

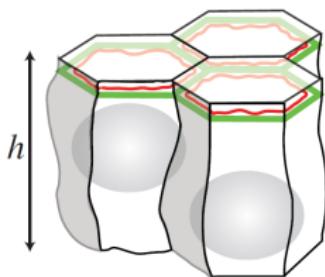
Robustness of epithelia tissue growth to cell mechanics

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

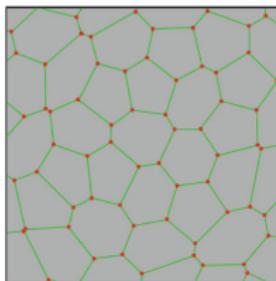
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22 October 2015, IEU/UZH, Switzerland.

Junctional network

A



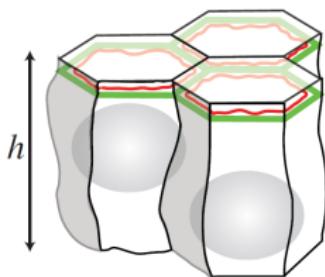
B



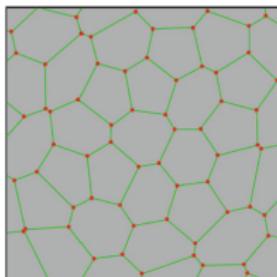
- ① Epithelia cells are connected to each other via adhesive molecules.

Junctional network

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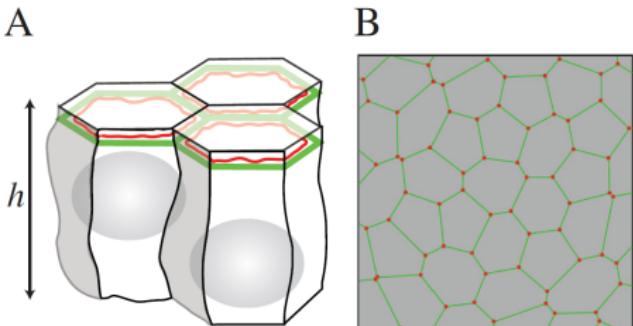


B



- 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

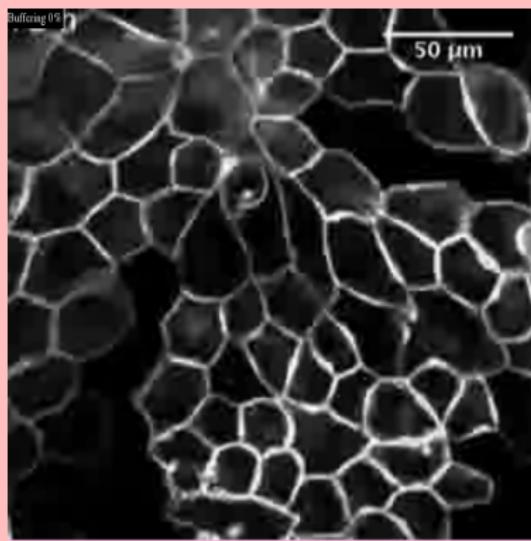


- 1 Epithelia cells are connected to each other via adhesive molecules.
 - 2 Epithelia cells establish a **junctional adherent network** near their apical region.
 - 3 Epithelia tissues are simpler to be studied (2-dimensional).

Tissue growth: cells as polygons, tissues as networks¹

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

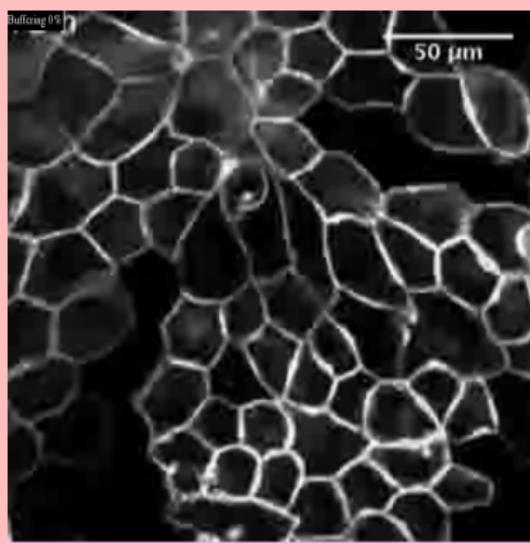
Tissue, cells, Edges, and Vertices



- ## 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.

