Modelling Drug Delivery and Tumour Growth

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PART ONE

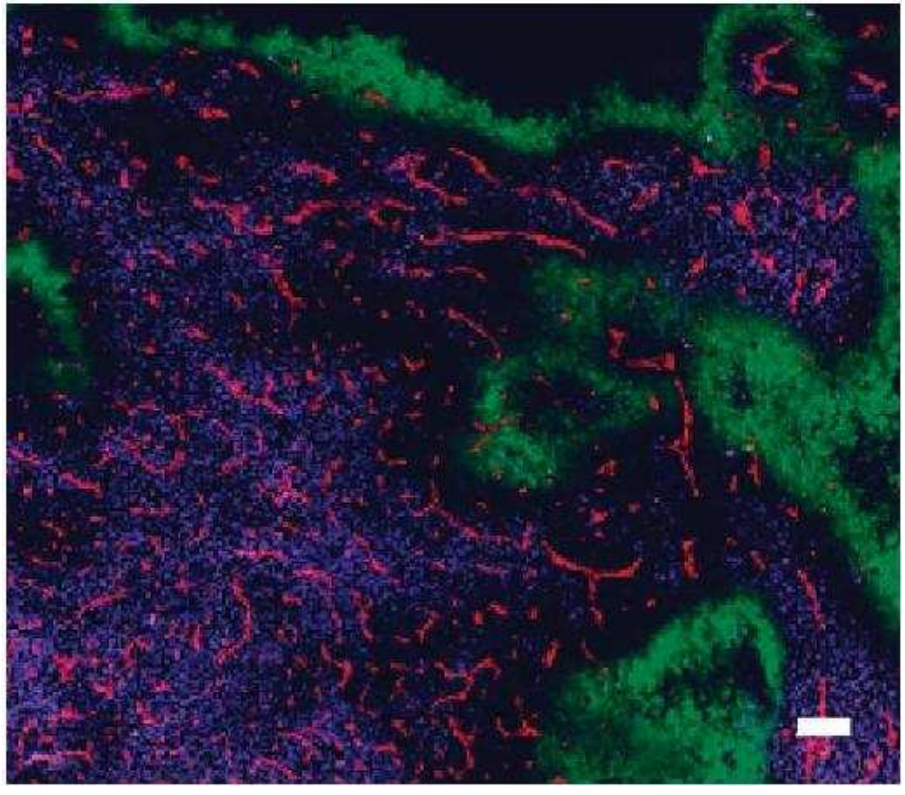
DRUG DELIVERY
(TO TUMOURS)

Drug Delivery

- Tumours contain poorly organised and dysfunctional vasculature.
- Hence, they are poorly perfused with blood.
- This difference in microenvironment has a profound effect on tumour response to chemotherapy.
- A major obstacle to effective chemotherapy is inadequate delivery of drug to cells.

Can we model the penetration of drug from blood vessels, through the surrounding layers of cells?

Drug Delivery



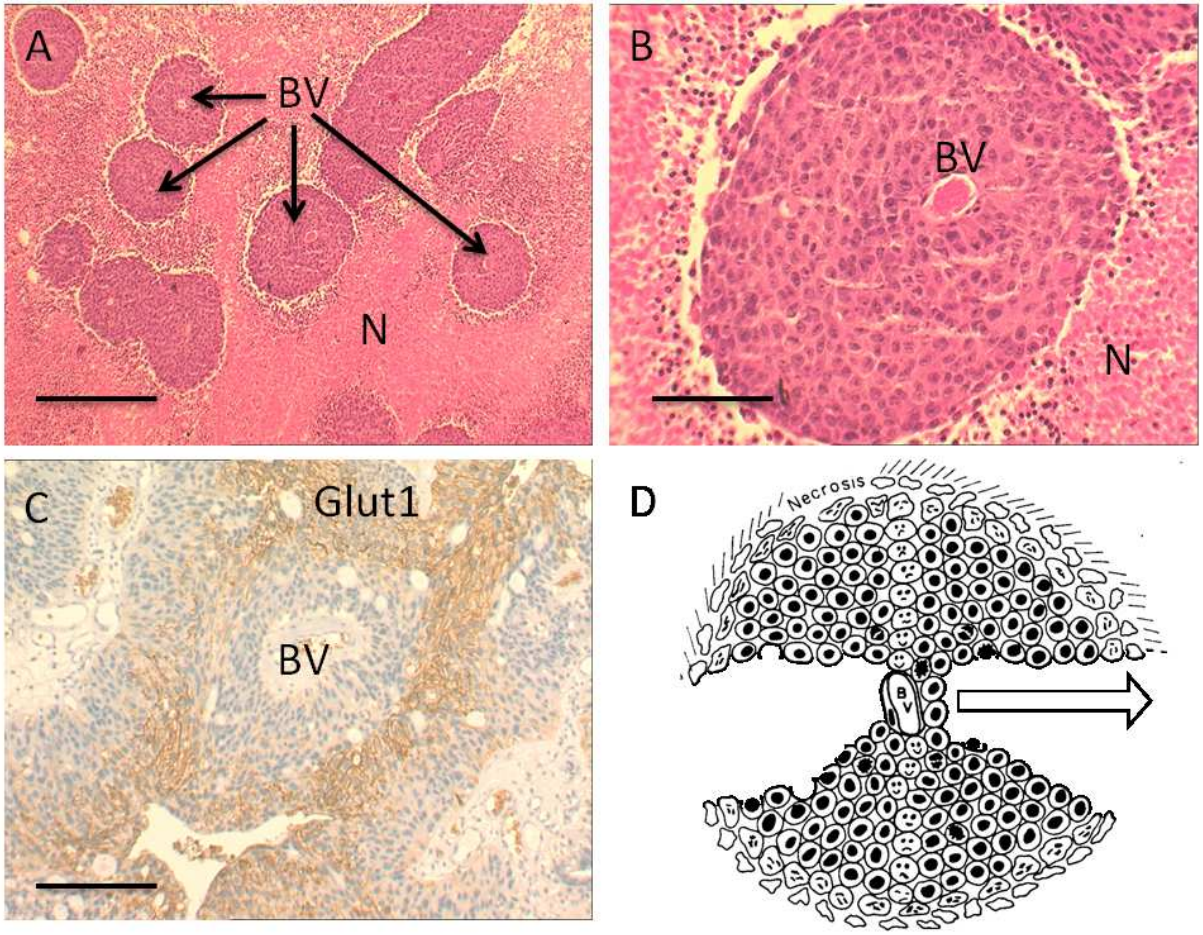
Blood Vessels (red): Drug (blue): Hypoxia (green)

Primeau, Rendon, Hedley, Lilge, Tannock (2005)

Drug Delivery

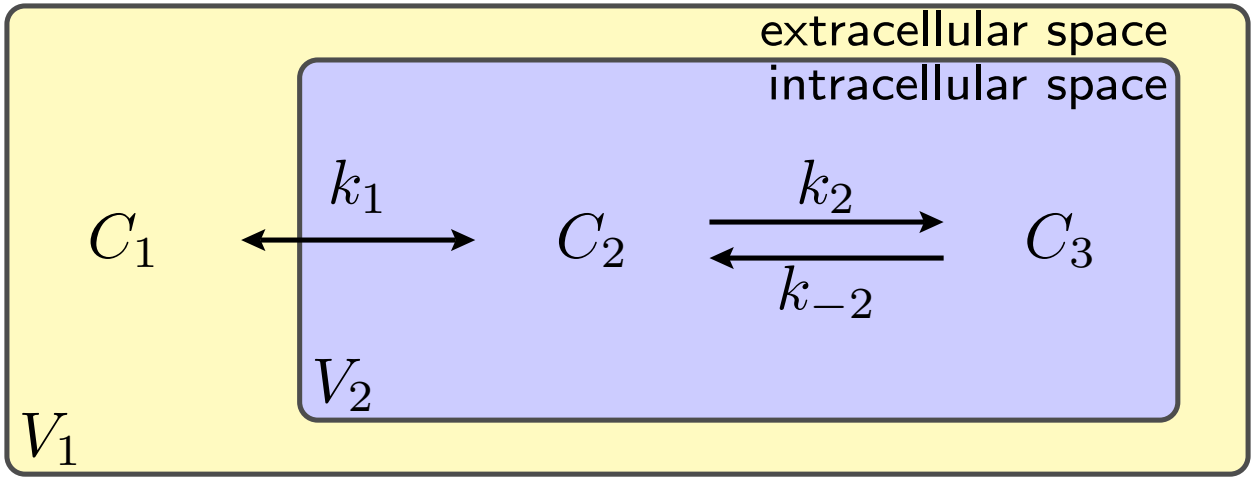
- Realistic tumour vasculatures are difficult to obtain.
- They would also be expensive to simulate.
- Start by considering a single blood vessel and the surrounding layers of cells.
- This set-up resembles a tumour cord.

Tumour Cords



BV = Blood Vessels, N = Necrosis, Glut1 $\Rightarrow$ Hypoxia

Cell Model



with $C_3 \leq C_0$

- Transport of drug across cell membrane (k_1)
- Binding and unbinding of drug in the cell (k_2,k_{-2})
- Potential saturation of binding sites (C_0)
- Interstitial drug diffusion will link the cells (D)

Mathematical Model

$$
\begin{aligned}
V_1 \frac{dC_1}{dt} &= a k_1 (C_2 - C_1) \\
V_2 \frac{dC_2}{dt} &= a k_1 (C_1 - C_2) - V_2 k_2 C_2 (C_0 - C_3) + V_2 k_{-2} C_3 \\
V_2 \frac{dC_3}{dt} &= V_2 k_2 C_2 (C_0 - C_3) - V_2 k_{-2} C_3
\end{aligned}
$$

- Biochemical parameters: k_1 k_2 k_{-2} C_0
  - Determined from *in vitro* experiments.
- Physical parameters: V_1 V_2 a
  - Determined by observation of tissue.

