

8.3 Nutrients: the Diffusion-limited Stage

In order to grow a tumour requires oxygen and other nutrients. Normal tissues have blood vessels passing through them, and nutrients in the blood pass into the tissues through the vessel walls. In the early stages of development tumours have no such blood supply, and rely on nutrients diffusing from the adjacent normal tissue. As the tumour grows, diffusion can no longer provide sufficient nutrient, nutrient concentrations near its centre fall and cells die, resulting in a *necrotic* core. The tumour can grow no further and reaches a *diffusion-limited steady state*. A similar situation can occur after vascularisation, i.e. after the tumour has triggered production of its own blood supply, if the pressure in the tumour gets high enough to collapse the blood vessels in the tumour. In this section we shall investigate the conditions under which a necrotic core is produced by modelling the nutrient concentration in this steady state. We shall assume that the problem is spherically symmetric, leading to simplifications in the equations which are summarised in Section C.2.3 of the appendix. Let $c(r)$ be the concentration of the limiting nutrient, which we assume for definiteness to be oxygen, at radius r . Let the radius of the necrotic core (when it exists) be r_1 and that of the tumour be r_2 . We shall take r_2 to be given and seek information on r_1 , so we are addressing the question of how large the necrotic core would be if the tumour were of a given size, rather than how large the tumour will become. Let c satisfy the steady-state diffusion equation

$$0 = -k + D\nabla^2 c = -k + D \frac{1}{r^2} \frac{d}{dr} \left(r^2 \frac{dc}{dr} \right) \quad (8.3.5)$$

for $r_1 < r < r_2$, where k is a constant representing the rate of uptake of oxygen and D is the constant diffusion coefficient. The oxygen is only taken up by living cells, so that

$$0 = D\nabla^2 c = D \frac{1}{r^2} \frac{d}{dr} \left(r^2 \frac{dc}{dr} \right) \quad (8.3.6)$$

for $r < r_1$. Let c_2 be the concentration in the normal tissue, provided by the perfusing blood vessels, and c_1 the concentration at or below which cells die. The fact that r_1 is unknown, so that the domains of Equations (8.3.5) and (8.3.6) are not given *a priori*, is a difficulty to be overcome. Such problems are known as *free boundary problems*.

Let us first consider small tumours, so small that there is no necrotic core. Then $r_1 = 0$ and the boundary conditions are

$$\frac{dc}{dr}(0) = 0, \quad c(r_2) = c_2, \quad (8.3.7)$$

using symmetry. Multiplying Equation (8.3.5) through by r^2 , integrating once, dividing through by r^2 and integrating again, we obtain

$$c(r) = \frac{1}{6} \frac{k}{D} r^2 + \frac{A}{r} + B, \quad (8.3.8)$$

where A and B are the two constants of integration, or using the boundary conditions (8.3.7),

$$c(r) = -\frac{1}{6} \frac{k}{D} (r_2^2 - r^2) + c_2. \quad (8.3.9)$$

This is valid as long as $c(0) \geq c_1$,

$$r_2^2 \leq r_c^2 = 6(c_2 - c_1) \frac{D}{k}. \quad (8.3.10)$$

Now assume $r_2 > r_c$, and is known, so that $r_1 > 0$, and is to be found. We may integrate Equation (8.3.5) in the necrotic core to deduce that c must be constant there, $c = \hat{c}$, say. By definition $\hat{c} \leq c_1$, but since no consumption of nutrient occurs for $c \leq c_1$ then we must have $\hat{c} = c_1$. (This may be made mathematically rigorous by using a maximum principle.) The boundary conditions for the region of living cells are now

$$c(r_1) = c_1, \quad J(r_1) = 0, \quad c(r_2) = c_2. \quad (8.3.11)$$

where $J = -D \frac{dc}{dr}$ is the (radial) flux of nutrient. The condition at $r = r_2$ is as before; the conditions at $r = r_1$ ensure continuity of concentration and flux at the boundary with the necrotic core. (There is no flux at all in the necrotic core, since $c = c_1$, constant, and so by continuity there can be none at r_1 .) Note that there are three boundary conditions, although Equation (8.3.5) is only a second order differential equation. The extra condition is crucial in allowing us to determine r_1 . *Continuity conditions* are often the key to a determination of an unknown boundary in a free boundary problem.

