Modelling Solid Tumour Growth
Lecture 1: Spatially-Averaged Models

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Outline

- Homogeneous growth laws
- Chemotherapy: continuous and periodic infusion
- Heterogeneous tumour growth
- Discussion

References

- M. Marusic et al (1994) *Bull. Math. Biol.* **56**:617-631.
- J.C. Panetta (1997). *Math. Biosci.* **146**:89-113
- D. Gammack, H.M. Byrne and C.E. Lewis (2001). *Bull. Math. Biol.* **63**: 135-166.

Homogeneous Tumour Growth

Modelling Assumptions

- Tumour contains one cell type
- No spatial variation
- No explicit mention of nutrients, growth factors or the host vasculature
- Tumour volume proportional to $N(t)$, the number of tumour cells at time t

General Model

$$\frac{dN}{dt} = f(N) \qquad \text{with} \quad N(t=0) = N_0$$

where $f(N)$ describes the tumour cell growth dyanmics

Examples of Heterogeneous Growth Models

I. Exponential Growth

$$f(N) = kN, \quad k = \text{proliferation rate} \qquad \Rightarrow N(t) = N_0 e^{kt}$$

II. Logistic Growth

$$f(N) = kN\left(1 - \frac{N}{\theta}\right), \qquad \theta = \text{carrying capacity}$$

$$\Rightarrow N(t) = \frac{\theta N_0}{N_0 + (\theta - N_0)e^{-kt}} \to \theta \text{ as } t \to \infty$$

III.

$$f(N) = \frac{kN}{\alpha}\left[1 - \left(\frac{N}{\theta}\right)^{\alpha}\right] \qquad (\alpha > 0)$$

$$\Rightarrow N(t) = \theta\left(\frac{N_0^{\alpha}}{N_0^{\alpha} + (\theta^{\alpha} - N_0^{\alpha})e^{-kt}}\right)^{1/\alpha}$$

Chemotherapy

Modelling Assumptions:

- Logistic growth when no drug present
- Drug delivered to tumour at prescribed rate $a(t)$
- Drug kills tumour cells at a rate μAN
- Drug undergoes natural decay and is degraded at rate γAN when it kills tumour cells

Model Variables

- $N(t)$ denotes number of tumour cells
- $A(t)$ denotes drug concentration within tumour

Homogenous Growth Models

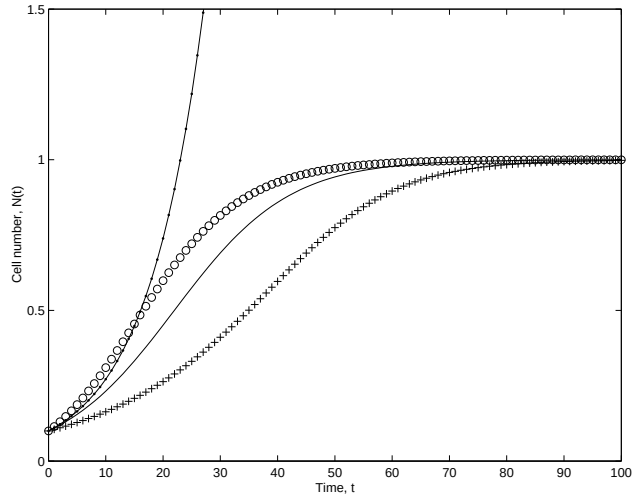


Diagram showing how the tumour evolves when growth laws I, II and III are used

Continuous Infusion ($a(t) = a_\infty$)

- When no drug is administered ($a_\infty = 0$), $N(t) \to \theta$ as $t \to \infty$
- When a tumour is continuously exposed to a drug, we expect that both $N(t)$ and $A(t)$ will evolve to time-independent, equilibrium values
- Therefore, we now identify and classify the equilibrium solutions
- Of interest is how these equilibrium solutions vary with the drug dosage, a_∞

