C5.12 Math Physiol 2012 q1

1/ (a)

$$\varepsilon \dot{v} = Av(v-a)(1-v) - w$$

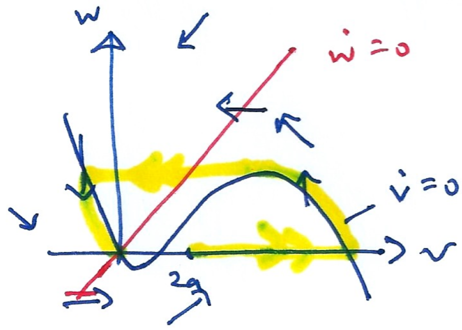
$$\dot{w} = -w + bv$$

$\varepsilon \ll 1$, $a \ll 1$

(i) v intracellular electrical potential relative to resting state

space clamped – forced to be independent of spatial variable x

ii.

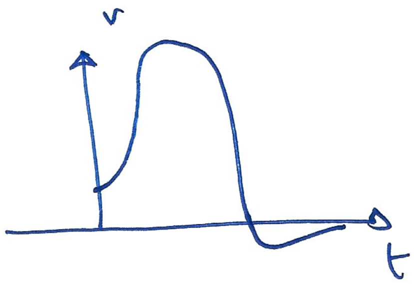


iii At large w, $\dot{v} < 0$, $\dot{w} < 0$ => trajectory arrows as shown

However, $\varepsilon \ll 1$ => almost horizontal away from v nullcline

=> excursion as shown (yellow)

iv



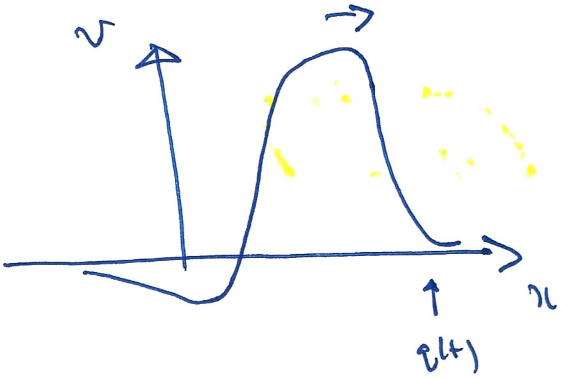
(b)

$$\varepsilon v_t = \varepsilon^2 v_{xx} + Av(v-a)(1-v) - (1+\delta \sin t)w$$

$$w_t = -w + bv$$

$v, w \to 0$ at $\pm\infty$

$\delta \ll 1$



(i) $y = x - q(t)$ $\quad \tau = t$

$$\Rightarrow \frac{\partial}{\partial x} = \frac{\partial}{\partial y}, \quad \frac{\partial}{\partial t} = \frac{\partial}{\partial \tau} - \dot{q}\frac{\partial}{\partial y}$$

$$\Rightarrow \quad w_\tau = \dot{q} w_y - w + bv$$

& $$\varepsilon(v_\tau - \dot{q} v_y) = \varepsilon^2 v_{yy} + Av(v-a)(1-v) - (1+\delta \sin \tau)w$$

(ii) ~~Now we~~ Now I suppose ~~we~~ ahead of the front, still in $y \sim O(1)$,

w and v are small, neglect ε

$$\Rightarrow \quad Av(v-a)(1-v) \simeq \cancel{Av} \simeq -aAv \approx (1+\delta \sin \tau)w$$

so $v \simeq -\dfrac{(1+\delta \sin \tau)w}{aA}$ $\quad$ also $a \ll 1$ but also $\delta \ll 1$ ... or.

suggests $$w_\tau - \dot{q} w_y \simeq -w \cancel{+} - \frac{b(1+\delta \sin \tau)}{a\cancel{\varepsilon}A} w$$

$$= -w\left[1 + \frac{b(1+\delta \sin \tau)}{\cancel{\varepsilon}\, aA}\right]$$

of required form with

$$f(\tau) = 1 + \frac{k(1+\delta\sin\tau)}{aA}$$

– well this is a bit loose as $a \ll 1$ but I suppose ok if $\varepsilon \ll 1$

in $$w_\tau - \dot{q}\, w_y = -f w$$

so $f > 0$ & $\dot{q} > 0$

can solve with characteristics

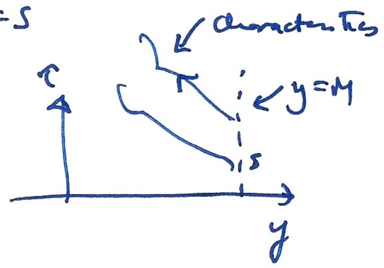
Note $\dot{y} = -\dot{q} < 0$ characteristics emerge from $y = \infty$!

since f = constant (as $\delta \ll 1$)

~~Suppose $w = w_\infty(s)$ at $y = s > 0$ at $\tau = 0$~~ ~~$\tau = s$,~~ y

~~then $\dot{y} = -\dot{q} \Rightarrow y = s + q(s) - q(\tau)$~~

Suppose we apply $w = w_M(s)$ at $y = M$ and $\tau = s$



then $\dot{w} = \cancel{-fw} - f w$

$$\dot{y} = -\dot{q}$$

$$\Rightarrow y = M - [q(\tau) - q(s)]$$

$$w \simeq w_M(s)\, e^{-f(\tau - s)}$$

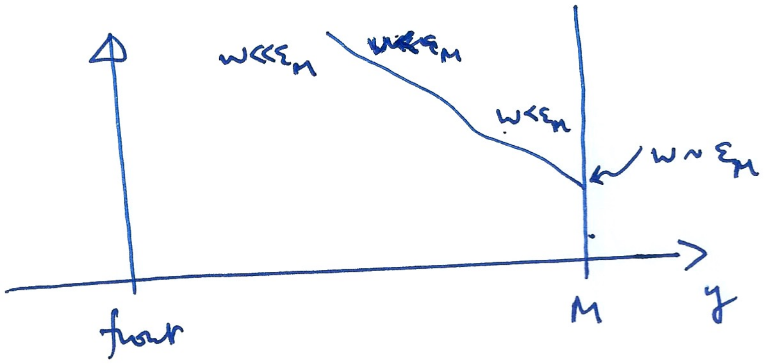
since $\delta \ll 1$ we have approximately $q = c\tau$ (convenient assumption)

so $$\tau - s \simeq \frac{M-y}{c}$$

$$\Rightarrow w \simeq w_M\left[\tau - \frac{(M-y)}{c}\right] \exp\left[\frac{y-M}{c}\right]$$

& in order for this to $\to 0$ at ∞ we need $w_M \to 0$ rapidly $\Rightarrow w \equiv 0$.

This is not very well put. Basically w decays exponentially along the characteristics as y ~~does~~ decreases, so if $w \to 0$ as $y \to \infty$, it enforces $w = 0$ ahead of the front.



If $M \gg 1$, $w \sim \varepsilon_M \ll 1$ for $y \sim 1$ for sufficiently large τ.

It's a bit awkward.

(iv) well, if we take $w = 0$ ahead of the front and now in the front $y = \varepsilon Y$

at leading order $\Rightarrow$ $-\dot{q}\, v_Y = v_{YY} + Av(v-a)(1-v)$ as $w = 0$

$v \to 0 \quad Y \to \infty$

& using the limit $\quad v \to 1 \quad Y \to -\infty$

$$v'' + \dot{q} v' - Av(v-a)(v-1)$$

$$U_0 = 0,\ U_1 = a,\ U_2 = 1 \qquad \begin{matrix} v \to U_0 = 0 & Y \to \infty \\ v \to U_2 = 1 & Y \to -\infty \end{matrix}$$

$$\Rightarrow c = \sqrt{\frac{A}{2}}\,(U_0 + U_2 - 2U_1)$$

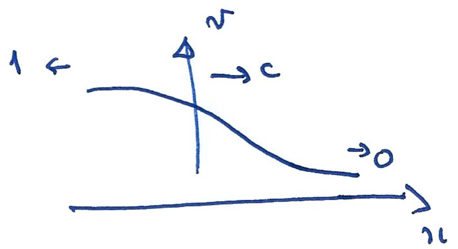
$$= \sqrt{\frac{A}{2}}\,(1 - 2a) > 0.$$

Rather weird question

C5.12 (C8.1b) Math Physiol 2012 Q2

(1

2/ $v_t = \nabla^2 v + v(1-v) f(v) \qquad f>0$



(a) plane waves $\nabla^2 v = v_{xx}$

$v = v(q) \qquad q = x - ct$

$-cv' = v'' + v(1-v) f(v)$

(b) 2-D

$\underline{x} = \underline{X}(\underline{a}, t) \qquad \underline{a} = \underline{A}(\underline{x}, t)$

$\underline{\nabla} v = \underline{e}_i \dfrac{\partial v}{\partial x_i} \qquad \& \qquad \dfrac{\partial}{\partial x_i} = \dfrac{\partial a_j}{\partial x_i}\dfrac{\partial}{\partial a_j} \qquad = \alpha_{ij}\dfrac{\partial}{\partial a_j}$

so $\underline{\nabla} v = \underline{e}_i \alpha_{ij} \dfrac{\partial v}{\partial a_j}$ Summation convention assumed

$\nabla^2 v = \cancel{\dfrac{\partial}{\partial x_j}\alpha_{ij}} \dfrac{\partial}{\partial x_k} \alpha_{kj} \dfrac{\partial v}{\partial a_j}$

$= \alpha_{kl}\dfrac{\partial}{\partial a_l}\left[\alpha_{kj}\dfrac{\partial v}{\partial a_j}\right]$

$= \underbrace{\alpha_{kl}\alpha_{kj}\dfrac{\partial^2 v}{\partial a_l \partial a_j}}_{\substack{k \to p \\ l \to i}} + \alpha_{kl}\dfrac{\partial \alpha_{kj}}{\partial a_l}\dfrac{\partial v}{\partial a_j}$

as given with

We need to show

$$\alpha_{kl}\frac{\partial \alpha_{kj}}{\partial a_l}\frac{\partial v}{\partial a_j} = \frac{\partial \alpha_{pi}}{\partial x_p}\frac{\partial v}{\partial a_i} + \alpha_{ij}\frac{\partial \overset{x_i}{\overset{\shortparallel}{X_i}}}{\partial t}\frac{\partial v}{\partial a_j}$$

$$= \frac{\partial \alpha_{kj}}{\partial x_k}\frac{\partial v}{\partial a_j} + \alpha_{kj}\frac{\partial X_k}{\partial t}\frac{\partial v}{\partial a_j}$$

$$= \left(\frac{\partial \alpha_{kj}}{\partial x_k} + \alpha_{kj}\frac{\partial X_k}{\partial t}\right)\frac{\partial v}{\partial a_j}$$

& note $\alpha_{kl} = \dfrac{\partial a_l}{\partial x_k}$

we want to show $\alpha_{kl}\dfrac{\partial \alpha_{kj}}{\partial a_l} = \dfrac{\partial \alpha_{kj}}{\partial x_k} + \alpha_{kj}\dfrac{\partial x_k}{\partial t}$

ugh

well I don't get this. I think he is now considering v as $v(\underline{a},t)$

So that $\cancel{\dfrac{\partial v(\underline{x},t)}{\partial t} = \dfrac{\partial v}{\partial t} + \dfrac{\partial v}{}}$ should be V really

$$\left(v(\underline{x},t) = v(\underline{x}(\underline{a},t),t) \equiv \overset{\downarrow}{V}(\underline{a},t)\right)$$

so $\dfrac{\partial v}{\partial t}\Big|_{\underline{a}} = \dfrac{\partial v}{\partial t}\Big|_{\underline{x}} + \dfrac{\partial x_i}{\partial t}\dfrac{\partial v}{\partial x_i}$

& his required eq

note this is particle velocity

$$\frac{\partial v}{\partial t}\Big|_{\underline{x}} = \frac{\partial v}{\partial t}\Big|_{\underline{a}} - \frac{\partial x_i}{\partial t}\frac{\partial v}{\partial x_i} = \nabla^2 v + \ldots$$

so $\dfrac{\partial v}{\partial t}\Big|_{\underline{a}} = \alpha_{kl}\alpha_{kj}\dfrac{\partial^2 v}{\partial a_l \partial a_j} + \overset{1}{\underbrace{\alpha_{kl}\dfrac{\partial \alpha_{kj}}{\partial a_l}}}\dfrac{\partial v}{\partial a_j} + \overset{2}{\dfrac{\partial x_i}{\partial t}\dfrac{\partial v}{\partial x_i}} + v(1-v)f(v)$

As before

2

$$\frac{\partial v}{\partial x_i} = \frac{\partial a_j}{\partial x_i}\frac{\partial v}{\partial a_j} = \alpha_{ij}\frac{\partial v}{\partial a_j}$$

and also

$$\frac{\partial \alpha_{ki}}{\partial x_k} = \frac{\partial \alpha_{ki}}{\partial a_j}\frac{\partial a_j}{\partial x_k} = \alpha_{kj}\frac{\partial \alpha_{ki}}{\partial a_j} \quad (1)$$

via (1)

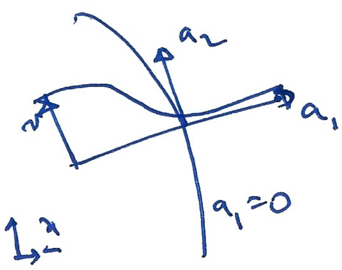
So

$$\left.\frac{\partial v}{\partial t}\right|_{\underline{a}} = \alpha_{kl}\alpha_{kj}\frac{\partial^2 v}{\partial a_l \partial a_j} + \frac{\partial \alpha_{kj}}{\partial x_k}\frac{\partial v}{\partial a_j} + \alpha_{ij}\frac{\partial v}{\partial a_j}\frac{\partial x_i}{\partial t} + v(1-v)f(v)$$

✓ $\quad k \to p,\ j \to i \quad$ ✓

I'm sure there is a prettier way

(c)



$\underline{\alpha} = (\alpha_{11}, \alpha_{21})$, $|\underline{\alpha}| = 1$

$$\underline{\alpha} = \left(\frac{\partial a_1}{\partial x_1}, \frac{\partial a_1}{\partial x_2}\right) = \underline{\nabla} a_1$$

(i) The normal to the wave front is $\underline{\nabla} a_1 = \underline{\alpha} \Rightarrow \square$.

(ii) We assume v changes rapidly in the front whose variation along the front is slow.

Specifically we suppose $\frac{\partial}{\partial a_1} \sim 1$ $\quad \frac{\partial}{\partial a_2} \sim \varepsilon$ say

Now note that the curvature is $2\kappa = \underline{\nabla}\cdot\underline{n} = \underline{\nabla}\cdot\underline{\alpha}$

and the front velocity is $\frac{\partial \underline{x}}{\partial t}\cdot\underline{n} = \frac{\partial x_i}{\partial t}\alpha_{i1}$

So approximately we have

$$\cancel{*} v_t = \cancel{\alpha_{p1}} \cancel{\alpha_{p1}}$$

$$\alpha_{p1}\alpha_{p1} v_{a_1 a_1} + \frac{\partial \alpha_{p1}}{\partial x_p} v_{a_1} + \alpha_{i1}\frac{\partial x_i}{\partial t} \cancel{*} v_{a_1} + v(1-v)f(v)$$

The front velocity is $v_n = \alpha_{i1}\dfrac{\partial x_i}{\partial t}$

the curvature say $K = 2\kappa = \nabla\cdot\underset{\sim}{\alpha} = \dfrac{\partial \alpha_{i1}}{\partial x_i}$

~~So we have~~ & $\alpha_{p1}\alpha_{p1} = \alpha_{11}^2 + \alpha_{21}^2 = 1$ as $|\underset{\sim}{\alpha}| = 1$

$$\Rightarrow v_t = v_{a_1 a_1} + (K + v_n) v_{a_1} + v(1-v)f(v)$$

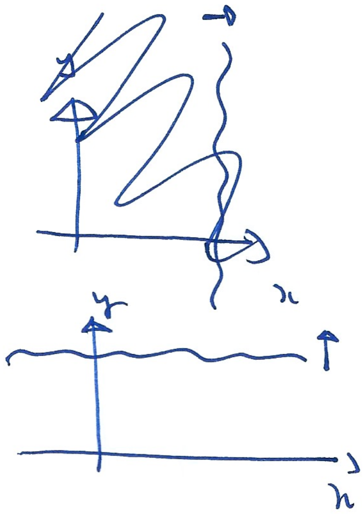
and this has a steady solution (we are in a travelling frame)

iff $K + v_n = c$

Since we know $v'' + cv' + v(1-v)f(v) = 0$ works.

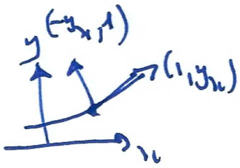
(d) wave front is

$$x = s, \quad y = ct + \delta h(s,t)$$



$$K = \frac{-\delta h_{ss}}{(1+\delta^2 h_s^2)^{3/2}}$$

$$\Rightarrow \quad \frac{-\delta h_{ss}}{(1+\delta^2 h_s^2)^{3/2}} + v_n = c$$



The curve is

$$y = ct + \delta h(x,t)$$

So $y_x = \delta h_x = \delta h_s$

$$\underset{\sim}{n} = \frac{(-\delta h_s, 1)}{(1+\delta^2 h_s^2)^{1/2}}$$

$$\underline{v} = (\dot{x}, \dot{y}) = (0, c + \delta h_t)$$

$$v_n = \frac{c + \delta h_t}{(1+\delta^2 h_s^2)^{1/2}} = F$$

So

$$\frac{-\delta h_{ss}}{(1+\delta^2 h_s^2)^{3/2}} + \frac{c + \delta h_t}{(1+\delta^2 h_s^2)^{1/2}} = c$$

ii

C6

Expanding for small δ

$$-\delta h_{ss} + c + \delta h_t + O(\delta^2) = c$$

$$\Rightarrow h_t = h_{ss}$$

diffusion so stable

[gosh what is this $h \in L^2$?!]

maybe he wants $\frac{d}{dt}\int_{-\infty}^{\infty} h^2 \, ds = -\int_{-\infty}^{\infty} h_s^2 \, ds < 0$!]

CS-12 Math Physiol ~~2013~~ 2013 q 1

(1

1/

$$\varepsilon \dot{v} = -m^3(v)(0.8-n)(v-1) - \gamma_K n^4 (v+v_K) = g(v,n)$$

$$\tau_n \dot{n} = n_\infty(v) - n$$

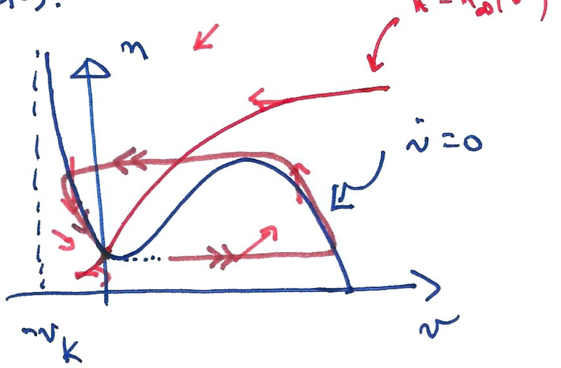
$\varepsilon = 2 \times 10^{-3}$

$v_K = 0.1$

Equilibrium is $v=0$, $n = n_{eqm}$, unique, stable

(a)(i) n is a gate variable for potassium ion channel transport (each channel has 4 n-gates): n represents the fraction of open n-gates.

(ii)



doesn't ask for proof of this

iii with also the n nullcline as above

- large n: $\dot{n}<0$, $\dot{v}<0$

⇒ as indicated by arrows, trajectories cycle round the equilibrium

⇒ $\varepsilon \ll 1$ ⇒ as shown in brown a small disturbance causes a large disturbance ⇒ excitable

(b) $\varepsilon v_t = \varepsilon^2 v_{xx} + g(v,n)$

(g as defined top of p1)

$\tau_n n_t = n_\infty(v) - n$

$v \to 0,\ n \to n_{eq}$ as $x \to \pm\infty$

(i) $y = x - ct$

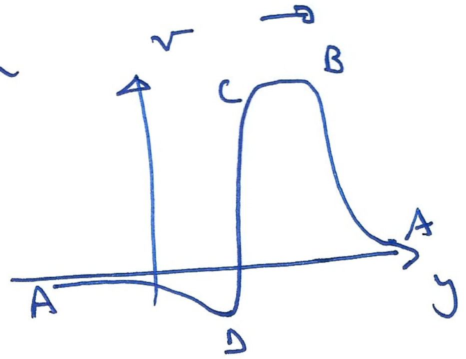
$Y = \frac{y}{\varepsilon}$, $c > 0$

$v(y)$ etc

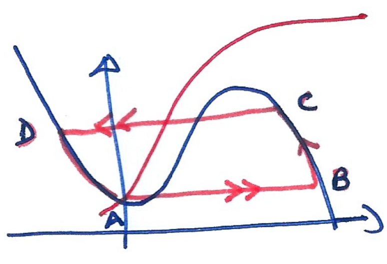
$-\varepsilon c v' = \varepsilon^2 v'' + g$

$-c\tau_n n' = n_\infty - n$

The wave will be as shown



& corresponding trajectory in (v,n) space



The wavefront is a fast phase, $y = \varepsilon Y$

$\Rightarrow \quad -cv' = v'' + g(v,n) \qquad ' = \frac{d}{dY}$

$-c\tau_n n' = \varepsilon(n_\infty - n)$

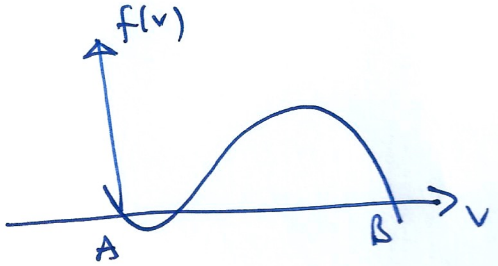
$\Rightarrow n \simeq n_{eq}, \quad v'' + cv' + f(v) = 0$ where $f(v) = g(v, n_{eq})$

from the figures above

$$v \to 0 \text{ as } y \to +\infty$$

(ii) Also as $y \to -\infty$ $v \to v_B$ where $f(v_B) = 0$

viz $-m^3(v_B)(0.8 - n_{eq})(v_B - 1) - \gamma_K n_{eq}^4 (v_B + v_K) = f(v_B)$



we note that $-m^3(0)(0.8 - n_{eq}).-1 - \gamma_K n_{eq}^4 v_K = 0$

(since $g(0, n_{eq}) \equiv 0$ & so $f(0) = 0$)

therefore v_B satisfies

$$-m^3(v_B)(0.8 - n_{eq})(v_B - 1) - \left(\frac{v_B}{v_K} + 1\right) m^3(0)(0.8 - n_{eq}) = 0$$

& thus $v_B - 1 = \left(\frac{v_B}{v_K} + 1\right) \dfrac{m^3(0)}{m^3(v_B)}$

and the approximate value of this for small $m^3(0)$

$(m^3(0) \ll \{ v_K m^3(v_B))$

is $v_B \approx 1$ (the other two values are $v_B = 0$ & $v_B \ll 1$)

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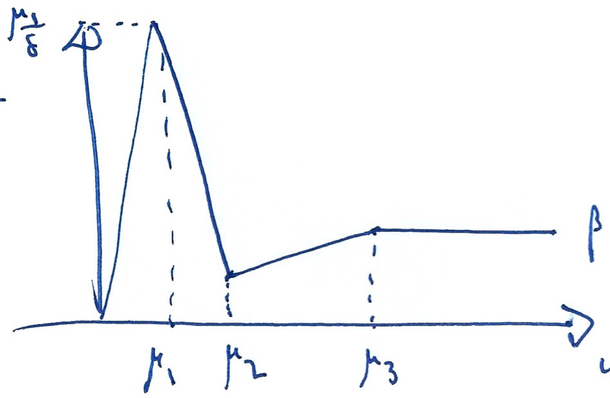
CS.12 Math Physiol 2013 q2

2/

$\dot{u} + \dot{v} = \mu - u$

$\varepsilon \dot{v} = -v + g(u)$



$\mu_1 = 2/3$

$0 < \varepsilon \ll \delta \ll 1$

$\beta = 0.1 \gg \delta$

μ_2 & μ_3 so g is cts.

$g(\mu_2) = \frac{\mu_1}{\delta} - \frac{1}{\delta}(\mu_2 - \mu_1) = \delta$

$g(\mu_3) = \delta + \delta(\mu_3 - \mu_2) = \beta$

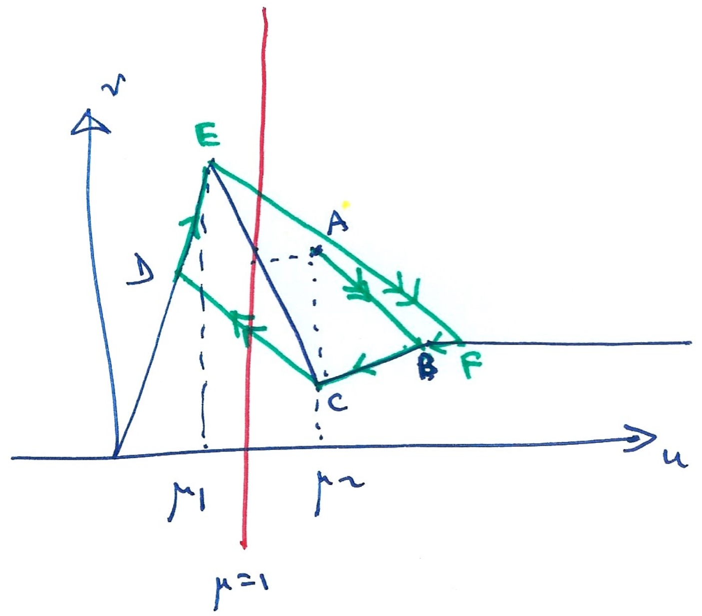
(a) (i) so $\mu_2 - \mu_1 = \mu_1 - \delta^2$ $\mu_2 = \frac{4}{3} - \delta^2$

& $\mu_3 - \mu_2 = \frac{\beta}{\delta} - 1$ $\Rightarrow$ $\mu_3 = \frac{4}{3} - \delta^2 + \frac{\beta}{\delta} - 1$

(ii) as above

$\mu = 1$ so $\mu_1 < \mu < \mu_2$

(b)



(i) Start at A $(\mu_2, g(1))$

v changes rapidly to get to $v = g(u)$

note at A $v > g(u)$ so $\dot{v} < 0$ so heads to right + down.

In this rapid change, $u + v \simeq$ constant

AB : rapidly to v nullcline

BC : slowly on v nullcline to $u = \mu_2$ (as $\dot{u} + \dot{v} < 0$)

CD : rapidly to v nullcline on $u+v$ constant

DE : slowly to $u = \mu_1$ on v nullcline

EF : rapidly to F on v nullcline along $u+v \simeq$ constant

Then repeat (oscillation) F C D E F....

(ii) On AB for $t \sim \varepsilon$ $\dot{u} + \dot{v} \approx 0$ So $u + v \simeq \mu_2 + g(1)$

Well $t_* \sim \varepsilon$. In more detail $t = \varepsilon T$ $(u+v)' \simeq 0$
$\Rightarrow u + v \approx \mu_2 + g(1)$

& $v' \simeq -v + \delta + S(u - \mu_2)$ at least while $u < \mu_3$

Thus $v' \approx -v + \delta + \delta\,[\,g(1) - v\,]$.

Better find where B is.

~~At B~~ At B $\dfrac{v - g(1)}{u - \mu_2} = -1$

$g(1) = \dfrac{2\mu_1 - 1}{\delta} = \dfrac{1}{3\delta}$

So $v = \dfrac{1}{3\delta} - u + \mu_2 = \dfrac{1}{3\delta} + \dfrac{\beta}{\delta} + \dfrac{4}{3} - 1 - \delta^2 - u$

Suppose $v < \beta$ then $\dfrac{\beta + \frac{1}{3}}{\delta} - u + \frac{1}{3} - \delta^2 < \beta$

$\Rightarrow u \approx \dfrac{\beta + \frac{1}{3}}{\delta} > \dfrac{\beta}{\delta} \approx \mu_3$

So B is actually on flat bit.