We again integrate Equation (8.3.5) to obtain

$$c(r) = \frac{1}{6} \frac{k}{D} r^2 + \frac{A}{r} + B. \quad (8.3.12)$$

Applying the boundary conditions (8.3.11), we obtain

$$c_1 = \frac{1}{6} \frac{k}{D} r_1^2 + \frac{A}{r_1} + B, \quad c_2 = \frac{1}{6} \frac{k}{D} r_2^2 + \frac{A}{r_2} + B, \quad 0 = \frac{1}{3} \frac{k}{D} r_1 - \frac{A}{r_1^2}. \quad (8.3.13)$$

Subtracting the first of these from the second, and substituting in the value of A obtained from the third, we obtain

$$\begin{aligned} c_2 - c_1 &= \frac{1}{6} \frac{k}{D} \left(r_2^2 - r_1^2 - 2r_1^3 \left(\frac{1}{r_1} - \frac{1}{r_2} \right) \right) \\ &= \frac{1}{6} \frac{k}{D} r_2^2 \left(1 + 2 \frac{r_1}{r_2} \right) \left(1 - \frac{r_1}{r_2} \right)^2 = \frac{1}{6} \frac{k}{D} \left(1 + 2 \frac{r_1}{r_2} \right) (r_2 - r_1)^2, \end{aligned} \quad (8.3.14)$$

from which r_1 may be found. If $r_2 \rightarrow \infty$, then from the second of these equalities $r_1/r_2 \rightarrow 1$, so from the third $r_2 - r_1 \rightarrow h$, a constant, where

$$h^2 = 2 \frac{D}{k} (c_2 - c_1). \quad (8.3.15)$$

In a large tumour there is a shell of proliferating cells, whose thickness depends on the excess nutrient concentration above a threshold, how fast the nutrient is consumed and how fast it diffuses, but not on the size of the tumour itself.

The condition $r_2 \rightarrow \infty$ above is a condition on a parameter of the problem, and should not be confused with the possible behaviour of the radius of the tumour as a function of time.

EXERCISES

8.3. Some tumours are better approximated by circular cylinders than by spheres.

a) For such a tumour, show that the analogue of Equation (8.3.12) is given by

$$c(R) = \frac{1}{4} \frac{k}{D} R^2 + A \log R + B.$$

b) Find the critical value of the outer radius R_2 above which a necrotic core begins to form.

c) Find the relationships between A , B and the necrotic radius R_1 .

d) Show that if the external radius of the cylinder is large, $R_2 - R_1 \rightarrow h$, where h is a constant to be found.

8.4. There is evidence in some tumours that intermediate levels of nutrient are sufficient for the cells to survive but not for them to proliferate, so that there is a layer of quiescent cells between the necrotic core and the outer proliferative layer, which consume nutrient at a lower rate than the proliferative cells. Set up a mathematical model for this situation. (You are not asked to solve it.) What conditions would you apply at the boundaries between the layers?

8.4 Moving Boundary Problems

In Section 8.3, we could not investigate the tumour growth because we neglected a fundamental principle, that of conservation of mass, which we shall now

include. We shall also include kinetics, so we now have $r_1 = r_1(t)$, $r_2 = r_2(t)$. The necrotic core occupies $0 \leq r < r_1(t)$ and the living cells $r_1(t) < r < r_2(t)$. Apart from this the problem for c is essentially unchanged if we make the reasonable (quasi-steady-state, see Chapter 6) assumption that the oxygen diffusion time-scale is much shorter than the tumour growth time-scale, so that Equation (8.3.5) still holds. A necrotic core forms for $r_2 > r_c$, and c is given by Equation (8.3.9) if $r_2 < r_c$, Equations (8.3.12) and (8.3.13) if $r_2 > r_c$. From now on we shall only consider the more difficult case $r_2 > r_c$, and leave the case $r_2 < r_c$ as an exercise. We must include the effects of proliferation of live cells and degradation of dead ones. We shall assume that all cells outside the necrotic core are proliferating, although there is some evidence that cells go through an intermediate non-proliferative stage before dying through lack of nutrients. The assumption on proliferation is that cell volume is produced by living cells at a specific rate P . In general this will depend on the nutrient concentration c . The assumption on degradation is that cell volume is lost at a specific rate L as necrotic cells and are broken down and their waste products removed. Let $\rho(r, t)$ be the density of the tumour, and $\mathbf{v}(r, t)$ the velocity field in the tumour, at radius r and time t . Then conservation of mass gives

