Mathematical Biology Assignment 3

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Q1. Morphogenesis

We will consider the general reaction diffusion system in dimensionless form on $0 < x < \pi$, given by

$$\frac{\partial u}{\partial t} = \frac{\partial^2 u}{\partial x^2} + \gamma f(u, v)\,, \tag{1.1}$$

$$\frac{\partial v}{\partial t} = 10\frac{\partial^2 v}{\partial x^2} + \gamma g(u, v)\,, \tag{1.2}$$

with no flux boundary conditions

$$\frac{\partial u}{\partial x}(0, t) = 0\,, \quad \frac{\partial u}{\partial x}(\pi, t) = 0\,, \tag{1.3}$$

$$\frac{\partial v}{\partial x}(0, t) = 0\,, \quad \frac{\partial v}{\partial x}(\pi, t) = 0\,. \tag{1.4}$$

Here $\gamma > 0$ is a dimensionless bifurcation parameter describing the relative strength of the diffusion terms compared to the interaction terms.

Let (u^*, v^*) be the spatially uniform steady state solution. The Jacobian matrix J of the linearisation of the system about (u^*, v^*) is given by

$$J = \gamma \begin{bmatrix} \frac{\partial f}{\partial u} & \frac{\partial f}{\partial v} \\ \frac{\partial g}{\partial u} & \frac{\partial g}{\partial v} \end{bmatrix}_{(u^*, v^*)} = \gamma \begin{bmatrix} 2 & -4 \\ 4 & -6 \end{bmatrix}. \tag{1.5}$$

Part a)

To show that (u^*, v^*) is stable in the absence of diffusion, we first calculate the eigenvalues of J:

$$\det \begin{bmatrix} 2\gamma - \lambda & -4\gamma \\ 4\gamma & -6\gamma - \lambda \end{bmatrix} = (2\gamma - \lambda)(-6\gamma - \lambda) - (4\gamma)(-4\gamma) = (\lambda + 2\gamma)^2 = 0\,,$$

$$\text{hence our eigenvalues are } \lambda = -2\gamma\,. \tag{1.6}$$

Since both (repeated) eigenvalues are negative, we see that (u^*, v^*) is a stable equilibrium as per standard linear stability analysis.

Part b)

We now investigate the scenario when diffusion is present, where we note that we have diffusion constants of $D_u = 1$ and $D_v = 10$. We start, as in J.D. Murray (Vol2 §2.3) by linearising around the steady state (u^*, v^*) (i.e. considering a perturbation about the steady state). In setting $\boldsymbol{w} = (u - u^*, v - v^*)$, we have

$$\frac{\partial \boldsymbol{w}}{\partial t} = \gamma J \boldsymbol{w} + D\frac{\partial^2 \boldsymbol{w}}{\partial x^2} \qquad \text{where} \quad D = \begin{bmatrix} 1 & 0 \\ 0 & 10 \end{bmatrix}. \tag{1.7}$$

We can define $\boldsymbol{W}(x) = (u(x), v(x))$ as the time independent solution to the spatial eigenvalue problem defined by

$$\frac{\partial^2 \boldsymbol{W}}{\partial x^2} + q^2 \boldsymbol{W} = 0 \tag{1.8}$$

with eigenvalues q. Our no flux boundary conditions at $x = 0$ and $x = \pi$ then give us that $\boldsymbol{W}(x) \propto \cos(qx)$, where we denote $\boldsymbol{W}_q$ as the eigenfunction corresponding to the qth eigenvalue. Hence we can look for Fourier solutions of the form

$$\boldsymbol{w}(x,t) = \sum_q c_q e^{\sigma t} \boldsymbol{W}_q(x)\,. \tag{1.9}$$

where c_q are the Fourier coefficients (largely irrelevant in our analysis) and σ is the exponential eigenvalue, which Murray calls the temporal growth rate. Substituting this equation into (1.7) and using the relation in (1.8), we have

$$\begin{gathered} \sigma \sum_q c_q e^{\sigma t} \boldsymbol{W}_q(x) = \gamma J \sum_q c_q e^{\sigma t} \boldsymbol{W}_q(x) - Dq^2 \sum_q c_q e^{\sigma t} \boldsymbol{W}_q(x) \\ \text{so} \quad (\gamma J - q^2 D - \sigma \mathbb{1}) \sum_q c_q \boldsymbol{W}_q(x) = 0\,. \end{gathered}$$

