ELSEVIER

Dendrites: bug or feature?

Michael Häusser*† and Bartlett Mel*‡

The integrative properties of dendrites are determined by a complex mixture of factors, including their morphology, the spatio-temporal patterning of synaptic inputs, the balance of excitation and inhibition, and neuromodulatory influences, all of which interact with the many voltage-gated conductances present in the dendritic membrane. Recent efforts to grapple with this complexity have focused on identifying functional compartments in the dendritic tree, the number and size of which depend on the aspect of dendritic function being considered. We discuss how dendritic compartments and the interactions between them help to enhance the computational power of the neuron and define the rules for the induction of synaptic plasticity.

Addresses
*Wolfson Institute for Biomedical Research and Department of Physiology, University College London, Gower Street, London WC1E 6BT, UK
†e-mail: m.hausser@ucl.ac.uk
‡Biomedical Engineering Department and Neuroscience Graduate Program, University of Southern California, Los Angeles, CA 90089, USA
e-mail: b.mel@ucl.ac.uk

Current Opinion in Neurobiology 2003, **13**:372–383

This review comes from a themed issue on
Signalling mechanisms
Edited by Morgan Sheng and Terrance P Snutch

0959-4388/03/$ – see front matter
© 2003 Elsevier Science Ltd. All rights reserved.

DOI 10.1016/S0959-4388(03)00075-8

Abbreviations

AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid
AP	action potential
BAC	backpropagation activated calcium spike
BPAP	backpropagating action potential
EPSP	excitatory postsynaptic potential
GABA	γ-aminobutyric acid
LTP	long-term potentiation
NMDA	*N*-methyl-D-aspartate

Introduction

Dendritic trees give neurons their personalities. They receive the vast majority of the cell's synaptic input, and act as the primary substrate for neuronal information processing. Nevertheless, despite more than 100 years of study the transformations dendrites perform on their inputs remain poorly understood. This is largely due to the inaccessibility of the extremely fine branches on which most of their synapses lie. In particular, we know little about the rules that govern signal integration in dendrites, how they influence (and react to) different forms of plasticity, and how they ultimately enrich the computational power of the brain.

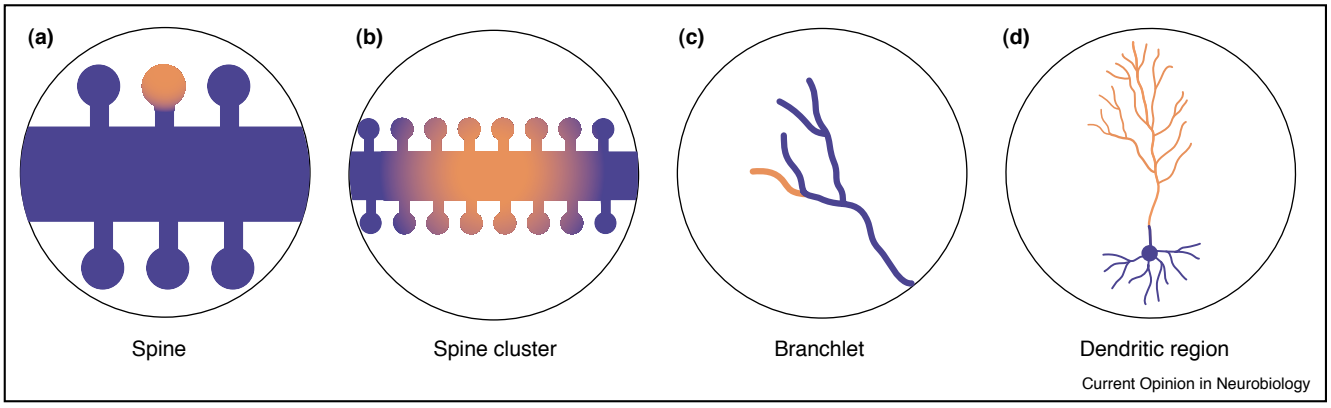
The past few years have seen an explosion of interest in dendrites, partly driven by the advent of powerful new imaging and recording techniques. However, as dendrites have taken centre stage in our search for an understanding of single-neuron computation, the mass of new data available has in some cases led to conflicting interpretations. Some findings, for example, seem consistent with the idea that dendrites impose obstacles to be overcome, necessitating biophysical 'corrective measures' to compensate for the signal attenuation and temporal distortion caused by the dendritic tree [1–4]. Other data support the idea that dendrites substantially enhance the neuron's computational power by introducing non-linear interactions between synapses and subcompartments of the cell. Taken to its logical extreme, this conceptual tension may be expressed as a simple question [5•,6•]: are dendrites a 'bug' or a 'feature'?

In this review, we begin by describing a loose hierarchy of models of the neuron, each of which emphasises a different granularity of dendritic processing (Figure 1). The models differ primarily in the number of functional compartments that they use to represent the dendritic tree. The models are not mutually exclusive, in the sense that each of the models may be valid at some level of analysis and provide a different insight into dendritic physiology. Our focus is on electrical rather than chemical compartments [7], and on pyramidal cells in the cortex and the hippocampus. We also discuss how the compartments that govern synaptic integration can influence synaptic plasticity, and how learning-induced changes in excitability may in turn alter the compartmental structure of the neuron.

How many compartments?

One of the central challenges in neuroscience has been to arrive at an appropriate abstraction for the individual neuron that captures the essence of the cell's information processing activities. In addressing this question, one of the main conceptual axes on which dendritic researchers have roamed relates to the number of independent electrical processing units operating — and cooperating — inside the neuron to produce its overall input–output behaviour [8]. For example, as complicated as a dendritic tree appears on the surface, it has long been considered a possibility that the whole cell nonetheless functions as a simple one-compartment summing unit, where, as in an idealised democracy, all synapses have an equal opportunity to influence neuronal output through the axon.

Figure 1



What are the functional compartments in neurons? A schematic representation of different levels of granularity in neuronal processing. **(a)** Calcium signalling restricted to single spines. **(b)** Signalling restricted to a small cluster of spines. **(c)** Signalling restricted to a single terminal branchlet. **(d)** Signalling extending across the entire apical dendritic tree.

The rule for combining the effects of many synapses under this model is generally assumed to be linear, and can thus be expressed as a weighted sum of all excitatory and inhibitory synaptic inputs. This view has been called the 'point neuron' hypothesis, and is arguably the default view of the neuron in most areas of neuroscientific inquiry. In addition, the point neuron and its variants have been almost universally adopted in the neural network and artificial intelligence fields [9–12].

Driving us to the other conceptual extreme are an array of spatio-temporal interactions among synaptic inputs and the local responses they trigger. Examples include dendritic spikes initiated by synaptic inputs to spatially defined dendritic compartments [13•,14], synergistic interactions between somatic and dendritic spike-generating mechanisms that depend on both intensity and timing of output [15,16••,17,18•,19•], the ability for properly timed synaptic inputs to boost (through excitation) or veto (through inhibition) back- and forward-propagating action potentials (APs) along the main apical trunk [18•,19•,20], and the consequences of all of these interactions for synaptic plasticity. These data suggest the importance of dendritic space and time for various aspects of neuronal information processing.

A modern take on the 'point neuron' hypothesis

The work of Wilfred Rall provided the first demonstration that from an electrical point of view, dendrites can be treated as spatially extended, branched coaxial cables subject to the laws of cable theory. Rall found that large dendritic trees could inflict significant spatio-temporal distortions on their synaptic inputs [21–23], and that in passive dendritic trees, this could lead to a marked breakdown in 'dendritic democracy' [24,25]: without compensatory mechanisms, distal synaptic inputs are heavily disadvantaged relative to proximal inputs [26••], as they give rise to somatic responses that are strongly attenuated and temporally smeared.

