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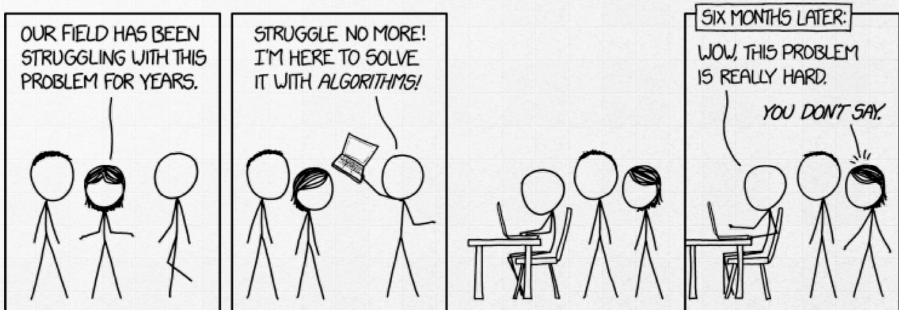
Shape, Stress and Division in Epithelia

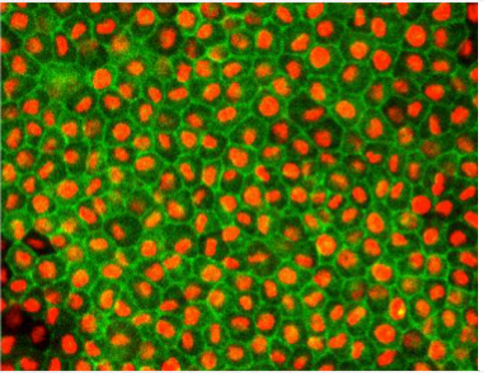
How does the mechanical environment affect cell division?
What is the relationship between stress and shape?

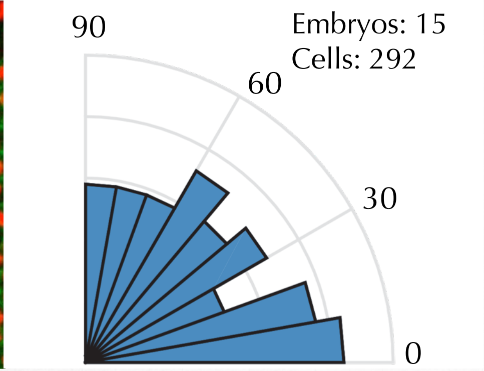
Alexander Nestor-Bergmann
Mathemologist

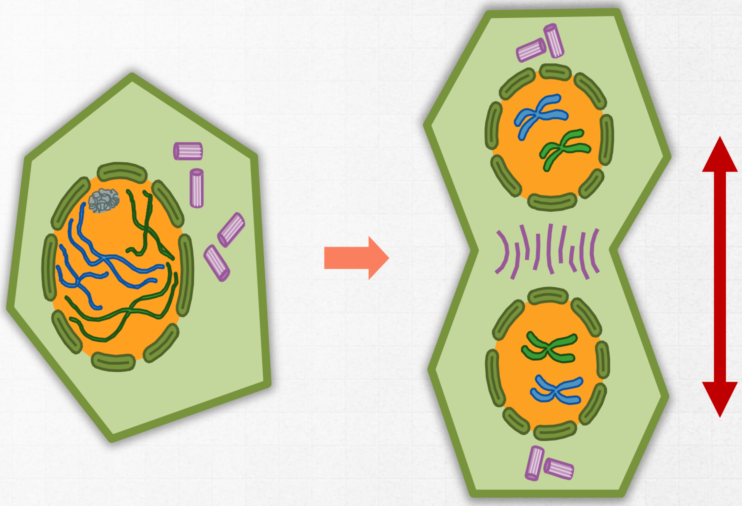


Motivation

PRELIMINARY OBSERVATIONS







Control Cells

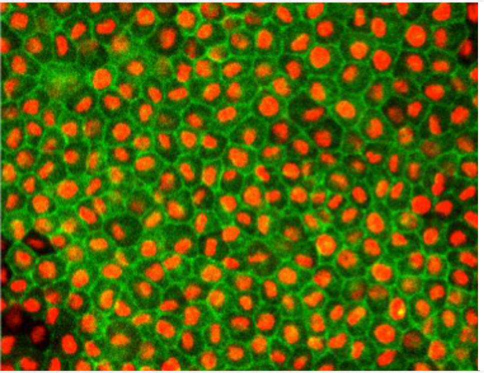
Randomly oriented, on average.

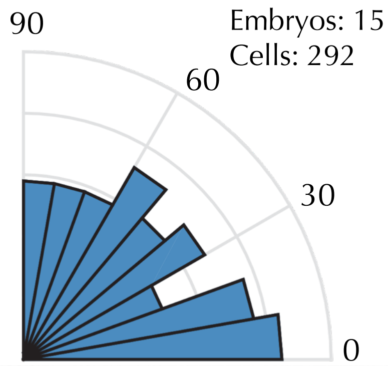
Division Angles

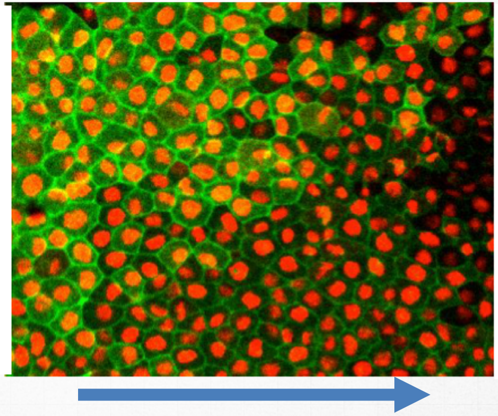
Division angles are uniformly distributed.

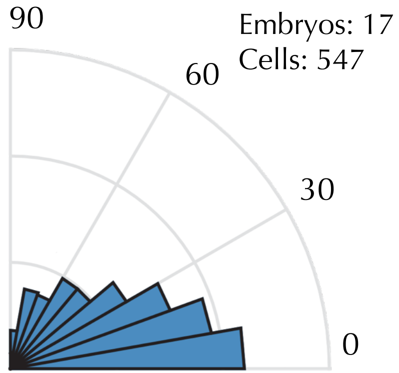
Some results

PRELIMINARY OBSERVATIONS









Control Cells

Randomly oriented, on average.

Division Angles

Division angles are uniformly distributed.

Stretched Cells

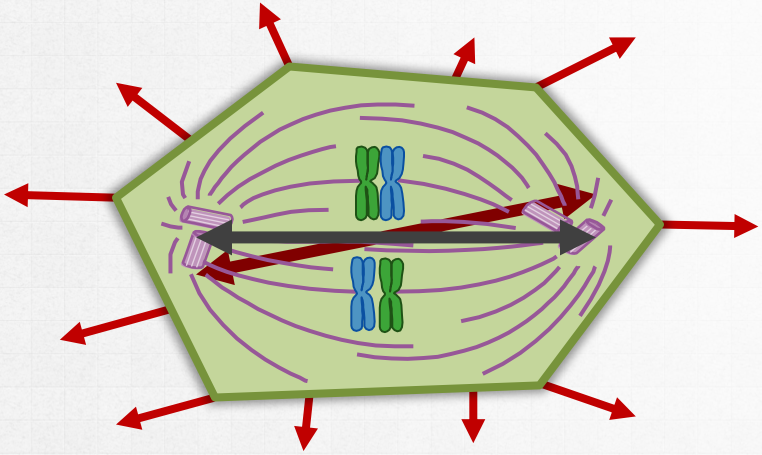
Oriented in direction of stretch.

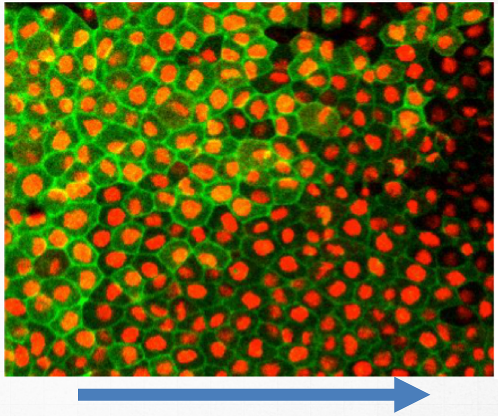
Division Angles

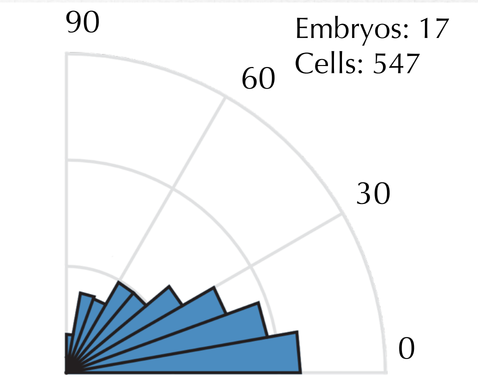
Division angles align with stretch.

