A Multi-scale Model Captures Stress Relaxation and Flow in Proliferating Tissues with Sub-cellular Elasticity

A Vertex-Based Model Computational Approach

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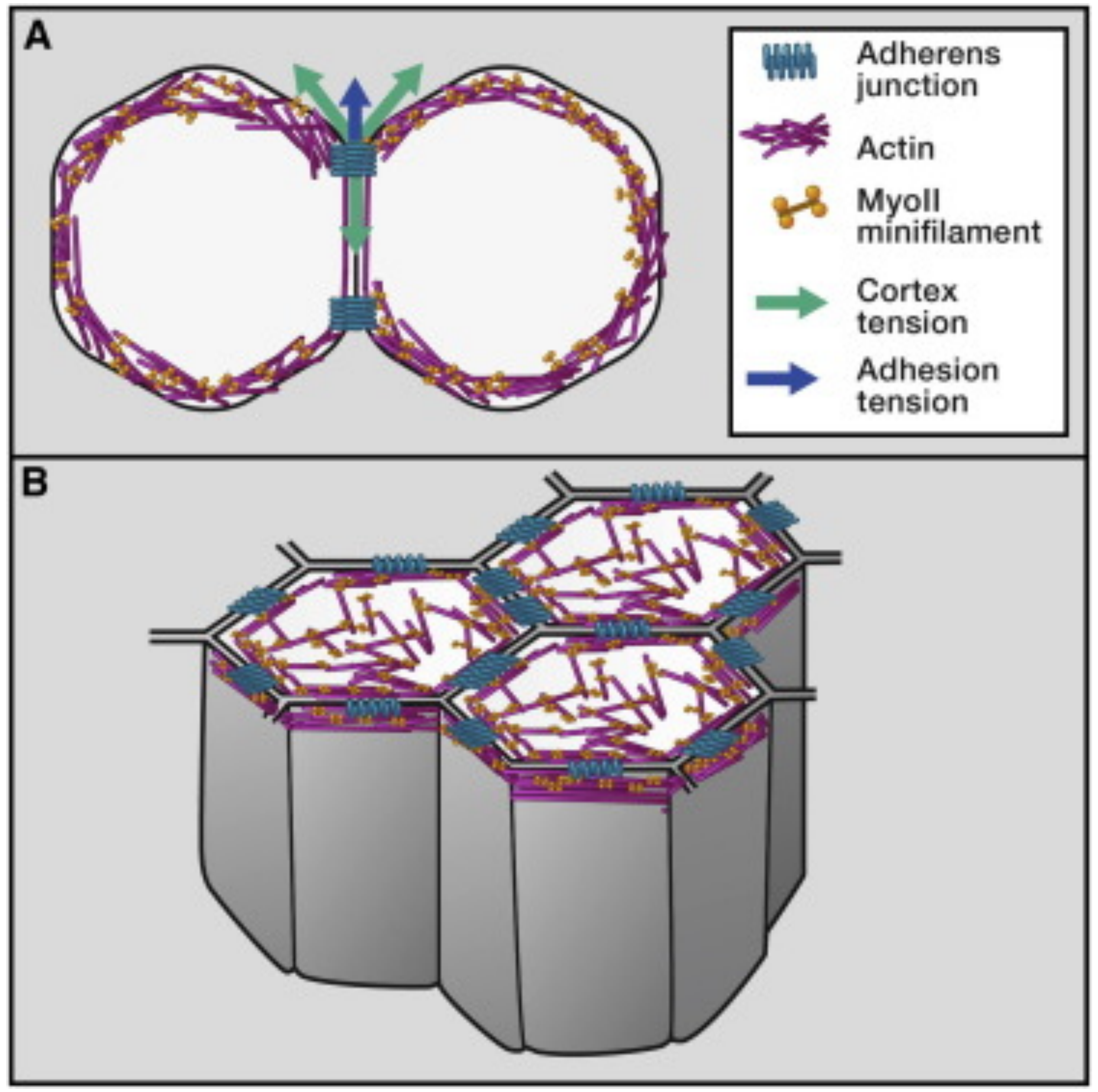
Contents

Background

Tissue Fluidity and Viscoelasticity

- Epithelial tissues are not passive materials: active, dynamic systems where cells generate force internally via actomyosin contractility, adhesion remodeling and turnover of structure components.
- Viscoelasticity
  - Elastic-like responses: When deformed quickly, tissue store mechanical energy/stress due to cytoskeletal tension and cell junction elasticity.
  - Viscous-like flow: Over longtime scales, junction remodel (e.g. via T1 transition), relaxing stress - this is tissue fluidization.

Lecuit, T., & Lenne, P.-F. (2007). *Cell surface mechanics and the control of cell shape, tissue patterns and morphogenesis*. **Nature Reviews Molecular Cell Biology**, 8(8), 633–644.



Self-Organization of Cells at Steady State Determined by Actin-Myosin Contractility and Cell Adhesion

Heisenberg CP, Bellaïche Y. Forces in tissue morphogenesis and patterning. Cell. 2013; 153(5):948– 962. https://doi.org/10.1016/j.cell.2013.05.008 PMID: 23706734

- How do tissues move and flow while growing?
  - Coupling of fluidity with nonlinear mechanics (e.g., elasticity + growth) remains poorly understood.
  - Current models often simplify tissues as either solid or fluid, missing the dynamic interplay.

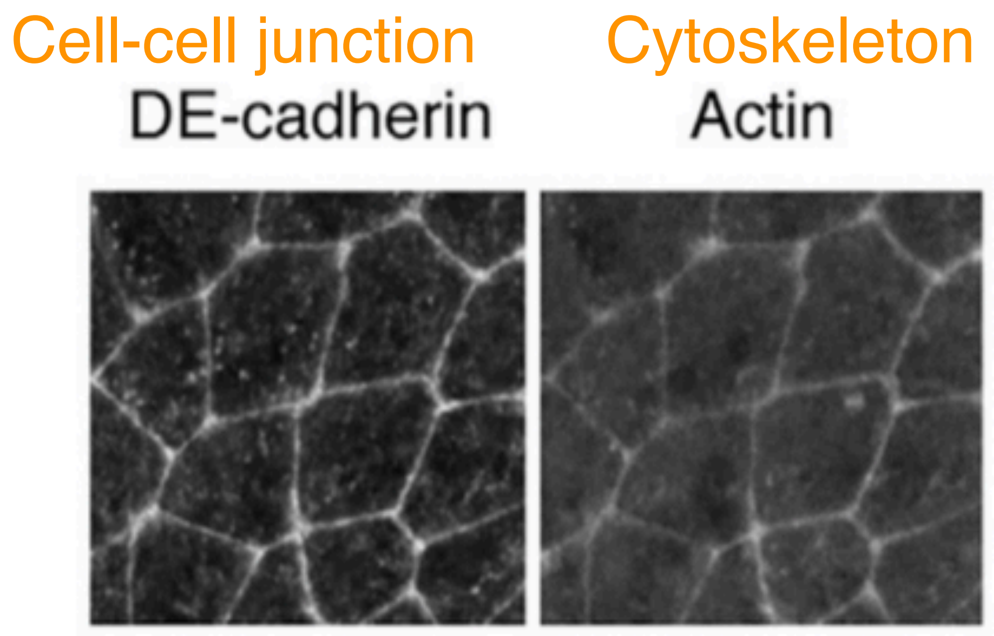
Background

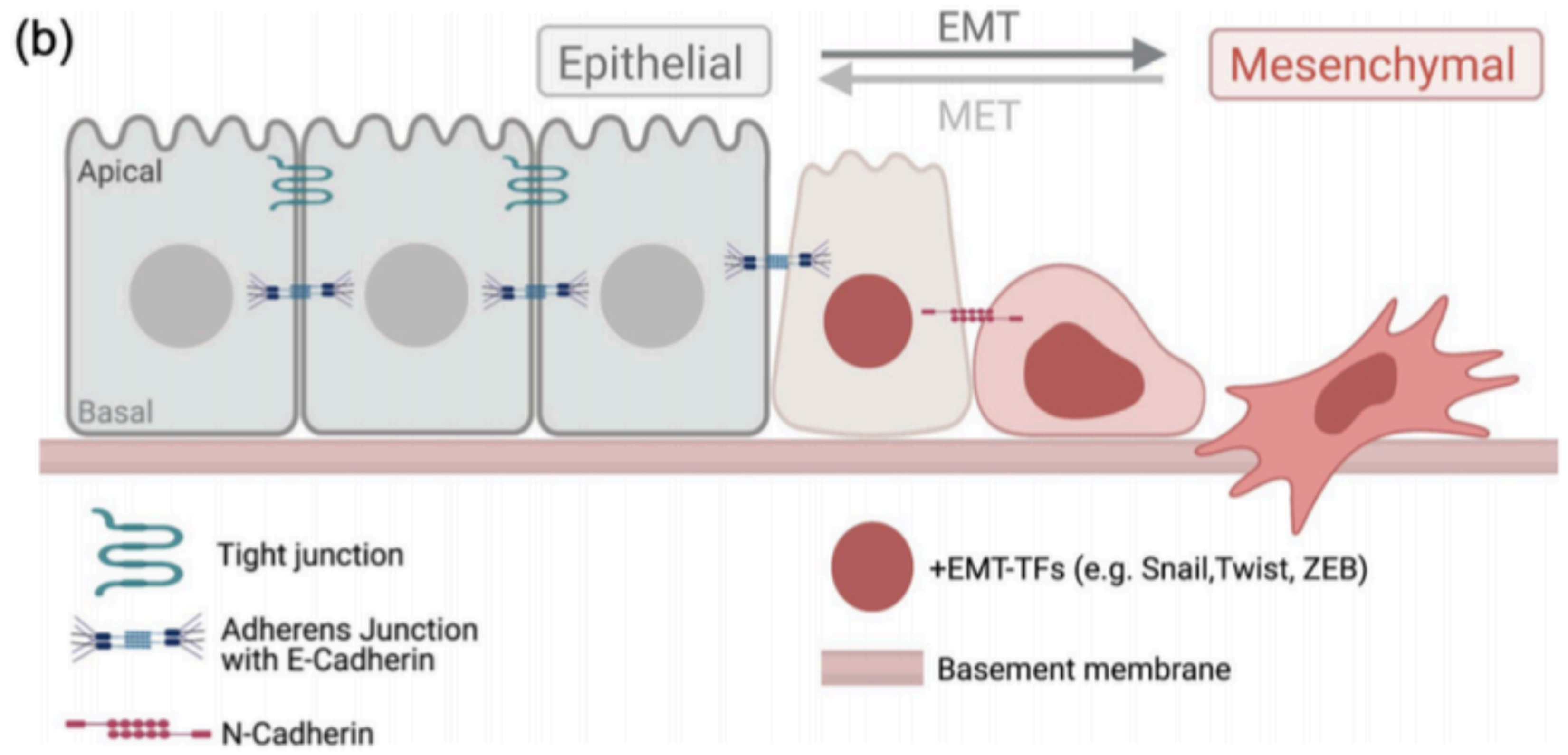
pEMT = hybrid epithelial/ mesenchymal phenotype

(retains adhesion + gains motility)

- Most previous studies view epithelial tissues as cohesive media connecting cells by intercellular junctions (a) while treating mesenchymal cells as individual particles (b).
- In development and cancer, cells often adopt a hybrid identity (c).
- How their fluidity is organized and controlled remains largely unknown. New modeling framework are needed to study interplay between actin structure, fluidity, and morphogenesis.

