Robustness of epithelia tissue growth to cell mechanics

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Institute of Evolutionary Biology and Environmental Studies, UZH.

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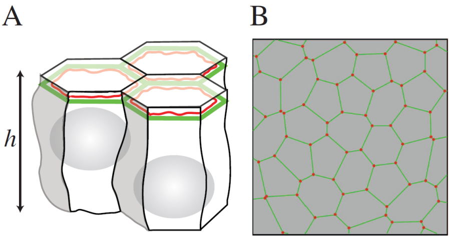
22 October 2015, IEU/UZH, Switzerland.

Junctional network



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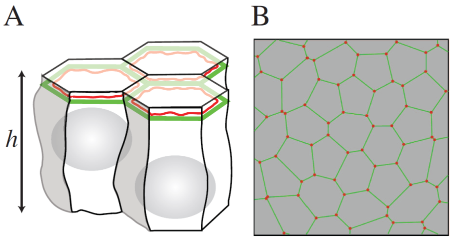

1. Epithelia cells are connected to each other via adhesive molecules.
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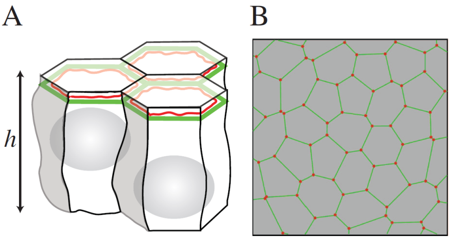
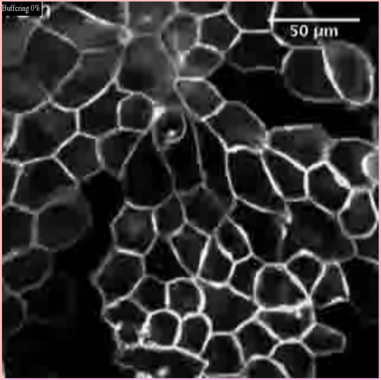


1. Epithelia cells are connected to each other via adhesive molecules.
2. Epithelia cells establish a **junctional adherent network** near their apical region.
3. Epithelia tissues are simpler to be studied (2-dimensional).

Tissue growth: cells as polygons, tissues as networks

Tissue, cells, Edges, and Vertices



1. Tissue as a network of cells[1].

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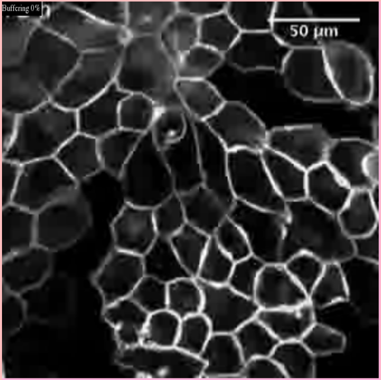

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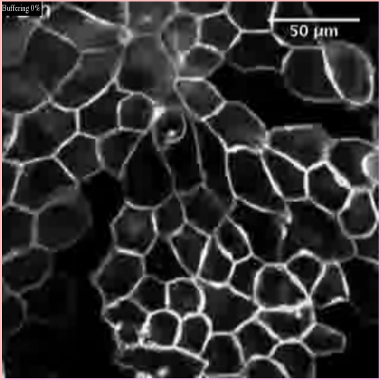

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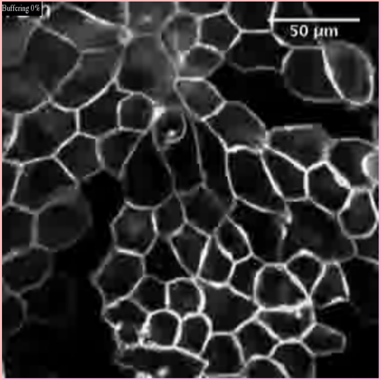

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4. Each Edge is composed by 2 Vertices[1].

