The University Of Sheffield.

SCHOOL OF MATHEMATICS AND STATISTICS **Spring Semester 2014–2015**

MAS377 Mathematical Biology **2 hours**

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

1 The population dynamics of a predator, P, and its prey, N, are given by the following ordinary differential equations,

$$\frac{dN}{dt} = rN(1 - N/K) - \rho(N)P,$$
$$\frac{dP}{dt} = \rho(N)P - dP,$$

where r, K and d are positive constants and $\rho(N)$ is a strictly increasing function of N.

(i) Give ecological meanings of the parameters r, K and d. ***(3 marks)***

(ii) Let $\rho(N) = bN$ where b is a positive constant. Sketch phase portraits for this system for when (a) $K < d/b$ and (b) $K > d/b$. Each should clearly show the nullclines, qualitative directions of flow and two sample trajectories. Hence infer the long-term behaviour in each case. ***(10 marks)***

(iii) Now let $\rho(N) = bN/(N + c)$ where b and c are positive constants. Sketch this function and explain why it might be more realistic than the function in part (ii). ***(2 marks)***

(iv) For $\rho(N) = bN/(N + c)$, show that there is a 'coexistence' equilibrium at,

$$N^* = \frac{cd}{b - d}, P^* = \frac{r}{b}\left(1 - \frac{N^*}{K}\right)(N^* + c).$$

(4 marks)

(v) The stability of this coexistence equilibrium is governed by the Jacobian,

$$\mathbf{J}^* = \begin{pmatrix} \dfrac{-rN^*}{K} + \dfrac{bN^*P^*}{(N^* + c)^2} & \dfrac{-bN^*}{N^* + c} \\ \dfrac{bcP^*}{(N^* + c)^2} & 0 \end{pmatrix}.$$

It can be shown that a unique stable cycle can emerge through a 'Hopf bifurcation' if the stability of this equilibrium changes from a stable spiral to an unstable spiral as a single parameter is varied. Using this definition, show that a Hopf bifurcation occurs at $K = 2N^* + c$. State whether the cycle occurs when K is greater or less than this value. ***(6 marks)***

2 The rubella virus is not only spread 'horizontally' between individuals, but also 'vertically' from parent to offspring. Assume a proportion v of offspring from infected parents are born with the virus. The dynamics of a human population exposed to rubella might then be described by the following ordinary differential equations:

$$\frac{dS}{dt} = \mu(S + (1 - v)I + R) - \beta SI - \mu S$$

$$\frac{dI}{dt} = \beta SI + v\mu I - (\mu + \gamma)I$$

$$\frac{dR}{dt} = \gamma I - \mu R,$$

where, S, I and R denote susceptible, infected and recovered individuals respectively, the parameters μ, β and γ are positive constants and $0 < v < 1$.

(i) Explain why we only need two of these equations to fully describe this system. Using $N = S + I + R$, show that the system can be re-written as

$$\frac{dS}{dt} = \mu(N - vI) - \beta SI - \mu S$$

$$\frac{dI}{dt} = \beta SI + v\mu I - (\mu + \gamma)I.$$

(2 marks)

(ii) State (in words) the definition of the basic reproductive number, R_0. Assuming $S(0) \approx N$, derive an expression for R_0 for this model such that $R_0 > 1$ is required for the infection to initially grow. ***(4 marks)***

(iii) Let $\beta = 0$ so that there is no horizontal transmission. By finding the possible equilibria and assessing their stability, show that the virus will never persist if it is spread only by vertical transmission. ***(5 marks)***

(iv) Now let $\beta > 0$ so that both forms of transmission occur. Show that there is an 'endemic' equilibrium at

$$(S^*, I^*) = \left(\frac{\mu - \mu v + \gamma}{\beta}, \frac{\mu(\beta N + \mu v - (\mu + \gamma))}{\beta(\mu + \gamma)} \right)$$

and that it is stable provided $R_0 > 1$. ***(10 marks)***

 Question 2 continued on next page

2 (continued)

(v) Now consider a wildlife population that is exposed to an infectious disease, with densities of susceptible and infected individuals given by S and I respectively. Use the information below to write down a set of ordinary differential equations that describe this system.

Susceptible hosts can reproduce at rate b and all offspring are born susceptible, but the disease prevents infected hosts from reproducing. All hosts die at natural mortality rate d and infected hosts suffer further mortality at rate α. Infection occurs through direct contact of susceptible and infected hosts, with the force of infection given by βI. Infected hosts can recover from disease at rate γ, but they do not gain immunity and instead return to being susceptible. ***(4 marks)***

3 A model for the expression of an auto-activating gene X is given by

$$\frac{dM}{dt} = -\mu M + k_1 f(P) \tag{1}$$

$$\frac{dP}{dt} = k_2 M - \nu P, \tag{2}$$

where $M(t)$ and $P(t)$ represent the concentrations of mRNA and protein associated with the gene, respectively, and k_1, k_2, μ and ν are positive constants.