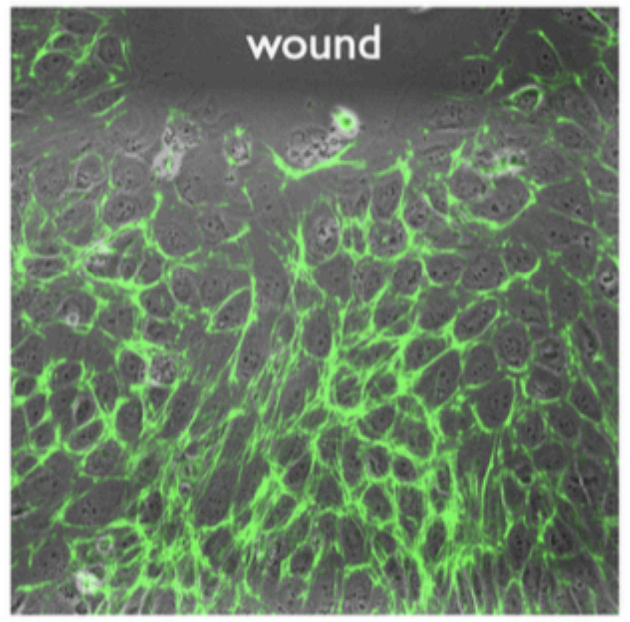
(a) Apical surface of *Drosophila* epithelium during metamorphosis





Amack. Cell Comm. Signal., 2021

(c) Epicardial monolayer with a wound region



Background

Large-scale planar tissue flow during wound closure

Monolayer wound closure with mouse embryonic epicardial cells (MEC-1)

