Dendritic processing

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Dendritic processing multiplies the computational power of a single neuron by enabling the processing of inputs in a spatio-temporally differentiated manner. Recently, the development of new and refined optical, electrophysiological and molecular-biological techniques has led to new insights into dendritic function and revealed an astonishing plethora of computational mechanisms.

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Abbreviations

AP	action potential
CF	climbing fiber
CFP	cyan fluorescent protein
GABA	γ-amino butyric acid
GFP	green fluorescent protein
LTD	long-term depression
NMDA	*N*-methyl-D-aspartate
PF	parallel fiber
YFP	yellow fluorescent protein

Introduction

Dendrites were first visualized by Camillo Golgi in 1873. A few years later, Santiago Ramón y Cajal proposed that dendrites are the input-receiving structures of neurons, and in 1889 William His finally coined the term 'dendrite'. Since the 1950s, dendritic function has continued to gain more attention, and in recent years — partly owing to the development of new techniques for studying it — dendritic information processing has been recognized as a widespread and important factor in neuronal computation [1,2]. In fact, the extent of dendritic processing is closely related to the number of computationally relevant degrees of freedom in the brain.

Comparing the information processing capacity of the brain with that of computing machinery, there is still not even a crude estimate of the number of 'elementary computational units' that the brain has. A reason for this is that the elementary computational unit in the nervous system is difficult to identify. In their original model of neuronal computation, McCulloch and Pitts [3] defined the basic computational unit as the simplest nonlinear element which they considered to be an individual neuron. Today, we now know that (nonlinear) neuronal computation happens at smaller, subcellular scales, such as in synaptic specializations (both pre- and postsynaptically), and may even occur in microdomains made up of a single supra-molecular assembly located in dendrites.

With regard to the function of a dendrite, there are two conceptual extremes. First, the dendrite can be considered as a largely passive current collector — as formulated in the cable theory [4] — with nonlinear (i.e., decision-making) processes occurring only at the zone of spike initiation. Second, the dendrite can be considered as a highly active (electrically and otherwise) nonlinear component that makes many local 'decisions'. At the soma, these local decisions may eventually be integrated into a single decision: to fire or not to fire an action potential (AP). Alternatively (or in addition), local 'decisions' may lead to local output either in the form of synaptic transmitter release (e.g. retinal amacrine cells or olfactory granule cells) or via retrograde messengers.

Before proceeding, we need to make clear what our definition of information processing shall be. Although linear filters are clearly relevant for both the shape of the frequency response and the combination of information, we would, for the purpose of this review, like to consider only such processes that depend nonlinearly on at least some of the inputs. Furthermore, there is the issue of timescale. For example, on the one hand neurons can act as 'coincidence detectors' by responding only to inputs concurring within a small time window — a function that requires fast nonlinearities, which clearly constitutes processing. On the other hand, would we consider the plasticity of existing synaptic connections, which is clearly nonlinear, to be 'processing'? We feel that this plasticity should be included because modifying a synaptic connection by a local signal is akin to 'output' to memory, even though there may be no immediate 'electrical' signature. Various forms of presynaptic potentiation and depression are clearly processing, but occur mostly in axons, which are not our subject here.

In this review, we begin with a short overview of some of the methods that are useful for studying dendritic processing, and then discuss some of the recently identified physiological mechanisms involved in processing. Finally, we conclude with a review of the most promising model systems.

