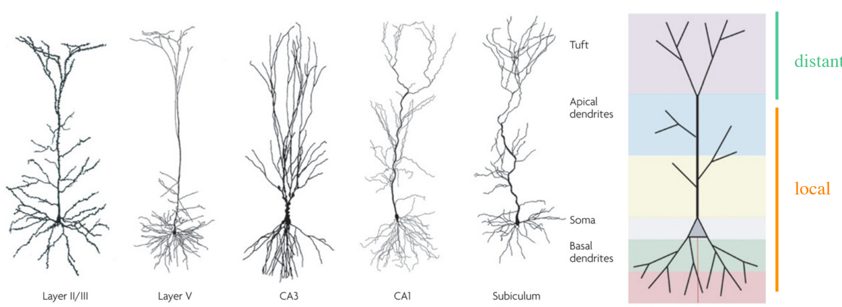
Dendritic processing in real neurons

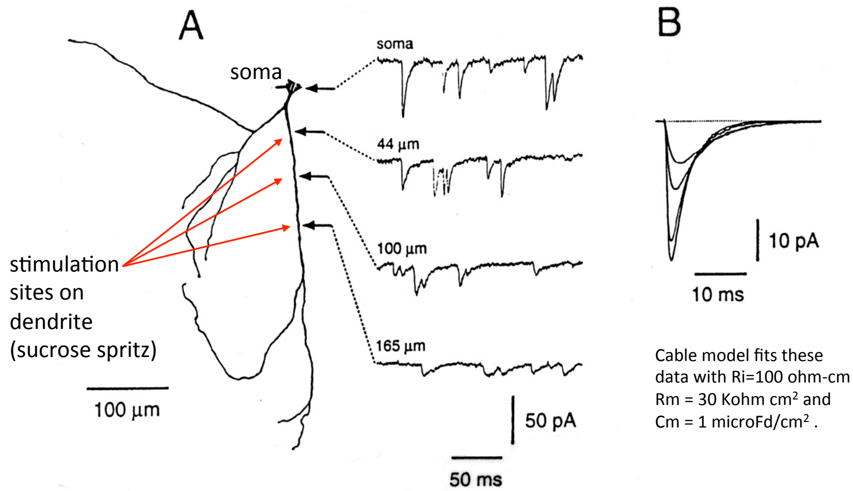
N Spruston (2008) Pyramidal neurons: dendritic structure and synaptic integration. *Nature Rev. Neurosci.* 9:206-221.

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

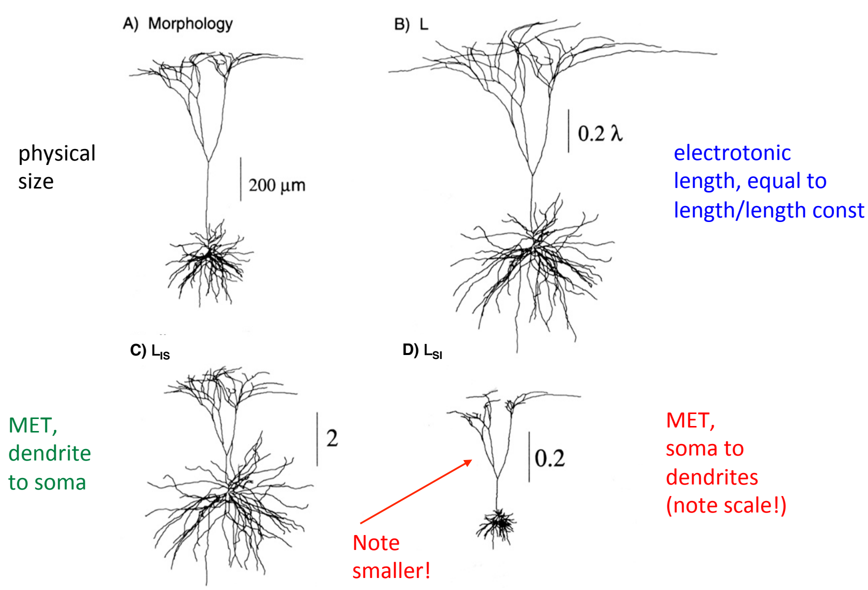
The cable model at work: mEPSCs recorded in the soma show the effects expected, depending on the dendritic source (smaller and slower if initiated further away)



Cable model fits these data with Ri=100 ohm-cm Rm = 30 Kohm cm^2 and Cm = 1 microFd/cm^2 .