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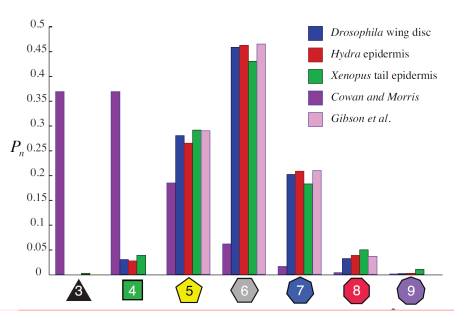
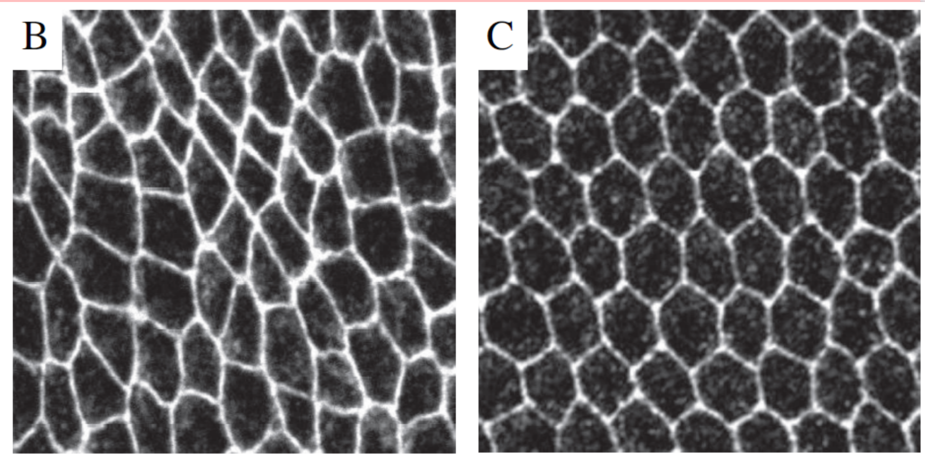
Different kind of tissues

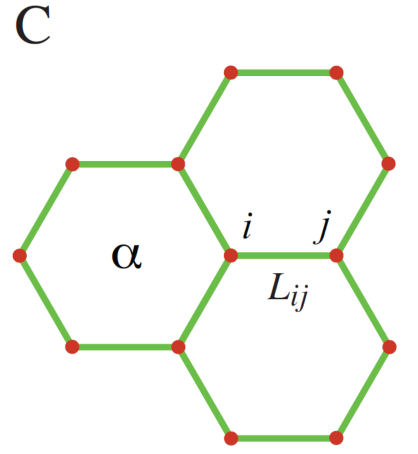


Different Developmental stages (Drosophila wings)

(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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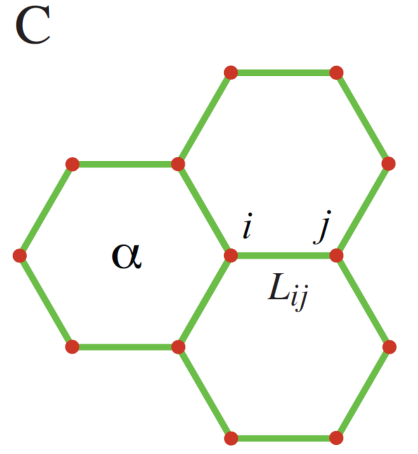

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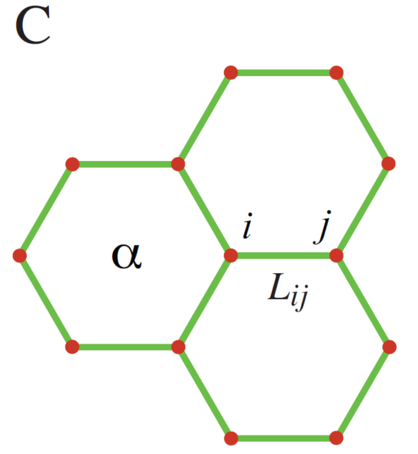

- Edge's Line tension (Λ) is associated to Edge's length[1].
- Cell's Contractility (Γ) is associated to Cell's Perimeter[1].
- Cell's Elasticity (K) is associated to Cell's Area[1].

