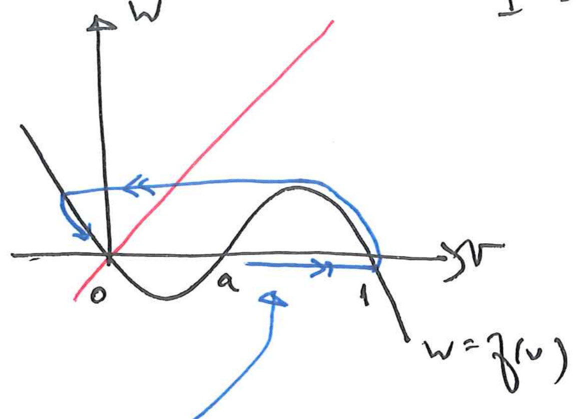
1 (a)

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

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

$$f = v(a-v)(v-1)$$

$I^* = 0$



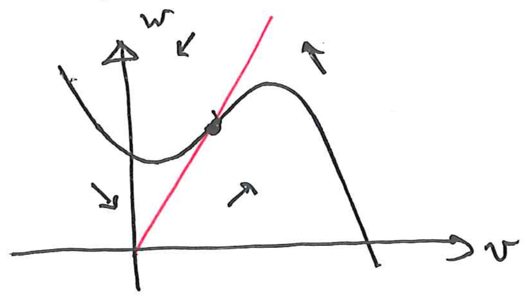
Perturb v ⇒ excitable

note $f = v(-v^2 + (a+1)v - a)$
$= -[v^3 - (a+1)v^2 + av]$

so $f' = -[3v^2 - 2(a+1)v + a]$
$= -3\left[\left\{v - \frac{a+1}{3}\right\}^2 - \frac{(a+1)^2}{9} + \frac{a}{3}\right]$
$= -3\left\{v - \frac{a+1}{3}\right\}^2 + \frac{1}{3}(a^2 - a + 1)$

So $\max f' = \frac{1}{3}(a^2 - a + 1) < \gamma$
⇒ only one root □

For $I^* > 0$, assume



Linearise $v = v^* + V$ $w = w^* + W$

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

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

$$\begin{pmatrix} \dot{V} \\ \dot{W} \end{pmatrix} = M \begin{pmatrix} V \\ W \end{pmatrix}, \quad M = \begin{pmatrix} f'/\varepsilon & -\frac{1}{\varepsilon} \\ \gamma & -1 \end{pmatrix}$$

obviously not a saddle.

⇒ unstable iff $\operatorname{tr} M > 0$, $\frac{f'}{\varepsilon} - 1 > 0$, $f'(v^*) > \varepsilon$

Approximately, instability if $v_- < v^* < v_+$

where $v_\pm$ roots of $f' = 0$

i.e. $v_\pm = \frac{a+1}{3} \pm \frac{1}{3}(a^2 - a + 1)^{1/2}$ $\left[a^2 - a + 1 = \frac{a^3+1}{a+1} > 0 \right]$

& thus instability occurs for

$$I_- < I^* < I_+$$

where $I_\pm = \gamma v_\pm - f(v_\pm)$

[& note $f(v_\pm) = -v_\pm^3 + (a+1)v_\pm^2 - a v_\pm$

while $f'(v_\pm) = 0 = -3v_\pm^2 + 2(a+1)v_\pm - a$

thus $v_\pm^2 = \frac{2}{3}(a+1)v_\pm - \frac{a}{3}$

so $f(v_\pm) = v_\pm\left[-v_\pm^2 + (a+1)v_\pm - a\right]$

$= v_\pm\left[-\frac{2}{3}(a+1)v_\pm + \frac{a}{3} + (a+1)v_\pm - a\right]$

$= \frac{1}{3}v_\pm\left[(a+1)v_\pm - 2a\right]$

$= \frac{1}{3}\left[(a+1)\left\{\frac{2}{3}(a+1)v_\pm - \frac{a}{3}\right\} - 2av_\pm\right]$

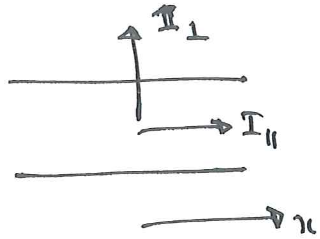
$= \frac{1}{9}\left[(2a^2 + 4a + 2 - 6a)v_\pm - a(a+1)\right]$

