Mechanobiology of Collective Cell Migration

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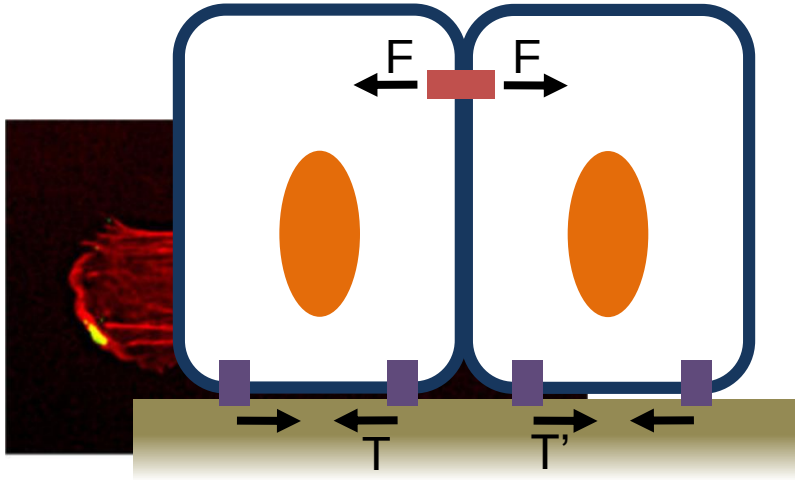
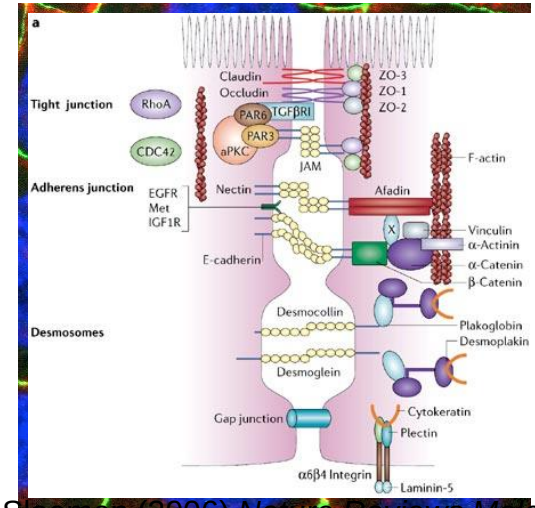
Mechanobiology of Cell Collectives

To understand the dynamics of many cells as a cohesive single group (‘Collective’) in a tissue or tissue-like system from the point of view of forces (‘mechanobiology’) that act on them.

Problem of length-scale: *Larger than single cells but smaller than a tissue!*





Thiery and Sleeman (2006) *Nature Reviews Molecular Cell Biology*, 7, 131

Acknowledgement

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Collaborators:

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Jeffrey Fredberg, Harvard Univ.
Christian Franck, Brown Univ.
Benjamin Geiger, Weizmann Institute

Collective Migration in Nature

Starling flocks

Source: telegraph.co.uk

Collective Movement/Migration = Correlated or aligned movements of several individuals

Fish school

Source: www.financialsense.com

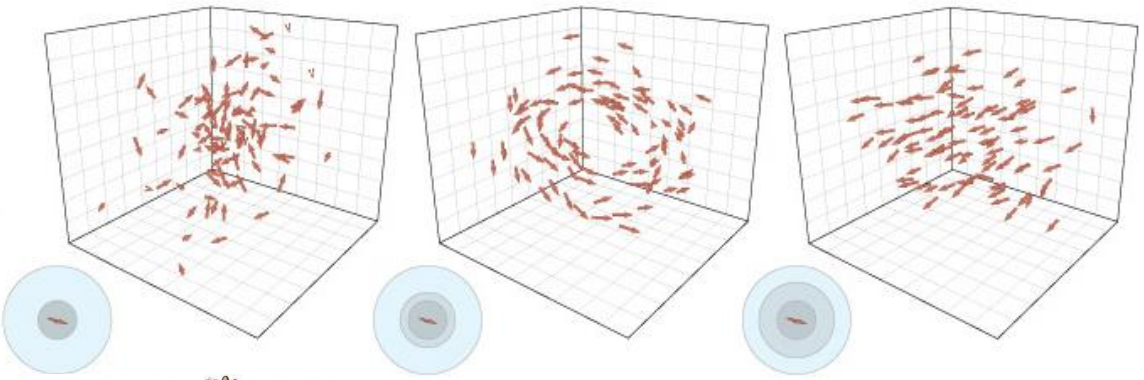
Sheep herd

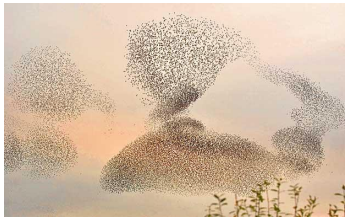
Source: www.wired.com

Behavioral Rules

3 Rules: Repulsion, Orientation, Attraction

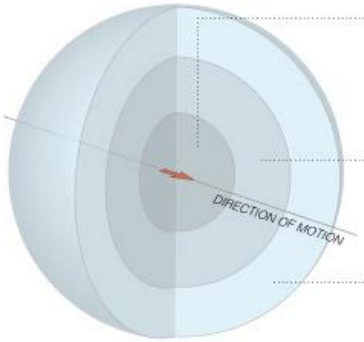
Swarm Torus Flock





Simulating Swarm Intelligence

Reseachers created a model of swarm behavior by programming individuals to maintain personal space while turning and moving in the same direction as others.



Area of repulsion
A simulated animal ( ) tries to maintain a spherical area of personal space by avoiding collision with other animals entering the area.

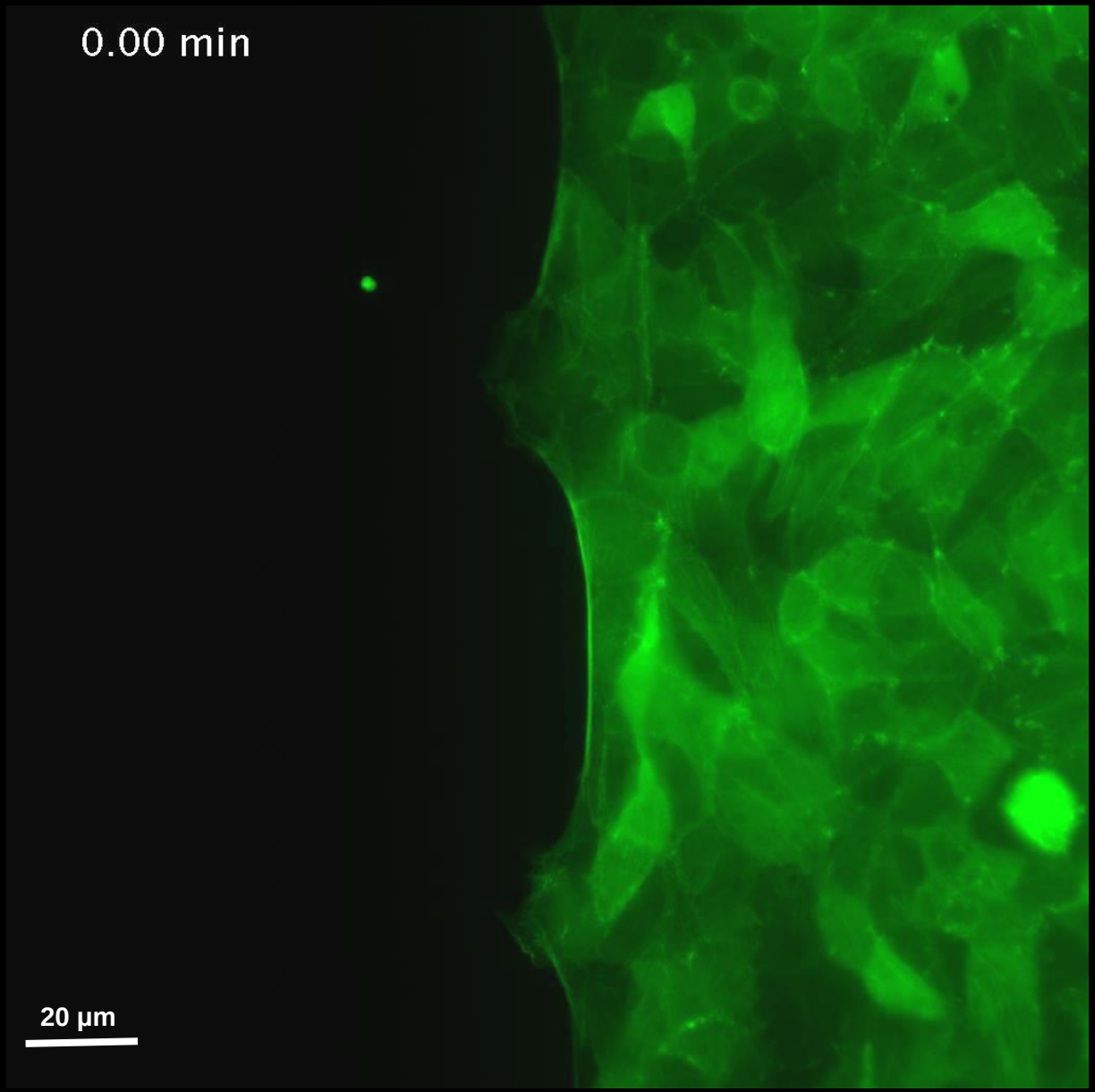
Area of orientation
The simulated animal will try to orient itself and move in the same direction as other animals in this region.

Area of attraction
The animal will try to move toward other animals in this region, encouraging group formation and cohesion.

Sources: Iain D. Couzin; Journal of Theoretical Biology

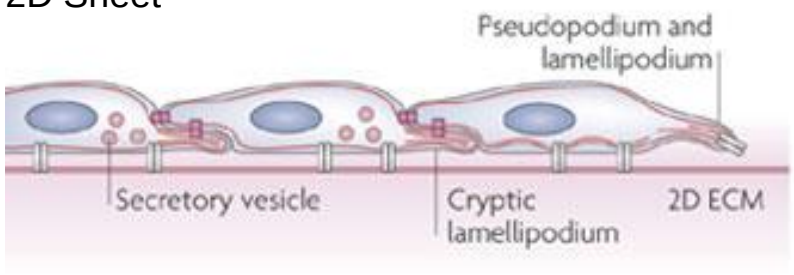
Collective Migration of Epithelial Cells

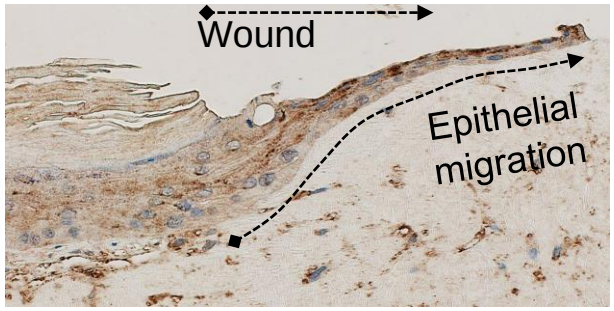
MDCK (Canine Kidney Epithelial) Cells expressing LifeAct-GFP



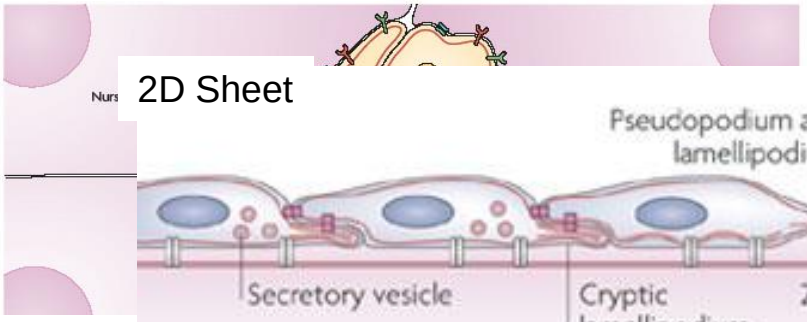
Collective Migration of Cells

2D Sheet



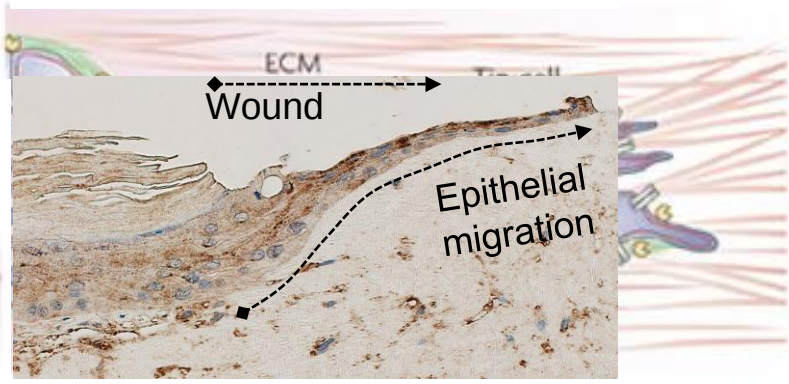


Border cell migration

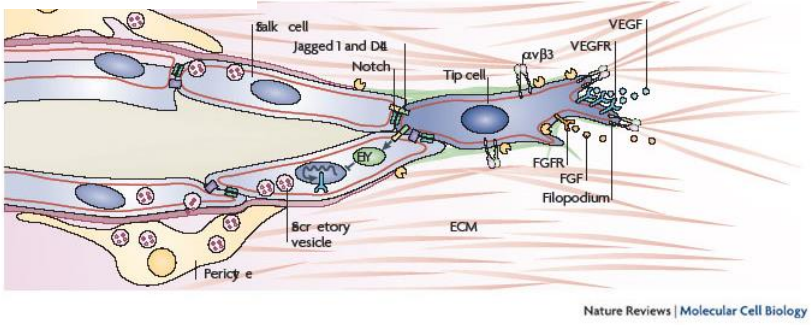


2D Sheet

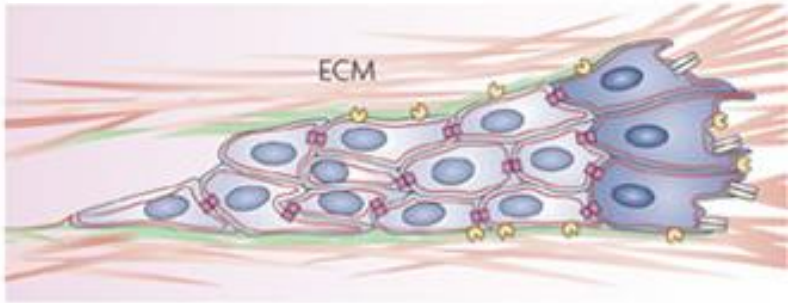
Metastatic invasion of cancer cells



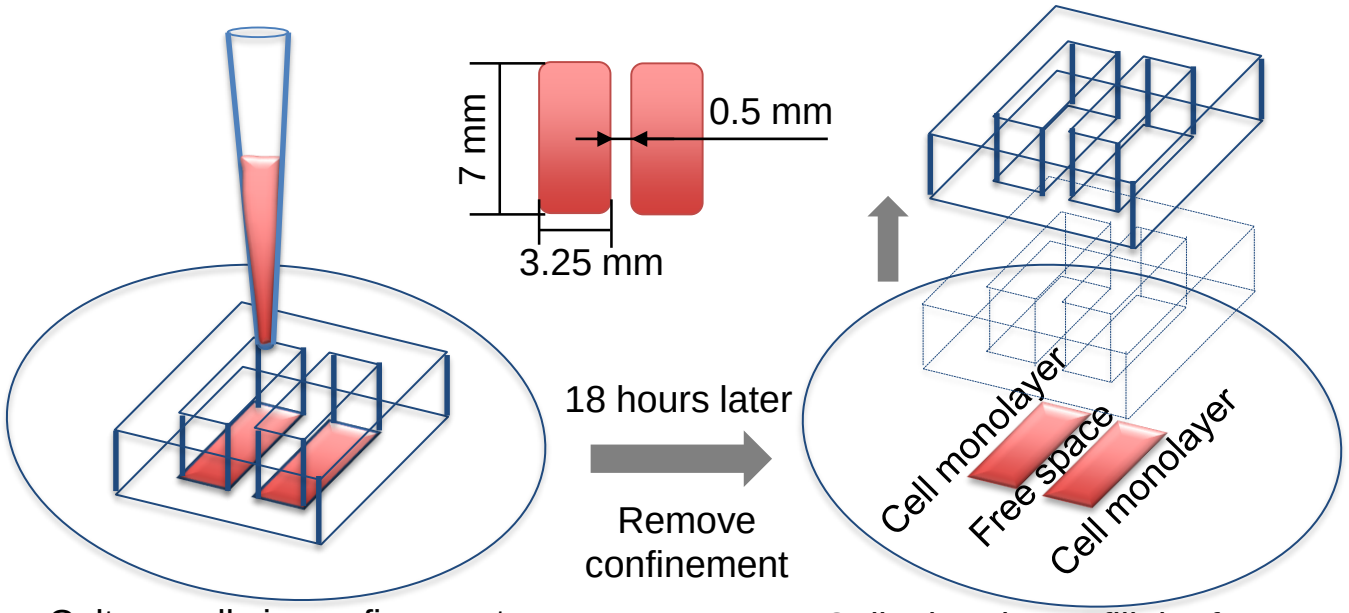
Angioge

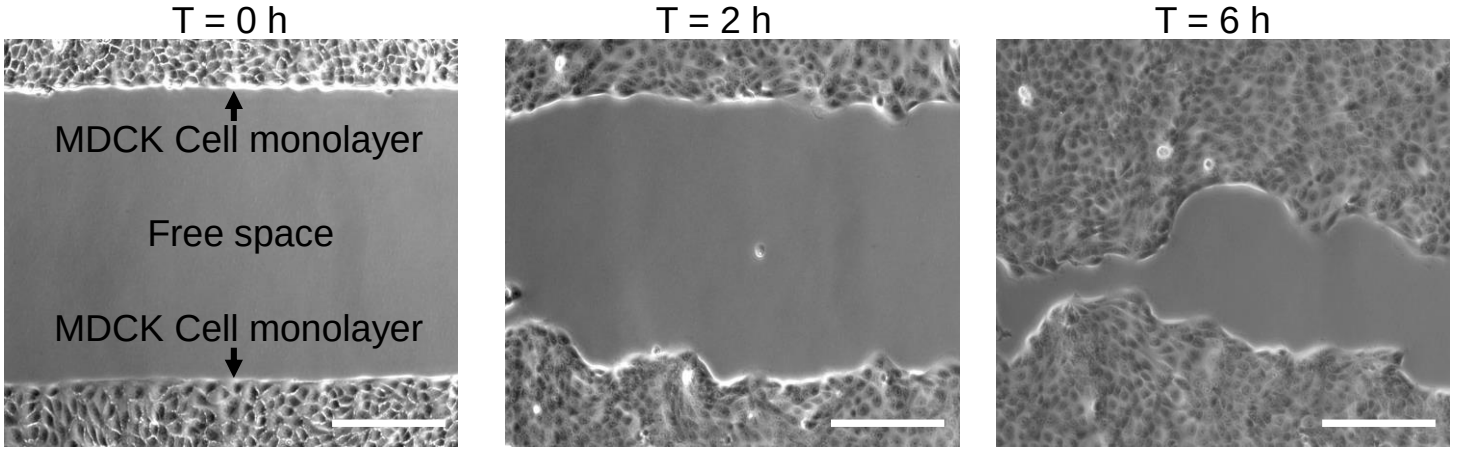


Invasion as isolated group



Epithelial Sheet Migration





Scale bars, 200 µm

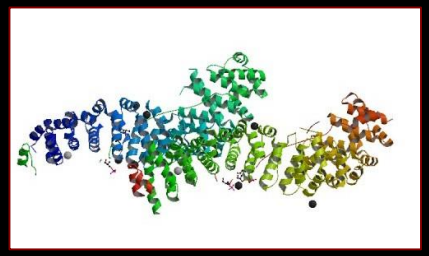
We are asking:

131.40 min

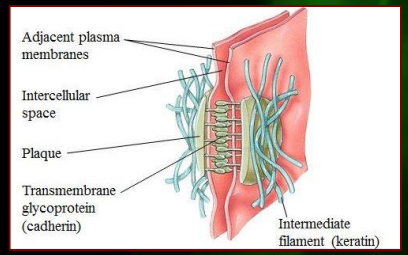
Can we find the rules or physical principles of collective cell migration?

