Further Mathematical Biology: Problem Sheet 4
Michaelmas Term 2018

Growing domains.

Question 1.

The following equations describe the growth of a tumour that is being radiated by an X-ray source.

$$\begin{aligned}
\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} - kC \quad &\text{for } |x| < R(t), \\
\frac{\partial C}{\partial x} = 0 \quad &\text{at } x = 0, \\
C(R(t), t) &= C_0, \\
\frac{dR}{dt} &= \int_0^{R(t)} (\alpha C - \beta) dx, \\
R(0) &= R_0,
\end{aligned}$$

where k is the rate of uptake of nutrient, the parameter α relates the tumour's growth rate to the nutrient concentration, and the parameter β relates the strength of the X-ray source to the rate of tumour cell death.

(a) Using the substitutions

$$x = R_0\xi, \quad R(t) = R_0 r(\tau), \quad C(x,t) = C_0 c(\xi, \tau), \quad t = \frac{\tau}{\alpha C_0},$$

and assuming that $\alpha C_0 R_0^2/D \ll 1$, show that the dimensionless system is

$$\begin{aligned}
0 = \frac{\partial^2 c}{\partial \xi^2} - \mu c \quad &\text{for } |\xi| < r(\tau), \\
\frac{\partial c}{\partial \xi} = 0 \quad &\text{at } \xi = 0, \\
c(r(\tau), \tau) &= 1, \\
\frac{dr}{d\tau} &= \int_0^{r(\tau)} (c - \gamma) d\xi, \\
r(0) &= 1.
\end{aligned}$$

State expressions for the dimensionless parameters μ and γ.

(b) Show that the concentration of nutrient inside the tumour is given by

$$c(\xi, \tau) = \frac{\cosh(\sqrt{\mu}\,\xi)}{\cosh(\sqrt{\mu}\,r(\tau))}, \quad |\xi| < r(\tau)$$

(c) Hence show that the differential equation governing the size of the tumour is

$$\frac{dr}{d\tau} = \frac{1}{\sqrt{\mu}}\tanh(\sqrt{\mu} r(\tau)) - \gamma r(\tau) \tag{1}$$

(d) Find an expression for the minimum dose, β^*, in terms of the other dimensional parameters, that will completely destroy the tumour. Discuss what will happen to the tumour in the cases $\beta = 0$ and $0 < \beta < \beta^*$ (Hint: sketch the two terms on the right-hand side of equation (1) as a function of r).

Question 2.

Justify the following model for the growth of a spherically-symmetric tumour of volume V:

$$\begin{aligned}
\frac{\partial C}{\partial t} = \frac{D}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial C}{\partial r}\right) - \lambda, \quad 0 \le r < R(t), \\
\frac{\partial C}{\partial r} = 0 \quad \text{at } r = 0, \\
C(R(t), t) = C^*, \\
\frac{dV}{dt} = 4\pi \int_0^{R(t)} P(C) r^2 dr, \\
R(0) = R_0.
\end{aligned}$$

Identify each term in the equations.

(a) Nondimensionalise the system, scaling lengths with R_0, concentrations with C^*, P with a typical tumour proliferation rate P_0, and time with $1/P_0$. Assuming that $R_0^2 P_0/D \ll 1$, show that the model reduces (approximately) to

$$\left.\begin{aligned}
\frac{1}{\rho^2}\frac{\partial}{\partial \rho}\left(\rho^2\frac{\partial c}{\partial \rho}\right) = \mu, \\
\frac{\partial c}{\partial \rho}(0, \tau) = 0, \\
c(s(\tau), \tau) = 1, \\
s^2\frac{ds}{d\tau} = \int_0^{s(\tau)} p(c)\rho^2 d\rho, \\
s(0) = 1,
\end{aligned}\right\} \tag{2}$$

where $s(\tau)$ is the dimensionless tumour radius, and μ is a dimensionless parameter that you should define.

