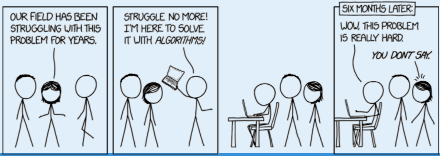


Stress and Disorder in a Confluent Epithelium

Inferring tissue mechanics from geometry

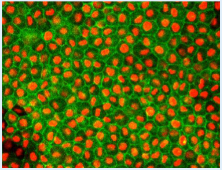
Alexander Nestor-Bergmann

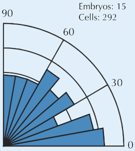
University of Cambridge

Institut Mittag-Leffler, 2018

Outline

The Biological Question





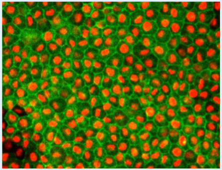
Control Cells

Randomly oriented on average

Division Angles

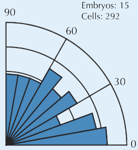
Uniformly distributed

The Biological Question



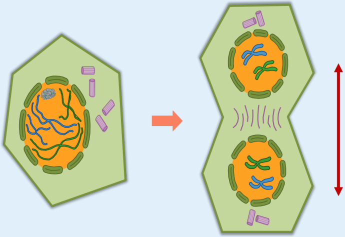
Control Cells

Randomly oriented on average

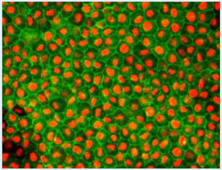


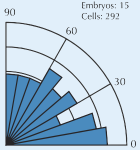
Division Angles

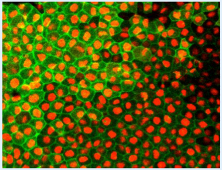
Uniformly distributed

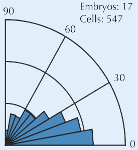


The Biological Question









Control Cells

Randomly oriented on average

Division Angles

Uniformly distributed

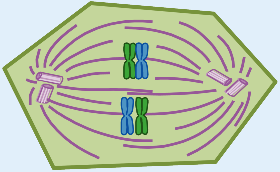
Stretched Cells

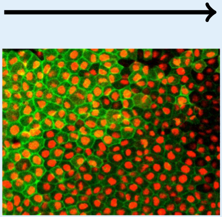
Aligned with direction of stretch

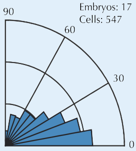
Division Angles

Align with stretch

The Biological Question







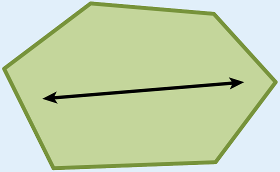
Stretched Cells

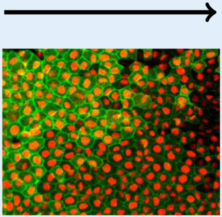
Aligned with direction of stretch

Division Angles

Align with stretch

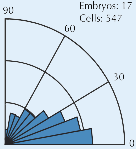
The Biological Question





Stretched Cells

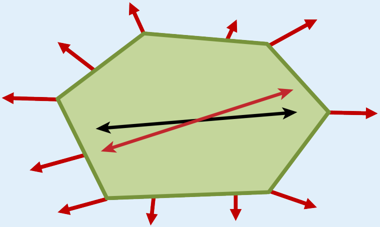
Aligned with direction of stretch

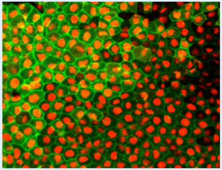


Division Angles

Align with stretch

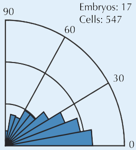
The Biological Question





Stretched Cells

Aligned with direction of stretch

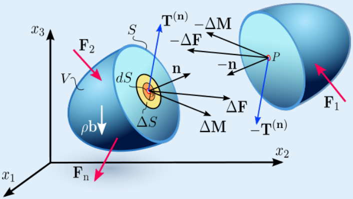


Division Angles

Align with stretch

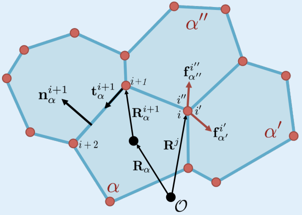
Modelling Approaches

Continuum mechanics



Capture tissue-level response to deformations.
– Bulk and shear modulus.

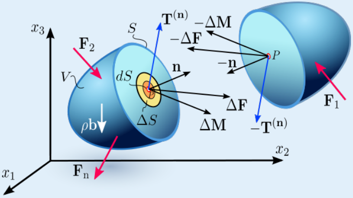
Discrete (vertex models)



Built from cell-level description.
Easy access to complex behaviours e.g. remodelling.

