

# Modelling Solid Tumour Growth

## Lecture 2: Spatially-Structured Models

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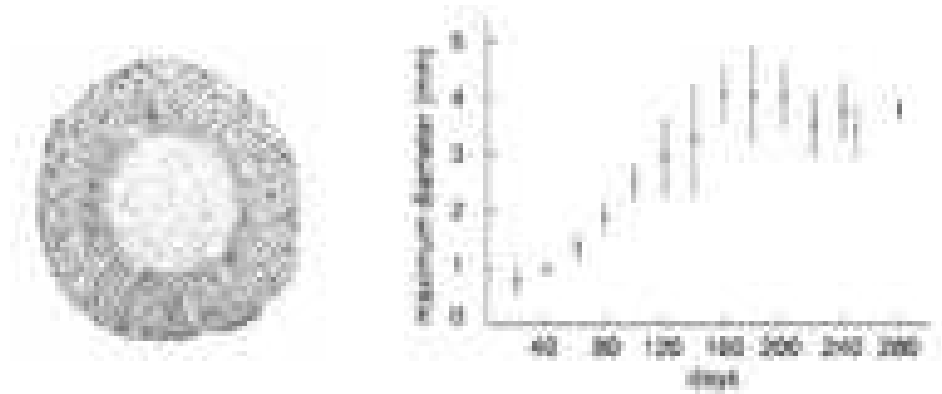
# Structure of Lecture

- Model development
- Model simplifications
- Model analysis
- Discussion

## References

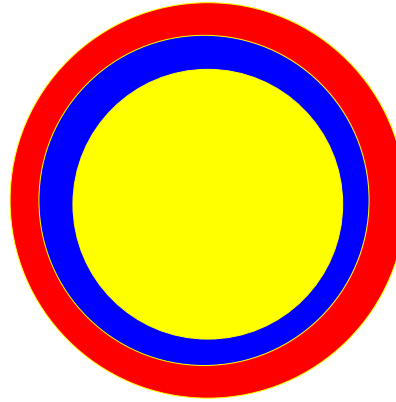
- H.P. Greenspan (1972) *Stud. Appl. Math.* **52**: 317-340.
- J.A. Adam (1986) *Math. Biosci.* **81**: 229-242.
- A.C. Burton (1966) *Growth* **30**: 157-176.

## *Background Biology*



Cross-section of a fully-developed avascular tumour and typical growth kinetics of an avascular tumour

# Modelling Assumptions



Schematic Diagram of a Fully-Developed Avascular Tumour

- 1-D, radial-symmetry
- Tumour contains uniform population of cells
- Single, growth-rate limiting nutrient (chemical), which is supplied at a constant rate from the surrounding medium
- Nutrient levels determine whether cells proliferate, become quiescent or die
- Key physical variables
  - Tumour radius,  $R(t)$
  - Nutrient concentration,  $c(r, t)$
  - Internal boundaries,  $R_H(t)$  and  $R_N(t)$

## Model Development: Nutrient Concentration, $c(r, t)$

$$\left( \begin{array}{c} \text{rate of change} \\ \text{of } c \end{array} \right) = \left( \begin{array}{c} \text{flux due to} \\ \text{diffusion} \end{array} \right) - \left( \begin{array}{c} \text{rate of} \\ \text{consumption} \end{array} \right).$$

$$\frac{\partial c}{\partial t} = \frac{D}{r^2} \frac{\partial}{\partial r} \left( r^2 \frac{\partial c}{\partial r} \right) - \Gamma(c, R, R_H, R_N).$$

where  $D$  = diffusion coefficient (assumed constant) and

$$\Gamma(c, R, R_H, R_N) = \Gamma H(r - R_N)$$

i.e. all viable (non-dead) cells consume nutrient at the constant rate  $\Gamma$ .

Boundary and initial conditions

$$\frac{\partial c}{\partial r} = 0 \quad \text{on } r = 0 \quad (\text{SYMMETRY})$$

$$c = c_\infty \quad \text{on } r = R(t)$$

$$c(r, 0) = c_0(r), \quad \text{specified}$$

## Model Development: Outer Tumour Radius, $R(t)$

$$\left( \begin{array}{c} \text{rate of change of} \\ \text{tumour volume} \end{array} \right) = \left( \begin{array}{c} \text{rate of cell} \\ \text{proliferation} \end{array} \right) - \left( \begin{array}{c} \text{rate of} \\ \text{cell death} \end{array} \right).$$

$$\Rightarrow \frac{d}{dt} \left( \frac{4\pi R^3}{3} \right) = \int [S - N] r^2 \sin \theta d\theta d\phi dr$$

where  $S = scH(r - R_H)$  and  $N = \underbrace{s\lambda_A}_{\text{apoptosis}} + \underbrace{s\lambda_N H(R_N - r)}_{\text{necrosis}}$

