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Functional implications of inhibitory synapse placement on signal processing in pyramidal neuron dendrites

Josiah R Boivin[1,2,3] and Elly Nedivi[1,2,3]

A rich literature describes inhibitory innervation of pyramidal neurons in terms of the distinct inhibitory cell types that target the soma, axon initial segment, or dendritic arbor. Less attention has been devoted to how localization of inhibition to specific parts of the pyramidal dendritic arbor influences dendritic signal detection and integration. The effect of inhibitory inputs can vary based on their placement on dendritic spines versus shaft, their distance from the soma, and the branch order of the dendrite they inhabit. Inhibitory synapses are also structurally dynamic, and the implications of these dynamics depend on their dendritic location. Here we consider the heterogeneous roles of inhibitory synapses as defined by their strategic placement on the pyramidal cell dendritic arbor.

Addresses
[1] Picower Institute for Learning and Memory, Massachusetts Institute of Technology, Cambridge, MA 02139, USA
[2] Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA 02139, USA
[3] Department of Biology, Massachusetts Institute of Technology, Cambridge, MA 02139, USA

Corresponding author: Nedivi, Elly (nedivi@mit.edu)

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Introduction

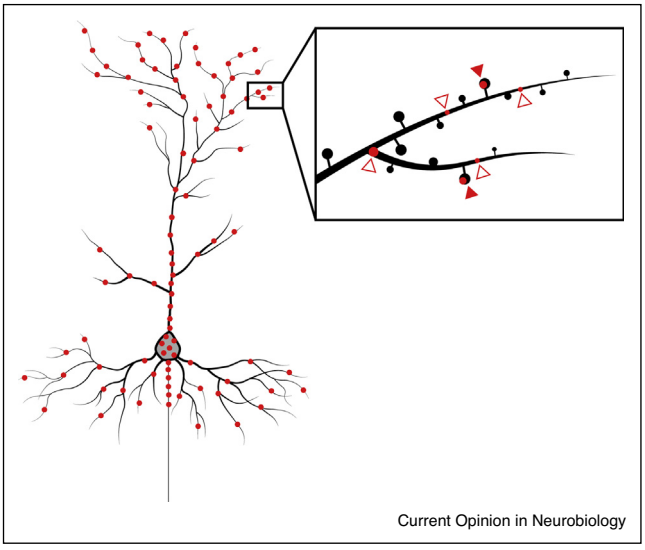
Each pyramidal neuron harbors thousands of excitatory and inhibitory synapses [1,2], and the integration of synaptic signals from different locales across these neurons ultimately determines their action potential output at any given time [3–8,9•]. A growing body of literature on inhibitory innervation of pyramidal cells has defined, in increasing detail, the inhibitory cell types that target distinct subcellular domains of postsynaptic pyramidal neurons (reviewed in [10,11•,12–15]). The influence of inhibitory inputs on action potential initiation at the soma or axon initial segment has received much attention (reviewed in [10,11•,14,15]). Yet, the vast majority of inhibitory synapses onto pyramidal neurons are located on the dendrites [1,2,11•,16], where they play an important role in shaping dendritic integration (Figure 1) [12]. Inhibitory synapses on dendrites arise from multiple inhibitory cell types, but are canonically thought to be mostly from somatostatin-expressing (SOM) interneurons [11•,17]. Despite their perceived monolithic innervation by SOM interneurons, dendritic inhibitory synapses can be considered heterogeneous based on their diverse effects on dendritic integration dependent on where they map onto the pyramidal dendritic arbor.

In contrast to excitatory synapses, which reside primarily on dendritic spines [1], dendritic inhibitory synapses reside on both the dendritic shaft and spines [1,2,18•,19,20]. Inhibitory shaft and spine synapses have distinct effects on the postsynaptic cell due to the compartmentalization of voltage within spines [21,22•]. The rich and complex structure of the dendritic arbor confers additional heterogeneity to inhibitory influence due to the asymmetric cable properties of dendrites, the influence of branch points on current propagation, and the differential impact of back propagating action potentials (bAPs) and excitatory synaptic inputs at proximal versus distal locations [3,8,9•]. In an added layer of complexity, inhibitory synapses are structurally dynamic, with turnover far outpacing that of excitatory synapses [18•,19,20], and the consequence of their removal or addition will also differ depending on dendritic location. Here, we discuss the location-dependent effects of dendritic inhibition on the detection and integration of excitatory signal, and the implications of inhibitory synapse structural dynamics based on dendritic placement.

