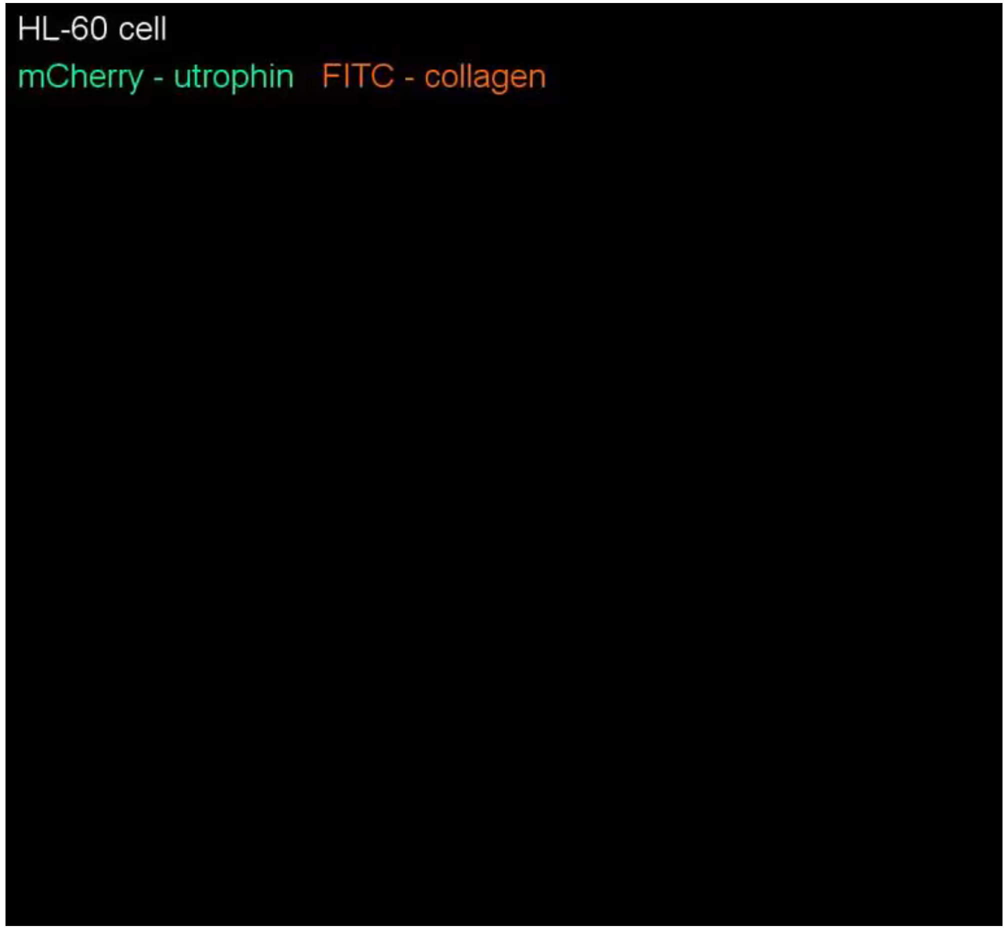
Biological physics and cell migration



Cancerous (leukemic) cell crawling through polymeric collagen environment

Chen… Betzig Science 2014

Brian Camley

Department of Physics & Astronomy
Department of Biophysics
Johns Hopkins University

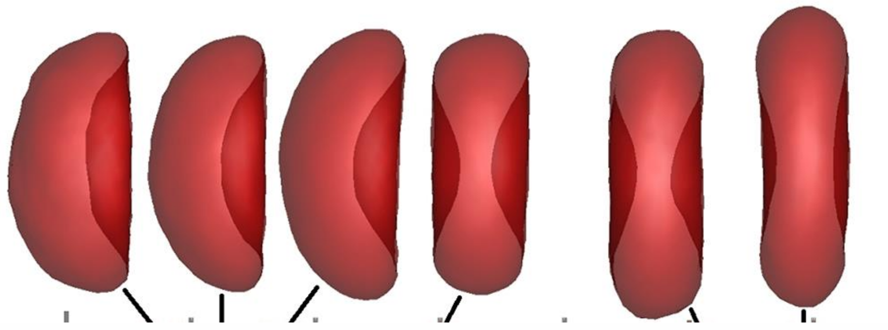
What is biological physics?

National Academies decadal survey: https://www.nationalacademies.org/our-work/biological-physicsphysics-of-living-systems-a-decadal-survey

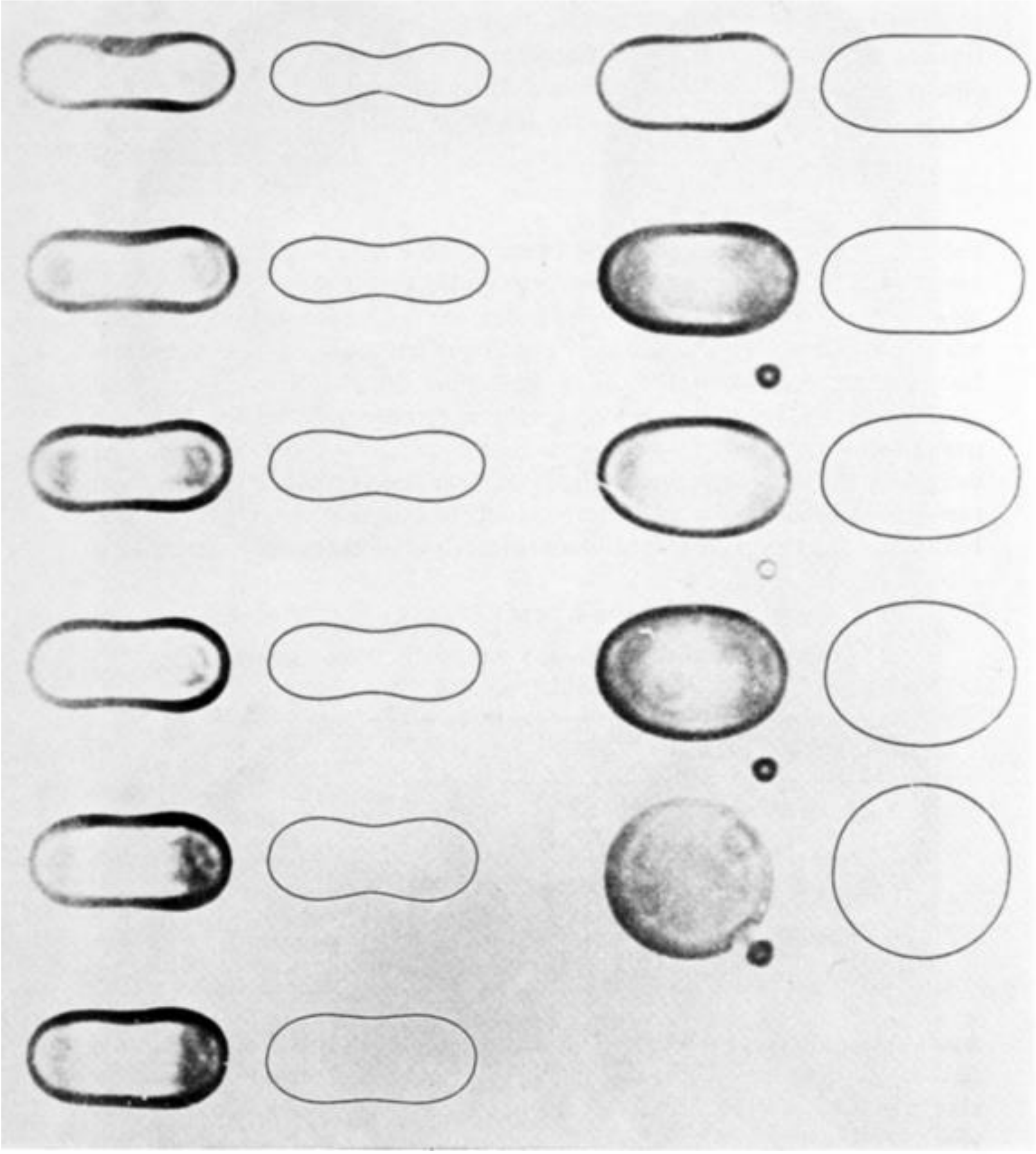
Huge scope!

Mechanics questions:

Why do red blood cells have their characteristic shapes?



Mauer et al. PLOS ONE 2017



Canham 1968

Huge scope!

Mechanics questions:

Why do red blood cells have their characteristic shapes?

How can you pack 1 meter of DNA into a nucleus of a cell (a few microns across)?

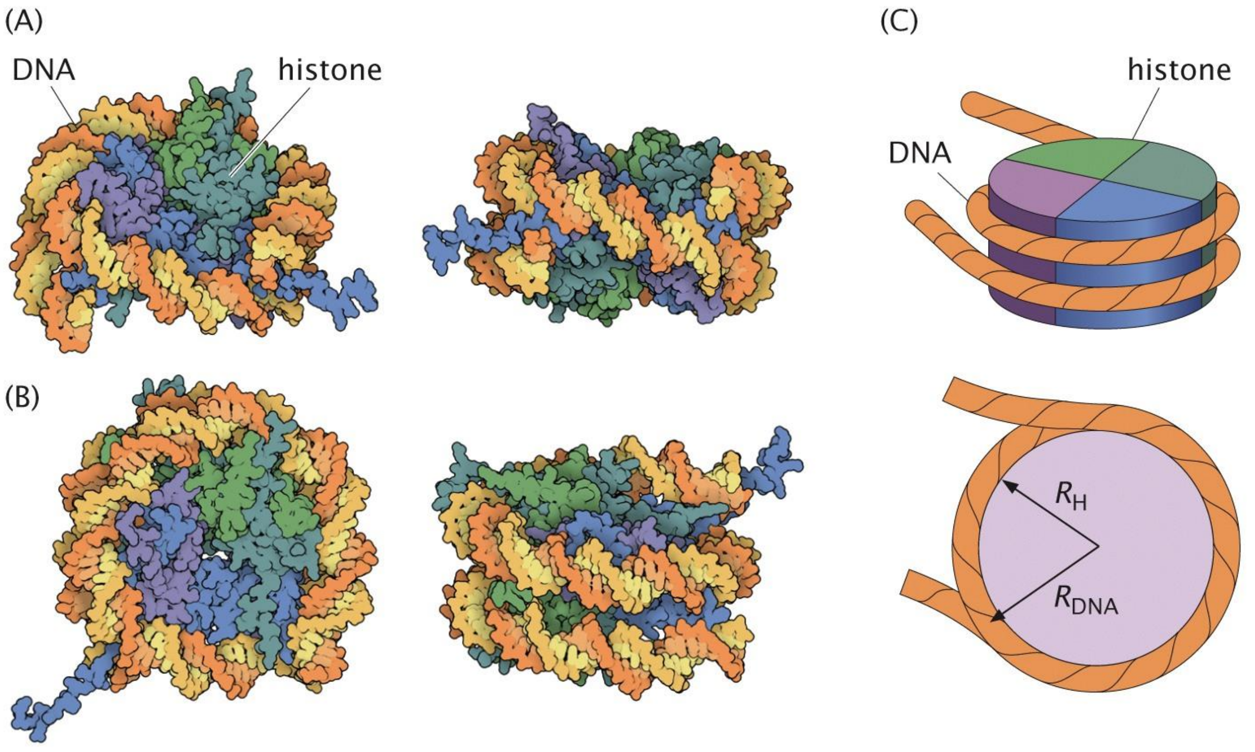


Figure 10.21 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Huge scope!

Mechanics questions:

Why do red blood cells have their characteristic shapes?

How can you pack 1 meter of DNA into a nucleus of a cell (a few microns across)?

Information questions:

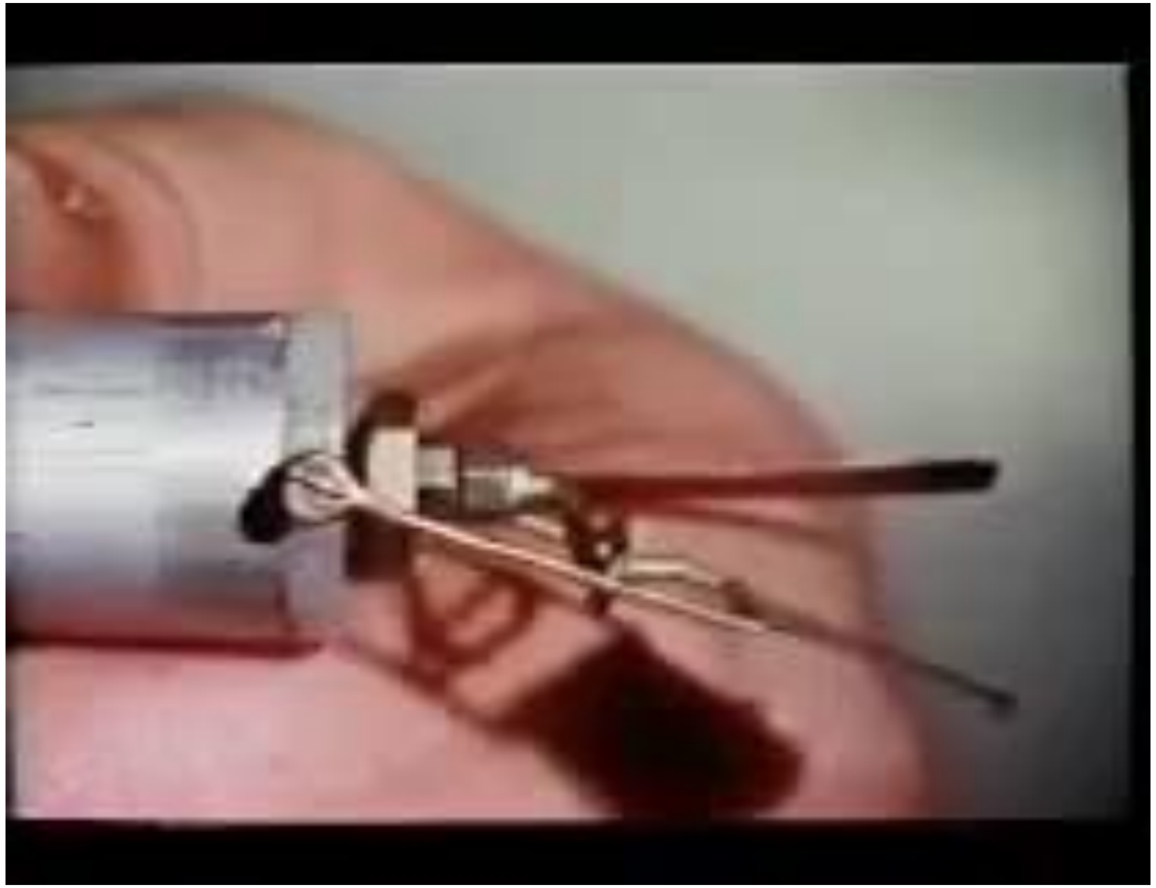
How do cells follow chemical cues?

How does the brain process information reliably?

How do groups of animals cooperate?

If you’re curious: https://www.nationalacademies.org/our-work/biological-physicsphysics-of-living-systems-a-decadal-survey

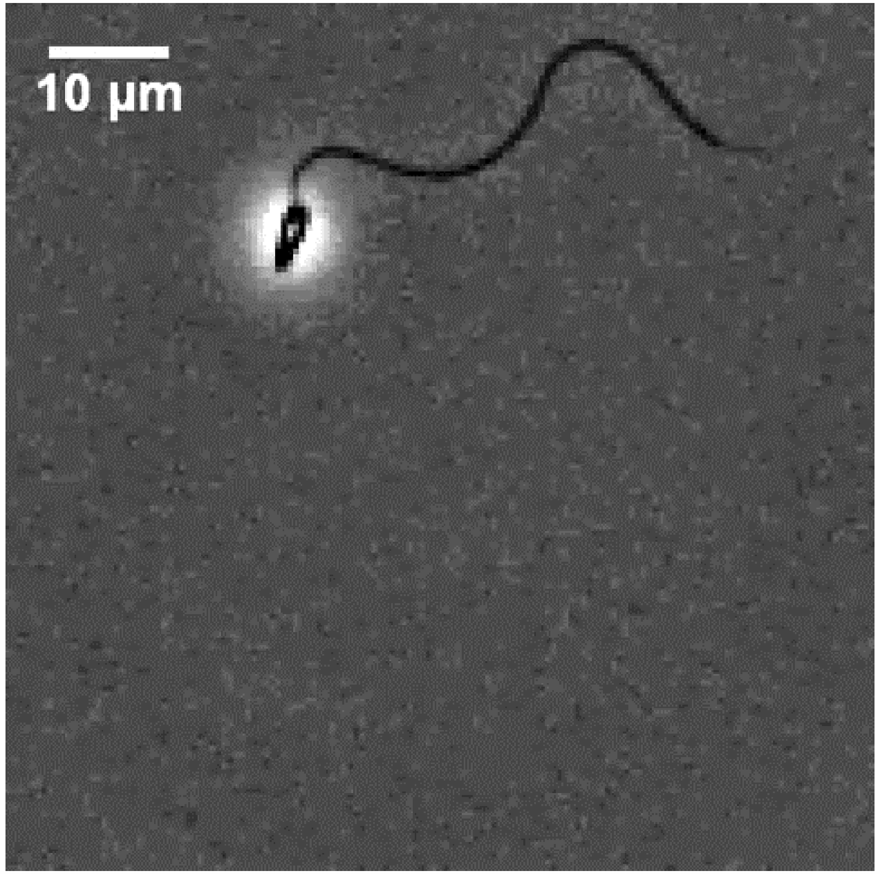
Swimming at low Reynolds numbers (high friction, low inertia)



See: “Life at Low Reynolds Number” by EM Purcell 1977

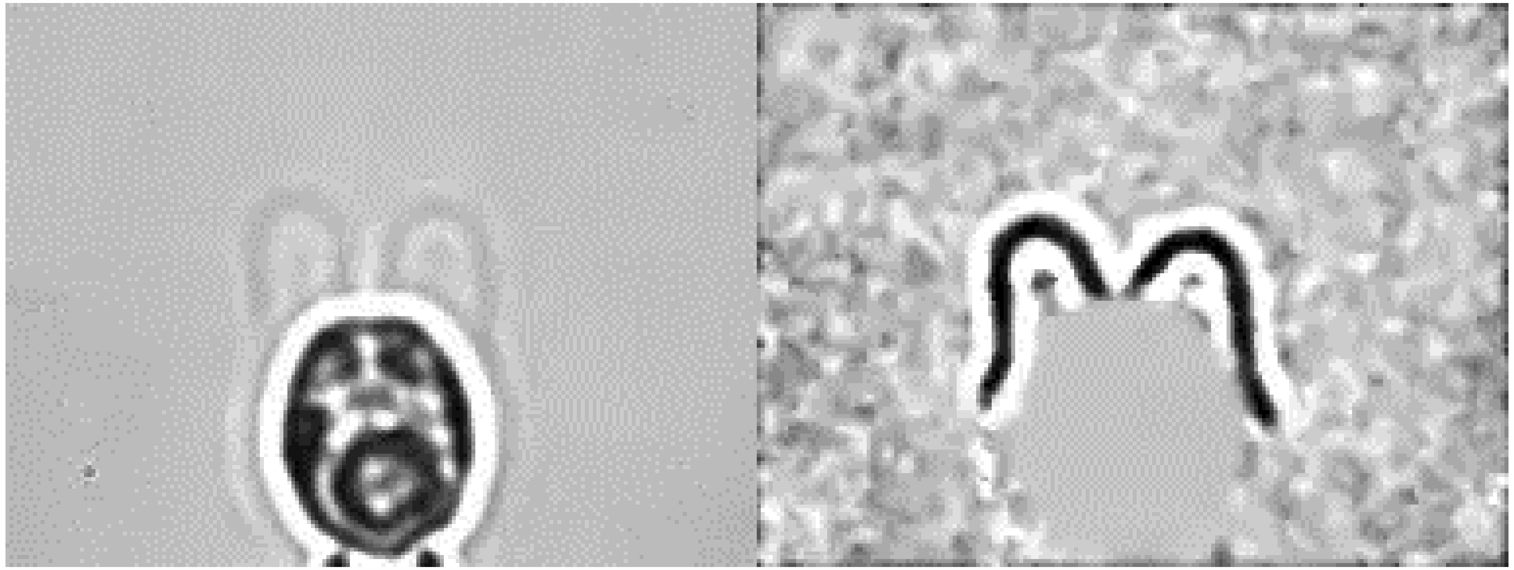
GI Taylor

Swimming at low Reynolds numbers



Sea urchin sperm (Jeffrey Guasto lab, Tufts)

