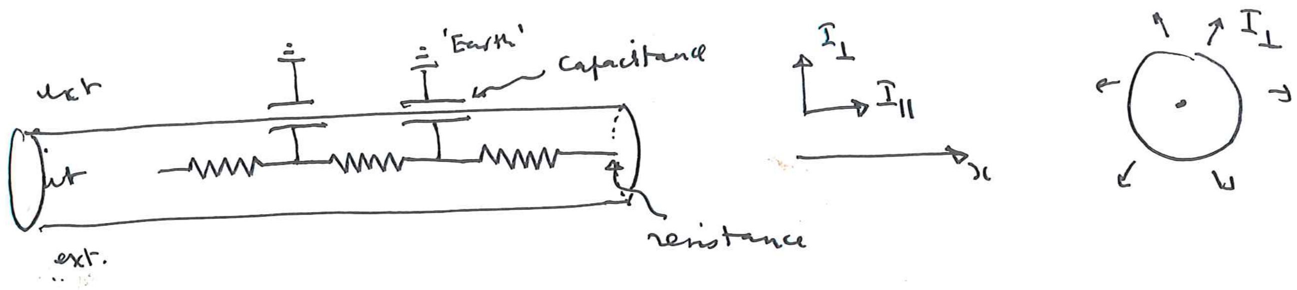
MP lecture 5

Signal propagation

The axon acts as a cable



With spatial variation (in x)

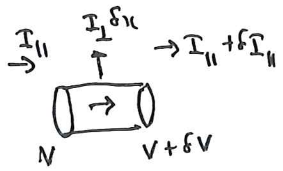
$I_\perp$ is the transmembrane current (per unit length) $A\ cm^{-1}$

$I_\parallel$ is the axial current in the x direction (A)

R is the axial resistance per unit length ($\Omega\ cm^{-1}$)

C is the capacitance per unit length ($F\ cm^{-1}$)

In a segment $(x, x+\delta x)$ the charge is $CV\delta x$



Charge conservation [current is charge flux]

$$\frac{\partial}{\partial t} CV\delta x \simeq -I_\perp \delta x - \frac{\partial I_\parallel}{\partial x}\delta x$$

thus $$C\frac{\partial V}{\partial t} = -I_\perp - \frac{\partial I_\parallel}{\partial x}$$

Constitutive law $$-\delta V = -\frac{\partial V}{\partial x}\delta x = I_\parallel \underbrace{R\,\delta x}_{\text{resistance of segment}}$$

$$\Rightarrow -\frac{\partial V}{\partial x} = RI_\parallel$$

$I_\perp = p(I_i - I_{app})$, p = perimeter, also $C = pC_m$ (C_m as earlier)

$$\Rightarrow \boxed{C_m V_t = I_{app} - I_i + \frac{1}{pR}V_{xx}}$$

[Note: the resistance per unit length $R = \frac{R_c}{A}$, A = area, R_c resistivity of the medium

so $C_m V_t = I_{app} - I_i + \frac{d}{4R_c} V_{xx}$, d = axon diameter.]

Non-dimensionalise (ex.)

As before, and choose

$$x \sim l = \left(\frac{r_H\, g_{Na}}{R_c}\right)^{1/2} \frac{\tau_n}{C_m}, \quad r_H = \frac{A}{p} = \frac{d}{4}$$

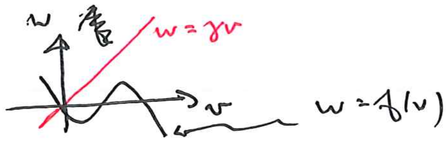
[Typical values as before & $d = 5\times10^{-2}$ cm, $R_c = 35\,\Omega$ cm $\Rightarrow l \sim 33$ cm.]

$$\Rightarrow \quad \varepsilon v_t = I^* - g(n,v) + \varepsilon^2 v_{xx}$$
$$n_t = n_\infty - n$$

When $I^* = 0$, perturbations lead to solitary travelling waves (neuron firing)

For simplicity, we will analyse these in the FitzHugh-Nagumo equation

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



— here $(0,0)$ is the equilibrium (& $I^* = 0$)

Travelling waves

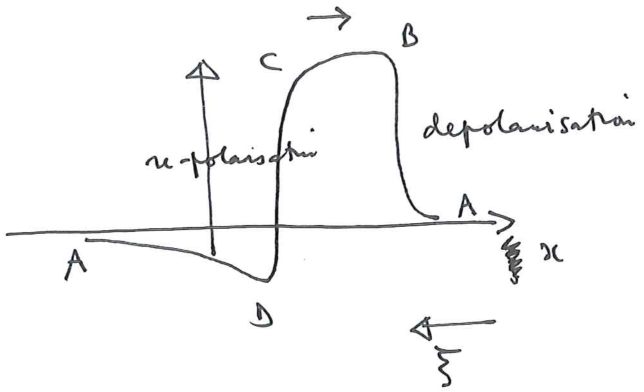
We seek a solution $v = v(\xi)$, $w = w(\xi)$, $\xi = ct - x$ $(c > 0)$

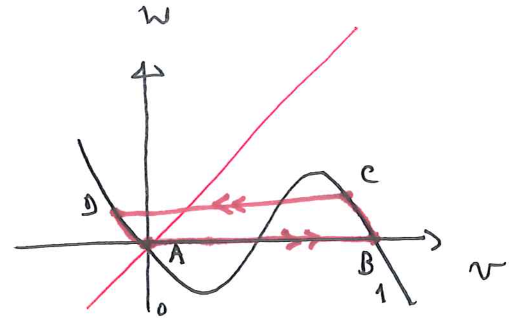
So

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

with $v = w = 0$ at $\pm\infty$

We seek / expect a wave of this form





Note: 1. The phase space is $\underset{\sim}{3\text{-D}}$

2. The waveform may not reach the maximum of f in $v>0$.

We construct the wave in four segments.