Location-specific effects of inhibition on the detection and integration of excitatory signal

Excitatory synapses onto pyramidal cells are located on dendritic spines that are widely spread across a complex dendritic arbor [1]. Dendritic inhibition can attenuate these excitatory synaptic inputs in a spatially restricted manner (Figure 2) [12,23,24,25•], with inhibitory synapses on the dendritic shaft affecting excitatory synaptic inputs located on the same dendritic branch [24]. The effects of inhibitory synapses onto dendritic spines is further compartmentalized within the spine, so that GABA uncaging onto a spine can inhibit calcium influx evoked by glutamate uncaging at that spine, with no effect on calcium influx in neighboring spines [23]. Inhibitory synapses on dendritic spines would likely have the most influence in distal locations, where bAPs are small or undetectable [3] and excitatory synaptic inputs

Figure 1



The vast majority of a cortical pyramidal cell's inhibitory synapses are located on the dendritic arbor, with a smaller number located on the soma and axon initial segment. Inhibitory synapses are schematized by red circles. Dendritic inhibitory synapses are found on both the shaft and spines, with inhibitory spine synapses located preferentially on distal dendrites. Spines that house inhibitory synapses also contain large, stable excitatory synapses (not pictured). Inset shows an enlarged version of the distal dendritic branches in the boxed region. Filled triangles point to inhibitory spine synapses; open triangles point to inhibitory shaft synapses.

are the primary source of depolarization. Interestingly, inhibitory synapses on dendritic spines are located preferentially in distal regions, more than 125 μm from the soma [20], where the relative influence of excitatory synaptic inputs compared to bAPs is greatest.

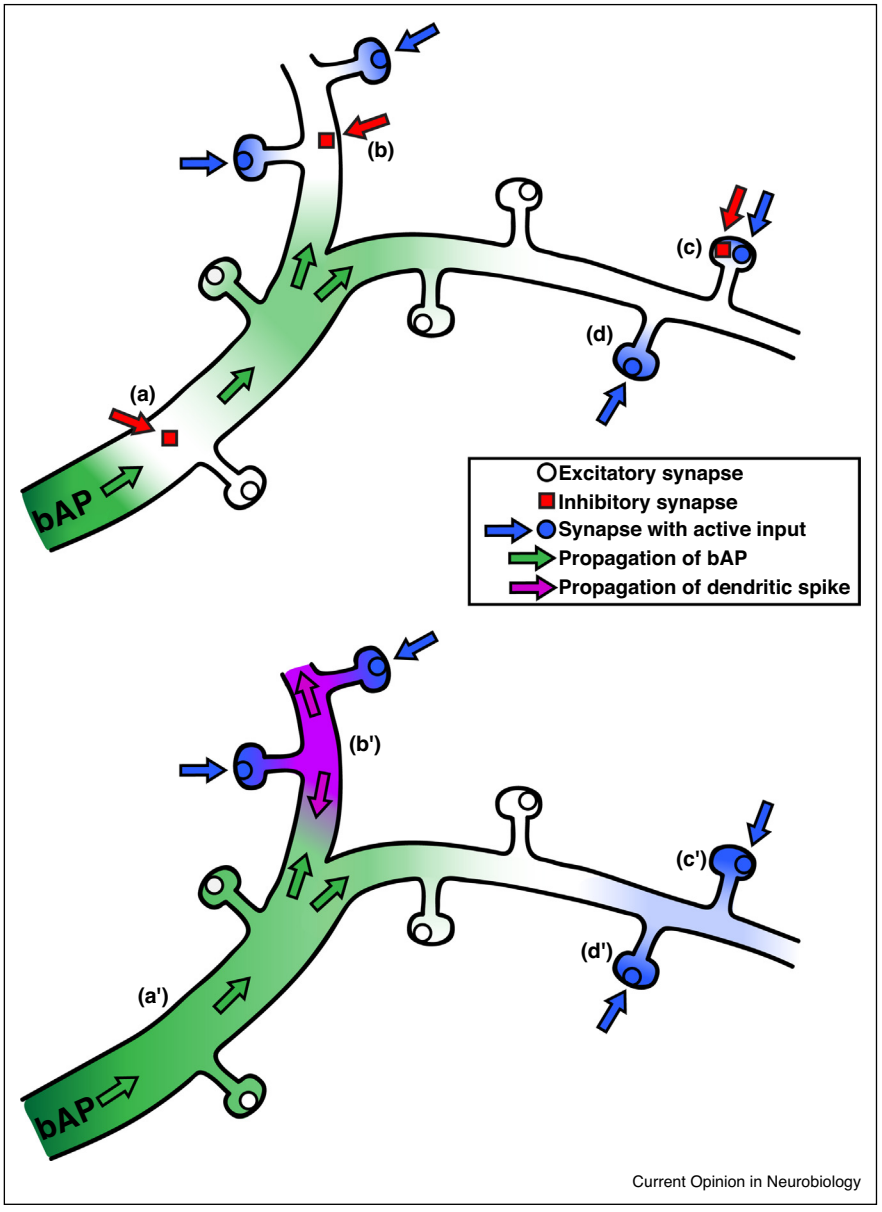
Modeling predicts that an inhibitory input onto a spine could reduce the amplitude of an excitatory postsynaptic potential by approximately 50% within the spine [11•]. Accordingly, experimental evidence indicates that GABA uncaging onto individual spines attenuates but does not fully eliminate calcium influx induced by localized glutamate uncaging [23]. Thus, an inhibitory synapse on a dendritic spine may not act as an on/off switch for the excitatory input, but rather would regulate the strength of this excitatory input in a graded fashion. Given that initial activation of a strong excitatory input may saturate the spine [26], attenuation by inhibitory synapses could serve to prevent saturation, effectively expanding the dynamic range of individual excitatory inputs.