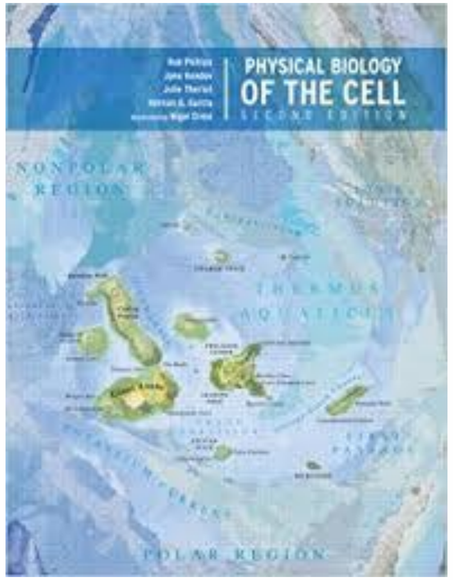
Chlamydomonas (K.C Leptos, Ray Goldstein lab)



See: “Life at Low Reynolds Number” by EM Purcell 1977

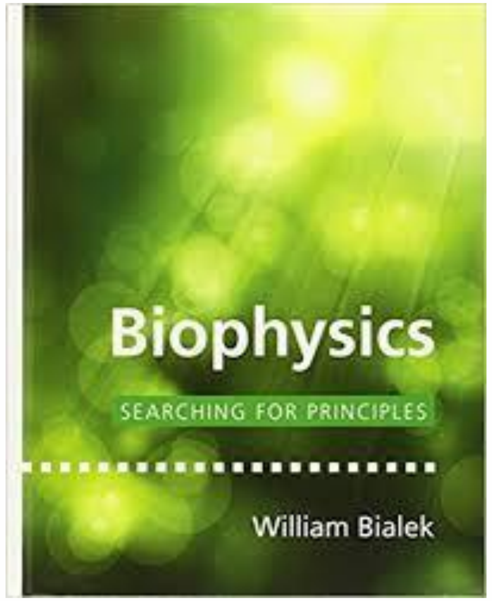
Some useful textbooks

Lots of material online: bionumbers.org



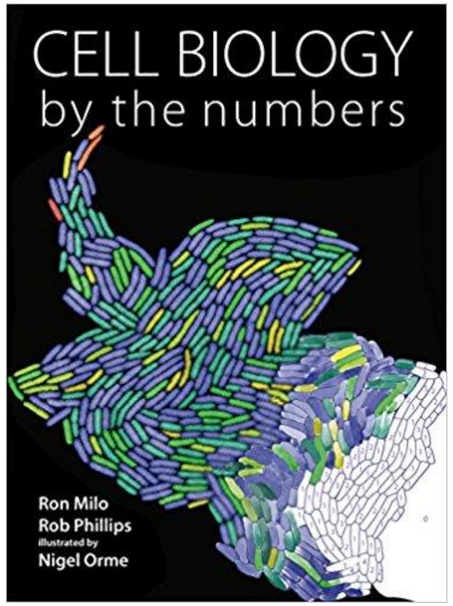
Physical Biology of the Cell
Philips, Kondev, Theriot, Garcia

Giant, useful reference
Digital copies of illustrations on website

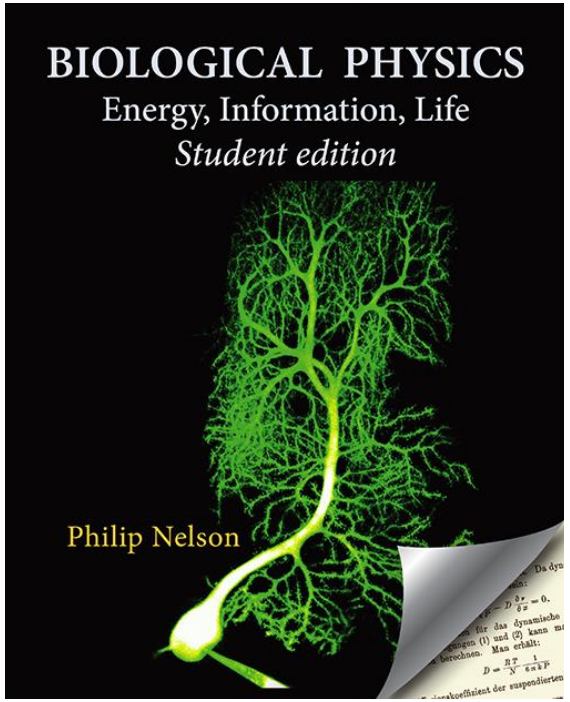


Biophysics:
Searching for Principles
Bialek

(draft copy freely available on Bialek's website)

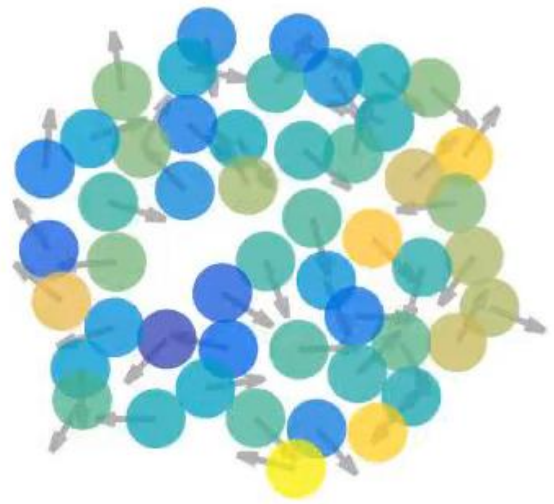


Cell Biology by the numbers
Milo and Philips



Biological Physics
Has some advanced material but most requires no math beyond calc
(~$30 in print, $10 kindle)

Story 1: Collective Chemotaxis, or How Cells Work Together by Competing



Chemotaxis in a single cell

~15 µm

About 60x realtime

Dictyostelium movie from RA Firtel group, UCSD

Collective cell motility

400 microns

1 second = 2 hrs
20 min real time

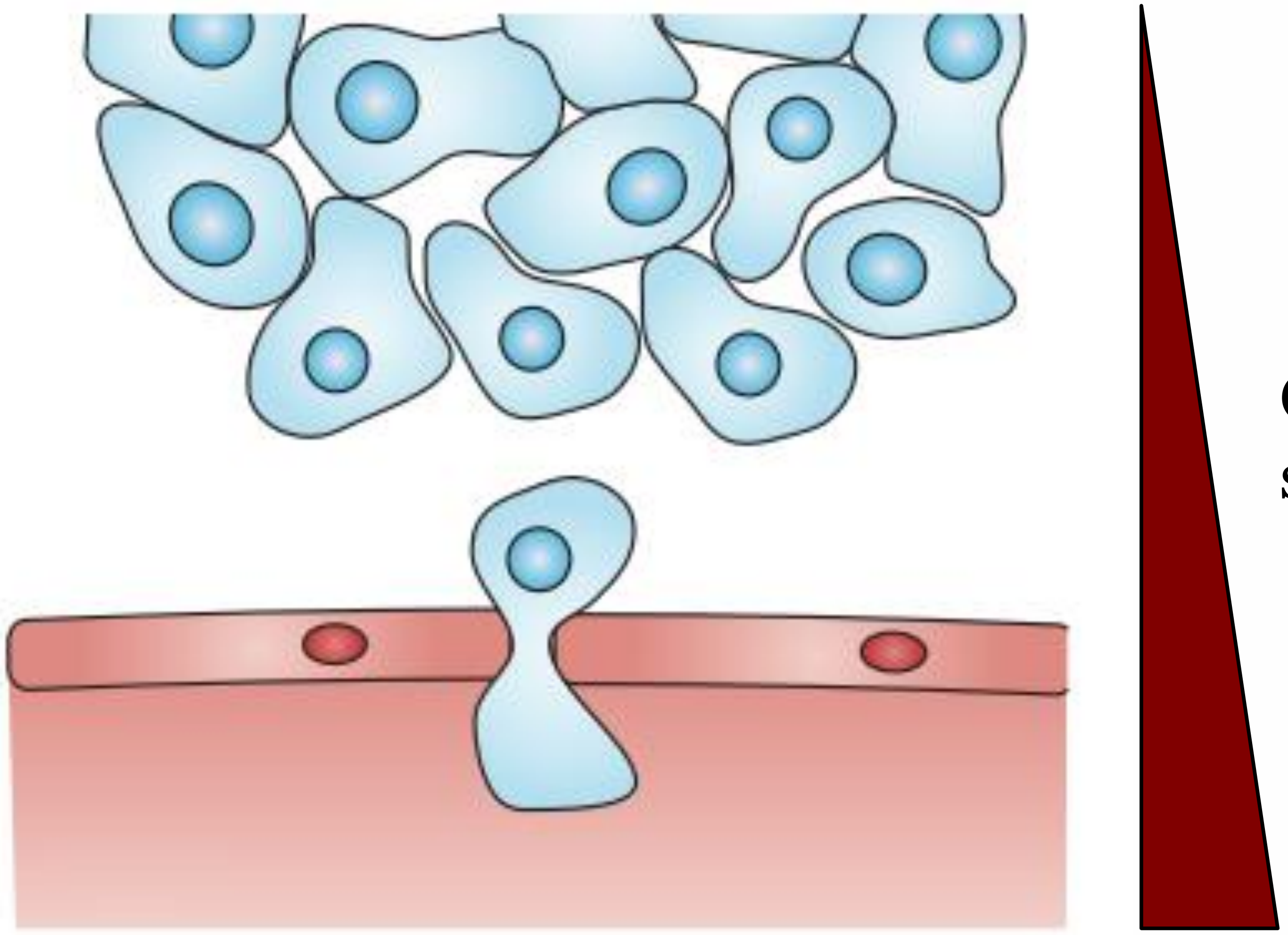
Vedula et al.
PNAS 2012

How does a collection of cells follow a chemical signal?

Why study chemotaxis?

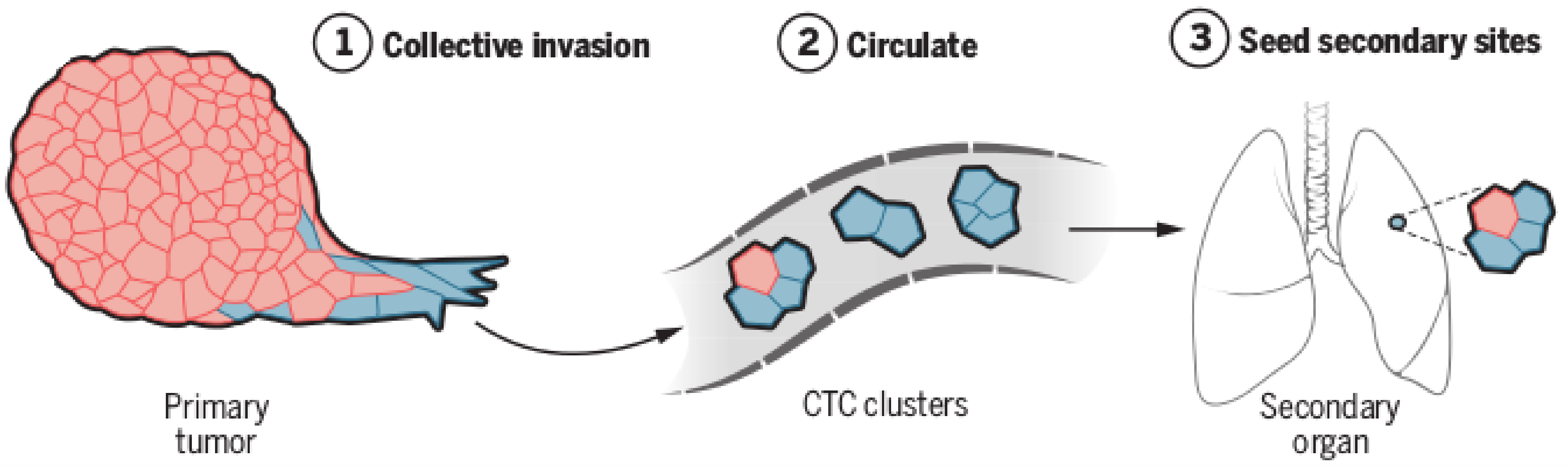
Neutrophil chasing bacterium
originally taken by David Rogers;
http://biochemweb.org/neutrophil.shtml

Why study chemotaxis?



See, e.g. “Chemotaxis in Cancer” Nat. Rev. Cancer 2011

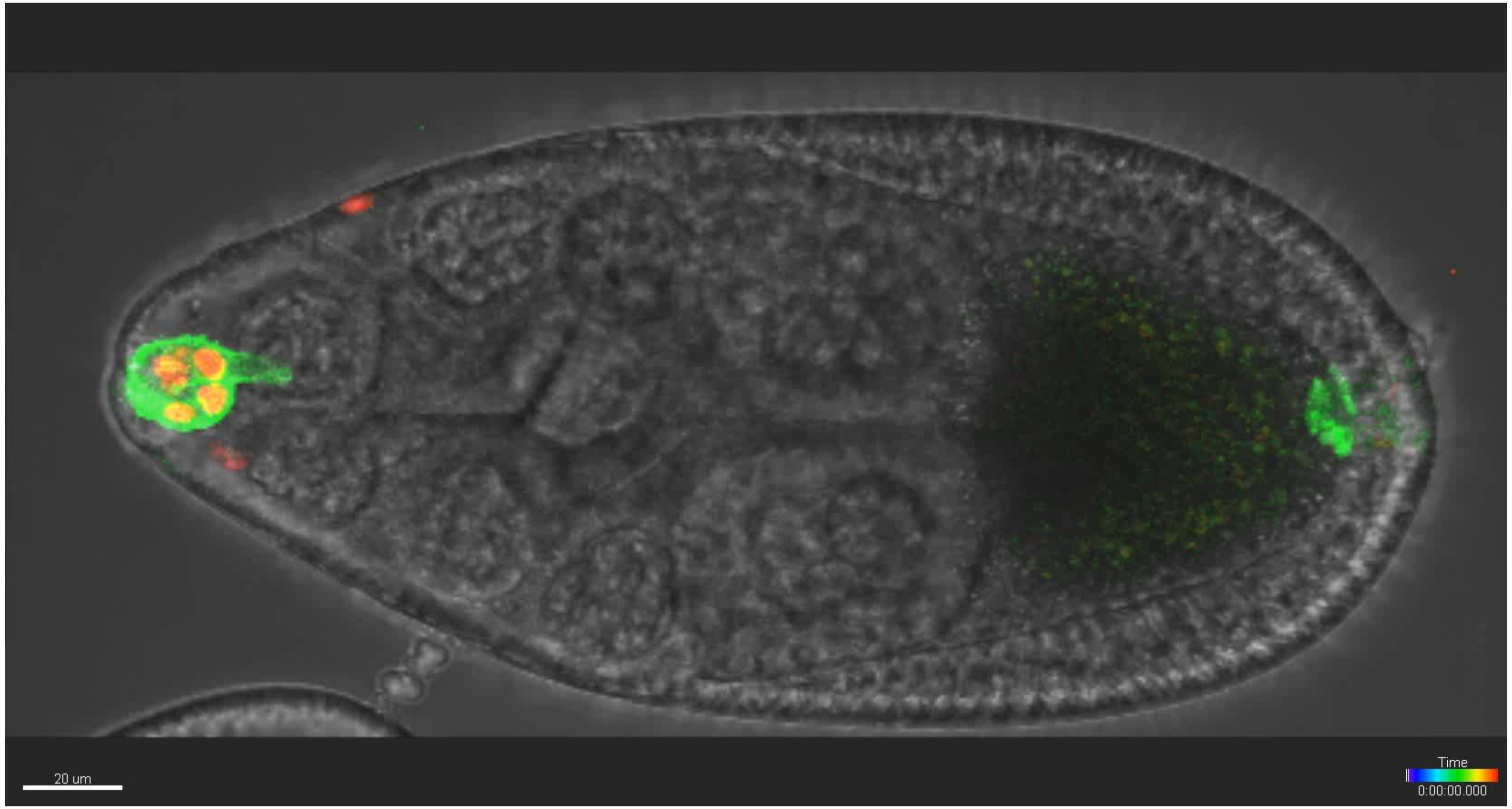
Why study clusters?



Cheung and Ewald, Science, 2016

Why study clusters?

Cells in the developing embryo travel together, too



Drosophila egg chamber: movie courtesy Wei Dai (Denise Montell group, UCSB)

Why do physicists bring to chemotaxis and cell motility?

Why should physicists study chemotaxis and cell motility?

Cells are soft matter

Why should physicists study chemotaxis and cell motility?

Cells are soft matter

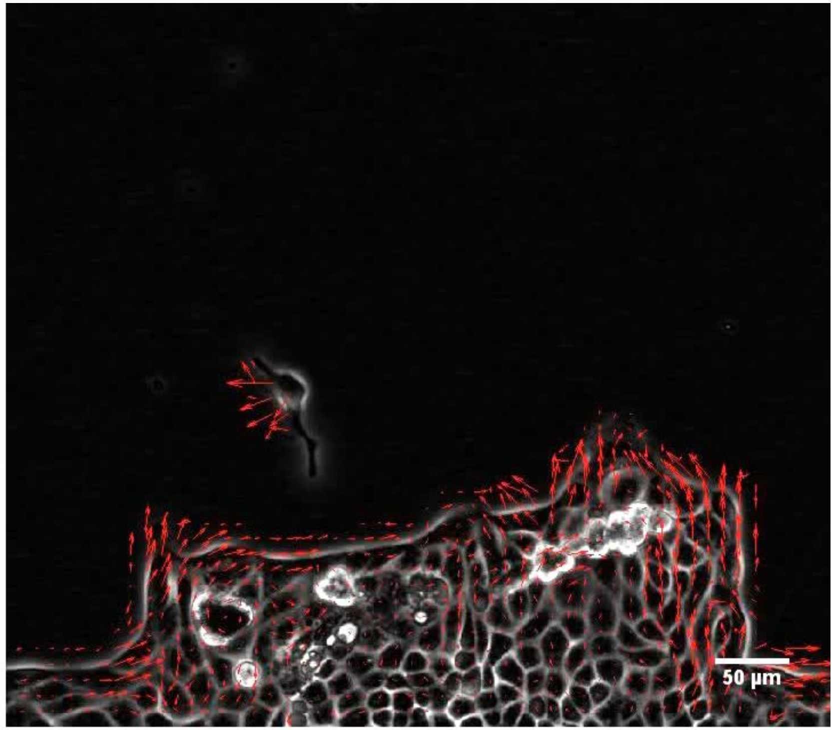
Cell motion is stochastic

Why should physicists study chemotaxis and cell motility?