Some results

PRELIMINARY OBSERVATIONS







Stretched Cells

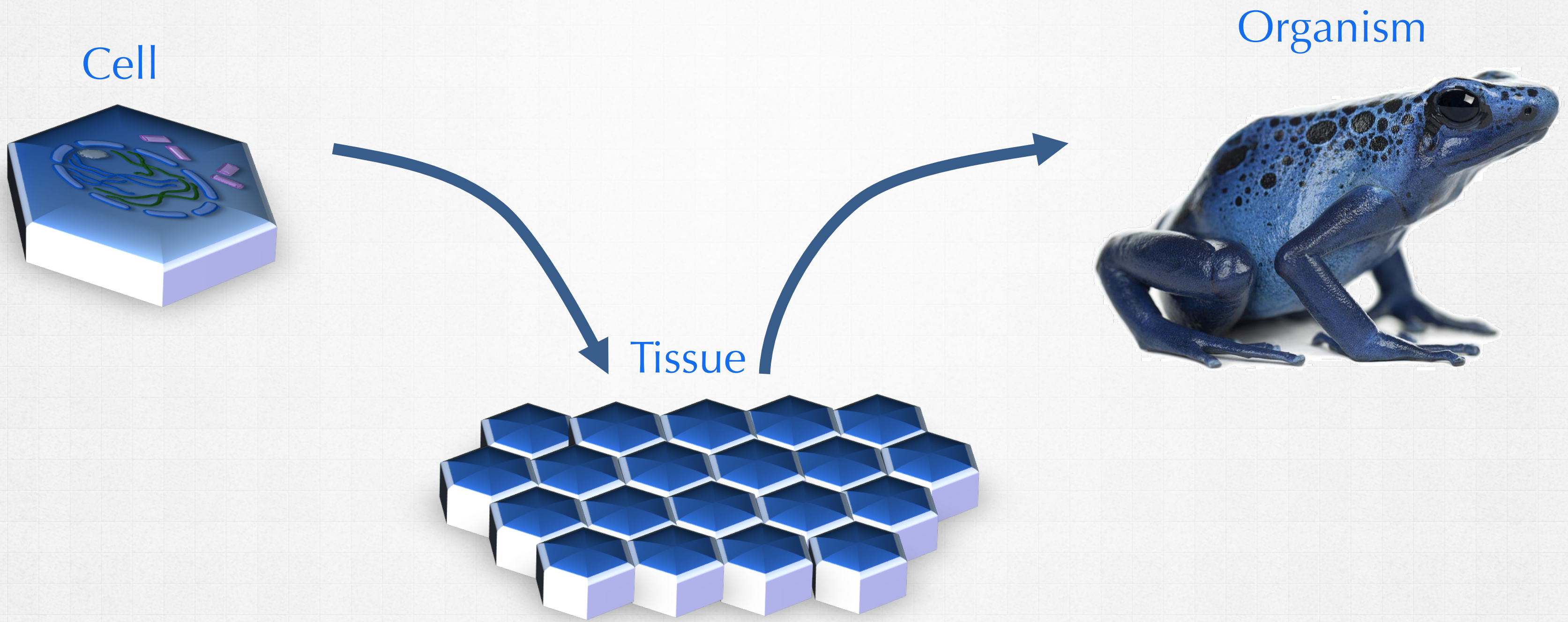
Oriented in direction of stretch.

Division Angles

Division angles align with stretch.

A Scaly Problem

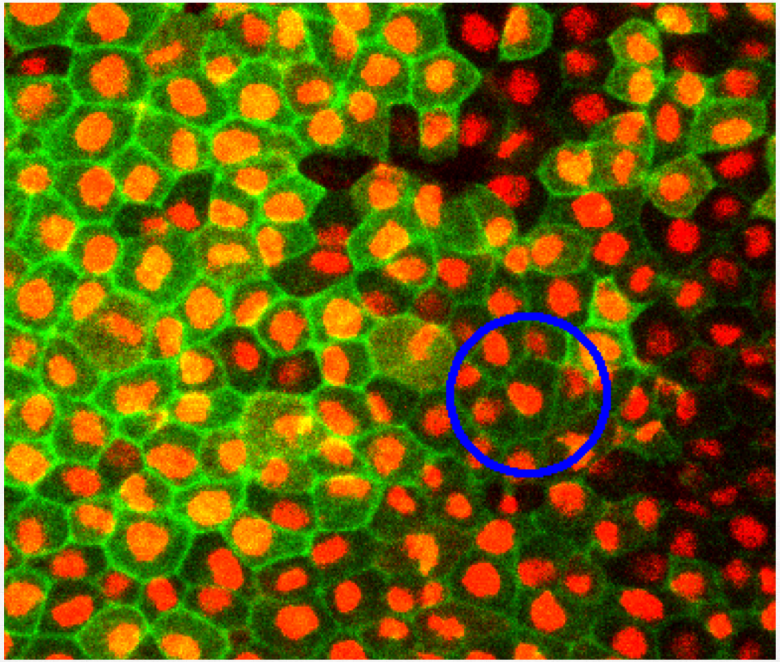
FORCES AT MULTIPLE SCALES



(thinkreptiles.com)

A Scaly Problem

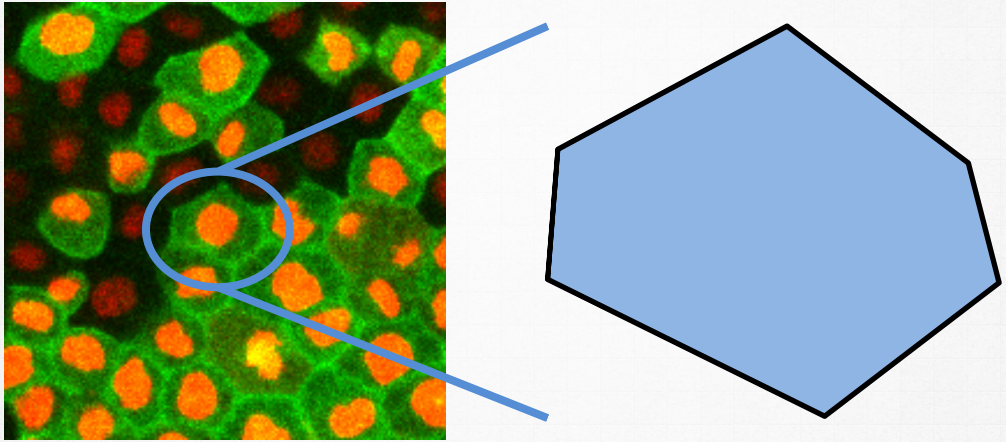
GLOBAL VS LOCAL STRESS



Stretched

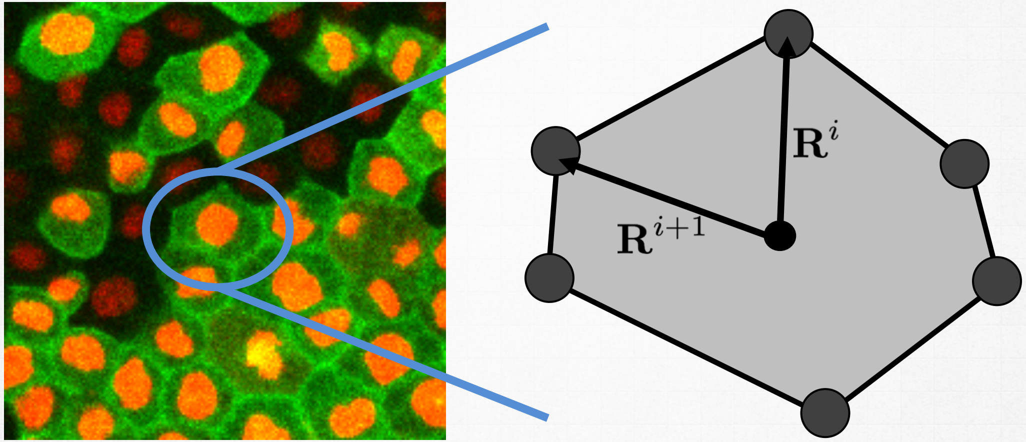
Getting into the mathematics

CHARACTERISING CELL SHAPE



Getting into the mathematics

CHARACTERISING CELL SHAPE



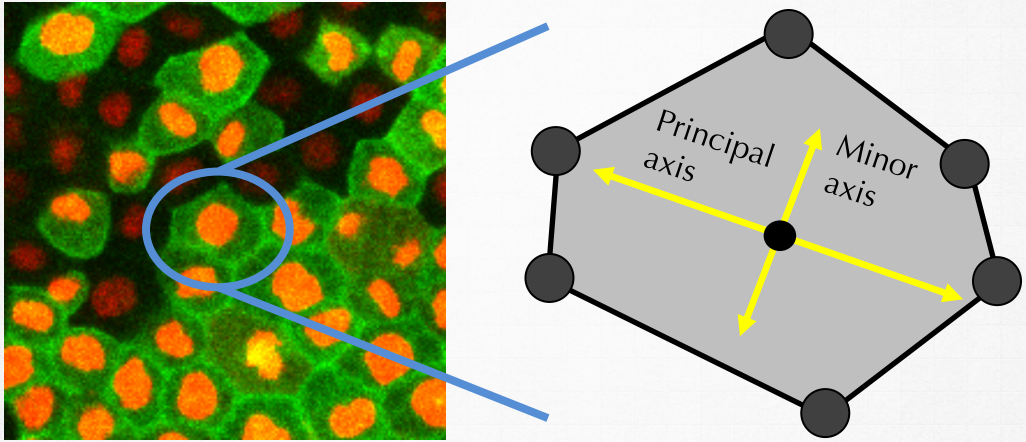
Shape tensor:

$$\mathsf{S} = \frac{1}{Z}\sum_{i=0}^{Z-1} \mathbf{R}^i \otimes \mathbf{R}^i \qquad (Z = \text{n}^{\underline{\text{o}}} \text{ vertices})$$

(Bosveld et al.; Bellaiche)

