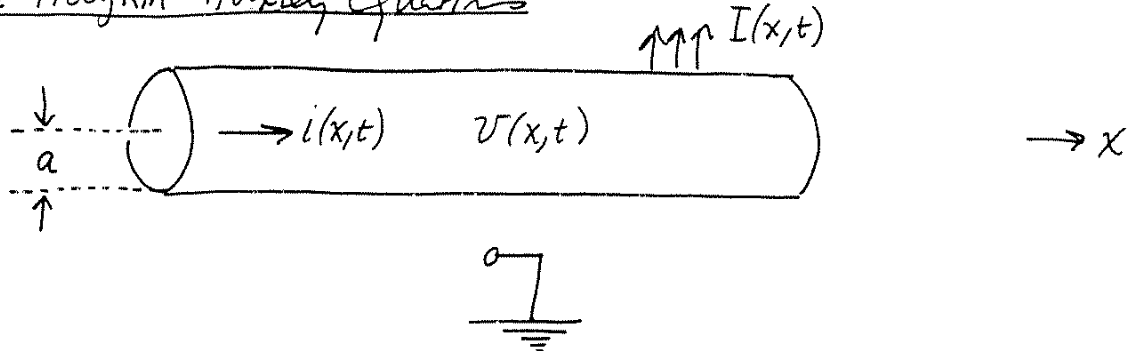
Charles S Peskin 10/11/91

The Hodgkin-Huxley equations



a = radius of axon
x = distance along axon
t = time
$i(x,t)$ = axial current
$V(x,t)$ = internal voltage
$I(x,t)$ = transmembrane current per unit area
C = membrane capacitance per unit area
g_{Na} = Na^+ conductance per unit area
g_K = K^+ conductance per unit area
g_L = leakage conductance per unit area
E_{Na} = equilibrium potential for Na^+
E_K = equilibrium potential for K^+
E_L = equilibrium potential for leakage current
ρ = resistivity of axoplasm

Current (charge) conservation:

$$i(b,t) - i(a,t) = -\int_a^b I(x,t)\, 2\pi a\, dx$$

$$\int_a^b \left(\frac{\partial i}{\partial x} + 2\pi a\, I\right) dx = 0$$

since a and b are arbitrary

$$\frac{\partial i}{\partial x} + 2\pi a\, I = 0$$

Ohm's law for axial current.

$$i = -\frac{\pi a^2}{\rho} \frac{\partial v}{\partial x}$$

Membrane current is the sum of capacitive and ionic components:

$$I = C\frac{\partial v}{\partial t} + g_{Na}(v - E_{Na}) + g_K(v - E_K) + g_L(v - E_L)$$

Combining the above:

$$C\frac{\partial v}{\partial t} + g_{Na}(v - E_{Na}) + g_K(v - E_K) + g_L(v - E_L) = \frac{a}{2\rho}\frac{\partial^2 v}{\partial x^2}$$

(This is called the cable equation)

The distinctive feature of the Hodgkin-Huxley equations is the dependence of g_{Na} and g_K on voltage and time*. Since it is simpler, consider g_K first:

Let the K^+ channel consist of 4 <u>identical</u> and <u>independent</u> subunits, each of which has two possible states (S and S^*) with voltage dependent transitions.

$$S \underset{\beta_n(v)}{\overset{\alpha_n(v)}{\rightleftharpoons}} S^*$$

Let the channel be OPEN if and only if <u>all 4</u> subunits are in the state S^*. Now consider a large population of channels, and let n be the fraction of <u>subunits</u> in the state S^*. Then n^4 is the fraction of channels in the OPEN state (recall independence of the subunits), and

$$g_K = \overline{g_K}\, n^4$$

where $\overline{g_K}$ is <u>the</u> (theoretical) K^+ conductance per unit area that would <u>be achieved</u> if all K^+ channels were open at once. According to the above kinetic scheme, n satisfies the differential equation

$$\frac{\partial n}{\partial t} = \alpha_n(v)(1-n) - \beta_n(v)\, n$$

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* g_L is constant: $g_L = \overline{g_L}$

Now consider g_{Na}. Let the Na^+ channel also consist of 4 <u>independent</u> subunits, but let 3 be of one type (S') and let 1 be of another type (S''). Let each type of subunits have two states with voltage dependent transitions:

$$S' \underset{\beta_m(v)}{\overset{\alpha_m(v)}{\rightleftharpoons}} (S')^*$$

$$S'' \underset{\beta_h(v)}{\overset{\alpha_h(v)}{\rightleftharpoons}} (S'')^*$$

and let the channel be open if and only if all 4 subunits are in the state $*$:

$$\text{OPEN CHANNEL} = ((S')^*)_3 (S'')^*$$

In a large population of such channels, let

m = fraction of ' subunits in state $(S')^*$
h = fraction of '' subunits in state $(S'')^*$

Then m^3h is the fraction of OPEN Na^+ channels (recall independence) and

$$g_{Na} = \overline{g_{Na}}\, m^3 h$$

According to the kinetic schemes given above for S' and S'', m and h satisfy the following differential equations

$$\frac{\partial m}{\partial t} = \alpha_m(v)(1-m) - \beta_m(v)\, m$$

$$\frac{\partial h}{\partial t} = \alpha_h(v)(1-h) - \beta_h(v)\, h$$

It is often useful to rewrite the equations for m, h, n as follows:

$$\frac{\partial m}{\partial t} = \frac{1}{\tau_m(v)}\left(m_\infty(v) - m\right)$$

$$\frac{\partial h}{\partial t} = \frac{1}{\tau_h(v)}\left(h_\infty(v) - h\right)$$

$$\frac{\partial n}{\partial t} = \frac{1}{\tau_n(v)}\left(n_\infty(v) - n\right)$$

where

$$m_\infty(v) = \frac{\alpha_m(v)}{\alpha_m(v) + \beta_m(v)} \qquad \tau_m(v) = \frac{1}{\alpha_m(v) + \beta_m(v)}$$

$$h_\infty(v) = \frac{\alpha_h(v)}{\alpha_h(v) + \beta_h(v)} \qquad \tau_h(v) = \frac{1}{\alpha_h(v) + \beta_h(v)}$$

$$n_\infty(v) = \frac{\alpha_n(v)}{\alpha_n(v) + \beta_n(v)} \qquad \tau_n(v) = \frac{1}{\alpha_n(v) + \beta_n(v)}$$

In summary we have the following system:

fast $$C\frac{\partial v}{\partial t} + \bar{g}_{Na}\, m^3 h\,(v - E_{Na}) + \bar{g}_K\, n^4 (v - E_K) + \bar{g}_L\,(v - E_L) = \frac{a}{2\rho}\frac{\partial^2 v}{\partial x^2}$$

fast $$\frac{\partial m}{\partial t} = \alpha_m(v)(1-m) - \beta_m(v)\, m = \frac{m_\infty(v) - m}{\tau_m(v)}$$

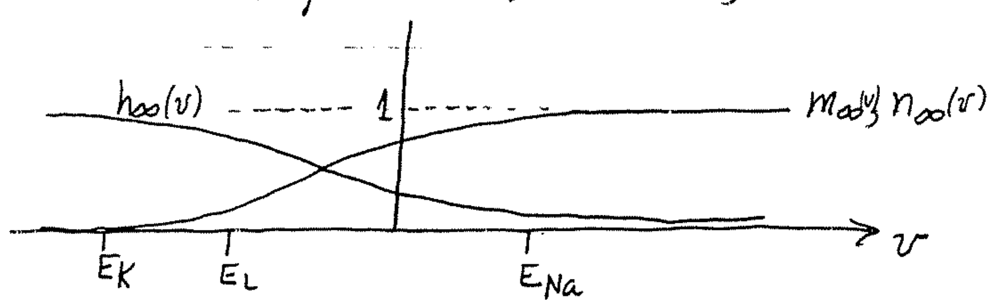
slow $$\frac{\partial h}{\partial t} = \alpha_h(v)(1-h) - \beta_h(v)\, h = \frac{h_\infty(v) - h}{\tau_h(v)}$$

slow $$\frac{\partial n}{\partial t} = \alpha_n(v)(1-n) - \beta_n(v)\, n = \frac{n_\infty(v) - n}{\tau_n(v)}$$

The essential qualitative facts which determine the behavior of this system are as follows. First

$$E_K < E_L < 0 < E_{Na}$$

Next, $m_\infty(v)$ and $n_\infty(v)$ are increasing functions, whereas $h_\infty(v)$ is a decreasing function; something like this:



Finally, (v, m) are fast variables, whereas (h, n) are slow.

Qualitative behavior of the "space-clamped" Hodgkin-Huxley equations.

Hodgkin and Huxley worked with the squid giant axon, an axon which is so large that it is possible to insert a silver wire along its length. Since silver is an excellent conductor, this forces $v(x,t)$ to be independent of x. Then m, h, and n rapidly fall into line with v and become x-independent also. (Think about how to show this!) In this space-clamped situation, then, we are dealing with a system of ordinary differential equations. The silver wire can also be used to apply current to the membrane. Thus, the first of the Hodgkin-Huxley equations becomes

$$C\frac{\partial v}{\partial t} + \bar{g}_{Na} m^3 h (v - E_{Na}) + \bar{g}_K n^4 (v - E_K) + \bar{g}_L (v - E_L) = I_0(t)$$

where $I_0(t)$ is the applied current (per unit area of membrane).

The m, h, n equations are the same as before. We shall give a qualitative analysis of this system based on the separation into fast and slow time scales.

Fast time-scale behavior: the (m,v) plane

On a fast time scale (~ 1 ms), h and n are effectively constant, and one can study the behavior of the system in the (m,v) plane. For now, let $I_0=0$. The first step is to plot the curves* along which $\partial m/\partial t=0$ or $\partial v/\partial t=0$. The curve $\partial m/\partial t=0$ is already known. it is $m=m_\infty(v)$. Setting $\partial v/\partial t=0$, we find

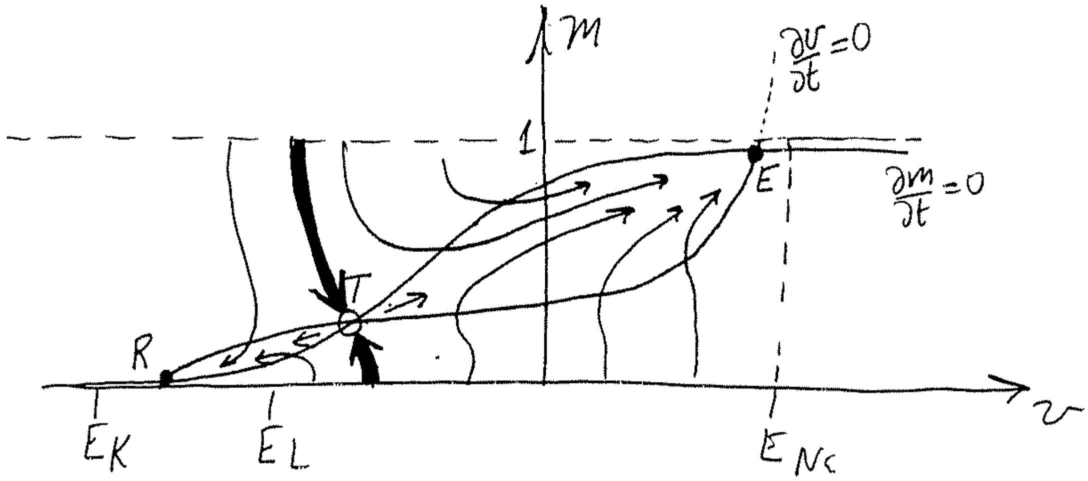
$$v = \frac{\bar{g}_{Na}\, m^3 h\, E_{Na} + \bar{g}_K\, n^4 E_K + \bar{g}_L E_L}{\bar{g}_{Na}\, m^3 h + \bar{g}_K\, n^4 + \bar{g}_L}$$

When $m=0$, $E_K < v < E_L$

As $m \to \infty$, $v \to E_{Na}$ (In fact $m \le 1$, but it helps in sketching the curve to know this limiting value.)

Depending on parameters and on the values of h and n (which are treated as parameters in the fast-scale analysis), the curves $\partial m/\partial t=0$ and $\partial v/\partial t=0$ may have one intersection or three (2 in border-line cases); we consider the situation where the number of intersections is 3.

