Modelling *in vitro* tissue growth

Open for Business INI Cambridge 24th June 2014

Reuben O'Dea
Centre for Mathematical Medicine and Biology
University of Nottingham

CMMB Centre for Mathematical Medicine and Biology
The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

Regenerative medicine

- "Replacement/regeneration of cells/tissues/organs to restore normal function"…

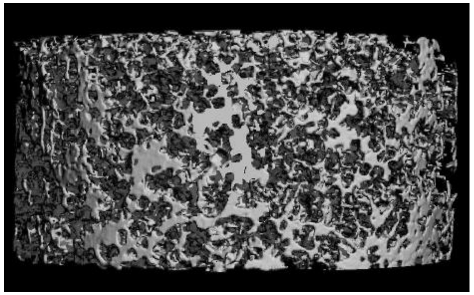
In vitro tissue engineering

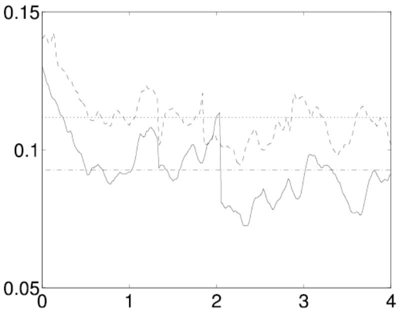
- Growth of tissues for implantation (*e.g.* bone)
- Toxicology screening, drug testing (NC3Rs)
- High demand – shortage of donor tissues
  - 2009/10: ~8000 waiting; 552 deaths
- **Generation of tissue with *in vivo* properties…**

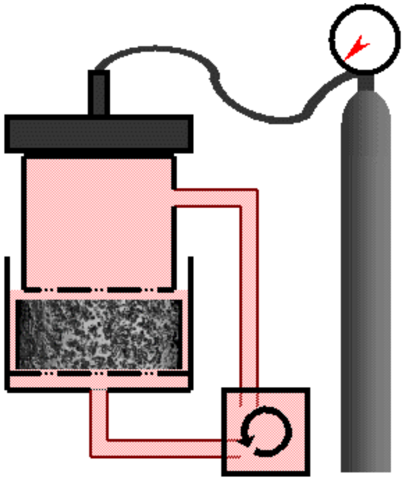
Modelling: (i) Quantitative understanding of complex problem
(ii) Emergent tissue-level properties

TE bioreactor system[1]

- Perfusion enhances nutrient delivery
- (Mechanotransduction) Bone cells sensitive to
  - Compressive strain
  - Fluid shear stress
- Mineralisation enhanced, localised in regions of stress







I. Phenomenological model

- Mechanotransduction
- Cell-cell/cell-scaffold interactions

II. Micro to Macoscale

- Microscale **FBP**
- Emergent macroscale model

[1] AJ El Haj et al. ISTM, Keele University

I Phenomenological model

Aims

- Develop a continuum macroscale model
- Accommodate:
  1. Cell-cell interactions
  2. Scaffold adhesion
  3. Mechanotransduction
- Obtain a ***minimal framework***

Multiphase approach

- Describe tissue as sets of interacting ***'phases'***
- 'Continuum mechanics'-type PDEs
- Naturally accommodates interactions within biological tissue

I Multiphase model – detail

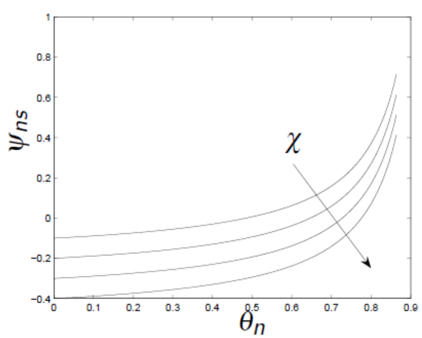
Phases

- Cells, culture medium: $\theta_n(\mathbf{x},t),\ \theta_w(\mathbf{x},t)$
- Substrate: PLLA scaffold, deposited ECM $\Theta(\mathbf{x},t) = \theta_s + \theta_e$
- Viscous fluids contained within porous scaffold

