Illuminating dendritic function with computational models

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Abstract | Dendrites have always fascinated researchers: from the artistic drawings by Ramon y Cajal to the beautiful recordings of today, neuroscientists have been striving to unravel the mysteries of these structures. Theoretical work in the 1960s predicted important dendritic effects on neuronal processing, establishing computational modelling as a powerful technique for their investigation. Since then, modelling of dendrites has been instrumental in driving neuroscience research in a targeted manner, providing experimentally testable predictions that range from the subcellular level to the systems level, and their relevance extends to fields beyond neuroscience, such as machine learning and artificial intelligence. Validation of modelling predictions often requires — and drives — new technological advances, thus closing the loop with theory-driven experimentation that moves the field forward. This Review features the most important, to our understanding, contributions of modelling of dendritic computations, including those pending experimental verification, and highlights studies of successful interactions between the modelling and experimental neuroscience communities.

Dendrites are thin processes that extend from the cell body of neurons. Their name originates from the Greek word 'dendron', owing to their obvious resemblance to 'trees'. Although first observed more than a century ago by Camillo Golgi[1] and Santiago Ramon y Cajal[2], the functional role of dendrites in the brain of behaving animals remains enigmatic. Golgi's proposition that dendrites served a nutrient role has long been disproved, whereas Ramon y Cajal's neuron doctrine, whereby dendrites provide the entry site and axons provide the output of neuronal cells, remains a very simplistic view of how dendrites operate.

Our limited understanding of dendritic function stems partly from technical barriers in manipulating dendritic properties and monitoring the effects of these manipulations across levels (synaptic, dendritic, neuronal, circuit and behavioural) while animals perform various naturalistic tasks. Technological advances[3–5] over the years have enabled certain types of cross-scale investigations, including the ability to optogenetically manipulate dendrites[6,7] and assess effects on behavioural correlates, such as sensory perception[7]. Assessing the network-level effects of dendrites and causally linking them to behaviour, however, remains a major challenge. Even if experimental techniques could provide all components necessary for understanding dendritic functions, an integrative approach is needed to put the pieces together.

Modelling provides a theoretical framework in which predictions and experimental evidence can be integrated to infer the key principles of dendritic operation. Computational models allow the fast, systematic, exhaustive and reversible manipulation of properties that may not be amenable to direct manipulation in living tissue, such as changes in dendritic morphology or the distribution of ionic channels in specific compartments and at specific time points. These interventions can, in turn, provide mechanistic explanations for experimental observations by identifying the key determinants of dendritic function. Conversely, hypothesis-driven modelling enables the synthesis of existing data into concrete theories and can lead to truly unexpected findings that guide further experimentation in a targeted manner.

This Review is centred on computational studies that link dendrites to brain function. Although dendritic processing has been investigated in various neuron types[8–11] and species (discussed elsewhere[12]), we focus mainly on dendritic models of neocortical and hippocampal neurons in rodents, as they provide the large bulk of the literature on dendritic computations. We address three levels of abstraction of modelling approaches — from the single neuron to the microcircuit and large-scale levels — and present select generic and function-specific predictions along with respective or pending experimental verifications (BOX 1). Rather than providing an exhaustive list, we aim to highlight the complementarity of computational and experimental techniques, and propose that such a synergistic approach is the way forward in hypothesis-driven research.

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Coincidence detectors
Parts of a neuron and/or neural circuit that show a supralinear increase of response upon coincident arrival of different input pathways.

Artificial neural networks
(ANNs). Versatile networks with weighted, directed connections organized in layers. ANNs are mathematical models capable of learning and are used mostly for classification tasks.

Rationale for modelling dendrites

Early models pioneered by Wilfrid Rall and colleagues[13–15] used a powerful theoretical tool, the cable theory, to study how dendrites influence neuronal computations. They predicted that, owing to the passive properties of neuronal membranes, the combined activation of nearby inputs to dendrites would result in a smaller depolarization than if those inputs were placed further apart. This sublinear integration was subsequently seen along the apical trunk of pyramidal neurons of hippocampal region CA1 (REF.[16]) and later in the dendritic branches of cerebellar neurons[17,18]. Moreover, sequential activation of the same synapses in opposite directions along a dendrite (towards or away from the soma) was predicted to produce different somatic responses, and this was confirmed experimentally in retinal[19] and cortical[20] neurons. These early models, extensively reviewed elsewhere[15,21,22], paved the way for modelling to become a key complementary technique in the quest for determining what dendrites do.

The advantages of modelling. Importantly, dendrites of most neuron types are morphologically complex and contain a rich repertoire of voltage-gated ion channels (also known as active channels)[23]. Activation of these channels alters synaptic integration in a non-linear manner, enabling dendrites to exhibit localized, regenerative electrical events termed dendritic spikes[24–27] and to support spatially restricted plasticity[28]. These properties furnish dendrites with a range of computational capabilities previously thought possible only at the level of neuronal networks. For example, non-linearities enable pyramidal neuron dendrites to act as coincidence detectors[29] and temporal sequence detectors[20]. They also allow individual neurons to integrate inputs similar to traditional two-layer[30–32] or complex multilayer[33] artificial neural networks (ANNs), while playing a critical role in information coding and memory capacity[34–36]. Moreover, recent studies in awake, behaving animals have demonstrated a key role of dendritic signals in brain functions, such as spatial navigation[37–39], sensory processing[40,41], sensory–motor integration[42], motor learning[43] and perception[7]. These findings implicate dendrites as key players in brain function in behaving animals and call for a deeper investigation of their role.

Experimental recording and manipulation of dendritic properties in vivo is especially challenging. These structures are much denser than cell bodies, are extensively tangled and receive a plethora of inputs organized in complex spatio-temporal ways from many different cell types. These properties make the study of dendritic contributions to behaviour much more challenging than respective interventions that target neuronal cell bodies, necessitating a battery of new, advanced techniques (BOX 2). Computational modelling is thus indispensable for the study of dendrites, as it provides unlimited power for probing and monitoring the effect of anatomical, physiological or plasticity changes at any location along even the most complex dendritic trees. When combined with experiments, modelling can help bridge the gap between high-level experimental interventions, their effect at the dendritic/neuronal or circuit levels and, ultimately, behaviour.

Choosing the best model. Dendritic models vary significantly, both in their level of biological realism (that is, in the extent to which they faithfully reproduce the system studied) and in their computational complexity (and, by extension, the resources and time required to simulate these models) (FIG. 1). There is no single answer to the quest of finding the 'best model', as this depends heavily on the question or questions asked. Perhaps the only universal advice that one can offer is based on Occam's razor: the best model is the one detailed enough to

Box 1 | Key predictions to be tested, and techniques needed to address them

Through the years, modelling studies have strived to identify the principles of dendritic and neuronal processing and how these are shaped when embedded in circuits. Inspired by experimental findings, these studies in turn aim to inform research efforts for the most promising experimental designs. For example, models can be used to test open questions by performing virtual manipulations that are only limited by the available computational resources and/or the imagination of the researchers. Through these manipulations and the ways that modelling predictions can be experimentally validated, models point to the key limitations and needed advances in experimental techniques. This crosstalk has proved to be effective for several predictions, as discussed throughout this Review, yet several predictions still await experimental verification. Here, we summarize the most important of these along with potential verification experiments.

Experiments that establish the functional role of patterned versus random activation of synapses in vivo should determine the extent to which synapse location on dendrites matters. More specifically, to test the model prediction that in-branch localization of spines affects output differently to a between-branch distribution[30,32,58], it would be useful to image the activity of individual spines at high spatio-temporal resolution on all of the dendrites of a single neuron in the behaving animal. Furthermore, a possible experiment to test the prediction that rewiring of axonal projections can result in the grouping of co-active axons onto the same dendritic branch[35,153,231] would involve identifying the presynaptic neurons for a given cell, and tracking axonal activity and mobility during development or learning, ideally capturing multiple dendrites of a single neuron.

The predictions that there are different dendritic integration modes that subserve different computations (for example, linear, supralinear, sigmoidal and so on[30,32,104]) and are mediated by different conductances and anatomical features can be tested by detecting dendritic integration modes while animals learn or execute different tasks. This can be done by recording the activity of individual spines and dendrites within single neurons and comparing this activity with circuit computations and behavioural read-outs. Moreover, future studies could assess the effects of targeted manipulation of specific dendritic inputs or conductances on dendritic responses, neuronal output and behaviour.

Another prediction that remains to be tested is whether single neurons acts as multilayer artificial neural networks[30,32,145]. High-resolution, single spine-level imaging, as well as holographic stimulation of individual spines that are distributed in different ways on a single neuron, coupled with somatic-activity measurements will be useful in determining how different compartments of a neuron contribute to dendritic and neuronal output.

To test whether error prediction is implemented in dendrites as an imbalance of excitatory and inhibitory input[159], researchers could record net excitatory and inhibitory currents from identified presynaptic neurons and specific to the apical tuft or basal tree, while simultaneously measuring dendritic responses and tracking plasticity induction in specific dendritic compartments. Relatedly, control of inhibitory inputs at specific locations on dendrites (through manipulation of select incoming axons) in vivo would be useful for ascertaining whether, as predicted[108,128], the inhibitory inputs regulate dendritic compartmentalization.

Last but not least, specific conductances could be manipulated — that is, activated or inactivated — in behaving animals while field potentials are recorded, to test the prediction that active dendritic conductances are visible in field potential recordings[183].

