Systems Biology II: Neural Systems (580.422)

Lecture 9, Nonlinear cable theory

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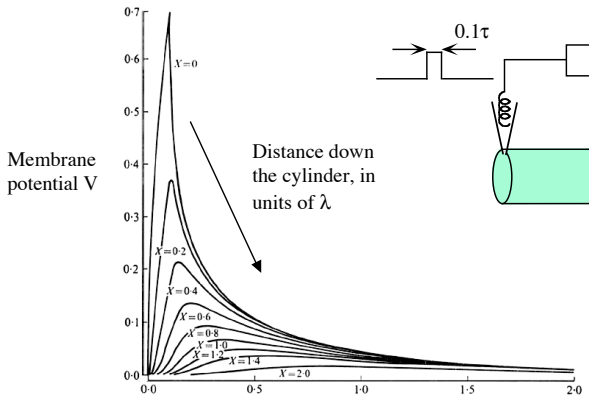
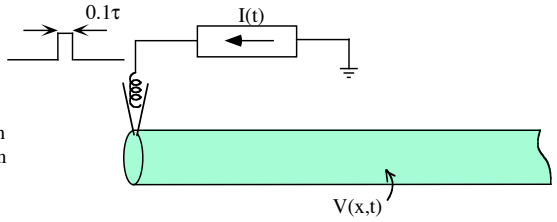
Linear cable theory ignores the presence of voltage-gated channels in the membrane. Potentials become smaller in amplitude and more spread out in time as they propagate away from the source, called electrotonic or passive conduction.

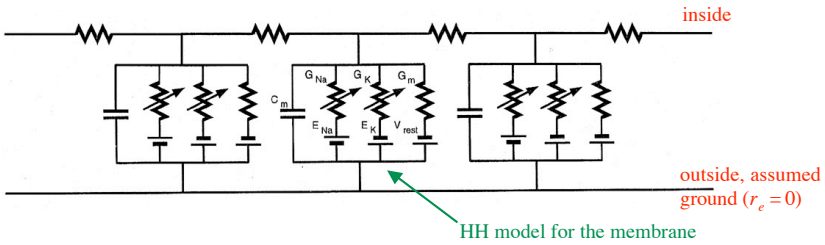




$$\lambda^2 \frac{\partial^2 V}{\partial x^2} = \tau \frac{\partial V}{\partial t} + V$$

Jack, Noble, & Tsien, 1975

Cable theory was originally developed (by Hodgkin and Rushton in the 50's) to apply to unmyelinated axons. In this case the cable is clearly non-linear.



The cable equation must includes the non-linearities in the transmembrane ion current term:

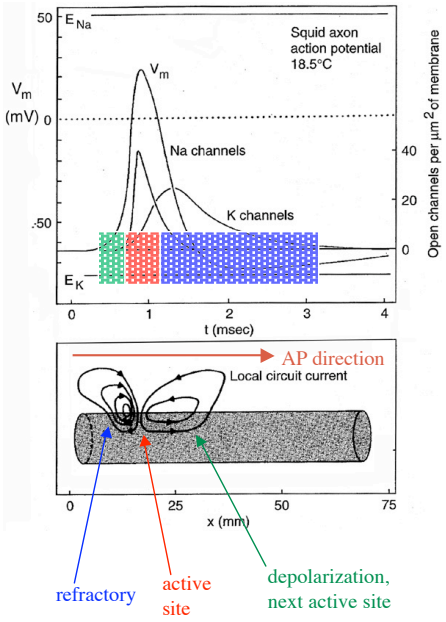
$$\frac{1}{r_i}\frac{\partial^2 V}{\partial x^2} = c_m \frac{\partial V}{\partial t} + I_{ionic} = c_m \frac{\partial V}{\partial t} + G_{Na} m^3 h (V - E_{Na}) + G_K n^4 (V - E_K) + G_m (V - E_{rest})$$

$= I_{Na} + I_K + I_m$

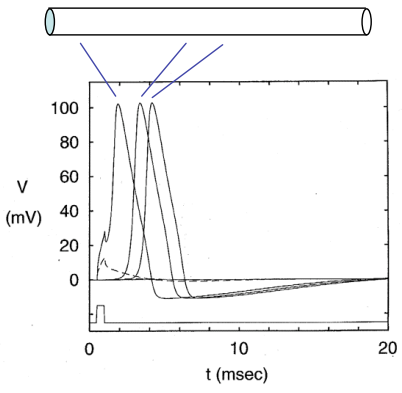
plus additional differential equations to describe the evolution of *m*, *h*, and *n*. An important test of the HH formulation is whether it can predict the propagation of the AP along an axon.