Bekkars and Stevens, 1996

How large is the dendritic tree? NOTE that the MET is different depending on the direction in which it is defined.



Zador, 1993

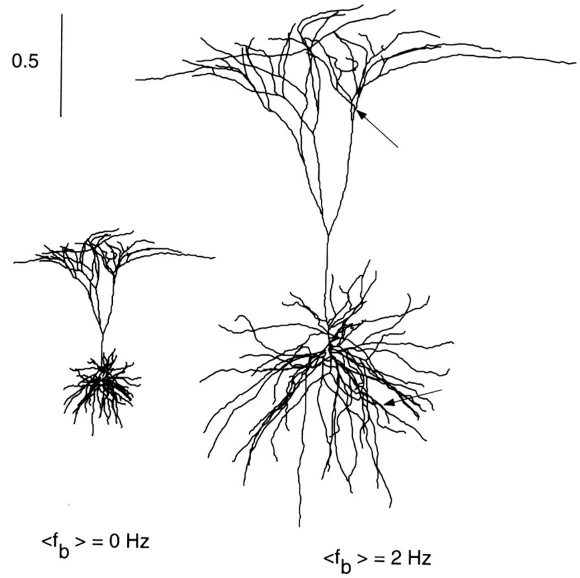
A cell's electrical size depends on the amount of synaptic input it receives.

The somaward METs at right are for a cell with no synaptic input (left) and a cell with substantial, randomly occurring, input (right).

Note the cell is electrically larger with synaptic input. This is explained as an effect of synaptic input on R_m and therefore on l, since

$$\lambda = \sqrt{\frac{R_m}{2R_i} a}$$

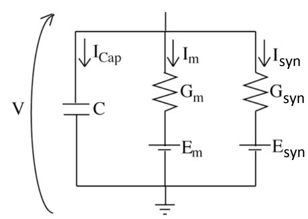
(l decreases as R_m decreases, making the cell electrically larger.)



Bernander et al., 1991

Simulations of synaptic inputs illustrate some important features of post-synaptic processing. In the model below, all the components of the membrane except the synaptic conductance are lumped together in G_m / E_m.

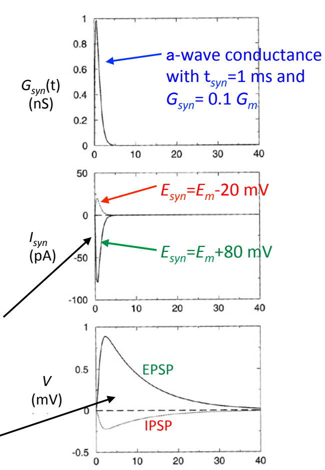
$$C\frac{dV}{dt} = -G_m(V - E_m) - G_{syn}(t)(V - E_{syn})$$



Solutions from this model are shown at right.

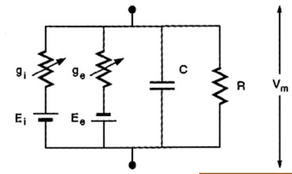
1. The excitatory synapse gives a larger current than the inhibitory synapse because of the difference in battery potentials.

2. The PSPs are longer lasting than the synaptic currents. This occurs because the membrane time constant C/G_m is 10 ms, longer than t_{syn}.



Koch, 1999

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



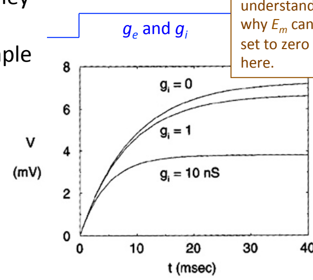
To see what this means, suppose the membrane has both an excitatory (g_e) and inhibitory (g_i) synapse and that they are activated simultaneously with a maintained step of conductance. This is not physiological, but makes it simple to solve the equations. Then:

$$C\frac{dV_m}{dt} = -\frac{1}{R}V_m - g_e(V_m - E_e) - g_i(V_m - E_i)$$

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

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

Make sure you understand why E_m can be set to zero here.



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

The plot shows the solution of the differential equation for the step of conductance. Note that the steady state value decreases as the inhibitory conductance increases. This occurs even though E_i=0 (so there is no IPSP). Thus inhibition can work by **shunting the currents** produced by an excitatory synapse.

!