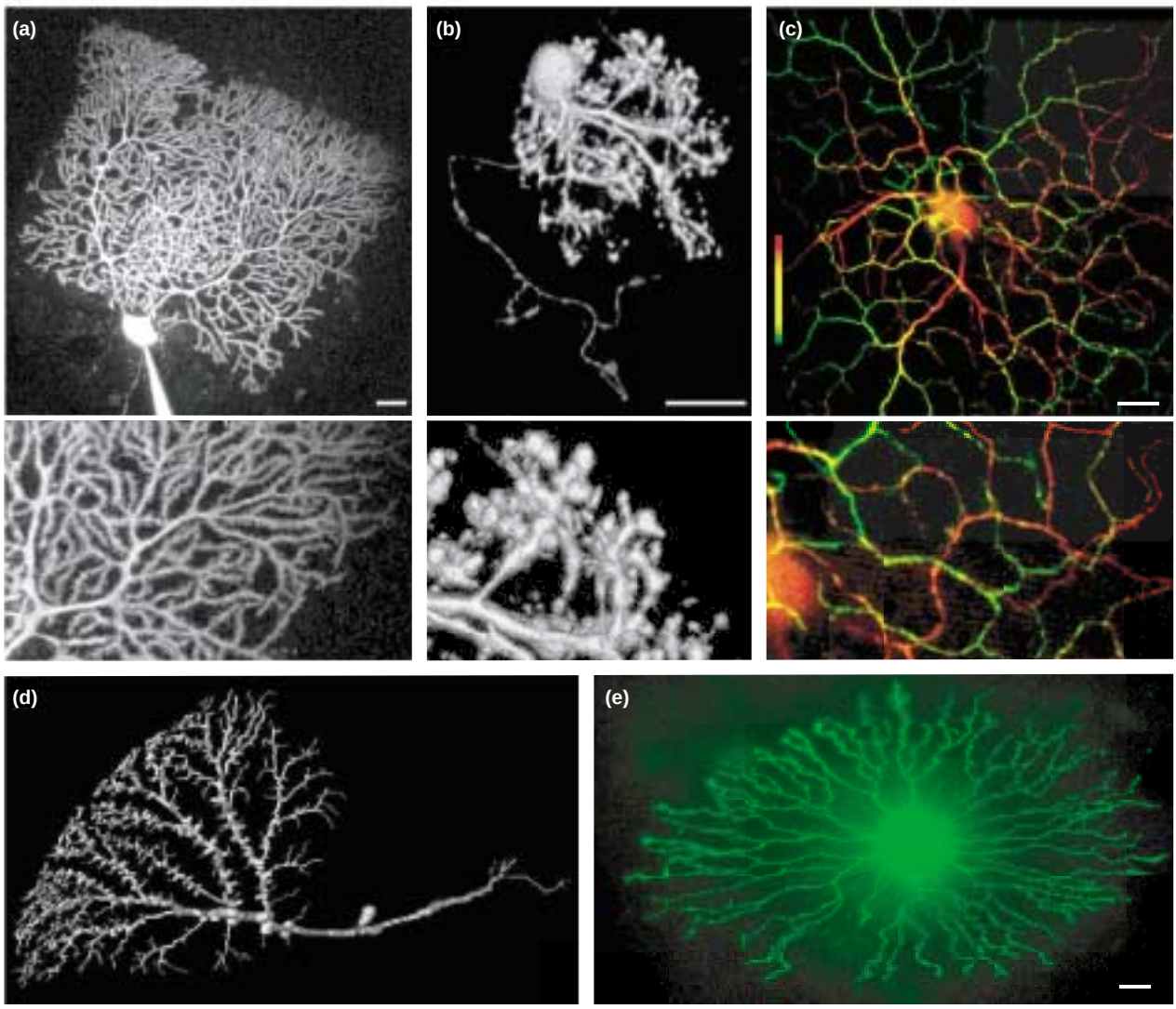
Methods of exploration

Functional morphology

One important aspect of dendritic processing is the interrelation between morphology and function. Here, we take a broad meaning of morphology that includes the distribution of active properties, such as voltage-gated channels and neurotransmitter receptors. For instance, the distribution of receptors or channels over a neuron's dendritic tree is usually neither homogenous nor random, but is well-organized and contributes decisively to the functional properties of the dendrite.

Immunocytochemistry with fluorescent probes and confocal microscopy can visualize these distributions in great

Figure 1



Dendritic morphologies. (a) Cerebellar Purkinje cell (image used with permission from [12••]). (b) Mitral cell from zebrafish olfactory bulb (kindly provided by R Friedrich). (c) Direction-selective ON/OFF ganglion cell from rabbit retina (injected by S He). Color coding indicates the depth (on the *z* axis) from the ganglion cell layer (red) to the outer border of the inner plexiform layer (green). (d) Visualization of a realistic model of a horizontal system north cell from fly lobular plate (kindly provided by A Borst). (e) Retinal starburst cell labeled with enhanced GFP using a gene gun (kindly provided by RH Masland). Scale bars, 20 μm.

detail. These methods are being augmented and extended by the use of chimeras of receptors and derivatives of green fluorescent protein (GFP) [5,6]. Such approaches, unlike antibody-based methods, are easily used on living tissue; nonetheless, they do not reveal the conditions under which the individual receptors are activated.