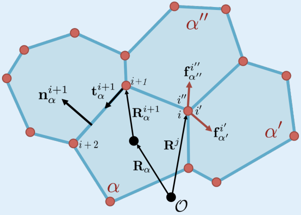
Modelling Approaches

Continuum mechanics



Capture tissue-level response to deformations.
– Bulk and shear modulus.

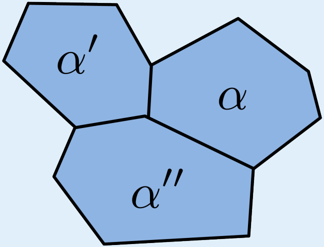
Discrete (vertex models)



Built from cell-level description.
Easy access to complex behaviours e.g. remodelling.

The Mechanical Energy of a Cell

$$\tilde{U}_\alpha = \frac{\tilde{K}}{2}\left(\tilde{A}_\alpha - \tilde{A}_0\right)^2 + \frac{\tilde{\Gamma}}{2}(\tilde{L}_\alpha - \tilde{L}_0)^2$$



$\tilde{A}_\alpha$ = Area of cell α

$\tilde{L}_\alpha$ = Perimeter of cell α

$\tilde{K}$ = Bulk stiffness

$\tilde{A}_0$ = Preferred area

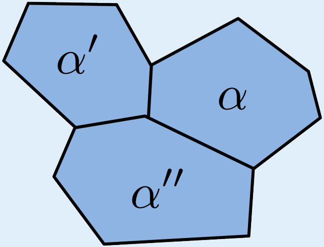
$\tilde{L}_0$ = Preferred Perimeter

$\tilde{\Gamma}$ = Contractility

Farhadifar et al. (2007) $>$ 600 citations!

The Mechanical Energy of a Cell

$$\tilde{U}_\alpha = \frac{\tilde{K}}{2}\left(\tilde{A}_\alpha - \tilde{A}_0\right)^2 + \frac{\tilde{\Gamma}}{2}(\tilde{L}_\alpha - \tilde{L}_0)^2$$



Nondimensionalise:

$$A_\alpha = \frac{\tilde{A}_\alpha}{\tilde{A}_0}$$

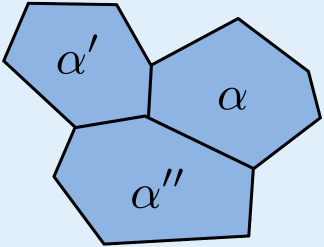
$$L_\alpha = \frac{\tilde{L}_\alpha}{\sqrt{\tilde{A}_0}}$$

$\ldots$

Farhadifar et al. (2007) $>$ 600 citations!

The Mechanical Energy of a Cell

$$U_\alpha = \frac{1}{2}\left(A_\alpha - 1\right)^2 + \frac{\Gamma}{2}(L_\alpha - L_0)^2$$



A_α = Area of cell α

L_α = Perimeter of cell α

L_0 = Preferred perimeter $(= -\frac{\Lambda}{2\Gamma})$

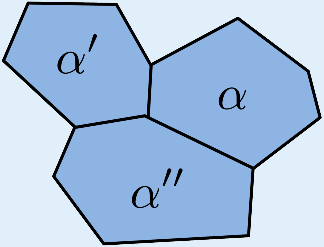
Λ = Line tension of cell edge

Γ = Cell contractility

Farhadifar et al. (2007) $>$ 600 citations!

The Mechanical Energy of a Cell

$$U_\alpha = \frac{1}{2}(A_\alpha - 1)^2 + \frac{\Gamma}{2}(L_\alpha - L_0)^2$$



A_α = Area of cell α

L_α = Perimeter of cell α

L_0 = Preferred perimeter $(= -\frac{\Lambda}{2\Gamma})$

Λ = Line tension of cell edge

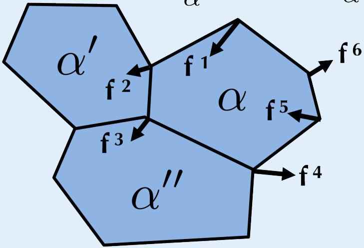
Γ = Cell contractility

Farhadifar et al. (2007) $>$ 600 citations!

The Mechanical Energy of a Cell

$$U_\alpha = \frac{1}{2}(A_\alpha - 1)^2 + \frac{\Gamma}{2}(L_\alpha - L_0)^2$$

$$\mathbf{f}^i_\alpha = -\nabla^i U_\alpha$$



A_α = Area of cell α

L_α = Perimeter of cell α

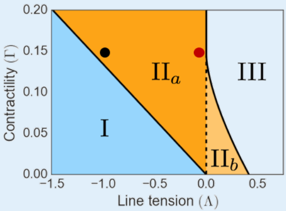
L_0 = Preferred perimeter $(= -\frac{\Lambda}{2\Gamma})$

Λ = Line tension of cell edge

Γ = Cell contractility

Farhadifar et al. (2007) $>$ 600 citations!