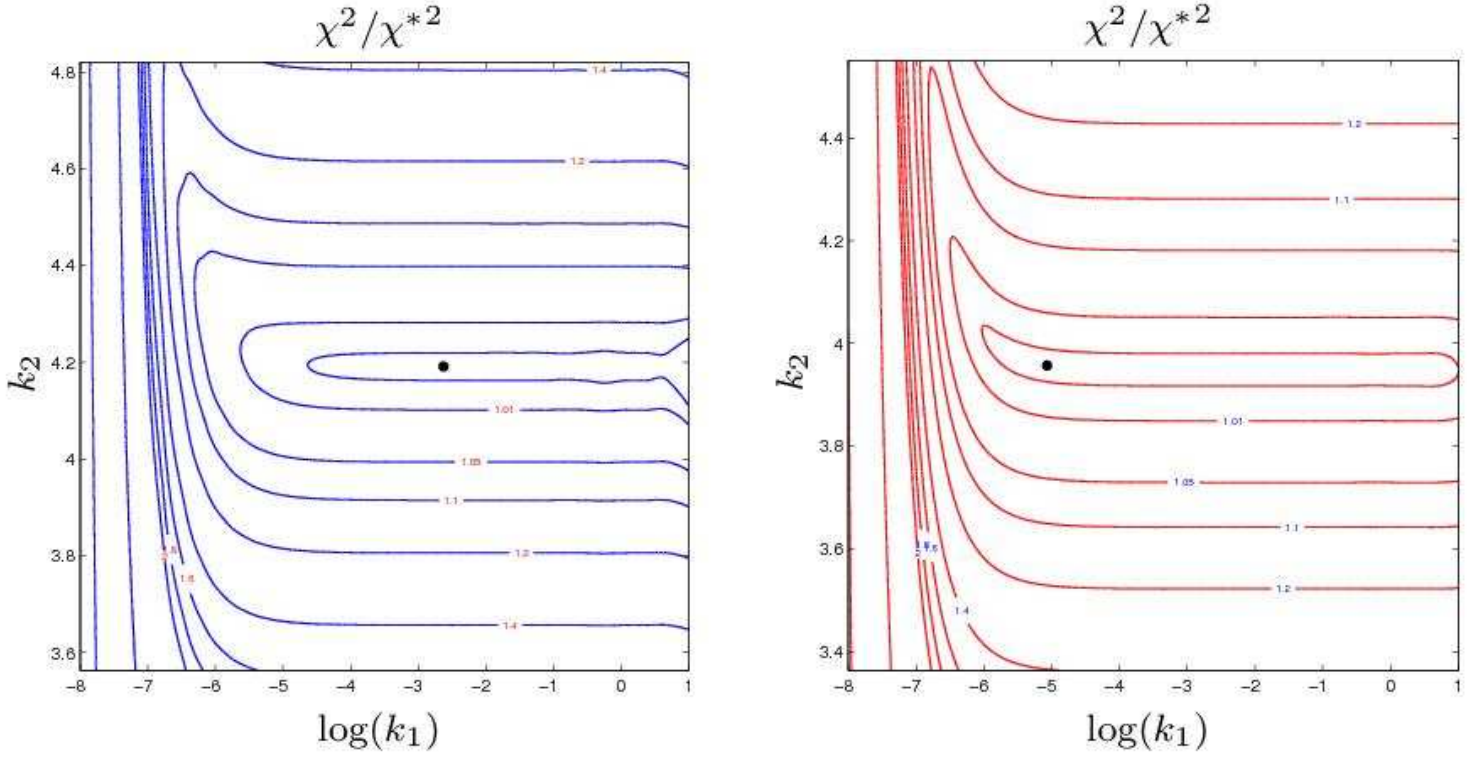
Binding Experiments

The *in vitro* experiments considered the action of the drug (Doxorubicin) on cells (DLD-1) in suspension.

- The initial extracellular drug concentration (C_1) was specified.
- Measurements were taken at later times of:
  - extracellular drug concentration (C_1),
  - intracellular drug concentration ($C_2 + C_3$).
- All the required parameters are identifiable from the data collected.

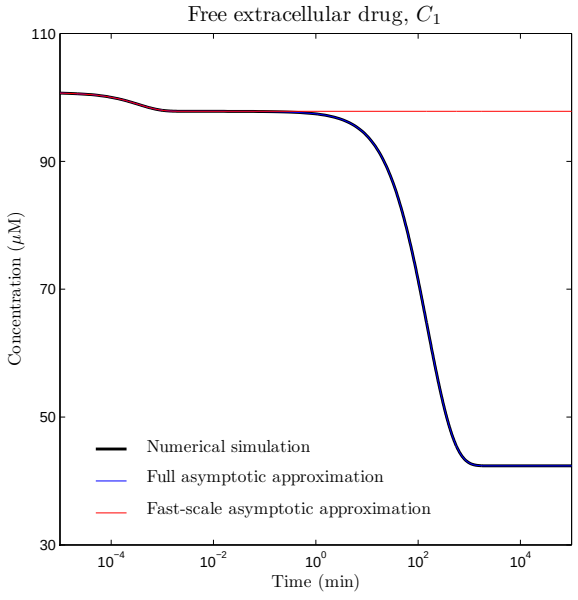
Parameter Sensitivity

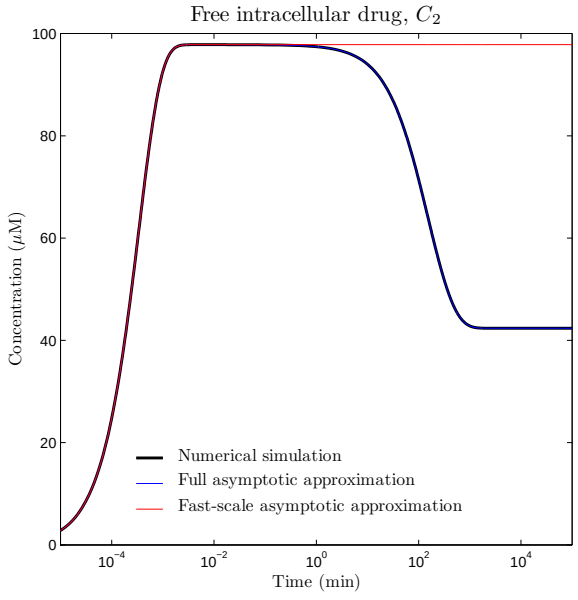
In fact, the model is extremely insensitive to the transmembrane transport rate (k_1) as long as it is fast enough.

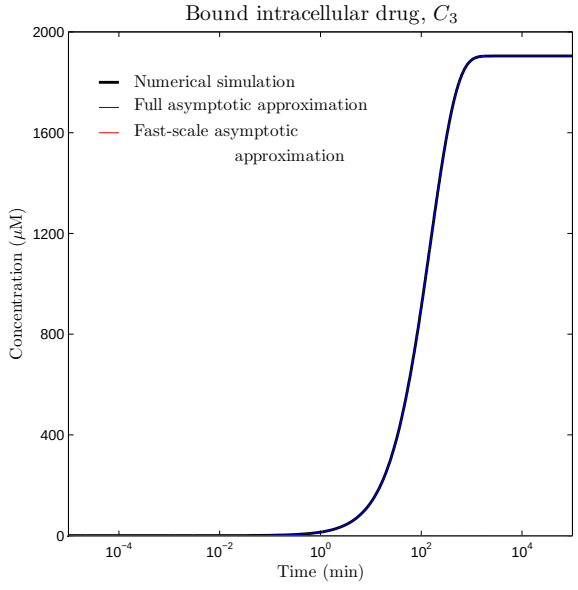


Timescales

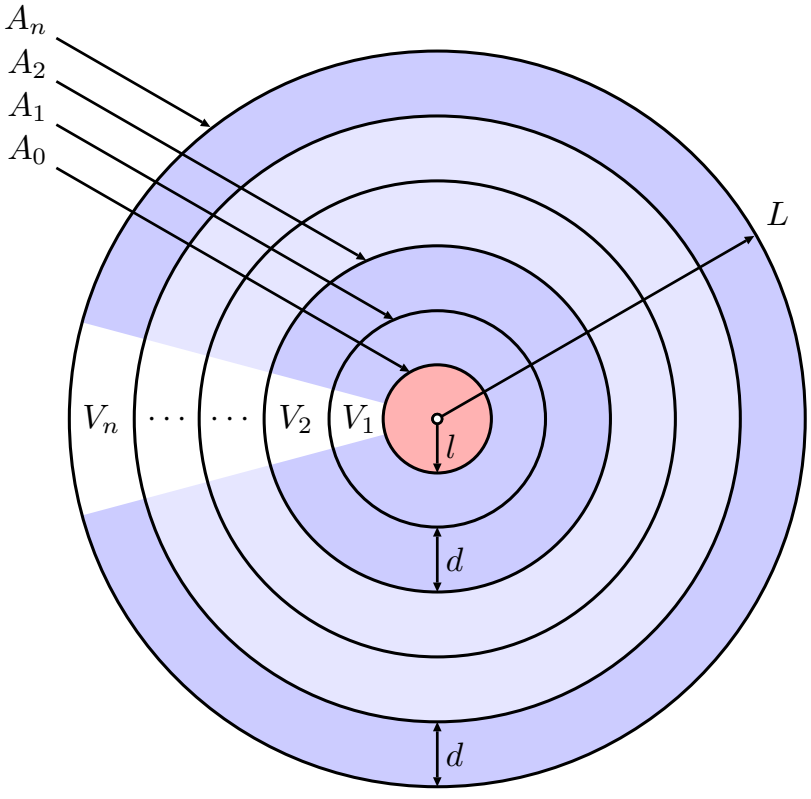
The fit to the data suggests two distinct time-scales, which are confirmed by mathematical analysis and can be linked to the literature.



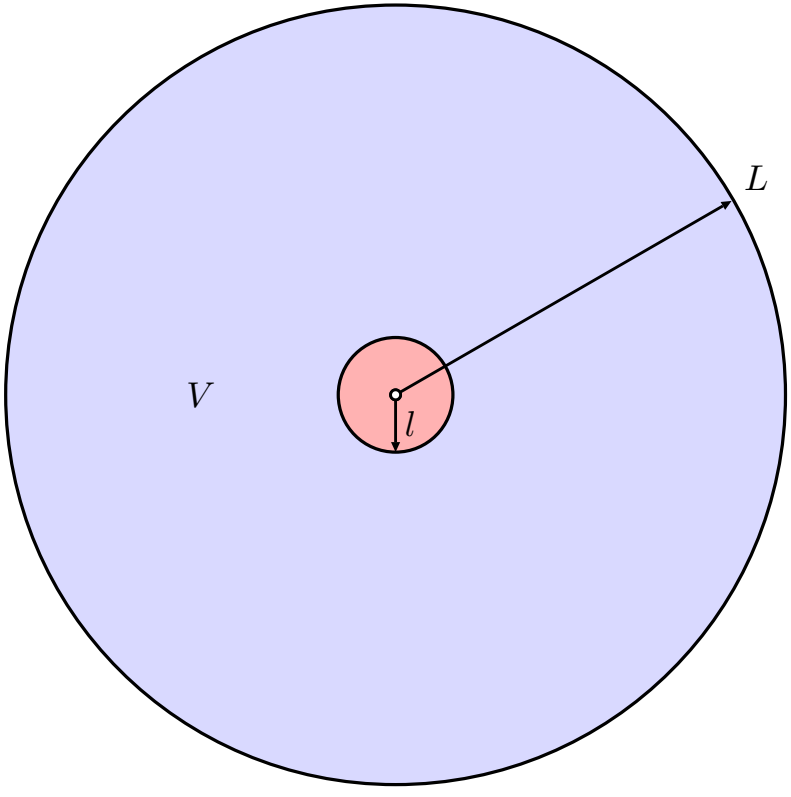




Radially Symmetric Models



Compartment Model



Continuum Model

Radially Symmetric Models

- A compartment model.
  - Each cell layer constitutes 3 compartments.
  - Drug is exchanged between layers and compartments within layers.
  - Effectively a finite volume approach with the mesh size dictated by the biological cell size.
- A continuum model.
  - Reaction-diffusion partial differential equations.
  - Discretised using a spectral approach.

Adaptive time-stepping is used (`ode15s` in Matlab).

Compartment Model

$$
\begin{aligned}
\delta_1 V_i \frac{dC_1^{(i)}}{dt} &= A_{i-1} k_0 (C_1^{(i-1)} - C_1^{(i)}) + A_i k_0 (C_1^{(i+1)} - C_1^{(i)}) \\
&+ a_i k_1 (C_2^{(i)} - C_1^{(i)}) \\
\delta_2 V_i \frac{dC_2^{(i)}}{dt} &= a_i k_1 (C_1^{(i)} - C_2^{(i)}) \\
&- \delta_2 V_i k_2 C_2^{(i)} (C_0 - C_3^{(i)}) + \delta_2 V_i k_{-2} C_3^{(i)} \\
\delta_2 V_i \frac{dC_3^{(i)}}{dt} &= \delta_2 V_i k_2 C_2^{(i)} (C_0 - C_3^{(i)}) - \delta_2 V_i k_{-2} C_3^{(i)}
\end{aligned}
$$

- $k_0 = D/d$ governs transport between layers.
- δ_1 and δ_2 are volume fractions ($\delta_1 + \delta_2 = 1$).

