Systems Biology II: Neural Systems (580.422)

Lecture 9, Nonlinear cable theory

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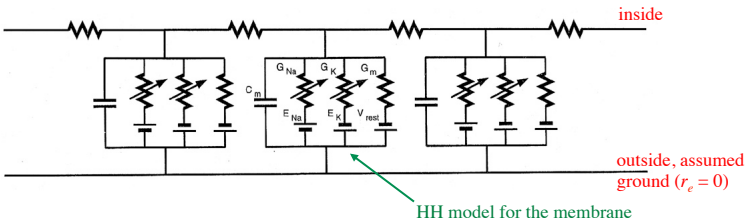
Reading

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).

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



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

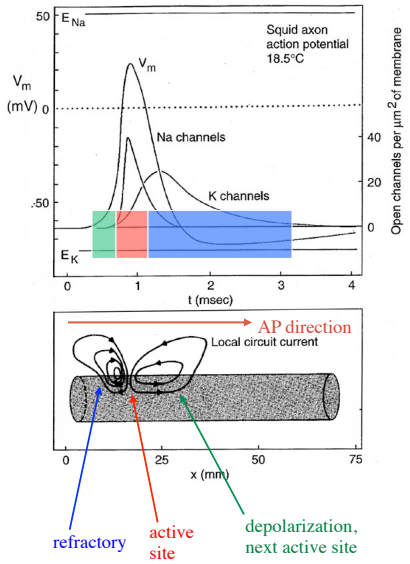
$$\frac{1}{r_i}\frac{\partial^2 V}{\partial x^2} = c_m\frac{\partial V}{\partial t} + I_{ionic} = c_m\frac{\partial V}{\partial t} + G_{Na}m^3h(V-E_{Na}) + G_K n^4(V-E_K) + G_m(V-E_{rest})$$

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.

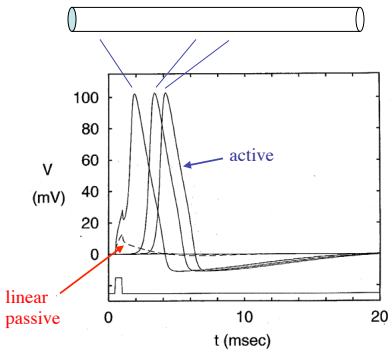
$=I_{Na}+I_K+I_m$

Koch, 1999

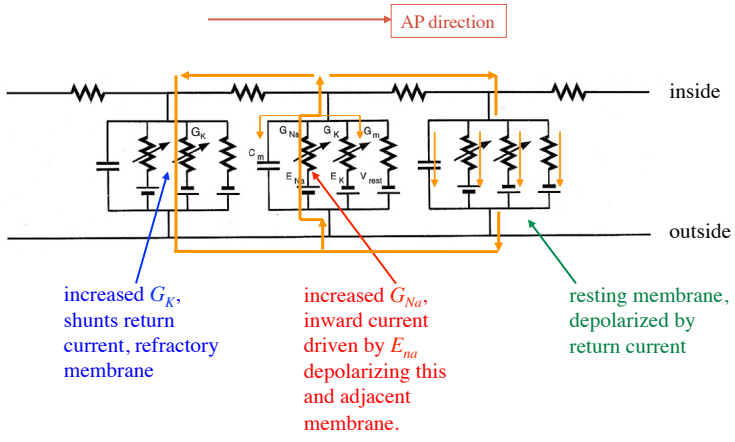
The action potential in axons moves at a constant velocity like a wave. The propagation of the AP depends on the spread of current away from the site of the current AP.



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



Koch, 1999 and Hille, 1992



An important aspect of action-potential conduction is its conduction velocity. H&H's model predicts that the conduction velocity of unmyelinated axons should vary as the square root of axon diameter (see the slides at the end of this lecture).