- **Proliferation** restricted to **non-quiescent regions** where it is proportional to  $c$
- Two cell death mechanisms are considered:
  - **Apoptosis** occurs for all values of  $c$
  - **Necrosis** occurs when  $c$  becomes too low to sustain live cells
- Since  $c = c(r, t)$ , we can integrate to get

$$R^2 \frac{dR}{dt} = \int_0^R [S(c, R, R_H, R_N) - N(c, R, R_H, R_N)] r^2 dr$$

with  $R(t = 0) = R_0$ , prescribed

# Model Development: Internal Boundaries, $R_H(t)$ and $R_N(t)$

- Uniformly proliferating tumour

$$c(r, t) > c_H \quad \forall r \in (0, R(t)) \Rightarrow R_H = R_N = 0$$

- Intermediate-sized tumour (prolif + quiescence)

$$\exists r \in (0, R(t)) \text{ such that } c_N < c(r, t) \leq c_H$$

$$\Rightarrow R_N = 0 < R_H < R \text{ with } c(R_H, t) = c_H$$

- Well-developed tumour (prolif, quiesc + dead)

$$\exists r \in (0, R(t)) \text{ such that } c(r, t) \leq c_N < c_H$$

$$\Rightarrow 0 < R_N < R_H < R$$

$$\text{with } c(R_H, t) = c_H \text{ and } c(R_N, t) = c_N$$

## Model Summary

$$\frac{\partial c}{\partial t} = \frac{D}{r^2} \frac{\partial}{\partial r} \left( r^2 \frac{\partial c}{\partial r} \right) - \Gamma H(r - R_N)$$

$$R^2 \frac{dR}{dt} = \int_0^R \{scH(r - R_N) - s\lambda_A - s\lambda_N H(R_N - r)\} r^2 dr$$

either  $R_H = 0$  if  $c > c_H \forall r$  or  $c(R_H, t) = c_H$

either  $R_N = 0$  if  $c > c_N \forall r$  or  $c(R_N, t) = c_N$

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

$$c = c_\infty \quad \text{on } r = R$$

$$c(r, 0) = c_0(r), \quad R(0) = R_0, \text{ prescribed}$$

**Note:**  $c_N < c_H$  and  $0 \leq R_N \leq R_H < R$



## Nondimensionalisation

$$c = Cc^*, \quad r = Xr^*, \quad t = Tt^*,$$

$$R = XR^*, \quad R_H = XR_H^*, \quad R_N = XR_N^*$$

where \*s denote dimensionless variables and  $C, X, T$ , etc are typical nutrient concentrations, etc

We rewrite model equations in terms of  $c^*$ , etc

$$\frac{\partial c^*}{\partial t^*} = \left( \frac{DT}{X^2} \right) \frac{1}{r^{*2}} \frac{\partial}{\partial r^*} \left( r^{*2} \frac{\partial c^*}{\partial r^*} \right) - \Gamma T H(r^* - R_N^*)$$

$$R^{*2} \frac{dR^*}{dt^*} = sT \int_0^{R^*} Cc^* H(r^* - R_N^*) r^{*2} dr^* - sT \int_0^{R^*} \lambda_A - \lambda_N H(R_N^* - r^*) r^{*2} dr^*$$

Timescales implicit in the model equations include

- The nutrient diffusion timescale
- The tumour doubling timescale
- The nutrient consumption timescale

## Nondimensionalisation (continued)

In practice

$$\left( \begin{array}{l} \text{nutrient diffusion} \\ \text{timescale, } X^2/D \\ \sim \text{mins or hours} \end{array} \right) \ll \left( \begin{array}{l} \text{tumour doubling} \\ \text{timescale, } 1/sC \\ \sim \text{weeks} \end{array} \right)$$