Box 2 | **Potential experimental approaches to test modelling predictions**

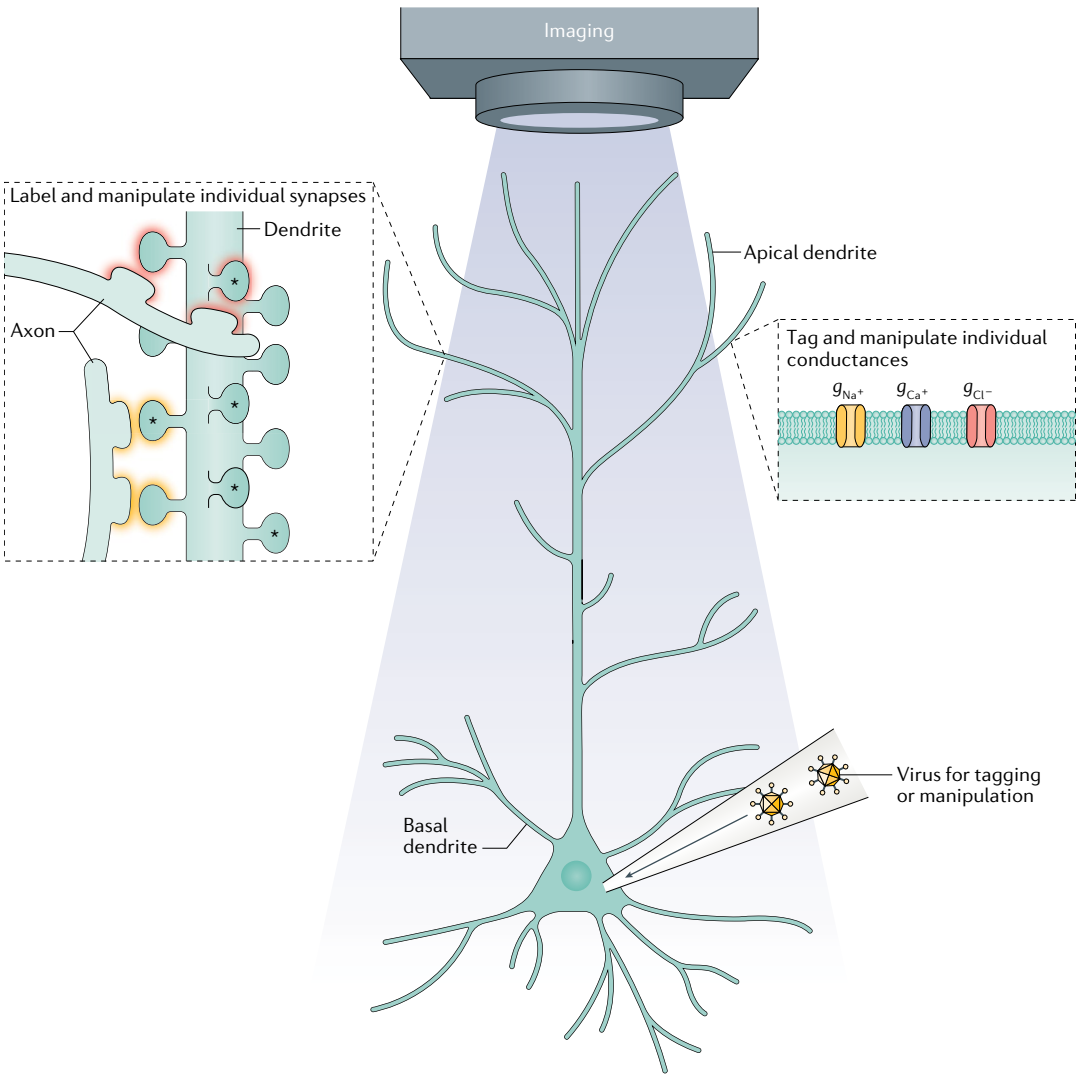
To effectively test the potential contributions of dendrites to circuit function and behaviour, technological advances are required. Currently, the most widely used activity-tracking technique — calcium imaging — provides reliable measurements of both subthreshold and suprathreshold activity in dendrites and spines, albeit with low temporal resolution. In the near future, high-frequency image acquisition[232,233] combined with genetically encoded voltage indicators[234,235] should allow for subthreshold and suprathreshold imaging of neuronal, dendritic and individual spine events in the same cell and/or in large populations of neurons.

Experimental techniques should enable the identification of presynaptic origins of specific spine inputs (marked with different colours) that participate in the formation (or not) of functional spine clusters, whereby neighbouring spines encode similar features, such as a specific line orientation[40]. Efforts towards this goal are emerging, including the anatomical identification of synaptic connections[236,237] and their functional characterization[210].

Selective manipulation of subcellular elements — for example, the selective activation or deactivation of individual spine structures corresponding to a given memory (marked with an asterisk in the figure) — is also important[238]. Although some structural manipulations, such as those driving the extension or retraction of dendrites, diameter modifications and changes in spine turnover rates, can be performed in cultures[239,240] or in genetically modified animals[36] as well as through the use of laser ablation in vivo[209], they are almost always non-reversible and typically unidirectional. Reversible approaches need to be developed.

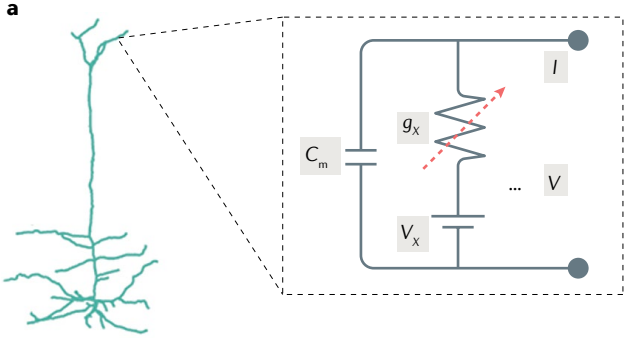
Teasing apart the effects of morphology from those of biophysical properties is a huge challenge, as these two factors often act in concert to produce a specific output, such as somatic bursting. Ideally, one would want to selectively tag and manipulate specific ionic conductances (such as g_{Na^+} or g_{Ca^+}) and synaptic conductances in vivo.

Finally, the expression of activity and plasticity markers or opsins targeted specifically to dendrites will be necessary to better understand their function. Selective tagging should also be tree-specific (for example, using distinct tags in apical and basal trees) or neuron-specific, and could be achieved through the use of transgenic animals[241] and/or cell type-specific viruses.



