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Modelling Drug Delivery and Tumour Growth

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PART ONE

DRUG DELIVERY

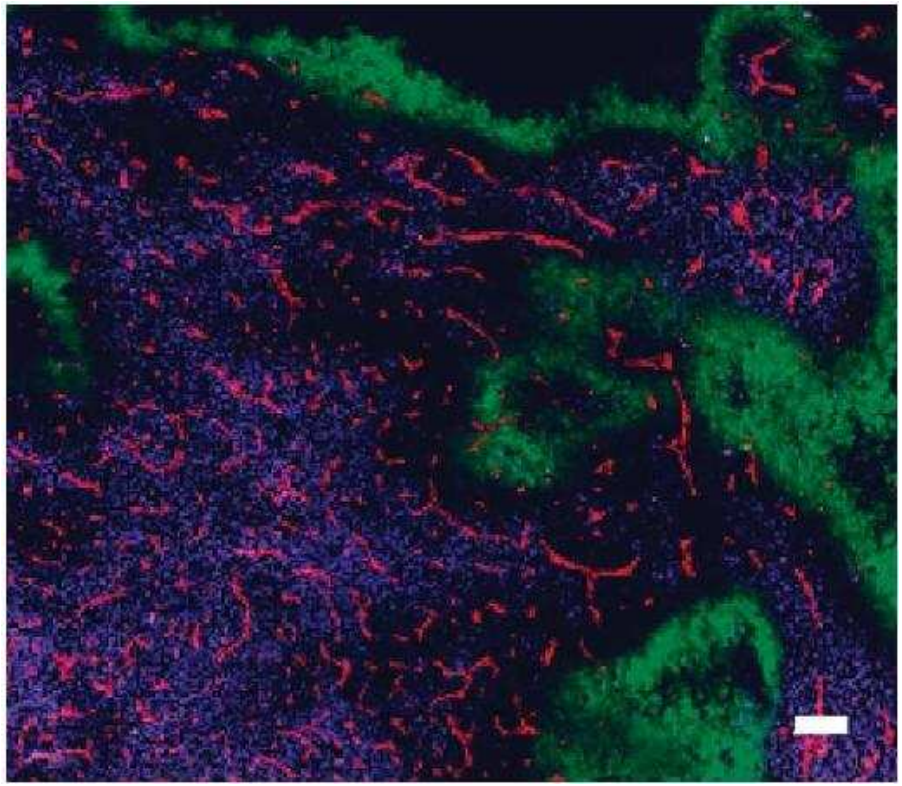
(TO TUMOURS)

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



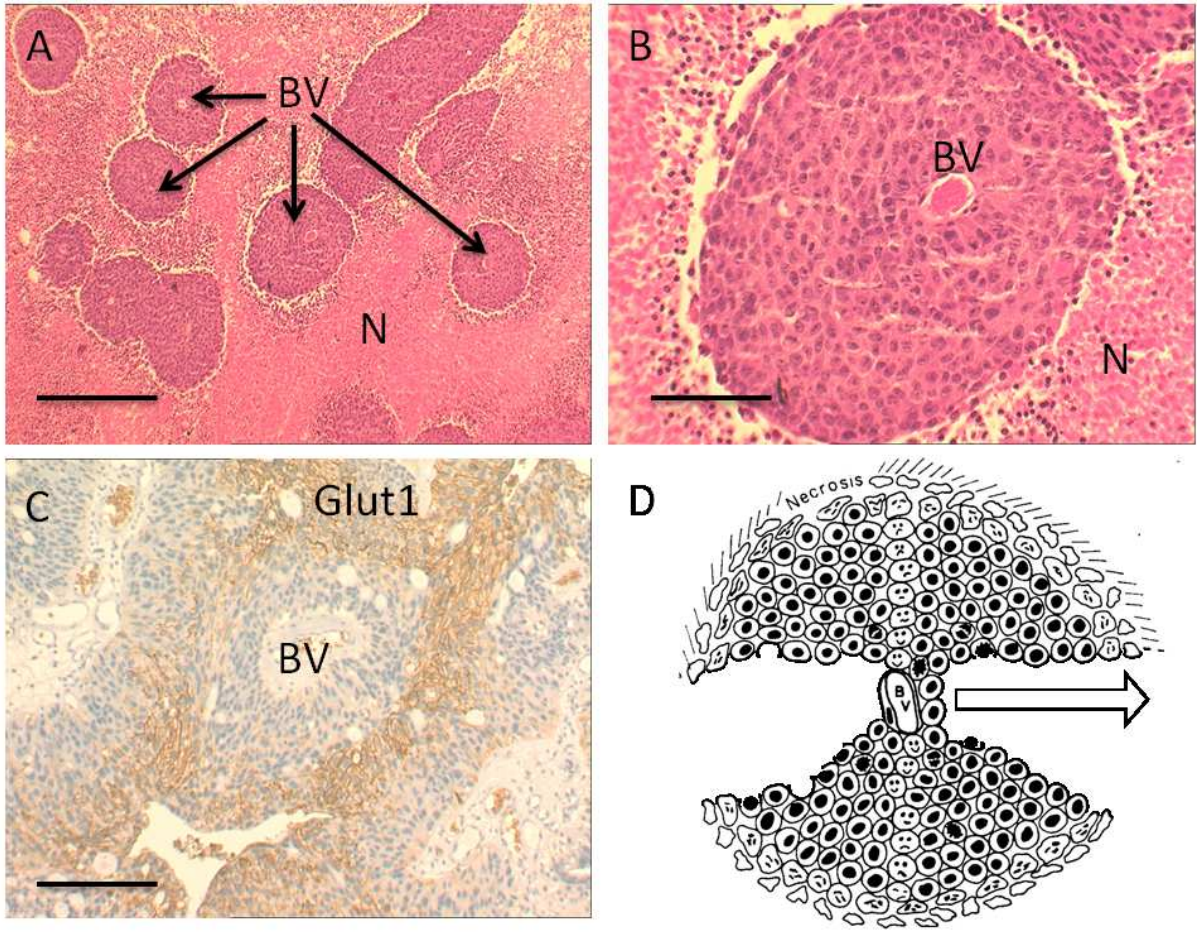
Blood Vessels (red): Drug (blue): Hypoxia (green)

Primeau *et al*, Clin Cancer Res, 11(24):8782–8788 (2005)

Drug Delivery

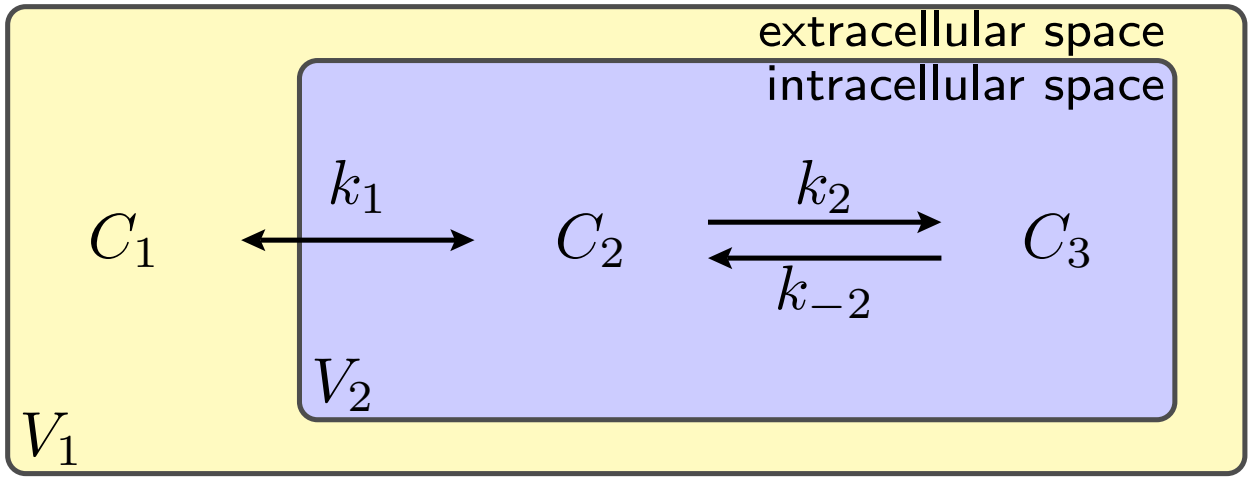
- Realistic tumour vasculatures are difficult to obtain.
- They would also be expensive to simulate.
- Start by considering a single blood vessel and the surrounding layers of cells.
- This set-up resembles a tumour cord.

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 or k_0)

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.

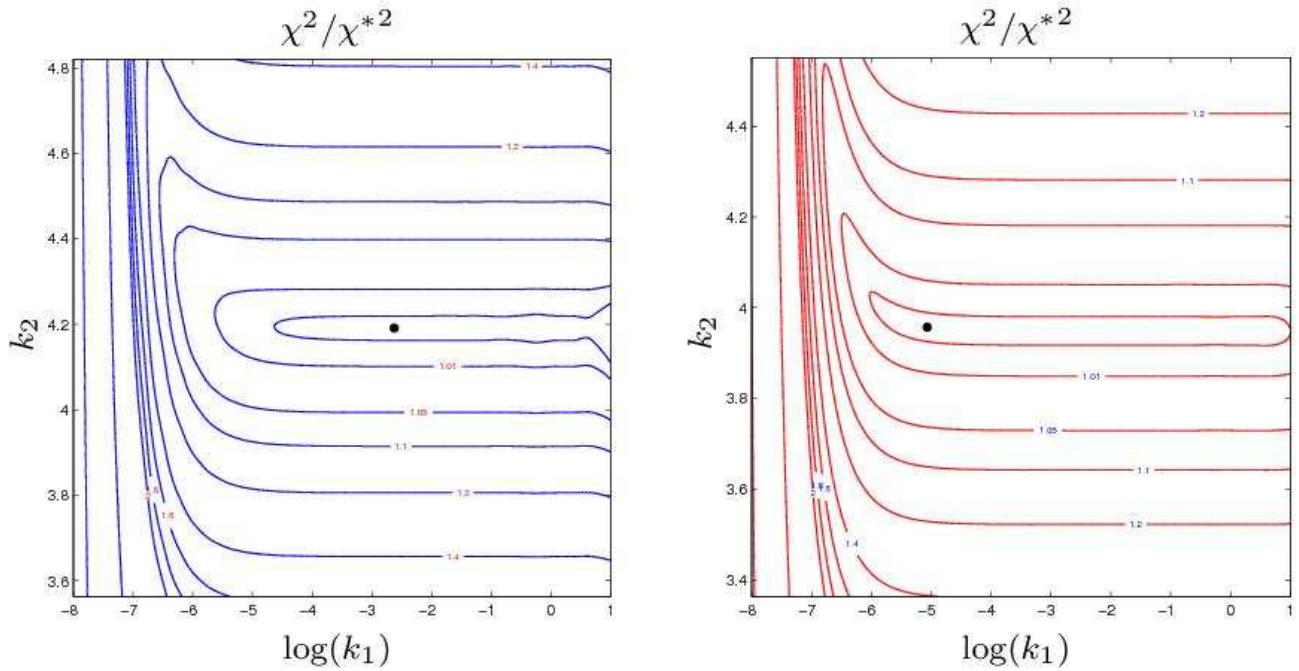
Binding Experiments

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.

