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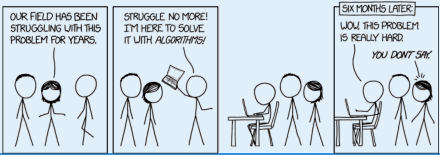


Mechanical Characterisation of Disordered and Anisotropic Cellular Monolayers

Inferring tissue mechanics from geometry

Alexander Nestor-Bergmann

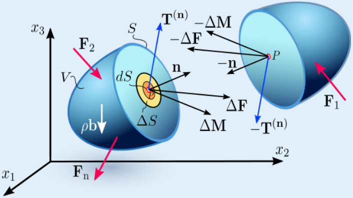
University of Cambridge

BAMC, 2019

Understanding Forces in Morphogenesis

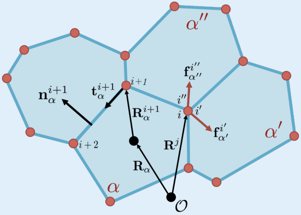
Modelling Approaches

Continuum mechanics



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

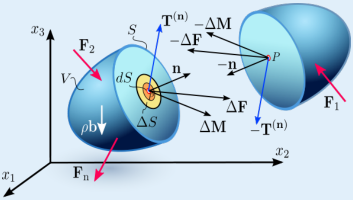
Discrete (vertex models)



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

Modelling Approaches

Continuum mechanics



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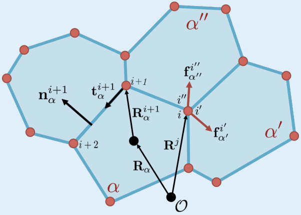

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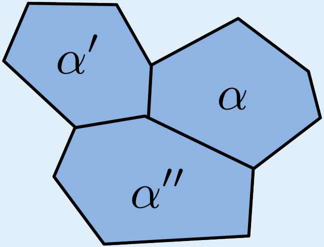
Easy access to complex behaviours e.g. remodelling.

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

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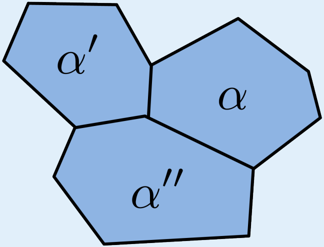


Nondimensionalise:

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

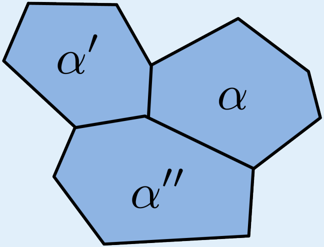
$$L_\alpha = \frac{\tilde{L}_\alpha}{\sqrt{\tilde{A}_0}}$$

$$\ldots$$

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

The Mechanical Energy of a Cell

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



A_α = Area of cell α

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

Λ = Line tension of cell edge

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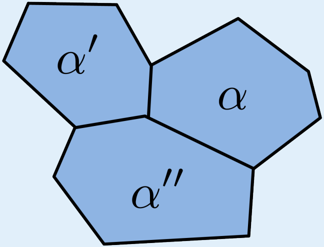

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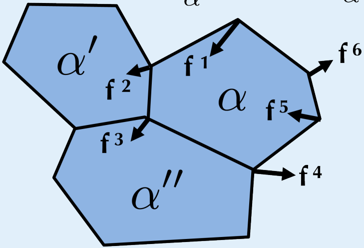

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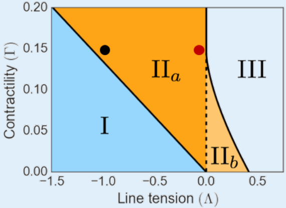
Parameter Selection



Play

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

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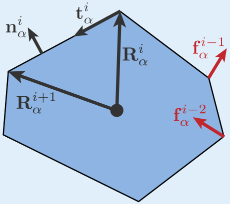
From Force to Stress

