EMERGING RULES FOR THE DISTRIBUTIONS OF ACTIVE DENDRITIC CONDUCTANCES

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A key goal in neuroscience is to explain how the operations of a neuron emerge from sets of active channels with specific dendritic distributions. If general principles can be identified for these distributions, dendritic channels should reflect the computational role of a given cell type within its functional neural circuit. Here, we discuss insights from experimental and computational data on the distribution of voltage-gated channels in dendrites, and attempt to derive rules for how their interactions implement different dendritic functions. We propose that this type of analysis will be important for understanding behavioural processes in terms of single-neuron properties, and that it constitutes a step towards a 'functional proteomics' of nerve cells, which will be essential for defining neuronal phenotypes.

COINCIDENCE DETECTION
The ability to sense the simultaneous occurrence of synaptic inputs at different points on the same cell.

INPUT RESISTANCE
The voltage change elicited by the injection of current into a cell, divided by the amount of current injected.

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Studies in the past decade have provided an increasing body of data on the presence and distribution of voltage-gated ion channels in the dendrites of pyramidal cells (reviewed in REFS 1–4). However, general rules to explain why these and other neurons acquire specific sets of channels in their dendrites, and why these channels have specific dendritic distributions, are still missing. Here, we address these questions by discussing direct experimental data and indirect evidence from comparisons that have been facilitated by the use of web-based databases and search tools such as NeuronDB. We focus primarily on insights from pyramidal cell dendrites, and compare these with the dendrites of other neuronal types.

Limitations of passive dendritic trees

Segev and London[5] have reviewed the possible roles of a dendritic tree in neuronal functions. Dendrites have been suggested to carry out several specific computational tasks, such as lateral inhibition by mitral cells in the olfactory bulb[6], motion detection by visual interneurons of *Drosophila*[7], direction selectivity in the visual cortex[8] and COINCIDENCE DETECTION in the auditory brainstem[9]. To illustrate how dendrites implement such tasks, and to provide a baseline for comparison with active dendrites, we use the mechanism of coincidence detection in a passive dendritic tree as an example (FIG. 1).

FIGURE 1A shows the peak somatic depolarization of a passive CA1 neuron during the activation of two synaptic inputs (S1 and S2) at the soma or at the most distal dendrites. As can be seen, when both inputs are at the soma (FIG. 1A and FIG. 1Ca), they may generate a somatic action potential within a temporal window that can be relatively narrow (green bar in FIG. 1A). When one of the inputs is at the soma and the other at the distal dendrite, the peak summation is shifted according to whether the initial response is somatic or dendritic. In the example shown (FIG. 1A), the peak occurs when the distal input leads the somatic input, because of better summation of the slowly spreading distal response with the faster, but later, somatic response, as first shown by Rall[10] (see also FIG. 1Cb, S2→S1). Theoretical studies[11] using passive reconstructions of neocortical pyramidal neurons have, in fact, indicated that a dendritically initiated distal signal would be elaborated at the soma with a time delay of up to ~50 ms, and within a large time window, with respect to a more proximal one. When both inputs are at the distal dendrite (FIG. 1A and FIG. 1Cc), two windows result, because the high INPUT RESISTANCE of the

