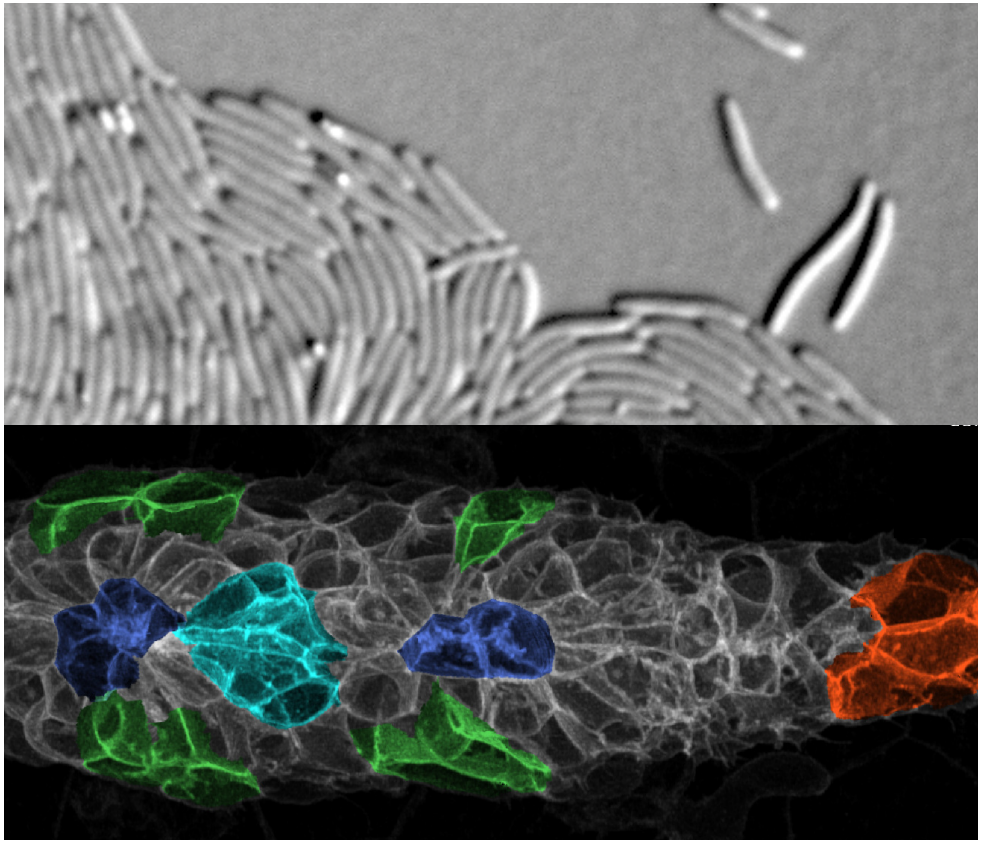
Collective Cellular Motility



Course 2: Mechanical guidance

Thomas Lecuit

chaire: Dynamiques du vivant

COLLÈGE DE FRANCE 1530

Single cell Motility: 3 general problems

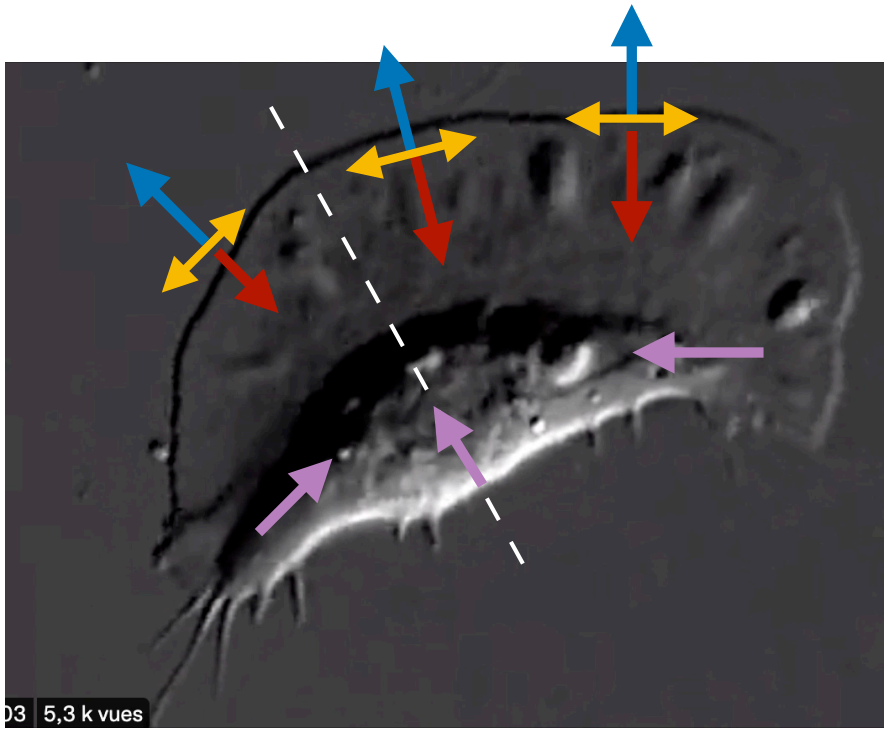
Mechanical Sensing and Guidance

1. Decoding the environment: What is the nature of cues?
   - Cells don't move randomly but sense an external cue
   - What is the nature of external cues? Diversity of cues (chemical, mechanical, electric, light)
   - Temporal vs spatial decoding

2. Processing the cue: Cell polarisation
   - Symmetry breaking: converting external gradient into vectorial cell organisation
   - Deterministic vs Stochastic processing
   - Polarisation of a cell or a trajectory

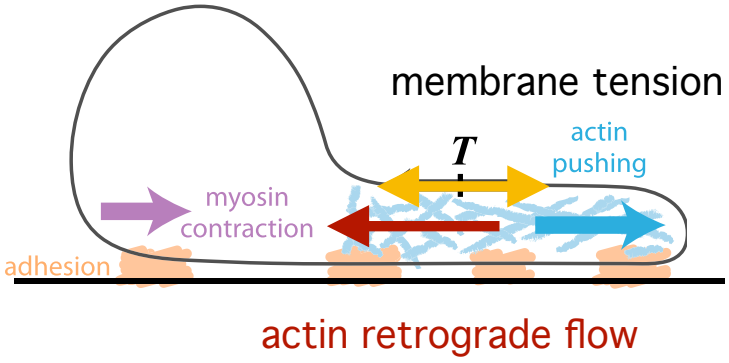
3. Mechanical response: Principles of movement
   - Depends on environment
   - **Force generation:** Active processes: actin pushing forces, actin flow, actomyosin contractility
   - **Force transmission:** Passive resistance: friction and adhesion

Crawling on a substrate (2D)



Dylan Burnette @MAG2ART

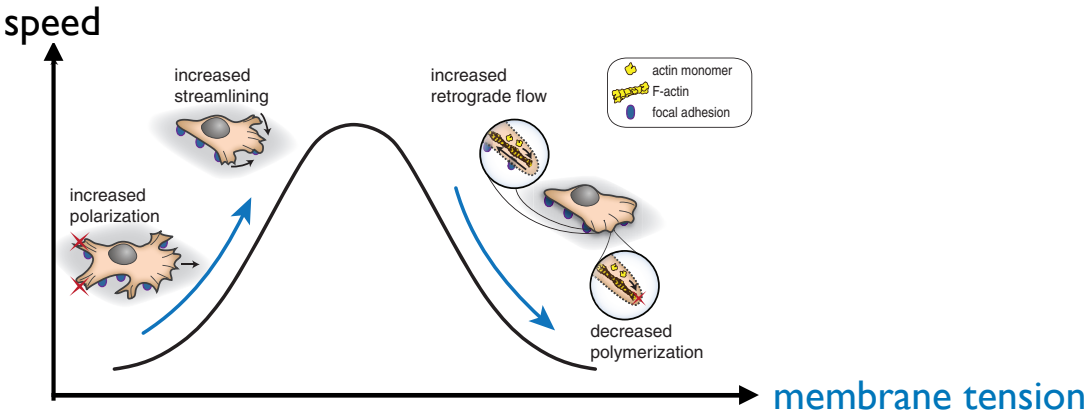
- **Force production:** actin polymerization
  — Brownian ratchet model
- **Force transmission:** actin retrograde flow and substrate adhesion
  — Clutch model (force dependent reinforcement)
- Membrane tension:
  — limits force production at front
  — couples front and back of cell
  — can be tuned



Crawling on a substrate (2D)

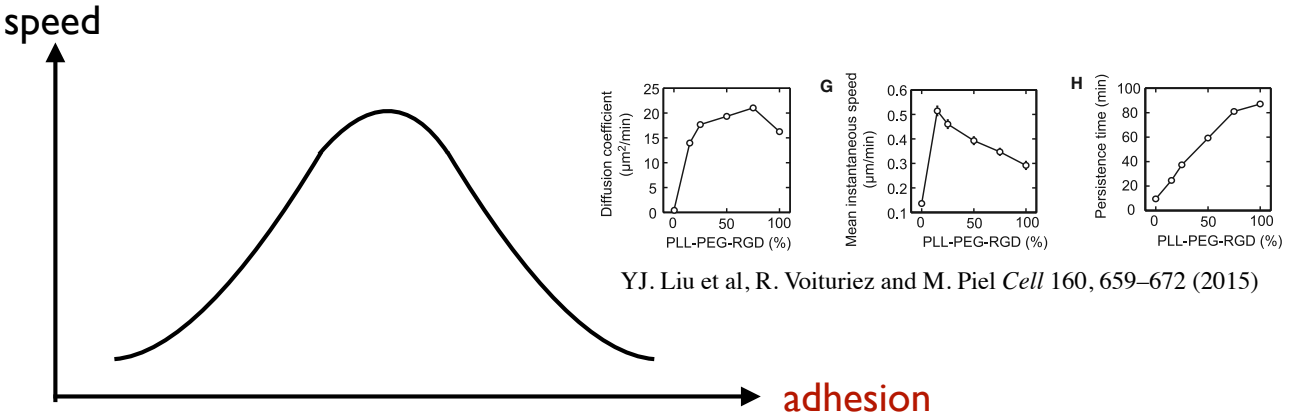
- Feedback regulation:
- Excess membrane tension and adhesion inhibit motility (negative feedback)
- Mechanical adaptation via feedbacks - impact on environment sensing

Membrane tension



P. Sens and J. Plastino. *J. Phys.: Condens. Matter* 27 (2015) 273103

Adhesion

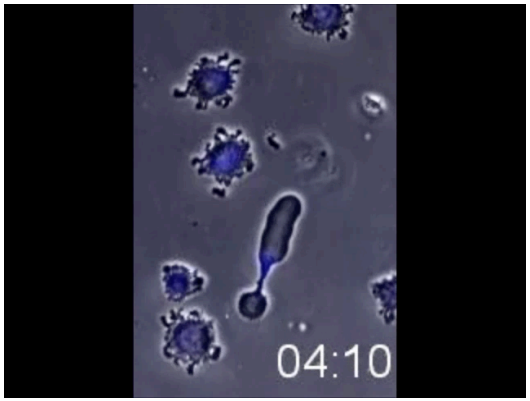


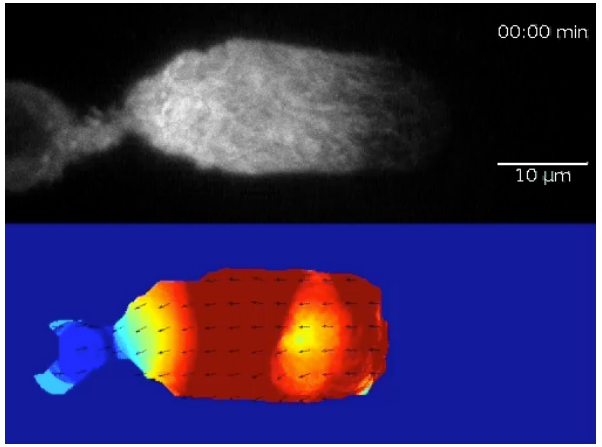
YJ. Liu et al, R. Voituriez and M. Piel *Cell* 160, 659–672 (2015)

P. DiMilla et al. and D. Lauffenburger *JCB* 122: 729-737 (1993)

Motility in confinement (3D)

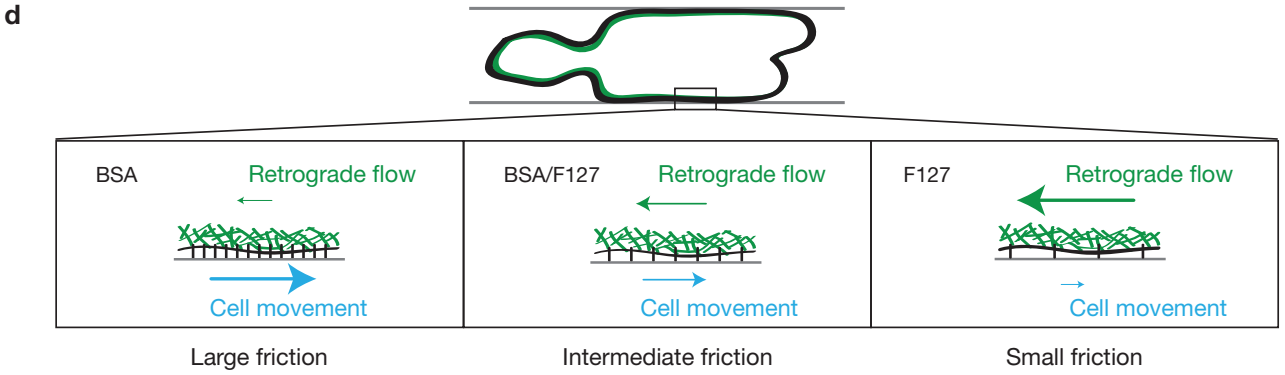
- Actin retrograde flow
- Gradient of cell contractility
- Feedback mechanism amplifies polarity and sustains motility
- Friction mediates adhesion independent motility





LifeAct-mCh (F-actin)

Retrograde flow



Comparison of adhesion and adhesion-free motility

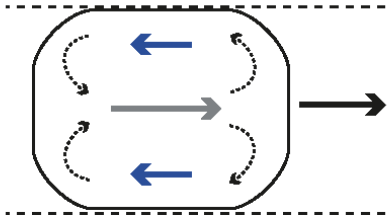
Migration Mode	Adhesive	Non-adhesive
Protrusion type	Usually lamellipodia	Usually blebs
Propelling force generation	Filament extension/actin flow	Cortex flow
Force transmission	Focal adhesion	Friction, protrusion intercalations, etc.
Substrate interaction	Specific	Non-specific
Duration of cell-substrate interactions	Longer than dwell time	Shorter than dwell time
Speed-substrate interaction strength relationship	Bell curve	Plateau
Environment	2D surfaces and 3D environments	3D confinement
Migration speed[a]	~0.1–1 μm/min	~1–10 μm/min
Stresses exerted on substrate[b]	~10^2 – 10^5 Pa	<1Pa
Actin flow profile	Mainly in lamellipodium	At the cortex all along the cell body, max velocity in cell center
Force dipole	Contractile	Expansile

Bodor et al. and E. Paluch. *Developmental Cell*. 52: 550-562 (2020)

- Friction-based migration is only possible in 3D confinement (unlike adhesion based motility)
- For 2D substrate motility, the strength and duration of molecular bonds must be strong enough to counteract Brownian motion (see catch bond and mechanical amplification mechanisms at Integrin foci)
- **In 3D, confinement prolongs the contacts of weak molecular interactions and multiply them over the entire cell surface**
- Cell substrate interactions shorter than cell dwell time in non-adhesive motility, but it is longer than cell dwell time in adhesive motility (thus requiring de-adhesion mechanisms). **In non-adhesive motion, friction does not interfere with cell retraction.**
- Therefore, **increasing friction does not lead to a plateau of migration speed, and no slowing down is expected even at very high friction.**

From cell to cell cluster motility: 3D

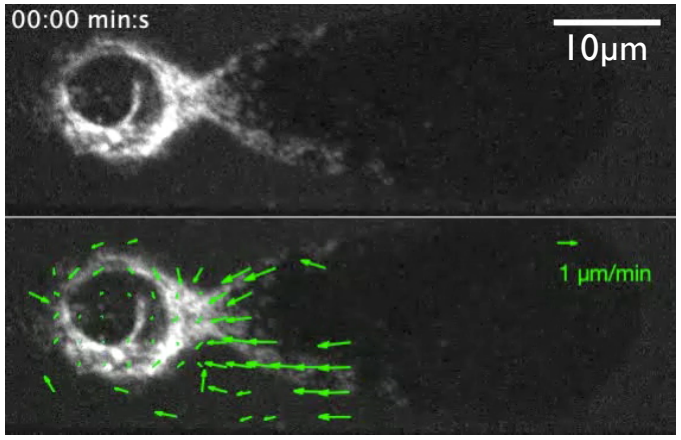
Retrograde flows
(of myosin or cells)



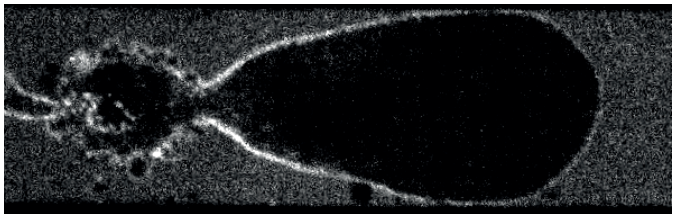
Cell

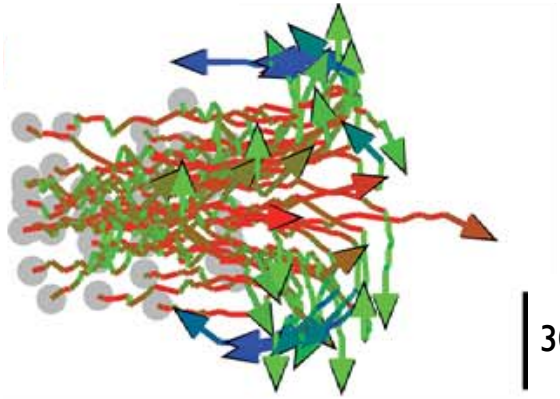
SupraCell

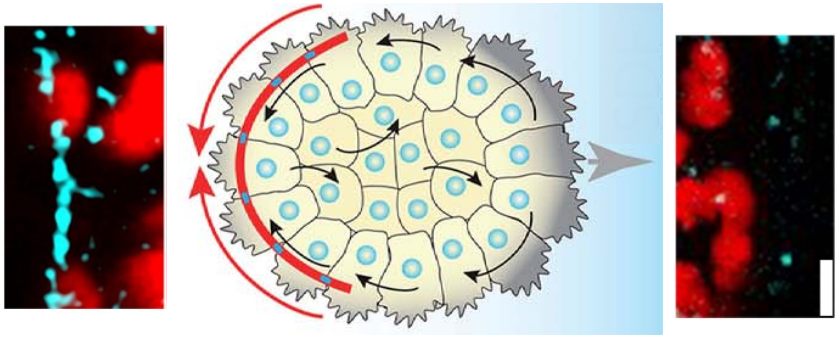
Myosin flow



Myosin polarity







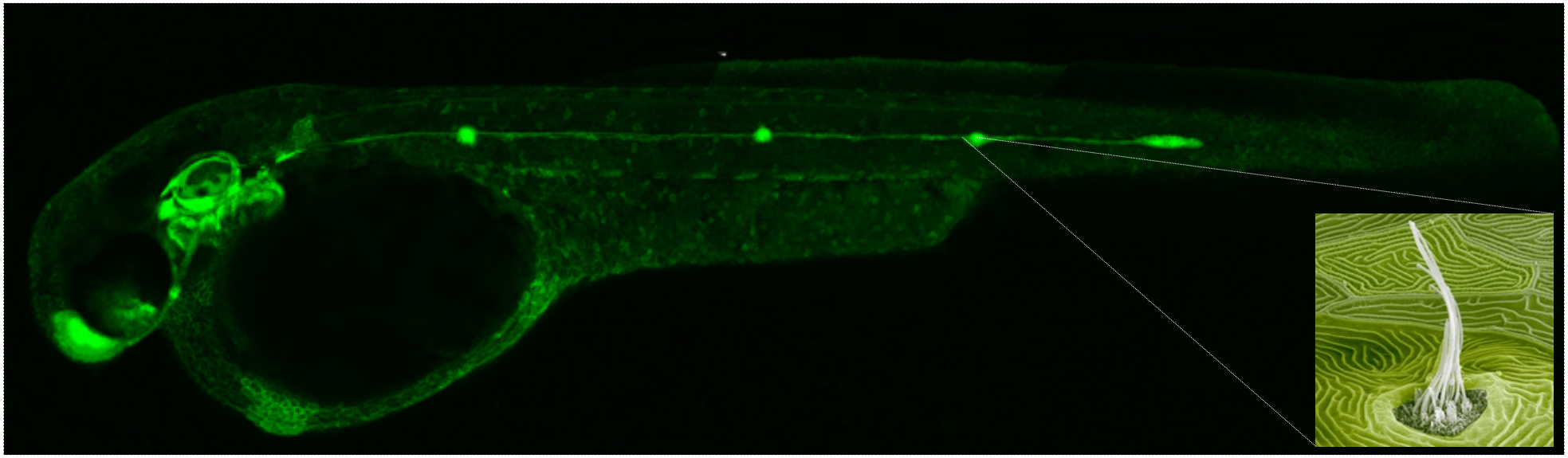
1 cell — L=30µm, U= 0.7µm.s^{-1}

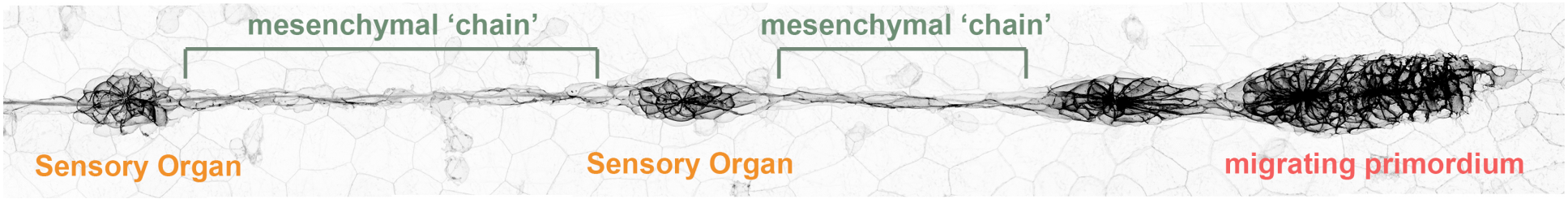
100 cells — L=120µm, U= 2-3$10^{-2}$µm.s^{-1}