Continuum Model

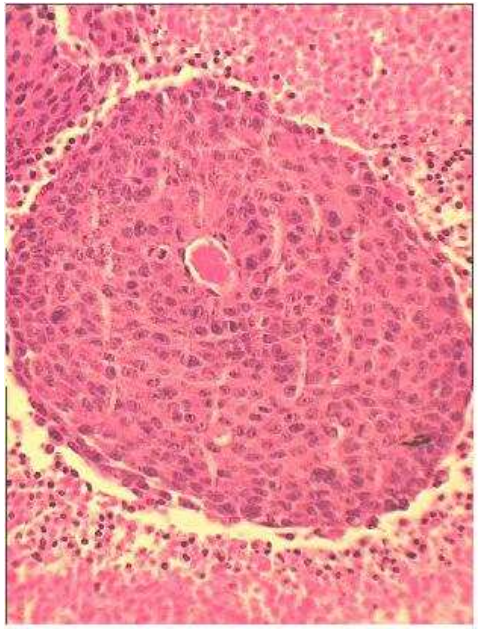
$$
\begin{aligned}
\delta_1 \frac{\partial C_1}{\partial t} &= D\left(\frac{\partial^2 C_1}{\partial r^2} + \frac{1}{r}\frac{\partial C_1}{\partial r}\right) \\
&+ \alpha k_1 \left(C_2 - C_1\right) \\
\delta_2 \frac{\partial C_2}{\partial t} &= \alpha k_1 \left(C_1 - C_2\right) - \delta_2 \left[k_2 C_2 \left(C_0 - C_3\right) - k_{-2} C_3\right] \\
\delta_2 \frac{\partial C_3}{\partial t} &= \delta_2 \left[k_2 C_2 \left(C_0 - C_3\right) - k_{-2} C_3\right]
\end{aligned}
$$

Both models have the boundary conditions

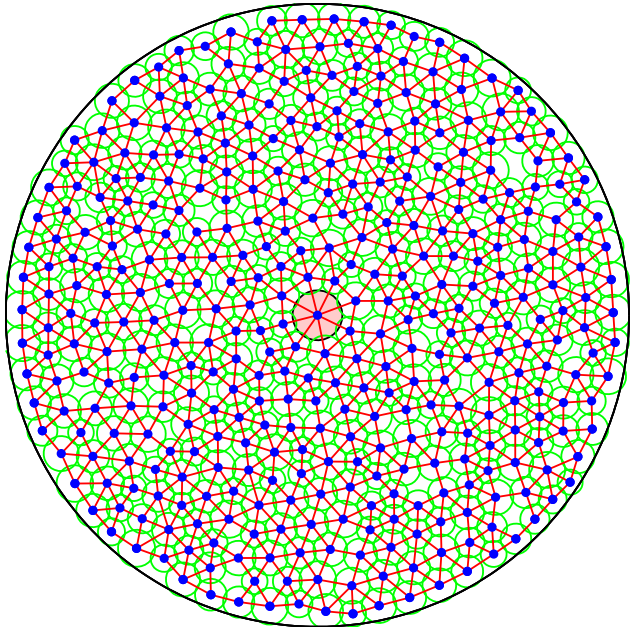
$$
D \left.\frac{\partial C_1}{\partial r}\right|_{r=l} = k_v (C_v - C_1|_{r=l}) \qquad D \left.\frac{\partial C_1}{\partial r}\right|_{r=L} = 0
$$

Cell-Centre Model

This is a multidimensional version of the compartment model.



Tumour cord



Discrete representation

Cell-Centre Model

$$
\begin{aligned}
\delta_1 V_i \frac{dC_1^{(i)}}{dt} &= \sum_{j \in \mathcal{N}_i} \frac{A_{ij}}{d_{ij}} D \left(C_1^{(j)} - C_1^{(i)} \right) + \sum_{j \in \mathcal{V}_i} A_{ij} k_v \left(C_v^{(j)} - C_1^{(i)} \right) \\
&+ a^{(i)} k_1 \left(C_2^{(i)} - C_1^{(i)} \right) \\
\delta_2 V_i \frac{dC_2^{(i)}}{dt} &= a^{(i)} k_1 \left(C_1^{(i)} - C_2^{(i)} \right) \\
&- \delta_2 V_i \left[k_2 C_2^{(i)} \left(C_0 - C_3^{(i)} \right) - k_{-2} C_3^{(i)} \right] \\
\delta_2 V_i \frac{dC_3^{(i)}}{dt} &= \delta_2 V_i \left[k_2 C_2^{(i)} \left(C_0 - C_3^{(i)} \right) - k_{-2} C_3^{(i)} \right]
\end{aligned}
$$

Numerical Experiments

To investigate:

- the differences between the compartment, continuum and cell-centre models;
- the effect of the pharmacokinetic profile;
- the influence of binding affinities.

Pharmacokinetic Profiles

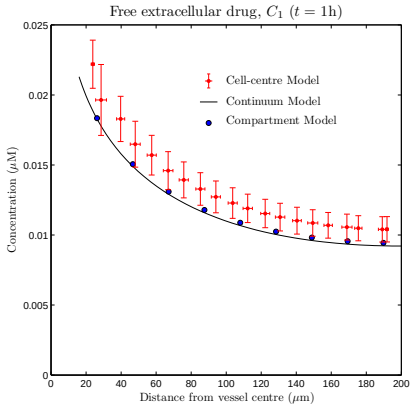
For a bolus injection the concentration of drug in the vessel ($c_v(t)$) is given by:

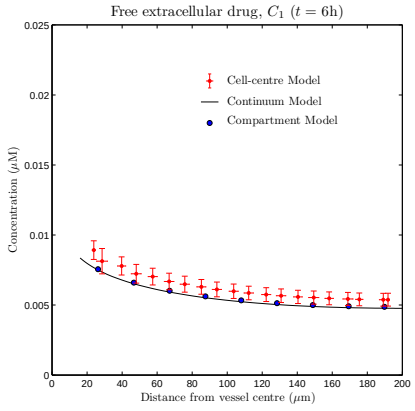
$$\begin{cases} \frac{D_0}{\tau}\left[\frac{A}{\alpha}\left(1-e^{-\alpha t}\right)+\frac{B}{\beta}\left(1-e^{-\beta t}\right)+\frac{C}{\gamma}\left(1-e^{-\gamma t}\right)\right] & t<\tau \\ \frac{D_0}{\tau}\left[\frac{A}{\alpha}\left(e^{\alpha\tau}-1\right)e^{-\alpha t}+\frac{B}{\beta}\left(e^{\beta\tau}-1\right)e^{-\beta t}+\frac{C}{\gamma}\left(e^{\gamma\tau}-1\right)e^{-\gamma t}\right] & t\geq\tau \end{cases}$$

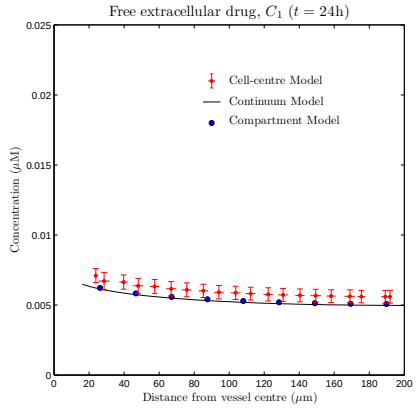
Robert, Illiadis, Hoerni, Cano, Durand, Lagarde (1982)

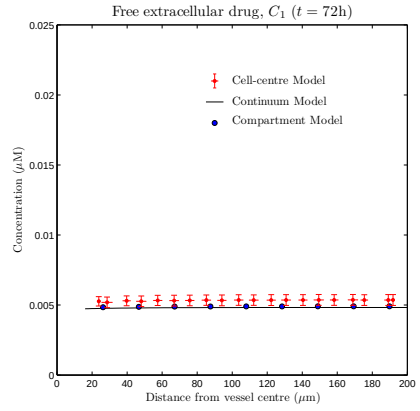
- A simplified form is given by $c_v(t) = Ae^{-\alpha t}$.
- Infusion can be simulated by $c_v(t) = K$.
- The parameters are chosen to give the same “area under curve”, *i.e.* $\int c_v \, \mathrm{d}t$.

