An Introduction to Mathematical Physiology

Michaelmas Term 2025

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General course information.

Lectures take place on Wednesdays 12-1 (L5) and Thursdays 11-12 (L4)

There will be 4 problem sheet classes. Each tutor will do 4 classes, each 90 mins and each covering 1 problem sheet.

CLASS OPTION 1

Georgina Ryan: Monday 9:30-11 Weeks 3, 5, 7, HT1 in C2

CLASS OPTION 2

Callum Marsh: Tuesday 11-12:30 Weeks 4, 6, 8 in C3, HT1 in C2

CLASS OPTION 3

Ramon Nartallo-Kaluarachchi: Wednesday 10:30-12 Weeks 4, 6, 8 in C2
HT1 in C3 (21/01/26)

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Problem Sheets: - Solutions to the B questions of Problem Sheet 1 and 3 should be submitted on Moodle by Friday 9 am on Weeks 2 and 6.

- Model answers will be provided to all questions and we'll go through these in the classes.

Special Topics: For those attending who need to write a special topic on this course. There is a list of possible topics on the course website.

Lectures: - Typeset lecture notes are detailed. But, everything you need will be covered in the lectures. Sometimes I'll point to the lecture notes for additional proofs.

- In this course there is just as much emphasis on coming up w/ the appropriate mathematical models as there is on solving them.
- Some guest appearances from research experts in the field (in brain modelling, calcium dynamics, ...)

[Notes based on those of Prof. Ian Griffiths]

Chapter 1: Enzyme kinetics

Enzymes are catalysts, they help convert other molecules known as substrates into products, but are not used up in the reaction themselves.

Applications: digestive system (glucose breakdown), DNA replication, liver enzymes (destroy toxins)

Consider chemicals A and B reacting on collision to form chemical C with a rate k: $A + B \xrightarrow{k} C$

This rate k depends on the molecule sizes, shapes, and the temperature.

Then we can write $\boxed{\frac{dC}{dt} = kAB}$

The rate at which the reaction takes place is proportional to the number of sufficiently energetic collisions bet^n molecules A & B $\propto$ concentrations of A and B.

[If you double the number of A you would expect the rate of reaction to double.

Note this means that $2A + B \xrightarrow{k} C$ is $\frac{dC}{dt} = kA^2B$

More on this on problem sheet 1 Q2.

you can think of $2A + B \xrightarrow{k} C$ as $A + A + B \xrightarrow{k} C$

This is called the **law of mass action** (the way in which chemical reactions & the consequent evolving concent. of their reactants are quantified)

Assumption: the mixture is well-stirred (i.e. concentrations of reactants uniform in space)

Michaelis-Menten kinetics (Section 1.2)

An enzyme reaction looks like this:

enzyme acts on single substrate

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

a complex, which breaks down into the enzyme and a product

(two-step process)

S: substrate; E: enzyme; k_1: a reversible reaction; C: enzyme is released when the complex breaks down into the product; E + P: enzyme, product

overall reaction rate

The overall reaction is $S \xrightarrow{r} P$. This looks like a simple reaction, but we know there are internal rate 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 constants

Thus the reaction rate is not a constant

But better to use the law of mass action:

$$\frac{dS}{dt} = k_{-1}C - k_1 SE \quad ①$$

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

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

$$\frac{dP}{dt} = k_2 C \quad ④$$

Michaelis-Menten kinetics

Can we simplify? Yes - P only appears in ④ so decouples.
I.e. it can be found by direct integration once the other 3 eqns for E, C, S have been solved.

Add ① + ③ to see that $\frac{dE}{dt} + \frac{dC}{dt} = 0 \Rightarrow E + C = \text{constant} = E_0$

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 $t = 0$.

We now non-dimensionalize the system to analyze it:

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

Thus,

$$\left[\frac{dS}{dt} = S_0 \frac{ds}{dt}, \quad \frac{dC}{dt} = E_0 \frac{dc}{dt} \quad dt = \frac{dt'}{k_1 E_0} \rightarrow \frac{d}{dt'} = \frac{1}{k_1 E_0} \frac{d}{dt}\right]$$

- The $\frac{dS}{dt}$ equation becomes:

$$k_1 S_0 E_0 \frac{ds}{dt'} = k_{-1} E_0 c - k_1 S_0 s (E_0 - E_0 c)$$

$$\Rightarrow k_1 S_0 \frac{ds}{dt'} = k_{-1} c - k_1 S_0 s (1 - c)$$

Divide through by $k_1 S_0$ to obtain $\frac{ds}{dt'} = \frac{k_{-1}}{k_1 S_0} c - s(1-c) = c\left(s + \frac{k_{-1}}{k_1 S_0}\right) - s$

$$\frac{ds}{dt'} = c\left(s + \underbrace{\frac{k_{-1}}{k_1 S_0} + \frac{k_2}{k_1 S_0}}_{K'} - \overbrace{\frac{k_2}{k_1 S_0}}^{\lambda}\right) - s = -s + c(s + K' - \lambda)$$

where $\boxed{K' = \frac{k_{-1} + k_2}{k_1 S_0}}$ and $\boxed{\lambda = \frac{k_2}{k_1 S_0}}$

- The $\frac{dC}{dt}$ equation becomes:

$$E_0 k_1 E_0 \frac{dc}{dt'} = k_1 S_0 s (E_0 - E_0 c) - (k_2 + k_{-1}) E_0 c$$

$$k_1 E_0 \frac{dc}{dt'} = k_1 S_0 s (1 - c) - (k_2 + k_{-1}) c$$

we divide now by $k_1 S_0$ again:

$$\underbrace{\frac{E_0}{S_0}}_{\varepsilon}\frac{dc}{dt'} = s(1-c) - \underbrace{\frac{(k_2+k_{-1})}{k_1 S_0}}_{K'} c$$

Note: the remarkable effectiveness of enzymes as catalysts is reflected in the extremely small concentrations needed in comparison to the substrate

$\Rightarrow \varepsilon \ll 1$

$$\Rightarrow \quad \varepsilon \frac{dc}{dt'} = s - (s+K')c \quad , \text{ where } \boxed{\varepsilon = \frac{E_0}{S_0}} \ll 1$$

because we only need a bit of enzyme.

Thus, the dimensionless system of equations becomes

$$\boxed{\begin{aligned} \frac{ds}{dt'} &= -s+c(s+K'-\lambda) \\ \varepsilon \frac{dc}{dt'} &= s-(s+K')c \end{aligned}}$$

with initial conditions $s(0)=1$, $c(0)=0$

$\varepsilon \ll 1$ means we can neglect the time derivative in the c-equation.

This makes a QUASI-STATIC system: s evolves through a time derivative, c evolves through an algebraic equation.

From $\varepsilon \to 0$ $\left(\varepsilon \frac{dc}{dt'} \to 0\right)$: $0 = s-(s+K')c \Rightarrow \boxed{c = \frac{s}{s+K'}}$

Thus, if we plug this into the 1st equation, we get $\frac{ds}{dt'} = -s + \frac{s}{s+K'}(s+K'-\lambda)$

$$\Rightarrow \quad \frac{ds}{dt'} = \frac{-s(\cancel{s+K'}) + s(\cancel{s+K'}-\lambda)}{s+K'} = -\frac{\lambda s}{s+K'}$$

$$\boxed{\frac{ds}{dt'} = -\frac{\lambda s}{s+K'}} \quad (\star)$$

$(\star)$ is known as the Michaelis-Menten law (and is for enzyme reactions)

(rate of transformation of the substrate)

What is the reaction rate?

This is $r \overset{\text{def}}{=} \frac{dP}{dt} = -\frac{dS}{dt} = -S_0 E_0 k_1 \frac{ds}{dt'}$ (non-dimensionalizing) — because it is more the state of depletion

$= -S_0 E_0 k_1 \left(-\frac{\lambda s}{s+k'}\right)$ (using (*)) — S

Now let's subst. $S = S_0 s$ and $\lambda = \frac{k_2}{k_1 S_0}$ to obtain

$$r = + E_0 k_1 \frac{k_2}{k_1 S_0} \frac{S'}{s+k'} = E_0 k_2 \frac{S'}{S_0 s + S_0 k'} = E_0 k_2 \frac{S'}{S' + S_0 k'}$$

$$= \frac{k_2 E_0 S'}{S' + S_0 \left(\frac{k_{-1}+k_2}{k_1 S_0}\right)} = \frac{k_2 E_0 S'}{S' + K}$$

So, reaction rate is

$$\boxed{r = \frac{dP}{dt} = \frac{k_2 E_0 S}{S+K}}$$

$$\boxed{K = \frac{k_{-1}+k_2}{k_1}}$$ This is the Michaelis constant

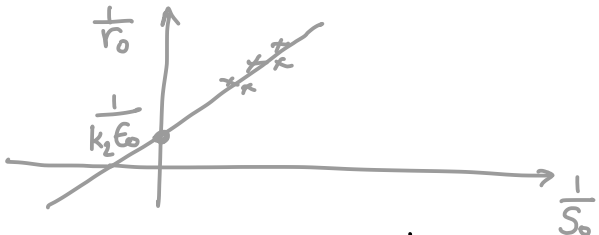
It's difficult to measure individual reaction rates experimentally.

But we can measure the overall reaction rate r and concentrations. So, if we look at the initial rate of reaction S_0:

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

slope

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



We can plot experimental data of $\frac{1}{r_0}$ versus $\frac{1}{S_0}$ and the slope is $\frac{K}{k_2 E_0}$ and intercept is $\frac{1}{k_2 E_0}$, which allows us to extract K and $k_2 E_0$.

These plots are Lineweaver-Burk plots.