Cells are soft matter

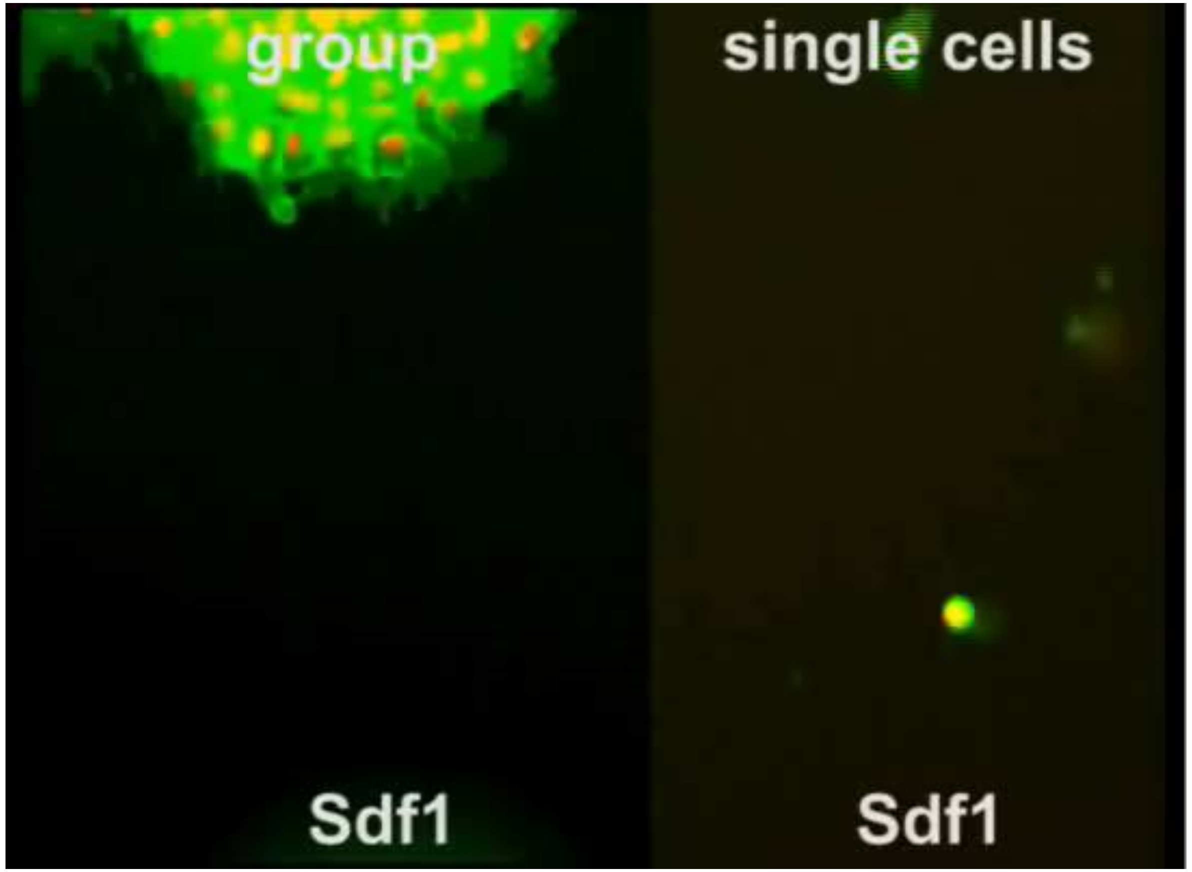
Cell motion is stochastic

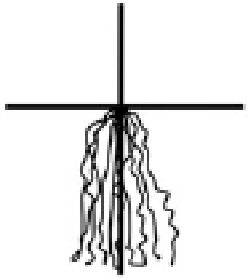
Collections of cells have emergent behaviors



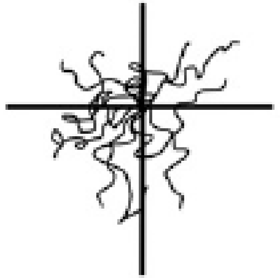
Interesting observations on collective gradient sensing

Neural crest chemotaxis *in vitro*

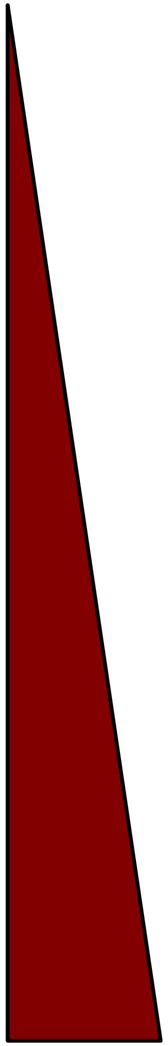




Aggregated cells

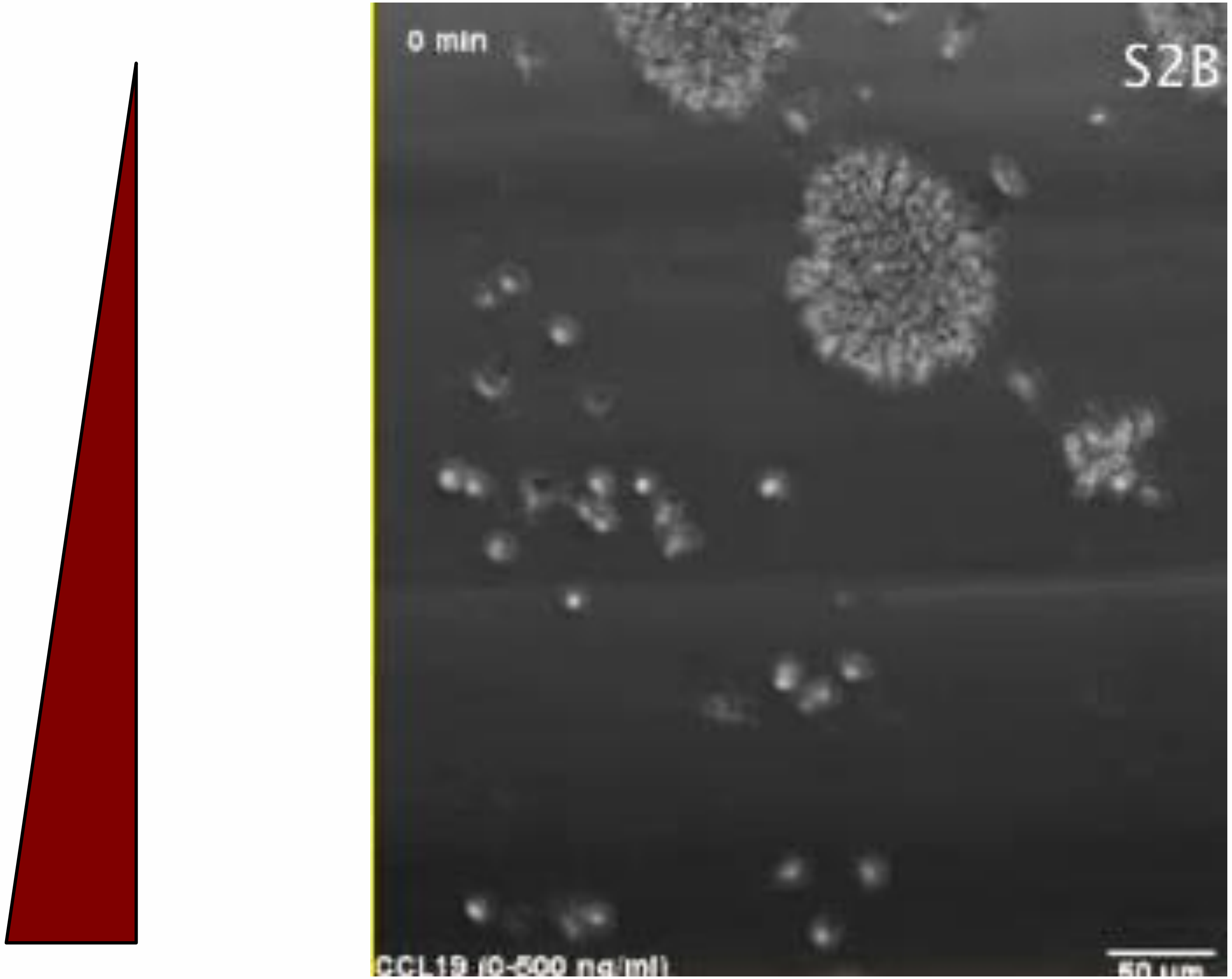


Single cells



Theveneau et al. Dev. Cell 2010

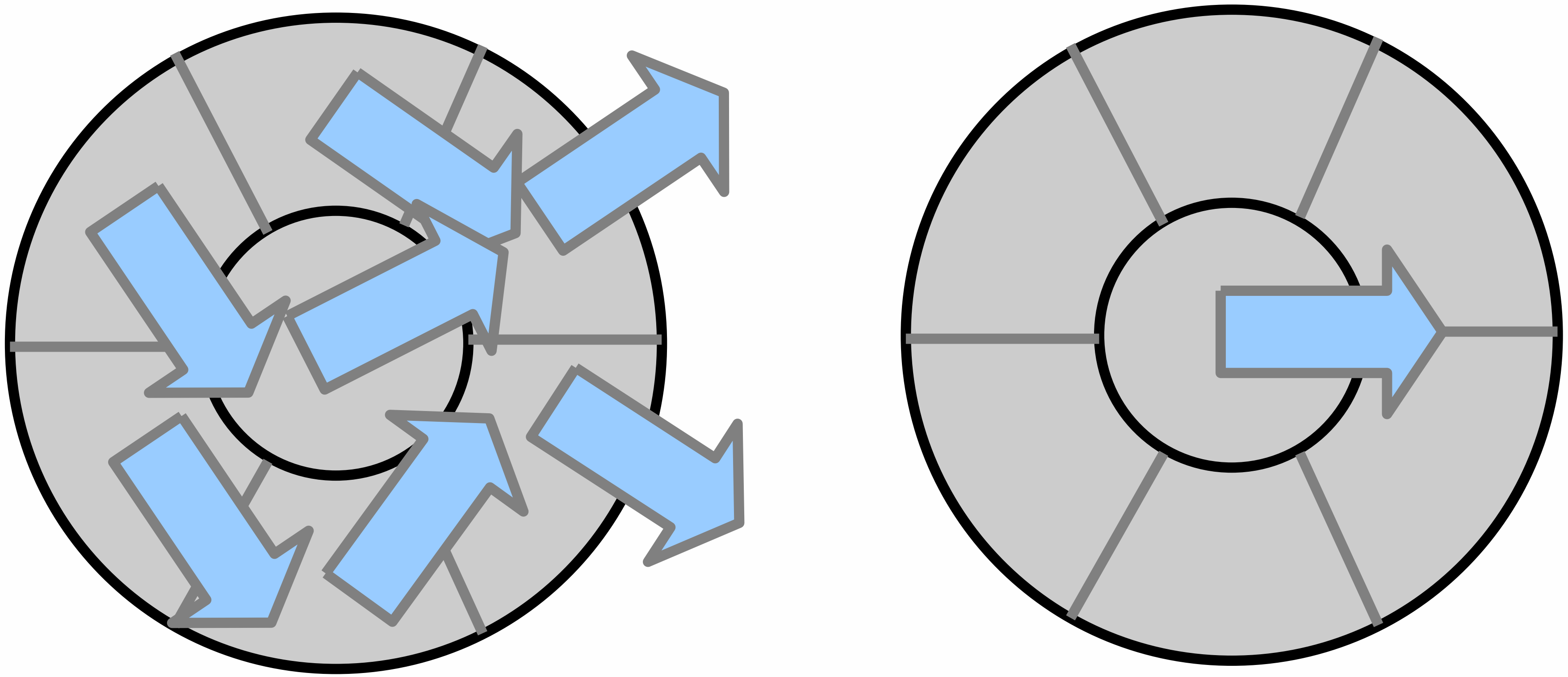
Lymphocytes being chemorepelled?



Malet-Engra et al. Current Biology 2015

How can a cluster of cells follow a gradient when the individual cells don't?

“Many wrongs”



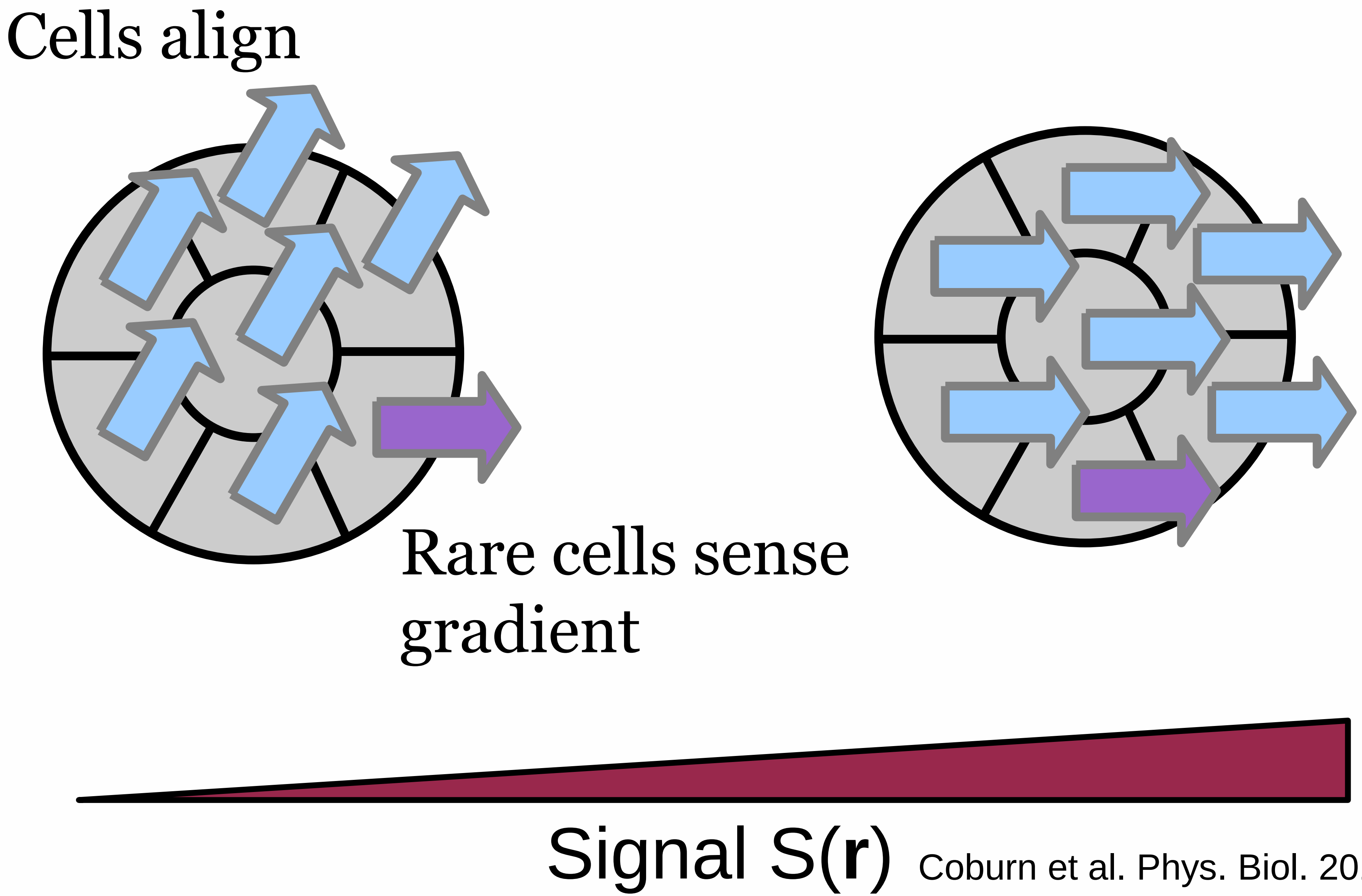
Noisy single-cell polarities

Cluster motion is less noisy

Signal S(**r**)

e.g. Simons Trends. Ecol. Evol. 2004

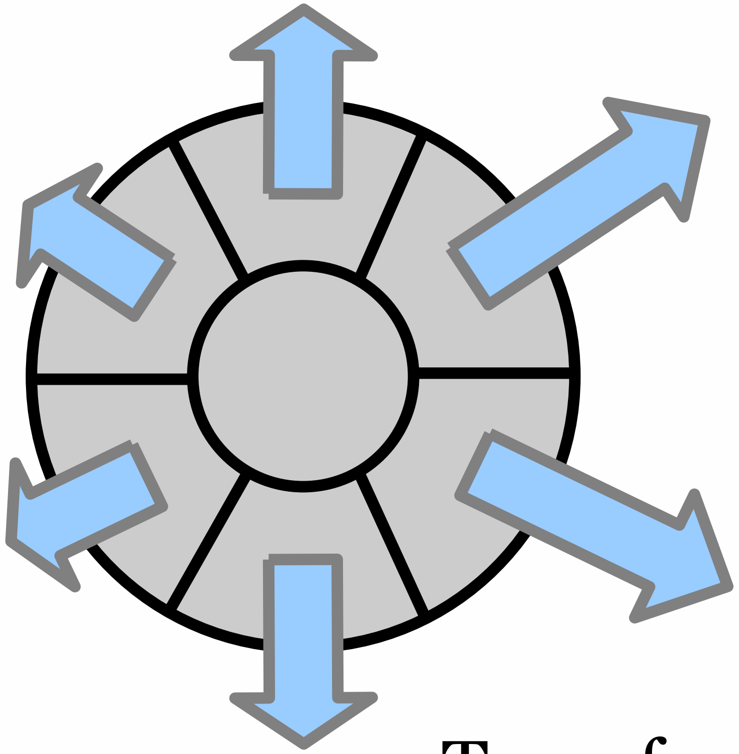
“Collective susceptibility”



Coburn et al. Phys. Biol. 2013
Hopkins and Camley, Phys. Rev. E 2019

"Collective guidance"

Cells sense *level* of signal

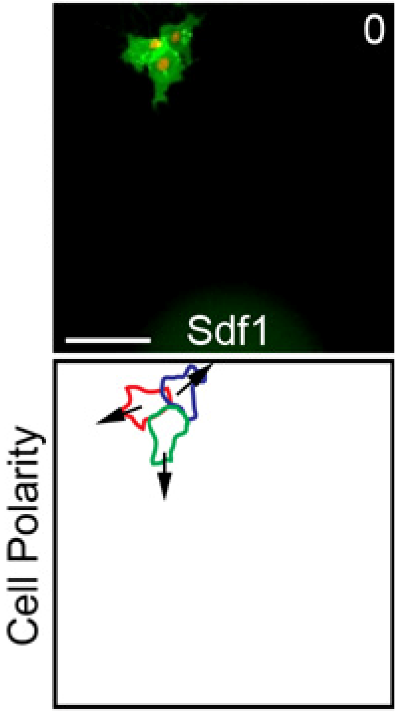


after Rørth, Curr. Opin. Cell Biol. 2007

A minimal model for “collective guidance” in neural crest

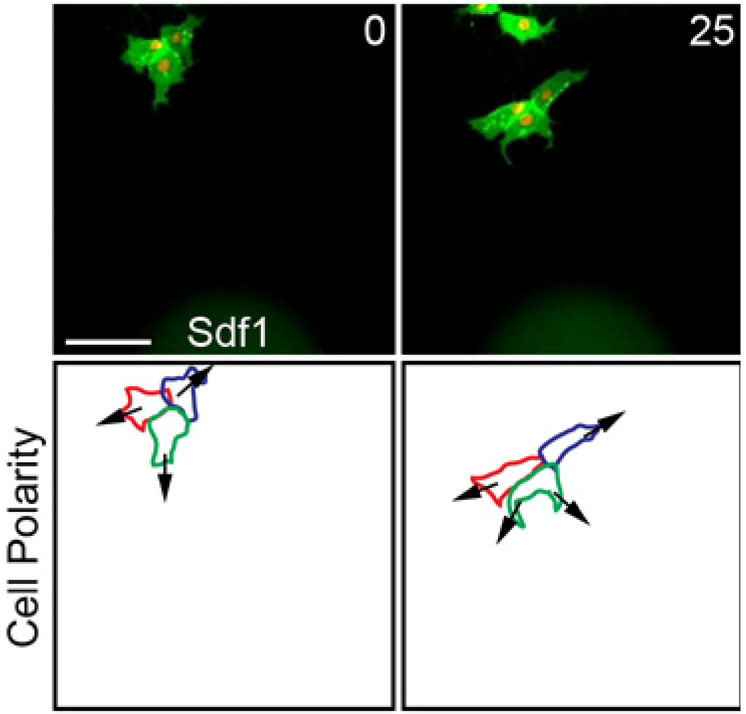
Work from Camley, Zimmermann, Levine, and Rappel, Phys. Rev. Lett. 2016

Contact inhibition of locomotion (CIL)



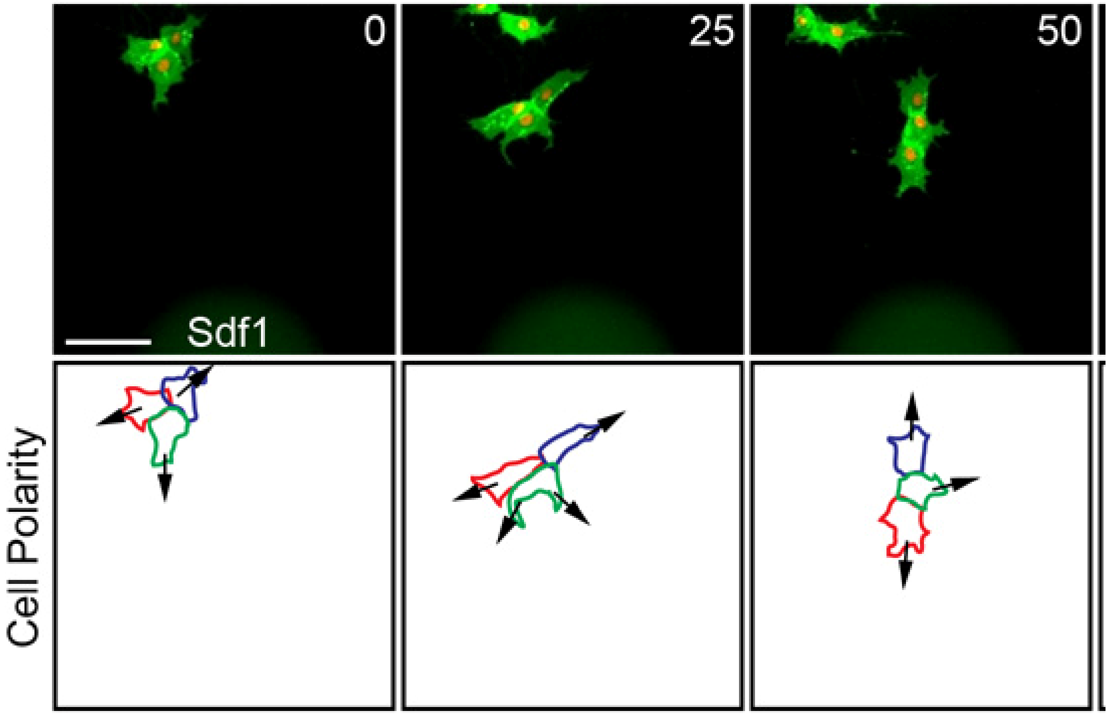
Theveneau et al. Dev. Cell 2010

Contact inhibition of locomotion (CIL)