Governing equations

Mechanotransduction

- Mass: $\frac{\partial \theta_i}{\partial t} + \nabla\cdot(\theta_i \mathbf{u}_i) = S_i$
- Momentum: $\nabla\cdot(\theta_i \sigma_i) + \sum_{j\neq i} \mathbf{F}_{ij} = 0$



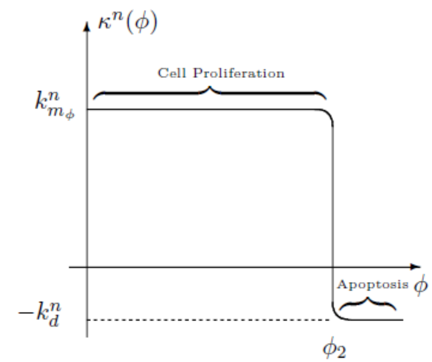
$$\psi_{ns} = -\chi + \frac{\delta_b \theta_n}{\theta_w}$$

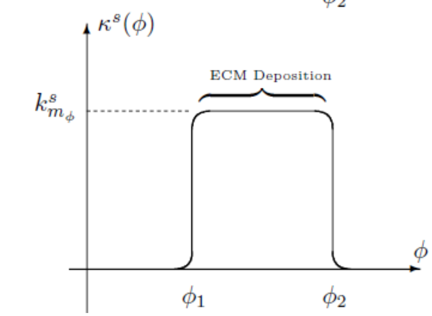
Cell-scaffold adhesion

Viscous drag + active forces

Cell aggregation

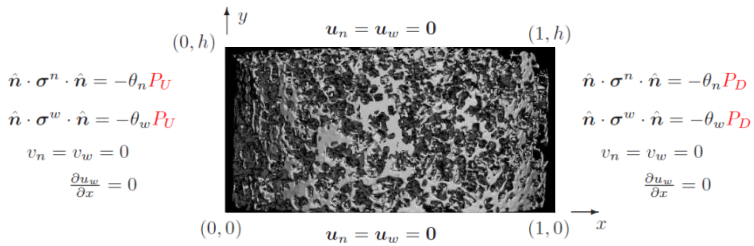
$$\Gamma_n = -\theta_n \nu + \frac{\delta_a \theta_n^2}{\theta_w}$$





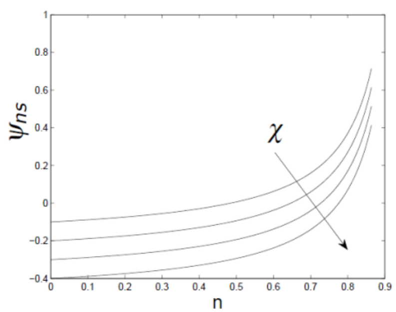
I Multiphase model – investigations

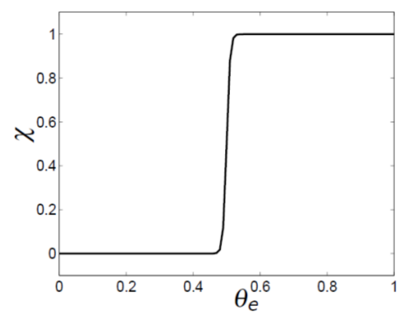
1. Geometry (2D vs 1D)