Koch, 1999

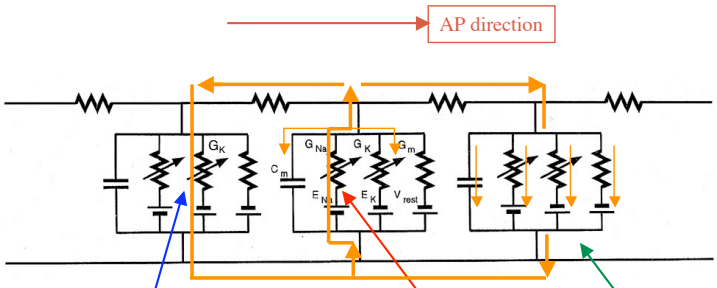
The action potential in axons moves at a constant velocity like a wave. The propagation of the AP depends on the spread of current away from the site of the current AP.



So that the action potential repeats itself at successive locations along the axon



Koch, 1999 and Hille, 1992



increased G_K, shunts return current, refractory membrane

increased G_{Na}, inward current driven by E_{na} depolarizing this and adjacent membrane.

resting membrane, depolarized by return current

Does the HH model predict the propagation of the action potential? An important attribute is that propagation is faster for larger cables. In fact, the HH equation predicts this behavior. To see how, first isolate the dependence of terms on the radius a of the membrane cylinder.

$$\frac{1}{r_i}\frac{\partial^2 V}{\partial x^2} = c_m \frac{\partial V}{\partial t} + G_{Na} m^3 h (V - E_{Na}) + G_K n^4 (V - E_K) + G_m (V - E_{rest})$$

membrane current as current/length of axon

Substitute for the constants that vary with cylinder radius and rewrite membrane currents as current/area of membrane

$$\frac{\pi a^2}{R_i}\frac{\partial^2 V}{\partial x^2} = 2\pi a C \frac{\partial V}{\partial t} + 2\pi a \left[\hat{G}_{Na} m^3 h (V - E_{Na}) + \hat{G}_K n^4 (V - E_K) + \hat{G}_m (V - E_{rest})\right]$$

membrane current as current/area of membrane

So that finally the effects of cylinder radius can be isolated in one term:

$$\frac{a}{2R_i}\frac{\partial^2 V}{\partial x^2} = C \frac{\partial V}{\partial t} + \hat{G}_{Na} m^3 h (V - E_{Na}) + \hat{G}_K n^4 (V - E_K) + \hat{G}_m (V - E_{rest})$$

H&H were unable to directly compute solutions to the non-linear cable equation. Instead, they argued that if the AP is to propagate without change in shape, then it must be described as a wave, as

$$V(x,t) = F(x - ut)$$

where u is the propagation velocity of the AP. With this assumption and the chain rule

$$\frac{\partial^2 V}{\partial x^2} = \frac{1}{u^2}\frac{\partial^2 V}{\partial t^2}$$

so that the non-linear cable equation can be written as an ordinary differential equation

$$\frac{a}{2R_i C u^2}\frac{d^2 V}{dt^2} = \frac{dV}{dt} + H(V,t)$$

The HH currents have been gathered up into the term $H(V,t)$, which does not vary with the radius of the axons. This equation could be solved by H&H (by hand). By trial and error, they found a value of the constants multiplying the leading term which gives a stable, propagating solution resembling an AP.

An important test of the theory is provided by two aspects of the constants:

1. The value of the constant found by HH predicted that u = AP propagation velocity = 18.8 m/s. The experimental value in squid giant axon was 21.2 m/s. Close!