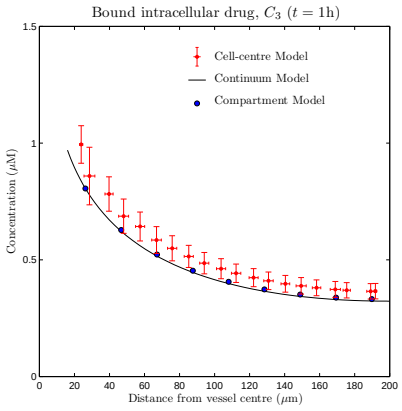
Bolus Injection

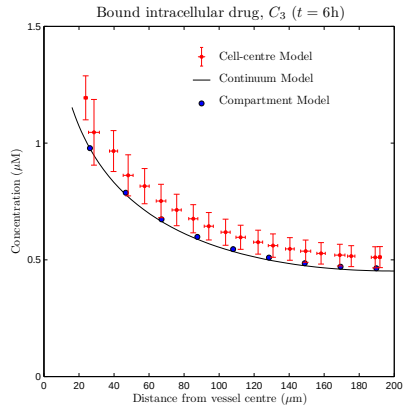


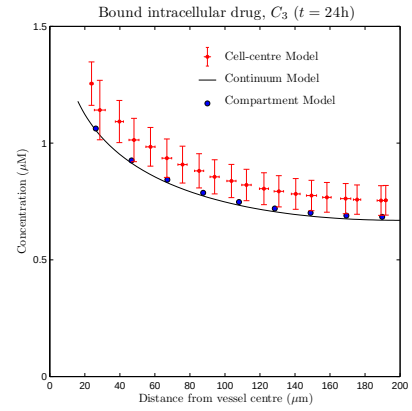


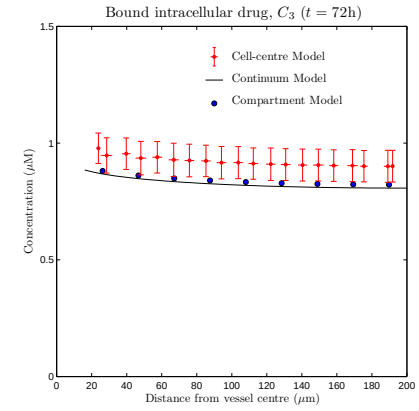






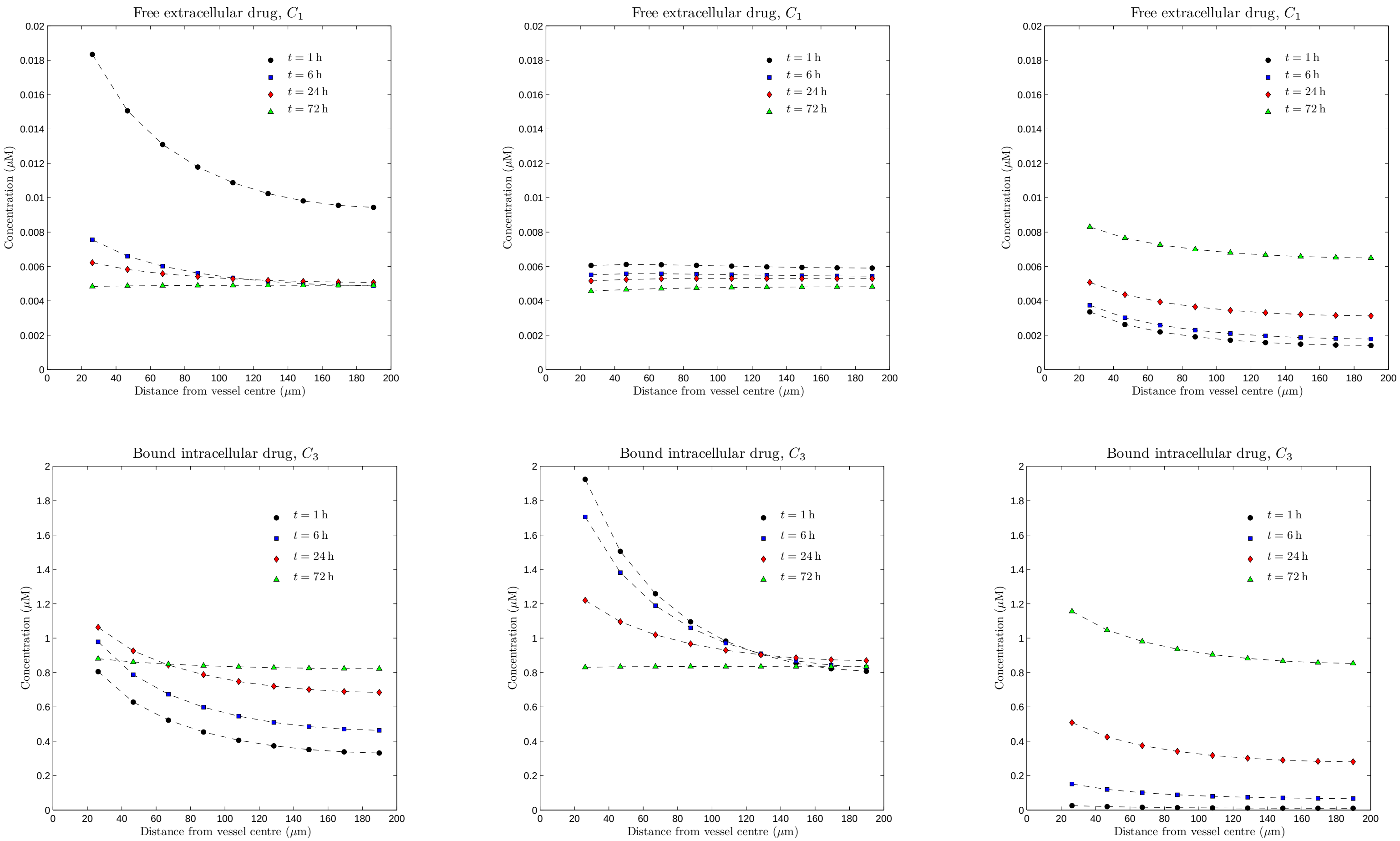






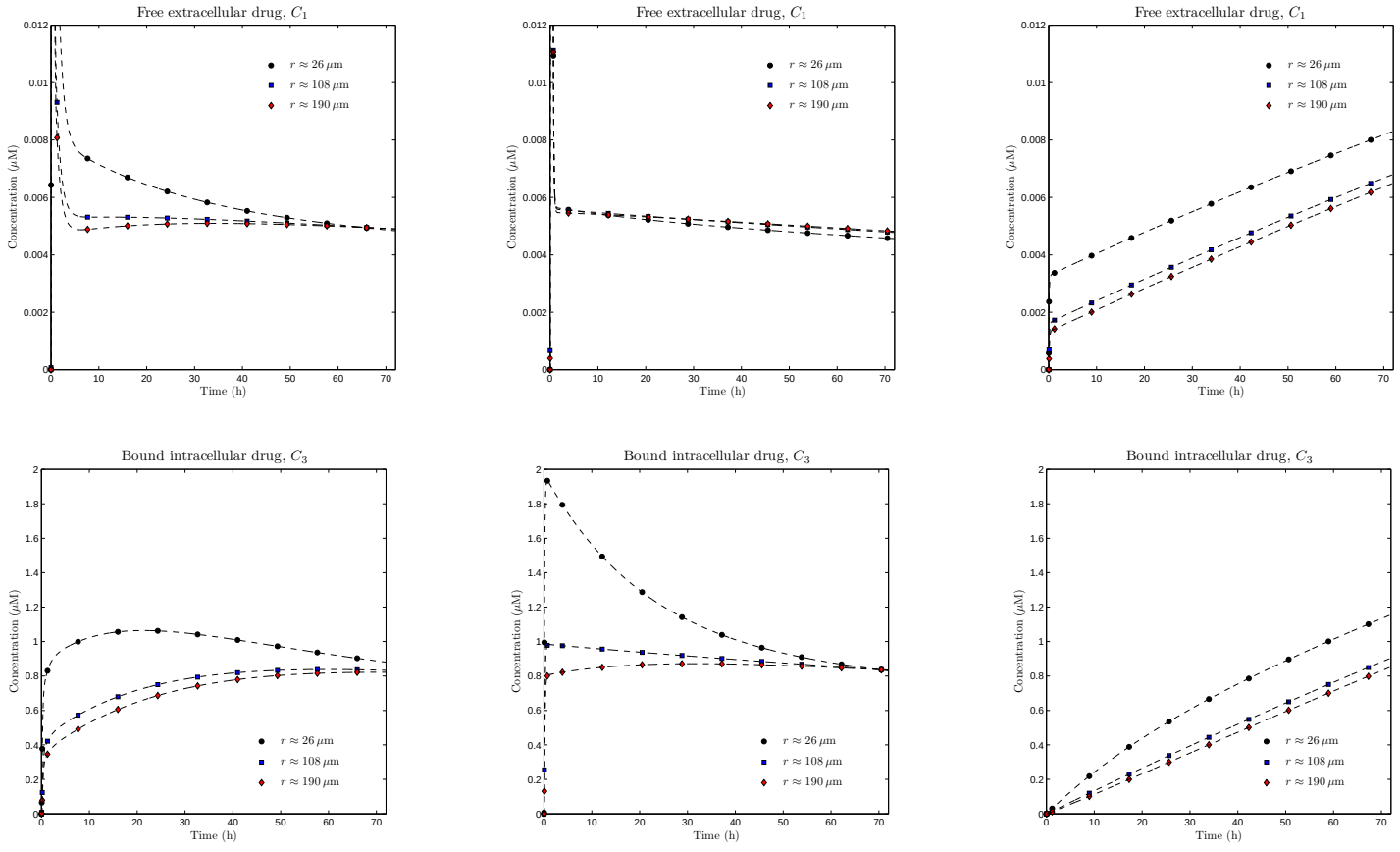
Drug distribution: extracellular (top), bound intracellular (bottom).
Snapshots at times 1h, 6h, 24h, 72h (left to right).

Spatial Variation



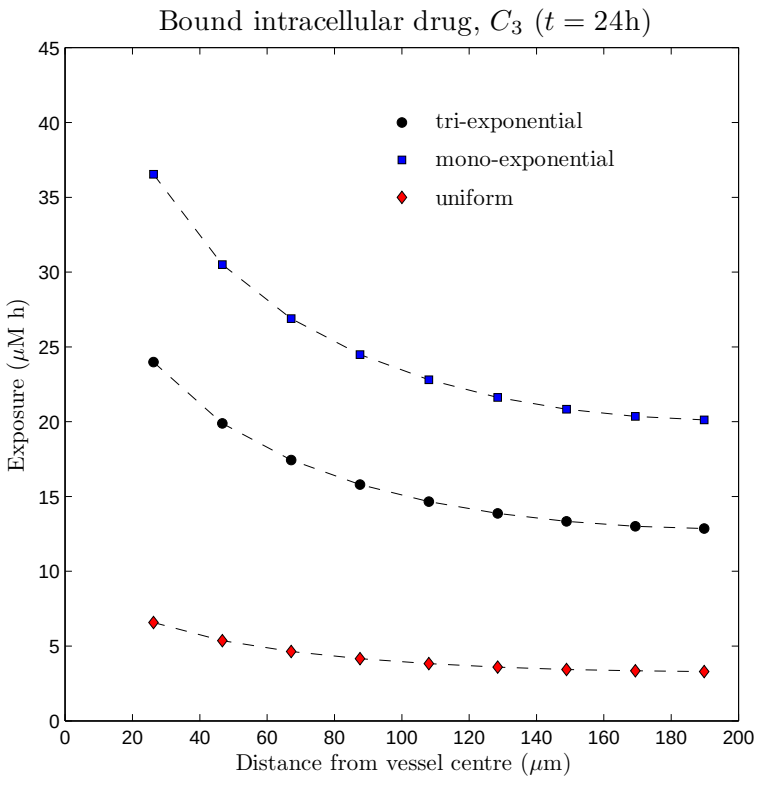
Drug distribution: extracellular (top), bound intracellular (bottom); for bolus (left), exponential (middle), infusion (right).

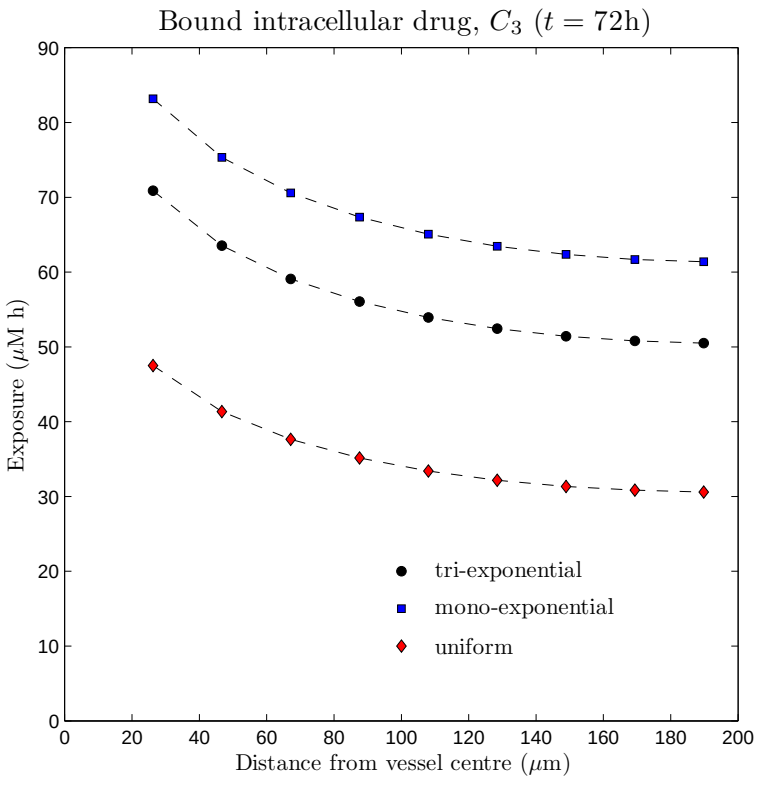
Temporal Variation



Drug evolution: extracellular (top), bound intracellular (bottom); for bolus (left), exponential (middle), infusion (right).