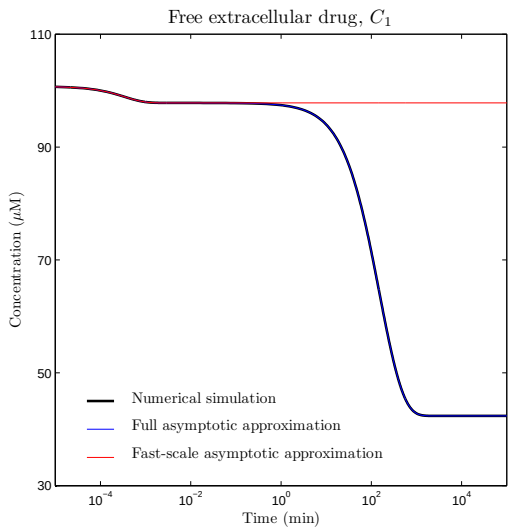
Parameter Sensitivity

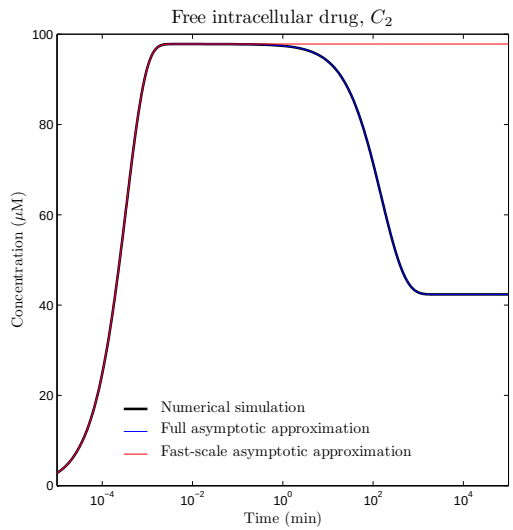
This system is extremely insensitive to the transmembrane transport rate (k_1)...as long as it is fast enough.

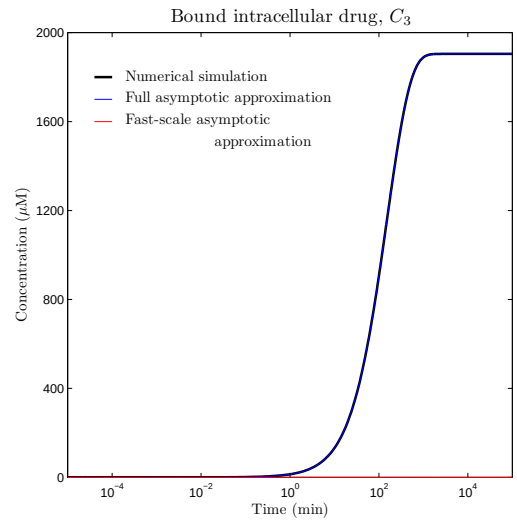


Timescales

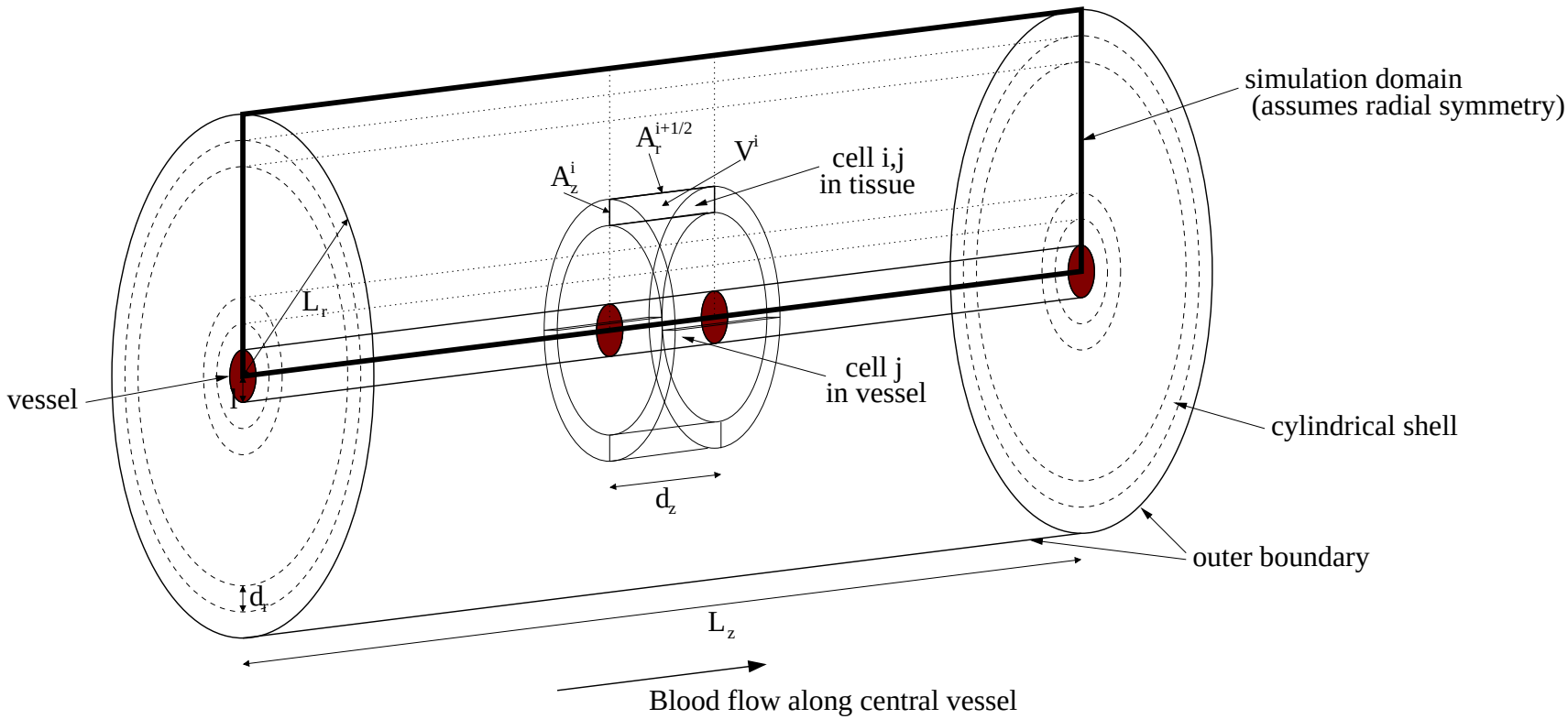
The fit to the data suggests two distinct time-scales. These are confirmed by mathematical analysis and can be linked to the literature.







A Cylindrically-Symmetric Model



A Cylindrically-Symmetric Model

A compartment model is implemented.

- Each computational cell constitutes 3 compartments.
- Drug is exchanged between cells and compartments within cells.
- This is effectively a finite volume approach with the mesh size dictated by the biological cell size.
- A continuum model could be used instead.

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

Transport Model

Tissue model (2D):

$$\begin{aligned}
\delta_1 V^i \frac{dC_1^{i,j}}{dt} &= A_r^{i-1/2} k_0 (C_1^{i-1,j} - C_1^{i,j}) + A_r^{i+1/2} k_0 (C_1^{i+1,j} - C_1^{i,j}) \\
&\quad + A_z^i k_0 (C_1^{i,j-1} - C_1^{i,j}) + A_z^i k_0 (C_1^{i,j+1} - C_1^{i,j}) \\
&\quad + a^i k_1 (C_2^{i,j} - C_1^{i,j}) \\
\delta_2 V^i \frac{dC_2^{i,j}}{dt} &= a^i k_1 (C_1^{i,j} - C_2^{i,j}) \\
&\quad - \delta_2 V^i k_2 C_2^{i,j} (C_0 - C_3^{i,j}) + \delta_2 V^i k_{-2} C_3^{i,j} \\
\delta_2 V^i \frac{dC_3^{i,j}}{dt} &= \delta_2 V^i k_2 C_2^{i,j} (C_0 - C_3^{i,j}) - \delta_2 V^i k_{-2} C_3^{i,j}
\end{aligned}$$

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

Transport Model

Vessel model (1D):

$$V_v^j \frac{d\,C_v^j}{dt} \;=\; -A_v^j \lambda (C_v^j - C_v^{j-1}) + A_r^{1/2} k_v (C_1^{1,j} - C_v^j)$$

Boundary conditions:

- For the tissue,

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

$$D \left.\frac{\partial C_1}{\partial r}\right|_{r=L_r} \;=\; D \left.\frac{\partial C_1}{\partial z}\right|_{z=0} \;=\; D \left.\frac{\partial C_1}{\partial z}\right|_{z=L_z} \;=\; 0$$

- For the vessel,

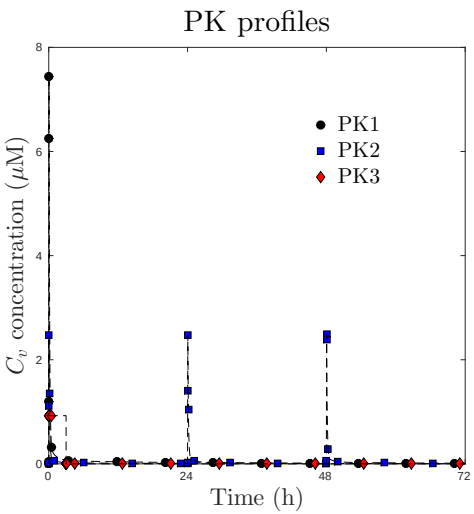
$$\left. C_v \right|_{z=0} \;=\; C_v(t)$$

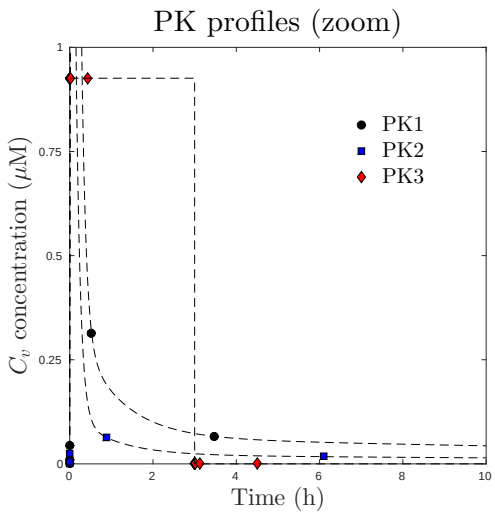
Numerical Experiments

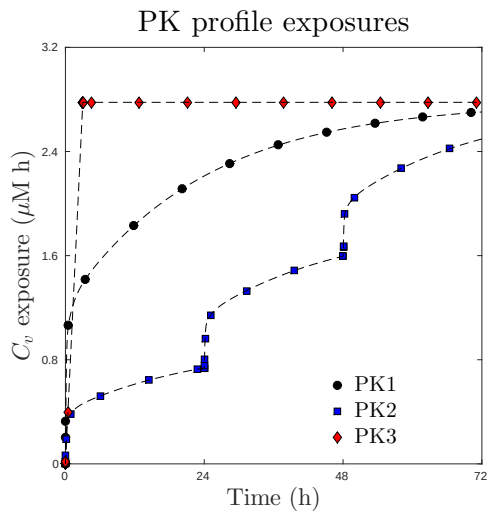
To investigate:

- the dependence on model parameters.
- the effect of changing the pharmacokinetic profile.
- the variation with distance from supply.

