Modelling Solid Tumour Growth
Lecture 3: Tumour Invasion and Symmetry Breaking

Helen Byrne

helen.byrne@nottingham.ac.uk

Centre for Mathematical Medicine, University of Nottingham

Outline

- Motivation
- Model development
- Model analysis
- Discussion

Motivation

- Why do tumours become irregular?
  - (A) Blood vessels that accompany angiogenesis lead to non-uniform nutrient delivery
  - (B) Inherent instability of the radially-symmetric avascular tumour configurations to asymmetric perturbations
- We explore alternative (B)

Model Development

Modelling Assumptions:

- Single, growth-rate limiting nutrient (e.g. oxygen, glucose)
- Cell proliferation and death generate spatial gradients in pressure within tumour
- Pressure variations drive cell motion, down pressure gradients
- Assume tumour's growth restrained by surface tension forces which maintain its compactness
- Neglect necrosis and quiescence ($R_H = 0 = R_N$)
- Restrict attention to 2-D (r, θ) geometry

Model Equations

- Nutrient concentration, $c(\boldsymbol{r}, t)$

$$0 = \nabla^2 c - \Gamma$$

with $\dfrac{\partial c}{\partial r} = 0$ at $r = 0$ and $c = c_\infty$ on $\Gamma(\boldsymbol{r}, t) = 0$

- Pressure, $p(\boldsymbol{r}, t)$, and velocity, $\boldsymbol{v}(\boldsymbol{r}, t)$
  - No voids and incompressibility (using kinetic terms from lecture 2) $\Rightarrow$

$$\nabla . \boldsymbol{v} = S(c) - N(c) = c - \lambda_A$$

  - Use Darcy's law to relate $\boldsymbol{v}$ and p

$$\boldsymbol{v} = -\mu \nabla p$$

where the permeability μ measures the sensitivity of the cells to pressure gradients

Model Equations (continued)

- Combine the above equations to eliminate $\boldsymbol{v}$

$$0 = \mu \nabla^2 p + (c - \lambda_A)$$

$$\text{with} \quad \frac{\partial p}{\partial r} = 0 \quad \text{at } r = 0 \quad \text{and} \quad p = 2\gamma\kappa \quad \text{on } \Gamma(\boldsymbol{r}, t) = 0$$

where κ = mean curvature of boundary and γ = surface tension coefficient

Tumour Boundary, $\Gamma(\boldsymbol{r}, t) = 0 = r - R(\theta, t)$

- Assume boundary moves with cell velocity there

$$\frac{\partial R}{\partial t} = \boldsymbol{v}.\boldsymbol{n} = -\mu \nabla p.\boldsymbol{n}, \quad \text{with } R(\theta, 0) = R_0(\theta)$$

where $\boldsymbol{n}$ = unit outward normal to tumour boundary

Model Summary

$$0 = \nabla^2 c - \Gamma = \mu \nabla^2 p + (c - \lambda_A)$$

$$\text{with} \quad \frac{\partial c}{\partial r} = 0 = \frac{\partial p}{\partial r} \quad \text{at } r = 0$$

$$c = c_\infty, \;\; p = 2\gamma\kappa \quad \text{on } \Gamma(\boldsymbol{r}, t) = 0$$

$$\frac{\partial R}{\partial t} = -\mu \nabla p . \boldsymbol{n} \quad \text{on } \Gamma(\boldsymbol{r}, t) = 0 = r - R(\theta, t)$$

$$\text{and} \quad R(\theta, 0) = R_0(\theta) \;\; \text{prescribed}$$

Model Analysis

• When $c = c(r,t), p = p(r,t)$ and $r = R(t)$ on the tumour boundary, the model equations reduce to give

$$0 = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 \frac{\partial c}{\partial r}\right) - \Gamma = \frac{\mu}{r^2}\frac{\partial}{\partial r}\left(r^2 \frac{\partial p}{\partial r}\right) + c - \lambda_A$$

$$\frac{dR}{dt} = -\mu \left.\frac{\partial p}{\partial r}\right|_{r=R(t)}$$

• Integrating the PDE for p, with $\frac{\partial p}{\partial r} = 0$ at $r = 0$

$$-\mu \frac{\partial p}{\partial r} = \frac{1}{r^2}\int_0^r (c - \lambda_A)\rho^2 d\rho$$

$$\Rightarrow R^2 \frac{dR}{dt} = \int_0^R (c - \lambda_A) r^2 dr$$

i.e. under radial symmetry we recover model from lecture 2

Model Analysis (continued)

