The University Of Sheffield.

SCHOOL OF MATHEMATICS AND STATISTICS **Spring Semester 2015–2016**

MAS377 Mathematical Biology **2 hours**

Marks will be awarded for your best ***three*** *answers.*

1 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,

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

where r, K and α are positive constants, and C_0 is also constant.

(a) Give biological meanings for each of the parameters r, K and α. ***(3 marks)***

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

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

stating how the non-dimensional parameter ρ is defined in terms of r, C_0 and α. Hence find a condition on the parameter α for the cells to successfully eradicate the virus. ***(6 marks)***

(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,

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

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

(a) Show that feasible equilibria exist if and only if $rK \geq 4s$. ***(6 marks)***

(b) Sketch the phase portrait for the case $rK > 4s$, showing the null-clines, equilibria, qualitative directions of flow and at least two example trajectories. Describe the possible long-term outcomes. ***(8 marks)***

(c) Explain why our assumption that the decay rate of cells is negligible causes unrealistic dynamics for initial conditions $V(0) \approx 0$. ***(2 marks)***

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

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

for positive constants β and γ, with $N = S + I + R$.

(a) Define, in words, the meaning of the term $R_0 = \beta N/\gamma$. ***(2 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 marks)***

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

$$\begin{aligned} \frac{dS}{dt} &= b(S + fI) - \beta SI - dS \\ \frac{dI}{dt} &= \beta SI - (\alpha + d)I \end{aligned}$$

where b, f, β, d and α are positive constants.

(a) What are the biological meanings of the parameters b and f? ***(2 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 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 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 marks)***

3 A model for the expression of a single gene is given by

$$\begin{aligned}\frac{dM}{dt} &= -d_m M + k_m \\ \frac{dP}{dt} &= k_p M - d_p P,\end{aligned}$$

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 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 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 $\dfrac{dM}{dt} = 0$), 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 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 marks)***

4 The *hes1* gene encodes a transcription factor that represses its own transcription. A simple model of *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 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 *sustained* oscillatory expression of the *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 marks)***

(iii) A revised model of the *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 marks)***

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

$$k_m k_p k_q \phi > 8D^3, \qquad (1)$$

where $\phi = -\left.\frac{df}{dQ}\right|_{Q_*}$. 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 marks)***

End of Question Paper