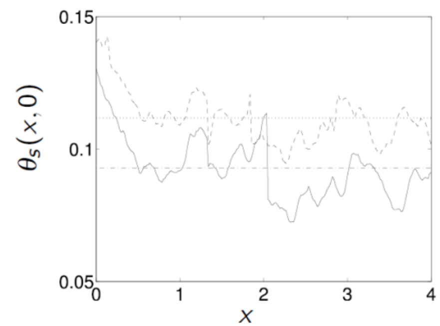


vs. $h \ll 1$

2. Cell-scaffold interaction model



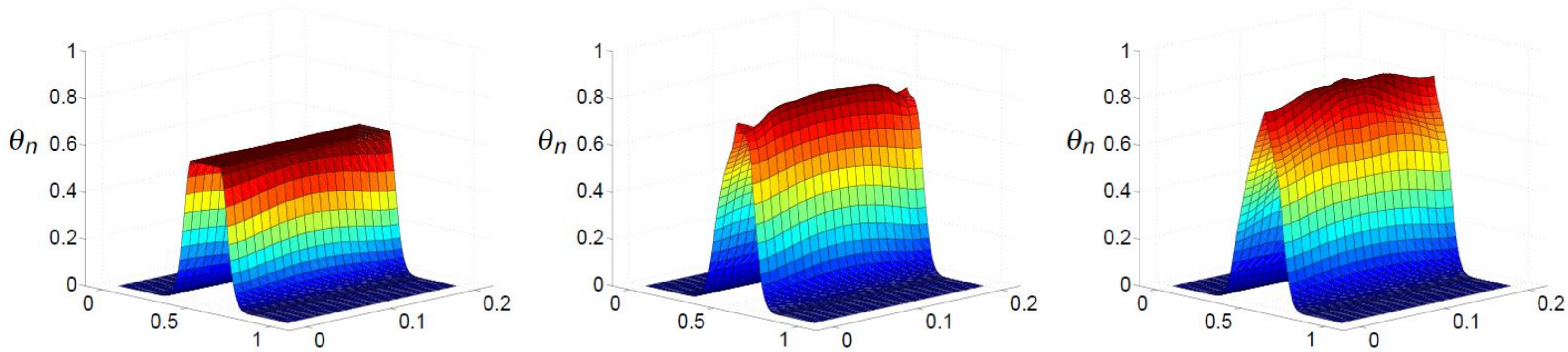




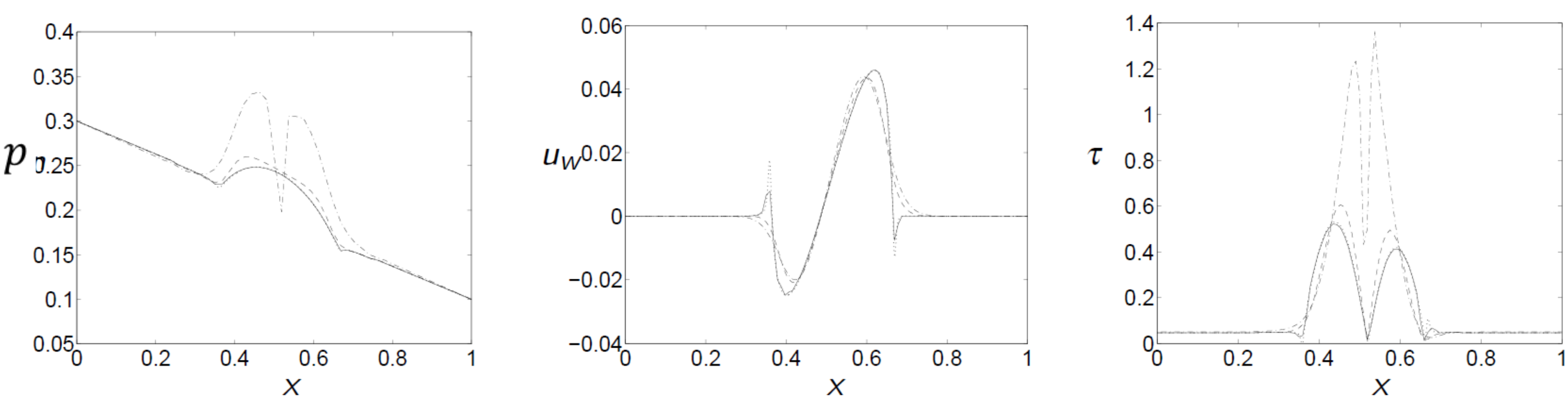
3. Scaffold heterogeneity

1. Results – geometry

Model predicts characteristic morphology due to culture conditions and regulatory mechanisms



How important is it to solve the full 2D equations? … very!