What would be the molecular mechanisms that decide these rules?

nm: Reaction



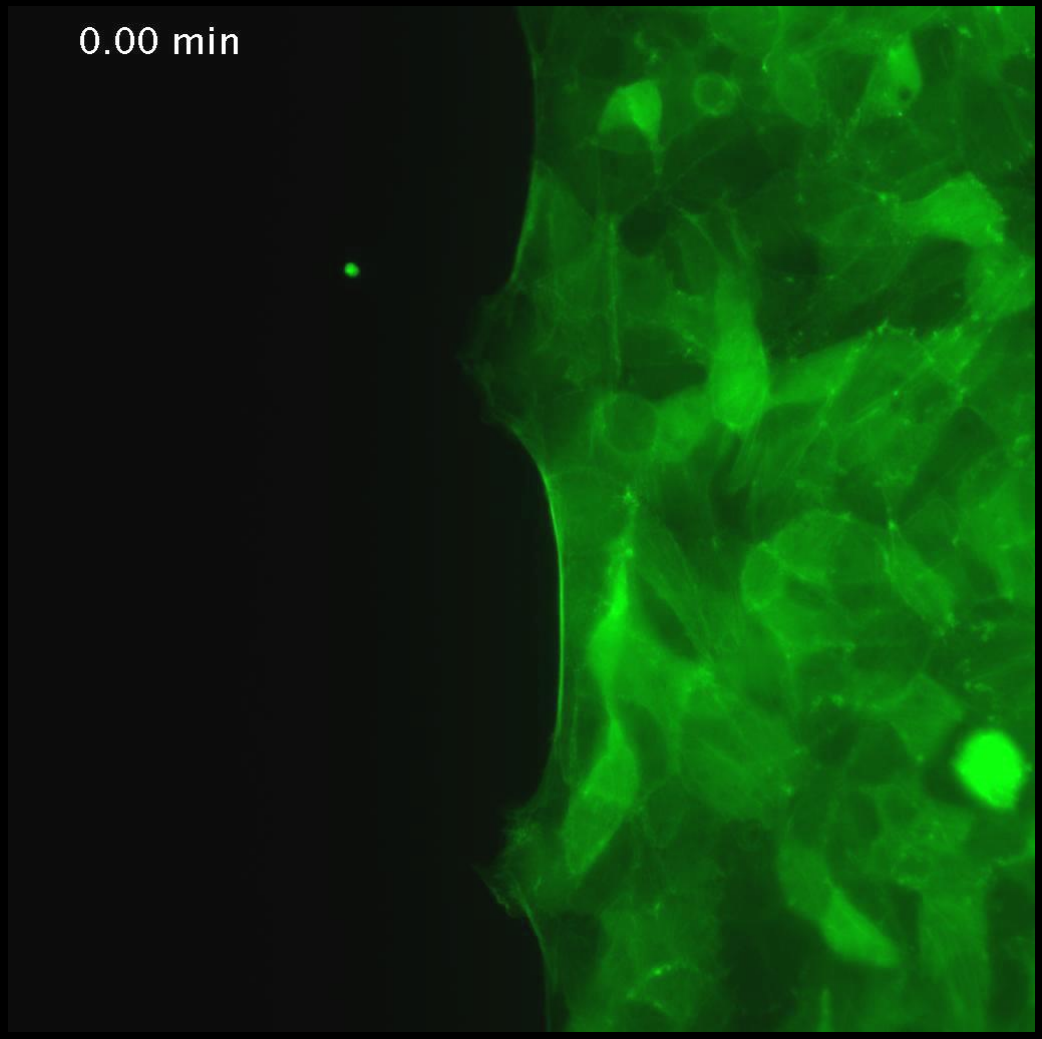
µm: Assembly



mm: Rules

<u>Answer can be found in how physical forces interact with the biochemical signaling</u>

Systematic Behavior?

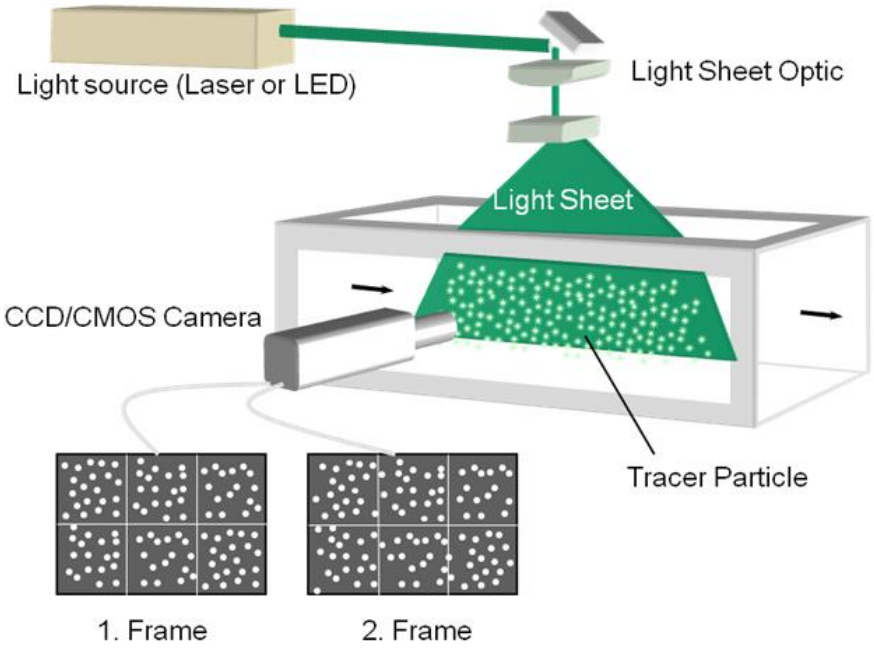


Physical Characterization

*** Motion**

*** Force**

Motion: Particle Image Velocimetry (PIV)



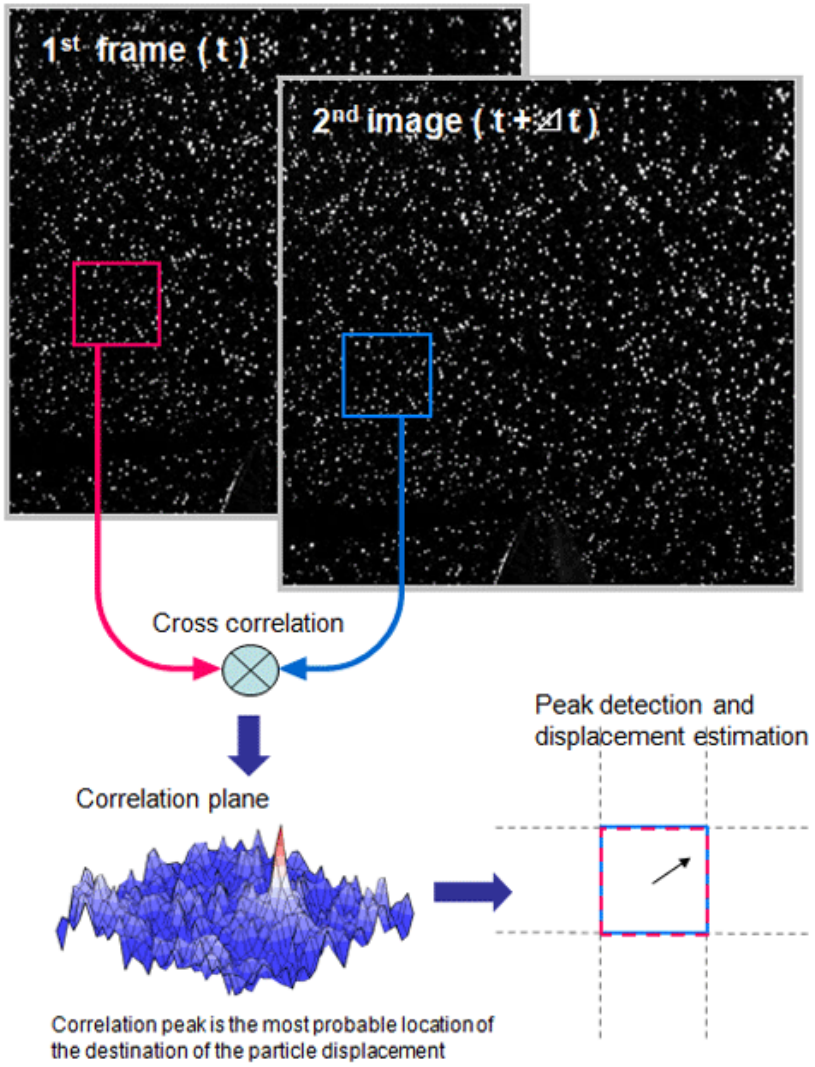
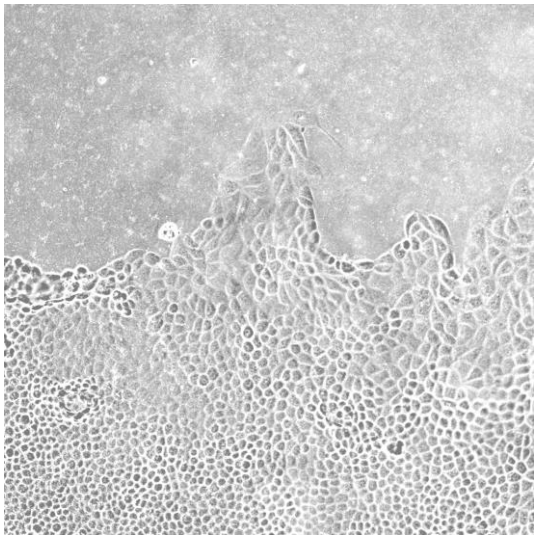
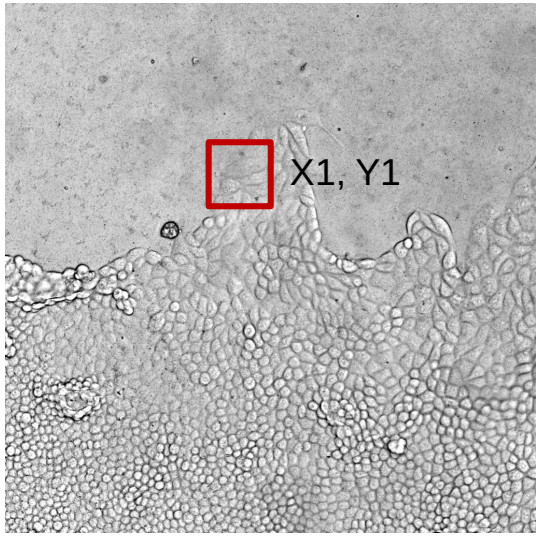


Image: Seika Digital Image Corp.

PIV in Collective Migration



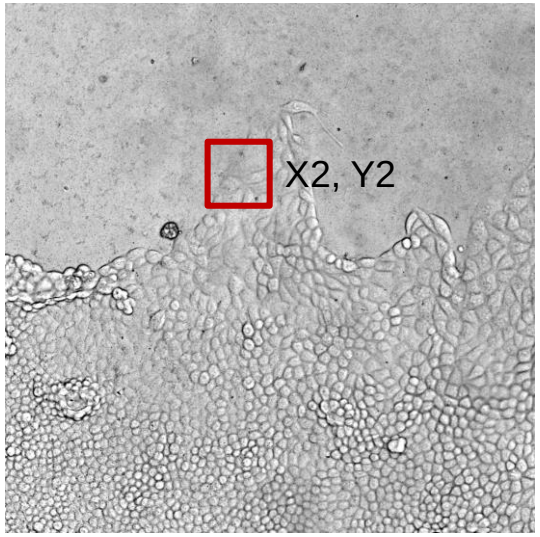


0, 0

$d_X = X2 - X1;$
$d_Y = Y2 - Y1;$
$d^2 = (d_X)^2 + (d_Y)^2$

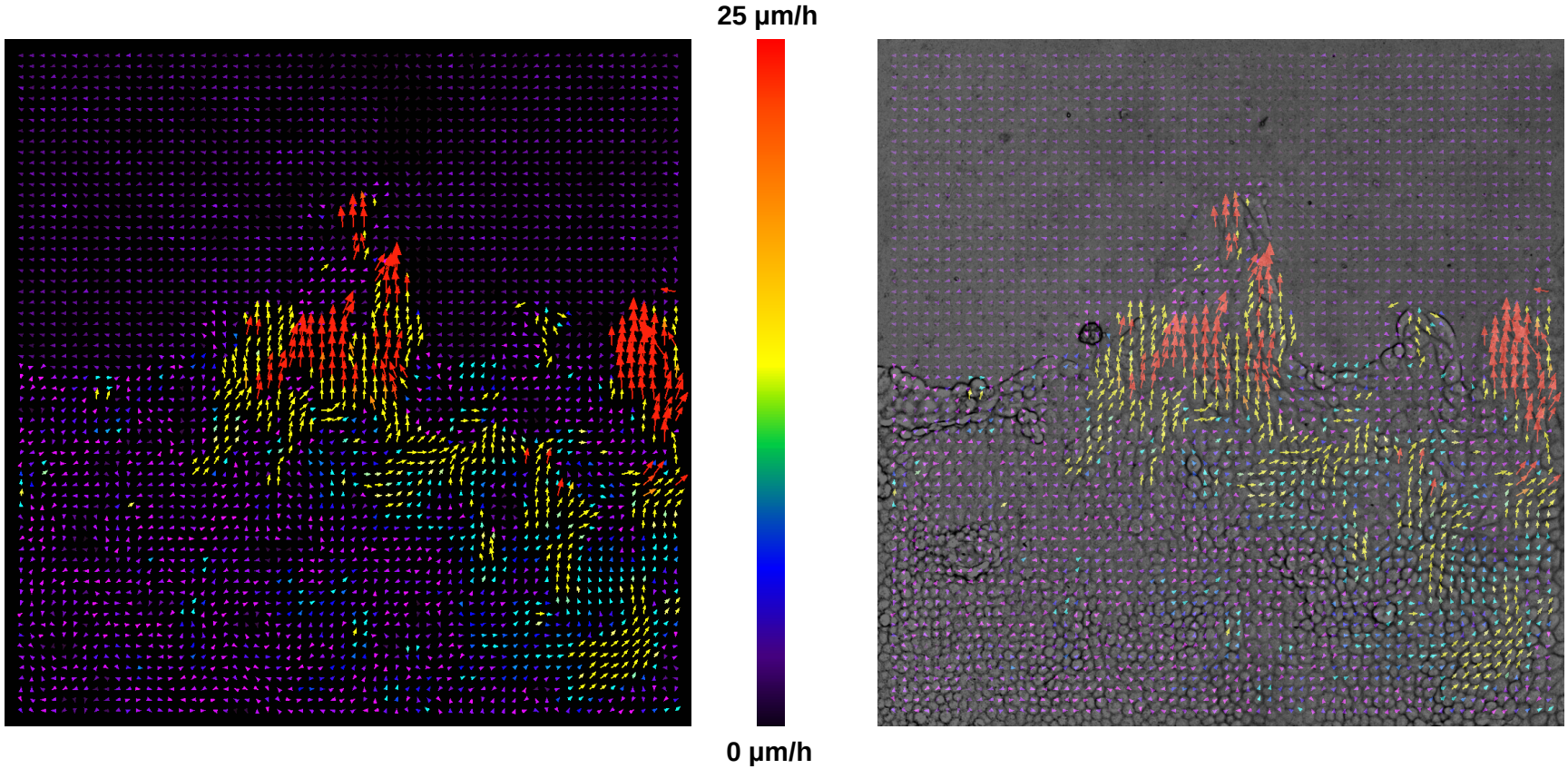
Δt = 10 minutes

$V_X = (X2 - X1)/\Delta t;$
$V_Y = (Y2 - Y1)/\Delta t;$
$V^2 = (V_X)^2 + (V_Y)^2$

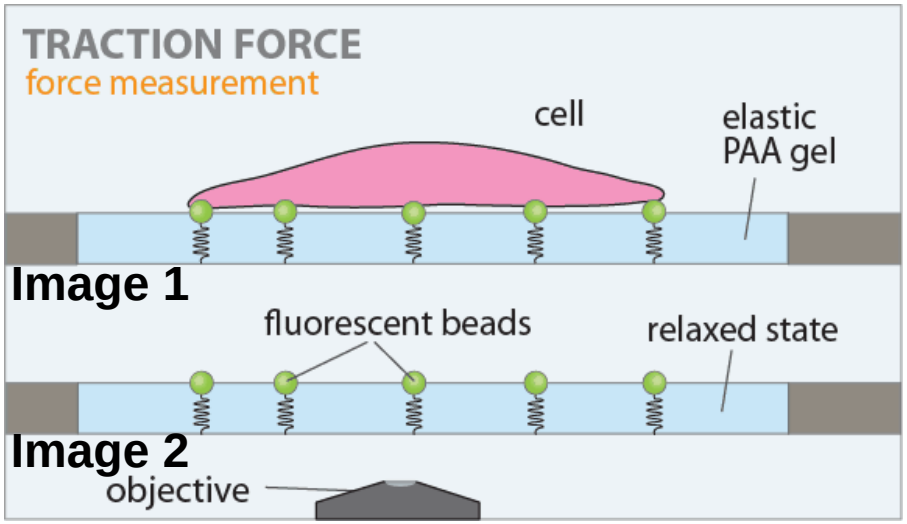


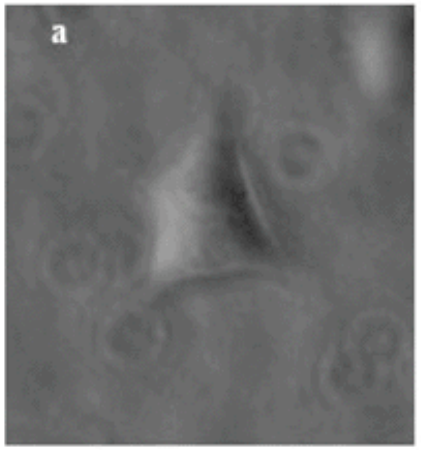
0, 0

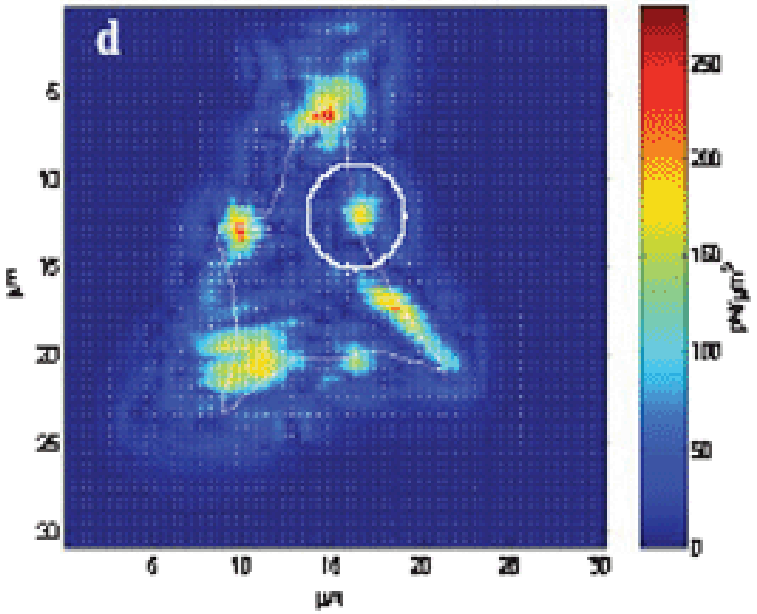
Velocity Field



Force: Traction Force Microscopy





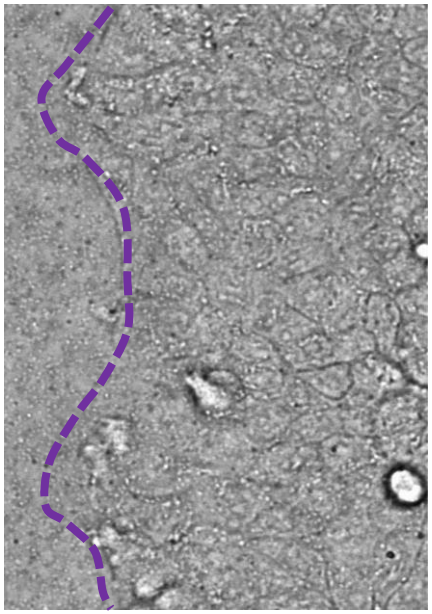


(Image 1 – Image 2) => Bead displacement => Traction Force (or Stress)