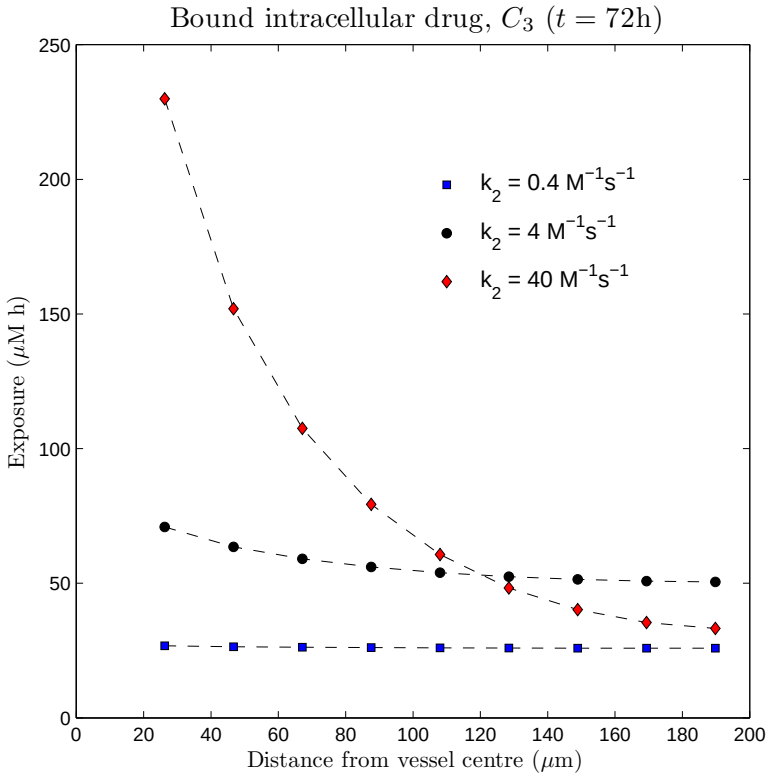
Exposure





Exposure to bound intracellular drug, $\int C_3 \, \mathrm{d}t$,
after 24h (left) and 72h (right).

Varying Binding Affinity



Exposure to bound intracellular drug, $\int C_3 \, \mathrm{d}t$, after 72h, for three different binding affinities.

Preliminary Observations

- The two discrete models and the discretised continuum model produce very similar results.
- The pharmacokinetic profile has less effect on the exposure than expected at long times.
- The exposure is sensitive to the binding rates.
- The model is extremely simple.
- The experimental measurements contain the largest source of variation.

The Next Steps

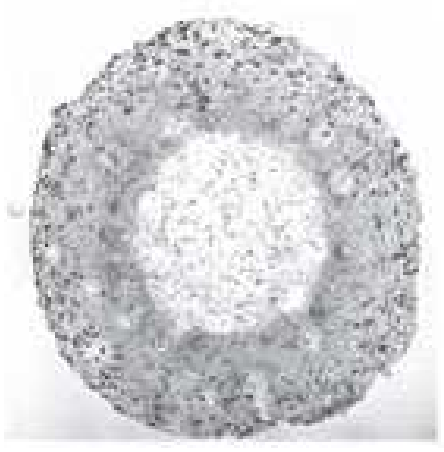
- Convective transport, validated by transwell experiments and possibly artificial tumour cords.
- More (parameterised?) processes and cell types.
  - Cell cycle (mitosis, apoptosis, necrosis).
  - Cell response (and a tumour growth model).
  - Drug clearance mechanisms, irreversible binding.
- With cell movement, realistic vasculature and three dimensions the scientific computing contribution becomes more significant.

PART TWO

TUMOUR GROWTH

Vascular Tumour Characteristics

- Rapid cell proliferation
  - Imbalance between mitosis and apoptosis
- Angiogenesis and co-option of vessels
- Can be spherical or irregular shapes
- Necrotic regions in tumour core and in avascular areas



A Continuum Multiphase Model

Based on Breward, Byrne and Lewis (2002,2003)

- Phases: cells, extracellular material, blood vessels
- Incompressible, viscous, fluids with drag between phases
- Cell-cell interactions included in stress tensors
- Includes mitosis, apoptosis/necrosis, angiogenesis, vessel occlusion
- A diffusible nutrient
- Tumour interacts with external tissue

Mass Balance

The tissue consists of N_p interacting phases, whose volume fractions θ_i are governed by mass conservation

$$\frac{\partial \theta_i}{\partial t} + \vec{\nabla} \cdot (\theta_i \, \vec{u}_i) = q_i \qquad i = 1, \ldots, N_p.$$

- $\vec{u}_i$ are phase velocities
- q_i allow conversion between phases
- Densities assumed to be constant and equal
- There are no “voids”, *i.e.*

$$\sum_{i=1}^{N_p} \theta_i = 1 \qquad \text{and} \qquad \sum_{i=1}^{N_p} q_i = 0 \, .$$

A Four-Phase Model

Four phases are chosen, to represent

- healthy cells (α_1)
- tumour cells (α_2)
- extracellular material (β)
- blood vessels (γ)

More could be added, *e.g.* different tumour cell phenotypes, mature/immature vessels.

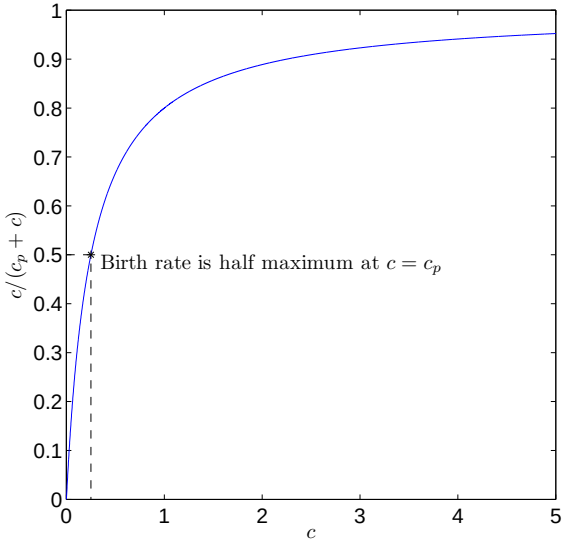
- The q_i are chosen to ensure $\theta_i \in [0, 1]$.

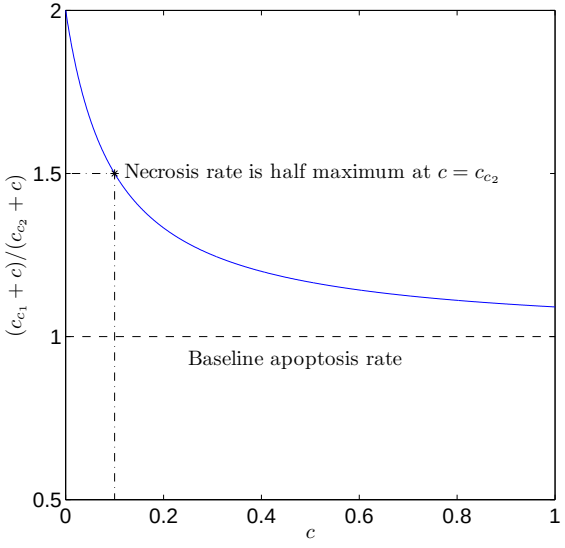
Mass Sources

For the cell phases:

$$q_{\alpha_j} = \underbrace{k_{1,j}\,\alpha_j\,\beta\left(\frac{c}{c_p + c}\right)}_{\text{cell birth}} \underbrace{- k_{2,j}\,\alpha_j\left(\frac{c_{c_1} + c}{c_{c_2} + c}\right)}_{\text{cell death}}$$

- k_* are rate constants
- c_* are concentration thresholds





Mass Sources

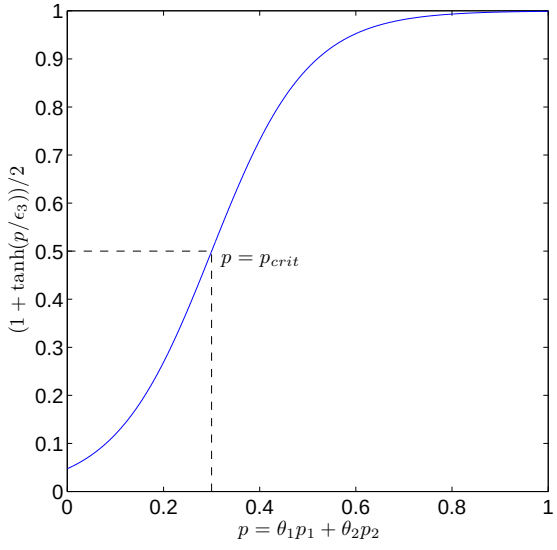
For the blood vessel phase:

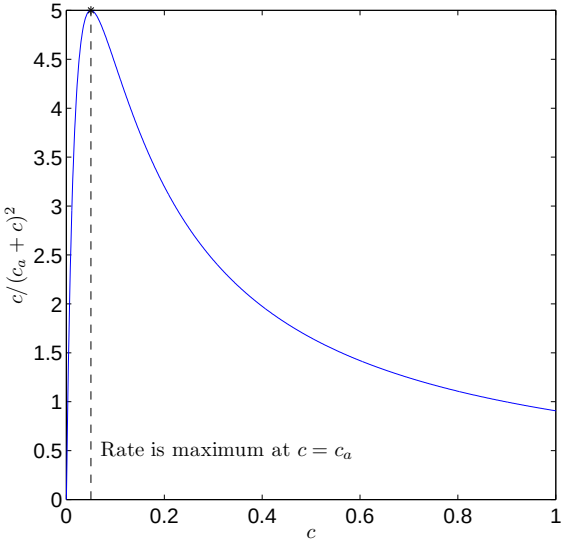
$$q_\gamma = \underbrace{-k_3\,\gamma\,\mathcal{H}(\alpha_1 p_{\alpha_1} + \alpha_2 p_{\alpha_2} - p_{crit}, \epsilon_3)}_{\text{occlusion}} + \underbrace{k_4\,(\alpha_1+\alpha_2)\,\gamma\left(\frac{\beta}{\varepsilon+\beta}\right)\left(\frac{c}{(c_a+c)^2}\right)}_{\text{angiogenesis}}$$

where $\mathcal{H}(\theta, \epsilon)$ is a smooth switch.

For the remaining material:

$$q_\beta = -q_{\alpha_1} - q_{\alpha_2} - q_\gamma$$





Momentum Balance

Assuming low Reynolds number flow,

$$\vec{\nabla} \cdot (\theta_i \, \boldsymbol{\sigma}_i) \; + \; \vec{F}_i \; = \; 0 \qquad\qquad i = 1, \ldots, N_p.$$

- $\boldsymbol{\sigma}_i$ are the phase stress tensors.
- $\vec{F}_i$ are momentum sources and sinks.
- Note that mass conservation implies

$$\sum_{i=1}^{N_p} \vec{\nabla} \cdot (\theta_i \, \vec{u}_i) \; = \; 0 \, .$$

Constitutive Laws

For viscous Newtonian fluids

$$\boldsymbol{\sigma}_i \;=\; -p_i\mathbf{I} + \mu_i(\vec{\nabla}\vec{u}_i + \vec{\nabla}\vec{u}_i^{\mathrm{T}}) + \lambda_i(\vec{\nabla}\cdot\vec{u}_i)\mathbf{I} \qquad i = 1,\ldots,N_p,$$

though $\lambda_i = -\frac{2}{3}\mu_i$ is assumed (local thermodynamic equilibrium).