Getting into the mathematics

CHARACTERISING CELL SHAPE



Circularity = minor axis/major axis

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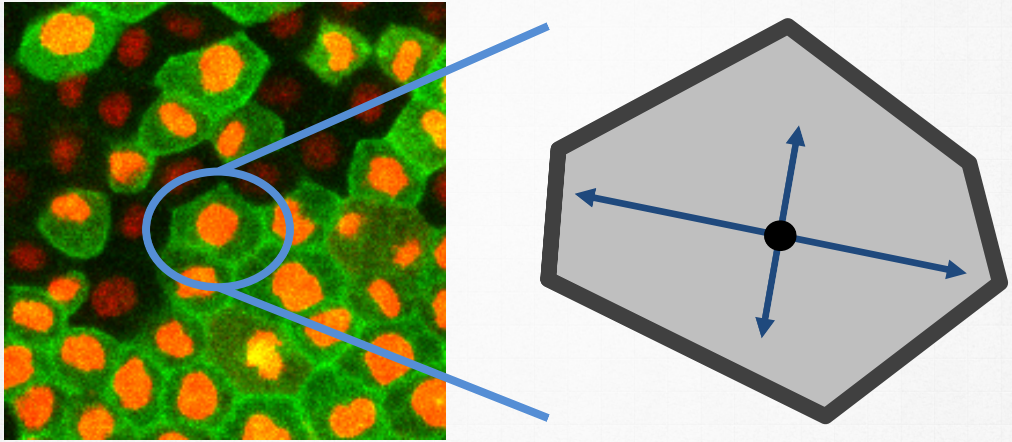
Getting into the mathematics

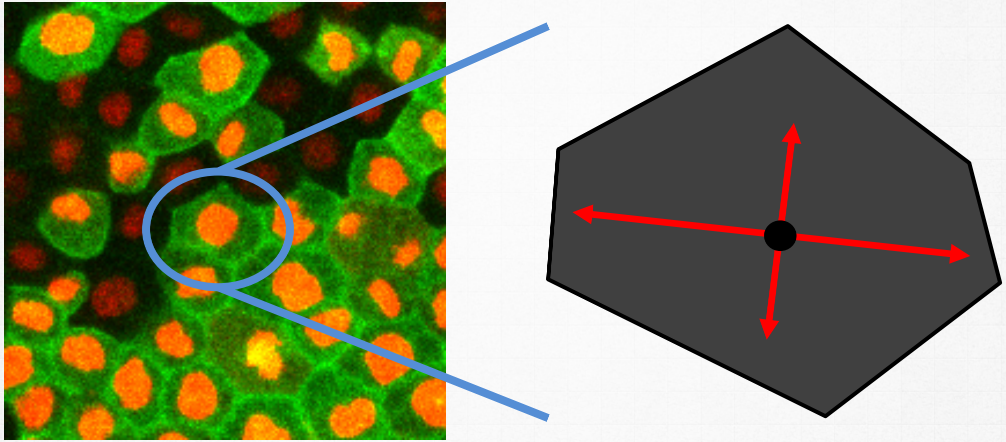
CHARACTERISING CELL SHAPE



Circularity = minor axis/major axis

Getting into the mathematics

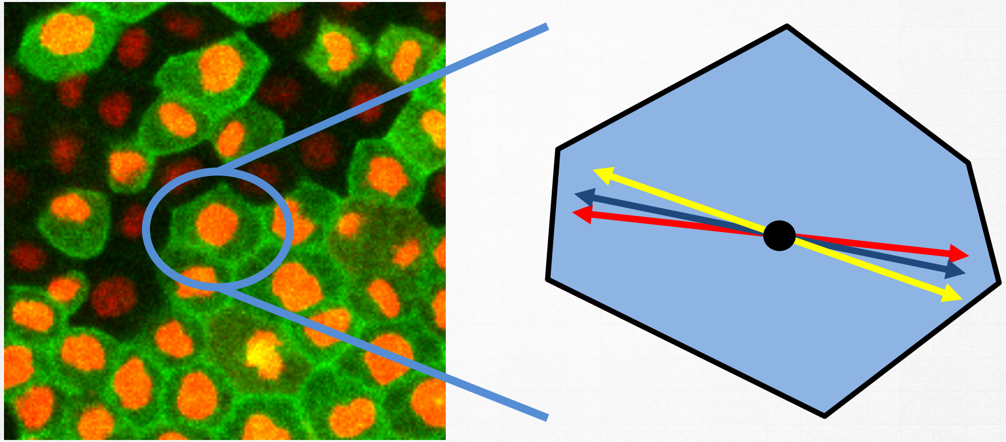
CHARACTERISING CELL SHAPE



Circularity = minor axis/major axis

Getting into the mathematics

CHARACTERISING CELL SHAPE



Circularity: C_V , C_P , C_A Orientation: θ_V , θ_P , θ_A

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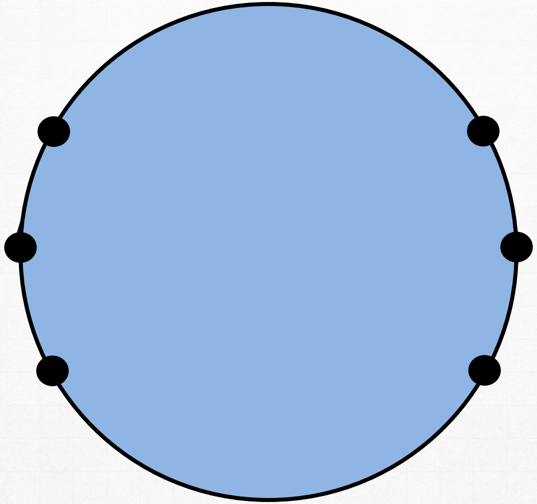
CHARACTERISING CELL SHAPE



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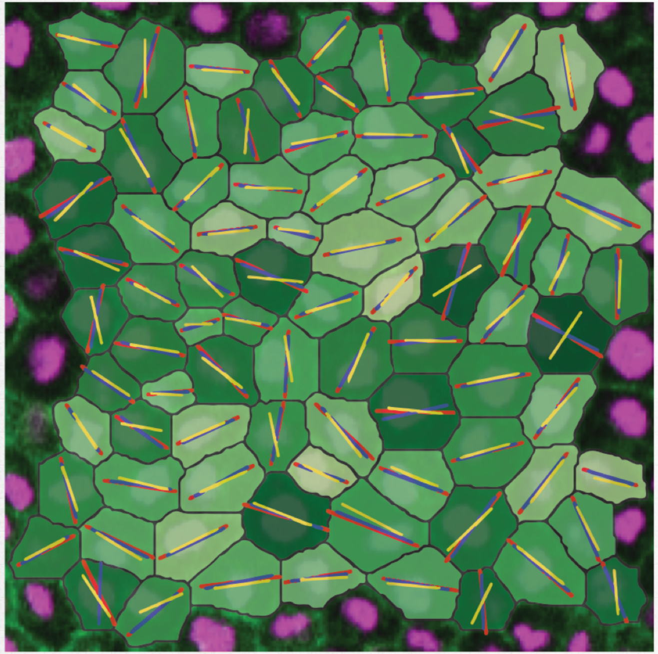
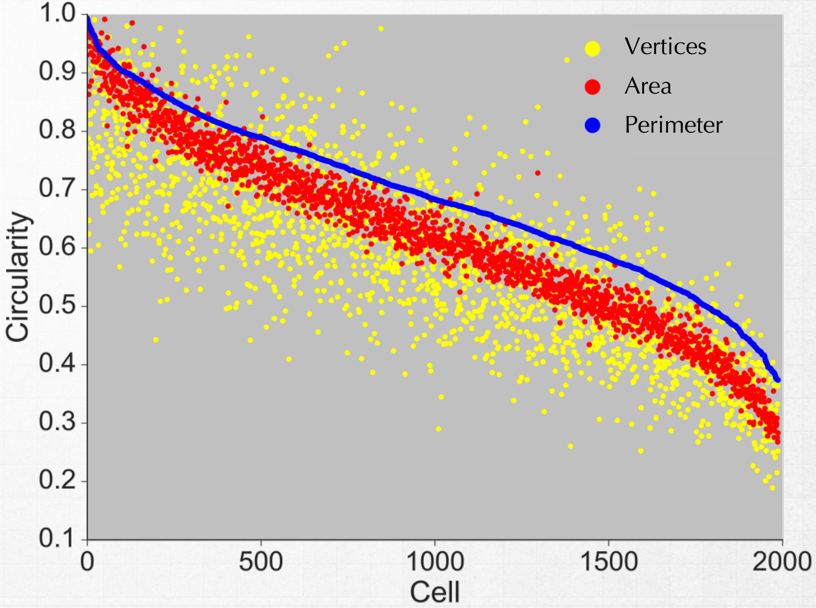
CHARACTERISING CELL SHAPE

