

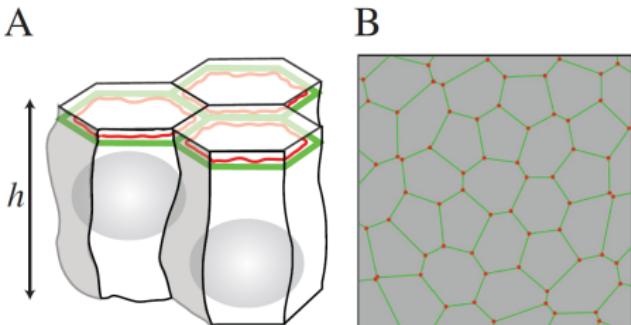
Robustness of epithelia tissue growth to cell mechanics

Charles N. de Santana,
Institute of Evolutionary Biology and Environmental Studies, UZH.

Robustness of epithelia tissue growth to cell mechanics,
22 October 2015, IEU/UZH, Switzerland.

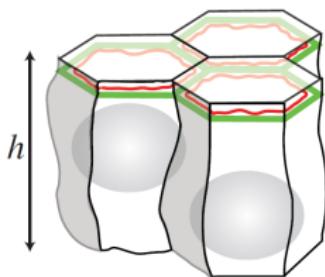
Junctional network

- 1 Epithelia cells are connected to each other via adhesive molecules.

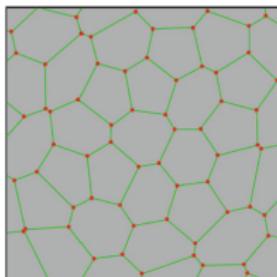


Junctional network

A

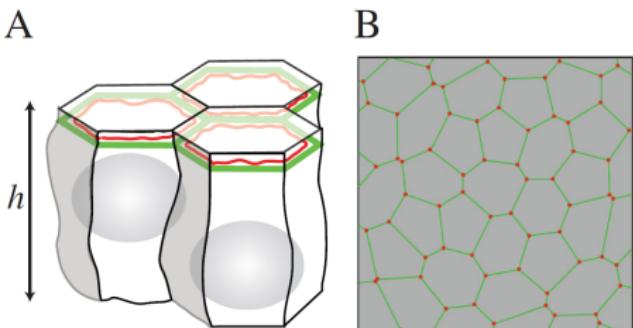


B



- 1 Epithelia cells are connected to each other via adhesive molecules.
 - 2 Epithelia cells establish a **junctional adherent network** near their apical region.

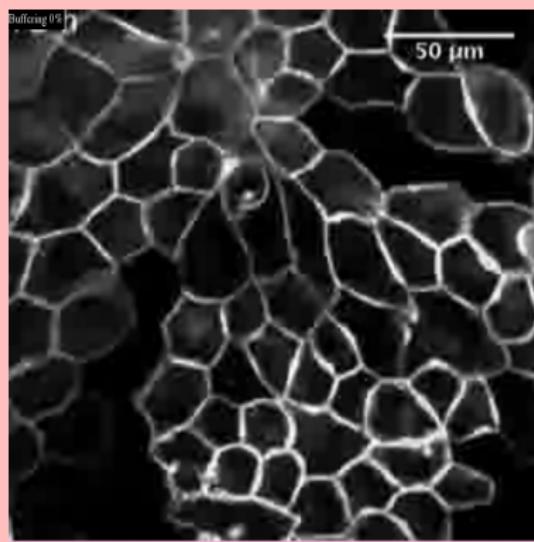
Junctional network



- 1 Epithelia cells are connected to each other via adhesive molecules.
 - 2 Epithelia cells establish a **junctional adherent network** near their apical region.
 - 3 Epithelia tissues are simpler to be studied (2-dimensional).

Tissue growth: cells as polygons, tissues as networks¹

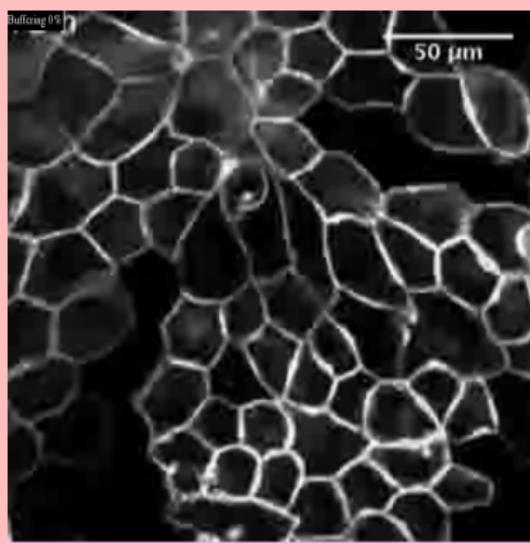
¹Canine kidney cells (kindly offered by Anastasia Trushko (UNIGE))



1 Tissue as a network of cells¹.

¹Farhadifar et al. *The influence of cell mechanics, cell-cell interactions, and proliferation on epithelial packing*. Current Biology 17.24 (2007): 2095-2104.

