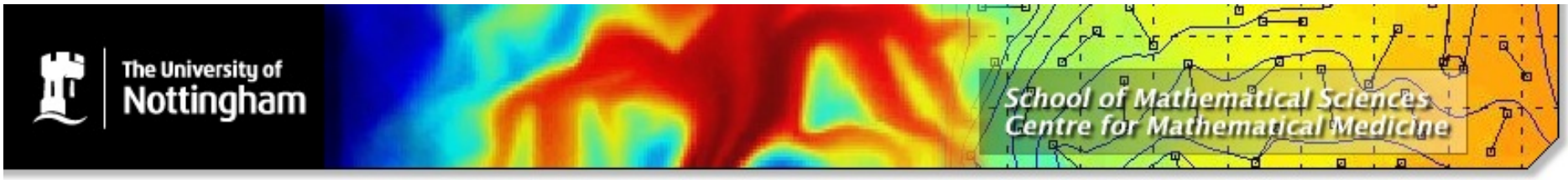
Modelling Solid Tumour Growth

Lecture 5: Summary and Future Directions

Helen Byrne

helen.byrne@nottingham.ac.uk



Outline

- Summary of Previous Lectures
- Current Modelling Challenges
- Therapeutic Challenges

Summary of Previous Lectures

- Avascular Growth
  - ODE models - spatially-averaged models
  - 1D PDE models - radially-symmetric models
  - 2- and 3D PDE models - symmetry-breaking or invasion
- Angiogenesis
  - PDE models - analytically tractable in 1D
  - Probabilistic models - realistic simulations in 2- and 3D

Current Modelling Challenges

- Tumour Progression and Initiation
- Cellular heterogeneity within tumour:
  - clonal cell populations, vasculature, ECM
- Coupling mechanical effects and growth:
  - stress may influence proliferation/death
  - proliferation/death may influence stress
- Coupling across spatial scales:
  - subcellular, cellular and macroscale phenomena are linked
  - hybrid models that couple PDE/ODE models to discrete models
- Specialising models:
  - e.g.gliomas and ductal carcinoma in situ (DCIS)

We will discuss briefly:

- Gliomas (Swanson et al. (2000) *Cell. Prolif.* **33**: 317-329)
- DCIS (Franks et al. (2005) *J. theor. Biol.* **232**: 523-543)
- Multiphase modelling (Breward et al. (2002) *J. Math. Biol.* **45**: 125-152)
- Genetic engineering of macrophages
  (Owen et al. (2004) *J. theor. Biol.* **226**: 377-391)
- Multiscale model of vascular tumour growth
  (Alarcon et al. (2003) *Prog. Biophys Mol Biol* **85**: 451-472)

Gliomas

- Let c = tumour cell density at location x and time t

- Assume that c satisfies

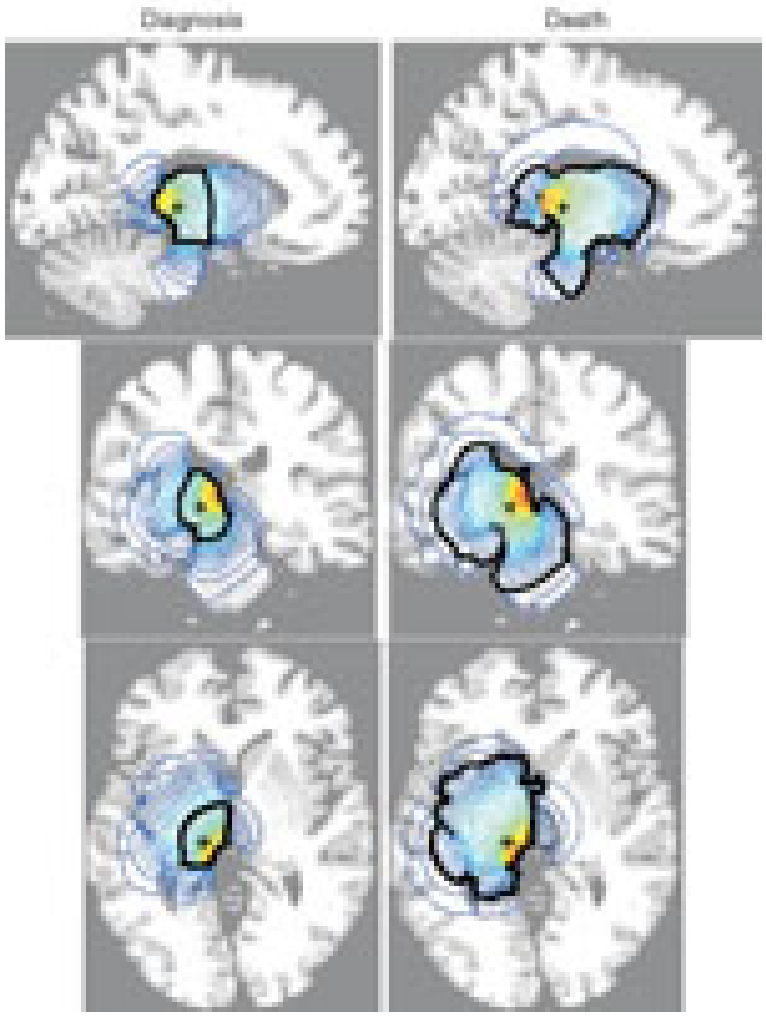
$$\frac{\partial c}{\partial t} = \nabla.(D\nabla c) + \rho c$$

