A phenomenological model of collective cell motion in some ex-vivo experiments

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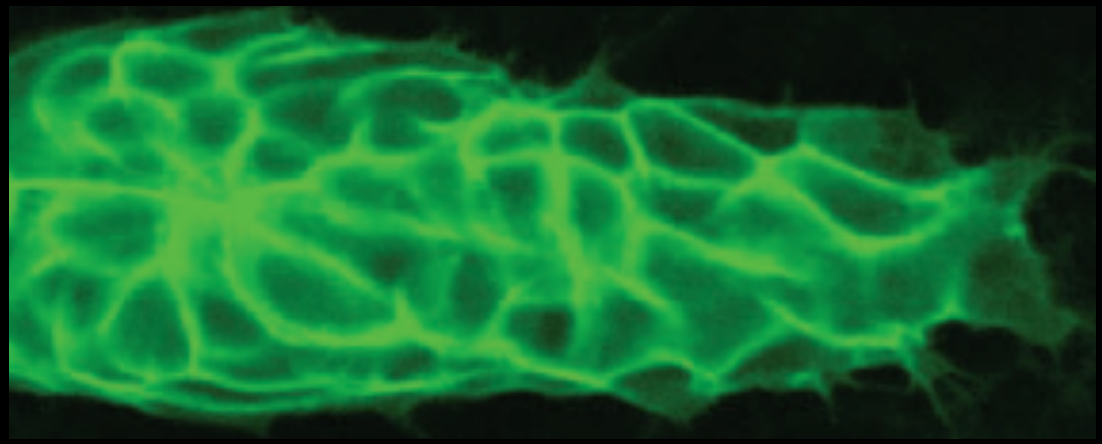
KITP, august 2013

Cells move collectively

Zebrafish lateral line



Lecaudey & Gilmour (2006)

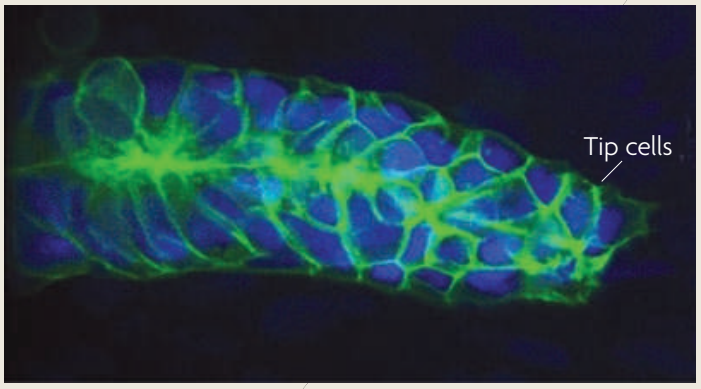
Collective cell motion in tumor

-Important during development

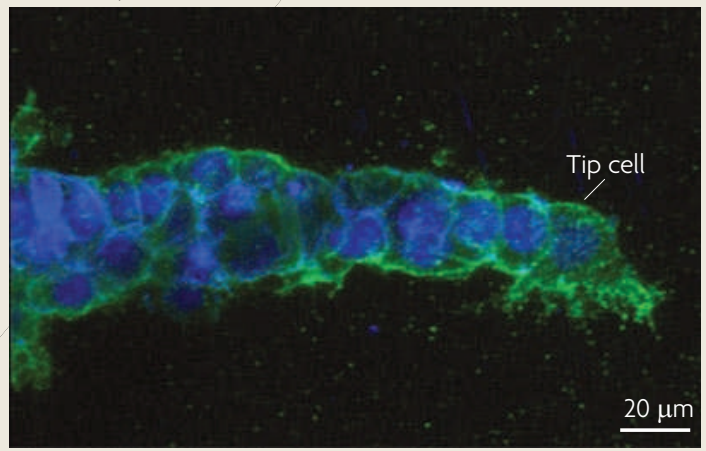
-for various physiological and pathological processes (wound healing, cancer,…)

Friedl Gilmour
Nat Rev M C B, 2009

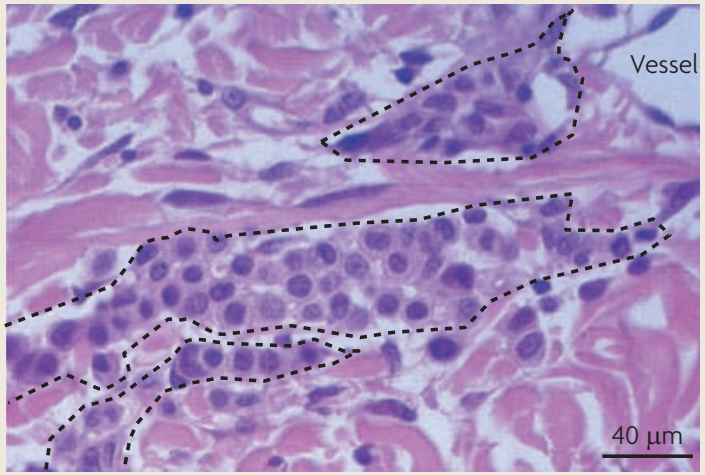
Lateral line primordium



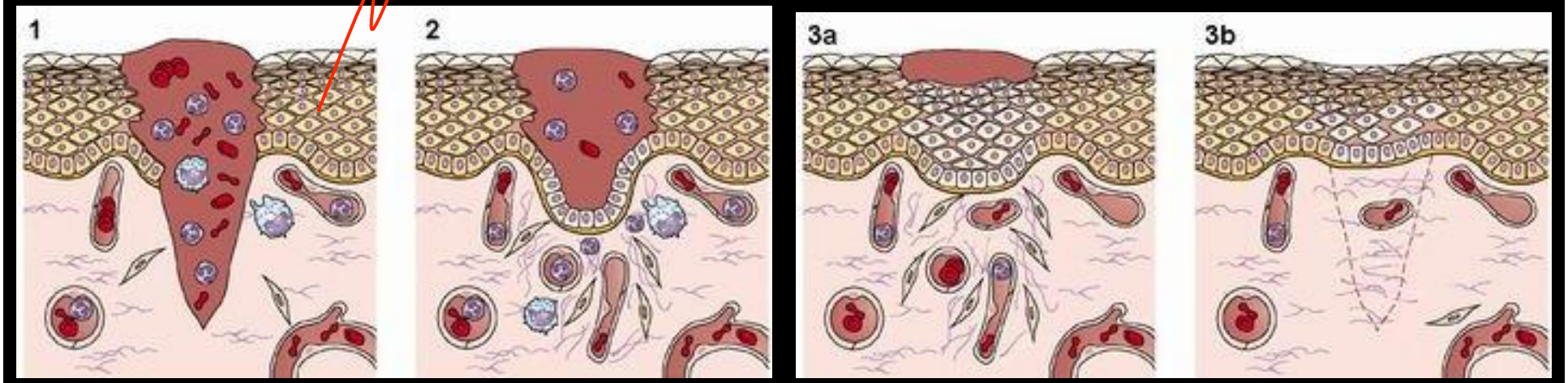
Mammary carcinoma



Human melanoma in deep dermis



« Real » wound



inflammation

Proliferation
+ migration

maturation

Collective motions of animals

Collective animal motion

A fascinating topic that has attracted the attention of physicists and mathematicians.

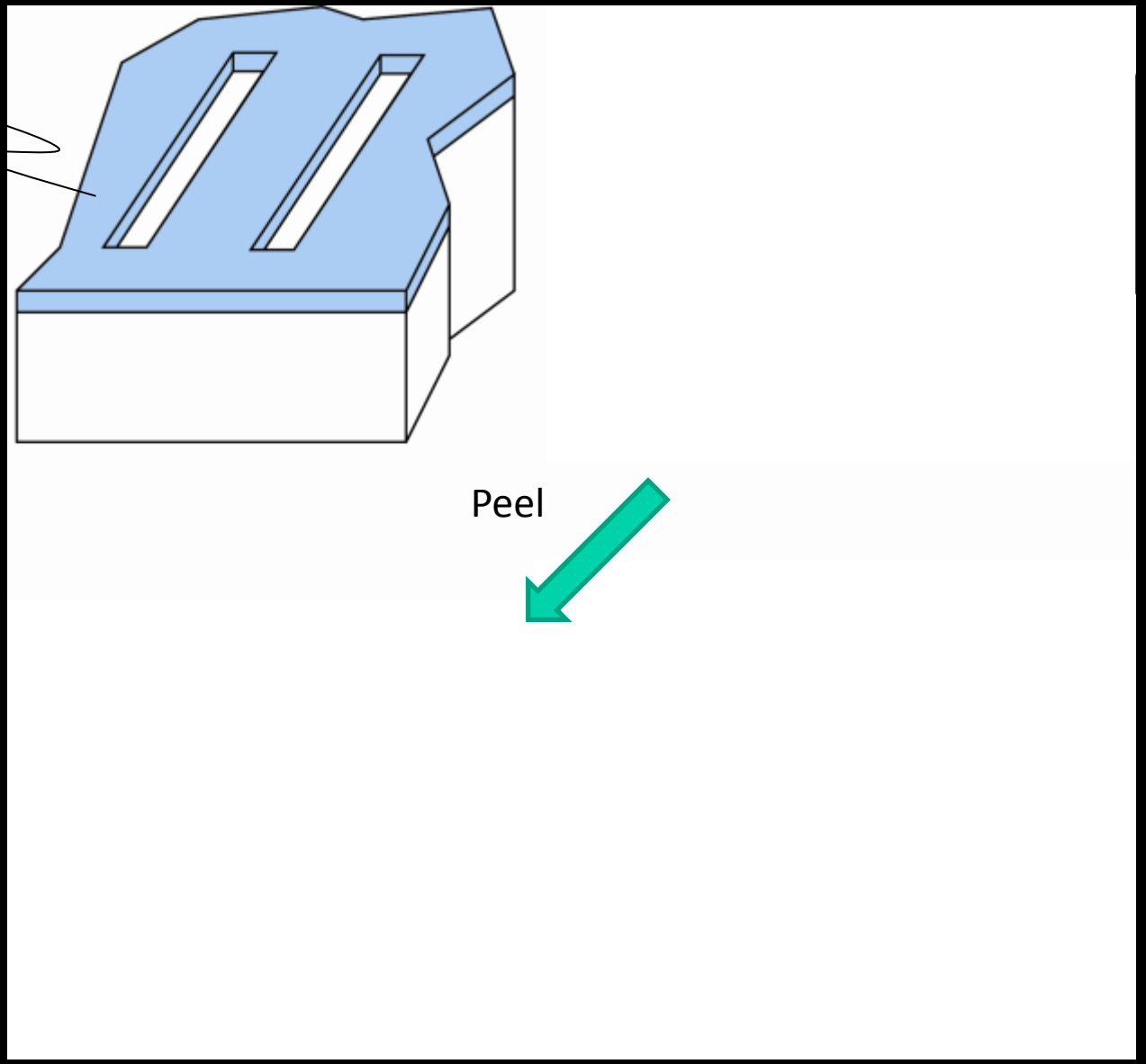
Simple models capture some qualitative features (Vicsek et al 1995, Toner and Tu, Chaté and Grégoire,...)

Experimental data is not abundant (but changes e.g. EU starflag , Giardina/Cavagna/Parisi, several cell tracking projects,…)

Detailed comparison between data and models is even less abundant but hopefully it is also changing.

