Using Macrophages to Treat Cancer

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Talk Outline

- Background biology
- Model development
- Numerical results
- Summary and discussion

Background Biology

Common anti-cancer strategies include:

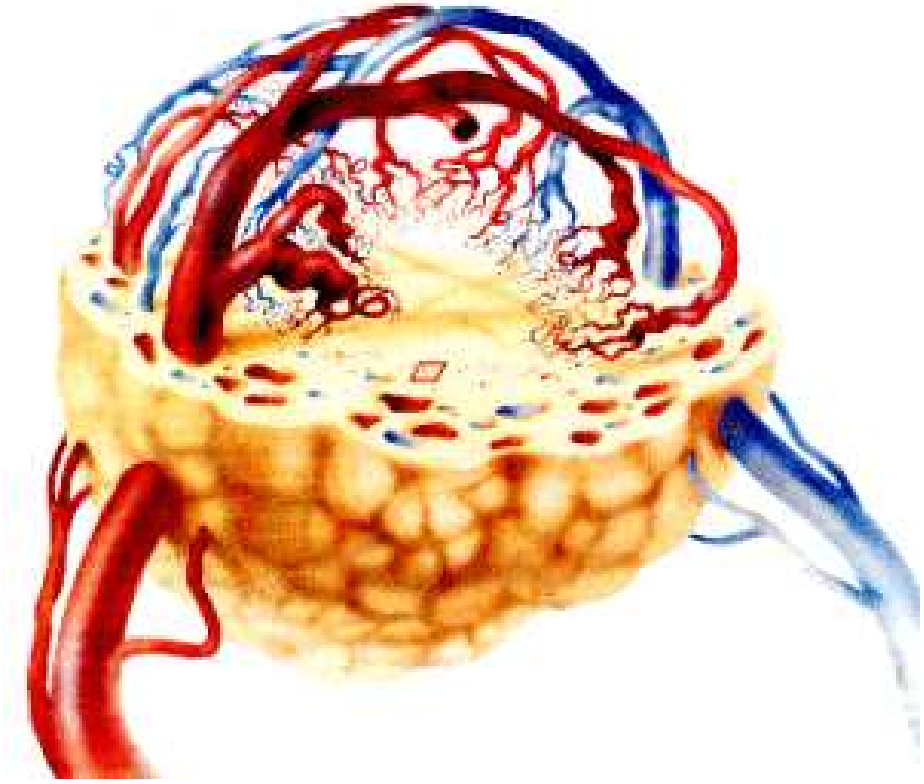
- Surgery
- Radiotherapy
- Chemotherapy

Limitations of these methods are driving the search for novel, complementary therapies.

In this talk, we will discuss a promising alternative.

Background Biology

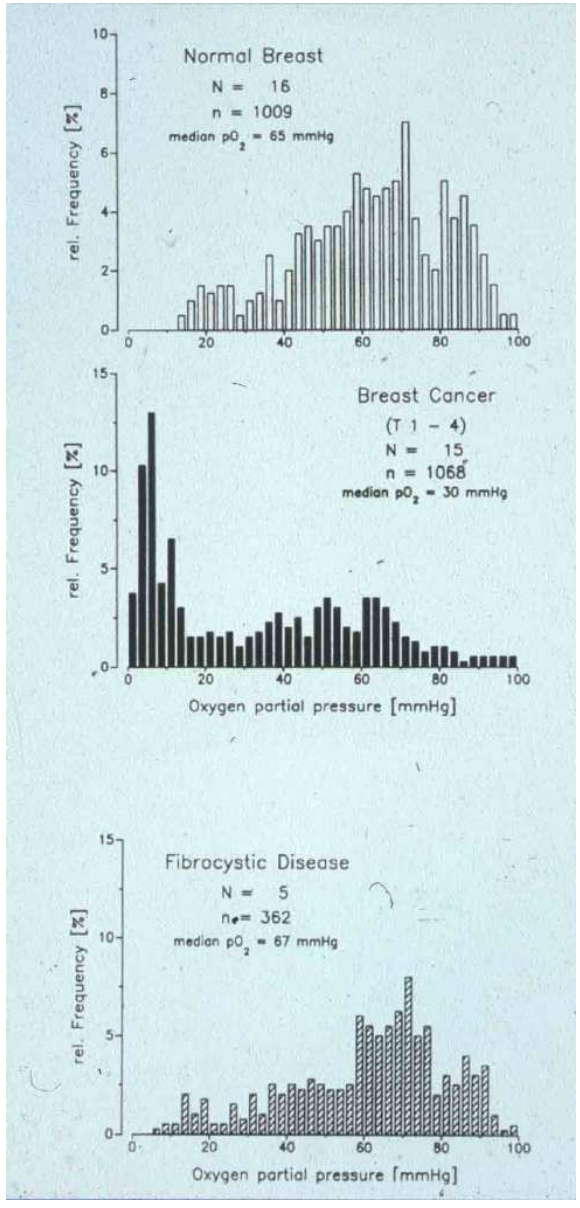
By the time tumours can be detected clinically, they usually have a blood supply:



Schematic Diagram of a Vascular Tumour

Background (continued)

And regions of low oxygen or hypoxia may be widespread:



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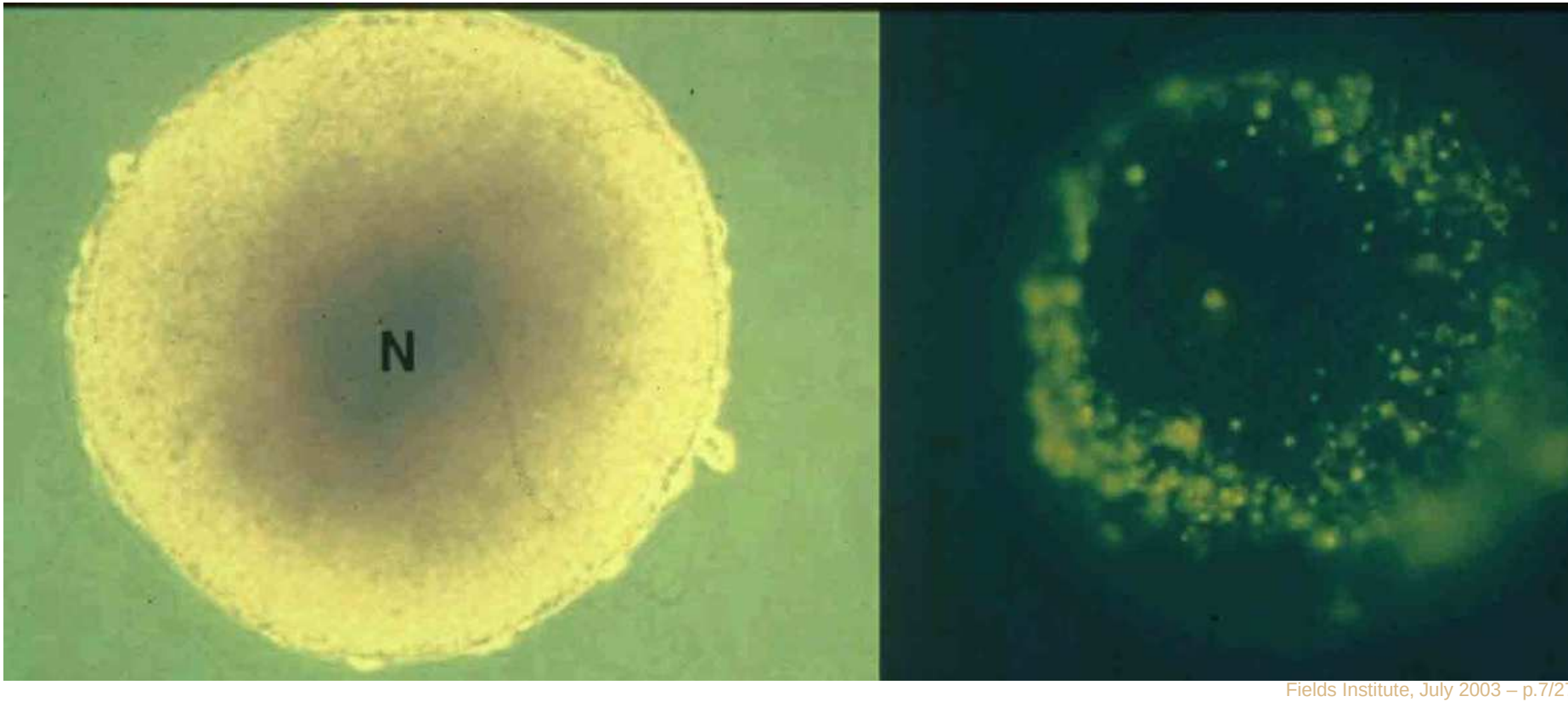
- Reduced cell kill
  - Drugs that target rapidly dividing tumour cells are less effective under hypoxia
- Initiators of angiogenesis
  - Many tumour cells respond to hypoxia by producing chemicals that stimulate the growth of new blood vessels to the tumour

Background (continued)

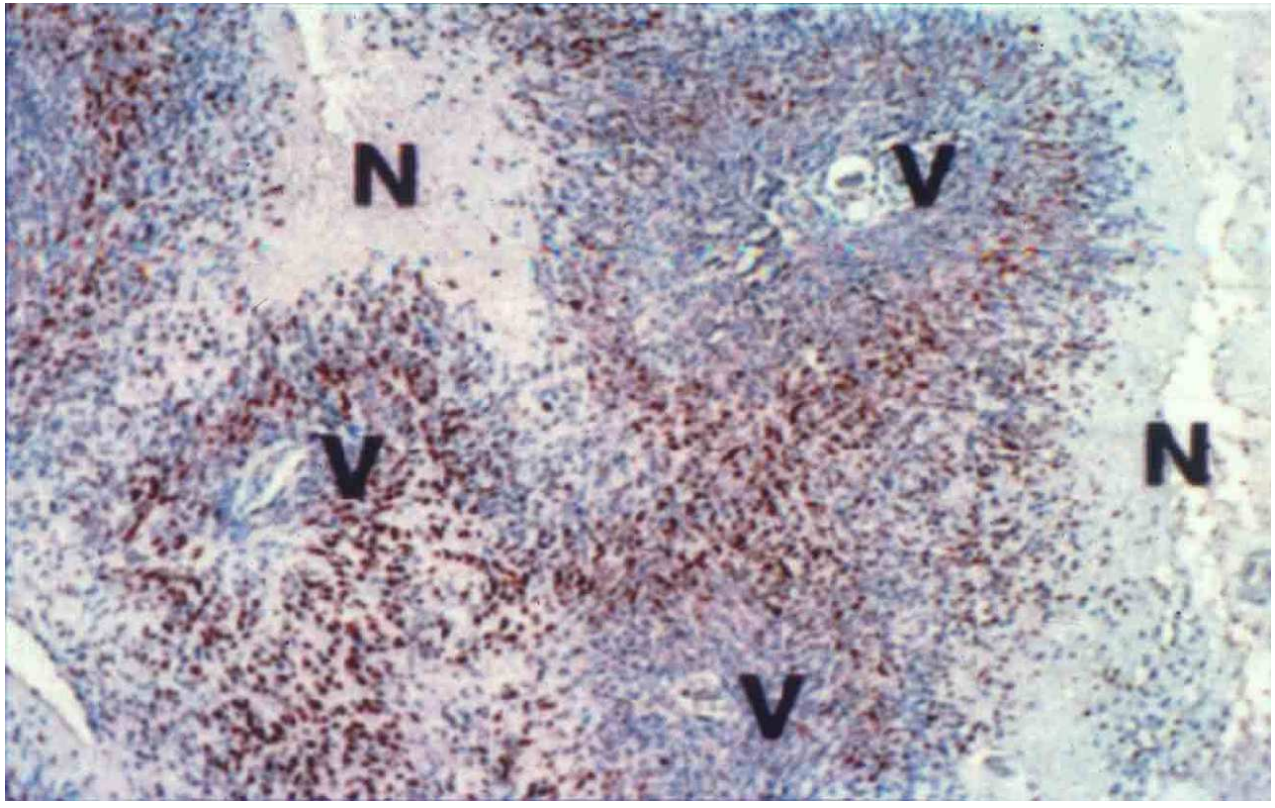
A possible life-line:

THE MACROPHAGE

Macrophages are white blood cells which accumulate in hypoxic tumour regions in vitro