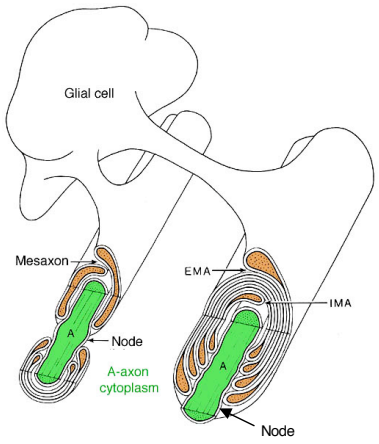
2. If $a/(2R_iCu^2)$ = constant, then it follows that the propagation velocity u in an axon should be proportional to the square root of the radius of the axon.

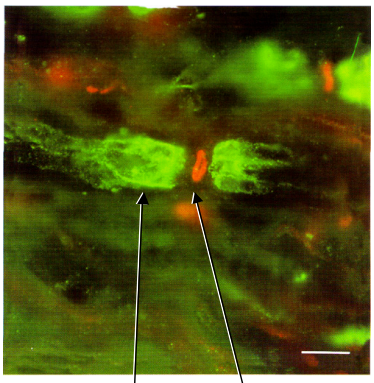
This prediction has been found to hold experimentally (?).

$$\frac{a}{2R_i C u^2}\frac{d^2 V}{dt^2} = \frac{dV}{dt} + H(V,t)$$

(constant)

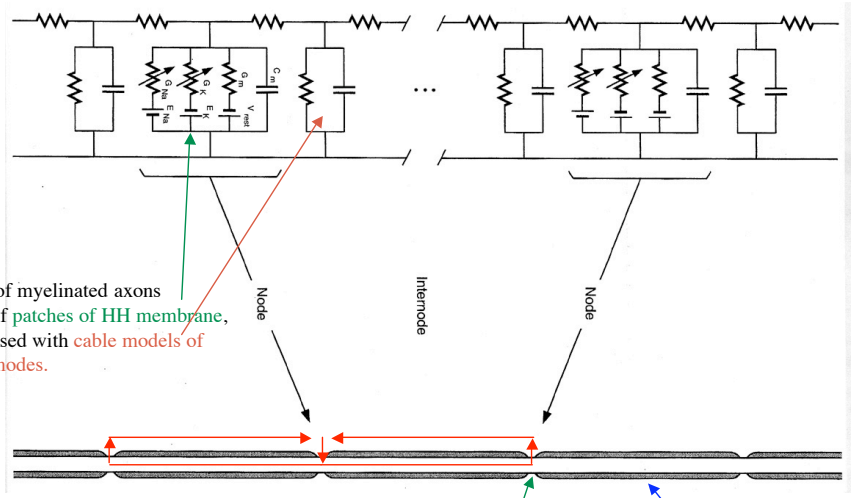
Axons that travel any distance in the brain are myelinated. This means that glial cells form an insulating layer around that axon by wrapping their membranes around the axon. At intervals the membrane of the axon is exposed at nodes of Ranvier. The sodium and potassium channels of these axons are concentrated at the nodes. Thus active currents associated with the action potential occur only at nodes, and the action potential jumps from node to node.





Jacobson, 1970; Levitan & Kaczmarek, 2002.

Myelinization changes AP propagation from a continuous process, as in the HH axon, to a discrete process in which the AP jumps from node to node. Propagation through the internodes is described by the cable equation, with nodal currents described by a HH-like model.

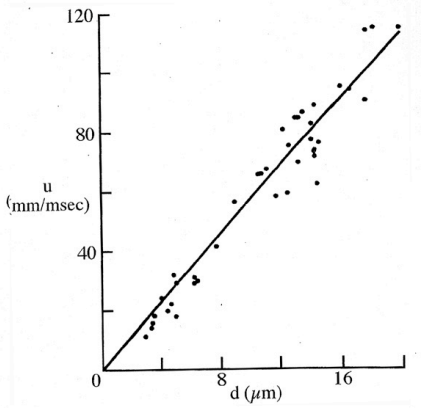


Models of myelinated axons consist of patches of HH membrane, interspersed with cable models of the internodes.