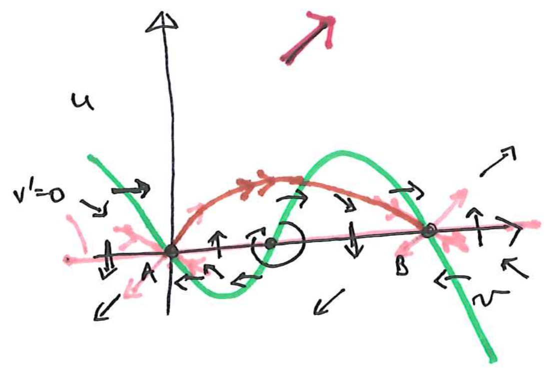
(i) AB : this is fast & we put $\xi = \varepsilon X$

So $cv' = f(v) - w + v''$, $cw' = \varepsilon(\gamma v - w)$

$\Rightarrow$ $w \simeq$ constant $= 0$, $cv' = f(v) + v''$

$\Rightarrow$ 2-D phase plane $\quad v' = u$

$\qquad\qquad\qquad\qquad\quad u' = cu - f(v)$



$(c>0)$

Phase plane as shown [nullclines, direction as $u \to \infty$

By inspection A & B are saddles (the other fixed pt is a spiral or node)

Choose c to connect the separatrices, as shown.

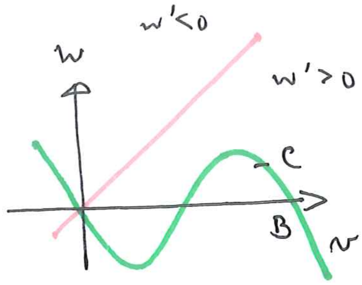
[In general, there will be discrete values for c. Sometimes, uniqueness can be shown by considering solutions of $\frac{du}{dv} = c - \frac{f(v)}{u}$ with $u \approx \lambda v$ as $v \to 0+$, $\lambda = c + \frac{|f'(0)|}{\lambda}$ $(\lambda>0)$ and proving monotonicity with c

— either works here.

(ii) BC is a slow phase:

$$0 \approx f(v) - w$$

$$cw' = \gamma v - w$$



$w \approx f(v)$ & w increases to C where $w = w_c$. This may or may not be at the maximum of f — we will assume not.

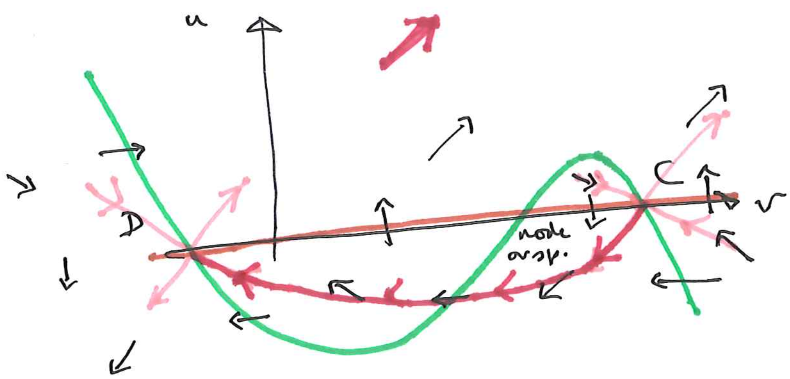
(iii) CD another fast phase, $\xi = \varepsilon X$

$w \approx w_c$ is constant & $cv' = f(v) - w + v''$

$$\Rightarrow \quad u' = cu + w_c - f(v)$$

$$v' = u$$

– Another (v, u) phase plane similar to AB but...



v-nullcline $u = 0$

u-nullcline

$$u = \frac{f(v) - w_c}{c}$$

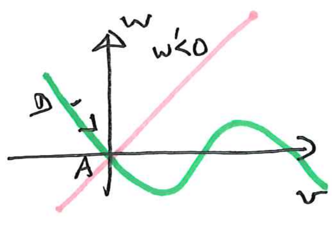
is lowered

directions as before but we seek a trajectory from C to D

This must pass in $u < 0$ & since c is already determined, we use the value of w_c to connect C to D as shown

(iv) Finally, the slow phase DA has $w \approx f(v)$

$cw' = \gamma v - w < 0$ so D approaches A.



□

MP Lecture 6 Calcium dynamics

Calcium (Ca^{2+}) is important in muscle contraction, cardiac signalling, etc.

Ca^{2+} is stored in bones, and released by hormonal stimulation.

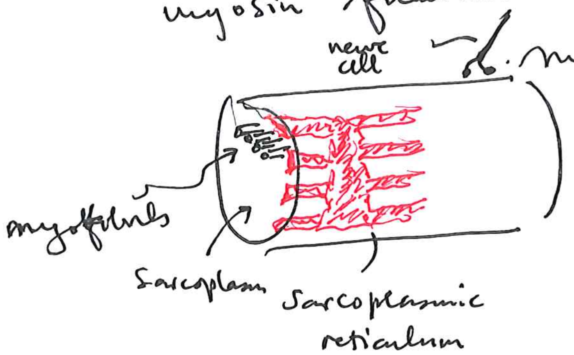
Extracellular Ca^{2+} concentrations are $\sim 10^{-3}$ M $= 1$ mM

Intracellular concentrations are $\sim 10^{-7}$ M $= 10^{-4}$ mM

So Ca^{2+} needs to be pumped out.

muscle cells

Muscles are bundles (fascicules) of muscle fibres (cells) each of which contains arrays of myofibrils which contain actin and myosin filaments – these contract under the action of Ca^{2+}



Under stimulation from a nerve cell, an action potential is triggered and propagates along the fibre:

Na^+ floods in as the cell depolarises & this allows Ca^{2+} in also.