where the diffusion coefficient D and cell proliferation rate ρ may vary with spatial location ie from grey to white matter

- Models yield predictions re true extent of tumour spread when calibrated against MRI scans

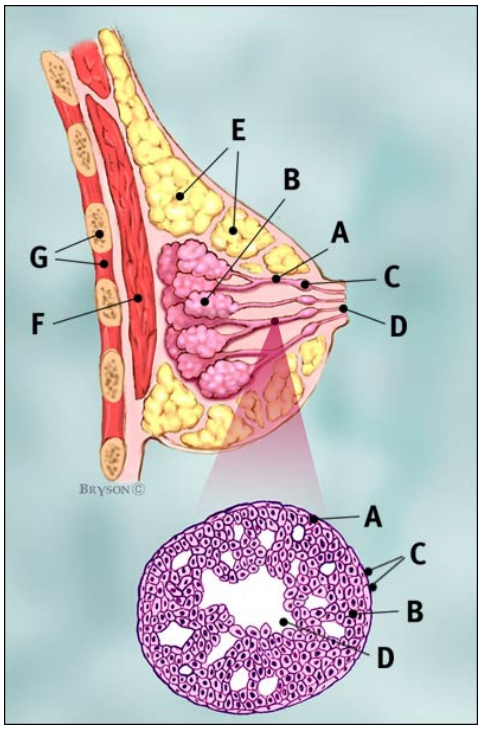
- See: Swanson et al. (2000) *Cell. Prolif.* **33**: 317-329

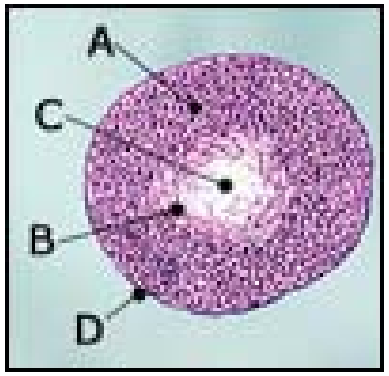
Gliomas

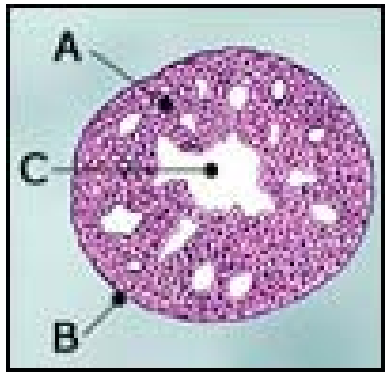


Series of images showing predicted spread of gliomas from detection to patient death