- We obtain following expressions for c, p and R:

$$c = c_\infty - \frac{\Gamma}{6}(R^2 - r^2)$$

$$p = \frac{\gamma}{R} - \frac{\Gamma}{120\mu}(R^2 - r^2)^2 + \frac{1}{6\mu}\left(c_\infty - \lambda_A - \frac{\Gamma R^2}{15}\right)(R^2 - r^2).$$

$$\frac{dR}{dt} = \frac{R}{3}\left(c_\infty - \lambda_A - \frac{\Gamma R^2}{15}\right)$$

- $\frac{dR}{dt} = 0 \Rightarrow R = 0$ (trivial solution) or $c = c_0(r), p = p_0(r)$ and $R = R_0$ where

$$c_0 = c_\infty - \frac{\Gamma}{6}(R_0^2 - r^2), \quad p_0 = \frac{\gamma}{R_0} - \frac{\Gamma}{120\mu}(R_0^2 - r^2)^2, \quad R_0^2 = \frac{15}{\Gamma}(c_\infty - \lambda_A)$$

Linear Stability Analysis

- What happens when radially-symmetric solutions subjected to asymmetric perturbations?

- Seek solutions for c, p and R of the form

$$c = c_0(r) + \epsilon c_1(r, \theta, t) + O(\epsilon^2)$$

- Substitute with trial solutions in model equations

$$0 = \nabla^2(c_0 + \epsilon c_1) - \Gamma$$

$$0 = \mu\nabla^2(p_0 + \epsilon p_1) + (c_0 + \epsilon c_1 - \lambda_A)$$

$$\frac{\partial}{\partial t}(R_0 + \epsilon R_1) = -\mu\nabla(p_0 + \epsilon p_1).\boldsymbol{n}$$

- Recover steady solutions at leading order.
- Equate to zero coefficients of $O(\epsilon)$:

$$0 = \nabla^2 c_1 = \mu\nabla^2 p_1 + c_1, \quad \epsilon\frac{\partial R_1}{\partial t} = -\mu\nabla(p_0 + \epsilon p_1).\boldsymbol{n}$$

Linear Stability Analysis (aside 1 – boundary conditions)

- Recall that $c = c_\infty$ on $\Gamma(\boldsymbol{r}, t) = 0$

$$\Rightarrow c_\infty \sim c_0 + \epsilon c_1 \quad \text{on } r = R_0 + \epsilon R_1(\theta, t)$$

$$c_\infty \sim c_0(R_0 + \epsilon R_1, t) + \epsilon c_1(R_0 + \epsilon R_1, t) = c_0(R_0) + \epsilon R_1 \frac{dc_0}{dr}(R_0) + \epsilon c_1(R_0, t) + O(\epsilon^2)$$

- Equate coefficients of $O(\epsilon^n)$:

$$\begin{aligned} O(1): &\quad c_0 = c_\infty &&\text{on } r = R_0 \\ O(\epsilon): &\quad c_1 = -R_1 \frac{\partial c_0}{\partial r} &&\text{on } r = R_0 \end{aligned}$$

- In the same way, using $p = 2\gamma\kappa$ on $r = R(\theta, t)$ we find

$$\begin{aligned} O(1): &\quad p_0 = \gamma / R_0 &&\text{on } r = R_0 \\ O(\epsilon): &\quad p_1 = -R_1 \frac{\partial p_0}{\partial r} + 2\gamma\kappa_1 &&\text{on } r = R_0 \end{aligned}$$

$$\text{where} \quad \kappa \sim \frac{1}{2R_0} + \epsilon\kappa_1$$

Linear Stability Analysis (aside 2 - normal derivatives)

Recall that

$$\epsilon \frac{\partial R_1}{\partial t} = -\mu \nabla (p_0 + \epsilon p_1).\boldsymbol{n} \quad \text{on } r = R_0 + \epsilon R_1(\theta, t)$$

where

$$\nabla (p_0 + \epsilon p_1) = \left(\frac{\partial p_0}{\partial r} + \epsilon \frac{\partial p_1}{\partial r}, \frac{\epsilon}{r} \frac{\partial p_1}{\partial \theta} \right) + O(\epsilon^2)$$