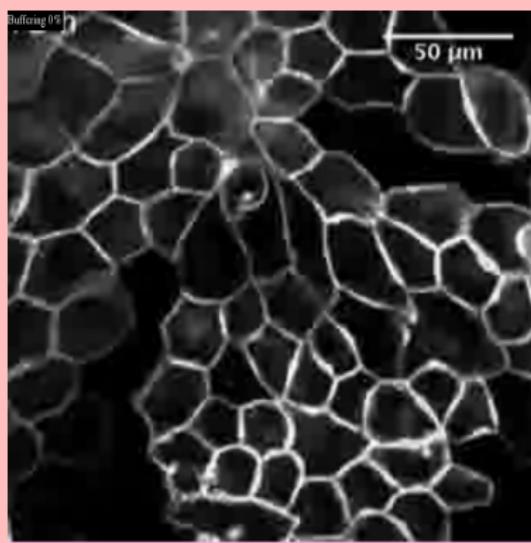
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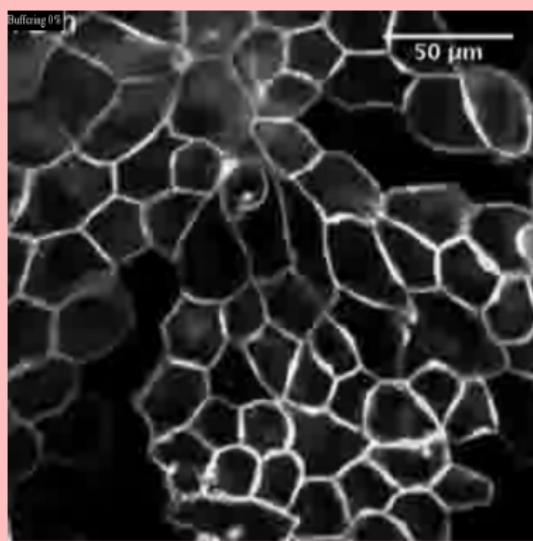
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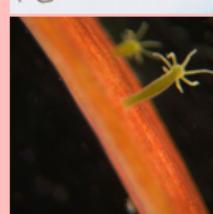
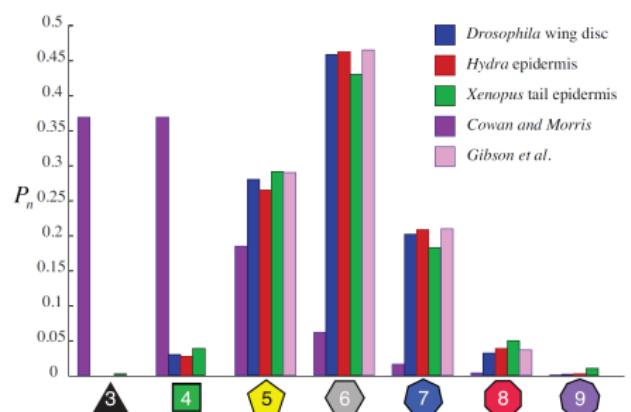
Tissue, cells, Edges, and Vertices



- ① Tissue as a network of cells¹.
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 - ④ Each Edge is composed by 2 Vertices¹.

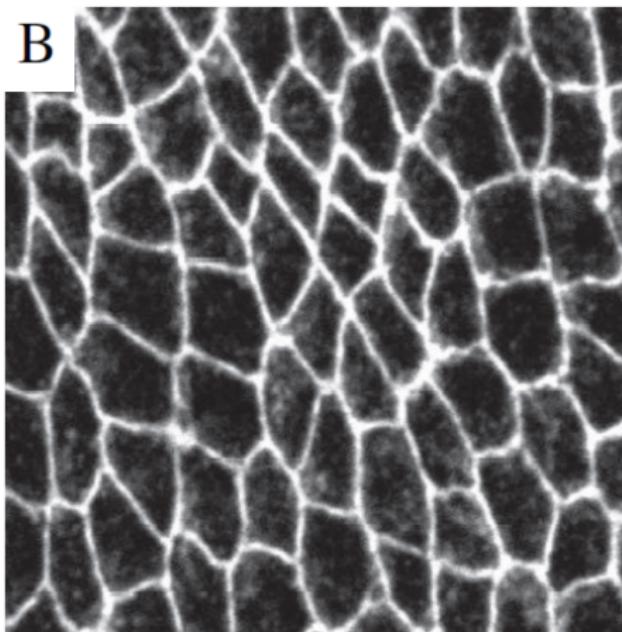
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Cell shapes and Different kind of tissues