Recent theoretical and experimental work has focused on several biophysical properties of dendrites that could help to mitigate the distance-dependent attenuation and low-pass filtering (i.e. temporal smoothing) of postsynaptic potentials within spatially extended dendritic trees. First, scaling of synaptic conductances depending on electrotonic distance from the soma could function to equalise the effects of synapses regardless of location. Evidence for this has been provided in motoneurons, and more recently in CA1 pyramidal neurons [2,27•]. On the other hand, the idea that this mechanism could function to equalise the effects of synapses regardless of location has been challenged on theoretical grounds [5•]. Moreover, no simple scaling principle has been found in neocortical pyramidal neurons [28••]. Second, dendritic voltage-dependent Na^+, Ca^{2+} and *N*-methyl-D-aspartate (NMDA) channels can boost the effectiveness of weak distal synaptic inputs [4,29•,30–33], whereas the hyperpolarization-activated cation current I_h can help to normalise their time courses [1,34]. A third type of dendritic normalisation, whose function is to counteract the classical synaptic saturation non-linearity, could result from a patch of voltage-dependent Ca^{2+} channels in the apical tree [3]. Taken together, these findings demonstrate that appropriate deployment of ion channels in the dendritic membrane can in principle help to 'correct' for signal distortions imposed by the dendritic tree. This means that a complicated and physically sprawling cell can be made to function (more) like a linear location-independent point neuron. Of course, although the data discussed above are thematically consistent with the point neuron hypothesis, they may be consistent with other models as well.

The two compartment world

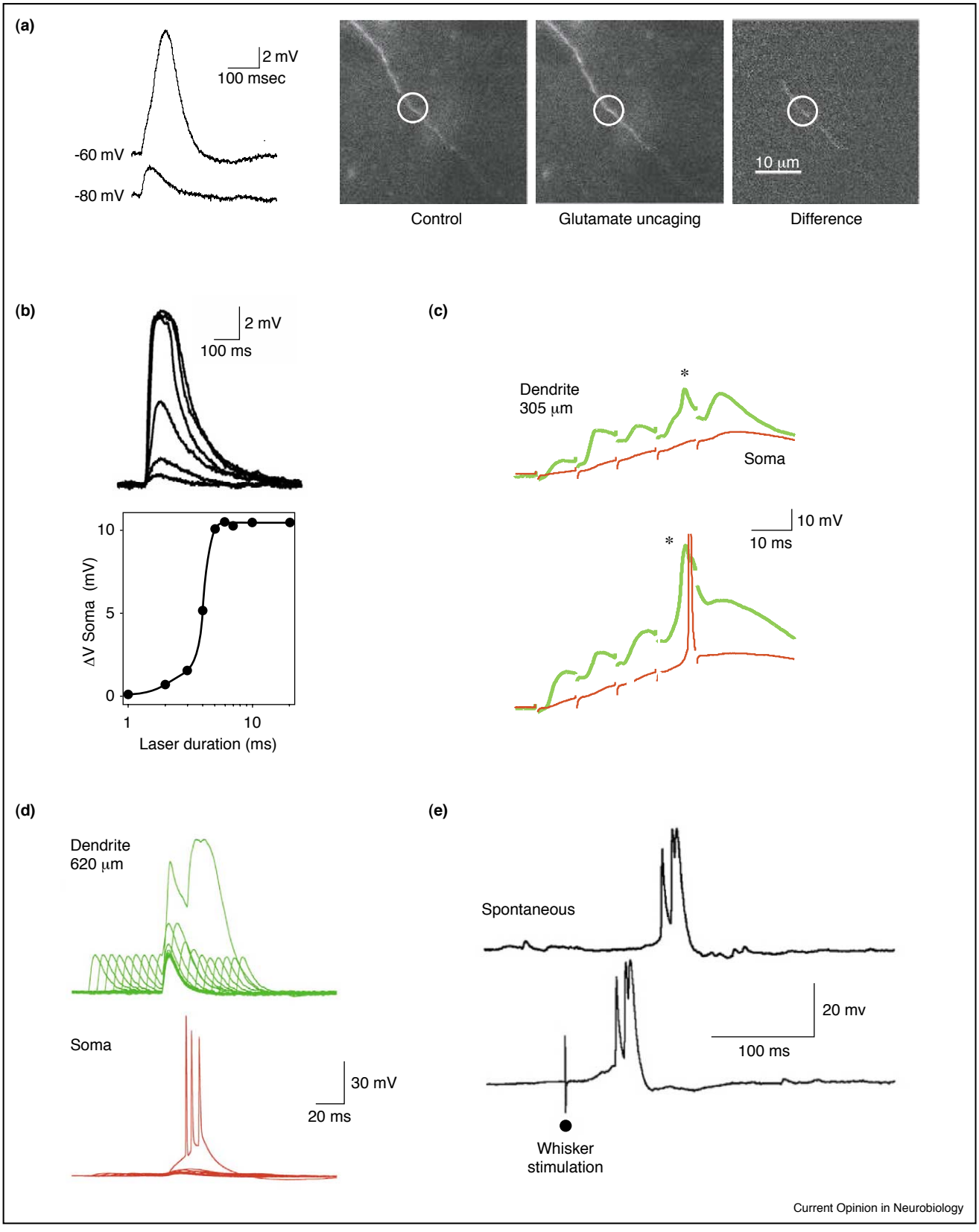
Since the work of Llinas and Sugimori [35] in Purkinje neurons more than two decades ago, it has become well established that the distal dendrites of many neuronal types can initiate regenerative spikes [3,16••,36–38]. Dendritic spikes (see Figure 2 for examples) have a clear voltage and stimulus intensity threshold and can occur without triggering axonal action potentials. Similarly, action potentials initiated in the axon do not propagate fully into the distal dendrites of many neurons [39,40•]. This attenuation of backpropagating action potentials (BPAPs) and dendritic spikes travelling in both directions between soma and dendrites is largely a consequence of dendritic morphology, acting in concert with the properties of dendritic voltage-gated channels [40•,41]. The resulting compartmentalisation of spiking behaviour is incompatible with the point neuron hypothesis, and has contributed to the development of the two-compartment view of the neuron. According to this model, the cell consists of one proximal compartment, usually including the soma, basal dendrites and axon, in which classical Na^+ action potentials are generated, and one distal compartment, representing the distal apical tree, in which fast Na^+ and slow Ca^{2+}-spikes are initiated. Lumping the apical tree into a single functional unit seems reasonable when it is considered that the apical trees of pyramidal cells are morphologically stereotyped [42•], and receive inputs from different sources than those of basal dendrites [43]. The adoption of the two-compartment model in the experimental community has also been spurred on by theoretical results that have highlighted the importance of compartments for the control of neuronal firing dynamics, particularly bursting [44–46].

Many of the interesting computational effects are likely to lie in the dynamic interactions between the proximal and distal compartments, and this is where the most significant progress has been made in recent years. A series of studies on layer 5 pyramidal neurons has investigated the interaction between BPAPs initiated in the axon and calcium spikes triggered in the distal dendritic compartment [6•,15–17,18•,47]. In an elegant recent study conducted by Larkum *et al.* [17], it was shown that single BPAPs can lower the threshold for initiation of distal calcium spikes, which in turn promotes burst firing at the soma (known as BAC firing for 'backpropagation activated calcium spike' firing). The relative timing of input to the two compartments was crucial, and BAC firing could be blocked by appropriately timed activation of an inhibitory input onto the cell (similar modulatory roles for inhibition have been previously reported by others [48,49]), which indicates that inhibition could be used to control the coupling between proximal and distal spike generation zones. The compartmentalisation is developmentally regulated and appears to be defined by a combination of the morphological elongation of the apical trunk and increases in dendritic channel densities [47]. In particular, a zone with a low threshold for initiation of calcium spikes appears to exist 550-900 μm from the soma [16••] in mature neurons. The coupling between this zone and the soma depends crucially on dendritic morphology [6•,40•], with the oblique dendrites playing an especially important role [6•]. This observation has led to the suggestion that the two compartment model of the layer 5 pyramidal cell should be elaborated to include a third compartment representing a central 'coupling zone' along the proximal apical dendrite. In this more refined model, inputs to oblique branches modulate the interaction between axonal and distal dendritic spikes [18•].