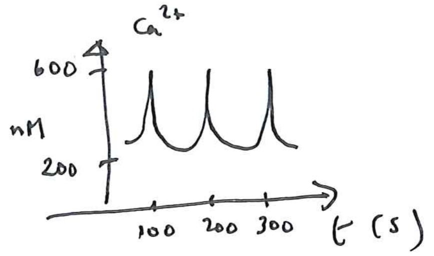
The internal store in the cell is the sarcoplasmic reticulum

It releases calcium by calcium-induced calcium release (CICR)

Muscle contraction

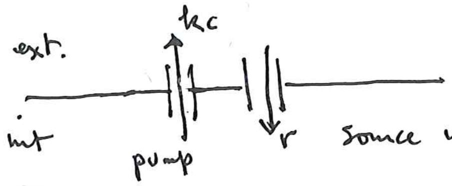
- We need a steady state with low intra-cellular Ca^{2+} which is excitable under a stimulus.
- Experiments show that oscillations can occur under stimulus in a limited range (of intensity); spiky; frequency increases with intensity.

eg Goldbeter p353

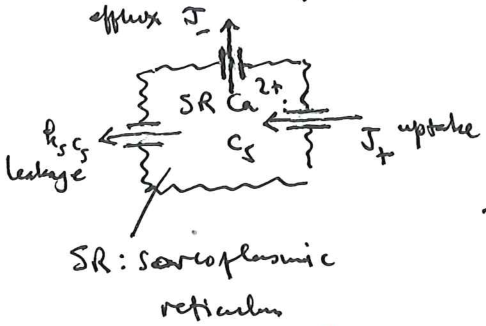


2-pool model

Note: this is very simplistic physiologically



source via opening of voltage-gated channels



Sarcoplasmic Ca^{2+}: c

The model is

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

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

& we assume the uptake $J_+ = \dfrac{V_1 c^n}{K_1^n + c^n}$ (to SR)

and the efflux $J_- = \dfrac{V_2 c_s^m}{K_2^m + c_s^m} \cdot \dfrac{c^p}{K_3^p + c^p}$

the CICR bit: increasing $c \Rightarrow$ increased output $\Rightarrow$ positive feedback

Non-dimensionalisation (ex.)

$c = K_1 u$, $\quad t \sim \frac{1}{k}$, $\quad c_s = K_2 v$

$$\Rightarrow \quad \dot u = \mu - u - \frac{\gamma}{\varepsilon} f(u,v)$$

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

$$f = \beta \frac{u^n}{1+u^n} - \frac{v^m}{1+v^m} \cdot \frac{u^p}{\alpha^p + u^p} - \delta v$$

$\mu = \frac{r}{k K_1}$

$\alpha = \frac{K_3}{K_1} \sim 0.9$

$\beta = \frac{V_1}{V_2} \sim 0.13$

$\gamma = \frac{K_2}{K_1} \sim 2$

Small leakage terms

- $\delta = \frac{k_s K_2}{V_2} \sim 0.004$
- $\varepsilon = \frac{k K_2}{V_2} \sim 0.04$

$m = n = 2$, $p = 4$

or

$$\boxed{\begin{aligned} \dot u + \gamma \dot v &= \mu - u \\ \varepsilon \dot v &= f(u,v) \end{aligned}}$$

$J(u) = \frac{\beta u^n}{1+u^n}$

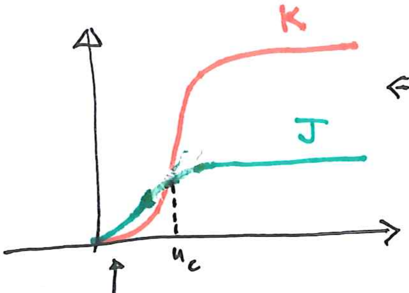
$K(u) = \frac{u^p}{\alpha^p + u^p}$

$L(v) = \frac{v^m}{1+v^m}$

Phase plane

v-nullcline $\quad \boxed{f = \cancel{\beta}\, J(u) - L(v) K(u) - \delta v = 0}$

$\delta \ll 1 \quad \Rightarrow \quad v \simeq L^{-1}\left[\frac{J(u)}{K(u)}\right]$



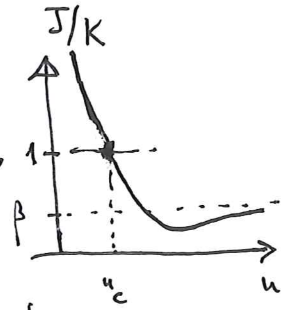
note $J \sim \beta u^2$, $K \sim u^4$

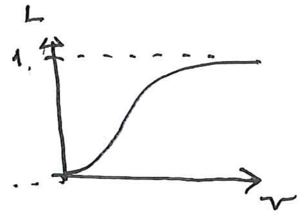
$\Leftarrow$ note $J \sim \beta\left[1 - \frac{1}{u^2} \cdots\right]$

$K \sim 1 - \frac{\alpha^4}{u^4} \cdots$

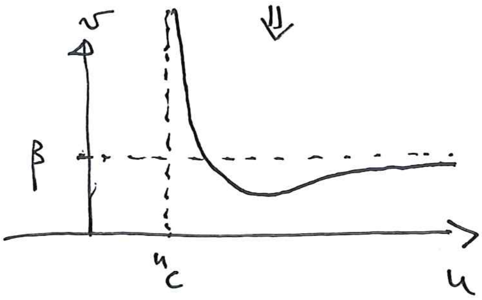
$\Downarrow$

$\frac{J}{K} \sim \beta\left(1 - \frac{1}{u^2} \cdots\right) \rightarrow$



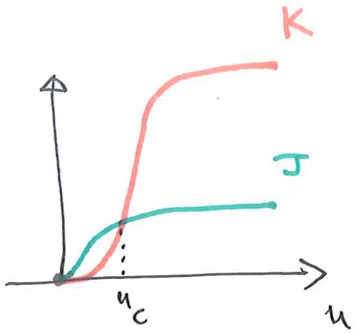


$\Downarrow$

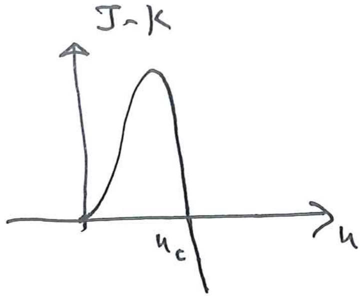


This gives the v-nullcline approximately, but is invalid for $v \gg 1$, specifically $v \sim \frac{1}{\delta}$

So ...



