Systems Biology II: Neural Systems (580.422)

Lecture 10, Neural integration

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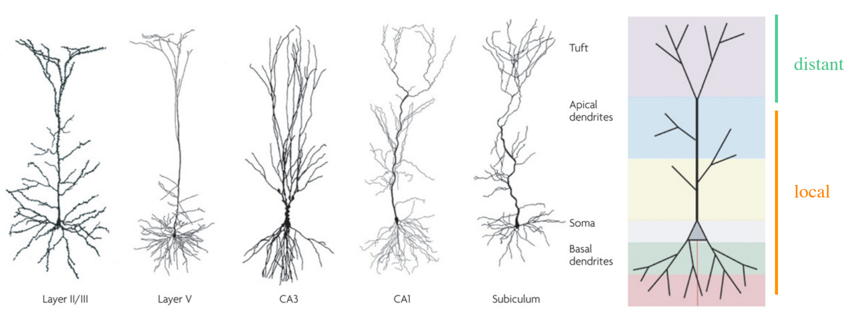
Reading

N. Spruston (2008) Pyramidal neurons, synaptic structure, and dendritic integration. *Nature Reviews: Neuroscience* 9:206-221.

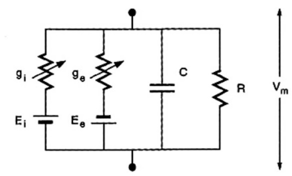
S.R. Williams and G.J. Stuart Role of dendritic synapse location in the control of action potential output. *Trends in Neurosciences* 26:147-154 (2003).

The shapes of cortical pyramidal neurons vary, but follow a common general plan. Usually there are basal dendrites near the soma and one or a few large apical dendrites that extend up to the cortical surface.
These trees tend to receive local inputs from nearby cells in the proximal part and distant inputs, e.g. from other parts of cortex, in the apical distal part.



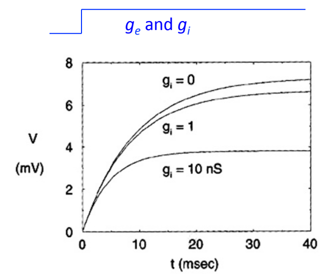
Spruston 2008

Synaptic interactions are inherently non-linear, because synapses change the conductance of the membrane, instead of performing some linear operation like injecting current.



The steady-state (dV_m/dt=0) value of V_m is

$$V_m(t \to \infty) = V_{\max} = \frac{g_e E_e + g_i E_i}{g_e + g_i + 1/R}$$



$1/R$=10 nS, g_e=1 nS
E_e=80 mV, E_i=0 mV

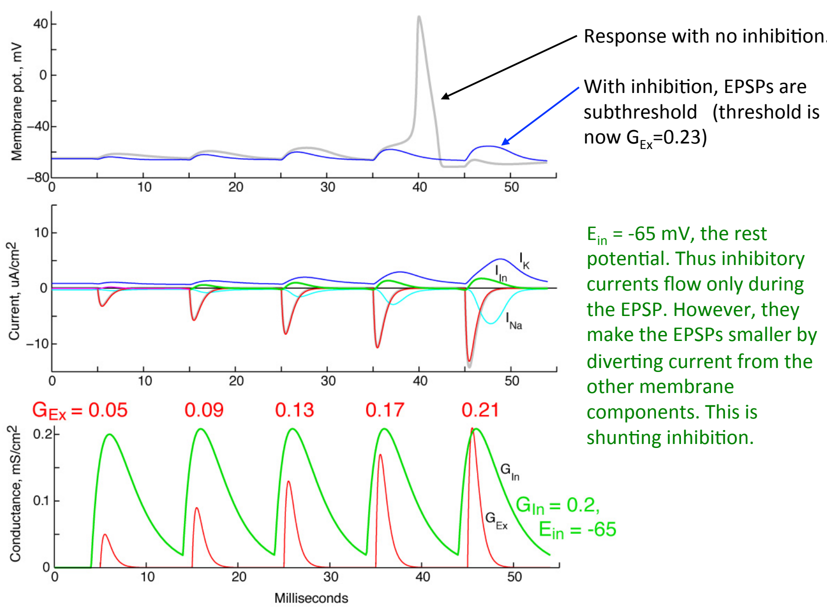
Note the nonlinear dependence of V_m on synaptic conductance g_e and g_i.

The excitatory response is saturating, so as g_e gets large compared to $1/R$, V saturates at E_e.

Note also that the synaptic inhibition can be effective even if E_i = 0 (the resting potential), called shunting inhibition.