* called isoclines



The three intersections have the following character:
- R = rest state (stable, node)
- T = threshold (unstable, saddle point)
- E = excited state (stable, node)

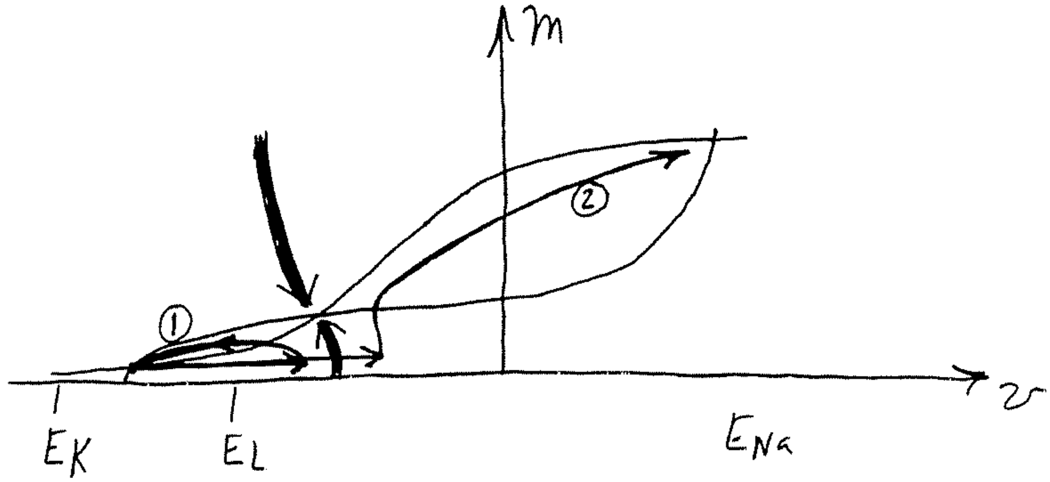
All trajectories that start near R end up at R
All trajectories that start near E end up at E

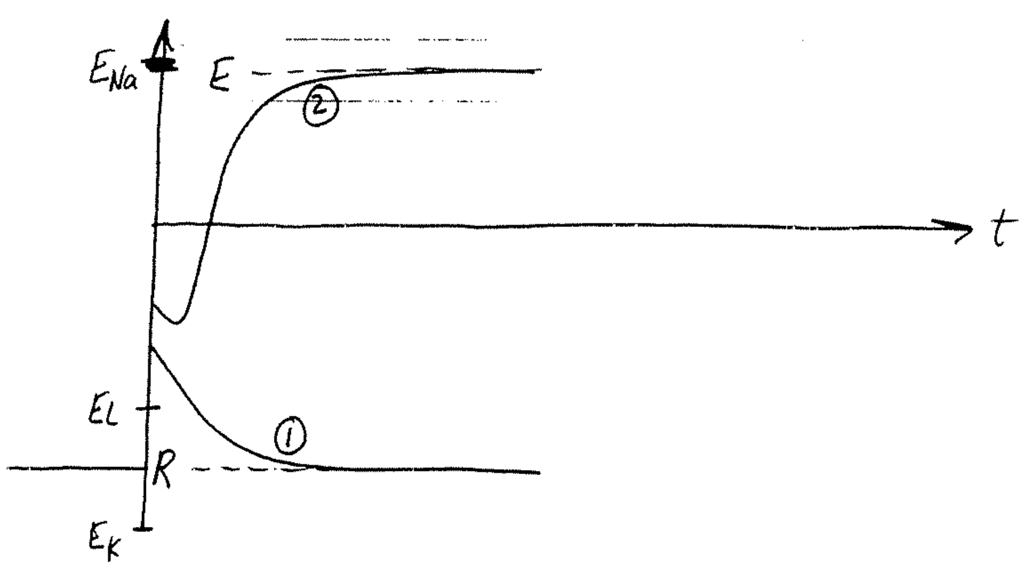
At T, there are two special trajectories, drawn dark, that end up at T itself; all others turn away from T and end up at R or E. The special trajectories form a <u>separatrix</u> which divides the phase plane into two parts. Any initial condition to the left of the separatrix has a trajectory that ends at state R; any initial condition to the right has a trajectory that ends at state E.

In summary, the fast-scale behavior is <u>bistable</u>.

Sub-threshhold and supra threshhold excitation :

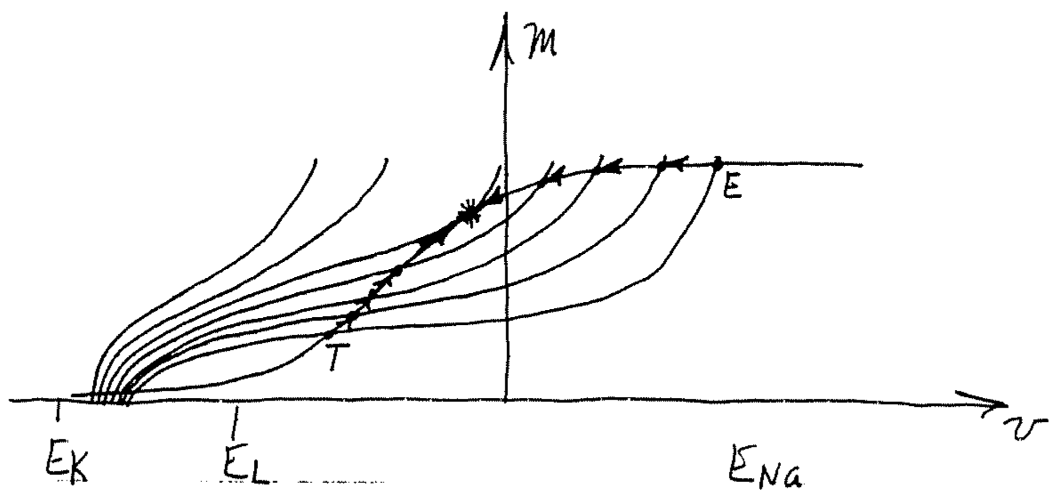
Let the system be in state R prior to $t=0$, and let $I_0(t)=Q_0\,\delta(t)$, so that Q_0 is the total charge per unit area delivered to the membrane by a current shock applied at $t=0$. This produces a jump in voltage $\Delta v = Q_0/C$. Since m cannot change instantaneously, the move in the phase plane is a horizontal shift Δv. If this takes the system past the separatrix, the result is excitation; otherwise, the system returns to rest.

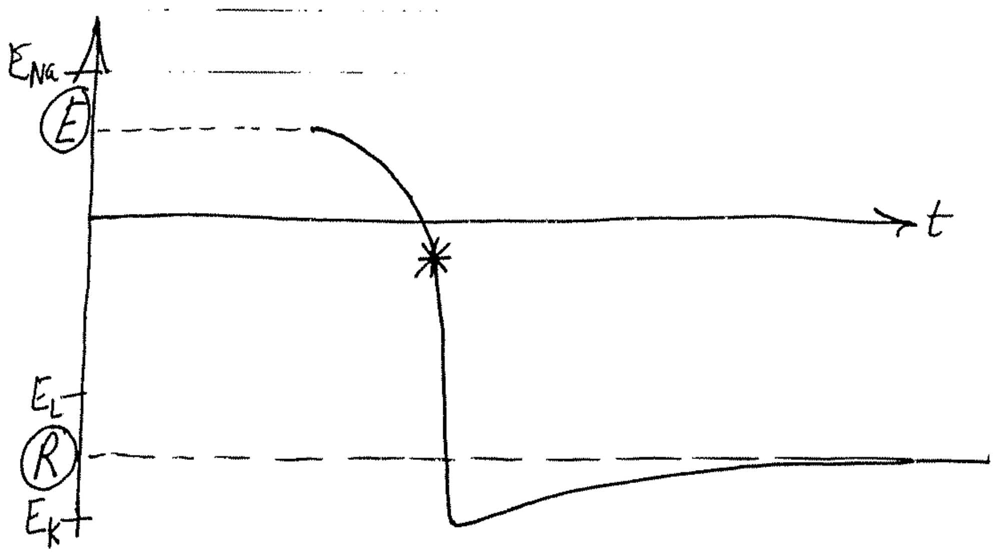




Recovery following excitation

If h and n were really constant, the excited state would persist indefinitely (unless a negative stimulus were applied of sufficient magnitude to cross the separatrix again and return the system to rest.) In fact, however, h and n change slowly, and the whole phase portrait evolves in such a way that the states E and T collide and mutually annihilate leaving only the state R, to which the system then returns. This process can be pictured as follows:





Slow time scale. the n, v plane

We have just been looking at a slow-scale process, in terms of the changes that it makes in the structure of the fast-scale phase plane. A more direct look at the slow time scale can be obtained as follows:

As a preliminary step, we simplify matters by setting

$$h = 1 - n$$

This is consistent with the Hodgkin-Huxley equations if

$$h_\infty(v) + n_\infty(v) = 1$$

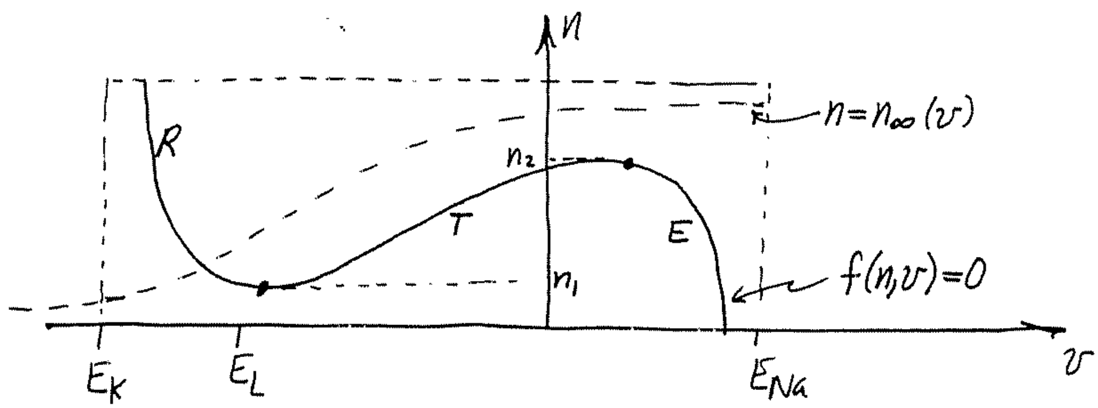
$$\tau_n(v) = \tau_h(v)$$

Next, we come to the essence of the slow-scale analysis, which is to assume that the fast scale variables (m, v) are always "at equilibrium" as n (and hence h) evolves. Thus

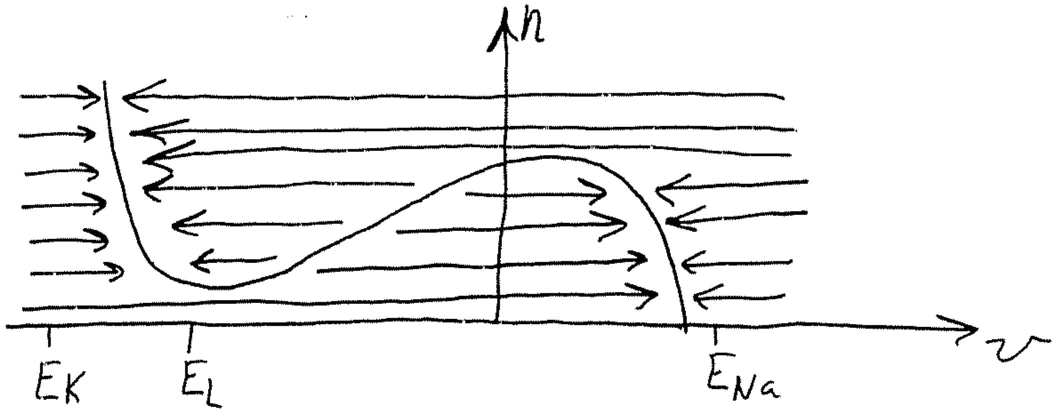
$$m = m_\infty(v)$$

$$f(n, v) = \bar{g}_{Na}\left(m_\infty(v)\right)^3(1-n)(v - E_{Na}) + \bar{g}_K n^4 (v - E_K)$$
$$+ \bar{g}_L(v - E_L) = 0$$

The curve $f(n,v)=0$ looks like this:



It is called the slow manifold. Note that there is an interval of n, between n_1 and n_2, where there are three values of v corresponding to each value of n. These correspond to the three constant states R, T, E of the fast (m,v) phase plane. Whenever the system is not on the slow manifold, it moves rapidly there by means of changes in the fast variables. On the slow time scale, these rapid changes look like jumps. Since n doesn't change during these jumps, they appear as horizontal lines in the (n,v) phase plane. From the fast-scale analysis, we know that the part of the slow manifold labeled T is unstable. Hence, all trajectories that start off the slow manifold jump horizontally (n = constant) to the branch R or **E** of the slow manifold, as shown below:

