13rd January 2025, Retreat for Women in Applied Mathematics

Oxford Mathematics
UNIVERSITY OF OXFORD
Mathematical Institute

Modelling the dynamic interplay between cells and the ECM

A hybrid approach to contact guidance

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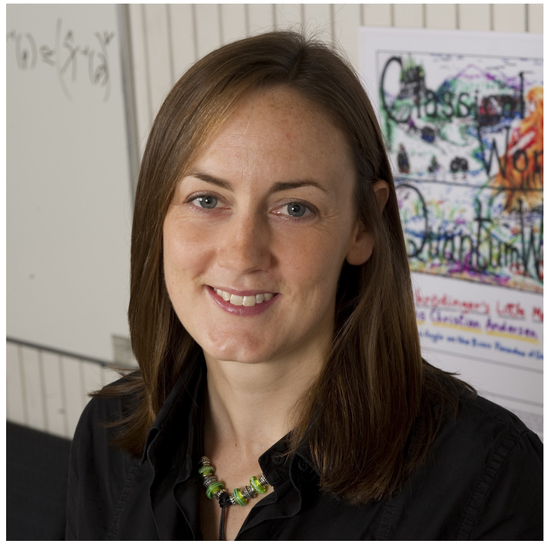

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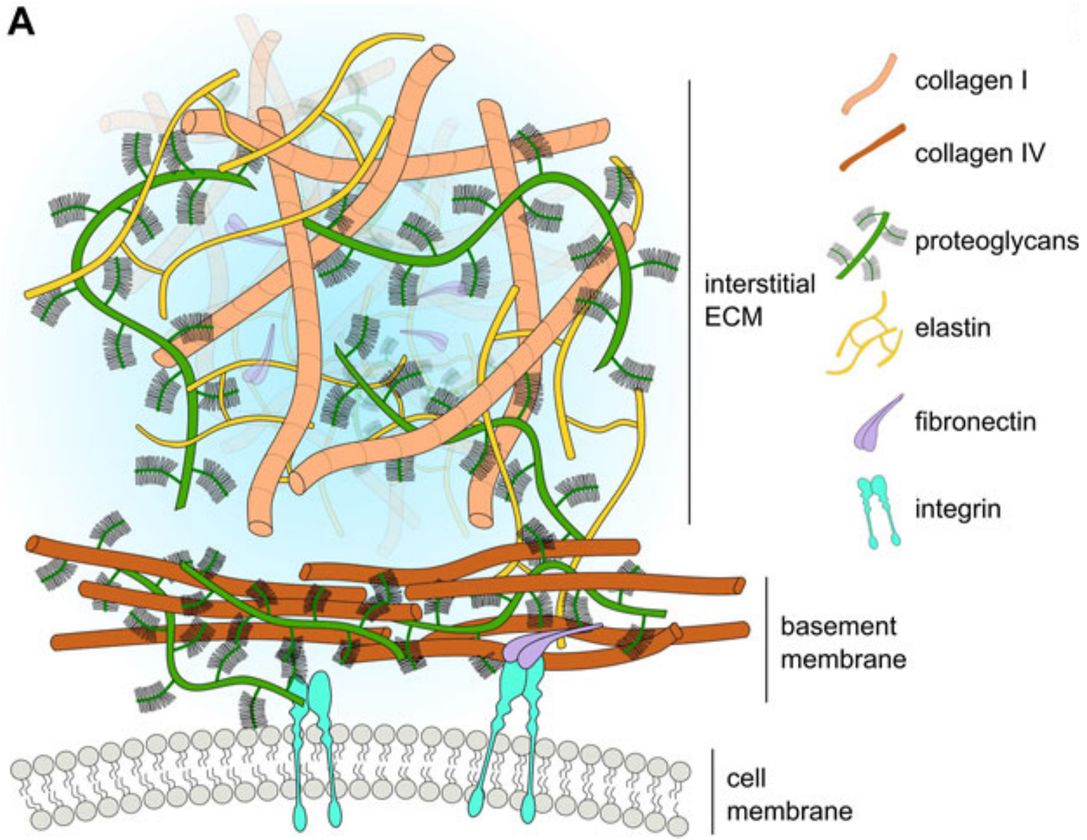
Extracellular Matrix (ECM)

Extracellular matrix (ECM) – A large network of proteins that surround, support, and give structure to cells and tissues in the body.

A real-life problem:
Fibrosis – excessive accumulation of extracellular matrix (ECM) that occurs during a **dysregulated tissue repair** response.

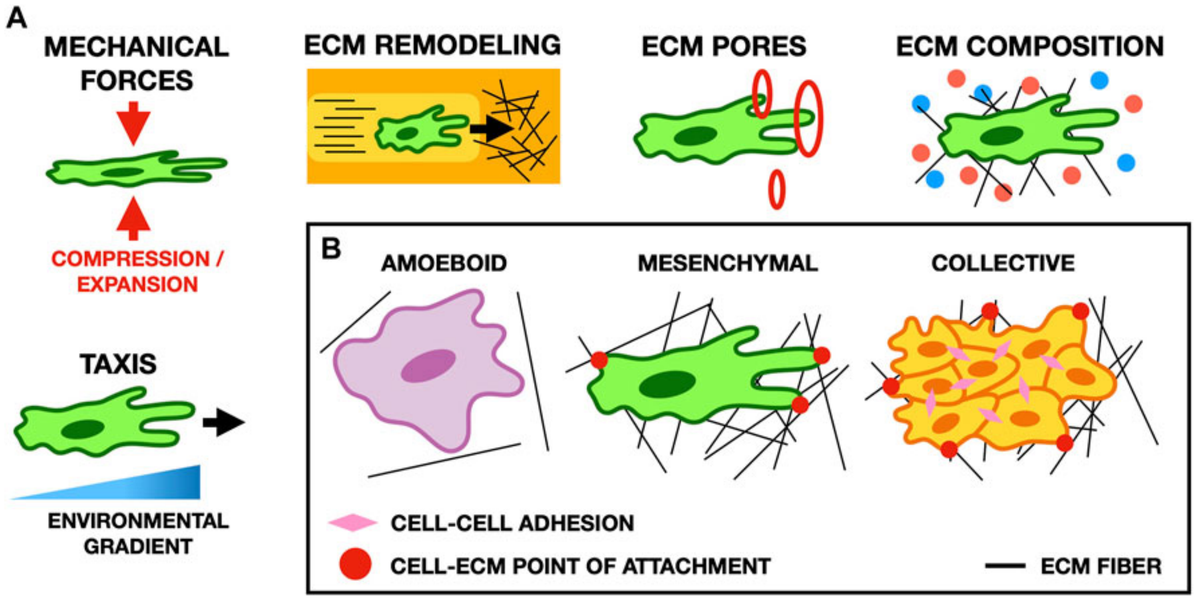
Major ECM compartments and their components



Crossley, Rebecca M., et al. "Modeling the extracellular matrix in cell migration and morphogenesis: a guide for the curious biologist." *Frontiers in cell and developmental biology* 12 (2024): 1354132.

ECM regulates cell activities

A. Cell-ECM interactions in migration;
B. Common migratory cell phenotypes.

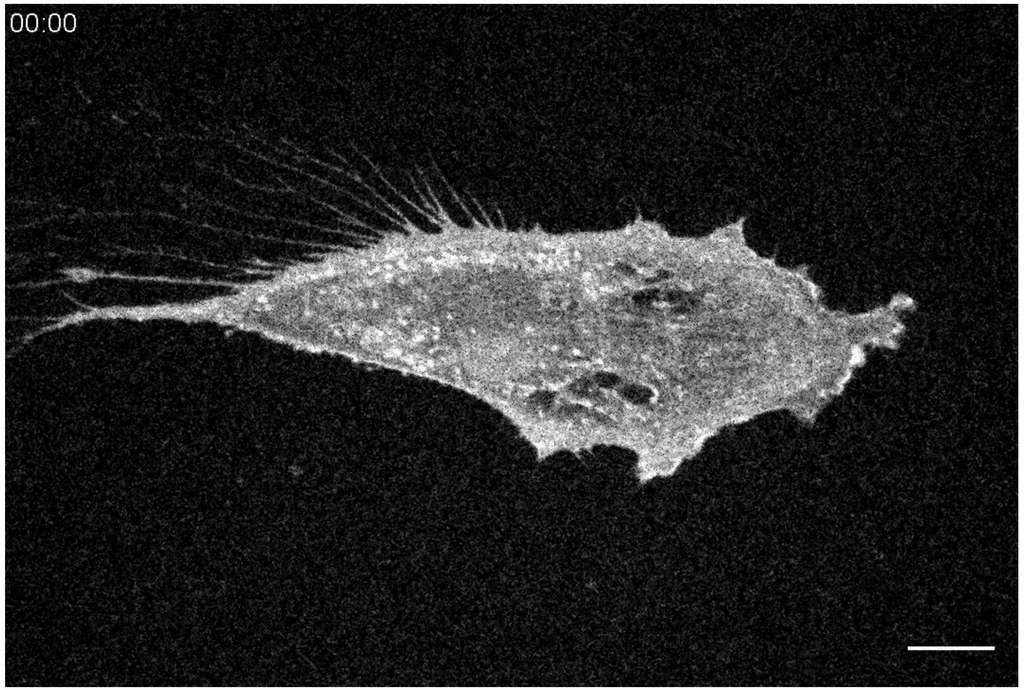


Crossley, Rebecca M., et al. "Modeling the extracellular matrix in cell migration and morphogenesis: a guide for the curious biologist." *Frontiers in cell and developmental biology* 12 (2024): 1354132.

