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
- Radiotherapy
- Discussion

References

- Wheldon et al, *Brit J Radiol* **50**: 681-682 (1977).
- 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 Homogeneous Growth Models

I. Exponential Growth ($k =$ proliferation rate)

$$f(N) = kN \qquad \Rightarrow N(t) = N_0 e^{kt}$$

II. Logistic Growth ($\theta =$ carrying capacity)

$$f(N) = kN\left(1 - \frac{N}{\theta}\right) \qquad \Rightarrow N(t) = \frac{\theta N_0}{N_0 + (\theta - N_0)e^{-kt}} \to \theta \text{ as } t \to \infty$$

III. (k, α, θ model parameters)

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

Homogenous Growth Models

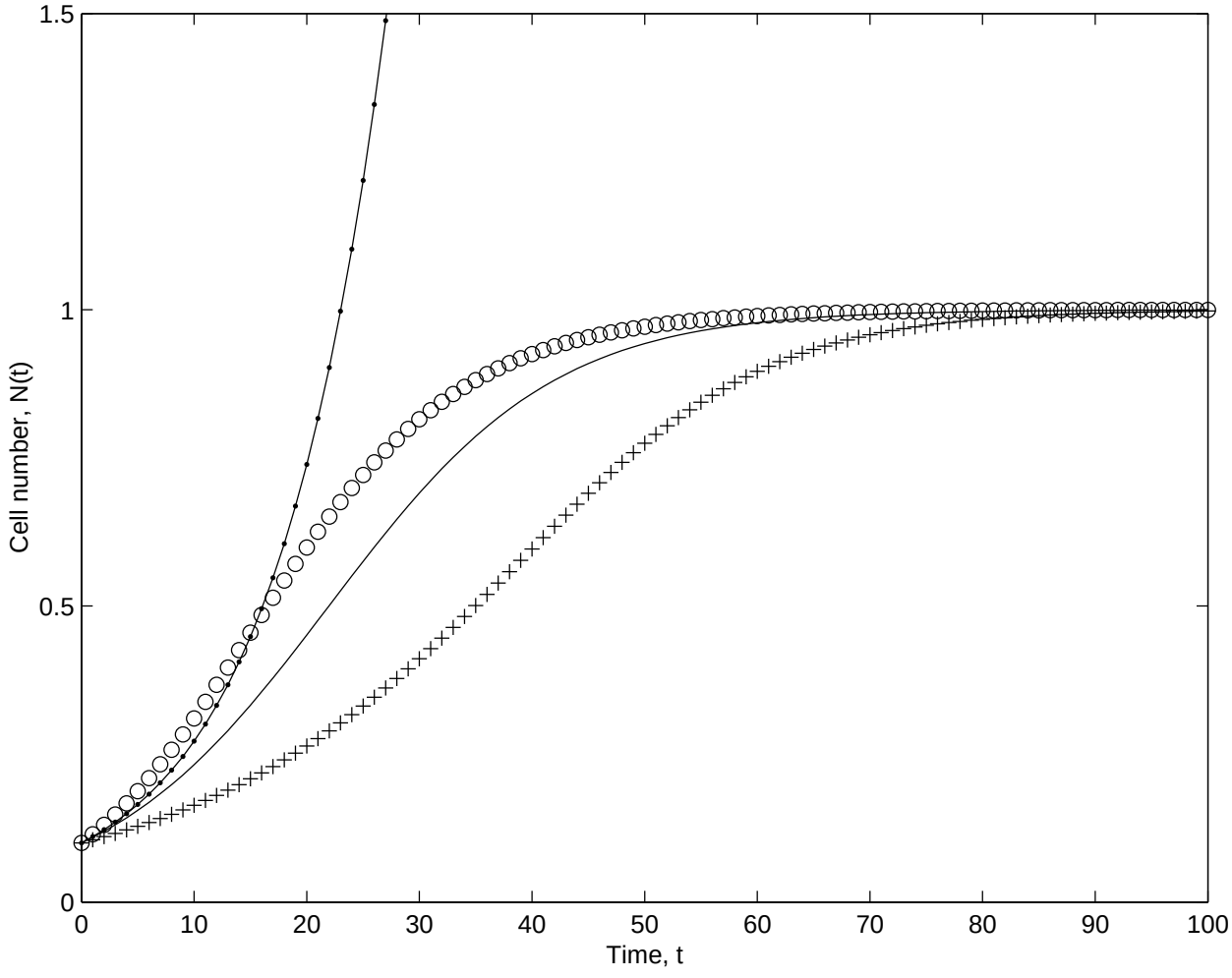


Diagram showing how the tumour evolves when growth laws I, II and III are used

Homogenous Growth Models

These are used to

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

However

- Often difficult to relate model parameters to biophysical behaviour of tumours
- Hence, development of more complex models in future lectures

