MATH377 School of Mathematics and Statistics

MATH377 Mathematical Biology

Marks will be awarded for your best three answers.
Consider a within-host virus population, $V$, that is attacked by immune cells, $C$.

(i) Assume that the number of immune cells is constant at density $C_0$. The dynamics of the virus are then given by the ordinary differential equation,

$$\frac{dV}{dt} = r V \left(1 - \frac{V}{K}\right) - \alpha V C_0$$

where $r$, $K$ and $\alpha$ are positive constants, and $C_0$ is also constant.

(a) Give biological meanings for each of the parameters $r$, $K$ and $\alpha$. 

(b) Taking the non-dimensional variables $n = \frac{V}{K}$ and $\tau = rt$, derive the non-dimensionalised system,

$$\frac{dn}{d\tau} = n(\rho - n),$$

stating how the non-dimensional parameter $\rho$ is defined in terms of $r$, $C_0$ and $\alpha$. Hence find a condition on the parameter $\alpha$ for the cells to successfully eradicate the virus.

(ii) Now assume that the density of the cells is no longer constant. Cells are produced by the body at a fixed rate $s$ but we assume that their decay rate is negligible. The dynamics of the coupled virus-cell system are now given by,

$$\frac{dV}{dt} = r V \left(1 - \frac{V}{K}\right) - \alpha V C$$

$$\frac{dC}{dt} = s - \alpha V C.$$

(a) Show that feasible equilibria exist if and only if $rK \geq 4s$.

(b) Sketch the phase portrait for the case $rK > 4s$, showing the nullclines, equilibria, qualitative directions of flow and at least two example trajectories. Describe the possible long-term outcomes.

(c) Explain why our assumption that the decay rate of cells is negligible causes unrealistic dynamics for initial conditions $V(0) \approx 0$. 

Continued
2 (i) The dynamics of susceptible (S), infected (I) and recovered (R) individuals in a human population can be modelled as follows,

\[
\frac{dS}{dt} = -\beta SI; \quad \frac{dI}{dt} = \beta SI - \gamma I; \quad \frac{dR}{dt} = \gamma I.
\]

for positive constants \( \beta \) and \( \gamma \), with \( N = S + I + R \).

(a) Define, in words, the meaning of the term \( R_0 = \frac{\beta N}{\gamma} \). \((2 \text{ marks})\)

(b) A disease outbreak is predicted in a town of 2000 people. The transmission coefficient is estimated to be \( \beta = 0.00075 \) and the daily recovery rate is \( \gamma = 0.15 \). Find how many individuals in the town must be vaccinated for herd immunity to prevent the outbreak. \((3 \text{ marks})\)

(ii) A plant population can be partitioned into either susceptible (S) or infected (I) compartments. The dynamics of this population are given by the ordinary differential equations,

\[
\frac{dS}{dt} = b(S + fI) - \beta SI - dS \\
\frac{dI}{dt} = \beta SI - (\alpha + d)I
\]

where \( b, f, \beta, d \) and \( \alpha \) are positive constants.

(a) What are the biological meanings of the parameters \( b \) and \( f \)? \((2 \text{ marks})\)

(b) Assume \( b = 1 \) and \( \beta = 1 \), and that \( d < 1 \) and \( f < 1 \). Find the endemic equilibrium \( (S^*, I^*) \) of the system and use linear stability analysis to show that it is stable only when \( f < \alpha + d \). \((9 \text{ marks})\)

(c) Sketch the phase portrait of this system for the case \( f < \alpha + d \), again assuming \( b = 1, \beta = 1, d < 1 \) and \( f < 1 \). This should show (within the biologically-feasible region) the nullclines, equilibria, qualitative directions of flow and at least two example trajectories. \((6 \text{ marks})\)

(d) Considering the phase portrait, suggest how increasing the value of \( f \) will alter the values of \( S^* \) and \( I^* \) at the endemic equilibrium. What will happen to the endemic equilibrium when \( f > \alpha + d \)? \((3 \text{ marks})\)
A model for the expression of a single gene is given by

\[
\begin{align*}
\frac{dM}{dt} & = -d_m M + k_m \\
\frac{dP}{dt} & = k_p M - d_p P,
\end{align*}
\]

where \( M = M(t) \) and \( P = P(t) \) represent the amounts of mRNA and protein, respectively, and \( k_m, k_p, d_m \) and \( d_p \) are positive constants.