When $\frac{dN}{dt} = 0 = \frac{dA}{dt}$, the model reduces to give

$$0 = kN\left(1 - \frac{N}{\theta} - \frac{\mu}{k}A\right) \quad \text{and} \quad 0 = a_\infty - \lambda A - \gamma NA.$$

$$\Rightarrow N = 0 \quad \text{and} \quad A = a_\infty \quad \text{(tumour-free solution)}$$

or $\quad 0 = N^2 + \frac{\lambda}{\gamma}\left(1 - \frac{\gamma\theta}{\lambda}\right)N + \frac{\lambda\theta}{\gamma}\left(\frac{a_\infty \mu}{\lambda k} - 1\right) \quad A = \frac{k}{\mu}\left(1 - \frac{N}{\theta}\right).$

Homogenous Growth Models

These are used to

- Fit experimental data
- Compare growth kinetics of different tumours
- Assess impact of therapy

However

- It is often difficult to relate the model parameters to the detailed biophysical behaviour of the tumours

Continuous Infusion: Linear Stability Analysis

Question: which solution is realised when more than one equilibrium solution occurs?

To determine the answer, we use linear stability analysis.

Linear Stability Analysis

- Perturb the system from an equilibrium point
- Determine how the perturbations evolve over time
  - Perturbation grows $\Rightarrow$ instability
  - Perturbation decays $\Rightarrow$ stability

Continuous infusion (continued)

$$0 = N^2 + \frac{\lambda}{\gamma}\left(1 - \frac{\gamma\theta}{\lambda}\right)N + \frac{\lambda\theta}{\gamma}\left(\frac{a_\infty \mu}{\lambda k} - 1\right)$$

Question: How do the equilibrium solutions vary with a_∞?

Let $$a_\infty^{max} \equiv \frac{\lambda k}{\mu}\left[1 + \frac{\lambda}{4\gamma\theta}\left(1 - \frac{\gamma\theta}{\lambda}\right)^2\right]$$

Using elementary analysis, we can show that

- $a_\infty > a_\infty^{max} \Rightarrow$ the tumour is erradicated, i.e. $N = 0$ is the steady solution
- $0 < a_\infty < a_\infty^{max} \Rightarrow$ outcome depends on $\gamma\theta/\lambda$:
  - **Case 1:** $\gamma\theta/\lambda < 1$.
    - $0 \leq a_\infty < \lambda k/\mu \Rightarrow$ single, nontrivial solution
    - $\lambda k/\mu < a_\infty \Rightarrow$ no nontrivial solutions
  - **Case 2:** $\gamma\theta/\lambda > 1$.
    - $0 \leq a_\infty < \lambda k/\mu \Rightarrow$ single nontrivial solution
    - $\lambda k/\mu < a_\infty < a_\infty^{max} \Rightarrow$ 2 physical solutions

Linear Stability Analysis (continued)

The Tumour-Free Solution, $(N, A) = (0, a_\infty/\lambda)$

- We introduce $\epsilon \ll 1$ and write:

$$N(t) = \epsilon\bar{N}(t) \quad \text{and} \quad A(t) = \frac{a_\infty}{\lambda} + \epsilon\bar{A}(t)$$

- We substitute with (N, A) in the model equations:

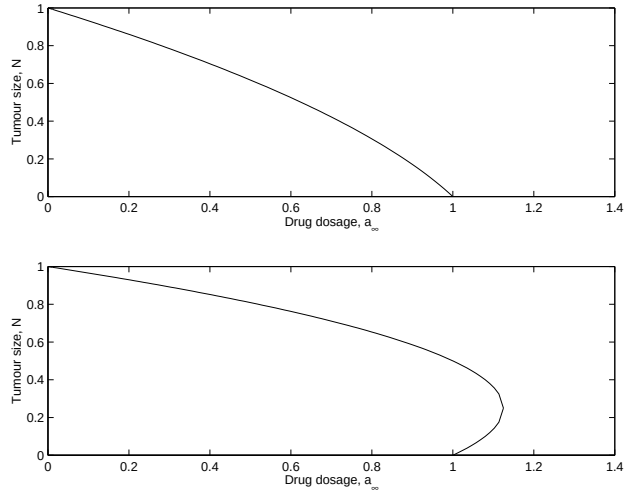
$$\frac{d}{dt}(\epsilon\bar{N}) = k\left(1 - \frac{\epsilon\bar{N}}{\theta}\right)(\epsilon\bar{N}) - \mu\left(\frac{a_\infty}{\lambda} + \epsilon\bar{A}\right)(\epsilon\bar{N})$$

$$\frac{d}{dt}\left(\frac{a_\infty}{\lambda} + \epsilon\bar{A}\right) = a_\infty - \left(\frac{a_\infty}{\lambda} + \epsilon\bar{A}\right)(\lambda + \epsilon\gamma\bar{N})$$