Pharmacokinetic Profiles

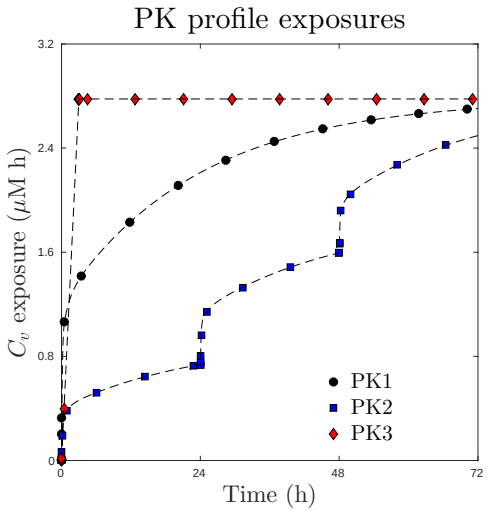


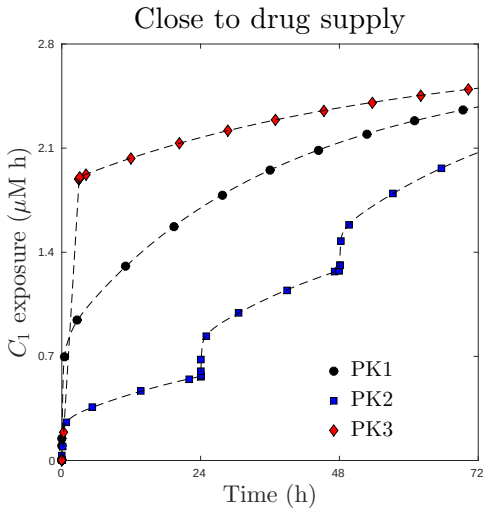


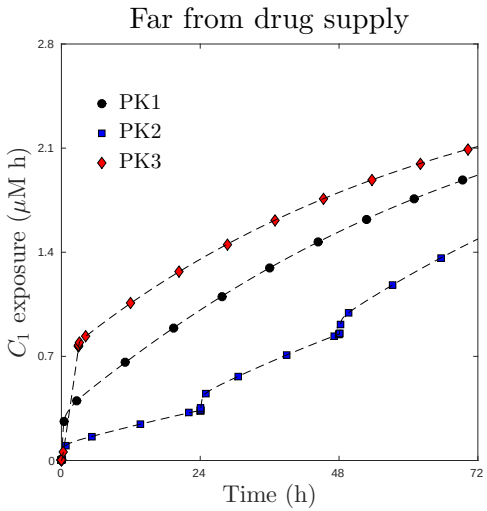


- A tri-exponential decay profile from patient data (PK1).
- A profile mimicking three rapid infusions, each one third the dose (PK2).
- A constant concentration profile (PK3).
- The parameters are chosen to give the same "area under curve", *i.e.* $\int_0^\infty c_v \, \mathrm{d}t$.

Free Extracellular Drug

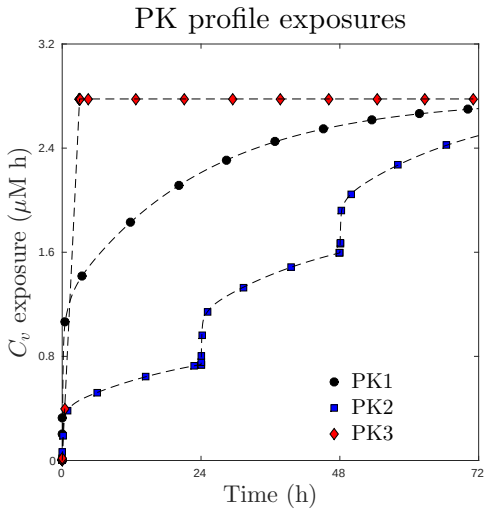


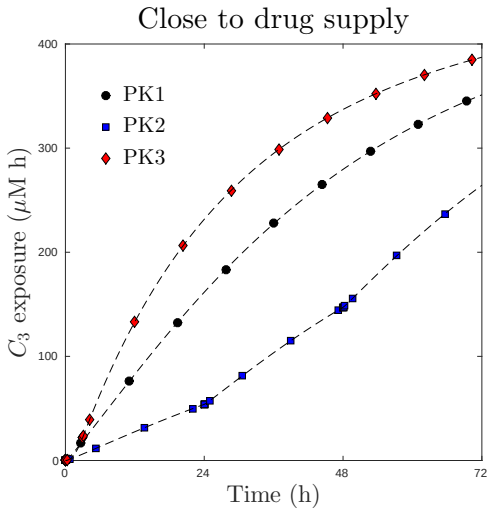


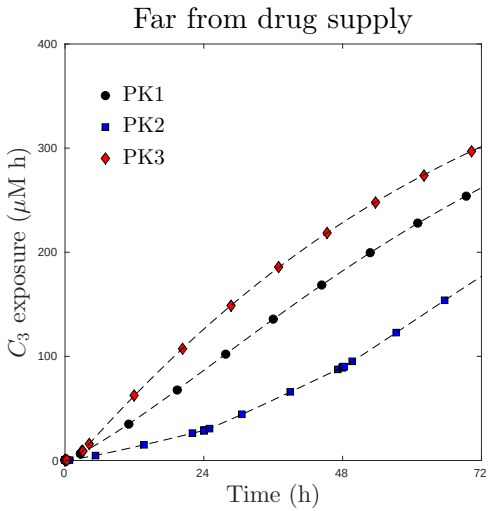


Dependence of free extracellular drug exposure on time: close to the supply (middle); far from the supply (right).

Bound Intracellular Drug



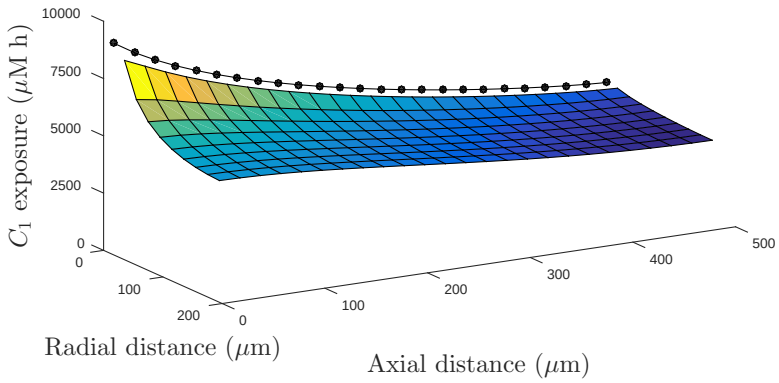




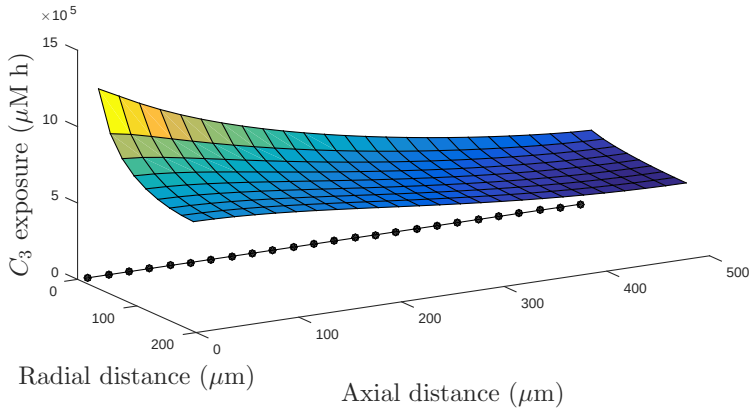
Dependence of bound intracellular drug exposure on time: close to the supply (middle); far from the supply (right).