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

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

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

3/



We have $-\frac{\partial V}{\partial x}\delta x = I_\parallel R\,\delta x$ where R is the resistance per unit length

and $\underset{\substack{\uparrow \\ \text{charge}}}{\frac{\partial}{\partial t} CV\delta x} = -I_\perp\,\delta x - \frac{\partial I_\parallel}{\partial x}\delta x$

where $I_\parallel$ is axial current, $I_\perp$ is ionic current per unit length & V is electric potential

$$\Rightarrow \quad I_\parallel = -\frac{1}{R}V_x\,, \quad CV_t = -I_\perp - \frac{\partial I_\parallel}{\partial x} = -I_\perp + \frac{1}{R}V_{xx}$$

Resting potential V_{eq} is where $I_\perp(V) = 0$.

Scale: $V - V_{eq} \sim v_{Na}$, $t \sim \tau_n$, $x \sim l$, $I_\perp = p\, g_{Na} v_{Na}\, g$

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

& $$\frac{C v_{Na}}{\tau_n} v_t = -p\, g_{Na} v_{Na}\, g + \frac{1}{R}\frac{v_{Na}}{l^2} v_{xx}$$

$$\Rightarrow \quad \varepsilon v_t = -g + \varepsilon^2 v_{xx}$$

$$\varepsilon = \frac{C v_{Na}}{\tau_n}\cdot\frac{1}{p\, g_{Na} v_{Na}} = \frac{c_m}{g_{Na}\tau_n}\,, \quad \varepsilon^2 = \frac{1}{R}\frac{v_{Na}}{l^2}\frac{1}{p\, g_{Na} v_{Na}} = \frac{1}{l^2 g_{Na}}\frac{A}{R_c\, p} = \frac{d}{4 l^2 g_{Na} R_c}$$

So choose $l = \frac{1}{2\varepsilon}\left(\frac{d}{g_{Na}R_c}\right)^{1/2} = \frac{g_{Na}\tau_n}{2C_m}\left(\frac{d}{g_{Na}R_c}\right)^{1/2}$

$$= \frac{\tau_n}{2C_m}\left(\frac{g_{Na}d}{R_c}\right)^{1/2}$$

Using values

& $\varepsilon = \frac{C_m}{g_{Na}\tau_n} \sim \frac{10^{-6}}{120\ 10^{-3}\ 5\ 10^{-3}}\ \frac{F\ \ cm^2}{\underbrace{cm^2\ S\ s}_{F s^{-1} = S}}$

$$\sim \frac{1}{600} = 1.6\times10^{-3}$$

$$l \sim \frac{5\ 10^{-3}}{2\ 10^{-6}}\ \frac{s\ cm^2}{F}\left(\frac{120\ 10^{-3}\ 5\ \ 10^{-2}}{35}\ \frac{S\ \ cm}{cm^2\ \Omega\ cm}\right)^{1/2}$$

note $1S = 1\Omega^{-1} = 1F s^{-1}$

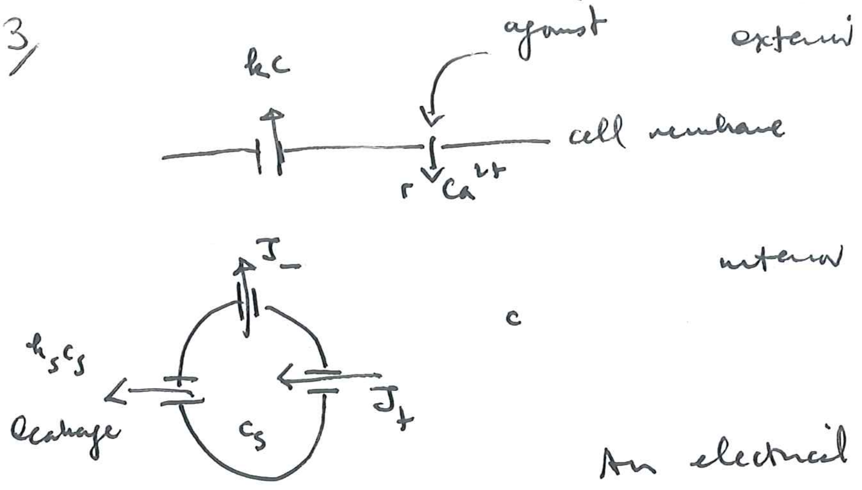
so $l = 2.5\times10^{3}\ \frac{s\ cm^2}{F}\left(\frac{60}{35}\ 10^{-4}\right)^{1/2}\frac{S}{cm}$

$$= 25\times\left(\frac{12}{7}\right)^{1/2} cm \simeq 32.7\, cm$$

— much longer than the axon itself!