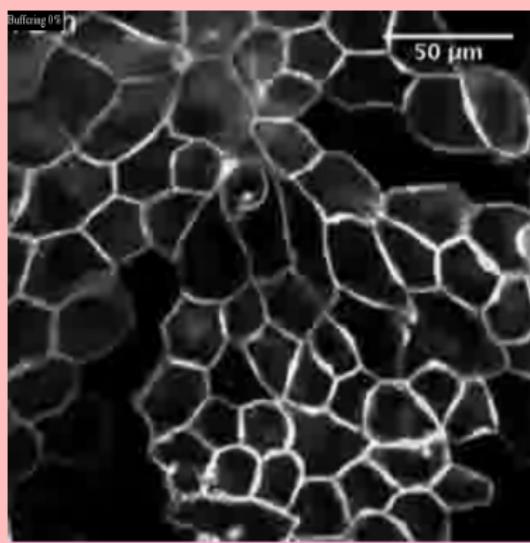
Tissue, cells, Edges, and Vertices



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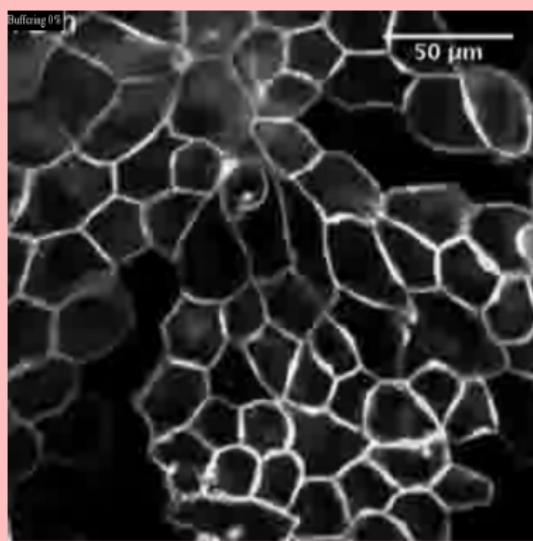
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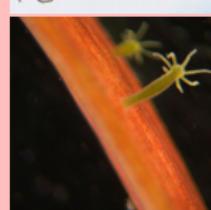
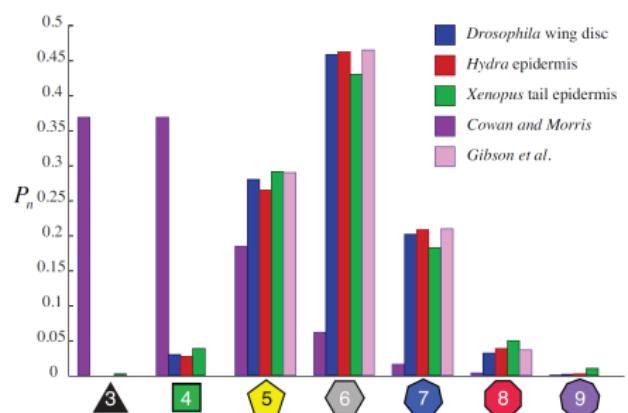
Tissue, cells, Edges, and Vertices



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 - ④ Each Edge is composed by 2 Vertices¹.

