Insights from mathematical models of micro-tissues for drug uptake & cancer spread

UNIVERSITY OF LIVERPOOL

Rachel Bearon
Dept. Mathematical Sciences

June 2023

Defining drug delivery into and across the oral mucosa, NC3Rs
2022

HoD;
Shape, shear, search & strife;
mathematical models of bacteria
2020

2018
Professor

Liverpool Centre for Mathematics in Health
2016

Lecturer
2005

2008
Systems biology
NfKB; HIF dynamic cell signalling

2007
Swimming phytoplankton in turbulence

School of Oceanography
University of Washington
2001- 2005

1998-2001

PhD: Run-and-tumble chemotaxis in an ambient fluid flow

University of Cambridge

UNIVERSITY OF LIVERPOOL

LIVERPOOL JOHN MOORES UNIVERSITY

EPSRC

Multiscale Modelling of Drug Transport & Metabolism in Multicellular Systems

Joe Leedale, Steve Webb, Rachel Bearon

AstraZeneca

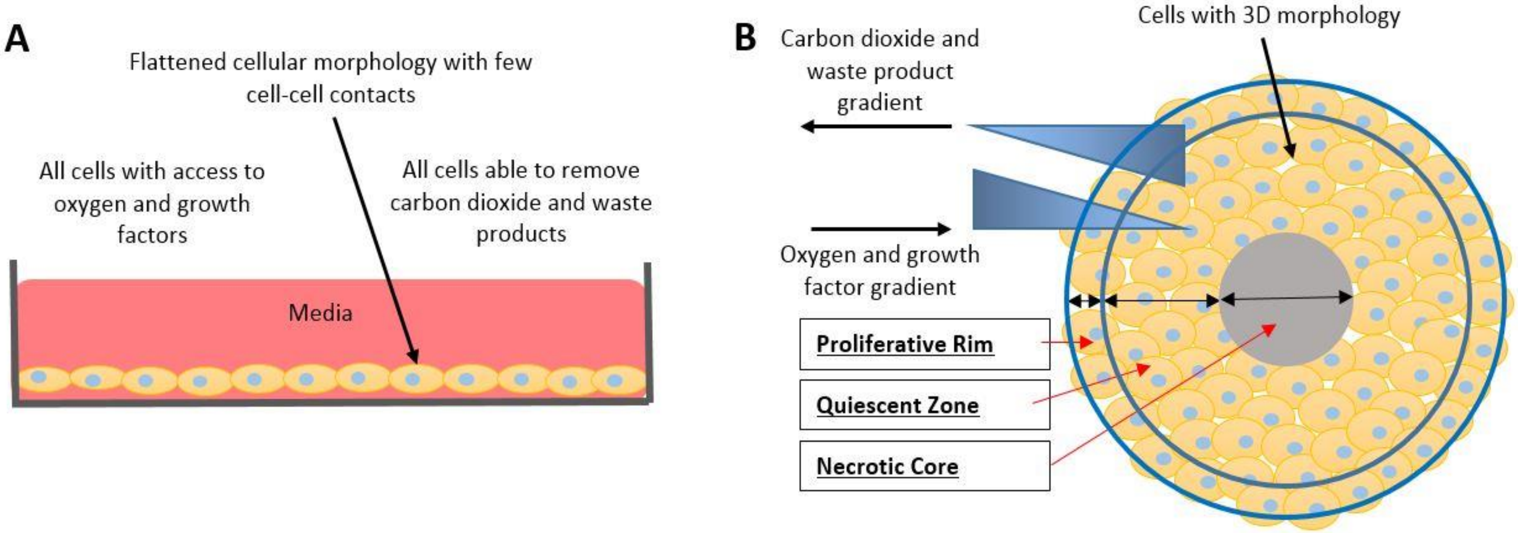
syngenta

Leedale, JA et al. (2020) *Interface Focus*, 10(2)

Healthcare challenge

Cellular spheroids

- 2D *in vitro* systems used to assess hepatotoxicity tend to lack physiological and xenobiotic competence.
- 3D spheroid cultures of hepatocytes *in vitro* are an improved platform to recapitulate the *in vivo* liver microarchitecture and function compared with 2D cultures.

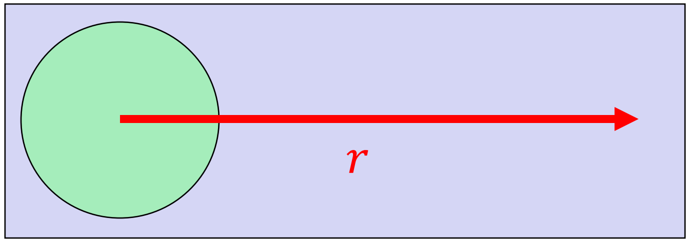


Kyffin J.A., Sharma P., Leedale J., Colley H.E., Murdoch C., Mistry P. and Webb S.D. (2018). Impact of cell types and culture methods on the functionality of in vitro liver systems-A review of cell systems for hepatotoxicity assessment. Toxicol. In Vitro 48: 262-275.

Microscale: drug diffusion & transport kinetics

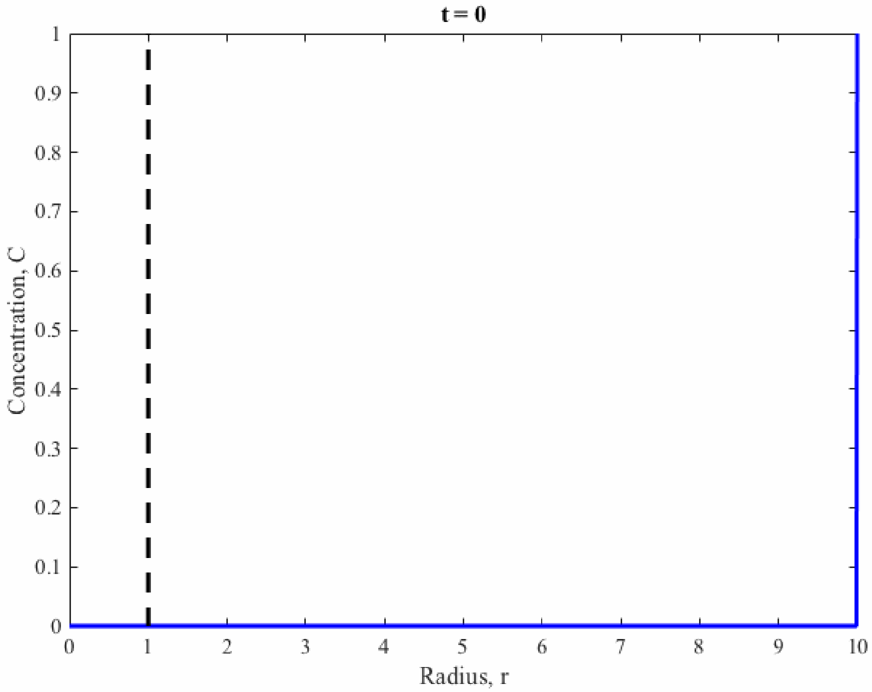
Inside cell:
Diffusion + Metabolism

$$\frac{\partial C_I}{\partial \tilde{t}} = \tilde{\nabla}^2 C_I - \frac{\tilde{V}_{max} C_I}{C_I + K_m}$$



Outside cell:
Diffusion only

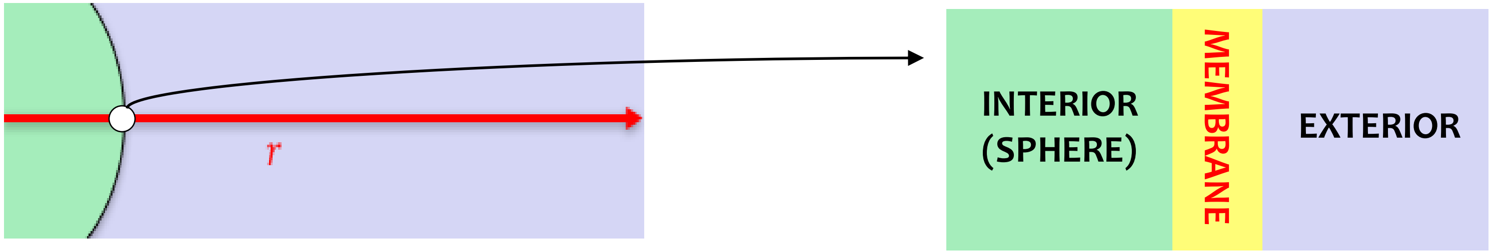
$$\frac{\partial C_E}{\partial \tilde{t}} = D\tilde{\nabla}^2 C_E$$

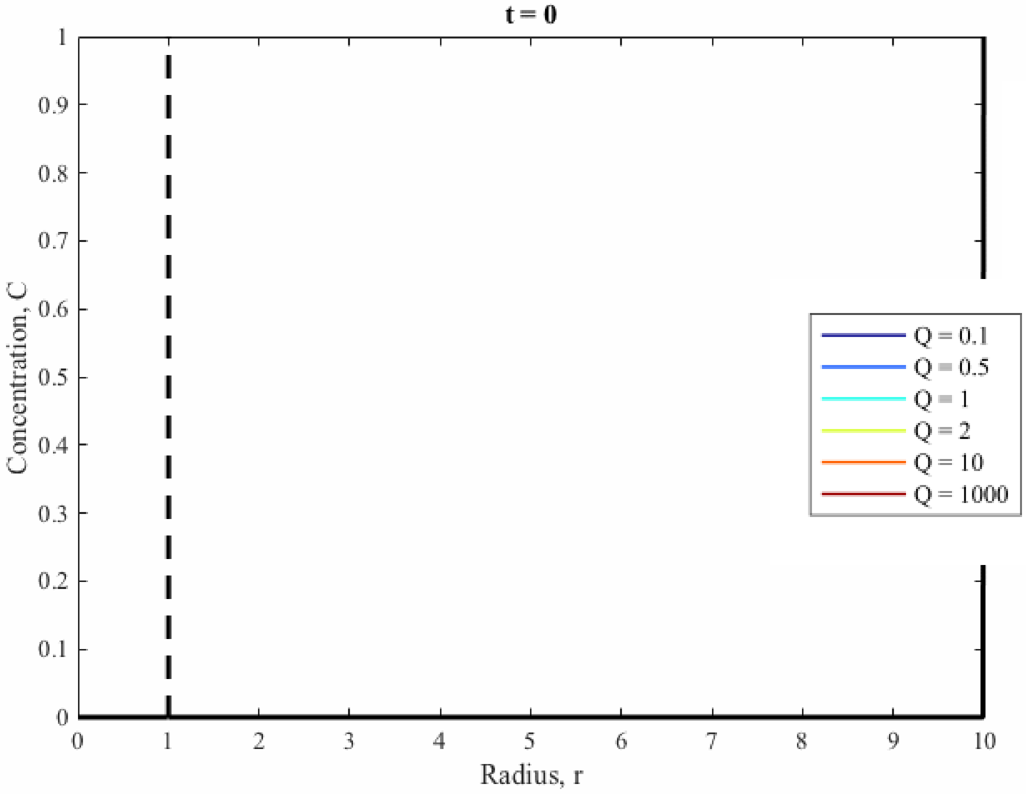


$$D_I \frac{\partial C_I}{\partial r} = D_E \frac{\partial C_E}{\partial r}, \qquad r = 1$$

$$C_I = C_E, \qquad r = 1$$

Effects of membrane barrier



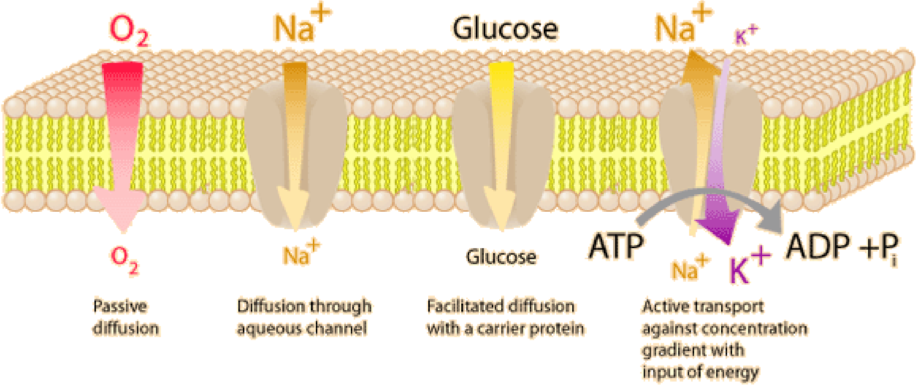


$$D_I \frac{\partial C_I}{\partial r} = D_E \frac{\partial C_E}{\partial r} = Q(C_E - C_I), \quad r = 1$$