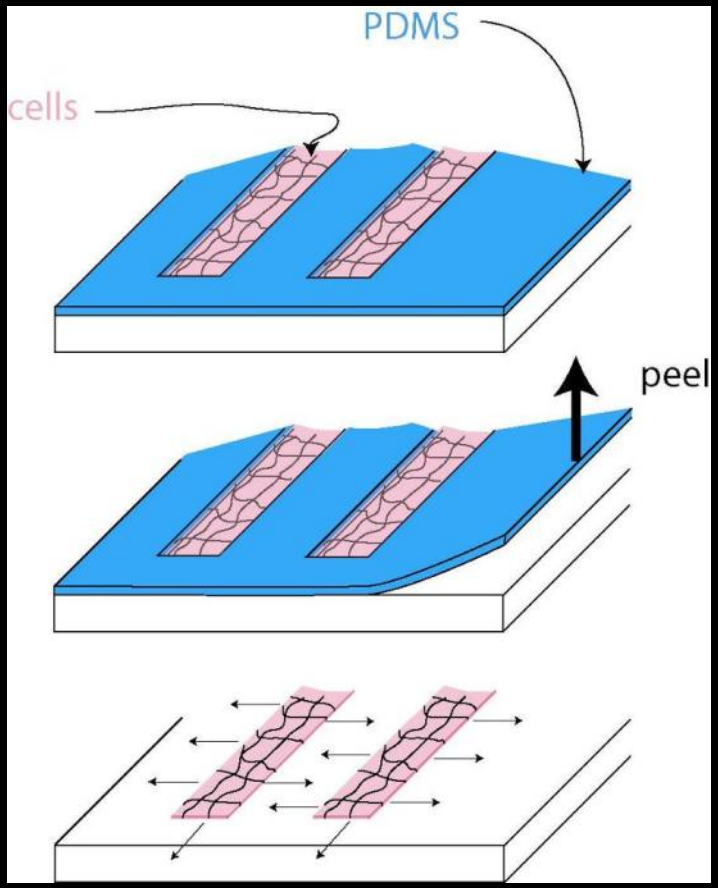
Model wounds

Poujade et al. PNAS 2007

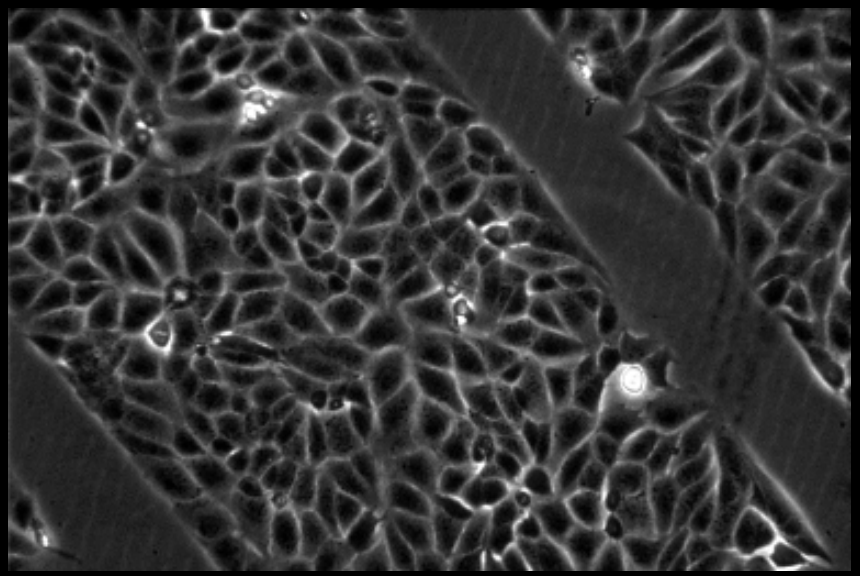


A model wound experiment

Micro-stencils



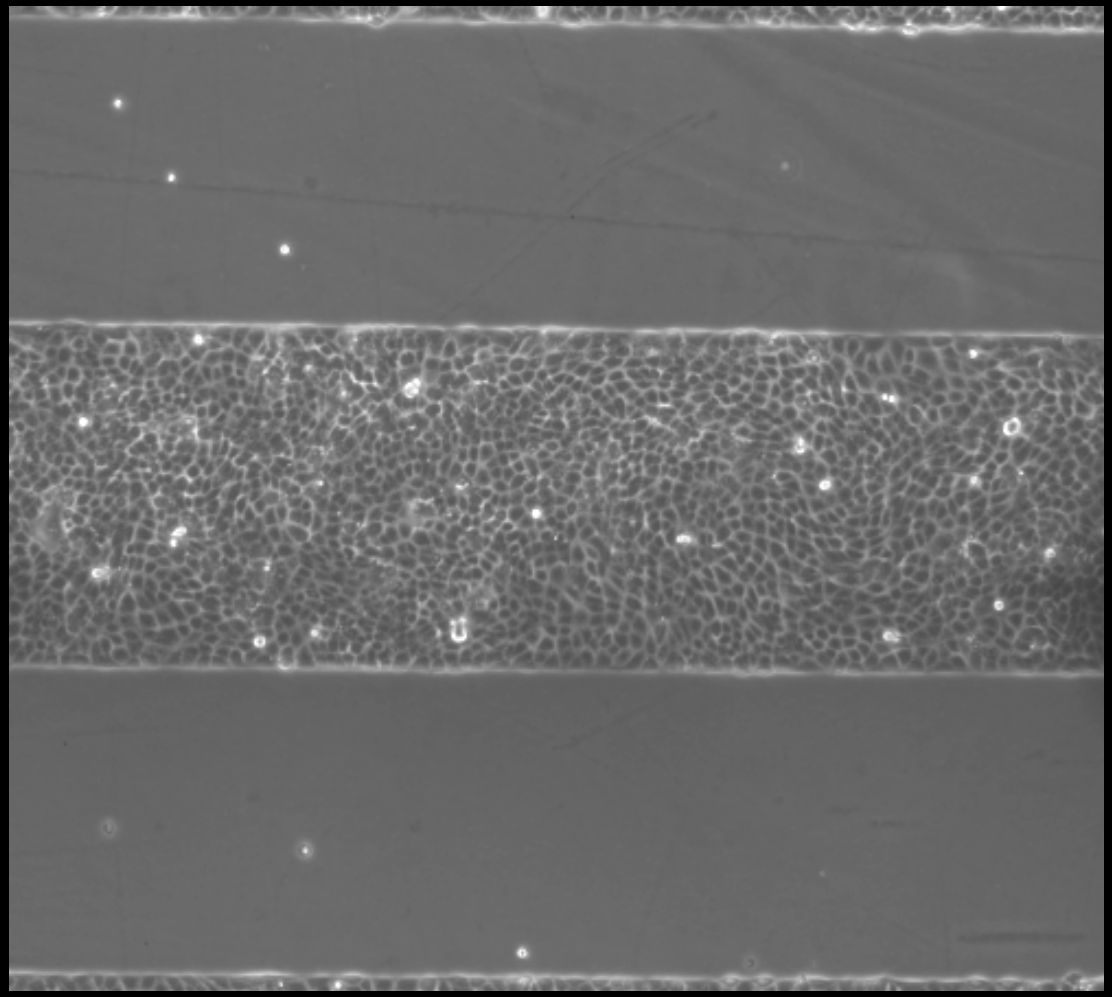
No damage to the cells



MDCK cells

Free surface sufficient to trigger motion

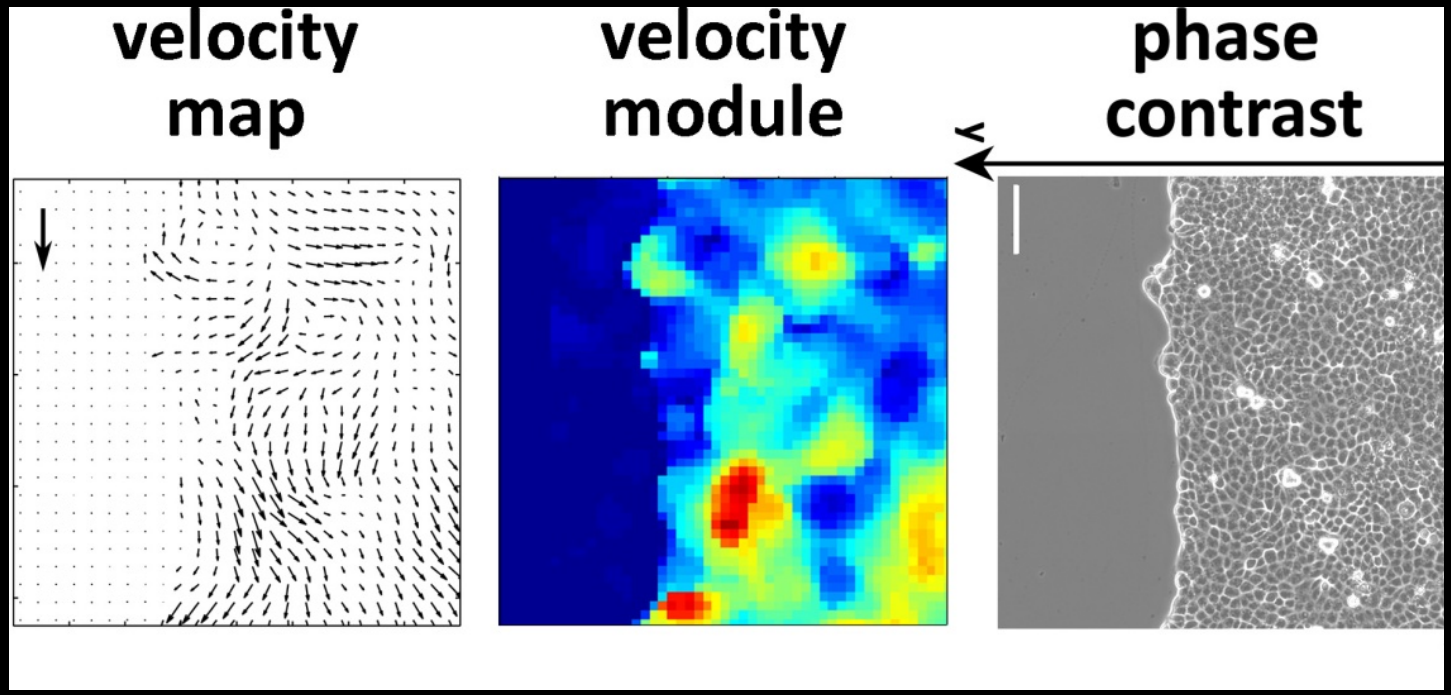
Poujade et al. PNAS 2007



MDCK cells
Total healing time : 15 h

Collective motion in the « bulk »

Detailed characterization of cell motion



L. Petitjean et al. Biophys. J 2010

Particle Image Velocimetry (PIV) analysis

similar set-up, D.Weitz, L. Hufnagel/B. Shraiman,…; simpler than birds in 3D

Can one describe the data in a simple way?

A simple model : interactive brownian particles

$$\frac{d\vec{v}_i}{dt} = -\alpha\vec{v}_i + \beta(\langle\vec{v}\rangle - \vec{v}_i) + \sigma\vec{\eta}_i + \vec{f}_i$$

friction coordination noise interactions

$$\tau\frac{d\eta_i}{dt} = -\eta_i + \xi_i,$$

Ornstein-Uhlenbeck

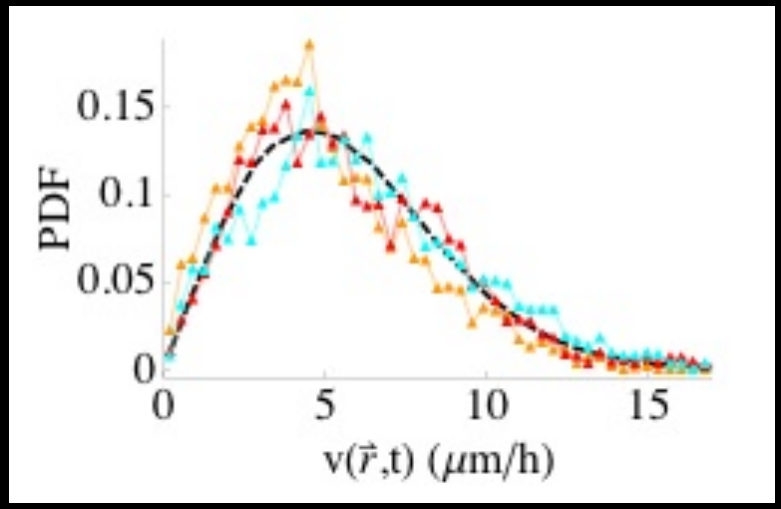
$$f_{ij} = -\nabla_i U(r_{ij})$$

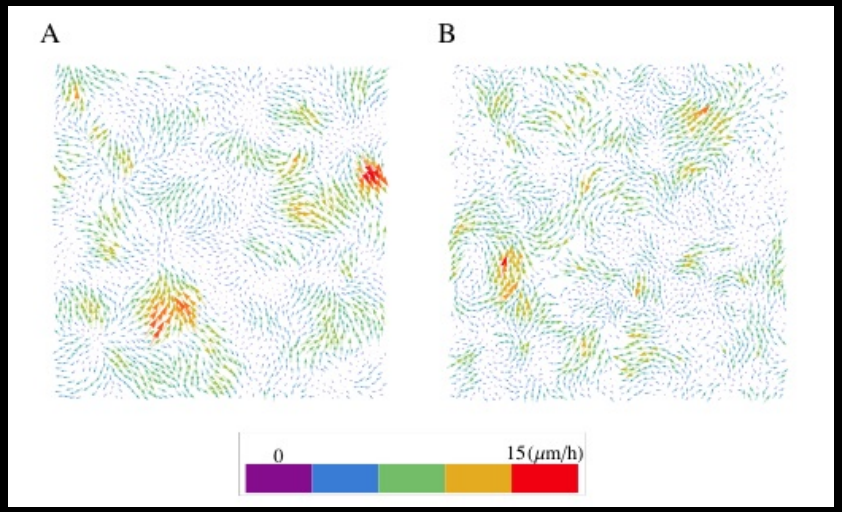
interaction between direct neighbors
short range repulsion
longer range attraction

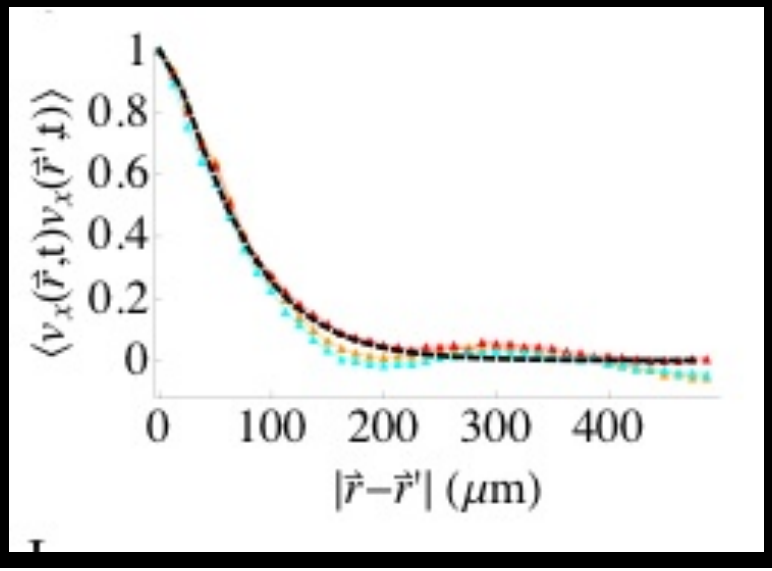
N Sepulveda, L Petitjean, O Cochet, P Silberzan &VH Plos Comp. Biol (2013)

