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School of Computing
Scientific Computation Group

Quantitative Cancer Therapeutics

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and

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(Funded by Yorkshire Cancer Research)

Scientific Computation Seminar, 8th February 2013

Drug Delivery

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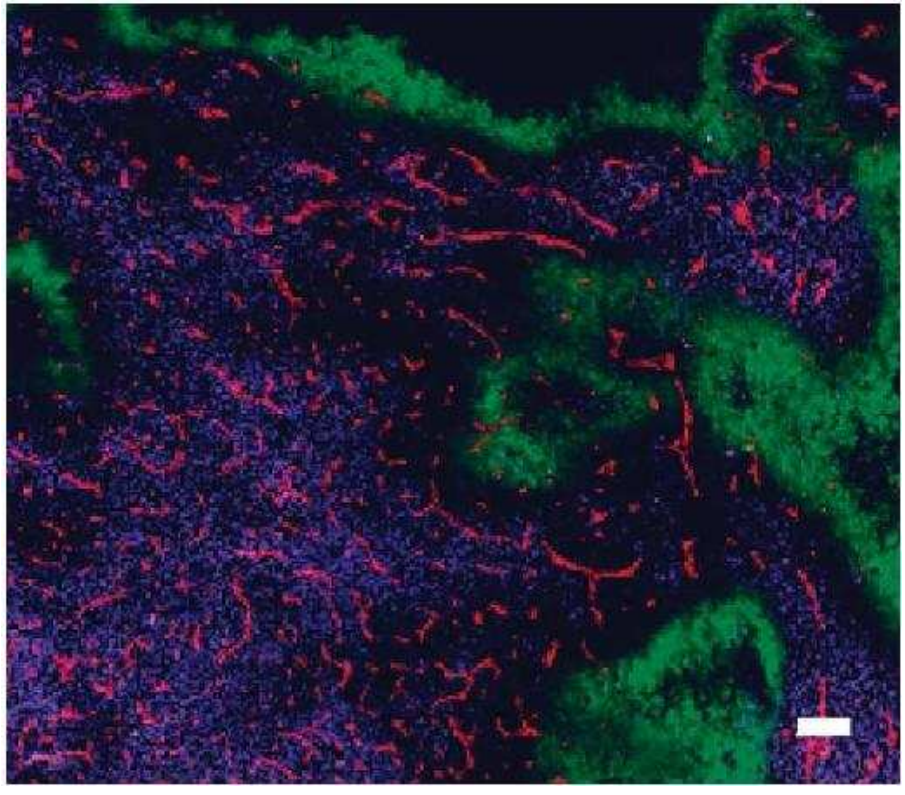

Blood Vessels (red): Drug (blue): Hypoxia (green)

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

Drug Delivery

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- 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

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- The details vary from drug to drug.
- Doxorubicin will be considered here.
  - It is used to treat many types of cancer, most commonly leukemia and Hodgkin's lymphoma.
  - It has been widely studied.
  - Most importantly (for our purposes) it can be made to fluoresce, making it easy to measure.

Drug Delivery

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

Tumour Cords

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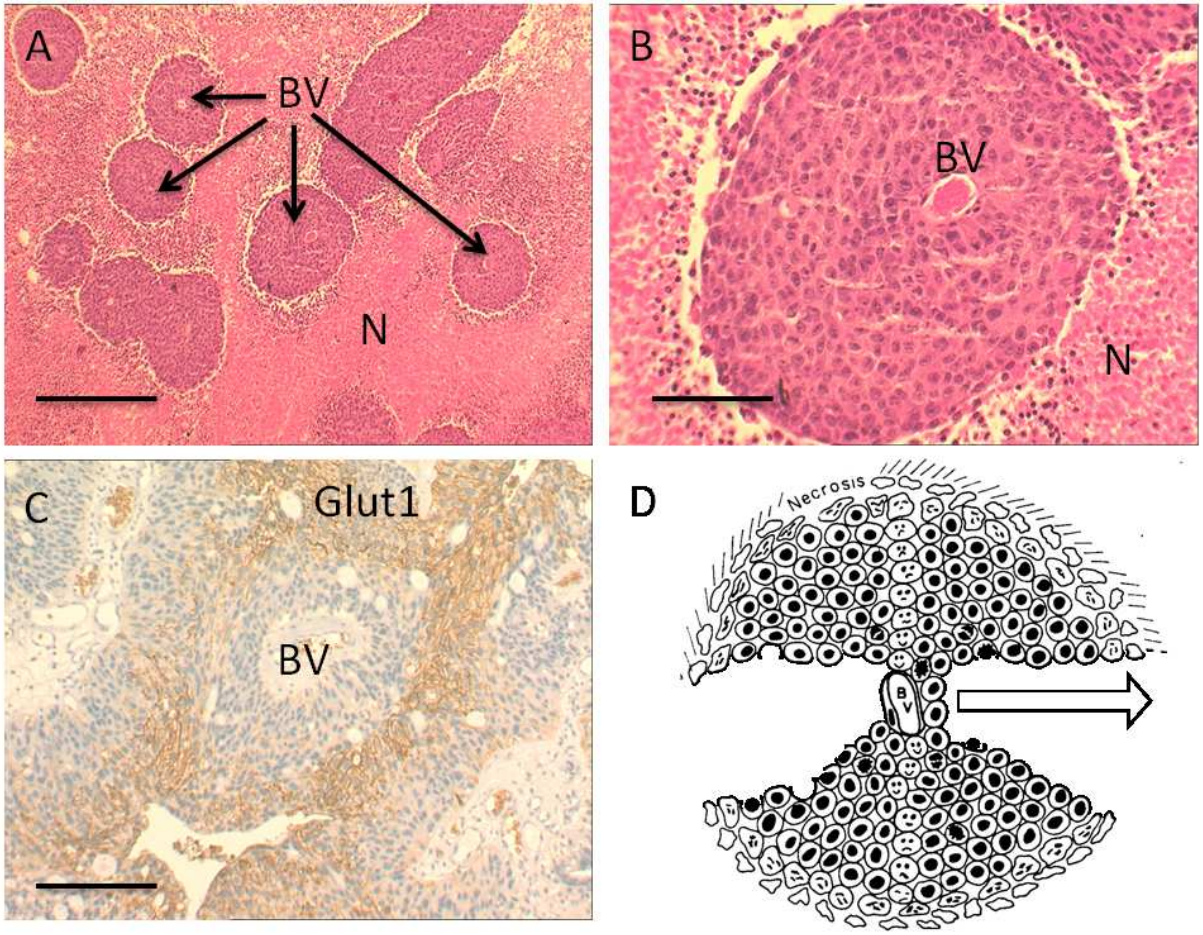

BV = Blood Vessels, N = Necrosis, Glut1 ⇒ Hypoxia

Drug Delivery

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This allows investigation of:

- the behaviour of discrete and continuous modelling frameworks;
- the effects of changing the models and delivery regimes, *e.g.*
  - pharmacokinetic profiles,
  - affinity for drug of cells.