Evaluating $\nabla (p_0 + \epsilon p_1)$ on tumour boundary, we have:

$$\nabla (p_0 + \epsilon p_1)|_{r=R_0+\epsilon R_1} = \left(\frac{dp_0}{dr} + \epsilon R_1 \frac{d^2 p_0}{dr^2} + \epsilon \frac{\partial p_1}{\partial r} \right)_{r=R_0} + O(\epsilon^2).$$

Also

$$\boldsymbol{n} = \frac{\nabla \Gamma}{|\nabla \Gamma|} = \left(1 + \frac{\epsilon^2 R_1^2}{R_0^2 + \epsilon^2 R_1^2} \right)^{-1/2} \left(\hat{\boldsymbol{r}} - \frac{\epsilon R_1}{R_0 + \epsilon R_1} \hat{} \right)$$

$$\Rightarrow \nabla (p_0 + \epsilon p_1).\boldsymbol{n} = \left. \frac{dp_0}{dr} \right|_{r=R_0} + \epsilon \left(R_1 \frac{d^2 p_0}{dr^2} + \frac{\partial p_1}{\partial r} \right)_{r=R_0} + O(\epsilon^2).$$

Linear Stability Analysis (continued)

- Combining above results we find that

$$0 = \nabla^2 c_1 = \mu \nabla^2 p_1 + c_1$$

$$\frac{\partial R_1}{\partial t} = -\mu \left[\frac{\partial p_1}{\partial r} + R_1 \frac{d^2 p_0}{dr^2} \right]_{r=R_0}$$

$$\text{with} \quad \frac{\partial c_1}{\partial r} = 0 = \frac{\partial p_1}{\partial r} \quad \text{on} \quad r = 0$$

$$c_1 = -R_1 \left. \frac{dc_0}{dr} \right|_{r=R_0} \quad \text{and} \quad p_1 = -\underbrace{R_1 \left. \frac{\partial p_0}{\partial r} \right|_{r=R_0}}_{\equiv 0} - \frac{\gamma}{R_0^2} \left(2R_1 + \mathcal{L}(R_1)\right)_{r=R_0}$$

$$\text{where} \quad \nabla^2 f = \frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial f}{\partial r} \right) + \frac{\mathcal{L}(f)}{r^2} \qquad \text{with} \qquad \mathcal{L}(f) = \frac{1}{\sin\theta} \frac{\partial}{\partial \theta} \left(\sin\theta \frac{\partial f}{\partial \theta} \right)$$

$$\text{and} \quad R_1(\theta, 0) = R_{10}(\theta), \quad \text{prescribed}$$

Aside ($\nabla^2 c_1 = 0$): separable solutions

$$0 = \nabla^2 c_1 = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 \frac{\partial c_1}{\partial r}\right) + \frac{1}{r^2 \sin\theta}\frac{\partial}{\partial\theta}\left(\sin\theta \frac{\partial c_1}{\partial\theta}\right)$$

- Let $c_1 = T(t)X(r)\Theta(\theta)$. Then

$$0 = \frac{T\Theta}{r^2}\frac{\partial}{\partial r}\left(r^2 \frac{\partial X}{\partial r}\right) + \frac{TX}{r^2 \sin\theta}\frac{\partial}{\partial\theta}\left(\sin\theta \frac{\partial\Theta}{\partial\theta}\right)$$

- Divide by $c_1 = TX\Theta$ (assuming $c_1 \neq 0$) and introduce separation constant, $\Lambda > 0$:

$$\frac{1}{X}\frac{\partial}{\partial x}\left(r^2 \frac{\partial X}{\partial r}\right) = \Lambda = -\frac{1}{\Theta \sin\theta}\frac{\partial}{\partial\theta}\left(\sin\theta \frac{\partial\Theta}{\partial\theta}\right)$$

Aside ($\nabla^2 c_1 = 0$): separable solutions

- Let $X = X_k(r) = r^k$ $(k = 0, 1, 2, \ldots)$

$$\Rightarrow \frac{1}{X_k}\frac{\partial}{\partial r}\left(r^2\frac{\partial X_k}{\partial r}\right) = k(k+1) = \Lambda_k$$