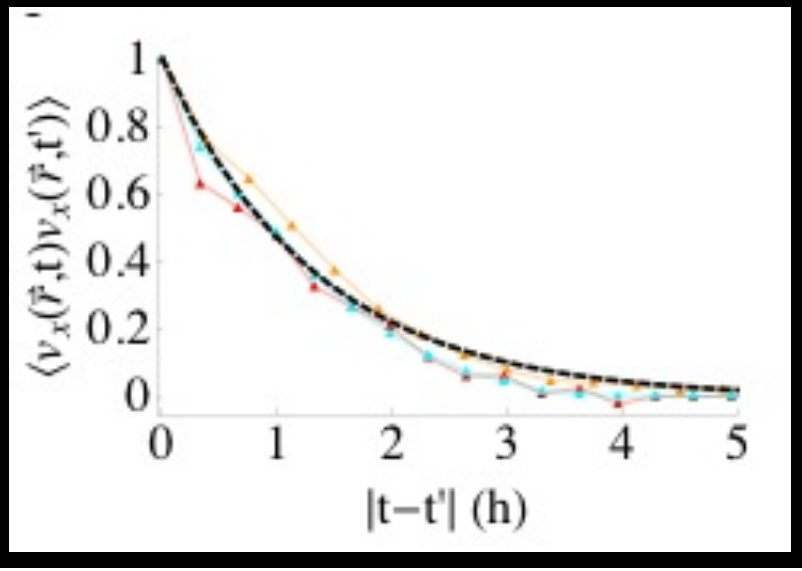
Comparison of velocity fields

Experiment Model

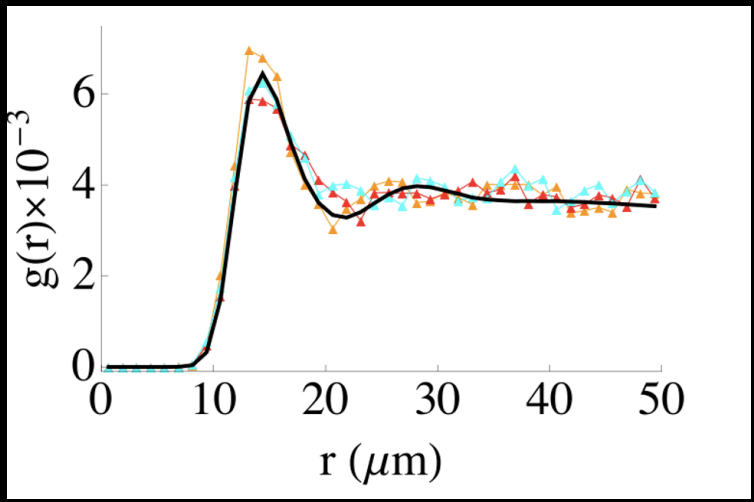




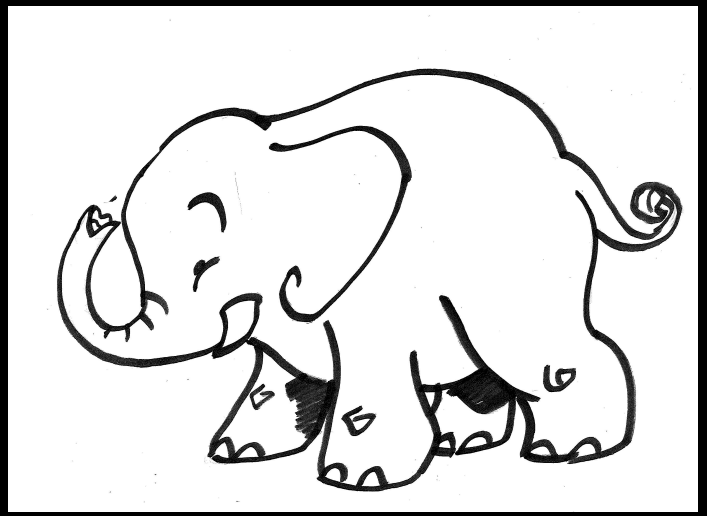




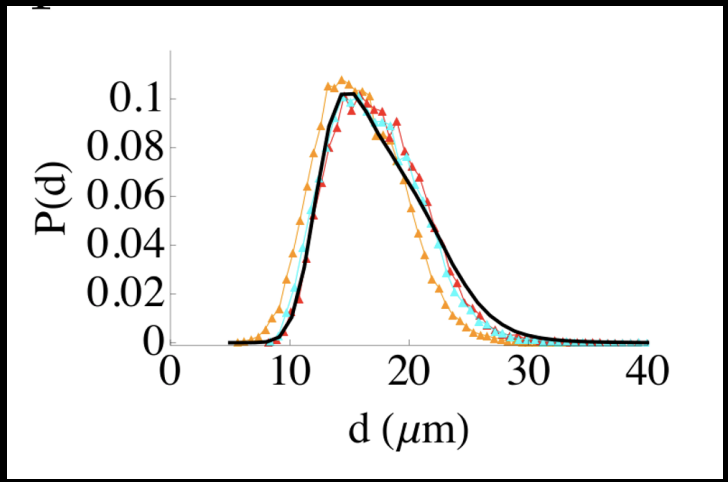
Cell positions



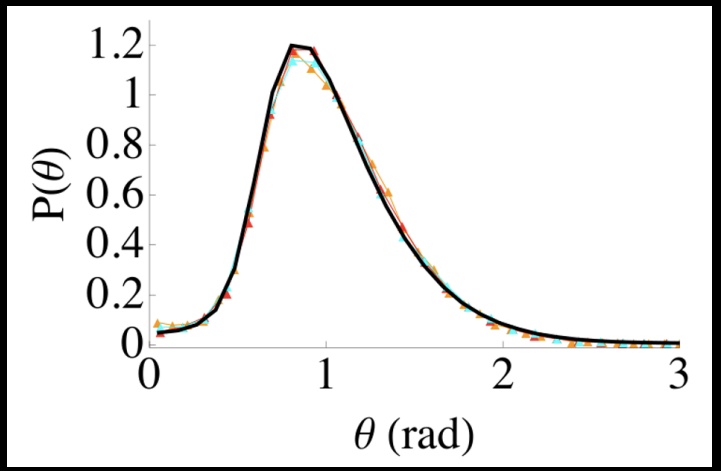
Pair distribution function



von Neumann's elephant?



Distance between neighbors



Angle between neighbors

Fixed-particle approximation to velocity correlations

-If cell/particle motions is neglected, the velocity eq. is linear

-Fix particle positions on the vertices of a triangular lattice

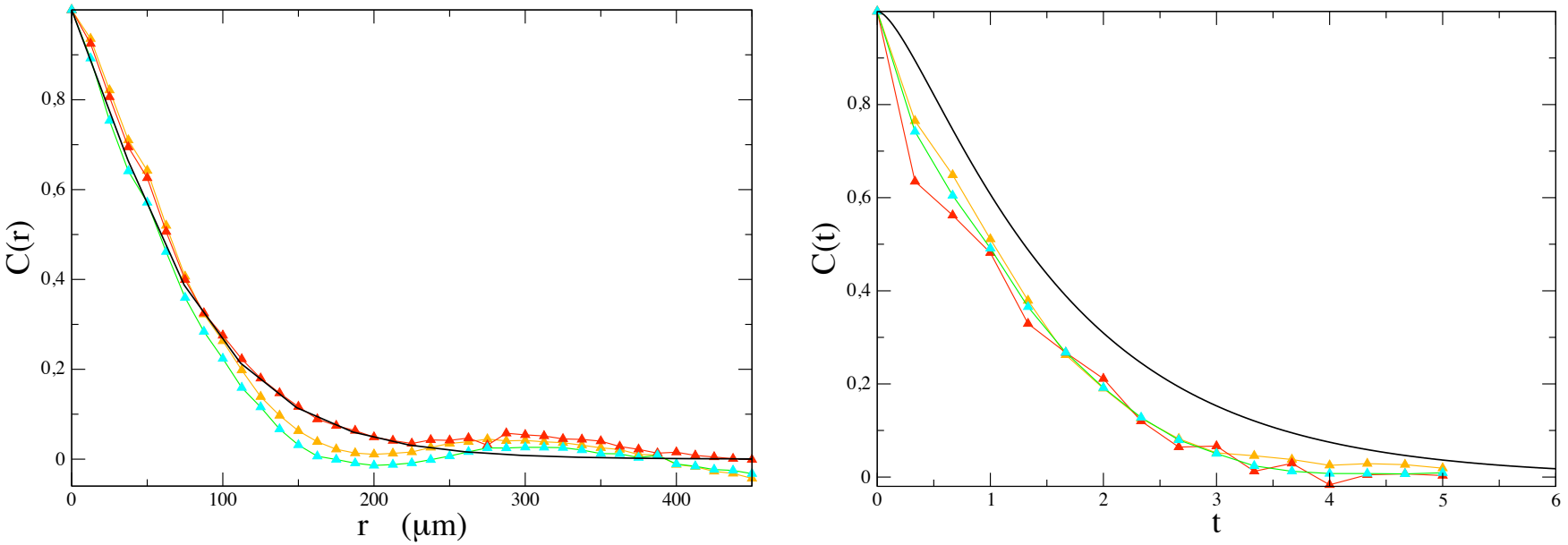
-Explicit solution by Fourier transformation

$$\langle v_{\mathbf{j}}(t) v_{\mathbf{k}}(t') \rangle = \sigma^2 \int D^2\mathbf{q} \frac{\exp[i[\mathbf{q}\cdot(\mathbf{j}-\mathbf{k})]}{2[1-\tau^2\gamma^2(\mathbf{q})]} \left\{ \frac{1}{\gamma(\mathbf{q})} \exp(-\gamma(\mathbf{q}) \mid t-t' \mid) - \tau \exp(\frac{-\mid t-t' \mid}{\tau}) \right\}$$

$$\gamma(\mathbf{q}) = \alpha + \frac{\beta}{3}[3 - \cos(\rho_1) - \cos(\rho_2) - \cos(\rho_1 - \rho_2)]$$

q=ρ1 q_1 + ρ2 q_2, vectors on the dual lattice

Fixed particle approximation of velocity correlations



-Spatial correlation functions very-well approximated

-velocity time auto-correlation less well :
motion decreases velocity auto-correlation

-Motion of cells is compatible with a very simple model

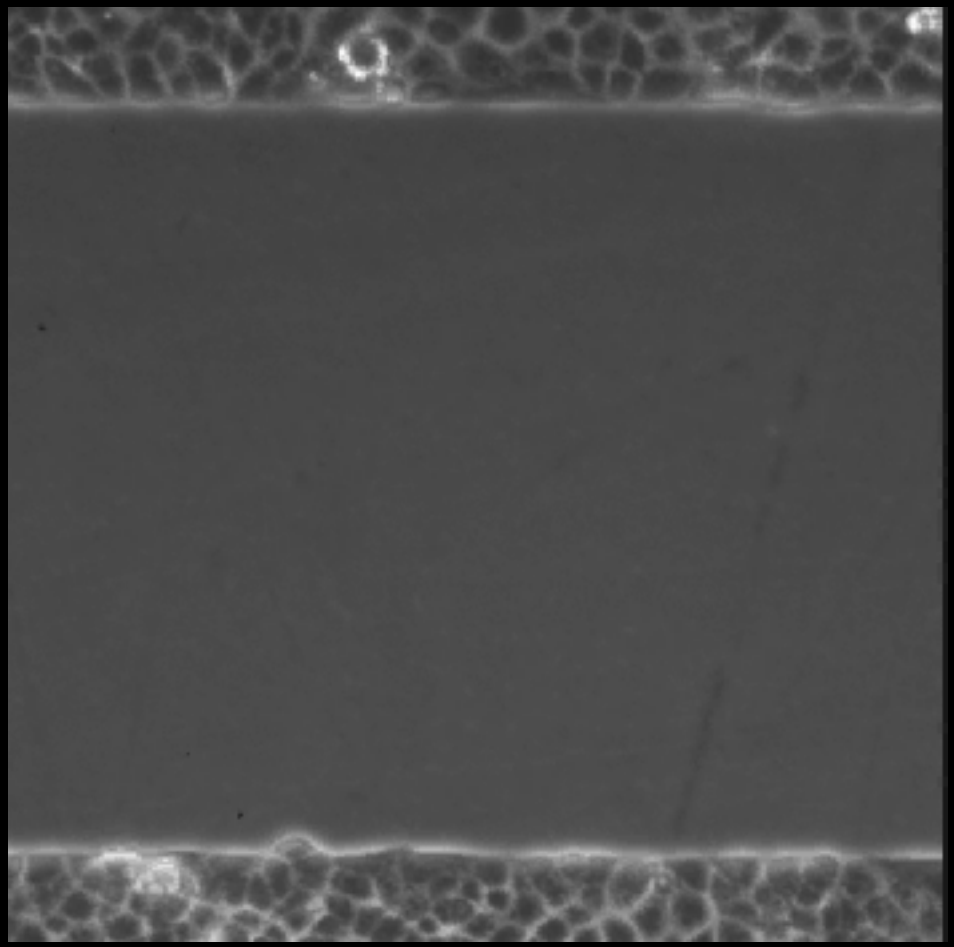
-Velocities are correlated over large lengths (~10 cells)