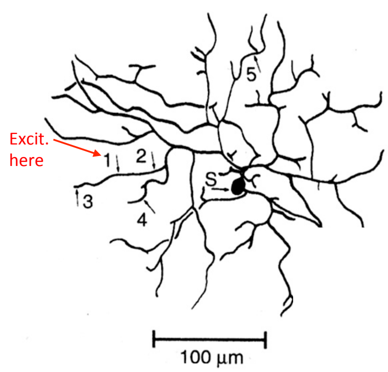
Koch, 1999

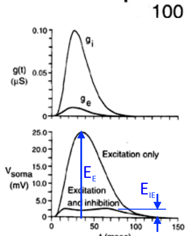
What is the effect of relative placement of synapses on the dendrites?

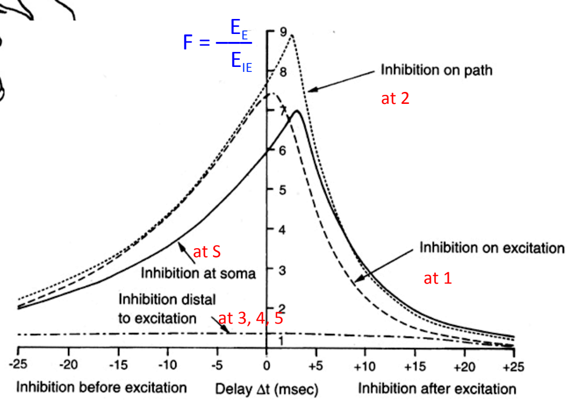
Because cells are not electrically compact, the relative placement of synapses on dendrites matters.

or

Why inhibitory synapses cluster near the soma.

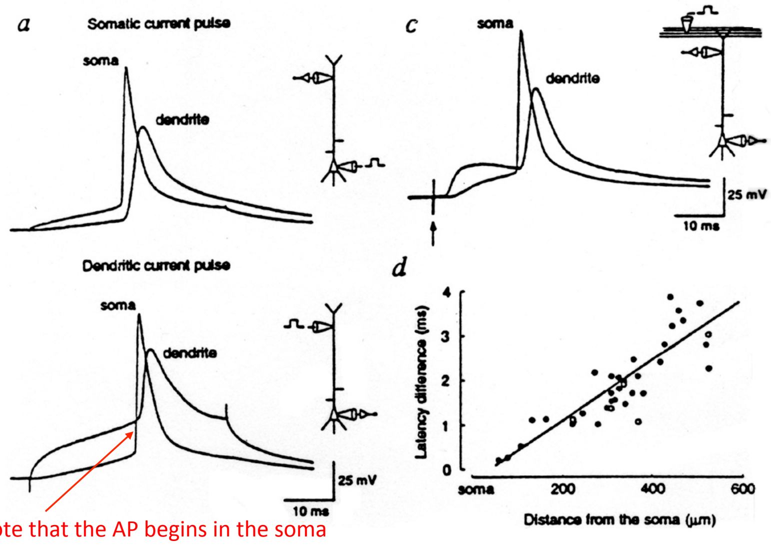






Koch et al., 1983

Dendritic trees are not passive: action potentials invade the dendritic tree from the soma, called backpropagation. This is consistent with the asymmetry in the MET.



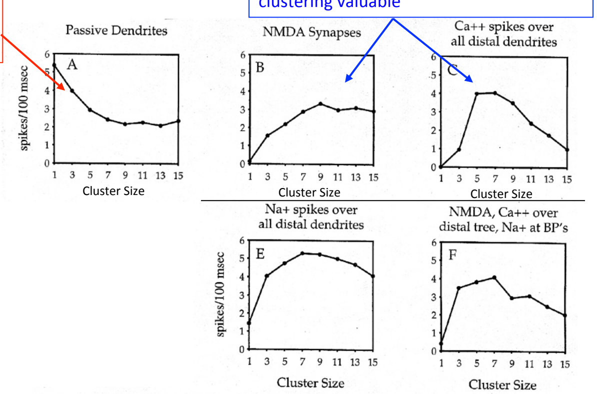
Note that the AP begins in the soma even if the stimulus is in the dendrite!

