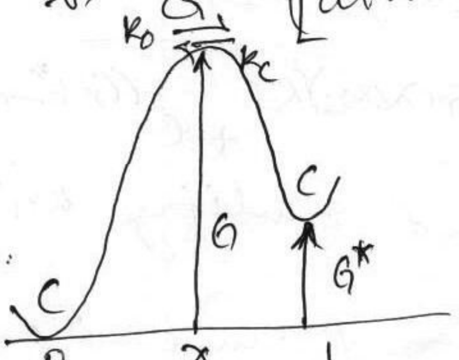
ASSIGNMENT - I

PROBLEM - 1

Let the free energy change needed at the barrier be G at location λ in moving from closed (C) at 0 to open (O) state at 1. Let the energy in open state be G^* [above (C)].



If d_c and d_o are lengths of the spring with channel closed and channel open respectively.

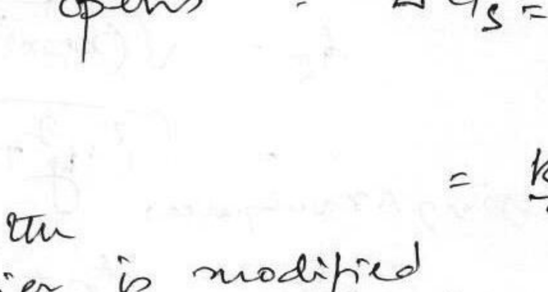
Thus change in potential energy when channel opens $= \Delta G_s = \int_{d_c}^{d_o} k\,x\,dx$

$$= \frac{k}{2}\left(d_o^2 - d_c^2\right)$$

Thus the barrier is modified by ramp of height ΔG_s. For

$$k_c = \alpha\, e^{-(G-G^*-\Delta G_s)/RT}$$

$$k_o = \alpha\, e^{-(G+\lambda\Delta G_s)/RT}$$



Rate of channel opening

$$\frac{dO}{dt} = -k_c O + k_o C = -k_c O + k_o (T-O)$$

where T is the total conc. of channels.

$$\Rightarrow \frac{dO}{dt} = k_O T - (k_O + k_C) O .$$

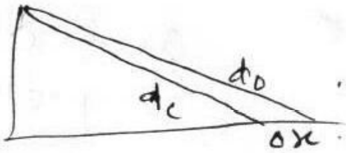
At steady state $\frac{dO}{dt} = 0$.

Probability of open channels

$$= \frac{O}{T} = \frac{k_O}{k_O + k_C} .$$

$$= \frac{e^{-(G + \lambda \Delta G_s)/RT}}{e^{-(G+\lambda \Delta G_s)/RT} + e^{-(G - G^* - \Delta G_s)/RT}} .$$

Take $\lambda = 1/2$ and simplify with $\Delta G_S = \frac{1}{2} k (d_O^2 - d_C^2)$



Assume Δx the separation is very small.

$$d_C = \sqrt{x^2 + y^2}$$

$$d_O = \sqrt{(x + \Delta x)^2 + y^2}$$

$$= \sqrt{x^2 + y^2 + 2x\Delta x + \Delta x^2}$$

using Δx very small,

$$d_O = d_C + \frac{x \Delta x}{d_C} .$$

$$\Delta G_S = \frac{1}{2} k \left(d_O^2 - d_C^2 \right) = \frac{1}{2} k \left[\cancel{d_C} + \frac{x\Delta x}{d_C} - \cancel{d_C} \right] \left[d_C + \frac{x\Delta x}{d_C} + d_C \right]$$

$$\approx K x \Delta x .$$

Substitute in O/T.

From above the rate constants are a function of separation x.

$$\frac{dO}{dt} = k_O(x_1)T - [k_O(x_1) + k_C(x_1)]O$$

when set apart to x_1,

at $t = 0^+$ the O value is

$$T \frac{k_O(x_0)}{k_O(x_0)+k_C(x_0)}$$ when held at x_0 for long.