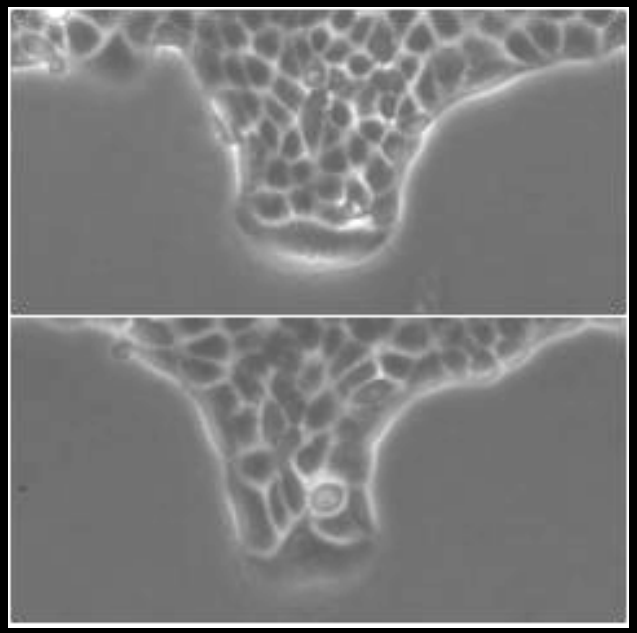
-Velocity alignment but no indication of preferred velocity (wo noise)

Useful to understand the evolution at later times?

Cell motion at the epithelium border

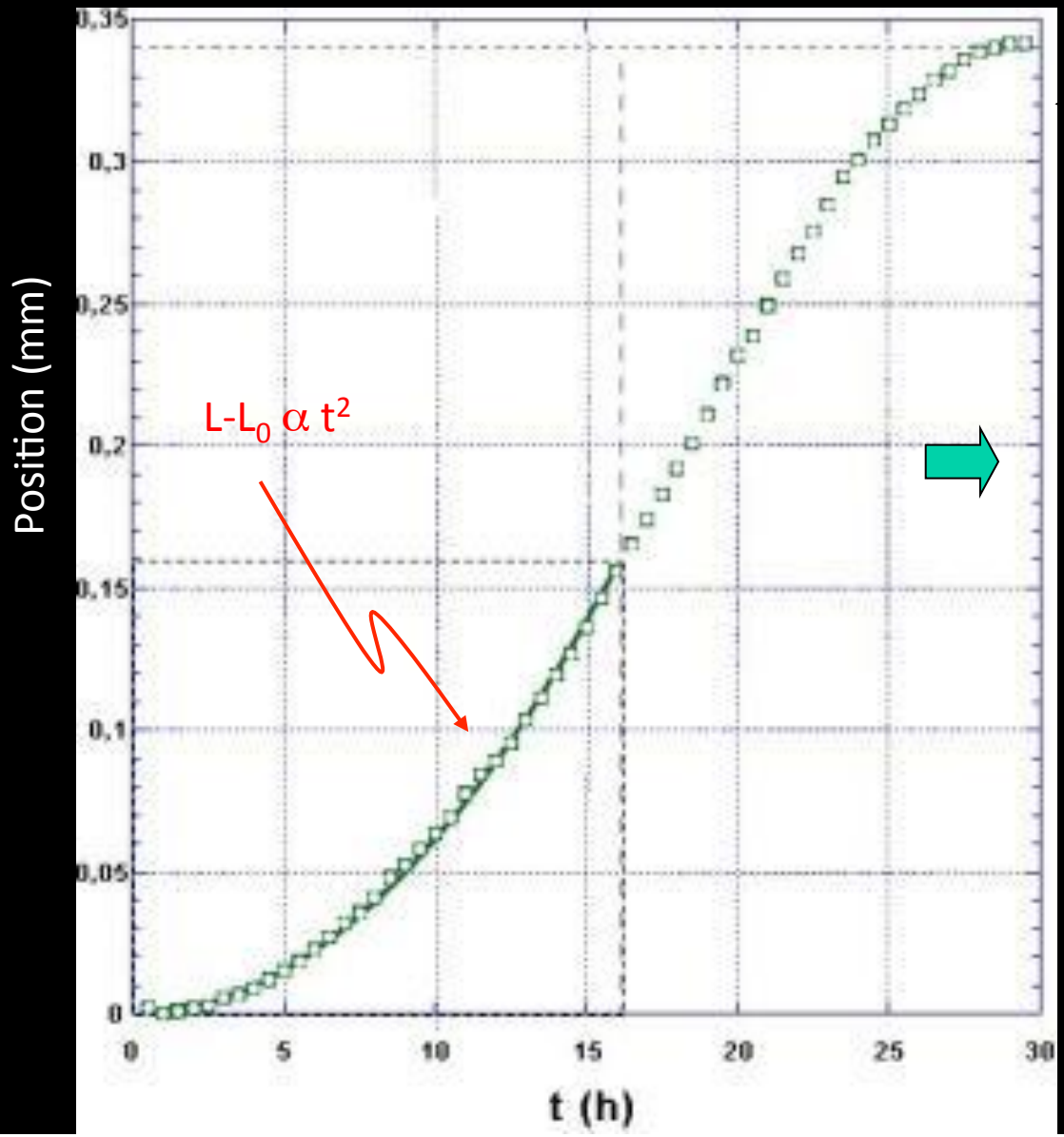
Fingering and « leader » cells





Total healing time : 15 h

Progression of the epithelium border



Complete healing

Parabolic at early times

Crossover to linear (constant velocity) at later time

4-6.10^5 cells/cm^2

Different hypotheses

Diffusion and chemotaxis mediated instability
(Ouaknin et al, 2003;…)

Motion by curvature: curved boundary regions move faster
(N Gov et al, 2010)

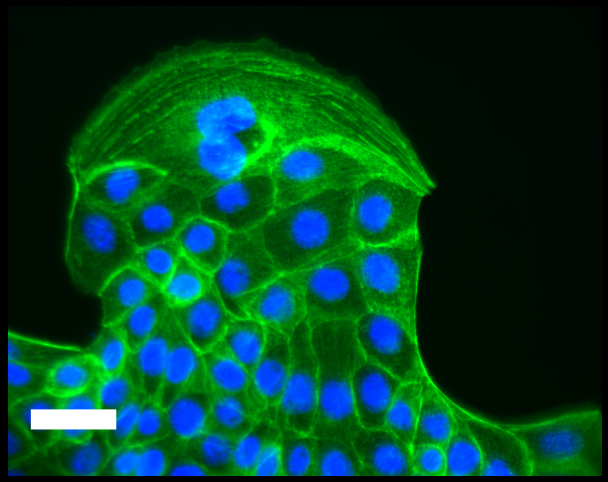
Our choice : leader cells are different

Leader cells have a different phenotype:

-Large, spread out cells.

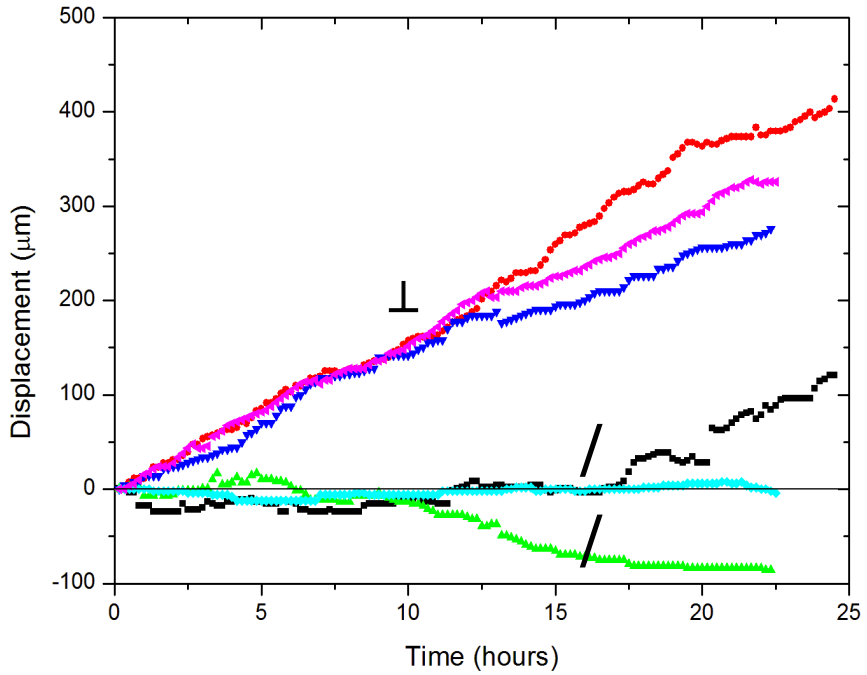
-Active lamellipodium

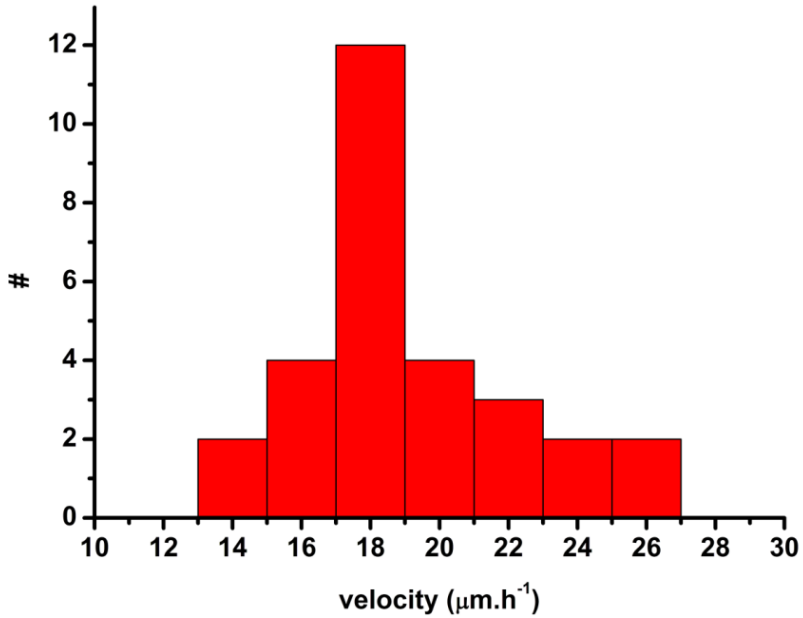
- Often binucleated



20 μm

Leader cell velocities





Very well defined,high, very directional velocities

Questions:

-can a faster cell entrain a cohort of followers?

-can it produce shapes that resemble the observed ones?

-can we understand border progression and the quadratic regime at early time?

Can a faster cell entrain followers?

-Different mechanisms tested (stronger influence on its neighbors, stronger adhesion between cells at the boundary,…)

-We did not find it possible to entrain cells (in the model) above their natural velocity

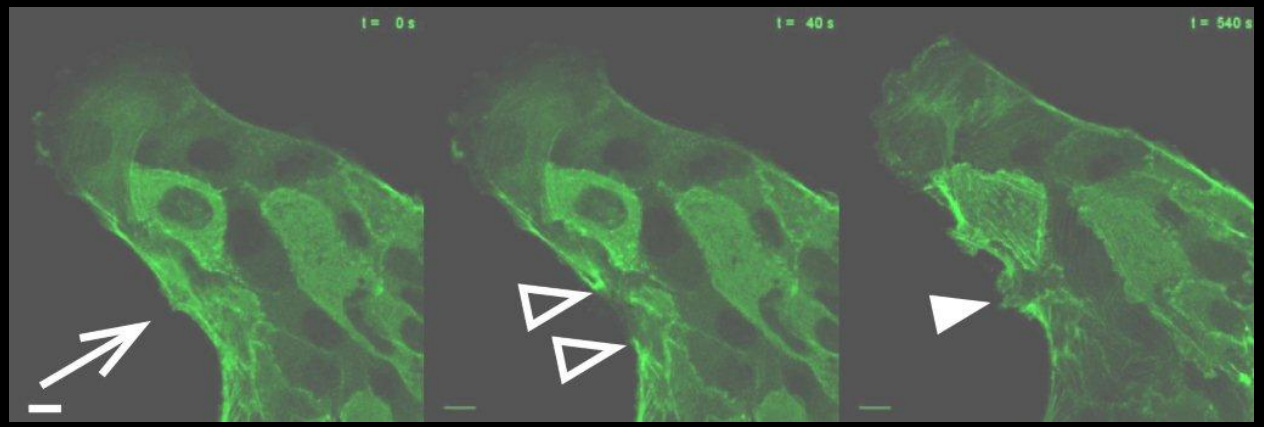
How can the border cells move much faster than than the cell in the bulk?

two possible mechanisms (not exclusive):

-pressure in the epithelium that pushes the border outward
-typical cell velocities increase when the local cell density decreases (reverse of contact inhibition)

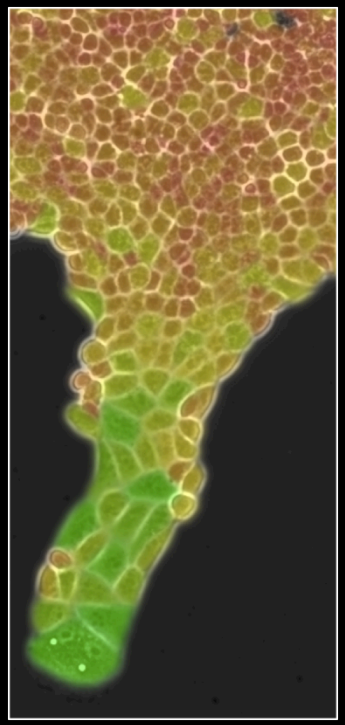
Why do cells only move fast behind a leader cell?