- We equate coefficients of $O(\epsilon)$:

$$\frac{d\bar{N}}{dt} = \left(k - \frac{\mu a_\infty}{\lambda}\right)\bar{N} \qquad \frac{d\bar{A}}{dt} = -\lambda\bar{A} - \frac{\gamma a_\infty}{\lambda}\bar{N}$$

Continuous Infusion (continued)



Bifurcation diagrams showing how the equilibrium size of the tumour varies with the drug dosage, a_∞, when $\gamma\theta/\lambda < 1$ and $\gamma\theta/\lambda > 1$. Parameter values: (a) $\theta = \lambda = \mu = k = 1, \gamma = 0.5$; (b) $\theta = \lambda = \mu = k = 1, \gamma = 2$.

Linear Stability Analysis (continued)

$$\Rightarrow \frac{d\bar{N}}{dt} = \bar{N}\frac{\partial f}{\partial N} + \bar{A}\frac{\partial f}{\partial A}, \qquad \frac{d\bar{A}}{dt} = \bar{N}\frac{\partial g}{\partial N} + \bar{A}\frac{\partial g}{\partial A}$$

- We seek solutions of the form

$$(\bar{N},\bar{A}) = (\tilde{N},\tilde{A})e^{\sigma t} \qquad \Rightarrow 0 = \begin{pmatrix} \sigma - \frac{\partial f}{\partial N} & \frac{\partial f}{\partial A} \\ \frac{\partial g}{\partial N} & \sigma - \frac{\partial g}{\partial A} \end{pmatrix} \begin{pmatrix} \tilde{N} \\ \tilde{A} \end{pmatrix}$$

- For nontrivial solutions ($(\tilde{N},\tilde{A}) \neq 0$)

$$0 = \sigma^2 - \left(\frac{\partial f}{\partial N} + \frac{\partial f}{\partial A}\right)\sigma + \left(\frac{\partial f}{\partial N}\frac{\partial g}{\partial A} - \frac{\partial f}{\partial A}\frac{\partial g}{\partial N}\right)$$

- For stability, $\Re(\sigma) < 0$

$$\Leftrightarrow \frac{\partial f}{\partial N} + \frac{\partial g}{\partial A} < 0 < \frac{\partial f}{\partial N}\frac{\partial g}{\partial A} - \frac{\partial f}{\partial A}\frac{\partial g}{\partial N}$$

Linear Stability Analysis (continued)

$$\bar{N}(t) = \bar{N}(0)e^{(k-\mu a_\infty/\lambda)t}$$

and

$$\bar{A}(t) = \left(\bar{A}(0) + \frac{\gamma a_\infty \bar{N}(0)}{\lambda^2 + k\lambda - \mu a_\infty}\right) e^{-\lambda t} - \left(\frac{\gamma a_\infty \bar{N}(0)}{\lambda^2 + k\lambda - \mu a_\infty}\right) e^{(k-\mu a_\infty/\lambda)t}$$

$$a_\infty > \frac{\lambda k}{\mu} \quad \Rightarrow \quad \bar{N}(t), \bar{A}(t) \to 0 \text{ as } t \to \infty$$
$$\Rightarrow \text{ trivial solution recovered: STABILITY}$$

$$a_\infty < \frac{\lambda k}{\mu} \quad \Rightarrow \quad \bar{N}(t), |\bar{A}(t)| \to \infty \text{ as } t \to \infty : \quad \text{INSTABILITY}$$

Linear Stability Analysis (continued)