Parameter Selection

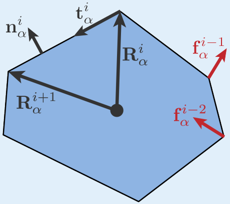


$$(\Lambda, \Gamma) = (-0.01, 0.15) \qquad (\Lambda, \Gamma) = (-0.1, 0.15)$$

Play

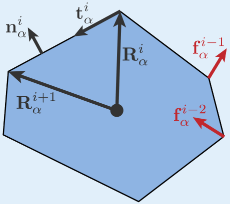
From Force to Stress

$$U_\alpha = \frac{1}{2}\left(A_\alpha - 1\right)^2 + \frac{\Gamma}{2}\left(L_\alpha - L_0\right)^2$$



From Force to Stress

$$U_\alpha = \frac{1}{2}\left(A_\alpha - 1\right)^2 + \frac{\Gamma}{2}(L_\alpha - L_0)^2$$

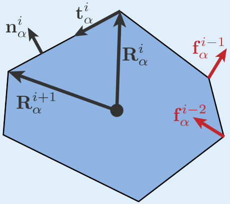


Define pressure and tension

$$P_\alpha = A_\alpha - 1$$
$$T_\alpha = \Gamma(L_\alpha - L_0)$$

From Force to Stress

$$U_\alpha = \frac{1}{2}\left(A_\alpha - 1\right)^2 + \frac{\Gamma}{2}(L_\alpha - L_0)^2$$



Elastic force

$$\begin{aligned}\mathbf{f}_\alpha^i &= \nabla^i U_\alpha \\ &= -\tfrac{1}{2} P_\alpha (\mathbf{n}_\alpha^i + \mathbf{n}_\alpha^{i-1}) + T_\alpha (\mathbf{t}_\alpha^i - \mathbf{t}_\alpha^{i-1})\end{aligned}$$

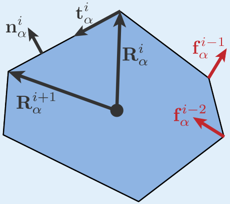
Define pressure and tension

$$\begin{aligned}P_\alpha &= A_\alpha - 1 \\ T_\alpha &= \Gamma(L_\alpha - L_0)\end{aligned}$$

UNIVERSITY OF CAMBRIDGE

From Force to Stress

$$U_\alpha = \frac{1}{2}\left(A_\alpha - 1\right)^2 + \frac{\Gamma}{2}\left(L_\alpha - L_0\right)^2$$



Elastic force

$$\mathbf{f}_\alpha^i = \nabla^i U_\alpha$$
$$= -\tfrac{1}{2}P_\alpha(\mathbf{n}_\alpha^i + \mathbf{n}_\alpha^{i-1}) + T_\alpha(\mathbf{t}_\alpha^i - \mathbf{t}_\alpha^{i-1})$$

Stress satisfies

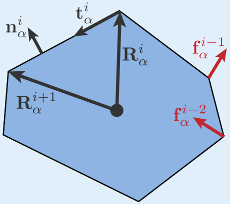
$$\boldsymbol{\sigma} = \nabla\cdot(\mathbf{R}\otimes\boldsymbol{\sigma})$$

Define pressure and tension

$$P_\alpha = A_\alpha - 1$$
$$T_\alpha = \Gamma(L_\alpha - L_0)$$

From Force to Stress

$$U_\alpha = \frac{1}{2}\left(A_\alpha - 1\right)^2 + \frac{\Gamma}{2}(L_\alpha - L_0)^2$$



Define pressure and tension

$$P_\alpha = A_\alpha - 1$$
$$T_\alpha = \Gamma(L_\alpha - L_0)$$

Elastic force

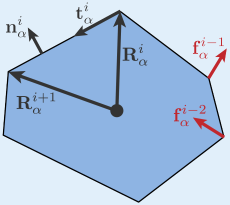
$$\begin{aligned}\mathbf{f}_\alpha^i &= \nabla^i U_\alpha \\ &= -\tfrac{1}{2}P_\alpha(\mathbf{n}_\alpha^i + \mathbf{n}_\alpha^{i-1}) + T_\alpha(\mathbf{t}_\alpha^i - \mathbf{t}_\alpha^{i-1})\end{aligned}$$

Stress satisfies

$$\int_{\mathcal{A}} \boldsymbol{\sigma}\,\mathrm{d}A = \int_{\mathcal{A}} \nabla\cdot(\mathbf{R}\otimes\boldsymbol{\sigma})\,\mathrm{d}A$$

From Force to Stress

$$U_\alpha = \frac{1}{2}\left(A_\alpha - 1\right)^2 + \frac{\Gamma}{2}(L_\alpha - L_0)^2$$