Cell Model

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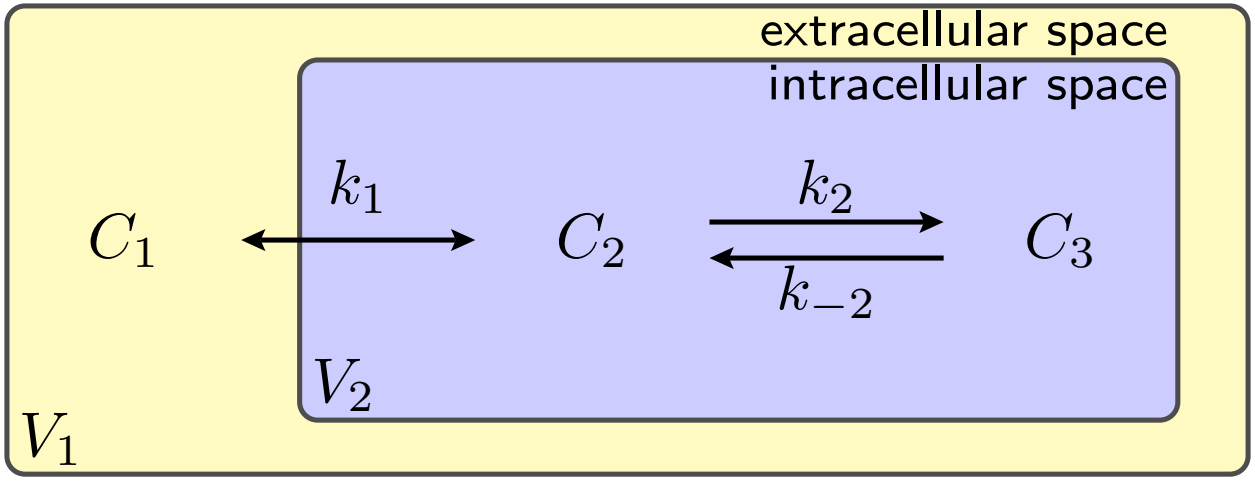

with $C_3 \leq C_0$

- 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

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

- Chemical 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

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The *in vitro* experiments considered the action of the drug on cells 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 ($C_2 + C_3$).

Steady-State Experiments

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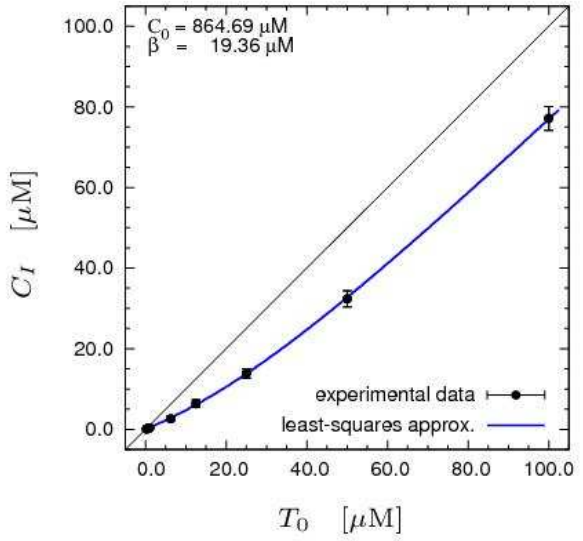
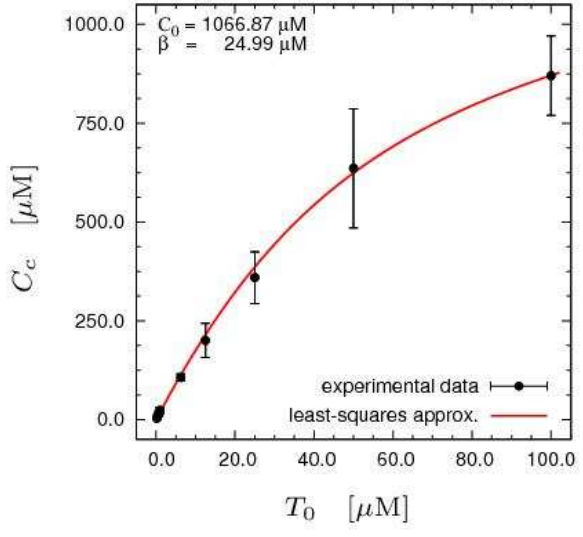
- Vary initial concentration (C_1).
- Measure C_1 and $C_2 + C_3$ at $t = 120$ minutes.
- Can solve the steady state equations for C_1, C_2, C_3.
- A least-squares fit estimates C_0 and $\beta = k_{-2}/k_2$.





Time-Dependent Experiments

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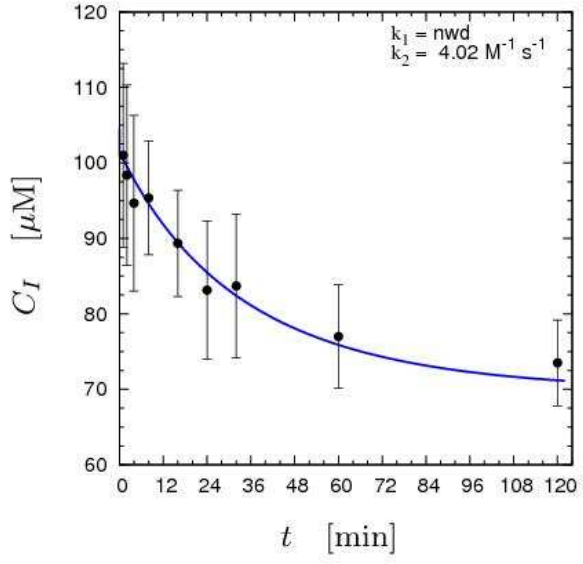
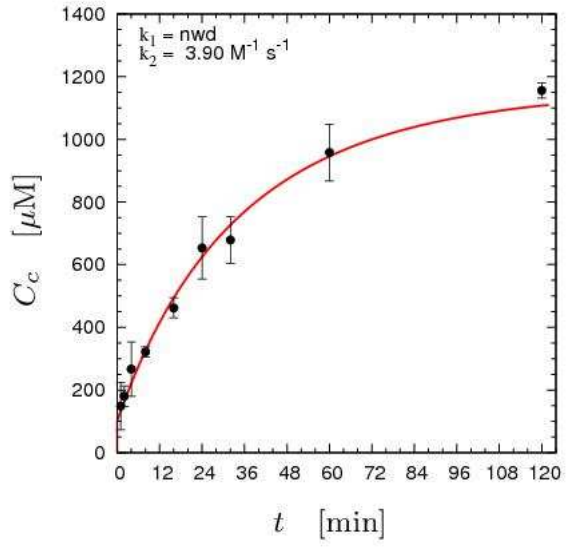
- Vary sample time (t).
- Measure C_1 and $C_2 + C_3$ at time t.
- Solve the time-dependent equations for C_1, C_2, C_3.
- A least-squares fit estimates k_1 and k_2 (hence k_{-2}).





