Robustness of tissue growth to cell mechanics

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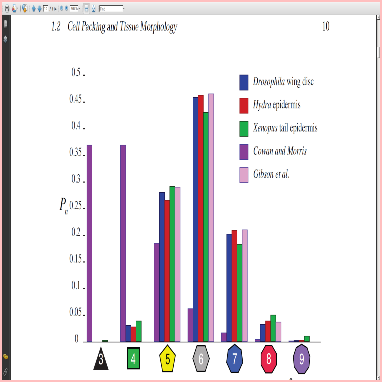
Tissue growth: cells as polygons, tissues as networks

Different kind of tissues



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- Different cells *shapes* distributions are related to **different kind** of tissues[1].

Developmental stages of tissues

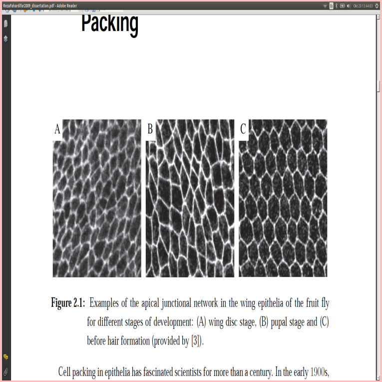

Figure 2.1: Examples of the apical junctional network in the wing epithelia of the fruit fly for different stages of development: (A) wing disc stage, (B) pupal stage and (C) before hair formation (provided by [3]).

Cell packing in epithelia has fascinated scientists for more than a century. In the early 1900s,

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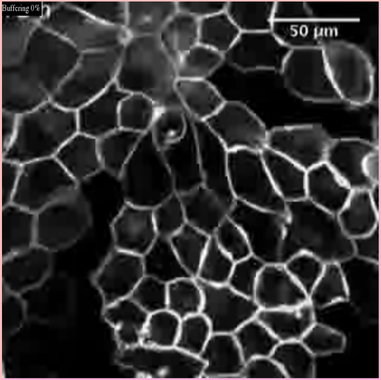
- Different cells *shapes* distributions are related to different **developmental stages** of a same tissue[2].

Tissue, cells, Edges, and Vertices



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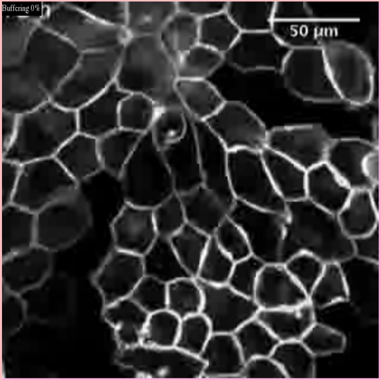
1. Tissue as a network of cells.

Tissue, cells, Edges, and Vertices



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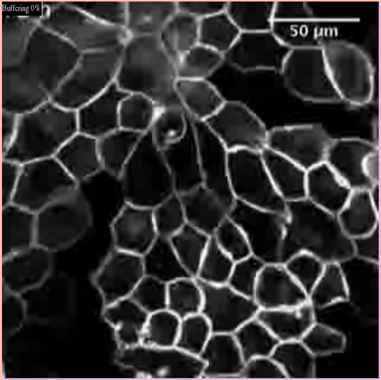

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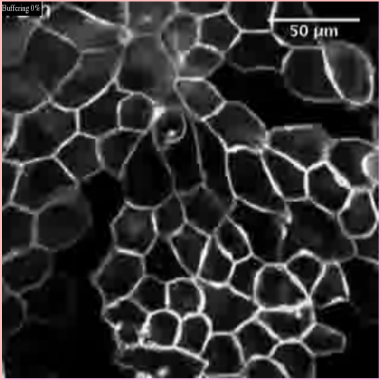
3. Each 2 Cells share 1 Edge.

Tissue, cells, Edges, and Vertices



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1. Tissue as a network of cells.
2. Cells as polygons.
3. Each 2 Cells share 1 Edge.
4. Each Edge is composed by 2 Vertices.

Edge's Line Tension

Include figure of a cell from Farhadifar

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

Cell's Contractility

Include figure of a cell from Farhadifar

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

Cell's Elasticity

Include figure of a cell from Farhadifar

- Cell's Elasticity (K) is associated to Cell's Area.

Force Balance Energy Function

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

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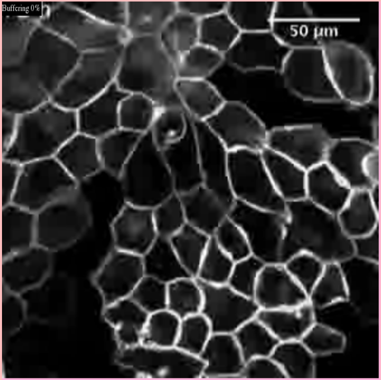
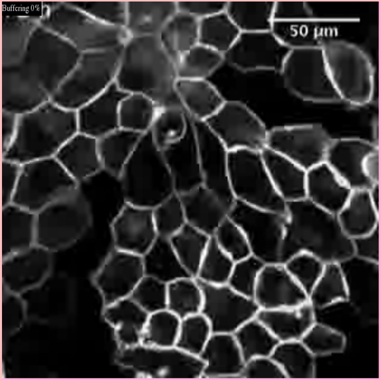


We keep the physical properties of the cells fixed during the simulation. So, in order to satisfy the **Minimal Energy's Assumption** theh positions of the vertices need to change.

