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 betⁿ molecules A & B ∝ 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

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

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

S: substrate

E: enzyme

k_{-1}: a reversible reaction

E + P: enzyme is released when the complex breaks down into the product

P: product

(two-step process)

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

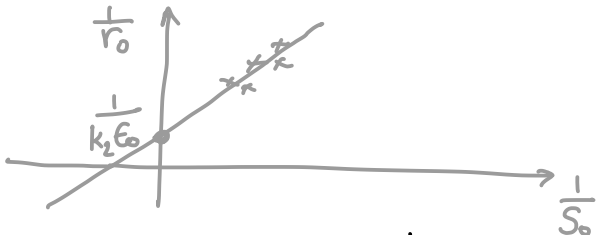
It's difficult to measure individual reaction rates experimentally.

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)

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

C_S: enzyme complex w/ substrate

and

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

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

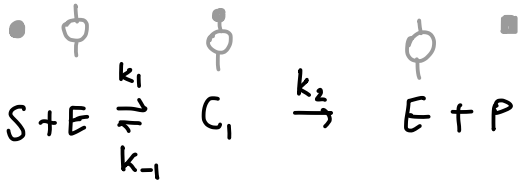
$$C_S + I \underset{k_1}{\overset{k_{-1}}{\rightleftharpoons}} C_I + S$$

(I: inhibitor)

(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).

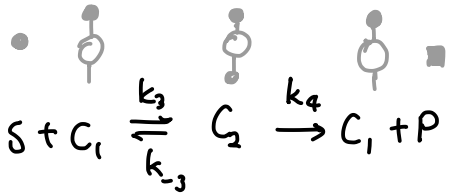
Cooperative systems – more than one binding site

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

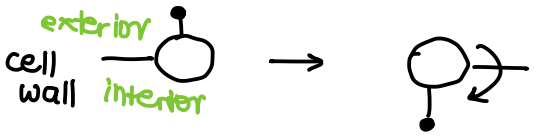
These exist both inside and outside the cell, creating a potential difference.

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

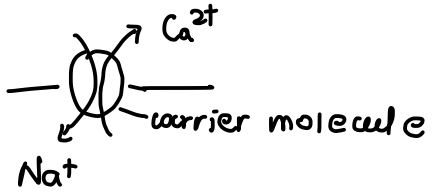
Osmosis is the mechanism by which water is transported across the cell membrane.

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.

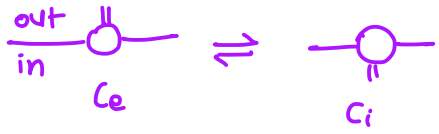
Carrier mediated transport - a molecule binds to a protein that has an active site that may be exposed to the interior or exterior of the cell (eg. glucose or amino acid transport)



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:

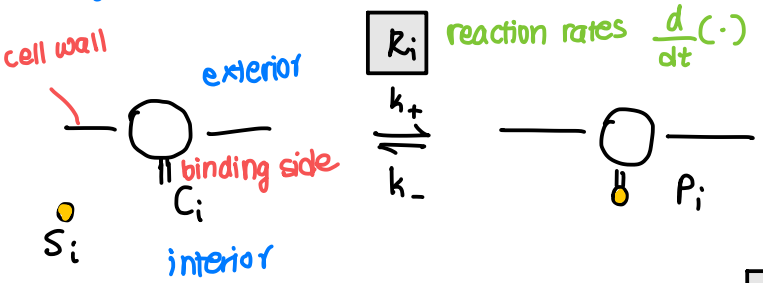
$$S_i + C_i \underset{k_-}{\overset{k_+}{\rightleftharpoons}} P_i \underset{k}{\overset{k}{\rightleftharpoons}} P_e \underset{k_+}{\overset{k_-}{\rightleftharpoons}} S_e + C_e \quad (*1)$$

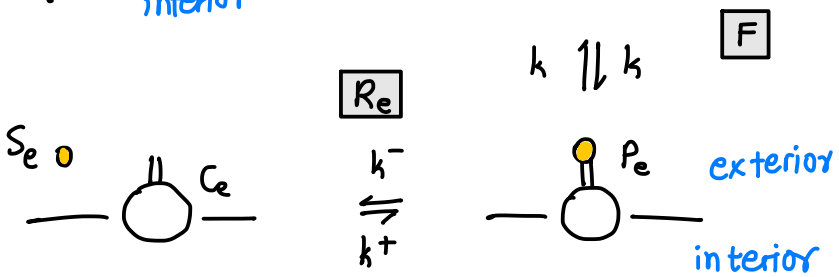
(2) (3) (1)

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

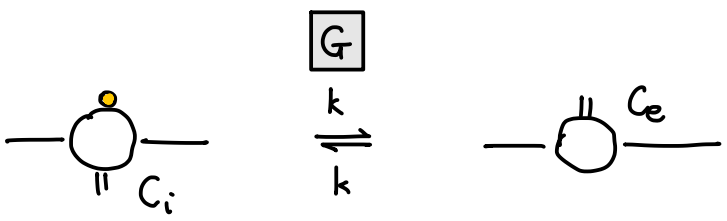
(*1):





"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

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

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: $\frac{dS}{dt'} = -\frac{\lambda S}{S + K'}$ 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.

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.