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



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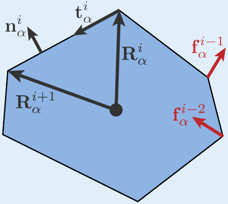

Define pressure and tension

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

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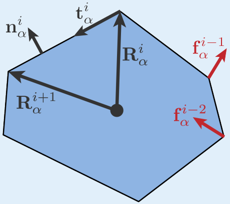

Elastic force

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

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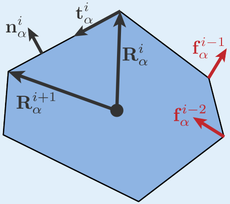

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Stress satisfies

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

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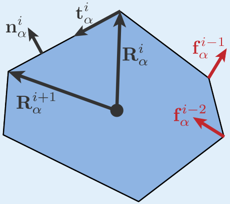

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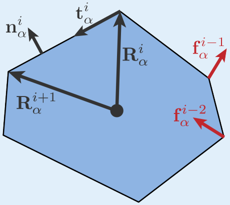

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$$\int_{\mathcal{A}} \boldsymbol{\sigma}\, \mathrm{d}A = \int_{\mathcal{A}} \nabla\cdot\left(\mathbf{R}\otimes\boldsymbol{\sigma}\right) \mathrm{d}A = \oint_{\mathcal{S}} \mathbf{R}\otimes\boldsymbol{\sigma}\cdot\mathbf{n}\, \mathrm{d}S$$

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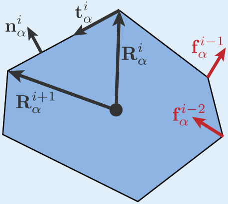

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Motivating the definition (Batchelor, 1970)

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

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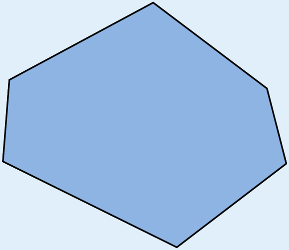
The Cell-Level Stress Tensor

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



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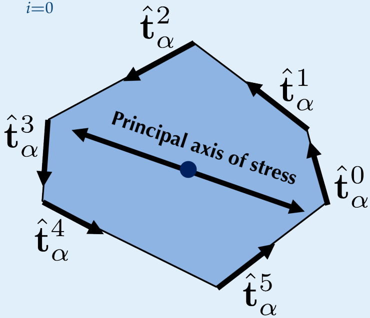
The Cell-Level Stress Tensor

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

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

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



Deviatoric stress

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

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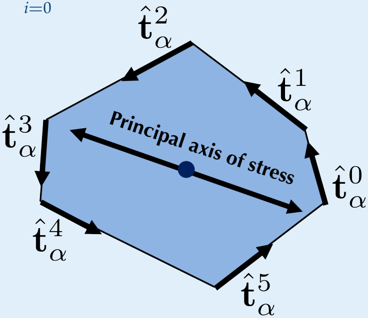

Deviatoric stress

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

Isotropic stress

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

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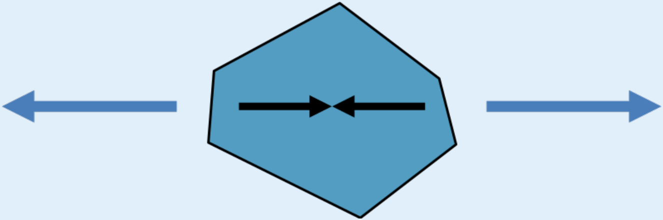
The Cell-Level Stress Tensor

