Multi-scale model for tissue engineered articular cartilage

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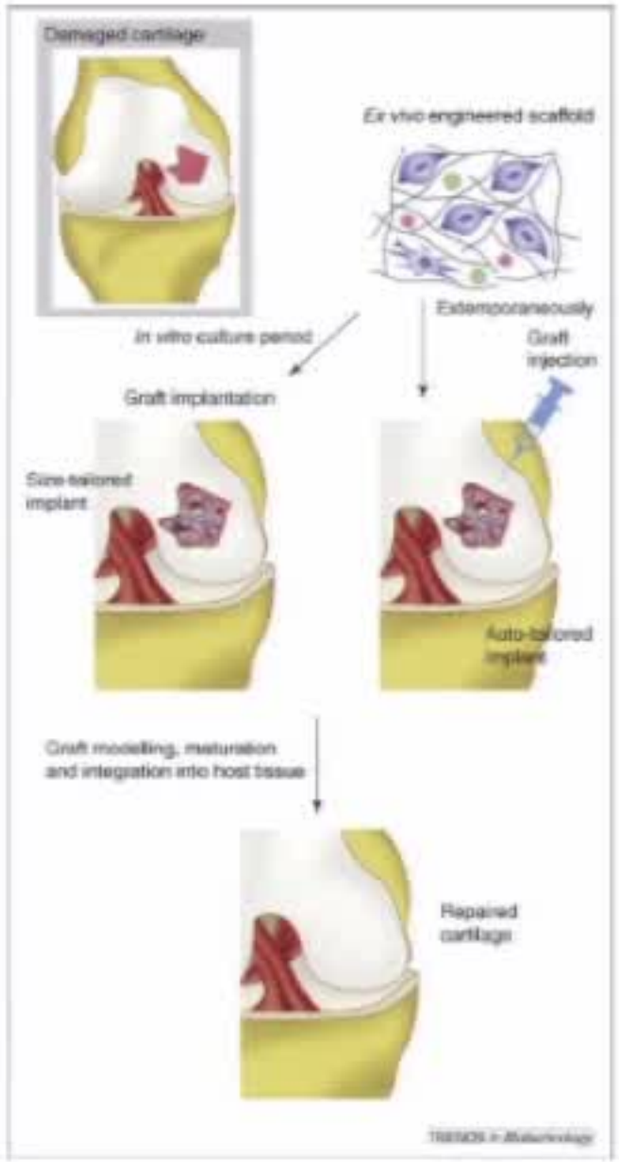
Introduction

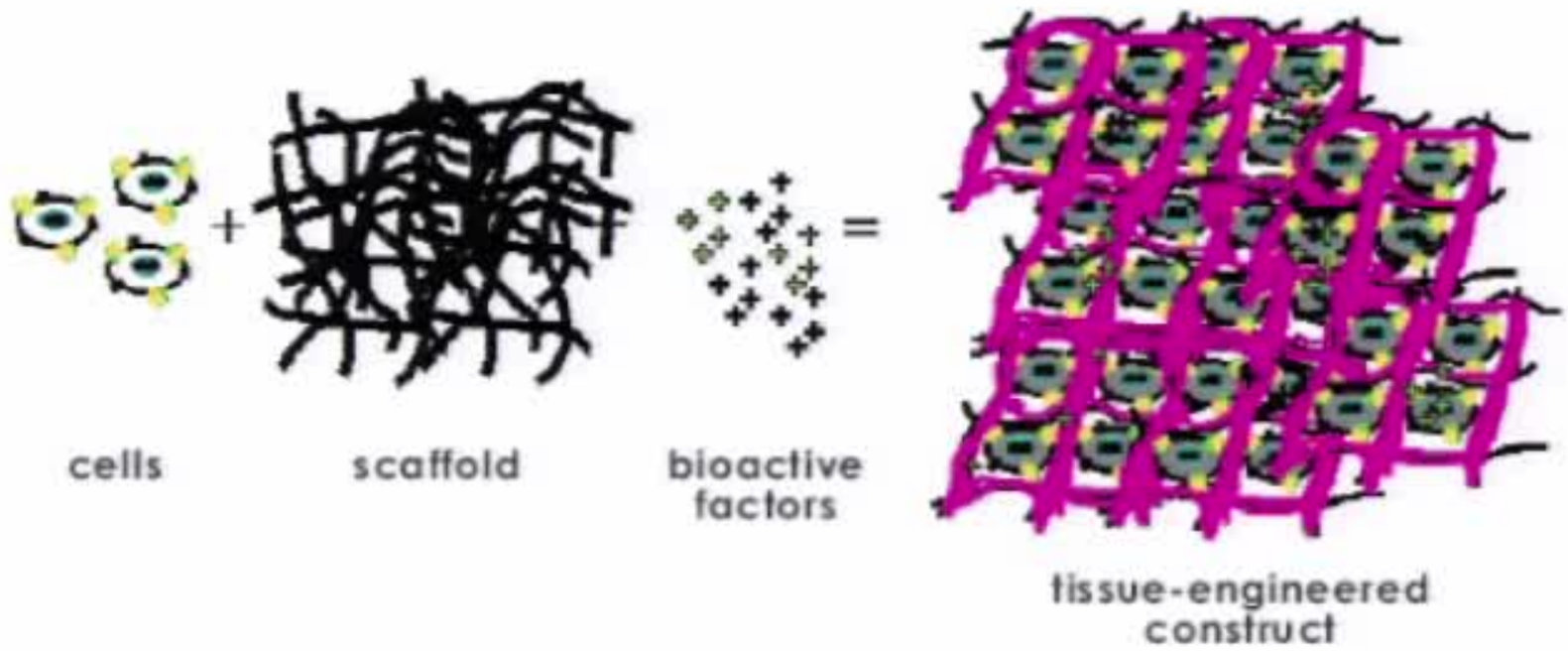
- Articular cartilage in the knee has a complex structure composed of a dense extracellular matrix (ECM), which includes fluid, a collagen network, and other proteins (proteoglycans).
- Distributed in the matrix there are chondrocytes (cells) that synthesize the building blocks of the ECM.
- Pathologies such as osteoarthritis and injuries can cause the erosion and damage of articular cartilage
- Cartilage has a low repair capability



Vinatier, C. et al. Trends in Biotechnology Vol. 27(5), 2009.

Introduction

Tissue engineering represents a promising path towards the treatment of damaged cartilage

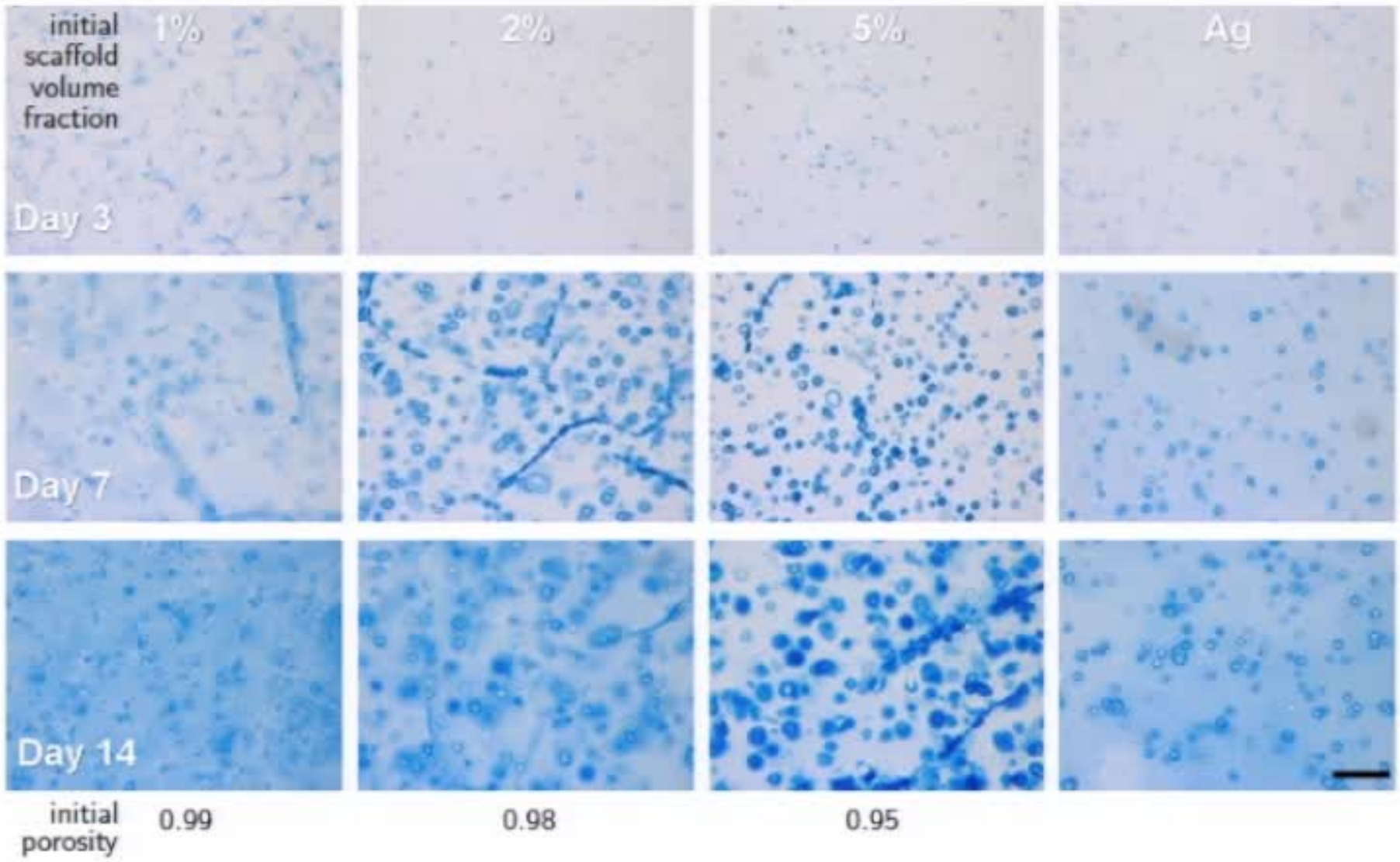


http://www.bioeng.nus.edu.sg/_images/gallery/research4.gif.