Example ($\theta = \lambda = \mu = k = 2, \gamma = 1/2$)

$$f(N,A) = N(1-N-A) \quad g(N,A) = a_\infty - A - \frac{NA}{2}$$

- Then (N_∞, A_∞) satisfy

$$0 = N_\infty^2 + N_\infty - 2(a_\infty - 1), \quad A_\infty = 1 - N_\infty$$

- In addition,

$$\begin{pmatrix} \frac{\partial f}{\partial N} & \frac{\partial f}{\partial A} \\ \frac{\partial g}{\partial N} & \frac{\partial g}{\partial A} \end{pmatrix} = \begin{pmatrix} 1 - 2N_\infty - A_\infty & -N_\infty \\ -A_\infty/2 & -1 - N_\infty/2 \end{pmatrix}$$

$$\Rightarrow \frac{\partial f}{\partial N} + \frac{\partial g}{\partial A} = -\frac{3}{2}N_\infty - A_\infty < 0 \qquad \text{and} \quad \frac{\partial f}{\partial N}\frac{\partial g}{\partial A} - \frac{\partial f}{\partial A}\frac{\partial g}{\partial N} = N_\infty^2 + \frac{N_\infty}{2} > 0$$

- Stability for all nontrivial solutions, where they exist.

Linear Stability Analysis (continued)

Nontrivial Solutions, $(N,A) = (N_\infty, A_\infty)$

- We seek solutions of the form

$$N(t) = N_\infty + \epsilon\bar{N}(t), \quad A(t) = A_\infty + \epsilon\bar{A}(t), \quad \epsilon \ll 1$$

where $f(N_\infty, A_\infty) = g(N_\infty, A_\infty) = 0$, so that.

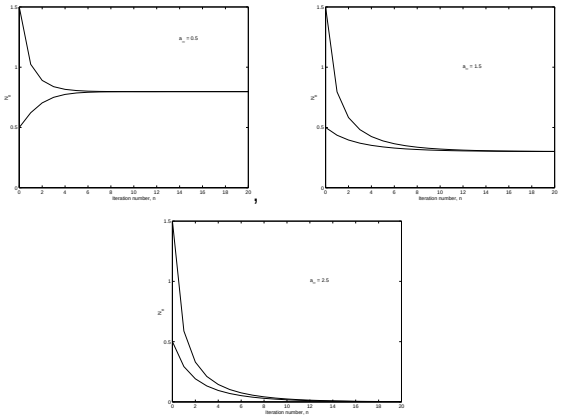
$$0 = N_\infty^2 + \frac{\lambda}{\gamma}\left(1 - \frac{\gamma\theta}{\lambda}\right)N_\infty + \frac{\lambda\theta}{\gamma}\left(\frac{a_\infty\mu}{\lambda k} - 1\right), \qquad A_\infty = \frac{k}{\mu}\left(1 - \frac{N_\infty}{\theta}\right)$$

- We substitute with (N,A) in the model equations:

$$\epsilon\frac{d\bar{N}}{dt} = f(N_\infty + \epsilon\bar{N}, A_\infty + \epsilon\bar{A}), \qquad \epsilon\frac{d\bar{A}}{dt} = g(N_\infty + \epsilon\bar{N}, A_\infty + \epsilon\bar{A}),$$

where
$$f(N_\infty + \epsilon\bar{N}, A_\infty + \epsilon\bar{A}) = \underbrace{f(N_\infty, A_\infty)}_{=0} + \epsilon\bar{N}\frac{\partial f}{\partial N}(N_\infty, A_\infty) + \epsilon\bar{A}\frac{\partial f}{\partial A}(N_\infty, A_\infty)$$

Periodic Infusion (ctd)



Series of diagrams showing the tumour's response to periodic infusion at different drug dosages. Parameter values: $\theta = 1 = \mu = k, \tau = 0.5$.

Periodic Infusion

Question: why is continuous infusion not a practical option for cancer treatment?

For simplicity, we consider the following, simplified model equations:

$$\frac{dN}{dt} = kN\left(1 - \frac{N}{\theta} - \mu A\right), \quad \text{with } N(0) = N_0,$$

$$\text{and} \quad A(t) = \begin{cases} a_\infty & n < t < n+\tau \\ 0 & n+\tau < t < n+1. \end{cases}$$

Note: $A(t)$ piecewise constant $\Rightarrow$ cells undergo logistic growth with variable carrying capacity and proliferation rate:

$$\frac{dN}{dt} = k\Lambda N\left(1 - \frac{N}{\theta\Lambda}\right) \quad \text{where} \quad \Lambda = \begin{cases} (1-\mu a_\infty) & \text{if } A = a_\infty \\ 1 & \text{if } A = 0 \end{cases}$$

Periodic Infusion (ctd)