The distribution of 'functional' receptors can, however, be mapped by photolyzing 'caged' neurotransmitter (or neurotransmitter analogs) while recording the cell's electrical response. Further improvement in spatial resolution has been made possible by the use of two-photon excitation ('optical two-photon uncaging') [7,8] and the development of double-caged substances, which require two photolysis steps and hence the absorption of two photons for conversion into the active form ('chemical two-photon uncaging') [9]. Both methods restrict the volume of agonist creation, thereby greatly reducing background activation.

Recently, chemical two-photon uncaging has been used to map glutamate and γ-amino butyric acid (GABA) receptors on CA1 pyramidal cells [10], revealing regional variations in the receptor distributions: receptor density increases with increasing distance from the soma. This finding is consistent with

electrophysiological studies [11], and may reflect a mechanism for equalizing synaptic weight (e.g. to compensate for the attenuation of a synapse by the distance from the soma). In another study, two-photon uncaging revealed the spatial extent of glutamate receptor modification followed by locally induced long-term depression (LTD) [12••].

Modeling

Realistic biophysical computer models are important for designing and directing experimental work, and for assessing the functional relevance of results; however, studies that involve both modeling and 'wet' science are still rare. for example, Schiller and co-workers [13] have shown that modeling can be helpful for understanding dendritic processing through studies of local dendritic spikes occurring in the basal dendrites of cortical pyramidal cells. Their compartmental model, which was based on experimental data, indicated that these spikes are largely mediated by *N*-methyl-D-aspartate (NMDA) receptors.

Furthermore, simulations can be useful in exploring the functional/computational benefits that may be provided by experimentally discovered mechanisms. For example, using modeling studies Song *et al.* [14] found that 'spike-timing-dependent plasticity' (reviewed in [15]) introduces competition among synapses, by promoting the synapses that consistently 'predict' the postsynaptic response, while weakening those that are randomly active — thus, fulfilling two requirements for Hebbian learning [16]. (In the late 1940s Hebb postulated that, under certain conditions, coincident activity in connected neurons may strengthen their synaptic connections.) The efficiency of spike-timing-dependent plasticity depends critically on the coincidence time window over which synaptic modification occurs; this time window, in turn, is determined by the local (active) properties of the dendrite.

Electrophysiology

The ability to make electrical recordings from dendrites — initially by using sharp microelectrodes [17] and later by using giga-seal patch-recordings [18] — has been crucial in the study of dendritic processing. The distribution of ion channels on a cell can be mapped by probing small patches of membrane at various locations using patch electrodes. The ion channels in these patches of membrane can be studied either *in situ* (cell-attached) or after being removed from the cell (excised patch). The local voltage response of the dendrites can be measured by using the whole-cell mode of the patch-clamp technique (to establish an electrical access to the cell). Using this latter approach, Häusser and colleagues have examined synaptic current shunting [19] and coincidence detection [20] by back-propagating APs. Nonetheless, electrophysiological approaches are restricted to those processes that are thick enough to be targeted by electrodes, often excluding large parts of the dendritic tree.

Optophysiology

Unlike electrophysiological methods, optical recording techniques can resolve activity patterns in dendritic processes. This allows both the mapping of local events (e.g. activity 'hot spots' such as calcium transients) in great detail and the correlation of the resulting activity map with the neuron's morphological specializations. Furthermore, two-photon laser-scanning microscopy allows the observation of single spine events with millisecond time resolution and high signal-to-noise ratio [21,22].

Recently, Sabatini and Svoboda [23] determined the number of voltage-activated calcium channels in single spines of pyramidal cells by using optical fluctuation analysis of AP-triggered calcium transients. (Optical, not unlike electrical, fluctuation analysis allows the determinations of the number of independently acting elements, for example ion channels, even if the switching of individual elements can not be resolved). Because the long wavelength of the excitation frequency penetrates deep into neural tissue, two-photon microcopy can also be used to study dendritic calcium dynamics [24,25] and spine morphology [26] *in vivo*.