Systems of ODEs

- Models thus far consist of single ODE
- Reasons for extending to systems of ODEs include:
  - tumour heterogeneity: cell cycle, clonal expansion, immune response, competition between normal and tumour cells, vascular tumour growth, ...
  - chemotherapy: tumour cells + drug
  - cell cycle dynamics: model intracellular protein levels throughout cell cycle
- Note: for details of subcellular dynamics, see: Tyson and Novak, J Theor Biol (2001) 210: 249-263; Alarcon et al, J Theor Biol (2004) 229: 395-411
- Note: the group project 'Antiangiogenic therapies for cancer' involves analysing (and extending) an ODE model of vascular tumour growth. With $V =$ tumour volume and $K =$ vascular volume, we have

$$\frac{dV}{dt} = -\lambda_1 V \log\left(\frac{V}{K}\right), \quad \frac{dK}{dt} = -\lambda_2 K + bV - dKV^{2/3}.$$

Chemotherapy

Model Variables

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

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 decays naturally and is degraded at rate γAN when it kills tumour cells

Model Equations:

$$\frac{dN}{dt} = kN\left(1 - \frac{N}{\theta}\right) - \mu AN, \quad \frac{dA}{dt} = a(t) - \lambda A - \gamma AN$$

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

- No drug ($a_\infty = 0$) $\Rightarrow N(t) \to \theta$ as $t \to \infty$
- When drug continuously infused, we expect $N(t)$ and $A(t)$ will evolve to time-independent, equilibrium values
- Therefore, we now identify and classify the equilibrium solutions, focussing on how they vary with the drug dosage, a_∞

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

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

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

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

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

Continuous infusion (continued)

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

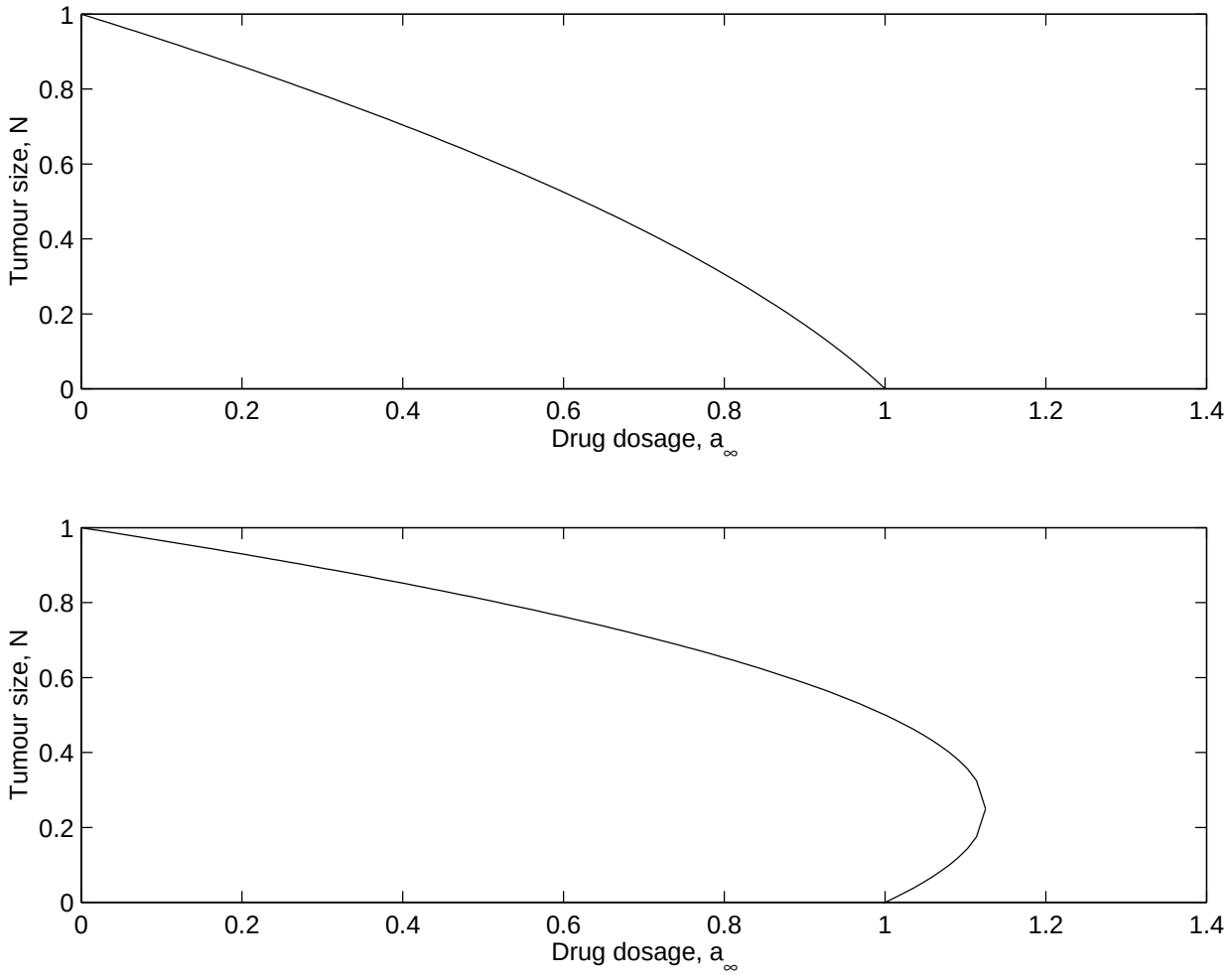
Question: How do the equilibrium solutions vary with a_∞?