Elastic force

$$\begin{aligned}\mathbf{f}_\alpha^i &= \nabla^i U_\alpha \\ &= -\tfrac{1}{2} P_\alpha (\mathbf{n}_\alpha^i + \mathbf{n}_\alpha^{i-1}) + T_\alpha (\mathbf{t}_\alpha^i - \mathbf{t}_\alpha^{i-1})\end{aligned}$$

Stress satisfies

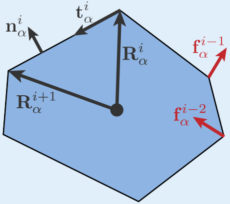
$$\int_{\mathcal{A}} \boldsymbol{\sigma}\, \mathrm{d}A = \int_{\mathcal{A}} \nabla\cdot(\mathbf{R}\otimes\boldsymbol{\sigma})\, \mathrm{d}A = \oint_{\mathcal{S}} \mathbf{R}\otimes\boldsymbol{\sigma}\cdot\mathbf{n}\, \mathrm{d}S$$

Define pressure and tension

$$\begin{aligned} P_\alpha &= A_\alpha - 1 \\ T_\alpha &= \Gamma(L_\alpha - L_0) \end{aligned}$$

From Force to Stress

$$U_\alpha = \frac{1}{2}\left(A_\alpha - 1\right)^2 + \frac{\Gamma}{2}\left(L_\alpha - L_0\right)^2$$



Elastic force

$$\begin{aligned}\mathbf{f}_\alpha^i &= \nabla^i U_\alpha \\ &= -\tfrac{1}{2} P_\alpha (\mathbf{n}_\alpha^i + \mathbf{n}_\alpha^{i-1}) + T_\alpha (\mathbf{t}_\alpha^i - \mathbf{t}_\alpha^{i-1})\end{aligned}$$

Stress satisfies

$$\int_{\mathcal{A}} \boldsymbol{\sigma}\, \mathrm{d}A = \int_{\mathcal{A}} \nabla\cdot(\mathbf{R}\otimes\boldsymbol{\sigma})\, \mathrm{d}A = \oint_{\mathcal{S}} \mathbf{R}\otimes\boldsymbol{\sigma}\cdot\mathbf{n}\, \mathrm{d}S$$

Define pressure and tension

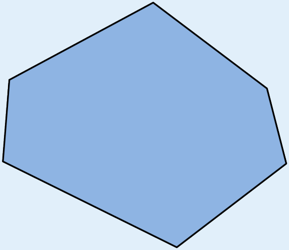
$$P_\alpha = A_\alpha - 1$$
$$T_\alpha = \Gamma(L_\alpha - L_0)$$

Motivating the definition (Batchelor, 1970)

$$A_\alpha \boldsymbol{\sigma}_\alpha = \sum_{i=0}^{Z_\alpha - 1} \mathbf{R}_\alpha^i \otimes \mathbf{f}_\alpha^i$$

The Cell-Level Stress Tensor

$$\boldsymbol{\sigma}_\alpha = -P_\alpha^{\text{eff}}\mathsf{I} + T_\alpha \mathsf{J}_\alpha$$



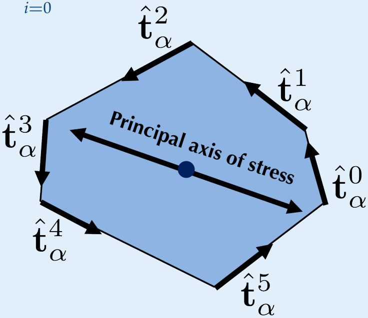
UNIVERSITY OF CAMBRIDGE

The Cell-Level Stress Tensor

Tension $T_\alpha = \Gamma(L_\alpha - L_0)$

$$\boldsymbol{\sigma}_\alpha = -P_\alpha^{\text{eff}}\mathsf{I} + T_\alpha \mathsf{J}_\alpha$$

$$\mathsf{Q} = \frac{1}{L}\sum_{i=0}^{Z_\alpha - 1} l_\alpha^i \hat{\mathbf{t}}_\alpha^i \otimes \hat{\mathbf{t}}_\alpha^i$$



Deviatoric stress

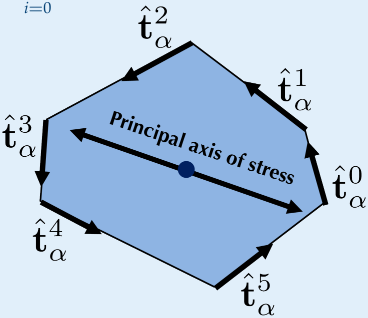
$$\mathsf{J}_\alpha = \frac{L_\alpha}{A_\alpha}\left(\frac{1}{2}\mathsf{I} - \mathsf{Q}\right)$$