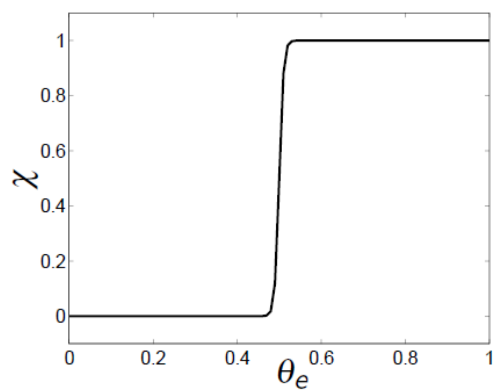


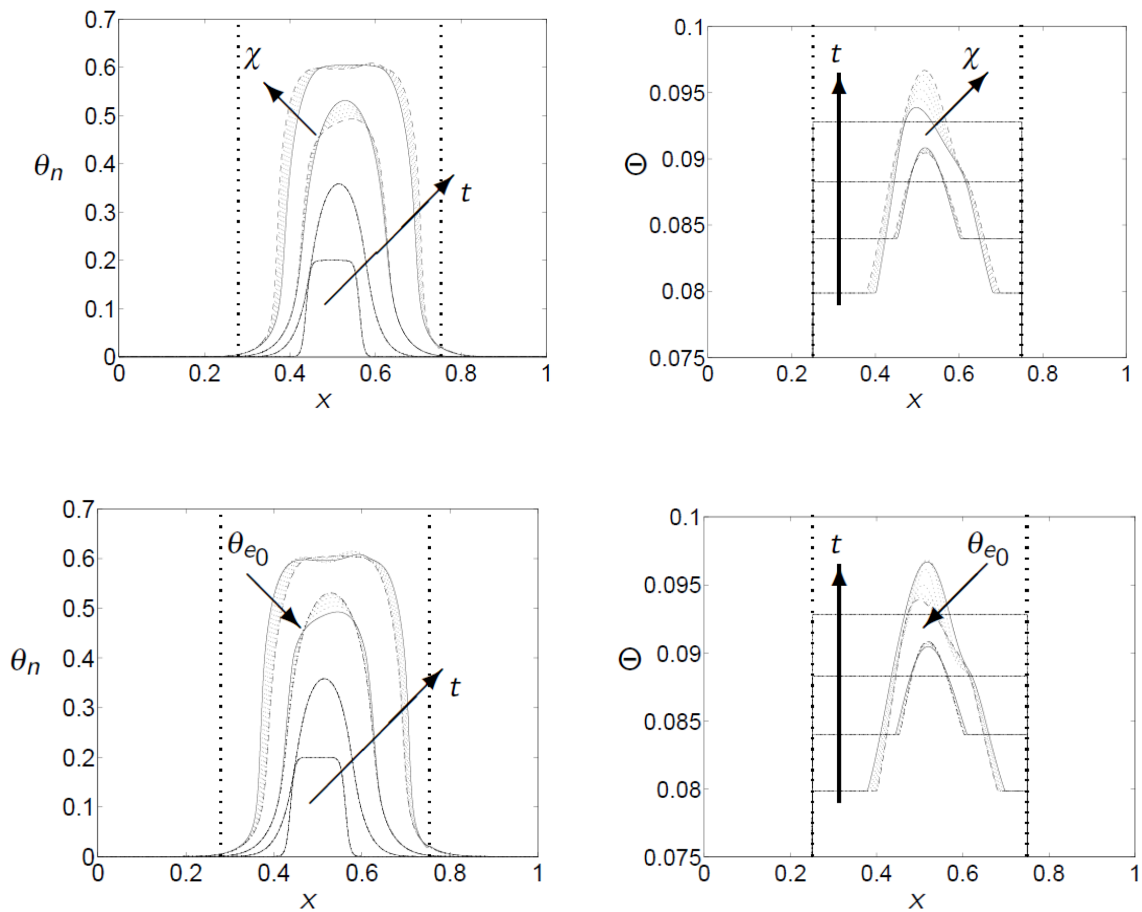
2. Results – adhesion

$$\Theta(\mathbf{x}, t) = \theta_s + \theta_e$$

$\chi = \text{constant}$

$\chi(\theta_e)$





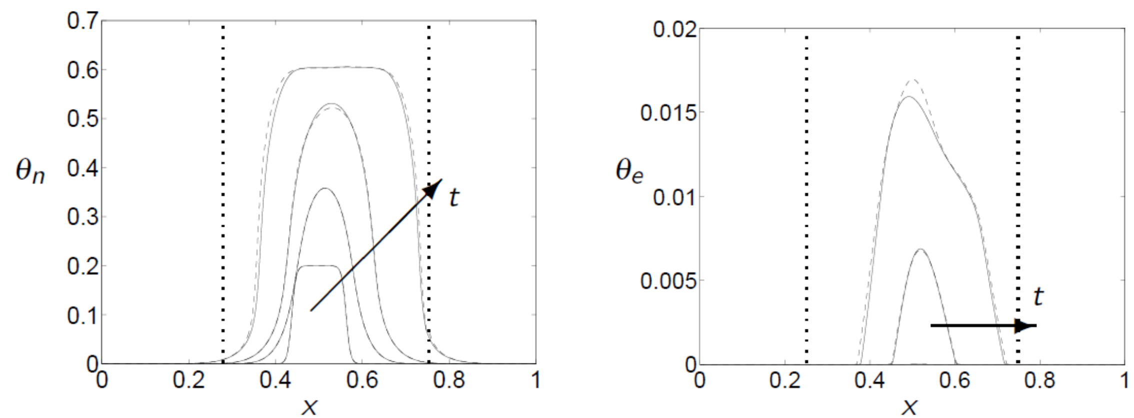
Simple adhesion model gives identical results!

