# Mathematical Biology Assignment 3 & 4

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Normally I would paraphrase the the questions, but instead I have appended the question sheet to the end

## 1 Assignment 3

1. to break down the problem into pieces:

   - The cells $(c, m, n)$ all proliferate logistically ($c$ greater rate than $n$).
   - $m$ increases (and saturates) with $a$
   - $c, n, m$ all move by random motion, and $m$ moves via chemotaxis with gradient of $a$
   - $a$ is produced constantly by $c$ and decays 'naturally'
   - $m$ kills $c$ at a rate proportional to $a$ concentration.
   - $a$ moves via diffusion

   Constants:

   - Proliferation rates of $c, m, n$ respectively $p_c, p_m, p_n$ with $p_c > p_n$
   - Carrying capacities for the cells $k_c, k_m, k_n$
   - $l_a$ describes the early growth rate of $m$ with respect to $a$
   - $\beta_m$ is the death rate of cancer cells due to macrophages and $\beta_a$ is the decomposition of MCP
   - $\chi$ is the chemotactic constant for the macrophages

$$
\begin{aligned}
\frac{\partial c}{\partial t} &= \nabla\left(D_c \nabla c\right) + p_c c(1 - \frac{c}{k_c}) - \beta_m m c \\
\frac{\partial n}{\partial t} &= \nabla\left(D_n \nabla n\right) + p_n n(1 - \frac{n}{k_n}) \\
\frac{\partial m}{\partial t} &= \nabla\left(D_m \nabla m\right) - \chi \nabla\left[m \nabla a\right] + \frac{p_m a}{l_a + a} m(1 - \frac{m}{k_m}) \\
\frac{\partial a}{\partial t} &= \nabla\left(D_a \nabla a\right) + p_a c - \beta_a
\end{aligned}
$$

   Where since this is for $1D$ $\nabla := \frac{d}{dx}$

2. (a) I'm going to let $(\tilde{b}, \tilde{p}) := \epsilon(b_1, p_1)e^{iqx+\lambda t}$

$$\frac{\partial b}{\partial t} = \mu\frac{\partial^2 b}{\partial x^2} + \frac{\gamma b}{1+b} - \frac{bp}{\kappa + b}$$
$$\lambda\tilde{b} = -q^2\mu\tilde{b} + \frac{\gamma\tilde{b}}{1+\tilde{b}} - \frac{\tilde{b}(1+\tilde{p})}{\kappa + b}$$
$$\lambda = -q^2\mu + \frac{\gamma}{1+\tilde{b}} - \frac{(1+\tilde{p})}{\kappa + \tilde{b}}$$

To leading order, $(\tilde{b}, \tilde{p})$ is negligible (assuming $\epsilon \ll 1$) this gives

$$\lambda = -q^2\mu + \gamma - \frac{p}{\kappa}$$

For the $p$ equation:

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

At order $\mathcal{O}(\epsilon)$

$$\lambda\tilde{p} = -q^2\tilde{p} - \delta\left(-q^2\tilde{b}\right) + \alpha(\sigma\tilde{b} - \tilde{p})$$
$$\lambda = -q^2 - \delta\left(-q^2\frac{b_1}{p_1}\right) + \alpha(\sigma\frac{b_1}{p_1} - 1)$$
$$\lambda = -q^2 - \alpha - \frac{b_1}{p_1}\left(-q^2\delta + \alpha\sigma\right)$$

Either $\frac{b_1}{p_1} = 0$ or $q^2\delta = \alpha\sigma$ for the answer required...

