Enzyme kinetics

Enzymes are catalysts - they help convert other molecules (called substrates) into products but are not used up in the reaction themselves.

Consider chemicals A and B reacting on collision to form chemical C with a rate k:

$$A + B \xrightarrow{k} C$$

this depends on the molecule shapes and sizes and the temperature.

Then we can write

$$\frac{dC}{dt} = k A B$$

Get students to think why this is true - if you double the number of A you would expect the rate of reaction to double

More on this on problem sheet 1 question 2.

Note this means that

$$2A + B \xrightarrow{k} C$$

is $\frac{dC}{dt} = k A^2 B$

This is called the law of mass action

Assumes that the mixture is well stirred (no spatial dependence).

An enzyme reaction looks like this:

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C \xrightarrow{k_2} E + P$$

- S: substrate
- E: enzyme
- k_1, k_{-1}: a reversible reaction
- C: a complex, which breaks down into the enzyme and a product.
- P: product

The overall reaction is $S \xrightarrow{r} P$

This looks like a simple reaction, but we know there are intermediate steps. You could just model the single reaction and capture all the intermediate steps with this overall reaction. This is the Hill equation:

$$r = \frac{r_0 S^n}{k^n + S^n}$$

k: some constant, n

But better to use the law of mass action:

$$\frac{dS}{dt} = k_{-1} C - k_1 S E \quad (1)$$

$$\frac{dE}{dt} = (k_{-1} + k_2) C - k_1 S E \quad (2)$$

$$\frac{dC}{dt} = k_1 S E - (k_2 + k_{-1}) C \quad (3)$$

$$\frac{dP}{dt} = k_2 C \quad (4)$$

Can we simplify? Yes -

E only appears in ① so decouples.

Add ② + ③ to ~~eliminate~~ see that $E + C =$ constant $= E_0$

initial value of E (since $C = 0$ initially)

This reduces the system to two ODEs:

$$\frac{dS}{dt} = k_1 C - k_1 S (E_0 - C)$$

$$\frac{dC}{dt} = k_1 S (E_0 - C) - (k_2 + k_1) C.$$

which can be solved subject to suitable initial conditions $S = S_0$, $C = 0$ at $t = 0$.

Non-dimensionalize to analyse the system:

$$S = S_0 s, \quad C = E_0 c, \quad t = \frac{t'}{k_1 E_0}$$

gives

$$\frac{ds}{dt'} = -s + c(s + k' - \lambda)$$

$$\varepsilon \frac{dc}{dt'} = s - (s + k') c$$

$$k' = \frac{k_1 + k_2}{k_1 S_0}$$

$$\lambda = \frac{k_2}{k_1 S_0}$$

$$s(0) = 1, \quad c(0) = 0$$

$$\varepsilon = \frac{E_0}{S_0} \ll 1$$

because we only need a bit of enzyme

$\varepsilon \ll 1$ means we can neglect the time derivative in the c equation. This makes a quasi-static system: s evolve through a time derivative; c evolves through an algebraic equation.

More on this in problem sheet 1, question 1!

$$\Rightarrow \quad c = \frac{s}{s + k'}, \qquad \boxed{\frac{ds}{dt'} = -\frac{\lambda s}{s + k'} \quad (*)}$$

(*) is known as the Michaelis Menten law (and is for enzyme reactions).

What is the reaction rate?

$$\text{This is} \quad r \overset{\text{def}}{=} \frac{dp}{dt}$$

$$= -\frac{ds}{dt} \qquad \text{(because it is minus the rate of depletion)}$$

$$= -s_1 E_0 k_1 \frac{ds}{dt'} \qquad \text{(non-dimensionalising}$$

$$= \frac{k_2 E_0 s}{k + s} \qquad \text{using (*)}$$

where $k = \dfrac{k_{-1} + k_2}{k_1}$ is the Michaelis constant.

It's difficult to measure individual reaction rates experimentally. But we can measure the overall reaction rate r and concentrations.

So, if we look at the initial rate of reaction r_0:

$$r_0 = \frac{k_2 E_0 S_1}{K + S_1} \Rightarrow \frac{1}{r_0} = \frac{1}{k_2 E_1} + \left(\frac{K}{k_2 E_1}\right)\frac{1}{S_0}$$

So $\frac{1}{r_0}$ is linear in $\frac{1}{S_0}$.

We can plot experimental data of $\frac{1}{r_1}$ versus $\frac{1}{S_0}$ and the gradient is $\frac{K}{k_2 E_0}$ and intercept is $\frac{1}{k_2 E_1}$ for different S_1's which allows us to extract K and $k_2 E_0$. These plots are called Lineweaver-Burk plots.

Our quasi-steady approximation does not satisfy our initial conditions

Now $c = \frac{s}{s+k}$

$s \to s_1$, $c = 0$. This is because there is a rapid transient

We see this by rescaling $t' = \varepsilon\tau$ to give

$$\frac{ds}{d\tau} = \varepsilon(-s + c(s + k' - \lambda)) = 0 \text{ to leading order}$$

$$\Rightarrow s = s_0$$

$$\frac{dc}{d\tau} = s - (s + k')c$$

$$\Rightarrow \frac{dc}{d\tau} = s_1 - (s_1 + k')c$$

$$\Rightarrow c = \frac{1}{1+k'}\left(1 - e^{-(1+k')\tau}\right)$$

This takes us from $c = 0$ at $t = 0$ to the initial quasi-static value.

Inhibitors are substances that inhibit the catalytic reaction of an enzyme ~~by binding reaction sites~~

eg 1 **competitive inhibition** - when the substrate can't bind if the inhibitor is bound to an enzyme

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C_S \xrightarrow{k_2} E + P$$

and $$E + I \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} C_I$$

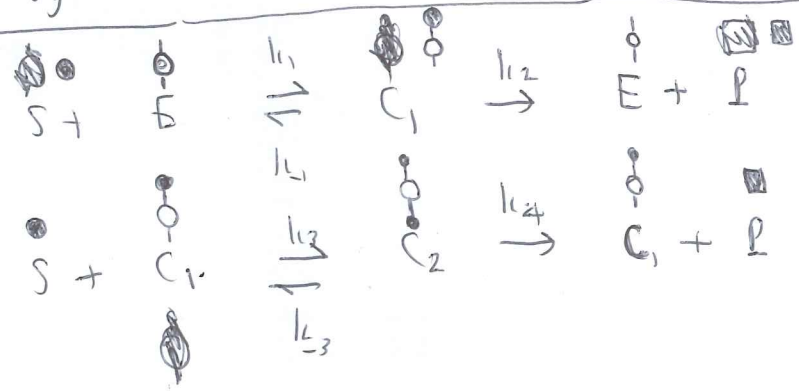
You can do law of mass action for these and analyse the reaction rate in a similar way to the previous case (see lecture notes)

eg 2 **allosteric inhibition**

As well as the previous two reactions we can also have the inhibitor binding to C_S to make a different product:

$$C_S + I \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C_I + S$$

Cooperative systems - more than one binding site



(catalytic reaction to make P from S using E as a catalyst)
(catalytic reaction to make P from S using the intermediate product C_1 as a catalyst too)

You can do the law of mass action analysis in this case and find that now

$$r = \frac{(k_2 k_2 + k_4 S) E_0 S}{k_1 k_2 + k_2 S + S^2}$$

$$k_1 = \frac{k_{-1} + k_2}{k_1}$$

$$k_2 = \frac{k_4 + k_3}{k_3}$$

Special cases: if the rates of binding and reaction are identical and independent at each site equal at each site then $k_1 = 2k_3$ (because k_3 is a reaction binding S with C_1 and C_1 has because there are

Special case: if the rate of binding of the first substrate molecule is small but the rate of binding of the second molecule is large then $k_1 \to 0$, $k_3 \to \infty$ with $k_1 k_3$ finite gives

$$r = \frac{k_4 E_0 S^2}{k_1 k_3 + S^2}$$

which is a Hill equation with exponent 2.

Trans-membrane ion transport

Cells are bags of water

The water contains dissolved salts: NaCl and KCl which dissolve into Na^+, Cl^-, K^+, ions.

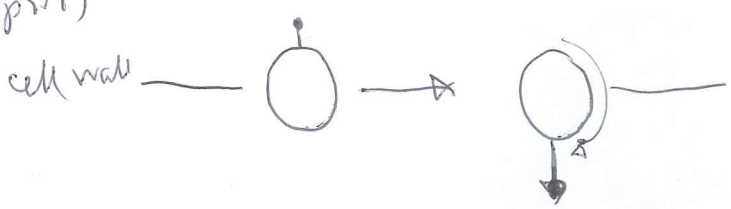
These exist both inside and outside the cell, creating a potential difference.

The cell walls are permeable - ions may be transported through the cell membrane, passing through pores called channels or gates.

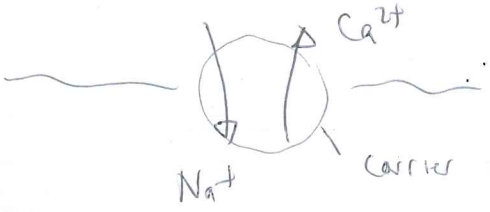
Osmosis is the mechanism by which water is transported across the cell membrane.

Carrier mediated diffusion - a molecule hitches a lift by binding to a carrier molecule which is lipid soluble and can move through the membrane

Carrier mediated transport - a molecule binds to a protein that has an active site that may be exposed to the interior or exterior of the cell (eg glucose or amino acid transport)



Pumps - these exchange one ion for another eg Na^+ and K^+ or Na^+ and Ca^{2+}



A model for carrier mediated transport

C_i = state with binding site exposed to the interior / exterior

C_e =

C_e can bind ~~to make a~~ with a substrate molecule in the exterior, S_e, ~~complex P_e.~~ to make a product P_e (1)

C_i can bind ~~with~~ a substrate molecule in the interior S_i to make a product P_i (with same rates as in the exterior) (2)

Further P_i can ~~react~~ turn into P_e. and vice versa (this is the carrier doing its 'rotation') (3)

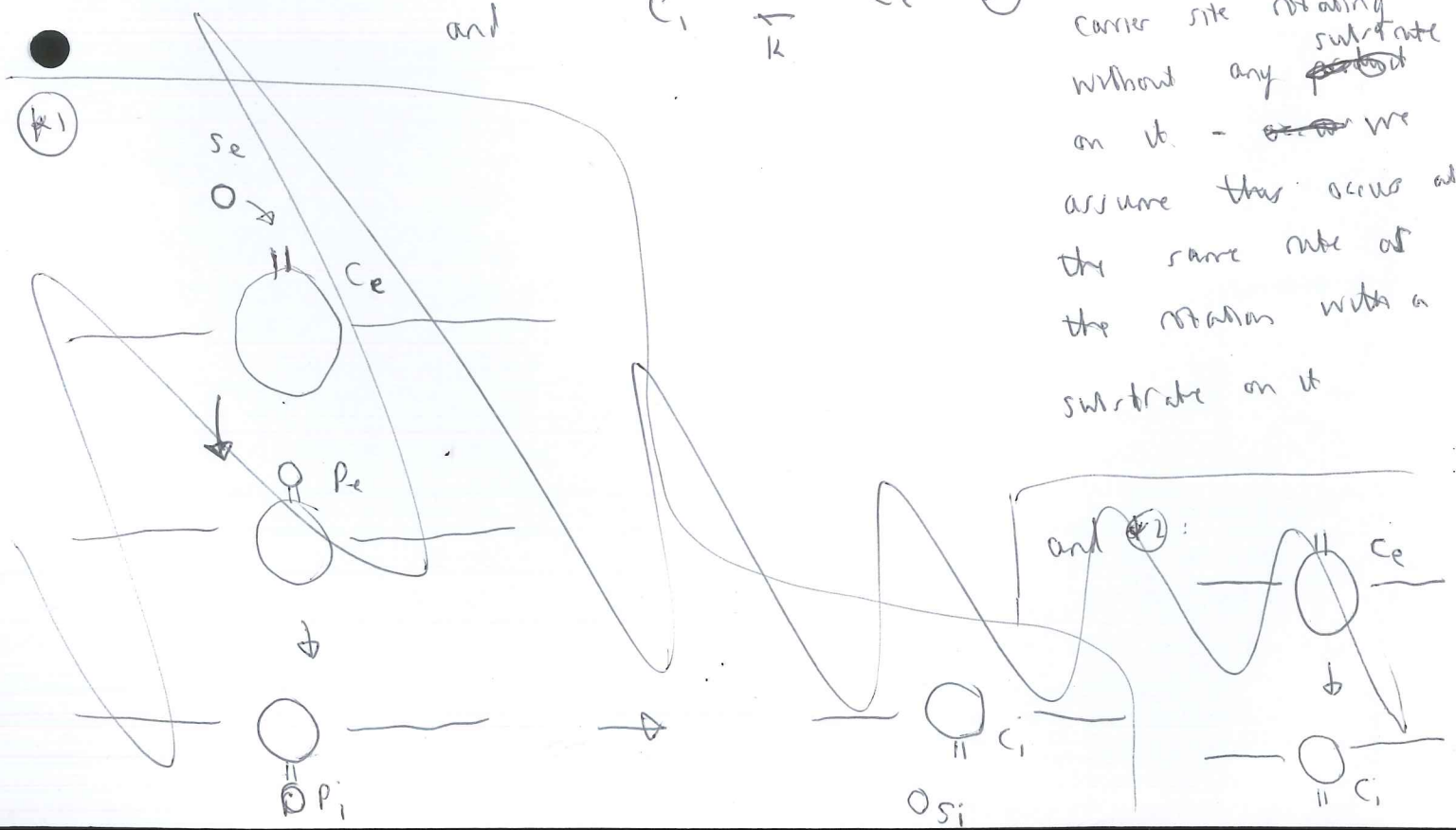
see next page for pictures.

The reaction scheme is:

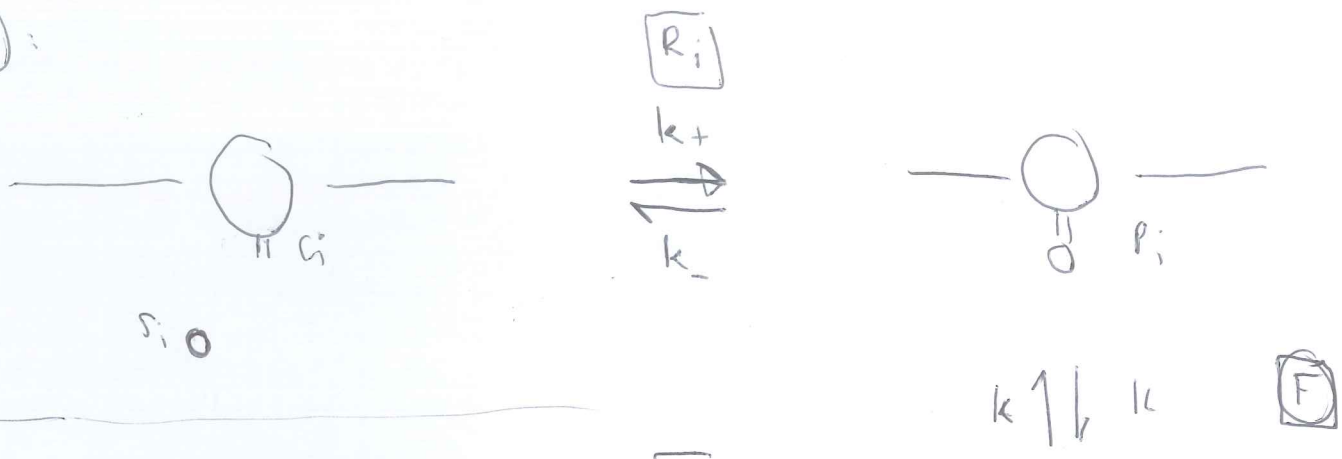
$$S_i + C_i \underset{k_-}{\overset{k_+}{\rightleftharpoons}} P_i \underset{k}{\overset{k}{\rightleftharpoons}} P_e \underset{k_+}{\overset{k_-}{\rightleftharpoons}} S_e + C_e \quad (*1)$$

(2) (3) (1)

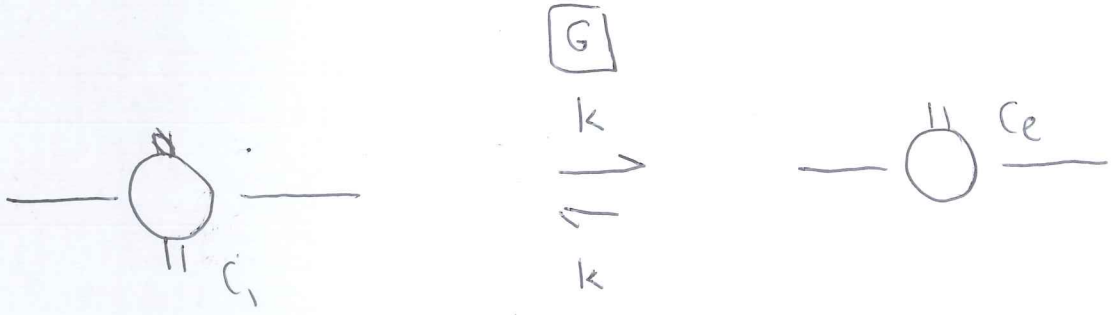
and $C_i \underset{k}{\overset{k}{\rightleftharpoons}} C_e$ (*2) this is the carrier site rotating without any substrate on it - we assume that occurs at the same rate as the rotation with a substrate on it



(*1):



(*2):



Finally, assume that substrate is supplied from the exterior at a rate J. and taken

Using the law of mass action we have

$$R_i = k_+ S_i C_i - k_- P_i$$

$$R_e = k_+ S_e C_e - k_- P_e$$

$$F = k P_i - k P_e$$

$$G = k C_i - k C_e$$

We are interested in finding a relationship for the rate of transfer of ions from one side to the other in steady state and how this depends on the parameters in all the individual reactions

Finally, suppose that substrate is supplied from the exterior at a rate J and taken away from the interior at the same rate.

Then:

$$\frac{dS_i}{dt} = -J - R_i \quad (1)$$

$$\frac{dS_e}{dt} = J + R_e \quad (2)$$

$$\frac{dP_i}{dt} = R_i - F \quad (3)$$

$$\frac{dP_e}{dt} = F - R_e \quad (4)$$

$$\frac{dC_i}{dt} = -G - R_i \quad (5)$$

$$\frac{dC_e}{dt} = +G + R_e \quad (6)$$

If J is unknown then there are six equations for seven unknowns.

Adding (3) + (4) + (5) + (6) gives

$$\frac{d}{dt}(P_i + P_e + C_i + C_e) = 0$$

$$\Rightarrow P_i + P_e + C_i + C_e = \text{constant}.$$

This is conservation of carrier.

And (1) + (2) + (3) + (4) gives $S_i + S_e + P_i + P_e = \text{constant}$.

This is conservation of substrate.

One can solve ① – ④ in steady state to find (see problem sheet 1, question 3)

$$J = \frac{k_- k\, C_{e_0}}{2k_0} \cdot \frac{S_e - S_i}{(K_m + S_i)(K_m + S_e) - K_d^2}$$

$$K_m = \frac{k_- + k_+}{k_+}$$

$$K_d = \frac{k}{k_+}$$

So this tells us the flux of ions transported across the cell membrane in steady state.