Vertices Area Perimeter

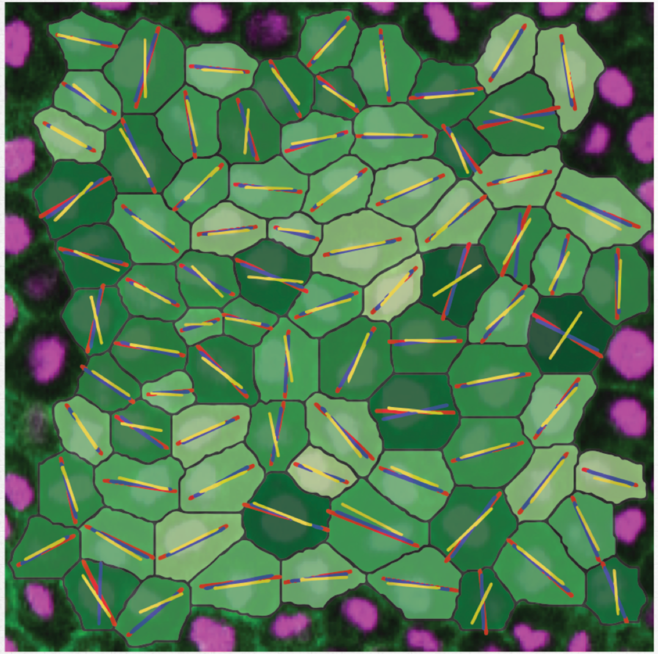


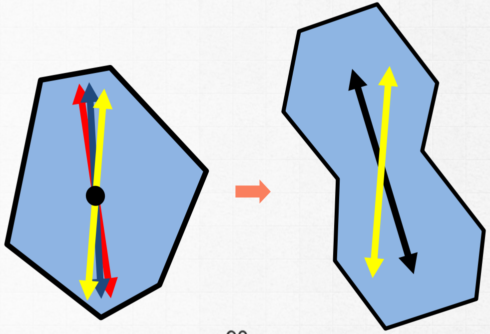


Getting into the mathematics

CHARACTERISING CELL SHAPE

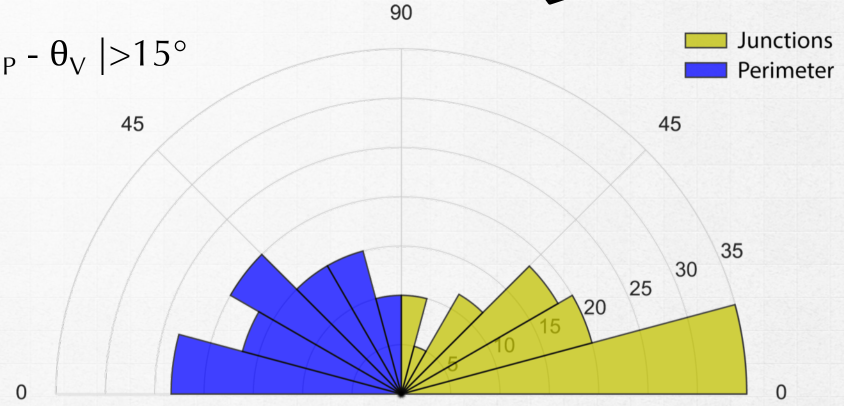
Vertices   Area   Perimeter





$|\theta_D - \theta_V|$

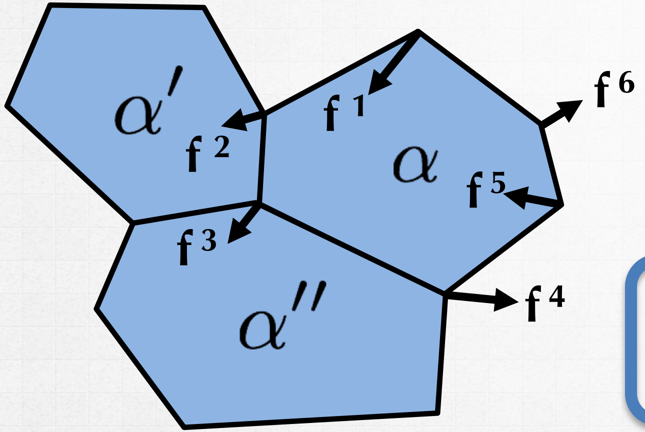
$|\theta_P - \theta_V| > 15°$



How do we model a cell?

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 of cell $\left(= -\frac{\Lambda}{2\Gamma}\right)$

Λ = Line tension of cell edge

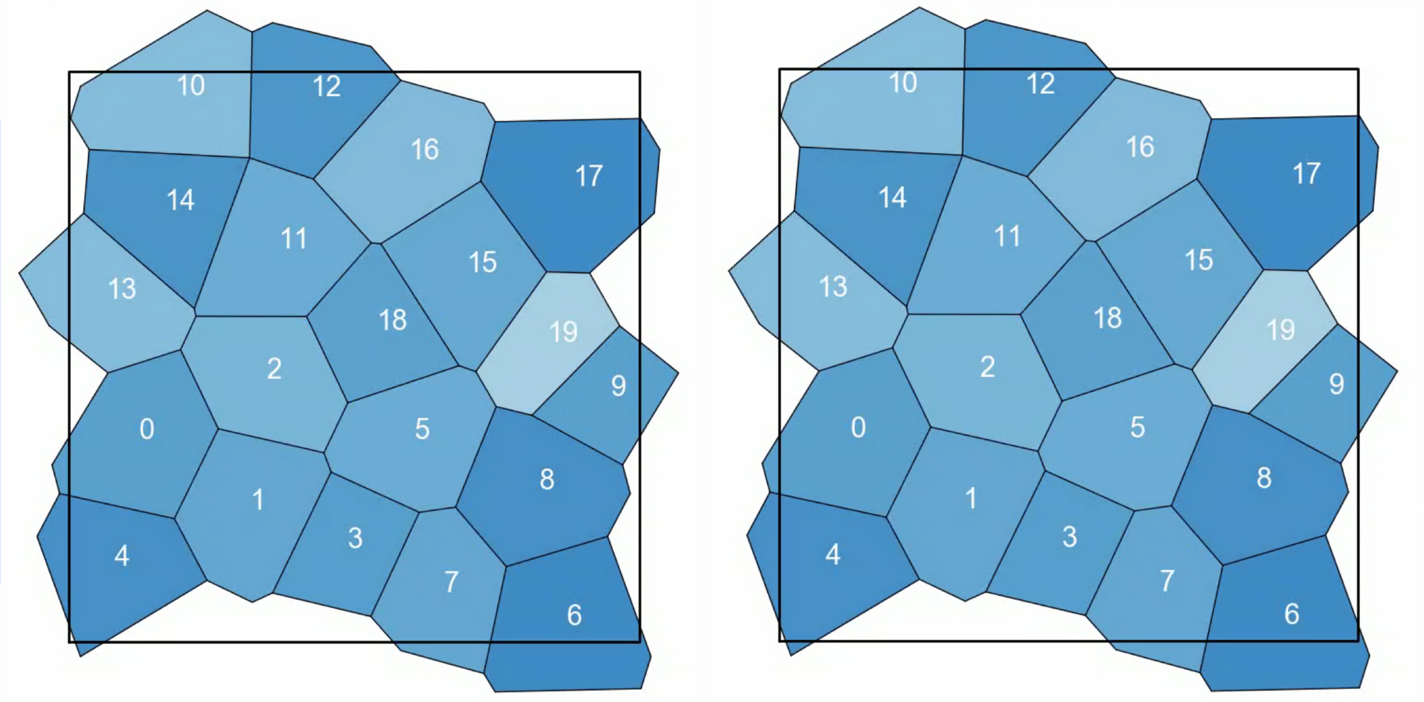
Γ = Cell contractility

Farhadifar et al. 2007

Relaxing

PARAMETER IMPORTANCE

Cell packing geometry is highly dependent on parameter selection.

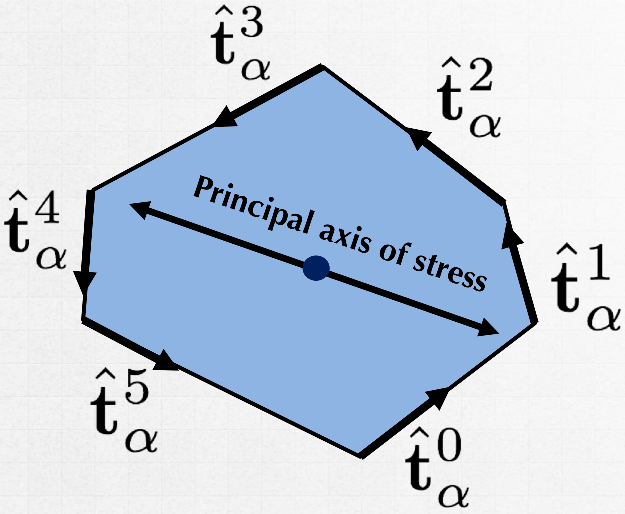


$(\Lambda, \Gamma) = (-1, 0.15)$ $(\Lambda, \Gamma) = (-0.01, 0.15)$

Coping with stress

THE CELL STRESS TENSOR

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



Deviatoric Stress

$$\mathsf{J}_\alpha = \mathsf{J}_\alpha(\mathbf{t}_\alpha^i)$$

Edge Tension

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

Effective Pressure

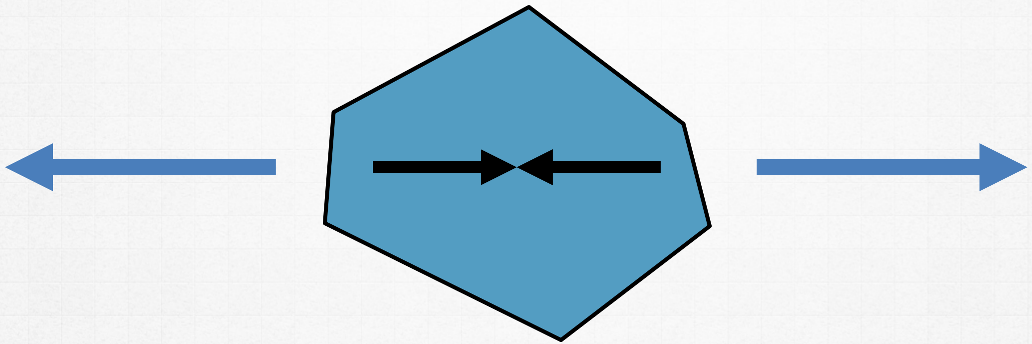
$$P_\alpha^{\text{eff}} = A_\alpha - 1 + \frac{T_\alpha L_\alpha}{2A_\alpha}$$