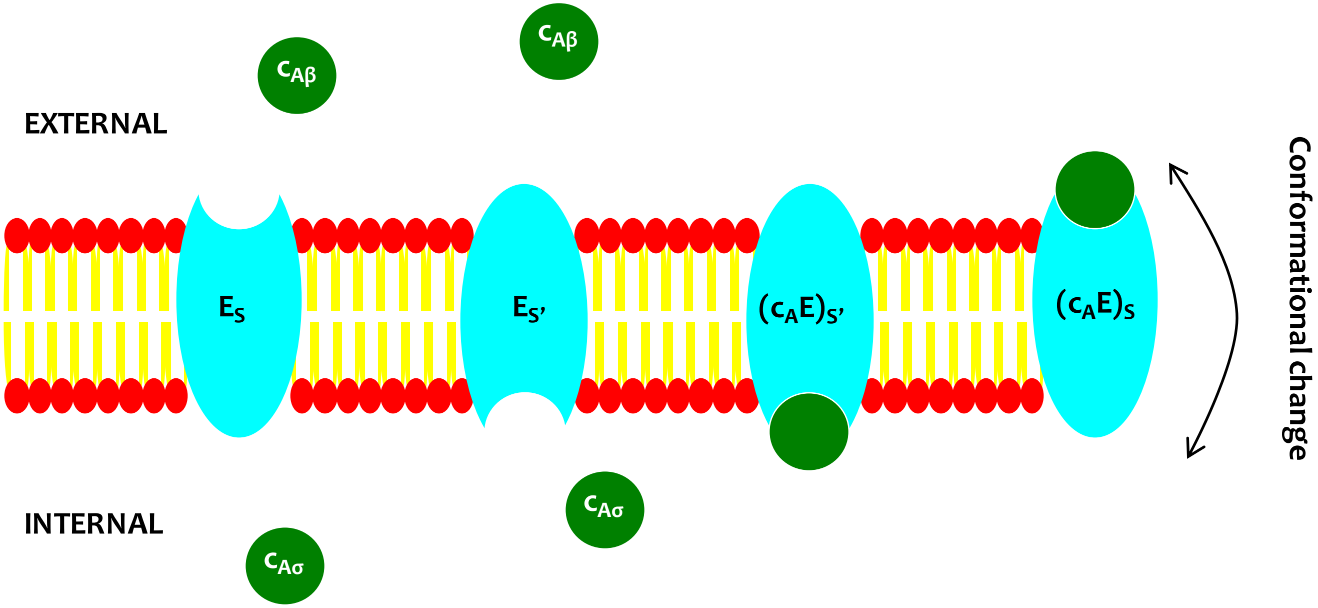
Effects of carrier-mediated transport

- Only small, lipophilic drugs enter the cell via diffusion directly through membrane.

- Other drugs use carrier proteins.

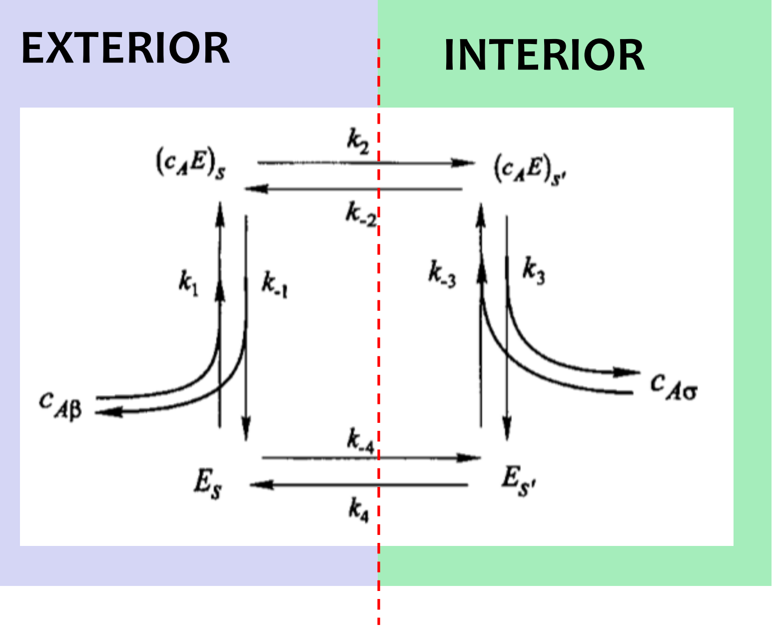


- Depend on carrier protein (or transporter) availability and properties of the transporter and this process can become saturated.

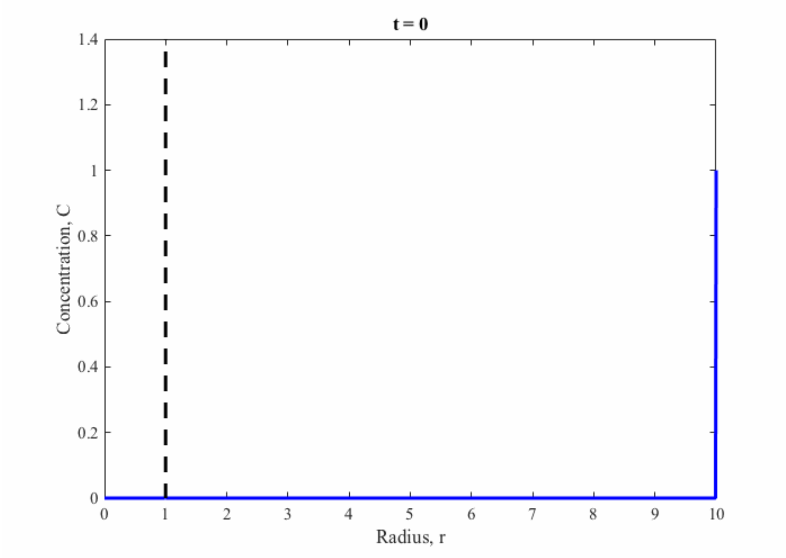


Effects of carrier-mediated transport

$$D_I \frac{\partial C_I}{\partial r} = \frac{Q(C_E - \alpha_1 C_I)}{\alpha_2 + \alpha_3 C_E + \alpha_4 C_I + \alpha_5 C_E C_I}, r = 1$$



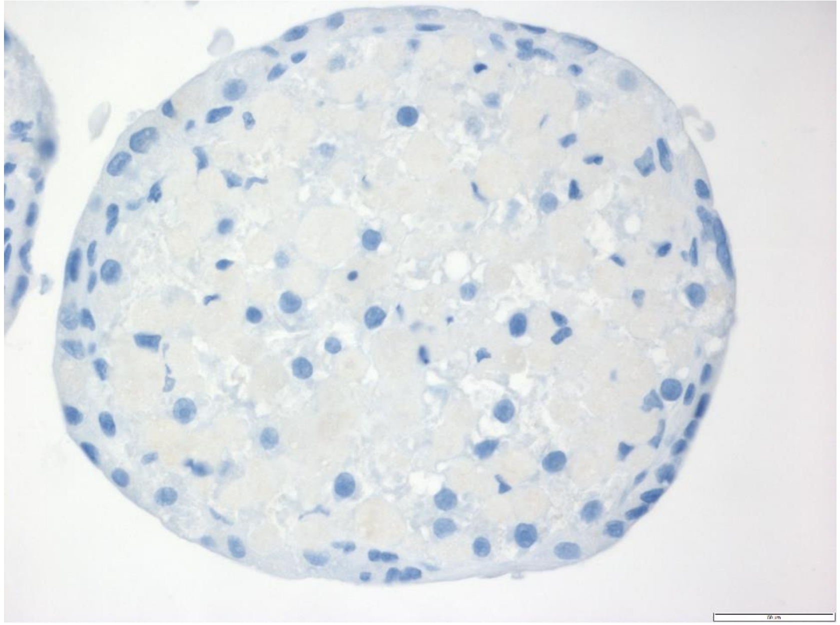
Wood, B. D. and S. Whitaker, 1998. Diffusion and reaction in biofilms. Chemical Engineering Science 53: 397-425.

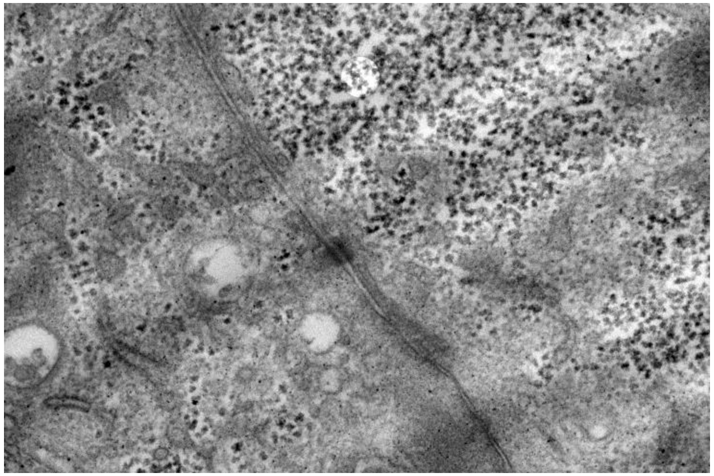


What if $\alpha_1 < 1$?