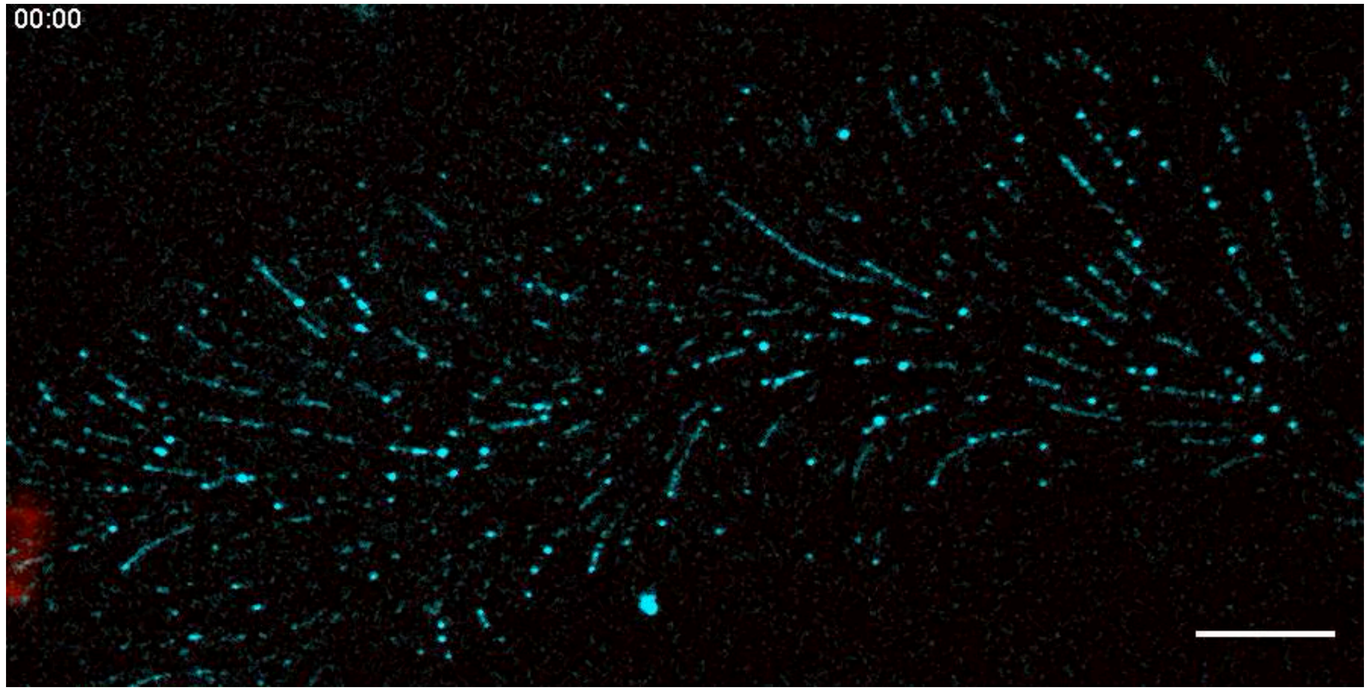
- **Contact guidance (CG):**
  Cells aligning and migrating along collagen fibres within the ECM.
- Haptotaxis
- Durotaxis
- …

Complex interactions bw cells and the ECM

CAF leaves an extended network of membranous material



MDA-MB-231 cells adheres to track regions



Baschieri, Francesco, et al. "Fibroblasts generate topographical cues that steer cancer cell migration." *Science Advances* 9.33 (2023): eade2120.

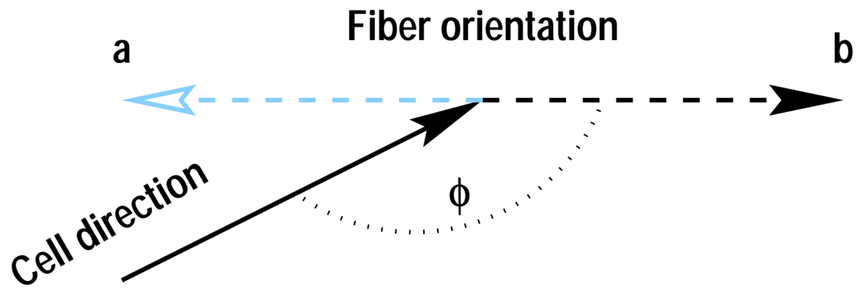
Structure of the talk

1. **General model framework**
   What are the different features that the model can capture?

2. **Application to a scratch assay system**
   What insights emerge from calibrating the model to Chloe's data?

Previous models for collagen fibres in CG

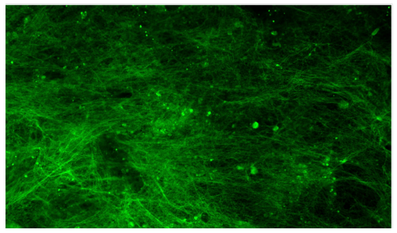
1. Continuous vector field



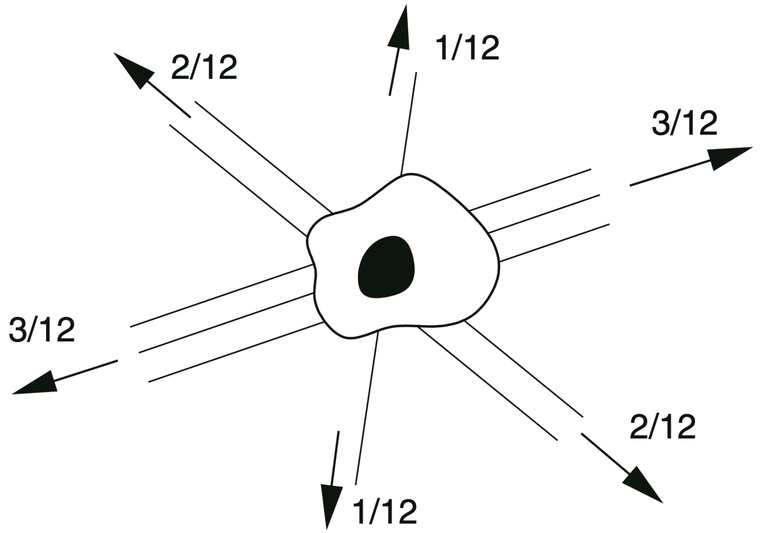
Dallon, John C., Jonathan A. Sherratt, and Philip K. Maini. "Mathematical modelling of extracellular matrix dynamics using discrete cells: fiber orientation and tissue regeneration." *Journal of theoretical biology* 199.4 (1999): 449-471.

Multiple collagen fibres, with distinct orientations

Data from Chloe



2. Probability distribution function

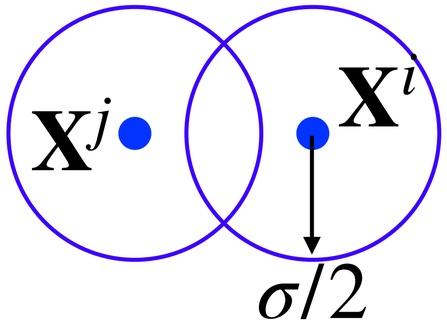


Painter, K. J. "Modelling cell migration strategies in the extracellular matrix." *Journal of mathematical biology* 58 (2009): 511-543.