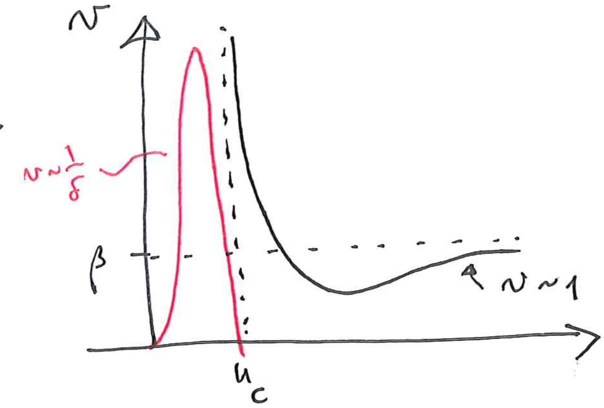
$\Rightarrow$



write $v = \frac{V}{\delta}$ $\Rightarrow$ $f \approx J(u) - K(u) - V$ $\quad (L \simeq 1)$

$\Rightarrow$ $V \simeq J(u) - K(u)$

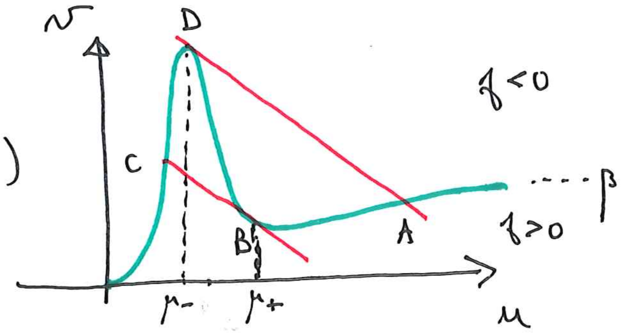
$\Rightarrow$



The two curves in fact match smoothly in a matching region where

$u - u_c \sim \delta^{\frac{m}{m+1}}$, $v \sim \frac{1}{\delta^{\frac{1}{m+1}}}$ [exo.]

So the v-nullcline is

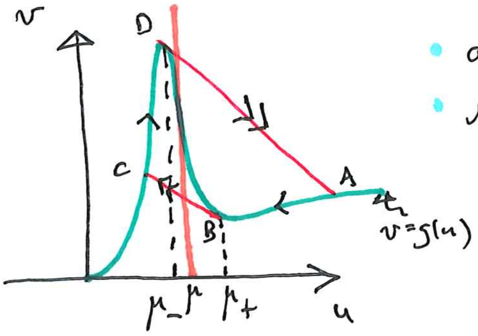


This defines a curve $v = g(u)$

(since $\frac{\partial f}{\partial v} < 0$)

Let B & D be the points where $g'(u) = -\frac{1}{\gamma}$ & $u|_B = \mu_+$, $u|_D = \mu_-$ (certainly exist for small δ)

then relaxation oscillations occur if $\mu_- < \mu < \mu_+$



- amplitude ~ constant
- period $\approx \int_{CD} + \int_{AB} dt \approx \int_{CD+AB} \frac{du + \gamma dv}{\dot{u} + \gamma \dot{v}} = \int_{CD+AB} \frac{[1+\gamma g'(u)]\,du}{\mu - u}$

$$= \underbrace{\int_{CD} \frac{[1+\gamma g']\,du}{\mu - u}}_{\text{decreases with } \mu \uparrow} \left(+ \int_{BA} \frac{[1+\gamma g']\,du}{u - \mu} \right)$$

MP lecture 7

Wave propagation

Excitable steady state + spatial variation (diffusion) $\Rightarrow$ travelling solitary wave (Hodgkin–Huxley)

Periodic solutions + diffusion $\Rightarrow$ periodic travelling waves

These have been observed in Xenopus oocytes : speeds $10-100\ \mu m\ s^{-1}$

Xenopus: sub-Saharan frog; oocytes: eggs

2-pool model + diffusion (1-D)

$$u_t + \gamma v_t = \mu - u + \nu u_{xx}$$

$$\varepsilon v_t = f(u,v)$$

(non-d with $x \sim l$, $\nu = \dfrac{D}{l^2 k}$, D = diffusion coefficient

We seek travelling waves $u = u(\xi)$, $v = v(\xi)$, $\xi = x + st$

& we choose l so that $\nu = \varepsilon$ $\Rightarrow$ $l = \left(\dfrac{D}{k\varepsilon}\right)^{1/2}$ $\sim 7\ \mu m$, wavespeed $lk \sim 70\ \mu m\ s^{-1}$

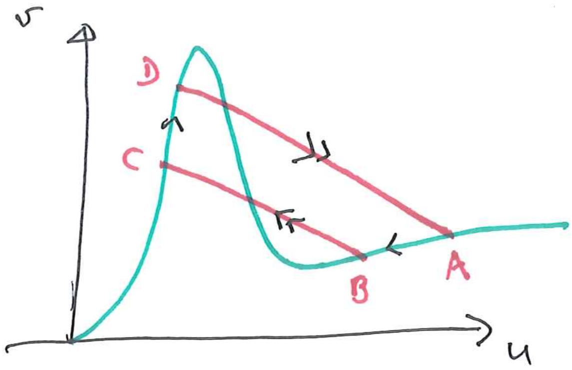
$$\Rightarrow \quad s(u' + \gamma v') = \mu - u + \varepsilon u'' \qquad ' = \frac{d}{d\xi}$$

$$\varepsilon s v' = f(u,v)$$

& we follow the FitzHugh–Nagumo type analysis for $\varepsilon \ll 1$, except we seek periodic solutions in ξ

Following FitzHugh-Nagumo, we seek a periodic solution as shown

(assuming $\mu_- < \mu < \mu_+$)