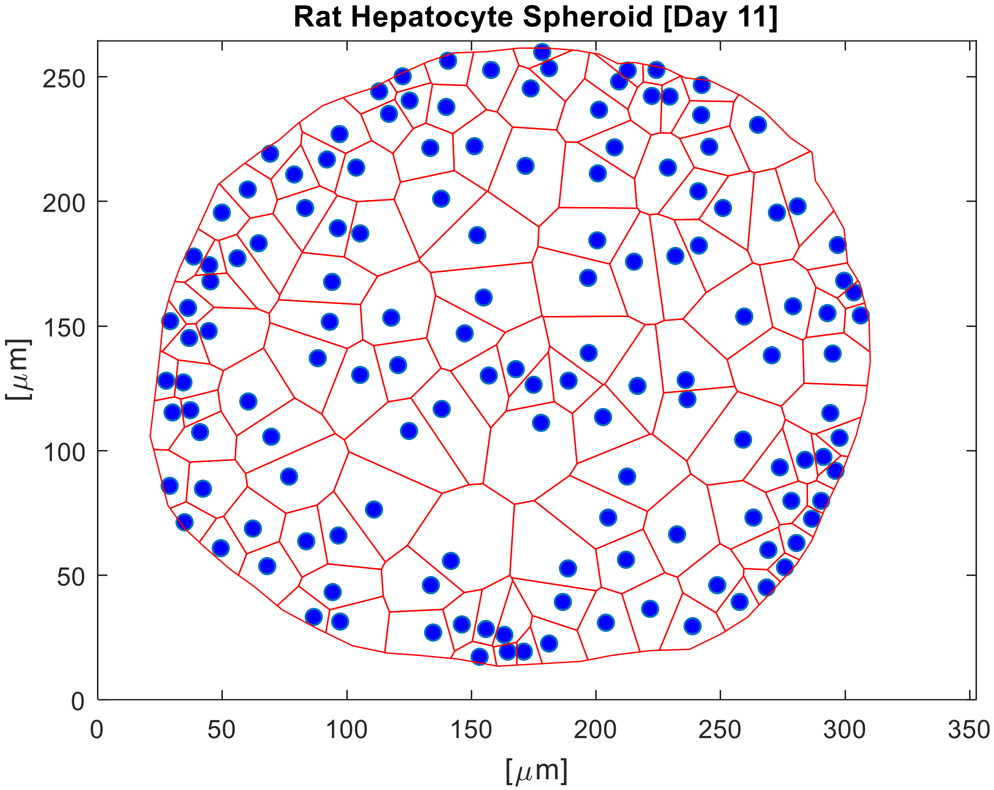
Active drug transport against concentration gradient.

Macroscale: hepatocyte spheroids





TEM – small intercellular gaps



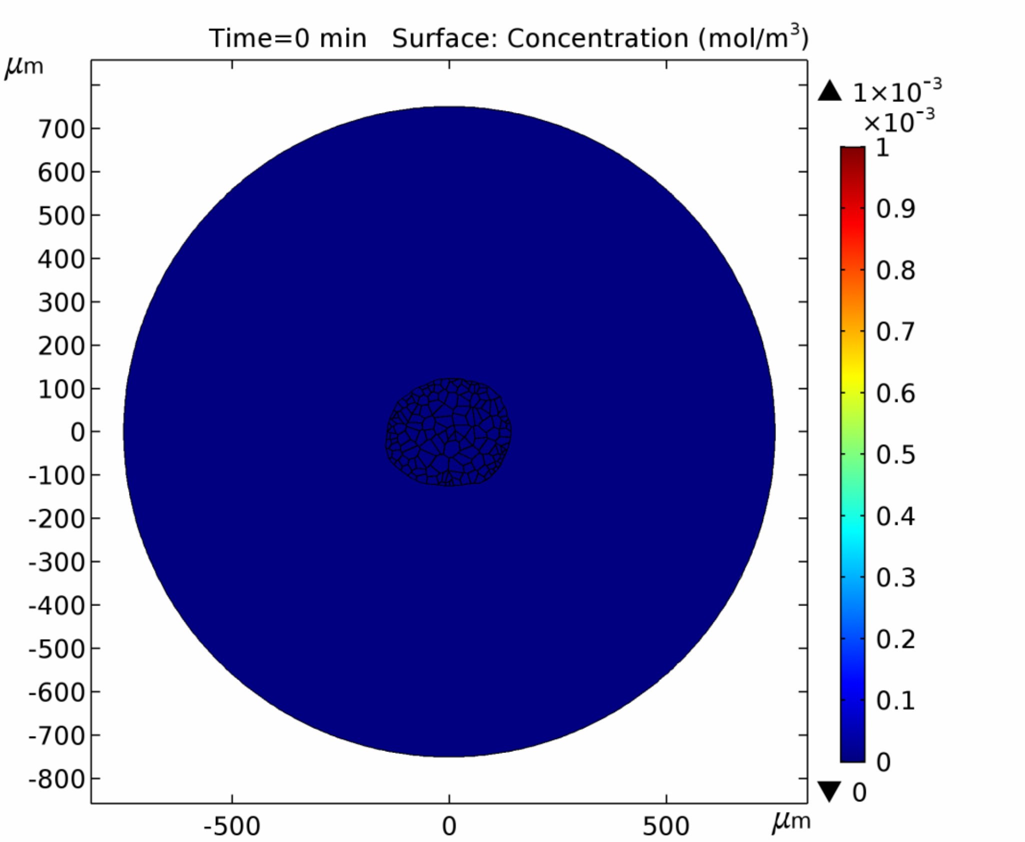
Rat Hepatocyte Spheroid [Day 11]

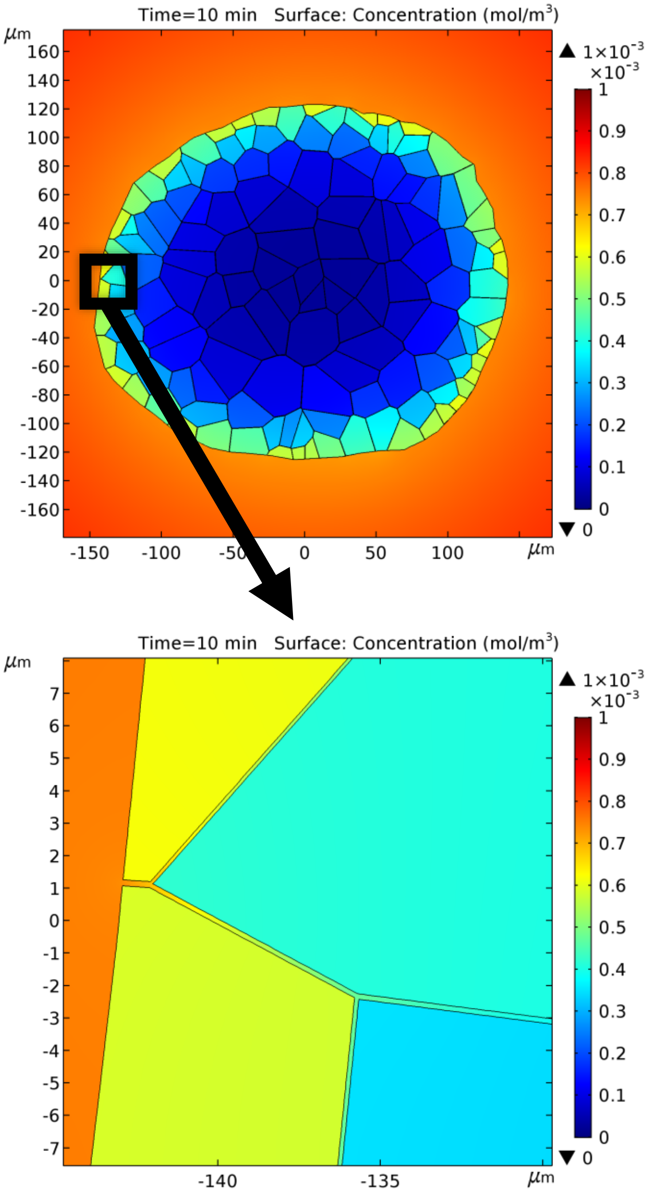
Craig Murdoch, Helen E. Colley,
University of Sheffield

Simulate multiscale model

$$\frac{\partial C_I}{\partial t} = D_I \nabla^2 C_I - \frac{V_{max} C_I}{C_I + K_m}, \qquad \text{INTERIOR}$$

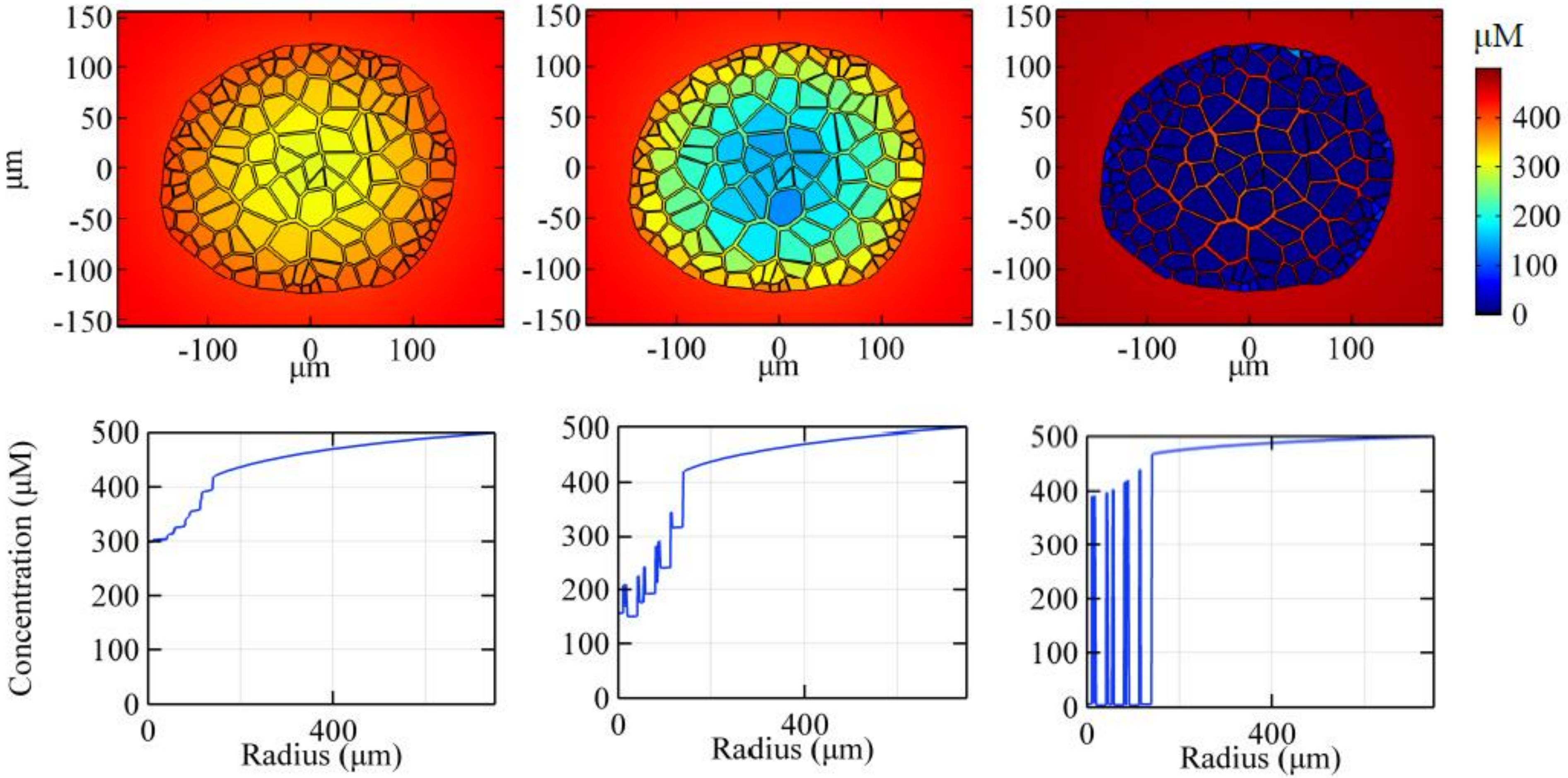
$$\frac{\partial C_E}{\partial t} = D_E \nabla^2 C_E\,, \qquad \text{EXTERIOR}$$