And in vivo

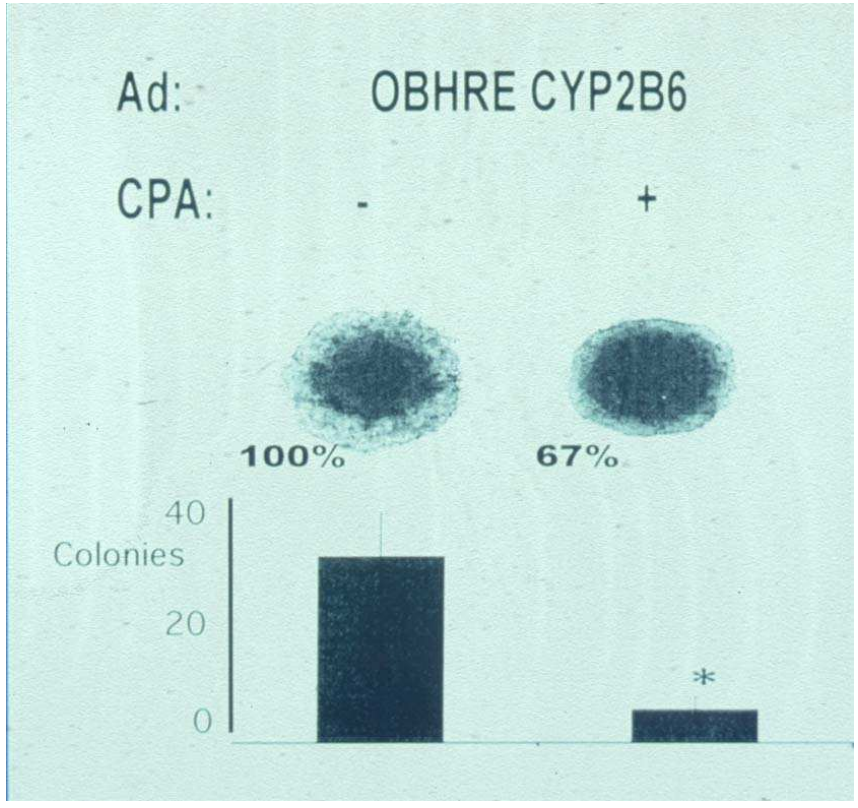


The Aim

- Extract and genetically engineer a patient's own macrophages
- Inject modified macrophages back into patient
- Macrophages migrate to hypoxic regions where they release chemicals which
  - kill tumour cells
  - halt the growth of new blood vessels

The Reality

Laboratory results are promising ...



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- Can engineered macrophages displace normal macrophages (and tumour cells)?
- How many macrophages should be engineered for optimum response?
- What drugs should be used?
- Coordination with other therapies?

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- Can engineered macrophages displace normal macrophages (and tumour cells)?
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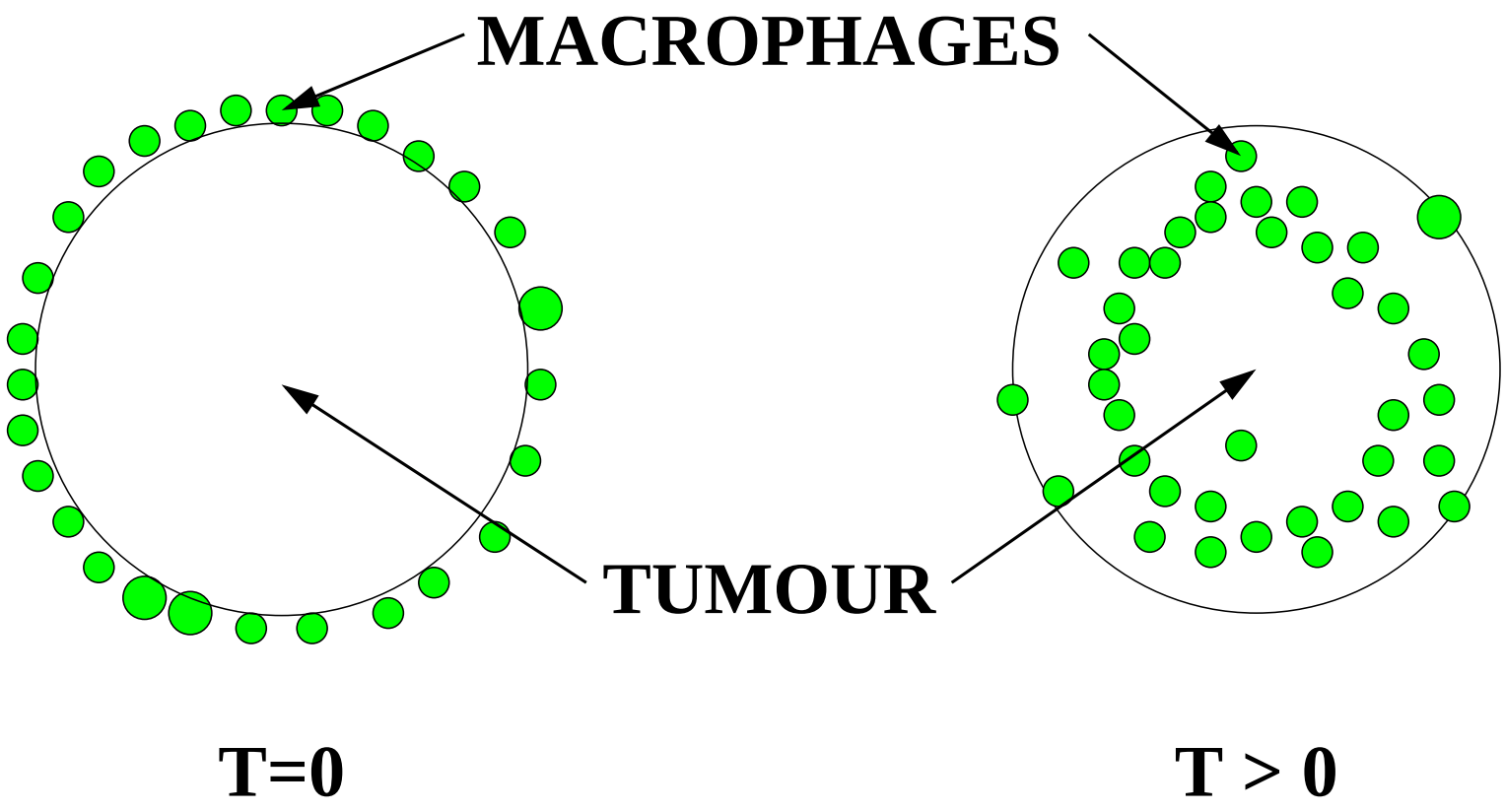
We now show how mathematical modelling can help to address these issues.