Parameter Sensitivity

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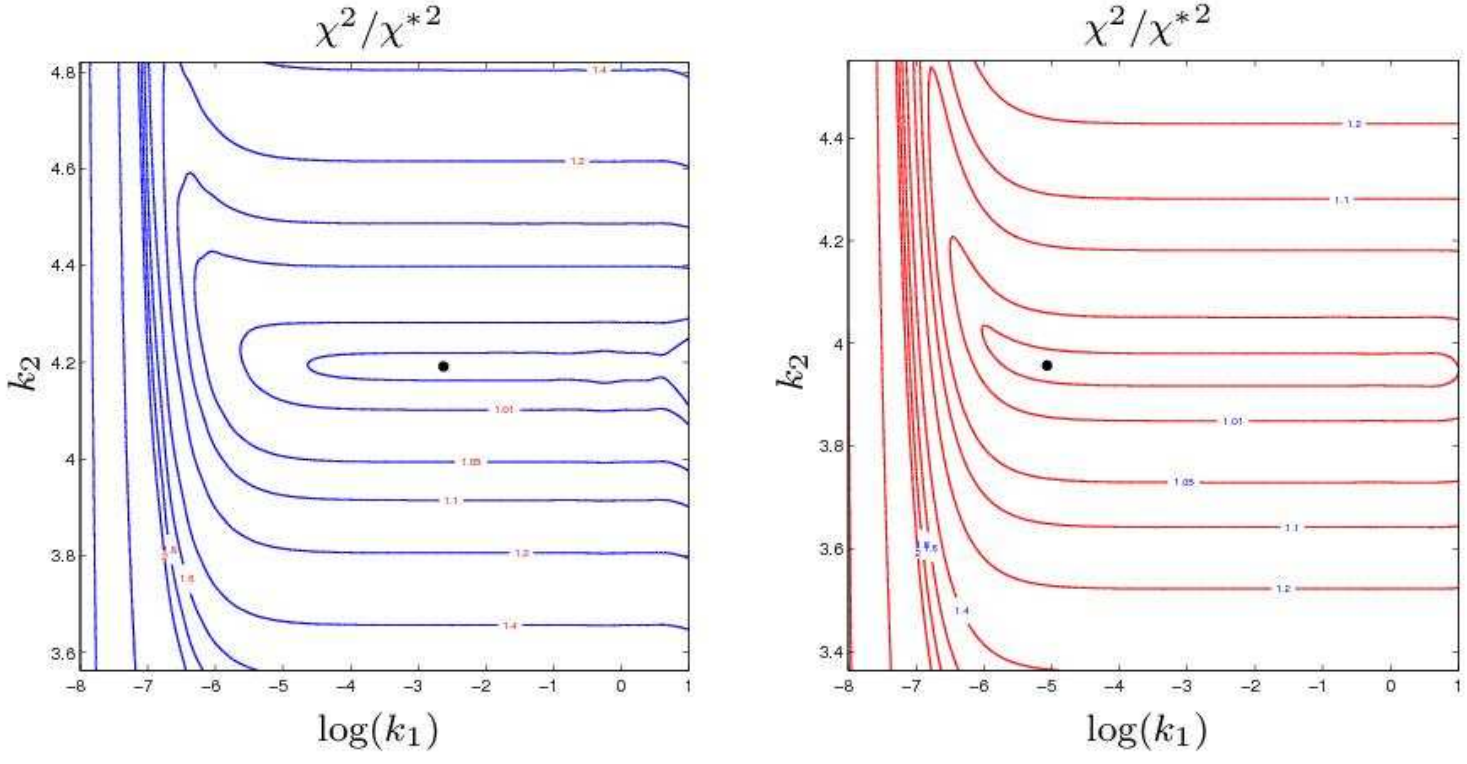
In fact, the model is extremely insensitive to the transmembrane transport rate (k_1) as long as it is fast enough.



Timescales

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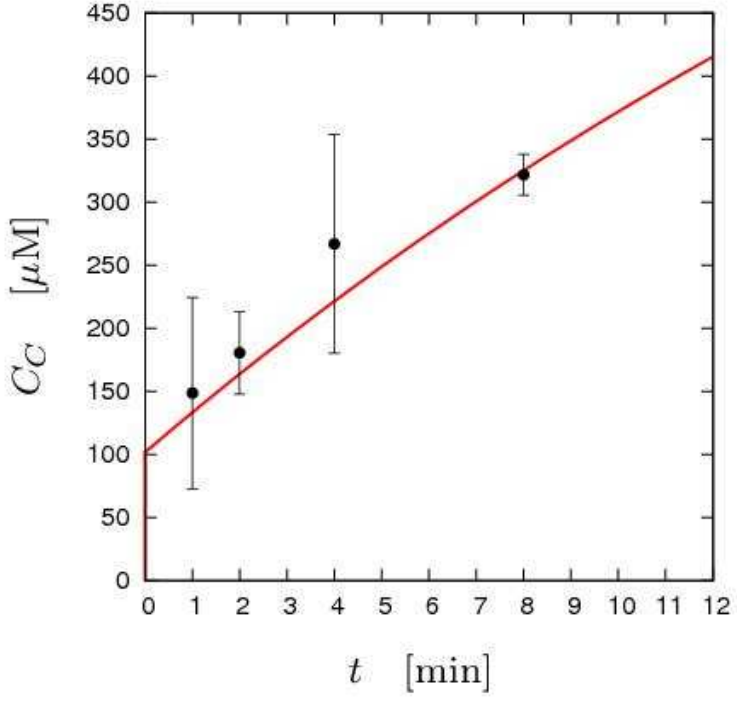
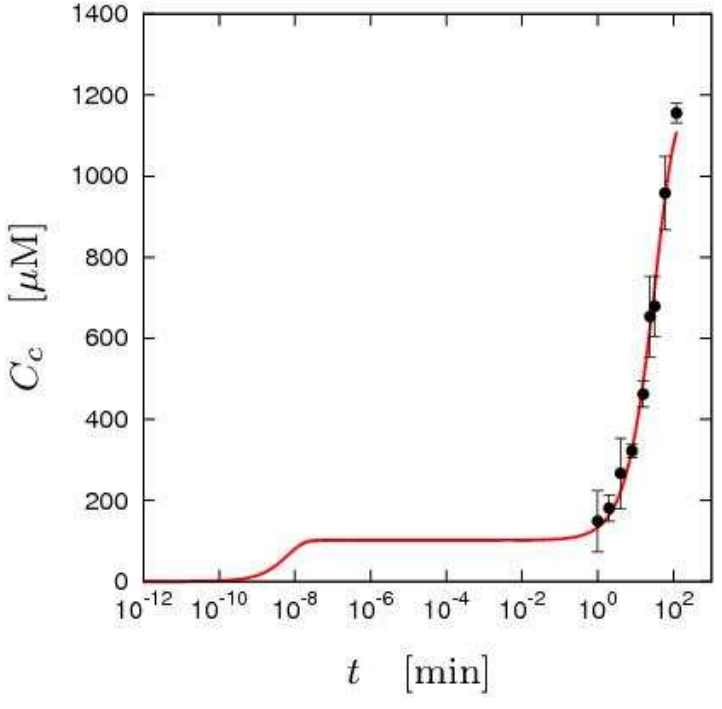
The fit to the data suggests two distinct time-scales, though care needs to be taken with how to link this with the literature.





Timescales

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"It is well-established, however, that transport across the cell membrane is **saturable** and that cellular transmembrane transport of doxorubicin takes hours and is *slower than the other transport steps*."