Effect of permeability on spatial distribution

Steady state distribution

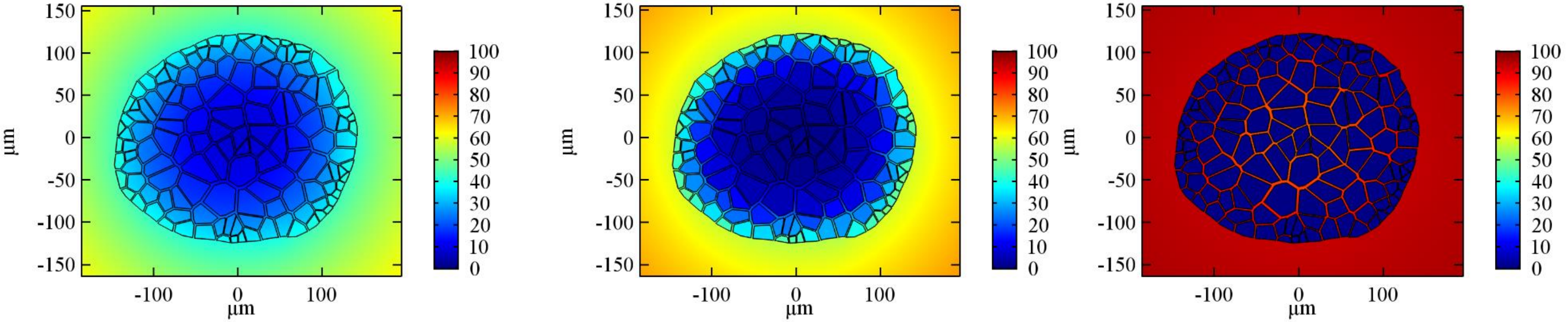


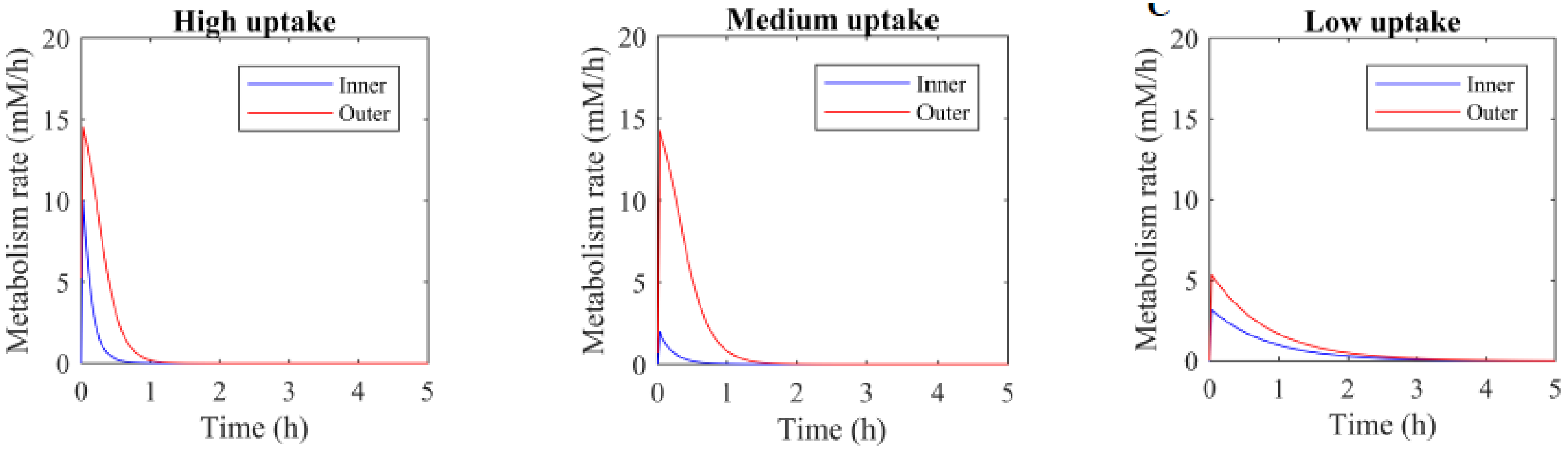
$$Q = \frac{P_{diff}}{4\pi R^2} = \frac{1}{10^6}\frac{10^{(0.6316\times \mathrm{LogD}_{7.4}-0.3143)}}{4\pi R^2}.$$

$\mathrm{LogD}_{7.4}=5$ **$\mathrm{LogD}_{7.4}=3$** **$\mathrm{LogD}_{7.4}=1$**

Uptake of fixed bolus of drug

Concentration after ~3.5 min





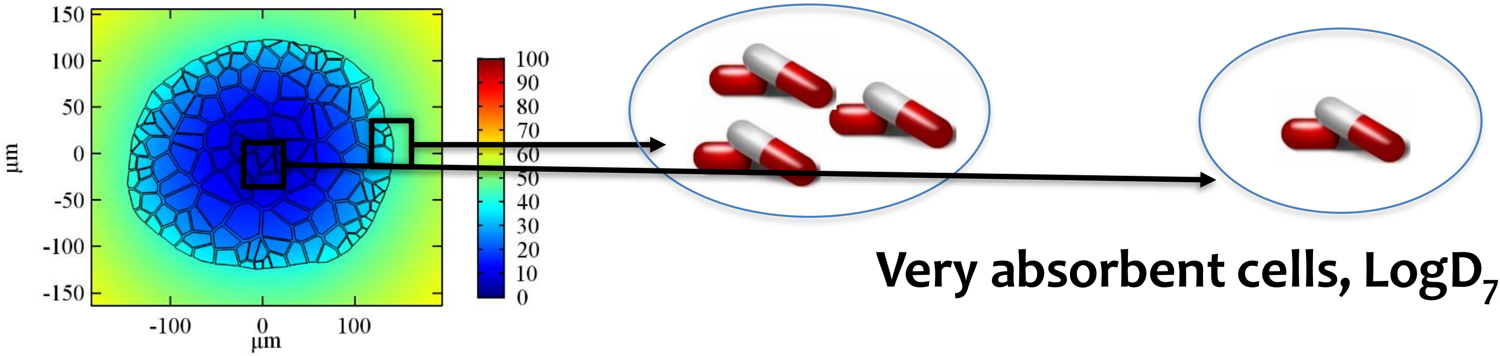
$$Q = \frac{P_{diff}}{4\pi R^2} = \frac{1}{10^6}\,\frac{10^{(0.6316\times \mathrm{LogD}_{7.4}-0.3143)}}{4\pi R^2}.$$

$\mathrm{LogD}_{7.4}=6$ **$\mathrm{LogD}_{7.4}=4$** **$\mathrm{LogD}_{7.4}=1$**

Drug uptake

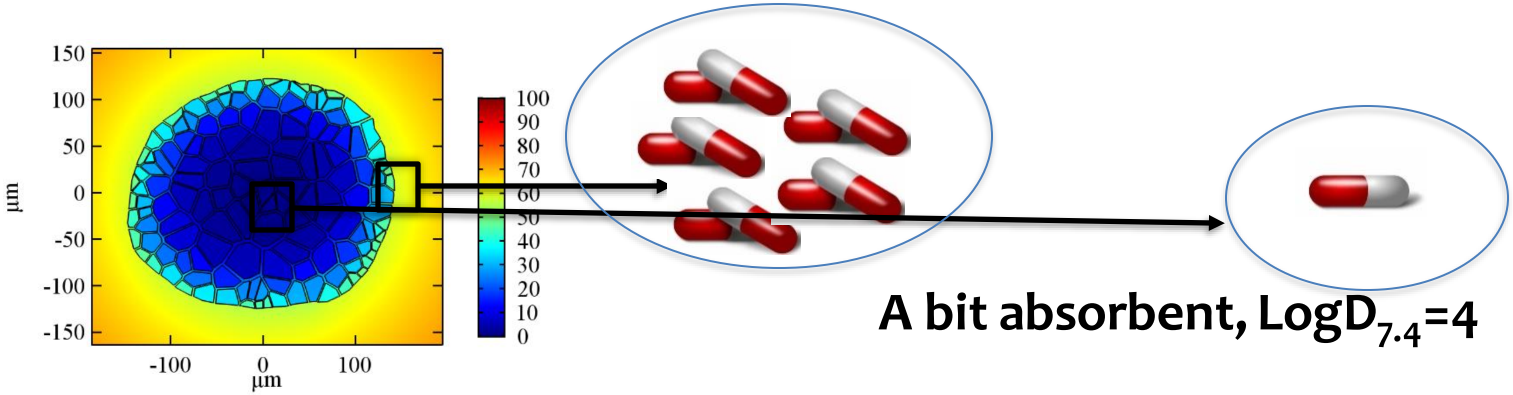
Concentration after ~3.5 min

Total drug uptake



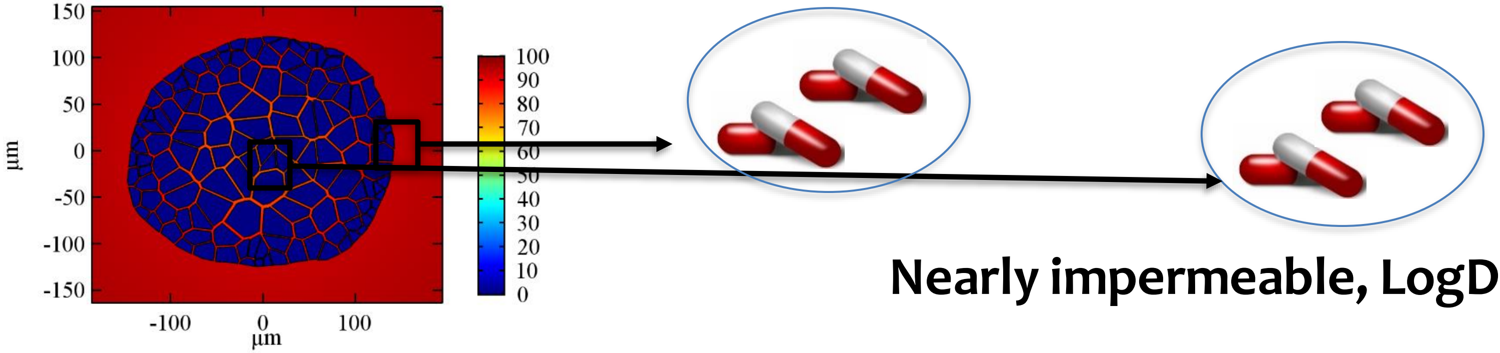
219% increase

Very absorbent cells, LogD$_{7.4}$=6



1250% increase

A bit absorbent, LogD$_{7.4}$=4



13% increase

Nearly impermeable, LogD$_{7.4}$=1

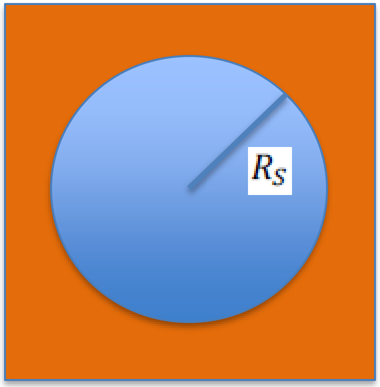
Homogenized sphere

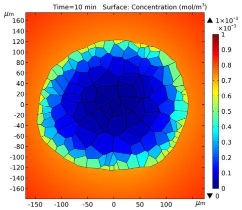
$$\frac{\partial C_S}{\partial t} = \frac{D_I^{Eff}}{r}\frac{\partial}{\partial r}\left(r\frac{\partial C_S}{\partial r}\right) - \frac{V_{max}C_S}{C_S + K_m}, \qquad r \le R_S,$$