The outcomes of tissue engineered cartilage experiments strongly depend on different factors such as the properties of the gel or scaffold (porosity of gel, mechanical properties, diffusion of nutrients)

Experiments: effect of porosity

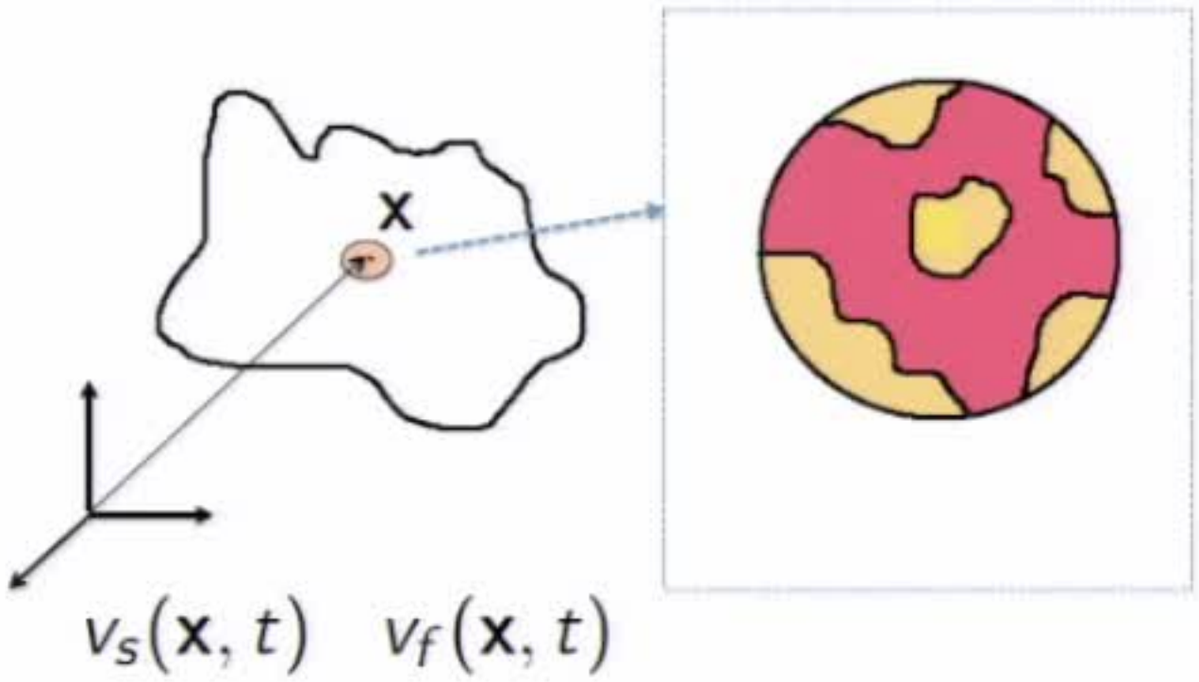
Porosity $= 1 -$ (solid volume fraction) $=$ fluid region

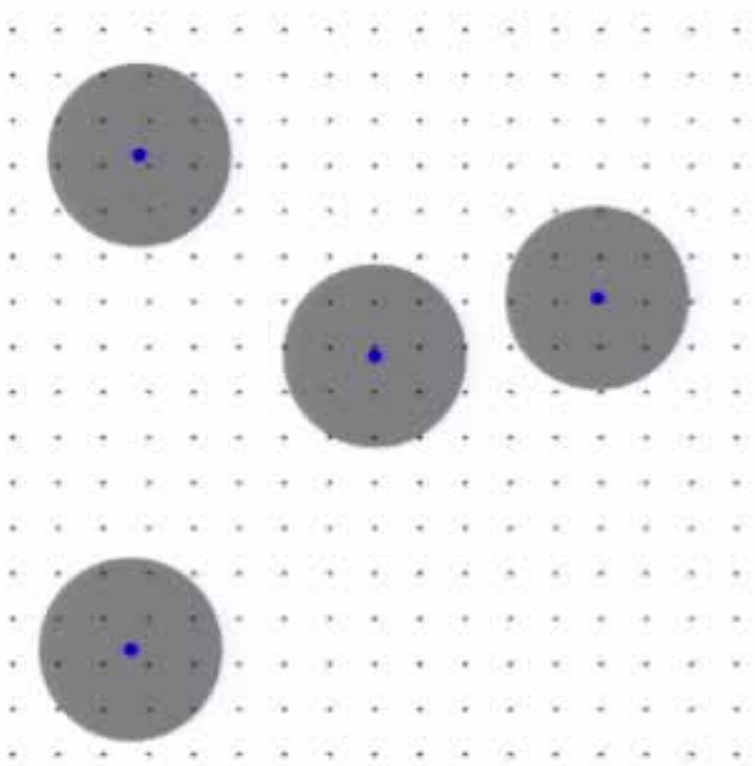


Localization of proteoglycans (blue) in gels of different porosity:
Erickson, I.E. et al Osteoarthritis and Cartilage Vol. 17, 2009.

Mathematical formulation

- Cell seeded gel - multiphase construct (solid + fluid)
- Porosity: multiphase quantity
- Possible approach: Mixture theory
- In this work: neglect fluid velocity





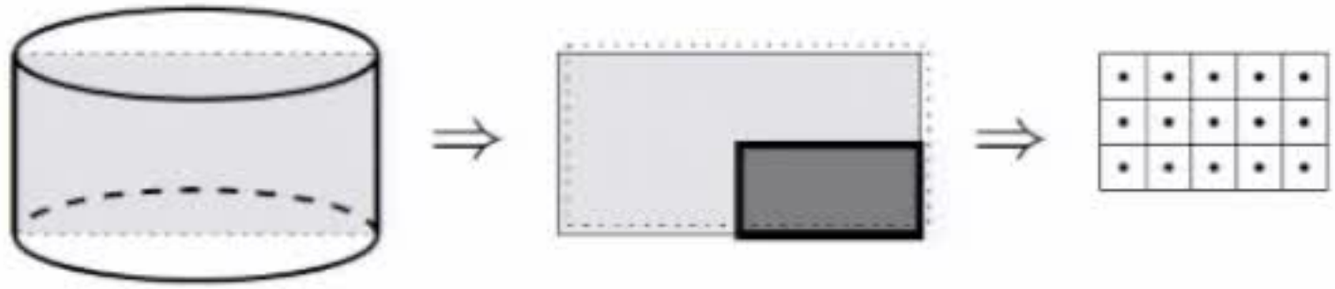
Goal

- Develop a model that describes the process of tissue growth of engineered cartilage
  - Utilize a hybrid cellular automata framework
  - First model to account for porosity
- Investigate the mechanisms governing the growth of tissue engineered cartilage

