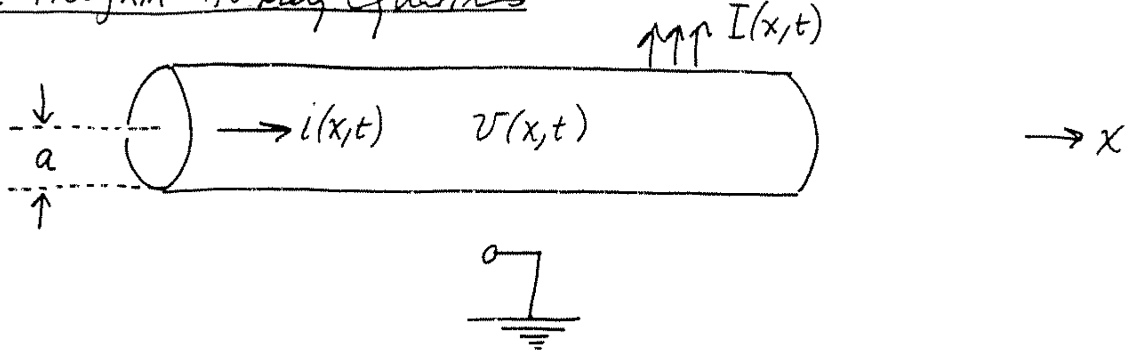
Charles S Peskin 10/11/91

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 *identical* and *independent* 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 *all 4* subunits are in the state S^*. Now consider a large population of channels, and let n be the fraction of *subunits* in the state S^*. Then n^4 is the fraction of channels in the OPEN state (recall independence of the subunits), and

$$g_K = \bar{g}_K n^4$$

where $\bar{g}_K$ is the (theoretical) K^+ conductance per unit area that would be achieved 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: $g_L = \bar{g}_L$

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:

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

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

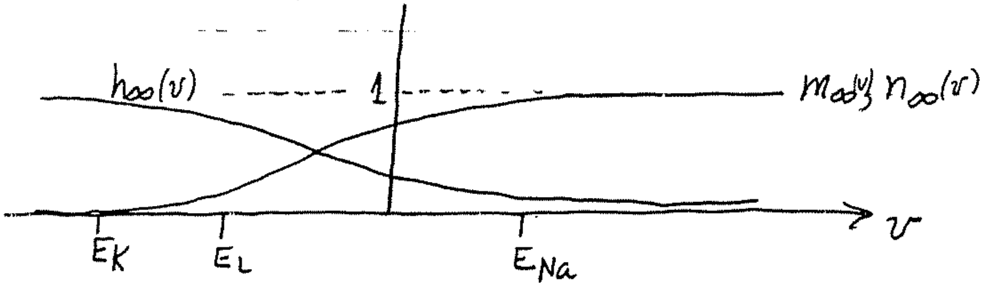
$$\text{slow}\quad \frac{\partial h}{\partial t} = \alpha_h(v)(1-h) - \beta_h(v)\,h = \frac{h_\infty(v) - h}{\tau_h(v)}$$

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

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 <u>fast</u> variables, whereas (h, n) are <u>slow</u>.

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

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

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 $m \leq 1$, 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.

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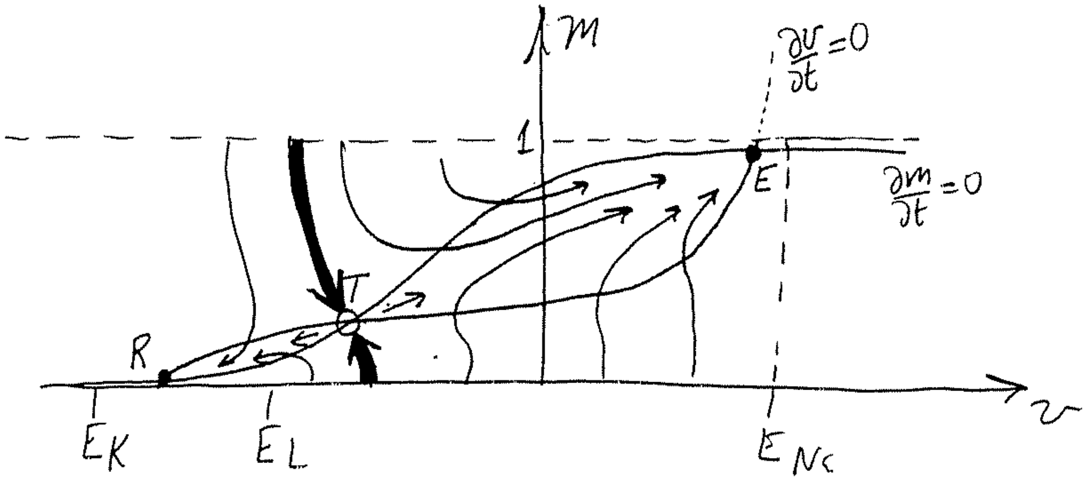
* called isoclines