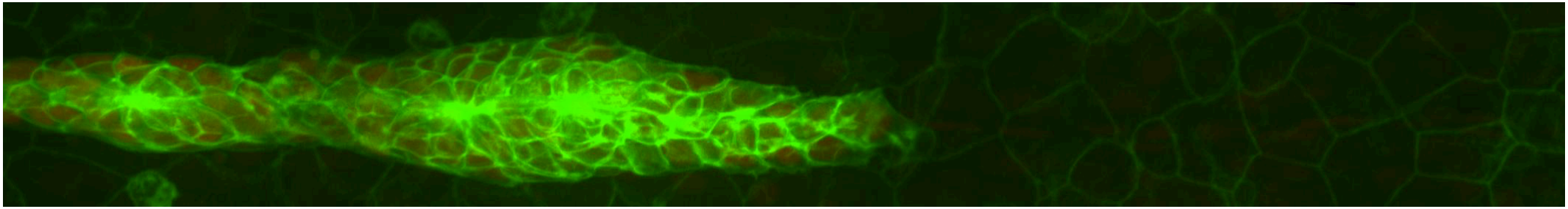
DL. Pagès et al., and R. Voituriez, M. Piel, F. Jaulin *Sci. Adv.* **8**, eabp8416 (2022)

Shellard et al., and R. Mayor. *Science* 362, 339–343 (2018)

Guidance of cell motility



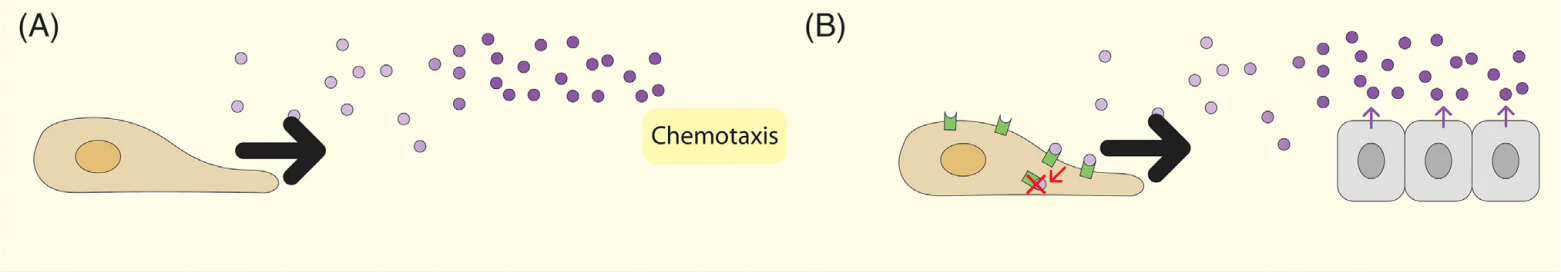




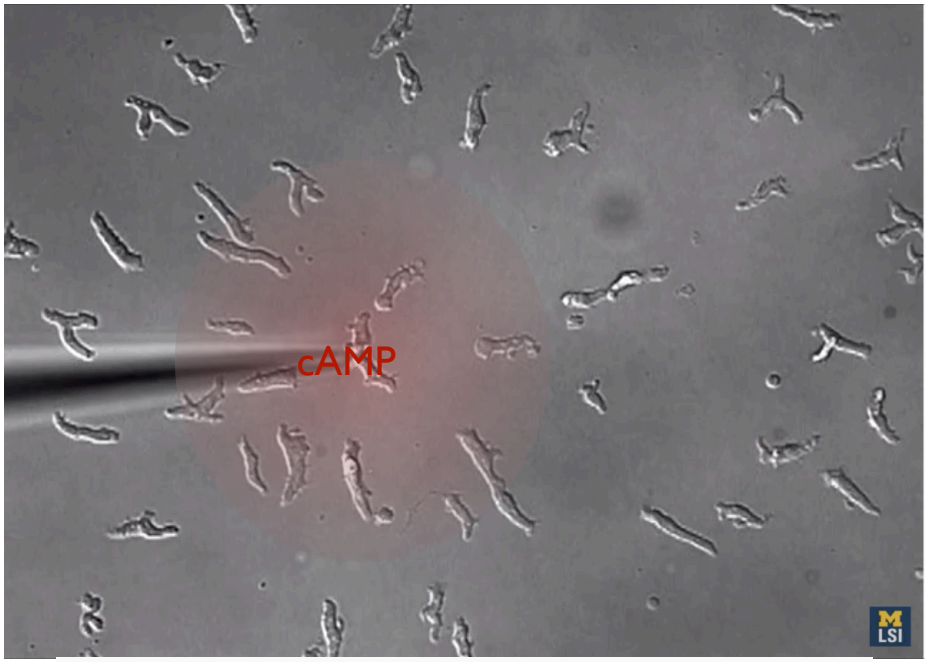
Darren Gilmour lab (Zürich)

Nature of guidance cues

– Chemotaxis



cAMP gradient



Carole Parent lab at the University of Michigan Life Sciences Institute.

Dictyostelium discoideum cells are attracted by cAMP released in a gradient from a pipette

Migration mode	Cue	Signal generation
Chemotaxis	Diffusible chemical released from cells or deposited extracellular vesicles	Simple diffusion Regulated removal by degradation of the chemoattractant or decoy receptors Release of extracellular vesicles

S. SenGupta, C. A. Parent and J. E. Bear, *Nature Rev Mol. Cell Biol.* 2021 https://doi.org/10.1038/ s41580-021-00366-6

Chemotaxis

1. Biased random walk characterizes chemotaxis across scales

2. Two different mechanisms of gradient sensing:

- Spatial mechanism: comparison of chemoattractant concentration along cell length. This requires often (always?) self-generated gradients by depletion of activity. More robust and long range.

- Temporal mechanism: comparison of chemoattractant at different positions and requires memory.

3. Adaptation and memory manifest in different ways across scales

- Temporal gradient sensing in prokaryotes
- Persistence of motility in eukaryotes (eg. Coupling between polarity and mechanics)

Mechanical guidance

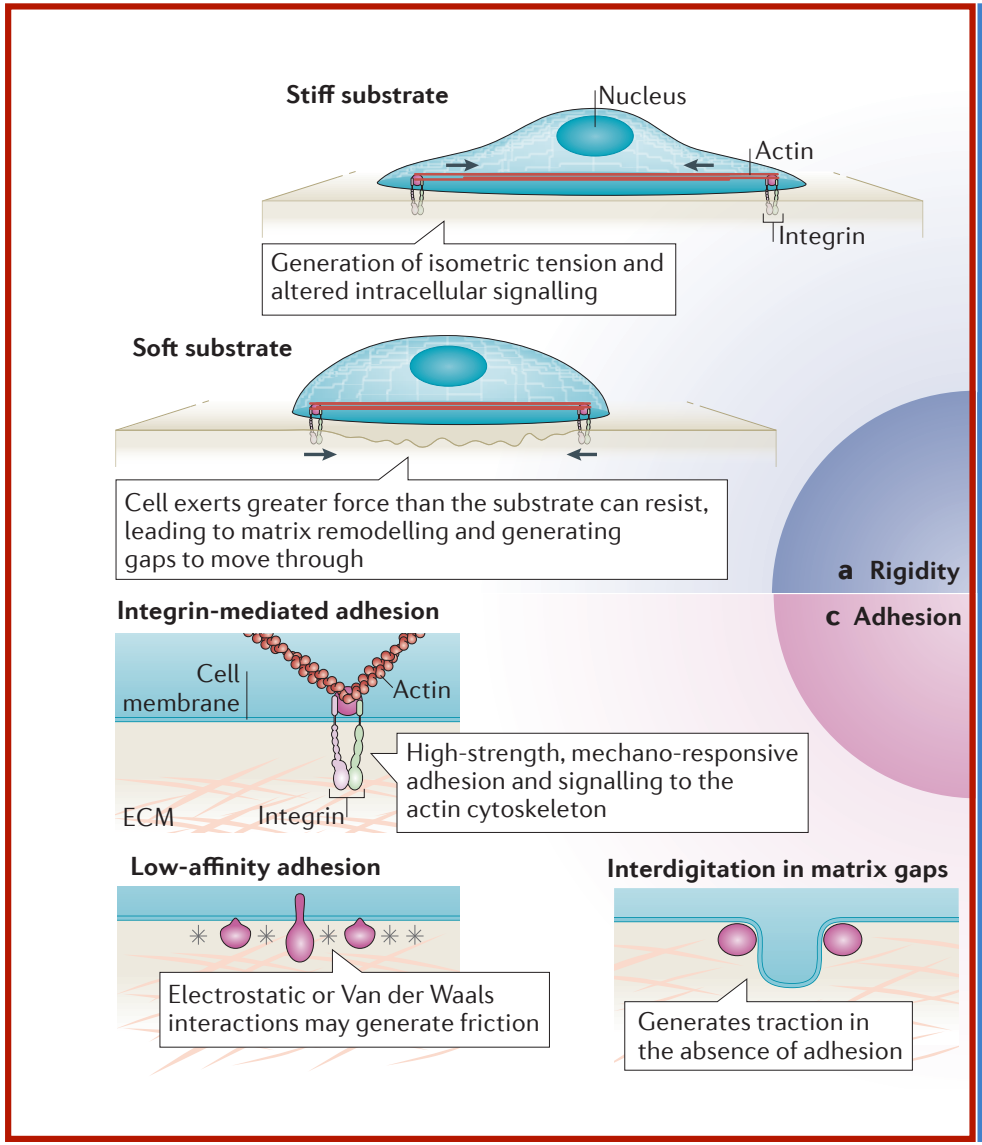
1. Substrate interactions in 2D and 3D are inherently mechanical

2. The stiffness, topography, etc of the environment can affect motility

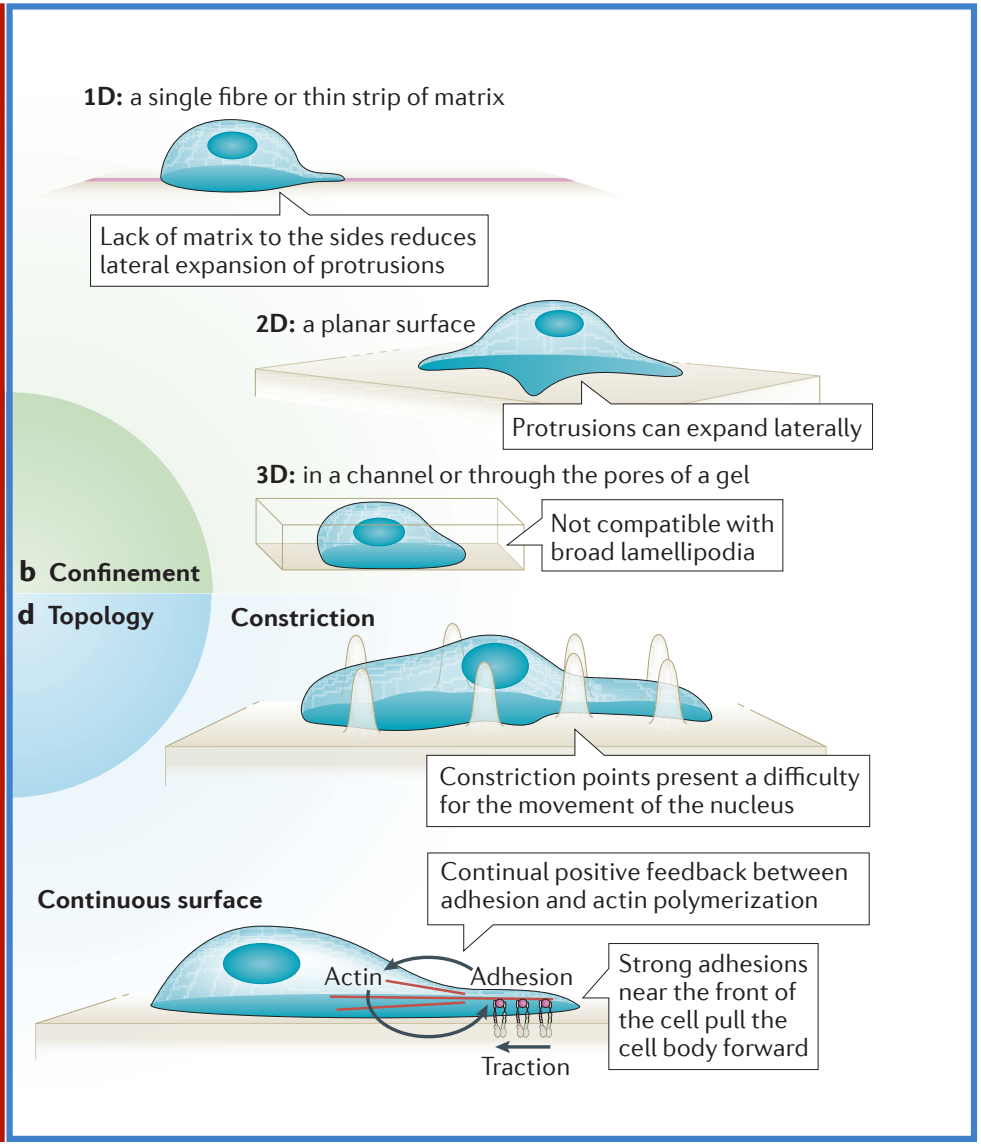
3. Cells also decode the mechanical properties of their environment

Physical variables of cell migration

Mechanics



Geometry

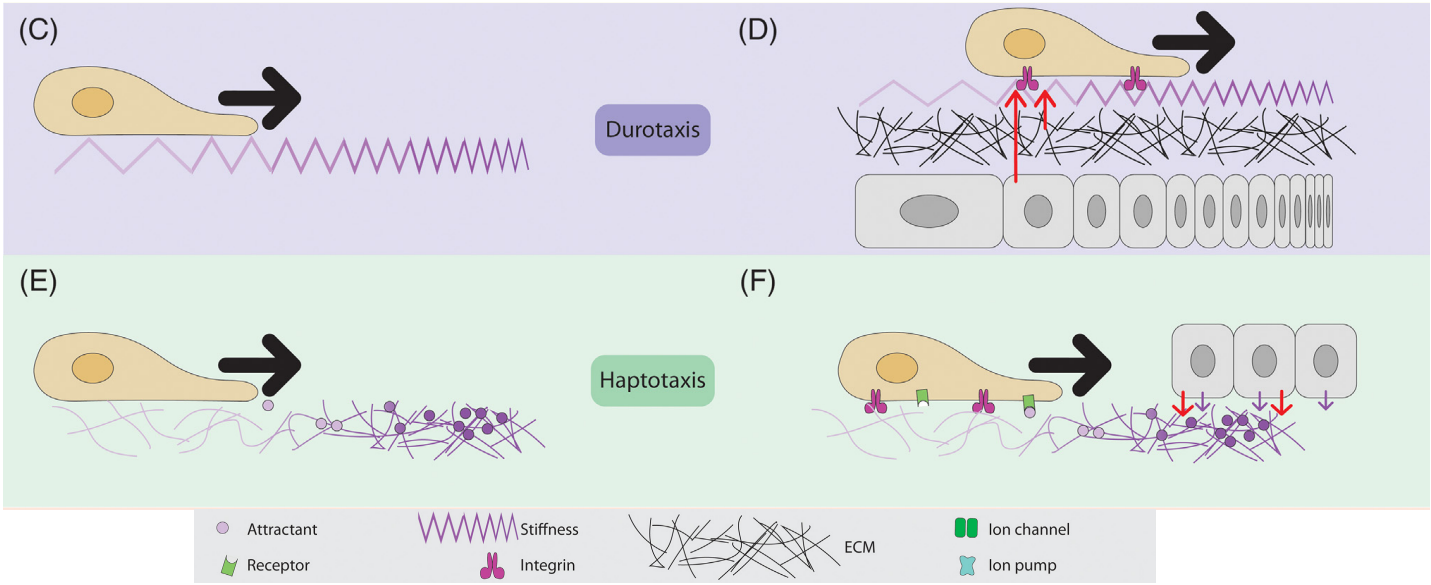


G. Charras and E. Sahai. *Nature Reviews MCB*, 15: 813-824 (2014)

Mechanical guidance

- Substrate stiffness gradient
  — Durotaxis

- Adhesion gradient
  — Haptotaxis

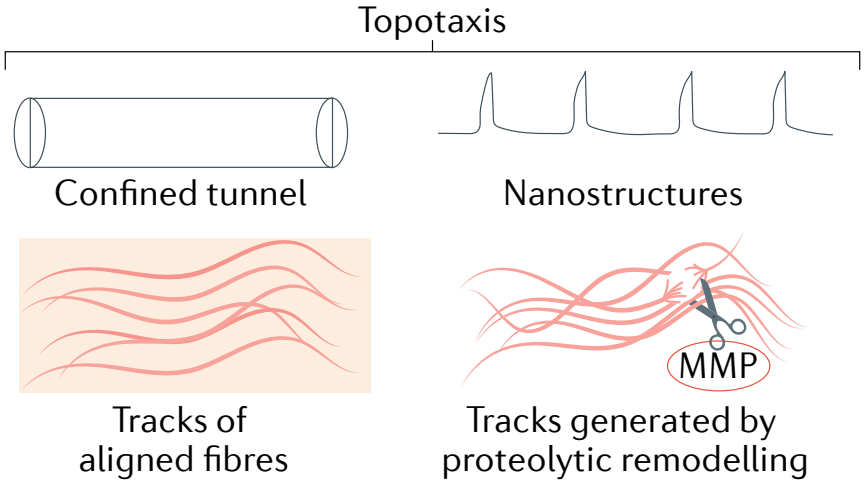


Migration mode	Cue	Signal generation
Haptotaxis	Substrate-bound chemical cues such as an immobilized chemokine or ECM	ECM secretion and deposition Binding of soluble factors to a substrate (mostly ECM) Exposing new sites on the substrate through enzymatic action
Durotaxis	Differential substrate compliance	Passive: creating a stiff substrate by crosslinking of ECM components or ECM deposition Active: cells or tissues exerting a force on the substrate that is sensed by other cells