(i) State the cellular processes that are represented by each term in the model equations. \((4 \text{ marks})\)

(ii) Find the steady state levels of mRNA and protein expression. Assuming initial conditions \( M(0) = 0, P(0) = 0 \), find expressions for \( M(t) \) and \( P(t) \). \((9 \text{ marks})\)

(iii) Show that if \( d_m = d_p \equiv D \) then the time \( T_1 \) taken for the protein level to reach half its steady state value is given by the solution of

\[ e^{DT_1} = 2 (1 + DT_1) . \]

A common simplification in cellular network models is to set mRNA dynamics to steady state (i.e. setting \( \frac{dM}{dt} = 0 \)), modelling explicitly only the protein dynamics. Show that this assumption leads to the reduced model

\[
\frac{dP}{dt} = \frac{k_m k_p}{D} - DP,
\]

and that the time \( T_2 \) taken for the protein level to rise from 0 to half its steady state level is given by \( e^{DT_2} = 2 \).

By comparing your expressions for \( T_1 \) and \( T_2 \) graphically, show that \( T_2 < T_1 \). \((5 \text{ marks})\)

(iv) Using your results from (iii), show that

\[ e^{D(T_1-T_2)} = 1 + DT_1 . \]

Using the approximation \( e^x \approx 1 + x + x^2 / 2 \), show that

\[
\frac{T_1}{T_2} \approx \frac{\ln 2 + \sqrt{2} \ln 2}{\ln 2} \approx 2.7 .
\]

Show that this approximation provides an overestimate of \( T_1/T_2 \).

If \( D = 0.02 \text{ min}^{-1} \), calculate \( T_2 \) and estimate \( T_1 \). \((7 \text{ marks})\)
The \textit{hes1} gene encodes a transcription factor that represses its own transcription. A simple model of \textit{hes1} gene expression is given by

\[
\frac{dM}{dt} = -d_m M + k_m f(P),
\]

\[
\frac{dP}{dt} = k_p M - d_p P,
\]

where \(M = M(t)\) and \(P = P(t)\) represent the amounts of mRNA and protein, respectively. \(d_m, d_p, k_m\) and \(k_p\) are positive constants.

(i) If \(f(P)\) is a monotonic decreasing function such that \(0 < f(P) \leq 1\), show graphically that the model has a unique steady state. Show that if the value of \(d_p\) is increased, then the steady state value of \(M\) increases. How does the steady state value of \(P\) change? \((5 \text{ marks})\)

(ii) By linearising the model equations about the steady state, determine whether or not the steady state is stable to small perturbations. Show that the model cannot account for \textit{sustained} oscillatory expression of the \textit{hes1} gene. Sketch a phase portrait for the model in the case when \(d_m = d_p\), and show on a separate sketch the qualitative form of the corresponding time courses of mRNA and protein expression. \((9 \text{ marks})\)

(iii) A revised model of the \textit{hes1} system includes an additional form \(Q\) of the Hes1 protein:

\[
\frac{dM}{dt} = -d_m M + k_m f(Q),
\]

\[
\frac{dP}{dt} = k_p M - d_p P,
\]

\[
\frac{dQ}{dt} = k_q P - d_q Q,
\]

where \(k_q\) and \(d_q\) are positive constants. Show that this model has a unique steady state \((M_*, P_*, Q_*)\). \((2 \text{ marks})\)

(iv) If \(d_m = d_p = d_q \equiv D\), show that the steady state is unstable if

\[
k_m k_p k_q \phi > 8D^3,
\]

where \(\phi = -\frac{df}{dQ} \bigg|_{Q_*}\). What type of bifurcation occurs when \(k_m k_p k_q \phi = 8D^3\)? Explain briefly why the model can account for sustained oscillatory expression of Hes1 if condition (1) is met (you do NOT have to try to prove this).

Show that if \(D = 0.03\text{min}^{-1}\), then the oscillatory period of Hes1 expression at the bifurcation point is approximately 2hrs. \((9 \text{ marks})\)

\textbf{End of Question Paper}