Main challenges

- Model calibration
- Efficiency

Model features



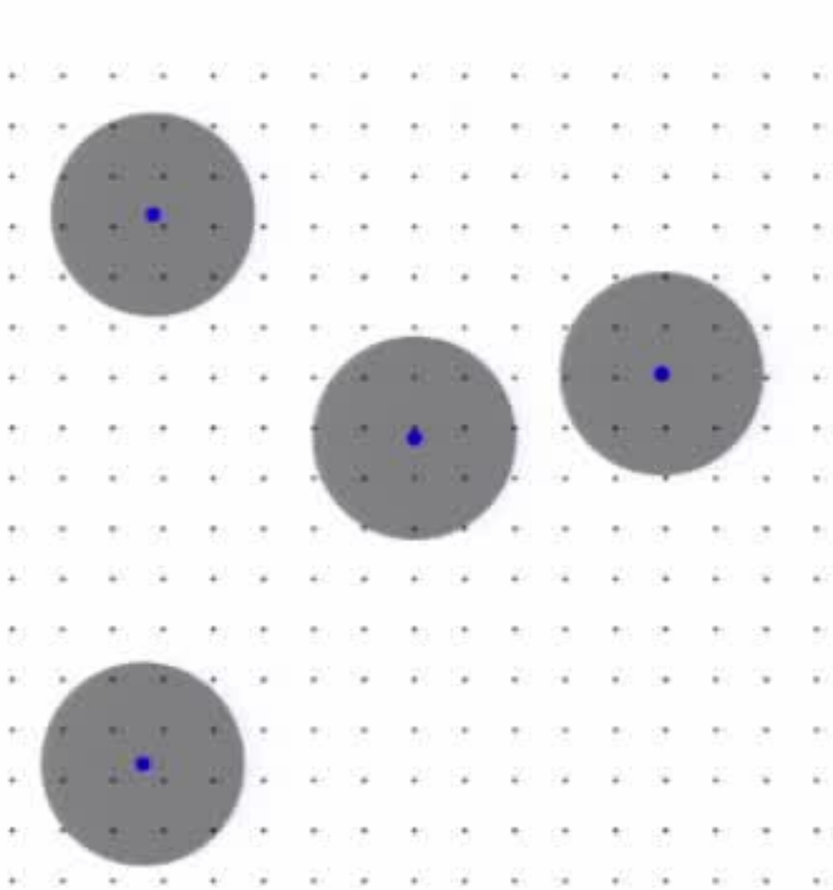
2D multiscale hybrid cellular automata model combining:

Discrete components

- Off-grid
- Chondrocyte cells
- Rule based
- Cell center and radius

Continuous components

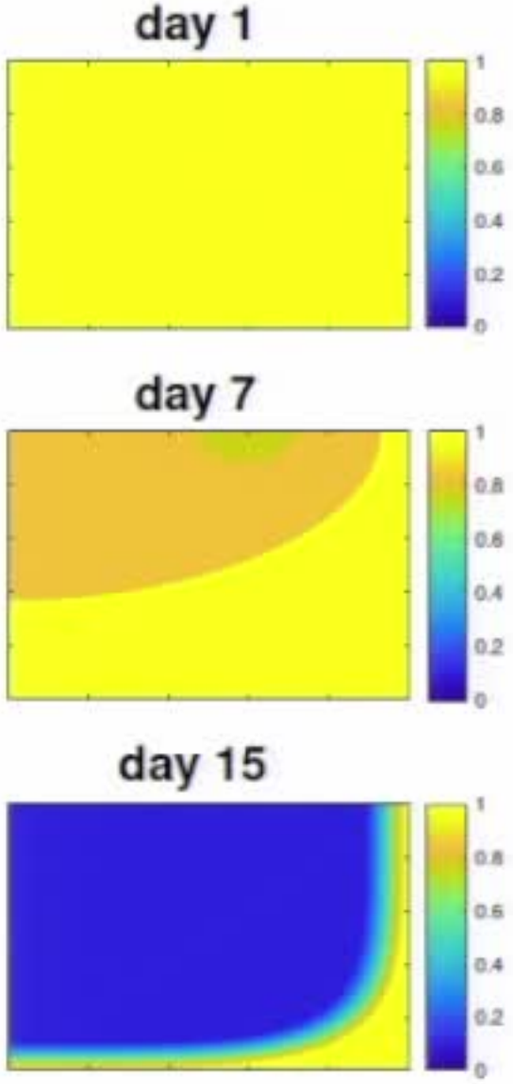
- On-grid
- Nutrient concentration, c
- Porosity, p



Continuous components - nutrient concentration

Nutrient concentration, c

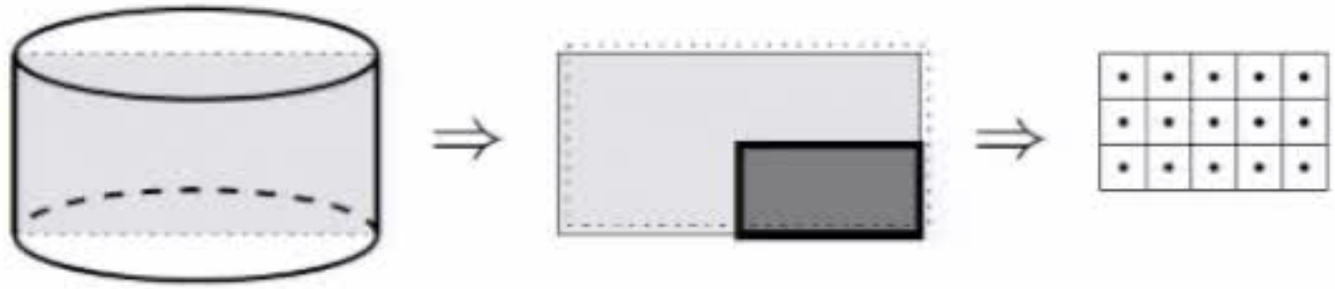
- Based on experiments
- Qualitative approach
- Non dimensional, on [0,1] range
- Slow timescale



Chung et al J Theor Biol Vol 262, (2010)

Bandeiras et al Biomech Model Mechanobiol Vol 14, (2015)

Model features



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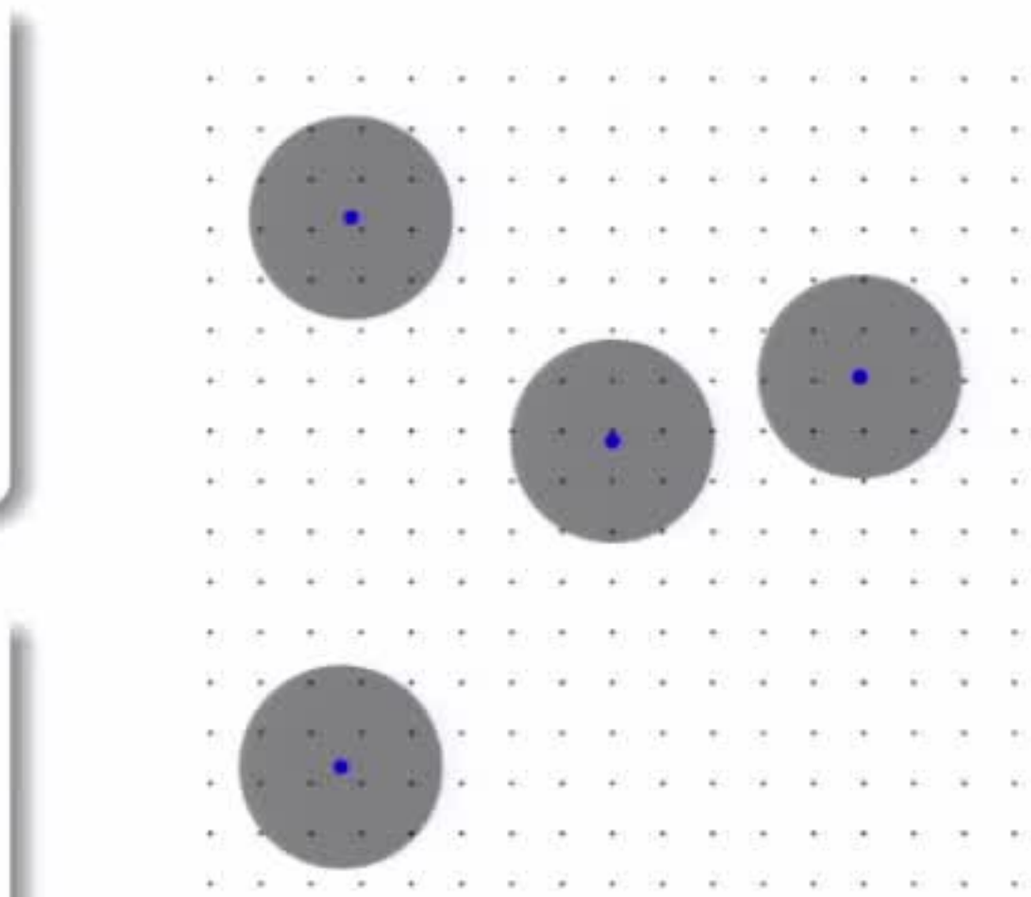