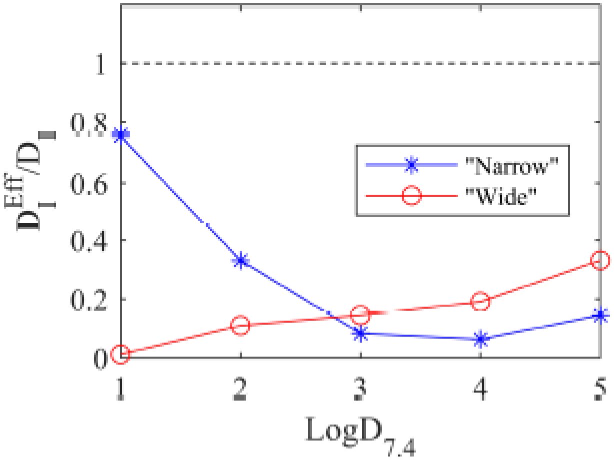
$$\frac{\partial C_O}{\partial t} = \frac{D_E}{r}\frac{\partial}{\partial r}\left(r\frac{\partial C_O}{\partial r}\right), \qquad r > R_S,$$

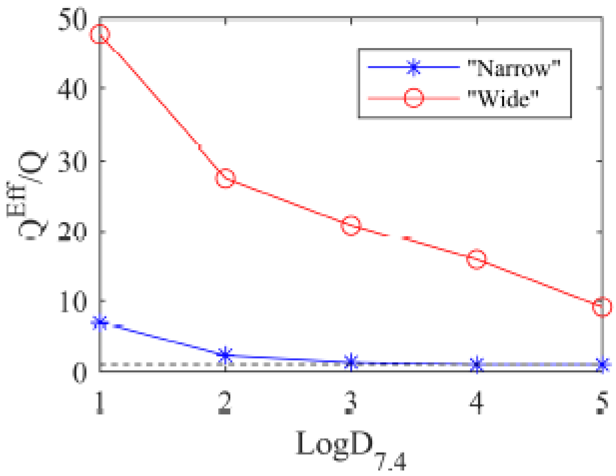
$$D_I^{Eff}\frac{\partial C_S}{\partial r} = 0, \qquad r = 0,$$

$$D_I^{Eff}\frac{\partial C_S}{\partial r} = D_E\frac{\partial C_O}{\partial r} = Q^{Eff}(C_O - C_S), \qquad r = R_S,$$









$$Error = \sum_i \left| \frac{C_{cont}(r_i, t^*) - \bar{C}_{cells}(r_i, t^*)}{\bar{C}_{cells}(r_i, t^*)} \right|$$

Music and mathematics interrogate brain tumour dissemination

Violaine See, Raphael Levy, Rachel Bearon, Emily Howard, Dave Mason

Marianne Scott

"Going into a project thinking like a biologist, keeps you focussed on the important biological questions. Bringing a mathematician on-board has helped us think about new ways to ask questions of our system."

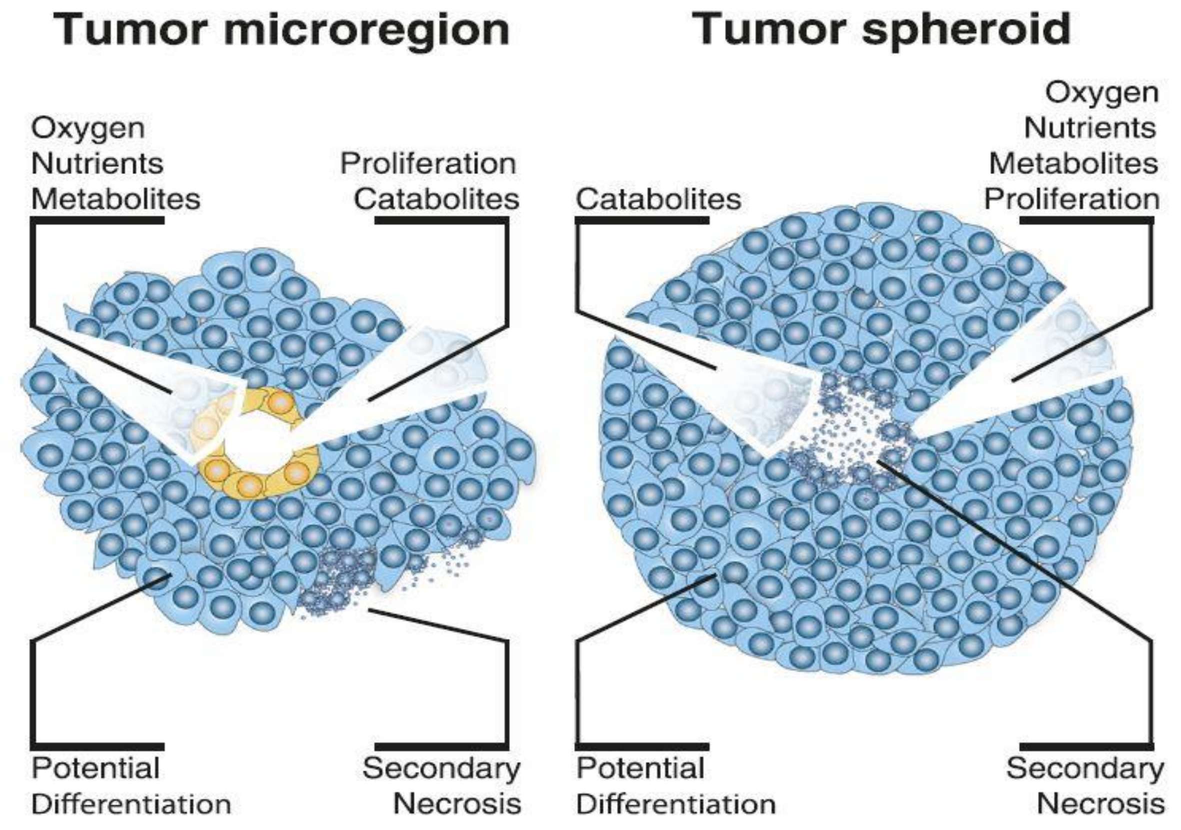
PRiSM

CCI
CENTRE FOR
CELL IMAGING

Kamila Zychaluk

Collaboration with Violaine See & Dave Mason

The Multicellular Tumour Spheroid Model



Phung et al. (2011) *J Cancer* 2: 507-514

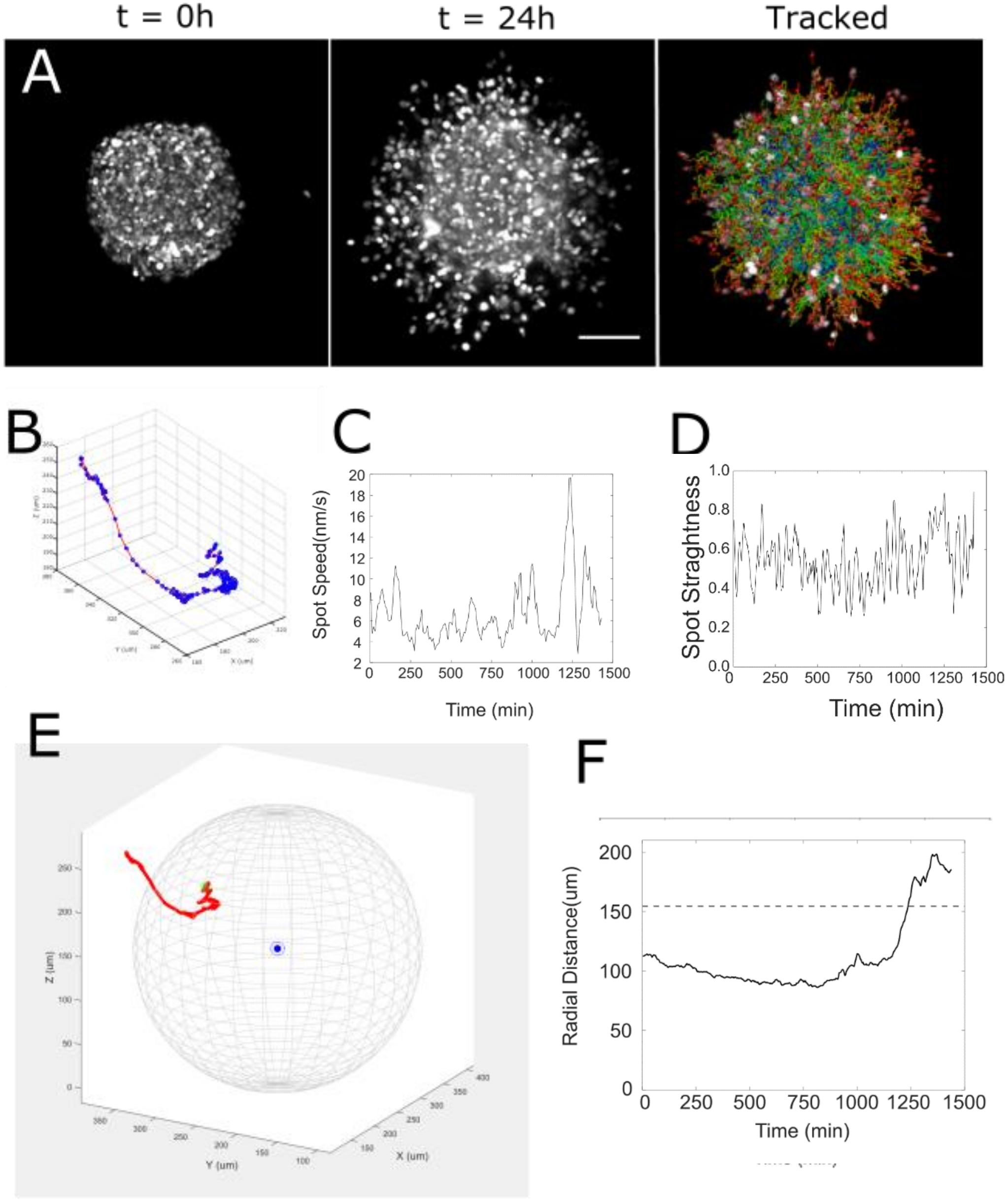
CCI
CENTRE FOR
CELL IMAGING

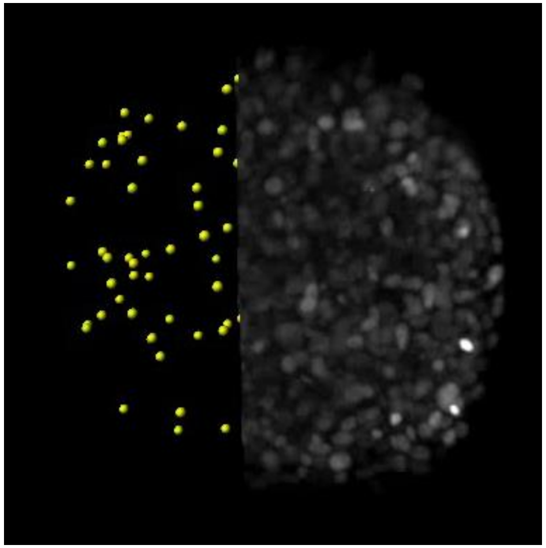
EPSRC Engineering and Physical Sciences Research Council

