Chapter 7

Moving boundary problems in biology

Free boundary problems have a long history of study in mathematics, and traditionally most applications have come from physics and engineering. However, there are also a number of biological scenarios that involve moving / free boundaries, in particular in the context of biological tissues which grow, develop and can be subject to a range of pathologies. Key examples include, but are not limited to, tumour growth, wound healing, tissue engineering and biofilms.

In this chapter we will focus on *in vitro* models for tumour growth. Common experimental assays involve culturing tumour cells as two-dimensional monolayers or as three-dimensional multicellular spheroids (see Figure 7.1). It is important to study the growth of monolayers and multicellular spheroids because they mimic the early stages of tumour growth, before the tumour has developed a blood supply. During this growth phase, tumour cells aggregate to form a mass which increases in size as the cells proliferate, with their growth and survival depending on local levels of vital nutrients (*e.g.* oxygen, glucose) that diffuse through the tissue. In addition, when developing and testing potential new drugs and treatments in the laboratory, experimentalists need an system which is reliable, safe and reproducible: in the context of cancer, *in vitro* models for tumour growth provide just this.

In order to model tumour growth we need to be able to predict nutrient concentration within the tumour (this determines how the tumour grows and will ultimately enable us to determine the position of the outer tumour boundary). As the tumour grows (or shrinks) the domain on which we will solve for the nutrient concentration changes – this is an example of a moving boundary problem.

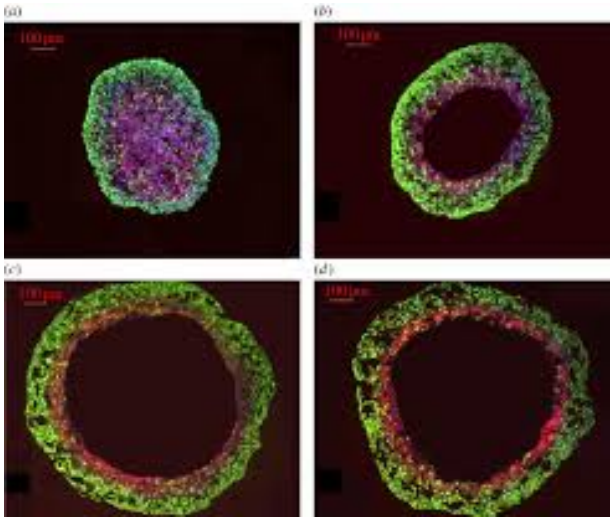

Figure 7.1: Series of images showing how the size and structure of multicellular tumour spheroids change over time.

7.1 A simple model of one-dimensional tumour growth

Consider a three-dimensional slab of tumour cells in which the cells are uniform in the y and z directions and $x = \pm R(t)$ denotes the position of the outer tissue boundary (see Figure 7.2). We would like to derive an equation for the nutrient concentration, $C(x,t)$, and suitable boundary conditions. For moving boundary problems, since the position of the boundary is unknown, we will need an extra condition to determine it. This will come from assumptions about how the tumour grows in response to consumption of nutrients.

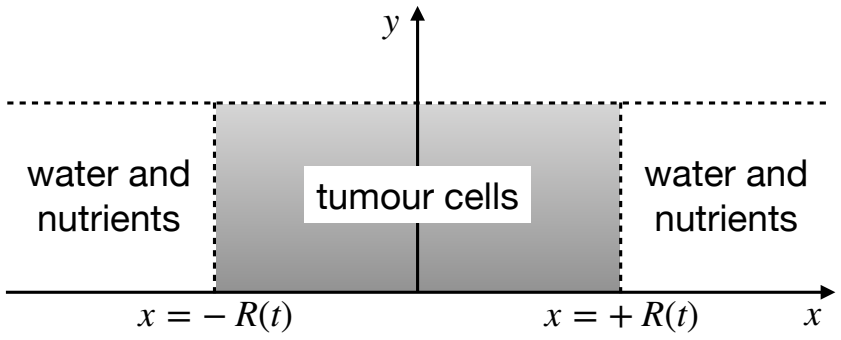

Figure 7.2: Schematic diagram of the one-dimensional tumour we will consider.