Koch, 1999

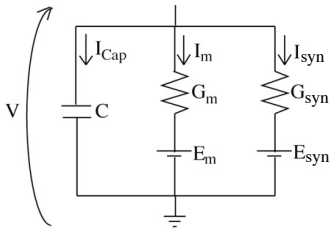
The advantage of myelin is that conduction velocity is now proportional to axon radius, not the square root of radius. This result is predicted by the equations for propagation of current through the model in the previous slide.

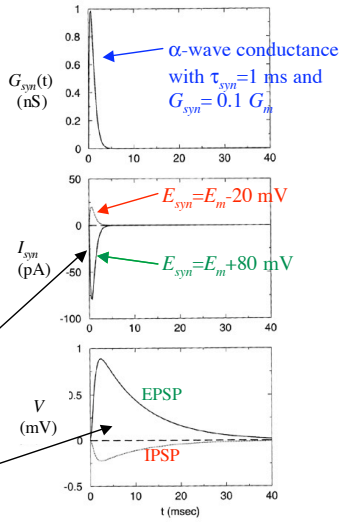
Of course, axons with velocity proportional to a instead of $\sqrt{a}$ are better for the brain, in that signals can be transmitted more quickly with less hardware (smaller axons) and with less energy.



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.

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





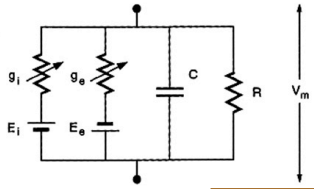
Solutions from this model are shown at right.

1. The excitatory synapse gives a larger current than the inhibitory synapse.

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 τ_{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.



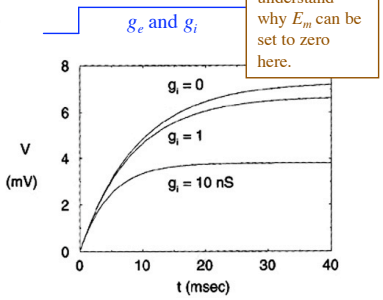
To see what this means, suppose the membrane has both an excitatory (g_e) and inhibitory (g_i) synapse and that they are activated simultaneously with a maintained step of conductance. This is not physiological, but makes it simple to solve the equations. Then:

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

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 if E_i=0 (meaning that the inhibitory equilibrium potential is at the resting potential)! Thus inhibition can work by shunting the currents produced by an excitatory synapse.

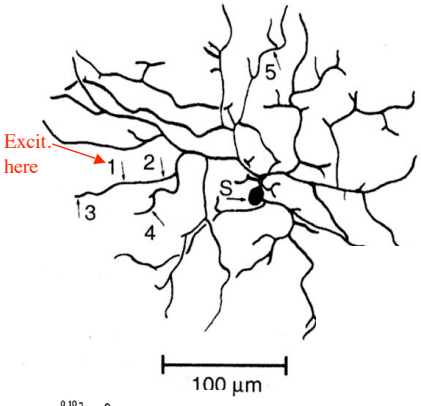
Koch, 1999

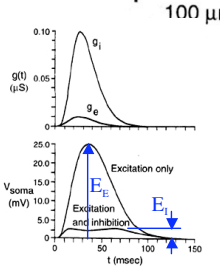
What is the effect of relative placement of synapses on the dendrites?

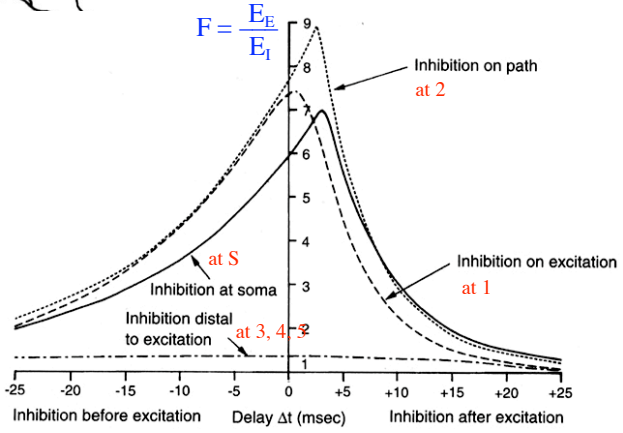
Because cells are not electrically compact, the relative placement of synapses on dendrites matters.

or

Why inhibitory synapses cluster near the soma.

