Dendritic Computation

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dendrites, coding, synaptic integration, spikes, ion channels

Abstract

One of the central questions in neuroscience is how particular tasks or computations, are implemented by neural networks to generate behavior. The prevailing view has been that information processing in neural networks results primarily from the properties of synapses and the connectivity of neurons within the network, with the intrinsic excitability of single neurons playing a lesser role. As a consequence the contribution of single neurons to computation in the brain has long been underestimated. Here we review recent work showing that neuronal dendrites exhibit a range of linear and nonlinear mechanisms that allow them to implement elementary computations. We discuss why these dendritic properties may be essential for the computations performed by the neuron and the network and provide theoretical and experimental examples to support this view.

Contents

INTRODUCTION

Brains compute. This means that they process information, creating abstract representations of physical entities and performing operations on this information in order to execute tasks. One of the main goals of computational neuroscience is to describe these transformations as a sequence of simple elementary steps organized in an algorithmic way. The mechanistic substrate for these computations has long been debated. Traditionally, relatively simple computational properties have been attributed to the individual neuron, with the complex computations that are the hallmark of brains being performed by the network of these simple elements. In this framework, the neuron (often called a "Perceptron," "Spin," or "Unit") sums up the synaptic input and, by comparing this sum against a threshold, "decides" whether to initiate an action potential. In computational terms this process includes only one nonlinear term (thresholding), which is usually counted as a single operation. Thus, the neuron operates as a device where analog computations are at some decision point transformed into a digital output signal. Such a design forms the backbone of many artificial neuronal networks, starting from the original work of McCullough & Pitts (1943) to the present day. In this review we argue that this model is oversimplified in view of the properties of real neurons and the computations they perform. Rather, additional linear and nonlinear mechanisms in the dendritic tree are likely to serve as computational building blocks, which combined together play a key role in the overall computation performed by the neuron.

In the first part of this review we describe the dendritic computational toolkit, i.e., the biophysical mechanisms in dendrites, which endow them with potential computational powers. We focus on the most recent findings and group them according to the type of computations being carried out. In the second part of the review, we present several examples where the role of dendritic mechanisms in computation has strong circumstantial support, such as directional selectivity in retinal neurons or coincidence detection in the auditory system. We conclude with a discussion of how we can ultimately prove the role of dendrites in neural computation and outline a process for achieving this goal. Throughout the review, we focus on the online aspects of computation. Naturally, the results of such computations must ultimately be read out and stored within the network. Given that dendrites are also the site where synaptic plasticity takes place, their properties are likely to

affect the induction and expression of plasticity. These issues have been discussed in several recent reviews (Häusser & Mel 2003, Linden 1999, Mainen 1999, Chklovskii et al. 2004), and we therefore do not address this aspect in detail here.

THE DENDRITIC "TOOLKIT"

Why discuss what a neuron does in terms of computation? We use a simple example to illustrate the problem. When one watches a movie, each frame is presented for about 50 ms, during which time we have to process any changes from the last frame before the next frame appears. To a first approximation the timescale of the computational cycle of a neuron involved in this computation is thus on the order of milliseconds to tens of milliseconds. Because a typical neuron in the brain receives thousands of synaptic inputs, a neuron involved in processing the visual input thus receives hundreds to thousands of 50-ms input spike trains. But the neuron has only one axon, which provides the output signal, and thus the final conversion represents a compression into a much smaller amount of information. Because there are so many inputs, an essential feature of this transformation is the amount of input information that must be discarded by the neuron. This process is analogous to what some mathematical functions are doing: projecting a huge space onto a narrow one. Thus, the neuron throws away the irrelevant information and selects only the information relevant to its function. The essence of computing a function in computer science is usually considered to be implementing an algorithm, that is, a sequence of simple computational steps organized in a flowchart that leads from the input to the output (**Figure 1**). Are there ways to deconstruct into such simpler building blocks the very complex mapping done by a neuron? Can we identify the crucial steps that occur during this process? Are decisions taken only at the final step of transforming the somatic voltage into an action potential, or are there decision points on the way?

Although the flowchart representation may not be the most appropriate and comprehensive way to describe what neurons are doing, it can nevertheless be very instructive to define and explore the computational building blocks (i.e., the boxes on the flowchart) that neurons can perform. During the past decade a rapidly increasing number of studies investigating signaling mechanisms in dendrites have appeared, and several recent reviews have discussed these findings in depth (Euler & Denk 2001, Häusser et al. 2000, Koch & Segev 2000, Magee 2000, Segev & London 2000, Williams & Stuart 2003). Rather than listing all the known facts about dendritic signaling, in this section we focus on identifying the unique dendritic mechanisms that can act as computational building blocks. We start with a brief discussion of how passive dendrites transform their inputs and implement nonlinear interactions between synaptic inputs. Then we review the role of dendritic voltage-dependent channels and conclude by evaluating the possible role of dendrites in chemical computation.

Computations in Passive Dendrites

It is important to recognize that the passive properties of the dendritic tree provide the backbone for the electrical signaling in dendrites, even when they are richly endowed with voltage-dependent ionic currents. For example, the threshold for initiation of a dendritic spike is determined in part by the availability of sodium channels, but perhaps even more by the passive load of the surrounding dendrites, which dictates how much of the input current will depolarize the membrane and how much will flow axially toward other dendritic regions (Segev & London 1999). Thus, understanding the passive properties of dendritic trees remains crucial for understanding computation in dendritic trees. Aside from their role in regulating the conditions for active dendritic signaling, the passive properties

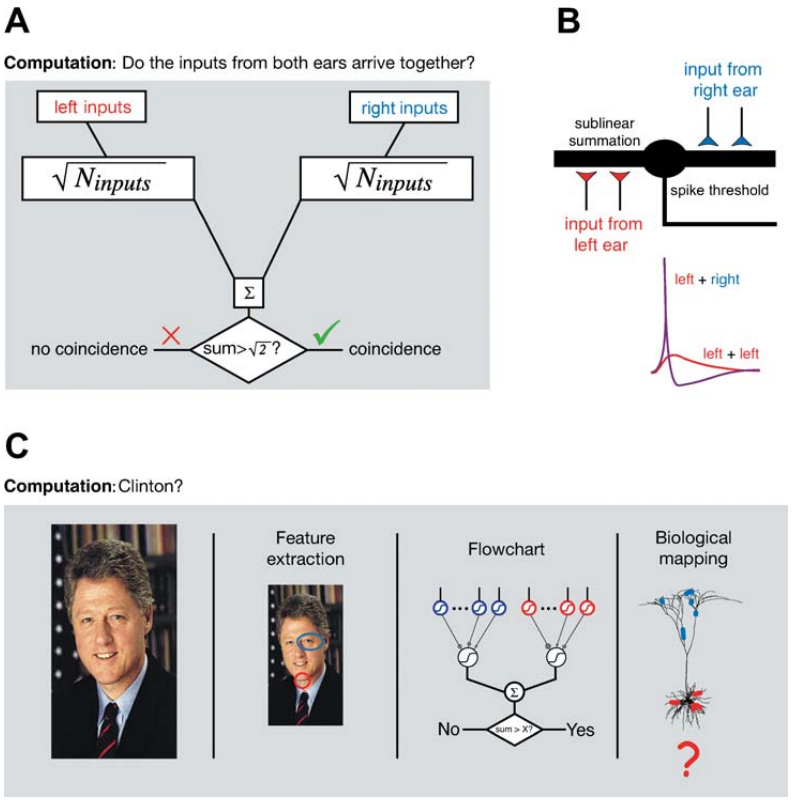


Figure 1

Dendritic computation. The task of a brainstem auditory neuron performing coincidence detection in the sound localization system of birds is to respond only if the inputs arriving from both ears coincide in a precise manner (10–100 μs), while avoiding a response when the input comes from only one ear. (A) A flowchart of a simplistic algorithm to achieve this computation. Inputs to each ear are summed sublinearly, and the input from both ears is then summed linearly and compared with threshold. Thus only if there are inputs from both ears will the sum exceed the threshold, whereas if the input arrives only to one ear the output is not large enough. (B) Agmon-Snir et al. (1998) showed that dendrites of these neurons might implement a similar algorithm. Inputs from each ear arrive on one dendrite. Sublinear summation is achieved by the mutual shunting of the excitatory inputs, and the threshold is implemented via the spike-generation mechanism. (C) Neurons are known to be involved in much more sophisticated computations, such as face recognition (Kreiman et al. 2000). An algorithm to solve a face recognition task is one of the holy grails of computer science. At present, we do not know precisely how single neurons are involved in this computation. An essential first step is feature extraction from the image, which clearly involves a lot of network preprocessing before features are fed into the individual cortical neuron. The flowchart implements a three-layer model of dendritic processing (see Häusser & Mel 2003) to integrate the input. The way such a flowchart is mapped onto the real geometry of a cortical pyramidal neuron (right panel) remains unknown.

of dendrites provide computational functions in their own right, as discussed below.

Delay lines via dendritic filtering. In terms of signal propagation, dendrites behave like electrical cables with medium-quality insulation. As such, passive dendrites linearly filter the input signal as it spreads to the site of initiation, where it is compared with the threshold. This filtering tends to attenuate the dendritic signal as a function of the distance it travels and the frequency of the original signal. Thus a brief and sharp excitatory postsynaptic potential (EPSP) that originates in the dendrite will be transformed into a much smaller and broader signal when it arrives at the soma (**Figure 2**). As a consequence, the time-to-peak of a synaptic event, and thus the delay of the resulting output spikes, depends on the location of the synapse in the dendritic tree. Rall (1964) recognized that this property may be exploited to perform simple computations. First, for single inputs, by acting as a delay line, the dendrites can thus "label" particular inputs on distinct regions of the dendritic tree by the latency of the resulting output spikes. In fact, EPSPs with different somatic shape are likely to affect the somatic output spike trains in different ways (Fetz & Gustafsson 1983). Second, for multiple inputs, the time course of the somatic voltage response depends on the temporal order of activation of the dendritic synapses (in contrast to the scenario where they are all located on the soma) (Rall 1964; see below, and see also **Figure 6**).