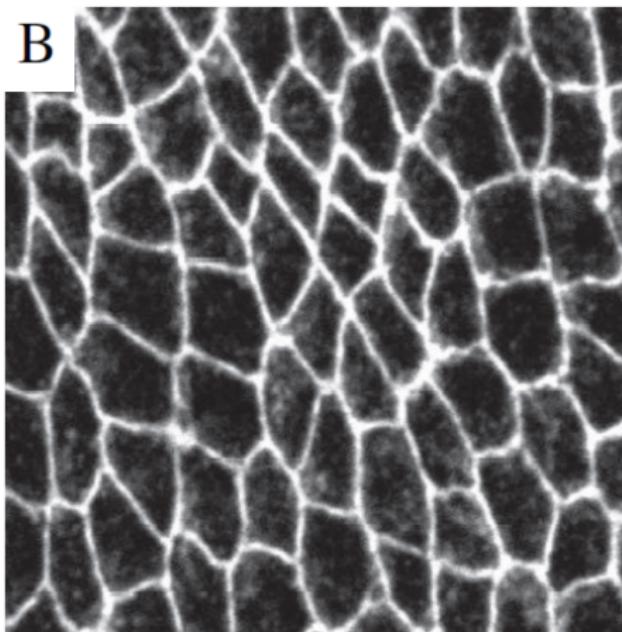
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Cell shapes and Different kind of tissues

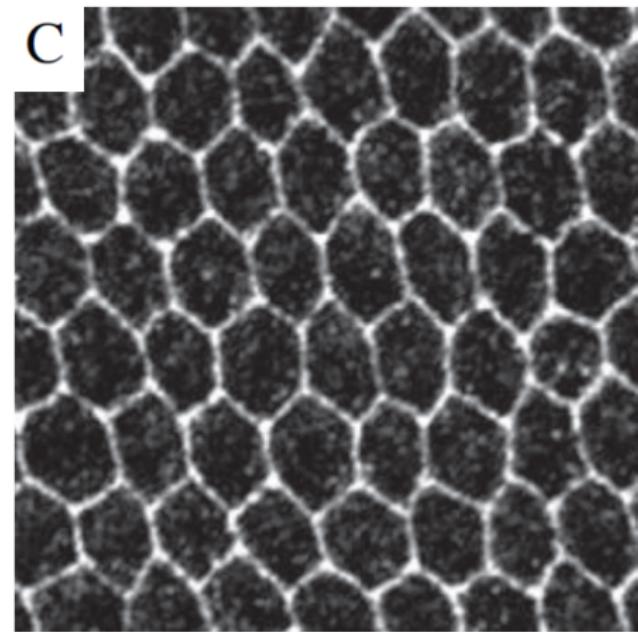


Cell shapes and Different Developmental stages (*Drosophila* wings)

(B) pupal stage

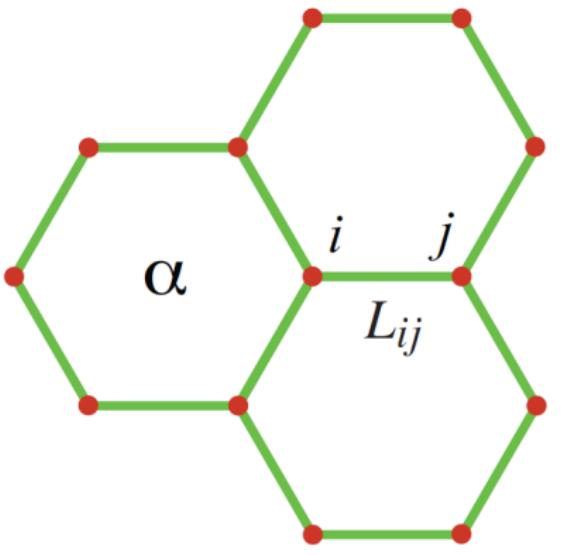


(C) before hair formation



Line Tension, Contractility, and Elasticity

C

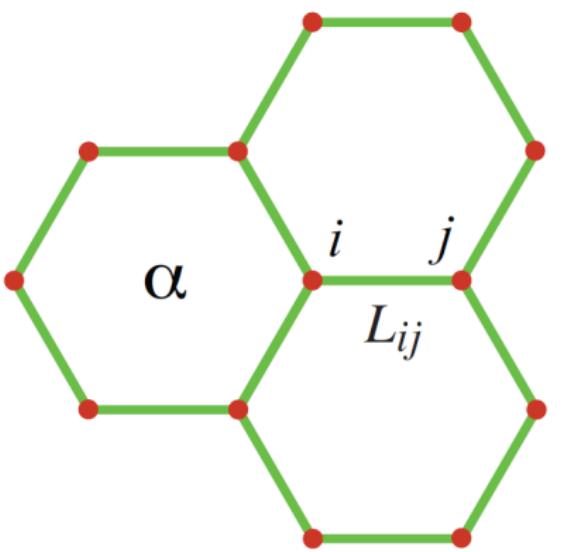


- Edge's Line tension (Λ) is associated to Edge's length¹.