The numerical results suggest that, under certain circumstances, the recurrence relation evolves so that

$$N_n = N_{n+1} = N_\infty$$

If this arises then,

$$N_\infty = \frac{\theta\Lambda(1 - e^{-k(1-\tau)}.e^{-k\Lambda\tau})}{\Lambda + (1-\Lambda)e^{-k(1-\tau)} - e^{-k(1-\tau)}.e^{-k\Lambda\tau}}$$

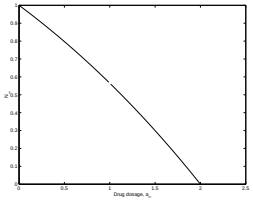


Diagram showing how N_∞ varies with a_∞ when periodic solutions emerge. Parameter values: $\theta = 1 = \mu = k, \tau = 0.5$.

Periodic Infusion (continued)

Assume continuity of $N(t)$ at $t = nT$ and $t = nT + \tau$:

$$N(t) = \begin{cases} \dfrac{\theta\Lambda N_n}{N_n + (\theta\Lambda - N_n)e^{-k\Lambda(t-n)}} & n < t < n+\tau \\ \dfrac{\theta N_{n+\tau}}{N_{n+\tau} + (\theta - N_{n+\tau})e^{-k(t-n-\tau)}} & n+\tau < t < n+1 \end{cases}$$

where $N_n = N(nT)$ and $N_{n+\tau} = N(nT+\tau)$ satisfy

$$N_{n+\tau} = \frac{\theta\Lambda N_n}{N_n + (\theta\Lambda - N_n)e^{-k\Lambda\tau}}$$

and

$$N_{n+1} = \frac{\theta\Lambda N_n}{\Lambda N_n + [(1-\Lambda)N_n + (\theta\Lambda - N_n)e^{-k\Lambda\tau}]e^{-k(1-\tau)}}$$

with $N_0 = N(t=0)$ prescribed.

Note: solutions depend on 4 parameter groupings:

$$\theta, \quad k, \quad \tau, \quad \Lambda = 1 - \frac{\mu a_\infty}{k}$$

Question: how does varying the drug dosage, a_∞, affect the outcome?

Heterogeneous Growth (ctd)

- Analysis proceeds as for earlier models
- Find and classify equilibrium solutions

Example ($k_{PD} = 0$: natural cell death negligible)

$$\frac{dP}{dt} = \frac{dQ}{dt} = \frac{dD}{dt} = 0$$

$\Rightarrow$ trivial and nontrivial solutions

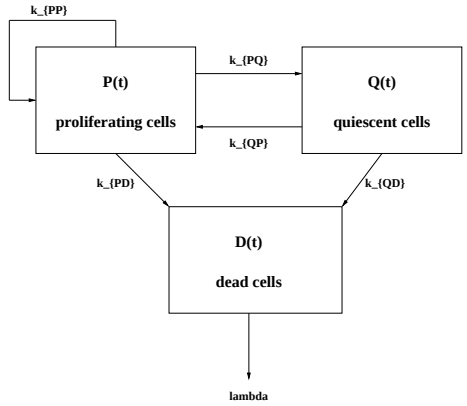
Trivial solution: $(P, Q, D) = (0, 0, 0)$

Nontrivial solutions:

$$0 = \left(\frac{\hat{k}_{PQ}}{\hat{k}_{QP}} - 1\right) P^2 + \left(\frac{\hat{k}_{QD}^2}{\hat{k}_{PP}\hat{k}_{QP}}\right)\left(1 - \frac{\hat{k}_{PQ}}{\hat{k}_{QP}} - \frac{\hat{k}_{PQ}}{\hat{k}_{QD}}\right) P + \left(1 + \frac{\hat{k}_{QD}}{\hat{k}_{QP}}\right)^2$$

with

Heterogeneous Growth



Schematic diagram of heterogeneous tumour growth model.