The three intersections have the following character:

R = rest state (stable, node)
T = threshhold (unstable, saddle point)
E = excited state (stable, node)

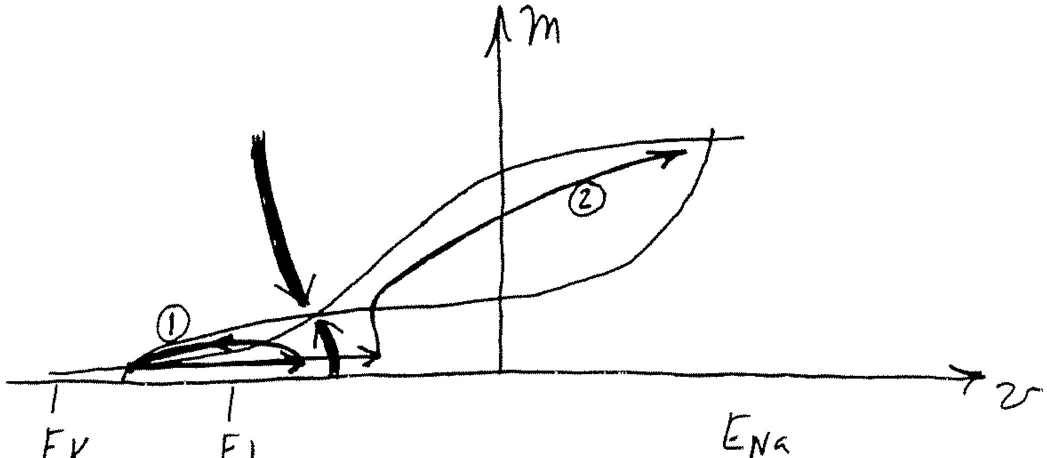
All trajectories that start near R end up at R
All trajectories that start near E end up at E

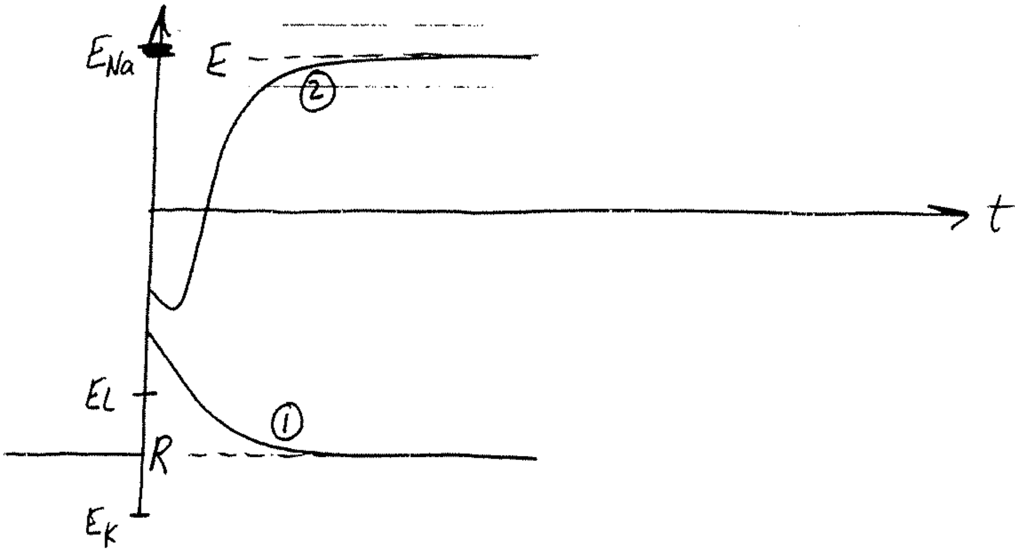
At T, there are two special trajectories, drawn dark, that end up at T itself; all others turn away from T and end ups at R or E. The special trajectories form a separatrix which divides the phase plane into two parts. Any initial condition to the left of the separatrix has a trajectory that ends at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

In summary, the fast-scale behavior is bistable.