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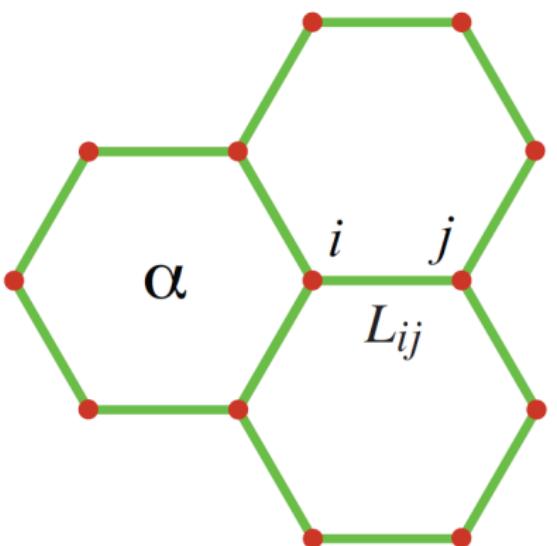


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Line Tension, Contractility, and Elasticity

C



- Edge's Line tension (Λ) is associated to Edge's length¹.
 - Cell's Contractility (Γ) is associated to Cell's Perimeter¹.
 - Cell's Elasticity (K) is associated to Cell's Area¹.

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Force Balance Energy Function¹

$$F = \sum_{\alpha} \frac{K_{\alpha}}{2} (A_{\alpha} - A_{\alpha}^{(0)})^2 + \sum_{(i,j)} \Lambda_{ij} L_{ij} + \sum_{\alpha} \frac{\Gamma_{\alpha}}{2} L_{\alpha}^2$$

- ## • Elasticity and Cell Area

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- Elasticity and Cell Area
 - Line tension and Edge length

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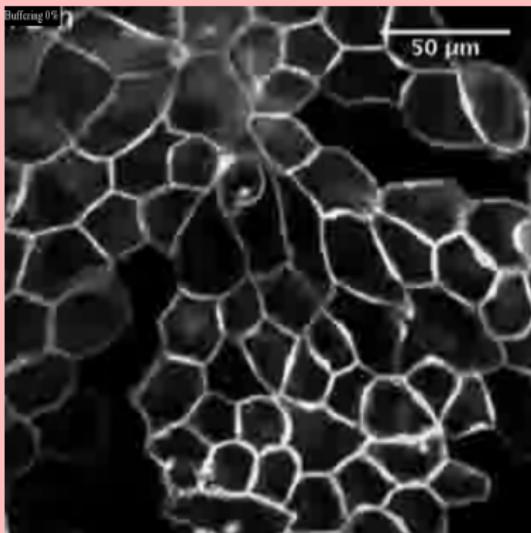
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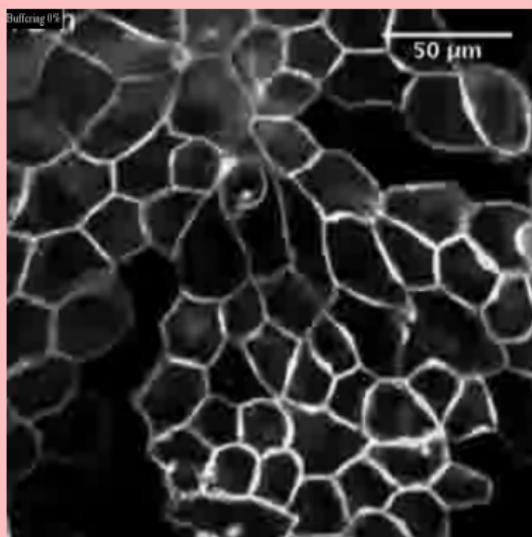
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The physical properties of the system are static. So, in order to satisfy the **Minimal Energy's Assumption**, the positions of the vertices change with different combination of parameters and different events (like the appearance of new cells).

Preferred Cell's Area $A_\alpha^{(0)}$

$$F = \sum_{\alpha} \frac{K_{\alpha}}{2} (A_{\alpha} - A_{\alpha}^{(0)})^2 + \sum_{(i,j)} \Lambda_{ij} L_{ij} + \sum_{\alpha} \frac{\Gamma_{\alpha}}{2} L_{\alpha}^2$$



$A_\alpha^{(0)}$ is the preferred area of cell α which is related to the volume, V_α and height, h_α of the cell: $A_\alpha^{(0)} = \frac{V_\alpha}{h_\alpha}$

Robustness question

How do mechanical properties of cells (Cells elasticity, Cells contractility, Edges line tension) affect the growth of tissues?