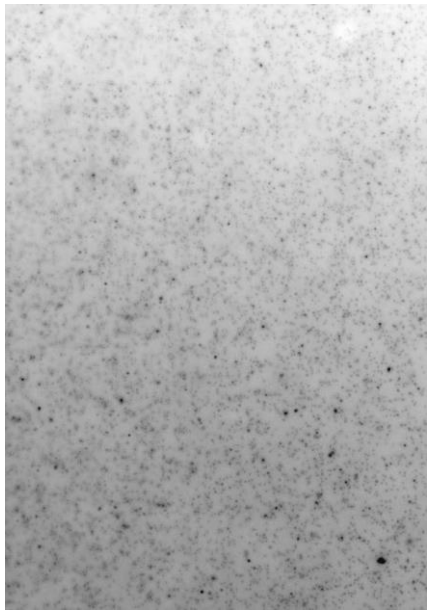
F = kx

Das *et al.* (2008) Lab on a Chip (RSC), 8, 1308-1318

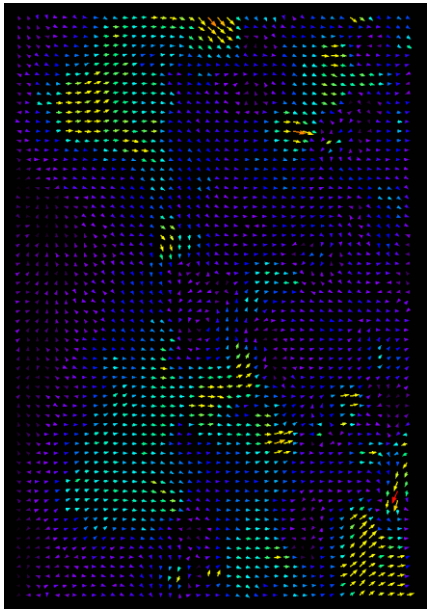
TFM in Collective Migration



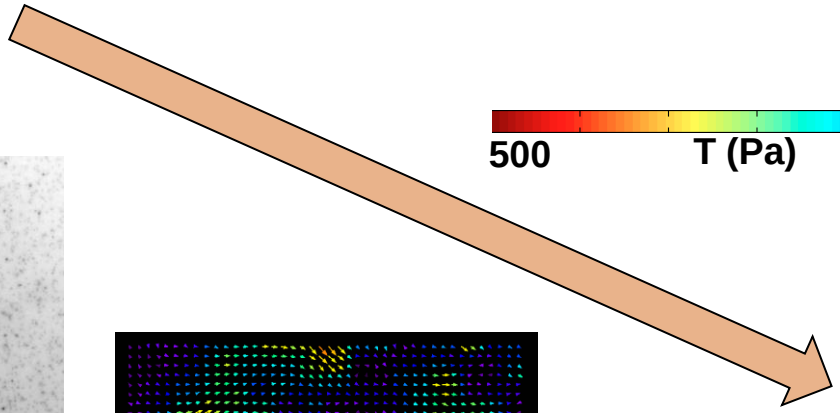
Phase contrast image of collective



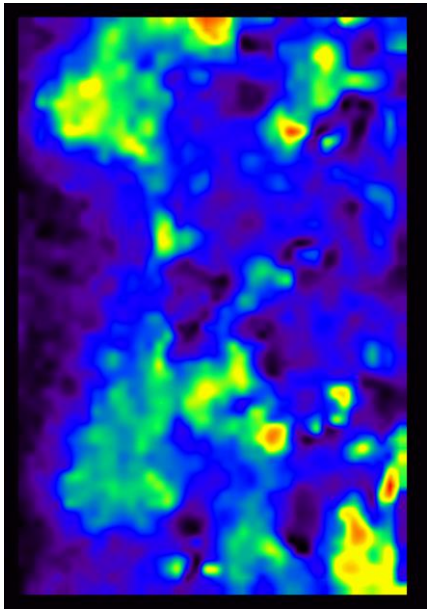
Displacement of beads underneath w.r.t. reference image



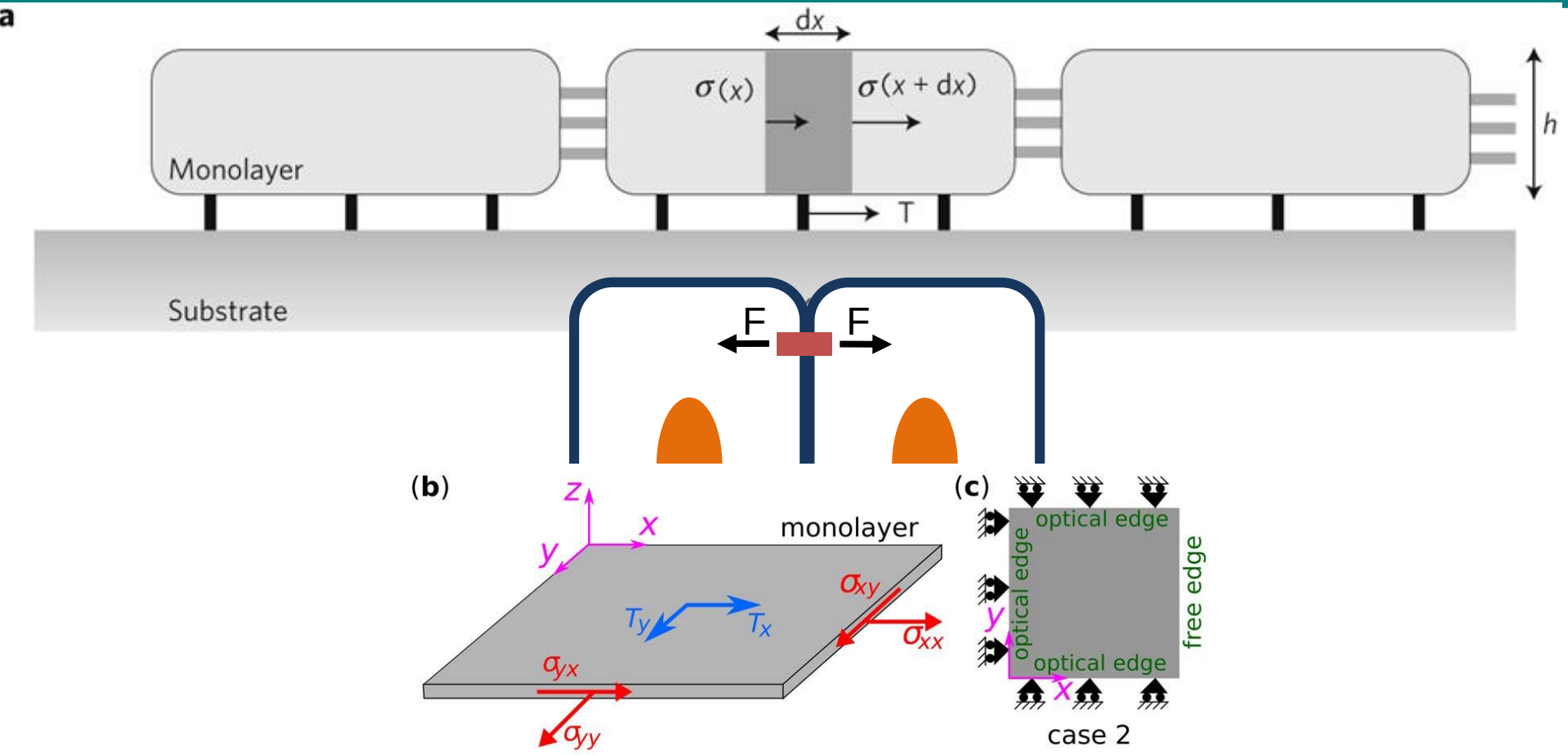
Bead displacement field



Traction force field

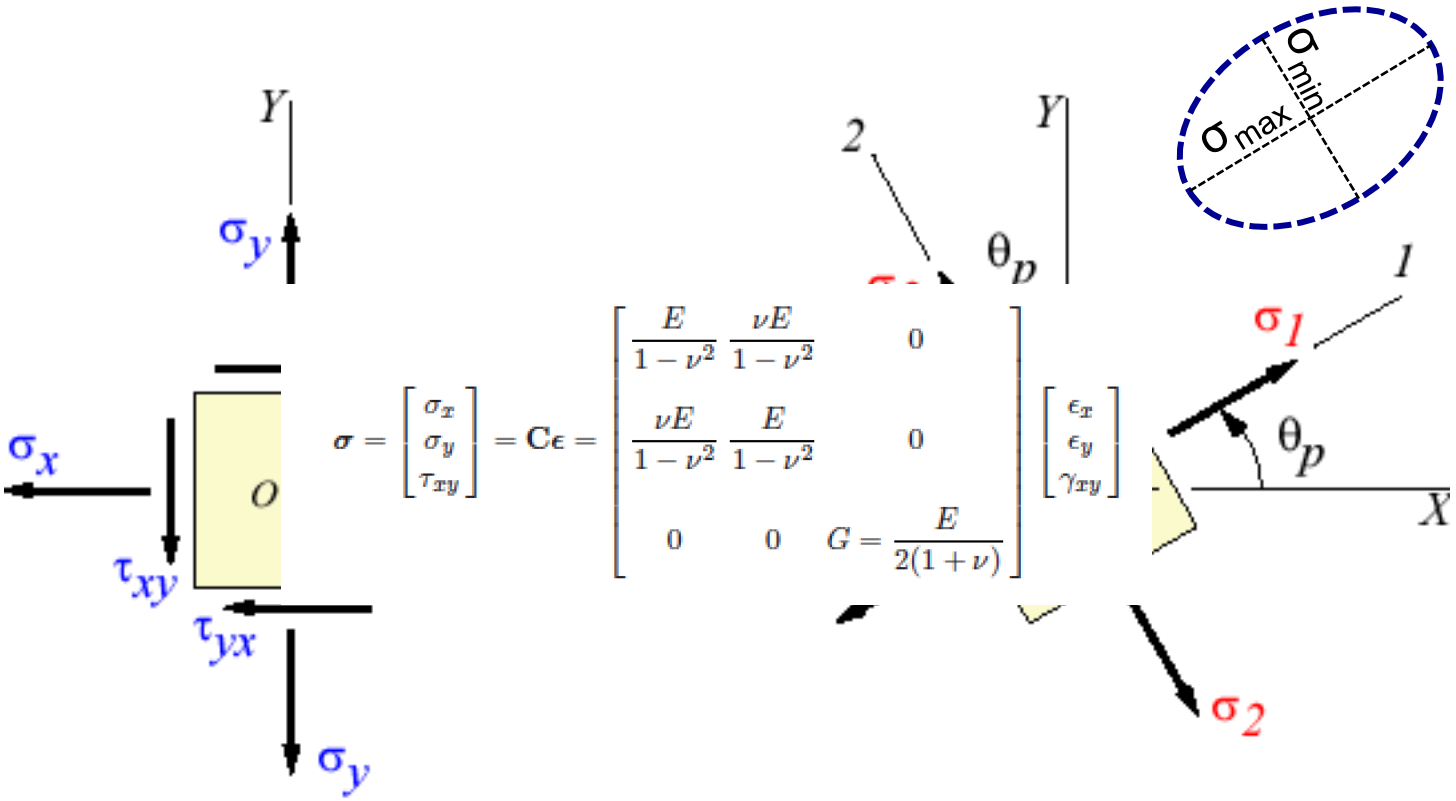


Monolayer Stress Microscopy



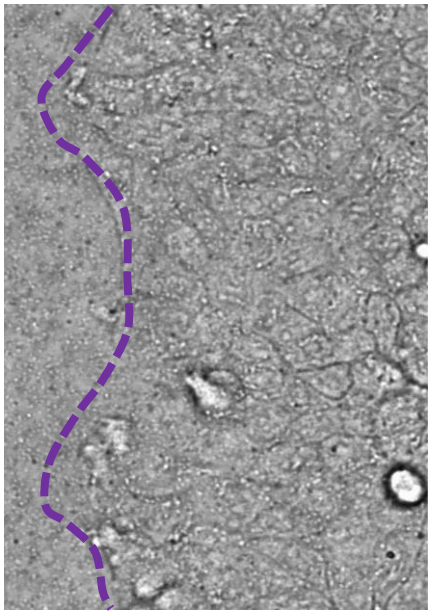
Tambe *et al.* (2011) *Nature Materials*, 10, 469–475

Stresses in 2D

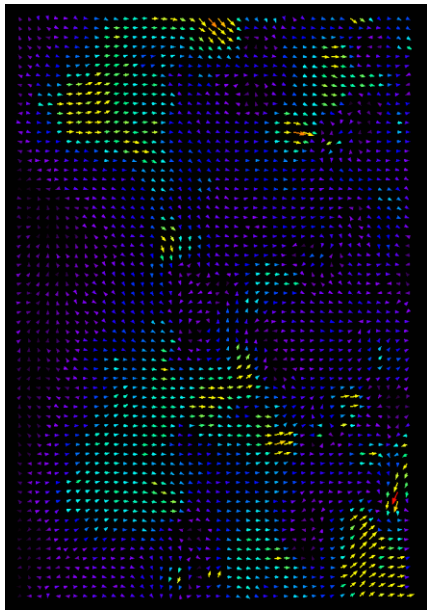


Average normal stress = $(\sigma_x + \sigma_y)/2 = (\sigma_{max} + \sigma_{min})/2$

Monolayer Stress Microscopy (MSM)



Phase contrast image of collective

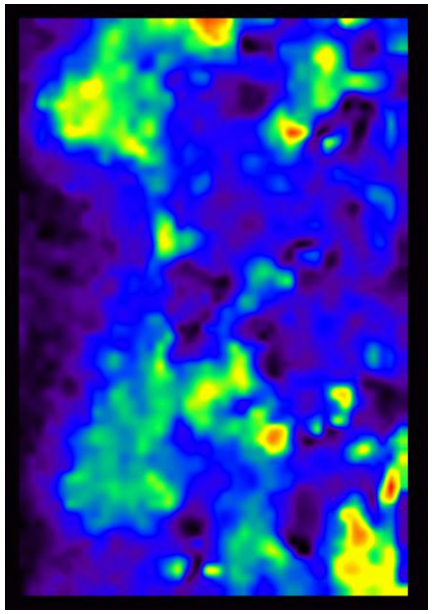


Bead displacement field

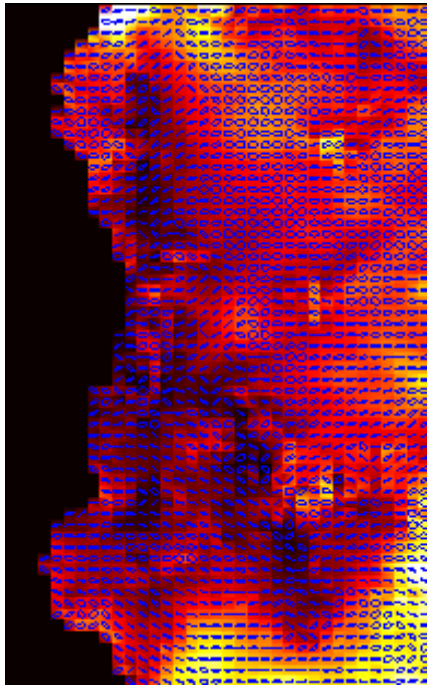
$\sigma_{max} = \sigma_{min}$ Isotropic

$\sigma_{max} >> \sigma_{min}$ Anisotropic

Traction force field



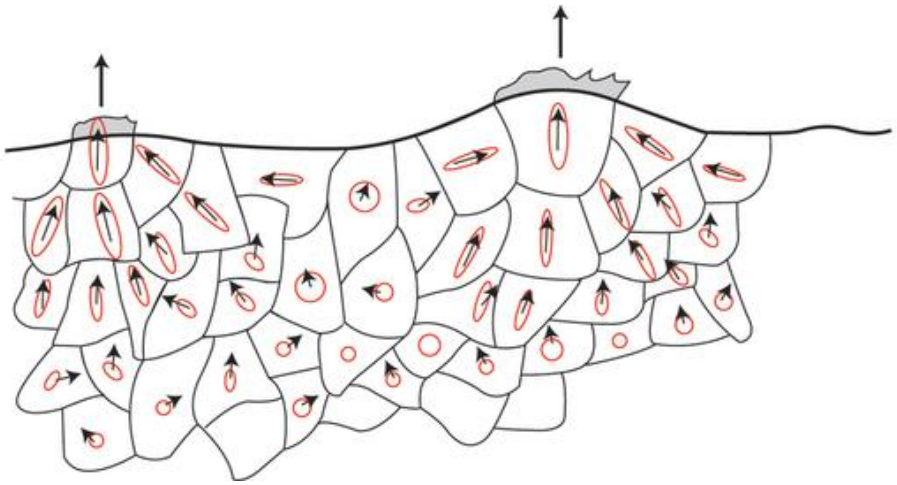
Average normal stress



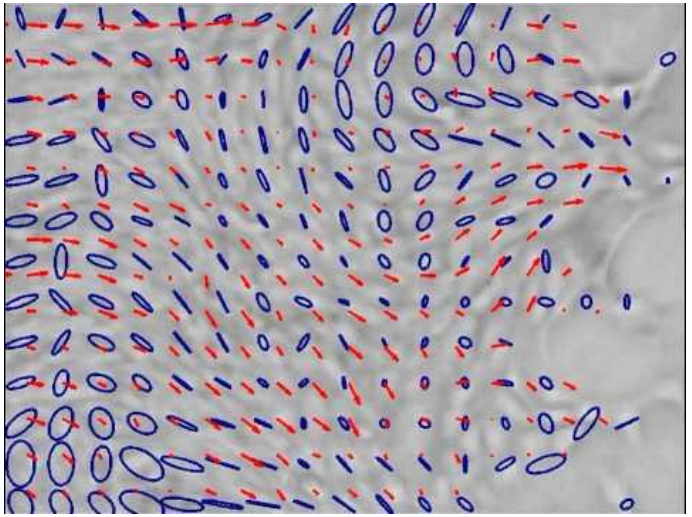
Systematic Behavior

Collective cell motion in a continuous tissue is guided by cooperative cell-cell pulling forces

