Modelling plasticity in dendrites: from single cells to networks

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Abstract

One of the key questions in neuroscience is how our brain self-organises to efficiently process information. To answer this question, we need to understand the underlying mechanisms of plasticity and their role in shaping synaptic connectivity. Theoretical neuroscience typically investigates plasticity on the level of neural networks. Neural network models often consist of point neurons, completely neglecting neuronal morphology for reasons of simplicity. However, during the past decades it became increasingly clear that inputs are locally processed in the dendrites before they reach the cell body. Dendritic properties enable local interactions between synapses and location-dependent modulations of inputs, rendering the position of synapses on dendrites highly important. These insights changed our view of neurons, such that we now think of them as small networks of nearly independent subunits instead of a simple point. Here, we propose that understanding how the brain processes information strongly requires that we consider the following properties: which plasticity mechanisms are present in the dendrites and how do they enable the self-organisation of synapses across the dendritic tree for efficient information processing? Ultimately, dendritic plasticity mechanisms can be studied in networks of neurons with dendrites, possibly uncovering unknown mechanisms that shape the connectivity in our brains.

Background

Dendritic spikes and dendritic computation

One of the distinguishing features of neurons is their remarkable morphology. Neurons possess long branch-like protrusions, called dendrites, that can extend hundreds of micrometers across the brain. Dendrites are not just passive cables conducting synaptic input to the soma. Instead, dendrites respond non-linearly to spatially clustered input, giving rise to action potentials mediated by diverse currents, called dendritic spikes [71]. We can distinguish three types of dendritic spikes based on the underlying ion channels: the first type is mediated by synaptic N-Methyl-D-Aspartate (NMDA)-receptors, and therefore called NMDA spikes. The opening of NMDA-receptor channels is glutamate- and voltage-dependent: upon pre-synaptic glutamate release, they contribute to the synaptic current once the local depolarisation crosses a threshold [65, 48]. Typically, they last for about 50-100 ms and allow a substantial influx of calcium ions. A second type of dendritic spike is mediated by voltage-gated calcium channels and therefore called dendritic calcium spike. This type is especially prominent in cortical layer 5 pyramidal neurons, which possess a calcium spike initiation zone close to the tuft dendrites [66]. Calcium spikes have two interesting properties: (1) they can cause somatic burst firing and thereby enable

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distal tuft inputs to interact with the soma and (2) they act as coincidence detectors between distal and proximal inputs as back-propagating action potentials substantially lower the threshold for calcium spike initiation [38]. In contrast to NMDA spikes, which usually do not propagate beyond the input dendrite [65, 11], calcium spikes can spread to larger regions of the apical dendritic tree [40]. Finally, the third type of dendritic spike is mediated by voltage-gated sodium channels. In contrast to the other types, it has fast dynamics and propagates quickly [20, 2, 54, 1].

All types of dendritic spikes were found to be correlated with important neuronal computations, including behaviorally relevant ones. For example, they have been implicated in determining tuning curves [41], orientation selectivity [69, 78], action potential generation [56] and action potential precision [2], as well as in modulating perception [** 72].

Parallel to these experimental findings, dendritic computation has been increasingly explored in theoretical models during the past decades. Pioneering work was performed by Mel and colleagues, showing how dendrites allow for 'cluster-sensitivity' towards inputs [51, 52]. Further research uncovered that dendritic non-linearities increase the computational capacity of neurons [59] and suggested to interpret a neuron as a two-layer network [58]. Recently, interactions among excitatory inputs [5] and between excitatory and inhibitory inputs [29, 18] across a dendritic branch have been studied more closely, and [** 4] showed that different branches operate as nearly independent processing units. These results suggest that a neuron acts as a network in which each subunit has non-trivial input-output functions [** 30]. Furthermore, the dendritic non-linearities enable a neuron to perform linearly non-separable computations, like exclusive-OR operations (XOR) [43, 9] and are critical for efficient computations with discrete somatic spikes [75].

Dendritic spikes and plasticity

Spike-timing-dependent plasticity (STDP) was shown to depend on dendritic location ([16], see [15] for a review). Moreover, STDP may be absent in distant synapses as back-propagating action potentials (bAPs) attenuate with somatic distance and sometimes fail to propagate into distal branches [70, 81]. The relevance of STDP is therefore debated, and it was argued that other plasticity mechanisms should exist within a neuron, independent of bAPs [44, 24, 45, 67, 8].