S. SenGupta, C. A. Parent and J. E. Bear, *Nature Rev Mol. Cell Biol.* 2021
https://doi.org/10.1038/ s41580-021-00366-6

Mechanical guidance

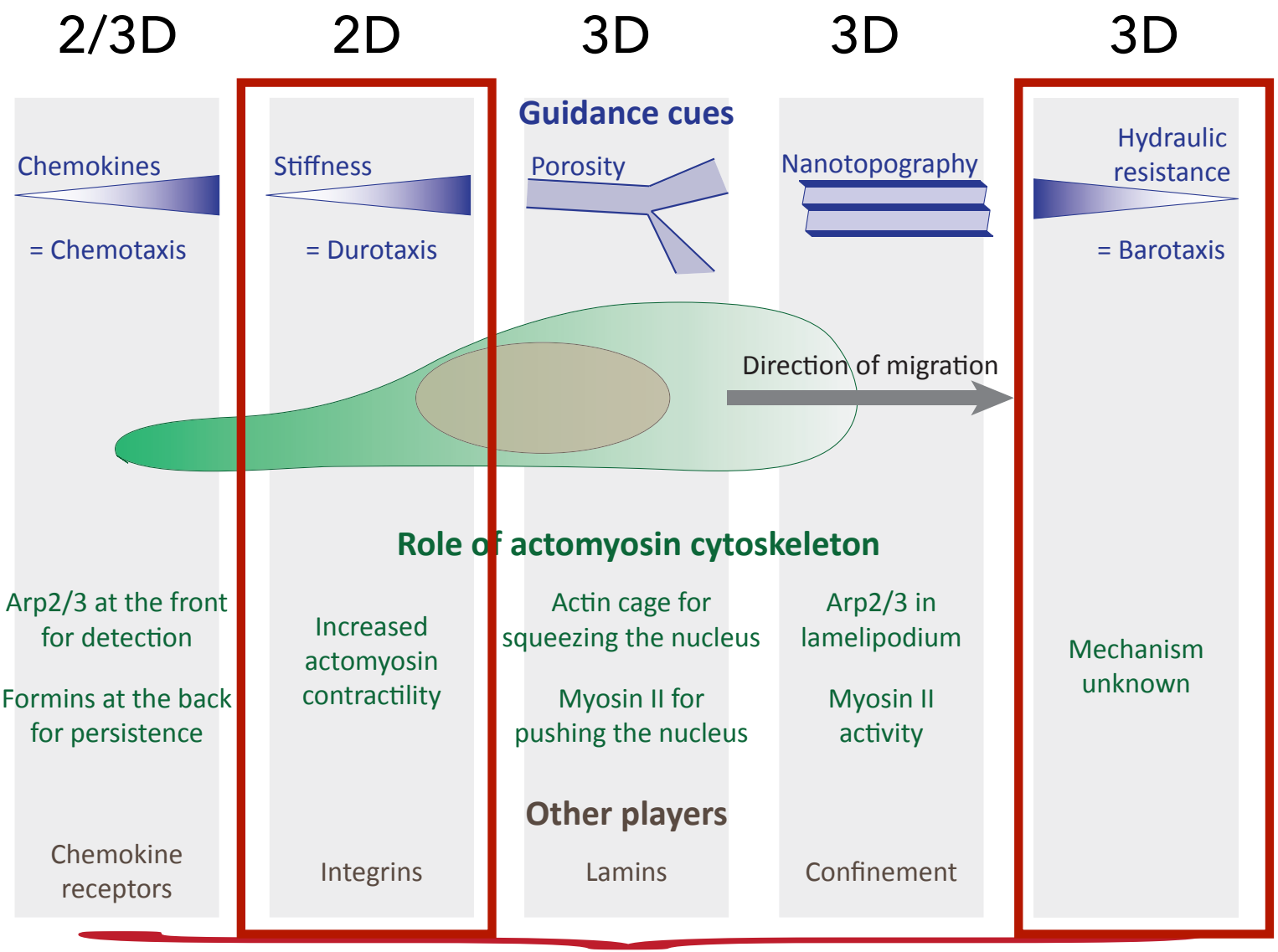
— Topotaxis



Migration mode	Cue	Signal generation
Topotaxis	Geometric properties of the migration substrate irrespective of mechanical or chemical properties	Preformed tunnels created by other cells Trails created by proteolytic ECM remodelling Topological features created by non-lytic ECM deformation 1D fibrils such as bundles of collagen Topology of natural tissue elements

S. SenGupta, C. A. Parent and J. E. Bear, *Nature Rev Mol. Cell Biol.* 2021 https://doi.org/10.1038/ s41580-021-00366-6

Mechanical guidance



Integrated migratory response to complex environmental guidance cues

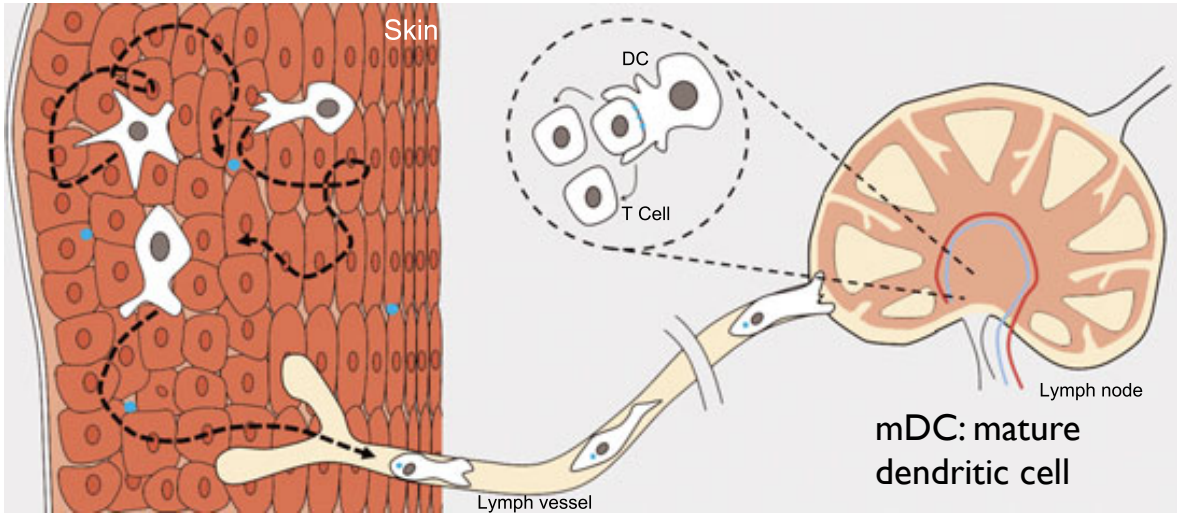
Mechanical guidance – *Barotaxis*

Barotaxis: pressure of fluid medium

- Principle
- Evidence
- A model
- Potential mechanisms
- Regulation
- Impact on navigation

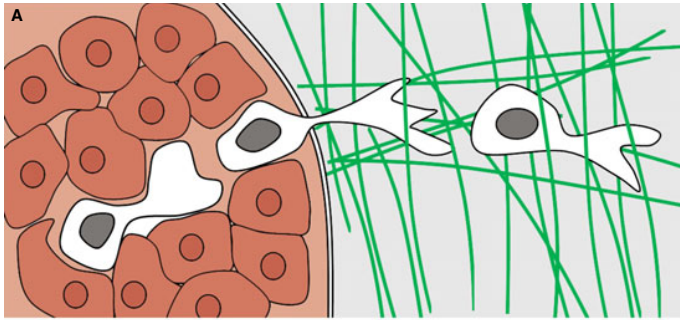
Potential context of barotaxis: 3D confined motility

Migration of dendritic cells *in vivo*

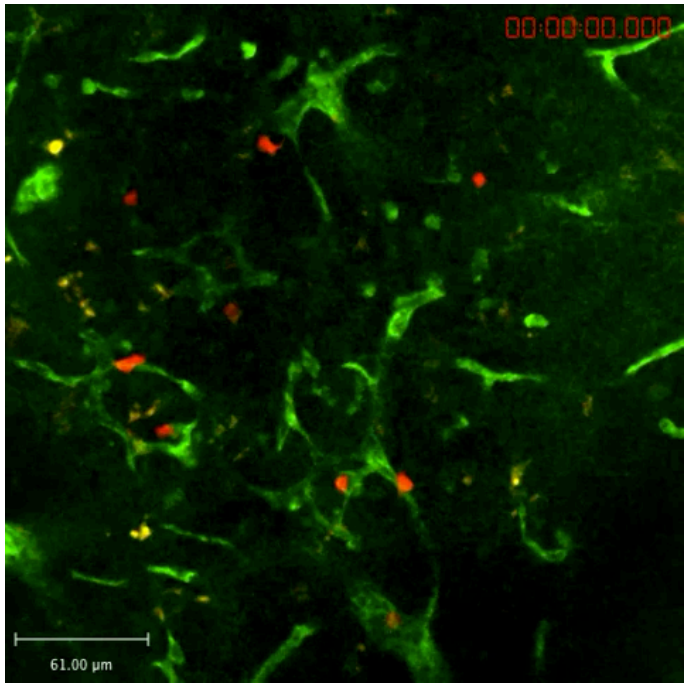


mDC: mature dendritic cell

iDC: immature dendritic cell



M. Heuzé et al., and AM. Lennon-Duménil. *Immunological Reviews* Vol. 256: 240–254 (2013)

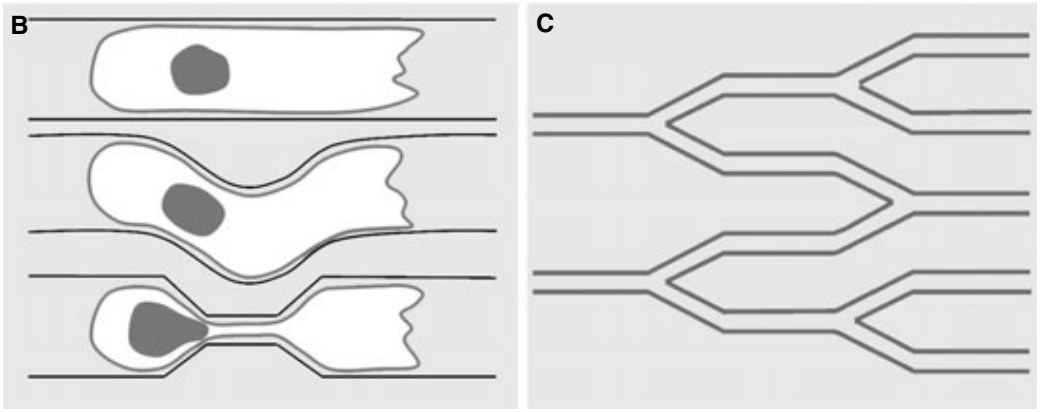


https://www.youtube.com/shorts/E4uU7kYY47U

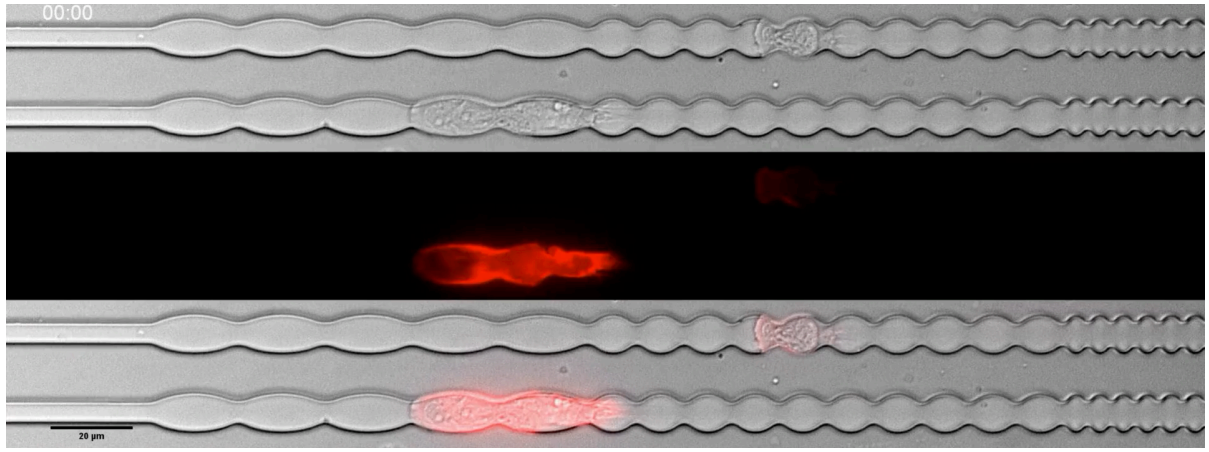
Cellular motility dynamics of transferred (red) and native (green) T cells in lymph node cortex.
Two-photon microscopy of T cell motility in S1P1-GFP mouse lymph node

Potential context of barotaxis: 3D confined motility

In vitro confinement



M. Heuzé et al., and AM. Lennon-Duménil. *Immunological Reviews* Vol. 256: 240–254 (2013)



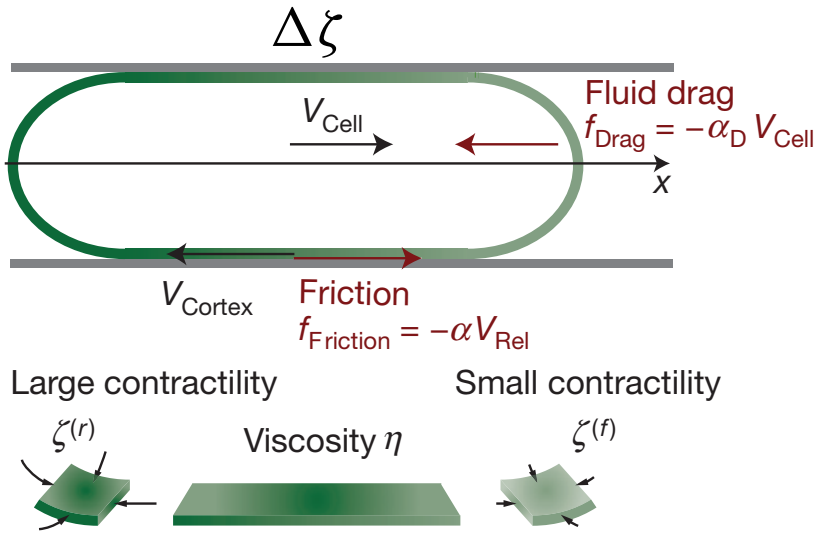
A. Reversat et al. and R. Voituriez and M. Sixt. *Nature*. 582(7813):582-585. (2020) doi: 10.1038/s41586-020-2283-z.

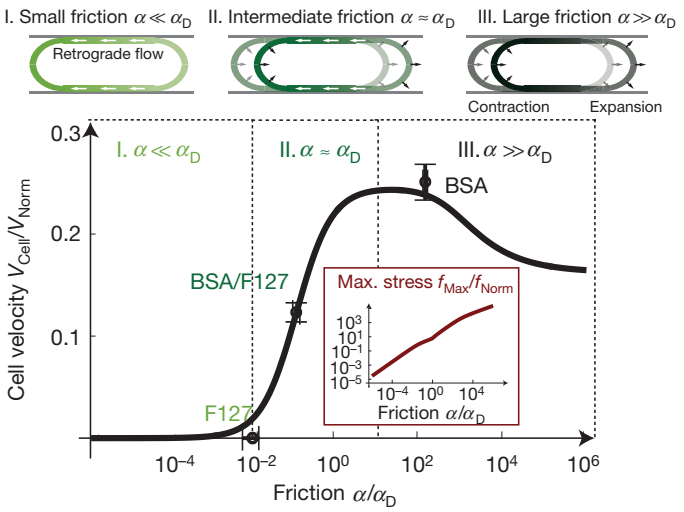
Principle of barotaxis

- Propulsive frictional forces result from retrograde actin flow velocity and allows forward movement

- Fluid drag force opposes forward movement

- Cell motility if frictional forces become equal to or larger than fluid drag force





$v_{norm} = (\zeta(r) - \zeta(f))L/\eta$

Bergert M, et al and G. Salbreux and E. Paluch. *Nat. Cell Biol.* 17:524–29 (2015)

Principle of barotaxis

- In some context, cell movement could be resisted by the extracellular fluid in the constrained geometry cells explore in vivo (capillary, fibrous network of ECM etc)

- Hydraulic resistance of water column ahead of moving cell:

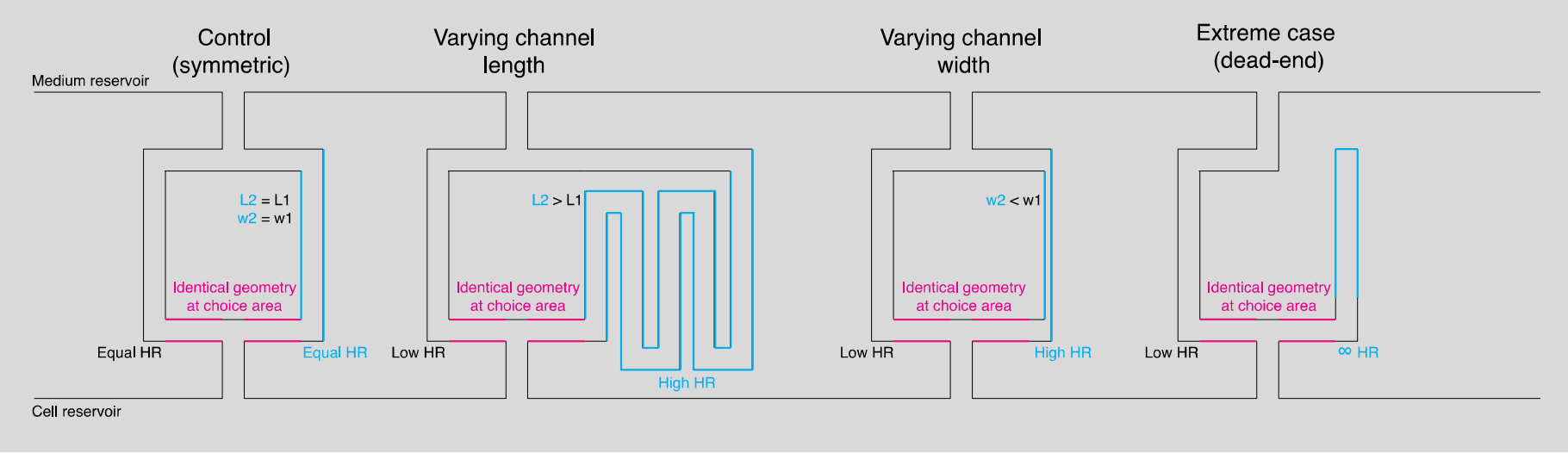
$$R_h = \Delta P/Q$$

Pressure drop/Flow rate (unit: Pa.s/m³)

$$R_h = \frac{12\mu L}{wh^3(1 - 0.63h/w)}$$

Fluid viscosity
Length (L), height (h) and width (w) of channel

Y. Belotti et al, and C. Weijer. *PNAS*. (2020) 117: 25553–25559



AM. Lennon-Dumenil and H. Moreau. *Current Opinion in Cell Biology* 2021, 72:131–136

Barotaxis in numbers

—The forces required to move a cell are of the same order as the forces required to move the surrounding fluid

- Load force exerted by fluid onto moving cell: $F = vRA^2$
  It depends on cell speed v, the hydraulic resistance R and the cross sectional area A.

  for immature dendritic cell, $\mu = 1$ mPa·s, $v = 8$ µm/min, $L = 250$ µm, $w = 3$ µm, $h = 2.5$ µm $\quad F = 0.5$ pN

  This is small: <pN/μm^2 or <Pa range

  Y. Belotti et al, and C. Weijer. *PNAS*. 117: 25553–25559 (2020)

- BUT, force for non-adhesive motility is in the range of <pN, so <Pa range at the cell scale.