Well no matter

on AB $(t = \varepsilon T)$ $v' \approx -v + \frac{1}{3} + O(\delta)$

Seems a bit of a vague question since ~~eat~~ within approximation it takes infinite T to get there.

Seems you should just say $t_* \sim \varepsilon$

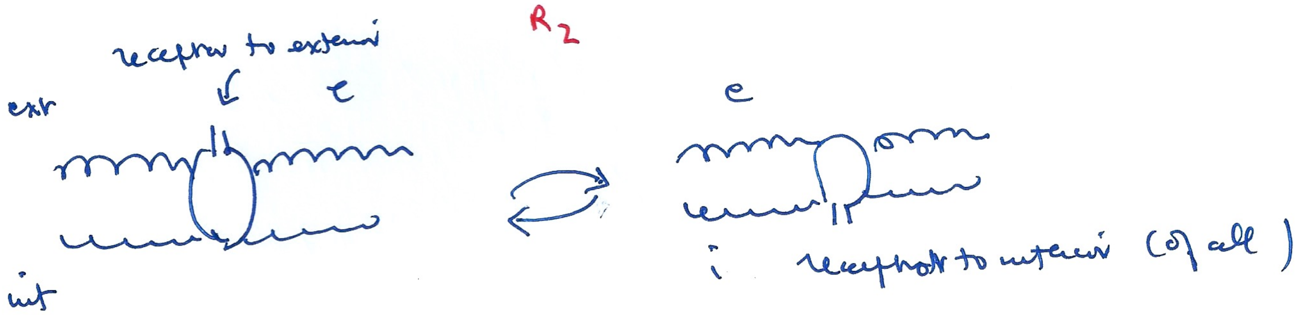
C5.12 (old C8.1b) Math Physiol 2014 q2

2/

(a)

$$S_i + C_i \overset{R_1}{\underset{k_-}{\overset{k_+}{\rightleftharpoons}}} P_i \overset{R_3}{\underset{k_2}{\overset{k_1}{\rightleftharpoons}}} P_e \overset{R_4}{\underset{k_+}{\overset{k_-}{\rightleftharpoons}}} S_e + C_e$$

$$C_i \underset{\underset{R_2}{k_4}}{\overset{k_3}{\rightleftharpoons}} C_e$$



S_i interior ~~bed~~ binds to C_i interior receptor $\to$ complex switches to exterior receptor complex releases exterior substrate

Law of mass action $A+B \xrightarrow{r} C$ rate of formation of C is $\propto AB$

(b) As in the question, overall rates as indicated in diagram above & then

$$\dot{s}_i = R_1 \qquad (1)$$

$$\dot{c}_i = R_1 + R_2 \qquad (2)$$

$$\dot{p}_i = -R_1 + R_3 \qquad (3)$$

$$\dot{p}_e = -R_3 + R_4 \qquad (4)$$

$$\dot{s}_e = -R_4 \qquad (5)$$

$$\dot{c}_e = -R_4 - R_2 \qquad (6)$$

C2

$c_i + c_e + p_i + p_e$:

Add (2) (6) (3) (4)

$\Rightarrow \dot{(c_i + c_e + p_i + p_e)} = R_4 + R_2 - R_4 - R_2$
$- R_1 + R_3 - R_3 + R_4 = 0$

So $c_i + c_e + p_i + p_e$ is constant

$\dot{(s_i + s_e + p_i + p_e)} = [(1) + (5) + (3) + (4)]$
$R_1 - R_4 - R_1 + R_3 - R_3 + R_4 = 0$

So $s_i + s_e + p_i + p_e$ = constant

p_i, c_i, p_e, c_e quasi-steady

$\Rightarrow R_1 + R_2 = -R_1 + R_3 = -R_3 + R_4 = -R_4 - R_2 = 0$

so $R_1 = -R_2 = R_3 = R_4$

(c) $k_\pm \to \varepsilon k_\pm$:
$$R_1 = \varepsilon[-k_+ s_i c_i + k_- p_i]$$
$$R_4 = \varepsilon[-k_- p_e + k_+ s_e c_e]$$
$$R_2 = k_4 c_e - k_3 c_i$$
$$R_3 = -k_1 p_i + k_2 p_e$$

we have $\dot{s}_e = -R_4 = -\varepsilon[k_+ s_e c_e - k_- p_e]$

So approximately

$$c_i = \frac{k_4}{k_3} c_e \quad , \quad p_i = \frac{k_2}{k_1} p_e \qquad (*)$$

Also

$$c_i + c_e + p_i + p_e = \text{constant}$$
$$s_i + s_e + p_i + p_e = \text{constant}$$

And

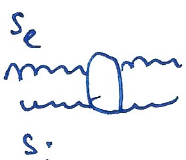
$$\dot{s}_e = \varepsilon [k_- p_e - k_+ c_e s_e]$$

The sneaky bit here is to spot that with $R_1 \approx R_4$

$$\dot{s}_i + \dot{s}_e = R_1 - R_4 \approx 0$$

So $s_i + s_e \approx$ constant
$\Rightarrow p_i + p_e \approx$ constant $\Rightarrow p_i, p_e$ constant
$\Rightarrow c_i + c_e =$ constant $\Rightarrow c_i, c_e$ constant
$\Big\}$ (due to (*))

So then $\dot{s}_e = \varepsilon [k_- p_e - k_+ c_e s_e]$ is a single equation for s_e.

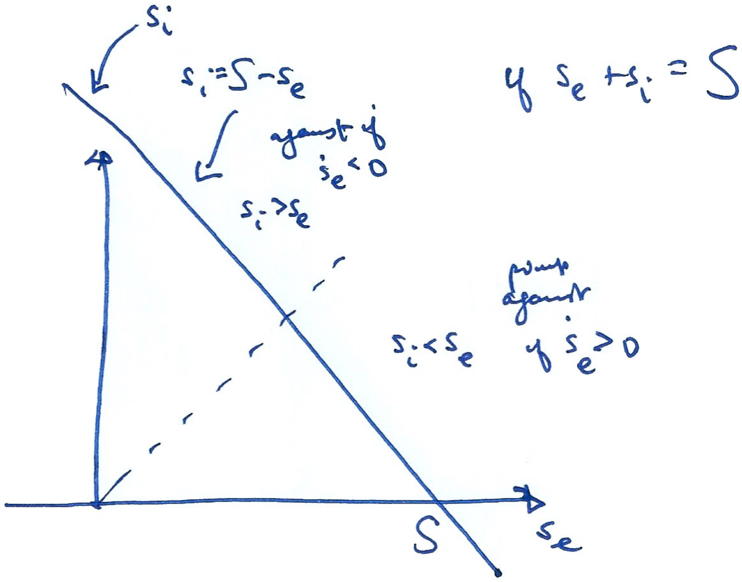


(ii) The pump acts against its gradient
if $\dot{s}_e > 0$ when $s_e > s_i$

Well this is obviously possible depend on values of

$$s_i + s_e = S, \quad p_i + p_e = P, \quad c_i + c_e = C$$

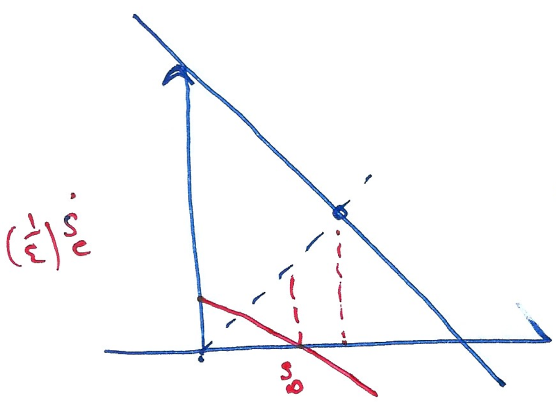
Since $s_e \to \frac{k_- p_e}{k_+ c_e} = S_\infty$



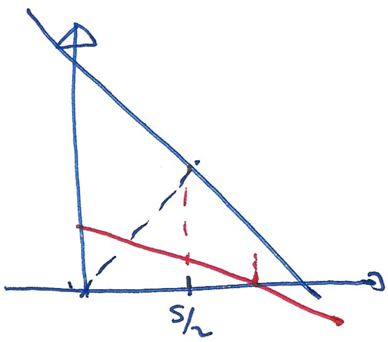
pump is against gradient if $\dot{s}_e > 0$ when $s_e > s_i$
or $\dot{s}_e < 0$ when $s_e < s_i$

3 ~~2~~ cases

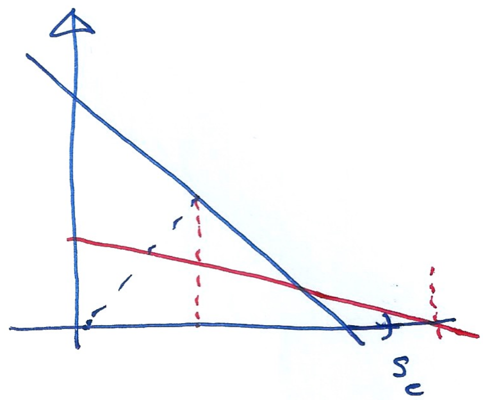
$s_\infty = \dfrac{k_- p e}{k_+ c_e} < S/2$



$S/2 < s_\infty < S$



$s_\infty > S$



$s_\infty < \frac{1}{2}S$ pumps against for $s_\infty < s_e < \frac{1}{2}S$

$\frac{1}{2}S < s_\infty < S$ " $\frac{1}{2}S < s_e < s_\infty$

$s_\infty > S$ " $\frac{1}{2}S < s_e < s_\infty$

So in all cases pump is against the gradient if s_e is between $\frac{1}{2}S$ and s_∞.

(5

iii Now $k_3 \to \varepsilon^2 k_3$

so $R_1 = \varepsilon[-k_+ s_i c_i + k_i p_i]$

$R_4 = \varepsilon[-k_- p_e + k_+ s_e c_e]$

$R_2 = \cancel{k_+ c_i \varepsilon^2 k_3 c_i}\ k_4 c_e - \varepsilon^2 k_3 c_i$

$R_3 = -k_1 p_i + k_2 p_e$

$R_1 \propto -R_2 = R_3 = R_4$

$c_i + c_e + p_i + p_e =$ constant

$s_i + s_e + p_i + p_e =$ constant

As before $\dot{s}_i + \dot{s}_e \simeq R_1 - R_4 \simeq 0$

$s_i + s_e = S$ constant

$c_i + c_e = C$ constant

$p_i + p_e = P$ constant

$R_1, R_4 = O(\varepsilon) \Rightarrow R_2, R_4 = O(\varepsilon)$

$\Rightarrow p_i = \frac{k_2}{k_1} p_e \Rightarrow p_i, p_e$ constant

$R_2 = O(\varepsilon) = c_e = O(\varepsilon)$

$\Rightarrow c_i \simeq C$ constant

$\dot{s}_e = -R_4 = \varepsilon[k_- p_e - k_+ s_e c_e]$

$\simeq \varepsilon[k_- p_e + O(\varepsilon)]$

Depends on p_e : if $P = O(\varepsilon)$ then it will be eventually ok

otherwise $s_e \uparrow$ until $s_e = O(\frac{1}{\varepsilon})$, $s_e = \frac{1}{\varepsilon} S_e \Rightarrow \dot{S}_e \simeq \varepsilon[k_- p_e - k_+ S_e(\frac{c_e}{\varepsilon})]$

6

but then this requires $S_e = O(\frac{1}{\varepsilon})$ $c_e = \varepsilon C_e$

& so we would have $(R_1 \to \varepsilon R_1$ but $R_4 = -\varepsilon[k_- P_e + k_+ S_e C_e]$

$$\dot{s}_i = \varepsilon R_1$$

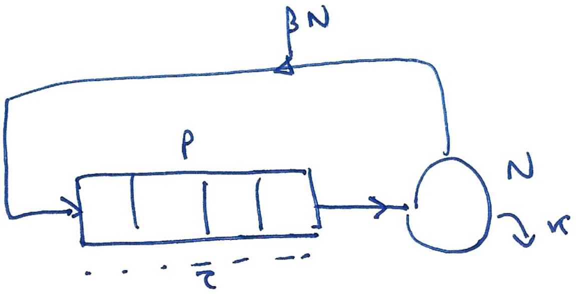
etc..

This is a bit open-ended since we are not told much about S, P etc.

Simple answer is it doesn't work straightforwardly.

CS-12 Math Physiol 2014 q3

3)



$$\dot{p} = -\gamma p + \beta(N)N - e^{-\gamma\tau}\beta(N_\tau)N_\tau$$

$$\dot{N} = -\beta(N)N - \kappa N + 2e^{-\gamma\tau}\beta(N_\tau)N_\tau$$

$$\beta = \beta_0 \exp\left[-N/\beta_1\right]$$

(a) γ apoptosis rate

κ rate of recruitment to maturation

$e^{-\gamma\tau}\beta(N_\tau)N_\tau$ loss to resting phase after passage through mitotic cycle (with delay τ)

$2e^{-\gamma\tau}\beta(N_\tau)N_\tau$ 2× above through cell division

specific recruitment rate to mitosis decreases with increasing N

(b) evidently $t \sim \tau$: scale $P \sim P_0$, $N \sim \beta_1$

$$\Rightarrow \frac{P_0}{\tau}\dot{p} = -\gamma P_0 p + \beta_0\beta_1 e^{-n} n - e^{-\gamma\tau}\beta_0\beta_1 e^{-n_1} n_1$$

$$\Rightarrow \dot{p} = -\gamma\tau p + \frac{\beta_0\beta_1\tau}{P_0} n e^{-n} - \beta_0\beta_1 e^{-\gamma\tau}\frac{\tau}{P_0} n_1 e^{-n_1}$$

$$\frac{\beta_1}{\tau}\dot{n} = -\beta_0\beta_1 n e^{-n} - \kappa\beta_1 n + 2e^{-\gamma\tau}\beta_0\beta_1 n_1 e^{-n_1}$$

$$\Rightarrow \dot{n} = -\beta_0\tau n e^{-n} - \kappa\tau n + 2\beta_0\cancel{\beta_1}\tau e^{-\gamma\tau} n_1 e^{-n_1}$$

and with $b = e^{-n}$ this is of the requested form if

$$c_0 = \gamma\tau$$

$$b_0 = \frac{\beta_0 \beta_1 \tau}{\rho_0}$$

$$b_0 e^{-c_0} = \frac{\beta_0 \beta_1 e^{-\gamma\tau}\tau}{\rho_0} = b_0 e^{-\gamma\tau}$$

and
$$b_0 = \beta_0 \tau$$

$$k_0 = \kappa\tau$$

$$2e^{-c_0} b_0 = 2\beta_0 \tau e^{-\gamma\tau}$$

so $c_0 = \gamma\tau$, $b_0 = \beta_0\tau$, $\rho_0 = \beta_1$

$k_0 = \kappa\tau$

equilibrium $\dot{n} = -b_0 n e^{-n} - k_0 n + 2b_0 e^{-c_0} n_1 e^{-n_1}$

$n = 0 \sim$ $k_0 = e^{-n}(2b_0 e^{-c_0} - b_0)$

$\Rightarrow e^{n} = (2e^{-c_0} - 1)\frac{b_0}{k_0}$

$\Rightarrow n_*$ if RHS > 1 ie $(2e^{-c_0} - 1) b_0 > k_0$

(c)

$n = n^* + m$

linearise $\dot{n} = -b_0 n e^{-n} - k_0 n + 2b_0 e^{-c_0} n_1 e^{-n_1}$

Define $g(n) = n e^{-n}$

$\dot{m} = -b_0 g' m - k_0 m + 2b_0 e^{-c_0} g' m_1$

where $g' = g'(n^*) = (1-n^*)e^{-n^*}$

$\Rightarrow \dot{m} = \alpha_1 m - \alpha_2 m_1$

$\alpha_1 = -b_0 g' - k_0$

$\alpha_2 = -2b_0 e^{-c_0} g'$

$k_0 = 0.1 \quad b_0 = 4 \quad e^{-c_0} = 0.6$

equilibrium $e^{n^*} = (1.2-1)\frac{4}{0.1} = 8 \qquad n^* = \ln 8 \simeq 2$

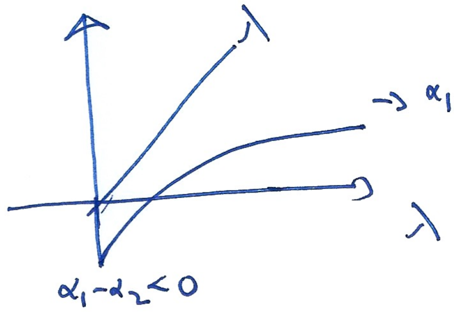
$g' \simeq -0.125$

$$\begin{cases} \alpha_1 \simeq 0.4 \\ \alpha_2 \simeq 0.6 \end{cases}$$

(d) $n = e^{\lambda t}$

(i) $\Rightarrow \lambda = \alpha_1 - \alpha_2 e^{-\lambda}$ $\qquad \alpha_1 = 0.4$, $\alpha_2 = 0.6$

I. +ve root?



slope of RHS $= \alpha_2 e^{-\lambda} < \alpha_2 < 1$ for $\lambda > 0$

& $\alpha_1 - \alpha_2 < 0 \Rightarrow$ no +ve root.

II. +ve real part?

$$\lambda = \alpha_1 - \alpha_2 e^{-\lambda}$$

Since $\alpha_1 < \alpha_2$, usual approach doesn't work

[$\mathrm{Re}\,\lambda > 0 \Rightarrow |\alpha_2 e^{-\lambda}| < \alpha_2$, no good]

If $\lambda = \lambda_R + i\lambda_I$ then

$$\lambda_R = \alpha_1 - \alpha_2 e^{-\lambda_R} \cos \lambda_I$$
$$\lambda_I = \alpha_2 e^{-\lambda_R} \sin \lambda_I$$

but $\dfrac{\sin \lambda_I}{\lambda_I} < 1 \quad \forall \lambda_I$ so $1 = \alpha_2 \dfrac{\sin \lambda_I}{\lambda_I} e^{-\lambda_R}$

$\Rightarrow \lambda_R < 0$ as $\alpha_2 < 1$ $\square$.

ii $k_0 \downarrow$ $b_0 \downarrow$ $\frac{k_0}{b_0}$ fixed.

$$e^{n^*} = (2e^{-c_0} - 1)\frac{b_0}{4k_0} \quad \text{is fixed}$$

$\Rightarrow |g'|$ is fixed

$$\alpha_1 = b_0\left[|g'| - \frac{k_0}{b_0}\right]$$

$$\alpha_2 = 2b_0 e^{-c_0}|g'|$$

so $\alpha_1 \downarrow \alpha_2 \downarrow$ with $\frac{\alpha_1}{\alpha_2}$ fixed

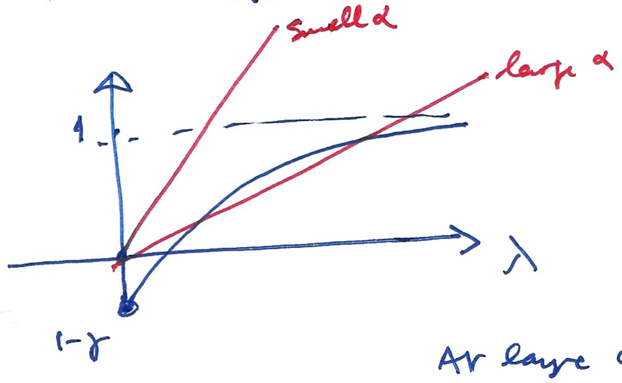
write $\alpha_1 = \alpha$, $\gamma = \cancel{\frac{\alpha_1}{\alpha_2}}$ $\frac{\alpha_2}{\alpha_1}$

$$\lambda = \alpha\left[1 - \gamma e^{-\lambda}\right]$$

for $\gamma > 1$, $\lambda = \lambda(\alpha)$. For $\alpha = 0.4$ $\mathrm{Re}\,\lambda < 0$
$(\gamma = 1.5)$.

The argument of part II above shows that $\exists\ \lambda_R < 0$ if λ is complex

$$1 - \gamma e^{-\lambda} = \frac{\lambda}{\alpha}, \quad \lambda \text{ real}, \quad \gamma > 1$$



~~It means λ with zero~~

~~Re λ to λ > 0~~

??

$\therefore$ λ never crosses zero

At large α, 2 +ve roots but via two complex roots becoming real

$\Rightarrow$ Hopf bifurcation at earlier (large α)

Hopf bifurcation?

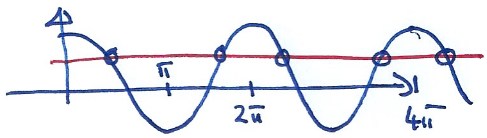
$$\lambda = \alpha\left[1 - \gamma e^{-\lambda}\right]$$

vary α $\quad \lambda = i\theta$

$$i\theta = \alpha\left[1 - \gamma e^{-i\theta}\right]$$

$$0 = 1 - \gamma\cos\theta$$

$$\theta = \alpha\gamma\sin\theta$$



$\theta = \cos^{-1}\frac{1}{\gamma}$ for $\gamma > 1$

or with $\phi = \cos^{-1}\frac{1}{\gamma} \in (0, \pi/2)$

$\theta = 2n\pi \pm \phi \qquad n = 0, 1 \ldots$

& $\alpha = \dfrac{\theta}{\gamma\sin\theta}$ gives sequence of increasing +ve values

$$\alpha_n = \frac{2n\pi + \phi}{\gamma\sin\phi} = \frac{2n\pi + \phi}{(\gamma^2 - 1)^{1/2}}$$

first is $\alpha_0 = \dfrac{\cos^{-1}\frac{1}{\gamma}}{\sqrt{\gamma^2 - 1}}$ $\qquad$ with $\gamma = 1.5$

$\alpha_0 \simeq 0.75$

Transversality $\lambda(\alpha)$

$$\lambda' = 1 - \gamma e^{-\lambda} + \alpha\gamma e^{-\lambda}\lambda'$$

$$= \frac{\lambda}{\alpha} + (\alpha - \lambda)\lambda'$$

so $\lambda' = \dfrac{\lambda}{\alpha(1 - \alpha + \lambda)}$, at $\lambda = i\theta$, $\lambda' = \dfrac{i\theta\left[1 - \alpha - i\theta\right]}{\alpha\left[(1-\alpha)^2 + \theta^2\right]}$

$\Rightarrow \mathrm{Re}\,\lambda' = \dfrac{\theta^2}{\alpha\left[(1-\alpha)^2 + \theta^2\right]} > 0$ so Hopf as α increases through

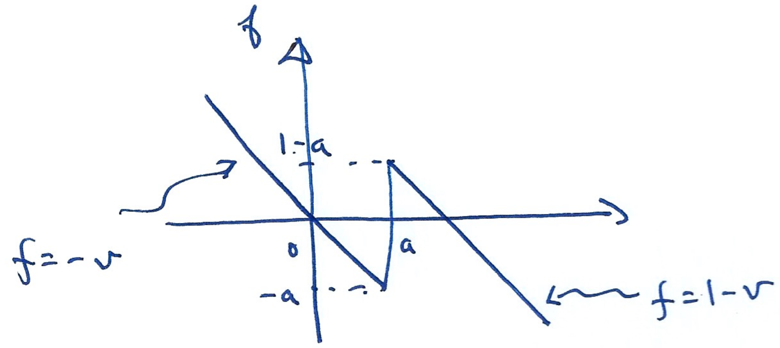
$\dfrac{\cos^{-1}\frac{1}{\gamma}}{\sqrt{\gamma^2 - 1}} \simeq 0.75$

not as $\alpha\downarrow$.

C5.12 Math Physiol 2015 q1 answer

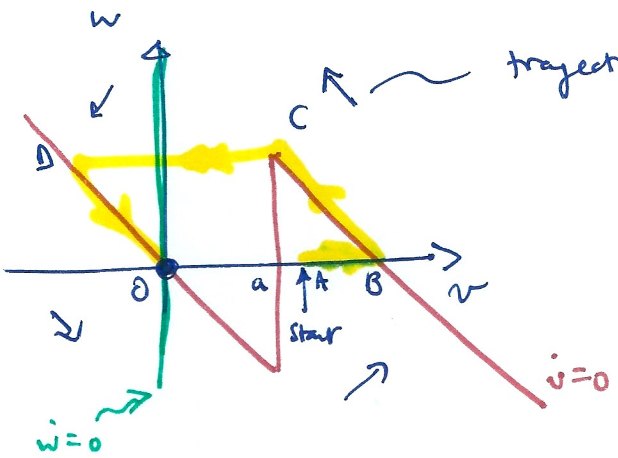
1, (a) $\varepsilon \dot{v} = f(v) - w$

$\dot{w} = v$



(i) v electrical potential etc

w gate variable etc



trajectories cycle as shown

(~~[illegible]~~ $v > 0$, $w > f(v)$ $\Rightarrow$ $\dot{v} < 0$, $\dot{w} > 0$)

(0,0) unique equilibrium

Near (0,0) $\begin{pmatrix}\dot{v}\\ \dot{w}\end{pmatrix} \approx \underbrace{\begin{pmatrix}-\frac{1}{\varepsilon} & -1\\ 1 & 0\end{pmatrix}}_{M}\begin{pmatrix}v\\ w\end{pmatrix}$ etc

$\det M = 1$

$\operatorname{tr} M = -\frac{1}{\varepsilon}$

$\Rightarrow$ stable

(2

Starting at A $(v^*, 0)$ $v^* > a$ trajectory is as

shown: ABCDO : AB fast to v nullcline as $\varepsilon \ll 1$

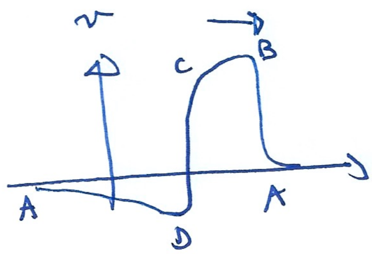
BC slow

CD fast

DO slow

$\Rightarrow$ steady state is excitable

(b)
$$\varepsilon v_t = \varepsilon^2 v_{xx} + f(v) - w$$
$$w_t = v$$



$y = x - ct$, $c > 0$

$v = v(y)$, $w = w(y)$

(i) $$-\varepsilon c v' = \varepsilon^2 v'' + f(v) - w$$
$$-cw' = v$$

(ii) $y = \varepsilon Y$ $\Rightarrow$ $$-cv' = v'' + f(v) - w$$

in front AB $$w' = \varepsilon v$$

$\Rightarrow w' \simeq 0 \Rightarrow w = 0$ $(w \to 0$ as $Y \to \infty)$

$$\Rightarrow v'' + cv' + f(v) = 0$$

BCS $v \to 0$ as $Y \to \infty$

$v \to 1$ (only other linearically stable steady state) as $Y \to -\infty$

(3

iii

we have to get from $v=1$ at $y=-\infty$

to $v=0$ at $y=+\infty$

for $v>a$ $\quad v''+cv'+1-v=0$

$f=1-v$

solutions exponentials

& $1-v \propto e^{\lambda y}$

$-\lambda^2 - c\lambda + 1 = 0$

$\lambda^2 + c\lambda - 1 = 0$

$\lambda = \frac{1}{2}\left[-c \pm \{c^2+4\}^{1/2}\right] = \lambda_\pm \qquad \lambda_+>0, \ \lambda_-<0$

we need $\lambda>0$ so $1-v \to 0$ as $y \to -\infty$

$\Rightarrow \quad 1-v = e^{\lambda_+ y}$ (coeff $=1$ wlog as just fixes origin)

till $v=a$ at $y = \frac{1}{\lambda_+}\ln(1-a) = y_a$

& $v' = -\lambda_+ e^{\lambda_+ y_a} = -\lambda_+(1-a)$

for $v<a$ $\quad v''+cv'-v=0$ $\quad$ solutions $e^{\lambda_\pm y}$ as before

~~Solution~~ we need λ_- so $v \to 0$ as $y \to \infty$

thus & require $v = a e^{\lambda_-(y-y_a)}$

& v' cts at y_a so $\lambda_- a = -\lambda_+(1-a)$

or $\frac{1}{2}\left[c+(c^2+4)^{1/2}\right]a = \frac{1}{2}\left[-c+(c^2+4)^{1/2}\right](1-a)$

