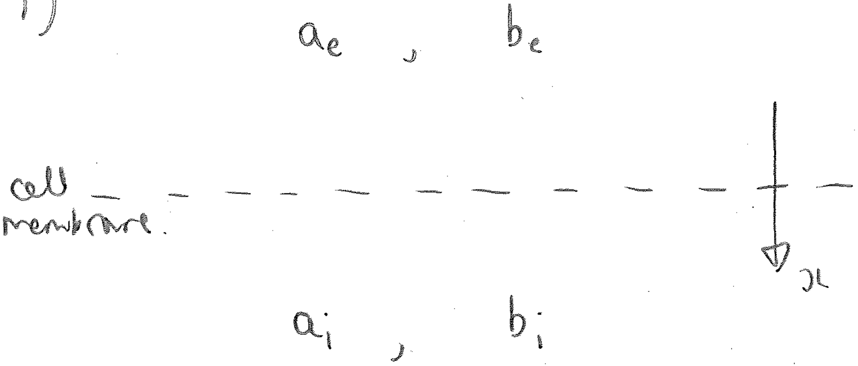
Problem Sheet 2

1)



$a_e + b_e = a_i + b_i$

$a_e > a_i$

- Initially since $a_e + b_e = a_i + b_i$, the system is electroneutral and there is no potential difference across the cell membrane.
- Na$^+$ gates open. Na$^+$ ions will flow from the exterior to the interior in response to the difference in concentrations. This corresponds to a diffusive flux $J_D = -D_a \frac{\partial a}{\partial x}$

D_a : diffusion coefficient.

- In doing so, this builds up a potential difference. The flux of ions due to a potential difference is $J_V = -\frac{u_a z_a a}{|z_a|} \frac{\partial \phi}{\partial x}$

u_a: ion mobility
z_a: ion valency (=+1 for Na$^+$)

ϕ = electric potential.

- The system reaches equilibrium when these fluxes are balanced : $J_D + J_V = 0$

$$\Rightarrow \quad D_a \frac{\partial a}{\partial x} = -\frac{u_a z_a a}{|z_a|} \frac{\partial \phi}{\partial x}$$

Now $D_a = \frac{u_a RT}{|z_a| F}$

(Einstein's relation)

R = universal gas constant

T = temperature

F = Faraday's constant

So $$\frac{u_a RT}{|z| F}\frac{\partial a}{\partial x} = -\frac{u_a z_a a}{|z_a|}\frac{\partial \phi}{\partial x}$$

$$\frac{RT}{z_a F}\frac{1}{a}\frac{\partial a}{\partial x} = -\frac{\partial \phi}{\partial x} \Rightarrow \phi = \frac{RT}{zF}\log(a) + \text{constant}$$

$$\frac{RT}{z_a F}\log\left(\frac{a_e^*}{a_i^*}\right) = \phi_i - \phi_e = V,$$ potential difference across the membrane

a_e^* = concentration of Na^+ at the cell membrane on the exterior

a_i^* = concentration of Na^+ at the cell membrane on the interior.

Due to the competing electric potential we will still have $a_e^* > a_i^*$

Now the K^+ gates open.

The initial diffusive flux is $-D_b \frac{\partial b}{\partial x}$.

There is also a flux due to the electric potential generated by the Na^+ ions. This is $\frac{u_b z_b b}{|z_b|} \frac{\partial \phi}{\partial x}$

where $\phi = \frac{RT}{z_a F} \log(a) +$ constant is the potential due to the Na^+ ions found earlier.

So the total initial flux is $J = -D_b \frac{\partial b}{\partial x} - \frac{u_b z_b b}{|z_b|} \frac{\partial \phi}{\partial x}$

and $D_b = \frac{u_b RT}{|z_b| F}$ by Einstein's relation and $z_b = 1$

gives the required result.

2.1

2)

$$\frac{dn}{dt} = \alpha(V)(1-n) - \beta(V)n$$

$$\frac{dn}{dt} = \alpha(V) - (\alpha(V)+\beta(V))n$$

$$\frac{1}{\alpha+\beta}\frac{dn}{dt} = \frac{\alpha}{\alpha+\beta} - n$$

$$\tau(V)\frac{dn}{dt} = n_\infty(V) - n \quad ①$$

where $\tau(V) = \frac{}{\alpha(V)+\beta(V)}$

$$n_\infty(V) = \frac{\alpha(V)}{\alpha(V)+\beta(V)}$$

n represents the fraction of open gates.