  Bergert M, et al and G. Salbreux and E. Paluch. *Nat. Cell Biol*. 17:524–29 (2015)

Multipole	Large friction	Intermediate friction	Low friction
τ (monopole)	$-1.55\ 10^{-12}$ N	$-1.04\ 10^{-12}$ N	$-1.37\ 10^{-13}$ N

Migration Mode	Adhesive	Non-adhesive
Protrusion type	Usually lamellipodia	Usually blebs
Propelling force generation	Filament extension/actin flow	Cortex flow
Force transmission	Focal adhesion	Friction, protrusion intercalations, etc.
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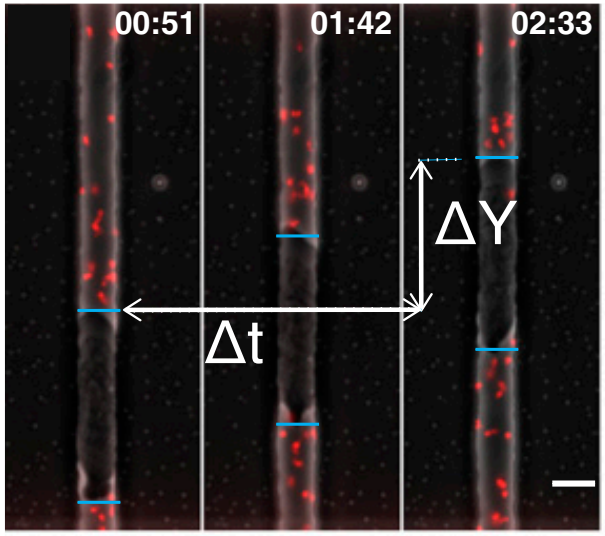
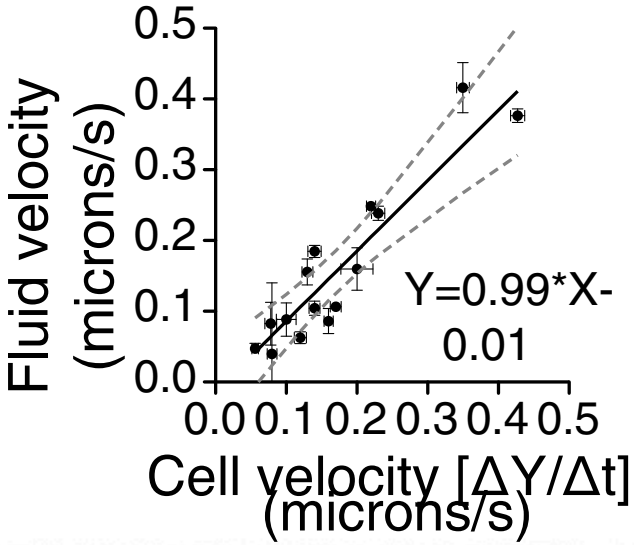
Force dipole	Contractile	Expansile

Bodor et al. and E. Paluch. *Developmental Cell*. 52: 550-562 (2020)

Evidence of Barotaxis

Cells displace the fluid ahead as they move in a capillary



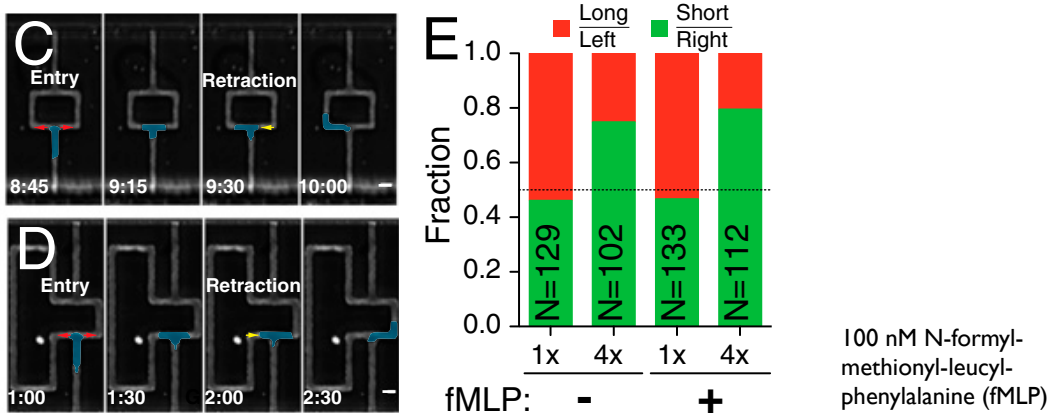


Harrison V. Prentice-Mott et al, and Jagesh V. Shah. (2013) *PNAS*, 110: 21006–21011

www.pnas.org/cgi/doi/10.1073/pnas.1317441110

Evidence of Barotaxis

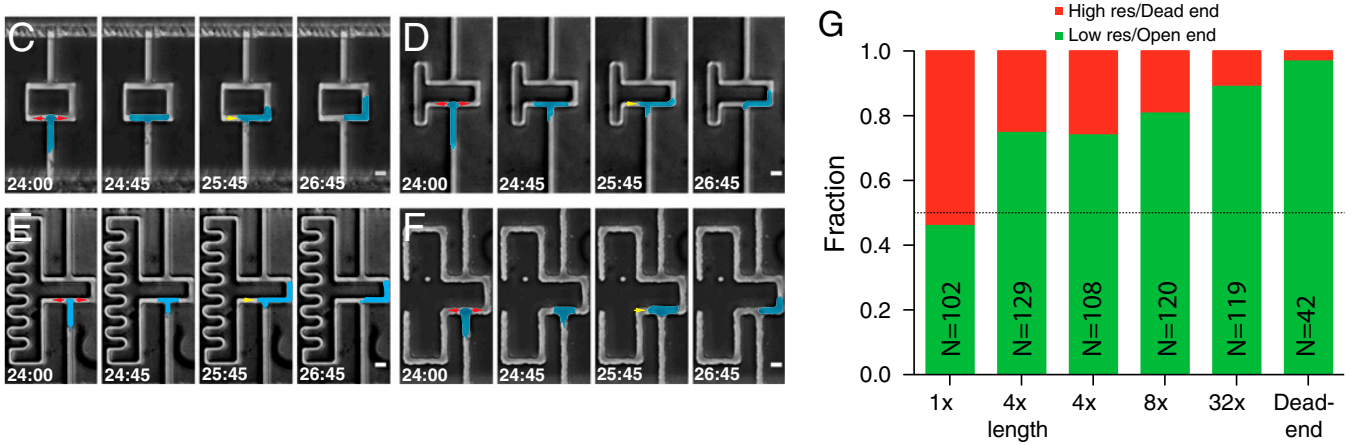
- Cells choose the shortest channel independent of any chemokine gradient in the system (fMLP).
- Length of channels: a 4 fold difference is detected by cells



100 nM N-formyl-methionyl-leucyl-phenylalanine (fMLP)

- The geometry of the path affects motility according to the Hydraulic resistance (based on length and height of channel)

$$R_h = \frac{12\mu L}{wh^3(1 - 0.63h/w)}$$



Harrison V. Prentice-Mott et al, and Jagesh V. Shah. (2013) *PNAS*, 110: 21006–21011

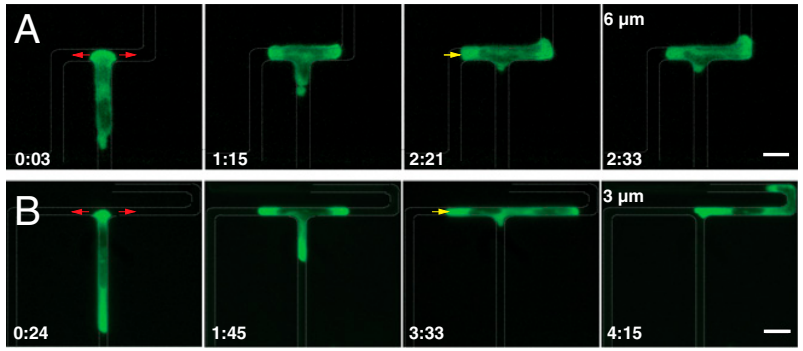
www.pnas.org/cgi/doi/10.1073/pnas.1317441110

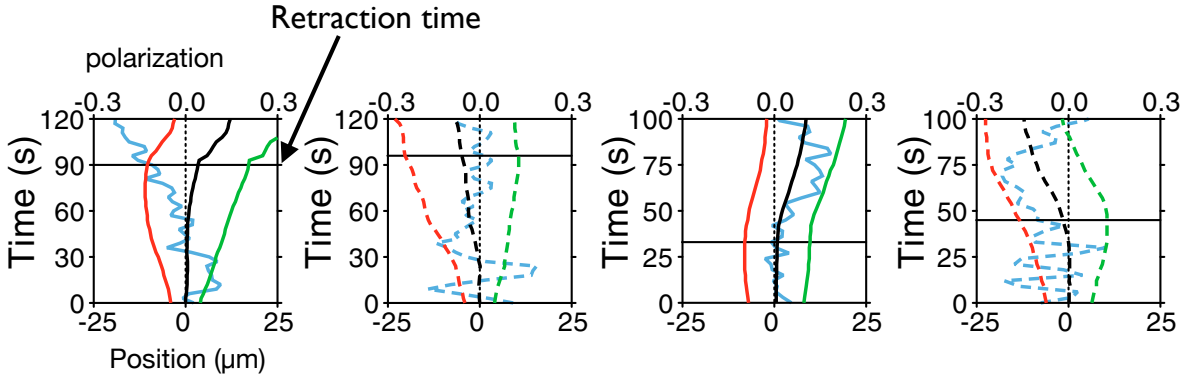
Evidence of Barotaxis

- Cells extend protrusions in both channels at a bifurcation
- One of the two pseudopods retracts and the cell moves towards the other extended pseudopod
- The competition between the extended pseudopods is **not mediated by differences in strength of canonical leading edge signaling**

- *Hypothesis:*
- The pseudopod that extends towards the Low Resistance channel grows faster
- This asymmetry in growth rates predicts cell movement

Akt::GFP: marks PI3K signalling at cell front





Left/High Resistance
Right/Low Resistance

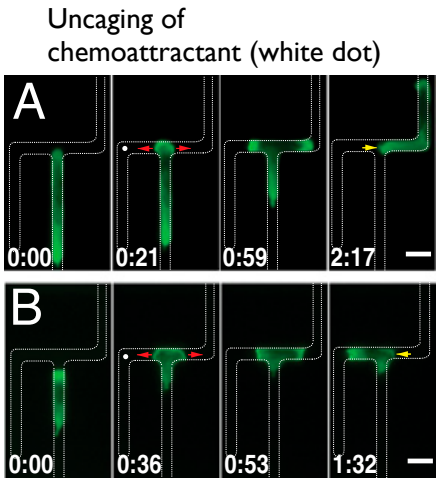
Cell mass
Cell biochemical polarization

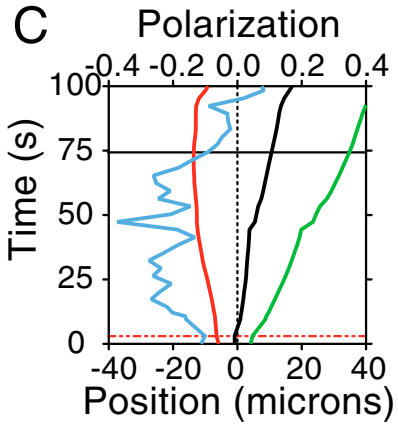
Harrison V. Prentice-Mott et al, and Jagesh V. Shah. (2013) *PNAS*, 110: 21006–21011
www.pnas.org/cgi/doi/10.1073/pnas.1317441110

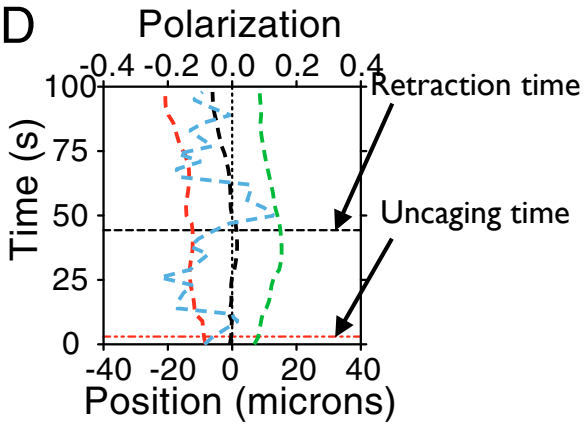
Evidence of barotaxis

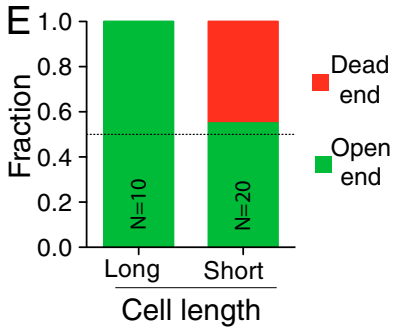
— Competition between chemotaxis and barotaxis

- Chemoattractant fMLP is uncaged in dead end.
- Cells respond by polarization towards chemoattractant in the dead end, but tend to extend stable extension towards the open channel.
- Majority of cells go towards the open end (70%) in spite of chemoattractant
- Barotaxis (response to hydraulic resistance) tends to override chemotaxis (in this system)









Harrison V. Prentice-Mott et al, and Jagesh V. Shah. (2013) *PNAS*, 110: 21006–21011

www.pnas.org/cgi/doi/10.1073/pnas.1317441110

Mechanical model of barotaxis

Model:

—Cells are described as an active poro-elastic material driven by the cortical actomyosin network

—Key parameters:

(1) **amplitude of the contractile stress** (interaction between myosin motors and cortical actin)

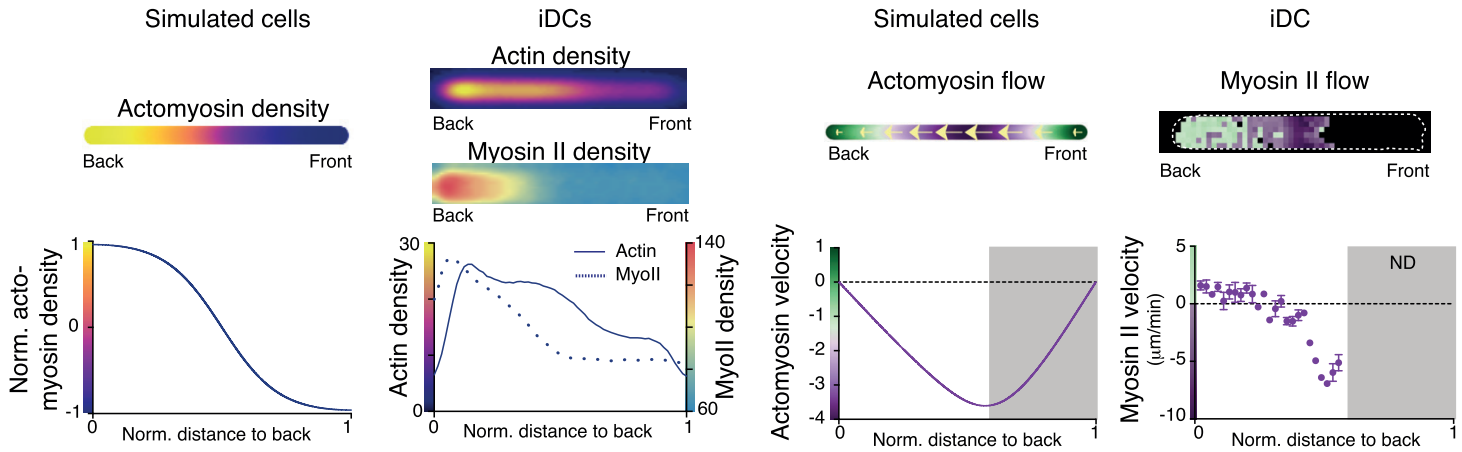
(2) **cell permeability** to the external fluid, which determines the force arising as the cell passes through the extracellular fluid.

—**Excitability**: above a threshold, cells exhibit spontaneous polarization

Random fluctuations of non-polarized cells are amplified leading to transient contractile activity at a pole. This drives spontaneous retrograde flow of the actin cortex, further amplifies and sustains it in a feedback.

Bergert M, et al and G. Salbreux and E. Paluch. *Nat. Cell Biol.* 17:524–29 (2015)
P. Maiuri, JF. Rupprecht, ..., M. Sixt, R. Voituriez *Cell 161*, 374–386 (2015)

iDC: immature dendritic cell



H. Moreau et al., and R. Voituriez, M. Piel and AM. Lennon-Duménil. *Developmental Cell* 49, 171–188 (2019)

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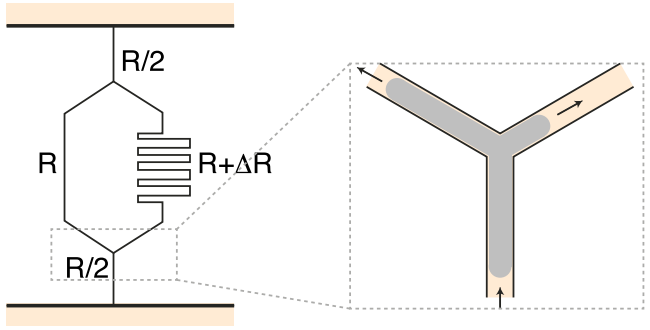
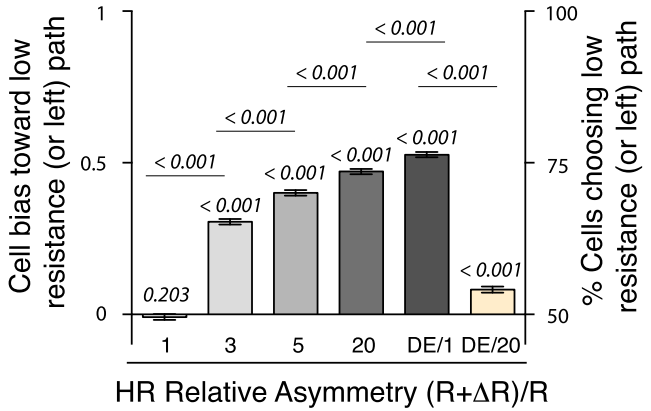
Schematic of the physical model



R: hydraulic resistance

Simulated cells

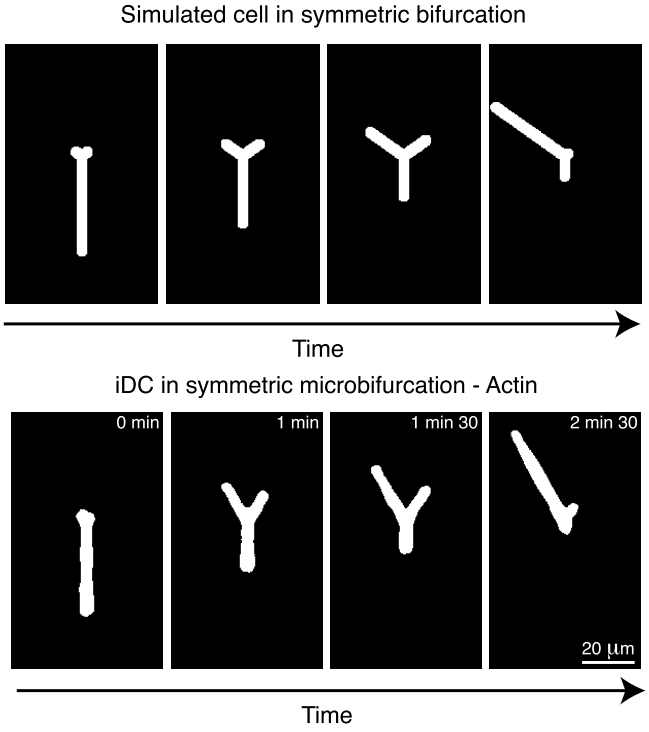


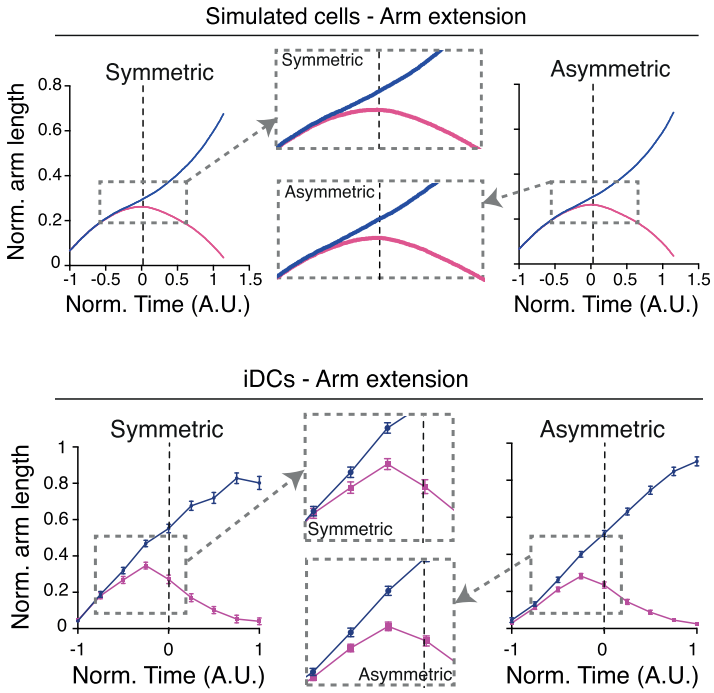
H. Moreau et al., and R. Voituriez, M. Piel and AM. Lennon-Duménil. *Developmental Cell* 49, 171–188 (2019)

Mechanism of barotaxis

— Role of hydraulic resistance on cell pseudopod extension rate?