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 (see exercise sheet)

- $a_\infty > a_\infty^{max} \Rightarrow$ 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
    - $0 < \lambda k/\mu < a_\infty \Rightarrow$ no nontrivial solutions
  - Case 2: $\gamma\theta/\lambda > 1$
    - $0 \leq a_\infty < \lambda k/\mu \quad \Rightarrow$ single nontrivial solution
    - $\lambda k/\mu < a_\infty < a_\infty^{max} \Rightarrow$ 2 physical solutions

Continuous Infusion (continued)



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

Continuous Infusion: Linear Stability Analysis

Use linear stability analysis to determine which solution is realised when more than one equilibrium solution occurs.

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 in model equations and equate coefficients of $O(\epsilon)$:

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

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

where $\Lambda = \gamma a_\infty \bar{N}(0)/(\lambda^2 + k\lambda - \mu a_\infty)$

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

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

Linear Stability Analysis (continued)

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

- Analysis proceeds as for trivial solutions, but algebra more involved
- 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

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

- We substitute in model equations and equate coefficients of $O(\epsilon)$:

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

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

$\Rightarrow$ Stability for all nontrivial solutions, where they exist.

Periodic Infusion

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

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

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

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

$A(t)$ 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 (continued)

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

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

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

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

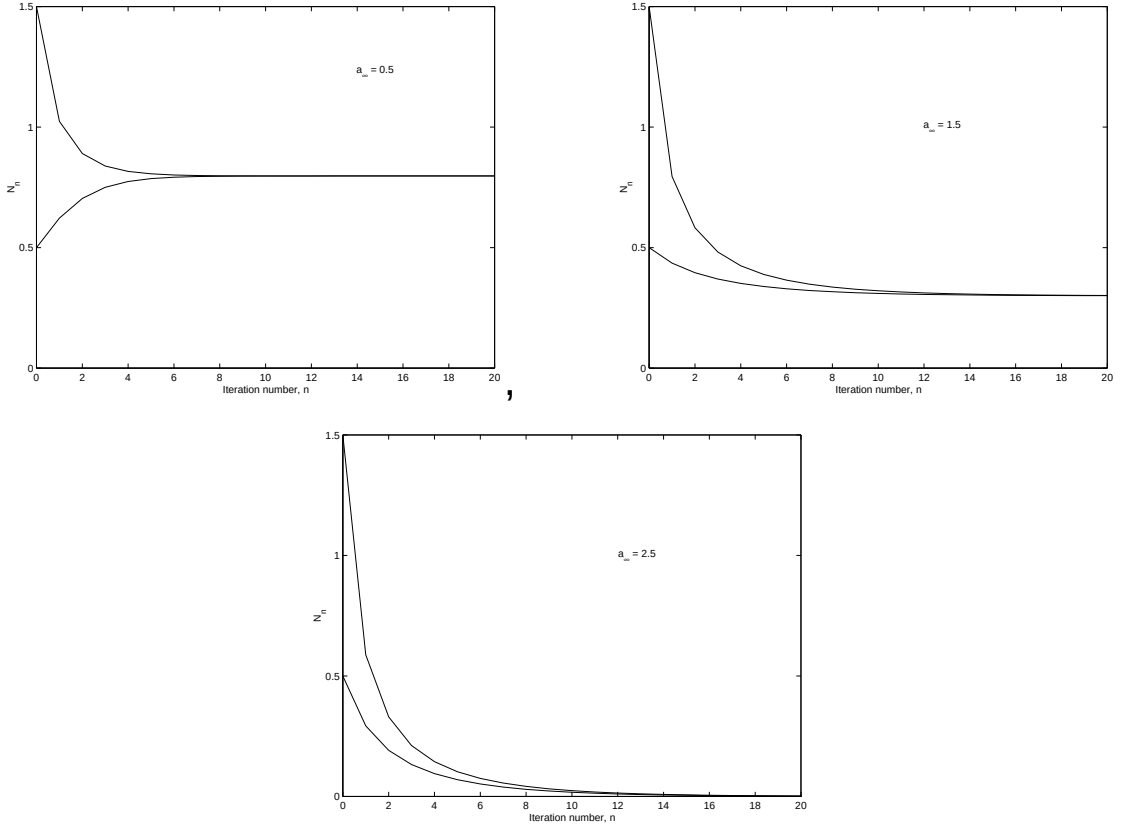
with $N_0 = N(t=0)$ prescribed.

