Further Mathematical Biology: Problem Sheet 1

Michaelmas Term 2019

Enzyme kinetics.

Question 1.

Use the Law of Mass Action to write differential equation models for the following reaction schemes

$$(i)\quad A{+}B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C \overset{k_2}{\rightarrow} D{+}B, \qquad (ii)\quad A{+}2B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C \overset{k_2}{\rightarrow} D{+}B, \qquad (iii)\quad A{+}3B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} 2B{+}C$$

Question 2 (a long question).

Consider the reaction

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} SE = C \overset{k_2}{\longrightarrow} P + E,$$

where S, E, C and P are substrate, enzyme, complex and product, respectively, and k_1, k_{-1} and k_2 are positive rate constants.

(a) Use the Law of Mass Action, which you should state, to write down four equations for the concentrations s, e, c and p of S, E, C and P, respectively.

(b) Initially $s = s_0$, $e = e_0$, $c = 0$ and $p = 0$, where s_0 and e_0 are constant. Show that the total amount of enzyme is conserved.

(c) Hence show that the system may be reduced to the following pair of equations

$$\frac{\mathrm{d}s}{\mathrm{d}t} = -k_1 e_0 s + (k_1 s + k_{-1})c, \tag{1}$$

$$\frac{\mathrm{d}c}{\mathrm{d}t} = k_1 e_0 s - (k_1 s + k_{-1} + k_2)c. \tag{2}$$

(d) With the non-dimensionalisation

$$u = \frac{s}{s_0}, \qquad v = \frac{c}{e_0}, \qquad \lambda = \frac{k_2}{k_1 s_0}, \qquad K = \frac{k_{-1} + k_2}{k_1 s_0}, \qquad \epsilon = \frac{e_0}{s_0},$$

use the rescaling in time $\sigma = \frac{k_1 e_0}{\epsilon} t$ to show that if $\epsilon \ll 1$ then there is an initial fast transient solution given by

$$u(\sigma) \approx 1 \text{ and } \frac{\mathrm{d}v(\sigma)}{\mathrm{d}\sigma} \approx 1 - (1 + K)v(\sigma).$$

(e) Use the rescaling in time, $\tau = k_1 e_0 t$ to show that the outer solution is given by

$$\frac{\mathrm{d}u(\tau)}{\mathrm{d}\tau} \approx -u + (u + K - \lambda)v \text{ and } v \approx \frac{u}{u + K}.$$

(f) [**Optional**] Show that the null clines for (**??**) and (**??**) are given by, respectively,

$$c = \frac{Ds}{\alpha + s} \text{ and } c = \frac{Ds}{\beta + s},$$

where α, β and D are to be found in terms of k_1, k_{-1}, k_2 and e_0.

(g) [**Optional**] Sketch the nullclines and draw the phase trajectory which begins at $s(0) = s_0$, $c(0) = 0$. Indicate the fast transient and pseudo-steady state portions on the trajectory.

Question 3.

An allosteric enzyme E reacts with a substrate S to produce a product P according to the mechanism

$$
\begin{aligned}
S + E \;&\underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}}\; C_1 \;\xrightarrow{k_2}\; P + E, \\
S + C_1 \;&\underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}}\; C_2 \;\xrightarrow{k_4}\; C_1 + P,
\end{aligned}
$$

where the k_i's are rate constants and C_1 and C_2 are enzyme-substrate complexes.

(a) With lowercase letters denoting concentrations, and initial conditions $s(0) = s_0$, $e(0) = e_0$, $c_1(0) = 0$, $c_2(0) = 0$ and $p(0) = 0$, write down the differential equation model for this system based on the Law of Mass Action.

(b) If

$$\epsilon = \frac{e_0}{s_0} \ll 1, \qquad \tau = k_1 e_0 t, \qquad u = \frac{s}{s_0}, \qquad v_i = \frac{c_i}{e_0},$$

show that the non-dimensional reaction mechanism reduces to

$$
\begin{aligned}
\frac{\mathrm{d}u}{\mathrm{d}\tau} &= f(u, v_1, v_2), \\
\epsilon \frac{\mathrm{d}v_1}{\mathrm{d}\tau} &= g_1(u, v_1, v_2), \\
\epsilon \frac{\mathrm{d}v_2}{\mathrm{d}\tau} &= g_2(u, v_1, v_2),
\end{aligned}
$$

where f, g_1 and g_2 should be determined.