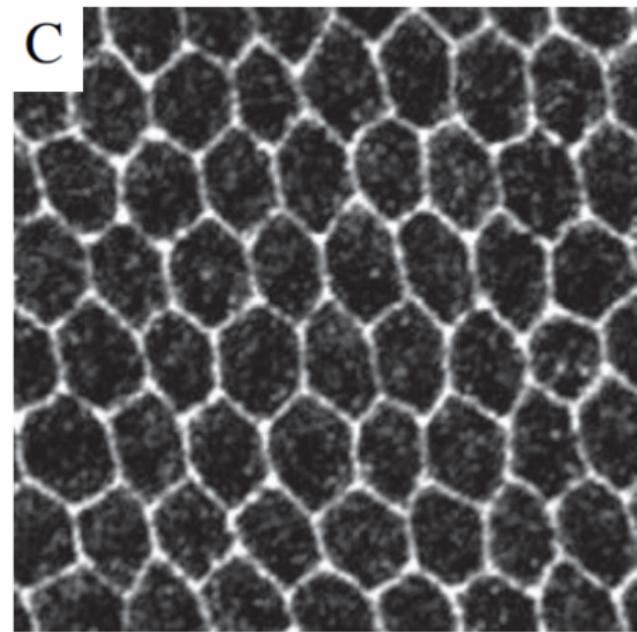


Cell shapes and Different Developmental stages (*Drosophila* wings)

(B) pupal stage

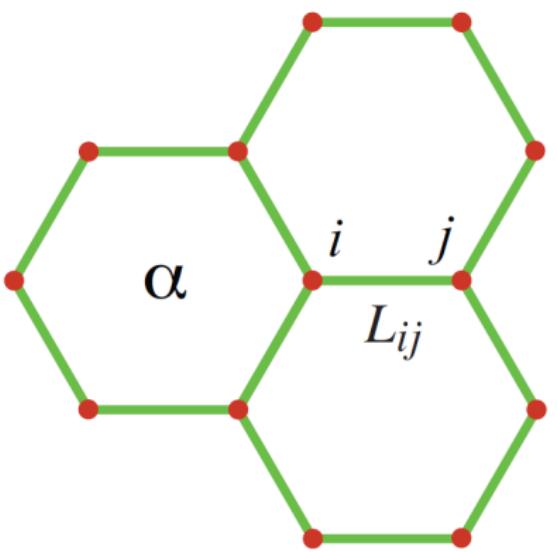


(C) before hair formation



Line Tension, Contractility, and Elasticity

C

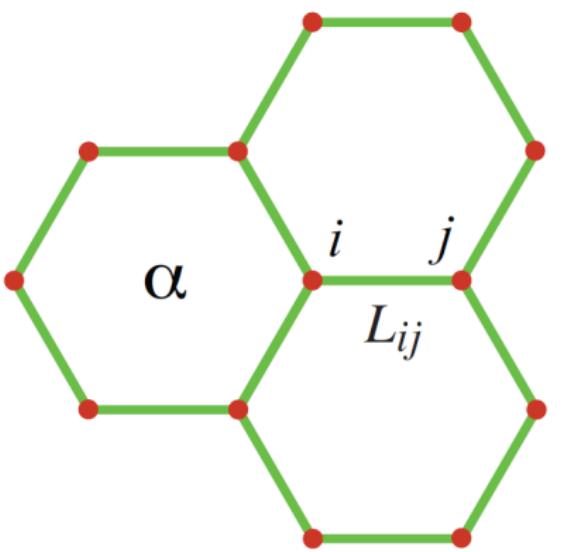


- Edge's Line tension (Λ) is associated to Edge's length¹.