Spatial Variation

Extracellular free drug, modified parameters

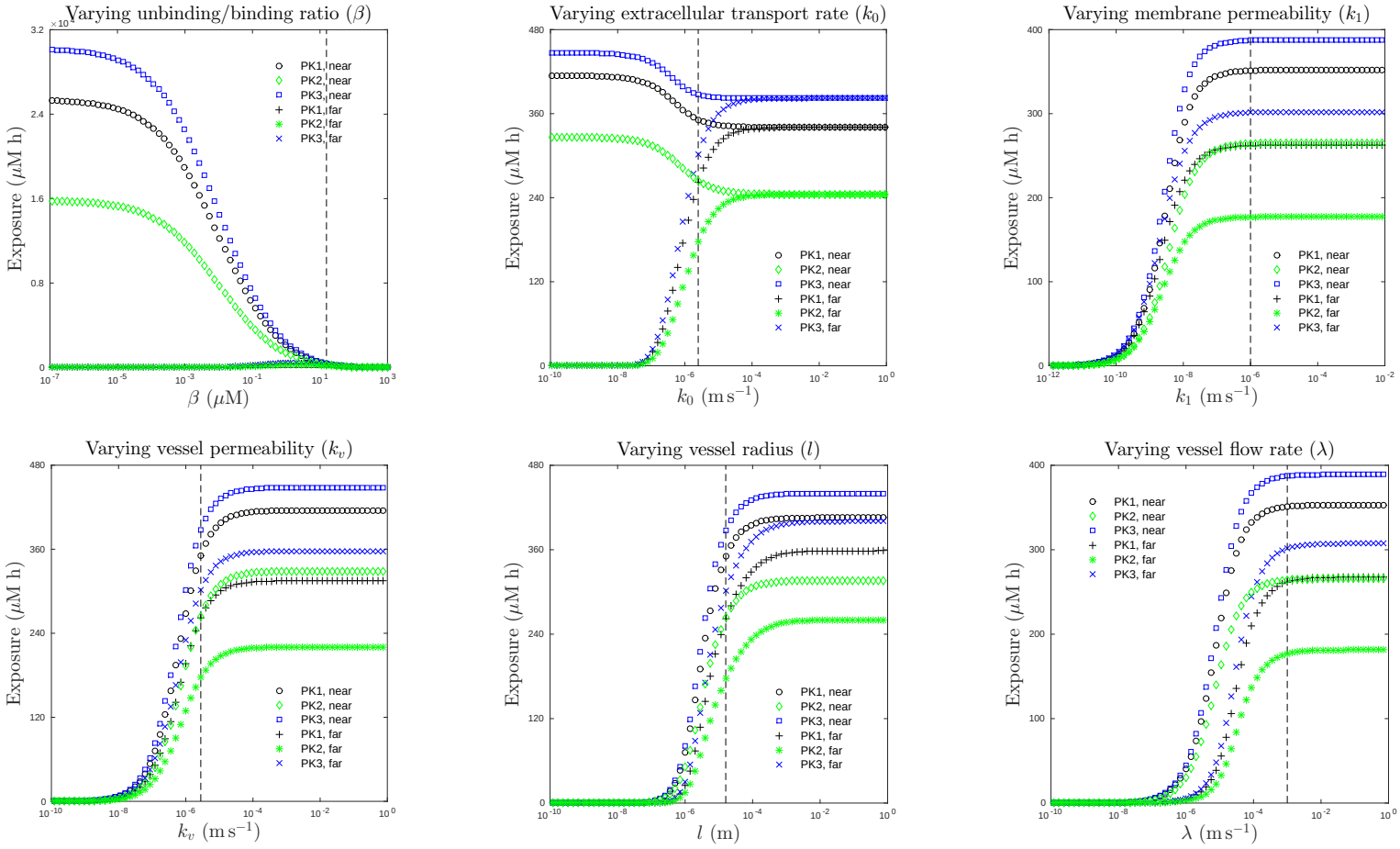


Intracellular bound drug, modified parameters



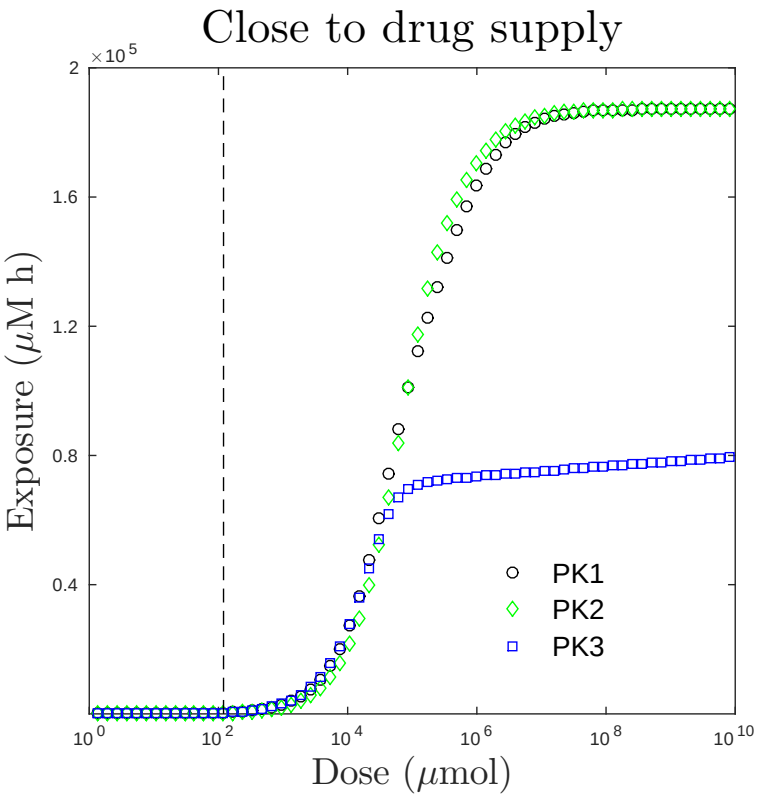
Variation of exposure in space:
free extracellular drug (left), bound intracellular drug (right).

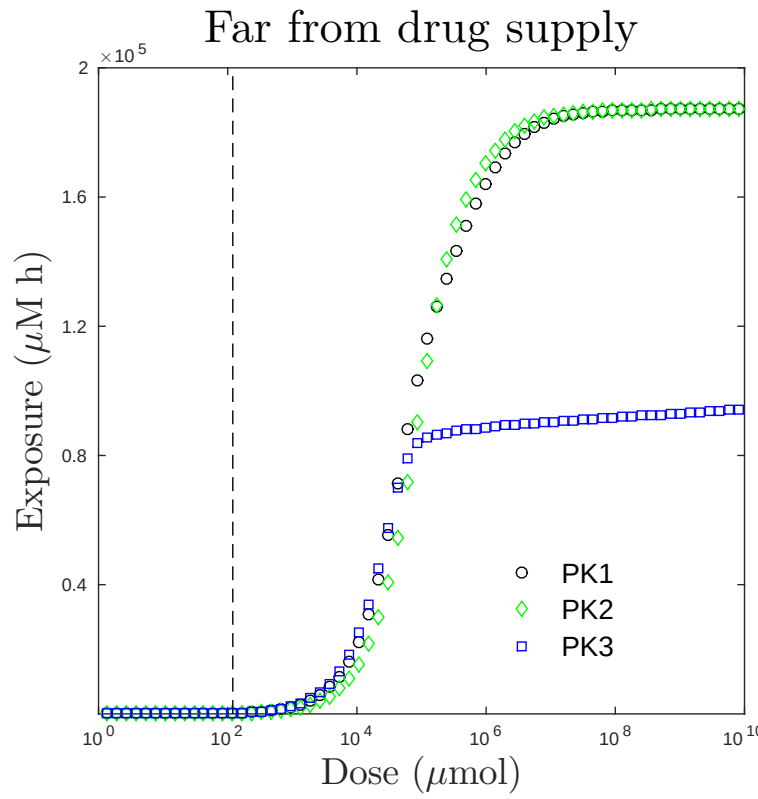
Varying Model Parameters



Dependence of bound intracellular drug exposure on β, k_0, k_1, k_v, l and λ.

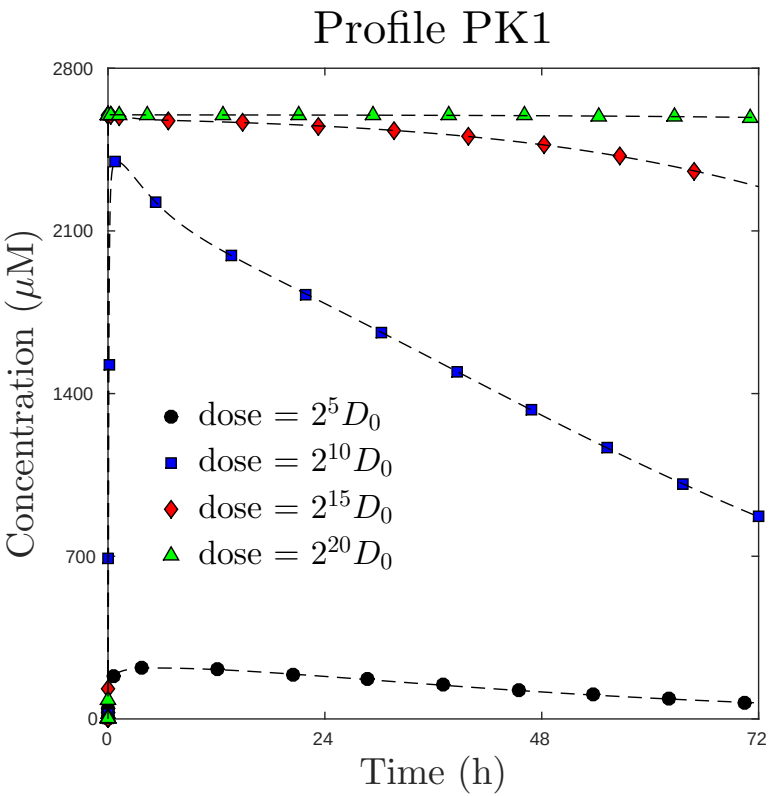
Varying Dose

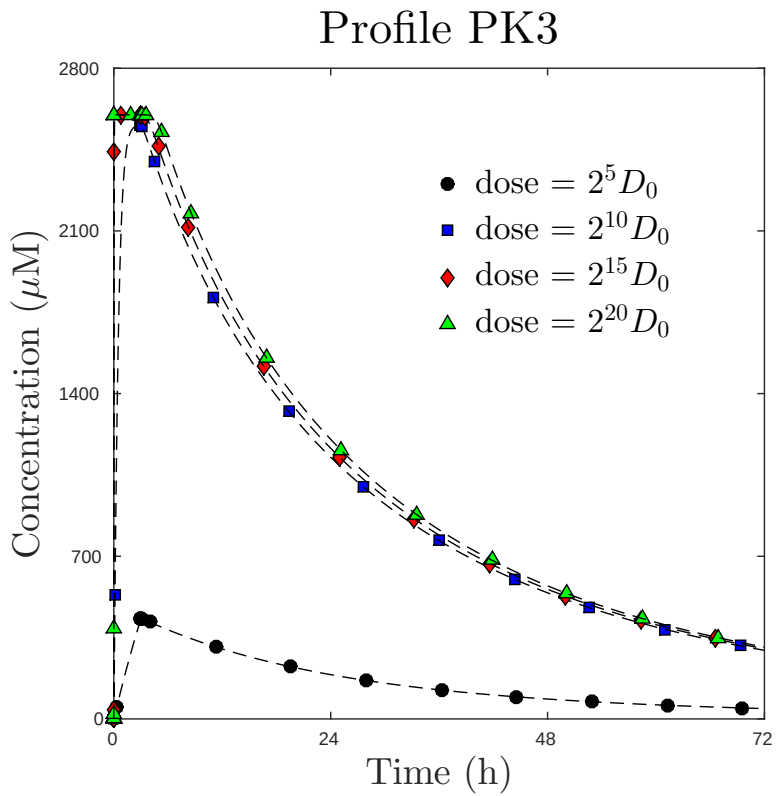




Dependence of bound intracellular drug exposure on dose.