Note the similarity in structure to the Michaelis-Menten flux we derived. ($\frac{dv}{dt} = \frac{V(S)}{(S)+K}$)

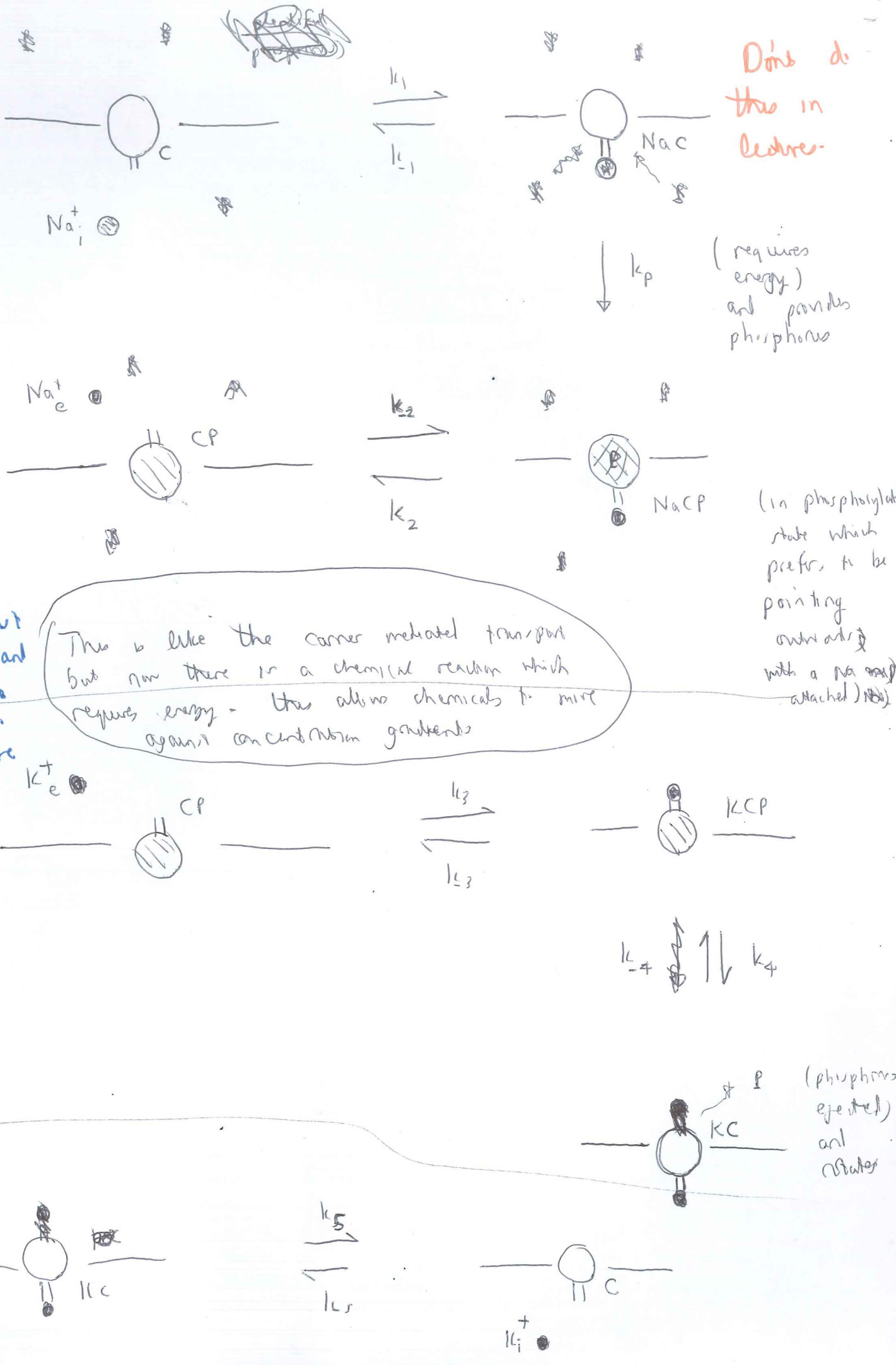
Active transport – the sodium–potassium pump

The carrier mediated transport described above moves molecules down chemical gradients.

To move molecules against a chemical gradient requires energy. This is known as an active transport mechanism.

One of the most important active transport mechanisms is the Na^+ K^+ pump.

For lectures just make the distinction from the carrier mediated transport before. Part on next page.

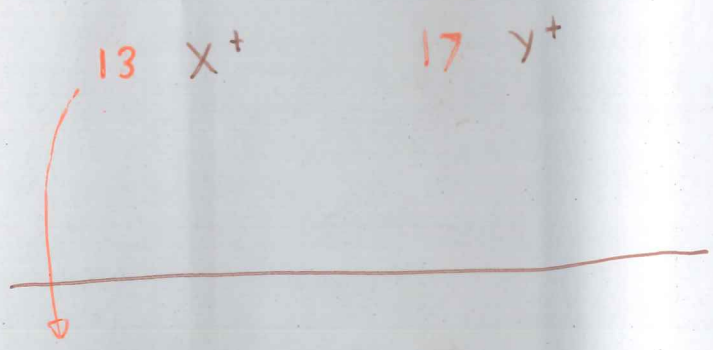

Don't do this in lecture.
C
k_1
k_{-1}
NaC
Na^+_i
k_p
(requires energy) and provides phosphorus
Na^+_e
CP
k_{-2}
k_2
NaCP
(in phosphorylated state which prefers to be pointing outwards with a Na attached)
This is like the carrier mediated transport but now there is a chemical reaction which requires energy - this allows chemicals to move against concentration gradients
Could just say this and no need to delve into the picture
K^+_e
CP
k_3
k_{-3}
KCP
k_{-4}
k_4
P
KC
(phosphorus ejected) and water
k_5
k_{-5}
C
K^+_i

The Nernst potential and the resting potential

The Nernst potential is that obtained when all gates are open and there is a balance between diffusive flux and electric flux. The system is in equilibrium

The resting potential is the difference between the potential outside and far from the cell and inside the cell, which may be different to the Nernst potential because gates open and close and ions are moved under different ionic and concentration gradients.

The Nernst potential



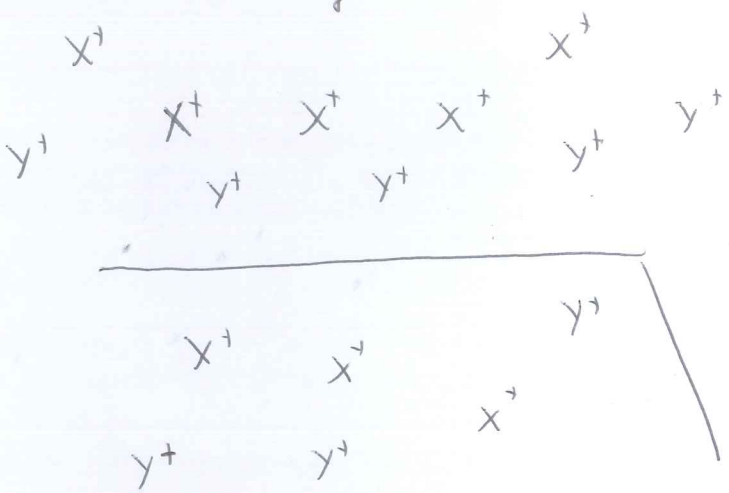
11 X^+ 17 Y^+

9 X^+ 23 Y^+

But doesn't reach 10 X^+ on each side because of electrostatic potential pushing back

The membrane potential

Consider the following set-up:



Equal positive and negative charges on each side but different amounts on the two sides.

a membrane permeable to X^+ but not Y^+

X^+ will diffuse through the membrane to balance the charge of X^+ on both sides.

The balancing will happen in a small region near the membrane (so far from the membrane the liquids will remain electroneutral).

The potential difference that builds up across the cell membrane as a result is called the Nernst potential

(ie. concentrations of X^+ will be equal across the membrane and concentrations

What is this potential?

There will be a flux of ions due to a concentration gradient

$\underline{J}_1 = -D \nabla c$ (regular diffusive flux)

D: ion diffusivity, c: concentration

ϕ: electric potential
$-\nabla\phi$ = electric field

There will be a flux of ions due to a potential difference

$\underline{J}_2 = -\frac{uzc}{|z|}\nabla\phi$

u = ion mobility = velocity under a constant electric field
z = valency of ion ($\frac{z}{|z|} = \pm 1$ giving ion charge)

So the total flux is $\underline{J} = \underline{J}_1 + \underline{J}_2$

$$\underline{J} = -D \nabla c - \frac{uzc}{|z|} \nabla \phi$$

or $J = -D \frac{\partial c}{\partial x} - \frac{uzc}{|z|} \frac{\partial \phi}{\partial x}$ (*) assuming set-up is one dimensional

Einstein's relation connects the diffusivity with the ion mobility:

$$\boxed{D = \frac{uRT}{|z|F}}$$

R = universal gas constant
T = absolute temperature
F = Faraday's constant

(cf Stokes Einstein:

$$D = \frac{k_B T}{6\pi \eta a}$$)

In equilibrium $J = 0$ (no flux)

We can integrate (*) to get $\boxed{V^{dif} = \phi_i - \phi_e = \frac{RT}{zF} \log\left(\frac{c_e}{c_i}\right)}$

Nernst potential

e = exterior
i = interior.

Now consider a

Ionic currents

The flow of ions across a membrane causes a build up of charge which means the membrane acts as a capacitor.

The voltage across the membrane is $V = \frac{Q}{C}$ ~ charge difference

capacitance

The current across the membrane is also $I = -\frac{dQ}{dt}$

Combining these gives $C\frac{dV}{dt} + I = 0$ (assuming C = constant)

This equation is the basis for much theoretical electrophysiology

We link the current to the voltage via $I_s = g_s(V - V_s)$ of each species of ion s

ion-specific membrane conductance

The total current $I = \sum_s I_s$.

(just $V = IR$ and conductance is $\frac{1}{R}$)

Gates But what does g_s look like? This is not a constant – it depends on ~~the~~ ~~many~~ the fraction of gates that are available that are open, n. Then $g_s = n g_{s\max}$ ↑ conductivity when all gates are open

closed

open

closed gate $\underset{\beta(V)}{\overset{\alpha(V)}{\rightleftharpoons}}$ open gate

$\alpha(V)$, $\beta(V)$ depend on the voltage

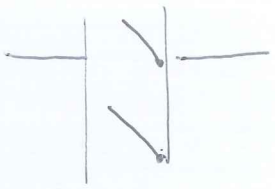
Law of mass action gives $\frac{dn}{dt} = \alpha(V)(1-n) - \beta(V)n$

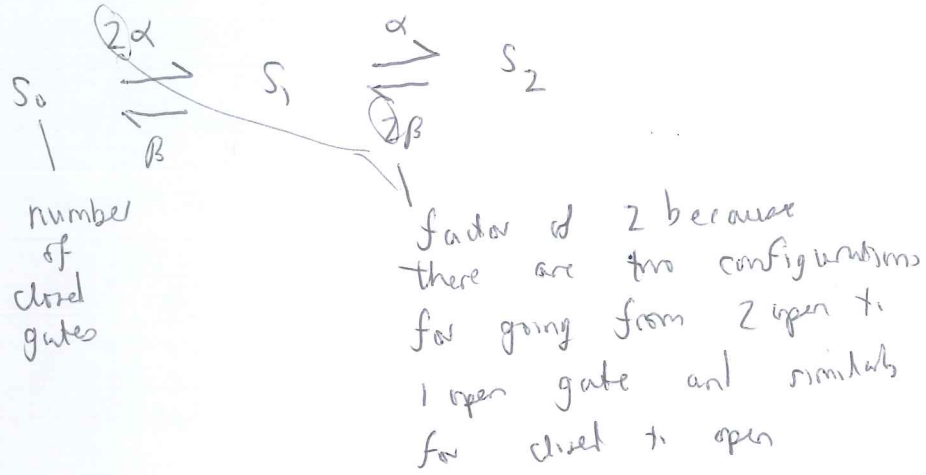
fraction of open gates

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

(where $n_\infty = \frac{\alpha(V)}{\tau(V)}$ and $\beta + \alpha = \frac{1}{\tau(V)}$)

You can also have multiple gates





Law of mass action gives $\frac{dS_1}{dt} = \beta S_1 - 2\alpha S_0$

$\frac{dS_1}{dt} = \alpha S_0 - 2\beta S_2$

and $\frac{dS_2}{dt}$ equation or just infer $S_0 + S_1 + S_2 = 1$ (conservation of gates)

We can reduce to one ODE by finding

Solution is $S_0 = (1-n)^2$, $S_1 = 2n(1-n)$, $S_2 = n^2$

where n satisfies $\frac{dn}{dt} = \alpha(1-n) - \beta n$ (i.e. the one-gate equation).

[Problem Sheet 2, question 1]

In this case the proportion of open channels is $S_2 = n^2$

so the conductivity in this case is $n^2 g_{max}$.

This result generalizes for N gates with a conductivity of $n^N g_{max}$

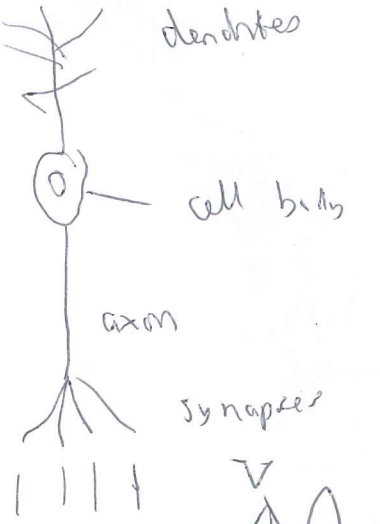
You can also look at the case of non-identical gates

You can also look at the case of non-identical gates – see lecture notes page 39 and problem sheet 2 question 3.1.

The Hodgkin-Huxley model

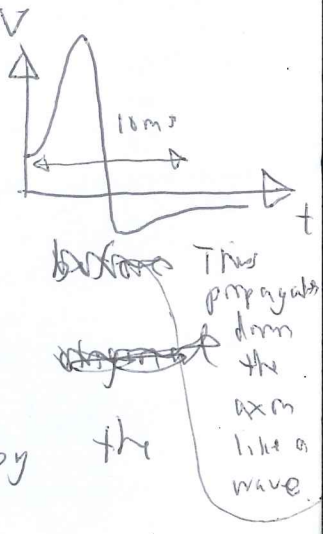
The nervous system is a communication system formed by nerve cells or neurons. Information is propagated along long cylindrical segments called axons by electrochemical signals.

Communication between cells occurs at junctions between synapses to the dendrites.

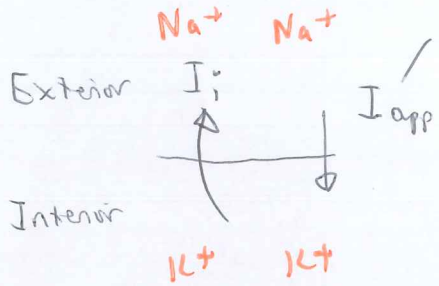


If a small current is applied for a short time then the membrane potential just returns to its resting potential when the current is removed.

But for a sufficiently high current the membrane potential undergoes a large excursion – an action potential – before returning to its resting value. Signals are transmitted by the propagation of these action potentials down an axon. Later on we will look at the spatial propagation but for now we



will look at a spatially independent model. This can be achieved in practice by inserting an electrode along the axon to spread the current out - this is called the space clamp technique.



Apply a current I_{app} to the axon and observe the ionic current that comes out, I_i.

Our earlier equation

$$C \frac{dV}{dt} + I = 0 \qquad (1)$$

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

C_m: Capacitance of the membrane

Potassium flow

Recall we have ~~[illegible]~~

our link between V and I_i: $I_i = g_s (V - V_s)$

and $g_s = \bar{n}^N g_{s\max}$ where N = number of gates

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

($g_{s,\max}$)

$g_s = n^4 g_{Na}$

What we find is that the potassium conductance may be controlled by this model when $N = 4$. Note, however that this is not due to four gates but just an experimental fit.

n is called the potassium activation

For the sodium conductance, ~~a model of the form~~ turns the sodium current on and another which turns it off. This can be described by

$$g_{Na} = \bar{g}_{Na} m^3 h$$

($\bar{g}_{Na}$ = $g_{Na,max}$)

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

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

Again, these powers are experimental fit rather than related to gates

is appropriate. This is like two gates

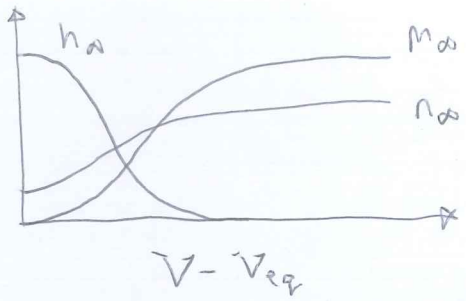
m is called the sodium activation
h is called the sodium inactivation.

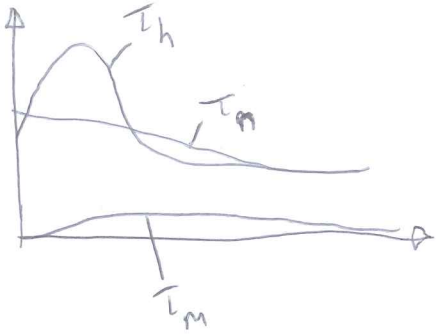
The Hodgkin-Huxley model for the current is then

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

(This model also comprises ~~equations~~ the DPE system (1)-(4).

What does the potential do?





1) Apply a current I_{app}.

2) V rises due to the current (equation ①) (graph 2)

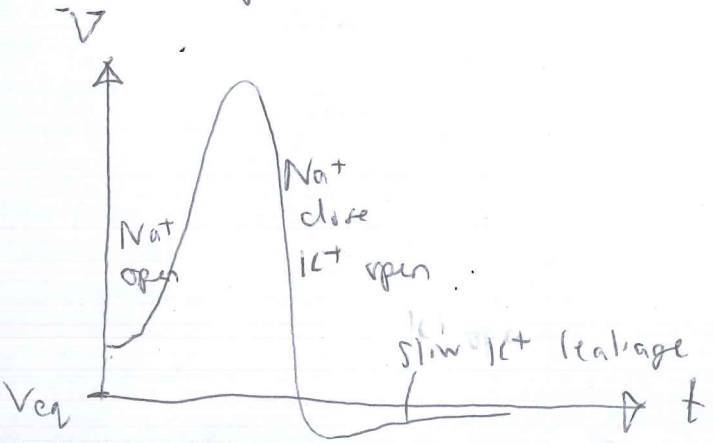
3) τ_m is small so m rises quickly (equation ③)

⇒ Na^+ floods into the axon from outside ($I_{Na} = m^3 h g_{Na}$)

4) This causes even more of a potential difference, causing m_∞ to rise (graph 1), which causes even more of a potential difference.

5) h_∞ falls causing Na^+ flow to slow as g_{Na} falls (gate closes)
n_∞ rises causing K^+ to flow out of the axon (g_K rises - gate opens) $g_K = n g_{Na}$
This causes an overshoot past V_{eq}

6) Slow leakage of K^+ back into the axon causes the system to go back to equilibrium.



The membrane is excitable

The equilibrium is a steady state but a large enough perturbation (which in practice is not too large) causes the potential to undergo an excursion - the action potential.

At the moment this is a four dimensional system (V, n, m, h described by equations ① - ④). This is not easy to analyse but we can reduce this to a two-dimensional system called the Fitzhugh-Nagumo equations. Model

The FitzHugh Nagumo model

Assumptions: 1) τ_m is small so $m \approx m_\infty(V)$
(m rapidly reaches its quasistatic value, using ③)

2) $\tau_n = \tau_h$ (not perfect, see graph 2, but a decent approximation).

3) $n_\infty + h_\infty =$ constant, $\bar{h}$ (motivated by graph 1).

$\Rightarrow n + h = \bar{h}$ (using ② and ④).

Thus reduces the Hodgkin-Huxley model (four ODEs for V, n, m, h) to the two-dimensional system for V and n:

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

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

See problem sheet 2 for this.

$$\frac{d}{dt}(n+h) = \bar{h} - (n+h)$$

$$\Rightarrow (n+h) = \bar{h} + ce^{-t}$$

This system is true for all time & eventually this settles to $n + h = \bar{h}$.

Non-dimensionalization

$$t = \tau_n t'$$

$$v = \frac{V - V_{eq}}{V_{Na} - V_{eq}}$$

V_{eq}: resting potential for Na^+

$$\Rightarrow \quad \frac{dn}{dt} = n_\infty(v) - n \qquad (1)$$

$$\varepsilon \frac{dv}{dt} = I^* - g(v, n) \qquad (2)$$

$$I^* = \frac{I_{app}}{g_{Na} V_{Na}} \qquad V_{1/2}^* = \frac{-V_{1/2}}{V_{Na}}$$

$$\gamma_K = \frac{g_K}{g_{Na}} \qquad V_L^* = \frac{V_L}{V_{Na}}$$

$$\gamma_L = \frac{g_L}{g_{Na}} \qquad \varepsilon = \frac{C_m}{g_{Na} \tau_n}$$

$$g(v, n) = \gamma_K (v + V_K^*) n^4 + \gamma_L (v - V_L^*) - (1 - v)(\bar{h} - n) m^3(v)$$

Key point: $\varepsilon << 1$

This is why you non-dimensionalize - to see the relative parameter sizes

Key point: $\varepsilon << 1$, so v & n quickly reaches quasistatic equilibrium in (2).

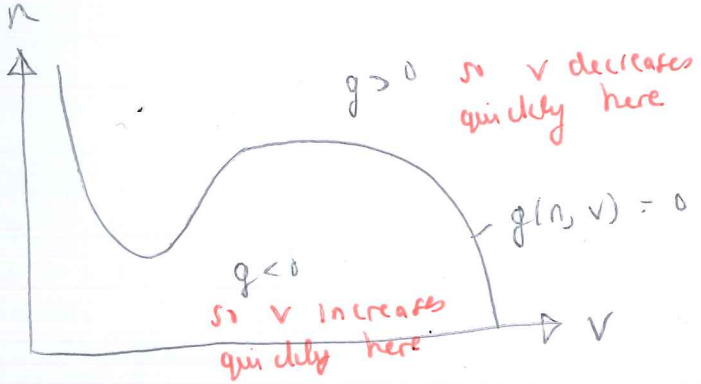
and $\gamma_L << 1$ so $g(v, n)$ simplifies

Phase plane analysis

start by considering the case $I^* = 0$.