7.1.1 Nutrient concentration, $C(x,t)$

We assume that the nutrient diffuses and is consumed by tumour cells at a constant rate. Thus, $C(x,t)$ satisfies

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} - \lambda \quad \text{for } |x| < R(t) \quad \text{(within the tumour)}, \tag{7.1}$$

where $D > 0$ is the diffusion constant and $\lambda > 0$ is the constant rate at which tumour cells consume nutrient. We assume that outside the tumour the nutrient is constantly replenished, so its concentration there is maintained at a constant value:

$$C(x,t) \equiv C^* \quad \text{for } |x| > R(t). \tag{7.2}$$

We assume that the tumour is symmetric about $x = 0$, so we only need solve on $0 \leq x \leq R(t)$, with boundary conditions

$$\frac{\partial C}{\partial x} = 0 \quad \text{at } x = 0, \tag{7.3}$$

$$C(R(t),t) = C^*. \tag{7.4}$$

We need an additional condition (or equation) that describes how tumour growth (represented by changes in $R(t)$) depends on nutrient levels.

7.1.2 Tumour boundary position, $x = R(t)$

The following equation defines how the growth of the tumour depends on the nutrient concentration:

$$\frac{\mathrm{d}R}{\mathrm{d}t} = \int_0^{R(t)} P(C)\,\mathrm{d}x, \tag{7.5}$$

where $P(C)$ represents the local proliferation rate at a given point within the tumour, and we assume that it depends only on the availability of nutrient at that point. In general, we expect $P(C)$ to be an *increasing* function of C. To close the model, we prescribe the initial position of the tumour boundary:

$$R(0) = R_0. \tag{7.6}$$

Note. Strictly speaking, we should impose initial conditions for the nutrient. However, in practice, as we explain below, it is not necessary to impose initial conditions for $C(x,t)$.

7.1.3 Model reduction

Our model of tumour growth consists of Equations (7.1)–(7.6). Before solving these equations, it is helpful to non-dimensionalise and then simplify them. We take

$$x = R_0\xi, \quad R(t) = R_0 r(\tau), \quad C(x,t) = C^* c(\xi,\tau), \quad P(C) = P_0 p(c), \quad t = \frac{\tau}{P_0}, \tag{7.7}$$

where P_0 is a typical tumour proliferation rate (*e.g.* when $C \equiv C^*$, the concentration of nutrient outside the tumour).

Equation (7.1) then becomes

$$\left(\frac{R_0^2 P_0}{D}\right)\frac{\partial c}{\partial \tau} = \frac{\partial^2 c}{\partial \xi^2} - \mu, \qquad \text{where } \mu = \frac{\lambda R_0^2}{C^* D}. \tag{7.8}$$

The coefficient $R_0^2 P_0/D$ is the ratio of the diffusion timescale, R_0^2/D, to a typical timescale for tumour proliferation, $1/P_0$. Typically, the diffusion timescale is much shorter (minutes, for a small tumour) than the proliferation timescale (tumour growth occurs over weeks) and, thus,

$$\frac{R_0^2 P_0}{D} \ll 1. \tag{7.9}$$

We can therefore neglect the time derivative in the diffusion equation and, to leading order, we obtain the following dimensionless model

$$\begin{aligned}
0 &= \frac{\partial^2 c}{\partial \xi^2} - \mu \quad \text{for } 0 \le \xi \le r(\tau), && (7.10)\\
c(\xi,\tau) &\equiv 1 \quad \text{for } \xi > r(\tau), && (7.11)\\
\frac{\partial c}{\partial \xi}(0,\tau) &= 0, && (7.12)\\
c(r(\tau),\tau) &= 1, && (7.13)\\
\frac{\mathrm{d}r}{\mathrm{d}\tau} &= \int_0^{r(\tau)} p(c)\,\mathrm{d}\xi, && (7.14)\\
r(0) &= 1. && (7.15)
\end{aligned}$$