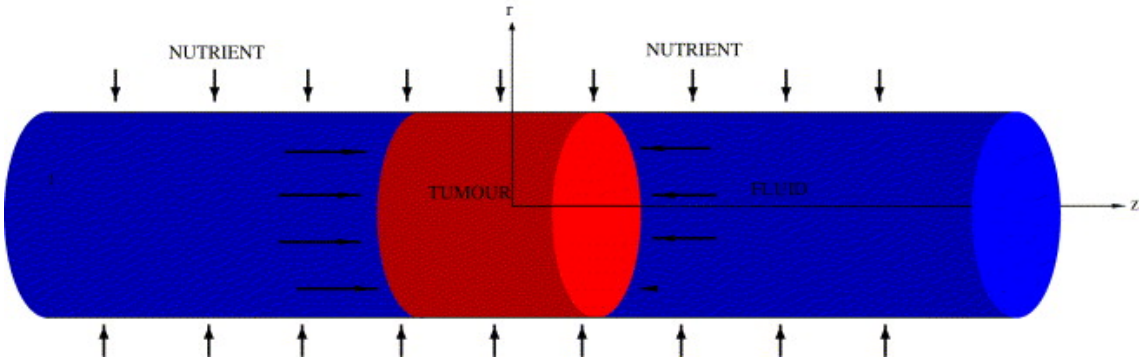
DCIS







DCIS

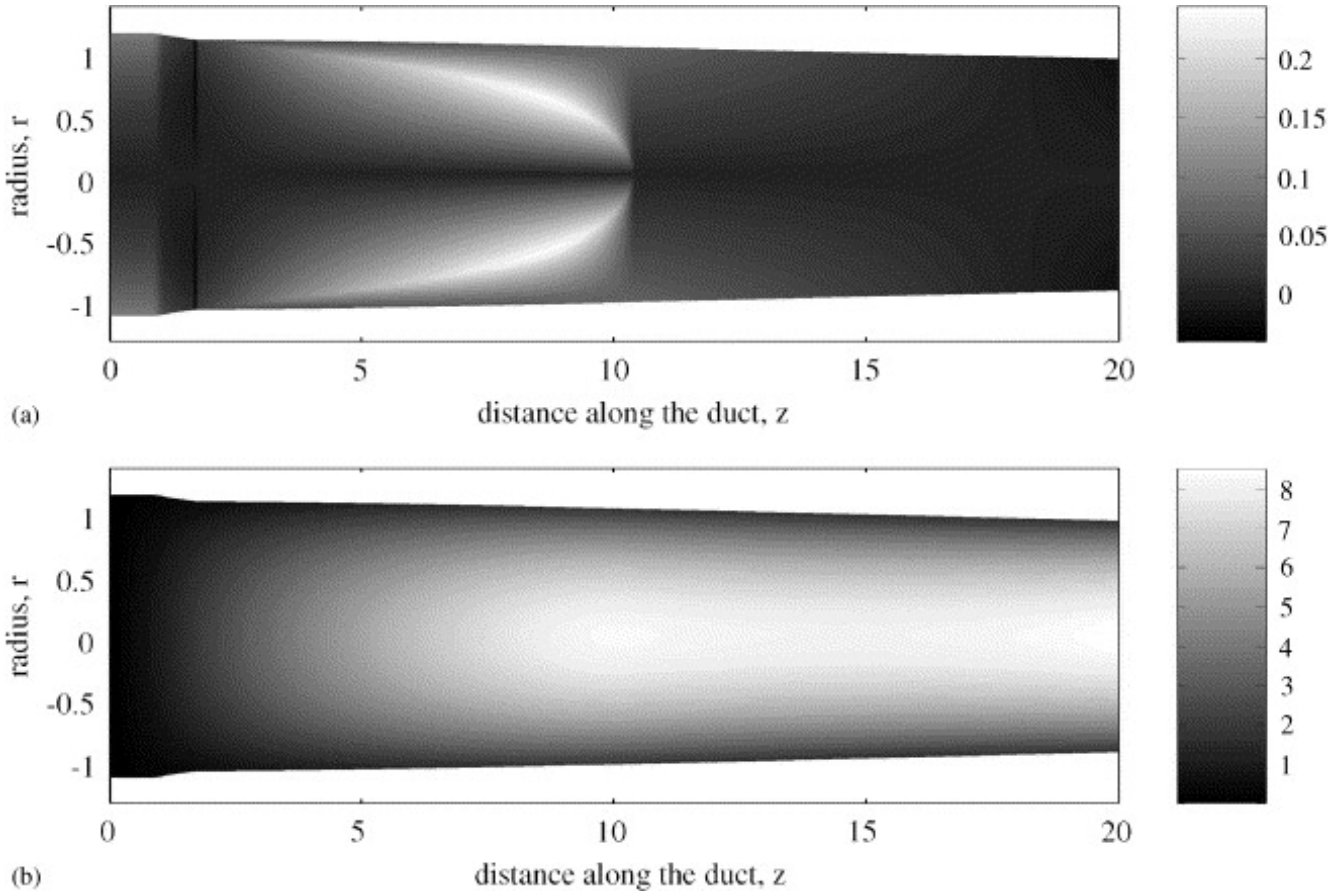


A schematic diagram showing the initial configuration of the duct and tumour

Model Framework

- Nutrient-limited model of avascular tumour growth within cylindrical duct
- Mechanical model of membrane deformation
- Models coupled via conditions on duct wall: expansive forces caused by net tumour growth balance forces that develop in membrane
- See: Franks et al. (2005) *J. theor. Biol.* **232**: 523-543

DCIS



Series of plots showing (a) the radial velocity and (b) the axial velocity of the tumour cells at $t = 2$

DCIS

- Models yield predictions about
  - Position at which duct wall likely first to be breached
  - Likely mechanism for production of membrane-degrading proteases i.e. mechanical stress rather than hypoxia