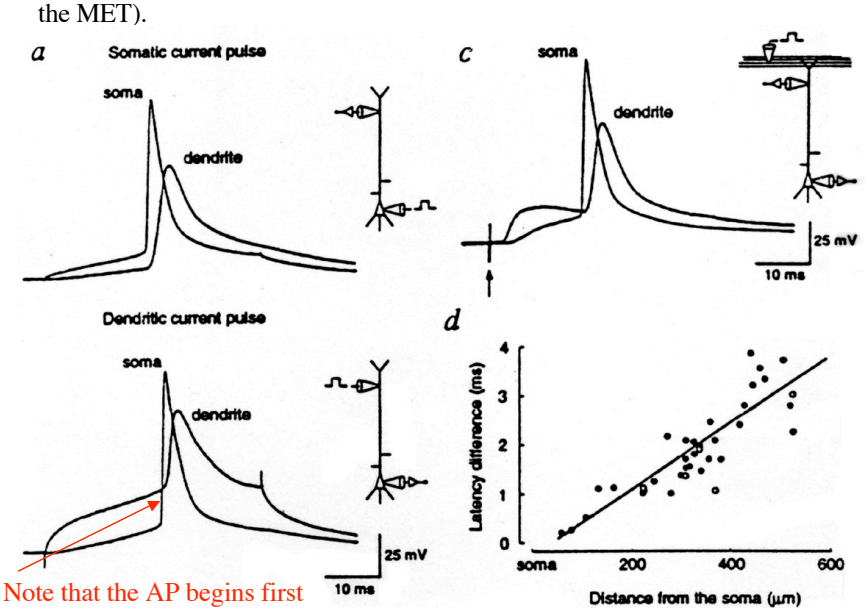






Koch et al., 1983

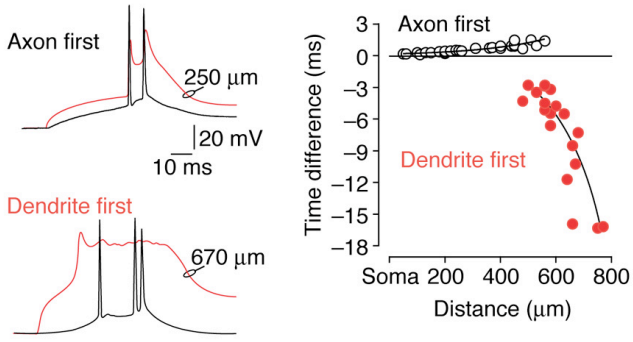
Dendritic trees are not passive: action potentials invade the dendritic tree from the soma, but not vice-versa (this is explained on the basis of the asymmetry in the MET).



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

Stuart and Sakmann, 1994

Action potentials can invade dendrites from the soma, as in the previous slide, 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, but probably occur elsewhere. They may help to couple distant synapses to the soma.



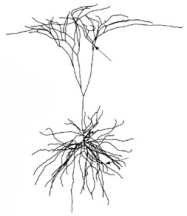
Simultaneous soma and dendritic patch recording, with current injection in either site. At proximal sites axon-first spikes were produced, but dendrite-first spikes were produced at distal sites.

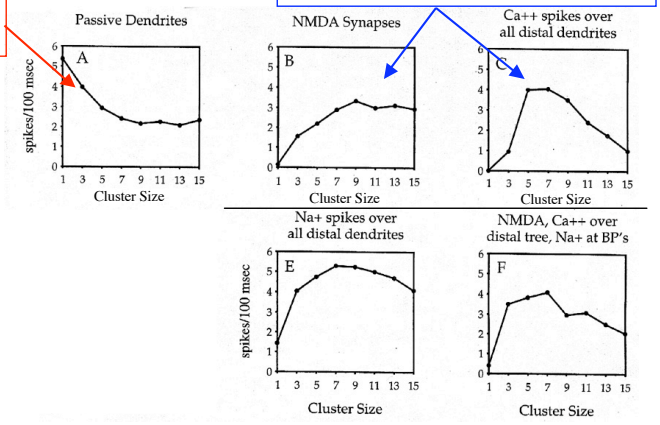
Williams & Stuart 2003

What is the effect of relative placement of synapses on the dendritic tree?
The answer 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

