School of Mathematical Sciences

Mathematical Biology (Honours)

Assignment 3 question sheet

Due: Friday, 1 November, by 5pm (leave in box on office door)

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1. Tumours contain a mixture of cancer cells, normal tissue cells and macrophages (a type of white blood cell). The proliferation rates of all three cell types are logistic, with the cancer cells proliferating more rapidly than their normal counterparts. The macrophage proliferation rate is an increasing, saturating function of a chemical, Monocyte Chemoattractant Protein or MCP, which is produced at a constant rate by the cancer cells and decays naturally. When MCP is present, the macrophages kill the cancer cells at a rate proportional to the MCP concentration. The cancer cells and normal cells move by random motion alone, whilst the macrophages move by a combination of random motion and chemotaxis up gradients of MCP. The MCP moves through the tumour domain by diffusion.

   Use the principle of conservation of mass to write down a mathematical model for this situation in a one-dimensional geometry. The model should consist of partial differential equations for the densities of the cancer cells $c(x,t)$, normal tissue cells $n(x,t)$ and macrophages $m(x,t)$, and the concentration of MCP $a(x,t)$ (where x and t denote position and time, respectively). You do not need to provide boundary or initial conditions, but you should carefully explain the reasoning behind each term in your model. [10 marks]

2. **(Response to bacterial infection)** Phagocytes are the class of white blood cells (including macrophages) which help to combat infections by engulfing and absorbing bacteria and other small cells. Consider the following dimensionless model for phagocyte chemotaxis towards bacterial cells, where p is the density of phagocytes, and b is the density of bacteria.

$$\frac{\partial b}{\partial t} = \mu \frac{\partial^2 b}{\partial x^2} + \frac{\gamma b}{1+b} - \frac{bp}{\kappa + b},$$

$$\frac{\partial p}{\partial t} = \frac{\partial^2 p}{\partial x^2} - \delta \frac{\partial}{\partial x}\left(p \frac{\partial b}{\partial x}\right) + \alpha(1 + \sigma b - p),$$

   where:

   - γ is the dimensionless maximum bacterial proliferation rate;
   - σ is the ratio of enhanced phagocyte production rate to normal 'background' production rate;
   - κ describes how bacteria-killing by phagocytes becomes less efficient at high bacterial densities;

- δ is the chemotaxis coefficient (sensitivity to gradients of bacteria density);
- α is the dimensionless phagocyte death rate.

(a) Carry out a linear stability analysis of the uninfected steady state $(b, p) = (0, 1)$ on an infinite domain by substituting solutions of the form

$$(b, p) = (0, 1) + \epsilon(b_1, p_1)e^{iqx+\lambda t},$$

(where the real part is to be understood) into the governing equations and linearising. Show that the roots of the resulting dispersion relation are

$$\lambda_1 = -\mu q^2 + \gamma - \frac{1}{\kappa}, \qquad \lambda_2 = -q^2 - \alpha.$$

[6 marks]

(b) Which mode (*i.e.* value of q) is most likely to cause instability? What is the implication of this? [2 marks]

(c) Show that a second, 'chronic infection' steady state can exist, with $(b, p) = (\bar{b}, \bar{p}) = (\bar{b}, 1 + \sigma\bar{b})$ (where $\bar{b} > 0$) and that this state will be linearly stable provided that

$$\frac{\gamma}{(1+\bar{b})^2} - \frac{\kappa\bar{p}}{(\kappa+\bar{b})^2} - \alpha - (1+\mu)q^2 < 0,$$

$$\frac{\alpha\kappa\bar{p}}{(\kappa+\bar{b})^2} - \frac{\alpha\gamma}{(1+\bar{b})^2} + \frac{\alpha\sigma\bar{b}}{\kappa+\bar{b}} + (\mu q^2 + \mu\alpha + \delta\bar{p}G(\bar{b}) - F(\bar{b}))q^2 > 0,$$

where the functions F and G are given by

$$F(b) = \frac{b(1+\sigma b)(1-\kappa)}{(1+b)(\kappa+b)^2}, \qquad G(b) = \frac{b}{(k+b)}.$$

[8 marks]