Koch, 1999

Adding shunting inhibitory inputs blocks the response to the excitatory input. The effect is mainly due to the inhibitory conductance change.



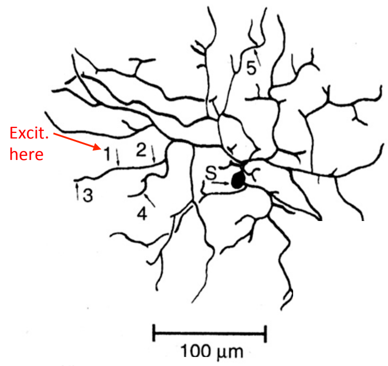
E_{in} = -65 mV, the rest potential. Thus inhibitory currents flow only during the EPSP. However, they make the EPSPs smaller by diverting current from the other membrane components. This is shunting inhibition.

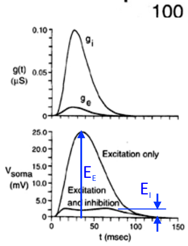
simp1.m

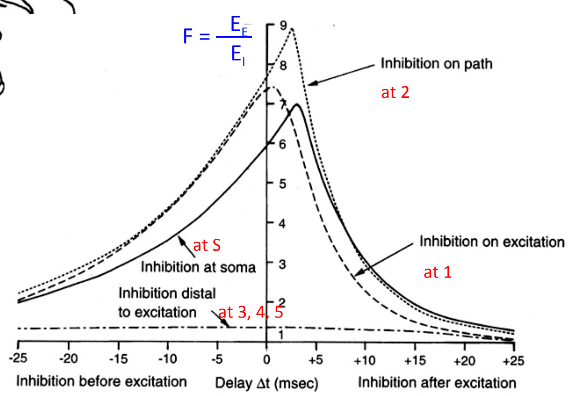
What is the effect of relative placement of synapses on the dendrites? Because cells are not electrically compact, the relative placement of synapses on dendrites matters.

or

Why inhibitory synapses cluster near the soma.





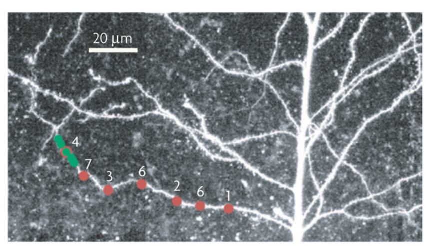


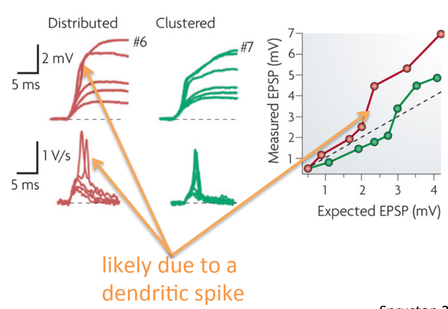
Koch et al., 1983

Because of the nonlinearity of the synaptic effect, clustering of inputs reduces the net synaptic effect. The red data show the response in the soma to (near) simultaneous glutamate uncaging at 7 sites spread out along a dendrite.

The green data show responses when the sites are clustered together.

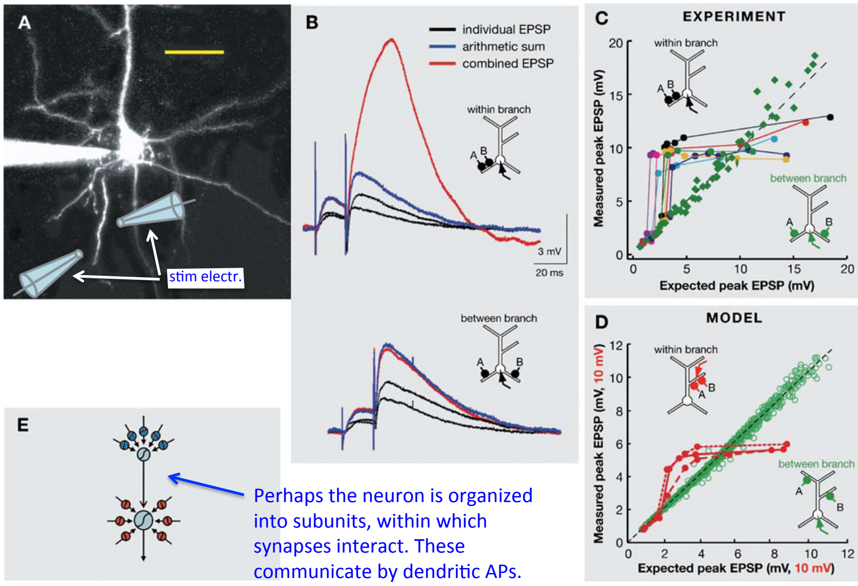
Note that the response is smaller when clustered for small EPSPs. Larger EPSPs (>3 mV in this case) show an increase in relative size, probably due to dendritic active channels.