As an intuitive argument, consider the linear cable equation:

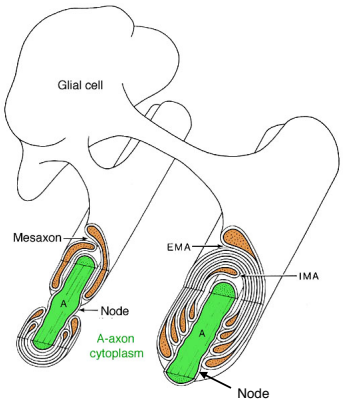
$$\lambda^2 \frac{\partial^2 V}{\partial x^2} = \tau \frac{\partial V}{\partial t} + V \quad \text{where} \quad \lambda = \sqrt{\frac{a R_m}{2 R_i}} \quad \text{and} \quad \tau = R_m C$$

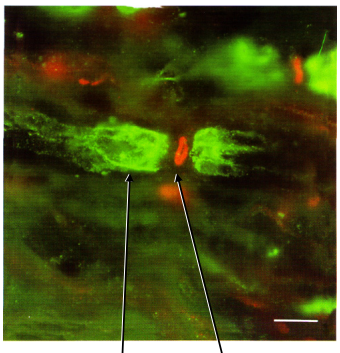
The distance through which disturbances travel is λ and the time scale for changes in membrane potential is τ. Events like the spread of the action potential that depend on the processes captured in the cable equation should spread with a velocity proportional to λ/τ.

$$velocity \approx \frac{\lambda}{\tau} = \frac{\sqrt{a}}{\sqrt{2 R_m R_i C}}$$

All the terms on the r.h.s. of this last equation are constants except a, the cylinder radius. This predicts that conduction velocity should vary as $\sqrt{a}$ in unmyelinated axons, which is the HH prediction (and is said to be supported by data).

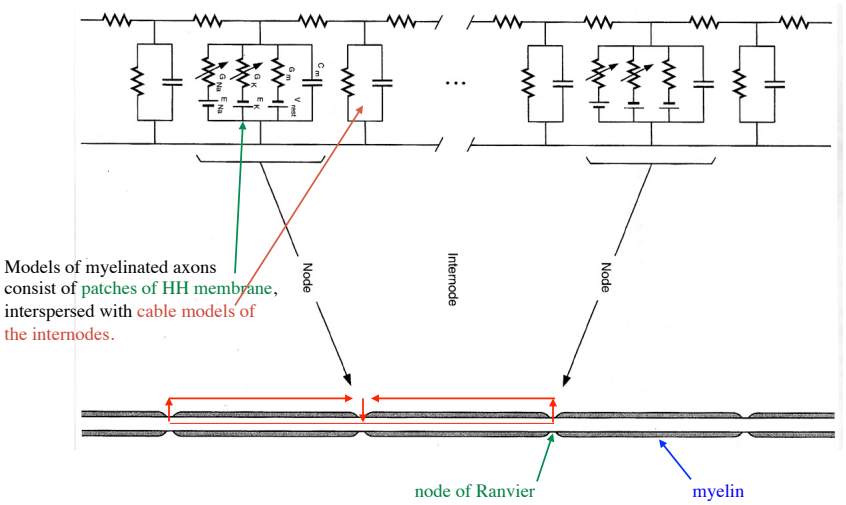
Axons that travel any distance in the brain are myelinated. This means that glial cells form an insulating layer around the axon by wrapping their membranes around it. At intervals the membrane of the axon is exposed at nodes of Ranvier. The sodium and potassium channels of these axons are concentrated 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.

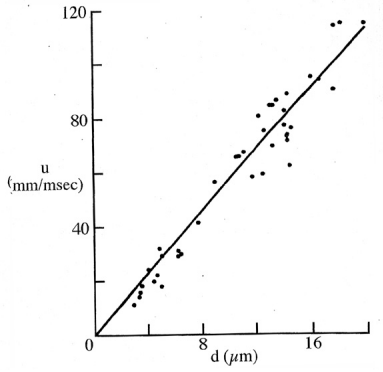
Myelinization changes AP propagation from a continuous process, as in the HH axon, to a discrete process in which the AP jumps from node to node. Propagation through the internodes is described by the cable equation, with nodal currents described by a HH-like model.