(8)

3/



An electrical (or other) stimulus opens ~~gat~~ channels in the cell membrane, allowing Ca^{2+} in. This is taken up by the Sarcoplasmic reticulum (J_+) which induces release (J_-).

c is the intra-cellular Ca^{2+}

c_s is the store in the S.R.

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

$$\dot{c}_s = J_+ - J_- - k_s c_s$$

$$J_+ - J_- - k_s c_s = \frac{V_1 c^n}{K_1^n + c^n} - \left(\frac{V_2 c_s^m}{K_2^m + c_s^m}\right)\left(\frac{c^p}{K_3^p + c^p}\right) - k_s c_s$$

To scale, balance terms as shown:

$$t \sim \frac{1}{k}, \quad c = K_1 u, \quad c_s = K_2 v, \quad J_+ - J_- - k_s c_s = V_2 f(u,v)$$

This leads to

$$K_1 k \dot{u} = r - k K_1 u - V_2 f$$

$$k K_2 \dot{v} = V_2 f$$

$$V_2 f = V_1 \frac{u^n}{1+u^n} - V_2 \frac{v^m}{(1+v^m)} \frac{u^p}{\left[\left(\frac{K_3}{K_1}\right)^p + u^p\right]} - k_s K_2 v$$

so $\quad \dot{u} = \mu - u - \gamma \dot{v}$

$$\varepsilon \dot{v} = f$$

$$f = \beta \frac{u^n}{1+u^n} - \left(\frac{v^m}{1+v^m}\right)\left(\frac{u^p}{\alpha^p + u^p}\right) - \delta v$$

where $\quad \mu = \dfrac{r}{K_1 k} \quad \dfrac{\gamma}{\varepsilon} = \dfrac{V_2}{K_1 k}, \quad \varepsilon = \dfrac{k K_2}{V_2} \quad \therefore \gamma = \dfrac{K_2}{K_1}$

$$\beta = \frac{V_1}{V_2}, \quad \alpha = \frac{K_3}{K_1}, \quad \delta = \frac{k_s K_2}{V_2}$$

use values: $\alpha \sim 0.9$

$\beta \sim 0.13$

$\gamma \sim 2$

$\delta \sim 0.004$

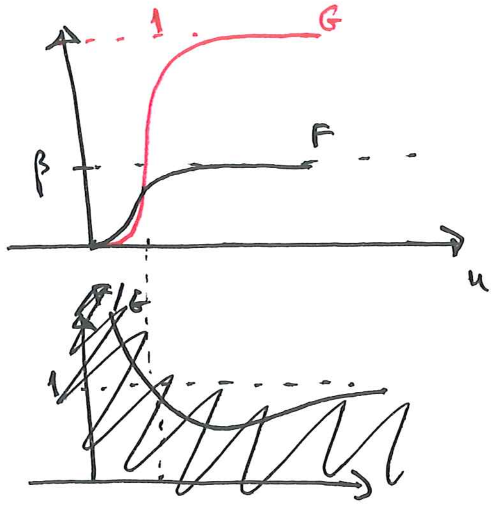
$\varepsilon \sim 0.04$

v nullcline

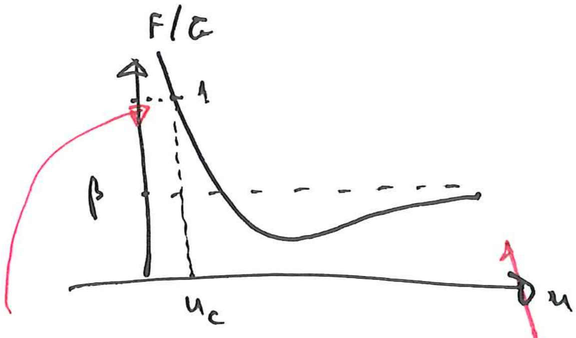
$$\beta \frac{u^n}{1+u^n} - \left(\frac{v^m}{1+v^m}\right)\left(\frac{u^p}{\alpha^p+u^p}\right) - \delta v = 0$$