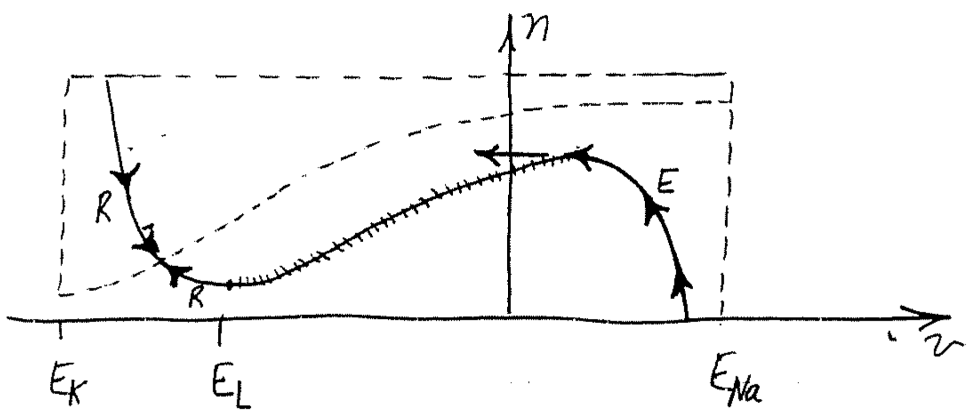


Once it reaches the slow manifold, the system evolves according to

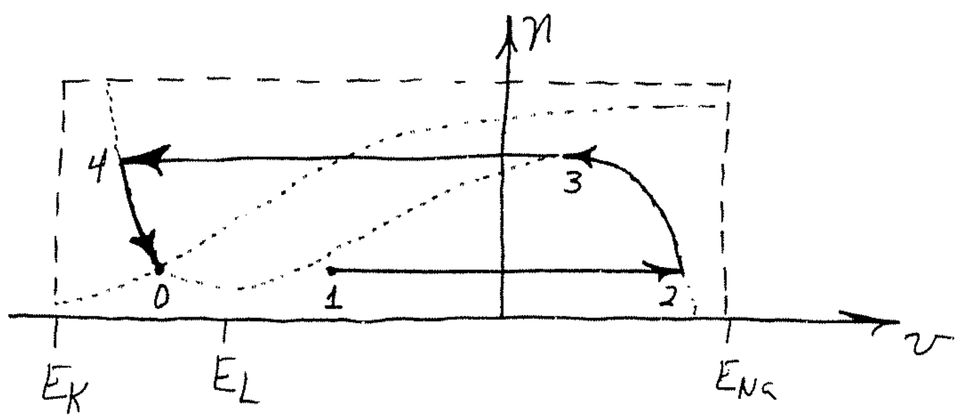
$$\frac{\partial n}{\partial t} = \frac{n_\infty(v) - n}{\tau_n(v)}$$

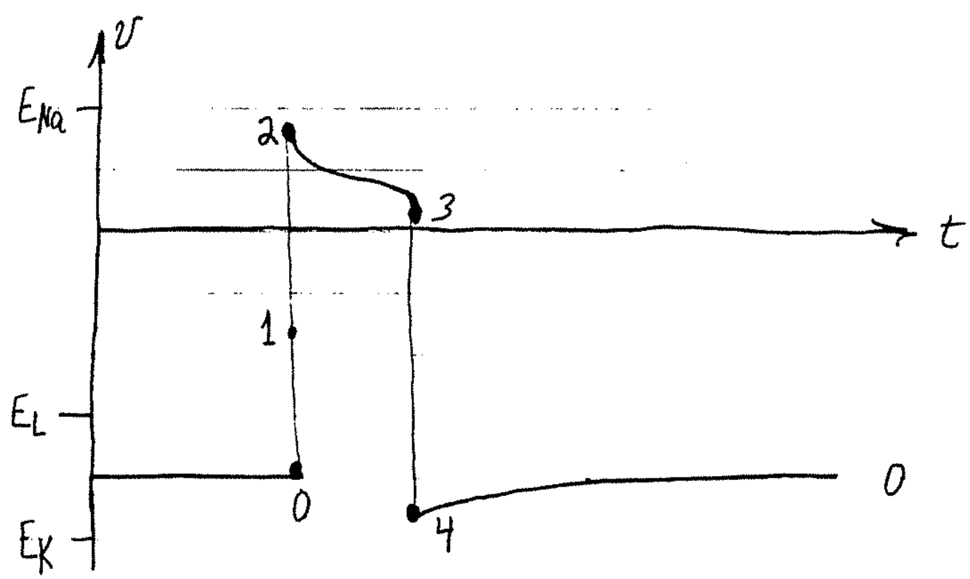
where $v = v_R(n(t))$ or $v = v_E(n(t))$ depending on whether the system happens to be on the rest (R) branch or on the excited (E) branch of the slow manifold. ($v_R(n)$ and $v_E(n)$ are the two stable solutions of $f(n,v)=0$. v_R is defined for $n_1 \le n \le 1$ and v_E is defined for $0 \le n \le n_2$. Since $n_1 < n_2$, their domains overlap.)

The evolution along the slow manifold carries n towards $n_\infty(v)$. The curve $n = n_\infty(v)$ intersects the R branch of the slow manifold, but not the E branch. Hence, on the R branch, the n dynamics carries the system towards a stable resting state, but on the E branch, the n dynamics drives the system towards and then past the value $n = n_2$, where the E branch terminates. The only possibility at that point is to jump to the R branch.



An action potential can now be understood as follows. The rest state of the neuron is the intersection of the curve $f(n,v)=0$ (the slow manifold) with the curve $n=n_\infty(v)$. Let a neuron be at rest there and let a current pulse be applied which is sufficient to step the voltage across the T branch of the slow manifold. Then the neuron jumps to the E manifold, where it evolves to the top, jumps back to the R manifold, and then recovers to its starting point.

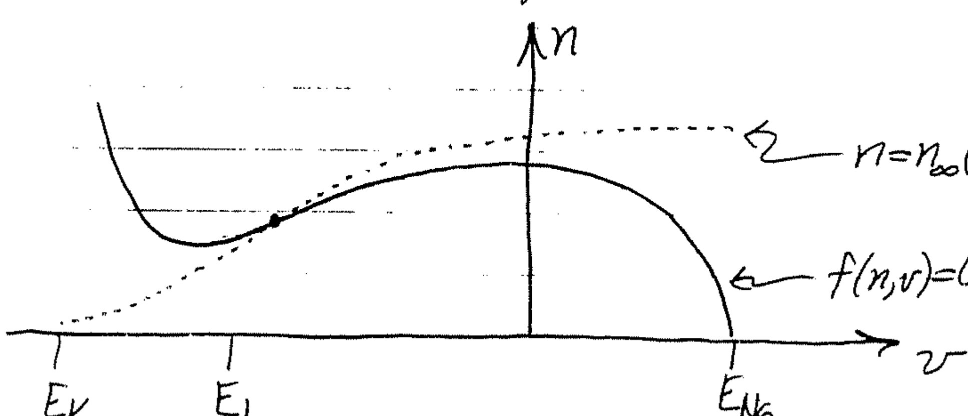




<u>Homework</u>: Use the (n,v) phase plane to discuss the following phenomena. (Don't just answer in words; draw pictures!)

1) <u>Relative refractory period</u>: Following an action potential, a second stimulus is given during the recovery phase (between point 4 and the return to point 0 in the diagrams on the previous page). What can you say about (i) the threshold voltage that must be reached to achieve an action potential, (ii) the size of the voltage step required to reach threshold, (iii) the peak voltage achieved during the action potential, (iv) the duration of the action potential.

2) <u>Spontaneous oscillations</u>: Suppose the slow manifold is shifted* so that it intersects the curve $n=n_\infty(v)$ somewhere on the unstable (T) branch of the slow manifold. Then the (n,v) phase plane looks like this:



What happens?

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*e.g. by application of steady current

3) <u>Anode-break excitation</u>*: From $t = -\infty$ until $t = 0$, the transmembrane potential is clamped at some value v_* which is sufficiently negative that

$$n_\infty(v_*) < n_1$$

(Recall that n_1 is the smallest value of n reached by the R branch of the slow manifold, see p. 13.)

At $t=0$, the voltage clamp is removed. What happens?

Would the result be the same if a membrane at rest were <u>suddenly</u> stepped to the voltage v_*? Explain the difference between these two situations. (Hint: think about n.)

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* Use the <u>un</u>-shifted slow manifold (as shown on pp. 13-16) to answer this question.

1

<u>Hodgkin-Huxley units.</u>

voltage. mV

current : μA

time : msec

length : cm

$\frac{\text{conductance}}{\text{area}}$: $\left(\frac{\mu A}{mV}\right) / cm^2$

$\frac{\text{capacitance}}{\text{area}}$: $\frac{(\mu A)(msec)}{mV \cdot cm^2} = \mu F / cm^2$

Hodgkin-Huxley parameters.

$$C = 1.0 \ \mu F/cm^2$$

$$\bar{g}_{Na} = 120 \left(\frac{\mu A}{mV}\right)/cm^2$$

$$\bar{g}_K = 36 \left(\frac{\mu A}{mV}\right)/cm^2$$

$$\bar{g}_L = 0.3 \left(\frac{\mu A}{mV}\right)/cm^2$$

$$E_{Na} = +45 \ mV$$

$$E_K = -82 \ mV$$

$$E_L = -59 \ mV$$

$$a = 0.0238 \ cm$$

$$\rho = 35.4 \ \Omega \ cm = 0.0354 \left(\frac{mV}{\mu A}\right) cm$$

Hodgkin-Huxley functions

$$m_\infty(V) = \frac{\alpha_m(V)}{\alpha_m(V)+\beta_m(V)}$$

$$\tau_m(V) = \frac{1}{\alpha_m(V)+\beta_m(V)}$$

and similarly for n_∞, τ_n, h_∞, τ_h

where the α's and β's are given on the next page.

$$\alpha_m(V) = \frac{\left(\frac{V+45}{10}\right)}{1 - \exp\left(-\frac{V+45}{10}\right)}$$

$$\beta_m(V) = 4\exp\left(-\frac{V+70}{18}\right)$$

$$\alpha_n(V) = (0.1)\frac{\left(\frac{V+60}{10}\right)}{1 - \exp\left(-\frac{V+60}{10}\right)}$$

$$\beta_n(V) = (0.125)\exp\left(-\frac{V+70}{80}\right)$$

$$\alpha_h(V) = (0.07)\exp\left(-\frac{V+70}{20}\right)$$

$$\beta_h(V) = \frac{1}{1 + \exp\left(-\frac{V+40}{10}\right)}$$

(V in mVolts, α and β in msec^{-1})

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Singular-perturbation analysis of the Hodgkin-Huxley equations

We introduce a parameter ε into the Hodgkin-Huxley equations as follows:

$$\varepsilon C \frac{\partial v}{\partial t} + \bar{g}_{Na} m^3 h (v - E_{Na}) + \bar{g}_K n^4 (v - E_K) + \bar{g}_L (v - E_L) = \varepsilon^2 \frac{a}{2\rho} \frac{\partial^2 v}{\partial x^2}$$

$$\varepsilon \tau_m(v) \frac{\partial m}{\partial t} = m_\infty(v) - m$$

$$\tau_h(v) \frac{\partial h}{\partial t} = h_\infty(v) - h$$

$$\tau_n(v) \frac{\partial n}{\partial t} = n_\infty(v) - n$$

Note that ε appears in 3 places: the $\partial v/\partial t$ term, the $\partial m/\partial t$ term, and the $\partial^2 v/\partial x^2$ term (in which it appears as ε^2).

Clearly, we recover the original Hodgkin-Huxley equations by setting $\varepsilon = 1$. We shall analyze the limit $\varepsilon \to 0$. If the parameter ε has been introduced cleverly enough, this limit will give a good approximation to the case $\varepsilon = 1$.

To simplify matters, consider a special case. Let

τ_m, τ_h, and τ_n be independent of v

$\tau_m = 0$

$$m_\infty(v) = 1 - h_\infty(v) = n_\infty(v) = \begin{cases} 1 & v > v_* \\ 0 & v < v_* \end{cases}$$

where

$$E_K < E_L < v_* < 0 < E_{Na}$$

Since $\tau_m = 0$, $m = m_\infty(v)$. Since $m_\infty(v)$ is 0 or 1, $m^3 = m$.

Thus, we have the simplified system:

$$\varepsilon C \frac{\partial v}{\partial t} + \bar{g}_{Na}\, m h (v - E_{Na}) + \bar{g}_K n^4 (v - E_K) + \bar{g}_L (v - E_L) = \varepsilon^2 \frac{a}{2\rho} \frac{\partial^2 v}{\partial x^2}$$