Schematic Diagram



Macrophages infiltrating a tumour spheroid.

Modelling Assumptions

- The tumour comprises three constituents
  - tumour cells, m,
  - macrophages, l
  - cellular material, n

- Cellular material is
  - produced on cell death
  - consumed during proliferation

- All constituents are transported with a common advection velocity, $\boldsymbol{v}$
- Cell proliferation and death are regulated by a generic nutrient, c (eg oxygen)
- Under hypoxia, the tumour cells (and macrophages) produce macrophage chemoattractant, a
- The macrophages bind to and kill tumour cells at a nutrient-dependent rate
- Radial symmetry

The Model Equations

Tumour cells, $m(r,t)$

$$\frac{\partial m}{\partial t} = \nabla.(\underbrace{D_m \nabla m - \boldsymbol{v} m}_{\equiv \boldsymbol{v}_m m}) + \underbrace{p_m(c) n m}_{\text{proliferation}} - \underbrace{d_m(c) m}_{\text{natural death}} - \underbrace{k(c) l m}_{\text{lysis}}$$

Macrophages, $l(r,t)$

$$\frac{\partial l}{\partial t} = \nabla.(D_l \nabla l - \chi l \nabla a - \boldsymbol{v} l) - d_l(c) l$$

Cellular material, $n(r,t)$

$$\frac{\partial n}{\partial t} = \nabla.(D_n \nabla n - \boldsymbol{v} n) + d_m(c) m + k(c) l m + d_l(c) l - p_m(c) n m$$

Nutrient, $c(r,t)$

$$0 = \nabla^2 c - d_c(c)(l+m)$$

Chemoattractant, $a(r,t)$

$$0 = \nabla^2 a + p_{al}(c) l + p_{am}(c) m - d_a a$$

The Model Equations (continued)

Advection velocity, $\boldsymbol{v} = (v(r,t), 0, 0)$

No voids $\Rightarrow n + m + l = 1$ so that

$$v = D_l \frac{\partial l}{\partial r} - \chi l \frac{\partial a}{\partial r} + D_m \frac{\partial m}{\partial r} + D_n \frac{\partial n}{\partial r}$$

Tumour boundary, $r = R(t)$

The boundary moves with the tumour cell velocity so that

$$\frac{dR}{dt} = v_m(R,t) = \left[v - \frac{D_m}{m} \frac{\partial m}{\partial r} \right]_{r=R(t)}$$

The Boundary and Initial Conditions

- Symmetry about $r = 0$
- On the tumour boundary, $r = R(t)$,

$$c = c_\infty \quad \text{and} \quad \frac{\partial a}{\partial r} = h_a(a_\infty - a)$$

$$-l(v_l - v_m) = h_l(l_\infty - l) \quad \text{and} \quad -n(v_n - v_m) = h_n(n_\infty - n)$$

- At $t = 0$

$$l(r,0) = 0, \;\; m(r,0) = m_0(r), \;\; n(r,0) = 1 - m_0(r), \;\; R(0) = R_0$$

NOTE

$$\frac{dR}{dt} = \left[v - \frac{D_m}{m}\frac{\partial m}{\partial r}\right]_{r=R(t)} \equiv [h_l(l_\infty - l) + h_n(n_\infty - n)]_{r=R(t)}$$

$$\Rightarrow \frac{d}{dt}\begin{pmatrix}\text{tumour}\\ \text{volume}\end{pmatrix} = [h_l(l_\infty - l) + h_n(n_\infty - n)] \times \begin{pmatrix}\text{tumour}\\ \text{surface area}\end{pmatrix}$$

Numerical Simulations

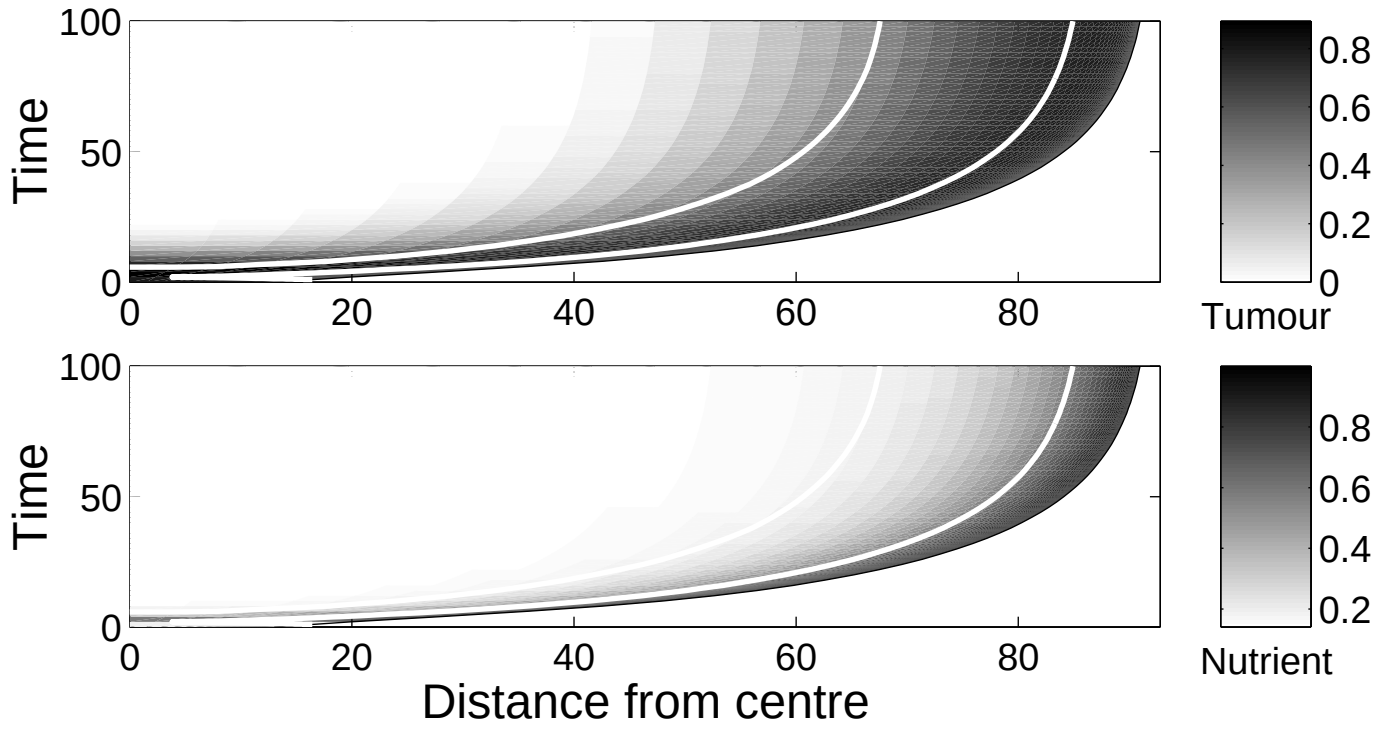
Recall the following questions of interest:

- Can engineered macrophages displace tumour cells (and normal macrophages)?
- What drugs should be used?
- How many macrophages should be engineered?

We address these questions by presenting a series of numerical simulations showing spheroid growth with:

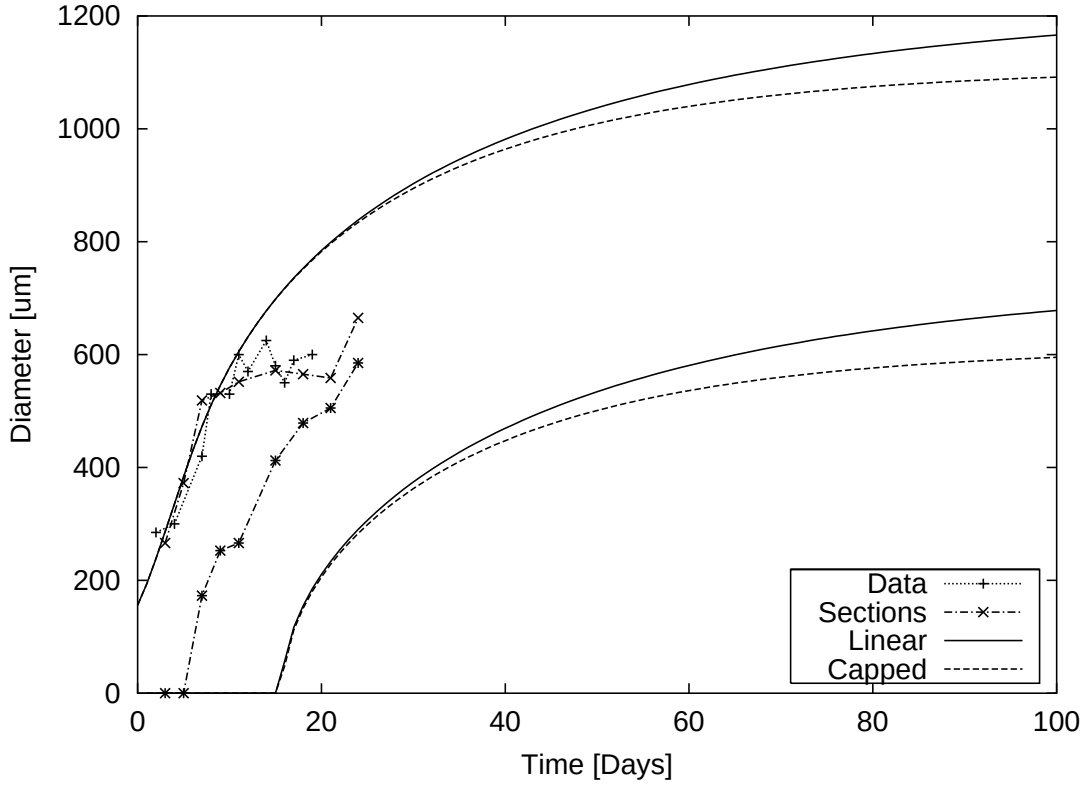
- (A) No macrophages
- (B) Infiltrating macrophages, with no tumour cell kill
- (C) Infiltrating macrophages, with tumour cell kill
- (D) Infiltration by normal and engineered macrophages