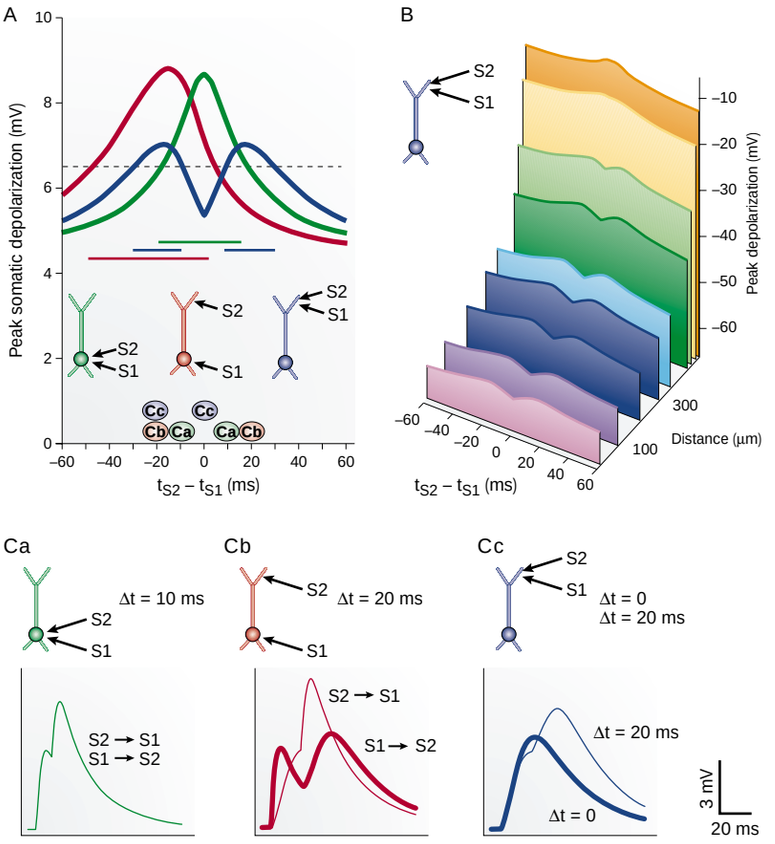

Figure 1 | **Effects of the dendritic tree on the integration of two synaptic inputs by a CA1 neuron.** All simulations were carried out using the NEURON simulation environment[70]. The morphology was based on a three-dimensional reconstruction[71], and synaptic conductances were modelled as an α-FUNCTION with a time constant of 3 ms, a reversal potential of 0 mV, and with peak values scaled in such a way as to obtain the same somatic depolarization when independently activated. The simulation files are publicly available in the ModelDB section of the SenseLab database. **A** | Peak somatic depolarization using passive dendrites with two synaptic inputs, S1 and S2, activated at different relative activation times ($t_{S2} - t_{S1}$) at the soma (green), at the soma and distant sites (red; S1 at the soma, S2 at 490 μm), or at a distal dendritic location (blue; 490 μm from the soma). The dotted line represents the threshold for an action potential in this model neuron. The temporal windows for synaptic integration are indicated by a coloured bar under each curve. Coloured labels are positioned close to the relative activation times used for the voltage traces shown in part **C**. **B** | Peak membrane depolarizing responses as a function of the distance from the soma, up to 490 μm along the apical dendrite. The inset represents the synaptic locations (S1 and S2 at 490 μm). **Ca**–**c** | Examples of somatic potential with different synaptic locations, relative activation times (Δt) and orders of activation (S1→S2 or S2→S1); trace colours as in **A**.

small branches gives large depolarizations, which bring the membrane potential close to the equilibrium potential of the synaptic conductances. There is therefore a mutual short-circuiting of the conductances when they are coincident. This effect is better illustrated in FIG. 1B, which shows the membrane potential as a function of distance from the soma for this case.

This example shows the way in which a passive dendritic tree with a long, thick APICAL DENDRITE would integrate two independent inputs. With a passive tree, the temporal integration window tends to be large for distal inputs and is static — dominated by the MEMBRANE TIME CONSTANT — without the possibility of activity-dependent shaping and modulation.

These limitations of passive dendrites are overcome when the dendritic membrane contains voltage-gated channels. The nature and distribution of such channels are crucial in shaping the dendritic responses. In the following sections, we review the findings on the main channels that have been identified so far, and discuss the implications for dendritic function.

Na^+ channels

The transient Na^+ channel is the basic current that underlies the generation and propagation of the action potential in virtually all axons. It is present to varying degrees in different dendrites, and its distribution is crucial for the functions of many types of dendrite.

Data on the distribution of Na^+ channels in the dendrites of different neuron types is summarized in FIG. 2a. In some cells, such as deep neocortical pyramidal neurons[12] and CA1 pyramidal neurons[13], Na^+ channel density is relatively high and constant throughout the dendritic tree. High densities are also found in the main apical trunk of the dendrites of mitral cells[14], in which action potential invasion throughout the lateral (secondary) dendrites has recently been reported[15] (but see REF. 16). The highest values in dendrites have so far been found in CA1 interneurons[17].

Other cells show wide variations in dendritic Na^+ channel density. For hippocampal CA3 pyramidal neurons, the density has not been directly estimated. In somatic intracellular recordings of CA3 cells, the CURRENT–VOLTAGE RELATIONSHIP was very similar to that of CA1 neurons[18]. But extracellular recording *in vivo*[19] indicated that the dendritic density of Na^+ channels decreases rapidly with distance from the soma. A decrease in density was observed in thalamocortical neurons, especially after branch points[20], and the density also decreased rapidly with distance from the soma in Purkinje cells[21] — a finding that is consistent with imaging studies of changes in intracellular Na^+ in this cell type[22].

Although this is the extent of quantitative studies of Na^+ channel dendritic distributions, other studies have provided indirect estimates. In spinal dorsal horn neurons, only ~20% of the total Na^+ conductance was estimated to be present in the dendrites[23]. In retinal ganglion cells, action potential propagation at reduced amplitude indicated a lower, but constant, density of dendritic channels[24]. In nigral dopaminergic neurons, full-amplitude dendritic action potential propagation pointed to a constant dendritic density[25].

In hippocampal granule neurons of the dentate gyrus, the somatic Na^+ channel density is similar to that of CA1 cells[26]. Indirect experimental evidence from laminar field potentials that were evoked by synchronous activation of granule cells[27] pointed to the presence of dendritic Na^+ channels, although at a density that was insufficient to support dendritic action potential initiation, even under strong dendritic stimulation. Only small Na^+ currents were measured in somatodendritic NUCLEATED PATCHES[28].

α-FUNCTION
The functional form $G(t) = (t/\alpha)e^{-\alpha t}$ is known as the α-function, and is widely used to represent the time course of a synaptic conductance. The value of α determines the rise and decay times.

APICAL AND BASAL DENDRITES
Cell types such as mitral cells and cortical pyramidal neurons have dendritic trees that are divided into two parts — an apical tree that ascends across layers and a basal tree that extends laterally.