Now, our quasi-steady approximation $c = \frac{s}{s+K'}$ does not satisfy our initial conditions $s=s_0$, $c=0$, since $c(0)=\frac{1}{1+K'} \neq 0$. This is because there is a rapid transient, $\Rightarrow s(0)=1$

when $t' = O(\varepsilon)$, during which the quasi-steady state approx. does not hold.

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

$$\frac{ds}{d\tau} = \varepsilon(-s + c(s + K' - \lambda)) = 0 \text{ to leading order since } \varepsilon \text{ is small} \Rightarrow \boxed{s = s_0}$$

($\frac{ds}{d\tau}=0 \Rightarrow s = \text{const.}$)

$$\frac{dc}{d\tau} = s - (s+K')c \xrightarrow{\text{subst. } s=s_0} \frac{dc}{d\tau} = s_0 - (s_0 + K')c$$

We solve this 1st order ODE $\frac{dc}{d\tau} + (s_0 + K')c = s_0$

We use the method of INTEGRATING FACTOR. $y = e^{(s_0+K')\tau}$

$$\frac{d}{d\tau}\left(e^{(s_0+K')\tau} c\right) = s_0 e^{(s_0+K')\tau}$$

$$e^{(s_0+K')\tau} c = \frac{s_0}{s_0+K'} e^{(s_0+K')\tau} + A \quad \text{/Const. of integration}$$

$$c = \frac{s_0}{s_0+K'} + A e^{-(s_0+K')\tau}$$

Using the initial condition $c(0)=0$: $0 = \frac{s_0}{s_0+K'} + A \Rightarrow A = -\frac{s_0}{s_0+K'}$, we obtain

$$c = \frac{s_0}{s_0+K'}(1 - e^{-(s_0+K')\tau})$$

If we use that $s(0) = s_0 = 1$, then this becomes

$$c = \frac{1}{1+K'}(1 - e^{-(1+K')\tau})$$

This takes us from $c=0$ at $t=0$ to the initial quasi-static value, and $c \sim \frac{1}{1+K'}$, as we move out of the boundary layer as $\tau \sim \infty$.

Inhibitors are substances that inhibit the catalytic reactions of an enzyme.

eg. 1 **COMPETITIVE INHIBITION** – when the substrate can't bind if the inhibitor is bound to an enzyme (other molecules w/ similar structure to substrate, can bind on the active site of the enzyme preventing the binding of the substrate)

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

↑ enzyme complex w/ substrate

and

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

↑ enzyme complex w/ inhibitor

You can do LAW OF MASS ACTION for these and analyze the reaction rate in a similar way to a previous case (see the typed lecture notes)

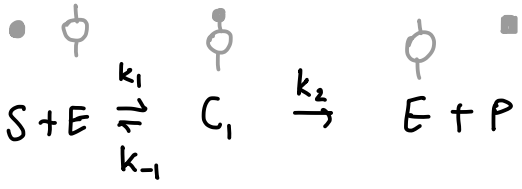
eg 2 **ALLOSTERIC INHIBITION** – As well as the previous two reactions we can also have the inhibitor binding to C_S to make a different product (other binding sites: a molecule can bind to one of these other sites, altering the 3D shape of the enzyme, and thus affecting the binding of the substrate on the active site).

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

↑ inhibitor

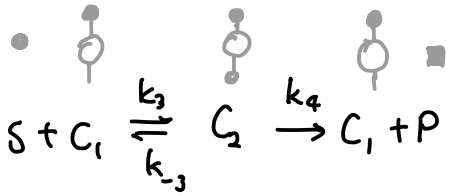
Cooperative systems – more than one binding site

enzyme w/ two active sites



$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C_1 \xrightarrow{k_2} E + P$$

Catalytic reaction to make P from S using E as a catalyst



$$S + C_1 \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} C_2 \xrightarrow{k_4} C_1 + P$$

Catalytic reaction to make P from S using the intermediate product C_1 as a catalyst too

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

$$r = \frac{(k_2 K_1 + k_4 S) E_0 S}{K_1 K_2 + K_2 S + S^2}$$

where $K_1 = \frac{k_{-1} + k_2}{k_1}$ and $K_2 = \frac{k_4 + k_{-3}}{k_3}$

For the derivation, please see the lecture notes

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

$$r = \frac{k_4 E_0 S^2}{K_1 K_2 + S^2}$$

Which is a Hill equation with exponent 2.

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

Recall this is the Hill equation

since $K_1 = \frac{k_{-1} + k_2}{k_1} \to \infty$ with $k_1 \to 0$ and $K_2 = \frac{k_3 + k_{-3}}{k_3} \to 0$ with $k_3 \to \infty$

CHAPTER 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

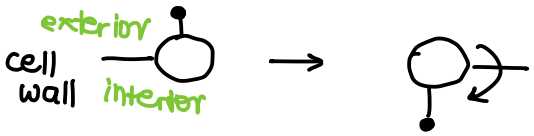
These exist both inside and outside the cell, creating a potential difference.

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

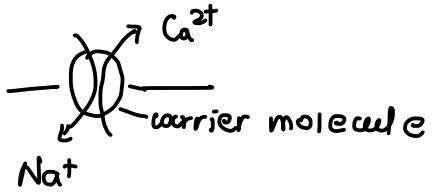
Osmosis is the mechanism by which water is transported across the cell membrane.

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

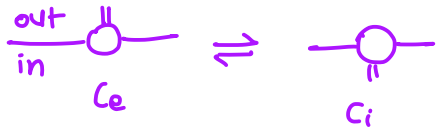
Carrier mediated transport - a molecule binds to a protein that has an active site that may be exposed to the interior or exterior of the cell (eg. glucose or amino acid transport)



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



A model for carrier mediated transport



carrier protein switches from binding-site-outwards to binding-site-inwards

C_i = state with binding site exposed to the interior

C_e = state with binding site exposed to the exterior

(binding/active site of the membrane can either be exposed in the interior or exterior)

C_e can bind with a substrate molecule in the exterior S_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 turn into P_e and vice versa. (This is the carrier during its 'rotation') (3)

[See below for pictures]

The reaction scheme is:

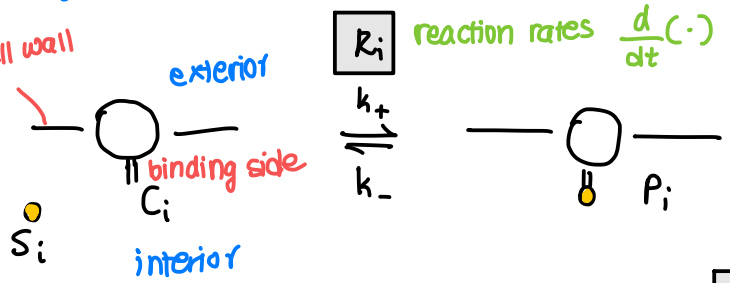
$$S_i + C_i \underset{k_-}{\overset{k_+}{\rightleftharpoons}} P_i \underset{k}{\overset{k}{\rightleftharpoons}} P_e \underset{k_+}{\overset{k_-}{\rightleftharpoons}} S_e + C_e \quad (*1)$$

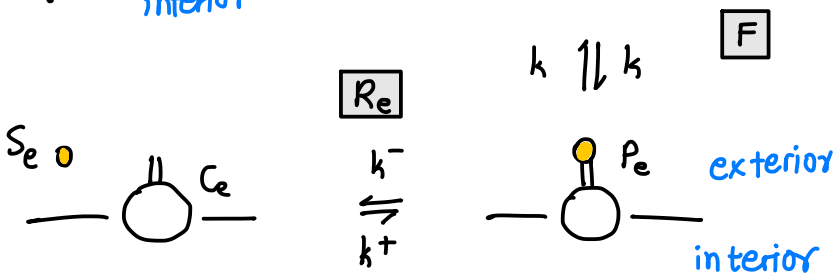
(2) (3) (1)

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

equally likely

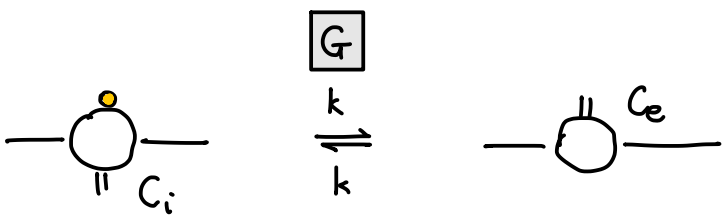
(*1):





" You can be on the inside or outside of the cell wall waiting for sth to bind "

(*2)



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 reaction.

Finally, suppose that substrate is supplied from the exterior at a const. rate J and taken away from the interior at the same rate. This is to avoid the system simply settling down to a steady state w/ zero flux.

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 this is 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 ①–⑥ in steady state to find

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

where $K_m = \frac{k_- + k_+}{k_+}$, $K_d = \frac{k}{k_+}$

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.

Recall: $\frac{dS}{dt'} = -\frac{\gamma S}{S + K'}$ Michaelis-Menten

($\frac{dS}{dt'} = J$)

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. [Sodium ions pumped out of the cell against the electrochemical gradient
Potassium ions pumped in]

Thus, the important distinction here to pay attention to is:

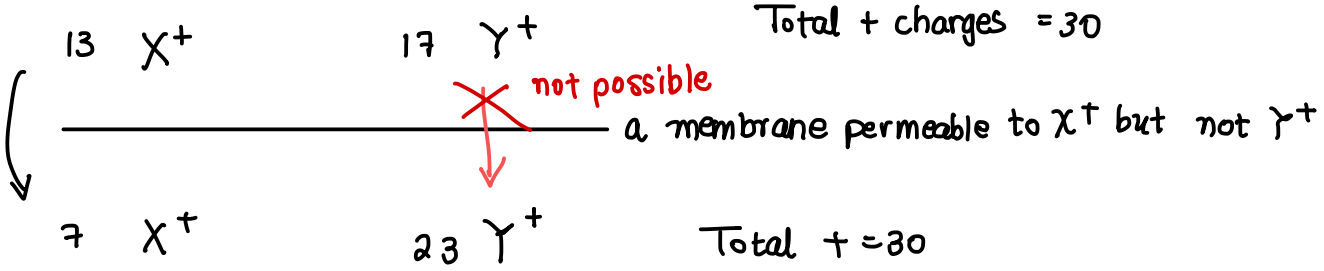
This is like the carrier mediated transport, but now there is a chemical reaction which requires energy. This allows chemicals to move against concentration gradients.