Sub-threshhold and supra threshhold excitation :

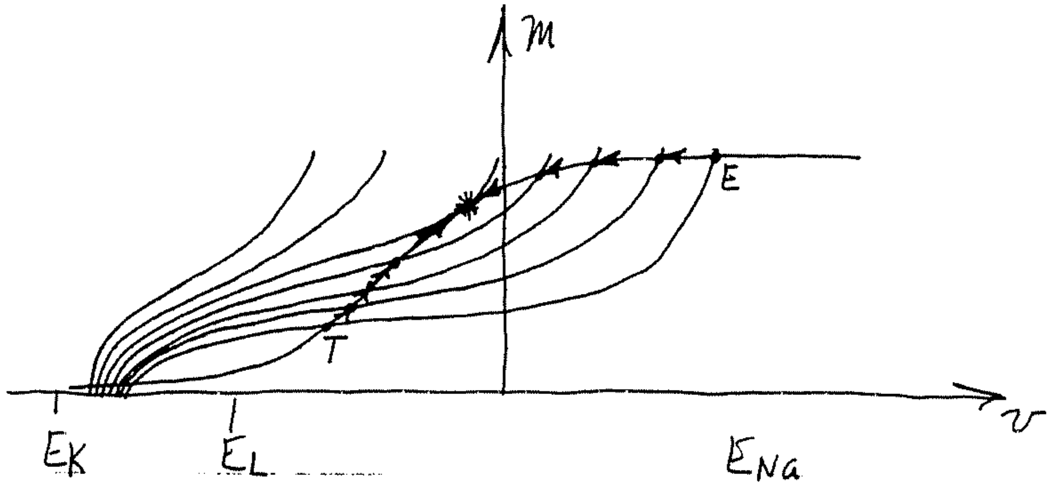
Let the system be in state R prior to $t=0$, and let $I_0(t)=Q_0\,\delta(t)$, so that Q_0 is the total charge per unit area delivered to the membrane by a current shock applied at $t=0$. This produces a jump in voltage $\Delta v = Q_0/C$. Since m cannot change instantaneously, the move in the phase plane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

