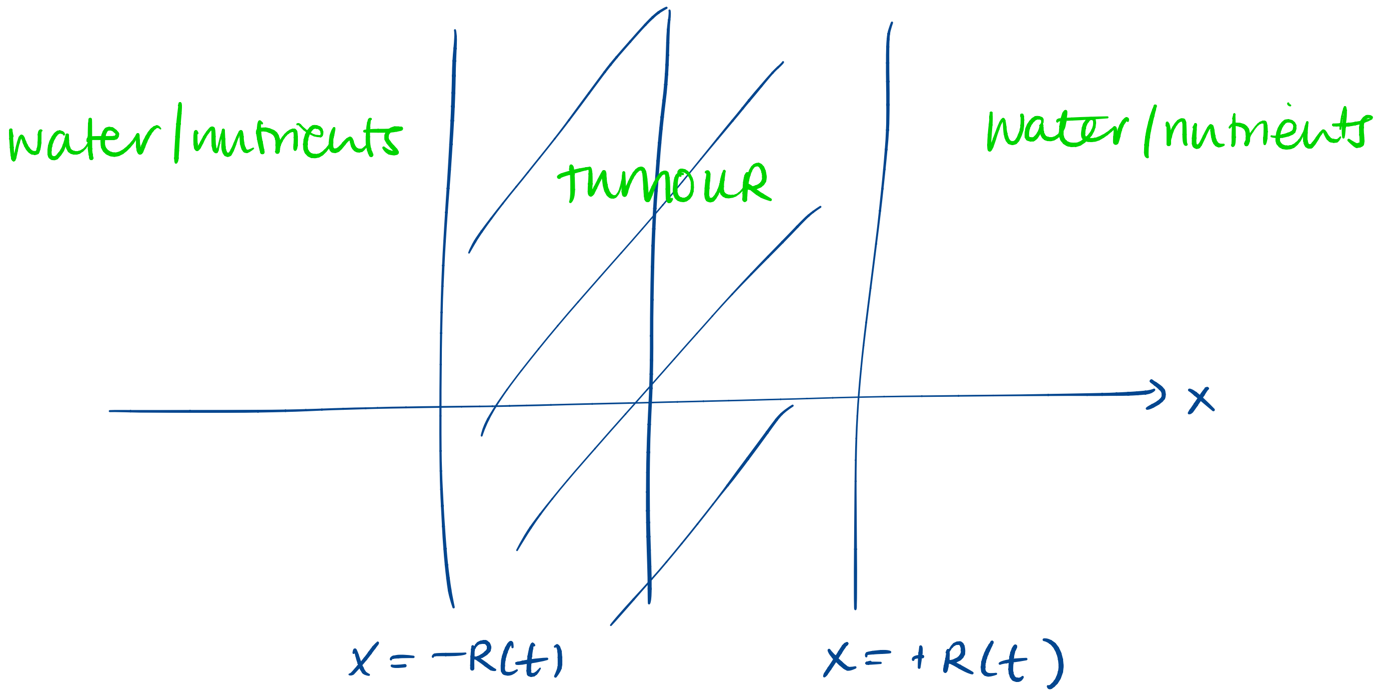
Chapter 7 – Moving boundary problems

§7.1 A 1D model



Model – evolution of the boundary, $R(t)$

– nutrient concentration, $c(x,t)$

Nutrient

$$\frac{\partial c}{\partial t} = \underbrace{D\frac{\partial^2 c}{\partial x^2}}_{\text{diffusion}} - \underbrace{\lambda}_{\text{uptake by tumour cells}} \qquad |x| < R(t)$$

$$c(x,t) = C^* \quad \text{for} \quad |x| > R(t).$$

Assume symmetric about $x=0$, solve on $0 \le x \le R(t)$

with $\frac{\partial c}{\partial x} = 0$ @ $x = 0$

$$c(R(t),t) = C^*$$

Tumour boundary

$$\frac{dR}{dt} = \int_0^{R(t)} \underset{\sim}{P(c)}\, dx$$

proliferation rate at concentration c.