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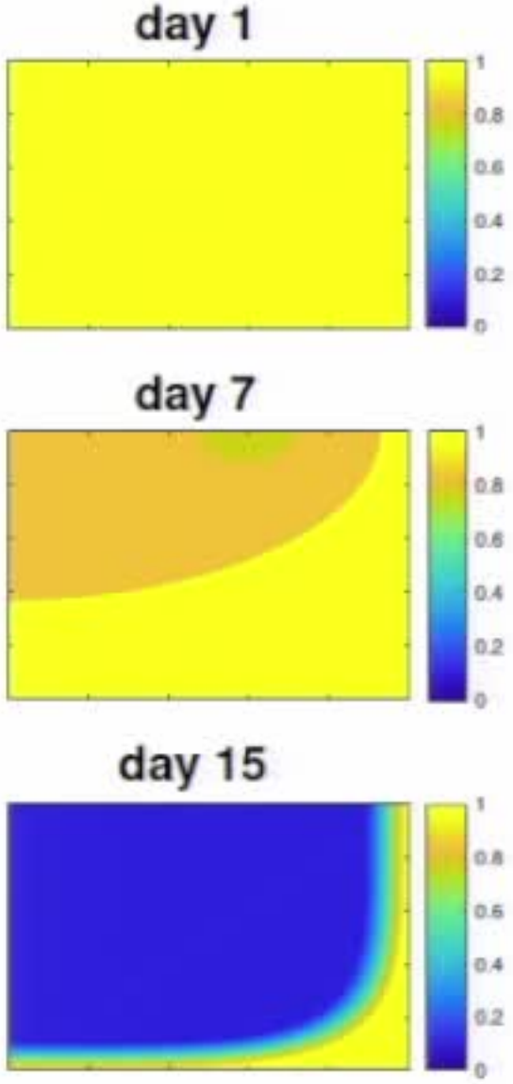

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Continuous components - porosity

Scaffold volume fraction, Φ_{SC} $^{(*)}$

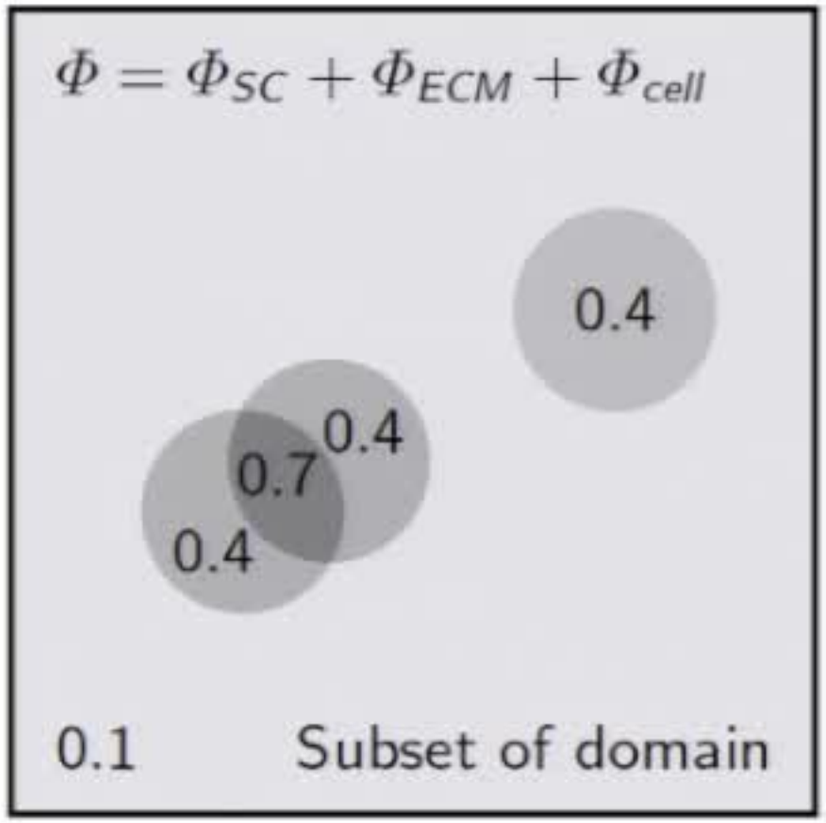
$$\Phi_{SC}(t) = \begin{cases} \Phi_{SC}^0, & t < \tau \\ \Phi_{SC}^0 e^{-k_{SC}(t-\tau)}, & t \geq \tau \end{cases}$$

ECM volume fraction, Φ_{ECM} $^{(*)}$

$$\Phi_{ECM}(t) = \Phi_{ECM}^{SS} \left(1 - e^{-k_{ECM} \cdot t}\right)$$

Cellular volume fraction, Φ_{cell}

- Depends on cell positions on grid
- Single cell contribution, $\widehat{\Phi}$



(*) Wilson C.G. et al Arch Biochem Biophys Vol 408, (2002)

- Solid Volume fraction $\Phi = \Phi_{SC} + \Phi_{ECM} + \Phi_{cell}$
- $p = 1 - \Phi$
- Fast timescale

Discrete components

Chondrocytes (cells)

- Cellular division
- Cell death
- Biased random movement
  - Chemotaxis
  - Porosoty
- Cell-to-cell contact inhibition

Numerical value	Cell status
0	moving
1	dividing
2	quiescent
3	dying

The variable `cell_status` monitor the current status of each cell.

Discrete components

Cell division: to perform cellular division a cell must

1. Not be in quiescent state
2. Have reached cellular maturity
3. Be in a region with enough nutrient
4. Be near to a region with high enough porosity to host a new cell

Cell death

- Determined by a random rule
- Removed from computational domain

Discrete components

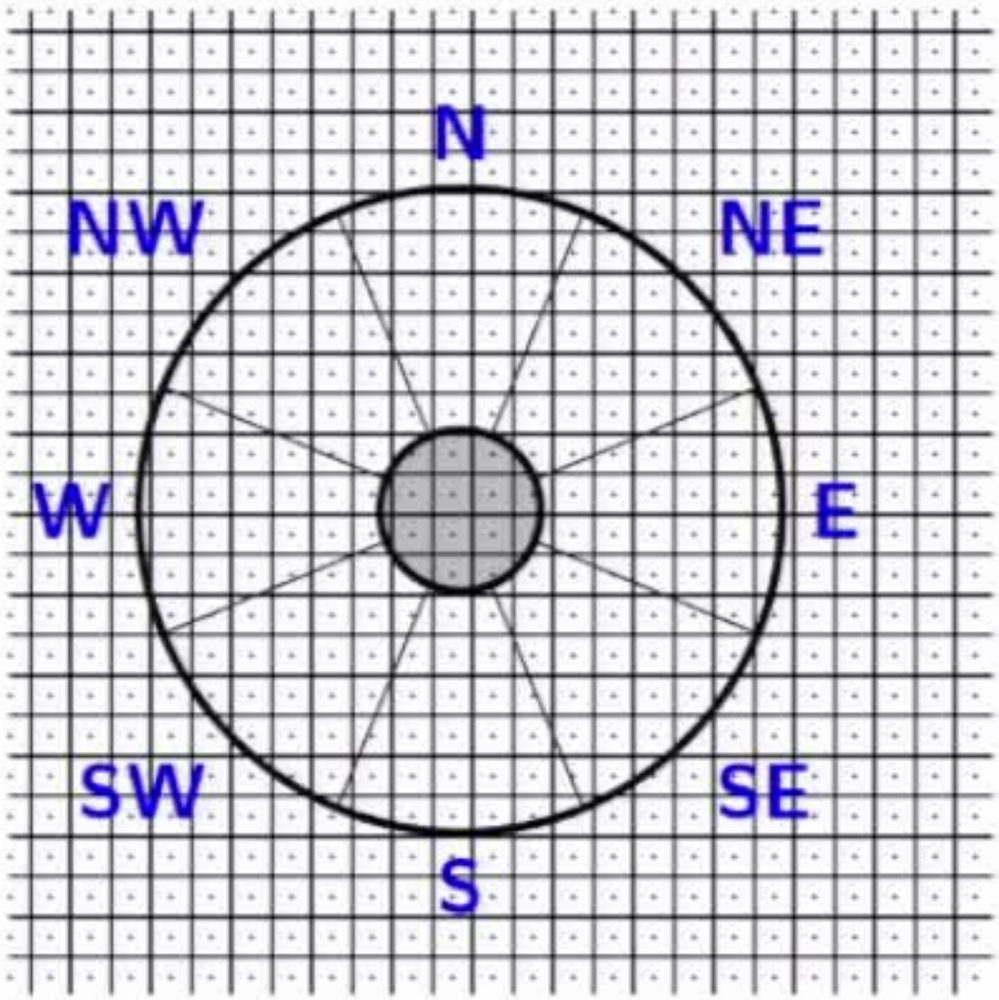
Cell movement

- Off-grid
- 8 possible directions
- Random, biased
  - towards higher c

$$\omega_{n,j} = \frac{c_{avg,j}}{\sum_{i=\varnothing}^{SE} c_{avg,i}}$$

  - towards higher p

$$\omega_{p,j} = \frac{p_{avg,j}}{\sum_{i=\varnothing}^{SE} p_{avg,i}}$$



k direction probability vectors (k cells)

$$\omega_j = \widehat{\omega}_{n,j} \cdot \widehat{\omega}_{p,j}, \quad j = \varnothing, \ldots, SE$$

∅	E	NE	N	NW	W	SW	S	SE

0 1

Discrete components

Cell-to-cell contact inhibition

- Collisions among cells
- Collided cells will enter the quiescent state
- Cells in quiescent state stay idle for a time t_{idle}
- No movement nor cell division