Strategy to answer the question

To explore a broad range of mechanical parameters (at high resolution) and study the effects of such parameters in the characteristics (**Phenotype**) of simulated cells and tissues.

Potential phenotypes to study:

- Cells shape distribution.

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- Cells *regularness* distribution.
- Edges angle distribution.

Sequence of Events¹

1 - Relaxation - Vertices change their position to guarantee the force balance to be equal to zero.

2 - Cell Proliferation - cells growth and cells division.

Initial conditions and constraints

Rectangular tissue with regular hexagonal cells (all the edges of the cells have

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Relaxation¹

Rectangular tissue with 5x5 cells

- 1 - Vertices change their position to guarantee the force balance equal to zero.

Relaxation¹

Rectangular tissue with 5x5 cells

- 2 - The position of the vertices is defined by a *Verlet Function* in which the acceleration is defined by the total force on the junctions of the tissue

$$r(t + \Delta t) = 2r(t) - r(t - \Delta t) + a(t)\Delta t^2.$$

Relaxation¹

Rectangular tissue with 5x5 cells

- 3 - Once the force is zero, the acceleration of the *Verlet Function* is also zero, and so the position of the vertices don't change from time step t to $t + \Delta t$.

Relaxation

Rectangular tissue with 5x5 cells

- 4 - Relaxation is finished once the length of the tissue remains *steady* (the position of its vertices don't change) along 100 time steps ($\frac{sd(\sum_{\alpha} L_{\alpha})}{mean(\sum_{\alpha} L_{\alpha})} \approx 0$).

Regularity of the tissue

- ① We define ***regularness*** as a dimensionless measure to say how regular the cells of a tissue are.

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- ② Regularness is defined as: $Reg = \frac{sd(L_{ij})}{mean(L_{ij})}$ accross all the edges.

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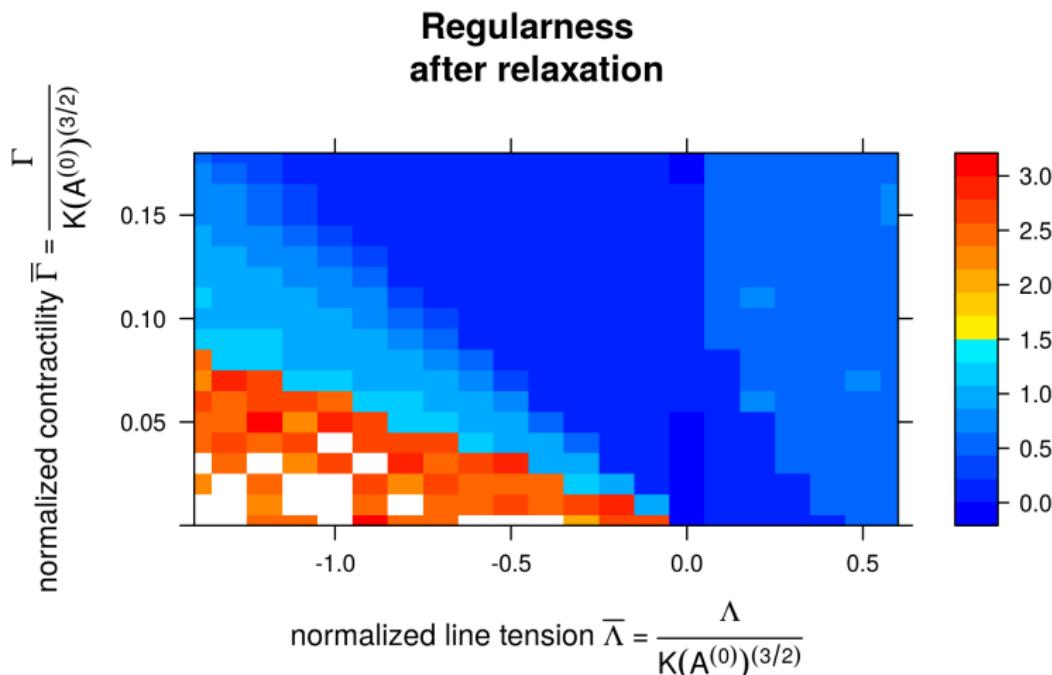
$$Reg \approx 0$$