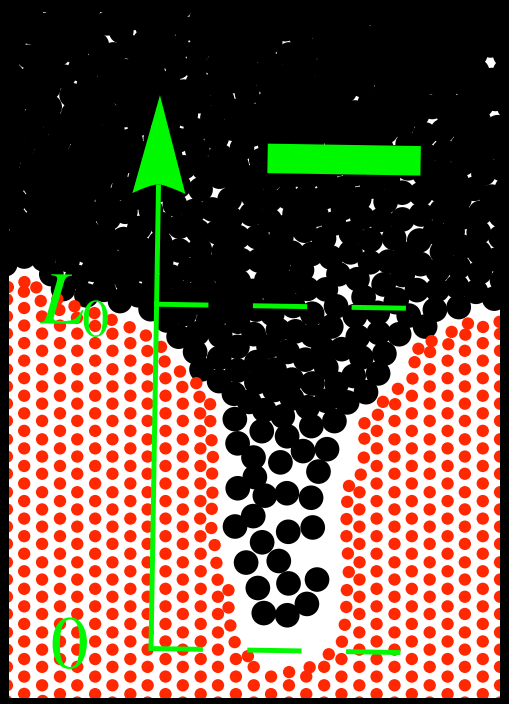
proposed mechanism :
-reduced velocity towards free space at the border
(actin cable?)

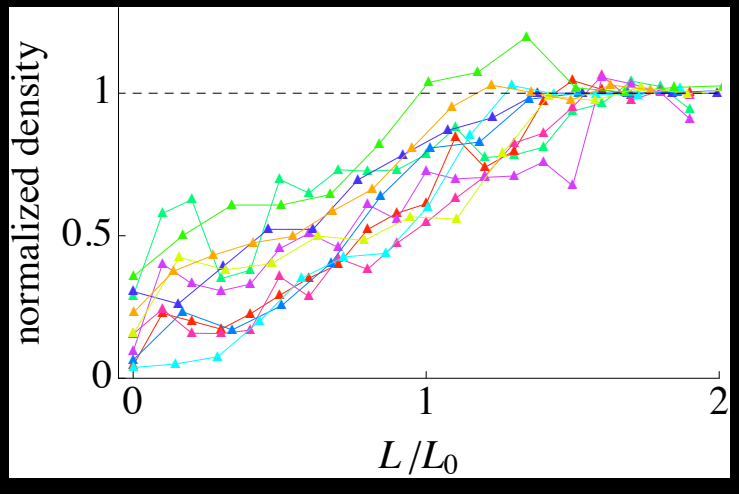


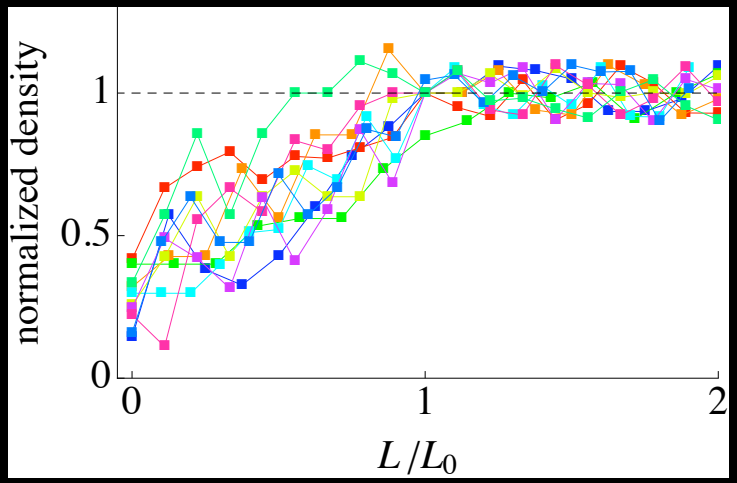
Implementation : repulsive force from free surface on non-leader cells
that disappear upon free-surface invasion

Shape and density in fingers









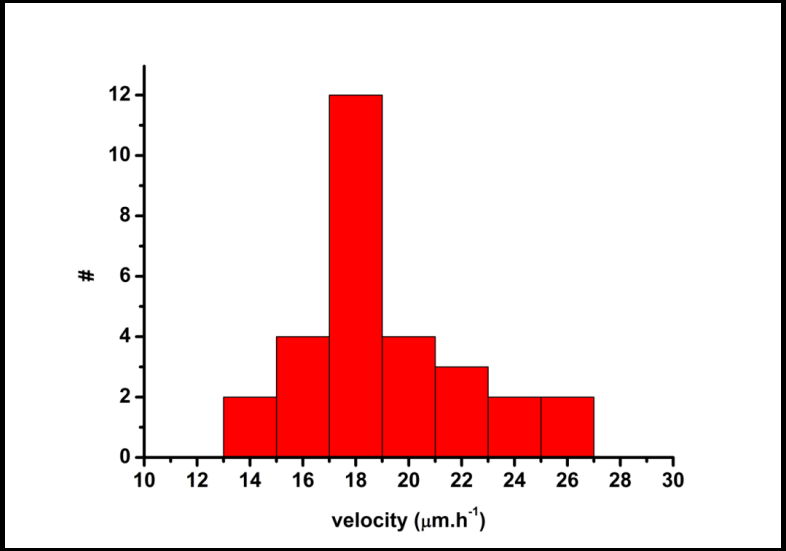
Outcome:

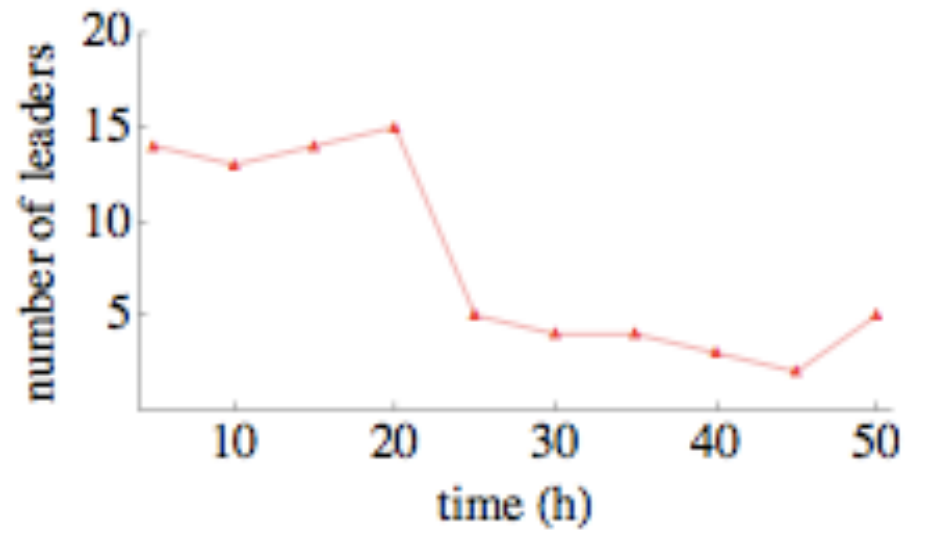
When some fast-moving cells are introduced four main properties seem important for the other cells to follow as in the experiments:

i) normal cells can autonomously move fast
ii) normal cell do not invade easily free surface (actin cable?)
iii) leader cells open the way to non-leader cell that crawl fast at low density
iv) leader cell coordinate their motion with their followers

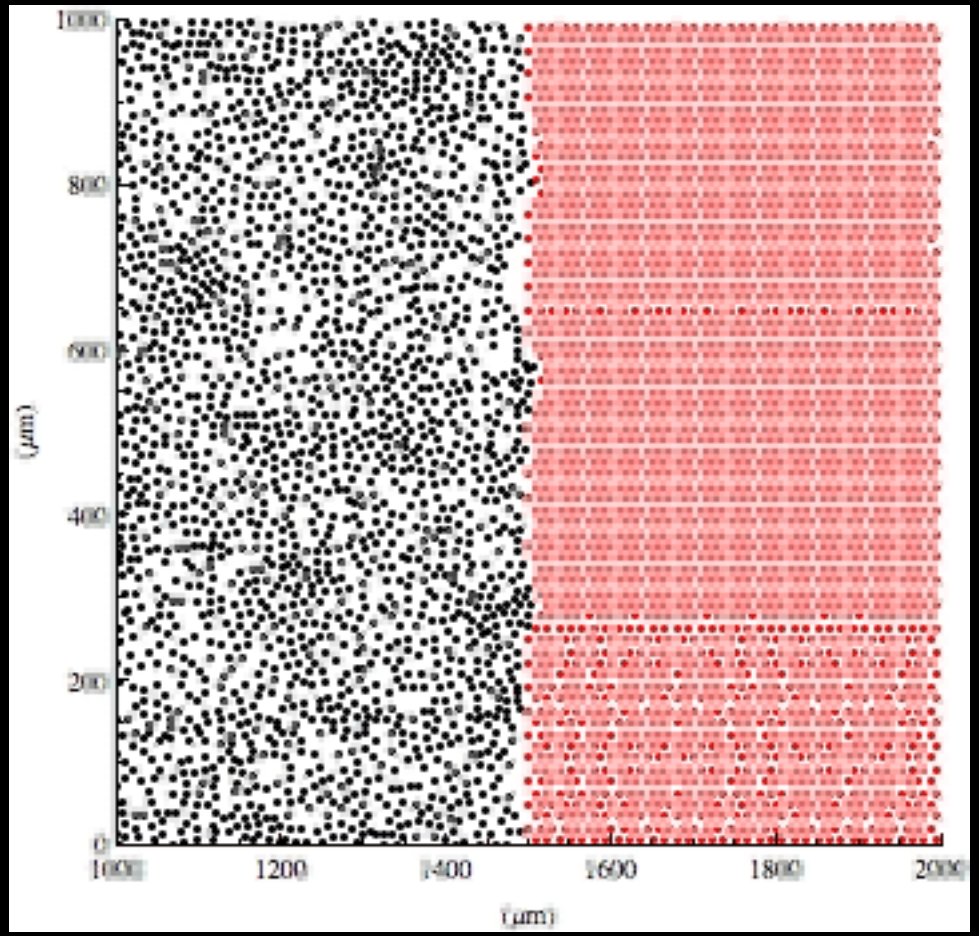
Introduction of many leader cells

Does the introduction of somefast-moving reproduce the full epithelium behavior?

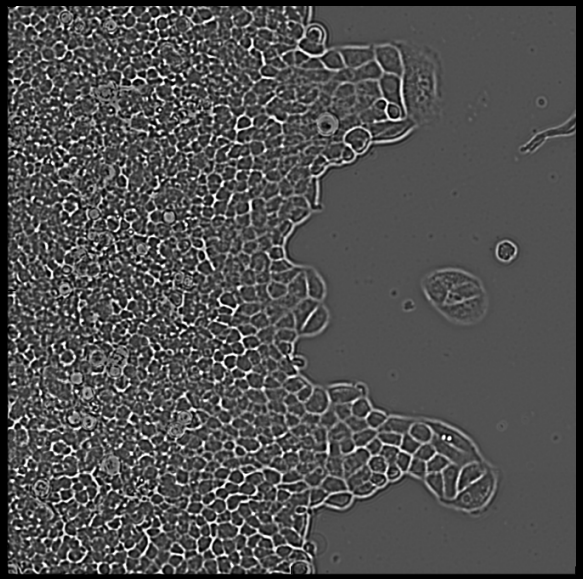


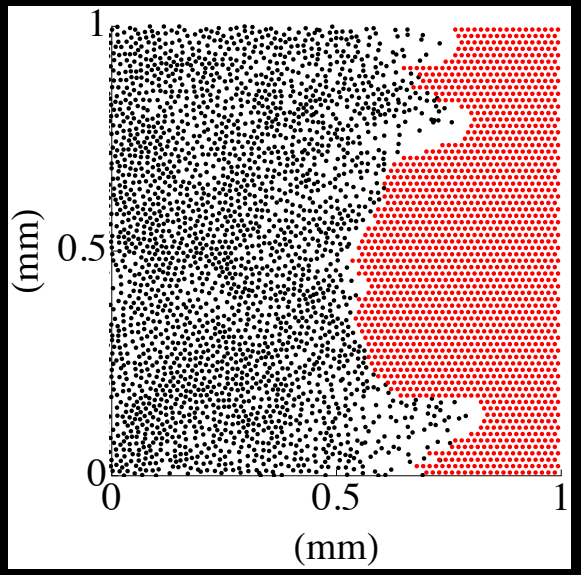


Link with cell cycle?