We start at D: DA is a fast phase, $\xi = \varepsilon X$

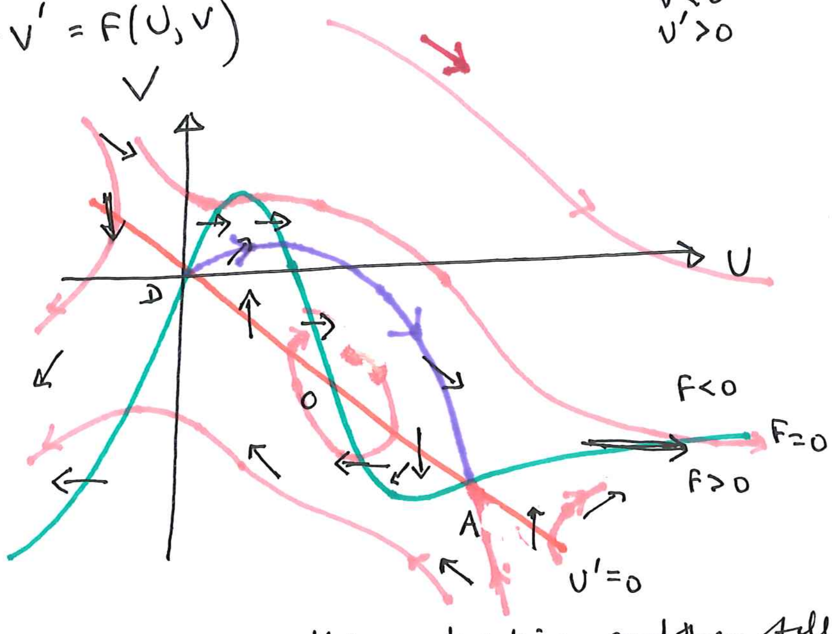
$$\Rightarrow \quad s(u' + \gamma v') \simeq u''$$

$$\Rightarrow \quad \begin{cases} u' \simeq s[u - u_D + \gamma(v - v_D)] \\ \text{and} \quad s v' = f(u,v) \end{cases}$$

Shift origin to $(0,0)$ by $u = u_D + U$, $v = v_D + V$, $f(u,v) = F(U,V)$

$$\Rightarrow \quad U' = s(U + \gamma V)$$

$$sV' = F(U,V)$$



Construct the phase plane: nullclines, directions and then fill in curves

D, A saddles, O node or spiral (could be stable or unstable

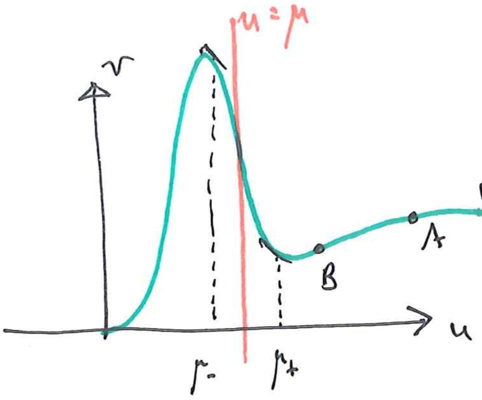
Select s so that D connects to A as shown [must be such a value as: $s \to 0$, D heads straight to O; $s \to \infty$ trajectory heads for $U = \infty$]

AB is a slow phase: $s(u'+\gamma v') = \mu - u + \epsilon u''$

$\epsilon s v' = f(u,v)$

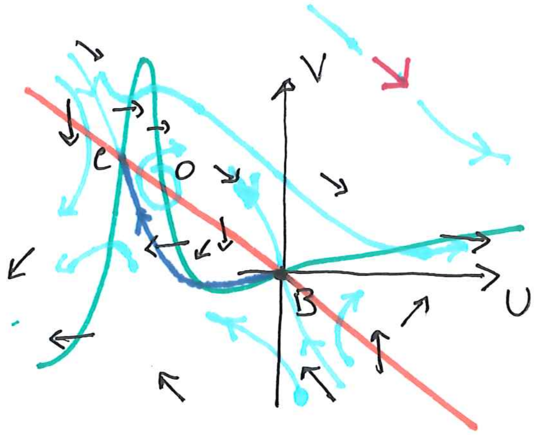
$\Rightarrow f(u,v) \simeq 0 \Leftrightarrow v = g(u)$, $u' \simeq \dfrac{\mu - u}{s[1+\gamma g'(u)]} < 0$

as $u > \mu$, $g' > 0$



till we get to B, BC fast phase $u = u_B + U$, $v = v_B + V$, $f(u,v) = F(U,V)$

$\Rightarrow$ $U' = s(U + \gamma V)$
$sV' = F(U,V)$ (again) but now



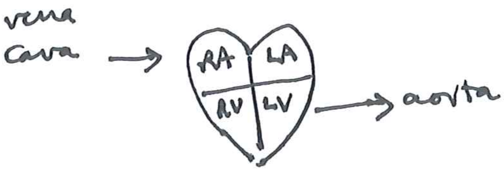
Phase plane similar to before : select u_B to connect to C

- Note: it is possible that B may be at the tangent (i.e. $u_B = \mu_+$). It appears (with the present parameters + choice of f) this is the case for $s \gtrsim 0.32$
- Since u_B was arbitrary there is a one-parameter family of periodic travelling waves

□

MP lecture 8

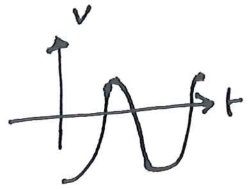
The electrochemical action of the heart



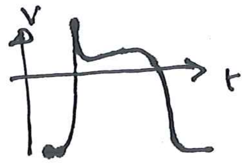
RA right atrium
LA left "
RV right ventricle
LV left "

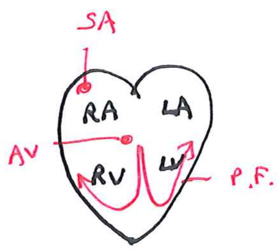
The heart has four chambers.
Blood flows into the RA from the venous system, to the RV, perfuses the lungs (gains O_2), to the LA, to the LV, then to the arteries.