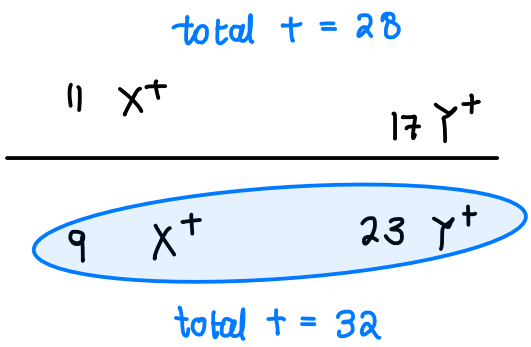
The Nernst potential and the resting potential

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.
high to low concent. ion charges moving

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





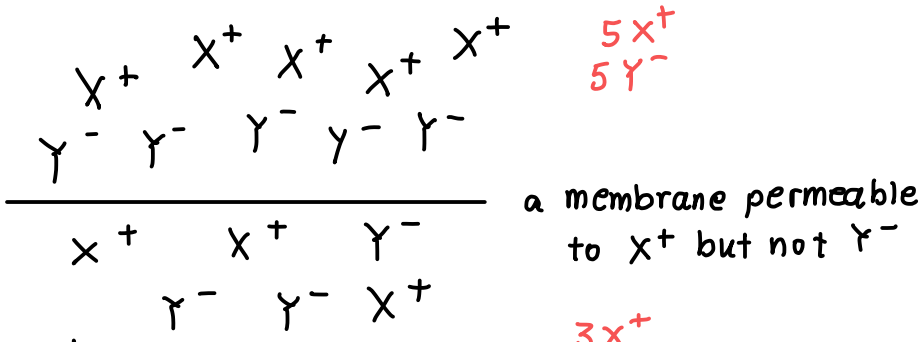
But doesn't reach 10 X^+ on each side because of electrostatic potential pushing back.

↳ charge imbalance sets up an electric field, which produces a force on the ions opposing further diffusion of X^+

Important: the actual amount of X^+ which diffuses through the membrane is small, and the excess charge all accumulates near the interface, so that to a good approx. the solutions on either side remain electrically neutral. The potential difference at which eqm is established and diffusion and electric-field-generated fluxes balance is the Nernst potential.

The membrane potential

Consider the following set-up:



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

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.

- What is this potential? There will be a flux of ions due to a concentration gradient.

$$\vec{J}_1 = -D\vec{\nabla}c$$

(D: ion diffusivity; c: concentration; regular diffusive flux)

There will be a flux of ions due to a potential difference (the ion carries a charge & is in the presence of an electric field)

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

- u = ion mobility = velocity under a constant electric field
- z = valence of the ion (i.e. valence = charge of ion (e.g. Na^+ has valence +1, O^{2-} has valence -2))
- $\frac{z}{|z|} = \pm 1$ giving ion charge (+ve ions move down potential gradients, -ve ions move up potential gradients)
- ϕ = electric potential $\Rightarrow \nabla\phi$ = electric field

So the total flux is $\vec{J} = \vec{J}_1 + \vec{J}_2 = -D\nabla\vec{c} - \frac{uzc}{|z|}\vec{\nabla}\phi$

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

Einstein's relation connects the diffusivity with the ion mobility: (look up Einstein relation in diffusion, or, kinetic theory)

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

R = universal gas constant

T = absolute temperature

F = Faraday's constant. (total electric charge divided by elementary charge carriers)

Note that (*) can be rewritten as $J = -D\left(\frac{\partial c}{\partial x} + \frac{Fzc}{RT}\frac{\partial \phi}{\partial x}\right)$, where x is a coordinate normal to the membrane.

In equilibrium, $J = 0$ (no flux) $\Rightarrow$ $\frac{\partial c}{\partial x} + \frac{zFc}{RT}\frac{\partial \phi}{\partial x} = 0$

We can integrate the flux J in (*) from $x=0$ (interior) to $x=L$ (exterior of membrane) to get:

$$V \overset{def}{=} \phi_i - \phi_e = \frac{RT}{zF}\log\left(\frac{c_e}{c_i}\right)$$

Nernst potential across cell membrane

e : exterior
i : interior

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 $V = \frac{Q}{C}$ (Q: charge difference, C: capacitance)

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

here I is the ionic current out of the cell (i.e. rate of flow of +ve charges outwards)

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

since $CV = Q$

$\frac{d}{dt}(CV) = \frac{dQ}{dt} \Rightarrow C\frac{dV}{dt} = -I$ if C = const

This eqn is the basis for much theoretical electrophysiology

We link the current of each species of ion S to the voltage via $I_S = g_S(V - V_S)$

(V_S: Nernst potential; g_S: ion-specific membrane conductance; $I_S = 0$ when $V = V_S$)

The total current is $I = \sum_S I_S$.

$\rightarrow$ just $V = IR$ (Ohm's law)

and conductance is $\frac{I}{V} = \frac{1}{R}$

Recall that conductance is a measure of how easily an electric current flows through a material. (It's the reciprocal of resistance)

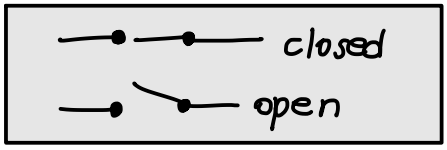
Def protein-lined pores which allow the passage of specific molecules

But what does g_S look like?

This is **not** a constant — it depends on the fraction of gates that are available (i.e that are open) (we know this experimentally) Let's denote the fraction of open channels by n

Then $g_S = n g_{S_{max}}$

↑ conductivity when all gates are open.



depend on the voltage

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

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

n: fraction of open gates; $(1-n)$: fraction of closed gates

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

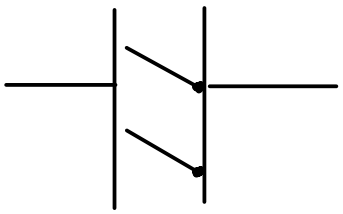
$$\Rightarrow \frac{1}{\alpha(V)+\beta(V)}\frac{dn}{dt} = \frac{\alpha(V)}{\alpha(V)+\beta(V)} - n$$

$$\Rightarrow \boxed{\tau(V)\frac{dn}{dt} = n_\infty - n} \quad \text{where } n_\infty = \frac{\alpha}{\alpha+\beta} \text{ (eqm value of } n\text{)} \quad \text{and} \quad \tau(V) = \frac{1}{\alpha+\beta}$$

$\tau(V)$: timescale for approach of the equilibrium n_∞

We note that both n_∞ and τ are determined experimentally.

You can also have **multiple gates**. Let S_i = density of states with i open gates. Then the transition between gate states is governed by the reaction:



$$S_0 \underset{\beta}{\overset{2\alpha}{\rightleftharpoons}} S_1 \underset{2\beta}{\overset{\alpha}{\rightleftharpoons}} S_2$$

number of closed gates

the factor of 2 is because there are two configurations for going from 2 open to 1 open gate and similarly for closed to open

Law of mass action gives

$$\frac{dS_0}{dt} = -2\alpha S_0 + \beta S_1$$

$$\frac{dS_2}{dt} = \alpha S_1 - 2\beta S_2$$

We could also write down an equation for S_1 but this equation is superfluous, since we can just infer it from $S_0 + S_1 + S_2 = 1$ (conservation of gates)

We can reduce to one ODE by finding that the solution is

$$S_0 = (1-n)^2, \quad S_1 = 2n(1-n), \quad S_2 = n^2$$ (we can see this by simple substitution)

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

[See 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 $n^2 g_{s_{max}}$.

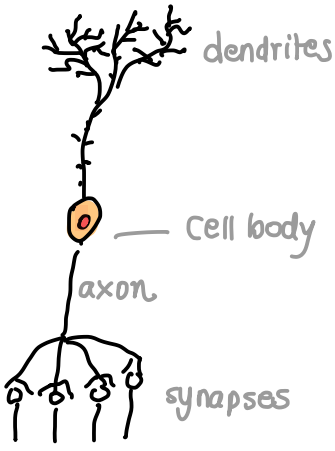
This result generalizes for N gates with a conductivity of $n^N g_{s_{max}}$

You can also look at the case of non-identical gates – see lecture notes on pg 34.

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.



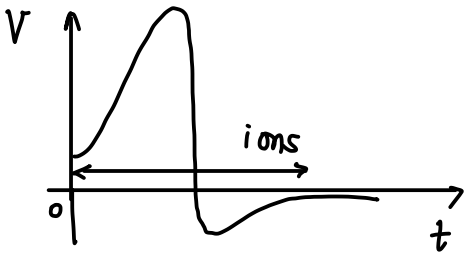
EXCITABILITY OF NEURONS

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 —

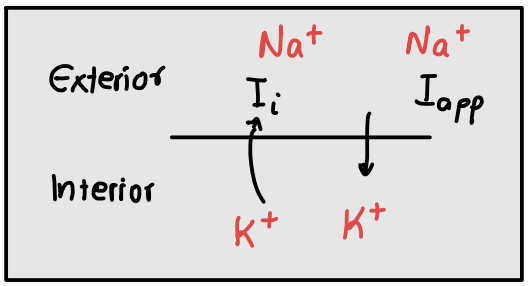
before returning to its resting volve.

