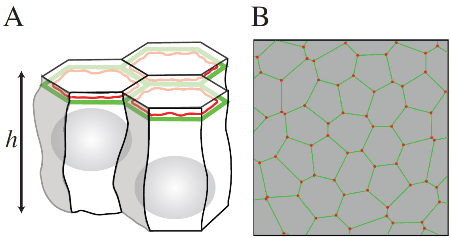
Robustness of epithelia tissue growth to cell mechanics

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



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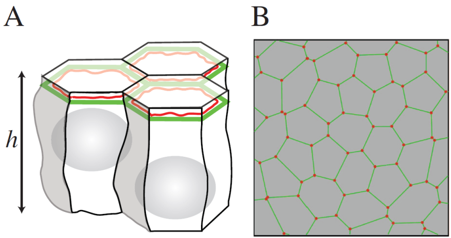

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2. These apical junctions can be considered as a two-dimensiona network (**junctional adherent network**) that defines the cell packing geometry.

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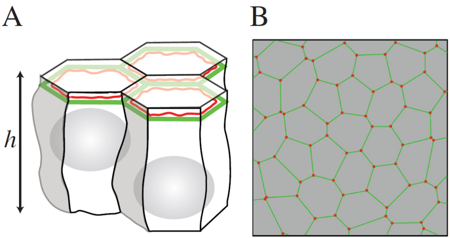

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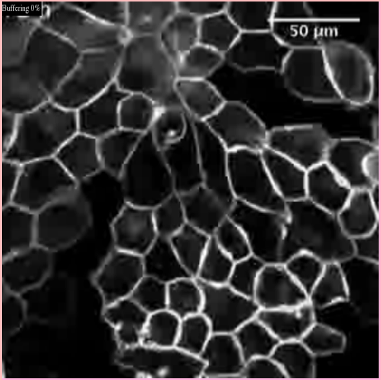
2. These apical junctions can be considered as a two-dimensiona network (**junctional adherent network**) that defines the cell packing geometry.
3. This 2-dimensional topology makes the study of Epithelia tissues simpler than the study of tissues in 3 dimensions.

Tissue growth: cells as polygons, tissues as networks[1]

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

Tissue, cells, Edges, and Vertices



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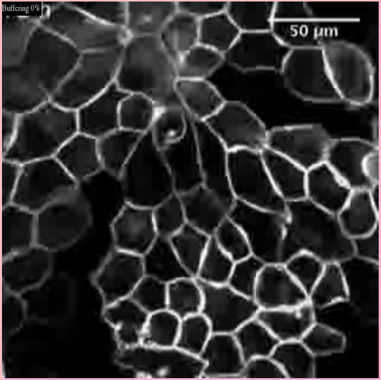

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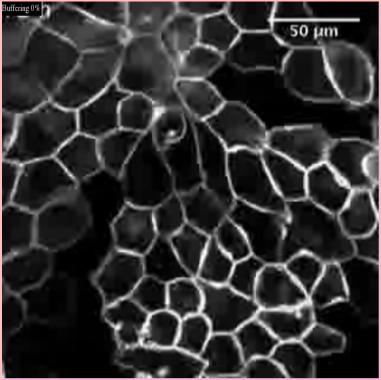

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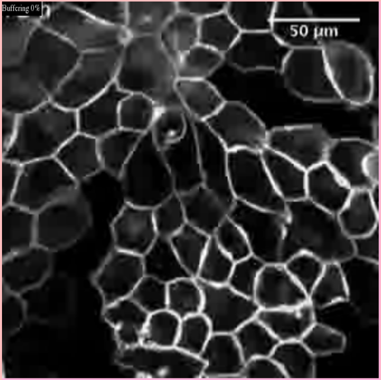

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4. Each Edge is composed by 2 Vertices[1].