7.1.4 Solution of the reduced model

Solving Equation (7.10) gives

$$c(\xi,\tau) = \frac{\mu \xi^2}{2} + A(\tau)\xi + B(\tau). \tag{7.16}$$

Although we have removed the explicit τ-dependence from the equation for nutrient concentration, c, the dependence of A and B on τ comes via the boundary conditions. Imposing the conditions given in Equations (7.12) and (7.13) gives

$$c(\xi,\tau) = 1 - \frac{\mu}{2}\left(r^2(\tau) - \xi^2\right). \tag{7.17}$$

The nutrient concentration, c, attains its minimum value at $\xi = 0$ where

$$c(0,\tau) = 1 - \mu r^2(\tau)/2. \tag{7.18}$$

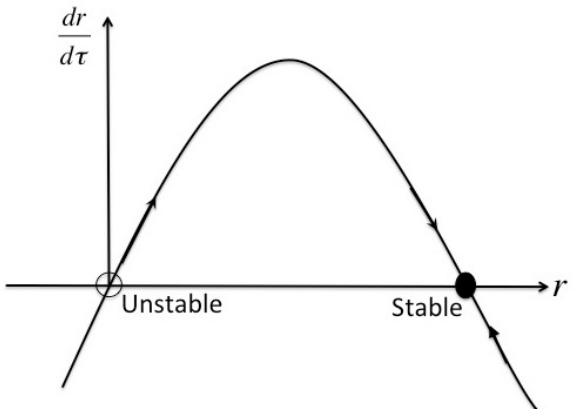

Figure 7.3: Phase-plot of $\mathrm{d}r/\mathrm{d}\tau$ versus $r(\tau)$, illustrating the steady states and their stability.

Note. As the tumour grows and $r(\tau)$ increases, the nutrient concentration at the tumour centre decreases. However, for physically realistic solutions, we require (at least) $c(0,\tau) \geq 0$.

7.1.5 Evolution of the tumour boundary, $r(\tau)$

Armed with the solution given in Equation (7.17) for the nutrient concentration, c, we can determine $r(\tau)$ via Equation (7.14). We consider the simplest case for which p is a linear function of c. A suitable nondimensionalisation of P can be chosen in order to make the coefficient of c unity, *i.e.* $p(c) = c$. Then Equation (7.14) becomes

$$\begin{aligned} \frac{\mathrm{d}r}{\mathrm{d}\tau} &= \int_0^{r(\tau)} c(\xi,\tau)\,\mathrm{d}\xi \qquad (7.19)\\ &= \int_0^{r(\tau)} \left[1 - \frac{\mu}{2}\left(r^2(\tau) - \xi^2\right)\right]\,\mathrm{d}\xi, \end{aligned}$$

and hence

$$\frac{\mathrm{d}r}{\mathrm{d}\tau} = r(\tau)\left(1 - \frac{\mu r^2(\tau)}{3}\right) = f(r), \qquad (7.20)$$

which is similar to logistic growth (indeed, $y = r^2$ undergoes logistic growth). We can integrate to find $r(\tau)$ explicitly, if required. However much information can be gained by considering the phase plane and / or carrying out linear stability analysis.

The steady states in the physically relevant regime ($r \geq 0$) are $r_1^* = 0$ and $r_2^* = \sqrt{3/\mu}$. Figure 7.3 shows the phase plane, with the steady states clearly marked. For values of r lying between $r_1^* = 0$ and $r_2^* = \sqrt{3/\mu}$, $\mathrm{d}r/\mathrm{d}t$ is positive. This means that the tumour-free state ($r_1^* = 0$) is unstable. On the other hand, perturbations about r_2^* decay over time and so the steady state is stable (if r is perturbed below r_2^* then $\mathrm{d}r/\mathrm{d}t$ is positive and r will increase until it reaches r_2^*, whereas if r is perturbed above r_2^* then $\mathrm{d}r/\mathrm{d}t$ is negative and r will decrease until it reaches r_2^*).