In the RA is the sino-atrial node (SA node) whose cells act as pacemaker with a periodic action potential

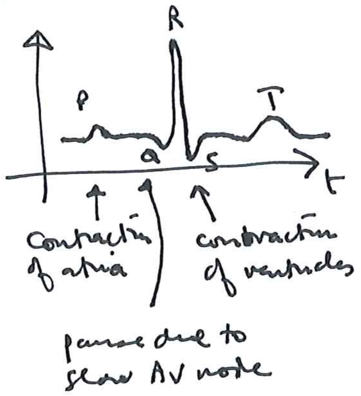


Other cells (atrial/ventricular myocytes, AV node, Purkinje fibres) are excitable, with distinct action potential





The electrocardiogram (ECG)



P: depolarisation of the atria via the SA node
QRS depolarisation of the ventricles
T repolarisation of the ventricles

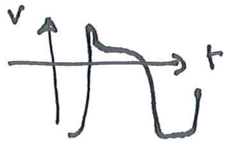
- Waves (2-D) propagate through the heart from the SA
- Blockage of conduction paths can lead to re-entrant spiral waves

e.g. due to dead core

- In the diseased heart, spiral waves can become chaotic → ventricular fibrillation

The Noble model (1962)

An early model for the action potential of ventricular myocytes [Purkinje fibres, pacemaker]



Cable equation $\quad C_m \dot{V} = -I_i \quad , \quad I_i = I_{Na} + I_K + I_L$

$$I_{Na} = \underbrace{[g_0}_{\text{residual}} + \underbrace{g_{Na} m^3 h}_{H \cdot H}](V - V_{Na}) \qquad V_{Na} \sim 40 \text{ mV}$$

$$I_K = (\underbrace{\gamma_K}_{\text{instant}} + \underbrace{g_K n^4}_{\text{long-lasting}})(V - V_K) \qquad V_K \sim -100 \text{ mV}$$

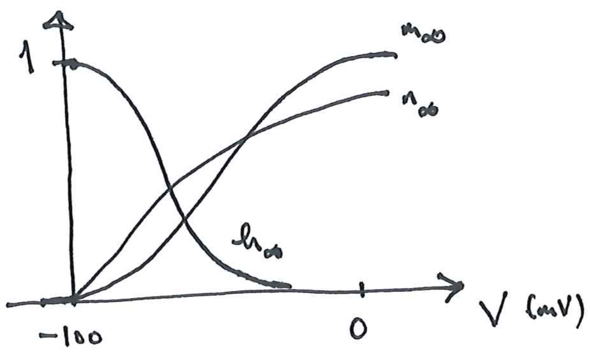
$$I_L = g_L (V - V_L) \quad \text{leakage} \qquad V_L \sim -60 \text{ mV}$$

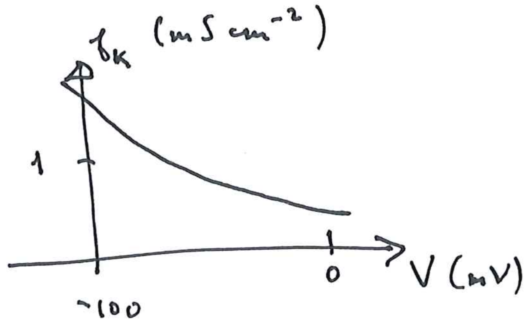
In practice $V_{eq} \sim -90$ mV

$$\tau_m \dot{m} = m_\infty - m \qquad \tau_m \sim 0.25 \text{ ms}$$

$$\tau_n \dot{n} = n_\infty - n \qquad \tau_n \sim 500 \text{ ms} \quad !$$

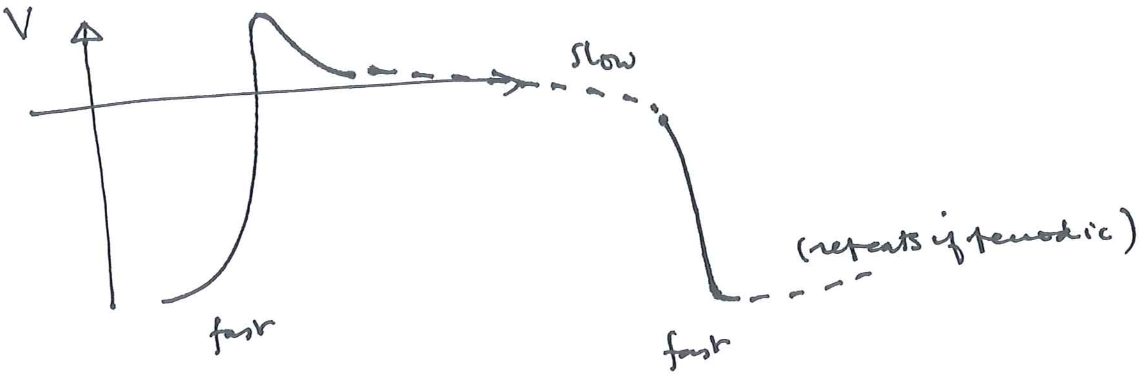
$$\tau_h \dot{h} = h_\infty - h \qquad \tau_h \sim 8 \text{ ms}$$





Potential time scale $\quad t_V \gtrsim \dfrac{C_m}{\bar{g}_{Na}} \sim 0.03 \text{ ms} \;!!\quad$ – but increased due to $m^3 h$ (~15 ms at equilibrium)