$\underline{\cdot}$ $\delta \ll 1$ $\qquad \frac{v^m}{1+v^m} \simeq \frac{\beta \frac{u^n}{1+u^n}}{\frac{u^p}{\alpha^p+u^p}}$ $\qquad m=2$, $n=2$, $p=4$

write $F = \frac{\beta u^n}{1+u^n}$ $\qquad G = \frac{u^p}{\alpha^p+u^p}$



due to $n > p$



Note as $u \to 0$ $\quad \frac{F}{G} \sim \frac{\beta}{u^{p-n}} = \frac{\beta}{u^2}$

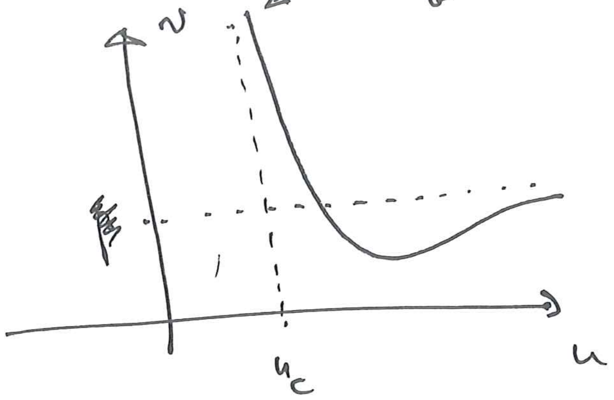
$u \to \infty \quad \frac{F}{G} \sim \frac{\beta\left(1+\frac{1}{u^n}\right)^{-1}}{\left(1+\frac{\alpha^p}{u^p}\right)^{-1}} \sim \beta\left(1-\frac{1}{u^n}\cdots+\frac{\alpha^p}{u^p}\cdots\right)$

$\sim \beta\left(1-\frac{1}{u^n}\right)$ is <u>increasing</u>

$\frac{v^m}{1+v^m} = \frac{F}{G}$, so $v = g(u)$ has same shape

but $v \to \infty$ as $\frac{F}{G} \to 1$ ie $u \to u_c$

$\Rightarrow$



ii $\quad v \sim \frac{1}{\delta}$ The approximation breaks down when $\delta v \sim 1$

& we rescale $v = \frac{V}{\delta}$, thus

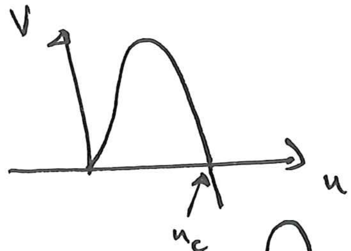
$$\beta\frac{u^n}{1+u^n} - \left(1+\frac{\delta^n}{V^n}\right)^{-1}\left(\frac{u^p}{\alpha^p+u^p}\right) - V = 0$$