So $ca + c(1-a) = -(c^2+4)^{1/2}a + (c^2+4)^{1/2}(1-a)$

~~i.e. $c(2-a) = (c^2+4)^{1/2}a$~~

$\Rightarrow c = (c^2+4)^{1/2}(1-2a)$ requires $a<\frac{1}{2}$ for $c>0$

$\Rightarrow c^2 = (c^2+4)(1-2a)^2$

~~$= c^2(1-2a) + 4(1-2a)$~~

~~$\Rightarrow c^2 = \frac{2(1-2a)}{}$~~

$c^2\left[1-(1-2a)^2\right] = 4(1-2a)^2$

$c^2\left[4a-4a^2\right]$

So $c = \dfrac{1-2a}{[a(1-a)]^{1/2}}$

(iv) well come on you already told us c was +ve

anyway what he wants is

$v'' + cv' + f(v) = 0$

$\frac{1}{2}v'^2\Big|_{-\infty}^{\infty} + c\int_{-\infty}^{\infty} v'^2\,dy + \int_1^0 f(v)\,dv = 0$

ie $c = \dfrac{\int_0^1 f(v)\,dv}{\int_{-\infty}^{\infty} v'^2\,dy} \gtrless 0$ if $\int_0^1 f(v)\,dv \gtrless 0$

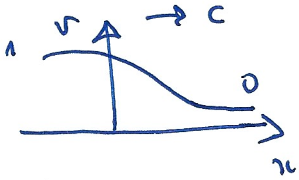
evidently if $a \lessgtr \frac{1}{2}$

(this sign is wrong)

C5.12 Math Physiol 2015 Q2 answer

2/

$$\varepsilon v_t = \varepsilon^2 \nabla^2 v + f(v) \quad , \quad f = Av(v-a)(1-v)$$



(a) $\underline{x} = \underline{x}(\underline{X}, t)$ Jacobian $\frac{\partial \underline{x}}{\partial \underline{X}} = \underline{J}$, $J_{ij} = \frac{\partial x_i}{\partial X_j}$

inverse is $\underline{X} = \underline{X}(\underline{x}, t)$ Jacobian $(=J^{-1}) = \underline{K}$, $K_{ij} = \frac{\partial X_i}{\partial x_j}$

note $JK = \underline{I}$.

$$\underline{e}_i = \frac{\partial \underline{x}}{\partial X_i}$$

(i) Since X_2 & X_3 define local cartesian coordinates in the interface, if we assume $\underline{X}$ is an orthogonal system, then X_1 is normal to the interface, so at $X_1 = 0$ (on the interface) $\underline{e}_1$ is normal to the interface.

this is just the material derivative

(ii) We have $\left.\frac{\partial v}{\partial t}\right|_{\underline{X}} = \left.\frac{\partial v}{\partial t}\right|_{\underline{x}} + \left.\frac{\partial x_i}{\partial t}\right|_{\underline{X}} \frac{\partial v}{\partial x_i}$ $\quad (v(\underline{x}, t) = v[\underline{x}(\underline{X}, t), t]$ $= v(\underline{X}, t))$

Also $\frac{\partial}{\partial x_i} = \frac{\partial X_j}{\partial x_i}\frac{\partial}{\partial X_j} = K_{ji}\frac{\partial}{\partial X_j}$ (use summation convention)

so $\frac{\partial v}{\partial x_i} = K_{ji}\frac{\partial v}{\partial X_j}$

$$\nabla^2 v = \frac{\partial^2 v}{\partial x_i \partial x_i} = \frac{\partial}{\partial x_i}\left[K_{ji}\frac{\partial v}{\partial X_j}\right] = K_{ki}\frac{\partial}{\partial X_k}\left[K_{ji}\frac{\partial v}{\partial X_j}\right]$$

$$= K_{ki}K_{ji}\frac{\partial^2 v}{\partial X_j \partial X_k} + K_{ki}\frac{\partial K_{ji}}{\partial X_k}\frac{\partial v}{\partial X_j}$$

So the equation is $(v = \underline{v}(\underline{X}, t))$, $\frac{\partial v}{\partial x_i} = K_{ji}\frac{\partial v}{\partial X_j}$

$$\varepsilon v_t = \varepsilon \frac{\partial x_i}{\partial t}\Big|_{\underline{X}} K_{ji}\frac{\partial v}{\partial X_j} + \varepsilon^2\left[K_{ki}K_{ji}\frac{\partial^2 v}{\partial X_j \partial X_k} + K_{ki}\frac{\partial K_{ji}}{\partial X_k}\frac{\partial v}{\partial X_j}\right]$$

Note $K_{ki}\frac{\partial K_{ji}}{\partial X_k} = \frac{\partial X_k}{\partial x_i}\frac{\partial K_{ji}}{\partial X_k} = \frac{\partial K_{ji}}{\partial x_i}$

in particular $\frac{\partial K_{1i}}{\partial x_i} = \frac{\partial}{\partial x_i}\left[\frac{\partial X_1}{\partial x_i}\right]$

note also $\underline{\nabla} X_1$ is the normal to the interface

thus $\frac{\partial K_{1i}}{\partial x_i} = \underline{\nabla}\cdot[\underline{\nabla} X_1]$

We can assume (otherwise rescale X_1) that in fact $\underline{\nabla} X_1 = \underline{n}$ (unit normal)

then $n_i = K_{1i}$ and $\underline{K_{1i}K_{1i} = 1}$

$$\text{So } \varepsilon v_t = \varepsilon \frac{\partial x_i}{\partial t}\Big|_{\underline{X}} K_{ji}\frac{\partial v}{\partial X_j} + \varepsilon^2 K_{ki}K_{ji}\frac{\partial^2 v}{\partial X_j \partial X_k} + \varepsilon^2\frac{\partial K_{ji}}{\partial x_i}\frac{\partial v}{\partial X_j}$$

Next we assume v changes rapidly with X_1, $X_1 = \varepsilon\xi$

then to leading order

$$0 = \underbrace{\frac{\partial x_i}{\partial t}\Big|_{\underline{X}} K_{1i}}_{K_{1i} = n_i}\frac{\partial v}{\partial \xi} + \underbrace{K_{1i}K_{1i}}_{=1}\frac{\partial^2 v}{\partial \xi^2} + \varepsilon\underbrace{\frac{\partial K_{1i}}{\partial x_i}}_{\underline{\nabla}\cdot\underline{n}}\frac{\partial v}{\partial \xi} + f(v)$$

$$\Rightarrow 0 = v_{\xi\xi} + \Big[\underbrace{\underline{n}\cdot\frac{\partial \underline{x}}{\partial t}\Big|_{\underline{X}}}_{\substack{u_n \\ \text{normal velocity} \\ \text{of front}}} + \varepsilon\,\underline{\nabla}\cdot\underline{n}\Big]v_\xi + f(v)$$

and we know that the solution of this is $V(\xi)$ satisfying

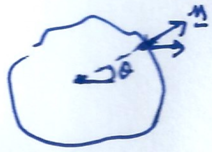
$$V'' + cV' + f(V) = 0$$

Therefore
$$\underbrace{\underline{n}\cdot\frac{\partial \underline{x}}{\partial t}}_{u_n} + \varepsilon \nabla\cdot\underline{n} = c$$

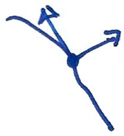
(iii) $\underline{n}\cdot\frac{\partial \underline{x}}{\partial t}$ is ~~norm.~~ front speed

$\nabla\cdot\underline{n}$ is curvature

(b) The wave front is at $r = R(\theta, t)$



So $x = R\cos\theta$
$y = R\sin\theta$



$$\underline{n} \propto (dy, -dx)$$

$$\propto \left(R'\sin\theta + R\cos\theta,\ -R'\cos\theta + R\sin\theta\right)$$

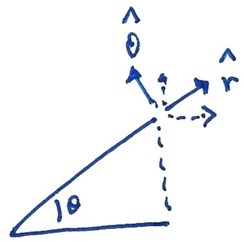
$$\text{so } \underline{n} = \frac{(R'\sin\theta + R\cos\theta,\ -R'\cos\theta + R\sin\theta)}{[R'^2\sin^2\theta + R^2\cos^2\theta + 2RR'\sin\theta\cos\theta + R'^2\cos^2\theta + R^2\sin^2\theta - 2RR'\sin\theta\cos\theta]^{1/2}}$$

$$= \frac{(R'\sin\theta + R\cos\theta,\ -R'\cos\theta + R\sin\theta)}{(R'^2 + R^2)^{1/2}}$$

$$\frac{\partial \underline{x}}{\partial t} = R_t(\cos\theta, \sin\theta)$$

$$\text{so } \underline{n}\cdot\frac{\partial \underline{x}}{\partial t} = \frac{R_t\,[R'\sin\theta\cos\theta + R\cos^2\theta - R'\sin\theta\cos\theta + R\sin^2\theta]}{(R^2 + R'^2)^{1/2}}$$

$$= \frac{RR_t}{(R^2 + R'^2)^{1/2}}$$



In cartesian coordinates

$$\underline{n} = \frac{(R'\sin\theta + R\cos\theta,\ -R'\cos\theta + R\sin\theta)}{(R^2+R'^2)^{1/2}}$$

we want this in cylindrical polars

note $\hat{\underline{r}} = \underline{i}\cos\theta + \underline{j}\sin\theta$

$\hat{\underline{\theta}} = -\underline{i}\sin\theta + \underline{j}\cos\theta$

so $\underline{i} = \hat{\underline{r}}\cos\theta - \hat{\underline{\theta}}\sin\theta$

$\underline{j} = \hat{\underline{r}}\sin\theta + \hat{\underline{\theta}}\cos\theta$

& so

$$\underline{n} = \frac{1}{(R^2+R'^2)^{1/2}}\Big[\overbrace{(R'\sin\theta + R\cos\theta)\cos\theta + (-R'\cos\theta + R\sin\theta)\sin\theta}^{\hat{r}},$$

$$\overbrace{-(R'\sin\theta + R\cos\theta)\sin\theta + (-R'\cos\theta + R\sin\theta)\cos\theta}^{\hat{\theta}}\Big]$$

$$= \frac{1}{(R^2+R'^2)^{1/2}}[R,\ -R']$$

$$\& \ \underline{\nabla}\cdot\underline{n} = \frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{R}{(R^2+R'^2)^{1/2}}\right) + \frac{1}{r}\frac{\partial}{\partial\theta}\left[\frac{-R'}{(R^2+R'^2)^{1/2}}\right]$$

at $r=R$,

$$= \frac{1}{R}\left[\frac{R}{(R^2+R'^2)^{1/2}} - \frac{R''}{(R^2+R'^2)^{1/2}} + \frac{R'(RR'+R'R'')}{(R^2+R'^2)^{3/2}}\right]$$

$$= \frac{1}{R(R^2+R'^2)^{3/2}}\left[R(R^2+R'^2) - R''(R^2+R'^2) + RR'^2 + R'^2R''\right]$$

$$= \frac{1}{R(R^2+R'^2)^{3/2}}\left[R^3 + 2RR'^2 - R^2R''\right]$$

$$= \frac{R^2+2R'^2-RR''}{(R^2+R'^2)^{3/2}}$$

phew

So $$c = \frac{RR_t}{(R^2+R'^2)^{1/2}} + \frac{\varepsilon(R^2+2R'^2-RR'')}{(R^2+R'^2)^{3/2}}$$

or $$R_t = \frac{c(R^2+R'^2)^{1/2}}{R} - \frac{\varepsilon(R^2+2R'^2-RR'')}{R(R^2+R'^2)}$$ $\left(R' = R'(\theta) = \frac{\partial R}{\partial \theta}\right)$

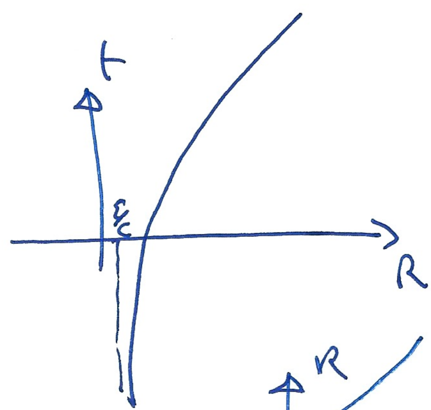
!!!

(ii) $R = R(t)$ $\Rightarrow$ $\dot{R} = c - \frac{\varepsilon}{R} = \frac{cR-\varepsilon}{R}$

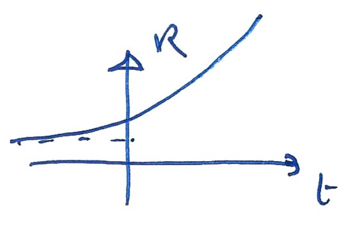
So $$\frac{R\dot{R}}{cR-\varepsilon} = 1$$

$$= \frac{R - \frac{\varepsilon}{c} + \frac{\varepsilon}{c}}{c(R-\frac{\varepsilon}{c})}$$

$$\Rightarrow \quad ct = R + \frac{\varepsilon}{c}\ln\left(R-\frac{\varepsilon}{c}\right)$$



So I suppose curvature blocking refers to the fact that it doesn't work for small R (curvature too large)



iii; seems a bit long....

$r = R(t) + \rho \qquad \rho(\theta, t)$ small

so $$\dot{R} + \rho_t = \frac{c\left(R^2 + 2R\rho \ldots \ldots\right)^{1/2}}{(R+\rho)} + \varepsilon\frac{\left[R\rho_{\theta\theta} \ldots - R^2 - 2R\rho \ldots\right]}{(R+\rho)(R^2 + 2R\rho \ldots)}$$

$\times$ by $R+\rho$

$$R\dot{R} + R\rho_t + \dot{R}\rho + \ldots = cR\left(1 + \frac{\cancel{2}\rho}{R}\ldots\right) \cancel{+} - \varepsilon + \frac{\varepsilon}{R}\rho_{\theta\theta}\ldots$$

$O(1)$ cancel so $(R\dot{R} = cR - \varepsilon)$

$$R\rho_t + \dot{R}\rho = \cancel{2}c\rho + \frac{\varepsilon}{R}\rho_{\theta\theta}$$

& $\dot{R} = c - \frac{\varepsilon}{R}$ $\qquad$ So $R\dot{\rho} = \frac{\varepsilon}{R}(\rho + \rho_{\theta\theta})$

& solutions are $\rho = \sum_m e^{im\theta}\rho_m(t)$ $\qquad$ ($m \neq 0$ as we can take mean of ρ to be 0 w.l.o.g.)

$$\Rightarrow R\dot{\rho}_m = \frac{\varepsilon}{R}(\rho_m - m^2\rho_m)$$
$$= -\frac{\varepsilon}{R}(m^2 - 1)\rho_m$$

so $|m| > 1$ decay

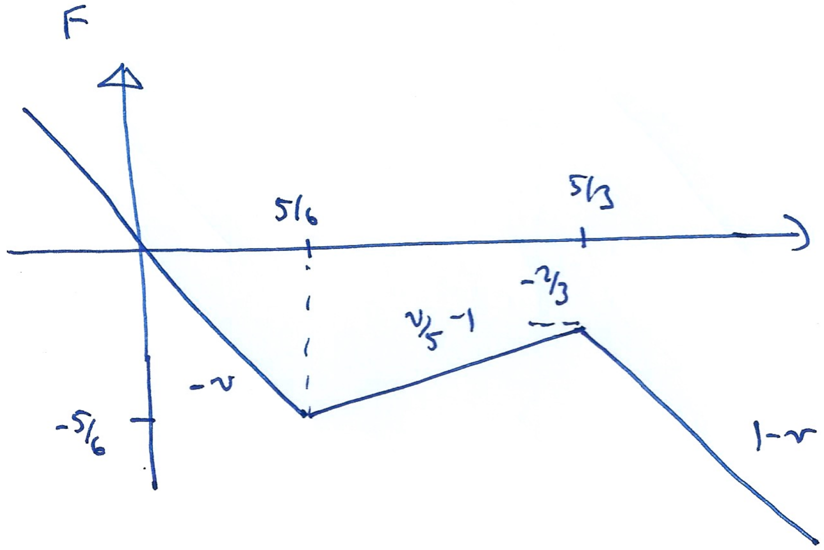
$|m| = 1$ neutrally stable apparently $\qquad$ (modulo algebra)

(1

C5.12 Math Physiol 2016 q 1

(a) $\quad \varepsilon \dot{v} = I + f(v) - w$

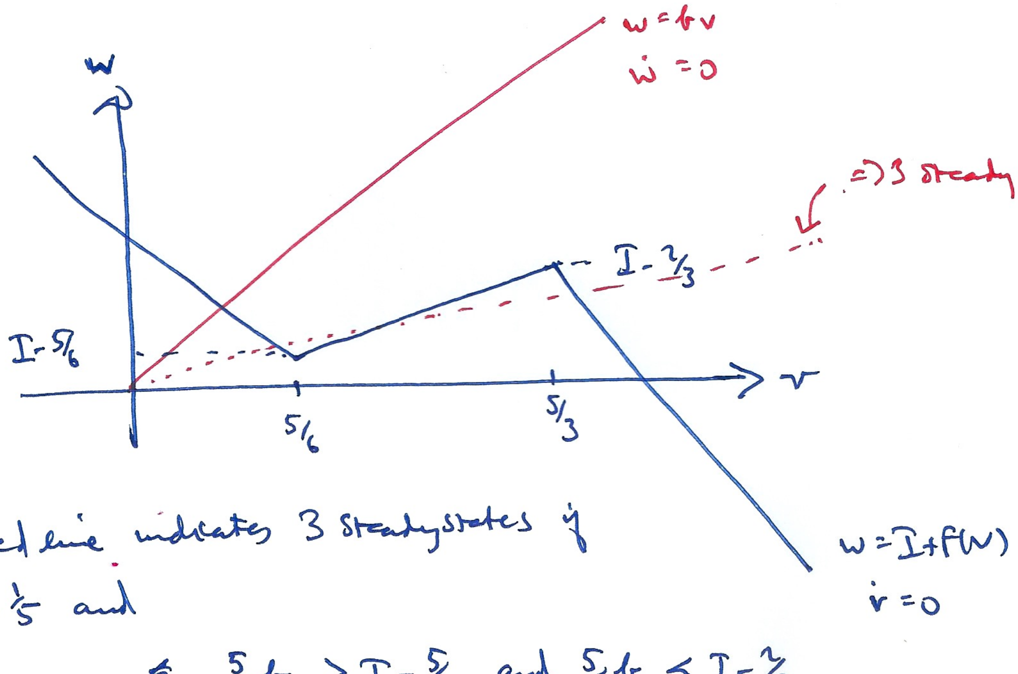
$\dot{w} = -w + bv \qquad I > 5/6$



v intracellular electric potential

w gate variable for K channel conductance

I applied current



The dotted line indicates 3 steady states if $b < \frac{1}{5}$ and

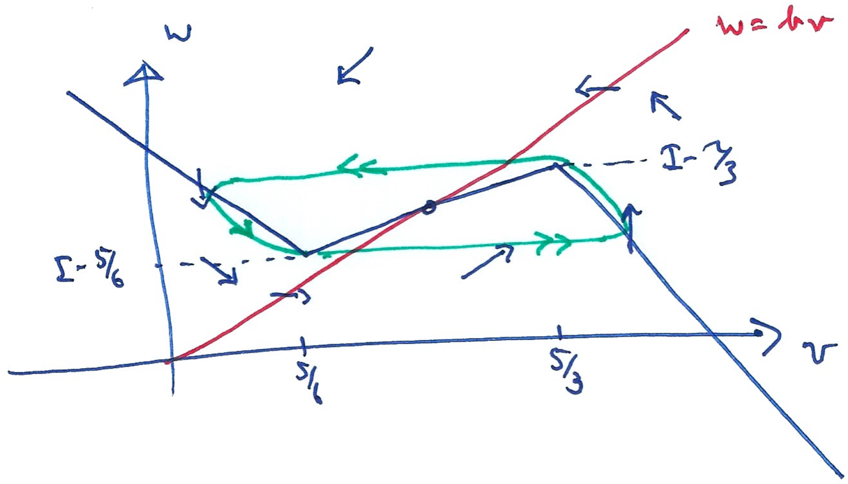
$$\frac{5}{6}b > I - \frac{5}{6} \quad \text{and} \quad \frac{5}{3}b < I - \frac{2}{3}$$

viz $\quad \dfrac{5b+2}{3} < I < \dfrac{5b+5}{6} \quad$ (which requires $b < \frac{1}{5}$)

(2

(b) 1 steady state $5/6 < v^* < 5/3$ requires

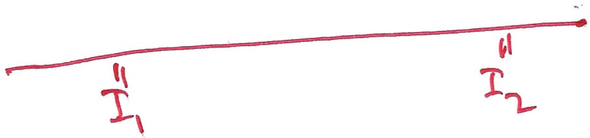
(i)



steady exists for

$$\tfrac{5}{6}b < I - \tfrac{5}{6} \quad \& \quad \tfrac{5}{3}b > I - \tfrac{7}{3}$$

$$\text{ie} \quad \frac{5}{6}(b+1) < I < \frac{5b+2}{3} \qquad (\text{note } b > 1/5)$$



At large w $\dot v < 0$ $\dot w < 0$ so trajectory directions as for arrows above in diagram

$\Rightarrow$ fixed point is node or spiral.

$\varepsilon \ll 1 \Rightarrow$ relaxation oscillations as indicated in green above

ii $\Rightarrow$ steady state is unstable

(but to do it formally, unstable if $\mathrm{tr}\,M = T > 0$

(det $M > 0$ as not a saddle)

$M = \begin{pmatrix} F'/\varepsilon & -1/\varepsilon \\ b & -1 \end{pmatrix}$ $\quad \mathrm{tr}\,M = \dfrac{F'}{\varepsilon} - 1 > 0$ as $\varepsilon \ll 1$ & $F' > 0$.

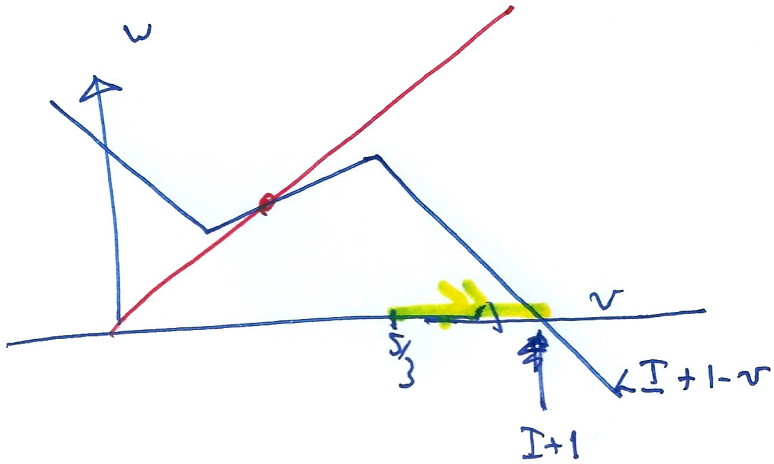
3

Depends on ε & b ? This is a bit vague as we are told $\varepsilon \ll 1$.

$T = \frac{1}{5\varepsilon} - 1$ so unstable for $\varepsilon < 0.2$.

Only depends on b if steady state not on middle branch.

iii



Start at $(5/3, 0)$ in yellow

$t = \varepsilon\tau$ $\quad v' = I + f(v) - w$

$\quad w' = \varepsilon[-w + b]$

$\Rightarrow w \simeq 0, \; v' \simeq I + f(v) = I + 1 - v$

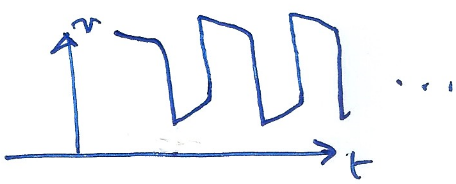
$v \to I+1$

iv Already done in (i) : v relaxes to v null cline rapidly

w trundles slowly on v null cline towards red

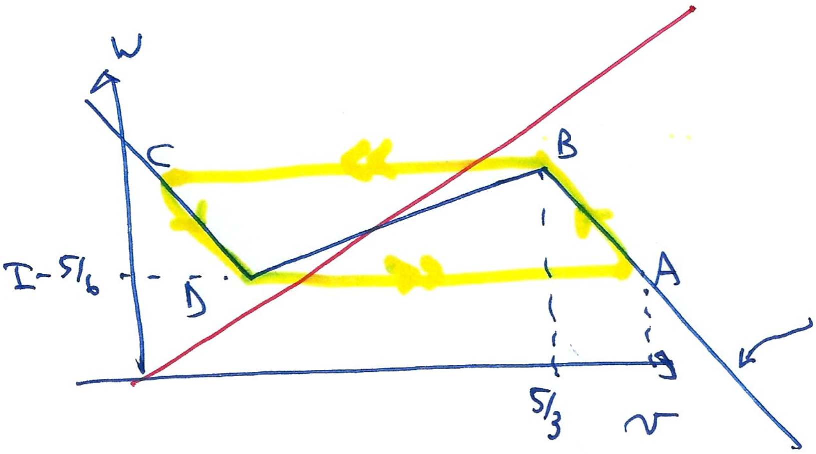
w null cline but can't stay on v null cline so hops rapidly

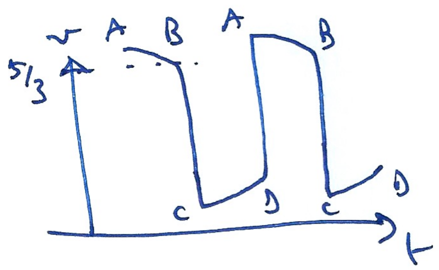
to other branch



(4

T = length of time $v > 5/3$ in oscillation:





$$T = \int_A^B dt = \int_A^B \frac{dw}{\dot{w}} = \int_A^B \frac{dw}{-w+bv}$$

and $w = I + 1 - v$

$$\text{so } T = \int_A^B \frac{-dv}{bv + v - (I+1)}$$

At A $I + 1 - v = I - 5/6 \Rightarrow v = \frac{11}{6}$

At B $v = 5/3$

$$\Rightarrow T = \int_{11/6}^{5/3} \frac{-dv}{(b+1)v - (I+1)}$$

$$= \frac{1}{b+1} \ln\Big[(b+1)v - (I+1)\Big]_{5/3}^{11/6}$$

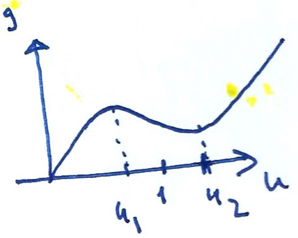
$$= \frac{1}{b+1} \ln\left[\frac{\frac{11}{6}(b+1) - I - 1}{\frac{5}{3}(b+1) - I - 1}\right] = \frac{1}{b+1} \ln\left[\frac{11b + 5 - 6I}{2(5b + 2 - 3I)}\right]$$

C5.12

Math Physiol 2016 q2

(1

2,
$$u_t + \gamma v_t = 1 - u + \varepsilon u_{xx}$$
$$\varepsilon v_t = -v + g(u)$$



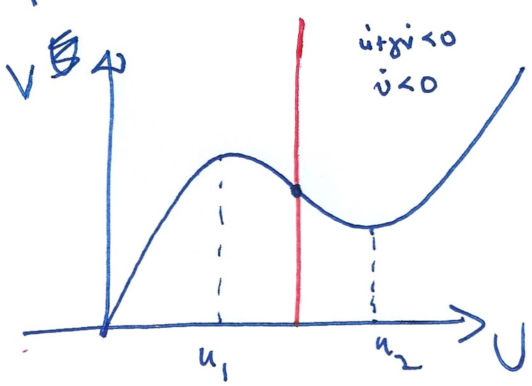
(a) v is the Ca^{2+}-sensitive store / concentration of Ca^{2+} in the cell (sarcoplasmic reticulum)

u is the cytosolic Ca^{2+} concentration in the cell.