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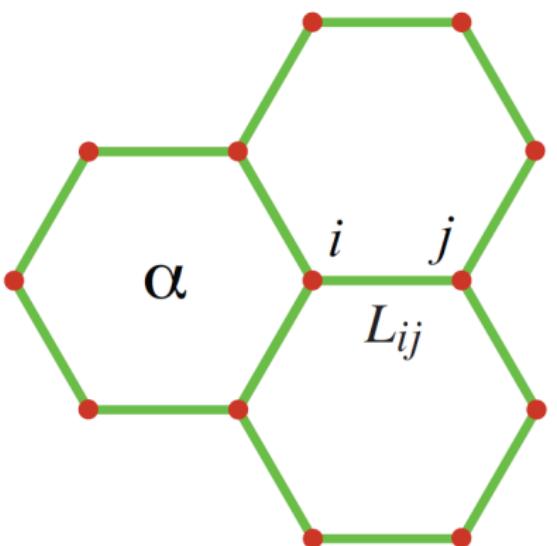


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 - Cell's Contractility (Γ) is associated to Cell's Perimeter¹.

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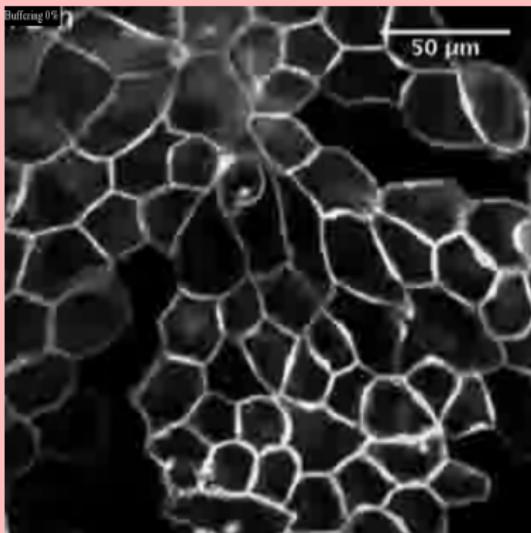
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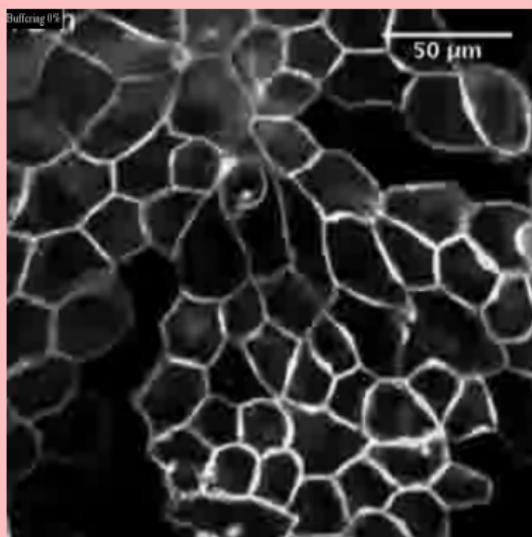
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The physical properties of the cells are static. So, in order to satisfy the **Minimal Energy's Assumption** the positions of the vertices change for different combination of parameters and different events (like the appearance of new cells).

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

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$A_\alpha^{(0)}$ 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.

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

Initial conditions and constraints

- ① Rectangular tissue with regular hexagonal cells (all the edges of the cells have the same length).

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- ② Non-boundary periodic conditions (the tissue is not *infinite*).
- ③ Line tension of boundary cells (Λ_b) is half the value of the other cells¹.

Relaxation¹

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

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Relaxation¹

- 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

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

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Relaxation¹

- 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 $t + \Delta t$.