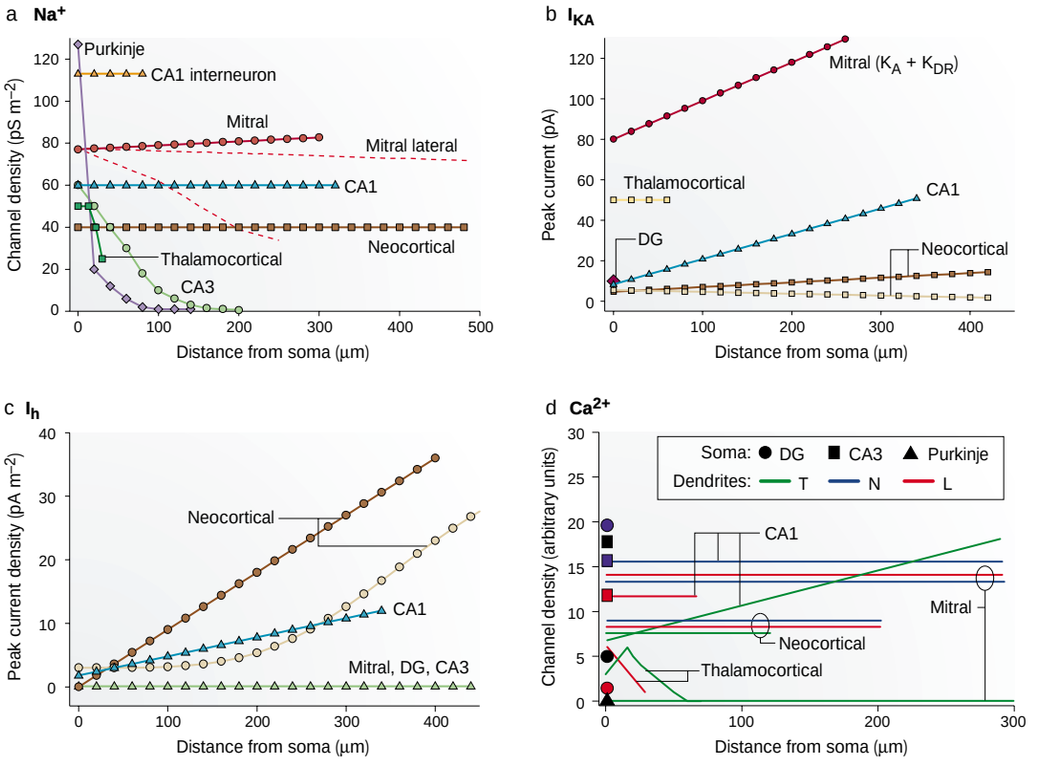

Figure 2 | **Dendritic distribution of active channels in different neuron types. a** | Na^+ channel density, directly estimated in the original experimental papers or indirectly inferred from the amplitude of action potential backpropagation or imaging studies. **b** | Peak dendritic K_A current presented as a function of the distance from the cell soma. **c** | Peak dendritic I_h density as a function of distance from the soma, directly estimated in the original experimental papers or indirectly inferred from the lack of a 'sag' in response to hyperpolarizing current injection. **d** | Schematic distribution of CaT, CaN and CaL Ca^{2+} channels as a function of distance from the soma. Graphs **a**, **b**, and **c** are based on quantitative experimental data; **d** is based on both the available quantitative data and on qualitative estimates. Further details, with search tools for comparative analysis, can be found in NeuronDB. DG, dentate gyrus granule cell.

MEMBRANE TIME CONSTANT
A quantity that depends on the capacitance and resistance of the cell membrane, and which sets a timescale for changes in voltage. A small time constant means that the membrane potential can change rapidly.

CURRENT–VOLTAGE RELATIONSHIP
A plot of the changes in ionic current as a function of membrane voltage.

NUCLEATED PATCHES
A special configuration of patch-clamp recording in which a membrane patch is pulled out of the cell together with the nucleus. The external face of the membrane still faces the extracellular medium, and the nucleus lies enclosed by this balloon-like patch.

K_A channels

These channels are involved in the repolarization phase of the action potential, and contribute to the control of action potential firing frequency. The data on K_A channel distribution in dendrites is summarized in FIG. 2b. It can be seen that there are two main patterns — their density is either relatively constant or it increases with increasing distance from the soma.

Two types of cell that show increasing K_A channel density are mitral/tufted cells[14] and CA1 pyramidal neurons[29]. Thalamocortical neurons[20] and deep neocortical neurons[30,31] have a relatively even distribution of K_A channels.

Among other cell types, recordings in mechanically isolated dentate gyrus granule cells with preserved dendrites of different length have indicated that K_A channels are concentrated in the axosomatic region; the dendrites were practically devoid of these channels[32]. For Purkinje cells, experimental data[33] and detailed modelling[34] indicated that a slower D-type K^+ conductance (rather than the faster A-type) might be present in the dendrites. In dissociated spinal dorsal horn neurons, only 17% of the total K_A current was estimated to be expressed in the dendrites[35].