- Cell principally under tension

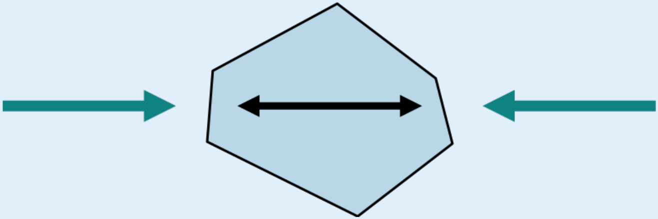
$$P_\alpha^{\text{eff}} > 0$$



The Cell-Level Stress Tensor

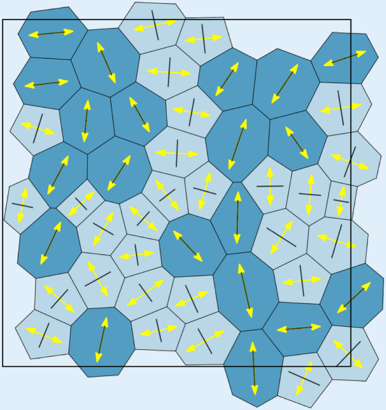
- Cell principally under compression

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



Cell-Level Stress and Shape Align

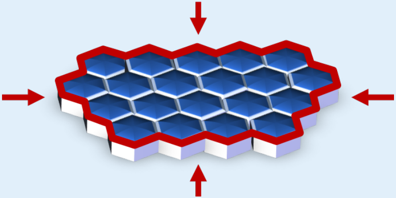
The principal axes of stress and shape align exactly.



The stress and shape tensors commute and so share eigenbases.

Local to Global Stress

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



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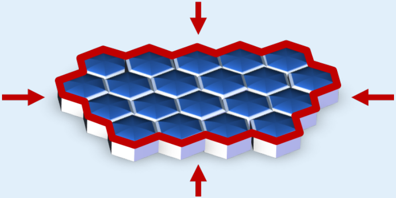
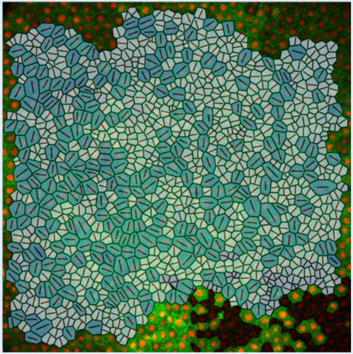
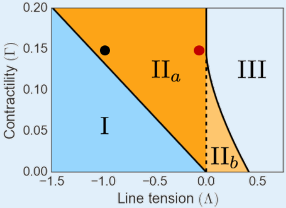
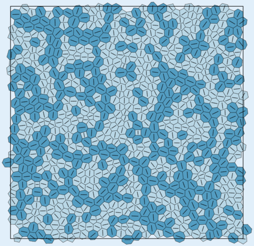




Heterogeneity of Stress

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





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

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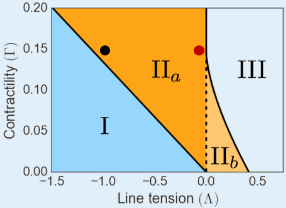

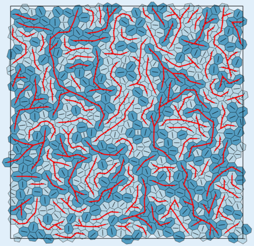

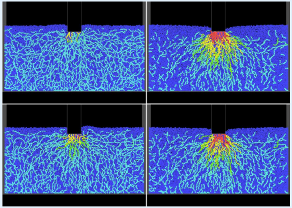

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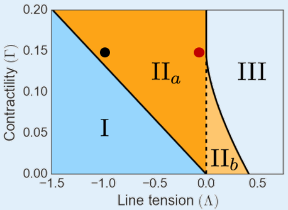
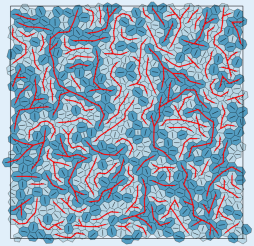
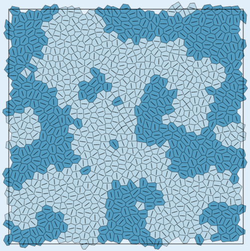