and approximately

$$V = \beta\frac{u^n}{1+u^n} - \frac{u^p}{\alpha^p+u^p}$$

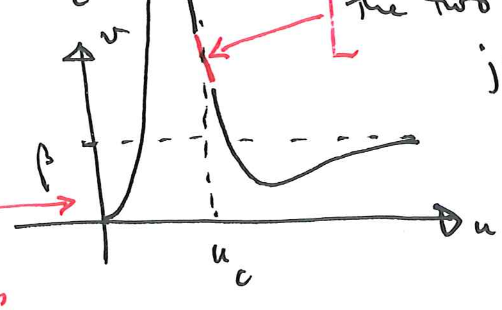
$$= F(u) - G(u)$$

& we see from F & G above



Suggest you do this – the rest I'll have done in lecture

Putting these together

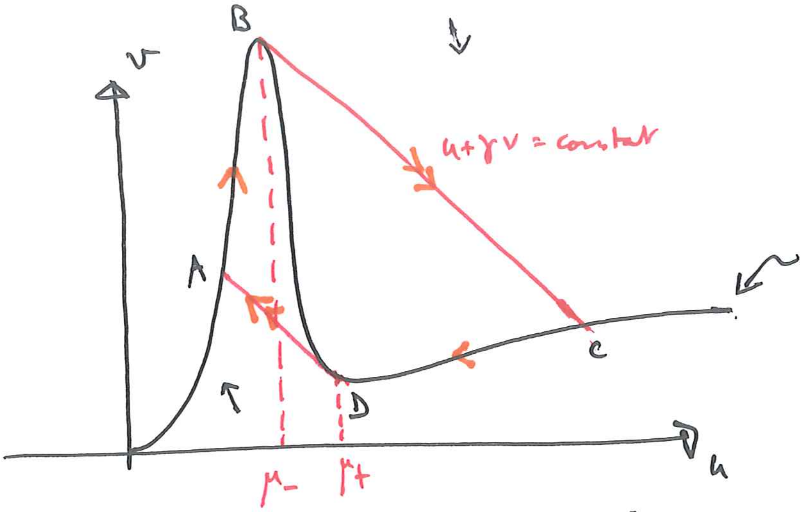


approx breaks down when $V \simeq 0$ but still ok more or less

the two approximations join via matching region where

$$\begin{cases} u = u_c + \nu U \\ V = \nu W \\ \nu = \delta^{\frac{m}{m+1}} \end{cases},$$

& we find $\underbrace{[G'(u_c) - F'(u_c)]}_{>0}U = \frac{G(u_c)}{W^m} - W \quad \ldots]$



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

$\varepsilon\dot{v} = f$. Large v, $f<0 \Rightarrow \dot{v}<0, \dot{u}>0$

So trajectories $\to f=0$ rapidly & along $u+\gamma v =$ constant

will be done in lecture...

Oscillations occur for $\mu_- < \mu < \mu_+$, as shown

do this

~~After~~ Amplitude evidently constant,

The period is approximately $P = \int_A^B dt + \int_C^D dt$

$$\Rightarrow P = \int_A^B + \int_C^D \frac{d(u+\gamma v)}{\dot{u}+\gamma\dot{v}} = \int_A^B + \int_C^D \frac{(1+\gamma g'(u))\,du}{\mu - u}$$

$$\simeq \int_{u_A}^{u_B} \frac{1+\gamma g'(u)}{\mu - u}\,du + \int_{u_D}^{u_C} \frac{1+\gamma g'(u)}{u-\mu}\,du$$

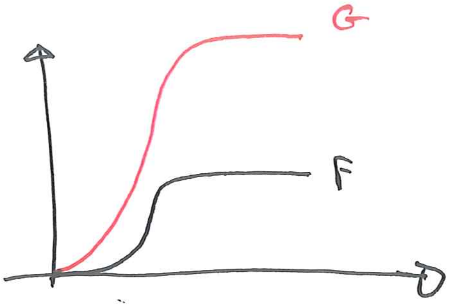
$$\simeq \int_{u_A}^{u_B} \frac{1+\gamma g'(u)}{\mu - u}\,du \qquad \text{since } g \sim \frac{1}{\delta} \text{ on } AB,\ g \sim 1 \text{ on } CD$$

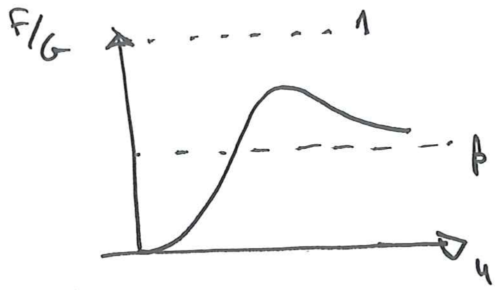
In fact

$$P \simeq \frac{\gamma}{\delta}\int_{u_A}^{u_B} \frac{F'(u) - G'(u)}{\mu - u}\,du \qquad \text{decreases with } \mu$$

If $n > p$ $F = \frac{\beta u^n}{1+u^n}$ $G = \frac{u^p}{\alpha^p + u^p}$

probably





$u \to 0$ $\frac{F}{G} \sim \beta u^{n-p}$

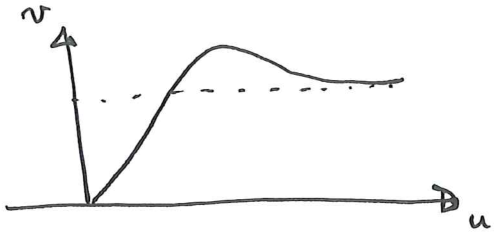
$u \to \infty$ $\frac{F}{G} \sim \frac{\beta\left(1+\frac{1}{u^n}\right)^{-1}}{\left(1+\frac{\alpha^p}{u^p}\right)^{-1}}$