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?

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 (ctd)

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

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

When this arises

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

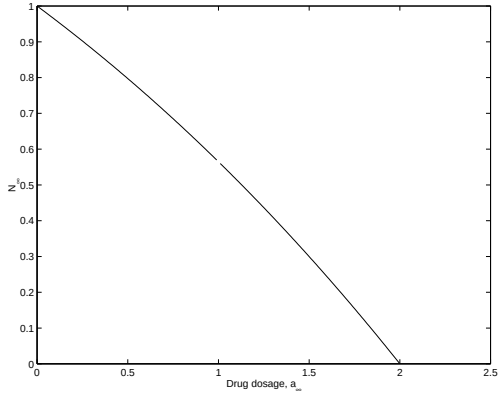
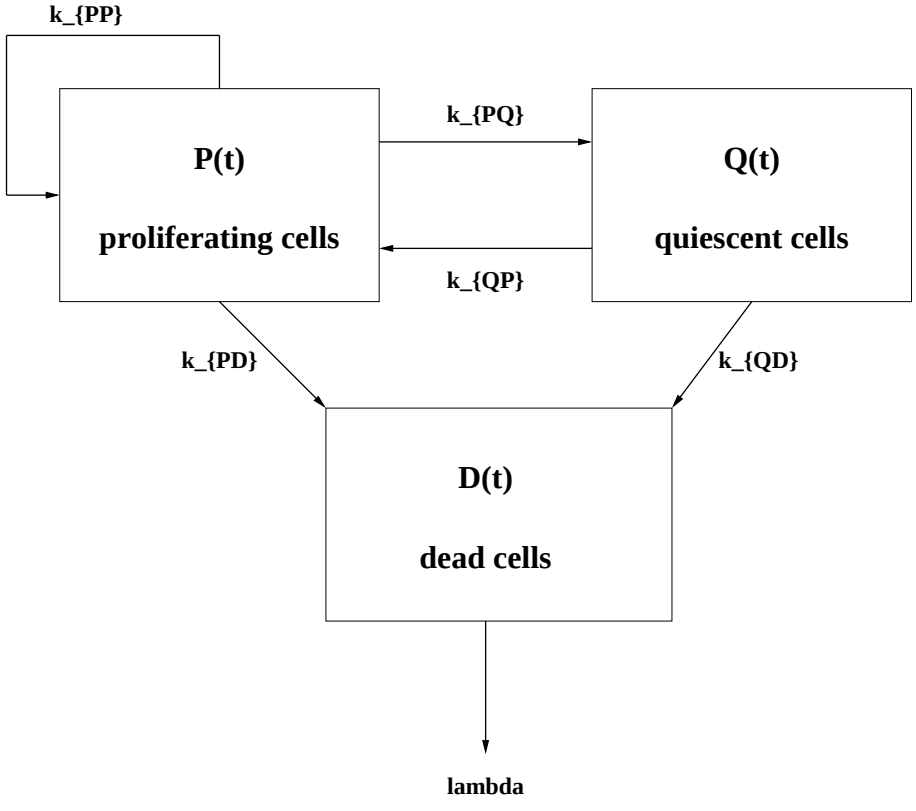


Diagram showing how N_∞ varies with a_∞ when periodic solutions emerge.

Note: same qualitative behaviour as for continuous infusion.

Parameter values: $\theta = 1 = \mu = k, \tau = 0.5$.

Heterogeneous Tumour Growth



Schematic diagram of heterogeneous tumour growth model.