Setting $\varepsilon = \gamma_L = 0$ in (2) gives $\frac{n^4}{\bar{h} - n} = \frac{(1 - v) m^3(v)}{\gamma_K (v + V_K^*)}$

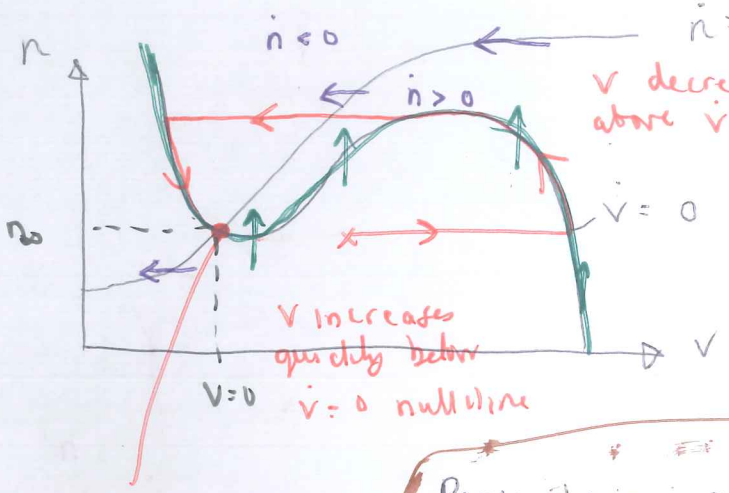
an algebraic relationship between n and v



Since $\varepsilon << 1$ we know that the system quickly jumps onto the nullcline

Note that including the γ_L term doesn't change these qualitative features

Now we just need to add the $\dot{n} = 0$ nullcline ($n = n_\infty(V)$)



Reaches this (unique) fixed point.

Proved below so don't need to say this

Perturbing around the fixed point we see that trajectories spiral around so the fixed point is a spiral.

Although this fixed point is stable, only a small increase in V will lead to a large excursion - this is the action potential again. If we plotted V versus t we would obtain the graph we drew earlier.

Stability

Linearize near the fixed point

Fixed point is $\dot{n} = 0$, $\dot{V} = 0$.

$\Rightarrow n = n_\infty$, $V = 0$

(By definition since V is the potential relative to the equilibrium)

Set $V = V$

$n = n_\infty + N$

and ODEs become

$$\frac{d}{dt}\begin{pmatrix} N \\ V \end{pmatrix} = \underbrace{\begin{pmatrix} -1 & \frac{dn_\infty}{dV} \\ -\frac{1}{\varepsilon}\frac{\partial g}{\partial n} & -\frac{1}{\varepsilon}\frac{\partial g}{\partial V} \end{pmatrix}}_{\underline{\underline{M}}} \begin{pmatrix} N \\ V \end{pmatrix}$$

Stability is given by $\det(\underline{\underline{M}})$ and $\mathrm{tr}(\underline{\underline{M}})$ / trace

$\det(\underline{\underline{M}}) < 0 \Rightarrow$ saddle

$\det(\underline{\underline{M}}) > 0$ and $\mathrm{tr}(\underline{\underline{M}}) < 0 \Rightarrow$ node or spiral

(See next page for why.)

Trace and determinant method

Eigenvalues can be written as

$$\lambda = \frac{\mathrm{Tr}(\underline{\underline{M}}) \pm \sqrt{(\mathrm{Tr}\,\underline{\underline{M}})^2 - 4\det(\underline{\underline{M}})}}{2}$$

We have $\det(\underline{\underline{M}}) = \frac{1}{\varepsilon}\left(\frac{\partial g}{\partial v}\Big|_{n=n^*} + \frac{\partial g}{\partial n}\Big|_{n=n^*} \frac{dn_\infty}{dv} \right)$

Now $\det(\underline{\underline{M}}) > 0$.

Proof

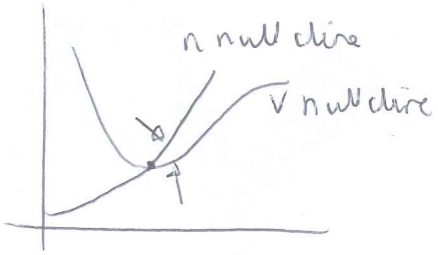
Now slope of n nullcline $= \frac{dn_\infty}{dv}$

Slope of v nullcline $= -\frac{\frac{\partial g}{\partial v}}{\frac{\partial g}{\partial n}}$ since $g(v, n) = 0$.

$$\frac{\partial g}{\partial n}\frac{dn}{dv} + \frac{\partial g}{\partial v} = 0.$$

$$\frac{dn}{dv} = -\frac{\frac{\partial g}{\partial v}}{\frac{\partial g}{\partial n}}$$

from graph, slope of n nullcline $>$ slope of v nullcline



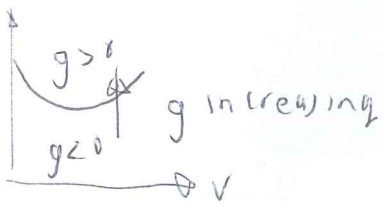
$\frac{dn_\infty}{dv} \to -\frac{\frac{\partial g}{\partial v}}{\frac{\partial g}{\partial n}}$

$\det(\underline{\underline{M}}) > 0$

$\mathrm{tr}(\underline{\underline{M}}) = -1 - \frac{1}{\varepsilon}\frac{\partial g}{\partial v}\Big|_{n=n^*}$

fixed point v stable if $\mathrm{tr}(\underline{\underline{M}}) < 0 \Rightarrow \frac{\partial g}{\partial v} > -\varepsilon$

$\frac{\partial g}{\partial v} > 0$ because of picture



fixed point v stable

Although the fixed point is stable, a small increase in v will lead to a large excursion - this is the action potential again. If we plotted v versus t we would obtain the graph we drew earlier.

Limit cycles

If we apply a current then this will push us off the equilibrium point and send us round the trajectory before starting the process all over again - we only need a bit of energy to achieve this.

Slightly different to a conventional limit cycle because in this case you need the giving a bit of energy to kick it round the cycle

The FitzHugh-Nagumo model is the reduction of the four dimensional Hodgkin-Huxley model to a two-dimensional system.

The FitzHugh-Nagumo equations are an analytically similar pair of equations that have the same behaviour

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

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

$$f(v) = v(v-a)(1-v) \quad \text{for } a < 1$$

FitzHugh-Nagumo equations

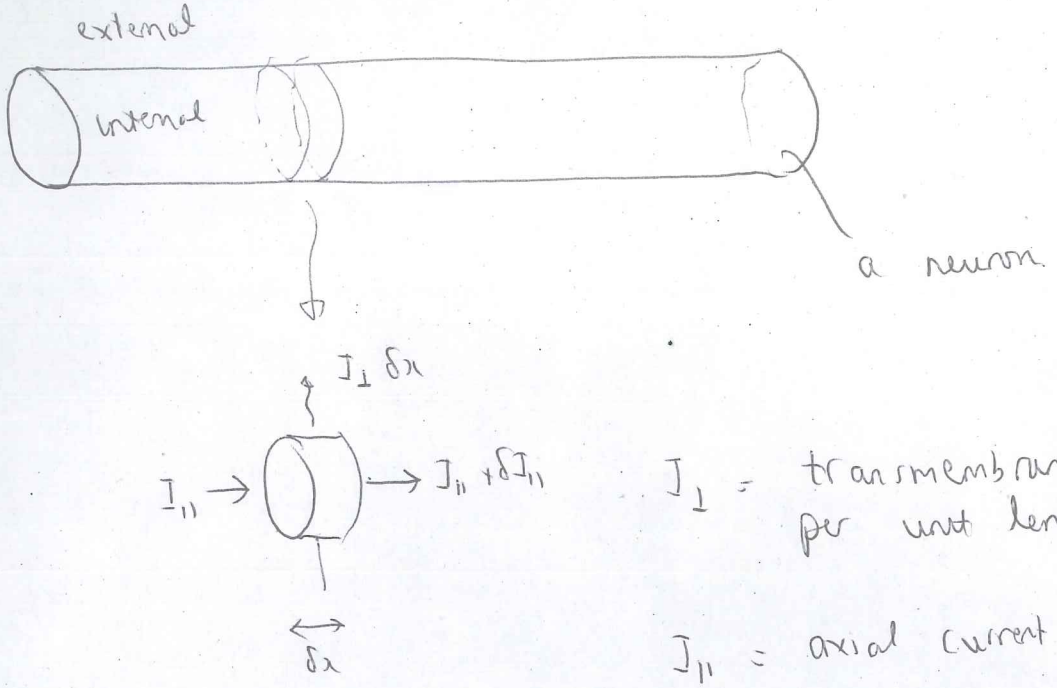
$$\varepsilon \dot{v} = I^{*} - g(v,n)$$

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

FitzHugh-Nagumo model

Wave propagation in neurons

We now explore spatial dependence of the Hodgkin-Huxley model.



$I_\perp$ = transmembrane current per unit length

$I_\parallel$ = axial current

R = axial resistance

C = capacitance per unit length

In a segment δx the total charge is $CV\,\delta x$

Charge conservation:

$$\frac{\partial}{\partial t}(CV\,\delta x) = -I_\perp \delta x + I_\parallel - (I_\parallel + \delta I_\parallel)$$

current lost through walls | current in left | current out right

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

assuming C = constant

$$C\frac{\partial V}{\partial t} = -I_\perp - \frac{\partial I_\parallel}{\partial x} \quad (*)$$

$-\delta V = I_{\parallel} R \delta x$ Definition of resistance (ie $\Delta V = I_{\parallel} R_{total}$)

$\Rightarrow \frac{\partial V}{\partial x} = -I_{\parallel} R.$

So in (*), $$\boxed{c\frac{\partial V}{\partial t} = -I_{\perp} + \frac{1}{R}\frac{\partial^2 V}{\partial x^2}} \quad (\dagger)$$

This is called the telegraph equation.
or the cable equation.

If the neuron ~~wave~~ perimeter is $p = \pi d$ then $I_{\perp} = p(\underbrace{I_i - I_{app}}_{\text{current per unit area between inside and outside as defined earlier}})$

(d: diameter)

and $C = p\, c_m$

(c_m: ~~actual capac~~ capacitance per unit area.)

If R_c = resistivity of medium then $R = \frac{R_c}{A}$

where $A = \frac{1}{4}\pi d^2$ is the neuron cross-sectional area.

In (†) this gives $c_m \frac{\partial V}{\partial t} = I_{app} - I_i + \frac{d}{4R_c}\frac{\partial^2 V}{\partial x^2}$

Non-dimensionalization

$$V = \frac{V - V_{eq}}{V_{Na} - V_{eq}}, \qquad I_1 = g_{Na}(V_{Na} - V_{eq}) \cdot g(n, V), \qquad x = l\hat{x}$$

$$t = \tau_n \hat{t}$$

where l is to be chosen later. (same as earlier non-dimensionalization)

This gives

$$\varepsilon \frac{\partial V}{\partial t} = I^+ - g(n, V) + \varepsilon^2 \frac{\partial^2 V}{\partial x^2}$$

$$\frac{\partial n}{\partial t} = n_\infty(V) - n.$$

(see problem sheet 2 for derivation of this)

This is the space dependent version of the FitzHugh-Nagumo ~~Hodgkin-Huxley~~ model - it's the same b.w pair with a $\frac{\partial^2 V}{\partial x^2}$ term.

Let's analyze action potentials in this case. We could analyze the equations above but it is easier to analyze the space-dependent FitzHugh-Nagumo equations (the equations that display the same qualitative behaviour but are easier to analyze):

$$\varepsilon \frac{\partial v}{\partial t} = f(v) - w + \varepsilon^2 \frac{\partial^2 v}{\partial x^2}$$

$$\frac{\partial w}{\partial t} = \gamma v - w.$$

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

and γ large enough that $(0,0)$ is the unique steady state.

Let's look for a travelling wave solution so we can find a wave travelling down the axon:

$$v = v(\xi), \quad w = w(\xi), \quad \xi = ct - x, \quad c > 0.$$

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

$$c w' = \gamma v - w.$$

with $v, w \to 0$ as $\xi \to \pm\infty$.

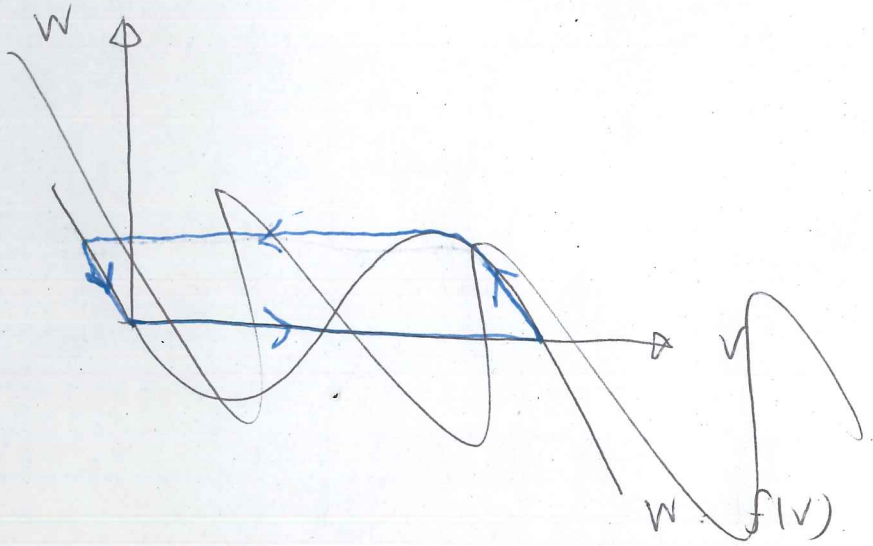
It is harder to do phase plane analysis now because the phase plane is three dimensional rather than two:

v, w, v'.

However, $\varepsilon \ll 1$ so this allows us to make progress without having to consider the three-dimensional phase space.

If we ignore the ε^2 then we have a picture like before:

There are four different regimes of behaviour.



i) To begin with, if we are not on the curve $w = f(v)$ then we quickly move there because of

$$\varepsilon v' = \underbrace{f(v) - w}_{\neq 0} + \varepsilon^2 v''$$

$\varepsilon v'$: fast motion; $f(v) - w$: just like before (ignoring higher order ε^2 term); $\varepsilon^2 v''$: higher order correction

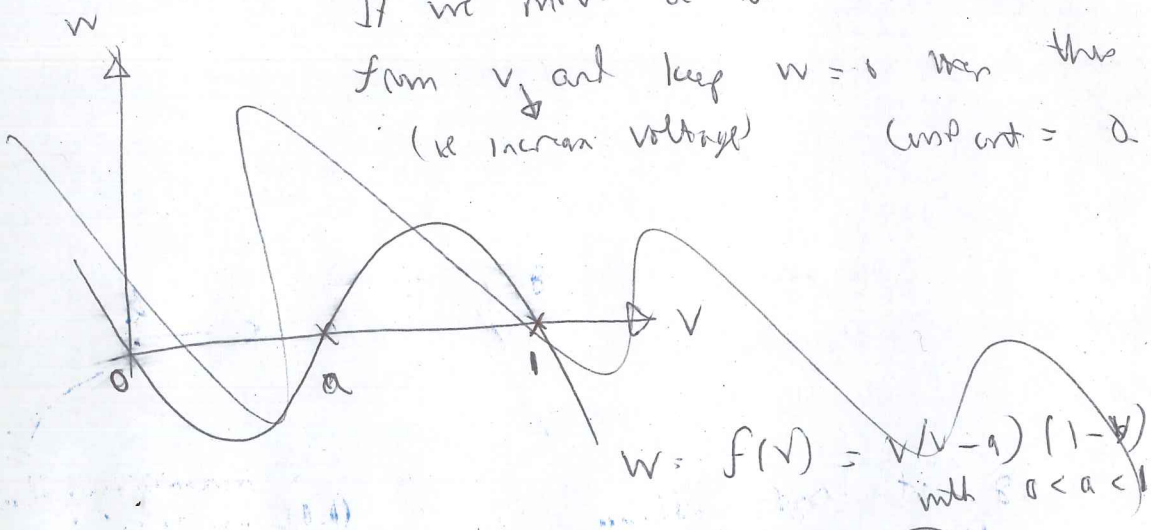
ii) In this region, things happen over a fast ξ scale. This suggests rescaling $\xi = \varepsilon \zeta$;

$$c \frac{dv}{d\zeta} = f(v) - w + \frac{d^2 v}{d\zeta^2}$$

and in this region, considering the other equation,

$$w' = \gamma v - w \Rightarrow c \frac{dw}{d\zeta} = \varepsilon(\gamma v - w) \Rightarrow w = \text{constant}.$$

If we move a little bit away from v_1 and keep $w = 1$ (ie increase voltage) then this constant $= a$



$w = f(v) = v(v-a)(1-v)$ with $0 < a < 1$

Fixed points of this rescaled system are $v = 0, a, 1$

Stability analysis (ie linearisation) shows that $v = 0, 1$ are saddles and $v = a$ is an unstable node or spiral (see lecture notes)

Now set $\frac{dv}{ds} = u$

Then our phase plane is $v' = u$

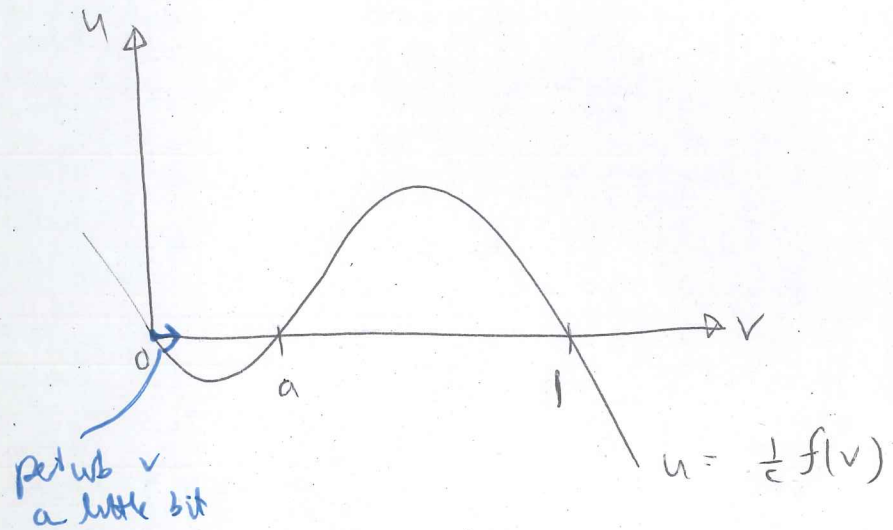
$u' = cu - f(v)$

$\| \quad v(v-a)(1-v)$

$0<a<1.$

~~Now only one to watch is~~

Fixed points of this reduced system are $u=0$, $v = 0, a, 1$



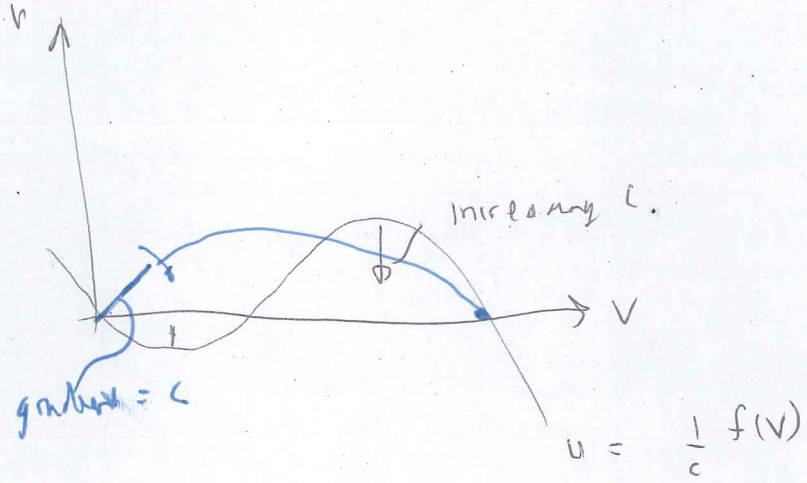
Linear stability analysis shows that $v=0,1$ are saddles and $v=a$ is an unstable node. So we are interested in the trajectory in the phase plane that goes from $v=0$ to $v=1$ fixed points (to ~~repeat~~ replicate the action potential we had in the space-clamped case where we had the fast behaviour jumping off the nullcline)

There is only one value of c that achieves this.

Now

$$\frac{du}{dv} = \frac{u'}{v'} = \frac{(u - f(v))}{u} = c \quad \text{at } v = 0$$ so gradient of

trajectory is c



Like a shooting problem.

This is how c is selected - this means there is a unique wave speed for the travelling wave.