BBSRC bioscience for the future

MRC Medical Research Council

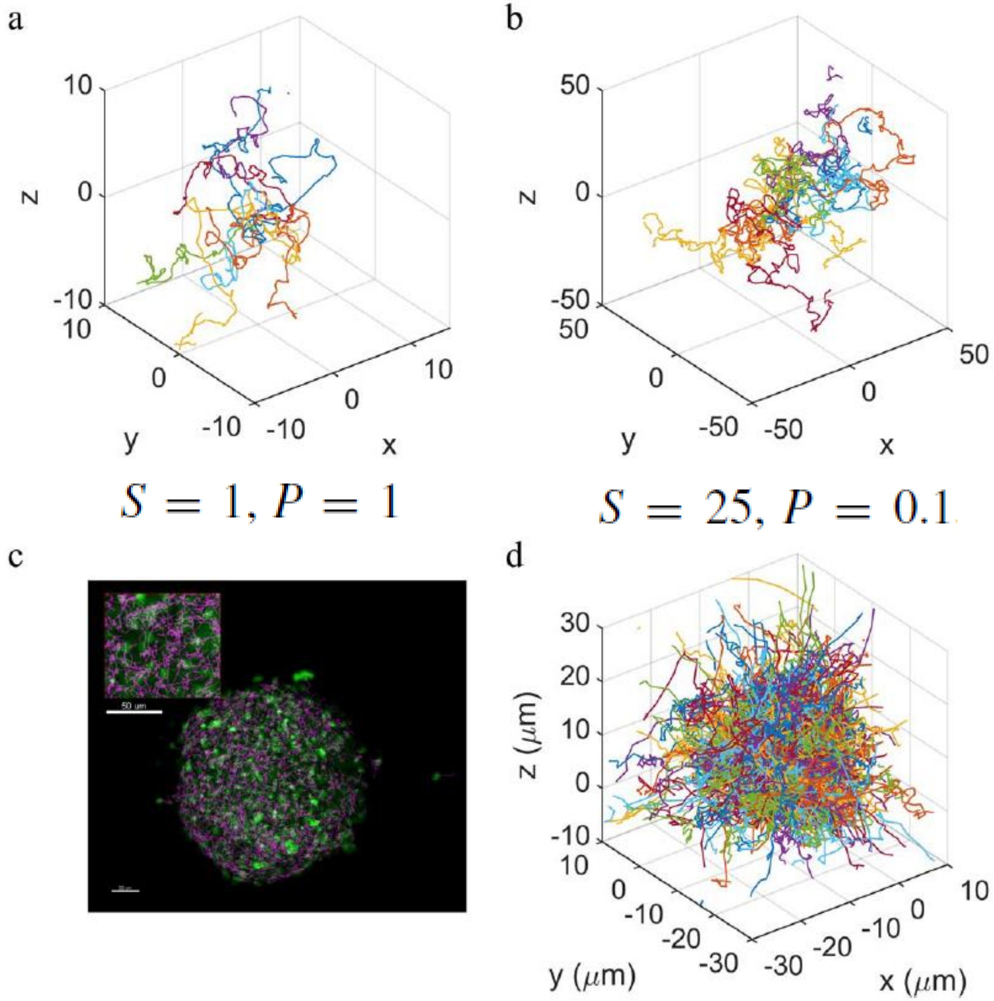
Single trajectory analysis





Rosalie Richards

Persistent random walk model for cell motility



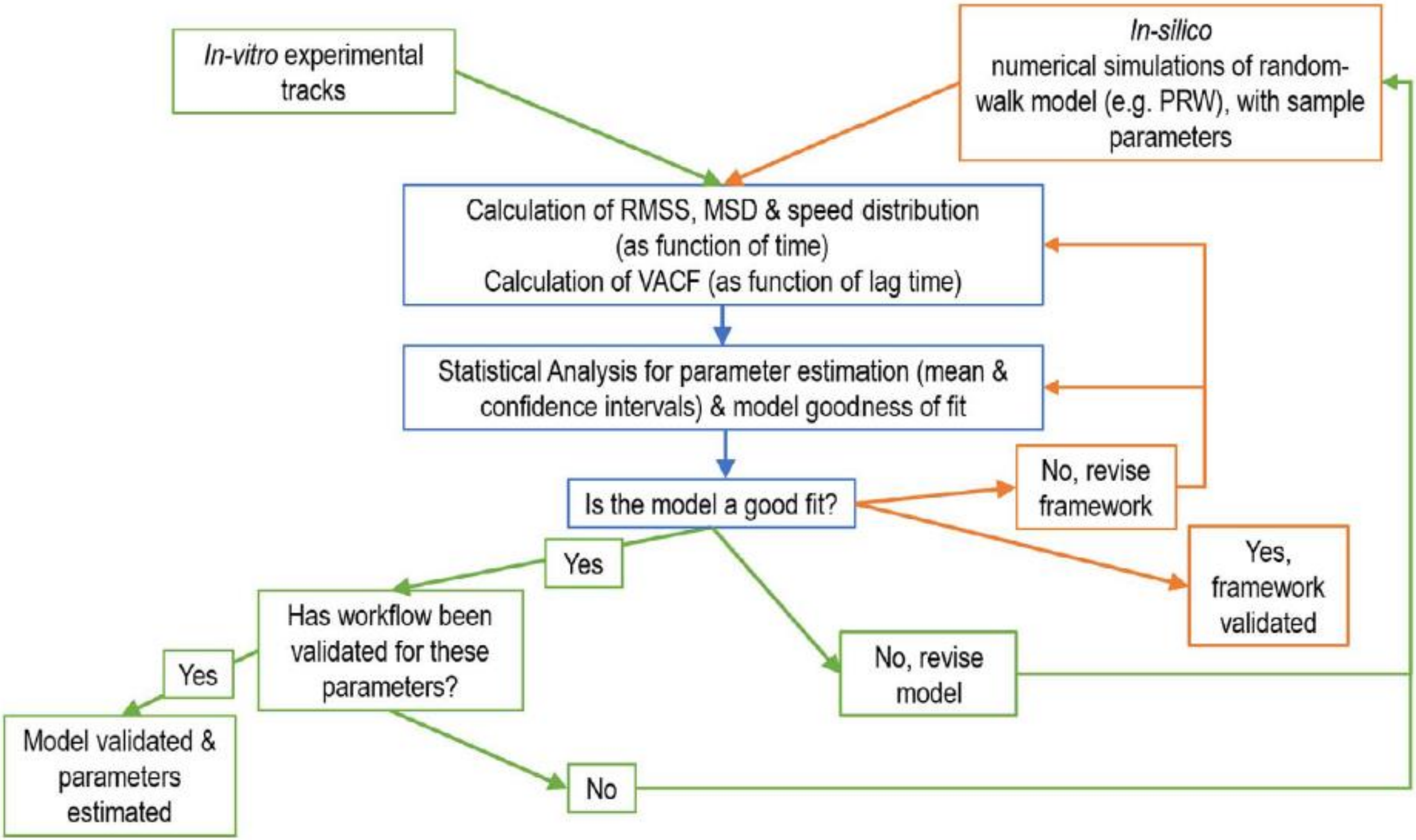
$S = 1, P = 1$

$S = 25, P = 0.1$

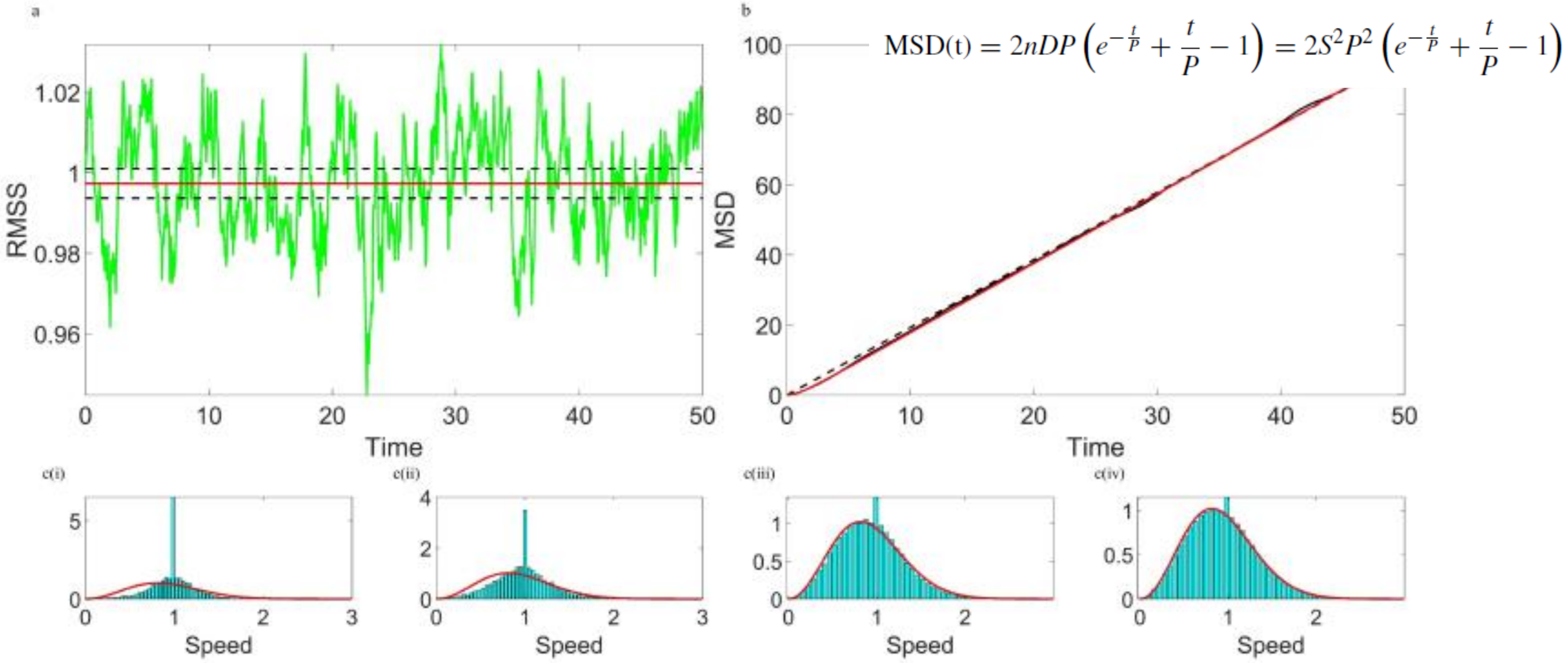
$$d\mathbf{v} = -\frac{1}{P}\mathbf{v}\,dt + \frac{\sqrt{2D}}{P}\,d\mathbf{W}(t)$$