α represents the rate of gate opening.

β represents the rate of gate closing

V represents the voltage.

V: V(t) prescribed so

$$\tau(t)\frac{dn}{dt} = n_\infty(t) - n$$

$$\frac{dn}{dt} + \frac{1}{\tau(t)}n = \frac{n_\infty(t)}{\tau(t)}$$

$$\frac{d}{dt}\left(n \exp\int_0^t \frac{ds}{\tau(s)}\right) = \frac{n_\infty(t)}{\tau(t)} \exp\int_0^t \frac{ds}{\tau(s)}$$

$$\boxed{n = \exp\left(-\int_0^t \frac{ds}{\tau(s)}\right)\int_0^t \frac{n_\infty(\tilde{t})}{\tau(\tilde{t})} \exp\int_0^{\tilde{t}} \frac{ds}{\tau(s)}\, d\tilde{t} + n(0)}$$

If $T = 1$, and $n_\infty = \cos(t) + 1$ then we may solve the ODE ① to get

$$n(t) = \tfrac{1}{2}(2n_0 - 3)e^{-t} + \tfrac{1}{2}(2 + \cos(t) + \sin(t))$$

$$= (n_0 - \tfrac{3}{2})e^{-t} + 1 + \frac{1}{2\sqrt{2}}\cos(t - \tfrac{\pi}{4})$$

$\uparrow$

out of phase with n_∞ by $\frac{\pi}{4}$

If $T = t+1$, $n_\infty =$ constant, n_∞^* say, then we may solve the ODE ① to get

$$n(t) = \frac{n_0 + n_\infty^* t}{1+t}$$

As $t \to \infty$,

$$n(t) = \left(n_\infty^* + \frac{n_0}{t}\right)\left(1 + \frac{1}{t}\right)^{-1}$$

$$\sim \left(n_\infty^* + \frac{n_0}{t}\right)\left(1 - \frac{1}{t}\right)$$

$$\sim n_\infty^* + \frac{(n_0 - n_\infty^*)}{t}$$

so approach to equilibrium is algebraic $(\propto \frac{1}{t})$

3) The Hodgkin-Huxley model is:

All of this is done in the lectures except for identifying the magnitude of the parameters

$$C_m \frac{dV}{dt} + (I_i - I_{app}) = 0 \quad ①$$

capacitance of the membrane

applied current

$$\tau(V) \frac{dn}{dt} = n_\infty(V) - n. \quad ②$$

n = potassium activation.

$$\tau_m(V) \frac{dm}{dt} = m_\infty(V) - m \quad ③$$

m = sodium activation.

$$\tau_h(V) \frac{dh}{dt} = h_\infty(V) - h \quad ④$$

h = sodium inactivation.

$$I_i = \underbrace{g_{Na} m^3 h (V - V_{Na})}_{Na^+ \text{ current}} + \underbrace{g_K n^4 (V - V_K)}_{K^+ \text{ current}} + \underbrace{g_L (V - V_L)}_{\text{leakage (mainly } Cl^- \text{ chloride ions)}} \quad ⑤$$

$\tau(V)$, $\tau_m(V)$, $\tau_h(V)$, $n_\infty(V)$, $m_\infty(V)$, $h_\infty(V)$, C_m, I_{app}, g_{Na}, g_K, g_L, V_{Na}, V_K, V_L are all known.

Assumptions : 1) $\tau_m \ll \tau$

③ $\Rightarrow$ $m \approx m_\infty(V)$.

2) $\tau \approx \tau_h$

3) $n_\infty + h_\infty$ = constant, $\bar{h}$ say

2), (3), ② + ④ $\Rightarrow$ $n + h = \bar{h}$

Then, ① and ⑤ gives

$$C_m \frac{dV}{dt} = I_{app} - \left[g_{Na} m^3 (\bar{h} - n)(V - V_{Na}) + g_K n^4 (V - V_K) + g_L (V - V_L) \right]$$

$$\tau(V) \frac{dn}{dt} = n_\infty(V) - n$$

Two equations for two unknowns : V and n.