Remarkably, *in vitro* experiments showed that synapses eliciting NMDA or calcium spikes undergo potentiation in the absence of somatic spikes [21, 22]. Golding et al. showed that potentiation was only abolished completely when both NMDA channels and voltage-gated calcium channels were blocked, showing a contribution to plasticity from both sources [21] . Interestingly, single occurrences of these dendritic spikes can induce LTP [62] or LTD [27] possibly enabling single-shot learning in contrast to STDP, which requires repeated pairings of pre- and postsynaptic spiking. These forms of local cooperative potentiation of nearby synapses could be restricted to early postnatal development [42]. Moreover, the temporal aspect of plasticity could be preserved in the presence of long-lasting dendritic spikes. *In vivo* results indicate that timing of inputs relative to the NMDA spike are indeed important: synapses active less than five seconds before an NMDA spike were depotentiated while coincident inputs were strengthened [11]. In this work, Cichon et al. propose that NMDA spike-dependent plasticity enables different inputs to be processed on different branches, reducing their interference. This is in line with the idea that functionally-related inputs form spatial clusters, which in turn are required for dendritic spikes and dendritic-spike mediated synaptic plasticity [46, 60]. Similar to NMDA spikes, pairing synaptic stimulation with dendritic calcium spikes can evoke both LTD and LTP [28]. Finally, also sodium spikes were shown to be crucial for potentiation in the tuft of CA1 pyramidal neurons [36]. It was suggested that synaptic inputs evoking sodium spikes in turn allow calcium influx

via NMDA-receptor channels and L-type voltage-gated calcium channels. Furthermore, dendritic sodium spikes can be impaired by bAPs [61], which could therefore affect this form of plasticity. Taken together, these experiments demonstrate interesting functional roles for dendritic spikes in plasticity.

Other mechanisms of plasticity in dendrites

As discussed in the previous sections, it is well established that clustered synapses can give rise to dendritic spikes and hence plasticity (for a recent review, see [** 34]). An important question is whether plasticity rules in turn promote the clustering of synapses. Various studies indeed found that plasticity of synapses is modified by activity at nearby locations. In hippocampal cells, it was found that inducing LTP at a synapse lowers the threshold for LTP in neighbouring synapses [25]. Another study showed how subthreshold activation of four spines within a 20 micron dendritic segment leads to LTP at those spines [** 76]. Such interactions between excitatory inputs would induce a bias towards the formation of functional clusters. However, direct measurements of neighbouring spines have argued both in favour [17, 13, 19] and against clustering [32, 10]. As suggested in [19], the discrepancy could be understood when considering that synapses involved in functional clusters are intermingled with other synapses.

On a longer timescale, homeostatic mechanisms maintain the stability of neuronal and network function. Homeostatic processes regulate synaptic strength to maintain a healthy range of neuronal activity. At sustained low activity levels, synapses tend to strengthen, while at sustained high activity levels, they tend to weaken [73], referred to as synaptic scaling. It is established that homeostatic mechanisms can act on a global (neuronal) level, affecting all synapses of a cell equally [74], while recently it was found that they can also act locally on the level of dendrites [7].

Finally, the communication between dendrites and the soma itself can be plastic. The density of potassium channels is regulated in an activity-dependent manner, which affects the forward- and backward-propagation of electrical signals [47, 49]. This mechanism is termed branch-strength plasticity, as it regulates which branches will have the strongest effect on the neuronal output. Moreover, the changes in ion channel density can affect the integration of local inputs and therefore the probability of evoking dendritic events.

Functional roles of plasticity in dendrites

While the computational advantages of dendrites have been extensively modeled, their influence on synaptic plasticity remains less explored.

A number of studies have tackled this question in single neuron models. A first body of work focussed on the role of inhibition in altering excitatory plasticity. It was shown that inhibition affects the excitatory learning window [3], that inhibition can gate the bAP and therefore STDP [* 77], and that inhibition enables a detailed excitatory-inhibitory balance on dendrites [* 26]. A second group focussed exclusively on excitatory plasticity in dendrites. Kumar et al. investigated the role of synaptic location and calcium saturation on plasticity. They showed that the amount of synaptic potentiation per spike is maximal at a preferred input rate, and this preferred rate itself is location dependent [37]. Combining branch strength plasticity with Hebbian and local learning rules, a single neuron was shown to solve a feature-binding problem [43]. Schiess et al. adopted a top-down approach. Starting from the task to be performed, they inferred a plasticity rule which allows to perform that task. Following this strategy, the authors proposed a

biologically plausible dendritic learning rule which can be interpreted as a version of the error-backpropagation algorithm [64].