(b) $u = U(\xi)$ $v = V(\xi)$ $\xi = x + st$

$$\Rightarrow \quad s(U' + \gamma V') = 1 - U + \varepsilon U''$$
$$\varepsilon s V' = -V + g(U)$$

(U,V) phase plane. Question a bit imprecise - periodic travelling waves? solitary travelling waves? ~~[illegible]~~c ~~[illegible]~~.



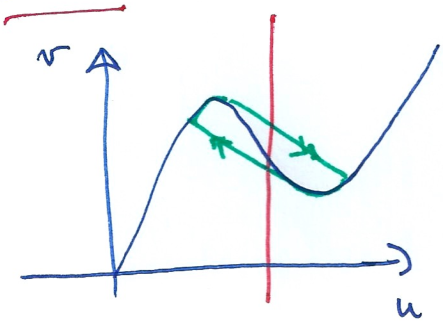
kinetics:
$$u_t + \gamma v_t = 1 - u$$
$$\varepsilon v_t = -v + g(u)$$

See below (p 3) for wave trajectory

(2

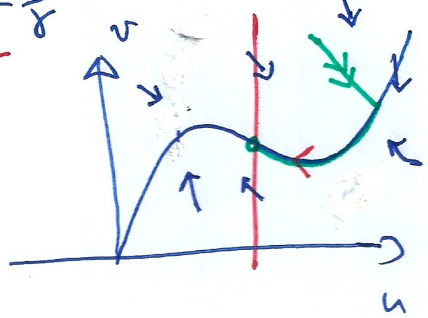
[Digression: whether the steady state is stable or unstable probably depends on whether $g' \gtrless -\frac{1}{\gamma}$ at the fixed point

if $g' < -\frac{1}{\gamma}$ $\left(-g' \gtrsim \frac{1}{\gamma}\right)$



we get oscillations

if $g' > -\frac{1}{\gamma}$



fixed point is stable

[Warning: see p2A for phase plane discussion]

Linearisation
$$\dot{u} = 1 - u - \frac{\gamma}{\varepsilon}\left[-v + g(u)\right]$$
$$\dot{v} = \frac{1}{\varepsilon}\left[-v + g(u)\right]$$

Near fixed pt community matrix is $M = \begin{pmatrix} -1-\frac{\gamma}{\varepsilon}g' & \frac{\gamma}{\varepsilon} \\ \frac{g'}{\varepsilon} & -\frac{1}{\varepsilon} \end{pmatrix}$

Phase plane indicates not saddle

Fixed pt unstable iff $\mathrm{tr}\, M > 0$

$$\Rightarrow -\frac{\gamma}{\varepsilon}g' - \frac{1}{\varepsilon} \gtrsim 0$$

$$\Leftrightarrow -g' \gtrsim \frac{1}{\gamma}$$]

[Further digression and salutary warning:

If you look at the trajectory directions on p 2

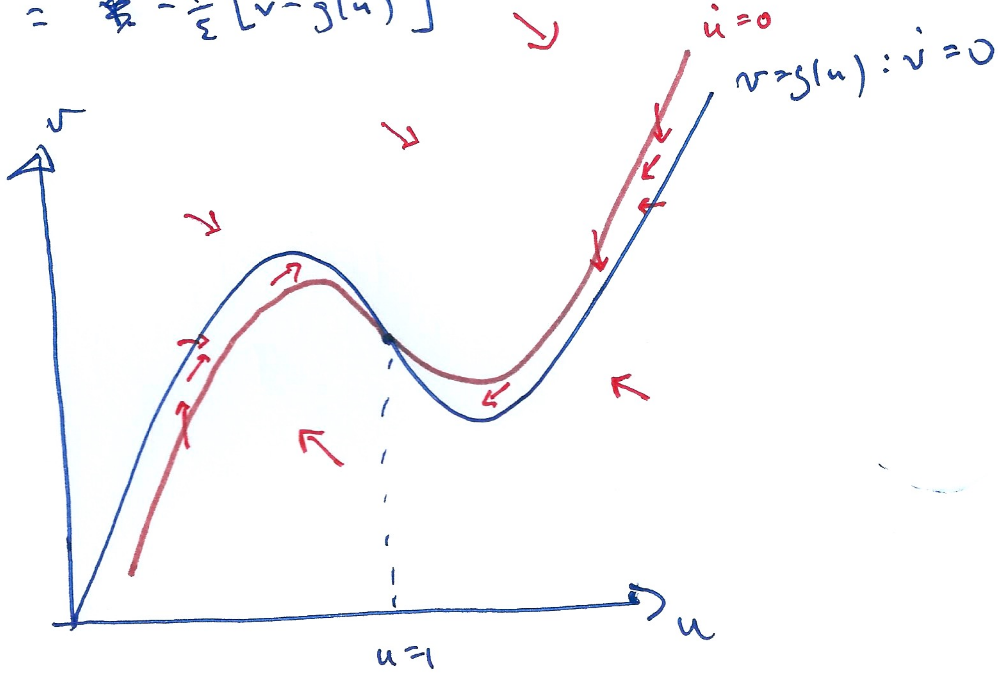
it looks as if $\dot u = 0$ on $v = g(u)$ instead of $\dot v$!?

In more detail:

$$\dot u = 1 - u + \frac{\gamma}{\varepsilon}\left[v - g(u)\right]$$

$$\dot v = -\frac{1}{\varepsilon}\left[v - g(u)\right]$$

Therefore



actual nullclines for u & v are

$\dot v = 0$ $\quad v = g(u)$ (blue)

$\dot u = 0$ $\quad v = g(u) + \frac{\varepsilon}{\gamma}(u-1)$ (brown)

and trajectory directions as shown in red

Warning: do not be overly simplistic with phase plane

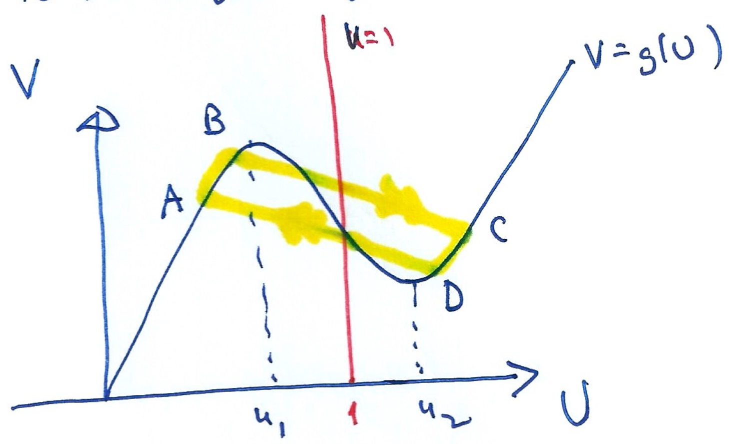
– rely on $\varepsilon \ll 1$]

(3

The diagram in the question is terrible!

But appears to indicate a solitary wave - but the system is not excitable, so let us assume periodic travelling waves

Then ($\sim$ Fitzhugh-Nagumo) I guess



(BC & AD not necessarily straight)

We don't know what U_B or U_A are

(c) Fast: $\xi = \varepsilon X$

$$\Rightarrow \quad s(U' + \gamma V') = \varepsilon[1 - U] + U''$$

$$sV' = -V + g(U)$$

$$\cancel{\Rightarrow sU' + \gamma[-V + g(U)] \approx U''}$$

lst is $\quad s(U' + \gamma V') \simeq U''$

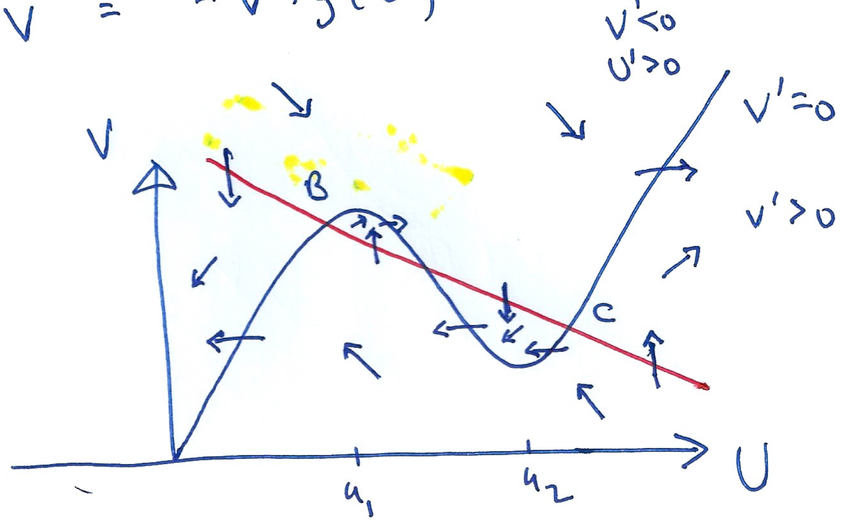
$$\Rightarrow \quad s[U - U_B + \gamma(V - V_B)] \simeq U' \qquad (U \to U_B,\ V \to V_B \text{ as } X \to -\infty)$$

~~[illegible]~~ as required

(i) Suitable choice of γ !! We already need to know this! It is $g'(1) < -\frac{1}{\gamma}$ (so oscillatory kinetics)

$$U' = s\left[U - U_B + \gamma(V - V_B)\right]$$

$$sV' = -V + g(U) \qquad s > 0$$



Phase portrait: nullclines (above), directions (above)

Whence it is clear that B & C are saddles

& intermediate fixed point is node or spiral

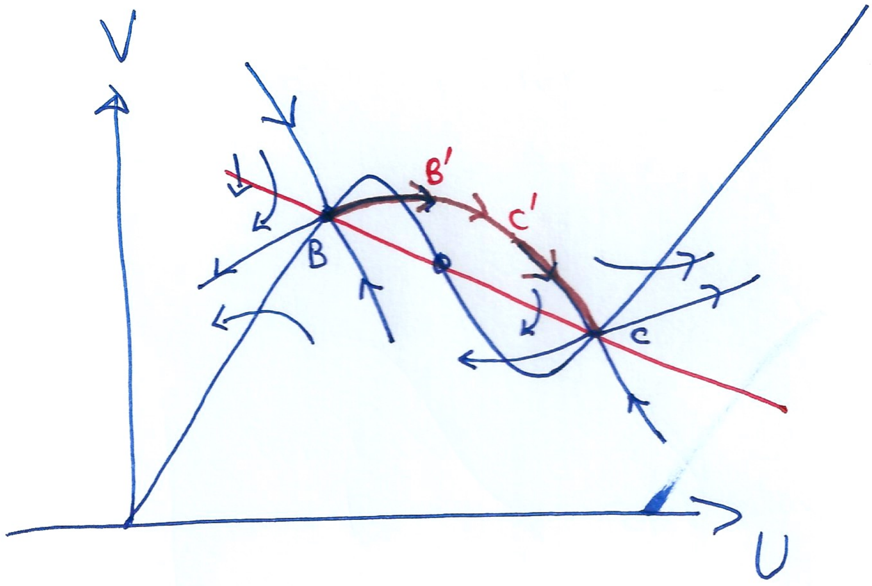
stability depends on $\mathrm{tr}\, M$, $M = \begin{pmatrix} s & \gamma s \\ g' & -1 \end{pmatrix}$

$\mathrm{tr}\, M = s - 1$

unstable if $s > 1$

stable if $s < 1$

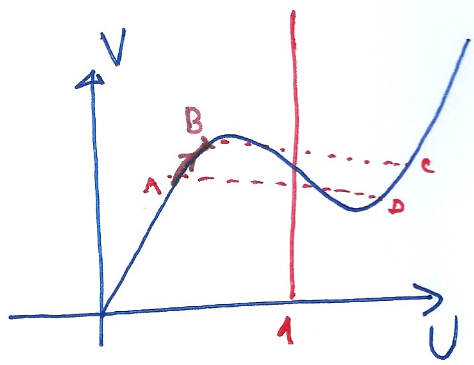
(5



ii To get from B to C the unstable separatrix BB' from B must join to the stable separatrix C'C to C. In general this will not occur. Given B, we choose s to make it happen.

(d) Back to ξ : $s(U' + \gamma V') = 1 - U + \varepsilon U''$
$\varepsilon s V' = -V + g(U)$

$\Rightarrow$ $V = g(U)$
$s(U' + \gamma V') = 1 - U$
$\Rightarrow$ $s[1 + \gamma g'(U)]U' = 1 - U$



"Hence show..." – imprecise. I think what is meant is that at B, $U_B < 1$, $U' > 0$,

$\Rightarrow$ $1 + \gamma g'(U_B) > 0$ so U_B is less than the value it obtains in the limit cycle (which has $\gamma g' = -1$)

[Note : U_B is not constrained : given U_B, choose s ; on the way back, select D to connect D to A. So there is a one-parameter family of periodic travelling waves]

C5.12 Math Physiol 2016 q3 (1

3/ $$\dot{E} = F(E_\tau) - \gamma E$$

(a) E circulating erythrocytes, γ loss term (life time ~ 100 d)

F production from pluripotential stem cells with a delay τ

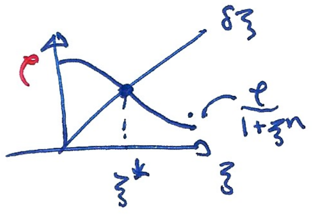
due to maturation time

(b) $$F(E) = \frac{F_0 \theta^n}{E^n + \theta^n}$$

(i) $E = \theta \xi \quad t = \tau T$

$$\Rightarrow \frac{\theta}{\tau}\dot{\xi} = \frac{F_0}{1+\xi_1^n} - \gamma\theta\xi$$

$$\Rightarrow \dot{\xi} = \frac{\rho}{1+\xi_1^n} - \delta\xi \qquad \rho = \frac{F_0 \tau}{\theta}, \quad \delta = \gamma\tau$$

(ii) 

Clearly unique steady state

(iii) linearise : write $h = \frac{\rho}{1+\xi^n}$

$\xi = \xi^* + \eta$

$$\dot{\eta} = h'(\xi^*)\eta_1 - \delta\eta$$

Define $\alpha = -h'(\xi^*) = \frac{\rho}{(1+\xi^n)^2} \cdot n\xi^{n-1}$. Note $1+\xi^n = \frac{\rho}{\delta\xi}$

$$\Rightarrow \alpha = \frac{\rho\,\delta^2\xi^2 \cdot n\xi^{n-1}}{\rho^2} = \frac{\delta^2 n}{\rho}\xi\left(\frac{\rho}{\delta\xi} - 1\right)$$

$$= \delta n\left[1 - \frac{\delta\xi^*}{\rho}\right] > 0$$

$$\dot{\eta} = -\alpha \eta_1 - \delta \eta$$

$$\eta = e^{\sigma t}$$

$$\sigma = -\delta - \alpha e^{-\sigma}$$

Question does not define ω !!

If α is small $\mathrm{Re}\,\sigma < 0$ (certainly if $\alpha < \delta$)

Fix δ, ~~$\sigma(\alpha)$~~ $\sigma(\alpha)$ has derivative

$$\sigma' = -e^{-\sigma} + \alpha e^{-\sigma} \sigma'$$

$$\Rightarrow \sigma' = \frac{e^{-\sigma}}{\alpha e^{-\sigma} - 1}, \quad \alpha e^{-\sigma} = -\sigma - \delta$$

$$\text{so } \sigma' = \frac{1}{\alpha}\left[\frac{-\sigma-\delta}{-\sigma-\delta-1}\right] = \frac{\sigma+\delta}{\alpha(\sigma+\delta+1)}$$

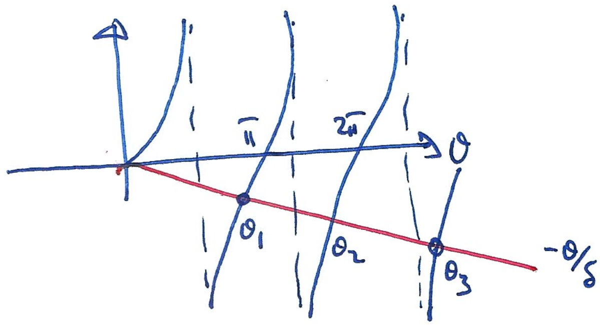
Suppose $\sigma = i\theta$ at some ~~critical~~ value of α

$$\text{then } i\theta = -\delta - \alpha e^{-i\theta}$$

$$\Rightarrow 0 = -\delta - \alpha \cos\theta$$

$$\theta = \alpha \sin\theta$$

$$-\delta = +\alpha\cos\theta$$



$$\Rightarrow \tan\theta = -\frac{\theta}{\delta}$$

$$\& \quad \alpha = \frac{\theta}{\sin\theta}$$

There are roots θ_i as shown

with $\theta_1 \in (\pi/2, \pi)$, $\theta_3 \in (5\pi/2, 3\pi)$ etc

& corresponding positive $\alpha_1 = \dfrac{\theta_1}{\sin\theta_1}$, $\alpha_3 = \dfrac{\theta_3}{\sin\theta_3}$ etc

& $\alpha_1 < \alpha_3 < .$

[the latter because also $\alpha = -\dfrac{\delta}{\cos\theta}$ & from the graph we

see ~~...~~ $\theta_r = r\pi - \phi_r$ where $\phi \in (0, \pi/2)$ is increasing with r

So $\theta_{2n-1} = (2n-1)\pi - \phi_{2n-1}$

$$\alpha = \frac{-\delta}{\cos\theta_{2n-1}} = \frac{\delta}{\cos\phi_{2n-1}}$$

$$\phi\uparrow \Rightarrow \cos\phi\downarrow \Rightarrow \frac{\delta}{\cos\phi}\uparrow$$]

Transversality : $$\sigma'\Big|_{i\theta} = \frac{\delta+i\theta}{\alpha(1+\delta+i\theta)} = \frac{(\delta+i\theta)(1+\delta-i\theta)}{\alpha[(1+\delta)^2+\theta^2]}$$

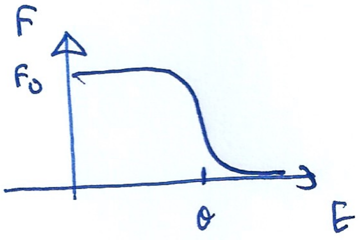
$$= \frac{\delta+i\theta+\delta^2+\theta^2}{\alpha[(1+\delta)^2+\theta^2]}$$

So $\mathrm{Re}\,\sigma'\Big|_{\sigma=i\theta} > 0$.

Therefore at $\alpha_1 = -\dfrac{\delta}{\cos\theta_1}$ instability occurs for $\alpha > \alpha_1$

So I suppose $\theta_1 = \omega^*$ not sure what A is about - seems to be upside down

(c) $n \to \infty$.



$$F = \frac{F_0}{1 + \left(\frac{E}{\theta}\right)^n}$$

$E < \theta \quad F \to F_0$

$E > \theta \quad F \to 0$

oops question has $\leq \theta$ & $\leq E_\tau$ should be $<$

$t \leq 0 \quad E = E_0 > \theta$, $E > \theta \quad -\tau \leq t \leq 0$

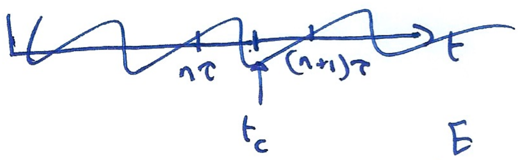
method of steps $\quad \dot{E} = F - \gamma E \quad$ $F = 0$ if $E_\tau > \theta$; $F = F_0$ if $E_\tau < \theta$

(i) $0 < t < \tau$: $\dot{E} = -\gamma E \Rightarrow E = E_0 e^{-\gamma t}$

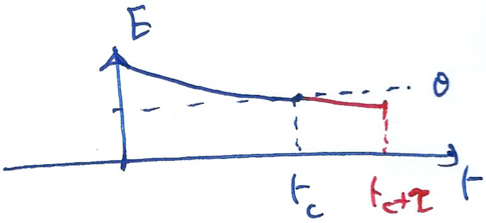
As long as $E_0 e^{-\gamma t} > \theta$ this solution carries on

~~Suppose~~ $\cancel{E_0 e^{-\gamma t}}$ At $t = t_c = \frac{1}{\gamma} \ln \frac{E_0}{\theta}$

$E = E_0 e^{-\gamma t} = \theta$



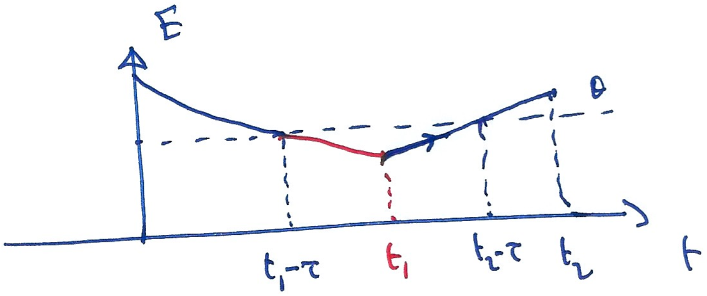
~~If $n\tau \leq t_c \leq (n+1)\tau$~~



For $t_c < t < t_c + \tau$ we still have $E_\tau > \theta$

so $E = E_0 e^{-\gamma t}$ till $t = t_c + \tau = \tau + \frac{1}{\gamma} \ln \frac{E_0}{\theta} = t_1$

& $E_1 = \theta e^{-\gamma \tau}$



Now for $t > t_1$, $E_\tau < \theta$ so $F = F_0$

& $\dot{E} = F_0 - \gamma E$ $\quad E = E_1$ at $t = t_1$

$$E - \frac{F_0}{\gamma} = \left(E_1 - \frac{F_0}{\gamma}\right)e^{-\gamma(t-t_1)}$$

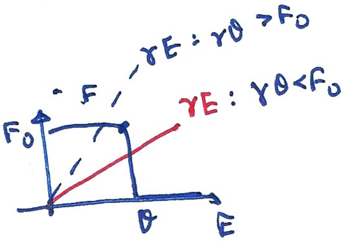
and this will carry on till $t = t_2$

where $E(t_2-\tau) = \theta$

ie $$\theta - \frac{F_0}{\gamma} = \left(E_1 - \frac{F_0}{\gamma}\right)e^{-\gamma[t_2-t_1-\tau]}$$

$$\Rightarrow \frac{\gamma\theta - F_0}{\gamma E_1 - F_0} = e^{-\gamma(t_2-t_1-\tau)}$$

[note:



Looking back at stability result – oscillations if $\alpha = -h'$ large enough

$\Rightarrow$ oscillations for $\gamma < \frac{F_0}{\theta}$

Stable if $\gamma > \frac{F_0}{\theta}$]

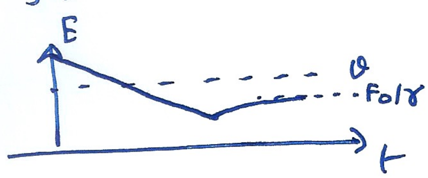
so ...

$$t_2 = t_1 + \tau + \frac{1}{\gamma}\ln\left[\frac{\gamma E_1 - F_0}{\gamma\theta - F_0}\right]$$

The sketch above (ie E becomes $> \theta$ again) only applies if $\frac{F_0}{\gamma}$ (where E is heading) is $> \theta$

ie if $\gamma < \frac{F_0}{\theta}$

If $\gamma < \frac{F_0}{\theta}$ then



(6

In fact for $t > t_1$ $\dot{E} = F_0 - \gamma E$

& if $\gamma E_1 > F_0$ solution will continue to decrease

& will approach $\frac{F_0}{\gamma}$ monotonically

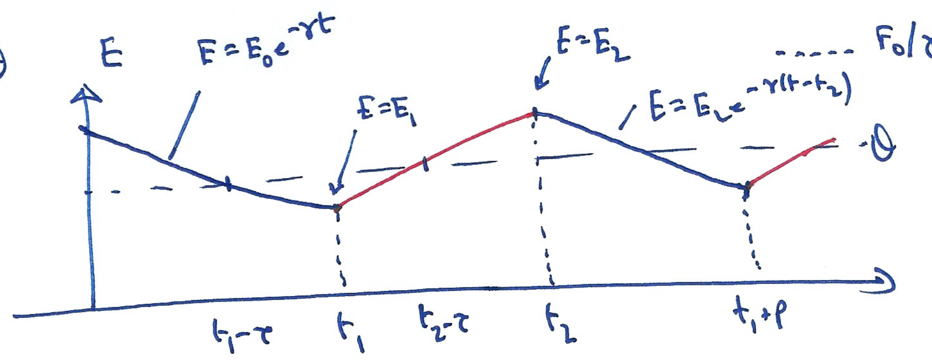
so $\gamma \theta e^{-\gamma\tau} > F_0$ solution decreases for ever

~~F_0~~ $F_0 < \gamma\theta e^{-\gamma\tau}$ decreases for ever, $t_1 = \infty$ $(\Rightarrow E \to \frac{F_0}{\gamma})$

$\gamma\theta e^{-\gamma\tau} < F_0 < \gamma\theta$ decreases till t_1, increases for ever after $t_2 = \infty$ $(E \Rightarrow F_0/\gamma)$

& if $F_0 > \gamma\theta$ oscillations. ~~ξ~~. [I think]

$F_0 > \gamma\theta$



At t_2, $E = E_2 = \frac{F_0}{\gamma} + \left(E_1 - \frac{F_0}{\gamma}\right)\left(\frac{F_0 - \gamma\theta}{F_0 - \gamma E_1}\right) e^{-\gamma\tau}$

thereafter $E = E_2 e^{-\gamma(t-t_2)}$ and the solution is periodic with period p

where $E_2 e^{-\gamma(t_1 + p - t_2)} = E_1$ ~~$\Rightarrow$~~, note $e^{-\gamma(t_1 - t_2)} = e^{\gamma\tau}\left(\frac{F_0 - \gamma E_1}{F_0 - \gamma\theta}\right)$

So $e^{\gamma p} = \frac{E_2}{E_1} e^{\gamma\tau}\left(\frac{F_0 - \gamma E_1}{F_0 - \gamma\theta}\right) = \frac{1}{E_1}\left[\frac{F_0}{\gamma}\left(\frac{F_0 - \gamma E_1}{F_0 - \gamma\theta}\right) e^{\gamma\tau} + E_1 - \frac{F_0}{\gamma}\right]$

$\Rightarrow p \ldots$

Question needed to state that $F_0 > \gamma\theta$.

C5.12 Math Physiol 2017 q1 answer

C1

1.
$$\varepsilon \dot{v} = I^* + f(v) - w$$
$$\dot{w} = \gamma v - w$$
$$f = -v(a-v)(1-v) \qquad 0<a<1$$

(a) v intracellular electric potential

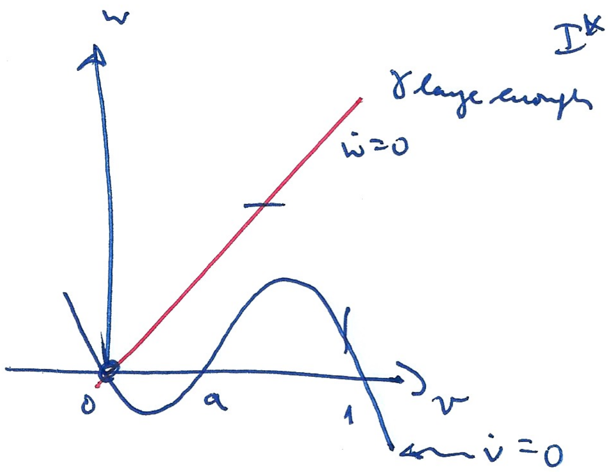
w gate variable

I^* applied current

$-f(v)+w$ ionic current out

Start with Hodgkin–Huxley, 3 gate variables m,h,n & telegraph equation for potential (via I_{ll} & $I_\perp$) : $\tau_m \ll 1 \Rightarrow m$ equilibrium, $n+h$ = constant.
$\Rightarrow$ FN reduction ...