(from $u' = (u - f(v))$)

(ii) The, once we land on the (u) nullcline $u = \frac{f(v)}{c}$ we slowly move up this. On this, $v' = \frac{f(v)}{\varepsilon}$

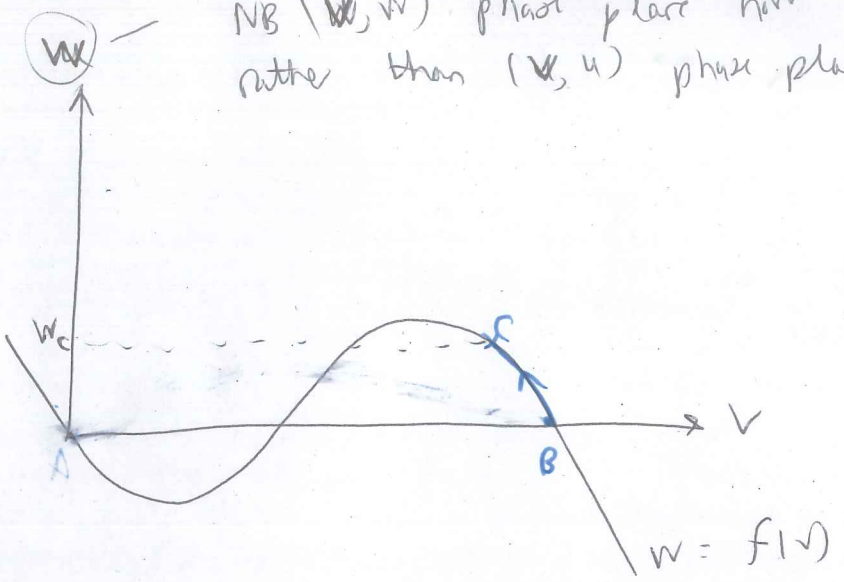
$$\varepsilon c v' = f(v) - w + \varepsilon^2 v''$$

$$\boxed{cw' = \gamma v - w} \quad (2)$$

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

$$\Rightarrow \boxed{w \approx f(v)} \quad (1)$$

This takes us up the curve $u = \frac{f(v)}{c}$ until we reach $w = \gamma v$ (the equilibrium of (2))



Note that C is not the maximum of $W = f(V)$ unlike in the space-clamped model. Now C is where $W = \gamma V$. We need to find what this V value (V_c) is, which we will find out in the next stage.

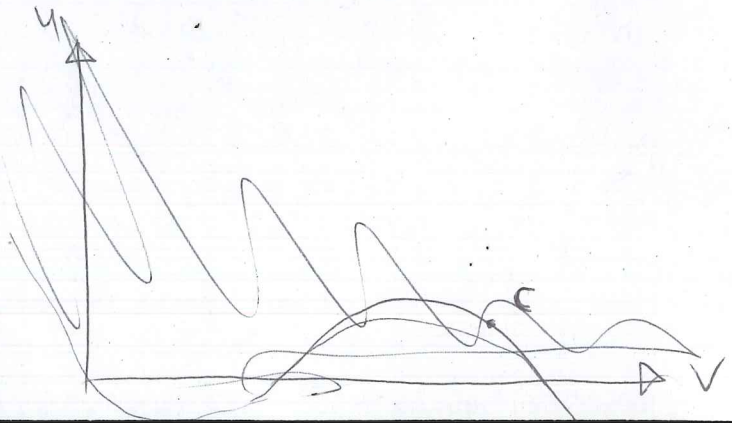
(iii). Once we have reached this point we enter another fast phase. Again rescale $\tilde{t} = \varepsilon t$ to capture this but this time $W = W_c$ (a non-zero constant). Then the system is

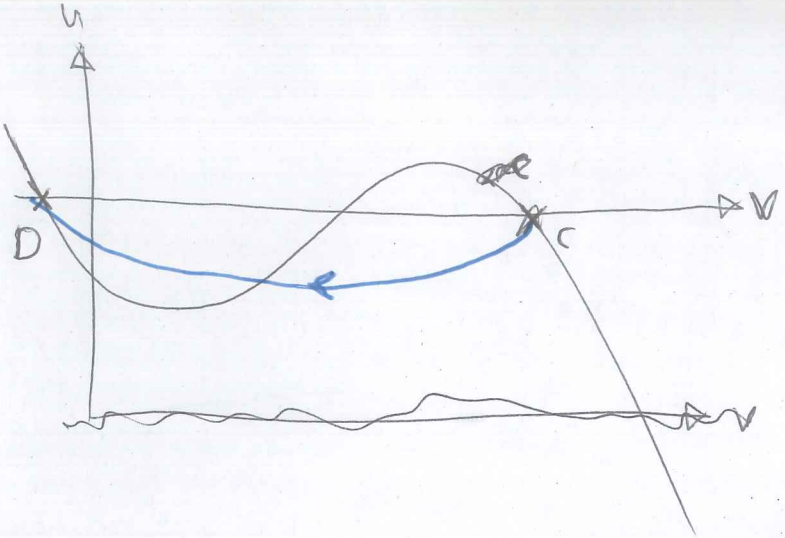
$$cV' = f(V) - W_c + V''$$

Which we need to find out what value it is

$$\Rightarrow \quad V' = u$$

$$u' = cu - f(V) + W_c$$



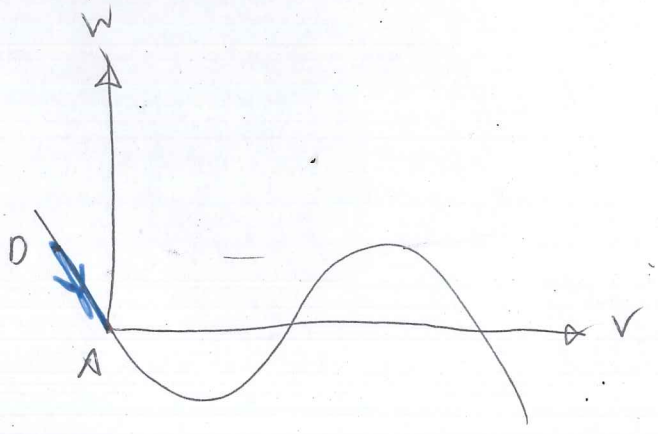


$$u = \frac{f(v)}{c} - \frac{w_c}{c}$$

(same curve as before just shifted down)

C and D are saddles and this time we have a trajectory that takes us from C to D. This time, to make sure these trajectories join up, it is we that we need to choose c correctly (just like we had to choose c correctly in phase (i))

Finally, a slow phase takes us back to A again on the (v, w) phase plane:

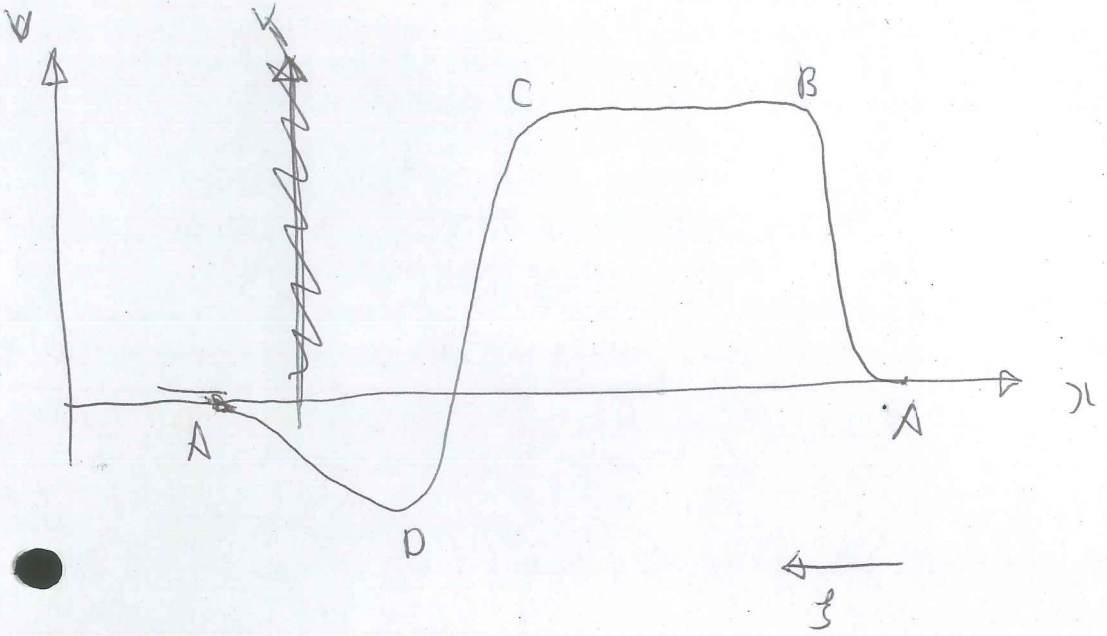


Again, on here,

$w \approx f(v)$

$w' = \gamma v - w$ (< 0 so motion is downwards, back to A)

The overall picture is a travelling wave that moves down the axis and looks like this:



Read from right to left

Calcium dynamics

Calcium (Ca^{2+}) is important in muscle dynamics and cell signalling.

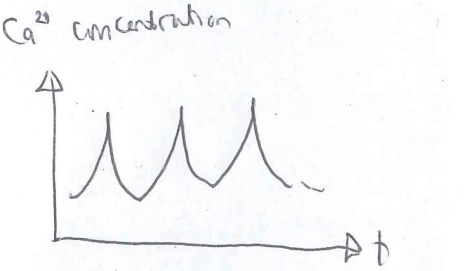
Ca^{2+} is stored in a cell in a bones and released by hormonal stimulation. The internal store is called the sarcoplasmic reticulum. It releases Ca^{2+} via calcium induced calcium release.

Extracellular Ca^{2+} concentrations are higher than intracellular concentrations so Ca^{2+} must be pumped out. The intracellular fluid matrix is called the sarcoplasm.

Muscle cells are bundles (fascicules) of muscle fibres (cells) each of which contains arrays of filament structures (microfibrils) which contract under the action of Ca^{2+}.

Under stimulation from a nerve cell, an action potential is triggered and propagates along the fibre as we have seen last lecture. Na^+ floods in and this allows Ca^{2+} in too.

The release of Ca^{2+} is quite spiky:



Can we derive a mathematical model in steady state for muscle contraction with a low Ca^{2+} concentration that is excitable under stimulus?

The two-pool model

We want to derive a model to explain how Ca^{2+} moves between the sarcoplasmic reticulum (the store) and the sarcoplasm.

c = concentration of Ca^{2+} in the sarcoplasm

c_s = concentration of Ca^{2+} in the sarcoplasmic reticulum (SR)

J_+ = rate of take-up of Ca^{2+} by the sarcoplasmic reticulum (SR) (by receptors) [active uptake]

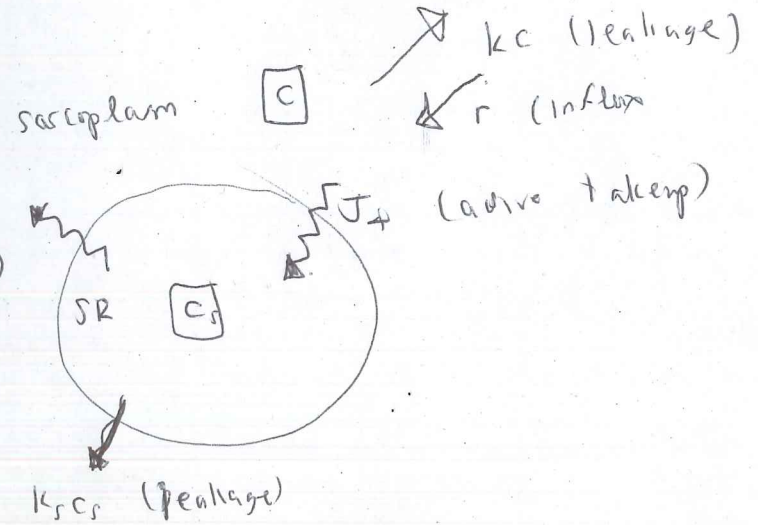
J_- = rate at which the SR releases its internal store (calcium-induced calcium release) [active release]

r = influx of Ca^{2+} into the sarcoplasm, because of an applied stimulus. from the outside world

~~k_c = rate of leakage of Ca^{2+} from sarcoplasm~~ (passive - proportional to concentration)

$k_s c_s$ = rate of leakage of Ca^{2+} from SR (passive - proportional to concentration) into the sarcoplasm

k_c = rate of leakage of Ca^{2+} from sarcoplasm to outside world (no path into the SR) (passive - proportional to concentration)



$$\frac{dc_s}{dt} = J_+ - J_- - k_c c_s \stackrel{\text{def}}{=} F$$

$$\frac{dc}{dt} = r - kc - (J_+ - J_- - k_s c_s)$$

$$= r - kc - F$$

We choose $J_+ = \dfrac{V_1 c^n}{K_1^n + c^n}$

NB V_1 not a voltage - this is a concentration rate

V_1, K_1, n are numbers.

This is a Hill function

There bits are important

$$J_- = \frac{V_2 c_s^m}{K_2^m + c_s^m} \left(\frac{c^p}{K_s^p + c^p} \right)$$

This is the important bit that causes the calcium induced calcium release

Non-dimensionalisation

$c = K_1 u, \quad c_s = K_2 v, \quad t = \frac{1}{k}\hat{t}, \quad F = V_2 f$

$$\frac{du}{dt} = \nu - u - \frac{\gamma}{\varepsilon} f(u,v)$$

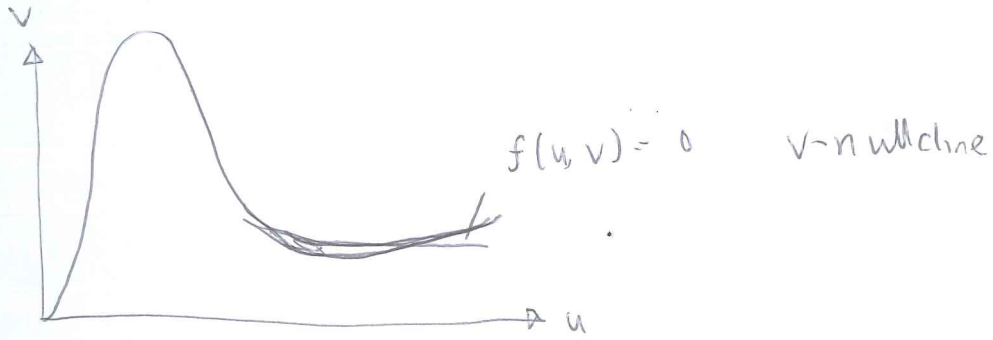
$$\frac{dv}{dt} = \frac{1}{\varepsilon} f(u,v)$$

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

$\nu = \frac{r}{kK_1}, \quad \gamma = \frac{K_2}{K_1}, \quad \varepsilon = \frac{K_1 K_2 \ll 1}{V_2}, \quad \alpha = \frac{K_3}{K_1}, \quad \beta = \frac{V_1}{V_2}, \quad \delta = \frac{K_s K_2 \ll 1}{V_2}$

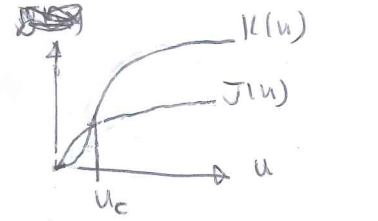
This is a two-dimensional system (u, v) so we may use phase-plane analysis

$\varepsilon \ll 1$ means that we quickly jump onto the v-nullcline, $f(u, v) = 0$

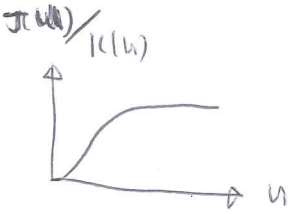


To plot this curve

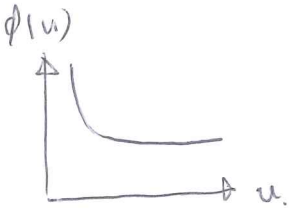
1) $\delta \ll 1$ so ignoring the δ term in $f(u, v)$ gives



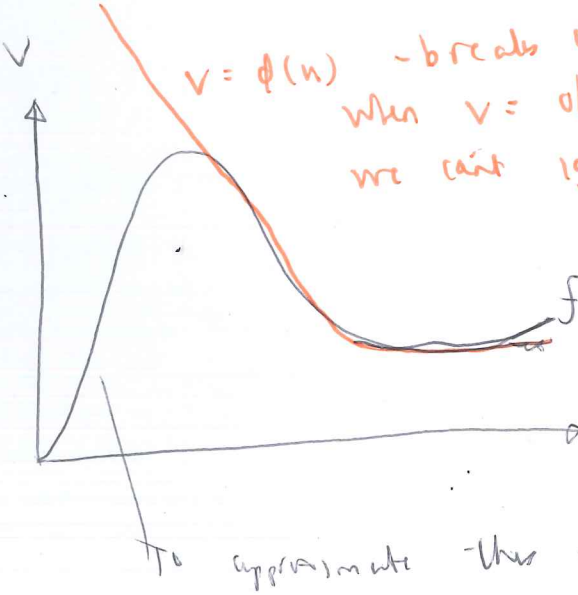
$$\frac{v_m}{1+v^m} = \frac{\frac{\beta u^n}{1+u^n}}{\frac{u^p}{\alpha^p + u^p}} \quad \text{def} \quad \frac{J(u)}{K(u)}$$



$$v = \left[\frac{J(u)}{K(u) - J(u)}\right]^{1/m} = \phi(u)$$

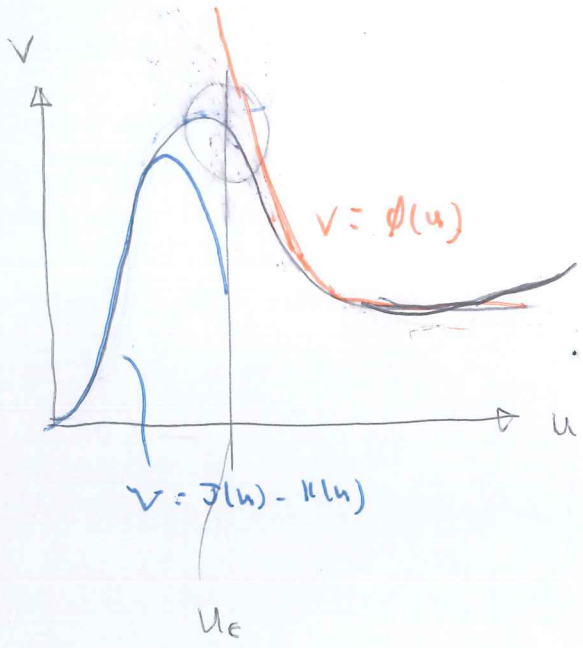


Don't do this in the lecture - This is a problem sheet question.



2) To get the bit when $V = O(\frac{1}{\delta})$, set $v = \frac{V}{\delta}$

Then $f(u,v) = 0 \Rightarrow V = J(u) - K(u)$



Don't do this in the lecture - there is a problem sheet question.

There is a matching region where neither are valid.

Here, we set $u = u_c + \delta^{m/(m+1)} U$,

$$V = \frac{1}{\delta^{1/(m+1)}} W$$

This approximation matches to the inner (blue) and outer (orange) regions.

Problem Sheet exercise?