Momentum sources include pressure effects and interphase drag (with coefficients d_{ij}):

$$\vec{F}_i \;=\; p_i\mathbf{I}\,\vec{\nabla}\theta_i \;+\; \sum_{j\neq i} d_{ij}\theta_i\theta_j\,(\vec{u}_j - \vec{u}_i) \qquad i = 1,\ldots,N_p.$$

Pressure Relations

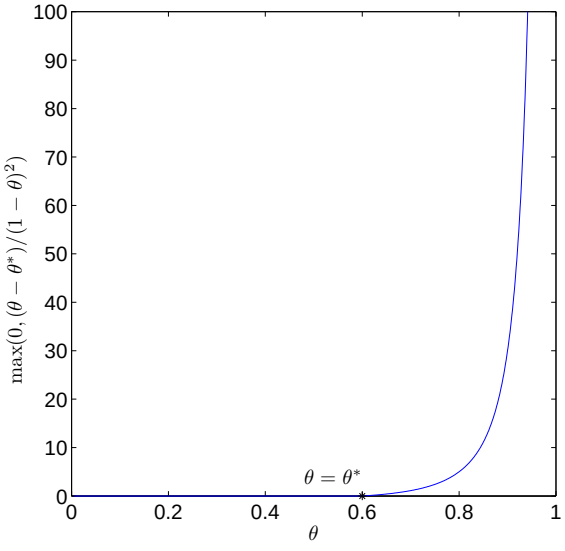
- Pressure due to the blood vessel phase is assumed independent of the local flow, *i.e.* $p_\gamma = p_\gamma^*$.
- Cells act like a fluid with additional cell-cell interactions, *i.e.*

$$p_{\alpha_1} = p_{\alpha_2} = p_\beta + \Sigma_\alpha$$

where

$$\Sigma_\alpha = \max\left(\frac{\Lambda(\alpha - \alpha^*)}{(1-\alpha)^2}, 0\right)$$

with $\alpha = \alpha_1 + \alpha_2$ and α^* a natural equilibrium density.



Diffusible Species

There are N_d additional species whose concentrations c_j are governed by

$$D_j \vec{\nabla}^2 c_j + q_j \;=\; 0 \qquad\qquad j = 1, \ldots, N_d \,.$$

- They are assumed to evolve much more rapidly than the tissue.
- They do not contribute to the volume.
- They provide non-local influence.

Diffusion Sources

A single species representing “nutrient” is used here, for which

$$q_c = \underbrace{k_5\,\gamma\,(c_v - c)}_{\text{replenishment}} \underbrace{- k_{6,1}\,\alpha_1\,c - k_{6,2}\,\alpha_2\,c}_{\text{baseline consumption}} \underbrace{- k_{7,1}\,\alpha_1\,\beta\left(\frac{c}{c_p + c}\right) - k_{7,2}\,\alpha_2\,\beta\left(\frac{c}{c_p + c}\right)}_{\text{consumption due to cell birth}}$$

- It would be simple to include others,
  e.g. VEGF, pH, glucose.

The Whole System

$$\frac{\partial \theta_i}{\partial t} + \vec{\nabla} \cdot (\theta_i \, \vec{u}_i) = q_i \qquad \sum_{i=1}^{N_p} \theta_i = 1$$

$$\vec{\nabla} \cdot (\theta_i [\mu_i (\vec{\nabla} \vec{u}_i + \vec{\nabla} \vec{u}_i^{\mathrm{T}}) + \lambda_i (\vec{\nabla} \cdot \vec{u}_i) \mathbf{I}]) + \sum_{j \neq i} d_{ij} \theta_i \theta_j \, (\vec{u}_j - \vec{u}_i) - \theta_i \, \vec{\nabla} \cdot (p_i \mathbf{I}) = 0$$

$$\sum_{i=1}^{N_p} \vec{\nabla} \cdot (\theta_i \, \vec{u}_i) = 0$$

$$D_j \vec{\nabla}^2 c_j + q_j = 0$$

Boundary Conditions

Mass balance:

- specify phase volume fractions at inflow.

Momentum balance:

- $\vec{u}_\beta = 0$ somewhere on the boundary;
- zero stress elsewhere.

Diffusible species:

- $\vec{\nabla} c \cdot \vec{n} = 0$ (zero flux).

The Whole System

The unknowns are

- θ_i – phase volume fractions
- $\vec{u}_i$ – phase velocities
- p_i – phase pressures
- c_j – diffusible species concentrations

Using unstructured triangular meshes in two space dimensions, evolve the phase volume fractions in time then update the other variables.

Numerical Approximation

Phase volume fractions

- Hyperbolic conservation laws with sources/sinks
- Important to remain within $[0, 1]$
- Cell-centre finite volume scheme on refined mesh
- Upwind with MUSCL slope limiting
- Forward Euler time-stepping

Numerical Approximation

Phase velocities and pressures

- A form of multicomponent Stokes flow
- Stable finite elements
  - quadratic velocities, linear pressures
- System is linear but not (quite) symmetric
- MUMPS (without the MP)
- Care is needed when $\theta_i = 0$

Numerical Approximation

Nutrient concentration

- Standard reaction-diffusion system
- Galerkin finite elements with linear elements on refined mesh
- Newton iteration combined with MUMPS
  - Allows nonlinear reaction terms
  - Jacobian approximated numerically

Test Case

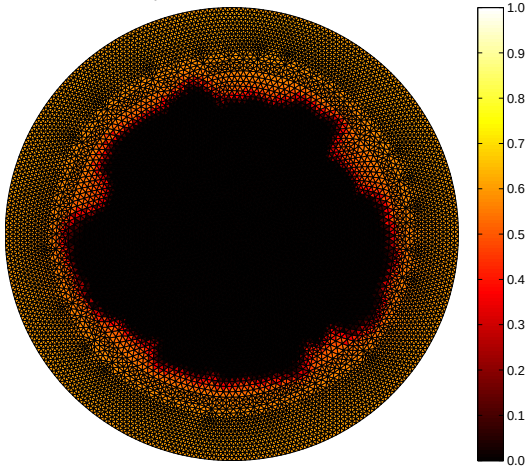
- Circular domain, radius 16
- Triangular mesh: 2349 nodes, 4539 elements
  - Gives 76237 DoFs in FEM solve
- “Free” boundaries: zero normal stress except β
- Seed “healthy tissue” in centre with

$$\alpha_2 = \begin{cases} 0.05\cos^2(\pi r/2) & \text{for } r \leq 1 \\ 0 & \text{otherwise} \end{cases}$$

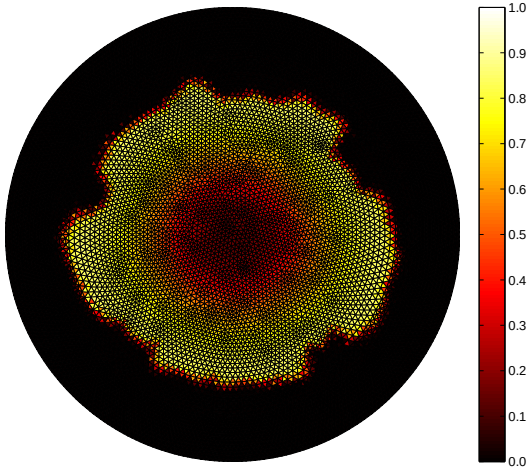
(animations)

Phase Volume Fractions

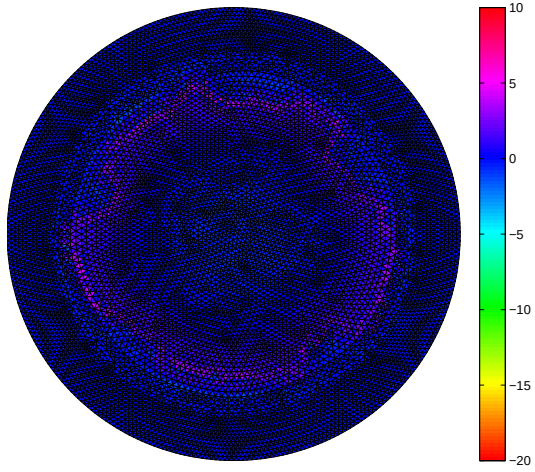
Healthy cells: θ_1 at $t = 300$



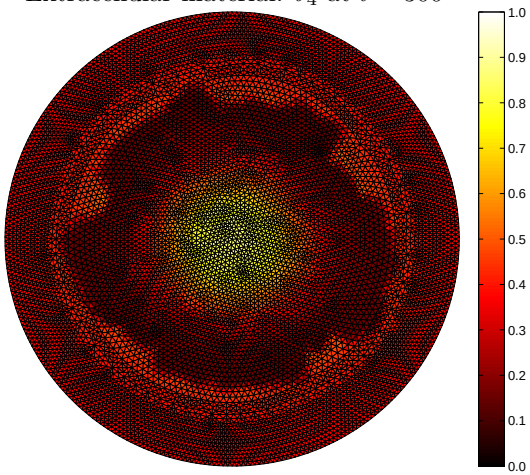
Tumour cells: θ_2 at $t = 300$



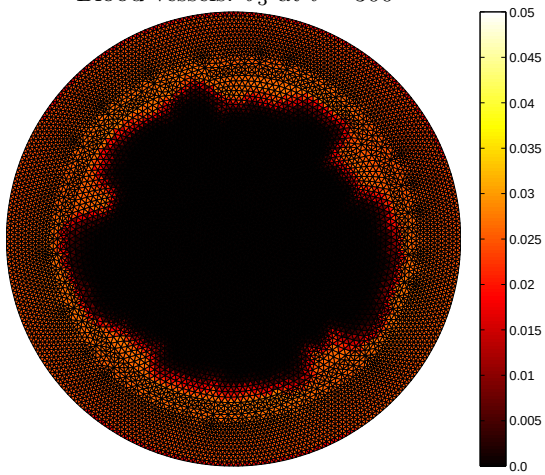
Cell pressure: p_1,p_2 at $t = 300$



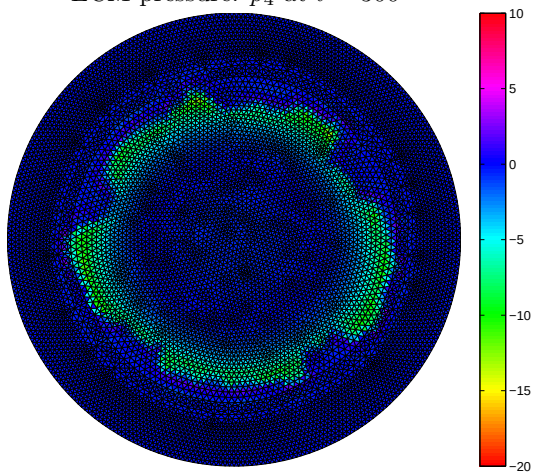
Extracellular material: θ_4 at $t = 300$