for all eigenvalues q. We seek non-trivial solutions for $\boldsymbol{W}_q(x)$, hence we want to solve $\det(\gamma J - q^2 D - \sigma \mathbb{1}) = 0$ for the eigenvalues σ, where we have

$$\begin{aligned} 0 = \det(\gamma J - q^2 D - \sigma \mathbb{1}) &= \det \begin{bmatrix} 2\gamma - q^2 - \sigma & -4\gamma \\ 4\gamma & -6\gamma - 10q^2 - \sigma \end{bmatrix} \\ &= \sigma^2 + (11q^2 + 4\gamma)\sigma + (10q^4 - 14\gamma q^2 + 4\gamma^2)\,. \end{aligned} \tag{1.10}$$

An elementary calculation using the quadratic formula shows that for any quadratic $a\sigma^2 + b\sigma + c = 0$ where $a > 0$ and $b > 0$ (which we have since $q^2, \gamma \geq 0$), there will be a positive solution for σ as long as $ac < 0$. Identifying these terms with (1.10), we see that our condition for instability of the qth node is

$$H(q^2) := 4\gamma^2 - 14\gamma q^2 + 10q^4 + < 0\,. \tag{1.11}$$

We note that here we have defined q to be the eigenvalues associated with (1.8) which yielded $\boldsymbol{W}(x) \propto \cos(qx)$. Our no flux boundary conditions then tell us that $q = \frac{n\pi}{L}$ for $n \in \mathbb{Z}$ where L is the length of the domain, but in our case we have $L = \pi$, that is, we have $q = n \in \mathbb{Z}$. So when we talk about the nth node, this is precisely the qth node.

Part c)

Solving for γ in $H(q^2) = 0$ we get

$$\gamma = \frac{1}{8}\left(14q^2 \pm \sqrt{196q^4 - 160q^4}\right) = q^2\,,\ \ \frac{5}{2}q^2\,. \tag{1.12}$$

Hence, since $H(q^2)$ is a positive quadratic in γ, we see that the condition on γ to ensure the qth node is unstable is

$$\gamma \in \left(q^2,\ \frac{5}{2}q^2\right)\,. \tag{1.13}$$

Part d)

Suppose we have $0 < \gamma < 10$. We can instead analyse $H(q^2) < 0$ in terms of q^2 now, where a similar analysis shows that $H(q^2) = 0$ when

$$q^2 = \frac{1}{20}\left(14\gamma \pm \sqrt{196\gamma^2 - 160\gamma^2}\right) = \frac{8}{20}\gamma\,,\ \ \gamma\,. \tag{1.14}$$

Hence, we have instability when $H(q^2) < 0$ which yields $q^2 \in (\frac{2}{5}\gamma,\ \gamma)$, so (noting the obvious negative symmetry in q) we have instability when

$$q \in \left(\sqrt{\frac{2\gamma}{5}},\ \sqrt{\gamma}\right)\,. \tag{1.15}$$

As can be seen in the graphs in part e), the modes $q = 1, 2, 3$ will be unstable for values of γ in various subintervals in $[0, 10]$. Using (1.13), we see that these nodes will be unstable when:

$$\underline{q=1}:\ \gamma \in (1, \frac{5}{2})\ ; \qquad \underline{q=2}:\ \gamma \in (4, 10)\ ; \qquad \underline{q=3}:\ \gamma \in (9, \frac{45}{2})\,. \tag{1.16}$$

In particular note that both $q = 2$ and $q = 3$ are unstable when $\gamma \in (9, 10)$. Interestingly, no nodes are unstable for $\gamma \in (0, 1)$ or $\gamma \in (\frac{5}{2}, 4)$.

Part e)

Using this analysis, we can use a graph to analyse which nodes, and how many, are unstable for $0 < \gamma < 10$ - this is shown in Figure 1.1. Note that we choose to depict this in the (γ, q) plane instead of (γ, q^2) plane simply as a matter of taste to keep the regions more compact to draw.