Computational complexity precludes systematic exploration across parameter space

Cumming *et al.* (2010) hybrid representation

Cells: discrete agents



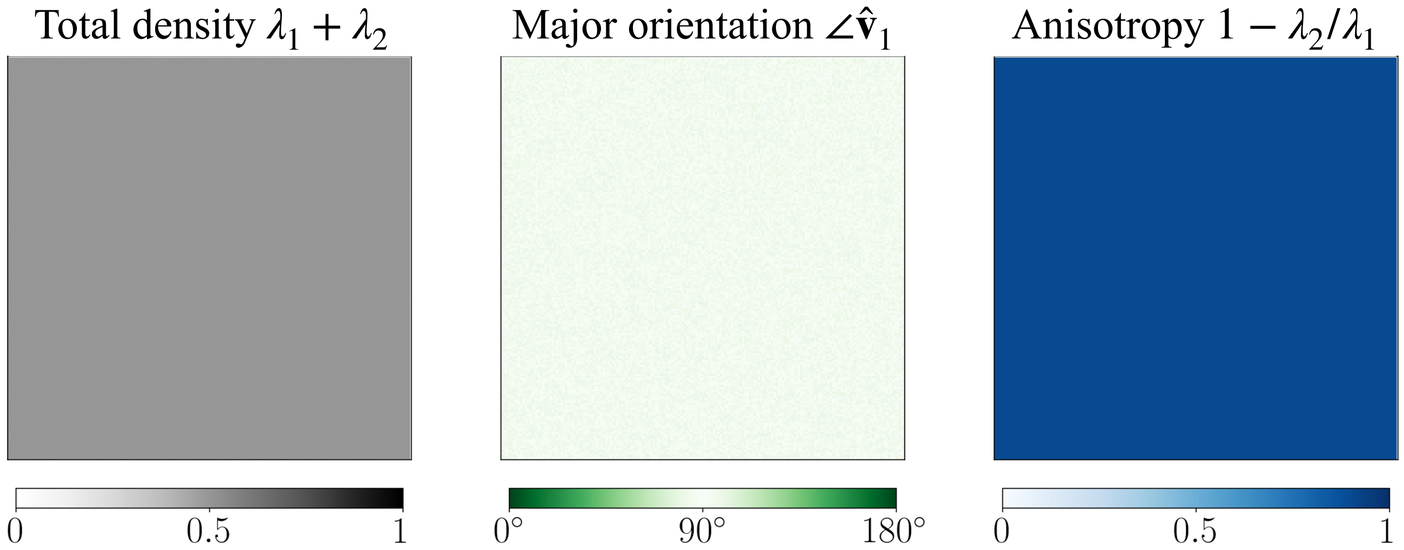
Collagen fibres: continuous tensorial field

$$\mathbf{\Omega}(\mathbf{x},t) = \frac{1}{\pi}\int_0^{\pi} \hat{\mathbf{u}}(\theta)\hat{\mathbf{u}}^T(\theta)\rho(\theta,\mathbf{x},t)\mathrm{d}\theta\,.$$

$$\mathbf{\Omega}(\mathbf{x},t) = \lambda_1\hat{\mathbf{v}}_1\hat{\mathbf{v}}_1^T + \lambda_2\hat{\mathbf{v}}_2\hat{\mathbf{v}}_2^T,\ 1 \geq \lambda_1 \geq \lambda_2 \geq 0$$

Our model's novelty:

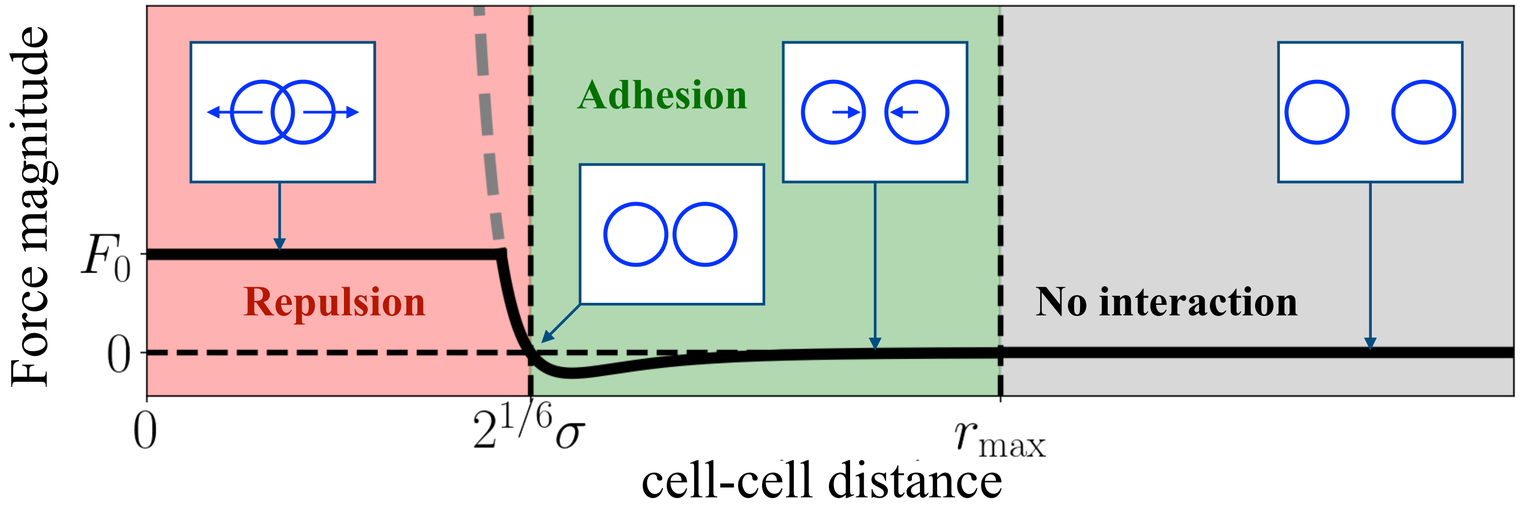
1. Simplest possible model encoding fibre distribution that focuses exclusively on contact guidance;
2. Nonlinear contact guidance on both total fibre density and anisotropy;
3. More realistic cell-cell interactions and cell secretion of collagen fibres.



Cell dynamics (1)

$$\frac{\mathrm{d}\mathbf{X}^i}{\mathrm{d}t} := \hat{\mathbf{M}}\left(\hat{\boldsymbol{\Omega}}\left(\mathbf{X}^i, t\right)\right)\left[\boldsymbol{\xi}^i + \sum_{j=1, j\neq i}^{N(t)} \mathbf{F}\left(\mathbf{X}^i - \mathbf{X}^j\right)\right], \quad i = 1, \ldots, N(t)$$

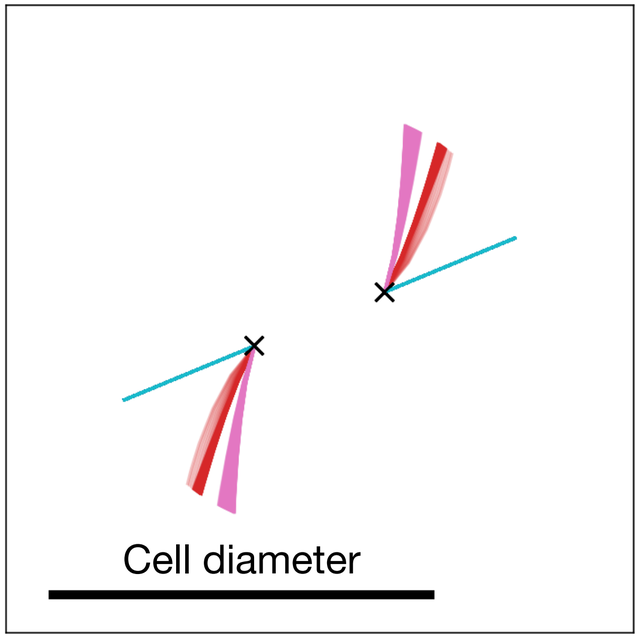
- $\boldsymbol{\xi}^i$: cell i's random motility.
- $\mathbf{F}\left(\mathbf{X}^i, \mathbf{X}^j\right)$: pairwise cell-cell interaction force between cell i and cell j with magnitude F.



Cell dynamics (2)

$$\frac{\mathrm{d}\mathbf{X}^i}{\mathrm{d}t} := \hat{\mathbf{M}}\left(\hat{\boldsymbol{\Omega}}\left(\mathbf{X}^i, t\right)\right)\left[\boldsymbol{\xi}^i + \sum_{j=1, j\neq i}^{N(t)} \mathbf{F}\left(\mathbf{X}^i - \mathbf{X}^j\right)\right], \quad i = 1, \ldots, N(t)$$

$[\hat{\cdot}]$: normalised (length-preserving) matrix.