We focus on the fast depolarisation



slow time scale is $\tau_n \sim 500$ ms

fast time scale is $\tau_h \sim 7$ ms

1. Assume ($\tau_m \sim 0.25$ ms) $\quad m \simeq m_\infty(V)$

2. Non-dimensionalise $\quad V \sim |V_K|$, $t \sim \tau_h$

$$\varepsilon = \frac{\tau_h}{\tau_n}$$

$$\Rightarrow \quad \dot n = \varepsilon(n_\infty - n)$$

$$\dot h = h_\infty - h$$

$$\dot V = -G(V,h,n)$$

$$G = -\{\underbrace{\gamma_0}_{\ll 1} + \underbrace{\gamma_{Na}}_{\sim 267} m_\infty^3(V)\, h\}(\underbrace{v_{Na}}_{0.4} - V) + \phi(V+1) \quad [+\gamma_L(V+\overbrace{v_L}^{0.6})]$$

Noble took $\gamma_L = 0$ to start

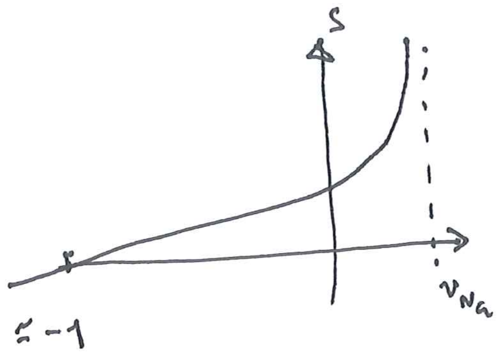
$$\phi = \underbrace{\phi_K(V)}_{\sim 1} + \underbrace{\gamma_K}_{\sim 1} n^4$$ — take as slowly varying (due to n)

Fast phase $\quad t \sim 1 \quad n \simeq$ constant

$$\begin{cases} \dot h = h_\infty - h \\ \dot V = -\gamma_{Na} m_\infty^3(V)\left[h_0(V) - h\right](v_{Na} - V) \end{cases}$$

$$h_0(V) = \frac{1}{\gamma_{Na} m_\infty^3(V)}\left[\underbrace{\frac{\phi(V+1) + \gamma_L(V+v_L)}{v_{Na} - V}}_{S} - \gamma_0\right]$$

note $S = \frac{\phi(V+1)\,[+\gamma_L(V+v_L)]}{v_{Na}-V}$



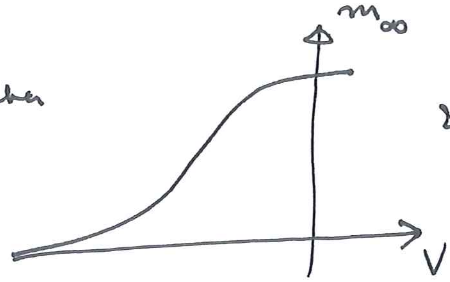
where $S = 0$

(more precisely at

$V = -\frac{[\phi+\gamma_L v_L - \gamma_0 v_{Na}]}{\phi+\gamma_L+\gamma_0}$)

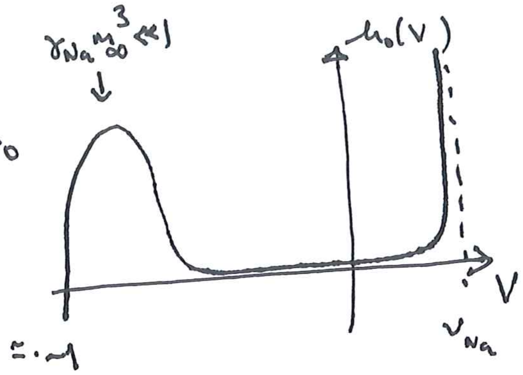
$= V_0$, say

Remember

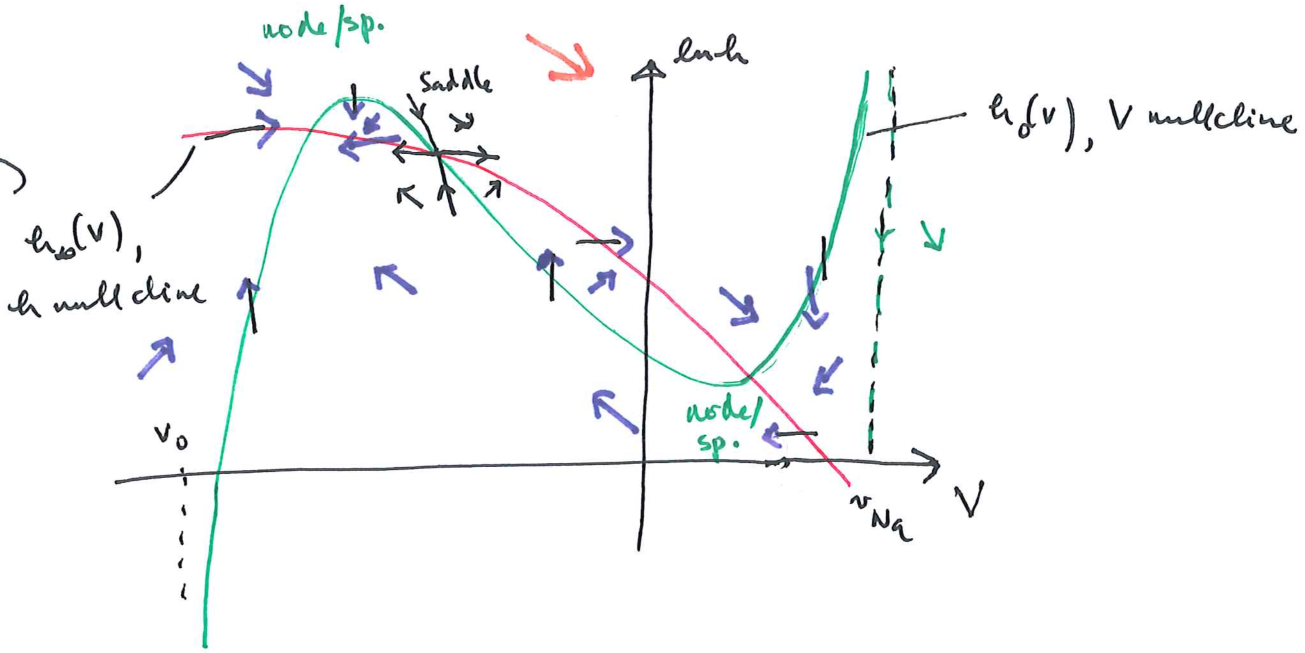


& $\gamma_{Na} \sim 267$

⇒ h_0



⇒



$\dot{h} = h_\infty - h$

$\dot{V} = -\gamma_{Na} m_\infty^3(V)\left[h_0(V) - h\right](v_{Na}-V)$

1. h, V nullclines
2. direction ($h\uparrow$: $\dot{h}<0, \dot{V}>0$
3. fill in rest