$$\frac{\partial \rho}{\partial t} = -\rho L - \nabla \cdot \mathbf{J} = -\rho L - \nabla \cdot (\rho \mathbf{v}) \quad (8.4.16)$$

in $0 < r < r_1(t)$ and

$$\frac{\partial \rho}{\partial t} = \rho P - \nabla \cdot \mathbf{J} = \rho P - \nabla \cdot (\rho \mathbf{v}). \quad (8.4.17)$$

in $r_1(t) < r < r_2(t)$. Here \mathbf{J} is the mass flux in the tumour, which is due simply to advection, so that $\mathbf{J} = \rho \mathbf{v}$ (see Chapter 5). This is a kinetic free boundary problem. Both r_1 and r_2 are unknown, although we know the relationship between them from the problem for the nutrient. We shall require an extra condition to determine them.

Let us assume that the density in the tumour is constant. Quoting Section C.2.3 of the appendix, the conservation of mass equations become

$$\nabla \cdot \mathbf{v} = \frac{1}{r^2} \frac{\partial}{\partial r} (r^2 v) = -L, \quad \nabla \cdot \mathbf{v} = \frac{1}{r^2} \frac{\partial}{\partial r} (r^2 v) = P, \quad (8.4.18)$$

in $0 < r < r_1(t)$ and $r_1(t) < r < r_2(t)$ respectively, where v is the radial velocity. Integrating and applying continuity of the velocity field at $r = r_1(t)$,

$$v = -\frac{1}{3} Lr, \quad v = \frac{1}{3} Pr - \frac{1}{3} (P + L) \frac{r_1^3}{r^2} \quad (8.4.19)$$

in $0 < r < r_1(t)$ and $r_1(t) < r < r_2(t)$ respectively.

So far in this section we have introduced a new unknown v and found a solution for it that would apply whatever r_1 and r_2 were. For the last piece in

the jigsaw we need to connect the v problem with r_1 or r_2 . We use the fact that the outermost cells in the tumour are moving at the velocity of expansion of the tumour, $\frac{dr_2}{dt}(t) = v(r_2(t))$. Hence

$$\frac{dr_2}{dt} = \frac{1}{3}Pr_2 \left(1 - \frac{P+L}{P} \frac{r_1^3}{r_2^3} \right). \quad (8.4.20)$$

Hence r_2 increases indefinitely or until $\frac{r_2^3}{r_1^3}$ becomes equal to $\frac{P+L}{P}$. If $L \ll P$ then $(P+L)/P \approx 1$, so in either case $r_2/r_1 \approx 1$, and we can use the approximation that $r_2 - r_1 = h$ given in Equation (8.3.15) to obtain $r_2 \approx 3hP/L$.

An alternative approach to this problem is to integrate Equations (8.4.16) and (8.4.17) over the volume $V(t)$ occupied by the tumour, again taking ρ to be constant. We obtain

$$\int_{V(t)} \nabla \cdot \mathbf{J} dV = \int_{V(t)} \nabla \cdot (\rho \mathbf{v}) dV = - \int_{V_1(t)} \rho L dV + \int_{V_2(t)} \rho P dV, \quad (8.4.21)$$

where $V_1(t)$ is the necrotic core and $V_2(t)$ the living cells. Using the divergence theorem,

$$\int_{V(t)} \nabla \cdot (\rho \mathbf{v}) dV = \int_{S(t)} \rho \mathbf{v} \cdot \mathbf{n} dS,$$