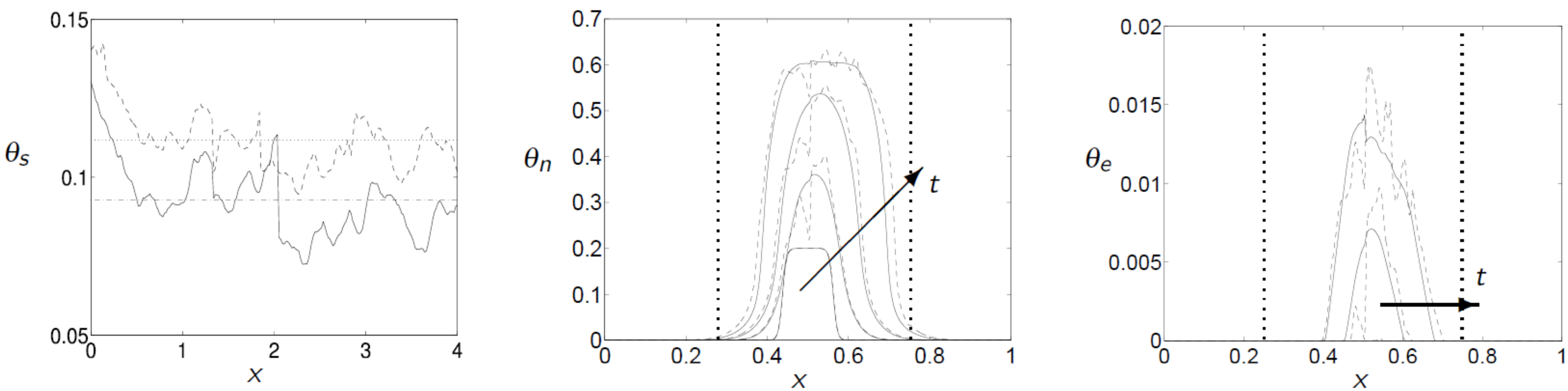
2. Results – scaffold heterogeneity

$\chi = \text{constant}$

$\chi = 0$: —

$\chi = 1$: – –

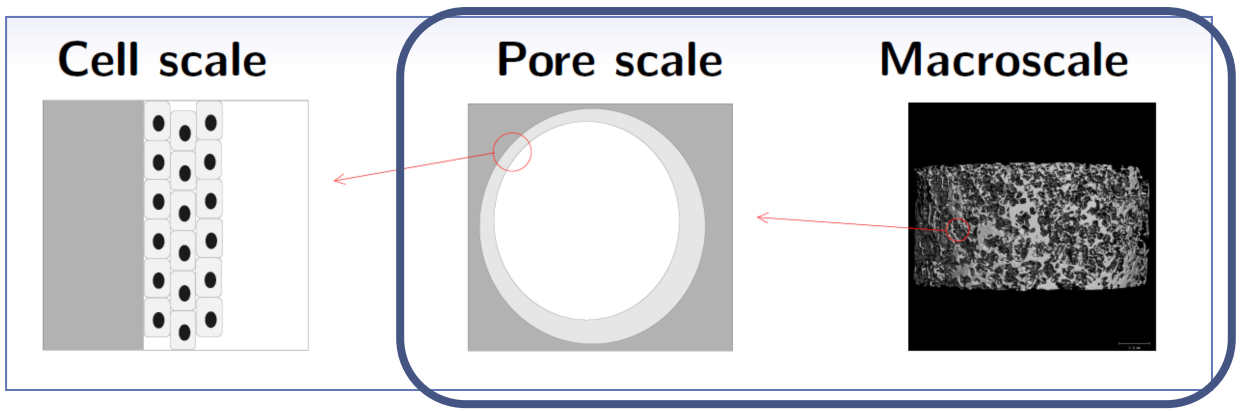




Cell-substrate adhesion → ECM profile mimics/exaggerates underlying heterogeneity

II Micro *vs.* macro models

- Tissue growth is inherently a ***multiscale*** process
- Phenomenological (macroscale) models