Thus
$$\frac{dO}{dt} = T\left[\cancel{k_O(x_1)}\; k_O(x_1) - [k_O(x_1)+k_C(x_1)]\frac{k_O(x_0)}{k_O(x_0)+k_C(x_0)} \right]$$

Rate of opening of channels.

<u>PROBLEM - 2.</u>

If before the change in voltage clamp voltage the voltage is held steady at V_1 and it is changed to V_2

then
$$\frac{dh}{dt} = \frac{h_\infty(V_2) - h}{\tau_H(V_2)}$$ describes the change in h.

with $h(t=0) = h_\infty(V_1)$.

The solution to the above diff. eqn. is

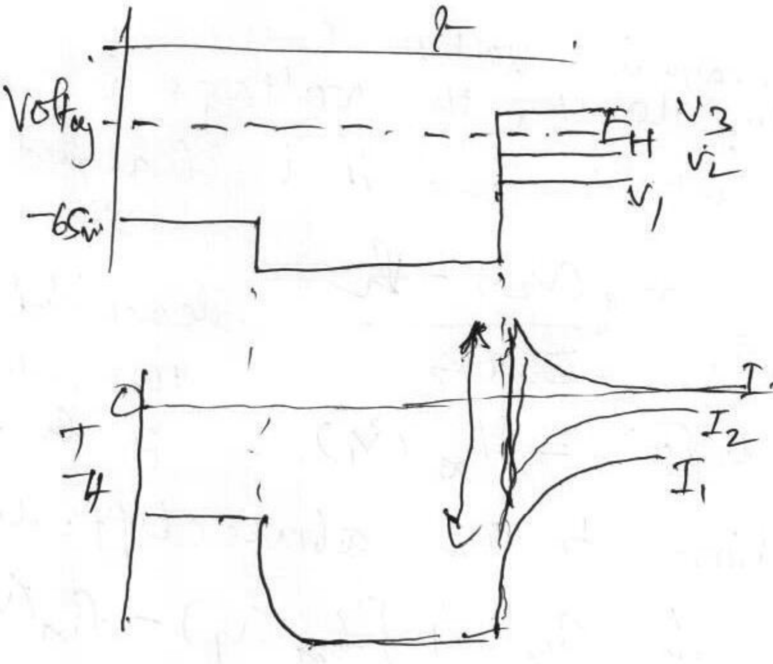
$$h(t) = h_\infty(V_2) + [h_\infty(V_1) - h_\infty(V_2)]e^{-t/\tau_H(V_2)}$$

h ~~decrea~~ changes exponentially from $h_\infty(V_1)$ to $h_\infty(V_2)$.

$$I_H(t) = \bar{g}_H\, [h_\infty(V_2) + [h_\infty(V_1) - h_\infty(V_2)]e^{-t/\tau_H(V_2)}] \times (V_2 - E_H)$$

$E_H = -43$ mV. All the clamp potentials used are below E_H. Thus all the currents are inward currents only increase or decrease from the holding current which is a high inward -ve current at the initial portion of the clamp. So there is no "actual" reversal in polarity.

To determine E_H, I_H must go to the from 0 current. Thus a clamp protocol when at the tail the clamp potential is changed to variety of values. like below.



Where this true reversal would take place is E_H.

Determining $h_\infty(V)$ & $\tau_H(V)$ was discussed in class. (like other HH gating variables).

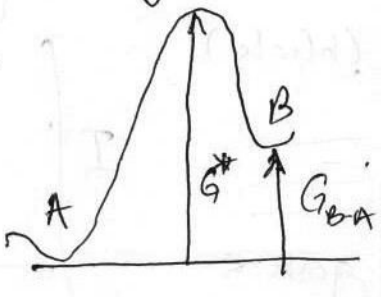
PROBLEM - 3

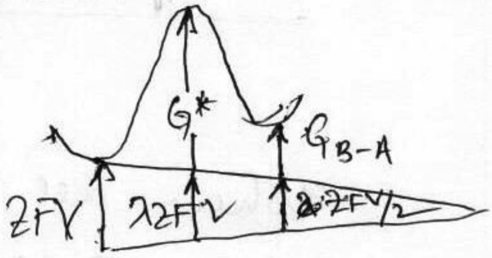
In the top model the binding of L^{2+} to the channel is not affected by the transmembrane potential because the ligand (ion) L^{2+} does not move through any fraction of the membrane. Whereas in the second case the L^{2+} ion goes through half of the membrane potential's field to the binding site.