The Cell-Level Stress Tensor

Tension $T_\alpha = \Gamma(L_\alpha - L_0)$

$$\boldsymbol{\sigma}_\alpha = -P_\alpha^{\mathrm{eff}}\mathsf{I} + T_\alpha \mathsf{J}_\alpha$$

$$\mathsf{Q} = \frac{1}{L}\sum_{i=0}^{Z_\alpha - 1} l_\alpha^i \hat{\mathbf{t}}_\alpha^i \otimes \hat{\mathbf{t}}_\alpha^i$$



Deviatoric stress

$$\mathsf{J}_\alpha = \frac{L_\alpha}{A_\alpha}\left(\frac{1}{2}\mathsf{I} - \mathsf{Q}\right)$$

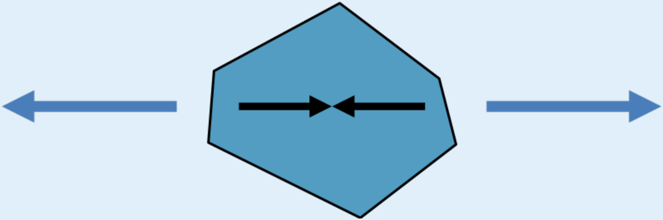
Isotropic stress

$$P_\alpha^{\mathrm{eff}} = A_\alpha - 1 + \frac{T_\alpha L_\alpha}{2A_\alpha}$$

The Cell-Level Stress Tensor

- Cell principally under tension

$$P_\alpha^{\mathrm{eff}} > 0$$

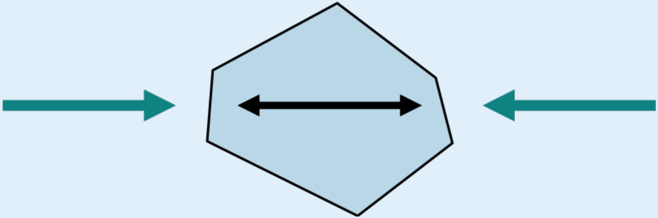


UNIVERSITY OF CAMBRIDGE

The Cell-Level Stress Tensor

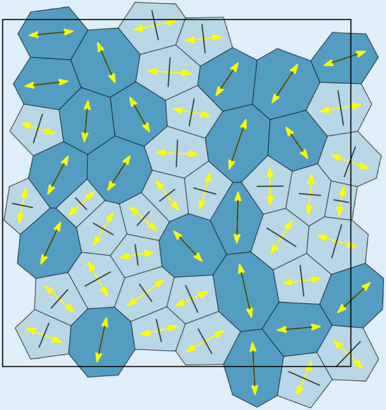
- Cell principally under compression

$$P_\alpha^{\text{eff}} < 0$$



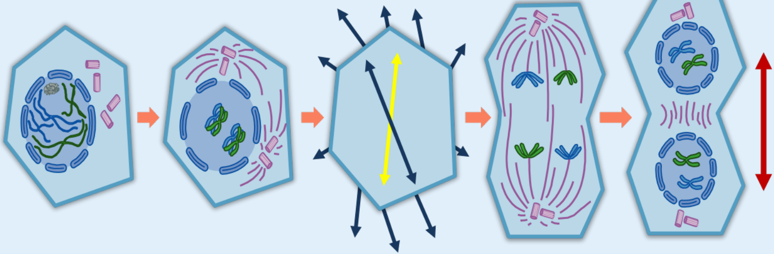
Cell-Level Stress and Shape Align

The principal axes of stress and shape align exactly.



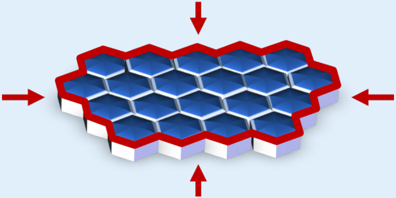
The stress and shape tensors commute and so share eigenbases.

Cell-Level Stress and Shape Align



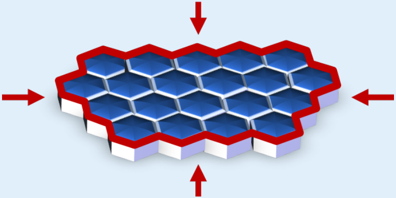
Local to Global Stress

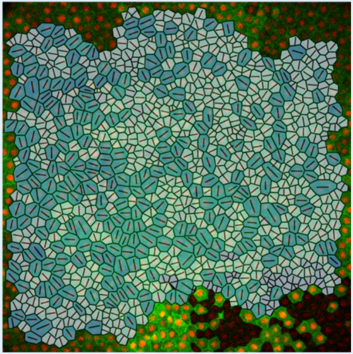
$$\boldsymbol{\sigma}^{\mathcal{M}} = \frac{1}{A^{\mathcal{M}}} \sum_{\alpha}^{N_c} A_\alpha \boldsymbol{\sigma}_\alpha$$