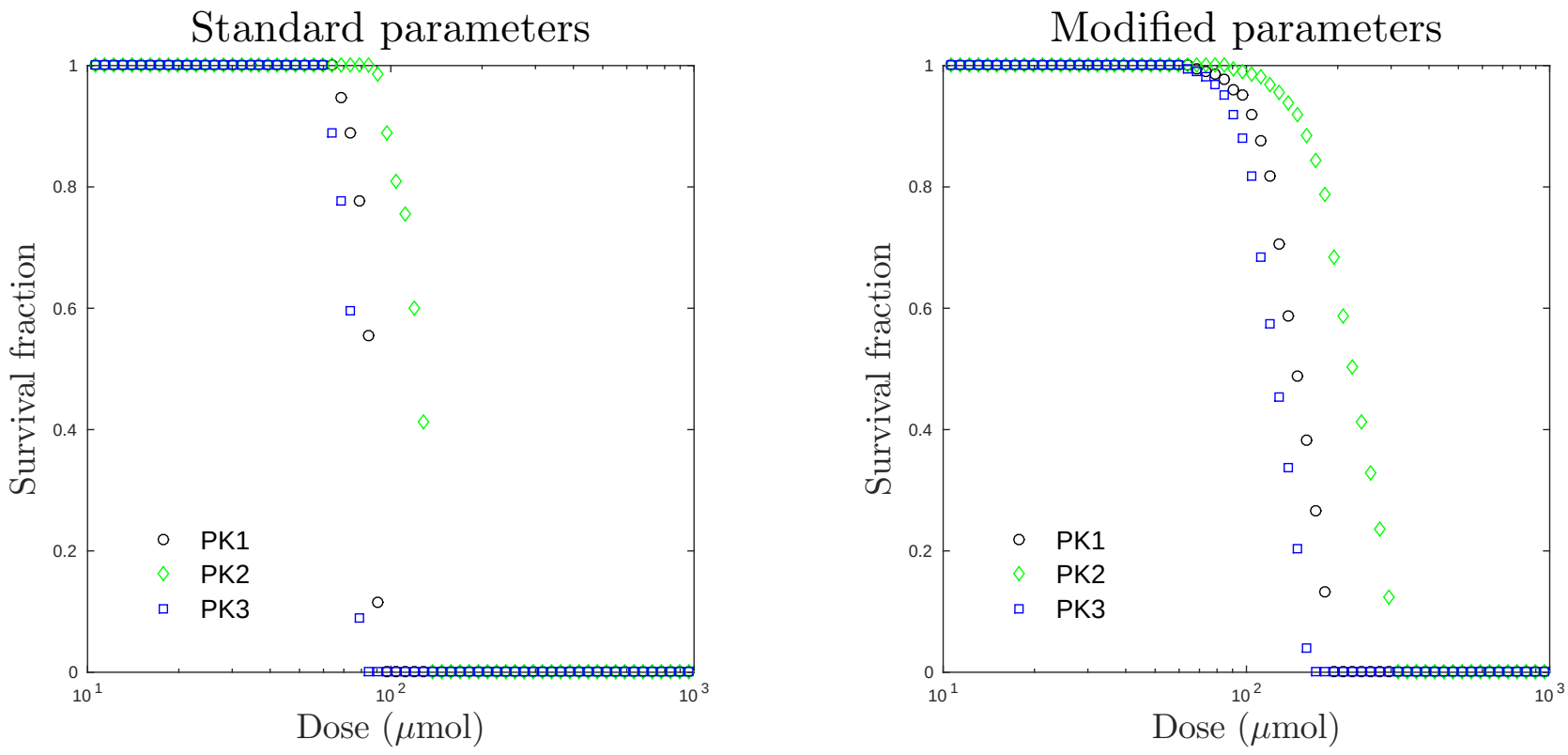
Varying Dose





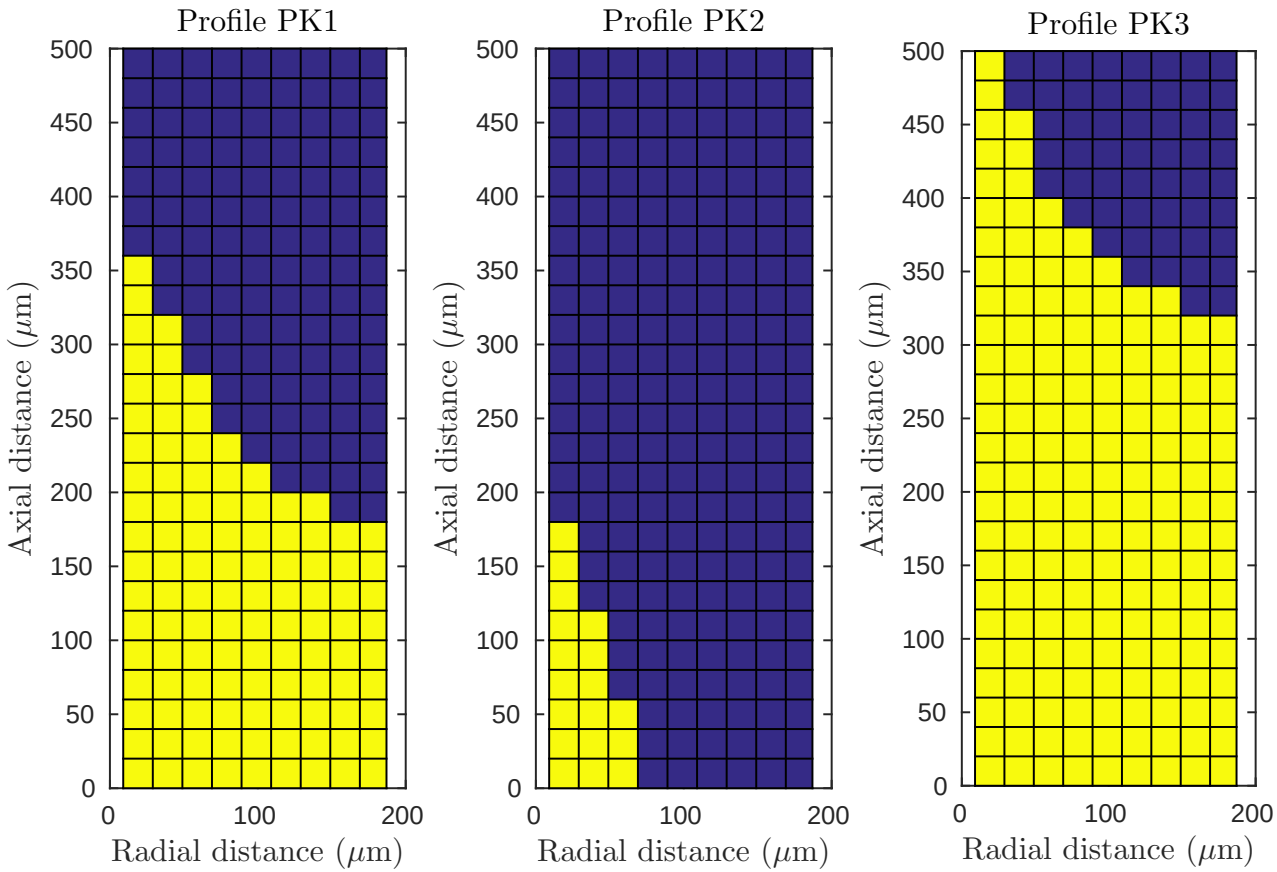
Dependence of bound intracellular drug exposure on time for two PK profiles.

Varying Dose



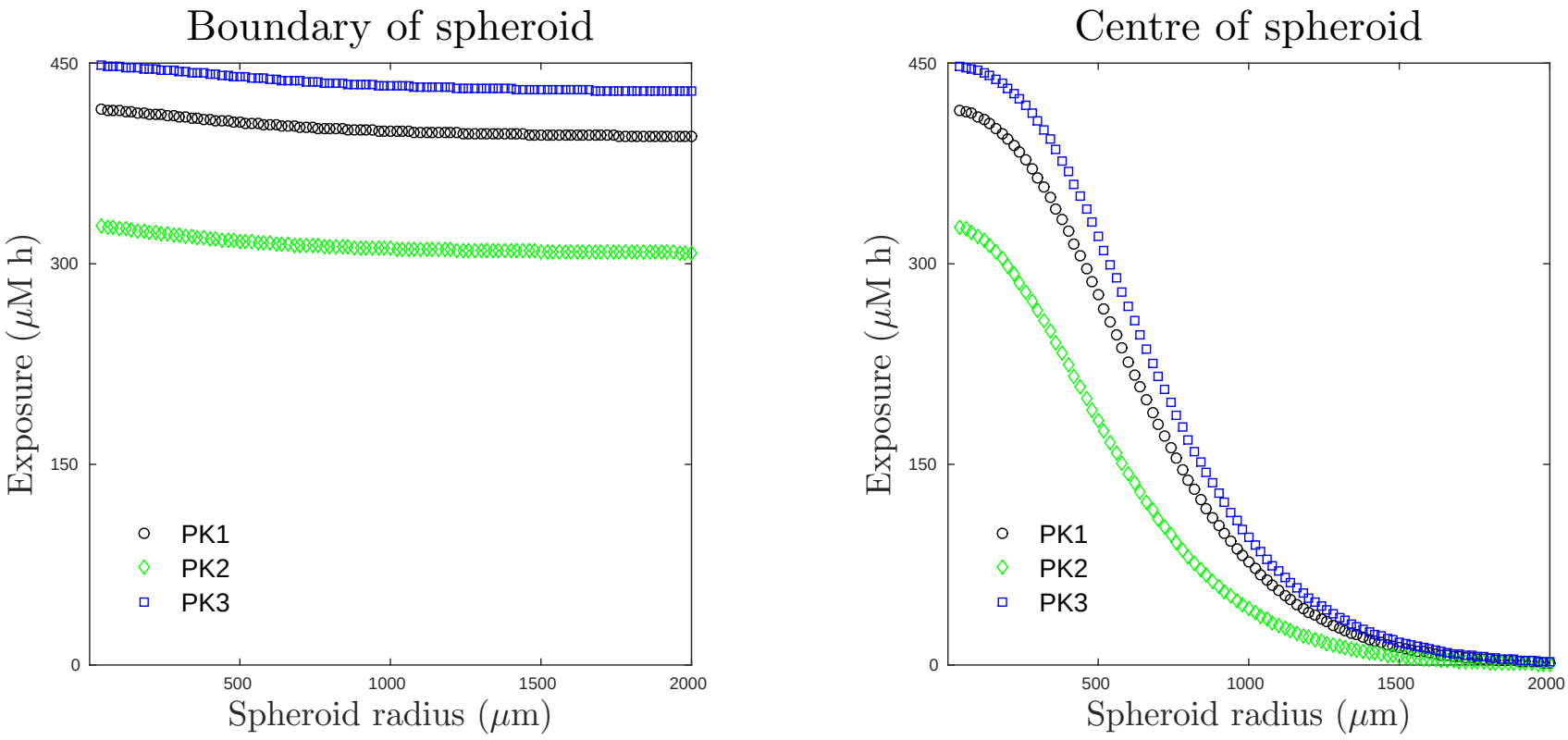
Dependence of survival fraction on dose.

Varying Dose



Surviving cells (blue) and dead cells (yellow) for different PK profiles.

Varying Distance From Source



Dependence of bound intracellular drug exposure on spheroid radius.

Preliminary Observations

- A simple transport model can be chosen because the main source of variation is in the experimental data.
- Exposure to bound drug decreases with distance from the source.
- The most effective mode of administration depends on the model parameters, *i.e.* it is potentially patient-specific.
- There is an optimal binding ratio beyond which stronger binding inhibits drug from reaching distant regions.
- Exposure to drug increases with transport rate across the cell membrane, vessel wall permeability, vessel radius and blood flow velocity.
- Rapid diffusion facilitates uniform drug distribution.

The Next Steps

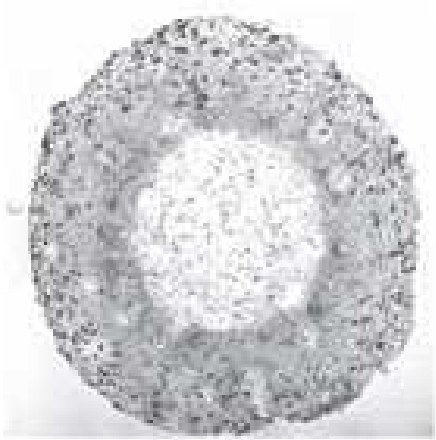
- Convective transport, validated by transwell experiments and possibly artificial tumour cords.
- Quantification of uncertainty in the model parameter values and the simulation results.
- More (parameterised?) processes and cell types.
  - Cell cycle (mitosis, apoptosis, necrosis)
  - Cell response (and a tumour growth model)
  - Drug clearance mechanisms
- Realistic vasculature in three dimensions, using either direct simulation or homogenisation (via multiscale asymptotics).
  - Good scientific computation becomes important.

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 models of Breward, Byrne and Lewis (2002,2003)

- Phases: cells (healthy and tumour), 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.

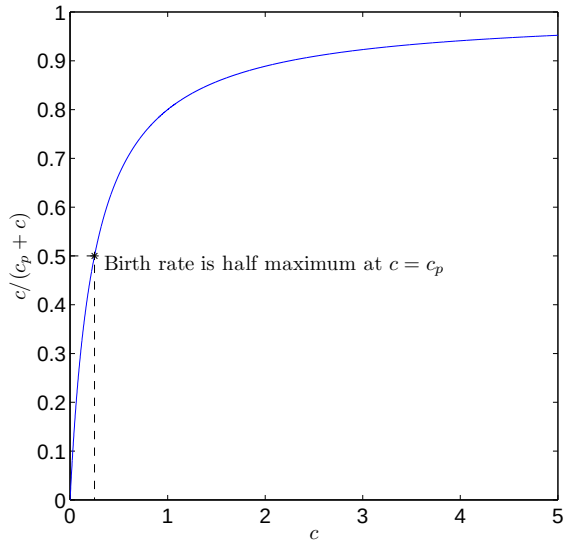
- The q_i are chosen to ensure $\theta_i \in [0, 1]$.