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Relaxation

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

Regularness of the tissue

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

Regularity of the tissue

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

Regularity of the tissue

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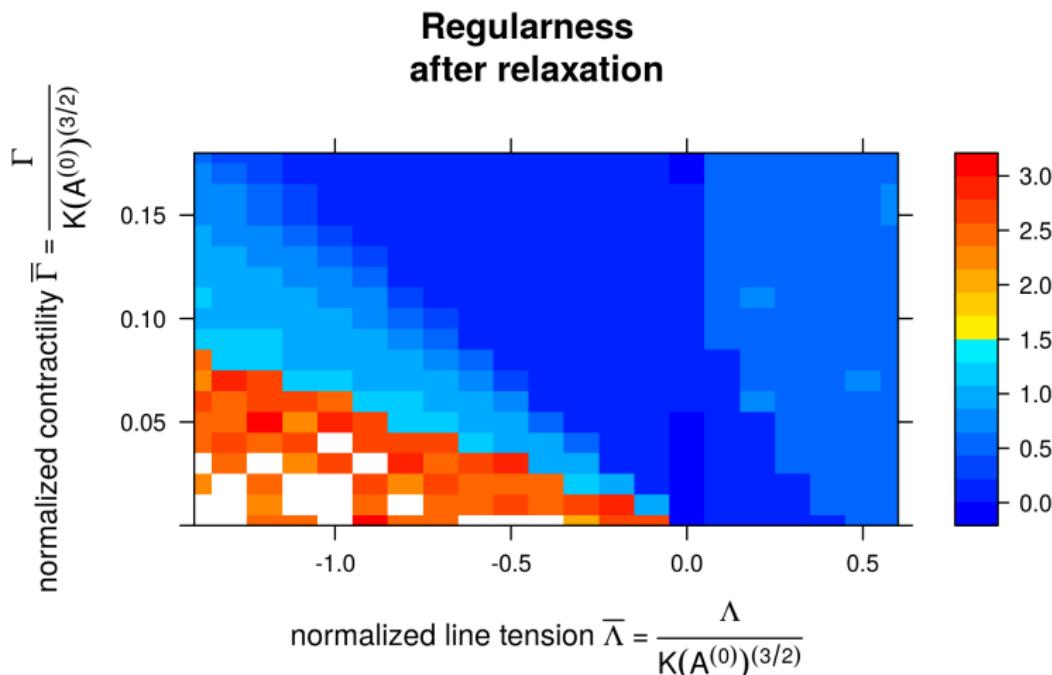
$$Reg \approx 0$$

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

$$Reg > 0$$

$$(-0.6, 0.08)$$

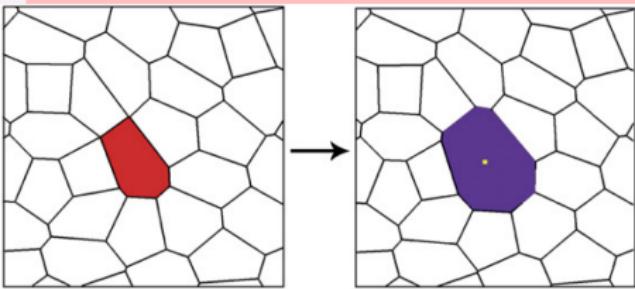
Phase space of Regularness



Cell Proliferation

- Cell Growth.
 - Cell Division

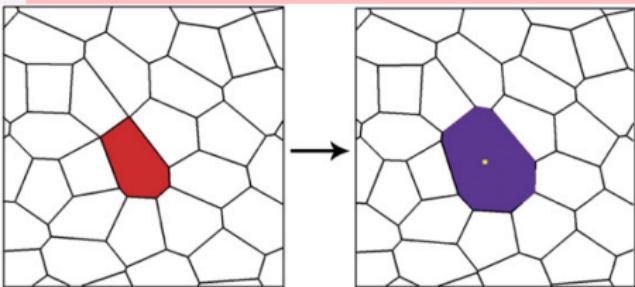
Cell Growth¹



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

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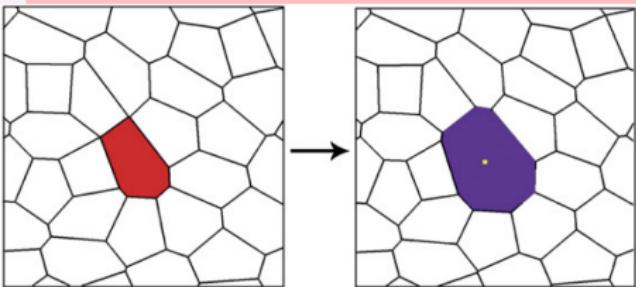
Cell Growth¹



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

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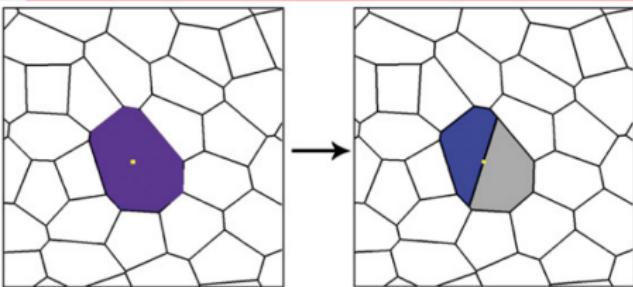
Cell Growth¹