I_h channels

I_h is a nonspecific cation current that is activated by hyperpolarization and deactivated by depolarization. It increases the membrane conductance at rest, thereby reducing the time course of subthreshold synaptic depolarizations, and it contributes to pacemaker functions. The distribution of dendritic I_h current is shown in FIG. 2c.

In CA1 neurons, I_h density increases progressively by more than sixfold from the soma to distal dendrites[36]. For somatosensory neocortical neurons of layer V, two different distributions have been suggested — an approximately linear, steep increase[37], and a lower density (comparable to that found in CA1 cells) up to 400 μm from the soma, strongly increasing in a nonlinear fashion for more distal locations[38].

Indirect evidence for the expression of this current in the soma of deep pyramidal cells of the piriform cortex can be inferred from the partially tetrodotoxin-sensitive 'sag' that is observed in response to hyperpolarizing current injection in intracellular recordings[39]. Recordings from thalamocortical neurons[40] and from periglomerular cells of the olfactory bulb[41] have shown that I_h is present, at least at the soma, although its

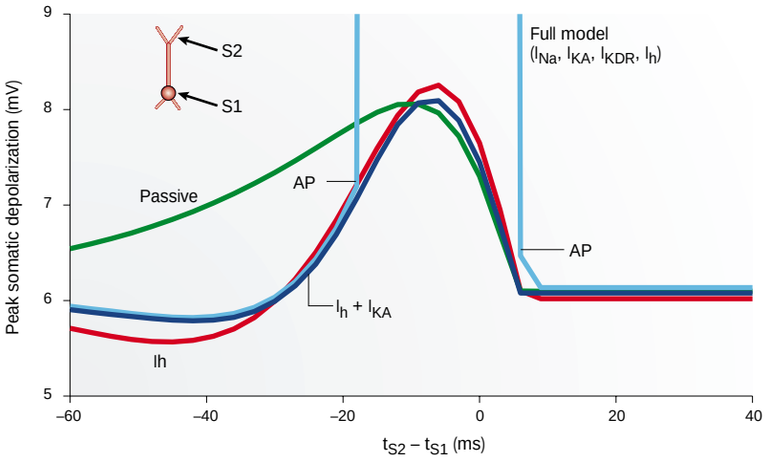

Figure 3 | **Effect of I_h on dendritic integration.** Peak somatic depolarization as a function of the relative activation times ($t_{S1} - t_{S2}$) using a passive model (green), as in FIG. 1A, a model with I_h (red) or $I_h + I_{KA}$ (dark blue), or a full model with $I_{Na} + I_{KA} + I_{KDR} + I_h$ (cyan) (from Migliore *et al.*[71]). The inset represents the synaptic locations (S1 at the soma, S2 at 418 μm) and indicates the relative activation times for which a somatic action potential (AP) was generated. In all cases, the peak synaptic conductances for S1 and S2 were scaled in such a way as to obtain a peak somatic depolarization of ~6 mV (for S1) and ~2.5 mV (for S2) when they were independently activated.

density and dendritic distribution were not estimated. Quantitative measures from patch recordings of I_h are not yet available for these cell types.

In Purkinje cells, a prominent sag that was attributed to I_h was observed in both somatic and dendritic recordings up to 150 μm from the soma[21], and this current was shown to have an important role in maintaining the tonic firing of these cells[42]. In dentate gyrus granule cells[43,44], CA3 cells[43] and mitral/tufted cells (W. Chen, personal communication), the lack of a prominent sag in response to hyperpolarizing current injections has indicated that I_h density in these cells is very low, if not absent.

Luthi and McCormick[45] have reviewed the functional role of the I_h current. Here, it is worth highlighting the role that this current can have in temporal integration by using a simulation (FIG. 3). The effect of I_h alone is to narrow significantly the temporal window for input summation. When combined with the properties of Na^+ currents, the occurrence of an action potential can signal coincidence detection. These combined effects can be compared with the responses in a passive dendritic tree (FIG. 1 and FIG. 3).

It has been shown that I_h modulates the TEMPORAL SUMMATION of excitatory postsynaptic potentials (EPSPs)[36,38]. In neocortical and CA1 pyramidal neurons, its non-uniform dendritic distribution normalizes the time course of EPSPs that are generated at different distances from soma[37,46]. Its high density in neocortical neurons points to the existence of a narrow time window for the integration of distant inputs[47]. I_h might therefore have a fundamental role in modulating the precise temporal dynamics of firing synchronization that is observed in the neocortex[48].

As mentioned above, I_h has also been suggested to generate pacemaker potentials, but its role is not consistent across different types of neuron. It has been shown to be important in thalamocortical cells, inferior olivary cells, CA1 interneurons and Purkinje cells. However, in other bursting cells, such as CA3 neurons, I_h does not seem to be important for pacemaking.

The effects of the experimentally observed dendritic distribution of I_h on the window for the temporal summation of two synaptic inputs on a CA1 neuron could be estimated from the simulations in FIG. 3. They indicate that the increasing density that is observed experimentally might be needed to reduce the time window during high-frequency synaptic activity, which inactivates K_A channels. Although the same result could probably be obtained with a uniform density (at average, not somatic, values), in this case, the higher I_h at the soma could make a CA1 neuron prone to generating intrinsic oscillatory firing.