Spruston 2008

Summation of dendritic inputs (electrical stimulation of small numbers of synapses): linear between branches and nonlinear (supralinear) within a branch.



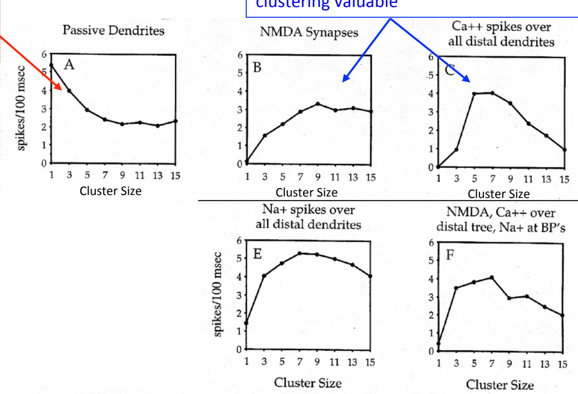
Perhaps the neuron is organized into subunits, within which synapses interact. These communicate by dendritic APs.

Polsky et al. 2004

The effect of relative placement of synapses on the dendritic tree depends on the properties of the cell and the type of synapse.
100 synapses were scattered on the dendrites of a model* of the cortical pyramidal cell at lower left. They were arranged in 100/*k* clusters of *k* synapses each. The synapses were then activated with independent 100 Hz spike trains and the postsynaptic firing rate determined in simulations. The higher the firing rate, the more effective is a particular distribution of synapses.

for a passive tree, it is best to spread the synapses out, so they can sum linearly

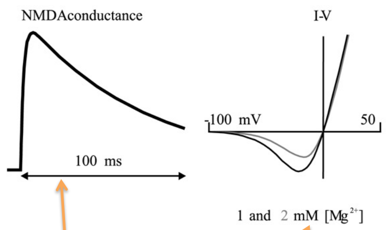
voltage-dependent (NMDA) synapses and active channels in the dendrites make clustering valuable

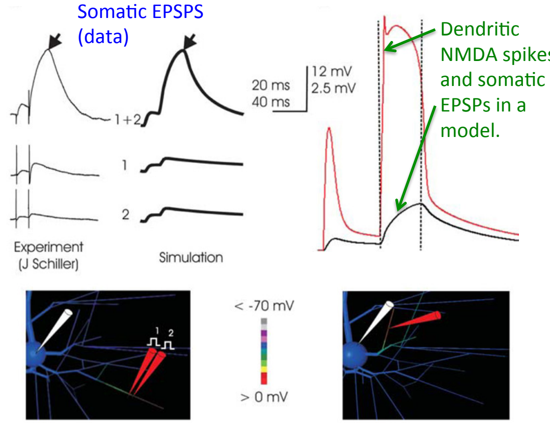


* (the model was a direct compartmental model of the neuron shown above.

Mel, 1993

Current evidence suggests that NMDA channels are responsible for dendritic "spikes" near the ends of small dendritic branches. These produce amplified EPSPs in the soma.



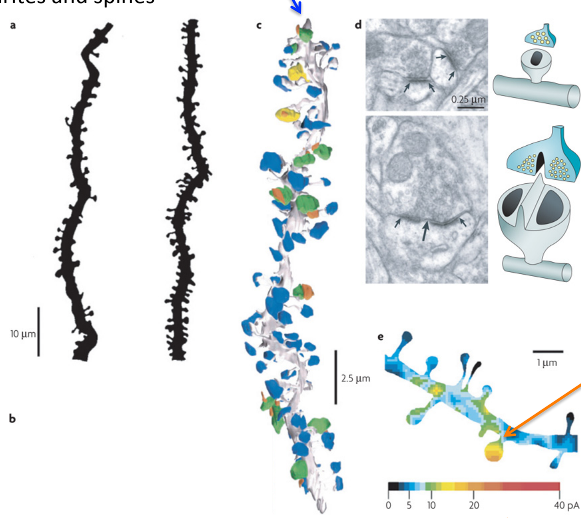


Properties of NMDA channels: left - gating time following neurotransmitter release; right – current-voltage plot in 1 and 2 mM Mg^{++}. Note the accelerating inward current, as in a sodium or calcium channel.