(b) Instabilities occur for lambda with positive real part. So, the most likely instabilities will occur for values of $q$ which give the largest $\lambda$. Hence in this case, the smallest values of $q$ will give the most likely instabilities. I.e. the wavenumbers with highest frequency

(c) I am going to drop the bars for simplicity sake, I.e. $(b, 1 + \sigma b)$

Existence :

$$\begin{aligned}\frac{\partial b}{\partial t} &= \mu\frac{\partial^2 b}{\partial x^2} + \frac{\gamma b}{1+b} - \frac{bp}{\kappa+b}\\ 0 &= \frac{\gamma b}{1+b} - \frac{b(1+\sigma b)}{\kappa+b}\\ 0 &= \gamma(\kappa+b) - (1+b)(1+\sigma b)\\ 0 &= \gamma\kappa + \gamma b - 1 - b - \sigma b - \sigma b^2\end{aligned}$$

$$\begin{aligned}\frac{\partial p}{\partial t} &= \frac{\partial^2 p}{\partial x^2} - \delta\frac{\partial}{\partial x}\left(p\frac{\partial b}{\partial x}\right) + \alpha(1+\sigma b - p)\\ &= \alpha(1+\sigma b - (1+\sigma b))\\ &= (1 - 1 + \sigma b - \sigma b) = 0\end{aligned}$$

Stability:

$$(b,p) = (\bar{b}, 1+\sigma\bar{b}) + \epsilon(\bar{b}_1, \bar{p}_1)e^{iqx+\lambda t}$$

I will call the perturbation part $(\hat{b}, \hat{p})$

$$\begin{aligned}\frac{\partial b}{\partial t} &= \mu\frac{\partial^2 b}{\partial x^2} + \frac{\gamma b}{1+b} - \frac{bp}{\kappa+b}\\ \lambda\hat{b} &= -\mu q^2\hat{b} + \frac{\gamma(\bar{b}+\hat{b})}{1+(\bar{b}+\hat{b})} - \frac{(\bar{b}+\hat{b})(1+\sigma\bar{b}+\hat{p})}{\kappa+(\bar{b}+\hat{b})}\end{aligned}$$

$$\begin{aligned}\frac{\partial p}{\partial t} &= \frac{\partial^2 p}{\partial x^2} - \delta\frac{\partial}{\partial x}\left(p\frac{\partial b}{\partial x}\right) + \alpha(1+\sigma b - p)\\ \lambda\hat{p} &= -q^2\hat{p} - \delta\left(-q^2\hat{b}\hat{p} - q^2\hat{b}(1+\sigma\bar{b}+\hat{p})\right) + \alpha(1+\sigma(\bar{b}+\hat{b}) - (1+\sigma\bar{b}+\hat{p}))\end{aligned}$$

This state will be linearly stable if both of these $\lambda$ equations give $\lambda < 0$

$$\begin{aligned}\lambda = \frac{1}{\hat{b}}\left(-\mu q^2\hat{b} + \frac{\gamma(\bar{b}+\hat{b})}{1+(\bar{b}+\hat{b})} - \frac{(\bar{b}+\hat{b})(1+\sigma\bar{b}+\hat{p})}{\kappa+(\bar{b}+\hat{b})}\right) < 0\\ -\mu q^2\hat{b} + \frac{\gamma(\bar{b}+\hat{b})}{1+(\bar{b}+\hat{b})} - \frac{(\bar{b}+\hat{b})(1+\sigma\bar{b}+\hat{p})}{\kappa+(\bar{b}+\hat{b})} < 0\end{aligned}$$

$$\lambda = \frac{1}{\hat{p}}\left(-q^2\hat{p} - \delta\left(-q^2\hat{b}\hat{p} - q^2\hat{b}(1+\sigma\bar{b}+\hat{p})\right) + \alpha(1+\sigma(\bar{b}+\hat{b}) - (1+\sigma\bar{b}+\hat{p}))\right) < 0$$

Need to get

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

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

Where

$$F(\bar{b}) = \frac{\bar{b}(1+\sigma\bar{b})(1-\kappa)}{(1+\bar{b})(\kappa+\bar{b})^2}, \quad G(\bar{b}) = \frac{\bar{b}}{\kappa+\bar{b}}$$

3. (a) The $\chi$ terms represent chemotaxis along a gradient. Since negative coefficients correspond to moving up a gradient (towards higher concentrations), $c_1$ is the $\beta$-amyloid, and $c_2$ is the TNF-$\alpha$.