Ca^{2+} channels

Ca^{2+} channels are crucial to many functions of the cell in general and of dendrites in particular. However, in contrast to the channels that we have discussed above, quantitative evidence for the density and distribution of Ca^{2+} channels is limited (FIG. 2d). We focus on the classical Ca^{2+} channel types — CaT (low-voltage activated, LVA), and CaL and CaN (high-voltage activated, HVA).

The dendritic distribution of the different kinds of Ca^{2+} channel has been characterized best in CA1 pyramidal neurons (reviewed in REF. 49). Although the total channel density was found to be reasonably uniform, there were significant differences in the distributions of Ca^{2+} channel types. The density of CaT channels was found to increase with distance from the soma[13]. CaL channels were localized chiefly in the more proximal dendrites[13,50]. CaN channels were found to be uniformly distributed on some, but not all, spines throughout the entire dendritic tree[51].

Evidence of Ca^{2+} channel types in other cells is more fragmentary. We will focus on evidence that is most relevant to the specific functions of dendrites. In neocortical neurons, dendritic Ca^{2+} transients that are evoked by BACKPROPAGATING ACTION POTENTIALS have indicated a fairly uniform distribution of CaL and CaN channels in the dendrites of these cells[52]. In addition, single subthreshold EPSPs[53] can activate LVA channels. A uniform distribution (as opposed to hot spots) of voltage-gated Ca^{2+} channels has also been suggested, although the relative contribution of the different channel subtypes has not been explored[54].

Evidence for Ca^{2+} spikes in mitral cells was found in the turtle[55]. Recordings in rat mitral cells[56] indicated that both HVA and LVA channels seemed to be expressed at the soma, although LVA channels were detected in only 65% of the tested neurons and, using Ca^{2+} imaging, no LVA channels were detected in the main apical dendritic trunk up to the distal tuft (arborization)[57].

Although it has been established for many years that Purkinje cell dendrites support prominent Ca^{2+} spikes in response to synaptic inputs[58], there are no data on the dendritic distribution of different types of Ca^{2+} channel in these neurons. In general, Ca^{2+}-imaging experiments

TEMPORAL SUMMATION
The way in which synaptic events add in time. One of the basic elements of synaptic integration.

BACKPROPAGATING ACTION POTENTIALS
Although action potentials typically travel down the axon towards the presynaptic terminal, they can also be initiated at the axon and propagate back into the dendrites, shaping the integration of synaptic activity and influencing the induction of synaptic plasticity.

have pointed to a homogeneous distribution of channels throughout the dendritic tree[59], with regenerative Ca^{2+} action potentials sometimes being restricted to a limited portion of the dendritic tree, and not involving the soma or the dendritic shaft. However, only HVA and no CaT channels have been found on the soma of adult cells[60].

In thalamocortical neurons, CaL channels were found to decrease rapidly with distance from the soma, with channels clustered around the base of dendrites, as observed in CA1 neurons[61]. A strong decrease in dendritic CaT channels with distance from the soma was also observed in dendritic patches, with no or few channels at the soma[20], as in Purkinje cells[60,62] and dentate gyrus granule cells[63].

General discussion

We can now discuss the interactions between the different channels in the dendrites of different types of neuron, and their possible relation to the functional characteristics of each cell type. First, it should be stressed that quantitative experimental estimates of channels or current densities, especially in dendrites, are complicated, and several caveats need to be considered. So, direct comparisons of the numerical values that have been estimated for a given channel type by different laboratories using different methods for different neurons might not be completely justified. We therefore focus on the most important qualitative differences, such as uniform or non-uniform distribution, or presence or absence of a given channel, which could be considered as more reliable, especially when the overall functional context of a given neuron is taken into account. For this reason, when analysing the experimental evidence reviewed in the previous sections, we will not make a direct comparison of quantitative data; rather, we will emphasize qualitative differences that might have functional consequences.

We begin by stressing that action potentials are energetically expensive owing to the requirement for ATP to fuel membrane pumps to restore ion gradients[64]. So, it is possible that the distinction between cells with and without dendritic Na^+ channels is an important one, and that Na^+ channels and the channels that interact with them are expressed only where they are specifically needed for functions related to action potential generation, propagation and modulation.

The best available data are for mitral cells, neocortical pyramidal neurons and CA1 pyramidal neurons, all of which have dendritic Na^+ channels. We discuss them in order of apparent increasing complexity of channel distributions.

Mitral cells. This cell type has the highest density of dendritic Na^+ channels among the principal neurons that have been studied[14]. This high density is evenly distributed throughout the apical, and probably also the basal, dendrites (FIG. 4a), and is associated with full action potential propagation along apical and basal dendrites in the backpropagating mode[15,65]. The dynamics of these action potentials are controlled by the high density of K_A channels, which would quench all action potential generation if it were not for their slow activation kinetics[14]. The slow kinetics seem to correlate with the relatively wide action potentials that are seen in these cells. The I_h current is not present in mitral cell dendrites, indicating that the temporal-integration window in these cells is relatively large. This would seem to correlate with the relatively slow time course of activation of dendritic tufts within an olfactory glomerulus[66].