Rhodes 2006

morphology of
dendrites and spikes

every spine (gray) has a synaptic terminal (colored)



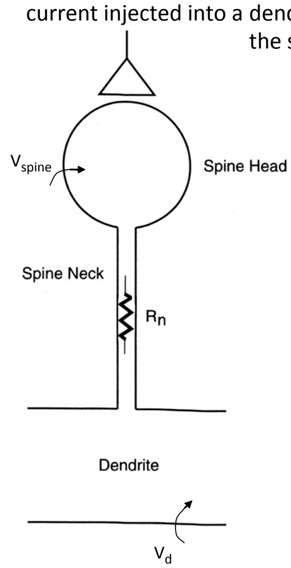
EM level pictures of spines, showing synaptic densities

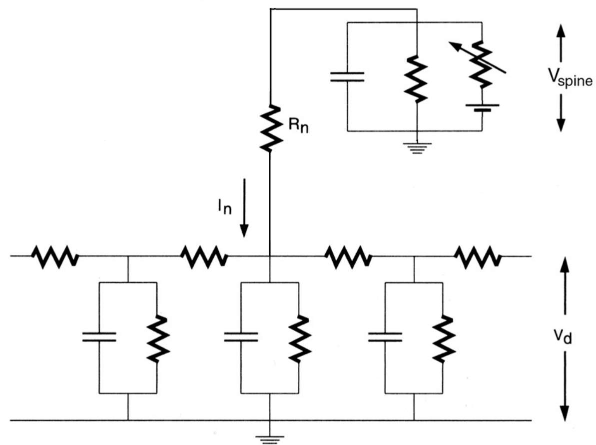
uncaging glutamate activates the soma only when it is done near a spine

Soma depolarization

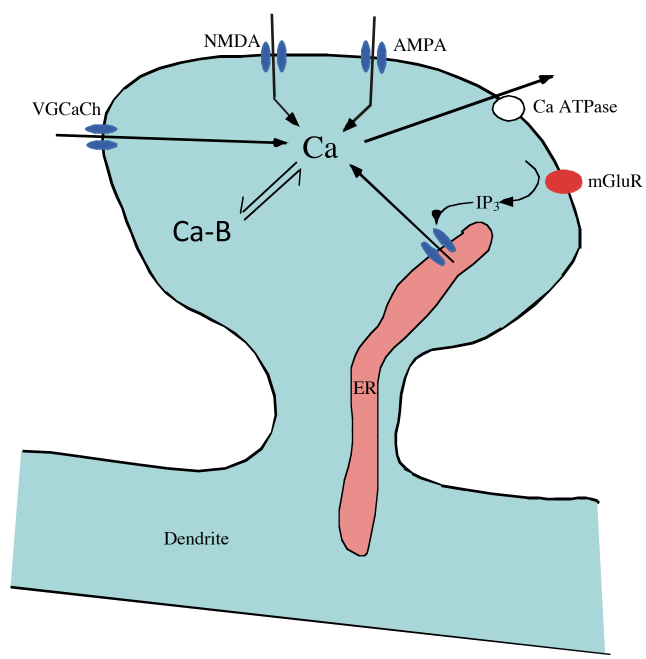
Spruston 2008

What is the effect of spines on input/output processing in a neuron? Spines do not have a significant electrical effect: the worst-case electrotonic length (*L*) of the spine neck is about 0.02, so there is negligible cable effect. Calculations show that the current injected into a dendrite by a synapse on a spine head is about the same as if the synapse were directly on the dendrite.





The calcium signal in spines is an essential message for postsynaptic plasticity, discussed in a subsequent lecture. Confining Ca to a single spine makes the changes produced by that Ca specific to the synapse on the same spine.