Koch, 1999

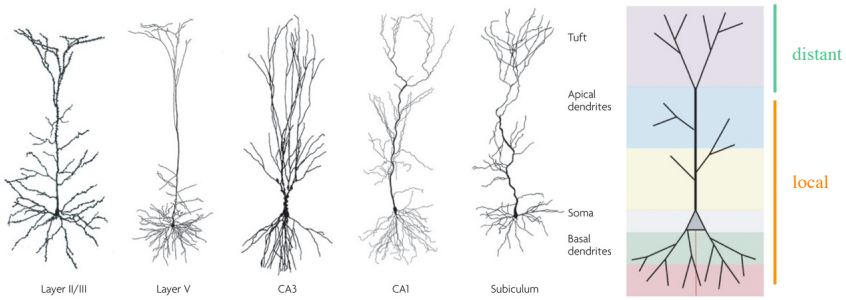
The advantage of myelin is that conduction velocity is now proportional to axon radius, not the square root of radius. This result is predicted by the equations for propagation of current through the model in the previous slide (a complex mess, not shown).

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.



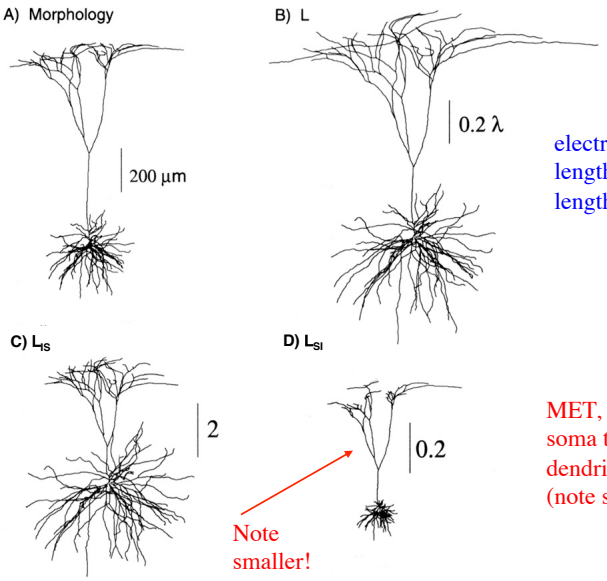
Ritchie et al 1982

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

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



physical size

electrotonic length, equal to length/length const

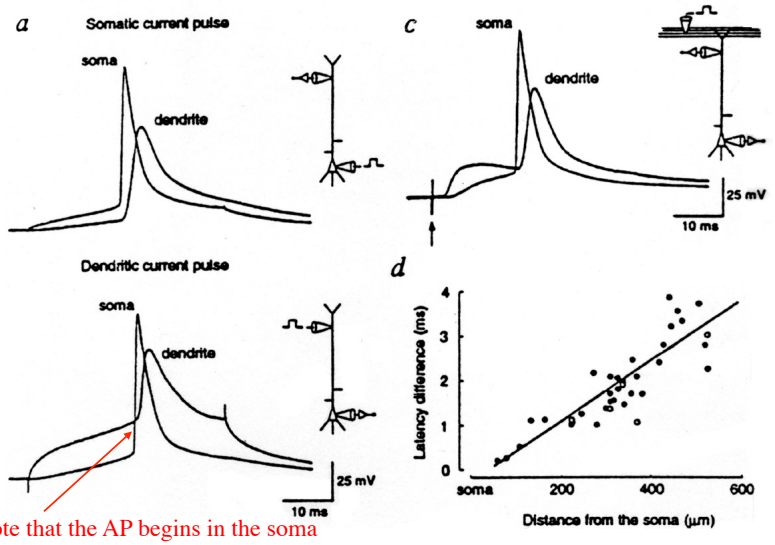
MET, dendrite to soma

MET, soma to dendrites (note scale!)

Note smaller!

Zador, 1993

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!