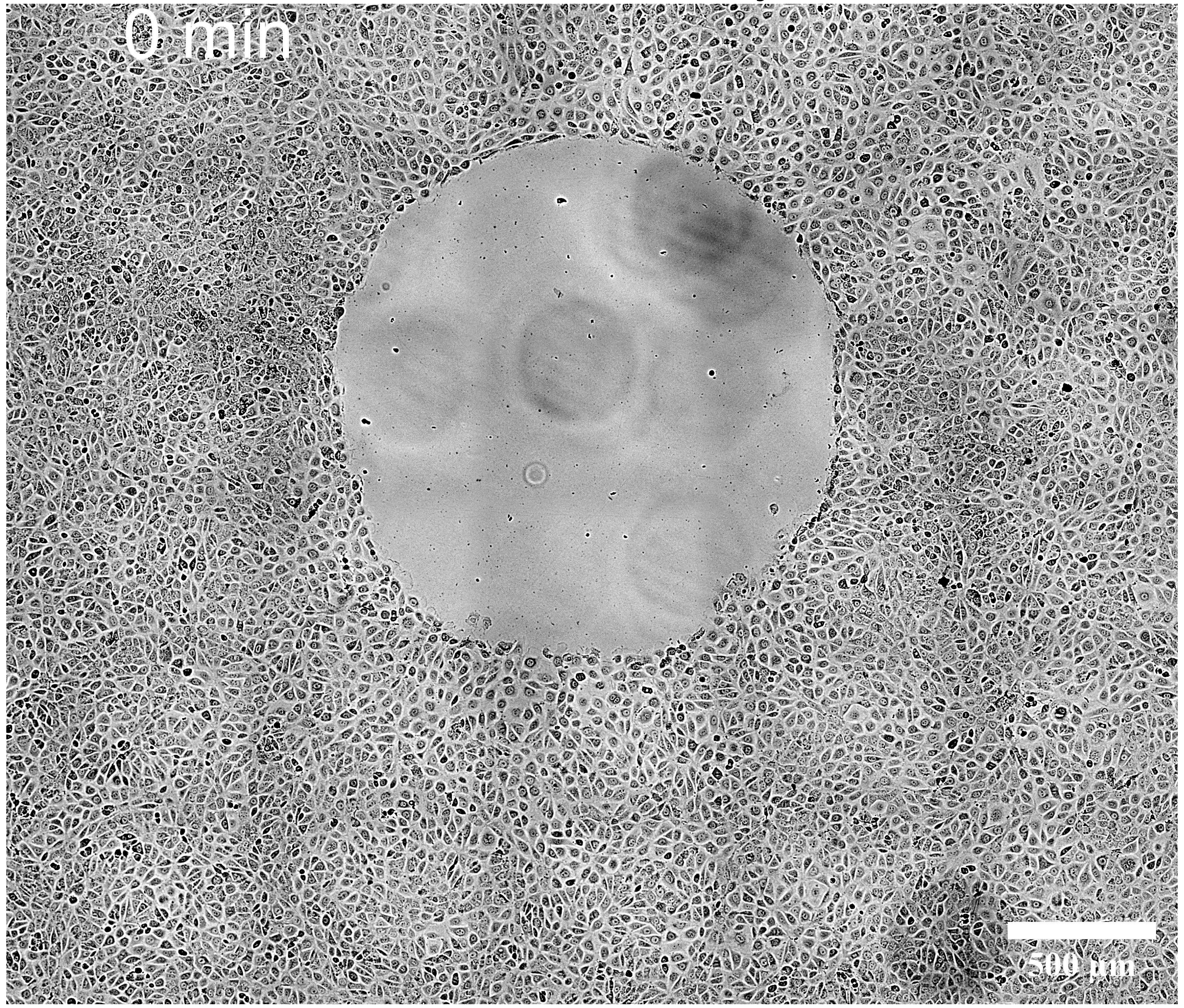
+TGFβ

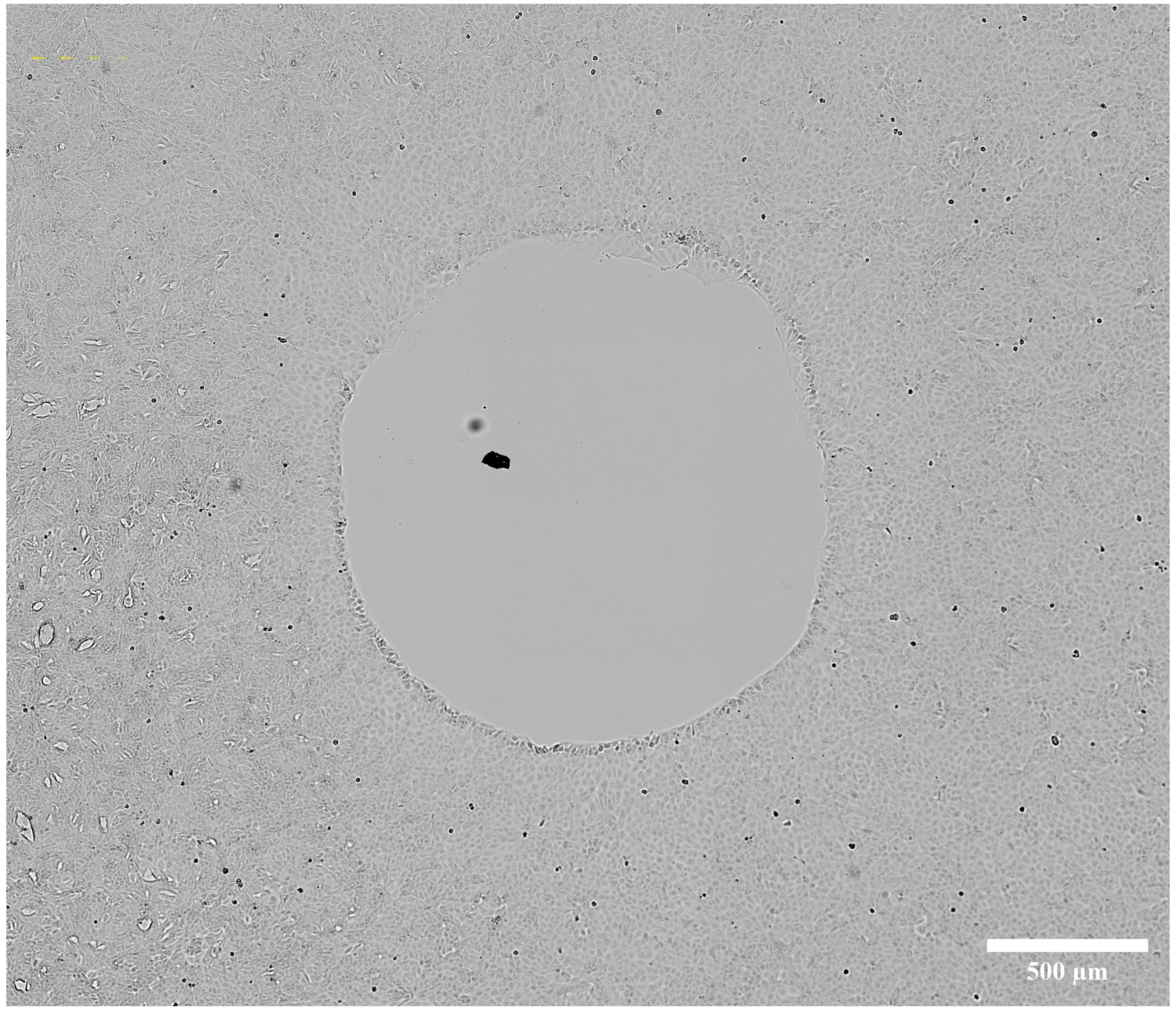
Closed ~ 1 days

More fluid vs less fluid

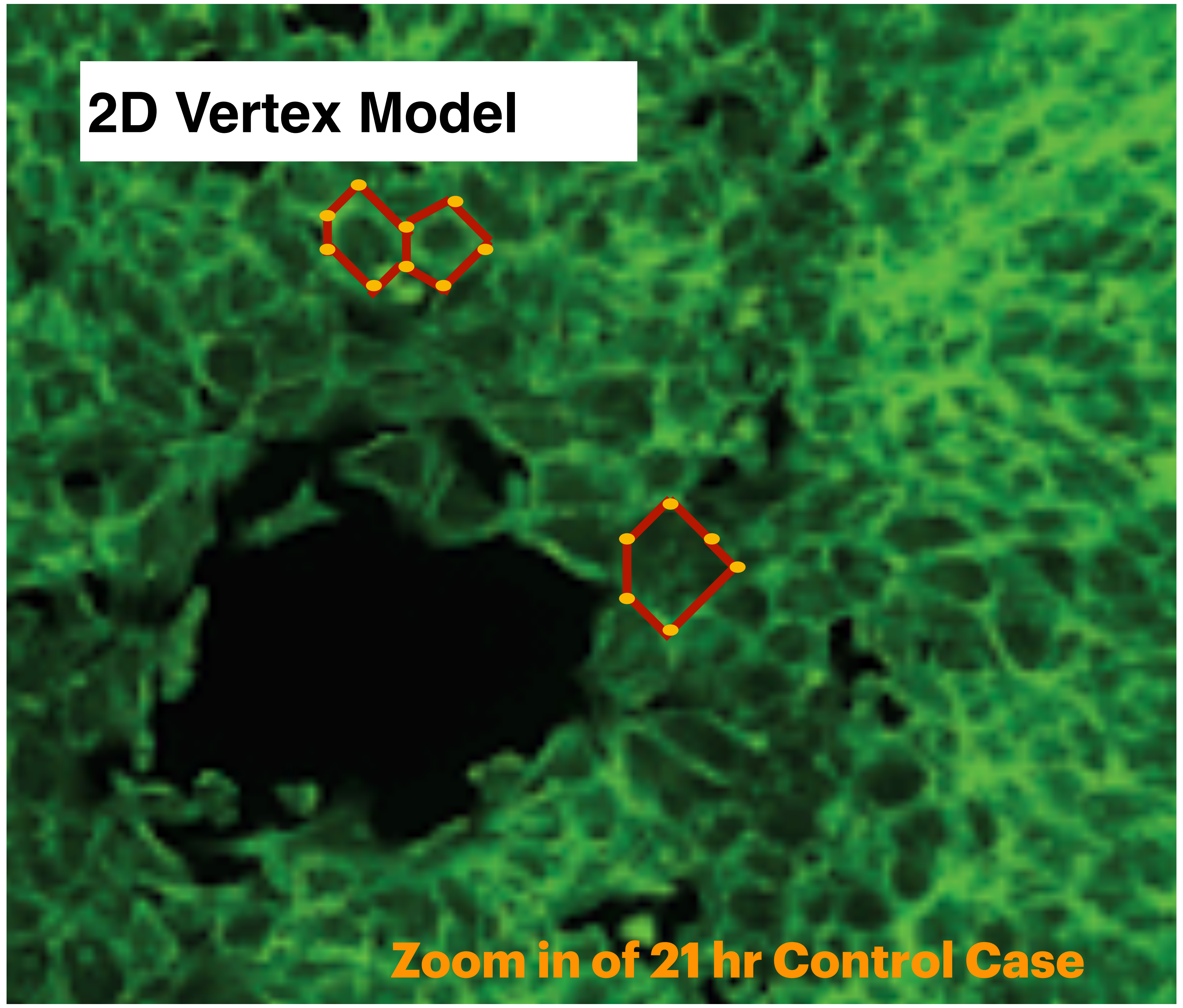
Monolayer wound closure with Madin-Darby canine kidney cells (MDCK)

Closed ~ 1.5 days





Modeling Framework



Actin fibers **do play a role**, but they are: Indirectly represented through the **force** along edges (linked to the actomyosin belt).

Modeling Framework

Energy-Based Model

$$E^e = \int_\Omega {J_e}^{-1} W(F_e) d\mathbf{X}$$

1. Elastic Energy

$$E^e = \sum_\eta E^{e,\eta}$$

Elastic Strain Energy per triangle

$$E^{e,\eta} = J_g^\eta A_0^\eta W^\eta$$

Elastic Energy per triangle

$$W^\eta = \frac{\mu}{2}(\det({\mathbf{F_e}}^\eta)^{-1} \mathrm{tr}({\mathbf{F_e}}^\eta {\mathbf{F_e}}^{\eta T}) - 2)$$