$$R(0) = R_0$$

Non-dimensionalisation / Model reduction

$$x = R_0 \xi \qquad t = \frac{\tau}{P_0} \qquad R(t) = R_0 r(\tau)$$

$$c(x,t) = c^* c(\xi, \tau)$$

$$\frac{\partial}{\partial x} = \frac{1}{R_0}\frac{\partial}{\partial \xi}, \quad \frac{\partial}{\partial t} = P_0 \frac{\partial}{\partial \tau} \qquad P(c) = P_0 p(c)$$

Nutrient

$$c^* P_0 \frac{\partial c}{\partial \tau} = \frac{D c^*}{R_0^2}\frac{\partial^2 c}{\partial \xi^2} - \lambda$$

$$\frac{R_0^2 \cancel{c^*} P_0}{D}\frac{\partial c}{\partial \tau} = \frac{\cancel{D}\cancel{c^*}}{\cancel{R_0^2}}\frac{\partial^2 c}{\partial \xi^2} - \frac{\lambda R_0^2}{c^* D}$$

$$\frac{R_0^2 P_0}{D}\frac{\partial c}{\partial \tau} = \frac{\partial^2 c}{\partial \xi^2} - \mu \qquad \mu = \frac{\lambda R_0^2}{c^* D}$$

$$\frac{R_0^2/D}{1/P_0}$$

R_0^2/D ← typical diffusion timescale ~ minutes

$1/P_0$ ← typical proliferation timescale ~ weeks

ie $\dfrac{R_0^2 P_0}{D} \ll 1$ assume in quasi-equilibrium.

ie $$0 = \frac{\partial^2 c}{\partial \zeta^2} - \mu \qquad 0 \le \zeta \le r(\tau)$$

$$c(\zeta, \tau) = 1 \qquad \zeta > r(\tau)$$

with $$\frac{\partial c}{\partial \zeta}(0,\tau) = 0 \qquad c(r(\tau), \tau) = 1.$$

Boundary $$\cancel{R_0}\, \cancel{P_0} \frac{dr}{d\tau} = \int_0^{r(\tau)} \cancel{P_0}\, p(c) . \cancel{R_0}\, d\zeta$$

$$\frac{dr}{d\tau} = \int_0^{r(\tau)} p(c)\, d\zeta \, , \quad r(0) = 1.$$

Solution

Nutrient: $$c(\zeta,\tau) = \frac{\mu\zeta^2}{2} + A(\tau)\zeta + B(\tau)$$

$$\left.\frac{\partial c}{\partial \zeta}\right|_{\zeta=0} = 0 \quad \Rightarrow \quad A(\tau) = 0$$

$$c(r(\tau),\tau) = 1 \quad \Rightarrow \quad 1 = \frac{\mu r^2(\tau)}{2} + B(\tau)$$

$$B(\tau) = 1 - \frac{\mu}{2} r^2(\tau)$$

$$\therefore \quad c(\zeta,\tau) = 1 - \frac{\mu}{2}\left(r^2(\tau) - \zeta^2\right) \qquad 0 \le \zeta < r(\tau)$$

$$c(\zeta,\tau) \equiv 1 \qquad \zeta \geqslant r(\tau).$$

Minimum value of nutrient concentration – at $z = 0$:

$$C_{min} = C(0, \tau) = 1 - \frac{\mu}{2} r^2(\tau)$$

NB C_{min} could become negative, which is infeasible. Hence model only valid until $r(\tau) = \sqrt{\frac{2}{\mu}}$.