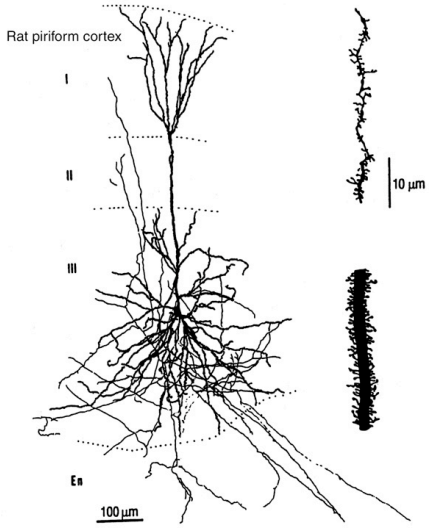


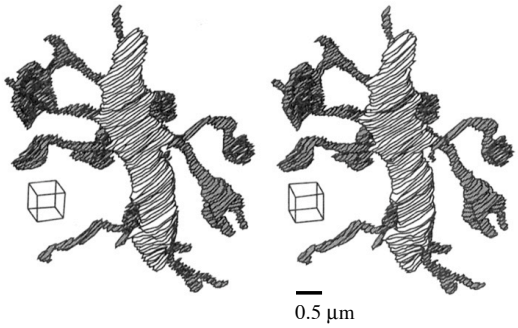


* (the model was a direct compartmental model of the neuron shown above.

Mel, 1993

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

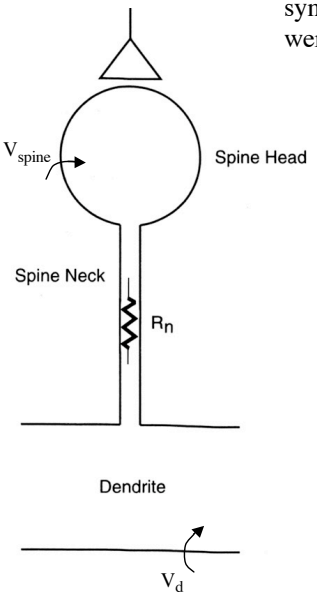


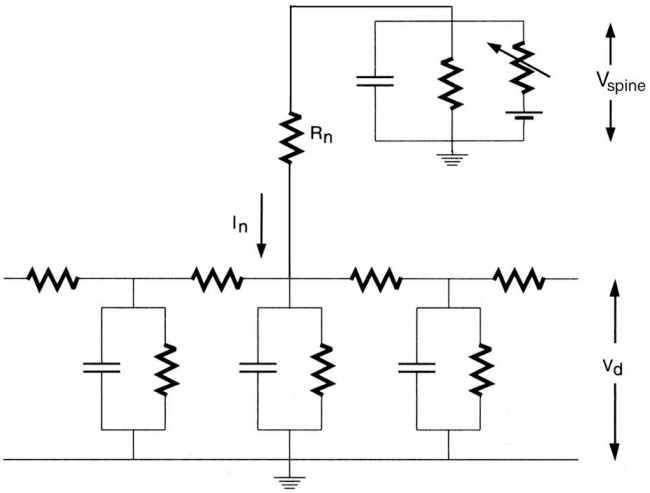


Wilson et al.,, 1992

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

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. 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.