- *In silico* and *in vivo:* Extension rates of both pseudopods are similar prior to retraction of one of the pseudopods, in both symmetric and asymmetric bifurcations.
- The fact that the behavior is the same in symmetric or asymmetric bifurcations indicate that the directional bias does not stem form hydraulic resistance slowing down pseudopod extension *per se,* and that there is an inherent instability in the system.



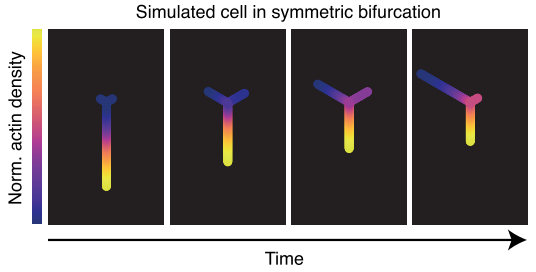


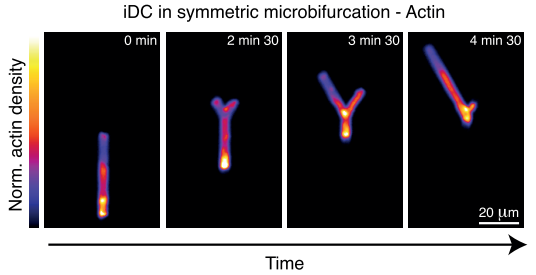
H. Moreau et al., and R. Voituriez, M. Piel and AM. Lennon-Duménil. *Developmental Cell* 49, 171–188 (2019)

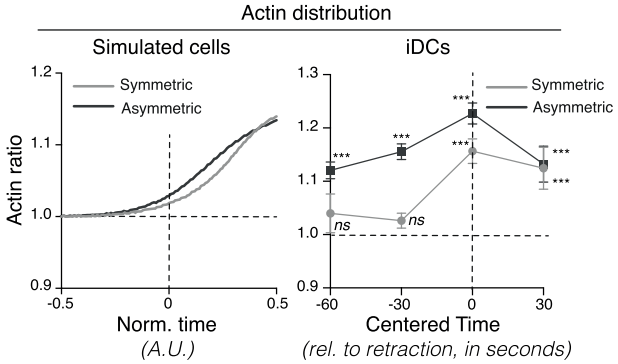
Mechanism of barotaxis

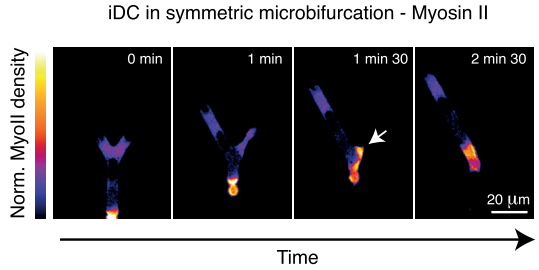
— Effect of hydraulic resistance is amplified by excitable contractility of cell cortex

- *In silico* and *in vivo:* Random cell repolarization of the cells: actin and myosinII accumulate in the stalling and retracting pseudopod
- A small force imbalance arising from asymmetry in hydraulic resistance between the two cell arms is amplified by the excitable actomyosin system

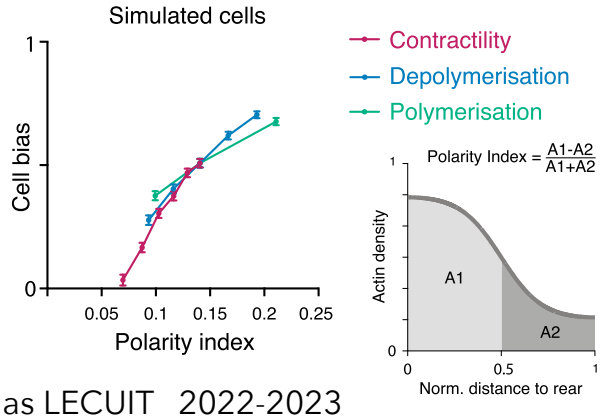


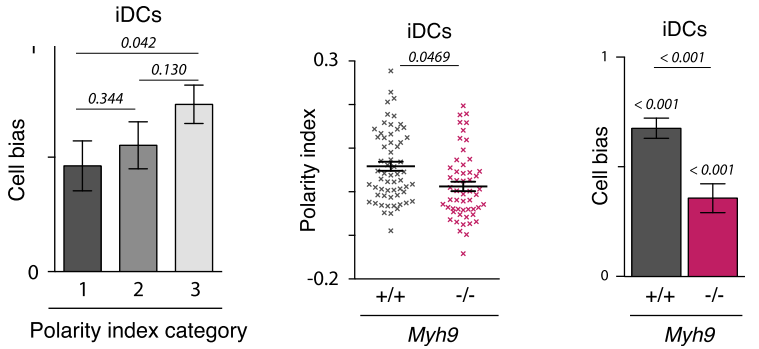






- Cell depolarization correlates with and is required for cell directional bias at a channel bifurcation



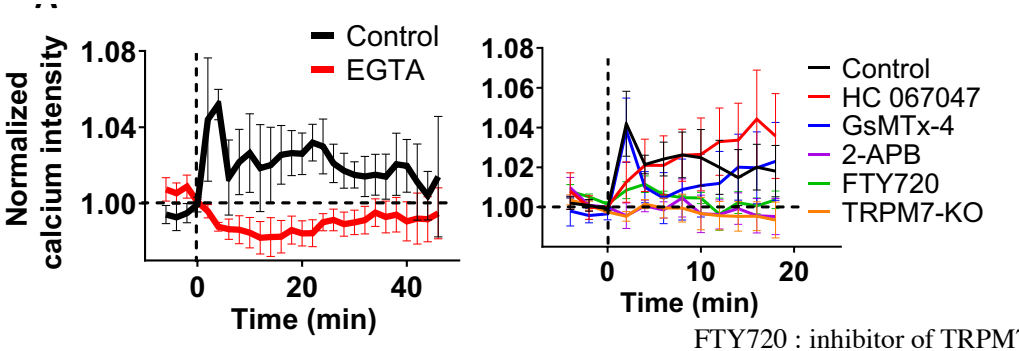


H. Moreau et al., and R. Voituriez, M. Piel and AM. Lennon-Duménil. *Developmental Cell* 49, 171–188 (2019)

Mechanism of barotaxis

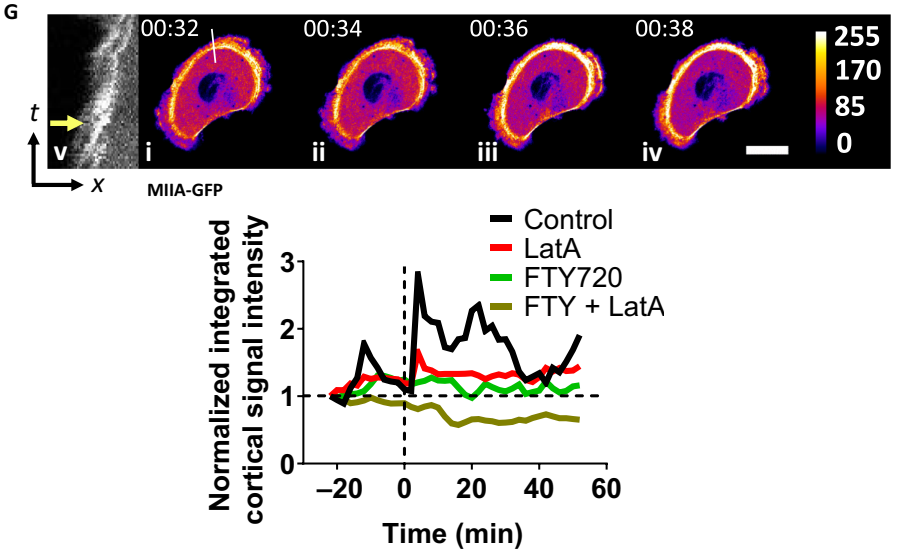
— Hydrostatic pressure induces cortical contractility

- Application of 3Pa hydrostatic pressure increases intracellular calcium concentration in cancer cell lines
- This requires presence and activation of the mechanosensitive, stretch-activated TRP channel TRPM7 (membrane tension)



FTY720 : inhibitor of TRPM7
GsMTx-4: Piezo1/2 inhibitor

- Cortical actomyosin is induced following application of hydrostatic pressure.
- This requires TRPM7 activation

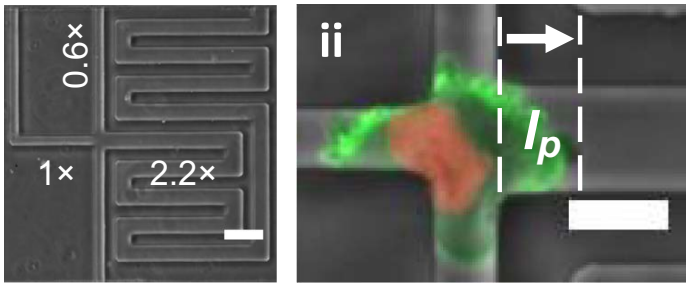


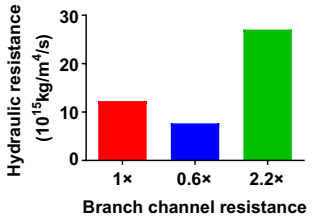
R. Zhao et al., and K. Konstantinopoulos. *Science. Advances*. 5:eaaw7243 (2019)

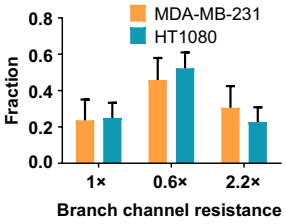
Mechanism of barotaxis

— Membrane tension sensing is required for barbotais

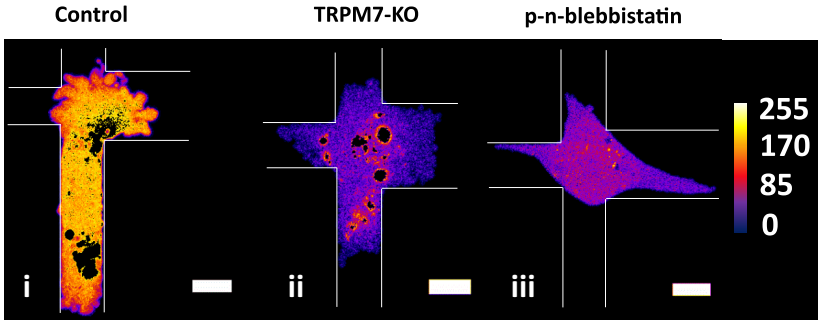
- At channel trifurcation cancer cells choose path of least hydraulic resistance

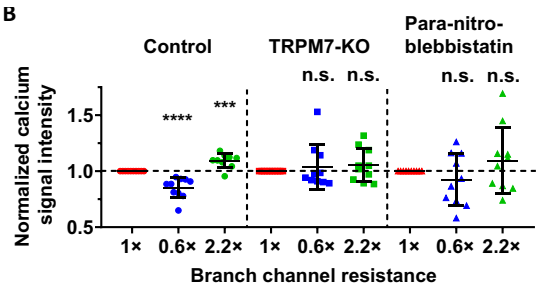






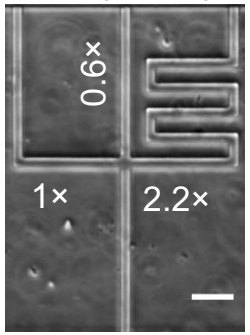
- Calcium is induced at cell trifurcation and its magnitude scales with the hydraulic resistance
- This requires TRPM7 and MyosinII contractility

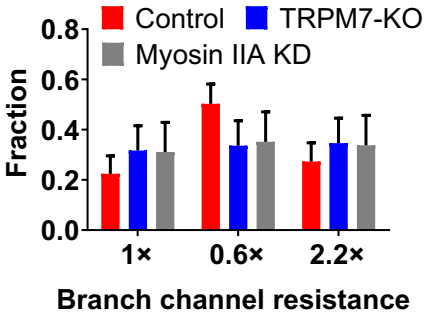




- In absence of TRPM7 activity cells are no longer barotactic

Same cross-sectional area (30 μm²)



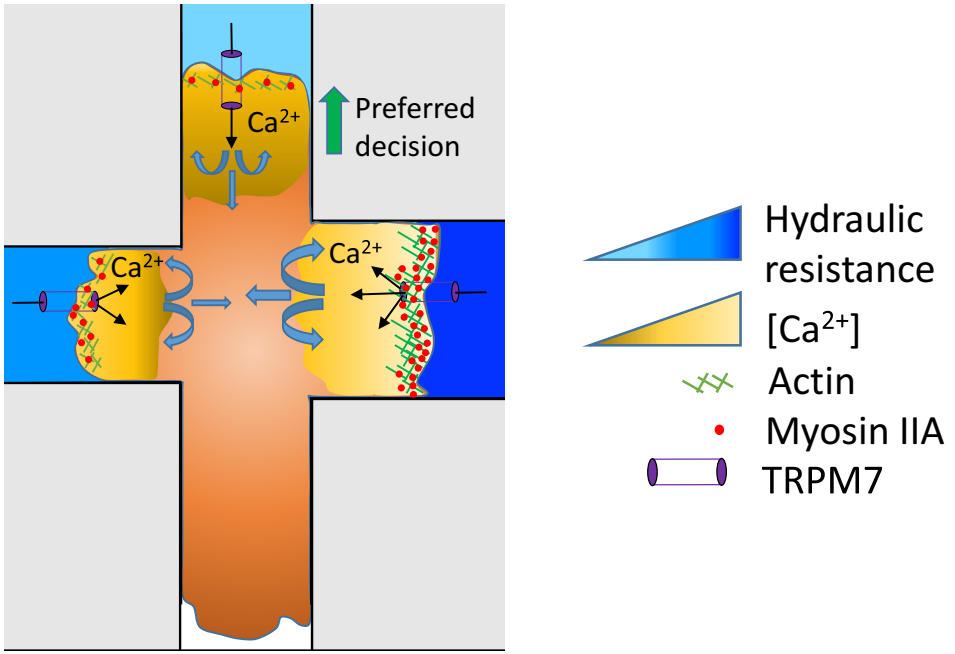


R. Zhao et al., and K. Konstantinopoulos. *Science. Advances*. 5:eaaw7243 (2019)

A possible *Mechanism* of barotaxis

- Hydrostatic pressure due to hydraulic resistance induces TRPM7 activation and calcium influx
- This leads to MyosinII activation and cortical contractility

- This induces (Zhao et al, 2019) or biases (Moreau et al, 2019) the cell repolarization at bifurcations
- Cell directionally bias follows from cell asymmetry/polarization (but not extension rate *per se?*, Prentice-Mott 2013))



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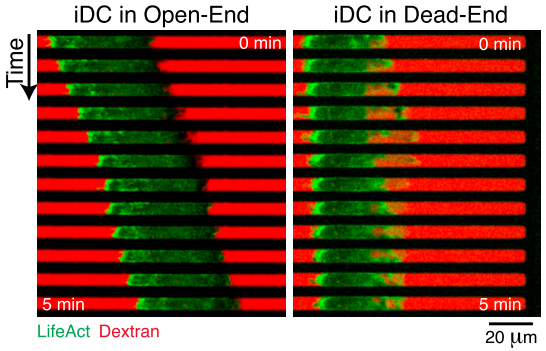
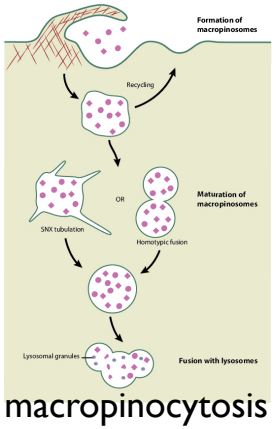
H. Moreau et al., and R. Voituriez, M. Piel and AM. Lennon-Duménil. *Developmental Cell* 49, 171–188 (2019)

Regulation of barotaxis: tuning cell permeability

— Cell permeability tunes barotactic response

- Immature dendritic cells (iDCs) in a dead-end (high HR) can sometimes become motile. Velocity is reduced and cells exhibit macropinocytic activity at the front

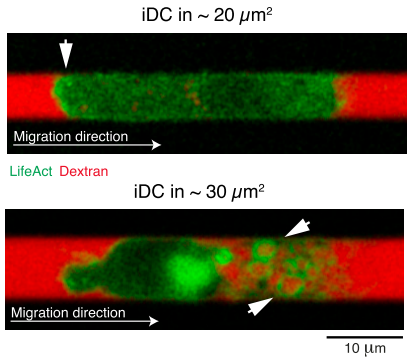


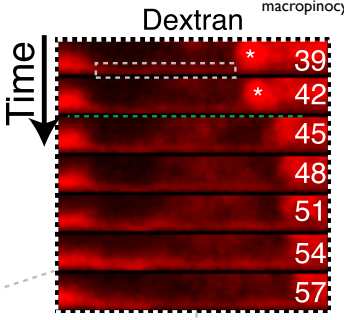


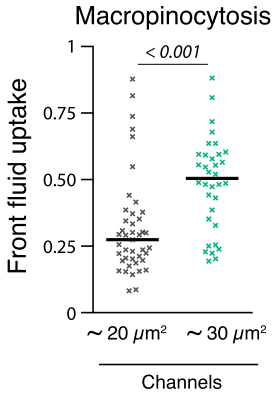
macropinocytosis

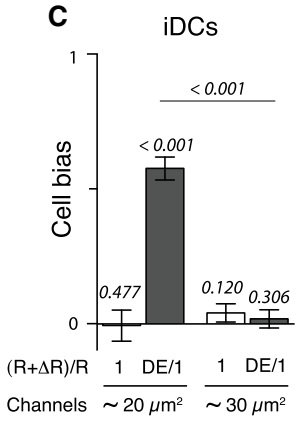
https://www.mechanobio.info/what-is-the-plasma-membrane/what-is-membrane-trafficking/what-is-macropinocytosis/

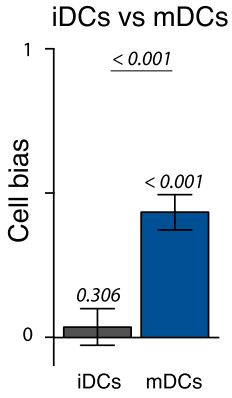
- In larger capillaries iDCs are no longer barotactic. This correlates with macropinocytosis.
- Macropinocytosis allows fluid transfer across cells in a channel
- Mature DCs (mDCs) in large capillaries are barotactic and have ***no*** macropinocytic activity.