Several other recent studies are consistent with the two-compartment view of the neuron. Pouille and Scanziani [50] examined the spatial organisation of feed-forward inhibition onto CA1 pyramidal neurons and showed that feed-forward inhibitory synapses appear to be concentrated primarily on the soma. As a consequence, the integration time of excitatory postsynaptic potentials (EPSPs) is far shorter at the soma than in the dendrites. In layer 5 pyramidal neurons, coincidence detection that results from pairing EPSPs and BPAPs [19•] or two independent strong synaptic inputs [51] is very different for inputs near the soma and for those in the distal dendrites. Similarly, it has been shown that out-of-phase sine wave or patterned input presented simultaneously to the soma and distal dendrites can mimic phase precession [52] in CA1 pyramidal cells [53] with the degree of phase precession regulated by the properties of ion channels in the distal dendritic compartment. Finally, the large conductances that underlie the action potential have been shown to shunt ongoing EPSPs in a manner that depends on the location, timing and kinetics of the underlying input [54•]. As the AP conductance is most concentrated in the axon, distal inputs are 'protected' from the shunt by

(Figure 2 Legend) Dendritic spikes of pyramidal cells. **(a)** Initiation and spatial spread of NMDA spikes in layer 5 pyramidal cells. Left panel, somatic voltage response to focal uncaging of glutamate from a basal dendrite at two holding potentials. Right panel, calcium response to glutamate uncaging on a basal dendrite. The difference image reveals the highly local nature of the calcium response. Taken from [14]. **(b)** Regenerative spikes in CA1 pyramidal dendrites. Top, somatic voltage response to glutamate uncaging of increasing duration at a distal dendrite. Bottom, plot of voltage response against laser pulse duration, showing marked sigmoidal non-linearity. Taken from [13•]. **(b)** Simultaneous somatic and dendritic recording from a CA1 pyramidal cell during theta-burst synaptic stimulation. Dendritic spikes (*) propagate incompletely to the soma and provide variable triggers of somatic APs. Taken from [94••]. **(d)** Simultaneous somatic and dendritic recording from a layer 5 pyramidal cell. Two simulated EPSPs were paired at varying intervals, with a dendritic calcium spike and corresponding somatic AP burst being generated only with a narrow coincidence time window. Taken from [28••]. **(e)** Dendritic recording from a rat layer 5 pyramidal cell *in vivo* (612 μm from soma). Top trace, spontaneous dendritic spike. Bottom trace, dendritic spike triggered by whisker stimulation. Taken from [16••].

Figure 2


(a)
2 mV
100 msec
-60 mV
-80 mV
10 μm
Control
Glutamate uncaging
Difference
(b)
2 mV
100 ms
ΔV Soma (mV)
10
5
0
1
10
Laser duration (ms)
(c)
Dendrite
305 μm
*
Soma
10 mV
10 ms
*
(d)
Dendrite
620 μm
Soma
30 mV
20 ms
(e)
Spontaneous
20 mv
100 ms
Whisker
stimulation
Current Opinion in Neurobiology

the intervening dendritic cable. The distal dendrites thus represent a separate functional compartment in which processing can continue relatively uninterrupted by somatic AP firing. Taken together, these results suggest that synaptic integration is regulated by a dance-like interplay between the cell's conventional fast spike-generating mechanism near the cell body and a spike generator in the distal dendrites, each of which read out the results of processing in their respective compartments.

What are the functional implications of proximal–distal interactions in the two-compartment model? Consider a possible scenario in the neocortex. Long-range horizontal and cortico–cortical connections provide association inputs to dendrites in layers 1 and 2, 'warming up' the distal apical tree and lowering its threshold for dendritic spike generation. Inputs to the apical oblique and basal dendrites, which may represent the contents of the cell's 'classical receptive field', drive the cell to fire fast spikes. Given the modulatory input to the apical tree, however, each somatic spike is multiplied into two or three spikes through the BAC firing mechanism. In this way, proximal–distal interactions could play a role in several modulatory effects that have been topics of active research in cortical sensory neurophysiology, including contextual effects that support contour completion [55], attentional modulation [56], and multiplicative 'gain fields' [57]. They could also provide a mechanistic basis for abstract learning rules that involve interactions among learning-related signals that are played out along two different time scales [58•,59].

Towards a finer-grained compartmentalisation

Despite the conceptual attractiveness of the two-compartment model, with its focus on the main proximal-distal axis, it is important to remember that the great majority of excitatory synapses on pyramidal neurons lie on the thin branches of the basal tree and apical oblique branches, which are particularly favourable sites for regenerative activation of dendritic voltage-gated channels. Schiller and co-workers [14] pushed the debate on dendritic compartmentalisation to a new level by using focal laser-activated release of caged glutamate, to stimulate clusters of excitatory synapses (within an approximately 10 micron radius) on fine basal dendrites of neocortical pyramidal cells. They found highly localised all-or-nothing spike-like responses that were initially triggered by α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors, and followed by co-activation of voltage-dependent Na^+, Ca^{2+} and NMDA channels. Given that the spikes could be evoked in the presence of tetrodotoxin (TTX), the sodium channel blocker, or cadmium, which blocks calcium channels, but were blocked by the NMDA antagonist AP5, they referred to these highly non-linear events as 'NMDA spikes'. A very similar set of findings was reported for the thin terminal branches of the apical trees of CA1 pyramidal cells [13•]. In addition, Oakley and co-workers [30] showed that all-or-none Ca^{2+}-dependent plateau potentials could be evoked virtually anywhere in the dendritic tree of a neocortical pyramidal cell, with the exception of a perisomatic exclusion zone.

Although evidence that suggests the existence of multiple dendritic spike-generating zones has been reported previously [60–63], these more recent reports are significant in two ways [64]. First, the number of dendritic spike-generating zones in a pyramidal cell, if they are identified within the thin terminal branches, could grow to several dozen or even 100 depending on the layer, area and species [65]. Second, the NMDA spikes identified by Schiller *et al.* [14] are unable to travel in most situations. Thus, unlike classical APs, which propagate with a high safety factor into unexcited stretches of axon, these dendritic spikes can evidently propagate effectively only when there is sufficient glutamate 'support' for them, that is, in situations where glutamate is bound to a sufficient number of postsynaptic receptors. Tying spikes to the site of synaptic excitation is likely to promote much greater independence among the different spike-generating zones within each of the thin branches.

Another example of highly localised dendritic processing can be found in the retina, in which a recent elegant study using calcium imaging techniques has demonstrated that individual dendritic branches of retinal starburst amacrine cells show directionally selective calcium signals, whereas the somatic voltage response shows no such selectivity [66••]. This finding bore out a longstanding prediction that direction selectivity is computed upstream from retinal ganglion cells, and that individual dendritic branches of amacrine cells can act as independent integrative units with branch-specific outputs [67]. Though evidence remains indirect, it is also likely that the specialised 'bottlebrush' endings of stratum griseum centrale type 1 (SGC-1) neurons in the chick tectum provide these cells with a moderately large number (e.g. 50) of independent active response zones in their distal dendrites. These distal compartments are thought to underlie the cell's chattering (bursting) responses and pronounced motion sensitivity [68].

Are dendritic compartments likely to exist on an even finer scale than the single thin branch, such as a small portion of a branch or even on an individual dendritic spine? This scenario could be favourable on computational grounds, as the greater the number of independent non-linear operations available to the neuron, the greater its potential computational power. It is also clear from imaging experiments that calcium and sodium signals can be compartmentalised within single spines [69,70]. However, the cable properties of neurites suggest that such a fine scale compartmentalisation for electrical signals may

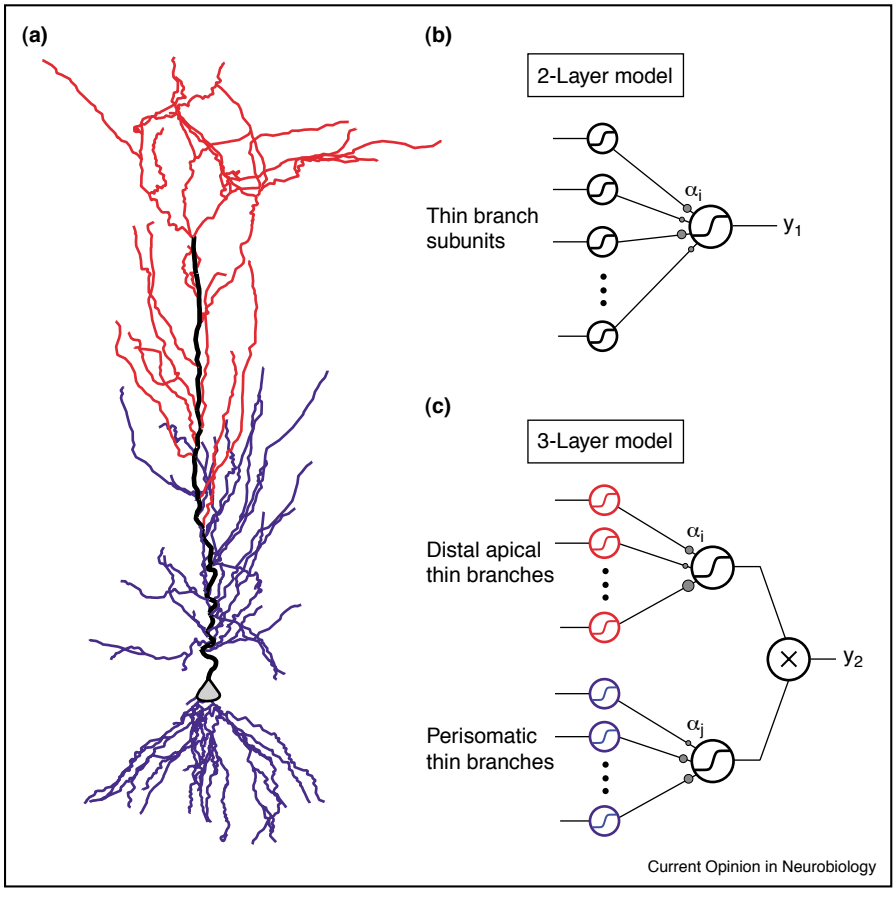
be difficult to achieve ([71]; see also Figure 7 in [72]). The precise lower limit on compartment size in the thin dendrites of pyramidal cells remains to be determined, perhaps through the use of voltage-sensitive dyes [73] and highly focal uncaging techniques [74].