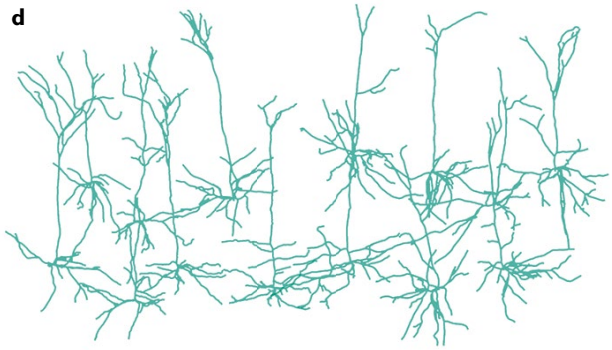
Detailed biophysical models

a



Multi-compartmental model

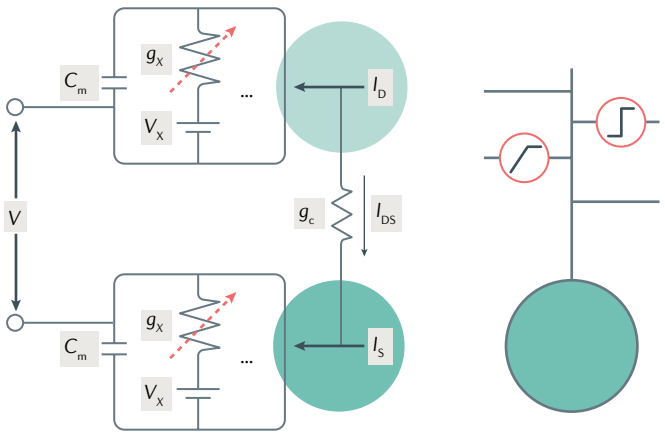
d



Multi-compartmental model

Reduced models

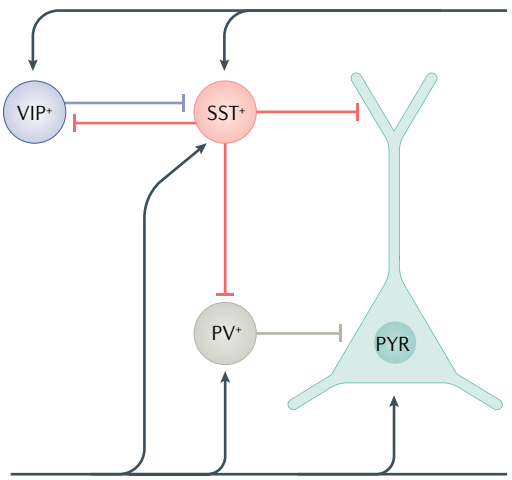
b



Two-compartment model

Two-stage integrate-and-fire model

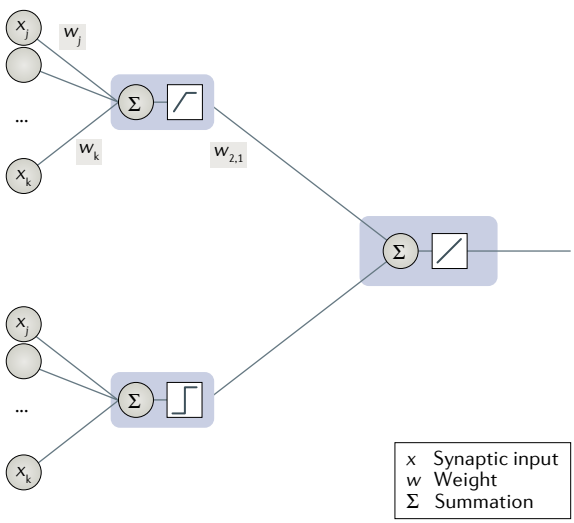
e



Few-compartment model

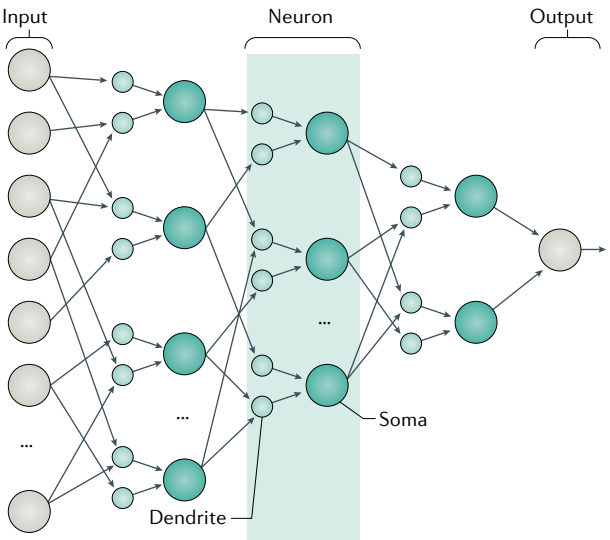
Mathematical abstractions

c



Two-layer modular ANN

f



Deep ANN architecture

Fig. 1 | **Levels of description in single-cell and circuit models with dendrites.** **a** | Detailed multi-compartmental models describe the morphology and biophysical properties of neurons by connecting together hundreds to thousands of electrical compartments each with their own conductances. These models are ideal for investigating how specific subcellular mechanisms (such as ionic conductances, receptors and synaptic machinery) or morphological features (for example, branch points) interact with one another and influence dendritic integration and/or neuronal output over time and/or space. These models provide mechanistic inferences that, in turn, allow for direct experimental testing of single neuron-level computational hypotheses. However, they are computationally costly, as they have hundreds to thousands of parameters and require solving numerous differential equations to simulate current (*I*) and voltage (*V*) changes over time and space. Various algorithms have been developed for the optimization of the respective parameters[223,224]. **b** | Examples of reduced models include simplification of multi-compartmental models to just two compartments or integrate-and-fire models[225] that use a few equations to describe somatic and dendritic activity[112,150,153]. These models are ideal for capturing simple features, such as the mean firing rate or the pattern of somatic output (for example, regular firing versus bursting). In such a model, the dendritic morphology and biophysics can be simplified or completely omitted. Reduced models ensure computational savings and also maintain the ability to probe the effects of selected mechanisms on neuronal output. Depending on the level of description implemented for dendrites, reduced models can account for some phenomena, such as the role of dendritic spikes in memory engrams[32,153] or information binding[216]. They are not appropriate, however, for studying the contributions of different membrane mechanisms to dendritic integration or the effect of morphological features on dendritic or neuronal output. **c** | Artificial neural network (ANN) abstraction of a neuron with two types of dendrites that are depicted as sigmoidal and saturating linear nodes. If the goal is not to simulate the activity of a neuron but, rather, to come up with a mathematical formalism that captures what a neuron computes, the best model can take the form of known statistical (for example, Bayesian), cascade (such as in linear–non-linear models) or other mathematical tools, such as ANNs. Theoretical models are ideal for formalizing neuronal computations and transferring insights from neuroscience to other disciplines (such as machine learning (ML) and artificial intelligence). They cannot, however, be used to identify the mechanistic underpinnings of the said computations in the neural tissue. **d** | Multi-compartmental models of neurons can be connected together to form detailed circuit models. These models can investigate network-level hypotheses and predict relevant biophysical mechanisms. **e** | Circuit models can be composed of different cell types that are represented by reduced compartmental or integrate-and-fire models with a small number of dendritic compartments. **f** | Deep ANN architectures can also consider dendrites through a structured connectivity scheme. Such architectures can be used to advance ML algorithms through the incorporation of biological features[226] and/or to provide insights regarding potential dendritic or neuronal contributions to specific functions[160,227]. C_m, specific membrane capacitance; g_x, conductance of ion x; I_D, dendritic current; I_S, somatic current; I_{DS}, dendro-somatic current; red dotted arrow, voltage-gated conductance; PV^+, parvalbumin-expressing; PYR, pyramidal; SST^+, somatostatin-expressing; VIP^+, vasoactive intestinal peptide-expressing. Parts **a**,**d** adapted with permission from REF.[201], American Physiological Society. Parts **b**,**c** adapted from REF.[32], CC BY 4.0 (https://creativecommons.org/licenses/by/4.0).

address the question of interest but requiring the smallest possible number of parameters. Various publicly available databases and simulators provide the necessary tools for modelling phenomena at the desired level of analysis (TABLE 1). In the following sections, we present successful examples of such modelling approaches and discuss their contributions to furthering our understanding of brain functions.

Single-neuron models

Single-neuron models that account for dendrites can be used to assess the effects of dendritic morphology, biophysics and plasticity on neuronal output. As discussed below, different approaches, including detailed biophysical models, reduced models and mathematical abstractions of single neurons, have explored these properties, providing important insights (FIG. 2).

Ionic channels
Protein structures that span the cell membrane, enabling the (selective) passage of ions from one side of the membrane to the other through the channel pore.

Effects of dendritic morphology on neuronal output. The quest to understand how the elaborated morphology of dendritic trees affects function dates back to the late 1800s[2]. Computational studies used elegant morphological modifications, such as reducing or enlarging the dendritic trees, or merely modifying their topological structure, to make causal predictions of how dendritic morphology affects neuronal responses[44–52]. For example, models investigated how the size and branching pattern of dendritic trees regulate burst or regular spiking of pyramidal neurons in CA3 (REF.[48]), the visual cortex[51] and the prefrontal cortex (PFC)[52]. CA3 pyramidal neurons with large dendritic trees are predicted to have lower burst rates, higher thresholds for state transitions (from quiescent to bursting and from bursting to regular spiking) and a higher tendency to burst from a plateau than CA3 pyramidal neurons with smaller dendritic trees. Similarly, in the PFC, the dendritic length, volume and branch number discriminate regular-spiking pyramidal neurons from intrinsic-bursting pyramidal neurons[52].

The geometrical features of dendritic bifurcations and their effect on signal integration were also identified in detailed CA1 pyramidal neuron models and validated by glutamate uncaging experiments[53]. In this study, morphological variations of branch points were predicted to greatly affect the ability of synaptic input to generate, propagate and time action potentials (APs), highlighting a feature largely ignored by previous studies of signal propagation. Another study went a step further to incorporate kinetic models of light-sensitive opsins, making its predictions (namely, that neuronal gain modulation depends on the morphological branching pattern) directly relevant to, and experimentally testable by, existing optogenetic methods[54].

Importantly, theoretical models that explain the rules underlying neuronal branching have enabled the generation of realistic synthetic geometries for many different neuronal types[55]. The main rule, a balance between path length and wiring costs, also determines the neuron's compartmentalization; that is, the independency of dendritic branches. Interestingly, the need for additions to this rule when artificially constructing a morphological type predicts the involvement of other mechanisms (such as developmental processes) that determine dendritic structure. Overall, the above modelling examples have illuminated how dendritic structure, even within the same morphological class, can dramatically influence signal integration and neuronal output — an issue that has mystified neuroscientists for decades[56].

Untangling the role of dendritic conductances. At the dawn of the twenty-first century, the function of the plethora of dendritic ionic channels was a mystery[57]. Now, despite years of intense investigations, a complete picture has yet to emerge. Biophysical modelling is ideal for teasing apart the effects of different ion channel features and properties, including their opening and closing kinetics, subunit composition, desensitization, localization and maximal conductance, as all of these can easily and reversibly be manipulated in computo. Models have revealed how specific conductances influence synaptic

Backpropagation
In neurophysiology, the active regeneration of somatic action potentials travelling backwards into the dendrites.

H-current
An inward current generated by the opening of hyperpolarization-activated cyclic nucleotide-gated cation channels; critical for synaptic integration and plasticity.

Point neuron view
Consideration of a neuron as a summation unit with a non-linear activation function and no internal (dendritic) morphology.

Active dendrites
Dendrites equipped with voltage-dependent ionic conductances.

integration, gate or amplify resulting depolarizations, modulate signal propagation and underlie the induction of dendritic spikes[58–65].

Biophysical modelling has been used to explain how A-type potassium channels in the dendrites of CA1 pyramidal neurons affect the backpropagation of APs[66] and reduce their amplitude as a function of the distance travelled[67]. The latter study predicted that appropriate timing of presynaptic and postsynaptic activity can enhance AP backpropagation into the distal dendritic tree by inactivating A-type channels. This type of channel was also experimentally shown to underlie Hebbian plasticity in the same cells[68].

Similarly, models have predicted a key role of the dendritic h-current in the temporal integration of incoming inputs[69–71]. A key prediction from these models is that because h-channels are highly abundant in the distal dendrites of CA1 pyramidal neurons, they can selectively block the summation of unsynchronized distal inputs. As such, h-channels can serve as coincidence detectors for distal inputs, a role later confirmed experimentally[72].

Computational modelling can also provide important insights about the characteristics of unidentified ionic conductances that underlie specific phenotypes. For example, biophysical modelling was used to explain how slow network depolarizations seen in vivo amplify small-amplitude synaptic inputs selectively at the basal dendrites[73]. The authors predicted that a postsynaptic voltage-gated channel may underlie this amplification, also suggesting suitable kinetics and subcellular distributions of the unidentified ionic conductances.

Dendritic spikes and their role in signal integration. The discovery of local spikes in the dendrites, first reported in cerebellar neurons[27] and later in cortical pyramidal neurons[24,25,29,74–84], marked a new era for dendrite research. These regenerative events were incompatible with the point neuron view, whereby dendrites were seen as passive conducting cables. New questions arose: how do these events influence neuronal integration, and under what conditions do they emerge? What functional roles do they subserve in the behaving animal? At a time when experimental techniques fell short of providing answers, computational models led the way.

In a 1979 study[85], Robert Traub built a simplified biophysical model of a CA1 pyramidal neuron based on electrophysiological data provided by Rodolfo Llinas. The model explained how calcium spikes originating in the dendrites extend the window for temporal integration of inputs, and thus contribute to burst firing and epileptogenesis. Similarly, the model was the first to explain how active dendritic integration influences somatic firing profiles[86]. Years later, Poirazi and colleagues[30,58] used a multi-compartmental CA1 pyramidal neuron model to explore the conditions enabling dendritic spikes and the arithmetic implemented by a neuron with active dendrites (FIG. 2a,b). An important prediction of this model was that, owing to local spiking, apical oblique dendrites integrate inputs in a sigmoidal, semi-independent manner. This prediction and its dependence on Na^+ and NMDA receptor (NMDAR)-mediated conductances[87] was later verified experimentally in hippocampal neurons[76] and in neocortical neurons[88].

