

## Location-Dependent Effects of Inhibition in a Pyramidal Neuron Model

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Inhibitory interneurons come in many shapes and sizes and shape the functioning of the cortical circuit in myriad ways. The precise roles played by the many types of inhibitory interneurons, however, remain poorly understood. One of the key features used to classify inhibitory interneurons is the subcellular distribution of the synaptic contacts they form on the dendrites/soma/axon of their target cells, especially pyramidal neurons. How does inhibition influence a pyramidal neuron's integrative behavior, or alter its firing rate or firing pattern, as a function of the inhibition's location?

Contrary to the expectation that (shunting) inhibition might act divisively on firing rates, given that it certainly acts divisively on subthreshold EPSPs (Koch, Poggio & Torre 1983), Holt and Koch (1997) showed that shunting inhibition on an integrate and fire neuron exhibited a largely subtractive influence on firing rates. Furthermore, in compartmental modeling studies of pyramidal cells with active dendrites, we found that divisive effects seemed to be primarily associated with distal rather than peri-somatic inhibition (Archie and Mel, 2000; Archie 2004).

To help clarify the "arithmetic" governing the integration of excitatory and inhibitory inputs in cells containing active channels, we have studied the effects of inhibitory inputs delivered at various locations on both the subthreshold and firing responses of a model neocortical pyramidal cell. Our preliminary results are as follows:

1. Increasing the intensity of excitatory stimulation to a branch containing high-NMDA/AMPA ratio synapses leads to a two-tiered accelerating nonlinear response; the first tier arises from the generation of a dendritic spike, which nonlinearly increases the response height when an NMDA spike is triggered, while the second tier arises from a nonlinear increase in the duration of the NMDA spike as the stimulus intensity is further increased.
2. Increasing the intensity of distal inhibitory stimulation leads to gradual suppression of the subthreshold somatic response, according to a law that is neither perfectly subtractive nor perfectly divisive of the output—but which nearly perfectly divides the input variable. Thus if the branch responds according to a sigmoidal function  $f(x)$  where  $x$  is the total excitatory input, the effect of inhibition is to divide the input variable  $x$ , giving  $f(x/i)$  for inhibitory level  $i$ .
3. Under circumstances so far modeled, somatic inhibition has a divisive over a substantial range of excitatory input intensities, but converts to a subtractive effect at very high excitatory intensities. In contrast, a constant hyperpolarizing current injection in the same cell leads to a uniformly subtractive effect.

In continuing work, our goal is to better define the conditions leading to the complex, heterogeneous interactions between excitatory and inhibitory inputs to pyramidal cells.