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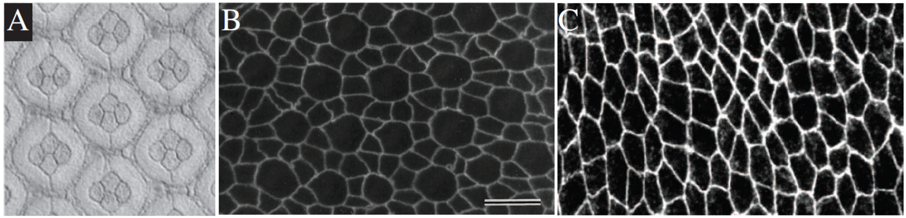
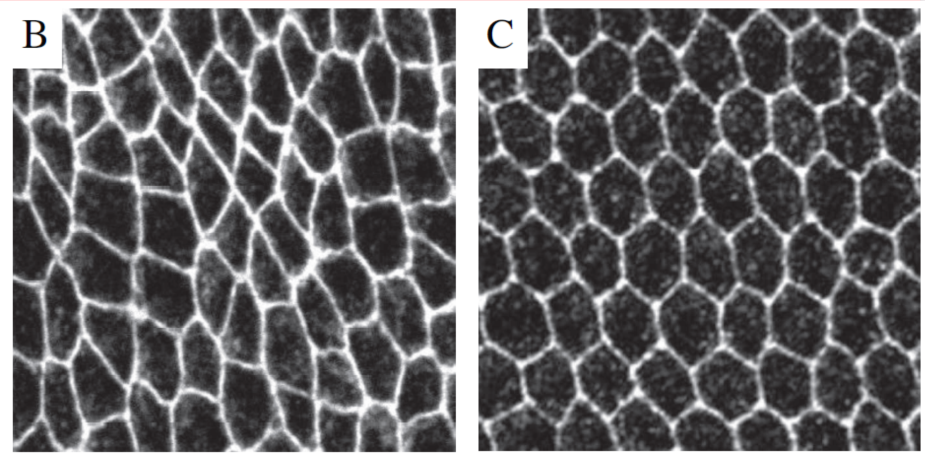
Cell shapes and Different kind of tissues



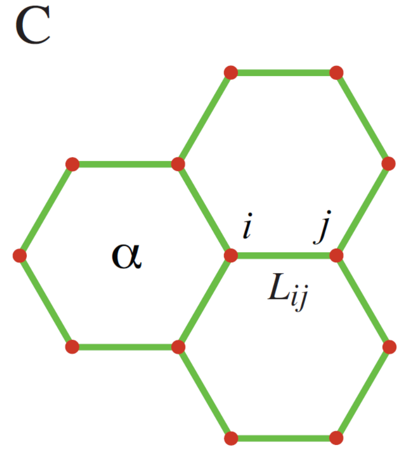
1. A - Drosophila retina ommatidium (eys of a fruit fly)
2. B - Basilar papilla of chicken embryo
3. **C - Drosophila wing disc**

Cell shapes and Different Developmental stages (Drosophila wings)

(B) pupal stage **(C)** before hair formation



Line Tension, Contractility, and Elasticity



- Edge's Line tension (Λ) is associated to Edge's length[1].

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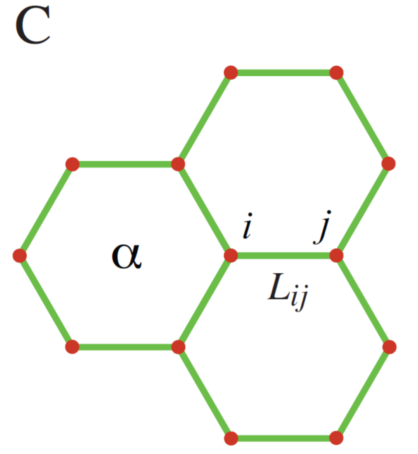

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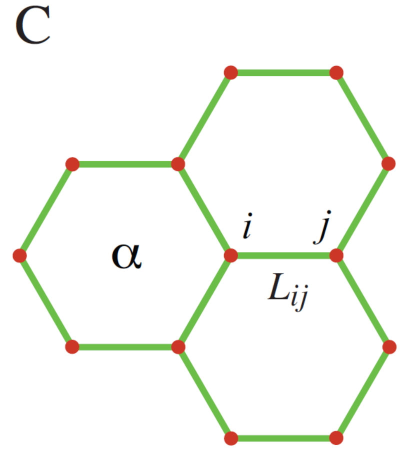

- Edge's Line tension (Λ) is associated to Edge's length[1].
- Cell's Contractility (Γ) is associated to Cell's Perimeter[1].
- Cell's Elasticity (K) is associated to Cell's Area[1].