Although we have a good variety of calcium sensors at our disposal, we still lack sensitive indicators for other ions and, in particular, voltage-sensitive dyes with a good signal-to-noise ratio [27,28]. However, major progress has been made in the development of GFP-based indicators that can be genetically targeted to specific types of neurons or even subcellular sites. Moreover, with interest in cellular chloride gradients growing, chloride indicators based on yellow fluorescent protein (YFP) have been developed. Recently, a mutant form of YFP (amino-acid mutation H1148Q), which is quenched by halides, has been shown to report physiological changes in chloride concentration at cytoplasmic pH [29,30].

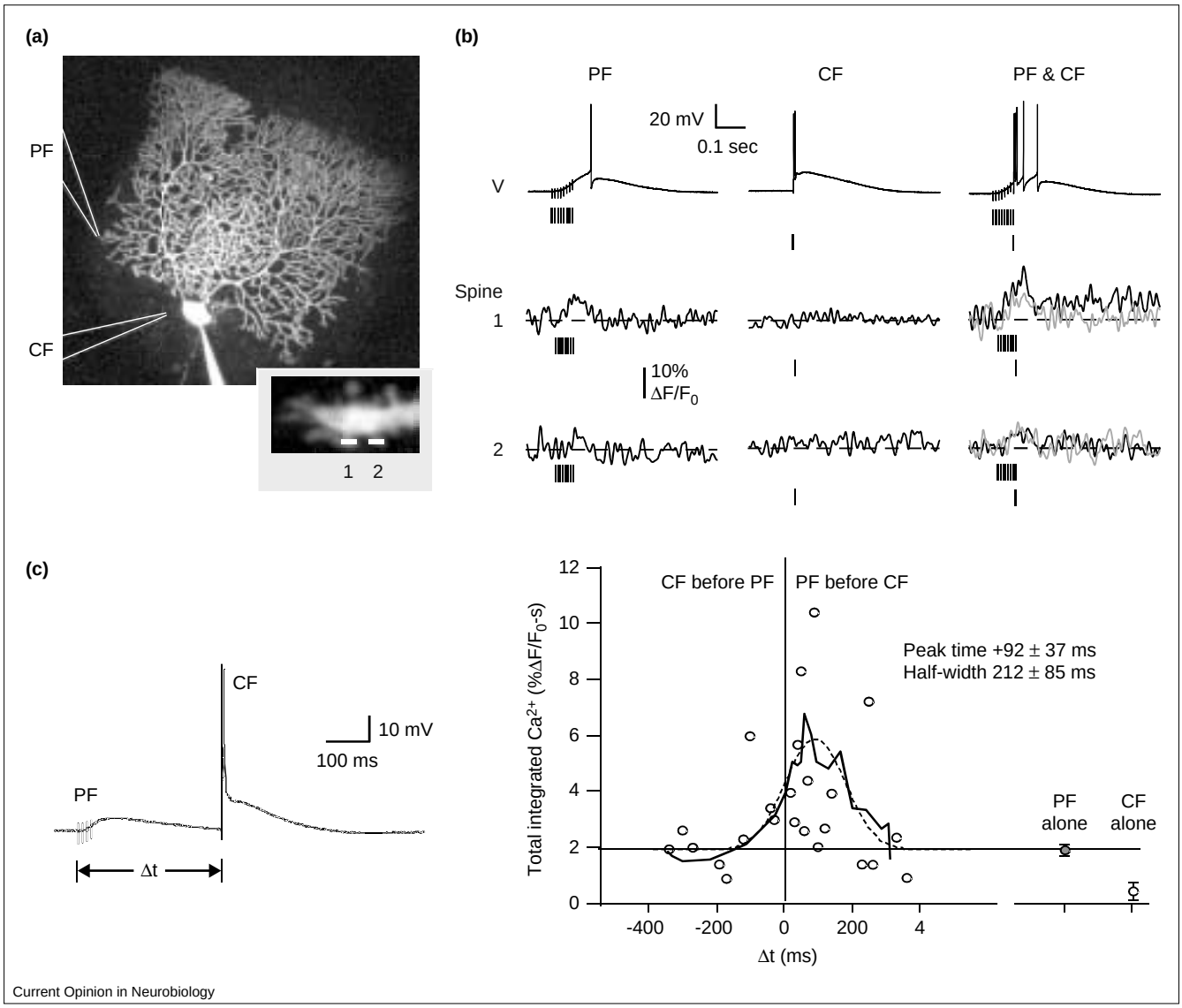
In analogy to the (genetically encoded) calmodulin-based calcium sensors, such as 'Cameleon' [31,32], a chloride sensor called 'Clomeleon' has been introduced [33]. Clomeleon, like the Cameleons, is a YFP/cyan fluorescent protein (CFP) fusion protein: the ratio of fluorescence resonance energy transfer dependent emission of the chloride-sensitive YFP to that of the chloride-insensitive CFP gives a measure of the intracellular chloride concentration. Furthermore, the discovery of other fluorescent proteins — such as dsRed from corals [34–36] — promises the development of probes with separable spectra, which are necessary for concurrent measurements of different physiological parameters.