Recall that if a node q is unstable then this corresponds to the existence of pattern. Further, the higher the value of q, the higher the frequency of the pattern in the domain, for example the shorter the width of a zebra's stripes. When there are multiple competing unstable nodes, it is assumed that the greatest q value will dominate the pattern formation.

If we extend our domain to $\gamma \in (0, 1000)$, we get an even better picture of how many nodes become unstable for a given γ value. It is clear that only the two γ intervals stated in part d) and depicted in purple in Figure 1.1 give rise to no unstable nodes, as we can clearly visually see that unstable nodes will exist for any $\gamma > 4$. Note that careful analysis of the number of perfect squares in some linear region would yield a relationship between the number of unstable nodes as a function of γ - we leave this as an exercise to the reader if they are so inclined.

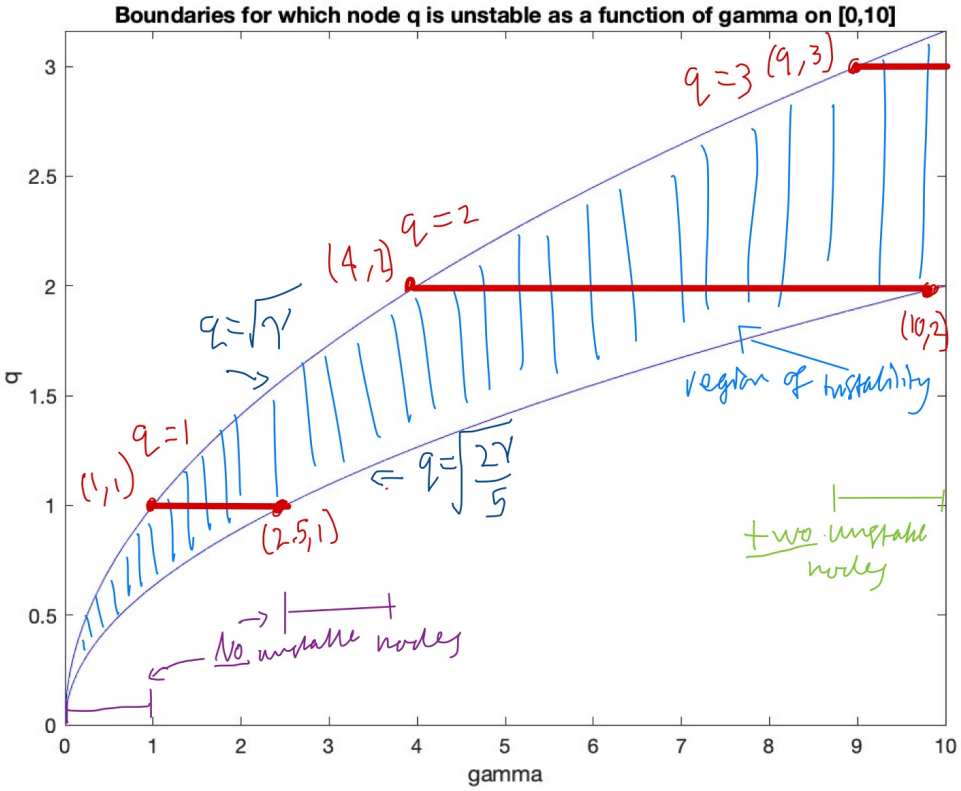

Figure 1.1: Plot depicting the region of instability and the corresponding unstable nodes q for different values of $\gamma \in (0, 10)$.