μ : elastic coefficient

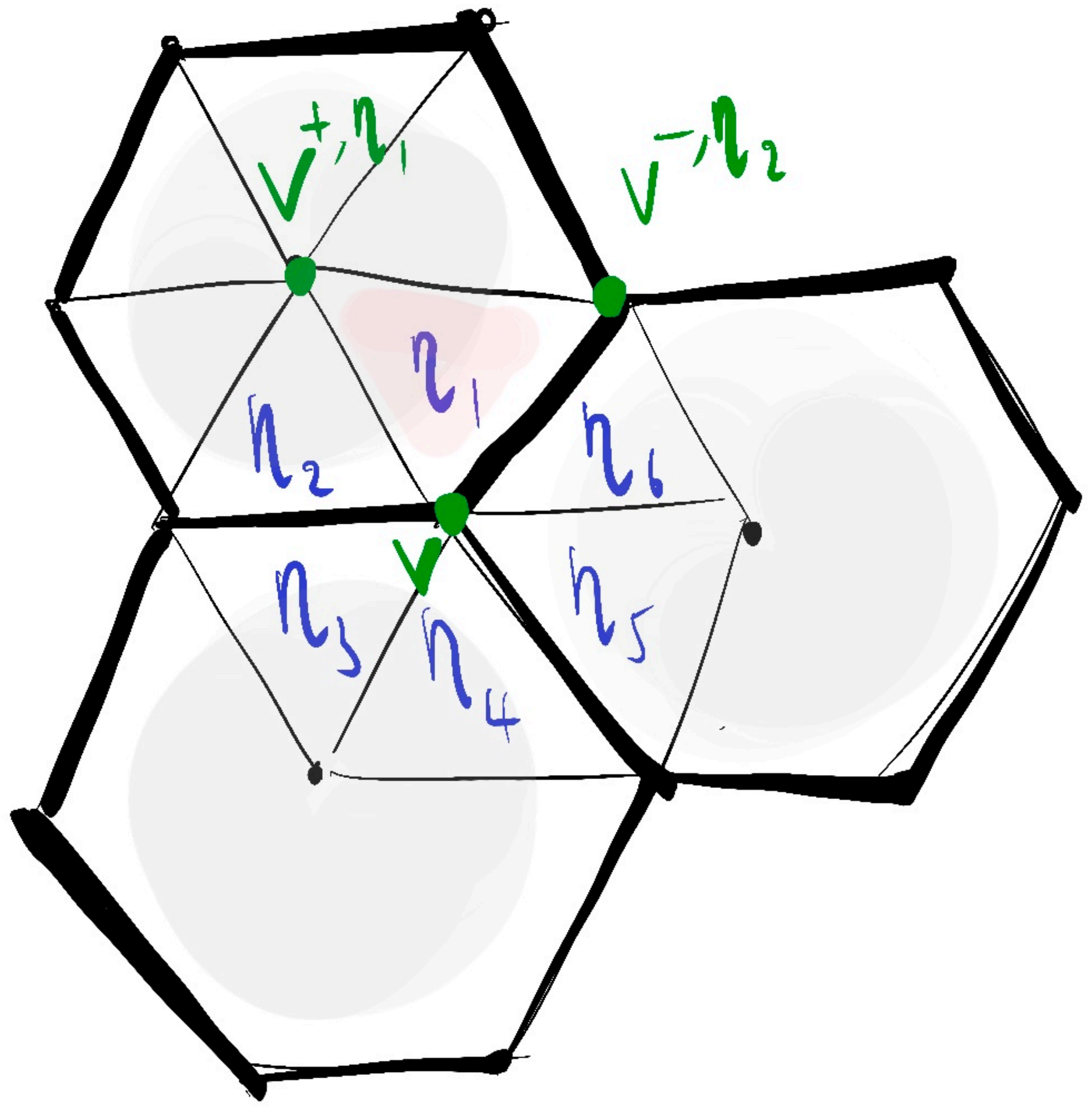
A_0^η : reference area of triangle η

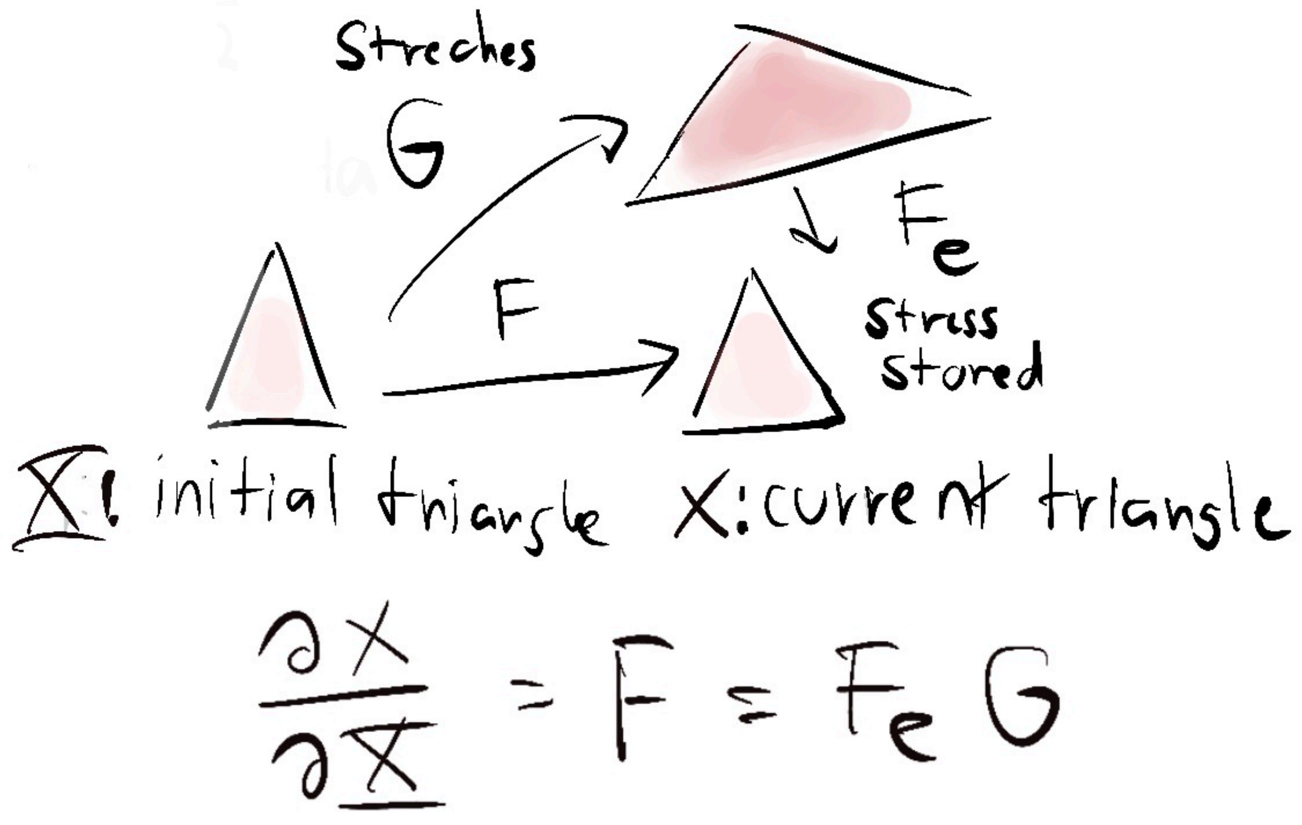
$\mathbf{F}$: deformation tensor

$\mathbf{F_e}$: elastic deformation tensor

$\mathbf{G}$: growth deformation tensor

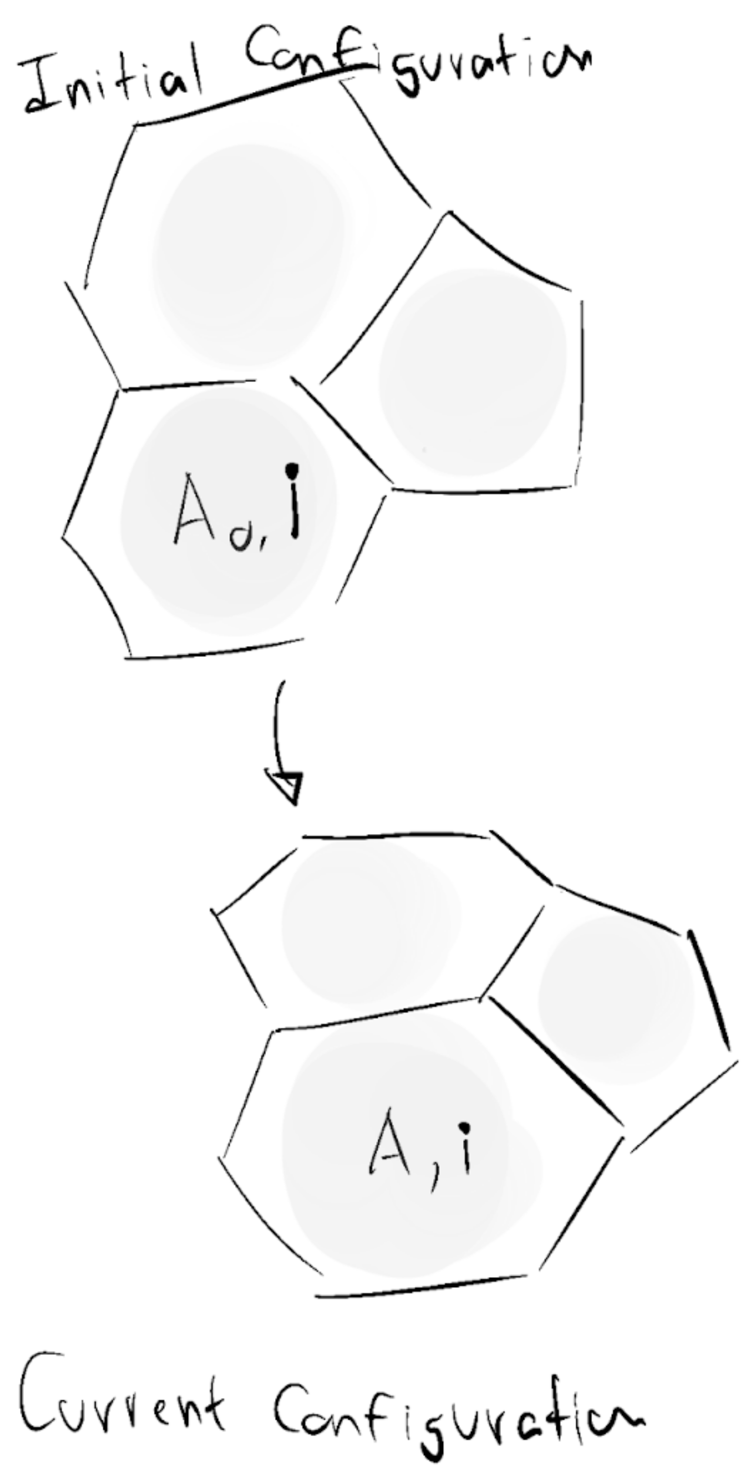
$J_g := \det(\mathbf{G})$ volumetric variation due to growth





Modeling Framework

Energy-Based Model



$$E^p = \int K(J_e - 1)^2 dA$$

2. Pressure Energy

$$E^p = \sum_i E^{p,i} \qquad E^{p,i} = \frac{K}{2} A_0^i \left(\frac{A^i}{A_0^i} - 1\right)^2$$

Pressure Energy per polygon

K : pressure coefficient

A_0^i : preferred area of polygon i

A^i : current area of polygon i

Assumption for tissue growth:

$$\frac{dA_0^i}{dt} = \gamma A_0^i$$

γ : growth coefficient

Tissue fluidity

$$\frac{d\mathbf{G}}{dt} = (\gamma \mathbf{I} + \frac{\beta}{\mu} \mathbf{F_e}^{-1} \boldsymbol{\sigma}_D \mathbf{F_e})\mathbf{G}$$

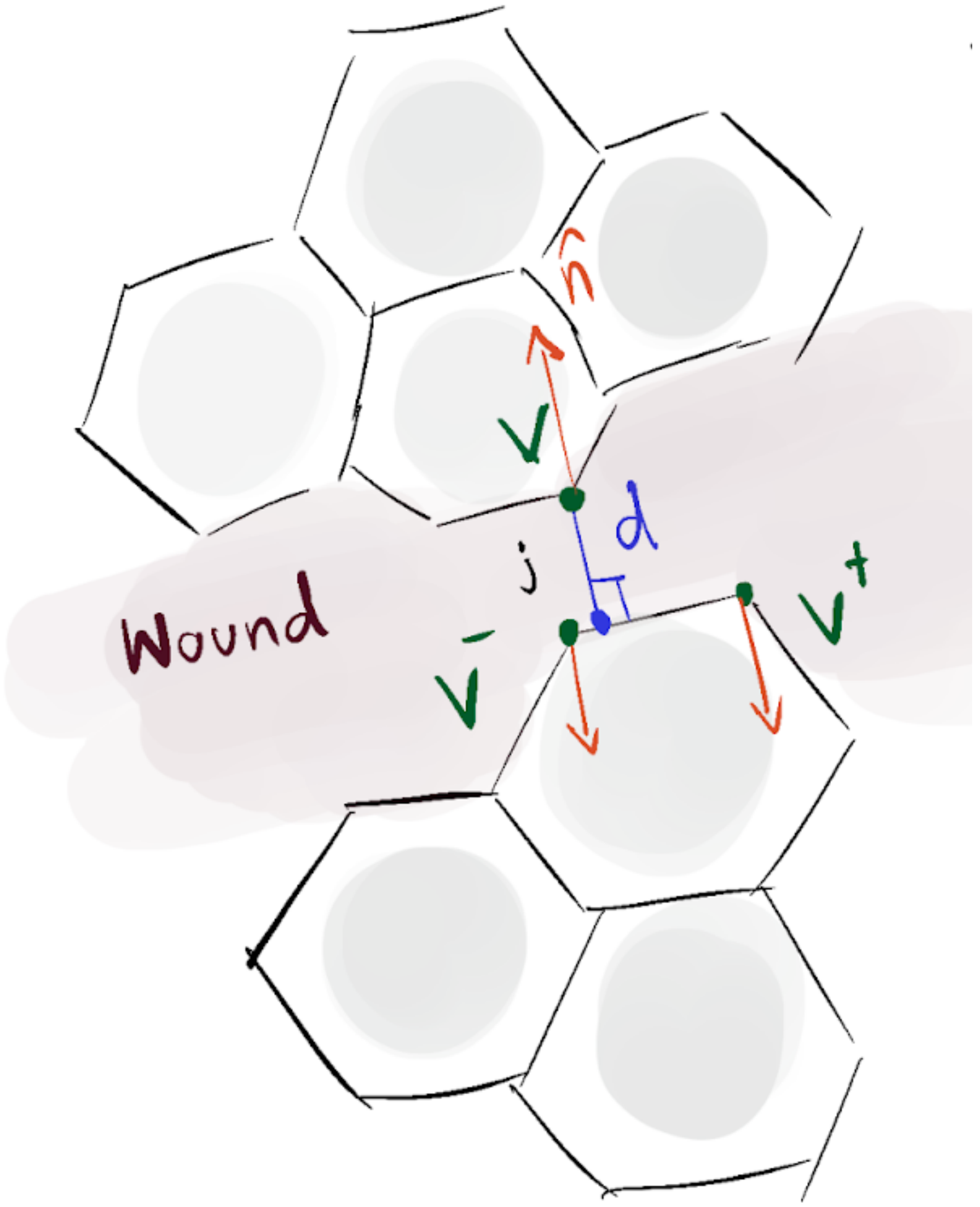
β : rearrangement rate

$\boldsymbol{\sigma}_D$: Cauchy stress for elasticity (deviatoric part)

Olaranont, Nonthakorn. *A Thermodynamically Chemomechanical Solid Tumor Growth Model*. Diss. University of California, Irvine, 2024.