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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

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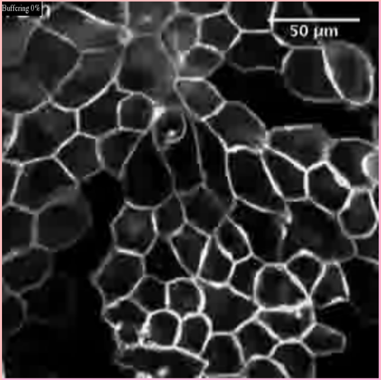
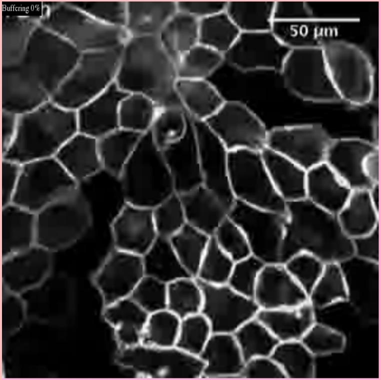


We keep the physical properties of the cells fixed during the simulation. So, in order to satisfy the **Minimal Energy's Assumption** the positions of the vertices need to change.

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: $A_\alpha^{(0)} = \frac{V_\alpha}{h_\alpha}$

Sequence of Events[1]

1. **Relaxation** (Vertices change their position to guarantee the force balance to be equal to zero).

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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).

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Relaxation[1]

Rectangular tissue with 5x5 cells

- 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*

Relaxation[1]

Rectangular tissue with 5x5 cells

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

[1]Farhadifar et al. *The influence of cell mechanics, cell-cell interactions, and*

Relaxation[1]

Rectangular tissue with 5x5 cells

- 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*

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 ($\frac{sd(\sum_\alpha L_\alpha)}{mean(\sum_\alpha L_\alpha)} \approx 0$).

Regularness 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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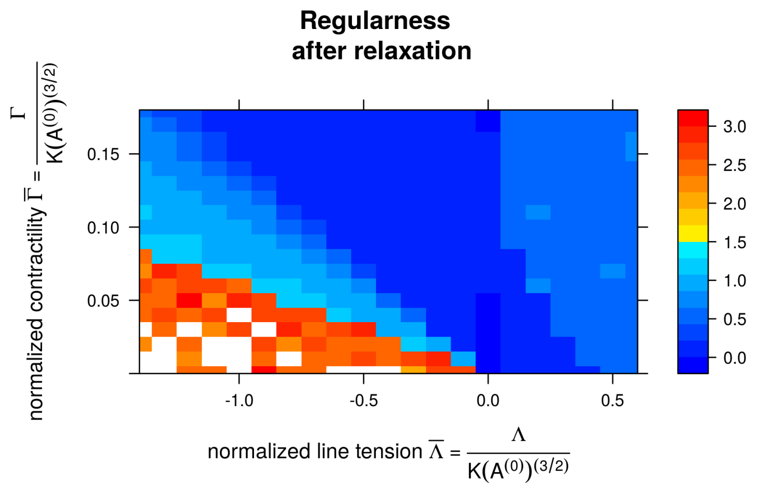
$Reg \approx 0$

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

$Reg > 0$

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

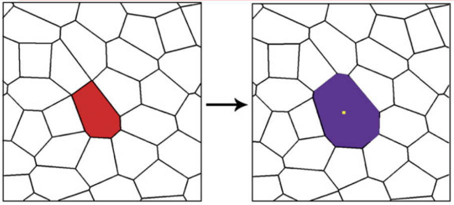
Phase space of Regularness



Cell Proliferation

- Cell Growth.
- Cell Division.