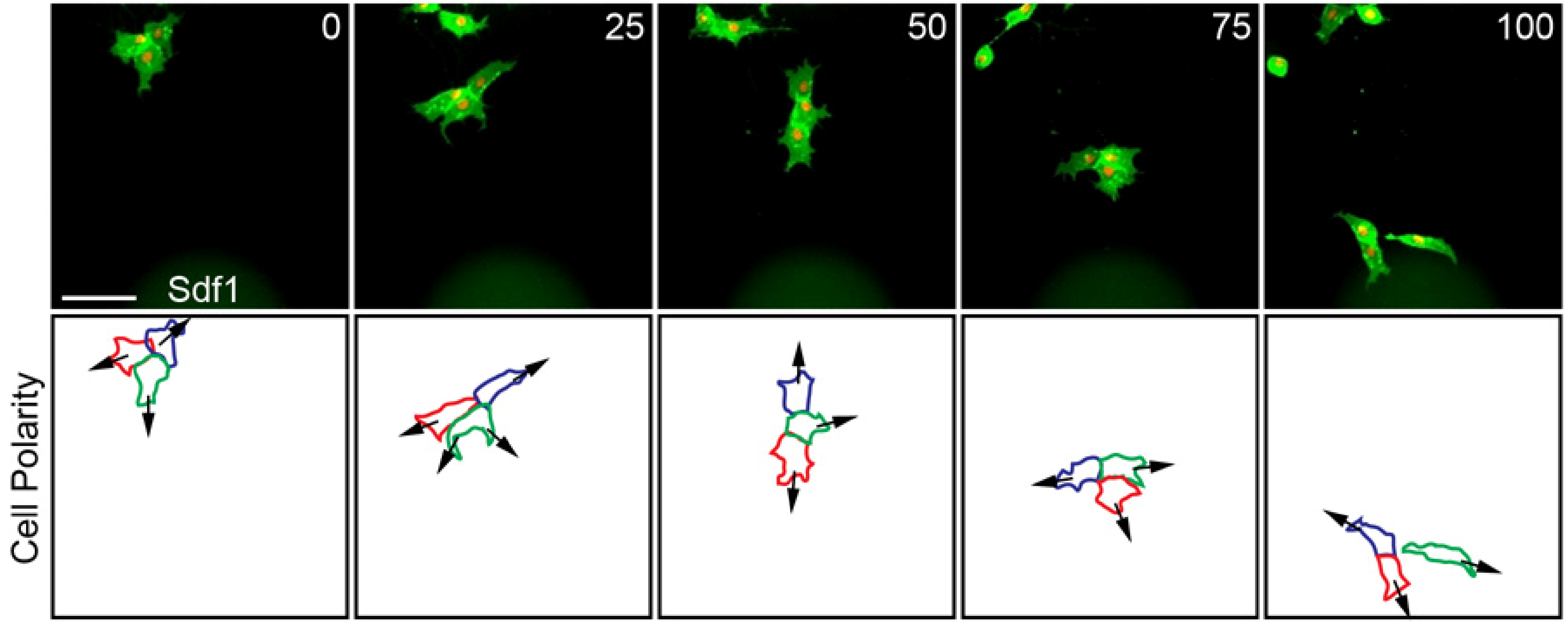
Theveneau et al. Dev. Cell 2010

Contact inhibition of locomotion (CIL)



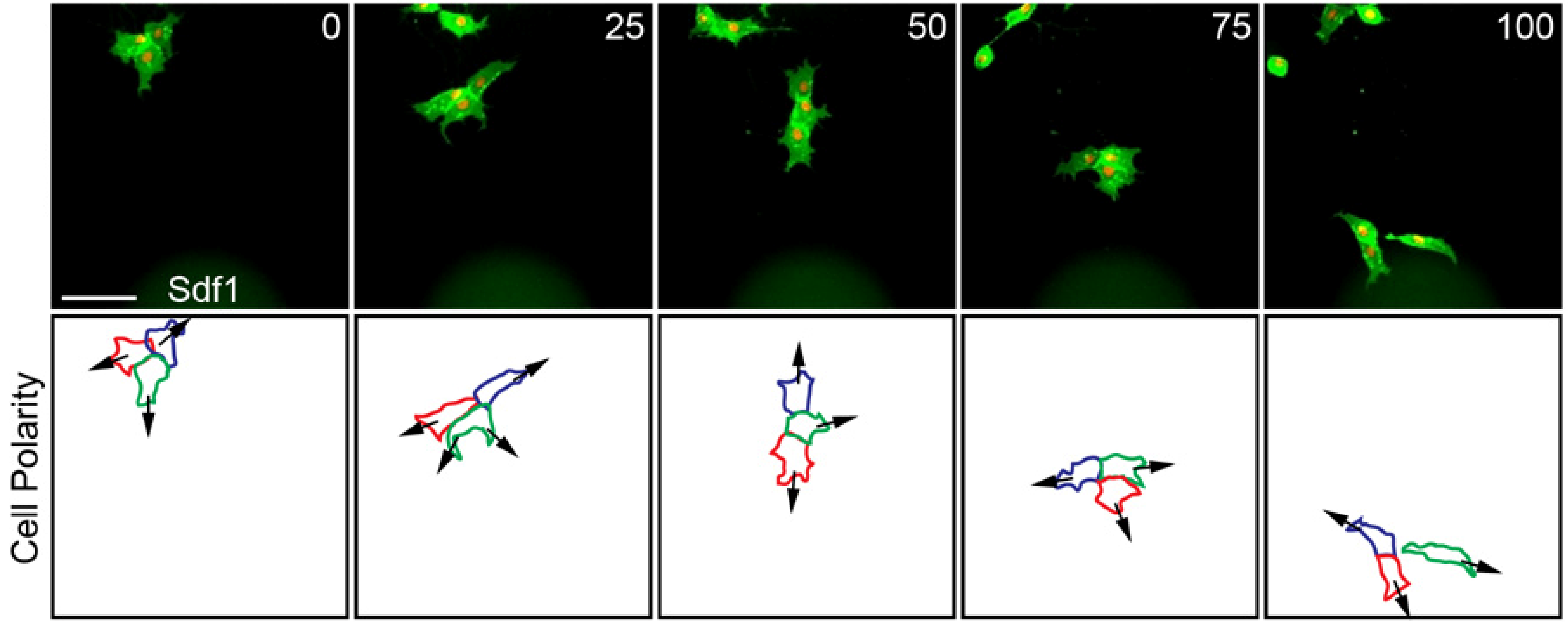
Theveneau et al. Dev. Cell 2010

Contact inhibition of locomotion (CIL)



Theveneau et al. Dev. Cell 2010

Contact inhibition of locomotion (CIL)

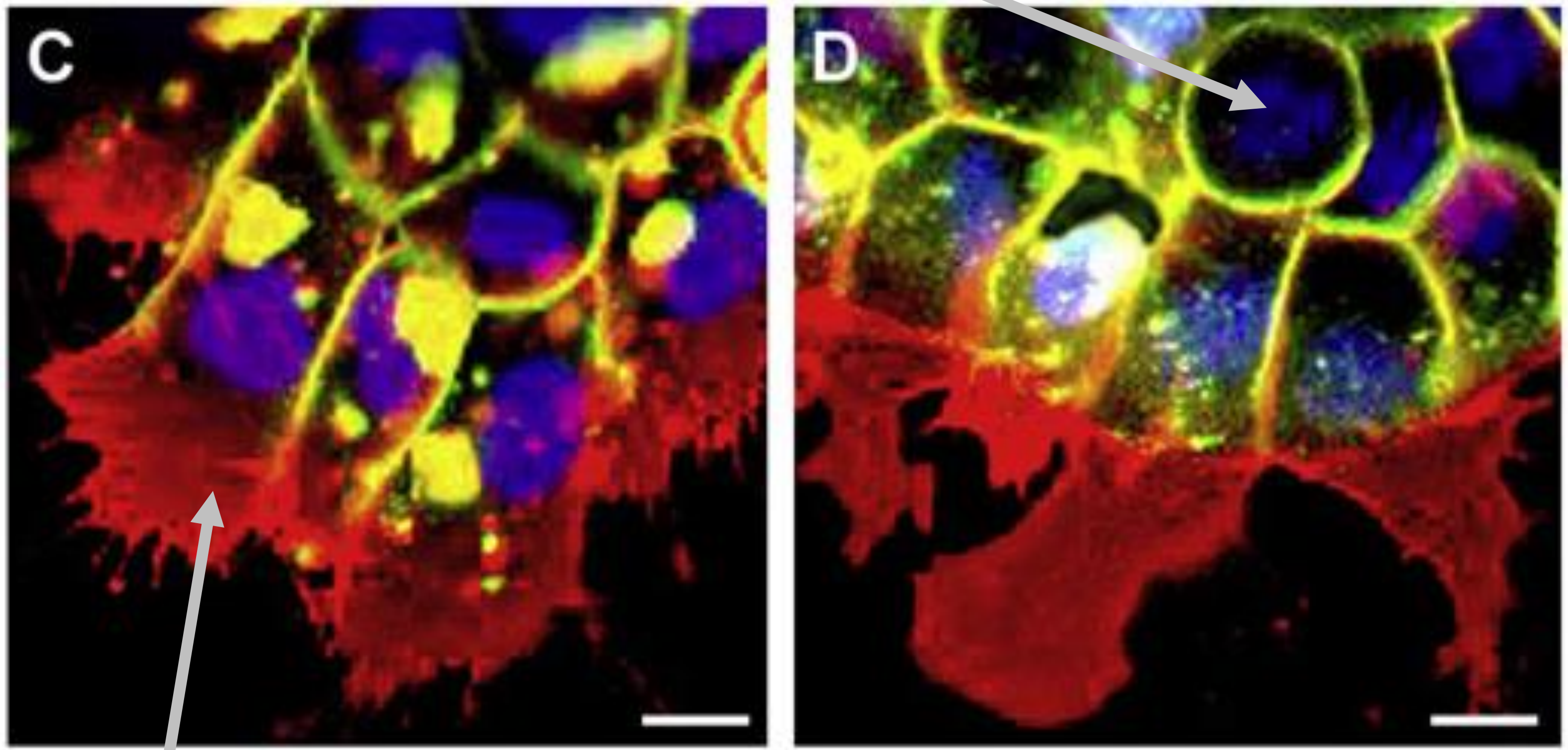


Neural crest cells protrude away from contact

Theveneau et al. Dev. Cell 2010

Contact inhibition of locomotion

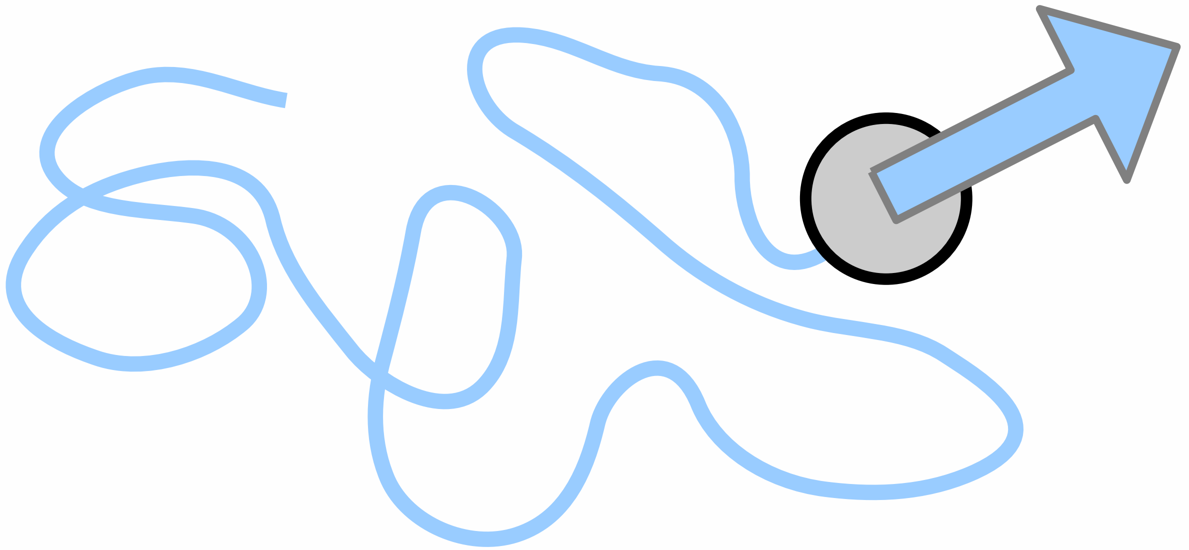
Inner cells have no protrusions



Outer cells have outward protrusions

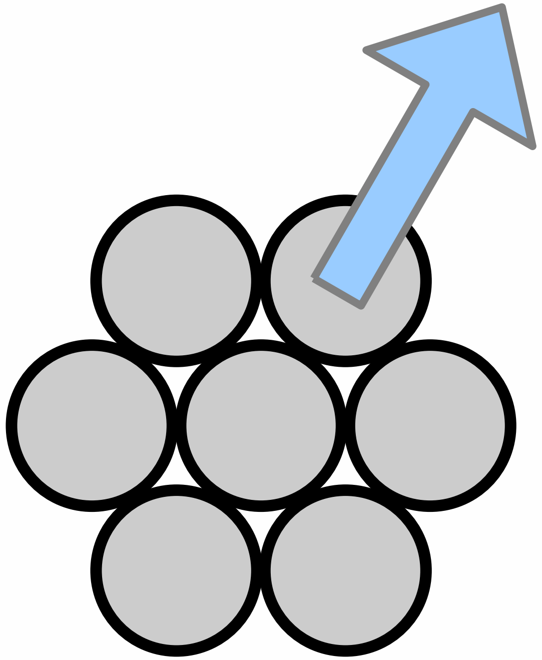
Theveneau et al. Dev. Cell 2010

Stochastic particle model



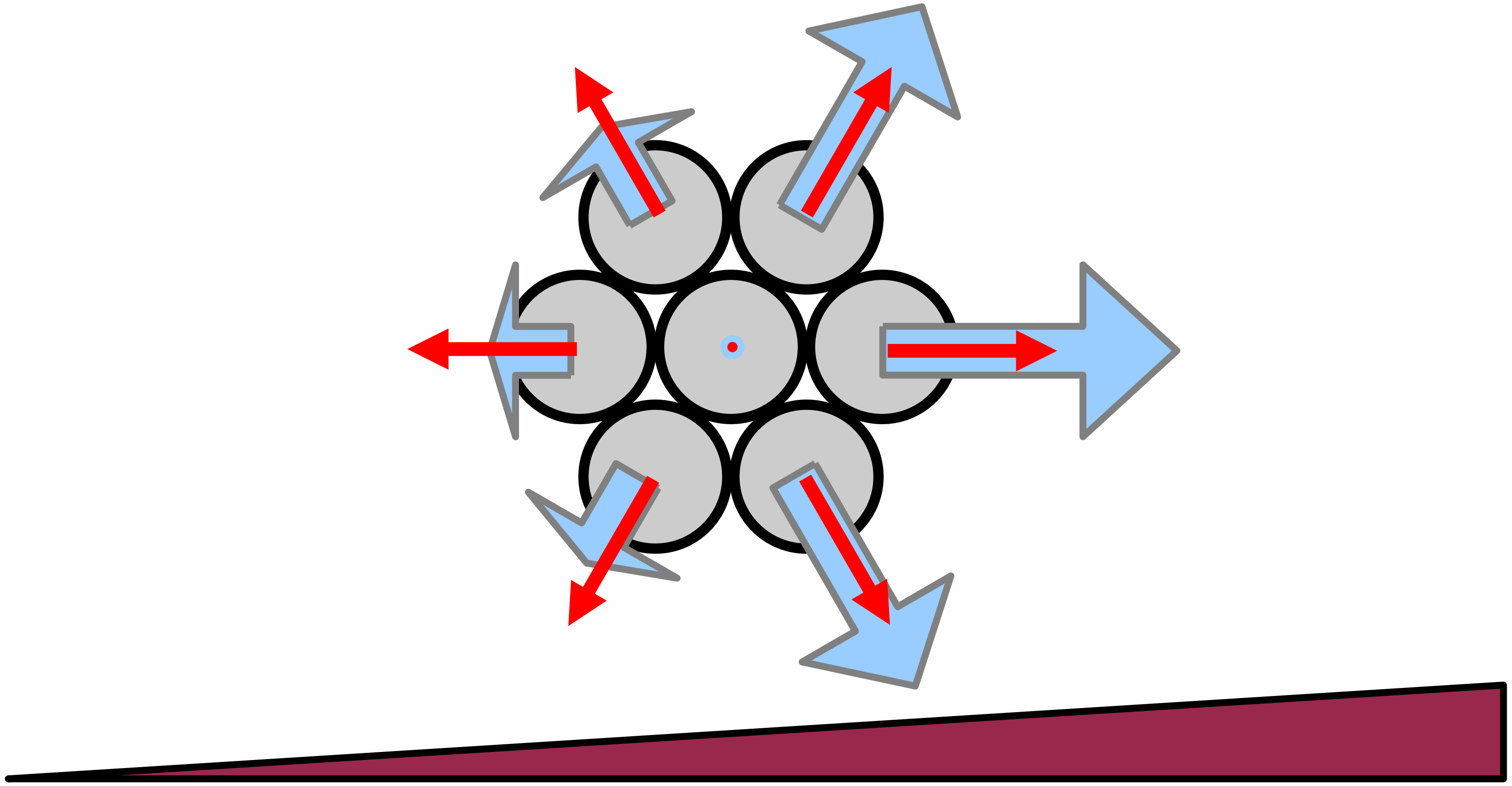
Single cells are random walkers

Stochastic particle model



Cells want to move away from their neighbors (CIL) but are stuck together mechanically

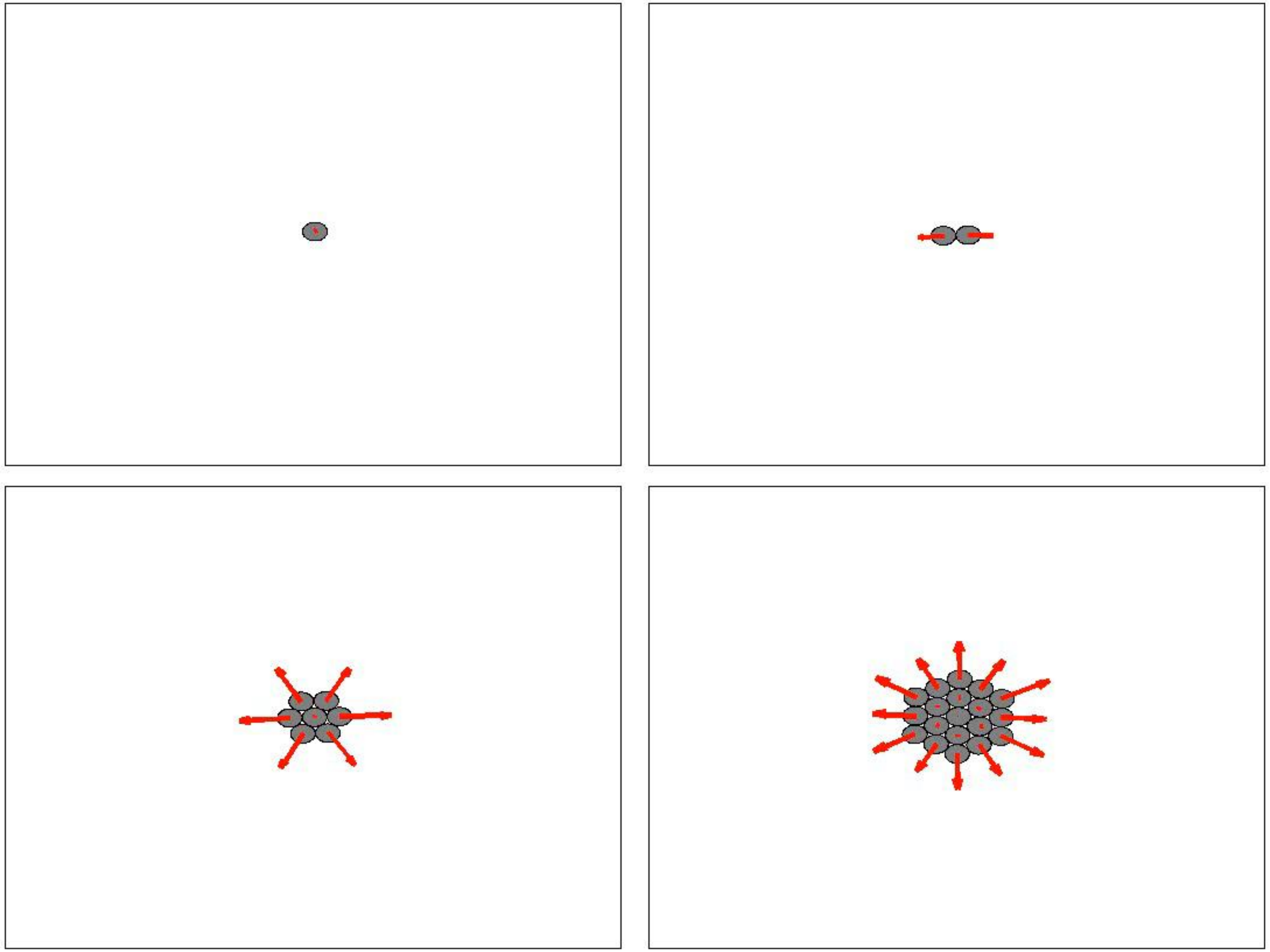
Stochastic particle model



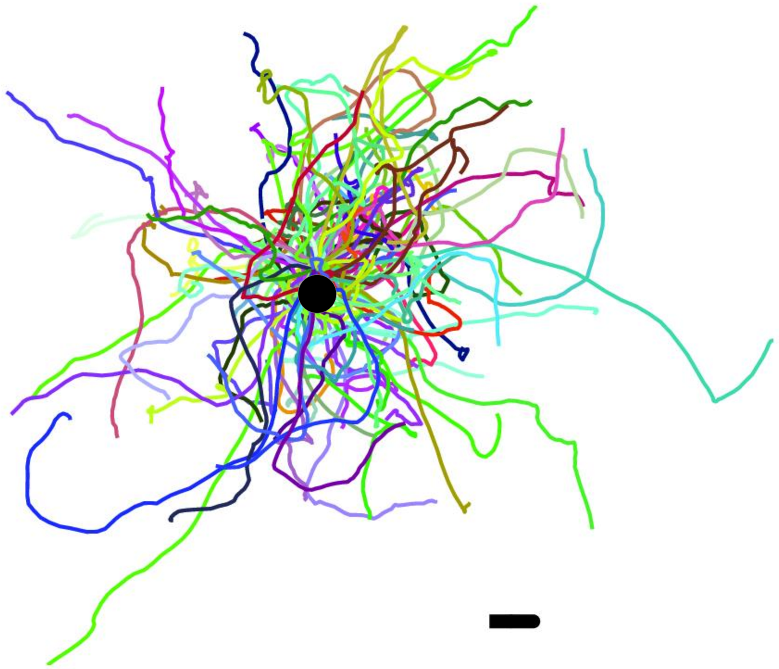
Signal S(**r**)

