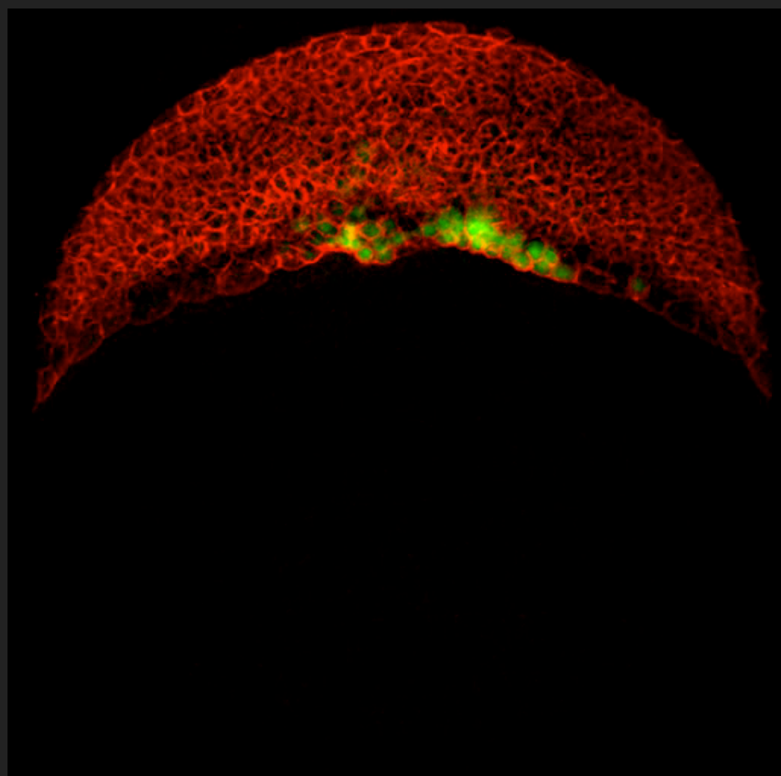
PRINCIPLES OF PHYSICAL MODELING



RODRIGO SOTO
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Optics, Forces & Development 2024

ACTIVE MATTER
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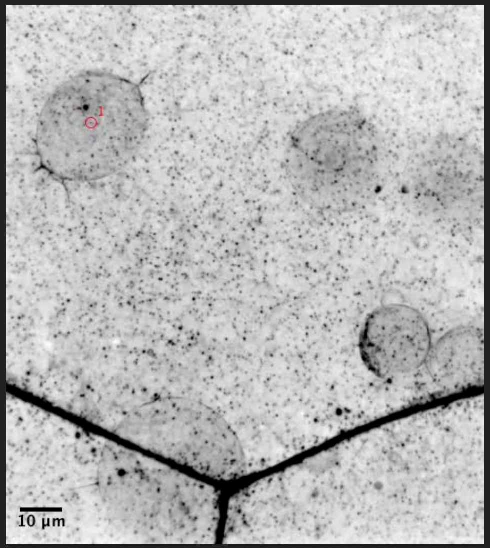
PHYSICAL MODELING

The objective is to use the concepts of physics to describe some biological process

Here, we will use mechanical models related to **development**

One key issue, not always trivial, is that a good model should:

- Give more than you put into
- Predict new phenomena or understand the origin of some phenomena
- Have the correct physics



APPROACHES TO PHYSICAL MODELING

There are different levels of description (level of detail)

1) Continuum description. Each element is a deformable body, with elastic and fluid properties. Very detailed

Need:
- The spatio-temporal distribution of active stresses
- The rheological properties of the material (elastic, viscous, etc)

2) Discrete element methods. Each element is a simple object. Interactions are relevant. Less detail

Here, we will consider this approach to mesenchymal cells and tissues

DISCRETE ELEMENT METHOD: MESENCHYMAL

Mesenchymal cells are described as single elements that:

- Cannot deform

- There are friction viscous forces with the substrate

- Move by generation of protrusions
  - This motion can be directed or random

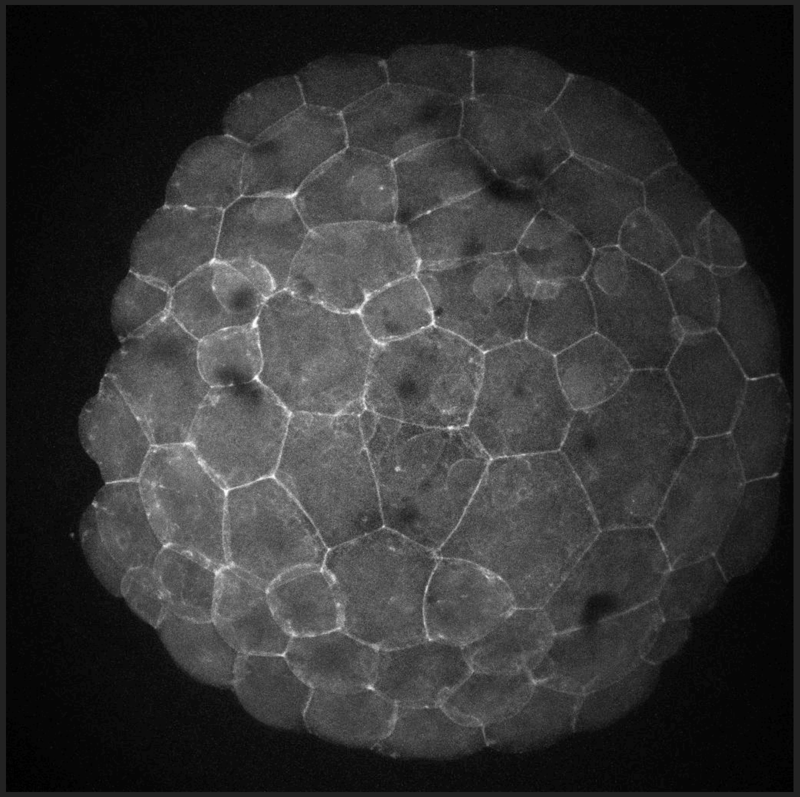
- There are interactions between neighbor cells
  - at short distance they repel due to excluded volume
  - at larger distances cells attract due to adhesive protrusions

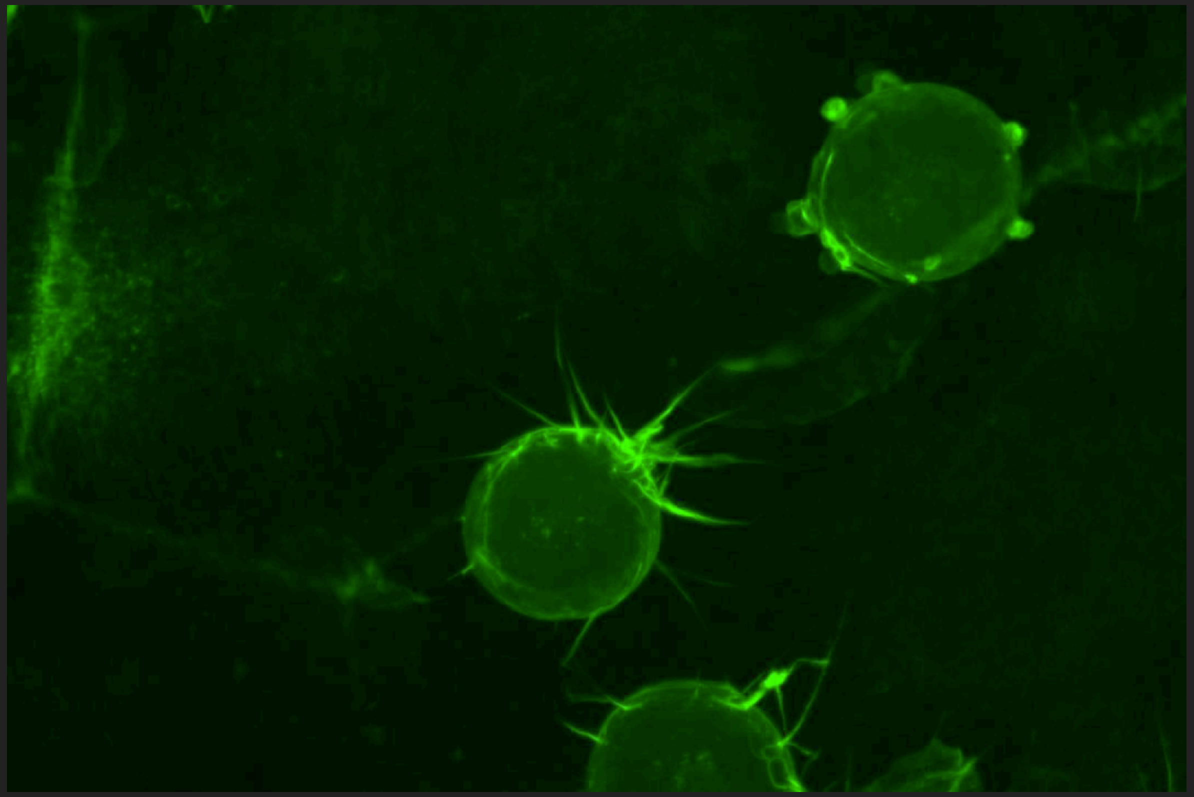
EFFECTIVE FORCES

Frictions viscous forces with the substrate

$$F = -\gamma V$$

But, in some cases, the cells move on a moving layer





$$F = \gamma(V_{\text{layer}} - V)$$

EFFECTIVE FORCES

Then, the total sum of forces is

$$F = \gamma(V_{\text{layer}} - V) + F_{\text{intra cells}} + F_{\text{others}} = 0$$

$$V = V_{\text{layer}} + (F_{\text{intra cells}} + F_{\text{others}})/\gamma$$

Looks like Aristotle….

This is what we call, an over-damped dynamics or non-inertial dynamics

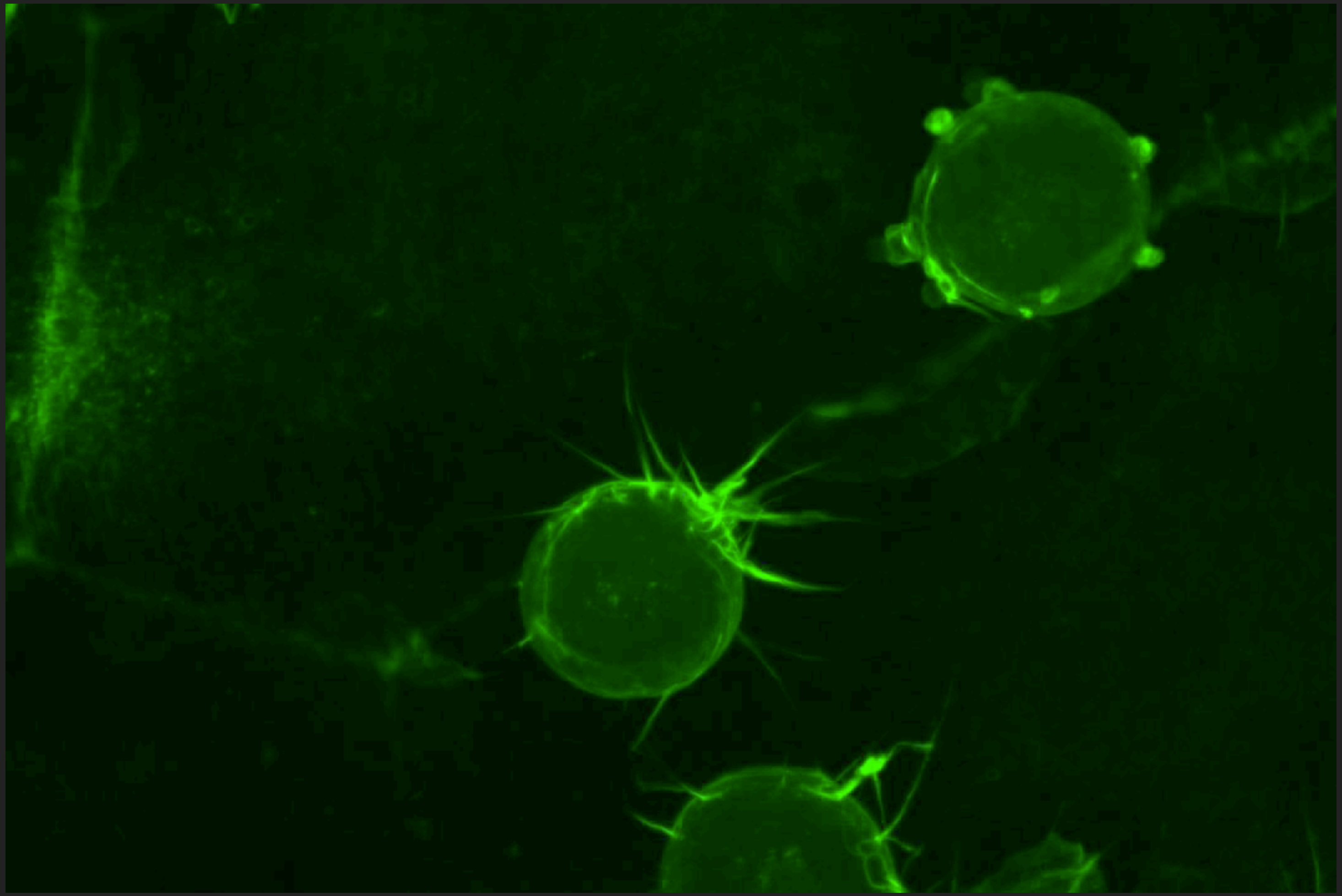
It simply reflects that applied forces are balanced by the friction force