$(\Lambda, \Gamma) = (-0.01, 0.15)$

Lengthscales diverge

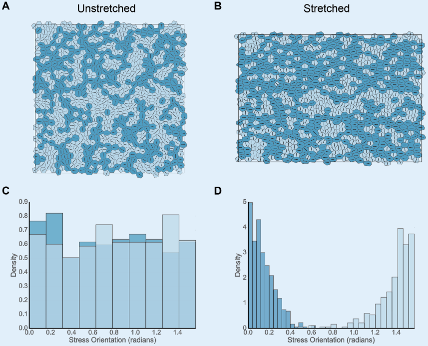


$(\Lambda, \Gamma) = (-0.1, 0.15)$

Deformation Promotes Organisation

Play

Small-on-Large Deformations Reveal Anisotropic Elasticity



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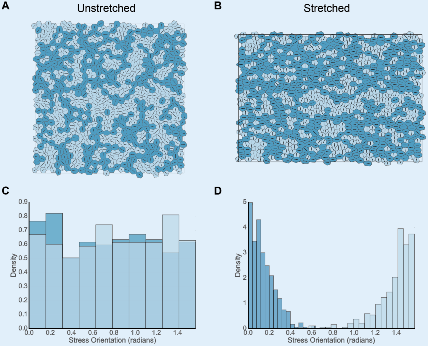

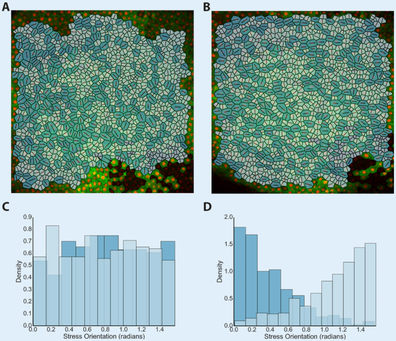

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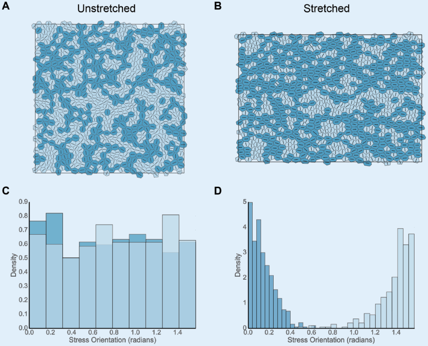

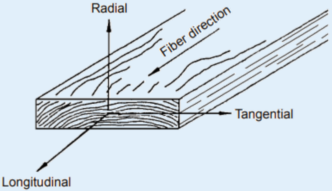

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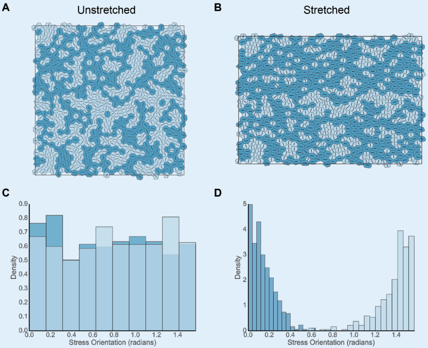
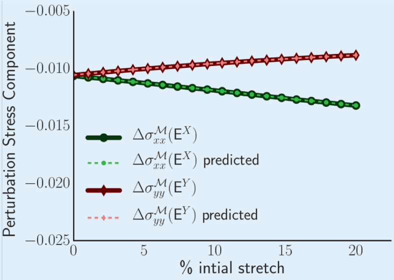
Small-on-Large Deformations Reveal Anisotropic Elasticity



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

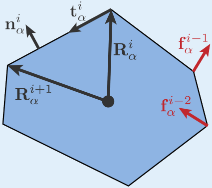
$$\mathbf{R}_{\alpha}^{i} \to \mathbf{R}_{\alpha}^{i} + \mathsf{E} \cdot \mathbf{R}_{\alpha}^{i} \tag{1}$$

- To linear order,

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

Expand stress,

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



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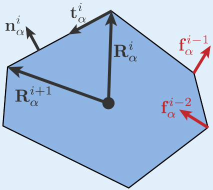
Expand stress,