Parallel processing and local computations. Synaptic inputs onto dendrites do not only inject current but also locally change the membrane conductance to certain ions. This leads to a nonlinear interaction between multiple inputs if they colocalize in time and space. When two excitatory inputs are active together at short distance, each depolarizes the membrane and reduces the driving force for the other input, and thus, theoretically, the response to the simultaneous activation is smaller than the sum of the individual responses (Rall et al. 1967). In this context, dendrites might be beneficial because they enable the spatial separation of inputs to minimize their interaction. In some cases, however, this possible sublinear summation may actually be advantageous (Agmon-Snir et al. 1998, section on coincidence detection in auditory neurons, p. 519) (see **Figure 1**). It also provides a mechanism for saturation of inputs, thus preventing overexcitation of the neuron by a group of synapses.

Nonlinear interactions are especially prominent between excitatory synapses and shunting inhibition. Shunting inhibition usually describes inhibition that changes the total conductance of the membrane but does not cause any voltage change when activated on its own. In this case it is more convenient to think of the inhibition as reducing the input resistance of the cell, effectively reducing the voltage response to excitatory current. This property of inhibition can be mathematically formulated as having a divisive effect on excitatory signals (Fatt & Katz 1953), providing a mechanism for simple arithmetic computation in dendrites (Blomfield 1974). Rall was the first to recognize that the effectiveness of this interaction has a strong spatial component. When excitatory and inhibitory inputs are widely separated from each other on different dendritic branches, then the inputs will tend to sum linearly at the soma. In contrast, when the excitatory and inhibitory inputs are located adjacent to each other, then the inhibition can produce a highly nonlinear "shunting" of the excitatory input (Rall 1964). An elegant recent experimental study by Liu (2004) demonstrated that such an inhibitory effect can be localized to a single dendritic branch. Theoretical work has shown that inhibition is also effective when it is located on the path between the excitatory input and the soma (Jack et al. 1975, Koch et al. 1983, Rall 1964). Thus, the relative location of synaptic inhibition versus excitation determines whether

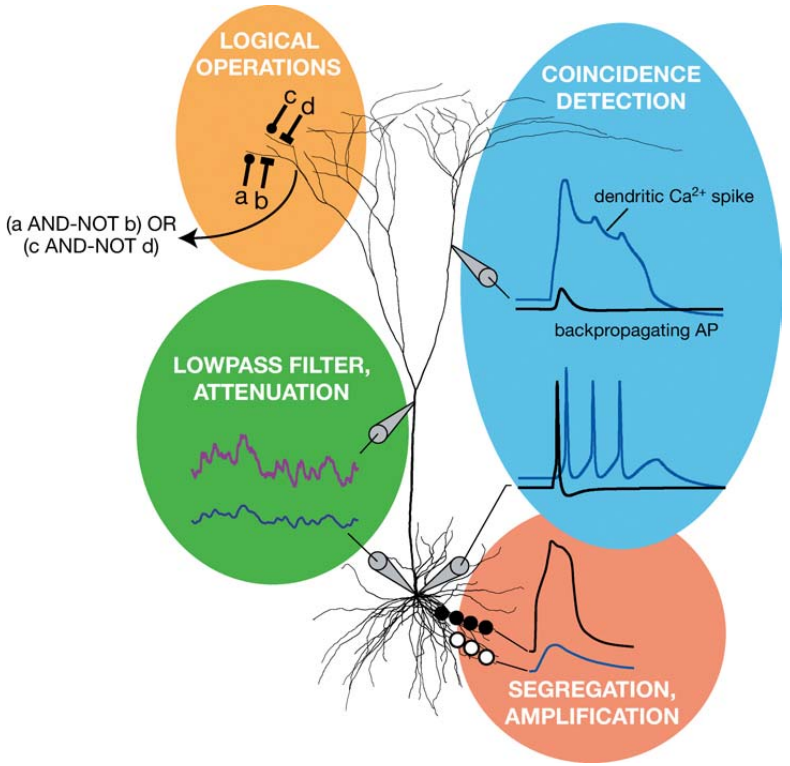


Figure 2

The dendritic computational toolkit. A schematic figure highlighting four key dendritic mechanisms, mapped onto a layer 5 pyramidal neuron morphology, which can allow dendrites to act as computational elements. These mechanisms can coexist in the same neuron and be active in parallel or in a hierarchical manner. Bottom left: Passive dendrites act as passive filters. A high-frequency fluctuating current injected in the dendritic pipette will evoke high-frequency and large-amplitude local voltage responses, but the response recorded by the somatic pipette will be attenuated and smoothed (low pass filtered). Top left: Nonlinear interaction between excitation and shunting inhibition on small dendritic branches can implement logical operations. The branch marked by an arrow sums up the current from the two subtrees, such that its output would be a logical OR on their output. Each of the subtrees will in turn inject current if and only if the excitation AND-NOT the inhibition will be active. Bottom right: Dendrites can help reduce or amplify the mutual interaction between excitatory inputs. Excitatory inputs to the same branch tend to sum sublinearly, whereas inputs on different branches sum linearly. Thus mapping input to different branches can reduce this effect. In neurons with active dendrites, however, clusters of inputs active synchronously on the same branch can evoke a local dendritic spike, which leads to significant amplification of the input. Synapses onto a different branch (open circles) are only slightly influenced by this spike. Top right: In layer 5 cortical pyramidal neurons, as depicted here, coincidence detection between the apical and basal dendritic compartments is achieved by active dendritic mechanisms. A backpropagating action potential, which coincides with a distal synaptic input, will trigger a dendritic Ca^{2+} spike, which depolarizes the whole apical dendrite and drives a burst of spikes in the axon. See text for further details.

inhibition predominantly counteracts a specific set of (neighboring) excitatory synapses or whether it acts on the global set of excitatory synapses.

Although inhibition can act in a graded manner, it has been predicted that, in principle, synaptic inhibition may be able to veto an excitatory signal effectively, depending on the location and the strength of the inhibitory conductances (Jack et al. 1975, Koch et al. 1983, Rall 1964). For example, the result of the combined operation of a neighboring pair of excitatory and inhibitory inputs will cause somatic depolarization if and only if excitatory input AND NOT inhibitory input is active (**Figure 2**). This AND-NOT function is a Boolean logical operation, of the exact same kind implemented in modern computers and studied in mathematical computational theory. Whether dendrites really implement a network of Boolean gates is not clear, but this is exactly the kind of formalism required for a deep understanding of dendritic computation, namely a formal mathematical entity that would clarify the operations performed by dendrites. Koch et al. (1983) cleverly showed that logic operations can be linked to the less formal notions of computation used by physiologists to devise a model of a retinal ganglion neuron that has a directional selectivity to moving visual inputs (**Figures 2** and **6**; see below). Because the branch points in the dendritic tree can be seen as summing up the currents in individual branches, each tree can be seen as summing over many logical gates, and thus the whole dendrite can implement complex functions. Note that a key issue in the implementation of such a mechanism is the addressing of the right synapses to the right dendrite. In fact, as a general rule, as we see below, any computation that exploits local nonlinearity mechanisms is bound to require the addressing of the relevant synaptic inputs to the relevant locality in the dendrite (Mehta 2004, Poirazi & Mel 2001). It remains to be seen whether the power of dendritic computation can itself provide a constraint for targeting of synaptic inputs at the appropriate locations and whether such addressing indeed takes place as a basic phenomenon in the brain (Chklovskii et al. 2004).

Computations in Active Dendrites

Dendritic excitability as a feedback mechanism. Solely on the basis of anatomical observations, Cajal formulated the law of dynamic polarization (Cajal 1911), which states that in the nervous system information flows in one direction: from dendrites to soma to axon. In the past decade it has become clear that in many types of neurons the presence of excitable ionic currents in the dendrites supports dendritic action potentials that travel in the reverse direction, from the soma into the dendrites (Stuart et al. 1997). Computationally this "backpropagation" has major consequences because it implies that the neuron is no longer an open-loop system but has an internal mechanism of feedback. It is thus no longer the case that feedback is a property only of the network, but rather it is a salient property of each element of the network. Moreover, the feedback conveyed by the backpropagating action potential is highly sophisticated and has many important consequences for dendritic function, and also for synaptic plasticity (Magee & Johnston 1997, Linden 1999). For example, a single backpropagating action potential can activate slow dendritic voltage-gated ionic currents, which in turn flow back towards the spike initiation zone in the axon, often resulting in additional action potentials (see below). Thus, the somatic action potential can under favorable conditions trigger a burst due to its interaction with the dendrites (Carruth & Magee 1999; Williams & Stuart 1999). Modeling studies show that this interaction between soma and dendrites can be captured by a reduced, two-compartment model of the neuron and critically depends on the coupling coefficient between the two compartments. This coupling is governed by dendritic morphology and the distribution and properties of dendritic voltage-gated channels and synaptic activity (Doiron et al. 2002, Mainen & Sejnowski 1996, Pinsky & Rinzel 1994, Schaefer et al. 2003, Vetter et al. 2001). The firing patterns of neurons are thus potentially tunable simply by changing dendritic properties. The interplay between somatic spikes and dendritic response could be exploited computationally, e.g., as a slope detector (Kepecs et al. 2002), or for feature detection in sensory systems (Oswald et al. 2004).