$$m = \begin{cases} 1 & v > v_* \\ 0 & v < v_* \end{cases}$$

$$\tau_h \frac{\partial h}{\partial t} = (1 - m) - h$$

$$\tau_n \frac{\partial n}{\partial t} = m - n$$

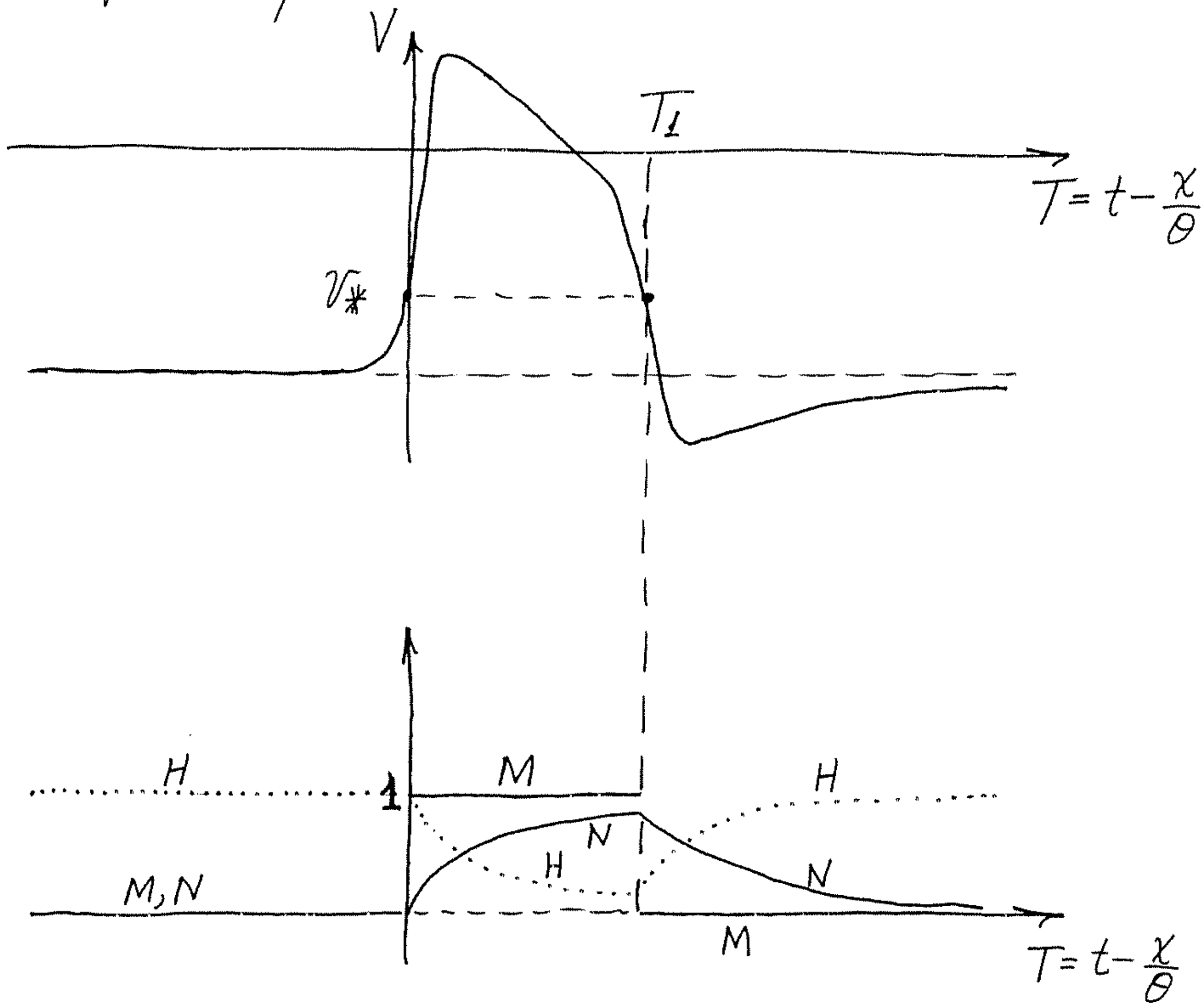
(Note that v_* plays the role of an explicit threshold.)

We seek traveling wave solutions:

$$v(x,t) = V\left(t-\frac{x}{\theta}\right) = V(T) \qquad m(x,t) = M\left(t-\frac{x}{\theta}\right) = M(T)$$

$$h(x,t) = H\left(t-\frac{x}{\theta}\right) = H(T) \qquad n(x,t) = N\left(t-\frac{x}{\theta}\right) = N(T)$$

with the following qualitative behavior:



For now, assume θ and T_1 are known. They will be determined later.

Solutions for M, H, N

$$M(T) = \begin{cases} 0, & T < 0 \\ 1, & 0 < T < T_1 \\ 0, & T_1 < T \end{cases}$$

$$H(T) = \begin{cases} 1, & T < 0 \\ \exp\left(-\frac{T}{\tau_h}\right), & 0 < T < T_1 \\ 1 - \left(1 - \exp\left(-\frac{T_1}{\tau_h}\right)\right)\exp\left(-\frac{T-T_1}{\tau_h}\right), & T_1 < T \end{cases}$$

$$N(T) = \begin{cases} 0, & T < 0 \\ 1 - \exp\left(-\frac{T}{\tau_n}\right), & 0 < T < T_1 \\ \left(1 - \exp\left(-\frac{T_1}{\tau_n}\right)\right)\exp\left(-\frac{T-T_1}{\tau_n}\right), & T_1 < T \end{cases}$$

Equation for V:

$$- \varepsilon^2 \frac{a}{2\rho\theta^2} V'' + \varepsilon C V'$$

$$+ \bar{g}_{Na} MH(V - E_{Na}) + \bar{g}_K N^4 (V - E_K) + \bar{g}_L (V - E_L) = 0$$

"Outer solution" (valid away from $T=0$ and $T=T_1$)
let $\varepsilon \to 0$ and solve for V:

$$V = \frac{\bar{g}_{Na} MH E_{Na} + \bar{g}_K N^4 E_K + \bar{g}_L E_L}{\bar{g}_{Na} MH + \bar{g}_K N^4 + \bar{g}_L}$$

where M, H, N are given on previous page. In particular

$$V = \begin{cases} E_L & T < 0 \\ \dfrac{\bar{g}_{Na} H E_{Na} + \bar{g}_K N^4 E_K + \bar{g}_L E_L}{\bar{g}_{Na} H + \bar{g}_K N^4 + \bar{g}_L}, & 0 < T < T_1 \\ \dfrac{\bar{g}_K N^4 E_K + \bar{g}_L E_L}{\bar{g}_K N^4 + \bar{g}_L}, & T_1 < T \end{cases}$$

"Inner solution" valid near $T=0$. Let $T=\varepsilon S$

$$V(T)=V(\varepsilon S)=U(S)$$

Then $U'(S)=\varepsilon V'(\varepsilon S) \qquad U''(S)=\varepsilon^2 V''(\varepsilon S)$

Substitute and then let $\varepsilon \to 0$

$$-\frac{a}{2\rho\theta^2}U''+CU'+\bar{g}_{Na}MH_0(U-E_{Na})+\bar{g}_K N_0^4(U-E_K)$$
$$+\bar{g}_L(U-E_L)=0$$

where $\quad H_0=\lim_{\varepsilon\to 0} H(\varepsilon S)=1$

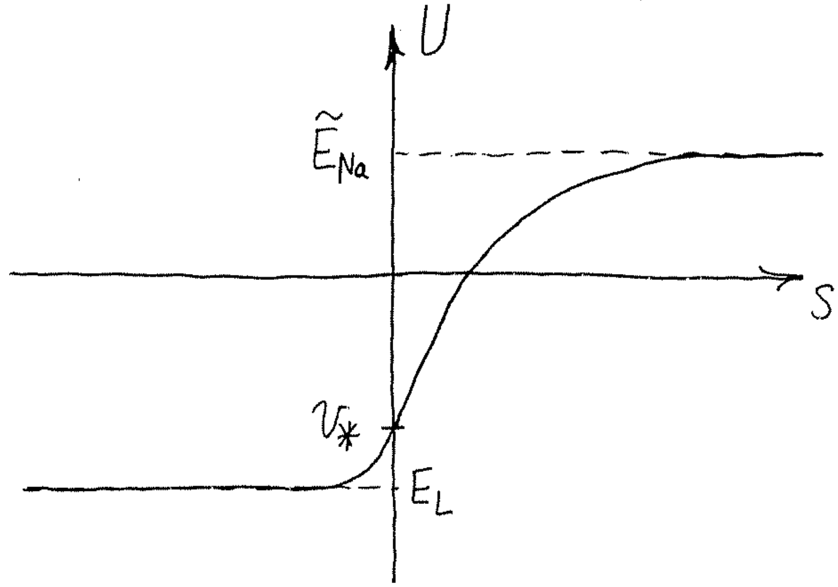
$$N_0=\lim_{\varepsilon\to 0} N(\varepsilon S)=0$$

$$M=\begin{cases}1 & S>0\\ 0 & S<0\end{cases}$$

Hence

$$-\frac{a}{2\rho\theta^2}U''+CU'+\bar{g}_{Na}M(U-E_{Na})+\bar{g}_L(U-E_L)=0$$

We seek a solution of the following form:



where
$$\tilde{E}_{Na} = \frac{\bar{g}_{Na} E_{Na} + \bar{g}_L E_L}{\bar{g}_{Na} + \bar{g}_L}$$

That is

$$U(S) = \begin{cases} E_L + (v_* - E_L)\exp(\lambda S) & S < 0 \\ \tilde{E}_{Na} + (v_* - \tilde{E}_{Na})\exp(\mu S) & S > 0 \end{cases}$$

where λ is the <u>positive</u> root of
$$-\frac{a}{2\rho\theta^2}\lambda^2 + C\lambda + \bar{g}_L = 0$$
and μ is the <u>negative</u> root of
$$-\frac{a}{2\rho\theta^2}\mu^2 + C\mu + (\bar{g}_{Na} + \bar{g}_L) = 0$$

It follows that

$$\lambda = \frac{\rho\theta^2 C}{a}\left(1 + \sqrt{1 + \frac{2a\bar{g}_L}{\rho\theta^2 C^2}}\right)$$

$$\mu = \frac{\rho\theta^2 C}{a}\left(1 - \sqrt{1 + \frac{2a(\bar{g}_L + \bar{g}_{Na})}{\rho\theta^2 C^2}}\right)$$

Note: The reason for choosing $\lambda > 0$ and $\mu < 0$ is to keep the solution bounded as $S \to \mp\infty$.

Because the equation for U is second-order, we require

$$U'(0^-) = U'(0^+)$$

$$(v_* - E_L)\lambda = (v_* - \tilde{E}_{Na})\mu = (\tilde{E}_{Na} - v_*)(-\mu)$$

$$\frac{\lambda}{-\mu} = \frac{\tilde{E}_{Na} - v_*}{v_* - E_L} = r$$

$$\frac{\sqrt{1 + \frac{2a\bar{g}_L}{\rho\theta^2 C^2}} + 1}{\sqrt{1 + \frac{2a(\bar{g}_L + \bar{g}_{Na})}{\rho\theta^2 C^2}} - 1} = r$$

Solve for θ as follows:

let

$$A = \sqrt{1 + \frac{2a\,\bar{g}_L}{\rho\theta^2 C^2}}$$

$$B = \sqrt{1 + \frac{2a(\bar{g}_L + \bar{g}_{Na})}{\rho\theta^2 C^2}}$$

Then

$$\frac{A+1}{B-1} = r \qquad \Rightarrow \qquad A - rB = -r - 1$$

and

$$\frac{A^2-1}{B^2-1} = \frac{\bar{g}_L}{\bar{g}_L + \bar{g}_{Na}} = \alpha$$

$$\left(\frac{A-1}{B+1}\right)\left(\frac{A+1}{B-1}\right) = \alpha$$

$$\frac{A-1}{B+1}\, r = \alpha \qquad \Rightarrow \qquad rA - \alpha B = r + \alpha$$

$$A = \frac{\alpha r + \alpha + r^2 + \alpha r}{r^2 - \alpha} = \frac{r^2 + 2\alpha r + \alpha}{r^2 - \alpha}$$

$$B = \frac{r + \alpha + r^2 + r}{r^2 - \alpha} = \frac{r^2 + 2r + \alpha}{r^2 - \alpha}$$

Check:

$$A+1 = \frac{2r^2+2\alpha r}{r^2-\alpha} \qquad A-1 = \frac{2\alpha r + 2\alpha}{r^2-\alpha}$$

$$B+1 = \frac{2r^2+2r}{r^2-\alpha} \qquad B-1 = \frac{2r+2\alpha}{r^2-\alpha}$$

$$\frac{A+1}{B-1} = \frac{2r(r+\alpha)}{2(r+\alpha)} = r \quad \checkmark$$

$$\frac{A-1}{B+1} = \frac{2\alpha(r+1)}{2r(r+1)} = \frac{\alpha}{r} \quad \checkmark$$

Now solve for θ from A or B. For example

$$\theta^2 = \frac{2a(\bar{g}_L+\bar{g}_{Na})}{\rho C^2}\,\frac{1}{B^2-1}$$

$$= \frac{2a(\bar{g}_L+\bar{g}_{Na})}{\rho C^2}\,\frac{(r^2-\alpha)^2}{2r(r+1)\,2(r+\alpha)}$$

$$= \frac{a(\bar{g}_L+\bar{g}_{Na})}{2\rho C^2}\,\frac{(r^2-\alpha)^2}{r(r+1)(r+\alpha)}$$

Note: This formula for θ^2 is only valid when $r^2 > \alpha$.