El-Kareh, Secomb (2000)

BUT

"The first (outer) cell compartment is a thin shell with a **high permeability** for drug transport between the interstitium and the inner cell compartment."

AND

"The drug adsorption process in the first (outer) cell compartment is so fast in comparison with drug diffusion in a tumor islet of densely packed cells, that for drug transport in a tumor islet we assume that the adsorbed drug accumulation per unit interstitial surface area in the first cell compartment is **constantly in equilibrium** with and proportional to the free drug concentration in the interstitium."

Lankelma, Luque, Dekker, Schinkel, Pinedo (2000)

Experimental Error

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- Initially, the time-varying in vitro experiments showed a systematic mass loss relative to the steady state experiments.
- This seems to have been due to differing experimental protocols for separating cells from supernatant.
- Even now, the variance in the experimental results is far more significant than most of the modelling issues that arise.

Radially Symmetric Models

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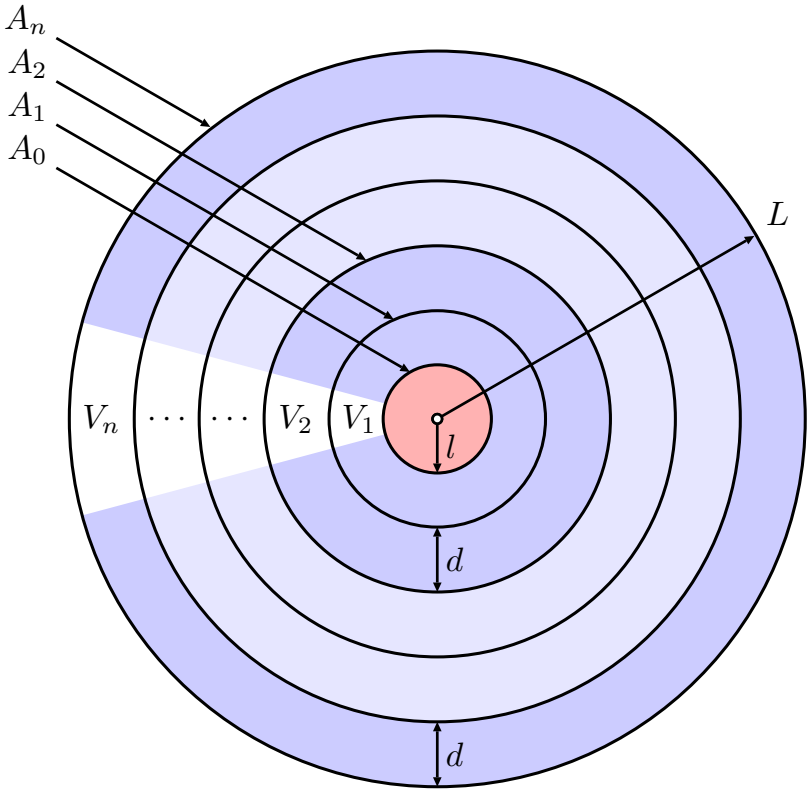
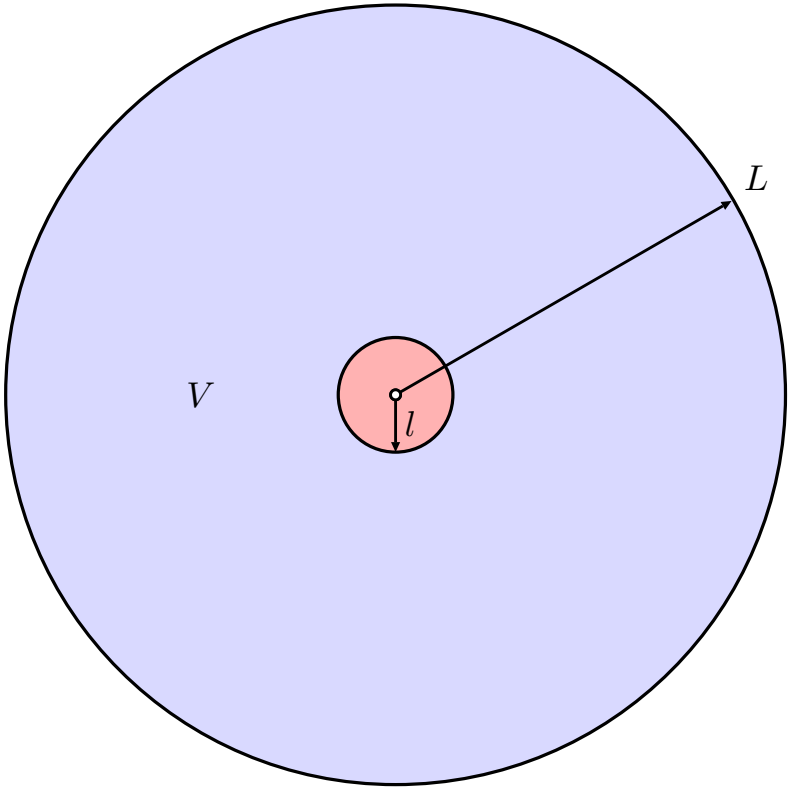


Compartment Model



Continuum Model

Radially Symmetric Models

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- 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

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

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

Continuum Model

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

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

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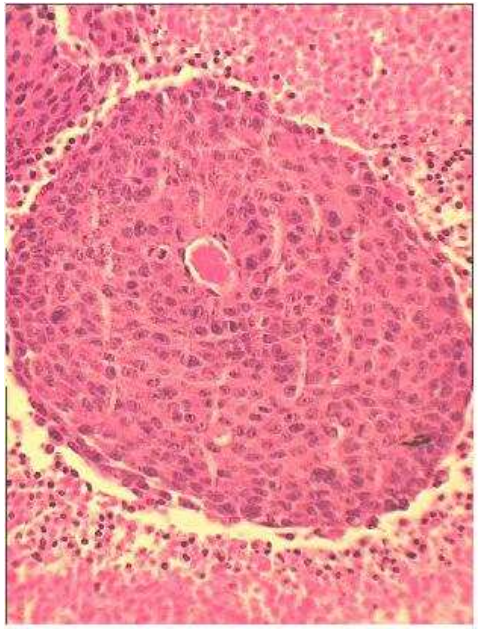
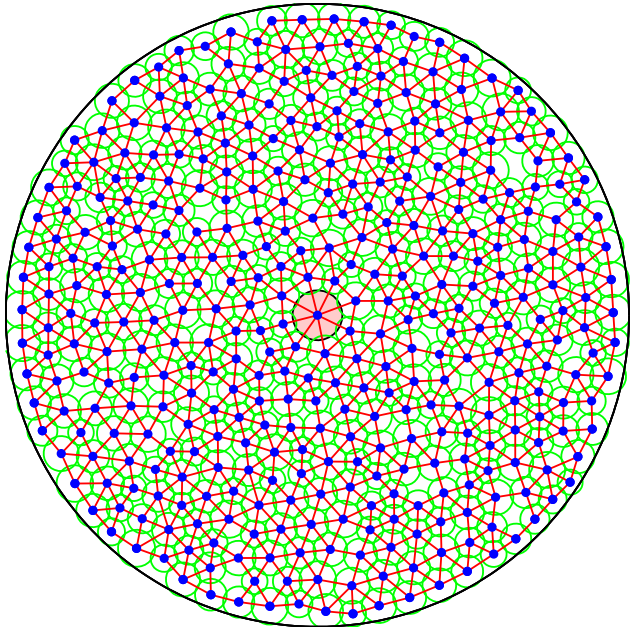
This is a multidimensional version of compartment model.