Now let's look at the dynamics. ~~The system relaxes~~ v rapidly approaches the v-nullcline that we have found, because of the ε in the $\frac{dv}{dt}$ equation. But now if we look at the $\frac{du}{dt}$ equation we have $\frac{du}{dt} = \mu - u - \frac{\gamma}{\varepsilon} f(u,v)$

↑ an ε here

So we don't just have u = constant unlike in the previous cases. Thus time we note that

$$\frac{du}{dt} + \gamma \frac{dv}{dt} = \mu - u$$

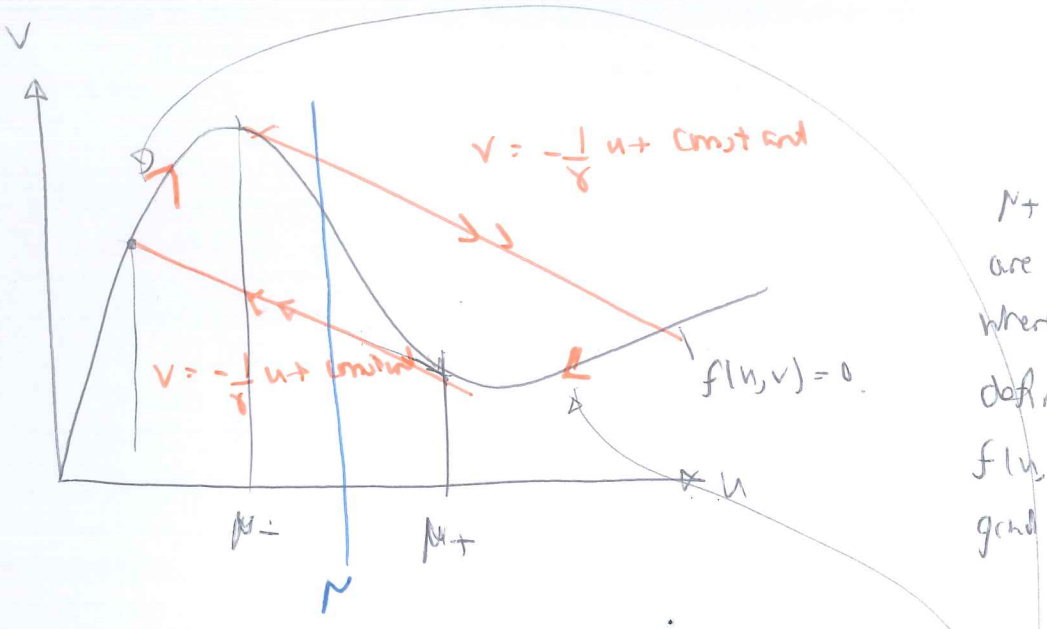
$$\varepsilon \frac{dv}{dt} = f(u,v),$$

So on the fast timescale ($t = \varepsilon T$) we have $\frac{dv}{dT} = f(u,v)$ giving the movement of v to the v-nullcline and $\frac{du}{dT} + \gamma \frac{dv}{dT} = \varepsilon(\mu - u)$

$$\Rightarrow u + \gamma v = \text{constant}$$

So we move to the v-nullcline along the line

$$v = \frac{\text{constant} - u}{\gamma}$$



N_+ and N_- are the places where the curve defined by $f(u,v) = 0$ has gradient $-\frac{1}{\gamma}$

Case (i) $N_- < N < N_+$

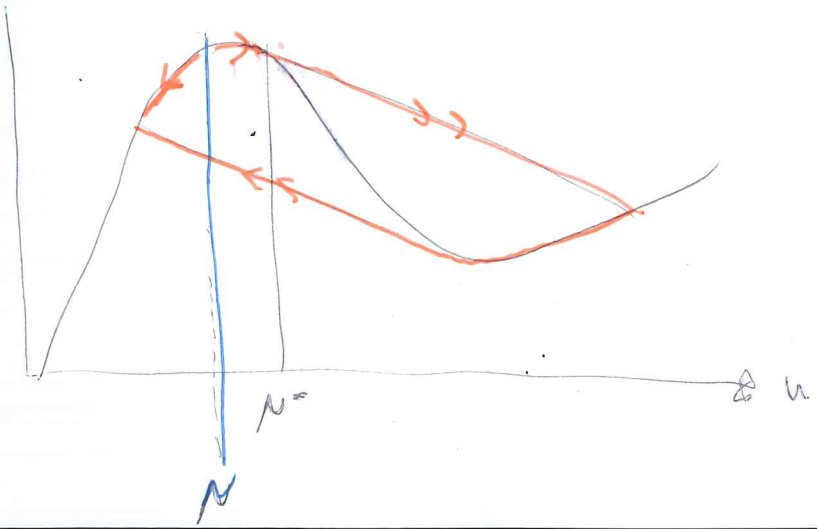
Then $\frac{d}{dt}(u + \gamma v) = N - u$ < 0 when $u > N_+$

> 0 when $u < N_-$

This leads to self-sustained or relaxation oscillations

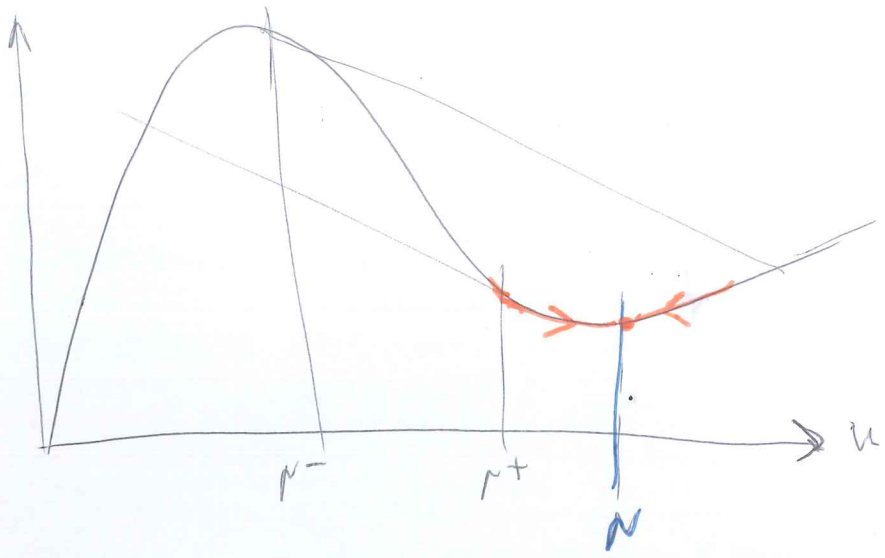
Case (ii) $N < N_-$

Then $\frac{d}{dt}(u + \gamma v) = N - u$ > 0 when $u < N_-$



Need a bit of excitation to get an excursion - a muscle contraction

Case (iii) $N > N_+$



$$\frac{d}{dt}(u + \gamma v) = N - u$$

Concentration of Ca^{2+} stays high always - cramp and rigor mortis.

Wave propagation

We have so far seen how an excitable steady state can (diffusion) and spatial variations can lead to travelling solitary waves (Hodgkin-Huxley)

(diffusion)

If you have periodic solutions and spatial variation this can lead to periodic travelling waves. These have been observed in Xenopus oocytes. (sub-stratum frog) (eggs)

Let's see if we can model this by adding in spatial dependence (diffusion) into our two-pool model:

$$u_t + \gamma v_t = f - u + D u_{xx}$$

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

Same model as before plus this extra term

Diffusion of Ca^{2+} in the sarcoplasm

$$D = \frac{\delta}{l^2 k}$$

δ: Diffusion coefficient of Ca^{2+} in the sarcoplasm

l: Length scale to be determined

k: Leakage rate

Define l so that $D = \varepsilon$ to give an interesting (and relevant) balance

This is similar to the FitzHugh-Nagumo equations with diffusion except that time the diffusion term is in the slow equation rather than the fast one.

Seek travelling wave solutions: $u = u(\xi)$, $v = v(\xi)$, $\xi = x + st$ $\quad s$ = wave speed.

$$\Rightarrow \quad s(u' + \gamma v') = \mu - u + \varepsilon u'' \qquad (1)$$

$$\varepsilon s v' = f(u, v). \qquad (2)$$

Now we follow the same analysis that we did for FitzHugh-Nagumo except now we are looking for periodic solutions in ξ rather than a solitary wave.

~~First look at the fast motion by~~

As before, (2) tells us that we quickly move onto the v nullcline $f(u, v) = 0$.

Rescale $\xi = \varepsilon X$ to see how we get there. This gives

$$s(u' + \gamma v') = u'' \quad (3) \qquad \left(' = \frac{d}{dX} \right)$$

$$sv' = f(u, v) \quad (4) \qquad \text{(to leading order in } \varepsilon)$$

Integrate (3) $\Rightarrow$ $\quad u' = s[u - u_0 + \gamma(v - v_0)]$

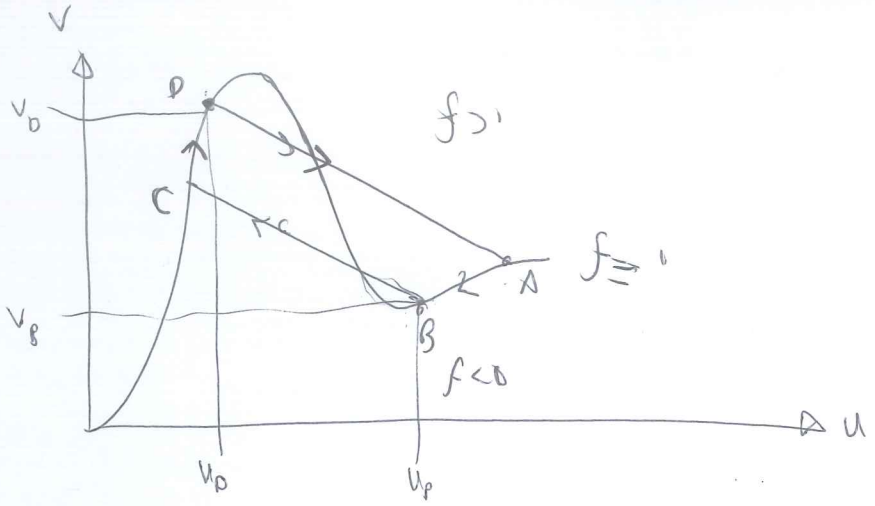
Where $u = u_0$, $v = v_0$ at the place where $u' = 0$ call this point P.

Now let's shift the origin to (u_0, v_0):

$u = u_0 + U$, $\quad v = v_0 + V$.

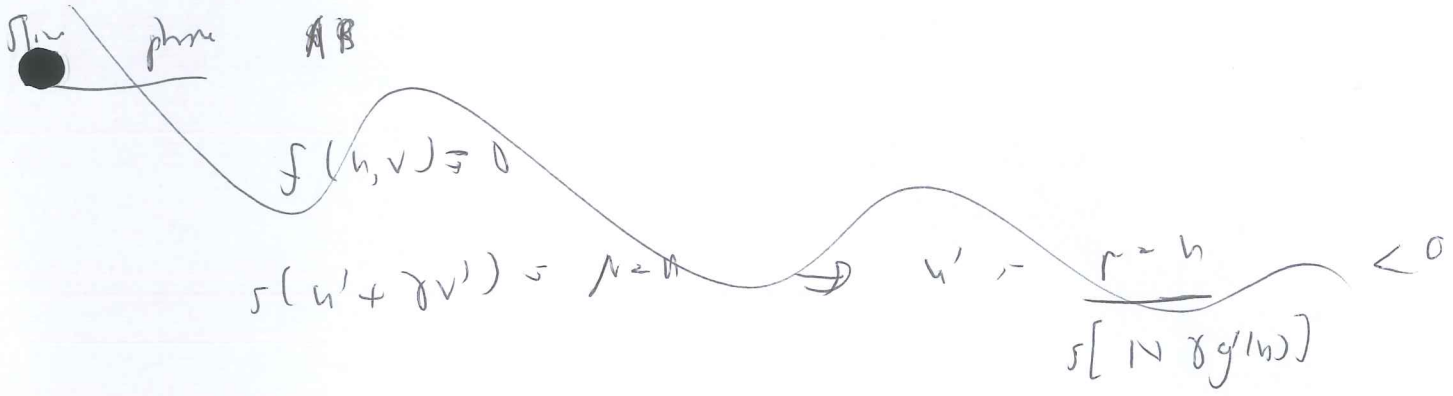
Then we have $\quad U' = s[U + \gamma V]$,

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



Hypothesized phase plane

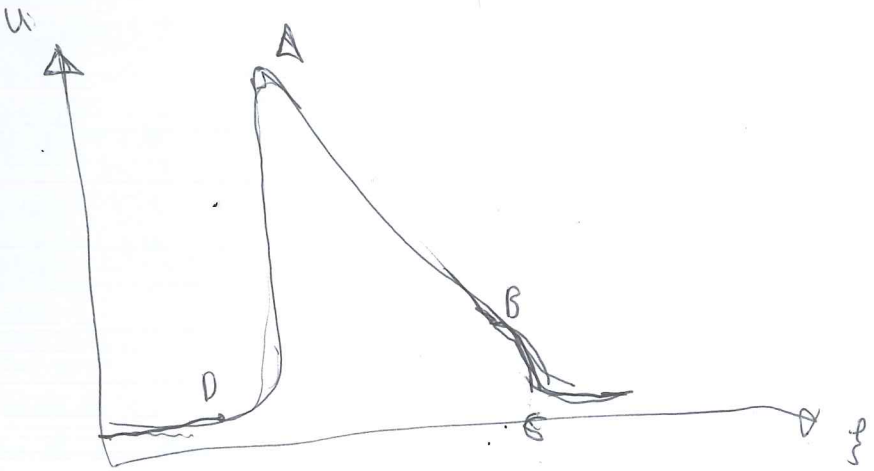
We will prove why N looks like this but good to know what we are shooting for.



the singular points

We don't know where $A(u_D, v_D)$ and (u_B, v_B) are and need to find them as part of the solution.

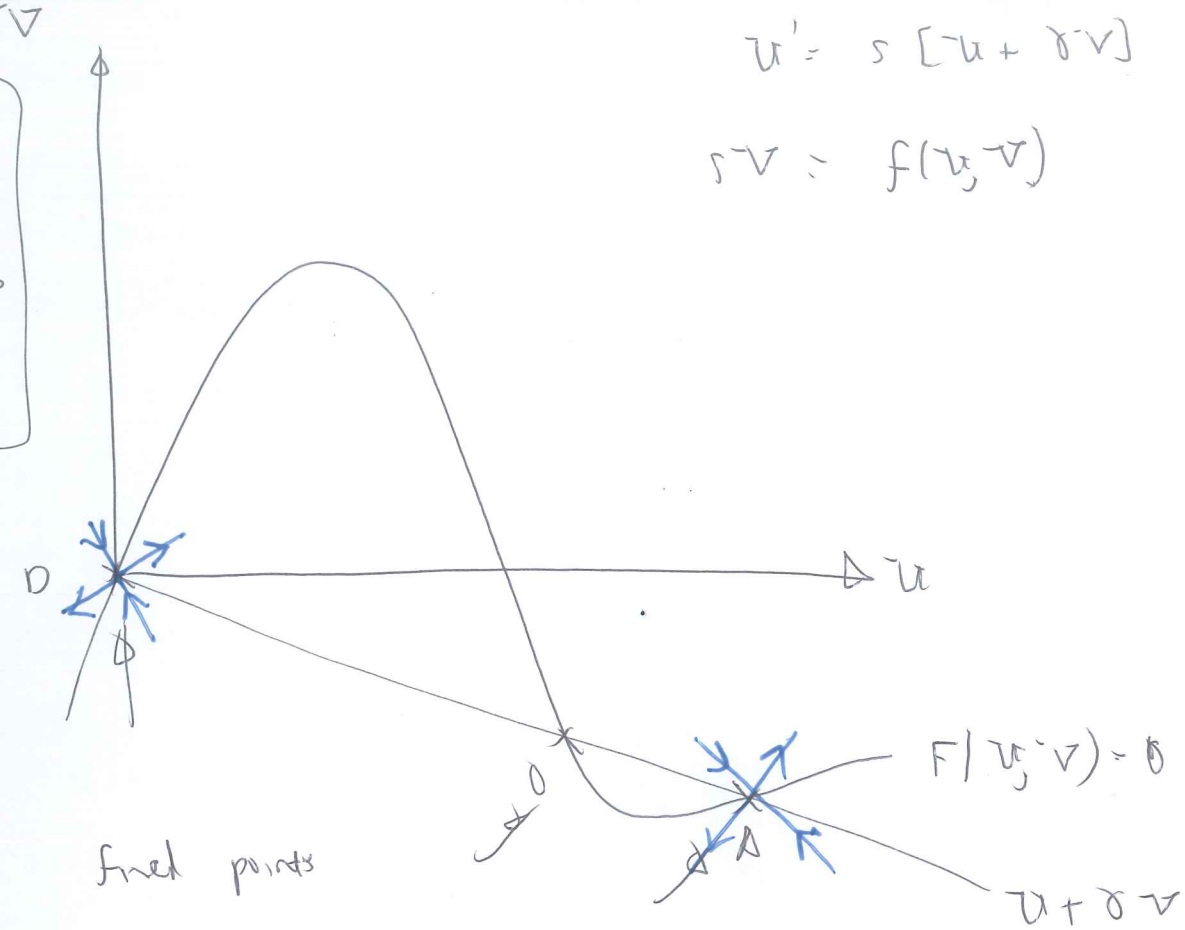
Hypothesized associated wave (which repeats periodically)



$$u' = s[-u + \gamma v]$$

$$s = f(u, v)$$

D and A are fixed points of the u, v system



fixed points

Fixed points: $u + \gamma v = 0$

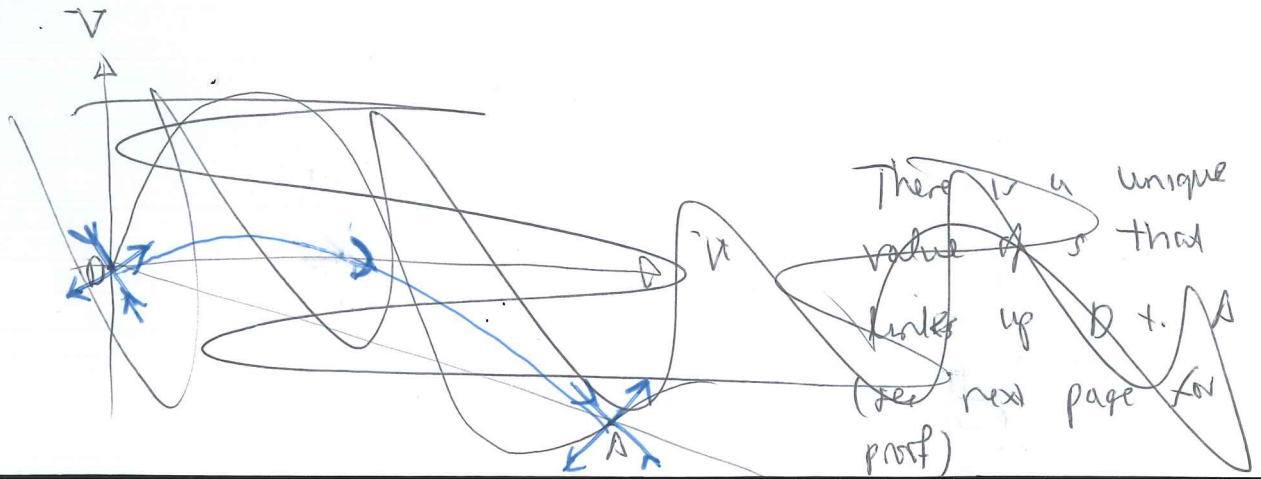
$f(u, v) = 0$

A and D are saddles

0 is an unstable node or focus

} Can be shown using standard linear stability analysis

Next step is to build up D and A:

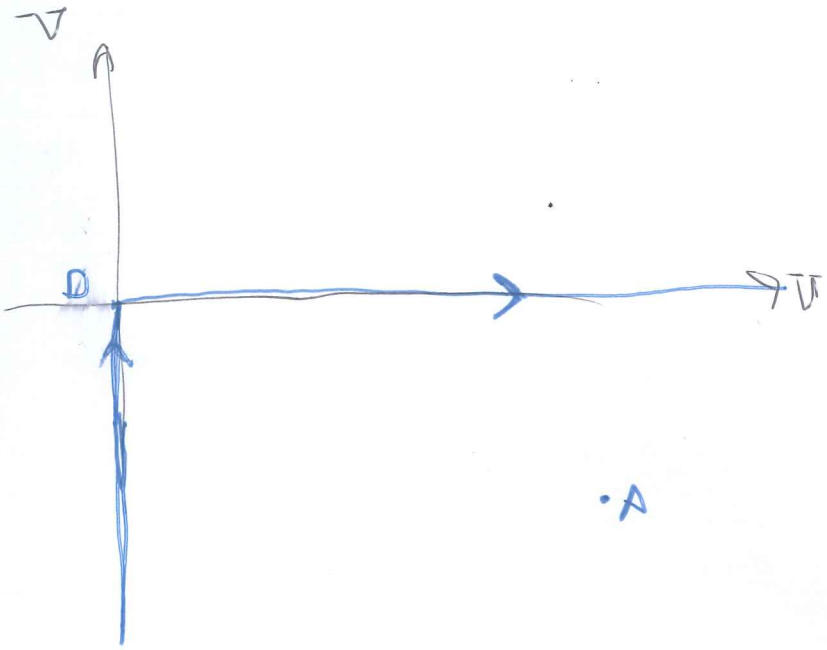


There is a unique value of s that joins D to A

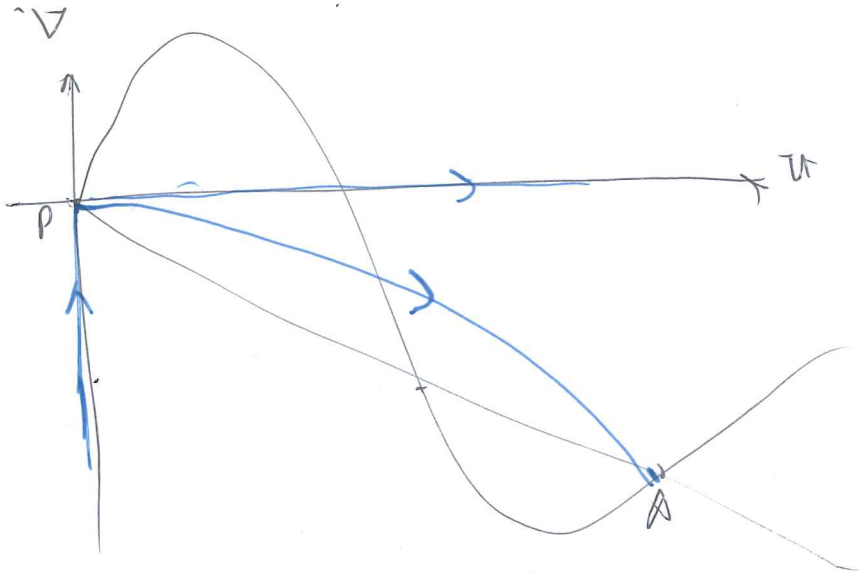
You can see this because if $s \to 1$ and $V < 0$

then U = constant and V goes up to D

And if $s \to \infty$ then $U \to \infty$:



∴ there must be something that joins D to A for an inbetween value of s.