Coping with stress

THE CELL STRESS TENSOR

- Cells principally under tension

$$P^{\text{eff}} > 0$$

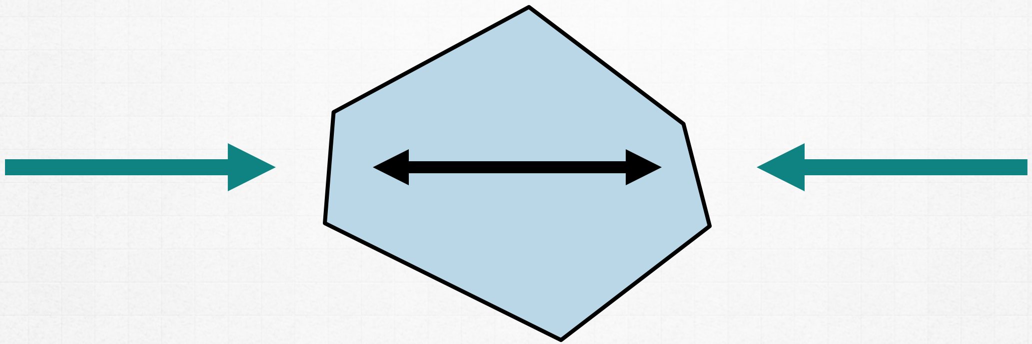


Coping with stress

THE CELL STRESS TENSOR

- Cells principally under compression

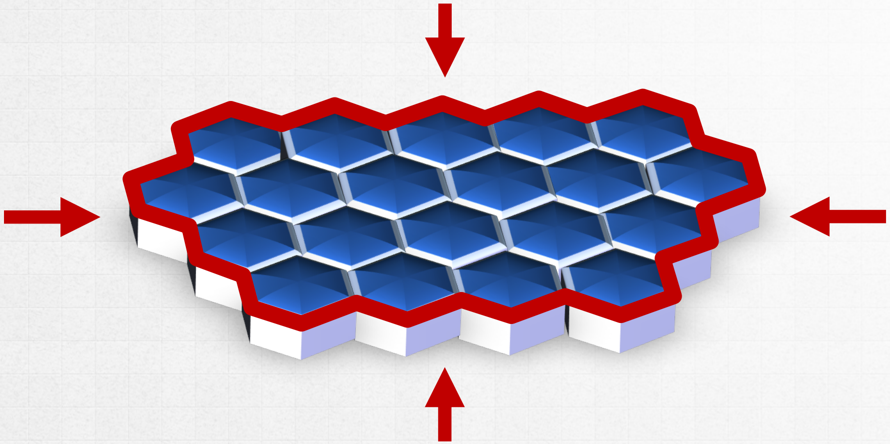
$$P^{\mathrm{eff}} < 0$$



Coping with stress

GLOBAL STRESS

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



- Bulk Modulus

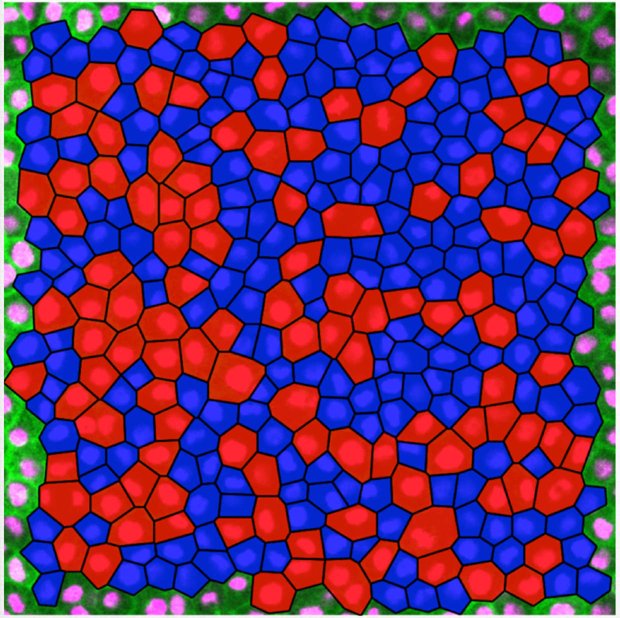
$$K = \sum_{\alpha=1}^{N_c} \frac{A_\alpha}{2A^{\mathcal{M}}} \left[2A_\alpha + \frac{\Gamma L_0 L_\alpha}{2A_\alpha} \right]$$

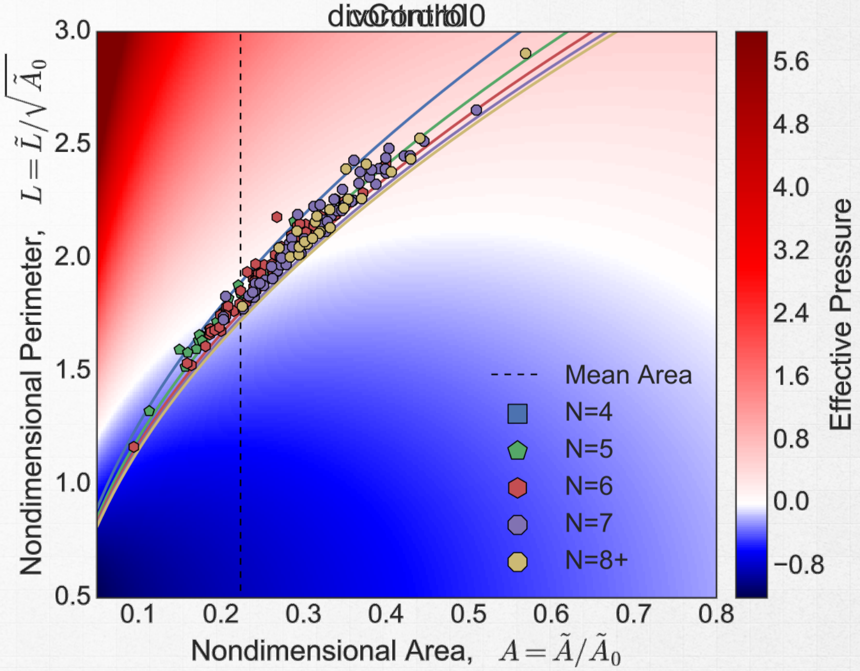
- Shear Modulus

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

Coping with stress

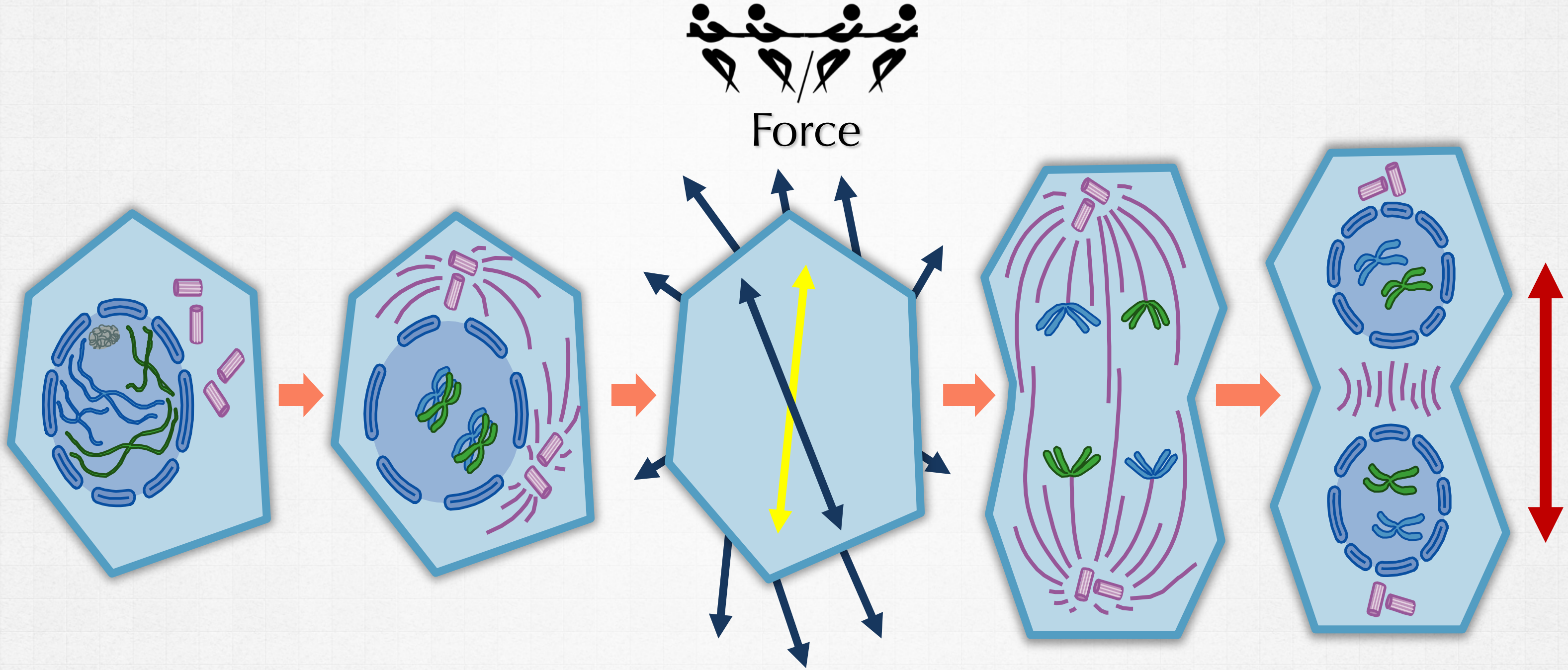
INFERRING STRESS IN EXPERIMENTS





Back to the Question!