Stuart and Sakmann, 1994

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

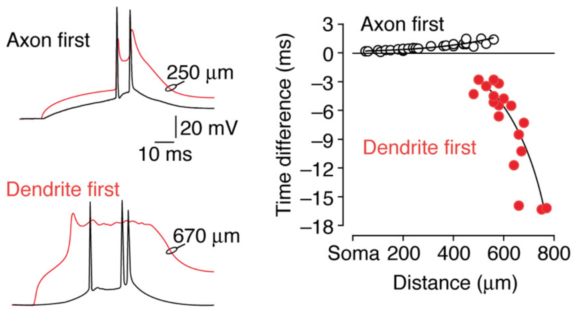
voltage-dependent (NMDA) synapses and active channels in the dendrites make clustering valuable



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

Mel, 1993

Action potentials can invade dendrites from the soma, as in the previous slides, or they can be initiated in dendrites. Usually the latter are calcium spikes. These tend to occur in neurons with large (electrotonically long) dendritic trees and are responses to strong inputs. They may help to couple distant synapses to the soma.



Simultaneous soma and dendritic patch recording, with current injection in either site. At proximal sites axon-first spikes were produced, but dendrite-first spikes were produced at distal sites.

Williams & Stuart 2003

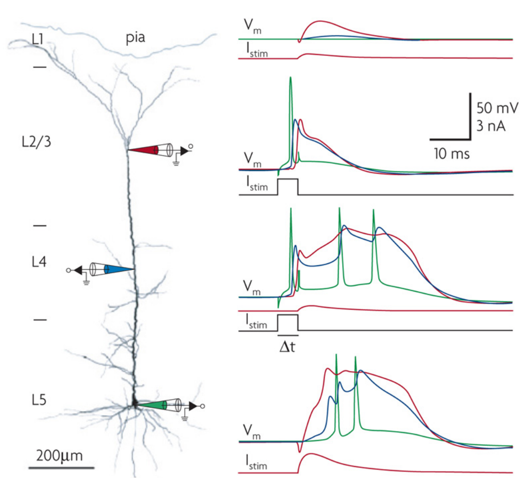
Forward and back-propagating potentials can interact, producing larger responses.

Top – dendritic current produces a small EPSP

Second – a back-propagating AP produced by current in the soma.,

Third – Coincidence of the two stimuli produces a dendritic Ca spike and a burst in the soma.

Bottom – a larger dendritic stimulus can produce the same effect (but now dendrite first).



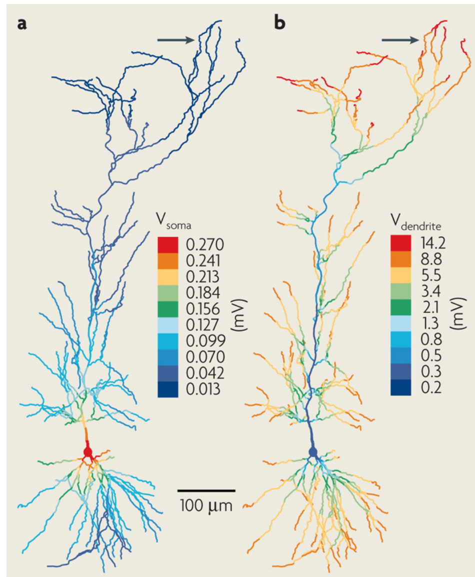
Spruston 2008

The nonlinearity of dendritic trees is potentiated by the large amplitudes of EPSPs there.

At left is the amplitude of the EPSP in the soma as a function of initiation site in the dendritic tree (a simulation). Cable effects are clear.

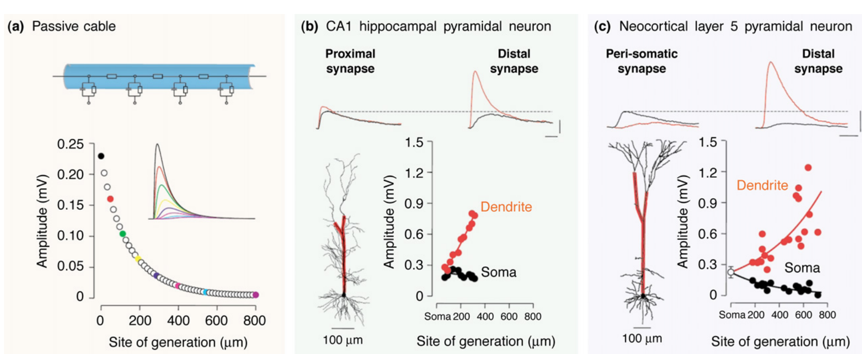
At right are the local EPSPs in the dendrite. These are much larger, because of the small size, and therefore high input impedance, of the smaller dendritic branches. These EPSPs are large enough to activate voltage-gated ion channels.