CaL and CaN channels are evenly distributed throughout the primary and secondary dendrites of mitral cells. One of their functions seems to be related to presynaptic transmitter release that is involved in the dendrodendritic interactions of this cell type with granule cell interneurons. CaT channels are absent, which is consistent with the need to avoid transmitter release at low depolarization levels. The high density of the fast K_A channels might also control the generation of Ca^{2+} spikes.

Neocortical pyramidal neurons. In this cell type, there is an even distribution of most channel types, with the exception of I_h, which increases with increasing distance from the soma (FIG. 4b). Na^+ channels are evenly distributed along the dendrites; K_A also has an even distribution at a relatively low density. This implies that action potentials can fully propagate backwards and also possibly forwards[67].

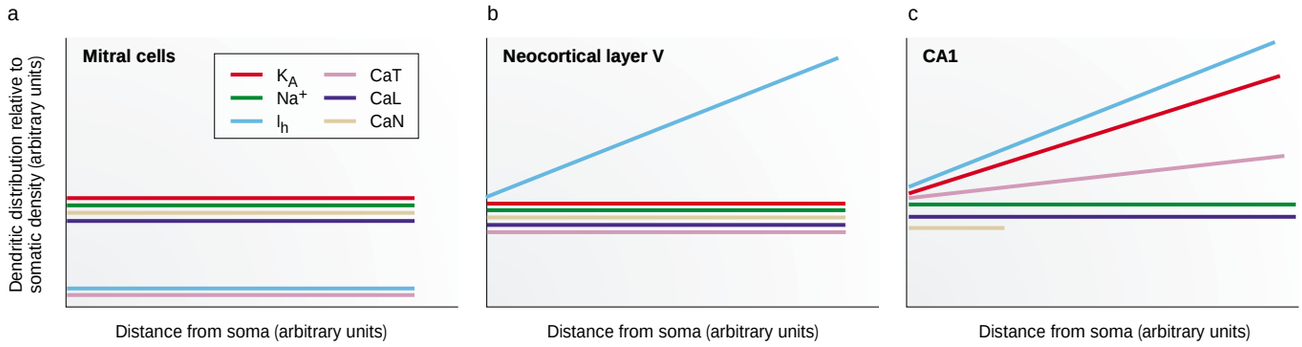

Figure 4 | **Dendritic distribution of active channels. a–c** | Schematic comparison of the dendritic distribution of active channels for mitral cells (**a**), layer V neocortical pyramidal neurons (**b**) and hippocampal CA1 pyramidal neurons (**c**). Further analysis of the channel combinations in these and other cell types can be carried out in NeuronDB, and realistic models from published papers for the neurons with these combinations of properties are in ModelDB.

The role of the weak, constant presence of K_A seems to be limited largely to repolarizing the membrane after the action potential, which might mean that inputs at different dendritic levels are not progressively dampened as in CA1 cells (see below). CaT channels in the dendrites might contribute to this equivalence by boosting local EPSPs.

I_h is present at low density at the soma, increasing to a high density in the distal dendrites. We suggest that this implies a close control over temporal summation, with the summation of EPSPs occurring within increasingly narrow time windows when they target more distal dendrites (see, for example, FIG. 3). Distal EPSPs therefore have large local amplitudes because of the high input resistance, and faster time courses because of the I_h current.

Ca^{2+} channel density is relatively uniform, and Ca^{2+} spikes might be more easily activated in neocortical cells because of the relatively low density of K_A channels.

CA1 hippocampal pyramidal neurons. Non-uniform densities of several channel types distinguish the distribution of channels in this cell type (FIG. 4c). Na^+ channels are present at uniform density along the long apical dendrite of CA1 pyramidal cells. K_A channels and I_h exist at a moderate but increasing density towards the periphery, and CaT channels are present at a moderately increasing density, whereas CaL and CaN channels have a relatively constant density.

On the basis of the principles that we have discussed above, we propose that this distribution implements the following dendritic functions. The Na^+ channels generate active depolarizations that can potentially support full action potentials. These depolarizations are controlled by K_A, depending on the intensity and time course of local EPSPs. The non-uniform distribution of I_h points to different modulations of the temporal window of summation of local synaptic inputs at the two extreme points of the dendritic tree — the PERFORANT PATH distally and the SCHAFFER COLLATERALS proximally — which are activated in sequence at different times. Dendritic Ca^{2+} spikes are opposed by the K_A current[29], but, under prolonged, strong excitatory responses, this current inactivates, allowing activation of different Ca^{2+} channels, depending on the amount of depolarization.

For comparison with the three cell types that we have just discussed, we now turn to three cell types that show bursting behaviour, have dendritic trees that lack a long, single apical dendrite, and are characterized by a relative lack of Na^+ channels in their dendrites — Purkinje cells, CA3 pyramidal neurons and thalamocortical cells.