Multiphase Modelling

- Theoretical framework that accounts for
  - Tumour heterogeneity (+ immune cells, ECM, vessels, ...)
  - Constitutive assumptions (eg elastic, visco-elastic, ...)
  - Mechanical effects (proliferation, ECM deformation, ...)
  - Interactions between species (eg cell-ECM drag, phase change)
- Builds on well-founded physical principles
  - Principles of Mass and Momentum Balance (solid mechanics!)
  - Closure by specification of suitable constitutive laws

Multicell Spheroids: Two Phase Model

The Mass Balance Equations

Tumour cells, $n(x,t)$:

$$\frac{\partial n}{\partial t} + \underbrace{\frac{\partial}{\partial x}(v_n n)}_{\text{advection}} = \underbrace{S_n}_{\substack{\text{net prolif.} \\ \text{rate}}}$$

Extracellular fluid, $w(x,t)$:

$$\frac{\partial w}{\partial t} + \frac{\partial}{\partial x}(v_w w) = S_w \equiv -S_n$$

The Momentum Equations

Tumour cells, $n(x,t)$:

$$0 = \frac{\partial}{\partial x}(n\sigma_n) + F_{nw} + p\frac{\partial n}{\partial x}$$

Extracellular fluid, $w(x,t)$:

$$0 = \underbrace{\frac{\partial}{\partial x}(w\sigma_w)}_{\substack{\text{internal} \\ \text{forces}}} - \underbrace{F_{nw}}_{\text{drag}} + \underbrace{p\frac{\partial w}{\partial x}}_{\substack{\text{interfacial} \\ \text{effects}}}$$

Multicell Spheroids: Constitutive Assumptions

No voids: $n + w = 1$

Stress tensors:

$$\sigma_w = -p_w = -p, \qquad \sigma_n = -p_n + \underbrace{2\mu_n \frac{\partial v_n}{\partial x}}_{\text{viscous effects}}, \qquad p_n = p + \Sigma_n(n)$$

$\mu_n \simeq$ cells' affinity for cells of same type: $\mu_n \downarrow$ as degree of differentiation $\uparrow$

Drag term: $F_{nw} = k(n)(v_w - v_n)$

Net proliferation rate: $$S_n = \left(\frac{S_0 c}{1 + S_1 c}\right) nw - \frac{S_2 + S_3 c}{1 + S_4 C} n$$

where nutrient $c(x,t)$ solves: $$0 = \frac{\partial^2 c}{\partial x^2} - \frac{Q_0 n c}{1 + Q_1 c}$$

Tumour boundary: $\frac{dR}{dt} = v_n(R,t)$

Multicell Spheroids: Model Simplification

'No voids' $\Rightarrow$ eliminate w: $\quad w = 1 - n$

Mass balances + 'no voids' (+ symmetry about $x = 0$) $\Rightarrow$ eliminate v_w:

$$nv_n + wv_w = 0 \quad \Rightarrow \quad v_w = -\frac{nv_n}{w}$$

Overall system momentum balance:

$$0 = \frac{\partial p}{\partial x} + \frac{\partial}{\partial x}(n\Sigma_n) - 2\mu_n \frac{\partial}{\partial x}\left(n\frac{\partial v_n}{\partial x}\right)$$

Momentum balance for w:

$$0 = -w\frac{\partial p}{\partial x} - k(v_w - v_n) \quad \Rightarrow \quad \frac{\partial p}{\partial x} = \frac{kv_n}{(1-n)^2}$$

Multicell Spheroids: Remarks

Substitute for w, v_w and $\frac{\partial p}{\partial x}$:

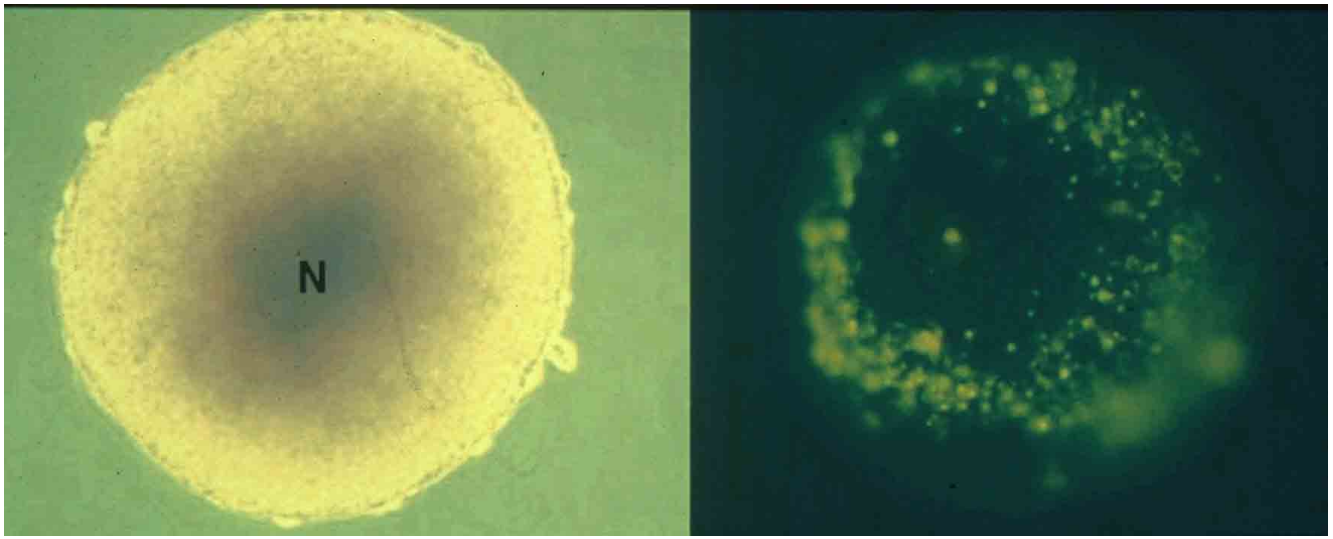
$$\frac{\partial n}{\partial t} + \frac{\partial}{\partial x}(n v_n) = 0,$$