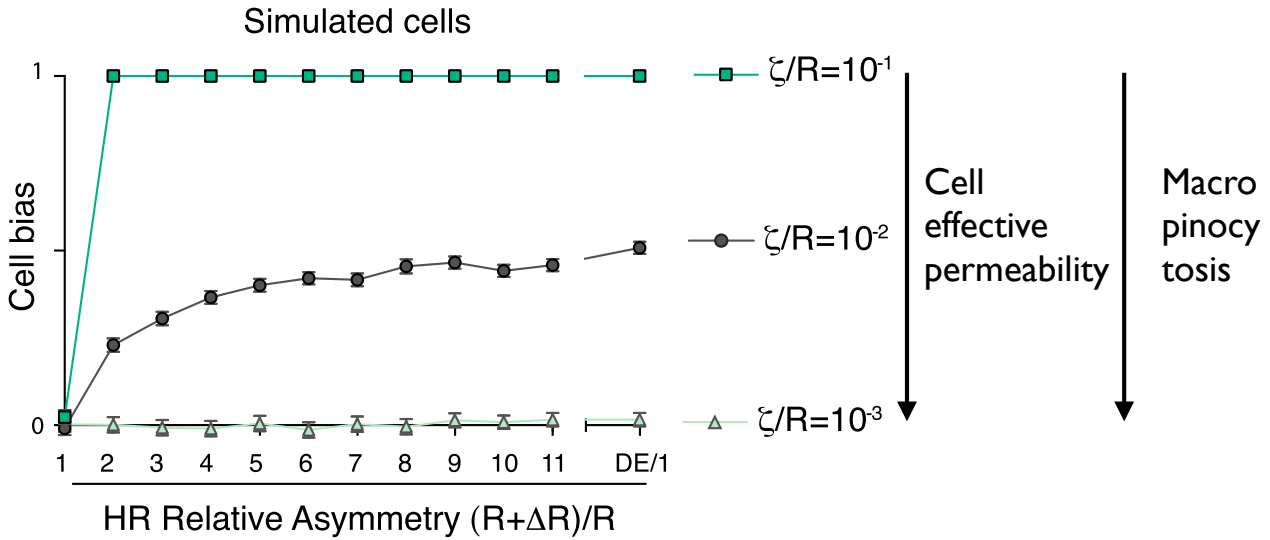
H. Moreau et al., and R. Voituriez, M. Piel and AM. Lennon-Duménil. *Developmental Cell* 49, 171–188 (2019)

Regulation of barotaxis: tuning cell permeability

- The effect of macropinocytosis can be modeled via the cell-fluid resistance parameter (which also includes permeability by leakage on the side of cells, or aquaporins etc)
- Increased cell-fluid resistance (for a given hydraulic resistance) increases cell directional bias *in silico* and barotaxis

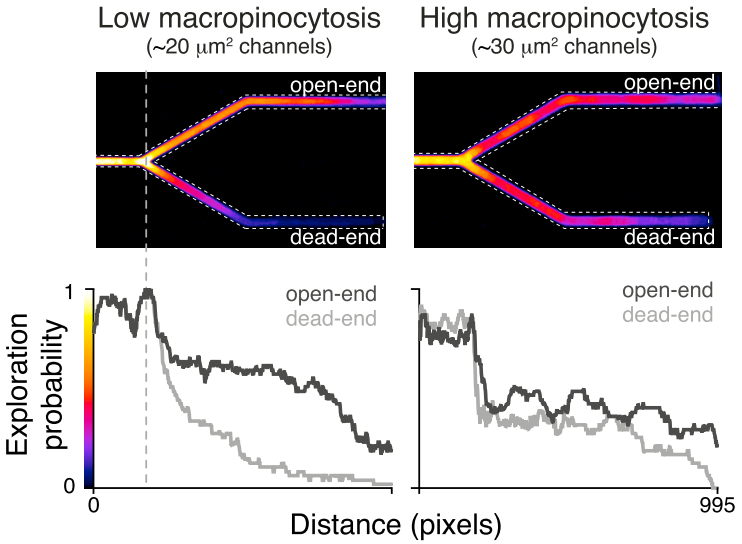
ζ Cell-fluid resistance (1/permeability)

R Hydraulic resistance



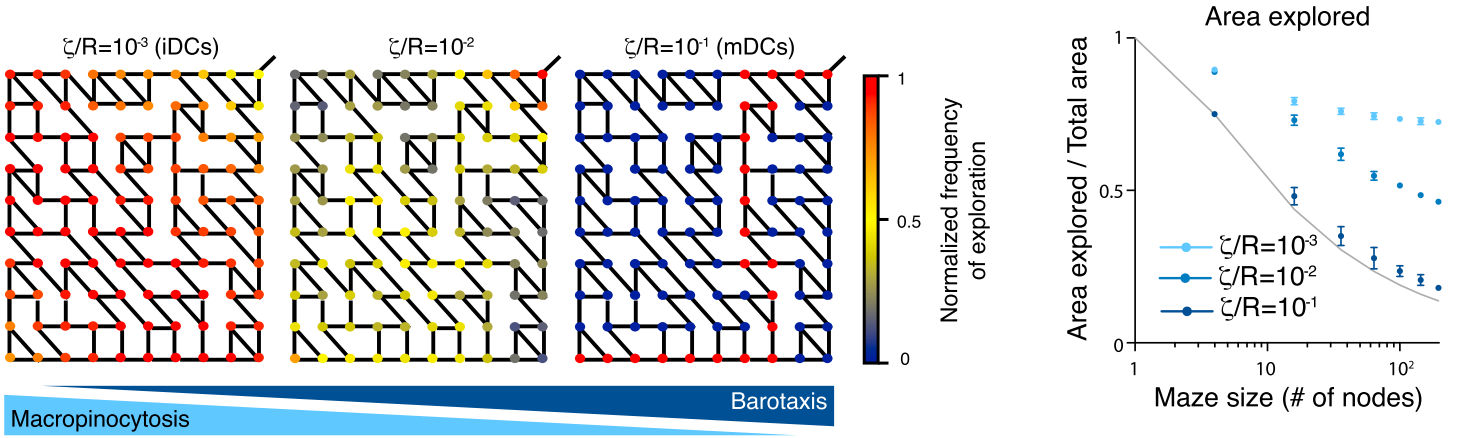
Regulation of barotaxis: consequences

- Cell permeability by macropinocytosis increases cell exploration in bifurcated channels (experiments in iDCs)



- Cells in a maze:

Patrolling behavior of non barotactic cells (eg. iDCs) and shortest path for barotactic cells (eg. mDCs)



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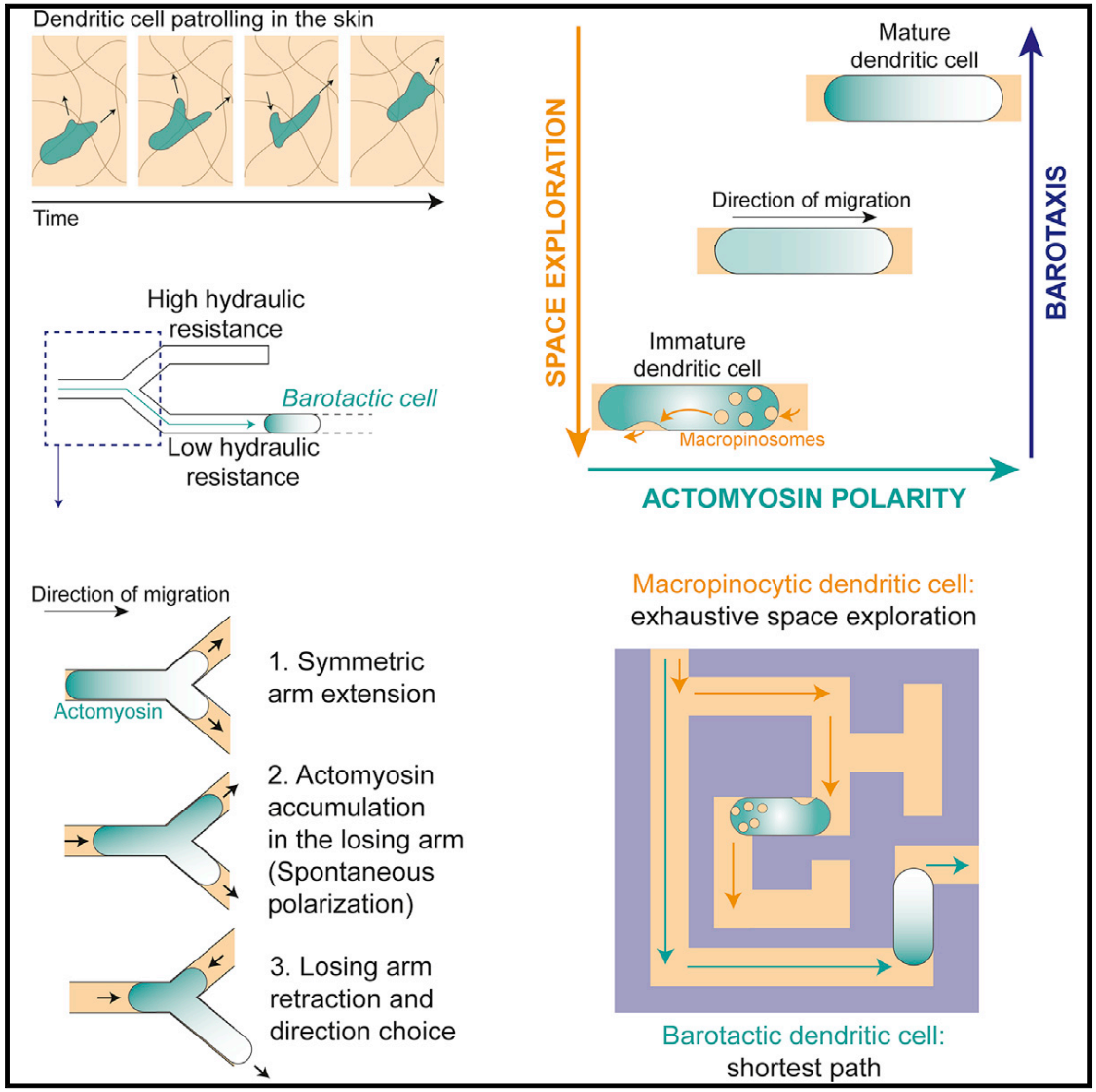
Regulation of barotaxis: tuning cell permeability



H. Moreau et al., and R. Voituriez, M. Piel and AM. Lennon-Duménil. *Developmental Cell* 49, 171–188 (2019)

Barotaxis: Non-local environment sensing in motility

- Barotaxis:

The hydraulic pressure is a mechanical signal sensitive to geometry of environment.

—Information about integration of path ahead of cell, rather than strictly local information

Chemotaxis: Non-local environment sensing in motility

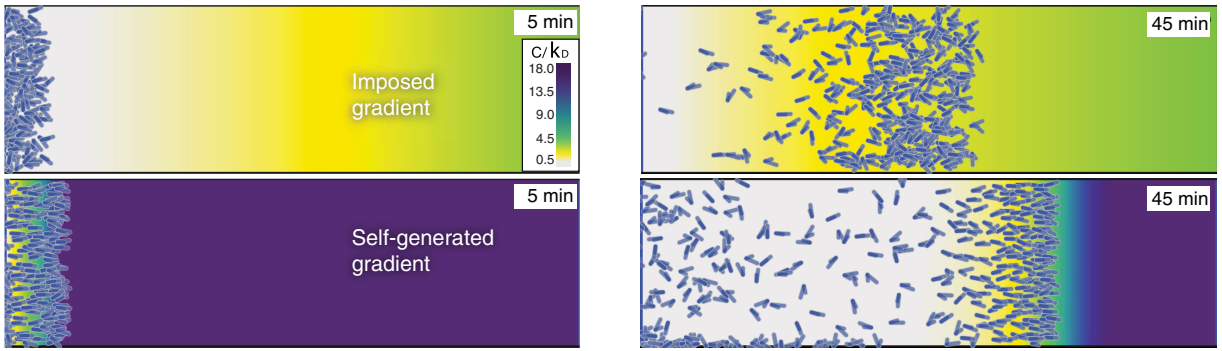
Cells detect and avoid dead ends with self-generated gradients

- **Chemical gradients**

  Imposed gradient:
  — chemotaxis is not efficient because it is too shallow

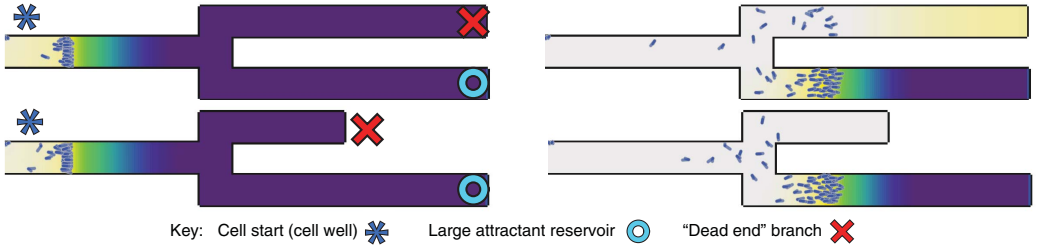
  Self-generated gradient:
  — chemotaxis works best at near saturation of receptor binding, allowing formation of a steep local gradient

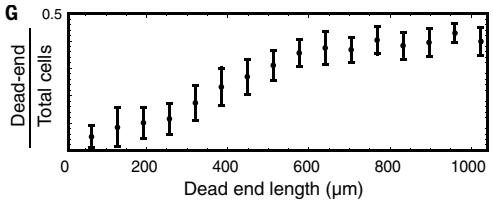
Persistent, biased random walk of cells in a bath with diffusion of attractant



- **Directional bias:**

In a dead end, the chemoattractant is rapidly degraded and follower cells avoid the dead end.
This results in a statistical bias in the distribution.
This bias increases as the dead end is shorter



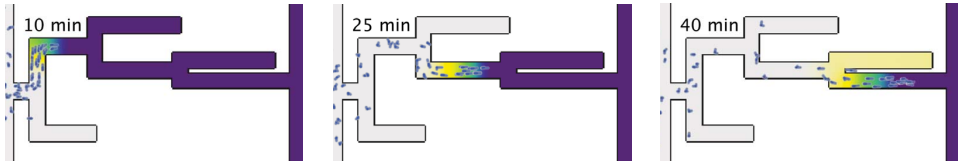


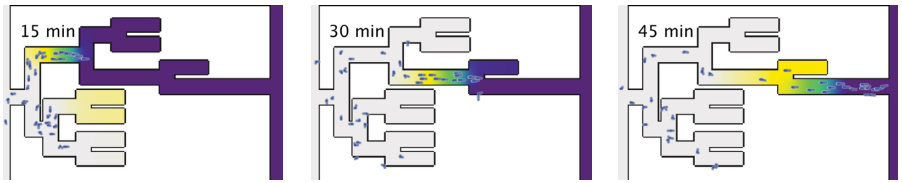
L. Tweedy et al., and R. Insall. *Science* 369, 1075 (2020)

Chemotaxis: Non-local environment sensing in motility

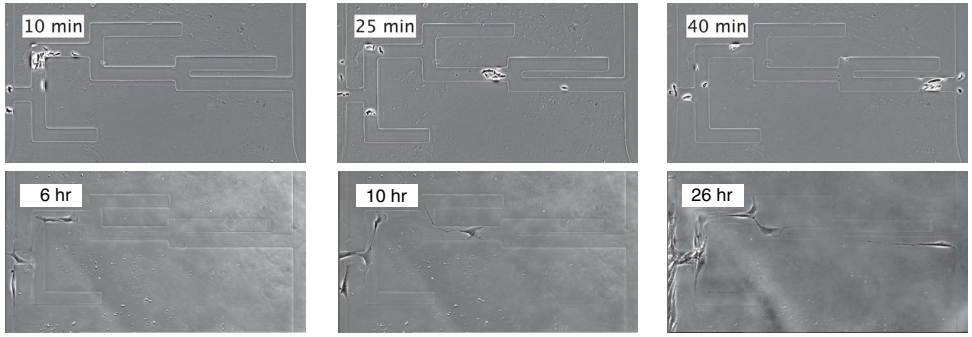
Pathfinding in a maze using self-generated gradients

Simulations



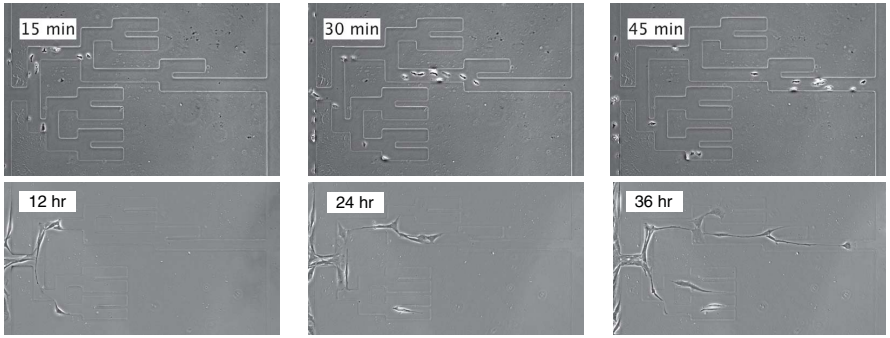


Dictyostelium cells



Pancreatic cancer cells

Dictyostelium cells



Pancreatic cancer cells

L. Tweedy et al., and R. Insall. *Science* 369, 1075 (2020)

Non-local environment sensing in motility

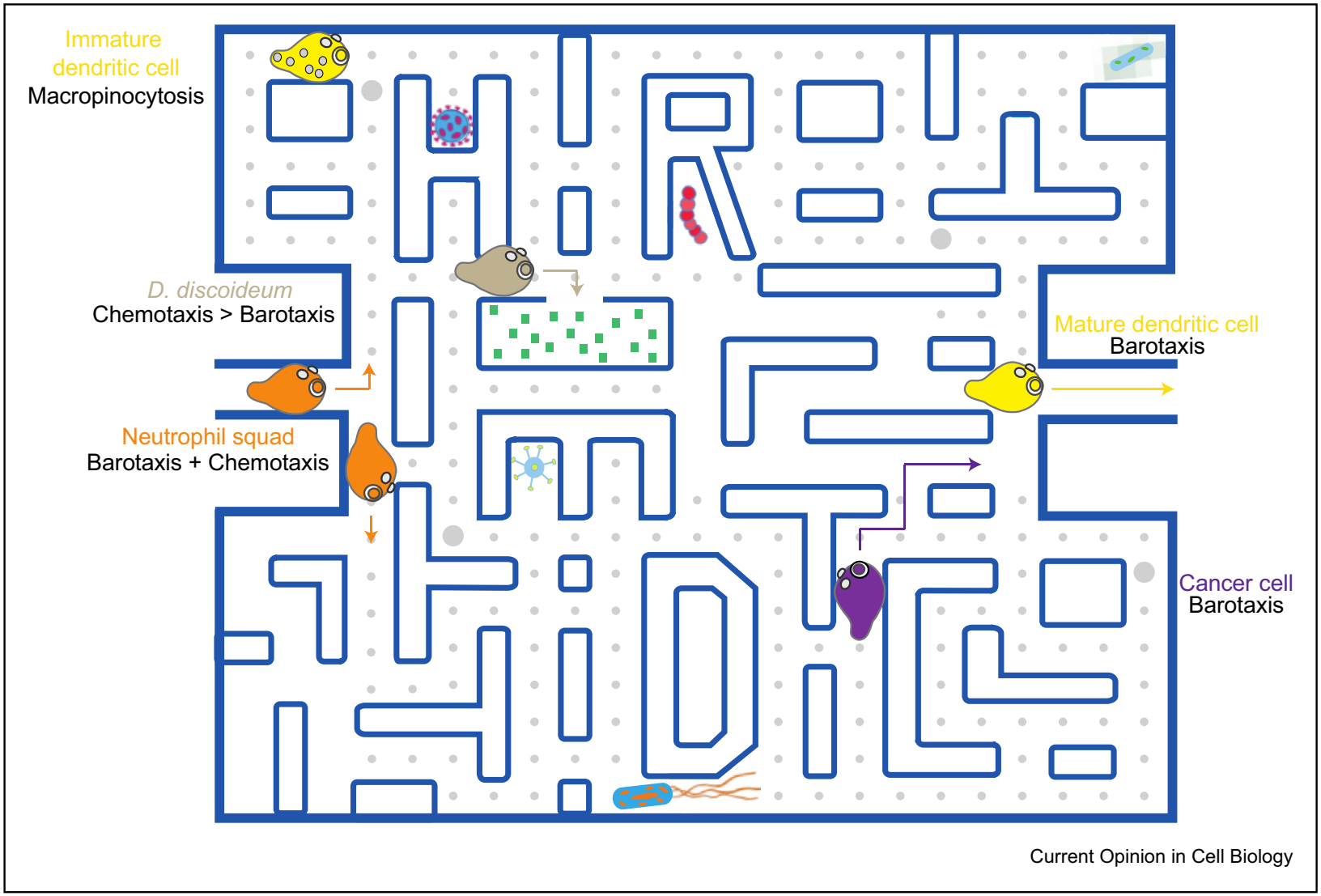
- Barotaxis:

The hydraulic pressure is a mechanical signal sensitive to geometry of environment.
—Information about integration of path ahead of cell, rather than strictly local information

- Chemotaxis:

The gradient generating mechanism dependent on geometry of the environment
Pathfinding in a maze through non-local sensing.

