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Dendrites: bug or feature?

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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.

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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.

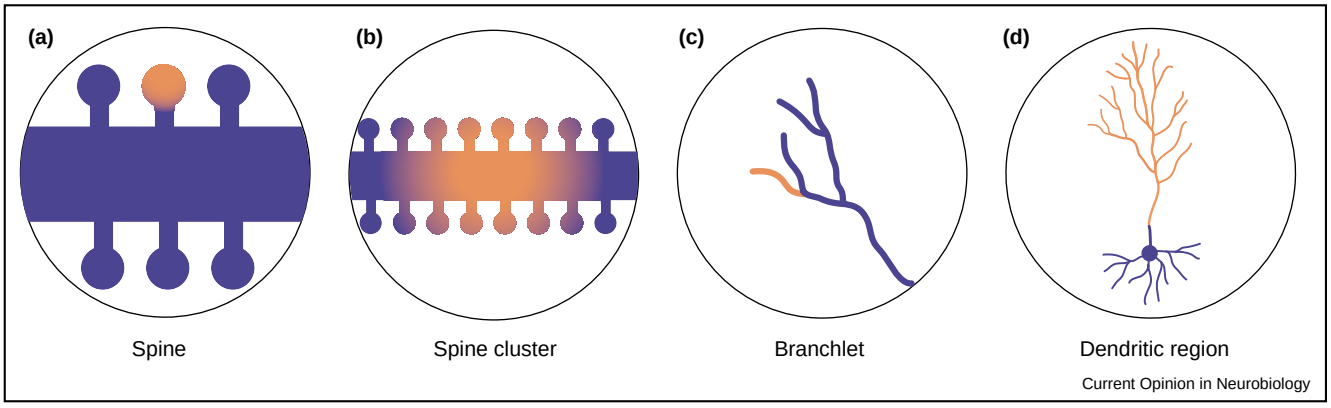
The past few years have seen an explosion of interest in dendrites, partly driven by the advent of powerful new imaging and recording techniques. However, as dendrites have taken centre stage in our search for an understanding of single-neuron computation, the mass of new data available has in some cases 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

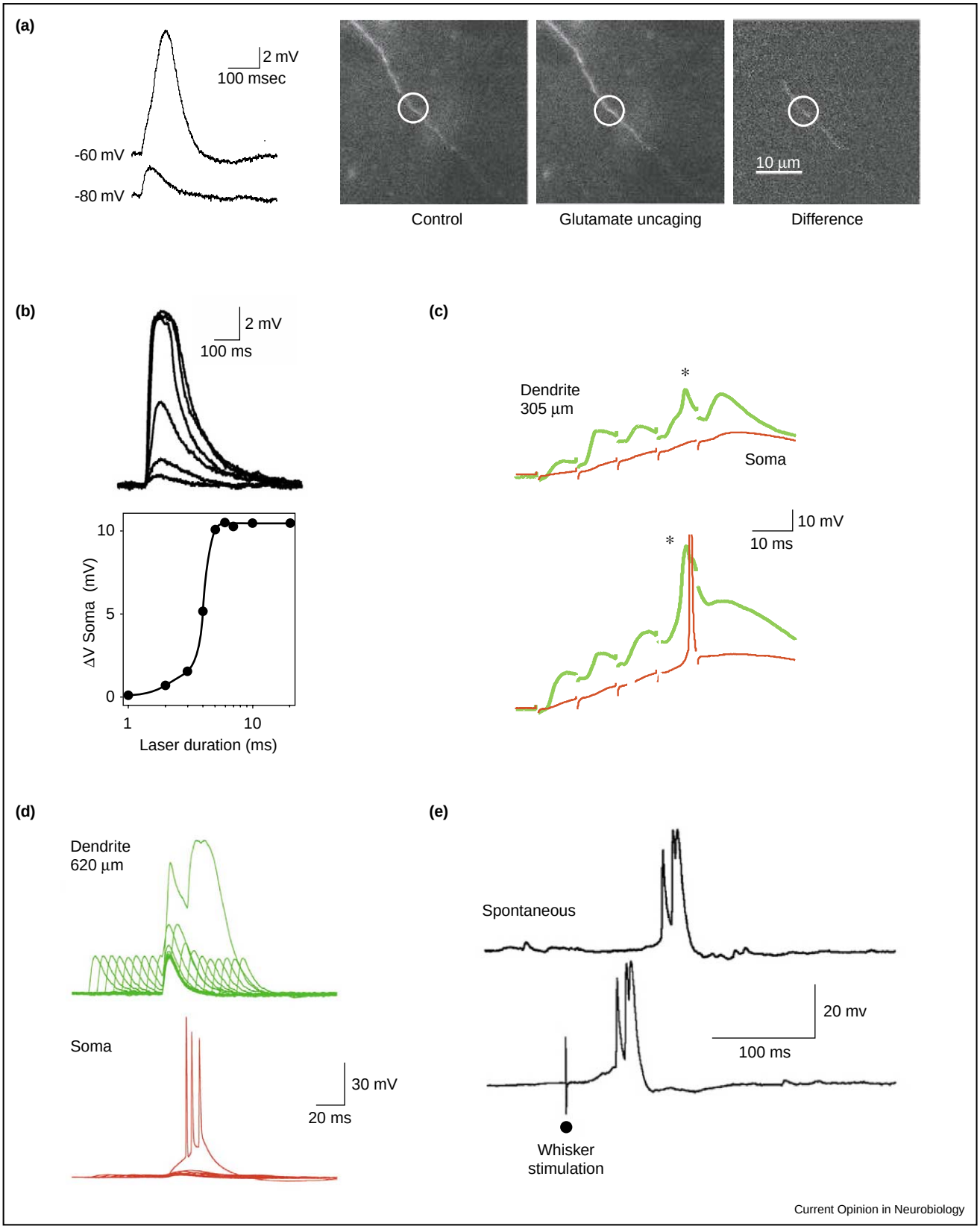
Since the work of Llinas and Sugimori [35] in Purkinje neurons more than two decades ago, it has become well established that the distal dendrites of many neuronal types can initiate regenerative spikes [3,16••,36–38]. Dendritic spikes (see Figure 2 for examples) have a clear voltage and stimulus intensity 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
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(d)
Dendrite
620 µm
Soma
30 mV
20 ms
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20 mv
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stimulation
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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