where $S(t)$ is the surface of $V(t)$, and since $\mathbf{v} \cdot \mathbf{n}$ is the normal component of velocity on the surface, this integral is equal to $\rho \frac{dV}{dt}$. (Alternatively, for those familiar with fluid dynamics, this is clear from the interpretation of $\nabla \cdot \mathbf{v}$ as the rate of dilatation.) The equation reduces to

$$\frac{dV}{dt} = - \int_{V_1} L dV + \int_{V_2} P dV \quad (8.4.22)$$

The interpretation of the terms in this equation is clear. For P and L constant it gives

$$\frac{dV}{dt} = P(V - V_1) - LV_1, \quad (8.4.23)$$

where V_1 is the volume of the necrotic core. In terms of the radii r_1 and r_2 ,

$$r_2^2 \frac{dr_2}{dt} = \frac{1}{3}P(r_2^3 - r_1^3) - \frac{1}{3}Lr_1^3,$$

and we have recovered Equation (8.4.20). In principle, we can now solve this equation by substituting in the formula obtained from Equation (8.3.14) for r_1 in terms of r_2 , and then integrating, but in practice this has to be done numerically.

However, we can obtain some useful information from the equation. Usually the loss rate L is much smaller than the proliferation rate P , and we can see that if $L \ll P$ the outside radius r_2 of the tumour satisfies $r_2(t) \rightarrow 3hP/L$ as $t \rightarrow \infty$. In other words, the tumour cannot grow beyond a certain size while its nutrient supply is diffusion-limited.

EXERCISES

- 8.5. Show that the model of this section with P constant predicts exponential growth of the tumour while $r_2 < r_c$.
- 8.6. Extend the model by including a layer of quiescent cells between the necrotic core and the outer proliferative layer.
- 8.7. In this exercise we analyse the steady state size r_2^* of the tumour model discussed in the last two sections.
- Find an expression for the steady state size r_2^* of the tumour as a function of the parameters c_1 , c_2 , k , D , P and L , all taken to be constant.
 - Confirm that $r_2^* \rightarrow 3hP/L$ as $L/P \rightarrow 0$, where h is given by Equation (8.3.15).

8.5 Growth Promoters and Inhibitors

A crucial feature of tissues is that they produce chemical substances that control (activate or inhibit) the growth of the surrounding tissue. These substances are known as local control or *paracrine* factors. One of the characteristic properties of tumour cells is their ability to escape from these local controls. Let us consider a homogeneous spherical tumour of radius R that secretes an inhibitory paracrine factor (growth inhibitor) c . We shall perform a spherically symmetric steady state analysis, as in Section 8.3. The equation satisfied by the growth inhibitor is

$$0 = \lambda - \mu c + D \nabla^2 c = \lambda - \mu c + D \frac{1}{r^2} \frac{d}{dr} \left(r^2 \frac{dc}{dr} \right) \quad (8.5.24)$$

in $0 < r < R$, where λ is the rate at which the chemical is secreted, μ the specific rate at which it is depleted, and D a constant diffusion coefficient. The boundary conditions are given by

$$\frac{dc}{dr}(0) = 0, \quad -D \frac{dc}{dr}(R) = Pc(R). \quad (8.5.25)$$

The first of these arises from symmetry, the second states that the flux of chemical out of the tumour is proportional to the concentration difference between the inside and the outside, assuming that the concentration outside is negligible. The constant P is known as the *permeability* of the interface between the

tumour and the normal tissue. The equation (8.5.24) is linear, and hence may be solved by the method of complementary function plus particular integral, with complementary function $A \exp(\alpha r)/r + B \exp(-\alpha r)/r$, where $\alpha = \sqrt{\mu/D}$, and particular integral λ/μ . The general solution satisfying the boundary condition at 0 is given by

$$c = \frac{\lambda}{\mu} + A \frac{\sinh(\alpha r)}{r} \quad (8.5.26)$$

for $0 < r < R$. The constant of integration A is then determined by the boundary condition at R , and we obtain

$$c(r) = \frac{\lambda}{\mu} \left(1 - \frac{R \sinh(\alpha r)}{r \sinh(\alpha R) f(\alpha R)} \right) \quad (8.5.27)$$

for $0 < r < R$, where

$$f(x) = 1 + \beta \left(\coth x - \frac{1}{x} \right) \quad (8.5.28)$$

and $\beta = \sqrt{\mu D}/P = \alpha D/P$. The function $c(r)$ is a decreasing function of r , shown in Figure 8.2.