   (b) Sub in $(m_0, c_{10}, c_{20})$. The first equation is trivially zero.

$$\begin{aligned}
\frac{\partial c_1}{\partial t} &= D_1\frac{\partial^2 c_1}{\partial x^2} + a_1 m - b_1 c_1 \\
0 &= 0 + a_1 m_0 - b_1 c_{10} \\
c_{10} &= \frac{a_1 m_0}{b_1}
\end{aligned}$$

$$\begin{aligned}
\frac{\partial c_2}{\partial t} &= D_2\frac{\partial^2 c_2}{\partial x^2} + a_2 m - b_2 c_2 \\
0 &= 0 + a_2 m_0 - b_2 c_{20} \\
c_{20} &= \frac{a_2 m_0}{b_2}
\end{aligned}$$

   (c) $\epsilon_1 = \frac{D_m}{D_1}$. This is the ratio of the rates of diffusion of glial cells and $\beta$-amyloid. Similarly, $\epsilon_2$ is the ratio of the rates of diffusion of glial cells and TNF-$\alpha$. Setting these simultaneously to zero corresponds to $D_m \ll D_1, D_2$. I.e. that the rate of diffusion of glial cells is significantly lower than that of the protein and chemical. Explicitly setting these to zero is by either letting $D_m = 0$ or both $D_1, D_2 \to \infty$. I.e. by assuming glial cells do not diffuse or that the protein and chemical both diffuse instantly.

   (d) Assume $(m, c_1, c_2) = (1, 1, 1)$. Linear stability analysis - using the fact that $\frac{\partial m}{\partial x} = \frac{\partial c_1}{\partial x} = \frac{\partial c_2}{\partial x} = 0$ for $x = 0, l$ (under the changed system):

$$(m, c_1, c_2) = \mathbf{1} + \epsilon(m_1, c_{11}, c_{21})\cos(qx)e^{\omega t}$$

Since we are setting $\epsilon_1 = \epsilon_2 = 0$ we only need to consider the first equation

$$\begin{aligned}
\frac{\partial m}{\partial t} &= \frac{\partial^2 m}{\partial x^2} - A_1\frac{\partial}{\partial x}\left(m\frac{\partial c_1}{\partial x}\right) + A_2\frac{\partial}{\partial x}\left(m\frac{\partial c_2}{\partial x}\right) \\
\omega\bar{m} &= -q^2\bar{m} - A_1\left(-q^2\bar{c_1}(1+\bar{m}) - q^2\epsilon^2 m_1 c_{11}\sin^2(qx)e^{2\omega t}\right) \\
&\quad + A_2\left(-q^2\bar{c_2}(1+\bar{m}) - q^2\epsilon^2 m_1 c_{21}\sin^2(qx)e^{2\omega t}\right)
\end{aligned}$$

To $\mathcal{O}(\epsilon)$

$$\begin{aligned}
\omega\bar{m} &= -q^2\bar{m} - A_1\left(-q^2\bar{c_1}\right) + A_2\left(-q^2\bar{c_2}\right) \\
\omega &= -q^2 - A_1\left(-q^2\frac{c_{11}}{m_1}\right) + A_2\left(-q^2\frac{c_{21}}{m_1}\right) \\
\omega &= -q^2 + q^2\left(A_1\left(\frac{c_{11}}{m_1}\right) - A_2\left(\frac{c_{21}}{m_1}\right)\right) \\
\omega &= -q^2 + q^2 A_2\left(\frac{A_1}{A_2}\left(\frac{c_{11}}{m_1}\right) - \left(\frac{c_{21}}{m_1}\right)\right)
\end{aligned}$$

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

Where $A = \frac{\chi_1 D_2 a_1}{\chi_2 D_1 a_2}$

(e) Growth of senile plaques will occur for $\omega > 0$

$$\begin{aligned} \omega = -q^2 + q^2 A_2 \left( \frac{A}{a^2 + q^2} - \frac{1}{q^2 + 1} \right) &> 0 \\ q^2 A_2 \left( \frac{A}{a^2 + q^2} - \frac{1}{q^2 + 1} \right) &> q^2 \\ \left( \frac{A}{a^2 + q^2} - \frac{1}{q^2 + 1} \right) &> \frac{1}{A_2} \end{aligned}$$

(f) The boundary conditions state $\frac{\partial m}{\partial x} = \frac{\partial c_1}{\partial x} = \frac{\partial c_2}{\partial x} = 0$ for $x = 0, l$ (under the changed parameters). So $q$ is restricted to force this condition, hence

$$q = \frac{2\pi n}{l}$$

For integer $n$.