Heterogeneous Tumour Growth: 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 $P(0) = P_0, Q(0) = Q_0, D(0) = D_0, N(t) = P(t) + Q(t) + D(t)$ and

$$k_{PP} = \hat{k}_{PP}, \quad k_{PQ} = \hat{k}_{PQ}P, \quad k_{PD} = \hat{k}_{PD}, \quad k_{QP} = \hat{k}_{QP}Q, \quad k_{QD} = \hat{k}_{QD}(P + Q)$$

- As for earlier models, find and classify equilibrium solutions

Heterogeneous Tumour Growth

Nontrivial Solutions

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

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

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

P, Q and D equations $\Rightarrow$

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

where

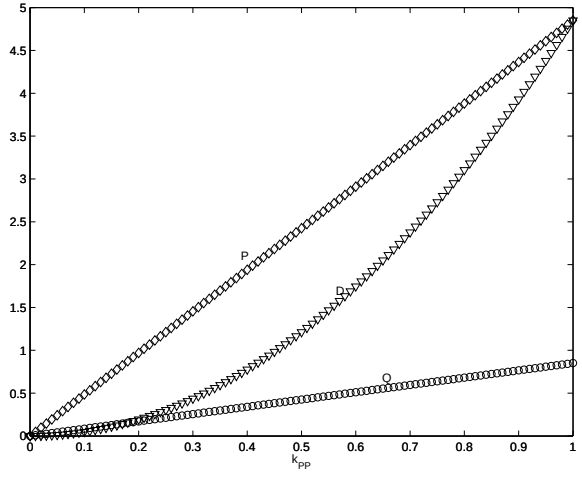
$$0 = \hat{k}_{QD}(\hat{k}_{QP} - \hat{k}_{PQ})Q^2 - \hat{k}_{PP}(\hat{k}_{QD} + 2\hat{k}_{QP})Q + \hat{k}_{PP}^2\left(1 + \frac{\hat{k}_{QP}}{\hat{k}_{QD}}\right)$$

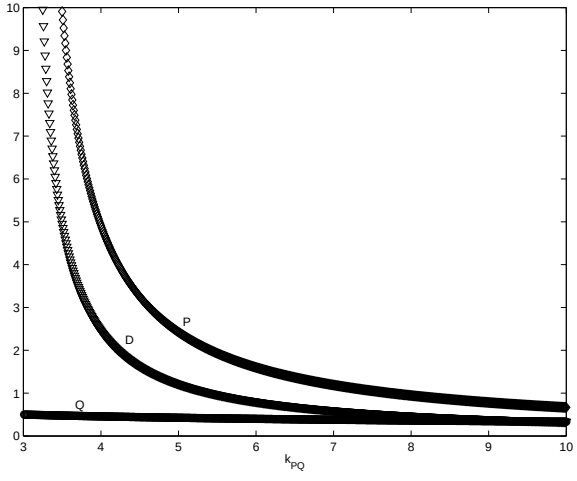
Heterogeneous Growth

Let $\hat{k}_{QD} = \hat{k}_{QP} = \lambda = 1$. Then

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

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



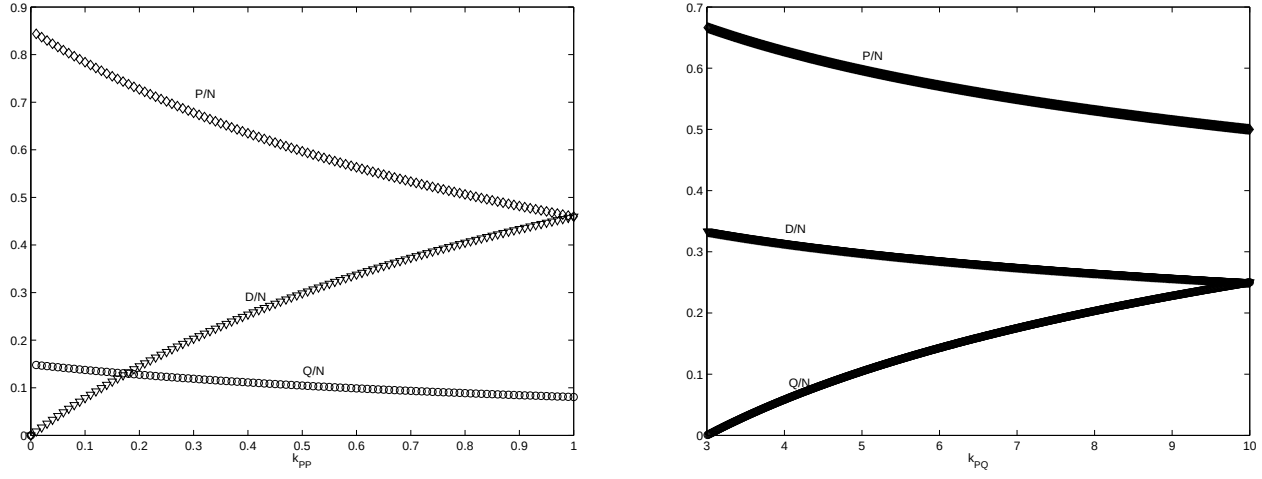


Diagrams showing how equilibrium solutions vary with $\hat{k}_{PP}$ and $\hat{k}_{PQ}$ when $\hat{k}_{QD} = \hat{k}_{QP} = \lambda = 1$: (a) $\hat{k}_{PQ} = 5, \hat{k}_{PP}$ varies; (b) $\hat{k}_{PP} = 0.5, \hat{k}_{PQ}$ varies.