  - ✓ 'Convenient'
  - ✗ Differ widely; neglect microscale phenomena

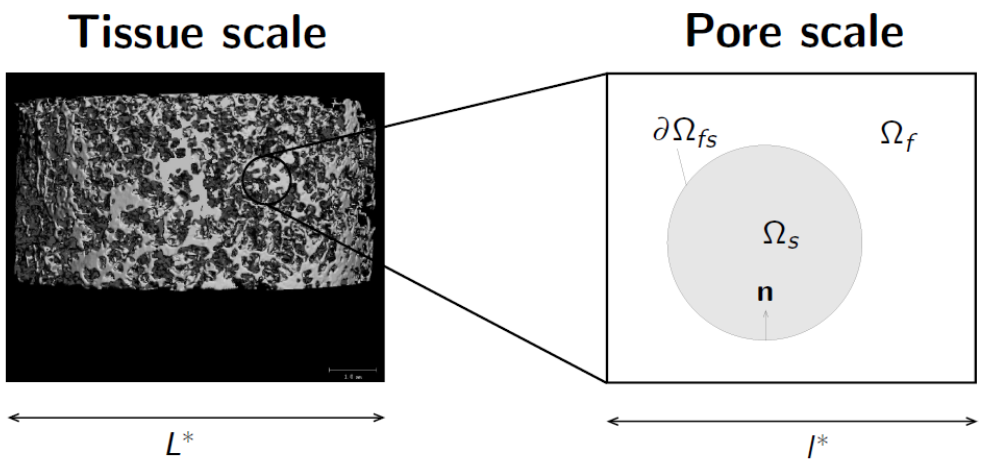


Aim: Derive a macroscale formulation able to embed microscale dynamics

meso

Multiscale methods exploit scale separation to do this

II Growth as a microscale FBP



- ❑ **Consider nutrient-limited growth in a TE scaffold**
- ❑ Rigid porous scaffold
- ❑ Viscous culture medium