Signals are transmitted by the propagation of these action potentials. Later on we will look at this spatial propagation down an axon, but for now we will look at a spatially independent model.



This propagates down the axon like a wave.

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.



(external inward current)

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

i.e.
How does I_i respond to I_{app}?
How much energy do we need for this Na^+-K^+ pump?

Our earlier equation $C\frac{dV}{dt} + I = 0$ ①

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

C_m: capacitance of the membrane

$(I_i - I_{app})$: total outward current

Now we'll figure out the eqns that are satisfied by Na & K using the eqns for the gates from before

Potassium flow

Recall we have our link between V (applied voltage) and I_i (resulting current): $I_i = g_s(V - V_s)$ and $g_s = n^N g_{s_{max}}$ (conductivity)

where N = number of gates and $\tau(V)\frac{dn}{dt} = n_\infty(V) - n$ ② ← true regardless of what the N is

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 as experimental fit. (the underlying physics is behaving like a 4-gate system but it's a bit more complicated than that)

$g_s = n^4 g_K$, $g_K = g_{s_{max}}$

n is called the potassium activation.

Sodium flow

For the sodium conductance there is a protein that turns the sodium current on and another which turns it off. This can be described by

$$g_s = g_{Na} m^3 h^1$$

again these powers are an experimental fit rather than related to gates

g_{Na} ~ $g_{s_{max}}$

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

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

is an appropriate model. This is like two gates:

m is called the sodium activation

h is called the sodium inactivation.

The Hodgkin-Huxley model for the outward ionic current is then

resting potentials

$$I_i = g_{Na} m^3 h (V - V_{Na}) + g_K n^4 (V - V_K) + g_L (V - V_L) \quad (5)$$

Na^+ current (sodium) | K^+ current (potassium) | leakage (mainly Cl^- chloride ions)

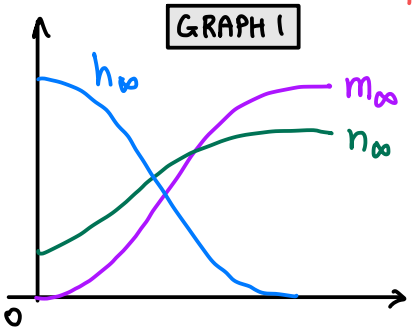
other ions flying around that contribute to the current

(This model also comprises the ODE system (1)–(4)). The closed system is (1)-(5).

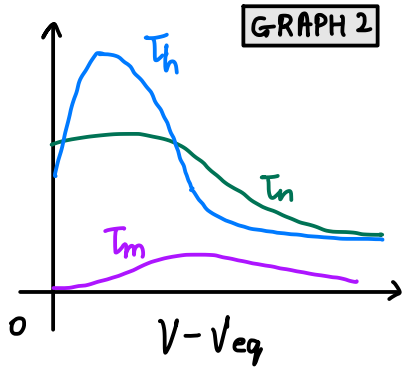
NB. The resting potential is the value of V when the outward ionic current is zero.

What does the potential do?

These values are experimentally measured



Eqm gate variables as fcns of potential relative to resting potential



Relaxation times as fcns of potential relative to resting potential

STEPS

(1) Apply a current I_{app}

(2) V rises due to the current (eqn ①) $C_m \frac{dV}{dt} + (I_i - I_{app}) = 0 \Rightarrow \uparrow C_m \frac{dV}{dt} = I_{app} - I_i \uparrow$

(3) τ_m is small (graph 2) so m rises quickly (eqn ③) $\frac{dm}{dt} = \left(\frac{m_\infty - m}{\tau_m \downarrow}\right) \uparrow$

$\Rightarrow Na^+$ floods into the axon from outside (since $g_s = m^3 h g_{Na}$) m increasing means more gates open for Na

Sodium activation

(4) This causes even more of a potential difference, causing m_∞ to rise (graph 1), which causes even more of a potential difference (from step (3) above) $\frac{dm}{dt} = \left(\frac{m_\infty \uparrow - m}{\tau_m}\right) \uparrow$

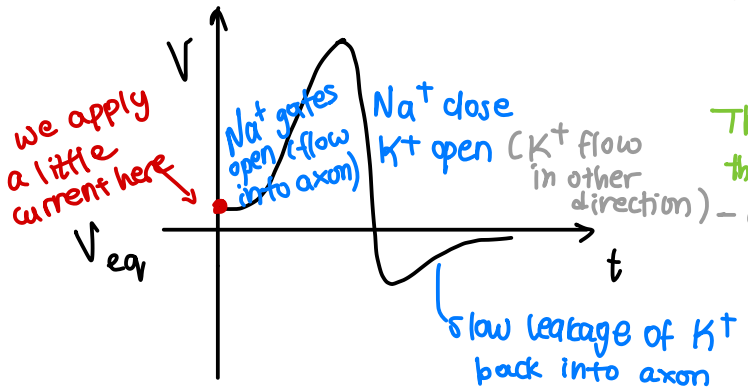
(5) h_∞ falls causing Na^+ flow to slow as g_{Na} falls (gate closes) activation gates ↑ deactivation gates ↓

n_∞ rises (graph 1) causing K^+ to flow out of the axon (g_{K^+} rises - gate opens) $g_s = n g_{Na}$

This causes an overshoot past V_{eq} (because $V_K < V_{eq}$)

Resting potential for K^+

(6) A slow leakage of K^+ back into the axon causes the system to go back to equilibrium (this recovers from the overshoot)



This is an action potential, obtained by solving the Hodgkin-Huxley model. (visualisation)

NB The I_{app} doesn't give a relaxation to V_{eq} immediately, but first an excitation that we are interested in.

The membrane is excitable. The equilibrium is a steady state but a large enough perturbation (which in practice isn't too large) that causes the potential to undergo an excursion – the action potential.

Note If we spatial independence:
We'll basically have a traveling wave of this action potential from the axon to the muscles that tells the muscles to do something

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

Section 2.3 . FitzHugh-Nagumo model [approximate asymptotic reduction of the Hodgkin-Huxley model]

Assumptions: 1) τ_m is small so $m \approx m_\infty(V)$ ($\tau_m \ll \tau_n, \tau_h$)

(m rapidly reaches its quasistable value, using ③) Recall eqn ③ $\frac{dm}{dt} = \frac{m_\infty - m}{\tau_m}$

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

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

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

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

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

This system is true for all time so it eventually settles to $n+h=\bar{h}$

This reduces the Hodgkin-Huxley model (four ODEs for V, n, m, h) to the two-dimensional system for V and n: (see problem sheet 2 for this)

$$C_m \frac{dV}{dt} = I_{app} - \left(g_k (V - V_k) n^4 + g_{Na} (V - V_{Na}) m_\infty^3(V)(\bar{h} - n) + g_h (V - V_h)\right)$$

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

We'll see if some of these parameters are small & negligible

Let's **non-dimensionalise** the system:

$$v = \frac{V - V_{eq}}{V_{Na} - V_{eq}} \quad \text{and.} \quad t = \tau_n(V_{eq})\, t'$$

voltage

(V_{eq}: resting potential for Na^+; v sets to 0 rather than V_{eq}.)

This leads to the dimensionless system

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

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

Dimensionless parameters

$$I^* = \frac{I_{app}}{g_{Na}(V_{Na} - V_{eq})} \qquad V_k^* = -\frac{(V_k - V_{eq})}{V_{Na} - V_{eq}}$$

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

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

where $g(v, n) = \gamma_k (v + V_k^*) n^4 + \gamma_L (V - V_L^*) - (1 - v)(\bar{h} - n) m^3(V)$ with

Key point: $\varepsilon \ll 1$ where $\varepsilon = \frac{C_m}{g_{Na}\tau_n}$

This is why we non-dimensionalize — to see the relative parameter sizes.

Key point: $\varepsilon \ll 1$, so V quickly reaches a quasisteady equilibrium in ② and $\gamma_L \ll 1$, so $g(V,n)$ simplifies: → you can see this through ②

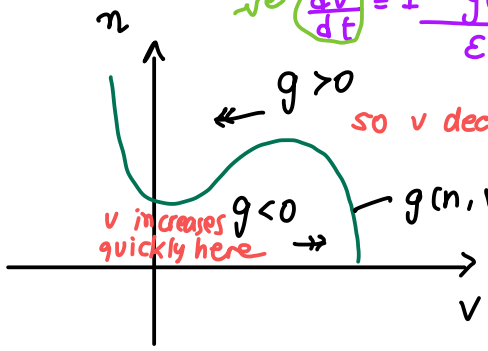
$$g(V,n) = \gamma_K (V+V_K^*) n^4 - (1-V)(\bar{h}-n) m_\infty^3(V) \qquad \frac{dV}{dt} = \frac{I^* - g(V,n)}{\varepsilon}$$

PHASE PLANE ANALYSIS

Start by considering the case $I^* = 0$ (i.e. no applied current, from ①, V is given by $g=0$)