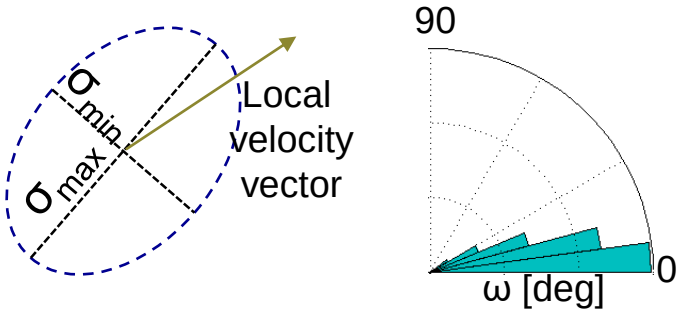
cooperative cell-cell pulling forces



‘Plithotaxis’

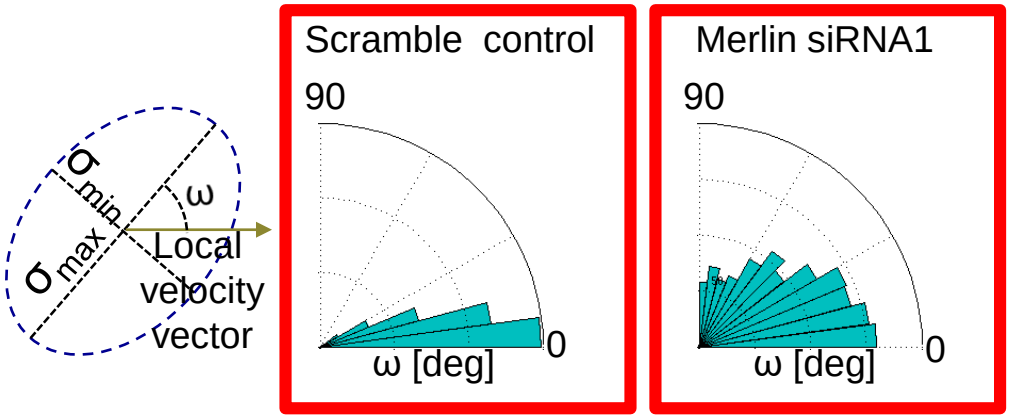


Tambe *et al*. (2011) *Nature Materials*, 10, 469–475

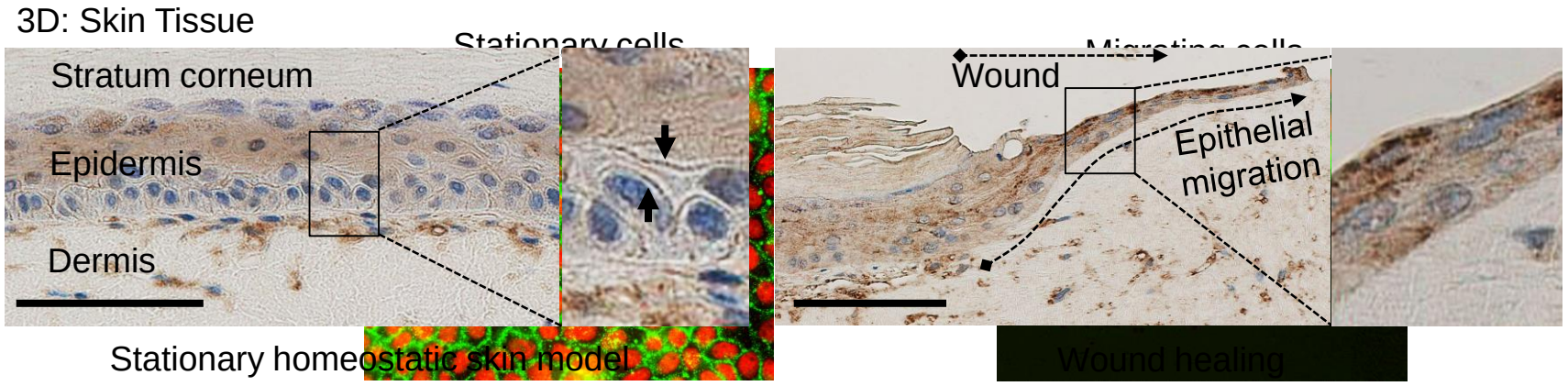


Das *et al.* (2015) *Nature Cell Biology*, 17, 276–287

A Tumor Suppressor Protein, Merlin



Breakdown of Stress-Velocity Alignment in Merlin-depleted Cells

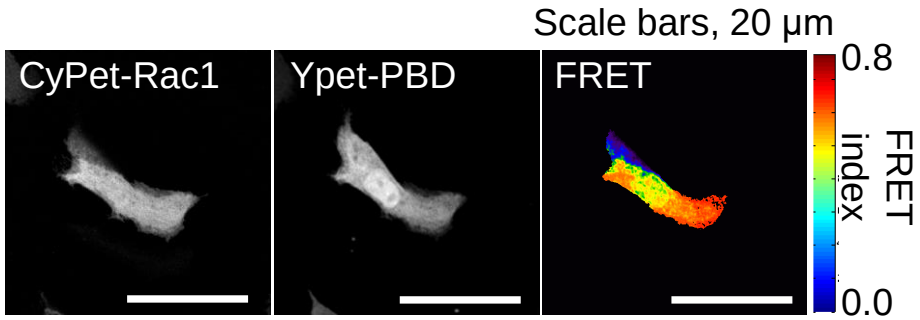


In collaboration with Niels Grabe's group in Heidelberg Univ.

Scale bars, 100 μm

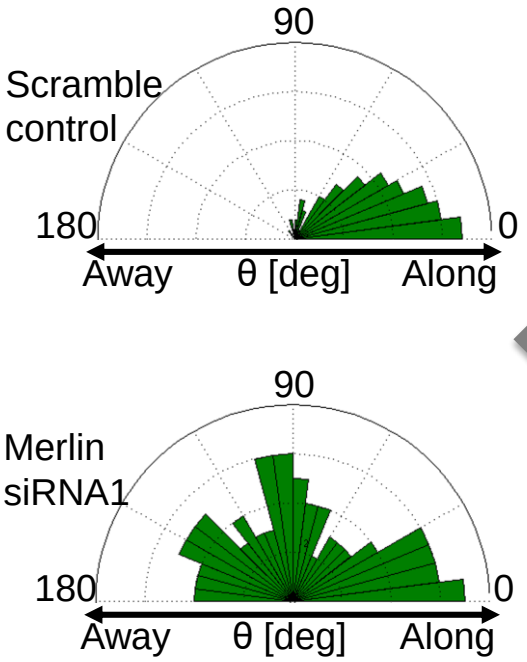
Das *et al.* (2015) *Nature Cell Biology*, 17, 276–287

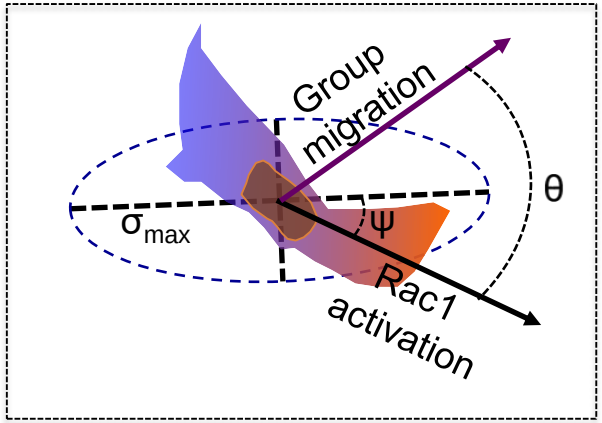
Collective Polarization of Active Rac1



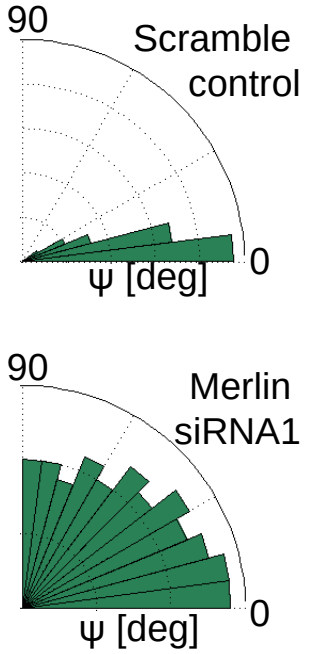
+ MSM + Phase contrast

Group migration-Rac1 activation (θ)



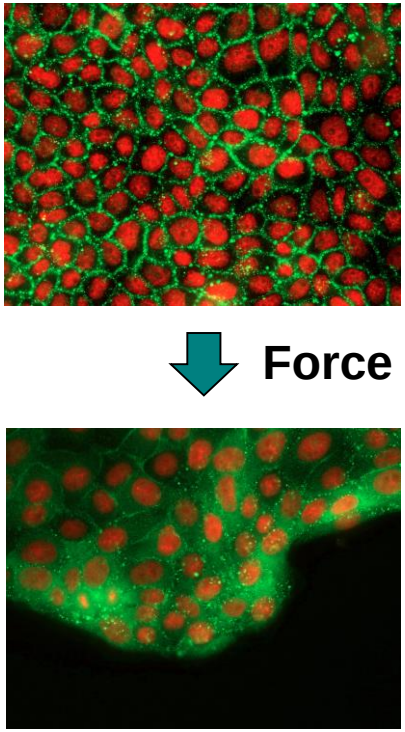


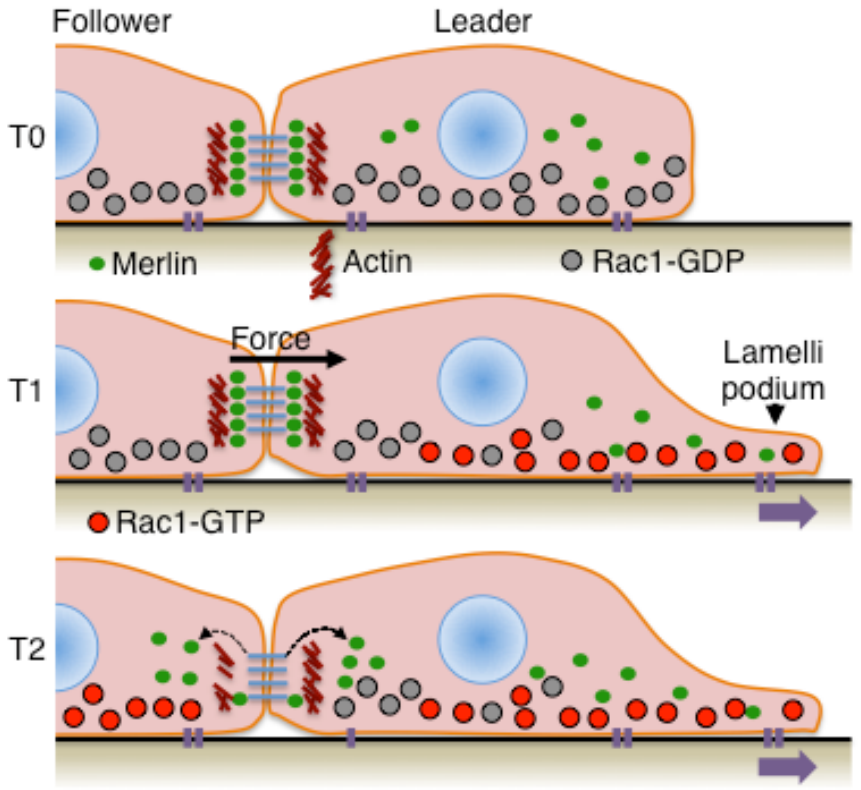
Stress-Rac1 activation (ψ)



Das *et al.* (2015) *Nature Cell Biology*, 17, 276–287

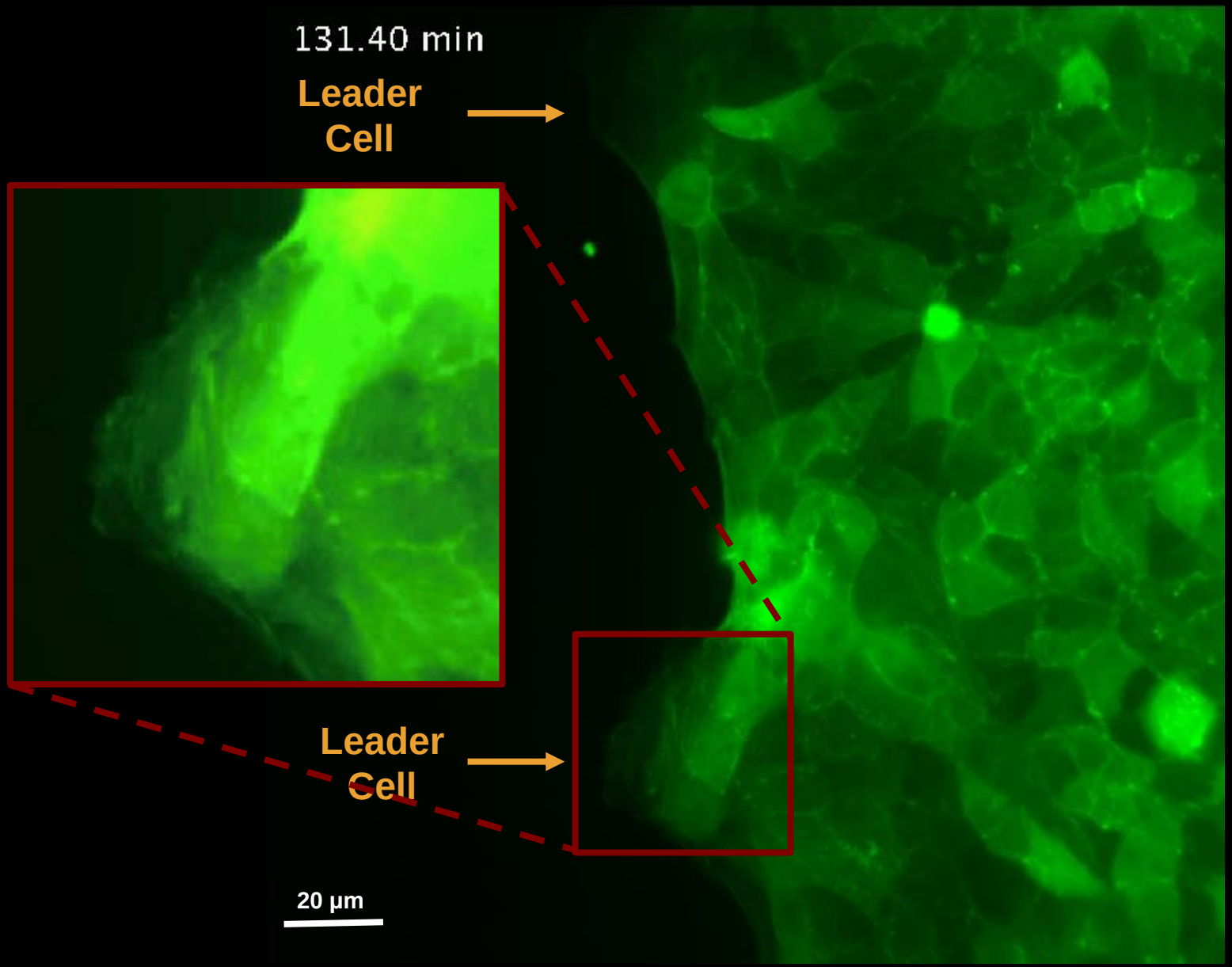
Molecular Model





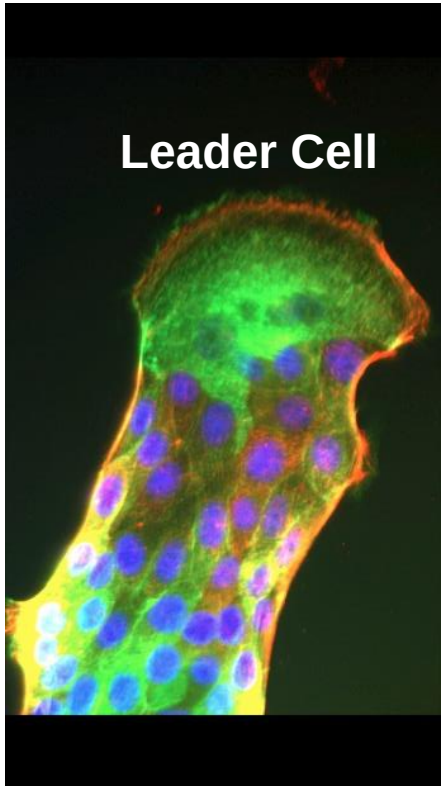
Problem of length-scale: Some of the molecular events do not make sense if you don't have the physical view of the phenomenon.

Leader Cells



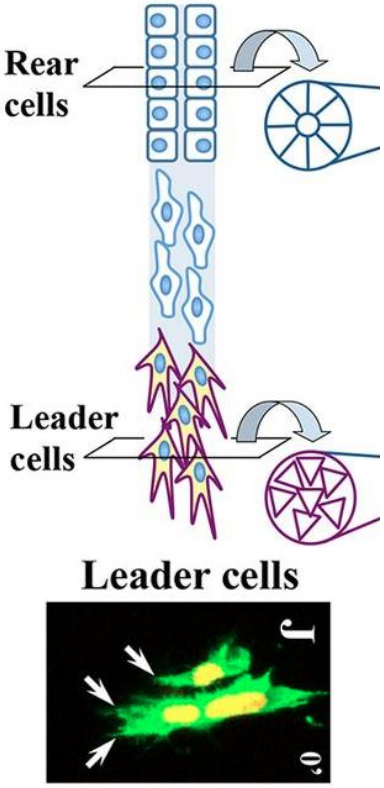
Importance of Leader Cells

Wound healing



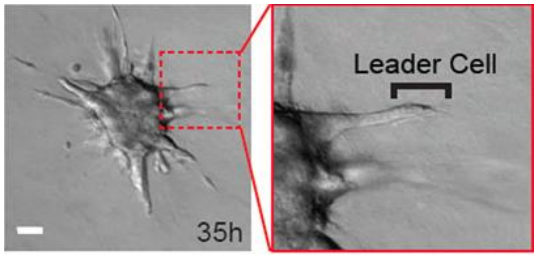
Reffay *et al.* (2014) *Nature Cell Biology*, 16, 217

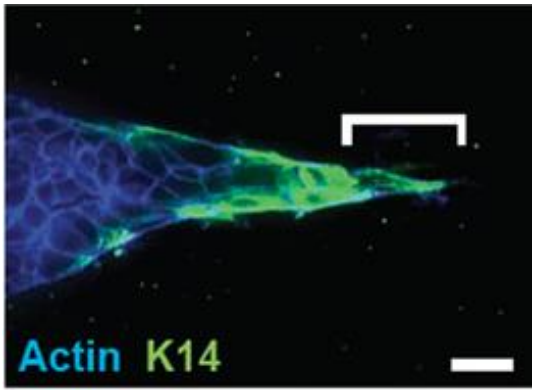
Branching morphogenesis



Atsuta *et al.* (2015) *Development*, 142, 2329

Metastatic invasion

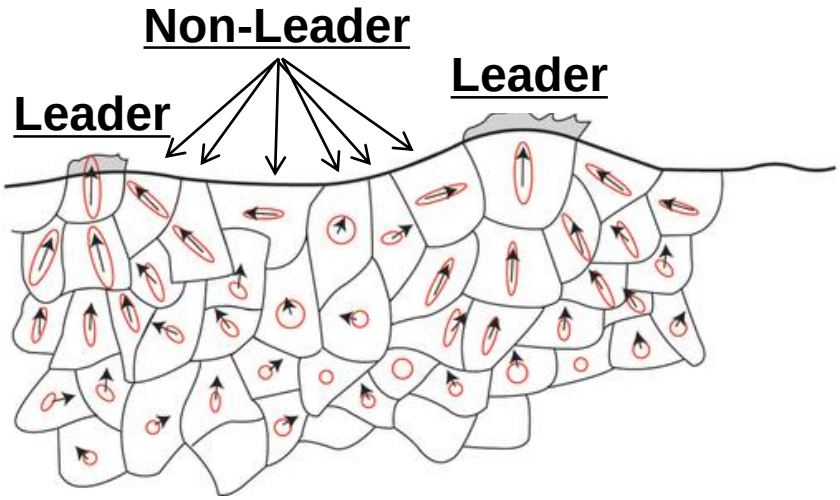




Cheung *et al.* (2013) *Cell*, 155, 1639

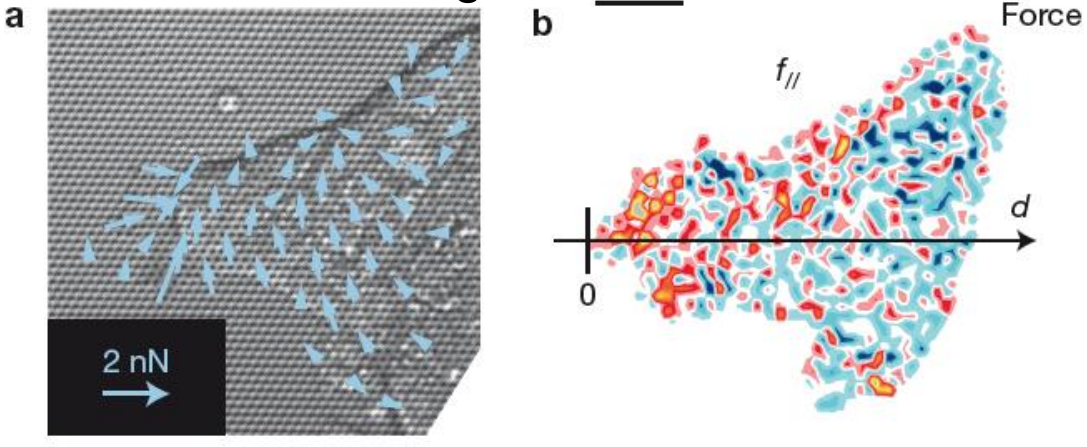
Leader Cell Biology

Why do only some cells become leaders?