$$(Lambda, Gamma) = (0, 0.15)$$

$$Reg > 0$$

$$(Lambda, Gamma) = (-0.6, 0.08)$$

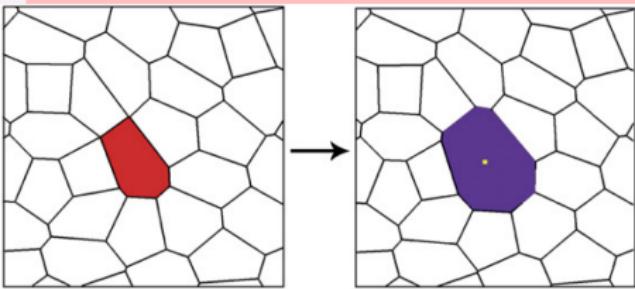
Phase space of Regularness



Cell Proliferation

- Cell Growth.
 - Cell Division

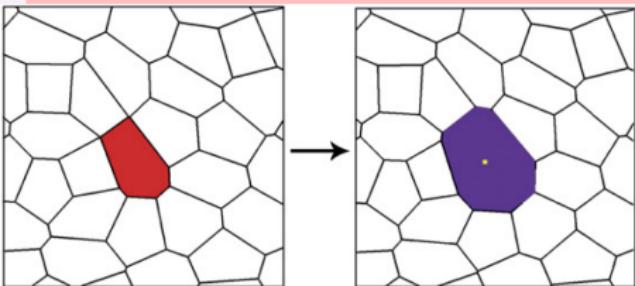
Cell Growth¹



- ① Cells are **randomly** triggered to increase their area.

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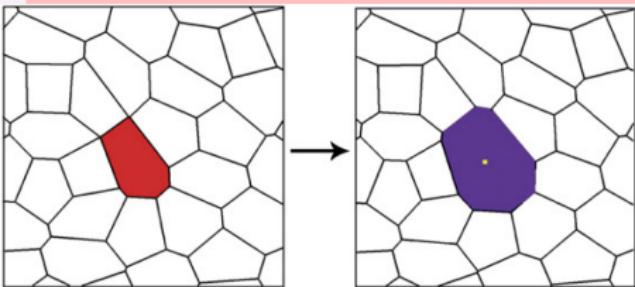
Cell Growth¹



- ① Cells are **randomly** triggered to increase their area.
- ② They increase their area by 10% each time step.

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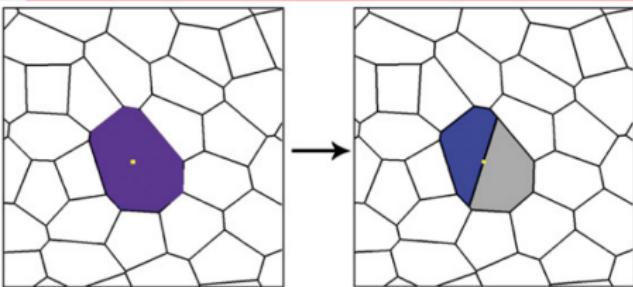
Cell Growth¹



- ① The increment of the area is given by changing the value of the preferred area parameter ($A_\alpha^{(0)}$) on the Force balance equation.

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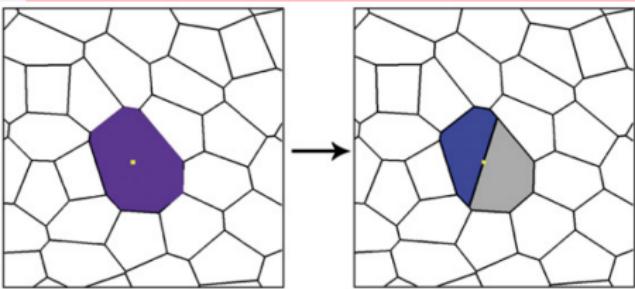
Cell Division¹



- ① Once a cell α reaches the **double** of the area it had **before starting to increase**, it is subdivided into two cells with half the current area of cell α .

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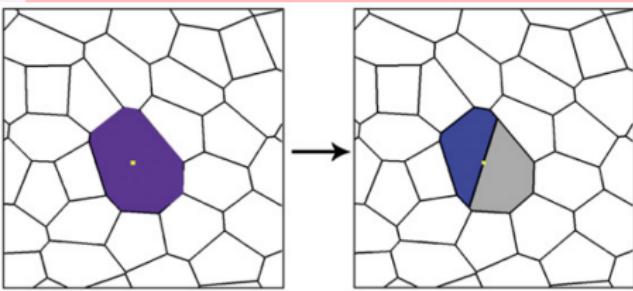
Cell Division¹



- ① The division consists in creating a new edge e_i that **crosses the centroid** of the original cell α with a **random direction**.