Amplification of synaptic inputs. The fact that passive dendrites attenuate the synaptic input on its way to the soma raises a long-standing question: Why have so many distal synapses if their activity is not going to affect the output whatsoever? Investigators have proposed that other mechanisms are involved in synaptic integration, effectively endowing each synapse with equal "vote" and creating a "dendritic democracy." Resolving the importance of these different mechanisms in different neuronal types is important because the presence or absence of compensatory mechanisms leads to fundamentally different views of neuronal function (Häusser & Mel 2003). Here we briefly outline the various scenarios and the supporting experimental evidence. Four major mechanisms have been proposed: synaptic scaling, synaptic boosting, local dendritic spikes, and global dendritic spikes.

1. Synaptic scaling: In this scenario, the conductances of distal synapses are scaled according to their distance from the soma, so as to equalize their efficacies. First, indirect evidence for this mechanism of "dendritic democracy" was found in motoneurons (Iansek & Redman 1973) and has been more recently supported by studies in hippocampal CA1 pyramidal neurons (Magee 2000). However, this mechanism may not be general because other major types of neurons do not seem to follow this rule (Williams & Stuart 2002).
2. Subthreshold boosting: Inward voltage-dependent dendritic currents can amplify synaptic inputs on their way to the soma, thus compensating for their attenuation. Although it is clear that there exist dendritic currents to support this scenario (Cook & Johnston 1997, 1999; Migliore & Shepherd 2002), there is contradictory experimental evidence regarding whether such boosting plays an important role, and whether it stems from dendritic or somatic currents (Oviedo & Reyes 2002, Schwindt & Crill 1995, Stuart & Sakmann 1995).
3. Local dendritic spikes: A powerful mechanism for overcoming dendritic attenuation is the local dendritic spikes triggered by coactivation of synaptic inputs. The regenerative inward currents required for triggering such spikes can be provided by voltage-gated sodium channels, voltage-gated calcium channels, or synaptically activated N-methyl-d-aspartate (NMDA) receptor channels. Such spikes could be triggered by synaptic inputs or local dendritic current injections. The spatial extent of these dendritic spikes is highly variable, and so is their effect on the somatic voltage (Gasparini et al. 2004, Golding & Spruston 1998, Mel 1993, Polsky et al. 2004, Schiller et al. 1997, Softky 1994, Stuart et al. 1997, Williams & Stuart 2002). Theoretical studies have recently shown that such a mechanism could lead to a substantial increase in the computational power of the neuron (see below; Poirazi & Mel 2001; **Figure 5**).
4. Global dendritic spikes: Layer 5 cortical pyramidal neurons represent an extreme case where, owing to the length of the apical dendrite, many synapses are located so distally that, in the absence of any compensation mechanisms, they would have virtually no effect on the somatic voltage (Cauller & Connors 1994; Stuart & Spruston 1998). Not

only is there marked passive attenuation in these neurons, but active currents may further attenuate the signal (see below). Recently experiments have shown that these neurons exhibit a second spike-initiation zone near the main branch point of the apical dendrite (about 500–650 μm from the soma). Investigators have suggested that the distal apical dendritic tree can act as a separate synaptic integration region, having its own separate spike-initiation zone at this location. When the distal compartment crosses the threshold, a dendritic Ca^{2+} spike is initiated, resulting in a huge dendritic depolarization that drives the somatic region to initiate action potentials. In this way the distal compartment communicates with the soma (Larkum et al. 1999b, 2001; Schiller et al. 1997; Williams 2004; Yuste et al. 1994) (**Figure 4**). To some extent this mechanism is also likely to be operational in other types of pyramidal neuron, such as those in hippocampal CA1 (Golding et al. 2002).

Compressive dendritic nonlinearities. Dendrites express not only voltage-gated inward currents, but also they are rich in other classes of voltage-gated currents that counteract regenerative excitation and thus can be thought to be responsible for maintaining the balance of excitability in the dendritic tree. Some of these currents, such as A-type K^+ currents or hyperpolarization-activated inward I_h currents, are located at higher densities in the distal part of the dendrites (Hoffman et al. 1997, Lörincz et al. 2002, Magee 1998, Williams & Stuart 2000; reviewed by Migliore & Shepherd 2002). This arrangement of nonregenerative currents in the dendrites is puzzling because it enhances the attenuation experienced by synaptic inputs. However, in view of the rich complement of excitable currents in the dendrites such mechanisms are likely required to maintain dendritic stability. In addition to their global balancing effect, these currents can take part in more local interactions. One example for such an interaction has been shown for A-type K^+ currents. When a synaptic input is active on a dendritic branch, the depolarization of the branch inactivates A-type K^+ currents in this branch. This in turn facilitates the ability of backpropagating action potentials to invade this branch more easily, which may provide a gating mechanism for plasticity in dendritic branches (Hoffman et al. 1997, Magee et al. 1998).

Coincidence detection. The simplest nonlinear operation is multiplication. In case of binary variables, multiplication is identical to the logical AND operation (the result is 1 if and only if the two inputs are 1), which can also be described in terms of coincidence detection. We have already described how the interaction of excitation and inhibition could implement this operation, but the regenerative inward currents expressed in the dendritic membrane provide numerous alternative mechanisms. These forms of coincidence detection can operate on a highly local scale (down to the level of a few spines) or on the scale of the entire neuron.

Numerous experimental studies have provided evidence that active dendrites can generate local dendritic spikes given synaptic input that is sufficiently clustered in space and time (the latter being the essential requirement for a coincidence detector). Such spikes can be generated by any combination of the voltage-gated regenerative inward currents known to be present in the dendritic membrane. For example, the current driven by NMDA receptor activation is known to be highly voltage dependent. Recently investigators (Cai et al. 2004, Polsky et al. 2004, Schiller et al. 2000) (see **Figure 5**) showed that synchronous synaptic inputs onto the same dendritic branch of layer 5 pyramidal neurons depolarize the membrane and create a positive feedback loop such that the current through the NMDA receptor depolarizes the membrane and recruits more NMDA-mediated current (supported by activation of dendritic Na^+ and Ca^{2+} channels). This all-or-none phenomenon is termed an NMDA spike, and its spatial extent is limited to a short region of the dendrite by active and passive mechanisms. In CA1 pyramidal neurons, a similar local coincidence-detection mechanism exists, based primarily on a different voltage-dependent current (Na^+) (Ariav et al. 2003). These dendritic mechanisms provide the neuron with the ability to detect coincidences in neighboring synaptic inputs on a very fast timescale, previously thought to be restricted to auditory neurons. The same mechanism was previously suggested in models to explain the variability in output spike trains of cortical neurons (Softky 1994).

Dendritic mechanisms also exist for reporting coincident pre- and postsynaptic activity. At distal synapses on the apical dendrite of layer 5 pyramidal neurons, pairing postsynaptic action potentials and synaptic input can trigger highly nonlinear amplification of backpropagating dendritic action potentials via recruitment of voltage-gated Na^+ channels (Stuart & Häusser 2001) (**Figure 3**). A similar supralinear interaction has also been observed in CA1 pyramidal neurons when pairing backpropagating spikes and EPSPs, where the contribution of A-type K^+ channel inactivation is more prominent (Johnston et al. 2000, Magee & Johnston 1997). This form of coincidence detection exhibits a narrow time window (~10 ms), similar to that required for induction of synaptic plasticity when pairing APs and EPSPs, and may thus act as a substrate for the induction of synaptic plasticity.

Finally, in layer 5 pyramidal neurons excitatory synaptic input to the distal apical tuft that coincides with backpropagation of the action potential results in a large dendritic Ca^+ spike, which in turn propagates toward the soma and drives the axon to fire a burst of action potentials (Larkum et al. 1999b, Schiller et al. 1997, Stuart & Häusser 2001) (**Figure 4**). This mechanism thus enables the detection of coincident activation of synaptic inputs to the two major compartments of the dendritic tree, and may thus be involved in reporting simultaneous activity across different cortical layers. This coincidence detection mechanism is potentially tunable, either by changing dendritic geometry or by modulating channel densities and properties (Vetter et al. 2001, Schaefer et al. 2003).

Dendritic subunits: neurons within a neuron. Nonlinear mechanisms in dendrites can vary widely in the spatial extent of the resulting electrical and chemical signals. Some events spread across the entire dendritic tree, whereas others remain very local (Häusser & Mel 2003). Focusing on the local mechanisms, Mel and colleagues (Mel 1993; Poirazi et al. 2003a; Poirazi & Mel 2001; Polsky et al. 2004) have developed a framework that breaks the dendrites into many tiny computational units. The basic nonlinearity in individual branchlets is based on the NMDA spike (Schiller et al. 2000, Schiller & Schiller 2001) and is modeled as a sigmoidal function (**Figure 5**). Each subunit thus integrates its inputs and passes them through a sigmodial nonlinearity function. This gives each piece of dendrite the computational power of a small unit similar to those conventionally used in neural networks. The output of each subunit is conveyed to the soma, in terms of passive dendritic integration. The picture that emerges from this analysis is of a two-layered neuronal network that resides within a single neuron. This analysis is supported by detailed modeling of single neurons, showing that the predictive power of the two-layer neural network description is very good (Poirazi et al. 2003b), and by experiments in layer 5 pyramidal neurons (Polsky et al. 2004). The attractiveness of this approach stems from the fact that two-layer neural networks are general-purpose computation machines, which have been extensively studied and can implement very powerful computations.