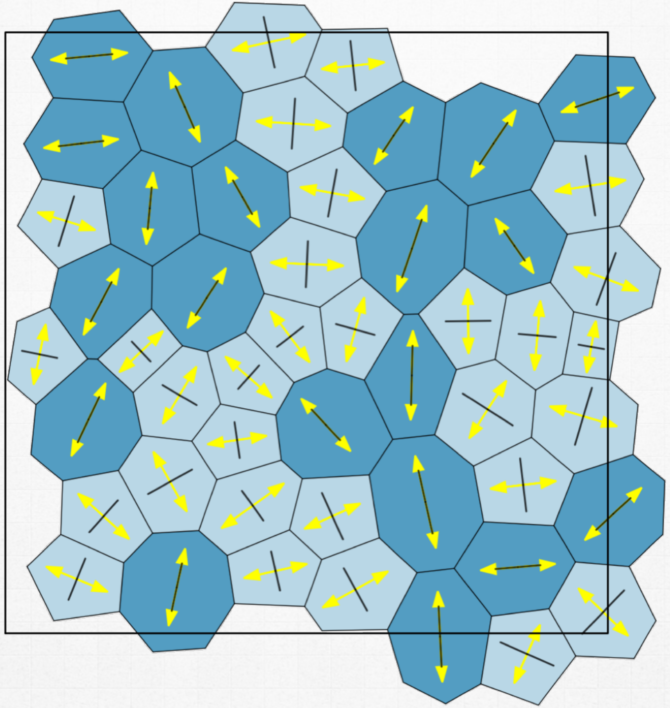
CELL DIVISION



The Result

STRESS AND SHAPE ALIGN

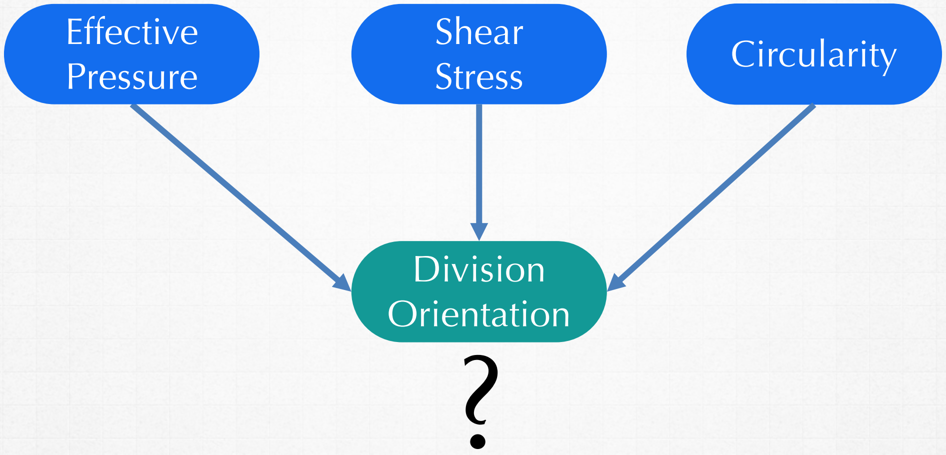
The principal axes of stress and shape align exactly



The stress and shape tensors commute, therefore they share eigenbases

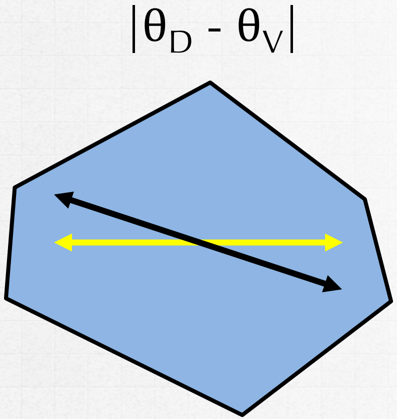
Back to the question

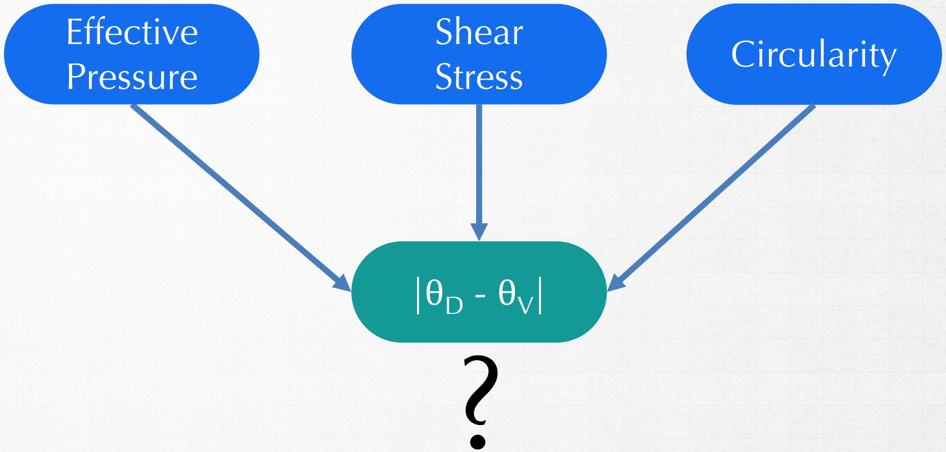
OTHER FEATURES OF STRESS/SHAPE



Stress vs shape

DIVISION MECHANISMS





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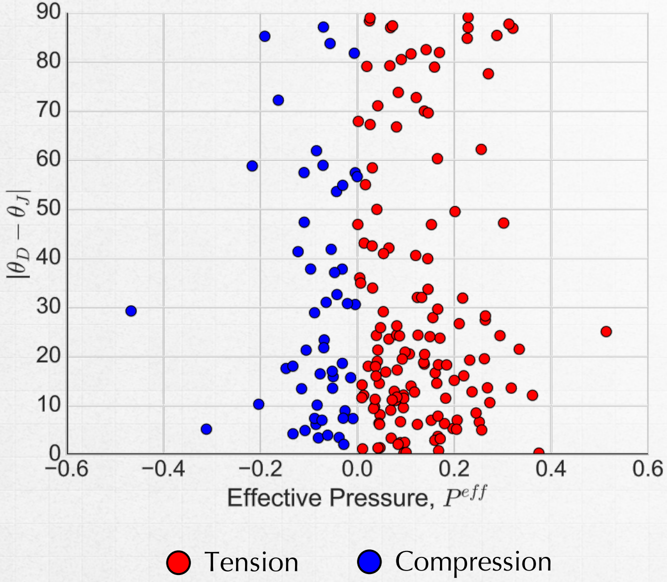
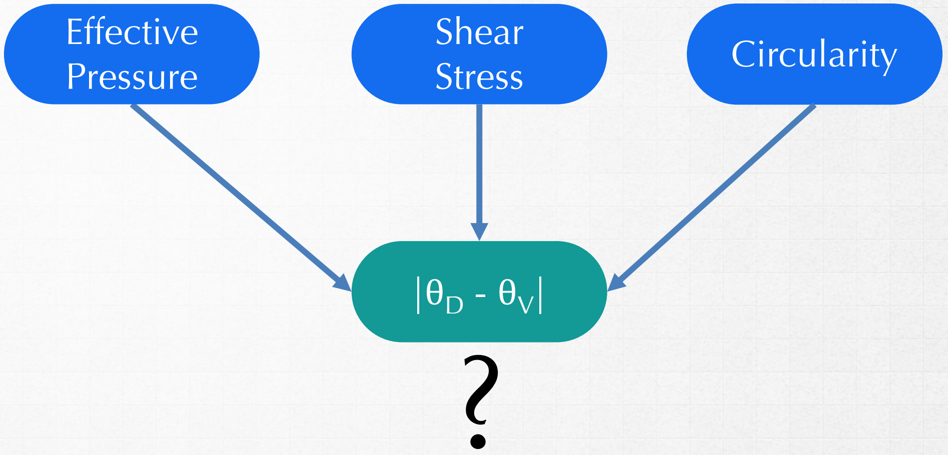
Coping with stress