No collagen fibres present

Vertically aligned collagen fibres

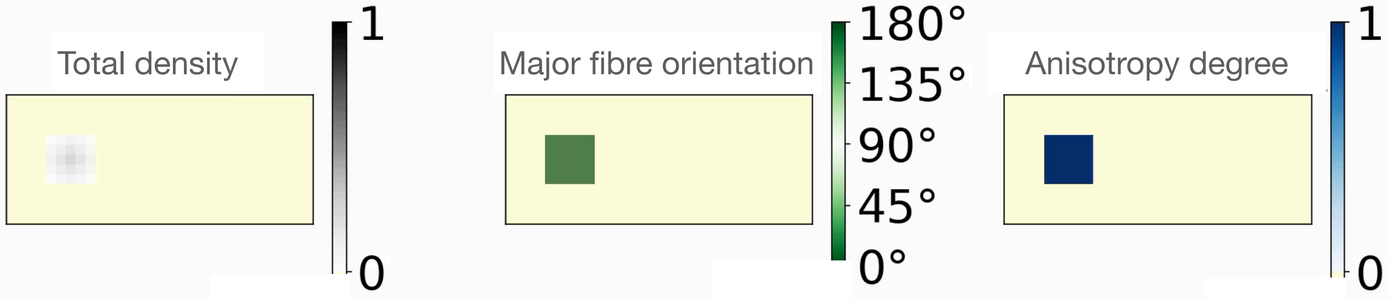
More anisotropic/denser collagen fibres

Hybrid model — fibre dynamics

$$\frac{\partial \boldsymbol{\Omega}(\mathbf{x},t)}{\partial t} = \sum_{i=1}^{N(t)} \omega\left(\mathbf{X}^i, \mathbf{x}; \sigma, \omega_0\right) \left[s\left(1-\lambda_1-\lambda_2\right) \hat{\mathbf{u}}^i_{\text{ave}} \left(\hat{\mathbf{u}}^i_{\text{ave}}\right)^T - d\boldsymbol{\Omega} \right]$$

Weight kernel

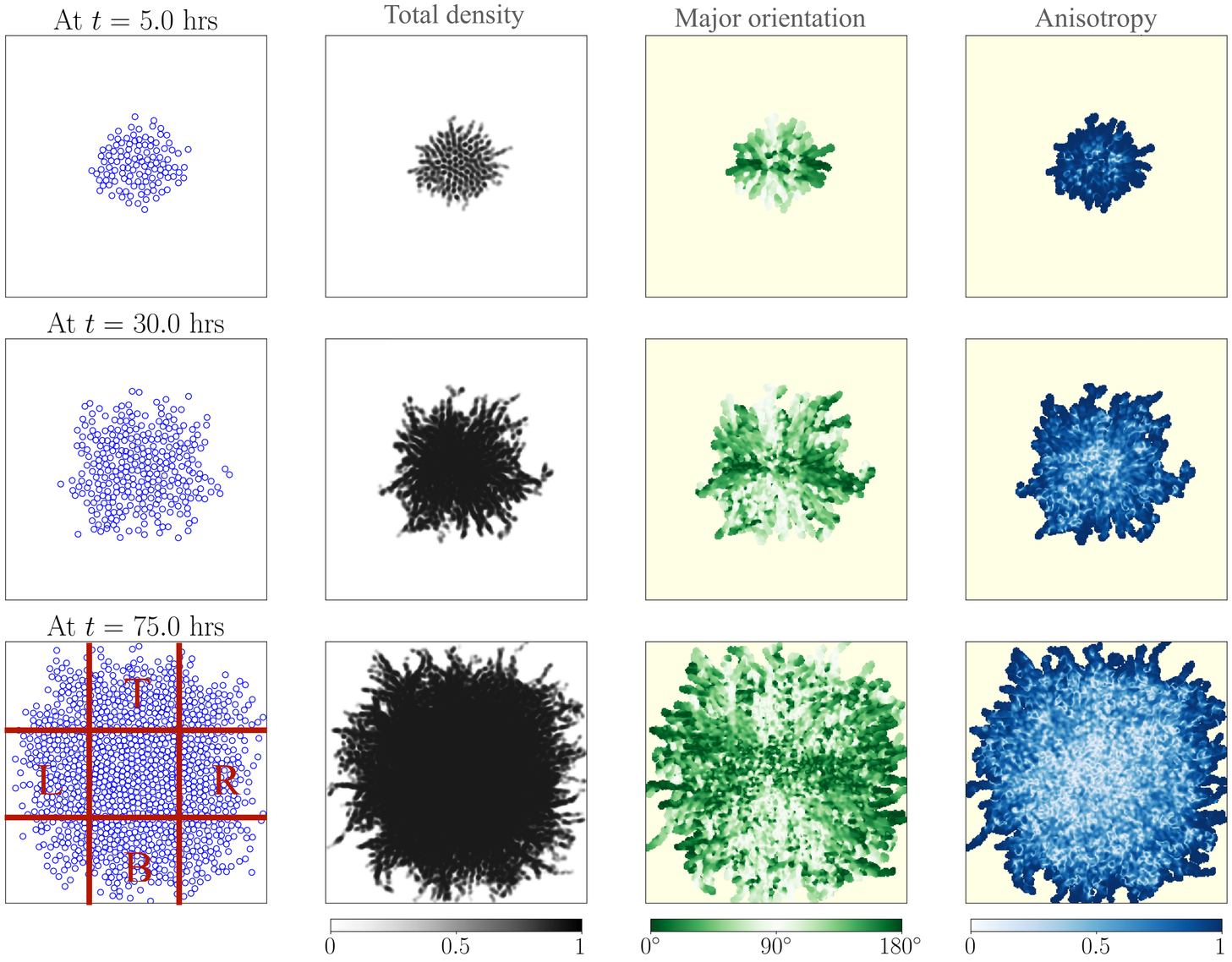
Fibre secretion with rate s in the direction of cell i's average velocity $\mathbf{u}^i_{\text{ave}}$.

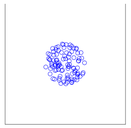


Fibre degradation with rate d without re-orientation.

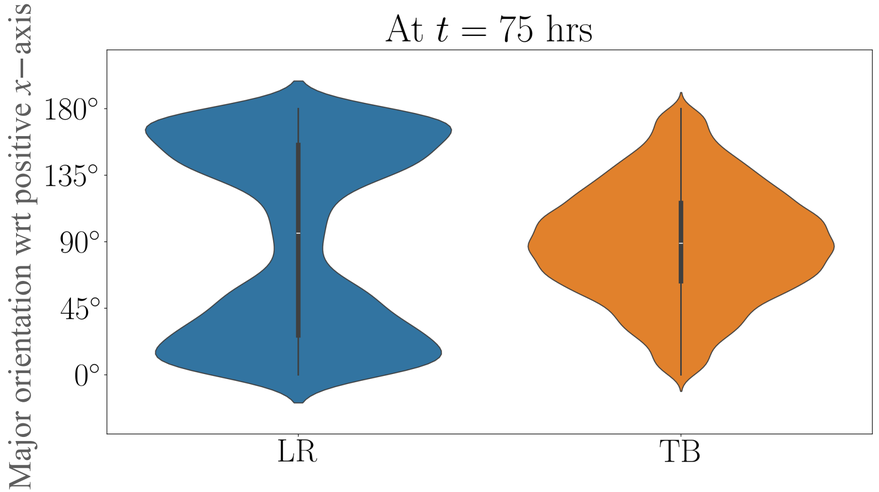
Key features (1)

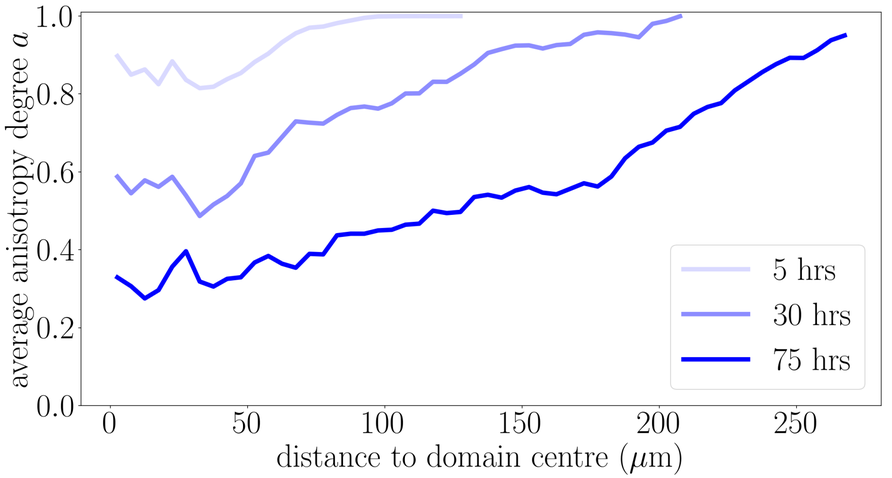
Collagen fibres encode cell migration information