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Force Balance Energy Function[1]

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

- Elasticity and Cell Area (K_{α}, and A_{α})

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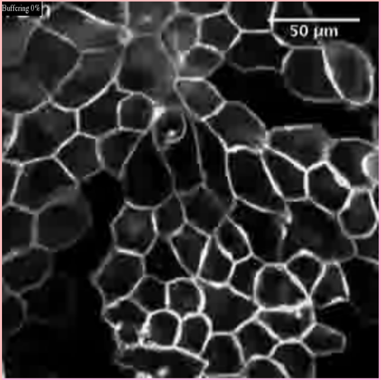
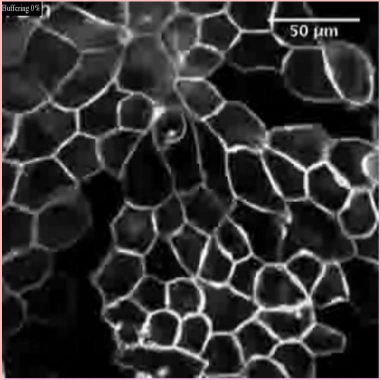


The physical properties of the cells are static. So, in order to satisfy the **Minimal Energy's Assumption** the positions of the vertices change for different combination of parameters and different events (like the appearance of new cells).

Preferred Cell's Area $A_\alpha^{(0)}$[1]

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



$A_\alpha^{(0)}$ 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 shape distribution.
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- Cells *regularity* distribution.

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Potential phenotypes to study:

- Cells shape distribution.
- Cells area distribution.
- Cells perimeter distribution.
- Cells *regularity* distribution.
- Edges angle distribution.

Sequence of Events[1]

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

2 - Cell Proliferation
cells growth and cells division.

[1] Farhadifar 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 constrains

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 cells[1].

Relaxation[1]

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

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

Relaxation[1]

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

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

Relaxation[1]

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

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

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 ***regularity*** 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.

Regularness of the tissue

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

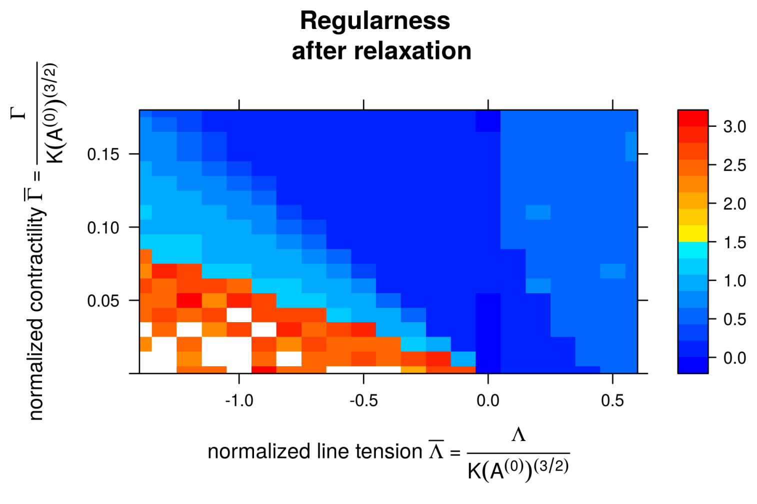
$Reg \approx 0$

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

$Reg > 0$

$(-0.6, 0.08)$

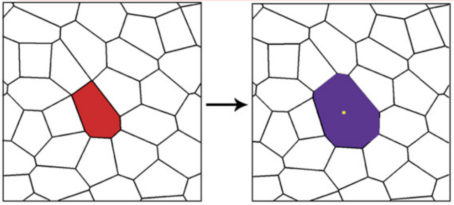
Phase space of Regularness



Cell Proliferation

- Cell Growth.
- Cell Division.

Cell Growth[1]



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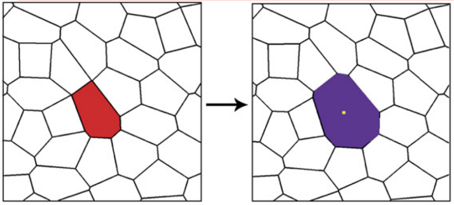

1. Cells are **randomly** triggered to increase their area.
2. They increase their area by 10% each time step.

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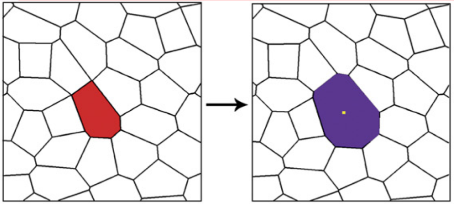
Cell Growth[1]



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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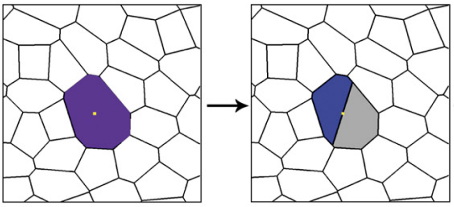
Cell Division[1]



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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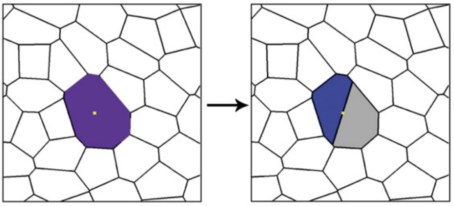
Cell Division[1]