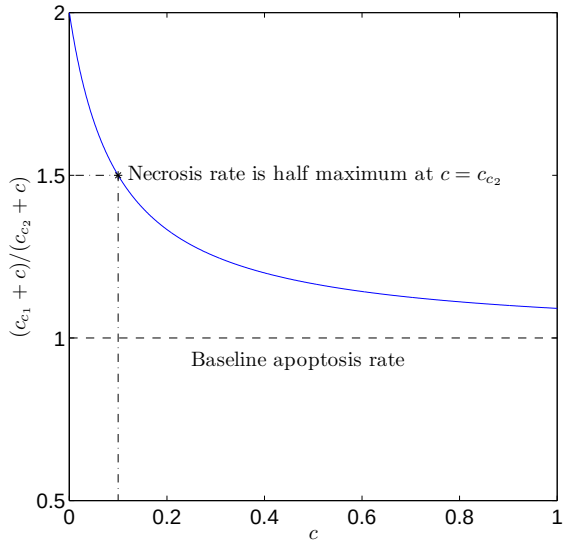
Mass Sources

For the cell phases (α_1, α_2):

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

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





Mass Sources

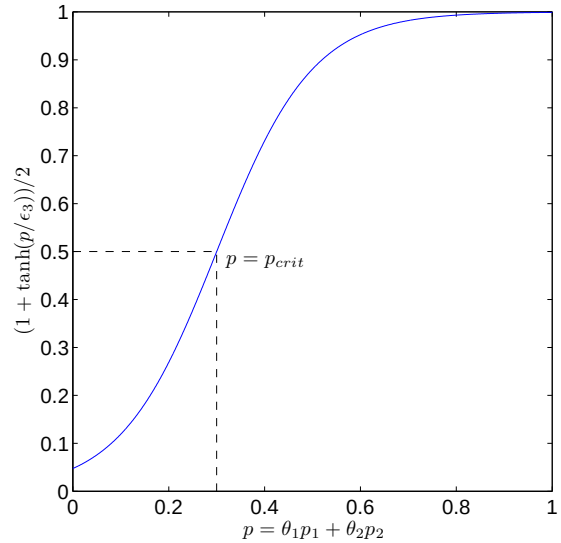
For the blood vessel phase (γ):

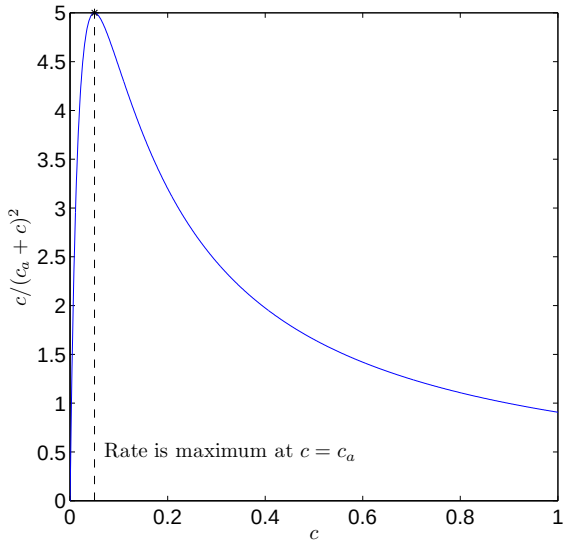
$$q_\gamma = \underbrace{-k_3\,\gamma\,\mathcal{H}(\alpha_1 p_{\alpha_1} + \alpha_2 p_{\alpha_2} - p_{crit}, \epsilon_3)}_{\text{occlusion}} + \underbrace{k_4\,(\alpha_1+\alpha_2)\,\gamma\left(\frac{\beta}{\varepsilon+\beta}\right)\left(\frac{c}{(c_a+c)^2}\right)}_{\text{angiogenesis}}$$

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

For the remaining material (β):

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





Momentum Balance

Assuming low Reynolds number flow, the phase velocities can be determined from momentum conservation,

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

- $\boldsymbol{\sigma}_i$ 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

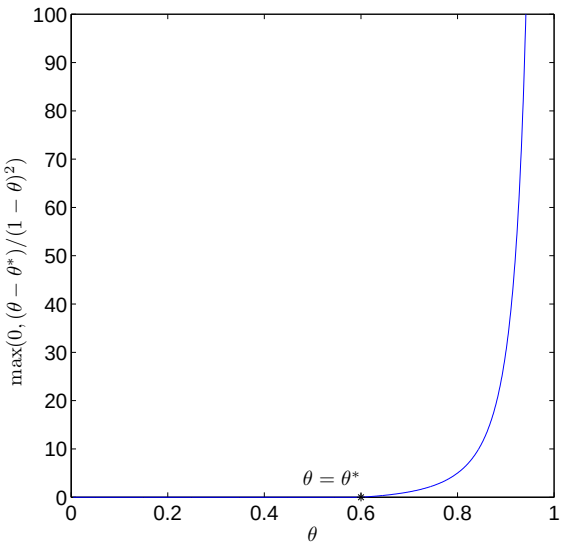
- Pressure due to the blood vessel phase is assumed independent of the local flow, *i.e.* $p_\gamma = p_\gamma^*$.
- Cells act like a fluid with additional cell-cell interactions, *i.e.*

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

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 reactive 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. drug, 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 normal 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

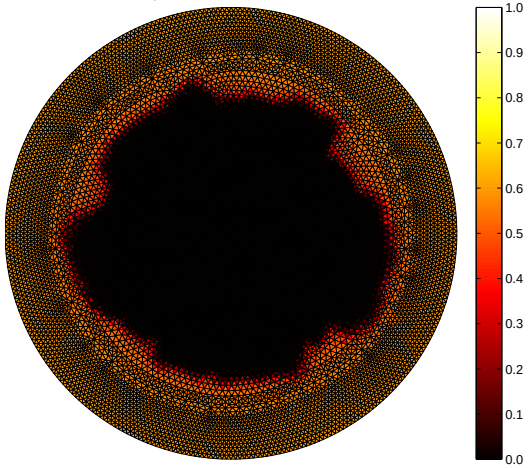
- Circular domain, radius 16
- Triangular mesh: 2349 nodes, 4539 elements
  - Gives 76237 DoFs in FEM solve
- "Free" boundaries: zero normal stress except β
- Seed "healthy tissue" in centre with

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

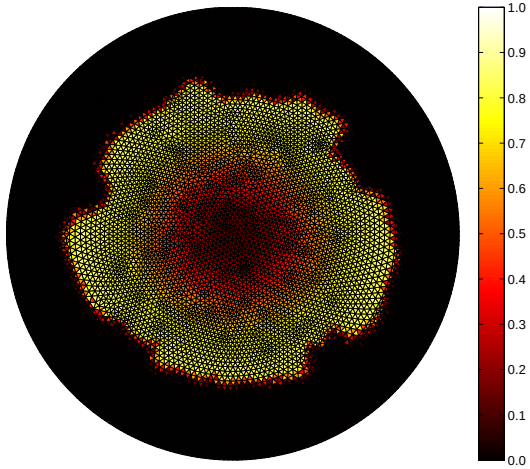
(animations)

Phase Volume Fractions

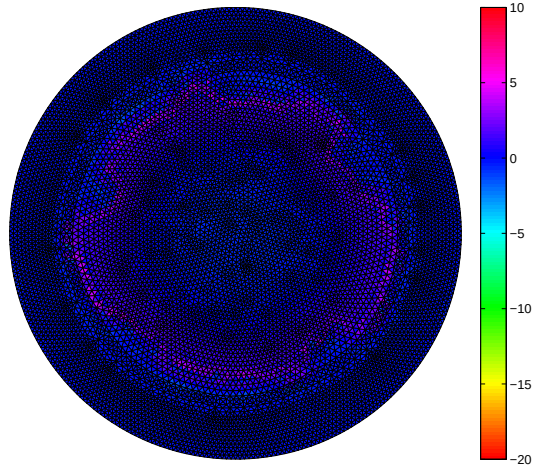
Healthy cells: θ_1 at $t = 300$



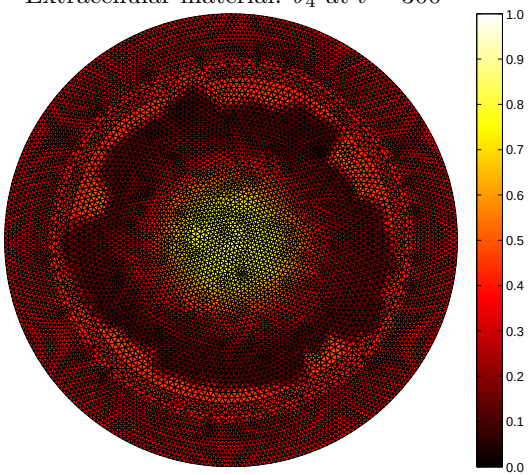
Tumour cells: θ_2 at $t = 300$



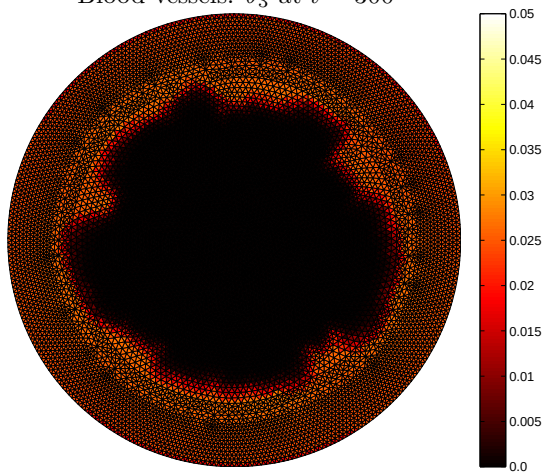
Cell pressure: p_1,p_2 at $t = 300$



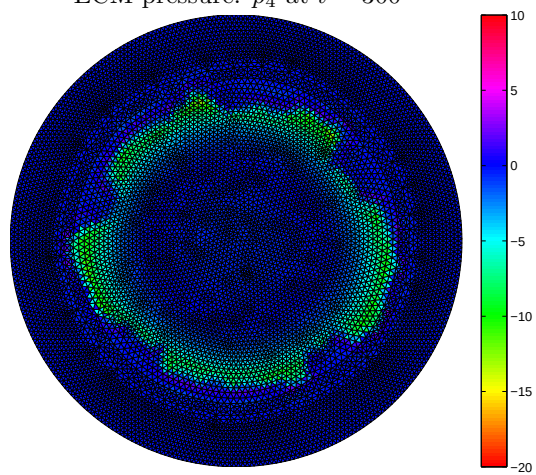
Extracellular material: θ_4 at $t = 300$