Cells feel CIL more strongly when the signal is large

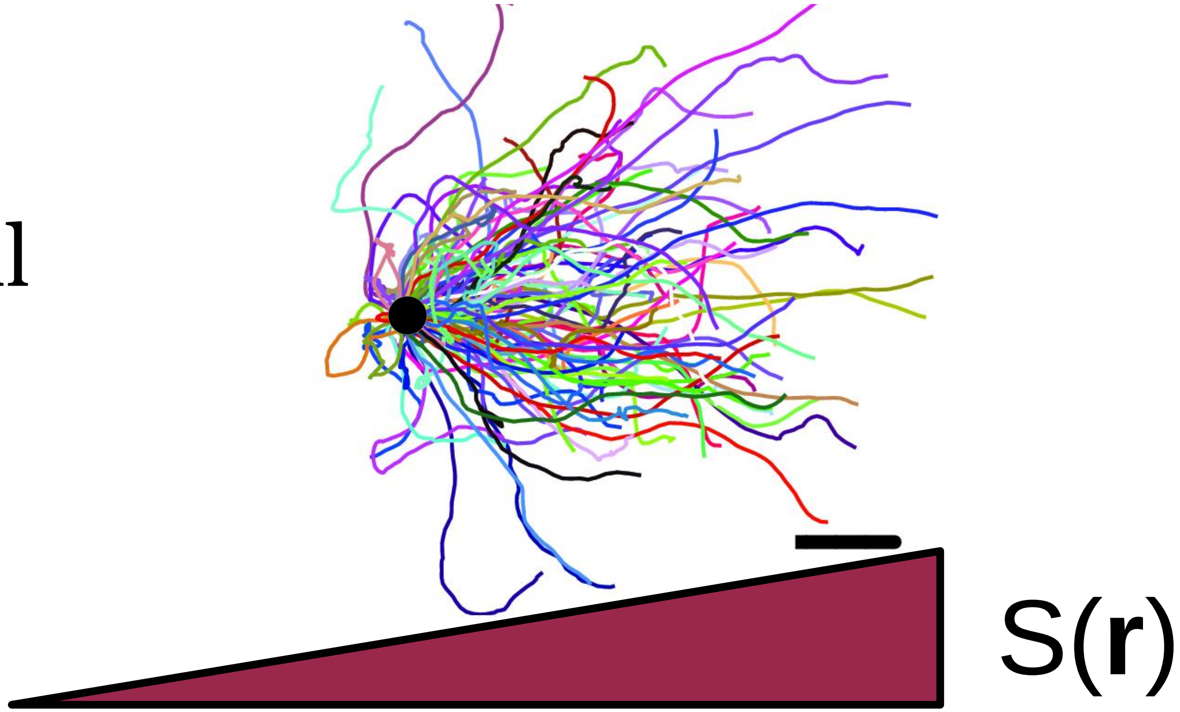
Simulations of the model



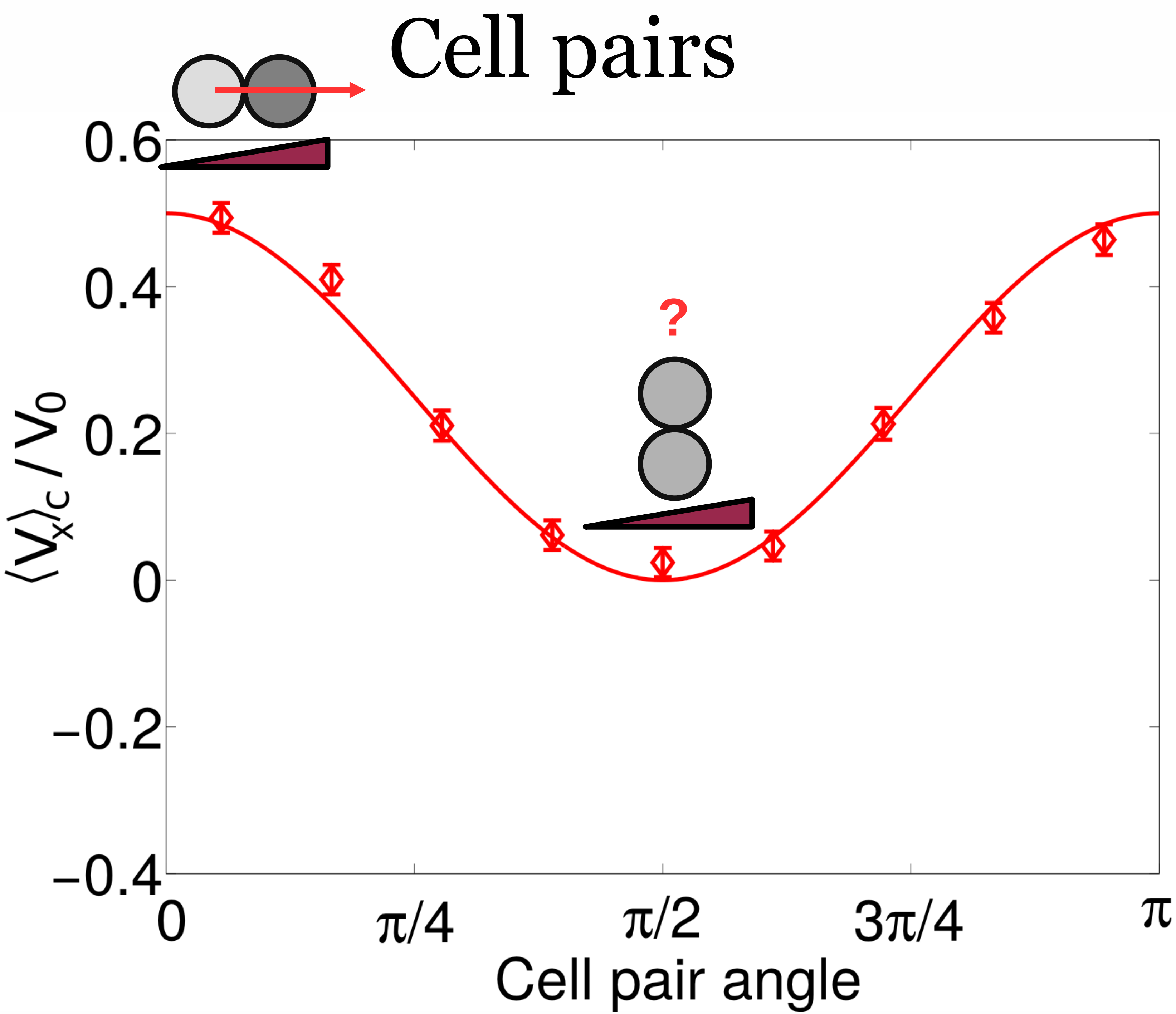
Single cells



Seven-cell clusters

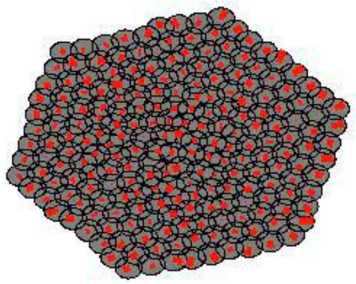


How can we tell if a cluster is using collective guidance?

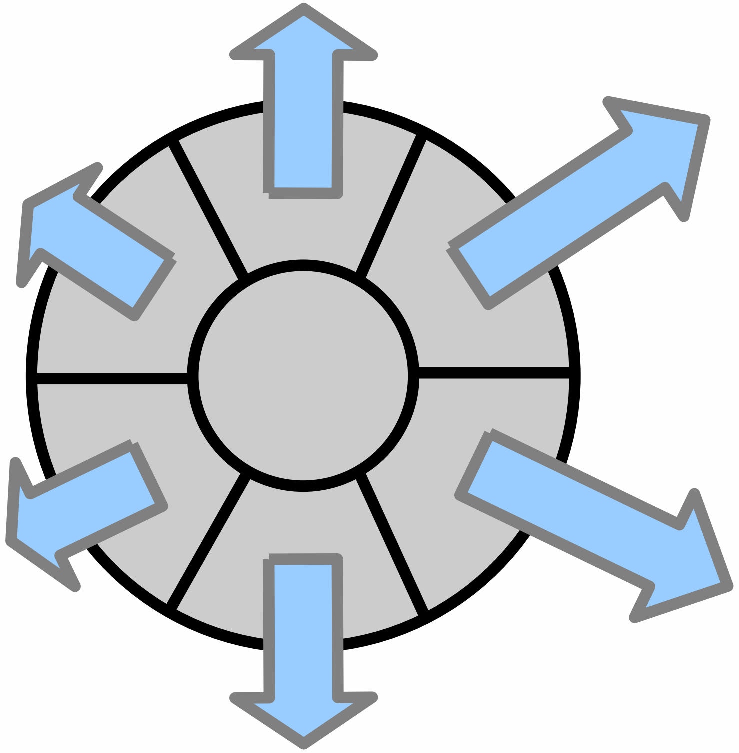


Cell pairs
?
0.6
0.4
0.2
0
−0.2
−0.4
⟨Vx⟩c / V0
0
π/4
π/2
3π/4
π
Cell pair angle

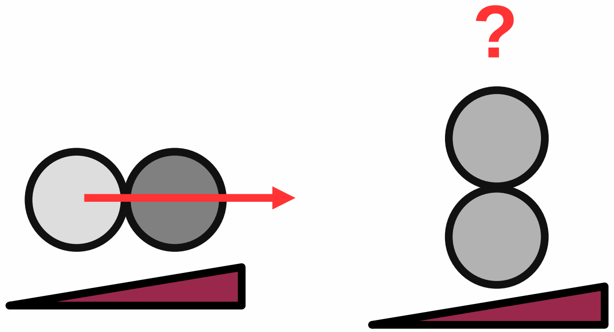
What if cells can’t hold together?



Conclusions

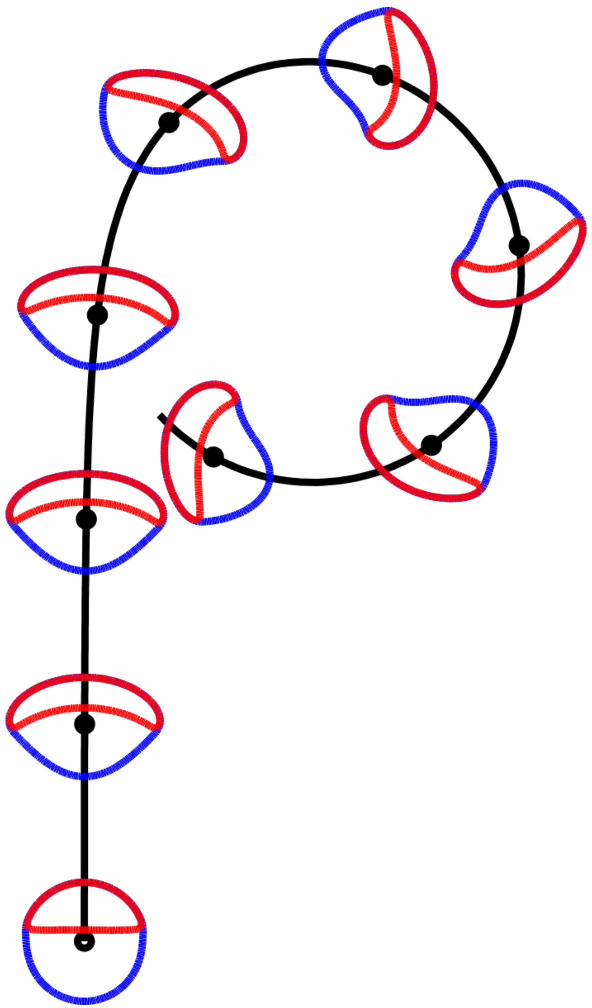


Cell clusters can have abilities that single cells don't!

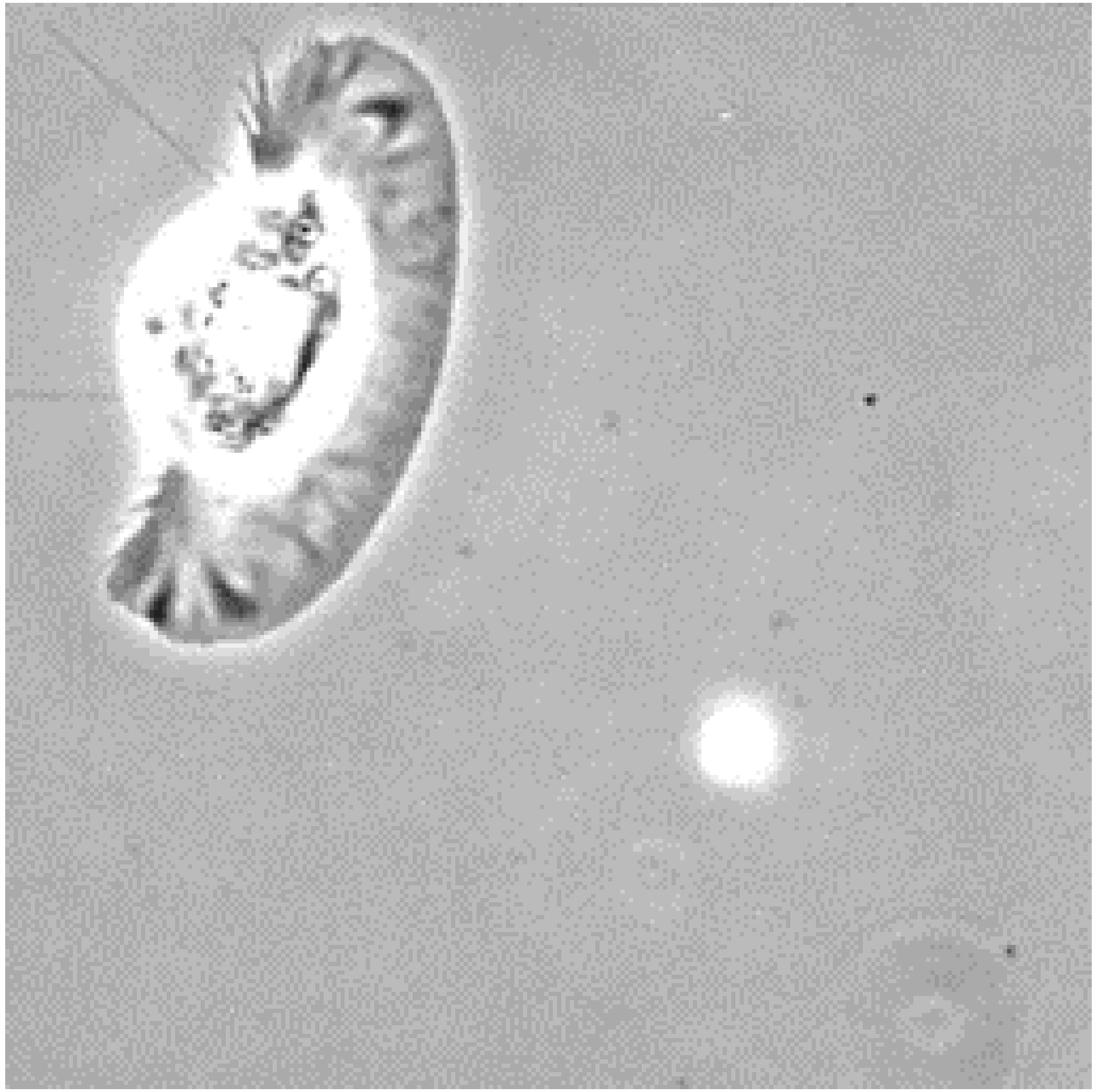


We can determine why by looking at cell pairs at different angles

Story 2: Circulating Cells, or How Water Droplets Create Rotation

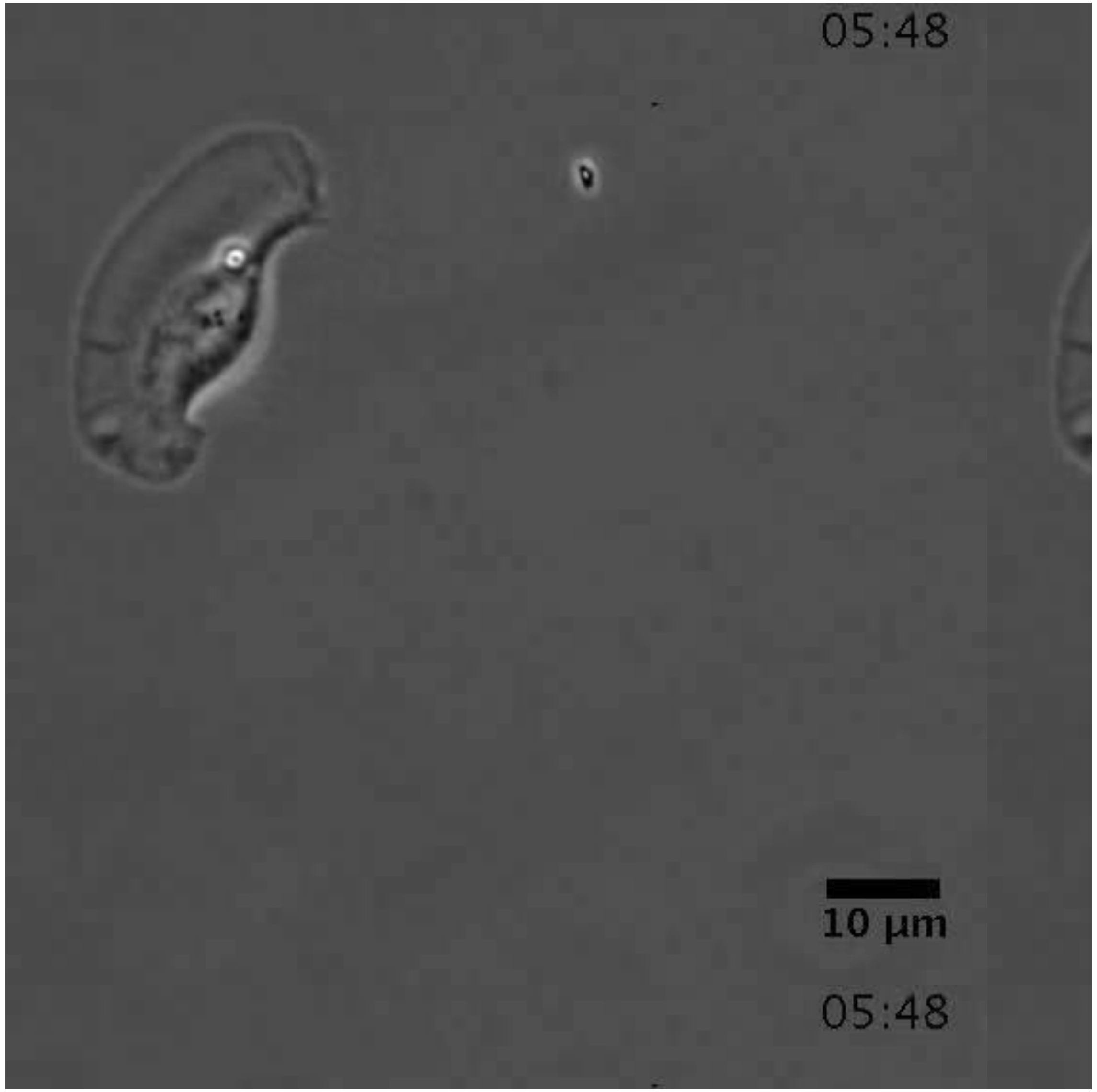


Eukaryotic cells typically crawl with a (persistent) random walk



Barnhart…. Theriot, Biophys. J. 2010

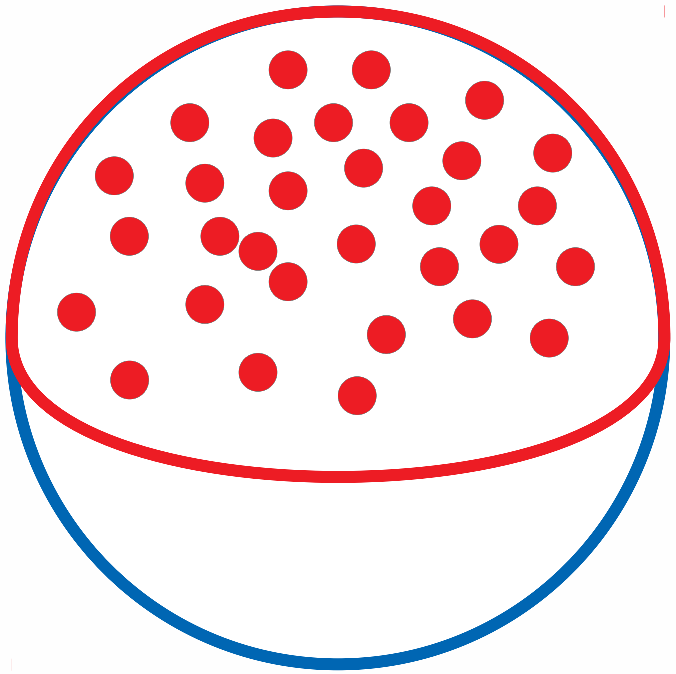
A surprise!