We follow tumour's development and, hence, focus on longer timescale, choosing

$$T = \frac{1}{sC}$$

and make the following quasi-steady assumption in the nutrient equation

$$O(\Gamma) = O\left(\frac{D}{X^2}\right) \gg O(T^{-1})$$

Then nutrient equation becomes

$$0 = \frac{1}{r^{*2}} \frac{\partial}{\partial r^*} \left( r^{*2} \frac{\partial c^*}{\partial r^*} \right) - \Gamma^* H(r^* - R_N^*)$$

$$\text{where } \Gamma^* = \frac{\Gamma X^2}{D} \sim O(1)$$

## Nondimensional Model Equations

$$0 = \frac{1}{r^{*2}} \frac{\partial}{\partial r^*} \left( r^{*2} \frac{\partial c^*}{\partial r^*} \right) - \Gamma^* H(r^* - R_N^*)$$

$$R^{*2} \frac{dR^*}{dt^*} = \int_0^{R^*} \{c^* H(r^* - R_N^*) - \lambda_A^* - \lambda_N^* H(R_N^* - r^*)\} r^{*2} dr^*$$

either  $R_H^* = 0$  if  $c^* > c_H^* \forall r$  or  $c^*(R_H^*, t^*) = c_H^*$

either  $R_N^* = 0$  if  $c^* > c_N^* \forall r$  or  $c^*(R_N^*, t^*) = c_N^*$

$\frac{\partial c^*}{\partial r^*} = 0$  at  $r^* = 0$ ,  $c^* = c_\infty^*$  on  $r^* = R^*$ ,  $R^*(0) = R_0^*$ , prescribed

$$\Gamma^* = \frac{\Gamma X^2}{D}, \quad \lambda_A^* = \frac{\lambda_A}{C}, \quad \lambda_N^* = \frac{\lambda_N}{C}, \quad c_\infty^* = \frac{c_\infty}{C}, \quad c_H^* = \frac{c_H}{C}, \quad c_N^* = \frac{c_N}{C}$$

### Notes:

- Henceforth we omit \*s for clarity
- We could choose  $C = c_\infty$  to eliminate  $c_\infty$ . Since we want to investigate effect of varying  $c_\infty$ , we retain  $c_\infty$  as an explicit model parameter
- Similarly, we choose not to scale lengths with  $R_0$

## *Model Simplification*

Our simple choices of the tumour cell proliferation rate, etc mean that

- $\exists$  analytical expressions for  $c = c(r, R, R_H, R_N)$
- $\exists$  algebraic equations relating  $R_H, R_N$  and  $R$
- Model reduces to ODE for  $R$  and algebraic equations for  $R_H$  and  $R_N$

The form of these relations depends on  $R(t)$

## Case 1: Uniformly Proliferating Tumour

Here the tumour is **small** and contains only **proliferating** cells:

$$c(r, t) = c_{\infty} - \frac{\Gamma}{6}(R^2 - r^2) \quad \text{with } R_H = 0 = R_N \quad \text{since } c > c_H \quad \forall r \in (0, R)$$

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

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

**Note:**

$$c_{min} = c(0, t) = c_{\infty} - \frac{\Gamma R^2}{6} \equiv c_H \quad \text{when } R^2 = \frac{6}{\Gamma}(c_{\infty} - c_H)$$

so that model ceases to be valid when  $R^2 = 6(c_{\infty} - c_H)/\Gamma$

This marks the appearance of a central region of **quiescence**, with  $R_H > 0$  (case 2)

## Case 2: Prolif + Quiescence

We have

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

$$\text{with } R_H^2 = R^2 - \frac{6}{\Gamma}(c_\infty - c_H)$$

and  $R_N = 0$  since  $c > c_N \forall r \in (0, R)$ . Then

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

$$\Rightarrow \frac{3}{R} \frac{dR}{dt} = \left( c_\infty - \frac{\Gamma R^2}{6} \right) \left( 1 - \frac{R_H^3}{R^3} \right) + \frac{\Gamma R^2}{10} \left( 1 - \frac{R_H^5}{R^5} \right) - \lambda_A$$

Model comprises ODE for  $R$  and algebraic equation for  $R_H$

## Case 2: Prolif + Quiescence

- $c(r, t) = c_\infty - \frac{\Gamma}{6}(R^2 - r^2) \Rightarrow c_{min} = c(0, t) = c_\infty - \Gamma R^2 / 6$

$\Rightarrow$  models breaks down when  $R^2 = 6(c_\infty - c_N) / \Gamma$

$\Rightarrow$  appearance of **central necrosis**, with  $R_N > 0$  (case 3)

- Differentiating equation for  $R_H$  with respect to  $t$ , model reduces to 2 ODEs:

$$\Rightarrow \frac{dR_H}{dt} = \frac{R}{R_H} \frac{dR}{dt} \quad \text{and} \quad \frac{dR}{dt} = \dots$$

- Since  $R_H < R$ , we deduce

$$\left| \frac{dR_H}{dt} \right| > \left| \frac{dR}{dt} \right|$$

i.e. quiescent region grows more rapidly than outer tumour boundary

## Case 3: Prolif, Quiesc + Dead

Algebra becomes more involved but ...