(all with 0.3 nS synaptic conductance)



Spruston 2008

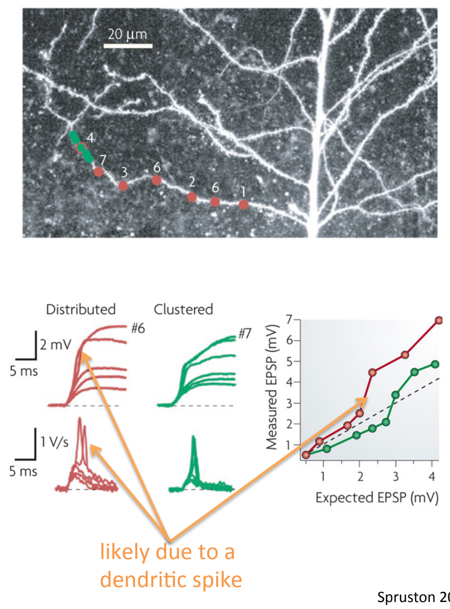
Synaptic democracy – despite attenuation of dendritic potentials by cable effects, EPSPs in the soma are independent of dendritic site in smaller cortical cells(data below for artificial synaptic currents of uniform amplitude). Caused by larger Z_{in} and larger $G_{synapse}$ at distal dendritic sites. Both effects are needed to compensate for cable effects.
In larger cells (layer 5), this synaptic conductance compensation is not seen. Recall that these are the cells with dendritic Ca action potentials. Perhaps synaptic conductance compensation cannot compensate for cable attenuation in these cells?



Williams and Stuart 2003

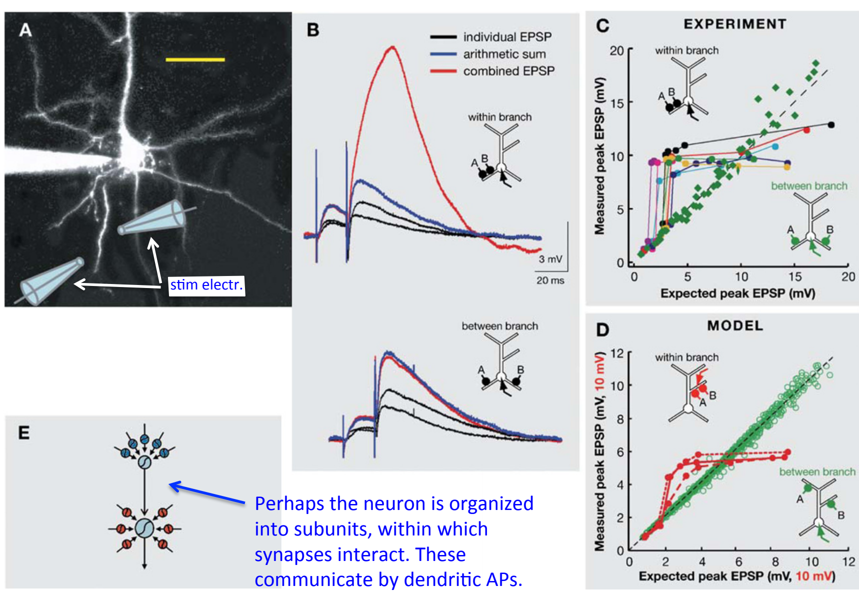
Because of the nonlinearity of the synaptic effect, clustering of inputs reduces the net synaptic effect. The red data show the response in the soma to (near) simultaneous glutamate uncaging at 7 sites spread out along a dendrite.
The green data show responses when the sites are clustered together.

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.