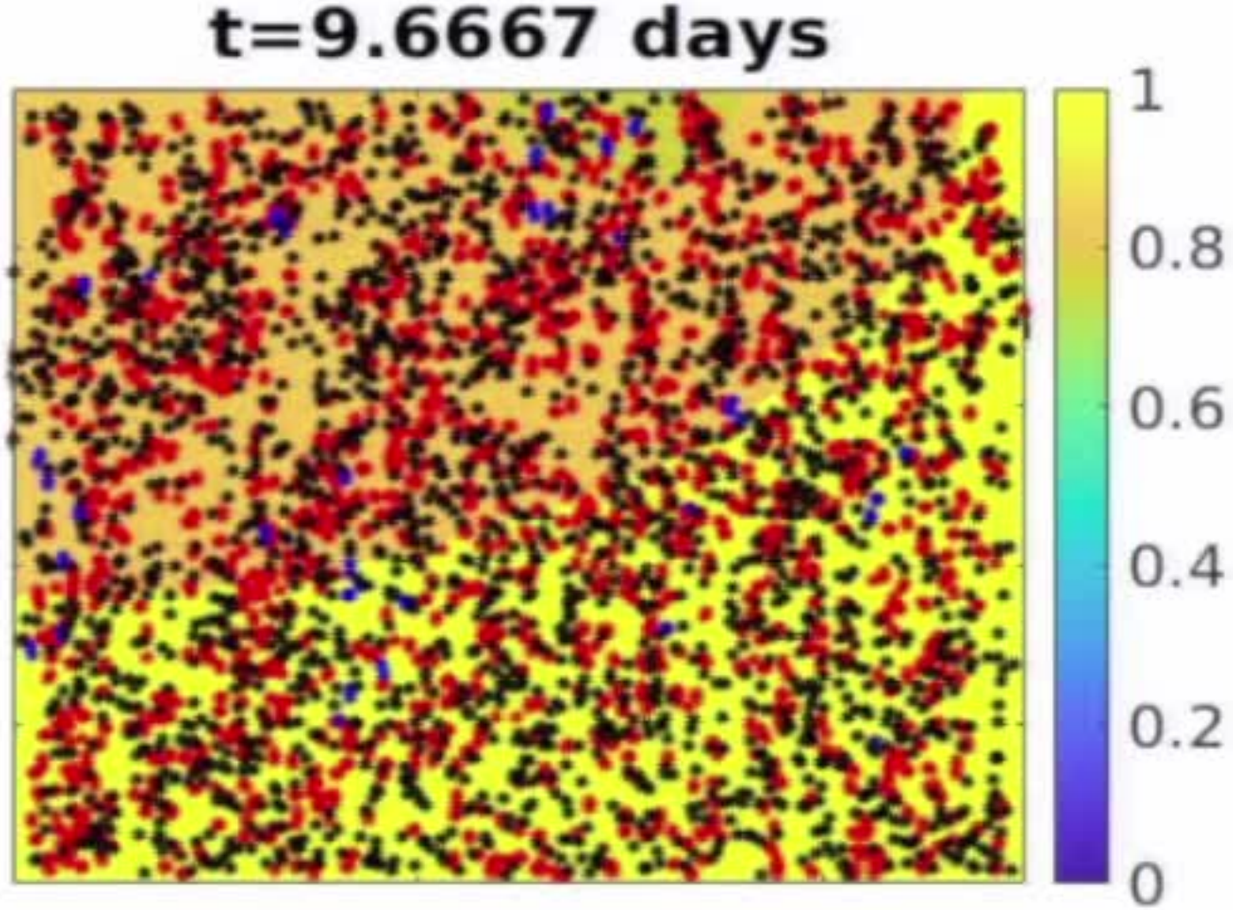
Boundary conditions

- No-flux bc
- Ghost nodes
- Trajectory corrections

Results

color nutrient concentration

* moving state
* dividing state
* quiescent state



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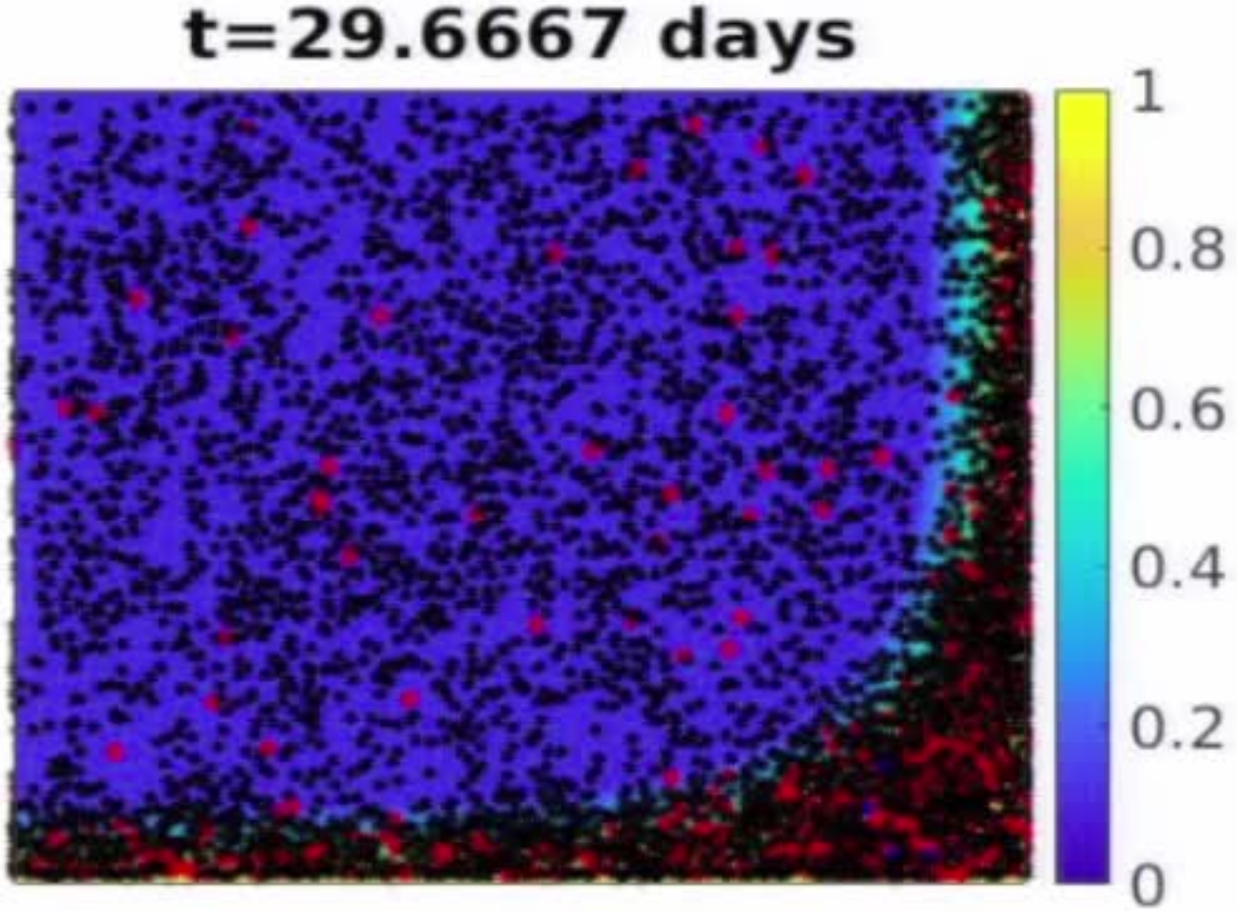