- 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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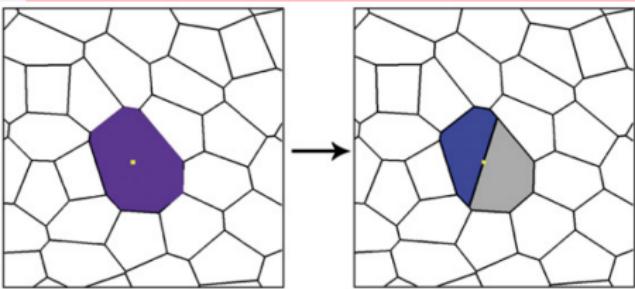
Cell Division¹



- 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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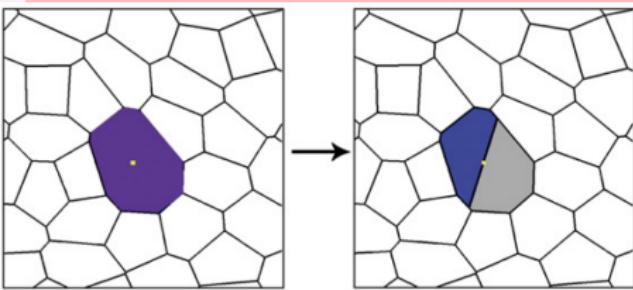
Cell Division¹



- 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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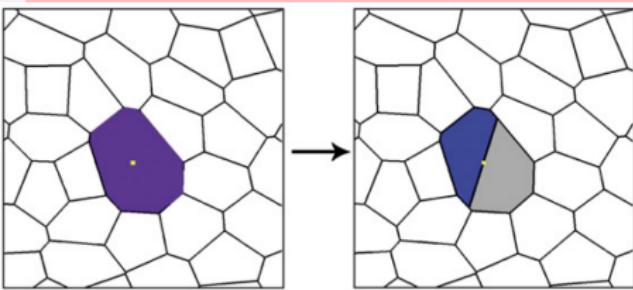
Cell Division¹



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

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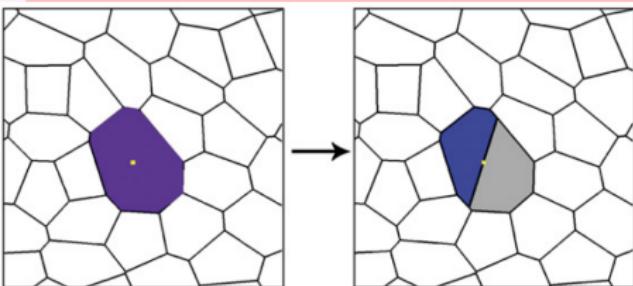
Cell Division¹



- 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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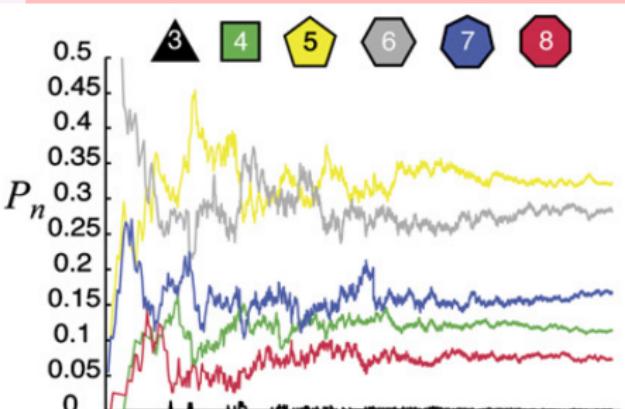
Cell Division¹