Modeling Framework

Energy-Based Model



3. Collision Energy

$$E^c = \sum_v E^{c,v} \qquad E^{c,v} = \begin{cases} K\bar{A}_0(\frac{d_0 - d^v}{\alpha d_0})^3, & \text{if } 0 \leq |d^v| \leq d_0 \\ 0, & \text{if otherwise} \end{cases}$$

d_0 : artificial distance constant b/w wound edges and vertices

α : collision energy sensitivity

$\bar{A}_0$: average initial polygons' areas of the entire tissue

Modeling Framework

Energy-Based Model

Force & Optimization

Total Force

$$\textbf{Force} := -\frac{\partial E^{tot}}{\partial \mathbf{r}}$$

where $E^{tot} = E^p + E^e + E^c$ is the total energy.

$\mathbf{r}$ is the position of a vertex.

Next we try to solve for positions of all $\mathbf{r}$ such that they makes the total force becomes zero.

Solver Optimizations

(Accelerated) Gradient Descent

i.e. heavy ball method (kinetic energy+friction+mass)

(Accelerated) Newton

Hessian: $\frac{\partial^2 E^{tot}}{\partial \mathbf{r}^2}$

Procedure

Step1: Define Parameters & Coefficients

Step2: Given a Configuration

Step3: Division Process (not including for now)

Step4: Growth & Fluidity (dA_0/dt & dG/dt)

Step5: Force Computation

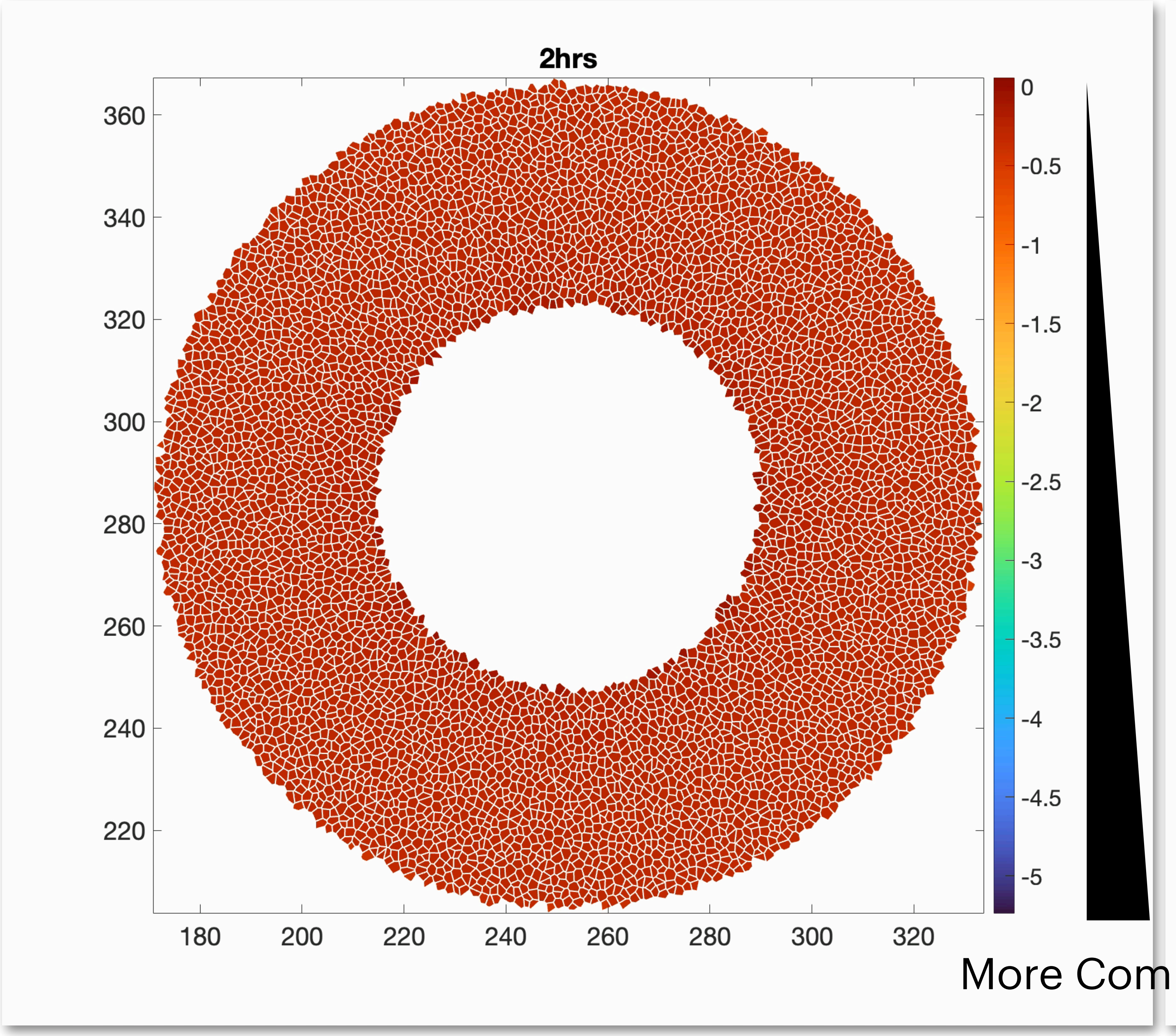
Step6: Apply a Solver Method (iteratively)