Purkinje cells. In this cell type, the classical evidence indicates that Na^+ channels are restricted to the most proximal dendrites and Ca^{2+} channels are present throughout the dendritic tree, although the specific types of Ca^{2+} channel have not been identified (FIG. 2). With this distribution, classical physiological studies established that the responses of Purkinje cells can distinguish between two distinct inputs — modulated spike discharge with PARALLEL FIBRE input, and burst responses with CLIMBING FIBRE input. This ability of the Purkinje cell might depend on the absence of Na^+, K_A and I_h channels along its dendrites, because of the following considerations. The presence of Na^+ channels would lead to intense depolarization and bursting in response to input from the parallel fibres. The presence of K_A channels would short-circuit any Ca^{2+} spike response to parallel fibre input. And the presence of I_h would reduce the temporal summation of asynchronous parallel fibre inputs. The apparent lack of CaT channels in Purkinje cells indicates a possible need for these cells to be activated only under strong synaptic inputs. In this case, the HVA channels CaN and CaL initiate Ca^{2+} spikes that might be restricted to isolated portions of the dendritic tree.

CA3 hippocampal pyramidal neurons. In this cell type, as in the Purkinje cell, the distribution of Na^+ channels seems to be restricted to the proximal dendrites. However, there is a high density of CaT channels at the soma, although data on the distribution of these channels are not available for the dendrites. We suggest that the distribution of CaT correlates with the bursting behaviour of these cells, and predict that these channels are not expressed in the dendrites. In fact, CA3 dendrites receive different afferent inputs that are activated at different times and at different distances from the soma, indicating a possible need to modulate their integration. With their amplifying effects on subthreshold inputs, CaT channels could readily initiate dendritic Ca^{2+} spikes. However, a bursting CA3 neuron might be needed to generate an output that can relieve the block of dendritic depolarization by K_A on CA1 neurons.

Although there is no evidence for K_A channels in the dendrites of CA3 cells, a modelling study has shown that a high density in the proximal dendrites would prevent bursting behaviour[68]. I_h is absent, indicating that the bursting behaviour is episodic rather than oscillatory, as in the case of thalamocortical cells (see below).

Thalamocortical neurons. In these cells, the Na^+ channel distribution is also limited to the soma and proximal dendrites. I_h is present at a high density on the soma, and it interacts with CaT channels to generate depolarizing–hyperpolarizing sequences that are responsible for the oscillatory behaviour that is characteristic of these cells in the bursting mode[69].

It is interesting to note that although both thalamocortical and Purkinje cells can generate spike output in either the transmission mode or the bursting mode, LVA channels are restricted to the proximal dendrites in thalamocortical cells, whereas HVA channels are uniformly distributed in the dendrites of Purkinje cells. These different distributions might be reflected in the firing modes of these cell types, which depend on different levels of background depolarization in thalamocortical cells and on the pattern of synaptic input in the Purkinje cell.

PERFORANT PATH
Axons of entorhinal cortex neurons that terminate largely in the hippocampal dentate gyrus. Some fibres from the entorhinal path reach the distal end of apical dendrites of CA1 neurons.

SCHAFFER COLLATERALS
Axons of the CA3 pyramidal cells of the hippocampus that form synapses with the apical dendrites of CA1 neurons.

PARALLEL FIBRES
The axons of cerebellar granule cells. Parallel fibres emerge from the molecular layer of the cerebellar cortex towards the periphery, where they extend branches perpendicular to the main axis of the Purkinje neurons and form the so-called *en passant* synapses with this cell type.

CLIMBING FIBRES
Cerebellar afferents that arise from the inferior olivary nucleus, each of which forms multiple synapses with a single Purkinje cell.

Summary
In this review of dendritic channel distributions, we have put forward several hypotheses on the defining characteristics of different neuronal types. These are summarized in FIG. 5, which attempts to organize the complex data into sequences that lead to a logical differentiation of neuronal phenotype.

We begin with the synaptic input and its reception by cells that are activated within relatively narrow or wide temporal windows. We propose that neurons with relatively narrow windows for temporal summation tend to have long dendrites that express Na^+ channels, whereas neurons with wide temporal windows tend to have dense branching trees that lack dendritic Na^+ channels. In both cases, cells also express HVA Ca^{2+} channels, presumably to mediate plastic processes and other Ca^{2+}-dependent functions.

The next crucial neuronal property to consider is the bursting behaviour of a given cell. If it bursts, it must have LVA Ca^{2+} channels on the soma, together with Na^+ channels to generate action potentials. This applies to both densely branching and apically branching dendritic trees.

For cells with long apical dendrites that show somatic bursts, we would predict a higher density of LVA channels than in cells that do not burst. All cells with long dendrites show action potential backpropagation, a product of the presence of dendritic Na^+ and K_A channels. Cells that do not modulate the temporal window for integration of subthreshold inputs, such as mitral cells, lack I_h currents, whereas cells that can exert such modulation require I_h. In the case of the latter, some cells, such as neocortical pyramidal neurons, do not have a high density of K_A channels, which precludes the modulation of backpropagation. By contrast, some cells, such as CA1 pyramidal neurons, have a high density of K_A channels, which modulate the extent of backpropagation of action potentials. This means that distal inputs must be stronger to have significant effects on the soma.