Few studies have investigated the role of dendritic plasticity in networks. Firstly, some studies looked at the effect of dendritic non-linearities on STDP-like learning rules. For example, dendritic sodium spikes were proposed to underlie sharp wave ripples during hippocampal replay of spike sequences [31], while inhibitory neurons gating dendro-somatic communication were proposed to improve context-dependent decision making [* 80]).

Secondly, some studies have explored novel plasticity mechanisms requiring dendrites. Wu et al. suggested a local learning rule dependent on dendritic depolarisation, which enhances the learning capacity [* 79]. O'Donnell et al. proposed a rule dependent on protein synthesis, which allows for selective memory consolidation even if the presynaptic activities overlap in time [55]. Kaifosh et al. proposed burst generation due to interacting bAPs and dendritic spikes as a plasticity mechanism, and showed how this enhances memory storage and recall in a hippocampal network [33].
The influence of NMDA spikes on plasticity in basal dendrites was studied in Bono et al. Exploiting the fact that NMDA spikes are more easily evoked further from the soma, they investigated how distal inputs can gate plasticity at other synapses and how the connectivity between neurons depends on synaptic location. Since NMDA spike mediated plasticity does not require somatic spikes, it decouples learning from the neuronal output. They proposed that this mechanism acts similarly to synaptic consolidation. In networks, they showed how NMDA spike mediated plasticity can protect stored associations from being overwritten when learning new associations [** 6].
Incorporating calcium-based learning rules, synaptic consolidation and plasticity-related protein synthesis, Kastellakis et al. showed in networks how associative memories can not only be linked on a cellular level, but lead to clusters sharing synapses from both memories, thus linking the memories on a sub-cellular level. Moreover, the authors investigate the role of the various sub-cellular mechanisms on shaping the synaptic arrangements and network activity [** 35].

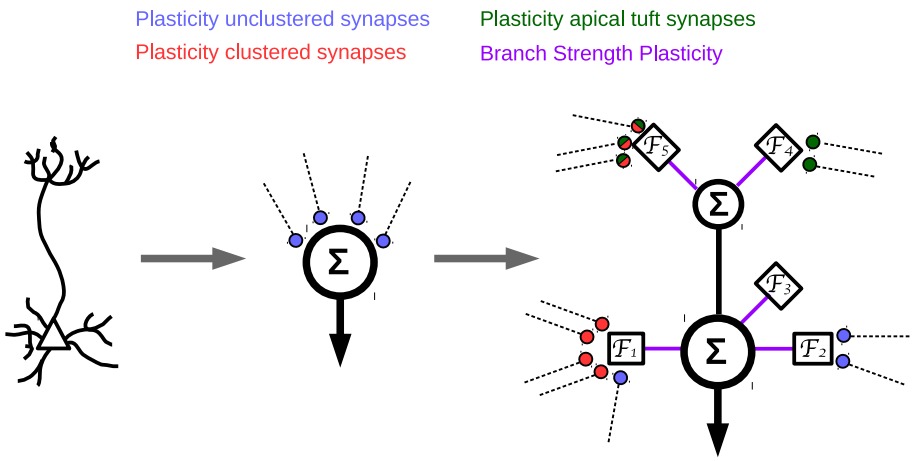

Figure 1 While most plastic models would reduce neurons to point units with the same plasticity rule for all synapses (middle), a more complex picture has emerged. Dendrites can allow for various non-trivial learning rules, depending on dendritic location and synaptic distribution (right). Moreover, plasticity mechanisms could interact and synapses could be under the influence of multiple mechanisms. In the schematics, different colours represent different (ficticious) learning rules. The Σ symbols denote units where inputs are summed and evoke a spike when inputs exceed a threshold. The $\mathcal{F}_i$ symbols denote multidimensional input-output functions, depending on input strength, dendritic morphology and synaptic location and distribution (see [** 30]).