# 2 Assignment 4

1. (a) $u$ is an activator, and $v$ is an inhibitor, as $u$ promotes the growth of $u$ and $v$, while $v$ inhibits the growth of $u$. This is shown by the signs of the $u$ and $v$ interaction terms (I'll show this further in part (c))

   (b) Spatially uniform steady state:

$$\frac{u^2}{v} - \beta u = 0$$
$$u^2 - v = 0$$

   Setting $v = u^2$ gives $u = \frac{1}{\beta}$. I.e. there is a unique spatially uniform steady state for $u = \frac{1}{\beta}$ and $v = \frac{1}{\beta^2}$.

   (c) For diffusion-driven instability, necessary conditions are:

$$f_a + g_b < 0$$
$$f_a g_b - f_b g_a > 0$$
$$df_a + g_b > 0$$
$$(df_a + g_b)^2 - 4d(f_a g_b - f_b g_a) > 0$$

   Where $f, g$ are the RHS portions of the $b, p$ DEs. And all of these equations are evaluated at the steady state, $\beta^{-1}, \beta^{-2}$.And in this case, $d = \delta$ and $a, b$ are $u, v$ respectively.

$$f = \frac{u^2}{v} - \beta u$$
$$g = u^2 - v$$

$$f_u = \frac{2u}{v} - \beta = 2\beta - \beta = \beta$$
$$f_v = -\frac{u^2}{v^2} = -\frac{\beta^4}{\beta^2} = -\beta^2$$
$$g_u = 2u = \frac{2}{\beta}$$
$$g_v = -1$$

$$M = \begin{pmatrix} \beta & -\beta^2 \\ \frac{2}{\beta} & -1 \end{pmatrix} \implies \begin{pmatrix} + & - \\ + & - \end{pmatrix}$$

   As in lectures, for $\beta > 0$, we clearly have activator-inhibitor due to the signs.
   Hence we require (at $\beta^{-1}, \beta^{-2}$):
   Plugging these into the $f_a, f_b, g_a, g_b$ equations.

$$\beta - 1 < 0$$
$$-\beta + 2\beta > 0$$
$$\delta\beta - 1 > 0$$
$$(\delta\beta - 1)^2 - 4\delta(-\beta + 2\beta) > 0$$

Hence requiring:

$$\beta < 1$$
$$\beta > 0$$
$$\beta > \frac{1}{\delta}$$

The last condition requires $\delta > 1$ to allow for all the others.
The last equation:

$$(\delta\beta - 1)^2 - 4\delta(-\beta + 2\beta) > 0 \, (\delta\beta - 1)^2 - 4\delta\beta > 0$$
$$\delta^2\beta^2 - 2\delta\beta + 1 - 4\delta\beta > 0$$
$$(\delta\beta)^2 - 6\delta\beta + 1 > 0$$

We would get equality for

$$\delta\beta = \frac{6 \pm \sqrt{36 - 4}}{2} = 3 \pm \sqrt{8} = 3 \pm 2\sqrt{2}$$