(b) By solving equations (2), show that when $p(c) = c$, the tumour radius $s(\tau)$ satisfies the first-order differential equation

$$\frac{ds}{d\tau} = \frac{s}{3}\left(1 - \frac{\mu s^2}{15}\right), \qquad s(0) = 1.$$

(c) What are the steady states for the tumour radius?

(d) Show that the tumour-free steady state is unstable and comment on whether the nontrivial steady state is physically realistic.

Question 3 (optional question).

Consider the following dimensionless model for the growth of a multicellular spheroid:

$$\frac{\partial^2 c}{\partial \xi^2} = \mu \quad -r(\tau) \leq \xi \leq r(\tau), \tag{3}$$

$$c(\xi, \tau) \equiv 1 \quad \xi \geq r(\tau), \tag{4}$$

$$\frac{\partial c}{\partial \xi}(0, \tau) = 0, \tag{5}$$

$$c(r(\tau), \tau) = 1, \tag{6}$$

$$\frac{dr(\tau)}{d\tau} = \int_0^{r(\tau)} p(c) d\xi, \tag{7}$$

$$r(0) = 1, \tag{8}$$

where the cells occupy $|\xi| \leq r(\tau)$, $c(\xi, \tau)$ is the nutrient concentration, μ is the rate at which it is taken up by the cells, and the cell proliferation rate, $p(c)$, is a function of the nutrient concentration.

(a) Suppose that the proliferation function p is given by $p(c) = c^2$. By solving equations (3)–(6), show that the position $r(\tau)$ of the outer radius of the spheroid is governed by the ordinary differential equation

$$\frac{dr}{d\tau} = r\left(1 - \frac{2}{3}\mu r^2 + \frac{2}{15}\mu^2 r^4\right). \tag{9}$$

(b) Find the steady states, and show that the only physically-relevant one is $r(\tau) \equiv 0$.

(c) By conducting a linear stability analysis of this trivial steady state deduce that it is unstable. What are the implications of these results for the growth of the spheroid in equation (9)?

(d) Assuming that the given form for p is realistic for all positive nutrient concentrations c, what would happen in the model to make the solution break down?

Discrete-to-Continuum and Age-Structured Models.

Question 1 (Fisher's Equation).

A population of cells is distributed along the real line which is decomposed into a series of boxes of width Δx. Denote by $N_i(t)$ the density of cells in the i-th box at time t. During the time period $(t, t + \Delta t)$, the cells in box i move to the right with probability p_R, to the left with probability p_L and do not move with probability $p_S = 1 - p_L - p_R$ where $0 \leq p_R, p_L, p_S \leq 1$. In addition to moving, the cells also reproduce at a constant rate λ and die due to competition for space at rate μ.

(a) Use the principle of mass balance to deduce discrete conservation equations (DCEs) for $N_i(t)$.

(b) Assume that the box size Δx is sufficiently small to identify a continuous density $n(i\Delta x, t) = n(x, t)$ with the discrete density $N_i(t)$. Use the DCEs from (a) to show that in the limit as $\Delta x, \Delta t \to 0$, $n(x, t)$ solves

$$\frac{\partial n}{\partial t} = D\frac{\partial^2 n}{\partial x^2} - c\frac{\partial n}{\partial x} + \hat{r}n\left(1 - \hat{\mu}n\right), \tag{10}$$

stating clearly how the constants $D, c, \hat{r}$ and $\hat{\mu}$ are defined.

(c) Seek travelling wave solutions to equation (10). Use phase plane techniques to determine the minimum wavespeed for a physically realistic travelling wave solution that connects the equilibrium points at $n = 0$ and $n = 1/\hat{\mu}$.

Question 2 (Chemotaxis).