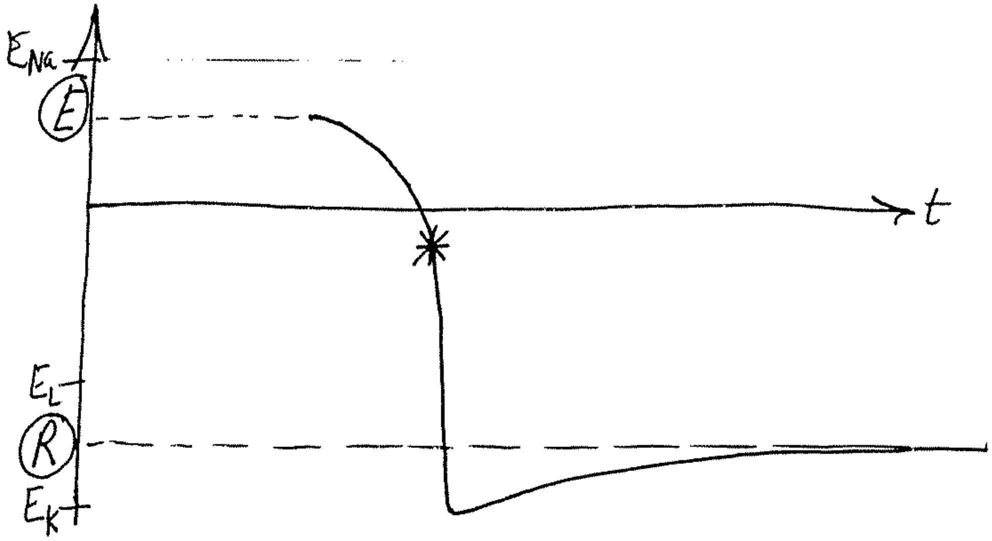




Recovery following excitation

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

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

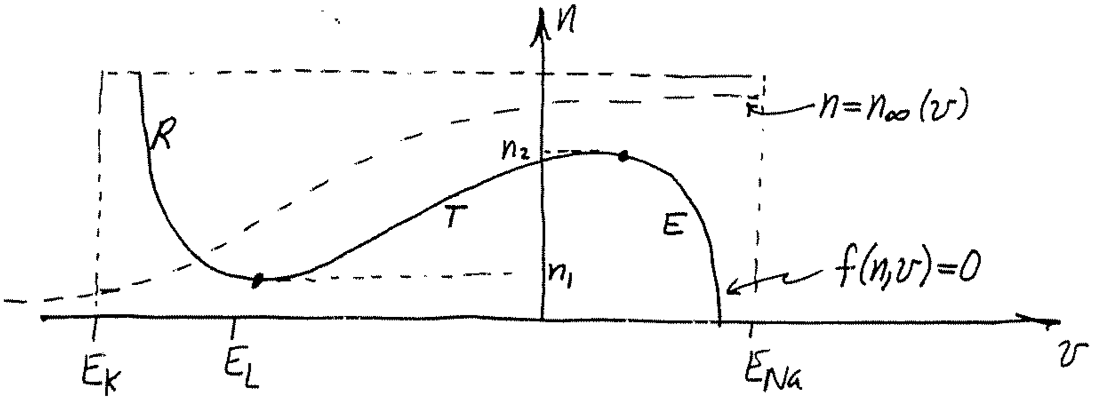
$$\tau_n(v) = \tau_h(v)$$

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

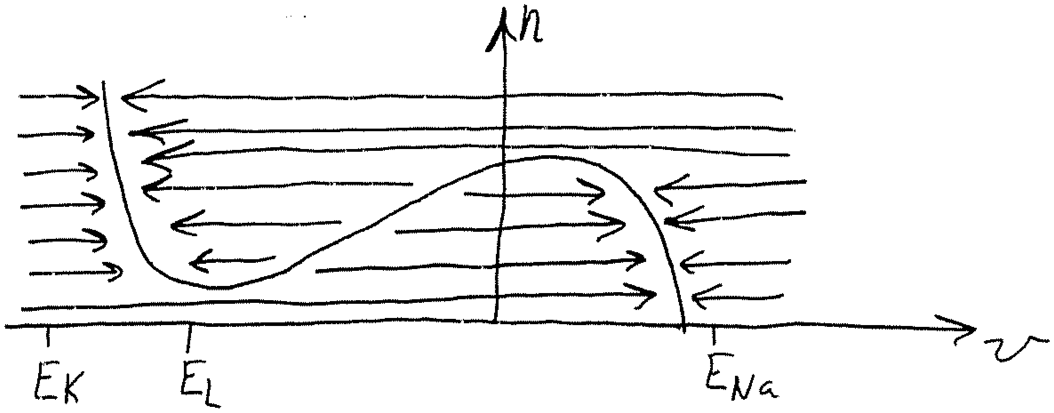
$$m = m_\infty(v)$$

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

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:

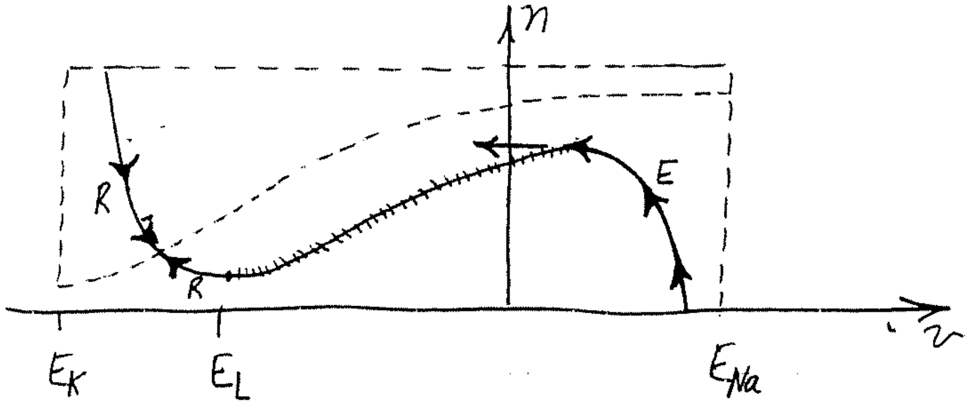


Once it reaches the slow manifold, the system evolves according to

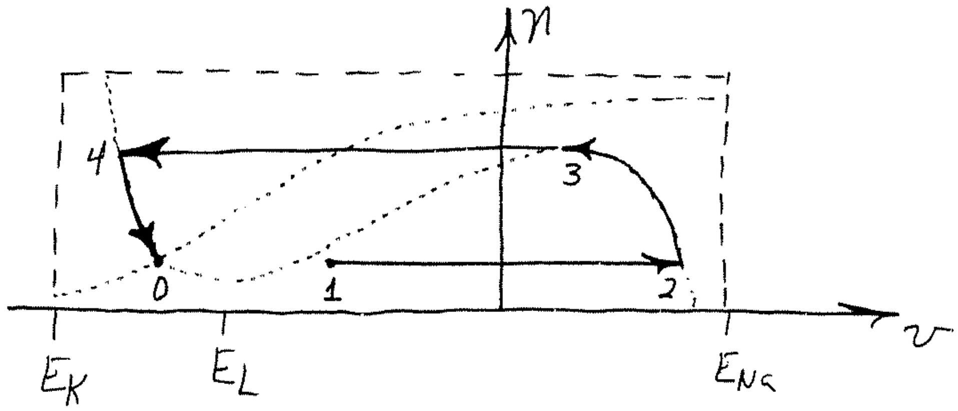
$$\frac{\partial n}{\partial t} = \frac{n_\infty(v) - n}{\tau_n(v)}$$