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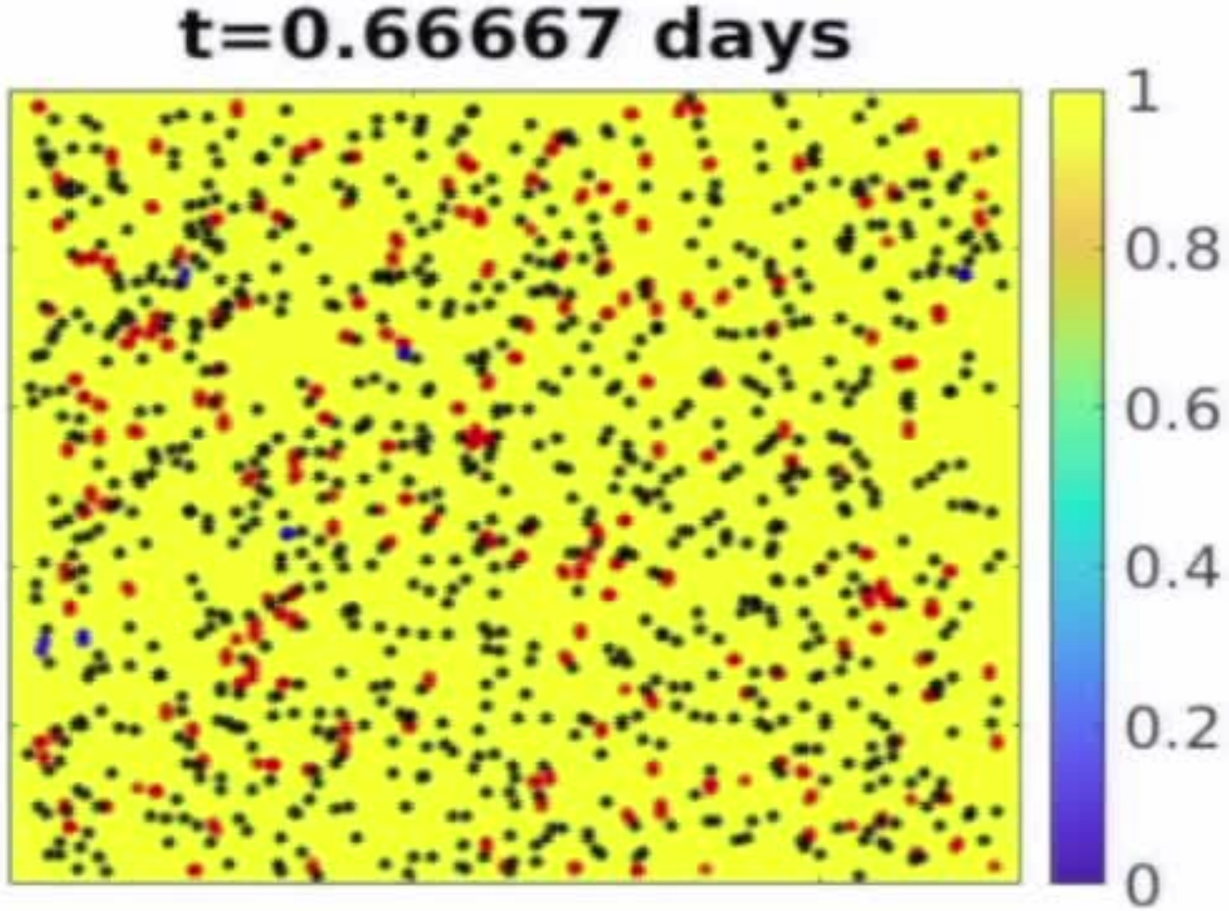
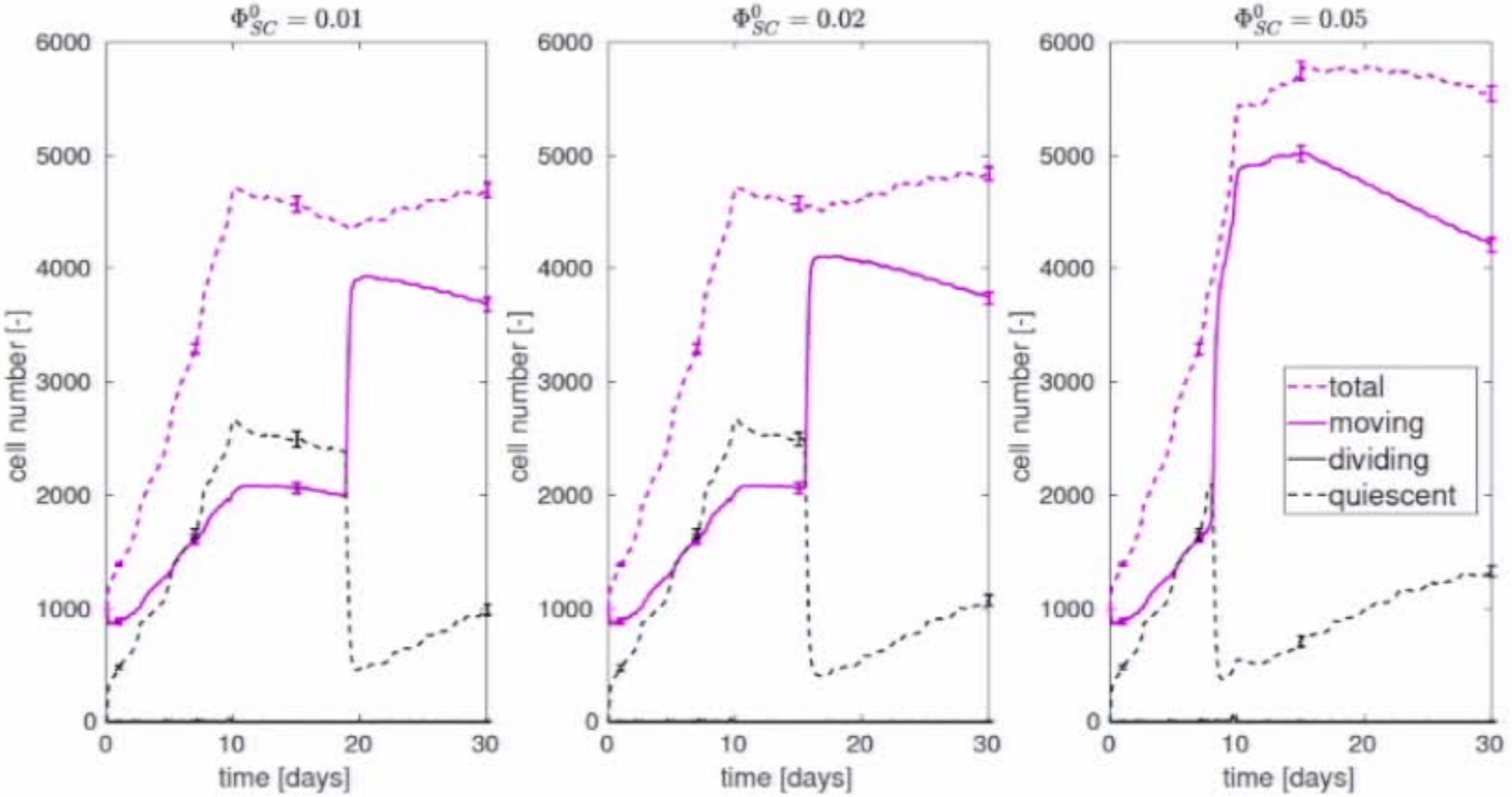
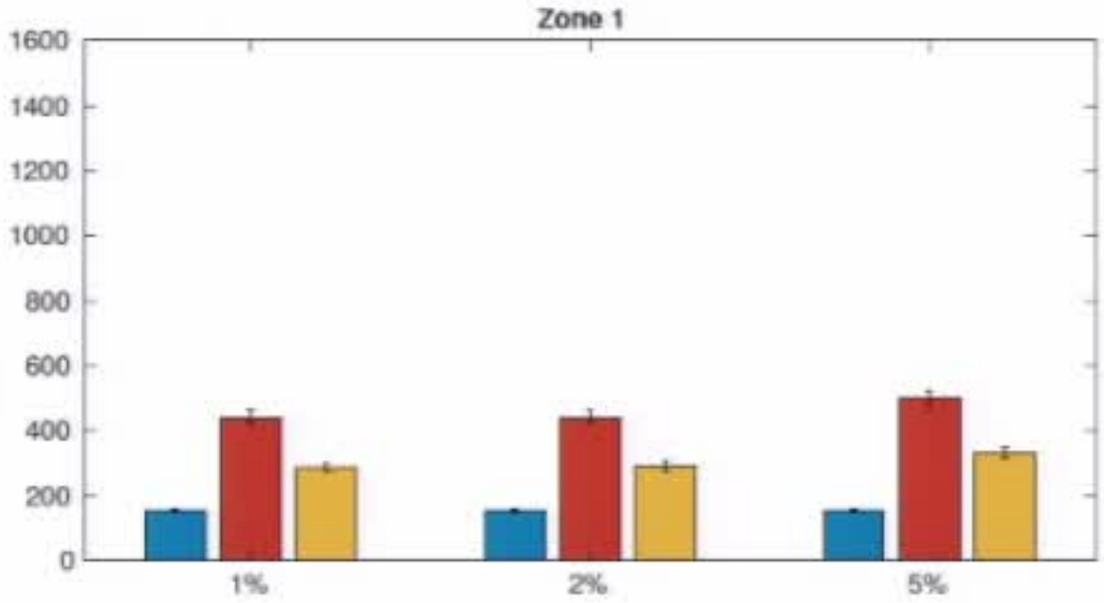