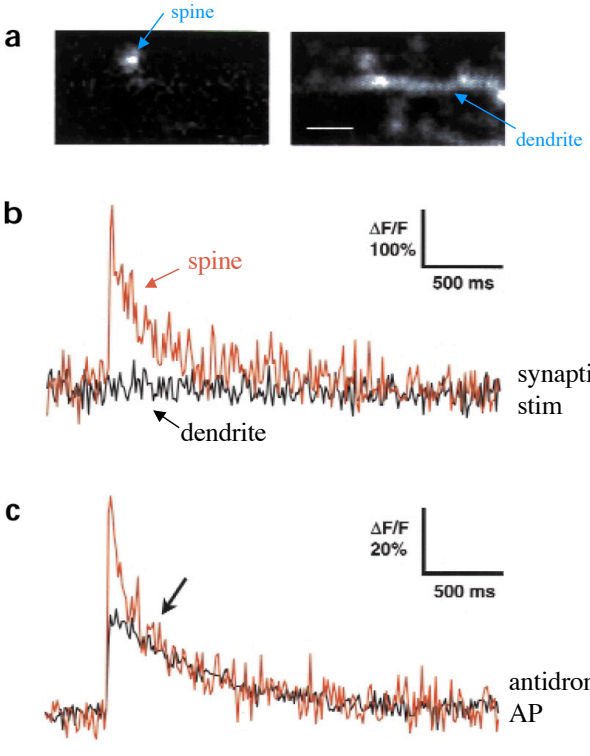


In fact, spines are calcium traps, the length constant for calcium diffusion in dendrites is very short, approximately the length of a spine neck.

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

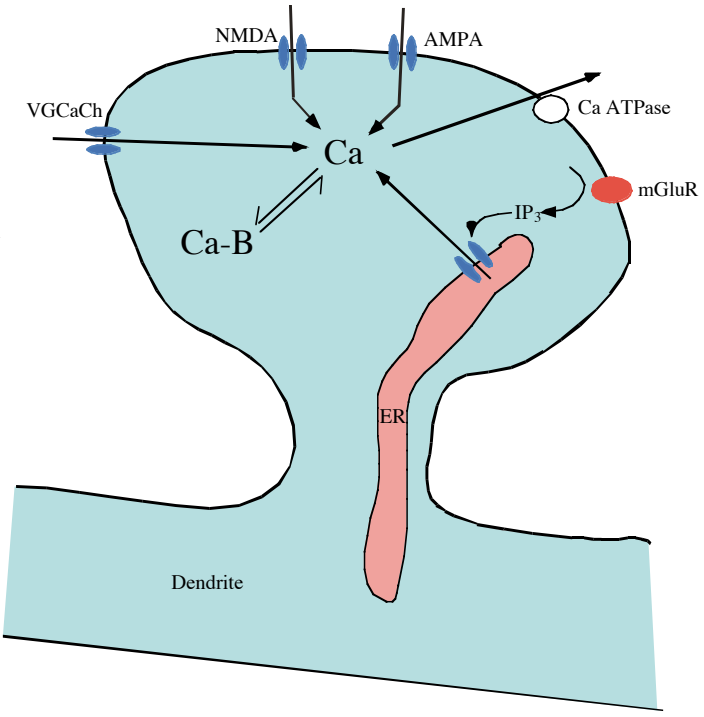
b. Shows the Ca signals in the spine (red) and dendrite (black) for synaptic stim.