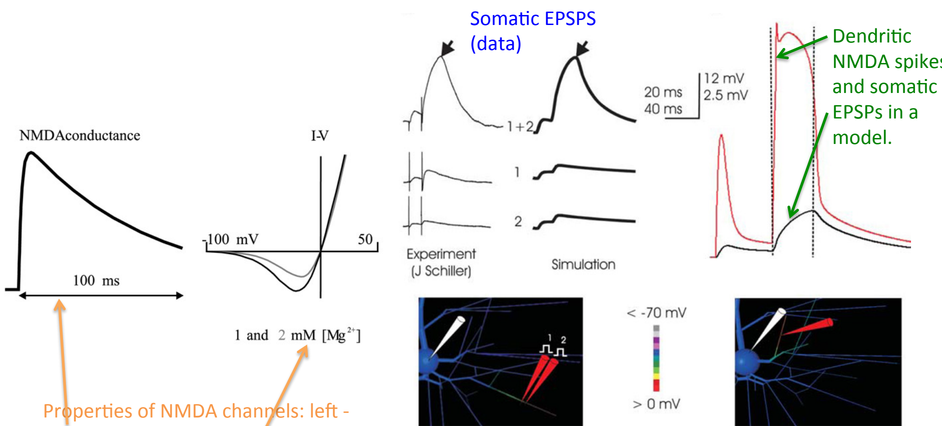
Spruston 2008

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



Polsky et al. 2004

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.

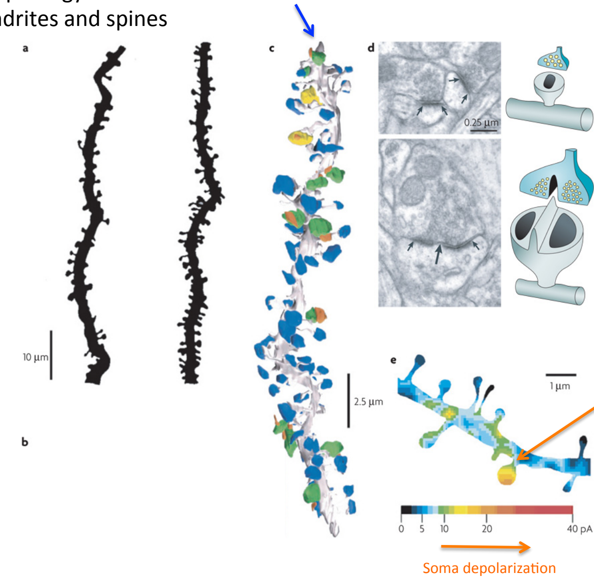


Properties of NMDA channels: left - gating time following neurotransmitter release; right – current-voltage plot in 1 and 2 mM Mg^{++}. Note the accelerating inward current, as in a sodium or calcium channel.

Rhodes 2006

morphology of dendrites and spikes

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

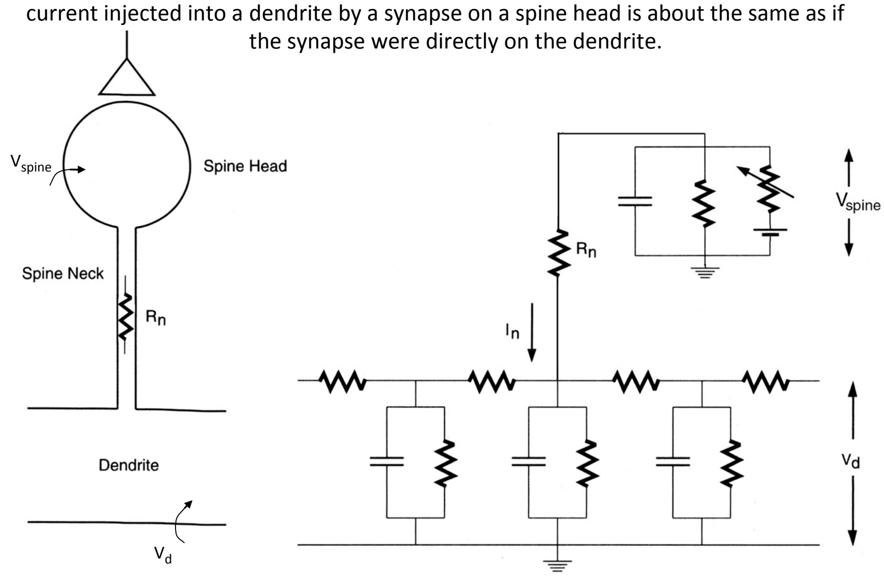


EM level pictures of spines, showing synaptic densities

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

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.