(c) Hence show that for $\tau \gg \epsilon$ the uptake of u is governed by

$$\frac{\mathrm{d}u}{\mathrm{d}\tau} = -r(u) = -u \frac{A + Bu}{C + u + Du^2},$$

where A, B, C and D are positive parameters.

(d) When $k_2 = 0$ sketch the uptake rate, $r(u)$, as a function of u and compare it with the Michaelis-Menten uptake.

Question 4 (another long question - optional - revision over the holidays?).

Many physiological processes involve the conversion of fructose-G phosphate (FGP) to adenosine diphosphate (ADP). There are two parallel conversion mechanisms:

$$FGP \xrightarrow{k_1} ADP \qquad \text{and} \qquad FGP + 2(ADP) \xrightarrow{k_2} 3(ADP).$$

(a) Explain why the second of these reactions is described as autocatalytic.

(b) Suppose further that ADP is converted into an end product with rate constant k_3, and that FGP is supplied at a constant rate (by other reactions). Write down a differential equation model, and, using a suitable nondimensionalisation, show that it reduces to the following system

$$\frac{dx}{dt} = \delta - kx - xy^2, \qquad \frac{dy}{dt} = kx + xy^2 - y,$$

where you should define all new constants and variables.

(c) Show that this system has a unique steady state.

(d) Show that if k is sufficiently large, then the steady state is stable, but that when $0 < k < 1/8$ it is unstable.

(e) Show further that when $k < 1/8$, suitable levels of autocatalysis can induce oscillations in the concentrations of FGP and ADP.

Ion Channels and Excitability.

Question 1.

Consider an ion channel that consists of subunits of two different types, m and h say, where each subunit is controlled by a gate that can be either open or closed. Suppose the channel has two m subunits and one h subunit. Let S_{ij} denote the channel with i open m subunits and j open h subunits, and let x_{ij} denote the fraction of channels in state S_{ij}.

(a) Assuming that α, β are the rates at which the m subunits open and close respectively, and δ, γ are the rates at which the h subunits open and close respectively, determine the differential equations governing the rate of change of each x_{ij}.

(b) Show that the reaction scheme is equivalent to

$$x_{21} = m^2 h \ , \ \frac{dm}{dt} = \alpha(1-m) - \beta m \ , \ \frac{dh}{dt} = \delta(1-h) - \gamma h \ ,$$

where the other variables are given by

$x_{00} = (1-m)^2(1-h)$, $x_{10} = 2m(1-m)(1-h)$, $x_{20} = m^2(1-h)$, $x_{01} = (1-m)^2 h$ and $x_{11} = 2m(1-m)h$.

(c) Suppose now that the channel consists of three m subunits and one h subunit. Considering the form of x_{21} above, can you suggest an expression for x_{31}, the proportion of channels with three open m subunits and one open h subunit.

(d) In the general case of a channel with A m subunits and B h subunits, what would be the expression for x_{AB}?

Question 2.

Consider the Fitzhugh Nagumo equations:

$$\begin{aligned} \epsilon \frac{\mathrm{d}u}{\mathrm{d}s} &= Au(u+\bar{a})(1-u) - v, \\ \frac{\mathrm{d}v}{\mathrm{d}s} &= -v + bu, \end{aligned}$$

where $0 < \bar{a} \ll 1$, $b > \epsilon > 0$, $0 < \epsilon \ll 1$, $A > 0$, $A \gg \bar{a}, \epsilon$ and $b > A\bar{a}$.

(a) Noting the sign of $\bar{a}$, sketch the phase plane.

(b) Show that there is a bifurcation, *i.e.* a destabilisation of the stationary point, as $\bar{a}$ is increased through $\bar{a}_* \stackrel{def}{=} \epsilon/A$.

(c) Briefly explain why this shows that the bifurcation corresponding to the destabilitation of the Fitzhugh Nagumo stationary point occures on the 2nd branch of the Fitzhugh Nagumo cubic nullcline, close to, but not exactly at, the local minimum of the cubic.

[In this question you may assume that the parameter values are always such that these equations only ever have one stationary point.]