Blood vessels: θ_3 at $t = 300$

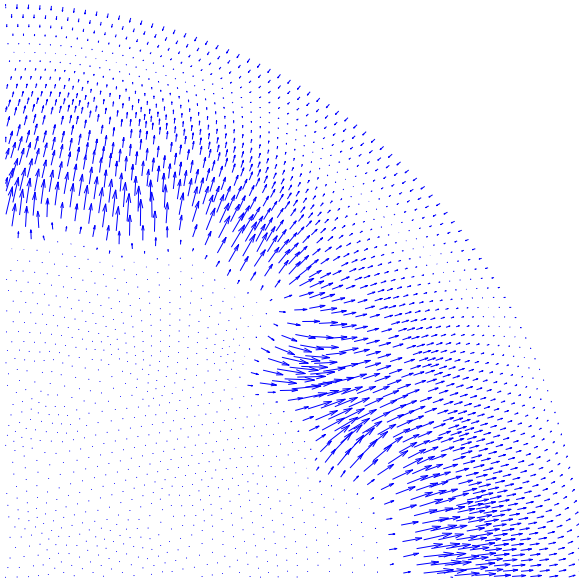


ECM pressure: p_4 at $t = 300$

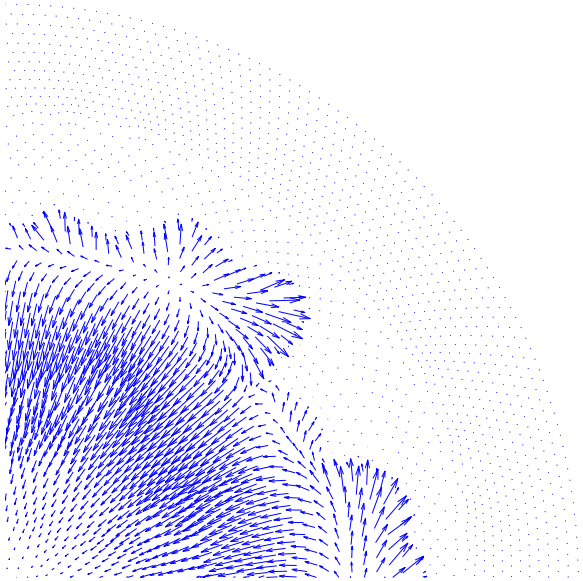


Phase Fluxes

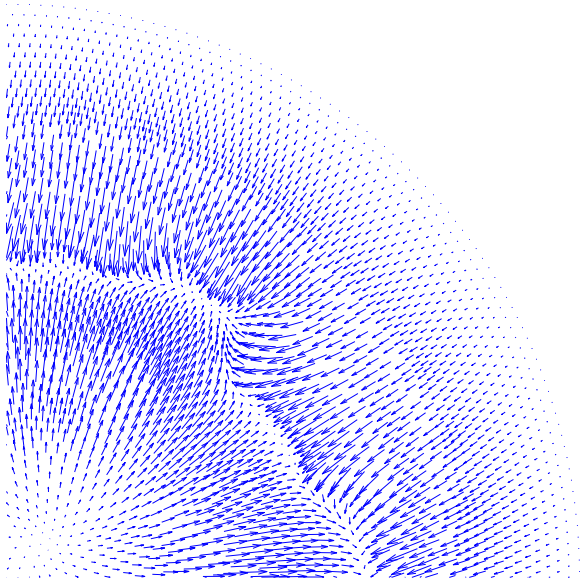
Healthy cells: $\theta_1 \vec{u}_1'$ at $t = 300$



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

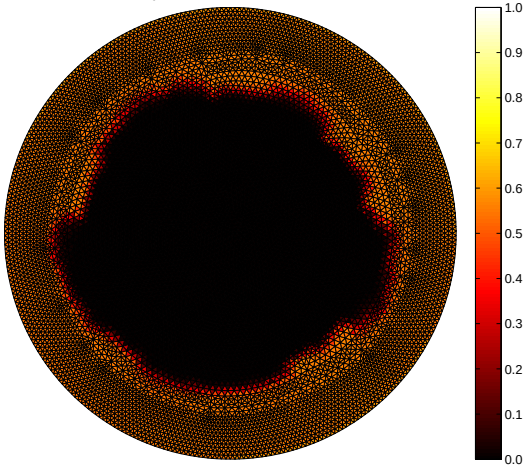


Extracellular material: $\theta_4 \vec{u}_4'$ at $t = 300$

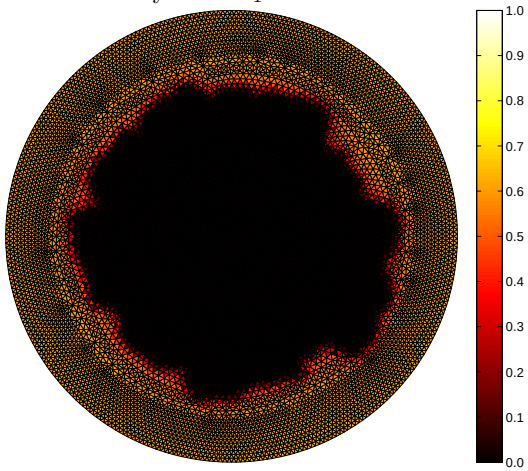


Varying Nutrient Diffusion

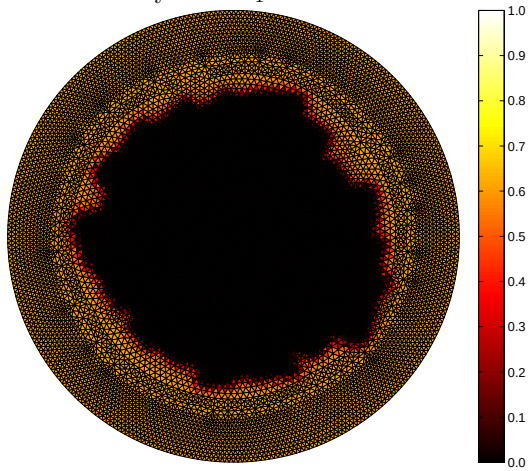
Healthy cells: θ_1 at $t = 225$



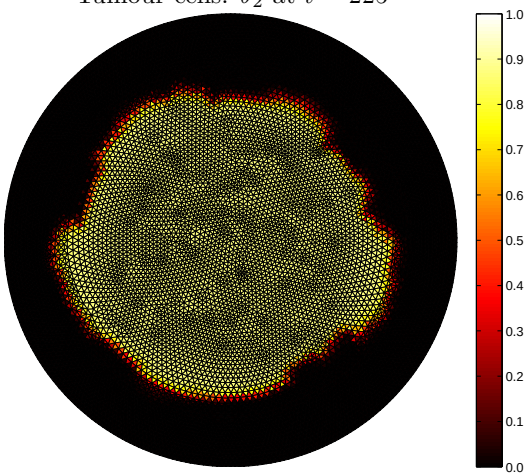
Healthy cells: θ_1 at $t = 525$



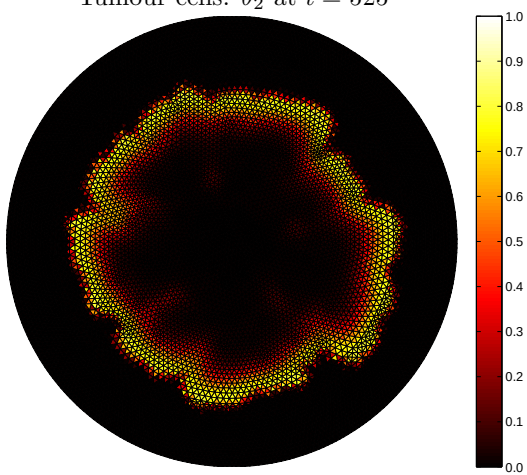
Healthy cells: θ_1 at $t = 800$



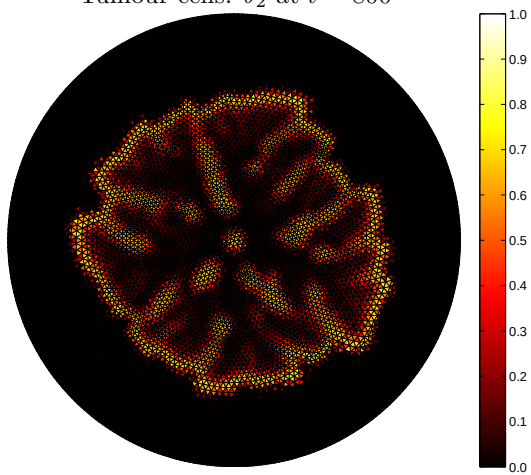
Tumour cells: θ_2 at $t = 225$



Tumour cells: θ_2 at $t = 525$

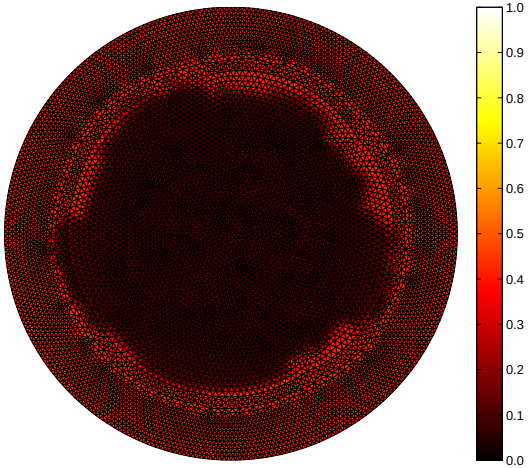


Tumour cells: θ_2 at $t = 800$

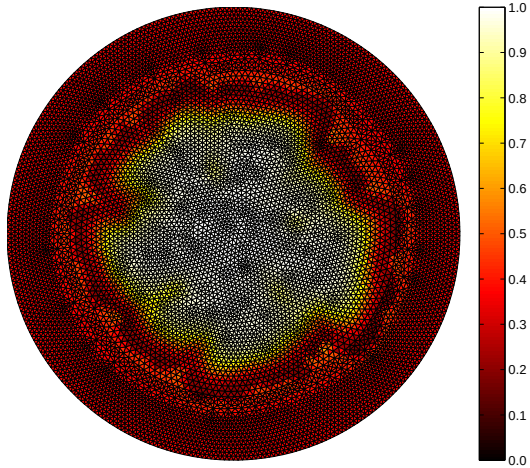


Varying Nutrient Diffusion

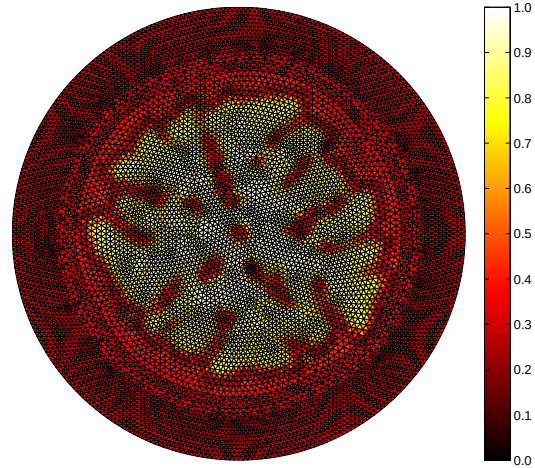
Extracellular material: θ_4 at $t = 225$