Getting at the inner neuron

What are the implications of these findings for single-neuron computation? Could there be an underlying principle that permits the full complexity of a dendritic tree to be represented in highly simplified terms? The available data suggest that the thin terminal branches of the apical and basal trees of pyramidal cells provide a set of independent non-linear 'subunits' that sum up their synaptic inputs and then apply a sigmoidal thresholding non-linearity to the output. In this scenario, how should the outputs of multiple subunits be combined to influence the cell's overall response? In the few experimental studies that have addressed the question of location dependent synaptic summation, so far only involving simple spatial integration scenarios, the data are most consistent with a linear or sublinear summation rule for signals that originate in different dendritic branches [30,75–78]. Building on these findings, one can formulate a working model in which the thin branches are the integrative subunits of pyramidal neurons. According to this model, each thin-branch subunit sums up its synaptic drive and then applies a sigmoidal thresholding non-linearity to the result, and the subunit outputs are summed linearly within the main trunks and cell body before output spike generation. This hypothesis is interesting, in that it states that an individual pyramidal neuron functions something like a conventional two-layer abstract 'neural network' [12], in which the thin dendritic branches themselves act like classical point neurons (Figure 3b).

Poirazi and co-workers [79••] used a detailed CA1 pyramidal cell model [80•] to test the two-layer neural network hypothesis. The authors used a complex set of

Figure 3



Simplified models of pyramidal cells. **(a)** CA1 pyramidal cell morphology [123]. A grey triangular soma was added for clarity. **(b)** Two-layer sum-of-sigmoids model as discussed by Poirazi *et al.* [79••]. All thin branches are treated as independent subunits with sigmoidal thresholds whose outputs are summed linearly in the main trunks and cell body. Small grey circles labelled α_i represent subunit weights, which might vary as a function of location or branch order. **(c)** A next generation single neuron model could include a multiplicative interaction between proximal and distal integrative regions of the cell. Overall output of such a three-layer model might be expressed using the form $y_1 + \alpha y_2$.

synaptic stimuli in which a varying number of excitatory synapses were distributed in a wide variety of spatial patterns. They found that the firing rate of the detailed biophysical model cell could be predicted by a two-layer abstract network model with sigmoidal subunits — amounting to a simple paper and pencil calculation. The predictions made by a point neuron model were much poorer, particularly for stimulus sets that involved variation in the spatial distribution of synaptic inputs (rather than variation in their number).

The two-layer sum-of-sigmoids model is attractive from a computational point of view, and could have broad implications for the information processing [72,81] and learning-related [82•, see also 83•] functions of the brain. However, in dealing only with steady state input and output variables (i.e. spike rates), the model does not address the question of spike timing, which the evidence suggests can be extremely important in dendrites [84,85]. In addition, in its simplest form (Figure 3b) the two-layer model cannot accommodate the proximal-distal interactions that are the hallmark of the two-compartment model (note the difference between the notion of compartments and the notion of layers). It is also the case that mechanisms other than synaptic boosting and dendritic spiking could contribute to non-linear dendritic integration. Shunting inhibition in dendrites is highly location- and state-dependent [50,86], and a theoretical study has shown that it could account for subtle aspects of the direction selective responses of cortical neurons [87]. In the future, it should be possible to formulate a next-generation single-neuron abstraction that incorporates and reconciles the key features of the two-compartment and multi-compartment views of the neuron (Figure 3c).

Dendritic coincidence detection and synaptic plasticity

The compartmentalisation of signalling in dendrites has important implications not only for information processing but also for the rules that govern the induction of synaptic plasticity [88,89]. In particular, recent studies suggest that synaptic plasticity appears to provide a local readout of integration in different compartments of the neuron. First, long-term synaptic plasticity in pyramidal neurons has been shown to depend crucially on the relative timing of presynaptic and postsynaptic spikes [84]. As backpropagation of the postsynaptic action potential is necessary for this form of coincidence detection [85], the regulation of backpropagation should in turn affect the induction of synaptic plasticity. In neocortical [19•] and hippocampal [20] pyramidal neurons, pairing APs with EPSPs amplifies the backpropagating AP in the distal dendrites, which will enhance the dendritic calcium channel activation and the relief of the Mg^{2+} block of NMDA receptors by the BPAP [90]. This EPSP-AP coincidence detection has a similar time window and amplitude-dependence as the induction of long-term potentiation (LTP) [91,92], which suggests that this mechanism may be involved in triggering LTP in distal dendrites. The dendritic morphology is critical for this effect, as boosting starts to occur in the region where the BPAP begins to fail [40•,41]. Other means of regulating AP backpropagation, for example through channel modulation [20] or inhibition, can thus gate or modulate the induction of plasticity that involves BPAPs. Second, postsynaptic bursts are a particularly effective conditioning stimulus for triggering synaptic plasticity [92,93]. In layer 5 pyramidal cells, bursts of somatic APs are more effective than single APs at triggering dendritic spikes in the apical tree [15,51]. This may provide a means by which proximal synapses can regulate plasticity at distal dendritic synapses. Third, dendritic spikes can themselves trigger synaptic plasticity. In CA1 pyramidal neurons, initiation of distal dendritic spikes can trigger LTP in the absence of somatic action potential firing [94••]. This indicates that the distal dendrites can operate as a compartment not only for signal processing but also for plasticity, in which distal dendritic inputs can locally and cooperatively control their own strength. The important corollary of this result is that the spatial extent of propagation of the dendritic spike will in turn define the spatial range of plasticity. It remains to be determined how spatially restricted the calcium spikes are that trigger plasticity, and whether the resulting degree of compartmentalisation conforms more to the two-compartment or the multi-compartment view of the neuron. Taken together, these findings imply that dendritic trees impose spatial restrictions on synaptic plasticity. Specifically, the rules for induction of synaptic plasticity may differ at proximal and distal synapses in a way that is defined by the properties of their respective compartments. A next step of key importance will be to determine whether or not the compartments for integration and plasticity are equivalent.

Synaptic plasticity triggers plasticity of dendritic integration

The fact that dendritic ion channels are subject to modulation by neurotransmitters and second messenger systems, together with the demonstration of homeostatic modulation of intrinsic excitability [95], has lent support to the idea that synaptic plasticity may also trigger changes in dendritic function. Indeed, it is known that LTP induction is accompanied by increases in the responsiveness of the postsynaptic neuron to the same inputs, a phenomenon known as E–S (EPSP–spike) coupling [96,97]. The key issue is whether such changes in excitability are restricted to the compartment bearing the synapses that have undergone plasticity, and thus affect only the efficacy of synapses within the compartment, or if there exist more global changes in excitability that affect all synapses. In CA1 pyramidal neurons, LTP induction is accompanied by changes in dendritic integration of neighbouring inputs along the apical dendrite

[78], which the authors interpreted to be associated with a decrease in the activity of I_h. Using direct dendritic recordings combined with imaging it has been possible to demonstrate spatially restricted changes in dendritic excitability following LTP, showing that EPSP shapes are altered and BPAPs and associated calcium signals are locally enhanced following LTP induction [98]. These local excitability changes do not, however, exclude more global changes in excitability. Indeed, E–S potentiation can be counterbalanced by a global decrease in excitability [99]. Taken together with the fact that postsynaptic activity alone can produce a downregulation of the excitability of dendritic spines [100], this suggests that homeostatic mechanisms may act to maintain the overall level of activity within the normal range [95]. These findings offer the intriguing prospect that synapses regulate the excitability of their local compartments, which in turn leads to more global changes and modifies the rules for induction of subsequent plasticity within that compartment. The mechanistic links between local and global changes in plasticity are sure to be fruitful avenues of investigation.