Mechanical and chemical guidance



AM. Lennon-Dumenil and H. Moreau. *Current Opinion in Cell Biology* 2021, 72:131–136

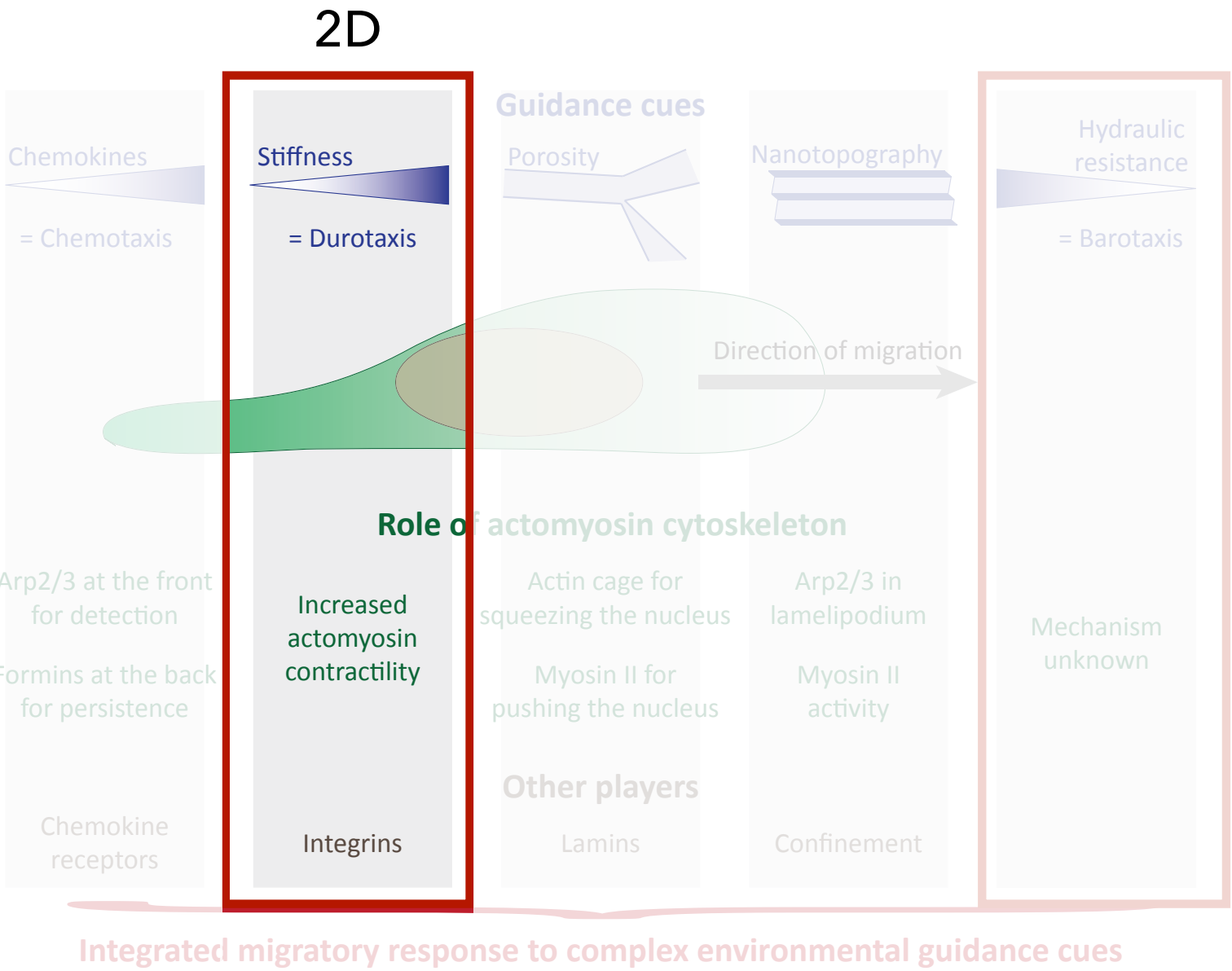
How do cells navigate over long range in situ (development, immune system, cancer)?

>>Interaction between cells and environment:

cells generate/modify their own guidance cue through such interactions

The structure of the environment matters (eg. confinement)

Durotaxis: substrate stiffness

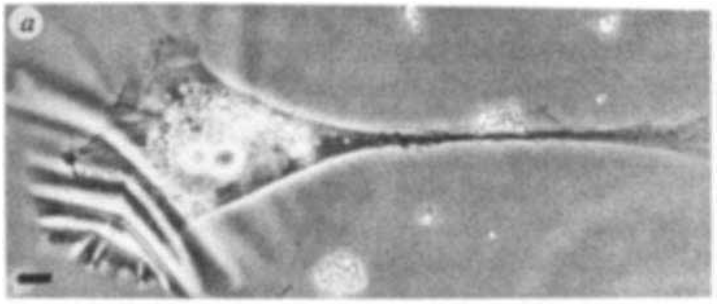


Cells exert traction on substrates

Fibroblast traction as a mechanism for collagen morphogenesis

Albert K. Harris, David Stopak & Patricia Wild

Department of Zoology, University of North Carolina, Wilson Hall 046-A, Chapel Hill, North Carolina 27514, USA

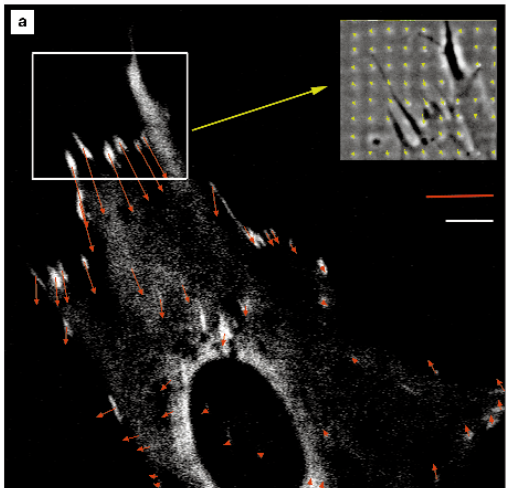


A. Harris, D. Stopak and P. Wild. *Nature*. 290:249-251 (1981)

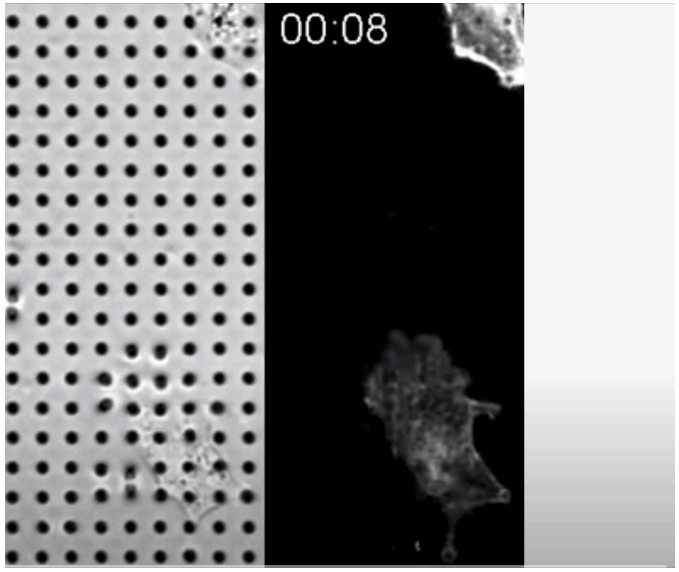
traction force microscopy

Human skin fibroblasts

GFP–vinculin



N. Balaban et al. and B. Geiger. *Nature Cell Biology*. 3: 466-472 (2001)

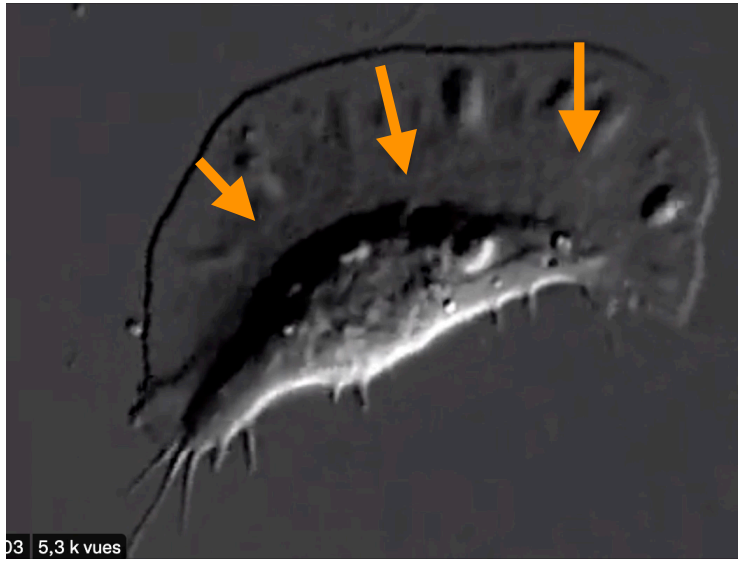


A GFP-integrin beta 1 expressing MDCK cell crawling on a miniature pillar array

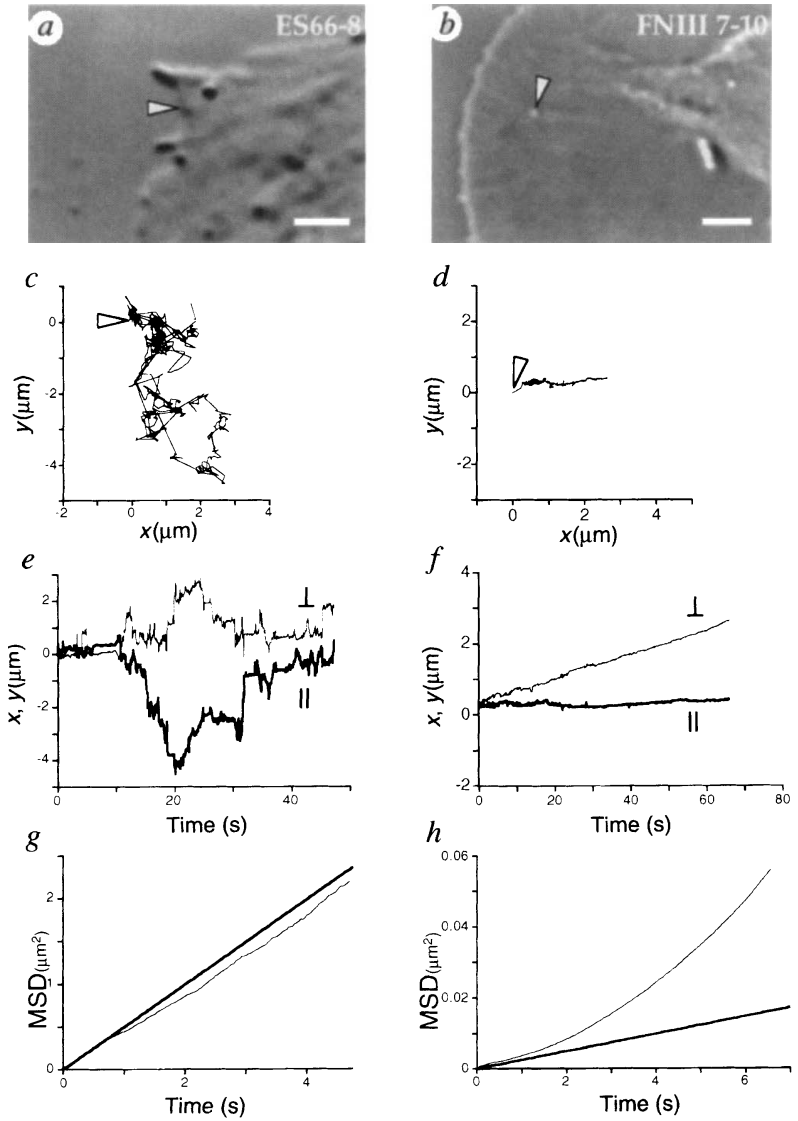
ECM induced Integrin coupling to actin

Binding of extracellular matrix ligand (Fibronectin) induces engagement of Integrin to retrograde actin flow

40 nm colloidal gold particles coated with
Anti ß1 Integrin antibody or Fibronectin type III domains



- Diffusive motion
  ß1 Integrin antibody
- Balistic motion
  Fibronectin domains



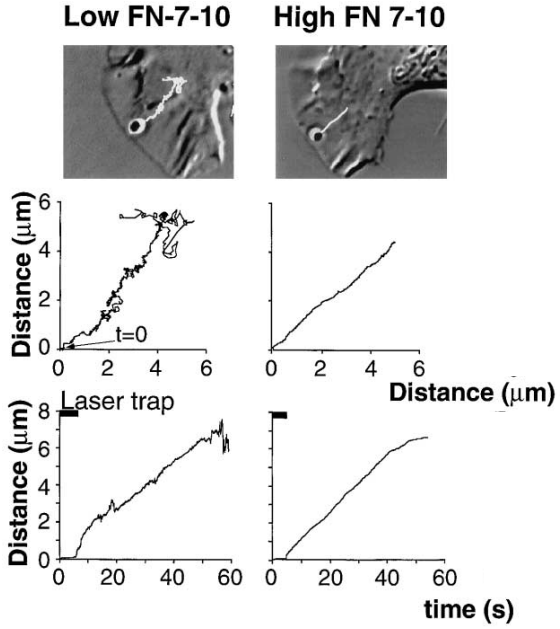
D. Felsenfeld, D. Choquet and M. Sheetz, *Nature*; 383:438-440 (1996)

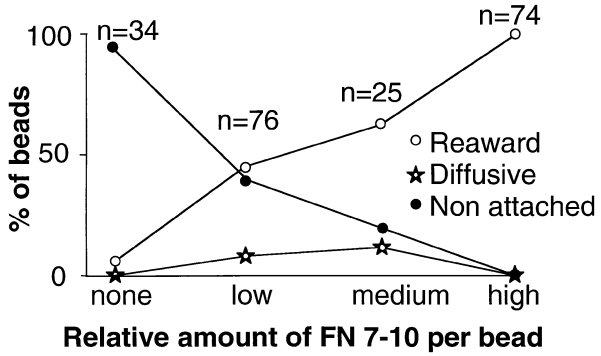
Evidence of Rigidity sensing

Extracellular Matrix Rigidity Causes Strengthening of Integrin–Cytoskeleton Linkages

Michael Sheetz

- Increasing the density of Fibronectin on beads increases directional rearward motion of beads



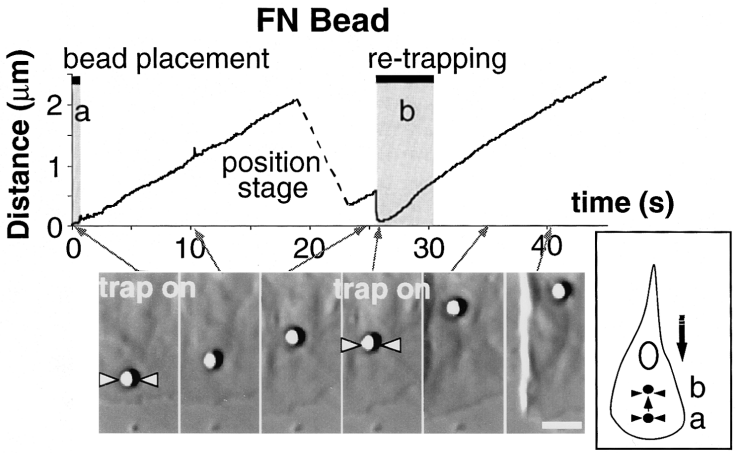


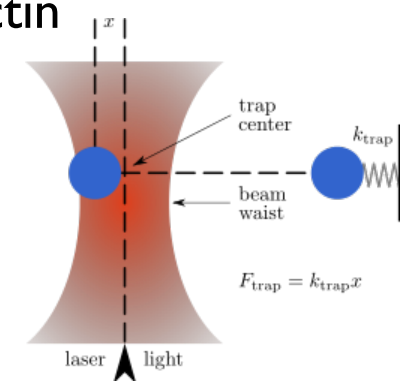
D. Choquet, D. Felsenfeld and M. Sheetz. *Cell*, 88: 39–48, (1997)

Evidence of Rigidity sensing

- Restraining bead motion induces reinforcement of anchoring to actin

Optical trapping of beads (>5pN)
Brief trapping (*a*, <2s), bead escapes the trap
Re-trapping (*b*) moves the beads to the center of the trap

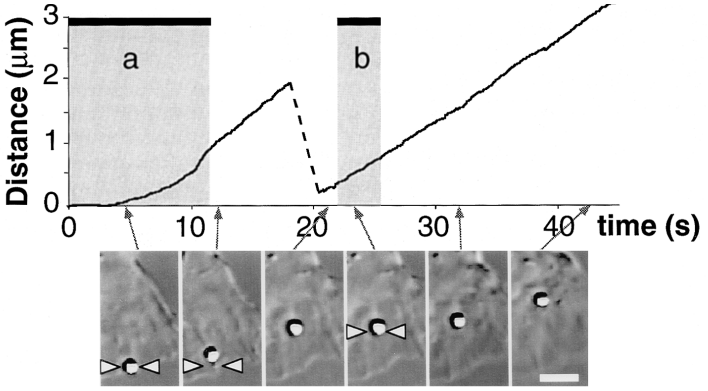




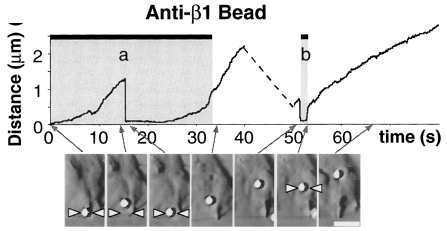
$$F_{min} = (k_{trap}\, k_B\, T)^{1/2}$$

Longer trapping (>10s) holds the bead, which eventually escapes (*a*)
Upon re-trapping (*b*), the bead does not center to the trap and continues rearward movement

—**Reinforcement of FN bead coupling** to actin
Increases with FN density



No reinforcement with anti ß1 coated bead (non-activating antibody)