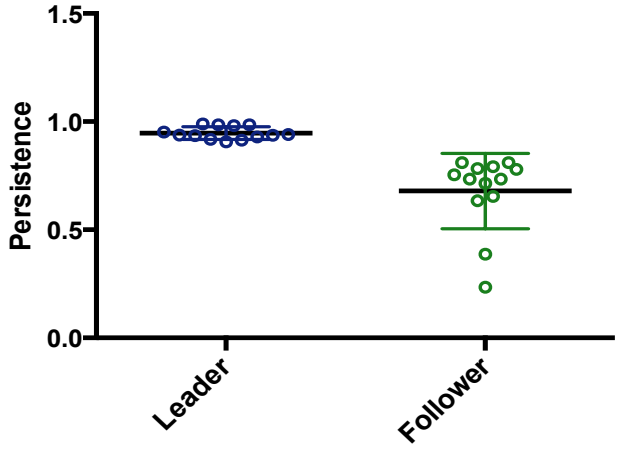


Medhavi

High traction

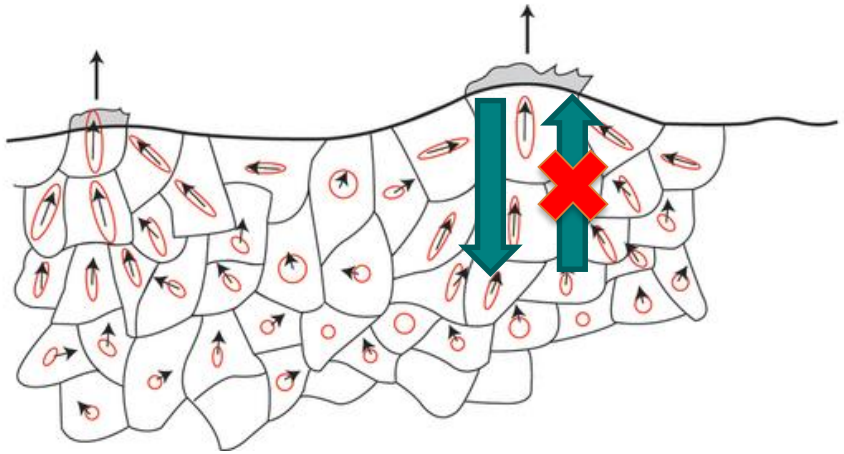


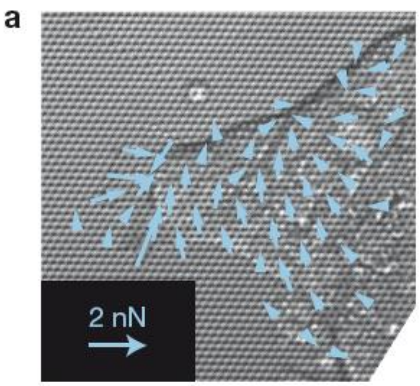
High persistence

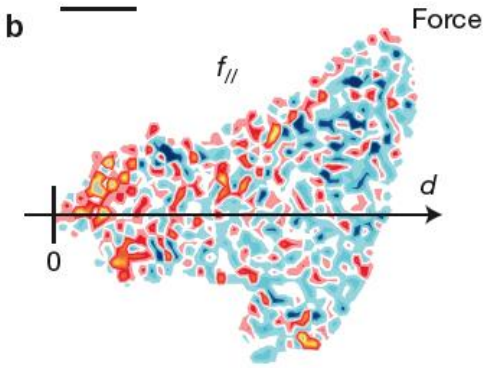


Reffay *et al.* (2014) *Nature Cell Biology*, 16, 217

Prevailing Concepts







Reffay *et al.* (2014) *Nature Cell Biology*, 16, 217

Review CellPress

Collective cell migration: guidance principles and hierarchies

Haeger *et al.* (2015) *Trends in Cell Biology*, 25, 556

Concepts:

1. Leader-Follower Hierarchy

2. Cell Autonomous

We asked:

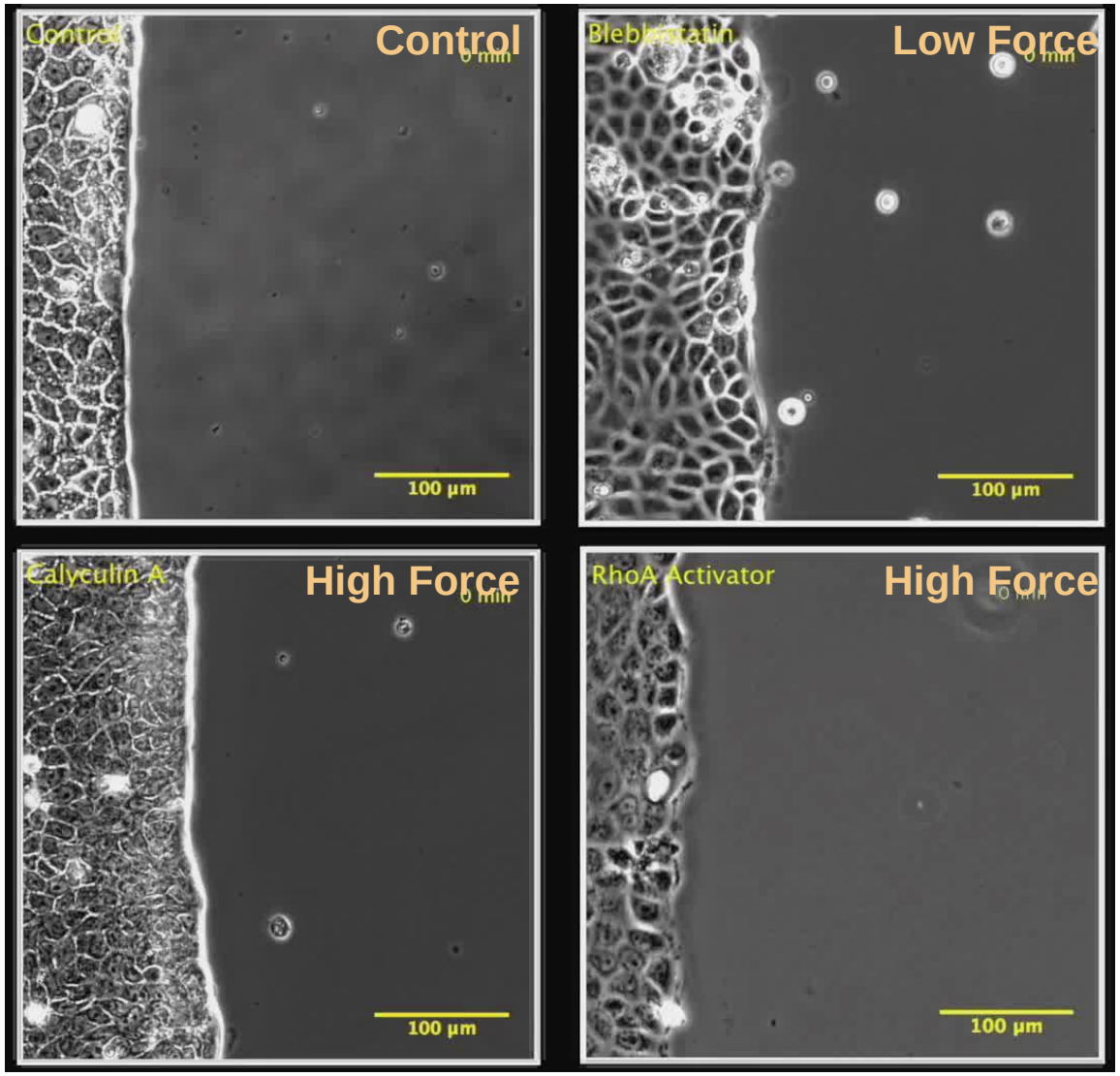
Correct?

Non-Cell Autonomous?

Nobody has followed them from the origin!!

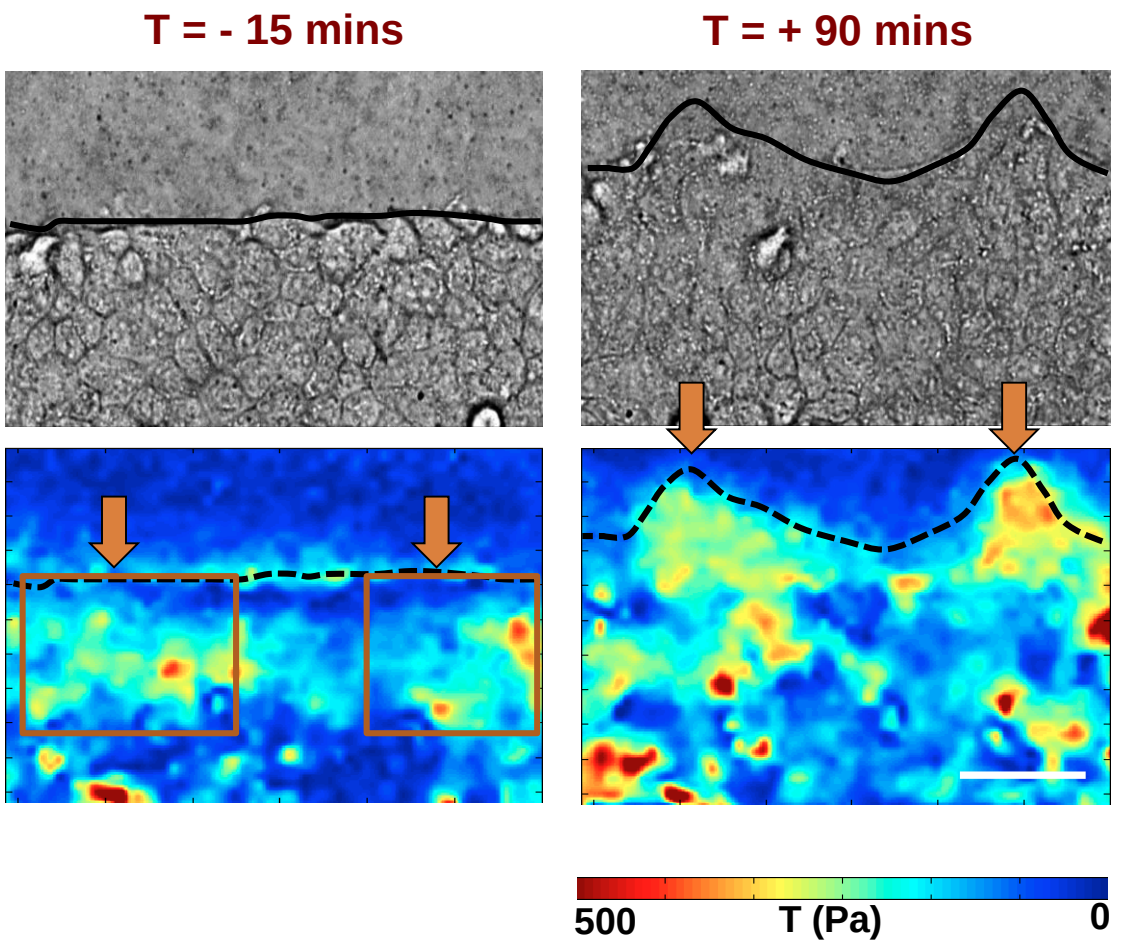
Forces Influence Leader Cell Formation

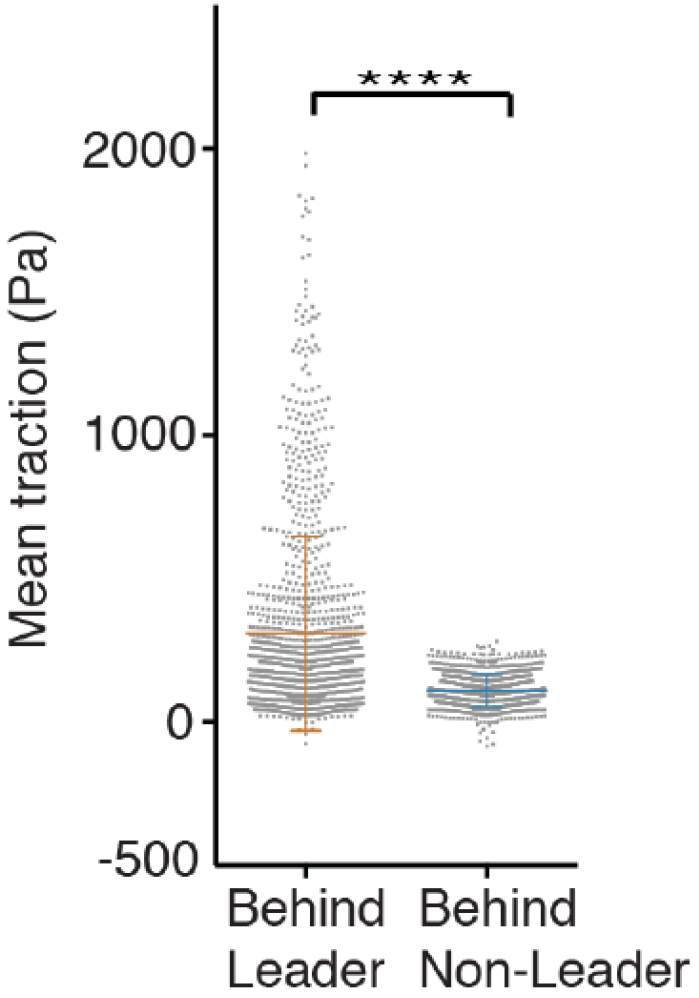
- Introduction
- Mechanobiology
- **Leader Cell**



Capturing Preparatory Rearrangement

Traction Force Landscape





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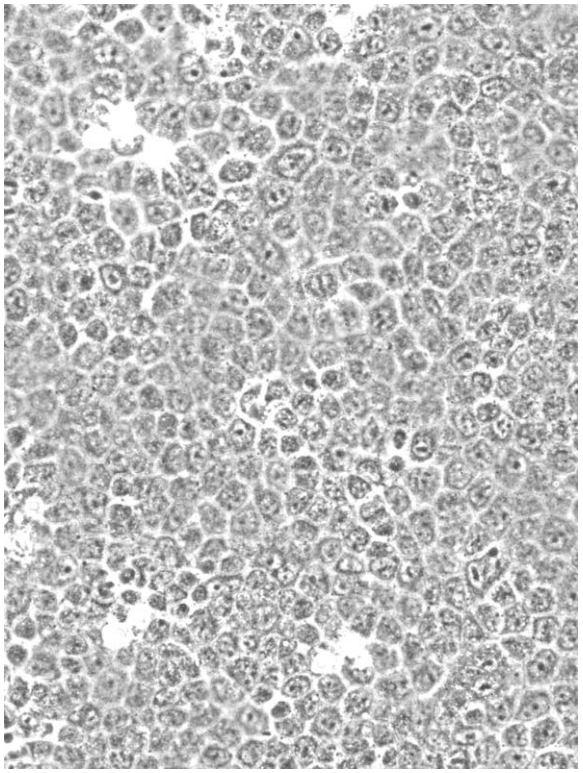
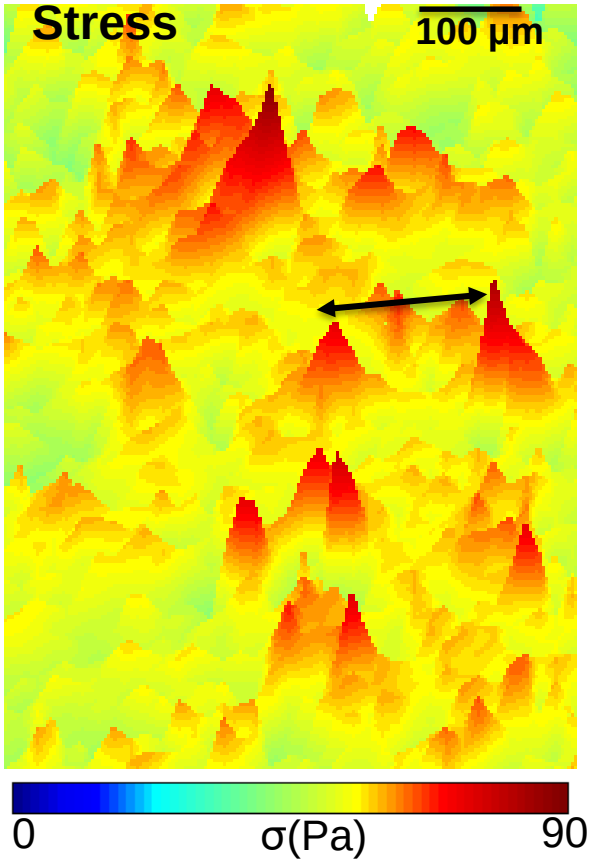
Scale bars, 50 μm