(b) $I^*=0$



Evidently one equilibrium $(0,0)$ for γ large

Linearise $\begin{pmatrix}\dot v\\ \dot w\end{pmatrix} \approx \underbrace{\begin{pmatrix}\frac{f'}{\varepsilon} & -\frac{1}{\varepsilon}\\ \gamma & -1\end{pmatrix}}_{M}\begin{pmatrix}v\\ w\end{pmatrix}$

$\operatorname{tr} M = \frac{f'}{\varepsilon} - 1 < 0$ at $(0,0)$, $\det M = -\frac{f'}{\varepsilon} + \frac{\gamma}{\varepsilon} > 0 \Rightarrow$ stable

L2

$t \sim 1$: $w \simeq f(v)$

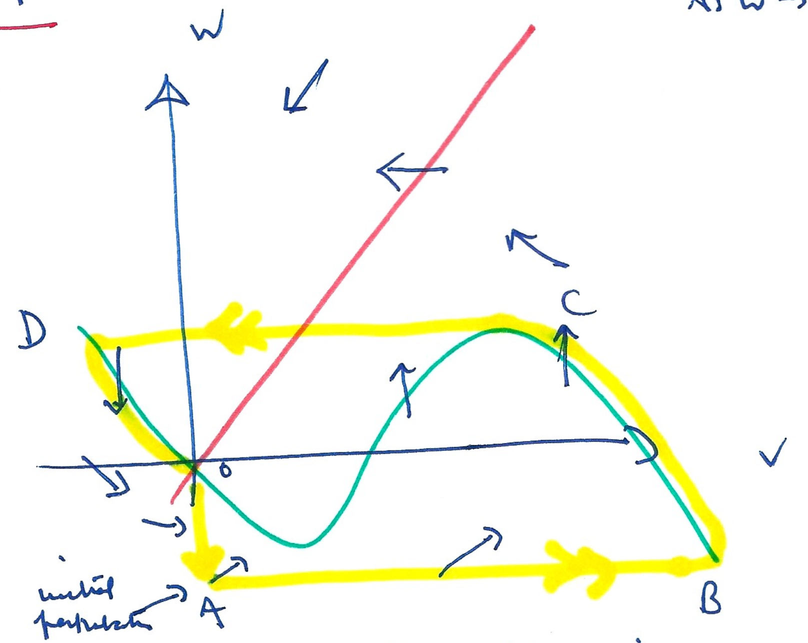
$\dot{w} = \gamma v - w$

$t \sim \varepsilon$, $t = \varepsilon T$ $\quad v' = f(v) - w$

$w' = 0$

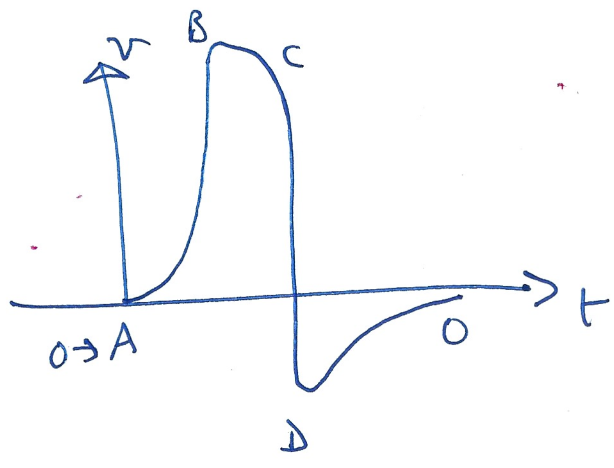
phase plane

As $w \to \infty$ & $\dot{v} < 0$
$\dot{w} < 0$



trajectories cycle round stable origin

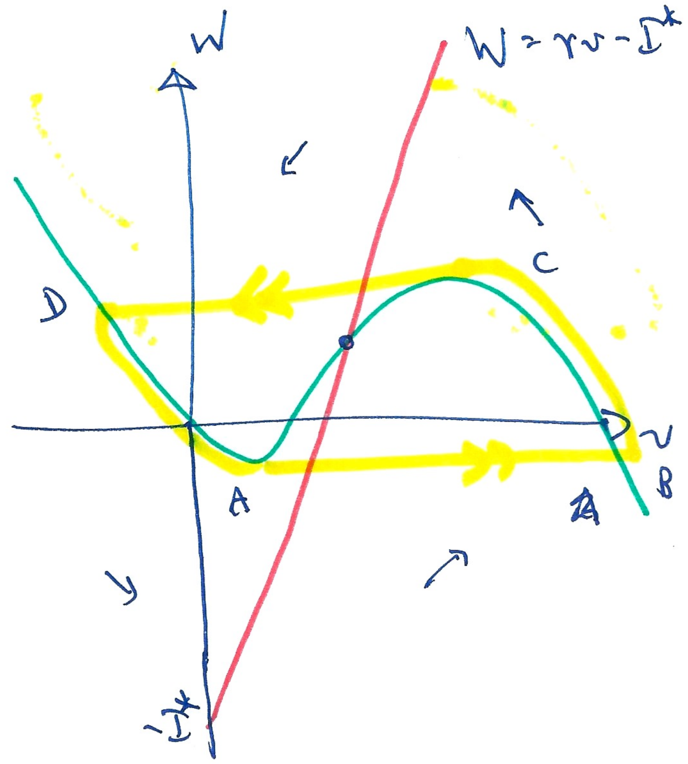
threshold : eg apply a state $I^{*} > 0$ for short time $\Longleftrightarrow$ lower $w \Rightarrow$ trajectory as shown : fast phases with $\twoheadrightarrow$



(e) $I^* = 0$, $W = w - I^*$

$$\varepsilon \dot v = f(v) - W$$

$$\dot W = \gamma v - I^* - W$$



$$P \approx \int_B^C dt + \int_D^A dt$$

$$\approx \int_B^C \frac{dW}{\dot W} + \int_D^A \frac{dW}{\dot W} \qquad \text{along } W = f(v)$$

$$= \int_B^C \frac{dW}{\gamma v - I^* - W} + \int_D^A \frac{dW}{\gamma v - I^* - W}$$

$$= \int_B^C \frac{f'(v)\,dv}{\gamma v - I^* - f(v)} + \int_D^A \frac{f'(v)\,dv}{\gamma v - I^* - W}$$

~~[illegible]~~ oh question leaves as W, how odd

(4

$$P \simeq \int_{W_B}^{W_C} \frac{dW}{\gamma v - I^* - W} + \int_{W_D}^{W_A} \frac{dW}{\gamma v - I^* - W}$$

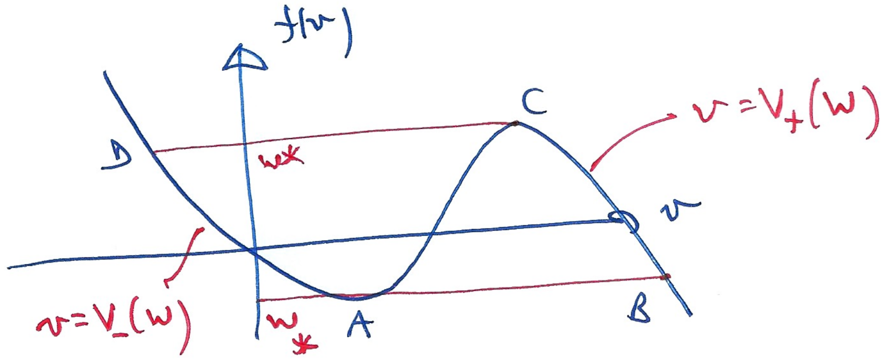
On BC $W < \gamma v - I^* - W$, denote $v = V_+(W)$ on BC

on DA $W > \gamma v - I^* - W$ denote $v = V_-(W)$ on AD

(see figure)

Also let $W = f(v) = w_*$ at A & B

$W = w^*$ at C & D



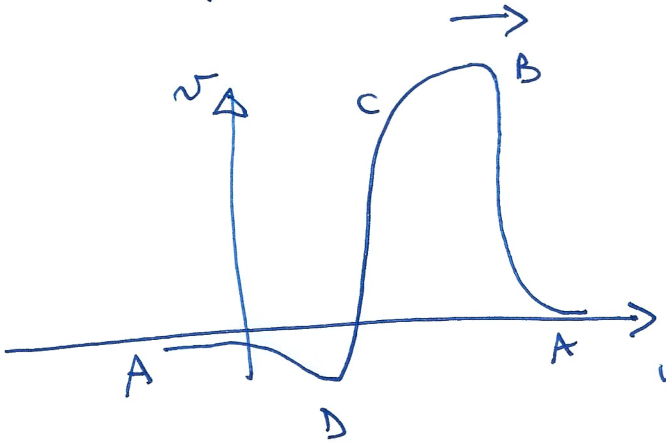
$$\text{So } P \simeq \int_{w_*}^{w^*} \frac{dW}{\gamma V_+(W) - I^* - W} + \int_{w^*}^{w_*} \frac{dW}{\gamma V_-(W) - I^* - W}$$

$$= \int_{w_*}^{w^*} \left[\frac{1}{\gamma V_+(W) - I^* - W} - \underbrace{\frac{1}{\gamma V_-(W) - I^* - W}}_{\text{note this is } > 0} \right] dW$$

5

(d) $\varepsilon v_t = f(v) - w + \varepsilon^2 v_{xx}$

$w_t = \gamma v - w$



$y = x - ct \qquad c > 0$

(i) $-\varepsilon c v' = f(v) - w + \varepsilon^2 v''$ $\qquad v(Y), w(Y)$

$-cw' = \gamma v - w$ $\qquad$ bcs $v, w \to 0$ at $\pm\infty$.

(ii) AB fast $y = \varepsilon Y$

$\Rightarrow \quad -cv' = f(v) - w + v''$

$-cw' = \varepsilon(\gamma v - w) \Rightarrow w \simeq 0$

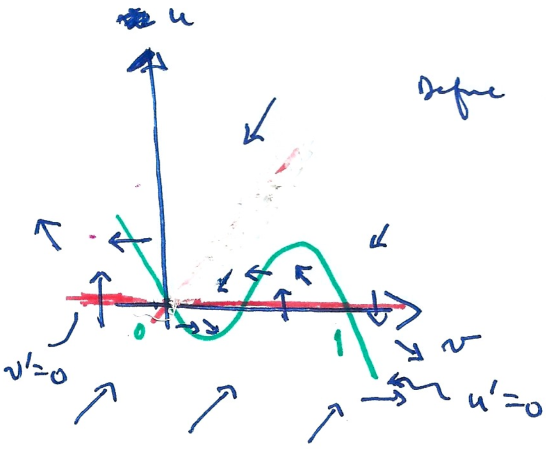
$\Rightarrow v'' + cv' + f(v) = 0$ on AB

$Y \to \infty \quad v \to 0$

$Y \to -\infty \quad v \to v_B$ (where $f(v_B) = 0$ $v_B = 1$

ie $v \to 1$ (or a).

(iii)



Define $v' = -u$

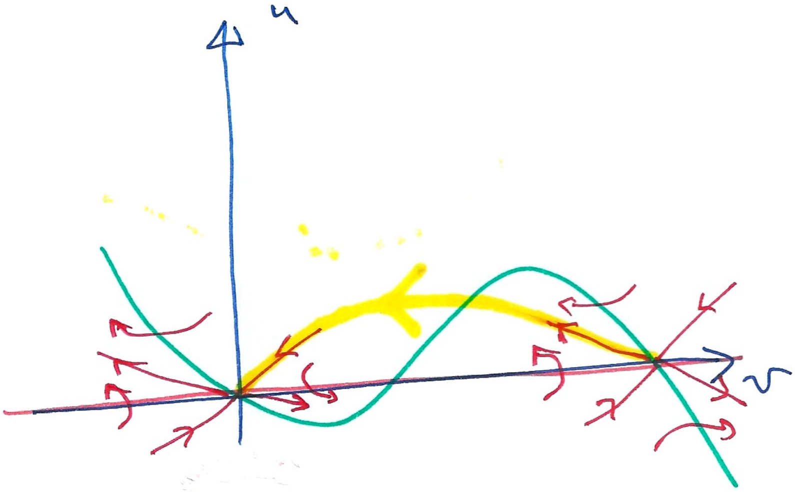
then $u' = f(v) - cu$

At large u $v' < 0$ $u' < 0$

$\Rightarrow$ trajectories as shown

Clearly $(0,0)$ & $(1,0)$ are saddles, $(a,0)$ a node or spiral

To connect $(1,0)$ $(y \to -\infty)$ to $(0,0)$ $(y \to \infty)$ we need to connect the unstable separatrix from $(1,0)$ in $v<1$ to the stable separatrix to $(0,0)$ in $v>0$:



This requires a choice of c to make them join.

$$v'' + cv' + f(v) = 0$$

So $(\times v')$

$$\tfrac{1}{2} v'^2 \Big|_{-\infty}^{\infty} + c \int_{-\infty}^{\infty} v'^2 \, dy + \int_1^0 f(v)\,dv = 0$$

$$\Rightarrow c = \frac{\int_0^1 f(v)\,dv}{\int_{-\infty}^{\infty} v'^2 \, dy}$$

which requires $\int_0^1 f(v)\,dv > 0$

viz $a < \frac{1}{2}$

C5.12 Math Physiol 2017 q2 answer (1

$$\dot{P} = -\gamma P + \beta(N)N - e^{-\gamma\tau}\beta(N_\tau)N_\tau$$

$$\dot{N} = -\beta(N)N - \kappa N + 2e^{-\gamma\tau}\beta(N_\tau)N_\tau$$

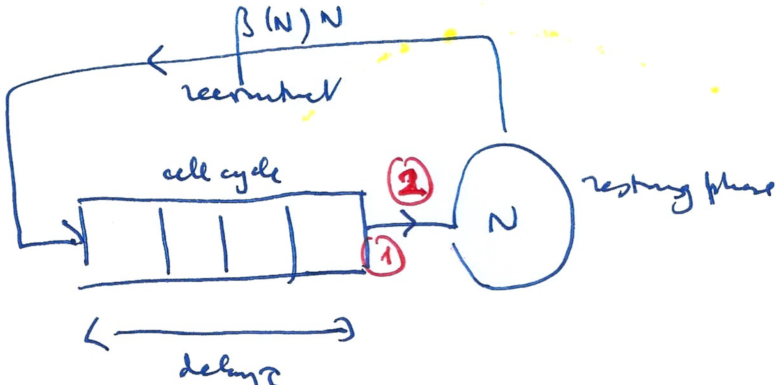
(a) γ apoptosis (cell death) rate

κ loss to maturation stage

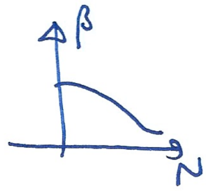
(i) $e^{-\gamma\tau}\beta(N_\tau)N_\tau$ (1) loss of cells from proliferative phase after cell cycle

(ii) $2e^{-\gamma\tau}\beta(N_\tau)N_\tau$ (2) supply to resting phase N after mitosis (factor of 2

(iii) β decreasing to effect control on production of N (high N causes less recruitment to proliferative phase)



(b) $\beta(N) = \beta_0 \,\mathrm{sech}\left(\frac{N}{\beta_1}\right)$



write $N = \beta_1 n$, $t \sim \tau$

$$\Rightarrow \frac{\beta_1}{\tau}\dot{n} = -\beta_0\beta_1 n \,\mathrm{sech}\, n - \kappa\beta_1 n + 2e^{-\gamma\tau}\beta_0\beta_1 n_1 \,\mathrm{sech}\, n_1$$

$$\Rightarrow \dot{n} = \beta_0\tau\left[n_1 \,\mathrm{sech}\, n_1 - n \,\mathrm{sech}\, n\right] - \kappa\tau n + \left[2e^{-\gamma\tau} - 1\right]\beta_0\tau\, n_1 \,\mathrm{sech}\, n_1$$

If we define $g = b n \,\mathrm{sech}\, n$ then, if $\underline{b = \beta_0\tau}$

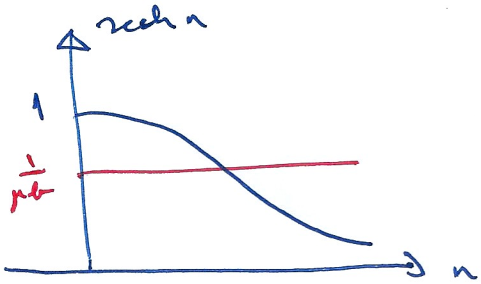
$$\dot{n} = g(n_1) - g(n) + \left[2e^{-\gamma\tau} - 1\right] g(n_1) - \kappa\tau n$$

Thus

$$\dot{n} = g(n_1) - g(n) + \varepsilon\left[\mu g(n_1) - n\right]$$

$$\underline{\varepsilon = \kappa\tau}, \quad \underline{\mu = \frac{2e^{-\gamma\tau} - 1}{\kappa\tau}} \qquad \underline{b = \beta_0 \tau}$$

(i) equilibrium



$n = \mu g(n)$

~~$= \mu b n\, \mathrm{sech}\, n$~~

$= \mu b n\, \mathrm{sech}\, n$

So $n = 0$ or $\mathrm{sech}\, n = \frac{1}{\mu b}$ if $\mu b > 1$

linearise $n = n^* + m$

$$\Rightarrow \dot{m} = g' m_1 - g' m + \varepsilon\left[\mu g' m_1 - m\right]$$

$g' = g'(n^*)$

$m = e^{\lambda t} \Rightarrow \quad \lambda = g' e^{-\lambda} - g' + \varepsilon \mu g' e^{-\lambda} - \varepsilon$

ie $\underline{\lambda = -\alpha - \delta e^{-\lambda}}$

where $\underline{\alpha = \varepsilon + g'}$

$\underline{\delta = -(1 + \varepsilon\mu) g' > 0}$

If $\alpha, \delta > 0$ then $\lambda < 0$ if real.

(ii)

Define $\tau = \varepsilon t$, $n = n(\tau) \Rightarrow n_1 = n(\tau - \varepsilon)$

$\Rightarrow$ Taylor expand $\quad n_1 = n - \varepsilon n' \ldots$

$\Rightarrow g(n_1) \simeq g(n) - \varepsilon n' g'(n) \ldots$

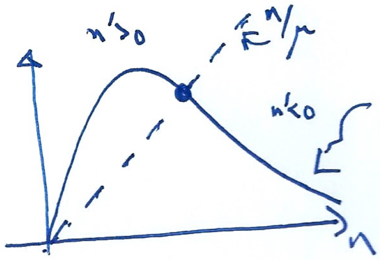
$$\varepsilon n' \simeq g(n) - \varepsilon n' g'(n) - g(n)$$
$$+ \varepsilon\left[\mu\{g(n) - \varepsilon n' g'(n) ..\} - n\right]$$

$$\Rightarrow n' \simeq -n'g'(n) + \mu g(n) - n$$

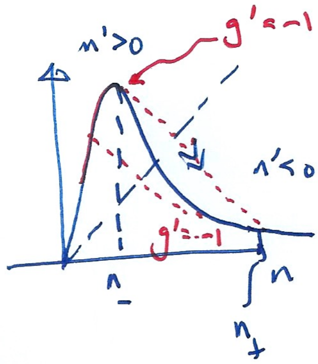
$$\Rightarrow n' \simeq \frac{\mu g(n) - n}{1 + g'(n)}$$

but for $t \sim 1$ $\quad \dot{n} \simeq g(n_1) - g(n)$

[The oscillations are actually of relaxation type, as on the slow time scale



or better



Slow phase finishes at $g' = -1$

$\Rightarrow$ fast phase & note if $n \to n_+$ as $t \to \infty$, $n \to n_-$ as $t \to -\infty$

$$n(t_+) - n(t_-) = \int_{t_-}^{t_+} g(n_1)\,dt - \int_{t_-}^{t_+} g(n)\,dt$$
$$= \int_{t_- - 1}^{t_+ - 1} g(n)\,dt - \int_{t_-}^{t_+} g(n)\,dt = \int_{t_- - 1}^{t_-} g\,dt - \int_{t_+ - 1}^{t_+} g\,dt$$

$\Rightarrow n_+ - n_- \simeq g(n_-) - g(n_+)$ so jump n_- to n_+ 'along' $n + g(n) = $ constant – red lines above]

C5·12 2017 q3

3/ (a) $C \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} O$ ← fraction n

$\dot n = \alpha(1-n) - \beta n$

$\Rightarrow \tau \dot n = n_\infty - n \qquad \tau = \cancel{\alpha+\beta}\ \frac{1}{\alpha+\beta} \quad , n_\infty = \frac{\alpha}{\alpha+\beta}$

τ_n relaxation time

n_∞ equilibrium

(b) $S_0 \underset{\beta}{\overset{l\alpha}{\rightleftharpoons}} S_1 \underset{2\beta}{\overset{(l-1)\alpha}{\rightleftharpoons}} \cdots \quad S_{l-1} \underset{l\beta}{\overset{\alpha}{\rightleftharpoons}} S_l$

(i) The reaction is $S_j \underset{(j+1)\beta}{\overset{(l-j)\alpha}{\rightleftharpoons}} S_{j+1}$

because S_j has j open gates, $l-j$ closed so $(l-j)$ chances of opening

S_{j+1} has $j+1$ so ~~the~~ $j+1$ chances of closing

(ii) $\dots \quad S_{j-1} \underset{j\beta}{\overset{(l-j+1)\alpha}{\rightleftharpoons}} S_j \underset{(j+1)\beta}{\overset{(l-j)\alpha}{\rightleftharpoons}} S_{j+1} \quad \dots$

$R_j \qquad R_{j+1}$

x_j = fraction of ~~open~~ S_j channels

~~$\dot x_j = (l-j+1)\alpha$~~

write $R_j = (l-j+1)\alpha x_{j-1} - j\beta x_j \qquad j = 1, \dots l$

then $\dot x_j = R_j - R_{j+1} \qquad j = 1, \dots l-1$

Also

$$\dot{x}_0 = -R_1$$

$$\dot{x}_\ell = R_\ell$$

(iii) To show a solution is $x_j = \binom{\ell}{j} n^j (1-n)^{\ell-j}$

a cute way is then $\sum_0^\ell x_j s^j = \sum_0^\ell \binom{\ell}{j} (ns)^j (1-n)^{\ell-j}$

~~$(1+x_j s)$~~

$$= (1-n+ns)^\ell$$

So define $\underline{\phi(s,t) = \sum_0^\ell x_j s^j}$

then $\phi_t = \sum_0^\ell \dot{x}_j s^j$

$$= \sum_0^\ell [R_j - R_{j+1}] s^j \quad \text{providing we define } R_0 = R_{\ell+1} = 0$$

$$= \sum_0^\ell R_j s^j - \frac{1}{s}\sum_0^\ell R_{j+1} s^{j+1}$$

$$= \sum_1^\ell R_j s^j - \frac{1}{s}\sum_0^{\ell-1} R_{j+1} s^{j+1}$$

$$= \sum_1^\ell R_j s^j - \frac{1}{s}\sum_1^\ell R_k s^k$$

$$= \left(1 - \frac{1}{s}\right)\sum_1^\ell R_j s^j$$

Also $\sum_1^\ell R_j s^j = \sum_1^\ell (\ell - j+1)\alpha x_{j-1} s^j - \sum_1^\ell \beta j x_j s^j$

$$= \sum_0^{\ell-1} (\ell-k)\alpha x_k s^{k+1} - \beta s \sum_1^\ell j x_j s^{j-1}$$

$(\ell-\ell=0)$: $= \sum_0^\ell (\ell-k)\alpha x_k s^{k+1} - \beta s \sum_0^\ell j x_j s^{j-1}$ $(0=0)$

$$= \sum_0^\ell \alpha \ell s\, x_k s^k - \sum_0^\ell \alpha s^2 k x_k s^{k-1} - \beta s \sum_0^\ell j x_j s^{j-1}$$

$$= \alpha \ell s \phi - \alpha s^2 \phi_s - \beta s \phi_s$$

Hence

$$\phi_t = \left(1-\frac{1}{s}\right)\left[\alpha l s\phi - (\alpha s^2+\beta s)\phi_s\right]$$

$$= (s-1)\left[\alpha l \phi - (\alpha s+\beta)\phi_s\right]$$

& if we put $\phi = (1-n+ns)^l$

$$\phi_t = l(1-n+ns)^{l-1}(s-1)\dot{n}$$

$$\phi_s = l(1-n+ns)^{l-1} \quad n$$

& this solves the pde (& thus the x_j eq^s) if

$$\phi_t = l(1-n+ns)^{l-1}(s-1)\dot{n}$$

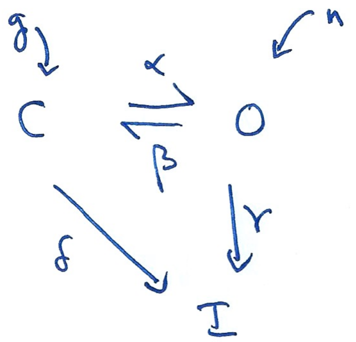
$$= (s-1)\left[\alpha l\phi - (\alpha s+\beta)\phi_s\right]$$

$$= (s-1)\left[\alpha l(1-n+ns)^l - (\alpha s+\beta)l(1-n+ns)^{l-1}n\right]$$

i.e [$\div$ by $l(1-n+ns)^{l-1}(s-1)$]

if $\quad \dot{n} = \alpha(1-n+ns) - (\alpha s+\beta)n$

$$= \alpha(1-n) - \beta n$$

(c) 

(i) $1-n-g$

(ii) $\dot n = \alpha g - \beta n - \gamma n$

$\dot g = -\alpha g + \beta n - \delta g$

(iii) $t=0$ $n=1$ $g=0$ all open

$$\begin{pmatrix}\dot n\\ \dot g\end{pmatrix} = \begin{pmatrix} -(\beta+\gamma) & \alpha \\ \beta & -(\alpha+\delta)\end{pmatrix}\begin{pmatrix} n\\ g\end{pmatrix}$$

$$\Rightarrow \begin{pmatrix} n\\ g\end{pmatrix} \sim \underset{\sim}{c_1} e^{\lambda_1 t} + \underset{\sim}{c_2} e^{\lambda_2 t}$$

$$(\lambda+\beta+\gamma)(\lambda+\alpha+\delta) - \alpha\beta = 0 \Rightarrow \lambda_1, \lambda_2$$

$\Rightarrow g = a(e^{\lambda_1 t} - e^{\lambda_2 t})$ $(\lambda_1 > \lambda_2)$ for $g=0$ at $t=0$

then (g eq) $n = \frac{1}{\beta}[\dot g + (\alpha+\delta) g]$

at $t=0$ $n = 1 = \frac{1}{\beta}[\dot g|_0] = \frac{a}{\beta}(\lambda_1 - \lambda_2)$

so $a = \dfrac{\beta}{\lambda_1 - \lambda_2}$

[(note $\lambda^2 - (\underbrace{\alpha+\beta+\gamma+\delta}_{T})\lambda + \underbrace{\alpha\gamma+\beta\delta+\delta\gamma}_{D} = 0$

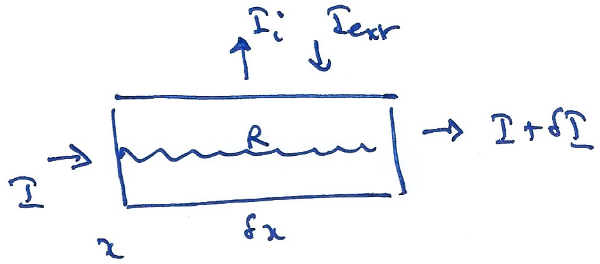
so $\lambda_{1,2} = \frac{1}{2}[T \pm (T^2 - 4D)^{1/2}]$

$\Rightarrow \lambda_1 - \lambda_2 = (T^2-4D)^{1/2} = [(\alpha+\beta+\gamma+\delta)^2 - 4(\alpha\gamma+\beta\delta+\gamma\delta)]^{1/2}$]

CS.12 C 1

Math Physiol 2018 q1

(a)



Conservation of charge (density) $Q = CV$

$$\frac{\partial}{\partial t} Q\,\delta x = I\Big|_{x+\delta x}^{x} + (I_{ext} - I_i)\,\delta x$$

$$\Rightarrow \underline{C\frac{\partial V}{\partial t} = -\frac{\partial I}{\partial x} + I_{ext} - I_i}$$

