the experimental recordings to the dendrite of the passive model and then fit the data with the LN model to describe its input/output function. As would be expected from Rall's passive theory of dendrites, the estimated filters and gain functions were identical for the low and high variance input conditions (Fig. 3B). In addition, the filters from the passive model's impulse-response function had no negativity and thus were not bandpass (inset) and the static-gain function was linear (Fig. 3C). Thus, the passive properties of dendrites in the compartmental model do not produce the same characteristics of the experimentally observed dendrite-to-soma input/output function.

We wanted to know what type of voltage- and time-dependent channels might account for our experimental observations. Active channels come in a variety of classes. Instead of focusing on one particular class, we used the freedom of computer simulations to construct a hypothetical channel. Using a generic channel, referred to as I_x, we systematically varied channel parameters to investigate how the voltage- and time-dependent properties affected temporal filtering and gain control in the ball & stick model. Our theoretical channel was based on the classic Hodgkin and Huxley formulation (Hodgkin and Huxley, 1952) that incorporated a voltage- and time-dependent activation variable, $n(v, t)$. This activation variable had sigmoidal voltage-dependent steady-state activation with first-order kinetics.

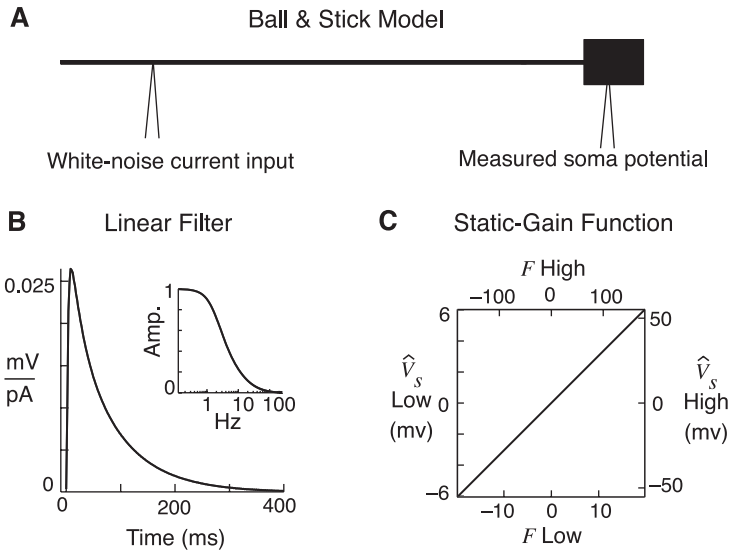

Fig. 3. Dendrite-to-soma input/output function of a passive neuron model. (A) The passive model had 20 dendrite compartments with a total length of 2000 μm and a diameter that tapered distally from 3 to 1 μm. The soma was a single 20 × 20 μm compartment. The passive parameters of the model were $R_m = 40{,}000\,\Omega\,cm^2$, $C_m = 2\,\mu F/cm^2$, and $R_a = 150\,\Omega\,cm$. (B) The optimized filters of the LN model were fit to the passive model. Filters for the low- and high-variance input were identical. (C) Static-gain functions of the optimized LN model were linear and had the same slope for both input conditions.

Mathematically, our hypothetical channel is described as

$$I_x = \bar{g}_x \cdot n(v,t) \cdot (v - E_{rev})$$
$$n_\infty = 1 - \frac{1}{1 + e^{-\beta(v - v_{1/2})}}$$
$$\frac{dn}{dt} = \frac{(n_\infty - n)}{\tau} \quad (2)$$

where n_∞ is the steady-state activation based on a sigmoid centered at $v_{1/2}$ with a slope of $1/\beta$, $\bar{g}_x$ the maximal conductance, τ the time constant of activation, and E_{rev} the reversal potential of the channel.

We first examined the effects of varying the steady-state voltage activation curve on the input/output function of the model. Voltage-dependent channels can have either depolarizing or hyperpolarizing activation curves. We inserted a uniform density of our I_x current throughout the dendrites and left the soma compartment passive. We set the parameters of I_x to have decreasing activation with depolarizing voltage (Fig. 4A) and stimulated the model with our low- and high-variance dendritic current injection. Fitting the LN model to the results of the simulation resulted in a bandpass filter and linear static-gain (Fig. 4A). The LN model accounted for greater than 98% of the somatic membrane potential and thus represented an excellent description of the input/output relationship of the compartmental model. It is worth mentioning that the simulated properties of I_x resembled the prominent dendritic current