Actually, ② + ④ gives $\tau \frac{d(n+h)}{dt} = \bar{h} - (n+h)$

$$\frac{d}{dt}\left[(n+h) \exp\left[\int_0^t \frac{dt'}{\tau(t')} \right] \right] = \bar{h} \exp\left[\int_0^t \frac{dt'}{\tau(t')} \right]$$

$$n + h = \bar{h} + A \exp\left[-\int_0^t \frac{dt'}{\tau(t')} \right]$$

$\rightarrow$ $\bar{h}$ as $t \to \infty$, or equals $\bar{h}$ if $n + h = \bar{h}$ at $t = 0$.

3.3

Non-dimensionalize:

$$v = \frac{V - V_{eq}}{V_{Na} - V_{eq}} , \qquad t = T_1 t'$$

$$\Rightarrow \quad \frac{dn}{dt} = n_\infty(v) - n$$

$$\varepsilon \frac{dv}{dt} = I^* - g(v,n)$$

$$g(v,n) = \gamma_K (v + v_K^*) n^4 + \gamma_L (v - v_L^*) - (1-v)(h-n) m^3(v)$$

NB
In lectures I said we should choose $t = \tau(V_{eq}) t'$. However, this should be $t = \tau(v) t'$. This means that you have time dependence in the $\tau(v(t))$.
This then gives $\varepsilon = \frac{C_m}{g_{Na} \tau(v(t))}$
So $\varepsilon = \varepsilon(t)$ however this doesn't matter as we only use the fact that $\varepsilon \ll 1$, which works even if ε is time dependent.

$$\gamma_K = \frac{g_K}{g_{Na}} , \qquad \gamma_L = \frac{g_L}{g_{Na}} , \qquad v_K^* = \frac{-V_K}{V_{Na}} , \qquad v_L^* = \frac{V_L}{V_{Na}}$$

Using the numbers given provides

$\gamma_K \sim 0.3,$

$\gamma_L \sim 0.003,$

$v_K^* \sim 0.1,$

$v_L^* \sim 0.1$

$\varepsilon \sim 1.6 \times 10^{-3}.$

We may exploit the fact that $\varepsilon \ll 1$ to perform fast-slow phase plane analysis; $\gamma_L \ll 1$ just simplifies the algebraic equation we must solve, $g(v,n) = 0$, for the nullcline.

4) $\varepsilon \dot{v} = J^* + f(v) - w$

$\dot{w} = \gamma v - w.$ $\varepsilon << 1$

$f = v(a-v)(v-1)$ $0 < a < 1.$

Steady states occur when $\dot{v} = \dot{w} = 0$

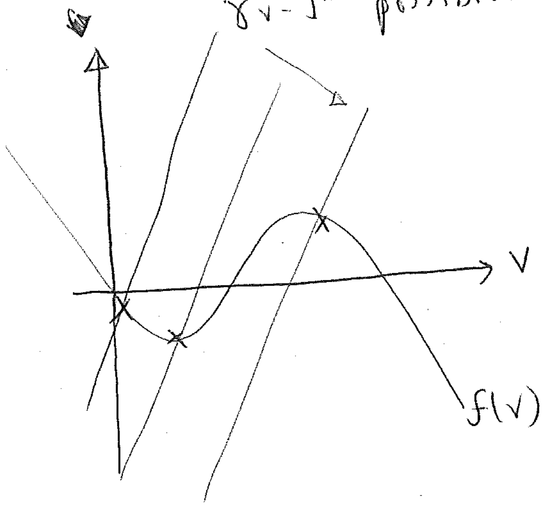
$\Rightarrow f(v) - w + J^* = 0$

$\gamma v = w.$

$\Rightarrow v(a-v)(v-1) - \gamma v + J^* = 0.$

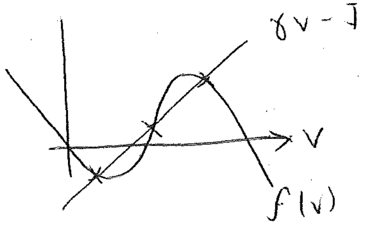
$f(v) = \gamma v - J^*$

$\gamma v - J^*$ possibilities, for different values of J^*.