This analysis also poses important questions about the way the neuron learns to

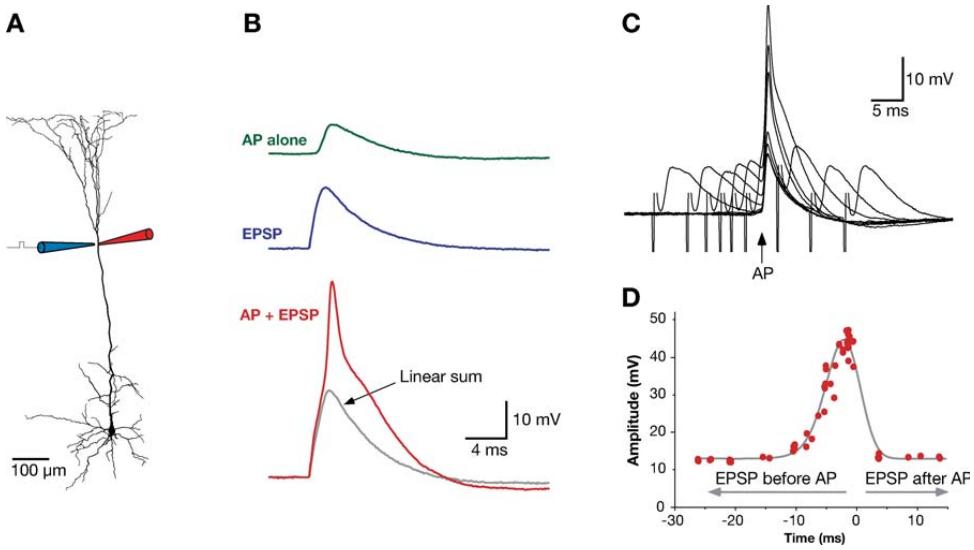
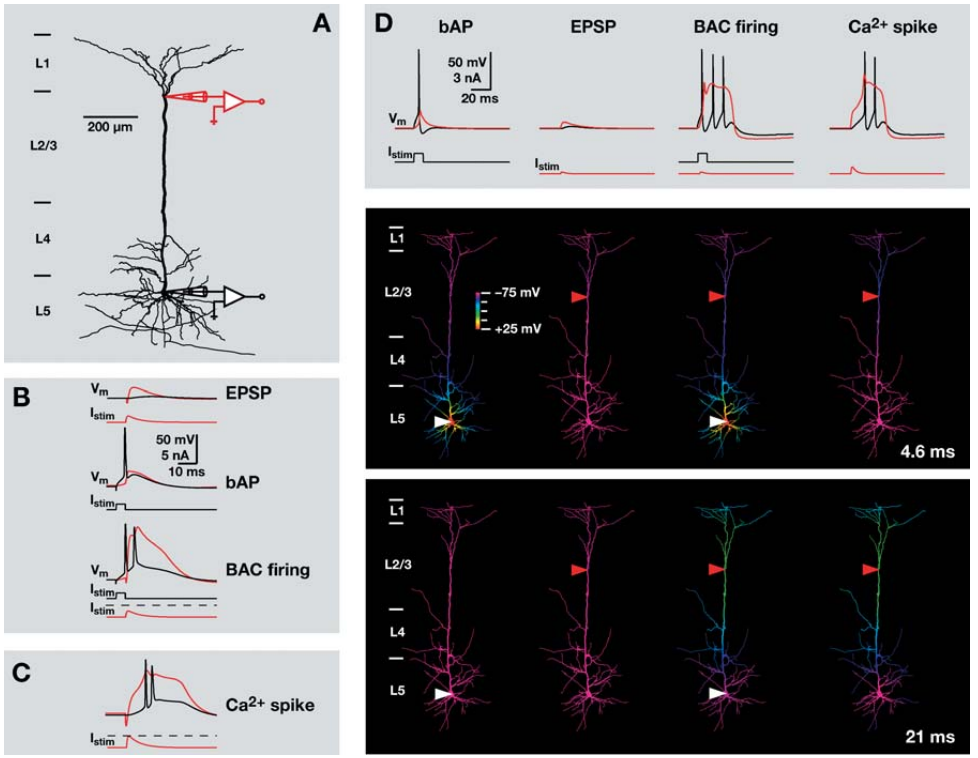


Figure 3

Coincidence detection of EPSPs and action potentials. (A) Schematic illustration of the recording configuration. A dendritic recording (red pipette) is made from the distal apical dendrite of a layer 5 pyramidal neuron, and synaptic input local to the recording site is activated with a stimulation electrode (blue pipette). (B) Top trace: backpropagating action potential initiated by somatic current injection (2.5 nA) recorded 720 μm from the soma. Middle trace: evoked EPSP recorded at the same dendritic location. Bottom trace: response to pairing the backpropagating action potential with the EPSP ("AP + EPSP"). For comparison, the linear sum of the action potential plus EPSP is also shown (grey trace). Stimulus artifacts are blanked for clarity. (C) Superimposed sweeps of evoked EPSPs at different times before and after action potentials initiated by somatic current injections (1.5 nA) at the time indicated by the arrow. Dendritic recording 480 μm from the soma. (D) Plot of action potential amplitude (measured at the time of action potential peak) versus the time difference between EPSP and somatic action potential onset (same cell as in C). The time of somatic action potential peak is defined as zero; negative time corresponds to when EPSPs were evoked before action potentials, and positive time corresponds to when EPSPs were evoked after action potentials. The smooth line is the fit with a skewed Gaussian. Modified from Stuart & Häusser (2001).

compute its input-output function. In this review we must assume that neurons are learning to compute what they compute. The leading theory for how this is achieved is Hebbian plasticity (Hebb 1949). But if dendrites are implementing these nonlinear subunits, Hebbian plasticity will not exploit the power of this model. Plasticity will help to drive learning within each individual subunit, but the number of inputs in each of these units is small and it is not clear how the relevant inputs will get there in the first place. Poirazi & Mel (2001) have proposed a learning algorithm by which synaptic connections are continuously remodelled until they hit the correct dendritic subunit. They show that such a learning algorithm implemented in a dendritic tree can be much more powerful than the Hebbian learning scheme. Although there exists conflicting evidence for ongoing remodeling of synaptic inputs in the adult brain (Grutzendler et al. 2002, Holtmaat et al. 2005, Mizrahi & Katz 2003, Trachtenberg et al. 2002), it is still an open question whether this algorithm indeed is implemented in real neural circuits. Other challenges for the model are its integration with the dendritic tree. All the model is currently taking from the dendritic tree is the ability to have independent subunits. However, it ignores global nonlinearities and modulations evident in the dendrites. Moreover, in a two-layer neural network, the coefficients from each unit in the first layer to the next are modifiable. Here, in comparison, they are fixed and determined by the dendritic tree. Finally, although the two-layer neural network model reliably predicts the steady-state firing rates of the pyramidal neurons, it neglects the temporal properties of spike firing that have been closely linked to dendritic excitability (e.g., Ariav et al. 2003, Larkum et al. 1999b).

Chemical computation. The expression of voltage-gated calcium channels in the dendritic membrane (Migliore & Shepherd 2002) immediately provides a biochemical readout of electrical excitability. In particular, dendritic calcium signals activated by backpropagating action potentials reliably encode the level of axonal spike firing in apical dendrites of pyramidal cells. This therefore provides a "frequency code" where firing rate is read out using a dendritic biochemical signal (Helmchen et al. 1996). This readout can also have a nonlinear frequency dependence if it involves activation of a dendritic calcium spike (Larkum et al. 1999a). The calcium signal can in turn activate voltage-gated potassium currents, thus acting as a feedback regulator of excitability, which changes the



input-output gain of the neuron (Sobel & Tank 1994) (see below). A similar readout of dendritic excitability can be provided by intracellular dendritic Na^+ signals (Rose & Konnerth 2001), which may in turn regulate excitability via activation of Na^+-activated K^+ channels.

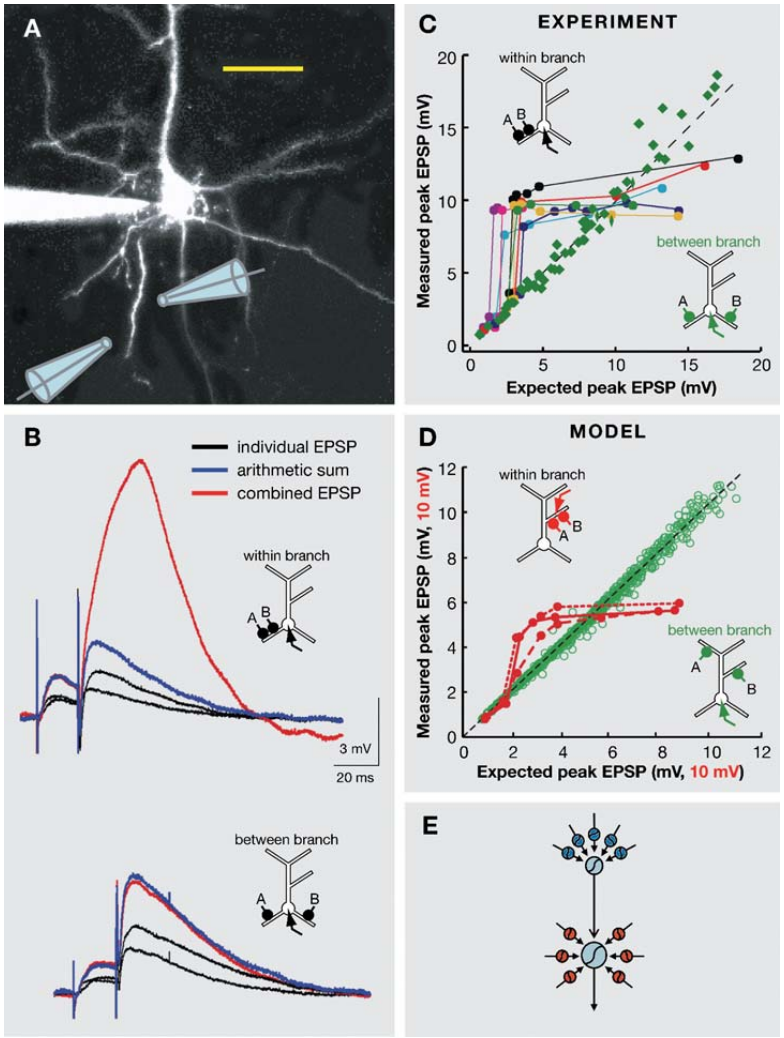
Whereas the various regenerative dendritic mechanisms for coincidence detection discussed above will also be read out via voltage-gated calcium channels to generate large dendritic calcium signals, the biochemical intracellular signaling pathways in dendrites may themselves contribute to coincidence detection in unique ways. For example, the IP3 receptor is cooperatively activated by both calcium and IP3, which allows for coincidence detection of calcium and IP3 delivered by different sources, such as action potentials and synaptic mGluR activation (Nakamura et al. 1999, Wang et al. 2000). This form of coincidence detection can be spatially segregated to particular types of dendrite (Nakamura et al. 2002). A further mechanism for coincidence detection and/or intracellular calcium amplification can be implemented via dendritic calcium-induced calcium release from stores (Emptage et al. 1999). Finally, the lowly calcium-buffering proteins localized in dendrites may themselves allow for a simple form of coincidence detection, generating a supralinear dendritic calcium signal by buffer saturation (Maeda et al. 1999). The large calcium signals generated by these different forms of coincidence detection can remain highly localized (Wang et al. 2000), or they can spread to other regions of the dendritic tree, assisted by further regenerative calcium release from stores (Larkum et al. 2003, Nakamura et al. 2002). Barlow proposed that such processing by intracellular networks can implement a second layer of computation coupled to, but semi-independent from, the electrical signaling in the plasma membrane (Barlow 1996). Such a "two level" arrangement could have enormous computational power, which is only beginning to be explored.