Some densely branching cells, such as dentate gyrus granule cells, lack LVA channels in both the soma and dendrites, and do not burst. Cells that express somatic LVA, such as CA3 pyramidal neurons, show episodic bursting. Other cells, exemplified by the Purkinje cells, show complex spikes and oscillations with the addition of I_h, at least at the soma. Furthermore, with the addition of LVA channels, the bursting behaviour of thalamocortical cells can be achieved.

These considerations are preliminary at this stage, but they indicate how rules for channel expression can determine functional properties that can be useful in defining neuronal phenotypes. On the basis of differences in dendritic channel distributions, we can predict, for example, that neocortical pyramidal neurons have narrower time windows for coincidence detection than CA1 pyramidal neurons and, in particular, mitral cells — a hypothesis that can be tested both experimentally and computationally.

The generation of Ca^{2+} spikes might indicate a learning mechanism in which local processing of the active inputs takes place within a large temporal window, controlled by the slower dynamics of the Ca^{2+} channels. This is a process that is fundamentally different from the global associative signal that is sent to all dendrites by a backpropagating action potential, which, being Na^+-dependent, could affect all the active synapses within a relatively short time window. An interesting hypothesis is that cells with long primary dendrites, such as CA1, deep neocortical and mitral cells, seem to implement a global rule, whereas multiple-branched neurons, such as Purkinje cells and CA3 pyramidal cells, implement a local one.

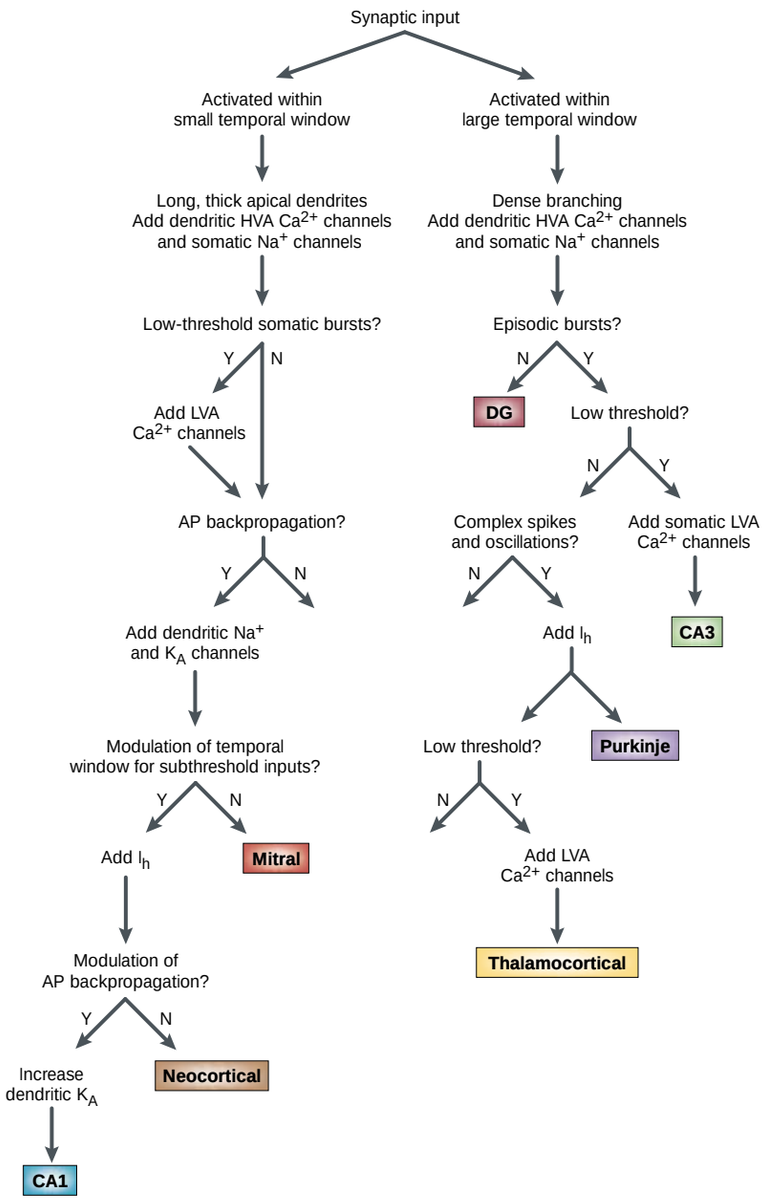

Figure 5 | **Schema for the differentiation of neuronal phenotypes.** Tentative flow chart showing how the specific distributions of ion channels might relate to morphological types of dendritic tree and the functional properties of neurons. AP, action potential; DG, dentate gyrus granule cell; HVA, high-voltage activated; LVA, low-voltage activated; N, no; Y, yes.

In conclusion, a detailed consideration of data on the distributions of dendritic active channels should lead to new ways of categorizing neuronal phenotypes. This might be regarded as the first step towards a 'proteomics' of dendritic function. Future studies will define better the precise distributions and functional properties of each channel type and their relation to the synaptic properties of the circuits of which each cell is a part.

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