Tumour boundary

$$\frac{dr}{d\tau} = \int_0^{r(\tau)} P(c)\, dz$$

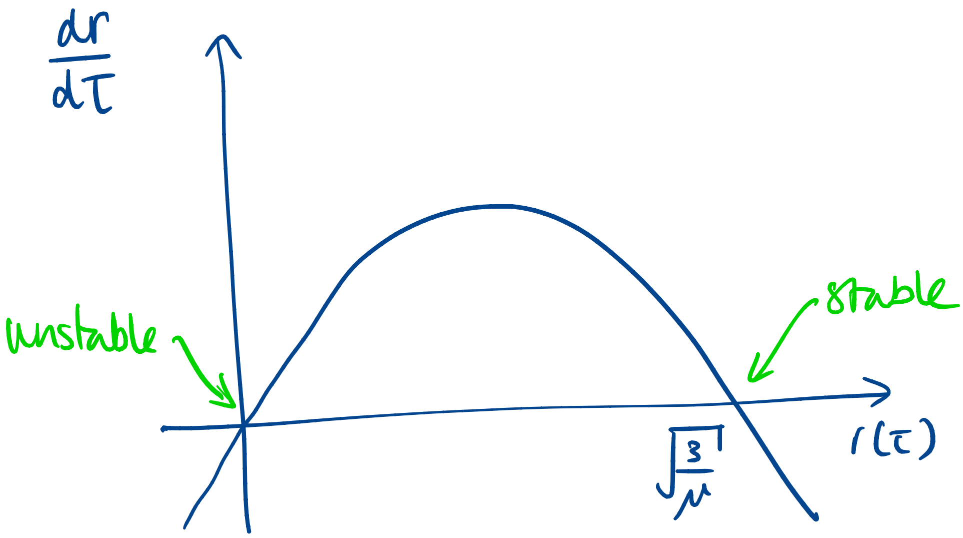
assume $p(c) = C$

$$= \int_0^{r(\tau)} C(z, \tau)\, dz$$

$$= \int_0^{r(\tau)} \left[1 - \frac{\mu}{2} r^2(\tau) + \frac{\mu}{2} z^2\right] dz$$

$$= r(\tau)\left[1 - \frac{\mu r^2(\tau)}{3}\right].$$

$r(0) = 1$.



Cell death at low nutrient concentration

Suppose $\exists\, c_N \in (0,1)$ s.t.

$c > c_N \Rightarrow$ cells can proliferate.

$c < c_N \Rightarrow$ cell will die and degrade.

Assume @ $\tau = 0$ $\quad c(0,0) = 1 - \frac{\mu}{2} > c_N$

Tumour boundary will evolve until either

① steady state attained ie $r = r^* = \sqrt{\frac{3}{\mu}}$

or

② minimum nutrient concentration reached at tumour centre ie $c(0,\tau) = c_N$

Q – which happens first??

Necrosis $\quad c_N = c(0,\tau) = 1 - \frac{\mu r_1^2}{2}$ $\quad$ tumour size when necrosis first occurs.

$$\Rightarrow r_1 = \sqrt{\frac{2(1-c_N)}{\mu}}$$

But $r^* = \sqrt{\frac{3}{\mu}}$ $\quad$ and $\quad 2(1-c_N) < 3$

$\Rightarrow$ always hit r_1 and necrosis first.

At what time?

$$\frac{dr}{d\tau} = r(\tau)\left[1 - \frac{\mu r^2(\tau)}{3}\right]$$

Integrate and solve:

$$\int_1^{r_1} \frac{dr}{r\left(1 - \frac{\mu r^2}{3}\right)} = \int_0^{\tau_1} d\tau = \tau_1$$

7.2 A revised model - including proliferation and necrosis

(Modify the model for $\tau > \tau_1$)

<u>Nutrient</u>

$$0 = \frac{\partial^2 c}{\partial \xi^2} - \mu H(c - c_N) \qquad 0 \leq \xi < r(\tau)$$

$$c(\xi, \tau) \equiv 1 \qquad \xi \geq r(\tau)$$

$$\left.\frac{\partial c}{\partial \xi}\right|_{\xi=0} = 0, \quad c(r(\tau), \tau) = 1$$

and $c(r_N(\tau), \tau) = c_N$, c cts across $\xi = r_N(\tau)$

$\frac{\partial c}{\partial \xi}$ cts across $\xi = r_N(\tau)$

<u>Boundary</u>

$$p(c) = \begin{cases} c & c > c_N \\ -\delta & c \leq c_N \end{cases}$$

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

$$r(\tau_1) = r_1 = \sqrt{\frac{2(1 - c_N)}{\mu}} .$$

For $\tau > \tau_1$ then $r(\tau)$ as given above.

NB r_N changes over time: $r_N = r_N(\tau)$.