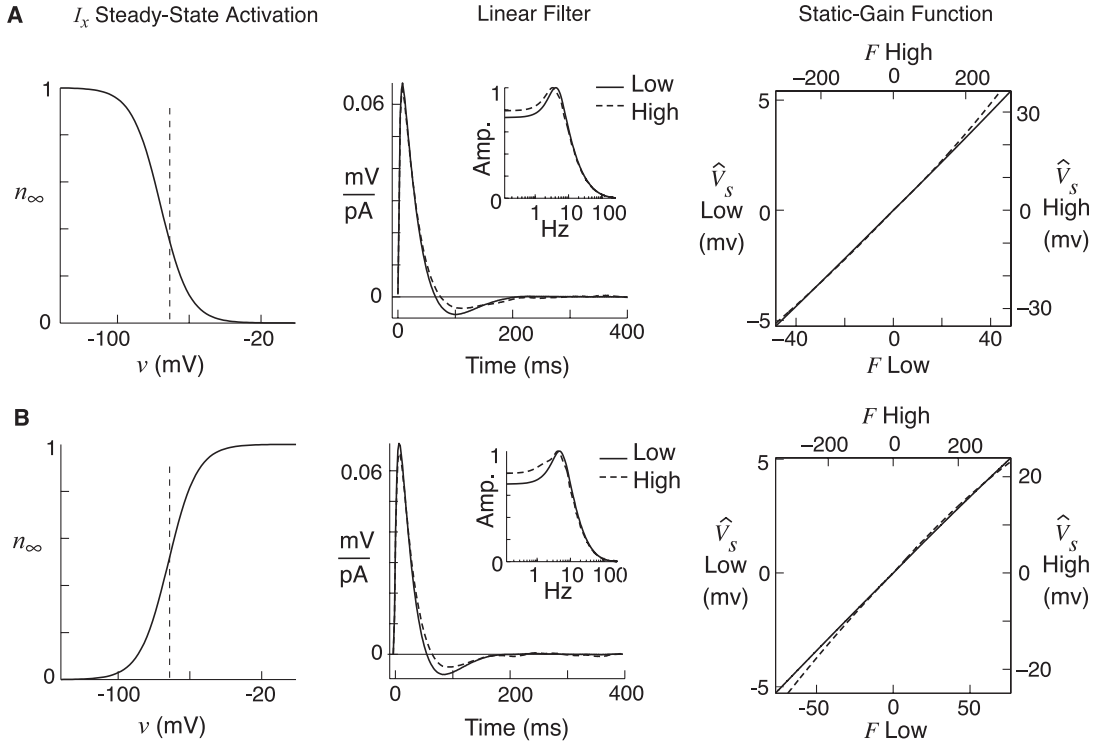

Fig. 4. The direction of steady-state voltage activation has little effect on bandpass features of the LN model. This figure shows the LN models that describe the dendrite-to-soma input/output function of the compartmental model containing the dendritic channel I_x. Two different steady-state activation curves were used for I_x. (A) Hyperpolarizing steady-state voltage activation of I_x produced bandpass features in the LN model (i.e., biphasic impulse-response function) but did not produce a reduction in gain between the low (solid line) and high (dashed line) variance input conditions. (B) Depolarizing steady-state voltage activation of I_x also produced bandpass features with no reduction in gain. In all simulations, I_x had a τ of 50 ms. The vertical dashed line in the activation plots indicates the resting membrane potential of -65 mV.

I_h (Magee, 1998). Thus, a simple voltage- and time-dependent channel can account for the bandpass filtering observed in our experimental data.

To see how the activation properties of the channel affected the input/output function, we reversed the activation curve of our hypothetical channel to have an increasing activation with depolarized potentials (Fig. 4B). The other parameters were the same except that the reversal potential of I_x was changed and the activation curve was shifted slightly to maintain stability. Injecting the low- and high-variance input current and fitting the LN model to the somatic potential, we found that this active current also produced a bandpass input/output function. Interestingly, there was still a lack of change in gain with input variance as can be seen in the static-gain function. Similar results were also observed when the slope of the activation curves was varied (data not shown).

From these simulations we can draw two conclusions. First, it appears that a variety of voltage dependencies can produce the bandpass filtering observed in neurons. Of course, this is only true when the membrane potential falls within the voltage activation range of the channel. In other words, a voltage-dependent channel that is always open or closed would not produce bandpass filtering. Second, a simple voltage-dependent mechanism does not seem to account for the experimentally observed change in gain between the low and high variance input conditions (compare the static-gain functions in Figs. 2D and 4).