Table 1 | **Popular modelling tools and databases**

Resource	Description	URL
Modelling tools		
NEURON	Simulator for detailed biophysical modelling	https://neuron.yale.edu/neuron/
BRIAN2	Spiking network simulator that also supports abstract dendritic modelling	https://brian2.readthedocs.io/en/stable/
GENESIS	Multilevel simulator that also supports biophysical modelling	http://genesis-sim.org/
LFPy	Enables the biophysical simulation of extracellular potentials	https://lfpy.readthedocs.io/en/latest/
OpenSourcebrain	Resource for sharing and collaboratively developing computational models of neural systems and generation of standardized models	http://opensourcebrain.org/
Trees toolbox	Morphological analysis, manipulations and artificially generated morphologies	https://www.treestoolbox.org/
Databases		
ModelDB	Repository of published models	https://senselab.med.yale.edu/modeldb/
NeuroMorpho	Repository of experimentally reconstructed single-neuron morphologies	http://neuromorpho.org/
ICGenealogy	Database of ion channel models	https://icg.neurotheory.ox.ac.uk/
Brain Observatory at the Allen Brain Institute	Provides access to the activity of different cell types of the mouse visual system	http://observatory.brain-map.org/visualcoding/
The Neocortical Microcircuit Collaboration Portal	Description of simulated microcircuit and associated NEURON models; repository of electrophysiological data; access to tools for morphological analyses and parameter optimization	https://bbp.epfl.ch/nmc-portal/welcome
Hippocampome	Portal for morphological, electrophysiological and anatomical data from the hippocampus and entorhinal cortex	http://hippocampome.org/php/index.php
MouseLight (Janelia)	Data set of whole mouse brains imaged at submicron resolution, allowing reconstructions of complete axonal arbours of individual neurons across the entire mouse brain	https://www.janelia.org/project-team/mouselight

Notably, both sublinear integration[17,18] and supralinear integration[89] have also been reported in the dendrites of different interneuron types[90]. In line with experiments, biophysical modelling of fast-spiking (FS) basket cells predicted two modes of dendritic integration: supralinear, resulting from the induction of local sodium spikes within large-volume branches; and sublinear, typically seen within small-volume branches[32].

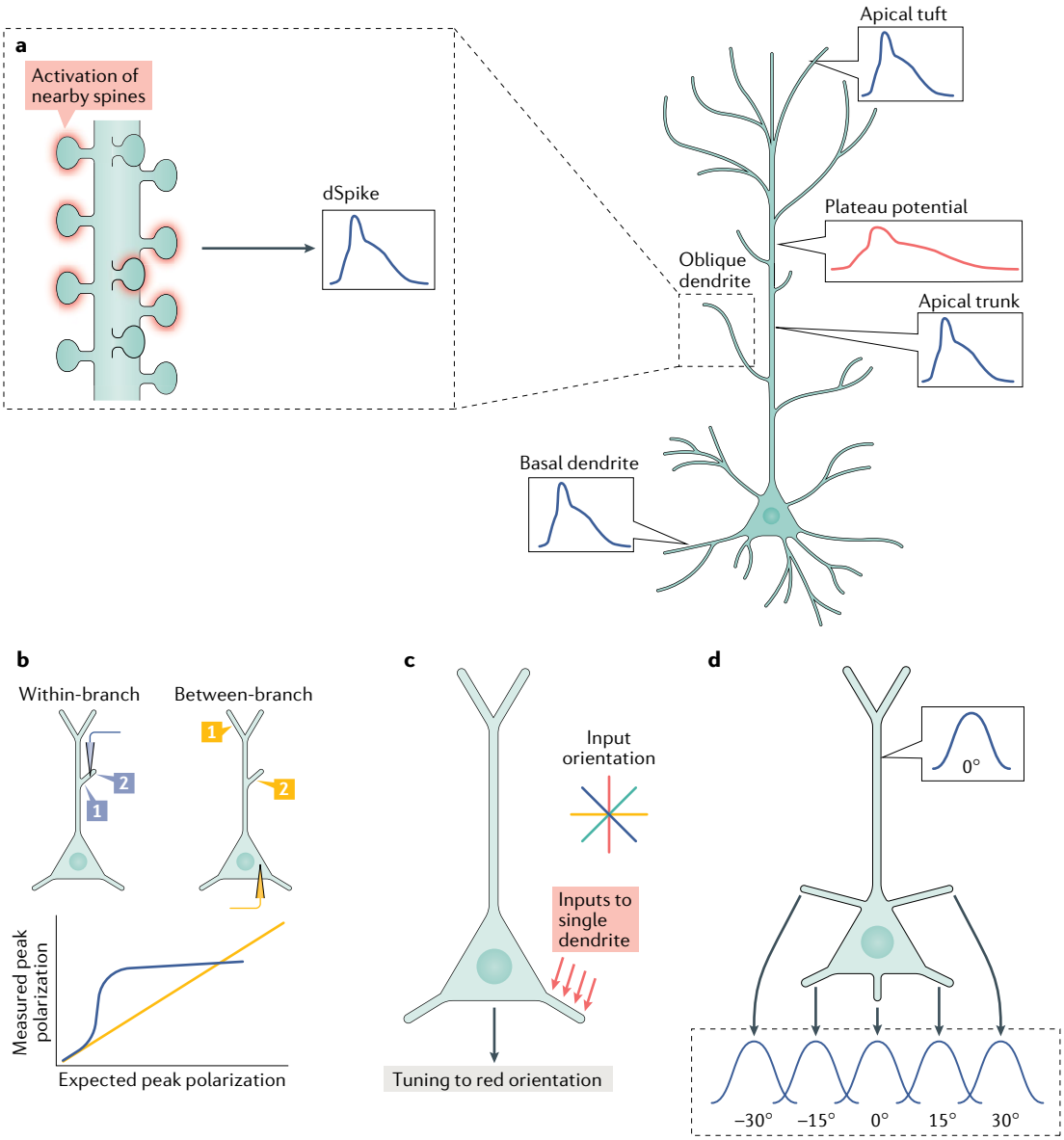


Fig. 2 | **Selected modelling predictions that have received experimental support. a** | One model predicted that co-activation of a few synapses grouped within a single dendrite could drive local spiking in oblique dendrites of CA1 pyramidal neurons (dSpike; blue trace)[58]. This prediction was verified experimentally in the same dendrites[76], and such dSpikes are now known to occur in several locations, including the basal, apical oblique and apical trunk dendritic branches[25,88,122,228], whereas longer-lasting dendritic plateau potentials are primarily restricted to the apical tuft[229]. **b** | Synaptic inputs (stimuli 1 and 2) that are co-activated within the same dendrite were predicted to integrate in a non-linear, sigmoidal manner[30], whereas the same inputs spread across different branches were predicted to sum linearly at the soma. This prediction was verified experimentally in the basal dendrites of neocortical neurons[88], and sigmoidal-like responses, due to local spiking, were also found in the apical oblique dendrites of CA1 pyramidal neurons[76]. Co-activation of nearby synapses similar to that predicted[30,35] has also been seen in vivo[230]. Schematic based on data in REF.[88]. **c** | According to a biophysical model of a pyramidal neuron in the primary visual cortex (V1)[61], a single dendrite containing similarly tuned inputs would induce somatic responses to the same orientation. Such a grouping of similarly tuned inputs was also seen experimentally in the visual cortex of ferrets[40]. **d** | By contrast, another model[209] predicted that single basal branches of layer 2/3 V1 pyramidal neurons sample from different yet overlapping distributions of orientation-tuned inputs. This explains somatic orientation tuning that is robust to the ablation of apical and a few basal dendrites. Such broad sampling was seen experimentally in the same neurons in mice[208] and there are indications for different distributions of inputs between branches[210].

In addition, models have predicted that dendritic spiking also depends on the stochastic gating properties of ionic channels, which in turn vary with morphological features[91] and ongoing membrane fluctuations[92]. These modelling results highlight the probabilistic nature of dendritic integration that should be considered in synaptic stimulation protocols when mapping dendritic input–output functions.

Overall, modelling studies have delved into the mysteries of dendritic spikes, explaining their dependence on ionic and synaptic conductances and their contribution to complex neuronal functions (see following sections).

Synaptic location and dendritic subunits. In light of active dendritic conductances, the long-standing inquiry of how synaptic location and dendritic compartmentalization into subunits affect neuronal responses has been revived.

According to early models, dendritic filtering of distal inputs reduces their effectiveness in influencing somatic output[95]. This reduced efficacy of distal inputs was verified experimentally using somato-dendritic patching in neocortical pyramidal neurons, and biophysical modelling predicted that passive properties, along with non-uniformly distributed ionic conductances (such as the h-current), were responsible for the severe attenuation of distal signals[63]. Although a progressive increase in AMPA receptor (AMPAR) density towards the distal sites can restore the effectiveness of distal dendritic inputs in CA1 pyramidal neurons[96], such compensation is not evident in layer 5 (L5) neocortical pyramidal neurons[97] (reviewed elsewhere[98]). Moreover, models[99] and experiments[100] showed that active conductances in dendrites can normalize the efficacy of distal synapses, restoring synaptic democracy. These studies revealed a new role of dendritic conductances: namely, that of democratizing dendrites (in certain neuron types) by making all synapses equally efficient in influencing somatic firing.

Importantly, depending on the spatial arrangement of incoming inputs, dendritic conductances can also boost dendritic signals and their impact on somatic output. Indeed, seminal work by Barlett Mel[60,101] predicted that neocortical pyramidal neurons respond maximally to spatially clustered inputs rather than randomly distributed inputs, a feature termed 'cluster sensitivity'. These studies were the first to identify an NMDAR-dependent boost in excitability, later shown experimentally[88,102], that was provided by the clustered arrangement of synapses. Mel also predicted the conditions that would cancel the boosting effects of clustering, such as the high resistance of spine necks, large synaptic conductances and high baseline levels of activity, inspiring further experiments[103]. In addition, theoretical modelling revealed that grouping of correlated synapses within the same dendritic branch, through a local plasticity rule, leads to a major increase in the information-storage capacity of a single neuron[35].

Crucially, the predicted effects of synaptic arrangement on neuronal computations are diverse[104]. For example, in a CA1 pyramidal neuron model[30], grouping of synapses within a few branches induced much stronger somatic responses than did the same number of randomly allocated synapses, whereas the opposite was true in detailed models of hippocampal and neocortical FS basket cells[32]. In the latter, somatic responses were strongest when excitatory inputs were distributed across the entire dendritic tree. This is puzzling given that both pyramidal and FS basket cells support dendritic spikes, as evidenced experimentally[76,78,89] and reproduced in models[32,58]. According to the FS basket cell models, differences in the dendritic diameter and the density of A-type channels, along with a small NMDAR-dependent conductance in the dendrites, explain the preference of these cells for dispersed input.

The above predictions suggest that dendritic — and, consequently, somatic — spiking is not necessarily facilitated by synaptic clustering, as was previously assumed[105,106]. Instead, other factors, such as the morphology and the interactions between ionic conductances that drive dendritic spikes (for example, Na^+ channels in FS basket cells versus Na^+ channels and NMDARs in pyramidal neurons) or oppose dendritic spikes (K^+ channels), ultimately determine whether a neuron will favour a specific arrangement of inputs. This point was also highlighted in a recent modelling study[107] showing that pyramidal neurons can generate dendritic spikes and express sharply tuned place cell responses even when inputs are randomly dispersed. Overall, the effect of synaptic distribution on local spiking is contingent to the degree of dendritic compartmentalization: in neurons with low dendritic compartmentalization, such as the pyramidal neurons of the superficial layers, the spatial arrangement of synaptic inputs can be of minimal importance and global dendritic spikes are predicted to emerge. Such global dendritic events can be further modulated by morphological and electrical properties[108,109] of dendrites as well as by the somatic input resistance[93].