Tumour cord



Discrete representation

Cell-Centre Model

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

Cell-Centre Model

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There are alternative approaches to approximating the V_i and A_{ij}, *e.g.*

- Voronoi tesselation
- Overlapping spheres

The domain is randomly seeded with cell centres (with associated cell radii) whose positions are iterated until they are in mechanical equilibrium.

A computational cell is **not** a biological cell.

Numerical Experiments

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To investigate:

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

Model Parameters

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Variable	Value	Description	Source of Data
l	$1.6 \times 10^{-5}\,\mathrm{m}$	Vessel radius	Histology
L	$2.0 \times 10^{-4}\,\mathrm{m}$	Cord radius (vessel + ~ 9 cells)	Histology
r	$\sim 1.0 \times 10^{-5}\,\mathrm{m}$	Cell radius	Histology
δ	0.0625	Intracellular : Extracellular volume ratio parameter	Histology
α	$\sim 1.94028 \times 10^{5}\,\mathrm{m}^{-1}$	Membrane surface : Tissue volume ratio	$2/(r\sqrt{1+\delta})$
k_1	$1.0 \times 10^{-6}\,\mathrm{m\,s}^{-1}$	Permeability across cell membrane	Experiment
k_2	$4.0 \times 10^{-6}\,\mathrm{l}\,\mu\mathrm{M}^{-1}\,\mathrm{s}^{-1}$	Drug association rate	Experiment
k_{-2}	$8.0 \times 10^{-5}\,\mathrm{s}^{-1}$	Drug disassociation rate	Experiment
k_v	$1.25 \times 10^{-7}\,\mathrm{m\,s}^{-1}$	Permeability across vessel wall	Estimate
D	$2.0 \times 10^{-12}\,\mathrm{m}^2\,\mathrm{s}^{-1}$	Interstitial diffusion rate	Literature
C_0	$1.5 \times 10^{3}\,\mu\mathrm{M\,l}^{-1}$	Binding site concentration	Experiment

Pharmacokinetic Profiles

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

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

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

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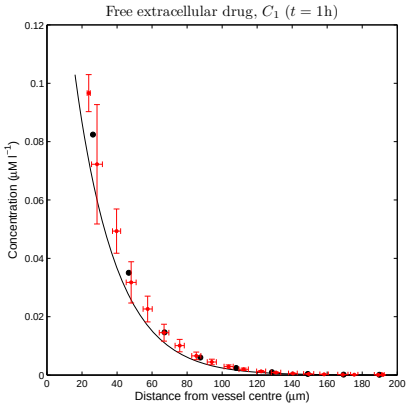

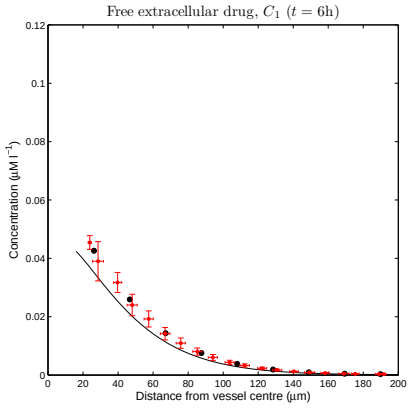

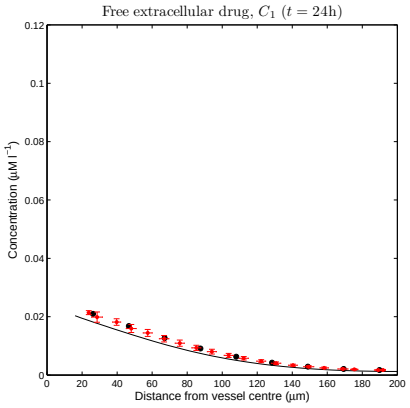

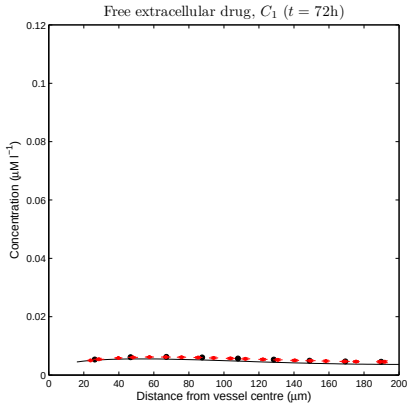

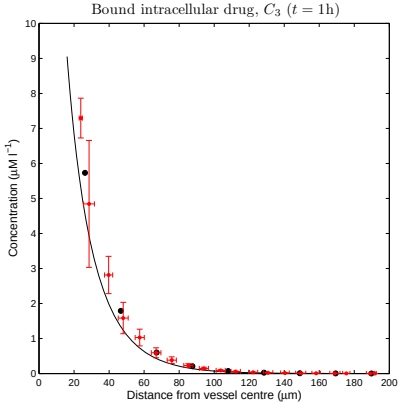

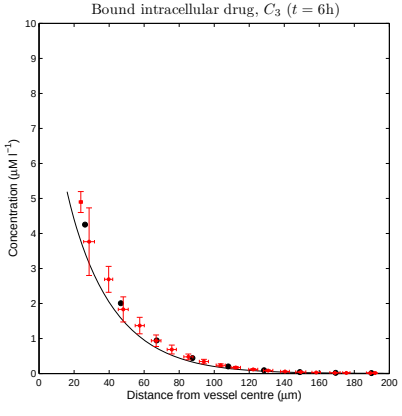

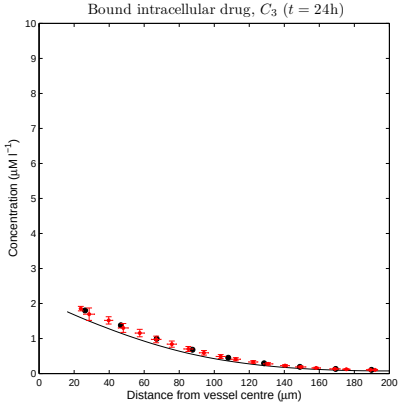

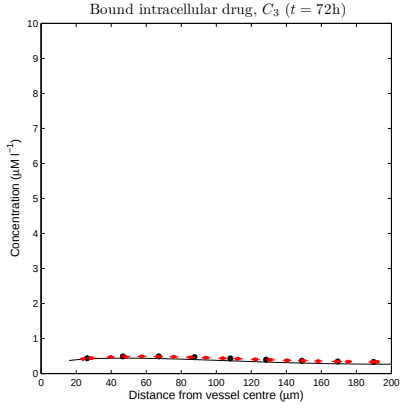

Drug distribution: extracellular (top), bound intracellular (bottom).
Snapshots at times 1h, 6h, 24h, 72h (left to right).