A is L^{2+} unbound to channel state & B is L^{2+} bound to channel state. The following barrier diagrams are appropriate.

If V is the membrane potential $V_{in} - V_{out}$

Top case





Problem 4 (Part A discussed in class)

Problem 4 (Part B)

$$\left.\begin{aligned} I_{ext} &= C\frac{dV}{dt} + \bar{g}_K n^4 (V - E_K) + \bar{g}_L (V - E_L) \\ \frac{dn}{dt} &= \alpha(V)(1-n) - \beta(V) n \end{aligned}\right] \cdots (1)$$

Small signal deviation

$$I_{ext} = I^r_{ext} + i_{ext} \qquad V = V^r + v \qquad n = n^r + \eta$$

$\alpha(V)$ & $\beta(V)$ linearized functions of v

$$\alpha(V) = \alpha^r + av \qquad \beta(V) = \beta^r + bv$$

Substituting the above in (1)

$$(2) \cdots \left[\begin{aligned} I^r_{ext} + i_{ext} &= C\frac{d(V^r+v)}{dt} + \bar{g}_K (n^r+\eta)^4 (V^r + v - E_K) \\ &\quad + \bar{g}_L (V^r + v - E_L) \\ \frac{d(n^r+\eta)}{dt} &= (\alpha^r + av)(1 - n^r - \eta) - (\beta^r + bv)(n^r + \eta) \end{aligned}\right.$$

Now $(n^r+\eta)^4 \simeq n^{r4} + 4n^{r3}\eta$ (neglecting higher power of η)

at V^r $\quad \frac{dV}{dt} = 0$ & $\frac{dn}{dt} = 0$

Thus $I^r_{ext} = g_K n^{r4}(V^r - E_K) + \bar{g}_L (V_L - E_L)$

& $\alpha^r(1-n^r) - \beta^r n^r = 0$

Using the above in (2) and neglecting second and higher order terms of the small variables (also ηv etc.)

$$i_{ext} \simeq C\frac{dv}{dt} + \bar{g}_K n^{r4} v + 4\bar{g}_K n^{r3}\eta(V^r - E_K) + \bar{g}_L v$$

$$\frac{d\eta}{dt} \simeq -\alpha^r\eta + a(1-n^r)v - \beta^r\eta - bn^r v.$$

PROBLEM 5

$$\frac{du}{dt} = 1-(b+1)u + au^2 v$$

$$\frac{dv}{dt} = bu - au^2 v.$$

Eq. pts are intersection of null clines.

$$\left.\begin{aligned} \frac{du}{dt} = 0 &\Rightarrow v_{u_{nc}} = -\frac{1-(b+1)u}{au^2} \\ \frac{dv}{dt} = 0 &\Rightarrow v_{v_{nc}} = \frac{b}{au} \end{aligned}\right\} \text{ So } u \neq 0.$$

$v_{u_{nc}} = v_{v_{nc}}$ for eq pt.

$$\Rightarrow -\frac{1-(b+1)u}{au^2} = \frac{b}{au}$$

$$\left.\begin{aligned} -1+(b+1)u &= bu \\ u_{eq} = 1 \quad v_{eq} &= b/a \end{aligned}\right] \text{ eq pt.}$$

$$J\Big|_{eq} = \begin{bmatrix} -(b+1)+2auv & au^2 \\ b-2auv & -au^2 \end{bmatrix}\Bigg|_{\text{at eq pt}}$$

$$= \begin{bmatrix} b-1 & a \\ -b & -a \end{bmatrix}$$

For eigen values.

$$\det\left[\lambda I - J\right] = 0$$

$$\Rightarrow \lambda^2 + (a-b+1)\lambda + a = 0$$

$$\lambda = \frac{b-a-1}{2} \pm \frac{\sqrt{(b-a-1)^2 - 4a}}{2}.$$

dividing 2nd term by $(b-a-1)$

$$\Rightarrow \lambda = \frac{b-a-1}{2}\left[1 \pm \sqrt{1-\frac{4a}{(b-a-1)^2}}\right]$$

$b-a-1 \neq 0$ for.