EFFECTIVE FORCES

If the cell is polarized in a direction, the protrusive force is in that direction

$$V = V_{\text{layer}} + (F_{\text{intra cells}} + F_{\text{others}})/\gamma$$

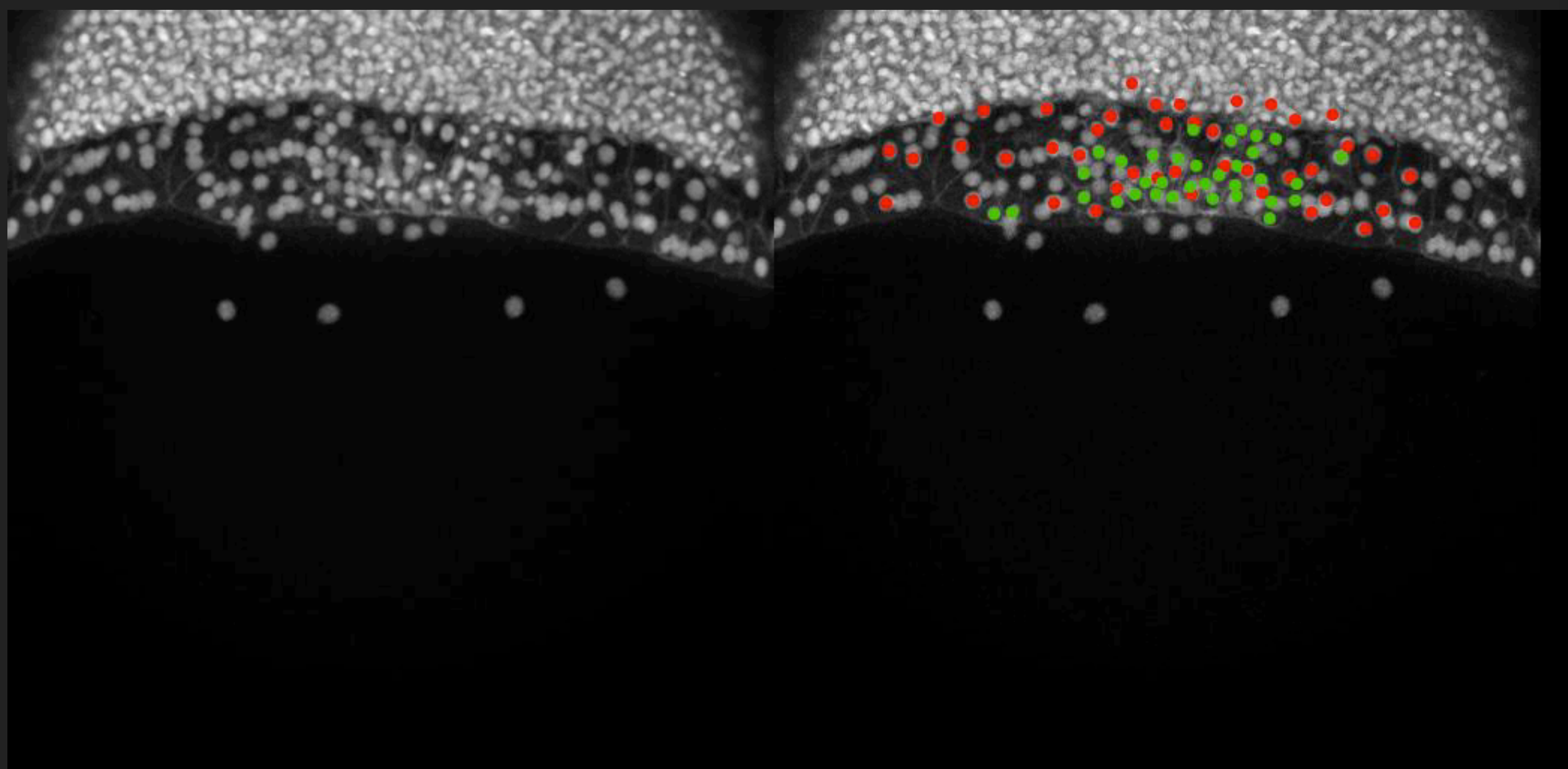
Gives rise to directed motion

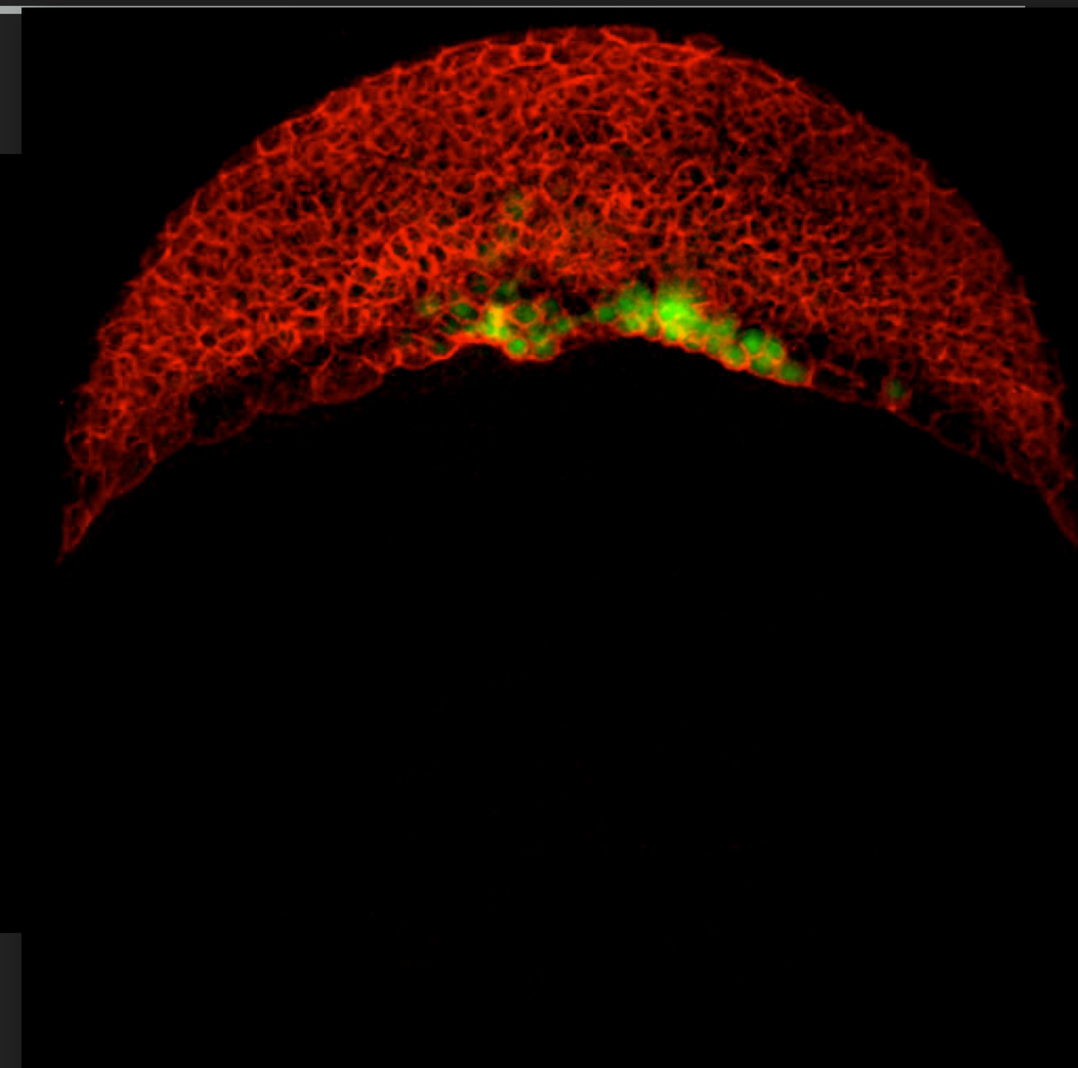


For non-polarized cells, The protrusive focus is erratic: in random directions

Gives rise to effective diffusion

APPLICATION: CELL MIGRATION IN ZEBRAFISH



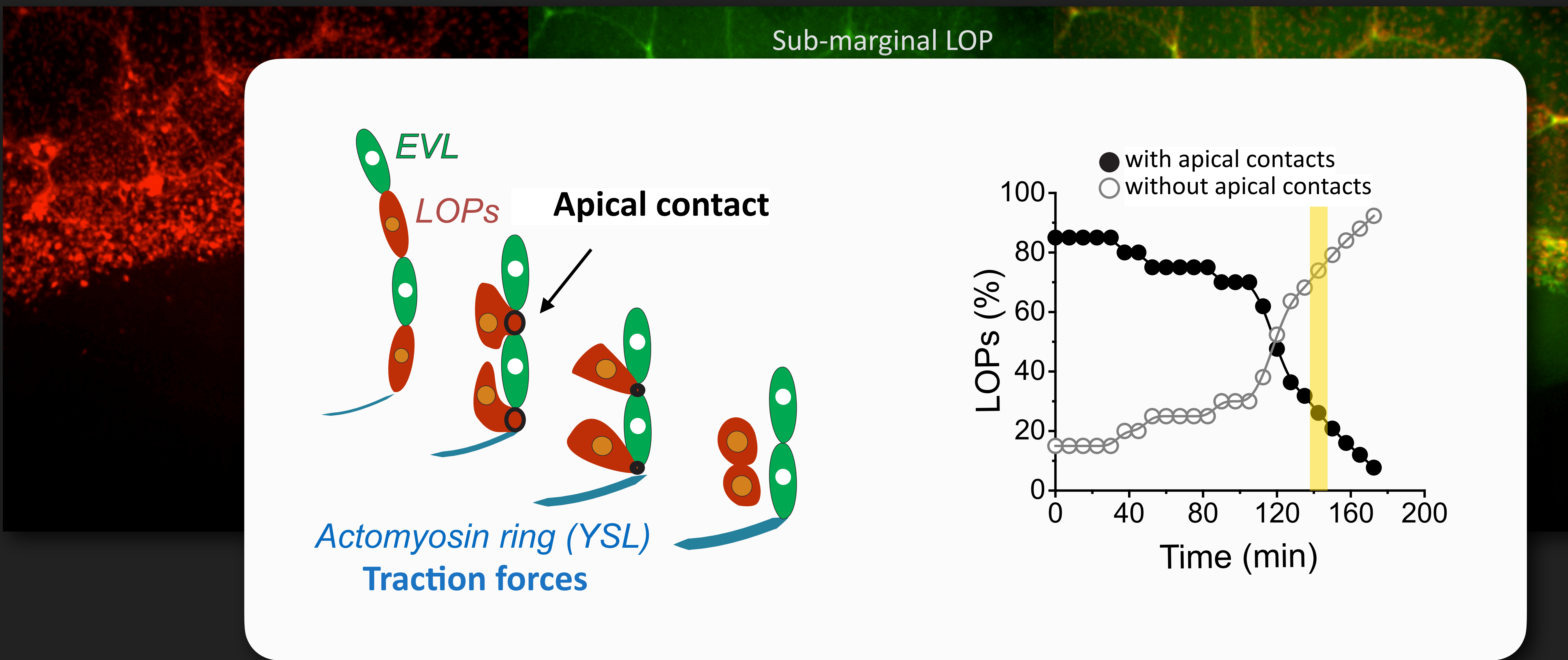


The protrusions are minority in the vegetal direction

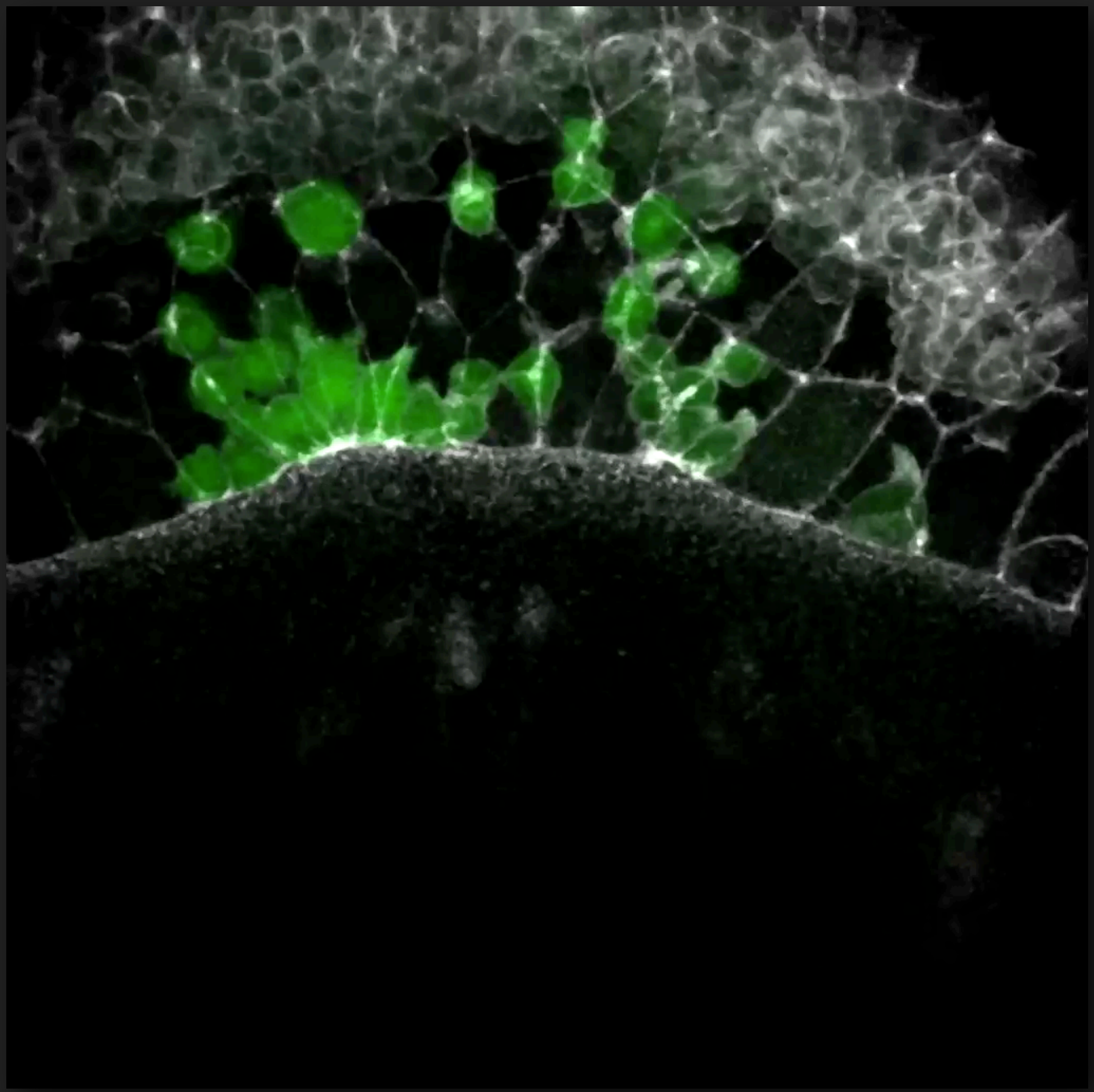
The migration is not due to cell polarization

What mechanism are responsible for the migration of the LOPs?