Setting $\varepsilon = \gamma_L = 0$ (identified as small) in ② gives $\frac{n^4}{\bar{h}-n} = \frac{(1-V)\, m_\infty^3(V)}{\gamma_K (V+V_K^*)}$ (*) an algebraic relationship between n and V

large & -ve $\frac{dV}{dt} = \frac{I^{*}{}^{>0} - g(V,n)}{\varepsilon}$

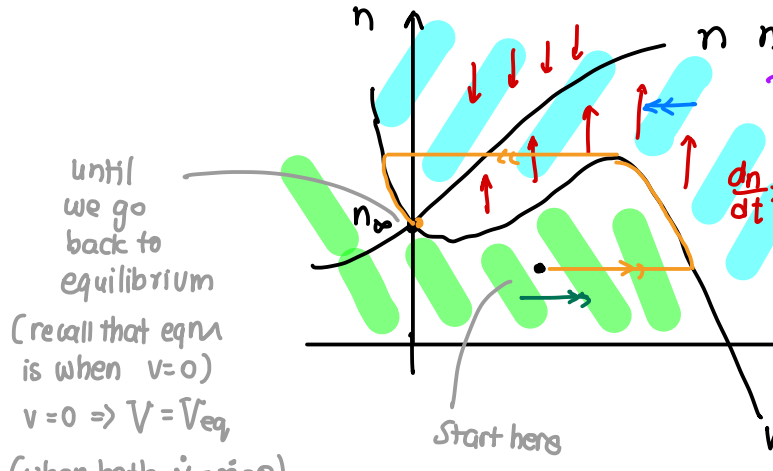


Since $\varepsilon \ll 1$ we know that the system quickly jumps onto this nullcline

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

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

(nullclines in general are when you set the $\frac{d}{dt}$ to zero)



PHASE PLANE ANALYSIS

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

STABILITY

Linearize near the fixed point, $n = n_\infty$, $v = 0$

Set $V = v$

$n = n_\infty + N$, $v, N \ll 1$

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

trace

$\det(\underline{\underline{M}}) > 0$ and $tr(\underline{\underline{M}}) < 0$

$\Rightarrow$ node or spiral

Trace and determinant method

Eigenvalues can be written as

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

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

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

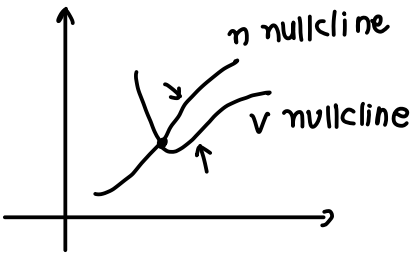
Proof Now slope of n nullcline $= \frac{dn_\infty}{dv}$

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

Differentiate $g(v, n(v)) = 0$ wrt v:

$\frac{\partial g}{\partial n}\frac{\partial n}{\partial v} + \frac{\partial g}{\partial v} = 0$, $\frac{\partial n}{\partial v} = \frac{-\frac{\partial g}{\partial v}}{\frac{\partial g}{\partial n}}$.

and from graph: slope of n nullcline $>$ slope of v nullcline



$\Rightarrow \frac{dn_\infty}{dv} > -\frac{\frac{\partial g}{\partial v}}{\frac{\partial g}{\partial n}}$. This implies that

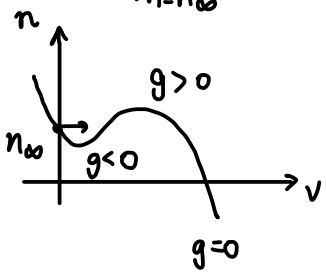
$\det(\underline{\underline{M}}) > 0$ and $\mathrm{tr}(\underline{\underline{M}}) = -\left(-\frac{1}{\varepsilon}\frac{\partial g}{\partial v}\Big|_{n=n_\infty}\right)$

Fixed point is stable if $\mathrm{tr}(M) < 0 \Rightarrow \frac{\partial g}{\partial v}\Big|_{n=n_\infty} > -\varepsilon$

$\frac{\partial g}{\partial v}\Big|_{n=n_\infty} > 0$ because of picture

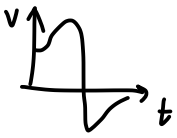
& definitely $\frac{\partial g}{\partial v}\Big|_{n=n_\infty} > -\varepsilon$

Fixed point is stable.



$\frac{\partial g}{\partial v}\Big|_{n=n_\infty}$ means: rate of change of g in the v direction while keeping n fixed (start on $g=0$, or v nullcline)

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 to give a bit of energy to kick it round the cycle (i.e. it doesn't continue on the loop w/o energy input)

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.

easier to handle this mathematically

FitzHugh-Nagumo model

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

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

FitzHugh-Nagumo equations

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

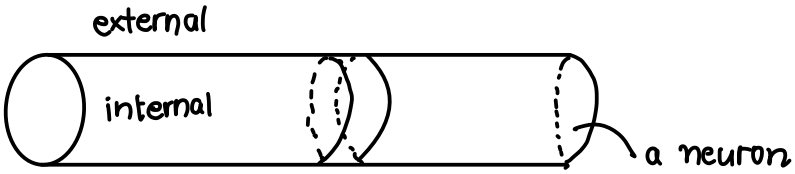
$\dot{w} = \gamma v - w$ ← linear fcn

$f(v) = v(v-a)(1-v)$ ← cubic fcn $\quad 0 \le a \le 1$

Fun fact of the day: Nerve signals can travel at speeds of 270 mph. This allows you to react quickly to various stimuli, such as pulling your hand away from a hot surface or reacting to a sudden loud noise

Wave propagation in neurons

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



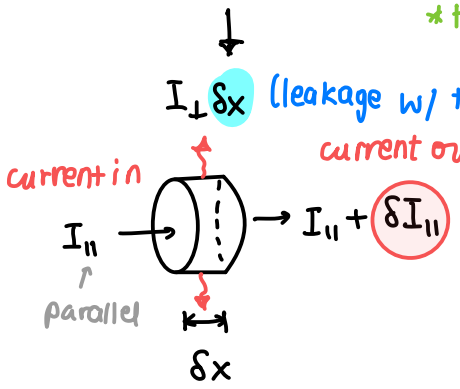
* the axon behaves like an electric cable

$I_\perp$ = transmembrane current per unit length

$I_\parallel$ = axial current

R = axial resistance (unwillingness of axon to transmit current down it)

C = capacitance per unit length (ability to store charge)



if I apply to something w/ capacitance C, a voltage V, then the total charge held by this small segment is $CV\delta x$

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

current out right

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

(only this increases the total charge $CV\delta x$)

Assuming C = const.

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

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

* the axon's internal electrical potential V is now a function of distance x along the cable and time t.

Taking the limit as $\delta x \to 0$

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

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

$$\Rightarrow \frac{\partial V}{\partial x} = -I_\parallel R \Rightarrow I_\parallel = -\frac{1}{R}\frac{\partial V}{\partial x}$$

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)

assuming the axon has a circular cross section

If the neuron perimeter is $p = \pi d$, then $I_\perp = p(I_i - I_{app})$

(p: diameter; $I_\perp$: need it per unit length; $(I_i - I_{app})$: current per unit area between inside and outside as defined earlier)

and $C = pC_m$

(C: capacitance per unit length; C_m: 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

$$\pi d C_m \frac{\partial V}{\partial t} = -\pi d(I_i - I_{app}) + \frac{\pi d^2}{4R_c}\frac{\partial^2 V}{\partial x^2}$$

$$\Rightarrow C_m \frac{\partial V}{\partial t} = I_{app} - I_i + \frac{d}{4R_c}\frac{\partial^2 V}{\partial x^2}$$

Non-dimensionalization

$$V = \frac{V - V_{eq}}{V_{Na} - V_{eq}}, \quad I_i = g_{Na}(V_{Na} - V_{eq})\, g(n, V), \quad x = l\hat{x}, \quad t = \tau_n \hat{t}$$

(l: to be chosen later)

(same as earlier non-dimensionalization)

where l is to be chosen later

This gives

$$\begin{cases} \varepsilon \frac{\partial v}{\partial t} = I^* - g(n, v) + \varepsilon^2 \frac{\partial^2 v}{\partial x^2} \\ \frac{\partial n}{\partial t} = n_\infty(v) - n \end{cases}$$

See problem sheet ② for derivation of this

This is the **space dependent version of the FitzHugh-Nagumo model** - it's the same but just with a $\frac{\partial^2 v}{\partial x^2}$ term. [spatial variation of V adds diffusion term]

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

$$\varepsilon \frac{\partial v}{\partial t} = f(v) - w + \varepsilon^2 \frac{\partial^2 v}{\partial x^2} \qquad f(v) = v(v-a)(1-v)$$

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

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 traveling down the axon

$v = v(\xi)$, $w = w(\xi)$, $\xi = ct - x$, $c > 0$ waves we'll draw at the end will go from right to left

$$\text{①} \quad \varepsilon c v' = f(v) - w + \varepsilon^2 v''$$

$$\text{②} \quad c w' = \gamma v - w$$

phase plane w/ v, w, v'

NB the primes are derivatives wrt ξ

with $v, w \to 0$ as $\xi \to \pm\infty$ (solitary waves in which the solution returns to the rest state at each end)

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.

There are four different regions of behaviour:

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

$$\text{①} \quad \varepsilon c v' = f(v) - w + \varepsilon^2 v''$$

$\varepsilon c v'$: fast motion; $f(v) - w \neq 0$; $\varepsilon^2 v''$: higher order correction

Just like before (ignoring the higher order ε^2 term)

In this region, things happen over a fast ξ scale. This suggests rescaling $\boxed{\xi = \varepsilon \xi}$

$$\text{①} \Rightarrow c \frac{dv}{d\xi} = f(v) - w + \frac{d^2 v}{d\xi^2} \quad \text{①'}$$

and in this region, considering the other equation, $cw' = \gamma v - w$ (② from above)

$$\Rightarrow c \frac{\partial w}{\partial \xi} = \varepsilon(\gamma v - w)$$

$$\Rightarrow w = \text{constant}.$$

We choose coordinates such that the resting state corresponds to $(v, w) = (0, 0)$.