Also Ohm's law with Resistance R / unit length

$$-\delta V = R\,\delta x\, I$$

$$\Rightarrow \underline{-\frac{\partial V}{\partial x} = RI}$$

C capacitance (/unit length)
R resistance (/unit length

(b) $I_i = g_1(V-V_1)n + g_2(V-V_2)(1-n)m$ $\qquad V_1 < V_2$

$$\tau \dot{n} = n_\infty(V) - n$$

(i) steady state $I_i = 0 \Rightarrow V = V_0$, $n = n_\infty(V_0) = n_0$ say

$$\Rightarrow 0 = g_1(V_0 - V_1)n_0 + g_2(V_0 - V_2)(1-n_0)m \qquad \text{er } m = m(V_0)?$$

$$\Rightarrow V_0 = \frac{g_1 n_0 V_1 + g_2(1-n_0)m V_2}{g_1 n_0 + g_2(1-n_0)m} \in (V_1, V_2)$$

since $g_1 n_0 > 0$
$g_2(1-n_0)m > 0$

ii

non-d $t \sim \tau$ $x \sim l$ $V = V_0 + V^* v$

$$CV_t = \frac{1}{R} V_{xx} + I_{ext} - I_i$$

& $I_i = g_1 [V_0 - V_1 + V^* v] n + g_2 [V_0 - V_2 + V^* v](1-n)m$

$$= g_1 V^* \left[\frac{V_0 - V_1}{V^*} + v\right] n + g_2 V^* \left[v - \frac{V_2 - V_0}{V^*}\right](1-n)m$$

$$= g_2 V^* I_i^*,$$

$$I_i^* = \frac{g_1}{g_2}\left[\frac{V_0 - V_1}{V^*} + v\right] n + \left[v - \frac{V_2 - V_0}{V^*}\right](1-n)m$$

chose $V^* = V_2 - V_0 > 0$

$$\Rightarrow I_i^* = \gamma(v + v_1) n + (v-1)(1-n)m$$

$$\gamma = \frac{g_1}{g_2}, \quad v_1 = \frac{V_0 - V_1}{V_2 - V_0} > 0$$

and $\frac{CV^*}{\tau} v_t = \frac{V^*}{Rl^2} v_{xx} + g_2 V^* (I_{ext}^* - I_i^*)$

where also $I_{ext} = g_2 V^* I_{ext}^*$

& $\dot{n} = n_\infty - n$

thus define $\varepsilon = \frac{CV^*}{\tau g_2 V^*} = \frac{C}{\tau g_2}$

& $\varepsilon^2 = \frac{1}{g_2 R l^2}$ ie $l = \frac{\tau g_2}{C\sqrt{g_2 R}} = \frac{\tau}{C}\sqrt{\frac{g_2}{R}}$

(e) $\qquad \varepsilon v_t = I_{exr}^* - I_i^* + \varepsilon^2 v_{xx}$ $\qquad$ 13

$$n_t = n_\infty - n$$

$$I_i^* = g(n,v) = \gamma(v+v_1)n + (v-1)(1-n)m$$

$$n = h(v) \longleftrightarrow g(n,v) = 0$$

explicitly $\quad [\gamma(v+v_1) - (v-1)m]\,n + (v-1)\,m = 0$

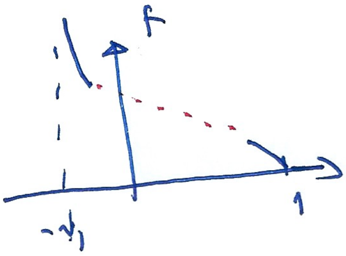
$$n = \frac{(v-1)\,m(v)}{(v-1)m(v) - \gamma(v+v_1)} = h(v) \qquad m>0,\ m'>0$$

equilibri: $\quad v=0,\ n = n_\infty(0)$

Consider the function $\quad f(v) = \dfrac{(1-v)\,m(v)}{\gamma(v+v_1)} \qquad \left(\text{so } h = \dfrac{1}{f+1}\right)$

For $-v_1 < v < 1$

$f > 0$



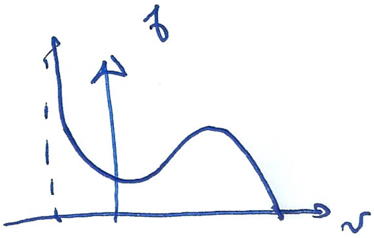
$f \to \infty$ at $-v_1$

$f \to 0$ at 1

so monotonically decreasing is possible

but clearly f will not be non-monotonic if

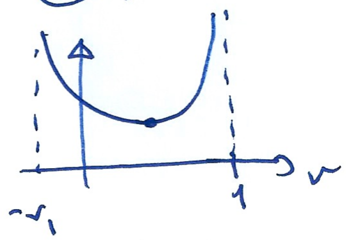
m' is large enough



....

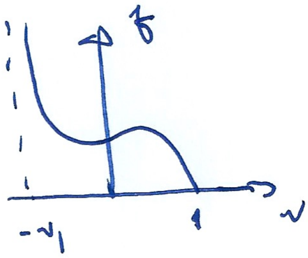
Explicitly $\frac{f'}{f} = \frac{-1}{1-v} + \frac{m'}{m} - \frac{1}{v+v_1}$

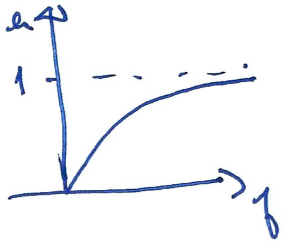
$$= \frac{m'}{m} - \underbrace{\left[\frac{1}{1-v} + \frac{1}{v+v_1}\right]}$$



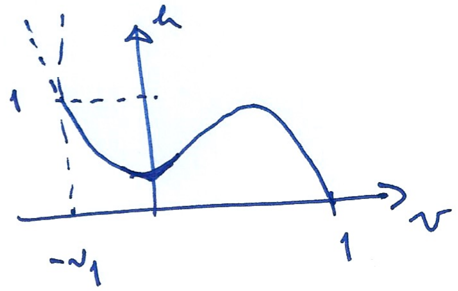
> 0 if $\frac{m'}{m}$ larger than $\min\limits_{-v_1<v<1} \left[\frac{1}{1-v} + \frac{1}{v+v_1}\right]$

then





$\Rightarrow$



(ii) obvious (already done). $h'(v) = h'(f)\, f'(v)$

$$= \frac{f}{(f+1)^2}\left[\frac{m'}{m} - \left\{\frac{1}{1-v} + \frac{1}{v+v_1}\right\}\right]$$

$\to -\infty$ as $v \to 1$

$h < 0$ as $v \to v_1$, $f \to \infty$

$\left(h' \approx \frac{1}{f} \cdot -\frac{1}{(v+v_1)} \approx -\frac{\gamma}{(1+v_1)\, m(-v_1)} \right)$

(5

$m = \exp[k(v-1)]$

$= \frac{m'}{m} = k$

non-monotonic if $k > \min\left[\frac{1}{1-v} + \frac{1}{v+v_1}\right]$

which is at $\quad +\frac{1}{(1-v)^2} = \frac{1}{(v+v_1)^2}$

ie $\quad 1-v = v+v_1$

$v = \frac{1-v_1}{2}$

min is $\left[\frac{1}{1-\left(\frac{1-v_1}{2}\right)} + \frac{1}{\frac{1-v_1}{2}+v_1}\right]$

$= \frac{4}{1+v_1}$

So if $k > \frac{4}{1+v_1}$

(iii) $n_\infty(v)$ increasing

~~At $x=0$, $f = \frac{m(0)}{\gamma v_1}$~~

$h'(v) = \frac{f}{(f+1)^2}\left[k - \left\{\frac{1}{1-v} + \frac{1}{v+v_1}\right\}\right]$

$h'(0) > 0 \quad$ if $[f(0) > 0$ as $m(0) > 0]$

$k > 1 + \frac{1}{v_1}$

[Note: question suggests $h'(0)>0$ as below. See p7 for $h'(0)<0$] (6

$\varepsilon\dot{v} = -g(n,v)$

$\dot{n} = n_\infty - n$

Note for $-v_1<v<1$, $n>0$

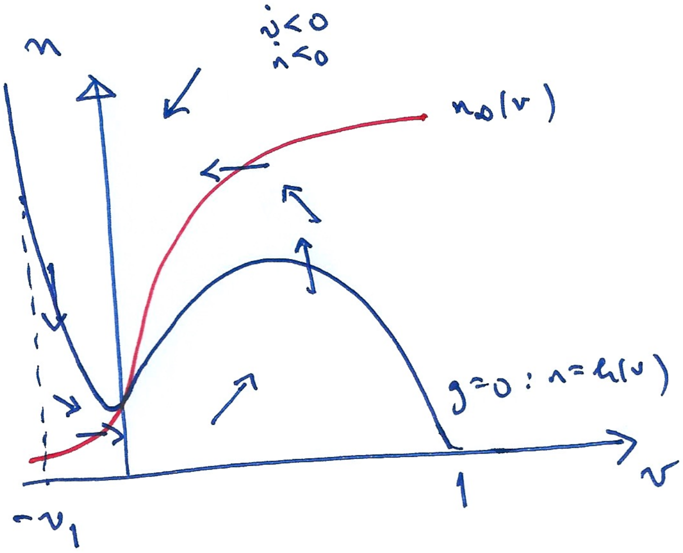
$g\to\infty$ as $n\to\infty$

so $\dot{v}<0$ for $n>h(v)$

$\downarrow$

trajectory directions as shown

$\Rightarrow$ fixed point is node or spiral

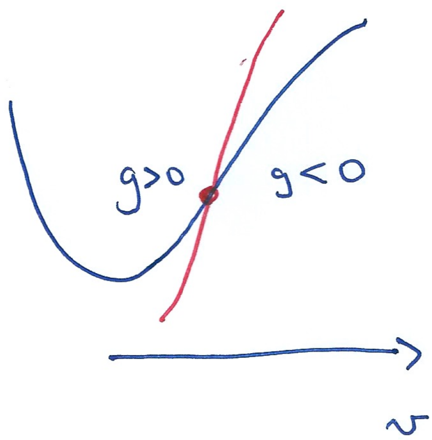


$\Rightarrow$ stable if $\mathrm{tr}\,M<0$ where $M=\begin{pmatrix} -\frac{1}{\varepsilon}g_v & -\frac{1}{\varepsilon}g_n \\ n_\infty' & -1 \end{pmatrix}$

ie $\mathrm{tr}\,M = -\frac{1}{\varepsilon}g_v - 1$

<0 if $g_v > -\varepsilon$

Now ~~suppose~~ if $h'(0)>0$



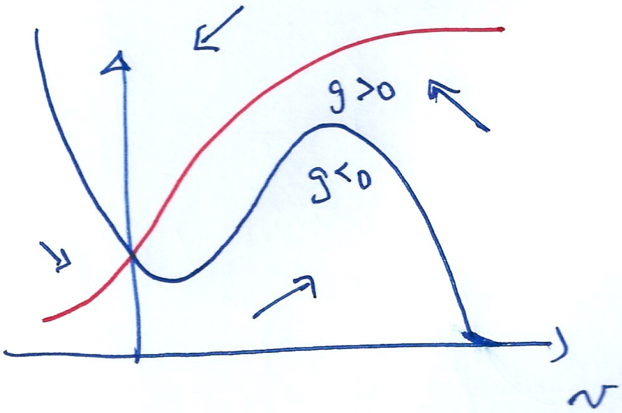
$\Rightarrow g_v<0$

and the steady state is Unstable !?

[The question is not specific, but the implication to me is that we should have $h'(0)<0$]

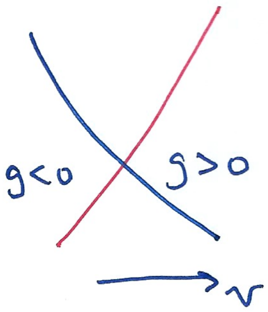
[I think the question ought to read:

Determine the conditions such that $h'(0) < 0$. Assuming this, use ...]



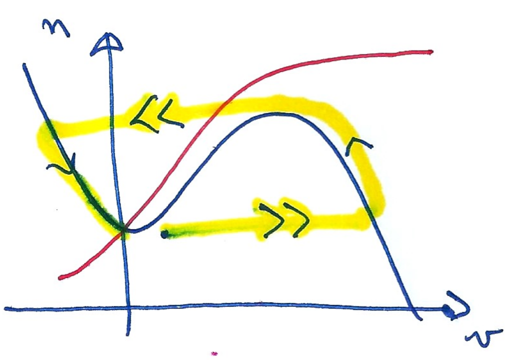
Steady state is stable if $g_v > -\varepsilon$

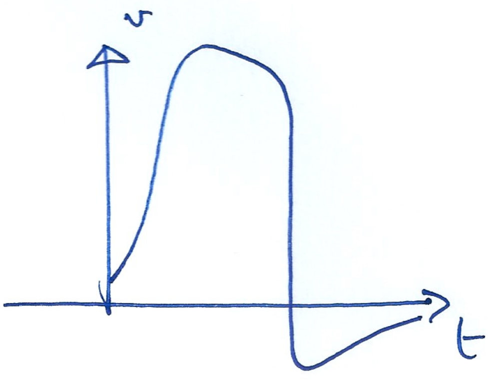
i.e. if $g_v \gtrsim 0$ $(\varepsilon \ll 1)$



$\Rightarrow g_v > 0$

Threshold phenomenon: increase v

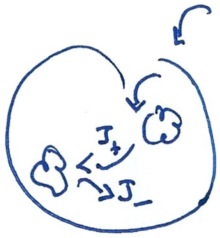




C1

CS.12 Math Physiol 2018 q 2

2/



$$\dot c = r - kc - [J_+ - J_- - k_s c_s]$$

$$\dot c_s = J_+ - J_- - k_s c_s$$

(a) r : production of cytoplasmic Ca^{2+} by stimulation of the IP_3 sensitive store

kc leakage of cytoplasmic Ca^{2+} through cell

kc_s leakage of Ca^{2+} sensitive store to cytoplasm

(b) $$J_- = \frac{V c_s^m}{K_1^m + c_s^m} \cdot \frac{c^p}{K_2^p + c^p}$$

This is the product of two Hill functions (analogous to cooperative enzyme production) : the release ~~depends~~ increases with c_s (as for example $c_s + \text{gate} \to c$) but is also stimulated by c (CICR) thus

$$c_s + \text{gate} \longrightarrow c \quad :$$

the cytoplasmic Ca^{2+} facilitates the release of the stored Ca^{2+}.

(c) 2

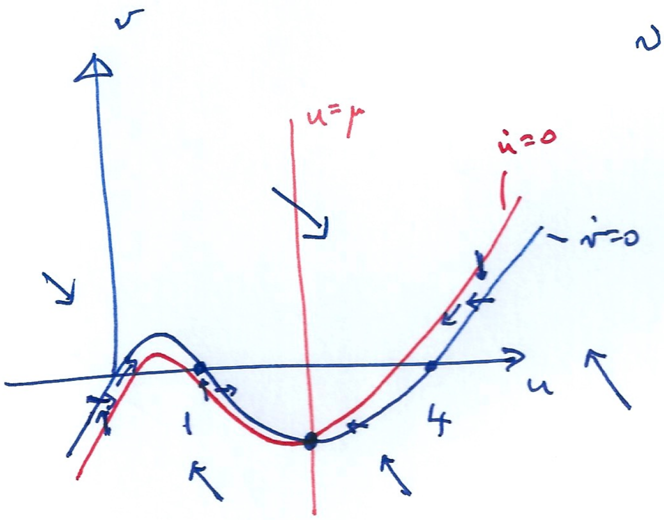
(c)

and $\dot{u} = \mu - u - \frac{5}{\varepsilon} f(u,v)$

$\dot{v} = \frac{1}{\varepsilon} f(u,v)$

$f = u[u^2 - 4u + 5] - v \quad \equiv g(u) - v$

(i)



v nullcline $f = 0$:

$v = u(u-4)(u-1)$

$\dot{u} = 0$ [not sure if the actual nullcline is required – would have depended how the lecturer presented it – I'll do the actual nullcline]

is (with $g(u) = u(u-4)(u-1)$)

$\frac{\varepsilon}{5}(\mu - u) = f = g - v \quad \Rightarrow v = g(u) - \frac{\varepsilon}{5}(\mu - u)$

example above uses $1 < \mu < 4$.

Large v: $\dot{v} < 0$, $\dot{u} > 0$ $\Rightarrow$ other trajectories as shown

Note unique steady state at $u = \mu$, $v = g(\mu)$

[Carrying on formally, linearise at steady state

$$u = \mu + U \qquad v = g(\mu) + V \quad \Rightarrow \text{ linearise } \begin{pmatrix} \dot U \\ \dot V \end{pmatrix} \approx M \begin{pmatrix} U \\ V \end{pmatrix}$$

$$M = \begin{pmatrix} -1 - \frac{5}{\varepsilon} f_u & -\frac{5}{\varepsilon} f_v \\ \frac{1}{\varepsilon} f_u & \frac{1}{\varepsilon} f_v \end{pmatrix}$$

So $\det M = -\frac{1}{\varepsilon} f_v$

$\operatorname{tr} M = -1 - \frac{5}{\varepsilon} f_u + \frac{1}{\varepsilon} f_v$

$f = g(u) - v$ so $\det M > 0$ never saddles

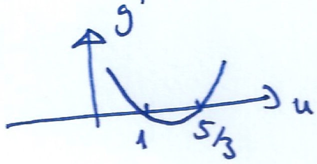
$\operatorname{tr} M = -1 + \frac{1}{\varepsilon}\left[-1 - 5g'\right]$

So $(\varepsilon \ll 1)$ steady state is stable if $-1 - 5g' \lesssim 0$

i.e. $g' \gtrsim -\frac{1}{5}$

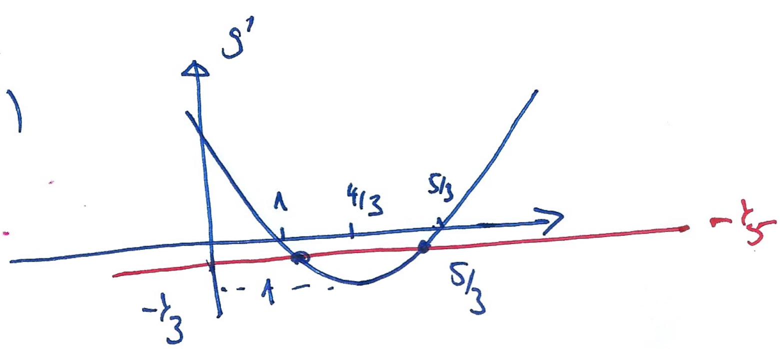
$$g' = \left[u^3 - 4u^2 + 5u\right]' = 3u^2 - 8u + 5$$

$$= (u-1)(3u-5)$$



min g' is at $u = \frac{4}{3}$, min $g' = 3 \cdot \frac{16}{9} - \frac{32}{3} + 5 = \frac{15-16}{3} = -\frac{1}{3}$

So $(u=\mu)$



values of u where $g' = -\frac{1}{5}$:

$$3u^2 - 8u + 5 = -\tfrac{1}{5}$$

are $\quad 3u^2 - 8u + \frac{26}{5} = 0$

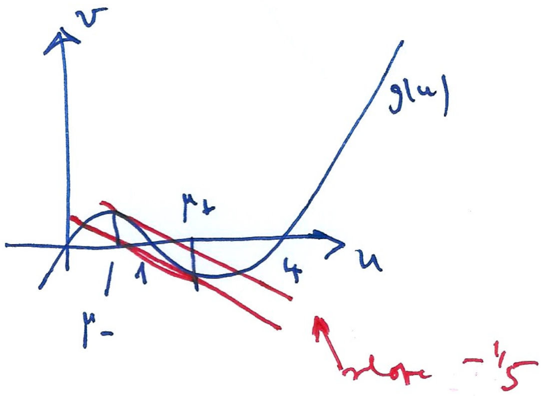
$$u = \frac{1}{6}\left[8 \pm \left\{ 64 - \frac{12.26}{5} \right\}^{1/2} \right]$$

$$= \frac{1}{6}\left[8 \pm \left\{ \frac{320 - 312}{5} \right\}^{1/2} \right]$$

$$= \frac{4}{3} \pm \frac{1}{3}\sqrt{\frac{2}{5}} \quad = \mu_\pm$$

So for $\mu_- \lesssim \mu \lesssim \mu_+$ steady state is unstable.]

But directly (perhaps all that is required)



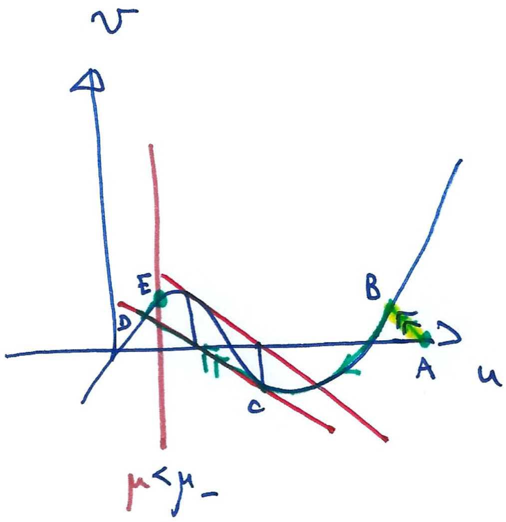
$$\varepsilon \dot{v} = f(u,v) = g(u) - v$$

$$(\dot{u + 5v}) = \mu - u$$

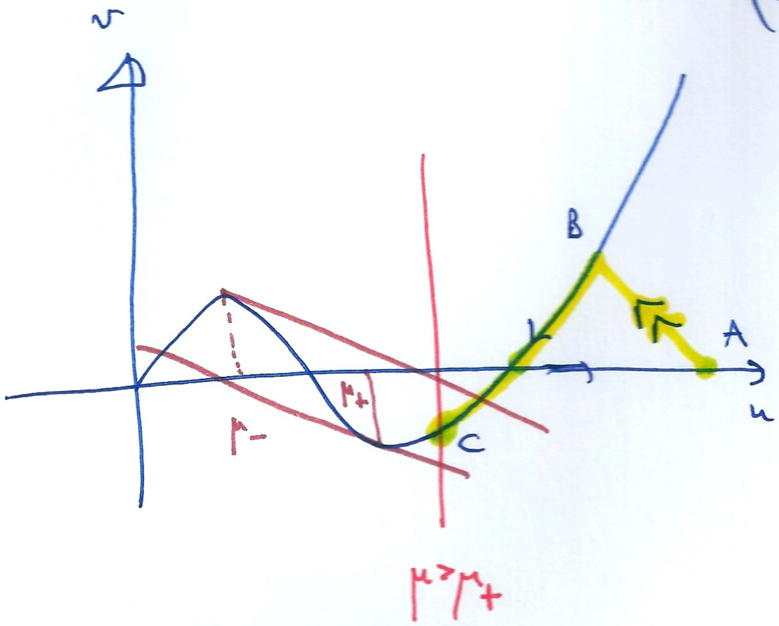
If we define $\mu_\pm$ to be where $g'(u) = -\frac{1}{5}$ (thus as above)

then we will get relaxation oscillations for $\mu_- < \mu < \mu_+$:

(5



trajectory follows ABCDE

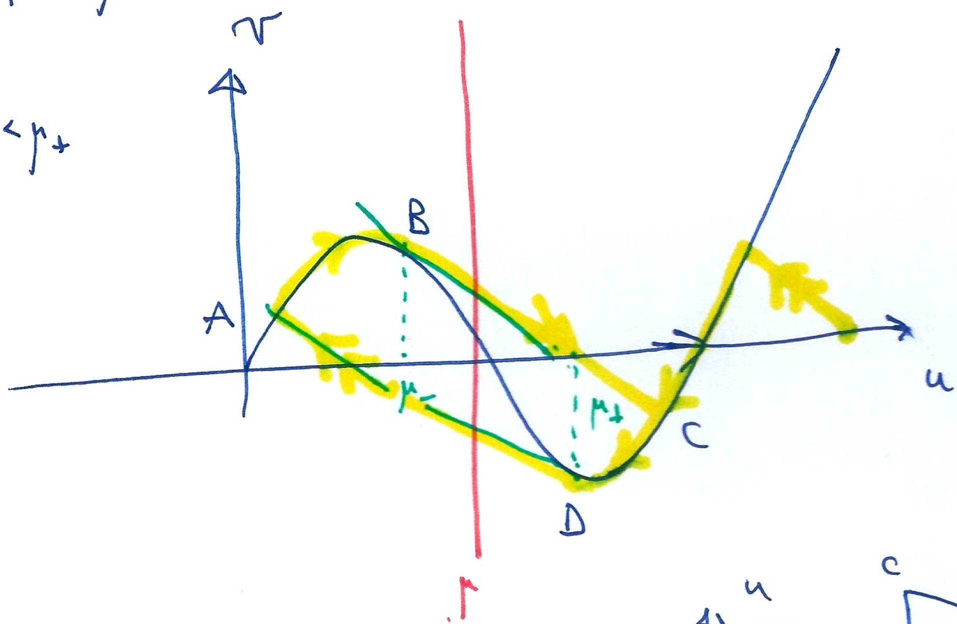


follows ABC

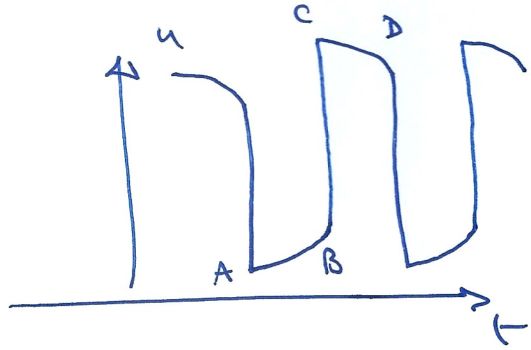
fast slow

(ii) μ_-, μ_+ done above

$\mu_- < \mu < \mu_+$



relaxation oscillation is ABCD

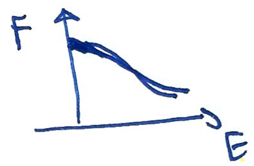


05·12 Math Physiol q3

(1

3, $\dot{E} = F(E_\tau) - \gamma E$

(a) E : erythrocytes produced at rate F which depends on E via feedback (eg via EPO) to stemcells which take time τ to mature : γ represents death rate of blood cells in circulation

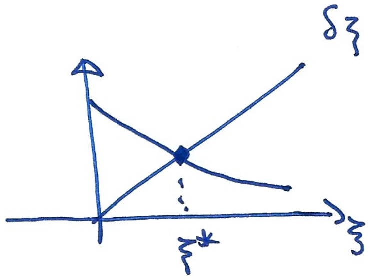
(b) 

production is reduced as E increases which acts to control numbers

(c) (i) $t \sim \tau$ $E = \theta \xi$, $F = \dfrac{F_0 \theta^n}{(E_\tau + \theta)^n}$

$$\Rightarrow \frac{\theta}{\tau} \dot{\xi} = \frac{F_0}{(1+\xi_1)^n} - \gamma \theta \xi$$

$$\Rightarrow \dot{\xi} = \frac{\rho}{(1+\xi_1)^n} - \delta \xi \qquad \left\{ \begin{array}{l} \rho = \dfrac{F_0 \tau}{\theta} \\ \delta = \gamma \tau \end{array} \right.$$

(ii) 

steady $\dfrac{\rho}{(1+\xi)^n} = \delta \xi$

decreasing increasing

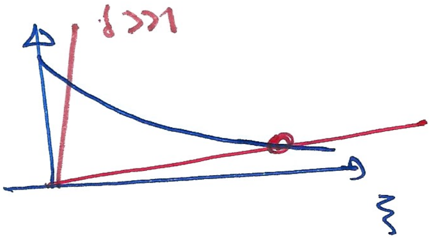
$\Rightarrow$ unique steady state

(2

$f(\xi) = \dfrac{1}{(1+\xi)^n}$

so $\dot{\xi} = \rho f(\xi_1) - \delta\xi$

$\delta \ll 1$



ξ^* is large

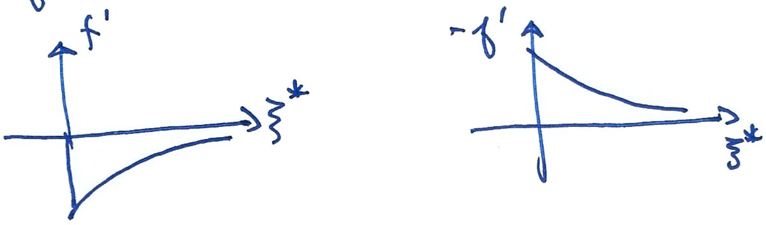
$\dfrac{\rho}{(1+\xi)^n} = \delta\xi \quad \Rightarrow \quad \xi^* \approx \left(\dfrac{\rho}{\delta}\right)^{\frac{1}{n+1}} \qquad \delta \ll 1$

if $\delta \gg 1$, $\xi \ll 1$, $\xi^* \approx \dfrac{\rho}{\delta} \qquad \delta \gg 1$

So $f' = \left(\dfrac{1}{(1+\xi)^n}\right)' = \dfrac{-n}{(1+\xi)^{n+1}} \approx -\dfrac{n\delta}{\rho} \qquad \delta \ll 1$

$\approx -n \qquad \delta \gg 1$

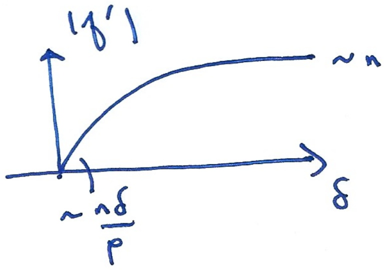
Clearly f' is monotonic in ξ



& ξ^* increases monotonically as δ decreases

$\Rightarrow |f'|$ increases with δ

$\Rightarrow$



(iii) $\delta \ll 1$

& perturb steady state $\xi = \xi^* + X$

$\Rightarrow \dot{X} = -p|f'(\xi^*)| X_1 - \delta X$

$X = e^{\sigma t}$ $\sigma = -p|f'| e^{-\sigma} - \delta$ ← note this is fine

$\delta \ll 1$, $p|f'| \simeq n\delta$ ← but this is misguided - see bottom p5

$\Rightarrow \sigma \simeq -\delta n e^{-\sigma} - \delta$

Clearly for $n<1$ all roots have $\mathrm{Re}\,\sigma < 0$

σ varies smoothly with n

If instability occurs then $\sigma = i\theta$ for some n

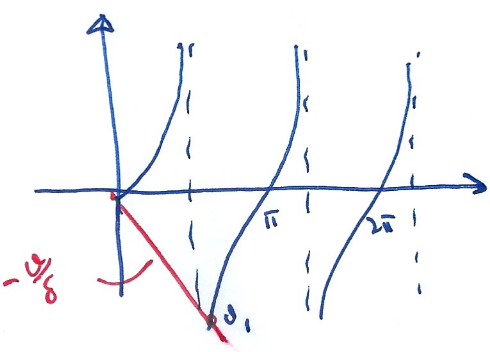
$\Rightarrow i\theta = -\delta n[\cos\theta - i\sin\theta] - \delta$

$\Rightarrow \theta = \delta n \sin\theta$

& $n\cos\theta + 1 = 0$

or $-1 = n\cos\theta$

$\Rightarrow -\frac{\theta}{\delta} = \tan\theta$



& then $n = \frac{-1}{\cos\theta}$

Note when $\delta \ll 1$

roots are $\theta_1 = \pi/2 + \phi_1 \qquad \phi_1 \ll 1$

$\theta_2 = 3\pi/2 + \phi_2 \qquad \phi_2 \ll 1$

$\vdots$

$\theta_m = (m - \tfrac{1}{2})\pi + \phi_m$ & ϕ_m decreases with m

so $$-\frac{1}{\cos\theta_m} = \frac{-1}{(-1)^m \cos(-\tfrac{1}{2}\pi + \phi_m)}$$

$$= \frac{(-1)^{m+1}}{\sin\phi_m}$$

only interested in m odd

corresponding $n_m = \dfrac{1}{\sin\phi_m}$ m odd

ϕ_m decreases with m

so does $\sin\phi_m$ $(\simeq \phi_m)$

so n_m increases with m

So $\min\limits_{m \text{ odd}} n_m = n_1$.