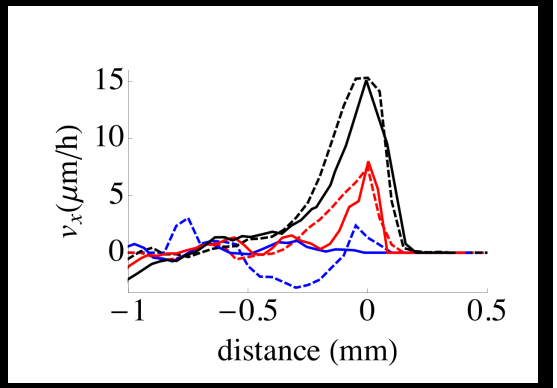

1000
800
600
400
200
0
(μm)
1000
1200
1400
1600
1800
2000
(μm)

Border and epithelium motion

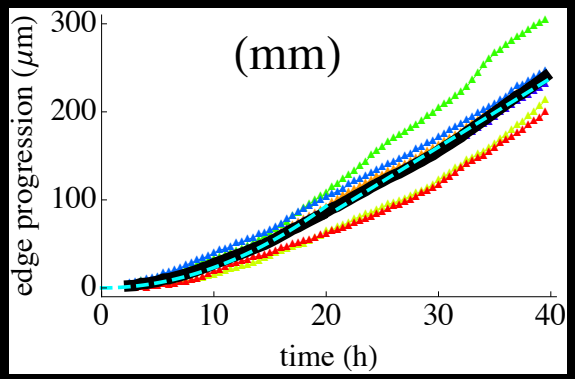




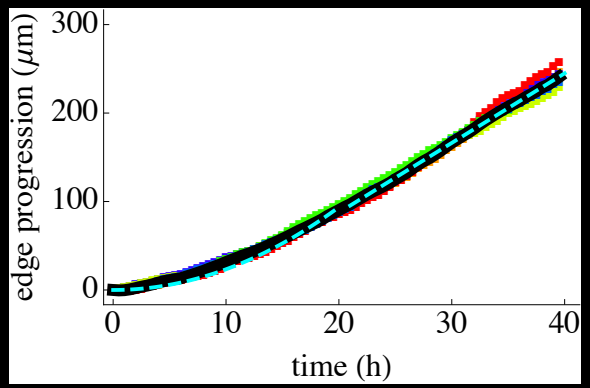
Velocity profiles



Experiments (dashed) vs.
Sim (solid); 0, 10, 20 h .



Experiments



Simulations

Early t^2 border progression : simple explanation

-Without leader cells the interface move at a slow velocity $\mathbf{v_s}$

-Leader cells appear at a uniform rate ρ (per unit border length)

-Each leader cell **i** guides a portion of the interface of width $\mathbf{w_i}$ at a high velocity $\mathbf{v_f}$

Mean border position : average of fingers and slow moving parts

$$x_b(t) = \frac{1}{L}\left[\sum_i w_i x_i(t) + v_s t\,(L - \sum_i w_i)\right]$$

Averaging over the stochastic leader creation, $\langle x_i(t)\rangle = (v_f + v_s)t/2$

$$\langle x_b(t)\rangle = \rho\, t\, \overline{w}\langle x_i(t)\rangle + v_s t(1 - \rho\overline{w}t) = \rho(v_f - v_s)\overline{w}\, t^2/2 + v_s t$$

Conclusions I:

-A simple model quantitatively accounts for the dynamics of cells in the epithelium bulk

-Proposed mechanisms for the action of leader cells

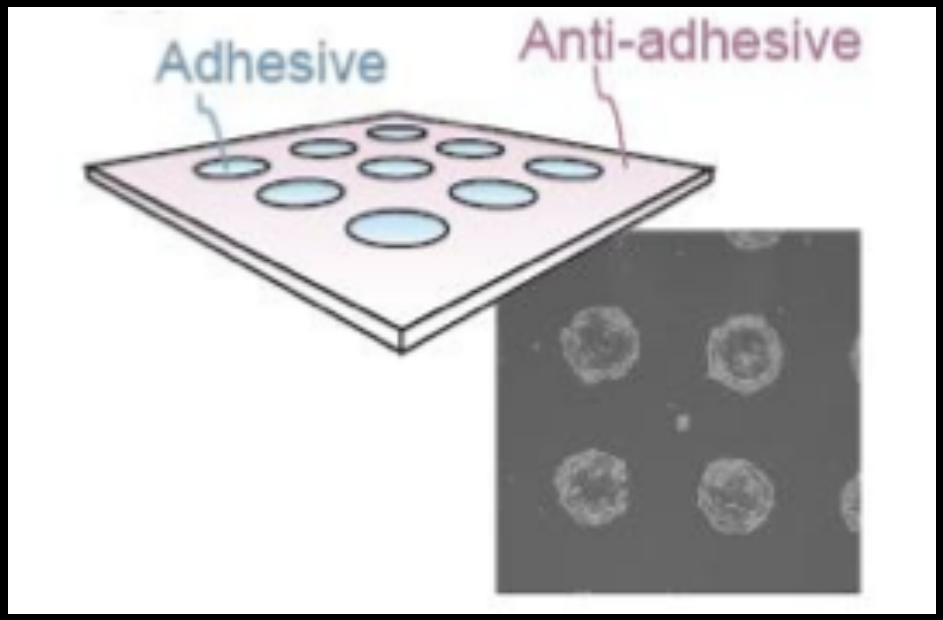
What's next?

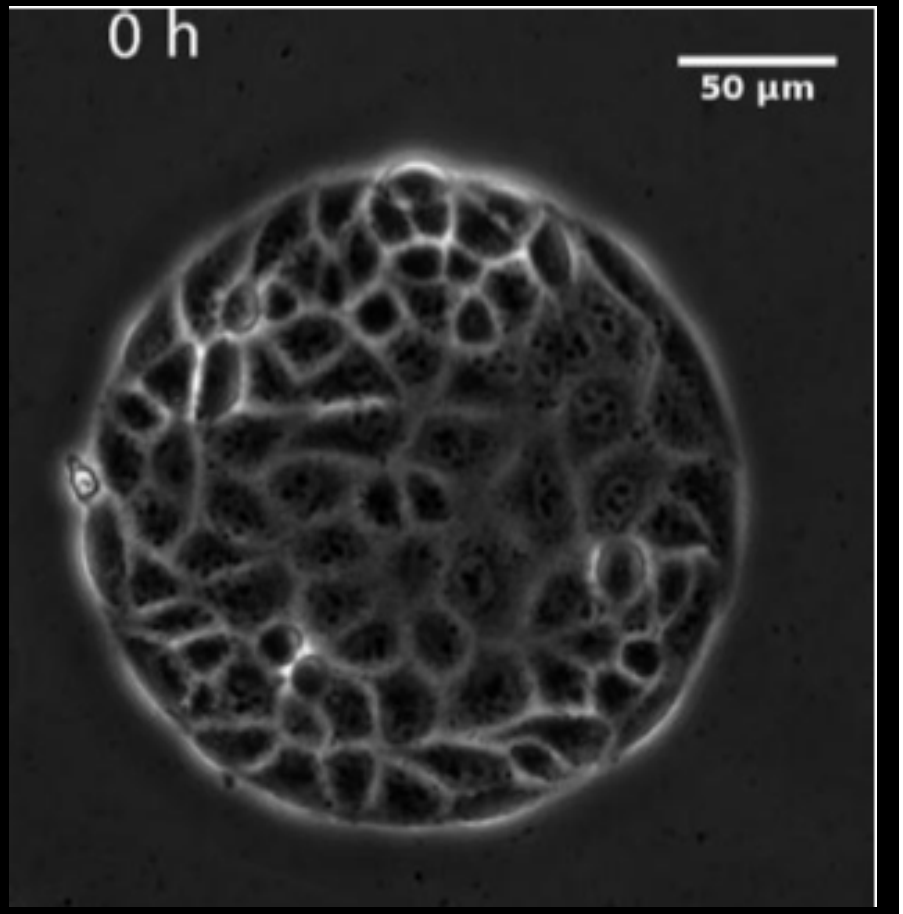
-Linking the model parameters to molecular mechanisms (and proteins/genes)

-Description of leader cell appearance

-Investigating the model usefulness for collective cell motions in other settings or other contexts (in vivo?).