Simplified Bolus Injection

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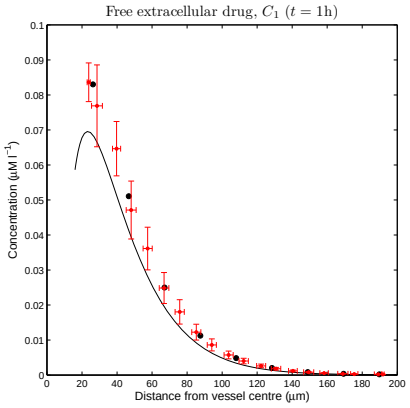

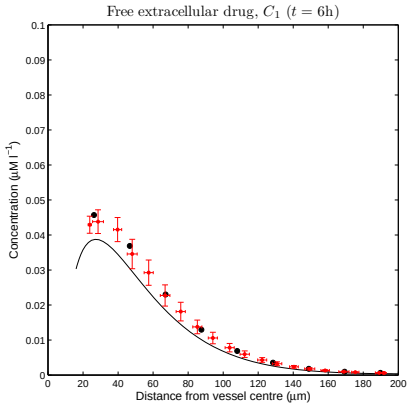

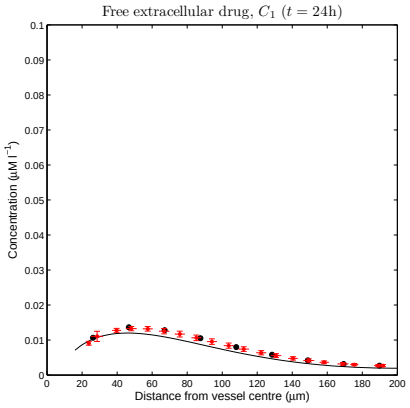

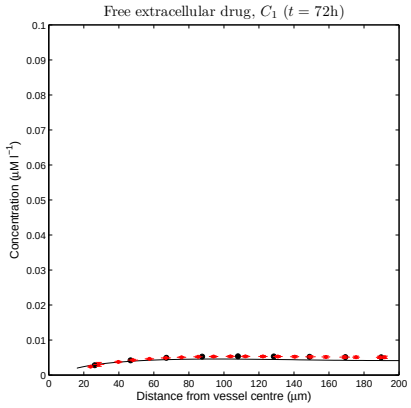

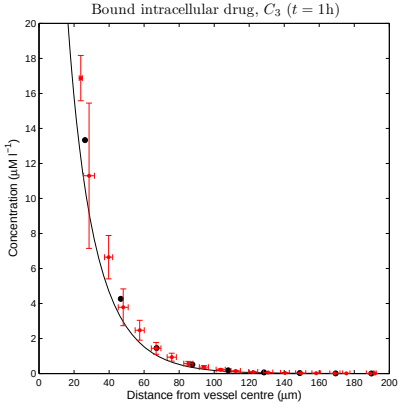

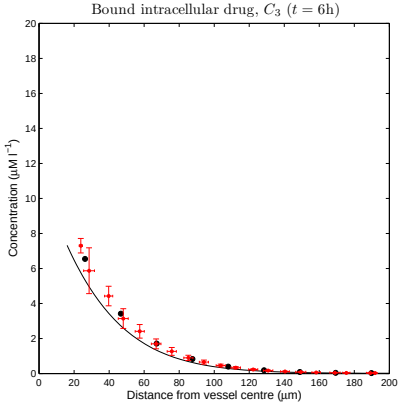

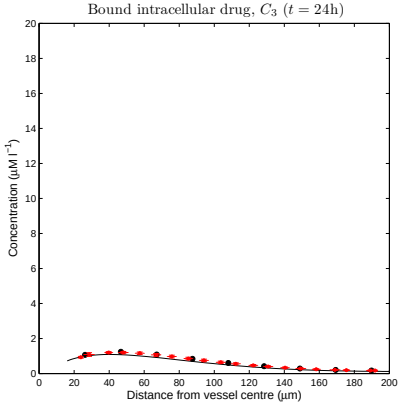

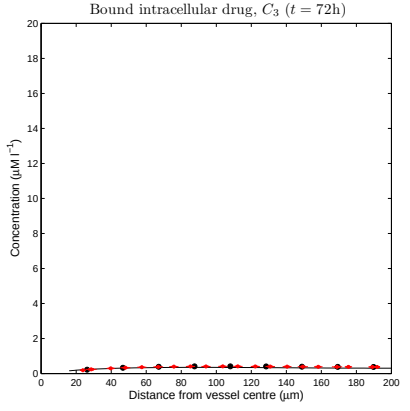

Drug distribution: extracellular (top), bound intracellular (bottom).
Snapshots at times 1h, 6h, 24h, 72h (left to right).

Infusion

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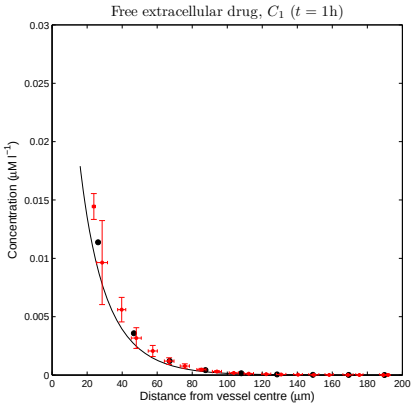