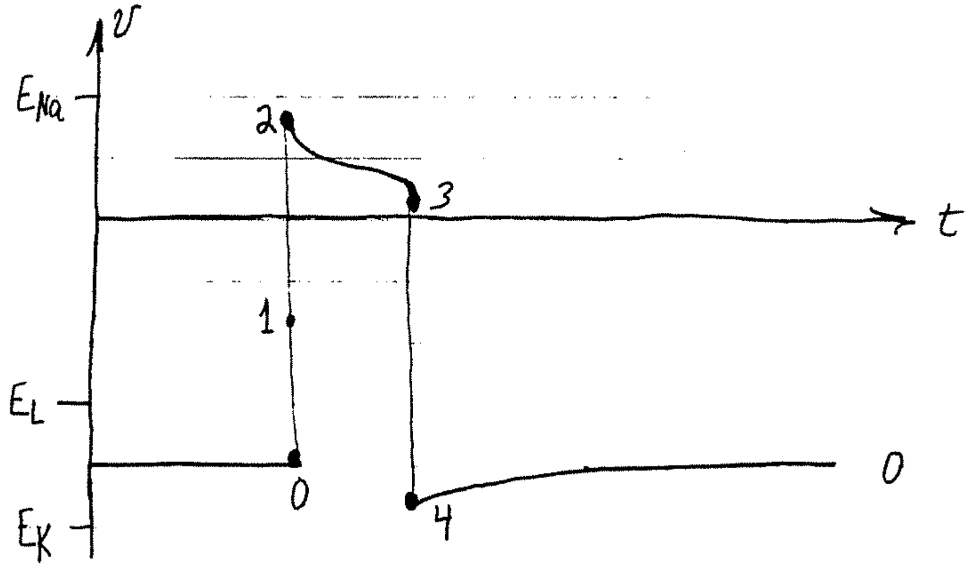
where $v = v_R(n(t))$ or $v = v_E(n(t))$ depending on whether the system happens to be on the rest (R) branch or on the excited (E) branch of the slow manifold ($v_R(n)$ and $v_E(n)$ are the two stable solutions of $f(n,v)=0$. v_R is defined for $n_1 \le n \le 1$ and v_E is defined for $0 \le n \le n_2$.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

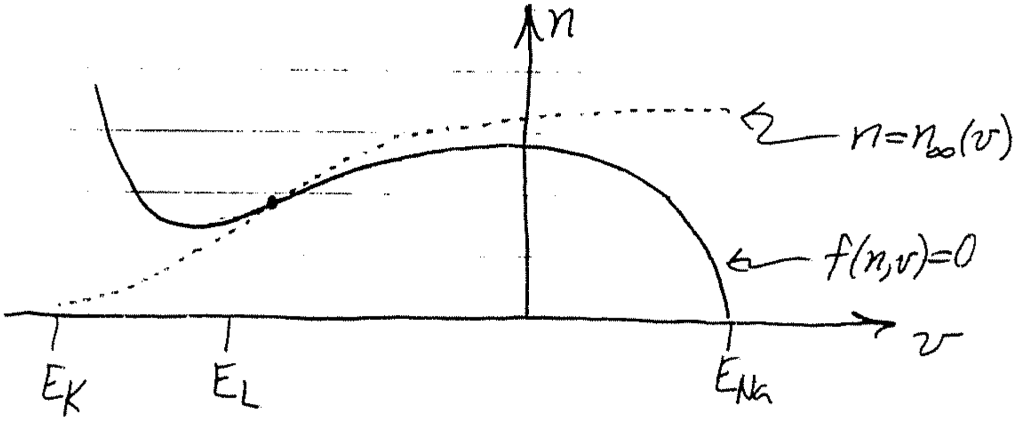




Homework: Use the (n,v) phase plane to discuss the following phenomena. (Don't just answer in words; draw pictures!)

1) Relative refractory period: 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) Spontaneous oscillations: 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) Anode-break excitation*: 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 suddenly stepped to the voltage v_*? Explain the difference between these two situations. (Hint: think about n.)

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* Use the un-shifted slow manifold (as shown in pp. 13-16) to answer this question.

Hodgkin-Huxley units.

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.

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

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

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

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

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

$$E_K = -82\,mV$$

$$E_L = -59\,mV$$

$$a = 0.0238\ cm$$

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

3

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})