$$c(r, t) = \begin{cases} c_N & 0 < r < R_N \\ c_N + \Gamma(r - R_N)^2(r + 2R_N)/6r & R_N < r < R \end{cases}$$

with

$$\frac{6}{\Gamma R^2}(c_\infty - c_N) = \left(1 - \frac{R_N}{R}\right)^2 \left(1 + \frac{2R_N}{R}\right)$$

$$\frac{6}{\Gamma R_H^2}(c_H - c_N) = \left(1 - \frac{R_N}{R_H}\right)^2 \left(1 + \frac{2R_N}{R_H}\right)$$

and

$$\begin{aligned} \frac{3}{R} \frac{dR}{dt} = & c_N \left(1 - \frac{R_H^3}{R^3}\right) - \left(\lambda_A + \lambda_N \frac{R_N^3}{R^3}\right) + \frac{\Gamma R^2}{10} \left(1 - \frac{R_H^5}{R^5}\right) \\ & - \frac{\Gamma R_N^2}{2} \left(1 - \frac{R_H^3}{R^3}\right) + \frac{\Gamma R_N^3}{2R} \left(1 - \frac{R_H^2}{R^2}\right) \end{aligned}$$



# *Summary bifurcation diagram*

# Model Analysis: Equilibrium Solutions

For steady state solutions,  $\frac{d}{dt} = 0$  in simplified model equations.

- For case 1 (unif prolif),  $R_H = R_N = 0$  and

$$R = 0 \quad \text{or} \quad R^2 = \frac{15}{\Gamma}(c_\infty - \lambda_A)$$

The nontrivial solution is valid iff  $c > c_H \forall r \in (0, R)$ . Now

$$c(0, t) = c_{min} = c_\infty - \frac{\Gamma R^2}{6} > c_H \Leftrightarrow c_\infty < \frac{2}{3} \left( \frac{5}{2} \lambda_A - c_H \right)$$

## Model Analysis: Equilibrium Solutions

- For case 2 (prolif + quiesc),  $0 = R_N < R_H < R$  with

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

and

$$0 = \left( c_\infty - \frac{\Gamma R^2}{6} \right) + \frac{\Gamma R^2}{10} \left( 1 - \frac{R_H^5}{R^5} \right) - \lambda_A$$

This solution is valid iff

$$\frac{6}{\Gamma}(c_\infty - c_H) < R^2 < \frac{6}{\Gamma}(c_\infty - c_N)$$

## Link with Spatially-Uniform Models

For case 1,

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

Let  $V = 4\pi R^3/3 = \text{volume of tumour}$ . Then

$$\frac{dV}{dt} = 4\pi R^2 \frac{dR}{dt} = V \left( c_\infty - \lambda_A - \frac{\Gamma}{15} \left( \frac{3}{4\pi} \right)^{2/3} V^{2/3} \right)$$

$$\Rightarrow \frac{dV}{dt} = \left( \frac{kV}{\alpha} \right) \left[ 1 - \left( \frac{V}{\theta} \right)^\alpha \right]$$

where

$$\alpha = 2/3, \quad k = \frac{2}{3}(c_\infty - \lambda_A), \quad \theta = \frac{4\pi}{3} \left[ \frac{15}{\Gamma}(c_\infty - \lambda_A) \right]^{3/2}$$

i.e. model equivalent to model 3 of lecture 1, with  $\alpha = 2/3$ .

## *Model Analysis (continued)*

In general, kinetic terms etc nonlinear  $\Rightarrow$  models don't yield simple analytical solutions

In such cases, numerical methods needed.

We can make some progress by studying special cases for which the model equations simplify

Three cases of interest are:

- Small tumour analysis ( $0 < R \ll 1$ )
- Onset of necrosis ( $0 < R_N \ll R$ )
- Fully-developed tumours with thin proliferating rims ( $0 < R - R_N \ll 1$ )

# 1. Small Tumour Analysis ( $0 < R \ll 1$ )

- If  $R_N = 0$  and  $0 < R \ll 1$  then

$$c \sim c_\infty \quad \forall r \in (0, R) \quad \text{and} \quad \frac{dR}{dt} \sim (c_\infty - \lambda_A) \frac{R}{3}$$

$$\Rightarrow R(t) \sim R(0) \exp \left\{ \frac{(c_\infty - \lambda_A)t}{3} \right\}$$

Tumour's growth rate depends on the balance between **proliferation** and **apoptosis**

- If  $c_\infty < \lambda_A$  then  $R(t) \rightarrow 0$  as  $t \rightarrow \infty$  i.e. the **tumour-free** solution is **linearly stable**: insufficient nutrient  $\Rightarrow$  apoptosis dominates proliferation
- If  $c_\infty > \lambda_A$  then tumour grows: **tumour-free** solution is **linearly unstable**.