Figure 4

Coincidence detection across dendritic compartments. (A) Reconstruction of a layer 5 pyramidal neuron; the locations of recording pipettes (soma, black; dendrite, red) are depicted schematically. (B) Distal current injection of 1.1 nA in the shape of an EPSP (I_{stim}, red) evoked only weak somatic (black) depolarization (upper panel). Threshold current injection (5 ms) into the soma (black) produced an AP that propagated back into the apical dendritic arbor (backpropagating action potential, bAP, red trace, middle panel). Combination of somatic and dendritic current injection generates several somatic APs and a dendritic Ca^{2+} spike (backpropagating action potential–activated Ca^{2+} spike firing, BAC firing; lower panel). The dashed line indicates the current threshold for a dendritic Ca^{2+} spike alone. (C) A dendritic Ca^{2+} spike was evoked by 2 nA current injection into the apical dendrite alone. Thus, the bAP reduced the threshold for dendritic Ca^{2+} spike by 0.9 nA (45% coupling). (D) A model of channel density distributions and kinetics was constructed to reproduce BAC firing in reconstructed model neurons (Schaefer et al. 2003). The electrical response of the reconstructed model neurons to dendritic and somatic current injection was investigated using the same protocols as in the experiment (A–C). (Upper panels) bAP: Threshold somatic current injection evoked a bAP (I_{stim} = 1.9 nA). EPSP: Distal EPSP-like current injection was adjusted to BAC firing threshold, which was 0.6 nA. Only a small somatic depolarization can be detected ($\Delta V \leq 2.5$ mV). BAC firing: Pairing the bAP with the dendritic EPSP-like current injection resulted in a large and long-lasting dendritic depolarization. Ca^{2+} spike: Large distal EPSP-like current injection (1.7 nA) elicited a Ca^{2+} spike. Thus, the bAP reduced the threshold for dendritic Ca^{2+} spikes by 1.1 nA, which resulted in a coupling of 1.1 nA/1.7 nA = 65%. Voltages were measured at the positions indicated by triangles in lower panels; (red: dendritic recording/current injection; black: somatic recording/current injection). (Lower panels) Same as upper panels but showing membrane potential in the entire dendritic tree. Voltages are color coded as indicated in the upper left. The position of current injection is indicated by the red (dendritic) and white (somatic) arrowheads. At the time of AP initiation (4.6 ms after the beginning of the somatic current injection), depolarization due to the bAP has already spread into the apical dendrite (in the case of bAP and BAC firing). After 21 ms, the voltage deflection due to the bAP has decayed back to baseline. Note that the spread of depolarization is almost the same for a dendritically elicited Ca^{2+} spike and BAC firing. Modified from Larkum et al. (1999b) and Schaefer et al. (2003).

EXAMPLES OF REAL-WORLD DENDRITIC COMPUTATION

In the previous section we described how the passive and active properties of the dendrites can endow them with computational features. The key question, of course, is whether the



brain takes advantage of these building blocks to perform computations. It is extremely difficult to show directly that a particular computational strategy is both necessary and sufficient to explain the computational behavior of networks. However, a few favorable cases have provided strong circumstantial evidence for dendritic computation playing a key and possibly essential role in computations performed by a neural network.

Directional Selectivity

Perhaps the most extensively studied computation on the single-cell level is direction selectivity. Direction-selective neurons respond to image motion in a preferred (PREF) direction but not in the opposite NULL direction. They can be found in many species from fly eyes to mammalian cortex, and in all these cases a role for dendritic computation has been proposed. One of the first and most convincing experiments demonstrating dendritic involvement in directional selectivity was provided by Single & Borst (1998). Using imaging of dendritic calcium signals in tangential cells of the fly visual system in vivo, they showed that the input to each dendritic branch, and thus the resulting dendritic calcium signal, is already directional selective, but the dendritic filtering is required to maintain a coherent response free from spatial pattern properties of the visual scene to ensure a purely direction-selective output signal in the axon.

In this section we focus on work on the direction-selective retinal ganglion cells (DSGC) described by Barlow & Levick (Barlow et al. 1964, Barlow & Levick 1965) as a case study for dendritic computation. Rall (1964) provided the first model for how dendrites can implement a directionally selective unit (**Figure 6**A). The idea is very simple: Synaptic input generated on the distal part of the dendrite is delayed at the soma by the dendritic filtering compared with proximal input. If synaptic inputs are activated in a sequence starting from the distal location of the dendrite toward the soma (the centripetal direction), then the EPSPs in the soma will sum effectively and the resulting somatic voltage would be large. In contrast, activating the same inputs in the centrifugal direction would result in a much lesser degree of summation because the proximal EPSP will decay by the time the distally originated EPSP will arrive. Assuming that the voltage peak is translated into action potentials, the neuron will show directional selectivity. Although the mechanism proposed is clearly feasible, there