Blood vessels: θ_3 at $t = 300$

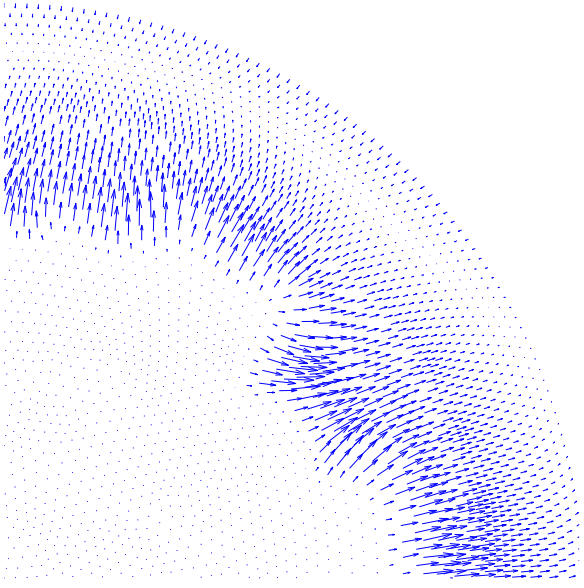


ECM pressure: p_4 at $t = 300$

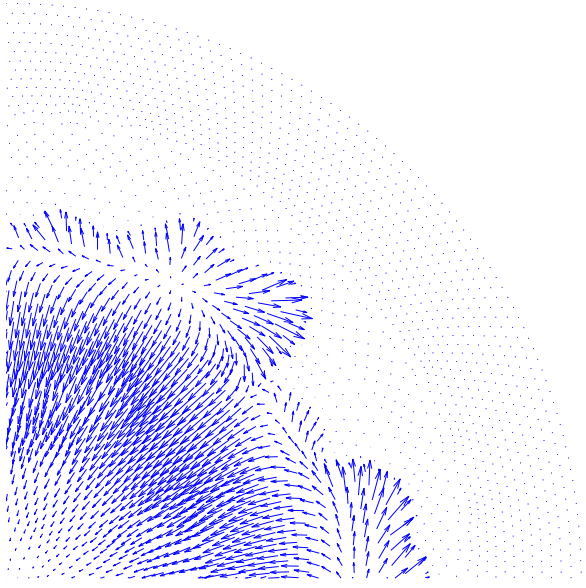


Phase Fluxes

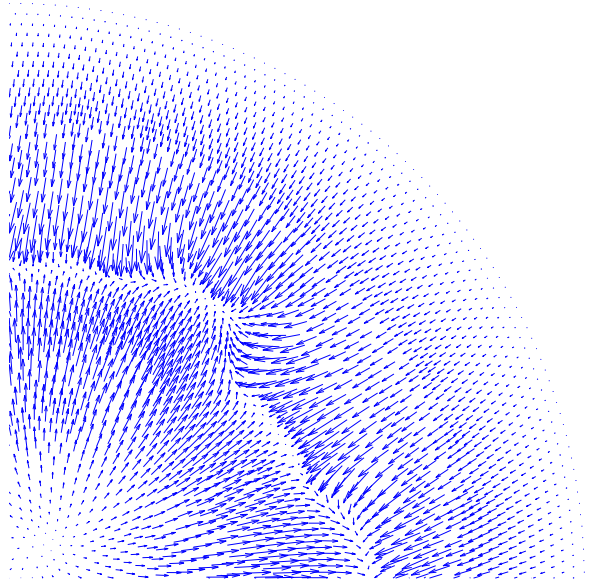
Healthy cells: $\theta_1 \vec{u}_1'$ at $t = 300$



Tumour cells: $\theta_2 \vec{u}_2'$ at $t = 300$

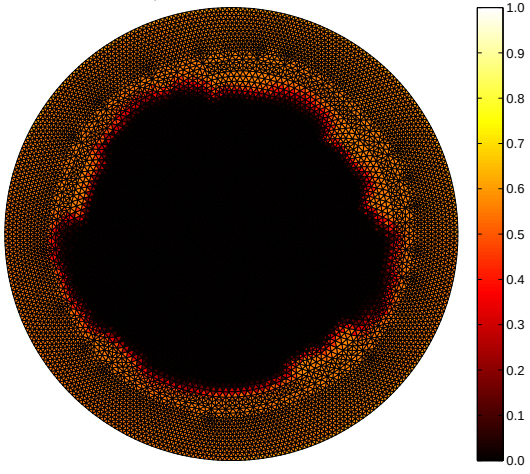


Extracellular material: $\theta_4 \vec{u}_4'$ at $t = 300$

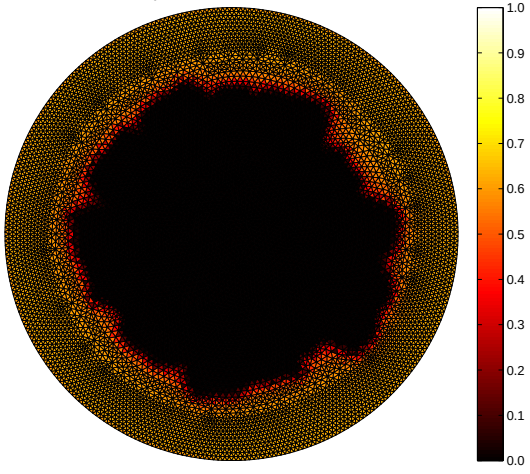


Varying Diffusion

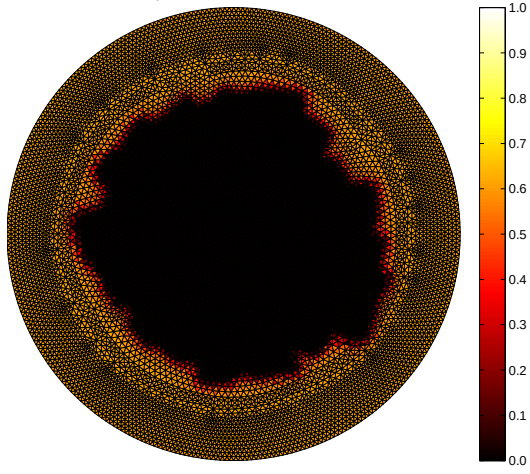
Healthy cells: θ_1 at $t = 225$



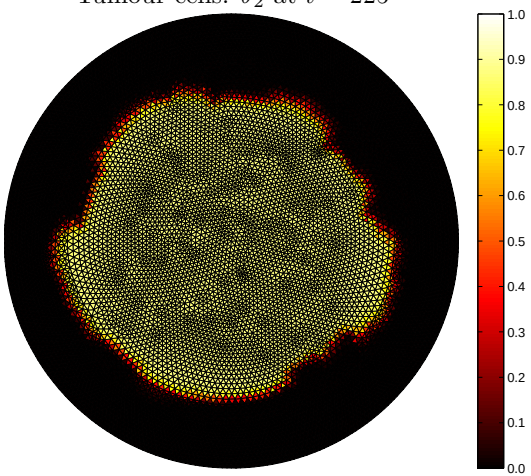
Healthy cells: θ_1 at $t = 525$



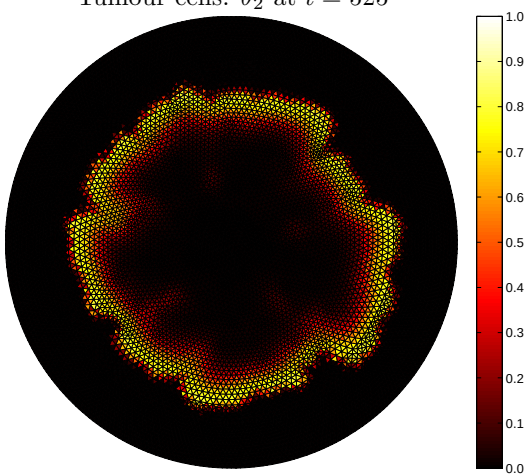
Healthy cells: θ_1 at $t = 800$



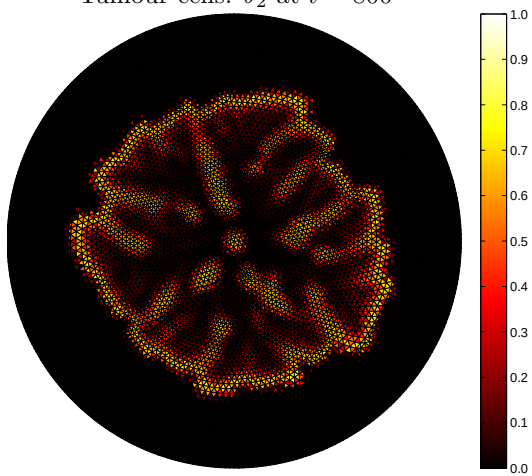
Tumour cells: θ_2 at $t = 225$



Tumour cells: θ_2 at $t = 525$

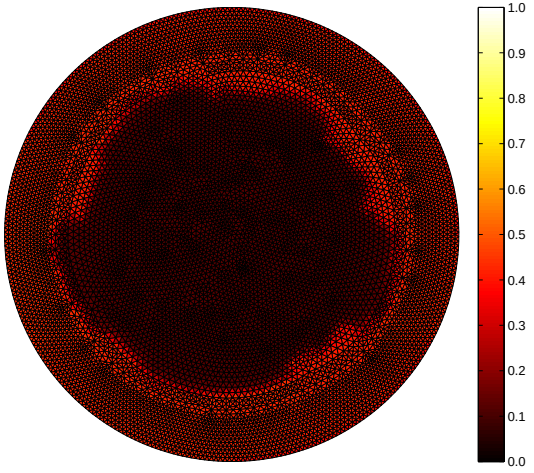


Tumour cells: θ_2 at $t = 800$

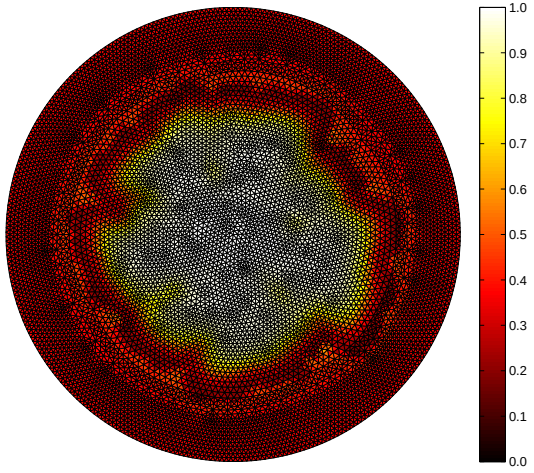


Varying Diffusion

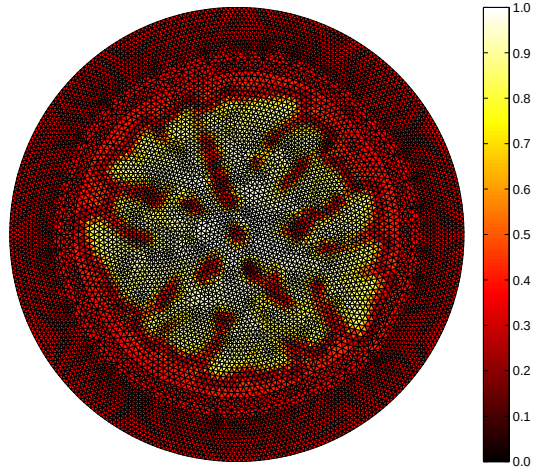
Extracellular material: θ_4 at $t = 225$