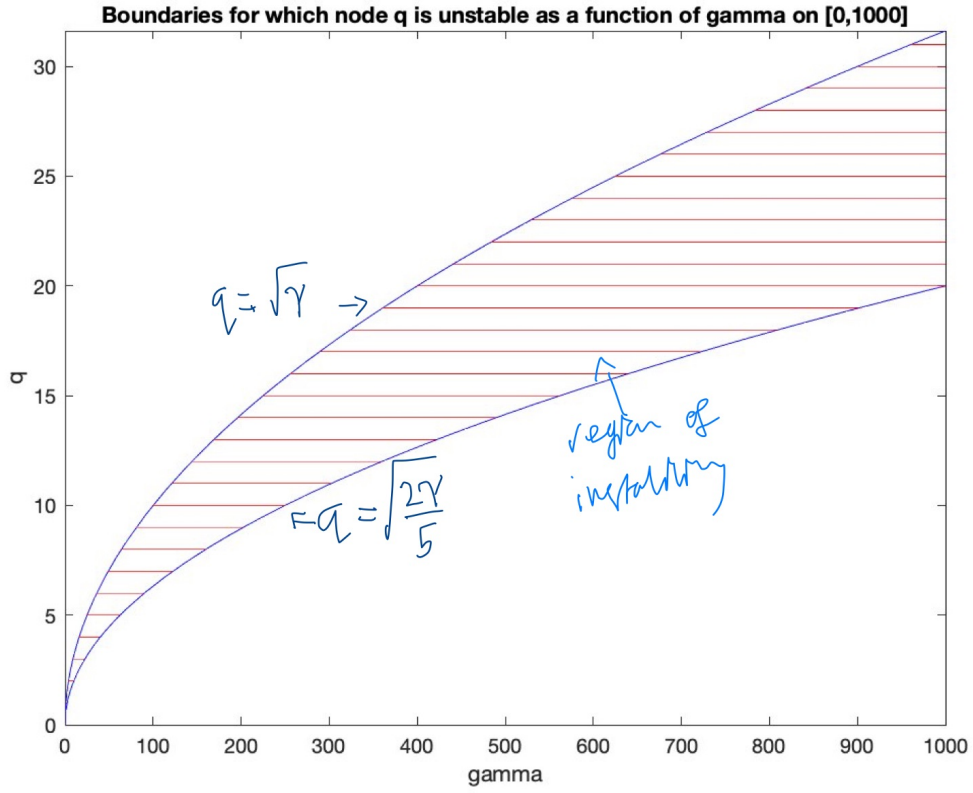

Figure 1.2: Plot depicting the region of instability and the corresponding unstable nodes q for different values of $\gamma \in (0, 1000)$.

Q2. 1D model in tissue engineering

Consider a region $0 \leq x \leq 1$ covered with cells with density $n(x,t)$. The cells need oxygen to survive. Let $c(x,t)$ denote the concentration of oxygen in the region. The equations governing $c(x,t)$ and $n(x,t)$ can be written as

$$\alpha \frac{\partial^2 c}{\partial x^2} - nF(c) = 0\,, \qquad \frac{\partial n}{\partial t} = nF(c)\,, \tag{2.1}$$

where α is a dimensionless diffusion parameter and $F(c)$ is a function describing the oxygen consumption by cells. The boundary and initial conditions are

$$c(0,t) = 1\,, \quad \frac{\partial c}{\partial x}(1,t) = 0\,, \quad n(x,0) = 1\,. \tag{2.2}$$

Note that we cannot set an initial condition for c nor a boundary condition for n. We shall consider the case where $F(c)$ is the Heaviside step function

$$F(c) = \begin{cases} 1 & \text{if } c > c^* \\ 0 & \text{if } c \leq c^* \end{cases}\,, \tag{2.3}$$

where c^* is a constant such that $0 < c^* < 1$. We will assume that $\alpha > 1/2$.

Part a)

As usual, the Heaviside step function acts as a kind of switch. In the context of our problem, we see that when the concentration of oxygen c is greater than some threshold c^*, $F(c) = 1$ turns on, which corresponds to $\frac{\partial n}{\partial t} = n$. This means that when the concentration reaches c^* in some region, the cells move to this region to consume said oxygen, which is represented by the solution $n(x,t) = N(x)e^t$ which shows that the density of cells increases exponentially when $c > c^*$. When the concentration of oxygen is low, so $F(c)$ is turned off, $n(x,t)$ will be constant in time, meaning the cells don't move as there is no oxygen to consume.