Thus $w \simeq \text{const} = w_{\text{resting}} = 0$. This is not saying that a const w must be zero but starting from rest, the slow variable w hasn't moved yet, so it equals its resting value (which is 0 in the shifted coords)

Now set $\frac{dv}{dJ} = u$. Then we can write (1') $c\frac{dv}{dJ} = f(v) - v + \frac{d^2v}{dJ^2} \Rightarrow cu = f(v) + u'$ where $'$ denotes derivative wrt J now

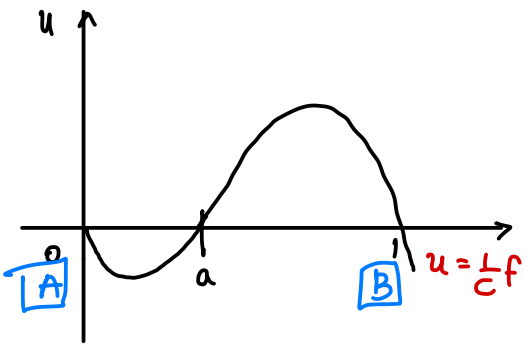
Then our phase plane system is $\begin{cases} v' = u \\ u' = cu - f(v) \end{cases}$ Phase plane system

stripped down eqns on pg 26 to phase plane in v, (1') which we called u (2D slice of 3D space)

$= v(v-a)(1-v), \quad 0 < a < 1$

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

the 3 equilibria are the zeros of $f(v)$ with $u = 0$



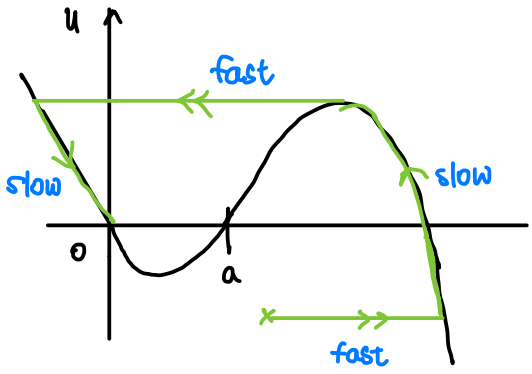
$u' = cu - f(v)$. Thus $u' = 0$
$\Rightarrow cu = f(v)$
$\Rightarrow u = f(v)/c$

can see this through linearisation

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 replicate the action potential we had in the space-clamped case where we had the fast behaviour jumping out of the nullcline.)

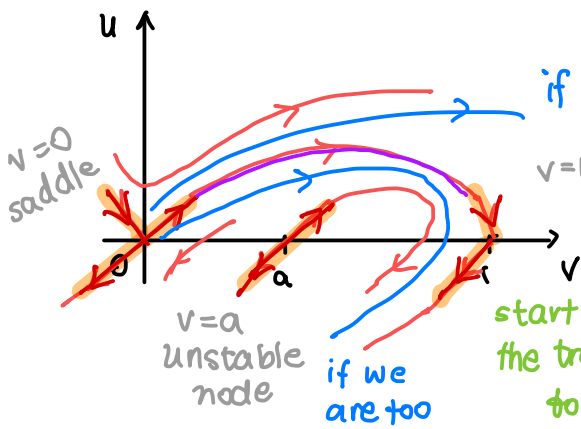
Similar to what we had before



There is only one value of c that achieves this now:

$$\frac{du}{dv} = \frac{u'}{v'} = \frac{cu - f(v)}{u} = c - \frac{f(v)}{u} = c$$ at $v = 0$, so gradient of trajectory is c

because $f(v=0) = 0$



"if we are too high" we will "fly off"

we are after the purple one that takes us from v=0 to v=1

start by drawing the trajectories close to v=0, a, 1 given their known nature & fill in the trajectories after

if we are too low we'll also fly off

Like a shooting problem. This is how c (wave speed) is selected - this means there is a unique wave speed for the travelling wave.

(ii). Thus, once we land on the u nullcline ($u = \frac{f(v)}{c}$, i.e. $v' = \frac{f(v)}{c}$) we slowly move on this. Specifically, on this we have

recall we set $u = v'$

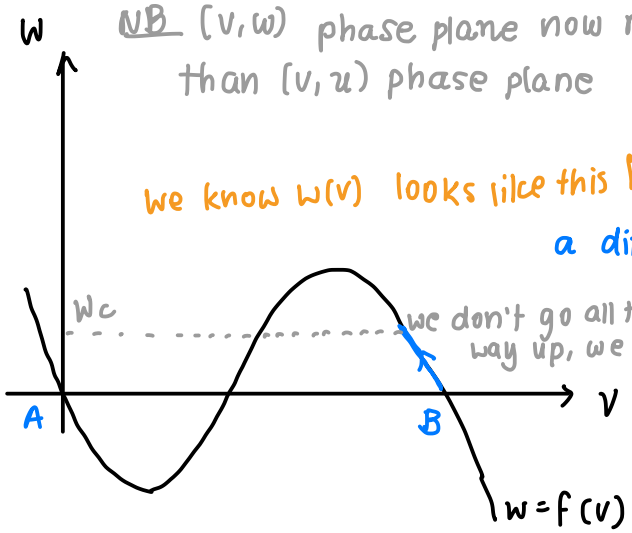
$\Rightarrow cv' = f(v)$

$$\left.\begin{aligned} \varepsilon c v' &= f(v) - w + \varepsilon^2 v'' \\ \Rightarrow \varepsilon f(v) &= f(v) - w + \varepsilon^2 v'' \end{aligned}\right\} \quad \boxed{cw' = \gamma v - w} \ (2) \text{ from before}$$

to leading order in ε

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

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

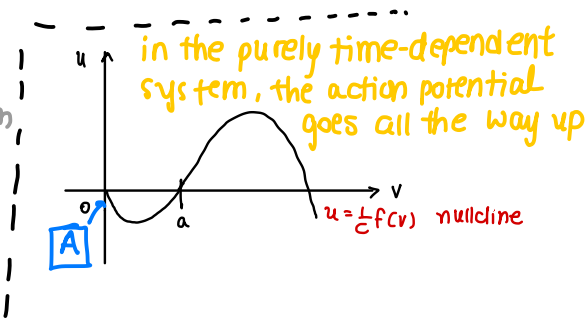


NB (v, w) phase plane now rather than (v, u) phase plane

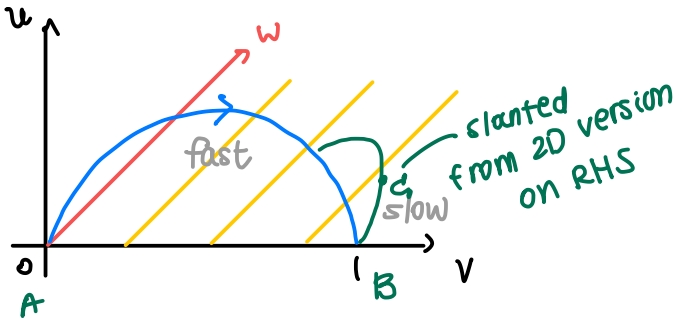
we know w(v) looks like this because $w = f(v) = v(v-a)(1-v)$ from (1) just above

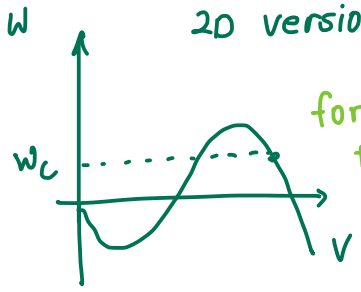
a different slice now

we don't go all the way up, we go in the 3rd dimension



in the purely time-dependent system, the action potential goes all the way up





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 value (w_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 $\boxed{\tau = \varepsilon t}$ to capture this, but this time $w = w_c$ (a nonzero constant, which we need to find out what value it is). Then the system is

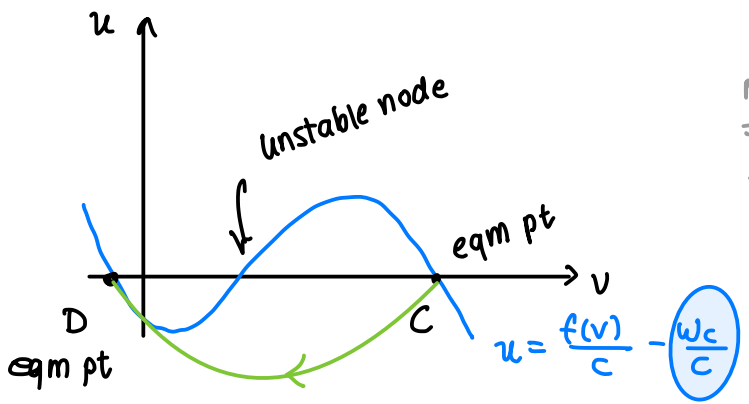
$$cv' = f(v) - w_c + v'' \qquad \text{where} \quad \cdot' = \frac{d\cdot}{d\tau}$$

The advantage of this now is we can again turn it into a phase plane, by writing it as a first-order system.

