Model for epithelial growth

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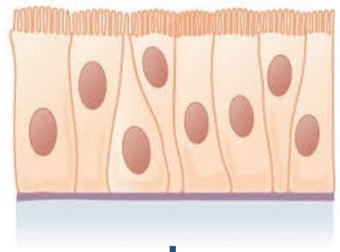
Motivation:
The mechanisms by which an organ knows when it has reached its adult size and shape and stops growing are poorly understood. Our focus here is the regulation of cell growth and proliferation.

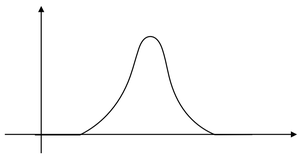
pseudo-stratified epithelia



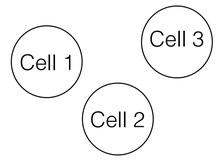
Hypothesis:
Mechanical feedback as compression or stretching plays a role in the regulation of cell growth at different scale.

Macroscopic model

We are working with biologists who study the development of the imaginal disc of drosophila. Among different hypothesis we study the influence of mechanical feedback.



We study a cell density



We study each cell individually

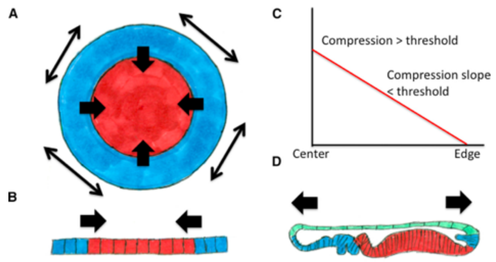


Fig 1: Hariharan, 2015. Developmental Cell, 34, 255-265

It has been showed that the imaginal disc can be divided in two categories of cells, the pouch (red) and the hinge (blue) which are not able to mix. This segregation could then create mechanical constraint as compression or stretching.

Hypothesis:
A possible regulator of tissue growth is the division of cells in two different categories that do not mix, with some elasticity constraint.

Microscopic model

To understand the regulation of cell growth, we want to study the deformation of each cell (nucleus, membrane). This may give us information on existence of stretching, compression...

Biologists aimed to give us 3D reconstruction of the pouch of the imaginal disc of the drosophila at different stages of the development. This will allow us to check the model we are developing.

Objective:
Create a mathematical model for cell packing in a tissue and implement the different steps of the cellular division (pick a cell, growth, migration to the top of the tissue, division...).

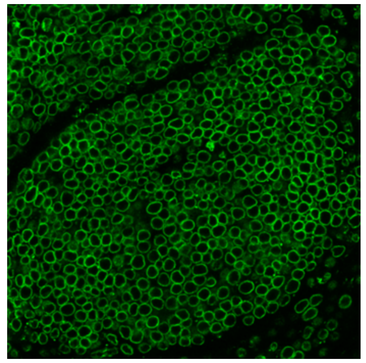


Fig 4: Dominik Schienstock

Mathematical model for 2 categories of cells unable to mix

To model the evolution of the cell density *n(x,t)* we use a simple **diffusion model** that has been previously proposed by Benoît Perthame [1] in the context of tumor growth.

$$\partial_t n - \nabla.(n\nabla p) = nG(p) \qquad (1)$$

The pressure *p(x,t)* expresses the volume exclusion and can be expressed by $p(n) = \epsilon\frac{n}{1-n}, \epsilon << 1$.This model derives from the following free energy, with *P* a primitive of *p*,

$$\mathcal{E}(n) = \int P(n(x))dx.$$

For the two species case we now have two different species of density $n_1(x,t)$ and $n_2(x,t)$. We modify the expression of the **free energy** by,

$$\mathcal{E}(n_1,n_2) = \lambda\int P((n_1+n_2)(x))dx + \mu\int Q((n_1n_2)(x))dx, \qquad (2)$$

where *P* expresses the volume exclusion pressure and *Q* corresponds to a **repulsion pressure** between the two different categories of cells.