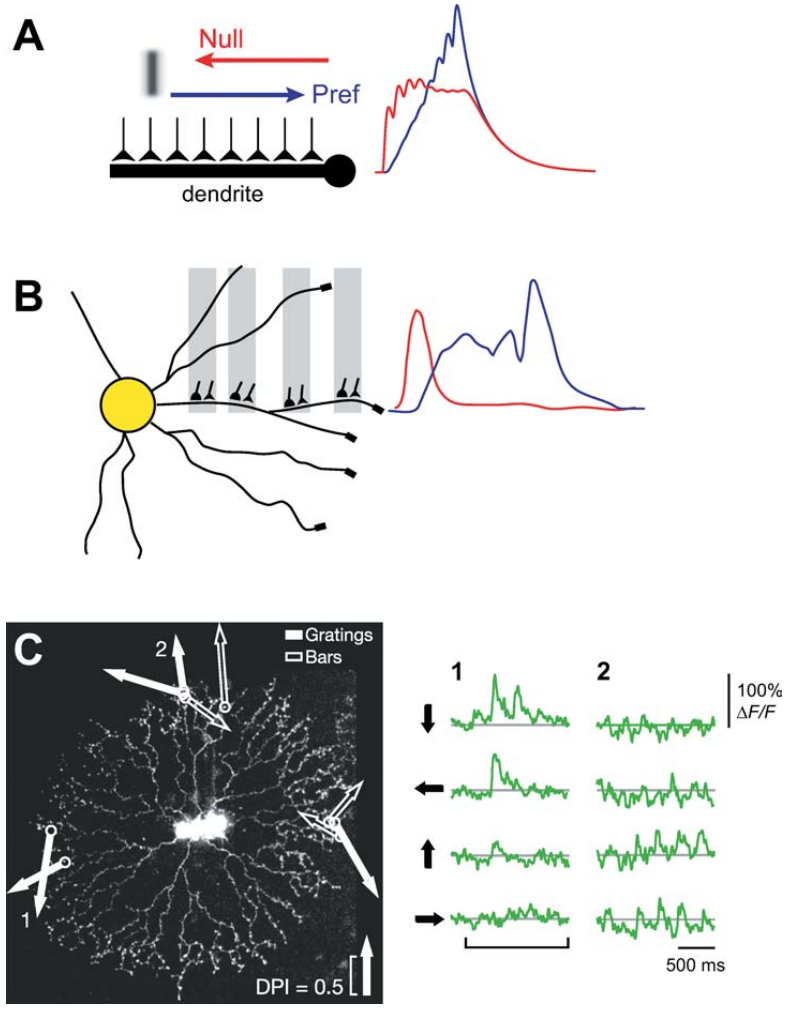


Figure 5

Dendritic multiplication in pyramidal cell dendritic branches. (A) Two stimulating electrodes were positioned near selected basal dendrites of a layer 5 pyramidal neuron filled with the calcium-sensitive dye Oregon Green BAPTA-1 (200 μM). A dendritic branch was visualized using a confocal microscope, and two stimulation electrodes were positioned in close proximity to the selected branch (blue). Scale bar, 75 μm. (B) Electrodes were activated first individually (black traces) and then simultaneously (red traces), and somatic EPSPs were recorded. Blue traces show the arithmetic sum of the two individual responses. Voltage traces are averages of four individual sweeps. Left traces show within-branch summation. The two electrodes were positioned near the same dendritic branch, separated by 20 μm (150 μm from the soma). Right traces show between-branch summation, where the two electrodes stimulated different branches and summation was linear. (C) Summary plot shows predicted versus actual combined responses in seven basal dendrites and one apical oblique dendrite (pink curve). Colored circles show sigmoidal modulation of within-branch summation (blue and yellow, without bicuculline to block GABAergic inhibition; dark green trace, with locally applied 10 μM bicuculline; five remaining traces, 1 μM bicuculline). Dashed line denotes exact linear summation. Green diamonds show between-branch summation experiments (12 branch pairs, 4 of them apical oblique dendrites). (D) Modeling data: Summation of single-pulse EPSPs in the apical oblique dendrites of a CA1 pyramidal cell model showed a similar overall pattern (Poirazi et al 2003a), including sigmoidally modulated within-branch summation (red circles) and linear between-branch summation (open green circles). Within-branch data for dendrites are attached to the apical trunk 92 μm (short dashes), 232 μm (solid), and 301 μm (long dashes) from the soma. Because of the uneven distances to the somatic recording electrode, recordings shown were made within the respective dendrite; for these data, axis values are scaled up 10, thus 0 mV, 20 mV, 40 mV, and so on. Modified from Polsky et al. 2004. (E) Schematic representation of a speculative neural network model based on the data shown in A–C and **Figure 4** (see also Häusser & Mel 2003). Blue branches represent the distal apical inputs, and red branches denote the basal inputs. Together, these inputs constitute the first layer of the network model, each performing supralinear summation of synaptic inputs as shown in B (small circles with sigmoids). The outputs of this first layer feed into two integration zones: one near the apical tuft (top) and one near the soma. These integration zones constitute the second layer of the network model (large circles with sigmoids).

is currently little direct evidence to support this model in cases where directional selectivity has been found (Anderson et al. 1999, Euler et al. 2002).

An ongoing debate exists about identifying the earliest level of neurons that show directional selectivity. Koch et al. (1982) proposed that the nonlinear interaction between the excitation and inhibition can explain directional selectivity in retinal ganglion cells. The essential assumption was that there is an asymmetry in the spatial distribution of inhibitory and excitatory inputs to the cell such that the inhibition biased and shifted to the NULL direction. In this way when the inputs are sweeping through the receptive field in the PREF direction the excitation is acting before the inhibition and the integration of excitatory inputs cause the neuron to respond. If the input moves in the NULL direction, then the inhibition is "on the path" of the excitation and vetoes it, preventing the neuron from responding. Recently, Taylor et al. (Taylor & Vaney 2002) showed, using intracellular recording from direction-selective retinal ganglion cells (DSRGC), that indeed such asymmetry in the inhibition exists, but these results are debatable (see also Borg-Graham 2001, Fried et al. 2002, Taylor & Vaney 2000).

The other possibility is that the input to the DSRGC is already direction selective. Using similar assumptions to the model by Koch, Borg-Graham & Grzywacz (1992) (**Figure 6**B) showed that the directional selectivity could be computed in the individual dendritic branches of starburst amacrine cells (SBAC), which are presynaptic to the retina ganglion cells. These cells do not have appropriate axons; rather each dendrite has an "output" synapse at its distal end. By using two-photon optical imaging of Ca^{2+} concentrations in the dendrites of SBAC, Euler et al. (2002) showed that indeed the Ca^{2+} concentration at the tip of the dendrites of SBAC is direction selective (**Figure 6**C). However, in contrast to the model, the response is still selective in the presence of $GABA_A$ blockers. In summary, it seems that directional selectivity is indeed computed by individual dendrites of SBAC, but the mechanism by which it is computed is still not fully understood.

Coincidence Detection in Auditory Neurons

Another system in which the contribution of the dendrites to computation has been demonstrated is the sound localization system of chicks (Agmon-Snir et al. 1998). In this system a special type of neuron is responsible for computing the time difference between sounds arriving to the two ears. Each neuron responds only to a very precise time difference, which corresponds to a specific location in space. The neurons contain only two major dendrites, and each dendrite receives inputs only from one ear. The inputs are supposedly arranged in such a way that there is a constant delay between the inputs arriving from one ear and the inputs arriving from the second. Coincident inputs from both ears arriving to the two dendrites are summed up at the soma and cause the neuron to emit action potentials. However, when coincident spikes arrive from the same ear, they arrive at the same dendrite and thus their summation is sublinear, resulting in a subthreshold response (**Figure 1**A). Moreover, Rubel and colleagues (Smith & Rubel 1979) showed that there is an inverse relationship between the preferred frequency of the neurons and their dendritic length, supporting the hypothesis that the dendrites are directly contributing to the computation. This is in agreement with the model because for high-frequency inputs the dendritic filtering causes accidental spikes that are out of phase to summate and cross the threshold. Thus the advantage of the dendrites in the low-frequency range becomes a burden in the high-frequency range, and the auditory coincidence detection neuron is better off with shorter dendrites.

Temporal Integration Over Long Timescales

All the computations discussed above take place on relatively short timescales; the neuron responds almost instantaneously to the input. Computations over longer timescales, such as those required for working memory, are usually attributed to network phenomena or involving molecular dynamics. In this context, computation of time integration becomes a challenging problem. How does a system integrate transients and maintain the computed integral for a long period, far longer than its intrinsic time constant? One example of such a system is the oculomotor system in the goldfish, where neurons maintain stable firing rates corresponding to the position of the eye and switch between them rapidly when saccades occur. Although previous work has focused largely on network explanations for such forms of time integration, dendritic mechanisms (Brody et al. 2003) in single neurons may also contribute. In particular, one intrinsic mechanism that could be involved in such a phenomenon is bistability. This is a property of a dynamical system exhibiting more than one stable point. Once driven to approach a stable point, it stays there. Neurons expressing specific types of voltage-gated ionic currents, for example, can show bistability. Some indirect evidence for dendritic bistability exists (Booth & Rinzel 1995, Milojkovic et al. 2004). Recently, Loewenstein & Sompolinsky (2003) presented a model in which a specifically dendritic bistability enables the dendrite to become a time integrator. In this model, the dendritic concentration of Ca^{2+} is bistable. If at one end of the dendrite it is forced to be in the up state, and at the other edge to be in the down state, then a standing wave of Ca^{2+} concentration is created. The location of the wavefront represents the result of the integral such that incoming transient synaptic input repositions the location of the front. As long as no input arrives, the front will keep its position and the dendrite will preserve the "working memory." A related study, based on an earlier model (Rosen 1972), has been proposed on the basis of dendritic bistability involving voltage-sensitive conductances (Goldman et al. 2003).

Image Processing in Dendrites of Fly Neurons

A key component of visual information processing by the fly nervous system is convolution, whereby an image is smoothed to remove noise and improve extraction of salient features. This operation is thought to be performed by a group of neurons in the lobula plate in the third visual ganglion known as the horizontally sensitive tangential cells. These

Figure 6

Dendritic mechanisms for directional selectivity. (A) A linear model exploiting the filtering properties of passive dendritic cables. When the input advances to the right (the preferred direction), the first EPSPs are widened by dendritic filtering, which gives time for the later input to sum temporally and build a large voltage response. When the input moves in the null direction, the first large EPSP decays by the time the last EPSP arrives at the soma, and a smaller peak response is achieved. Note that this mechanism is not very robust because the difference in peak amplitude between the two scenarios is small, and the time integral of the voltage (corresponding to the total amount of charge) is identical. (B) A model of the starburst amacrine cell in the retina (Borg-Graham 1992). The input to each amacrine dendrite is composed of excitatory and inhibitory inputs that have symmetric receptive fields. Although the starburst cell is radially symmetric, the symmetry breaks with respect to the direction-selective circuit because the outputs to the directionally selective ganglion cells are on the distal tip of each dendrite. Furthermore, these outputs are formally direction selective, in the sense that the integral of the response depends on direction, because of the nonlinear interaction between excitation and inhibition, as described by Rall (1964) and Koch et al. (1982). (C) Imaging of internal Ca^{2+} concentration from dendrites of starburst amacrine cells shows that these dendrites are indeed direction selective (Euler & Denk 2002). The experiments are not consistent with the mechanism in A, but they do not completely agree with the model in B either, because blocking $GABA_A$ receptors retains some of the directional selectivity.