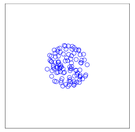
with no fibres as IC



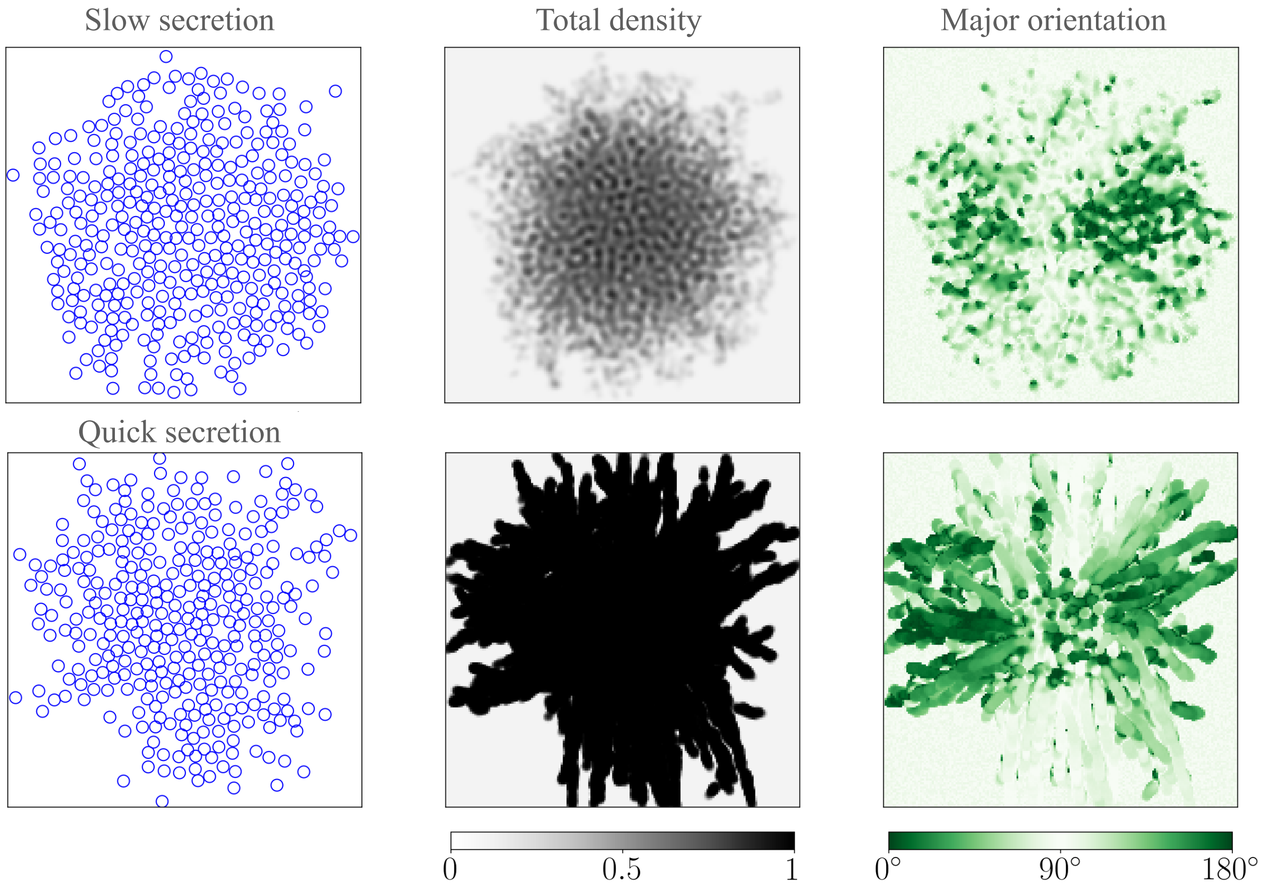


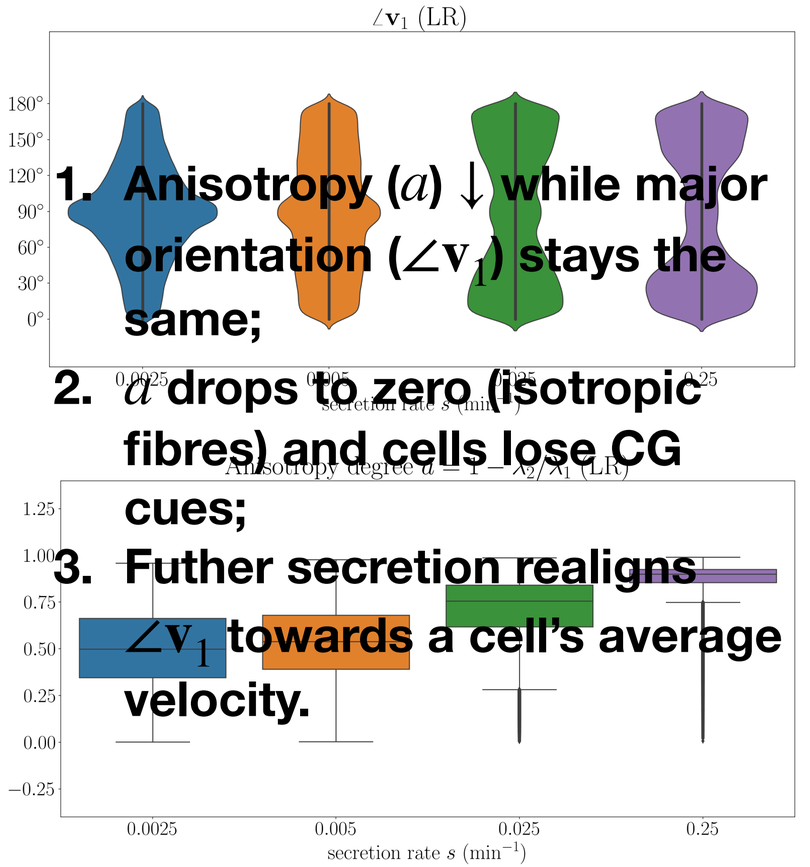
Key features (2)