Mechanisms

Electrical compartmentalization

Electrical signals are by far the fastest means of neural communication. Of all the intracellular 'messengers', voltage spreads most readily throughout the cell, owing to the fact that electric fields are not well confined along a neurite. Even so, there are cases in which significant gradients and compartmentalization can be observed and a biological role can be assigned [37••,38•]. For example, tangential cells in the fly (see below) show different degrees of voltage spread across their dendritic tree,

Figure 2



Coincidence detection and supralinear calcium signals in single Purkinje cell spines. (a) Purkinje neuron filled with magnesium green through a patch pipette (bottom), with marks (white lines) representing the glass pipettes for parallel fiber (PF) and climbing fiber (CF) activation. The inset shows higher magnification views of two spines in which the calcium transients were monitored. (b) Traces, somatic voltage (V) and fluorescence responses (spines 1 and 2). PF stimulation alone elicits a small calcium response in spine 1 but not in spine 2 (first column), whereas CF stimulation alone fails to induce a calcium response in either spine (second column). PF stimulation in conjunction with a brief CF stimulus (third column) evokes a calcium transient in both spines, with the response in spine 1 being larger than the linear sum of PF- and CF-evoked responses (gray curve), indicating supralinearity. (c) For eliciting a supralinear response, PF and CF stimulation have to occur within a narrow time window, with PF stimulation slightly preceding. Right: solid trace – box-smoothed average over three points; dashed curve – best fit of raw data points to Gaussian function. Figure modified with permission from [12••].

depending on the site of stimulation [37••]. When stimulated with an axonal current injection the resulting potential spread readily throughout the tree, however, when current was injected locally in a dendrite, the potential fell off steeply in a short distance from the injection site. This 'compartmentalization' of the membrane potential allows the dendrites to accomplish local computations (and possibly even local motion adaptation) without interfering with the integrative functions of the cell.

Amplification

Active (voltage-gated) currents can greatly sharpen both spatial and temporal gradients [39] and can, particularly when poised near instability, serve to amplify small differences. Well-studied examples of active currents include dendritic calcium spikes in Purkinje cells [40] and layer 5 pyramidal neurons [25,41,42].

Regenerative events in dendrites do not necessarily require 'classical' voltage-gated channels. For example,

NMDA receptors have been shown to contribute largely to spikes occurring in the basal dendrites of cortical pyramidal cells [13]. It may be possible that such a mechanism could dynamically create 'zones' of excitability set up by glutamate that is pre-bound in parts of the cell's dendritic tree.

Back-propagation

Back-propagating sodium APs — like calcium spikes — can act as a 'global' signal. Back-propagation is strongly dependent on dendritic morphology [38•] and can be modulated with high-precision timing by synaptic inputs [20] and probably on a slower timescale by modulatory inputs.

Conversely, the weight of synaptic input can be shunted by coincident spikes [19]. The strength of this modulation depends on the dendritic morphology and on the kinetics, location and timing of the synaptic inputs present. For example, distal input via receptors with slow kinetics may dominate during AP firing, because they may reach maximal activation after the shunting effect of the AP has ceased. NMDA receptor mediated inputs may even be enhanced due to the release of the magnesium block by appropriately timed APs.