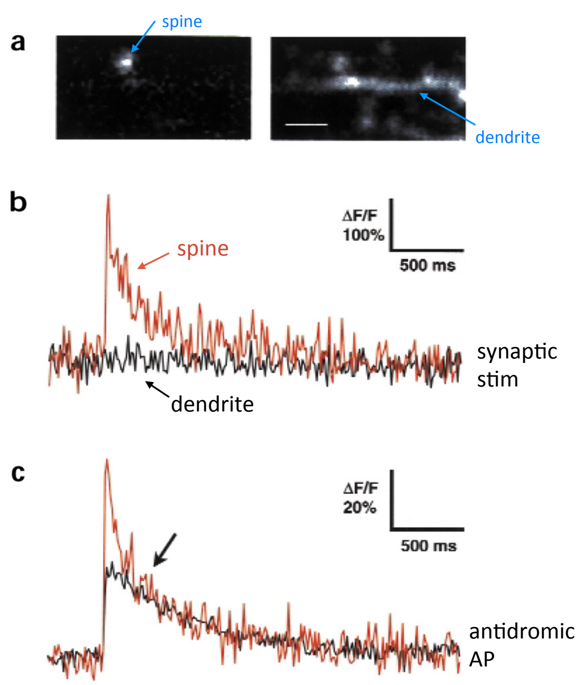


In fact, spines are calcium traps, the length constant for calcium diffusion in dendrites is very short, approximately the length of a spine neck.

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

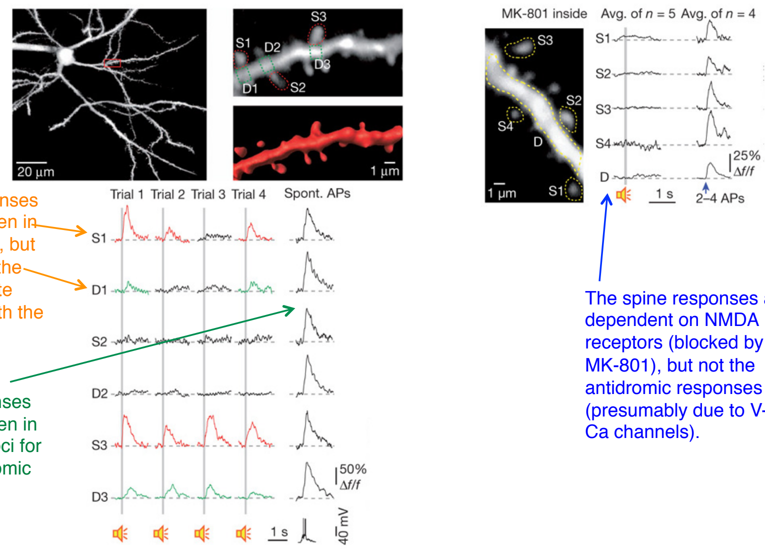
b. Shows the Ca signals in the spine (red) and dendrite (black) for synaptic stim.

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



Yuste et al., 2000

Another example of the Ca trapping function of spines: calcium signals from spines in auditory cortex neurons, showing responses to sound.



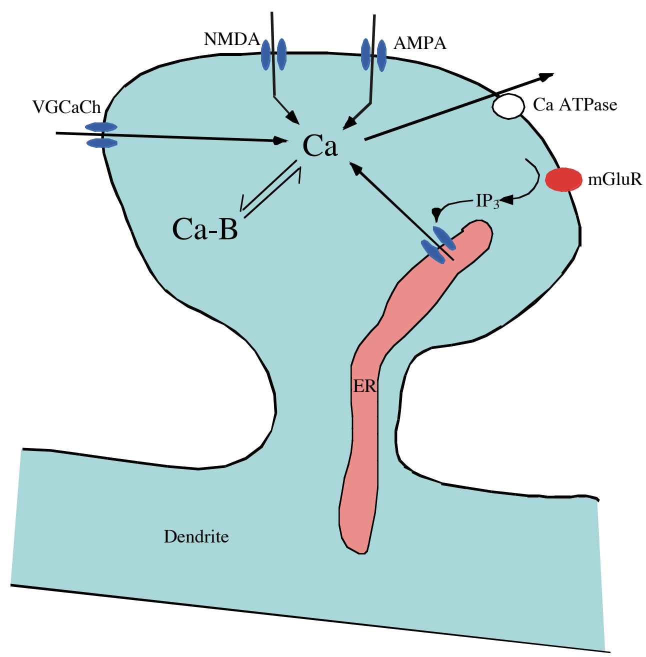
Responses are seen in spines, but not in the dendrite beneath the spine