To complicate matters further, the effects of incoming input arrangement on dendritic responses are subject to ongoing background activity, which in turn depends on the behavioural state (see REF.[110] and references therein). For instance, depolarized neuronal states and membrane fluctuations are predicted to increase both the attenuation of synaptic signals and the probability of dendritic spike initiation, while also promoting the forward propagation of dendritic events and enhancing temporal discrimination[110]. The effect of in-vivo-like activity on the forward propagation of dendritic spikes was verified experimentally[111]. Modelling further predicts that correlated background activity results in a counter-intuitive reduction of somatic firing, owing to the collision of dendritic spikes[112]. Importantly, in the presence of active dendritic conductances, widespread input promotes synaptic democracy, whereby distal and proximal inputs have the same synaptic efficacy (location invariance) and the collaboration of inputs from multiple sites is required for somatic spiking[92,113,114]. Various modelling studies have also shown that dendritic compartmentalization is dynamic; it can be regulated by widespread excitation[115] and inhibition[108]. These studies reveal that the level of dendritic independence is not a fixed quantity; rather,

Fast-spiking (FS) basket cells
Inhibitory neurons characterized by brief and high-frequency action potentials. Usually, FS basket cells innervate the perisomatic region of pyramidal neurons and other interneurons.

Synaptic democracy
Location independence of the efficacy of synaptic inputs in evoking somatic depolarization and/or action potentials.

Place cell
A type of neuron mostly found in the hippocampus that fires at a high rate whenever an animal enters a particular location (place field) within its environment.

Global dendritic spikes
Non-linear depolarizations generated en masse in the dendrites of neurons, usually in response to dispersed input.

the number of dendritic subunits is determined by the neuronal type and network state.

Finally, on top of synaptic arrangement effects at the dendritic tree level, both models and experiments suggest that the placement and interaction of inputs within a given dendrite also influence local and somatic output[59]. For example, both the amplitude of excitatory postsynaptic potentials (EPSPs) and the supralinearity of synaptic integration increase with the distance from the branch point towards the tip of a single dendrite[59,116]. Moreover, distal excitation lowers the threshold for dendritic spike initiation by more proximal (near the branch point) inputs, whereas proximal excitation lowers the threshold and increases the gain in amplitude of distal inputs[117]. Thus, even single branches can be equipped with multiple integration units that cooperate to produce a specific neuronal output[118].

Overall, computational models have been crucial for dissecting how the spatial organization of inputs, along with the compartmentalized features of dendrites, enables neurons to implement different integration schemes in dynamic and flexible ways.

Dendritic contributions to generic neuronal computations. The ability to exhibit a coincidence detection function — whether this refers to detecting coincident synaptic inputs within a branch (through dendritic spikes), between distinct branches (through the generation of an AP) or between dendritic trees (through the induction of somatic bursting) — has also been attributed to various dendritic conductances[23,119]. Computational modelling has been instrumental in delineating the interactions between active conductances, morphology and the timing constraints that underlie a coincidence detection function[45,87,120–122].

Although early models of passive dendrites suggested that the membrane time constant sets the upper limit on the time window over which EPSPs can sum[123,124], a narrower window is required for this summation to induce dendritic spikes. According to biophysical models, Na^+-dependent and NMDAR-dependent dendritic spiking in basal dendrites of CA1 pyramidal neurons results from highly coincident synaptic input (less than 3 ms apart) and leads to reliable and temporally precise generation of somatic APs[122]. As a result, dendritic spikes may serve as precise 'timers' of somatic APs. Similar coincidence requirements were seen in the apical dendrites of these neurons: according to a CA1 pyramidal neuron model, spike initiation in the apical tuft or apical trunk requires near-synchronous (within 3 ms) activation of approximately 50 synapses[120]. Such tight synchronicity was also seen experimentally in apical oblique dendrites of these cells[76]. Computational modelling[87], however, challenged this requirement, suggesting that the emergence of dendritic spikes also depends on the pattern of synaptic stimulation: synapses activated by short bursts — a pattern frequently seen in theta-modulated CA3 afferents in vivo — extend the temporal window for dendritic spike initiation to more than 10 ms. This extension is due to the non-saturating properties of NMDARs, which, unlike AMPARs, are not fully activated by a single spike[125]. These predictions raise an important issue with respect to the interpretation of both modelling and experimental findings: the effects of the specific protocol used must be considered.

Coincidence detection is also realized through somatic bursting, which is supported by calcium regenerative potentials in the apical dendrites that are induced by synaptic input coinciding with a backpropagating AP[29]. Modelling work has helped delineate the conditions enabling the occurrence of these burst events. For example, in the presence of calcium regenerative potentials, the interaction between apical tuft and basal inputs is best represented as a composite-sigmoid integration, such that apical input lowers the threshold for somatic bursting and amplifies basal-tree inputs[121]. The simplicity of this phenomenological model provides an experimentally testable proof-of-concept prediction for interactions between apical and basal dendrites. Moreover, experiments and biophysical models of L5 neocortical pyramidal neurons revealed that increased numbers of apical oblique branches close to (that is, less than 140 µm from) the soma strengthen the coupling of the apical and somatic AP initiation zones, thus facilitating coincidence detection in neurons with elaborate proximal apical trees[45].

The above examples highlight how dendritic models have contributed to our understanding of coincidence detection functions, by revealing the effects of dendritic anatomy, ionic conductances and their spatial distributions on this important and generic computation that spans different cortical and hippocampal regions.

Inhibitory control of dendrites. Inhibition is a major determinant of dendritic integration and its effects on neuronal output. According to biophysical models, the rules underlying the summation of excitatory and inhibitory inputs depend on their relative position: in passive models of retinal ganglion cells, shunting inhibitory conductances on the path of excitation to the soma (on-path inhibition) strongly reduce somatic EPSPs[126]. The same result was later seen in CA1 pyramidal neurons through the use of experimental and modelling approaches[127]. Interestingly, models also predict that distal (off-path) inhibition gates dendritic spike initiation[128–130] and thus can have a larger somatic impact than on-path inhibition. This strategic control of dendritic spikes through distal inhibition has also been shown experimentally[29].

The position of inhibitory synapses on the dendritic tree has also been predicted to gate backpropagating APs while leaving forward propagation intact. In this scenario, appropriately timed EPSPs can still trigger somatic APs whereas backpropagating signals are abolished[131]. Surprisingly, models[128] predict that the spatial spread of inhibitory shunt from multiple distal inputs towards the soma can effectively control excitation even in dendrites that are not directly targeted by inhibition. In general, once a dendritic spike is generated, local inhibition can either transiently or permanently terminate it, depending on their relative timing[94,129]. Some of these predictions were verified and further elaborated by experiments[130,132] that suggested that the location

AP initiation zones
Specialized domains of a neuron enriched with sodium and potassium channels, where propagated synaptic potentials are summated and an action potential (AP) is initiated.

Inhibitory shunt
Activation of an inhibitory synapse that adds a conductance value to the membrane. This reduces input resistance and thus has a divisive effect on excitatory inputs.

and timing of inhibition that pyramidal neurons receive in different dendritic pathways can dynamically tailor their output. In support of this conjecture, recent anatomical data suggest a fine-scale regulation of the number and location of excitatory and inhibitory synapses within individual dendrites of pyramidal neurons, and modelling further predicts that this local structure can effectively control dendritic integration[133] and somatic firing[134].

Dendritic computations in human neurons. Although many lessons have been learnt about dendritic function in rodents, to establish their relevance for humans, the community has had to invest resources in the study of human neurons. Compared with other species, human pyramidal neurons differ in their size, their dendritic complexity and their number and density of dendritic spines[135,136], all of which can impact their processing capabilities.

According to single-neuron models, the large dendritic trees of human neurons enable the detection of rapid changes in incoming inputs[137] while also restricting the propagation of dendritic signals, thus promoting compartmentalization[136,138]. According to one study, this compartmentalization is further enhanced by low dendritic channel densities and persists even in the presence of dendritic spikes[139].

In addition, a new mechanism was recently discovered that consists of calcium-dependent dendritic spikes with attenuating amplitude (dCaAPs). A combination of experiments and single-neuron modelling revealed that dCaAPs enable single human neurons — or rather, their apical dendrites — to solve the exclusive-or (XOR) operation[140], a computation that was considered solvable only by networks of neurons. Single-neuron modelling has also predicted the generation of NMDAR-dependent spikes in multiple independent dendritic sites in human neurons[141], typically thought to serve as AND gates. In combination with dCaAPs, these dendritic non-linearities furnish human neurons with a much greater repertoire of computing abilities than have yet been reported in other species.

Finally, connectivity motifs in human circuits could be somewhat different from those in rodents: for example, a newly identified type of L1 interneuron, not documented in rodents, targets the distal dendritic shafts of L3 pyramidal neurons and controls the backpropagating APs in a compartmentalized manner[142]. Whether these computations are qualitatively similar to, or different from, those in other species remains an open question, and detailed biophysical modelling will be crucial in addressing this.

Simplified, abstract neuron models with dendrites. Dendritic models often have to account for the detailed morphology and/or biophysics of dendritic trees, a deed that comes with high computational complexity. This complexity can be reduced through mathematical abstractions that are effective in both capturing key dendritic properties and minimizing computational cost[22].

Early theoretical work used abstract mathematical neurons furnished with non-linearly integrating dendrites described by quadratic equations[35]. This work revealed that neurons equipped with non-linearly integrating dendrites have a much higher capacity for discriminating patterns from different classes (for example, cats versus dogs) than do neurons with linearly integrating dendrites, as also seen in reduced CA1–CA3 circuit models[143]. Inspired by these findings, a mathematical reduction based on ANNs was developed, whereby the first layer corresponded to the apical dendrites and the second layer to the cell body[30]. Units in both layers had a sigmoidal-like transfer function to represent their spiking abilities. This two-stage mathematical abstraction is supported by anatomical findings[31] and was demonstrated to explain the firing rates of a detailed CA1 pyramidal neuron[30] and the processing of basal-tree inputs to L5 pyramidal neurons[144]. A similar two-stage ANN model in which the hidden layer represented two types of dendritic non-linearities — sublinear and sigmoidal — was recently shown to account for the firing variability of FS basket cells[32]. Reducing complex neurons in ANNs is especially powerful, as it allows their incorporation into deep neural networks (DNNs), thus enabling fields such as machine learning (ML) and artificial intelligence (AI) to account for dendritic computations.