$$0 = \frac{\partial^2 c}{\partial x^2} - \frac{Q_0 n c}{1 + Q_1 c}, \quad \frac{dR}{dt} = v_n(R, t)$$

$$0 = 2\mu_n \frac{\partial}{\partial x}\left(n \frac{\partial v_n}{\partial x}\right) - \frac{k v_n}{(1-n)^2} - \frac{\partial}{\partial x}(n \Sigma_n)$$

- If $\mu_n \longrightarrow 0$ model is similar to early tumour growth models but may become ill-posed
- Extensions to include ECM, vessels are (relatively) straightforward
- Many modelling challenges: interactions between 2+ phases, choice of consitutive laws, ...

Genetically Engineered Macrophages

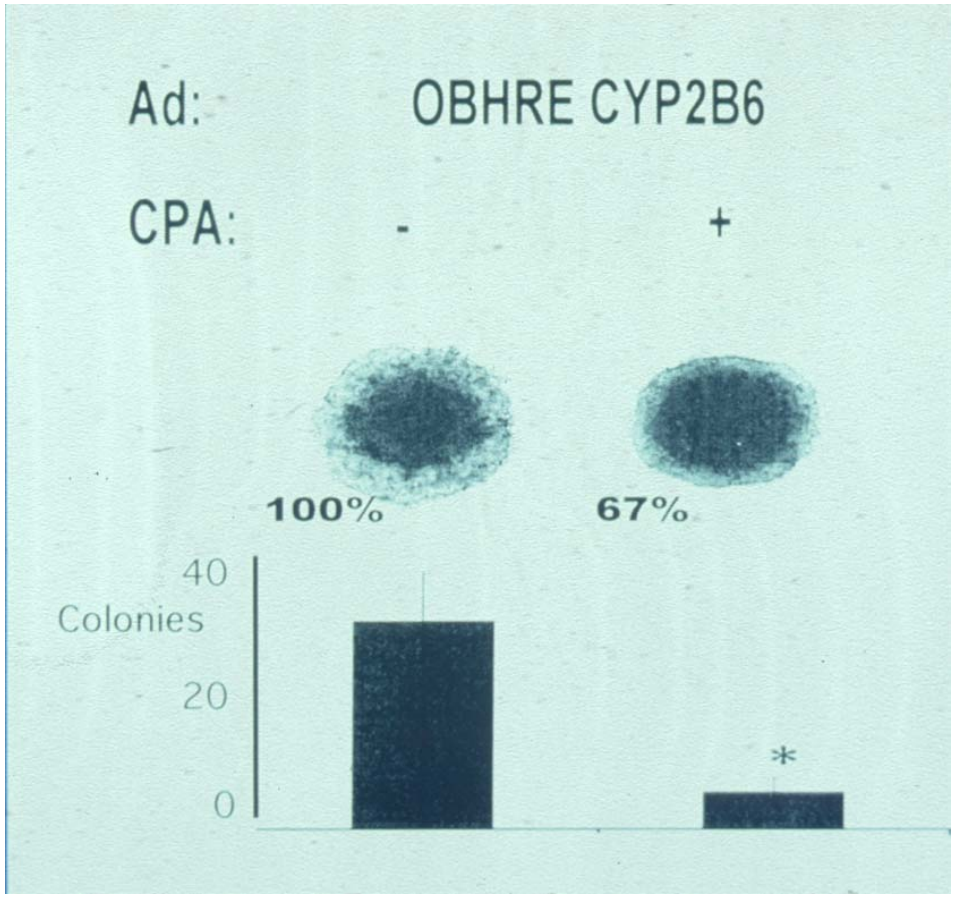


Macrophages are white blood cells which accumulate in hypoxic tumour regions

Genetically Engineered Macrophages: 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