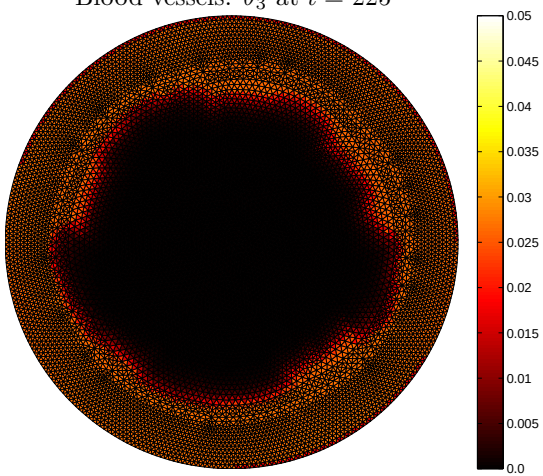
Extracellular material: θ_4 at $t = 525$



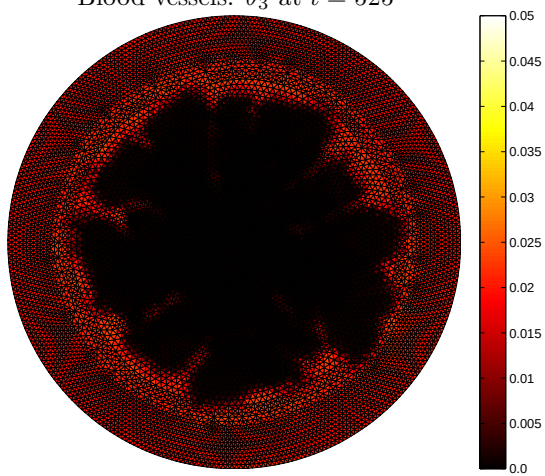
Extracellular material: θ_4 at $t = 800$



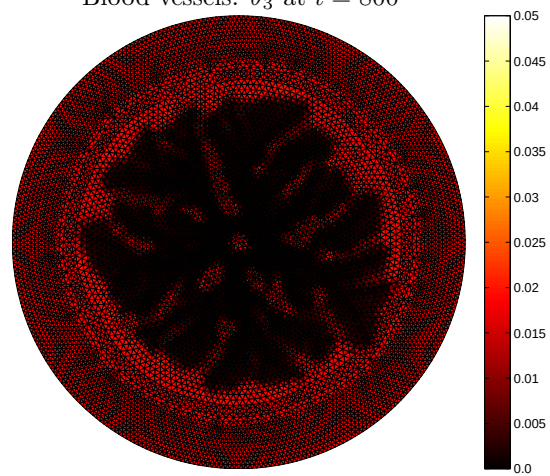
Blood vessels: θ_3 at $t = 225$



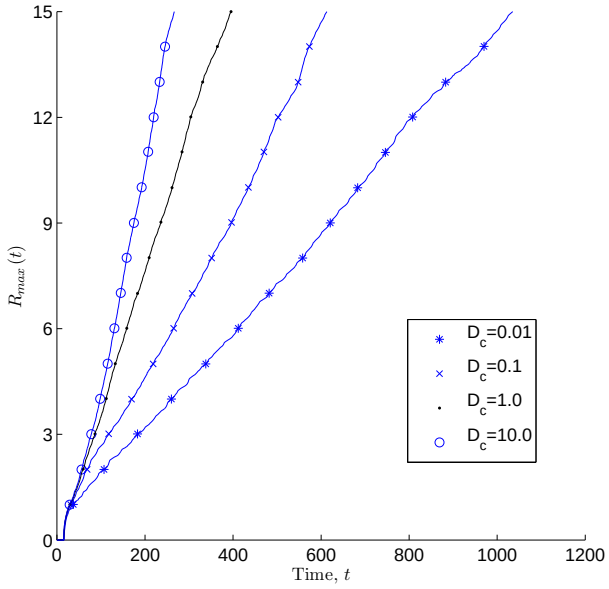
Blood vessels: θ_3 at $t = 525$

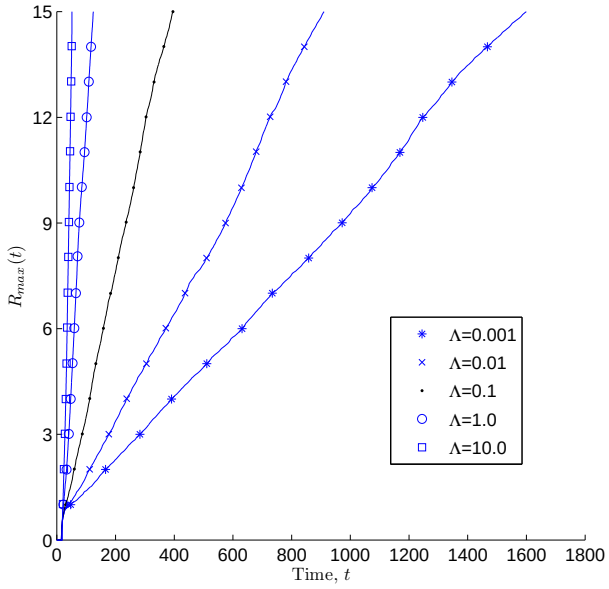


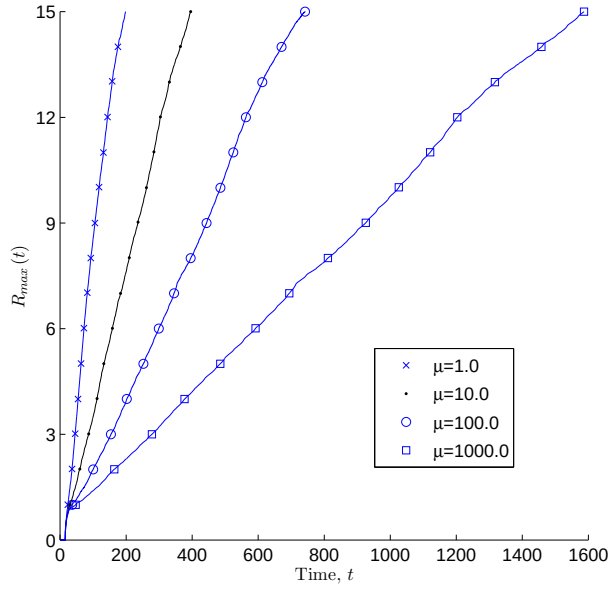
Blood vessels: θ_3 at $t = 800$



Parameter Dependence

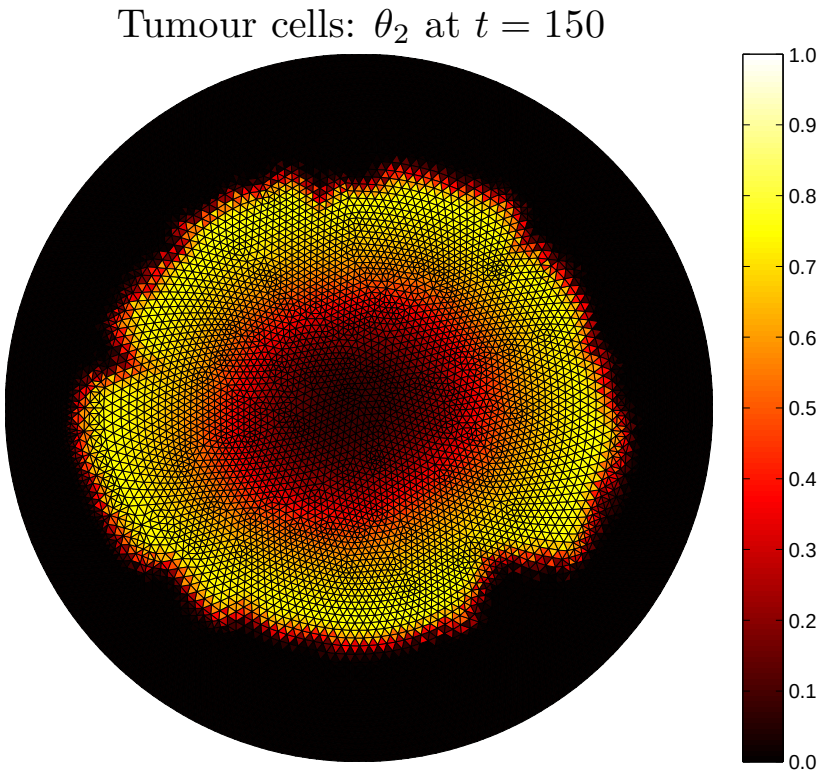


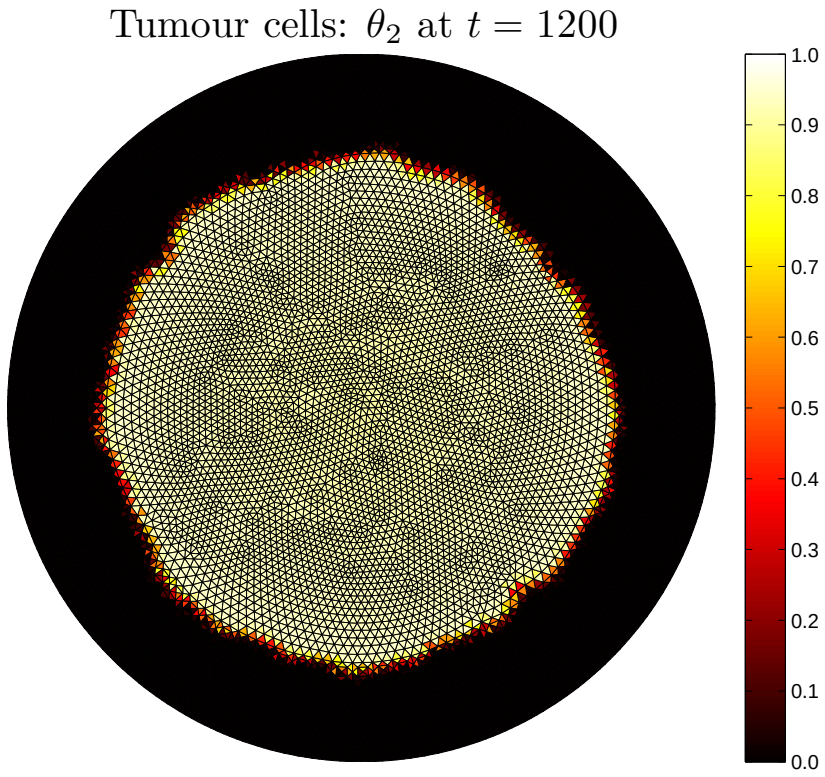




Nutrient diffusion rate (left), cell tension (middle), phase viscosity (right).

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 highly irregular.
- The regularity is most sensitive to the phase viscosities and the cell tension constant.
- Tumour growth is approximately linear in both one and two dimensions.
- 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, node reordering, preconditioning, multigrid
  - Better efficiency needed for 3D, more phases, etc.
- Physical/biological realism
  - Measurable model parameters
- Numerical artefacts, resolution issues
  - Adaptive approaches?

Related Work

- Multiscale asymptotic analysis for more efficient representation of multiphase dynamics.
- Combining drug delivery (and radiation therapy) with tumour response.
- Uncertainty quantification of parameterisation and simulation results in drug delivery and tumour growth.
- The ultimate aim is to devise optimal, personalised, treatment strategies.