The eq pt. in the system would be spiral if

For that case λ is imaginary.

$$\frac{4a}{(b-a-1)^2} > 1 \Rightarrow a^2 - 2ab - 2a + 1 - 2b + b^2 < 0 \quad \text{(1)}$$

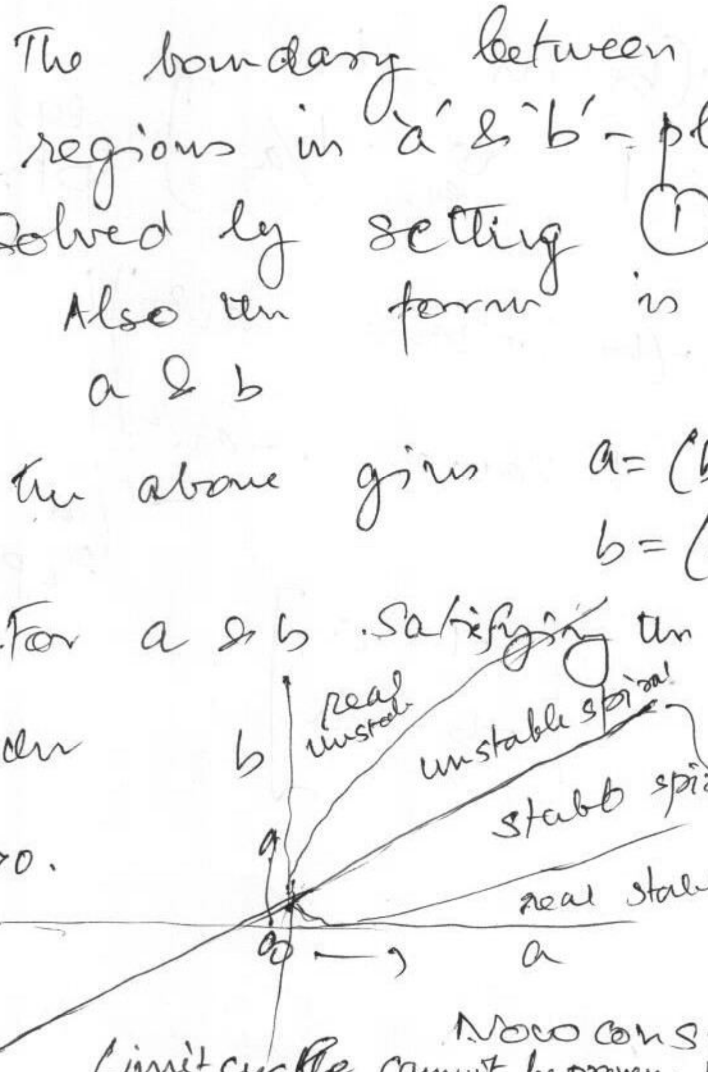
The boundary between real and complex regions in 'a' & 'b' - plane can be solved by setting (1) to 0.
Also the form is symmetric in a & b

the above gives $a = (b+1) \pm 2\sqrt{b}$.
$b = (a+1) \pm 2\sqrt{a}$

As above a & b are real $a \neq 0$ $b \neq 0$

For a & b satisfying the above

Consider only $a>0, b>0$.



$b-a-1=0 \rightarrow \lambda$ imaginary.

$Re[\lambda] < 0$ for $b-a-1<0$
$b < a+1$

Now consider for other 3 quadrants.
Limit cycle cannot be proven - Why? (FOR YOU TO DO)