$\sim \beta\left(1 - \frac{1}{u^n} + \frac{\alpha^p}{u^p}\right)$

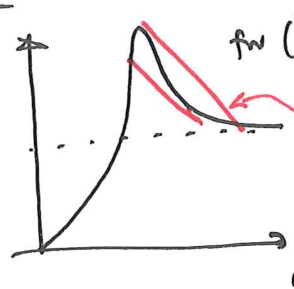
$\sim \beta\left(1 + \frac{\alpha^p}{u^p} \dots\right)$

& if β is low enough that $F/G < 1$

then



or



for $\left(\frac{F}{G}\right)_{max}$ nearer to 1

$u + \gamma v$ const

$-\frac{dv}{du} = \frac{1}{\gamma}$

$\Downarrow$

no oscillations unless $\frac{1}{\gamma}$ small i.e γ large

$\Downarrow$

oscillations

Mathematical Physiology Problem sheet 2

answers

4/

$$u_t = \mu - u - \gamma\frac{f}{\varepsilon}$$

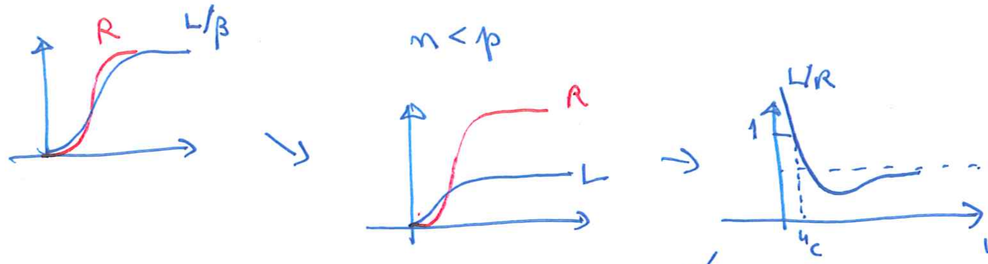
$$v_t = \frac{f}{\varepsilon}$$

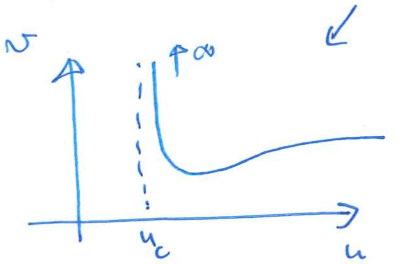
$$f = \beta\left(\frac{u^n}{1+u^n}\right) - \left(\frac{v^m}{1+v^m}\right)\left(\frac{u^p}{\alpha^p+u^p}\right) - \delta v$$

not necessary really

For $v \sim 1$, $\delta \ll 1$ $\qquad \frac{v^m}{1+v^m} \simeq \frac{L(u)}{R(u)}$ $\qquad L = \frac{\beta u^n}{1+u^n}$, $R = \frac{u^p}{\alpha^p+u^p}$

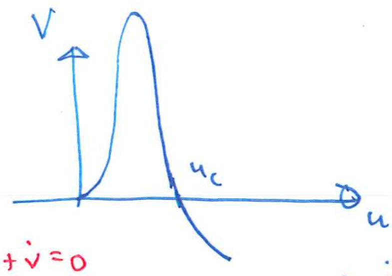
$n < p$



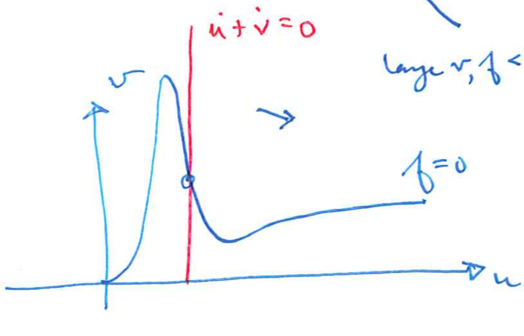


Note $L = R$ at $u = u_c$

For $v = \frac{V}{\delta}$, $V \simeq L - R$



Composite



large v, $f<0 \Rightarrow \dot v < 0$, $\dot u + \gamma \dot v > 0$

Since $f=0$ defines $v = g(u)$ uniquely steady state is

$u = \mu$, $v = g(\mu)$

Linear Stability

$u = \mu + U$

$v = g(\mu) + V$

$$\begin{pmatrix} \dot{U} \\ \dot{V} \end{pmatrix} = \begin{pmatrix} -1 - \frac{\gamma f_u}{\varepsilon} & -\frac{\gamma f_v}{\varepsilon} \\ \frac{f_u}{\varepsilon} & \frac{f_v}{\varepsilon} \end{pmatrix}$$

determinant $D = -\frac{f_v}{\varepsilon}$, $f_v < 0$ so $D > 0$.