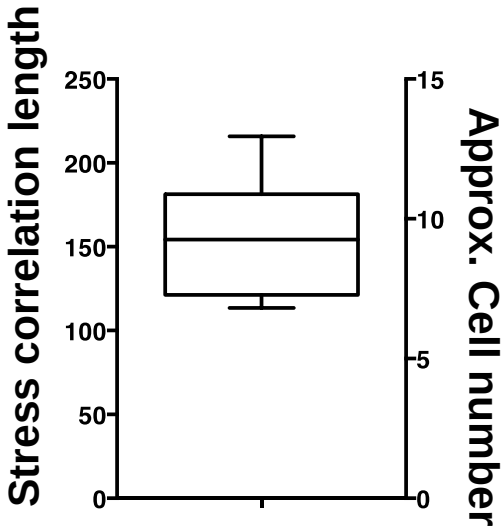
Dynamic Heterogeneity

Phase contrast

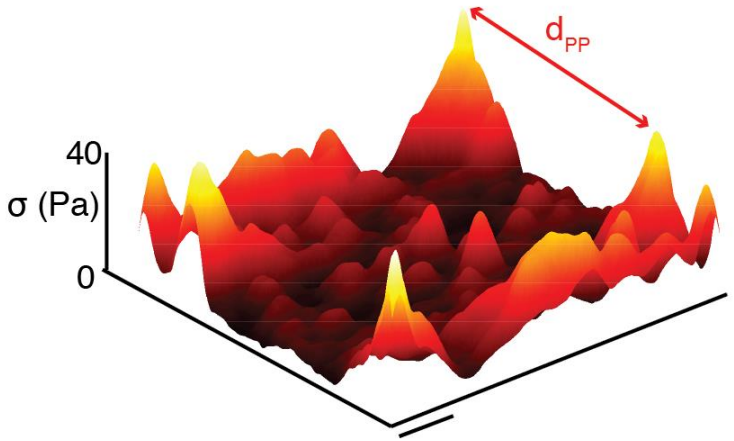


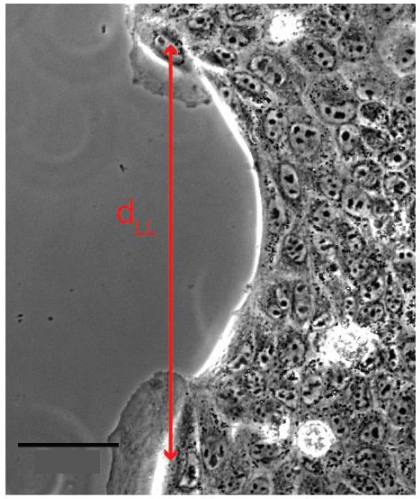
Average Normal Stress

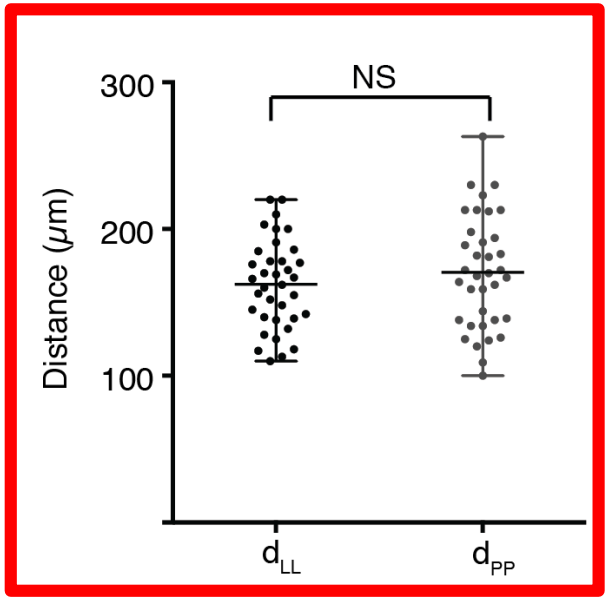




Length of Dynamic Fluctuations







d_{LL}: Leader-to-leader distance
d_{PP}: Peak-to-peak distance

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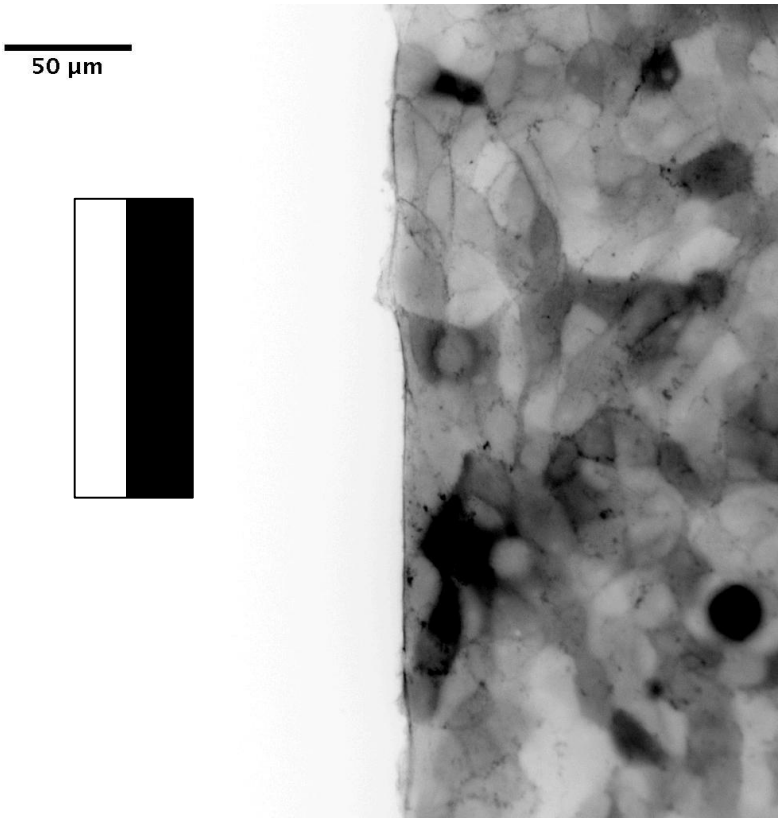
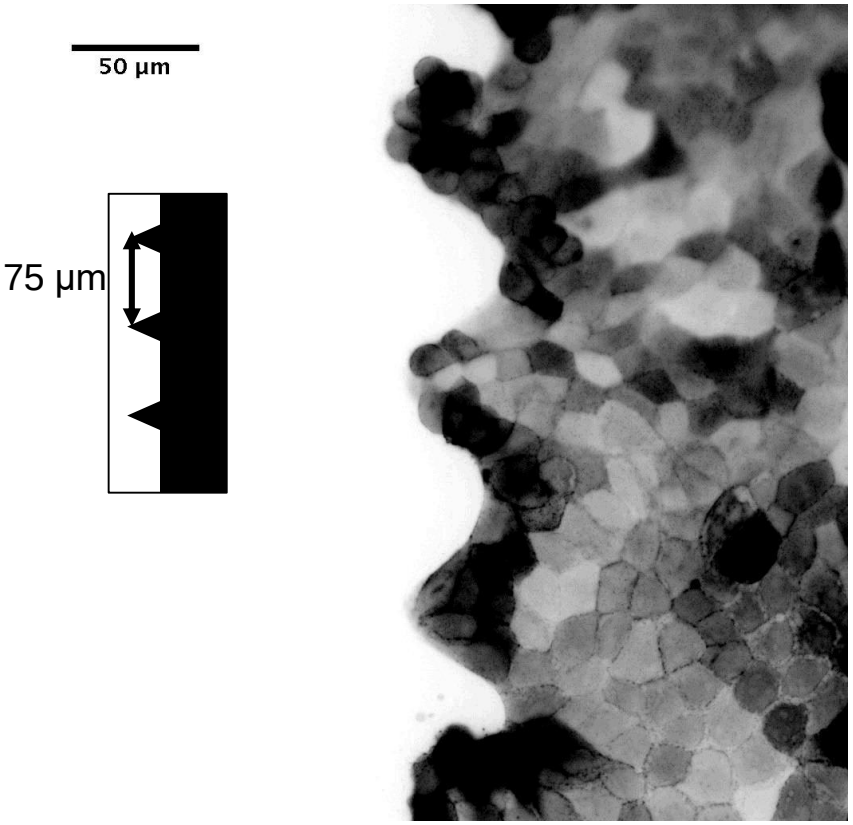
Interface versus System





***LifeAct* MDCK cells**

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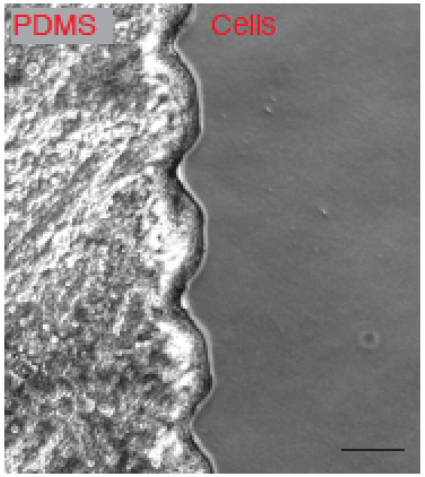
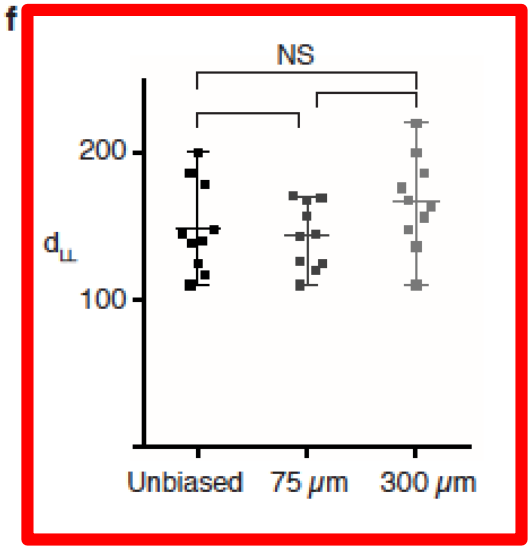
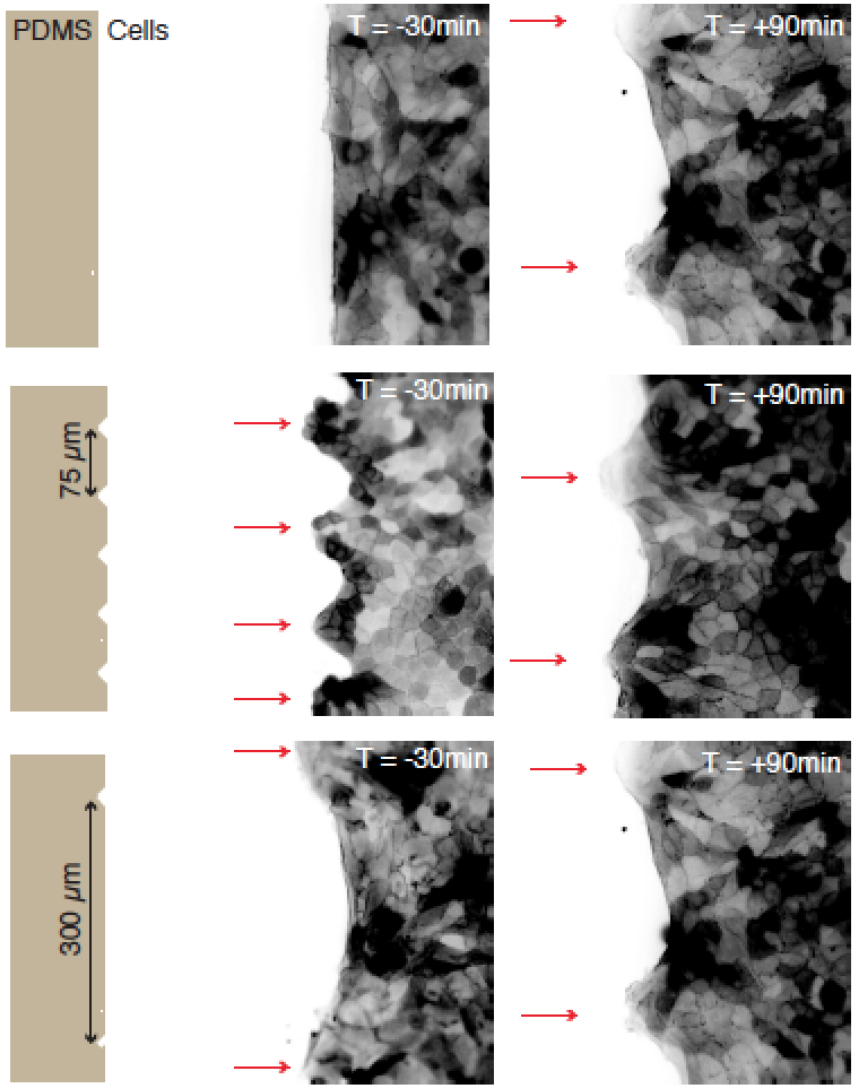
Interface versus System







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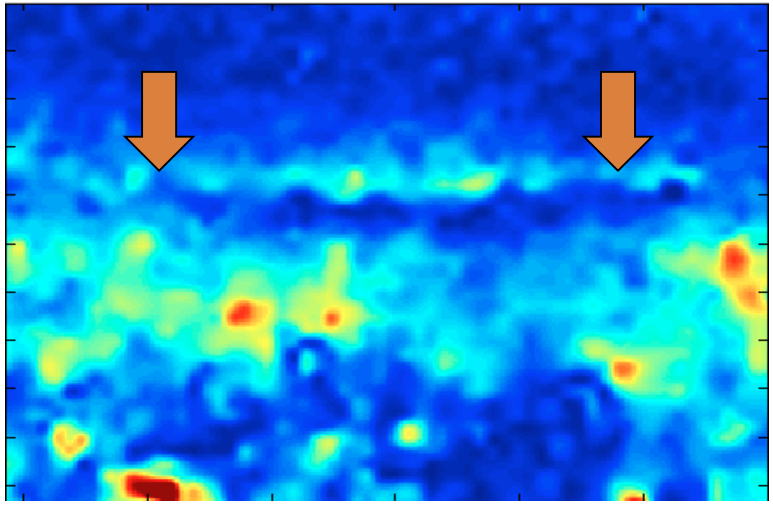
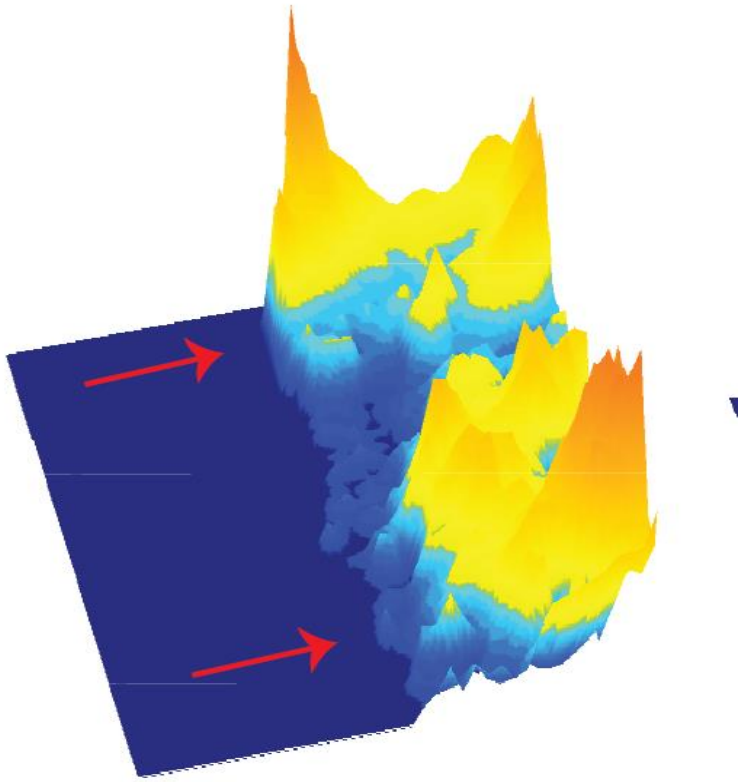
What does the stress build-up mean?





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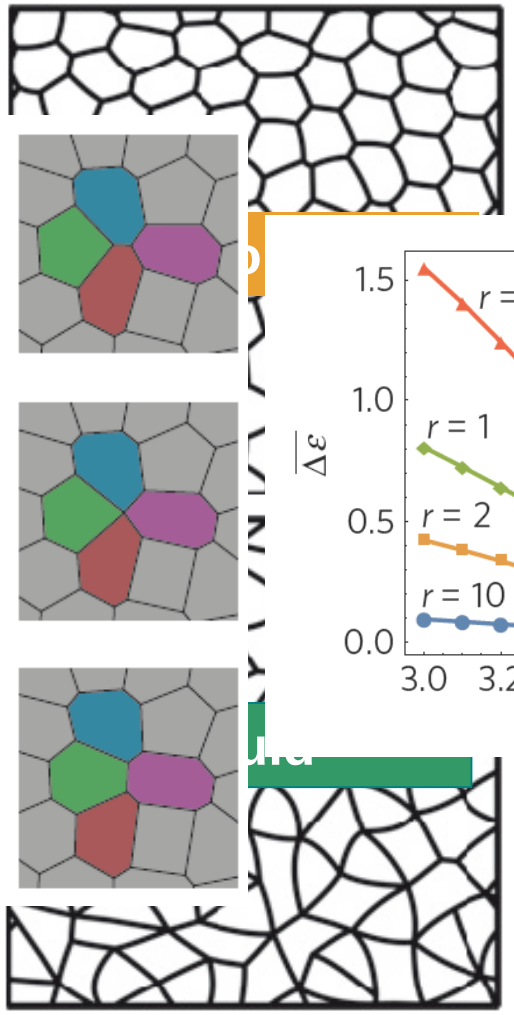
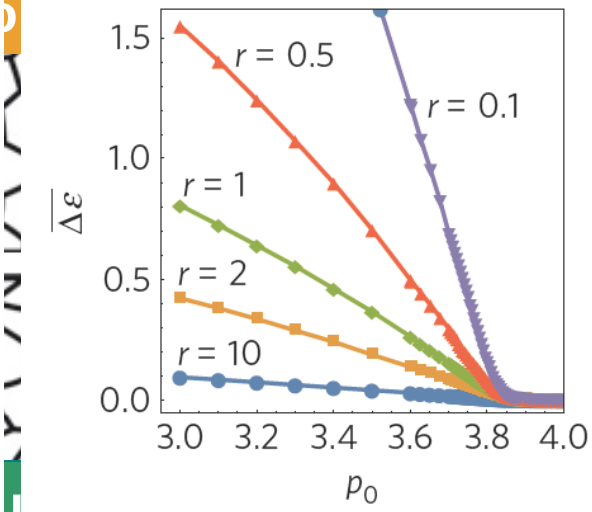
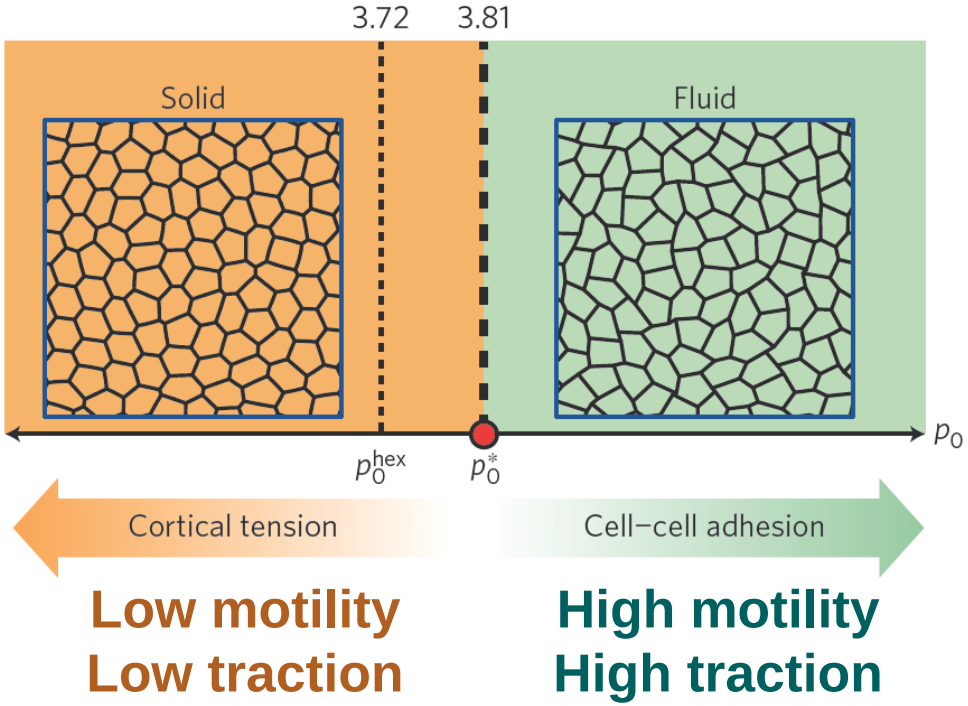
Jamming in Monolayer