Heterogeneous Tumour Growth

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

$$N = P + Q + D$$



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

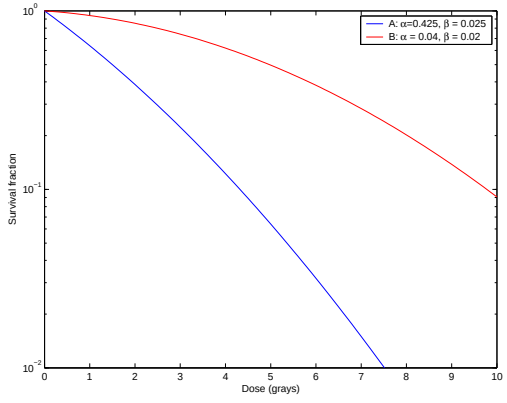
Suggestions

- Combine with earlier models to investigate the impact of different chemotherapeutic drugs eg target proliferating cells, target live tumour cells
- Adapt model to study interactions between normal and cancer cells and their differential response to therapy

Radiotherapy

- Let N_t denote the number of tumour cells at time t
- Experiments $\Rightarrow$ fraction of cells surviving dose D of radiotherapy is

$$\left(\begin{array}{c}\text{survival}\\ \text{fraction}\end{array}\right) = \frac{N_t^{after}}{N_t^{before}} = e^{-(\alpha D+\beta D^2)} \qquad \text{(the Linear-Quadratic Model)}$$



Typical cell survival curves based on the linear-quadratic model following a dose D of radiotherapy. The parameters α and β characterise the tissue's response to radiotherapy: α relates to cells that are killed instantly; $beta$ to cells that are damaged and die when they next try to divide.

Tried and Tested - Radiotherapy

- We assume that
  - Radiation is given at regular intervals, at times $\Delta t, 2\Delta t, \ldots$
  - The tumour grows exponentially between treatments so that

$$N_{t+\Delta t}^{before} = N_t^{after} e^{g\Delta t} \qquad \text{where } g = \text{tumour's growth rate}$$

- so that the tumour doubling time $t_2 = \ln 2/g$
- We now predict how tumour's size changes during a course of radiotherapy
  - Periods of exponential growth (between treatments)
  - Step changes in cell number (when treatment given)

Tried and Tested - Radiotherapy

- Let $N_0 =$ tumour size at $t = 0$
- When dose 1 given (at $t = \Delta t$) we have

$$N_{\Delta t}^{before} = \underbrace{N_0 e^{g\Delta t}}_{\text{growth between doses}} \quad \text{and} \quad N_{\Delta t}^{after} = \underbrace{N_{\Delta t}^{before}\, e^{-(\alpha D+\beta D^2)}}_{\text{shrinkage after therapy}}$$