unstable iff $T > 0$ i.e

$$-1 - \gamma \frac{f_u}{\varepsilon} + \frac{f_v}{\varepsilon} > 0$$

$$\text{i.e } \underline{\varepsilon - f_v < -\gamma f_u}$$

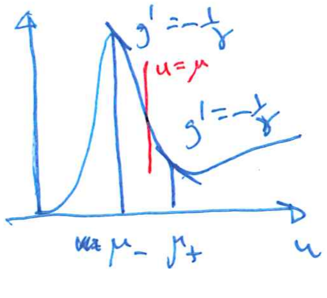
approximately if

$$f_v > \gamma f_u$$

or $(f_v < 0)$ $\frac{1}{\gamma} < \frac{f_u}{f_v}$

or $-\frac{1}{\gamma} > -\frac{f_u}{f_v}$. now $g' = -\frac{f_u}{f_v}$

i.e $\underline{g' < -\frac{1}{\gamma}}$



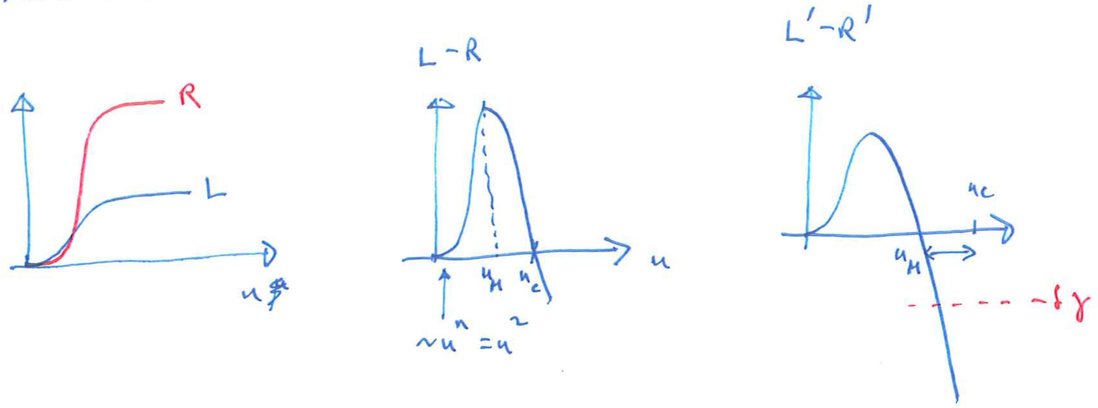
instability if $\mu_- < \mu < \mu_+$.

In terms of δ, near μ_+, little effect

For $v \sim \frac{1}{\delta}$, $v \simeq \frac{1}{\delta}\left[L(u) - R(u)\right]$

So $g'(\mu) \simeq \frac{1}{\delta}\left[L'(\mu) - R'(\mu)\right]$

thus unstable $(\varepsilon \to 0)$ if $L'(\mu) - R'(\mu) < -\delta\gamma$



Note $u_M \simeq \mu_-$

Effect of increasing δ is to increase μ_-, little effect on μ_+ □.

5/ $u_t = \mu - u - \dfrac{\gamma f}{\varepsilon} + \varepsilon u_{xx}$

$\varepsilon v_t = f$

u is cytosolic Ca^{2+} & can diffuse in the cytoplasm.

v is in the calcium store (the sarcoplasmic reticulum)

so does not diffuse.