Cells produce a signalling molecule as they move along the real line which we view as a series of compartments of width δx. We denote by $n_i(t)$ the cell density and by and $a_i(t)$ the concentration of the chemical in compartment i at time t. During the time step δt, a cell in box i moves to the right or left with probabilities p_R^i and p_L^i where

$$p_R^i = p + \theta(a_{i+1} - a_i) \quad \text{and} \quad p_L^i = p + \theta(a_{i-1} - a_i),$$

where p, θ are positive constants and $0 \leq p_R^i, p_L^i \leq 1 \ \forall i$. Each cell produces the chemical at a constant rate $\hat{\lambda} > 0$. The chemical also moves via an unbiased random walk and decays naturally at rate $\hat{\mu} > 0$.

(a) Use the principle of mass balance to derive discrete conservation equations for $n_i(t)$ and $a_i(t)$.

(b) Assume that the box size δx is sufficiently small to identify continuous densities $N(i\delta x, t) = N(x,t)$ and $A(i\delta x, t) = A(x,t)$ with the discrete densities $n_i(t)$ and $a_i(t)$. Use the DCEs from (a) to show that in the limit as $\delta x, \delta t \to 0$, $N(x,t)$ and $A(x,t)$ solve the following partial differential equations

$$\frac{\partial N}{\partial t} = D_N \frac{\partial^2 N}{\partial x^2} - \chi \frac{\partial}{\partial x}\left(N \frac{\partial A}{\partial x}\right), \tag{11}$$

$$\frac{\partial A}{\partial t} = D_A \frac{\partial^2 A}{\partial x^2} + \lambda N - \mu A, \tag{12}$$

stating clearly how the constants D_N, D_A, χ, λ and μ are defined.

(c) [revision of pattern formation] Identify the spatially uniform steady states of equations (11)-(12) and examine their linear stability. Derive the dispersion relation and, hence, obtain the conditions on the parameters under which the system will give rise to spatially heterogeneous solutions. Comment briefly on how the initial cell seeding density influences the formation of spatial patterns.

Question 3.

The evolution of an age-structured population $N(t,a)$ satisfies

$$\frac{\partial N}{\partial t} + \frac{\partial N}{\partial a} = -\mu(a) N,$$

with $N(0,a) = F(a)$ and $N(t,0) = B(t) = \int_0^\infty \beta(a) N(t,a) da$, for some positive functions $\mu(a), F(a)$ and $\beta(a)$.

(a) Use the method of characteristics to show that

$$N(t,a) = \begin{cases} F(a-t)\exp\left(-\int_{a-t}^{a} \mu(\tau)d\tau\right) & \text{for } 0 < t < a, \\ B(t-a)\exp\left(-\int_0^a \mu(\tau)d\tau\right) & \text{for } a < t, \end{cases}$$

$$\text{where } B(t) = \int_0^t \beta(\tau) B(t-\tau) e^{-\int_0^\tau \mu(\theta)d\theta} d\tau + \int_t^\infty \beta(\tau) F(\tau - t) e^{-\int_{\tau-t}^{\tau} \mu(\theta)d\theta} d\tau.$$

(b) Suppose that $\beta(a) = \beta > 0$, $\mu(a) = \mu > 0$ and that $N(t, a) \sim e^{\gamma t} S(a)$ as $t \to \infty$. Show that the growth rate γ is given by $\gamma = \beta - \mu$.

(c) Sketch the corresponding profiles $S(a)$ for the cases $\gamma > 0, \gamma = 0$ and $\gamma < 0$. Comment briefly on your results.

Question 4.

Consider a population of cells that are executing the cell cycle. We denote by $n(\phi, t)$ the number of cells at position $0 \leq \phi \leq 1$ in their cycle at time t. We introduce the following partial differential equation to model the evolution of the cells:

$$\frac{\partial n}{\partial t} + (1 + \beta\phi)\frac{\partial n}{\partial \phi} = -\mu n,$$

with $n(\phi, 0) = f(\phi)$ and $n(0, t) = 2n(1, t)$ for some positive function $f(\phi)$ and positive constants β and μ.

By seeking a separable solution of the form $n(\phi, t) = e^{\gamma t} N(\phi)$, derive an expression for the unique value of $\mu = \mu^*(\beta)$ for which the population evolves, at long times, to a non-trivial, time-independent solution.