Chemical compartments and second messengers

Although widely branched dendritic trees can support several independent electric compartments, the same geometry can support many more chemical compartments. The reason for this is that diffusion — even that of small molecules or ions — is slow, particularly in the spiny geometry that is so typical of the dendrites of many types of neurons in the brain [43].

Over the years, several studies have shown that spines in different cell types can act as individual compartments for calcium and other second messengers ([12••,21,22,44]; reviewed in [45]); these compartments are, in addition, capable of performing biochemical computations [12••,21]. It is also becoming increasingly clear that the spatio-temporal stimulation pattern can determine which type of physiological mechanism dominates the cell's response, in particular, when metabotropic receptors and release from intracellular stores are involved [12••,46•,47,48,49••].

Not only Ca^{2+}, but also other ions may be functionally compartmentalized in neurons. For example, intracellular chloride gradients offer a way to modulate GABA and glycine receptor-mediated inhibition differentially in distinct compartments of a neuron [33]. Using the 'Clomeleon' indicator discussed above, Kuner and Augustine [33] have visualized chloride gradients in cultured hippocampal neurons. Focal GABA application led to accumulation of chloride that spread to other parts of the cell — possibly constituting a mechanism for use-dependent suppression of GABA-mediated input. Furthermore, neurons may be able to adjust the local chloride concentration such that activation of GABA receptors induces inhibition in one compartment but excitation in another one — for instance, by differential expression of chloride-extruding and chloride-accumulating transporters (e.g. the K^+/Cl^--cotransporter KCC2 and the $Na^+/K^+/Cl^-$-cotransporter NKCC, respectively). Immunohistochemical evidence indicates that this could be the case in the retinal bipolar cells that depolarize at light-onset (ON cells). ON bipolar cells receive at their dendrites GABAergic input from horizontal cells which depolarize at light-offset (OFF cells). If this horizontal cell input were inhibitory, the bipolar cells would receive surround inhibition at light-off and not, as one would expect, at light-on. A high chloride concentration in the bipolar cell's dendrites may provide an excitatory GABAergic input and thus, the correct conversion of the input signals from horizontal cells [50].

Coincidence detection

Recognizing temporal relationships is a crucial computational operation and prerequisite for plasticity and learning. Dendritic coincidence detection is implemented at different temporal and spatial scales, involving various mechanisms, and can affect single dendritic spines or branches [12••,21,24] or can modulate the response of the whole cell [20]. Even a particularly shaped dendritic tree can facilitate coincidence detection — as has been demonstrated in simulations of bipolar neurons in the auditory brainstem [51].

The detection of signal concurrency within a very small time window suffers from the temporal filtering and attenuation that occurs as synaptic signals travel to the soma. Although active channels in dendrites can partially overcome this signal degradation, local dendritic coincidence detection may be essential for precise timing in the submillisecond range [52,53].

Model systems

In recent years, most experimental studies on dendritic processing have concentrated on hippocampal and cortical pyramidal cells or Purkinje cells, resulting in a wealth of detailed knowledge (see above). Beyond doubt, the hippocampus and cortex will continue to provide fascinating insight in dendritic computation. Here, however, we would like to discuss a selection of other model systems in which a crucial role for dendritic computation has been either proposed or convincingly demonstrated.

In the visual system of the fly, a small population of large interneurons in the lobular plate — the tangential cells — spatially integrates the output of a great number of columnar neurons, which each observe a small patch of the visual field. Tangential cells are selective to direction; that is, they are excited by motion in a preferred direction and inhibited by motion in the opposite direction [54,55]. Furthermore, the velocity of the motion is represented by the amplitude of the (graded) output potential of the cell.

When measuring the spatio-temporal calcium changes in the neuron's dendritic tree *in vivo*, Single and Borst [56]

found that the local calcium signals indicate the motion, the velocity, and also some spatial properties of the stimulus (a moving grating). Dendritic low-pass filtering, however, eliminates the signals introduced by the grating properties, resulting in a purely direction-selective signal [56]. (One type of tangential cell possesses active dendritic sodium conductances, and Haag and Borst [57] have shown that oscillations evoked by the stimulus frequency are amplified in this cell.)