DIVISION MECHANISMS





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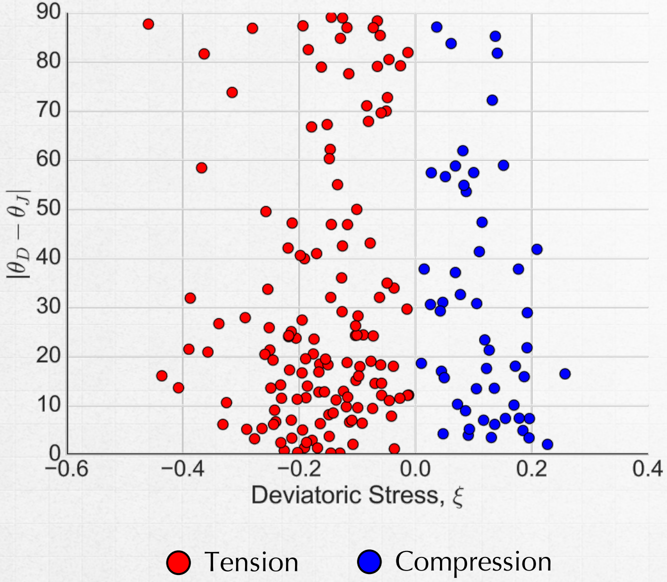
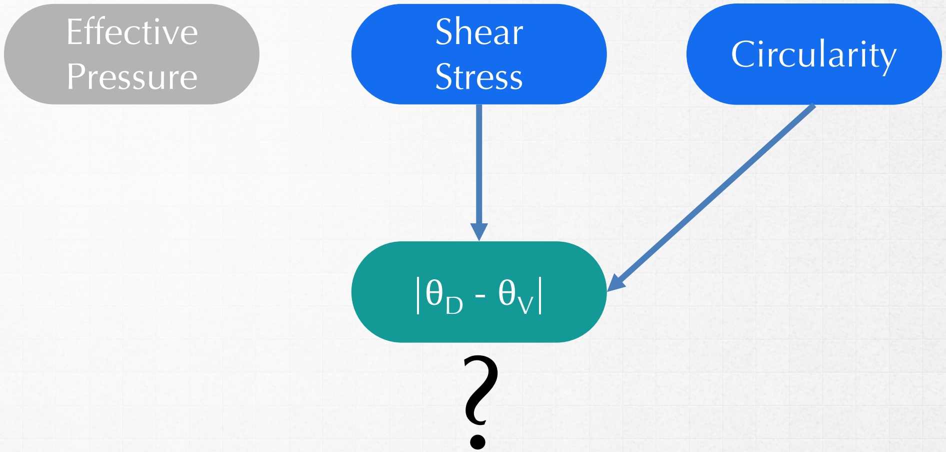
DIVISION MECHANISMS





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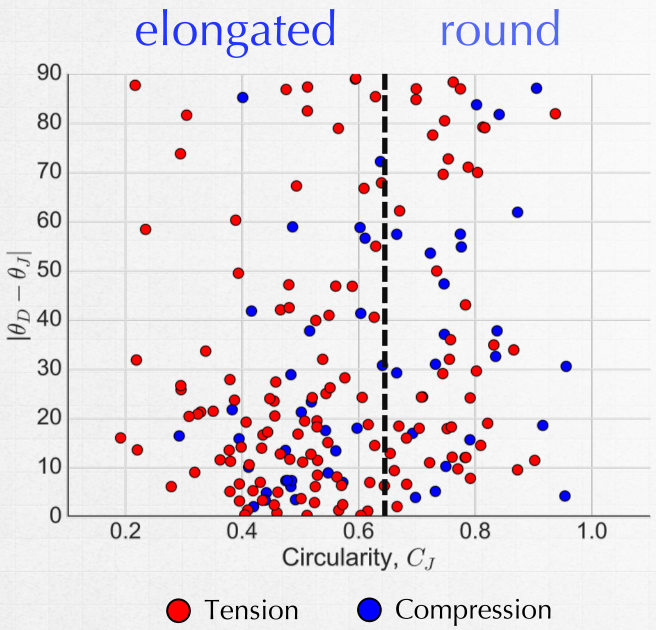
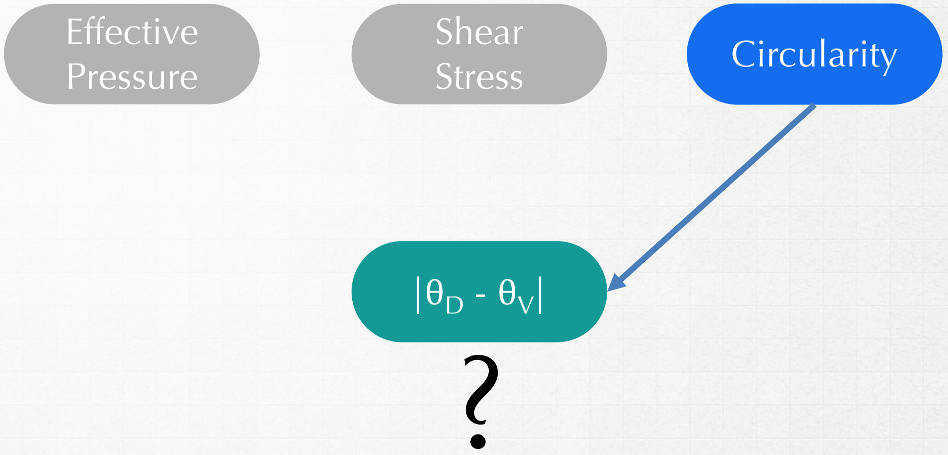
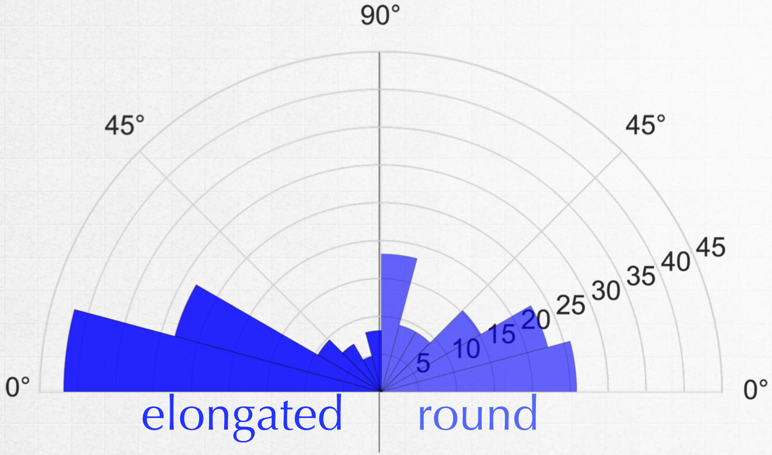
DIVISION MECHANISMS





Coping with stress

DIVISION MECHANISMS



Effective Pressure

Shear Stress

Circularity

$|\theta_D - \theta_V|$

?

Summing up

IN CONCLUSION

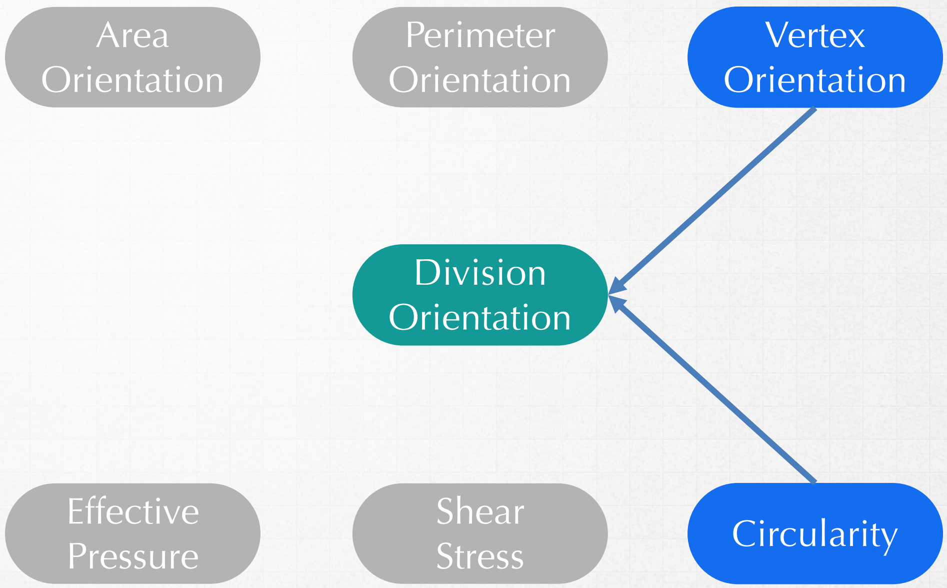
Division orientation is best predicted by cell vertices (tricellular junctions).

We can noninvasively infer stress in experimental data using a model.

The model predicts cell stress aligns with vertex orientation.

We find division alignment correlates with circularity, but not isotropic or shear stress.

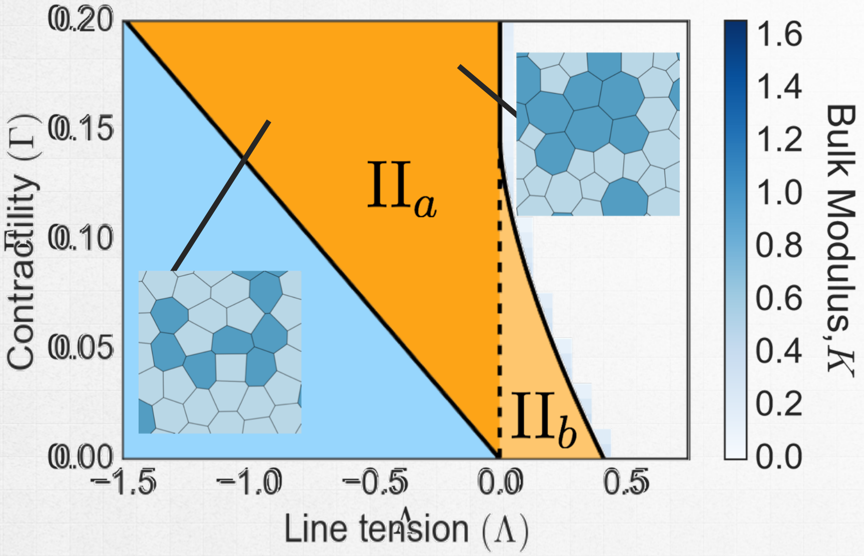
According to the model!