dt

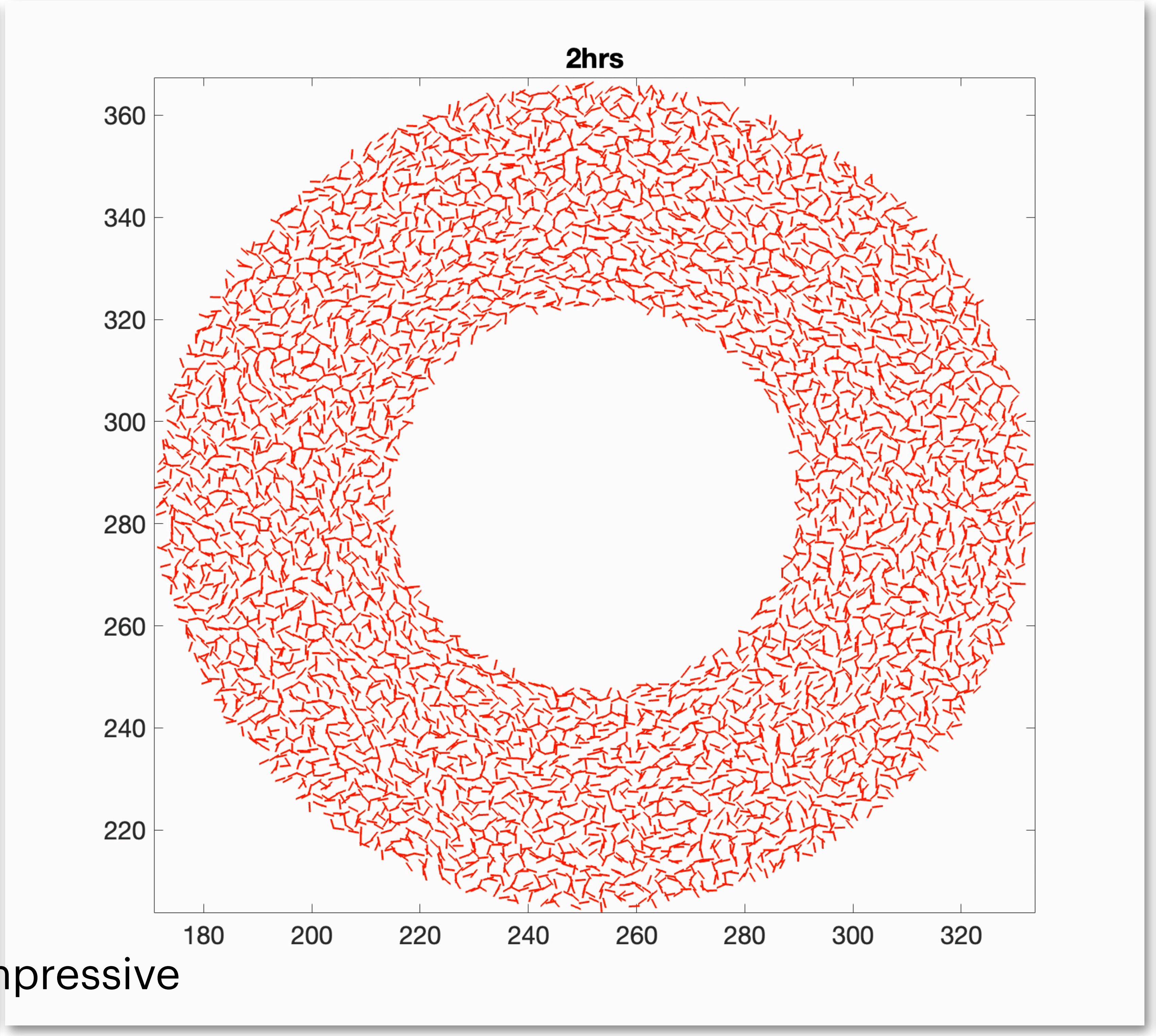
Results

Wound Closure Simulation

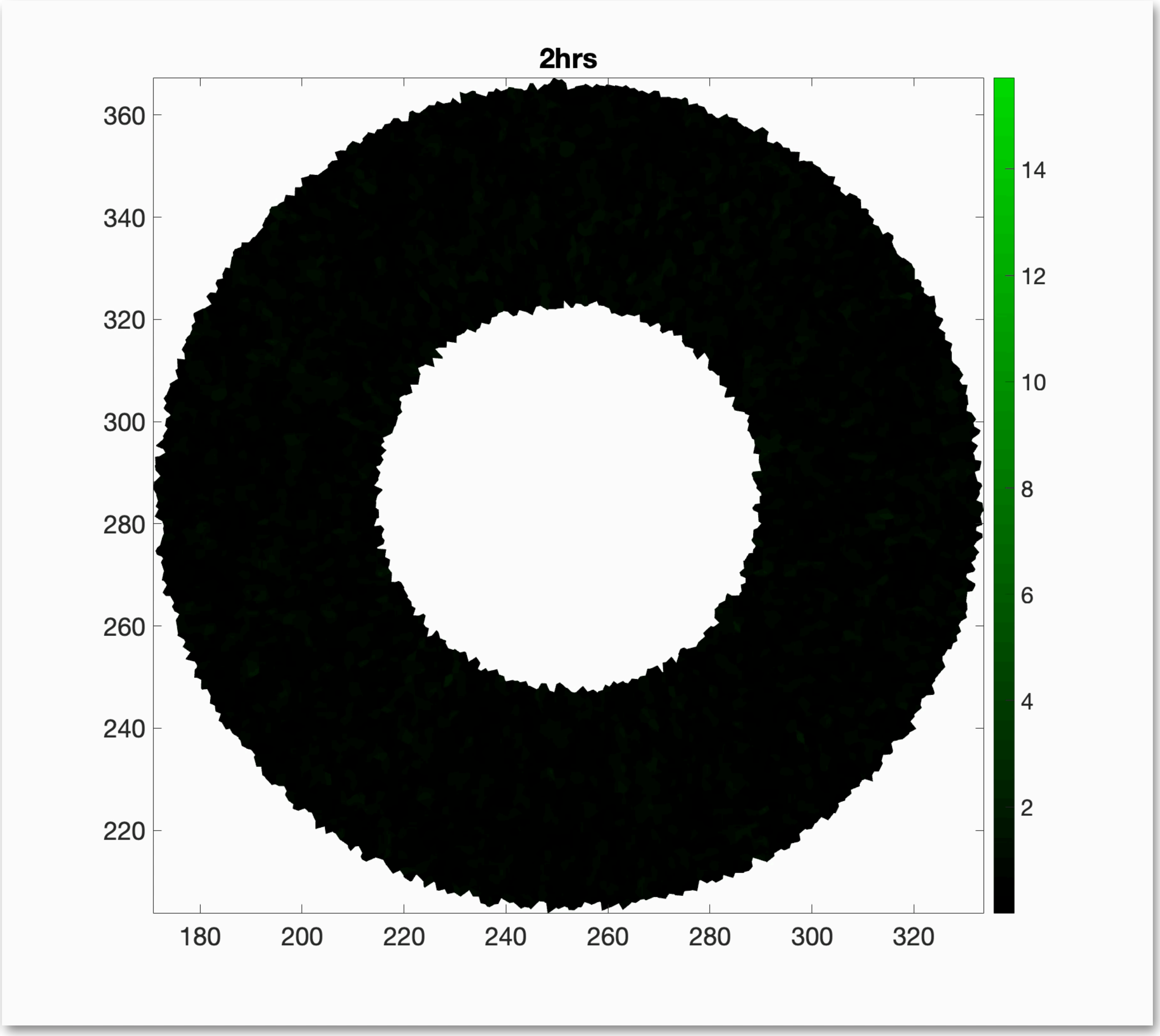
Negative pressure in each polygon



Direction of the compression



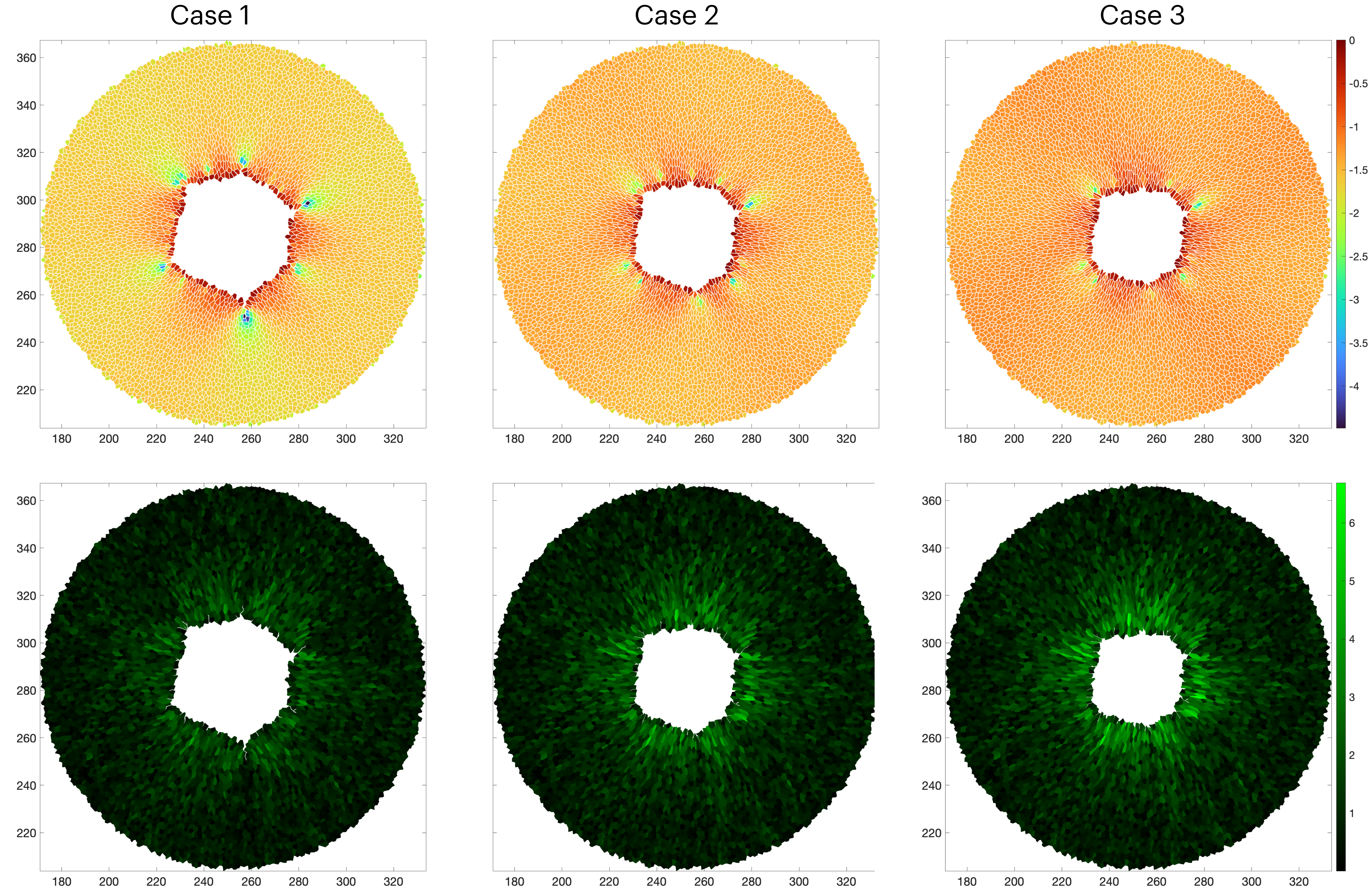
Shape Anisotropic

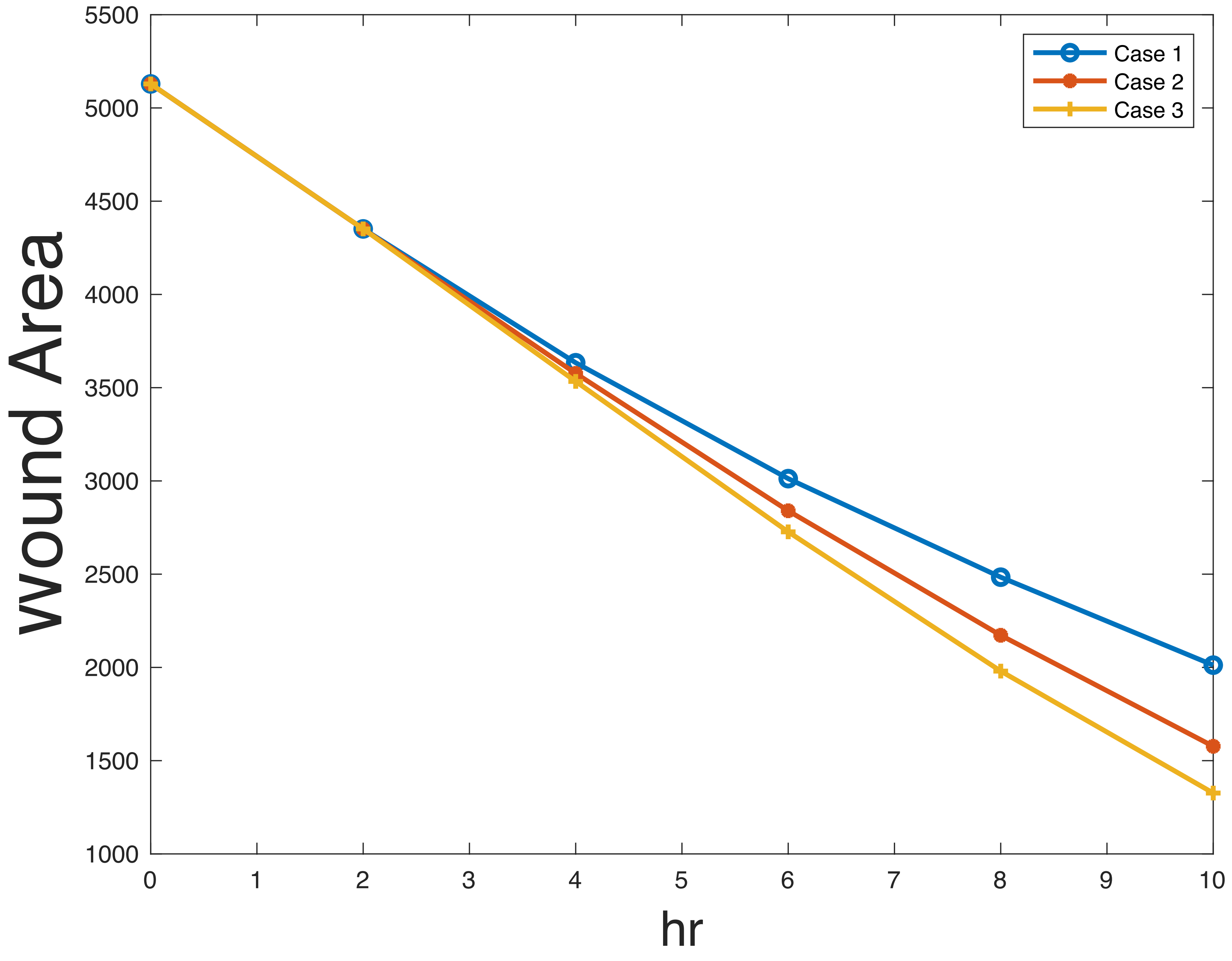


Results

Wound Closure Simulation

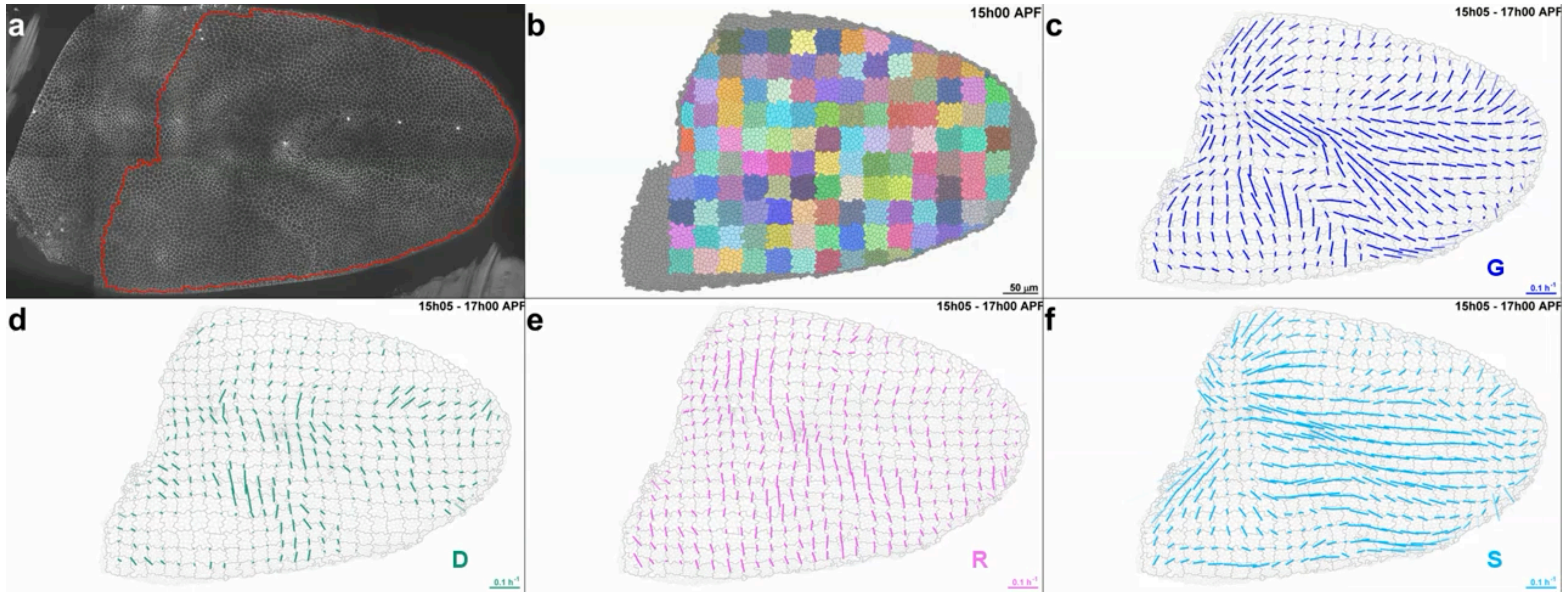
Compare different β : 0,0.075,0.15 at 10 hrs respectively





Results