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

Sequence of Events

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

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2. **Cell Proliferation** (cells growth and cells division).

Relaxation

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

Relaxation

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

Relaxation

- 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 $t + \Delta t$.

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.

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

Regularness of the tissue

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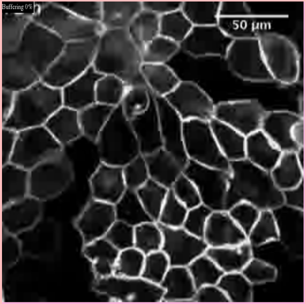
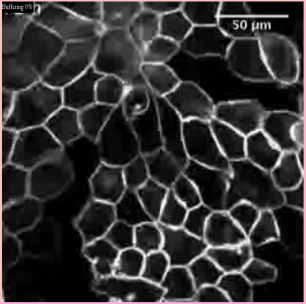
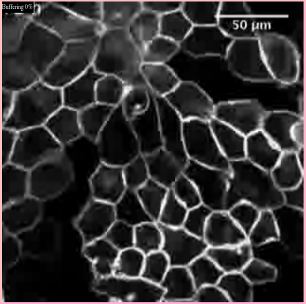
$$Reg \approxeq 0$$



$$Reg > 0$$



Phase space of Regularness



Phase space of Regularness in Time

Cell Proliferation

- Cell Growth.
- Cell Division.

Cell Growth

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

Cell Growth

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2. They increase their area by 10% each time step.

Cell Growth

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

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.

Cell Division

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

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.

Cell Division

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

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

Cell Division

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

Cell Division

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

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

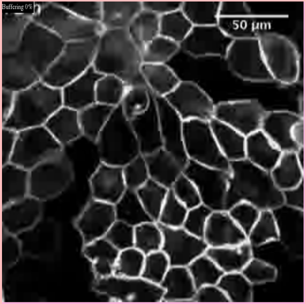
Cell Division

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

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.

Steady state

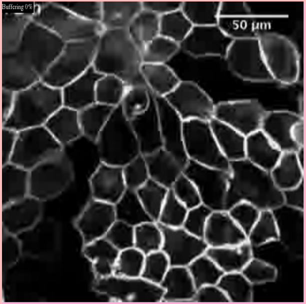
$$F = \sum_\alpha \frac{K_\alpha}{2}(A_\alpha - A_\alpha^{(0)})^2 \; + \; \sum_{(i,j)} \Lambda_{ij} L_{ij} \; + \; \sum_\alpha \frac{\Gamma_\alpha}{2} L_\alpha^2$$



1. The steady state of the cell division proccess is observed once the relative proportion of cells don't change along 1000 time steps.

Phase Space: Mean shape of cells

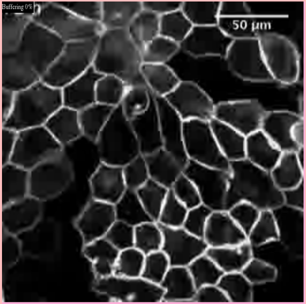
$$F = \sum_\alpha \frac{K_\alpha}{2}(A_\alpha - A_\alpha^{(0)})^2 \; + \; \sum_{(i,j)} \Lambda_{ij} L_{ij} \; + \; \sum_\alpha \frac{\Gamma_\alpha}{2} L_\alpha^2$$



1. We observed the following Phase space of shape of cells after 10 replicates.

Phase Space: Deviation of shapes of cells

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



1. We observed the following Phase space of the variation in the shape of cells after 10 replicates.

Phase Space: Mean shape of cells

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

1. Increase the number of replicates.

Phase Space: Mean shape of cells

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1. Increase the number of replicates.
2. Change initial conditions of the tissues.

Phase Space: Mean shape of cells

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1. Increase the number of replicates.
2. Change initial conditions of the tissues.
3. Change choice of cells to proliferate.

Phase Space: Mean shape of cells

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1. Increase the number of replicates.
2. Change initial conditions of the tissues.
3. Change choice of cells to proliferate.
4. Change the way cells are divided.

Phase Space: Mean shape of cells

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1. Increase the number of replicates.
2. Change initial conditions of the tissues.
3. Change choice of cells to proliferate.
4. Change the way cells are divided.
5. Change the shape of the tissue.

Thank you!

- SystemsX Initiative.
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- Wagner's Group members (UZH).
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