Allen… Theriot, Mogilner, Cell Systems 2020

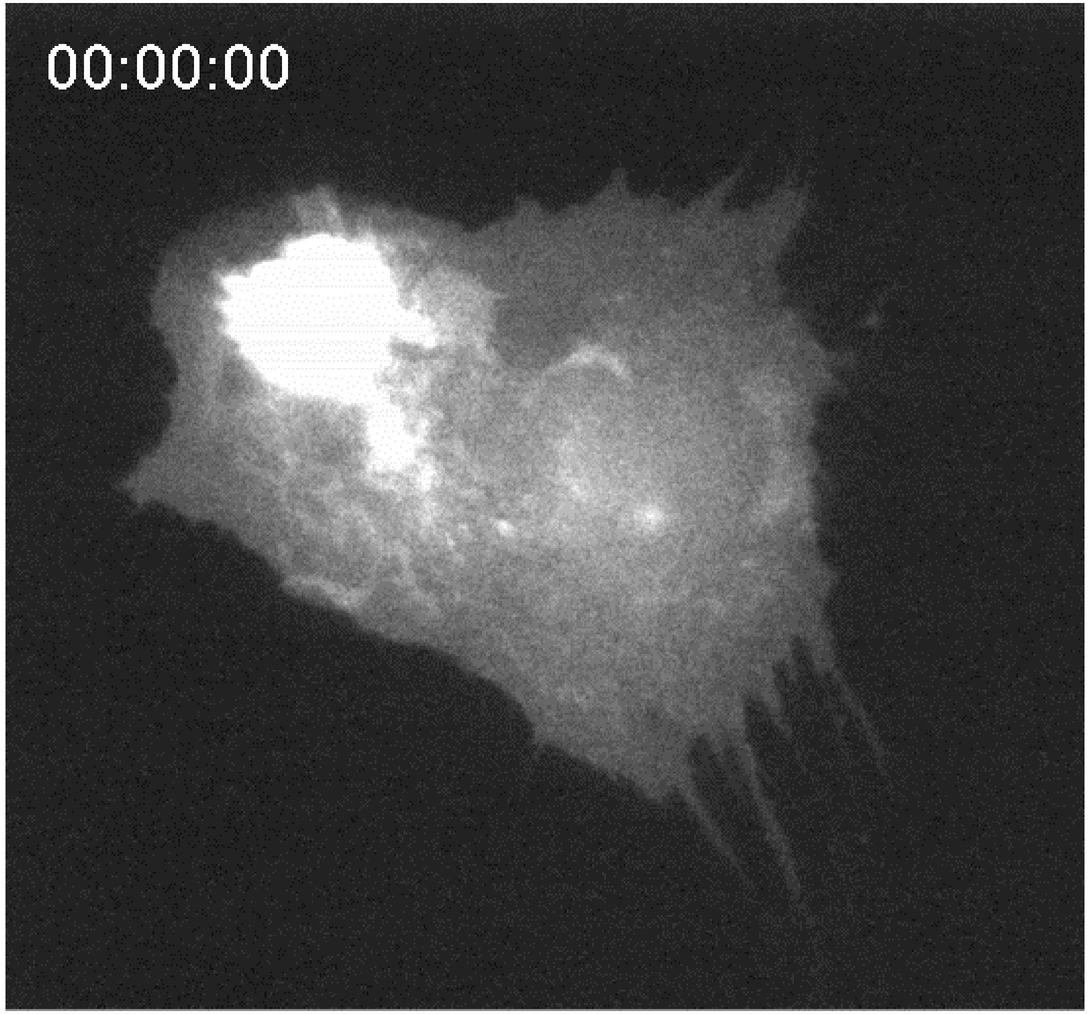
Cell polarity: what is the front?

Deliberately oversimple view:



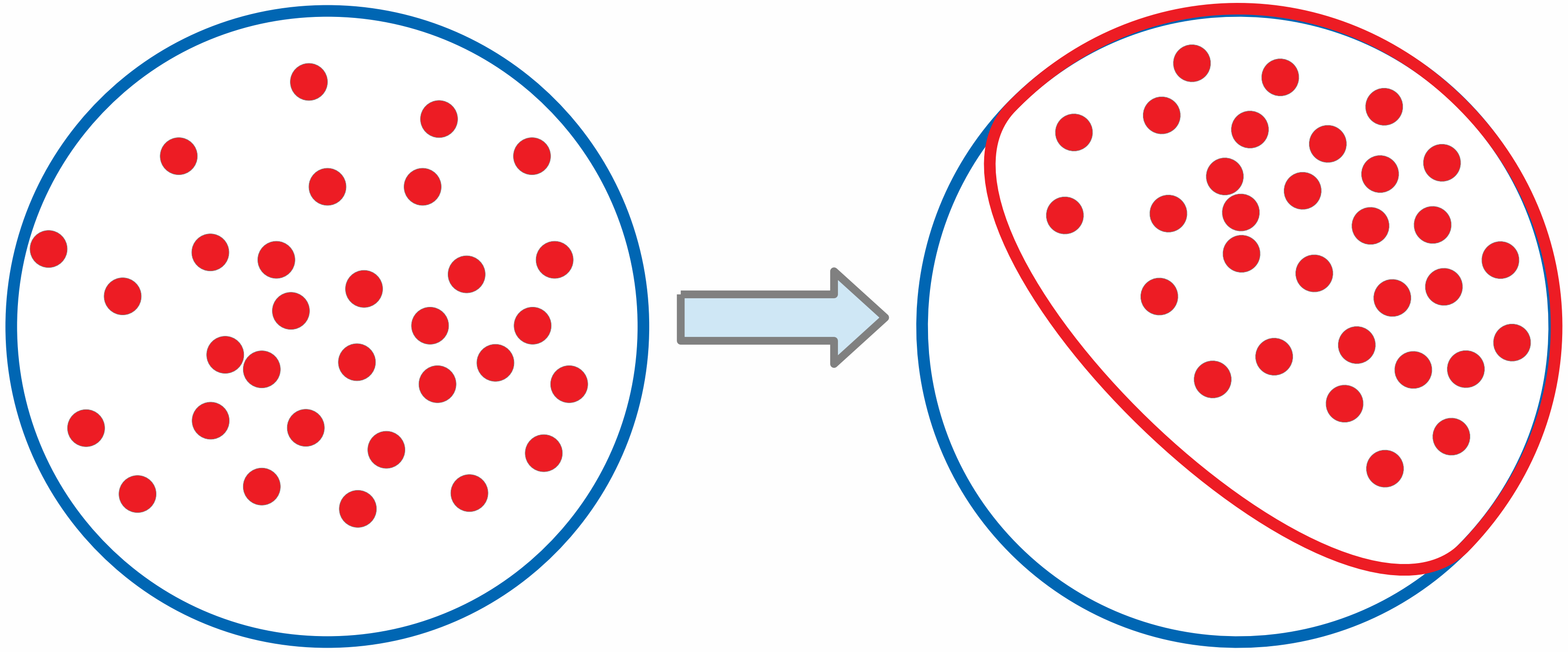
There are more proteins of certain types at the front!

(Active) Rac is one of the proteins that defines the cell front



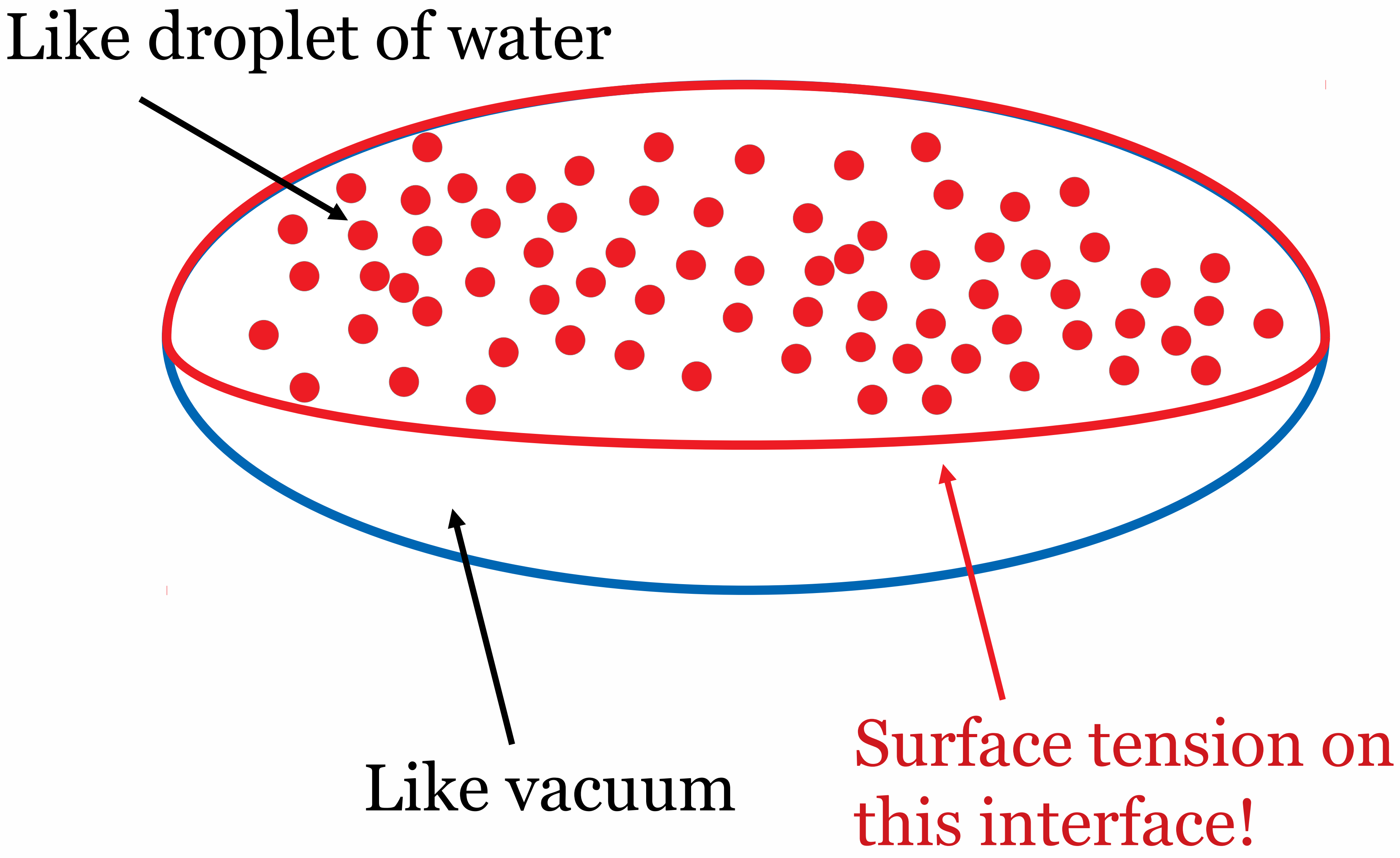
Rac activation by light, Wu… Hahn, Nature 2009

Even if there is no signal, the cell will pick a front randomly

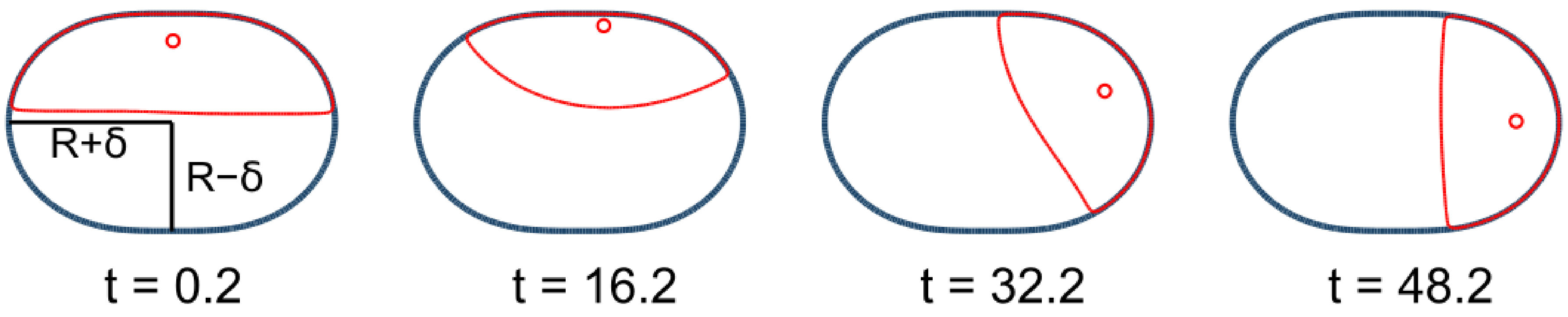


Think (not quite right): proteins like to clump together

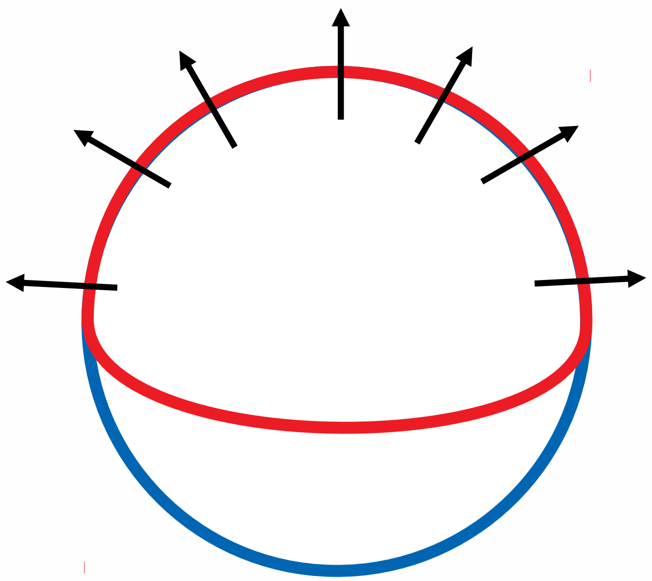
What if cell isn't circular?



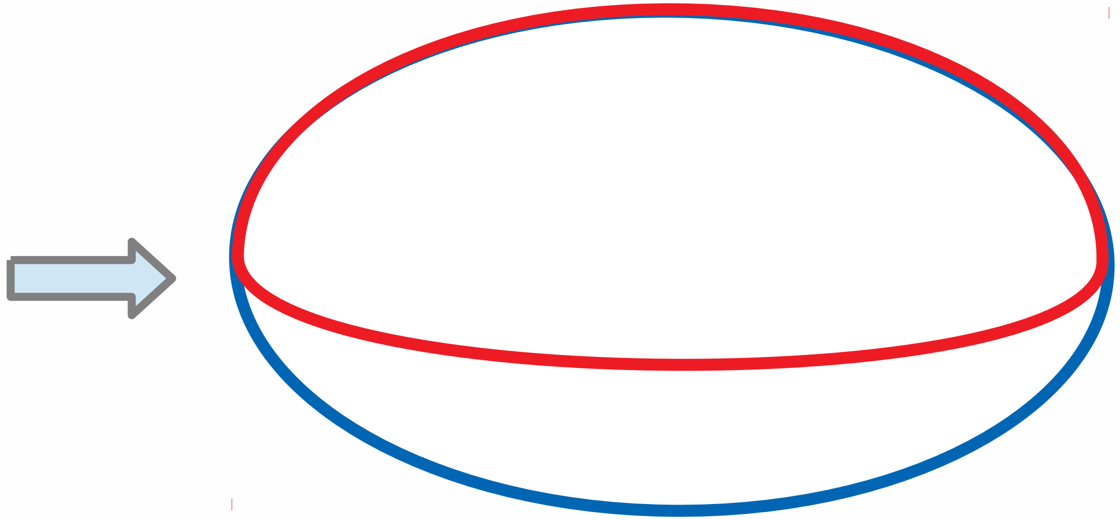
The interface of the high-protein area should be minimized!



Now we can understand turning!