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



Tangents: $\mathbf{t}^i = \mathbf{R}^{i+1} - \mathbf{R}^i$, 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: $l^i = (\mathbf{t}^i \cdot \mathbf{t}^i)^{\frac{1}{2}} \ldots$

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Small-on-Large Deformations Reveal Anisotropic Elasticity

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

$$\mathbf{R}^i_\alpha \to \mathbf{R}^i_\alpha + \mathsf{E}\cdot\mathbf{R}^i_\alpha \qquad (1)$$

- To linear order,

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

Expand stress,

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

Hooke's Law:

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

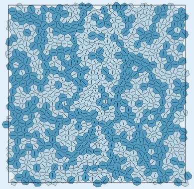
giving the stiffness tensor

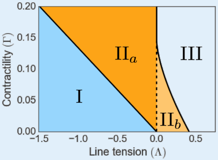
$$\mathsf{C} = \frac{1}{A^{\mathcal{M}}}\sum_{\alpha}^{N_c}\left[A^2_\alpha \mathsf{I}\otimes\mathsf{I} + \Gamma L^2_\alpha \mathsf{Q}_\alpha\otimes\mathsf{Q}_\alpha + L_\alpha T_\alpha(\mathsf{B}_\alpha - \mathsf{Q}_\alpha\otimes\mathsf{I})\right]$$

where

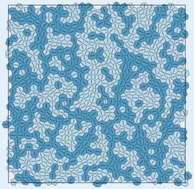
$$\mathsf{B}_\alpha : \mathsf{E} = \frac{1}{L_\alpha}\sum_{i=0}^{N_v-1} l^i_\alpha\left[\hat{\mathbf{t}}^i_\alpha\otimes(\mathsf{E}\cdot\hat{\mathbf{t}}^i_\alpha) = (\mathsf{E}\cdot\hat{\mathbf{t}}^i_\alpha)\otimes\hat{\mathbf{t}}^i_\alpha - \hat{\mathbf{t}}^i_\alpha\otimes\hat{\mathbf{t}}^i_\alpha(\hat{\mathbf{t}}^i_\alpha\cdot\mathsf{E}\cdot\hat{\mathbf{t}}^i_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

Elastic Moduli for Isotropic Tissues



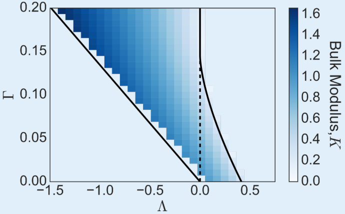


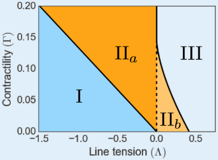
Elastic Moduli for Isotropic Tissues



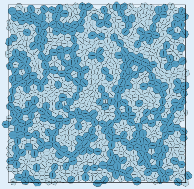
Bulk modulus

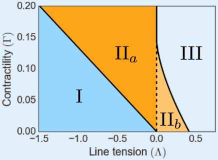
$$K = \frac{1}{2A^{\mathcal{M}}} \sum_{\alpha=1}^{N_c} 2A_\alpha^2 + \tfrac{1}{2}\Gamma L_0 L_\alpha$$





Elastic Moduli for Isotropic Tissues



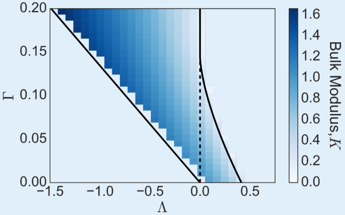


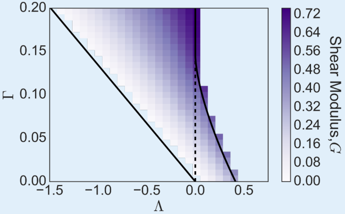
Bulk modulus

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

Shear modulus

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





Understanding Forces in Morphogenesis

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