Open questions and challenges

In the previous sections, we provided a concise overview of the recent advances in our understanding of neuronal processing. However, many aspects about the role of dendritic processes for plasticity remain unknown. In the following, we formulate questions that we think need to be addressed next.

• Does the location of synapses relative to the site of dendritic spike initiation play a role in determining the direction of plasticity (increase or decrease of synaptic strength), as suggested in [28]? A related question is: in which spatial range do synapses need to be to affect each other's plasticity?

• For plasticity mediated by dendritic spikes, does timing play a role for the direction of plasticity, as suggested in [50, 11]? Are there mechanisms similar to those underlying STDP at work? If timing does not play a role, are there other mechanisms that influence whether potentiation or depression will occur (for example mechanisms sensitive to input rate, or inhibition)?

• Only few experimental studies have investigated learning rules at more distal synapses, all yielding a distance-dependence of STDP, albeit with diverse results (see [15] for a review). Given that the back-propagating action potential and hence STDP are less powerful in pyramidal tuft dendrites, does the calcium spike dominate plasticity in the apical tuft? Along these lines, Sandler et al. showed a form of plasticity in tuft dendrites, which was not present in basal dendrites [** 63]. Are there more differences between basal and tuft dendrites and are they adjusted to the functionality of their inputs? For example, apical tuft inputs are thought to originate from higher order areas, providing feedback and contextual information [14]. Understanding how synapses are modified in these regions could be crucial for the understanding of cognitive processes like

attention and perception (see e.g. [** 72, 39]).

• What is the relation between the tuning of inhibitory inputs and neighbouring excitatory inputs. How does inhibition interact with excitatory plasticity and affect synaptic distributions? Is inhibitory plasticity itself dependent on synaptic location?

• Do homeostasis and excitatory/inhibitory balance operate on different spatial scales (e.g. branch versus neuronal level)? How do they interact and what are the computational advantages of having multiple mechanisms?

• Do the learning rules within a neuron change during development, as suggested by Lee et al. [42]?

• Which mechanisms encourage binding of inputs, and which mechanisms foster competition between inputs? Binding of inputs is important for associative memory, while competition is important for selectivity and sparsity. How can and do these mechanisms co-exist?

• Which of all these dendritic plasticity mechanisms are relevant on a network level, especially when recurrent connections are prominent?

Outlook

Experimental results point towards a mixture of many learning mechanisms within a single neuron. Each one of those can have diverse impact in various regions of the dendritic tree. For example, plasticity at synapses closer to the soma can be different than at synapses further from the soma, and neighbouring synapses can affect each other's plasticity (Figure 1). This sophisticated mixture further depends on cell type and brain region. To better understand how these mechanisms act and interact, theoretical models can be valuable since they provide complete control over all parameters [53]. However, it is important to characterise and constrain these models according to the available experimental data.

Especially when studying how dendritic plasticity affects network computations, theoretical models can be useful. It is often sufficient to reduce dendrites to a few compartments capturing the relevant behaviour (e.g. see [* 80, ** 6, ** 35]). This is both computationally efficient and the abstraction makes the model components and their interactions easier to understand. Dendritic plasticity mechanisms can be implemented using phenomenological plasticity rules that capture many of the phenomena described in this article, e.g. the calcium-dependent [68, 23] and voltage-dependent [12] models, and possibly combining multiple plasticity rules (e.g. [** 35]). These rules could be further simplified to abstract versions capturing only the essential features (e.g. see [* 79, 43, 33]).

The few studies investigating the network effects of such learning rules showed how they can alter storage capacity, memory consolidation and association of memories. In particular, dendritic spike mediated plasticity decouples the learning mechanism from the neuronal output [** 6], which can profoundly alter the learning dynamics in networks. Furthermore, different pathways could be modified in distinct ways [57]. For example, feedback versus feedforward streams, inputs converging from different modalities (e.g. visual versus auditory streams), and driver versus modulator inputs could all obey different learning rules.

To conclude, research on dendrites has shown that neurons are even more remarkable than previously thought. Dendrites considerably enhance the possible computations on a cellular level

and allow for multiple plasticity mechanisms. In which way these mechanisms orchestrate the arrangement of synapses on dendrites and shape network connectivity is still poorly understood; it poses one of the current challenges both in experimental and theoretical neuroscience.

Acknowledgements

This work has been supported by the Wellcome Trust.

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