Cell secretion modulates collagen fibres in three consecutive steps



with anisotropically vertically aligned fibres

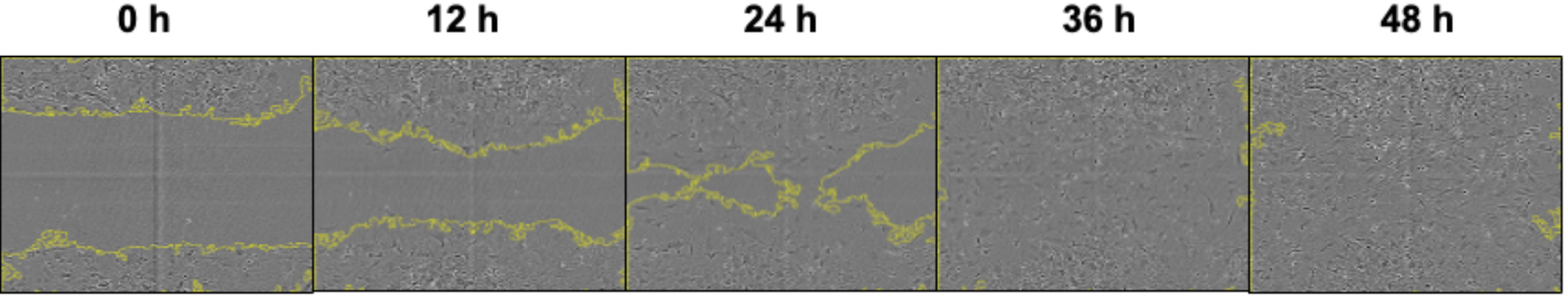


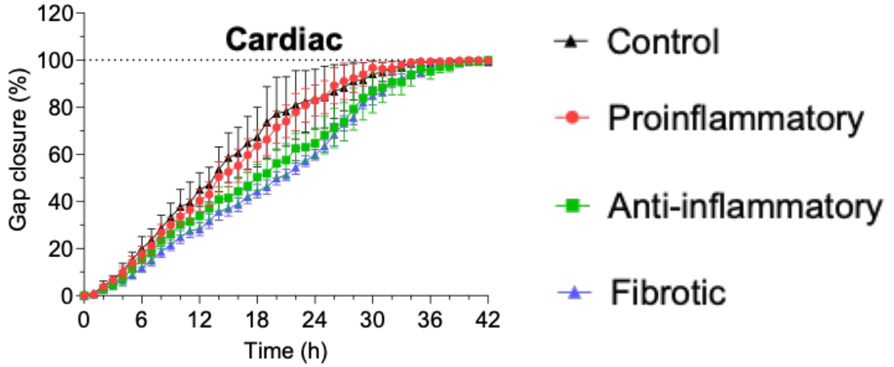


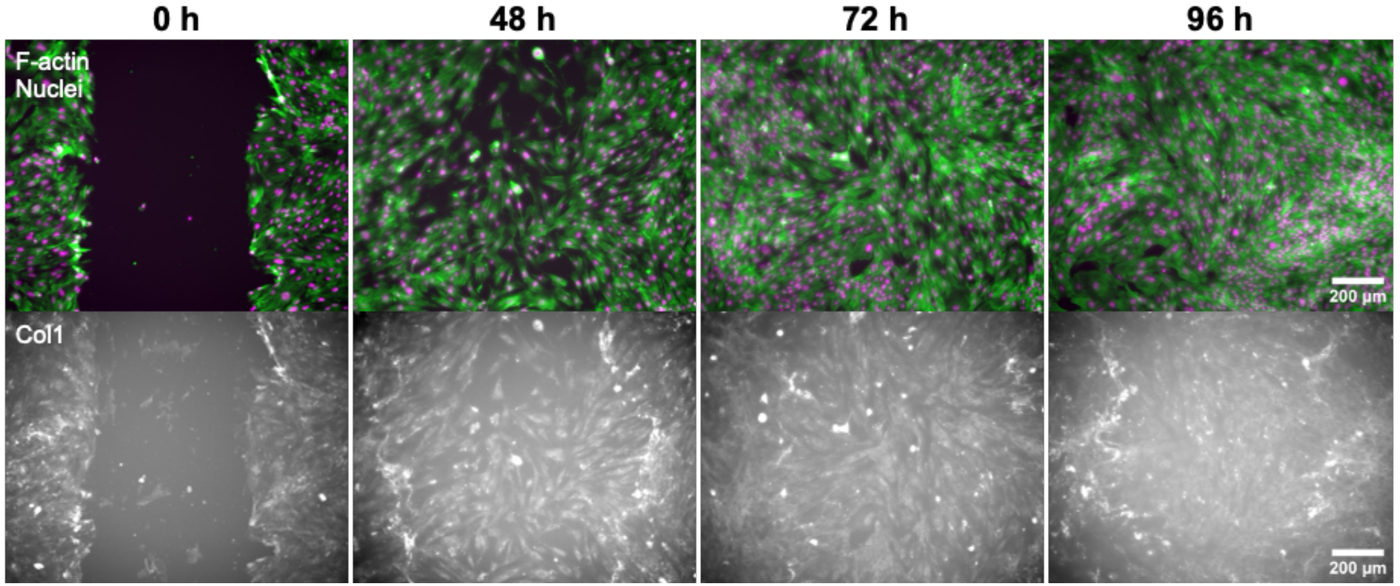
1. Anisotropy (a) ↓ while major orientation ($\angle \mathbf{v}_1$) stays the same;
2. a drops to zero (isotropic fibres) and cells lose CG cues;
3. Futher secretion realigns $\angle \mathbf{v}_1$ towards a cell's average velocity.

Application to a scratch assay system

Scratch assay data show how collective cell migration closes the wound







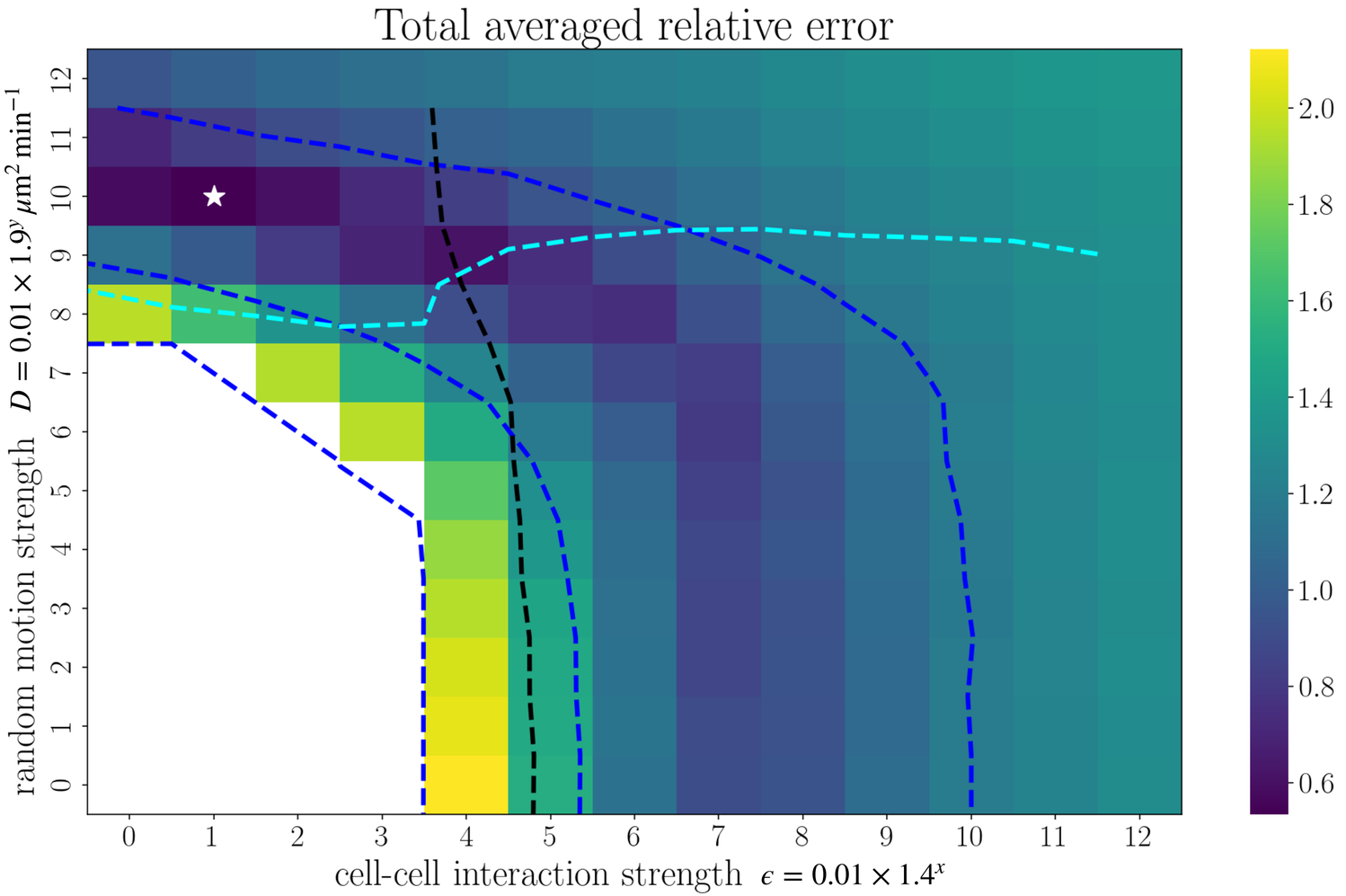
Data from Chloe: Collagen I production post-scratch in pro-inflammatory condition for lung fibroblasts.

Model improvements:

- Cell i's random motion depends on local fibre density.
- Cell i's collagen fibre secretion rate depends on local cell density.