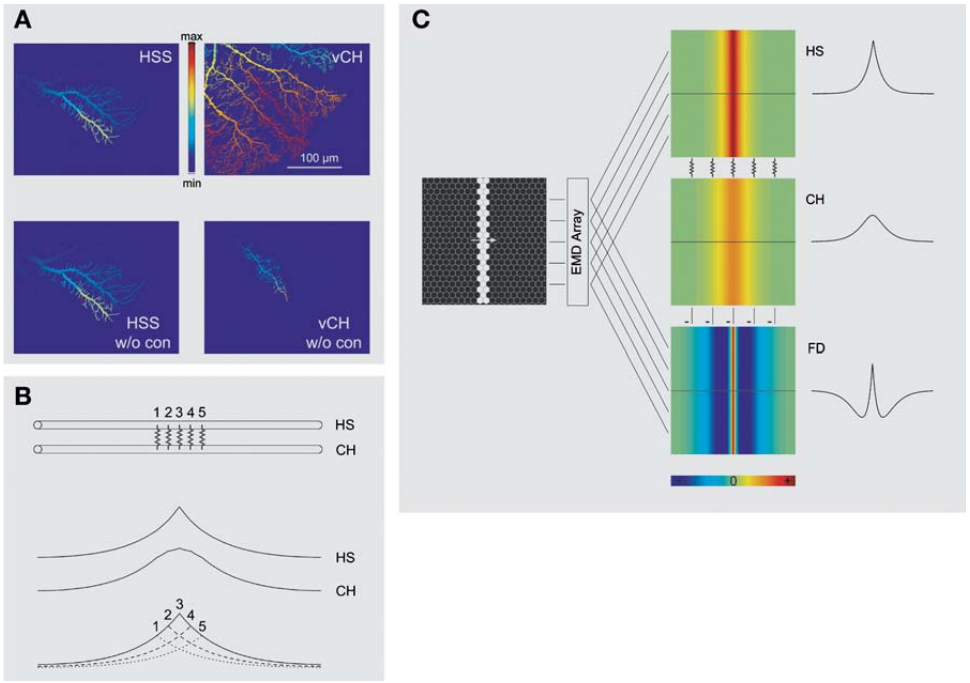


Figure 7

Image processing in visual interneurons of the fly. (A) Top: Spread of membrane potential in a model of neurons, which are horizontally sensitive of the southern area of the visual field (HSS) (left) and ventral centrifugal horizontal cells (vCH) model (right) after local current injection into HSS. Bottom: same as top panels, but HSS and vCH models were not connected to each other. Current was injected in HSS (left) and vCH (right). (B) Simplified model of HS and CH neurons. Top: Two cylinders (HS and CH) are connected by five linear conductances surrounding the location of current injection. Middle panel: in HS, the signal spreads with an exponential decay. The CH spread is broader. Bottom panel: The CH spread can be approximated by the sum of passive spread through each conductance. (C) Consequences of the CH cell dendritic image blurring for relative motion detection. An array of elementary motion detectors computes the image motion in a retinotopic way, feeding onto the dendrites of HS and figure-detection (FD) cells. This motion representation is blurred in the dendrites of the CH cell via dendro-dendritic connections between HS and CH cells. By conveying inhibitory dendro-dendritic input to FD cells, being subtracted from the retinotopic input, an enhancement of the motion edges is achieved. Modified from Cuntz et al. 2003.

neurons respond to visual motion in a directionally selective way and can be divided into two groups of neurons: the horizonal system (HS) cells and the centrifugal horizonal (CH) cells. Specific CH cells, the ventral CH (vCH) cells, are electrically coupled via dendritic gap junctions to HS cells. Retinotopic input to HS cells is already filtered by the electrotonic decay of membrane potential in HS cell dendrites. As shown in **Figure 7** (Cuntz et al. 2003), the coupling via gap junctions then imposes the filtered membrane potential of the HS cell onto the CH dendritic tree, where another round of low-pass filtering takes place. The end result is a blurred and de-noised version of the original image. Thus, the biophysical properties of dendritic trees can implement non-trivial image processing operations in a simple and elegant manner.

Looming Sensitive Neurons in the Locust

The lobula giant movement detector (LGMD) is an identified neuron in the locust visual system whose output firing rate is most sensitive to objects approaching a collision course (looming visual stimuli), indicating a forthcoming collision (**Figure 8**). The timing of the peak firing rate comes with a fixed delay after the time at which a looming object reaches a fixed-threshold angular size, on the retina, independent of the object's approach speed or size (Gabbiani et al. 1999, 2004). A mathematical model supported by experimental results predicts that this behavior could be explained as a multiplication of two parameters of the approaching object, namely its angular size and speed of approach (Gabbiani et al. 2002). The LGMD neuron has a unique dendritic structure composed of a fan-like tree and two additional sub trees. The synaptic input is segregated such that excitatory, motion-sensitive input arrives on the major fan-like tree, and inhibitory size-sensitive inputs arrive in separated ON/OFF channels at the remaining two subtrees. The multiplication is thought to be implemented such that each of the relevant parameters is encoded logarithmically in one of these subtrees, and the dendritic sum of the two types of inputs results with the sum of logarithm (corresponding to the logarithm of the multiplication). The spiking mechanism on this combined input implements an approximate exponentiation that inverses the logarithm, and the result of the multiplication is thus encoded in the firing rate. The accessibility of the LGMD neuron to dendritic recordings and optical imaging in vivo makes it a promising candidate for understanding the biophysics of a high-level computation in dendrites in the near future.

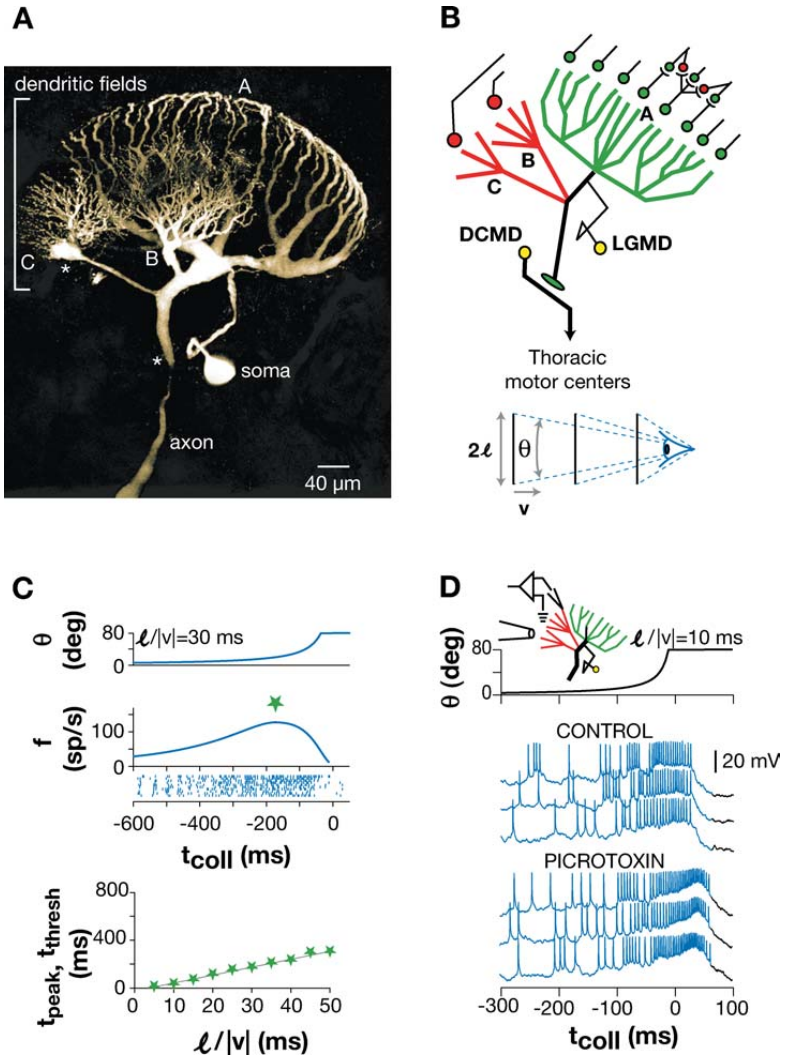
Forward Masking of Cricket Songs

Omega neurons in female crickets respond to the male calling song with bursts of action potentials. The response of an omega to a particular sound can be dramatically attenuated if it is preceded by an identical but louder sound. This suppression is known as

Figure 8

Computation in dendrites of locust looming-sensitive neurons. (A) The LGMD neuron's dendritic tree consists of three distinct subfields (A–C). Subfield A receives motion-sensitive excitatory inputs, whereas subfields B and C receive phasic inhibition related to object size. As in many invertebrate neurons the soma lies outside the electrical signal propagation path, and spikes are generated at the point where the axon is thinnest. (B) Schematic illustration of the neuronal inputs received by the LGMD. Postsynaptic inhibitory regions of the LGMD are illustrated in red and excitatory ones in green. Green and red dots represent inhibitory and excitatory synapses, respectively. Yellow dots indicate cell bodies. Bottom: A solid object of size 2ℓ is approaching the animal on a direct collision course with a constant velocity v. The angle subtended by the object is represented by θ. (C) Top panel shows the time course of θ for the looming stimulus, and the middle panel shows individual spike trains of the LGMD neuron in response to repetitions of this stimulus. The blue line above the spike trains represents the average instantaneous firing rate, and its peak is marked by a star. Bottom: The relation between the peak firing time relative to collision as a function of $\ell/|v|$ is nearly linear. This is equivalent to the angular size subtended by the object being a fixed constant δ ms prior to the peak, independent of the stimulation. This angular size is typically in the range of 15°–35°. Thus, LGMD's peak firing time acts as an angular threshold detector. (D) Top three traces are intracellular dendritic recordings in response to a looming stimulus, and bottom three traces show the response after picrotoxin injection to the lobula. Picrotoxin prolongs the responses, and the peak firing rate no longer predicts collisions. Adapted from Gabbiani et al. 2004.

forward masking and represents a simple form of gain control, allowing the female cricket to focus on the loudest male in the presence of multiple competing males. Sobel & Tank (1994) have shown that biochemical dendritic signaling underlies this simple computation. By imaging dendritic calcium signals in omega neurons, they showed that a loud simulated calling song triggers a large, long-lasting dendritic calcium transient associated with a potassium conductance that suppresses excitability. The time course of the calcium signal was tightly correlated with the time course of forward masking. To demonstrate a causal relationship, Sobel & Tank showed that buffering dendritic calcium prevents the hyperpolarization and reduction in excitability. They also demonstrated that uncaging calcium in the dendrite produces a similar hyperpolarization and dampening of excitability to that generated by the sound. These findings demonstrate how dendritic mechanisms—conversion of action potentials into a calcium signal and then activation of a potassium conductance—can be directly linked to a computational task relevant to behavior.



Dendritic Mechanisms and Behavior

Two recent pioneering experimental studies have opened the door for exploring dendritic function of mammalian neurons in an entirely new framework. By using molecular techniques to manipulate dendritic ion channels in transgenic animals, Nolan et al. (2004) and Bernard et al. (2004) have demonstrated that it is possible to link the excitable properties of distal dendrites with network-level and behavioral phenomena. Bernard et al. (2004) demonstrated that in an animal model of temporal lobe epilepsy, the excitability of CA1 pyramidal cell dendrites is enhanced by downregulation of dendritic A-type K^+ channels by phosphorylation, combined with reduced expression of these channels. Although the evidence remains indirect, the enhanced dendritic excitability associated with this channelopathy may contribute to the observed reduction in seizure threshold in the hippocampus.