$\mathbf{v}$	Cell velocity
P	Correlation time
S	RMS speed
$D=S^2P/n$	Spatial Diffusion in n dimensions

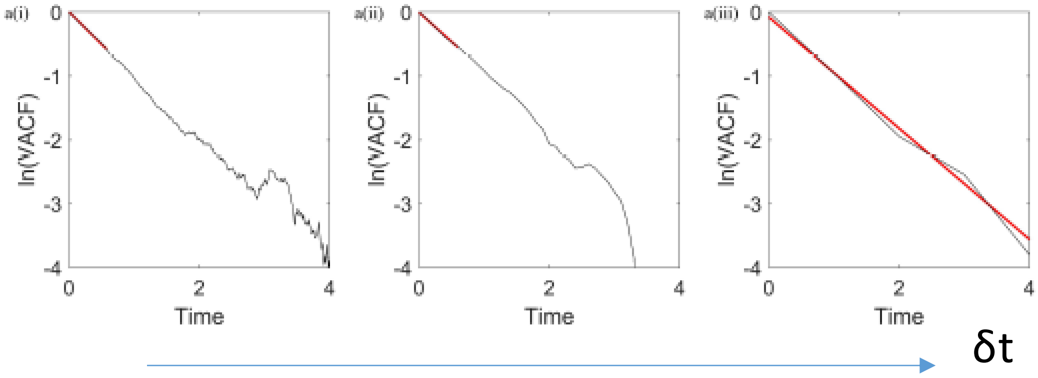
M. SCOTT, K. ZYCHALUK AND R. N. BEARON (2021), *Math. Medicine & Biol.*
A mathematical framework for modelling 3D cell motility; applications to Glioblastoma cell migration


In-vitro experimental tracks
In-silico numerical simulations of random-walk model (e.g. PRW), with sample parameters
Calculation of RMSS, MSD & speed distribution (as function of time)
Calculation of VACF (as function of lag time)
Statistical Analysis for parameter estimation (mean & confidence intervals) & model goodness of fit
Is the model a good fit?
No, revise framework
Yes, framework validated
Yes
No, revise model
Has workflow been validated for these parameters?
Yes
Model validated & parameters estimated
No

Statistical properties (in-silico), *S=1; P=1*



$$\mathrm{MSD(t)} = 2nDP\left(e^{-\frac{t}{P}} + \frac{t}{P} - 1\right) = 2S^2P^2\left(e^{-\frac{t}{P}} + \frac{t}{P} - 1\right)$$

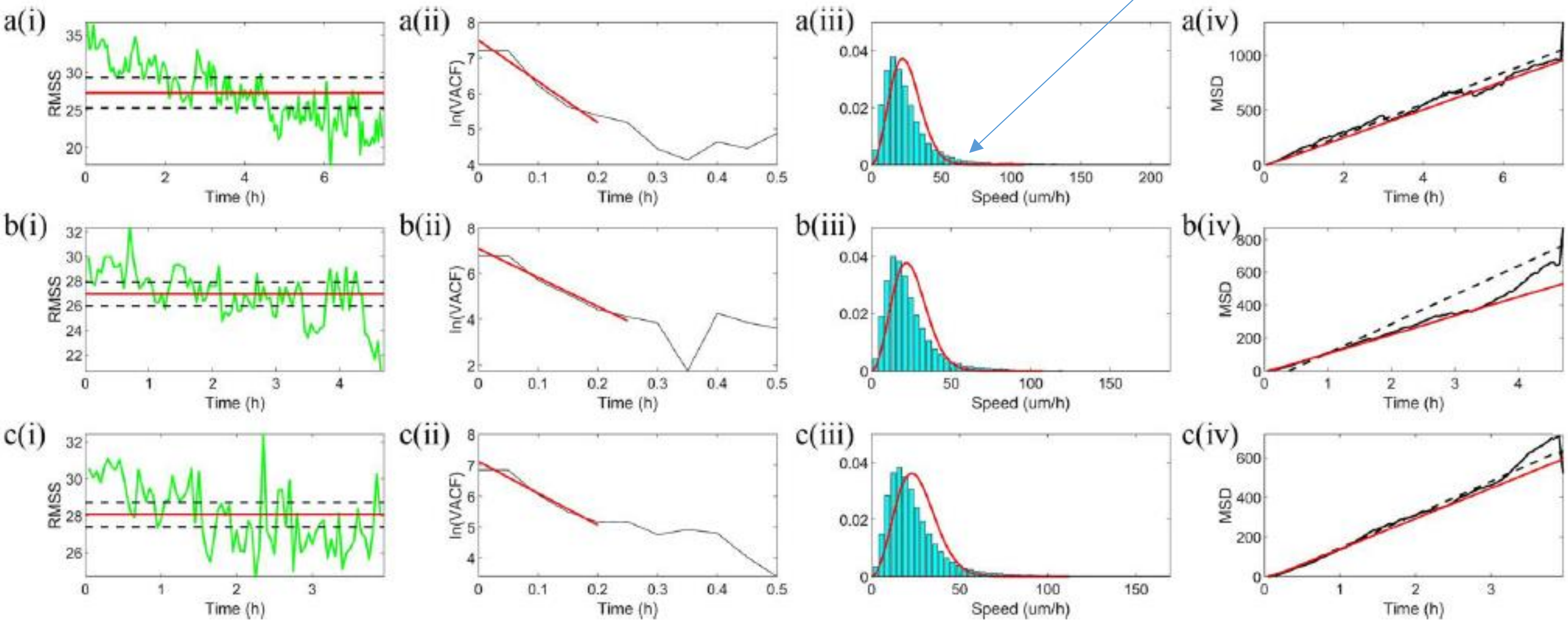


δt

Velocity autocorrelation (P=1)

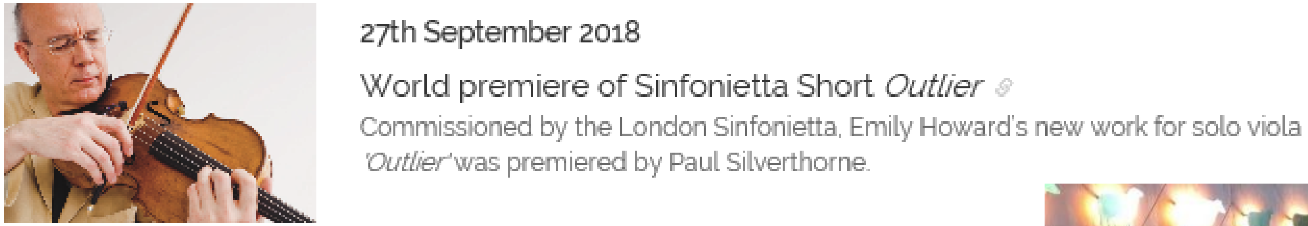
$$\mathrm{VACF(t)} = \frac{nD}{P}e^{-\frac{t}{P}} = S^2e^{-\frac{t}{P}}$$

Statistical properties (experimental) (S=?, P =?):



Outliers?

(a) *S*=27microns/h [25.3-29.3]	*P*=0.086h [0.070,0.113]
(b) *S*=27microns/h [26.0-27.9]	P=0.079h [0.068-0.095]
(c) *S*=28microns/h [27.4-28.7]	P=0.098h [0.080-0.124]



27th September 2018

World premiere of Sinfonietta Short *Outlier*

Commissioned by the London Sinfonietta, Emily Howard's new work for solo viola *'Outlier'* was premiered by Paul Silverthorne.

PRiSM 8 Cubed 2020

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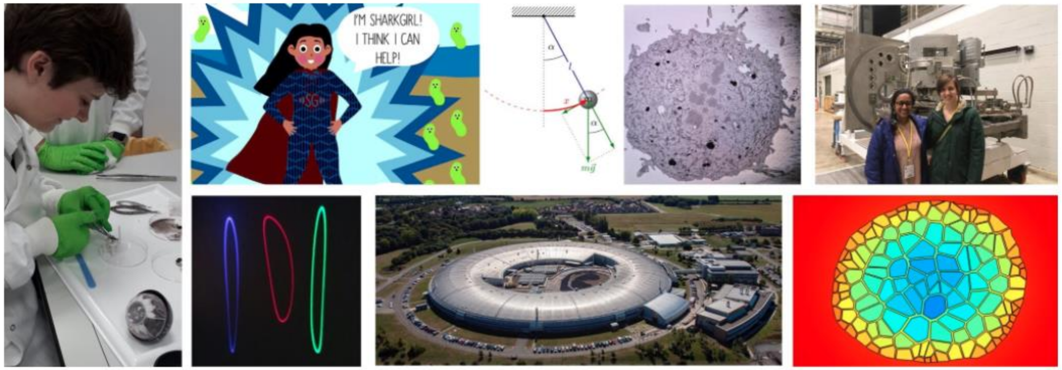
8 composers x 8 scientists x 8 performers

10 July 2020



8³ 2020 is a collaboration between 8 composers, 8 scientists and 8 performers from the RNCM and the University of Liverpool, in which music and science entwine in the creation of new works.