Then $\Theta = \Theta_k(\theta)$ where

$$0 = \frac{1}{\sin\theta}\frac{\partial}{\partial\theta}\left(\sin\theta\frac{\partial\Theta_k}{\partial\theta}\right) + k(k+1)\Theta_k$$

- Let $z = \cos\theta$ and $\Theta_k(\theta) = P_k(z)$

$$\Rightarrow 0 = \frac{d}{dz}\left[(1-z^2)\frac{dP_k}{dz}\right] + k(k+1)P_k \qquad \text{Legendre's Equation}$$

- Combine results, setting $T(t) = \chi_k(t)$, to get

$$c_1(r,\theta,t) = \chi_k(t)r^k P_k(\cos\theta)$$

Linear Stability Analysis (continued)

- Using $0 = \nabla^2 c_1 = \mu \nabla^2 p_1 + c_1$, we have

$$c_1(r, \theta, t) = \chi_k(t) r^k P_k(\cos\theta)$$

$$p_1(r, \theta, t) = \left(\pi_k(t) - \frac{\chi_k(t) r^2}{2\mu(2k+3)} \right) r^k P_k(\cos\theta)$$

Note:

$$\frac{\partial c_1}{\partial r} = 0 = \frac{\partial p_1}{\partial r} \quad \text{at } r = 0$$

- We assume that

$$R_1(\theta, t) = \rho_k(t) P_k(\cos\theta)$$

Linear Stability Analysis (continued)

- Determine χ_k, π_k and ρ_k by imposing BCs:

$$c_1 = -R_1 \left.\frac{dc_0}{dr}\right|_{r=R_0} \Rightarrow \chi_k R_0^k = -\left(\frac{\Gamma R_0}{3}\right)\rho_k$$

$$p_1 = -\frac{\gamma}{R_0^2} \left.\left(2R_1 + \mathcal{L}(R_1)\right)\right|_{r=R_0} \Rightarrow \pi_k R_0^k = \frac{\gamma}{R_0^2}(k-1)(k-2)\rho_k + \frac{\chi_k R_0^{k+2}}{2\mu(2k+3)}$$

$$\frac{\partial R_1}{\partial t} = -\mu \left(\frac{\partial p_1}{\partial r} + R_1 \frac{d^2 p_0}{dr^2}\right)_{r=R_0} \Rightarrow \frac{1}{\rho_k}\frac{d\rho_k}{dt} = (k-1)\left[\frac{2\Gamma R_0^2}{15(2k+3)} - \frac{\gamma\mu}{R_0^3}k(k+2)\right]$$

Linear Stability Analysis

- $R \sim R_0 + \epsilon \rho_k(t) P_l(\cos\theta)$ where

$$\frac{1}{\rho_k}\frac{d\rho_k}{dt} = (k-1)\left[\frac{2\Gamma R_0^2}{15(2k+3)} - \frac{\gamma\mu}{R_0^3}k(k+2)\right]$$

- Notes:
  - $\frac{d\rho_k}{dt} = 0 \Rightarrow$ system insensitive to perturbations involving $P_{k=1}(\cos\theta)$. Such perturbations correspond to translation of coordinate axes
  - If surface tension effects neglected ($\gamma = 0$)

$$\frac{1}{\rho_k}\frac{d\rho_k}{dt} = \left(\frac{2\Gamma R_0^2}{15}\right)\left(\frac{k-1}{2k+3}\right)$$

    $\Rightarrow$ system unstable to all asymmetric pertubations
  - If $\gamma > 0$ (and $k > 1$), then steady state is unstable to finite number of perturbations

$$\frac{1}{\rho_k}\frac{d\rho_k}{dt} > 0 \text{ if } k(k+2)(2k+3) < \frac{4\Gamma R_0^5}{15\mu\gamma}$$

Summary

- We have developed a model that can describe 2- and 3D tumour growth (or invasion)
- Using linear stability analysis we have identified
  - Conditions under which radially-symmetric steady state is stable to asymmetric perturbations involving Legendre polynomials
  - Conditions under which tumour is likely to be asymmetric (i.e. invasive or infiltrative)
- Model Extensions
  - Multiple growth factors
  - Weakly nonlinear analysis ($O(\epsilon^2)$-terms)
  - Mode interactions
  - Numerical methods