⇒ 4. outer fixed points node/spiral
intermediate saddle

5. Stability

Stability of outer fixed points

- Linearise at a fixed point

$$\begin{cases} \dot{h} = h_\infty - h \\ \dot{V} = A[h - h_0(V)] \end{cases}$$

$$h = h^* + H, \quad V = V^* + W$$

$$A = \gamma_{Na} m_\infty^3 (v_{Na} - V)$$

$$\begin{pmatrix} \dot{H} \\ \dot{W} \end{pmatrix} \simeq \underbrace{\begin{pmatrix} -1 & h_\infty' \\ A & -Ah_0' \end{pmatrix}}_{M} \begin{pmatrix} H \\ W \end{pmatrix}$$

$$\mathrm{tr}\, M = -1 - Ah_0'$$

Note: only need to linearise bit that vanishes at fixed pt.

Left hand fixed pt $h_0' > 0$ probably & in any case $A \ll 1 \Rightarrow \mathrm{tr}\, M < 0 \rightarrow$ stable

Right hand fixed pt. A is large so stable if $h_0' > 0$ as in figure.

In more detail, $h_0 = \dfrac{S}{\gamma_{Na} m_\infty^3} = \dfrac{S(v_{Na} - V)}{A} = \dfrac{N}{A}$

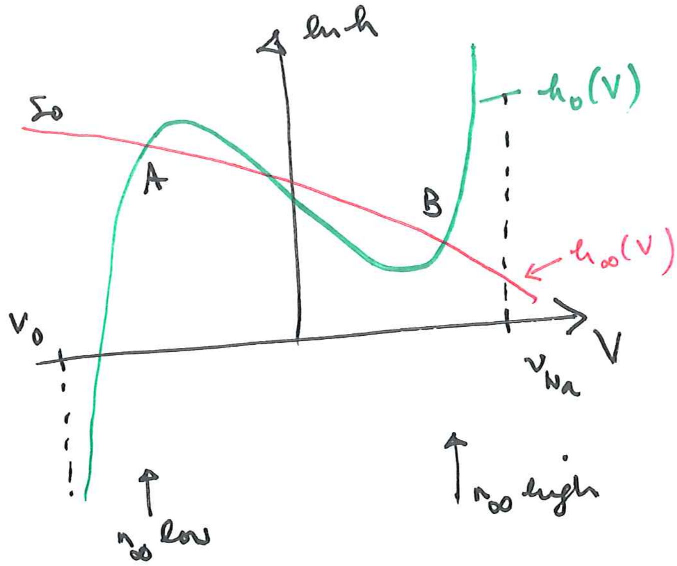
$$N = \phi(V+1) + \gamma_L(V + v_L) - \gamma_0(v_{Na} - V)$$

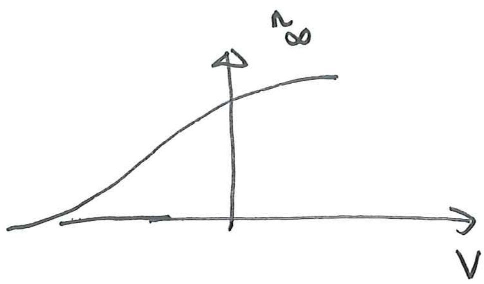
so $h_0' = \dfrac{N'}{A} + N\left(\dfrac{1}{A}\right)'$; but $\dfrac{1}{A} \ll 1$ so actually $h_0' \ll 1$

So both fixed points are stable + no connecting trajectory.

Finally consider the slow variation of n (with intersections as shown for $n \simeq 0.5$)

$$n \text{ increase} \Rightarrow \phi = d_K + \gamma_K n^4 \uparrow \Rightarrow S = \frac{\phi(V+1)}{v_{Na} - V} + \dots \uparrow \Rightarrow h_0 \uparrow$$

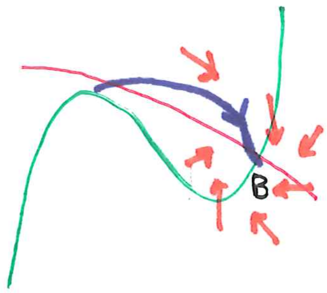




If at A at $n \simeq 0.5$ say $\quad n > n_\infty$, $\dot{n} = \varepsilon(n_\infty - n) < 0$

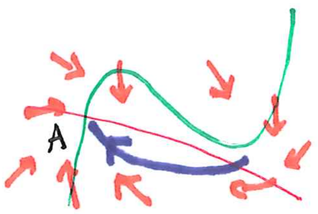
$\Rightarrow n\downarrow \Rightarrow h_0\downarrow \Rightarrow$

trajectory $\rightarrow$ B



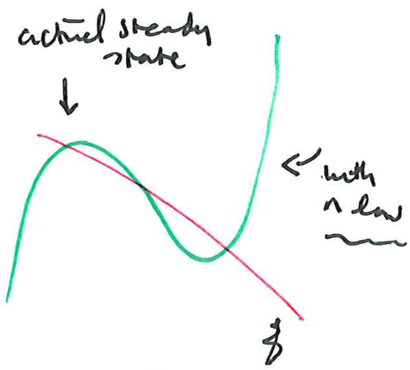
At B $\quad n_\infty$ high $\quad n < n_\infty \quad \dot{n} > 0$

$\Rightarrow n\uparrow \Rightarrow h_0\uparrow \Rightarrow$



and cycle repeats periodically

to obtain excitability in this model, we need



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