An individual excitatory synaptic input can produce a large voltage change within the spine head on which it is located, but this depolarization attenuates sharply as current flows from the spine into the dendritic shaft, and through dendritic branching points to larger-diameter, more proximal regions of dendrite [3,21,27]. To propagate excitatory synaptic inputs to the soma, particularly when inputs are located on distal dendrites, pyramidal neurons rely on regenerative dendritic spikes that occur when multiple sources of depolarization converge [3,5,6,8,9•,28–31]. For example, depolarization from nearby co-active excitatory synapses can sum non-linearly to initiate a dendritic spike [28,29,32–34]. Depolarization from a bAP or an earlier dendritic spike can also lower the threshold for initiating a dendritic spike in response to excitatory synaptic input [3,28]. Dendritic inhibition regulates this process of coincidence detection and signal propagation by attenuating bAPs and by directly curtailing dendritic spikes [12].

Modeling predicts that an individual inhibitory synapse on the dendritic shaft could substantially reduce bAP-induced depolarization and the resulting calcium influx within the dendritic branch in which it resides (Figure 2) [35]. Experimental evidence bears out this prediction: GABA uncaging at a single site on the dendrite can attenuate bAP-induced calcium influx within approximately 20 μm of the uncaging site on the same dendritic branch [36,37]. Similarly, stimulation of an individual inhibitory interneuron can attenuate bAP-induced calcium influx within a spatially restricted region of the dendritic branch on which a putative synaptic contact is located, with negligible effects on neighboring branches [35,38•]. Inhibitory synapses on dendritic spines have a more compartmentalized effect on bAPs: GABA uncaging onto a single spine can attenuate bAP-induced calcium influx within the same spine, with no detectable influence on neighboring spines [23]. These effects of inhibitory synapses on the spread of bAPs are likely to be most influential in proximal regions of the dendritic tree that are readily invaded by bAPs, as opposed to distal regions in which bAPs are smaller or undetectable [3].

In addition to attenuating bAPs, inhibition can curtail dendritic spikes within specific dendritic branches (Figure 2). For example, GABA iontophoresis onto a pyramidal dendrite increases the threshold amount of glutamate uncaging necessary for eliciting a dendritic spike [39]. GABA iontophoresis is most effective at raising the threshold for dendritic spike initiation when it is co-localized with, or slightly distal to, the sites of glutamate receptor activation, while GABA iontophoresis proximal to the sites of glutamate uncaging is most effective at reducing the amplitude of the spike once it is initiated [39]. These results are bolstered by modeling data suggesting that a single inhibitory synapse placed at the site of, or slightly distal to, co-active excitatory synaptic inputs can curtail the resulting NMDA spike within the same dendritic branch [40•]. Thus, the placement of an inhibitory synapse in relation to nearby excitatory inputs can determine its effects on dendritic spiking.