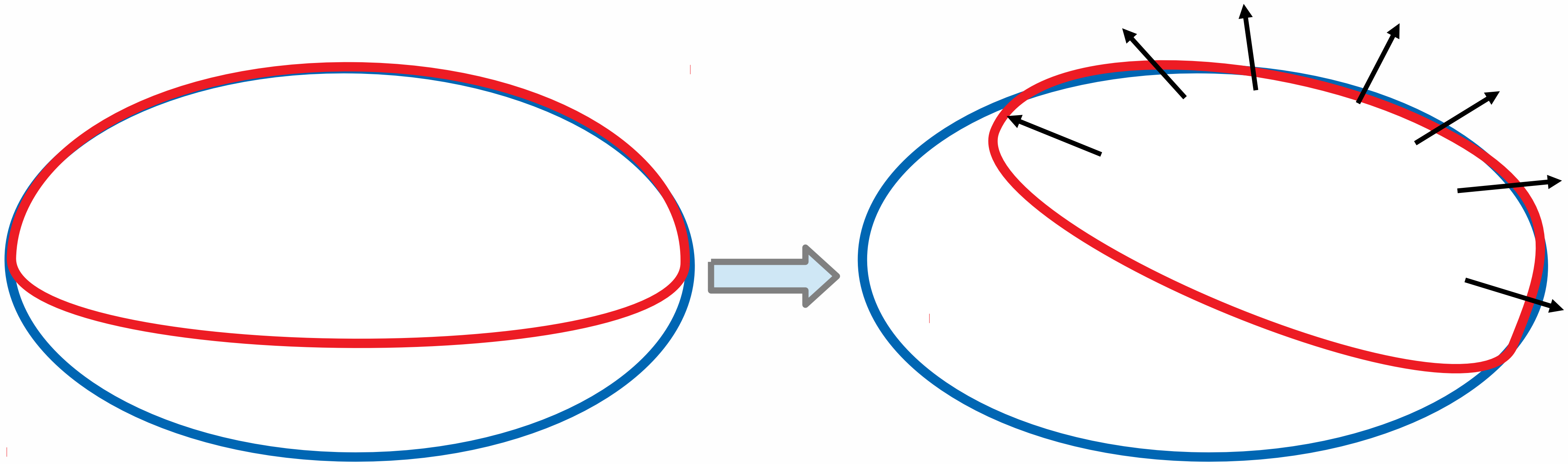


Cell pushes forward
where Rac is high



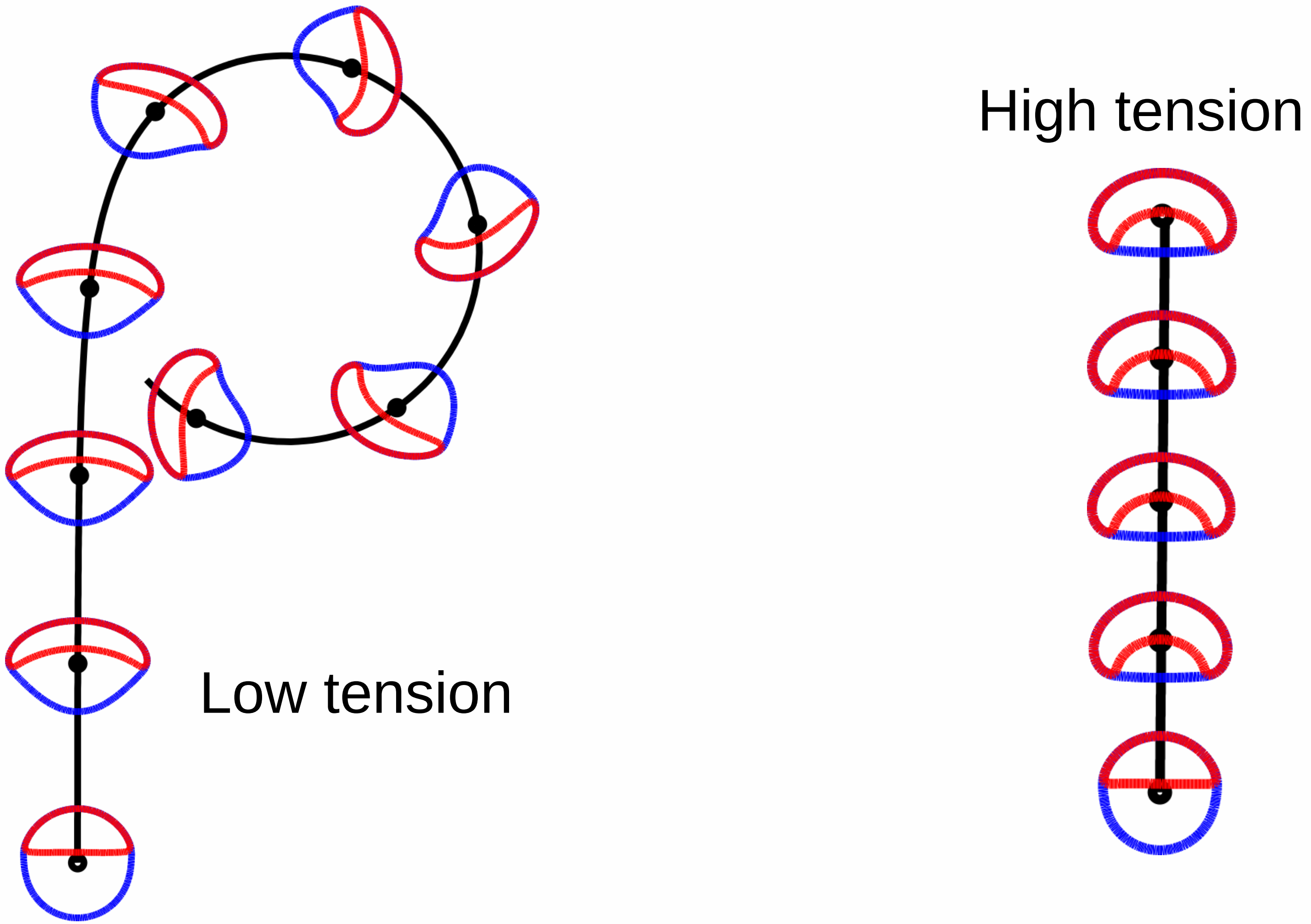
Cell becomes elongated

Now we can understand turning!



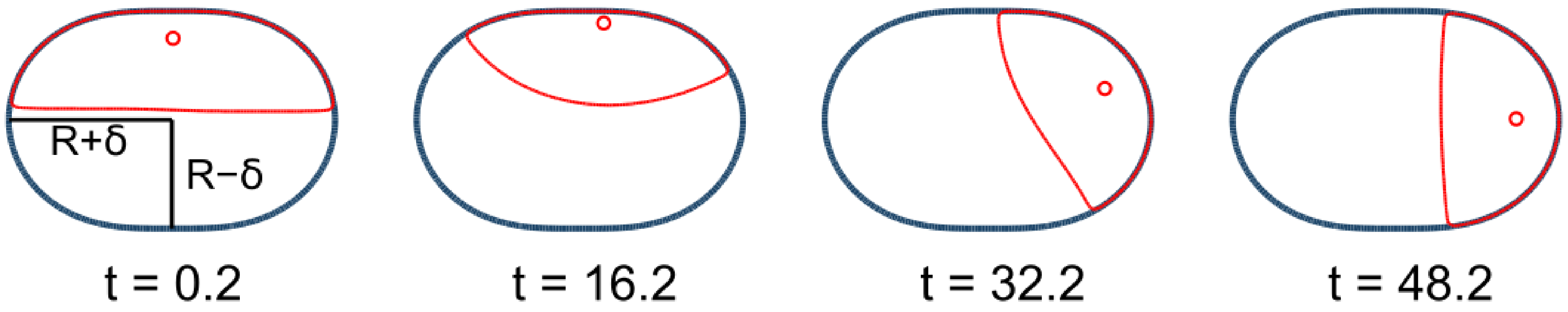
Rac reorients to minimize interface length

Turning happens if the cell shape is sufficiently deformable

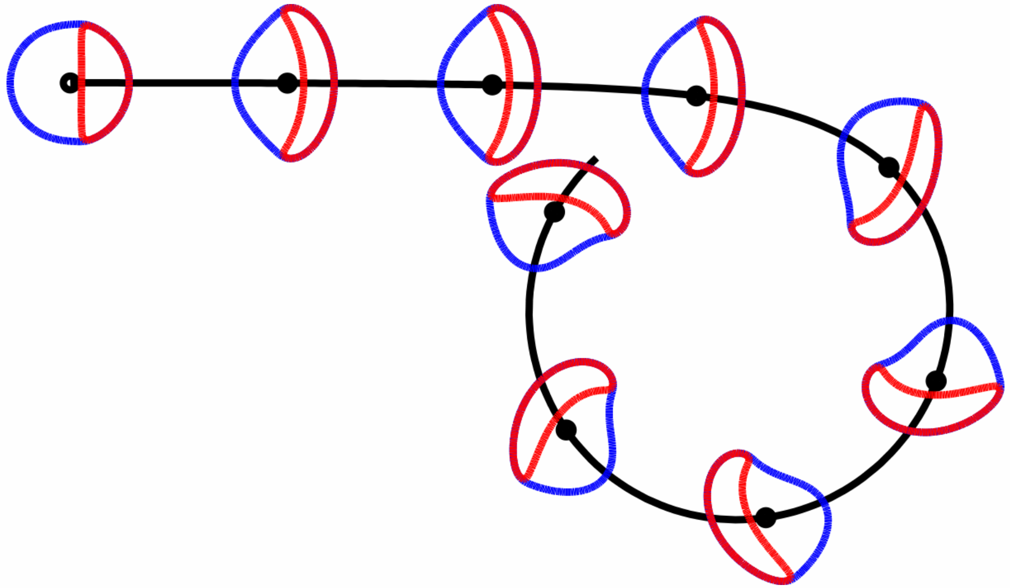


Camley*, Zhao*, et al. Phys. Rev. E.2017

Conclusions



Cell shape and the reactions within it are coupled, in part because high Rac areas are like a water droplet



This suggests turning will happen if cell shape is deformable enough

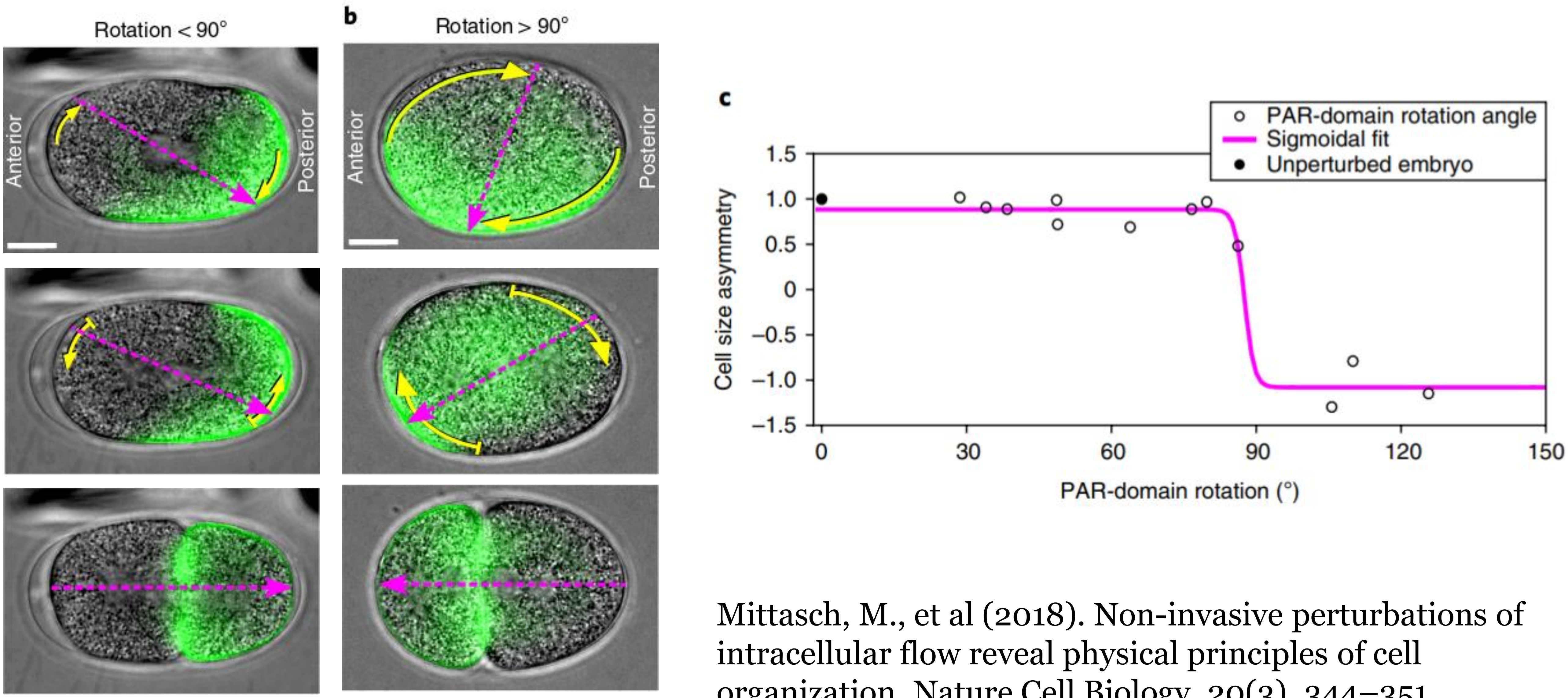
Bonus results on patterning!

“Sensing the shape of a cell with reaction-diffusion and energy minimization”
Singh, Leadbetter, Camley arXiv:2111.08496 (2021)
In press at PNAS 2022

Sensing the long axis in development?

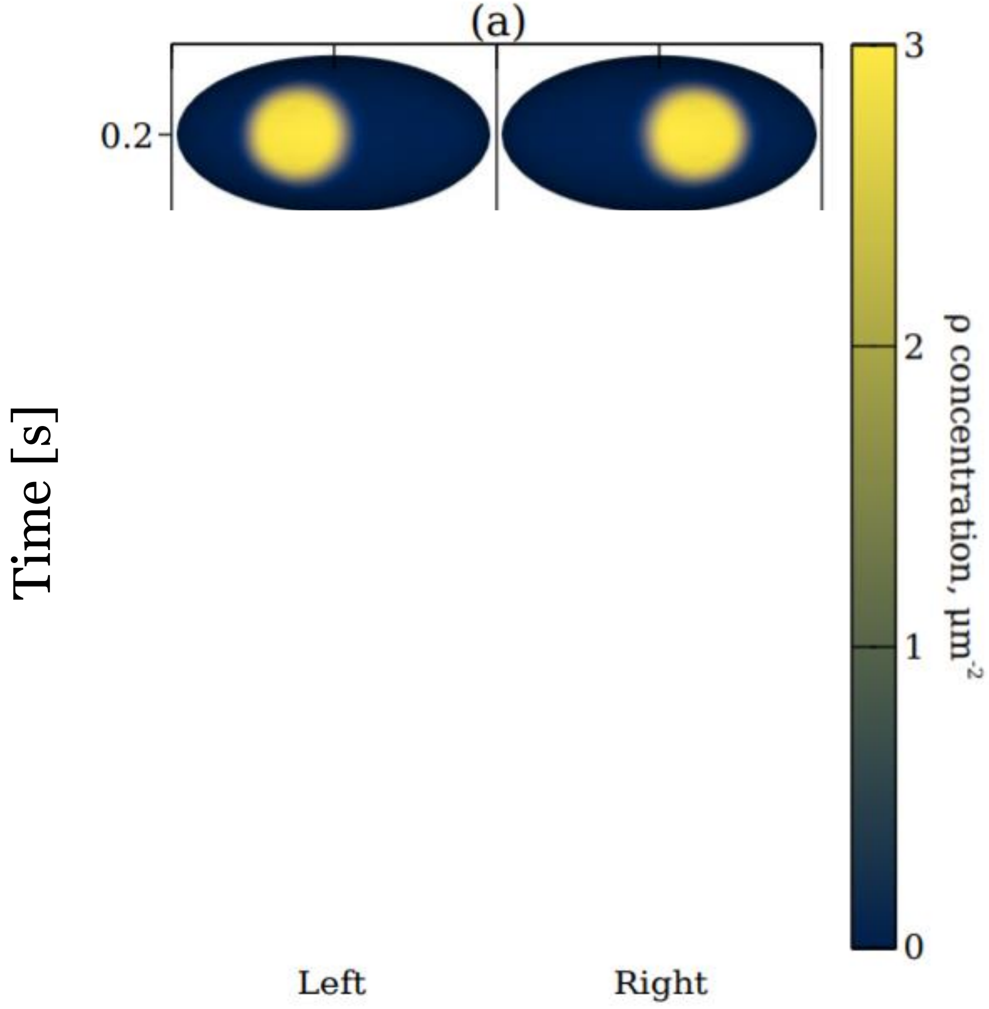
C elegans zygote:

Sensing the long axis in development?



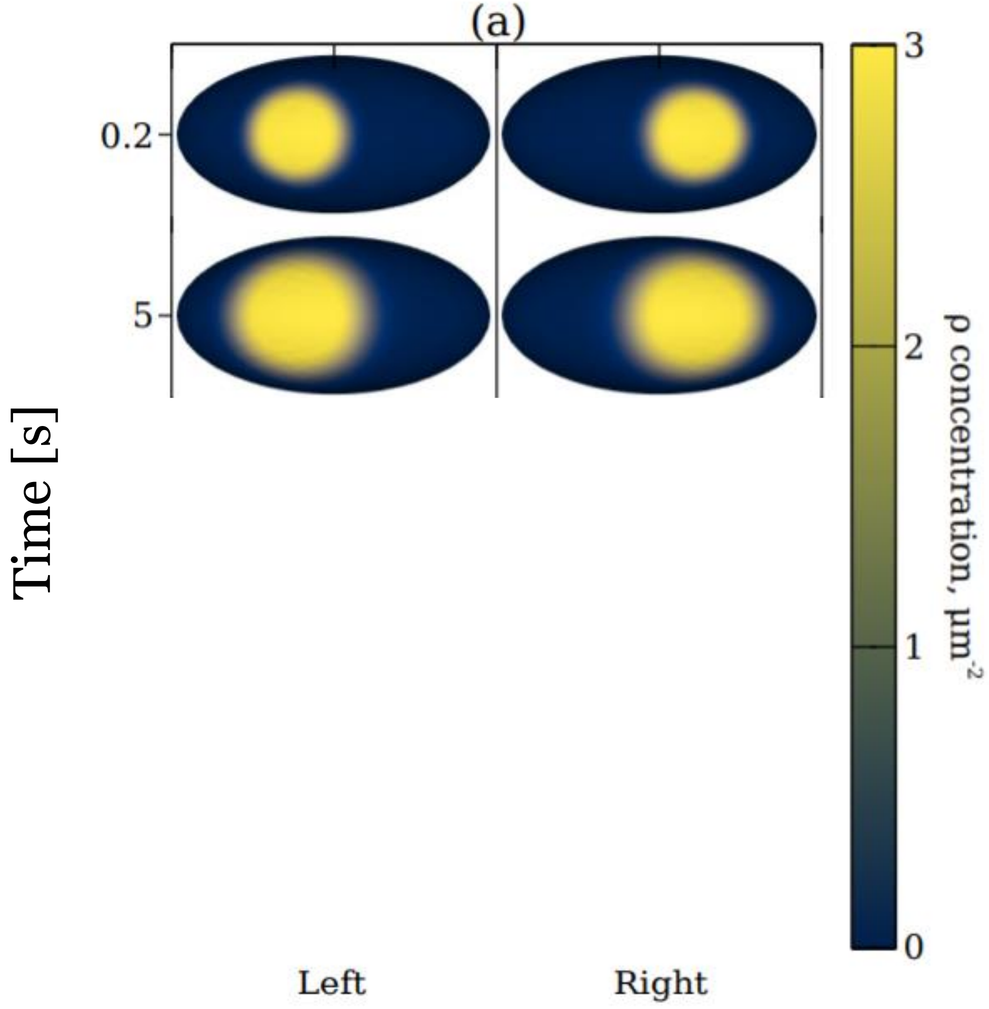
Mittasch, M., et al (2018). Non-invasive perturbations of intracellular flow reveal physical principles of cell organization. Nature Cell Biology, 20(3), 344–351.

Minimal model senses the long axis!



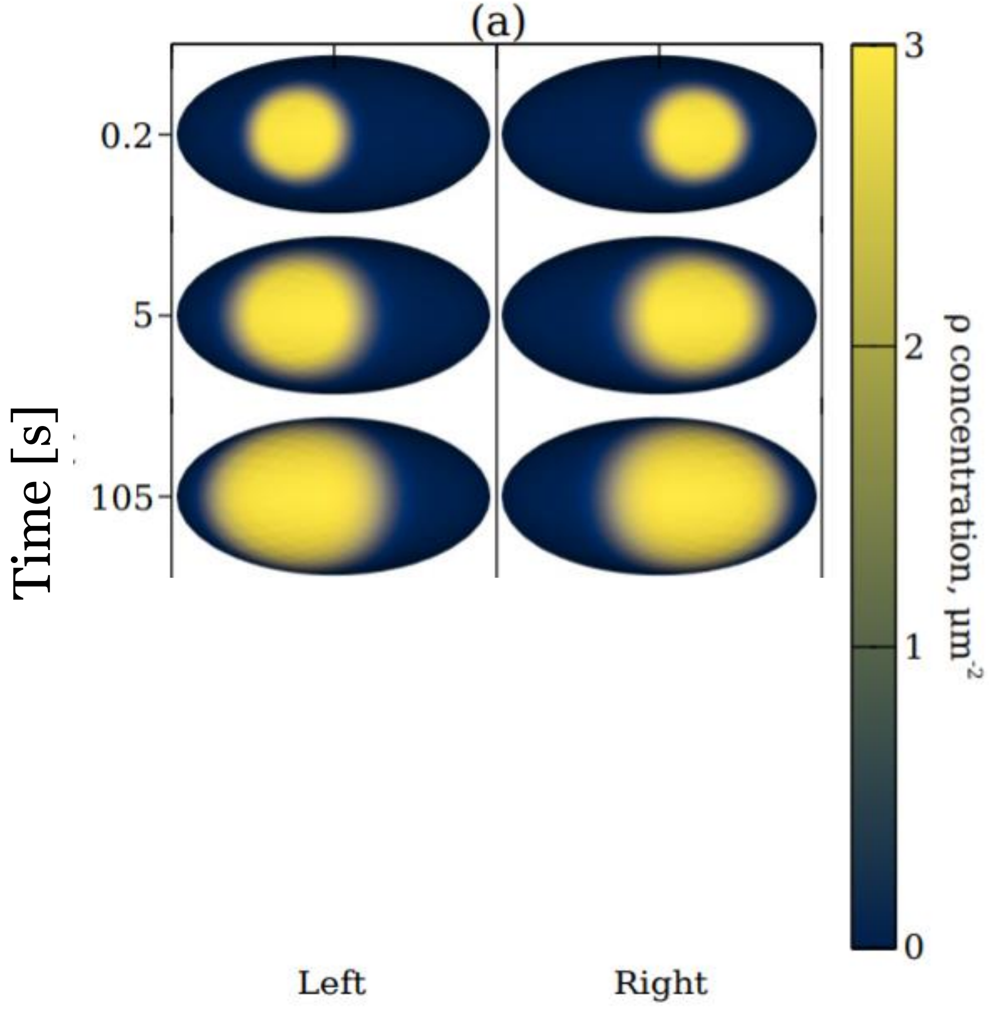
Simulating the minimal cell polarity model

Minimal model senses the long axis!



Simulating the minimal cell polarity model

Minimal model senses the long axis!