Local to Global Stress

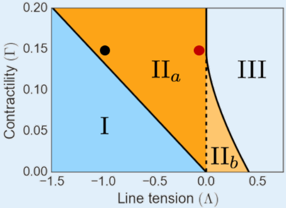
$$\boldsymbol{\sigma}^{\mathcal{M}} = \frac{1}{A^{\mathcal{M}}} \sum_{\alpha}^{N_c} A_\alpha \boldsymbol{\sigma}_\alpha$$

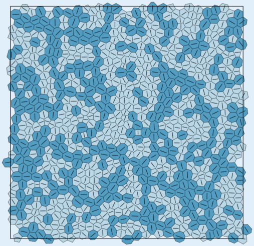




Heterogeneity of Stress

$$U_\alpha = \frac{1}{2}(A_\alpha - 1)^2 + \frac{\Gamma}{2}(L_\alpha - L_0)^2$$



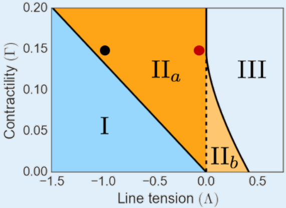


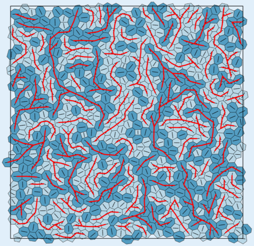
$$(\Lambda, \Gamma) = (-0.01, 0.15)$$

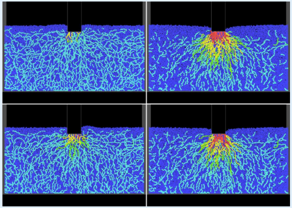
UNIVERSITY OF CAMBRIDGE

Heterogeneity of Stress

$$U_\alpha = \frac{1}{2}(A_\alpha - 1)^2 + \frac{\Gamma}{2}(L_\alpha - L_0)^2$$



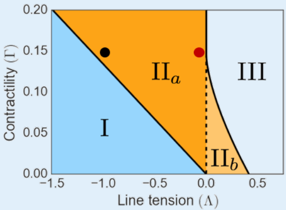


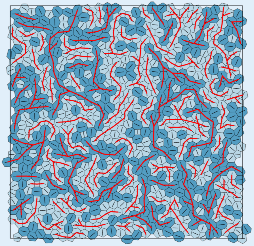


$$(\Lambda, \Gamma) = (-0.01, 0.15)$$

Heterogeneity of Stress

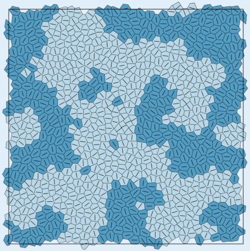
$$U_\alpha = \frac{1}{2}(A_\alpha - 1)^2 + \frac{\Gamma}{2}(L_\alpha - L_0)^2$$





$(\Lambda, \Gamma) = (-0.01, 0.15)$

Lengthscales diverge

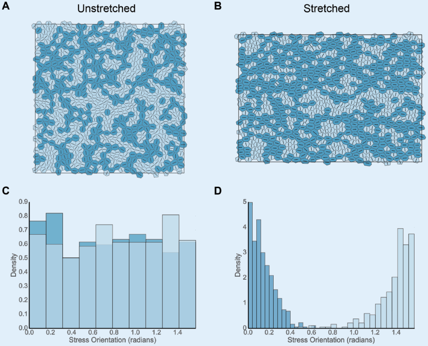


$(\Lambda, \Gamma) = (-0.1, 0.15)$

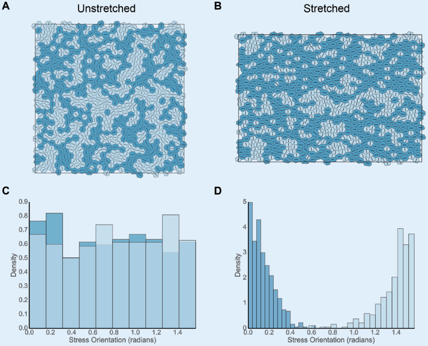
Deformation Promotes Organisation

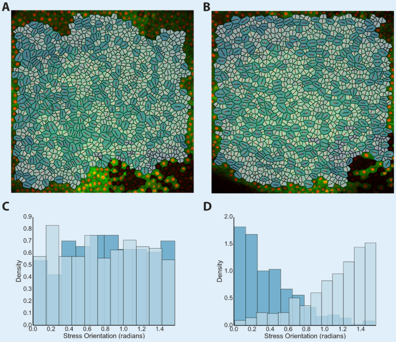
Play

Small-on-Large Deformations Reveal Anisotropic Elasticity



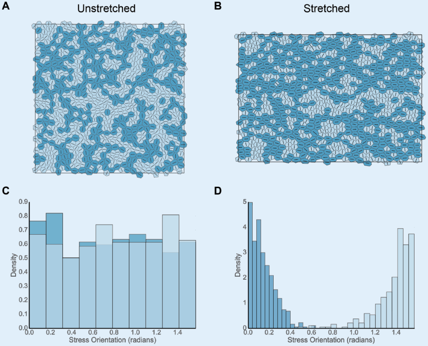
Small-on-Large Deformations Reveal Anisotropic Elasticity