If $r^2 \leq \alpha$, there is no solution. To see this recall that

$$r = \frac{A+1}{B-1}$$

$$\frac{r}{\alpha} = \frac{B+1}{A-1}$$

$$\frac{r^2}{\alpha} = \frac{A+1}{A-1}\,\frac{B+1}{B-1} > 1 \qquad (\text{since } A > 1 \text{ and } B > 1)$$

In summary, for $r^2 > \alpha$

$$\theta = \pm\,(r^2 - \alpha)\sqrt{\frac{a\,(\bar{g}_L + \bar{g}_{Na})}{2\rho C^2\, r(r+1)(r+\alpha)}}$$

where

$$r = \frac{\tilde{E}_{Na} - v_*}{v_* - E_L}$$

"Inner solution" valid near $T=T_1$. Let $T=T_1+\varepsilon S$

$$V(T)=V(T_1+\varepsilon S)=U(S)$$

$$U'(S)=\varepsilon V'(T_1+\varepsilon S) \qquad U''(S)=\varepsilon^2 V''(T_1+\varepsilon S)$$

Substitute and then let $\varepsilon \to 0$:

$$-\frac{a}{2\rho\theta^2}U''+CU'+\overline{g}_{Na}MH_1(U-E_{Na})$$
$$+\overline{g}_K N_1^4(U-E_K)+\overline{g}_L(U-E_L)=0$$

where

$$H_1=\lim_{\varepsilon\to 0}H(T_1+\varepsilon S)=\exp\left(-\frac{T_1}{\tau_h}\right)$$

$$N_1=\lim_{\varepsilon\to 0}N(T_1+\varepsilon S)=1-\exp\left(-\frac{T_1}{\tau_n}\right)$$

$$M=\begin{cases}1, & S<0\\ 0, & S>0\end{cases}$$

Let

$$g_1 = \overline{g}_K N_1^4 + \overline{g}_L$$

$$g_1^+ = \overline{g}_{Na} H_1 + \overline{g}_K N_1^4 + \overline{g}_L$$

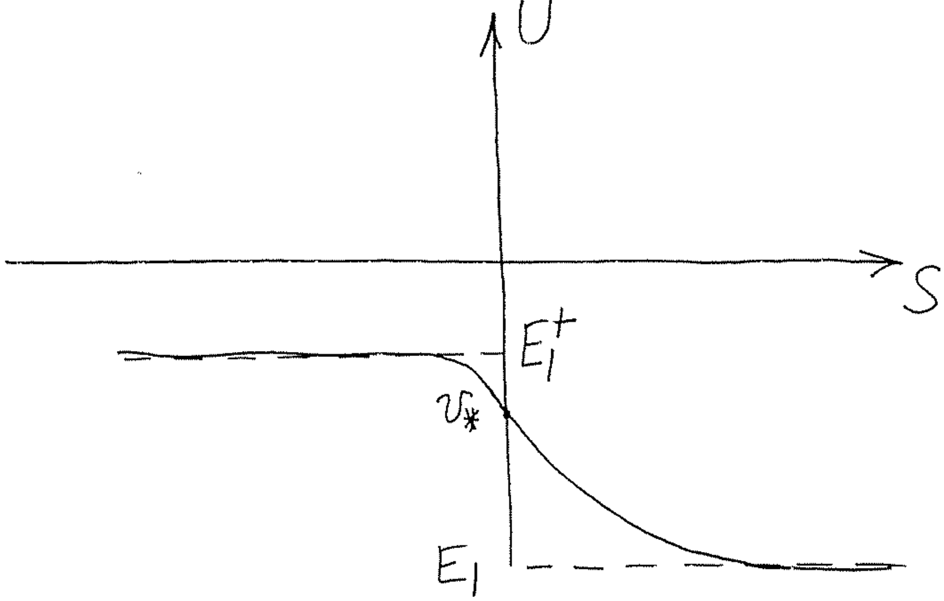
$$E_1 = \frac{\overline{g}_K N_1^4 E_K + \overline{g}_L E_L}{\overline{g}_K N_1^4 + \overline{g}_L}$$

$$E_1^+ = \frac{\overline{g}_{Na} H_1 E_{Na} + \overline{g}_K N_1^4 E_K + \overline{g}_L E_L}{\overline{g}_{Na} H_1 + \overline{g}_K N_1^4 + \overline{g}_L}$$

Then

$$-\frac{a}{2\rho\theta^2} U'' + C U' + \begin{Bmatrix} g_1^+(U - E_1^+) & S<0 \\ g_1(U - E_1) & S>0 \end{Bmatrix} = 0$$

Look for a solution of the following form



$$U(S) = \begin{cases} E_1^+ + (v_* - E_1^+)\exp(\lambda S) & S<0 \\ E_1 + (v_* - E_1)\exp(\mu S) & S>0 \end{cases}$$

where λ is the <u>positive</u> root of

$$-\frac{a}{2\rho\theta^2}\lambda^2 + C\lambda + g_1^+ = 0$$

and μ is the <u>negative</u> root of

$$-\frac{a}{2\rho\theta^2}\mu^2 + C\mu + g_1 = 0$$

Thus
$$\lambda = \frac{\rho\theta^2 C}{a}\left(1+\sqrt{1+\frac{2ag_1^+}{\rho\theta^2 C^2}}\right)$$
$$\mu = \frac{\rho\theta^2 C}{a}\left(1-\sqrt{1+\frac{2ag_1}{\rho\theta^2 C^2}}\right)$$

Match slopes at $S=0$:
$$U'(0^-) = U'(0^+)$$
$$(V_* - E_1^+)\lambda = (V_* - E_1)\mu$$
$$\frac{\lambda}{-\mu} = \frac{V_* - E_1}{E_1^+ - V_*} = r_1 \qquad \text{(This defines } r_1\text{)}$$

Then:
$$\frac{\sqrt{1+\frac{2ag_1^+}{\rho\theta^2 C^2}}+1}{\sqrt{1+\frac{2ag_1}{\rho\theta^2 C^2}}-1} = r_1$$

This equation determines T_1 (see below)

How does $r_1 = \dfrac{v_* - E_1}{E_1^+ - v_*}$ depend on T_1 ?

It is easy to check that

i) E_1 is decreasing

$E_1(0) = E_L < v_*$

Hence $E_1(T_1) < v_*$ for all T_1

ii) E_1^+ is decreasing

$E_1^+(0) = \tilde{E}_{Na} > v_*$ $\qquad$ $E_1^+(\infty) = \dfrac{\bar{g}_K E_K + \bar{g}_L E_L}{\bar{g}_K + \bar{g}_L} < v_*$

Hence there is some T_1^* for which

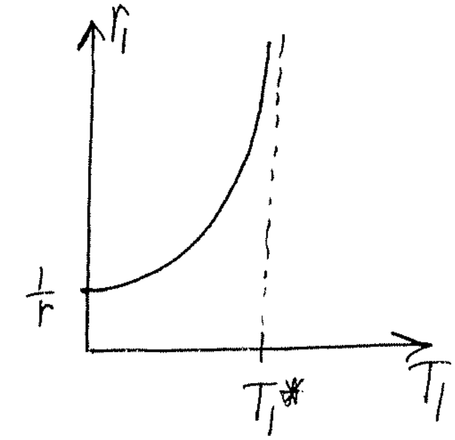
$$E_1^+(T_1^*) = v_*$$

It follows that:

$$r_1(0) = \frac{v_* - E_L}{\tilde{E}_{Na} - v_*} = \frac{1}{r}$$

r_1 is increasing

r_1 blows up at $T_1 = T_1^*$



Let

$$f_1(T_1) = \frac{\sqrt{1 + \dfrac{2a g_1^{+}(T_1)}{\rho \theta^2 C^2}} + 1}{\sqrt{1 + \dfrac{2a g_1(T_1)}{\rho \theta^2 C^2}} - 1}$$

First, note that

$$f_1(0) = \frac{\sqrt{1 + \dfrac{2a(\bar{g}_{Na} + \bar{g}_L)}{\rho \theta^2 C^2}} + 1}{\sqrt{1 + \dfrac{2a \bar{g}_L}{\rho \theta^2 C^2}} - 1}$$

$$> \frac{\sqrt{1 + \dfrac{2a(\bar{g}_{Na} + \bar{g}_L)}{\rho \theta^2 C^2}} - 1}{\sqrt{1 + \dfrac{2a \bar{g}_L}{\rho \theta^2 C^2}} + 1} = \frac{1}{r} = r_1(0)$$

We have shown that $f_1(0) > r_1(0)$

Next consider $f_1'(T_1)$. We have the following properties

$$g_1^+(T_1) > g_1(T_1) \qquad \text{(because of } g_{Na}\text{)}$$

$$(g_1^+)'(T_1) < g_1'(T_1) \qquad \text{(because } g_{Na} \text{ is decreasing)}$$

$$0 < g_1'(T_1) \qquad \text{(because of } g_K\text{)}$$

It follows that $f_1'(T_1) < 0$. To show this, let

$$A_1 = \sqrt{1 + \frac{2a\, g_1^+(T_1)}{\rho\theta^2 C^2}}$$

$$B_1 = \sqrt{1 + \frac{2a g_1}{\rho\theta^2 C^2}}$$

$$f_1 = \frac{A_1 + 1}{B_1 - 1}$$

$$f_1' = \frac{(B_1 - 1)A_1' - (A_1 + 1)B_1'}{(B_1 - 1)^2}$$

Now
$$A_1' = \frac{a}{\rho\theta^2 C^2} \frac{1}{A_1} (g_1^+)'$$

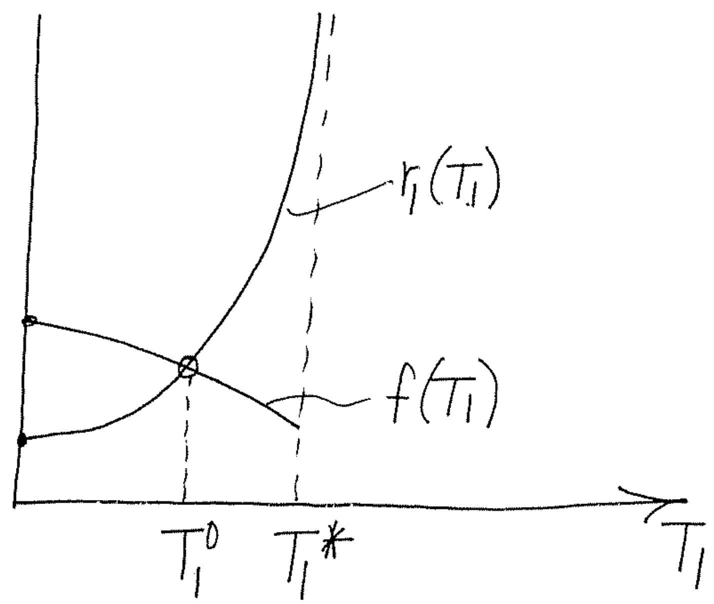
$$B_1' = \frac{a}{\rho\theta^2 C^2} \frac{1}{B_1} g_1'$$

$$f_1' = \frac{a}{\rho\theta^2 C^2 (B_1-1)^2} \left[\frac{(B_1-1)}{A_1} (g_1^+)' - \frac{(A_1+1)}{B_1} g_1' \right]$$

Now:
$$B_1 < A_1$$
$$B_1 - 1 < A_1 + 1$$
$$\frac{B_1-1}{A_1} < \frac{A_1+1}{B_1}$$
and $(g_1^+)' < g_1'$

Hence $f_1' < 0$ as claimed

We have shown that there is a unique T_1^0 for which
$f_1(T_1^0) = r_1(T_1^0)$:

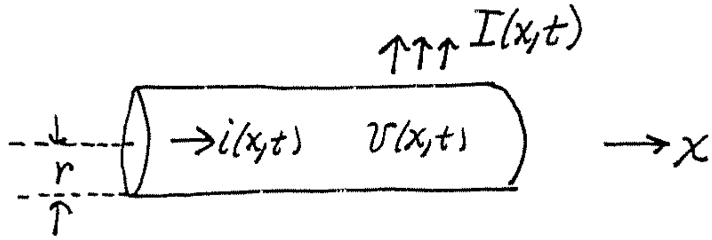


Thus $T_1 = T_1^0$ is the duration of the pulse. Note that $T_1^0 < T_1^*$, the time at which the excited state would reach threshhold. The pulse "jumps" across threshhold on the downstroke just as on the upstroke. (It looks more and more like a jump as $\varepsilon \to 0$!)

C. Peskin 11/5/98

NUMERICAL SOLUTION OF THE THE HODGKIN-HUXLEY EQUATIONS

Derivation of the Cable equation*:



$i(x,t)$ = axial current
$I(x,t)$ = transmembrane current (positive outward)
$v(x,t)$ = transmembrane voltage (inside − outside)
r = radius of cable

Current conservation:

$$i(x_1,t) - i(x_2,t) = \int_{x_1}^{x_2} I(x,t)\, 2\pi r\, dx \qquad (1)$$

$$0 = \int_{x_1}^{x_2} \left(\frac{\partial i}{\partial x} + I\, 2\pi r \right) dx \qquad (2)$$

Since x_1 and x_2 are arbitrary

$$\frac{\partial i}{\partial x} + I\, 2\pi r = 0 \qquad (3)$$

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* First few pages here repeat earlier material, but are included to fix notation, which is slightly different.

Equation of transmembrane current:

$$I = C\frac{\partial v}{\partial t} + g(v-E) \qquad (4)$$

where C = capacitance per unit area of membrane
g = conductance per unit area of membrane
E = reversal potential (see below)

Equation of axial current

$$i = -\frac{\pi r^2}{\rho}\frac{\partial v}{\partial x} \qquad (5)$$

where ρ = resistivity of internal medium.

Substituting I and i into the equation of charge conservation. The result is

$$C\frac{\partial v}{\partial t} + g(v-E) = \frac{r}{2\rho}\frac{\partial^2 v}{\partial x^2} \qquad (6)$$

Ionic current:

The ionic transmembrane current, denoted above as $g(v-E)$ actually has three components that flow through different membrane channels:

$$g(v-E) = g_{Na}(v-E_{Na}) + g_K(v-E_K) + g_L(v-E_L) \tag{7}$$

The first two are carried by Na^+ and K^+ ions, respectively. The third type of ion channel is less specific and is denoted by the subscript L, for "Leakage." From Eq. 7, we have

$$g = g_{Na} + g_K + g_L \tag{8}$$

$$E = \frac{g_{Na}E_{Na} + g_K E_K + g_L E_L}{g_{Na} + g_K + g_L} \tag{9}$$

The quantities E_{Na}, E_K, and E_L are constants. They are known as "equilibrium potentials" in the case of channels that admit only one species of ion like the Na^+ and K^+ channels. More generally, these constants are called "reversal potentials." They describe the voltage that must be applied to counterbalance the concentration difference of ions across the channels, and thus yield zero current.