Calcium transients are restricted in a retinotopic fashion to the stimulated branches of the dendritic tree [54]. The local confinement of the calcium transient (and presumably the underlying membrane depolarization) has been shown to result mainly from the geometry of the dendritic tree and its membrane properties [37••]. Comparison of the calcium dynamics of two classes of tangential neurons, which are known to receive similar retinotopic input, revealed class-specific differences in calcium response, suggesting that these neuron classes have differences in dendritic processing [58] even though their electrical responses are very similar. Furthermore, calcium accumulation in tangential cells may also play a role in a postsynaptic form of motion adaptation [59].

The vertebrate retina is a well-established model system in which dendritic processing may have a prominent role. With the advent of two-photon microscopy, optical recordings from intact, light-sensitive retina have become feasible [60], and provide the basis for studying light-driven local dendritic events.

For example, amacrine cells — which mostly lack a discernible axon [61] — represent, in a way, a 'prototype' of a neuron that processes signals with its dendrites. They come in 20–30 morphological flavors (reviewed in [62]), indicating a rich functional diversity. Amacrine cells are retinal interneurons that relay signals among bipolar cells, other amacrine cells and ganglion cells. Their dendrites both receive synaptic input and make output synapses: in some amacrine types inputs and outputs are co-localized (e.g. A17) [63], whereas in others they are at least partially separated (e.g. starburst amacrine cells) [64]. In retinal ganglion cells, back-propagation and dendritic spike initiation has been observed [65].

However, the most prominent example for retinal dendritic processing is probably the mechanism on which direction selectivity in some ganglion cell is based [66]. Only recently, Taylor *et al.* [67•] provided evidence that the computation of direction selectivity — the interaction between excitatory and inhibitory inputs — is situated postsynaptically in the DS (direction-selective) ganglion cell dendrite (but see [68•]).

In the olfactory bulb, the first levels of signal processing are performed through reciprocal dendro-dendritic synaptic interactions between dendrites of mitral and granule cells (reviewed in [69]). The release of glutamate from mitral cell dendrites onto axonless granule cells evokes feedback inhibition of the excited mitral cell, as well as lateral inhibition of neighboring, mitral cells. The inhibition by granule cells is controlled by both the extent of AP propagation and concurrent changes in calcium concentration in the lateral mitral cell dendrites [70]. GABA release from granule cells can be induced locally by coincident glutamate release from mitral cells and granule cell depolarization through an NMDA receptor-mediated mechanism.

Using caged calcium compounds, Chen *et al.* [71] have provided evidence that calcium influx through NMDA receptors alone can directly trigger the feedback inhibition onto mitral cells. A stronger stimulation of granule cells eliciting an AP would be expected to cause GABA release from all synaptic sites. A recent study by Isaacson [72] supports further the idea that the sites of GABA release and calcium influx are co-localized in granule cells (suggesting highly localized interactions); however, this study also found that calcium influx is mediated mainly by voltage-gated calcium channels rather than NMDA receptors. Dendritic processing may thus enable granule cells to operate in different 'modes': a local mode (subthreshold, only recurrent inhibition) and a more extended mode (APs, recurrent and lateral inhibition).

Conclusions

Although we are still far from a general understanding of dendritic processing, we have gained some insight into its importance for neuronal computation. The great diversity of dendritic morphology — already appreciated more than 100 years ago — (probably) corresponds to an equally large variety of dendritic mechanisms and functions. Dendrites have turned out to be complex, multifaceted computing devices, which can operate in a highly nonlinear fashion. Dendritic processing can be locally confined or operate over large branches or subtrees, depending on the spatio-temporal pattern of the input that is received. Remarkably, Cajal may have sensed that dendrites are much more than simple input receiving structures. More than 100 years ago he wrote [73]: "…Besides, it appeared to me that certain facts were definitely contrary to the supposed exclusively cellulipetal conduction of the dendrites and cellulifugal of the axons…In such cases it was necessary to admit contact between dendrites of diverse origins and hence conduction indifferently cellulipetal or cellulifugal."

Today, newly developed (or refined) techniques allow us to 'look' into single dendrites, to genetically alter their components, or to map their functional synaptic inputs. This results in detailed, but often descriptive information on dendritic processing mechanisms. For the future, it will be essential to associate these mechanisms with the functional role of the neuron, the network (or local circuit) that the neuron belongs to, and, if possible, with behavior.

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See annotation to Borg-Graham [68•].

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