Large responses are seen in both loci for antidromic APs

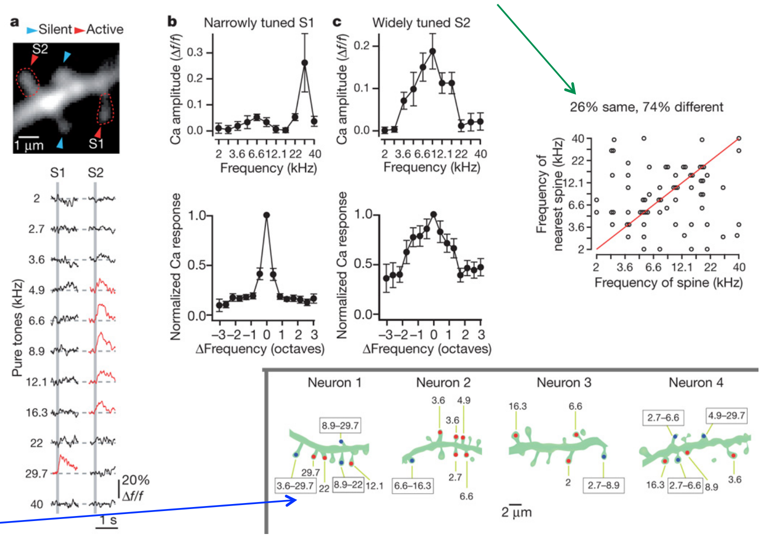
The spine responses are dependent on NMDA receptors (blocked by MK-801), but not the antidromic responses (presumably due to V-gated Ca channels).

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

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.



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



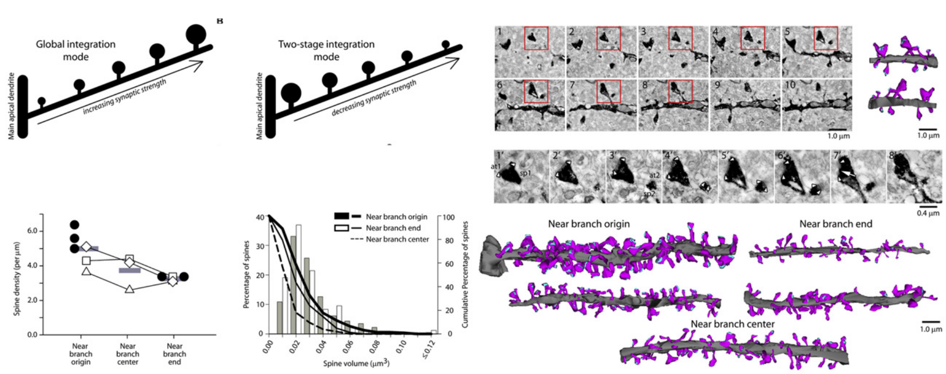
Spines are tuned (red vs black responses)

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

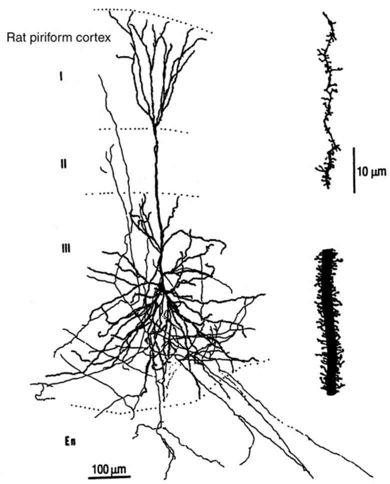
Chen, Leischner, Rochefort, Nelken, Konnerth. Nature (2011) doi:10.1038/nature10193

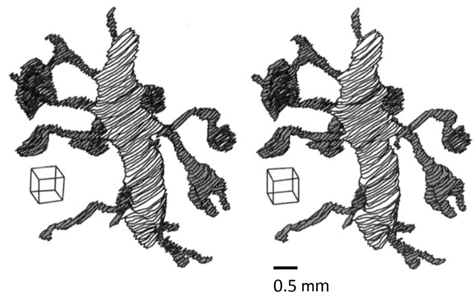
Evidence that spines are organized in a way consistent with the two-stage integration model discussed in a previous slide (on subunits).

Spines are organized in terms of a local model (right) rather than a synaptic democracy model (left).



Neurons often are covered in <u>spines</u>, small extensions of dendrites on which excitatory synapses are made. Inhibitory synapses tend to occur on dendritic shafts.





Wilson et al.,, 1992

Typically, spines are 0.1-0.4 mm in diameter, and 0.4-2 mm long