7.1.6 Cell death at low nutrient concentration

As nutrient levels fall the ability of a cell to proliferate and remain alive diminishes. We model these effects by assuming that there exist a threshold nutrient concentration, $c_N \in (0,1)$, such that:

- $c > c_N \implies$ cells can proliferate;
- $c < c_N \implies$ cells die and degrade (known as "necrosis").

At time $\tau = 0$, the tumour has unit radius ($r(0) = 1$), and nutrient concentration given by Equation (7.17), where we assume that

$$c(0,0) = 1 - \frac{\mu}{2} > c_N, \tag{7.21}$$

so that initially the tumour is well-nourished.

The tumour boundary evolves according to Equation (7.20) until either the steady state is attained, or until the minimum nutrient concentration is reached at the centre of the tumour, $c(0,\tau) = c_N$, and necrosis takes place there. The question is then one of which occurs first?

We determine whether necrosis occurs before the tumour attains a steady state by determining the tumour size, $r = r_1$, at which necrosis first occurs. We do this by setting $c(0,\tau) = c_N$ in Equation (7.17):

$$c_N = 1 - \frac{\mu r_1^2}{2} \quad \implies \quad r_1 = \left(\frac{2(1-c_N)}{\mu}\right)^{1/2}. \tag{7.22}$$

Noting that $r_1 < r_* = \sqrt{3/\mu}$ we see that the tumour always reaches size r_1 before the steady state is reached *i.e.* the steady state is never physically realised.

To calculate the time $\tau = \tau_1$ of necrosis onset, we separate variables and integrate Equation (7.20), between the appropriate limits:

$$\int_1^{r_1} \frac{\mathrm{d}r}{r(1-\mu r^2/3)} = \int_0^{\tau_1} \mathrm{d}\tau = \tau_1. \tag{7.23}$$

7.2 Revised model: including proliferation and necrosis

It is clear that in order to be able to describe tumour evolution after the onset of necrosis (*i.e.* for $\tau > \tau_1$), we must modify the model for $\tau > \tau_1$.

7.2.1 Model derivation for $\tau > \tau_1$

In the original model, the parameter λ in Equation (7.1) (or μ in Equation (7.10)) represents uniform nutrient uptake across the tumour. In reality, however, only live cells will absorb nutrient. Thus we replace Equation (7.10) by

$$\frac{\partial^2 c}{\partial \xi^2} = \mu H(c - c_N) \quad 0 \le \xi \le r(\tau), \quad \text{where} \quad H(c - c_N) = \begin{cases} 1 & \text{if } c > c_N, \\ 0 & \text{if } c \le c_N. \end{cases} \tag{7.24}$$

Equations (7.11), (7.12) and (7.13) are unchanged but the tumour growth equation, Equation (7.14), must be modified since only live cells proliferate and contribute to growth, while dead cells degrade and effectively remove mass from the system. Thus, again assuming proliferation (where it occurs) to be linear in c, we take

$$\frac{\mathrm{d}r}{\mathrm{d}\tau} = \int_0^{r(\tau)} p(c)\,\mathrm{d}\xi = \int_{r_N(\tau)}^{r(\tau)} c\,\mathrm{d}\xi - \int_0^{r_N(\tau)} \delta\,\mathrm{d}\xi. \tag{7.25}$$

That is, the net proliferation function $p(c)$ has the form

$$p(c) = \begin{cases} c & \text{if } c > c_N \\ -\delta & \text{if } c \le c_N, \end{cases} \tag{7.26}$$

where $\delta > 0$ is the death rate when nutrient levels are too low ($c \le c_N$) to sustain viable cells.