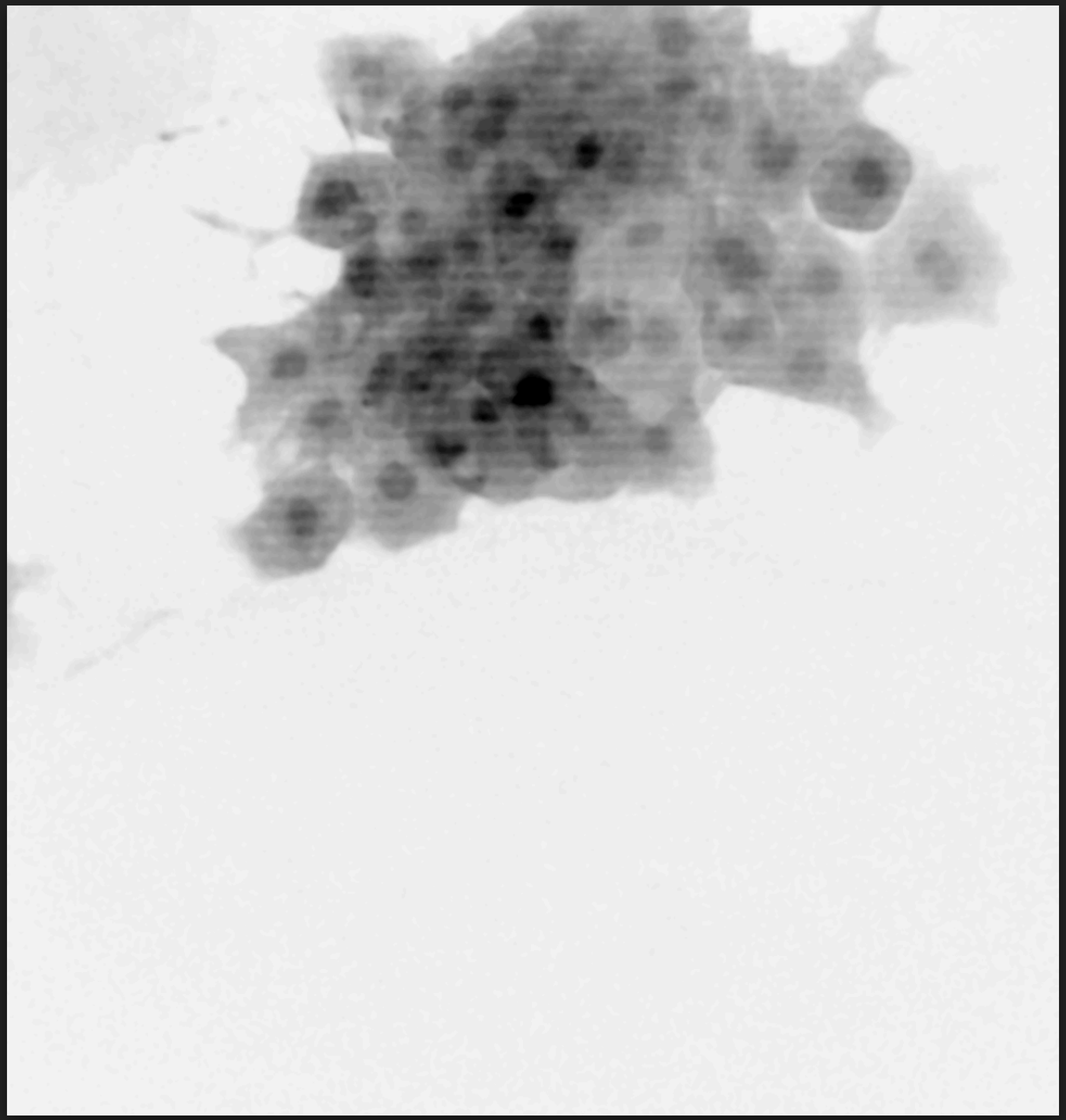
LOPS ORIGINATE FROM EVL DELAMINATION



LOP-LOP INTERACTION



cad1(E-cad) Mo

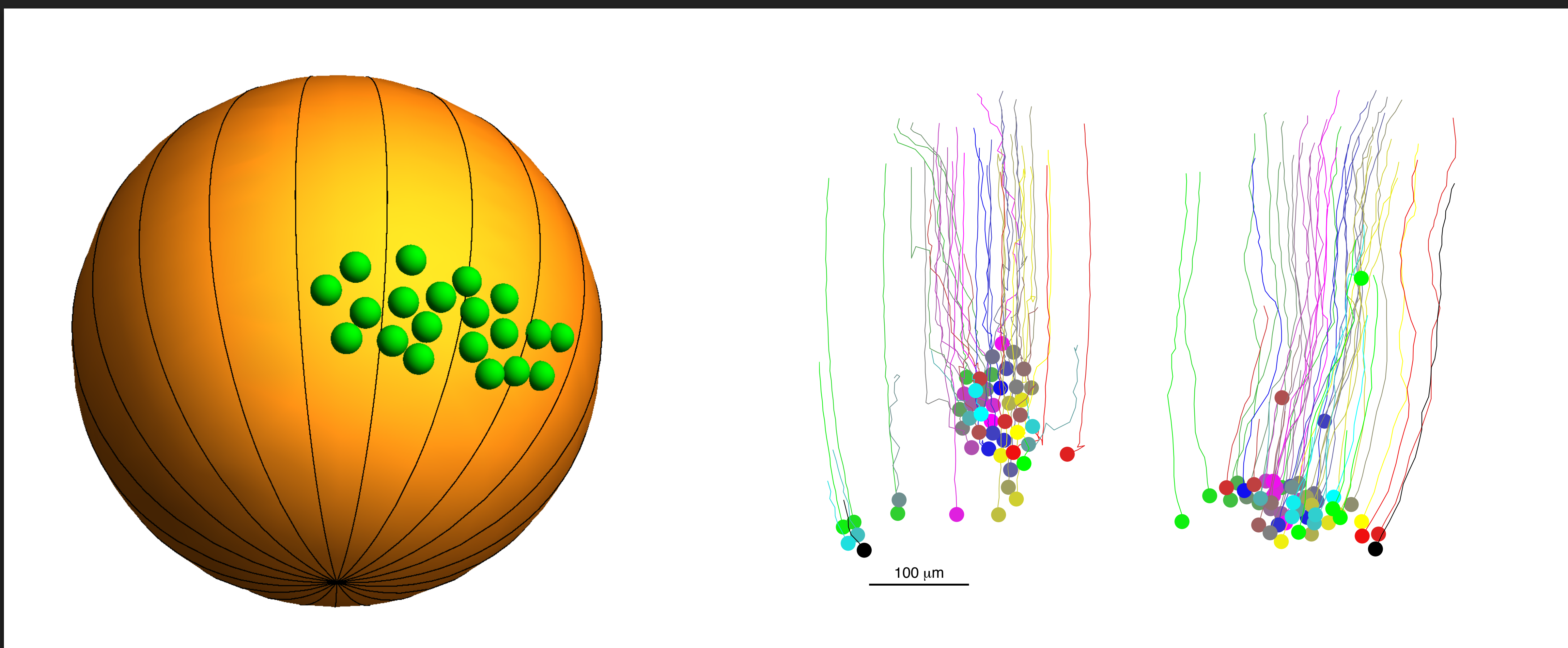


- **Lack of cell adhesions destroys the cluster integrity**
- **Large protrusions attract cells and keep to cluster together**
- **Interactions avoid loosing cells, protecting the integrity of the Laterality Organ**

PHYSICAL MODELING

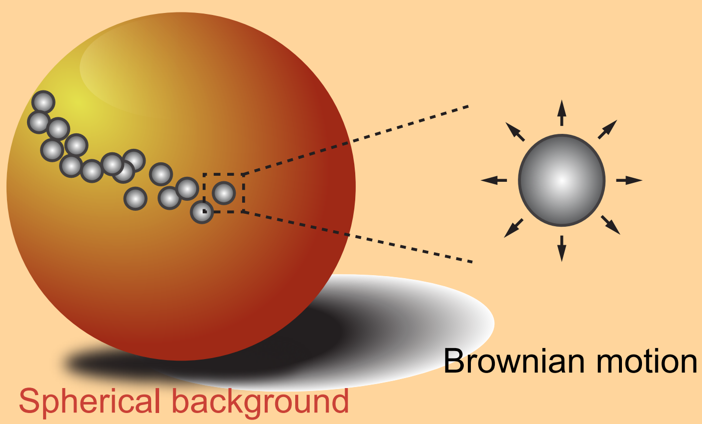
$$V = V_{\text{layer}} + (F_{\text{intra cells}} + F_{\text{others}})/\gamma$$

Intracell forces: adhseion-attraction
Other forces: random force, EVL traction



PHYSICAL MODELING

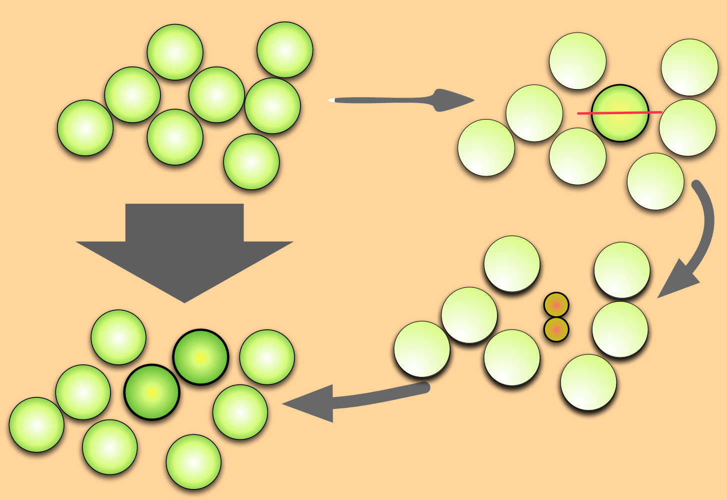
LOPs: Brownian circular particles moving on the egg's spherical surface



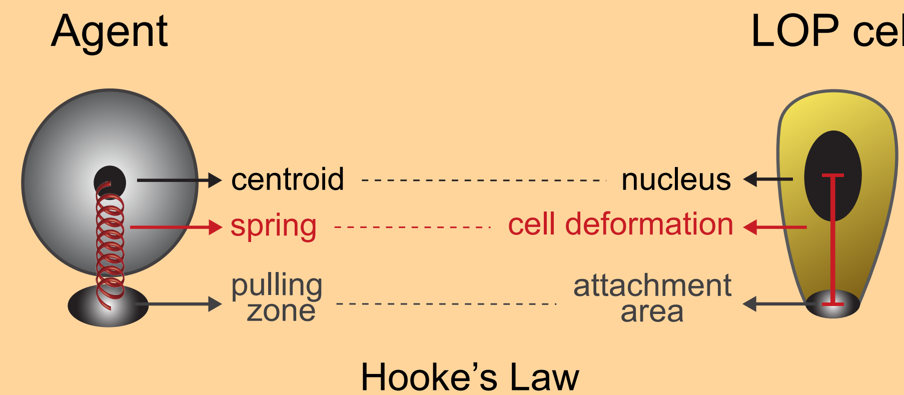
Overdamped dynamics

$$\frac{d\vec{r}_i}{dt} = \overrightarrow{F}_i + \vec{\xi}_i = -\frac{\partial U}{\partial \vec{r}_i} + \vec{\xi}_i$$

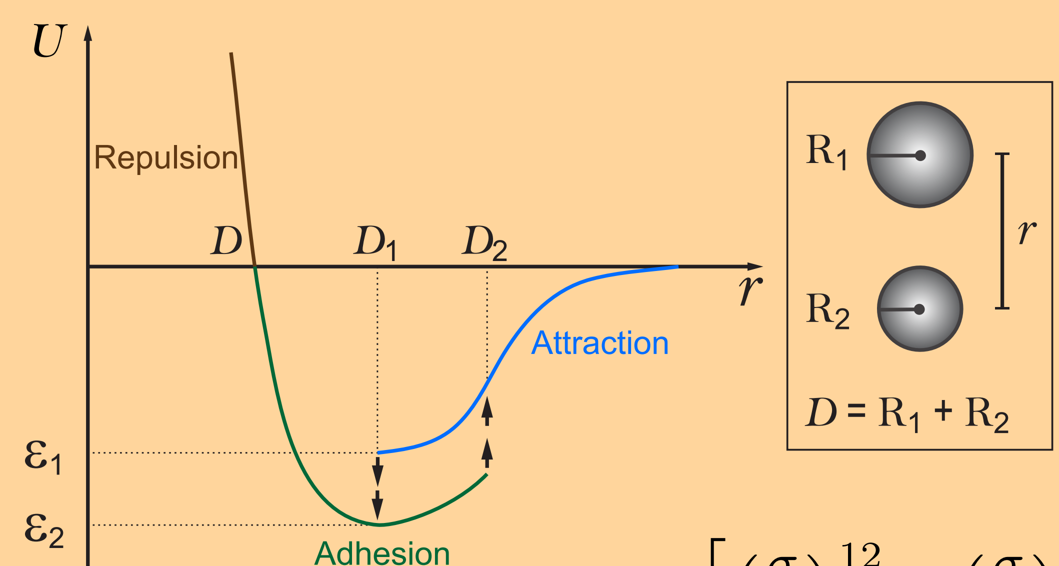
LOPs divide



Attachment with EVL modeles as an elastic spring. Number of attachments is gradually lost



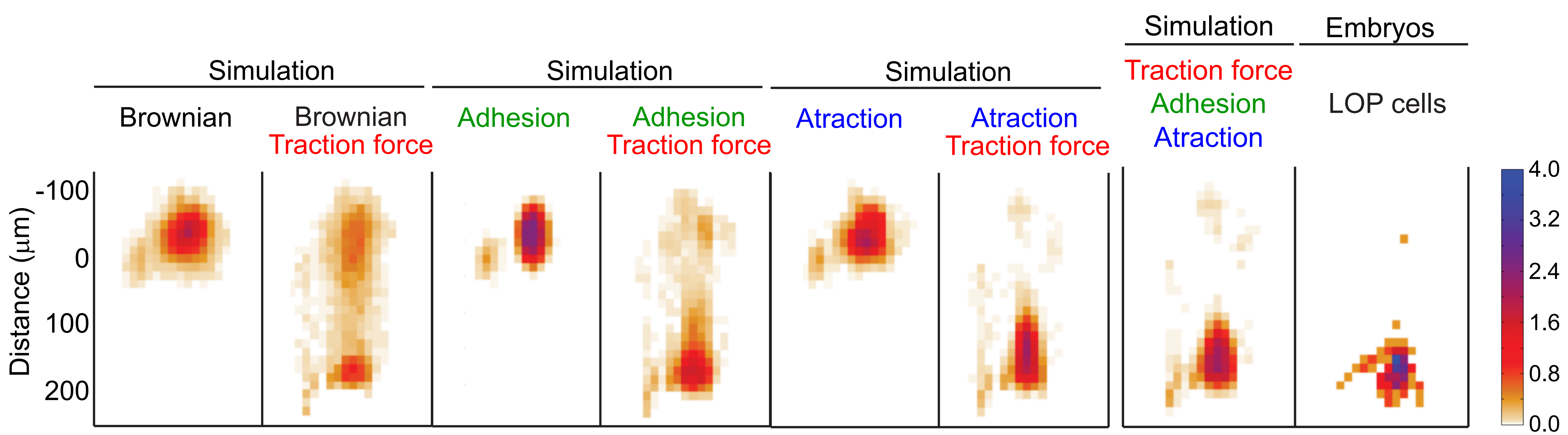
LOP-LOP interaction: potential with hysteresis