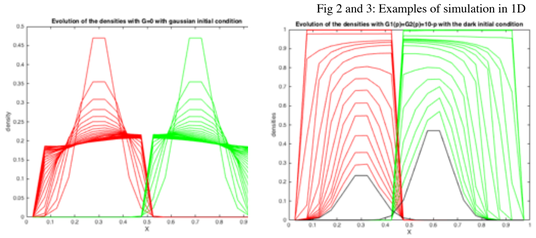
$$P(n_1{+}n_2) = -\epsilon(n_1{+}n_2{+}ln(1{-}(n_1{+}n_2))), \text{ and } Q(n_1n_2) = \frac{\widetilde{p}n_r}{m-1}(\frac{n_1n_2}{n_r^2}{+}1)^m, m >> 1.$$

We can derive from this free energy the system of equations

$$\partial_t n_1 + \nabla_x(n_1v_1) = n_1G_1, \qquad (3)$$
$$\partial_t n_2 + \nabla_x(n_2v_2) = n_2G_2, \qquad (4)$$
$$v_1 = -\nabla_x(\lambda p(n_1+n_2) + \mu n_2 q(n_1n_2)), \qquad (5)$$
$$v_2 = -\nabla_x(\lambda p(n_1+n_2) + \mu n_1 q(n_1n_2)). \qquad (6)$$

where *p* and *q* are respectively the derivative of *P* and *Q*.

Fig 2 and 3: Examples of simulation in 1D



Mathematical model for cell packing in a tissue

The first step is to create a model for a stationary tissue, without cellular division. We consider the tissue as an **elastic box**, and we model only cell by nucleus which are represented by spheres floating in the tissue.

The elastic box is delimitated by the points $(Y_i)_{i\in[1;S]}$. Points of the elastic box are linked by strings and torques so the according energy is expressed by

$$E_{spring}(Y) = \sum_{i=1}^{S}\frac{1}{2}k_i(|Y_{i+1}-Y_i| - l_i)^2,$$

$$E_{torque}(Y) = \sum_{i\in T_S}\frac{1}{2}c_i(\frac{Y_{i+1}-Y_i}{|Y_{i+1}-Y_i|}.\frac{Y_{i-1}-Y_i}{|Y_{i-1}-Y_i|}+1)^2 + \sum_{i\in T_c}\frac{1}{2}c_i(\frac{Y_{i+1}-Y_i}{|Y_{i+1}-Y_i|}.\frac{Y_{i-1}-Y_i}{|Y_{i-1}-Y_i|})^2$$

where $(k_i)_{i\in[1;S]}$ is the stiffness and $(l_i)_{i\in[1;S]}$ the rest length of the spring, and *Tc*, *Ts* are respectively the points lying at the corner and the side of the box. So we want to **minimise** the energy

$$E(Y) = E_{spring}(Y) + E_{torque}(Y),$$

with the **constraint** that each sphere$(X_i)_{i\in[1,N]}$ of radius $(R_i)_{i\in[1,N]}$ stays inside the box and without overlapping. These conditions can be expressed by

$$\forall i,j \in [1,N]\times[1,S], \psi_{i,j}(X,Y) < 0 \text{ and } \forall i,j\in[1,N]^2, \phi_{i,j}(X,Y) < 0$$

with

$$\psi_{i,j}(X,Y) = R_i - |X_i - Y_j|$$

and

$$\phi_{i,j}(X,Y) = R_i + R_j - |X_i - X_j|.$$

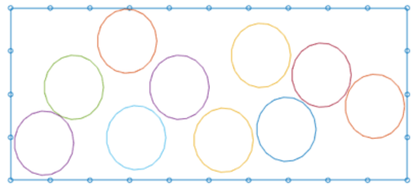


Fig 4: scheme of the system: colored circles are the cells and blue lines define the elastic box

Reference:
[1] Benoit Perthame, Fernando Quiros, and Juan-Luis Vasquez, The hele-shaw asymptotics for mechanical model of tumor growth. *hal-00831932*.
[2] Richard Jordan, David Kinderlehrer and Felix Otto. The variational formulation of the fokker-Planck equation. *SIAM J.MATH ANAL, 1998*
[3] David Kinderlehrer and Noel J. Walkington. Approximation of parabolic equations using the Wasserstein metric. *M2AN, Vol. 33, No 4, 1999*

Conclusion/work to do:
- 2D simulation for the macroscopic model and add stretching,
- Simulation for the microscopic model,
- Add cellular division in the microscopic model.

Keywords:
diffusion model, free energy, repulsion pressure, elastic box, minimise with constraint.