In the case of a channel that admits only one species of ion, it can be shown from thermodynamic considerations that the equilibrium potential is given by the Nernst equation

$$E_{Na} = \frac{kT}{q} \log \frac{[Na^+]_o}{[Na^+]_i} \tag{10}$$

$$E_K = \frac{kT}{q} \log \frac{[K^+]_o}{[K^+]_i} \tag{11}$$

where

k = Boltzmann's constant
T = absolute temperature
q = charge on a proton

$\log$ = natural logarithm
$[\ ]_o$ = concentration outside cell
$[\ ]_i$ = concentration inside cell

For less specific ion channels, the situation is more complicated, but one can still measure the voltage at which the current is zero, and that defines the reversal potential.

In typical neurons, the flow of current during an action potential is not sufficient to change the ion concentrations appreciably. Therefore, the quantities E_{Na}, E_K, and E_L may be treated as constants. These constants satisfy

$$E_K < E_{rest} < E_L < 0 < E_{Na} \qquad (12)$$

where $E_{rest} = -70$ mV is the rest potential of the neuron.

<u>Dynamics of the conductances:</u>

The conductances g_{Na}, g_K, and g_L obey the following equations:

$$g_{Na} = \overline{g_{Na}}\, m^3 h \qquad (13)$$

$$g_K = \overline{g_K}\, n^4 \qquad (14)$$

$$g_L = \overline{g_L} \qquad (15)$$

where

$$\frac{\partial m}{\partial t} = \alpha_m(v)(1-m) - \beta_m(v)m \qquad (16)$$

$$\frac{\partial h}{\partial t} = \alpha_h(v)(1-h) - \beta_h(v)h \qquad (17)$$

$$\frac{\partial n}{\partial t} = \alpha_n(v)(1-n) - \beta_n(v)n \qquad (18)$$

where $\overline{g_{Na}}, \overline{g_K}, \overline{g_L}$ are given constants, and where

$\alpha_m, \beta_m, \alpha_h, \beta_h, \alpha_n, \beta_n$ are given functions

The following model of a K^+ channel was proposed by Hodgkin and Huxley as a way of understanding Eqs. 14 and 18:

i) Each K^+ channel contains 4 identical gates
ii) The gates open and close independently of each other
iii) The rate constants for opening and closing a gate are voltage-dependent:

$$\text{CLOSED} \underset{\beta_n(v)}{\overset{\alpha_n(v)}{\rightleftharpoons}} \text{OPEN}$$

iv) The K^+ channel as a whole is open if and only if all four gates are open.

If we then let n = probability that a gate is open, and if we consider a large population of channels, Eqs. 14 and 18 follow.

Similarly, Eqs. 13,16,17, which describe the population of Na^+ channels, can be understood in terms of the following model, proposed by Hodgkin and Huxley:

i) Each Na^+ channel contains 4 gates: 3 "m-gates" and 1 "h-gate."

ii) All four gates open and close independently of each other.

iii) The rate constants for opening and closing a gate are voltage dependent, with different voltage dependence for the m-gates and the h-gates. (Indeed, that is what distinguishes them from each other.)

m-gates (3): $\text{CLOSED} \underset{\beta_m(V)}{\overset{\alpha_m(V)}{\rightleftharpoons}} \text{OPEN}$

h-gate (1): $\text{CLOSED} \underset{\beta_h(V)}{\overset{\alpha_h(V)}{\rightleftharpoons}} \text{OPEN}$

iv) The Na^+ channel as a whole is open if and only if all four gates are open.

If we then let

m = probability that an m-gate is open
h = probability that an h-gate is open

and consider a large population of channels, Eqs. 13,16,17 follow.

Summary of the Hodgkin-Huxley equations:

$$C\frac{\partial v}{\partial t} + g(v-E) = \frac{r}{2\rho}\frac{\partial^2 v}{\partial x^2} \qquad (19)$$

$$g = g_{Na} + g_K + g_L \qquad (20)$$

$$E = \frac{g_{Na}E_{Na} + g_K E_L + g_L E_L}{g_{Na} + g_K + g_L} \qquad (21)$$

$$g_{Na} = \overline{g_{Na}}\, m^3 h \qquad (22)$$

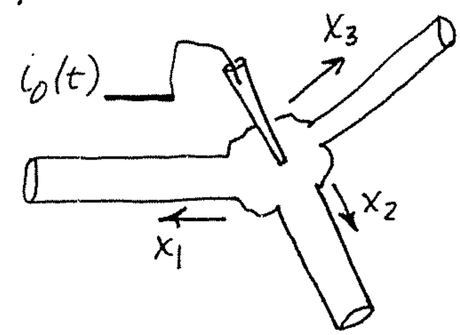
$$g_K = \overline{g_K}\, n^4 \qquad (23)$$

$$g_L = \overline{g_L} \qquad (24)$$

$$\frac{\partial s}{\partial t} = \alpha_s(v)(1-s) - \beta_s(v)s \qquad (25)$$

where $s = m, h,$ or n

Boundary conditions



$L = 3$

Consider a junction at which L cables come together, numbered $l = 1 \cdots L$. There may be a cell body or other varicosity at the junction which we designate by the subscript 0; in particular its membrane area is A_0, and the current injected at the junction (if any) is denoted $i_0(t)$. This current could be an experimental stimulus, as shown above, or a synaptic current. For simplicity of notation, we assume that x is measured away from the junction in all of the cables that meet there. Thus, the junction itself is given by $x_1 = \cdots = x_L = 0$.

The boundary conditions are that the voltage is continuous and the currents add up:

$$v_0(t) = v_1(0,t) = v_2(0,t) = \cdots = v_L(0,t) \qquad (26)$$

$$i_0(t) = A_0\left(C\frac{\partial v_0}{\partial t} + g_0(v_0 - E_0)\right) + \sum_{l=1}^{L}\left(-\frac{\pi r_l^2}{\rho}\right)\frac{\partial v_l}{\partial x_l}(0,t)$$

(27)

In Eq. 27, g_0 and E_0 are not constants. Instead, they are given by equations like Eqs. 20-25. Details of these equations may be different in different branches, and also different in the cell body (or other varicosity).

There are many special cases of the above boundary conditions that cover different situations of interest:

i) If no current is applied, $i_0(t) = 0$.

ii) If there is no cell body or varicosity at a junction, $A_0 = 0$.

iii) At the terminal end of a branch, $A_0 = 0$ and $L = 1$.

iv) If current is applied in the interior of a branch, the point where it is applied can be regarded as a junction between two branches with identical properties. Thus $L = 2$, $r_1 = r_2$, $A_0 = 0$.

Initial conditions

Initial data for the Hodgkin-Huxley equations are the values of v, m, h, n at $t=0$. That is, we need to specify

$$v(x,0),\ m(x,0),\ h(x,0),\ n(x,0)$$

In an important special case, the neuron is initially "at rest." This means that $v(x,0)=v_r$, where v_r is a constant, the determination of which will be discussed below. The corresponding values of m,h,n are found by setting $\partial m/\partial t = \partial h/\partial t = \partial n/\partial t = 0$ with $v = v_r$. The results may be summarized:

$$s_r = s_\infty(v_r) \tag{28}$$

where

$$s_\infty(v) = \frac{\alpha_s(v)}{\alpha_s(v)+\beta_s(v)} \tag{29}$$

and $s = m,h,n$. Then v_r itself is the solution of $\partial v/\partial t = 0$, or

$$v_r = E_r = \frac{\bar{g}_{Na}\,(m_\infty(v_r))^3 h_\infty(v_r)\,E_{Na} + \bar{g}_K (n_\infty(v_r))^4 E_K + \bar{g}_L E_L}{\bar{g}_{Na}\,(m_\infty(v_r))^3 h_\infty(v_r) + \bar{g}_K (n_\infty(v_r))^4 + \bar{g}_L}$$

(30)

Numerical method for the Hodgkin-Huxley equations

let

$$v_j^k = v(j\Delta x, k\Delta t) \tag{31}$$

$$s_j^{k+1/2} = s(j\Delta x, (k+\tfrac{1}{2})\Delta t) \tag{32}$$

where $s = m, h, n$, and similarly for other variables related to m, h, n. Then let

$$\frac{s_j^{k+1/2} - s_j^{k-1/2}}{\Delta t} = \alpha_s(v_j^k)\left(1 - \frac{s_j^{k+1/2} + s_j^{k-1/2}}{2}\right)$$

$$- \beta_s(v_j^k)\left(\frac{s_j^{k+1/2} + s_j^{k-1/2}}{2}\right) \tag{33}$$

$$C\,\frac{v_j^{k+1} - v_j^k}{\Delta t} + g_j^{k+1/2}\left(\frac{v_j^{k+1} + v_j^k}{2} - E_j^{k+1/2}\right)$$

$$= \frac{r}{2\rho}\left(D^+D^-\,\frac{v^{k+1} + v^k}{2}\right)_j \tag{34}$$

where

$$\left(D^{+}\phi\right)_j = \frac{\phi_{j+1} - \phi_j}{\Delta x} \tag{35}$$

$$\left(D^{-}\phi\right)_j = \frac{\phi_j - \phi_{j-1}}{\Delta x} \tag{36}$$

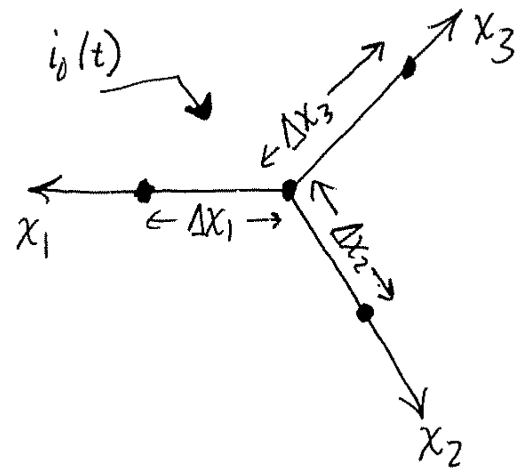
So that

$$\left(D^{+}D^{-}\phi\right)_j = \left(D^{-}D^{+}\phi\right)_j = \frac{\phi_{j+1} + \phi_{j-1} - 2\phi_j}{(\Delta x)^2} \tag{37}$$

Eqs. 33 are to be solved for $S_j^{k+1/2}$, and Eqs. 34 are to be solved for v_j^{k+1}.

Note that in Eqs. 33, the unknowns at different j are uncoupled, but in Eqs. 34 they are coupled through the operator $D^{+}D^{-}$. Thus Eq. 34 is a <u>system</u> to be solved simultaneously for all of the v_j at the particular time $(k+1)\Delta t$. This system is not completely specified, however, until we consider boundary conditions. (Eq. 34 only makes sense for interior points.)

Discretization of the boundary (junction) conditions



Since the voltage is continuous at a junction, we only need one node there. Let the junction voltage be denoted $v_0(t)$. This takes care of Eq. 26.

In order to discretize Eq. 27, we need a formula for $\frac{\partial v_\ell}{\partial x_\ell}(0,t)$. This is found from Taylor series:

$$v_\ell(\Delta x_\ell, t) = v_\ell(0,t) + \Delta x_\ell \frac{\partial v_\ell}{\partial x_\ell}(0,t) + \frac{1}{2}(\Delta x_\ell)^2 \frac{\partial^2 v_\ell}{\partial x_\ell^2}(0,t) + O\left((\Delta x_\ell)^3\right) \qquad (38)$$

Note that the cable equation (Eq. 19) may be solved for $\frac{\partial^2 v_\ell}{\partial x_\ell^2}$:

$$\frac{\partial^2 v_\ell}{\partial x_\ell^2} = \frac{2\rho}{r_\ell}\left(C\frac{\partial v_\ell}{\partial t} + g_\ell\left(v_\ell - E_\ell\right)\right) \qquad (39)$$

Substitute Eq. 39 into Eq. 38, and solve for $\frac{\partial v_\ell}{\partial x_\ell}(0,t)$.

$$\frac{\partial v_\ell}{\partial x_\ell}(0,t) = \frac{v_{\ell 1} - v_0}{\Delta x_\ell} - \frac{2\Delta x_\ell \rho}{2 r_\ell}\left(C\frac{\partial v_0}{\partial t} + g_{\ell 0}\left(v_0 - E_{\ell 0}\right)\right)$$

$$+ O\left(\left(\Delta x_\ell\right)^2\right) \qquad (40)$$

Substitute this result into Eq. 27 and collect terms:

$$i_0(t) = \tilde{A}_0\left(C\frac{\partial v_0}{\partial t} + \tilde{g}_0\left(v_0 - \tilde{E}_0\right)\right)$$

$$+ \sum_{\ell=1}^{L}\left(-\frac{\pi r_\ell^2}{\rho}\right)\frac{v_{\ell 1} - v_0}{\Delta x_\ell}$$

$$+ O\left(\left(\Delta x\right)^2\right) \qquad (41)$$

where

$$\tilde{A}_0 = A_0 + \sum_{l=1}^{L} \frac{1}{2}\left(2\pi r_l \Delta x_l\right)$$

$$\tilde{g}_0 = \frac{A_0 g_0 + \sum_{l=1}^{L} \frac{1}{2}\left(2\pi r_l \Delta x_l\right) g_{l0}}{\tilde{A}_0}$$

$$\tilde{E}_0 = \frac{A_0 g_0 E_0 + \sum_{l=1}^{L} \frac{1}{2}\left(2\pi r_l\right)\Delta x_l \, g_{l0} E_{l0}}{\tilde{A}_0 \tilde{g}_0}$$

and where we have assumed that all the Δx_l are the same order of magnitude, denoted $O(\Delta x)$.