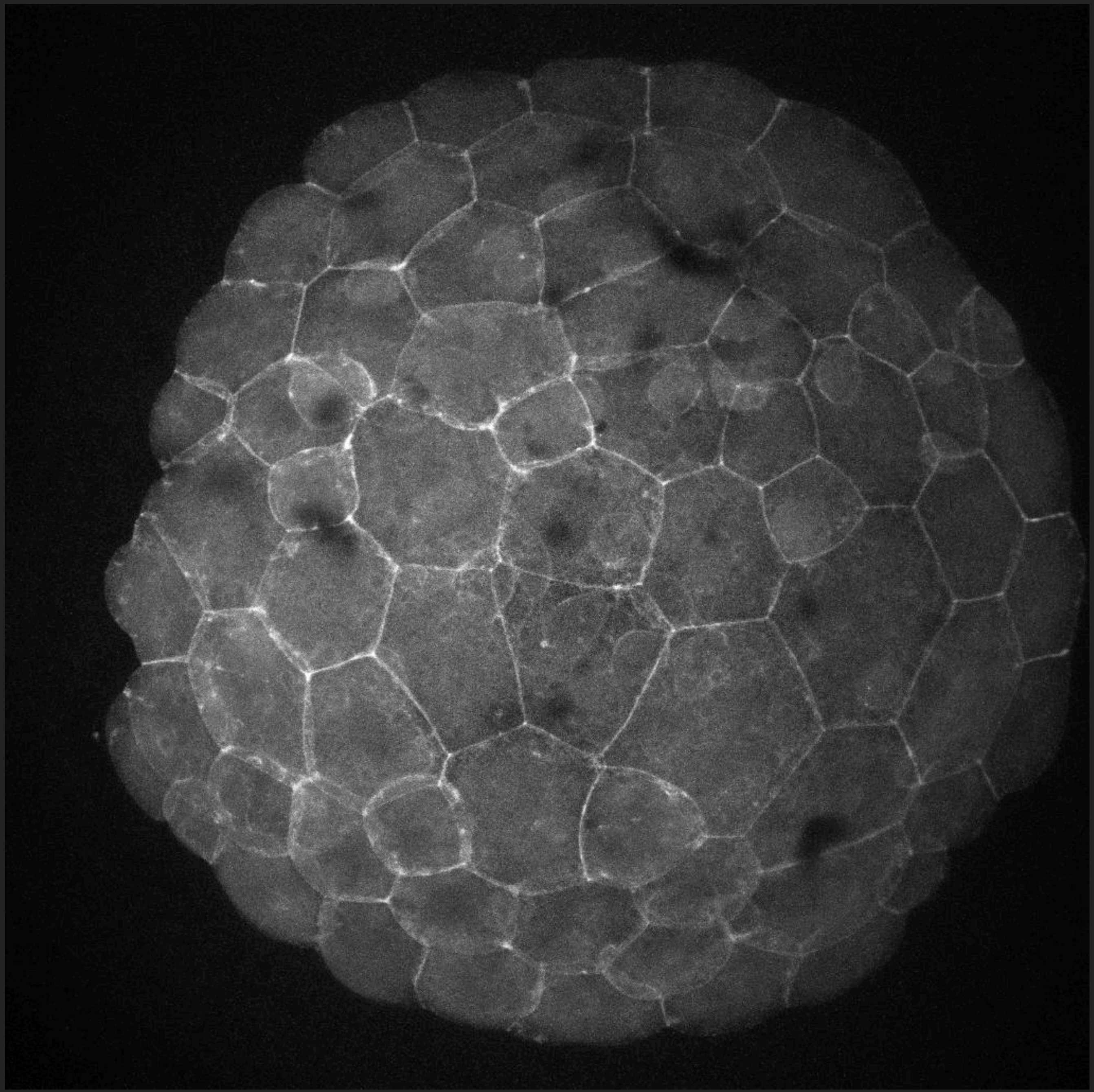
$$U = 4\varepsilon\left[\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^{n}\right]$$

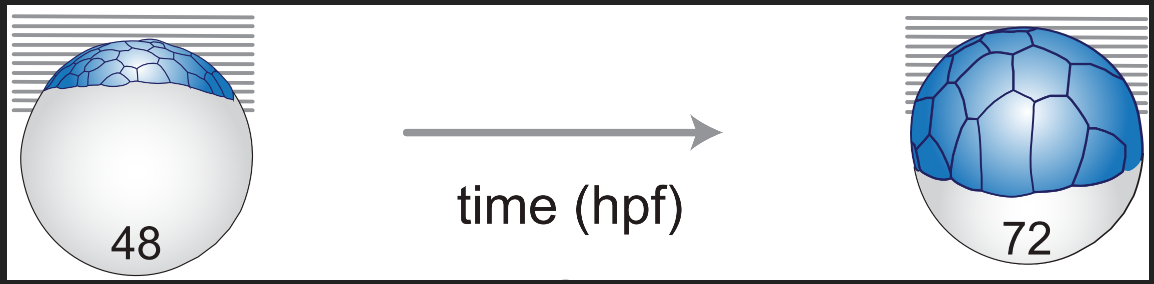
RESULTS

Cell density in the final state (after 200 mins)
Averaged over the 3 ICs



TISSUES: VERTEX MODEL



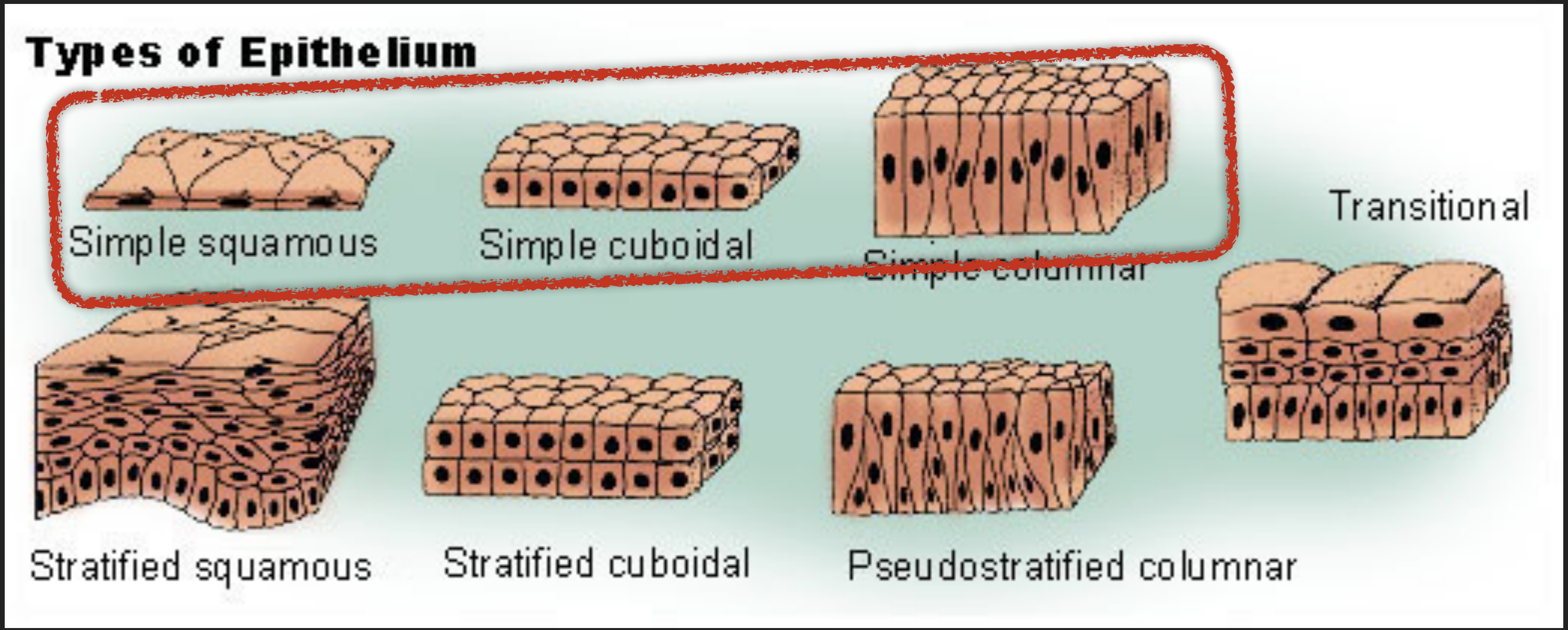


The tissue responds elastically

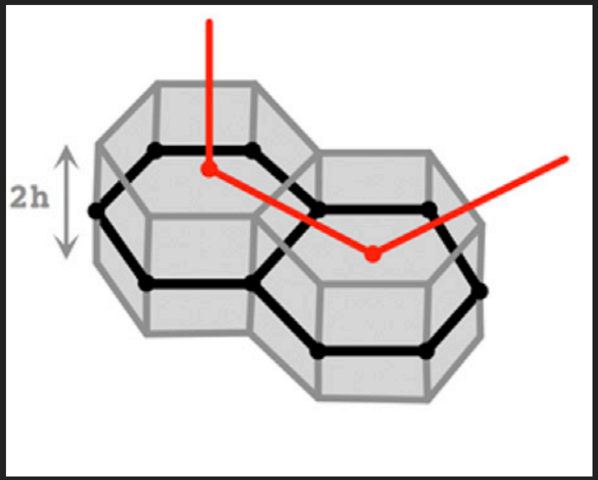
Time-dependent active stresses

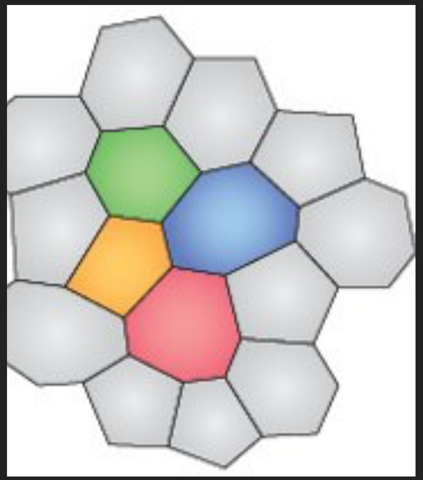
The active stresses change shapes

TISSUES: VERTEX MODEL



Instead of giving all the detail, we describe it as a tiling of polygons or polyhedra (cells)





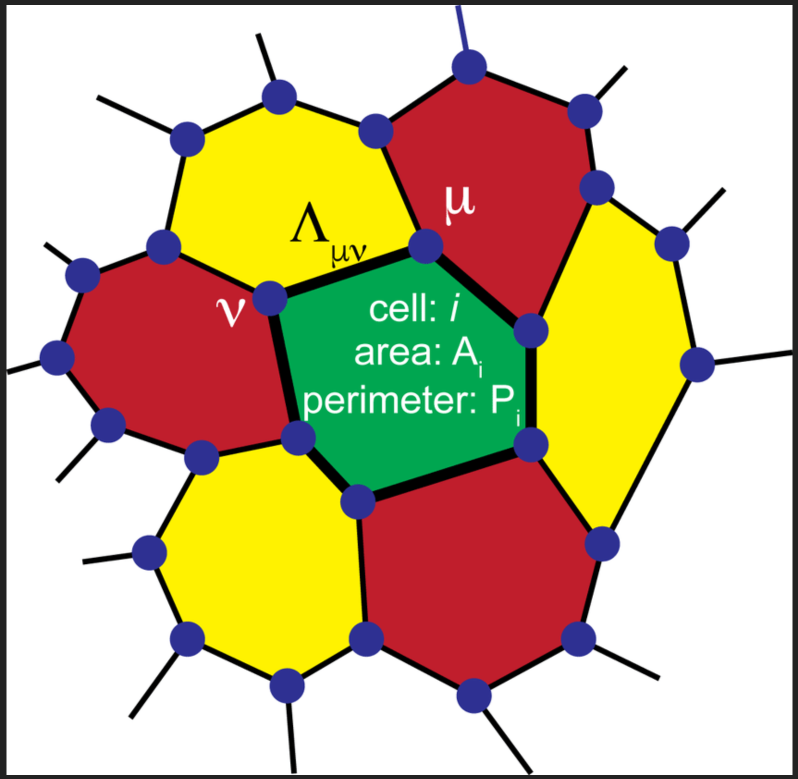
The polygons (polyhedra) are defined by the positions of their vertices

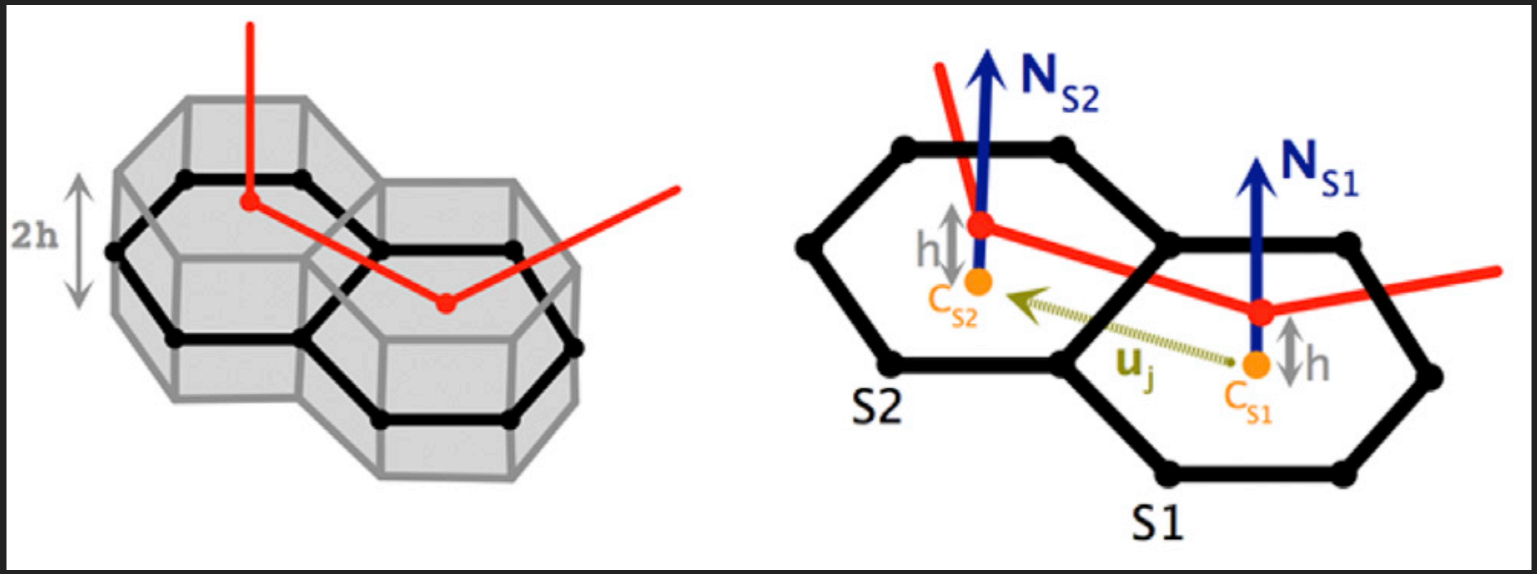
TISSUES: VERTEX MODEL

The polygons are defined by the positions of their vertices

Cells are characterized by their:

- Area, perimeter, length of edges, orientation (for polygons)
- Volume, areas, lengths, and orientation (for polyhedra)





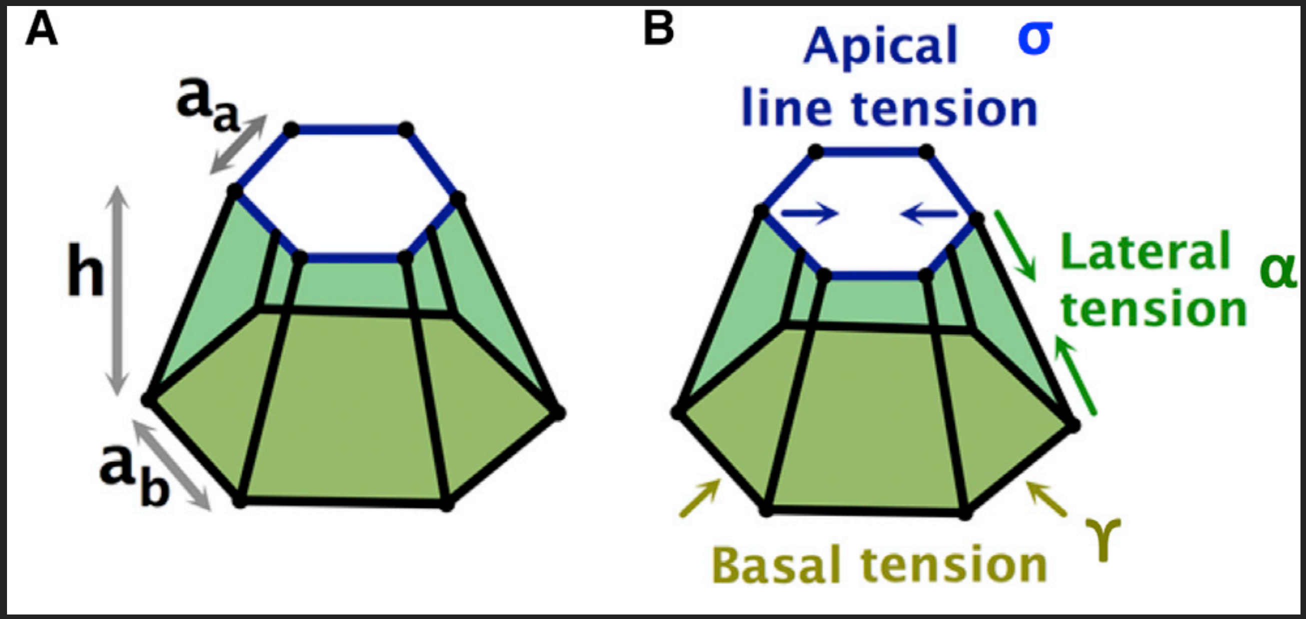
Misra et al. 2016

TISSUES: VERTEX MODEL

We define an “objective function” E, which measures the deviation of the cell to their preferred state

For polyhedra:

$$E_{3D} = \sigma \sum_{e} l_e + \alpha \sum_{l} S_l + \gamma \sum_{b} S_b + B \sum_{c} \left(V_c - V_c^0\right)^2.$$



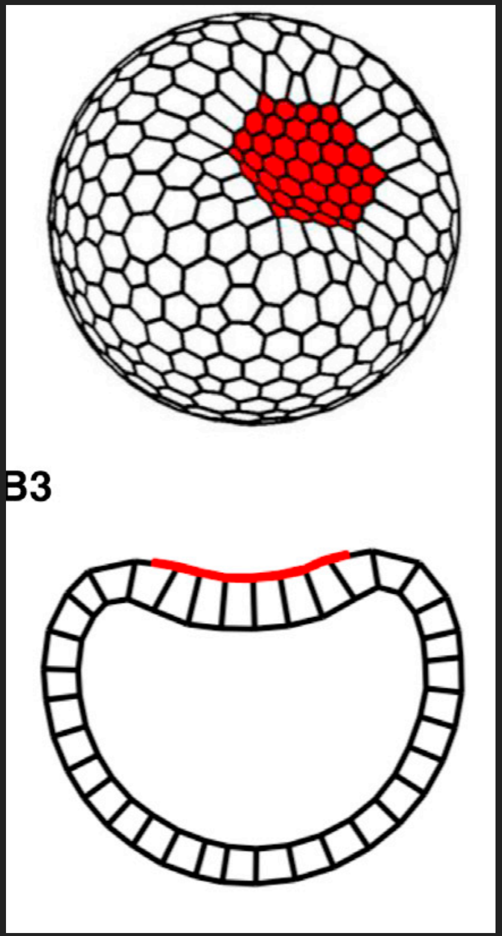
Cells deform (move the vertices) as to minimize E

ACTIVITY

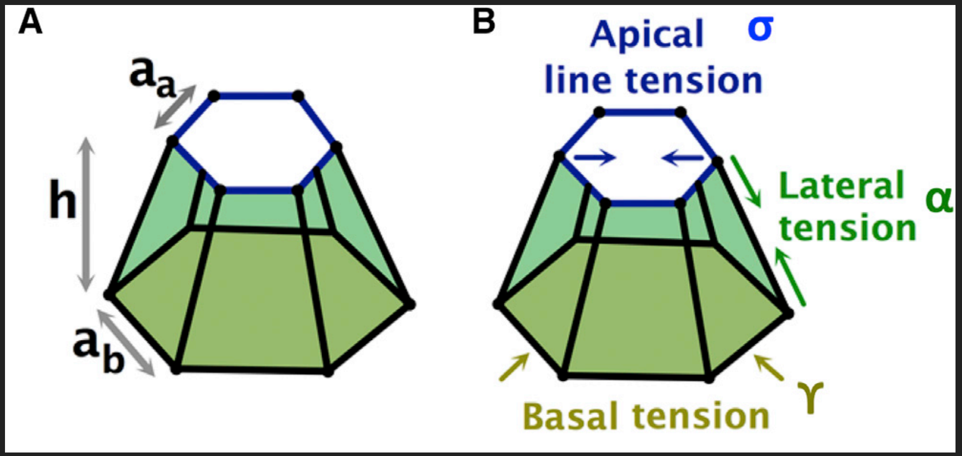
Cells deform (more the vertices) as to minimize E

$$E_{3D} = \sigma \sum_{e} l_e + \alpha \sum_{l} S_l + \gamma \sum_{b} S_b + B \sum_{c} \left(V_c - V_c^0\right)^2.$$

For example, increasing the apical line tension



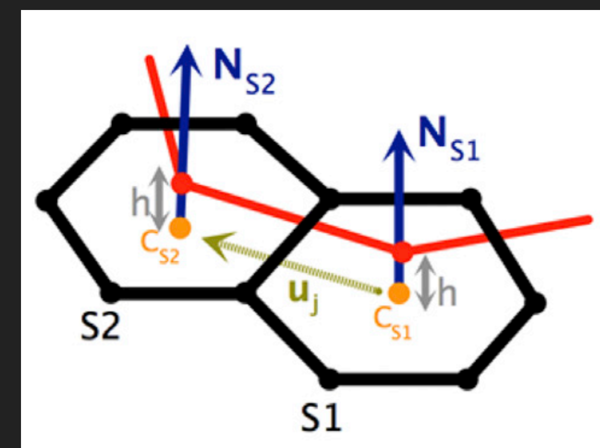
Misra et al. 2016



ACTIVITY

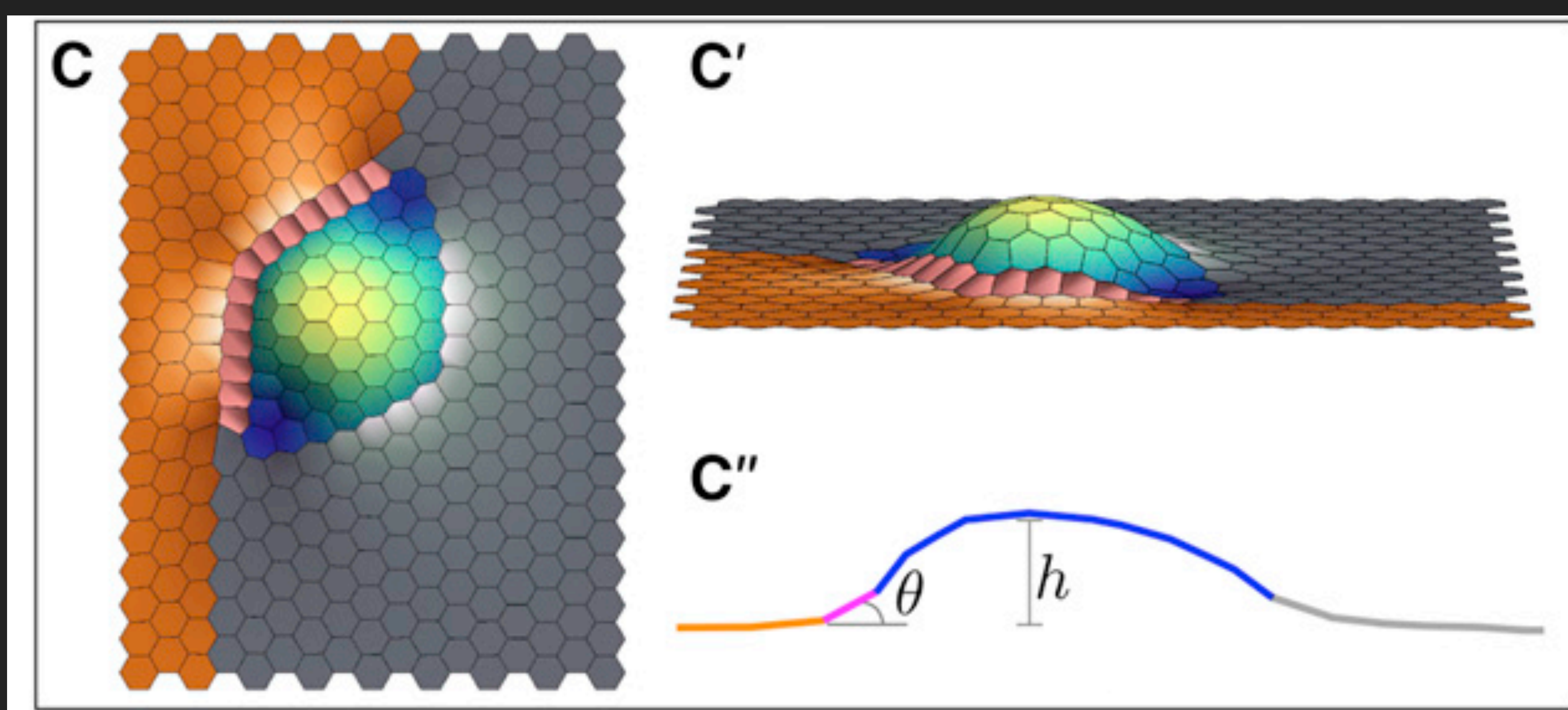
Also, we can model them as polygons. The objective function is

$$E_{2D} = \mu \sum_{c} \left(A_c - A_c^0\right)^2 + \sigma \sum_{j} l_j + \beta \sum_{j'} \left(\left(1 - \boldsymbol{N}_{s2(j')} \cdot \boldsymbol{N}_{s1(j')}\right)\right)$$