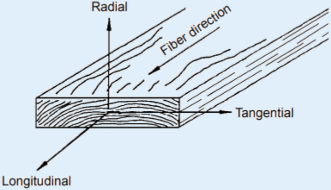




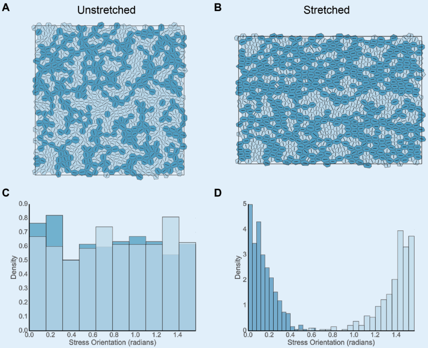
UNIVERSITY OF CAMBRIDGE

Small-on-Large Deformations Reveal Anisotropic Elasticity

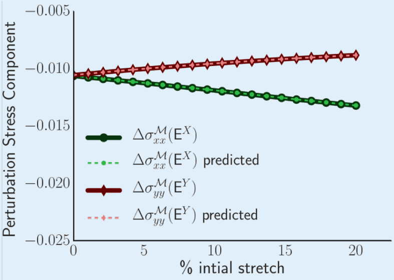




Small-on-Large Deformations Reveal Anisotropic Elasticity



Apply strain in x: E^x . . . and in y: E^y



Small-on-Large Deformations Reveal Anisotropic Elasticity

- Take pre-stressed base state, $\boldsymbol{\sigma}^{\mathcal{M}}$
- Impose homogenous strain, E
- Position vectors transform as

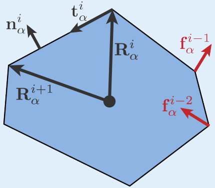
$$\mathbf{R}_\alpha^i \rightarrow \mathbf{R}_\alpha^i + \mathsf{E} \cdot \mathbf{R}_\alpha^i \qquad (1)$$

- To linear order,

$$\boldsymbol{\sigma}^{\mathcal{M}} \rightarrow \boldsymbol{\sigma}^{\mathcal{M}} + \Delta\boldsymbol{\sigma}^{\mathcal{M}}$$

Expand stress,

$$\boldsymbol{\sigma}^{\mathcal{M}}(\{\mathbf{R}_\alpha^i\}) \rightarrow \boldsymbol{\sigma}^{\mathcal{M}}(\{\mathbf{R}_\alpha^i + \mathsf{E} \cdot \mathbf{R}_\alpha^i\})$$



Small-on-Large Deformations Reveal Anisotropic Elasticity

- Take pre-stressed base state, $\boldsymbol{\sigma}^{\mathcal{M}}$
- Impose homogenous strain, E
- Position vectors transform as

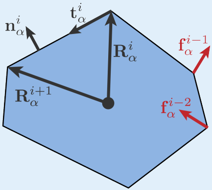
$$\mathbf{R}_\alpha^i \rightarrow \mathbf{R}_\alpha^i + \mathsf{E} \cdot \mathbf{R}_\alpha^i \tag{1}$$

- To linear order,

$$\boldsymbol{\sigma}^{\mathcal{M}} \rightarrow \boldsymbol{\sigma}^{\mathcal{M}} + \Delta\boldsymbol{\sigma}^{\mathcal{M}}$$

Expand stress,

$$\boldsymbol{\sigma}^{\mathcal{M}}(\{\mathbf{R}_\alpha^i\}) \rightarrow \boldsymbol{\sigma}^{\mathcal{M}}(\{\mathbf{R}_\alpha^i + \mathsf{E} \cdot \mathbf{R}_\alpha^i\})$$



Tangents: $\mathbf{t} = \mathbf{R}^{i+1} - \mathbf{R}^i$, and using (1):

$$\mathbf{t}^i + \Delta\mathbf{t}^i = \mathbf{R}^{i+1} - \mathbf{R}^i + \mathsf{E} \cdot (\mathbf{R}^{i+1} - \mathbf{R}^i),$$

such that $\Delta\mathbf{t}^i = \mathsf{E} \cdot \mathbf{t}^i$

Then lengths: $l^i = (\mathbf{t}^i \cdot \mathbf{t}^i)^{\frac{1}{2}} \ldots$

UNIVERSITY OF CAMBRIDGE

Small-on-Large Deformations Reveal Anisotropic Elasticity

- Take pre-stressed base state, $\boldsymbol{\sigma}^{\mathcal{M}}$
- Impose homogenous strain, E
- Position vectors transform as

$$\mathbf{R}_\alpha^i \to \mathbf{R}_\alpha^i + \mathsf{E} \cdot \mathbf{R}_\alpha^i \tag{1}$$