Dendrites as presynaptic elements

Dendritic release of neurotransmitter, which has been found in several cell types [101–108], may provide another mode of dendritic 'readout' tied to the cell's compartment structure. Starburst amacrine cells in the retina release both γ-aminobutyric acid (GABA) and acetylcholine from their dendrites, making it likely that the local branch-specific calcium signals recently shown to be triggered by directionally-selective light stimuli will in turn trigger dendrite-specific transmitter release [66••]. Dendritic control of release is also seen in hypothalamic oxytocin neurons, in which dendritic secretion of oxytocin appears to occur independently of axonal spiking [109]. This supports the idea that regulation of the dendritic release compartment is separate from that of the axon. In the thalamus, local-circuit thalamic interneurons release GABA from their dendrites, which take part in a unique triadic structure, in which they are postsynaptic to the sensory afferents but presynaptic to the dendrites of thalamocortical cells and other interneurons. Muscarinic activation evidently switches the cell's firing from burst to tonic mode by uncoupling the distal dendrites from the soma and axon; this leads to dendritic release within the triad being favoured over axonal release [110]. The release of GABA from the dendrites also appears to be under tight local control [111], further supporting the idea that dendrites act as local processing compartments. In the olfactory bulb, the glutamatergic lateral dendrites of mitral cells form dendro–dendritic reciprocal synapses with inhibitory granule cells. APs backpropagate actively but decrementally in the lateral dendrite [112–116], and backpropagation is potently regulated by local inhibition [113–115] and A-type potassium channels [116]. This provides a means of modulating long-range lateral inhibition of neighbouring glomeruli, and supports the idea that the lateral dendrites act as a different functional compartment from the apical dendrite (in which AP backpropagation is highly reliable). Finally, the recent excitement with regards to the role of cannabinoids as a retrograde messenger [117] should focus interest on the mechanisms for regulating cannabinoid release from dendrites. In particular, it would be interesting to determine whether or not such release, which is known to be calcium-dependent, can be linked to calcium signalling in restricted dendritic compartments, and whether or not such release obeys spike timing-dependent plasticity rules that are defined by dendritic properties [84].

Conclusions: a view of the brain

Many of our recent insights into dendritic function have been obtained from *in vitro* and modelling studies. Ultimately, whether particular dendritic properties represent bugs or features must be determined in the context of the intact brain. Two-photon imaging experiments [118] and whole-cell recordings [16••] in anaesthetised animals have demonstrated that dendritic spikes can occur *in vivo*. To link these and other aspects of dendritic phenomenology to behaviour, it is essential to develop techniques that make this possible in the awake animal. An important step in this direction has been provided by Helmchen and co-workers [119], who have developed a miniaturised two-photon microscope that can be used to visualise neurons in the awake, freely-moving animal. In conjunction with intracellular recordings from neurons in awake [120,121] and freely moving animals [122], these new approaches will help us to determine when and how dendrites, and their compartments, contribute to the brain's remarkable capacities for perception, action and memory.

Acknowledgements

We thank the Human Frontier Science Program, the European Union, Wellcome Trust and Gatsby Foundation for support, and Mark Farrant, Mickey London, Troy Margrie, and Arnd Roth for comments.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Magee JC: **Dendritic Ih normalizes temporal summation in hippocampal CA1 neurons**. *Nat Neurosci* 1999, **2**:848.
2. Magee JC, Cook EP: **Somatic EPSP amplitude is independent of synapse location in hippocampal pyramidal neurons**. *Nat Neurosci* 2000, **3**:895-903.
3. Bernander O, Koch C, Douglas RJ: **Amplification and linearization of distal synaptic input to cortical pyramidal cells**. *J Neurophysiol* 1994, **72**:2743-2753.
4. Cauller LJ, Connors BW: **Synaptic physiology of horizontal afferents to layer I in slices of rat SI neocortex**. *J Neurosci* 1994, **14**:751-762.
5. • London M, Segev I: **Synaptic scaling *in vitro* and *in vivo***. *Nat Neurosci* 2001, **4**:853-855.

The authors demonstrate that scaling of synaptic conductances by their electronic distance, as measured for single synaptic inputs in CA1 pyramidal cells in slices, becomes 'self-defeating' *in vivo*. This is because as more inputs become active, the resulting increase in membrane conductance shunts the propagation of distal inputs towards the soma.

6. • Schaefer AT, Larkum ME, Sakmann B, Roth A: **Coincidence detection in pyramidal neurons is tuned by their dendritic branching pattern.** *J Neurophysiol* 2003, in press.

This study examines the factors that determine the coupling between the somatic and distal spike initiation zones in layer 5 pyramidal neurons. The position and number of oblique branches along the apical trunk are shown to play a crucial role.

7. Helmchen F: **Dendrites as biochemical compartments.** In *Dendrites*. Edited by Stuart GJ, Spruston N, Häusser M. Oxford UK: Oxford University Press; 1999:160-192.

8. Koch C, Poggio T, Torre V: **Retinal ganglion cells: a functional interpretation of dendritic morphology**. *Philos Trans R Soc Lond B Biol Sci* 1982, **298**:227-263.

9. McCulloch WS, Pitts WH: **A logical calculus of the ideas immanent in nervous activity**. *Bull Math Biophys* 1990, **99**:99-115.

10. Minsky M, Papert S: *Perceptrons*. Cambridge, MA: MIT Press; 1969.

11. Rumelhart D, McClelland J: *Parallel Distributed Processing: Explorations in the Microstructure of Cognition*. Cambridge, MA:MIT Press; 1986.

12. Bishop C: *Neural Networks for Pattern Recognition*. Oxford UK: Oxford University Press; 1995.

13. • Wei DS, Mei YA, Bagal A, Kao JP, Thompson SM, Tang CM: **Compartmentalized and binary behavior of terminal dendrites in hippocampal pyramidal neurons**. *Science* 2001, **293**:2272-2275.

Similar to the findings of Schiller *et al.* [14] in basal dendrites of neocortical cells, the authors reported that thin branches in the apical trees of CA1 pyramidal cells generated powerful slow spike-like responses when a threshold level of synaptic input (mimicked through glutamate uncaging) was reached.

14. Schiller J, Major G, Koester HJ, Schiller Y: **NMDA spikes in basal dendrites of cortical pyramidal neurons**. *Nature* 2000, **404**:285-289.

15. Larkum ME, Kaiser KM, Sakmann B: **Calcium electrogenesis in distal apical dendrites of layer 5 pyramidal cells at a critical frequency of back-propagating action potentials**. *Proc Natl Acad Sci USA* 1999, **96**:14600-14604.

16. •• Larkum ME, Zhu JJ: **Signaling of layer 1 and whisker-evoked Ca^{2+} and Na^{+} action potentials in distal and terminal dendrites of rat neocortical pyramidal neurons *in vitro* and *in vivo***. *J Neurosci* 2002, **22**:6991-7005.

Using a combination of *in vitro* and *in vivo* recording, the authors investigate the coupling of somatic and distal dendritic integration zones, and the dependence of threshold for axonal APs and dendritic spikes on dendritic location. They also demonstrate dendritic spikes evoked by whisker stimulation.

17. Larkum ME, Zhu JJ, Sakmann B: **A new cellular mechanism for coupling inputs arriving at different cortical layers**. *Nature* 1999, **398**:338-341.

18. • Larkum ME, Zhu JJ, Sakmann B: **Dendritic mechanisms underlying the coupling of the dendritic with the axonal action potential initiation zone of adult rat layer 5 pyramidal neurons**. *J Physiol* 2001, **533**:447-466.