Solution

Nutrient

$$\frac{\partial^2 c}{\partial \zeta^2} = \begin{cases} 0 & 0 \le \zeta \le r_N(\tau) \\ \mu & r_N(\tau) < \zeta \le r(\tau) \end{cases}$$

$$c(\zeta,\tau) = \begin{cases} A_1(\tau)\zeta + B_1(\tau) & 0 \le \zeta \le r_N(\tau) \\ \frac{1}{2}\mu\zeta^2 + A_2(\tau)\zeta + B_2(\tau) & r_N(\tau) < \zeta \le r(\tau) \end{cases}$$

At $\zeta = 0$ $\quad \frac{\partial c}{\partial \zeta} = 0 \quad \Rightarrow \quad A_1(\tau) = 0$

At $\zeta = r_N$, $c = c_N \quad \Rightarrow \quad B_1(\tau) = c_N$

At $\zeta = r(\tau)$, $c = 1 \quad \Rightarrow \quad \frac{1}{2}\mu r^2(\tau) + A_2(\tau) r(\tau) + B_2(\tau) = 1$

At $\zeta = r_N(\tau)$, $c = c_N \quad \Rightarrow \quad \frac{1}{2}\mu r_N^2(\tau) + A_2(\tau) r_N(\tau) + B_2(\tau) = c_N$

$$\frac{\partial c}{\partial \zeta} \text{ cts} \Rightarrow 0 = \mu r_N(\tau) + A_2$$

$$\Rightarrow \quad A_2 = -\mu r_N(\tau)$$

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

$$\therefore \; c(\zeta,\tau) = \begin{cases} c_N & 0 \le \zeta \le r_N(\tau) \\ \frac{1}{2}\mu(\zeta - r_N(\tau))^2 + c_N & r_N(\tau) < \zeta \le r(\tau) \\ 1 & \zeta > r(\tau) \end{cases}$$

Then, using the final condition

$$1 - C_N = \frac{1}{2}\mu^2 \left(r(\tau) - r_N(\tau) \right)^2$$

– relates $r(\tau)$ and $r_N(\tau)$

Width of the proliferating rim:

$$r(\tau) - r_N(\tau) = \sqrt{\frac{2(1-C_N)}{\mu^2}} := \alpha$$

(constant).

<u>Boundary</u>

$(r(\tau_1) = r_1)$

$$\frac{dr}{d\tau} = \int_{r_N(\tau)}^{r(\tau)} \left[\frac{1}{2}\mu(\xi - r_N(\tau))^2 + C_N \right] d\xi + \int_0^{r_N(\tau)} \delta \, d\xi$$

$$= \frac{1}{6}\mu\alpha^3 + C_N\alpha - \delta(r(\tau) - \alpha)$$

$$= \frac{1}{6}\mu\left(r(\tau) - r_N(\tau)\right)^3 + C_N\left(r - r_N(\tau)\right) - \delta r_N(\tau)$$

Note that $1 - C_N = \frac{1}{2}\mu^2\alpha$

$$\therefore \quad \frac{dr}{d\tau} = \frac{1}{3}\alpha(1 - C_N) + C_N\alpha + \delta\alpha - \delta r(\tau)$$

$$= -\delta r(\tau) + \underbrace{\frac{1}{3}\alpha\left[1 + 2C_N - 3\delta\right]}_{\beta}$$

Solve for $r(\tau)$: $\quad \dfrac{dr}{d\tau} = -\delta r(\tau) + \beta$

PTO

$$\int_{r_1}^{r} \frac{1}{\beta-\delta\bar{r}}\, d\bar{r} = \int_{\tau_1}^{\tau} d\bar{\tau} = (\tau-\tau_1)$$

$$\Rightarrow \quad r(\tau) = \frac{\beta}{\delta} + \left(r_1 - \frac{\beta}{\delta}\right) e^{-\delta(\tau-\tau_1)} \qquad (\delta \neq 0)$$

$$\rightarrow \frac{\beta}{\delta} \quad \text{as } \tau \to \infty$$

(For $\delta = 0$: $\frac{dr}{d\tau} = \beta$ ie linear growth)