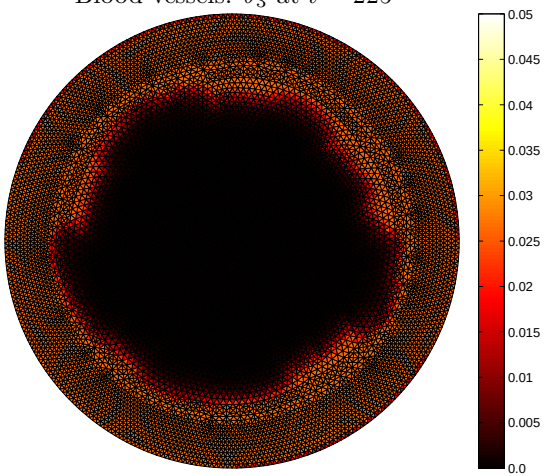
Extracellular material: θ_4 at $t = 525$



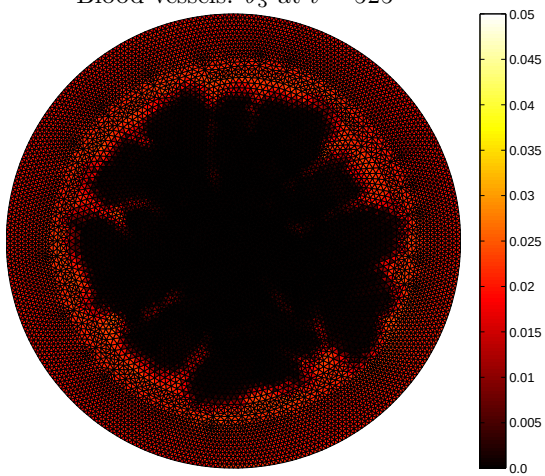
Extracellular material: θ_4 at $t = 800$



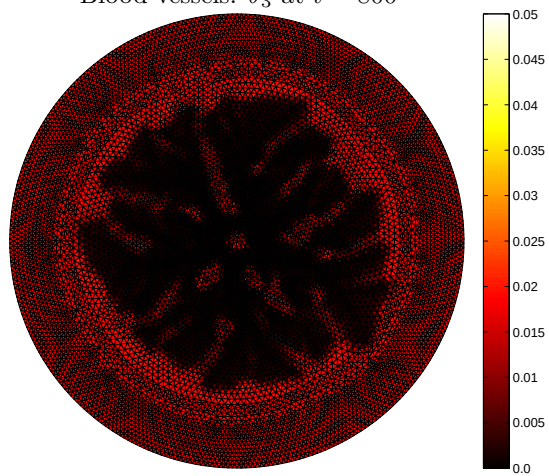
Blood vessels: θ_3 at $t = 225$



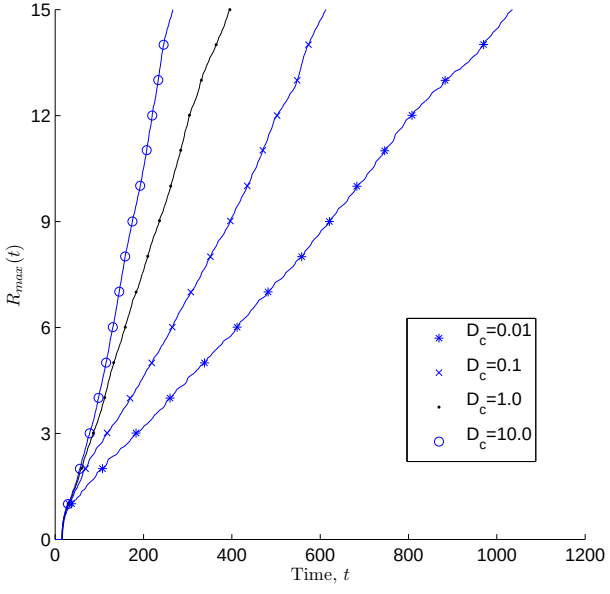
Blood vessels: θ_3 at $t = 525$

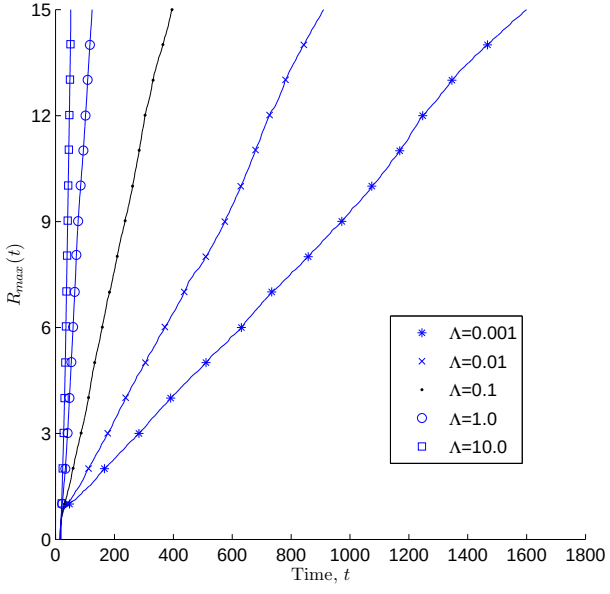


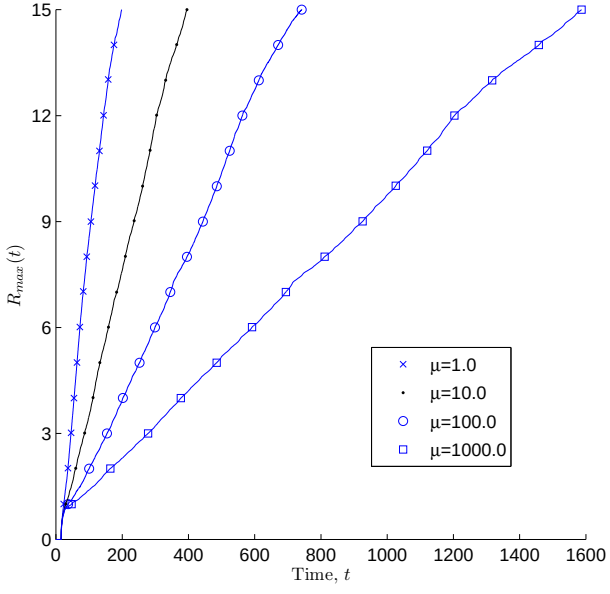
Blood vessels: θ_3 at $t = 800$



Parameter Dependence

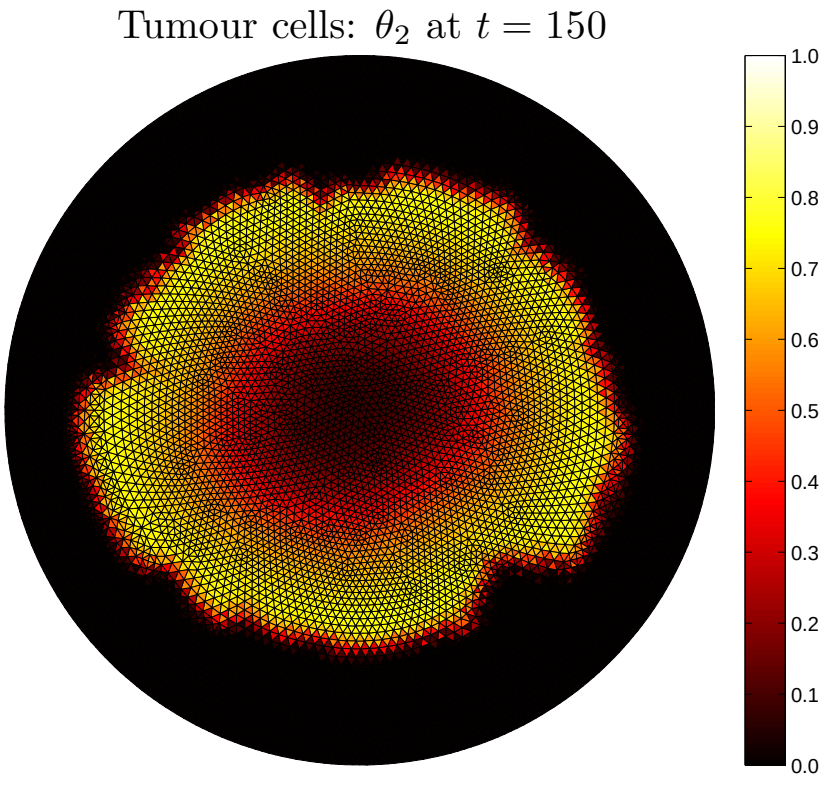


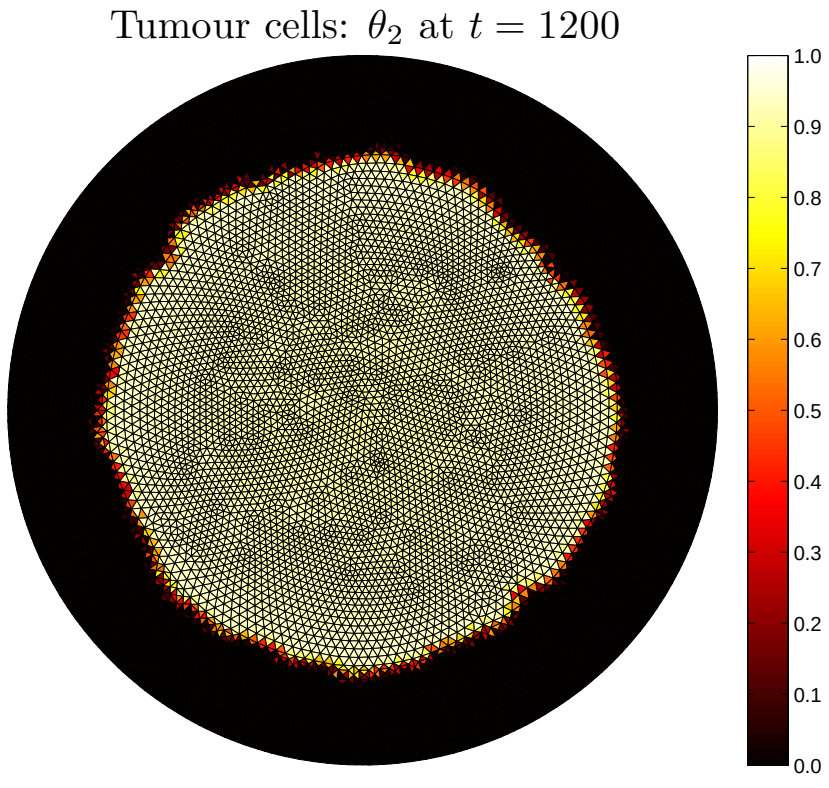




Nutrient diffusion rate (left), cell tension (middle), phase viscosity (right).

Front Irregularity





Variable phase viscosities: low (left), high (right).

Model Behaviour

- The proliferating rim/necrotic core structure is reproduced.
- Shapes can be almost circular (in 2D) or irregular.
- The regularity is most sensitive to the phase viscosities and the cell tension constant.
- Tumour growth is approximately linear.
- The growth rate is increased by increasing nutrient diffusion rates, cell birth rates or cell tension, or decreasing phase viscosities or cell death rates.

Issues

- Speed and memory
  - Iterative solvers, preconditioning, multigrid
  - Better efficiency needed for 3D, more phases, etc.
- Physical/biological realism
  - Measurable model parameters
- Numerical artefacts, resolution issues
  - Adaptive approaches?

Current Developments

- Multiscale asymptotic analysis is allowing us to scale the effects of the capillary-level drug delivery model up to the scale of a full tumour.
- The large-scale drug delivery model will be linked with a tumour response model.
- The response model will investigate the combined effects of chemotherapy and radiotherapy.
- The ultimate aim is to devise optimal, personalised, treatment strategies.