Now we go from A to B along ~~[illegible]~~ $f(u,v) > 0$ on the v-nullcline. This is the slow part:

$$s(u' + \gamma v') = \mu - u + \varepsilon u'' \quad \Rightarrow \quad s(u' + \gamma v') = \mu - u$$

$$\varepsilon s v' = f(u,v) \qquad\qquad f(u,v) = 0$$

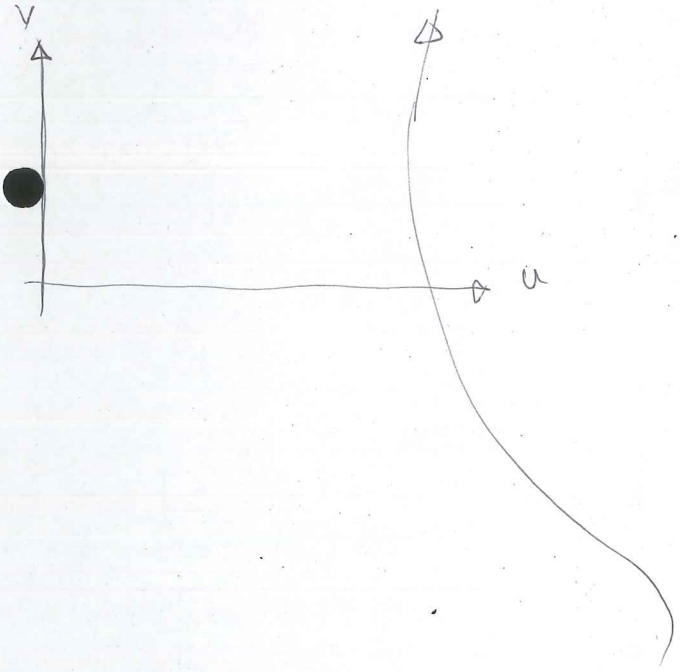
to leading order in ε.

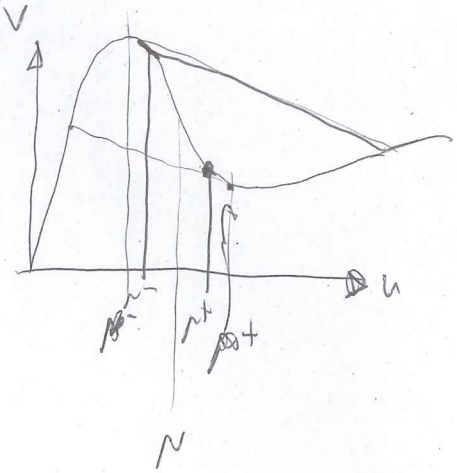
We know that B is to the left of A because we can show that $u' < 0$ on this slow phase.

Proof

$$u' = \frac{\mu - u}{s\left(1 + \gamma \frac{v'}{u'}\right)}$$

$= \frac{dv}{du}$





We will assume $\mu_- < \mu < \mu_+$

so $\mu - u < 0$

Recall μ^-, μ^+ are the places where the gradient of the curve $f(u,v) = 0$ equals $-\frac{1}{\gamma}$

so we know this is $> -\frac{1}{\gamma}$

so denominator > 0 $\therefore u' < 0$ $\therefore$ trajectory moves along $f(u,v)=0$ to the left.

Now do we know where B is? The b the (unique) place where we link back on a fast trajectory

To analyse this, we set $u = u_B + U$,

$V = v_B + V$

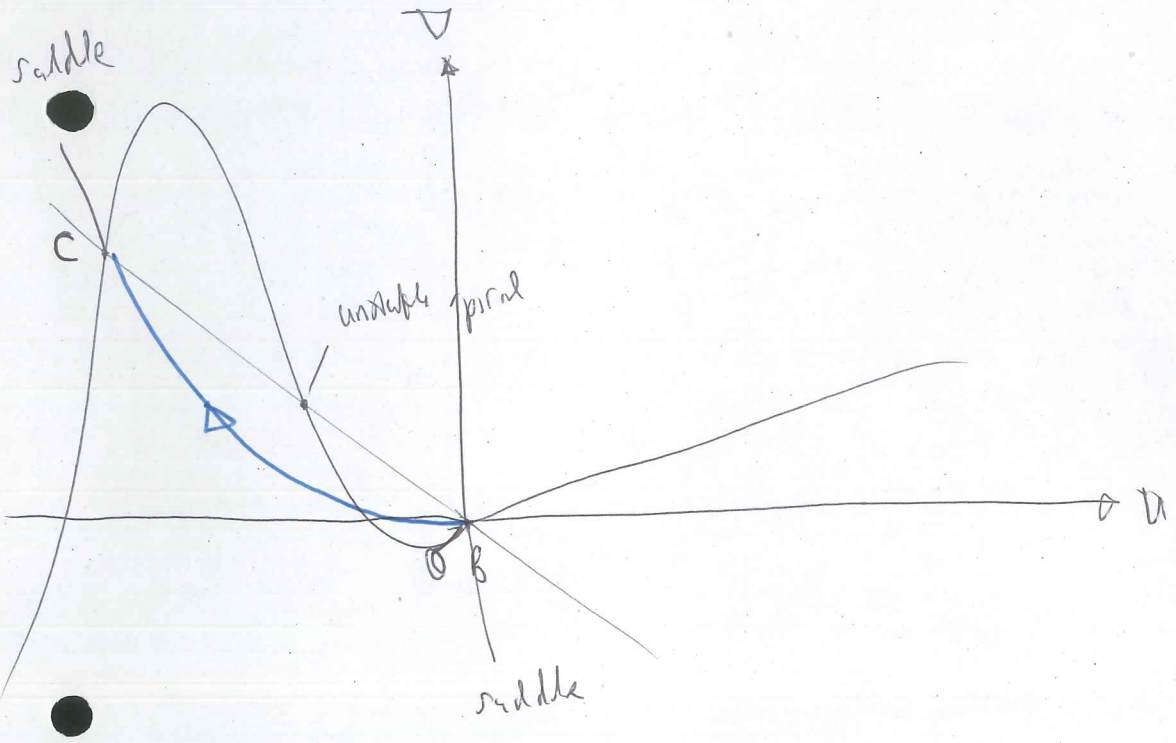
to get (like before) $U' = s(U + \gamma V)$

$sV = F(U, V)$

Fixed points:

$U + \gamma V = 0$

$F(U, V) = 0$



B and C are fixed points of the (U, V) system

The values of u_B, v_B are set so that we link back up to the other fixed point, C, in the new (U, V) phase plane (note that one is different to the previous (u, v) phase plane because now we are centred around (u_B, v_B) rather than (u_0, v_0).

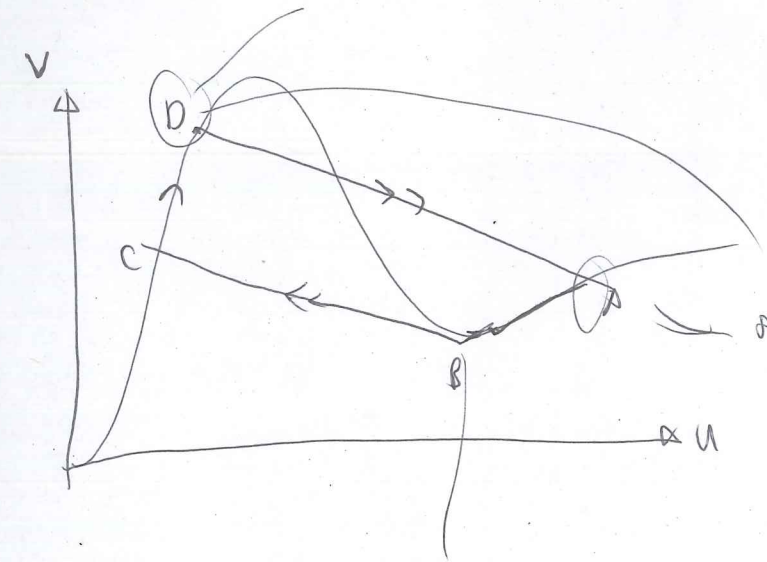
This then leaves the final slow phase C + D.

As on B t. C we have u's $\frac{\rho - u}{s\left[1 + \gamma \frac{dv}{du}\right]} > 0$ as $u < \rho$

so thus takes us to the right on the curve $f(u,v) = 0$

~~And that although~~

So overall we have: ~~Set by fixed point of (u,v) system~~



fixed

Set by fixed points of (u,v) system; ~~P~~ S chosen to limit the two trajectories

Set by fixed points of ~~first~~ second (u,v) system; (u_B ~~v_B~~) chosen to limit the two trajectories

Note that although u_B (and thus v_B) were fixed, u_D (and thus v_B) were not. So there is a one-parameter family of periodic travelling wave, with corresponding wave speeds.

The heart

There are two parts to the heart function:

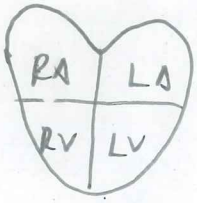
1) Electrochemical action – causes muscle contraction to pump blood around the body

2) Mechanical action – enables unidirectional circulation via a system of valves.

We will begin by studying 1 and then move onto 2

The electrochemical action of the heart

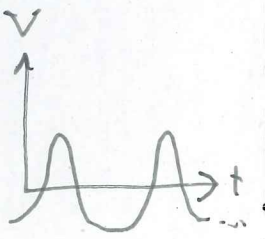
The heart has four chambers



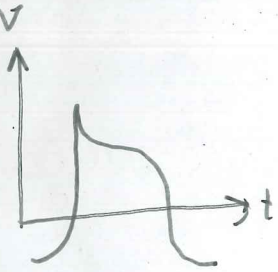
RA: right atrium
LA: left atrium
RV: right ventricle
LV: left ventricle

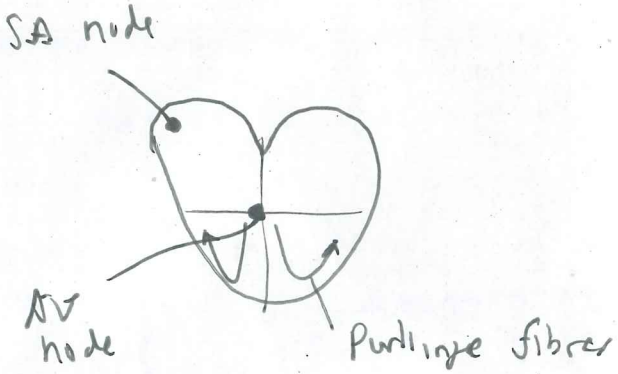
Blood flows into the RA from the venous system, to the RV, perfuses through the lungs (gains oxygen), moves to the LA then the LV then to the arteries

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

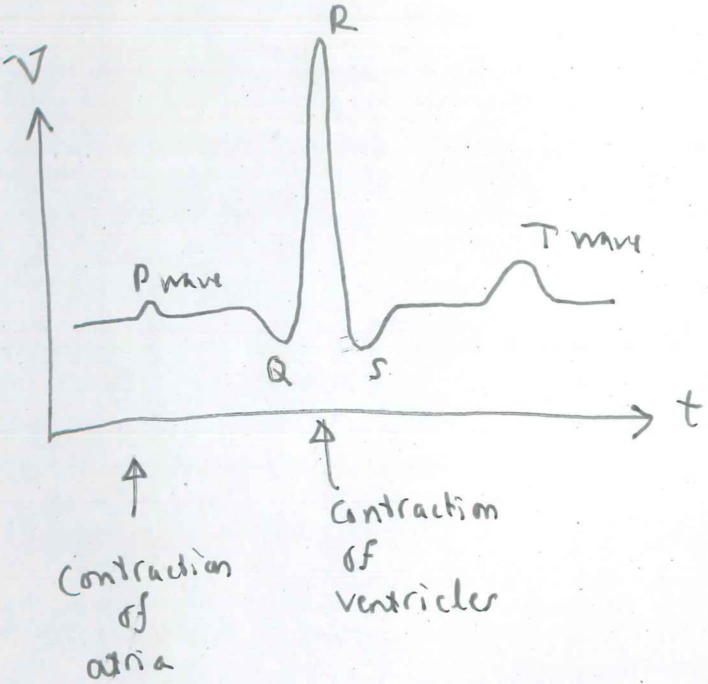


Other cells (atrial / ventricular (AV) myocyter, AV node, Purkinje fibres) are excitable with a distinct action potential.





The echocardiogram (ECG)



P = depolarisation of the atria

Q,R,S = depolarisation of the ventricles

T = repolarisation of the ventricles

Approximately) 2D waves propagate through the heart from the SA. We will learn about these

Blockage of conduction paths can lead to 're-entrant' spiral waves, which cycle round the diseased tissue. This causes ventricular tachycardia.

In the diseased heart, spiral waves can become chaotic. This causes ventricular fibrillation.

The Noble model (1962)

This was an early model for the action potential of ventricular myocytes.

Similar to Hodgkin-Huxley but more variables due to greater number of currents involved.

Represents the ionic current as the sum of sodium, potassium and leakage currents:

$$C_m \frac{dV}{dt} = -I_i \qquad I_i = I_{Na} + I_K + I_L$$

residual — Hodgkin-Huxley

$$I_{Na} = [g_0 + g_{Na} m^3 h](V - V_{Na})$$

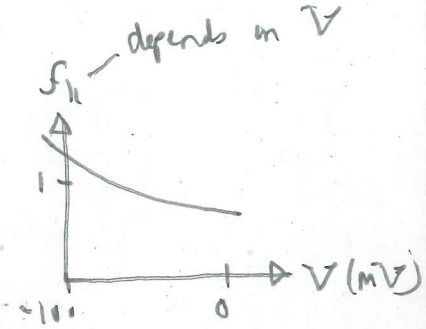
switching on gate — switching off gate

Conductivity of Na (m and h gates)

instant — long lasting

$$I_K = [f_K + g_K n^4](V - V_K)$$

Conductivity of K (n gate only)



$$I_L = g_L (V - V_L)$$

constant leakage conductivity.

eg this

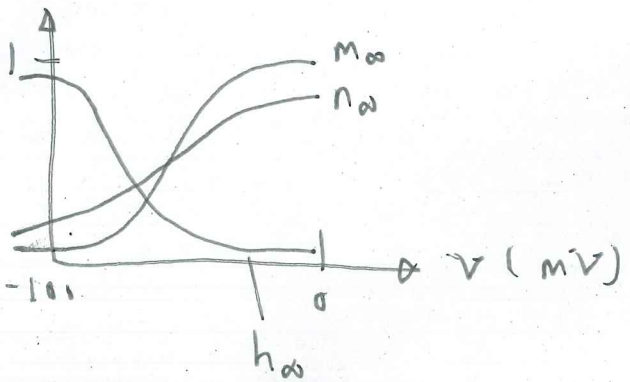
[All of this comes largely from experimental fitting but the key idea is the gate]

and the gate variables satisfy:

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

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

$$\tau_n \dot{n} = n_\infty - n \qquad \tau_n \sim 50 ms$$ - much longer.



We non-dimensionalize via

$$V = |V_k|\,\hat{V}, \qquad t = \tau_h\,\hat{t}$$

$(V_k < 0)$

to get

$\tau_m / \tau_n \ll 1$: $\dot{m} = m_\infty - m \Rightarrow m \approx m_\infty$ (rapidly reached)

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

$\tau_n / \tau_m \gg 1 = \frac{1}{\varepsilon}$, say ($\varepsilon \simeq 0.016$)

$$\dot{n} = n_\infty - n \qquad \dot{n} = \varepsilon (n_\infty - n)$$

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

This is the dimensionless form of $C_m \dot{V} = -I_i$ from previous page

(dropping hats on dimensionless V)

with $G = -\left[\gamma_0 + \gamma_{Na}\, m_\infty^3(V)\, h\right](V_{Na} - V)$

$\gamma_0 \ll 1$, $\gamma_{Na} \gg 1$

$$+ \phi(V+1) + \gamma_L (V + V_L)$$

Note from $\gamma_L = 0$ to begin with (This is the leakage part)

we will use this later.

$$= \phi_{fl}(V) + \gamma_{fl}\, n^4$$

we will use this later

First consider the fast phase. (ie no time rescalings)

This gives n = constant to leading order in ε.

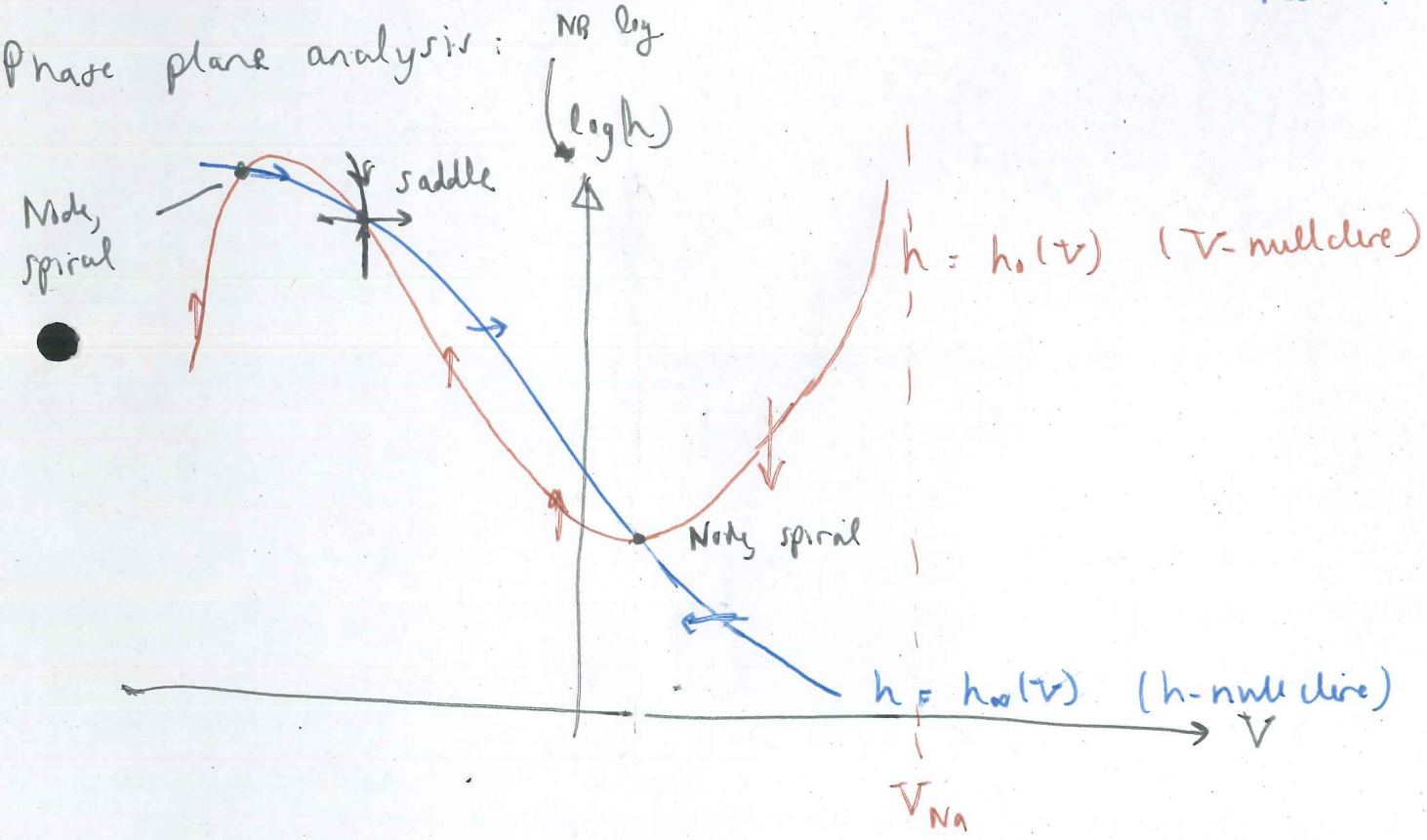
$$\dot{h} = h_\infty - h$$

$$\dot{V} = -\gamma_{Na}\, m_\infty(V)^3 \,[\, h_\infty(V) - h \,]\,(V_{Na} - V]$$

where $h_\infty(V) \stackrel{\text{def}}{=} \frac{1}{\gamma_{Na}\, m_\infty(V)^3} \left(\left[\frac{\phi(V+1) + \gamma_L(V+V_L)}{V_{Na} - V} - \gamma_h \right] \right.$

$\stackrel{\text{def}}{=}$? NB sure if this is needed

Phase plane analysis:



We need to find the stability of the two nodes

Linearising about these fixed points (h^*, v^*), via

$h = h^* + N$, $v = v^* + w$ gives

Maybe we don't need to do this in lectures and we can just say they are stable

$$\frac{d}{dt}\begin{pmatrix} N \\ w \end{pmatrix} = \underbrace{\begin{pmatrix} -1 & h_\infty' \\ A & -A h_\infty' \end{pmatrix}}_{\underline{\underline{M}}} \begin{pmatrix} N \\ w \end{pmatrix}$$

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

$$\mathrm{tr}(\underline{\underline{M}}) = -1 - A h_\infty'$$

Left fixed point

Here, $h_\infty' > 0$ and m_∞ is quite small for low v values (see earlier graph) so $m_\infty \ll 1$ so $A \ll 1$.