An augmented version of the two-stage model for cortical pyramidal neurons has also been proposed that separates computations in basal and apical tuft regions, and accounts for the spatial profile of excitatory and inhibitory inputs[145]. When further considering the potential for targeted modulation of dendritic conductances by neuromodulators[146,147], each dendritic subunit of a neuron may be able to implement its own, adaptive form of local integration. In this augmented model, the morphology and biophysical properties of neurons determine the complex arrangement of dendritic subunits[33].

Another reductionist strategy is to consider simple extensions of 'integrate-and-fire' point neurons that include dendrites. In most of these cases, dendrites are included as passive compartments[148–150], and non-linear synaptic currents can be added to capture the subthreshold activity of neurons and their dendrites[148]. Integrate-and-fire models that support dendritic spiking have also been developed[151,152] and used to study different functions, including the role of dendritic non-linearities in associative memory engrams[32,153] and the effect of input correlations on the forward propagation of dendritic spikes[112]. An important outcome of the latter study is a 'discrete state' model that efficiently describes dendritic spike propagation and collision. Finally, in an elegant study[154], hierarchical linear–non-linear (LN) models were used to describe the somatic membrane potential (without APs) in response to in vivo-like inputs. Dendrites were represented as hierarchical sequences of nested, LN units (resembling perceptrons), as a function of time. The main advantage of this LN abstraction for dendritic processing is that it provides a principled, statistical inference-based method to account for neuronal responses.

Overall, these mathematical abstractions increase tractability and reduce the computational cost of detailed

Associative memory engrams
Memory traces that consist of different types of information that become bound together, possibly through their storage in common neurons.

Linear–non-linear (LN) models
Phenomenological models in which the outputs are estimated by successively applying linear temporal filters to the inputs, followed by static non-linear transformations.

Perceptrons
Binary classification algorithms each consisting of weighted inputs, a bias and a thresholding function that generates an output decision.

single-neuron models while also setting the ground for incorporating dendrites in other systems, such as neuromorphic devices[155–158] and ML algorithms[159–161].

Microcircuit models

Neurons — and thus their dendrites — are embedded in highly complex local and long-range circuits, receiving, processing and sending various types of information. Similarities in microcircuit organization across areas, seen as connectivity motifs, suggest the use of similar strategies for encoding and decoding incoming signals (reviewed elsewhere[162,163]). The most widely reported motifs involve vasoactive intestinal polypeptide-expressing (VIP^+), somatostatin-expressing (SST^+) or parvalbumin-expressing (PV^+) interneurons. In these motifs, VIP^+ and SST^+ interneurons are reciprocally inhibited; SST^+ interneurons inhibit the apical dendrites of pyramidal neurons and the somata of PV^+ interneurons, and PV^+ interneurons target the perisomatic regions of pyramidal neurons (FIG. 3). Models predict that these interneuronal circuits have key roles in regulating the interaction between the mainly feedforward and largely feedback information streams arriving at the basal and apical dendritic trees of pyramidal neurons, respectively[119]. The coincident arrival of both inputs is predicted to underlie various circuit-level functions, such as cortical associations[119] and predictive coding[164]. Below, we highlight examples of microcircuit models in which the dendrites of interconnected neurons interact with local inhibitory circuits to efficiently process these different information streams (FIG. 3).

Dynamic regulation of dendritic input streams by inhibition. VIP^+, SST^+ and PV^+ interneurons tightly control dendritic integration in pyramidal neurons[163,165–167], in non-trivial ways. According to a circuit model of two-compartment neurons[168], SST^+ neurons dynamically regulate the integration of different input pathways: strong activation of these neurons attenuates apical signals and, by inhibiting PV^+ neurons, facilitates the processing of perisomatic inputs to pyramidal neurons. Conversely, reductions in SST^+ neuron activity promote the integration of apical inputs and indirectly suppress perisomatic inputs. Although such dynamic control of signal integration in pyramidal neurons by soma-targeting and dendrite-targeting inhibition has been reported experimentally[169], the underlying interneuron types and their causal interactions remain unclear.

Moreover, the reciprocal inhibition of VIP^+ and SST^+ interneurons is predicted to amplify their own excitatory inputs and thus the somato-centric or dendro-centric inhibition of pyramidal neurons: when VIP^+ neurons receive weak excitatory input, they weakly inhibit SST^+ neurons, which in turn release their reciprocal inhibition onto VIP^+ neurons, leading to a circular amplification of the weak input to the VIP^+ neurons. The same happens with weak input to SST^+ cells (see FIG. 3 for VIP^+ neuron–SST^+ neuron connectivity). It remains unknown whether this reciprocally inhibitory interaction amplifies the responses of VIP^+ and SST^+ neurons and, in turn, regulates the integration of apical and basal input streams in vivo.

Pathway integration. The simultaneous encoding of both feedback and feedforward input, termed 'multiplexing', was investigated in a circuit model of reduced, two-compartment L5 neurons[170]. Multiplexing emerged when feedforward information was encoded by single spikes (events) and feedback information by the probability of bursting. The multiplexed signal was in turn predicted to be decoded by different mechanisms: short-term depression (STD) allowed for the decoding of feedforward information (events), whereas short-term facilitation (STF) detected the conjugative effect of the two pathways. Excitatory input to SST^+ neurons through STF synapses, and to PV^+ neurons through STD synapses, followed by PV^+-neuron-mediated inhibition to SST^+ neurons, decodes feedback information. When SST^+ neurons of the latter motif project back to the apical trees of the same excitatory population, they are predicted to control the gain of the dendritic signal, thus linearizing the input–output function of pyramidal neurons. In accordance, circuit modelling and experiments show that local and feedforward excitation of SST^+ neurons regulate the gain and threshold, respectively, of non-linear dendritic responses in L5 pyramidal neurons by suppressing calcium spikes[171].

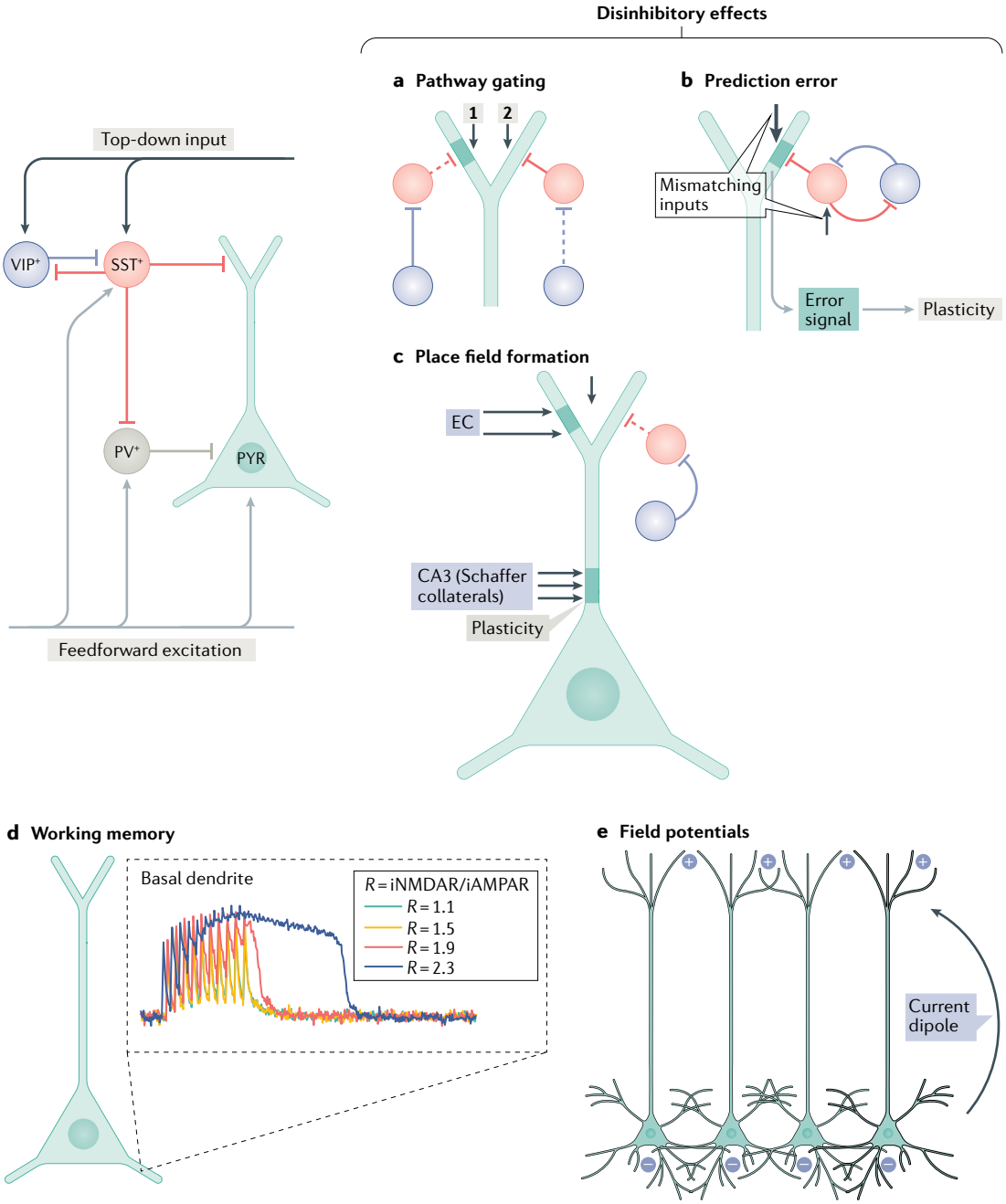
Pathway-specific gating. The above studies place SST^+ interneurons in control of pathway integration within dendrites. Recent modelling[172] further predicts that these cells may act as pathway gatekeepers, to enable, for example, attention to a specific input stream. In this model, simplified pyramidal neurons (comprising a soma plus a few active dendrites) receive input from different pathways, each of which forms clustered synapses within different branches (FIG. 3a). Gate opening for one pathway is achieved through selective disinhibition of the branches receiving input from this particular pathway. The model predicts that such a selective alignment of disinhibition and excitation requires sparse SST^+ interneuron-to-pyramidal dendrite connectivity, and can be shaped by plasticity or by context-dependent activation of VIP^+ (or SST^+) interneurons. This prediction is supported by indirect experimental evidence: selective attention recruits VIP^+ neurons in a spatially restricted manner[173] and VIP^+ neurons disinhibit a functionally specific subset of inhibitory neurons[174].