We have $-\dfrac{\theta}{\delta} \simeq \tan\theta$ & $\theta_1 = \pi/2 + \phi_1$

$$-\frac{\pi}{2\delta} \simeq \frac{\cos\phi_1}{-\sin\phi_1} \simeq -\frac{1}{\phi_1} \Rightarrow \phi_1 \simeq \frac{2\delta}{\pi}$$

$$\Rightarrow n_1 \simeq -\frac{1}{\cos\theta_1} = \frac{1}{\sin\phi_1} \simeq \frac{\pi}{2\delta}$$

So the steady state is unstable for $n \gtrsim \frac{\pi}{2\delta}$

(assuming some approximation works).

Transversality $\sigma(n)$

$$\sigma = -\delta n e^{-\sigma} - \delta$$

$$\sigma' = -\delta e^{-\sigma} + \delta n e^{-\sigma} \sigma'$$

$$= \frac{\sigma+\delta}{n} - (\sigma+\delta)\sigma'$$

$$\Rightarrow \sigma' = \frac{1}{n}\left[\frac{\sigma+\delta}{\sigma+\delta+1}\right]$$

at $\sigma = i\theta$ $\quad \sigma' = \frac{1}{n}\left[\frac{(1+\delta-i\theta)(\delta+i\theta)}{(1+\delta)^2+\theta^2}\right]$

$$= \frac{1}{n}\left[\frac{\delta+i\theta+\delta^2+\theta^2}{(1+\delta)^2+\theta^2}\right]$$

$\Rightarrow \operatorname{Re}\sigma' > 0$ transversality.

[Actually the part ii is a bit off-putting. Linear stability is $\sigma = -p|f'|e^{-\sigma} - \delta = -\beta e^{-\sigma} - \delta$ say in any case so all the above, replacing δn by $p|f'| = \beta$ still works, so the condition is $p|f'| \gtrsim \pi/2$ – independently of whether the approximation for f' still works. In fact if you put $p|f'| = \pi/2$ you find $\xi^* = \frac{1}{\frac{2n\delta}{\pi}-1}$ which is $O(1)$ if $n\delta = O(1)$ so (ii) seems irrelevant]

(1

Mathematical Physiology fhs 2018-2019

Answers

B = bookwork

V = variant of [or similar to] material seen before (e.g. on problem sheet)

N = new

1. (a) S = concentration of ion

so $-D\nabla S$ is diffusive flux

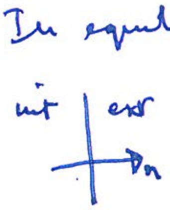
V = electrical potential

drives current $\propto -\nabla V$

i.e. each ion moves in the direction of $-\nabla V$ at a rate u (if +vely charged) or $-u$ (if -vely charged), i.e at rate $u \,\mathrm{sgn}\, z$, z = valency, and thus the ionic flux due to V is $-u \,\mathrm{sgn}\, z\, S \nabla V$

Total flux is $\mathbf{J} = -D\nabla S - u \,\mathrm{sgn}\, z\, S\nabla V$

In equilibrium $\mathbf{J} = \mathbf{0}$ & across a membrane this gives



$$-D\frac{\partial S}{\partial n} - u \,\mathrm{sgn}\, z\, S\frac{\partial V}{\partial n} = 0$$

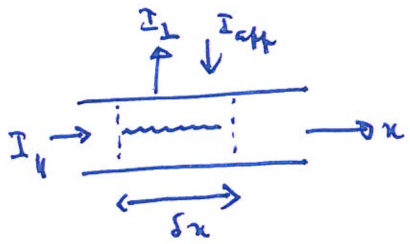
$$\text{i.e.} \quad -\frac{\partial V}{\partial n} = \frac{D}{u \,\mathrm{sgn}\, z}\frac{1}{S}\frac{\partial S}{\partial n}$$

$$\Rightarrow \quad -[V]_i^e = \frac{D}{u \,\mathrm{sgn}\, z}[\ln S]_i^e$$

with $u = \frac{|z|FD}{RT}$, $\frac{D}{u \,\mathrm{sgn}\, z} = \frac{D}{|z|\,\mathrm{sgn}\, z}\frac{RT}{FD} = \frac{RT}{Fz}$ & $V = [V]_e^i = \frac{RT}{zF}\ln\frac{S_e}{S_i}$

5 B

(b) C 2



If V is the (internal) potential then $CV\delta x$ is the charge in the segment $(x, x+\delta x)$, C = capacitance per unit length

So conservation of charge gives

$$\frac{\partial}{\partial t} CV\delta x = -I_\perp \delta x + I_{app}\delta x + I_\parallel\big|_x - I_\parallel\big|_{x+\delta x}$$

& thus $$C\frac{\partial V}{\partial t} = -I_\perp + I_{app} - \frac{\partial I_\parallel}{\partial x}$$

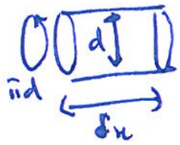
The axial current is given by Ohm's law:

$$V\big|_x - V\big|_{x+\delta x} = I_\parallel R\,\delta x$$ where R = resistance per unit length,

so $$I_\parallel = -\frac{1}{R}\frac{\partial V}{\partial x}$$

& $$CV_t = -I_\perp + I_{app} + \frac{1}{R}V_{xx}$$

5 B



If C_m is the capacitance per unit area, then $\pi d\,\delta x\, C_m = \delta x\, C$

i.e. $C = \pi d C_m$

(3

(c)

$$I_i = g_{Na} m^3 h (V - V_{Na}) + g_K n^4 (V - V_K) + g_L (V - V_L)$$

is current per unit area. Thus $\pi d \delta x\, I_i = \delta x I_\perp$, i.e. $\underline{I_\perp = \pi d I_i}$

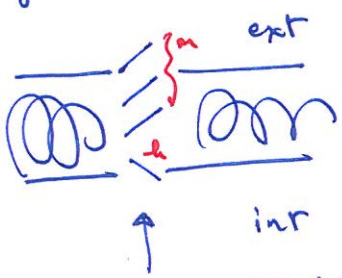
Each term is an ionic flux due to sodium (Na), potassium (K) and leakage (L) - e.g. (mostly) chloride

g_{Na} etc are conductances

V_{Na} etc are Nernst potentials

m, h, n are gate variables

e.g.



3 m gates & 1 h gate

$m^3 h$ is the proportion of open channels with 3 m gates & 1 h gate.

Gate equations: $\quad \tau_k \dot{k} = k_\infty(V) - k$

for $k = m, n, h$.

$$\tau_m \dot{m} = m_\infty - m$$
$$\tau_n \dot{n} = n_\infty - n$$
$$\tau_h \dot{h} = h_\infty - h$$

$\tau_m \ll \tau_n, \tau_h \Rightarrow m \to m_\infty$ rapidly $\Rightarrow \underline{m \approx m_\infty(V)}$

$\tau_n = \tau_h$, $n_\infty + h_\infty = \bar{h} \Rightarrow \quad \tau_n \dot{(n+h)} = \bar{h} - (n+h)$

$\Rightarrow n + h \to \bar{h}$ so take $\underline{n + h = \bar{h}}$

6 B

(d)

$$V - V_{eq} = (V_{Na} - V_{eq})\, v \qquad t \sim \tau_n \qquad x \sim l$$

$$\Rightarrow V - V_{Na} = V_{eq} - V_{Na} + (V_{Na} - V_{eq})\, v$$

write $\Delta V = V_{Na} - V_{eq}$

$$\Rightarrow V - V_{Na} = \Delta V\,(v - 1)$$

$$V - V_K = V_{eq} - V_K + \Delta V\, v$$

$$V - V_L = V_{eq} - V_L + \Delta V\, v$$

Define
$$V_{eq} - V_K = \Delta V_K = 12\ \text{mV}$$
$$V_L - V_{eq} = \Delta V_L = 10.6\ \text{mV}$$
$$\Delta V = 115\ \text{mV}$$

so
$$V - V_{Na} = \Delta V\,(v - 1)$$
$$V - V_K = \Delta V\left(v + \frac{\Delta V_K}{\Delta V}\right)$$
$$V - V_L = \Delta V\left(v - \frac{\Delta V_L}{\Delta V}\right)$$

Define
$$v_K^* = \frac{\Delta V_K}{\Delta V} = \frac{12}{115} \sim 0.1$$
$$v_L^* = \frac{\Delta V_L}{\Delta V} = \frac{10.6}{115} \sim 0.09$$

Then
$$I_i = g_{Na} m^3 h\, \Delta V\,(v-1) + g_K n^4\, \Delta V\,(v + v_K^*) + g_L\, \Delta V\,(v - v_L^*)$$
$$= g_{Na}\Delta V\left[-(1-v)\, m^3 h + \gamma_K n^4 (v + v_K^*) + \gamma_L (v - v_L^*)\right]$$

$$\gamma_K = \frac{g_K}{g_{Na}} = \frac{36}{120} = 0.3$$
$$\gamma_L = \frac{g_L}{g_{Na}} = \frac{0.3}{120} = \frac{3\times10^{-1}}{1.2\times10^{2}} = 2.5\times10^{-3}$$

Thus, with $I_i = g_{Na}\Delta V\, I_i^*$

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

The cable equation is (non-d)

$$\frac{C}{\tau_n}\Delta V\, v_t = I_{app} - \pi d g_{Na}\Delta V\, I_i^* + \frac{1}{R}\frac{\Delta V}{\ell^2} v_{xx}$$

Thus with $I^* = \cancel{\frac{I_{app}\tau_n}{C\Delta V}}\ \frac{I_{app}}{\pi d g_{Na}\Delta V}$, this is

$$\frac{C}{\pi d \tau_n g_{Na}} v_t = I^* - I_i^* + \frac{1}{\pi d R \ell^2 g_{Na}} v_{xx}$$

So we define ($C = \pi d C_m$)

$$\varepsilon = \frac{C_m}{\tau_n g_{Na}} = \frac{10^{-6}}{5\;10^{-3}\;120\;10^{-3}}\;\frac{F}{cm^2}\;\frac{cm^2}{s\;S}$$

$$= \frac{1}{600} = \frac{1}{6\times10^2} \sim 0.16\times10^{-2}$$

and $\frac{1}{\pi d R \ell^2 g_{Na}} = \varepsilon^2 = \frac{C_m^2}{(\tau_n g_{Na})^2}$

$$\Rightarrow \ell = \frac{1}{\sqrt{\pi d R g_{Na}}}\frac{\tau_n g_{Na}}{C_m} = \frac{\tau_n}{C_m}\sqrt{\frac{g_{Na}}{\pi d R}}$$

$$= \frac{5\;10^{-3}}{10^{-6}}\left(\frac{0.12\;10^{-4}}{3.14\times5\times10^{-2}\;1.5}\;\frac{S\;cm}{cm^2\;cm\;\Omega}\right)^{1/2}\frac{s\;cm^2}{F}$$

$$= 5\times10\left(\frac{12}{15.7}\right)^{1/2}\frac{S}{cm}\;\frac{s\;cm^2}{F}$$

$$\sim 50\times\frac{\sqrt{3}}{2}\;cm \sim 43\;cm$$

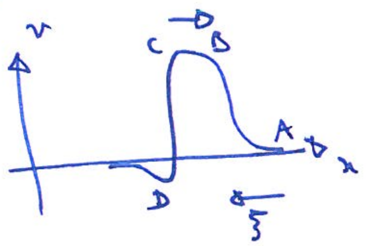
5 V

(e) $I^* = 0$

$$\varepsilon v_t = -g(v,n) + \varepsilon^2 v_{xx}$$

$$n_t = n_\infty - n$$

travelling wave n, v function of $\xi = ct - x$, $c > 0$

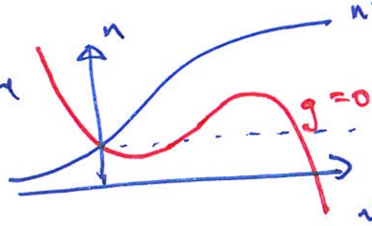


$\Rightarrow$ $\varepsilon c v' = -g + \varepsilon^2 v''$

$c n' = n_\infty - n$

$\Rightarrow$ phase plane n, v, v'

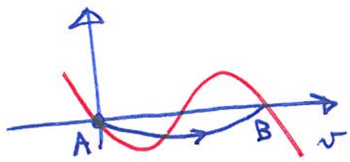
Assume



… 3 roots $g = 0$ at $n = n_\infty(0)$

Fast phase $\xi = \varepsilon X$: $cv' = -g + v''$, $n \simeq$ Constant

phase plane



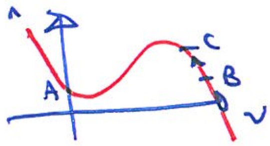
$v' = -w$

$w' = cw - g$

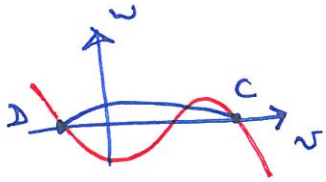
pick c so $A \to B$

Slow phase $g = 0$ $cn' = n_\infty - n$

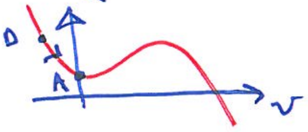
$B \to C$, $n = n^*$ to be found



fast phase: pick n^* so $C \to D$

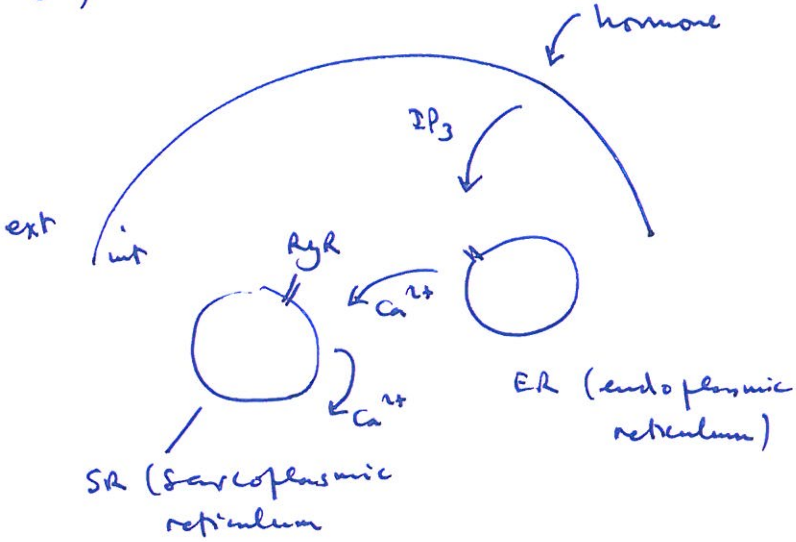


Slow phase $D \to A$



4 V

2. (a)



Stimulation of a cell by an agonist causes release of IP_3 to the ER which releases Ca^{2+} to the SR which releases stored Ca^{2+}.

<u>Model</u>

$$\dot{c} = r - kc - \overbrace{[J_+ - J_- - k_s c_s]}^{-J}$$

$$\dot{c}_s = J_+ - J_- - k_s c_s = J, \text{ say}$$

$$J_+ = \frac{V_1 c^n}{K_1^n + c^n} \qquad J_- = \frac{V_2 c_s^m}{K_2^m + c_s^m} \cdot \frac{c^p}{K_3^p + c^p}$$

$$J = \frac{V_1 c^n}{K_1^n + c^n} - \frac{V_2 c_s^m}{K_2^m + c_s^m} \cdot \frac{c^p}{K_3^p + c^p} - k_s c_s$$

Balances as shown: scale $t \sim \frac{1}{k}$, $c = K_1 u$, $c_s = K_2 v$

$$J = V_2 f$$

8

Then $k K_1 \dot{u} = r - k K_1 u - V_2 f$

$k K_2 \dot{v} = V_2 f$

$$V_2 f = V_1 \frac{u^n}{1+u^n} - \frac{V_2 v^m}{1+v^m} \cdot \frac{u^p}{\left(\frac{K_3}{K_1}\right)^p + u^p} - k_s K_2 v$$

Thus

$$\dot{u} = \mu - u - \gamma \dot{v}$$

$$\varepsilon \dot{v} = f$$

$$f = F(u) - \frac{G(u) v^m}{1+v^m} - \delta v, \qquad F = \frac{\beta u^n}{1+u^n}, \quad G = \frac{u^p}{\alpha^p + u^p}$$

if $\mu = \frac{r}{k K_1}$, $\frac{\gamma}{\varepsilon} = \frac{V_2}{k K_1}$, $\varepsilon = \frac{k K_2}{V_2} \Rightarrow \gamma = \frac{K_2}{K_1}$

$\beta = \frac{V_1}{V_2}$, $\alpha = \frac{K_3}{K_1}$, $\delta = \frac{k_s K_2}{V_2}$

1(b) B

(b) $\alpha = \frac{K_3}{K_1} = 0.9$, $\beta = \frac{65}{500} = 0.13$, $\gamma = 2$, $\delta = \frac{1 \times 2}{500} \frac{s^{-1}\,\mu M}{\mu M\, s^{-1}} = 0.004$

$\varepsilon = \frac{10 \times 2}{500} \frac{s^{-1}\,\mu M}{\mu M\, s^{-1}} = 0.04$

2 B

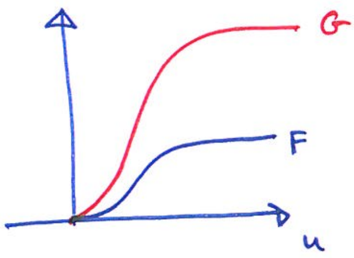
(c) Since $\delta \ll 1$, $f = 0$ if $\frac{v^m}{1+v^m} = \frac{F(u)}{G(u)}$

& this is $v = V(u)$, V has same shape as F/G

as $\frac{v^m}{1+v^m}$ is monotonically increasing ($\lambda < 1$, but this is only if $F/G < 1$)

$m = 2,\ n = 4,\ p = 2$

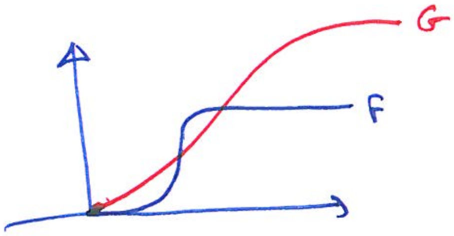
So $f = F(u) - G(u)\dfrac{v^2}{1+v^2} - \delta v,\qquad F = \dfrac{\beta u^4}{1+u^4},\quad G = \dfrac{u^2}{\alpha^2+u^2}$



possible : $F < G$ initially & finally

(& then $F < G$)

but



is possible if $F = G$ has 2 +ve roots

In the latter case $\dfrac{\beta u^4}{1+u^4} = \dfrac{u^2}{\alpha^2+u^2}$

$$\Rightarrow \beta u^2(\alpha^2+u^2) = 1+u^4$$

$$\Rightarrow (1-\beta)u^4 - \beta\alpha^2u^2 + 1 = 0$$

$$\Rightarrow u^2 = \frac{1}{2(1-\beta)}\left[\beta\alpha^2 \pm \left\{\beta^2\alpha^4 - 4(1-\beta)\right\}^{1/2}\right]$$

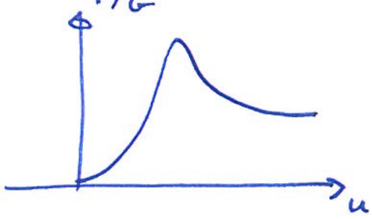
gives ~~have~~ 2 +ve roots iff $\beta^2\alpha^4 > 4(1-\beta)$

i.e. $\alpha^2 > \frac{2}{\beta}(1-\beta)^{1/2}$

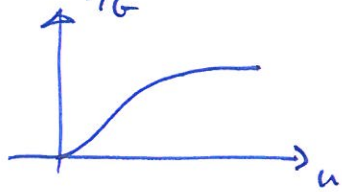
or $\alpha > \sqrt{\frac{2}{\beta}}\,(1-\beta)^{1/4}$

So $F<G$ (1st picture) if $\alpha < \sqrt{\frac{2}{\beta}}\,(1-\beta)^{1/4}$

In that case



(or



)

to show F/G has a maximum, show $\left(F/G\right)' = 0$ has a +ve root

i.e. $F'G - FG' = 0$

Do these derivatives w.r.t. $\xi = u^2$, $F = \dfrac{\beta\xi^2}{1+\xi^2}$, $G = \dfrac{\xi}{\alpha^2+\xi}$

$$\Rightarrow F' = \frac{2\beta\xi}{1+\xi^2} - \frac{2\beta\xi^3}{(1+\xi^2)^2} = \frac{2\beta\xi}{(1+\xi^2)^2}$$

$$G' = \frac{1}{\alpha^2+\xi} - \frac{\xi}{(\alpha^2+\xi)^2} = \frac{\alpha^2}{(\alpha^2+\xi)^2}$$

so need
$$\underbrace{\frac{\beta\xi^2}{1+\xi^2}}_{F}\ \underbrace{\frac{\alpha^2}{(\alpha^2+\xi)^2}}_{G'} = \underbrace{\frac{2\beta\xi}{(1+\xi^2)^2}}_{F'}\ \underbrace{\frac{\xi}{\alpha^2+\xi}}_{G}$$

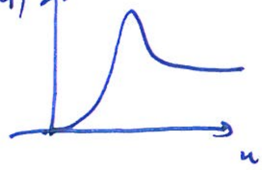
$\div \beta\xi^2$ i.e. $\alpha^2(1+\xi^2) = 2(\alpha^2+\xi)$

i.e. $\alpha^2\xi^2 - 2\xi - \alpha^2 = 0$

$$\Rightarrow \xi = \frac{1}{\alpha^2}\left[1 \pm \{1+\alpha^2\}^{1/2}\right]$$
$$= u^2$$

So $u = \dfrac{1}{\alpha}\left[1 + (1+\alpha^2)^{1/2}\right]^{1/2}$ & there is always a maximum

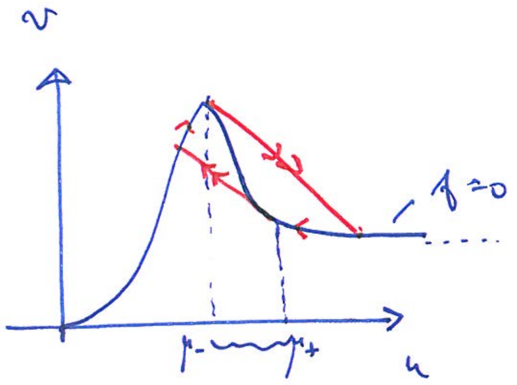
So $V(u)$



Small ~~[illegible]~~ $\max \dfrac{F}{G} < 1$

10 V/N

(d)



$\dot{u} + \gamma \dot{v} = \mu - u$

$\varepsilon \dot{v} = f$

v rapidly → f = 0 along u + γv = constant

& give oscillations as shown if $\mu_- < \mu < \mu_+$

V_{max} needs to be large enough so that lines $\frac{dv}{du} = -\frac{1}{\gamma}$ can

traverse f = 0 as shown.

3 V/N

3, (a)

$$\sigma = -\beta - \gamma e^{-\sigma}$$

Consider the function $(\sigma+\beta)e^{\sigma} = f(\sigma)$

This has an essential singularity at ∞

& $f = 0$ only at $\sigma = -\beta$

Therefore in any neighbourhood of ∞ $f = -\gamma$ has a root

$\Rightarrow \exists\, \infty$ roots of $\sigma = -\beta - \gamma e^{-\sigma}$ as $\sigma \to \infty$

As $\sigma \to \infty$, we must have $e^{-\sigma} \to \infty \Rightarrow \mathrm{Re}\,\sigma \to -\infty$

Actually $\sigma(\gamma)$ is analytic,

$$\sigma' = -e^{-\sigma} + \gamma e^{-\sigma}\sigma' \Rightarrow \sigma' = \frac{-e^{-\sigma}}{1-\gamma e^{-\sigma}} = \frac{1}{\gamma - e^{\sigma}}$$

Evidently there are singularities (branch points) when $\gamma e^{-\sigma} = 1$,

but at such values $\sigma = -\beta - 1$ is real (& $-$ve), so the complex roots

vary analytically with γ.