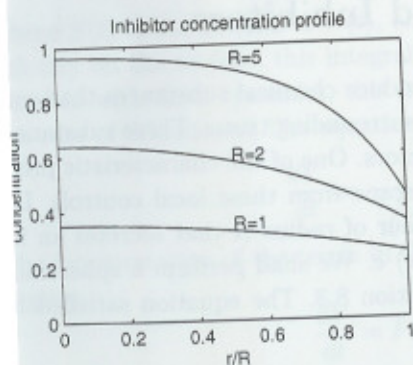


Figure 8.2 The inhibitor profile. If growth were completely inhibited for $c > c_1 = 0.4$, say, then growth would occur throughout the tumour for $R = 1$, only in a thin outer shell for $R = 2$, and nowhere in the tumour for $R = 5$ (so that the tumour would in fact never reach this size).

As the radius R of the tumour increases, then it is easy (although algebraically messy) to show that $c(0)$ increases from 0 to λ/μ , and $c(R)$ increases from 0 to $\frac{\lambda\beta}{\mu(1+\beta)}$. The concentration of the inhibitor inside the tumour increases as the tumour grows.

Now if we suppose that growth is very precisely controlled by the inhibitor, in the manner of a strongly cooperative modifier as discussed in Chapter 6, we can assume that growth only occurs where $c < c_1$. Hence growth ceases everywhere in the tumour as long as $c(R) > c_1$,

$$\frac{\lambda}{\mu} \left(1 - \frac{1}{f(\alpha R)} \right) > c_1. \quad (8.5.29)$$

If αR is small, this can never hold, whereas if αR is large, it approximates $c_1 < \frac{\lambda\beta}{\mu(1+\beta)}$. If $c_1 < \frac{\lambda\beta}{\mu(1+\beta)}$, the tumour will cease growing at some finite value of R , but if $c_1 > \frac{\lambda\beta}{\mu(1+\beta)}$, tumour growth cannot be controlled by the inhibitor (It may of course still be controlled by some other mechanism, such as lack of nutrient.) We suppose that normal tissue is sensitive to inhibitor, so c_1 is relatively low and tissue growth is under control, but that a tumour is relatively insensitive, so c_1 is larger and it escapes inhibitory control.

EXERCISES

- 8.8. On the assumption that there is no other growth control mechanism sketch the bifurcation diagram for the steady state tumour radius R^* with bifurcation parameter c_1 .
- 8.9. Let the concentration c of an inhibitor satisfy $0 = \lambda - \mu c + D\nabla^2 c$ within a tumour, $0 = -\mu c + D\nabla^2 c$ outside it.
 - a) What is the rationale behind this model?
 - b) What boundary conditions would you impose at the boundary between normal and tumour tissue?
 - c) Solve the problem in one spatial dimension (for algebraic simplicity), assuming the tumour occupies the region $-L < x < L$.
 - d) Sketch the bifurcation diagram for the steady state tumour size $2L^*$ with bifurcation parameter c_1 .

8.6 Vascularisation

In order to grow beyond the diffusion-limited stage, tumours have to have a blood supply. They seem to achieve this by secreting a *tumour angiogenesis factor* (TAF) which diffuses across the tissue between the tumour and a blood vessel, activates new blood vessel formation (angiogenesis), and attracts these vessels towards the tumour. Let c be the concentration of TAF in the region between the tumour and the target blood vessel. Then it can be modelled by

$$\frac{\partial c}{\partial t} = -f(c)g(n) - h(c) + D_c \nabla^2 c. \quad (8.6.30)$$

Here $h(c)$ represents the rate of decay of the TAF and $f(c)g(n)$ the rate of take-up by the cells n which make up the new blood vessels. The equation for