Next, we examined the effect of the time dependencies of our theoretical channel on the neuronal input/output function. In the above simulations, we held the τ of I_x fixed at 50 ms. By varying τ we found that the time dependencies of the channel greatly affected the filtering properties. A shorter τ of 8 ms produced a model with an input/output function that exhibited less bandpass filtering that was shifted to higher frequencies (Fig. 5A). The shorter τ, however, created a slight increase in gain

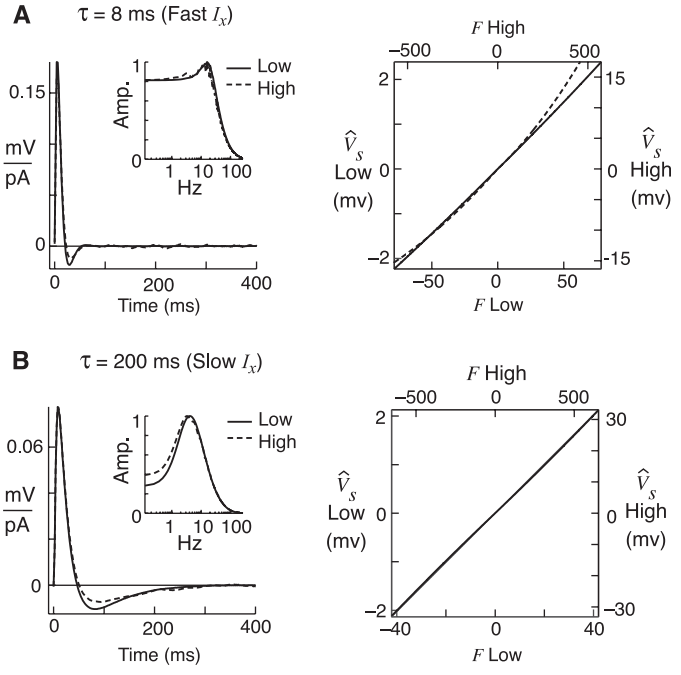

Fig. 5. Temporal channel properties determine bandpass features of the LN model. Shown are the LN models for both the low (solid line) and high (dashed line) variance input conditions. Except for τ, the parameters for I_x were the same as in Fig. 4A. (A) Fast activation of I_x ($\tau = 8$ ms) moved the bandpass to higher frequencies, but did not produce a reduction in gain with increased input variance. (B) Slow activation of I_x ($\tau = 200$ ms) increased the bandpass property of the filter and moved it toward lower frequencies with no reduction in gain.

for the high-variance input compared with the low-variance input, which is opposite to the gain change observed experimentally. In comparison, increasing τ to 200 ms had the opposite effect of enhancing the bandpass filtering of the model (Fig. 5B). Compared with a τ of 50 ms (Fig. 4A), the slower channel also moved the bandpass region to a lower frequency range. However, increasing τ produced no change in the gain of the neuron from the low-variance to the high-variance condition.

Discussion

Determining how neurons integrate synaptic input is critical for revealing the mechanisms underlying higher brain function. A precise description of the dendrite-to-soma input/output function is an important step. We found that the dendrite-to-soma input/output function of CA1 pyramidal neurons is well described by a simple functional LN model that combines linear filtering with static nonlinear gain control. The fact that the LN model accounted for over 97% of the somatic potential variance during a relatively long random input cannot be overemphasized. Even when producing action potentials during the high-variance input, the neuronal input/output function was well described by the LN model. The combination of bandpass filtering characteristics and nonlinear gain changes suggests that the input/output function cannot be explained by passive cellular properties, but requires active membrane mechanisms.

The advantages of characterizing the neuronal input/output relationship using a functional LN model are many. This model allows us to describe neuronal processing using the well-defined signal processing concepts of linear filtering and gain control. Although useful in understanding the biophysical aspects of neurons, a realistic compartmental model of a neuron would not allow such a clear description of the dendrite-to-soma input/output function. As demonstrated by our modeling of a hypothetical voltage-dependent conductance, I_x, different channel parameters can produce the same qualitative input/output characteristics of a compartmental neuron model.

That a simple functional model accounted so well for the dendrite-to-soma processing was initially surprising given that dendrites contain a wide range of nonlinear voltage- and time-dependent channels (Johnston et al., 1996). However, our subsequent computer simulations using a compartmental model indicate that nonlinear channels can underlie the linear temporal dynamics observed experimentally. The bandpass filtering produced by our theoretical voltage- and time-dependent channel is a result of a complex interaction between the passive filtering properties of the membrane and the temporal dynamics of the channel (for review, see Hutcheon and Yarom, 2000). Although the steady-state activation curve also influenced the bandpass filtering, we found that channel kinetics had the greatest effect on the temporal filtering of the model.