Cell Growth[1]



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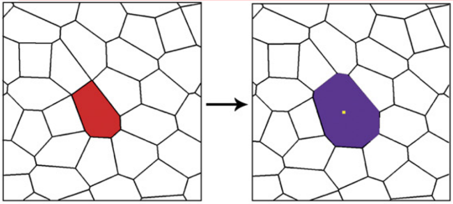

1. Cells are **randomly** triggered to increase their area.
2. They increase their area by 10% each time step.

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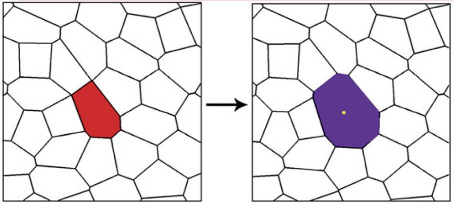
Cell Growth[1]



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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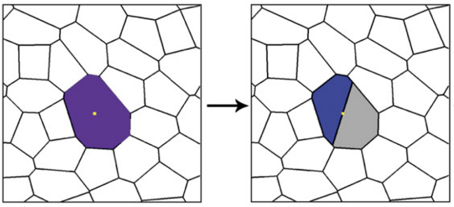
Cell Division[1]



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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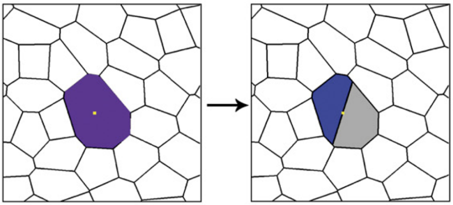
Cell Division[1]



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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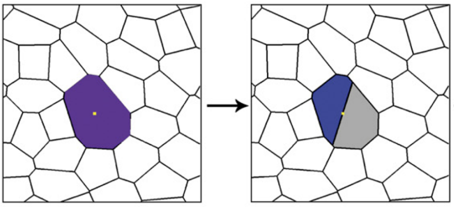
Cell Division[1]



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

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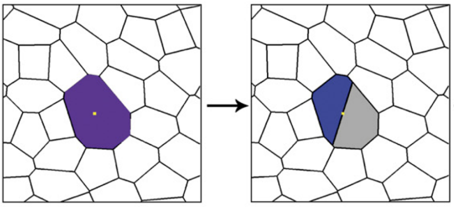
Cell Division[1]



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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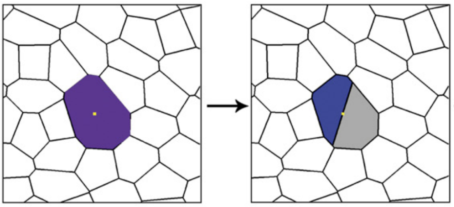
Cell Division[1]



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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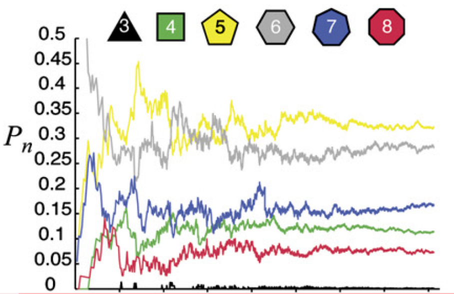
Steady state



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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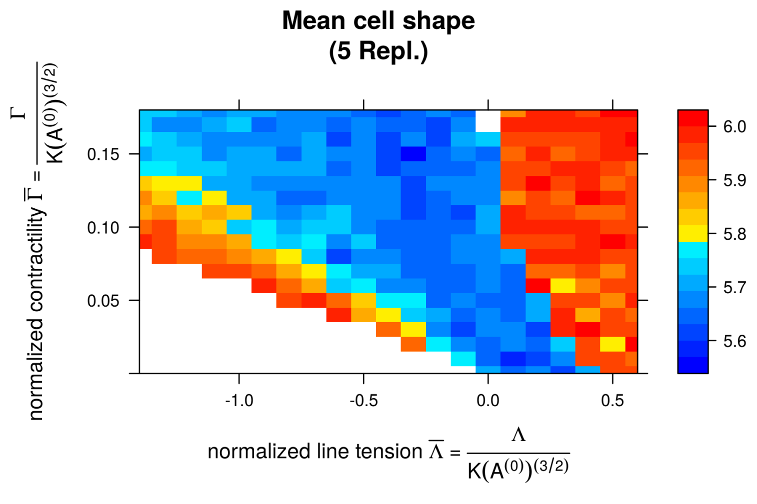
Phase space: Mean shape of cells (10 Repl.)



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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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4. Change the way cells are divided.
5. Change the shape of the tissue.

Thank you!

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