For there to be a unique root, we need $f'(v) < \gamma$

- otherwise we could have more than one root :



Now $f'(v) = \frac{d}{dv}\left[-v^3 + (a+1)v^2 - av \right]$

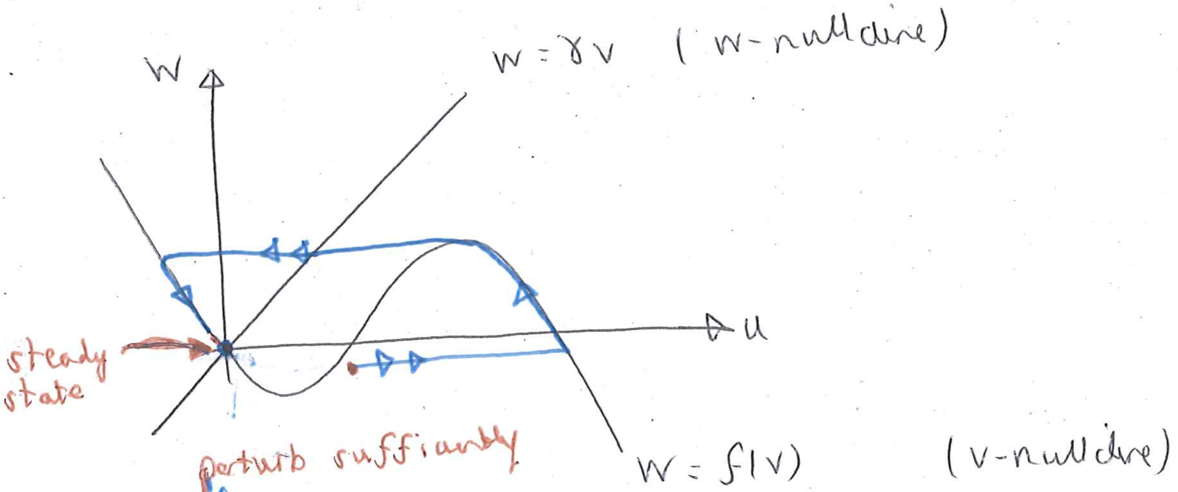
$= -3v^2 + 2v(a+1) - a$

$= -3\left(v - \frac{a+1}{3} \right)^2 + \frac{1}{3}(a^2 - a + 1)$ (completing the square)

So $f'(v) < \frac{1}{3}(a^2 - a + 1)$

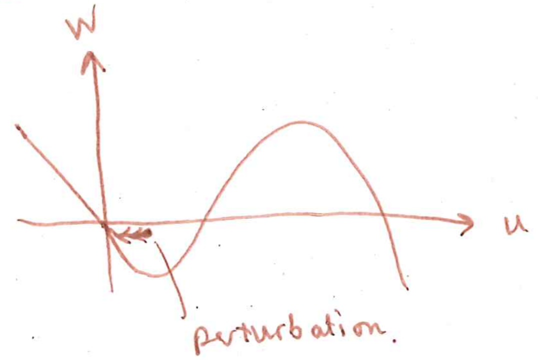
So we have a unique root if $\frac{1}{3}(a^2 - a + 1) < \gamma$ as required.

If $I^* = 0$ we have the phase plane:

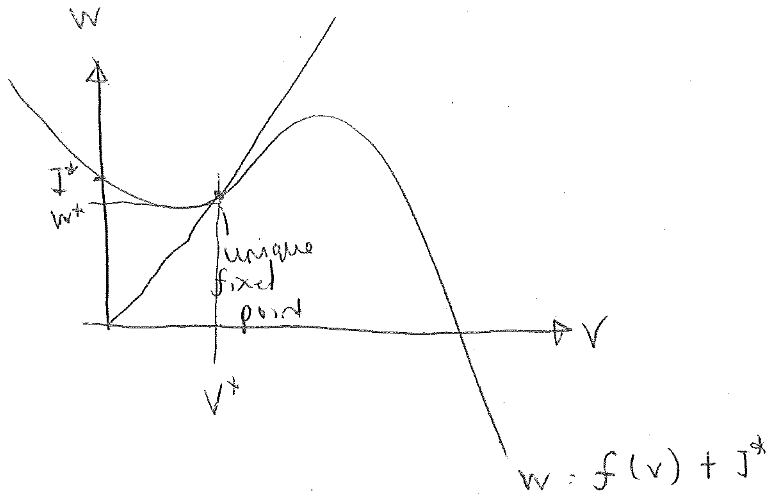


perturb sufficiently from steady state and we make an excursion ∴ system is excitable

If we don't provide enough of a perturbation then we do not make an excursion and we relax back to the equilibrium.