(i) Suggest biological meanings for k_2, μ and ν. What properties should the function $f(P)$ have? ***(3 marks)***

(ii) If $f(P) = B + \dfrac{P^n}{\theta^n + P^n}$, where B, θ and n are positive constants, sketch the nullclines of the model described by Eqs. (1) and (2) for $n > 1$. Hence show that the model can have either one or three steady states. ***(3 marks)***

(iii) Explain the meaning of the term *bistability*. Linearise the model described by Eqs. (1) and (2) and show that when the model has three steady states, then it exhibits bistability. Sketch the phase portrait in this case, showing example trajectories. What does this mean in terms of the expression of the gene X? ***(9 marks)***

(iv) Show that when $B = 0$ and $n = 2$, the model exhibits bistability if

$$\theta < \theta_c = \frac{k_1 k_2}{2\mu\nu}.$$

Show graphically that if $\theta < \theta_c$ and B is increased above a critical level B_c (which you should *not* attempt to find an expression for), then the system becomes monostable, with P expressed at a high level.

High expression levels of gene X result in a clinical disease. In a healthy individual, $B = 0$, $\theta < \theta_c$, and gene X is not expressed ($P = 0$). In a patient with the disease, B is increased above B_c, resulting in high levels of expression of P. Sketch the healthy and diseased states on a phase portrait, indicating the relevant steady states. ***(4 marks)***

(v) Two drugs that affect the expression of gene X are available. Drug 1 decreases B to $B = 0$. Show from your phase portrait that if Drug 1 is given to a patient with the disease, then the expression level of gene X will remain high (and the drug will therefore be ineffective).
Drug 2 increases the degradation rate of proteins. Show from your phase portrait that Drug 2 can decrease the level of expression of P if given to a patient with the disease. Drug 2 has severe side effects, and cannot be tolerated by patients for very long. Show that if Drug 2 is removed, expression of gene X will return to a high level.
Show that if Drug 1 and Drug 2 are given *simultaneously*, then the expression level of gene X can be reduced to zero. Show that this state is maintained if Drug 2 is now removed. ***(6 marks)***

4 A model for the auto-regulation of the Hes1 gene is given by

$$\frac{dM}{dt} = -\mu M + g[P(t-\tau_1)] \tag{3}$$

$$\frac{dP}{dt} = M(t-\tau_2) - \nu P, \tag{4}$$

where $M(t)$ and $P(t)$ represent the concentrations of *hes1* mRNA and Hes1 protein, respectively, τ_1 and τ_2 are non-negative constants, μ and ν are positive constants, and $g(P)$ is a monotonic decreasing function with $g(0) = 1$ and $\lim_{P\to\infty} g(P) = 0$.

(i) Explain the biological meaning of τ_1 and τ_2. ***(2 marks)***

(ii) Show that the model always has a unique steady state $P_* > 0$. Sketch the phase portrait for the model when $\tau_1 = 0$ and $\tau_2 = 0$, and show that in this case the steady state is stable. Show that if $\mu = \nu$, then this steady state is a stable spiral. ***(7 marks)***

(iii) Show that the model can be written as a single second-order equation for P:

$$\frac{d^2P}{dt^2} + (\mu+\nu)\frac{dP}{dt} + \mu\nu P = g[P(t-\tau)],$$

where $\tau = \tau_1 + \tau_2$.
By linearising this equation around the steady state $P = P_*$, show that solutions of the form $P = P_* + p_0 e^{\lambda t}$ (p_0 small) satisfy

$$\lambda^2 + (\mu+\nu)\lambda + \mu\nu = -\gamma e^{-\lambda\tau}, \quad \gamma > 0, \tag{5}$$

and explain what γ is. ***(5 marks)***

(iv) If $\mu = \nu$, show that if Eq. (5) has a pure imaginary solution $\lambda = i\omega,\ \omega \in \mathbb{R}$ then

$$\omega^2 - \mu^2 = \gamma\cos\omega\tau \quad \text{and} \quad 2\mu\omega = \gamma\sin\omega\tau.$$

Show that a necessary condition for this to be possible is that $\gamma > \mu^2$. If this condition is met, explain what happens as τ is increased from zero. What is the biological significance of this? ***(7 marks)***

(v) For Hes1, $\mu = 0.03\text{min}^{-1}$. If $\gamma = 0.0034\text{min}^{-2}$, show that sustained oscillations in Hes1 expression can occur if $\tau \geq 21.6\text{min}$. What is the period of these oscillations when $\tau = 21.6\text{min}$? ***(4 marks)***

End of Question Paper