(A) No macrophages



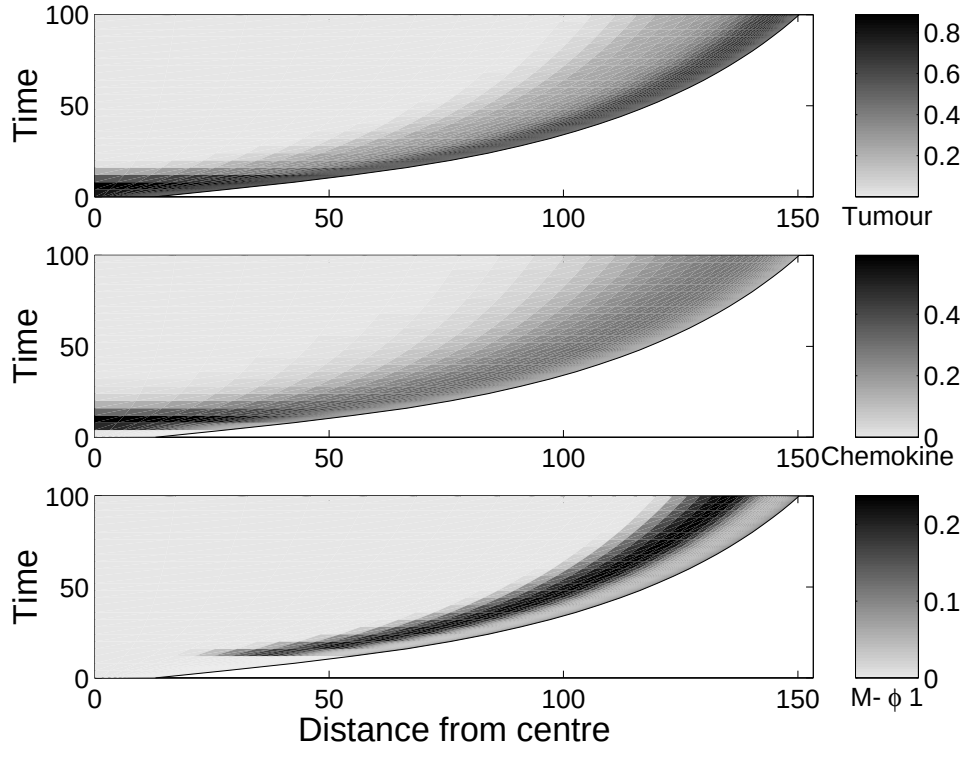
Spheroid growth

(A) No macrophages



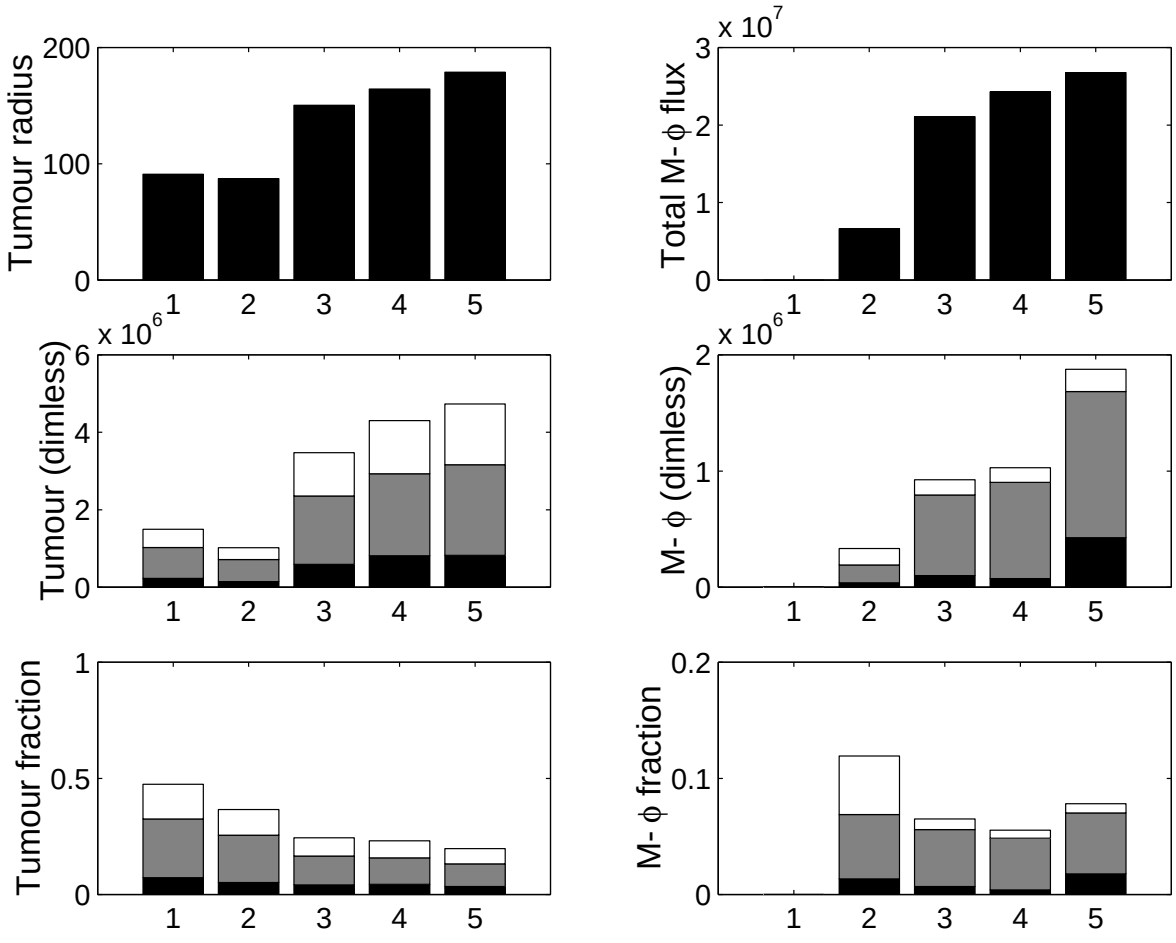
Spheroid growth alone: comparison with experimental data.

(B) Infiltrating macrophages, with no cell kill



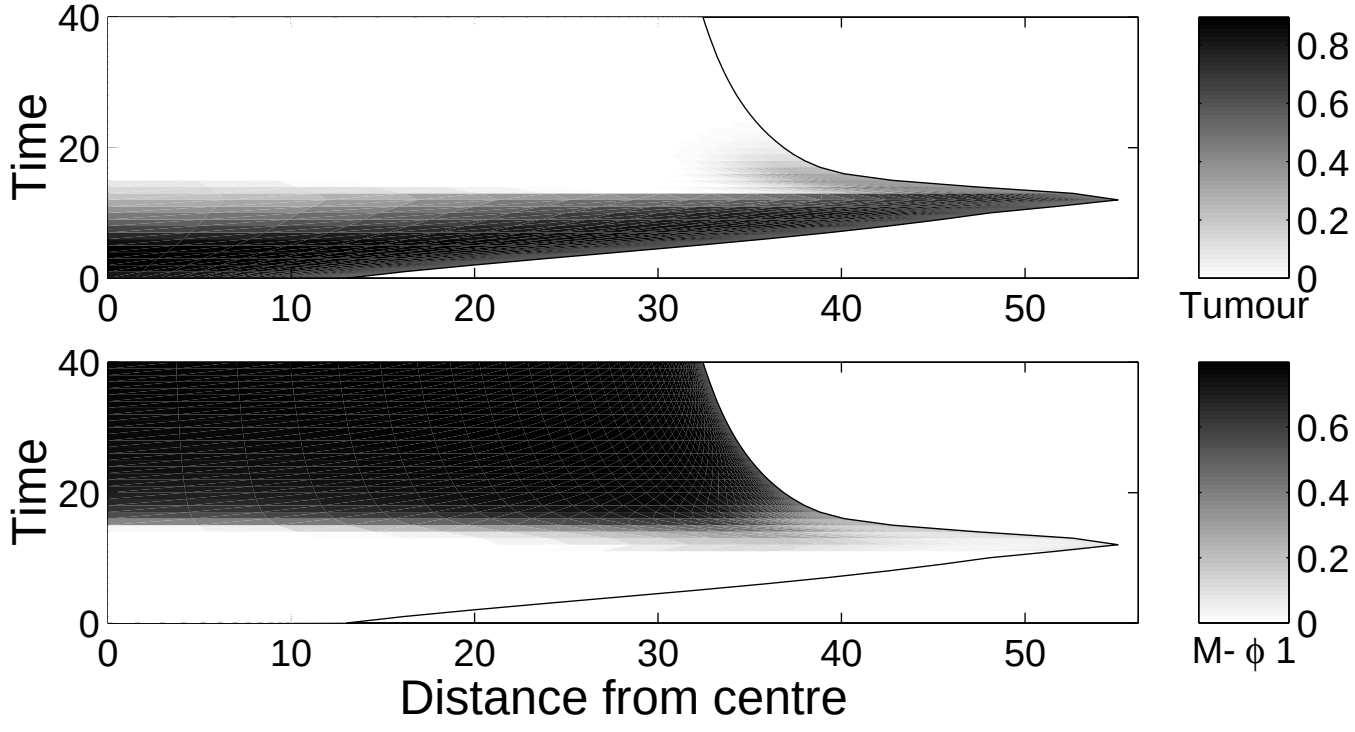
With chemotaxis, significant macrophage accumulation occurs in the hypoxic region.