- Uptake Anna Appleby (Composer, RNCM) and Rachel Bearon (Professor of Mathematical Biology, Liverpool)

https://www.youtube.com/watch?source_ve_path=Mjg2NjQsMTY0NTA2&feature=emb_share&v=0_obEP1Nl4U

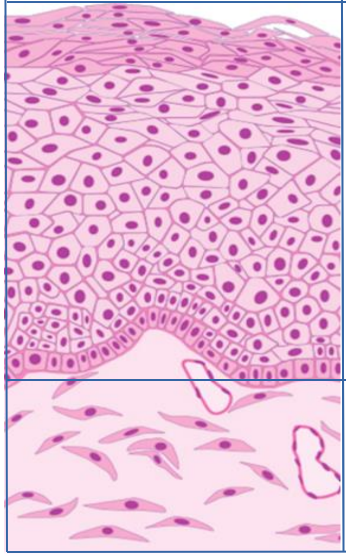
Mathematical modelling of trans-oromucosal drug permeation

- Sean Edwards (UoL)
- Craig Murdoch (UoS)
- Helen Colley (UoS)
- Amy Harding (UoS)
- Stephen Webb (Syngenta)
- Joseph Leedale (Syngenta)

In silico models

Application

Diffusion



Epithelium

Diffusion

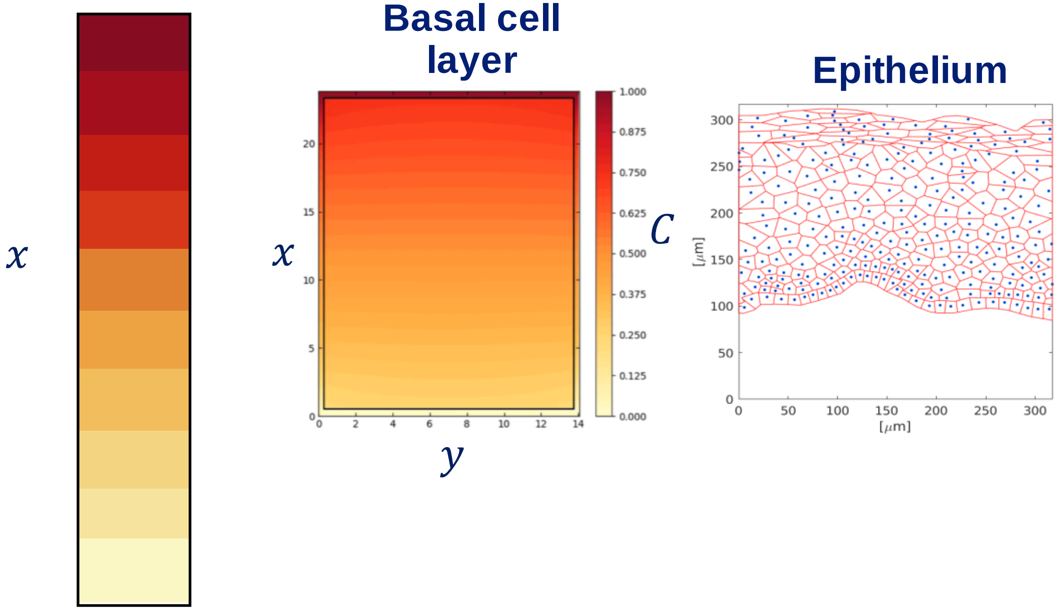
Membrane permeation

Metabolism

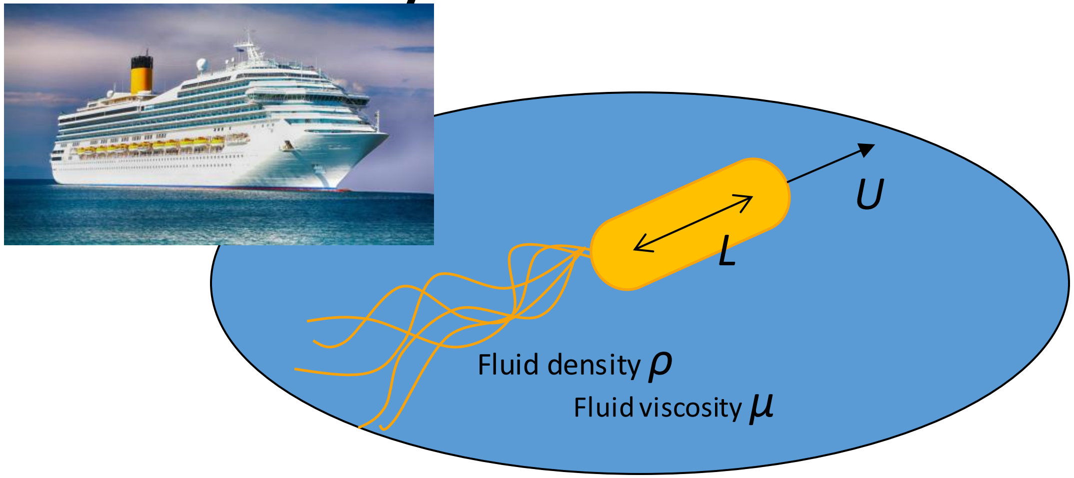
Lamina Propria

Diffusion
Systemic Uptake

1D Continuum



The dynamics of swimming bugs



Bacteria in water

$$U \sim 30\ microns/s$$

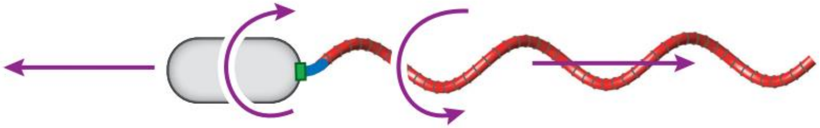
$$L \sim 1\ micron$$

$$R \sim 3 \text{ x } 10^{-5}$$

coasting distance ≃ 0.1 Å

coasting time ≃ 0.3 microsec.

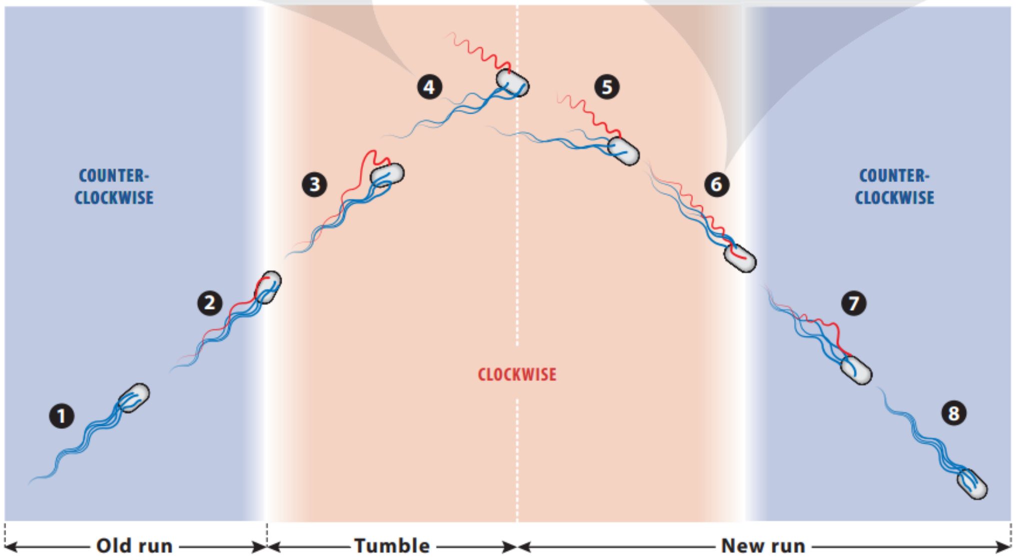
$$\frac{inertial\ forces}{viscous\ forces} \sim R = \frac{\rho U L}{\mu}$$



Lauga 2016,`Bacterial Hydrodynamics'

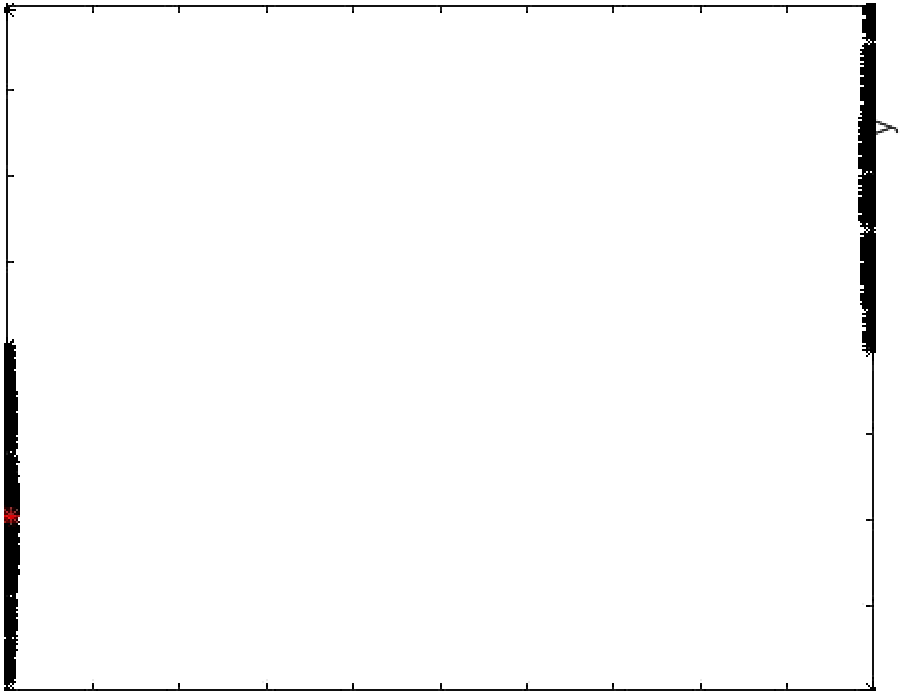
Cara Neal:
Swimming in complex fluids

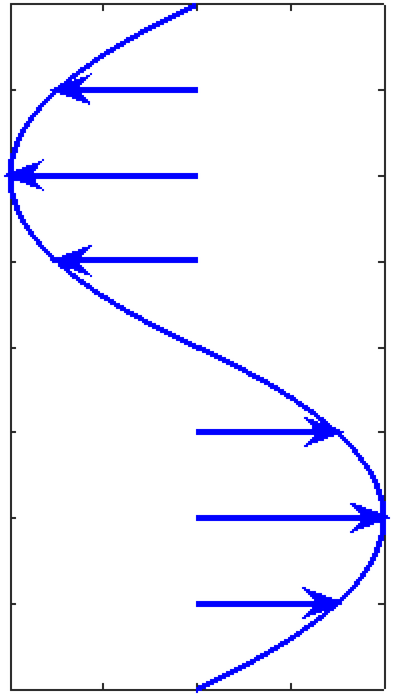
Purcell 1976 'Life at Low Reynolds number'

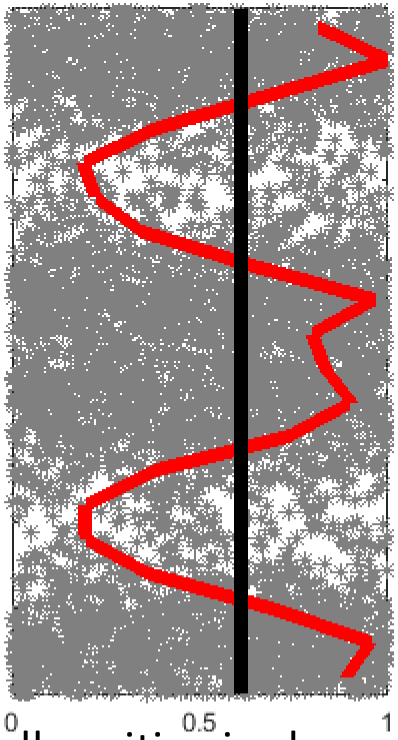


Trapping of swimmers in high shear

Illustrative IBM simulation of random walk of ellipsoids in periodic Poiseuille flow







Red line: histogram of cell position in shear

Smitha Maretvadakethope
Shape, shear, search & strife; mathematical models of bacteria

Closing comments

- 3D micro-tissues provide fantastic data for developing mathematical models
- Data can be used to parameterise and test models
- Validated models can then be used to extrapolate from 3D micro-tissue to more complex 3D geometries/PKPB models
- Examine effects of perturbation (e.g. drug dosing, mutants)
- Combine rigorous statistical methodology to parameterise & test models, leading to better understanding
- Follow your interests