Part b)

Assume that for an initial time period the oxygen concentration is strictly $c > c^*$ everywhere - we can then solve for $n(x,t)$ and $c(x,t)$ for these early times. We first have

$$\frac{\partial n}{\partial t} = n\,, \qquad \text{so} \quad n(x,t) = N(x)e^t\,,$$

and then using the condition $n(x,0) = 1$, this yields $N(x) = 1$, hence $n(x,t) = e^t$. Substituting this into the first equation gives

$$\frac{\partial^2 c}{\partial x^2} = \frac{1}{\alpha}e^t\,, \qquad \text{so} \quad \frac{\partial c}{\partial x} = \frac{1}{\alpha}xe^t + C_1(t)\,,$$

and since we have $\frac{\partial c}{\partial x}(1,t) = 0$, this gives $C_1(t) = -\frac{1}{\alpha}e^t$ so we have

$$\frac{\partial c}{\partial x} = \frac{1}{\alpha}xe^t - \frac{1}{\alpha}e^t\,.$$

Performing integration one final time then gives us

$$c(x,t) = \frac{1}{2\alpha}x^2e^t - \frac{1}{\alpha}xe^t + C_0(t)\,,$$

and using $c(0,t) = 1$ we finally arrive at our early time solutions for $c(x,t)$ and $n(x,t)$,

$$c(x,t) = \frac{1}{2\alpha}x^2e^t - \frac{1}{\alpha}xe^t + 1 \quad \text{and} \quad n(x,t) = e^t\,. \tag{2.4}$$

We can then analyse $c(x,0)$ as a function of $x \in [0,1]$, where

$$c(x,0) = \frac{1}{2\alpha}x^2 - \frac{1}{\alpha}x + 1\,. \tag{2.5}$$

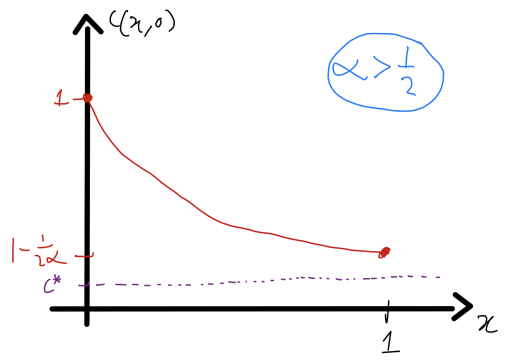

Figure 2.1: Plot of $c(x,0)$ for $x \in [0,1]$.

A simple calculation shows that (supposing α is a positive dimensionless parameter) this is minimised at $x = 1$, the edge of the boundary. Here we have a concentration of

$$c(1,0) = 1 - \frac{1}{2\alpha}\,,$$

and so in order to ensure that $c(x,0)$ is positive for each $x \in [0,1]$, which is the only biologically reasonable option, we must have $1 - \frac{1}{2\alpha} > 0$, so $\alpha > \frac{1}{2}$ as outlined in the question. A small schematic can be seen in Figure 2.1.

Part c)

Suppose we have a critical oxygen level c^* as outlined in the preamble, and a critical time t_c such that the oxygen falls to c^* at t_c, that is, $c(1,t_c) = c^*$, hence

$$c(1,t_c) = \frac{1}{2\alpha}e^{t_c} - \frac{1}{\alpha}e^{t_c} + 1 = c^*\,.$$

A short calculation then gives us an expression for t_c in terms of the fixed c^* as

$$t_c = \log(2\alpha(1-c^*))\,. \tag{2.6}$$

Part d)

For times $t > t_c$ there is a moving point $X(t)$ where the oxygen concentration first reaches c^*, i.e. there is an $X(t)$ defined by

$$c(x,t) > c^* \quad \text{for} \;\; 0 < x < X(t), \quad c(X(t),t) = c^*\,. \tag{2.7}$$

The region $0 < x < X(t)$ corresponds to $c > c^*$, hence $F(c) = 1$. By contrast, $X(t) < x < 1$ corresponds to $c < c^*$ hence $F(c) = 0$. Therefore our PDEs become

$$\underline{0 < x < X(t):} \qquad \alpha\frac{\partial^2 c}{\partial x^2} = n \quad \text{and} \quad \frac{\partial n}{\partial t} = n\,, \tag{2.8}$$

$$\underline{X(t) < x < 1:} \qquad \alpha\frac{\partial^2 c}{\partial x^2} = 0 \quad \text{and} \quad \frac{\partial n}{\partial t} = 0\,. \tag{2.9}$$