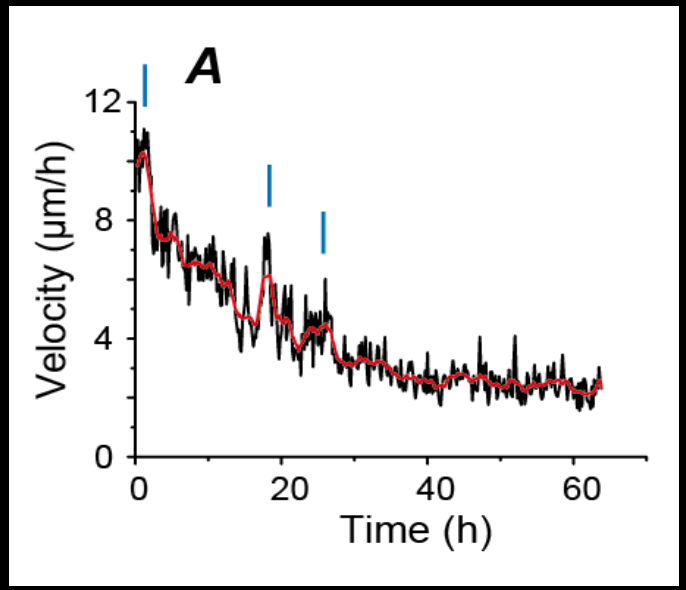
Dynamics of cells in confined patches

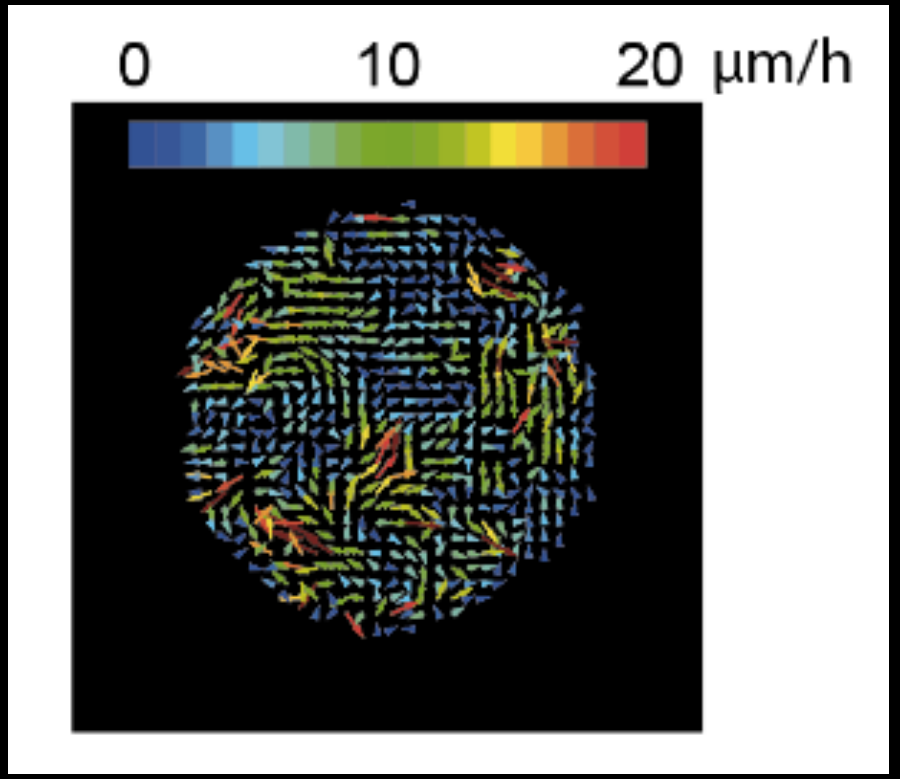


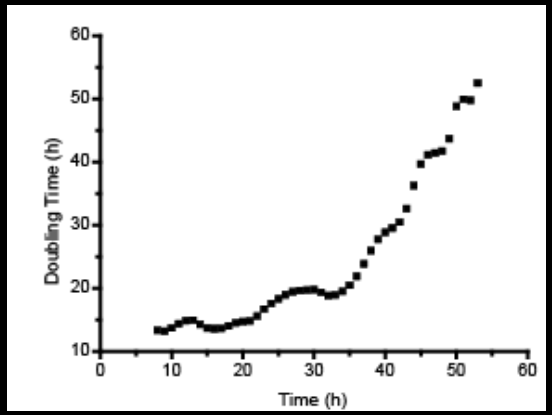


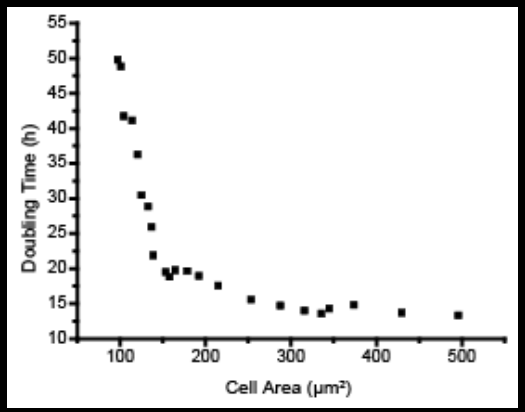
M Deforet

Dynamics of cells in confined patches



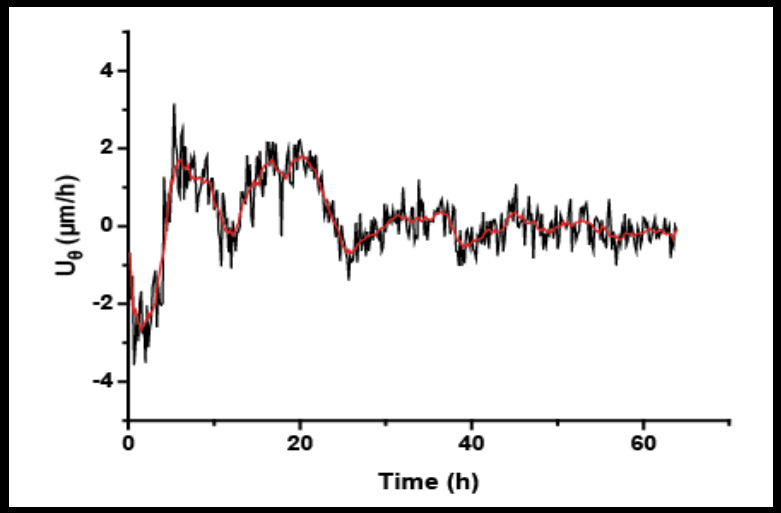


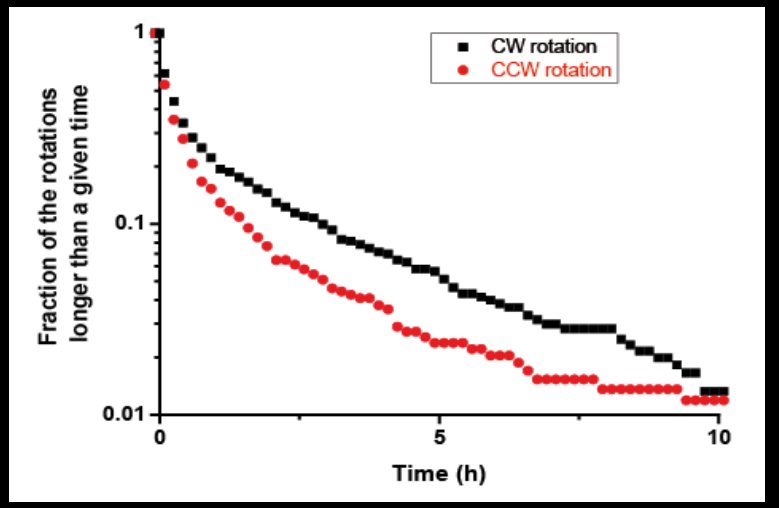


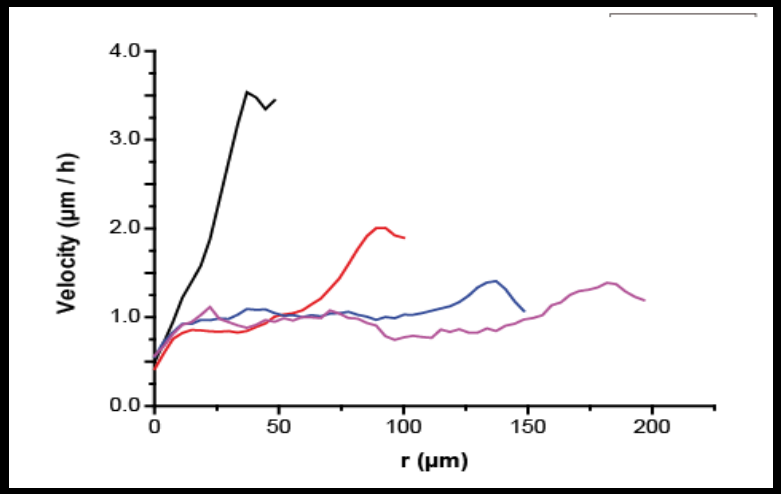


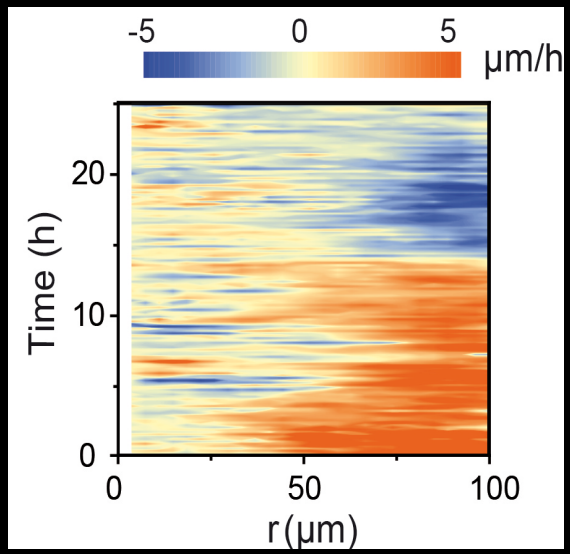
M Deforet

I. Global rotation with stochastic reversals









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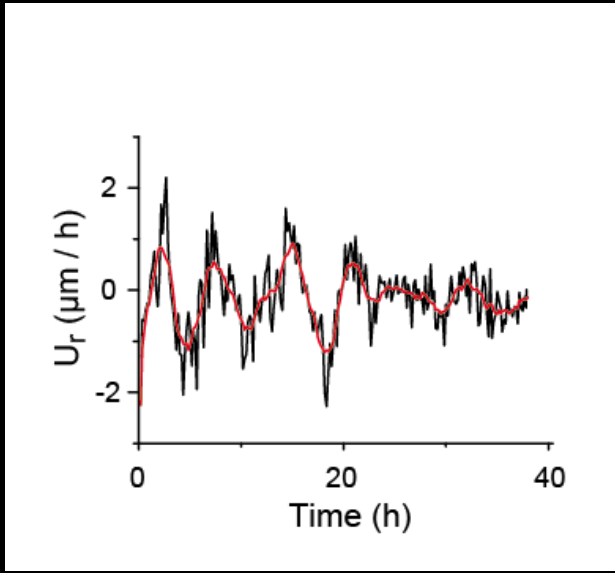
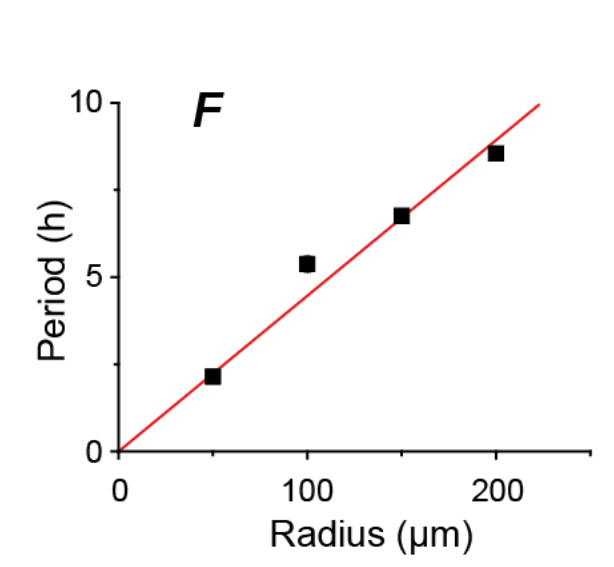
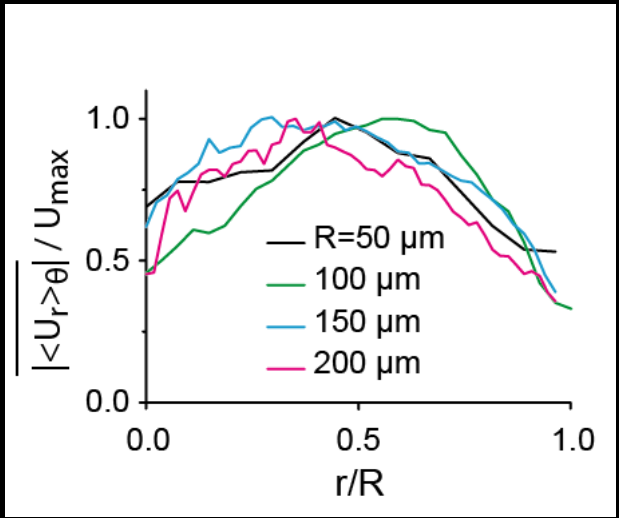
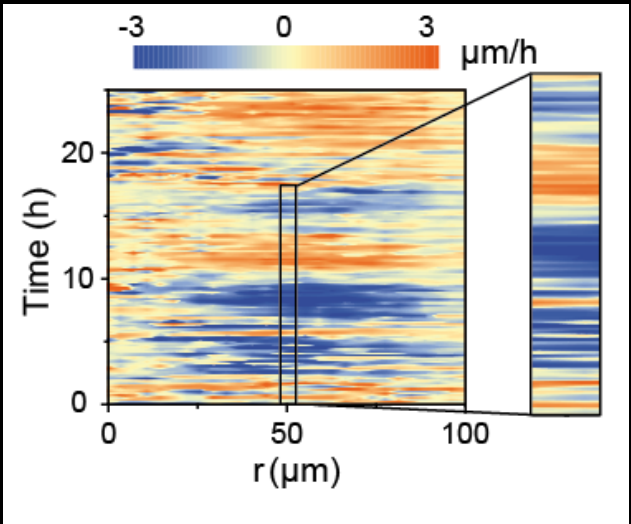
II. Radial breathing oscillations as cells reach confluence









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Questions:

-Where are these global behaviors coming from?

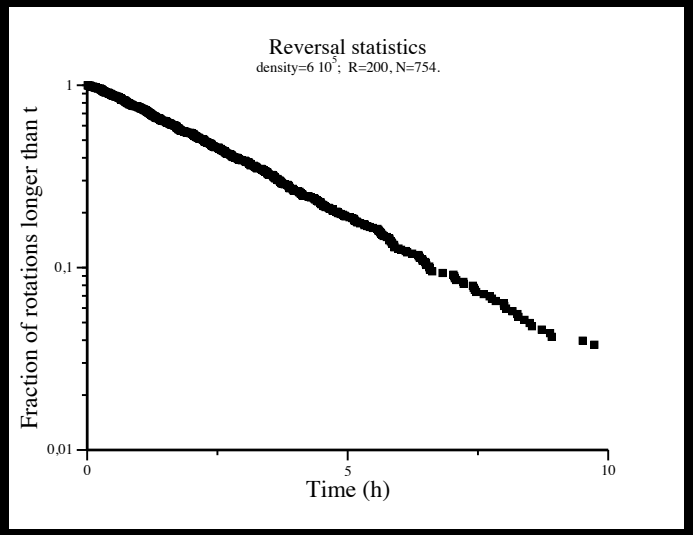
-Are they arising from some new mechanisms (signalling and waves?) induced by confinement?

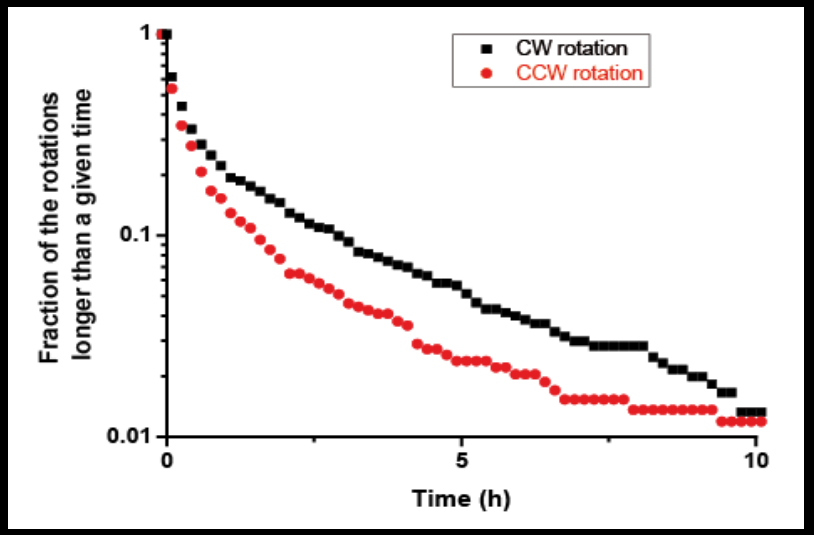
A simple approach:

- To better see what is required, let us see what our simple model does in this geometry :