In studying coupling between somatic and apical dendritic spike-generating zones, the authors showed that either small dendritic current injections or a distal synaptic input paired with a single backpropagating action potential evoked at the soma led to a BAC spike, which in turn caused a burst of 2–3 spikes at the soma. They also found that properly timed inhibition could interrupt the soma-dendritic spike coupling, and examined how current injected in the middle of the apical dendrite can modulate forward and backpropagation of APs, leading to the formulation of a three-compartment model.

19. • Stuart GJ, Häusser M: **Dendritic coincidence detection of EPSPs and action potentials**. *Nat Neurosci* 2001, **4**:63-71.

This study shows that pairing EPSPs with single APs substantially boosts the amplitude of BPAPs in the distal dendrites of layer 5 pyramidal cells with a time window similar to that required for the induction of synaptic plasticity. The mechanism relies on non-linear recruitment of dendritic Na^{+} channels.

20. Watanabe S, Hoffman DA, Migliore M, Johnston D: **Dendritic K^{+} channels contribute to spike-timing dependent long-term potentiation in hippocampal pyramidal neurons**. *Proc Natl Acad Sci USA* 2002, **99**:8366-8371.

21. Rall W: **Theoretical significance of dendritic trees for neuronal input-output relations.** In *Neural Theory and Modeling*. Edited by Reiss RF. Palo Alto: Stanford University Press, 1964: 73-97.

22. Segev I, Rall W: **Excitable dendrites and spines: earlier theoretical insights elucidate recent direct observations**. *Trends Neurosci* 1998, **21**:453-460.

23. Segev I, London M: **Untangling dendrites with quantitative models**. *Science* 2000, **290**:744-750.

24. Häusser M: **Synaptic function: dendritic democracy**. *Curr Biol* 2001, **11**:R10-12.

25. Williams SR, Stuart GJ: **Role of dendritic synapse location in the control of action potential output**. *Trends Neurosci* 2003, **26**:147-154.

26. •• London M, Schreibman A, Häusser M, Larkum ME, Segev I: **The information efficacy of a synapse**. *Nat Neurosci* 2002, **5**:332-340.

The authors use information theory to define a new measure of synaptic efficacy, the synaptic information efficacy (SIE) that captures the impact of a single synaptic input on the output. This offers a more rigorous way of quantifying changes in synaptic strength following synaptic plasticity, and of determining which biophysical factors are most important in determining synaptic efficacy measured in terms of spike output.

27. • Andrasfalvy BK, Magee JC: **Distance-dependent increase in AMPA receptor number in the dendrites of adult hippocampal CA1 pyramidal neurons**. *J Neurosci* 2001, **21**:9151-9159.

Using outside-out patches to study the properties and distribution of synaptic glutamate receptors, the authors found that AMPA receptor number increased by a factor of two over a several hundred μm stretch of the apical dendritic tree. This finding helps account for the surprising earlier observation [2] that somatic EPSP amplitude is nearly independent of synaptic location over this same range.

28. •• Williams SR, Stuart GJ: **Dependence of EPSP efficacy on synapse location in neocortical pyramidal neurons**. *Science* 2002, **295**:1907-1910.

The authors show that in layer 5 pyramidal neurons, unlike in CA1 pyramidal neurons, synaptic conductance is not scaled by electrotonic location. The substantial attenuation of distal dendritic inputs can be overcome by the boost provided by dendritic calcium spikes initiated by synchronous distal synaptic input.

29. • Oviedo H, Reyes AD: **Boosting of neuronal firing evoked with asynchronous and synchronous inputs to the dendrite**. *Nat Neurosci* 2002, **5**:261-266.

The authors found that simulated EPSP barrages delivered by current injection to the distal apical trunk led to higher axonal firing rates than identical EPSP trains delivered to the soma. The primary mechanism is used when the distal input combines with backpropagating spikes to enhance dendritic Na^{+} channel activation, which helps to further drive spiking.

30. Oakley JC, Schwindt PC, Crill WE: **Dendritic calcium spikes in layer 5 pyramidal neurons amplify and limit transmission of ligand-gated dendritic current to soma**. *J Neurophysiol* 2001, **86**:514-527.

31. De Schutter E, Bower JM: **Simulated responses of cerebellar Purkinje cells are independent of the dendritic location of granule cell synaptic inputs**. *Proc Natl Acad Sci USA* 1994, **91**:4736-4740.

32. Cook EP, Johnston D: **Voltage-dependent properties of dendrites that eliminate location-dependent variability of synaptic input**. *J Neurophysiol* 1999, **81**:535-543.

33. Rudolph M, Destexhe A: **A fast-conducting, stochastic integrative mode for neocortical neurons *in vivo***. *J Neurosci* 2003, **23**:2466-2476.

34. Williams SR, Stuart GJ: **Site independence of EPSP time course is mediated by dendritic I(h) in neocortical pyramidal neurons**. *J Neurophysiol* 2000, **83**:3177-3182.

35. Llinas R, Sugimori M: **Electrophysiological properties of *in vitro* Purkinje cell dendrites in mammalian cerebellar slices**. *J Physiol* 1980, **305**:197-213.

36. Yuste R, Gutnick MJ, Saar D, Delaney KR, Tank DW: **Ca^{2+} accumulations in dendrites of neocortical pyramidal neurons: an apical band and evidence for two functional compartments**. *Neuron* 1994, **13**:23-43.

37. Kim HG, Connors BW: **Apical dendrites of the neocortex: correlation between sodium- and calcium-dependent spiking and pyramidal cell morphology**. *J Neurosci* 1993, **13**:5301-5311.

38. Schiller J, Schiller Y, Stuart G, Sakmann B: **Calcium action potentials restricted to distal apical dendrites of rat neocortical pyramidal neurons**. *J Physiol* 1997, **505**:605-616.

39. Stuart G, Spruston N, Sakmann B, Häusser M: **Action potential initiation and backpropagation in neurons of the mammalian CNS**. *Trends Neurosci* 1997, **20**:125-131.

40. • Vetter P, Roth A, Häusser M: **Propagation of action potentials in dendrites depends on dendritic morphology**. *J Neurophysiol* 2001, **85**:926-937.
This study demonstrates that dendritic geometry, together with channel densities and properties, plays a crucial role in determining both forward and backpropagation of action potentials and dendritic spikes. The range of backpropagation efficacies observed experimentally can thus be linked to diversity in dendritic geometry. It is also shown that the sensitivity to channel modulation depends on the details of the dendritic geometry. These features are explained by a simple cable model of the neuron.

41. Golding NL, Kath WL, Spruston N: **Dichotomy of action-potential backpropagation in CA1 pyramidal neuron dendrites**. *J Neurophysiol* 2001, **86**:2998-3010.

42. • Rhodes PA, Llinas RR: **Apical tuft input efficacy in layer 5 pyramidal cells from rat visual cortex**. *J Physiol* 2001, **536**:167-187.
Using a compartmental model of a thick tufted layer 5 pyramidal cell, the authors found that in comparison to the oblique branches of the apical tree, the electrotonic structure of the apical tuft particularly lends itself to maintenance of prolonged depolarisations, thus facilitating the triggering of slow calcium spikes characteristic of this dendritic region.

43. Cauller LJ, Clancy B, Connors BW: **Backward cortical projections to primary somatosensory cortex in rats extend long horizontal axons in layer I**. *J Comp Neurol* 1998, **390**:297-310.

44. Pinsky PF, Rinzel J: **Intrinsic and network rhythmogenesis in a reduced Traub model for CA3 neurons**. *J Comput Neurosci* 1994, **1**:39-60.

45. Mainen ZF, Sejnowski TJ: **Influence of dendritic structure on firing pattern in model neocortical neurons**. *Nature* 1996, **382**:363-366.

46. Kepecs A, Wang XJ, Lisman J: **Bursting neurons signal input slope**. *J Neurosci* 2002, **22**:9053-9062.

47. Zhu JJ: **Maturation of layer 5 neocortical pyramidal neurons: amplifying salient layer 1 and layer 4 inputs by Ca^{2+} action potentials in adult rat tuft dendrites**. *J Physiol* 2000, **526**:571-587.

48. Miles R, Toth K, Gulyas AI, Hajos N, Freund TF: **Differences between somatic and dendritic inhibition in the hippocampus**. *Neuron* 1996, **16**:815-823.

49. Tsubokawa H, Ross WN: **IPSPs modulate spike backpropagation and associated $[Ca^{2+}]i$ changes in the dendrites of hippocampal CA1 pyramidal neurons**. *J Neurophysiol* 1996, **76**:2896-2906.