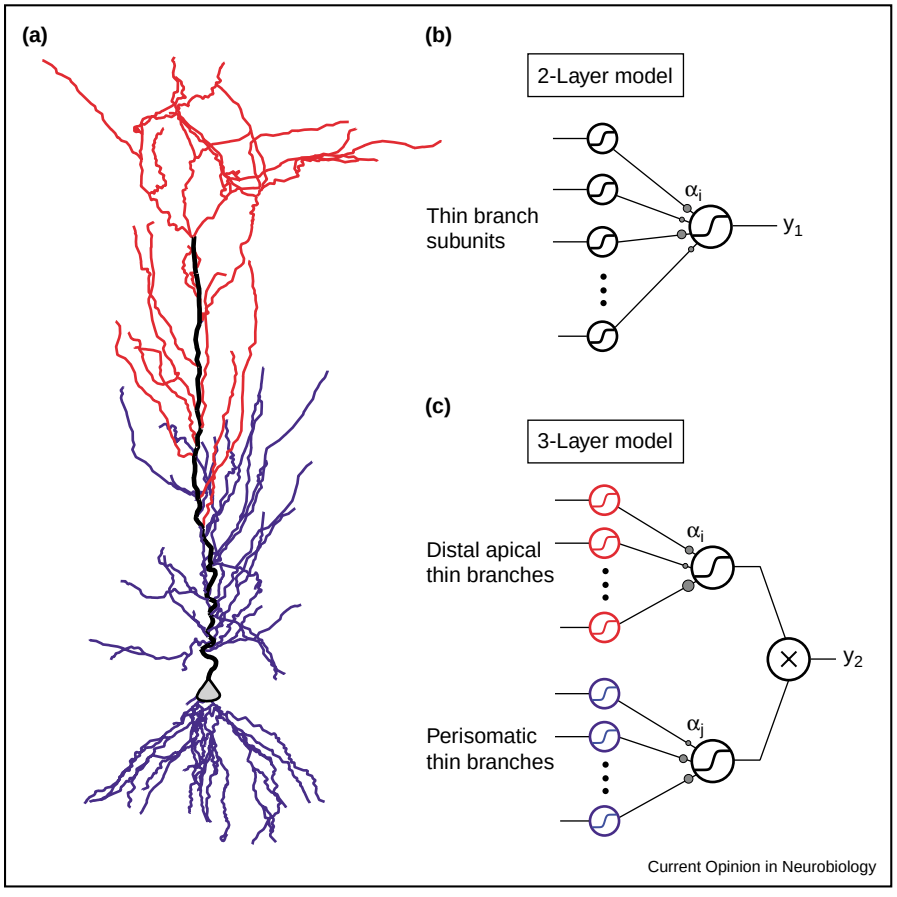
be difficult to achieve ([71]; see also Figure 7 in [72]). The precise lower limit on compartment size in the thin dendrites of pyramidal cells remains to be determined, perhaps through the use of voltage-sensitive dyes [73] and highly focal uncaging techniques [74].

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.

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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.

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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.

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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.

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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.

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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.

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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.

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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.

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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.

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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.

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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.

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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.

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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.

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