In summary, the full model is

$$\begin{aligned}
\frac{\partial^2 c}{\partial \xi^2} &= \mu H(c - c_N) \quad 0 \le \xi \le r(\tau), && (7.27)\\
c(\xi, \tau) &\equiv 1 \quad \xi > r(\tau), && (7.28)\\
\frac{\partial c}{\partial \xi}(0, \tau) &= 0, && (7.29)\\
c(r(\tau), \tau) &= 1, && (7.30)\\
c(r_N(\tau), \tau) &= c_N, \quad \text{with } c \text{ continuous across } \xi = r_N(\tau), && (7.31)\\
\frac{\partial c}{\partial \xi} & \quad \text{continuous across } \xi = r_N(\tau), && (7.32)\\
\frac{\mathrm{d}r}{\mathrm{d}\tau} &= \int_0^{r(\tau)} p(c)\,\mathrm{d}\xi = \int_{r_N(\tau)}^{r(\tau)} c\,\mathrm{d}\xi - \int_0^{r_N(\tau)} \delta\,\mathrm{d}\xi, && (7.33)\\
r(\tau_1) &= r_1 = \left(\frac{2(1 - c_N)}{\mu}\right)^{1/2}. && (7.34)
\end{aligned}$$

Note that for $\tau > \tau_1$, the outer moving boundary, $r(\tau)$, is determined by Equation (7.33). The edge of the necrotic region, $\xi = r_N(\tau)$, say, will also move in time: it is located where the nutrient

concentration first dips below the threshold value, $c(r_N(\tau), \tau) = c_N$. We now have two moving boundaries to determine.

7.2.2 Model solution

We solve for c in each of the two regions, noting that Equation (7.27) is equivalent to

$$\frac{\partial^2 c}{\partial \xi^2} = \begin{cases} 0 & \text{for } 0 \leq \xi \leq r_N(\tau), \\ \mu & \text{for } r_N(\tau) \leq \xi \leq r(\tau), \end{cases} \tag{7.35}$$

and hence

$$c(\xi, \tau) = \begin{cases} A_1(\tau)\xi + B_1(\tau) & \text{for } 0 \leq \xi \leq r_N(\tau), \\ \frac{\mu\xi^2}{2} + A_2(\tau)\xi + B_2(\tau) & \text{for } r_N(\tau) \leq \xi \leq r(\tau). \end{cases} \tag{7.36}$$

We fix $A_1(\tau)$ and $B_1(\tau)$ by imposing the conditions stated in Equations (7.29) and (7.31), which give

$$A_1 = 0 \quad \text{and} \quad B_1 = c_N. \tag{7.37}$$

The conditions stated in Equations (7.30), (7.31) and (7.32) supply

$$\frac{1}{2}\mu r^2(\tau) + A_2 r(\tau) + B_2 = 1, \tag{7.38}$$

$$\frac{1}{2}\mu r_N^2(\tau) + A_2 r_N(\tau) + B_2 = c_N, \tag{7.39}$$

$$\mu r_N(\tau) + A_2 = 0. \tag{7.40}$$

In this way we obtain $A_2(\tau)$ and $B_2(\tau)$ in terms of $r_N(\tau)$

$$A_2 = -\mu r_N(\tau) \quad \text{and} \quad B_2 = c_N + \frac{\mu r_N^2(\tau)}{2}, \tag{7.41}$$

and an equation relating $r_N(\tau)$ to $r(\tau)$:

$$1 - c_N = \frac{\mu}{2}\left(r(\tau) - r_N(\tau)\right)^2. \tag{7.42}$$

Equation (7.42) predicts that the width of the tumour's proliferating rim remains fixed after the onset of necrosis:

$$r(\tau) - r_N(\tau) = \sqrt{\frac{2}{\mu}(1 - c_N)} = \alpha. \tag{7.43}$$

The nutrient concentration in each region is given by

$$c(\xi,\tau) = \begin{cases} c_N & \text{for } 0 \le \xi < r_N(\tau), \\ c_N + \frac{\mu}{2}\left(\xi - r_N(\tau)\right)^2 & \text{for } r_N(\tau) \le \xi \le r(\tau), \\ 1 & \text{for } \xi > r(\tau), \end{cases} \tag{7.44}$$

with Equation (7.42) relating $r_N(\tau)$ and $r(\tau)$ and ensuring continuity of c at the tumour boundary, $r(\tau)$.