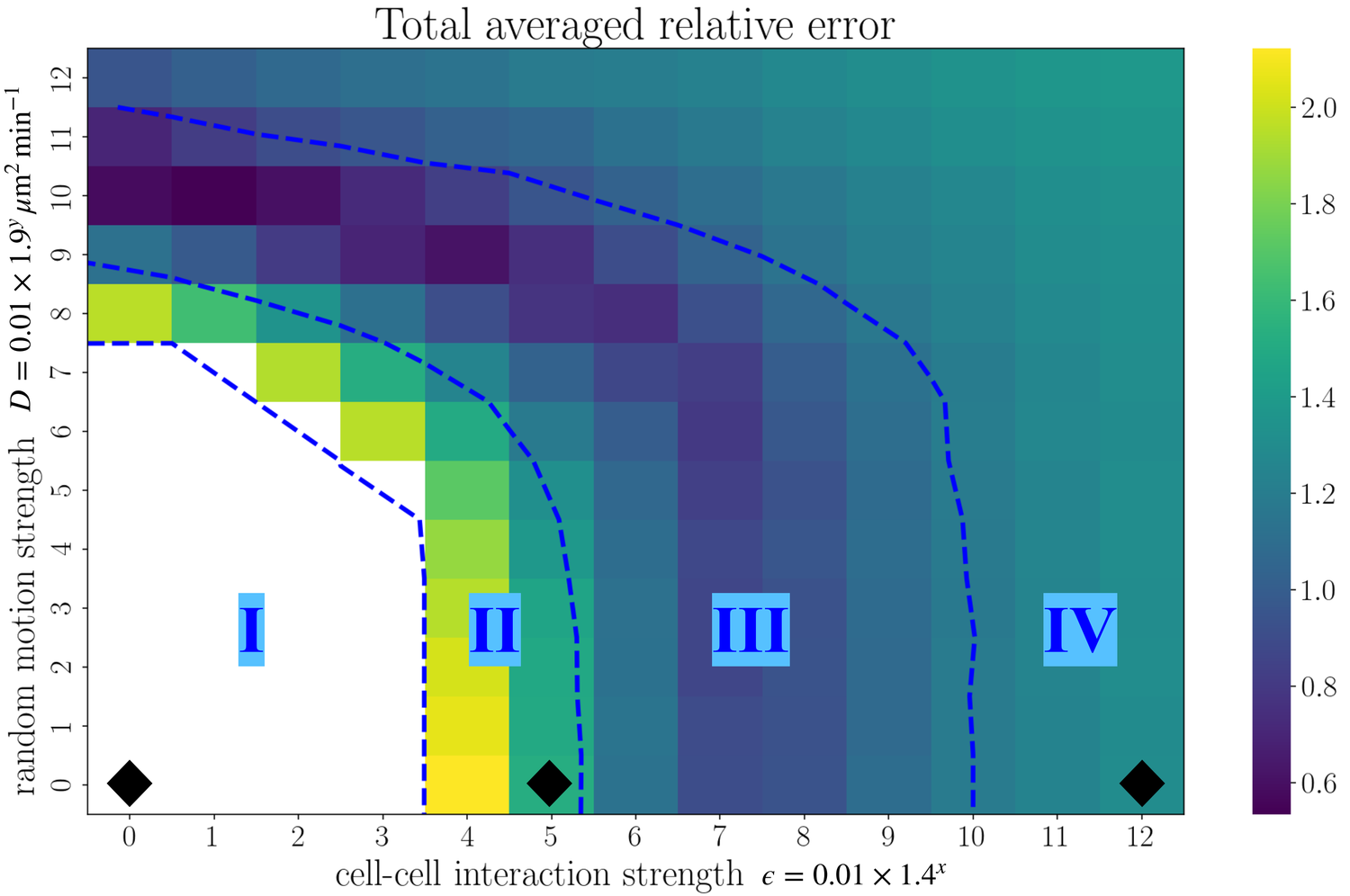
Calibration gives cell motility properties