The first condition $c(0,t) = 1$ remains unchanged, as does the second $\frac{\partial c}{\partial x}(1,t) = 0$ although it is now relevant to the region $X(t) < x < 1$. The third, $n(x,0) = 1$, is now irrelevant since we are away from $t = 0$. Since $c(x,t)$ represents the concentration of oxygen and, importantly, is diffusing, biologically we should ensure that $c(x,t)$ is a smooth function across the $x = X(t)$ boundary. Since $n(x,t)$ is not diffusing, we only need to ensure it is continuous. Further, our solutions for both c and n should be continuous along the the $t = t_c$ boundary. Putting all of this together, our new initial and boundary conditions are:

$\underline{0 < x < X(t):}$	$c(0,t) = 1$
$\underline{X(t) < x < 1:}$	$\frac{\partial c}{\partial x}(1,t) = 0$
$\underline{\text{Continuity of } n}$	$n(X(t)^-,t) = n(X(t)^+,t)$
$\underline{\text{Smoothness of } c:}$	$c(X(t)^-,t) = c(X(t)^+,t)\,, \qquad \frac{\partial c}{\partial x}(X(t)^-,t) = \frac{\partial c}{\partial x}(X(t)^+,t)$
$\underline{\text{Continuity across } t = t_c:}$	$c(x,t_c^-) = c(x,t_c^+)\,, \qquad n(x,t_c^-) = n(x,t_c^+)$

Part e)

We shall now solve these equations on the whole domain $0 \le x \le 1$. For clarity, let $c_1(x,t)$ and $n_1(x,t)$ denote the solutions (2.4) we found in part b) for $t < t_c$, let $c_2(x,t)$ and $n_2(x,t)$ for $t > t_c$ in $0 < x < X(t)$, and then let $c_3(x,t)$ and $n_3(x,t)$ for $t > t_c$ in $X(t) < x < 1$.

We first solve for the second case. We immediately see that $n_2(x,t) = N_2(x)e^t$, and since this must match $n_1(x,t)$ at $t = t_c$, we have $n_2(x,t_c) = N_2(x)e^{t_c} = e^{t_c} = n_1(x,t_c)$ and so $N_2(x) = 1$, hence

$$n_2(x,t) = e^t\,. \tag{2.10}$$

Thus the solution for c_2 will take the same form as in (2.4), namely

$$c_2(x,t) = \frac{1}{2\alpha}x^2e^t + A_2(t)x + B_2(t)\,.$$

Using the $c(0,t) = 1$ condition, we have $B_2(t) = 1$. We will return to $A_2(t)$ later.

Next, solving on $X(t) < x < 1$ yields

$$c_3(x,t) = A_3(t)x + B_3(t)\,, \quad \text{and} \quad n_3(x,t) = N_3(x)\,.$$

Then $\frac{\partial c}{\partial x}(1,t) = 0$ gives $A_3(t) = 0$. We then match $c_1(x,t_c^-) = c^* = B_3(t) = c_3(x,t_c^+)$, so

$$c_3(x,t) = c^*\,. \tag{2.11}$$

We will deal with $N_3(x)$ later.

Returning to $A_2(t)$, we now see that we can use the smoothness at $x = X(t)$ condition to conclude

$$\frac{\partial c_2}{\partial x}(X(t),t) = \frac{1}{\alpha}X(t)e^t + A_2(t) = 0 = \frac{\partial c_3}{\partial x}(X(t),t)\,.$$

Hence, we see that $A_2(t) = -\frac{1}{\alpha}X(t)e^t$. We can then finally solve for $X(t)$ which is defined by,

$$c_2(X(t),t) = \frac{1}{2\alpha}e^tX(t)^2 - \frac{1}{\alpha}e^tX(t)^2 + 1 = c^*\,,$$

and so solving for $X(t)$ (taking the positive square root since $0 \le x \le 1$) we have

$$X(t) = \sqrt{2\alpha e^{-t}(1-c^*)}\,. \tag{2.12}$$

Note then that $e^tX(t) = \sqrt{2\alpha e^t(1-c^*)}$.