3. **(Formation of senile plaques in Alzheimer's disease)** Senile plaques are lesions which occur in the brains of patients with Alzheimer's disease, and are implicated in its progression. They consist of aggregations of non-neuronal cells called glial cells, and a protein called β-amyloid, together with degenerating neurons (brains cells) and other chemical factors, including TNF-α (tumour necrosis factor-α). The glial cells produce both factors (β-amyloid and TNF-α), and are attracted to β-amyloid, but repelled by TNF-α. Luca *et al.* [1] developed the following one-dimensional model to study the formation of these plaques:

$$\frac{\partial m}{\partial t} = D_m\frac{\partial^2 m}{\partial x^2} - \chi_1\frac{\partial}{\partial x}\left(m\frac{\partial c_1}{\partial x}\right) + \chi_2\frac{\partial}{\partial x}\left(m\frac{\partial c_2}{\partial x}\right)$$

$$\frac{\partial c_1}{\partial t} = D_1\frac{\partial^2 c_1}{\partial x^2} + a_1m - b_1c_1, \qquad \frac{\partial c_2}{\partial t} = D_2\frac{\partial^2 c_2}{\partial x^2} + a_2m - b_2c_2,$$

where $m(x, t)$ is the density of glial cells. The model is to be solved in the domain $0 \leq x \leq L$, subject to the boundary conditions

$$\frac{\partial m}{\partial x} = \frac{\partial c_1}{\partial x} = \frac{\partial c_2}{\partial x} = 0 \quad \text{on } x = 0, L,$$

and suitable initial conditions.

(a) By considering the signs of the chemotactic flux terms, determine which of c_1 or c_2 represents the concentration of β-amyloid protein, and which represents the concentration of TNF-α. [2 marks]

(b) Show that for any positive constant value m_0, the model equations have a spatially uniform steady state $(m, c_1, c_2) = (m_0, c_{1_0}, c_{2_0})$, where c_{1_0} and c_{2_0} are constants which you should determine. [2 marks]

The model can be written in dimensionless variables (indicated by tildes) using the scalings

$$x = \sqrt{\frac{D_2}{b_2}}\tilde{x}, \quad t = \frac{D_2}{b_2 D_m}\tilde{t}, \quad m = m_0\tilde{m}, \quad c_1 = c_{1_0}\tilde{c}_1, \quad c_2 = c_{2_0}\tilde{c}_2.$$

The dimensionless equations (dropping tildes) are:

$$\frac{\partial m}{\partial t} = \frac{\partial^2 m}{\partial x^2} - A_1 \frac{\partial}{\partial x}\left(m\frac{\partial c_1}{\partial x}\right) + A_2 \frac{\partial}{\partial x}\left(m\frac{\partial c_2}{\partial x}\right)$$

$$\epsilon_1 \frac{\partial c_1}{\partial t} = \frac{\partial^2 c_1}{\partial x^2} + a^2(m - c_1), \epsilon_2\frac{\partial c_2}{\partial t} = \frac{\partial^2 c_2}{\partial x^2} + m - c_2,$$

which are to be solved in $0 \le x \le l$. The dimensionless parameters are:

$$A_1 = \frac{\chi_1 a_1 m_0}{D_m b_1}, \quad A_2 = \frac{\chi_2 a_2 m_0}{D_m b_2}, \quad \epsilon_1 = \frac{D_m}{D_1},$$

$$\epsilon_2 = \frac{D_m}{D_2}, \quad a = \sqrt{\frac{D_2 b_1}{D_1 b_2}}, \quad l = L\sqrt{\frac{b_2}{D_2}}.$$

(c) For the remaining parts of the question, let $\epsilon_1 = \epsilon_2 = 0$. Give a physical interpretation of this assumption. [1 marks]

(d) In a normal brain, assume that $(m, c_1, c_2) = (1, 1, 1)$. Perform a linear stability analysis of this steady state and show that it leads to the dispersion relation:

$$\omega = -q^2 + q^2 A_2 \left(\frac{A}{a^2 + q^2} - \frac{1}{q^2 + 1}\right),$$

where $A = \dfrac{\chi_1 D_2 a_1}{\chi_2 D_1 a_2}$. [6 marks]

(e) Hence determine that a necessary and sufficient condition for the growth of senile plaques is

$$\frac{A}{a^2 + q^2} - \frac{1}{q^2 + 1} > \frac{1}{A_2}.$$

[2 marks]

(f) Are there any restrictions on the permissible wavenumbers, q? If so, what are they? [1 marks]

Total: 40 marks

References

[1] M. Luca, A. Chavez-Ross, L. Edelstein-Keshet, and A. Mogilner. Chemotactic signalling, microglia and Alzheimer's disease senile plaques: Is there a connection? *Bull. Math. Biol.*, 65:693–730, 2003.