It is significant that the dendrite-to-soma input/output relationship contains a prominent bandpass in the theta frequency range. Neuronal networks in the hippocampus have prominent theta oscillations that are correlated with specific cognitive and behavioral states. Hippocampal theta 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). Thus, the bandpass dynamics of the dendrite-to-soma input/output function may contribute directly to network-level oscillations in the hippocampus and other brain areas such as the neocortex (Ulrich, 2002).

Adaptation of gain is an important signal-processing mechanism because it ensures that the amplitude of the stimulus is maintained within the dynamic range of the system (for review, see Salinas and Thier, 2000). Information theory provides a basis for the popular idea that the brain adapts to the statistical properties of the signals encoded for efficient representation (e.g., Barlow, 1961; Atick, 1992; Bialek and Rieke, 1992; Hosoya et al., 2005). For example, the spike activity of neurons in the visual system has repeatedly been shown to adapt to the variance (or contrast) of a visual stimulus (e.g., Maffei et al., 1973; Movshon and Lennie, 1979; Albrecht et al., 1984; Fairhall et al., 2001; Kim and Rieke, 2001; Baccus and Meister, 2002). We found a similar change in gain to the variance

of the injected current, suggesting that the intrinsic properties of dendrites may provide part of the foundation for gain adaptation observed at the circuit and systems level. Recent studies have reported similar changes in the gain of signals injected into the soma of cortical neurons in vitro. It has been proposed that this regulation of gain may be due to either intrinsic channel mechanisms (Sanchez-Vives et al., 2000), changes in background synaptic activity (Chance et al., 2002; Rauch et al., 2003; Shu et al., 2003), or both (Higgs et al., 2006). Because of the importance of maintaining the optimal level of activity in the brain, it is not surprising that there may exist multiple mechanisms for regulating gain.

With our computer simulations, however, we were not able to link the properties of our simple theoretical channel to the experimentally observed adaptation of the static-gain function. Although we observed changes in gain that occurred between the low- and high-variance input conditions, these were in the wrong direction (compare Fig. 2D and 5A). In addition, the model did not produce the compressive reduction in gain observed at depolarized potentials with the high-variance input. This suggests that the experimentally observed change in the static-gain function may be due to other mechanisms such as an increase in intracellular Ca^{2+} during the high-variance input. Another possibility is that the reduction in gain with increased input variance may arise from the interaction of many different channel types and mechanisms.

The theoretical channel model in Fig. 4A is based closely on the voltage-dependent current, I_h. This channel is expressed throughout the dendrites and has been shown to affect the temporal integration of synaptic inputs (Magee, 1999). Using a "chirp" sinusoidal stimulus, Ulrich showed that I_h plays a role in dendrite-to-soma bandpass filtering in neocortical neurons (Ulrich, 2002). Our preliminary experiments conducted in the presence of pharmacological blockers suggest that I_h may have a similar role in hippocampal pyramidal cells. However, dendrites contain many other voltage-dependent mechanisms and understanding how they work together to shape the dendrite-to-soma input/output function is an important topic for future studies.

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CHAPTER 2

A simple growth model constructs critical avalanche networks

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Abstract: Neurons recorded from electrode arrays show a remarkable scaling property in their bursts of spontaneous activity, referred to as ''avalanches'' (Beggs and Plenz, 2003, 2004). Such scaling suggests a critical property in the coupling of these circuits. We show that similar scaling laws can arise in a simple model for the growth of neuronal processes. In the model (Van Ooyen and Van Pelt, 1994, 1996), the spatial range of the processes extending from each neuron is represented by a circle that grows or shrinks as a function of the average intracellular calcium concentration. Neurons interact when the circles corresponding to their processes intersect, with a strength proportional to the area of overlap.