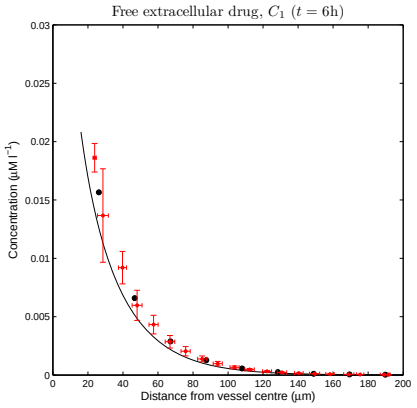

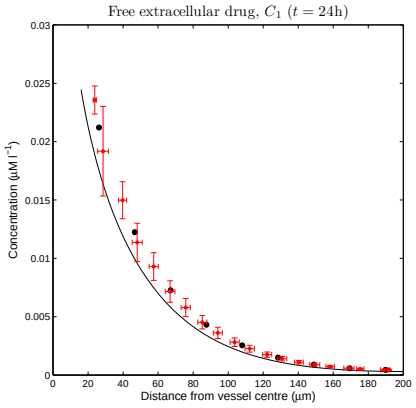

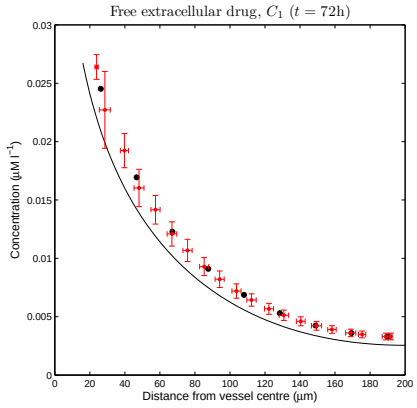

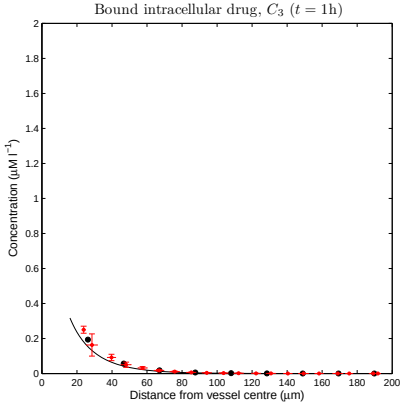

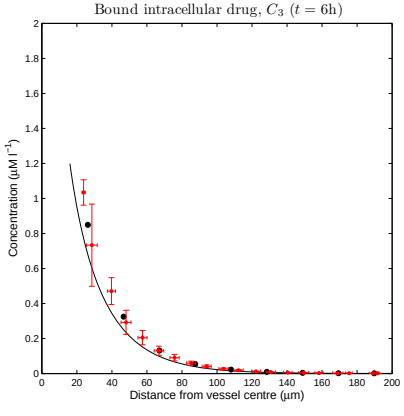

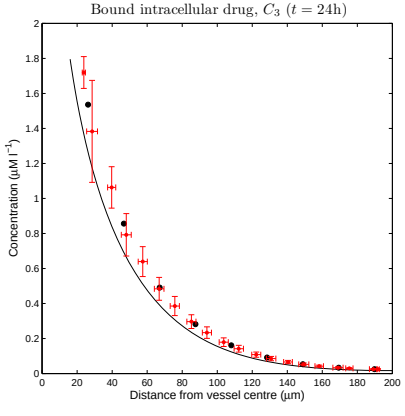

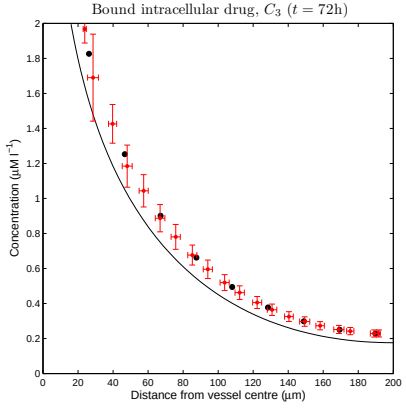

Drug distribution: extracellular (top), bound intracellular (bottom).
Snapshots at times 1h, 6h, 24h, 72h (left to right).

Time Variation

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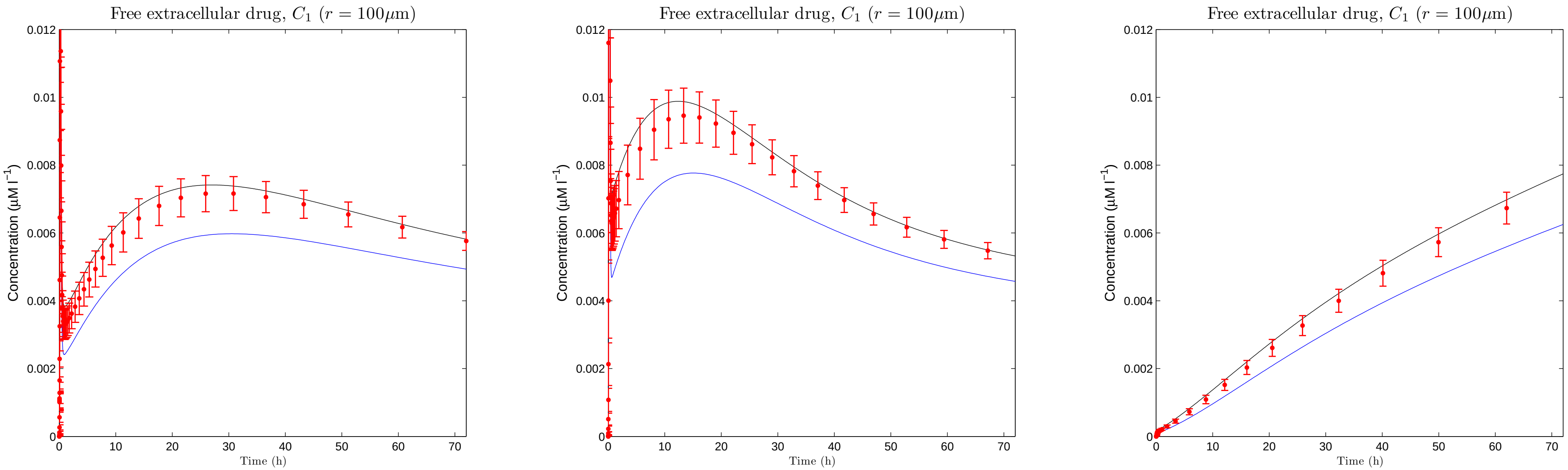

Extracellular drug concentration at $r = 100\,\mu$m
for bolus (left), exponential (middle), infusion (right).

Time Variation

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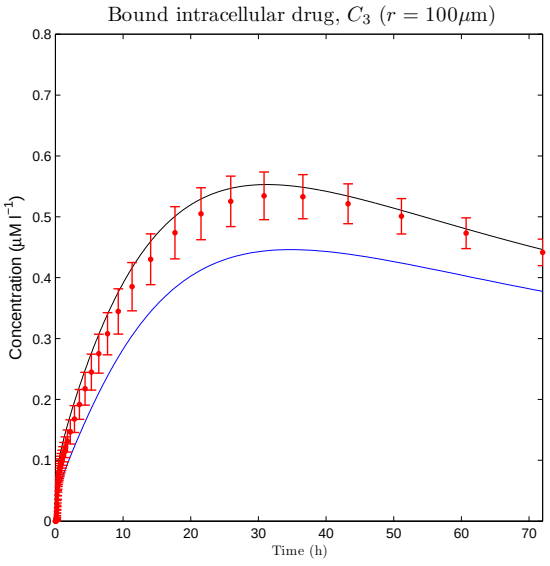

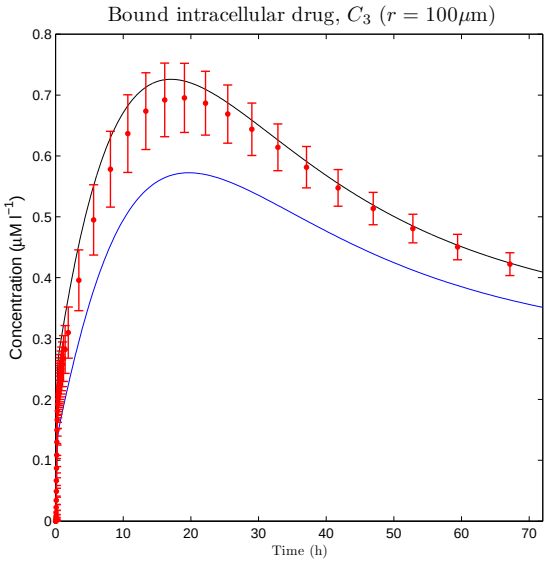

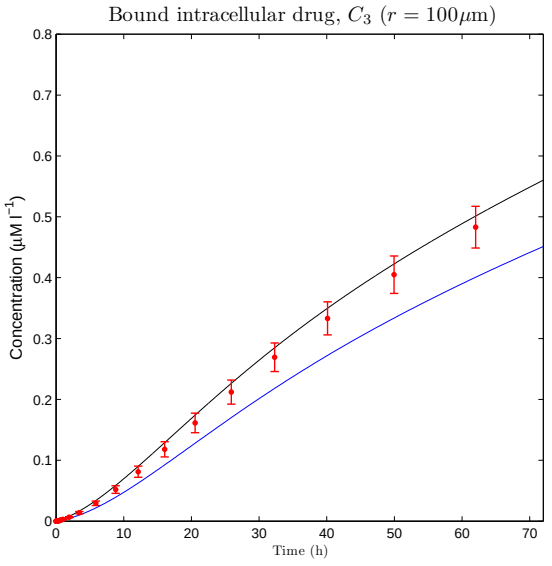

Bound intracellular drug concentration at $r = 100\,\mu$m for bolus (left), exponential (middle), infusion (right).