(B) Infiltrating macrophages, with no cell kill



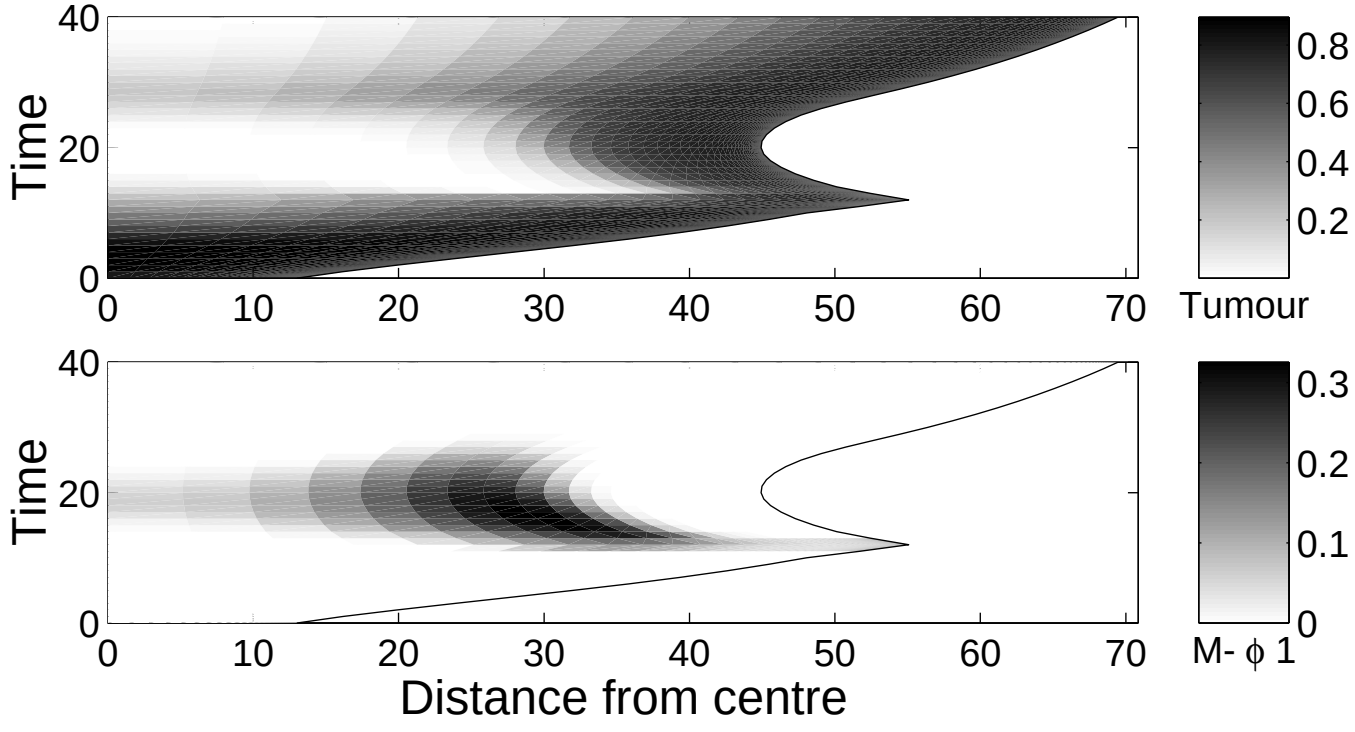
Spheroid properties at $t = 100$. (1) spheroid only; (2) spheroid and macrophages with random motion alone; (3) spheroid and macrophages with chemotaxis; (4) as (3), but macrophages produce chemoattractant; (5) as (3), but macrophage death rate halved.