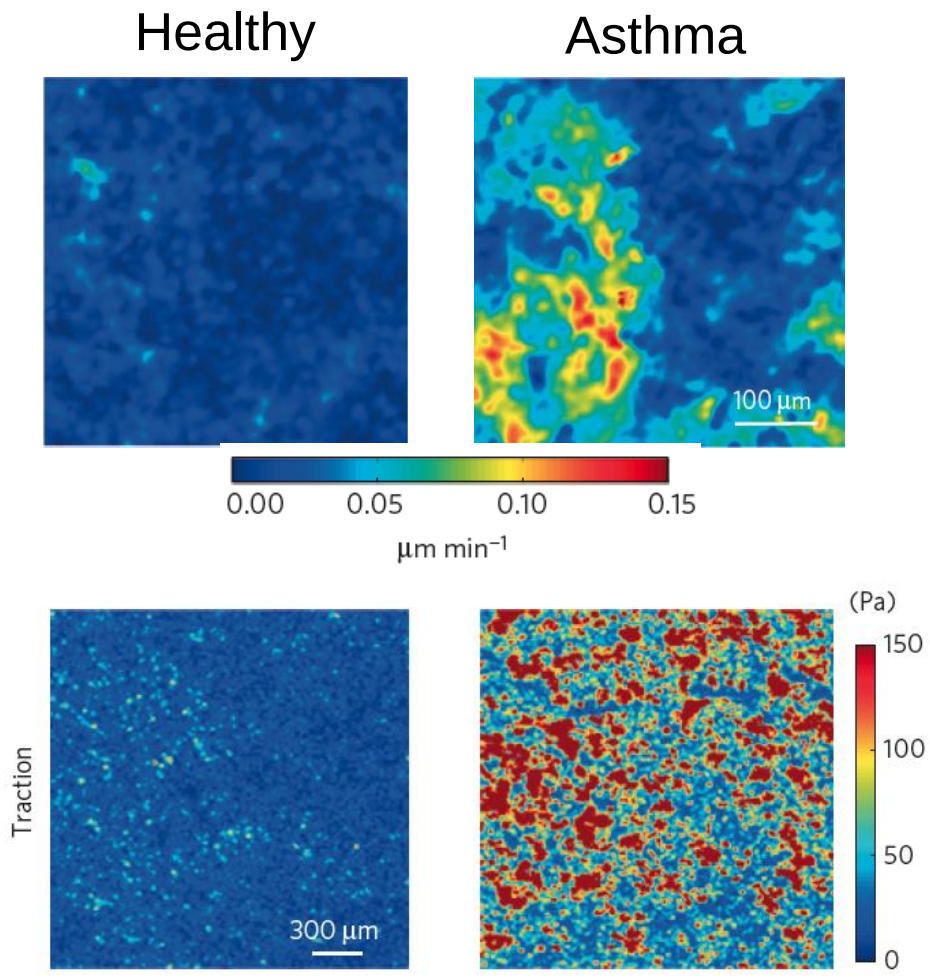
$$p_0 = P_0 / \sqrt{A_0}$$



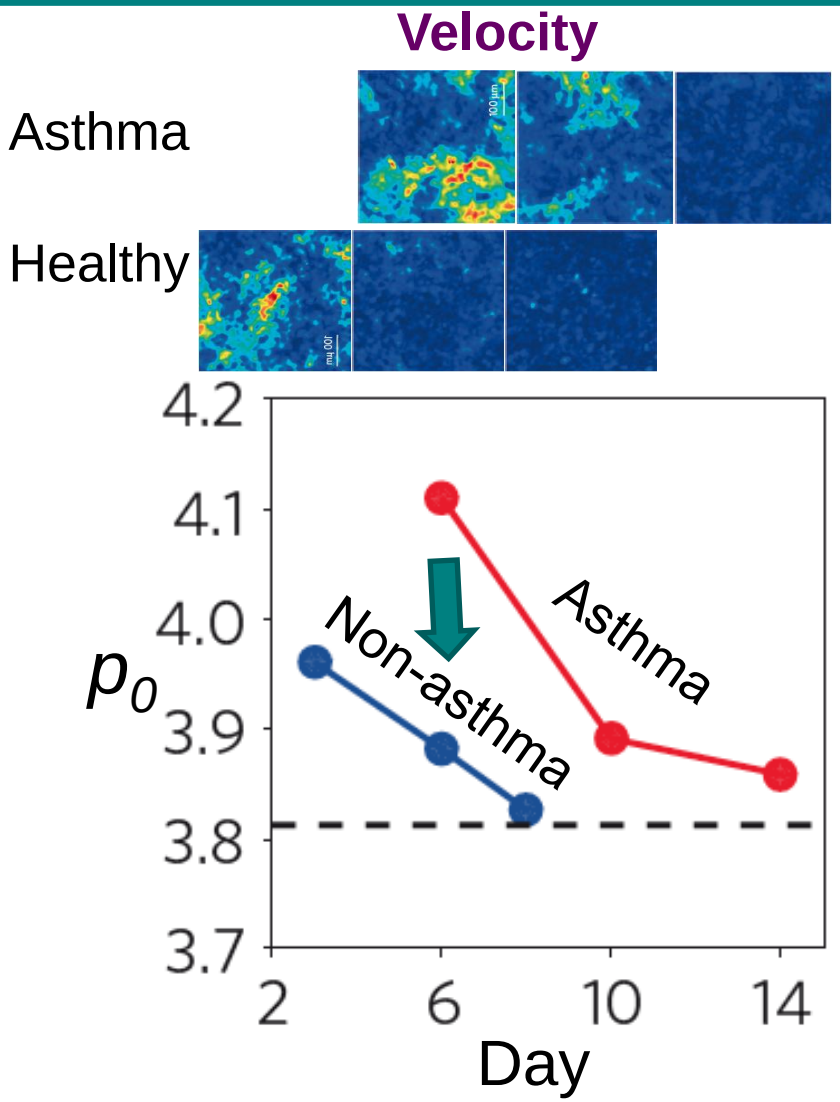
Bi *et al.* (2015) *Nature Physics*, 11, 1074

Cell Shape in Motility Transition

Bronchial epithelium

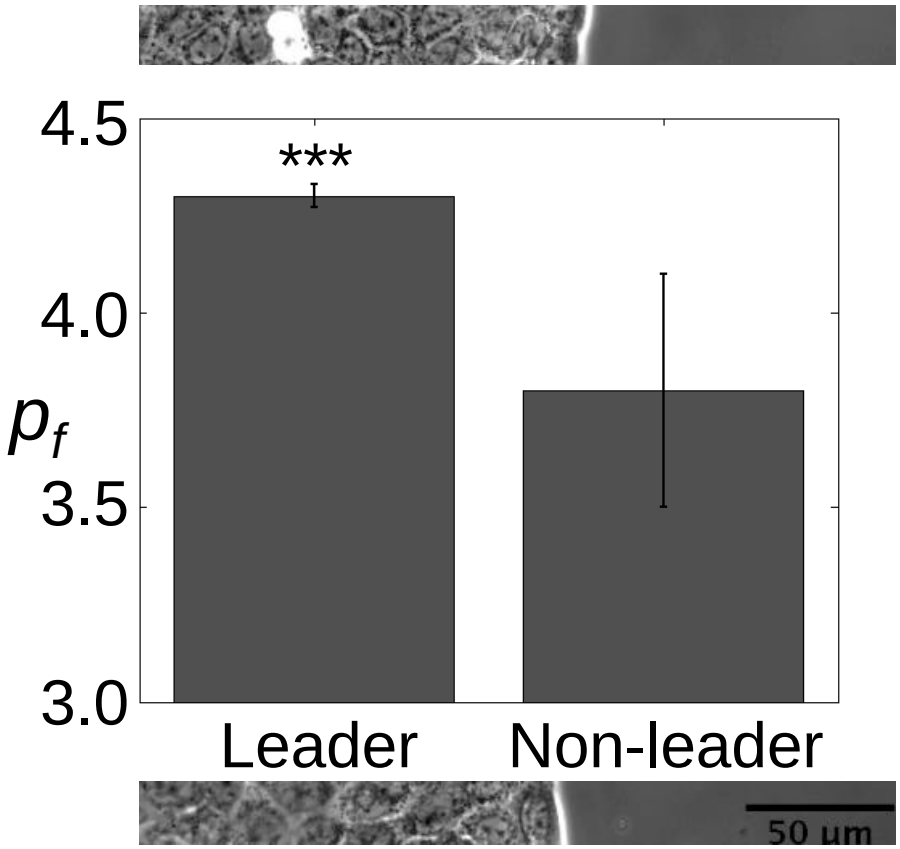


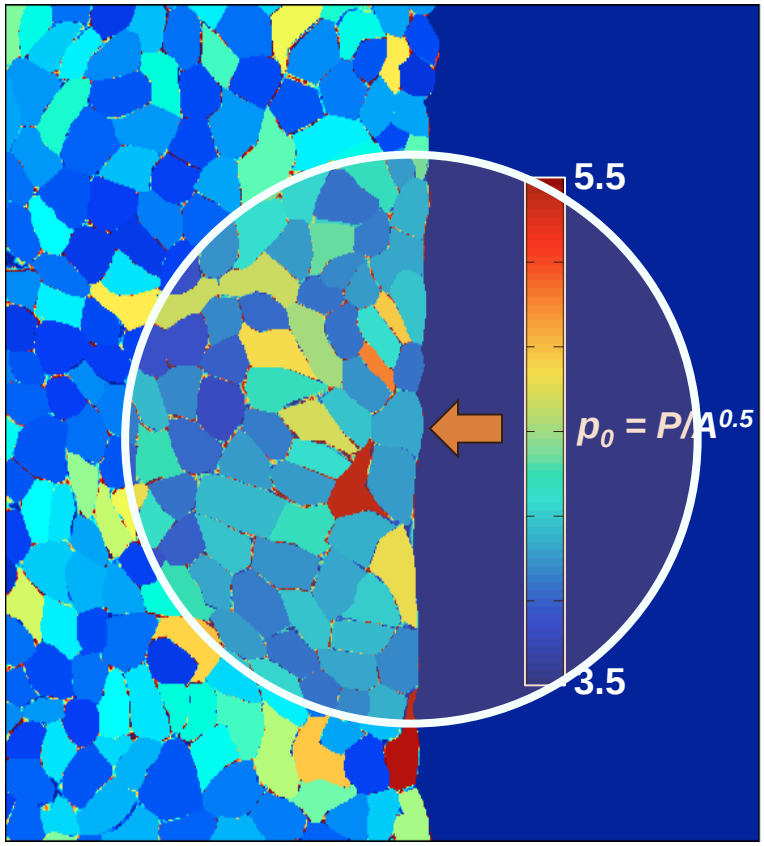
Day 6



Park *et al.* (2015) *Nature Materials*, 14, 1040

Geometry of the Follower





p_f = Mean shape-index (distance corrected) of followers

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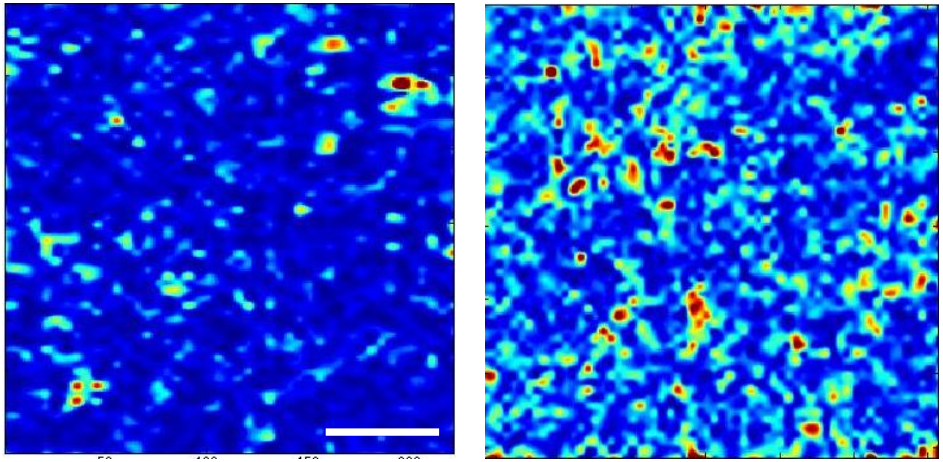
Does Introducing Fluid Followers Help?

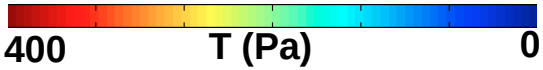
Control | Merlin-depleted



Scale bar, 100 μm

Low motility
Low traction
Low p_0

High motility
High traction
High p_0



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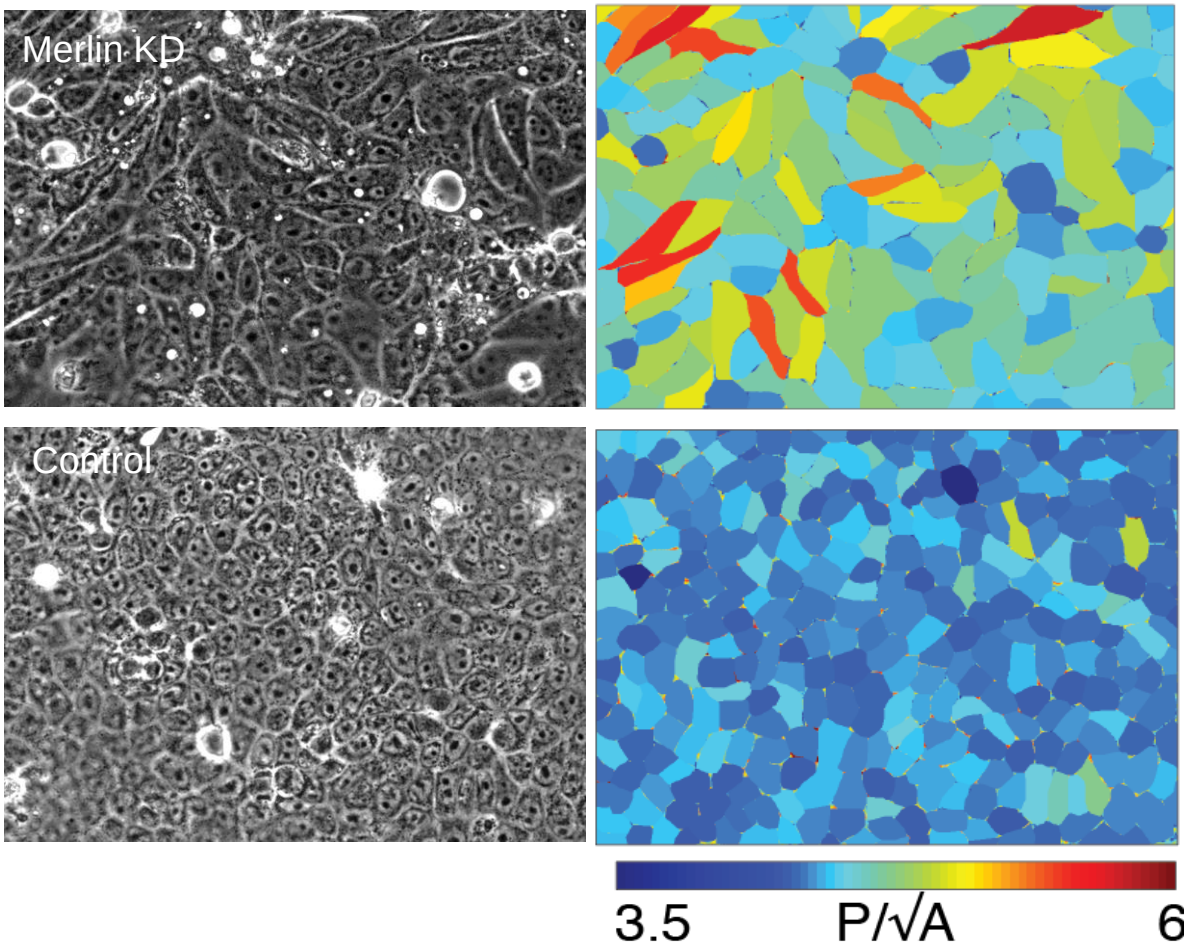
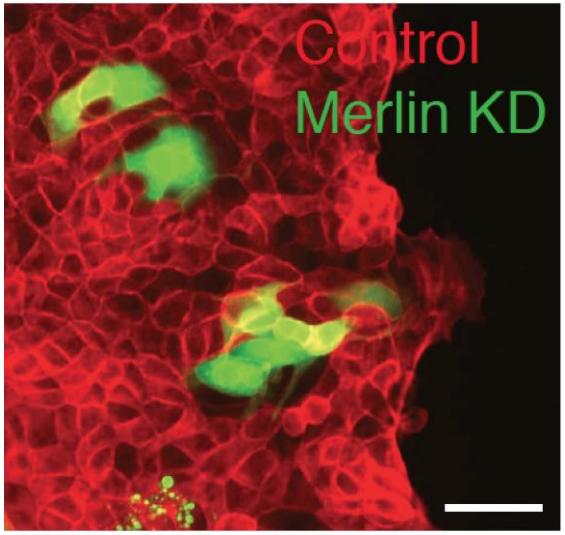
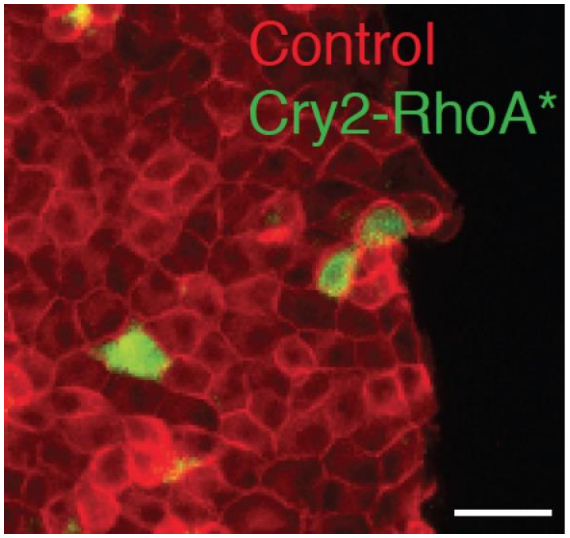
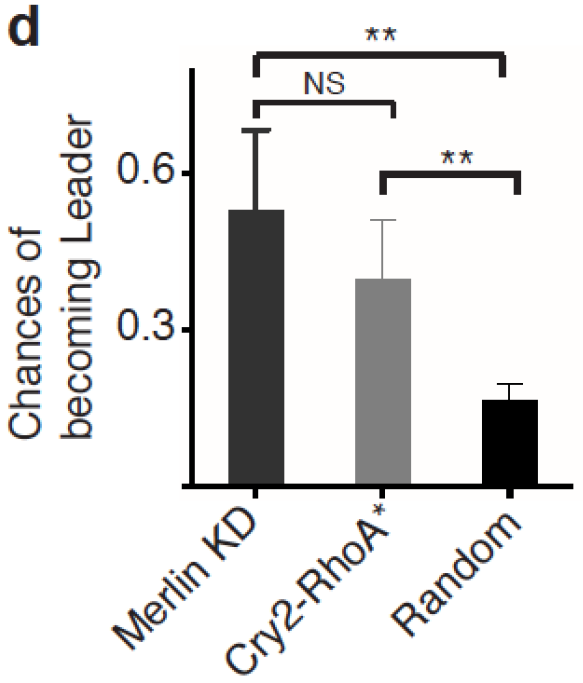
Perpetually Unjammed Monolayer



