The University Of Sheffield.

SCHOOL OF MATHEMATICS AND STATISTICS **Autumn Semester 2019–20**

MAS377 Mathematical Biology **2 hours**

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

1 Consider a fish population, N, that is commercially fished. The dynamics of the population are governed by the following ordinary differential equation,

$$\frac{dN}{dt} = r(N)N - f(N)N, \tag{1}$$

where $r(N) = r_0(1 - N/K)$ is the *per-capita* growth rate of the population in the absence of fishing, $f(N)$ is the *per-capita* rate of removal due to fishing, and r_0 and K are positive constants.

(i) A researcher proposes that the fishing rate should be given by $f(N) = \phi$, where ϕ is a positive constant.

(a) What are the biological meanings of r_0 and K? ***(2 marks)***

(b) Find the equilibrium values, N^*, of the fish population, and determine when each is stable by linear stability analysis. ***(7 marks)***

(c) Using the values from part (b), sketch a bifurcation diagram for the system, with r_0 on the horizontal axis and N^* on the vertical axis. Use a solid line to denote stable equilibria and a dashed line for unstable equilibria. State the type of bifurcation that occurs in your diagram. ***(4 marks)***

(ii) A second researcher claims that a more realistic fishing rate is,

$$f(N) = \frac{\rho N}{N^2 + A^2}, \tag{2}$$

where ρ and A are positive constants.

(a) Sketch $f(N)$. (Hint: you may find it useful to calculate $f'(N)$). ***(3 marks)***

(b) Now produce three further plots which will each identify different qualitative behaviours of the dynamics. In each plot, sketch both $f(N)$ and $r(N)$ as functions of N on the same axes. You may assume that $f(N)$ is identical in each case, and that in case (1) r_0 and K are small, in case (2) r_0 and K are intermediate, and in case (3) r_0 and K are large. ***(6 marks)***

(c) Using the sketches above, describe the likely outcomes of the system in each case. ***(3 marks)***

2 (i) 'Naive' immune cells, C, are produced by the body at a constant rate, s, and decay at rate μ, giving dynamics of,

$$\frac{dC}{dt} = s - \mu C. \tag{3}$$

Assuming that there is an initial density of cells, C_0, at $t = 0$, find the explicit solution $C(t)$. Hence or otherwise find the equilibrium density of naive immune cells in the body. ***(4 marks)***

(ii) Assume these naive immune cells stay at this fixed density, C^*, as they respond to an infectious bacteria, B. Bacteria are 'eaten' by cells at *per-capita* rate $pC^*/(B + A)$ (where A is a constant), becoming a new type of 'active' immune cell, D. These active cells then undergo programmed cell death, killing the bacteria they have ingested, at rate ν. It is proposed that the dynamics of bacteria and active cells are therefore governed by the following ordinary differential equations,

$$\frac{dB}{dt} = rB - \frac{pC^*B}{B+A} \tag{4}$$

$$\frac{dD}{dt} = \frac{pC^*B}{B+A} - \nu D, \tag{5}$$

with all parameters being positive (and $C(t) = C^*$).

(a) Explain why the given ingestion function, $pC^*B/(B + A)$, is more realistic than a constant *per-capita* rate (i.e. pC^*B). ***(2 marks)***

(b) Let $r < pC^*/A$. Sketch the phase portrait of this system. You should clearly show the nullclines, equilibria, directions of flow and four example trajectories (one starting in each region separated by your nullclines). ***(8 marks)***

(c) Using your phase portrait, describe in words the possible outcomes. ***(5 marks)***

(d) Perform linear stability analysis of the system, and therefore confirm the stabilities of the equilibria you found in your phase portrait (again assuming $r < pC^*/A$). Note, you do not necessarily need to calculate the equilibrium values of B and D. ***(6 marks)***

3 A model for the expression of an autoregulatory gene is given by

$$\frac{dM}{dt} = f(P) - \mu M \qquad (6)$$

$$\frac{dP}{dt} = kM - \nu P, \qquad (7)$$

where M and P represent the concentrations of mRNA and protein encoded by the gene, respectively, μ, ν and k are positive constants, and

$$f(P) = \frac{P^2}{1 + P^2}.$$

(i) What are the biological meanings of μ, ν and k? Is the gene auto-activating or auto-repressive? ***(4 marks)***

(ii) Write down a polynomial equation that is satisfied by steady state values of P. Show that if $2\mu\nu > k$, then the model has a unique steady state. What are the values of M and P at this steady state? ***(6 marks)***

(iii) Write down the Jacobian matrix of the model. ***(2 marks)***

(iv) What does it mean for a system to be bistable? Assume now that $2\mu\nu < k$. Sketch the nullclines of the model. By considering the gradients of the nullclines at each steady state, show that the model is bistable. ***(8 marks)***

(v) Consider a scenario where stable non-zero expression of this gene results in an undesirable clinical condition. It is proposed to treat this with a drug that reduces the efficiency of transcription, so that the dynamics of M are governed by the equation

$$\frac{dM}{dt} = \alpha f(P) - \mu M,$$

where $\alpha < 1$ measures the efficiency of transcription. The equation governing the dynamics of P is unchanged. Assuming that $\mu = 2$, $\nu = 1$ and $k = 10$, show that application of the drug will be effective (by eliminating the non-zero steady state of the model) if $\alpha < 0.4$. ***(5 marks)***

4 The regulated transcription of a gene is represented by the differential equation

$$\frac{dm}{dt} = -\mu m + f(t), \quad t \geq 0, \tag{8}$$

where $m(t)$ represents the concentration of the mRNA transcript associated with the gene, and μ is a positive constant.

(i) What are the meanings of the parameter μ and the function $f(t)$? ***(2 marks)***

(ii) Why should $f(t)$ be non-negative and bounded above? ***(2 marks)***

(iii) If $f(t) = 1$ for all $t \geq 0$, what is the steady state value of m? Is this steady state stable or unstable? ***(4 marks)***

(iv) Consider the case when transcription occurs at a constant rate for a finite time interval T, where $f(t)$ is given by

$$f(t) = \begin{cases} 1, & 0 \leq t \leq T \\ 0, & t > T \end{cases}$$

where T is a positive constant. Sketch $f(t)$. By solving (8), show that if $m(0) = 0$, then

$$m(t) = \begin{cases} \dfrac{1}{\mu}\left(1 - e^{-\mu t}\right), & 0 \leq t \leq T \\ \dfrac{1}{\mu}\left(e^{\mu T} - 1\right) e^{-\mu t}. & t > T \end{cases}$$

Sketch $m(t)$. ***(9 marks)***

(v) Protein P is produced by translation of the mRNA at a rate km, where k is a positive constant. If the protein is stable (i.e. if its degradation rate $= 0$), then the dynamics of the concentration of the protein, $p(t)$ are governed by the differential equation

$$\frac{dp}{dt} = km.$$

Using the result from (iii), and setting $p(0) = 0$, find $p(t)$ for $t > 0$. ***(5 marks)***

(vi) Show that, as $t \to \infty$, $p(t)$ approaches a steady state value that is proportional to T. What is the constant of proportionality? ***(3 marks)***

End of Question Paper