50. Pouille F, Scanziani M: **Enforcement of temporal fidelity in pyramidal cells by somatic feed-forward inhibition**. *Science* 2001, **293**:1159-1163.

51. Williams SR, Stuart GJ: **Backpropagation of physiological spike trains in neocortical pyramidal neurons: implications for temporal coding in dendrites**. *J Neurosci* 2000, **20**:8238-8246.

52. Magee JC: **A prominent role for intrinsic neuronal properties in temporal coding**. *Trends Neurosci* 2003, **26**:14-16.

53. Magee JC: **Dendritic mechanisms of phase precession in hippocampal CA1 pyramidal neurons**. *J Neurophysiol* 2001, **86**:528-532.

54. • Häusser M, Major G, Stuart GJ: **Differential shunting of EPSPs by action potentials**. *Science* 2001, **291**:138-141.
The authors show that the large conductances activated by the axonally initiated AP substantially shunt appropriately timed EPSPs. Synaptic inputs with slow kinetics, or arising at distal synapses, are relatively spared by this shunting mechanism. These findings suggest that for proximal synapses synaptic integration time depends on firing rate and that integration of distal inputs can proceed uninterrupted by somatic AP firing. The difference in shunting between pyramidal and Purkinje neurons indicates that shunting may be regulated on a cell-specific level.

55. Kapadia MK, Ito M, Gilbert CD, Westheimer G: **Improvement in visual sensitivity by changes in local context: parallel studies in human observers and in V1 of alert monkeys**. *Neuron* 1995, **15**:843-856.

56. McAdams CJ, Maunsell JH: **Attention to both space and feature modulates neuronal responses in macaque area V4**. *J Neurophysiol* 2000, **83**:1751-1755.

57. Salinas E, Abbott LF: **Coordinate transformations in the visual system: how to generate gain fields and what to compute with them**. *Prog Brain Res* 2001, **130**:175-190.

58. • Körding KP, König P: **Supervised and unsupervised learning with two sites of synaptic integration**. *J Comput Neurosci* 2001, **11**:207-215.
The authors show that an abstract neuron-like unit with two sites of synaptic integration, one that generates fast spikes (i.e. the soma) and the other slow spikes (i.e. the distal dendrites), could provide a mechanism whereby a network of neurons efficiently learns to respond to spatially invariant structures in the outside environment.

59. Körding KP, König P: **Neurons with two sites of synaptic integration learn invariant representations**. *Neural Comput* 2001, **13**:2823-2849.

60. Llinas R, Nicholson C, Precht W: **Preferred centripetal conduction of dendritic spikes in alligator Purkinje cells**. *Science* 1969, **163**:184-187.

61. Kamondi A, Acsady L, Buzsaki G: **Dendritic spikes are enhanced by cooperative network activity in the intact hippocampus**. *J Neurosci* 1998, **18**:3919-3928.

62. Golding NL, Spruston N: **Dendritic sodium spikes are variable triggers of axonal action potentials in hippocampal CA1 pyramidal neurons**. *Neuron* 1998, **21**:1189-1200.

63. Stuart G, Spruston N, Sakmann B, Häusser M: **Action potential initiation and backpropagation in neurons of the mammalian CNS**. *Trends Neurosci* 1997, **20**:125-131.

64. Schiller J, Schiller Y: **NMDA receptor-mediated dendritic spikes and coincident signal amplification**. *Curr Opin Neurobiol* 2001, **11**:343-348.

65. Elston GN, Rosa MG: **Morphological variation of layer III pyramidal neurones in the occipitotemporal pathway of the macaque monkey visual cortex**. *Cereb Cortex* 1998, **8**:278-294.

66. •• Euler T, Detwiler PB, Denk W: **Directionally selective calcium signals in dendrites of starburst amacrine cells**. *Nature* 2002, **418**:845-852.
The authors found that stimulus evoked Ca^{2+} signals in the branches of starburst amacrine cells in the retina were larger when a light was moved radially outward along the branch, confirming the predictions of Borg-Graham and Grzywacz [67]. Given the synaptic release sites are located distally in these cells, the suggestion is that each dendritic tip provides a direction-selective output onto their targets.

67. Borg-Graham LJ, Grzywacz N: **A model of the direction selectivity circuit in retina: transformations by neurons singly and in concert.** In *Single Neuron Computation*. Edited by McKenna T, Davis J, Zornetzer SF. Boston MA: Academic Press; 1992:347-375.

68. Luksch H, Karten HJ, Kleinfeld D, Wessel R: **Chattering and differential signal processing in identified motion-sensitive neurons of parallel visual pathways in the chick tectum**. *J Neurosci* 2001, **21**:6440-6446.

69. Sabatini BL, Maravall M, Svoboda K: **Ca^{2+} signaling in dendritic spines**. *Curr Opin Neurobiol* 2001, **11**:349-356.

70. Rose CR, Konnerth A: **NMDA receptor-mediated Na^{+} signals in spines and dendrites**. *J Neurosci* 2001, **21**:4207-4214.

71. Koch C, Zador A: **The function of dendritic spines: devices subserving biochemical rather than electrical compartmentalization**. *J Neurosci* 1993, **13**:413-422.

72. Archie KA, Mel BW: **A model for intradendritic computation of binocular disparity**. *Nat Neurosci* 2000, **3**:54-63.

73. Djurisic M, Zecevic DP: **Voltage imaging of action potentials and synaptic potentials in the primary and secondary dendrites of mitral cells**. *SFN Abstr* 2002, **32**:202-208.

74. Matsuzaki M, Ellis-Davies GC, Nemoto T, Miyashita Y, Iino M, Kasai H: **Dendritic spine geometry is critical for AMPA receptor expression in hippocampal CA1 pyramidal neurons**. *Nat Neurosci* 2001, **4**:1086-1092.

75. Cash S, Yuste R: **Linear summation of excitatory inputs by CA1 pyramidal neurons**. *Neuron* 1999, **22**:383-394.

76. Urban NN, Barrionuevo G: **Active summation of excitatory postsynaptic potentials in hippocampal CA3 pyramidal neurons**. *Proc Natl Acad Sci USA* 1998, **95**:11450-11455.

77. Tamas G, Szabadics J, Somogyi P: **Cell type- and subcellular position-dependent summation of unitary postsynaptic potentials in neocortical neurons**. *J Neurosci* 2002, **22**:740-747.

78. Wang Z, Xu N, Wu C, Duan S, Poo M: **Bidirectional changes in spatial dendritic integration accompanying long-term synaptic modifications**. *Neuron* 2003, **37**:463-472.

79. •• Poirazi P, Brannon T, Mel BW: **Pyramidal neuron as a 2-layer neural network**. *Neuron* 2003, **37**:989-999.
The authors test the power of several simple abstract models to predict the firing rate of their complex biophysical CA1 pyramidal cell model. They found that the best predictions were produced by a simple formula that mapped the physical subcomponents of the cell onto those of an abstract two-layer 'neural network'. In the first layer, synaptic inputs drive dozens of independent sigmoidal subunits corresponding to the long, thin terminal dendrites that make up the bulk of the cell's receptive surface. In the second layer, the thin branch outputs are summed within the main trunk and cell body before final thresholding.

80. • Poirazi P, Brannon T, Mel BW: **Arithmetic of subthreshold synaptic summation in a model of a CA1 pyramidal cell**. *Neuron* 2003, **37**:977-987.
The authors replicate a wide variety of *in vitro* data in a detailed compartmental model of a CA1 pyramidal neuron, and then use the model to address an array of methodological issues that can complicate the interpretation of dual input synaptic summation data. New experiments are proposed along with predicted outcomes.

81. Mel BW, Ruderman DL, Archie KA: **Translation-invariant orientation tuning in visual 'complex' cells could derive from intradendritic computations**. *J Neurosci* 1998, **18**:4325-4334.

82. • Poirazi P, Mel BW: **Impact of active dendrites and structural plasticity on the memory capacity of neural tissue**. *Neuron* 2001, **29**:779-796.
The authors used combinatorial analysis and computer simulations to quantify memory capacity as a function of dendritic geometry, finding that the long-term storage capacity of neural tissue may lie primarily in the selective addressing of synaptic contacts onto dendritic subunits.