Genetically Engineered Macrophages: The Reality



Laboratory results are promising

Genetically Engineered Macrophages: The Reality

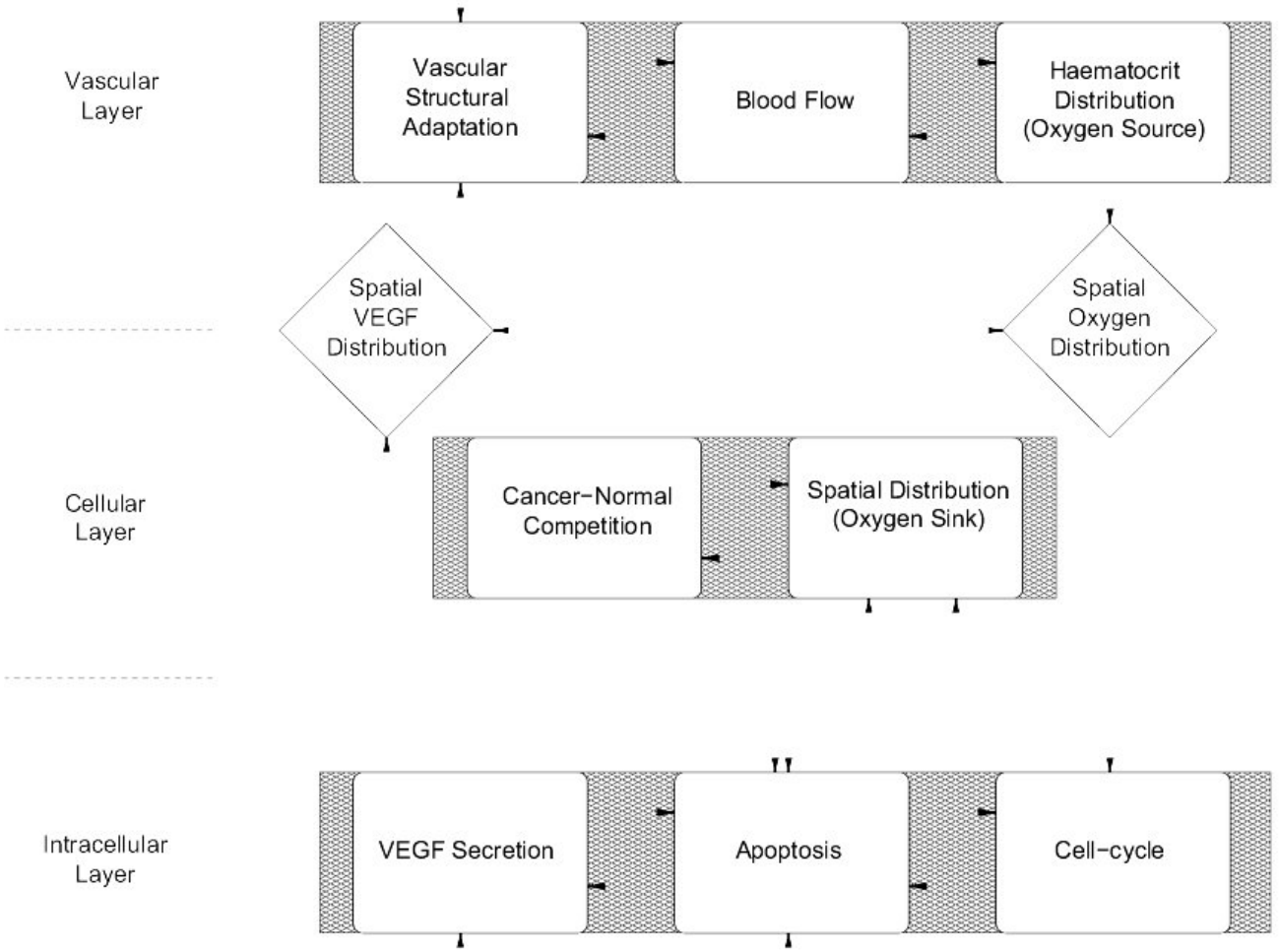
Many issues that need to be resolved are being studied using a combination of mathematical modelling and experiments

- Can engineered macrophages displace normal macrophages (and tumour cells)?
- How many macrophages needed for optimum response?
- What drugs should be used?
- Coordination with other therapies?
- See: Owen et al. (2004) *J. theor. Biol.* **226**: 377-391.