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

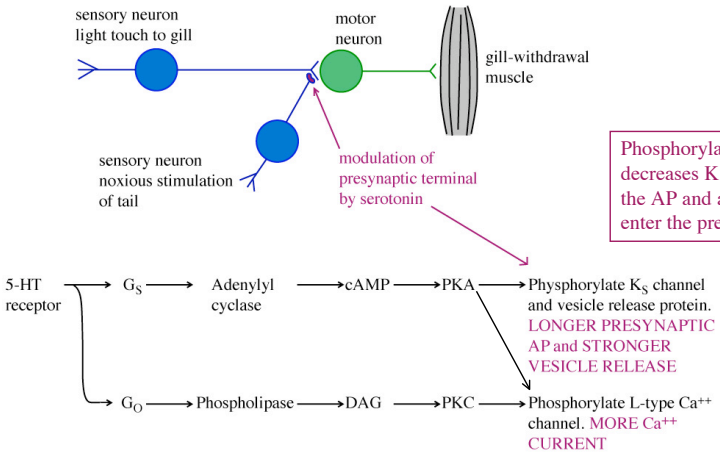


Yuste et al., 2000

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



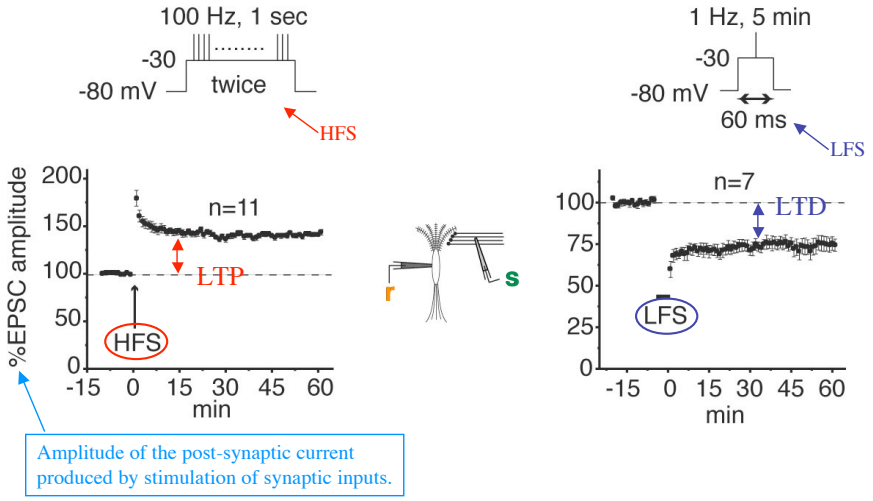
Strength of synapses again. Synaptic strength can be modulated under behavioral conditions by metabotropic mechanisms, exemplified by postsynaptic sensitization in the aplysia gill-withdrawal reflex. The reflex protects the gill from damage using the warning signal of strong stimulation of the tail. These effects can last for up to several days, if the stimulus is repeated enough times.



Phosphorylating K_S channels decreases K^+ currents, prolonging the AP and allowing more Ca^{++} to enter the presynaptic terminal.

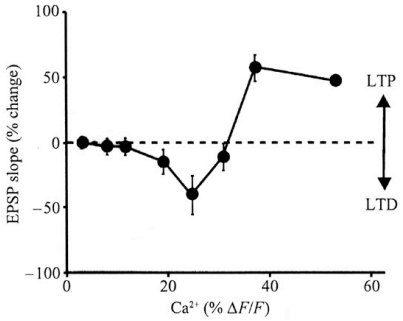
Longer-term changes in the strength of a synape occur due to use of the synapse. Below are an example of long-term potentiation (LTP, left) and long-term depression (LTD, right). The stimulus protocol involves two components:

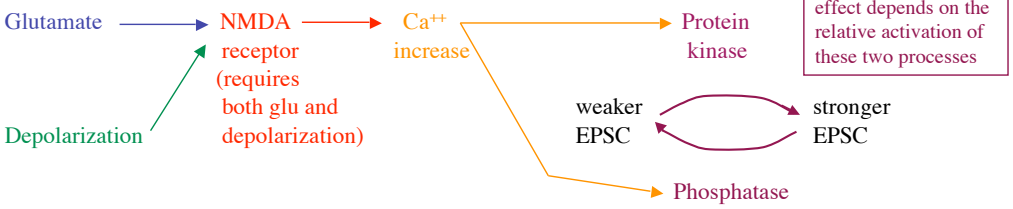
1. Stimulation of presynaptic fibers (s)
2. Depolarization of the postsynaptic cell through the recording electrode (r)



Fujino and Oertel, 1999

LTP and LTD can both occur at the same synapse, as in the example on the previous slide. The difference seems to depend on the strength of the Ca signal in the postsynaptic terminal. The sequence of events occurring in the postsynaptic cell is known partially and is described below.





Presumably the net effect depends on the relative activation of these two processes

The actual mechanisms of strengthening the postsynaptic EPSC probably include several; 1) changes in ion currents due to phosphorylation; 2) the number of AMPA receptors in the postsynaptic terminal can change; 3) ??

Johnston et al. 2002