The length scale is εu_{xx} because periodic wave trains exist

$u = u(\xi)$, $v = v(\xi)$, $\xi = x + ct$

& then $+cu' = \mu - u - \dfrac{\gamma f}{\varepsilon} + \varepsilon u''$

$\varepsilon c v' = f$

So we get slow phases where $f \simeq 0$ & $cu' = \mu - u$

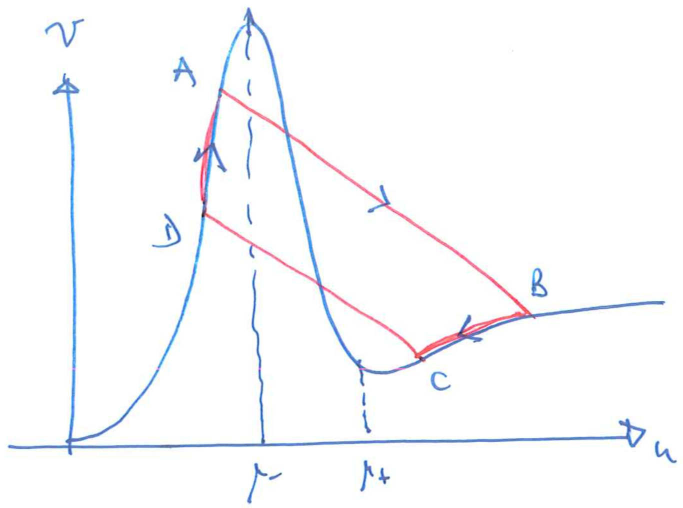
and fast phases where $\xi = \varepsilon X$

& so $\dfrac{c}{\varepsilon} u_X = \mu - u - \dfrac{\gamma f}{\varepsilon} + \dfrac{1}{\varepsilon} u_{XX}$

$c v_X = f$

$\begin{cases} c u_X = -\gamma f + u_{XX} \\ c v_X = f \end{cases}$ gives correct scale for transition

(& $c(u+\gamma v)_X = u_{XX} \Rightarrow c(u+\gamma v) = u_X$ etc..



In the slow phases AD, BC $f \simeq 0$

& $c(u+\gamma v)' = \mu - u$

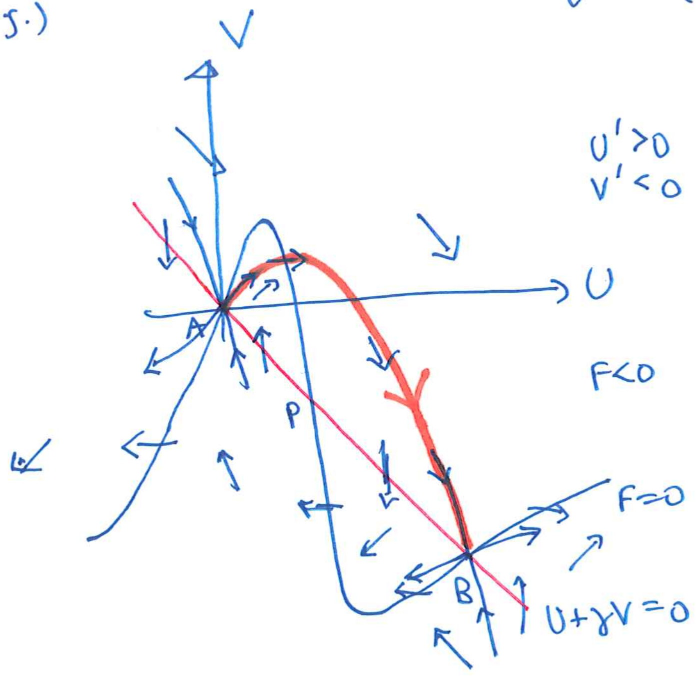
so D to A if $u < \mu$
& B to C if $u > \mu$

certainly if $\mu_- < \mu < \mu_+$.

$u = u_A + U$
$v = v_A + V$
$f = F(U,V)$

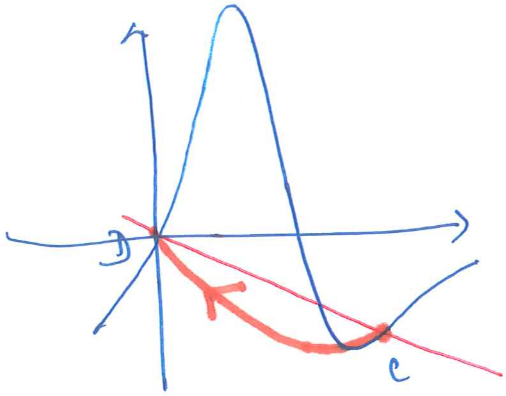
Fast phase, shift origin to A
AB (e.g.) $\Rightarrow$ $cV' = F$

$U' = c(U + \gamma V)$



3 fixed points. Clearly P is a node or spiral, A, B saddles.
To get from A to B we need separatrices to connect as shown
$\Rightarrow$ requires (unique) c.

To get from C to D is essentially the same picture but choose value of u_C to connect.



gives a one-parameter family as u_A was arbitrary (within a finite range