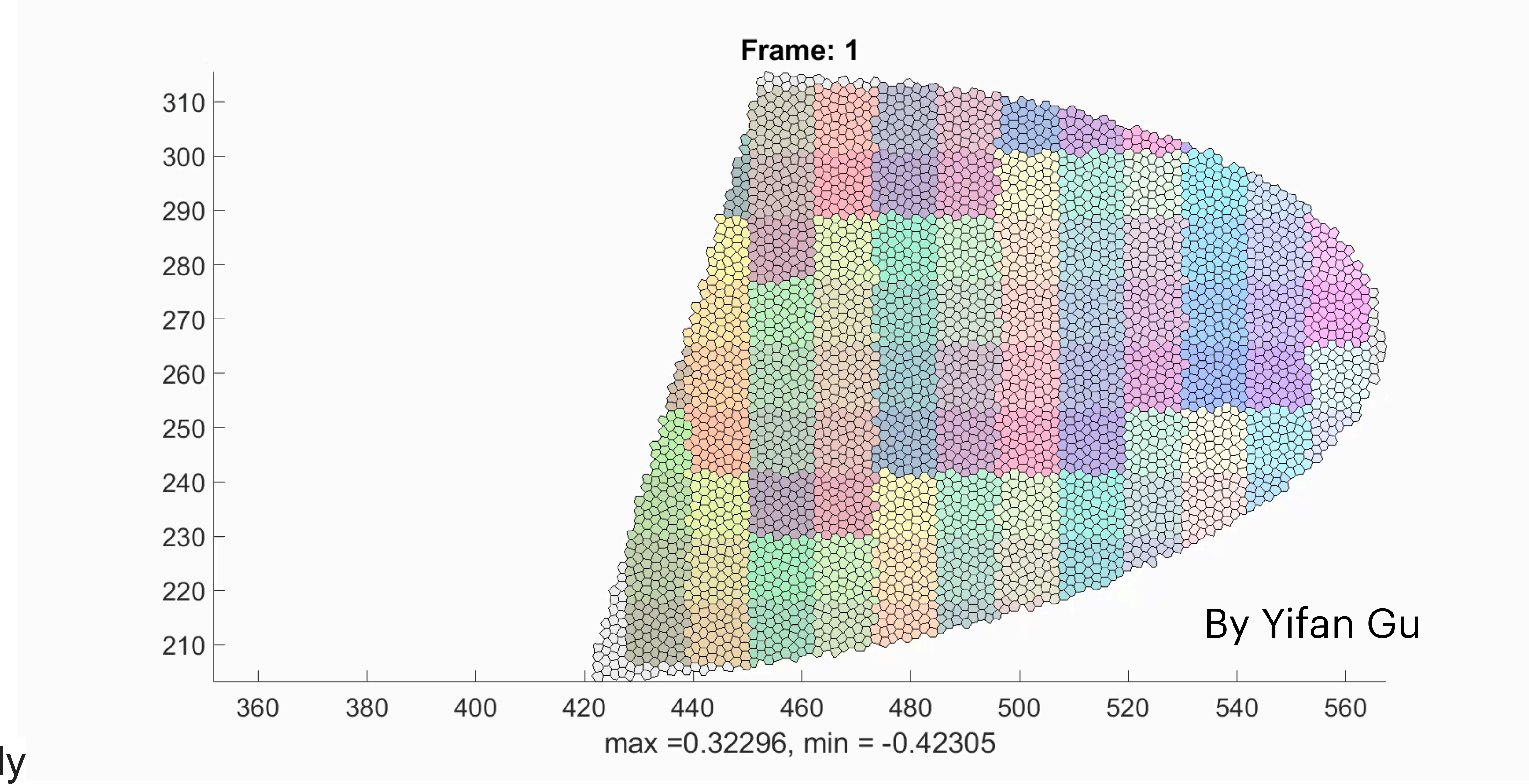
Wing Simulation



Growth and morphogenesis of cell patches during wing development of a Drosophila adult fly

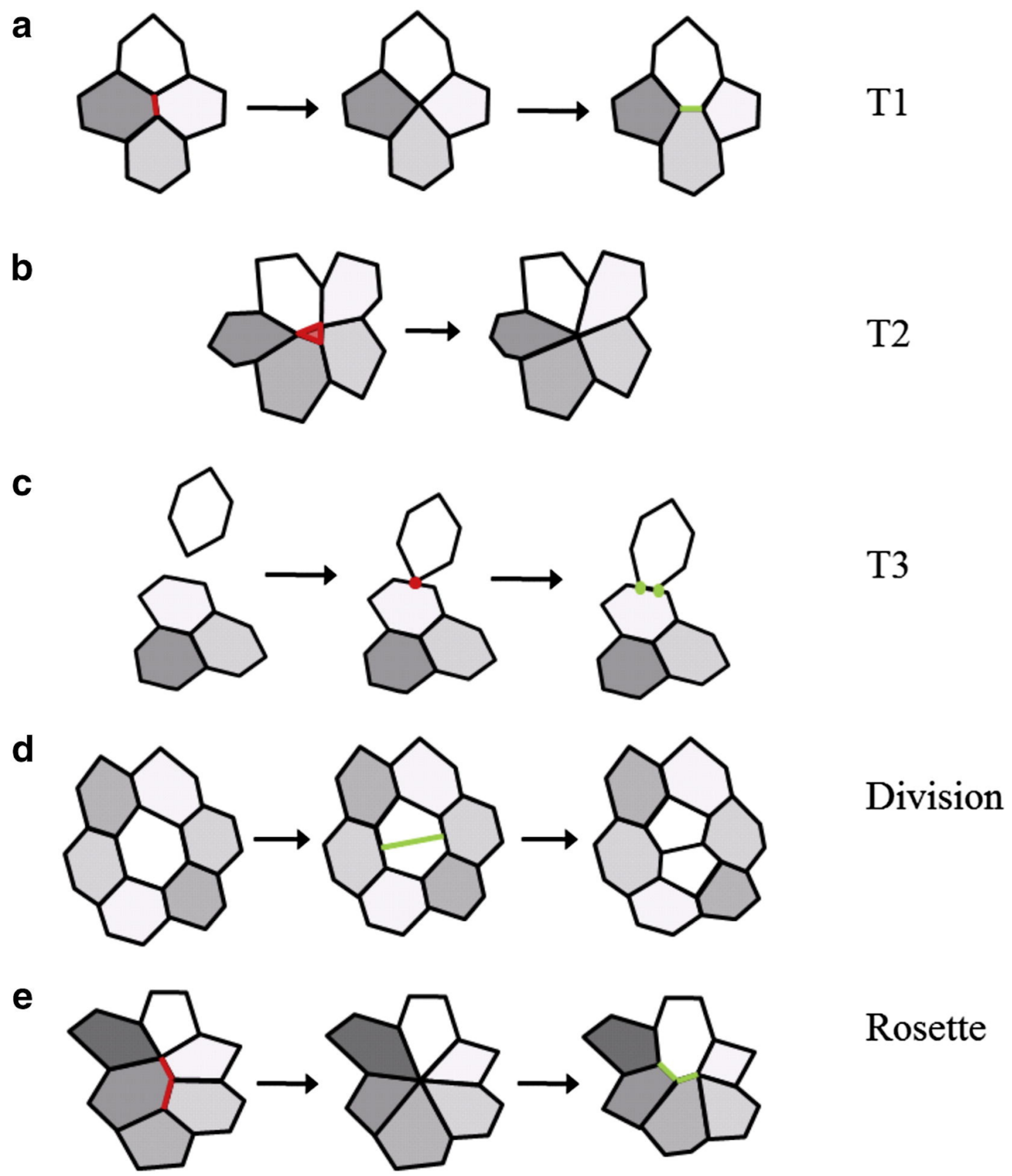
Boris Guirao, Stéphane U Rigaud, Floris Bosveld, Anaïs Bailles, Jesús López-Gay, Shuji Ishihara, Kaoru Sugimura, François Graner, Yohanns Bellaïche (2015) Unified quantitative characterization of epithelial tissue development eLife 4:e08519