Dendrites and predictive coding. The dynamic control of pathway-specific information at the dendritic level has also been a subject of intense investigation in the field of predictive coding (see REF.[175] and references therein). This line of work refers to the generation of an error signal in the dendrites of pyramidal neurons that is used to update the hypothesis of a sensory experience with the actual sensory input. According to a compartmental circuit model[159], prediction errors at the apical tree of pyramidal neurons are generated by the excess of feedback excitation compared with local inhibition (for example, from SST^+ interneurons). These error signals drive learning of the feedforward connections through local synaptic plasticity. Moreover, the excitation of VIP^+ interneurons is predicted[168] to increase the strength of these error signals owing to their aforementioned

Predictive coding
The comparison of sensory inputs with prior expectations (to create a 'prediction'), and propagation of an 'error' signal to the brain areas responsible for the expectations.

Short-term depression
(STD). A negative change in postsynaptic potentials following repetitive stimulation of a synapse.

Short-term facilitation
(STF). A positive change in postsynaptic potentials following repetitive stimulation of a synapse.



reciprocal inhibition of SST$^+$ neurons. In agreement, recent experiments show that feedback input can gate plasticity of the feedforward synapses through VIP$^+$ neuron-mediated disinhibition[176] and that pyramidal neurons indeed recruit inhibitory populations to produce a predictive error[177] (FIG. 3b).

Together, the above modelling studies highlight the key role of dendritic signals and their dynamic regulation by local interneurons in the implementation of complex, circuit-level functions, leading to several predictions that await experimental testing.

Large-scale network models

Detailed, large-scale network models are used to investigate the conjugative effect of neuronal populations within or between areas, aiming to infer the mechanisms that underlie complex dynamics, such as oscillations. Recent efforts from the Allen Institute and the Human Brain Project have produced benchmarking data about the diversity of neurons that can be used for constraining detailed models of the somatosensory[178] and visual[179] areas. These large-scale models have produced several interesting predictions regarding the neuronal and circuit mechanisms underlying, for example, cortical state transitions[178] and visual tuning[179]. Yet the role of dendrites in these computations has not been explicitly addressed.

An interesting example where biophysical large-scale modelling has highlighted the impact of dendritic processing in population dynamics is field potentials. Field potentials, such as the local field potential (LFP) and electroencephalography (EEG)-recorded potentials, are widely used as measures of neuronal activity, although

Field potentials
Extracellular measurements of the activity of a population of neurons, reflecting neuronal transmembrane currents that are mainly due to synaptic activity.

◀ Fig. 3 | **Examples of experimentally supported modelling predictions of dendritic contributions to circuit functions.** Many models have simulated interactions in a cortical circuit receiving feedforward and top-down inputs; the circuit involves a pyramidal (PYR) neuron that receives inhibition at the apical dendrites from somatostatin-expressing (SST^+) neurons, which in turn have a reciprocal inhibitory interaction with vasoactive intestinal peptide-expressing (VIP^+) interneurons. By contrast, parvalbumin-expressing (PV^+) interneurons inhibit the soma of pyramidal neurons. **a** | Computational modelling has predicted that dendritic (dis)disinhibition can be a mechanism for selective gating of different input streams (1 and 2) targeting distinct branches of the same neurons. Specifically, disinhibition mediated by a VIP^+ neuron targeting an SST^+ neuron can selectively gate the respective pathway (here, input stream 1), allowing for the generation of dendritic NMDA receptor (NMDAR)-dependent spikes that in turn drive somatic spikes[172]. **b** | Feedforward excitation of SST^+ neurons (either directly or through their activation from the local population of pyramidal neurons) has been predicted to match the excitatory top-down input to the apical dendrites of pyramidal neurons[159]. Any resulting mismatch produces a prediction-error signal (which manifests as a calcium spike) that is suggested to guide plasticity. **c** | In a CA1 circuit model, the interaction of distal cortical and intrahippocampal inputs to pyramidal neurons with active dendrites is predicted to be regulated by local disinhibitory (VIP^+) neurons. Disinhibition influences the probability that silent model cells become place cells during a simulated learning task, through enhanced plasticity of CA3 inputs[193]. These predictions suggest that dendritic non-linearities and their control by disinhibition may play a key role in hippocampal functions, such as spatial navigation. In accordance, dendritic spikes have been shown to precede and dictate the formation of place cells in new environments[222]. **d** | In a recurrent prefrontal cortex network model of working memory, NMDAR-dependent dendritic spikes maintain the online activity needed for working memory[200]. Graph shows the dendritic membrane potential when the ratio of AMPA receptor (iAMPAR) current to NMDAR current (iNMDAR) is increased. **e** | Large-scale modelling studies suggest that layer 5 pyramidal neurons, characterized by their asymmetrically extended dendritic trees and their active membrane currents, create large current dipoles, making dendritic currents detectable in the local field potential[180]. Support for this prediction comes from experiments showing that calcium spikes can be detected from surface potentials[185]. EC, entorhinal cortex. Part **d** is adapted from REF.[200], CC BY 4.0 (https://creativecommons.org/licenses/by/4.0).

they cannot resolve the activity of individual neurons. Models of field potentials investigate how they are shaped by the anatomical, biophysical and activity features of the cortex, and can thereafter be used, at least partially, to reverse-engineer neuronal activity from extracellular recordings.

The biophysical mechanisms that contribute to field potentials and the respective models have been extensively reviewed elsewhere[180,181]. In short, large-scale modelling of morphologically and biophysically detailed neurons shows that neurons with asymmetrically extended dendrites (such as L5 pyramidal neurons) create the largest current dipoles (FIG. 3e). Moreover, active membrane currents and their somato-dendritic distributions shape field-potential properties, whereas asymmetric spatial organization of inputs along the dendrites and their temporal correlations modulate the amplitude of field potentials[182–184]. In vivo experimental verification of a biophysical mechanism predicted by these models[185] showed that calcium spikes in the apical dendrites of L5 neurons are indeed visible in field potentials. This study opens new avenues into the use of field potentials to understand dendritic and neuronal processing.

Complex brain functions

In addition to the generic computations discussed in the previous sections, dendritic modelling has been instrumental in delineating various region-specific functions. Below we review some of these studies, focusing on how model predictions can inform new experiments.

Hippocampal functions. The hippocampus is a key brain area involved in episodic memory, navigation and cognition, yet its precise computations remain controversial[186]. The ability of animals and humans to discriminate and recall information is attributed to respective computations such as pattern separation and pattern completion that take place in the dentate gyrus (DG) and CA3 areas of the hippocampus, respectively[187]. CA1 neurons support various functions, including information binding and spatial navigation. The latter is realized through the formation of place cells, the Nobel Prize-winning neurons that encode specific locations in space[188].

Granule cells (GCs), the principal excitatory neurons of the DG, are believed to be the key neurons that discriminate between similar environments or objects, a process termed pattern separation[189]. According to a computational model[190], pattern separation is enhanced when network activity is sparse — a condition achieved by the requirement of at least two dendrites being active for a GC neuron to fire. Sparsity is further predicted to be increased by alternative intrinsic and synaptic mechanisms (reviewed in REF.[191]), making dendrites a sufficient but not necessary condition for pattern separation efficiency.

According to a CA3 network model, inputs from the entorhinal cortex (EC) and DG to CA3 neurons interact non-linearly to ensure optimal encoding of memories[143]. In this model, dense, correlated distal inputs from the EC promote the efficient encoding of similar memories (pattern completion), whereas sparse, decorrelated inputs to proximal dendrites from the DG reduce memory interference. The opposite occurs in the CA1 area: sparse EC input to the distal dendrites of CA1 pyramidal neurons is predicted to bind information arriving from CA3 at the proximal dendrites with a specific context. Feature binding in proximal (oblique) dendrites of single CA1 pyramidal neurons has been proposed to arise when somatic firing is induced by the collective activation of oblique dendrites receiving independent inputs[192]. This model further suggests an optimal number of dendrites for feature binding. Overall, these studies predict that the binding versus the separation of memories in the hippocampus depends on the compartmentalization and specific patterning of inputs to the dendrites of DG GCs and CA3 and CA1 pyramidal neurons, and these predictions remain exciting open questions.

Dendritic inhibition is uniquely positioned to manipulate excitatory dendritic input and thus influence the encoding of information in the hippocampus. The role of dendritic inhibition in CA1 place cell remapping has been investigated with a combination of circuit models and in vivo experiments. In an elegant study where animals learned the location of reward along a linear track, the place cell population encoding the reward location increased substantially after learning, in a phenomenon termed enrichment[193]. Optogenetic silencing of VIP^+ cells eliminated this enrichment, revealing a new role of these neurons in spatial learning (FIG. 3c). However, discriminating between inhibitory and disinhibitory subtypes of VIP^+ cells was hindered by the lack of respective Cre lines (BOX 2). Circuit modelling including both subtypes of VIP^+ cells (expressing calretinin

Pattern separation
The process that minimizes the overlap between the neuronal populations that encode for similar input patterns.

Pattern completion
The process during which a learned pattern is recalled upon presentation of a degraded or partial version of the original stimulus.

(CR) or cholecystokinin (CCK)) predicted that the CR^+ disinhibitory subtype was responsible for the observed learning-induced enrichment, potentially through gating the plasticity of CA3 inputs[193]. A similar modelling investigation helped dissect the effects of reduced inhibition (by SST^+ and PV^+ interneurons) versus the de-synchronization of DG–CA1 inhibitory networks on the spatial tuning of CA1 place cells in epileptic mice[194]. Modelling predicted that the experimentally reported loss of inhibition is not sufficient to explain defects in spatial tuning, and further experimentation validated this prediction. By contrast, the loss of synchronicity between DG and CA1 interneurons was predicted to account for the spatial deficits.

Biophysical models of the CA1 area have also been used to study phenomena that only emerge at large scales, such as the theta-cycle phase precession of excitatory and inhibitory neurons[195]. Using a regional model of the CA1 consisting of one excitatory and eight inhibitory cell types, this study demonstrated the spontaneous emergence of theta waves and phase-locked gamma oscillations. By manipulating the circuit and input properties of the model neurons, the authors identified the main cell types and connections that are relevant for the intrinsically generated theta cycle and predicted that interneuron diversity is critical for oscillations.