83. • Stepanyants A, Hof PR, Chklovskii DB: **Geometry and structural plasticity of synaptic connectivity**. *Neuron* 2002, **34**:275-288.
To address the issue of structural plasticity on a short time scale and its consequences for storage capacity, the authors use simple but elegant geometric arguments to calculate the 'filling fraction' of cortical tissue. The filling fraction is the number of synaptic contacts actually made by the dendrite divided by the number of axons that are in principle accessible to the dendrite, that is, within a distance of one spine length.

84. Sjöström PJ, Nelson SB: **Spike timing, calcium signals and synaptic plasticity**. *Curr Opin Neurobiol* 2002, **12**:305-314.

85. Magee JC, Johnston D: **A synaptically controlled, associative signal for Hebbian plasticity in hippocampal neurons**. *Science* 1997, **275**:209-213.

86. Gulledge AT, Stuart GJ: **Excitatory actions of GABA in the cortex**. *Neuron* 2003, **37**:299-309.

87. Mo C, Koch C: **Modeling revers-phi motion selective neurons in cortex: double synaptic veto mechanism.** *Neural Comput* 2003, in press.

88. Mainen ZF: **Functional plasticity at dendritic synapses.** In *Dendrites*. Edited by Stuart G, Spruston N, Häusser M. Oxford, UK: Oxford University Press; 1999:310-338.

89. Goldberg J, Holthoff K, Yuste R: **A problem with Hebb and local spikes**. *Trends Neurosci* 2002, **25**:433-435.

90. Vargas-Caballero M, Robinson HPC: **A slow component of voltage-dependent Mg^{2+} unblock of NMDA receptors limits their contribution to spike generation in cortical pyramidal neurons**. *J Neurophysiol* 2003, **89**:2778-2783.

91. Markram H, Lubke J, Frotscher M, Sakmann B: **Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs**. *Science* 1997, **275**:213-215.

92. Sjöström PJ, Turrigiano GG, Nelson SB: **Rate, timing, and cooperativity jointly determine cortical synaptic plasticity**. *Neuron* 2001, **32**:1149-1164.

93. Pike FG, Meredith RM, Olding AW, Paulsen O: **Postsynaptic bursting is essential for 'Hebbian' induction of associative long-term potentiation at excitatory synapses in rat hippocampus**. *J Physiol* 1999, **518**:571-576.

94. •• Golding NL, Staff NP, Spruston N: **Dendritic spikes as a mechanism for cooperative long-term potentiation**. *Nature* 2002, **418**:326-331.
The authors show that dendritic spikes triggered by cooperative synaptic input to the distal dendrites of CA1 pyramidal cells contribute to the postsynaptic depolarisation and calcium entry necessary to trigger LTP. This form of plasticity does not require axonal action potentials, suggesting that dendritic spikes may functionally link together neighbouring groups of synapses by triggering plasticity in local dendritic domains.

95. Turrigiano GG, Nelson SB: **Hebb and homeostasis in neuronal plasticity**. *Curr Opin Neurobiol* 2000, **10**:358-364.

96. Bliss TV, Lomo T: **Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path**. *J Physiol* 1973, **232**:331-356.

97. Daoudal G, Hanada Y, Debanne D: **Bidirectional plasticity of excitatory postsynaptic potential (EPSP)-spike coupling in CA1 hippocampal pyramidal neurons**. *Proc Natl Acad Sci USA* 2002, **99**:14512-14517.

98. Frick AA, Magee JC, Schexnayder L, Inoue M, Miyakawa H, Johnston D: **LTP induction enhances locally the back-propagation of action potentials into dendrites**. *SFN Abstr* 2002, **32**:442-443.

99. Fricker D, Johnston D: **Plastic changes in intrinsic excitability associated with long-term synaptic potentiation in CA1 pyramidal neurons**. *SFN Abstr* 2001, **31**:1.

100. Yasuda R, Sabatini BL, Svoboda K: **All-or-none, stochastic depression of R-type calcium channels in dendritic spines**. *SFN Abstr* 2002, **32**:435-437.

101. Häusser M, Stuart G, Racca C, Sakmann B: **Axonal initiation and active dendritic propagation of action potentials in substantia nigra neurons**. *Neuron* 1995, **15**:637-647.

102. Zilberter Y, Kaiser KM, Sakmann B: **Dendritic GABA release depresses excitatory transmission between layer 2/3 pyramidal and bitufted neurons in rat neocortex**. *Neuron* 1999, **24**:979-988.

103. Zilberter Y: **Dendritic release of glutamate suppresses synaptic inhibition of pyramidal neurons in rat neocortex**. *J Physiol* 2000, **528**:489-496.

104. Falkenburger BH, Barstow KL, Mintz IM: **Dendrodendritic inhibition through reversal of dopamine transport**. *Science* 2001, **293**:2465-2470.

105. Urban NN, Sakmann B: **Reciprocal intraglomerular excitation and intra- and interglomerular lateral inhibition between mouse olfactory bulb mitral cells**. *J Physiol* 2002, **542**:355-367.

106. Isaacson JS: **Mechanisms governing dendritic gamma-aminobutyric acid (GABA) release in the rat olfactory bulb**. *Proc Natl Acad Sci USA* 2001, **98**:337-342.

107. Schoppa NE, Westbrook GL: **Glomerulus-specific synchronization of mitral cells in the olfactory bulb**. *Neuron* 2001, **31**:639-651.

108. Halabisky B, Friedman D, Radojicic M, Strowbridge BW: **Calcium influx through NMDA receptors directly evokes GABA release in olfactory bulb granule cells**. *J Neurosci* 2000, **20**:5124-5134.

109. Ludwig M, Sabatier N, Bull PM, Landgraf R, Dayanithi G, Leng G: **Intracellular calcium stores regulate activity-dependent neuropeptide release from dendrites**. *Nature* 2002, **418**:85-89.

110. Zhu J, Heggelund P: **Muscarinic regulation of dendritic and axonal outputs of rat thalamic interneurons: a new cellular mechanism for uncoupling distal dendrites**. *J Neurosci* 2001, **21**:1148-1159.

111. Cox CL, Sherman SM: **Control of dendritic outputs of inhibitory interneurons in the lateral geniculate nucleus**. *Neuron* 2000, **27**:597-610.

112. Charpak S, Mertz J, Beaurepaire E, Moreaux L, Delaney K: **Odor-evoked calcium signals in dendrites of rat mitral cells**. *Proc Natl Acad Sci USA* 2001, **98**:1230-1234.

113. Margrie TW, Sakmann B, Urban NN: **Action potential propagation in mitral cell lateral dendrites is decremental and controls recurrent and lateral inhibition in the mammalian olfactory bulb**. *Proc Natl Acad Sci USA* 2001, **98**:319-324.

114. Lowe G: **Inhibition of backpropagating action potentials in mitral cell secondary dendrites**. *J Neurophysiol* 2002, **88**:64-85.

115. Xiong W, Chen WR: **Dynamic gating of spike propagation in the mitral cell lateral dendrites**. *Neuron* 2002, **34**:115-126.

116. Christie JM, Westbrook GL: **Regulation of backpropagating action potentials in mitral cell lateral dendrites by A-type potassium currents**. *J Neurophysiol* 2003, **89**:2466-2472.

117. Wilson RI, Nicoll RA: **Endocannabinoid signaling in the brain**. *Science* 2002, **296**:678-682.

118. Helmchen F, Svoboda K, Denk W, Tank DW: ***In vivo* dendritic calcium dynamics in deep-layer cortical pyramidal neurons**. *Nat Neurosci* 1999, **2**:989-996.

119. Helmchen F, Fee MS, Tank DW, Denk W: **A miniature head-mounted two-photon microscope. High-resolution brain imaging in freely moving animals**. *Neuron* 2001, **31**:903-912.

120. Margrie TW, Brecht M, Sakmann B: ***In vivo*, low-resistance, whole-cell recordings from neurons in the anaesthetized and awake mammalian brain**. *Pflugers Arch* 2002, **444**:491-498.

121. Steriade M, Timofeev I, Grenier F: **Natural waking and sleep states: a view from inside neocortical neurons**. *J Neurophysiol* 2001, **85**:1969-1985.

122. Luo M, Katz LC, Fee MS: **Encoding pheromonal signals in the accessory olfactory bulb of behaving mice**. *Science* 2003, **299**:1196-1201.

123. Cannon RC, Turner DA, Pyapali GK, Wheal HV: **An on-line archive of reconstructed hippocampal neurons**. *J Neurosci Methods* 1998, **84**:49-54.