Preliminary simple ellipsoid wing simulation



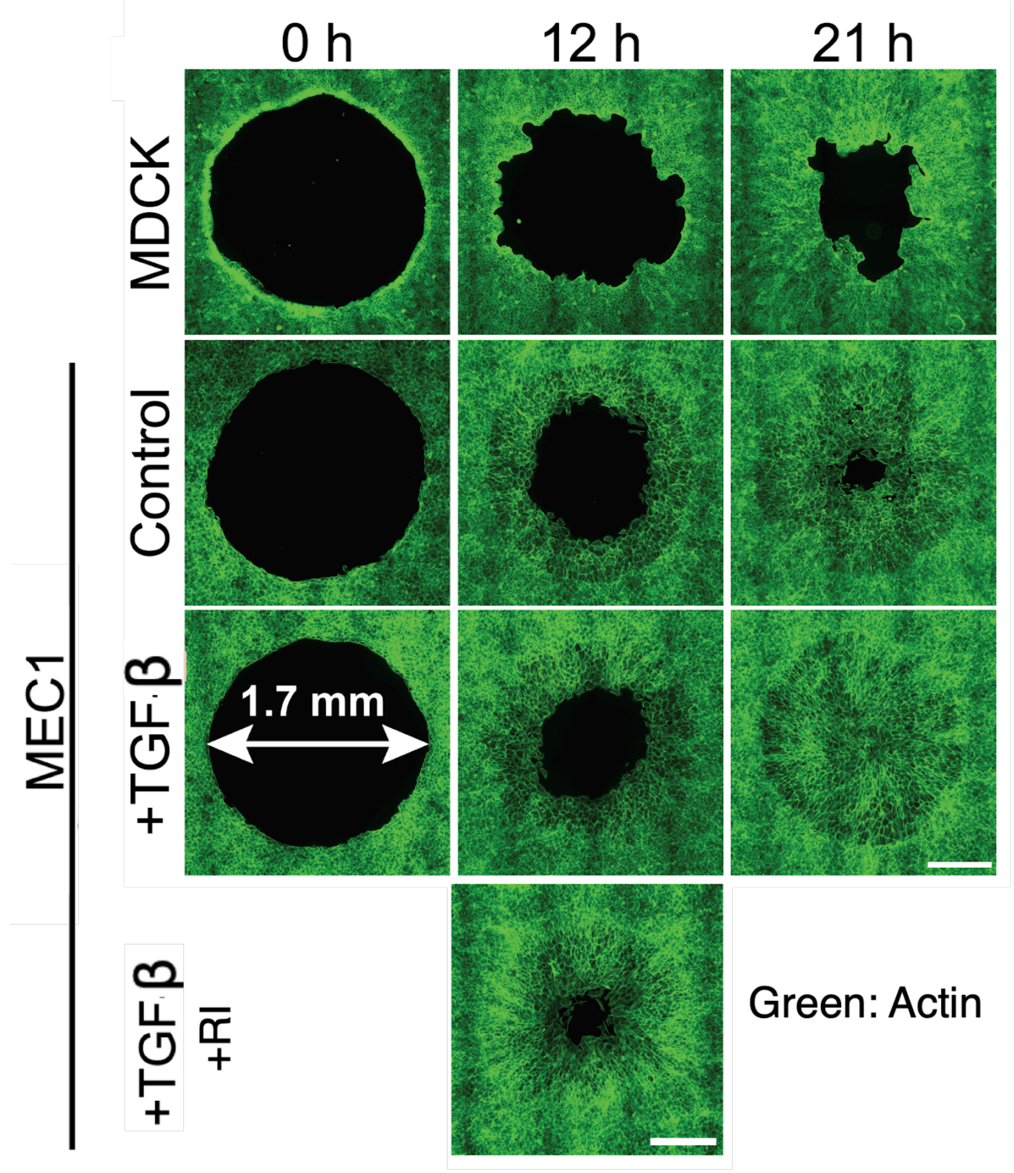
Equilibrium solution at 1 hr for $\gamma := 0.55$

Future Work

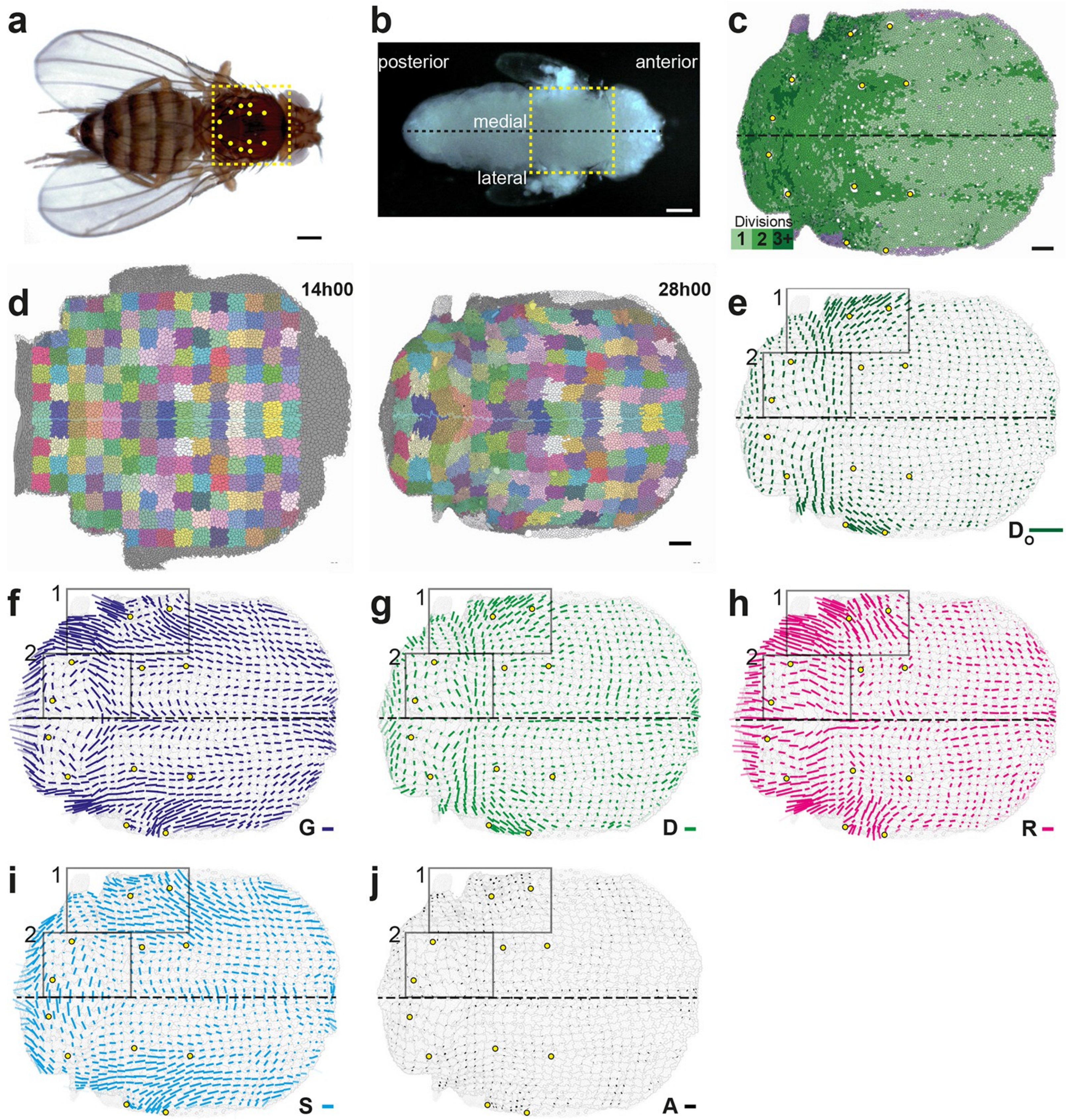


Fletcher, Alexander G., et al. "Vertex models of epithelial morphogenesis." Biophysical journal 106.11 (2014): 2291-2304.

Wound Closure



Jiang, Wei, Wang, Gu, Olaranont, Wen, Sun and Wu, in preparation.



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Tissue morphogenesis of the whole Drosophila notum

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Q/A