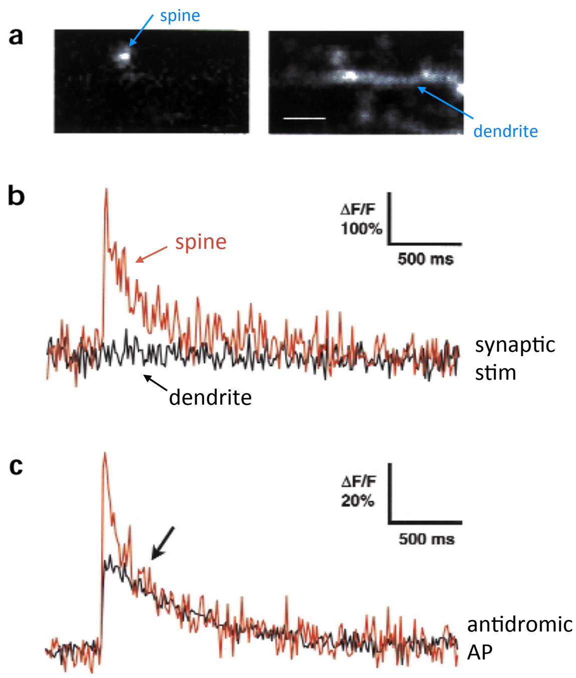


In fact, spines are calcium traps, the length constant for calcium diffusion in dendrites is very short, approximately the length of a spine neck.

a. shows 2-photon images of Ca in a spine and dendrite (right) and the Ca difference signal following synaptic stimulation

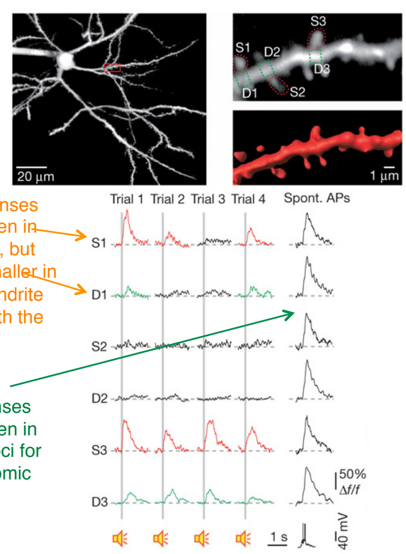
b. Shows the Ca signals in the spine (red) and dendrite (black) for synaptic stim.

c. Shows the Ca signals in spine and dendrite following anti-dromic AP invasion



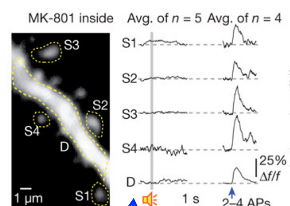
Yuste et al., 2000

How are inputs distributed on dendritic trees? The answer is beginning to emerge from studies of calcium imaging of dendritic spines in cortical neurons. Below are calcium signals from spines in auditory cortex neurons, showing responses to sound.



Responses are seen in spines, but are smaller in the dendrite beneath the spine

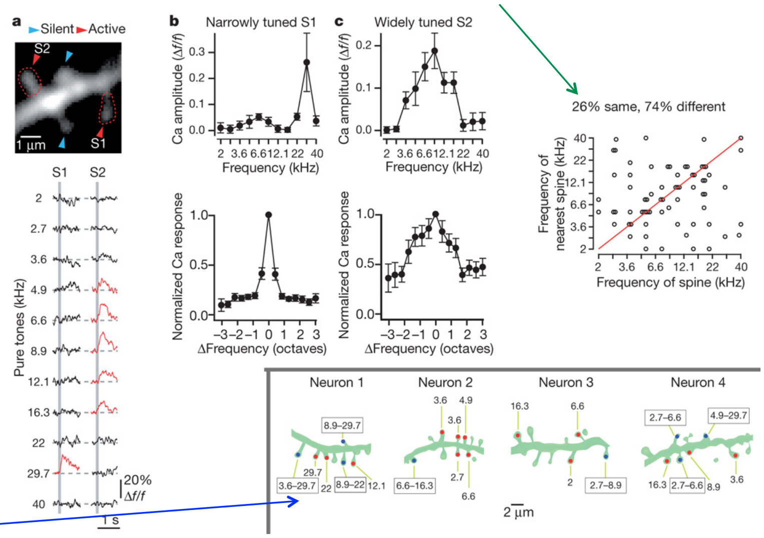
Large responses are seen in both loci for antidromic APs



The spine responses are dependent on NMDA receptors (blocked by MK-801), but not the antidromic responses (presumably due to V-gated Ca channels).

Chen, Leischner, Rochefort, Nelken, Konnerth. Nature (2011) doi:10.1038/nature10193

Auditory neurons are generally tuned to different frequencies. Surprisingly, inputs to adjacent spines on a cortical neuron can have widely different frequency tuning.



Spines are tuned (red vs black responses)

The tuning of adjacent spines on the same dendrite varies (wide tuning blue, narrow red)

Chen, Leischner, Rochefort, Nelken, Konnerth. Nature (2011) doi:10.1038/nature10193