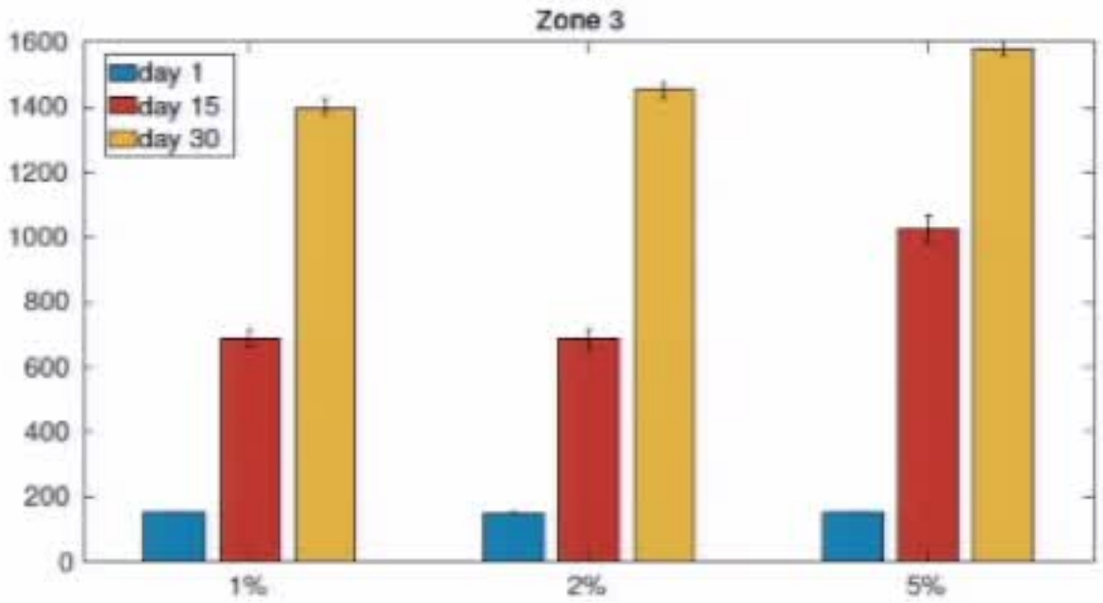
Results - cell status and porosity

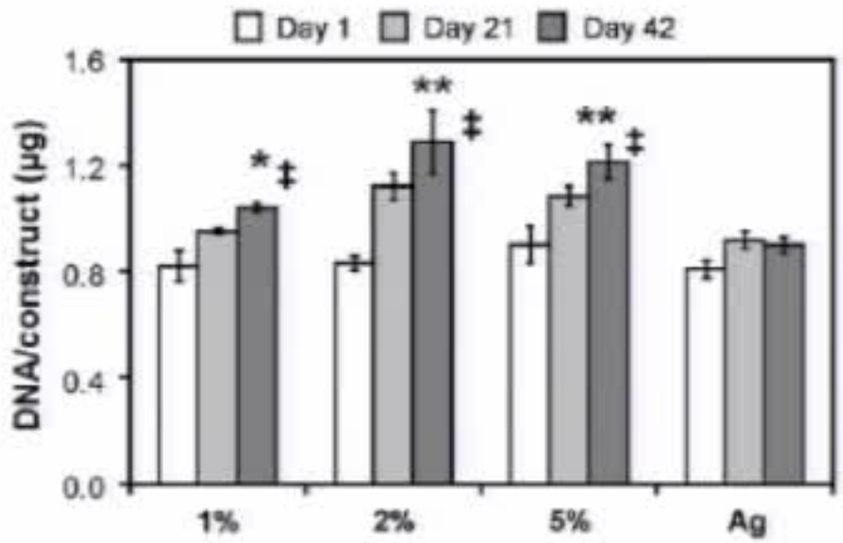


Results - spatial variability



Zone 1		
		Zone 3





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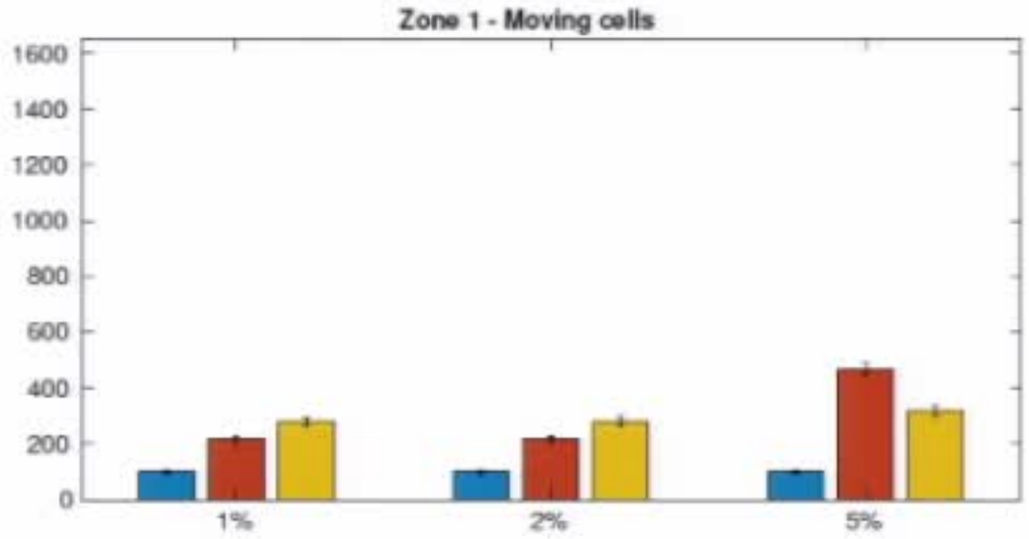
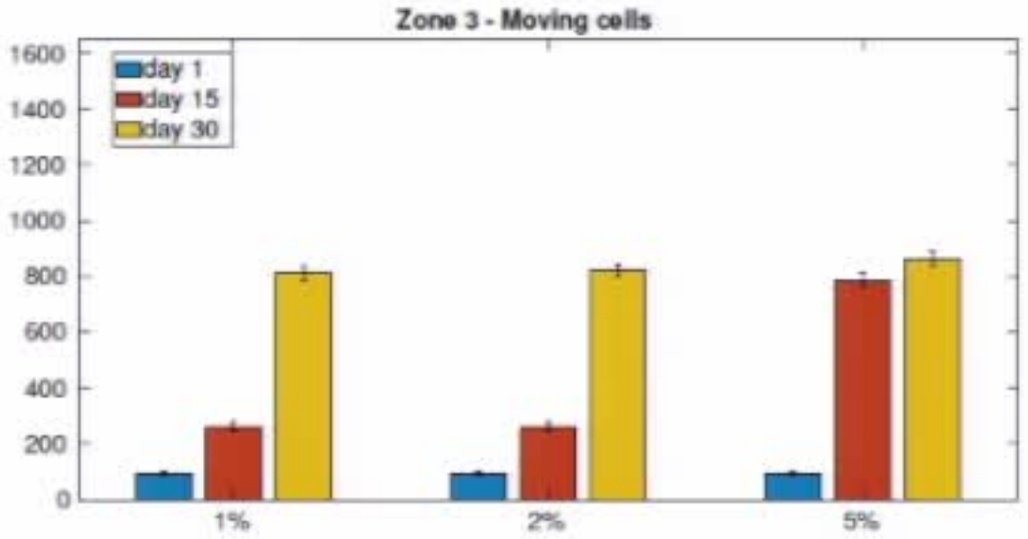
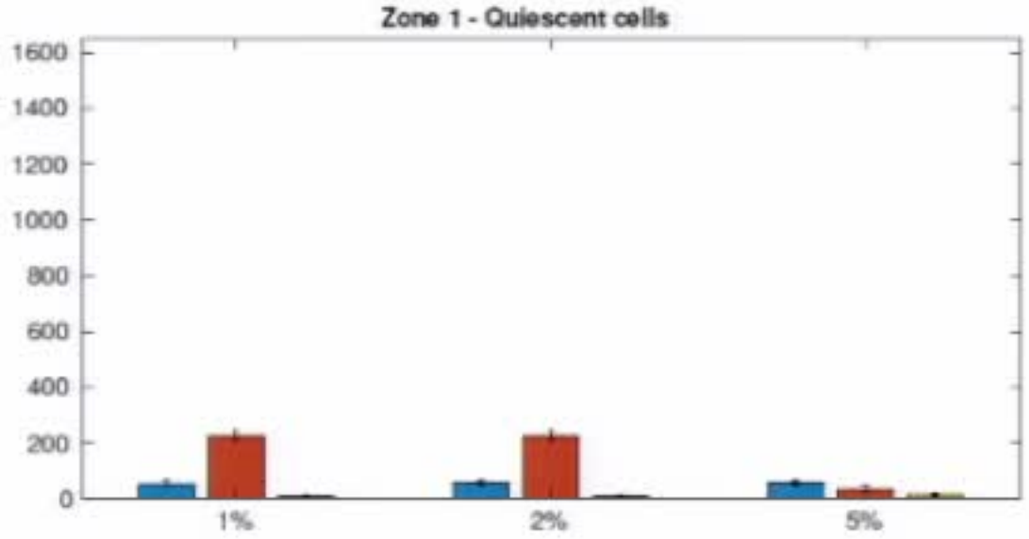
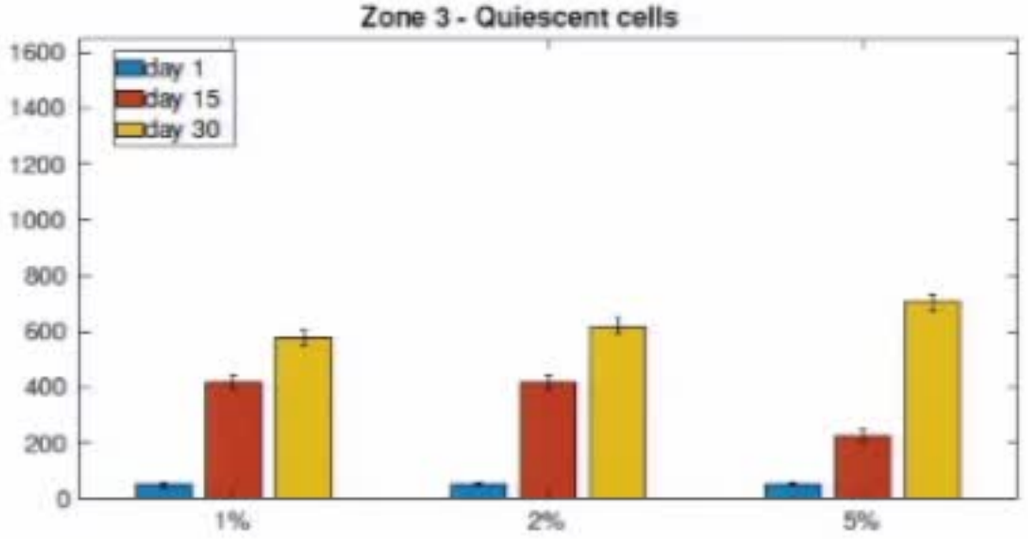
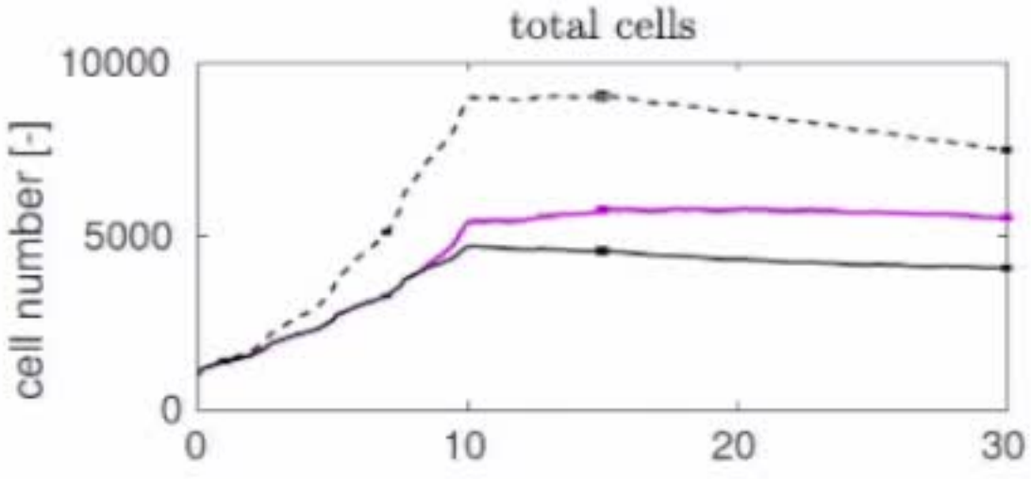