Introducing Fluid Followers Helps







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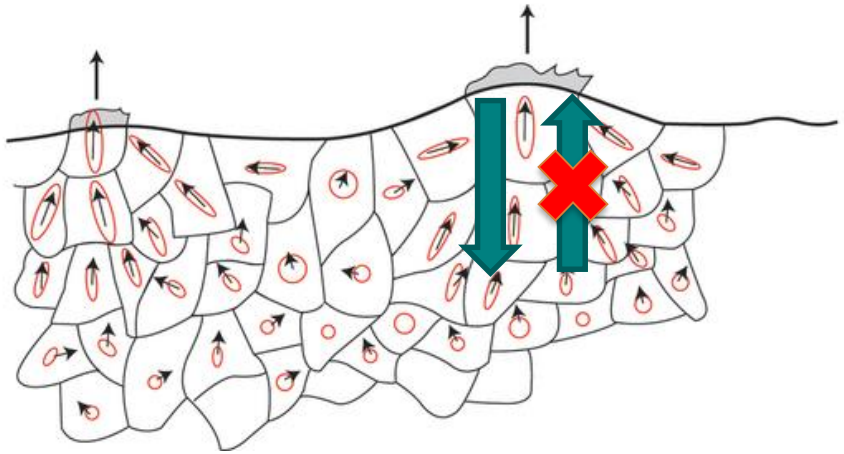
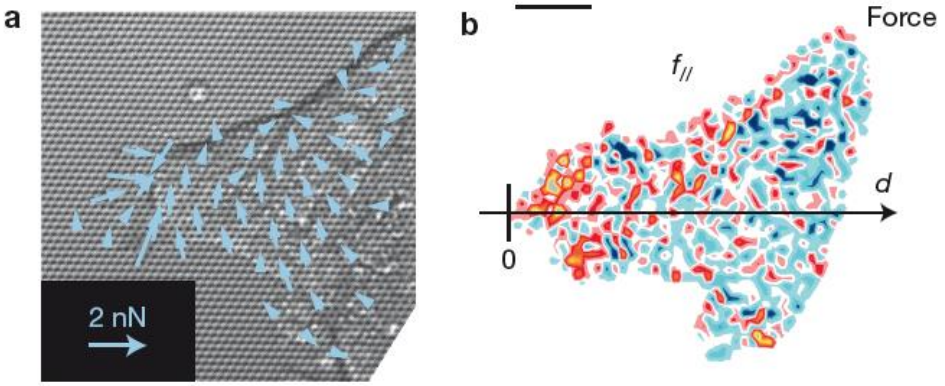
Prevailing Concepts





Reffay *et al.* (2014) *Nature Cell Biology*, 16, 217

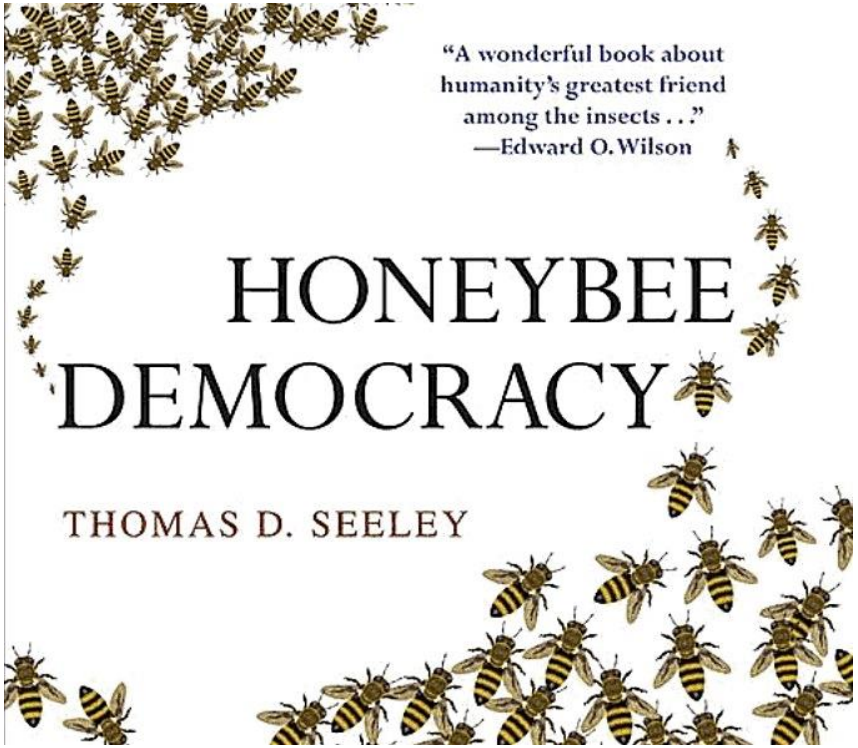
Concepts:

1. Leader-Follower Hierarchy → **Correct? Not Really**

2. Cell Autonomous → **Non-Cell Autonomous? Yes**

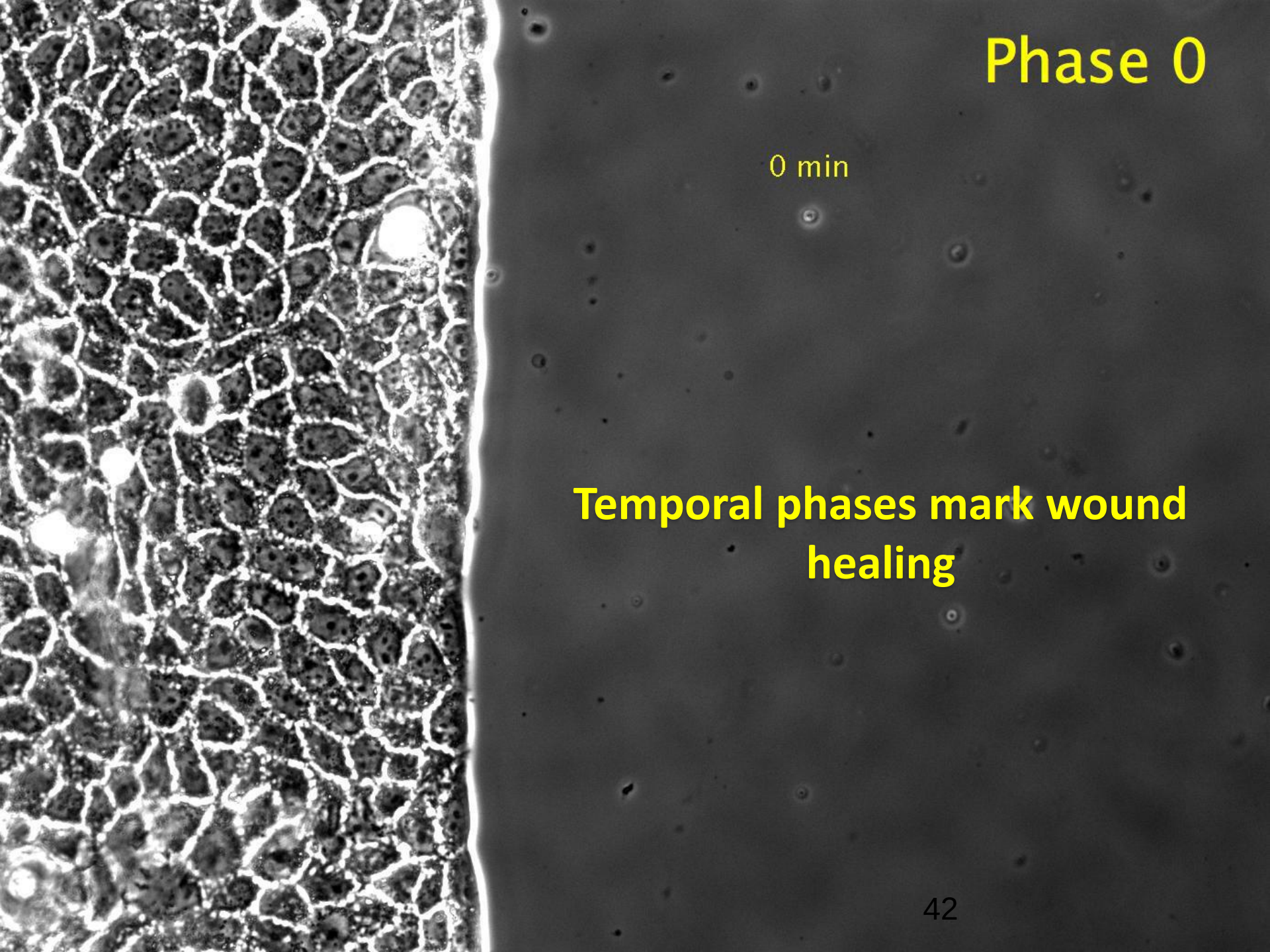
‘Democratic’ or System-driven process, which calls for novel ways of treating leader cells in pathological situations!

Dynamic Democracy Prevails in Nature



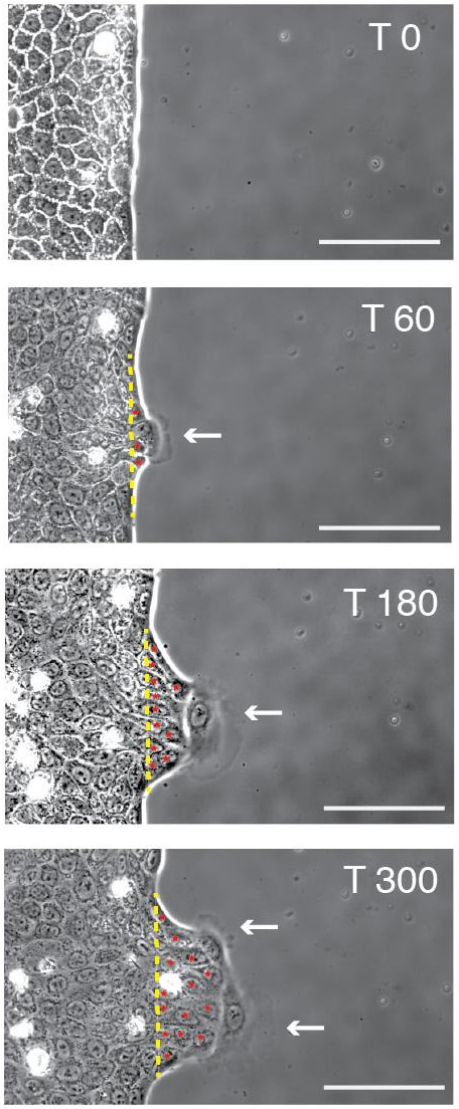
"Shared decision-making drives collective movement in wild baboons"

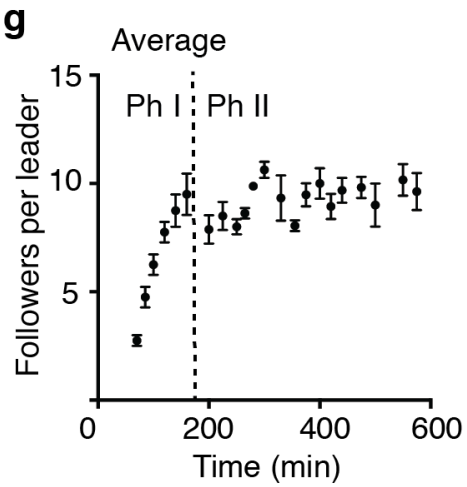
Strandburg-Peshkin *et al.* (2015) *Science*, 348, 1358

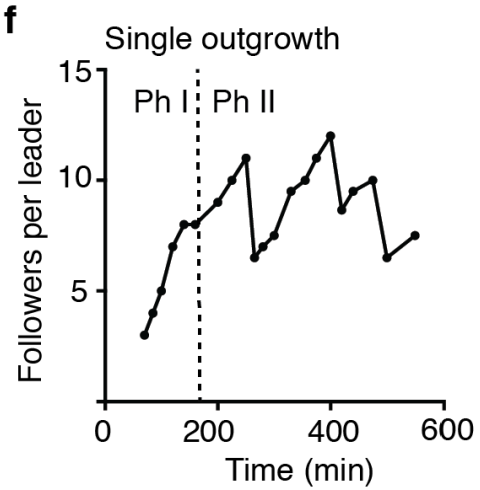


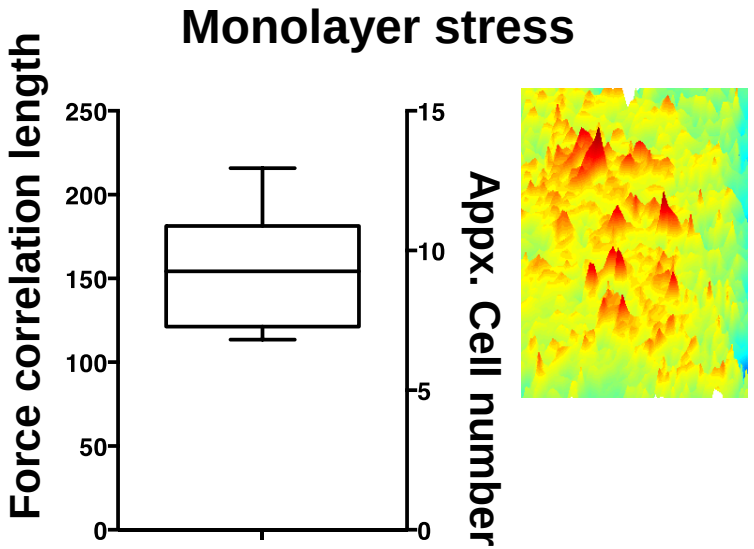
Temporal phases mark wound healing

Multicellular Mechanical Entity









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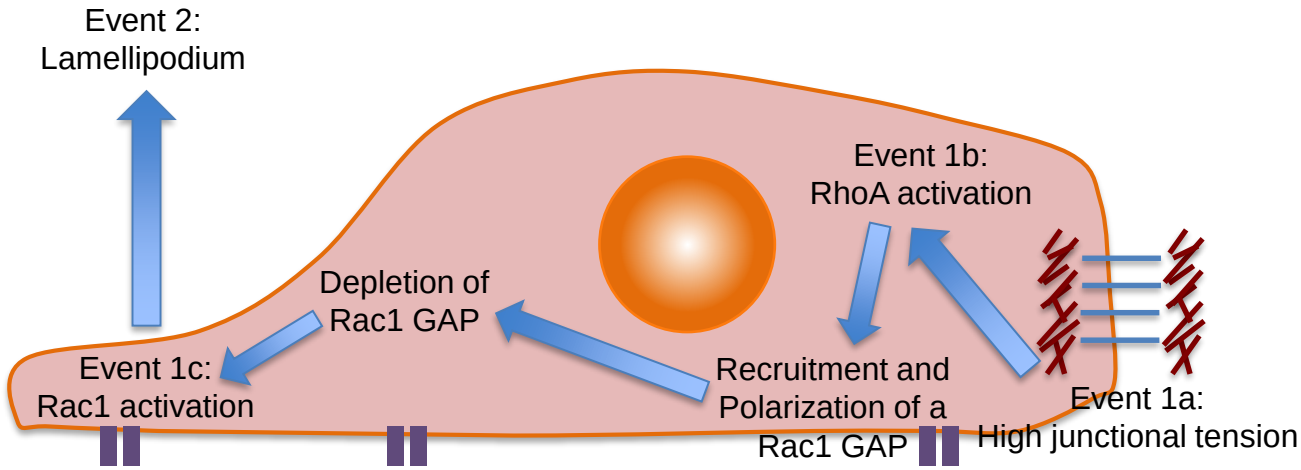
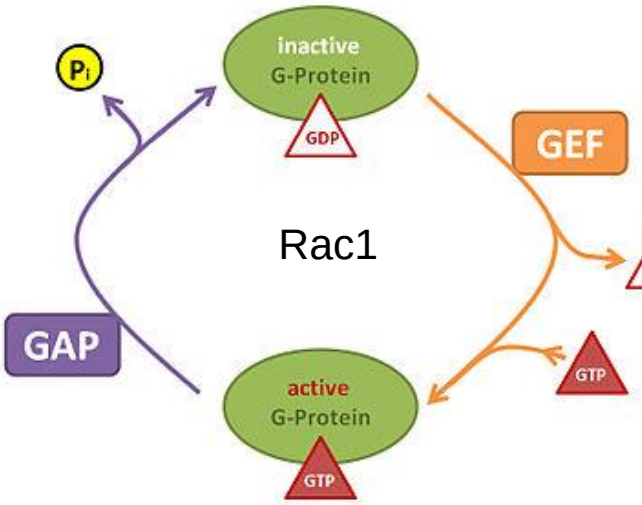
Exploring Molecular Mechanism

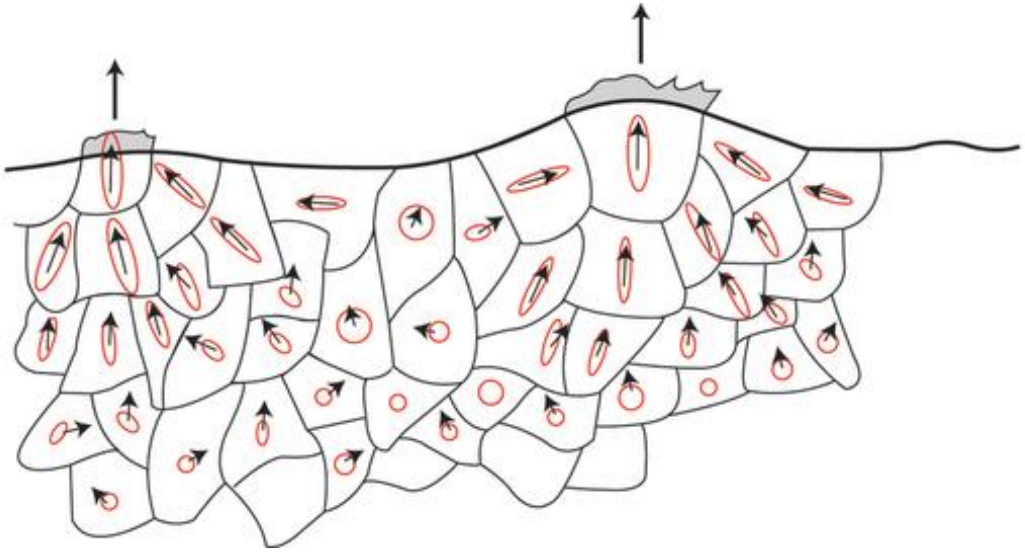


Rac1 GAPs:
Arhgap24 (FilGAP)
Arhgap22
Arhgap17 (Nadrin)



Rac1 GEFs:
FGD5
Tuba
Arhgef15
Arhgef7
Vav2
Tiam1

Perspective



It's important to look at biological problems from a physicist's point of view to make sense of 'noisy' molecular data!!!


Thank
You!