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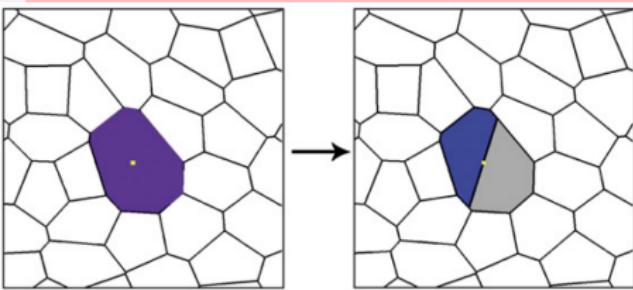
Cell Division¹



- ① The former cell α is replaced by two new cells that share the edge e_i .

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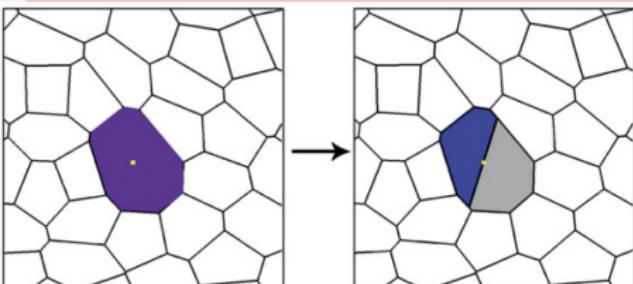
Cell Division¹



- ① Edges in neighbour cells that are now connected to one of the vertices of e_i need to be splitted into two edges.

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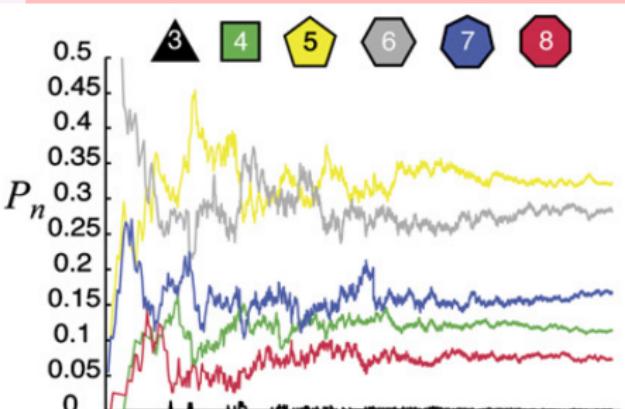
Cell Division¹



- ① This procedure changes the *shape* of the cells in the neighbourhood of α , as well as it creates new cells to replace α that not necessarily have the same *shape* as α .

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Steady state



- ① The steady state of the cell division process is observed once the relative proportion of cells don't change along 100 time steps.