Our boundary or junction condition will be Eq. 41 with the $O((\Delta x)^2)$ term deleted, and also discretized with respect to time:

$$i_0^{k+1/2} = \tilde{A}_0\left(C\,\frac{v_0^{k+1}-v_0^{k}}{\Delta t} + \tilde{g}_0^{k+1/2}\left(\frac{v_0^{k+1}+v_0^{k}}{2} - \tilde{E}_0^{k+1/2}\right)\right)$$

$$+\sum_{l=1}^{L}\left(-\frac{\pi r_l^2}{\rho}\right)\frac{\left(\frac{v_{l1}^{k+1}+v_{l1}^{k}}{2}\right)-\left(\frac{v_0^{k+1}+v_0^{k}}{2}\right)}{\Delta x_l}$$

(42)

Like the interior equations, this couples the junction point to its immediate neighbors only.

Next, we consider the solution of the resulting system of equations for v^{k+1}.

Generalized tridiagonal system on a tree of nodes

Consider an arbitrary connected graph $\mathcal{G}$ with no loops.

Let the nodes of $\mathcal{G}$ be numbered $1 \cdots N$, and let node 1 be called the root. (This can be any node of the graph; we choose it arbitrarily.

Now consider some specified node i, where $i \neq 1$. Since $\mathcal{G}$ is connected, it is possible to find a chain of nodes connecting node 1 and node i. This is a sequence of node indices

$$\left(1, n_1, n_2, \cdots, i\right)$$

such that the first element is 1, the last is i, there are no repetitions, and any two successive nodes in the chain are neighbors in $\mathcal{G}$.

Since $\mathcal{G}$ has no loops, the chain of nodes connecting node 1 and node i is unique.

Let $R(i)$ be the node that immediately precedes i in this chain. Then $R(i)$ is the "rootward neighbor" of node i. This defines $R(i)$ for all $i \neq 1$. By convention, we say that $R(1)=0$.

Let $\mathcal{L}(i)$ be the <u>set</u> of all neighboring nodes of node i <u>except</u> $R(i)$. These will be called the "leafward" neighbors of node i. A node i is said to be a "leaf" if it has no leafward neighbors; that is, if $\mathcal{L}(i) = \phi$.

Thus, by choosing a <u>root</u>, we have made the graph $\mathcal{G}$ into a <u>tree</u>. This was only possible, of course, because $\mathcal{G}$ has no loops.

Now a <u>generalized tridiagonal system</u> on the tree defined above is a linear system of equations of the form

$$-a_i V_{R(i)} + b_i V_i - \sum_{j \in \mathcal{L}(i)} \bar{c}_{ij} V_j = W_j$$

$$i = 1 \cdots N \tag{43}$$

where $a_1 = 0$ and where the summation is understood to yield 0 when $\mathcal{L}(i) = \phi$.

An important simplification of the notation can be made by noting that

$$j \in \mathcal{L}(i) \iff i = R(j) \tag{44}$$

Thus, for $j \in \mathcal{L}(i)$

$$\bar{c}_{ij} = \bar{c}_{R(j),j} \tag{45}$$

which is a function of j only. Thus we may write

$$\bar{c}_{ij} = c_j \tag{46}$$

and our linear system becomes

$$-a_i V_{R(i)} + b_i V_i - \sum_{j \in \mathcal{L}(i)} c_j V_j = W_j \tag{47}$$

for $i = 1 \cdots N$. This system is solved by reducing it to a pair of generalized bidiagonal systems:

$$b_i' U_i - \sum_{j \in \mathcal{L}(i)} c_j' U_j = W_i \qquad (48)$$

$$-a_i' V_{R(i)} + V_i \qquad = U_i \qquad (49)$$

where the a_i', b_i', and c_j' are to be determined so that Eqs. 48–49 are equivalent to Eq. 47.

To find out how these new coefficients are related to the original a_i, b_i, c_j, we substitute Eq. 49 into Eq. 48, and collect terms

$$b_i'\left(-a_i' V_{R(i)} + V_i\right) - \sum_{j \in \mathcal{L}(i)} c_j'\left(-a_j' V_{R(j)} + V_j\right) = W_j \qquad (50)$$

$$-b_i' a_i' V_{R(i)} + \left(b_i' + \sum_{j \in \mathcal{L}(i)} c_j' a_j'\right) V_i$$

$$+ \sum_{j \in \mathcal{L}(i)} \left(-c_j' V_j\right) = W_j \qquad (51)$$

The crucial step in the foregoing was to notice that for $j \in \mathcal{L}(i)$, $R(j) = i$.

It is interesting to note that if instead of Eqs. 48–49, we had tried

$$-\tilde{a}_i' \tilde{U}_{R(i)} + \tilde{b}_i' \tilde{U}_i = W_i \quad (52)$$

$$\tilde{V}_i - \sum_{j \in \mathcal{L}(i)} \tilde{c}_j' \tilde{V}_j = \tilde{U}_i \quad (53)$$

we would not have been able to proceed. The reason can be seen when we substitute Eq. 53 into Eq. 52, to get

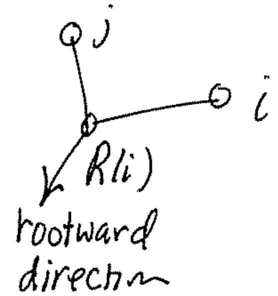
$$-\tilde{a}_i' \left(\tilde{V}_{R(i)} - \sum_{j \in \mathcal{L}(R(i))} \tilde{c}_j' \tilde{V}_j \right)$$

$$+ \tilde{b}_i' \left(\tilde{V}_i - \sum_{j \in \mathcal{L}(i)} \tilde{c}_j' \tilde{V}_j \right) = W_i \quad (54)$$

Eq. 54 is a dead end because

$$j \in \mathcal{L}(R(i)) \not\Rightarrow j = i \qquad (55)$$

as shown by the following counterexample



Returning now to Eq. 51, and comparing it to Eq. 47, we see that the two are indeed of the same form and moreover that they can be made identical if we can choose a_i', b_i', and c_j' to satisfy

$$a_i' b_i' = a_i \qquad (56)$$

$$b_i' + \sum_{j \in \mathcal{L}(i)} c_j' a_j' = b_i \qquad (57)$$

$$c_j' = c_j \qquad (58)$$

Of course, Eq. 58 is easily satisfied merely by dropping the primes on the c_j' and using instead the original coefficients c_j.

An algorithm will be stated below to find the a_i' and b_i' given the a_i and b_i. This algorithm depends on the nodes of the graph $\mathcal{G}$ being numbered in such a manner that

$$j \in \mathcal{I}(i) \Rightarrow j > i \qquad (59)$$

Such a numbering (of which there are many) can be found by induction. Start by assigning the number 1 to the root. Then, when the numbers $1 \cdots n$ have already been assigned, assign the number $n+1$ to any node that does not yet have a number and which is connected by an edge of $\mathcal{G}$ to some node that has already been numbered. Clearly, such a node exists since $\mathcal{G}$ is connected, unless of course, $n = N$ in which case we are done. Moreover, this procedure guarantees that

$$R(i) < i \qquad (60)$$

for all i. To see this, recall the definition of $R(i)$ as the node that immediately precedes i in the unique chain from the root to i. If

i were numbered before $R(i)$, this would mean that there is some other chain from the root to i, one that does not involve $R(i)$. This is impossible, by the hypothesis that G has no loops.

But

$$j \in \mathcal{L}(i) \Rightarrow R(j) = i \Rightarrow j > R(j) = i \Rightarrow j > i \quad (61)$$

where the second implication makes use of Eq. 60. Thus, we have proved Eq. 59. From now on, we assume that the nodes have been numbered in such a manner that Eq 59 is satisfied.

Then the following algorithm finds the a_i' and b_i', and moreover, it uses them to determine the U_i and finally the V_i :

for $i = N : (-1) : 1$

$$b_i' = b_i - \sum_{j \in \mathcal{L}(i)} c_j a_j'$$

$$a_i' = a_i / b_i'$$

$$U_i = \Big(W_i + \sum_{j \in \mathcal{L}(i)} c_j U_j \Big) / b_i'$$

end

$$V_1 = U_1$$

for $i = 2 : (+1) : N$

$$V_i = U_i + a_i' V_{R(i)}$$

end

Eqs. 59 and 60 guarantee that all quantities have already been computed by the time they are needed.

The efficient implementation of the above algorithm requires a good data structure for trees.

We shall call the nodes in the set $\mathcal{L}(i)$ the "children" of node i.

Note that each node j other than the root ($j=1$) is in exactly one of the sets $\mathcal{L}(i)$, namely $\mathcal{L}(R(j))$.

Let $\mathcal{S}(j) = \mathcal{L}(R(j))$. Eq. 62 This is the set of "siblings" of node j. Also let

$$\mathcal{S}_+(j) = \{k : k \in \mathcal{S}(j) \text{ and } k > j\} \tag{63}$$

We shall think of this as the set of "younger siblings" of node j. Now let:

$$fc(i) = \begin{cases} \mathrm{Min}(\mathcal{L}(i)), & \mathcal{L}(i) \neq \phi \\ 0, & \mathcal{L}(i) = \phi \end{cases} \tag{64}$$

$$ns(j) = \begin{cases} \mathrm{Min}(\mathcal{S}_+(j)), & \mathcal{S}_+(j) \neq \phi \\ 0, & \mathcal{S}_+(j) = \phi \end{cases} \tag{65}$$

Thus $fc(i)$ denotes the "first child" of node i, and $ns(j)$ denotes the "next sibling" of node j. The entire tree can be reconstructed from these two arrays.

We now write a matlab program that uses the arrays fc, ns, and R to implement the algorithm stated on page 26. This program stores a_i' in the same location as a_i, b_i' in the same location as b_i, and U_i and W_i in the same location as V_i.

The main point of interest is the "while" loop that computes the sums over $j \in \mathcal{L}(i)$.

```
for i = N:(-1):1
  j = fc(i)
  while (j ~= 0)
      b(i) = b(i) - c(j) * a(j)
      V(i) = V(i) + c(j) * V(j)
      j = ns(j)
  end
  a(i) = a(i)/b(i)
  V(i) = V(i)/b(i)
end
for j = 2:(+1):N
    V(i) = V(i) + a(i) * V(R(i))
end
```

Convergence of the proposed numerical method as applied to the cable equation on a periodic domain

In this section we consider the cable equation

$$C \frac{\partial v}{\partial t} + g(x,t)\big(v - E(x,t)\big) = \frac{r}{2\rho} \frac{\partial^2 v}{\partial x^2} \qquad (66)$$

on $0 \leq x \leq L$ with periodic boundary conditions, and $t > 0$. The functions $g(x,t)$ and $E(x,t)$ are here regarded as known. This is, of course, a big simplification of the Hodgkin-Huxley case, in which g and E have to be determined by solving for m, h, n, which are themselves influenced by the voltage. The initial data are

$$v(x,0) = v^0(x), \text{ a given function} \qquad (67)$$

The exact solution of the above problem, $v(x,t)$, also satisfies exactly the following difference scheme with remainder

$$C\frac{v^{n+1} - v^n}{\Delta t} + g^{n+1/2}\left(\frac{v^{n+1} + v^n}{2} - E^{n+1/2}\right)$$

$$= \frac{r}{2\rho} D^+D^- \frac{v^{n+1} + v^n}{2} + R^{n+1/2} \qquad (68)$$

Later, we shall use Taylor series to derive bounds on $R^{n+1/2}$, but for now we just regard it as some given function. Eq. 68 motivates the difference scheme

$$C\frac{V^{n+1}-V^{n}}{\Delta t}+g^{n+1/2}\left(\frac{V^{n+1}+V^{n}}{2}-E^{n+1/2}\right)$$

$$=\frac{r}{2\rho}D^{+}D^{-}\frac{V^{n+1}+V^{n}}{2} \qquad (69)$$

let

$$U=V-v \qquad (70)$$

so that U is the error. Subtracting Eq. 68 from Eq. 69, we see that U satisfies

$$C\frac{U^{n+1}-U^{n}}{\Delta t}+g^{n+1/2}\frac{U^{n+1}+U^{n}}{2}$$

$$=\frac{r}{2\rho}D^{+}D^{-}\frac{U^{n+1}+U^{n}}{2}-R^{n+1/2} \qquad (71)$$

Also, if we set $V^{0}=v^{0}$, then

$$U^{0}=0 \qquad (72)$$

At this point we need the inner product defined by

$$(\phi, \psi) = \sum_{j=0}^{N-1} \phi_j \psi_j \, \Delta x \qquad (73)$$

where $\Delta x = L/N$. Also, we shall use the corresponding norm

$$\| \phi \| = \sqrt{(\phi, \phi)} \qquad (74)$$

Taking periodicity into account, it is easy to show by "summation by parts" (shifting indices) that

$$(\phi, D^+ \psi) = -(D^- \phi, \psi) \qquad (75)$$

That is, D^+ and $(-D^-)$ are adjoint operators.