- 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



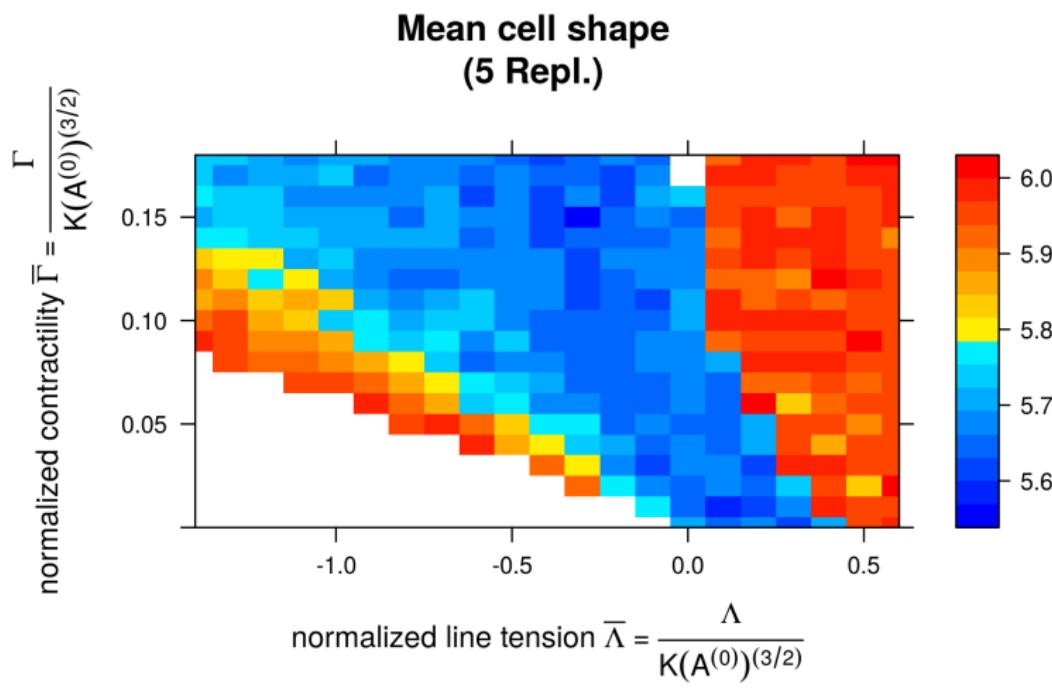
- ① The steady state of the cell division process is observed once the relative proportion of cells don't change along 100 time steps.

Change in shapes distribution

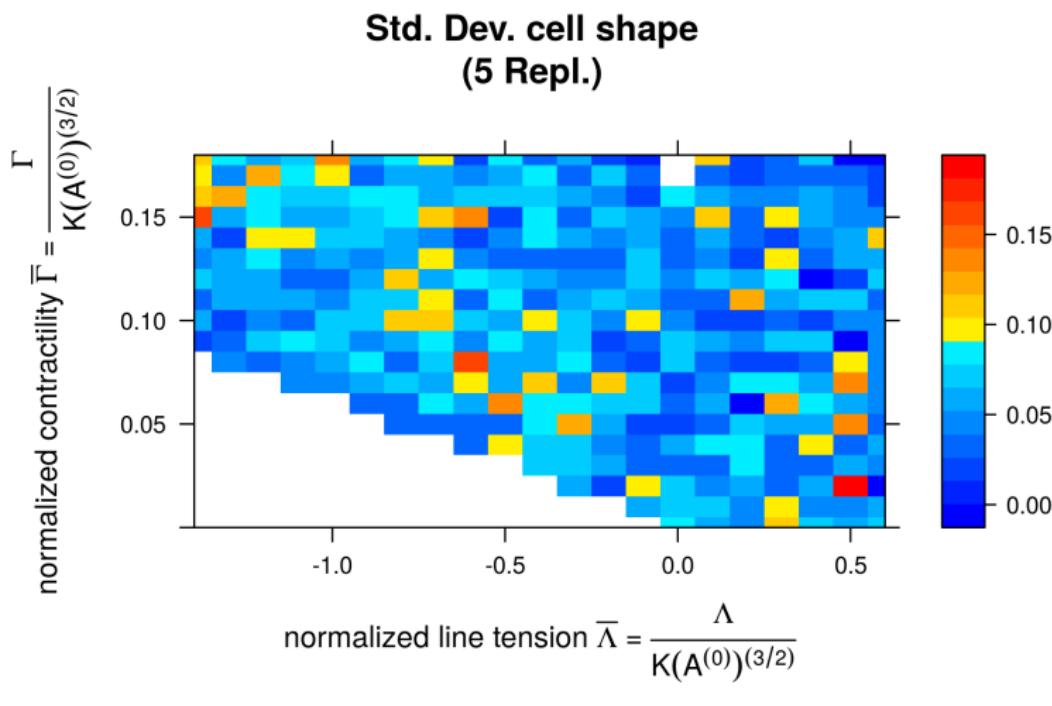
$Reg \approx 0$
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$Reg > 0$
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Phase space: Mean shape of cells (5 Repl.)



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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- 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.