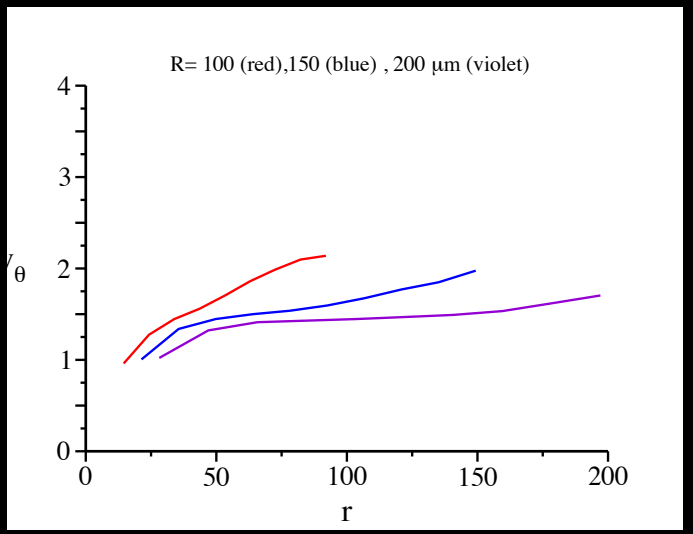
Simulations (at fixed density) with an added external repulsive potential that confines particles in a circular disk

I. Rotation and reversals : model vs. experiments

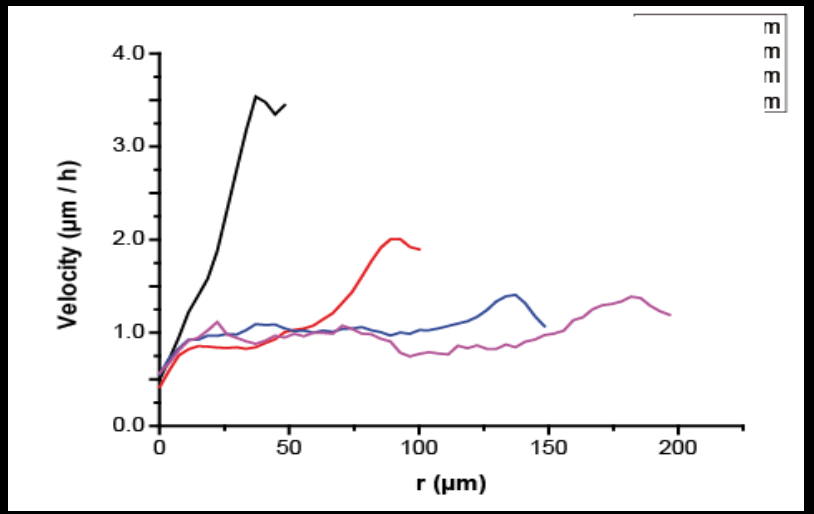




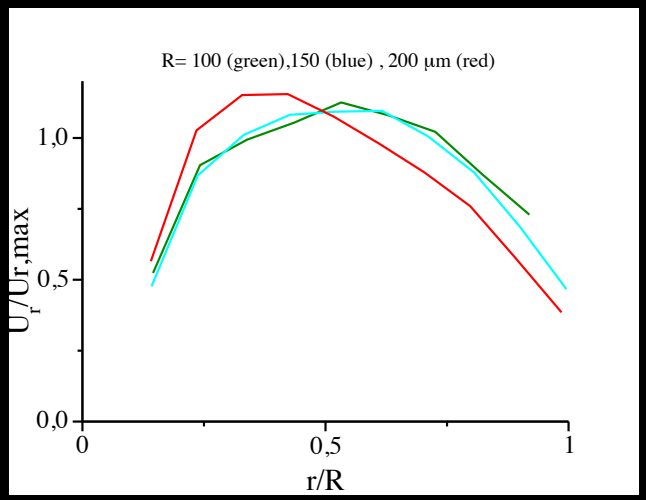
Simulations

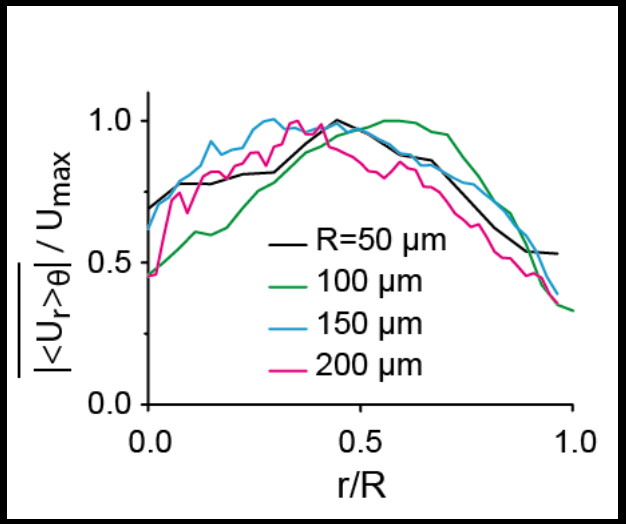


Experiments

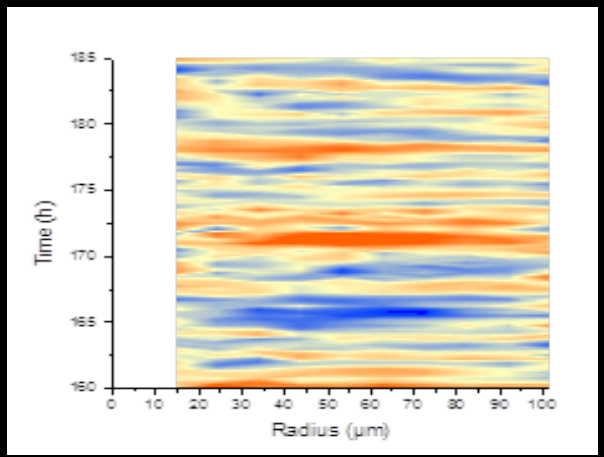


II. Radial breathing oscillations : model vs. experiments

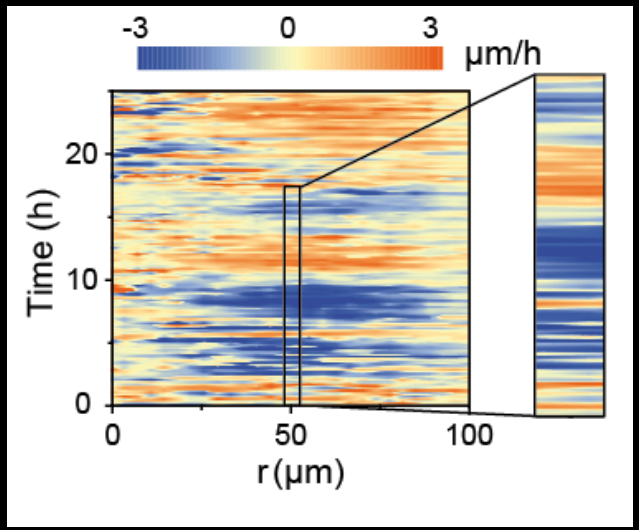




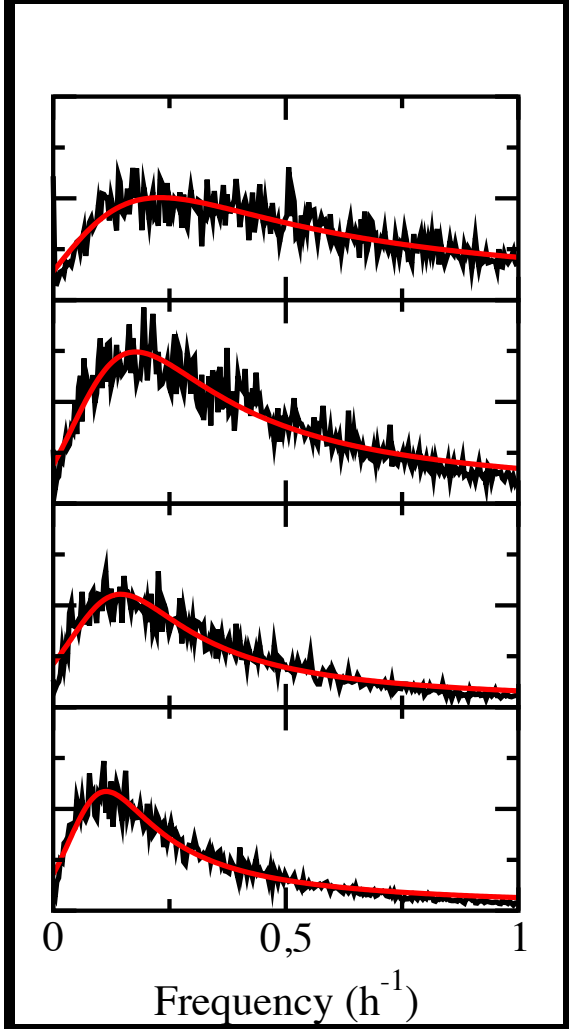
Simulations



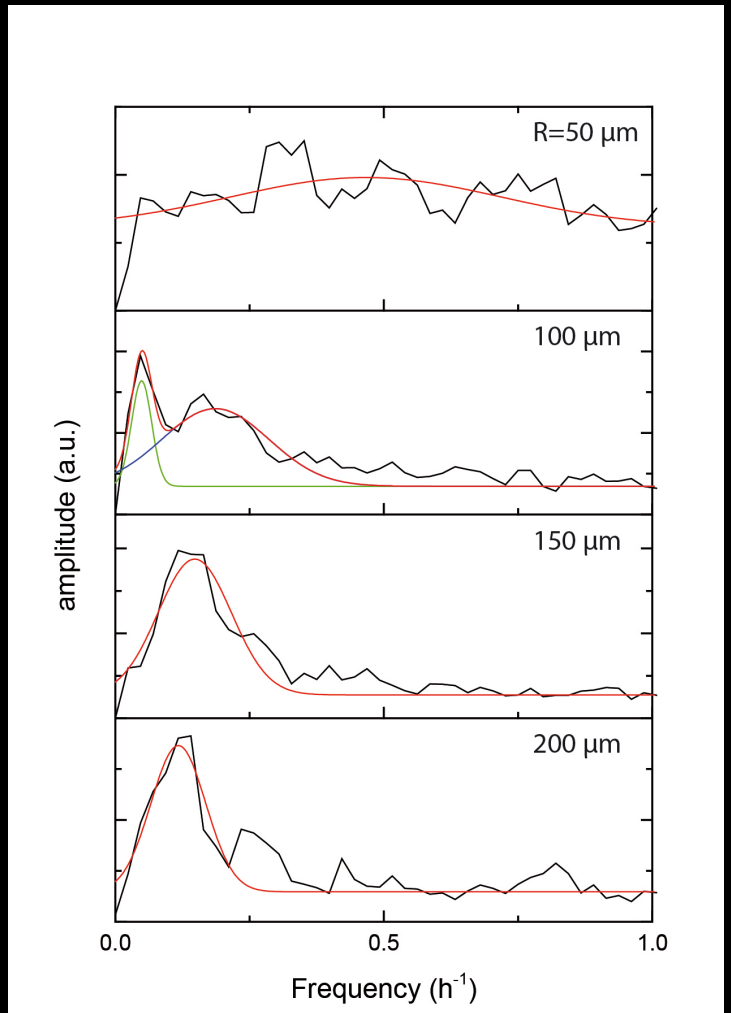
Experiments



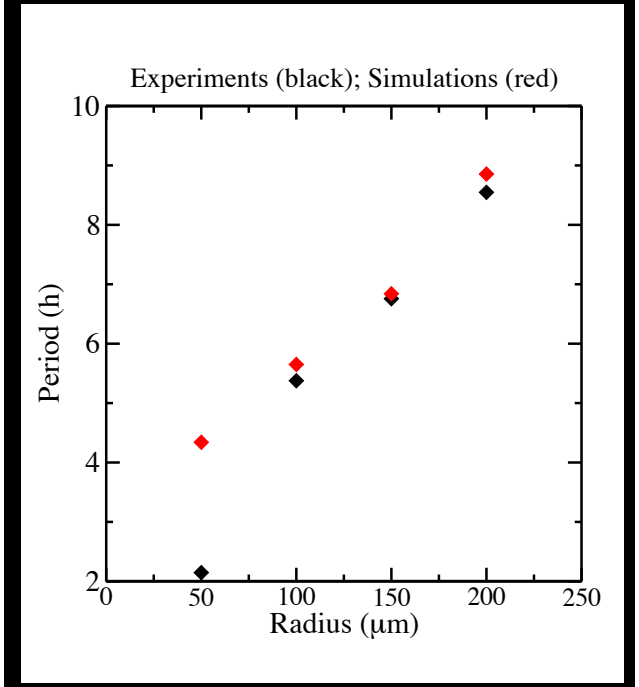
II. Radial breathing oscillations : model vs. experiments



Simulations



Experiments

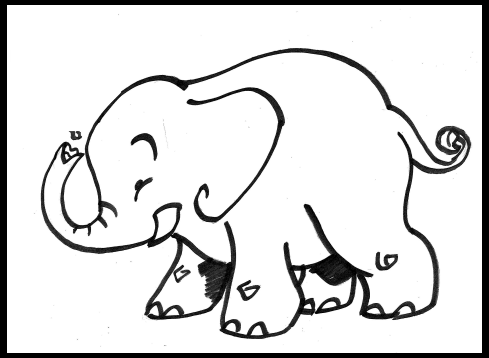


Conclusions

-A simple model quantitatively accounts for the dynamics of cells in the epithelium bulk

-It seems useful to see what naturally follows from the included features (noise, persistence, coordination) from what requires supplementary mechanisms

-From a more theoretical point of view : analysis to be done to derive the cell assembly dynamics characteristics from the (model) individual cell properties.



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Thank you!



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M Deforet

N Sepulveda