Phase plane system $\begin{cases} v' = u \\ u' = cu - f(v) \end{cases}$ from before, becomes now

$$\Rightarrow \boxed{\begin{aligned} v' &= u \\ u' &= cu - f(v) + w_c \end{aligned}}$$

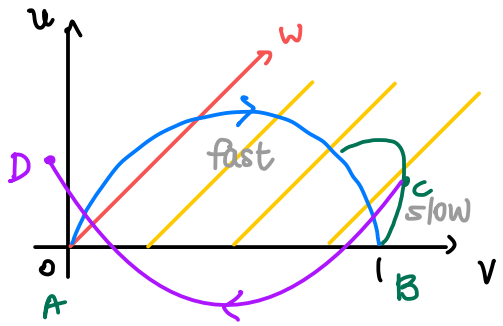
Going back into the (u,v) plane again we end up w/ something quite similar



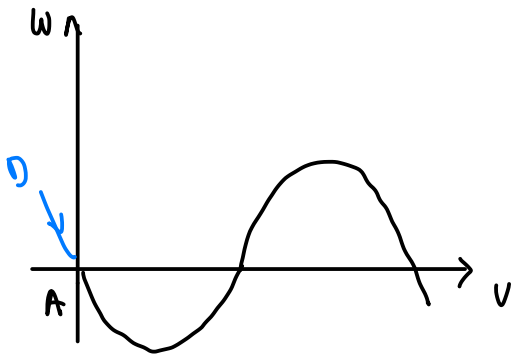
Nullcline : $u' = 0$
$\Rightarrow 0 = cu - f(v) + w_c$
$\Rightarrow u = (f(v) - w_c)/c$
same curve as before but shifted down by this amount

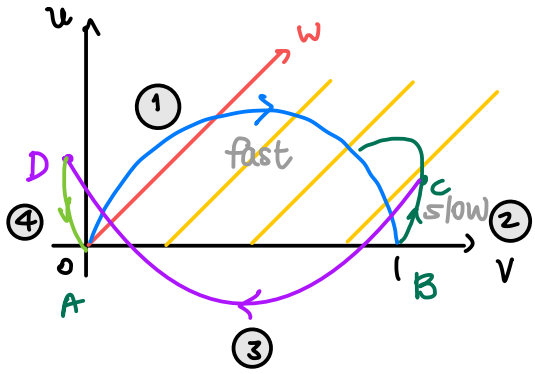
C & D are saddles and this time we have a trajectory that takes us from C to D.

This time it is w_c that we need to choose correctly (just like we had to choose the wave speed c correctly in part (i)).



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

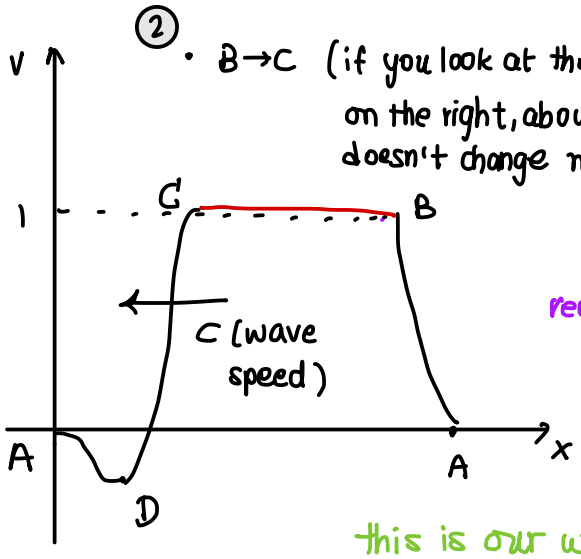




A → B, B → C, C → D, D → A
fast slow fast slow

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

The trajectories
A → B
B → C
C → D
D → A
take a certain amount of time but we are interested in the voltage



② • B → C (if you look at the plot on the right, above, B doesn't change much)

① • A → B
v goes from 0 to 1
& it happens quickly

recall that since we chose $\tau = ct - x$, $c > 0$ we go from right to left

this is our wave train which propagates w/ speed c

③ C→D This takes us from $v \approx 1$ to $v \approx 0$ (but a bit negative)

* Same as the space-clamp version, but in that case the wave train above would be a time trace whereas the one above is moving down the axon.

The section above is about how a signal propagates from our brain to our muscles to say "do something". But the muscle then has to do something. This is what we will cover next.

Chapter 4: CALCIUM DYNAMICS

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

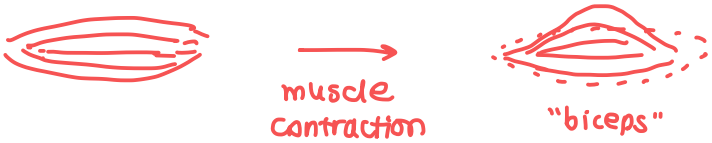
Ca^{2+} is stored in cells in bones & released by hormonal stimulation. The internal store is called the sarcoplasmic reticulum.

It releases Ca^{2+} via calcium induced release

The intracellular fluid matrix is called the sarcoplasm.

Extracellular Ca^{2+} concentrations are higher than intracellular concentrations so Ca^{2+} must be pumped out.

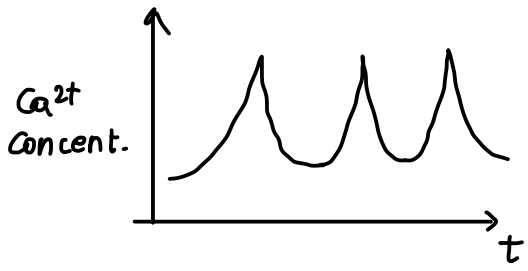
Muscle cells are bundles (fascicules) of muscle fibres (cells) each of which contains arrays of filament structures (microfibrils) which contract under the action of Ca^{2+}



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

Na^+ floods in and this allows Ca^{2+} in too

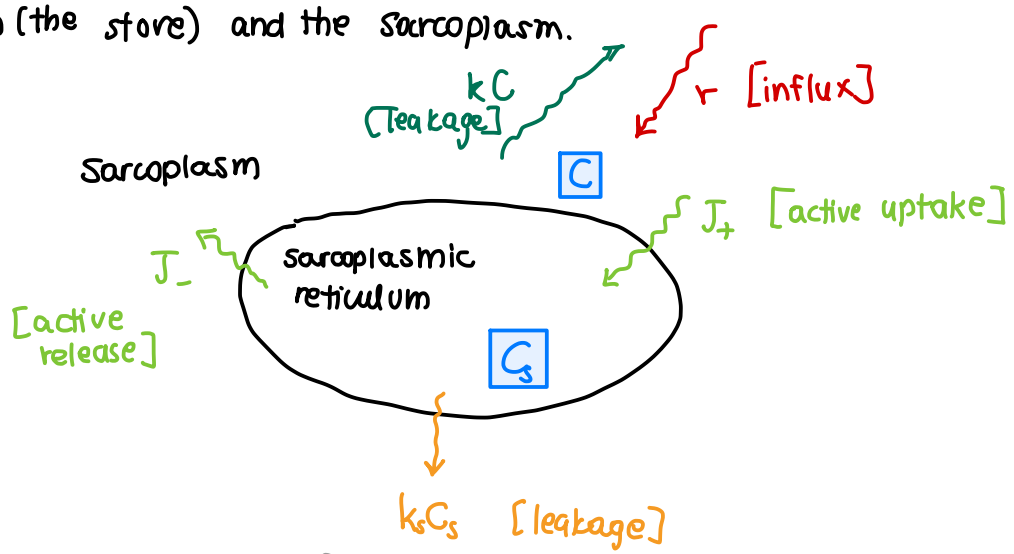
The release of Ca^{2+} is quite spiky



Can we derive a mathematical model for muscle contraction with a low Ca^{2+} concentration in steady state 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.



(it makes sense that the leakage is proportional to the conc. C_s. If we double C_s, we'll have more leakage)

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

C_s = " " Sarcoplasmic reticulum (SR)

J_+ = rate of take up of Ca^{2+} by the sarcoplasmic reticulum (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 from the outside world because of an applied stimulus.

k_sC_s = rate of leakage of Ca^{2+} from SR into the sarcoplasm [passive - proportional to concentration]

k_C = rate of leakage of Ca^{2+} from sarcoplasm to outside world [passive - proportional to concentration]

$$\frac{dC_s}{dt} = J_+ - J_- - k_s C_s \overset{\text{def}}{=} F$$

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

$$= r - kc - F$$

We choose $J_+ = \dfrac{V_1 c^n}{K_1^n + c^n}$ (from experiments) — constants; Hill function again

NB V_1 is not a voltage, it is a concentration rate.

V_1, K_1, n are just numbers

these bits aren't important

$$J_- = \left(\frac{V_2 C_s^m}{K_2^m + C_s^m}\right)\left(\frac{c^p}{K_3^p + c^p}\right)$$ Hill function

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

Non-dimensionalisation

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

$\Big\|$ $u, v, \hat{t}, f$ all dimensionless counterparts

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

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

implicit function of u and v that we can plot

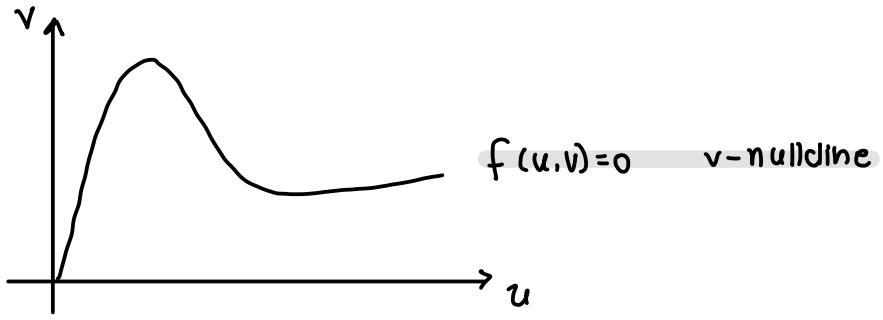
where $f = \beta\left(\dfrac{u^n}{1+u^n}\right) - \left(\dfrac{v^m}{1+v^m}\right)\left(\dfrac{u^p}{\alpha^p + u^p}\right) - \delta v$

with $\mu = \dfrac{r}{kK_1}$, $\gamma = \dfrac{K_2}{K_1}$, $\varepsilon = \dfrac{kK_2}{V_2} \ll 1$, $\alpha = \dfrac{K_3}{K_1}$, $\beta = \dfrac{V_1}{V_2}$, $\delta = \dfrac{k_s K_2}{V_2} \ll 1$

as our dimensionless parameters.

