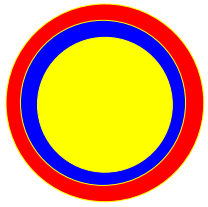
Modelling Assumptions



Schematic Diagram of a Fully-Developed Avascular Tumour

- 1-dimensional, radially-symmetric growth
- Tumour contains uniform population of cells
- Single, growth-rate limiting nutrient (chemical), which is supplied at a constant rate from the surrounding medium
- Local nutrient concentration determines 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 $R_N(t)$

Modelling Solid Tumour Growth
Lecture 2: Spatially-Structured Models

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Model Development (continued)

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 Γ.

Nutrient boundary and initial conditions

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

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

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

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.

Model Development (continued)

Internal Boundaries, $R_H(t)$ and $R_N(t)$

- Uniformly proliferating tumour

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

- Intermediate-sized tumour

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

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

- Well-developed tumour

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

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

with $c(R_H, t) = c_H$ and $c(R_N, t) = c_N$

Model Development (continued)

Outer Tumour Radius, $R(t)$

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

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

where $\quad S = S(c, R, R_H, R_N) = scH(r - R_H)$

and $\; N = N(c, R, R_H, R_N) = \underbrace{s\lambda_A}_{\text{apoptosis}} + \underbrace{s\lambda_N H(R_N - r)}_{\text{necrosis}}$

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 $c(R_N, t) = c_N$

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

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

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

Model Development (continued)

Notes:

- Proliferation restricted to proliferating, non-quiescent regions where it occurs at rate proportional to c
- 2 cell death mechanisms:
  - 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 perform (θ, ϕ)- integrations to obtain following integro-differential equation for $R(t)$:

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

with $\quad R(t = 0) = R_0, \;$ prescribed

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 $c^*(R_N^*, t^*) = c_N^*$

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

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

Notes:

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

Nondimensionalisation

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

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

where c^*, r^*, t^*, etc are dimensionless variables and C, X, T, etc are typical nutrient concentrations, etc

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

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: $0 < R^2 < 6(c_\infty - c_H)/\Gamma$

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

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

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

Here tumour contains proliferating cells only.

Nondimensionalisation (continued)

In practice

$$\begin{pmatrix} \text{nutrient diffusion} \\ \text{timescale, } X^2/D \\ \sim \text{mins or hours} \end{pmatrix} \ll \begin{pmatrix} \text{tumour doubling} \\ \text{timescale, } 1/sC \\ \sim \text{weeks} \end{pmatrix}$$

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

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

Then nutrient equation becomes

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

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

Case 2: $6(c_\infty - c_H)/\Gamma < R^2 < 6(c_\infty - c_N)/\Gamma$

Notes:

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

  $\Rightarrow$ 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:

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

- Since $R_H < R$, we deduce

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

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

Case 1: $0 < R^2 < 6(c_\infty - c_H)/\Gamma$

Note:

$$\begin{aligned} c(r,t) &= c_\infty - \frac{\Gamma}{6}(R^2 - r^2) \\ \Rightarrow c_{min} &= c(0,t) = c_\infty - \frac{\Gamma R^2}{6} \equiv c_H \text{ when } R^2 = \frac{6}{\Gamma}(c_\infty - c_H) \end{aligned}$$

i.e. 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 3: $(6(c_\infty - c_N)/\Gamma < R^2)$

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

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

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

Case 2: $6(c_\infty - c_H)/\Gamma < R^2 < 6(c_\infty - c_N)/\Gamma$

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

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

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

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

Tumour contains proliferating and quiescent cells

Model comprises ODE for R and algebraic equation for R_H

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 $V = 4\pi R^3/3 =$ 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: Equilibrium Solutions

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

For case 1

$$R_H = R_N = 0 \quad \text{and} \quad 0 = R\left(c_\infty - \frac{\Gamma R^2}{15} - \lambda_A\right)$$

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

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

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

Model Analysis (continued)

In general, kinetic terms etc will be nonlinear and resulting models may not yield simple analytical solutions

In such cases, we must use numerical methods to construct approximate solutions.

We may be able to make analytical progress by studying special cases for which the model equations simplify

Three cases that may be 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 ($0 < R - R_N \ll 1$)

Model Analysis: Equilibrium Solutions

For case 2

$$R_N = 0 \quad R_H^2 = R^2 - \frac{6}{\Gamma}(c_\infty - \lambda_A)$$

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

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

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)

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

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

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

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

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

- If $c_\infty < \lambda_A$ then $R(t) \to 0$ as $t \to \infty$ 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.

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

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

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

- Substituting for R_N in the algebraic identity yields

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

- Substituting for R_N in the ODE yields

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

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

- If $c_N, R_{N1} \sim O(1)$ then

$$R_\infty \sim O\left(\frac{\delta}{\lambda_A + \lambda_N}\right)$$

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

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

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

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

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

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

- 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

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_∞) 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 Weaknesses

- Cellular heterogeneity
- 2- and 3-D tumour growth/invasion