So $\mathrm{tr}(\underline{\underline{M}}) < 0 \Rightarrow$ stable

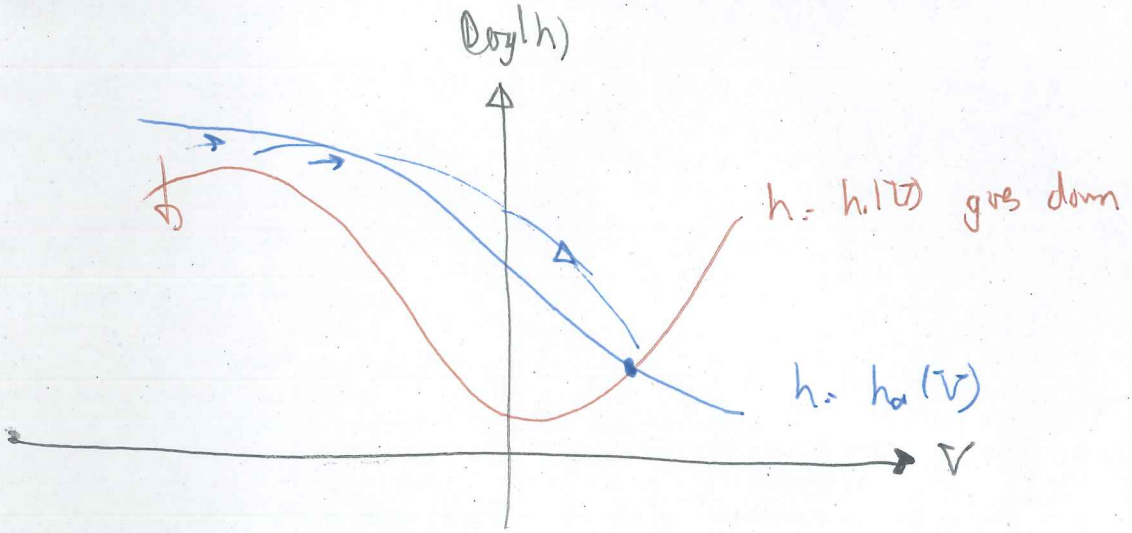
Right fixed point

$h_\infty' < 0$ so $\mathrm{tr}(\underline{\underline{M}}) < 0$ so stable too.

Now we need to consider the slow variation in n.

$\dot{n} = \varepsilon(n_\infty - n)$.

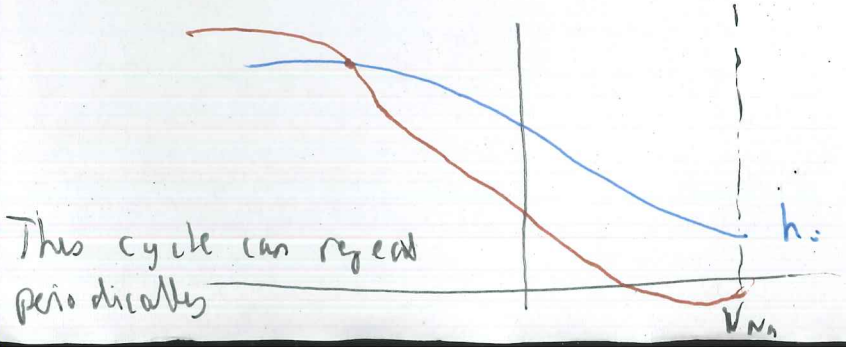
When solution is at left fixed point, V is low so n_∞ is low (from previous graph) so $n_\infty - n < 0$ so n goes down so ϕ goes down (recall $\phi = \bar{\phi}_{ik}(V) + \gamma_k \underline{n}^4$) so $h_i(V)$ goes down (see definition of $h_i(V)$ so phase (and actually changes shape) plane evolves to:



So this is something different because in this phase plane the nullclines are moving

In doing so the left fixed point disappears and so the system jumps to the right fixed point

From here, n_∞ is now high so $n_\infty - n > 0$ so n goes up so the $h = h_\infty(V)$ curve moves up until we get a loss of the right fixed point:



The left fixed point reappears as $h = h_\infty(V)$ graph also changes shape.

Waves in two or three dimensions

Waves propagate through the heart in approximately two dimensions

Periodic wave propagation

Let $\underline{w}$ be a vector of 'reactants' (eg v, m, n, h) with kinetics $\frac{\partial \underline{w}}{\partial t} = f(\underline{w})$.

Suppose $\underline{w}$ has a stable limit cycle behaviour $\underline{w} = \underline{W}_0(t)$ with period T.

Now consider weak diffusion to add spatial dependence:

$$\frac{\partial \underline{w}}{\partial t} = f(\underline{w}) + \varepsilon \nabla^2 \underline{w} \quad (1) \qquad \varepsilon << 1.$$

(This assumes all reactants have the same diffusion coefficient.)

The weak coupling causes $\underline{w}$ to evolve on a slow time scale, $\tau = \varepsilon t$.

We seek a multiple scales approximation: $\underline{w} = \underline{w}(x, t, \tau)$.

Then (1) becomes $\frac{\partial \underline{w}}{\partial t} + \varepsilon \frac{\partial \underline{w}}{\partial \tau} = f(\underline{w}) + \varepsilon \nabla^2 \underline{w}$. (2)

We seek a series approximation $\underline{w} = \underline{w}_0 + \varepsilon \underline{w}_1 + \dots$

At $O(1)$ in ② this gives

$$\frac{\partial \underline{w}_0}{\partial t} = f(\underline{w}_0)$$

$$\Rightarrow \quad \underline{w}_0 = W_0(t + \psi(\underline{x}, \tau))$$

↑ This tells us how the phase can shift in space and on the long time τ.
(Recall W_0 is the solution to $\frac{\partial \underline{w}}{\partial t} = f(\underline{w})$ so this phase shift is like the constant of integration and the only way to get the $\underline{x}$ and τ dependence in.)

At $O(\varepsilon)$ we get

$$\frac{\partial \underline{w}_1}{\partial t} - J\underline{w}_1 = -\left(\frac{\partial \psi}{\partial \tau} - \nabla^2\psi\right)\underline{w}_0' + |\nabla\psi|^2 \underline{w}_0''$$

where $J = Df(W_0(t))$

↑ Derivative with respect to w_0.

This is a linear inhomogeneous equation.

We also note that $\underline{s} \overset{\text{def}}{=} \underline{w}_0'$ satisfies

$$\frac{\partial \underline{s}}{\partial t} - J\underline{s} = 0$$

(since $\frac{\partial \underline{w}_0}{\partial \tau} = f(w_0)$

$$\Rightarrow \frac{\partial}{\partial t}(\underline{w}_0') = \frac{df}{dw} w_0' = Jf\, w_0' \quad)$$

Thus we may use the Fredholm alternative to determine the solution for $\underline{w}_1$, which gives

$$\underline{w}_1 = -t\left[\frac{\partial \psi}{\partial \tau} - \nabla^2\psi\right]\underline{s} + |\nabla\psi|^2\underline{u} \quad \text{as } t \to \infty$$

where $\underline{u} = \underline{s}\left[\bar{\alpha}\, t + p(t)\right]$

$\bar{\alpha}$: a parameter that depends on $\underline{s}$

$p(t)$: a periodic function

(No need to know the details of this.)

Now we choose ψ to remove the secular terms that grow unboundedly with time (underlined in orange)

Thus we choose

$$\boxed{\frac{\partial \psi}{\partial \tau} = \nabla^2\psi + \bar{\alpha}\,|\nabla\psi|^2}$$

This is an integrated version of Burgers' equation – in one dimension, $u = -\dfrac{\partial \psi / \partial x_1}{2\bar{\alpha}}$ satisfies $\dfrac{\partial u}{\partial \tau} + u\dfrac{\partial u}{\partial x_1} = \dfrac{\partial^2 u}{\partial x_1^2}$

(Burgers' equation).

Solutions of Burgers' equation include shocks.

Target patterns

Consider the equation $\frac{\partial \psi}{\partial \tau} = \nabla^2 \psi + \bar{\alpha} |\nabla \psi|^2$

with boundary conditions $\psi = \Omega \tau$ at $r = b$

(this could correspond to an impurity)

↑ radial coordinate.

This corresponds to patterns that are formed by a pacemaker in the heart in the SA node and a radiation condition $\frac{\partial \psi}{\partial r} < 0$ as $r \to \infty$

- this generates circular patterns that originate from a point. (This ensures that the waves move outwards.)

We make the ansatz $\psi = \Omega \tau - f(r)$

This then gives

$$f'' + \frac{1}{r} f' - \bar{\alpha} (f')^2 + \Omega = 0$$

with $f(b) = 0$

and $f' \to 0$ as $r \to \infty$

The solutions to this are

$$f(r) = -\frac{1}{\bar{\alpha}} \log \left[\frac{K_0(\sqrt{\bar{\alpha}\Omega}\, r)}{K_0(\sqrt{\bar{\alpha}\Omega}\, b)} \right]$$

K_0 = modified Bessel function of the second kind of order zero

K_0 is the solution to

$g'' + \frac{1}{s} g' - g = 0$

that decays as $s \to \infty$ (The other solution, which $\to \infty$ as $s \to \infty$ is I_0)

Spiral waves

Now consider the ansatz $\psi = \Omega T + m\theta - g(r)$ $\quad m \in \mathbb{N}$

with boundary condition $\psi = \Omega T + m\theta$ at $r = b$

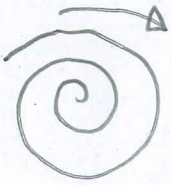
and the radiation condition again, $\frac{\partial \chi}{\partial r} < 0$ as $r \to \infty$.

This time, the solution is

$$g = -\frac{1}{\bar{\alpha}} \log \left[\frac{K_\nu(\sqrt{\bar{\alpha}\Omega}\, r)}{K_\nu(\sqrt{\bar{\alpha}\Omega}\, b)} \right] \qquad \nu = i\bar{\alpha} m$$

and $\chi \sim \Omega T + m\theta - \sqrt{\frac{\Omega}{\bar{\alpha}}}\, r$ as $r \to \infty$

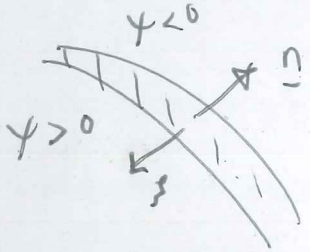
This is an Archimedean spiral



This spiral rotates and continues to excite the tissue.

Curved front propagation

Consider a wave in which the phase ψ of the potential vary rapidly within a thin region (the wave front) which curve more slowly in other directions



● Suppose that the equation $v_t = f(v) + \nabla^2 v$ (*)

has a one-dimensional travelling wave solution

$v = v(s)$, $s = ct - x$, $c > 0$, $v(\infty) = 0$, $v(-\infty) = 0$

$$\Rightarrow \quad cv' = f(v) + v'' \qquad (\dagger)$$

L● ψ denote the phase of the wave.

We define the location of the wave front as $\psi(\underline{x}, t) = 0$

(eg $\psi = ct - r$ is a target pattern)

Let s be the distance along the normal $\underline{n}$ in the inward direction (see above sketch) $\underline{n} = -\dfrac{\nabla\psi}{|\nabla\psi|}$ by definition of the normal to a surface ψ.

So $\delta\psi = \nabla\psi . \delta\underline{x}$

$= -|\nabla\psi| \underline{n} . \delta\underline{x}$

$= -|\nabla\psi| \delta s$ $\Rightarrow$ $\psi_s = |\nabla\psi|$

We look for a solution of the form $v(\psi)$

In (*) this gives

$$v'(\psi)\left(\psi_t - \nabla^2\psi\right) = f(v) + v''(\psi)|\nabla\psi|^2$$

Since the front is thin this allows us to make a quasi one dimensional approximation: $v_s \approx |\nabla\psi|\, v'(\psi)$

$$\Rightarrow \quad v_{ss} + \frac{v_s}{|\nabla\psi|}\left[\nabla^2\psi - \frac{\partial}{\partial s}|\nabla\psi| - \psi_t\right] + f(v) = 0$$

Comparing this with (†) which holds if we have a travelling wave solution, we see that we need

$$\frac{1}{|\nabla\psi|}\left[\nabla^2\psi - \frac{\partial}{\partial s}|\nabla\psi| - \psi_t\right] = -c$$

$$\Rightarrow \quad \psi_t = \nabla^2\psi - \frac{\partial}{\partial s}|\nabla\psi| + c|\nabla\psi|$$

$$\Rightarrow \quad \frac{\psi_t}{|\nabla\psi|} = c - \nabla\cdot\underbrace{\left(-\frac{\nabla\psi}{|\nabla\psi|}\right)}_{\underline{n}} \qquad (X)$$

But now $\psi = 0$ denotes the front so $\dfrac{D\psi}{Dt} = 0$

$$\Rightarrow \quad \psi_t + \underline{v}\cdot\nabla\psi = 0$$

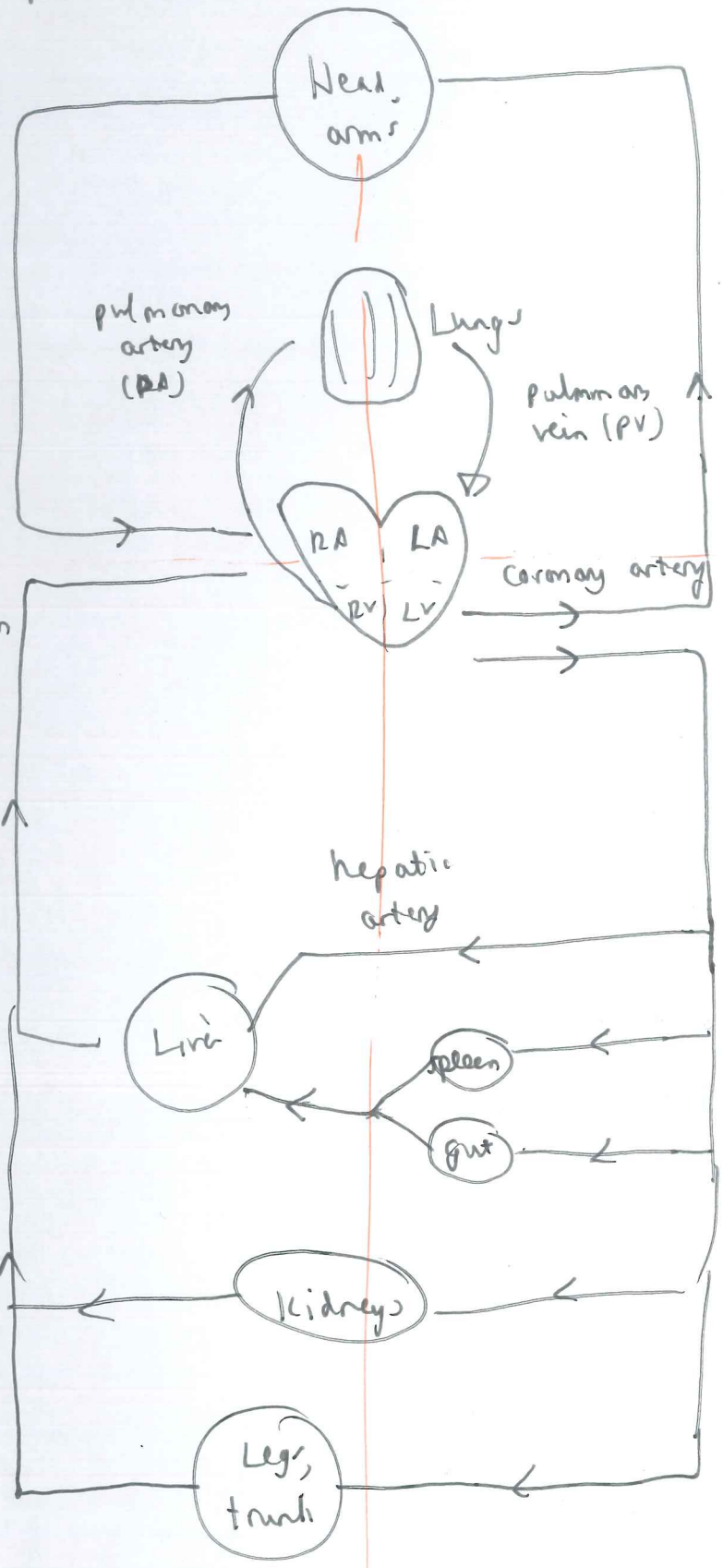
$$\Rightarrow \quad \psi_t + v_n|\nabla\psi| = 0$$

$$\Rightarrow \quad v_n = -\frac{\psi_t}{|\nabla\psi|}$$

So in (X) $\Rightarrow$ $\boxed{v_n = c - \nabla\cdot\underline{n}}$ This is the Eikonal equation

The heart as a pump

We have so far looked at the electrochemical action of the heart. Now we will move on to look at the mechanical action.



superior vena cava (SVC)

femoral large vein in the human body

Inferior vena cava (IVC) largest vein in the body

RA = right atrium

RV = right ventricle

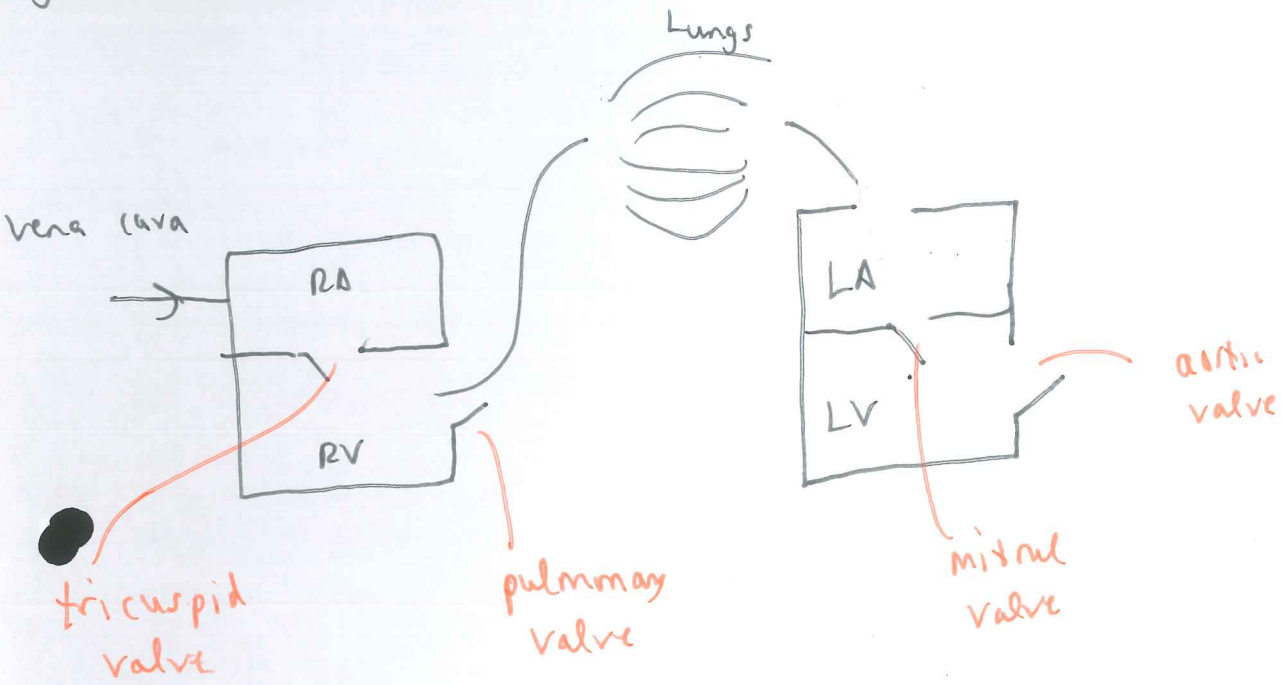
LA = left atrium

LV = left ventricle

splanchnic circulation (gastric, small intestinal, colonic, pancreatic, hepatic and spleen circulations) is parallel with one another.

renal system

Blood collects oxygen (O_2) from the lungs and delivers this to the tissues and collects CO_2 from tissue and dumps this to the lungs (to exhale)



There are two parts to the heart function:

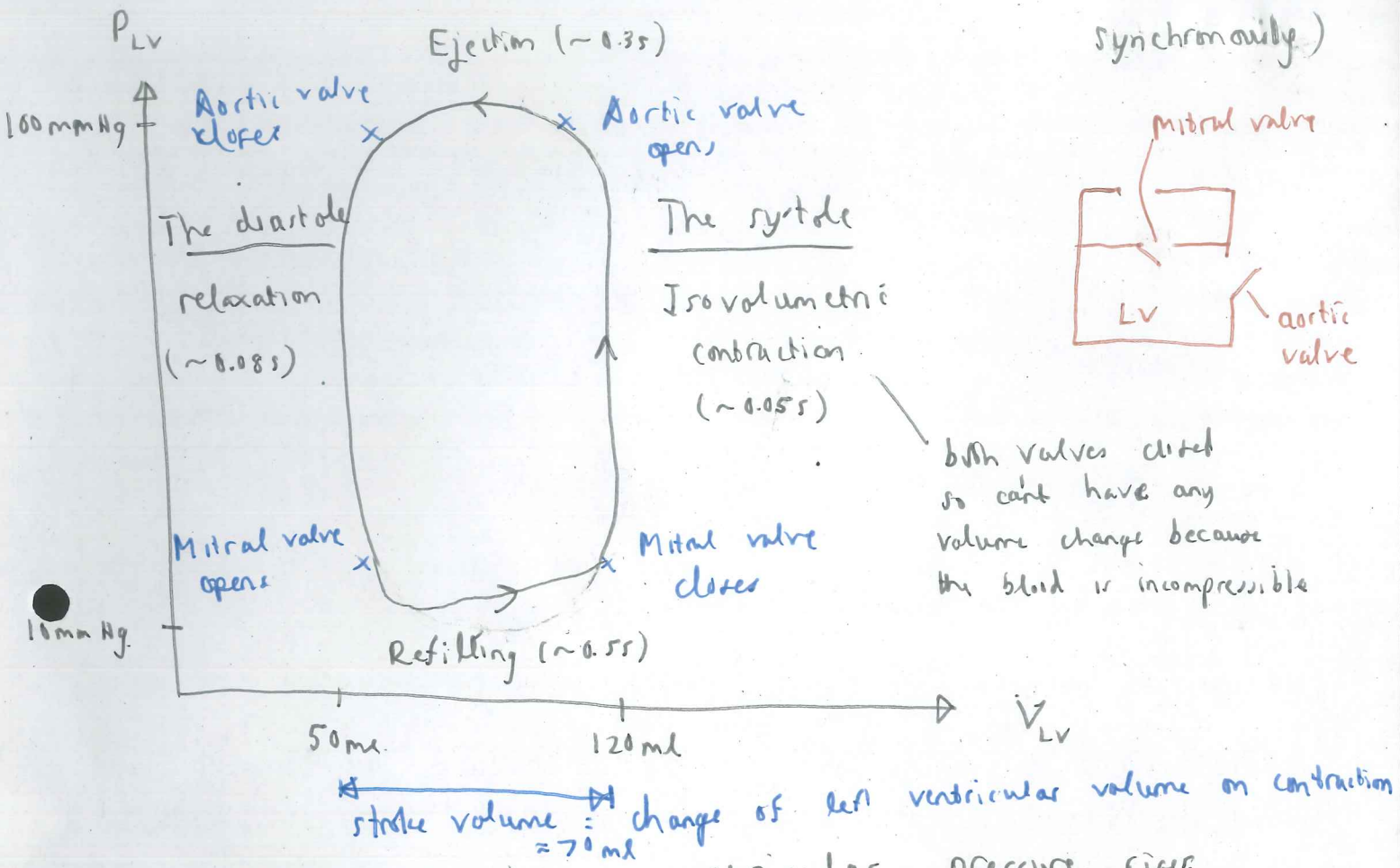
1) electrochemical action - causes muscle contraction to pump blood around the body.