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, $f(u,v)=0$



How to plot this curve?

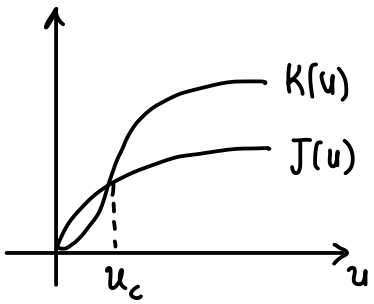
① $\delta \ll 1$ so ignoring the δ-term in $f(u,v)$ gives

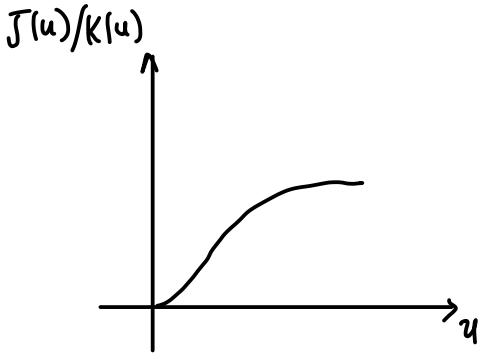
$$f = \beta\left(\frac{u^n}{1+u^n}\right) - \left(\frac{v^m}{1+v^m}\right)\left(\frac{u^p}{\alpha^p+u^p}\right) - \delta v = 0$$

$-\delta v \approx 0$ since $\delta \ll 1$

$= 0$ in the nullcline

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



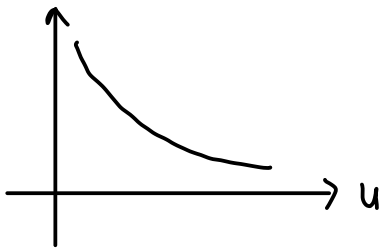


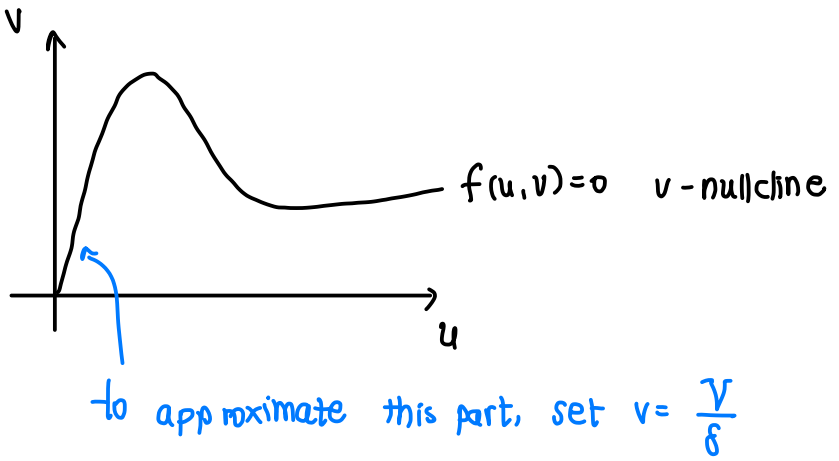
$$\Rightarrow \quad v^m = (1+v^m)\frac{J(u)}{K(u)} \Rightarrow \quad v^m\left(1-\frac{J(u)}{K(u)}\right) = \frac{J(u)}{K(u)}$$

$$v^m\left(\frac{K(u)-J(u)}{K(u)}\right) = \frac{J(u)}{K(u)}$$

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

$\phi(u)$





For the rest of this, see problem sheet.

Now let's look at the dynamics. 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 $u = \text{const}$ unlike in the previous cases. This time we note that

since $\frac{dv}{dt} = \frac{1}{\varepsilon} f(u,v)$ $\Rightarrow$ $\frac{du}{dt} = \mu - u - \gamma \frac{dv}{dt}$

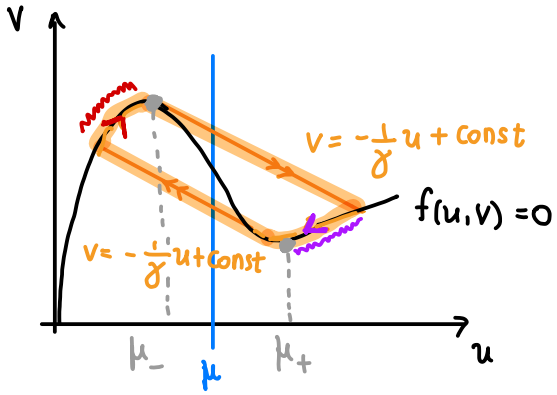
$\Rightarrow$ $\frac{du}{dt} + \gamma \frac{dv}{dt} = \mu - u$

On the fast timescale $\boxed{t = \varepsilon\tau}$ we have $\varepsilon \frac{dv}{dt} = f(u,V)$ becomes $\frac{dv}{d\tau} = f(u,V)$ giving the movement of v to the v-nullcline and $\frac{du}{d\tau} + \gamma \frac{dv}{d\tau} = \varepsilon(\mu - u)$

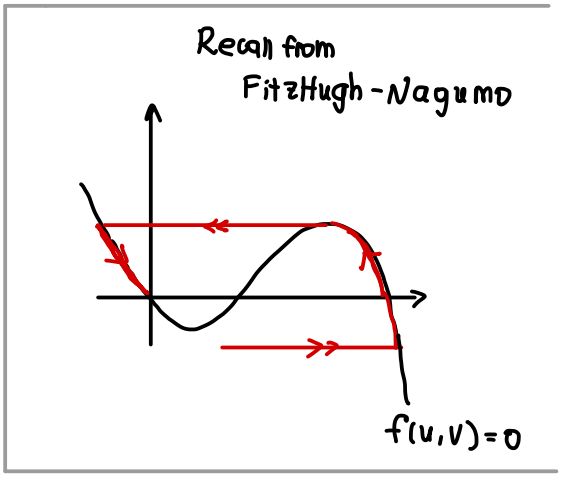
↑ these are $\frac{d}{d\tau}$ not $\frac{d}{dt}$

$\Rightarrow u + \gamma v = \text{const.}$ to leading order in ε.

So we move to the v-nullcline along the line $v = \frac{\text{const} - u}{\gamma} = -\frac{1}{\gamma} u + \frac{\text{const}}{\gamma}$



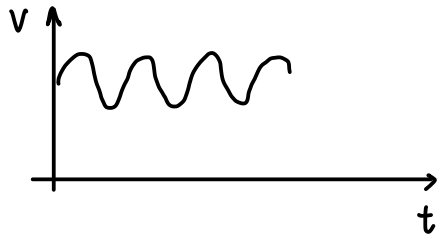
μ_+ and μ_- are the points where the gradient of the curve $f(u,v)=0$ is $-\frac{1}{\gamma}$

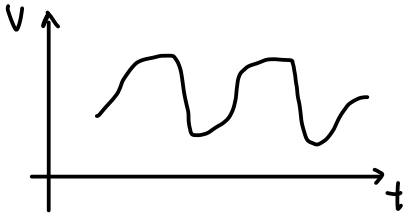


Case (i): $\mu_- < \mu < \mu_+$

Then $\frac{d}{dt}(u+\gamma v) = \mu - u$. When $u<\mu$, we move to the right
When $u>\mu$, we move to the left

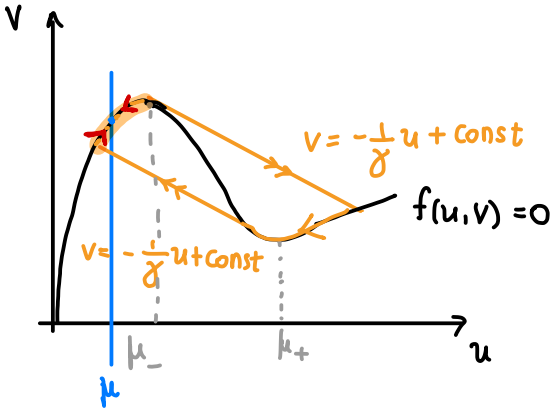
This leads to **self-sustained** or **relaxation oscillations**. $\frac{d}{dt}(u+\gamma v) = \mu - u < 0$ when $u > \mu_+$
> 0 when $u < \mu_-$





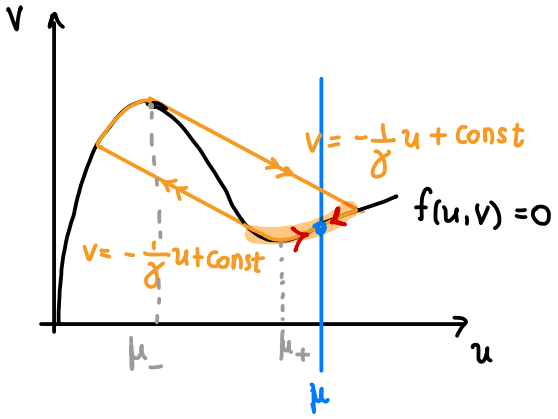
Case (ii): $\mu < \mu_-$

Then $\frac{d}{dt}(u+\gamma v) = \mu - u < 0$ when $u < \mu$ $(<\mu_-)$ we move to the right
when $u > \mu$ we move to the left



We need a bit of energy / excitation to move away from the blue equilibrium point, and then we get an excursion — a muscle contraction!

Case (iii): $\mu > \mu_+$



$\frac{d}{dt}(u + \gamma v) = \mu - u$. When $u < \mu$ we move to the right

$u > \mu$ we move to the left

The equilibrium lies at $u > \mu_+$, which is high. This leads to cramps ☹ and rigor mortis 💀

⇓

i.e. concentration of Ca^{2+} stays high always