We can then use this information to solve for $N_3(x)$, using the fact that $n_2(X(t),t) = n_3(X(t),t)$ when $x = X(t)$, or better yet when $t = X^{-1}(x)$. For a fixed x, we can rearrange (2.12) to get $t = -\log(\frac{x^2}{2\alpha(1-c^*)})$. That is, we can then match

$$n_2(x, X^{-1}(x)) = \exp\left(-\log\left(\frac{x^2}{2\alpha(1-c^*)}\right)\right) = \frac{2\alpha(1-c^*)}{x^2} = N_3(x) = n_3(x, X^{-1}(x))\,,$$

hence giving us $N_3(x)$.

We can finally put all of this unwieldy information together and arrive at our final solution for $c(x,t)$ and $n(x,t)$ when $t > t_c$,

$$c(x,t) = \begin{cases} \frac{1}{2\alpha}x^2e^t - \frac{1}{\alpha}x\sqrt{2\alpha e^t(1-c^*)} + 1 & \text{if } 0 < x < X(t) \\ c^* & \text{if } X(t) < x < 1 \end{cases}, \tag{2.13}$$

$$\text{and} \quad n(x,t) = \begin{cases} e^t & \text{if } 0 < x < X(t) \\ \frac{2\alpha(1-c^*)}{x^2} & \text{if } X(t) < x < 1 \end{cases}. \tag{2.14}$$

Part f)

We set $\alpha = 2$ and $c^* = \frac{1}{2}$ to plot $c(x,t)$ and $n(x,t)$ for $t = 1, 2, 3, 4$. Note that for these values we have $t_c = \log 2 < 1$, hence we are only in the regime specified by (2.13) and (2.14). These plots are seen in Figures 2.3 and 2.2.

Note that in these figures, t increasing corresponds to reading the plot "from right to left" when analysing the critical points $x = X(t)$. We see that at small time $t = 1$, the cells are very spread out across the domain. The cells remain at a fixed x value until the concentration of oxygen reaches c^*, which effectively acts as a trigger to move towards the origin where, as is seen in the $c(x,t)$ plot, there is a higher concentration of oxygen at every t value. Viewing $n(x,t)$, some cells get stuck around $x = 1$, but most are able to continue moving towards the origin in pursuit of more oxygen. In particular, the cell density becomes very singular as $t \to \infty$ as the only remaining oxygen quickly becomes concentrated at $x = 0$.

Part g)

As discussed above, the cell density approaches a singularity at $x = 0$ as $t \to \infty$, which is clearly unphysical. As is natural in these scenarios, this behaviour typically has something to do with carrying capacities, or lack thereof, in the system. Indeed, the governing equation $\frac{\partial n}{\partial t} = nF(c)$ allows for unbounded growth in $n(x,t)$ as $t \to \infty$. Of course, there is typically a good fix for this by ensuring that there is a carrying capacity in the model to prevent unbounded growth. Hence for some carrying capacity K we could alternatively have

$$\frac{\partial n}{\partial t} = n\left(1 - \frac{n}{K}\right)F(c) \tag{2.15}$$

which would ensure there is no singularity behaviour at the origin, hence a much more physical biological model.