Calibrate the improved model to data and obtain cell motility properties



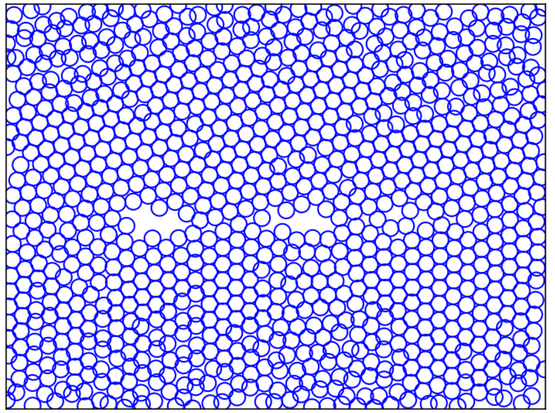
Breakdowns in the next slide

The time point when wound gets closed

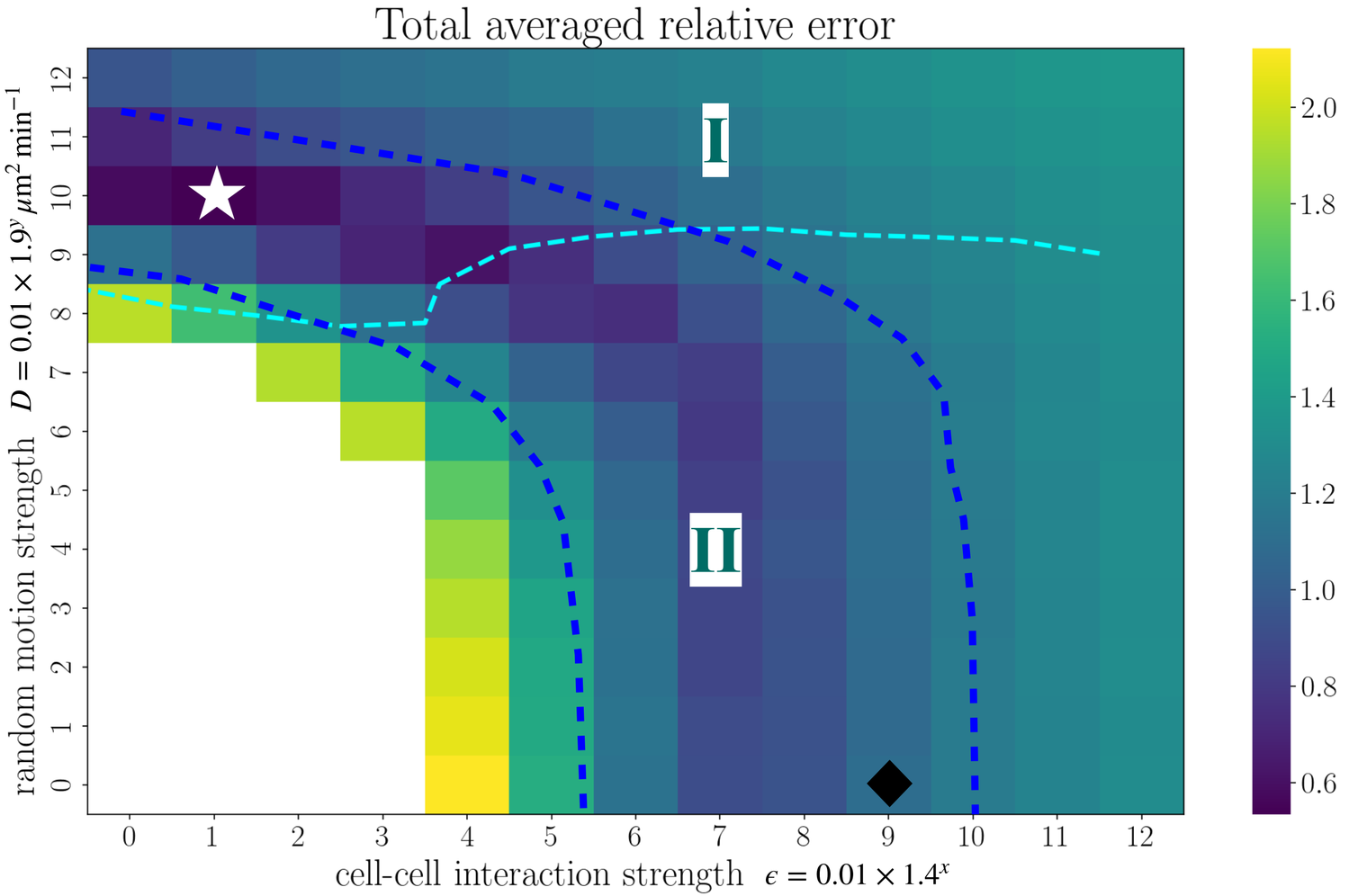


IV: Wound gets closed after 24 hours

$t = 12$ hrs

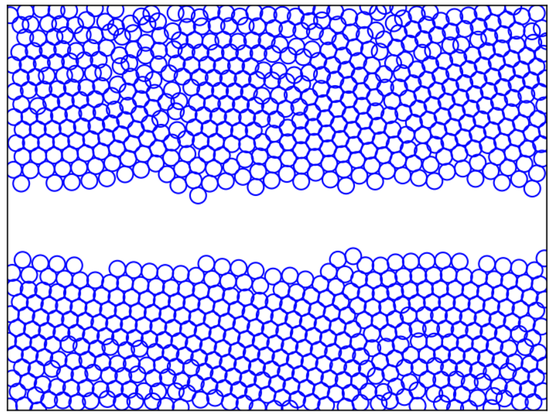


How clustered cells are

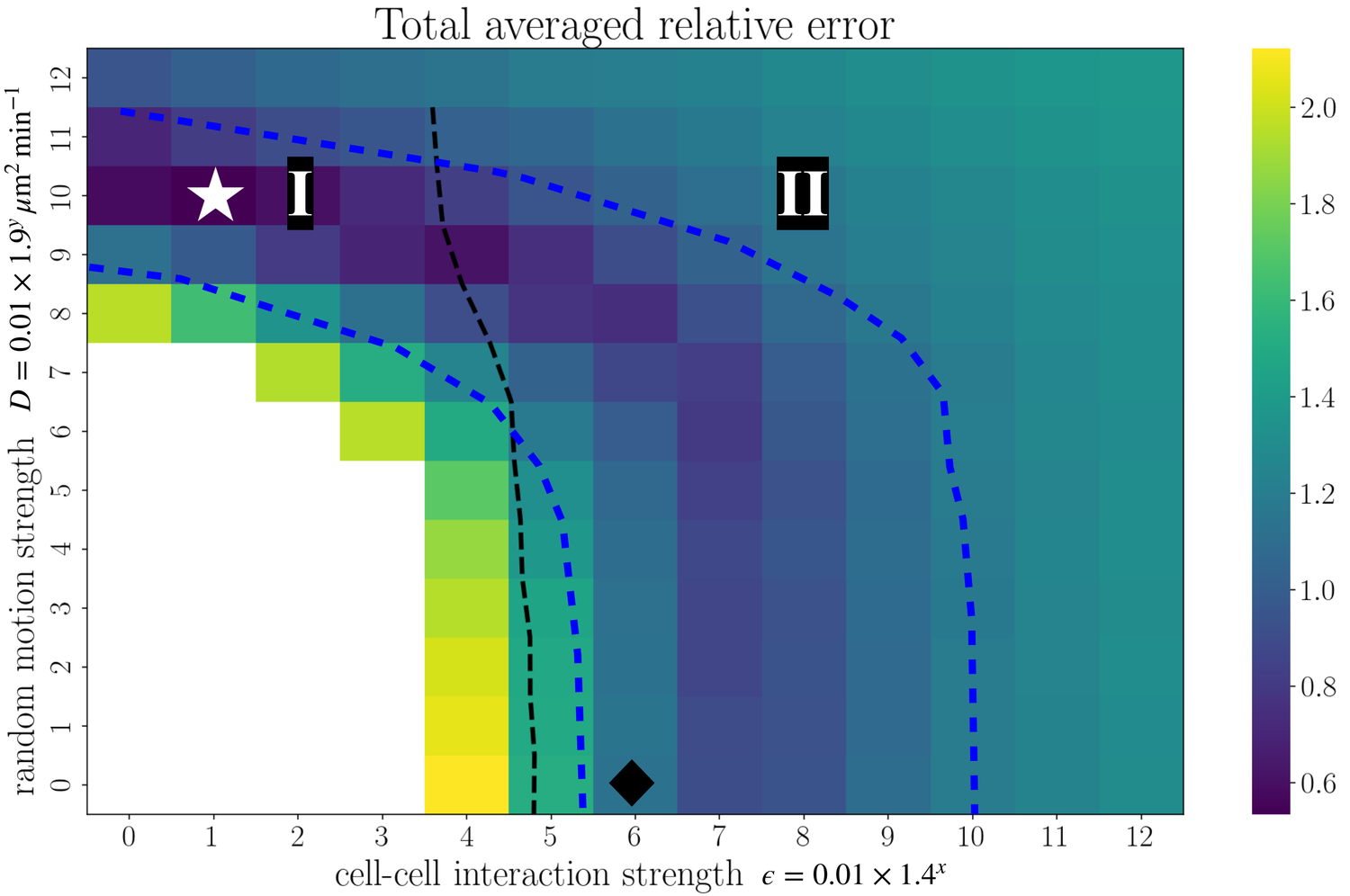


II: More dispersed

$t = 12$ hrs

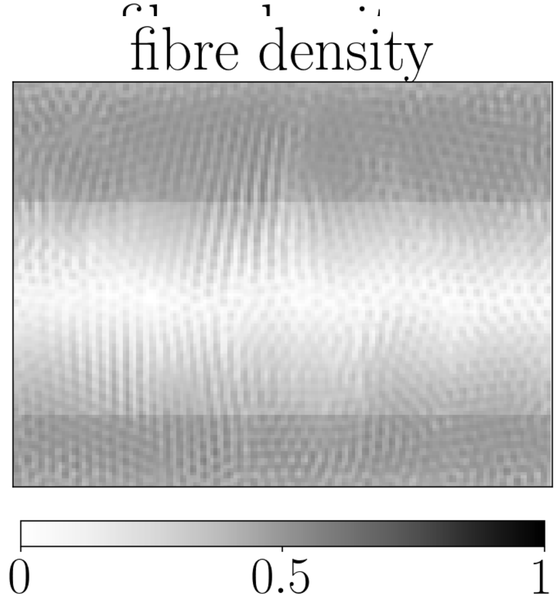


The amount of collagen fibres



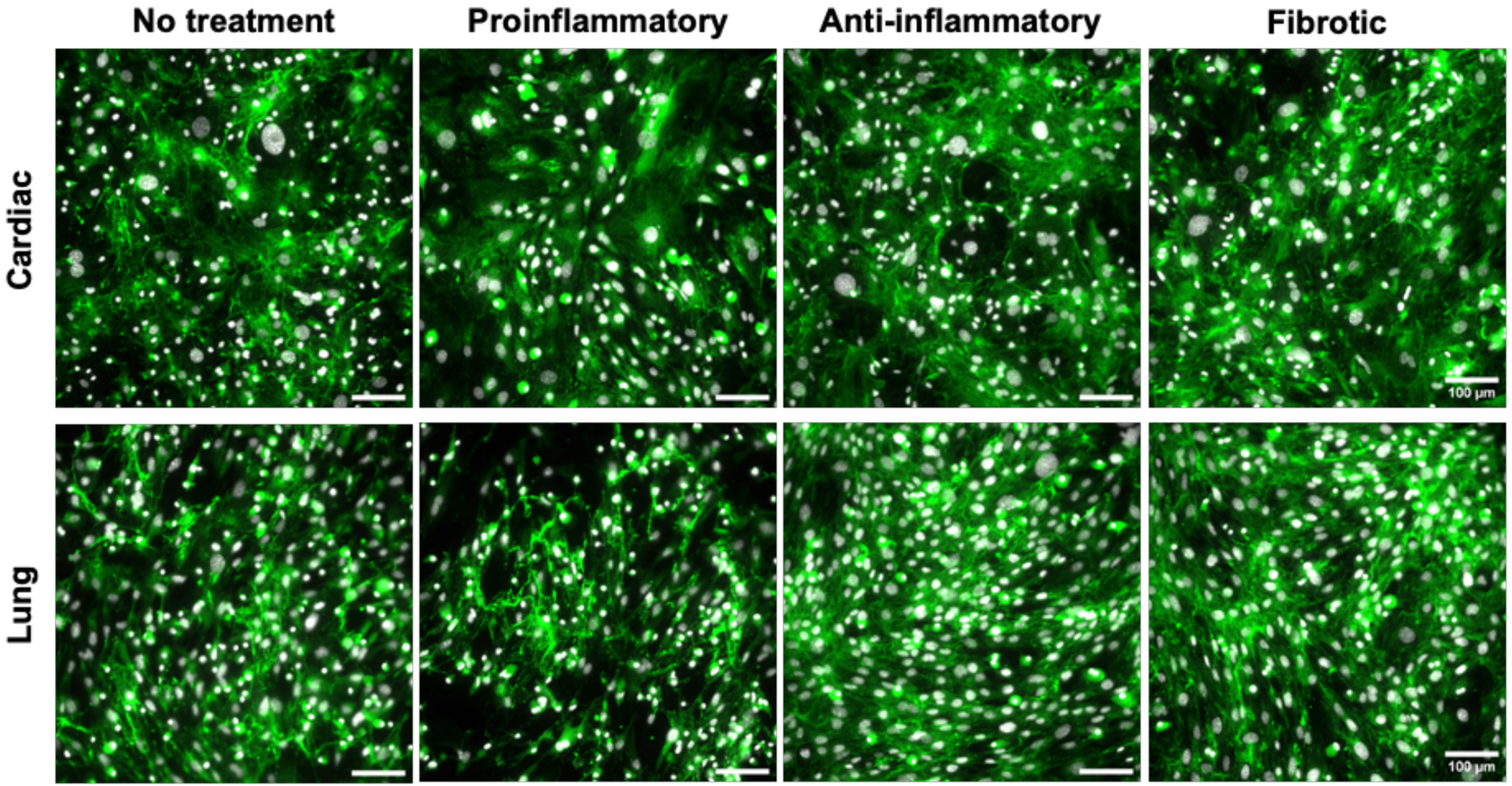
I: Less than 20% of space is filled with collagen fibres in the wound area

II: More than 20% of space is filled with collagen fibres in the wound area



Outlook

Collagen I data from Chloe at 72 hours



Not in the scratch assay setting

Tune parameters to:

1. Resemble differences in collagen distribution;
2. Hypothesis how varying cell types and cytokine conditions impact dynamics.

Thanks for your attention!

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