If γ is small, then $\sigma = -\beta + O(\gamma)$, $\mathrm{Re}\,\sigma < 0$, unless

$e^{-\sigma}$ is large — which requires $\mathrm{Re}\,\sigma < 0$;

so $\mathrm{Re}\,\sigma < 0$ $\forall$ small γ.

From above, if $\sigma = i\omega$, $\mathrm{Re}\,\frac{d\sigma}{d\gamma} = \frac{d\,\mathrm{Re}\,\sigma}{d\gamma} = \mathrm{Re}\,\frac{1}{\gamma - e^{\sigma}} = \mathrm{Re}\left[\frac{1}{\gamma + \frac{\gamma}{\sigma+\beta}}\right]$

$$= \mathrm{Re}\left[\frac{i\omega+\beta}{i\gamma\omega + \gamma(1+\beta)}\right] = \mathrm{Re}\left[\frac{(i\omega+\beta)\{-i\gamma\omega + \gamma(1+\beta)\}}{\gamma^2(1+\beta)^2 + \gamma^2\omega^2}\right] = \frac{\beta\gamma(1+\beta) + \gamma\omega^2}{\gamma^2(1+\beta)^2 + \gamma^2\omega^2} > 0$$

Hence $\mathrm{Re}\,\sigma > 0$ for $\gamma > \gamma_c$

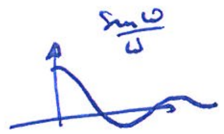
where γ_c is smallest root of $i\omega = -\beta - \gamma e^{-i\omega}$

i.e $\omega = \gamma \sin \omega$, $\quad 0 = -\beta - \gamma \cos \omega$

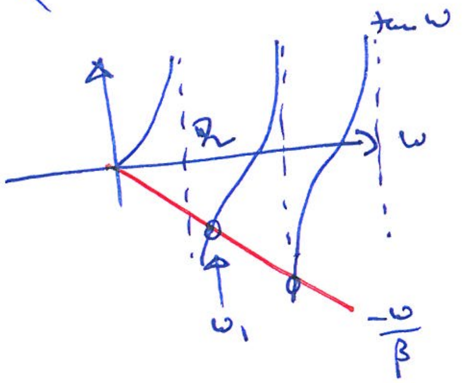
$\Rightarrow -\beta = \gamma \cos \omega$

thus $-\dfrac{\omega}{\beta} = \tan \omega$ determines ω given β

& then $\gamma = \dfrac{\omega}{\sin \omega}$



so γ increases as ω increases (can elaborate ..)



gives a sequence $\omega_1 < \omega_2 < \ldots$ & corresponding $\gamma_1 < \gamma_2 < \ldots$

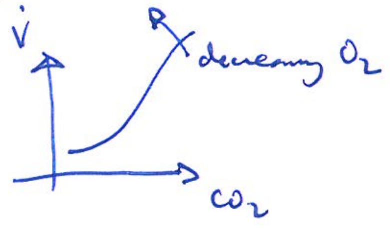
As $\beta \to 0$, $\omega_1 \to \pi/2 \Rightarrow \gamma_1 = \gamma_c = \pi/2$

10 B/V

(b) minute ventilation : volume of air inspired in a minute, $\dot{V}$

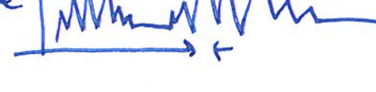
central chemoreceptor responds (via H^+) to CO_2

peripheral chemoreceptor responds to O_2, modulated by CO_2



4 B

Cheyne-Stokes : periodic with apnea



etc

(5)

$$K\dot{p} = M - pG\overbrace{\left[p_\tau - p_0\right]_+}^{\dot{V}}$$

M metabolic CO_2 production rate

K compartment (tissue) volume

G gain of controller

$p_\tau = p_{CO_2}(t-\tau)$

Steady $\quad M = pG(p-p_0) \qquad$ (as $p > p_0$)

$$\frac{M}{Gp_0^2} = \frac{p}{p_0}\left(\frac{p}{p_0} - 1\right) \quad \text{is small,}$$

so $\quad \dfrac{p}{p_0} = 1 + \dfrac{M}{Gp_0^2}\cdot\dfrac{p_0}{p}$

$\dfrac{p}{p_0} \simeq 1$ so $\dfrac{p}{p_0} \simeq 1 + \dfrac{M}{Gp_0^2}$, $\quad p \simeq p_0 + \dfrac{M}{Gp_0} = p^*$

6 $\quad$ B/V

(d) $\quad p = p^* + \rho$, linearise ..

$$K\dot{\rho} = - p^* G \rho_\tau - \rho G(p^* - p_0)$$

$$\rho = e^{\sigma t/\tau} \Rightarrow \frac{K\sigma}{\tau} = -p^* G e^{-\sigma} - G(p^* - p_0)$$

$$\text{or } \sigma = -\frac{p^* G\tau}{K} e^{-\sigma} - \frac{G\tau}{K}(p^* - p_0)$$

$$= -\beta - \gamma e^{-\sigma} \qquad \gamma = \frac{p^* G\tau}{K}, \quad \beta = \frac{G\tau}{K}(p^* - p_0)$$

If $M \ll G p_0^2$, then

$$\gamma \simeq \frac{p_0 G \tau}{K}, \quad \beta \approx \frac{G\tau}{K} \frac{M}{G p_0} = \frac{M\tau}{K p_0}$$

Note that
$$\frac{\beta}{\gamma} = \frac{M\tau}{K p_0} \cdot \frac{K}{p_0 G \tau} = \frac{M}{G p_0^2} \ll 1$$

So $\beta \ll \gamma$.

Assuming $\beta \ll 1$ then instability occurs if $\gamma \gtrsim \pi/2$

Since $\gamma = O(1)$ at this value, then indeed $\beta \ll 1$.

This criterion is $\frac{p_0 G \tau}{K} \gtrsim \frac{\pi}{2}$ i.e. $\tau \gtrsim \frac{\pi K}{2 p_0 G}$.

5 v/N

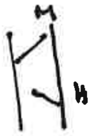
Mathematical Physiology FHS 2020 Answers (1

B = bookwork
V = variant / homework
N = new

1 (a) $$C \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} O$$

n open gates so $\dot{n} = \alpha(1-n) - \beta n$
$= \alpha - (\alpha+\beta)n$

4 B $n \to n_\infty = \dfrac{\alpha}{\alpha+\beta}$ as $t \to \infty$

(b) 

S_{ij} : i open M gates (fraction)
j open H gates

reaction scheme

$$\begin{tikzcd}
S_{00} \arrow[r, shift left, "\gamma"] \arrow[d, shift right, "\alpha"'] \arrow[r, bend left=60, "R_1"] \arrow[d, bend right=60, "R_2"'] & S_{01} \arrow[l, shift left, "\delta"] \arrow[d, shift right, "\alpha"'] \arrow[d, bend left=60, "R_4"] \\
S_{10} \arrow[r, shift left, "\gamma"] \arrow[u, shift right, "\beta"'] \arrow[r, bend right=60, "R_3"'] & S_{11} \arrow[l, shift left, "\delta"] \arrow[u, shift right, "\beta"']
\end{tikzcd}$$

overall reaction rates

$$R_1 = \gamma S_{00} - \delta S_{01}$$
$$R_2 = \alpha S_{00} - \beta S_{10}$$
$$R_3 = \gamma S_{10} - \delta S_{11}$$
$$R_4 = \alpha S_{01} - \beta S_{11}$$

rate equations
$$\dot{S}_{00} = -R_1 - R_2$$
$$\dot{S}_{01} = R_1 - R_4$$
$$\dot{S}_{10} = R_2 - R_3$$
$$\dot{S}_{11} = R_3 + R_4$$

Adding, we see $\sum S_{ij}$ = constant $= 1$

12

$h = S_{01} + S_{11}$

$m = S_{10} + S_{11}$

$\Rightarrow 1-h = S_{10} + S_{00}$

$1-m = S_{01} + S_{00}$

$\Rightarrow \dot{h} = \dot{S}_{01} + \dot{S}_{11} = R_1 - R_4 + R_3 + R_4 = R_1 + R_3$

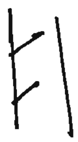
$= \gamma(S_{00} + S_{10}) - \delta(S_{01} + S_{11})$

$= \gamma(1-h) - \delta h$

& $\dot{m} = \dot{S}_{10} + \dot{S}_{11} = R_2 + R_4 = \alpha(S_{00} + S_{01}) - \beta(S_{10} + S_{11})$

$= \alpha(1-m) - \beta m$

8 V

(5) 

$$S_0 \underset{\beta}{\overset{2\alpha}{\rightleftharpoons}} S_1 \underset{2\beta}{\overset{\alpha}{\rightleftharpoons}} S_2$$

R_1 R_2

2 open

$R_1 = 2\alpha S_0 - \beta S_1$

$R_2 = \alpha S_1 - 2\beta S_2$

$\dot{S}_0 = -R_1$

$\dot{S}_1 = R_1 - R_2$

$\dot{S}_2 = R_2$

$S = S_0 + S_1 x + S_2 x^2$

$\Rightarrow S_t = -R_1 + (R_1 - R_2)x + R_2 x^2 = (x-1)[R_1 + R_2 x]$

& $S_x = S_1 + 2S_2 x$

$\cancel{\text{so } S_t = -2\alpha S_0 + \beta S_1 + 2\alpha S_0 x - \beta S_1 x - \alpha S_1 x + 2\beta S_2 x + \alpha S_1 x^2 - 2\beta S_2 x^2}$

$\cancel{= 2\alpha S_0(x-1) - \beta S_1(x-1) + \alpha S_1 x(x-1) - 2\beta S_2 x(x-1)}$

$\cancel{= (x-1)[2\alpha S_0 - \beta S_1 + \alpha S_1 x - 2\beta S_2 x]}$

$\cancel{= (x-1)[2\alpha S_0 + 2\alpha S_1 x + 2\alpha S_2 x^2 - \alpha S_1 x - \beta S_1 + 2\beta S_2 x - 2\alpha S_2 x^2]}$

$\cancel{= (x-1)[2\alpha S - \alpha x(S_1 + 2S_2 x)}$

So $S_t = (x-1)\left[(2\alpha S_0 - \beta S_1) + (\alpha S_1 - 2\beta S_2)x\right]$

$$= (x-1)\Big[\, 2\alpha S_0 + 2\alpha S_1 x + 2\alpha S_2 x^2 - 2\alpha S_1 x - 2\alpha S_2 x^2 - \beta S_1 + \alpha S_1 x - 2\beta S_2 x \,\Big]$$

$$= (x-1)\left[2\alpha S \;\cancel{-\beta S_1} + S_1[-\beta - \alpha x] - 2S_2 x(\beta + \alpha x)\right]$$

$$= (x-1)\left[2\alpha S - (\beta + \alpha x)(S_1 + 2S_2 x)\right]$$

$$= (x-1)\left[2\alpha S - (\beta + \alpha x) S_x\right]$$

Try $S = [1 - g(t) + g(t)x]^2$

$$\Rightarrow S_t = 2[1 - g + gx](x-1)\dot{g}$$

$$S_x = 2[1 - g + gx]\,g$$

So we require

that $2(1-g+gx)(x-1)\dot{g} = (x-1)\left[2\alpha\{1-g+gx\}^2 - (\beta+\alpha x).2\{1-g+gx\}g\right]$

viz $\dot{g} = \alpha(1-g+gx) - (\beta + \alpha x)g$

$$= \alpha(1-g) - \beta g$$

For this solution $S = (1-g)^2 + 2g(1-g)x + g^2x^2$

$$\Rightarrow S_2 = g^2$$

8 B/N

(4

(d)

If $S = [1-g+gx]^2 + u(x,t)$

$S(1,t) = 1 + u(1,t) = S_0 + S_1 + S_2 = 1 \Rightarrow u(1,t) = 0$

We have

$$S_t + (x-1)(\alpha x+\beta) S_x = 2\alpha(x-1)S$$

$S = (1-g+gx)^2$ is a solution of $\dot{g} = \alpha(1-g) - \beta g$

Eq is linear so

$$u_t + (x-1)(\alpha x+\beta) u_x = 2\alpha(x-1)u$$

Characteristics
$$\dot{x} = (x-1)(\alpha x+\beta)$$
$$\dot{u} = 2\alpha(x-1)u$$

B.c. ~~...~~

$u = u_0(x)$ at $t=0$

i.e. $u = u_0(\sigma)$, $x=\sigma$, $t=0$

$$\frac{dx}{\alpha+\beta}\left[\frac{1}{x-1} - \frac{\alpha}{\alpha x+\beta}\right] = dt$$

$$\ln\left(\frac{x-1}{\alpha x+\beta}\right) = \ln\left(\frac{\sigma-1}{\alpha\sigma+\beta}\right) + (\alpha+\beta)t$$

$$\Rightarrow \frac{x-1}{\alpha x+\beta} = \frac{\sigma-1}{\alpha\sigma+\beta} e^{(\alpha+\beta)t}$$

& then $\frac{du}{dx} = \frac{2\alpha u}{\alpha x+\beta} \Rightarrow \ln u = 2\ln(\alpha x+\beta) + \ldots$

$$\Rightarrow u = u_0(\sigma)\left(\frac{\alpha x+\beta}{\alpha\sigma+\beta}\right)^2$$

Note when $x=1$, $\sigma=1$, $u=0 \Rightarrow$ $u_0(1)=0$ (as just $u(1,t)=0$ at $t=0$)

As $t\to\infty$, $\sigma\to 1 \Rightarrow u\to 0$. □

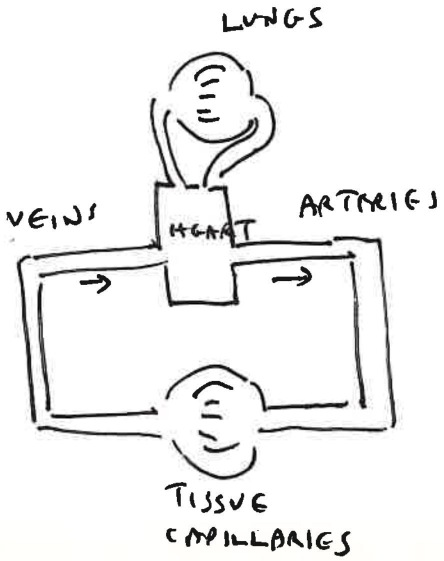
5 N

5

2 (a)

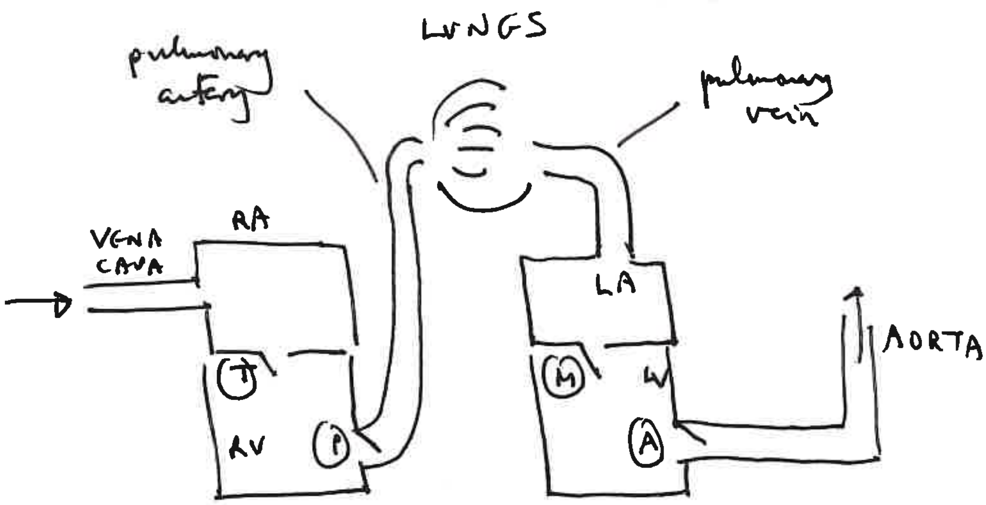
(i) Periodic action potentials occur in the sino-atrial node and the resultant signal is propagated through the myocardium causing contraction of the heart muscle cells

(ii)



Contraction of the heart causes blood to flow from the heart to the lungs where it collects oxygen, back to the heart, where it is expelled to the arteries, then tissues & back to the heart via the veins.

(iii)



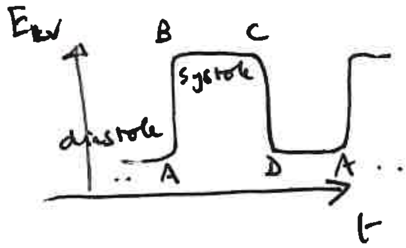
valves: T	tricuspid	RA:	right atrium
P	pulmonary	RV	right ventricle
M	mitral	LA	left atrium
A	aortic	LV	left ventricle

6 B

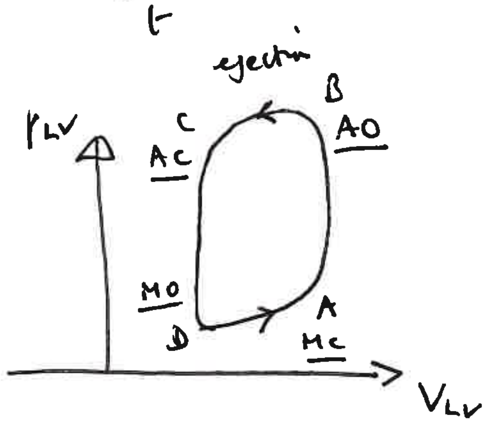
(b) Compliance : volume / pressure (looseness)

Elastance : compliance^{-1} (pressure / volume) (stiffness)

resistance : pressure drop / flow rate



$$p_{LV} = E_{LV}(V_{LV} - V_{LV0})$$



Left ventricular valves

A (aortic) outlet

M (mitral) inlet

AO A opens

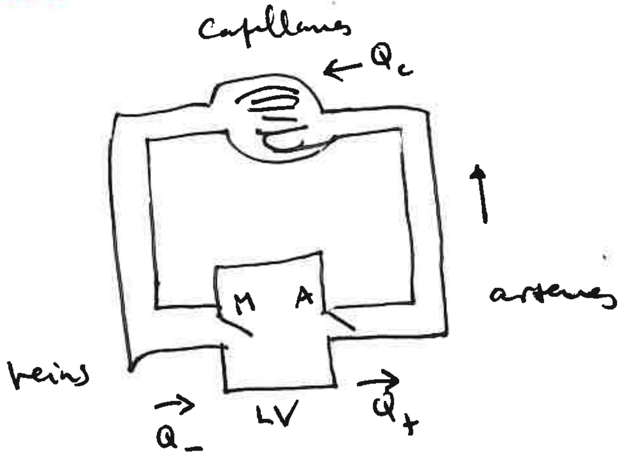
AC A closes

MO M opens

MC M closes

7 B

(c)



V_a arterial volume

V_v venous volume

V_{LV} left ventricular volume

Q_+ flow from LV

Q_- flow to LV

Q_c flow through capillaries

$p_{a,v,LV}$ pressure in arteries, veins, left ventricle

mass conservation ⟹ $\dot{V}_a = Q_+ - Q_c$

$\dot{V}_v = Q_c - Q_-$

$\dot{V}_{LV} = Q_- - Q_+$

& $Q_c = \dfrac{p_a - p_v}{R_c}$ $\quad Q_+ = \dfrac{[p_{LV} - p_a]_+}{R_a}$ $\quad Q_- = \dfrac{[p_v - p_{LV}]_+}{R_v}$ resistances R

compliances C

6 B

$V_a = V_{a0} + C_a p_a$, $V_v = V_{v0} + C_v p_v$: capillary volume is zero.

7

Ejection : aortic valve open
mitral valve closed

$\Rightarrow \quad p_{LV} > p_a , p_v \quad \Rightarrow \quad Q_+ = \frac{p_{LV} - p_a}{R_a} \quad Q_- = 0$

$$\Rightarrow \quad C_a \dot{p}_a = \frac{p_{LV} - p_a}{R_a} - \frac{(p_a - p_v)}{R_c}$$

$$C_v \dot{p}_v = \frac{p_a - p_v}{R_c}$$

$$\frac{1}{E_s} \dot{p}_{LV} = - \frac{(p_{LV} - p_a)}{R_a}$$

$\frac{0.09}{1.8} = 0.05$

or

$$\underbrace{R_a C_a}_{0.095} \dot{p}_a = p_{LV} - p_a - \frac{R_a}{R_c} (p_a - p_v)$$

$$\underbrace{R_c C_v}_{60\,s} \dot{p}_v = p_a - p_v$$

$$\underbrace{\frac{R_a}{E_s}}_{0.02\,s} \dot{p}_{LV} = p_a - p_{LV} \qquad \left(\text{note } E_s = \frac{1}{C_s}\right)$$

Based on the values given above, during systole $(0.3\,s)$

$p_a \simeq p_{LV}$ due to $\frac{R_a}{E_s} \sim 0.02\,s \ll 0.3\,s$

thus $p_a - p_{LV} = R_a C_s \dot{p}_{LV} \simeq R_a C_s \dot{p}_a$

$p_v \simeq$ constant as $60\,s \gg 0.3\,s$

p_a eqn $\Rightarrow \quad R_a (C_a + C_s) \dot{p}_a \simeq - \frac{R_a}{R_c} (p_a - p_v)$

$\Rightarrow \quad \dot{p}_a \simeq - \frac{(p_a - p_v)}{R_c (C_a + C_s)} \quad \Rightarrow \quad p_a - p_v \propto \exp\left[-\frac{t}{\tau}\right],$

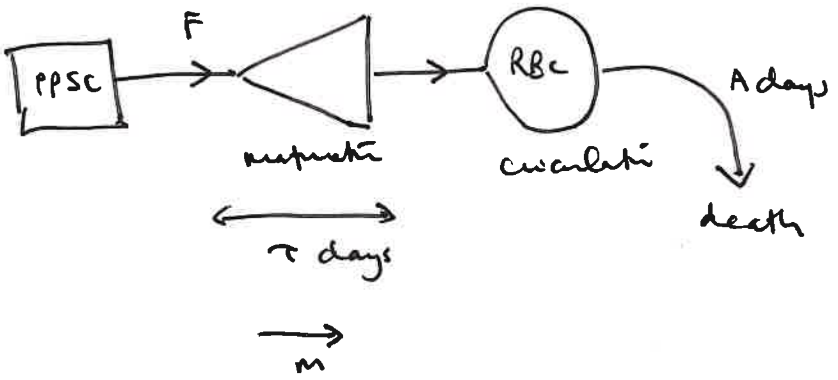
$\tau = R_c (C_a + C_s)$

6 N

Value is $R_c C_a + \frac{R_c C_a}{R_a C_a} . R_a C_s = 1.8 + \frac{1.8}{0.09} 0.02 = 2.2\,s$

3/(a) red blood cells, white blood cells (of many types)

produced by maturation of pluripotential stem cells in the bone marrow & released to the blood circulation from there.



The maturing cell concentration c satisfies the characteristic equation

$$\frac{dc}{dt} = -\delta c \qquad \Rightarrow \quad c_t + c_m = -\delta c \qquad \delta = \text{cell death rate}$$

$$\frac{dm}{dt} = 1$$

Similarly if RBC population r has age a,

$$r_t + r_a = -\gamma r \qquad \gamma = \text{RBC death rate}$$

Evidently $r(t,0) = c(t,\tau)$:

Also $\frac{d}{dt}\int_0^\tau c\,dm = \int_0^\tau c_t\,dm = \underbrace{-\delta\int_0^\tau c\,dm}_{\text{death rate}} \underbrace{-c|_\tau}_{\text{loss to RBC}} + \underbrace{c|_0}_{\text{source from PPSC}}$

So $c|_{m=0} = F(t)$

5 B/V

(f)

$\dot{c} = -\delta c \qquad m = 0$

$\dot{m} = 1 \qquad t = s > 0$

$\qquad\qquad c = F(s)$

$\Rightarrow c = F(s)e^{-\delta(t-s)}, \quad m = t-s$

$\Rightarrow c = F(t-m)e^{-\delta m}$

$\Rightarrow c(t,\tau) = F(t-\tau)e^{-\delta\tau} \qquad$ if $t > \tau$ (so $s > 0$)

$\Rightarrow r(t,0) = F(t-\tau)e^{-\delta\tau}$

So $\dot{r} = -\gamma r \qquad a = 0$

$\dot{a} = 1 \qquad t = \eta > 0$

$\qquad\qquad r = F(\eta - \tau)e^{-\delta\tau}$

$\Rightarrow a = t - \eta$

$r = F(\eta-\tau)e^{-\delta\tau}e^{-\gamma(t-\eta)}$

$\Rightarrow r = F(t-a-\tau)e^{-\delta\tau-\gamma a}$

$= F_{a+\tau}e^{-\delta\tau-\gamma a} \qquad t > \tau + a$ (so $\eta > 0$)

5 B/V

(c) $R = \int_0^A r\, da$

If $t > \tau + A$ then $R = \int_0^A F(t-a-\tau)e^{-\delta\tau-\gamma a}\, da$

we have $\dot{R} = \int_0^A r_t\, da = \int_0^A (-\gamma r - r_a)\, da = -\gamma R + r|_{a=0} - r|_{a=A}$

$= -\gamma R + F_\tau e^{-\delta\tau} - F_{A+\tau}e^{-\delta\tau-\gamma A}$ from solutions above

5 V

(d)

$$F = \frac{F_0 R_0^n}{R^n + R_0^n}$$

Scale $t \sim \tau$, $R \sim R_0$ define $h(R) = \frac{1}{1+R^n}$

so non-d $F = F_0 h(R)$

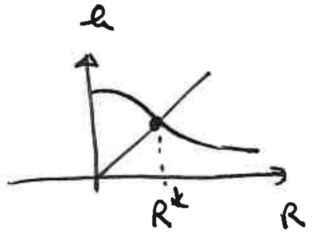
$$\underset{\text{non-d}}{\Rightarrow} \quad \frac{R_0}{\tau}\dot{R} = -\gamma R_0 R + F_0 h(R_1) e^{-\delta\tau} - F_0 h(R_{1+\frac{A}{\tau}}) e^{-\delta\tau - \gamma A}$$

$$\Rightarrow \quad \dot{R} = -\gamma\tau R + \frac{\tau F_0 e^{-\delta\tau}}{R_0} h(R_1) - \frac{\tau F_0}{R_0} h(R_{1+\Lambda}) e^{-\delta\tau - \gamma A}$$

or $\dot{R} = \beta[h(R_1) - \nu h(R_{\Lambda+1})] - \mu R$

with $\Lambda = \frac{A}{\tau}$, $\mu = \gamma\tau$, $\beta = \frac{\tau F_0 e^{-\delta\tau}}{R_0}$, $\nu = e^{-\gamma A}$

Steady state, $\mu R = \beta(1-\nu)h(R)$



Unique if $\nu < 1$

5 V/N

(e) If $\nu \ll 1$, $\dot{R} \simeq \beta h(R_1) - \mu R$

linearise $R = R^* + r$, $\dot{r} = \beta h'(R^*) r_1 - \mu r$

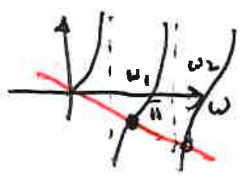
$r = e^{\sigma t}$ $\Rightarrow$ $\sigma = \beta h'(R^*) e^{-\sigma} - \mu$ $= -B - Ge^{-\sigma}$

$B = \mu$, $G = \beta|h'(R^*)|$

Instability: G small: $\mathrm{Re}\,\sigma < 0$

Instability at $i\omega = -B - Ge^{-i\omega}$, $\omega = G\sin\omega$, $B = -G\cos\omega$ $\Rightarrow$ $\tan\omega = -\frac{\omega}{B}$

5 V/N



Unstable for $G > \frac{\omega_2}{\sin\omega_2}$ $\left(\frac{\omega_1}{\sin\omega_1} < 0\right)$