Exposure

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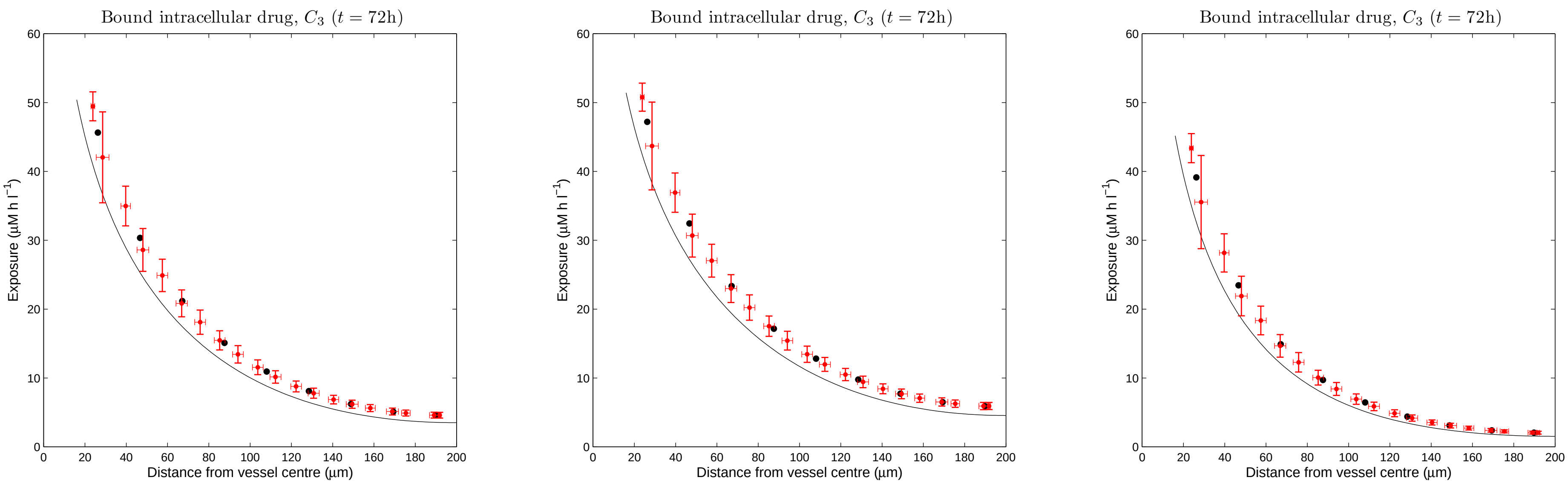

Exposure to bound intracellular drug, $\int C_3 \, \mathrm{d}t$, after 72h for bolus (left), exponential (middle), infusion (right).

Varying Binding Affinity

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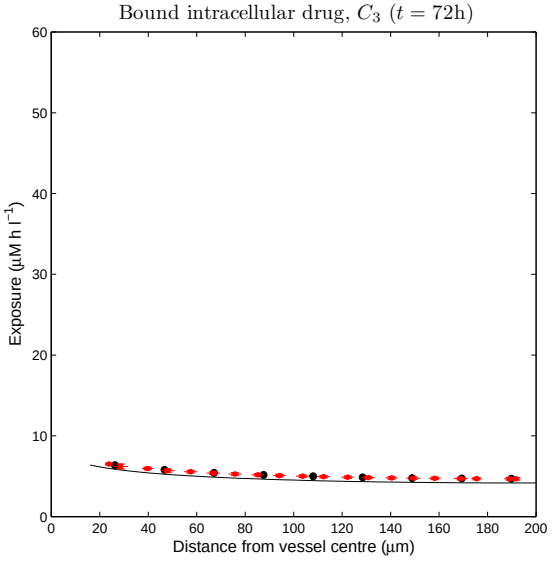

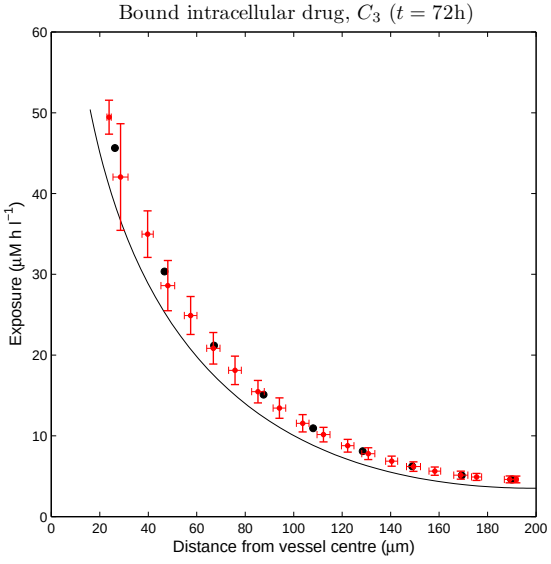

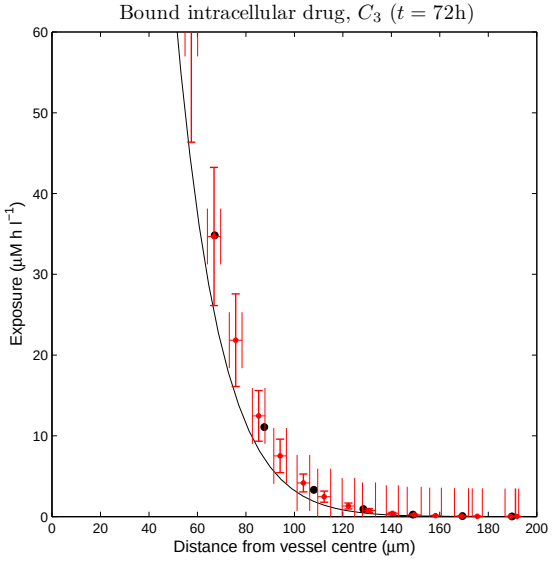

Exposure to bound intracellular drug, $\int C_3 \, \mathrm{d}t$, after 72h for bolus injection with $k_2/10$ (left), k_2 (middle), $k_2 \times 10$ (right).

Preliminary Observations

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- The two discrete models produce very similar results which differ from those of the continuum model.
- The pharmacokinetic profile has less effect on the exposure than expected.
- 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

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- Convective transport, validated by transwell experiments and possibly artificial tumour cords.
- Add more processes and cell types...but how should they be parameterised?
  - Cell cycle (mitosis, apoptosis, necrosis)
  - Cell response (and a tumour growth model)
  - Combination therapy (EPSRC sandpit grant)
- With cell movement, realistic vasculature and three dimensions the scientific computing contribution becomes more significant.