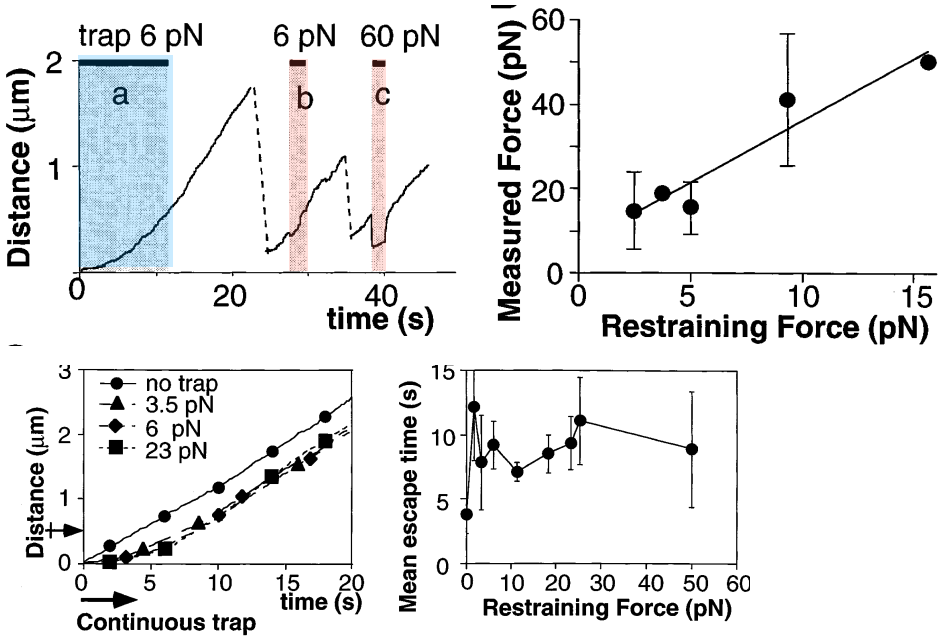


D. Choquet, D. Felsenfeld and M. Sheetz. *Cell*, 88: 39–48, (1997)

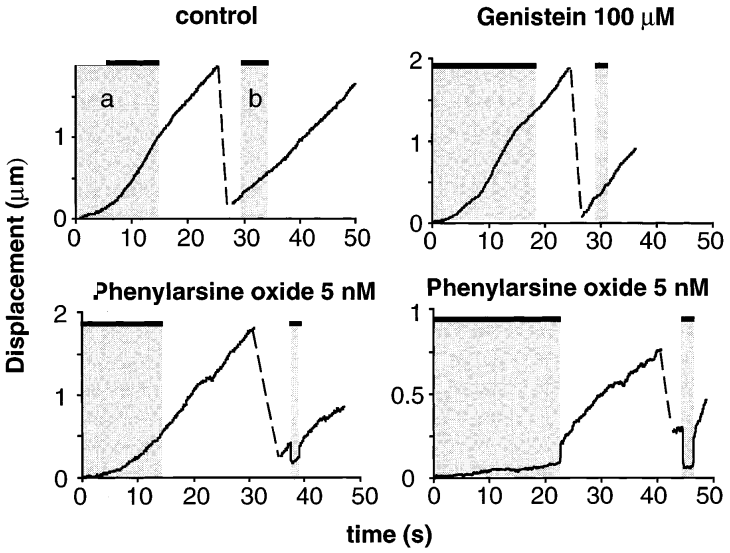
Evidence of Rigidity sensing

- Amount of reinforcement to actin cytoskeleton depends on strength of restraining force
  - The force to hold is ~3times higher than restraining force
  - Kinetics of reinforcement is independent of restraining force
  - Reinforcement is localized (a neighboring (~2µm) bead is unaffected)

Restraining force Measured force to move the bead

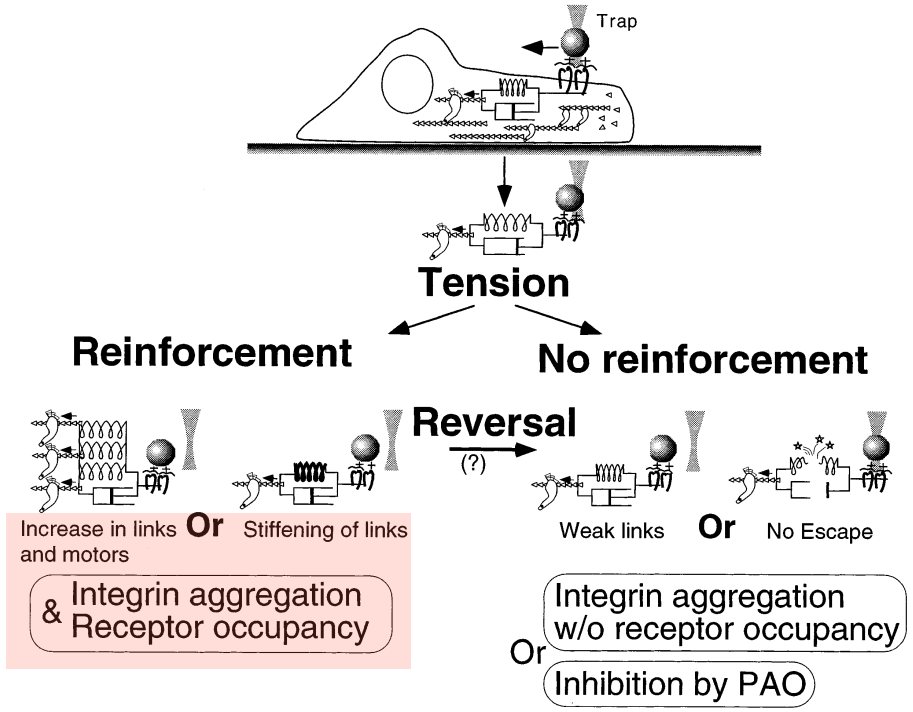


- Reinforcement requires post-translational modifications (tyrosine phosphorylation)



D. Choquet, D. Felsenfeld and M. Sheetz. *Cell*, 88: 39–48, (1997)

Possible mechanisms of Rigidity sensing
Implications: rigidity as a guidance cue



Most models for substrate-based cell guidance have relied on the biochemical nature of the cues delivered to the cell. We propose here that the physical characteristic, namely the resistance to displacement of the substrate, is an additional cue that cells can use to orient during migration.

D. Choquet, D. Felsenfeld and M. Sheetz. *Cell*, 88: 39–48, (1997)

Hypothesis: rigidity as a guidance cue

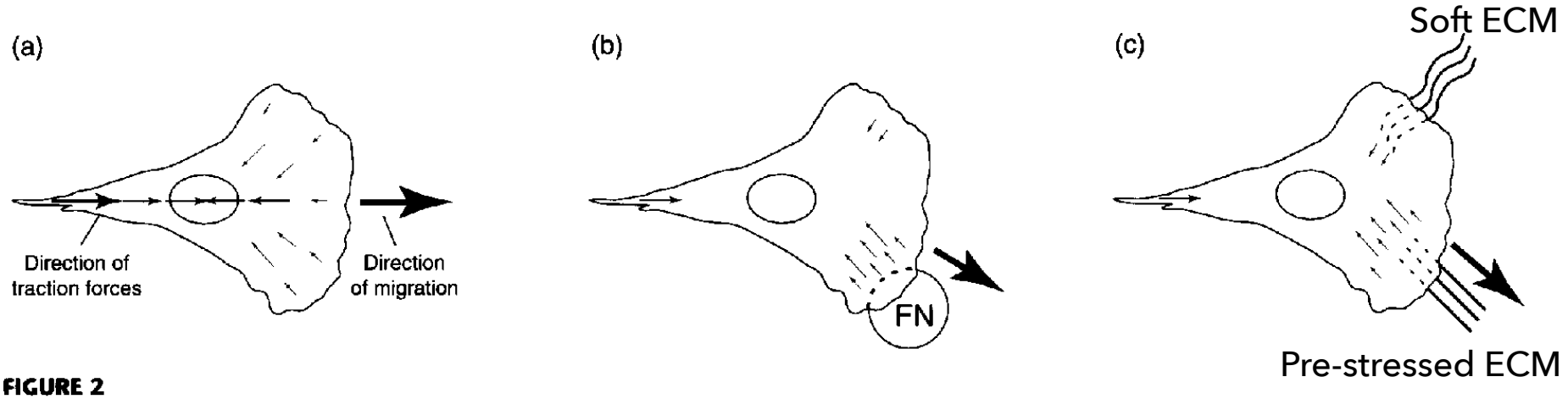


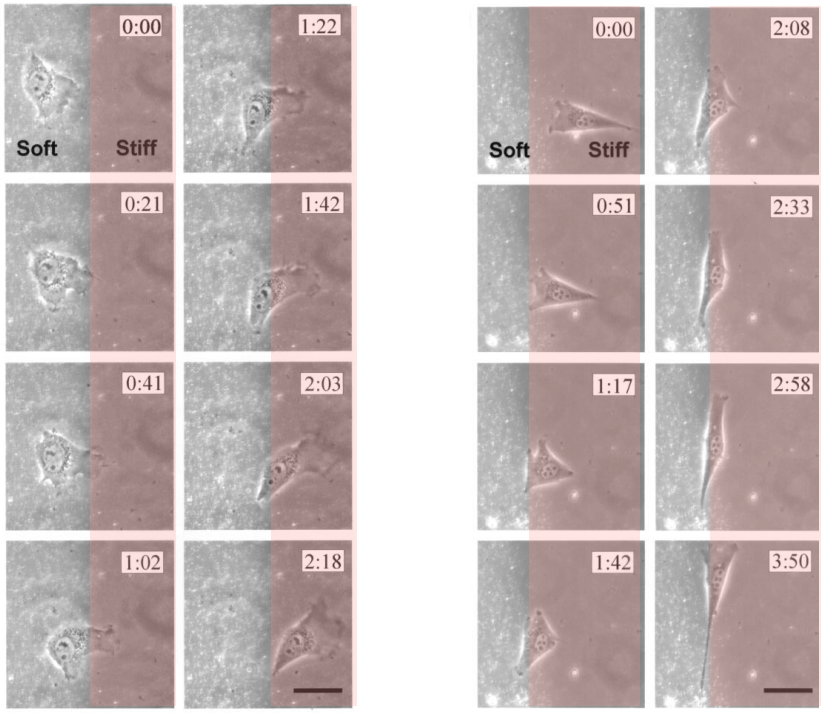
FIGURE 2

Orientation of traction forces in response to environmental cues. (a) When there are no external cues, traction forces (small arrows) in the front of the cell are oriented rearward and traction forces in the back of the cell are oriented forward. For net forward movement to occur (large arrow), the forces in the front of the cell must exceed the forces in the rear by an amount equal to the fluid drag, which is the force imposed on the cell by the surrounding media. (b) When a migrating cell encounters an appropriate molecular cue in its environment [indicated as fibronectin (FN)], the receptors that recognize the cue associate with force-generating components of the cytoskeleton. The increase in traction force generated at that side of the cell (small arrows) causes the cell to turn (large arrow) towards the location of the ligand. (c) The stiffness of the extracellular matrix (ECM) in the cellular environment might also orient the direction of cell migration. The binding of integrins to pre-stressed ECM fibres (straight lines; relaxed ECM shown as wavy lines) would selectively strengthen the linkage between those receptors and the force-generating cytoskeleton at that side of the cell. The localized increase in traction forces (small arrows) causes the cell to turn (large arrow) towards the rigid substrate.

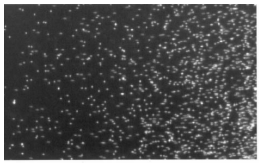
Sheetz, M. P., D. P. Felsenfeld, and C. G. Galbraith. *Trends Cell Biol*. 8:51–54. (1998)

Durotaxis: cell guidance by the rigidity of substrate

In this study, we demonstrate that cell movement can also be guided by purely physical interactions at the cell-substrate interface. We cultured National Institutes of Health 3T3 fibroblasts on flexible polyacrylamide sheets coated with type I collagen. A transition in rigidity was introduced in the central region of the sheet by a discontinuity in the concentration of the bis-acrylamide cross-linker. Cells approaching the transition region from the soft side could easily migrate across the boundary, with a concurrent increase in spreading area and traction forces. In contrast, cells migrating from the stiff side turned around or retracted as they reached the boundary. We call this apparent preference for a stiff substrate "durotaxis."



Collagen density
(rigidity 140-300 kdyn/cm^2)



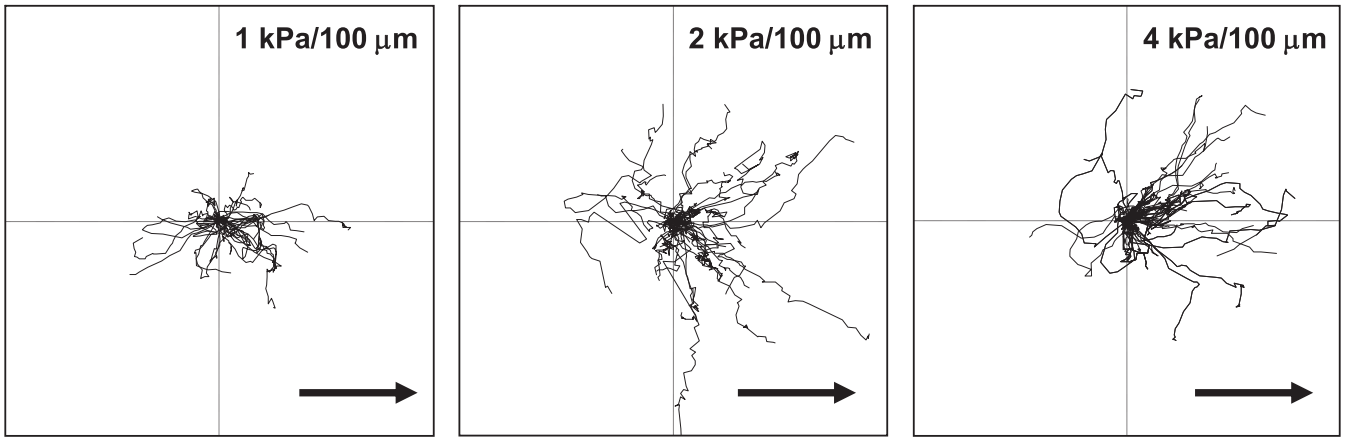
1 dyn = 10^{-5} N
1 kdyn/cm^2 = 100Pa

Young's modulus (kdyn/cm^2)	Traction forces (kdyn/cm^2)	Cell speed (μm/min)
140	6.2 ± 1.3 (n = 6)	0.44 ± 0.23 (n = 33)
300	10.9 ± 3.4 (n = 6)	0.26 ± 0.13 (n = 24)

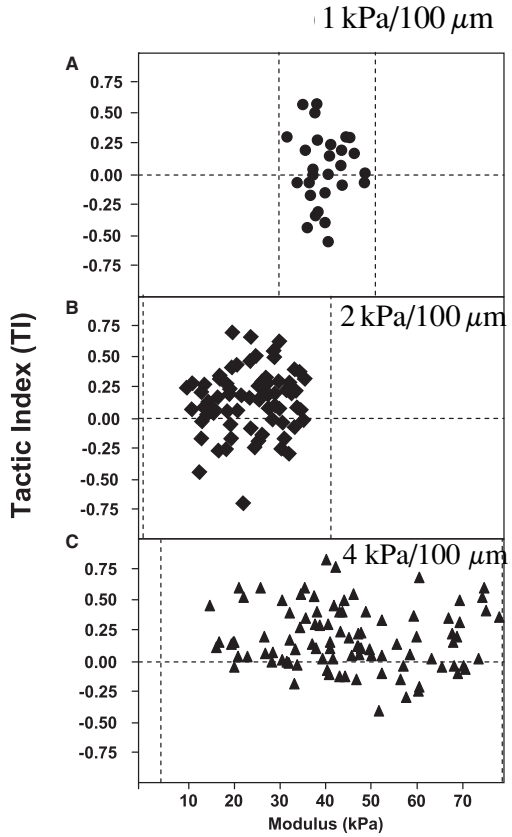
Chun-Min Lo, et al and Yu-loi Wang. *Biophysical Journal* 79:144–152 (2000)

Durotaxis: cell guidance by the rigidity of substrate

Traction index depends only on gradient strength, not on absolute stiffness



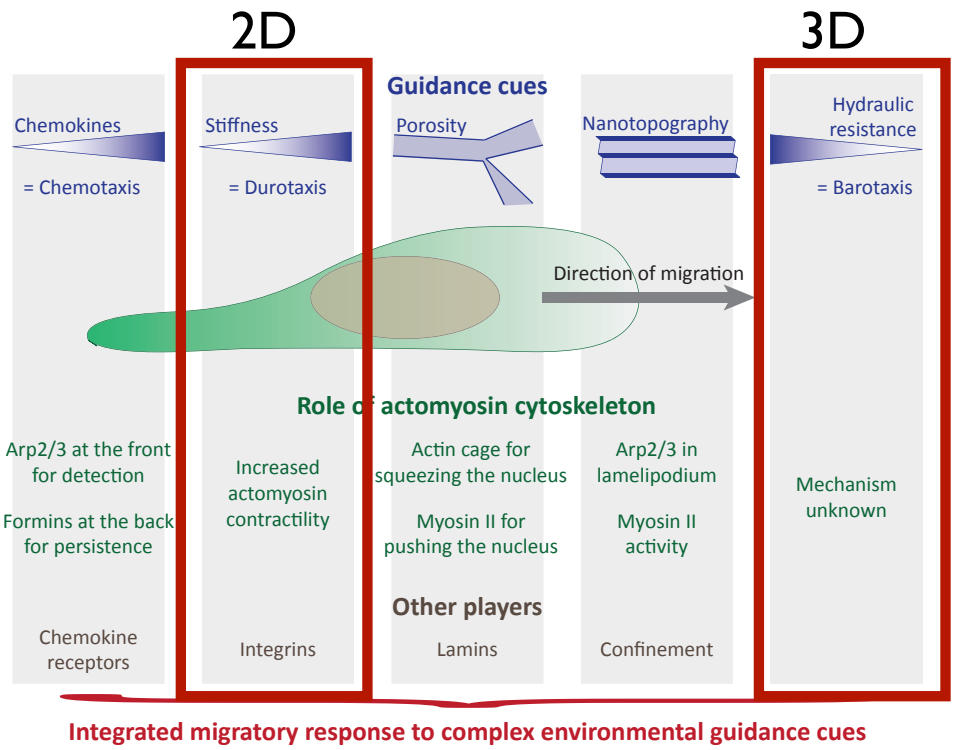
Vascular smooth muscle cells



B. Isenberg et al, and JY Wong *Biophysical Journal* 97:1313–1322 (2009)

Conclusions Course #2

1. Substrate interactions in 2D and 3D are inherently mechanical
2. Cells also decode the mechanical properties of their environment
3. Barotaxis: Hydraulic resistance of fluid can bias cell movement
4. Durotaxis: Substate stiffness gradient can also bias cell movement

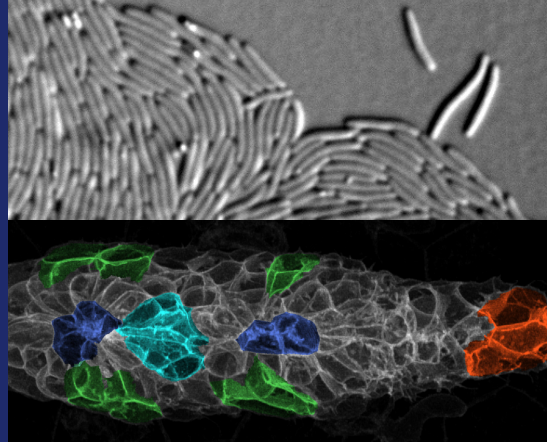


Thomas LECUIT

CHAIRE DYNAMIQUES DU VIVANT

Motilité cellulaire collective

15 novembre > 13 décembre



COURS

Les mardis de 10 h 00 à 11 h 30 – Amphithéâtre Guillaume Budé

15 novembre 2022
Introduction : de la cellule à la supra-cellule

22 novembre 2022
Tactisme mécanique — barotaxie

29 novembre 2022
Tactisme mécanique — durotaxie individuelle et collective

6 décembre 2022
Motilité collective au cours du développement

13 décembre 2022
Motilité collective des bactéries

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Amphithéâtre Maurice Halbwachs

Lundi 19 Juin 2023
Growth and Form

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Thomas Römer
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