Genetically Engineered Macrophages

- Models yield range of predictions, including:
  - When used *in vitro*, cell kill localised in outer, proliferating region and similar to that for standard chemotherapeutic drug
  - When used *in vivo*, cell kill localised in tumour region and side-effects (cell kill) in healthy tissue reduced
- Example illustrates benefit of mathematical modelling: *in vitro* results alone suggest that not worth developing therapy!

Multiscale modelling of vascular tumour growth

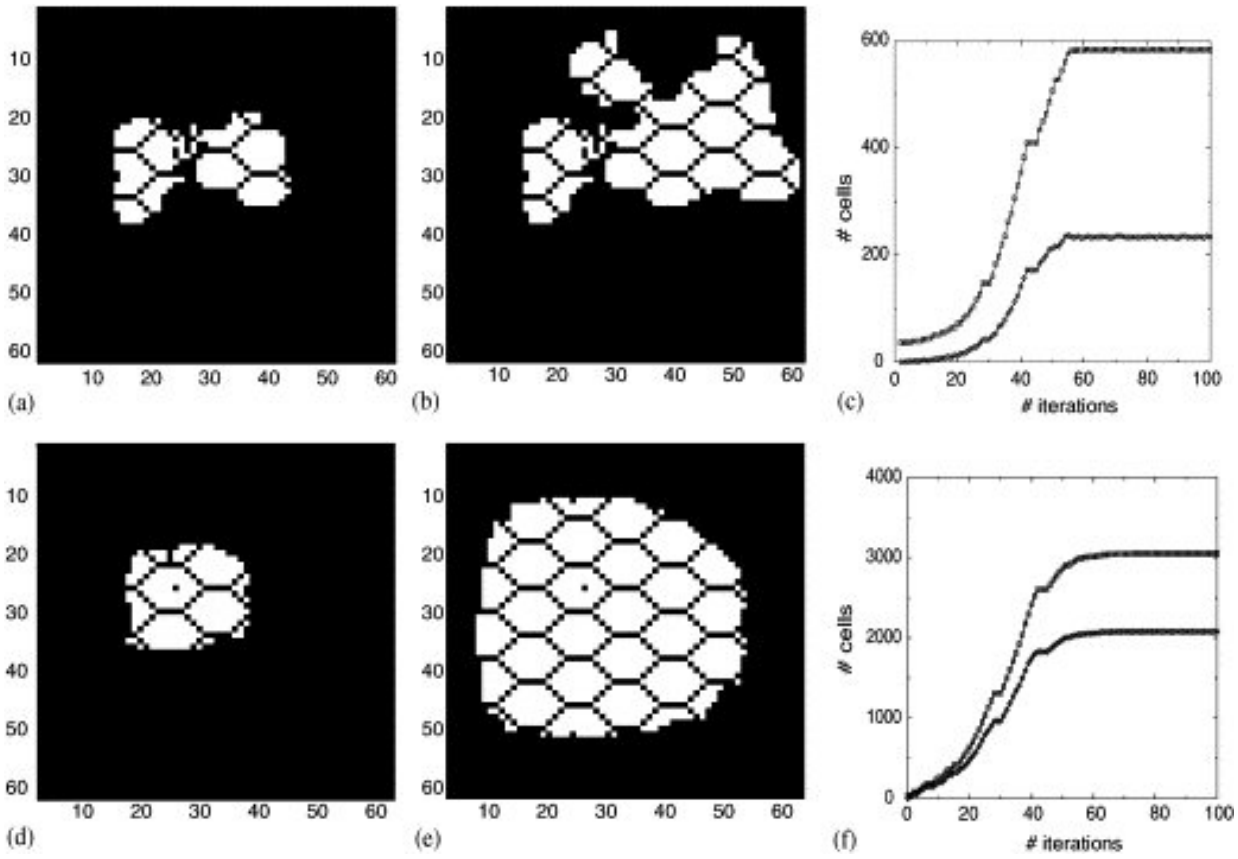


Schematic representation of our hybrid cellular automaton

Multiscale modelling of vascular tumour growth

- The subcellular level: ODE model of cell cycle based on the proteins cyclin and CDK (Tyson and Novak, 2001)
- The cellular level: 2D hybrid cellular automaton for vessels, tumour cells and normal cells; reaction-diffusion equation for oxygen, with distributed sources (vessels) and sinks (cells)
- The vessels: hexagonal network of blood vessels; pressure drop imposed across domain; Kirchoff's laws to determine flow in each vessel; vessel radii adapt to demands of surrounding tissue
- Time for a movie?
- See: Alarcon et al. (2003) *Prog. Biophys Mol Biol* **85**: 451-472