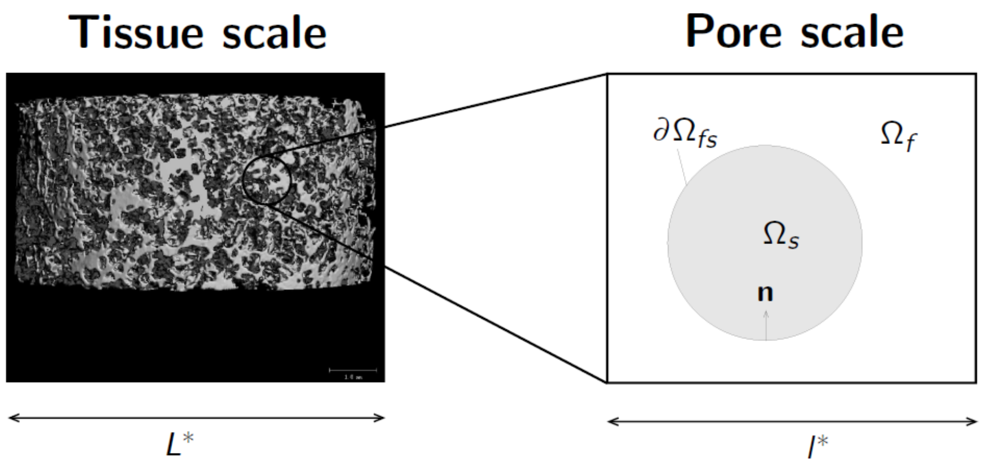
➢ Growth/deposition as evolution of interface

Simple method to accommodate **microscale flow, transport, microstructure**

➢ Multiscale method relies on:

- ❑ Scale separation: $\varepsilon = \frac{l^*}{L^*} \ll 1$
- ❑ Local periodicity

II Growth as a microscale FBP



- Consider nutrient-limited growth in a TE scaffold
- Rigid porous scaffold
- Viscous culture medium

Fluid flow:

$$\begin{cases} \rho_f^* \left(\frac{\partial \mathbf{v}^*}{\partial t^*} + (\mathbf{v}^* \cdot \nabla^*)\mathbf{v}^* \right) = -\nabla^* p^* + \mu^* \nabla^{*2} \mathbf{v}^* \\ \nabla^* \cdot \mathbf{v}^* = 0 \end{cases}$$

Nutrient transport:

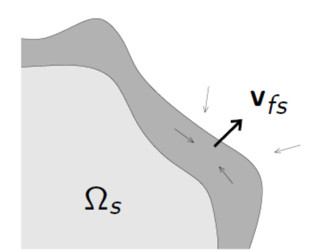
$$\frac{\partial c^*}{\partial t^*} + \mathbf{v}^* \cdot \nabla^* c^* = D^* \nabla^{*2} c^*$$

Nutrient uptake:

$$c\, \mathbf{v}_{fs}^* \cdot \mathbf{n} = -\frac{1}{\rho_s^*} S^*(Q^*) \nabla^* c^* \cdot \mathbf{n} = Q^*$$

Growth:

$$\rho_f^* \mathbf{v}^* \cdot \mathbf{n} = \left(\frac{1}{\rho_f^*} - \frac{1}{\rho_s^*} \right) S^*(Q^*) = S^*(Q^*)$$



Macroscale model

- Separate microscale (x) and macroscale dependence (*X*)
- 'Average' microscale equations over the pore domain, … , obtain ***macroscale*** flow, transport equations:

Flow
Influenced by
microstructure

Flow
Influenced by
microscale growth

$$\mathbf{v} = -\mathbf{K} \cdot \nabla_X p$$

$$\nabla_X \cdot (\mathbf{K} \nabla_X p) = (\rho - 1) S$$

$$\Phi \frac{\partial c}{\partial t} + \mathbf{v} \cdot \nabla_X c = \rho c S + Q$$

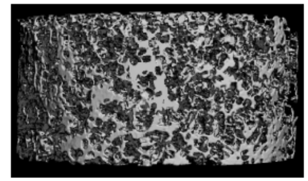
Transport
Influenced by
microstructure and growth

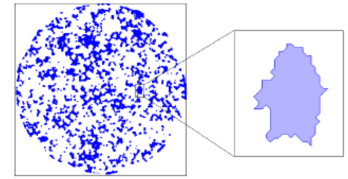
Transport
Influenced by
uptake and growth