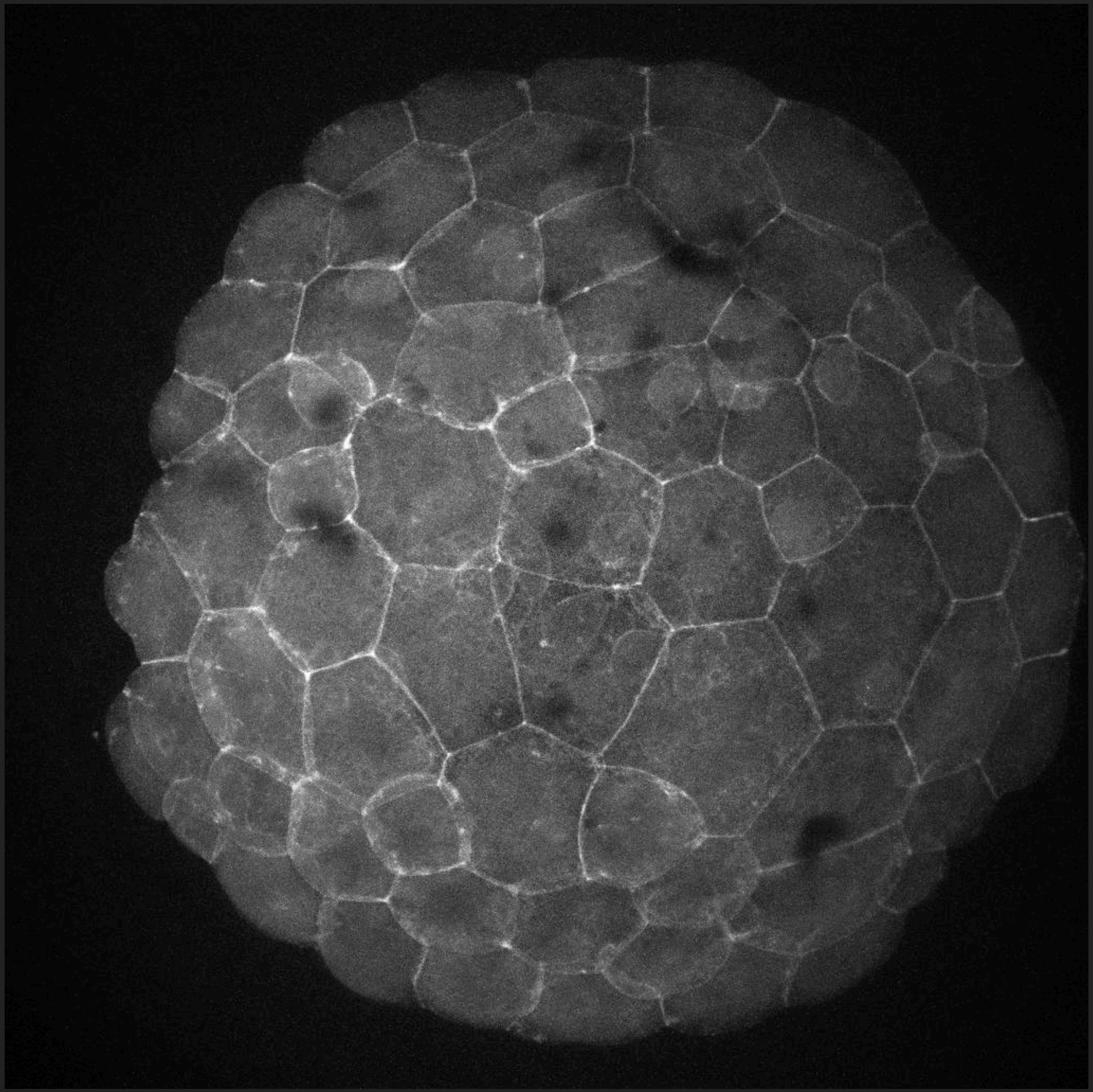
Misra et al. 2016

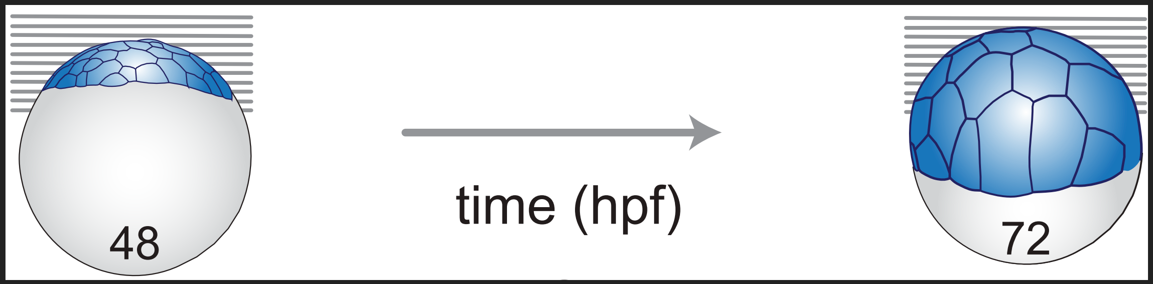
Modulating the line tension

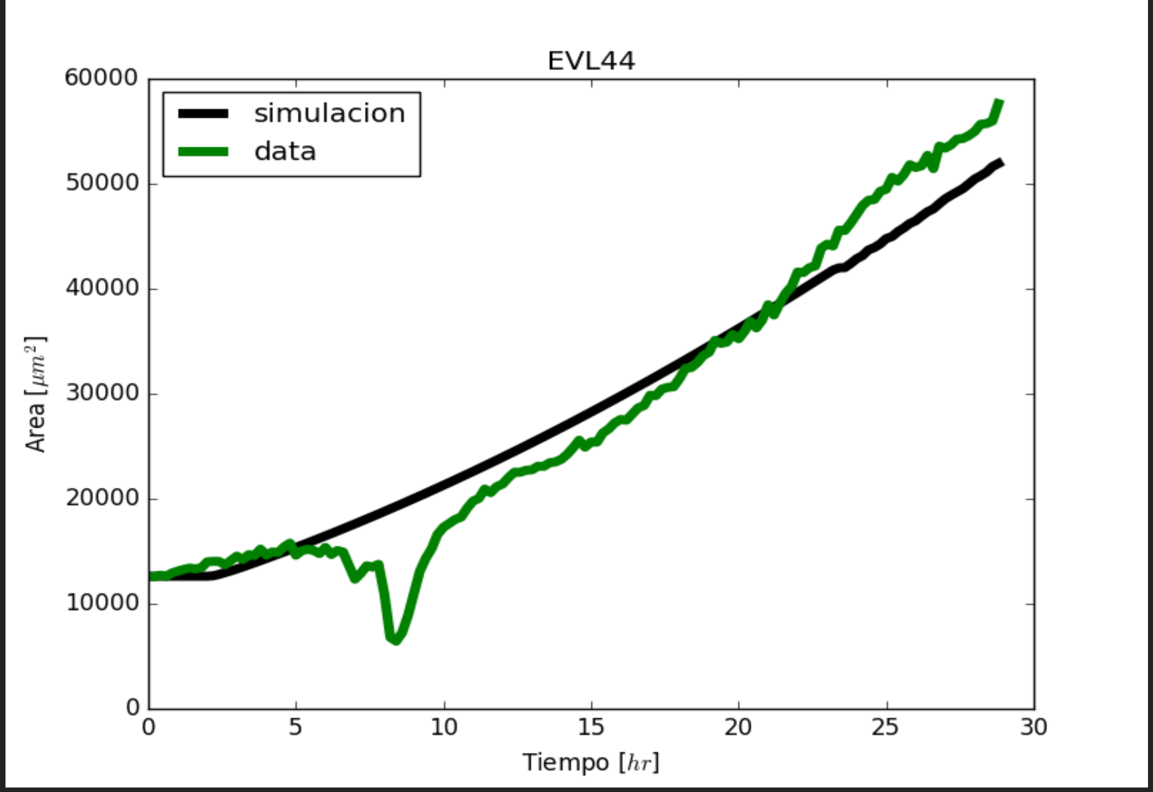


Osterfield et al. 2013

CELL CONTRACTION IN ANNUAL KILLIFISH AUSTROLEBIAS NIGRIPINNIS







SINGLE CELLS CONTRACT
THE TISSUE RESPONDS ELASTICALLY

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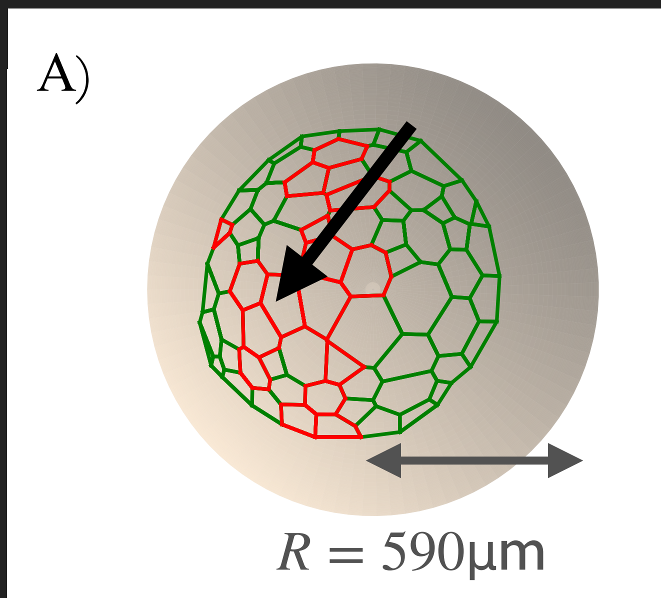
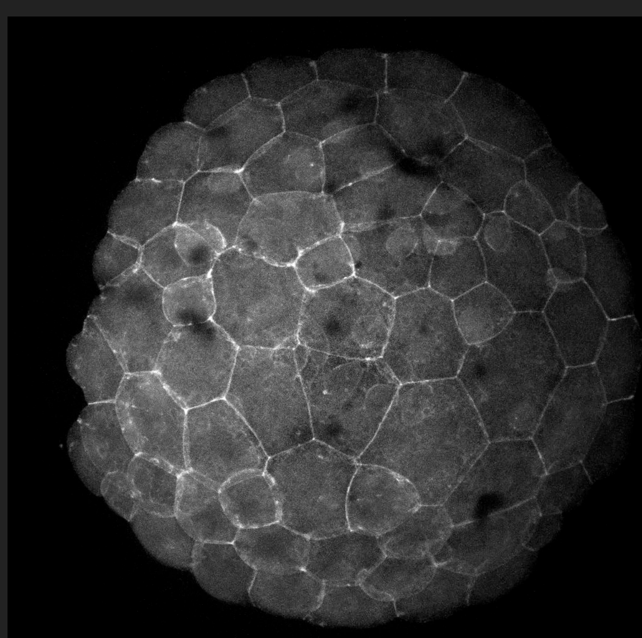
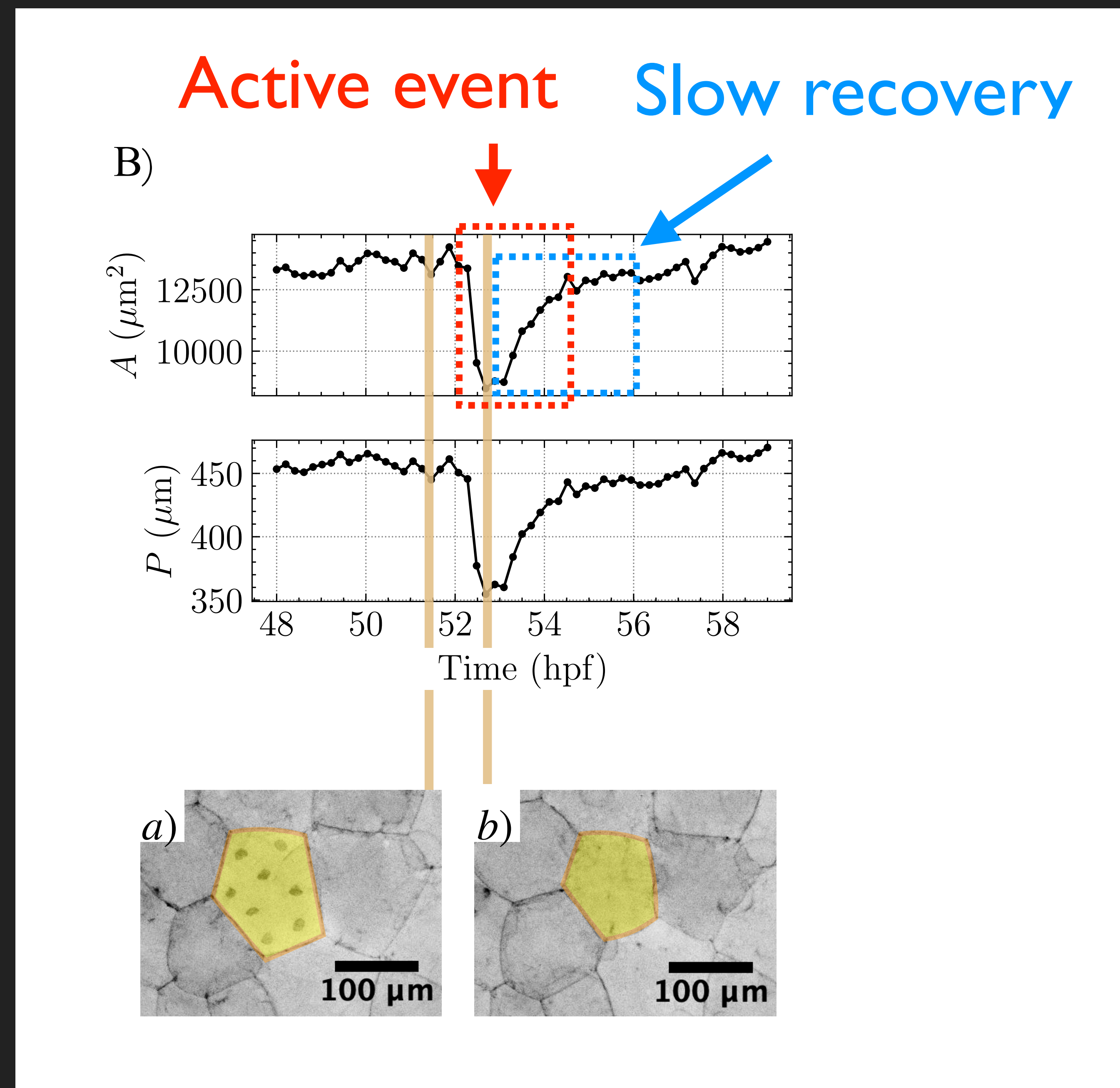
CELL CONTRACTION IN ANNUAL KILLIFISH AUSTROLEBIAS NIGRIPINNIS

Initial state: $t = 48$ hpf





Confocal microscopy using an embryo microinjected with lifeact-GFP.

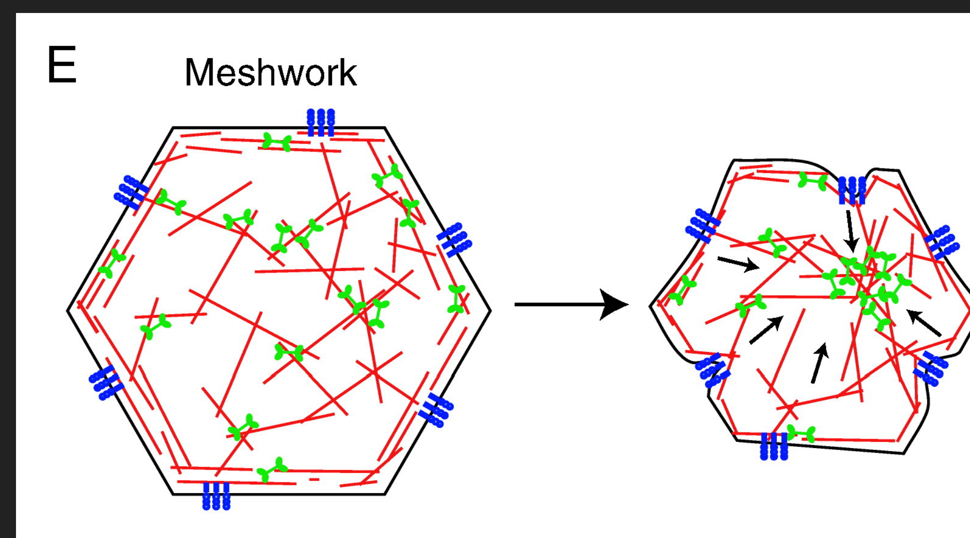


MODELS OF APICAL CONTRACTIONS?

Can we identify and quantify the forces that act during the contraction pulse?

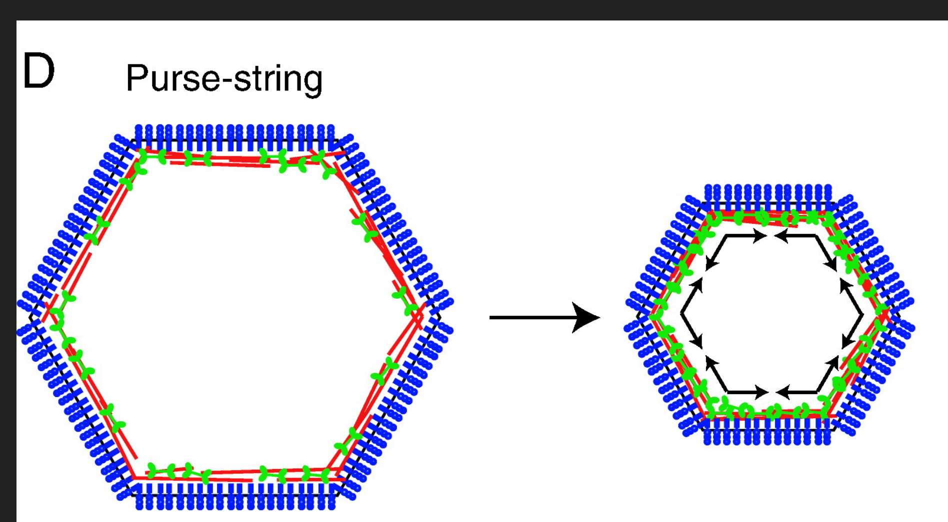
What is the origin of the contraction? Where do the forces act?