Figure 2



Effects of inhibitory synapses on the propagation of depolarization in the dendritic shaft and spines. The effects of inhibitory synaptic inputs are illustrated at sites labeled **a**–**d** in the top figure. The same regions of dendrite are shown without inhibition and labeled **a**′–**d**′ in the bottom figure. (**a**) An inhibitory synapse on the dendritic shaft reduces the spread of the bAP (denoted by green fill) in a restricted region of the dendritic shaft and an adjacent spine. (**a**′) Without inhibition, the bAP propagates along the same branch with only slight attenuation, but then weakens substantially as it crosses a branching point and reaches more distal regions of dendrite. (**b**) An inhibitory synapse on the dendritic shaft prevents the detection of two convergent excitatory inputs (denoted by blue fill) and the bAP within the adjacent dendritic shaft. (**b**′) Without inhibition, the convergence of excitatory synaptic input with the bAP initiates a dendritic spike (denoted by purple fill). (**c**) An inhibitory synapse on a dendritic spine attenuates an excitatory input onto that spine, while an adjacent spine (**d**) is unaffected. (**c**′,**d**′) Without inhibition, the two distal excitatory inputs produce depolarization shown in blue.

A relatively small dendritic spike in a thin dendrite may fail to propagate to the soma, but multiple dendritic spikes can converge and summate, producing cooperativity among co-active excitatory inputs on a larger scale [3,28]. Multiple co-active inhibitory synapses can produce far-reaching inhibition of dendritic spikes in the pyramidal arbor [41–44,45•]. Modeling based on a reconstructed cortical pyramidal neuron and its SOM cell inputs suggests that coordinated inhibition from sparse, distally located inhibitory synapses can spread centripetally, ultimately blocking the initiation of calcium spikes at the main branch point of the apical dendrite [41]. This

inhibition is predicted to decouple the two main sites of spike initiation in the cortical pyramidal neuron, the somatic/axonal region and the main branch point of the apical dendrite, substantially altering the firing of the neuron [41]. Slice [42,43,46–48] and *in vivo* [48] electrophysiology studies confirm that precisely timed stimulation of distal inhibitory inputs can indeed block the initiation of spiking in the apical dendrite. Further, this blockade of spiking in the apical dendrite can prevent bursts of somatic action potentials in response to simultaneous current injections at the soma and distal dendrites [47]. These studies suggest that the coordinated action of even a few strategically placed inhibitory synapses can not only gate the detection of individual excitatory inputs or bAPs, but can regulate the integration of multiple sources of excitatory signal, ultimately influencing a neuron's action potential output.

Role of inhibition in synaptic plasticity

Spike timing dependent plasticity (STDP), which can produce strengthening or weakening of synapses, is dependent on the correlated or uncorrelated, respectively, nature of depolarizing events [3,49–51]. STDP provides a mechanism by which individual pyramidal neurons can associate inputs arriving within a specific time window, but potentially at disparate locations on the dendritic arbor [49]. The changes in the weights of excitatory synapses that participate in correlated events (reviewed in [3,49]) often go hand in hand with changes in synapse size and spine morphology, i.e. spine head expansion or shrinkage, and can ultimately lead to spine gain or loss [52,53].

Since inhibition can attenuate the detection or summation of what would otherwise be correlated synaptic inputs, inhibitory synapse activity can have a profound effect not only in attenuating the spread and integration of convergent sources of depolarization, but also on whether they lead to synapse strengthening or weakening [3,12]. Modeling predicts that individual inhibitory synapses on a pyramidal dendrite can alter the propensity for long-term potentiation or long-term depression at nearby excitatory synapses, with inhibitory inputs differentially affecting the weights of excitatory synapses dependent on their location proximal or distal to these excitatory synapses [54].