- Combining these expressions we have

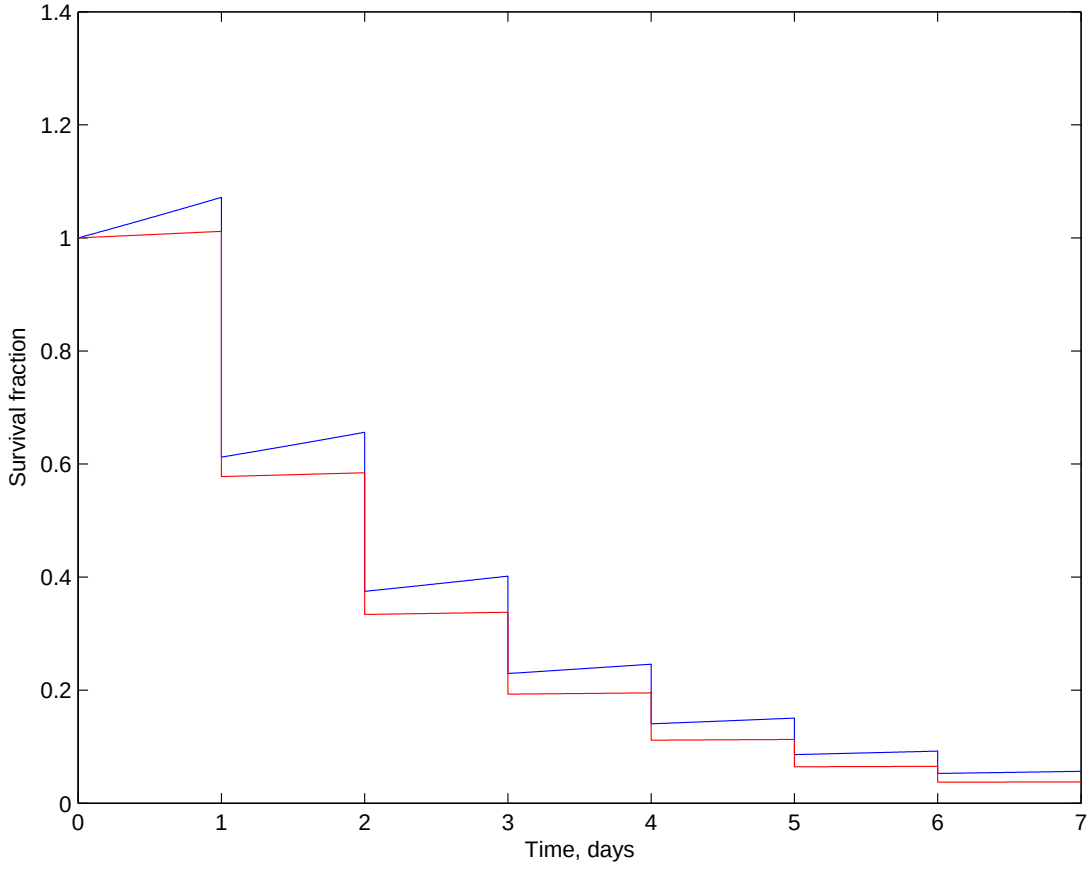
$$N_{\Delta t}^{after} = N_0\, e^{g\Delta t-(\alpha D+\beta D^2)}$$

- Similarly, after dose n (at $t = n\Delta t$)

$$N_{n\Delta t}^{after} = N_0\, e^{n[g\Delta t-(\alpha D+\beta D^2)]}$$

$$\Rightarrow \left(\begin{array}{c}\text{survival fraction}\\ \text{at end of schedule}\\ \text{i.e. after } n \text{ doses}\end{array}\right) = e^{n[g\Delta t-(\alpha D+\beta D^2)]}$$

Tried and Tested - Radiotherapy



Change in survival fraction following 1 week of conventional treatment ($D = 200$ rads) administered to tumours with different doubling times (Key: $t_2 = 10$ days, $t_2 = 60$ days). In both cases, $\alpha = 2 \times 10^{-3}$ rad^{-1} and $\beta = 4.0 \times 10^{-6}$ rad^{-2}.

Tried and Tested - Optimal Radiotherapy

- After n rounds of radiotherapy,

$$\text{(survival fraction)} = e^{n[g\Delta t-(\alpha D+\beta D^2)]}$$

- In practice, radiologists select n, Δt and D to minimise the survival fraction.

What prevents them using the largest doses possible?

SIDE EFFECTS: damage to healthy tissue

Which tissues will be most affected?

Tissues with rapid turnover eg normal connective tissue

Tried and Tested - Optimal Radiotherapy

- We estimate the damage following n rounds of radiotherapy to be

$$\text{Damage} = D\, n^a\, (\Delta t)^{-b} \qquad \text{where} \quad a = 0.65, \;\; b = 0.11$$