MESHWORK MODEL



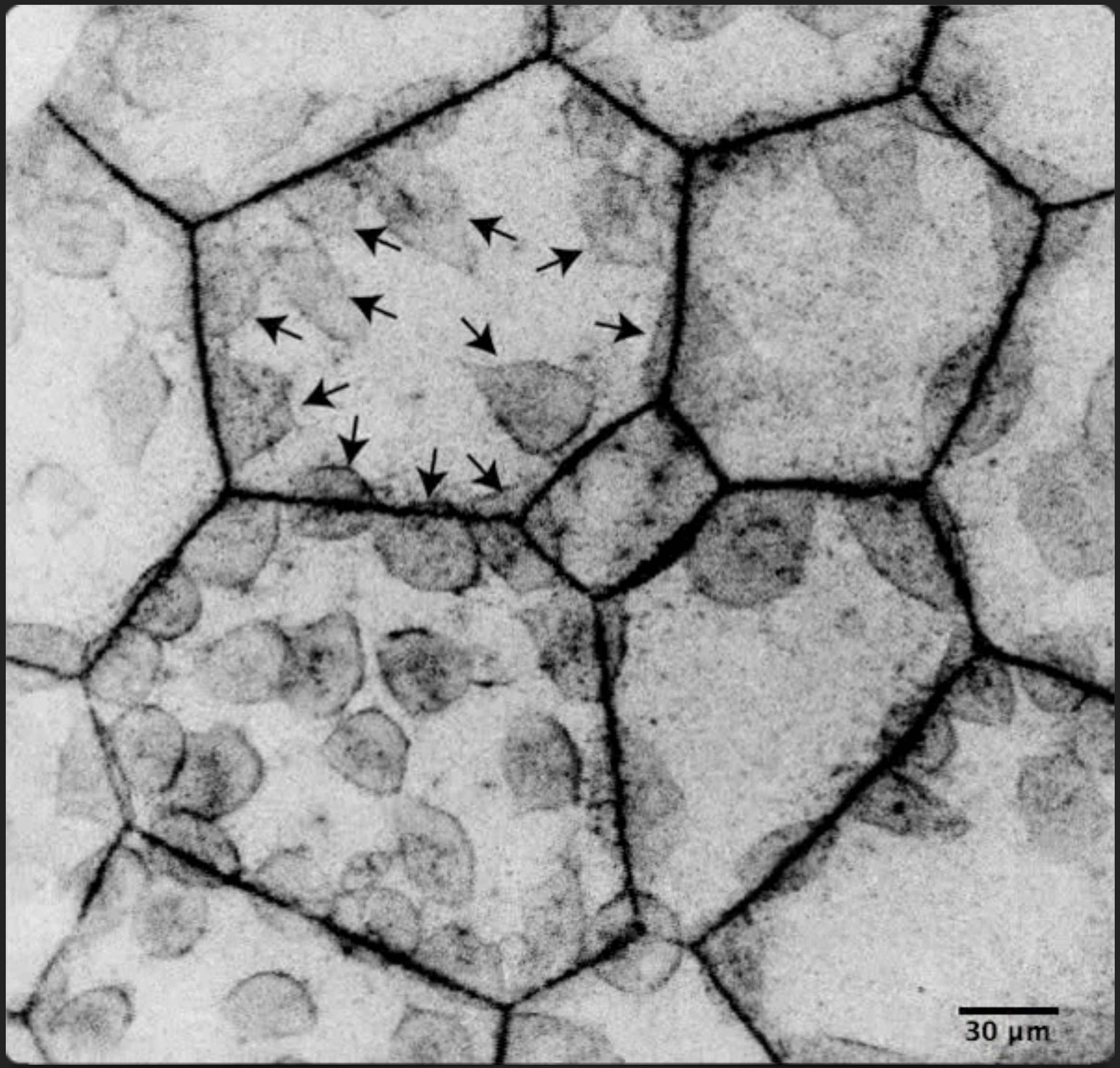
Adam C Martin, Dev.Bio. 341, 2010.

PURSE-STRING MODEL



Adam C Martin, Dev.Bio. 341, 2010.

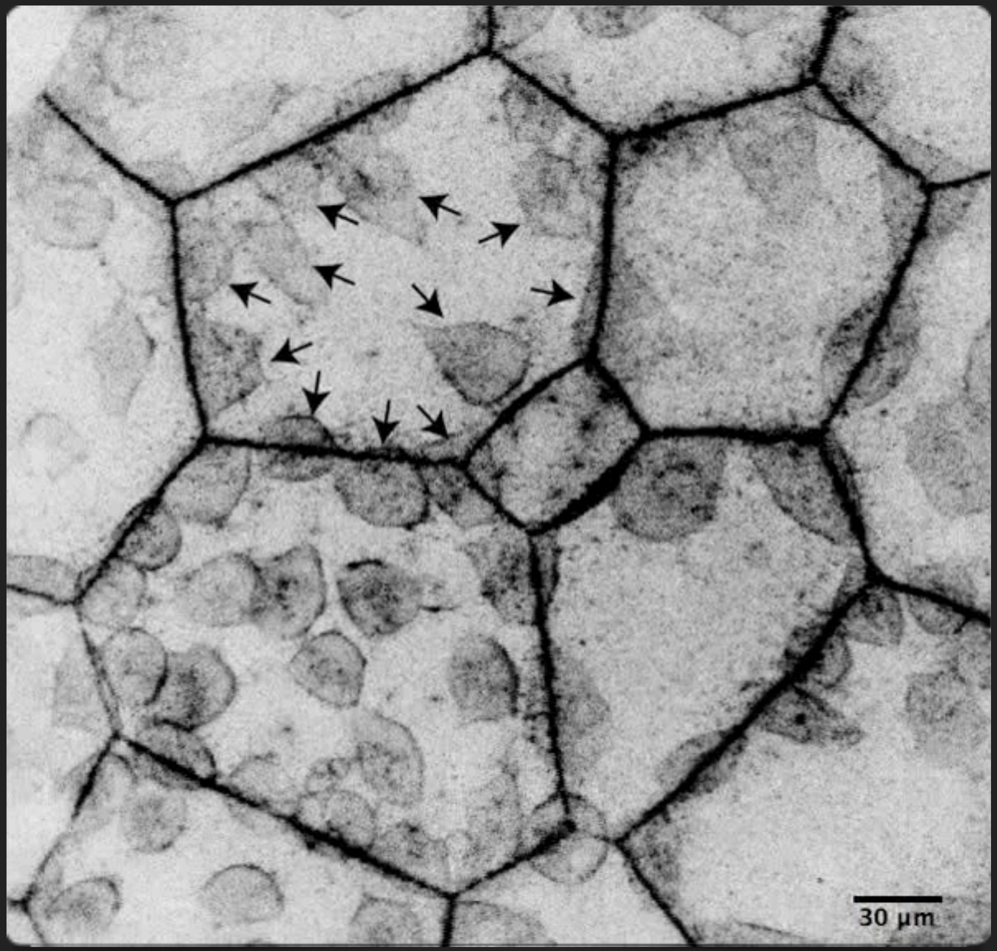
VERTEX MODEL



- Each cell is modeled as a polygon with area A_c and perimeter P_c
- The degrees of freedom are the vertex positions r_i
- Evolve to minimize an elastic energy $\frac{d\mathrm{r}_i}{dt} = -\gamma \frac{\partial E}{\partial \mathrm{r}_i}$ with

$$E = \frac{K_A}{2} \sum_c (A_c - A_{c0})^2 + \frac{K_P}{2} \sum_c (P_c - P_{c0})^2 + J \sum_{\langle ij \rangle} l_{ij}$$

MODELING APICAL CONTRACTIONS



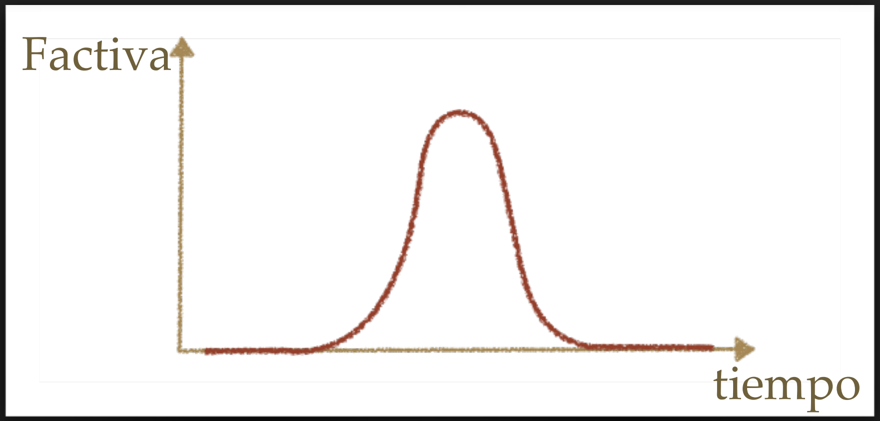
- This dynamics with

$$E = \frac{K_A}{2}\sum_c (A_c - A_{c0})^2 + \frac{K_P}{2}\sum_c (P_c - P_{c0})^2 + J\sum_{\langle ij\rangle} l_{ij}$$

is purely passive

- The activity enters as changes in the cell reference perimeter or area

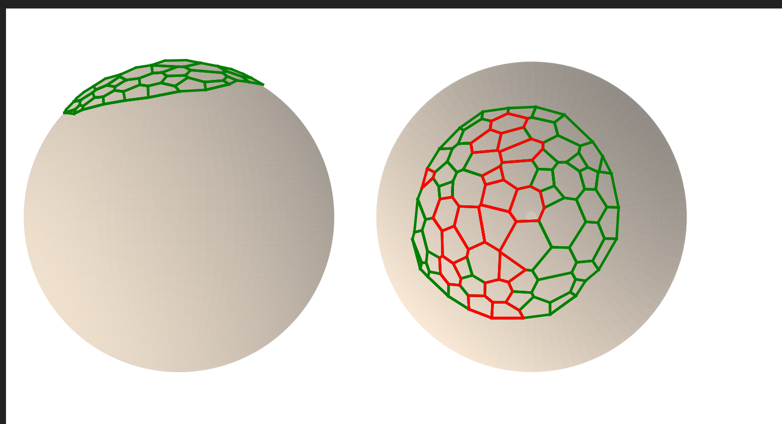
$$A_{0c} \to (1-\lambda_A)A_{0c}$$
$$P_{0c} \to (1-\lambda_P)P_{0c}$$



- How does the tissue reacts?