- *K, S,* **Q** depend on the **domain** through: ***Ω* and *∂Ω***

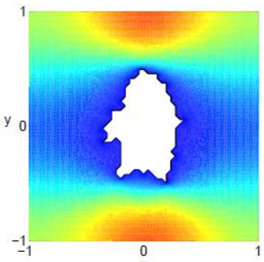
Macroscale model – results

- Use scaffold to define the microstructure: **domain *Ω***





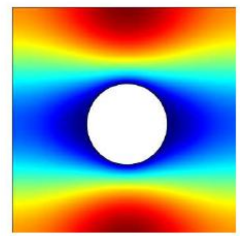
- ***K, S, Q*** depend on the **domain** through ***Ω* and *∂Ω***; e.g.:



$$\mathbf{K} = \begin{pmatrix} 0.37 & 0.0014 \\ 0.0014 & 0.64 \end{pmatrix}$$

$$|\partial\Omega_{fs}| = 3.36$$

$$\Phi = 0.9$$

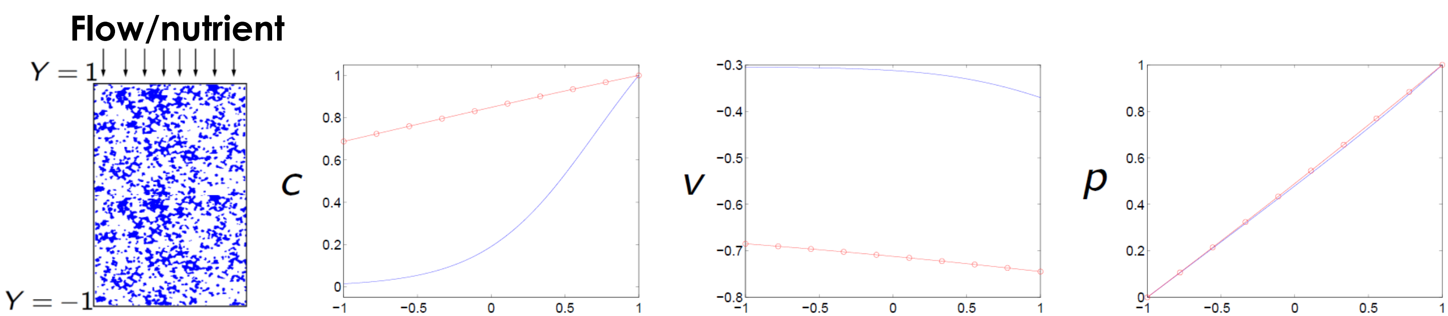


$$\mathbf{K} = \begin{pmatrix} 1.46 & 0 \\ 0 & 1.46 \end{pmatrix}$$

$$|\partial\Omega_{fs}| = 1.13$$

$$\Phi = 0.9$$

- Macroscale bioreactor 'model'; simple **uptake/growth:** $Q \propto c$, $S \propto Q$



Summary

Phenomenological model

- Continuum macroscale model for TE applications
- Accommodates:
    1. Cell-cell interactions; 2. Scaffold adhesion; 3. Mechanotransduction
- Investigated a ***minimal framework***

Multiscale analysis

- Rigorous development of macroscale growth model via microscale FBP formulation
- Obtain fully-coupled growth/flow/transport within well-studied PDE formulation

Thanks!

INSTITUTE FOR SCIENCE AND TECHNOLOGY IN MEDICINE

NOTTINGHAM TRENT UNIVERSITY

AJ El Haj

MR Nelson

UNIVERSITY OF OXFORD Mathematical Institute

OCCAM Oxford Centre for Collaborative Applied Mathematics

SL Waters, HM Byrne
JM Osborne, J Whiteley

Multiphase modelling

- O'Dea, Waters & Byrne (2008) *EJAM*, 19:607–634
- O'Dea, Waters & Byrne (2010) *Math. Med. Biol.*, 27(2):95–127
- O'Dea, Osborne, Whiteley, Byrne & Waters (2010) *ASME J. Biomech.*, 132(5)
- O'Dea, Osborne, El Haj, Byrne & Waters (2013) *J. Math. Biol.* 67(5):1199–1225
- O'Dea, Byrne & Waters (2013) *Computational modelling in TE* (Review) 229–266

Multiscale analysis

- O'Dea, Nelson, El Haj, Waters, & Byrne (2014; in press) *Math. Med. Biol.*