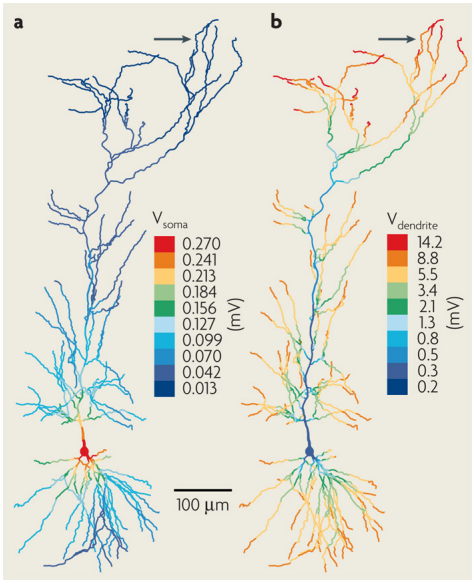
Stuart and Sakmann, 1994

(all with 0.3 nS synaptic conductance)

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

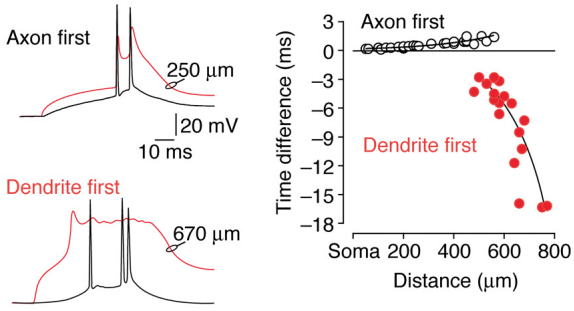
At left is the amplitude of the EPSP in the soma as a function of initiation site in the dendritic tree (a simulation). Cable effects are clear.

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.



Spruston 2008

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 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

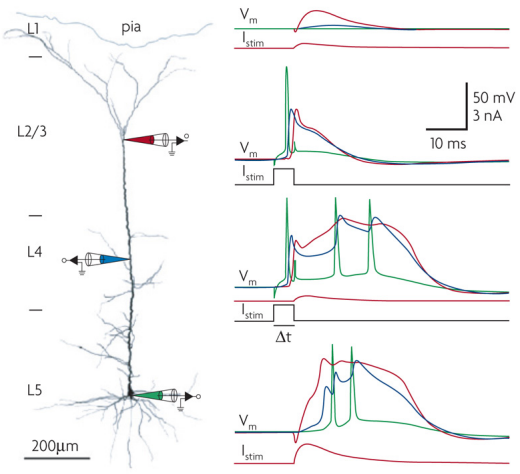
Forward and back-propagating potentials can interact, producing larger responses.

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).