2) mechanical action - enables unidirectional circulation via a system of valves.

We will begin by studying 1 and then move onto 2.

Pressure - volume cycle of the left ventricle

(The right acts almost synchronously)



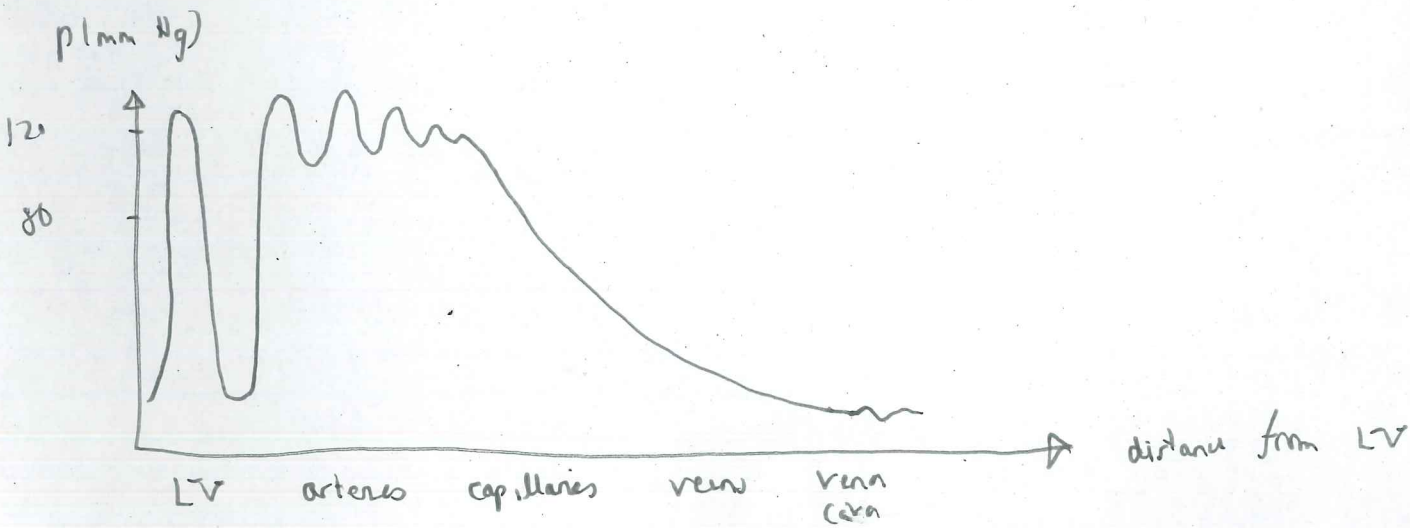
both valves closed so can't have any volume change because the blood is incompressible

Systole = contraction phase - ventricular pressure rises

Diastole = relaxation phase - ventricular pressure falls.

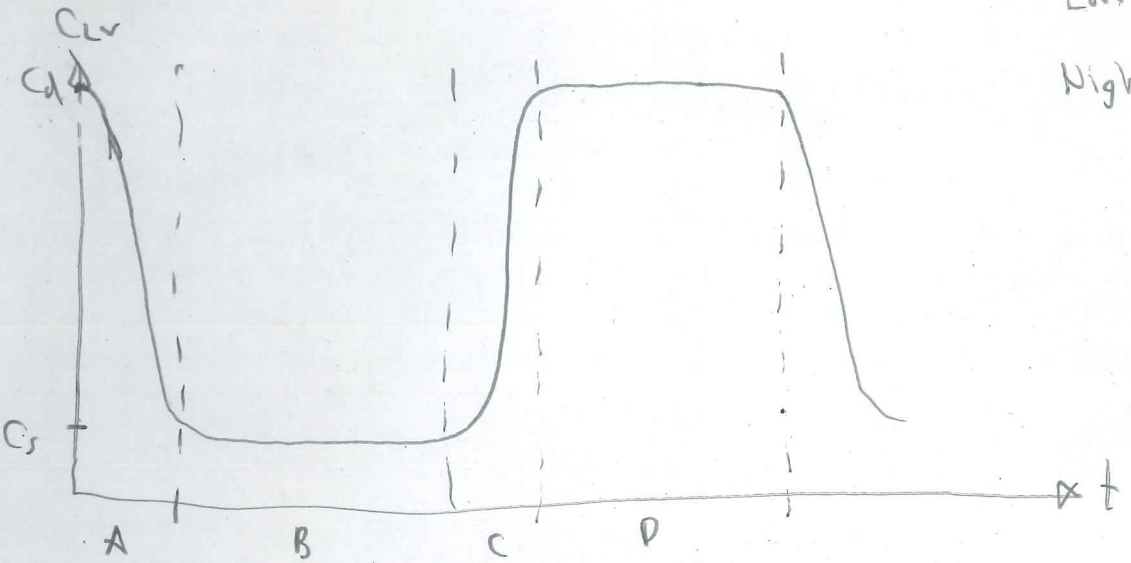
Heart rate = $\frac{1}{\text{period of the sino atrial node cells}}$

[Do next page before the picture]



The compliance can be thought of as a prescribed periodic function: C_{LV} ✓ $\frac{1}{\text{elastance}}$ of the heart

Low C = tight
High C = loose.



A. The systole: Isovolumetric contraction. The compliance falls as the heart tightens.

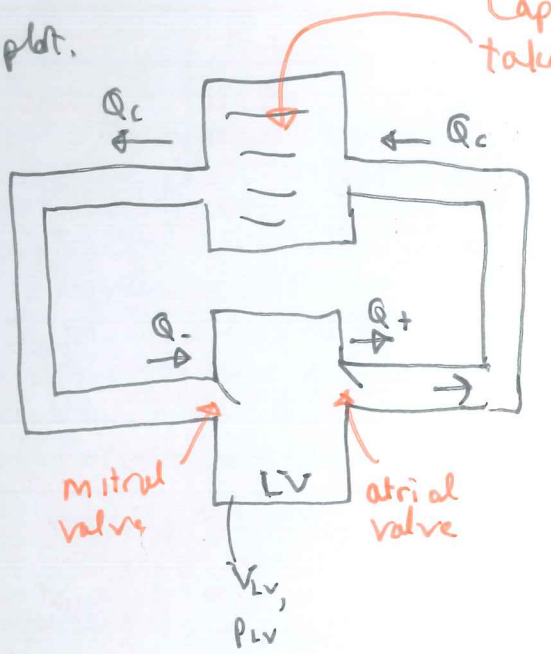
B. Ejection. Constant low compliance C_d (tight) pushes blood out

C. The diastole. Isovolumetric contraction. The compliance rises as the heart loosens.

D. Refilling. Constant high compliance C_s (loose) allows blood in.

A simple mechanical model of the circulation

We would like to write down a mathematical model to explain the $P_{LV} - V_{LV}$ plot.



Veins
volume in veins: V_v
pressure: P_v
(assume no pressure loss from start to end)

arteries
volume in arteries: V_a
pressure: P_a

Q_+, Q_-, Q_c = blood flows

V_a, V_v, V_{LV} = compartment volumes

Blood is incompressible but blood vessels are compliant (so blood flows at different points along the network can differ from one another and change with time)

Conservation of blood:

$$\dot{V}_a = Q_+ - Q_-$$

$$\dot{V}_v = Q_c - Q_-$$

$$\dot{V}_{LV} = Q_- - Q_+$$

Compliance.

Increasing pressure distends blood vessels:

$$V_a = V_{a0} + C_a P_a$$

$$V_v = V_{v0} + C_v P_v$$

$$V_{LV} = V_{LV0} + C_{LV} P_{LV}$$

C = compliance $= \frac{1}{\text{elastance}}$

Low C = tight, high C = loose

Resistances:

Capillaries occupy no volume but offer resistance:

$$Q_c = \frac{P_a - P_v}{R_c}$$

$$Q_+ = \frac{[P_{LV} - P_a]_+}{R_a}$$ ← the positive part

$$Q_- = \frac{[P_v - P_{LV}]_+}{R_v}$$

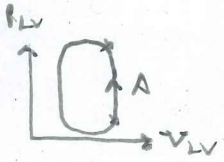
Writing the model in terms of just pressures:

$$\frac{dp_a}{dt} = \frac{[p_{LV} - p_a]_+}{R_a C_a} - \frac{p_a - p_v}{R_c C_a} \quad (1)$$

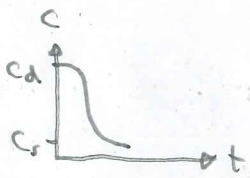
$$\frac{dp_v}{dt} = \frac{p_a - p_v}{R_c C_v} - \frac{[p_v - p_{LV}]_+}{R_v C_v} \quad (2)$$

$$\frac{d}{dt}(C_{LV} p_{LV}) = \frac{[p_v - p_{LV}]_+}{R_v} - \frac{[p_{LV} - p_a]_+}{R_a} \quad (3)$$

A. Isovolumetric contraction



(Both valves closed) (0.05 s)



Initial conditions:

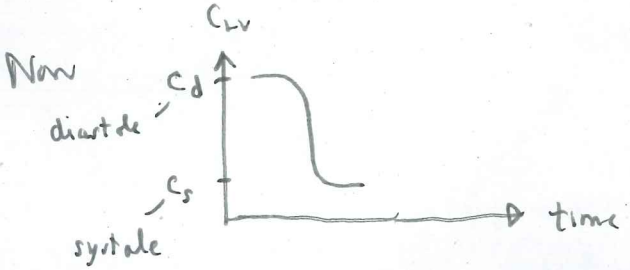
$p_{LV} < p_v \ll p_a$

(1) $\Rightarrow$ $\frac{dp_a}{dt} = -\frac{p_a}{R_c C_a}$

$R_c C_a \approx 1.8$ s and time of contraction ≈ 0.05 s so $p_a \approx$ constant on this phase

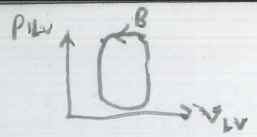
Similarly, (2) $\Rightarrow$ $p_v \approx$ constant on this phase

(3) $\Rightarrow$ $\frac{d}{dt}(C_{LV} p_{LV}) = 0$



so C_{LV} falls, p_{LV} rises

B. Ejection



(Atrial valve open) (0.3 s) (C_{LV} constant $= C_s$) 77

$P_V \ll P_a < P_{LV}$ (because now P_{LV} is much higher)

① ⇒ $$\frac{dP_a}{dt} = \frac{P_{LV} - P_a}{R_a C_a} - \frac{P_a - P_V}{R_c C_a} \quad (*)$$

$\frac{dP_a}{dt}$: 0.3 s; $R_a C_a$: 0.095 s; $R_c C_a$: 1.8 s

much smaller than the other two

⇒ $\boxed{P_{LV} \approx P_a}$

② ⇒ $$\frac{dP_V}{dt} = \frac{P_a - P_V}{R_c C_V}$$

$\frac{dP_V}{dt}$: 0.3 s; $R_c C_V$: 60 s

⇒ $\boxed{P_V \approx \text{constant}}$

③ ⇒ $$\frac{d}{dt}(C_{LV} P_{LV}) = -\frac{P_{LV} - P_a}{R_a}$$

Now C_{LV} = constant $= C_s$ so substituting this into (*) gives

$$\frac{dP_a}{dt} = -\frac{C_s}{C_a}\frac{dP_a}{dt} - \frac{P_a - P_V}{R_c C_a}$$

$$(C_a + C_s)\frac{dP_a}{dt} = -\frac{P_a}{R_c} \quad \text{(since } P_a \gg P_V\text{)}$$

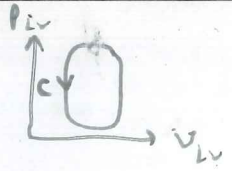
$$\boxed{P_a \propto \exp\left[\frac{-t}{R_c(C_a + C_s)}\right]}$$

0.3 s

2.2 s

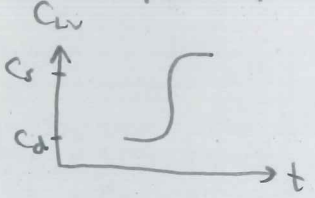
⇒ P_a falls by ~ 0.87 in this phase.

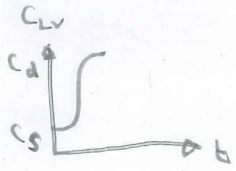
C. Isovolumetric relaxation



(Both valves closed) (0.085)

$P_v < P_{LV} < P_a$





P_a = constant

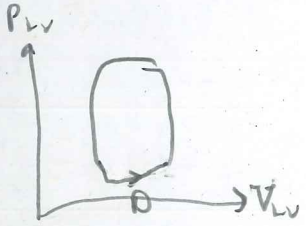
P_v = constant

C_{LV} rises.

As before, $\frac{d}{dt}(C_{LV} P_{LV}) = 0$

So now P_{LV} falls until $P_{LV} = P_v$. and mitral valve open to commence filling

D. Refilling



(Mitral valve open) (0.5s) | (C_{LV} = constant = C_d)

$P_{LV} < P_v << P_a$

① $\Rightarrow \frac{dP_a}{dt} = -\frac{P_a - P_v}{R_c C_a} \approx -\frac{P_a}{R_c C_a}$ since $P_a >> P_v$

② $\Rightarrow \frac{dP_v}{dt} = \frac{P_a - P_v}{R_c C_v} - \frac{P_v - P_{LV}}{R_v C_v}$

$R_c C_v$ 0.8s — neglects compared with — $R_v C_v$ 0.8s

③ $\Rightarrow \frac{dP_{LV}}{dt} = \frac{P_v - P_{LV}}{C_d R_v}$ (since C_{LV} = constant = C_d)

④ $\Rightarrow$ $P_a \propto \exp\left[-\frac{t}{R_c C_a}\right]$ $\Rightarrow$ P_a falls by ≈ 0.76 in this phase.

So total fall in P_a N $0.87 \times 0.76 = 0.66$

(ejection) (refilling)

(120 mm Hg to 80 mm Hg)

② − ③ gives

$$\dot{P}_v - \dot{P}_{LV} = -\left(\frac{1}{R_v C_v} + \frac{1}{R_v C_a}\right)(P_v - P_{LV})$$

since (C_v = constant)

$$P_v - P_{LV} \propto \exp\left[-\frac{1}{R_v}\left(\frac{1}{C_v} + \frac{1}{C_a}\right)t\right]$$

Nervous control of the heart

This is what controls the heart rate, stroke volume and arterial blood pressure.

There are two parts of the nervous system that control cardiac output - the sympathetic and parasympathetic systems.

Nervous control is effected by - afferent nerves (to the brain)

efferent nerves (from the brain)

The sympathetic system releases noradrenaline and adrenaline and other neurotransmitters

There are two parts to the sympathetic system -

α-sympathetic (peripheral vessels) — release of neurotransmitters here causes vasoconstriction which causes an increase in blood pressure.

β-sympathetic (ventricular muscle) — release of neurotransmitters here causes an increase in the firing of the SA node (ie increase in heart rate)

The sympathetic system acts slowly (~10s)

The parasympathetic system releases acetylcholine (another neurotransmitter)

This decreases the heart rate and causes vasodilation

This acts quickly.

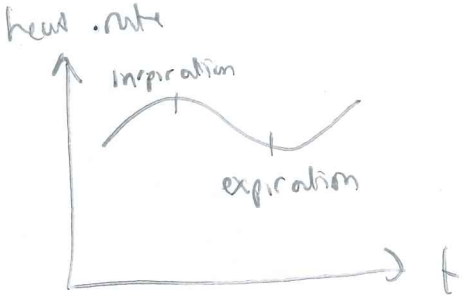
The baroreceptors control the blood flow and blood pressure. They are located in the aortic arch of the chest and the carotid sinus in the chest. The control response is called the baroflex.

Oscillatory patterns

Respiratory sinus arrythmia (RSA)

- heart rate is faster breathing in than breathing out (can get a different resting heart rate depending on which of these you are doing while measuring it)

realm:
- inspiration leads to low pressure which increases the heart rate because it is easier to flow



Mayer waves

- due to the sympathetic system.
- ~10s time period (same as timescale of sympathetic system).

Mathematical model of the baroflex: the Ottesen model (1997)

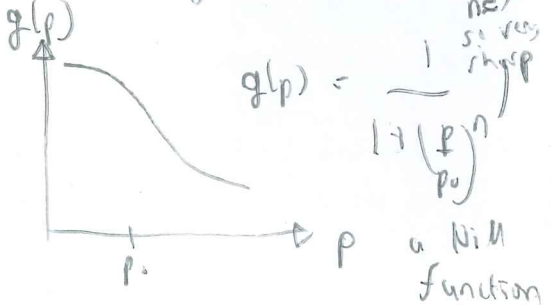
Three variables: average arterial and venous pressures p_a and p_v and the heart rate

Control is effected by sympathetic and parasympathetic tones:

Sympathetic tone:

$$T_s = g(p_a^\tau)$$

$$p_a^\tau = p_a(t-\tau)$$ (a delay because its effects are delayed after release - slow)



$$g(p) = \frac{1}{1+\left(\frac{p}{p_0}\right)^n}$$ n=7 sympathetic, n=2 parasympathetic

a Hill function

Parasympathetic tone : $T_p = 1 - g(p_a)$

Heart rate, N : $\dot{N} = \delta_H (N_0 - N) + \lambda_N T_s - \nu_N T_p$

(taken as a continuous variable - ie the average heart rate)

N_0: natural resting heart rate in the absence of tones

ν_N: parameter describing the strength of the sympathetic and parasympathetic tones

$$C_a \dot{p}_a = -\frac{p_a}{R_c} + H \Delta V$$

C_a: compliance (as introduced before)

R_c: resistance as introduced before

H: stroke volume

Non-dimensionalisation

$N = N_0 h, \quad p_a = p_0 p, \quad t = \tau \hat{t}$

$$\Rightarrow \quad \dot{p} = \kappa (-p + \nu h)$$

$$\varepsilon \dot{h} = \delta(1 - h) + \lambda g(p_1) - \nu (1 - g(p)) \qquad (\varepsilon \ll 1)$$

(other parameters roughly $O(1)$)

$p_1 = p(t-1), \quad g(p) = \frac{1}{1 + p^n} \qquad n \approx 7$