Applying this application, we take the inner product of both sides of Eq. 71 with $\frac{U^{n+1} + U^n}{2}$. The result is

$$\frac{C}{2\Delta t}\left(\|U^{n+1}\|^2 - \|U^n\|^2\right) + \left(\frac{U^{n+1}+U^n}{2}, g^{n+1/2}\frac{U^{n+1}+U^n}{2}\right)$$

$$= \frac{r}{2\sigma}\left(\frac{U^{n+1}+U^n}{2}, D^+D^-\frac{U^{n+1}+U^n}{2}\right) - \left(\frac{U^{n+1}+U^n}{2}, R^{n+1/2}\right)$$

(76)

Since $g \geq 0$

$$\left(\frac{U^{n+1}+U^n}{2}, g\frac{U^{n+1}+U^n}{2}\right) \geq 0 \tag{77}$$

Also

$$\left(\frac{U^{n+1}+U^n}{2}, D^+D^-\frac{U^{n+1}+U^n}{2}\right) = -\left\|D^-\frac{U^{n+1}+U^n}{2}\right\|^2 \leq 0$$

(78)

Therefore, with the help of the Schwarz inequality

$$\frac{C}{2\Delta t}\left(\|U^{n+1}\|^2 - \|U^n\|^2\right) \leq \left\|\frac{U^{n+1}+U^n}{2}\right\| \left\|R^{n+1/2}\right\| \tag{79}$$

$$C\left(\frac{\|U^{n+1}\| + \|U^n\|}{2}\right)\left(\frac{\|U^{n+1}\| - \|U^n\|}{\Delta t}\right) \leq \left\|\frac{U^{n+1}+U^n}{2}\right\| \left\|R^{n+1/2}\right\|$$

(80)

By the triangle inequality

$$\left\| \frac{U^{n+1}+U^{n}}{2} \right\| \le \frac{\|U^{n+1}\| + \|U^{n}\|}{2} \qquad (81)$$

So
$$\|U^{n+1}\| - \|U^{n}\| \le \frac{\Delta t}{C} \|R^{n+1/2}\| \qquad (82)$$

Recall $\|U^{0}\| = 0$. It then follows by induction that for $n\Delta t \le t_{max}$

$$\|U^{n}\| \le \frac{t_{max}}{C} \left(\max_{m:\,(m+1)\Delta t \le t_0} \|R^{m+1/2}\| \right) \qquad (83)$$

We now turn to the task of finding bounds on R. This is done using Taylor series with remainder. Let * denote the (unknown) time at which the remainder term is to be evaluated, and similarly, let $_*$ denote the (unknown) spatial location. Different instances of * or $_*$ may correspond to different values of t or x.

First, consider a Taylor series expansion in time about $(j\Delta x, (n+\frac{1}{2})\Delta t)$

$$v_j^{n+1} = v_j^{n+1/2} + \left(\frac{\Delta t}{2}\right)\left(\frac{\partial v}{\partial t}\right)_j^{n+1/2} + \frac{1}{2}\left(\frac{\Delta t}{2}\right)^2\left(\frac{\partial^2 v}{\partial t^2}\right)_j^{n+1/2} + \frac{1}{6}\left(\frac{\Delta t}{2}\right)^3\left(\frac{\partial^3 v}{\partial t^3}\right)_j^{*} \qquad (84)$$

$$v_j^{n} = v_j^{n+1/2} - \left(\frac{\Delta t}{2}\right)\left(\frac{\partial v}{\partial t}\right)_j^{n+1/2} + \frac{1}{2}\left(\frac{\Delta t}{2}\right)^2\left(\frac{\partial^2 v}{\partial t^2}\right)_j^{n+1/2} - \frac{1}{6}\left(\frac{\Delta t}{2}\right)^3\left(\frac{\partial^3 v}{\partial t^3}\right)_j^{*} \qquad (85)$$

It follows that

$$\frac{v_j^{n+1} - v_j^{n}}{\Delta t} = \left(\frac{\partial v}{\partial t}\right)_j^{n+1/2} + \frac{(\Delta t)^2}{48}\left(\left(\frac{\partial^3 v}{\partial t^3}\right)_j^{*} + \left(\frac{\partial^3 v}{\partial t^3}\right)_j^{*}\right) \qquad (86)$$

A similar argument shows that

$$\frac{v_j^{n+1} + v_j^{n}}{2} = v_j^{n+1/2} + \frac{(\Delta t)^2}{16}\left(\left(\frac{\partial^2 v}{\partial t^2}\right)_j^{*} + \left(\frac{\partial^2 v}{\partial t^2}\right)_j^{*}\right) \qquad (87)$$

Next, considering a Taylor series expansion in space about the ~~same~~ point $(j\Delta x, (n)\Delta t)$, we have

$$v_{j+1}^{n} = v_j^{n} + (\Delta x)\left(\frac{\partial v}{\partial x}\right)_j^n + \frac{1}{2}(\Delta x)^2\left(\frac{\partial^2 v}{\partial x^2}\right)_j^n$$

$$+ \frac{1}{6}(\Delta x)^3\left(\frac{\partial^3 v}{\partial x^3}\right)_j^n + \frac{1}{24}(\Delta x)^2\left(\frac{\partial^4 v}{\partial x^4}\right)_*^n \quad (88)$$

$$v_{j-1}^{n} = v_j^{n} - (\Delta x)\left(\frac{\partial v}{\partial x}\right)_j^n + \frac{1}{2}(\Delta x)^2\left(\frac{\partial^2 v}{\partial x^2}\right)_j^n$$

$$- \frac{1}{6}(\Delta x)^3\left(\frac{\partial^3 v}{\partial x^3}\right)_j^n + \frac{1}{24}(\Delta x)^2\left(\frac{\partial^4 v}{\partial x^4}\right)_*^n \quad (89)$$

It follows that

$$\frac{v_{j+1}^{n} + v_{j-1}^{n} - 2v_j^{n}}{(\Delta x)^2} = \left(\frac{\partial^2 v}{\partial x^2}\right)_j^n + \frac{(\Delta x)^2}{24}\left(\left(\frac{\partial^4 v}{\partial x^4}\right)_*^n + \left(\frac{\partial^4 v}{\partial x^4}\right)_*^n\right) \quad (90)$$

Of course, Eq. 90 also holds with n replaced by $n+1$:

$$\frac{v_{j+1}^{n+1} + v_{j-1}^{n+1} - 2v_j^{n+1}}{(\Delta x)^2} = \left(\frac{\partial^2 v}{\partial x^2}\right)_j^{n+1} + \frac{(\Delta x)^2}{24}\left(\left(\frac{\partial^4 v}{\partial x^4}\right)_*^{n+1} + \left(\frac{\partial^4 v}{\partial x^4}\right)_*^{n+1}\right), \quad (91)$$

Averaging Eq. 90 and Eq. 91, we get

$$\left(D^+D^-\frac{v^{n+1}+v^n}{2}\right)_j$$

$$= \frac{1}{2}\left(\left(\frac{\partial^2 v}{\partial x^2}\right)_j^{n+1} + \left(\frac{\partial^2 v}{\partial x^2}\right)_j^n\right)$$

$$+ \frac{(\Delta x)^2}{48}\left(\left(\frac{\partial^4 v}{\partial x^4}\right)_*^{n+1} + \left(\frac{\partial^4 v}{\partial x^4}\right)_*^{n+1} + \left(\frac{\partial^4 v}{\partial x^4}\right)_*^n + \left(\frac{\partial^4 v}{\partial x^4}\right)_{**}^n\right)$$

(92)

Note that Eq. 87 applies not only to v but also to $\partial^2 v/\partial x^2$. In this form, it reads

$$\frac{1}{2}\left(\left(\frac{\partial^2 v}{\partial x^2}\right)_j^{n+1} + \left(\frac{\partial^2 v}{\partial x^2}\right)_j^n\right)$$

$$= \left(\frac{\partial^2 v}{\partial x^2}\right)_j^{n+1/2} + \frac{(\Delta t)^2}{16}\left(\left(\frac{\partial^4 v}{\partial x^2 \partial t^2}\right)_j^{*} + \left(\frac{\partial^4 v}{\partial x^2 \partial t^2}\right)_j^{**}\right)$$

(93)

Substituting Eq. 93 into Eq. 92, we get

$$\left(D^+D^- \frac{v^{n+1}+v^n}{2}\right)_j = \left(\frac{\partial^2 v}{\partial x^2}\right)_j^{n+1/2} + \frac{(\Delta t)^2}{16}\left(\left(\frac{\partial^4 v}{\partial x^2 \partial t^2}\right)_j^* + \left(\frac{\partial^4 v}{\partial x^2 \partial t^2}\right)_j^*\right)$$
$$+ \frac{(\Delta x)^2}{48}\left(\left(\frac{\partial^4 v}{\partial x^4}\right)_*^{n+1} + \left(\frac{\partial^4 v}{\partial x^4}\right)_*^{n+1} + \left(\frac{\partial^4 v}{\partial x^4}\right)_*^{n} + \left(\frac{\partial^4 v}{\partial x^4}\right)_*^{n}\right) \quad (94)$$

Eq. 86 can be solved for $(\partial v/\partial t)_j^{n+1/2}$.

Eq. 87 can be solved for $v_j^{n+1/2}$.

Eq. 94 can be solved for $(\partial^2 v/\partial x^2)_j^{n+1/2}$.

Substituting these results into the cable equation, Eq 66, we get Eq. 68 with

$$R_j^{n+1/2} = C' \frac{(\Delta t)^2}{48}\left(\left(\frac{\partial^3 v}{\partial t^3}\right)_j^* + \left(\frac{\partial^3 v}{\partial t^3}\right)_j^*\right)$$
$$+ g_j^{n+1/2} \frac{(\Delta t)^2}{16}\left(\left(\frac{\partial^2 v}{\partial t^2}\right)_j^* + \left(\frac{\partial^2 v}{\partial t^2}\right)_j^*\right)$$
$$- \frac{r}{2\rho}\left[\frac{(\Delta t)^2}{16}\left(\left(\frac{\partial^4 v}{\partial x^2 \partial t^2}\right)_j^* + \left(\frac{\partial^4 v}{\partial x^2 \partial t^2}\right)_j^*\right)\right.$$
$$\left. + \frac{(\Delta x)^2}{48}\left(\left(\frac{\partial^4 v}{\partial x^4}\right)_*^{n+1} + \left(\frac{\partial^4 v}{\partial x^4}\right)_*^{n+1} + \left(\frac{\partial^4 v}{\partial x^4}\right)_*^{n} + \left(\frac{\partial^4 v}{\partial x^4}\right)_*^{n}\right)\right] \quad (95)$$

Let $$\|\phi\|_{max} = \max_{\substack{0 \le x \le L \\ 0 \le t \le t_{max}}} |\phi(x,t)| \qquad (96)$$

Then, for $0 \le (n+\frac{1}{2})\Delta t \le t_{max}$,

$$\left|R_j^{n+1/2}\right| \le A_1 (\Delta t)^2 + A_2 (\Delta x)^2 \qquad (97)$$

where

$$A_1 = \frac{c}{24} \left\| \frac{\partial^3 v}{\partial t^3} \right\|_{max} + \frac{\|g\|_{max}}{8} \left\| \frac{\partial^2 v}{\partial t^2} \right\|_{max}$$

$$+ \frac{r}{2\rho} \frac{1}{8} \left\| \frac{\partial^4 v}{\partial x^2 \partial t^2} \right\|_{max} \qquad (98)$$

$$A_2 = \frac{r}{2\rho} \frac{1}{12} \left\| \frac{\partial^4 v}{\partial x^4} \right\|_{max} \qquad (99)$$

Thus, A_1 and A_2 are constants, independent of Δt and Δx

It follows from Eq. 97 that for $0 \le (n+\frac{1}{2})\Delta t \le t_{max}$,

$$\| R^{n+1/2} \| \le \left(A_1 (\Delta t)^2 + A_2 (\Delta x)^2\right)\sqrt{L} \qquad (100)$$

Thus, finally, Eq. 83 becomes

$$\| V^n - v^n \| = \| U^n \| \le \frac{t_{max}\sqrt{L}}{C} \left(A_1 (\Delta t)^2 + A_2 (\Delta x)^2\right) \qquad (101)$$

where A_1 and A_2 are given by Eqs. 98-99.

Note that in the fixed time interval $(0, t_{max})$, we can make the error as small as we like by appropriate choice of Δt and Δx. This is called <u>convergence</u> of the numerical scheme.

Note that there is no restriction on Δt and Δx. This is called <u>unconditional stability</u>.

Finally, the error is $O((\Delta t)^2) + O((\Delta x)^2)$. This is called <u>second-order accuracy</u>.