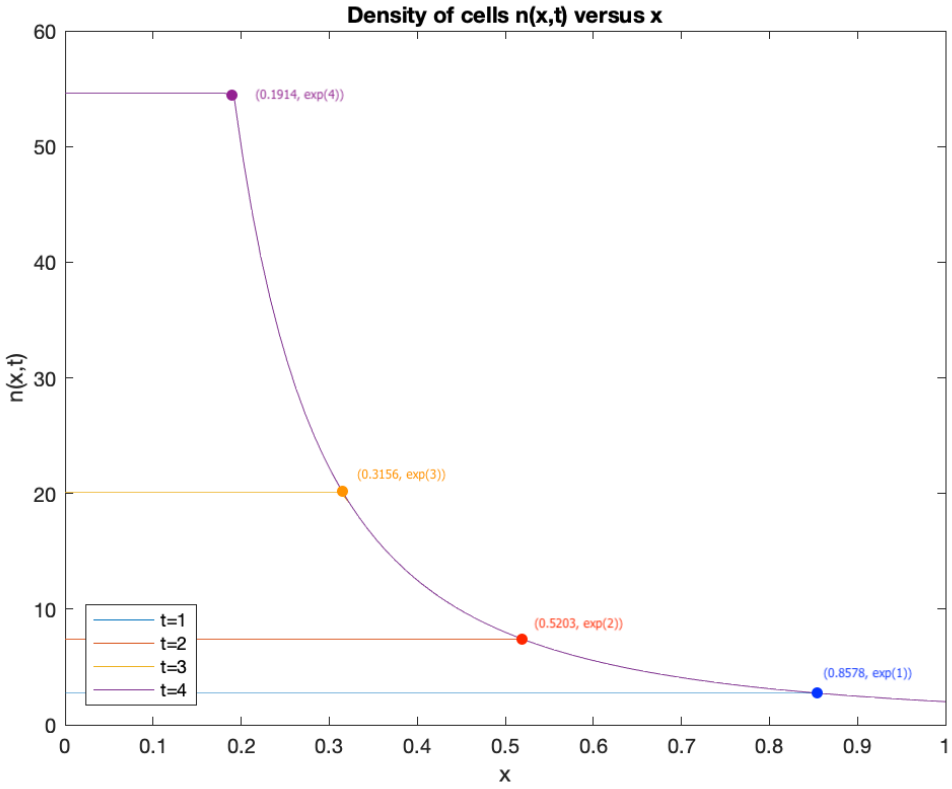

Figure 2.2: Plot of cell density $n(x,t)$ versus x for $t = 1, 2, 3, 4$.

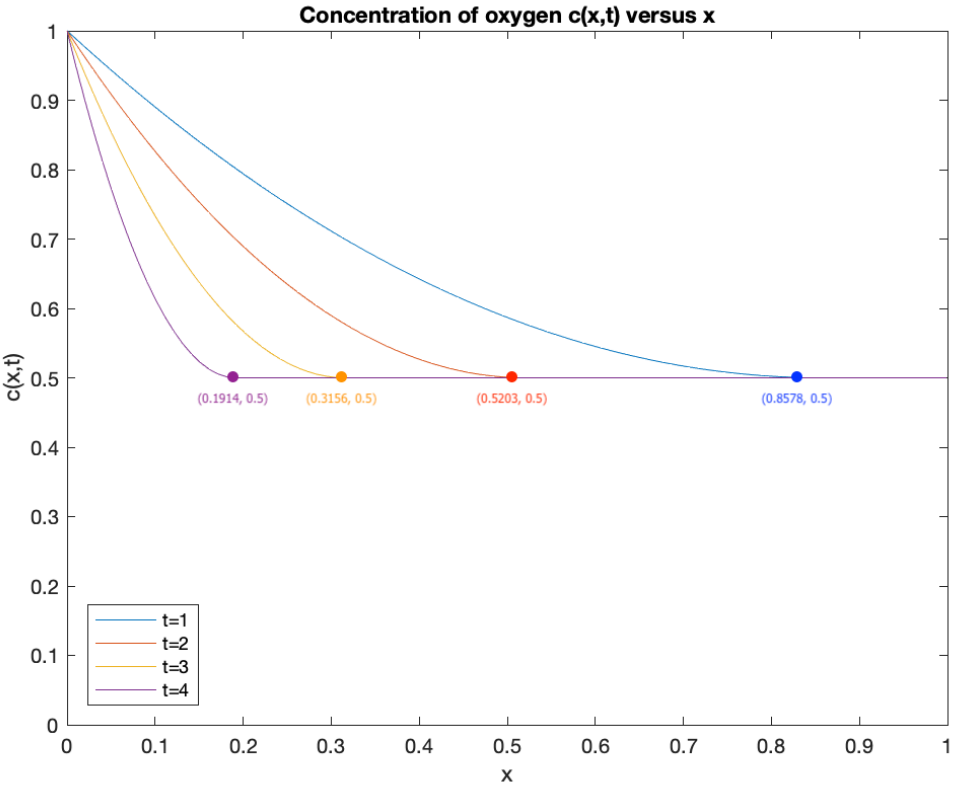

Figure 2.3: Plot of concentration $c(x,t)$ versus x for $t = 1, 2, 3, 4$.