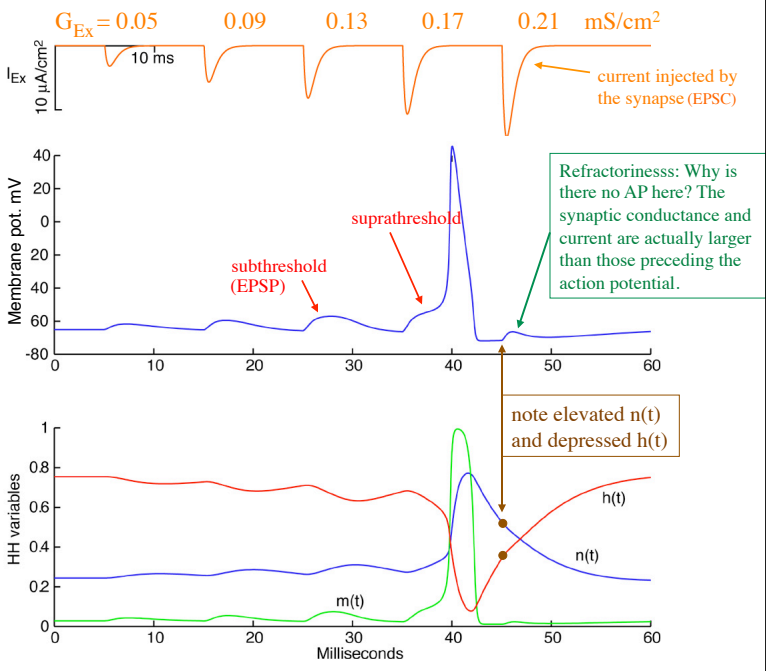


Spruston 2008

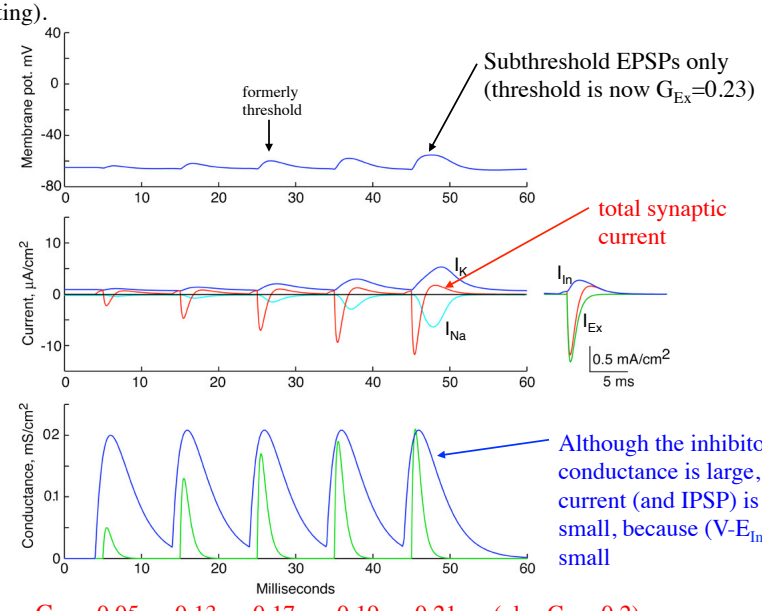
A simulation of excitatory synaptic inputs to a simple (HH) neuron.

This shows sub- and suprathreshold behavior, depending on synaptic conductance.

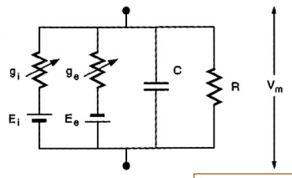
This could also be spatial summation, i.e. simultaneous activation of several synapses.



Adding inhibitory inputs blocks the response to the excitatory input. The effect is due to hyperpolarizing current and the inhibitory conductance change (inhibitory shunting).



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:

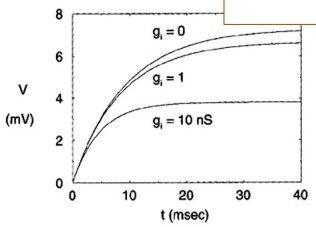
$$C\frac{dV_m}{dt} = -\frac{1}{R}V_m - g_e(V_m - E_e) - g_i(V_m - E_i)$$

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.

g_e and g_i



$1/R$=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.

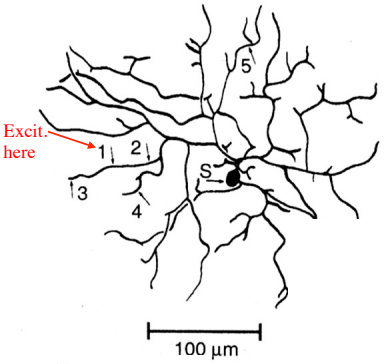
Koch, 1999

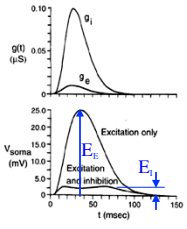
What is the effect of relative placement of synapses on the dendrites?

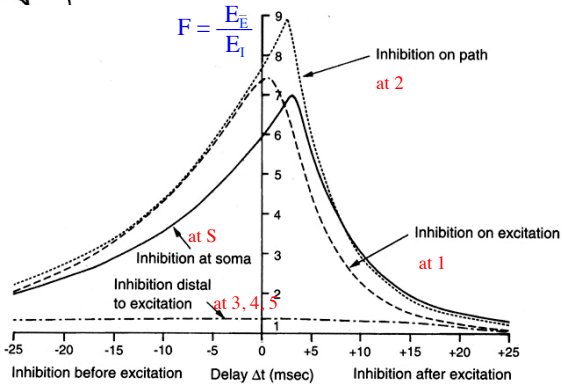
Because cells are not electrically compact, the relative placement of synapses on dendrites matters.

or

Why inhibitory synapses cluster near the soma.







Koch et al., 1983

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)