It remains to solve Equation (7.33) subject to the "initial" condition give in Equation (7.34):

$$\begin{aligned} \frac{\mathrm{d}r}{\mathrm{d}\tau} &= \int_{r_N(\tau)}^{r(\tau)} c\,\mathrm{d}\xi - \int_0^{r_N(\tau)} \delta\,\mathrm{d}\xi & (7.45)\\ &= \int_{r_N(\tau)}^{r(\tau)} \left[\frac{\mu}{2}\left(\xi - r_N(\tau)\right)^2 + c_N\right]\,\mathrm{d}\xi - \int_0^{r_N(\tau)} \delta\,\mathrm{d}\xi & (7.46)\\ &= \left(r(\tau) - r_N(\tau)\right)\left[\frac{\mu}{6}\left(r(\tau) - r_N(\tau)\right)^2 + c_N\right] - \delta r_N(\tau) & (7.47)\\ &= -\delta r(\tau) + \frac{\alpha}{3}\left(1 + 2c_N + 3\delta\right), \quad \text{with} \quad r(\tau_1) = r_1, & (7.48) \end{aligned}$$

where Equation (7.43) was used in the last line to eliminate $r_N(\tau)$. This ordinary differential equation for $r(\tau)$ is readily solved to give

$$r(\tau) = \left(r_1 - \frac{\beta}{\delta}\right) e^{-\delta(\tau-\tau_1)} + \frac{\beta}{\delta}, \qquad \beta = \frac{\alpha}{3}(1 + 2c_N + 3\delta), \tag{7.49}$$

when $\delta \neq 0$. In this case, the tumour evolves to a final dimensionless radius of β/δ.

If $\delta = 0$ (dead cells do not degrade) then we have constant growth,

$$\frac{\mathrm{d}r}{\mathrm{d}\tau} = \beta, \qquad r(\tau_1) = r_1. \tag{7.50}$$

In this case, the tumour radius does not attain a steady state: it grows linearly with τ.

7.3 Summary

Processes such as tissue growth can give rise to moving boundaries in mathematical models. In this chapter we considered simple models for tumour growth in which domain growth is driven entirely by nutrient consumption. As a result, we also needed to account for nutrient transport and uptake within the domain. As the timescale for tumour growth is typically much longer than the timescale for nutrient diffusion we were able to consider the a simplified model in which the diffusion equation is quasi-steady. We showed that, for a simple one-dimensional model

with symmetry about the ξ-axis, uniform nutrient concentration outside the tumour, and a cell proliferation rate that is linear in c, we can obtain an ordinary differential equation for the position of the tumour boundary $r(\tau)$. We demonstrated that this model is breaks down for large times because the nutrient concentration at the centre of the tumour becomes negative (before the steady state can be attained). To tackle this issue, we modified the model to allow cells to die when insufficient nutrient, $c < c_N$, is available. This modification lead to a model with two moving boundaries: the edge of the tumour (fixed by the proliferation condition) and edge of necrotic core (fixed by the condition $c = c_N$). Finally, we showed that if dead cells degrade then the new model leads to a steady state for the tumour, and otherwise linear growth ensues. There are many ways in which we could make the model more realistic, for example, we could solve in three-dimensional geometry. In addition, we could incorporate the effects of an externally-supplied drug (*e.g.* chemotherapy).

Suggested reading.

- H. P. Greenspan (1972). Models for the growth of a solid tumour by diffusion. *Stud. Appl. Math.* 52:317–344.
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- D. S. Jones and B. D. Sleeman (2004). *Differential Equations and Mathematical Biology,* (Taylor and Francis).