- To linear order,

$$\boldsymbol{\sigma}^{\mathcal{M}} \to \boldsymbol{\sigma}^{\mathcal{M}} + \Delta\boldsymbol{\sigma}^{\mathcal{M}}$$

Expand stress,

$$\boldsymbol{\sigma}^{\mathcal{M}}(\{\mathbf{R}_\alpha^i\}) \to \boldsymbol{\sigma}^{\mathcal{M}}(\{\mathbf{R}_\alpha^i + \mathsf{E} \cdot \mathbf{R}_\alpha^i\})$$

Hooke's Law:

$$\Delta\boldsymbol{\sigma}^{\mathcal{M}} = \mathsf{C} : \mathsf{E}$$

giving the stiffness tensor

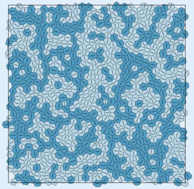
$$\mathsf{C} = \frac{1}{A^{\mathcal{M}}} \sum_{\alpha}^{N_c} [A_\alpha^2 \mathsf{I} \otimes \mathsf{I} + \Gamma L_\alpha^2 \mathsf{Q}_\alpha \otimes \mathsf{Q}_\alpha + L_\alpha T_\alpha (\mathsf{B}_\alpha - \mathsf{Q}_\alpha \otimes \mathsf{I})]$$

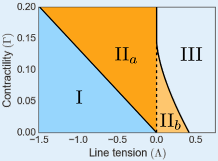
where

$$\mathsf{B}_\alpha : \mathsf{E} = \frac{1}{L_\alpha} \sum_{i=0}^{N_v - 1} l_\alpha^i \left[\hat{\mathbf{t}}_\alpha^i \otimes (\mathsf{E} \cdot \hat{\mathbf{t}}_\alpha^i) = (\mathsf{E} \cdot \hat{\mathbf{t}}_\alpha^i) \otimes \hat{\mathbf{t}}_\alpha^i - \hat{\mathbf{t}}_\alpha^i \otimes \hat{\mathbf{t}}_\alpha^i (\hat{\mathbf{t}}_\alpha^i \cdot \mathsf{E} \cdot \hat{\mathbf{t}}_\alpha^i)\right]$$

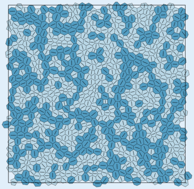
UNIVERSITY OF CAMBRIDGE

Elastic Moduli for Isotropic Tissues



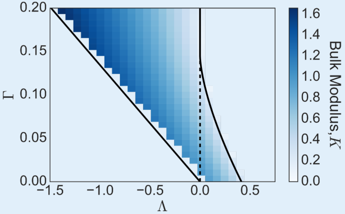


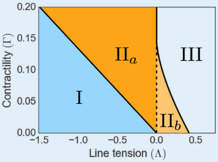
Elastic Moduli for Isotropic Tissues



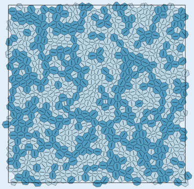
Bulk modulus

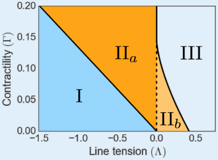
$$K = \frac{1}{2A^{\mathcal{M}}} \sum_{\alpha=1}^{N_c} 2A_\alpha^2 + \frac{1}{2}\Gamma L_0 L_\alpha$$





Elastic Moduli for Isotropic Tissues



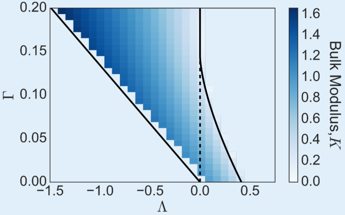


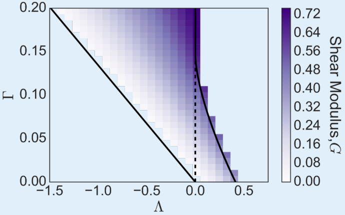
Bulk modulus

$$K = \frac{1}{2A^{\mathcal{M}}} \sum_{\alpha=1}^{N_c} 2A_\alpha^2 + \tfrac{1}{2}\Gamma L_0 L_\alpha$$

Shear modulus

$$G = \frac{3}{8A^{\mathcal{M}}} \sum_{\alpha=1}^{N_c} \Gamma L_\alpha (L_\alpha - L_0)$$





Murisic et al. (2015)

Understanding Forces in Morphogenesis

The Research Group

Sarah Woolner

MANCHESTER 1824
The University of Manchester

UNIVERSITY OF CAMBRIDGE

Oliver Jensen

MANCHESTER 1824
The University of Manchester