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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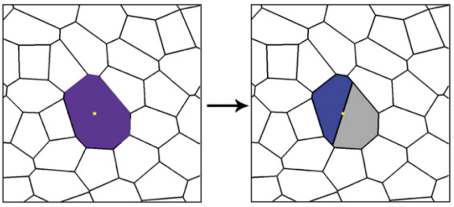
Cell Division[1]



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

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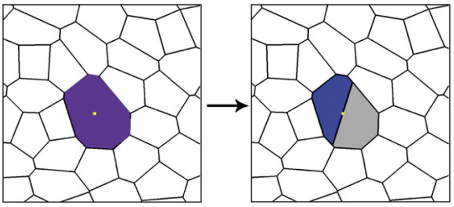
Cell Division[1]



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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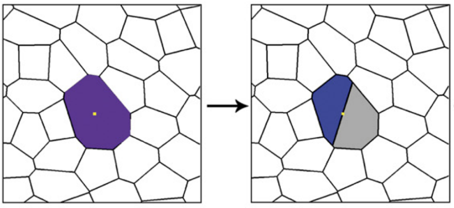
Cell Division[1]



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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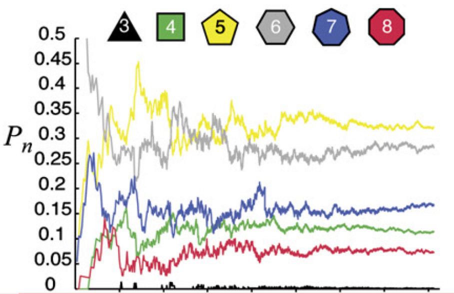
Steady state



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

Change in shapes distribution

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$Reg > 0$

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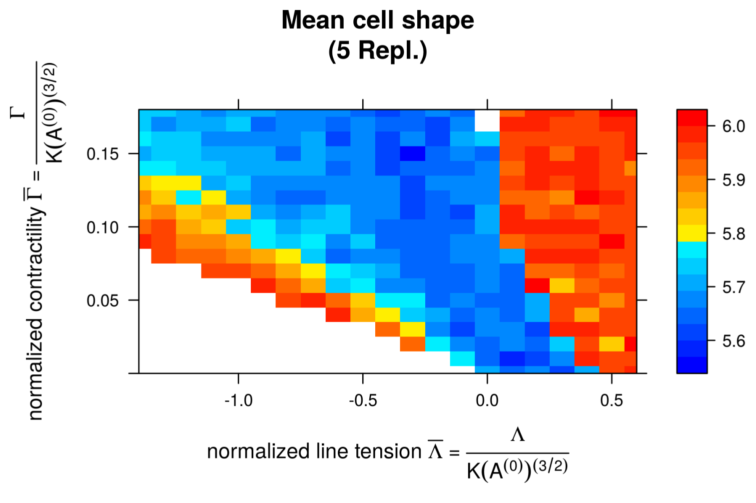
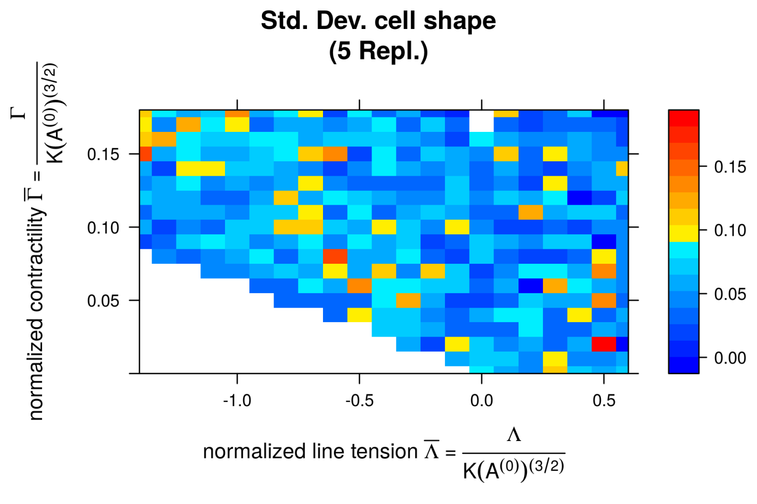
Phase space: Mean shape of cells (5 Repl.)



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



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

Technologies

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4. Slides made with **LaTeX**.

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5. Study the Phase Space of **Perimeter** of cells.
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.