Nolan and colleagues (2004) generated a transgenic mouse with a forebrain-restricted deletion of the HCN1 gene, which encodes the hyperpolarization-activated cation current I_h. These mice exhibit enhanced performance in hippocampal-dependent learning and memory tasks. On the cellular and network level, the mice demonstrate enhanced theta oscillations and LTP. Because previous work has demonstrated that HCN1 channels are highly concentrated in the distal dendrites of CA1 pyramidal neurons (Magee 1998), the authors examined integration of proximal and distal synaptic input to CA1 pyramidal neurons. They demonstrated that distal perforant path synaptic inputs are selectively enhanced in the HCN1 knockout and that LTP of these inputs is also enhanced, whereas LTP at the more proximal Schaffer collateral input is unchanged. These results provide some of the best available evidence linking integration of distal dendritic synaptic input with behavior and point to the importance of independent regulation of excitability in subcompartments of the dendritic tree.

CHALLENGES FOR THE FUTURE: A WISH LIST FOR DENDRITIC COMPUTATION

The ultimate challenge for those interested in dendritic computation is to show that computation conveys a significant advantage in the operation of real neural circuits. This advantage is difficult to show directly, given that dendrites also have other properties not directly related to computation, such as their important structural role in determining brain wiring (Chklovskii 2004). Here we outline several of the key challenges faced by experimenters working at different levels to understand the contribution of dendrites to computation in the mammalian brain.

For Molecular Biologists: Designer Dendrites

To manipulate the computational properties of dendritic trees, we want to be able to manipulate dendritic shape and the spatial distribution and properties of voltage-gated channels using genetic tools. The molecular regulation of dendritic growth and shape has become a burgeoning field over the past decade, and many kinases have been identified that can be regulated to produce changes in dendritic form (Scott & Luo 2001). In parallel, our understanding of ion channel trafficking

regulation and the local synthesis of ion channels in dendrites has also made substantial progress (Horton & Ehlers 2003, Misonou et al. 2004, Misonou & Trimmer 2004). Within the next decade it should be possible, using transgenic and viral techniques, to selectively modify single neurons or entire populations of neurons to generate dendritic subunits with defined shapes and electrical properties. Such "designer dendrites" can be used to identify the role of specific dendritic mechanisms, such as action potential backpropagation, for the function and formation of specific neural networks and ultimately can serve as a well-defined bridge between molecules and behavior.

Many dendritic mechanisms require that specific kinds of synaptic input are addressed to specific regions of the dendritic tree or furthermore require that synaptic inputs are highly spatially clustered. Although there is already considerable evidence from decades of anatomical work that precise spatial targeting of certain kinds of synaptic inputs is achieved in some cell types (Freund & Buzsaki 1996, Somogyi et al. 1998), identifying the molecular mechanisms responsible for such targeting will be very important for understanding how synaptic connectivity interacts with and defines dendritic computational mechanisms (Ango et al. 2004). It will be of great interest to harness these mechanisms to identify and manipulate the spatial arrangement of specific types of synaptic inputs to the dendritic tree. These mechanisms could be exploited first to label inputs selectively conveying different streams of information. This will allow us to test directly to what extent inputs carrying similar or divergent information are clustered on neighboring stretches of dendrite, or whether targeting is essentially random on the scale of microns to dozens of microns. Second, once patterns of spatial clustering have been identified, then by manipulating molecular mechanisms it may be possible to disrupt or redirect such clustering in a defined way to permit causal links to be made between the local nonlinear computations described above and behavior.

HOW CAN WE PROVE THAT DENDRITES ARE INVOLVED IN COMPUTATION?

Proving that dendrites are both necessary and sufficient for a particular computation relevant to behavior is a very difficult challenge. Necessity is within reach for the relatively simple case where the computation is accomplished by a single identified neuron, as is the case for some invertebrate sensory neurons (see text) or when the underlying biophysical mechanism depends on a single channel type. Demonstrating sufficiency is much more difficult, particularly because dendritic computation is a process that is tightly interlinked with the proper functioning of the entire system. Nevertheless, we outline here a list of objectives that must be achieved to prove that dendrites are required for computation. These should not necessarily be addressed in a linear sequence; rather, it will be beneficial to attack these problems in parallel.

Identify the Computation:

Probing the contribution of dendrites to computation is possible only when the computation of the neuron bearing the dendrites is identified. This requires identifying a simple behavior that involves a recognizable kind of computation (e.g., filtering, convolution, pattern recognition) and tracing it to the neurons responsible.

Defining the Mechanism:

Use recordings (e.g., electrophysiological or imaging) from dendrites of these neurons in an accessible preparation (e.g., brain slices) to define the dendritic signals and biophysical mechanisms that may underlie the behavior.

Correlation in the Intact Preparation:

Use recordings from dendrites in an intact preparation to show strong correlations between dendritic signals linked with the identified computation and the behavior of the animal.

Manipulation to Define a Causal Link:

Manipulate a dendritic mechanism to determine if it is both necessary and sufficient to explain the computation. Selectively knock out the mechanism and demonstrate that the behavior is impaired. Activate or modify the dendritic mechanism to demonstrate that the behavior is modified in the expected direction.

Modeling the Computation:

Use modeling to define an algorithm that describes the computation, or sequence of computations, performed by the dendrites that can plausibly explain the behavior. Modeling of single neurons and neural networks can also be used to confirm that the computation can convey a significant benefit (which can help to establish sufficiency).

bAP: backpropagating action potential

CH: centrifugal horizontal

DSGC: direction-selective retinal ganglion cells

EPSP: excitatory postsynaptic potential

$GABA_A$: γ-aminobutyric acid type A

HS: horizontal system

LGMD: lobula giant movement detector

NMDA: N-methyl-d-aspartate

SBAC: starburst amacrine cells

VCH: ventral centrifugal horizontal

For Neurophysiologists: Putting Dendrites Back into the Network

Most of our understanding of dendritic function has come from studies in isolated preparations (brain slices and culture preparations). Although this approach has been very successful in defining the biophysical basis of dendritic excitability and identifying computational subunits in neurons, it is associated with two main problems. First, the baseline conditions in these preparations are often very different from those pertaining in the intact brain, where the presence of high levels of background synaptic input can fundamentally change dendritic processing (Destexhe et al. 2003, Williams 2004). Second, the technical limitations imposed by slice experiments, together with uncertainty about the spatiotemporal pattern of synaptic inputs to single neurons in the intact brain, have made it difficult to identify which of the many mechanisms studied in vitro are also operating in vivo and may actually be relevant for computation in the intact brain. Fortunately, it is now possible to investigate dendritic function directly in vivo. Both electrophysiological (Buzsaki & Kandel 1998, Kamondi et al. 1998, Larkum & Zhu 2002, Loewenstein et al. 2005) and optical (Helmchen et al. 1999, Svoboda et al. 1999, Waters et al. 2004) techniques now exist for recording electrical and chemical dendritic signaling in anesthetized and awake, head-restrained animals. The prospect of using two-photon imaging techniques to monitor dendritic signaling in freely moving animals (Helmchen et al. 2001) should permit correlations to be established between dendritic events associated with computation (e.g., dendritic spikes) and behavior. In combination with the molecular tools outlined above and new tools for noninvasively manipulating neuronal activity in defined populations (Fetcho & Bhatt 2004, Lima & Miesenböck 2005), it should be possible to identify the causal links between dendritic computation and behavior.

For the Theorist: Proving the Benefits of Dendritic Computation

Ultimately, understanding the role of dendrites in neural computation requires a theory. This theory must identify the benefits of having dendrites and reveal the basic principles used to provide these benefits. To make advances toward such a theory, efforts should be made in three major directions. First, we need to construct algorithms based on the dendritic toolkit and show how specific computations can be achieved, making predictions that are experimentally testable (e.g., Agmon-Snir et al. 1998). Second, given that realistic modeling of single neurons has reached a relatively mature phase, we need to take advantage of the capability of such models to simulate conditions that are very difficult to test experimentally. One important task is to explore how different components of the dendritic toolkit interact with each other (e.g., how do local interactions between excitation and inhibition influence local dendritic spikes?). It is also essential to use these models to see how realistic conditions, such as noise, neuromodulation, and adaptation, affect the computational properties of the dendrites. It is a major challenge to understand how stability of the algorithmic computation can be maintained in the face of these variables, such that it is resistant to them or such that these variables can be synergistically exploited. The third challenge is to put dendrites back into networks. This will be greatly aided by the construction of reduced models of dendritic neurons (e.g., Rall 1964, Pinsky & Rinzel 1994) which capture essential features of dendritic function that could be exploited for computation. The ultimate step will be to build artificial neural networks incorporating such reduced models of the single neuron to demonstrate to what degree dendritic algorithms enhance the performance of neural networks in well-defined tasks.

CONCLUSIONS

Although dendrites have been studied for decades, the field of dendritic computation is still in its infancy. This is partly because dendrites remain relatively inaccessible and have only recently begun to yield their secrets to the onslaught of multiple new experimental tools. However, the real challenge is a deeper one, faced by many areas of neuroscience (and biology in general): how to evaluate the importance of mechanisms on the molecular and cellular level for computation at the behavioral level. The ability not only to record electrical and chemical signals in the intact brain but also to manipulate the structure and function of dendrites using molecular tools will hopefully allow us to move from the descriptive level, correlating dendritic signals linked to computation with behavior, toward directly testing the causal nature of these links. Such experiments will provide a deeper understanding of how single neurons contribute to computation in the brain and should inspire the development of novel neural network architectures with the computational powers of real brains.

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Neuroscience

Volume 28, 200

Contents