Keywords: network activity; homeostasis; plasticity; network development

Introduction

Theoretical (also known as computational) neuroscience seeks to use mathematical analysis and computer simulation to link the anatomical and physiological properties of neural circuits to behavioral and cognitive functions. Often, researchers working in this field have a general principle of circuit design or a computational mechanism in mind when they start to work on a project. For the project to be described here, the general issue concerns the connectivity of neural circuits. For all but the smallest of neural circuits, we typically do not have a circuit diagram of synaptic connectivity or a list of synaptic strengths. How can we model a circuit when we are ignorant of such basic facts about its structure? One answer is to approach the problem statistically, put in as much as we know and essentially average over the rest. Another approach, and the one that inspires this work, is to hope that we can uncover properties of a neural circuit from basic principles of synapse formation and plasticity. In other words, if we knew the rules by which neural circuits develop, maintain themselves, and change in response to activity, we could work out their architecture on the basis of that knowledge. To this end, we need to uncover the basic rules and principles by which neural circuits construct themselves.

When neurons are removed from the brain and grown in culture, they change from disassociated neurons into reconnected networks or, in the case of slice cultures, from brain slices to essentially two-dimensional neural circuits. These re-development processes provide an excellent opportunity for exploring basic principles of circuit formation. Using slice cultures from rat cortex (and also acute slices),

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Beggs and Plenz (2003, 2004) uncovered an intriguing property of networks of neurons developed in this way. By growing neural circuits on electrode arrays, they were able to record activity over long periods of time and accumulate a lot of data on the statistical properties of the activity patterns that arise spontaneously in such networks. Of particular interest are the observations of scaling behavior and criticality. These results provide the inspiration for the model we construct and study here.

The networks recorded by Beggs and Plenz (2003, 2004) are often silent, but silent periods are punctuated by spontaneous bursts of activity observed on variable numbers of electrodes for different periods of time. Beggs and Plenz called these bursts avalanches. To define and parameterize neural avalanches, they divided time into bins of size t_{bin} through a procedure that selects an optimal size. Here, we simply use $t_{\text{bin}} = 10\,\text{ms}$, typical of the values they used. An avalanche is defined as an event in which activity is observed on at least one electrode for a contiguous sequence of time bins, bracketed before and after by at least one bin of silence on all electrodes. We use an identical definition here, except that electrode activity is replaced by neuronal activity, because our model has no electrodes and we can easily monitor each neuron we simulate.

The results of Beggs and Plenz (2003, 2004) of particular importance for our study are histograms characterizing both the durations and sizes of the avalanches they recorded. Duration was determined by counting the number of consecutive bins within an avalanche. Size was measured either in terms of the number of electrodes on which activity was recorded during an avalanche, or by a measure of the total signal seen on all electrodes during the course of an avalanche. In our modeling work, we measure the size of an avalanche by counting the total number of action potentials generated during its time course.

The histograms of duration and size constructed from the data revealed a fascinating property (Beggs and Plenz, 2003, 2004; Fig. 1); both were of a power-law form. The number of events of a given size fell as the size to the $-3/2$ power, and the number of events of a given duration fell as the duration to the -2 power. Power-law distributions are interesting because they contain no natural scale. For example, in this context we might expect the typical size of a neuronal dendritic tree or axonal arbor (around 100 μm) to set the spatial scale for avalanches. Similarly, we might expect a typical membrane time constant of around 10 ms to set the scale for avalanche durations. If this were true, the distributions should be exponential rather than power-law. Power-law distributions indicate that these networks can, at least occasionally, produce activity patterns that are much larger and much long-lasting that we would have expected. This is what makes power-law distributions so interesting. Another intriguing feature is that power-law behavior typically arises in systems

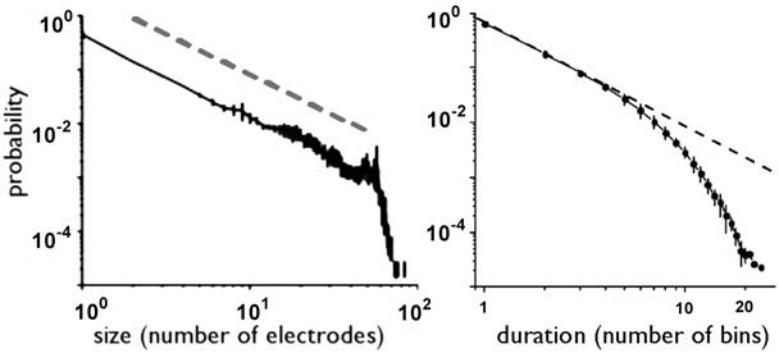

Fig. 1. Results of Beggs and Plenz on avalanche distributions. Left: probability of avalanches of different spatial sizes. The dashed line corresponds to a $-3/2$ power. Right: probability of avalanches of different durations. The dashed line corresponds to a -2 power. (Adapted with permission from Beggs and Plenz, 2004).