Along with its influence on synaptic strength, dendritic inhibition can influence excitatory synaptic structural plasticity and circuit remodeling [12]. For example, GABA uncaging at the site of convergent bAPs and glutamate uncaging can induce the shrinkage and elimination of nearby spines, which likely represents the weakening and removal of excitatory synapses [37]. The ability of GABA uncaging onto the dendritic shaft to induce spine shrinkage is limited to spines within 15 μm of the uncaging site [37]. Thus, the specific location of an inhibitory synapse also determines its effects on excitatory circuit remodeling.

Implications of inhibitory synapse structural dynamics

Dendritic inhibitory synapses are highly dynamic [18•,19,20]. Both shaft and spine synapses show repeated removal and recurrence at stable sites, suggesting they may reversibly modulate the ability of individual spines or dendritic branches to detect and participate in plasticity-inducing events [18•].

In response to monocular deprivation, recurrent inhibitory synapses shift to a dynamic state in which their average lifetime is reduced and the time between reappearances is lengthened [18•]. When these inhibitory synapses are absent, excitatory inputs and bAPs that were once attenuated may now be detected, allowing the disinhibited dendrite to integrate convergent excitatory inputs. This disinhibition may play a critical role in ocular dominance plasticity by creating an environment that is permissive for STDP of excitatory synapses, enabling disinhibited dendritic branches to participate in experience-dependent circuit remodeling [55,56].

The most dynamic inhibitory synapses are those located on spines [18•,20]. These dually innervated spines (DiS), which also house an excitatory synapse, are extremely stable, as are the excitatory synapses they house [18•]. The apposition of a stable excitatory input with a highly dynamic inhibitory input on the same spine potentially enables rapidly reversible inhibitory modulation of input efficacy at stable excitatory synapses [18•]. This could dynamically regulate not only the magnitude of specific excitatory synaptic inputs [23], but also their integration with bAPs or other nearby excitatory synaptic and local regenerative events. Thus, inhibitory spine synapse dynamics would allow both spatially and temporally restricted exclusion of specific excitatory connections from circuit activity and synaptic plasticity.

The ability of inhibitory shaft and spine synapses to reversibly modulate excitatory circuits that appear structurally stable may generalize more broadly. For example, *in vivo* imaging studies show that monocular deprivation does not alter spine dynamics on L2/3 pyramidal neurons in primary visual cortex [20,57], but it does alter the structural dynamics of inhibitory synapses on the dendritic spines and shafts of these same neurons [18•,19,20]. In this case, the absence of structural excitatory circuit change as inferred by spine dynamics does not necessarily indicate a lack of functional rewiring that could be powered by structural remodeling of inhibitory synapses.

Conclusion and future directions

In vivo imaging of genetically labeled inhibitory synapses has revealed structurally dynamic synapses distributed

strategically throughout the pyramidal dendritic tree. Slice electrophysiology and calcium imaging suggest that by influencing the detection and integration of multiple sources of excitatory signal, these inhibitory synapses may alter information processing and the propensity for synaptic plasticity within their local circuit. Extending such studies to an *in vivo* context and establishing their relevance during a behavioral task is significantly more challenging. Recently, new *in vivo* functional manipulation and imaging tools have enabled experiments demonstrating dendritic integration within intact circuits in specific behavioral contexts [58–62]. However, we lack explicit knowledge of the type of information being integrated, and our knowledge related to inhibition in these *in vivo* paradigms is still in its infancy. Pioneering *in vivo* studies show that inhibition can suppress calcium spikes in the apical dendrites of pyramidal cells [61,63] and demonstrate the feasibility of calcium imaging of GABAergic axons in awake behaving animals [64,65]. One of the limitations to combining synaptic resolution functional studies of both excitatory and inhibitory activity has been the ability to concurrently monitor both elements *in vivo*. Development of tools for functional imaging in multiple colors [66], would open the door to future *in vivo* studies that include simultaneous monitoring of inhibitory afferent activity and the integration of excitatory signal in the pyramidal dendrites they target. Further, expanding the palette of genetic calcium sensors and integrating their use with new methods for genetically labeling inhibitory postsynaptic sites *in vivo* [18•,19,20] would allow monitoring of dendritic function in relation to the placement and structural dynamics of dendritic inhibitory synapses. Ultimately, future studies may reveal the effects of strategically placed inhibitory inputs on the integration of excitatory signal across the full dendritic arbor within the brain of an animal performing a well-defined behavioral task.

Conflict of interest statement

Nothing declared.

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