Change in shapes distribution

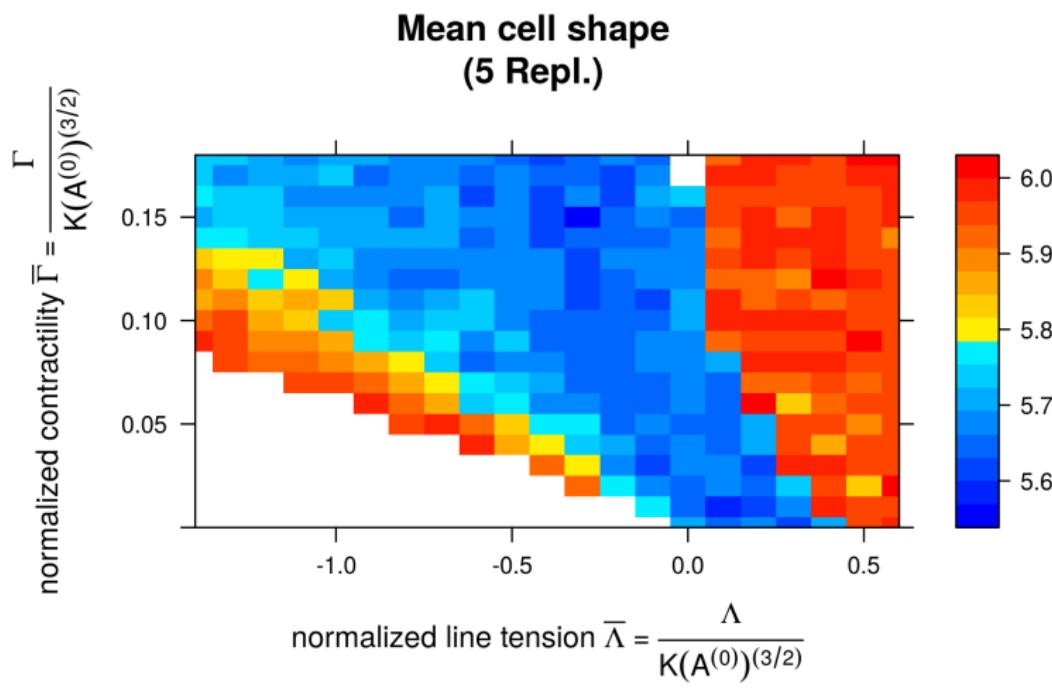
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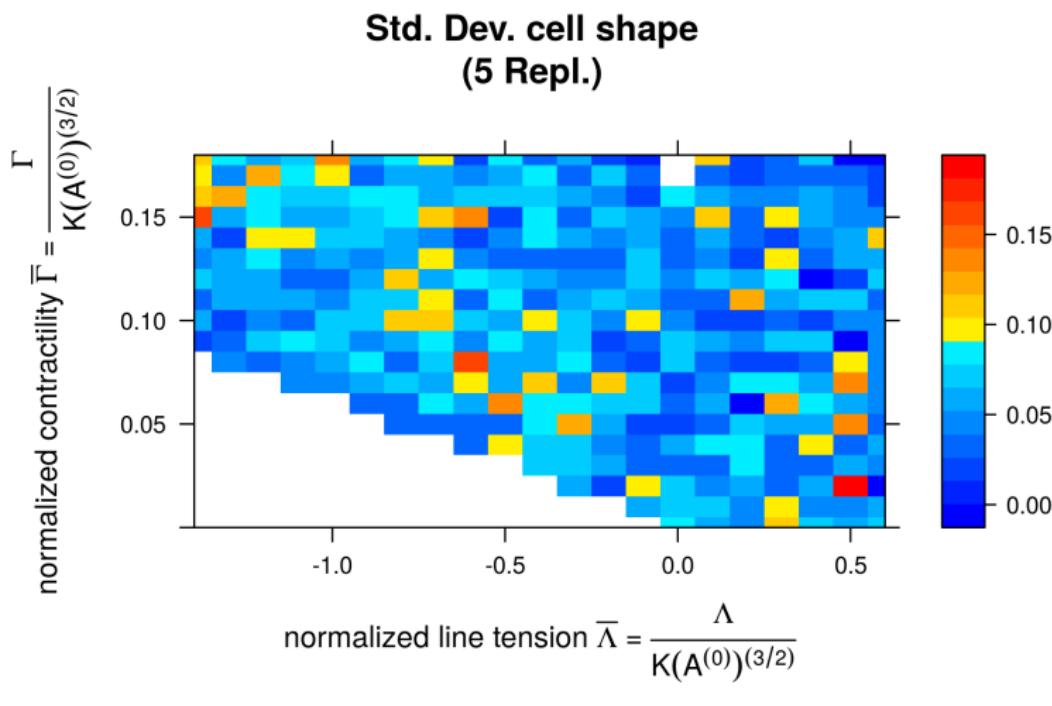
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Phase space: Mean shape of cells (5 Repl.)



Phase space: Std. Dev. of shape of cells (5 Repl.)



Interesting numbers

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- 5 Written by *6 hands*: Aziza Merzouki, Orestis Malaspina, Charles de Santana.

Technologies

① Programming language: C++.

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- 4 Slides made with **LATEX**.

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- 6 Study the Phase Space of **Direction of edges** of cells.

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- ① Change initial organization of cells in the tissues (starting from non-regular tissues).

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- ④ Change the way cells are divided (the splitting edge e_i depends on the number of edges of neighbour cells).
- ⑤ Study 3D tissues.

Thank you!

- SystemsX Initiative.
- ***EpiphysX*** members: Andreas Wagner (UZH), Aziza Merzouki, Orestis Malaspinas, Bastien Chopard, Aurélien Roux, Michel Milinkovitch, Marcos Gonzalez-Gaitan, Anastasia Trushko, Antonio Martins (UNIGE)
- Chopard's Group members (UNIGE).
- Wagner's Group members (UZH).
- You, for the attention and patience.