Heterogeneous Growth

Nontrivial Solutions

$$\frac{dP}{dt} = 0 \Rightarrow 0 = (k_{PP} - k_{PQ})P + k_{QP}Q^2$$

$$\frac{dQ}{dt} = 0 \Rightarrow 0 = k_{PQ}P^2 - [k_{QP}Q + k_{QD}(P + Q)]Q$$

$$\frac{dD}{dt} = 0 \Rightarrow 0 = k_{QD}(P + Q)Q - \lambda D$$

P, Q and D equations $\Rightarrow$

$$P = \frac{k_{QD}Q^2}{k_{PP} - k_{QD}Q} \quad \text{and} \quad D = \frac{k_{QD}}{\lambda}(P + Q)Q$$

where

$$0 = k_{QD}(k_{QP} - k_{PQ})Q^2 - k_{PP}(k_{QD} + 2k_{QP})Q + k_{PP}^2\left(1 + \frac{k_{QP}}{k_{QD}}\right)$$

Heterogeneous Growth (ctd)

Model Equations:

$$\frac{dP}{dt} = (k_{PP} - k_{PQ} - k_{PD})P + k_{QP}Q,$$

$$\frac{dQ}{dt} = k_{PQ}P - (k_{QP} + k_{QD})Q,$$

$$\frac{dD}{dt} = k_{PD}P + k_{QD}Q - \lambda D,$$

with $P(0) = P_0, Q(0) = Q_0, D(0) = D_0$.

$$k_{PP} = \frac{\hat{k}_{PP}}{\hat{N} + N}, \quad k_{PQ} = \frac{\hat{k}_{PQ}P}{\hat{N} + N}, \quad k_{PD} = \hat{k}_{PD},$$

$$k_{QP} = \frac{\hat{k}_{QP}Q}{\hat{N} + N}, \quad k_{QD} = \frac{\hat{k}_{QD}(P + Q)}{\hat{N} + N}$$

and $N(t) = P(t) + Q(t) + D(t)$

Discussion

Summary

- Simple ODE models studied
- Many features of tumour growth neglected
- Models can explain solid tumour growth dynamics (and their response to different drug protocols)
- How can simple models be improved to provide better physical insight?
  - Spatial-structure - Lectures 2 and 4
  - Cell-cycle-kinetics $\Rightarrow$ response to cell-cycle specific drugs
  - ...

Suggestions

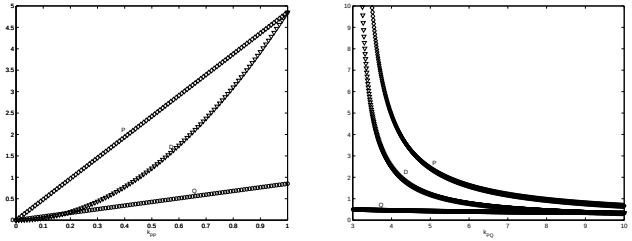
- Extend chemotherapy models to include the response of normal cells
- Include chemotherapy in heterogeneous models of tumour growth

Heterogeneous Growth

Let $k_{QD} = k_{QP} = \lambda = 1$. Then

$$0 = (1 - k_{PQ})Q^2 - 3k_{PP}Q + 2k_{PP}^2 \quad \Rightarrow \quad Q = \frac{3k_{PP} \pm \sqrt{k_{PP}^2(1 + 8k_{PQ})}}{1 - k_{PQ}}$$

$k_{PQ} \neq 1 \Rightarrow$ 1 positive, physically realistic root

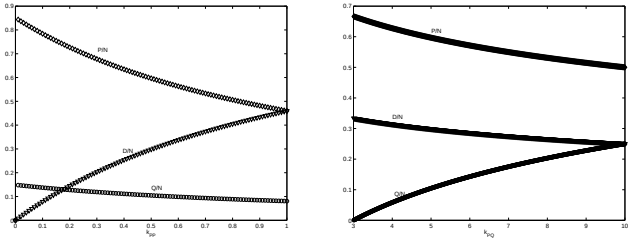


Diagrams showing how equilibrium solutions vary with k_{PP} and k_{PQ} when $k_{QD} = k_{QP} = \lambda = 1$: (a) $k_{PQ} = 5, k_{PP}$ varies; (b) $k_{PP} = 0.5, k_{PQ}$ varies.

Heterogeneous Growth

$$Q = \frac{3k_{PP} \pm \sqrt{k_{PP}^2(1 + 8k_{PQ})}}{1 - k_{PQ}}, \quad P = \frac{Q^2}{k_{PP} - Q}, \quad D = (P + Q)Q,$$

$$N = P + Q + D$$



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