## 2. Onset of Necrosis ( $0 < R_N \ll R$ )

- When  $0 < R_N = R_H \ll 1$

$$\frac{3}{R} \frac{dR}{dt} = c_N \left( 1 - \frac{R_N^3}{R^3} \right) - \left( \lambda_A + \lambda_N \frac{R_N^3}{R^3} \right) + \frac{\Gamma}{10} \left( 1 - \frac{R_N^5}{R^5} \right) - \frac{\Gamma R_N^2}{2} \left( 1 - \frac{R_N}{R} \right)$$

$$\text{with } \frac{6}{\Gamma R^2} (c_\infty - c_N) = \left( 1 - \frac{R_N}{R} \right)^2 \left( 1 + \frac{2R_N}{R} \right)$$

- We introduce  $0 < \epsilon \ll 1$  and assume

$$R \sim R_0 + \epsilon R_1 + \epsilon^2 R_2 \quad \text{and} \quad R_N \sim \epsilon R_{N1}$$

- Substituting in the algebraic identity and equating coefficients of  $O(\epsilon)$  we deduce

$$R_0^2 = \underbrace{\frac{6}{\Gamma} (c_\infty - c_N)}_{\text{constant}}, \quad R_1 = 0, \quad R_2 = \frac{3R_{N1}^2}{2R_0}$$

- Note:**

- $R_0$  = radius at which necrosis is initiated
- $O(\epsilon^2)$  variations in  $R$  and  $O(\epsilon)$  variations in  $R_N \Rightarrow$  rapid evolution of necrotic core while overall tumour volume remains approximately constant

## 2. Onset of Necrosis ( $0 < R_N \ll R$ )

- Substituting with  $R$  and  $R_N$  in the ODE

$$\left(\frac{3\epsilon^2}{R_0}\right) \frac{dR_2}{dt} = c_N - \lambda_A - \frac{\Gamma R_0^2}{10}$$

- We **regularise** this ODE by introducing a short timescale  $\tau = \frac{t}{\epsilon^2}$

$$\Rightarrow R_2(\tau) = R_2(0) + \left(\frac{1}{5}(c_\infty - c_N) - \frac{1}{3}(\lambda_A - c_N)\right) R_0 \tau$$

- Hence the necrotic core persists if

$$c_\infty > c_N + \frac{5}{3}(\lambda_A - c_N)$$

- **Note:** agreement with experimental results by Groebe and Muller-Kleiser (1996)



### 3. Thin Proliferating Rim ( $0 < R - R_N \ll 1$ )

- We introduce  $0 < \delta \ll 1$  and assume

$$R_N \sim R - \delta R_{N1}$$

- Substituting for  $R_N$  yields

$$c_\infty - c_N \sim \frac{\Gamma}{2}(\delta R_{N1})^2 = \frac{\Gamma}{2}(R - R_N)^2$$

$$\text{and } \frac{dR}{dt} \sim -\frac{1}{3}(\lambda_A + \lambda_N)R + \delta(c_N + \lambda_N)R_{N1}$$

$$\Rightarrow R(t) \rightarrow R_\infty \sim \frac{3\delta(c_N + \lambda_N)R_{N1}}{\lambda_A + \lambda_N} \quad \text{as } t \rightarrow \infty$$

$$c_N, R_{N1} \sim O(1) \quad \Rightarrow \quad R_\infty \sim O\left(\frac{\delta}{\lambda_A + \lambda_N}\right)$$

- Hence, if experiments indicate that  $R_\infty \sim O(1)$  we deduce

$$\lambda_A + \lambda_N \sim O(\delta)$$

# Summary of Results

The spatially-structured models reproduce the main features of avascular tumour growth (i.e. quiescence, necrosis and growth saturation)

- Rapid expansion of the necrotic core following the onset of necrosis

We can use models to predict how changes to system parameters (eg  $c_\infty$ ) affect tumour's growth and equilibrium configuration

We can identify conditions under which certain equilibrium configurations will be realised

- Thin proliferating rim if  $c_\infty \sim c_N$

# *Discussion*

## Model Extensions

- Response to chemotherapy
- Response to multiple growth factors (GFs)
  - Supplied externally
  - Produced by tumour cells
  - GFs promote or inhibit cell proliferation

## Model Deficiencies

- Cellular heterogeneity (lecture 5)
- 2- and 3-D tumour growth/invasion (lecture 3)