and Damage $< R_{tol} = 1800 =$ maximum damage that can be tolerated

- To design an optimal schedule,

Choose $n, \Delta t$ and D

to minimise survival fraction and damage to normal tissue

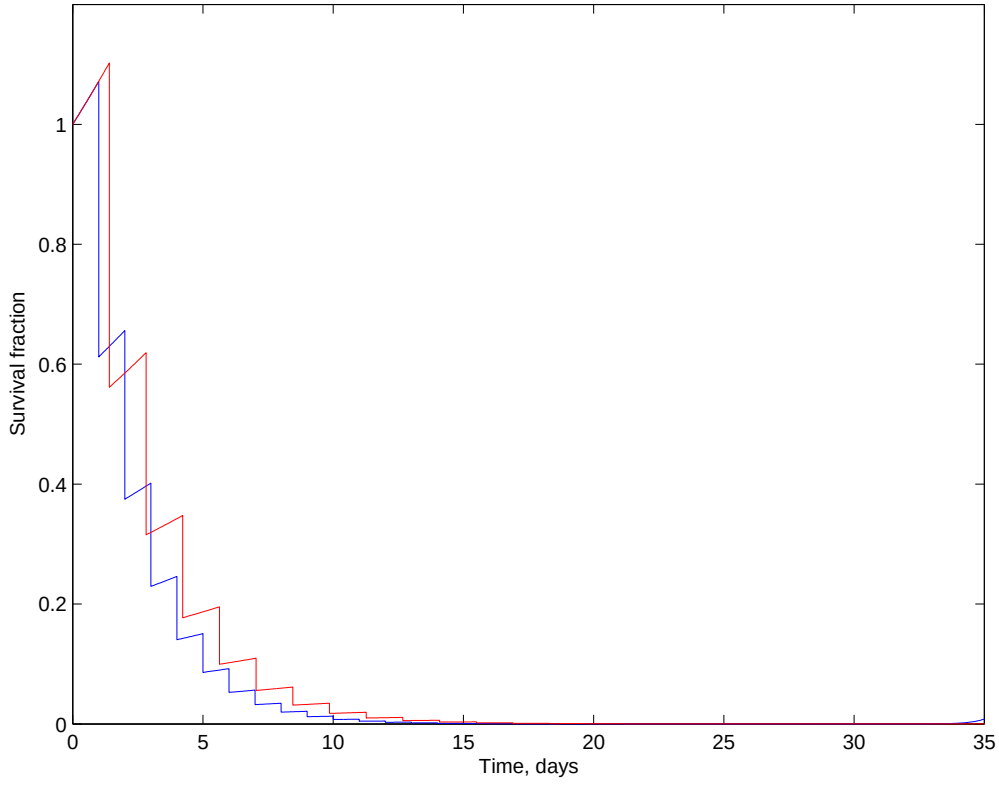
where

$$\text{(survival fraction)} = e^{n[g\Delta t - (\alpha D + \beta D^2)]}$$

- Using calculus, it is possible to show that the optimal schedule has

$$D = \frac{\alpha}{\beta}\,\frac{[1-(a+b)]}{[2(a+b)-1]}, \qquad \Delta t = \frac{b(\alpha D + \beta D^2)}{g(a+b)}, \qquad n = \left(\frac{R_{tol}}{D}\right)^{1/a} (\Delta t)^{b/a}$$

Tried and Tested - Optimal Radiotherapy



Comparison of response to conventional and optimal radiotherapy schedules (Key: conventional: $D = 200$ rads, $\Delta t = 1$ day, $n = 30$ days, optimal: $D = 230.8$ rads, $\Delta t = 1.41$ day, $n = 25$). Benefit from optimal therapy evident at later times.

Tried and Tested - Optimal Radiotherapy

Doubling Time t_2 (days)	Dose D (rads)	Interval Δt (days)	Number of doses, n	Survival Fraction	Survival Fraction
1	230.8	0.14	17	5.8×10^{-5}	5.4×10
10	230.8	1.4	25	5.5×10^{-7}	4.0×10^{-7}
30	230.8	4.23	30.0	2.9×10^{-8}	1.0×10^{-7}
60	230.8	8.45	34	3.3×10^{-9}	7.1×10^{-8}
90	230.8	12.70	36	8.3×10^{-10}	6.4×10^{-8}

Table highlighting the difference between conventional and optimal radiotherapy schedules for tumours with different doubling times

Notes:

- At end of treatment, tumour recommences exponential growth
- Also

$$\left(\begin{array}{c}\text{damage due to}\\ \text{conventional schedule}\end{array}\right) = 1825 > \left(\begin{array}{c}\text{tolerated}\\ \text{damage}\end{array}\right) = R_{tol} = 1800$$

For further details, see, for example: Wheldon et al, *Brit J Radiol* **50**: 681-682 (1977).

Radiotherapy - Comments

- We've used a simple model to determine optimal radiotherapy protocols for tumours with different doubling times.
- Could we do better?
  - Not all tumours undergo exponential growth
  - Tumours are highly irregular, their spatial structure changing markedly over time
  - A tissue's response to radiotherapy depends on the local oxygen concentration
- We could extend our model in many ways
  - Different tumour growth laws (e.g. Gompertz, logistic)
  - Model tumour's spatial structure and include local oxygen concentration
  - Allow multiple tumour populations, with different radio-sensitivity
  - Different radiotherapy protocols
- It is often difficult (impossible) to obtain accurate estimates of parameters associated with more complex models.
- Hence, we must compromise, using a model which exploits information that can be reliably and accurately collected

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
  - ...

Ideas for Future Work

- Extend chemotherapy models to include the response of normal cells
- Include chemotherapy in heterogeneous models of tumour growth
- Introduce time delays to model e.g. immune response (c.f. Leon Glass' lectures)