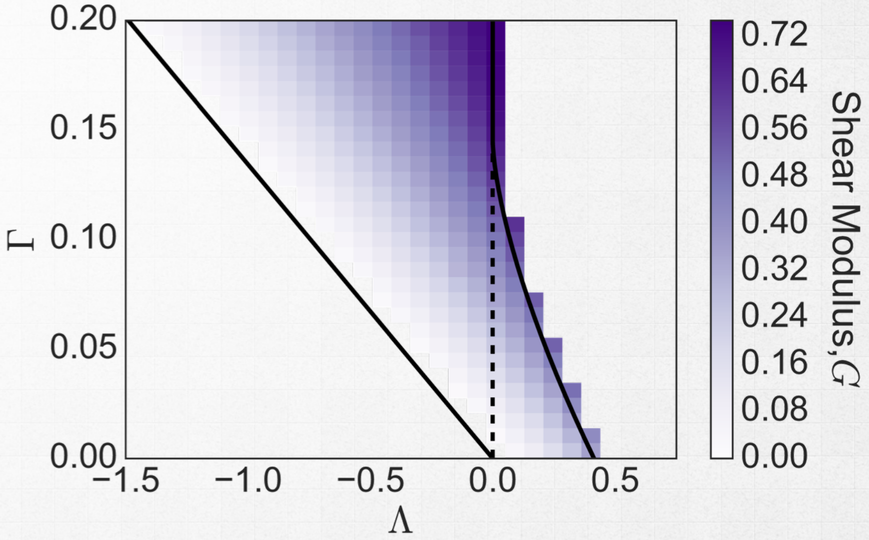
BULK VS SHEAR MODULI

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

Bulk Modulus

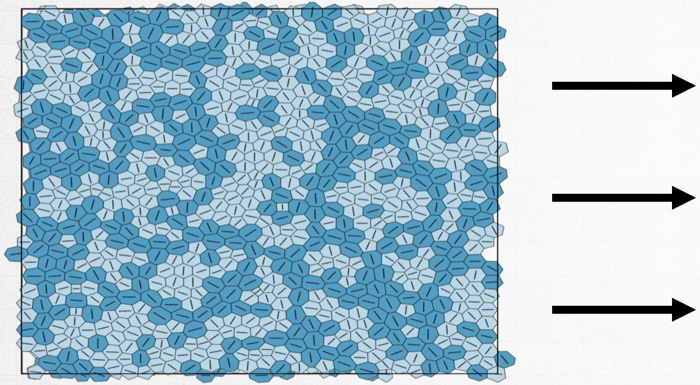


Shear Modulus



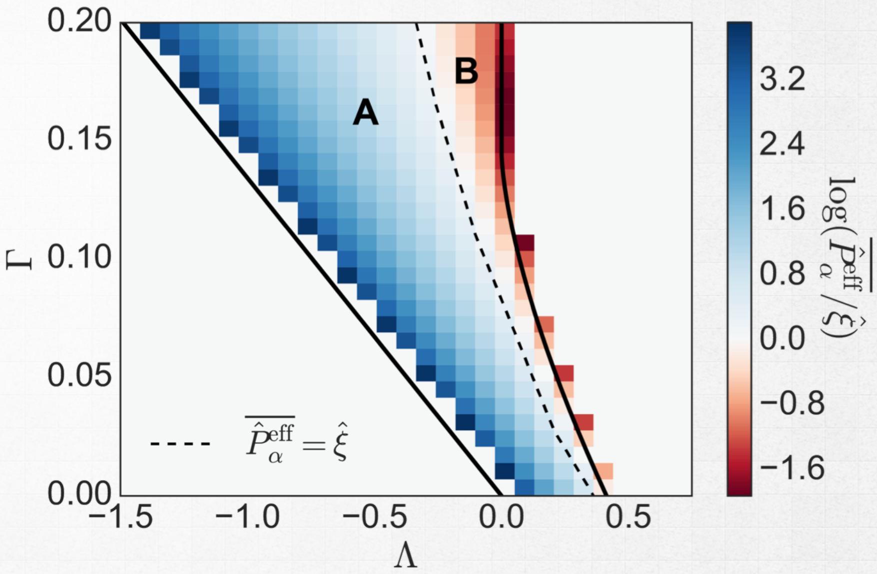
Coping with stress

RESISTANCE TO DEFORMATIONS



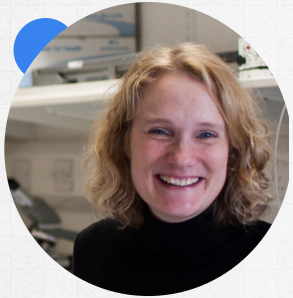
Shear Stress ξ

Isotropic Stress $\overline{\hat{P}^{\mathrm{eff}}_{\alpha}}$



Meet the Gang

THE RESEARCH GROUP



Sarah Woolner

Principal Investigator

Principal investigator in the Matrix Centre, University of Manchester.

The lab

Georgina Stooke-Vaughan, Georgina Goddard
Megan Moruzzi, Mark Johnston

Oliver Jensen

Professor of Mathematics

Sir Horace Lamb Professor of Mathematics at the University of Manchester.

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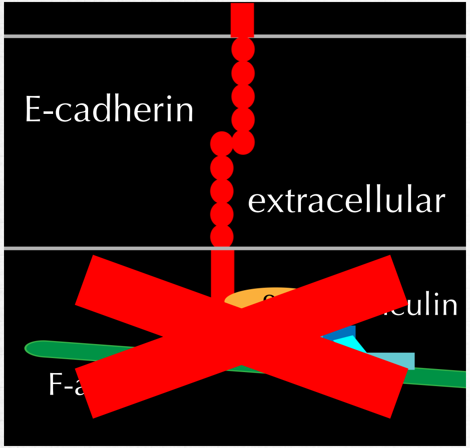
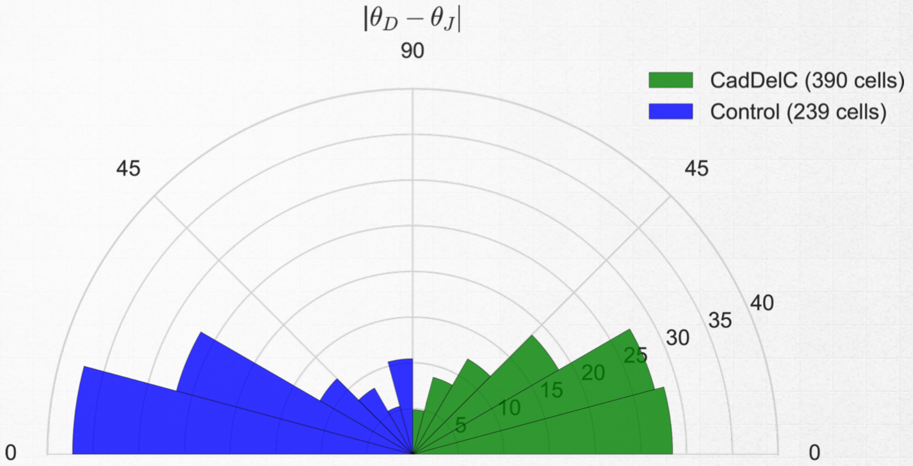
Something interesting

E-CADHERIN IN DIVISION

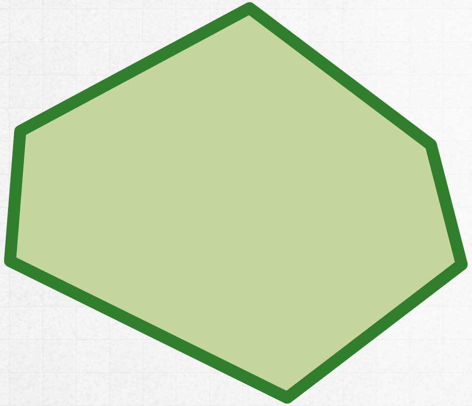




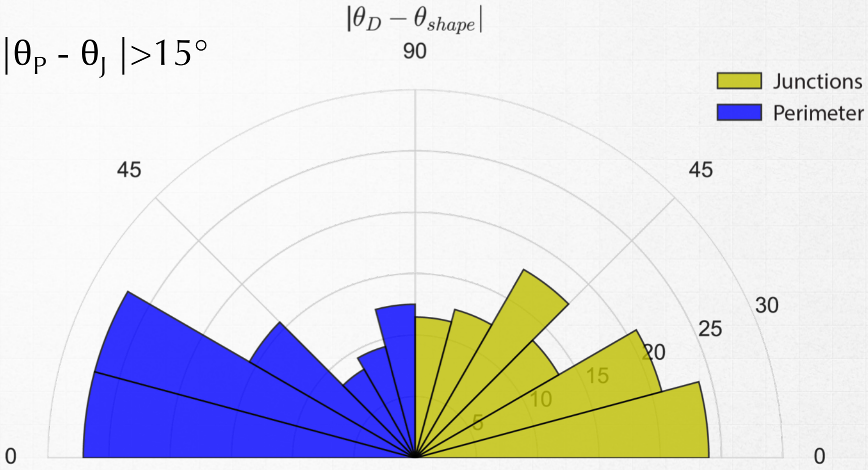
Expression of Cad-DelC reduces division orientation to principal axis

Something interesting

E-CADHERIN IN DIVISION



$|\theta_P - \theta_J| > 15°$



Over expression of Cadherin around perimeter results in division aligning better with perimeter than junctions

Coping with stress

GLOBAL STRESS