If $J^* > 0$ we have the following phase plane:



Fixed point (v^*, w^*) satisfies $\quad J^* + f(v^*) - w^* = 0$

L. ~~[illegible] about fix~~ $\quad \gamma v^* - w^* = 0$

Linearize about this fixed point : $\quad v = v^* + V$

$w = w^* + W$

$$\Rightarrow \quad \varepsilon \dot{V} = f'(v^*) V - W$$

$$\dot{W} = \gamma V - W$$

$$\begin{pmatrix} \dot{V} \\ \dot{W} \end{pmatrix} = \underbrace{\begin{pmatrix} f'(v^*)/\varepsilon & -1/\varepsilon \\ \gamma & -1 \end{pmatrix}}_{\underline{M}} \begin{pmatrix} V \\ W \end{pmatrix}$$

The system is unstable iff $\operatorname{tr}(\underline{m}) > 0 \Rightarrow f'(v^*) > \varepsilon$ and so if $f'(v^*) > \varepsilon$ then oscillations will occur.

Since $\varepsilon << 1$, oscillations will occur if $f'(v^*) \gtrsim 0$

Thus, oscillations will occur if $V_- < V^* < V_+$ where $V_\pm$ are the roots of $f' = 0$.

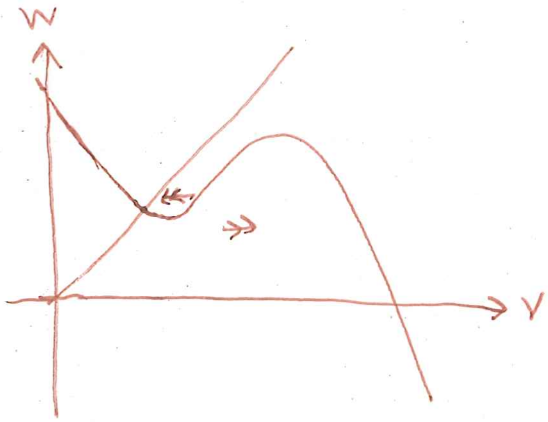
i.e. $$V_\pm = \frac{a+1}{3} \pm \frac{1}{3}\sqrt{(a^2 - a + 1)}$$

Thus, instability occurs for $I_- < I^* < I_+$ where

$$I_\pm = \gamma V_\pm - f(V_\pm)$$

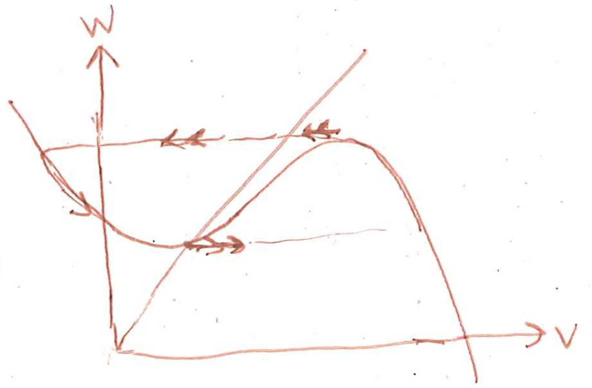
Substituting ① into ② gives (after algebra):

$$I_\pm = \frac{1}{3}\left[\gamma - \frac{2}{9}(a^2 - a + 1)\right]\left[(a+1) \pm (a^2 - a + 1)^{\frac{1}{2}}\right] + \frac{1}{9}a(a+1)$$



$f'(v^*) < 0$

Need to perturb beyond dip



$f'(v^*) > 0$

Infinitely small perturbation gives rise to an excursion.