Plot $\beta, \delta$ in the region, $\beta \in (0, 1)$

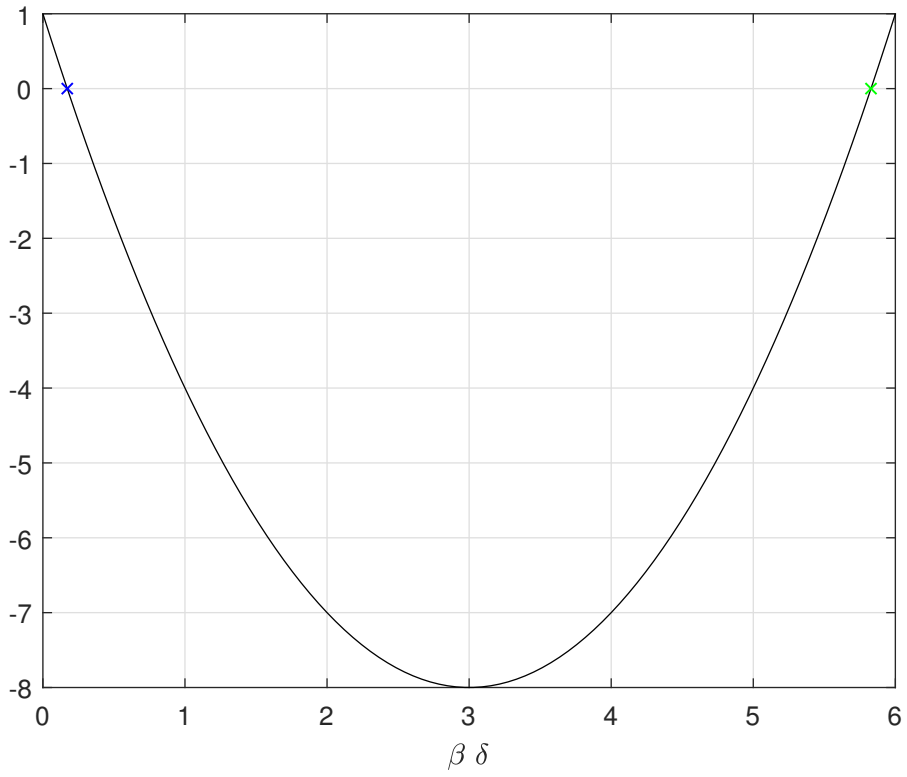


Figure 1: A plot of the final condition with the positions of the zeros plotted

Figures 1 and 2 both show equalities for this to hold true. The colour coding is set to match the two plots together.
To satisfy the conditions the values of $\beta$ and $\delta$ must be above the green plot, as the blue plot is not in the valid region.

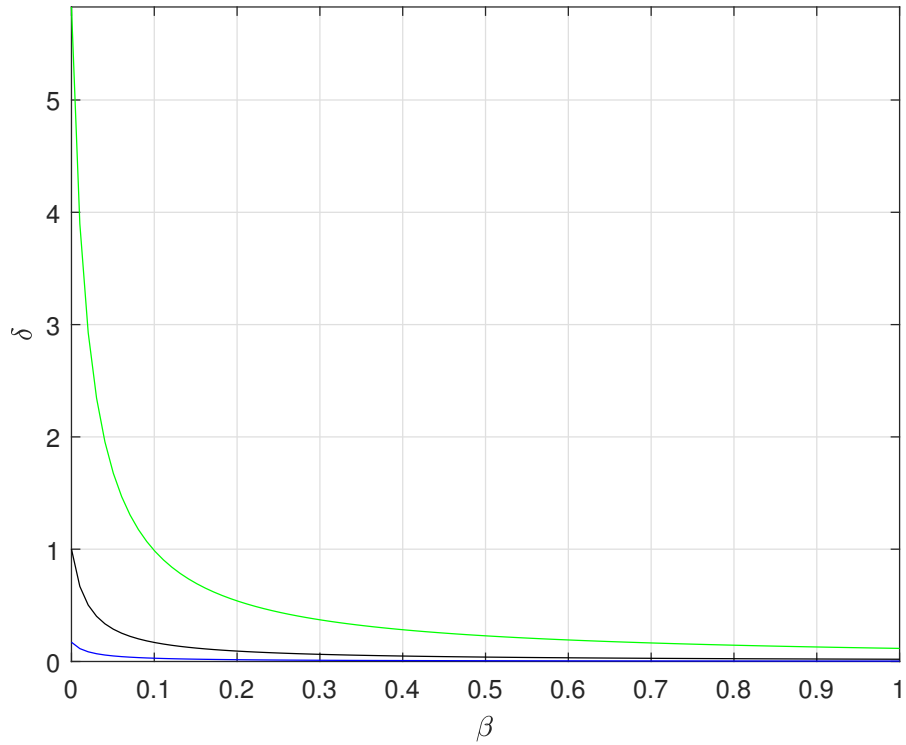


Figure 2: A plot of the conditions together - colour coded to match the previous

(d) From lectures $q = 0$ is stable, and as $q^2 \to \infty$ we have stability. The $q$ with instability will be $q \in (q_1, q_2)$, where $(q_1, q_2)$ are the zeros of $h(q^2)$:

$$\begin{aligned} h(q^2) &= \delta q^4 - \gamma(\delta f_a + g_b)q^2 + \gamma^2 \det M \\ h(q^2) &= \delta q^4 - (\delta f_a + g_b)q^2 + (f_a g_b - f_b g_a) \\ &= \delta q^4 - (\delta\beta - 1)q^2 + \delta\beta \end{aligned}$$

$$q^2 = \frac{\beta\delta - 1 \pm \sqrt{\beta^2\delta^2 - 4\beta\delta^2 - 2\beta\delta + 1}}{2\delta}$$

So the unstable wavenumbers are

$$q^2 \in \left( \frac{\beta\delta - 1 - \sqrt{\beta^2\delta^2 - 4\beta\delta^2 - 2\beta\delta + 1}}{2\delta}, \frac{\beta\delta - 1 + \sqrt{\beta^2\delta^2 - 4\beta\delta^2 - 2\beta\delta + 1}}{2\delta} \right)$$

(e) By changing the rate of diffusion for $v$ to relate to $u$, at any instant, the rate of diffusion of $v$ could become quite small due to small $u$, and effectively bringing $\delta < 1$, hence ruining the possibility for the Turing instabilities to occur for small $u$. Near the steady state $(\beta^{-1}, \beta^{-2})$ from before, the diffusion for $v$ would be approximately $\delta\beta^{-1}$.

2. (a) Information:

- nutrient diffuses, with diffusion coeff $D = 1$
- Boundary conditions $c(x \geq L(t)) = c_\infty$.
- No flux at $x = 0$, i.e. $\frac{dc}{dx}\Big|_{x=0} = 0$
- $c < c_n$ causes necrotic cells

- necrotic cells do not consume nutrient
- necrotic cells decay at rate $\beta$.
- Diffusion of nutrient occurs faster than tumour growth
- Cell density is constant

Conservation of cells and nutrient give

$$\frac{\partial n}{\partial t} + \nabla \cdot (nv) = f(c, \mathbf{x}, t)$$
$$\frac{\partial c}{\partial t} = D\nabla^2 c - \lambda n$$

Given that the density of cells is constant$D = 1$, and prior to the necrotic region appearing, the reaction (proliferation) is $f \propto c$

$$\frac{dv}{dx} = \gamma(c_n - c)$$
$$\frac{dc}{dt} = \frac{d^2c}{dx^2} - \lambda$$

Where $v$ is the velocity of cells, and $\gamma$ is the cell proliferation rate. For $0 < x < L(t)$, where $k$ is some constant consumption rate.

The quasi-steady assumption gives $c = \frac{\lambda}{2}x^2 + bx + d$. $\frac{dc}{dx}\Big|_{x=0} = 0$ implies $b = 0$.

We have $c(L(t)) = c_\infty$

$$c_\infty = \frac{\lambda}{2}L^2 + d$$

$$c = sc_\infty - \lambda$$

Using this in the $v$ equation:

$$\frac{dv}{dx} = \gamma(c_n - c)$$
$$\frac{dv}{dx} = sc_\infty - \lambda s x^2$$
$$v(x,t) = sc_\infty x - \frac{\lambda s x^3}{3}$$
$$v(L(t),t) = sc_\infty L - \frac{\lambda s L^3}{3}$$