Overall, these studies highlight how modelling can bridge pieces of experimental evidence when the necessary technology is not yet in place and can drive targeted experimentation.

Working memory. Working memory — that is, the ability to retain information for a short period of time — is attributed to PFC circuits[196]. An important feature of these circuits is the hyper-reciprocal connectivity of pyramidal neurons[197]. Modelling revealed that the stability of L5 PFC circuit activity depends on the dopaminergic regulation of ionic properties (such as persistent Na^+ channels)[198] and of synaptic properties, such as the NMDAR[199]. Specifically, NMDAR-mediated dendritic spikes are predicted to alleviate the need for large networks of neurons to maintain online activity[200] (FIG. 3d). Modelling further predicts that the morphology of the basal trees segregates L5 PFC pyramidal neurons into distinct subtypes, and that their respective microcircuits support either temporal integration or coincidence detection, diversifying processing within the same layer[201]. Moreover, according to biophysical models of L5 PFC pyramidal neurons, synapses positioned towards the tips of the basal dendrites facilitate NMDAR-dependent dendritic spiking, and therefore increase the probability of persistent firing and serve as a mechanism for feature selectivity[116]. These predictions provide a mechanistic explanation for the experimentally reported dependence of persistent activity on NMDARs[202], whereas the predicted necessity for NMDAR-mediated spikes has also received experimental support, albeit in the EC[203]. Moreover, NMDAR-dependent stimulus selectivity has been reported experimentally in the visual[75] and barrel[41] cortices.

Finally, differences in the somato-dendritic balance of excitation and inhibition have been proposed to regulate persistent firing in PFC circuit models. Specifically, soma-targeting interneurons that provide widespread inhibition silence other pyramidal neurons in a stimulus-non-selective manner[204] and are crucial for the induction and synchronicity of persistent firing[205]. Locally, pyramidal neurons that receive the stimulus inputs excite inhibitory neurons that project to the dendrite-targeting interneurons, thus disinhibiting the local excitatory population. The control of gain in a subpopulation of pyramidal neurons through the activation of interneuron-targeting interneurons has since been shown experimentally in the PFC[174].

Overall, the above studies show that PFC dendritic features, including dendritic-tree morphology, dendritic integration and dendritic inhibition, promote PFC-dependent functions, including temporal integration, persistent firing and selectivity. The in vivo validity of these findings remains to be explored.

Stimulus selectivity. The ability of pyramidal neurons in sensory cortices to selectively respond to specific stimuli, such as a certain line orientation in the primary visual cortex (V1), has also been investigated with dendritic models. In both simplified and detailed pyramidal neuron models, dendritic spikes have been proposed to underlie orientation selectivity and visual processing[61,121,206] (FIG. 2c). Moreover, dendritic non-linearities and in-branch (clustered) localization of inputs were predicted to underlie the ability of complex cells to respond preferentially to specific line orientations, irrespective of the line location in the visual field[206].

The predicted role of dendritic supralinearities in orientation-tuning properties has recently received experimental support[40,41,75]. Interestingly, sublinear dendritic integration supported by a dispersed distribution of similarly tuned synaptic inputs can also underlie orientation selectivity[207,208]. Finally, dendritic contributions to orientation tuning were investigated through a combination of in vivo microdissection of dendritic branches and trees and biophysical modelling[209] (FIG. 2d). Experiments showed that somatic tuning was robust to ablation of the apical dendrite, whereas gradual removal of basal branches caused gradual shifts in somatic tuning. According to the model, these data are explained if each basal dendrite samples broadly from different yet overlapping distributions of orientation-tuned inputs. In other words, each basal dendrite conveys a slightly different message to the cell body. This predicted between-branch variability has recently received experimental support in the V1 (REF.[210]) and the CA1 area of the hippocampus[211]. The computational benefits of such synaptic organization, however, remain unknown.

Amplification of stimulus selectivity has been experimentally shown to depend on intracortical input, at least in L4 neurons in mice[212]. This amplification is predicted to arise from dendritic non-linearities (such as the induction of NMDAR-mediated and/or calcium spikes) and the recurrent connectivity of L5 pyramidal neurons[213]. Specifically, the coincidence of feedforward, perisomatic thalamic input with dendritic input from the local L5 population promotes the induction of dendritic spikes, thus amplifying the thalamic input. Experiments in mice

Theta-cycle phase precession
The advancement of spike timing of a particular place cell to earlier phases of the theta cycle as the animal passes through its place field.

confirmed that NMDARs shape orientation selectivity in L2/3 neurons[75] and that backpropagation-activated calcium spikes are generated in L5 pyramidal neurons of the visual cortex[121].

Interestingly, stimulus selectivity in inhibitory circuits is also shaped by dendritic properties. In a detailed biophysical model of L2/3 basket cells, the electrical coupling between their dendrites (through gap junctions) decreased input resistance and the membrane time constant, thus reducing the time window for synaptic integration[214]. As a result, the circuit dynamically fluctuated between two states: an asynchronous one, where the small time constant allows basket cells to respond to high-frequency inputs; and another in which basket cells are synchronously active, extending the time window for coincidence detection. The latter state decreases orientation selectivity (or even changes orientation preference) of inhibitory neurons, by homogenizing the response of the different neurons.

The above studies highlight how synaptic location, dendritic integration and interactions between dendritic compartments influence stimulus selectivity in both excitatory and inhibitory neurons. They further emphasize how causal manipulations of anatomical, electrophysiological or input properties of dendrites that cannot be performed experimentally help identify the key players in specific brain functions.

Plasticity. Implementation of biologically realistic plasticity rules in neuron models with non-linear dendrites can help investigating memory-related phenomena and predicting their properties. Although it is beyond the scope of this Review to discuss plasticity models in depth (see recent reviews[105,215]), the predictions of these models highlight the dual role of dendrites as both processing and memory-storage units. For example, information binding is predicted to occur through the formation of synaptic clusters within dendrites and the strengthening of dendritic coupling to the cell body[216]. Furthermore, memories are predicted to become linked across time through the formation of synaptic clusters in the dendrites of a shared ensemble of neurons, with the extent of linking depending on the locus of protein synthesis[105]. The rescue of weak memories by a strong one is predicted to depend on the spatial arrangement of synapses and the population overlap of ensembles of neurons encoding the weak and strong memories[217]. Moreover, plasticity rules are expected to follow a gradient along the dendrites, with spike timing-dependent plasticity dominating proximal inputs and a dendritic spike-dependent LTP operating distally. Relatedly, the distal clustering of inputs dictates whether connectivity is unidirectional or bidirectional[218]. One-shot learning is predicted to be maximally efficient when a few synapses are modified to store a memory through use of binary (instead of graded) weights and a dual-threshold plasticity rule[34]. Moreover, recognition memory is better if the oldest patterns are preferentially erased when a new pattern is stored, through age-ordered synaptic depression[219]. In addition, mismatches in somatic firing and dendritic membrane potential are expected to produce prediction errors that drive synaptic plasticity[220].

Spike timing-dependent plasticity
A type of Hebbian learning where plasticity is regulated by the relative timing of the presynaptic and postsynaptic action potentials.

Perhaps the most important finding about dendritic-related plasticity is that of behavioural time-scale plasticity (BTSP) reported experimentally in CA1 pyramidal neurons and explained with computational models[38]. In this study, dendritic calcium plateau potentials predicted the location preference of new place cells within a window of up to 3 s, long before (or after) the animal passed over that specific location. Overall, the role of dendritic plasticity in neuronal and circuit computations is another major domain in which the synergy of models and experiments have made important contributions.

Conclusions and future perspectives

The beauty of neuronal models lies in their power to simulate any imaginable scenario, given sufficient computational power. It is precisely this flexibility that allowed the numerous modelling discoveries about dendrites discussed in this Review to occur well before their experimental verification, while waiting for the necessary technologies to become available (BOX 2). The lessons learned begin at the subcellular level — such as the contributions of ionic mechanisms, dendritic morphology and input structure — and develop into single-neuron computations and the effects of dendritic properties at the network level and on large-scale phenomena, such as field potentials. Such predictions lead to further experimentation that extends our understanding and helps refine models, thus closing a fruitful loop. Future work should capitalize on the complementarity of modelling and experimental efforts to address the major challenge of establishing causal links between dendrites, neurons and circuit functions to naturalistic behaviours[221]. Experimental attempts towards this goal are scarce and limited to single brain areas and relatively simple tasks, such as 1D spatial navigation[37,38,77,193,222], sensory processing[40,41,209], sensory–motor integration[42], motor learning[43] and sensory perception[7]. Complex behaviours, however, involve several brain areas and are influenced by a multitude of factors, making it extremely difficult to dissect the specific contributions of dendrites. Accordingly, dendritic modelling has been successful in identifying the computations and neuronal correlates of simple behaviours, but has yet to be applied, at least to our knowledge, for diverse naturalistic behaviours. This impasse should be the focus of future studies, with a tight interaction between modelling and experimental approaches leading the way.

As discussed throughout this Review, models and experiments are currently used as complementary yet parallel modules. Although their combination has proved greatly beneficial for understanding dendritic function, true synergy is still missing. Drawbacks of the current approach include the offline character of models, as data for constraining them are typically collected in advance and are limited in breadth (for example, concerning a single cell type) and/or spatio-temporal resolution (for example, two-photon imaging versus wide-field calcium imaging). Some of these limitations will soon be eliminated by emerging technologies, such as voltage dyes and dendrite-targeted optogenetic tools, allowing researchers to record from multiple areas and manipulate dendrites

during behaviour. Such advances will facilitate the development of better models and the testing of predictions, making the combination of modelling with experimental approaches an indispensable tool for dendritic research.

The next step forward requires true synergy, whereby the crosstalk of experiments and modelling is realized in real time. One such scenario could be the development of hybrid systems, whereby circuit models are driven online by neuronal activity of living organisms during complex behaviours. Such systems would enable the continuous refinement of model parameters using the produced data. Once optimized, targeted manipulations of dendrites performed in models will be directly linked to complex behaviours and can guide experiments in more efficient ways.

Overall, a carefully designed integration of modelling and experimental tools will be key to our understanding of how dendrites contribute to behaviour. As new knowledge accumulates, we expect that refined models will unify fragmented data and help infer the repertoire of computations and functions supported by dendrites, neurons and circuits.

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