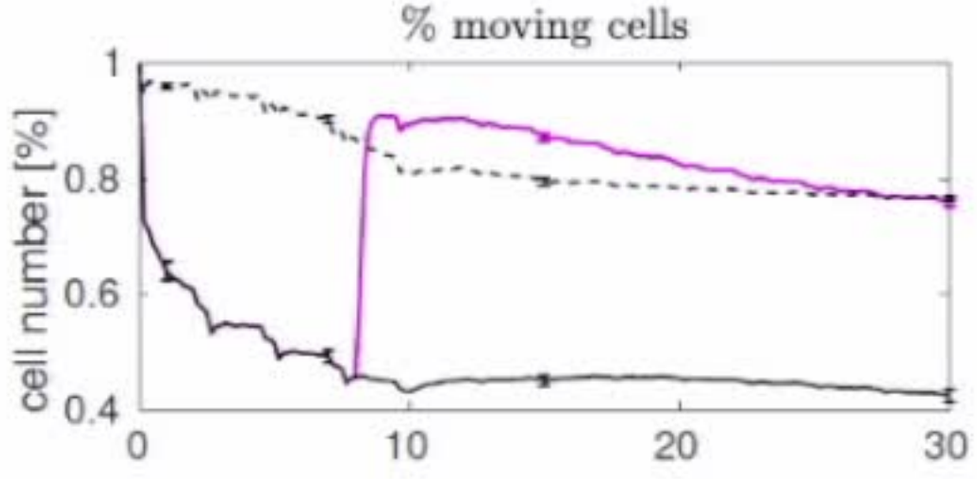


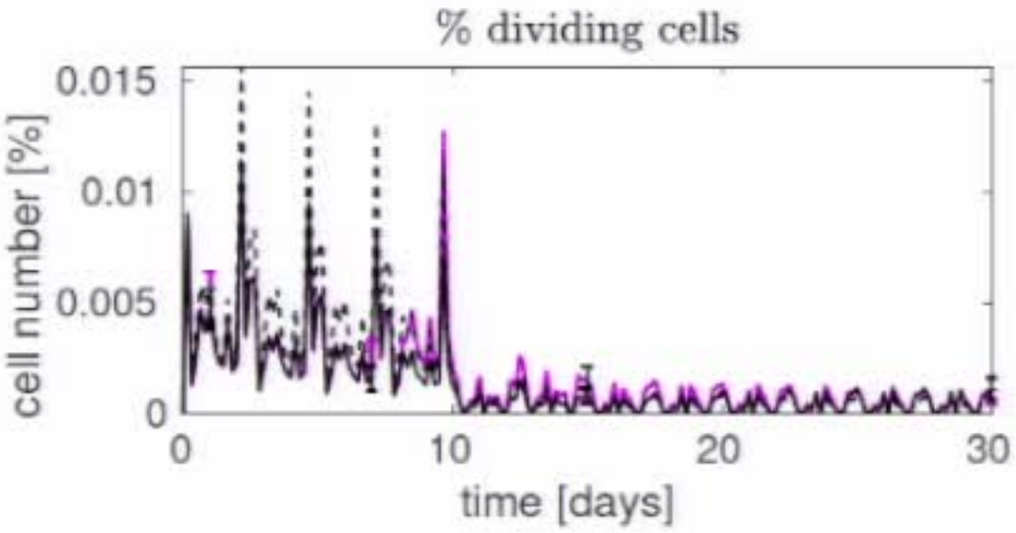


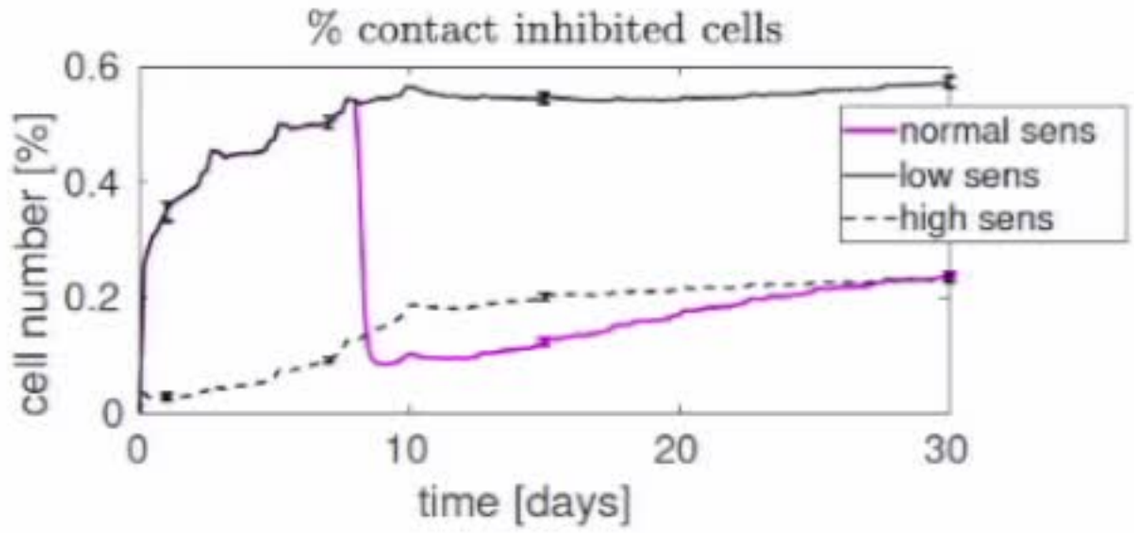


Results - sensitivity to porosity









Conclusions and future works

- Developed a hybrid model that describes the process of tissue growth of engineered cartilage accounting for porosity.
- Captures different behavior for low (0.95) and high (0.99,0.98) initial value of porosity.
- Spatial heterogeneity.
- Non trivial dynamics due to different sensitivity to porosity.

- Refine rules to capture differences between 1% and 2% cases.
- Develop cell dependent nutrient and ECM production.
- Expand the model to include a mixture theory formulation.

Results - sensitivity to porosity