The substitution $s = 2\gamma$ implies that $s$ is twice the proliferation rate. Hence

$$\frac{dL}{dt} = sc_\infty L - \frac{\lambda s L^3}{3}$$

(b) The steady state $L = 0$ is trivial:

$$\frac{dL}{dt} = sc_\infty L - \frac{\lambda s L^3}{3}$$
$$\frac{dL}{dt} = 0$$

Stability:

$$\begin{aligned}\frac{d}{dL}\left(sc_\infty L - \frac{\lambda s L^3}{3}\right) &= sc_\infty - \lambda s L^2 \\ &= sc_\infty\end{aligned}$$

Given $s, c_\infty > 0$ this is unstable.
The $L = L_* \geq 0$ steady state:

$$\begin{aligned}\frac{dL}{dt} &= sc_\infty L - \frac{\lambda s L^3}{3} \\ 0 &= sc_\infty - \frac{\lambda s L^2}{2} \\ L^2 &= \frac{2c_\infty}{\lambda} \\ L &= \sqrt{\frac{2c_\infty}{\lambda}}\end{aligned}$$

Ignoring the negative case since $L \geq 0$. Stability:

$$\begin{aligned}sc_\infty - \lambda s L^2 &= sc_\infty - \lambda s \frac{2c_\infty}{\lambda} \\ &= sc_\infty (1-2) \\ &= -sc_\infty\end{aligned}$$

Given $s, c_\infty > 0$ this is stable.
It cannot exist as

(c) Inside the region $0 < x < L_n$, the $c$ DE

$$\frac{dc}{dt} = \frac{d^2c}{dx^2}$$

With $\lim_{x^- \to L_n} c(L_n) = \lim_{x^+ \to L_n} = c(L_n) = c_n$ and $\lim_{x^- \to L_n} \frac{dc}{dx} = \lim_{x^+ \to L_n} \frac{dc}{dx}$

(d) Need to get

$$\frac{dL}{dt} = s(L - L_n)\left(c_n + \frac{\lambda}{6}(L - L_n)^2\right) - \beta L_n$$

# Code

```
close all
clear all

x = linspace(0,6);
plot(x,x.^2 - 6*x +1,'k')
hold on
plot((3 + 2 *sqrt(2)),0,'gx')
plot((3 - 2 *sqrt(2)),0,'bx')
xlabel('\beta \delta')
grid on
```

```
11 saveas(gcf,'bdregion.eps','epsc')
12
13 figure
14 beta = linspace(0,1);
15 delta = linspace(1,50);
16
17 %plot beta = delta
18 plot(beta,1./delta,'k')
19 %plot the last condition
20 hold on
21 %fimplicit(@(beta,delta) delta.^2.*beta.^2 - 6*delta.*beta +
       ↪ 1,[0,1,1,50])
22 dbplus= (3 + 2 *sqrt(2))./delta;
23 dbminus= (3 - 2 *sqrt(2))./delta;
24 plot(beta,dbplus,'g')
25 plot(beta,dbminus,'b')
26
27 axis([0,1,0,inf])
28 xlabel('\beta')
29 ylabel('\delta')
30 grid on
31 saveas(gcf,'betaVdelta.eps','epsc')
```

# 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:

   - $\gamma$ is the dimensionless maximum bacterial proliferation rate;
   - $\sigma$ is the ratio of enhanced phagocyte production rate to normal 'background' production rate;
   - $\kappa$ describes how bacteria-killing by phagocytes becomes less efficient at high bacterial densities;

- $\delta$ is the chemotaxis coefficient (sensitivity to gradients of bacteria density);
- $\alpha$ 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 $\beta$-amyloid, together with degenerating neurons (brains cells) and other chemical factors, including TNF-$\alpha$ (tumour necrosis factor-$\alpha$). The glial cells produce both factors ($\beta$-amyloid and TNF-$\alpha$), and are attracted to $\beta$-amyloid, but repelled by TNF-$\alpha$. Luca *et al.* [1] developed the following one-dimensional model to study the formation of these plaques:

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

$$\frac{\partial c_1}{\partial t} = D_1\frac{\partial^2 c_1}{\partial x^2} + a_1 m - b_1 c_1, \qquad \frac{\partial c_2}{\partial t} = D_2\frac{\partial^2 c_2}{\partial x^2} + a_2 m - b_2 c_2,$$

where $m(x, t)$ is the density of glial cells. The model is to be solved in the domain $0 \le x \le L$, 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 $\beta$-amyloid protein, and which represents the concentration of TNF-$\alpha$. [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 $0 \leq x \leq l$. 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.