APPLICATION TO THE FISH EMBRYO

2D VERTEX MODEL CONSTRAINED TO THE SPHERE



$R = 590\mu\text{m}$

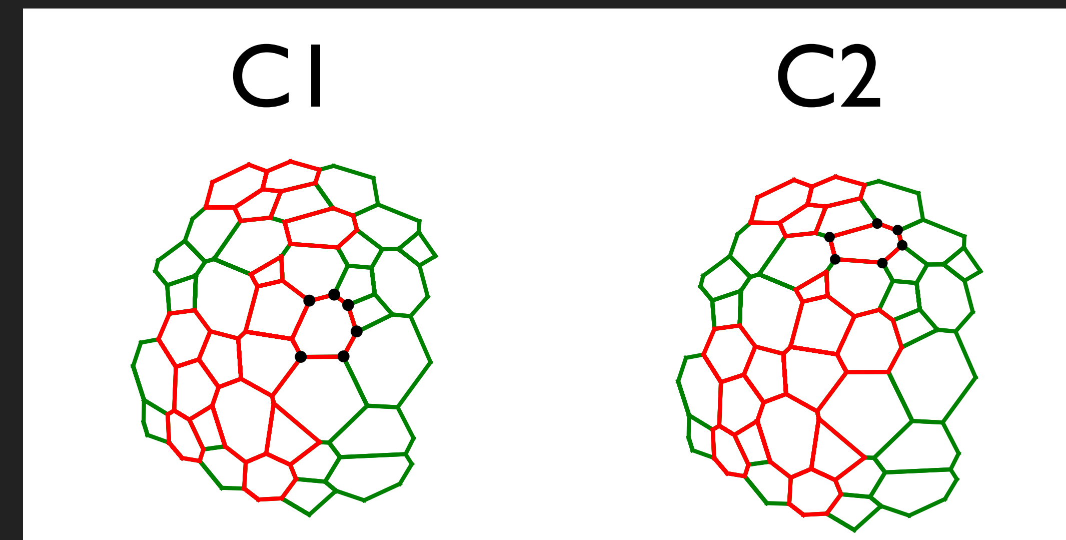
$h \sim 5\mu\text{m}$

68 cells

$l_0 \sim 0.1R$

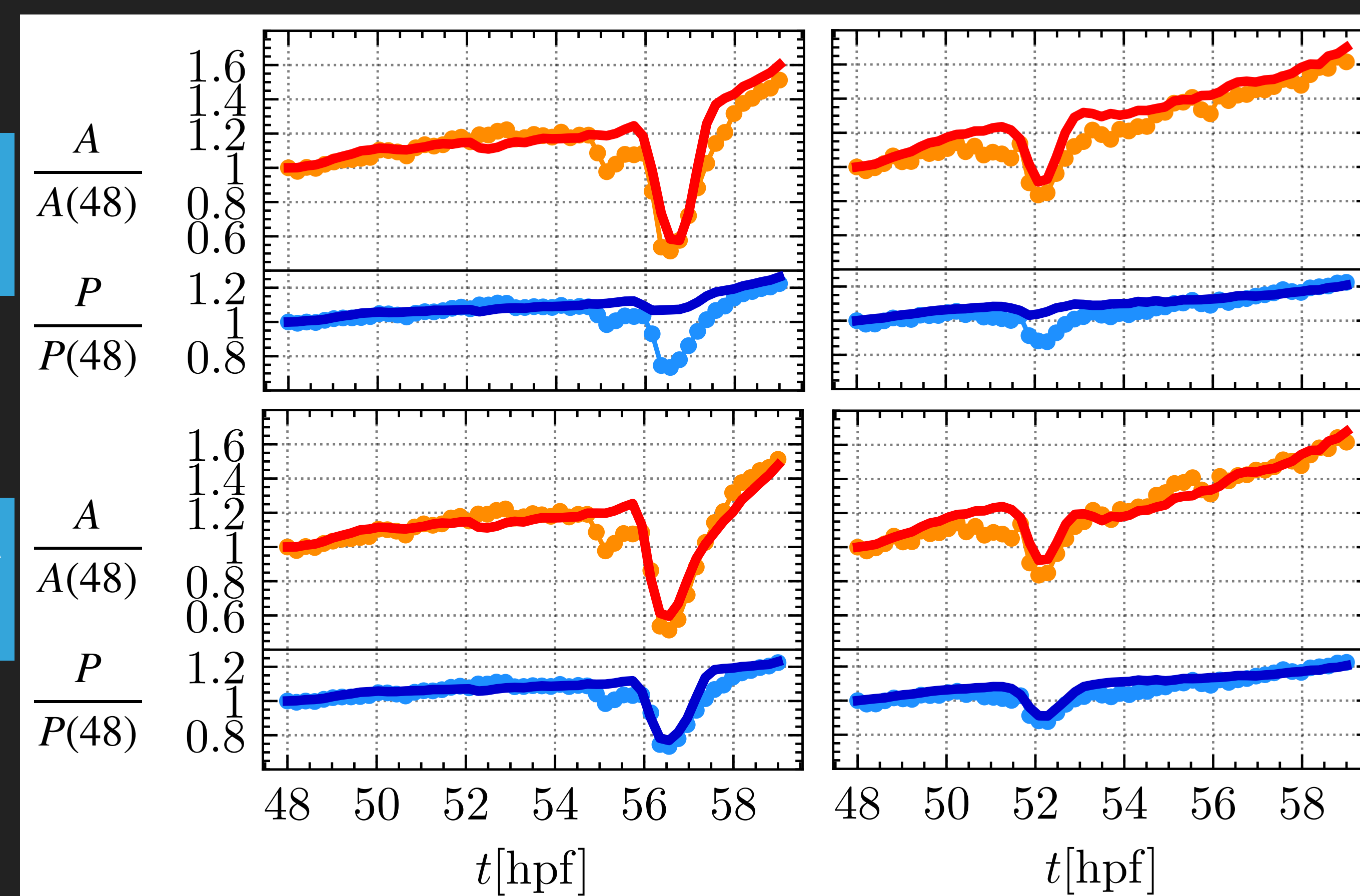
$t_{\text{tot}} = 11\text{hr}$

16 active events of 1.5 to 3.5hr



MEDIAL ACTIVITY

PERIMETER ACTIVITY



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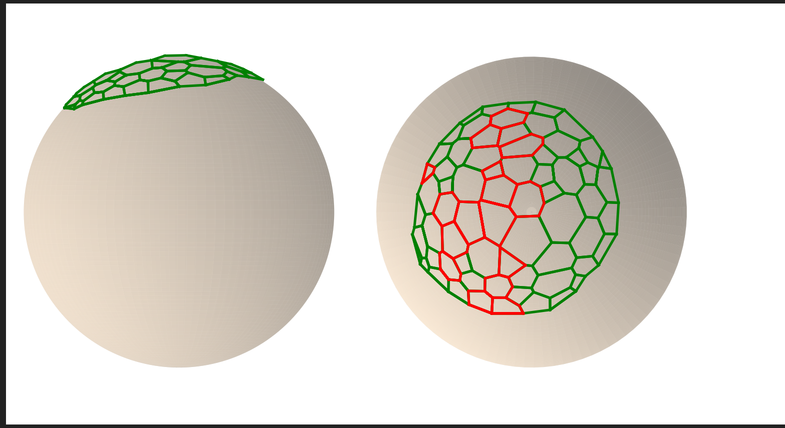

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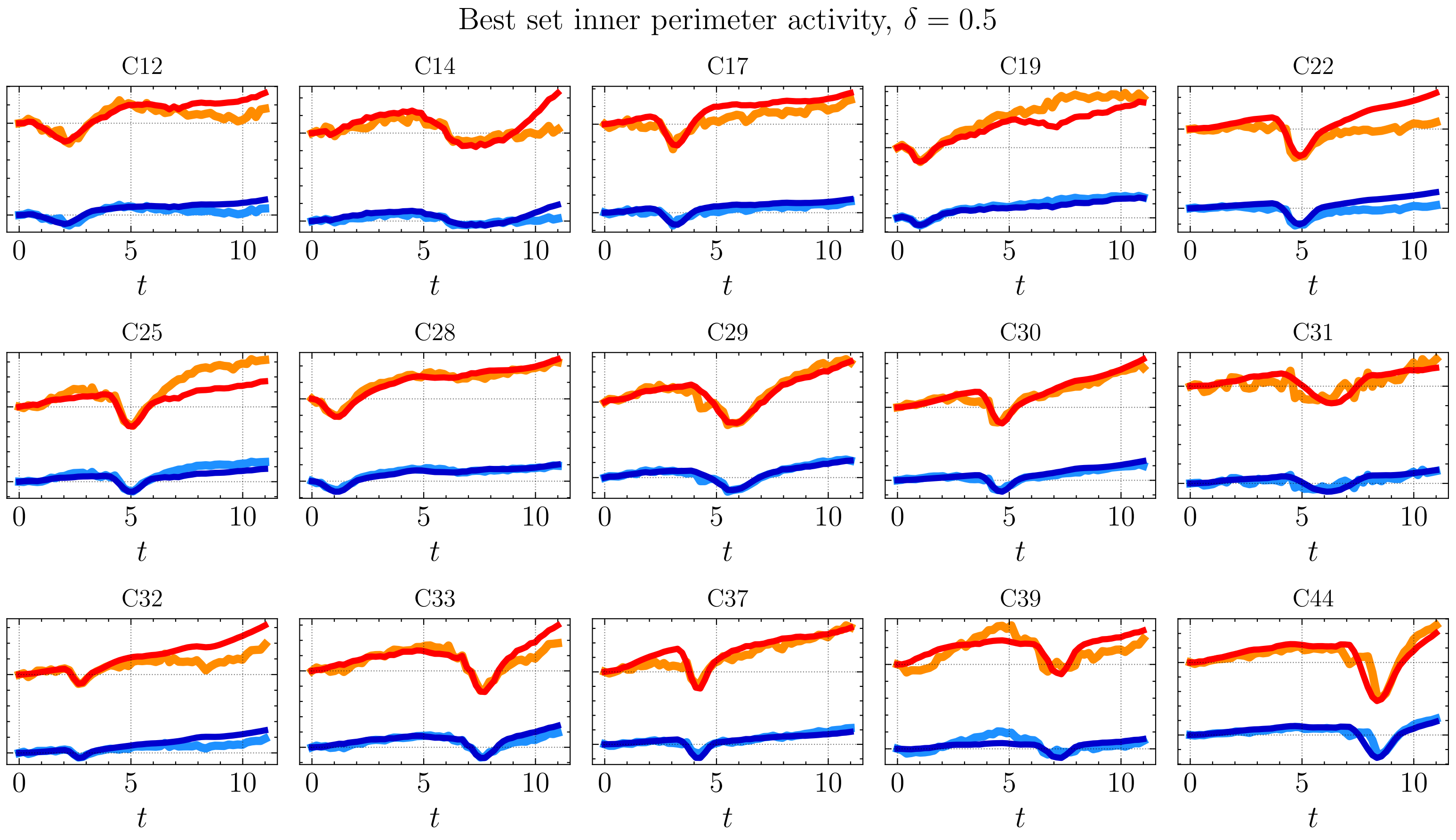
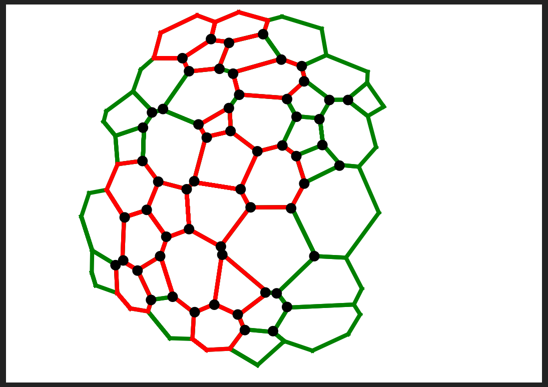


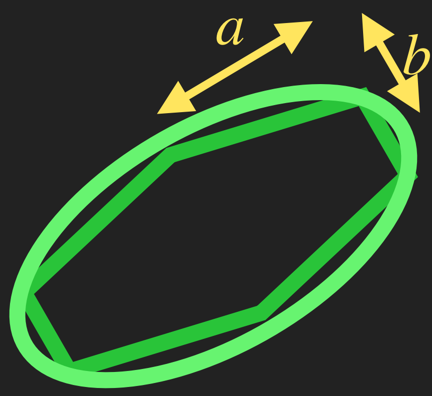


ALL PULSES WERE PRODUCED BY PERIMETER ACTIVITY
GIVE RISE TO MORE CIRCULAR SHAPES

CAN WE UNDERSTAND THIS FROM THE MECHANICS?

STRESSES IN THE VERTEX MODEL

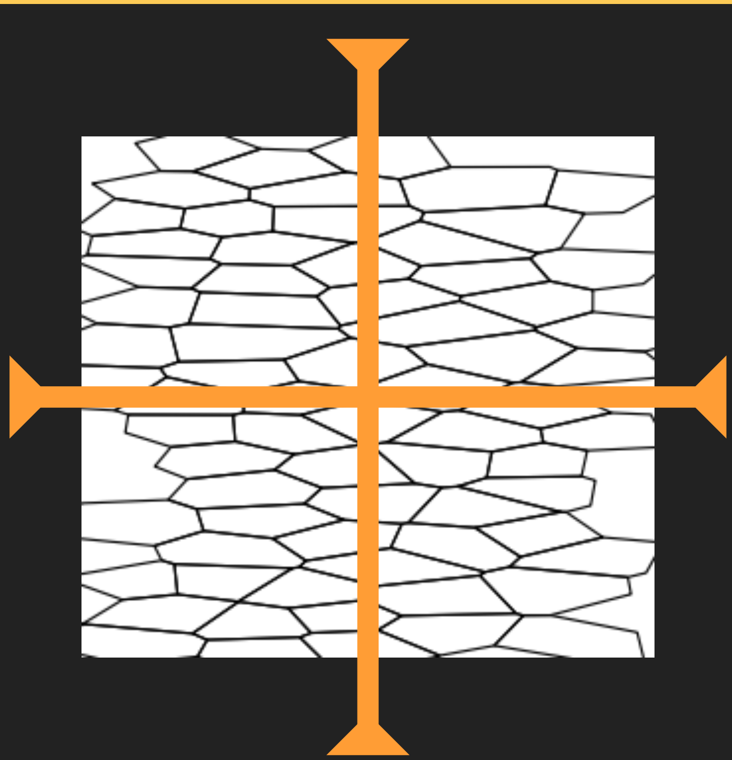
Texture matrix: $\mathbb{M} = \begin{pmatrix} a^2 & 0 \\ 0 & b^2 \end{pmatrix}$

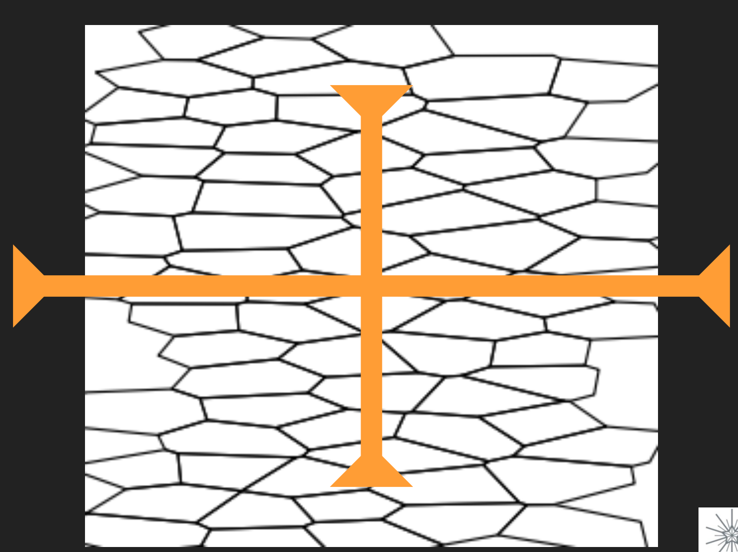


Stress tensor: $\sigma_e = K_A \left(A_c - A_0\right) \mathbb{I} + \gamma K_P \left(P_c - P_0\right) \mathbb{M}$

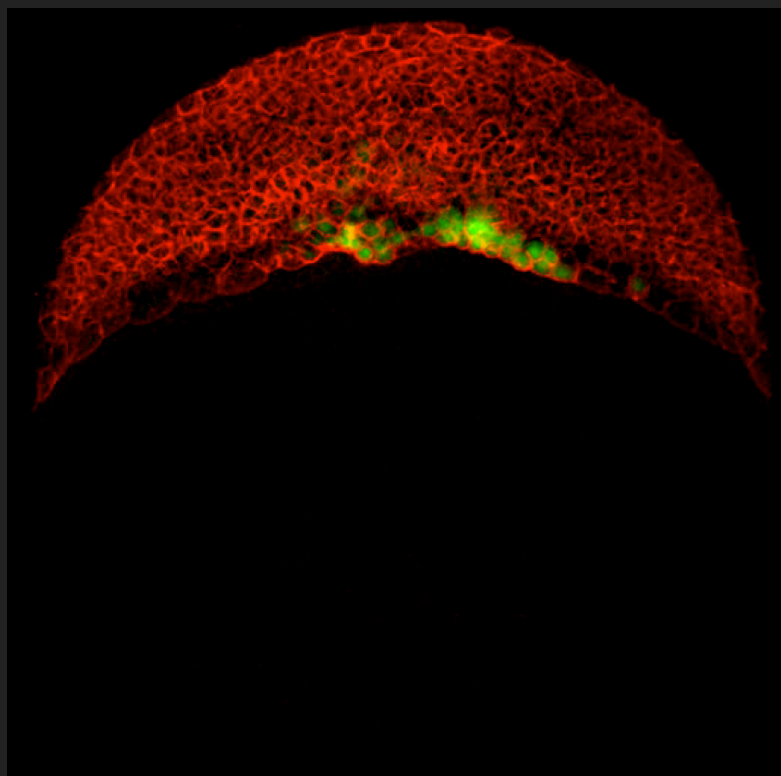
THE ACTIVE PULSE
$A_{0c} \rightarrow (1+\lambda_A)A_{0c}$
CREATES ISOTROPIC STRESSES

THE PULSE $P_{0c} \rightarrow (1+\lambda_P)P_{0c}$
CREATES A STRESS THAT DEPENDS ON CELL SHAPE





PRINCIPLES OF PHYSICAL MODELING



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