Multiscale modelling of vascular tumour growth

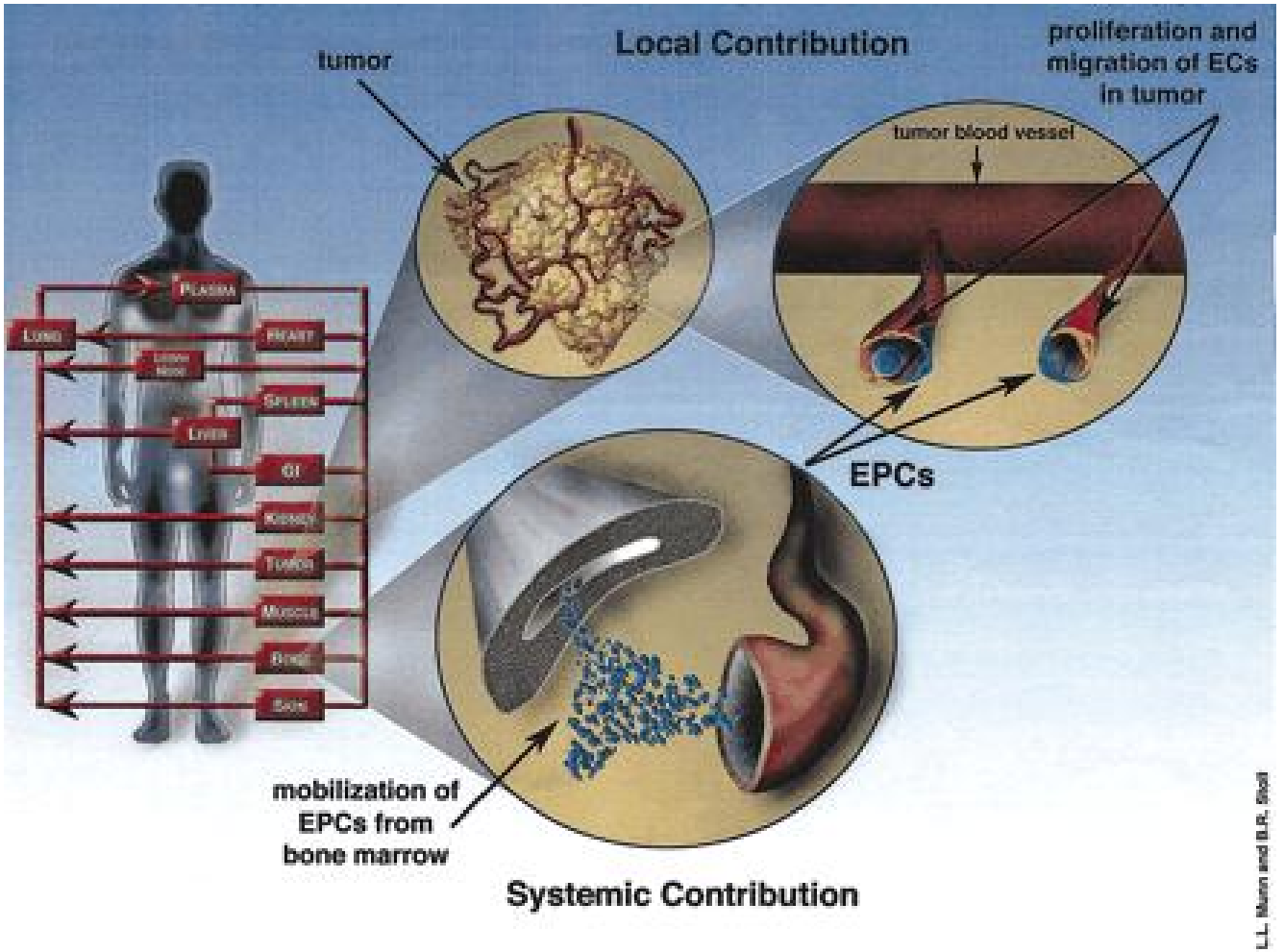


Tumour growth in homogenous and inhomogenous environments. **Key:** heterogenous (upper panels); homogeneous (lower panels). In (c) and (f), squares represent total number of tumour cells (proliferating + quiescent), diamonds denote quiescent cells.

Therapeutic Challenges

- Gene-based and viral therapies
- DNA condensation
- Anti-angiogenic treatments
- Hyperthermia
- Magnetically-tagged drugs

Therapeutic Challenges



Effective anti-angiogenic therapies will need to account for recruitment of EC stem cells to tumour sites.

Summary

Summary

▶ Modelling solid tumour growth is an exciting and challenging area of mathematical research.

▶ In order to be of clinical value, these models need to become more specific (eg particular tumour, particular mutation).

▶ Many parts of the cancer jigsaw have now been identified (ie subcellular, cellular and macroscopic phenomenon).

▶ Mathematics provides framework with which to assemble the jigsaw and thereby to help improve our understanding and treatment of cancer