# School of Mathematical Sciences

## Mathematical Biology (Honours)

### Assignment 4 question sheet

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

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1. Two chemicals, which control the pigmentation of an animal's skin, have concentrations $u$ and $v$, diffuse and interact on $-\infty < x < \infty$ according to the (dimensionless) equations

$$\frac{\partial u}{\partial t} = \frac{u^2}{v} - \beta u + \frac{\partial^2 u}{\partial x^2}, \qquad \frac{\partial v}{\partial t} = u^2 - v + \delta \frac{\partial^2 v}{\partial x^2},$$

where $\beta$ and $\delta$ are positive constants.

   (a) Which chemical plays the role of activator, and which is the inhibitor? [1 marks]

   (b) Show there is a unique spatially uniform steady state with $u, v > 0$. [2 marks]

   (c) Carry out a linear stability analysis of this steady state by considering solutions of the form

$$(u, v) = (u_0, v_0) + \epsilon(u_1, v_1)e^{iqx+\lambda t} + \ldots,$$

   (where the real part is to be understood). Hence, determine the conditions for a diffusion-driven (Turing) instability to occur, and sketch the corresponding region in the $(\beta, \delta)$ plane. [6 marks]

   (d) When a diffusion-driven instability occurs, what are the unstable wave numbers? [4 marks]

   (e) Briefly explain how your results would change if the diffusion coefficient for $v$ was proportional to $u$, so the second of the two equations would become:

$$\frac{\partial v}{\partial t} = u^2 - v + \delta \frac{\partial}{\partial x}\left(u \frac{\partial v}{\partial x}\right),$$

   [3 marks]

2. Tumour cells are grown in a tube, occupying the region $0 < x < L(t)$, where $x$ is the distance along the tube. The region $x > L(t)$ contains nutrient medium, where the nutrient concentration, $c$, is maintained at a constant level, $c_\infty$. Nutrient diffuses through the tumour cells (whether alive or dead), with diffusion coefficient, $D = 1$. There is no flux of cells or nutrient through the bottom of the tube, $x = 0$. Provided $c > c_n$, tumour cells consume nutrient at a constant rate, $\lambda$, and proliferate at a rate proportional to the nutrient concentration. However, if $c < c_n$, the cells become necrotic; necrotic cells do not consume nutrient and decay at a constant rate, $\beta$. You may assume that the diffusion of nutrient occurs much faster than the growth of the tumour, and that the density of cells within the tumour region remains constant at all times.

   (a) Assuming that the tumour is small enough not to have developed a necrotic region, show that the length of the tumour region $L(t)$ satisfies

   $$\frac{dL}{dt} = sc_\infty L - \frac{\lambda s L^3}{3}, \tag{1}$$

   where $s$ is constants, whose meaning you should explain. [6 marks]

   (b) Show, from equation (1) above that there are two steady states, $L = 0$, and $L = L^* > 0$, which are unstable and stable, respectively. Explain why, in reality, the $L = L^*$ steady state will not be attained. (*Hint: consider the nutrient level at* $x = 0$.) [4 marks]

   (c) Now consider a tumour which has a necrotic region $0 < x < L_n(t)$. Find the nutrient concentration throughout the entire tumour ($0 < x < L(t)$), assuming that both the nutrient concentration and its derivative are continuous at $x = L_n$. Hence, obtain an equation for the length of the proliferating region, $L - L_n$ in terms of $\lambda$, $c_\infty$ and $c_n$. [5 marks]

   (d) Solve for the cell velocity, and thus show the length of the tumour region satisfies

   $$\frac{dL}{dt} = s(L - L_n)\left(c_n + \frac{\lambda}{6}(L - L_n)^2\right) - \beta L_n.$$

   [3 marks]

*Total: 34 marks*