(C) Infiltrating macrophages, with cell kill



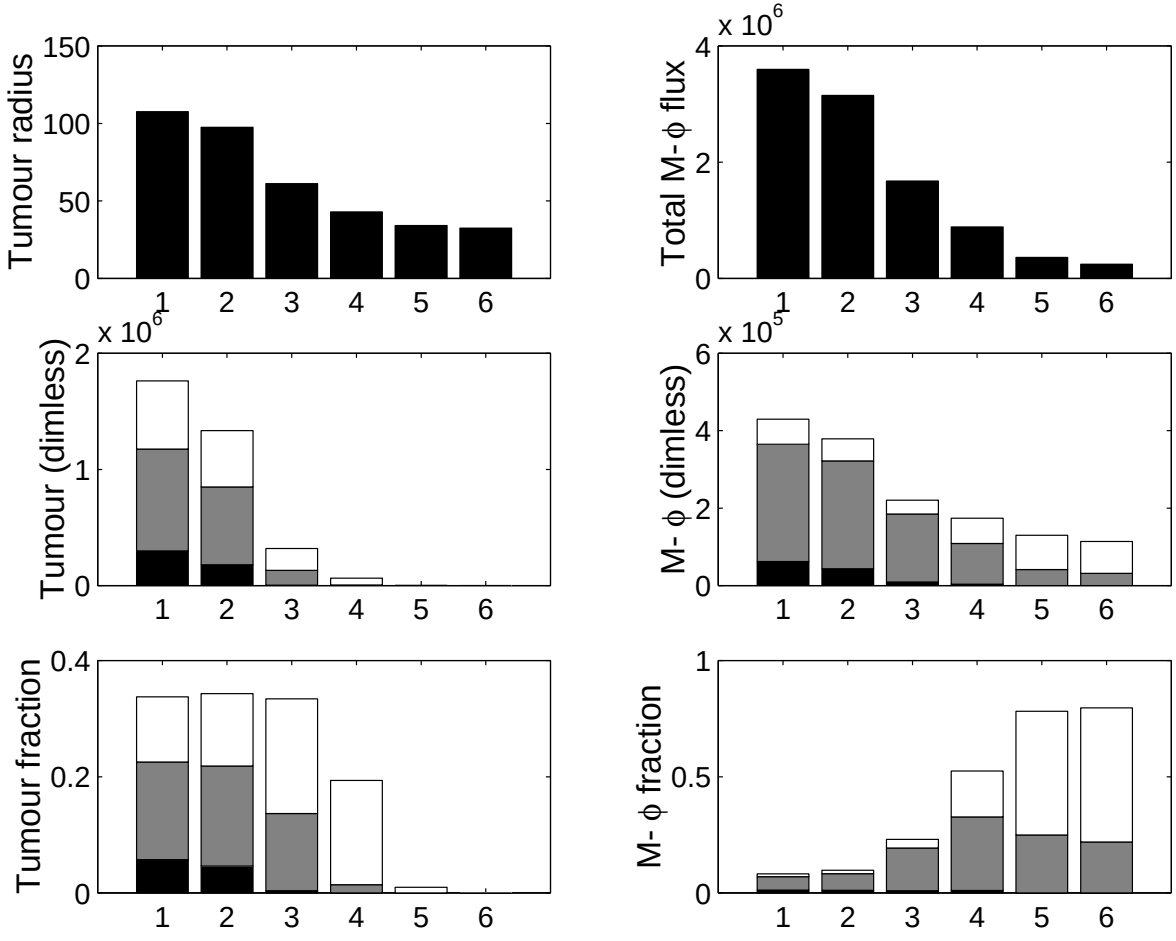
Reduction in spheroid growth caused by continuous infusion with engineered macrophages.

(C) Infiltrating macrophages, with cell kill



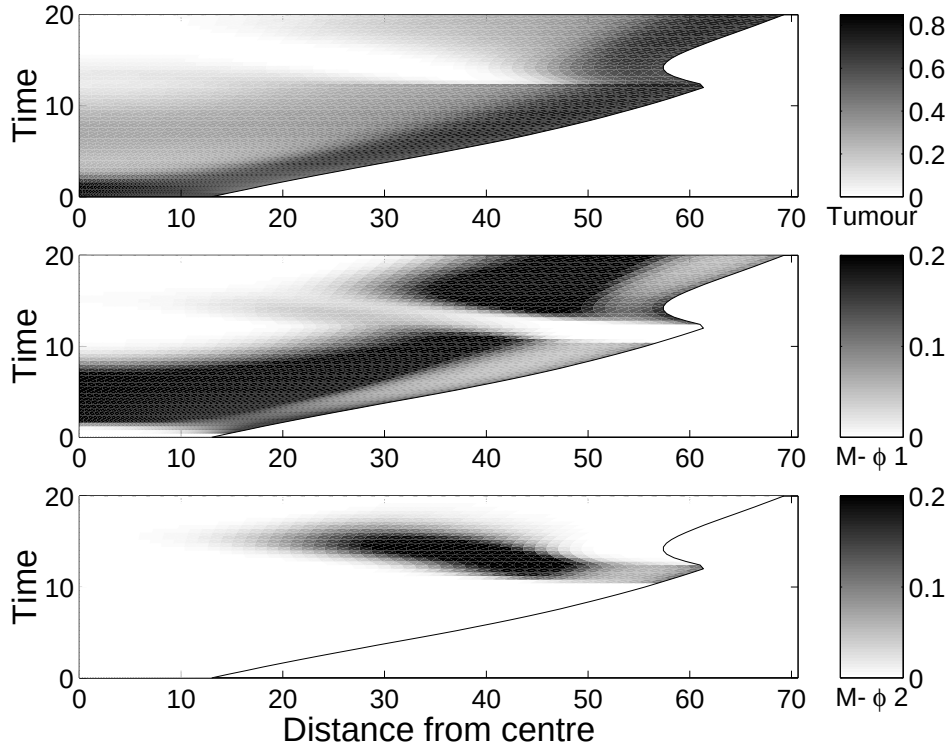
Macrophages are applied between days 10 and 12. The spheroid shrinks until macrophage levels decline and growth resumes.

(C) Infiltrating macrophages, with cell kill



Spheroid properties at $t = 40$. Macrophage lysis rate increases from (1) through to (6).

(D) Infiltration by normal and engineered macrophages



Infiltration by two macrophage populations. The second population kills the tumour cells under hypoxia

Discussion

- Macrophages may displace tumour cells within hypoxic tumour regions
- Genetically-engineered can produce tumour shrinkage and may erradicate all hypoxic tumour cells
- We can use our model framework to test different treatment protocols
  - Timing and strength of repeat macrophage injections
  - Coordination with therapies that target proliferating cells
  - Comparison with ongoing experiments
  - More accurate description of drug activity (the bystander effect)
  - Manipulate engineered macrophages (alter chemokine receptor expression) to optimise therapeutic response
- We have considered avascular tumours growing in vitro.
- To assess the value of this therapy in vivo, we need to develop realistic models of vascular tumour growth.
- First, however, we should consider avascular growth in vivo

Summary

- There is now a well-established, theoretical literature describing many aspects of solid tumour growth, including:
  - avascular tumour growth
  - tumour invasion
  - angiogenesis
- We are now in a unique position to tailor these models to specific situations.
- Such modifications present numerous mathematical challenges.
- By working with biomedical researchers, we can generate complementary insight into new therapies as they are being developed.