Simulating the minimal cell polarity model

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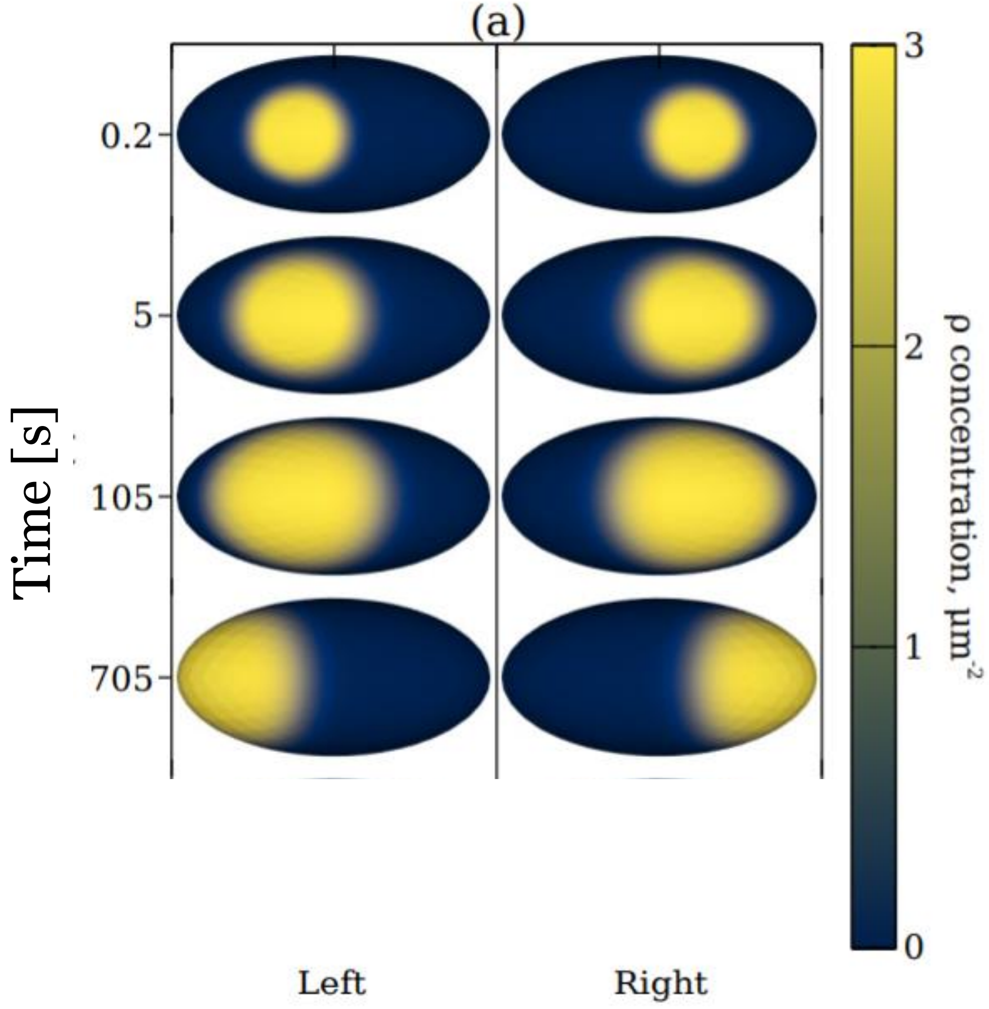
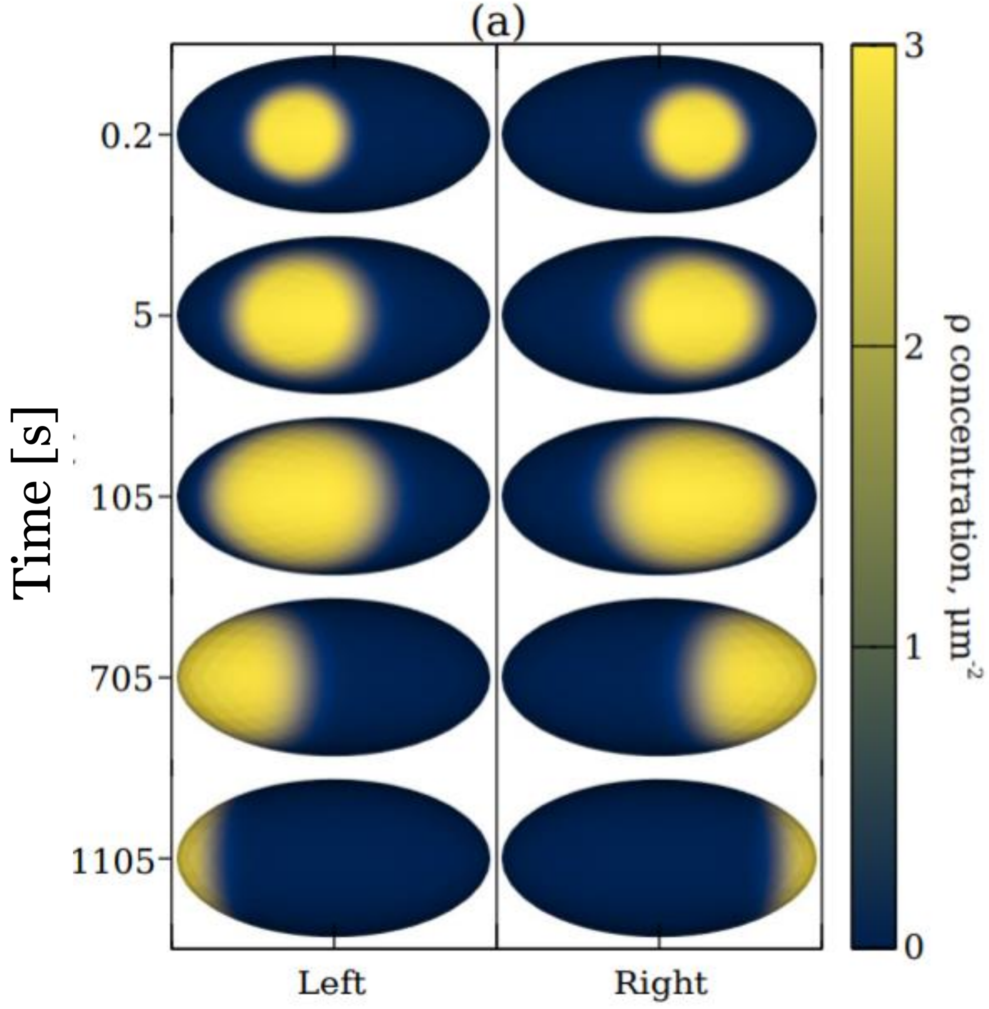


Simulating the minimal cell polarity model

Minimal model senses the long axis!



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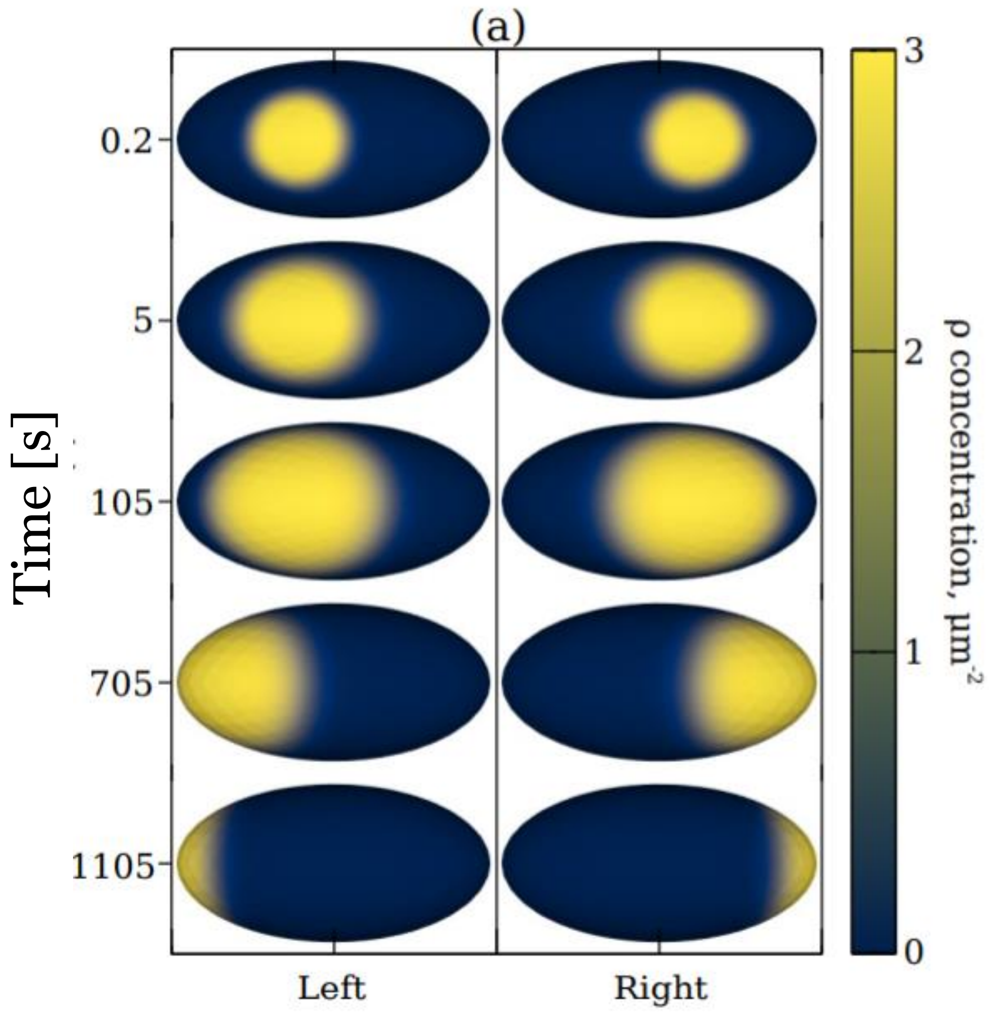
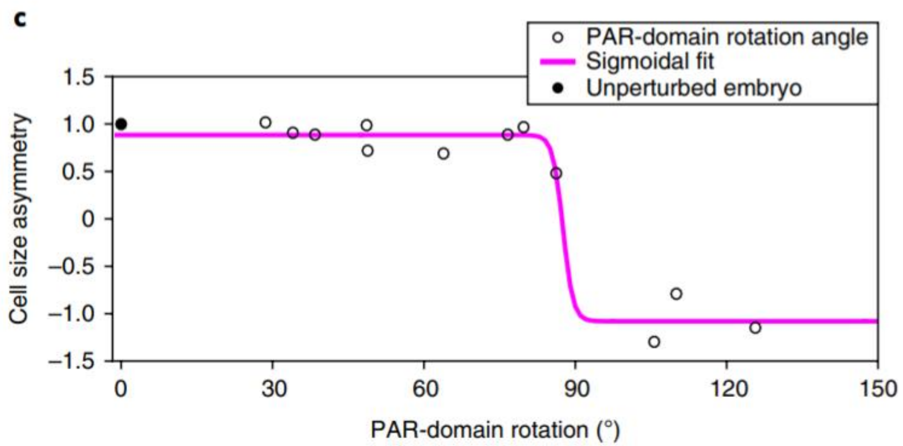
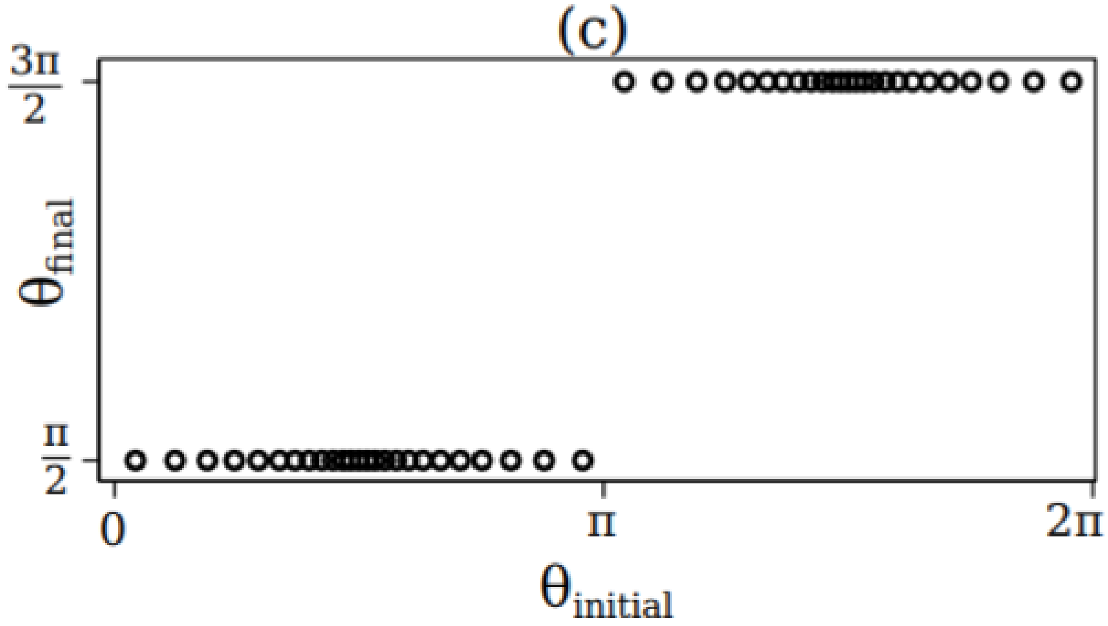
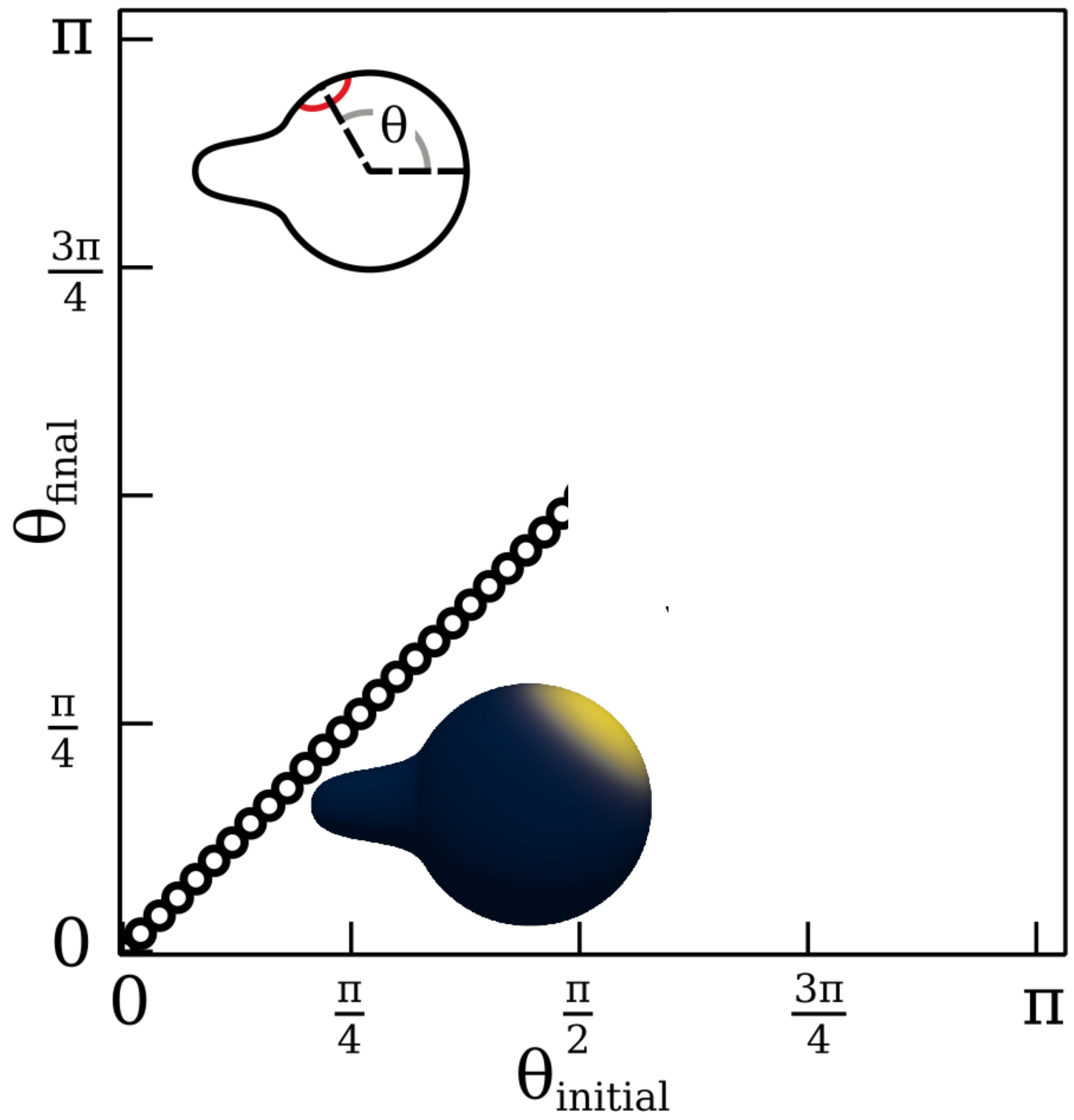


Simulating the minimal cell polarity model

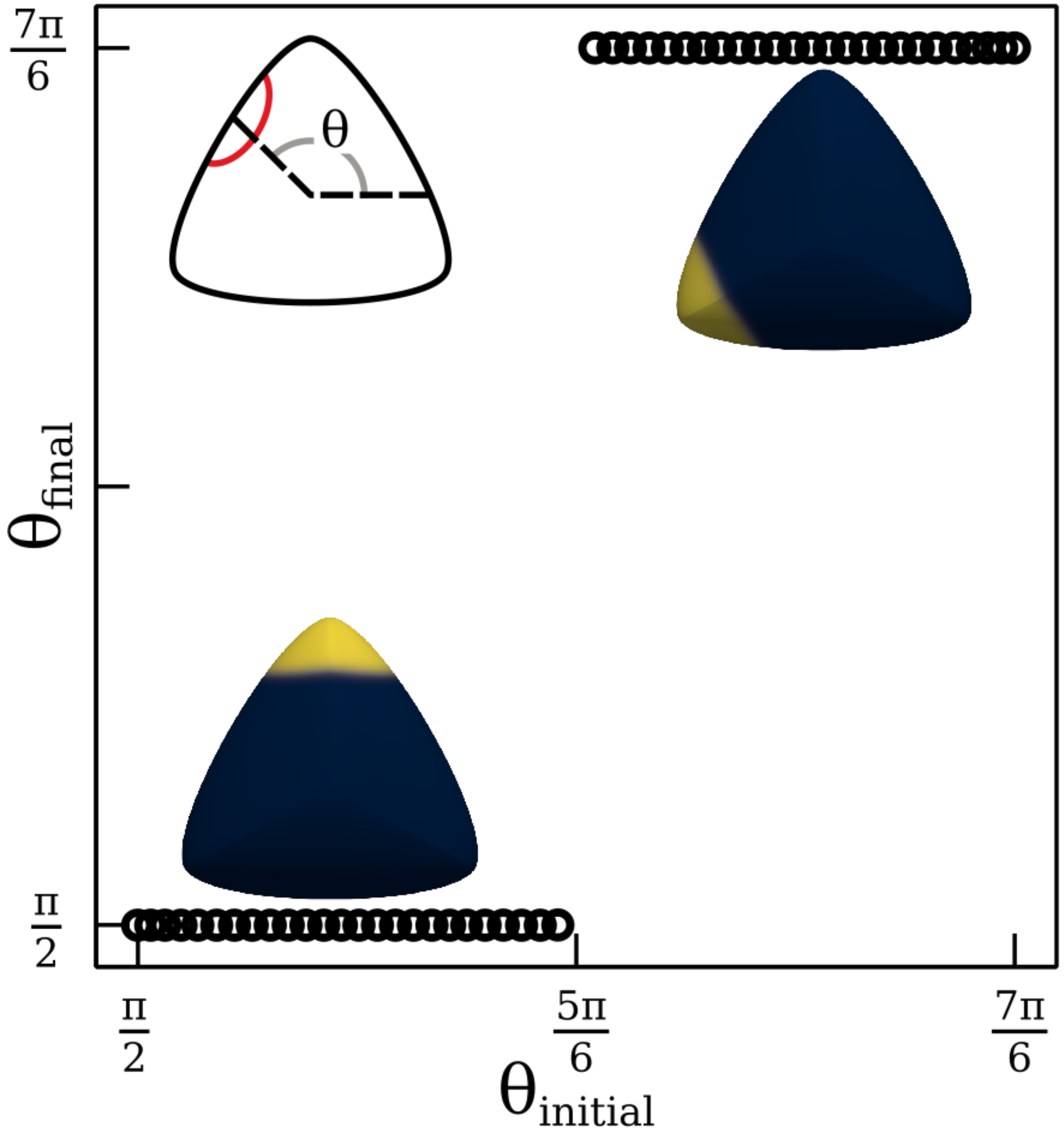


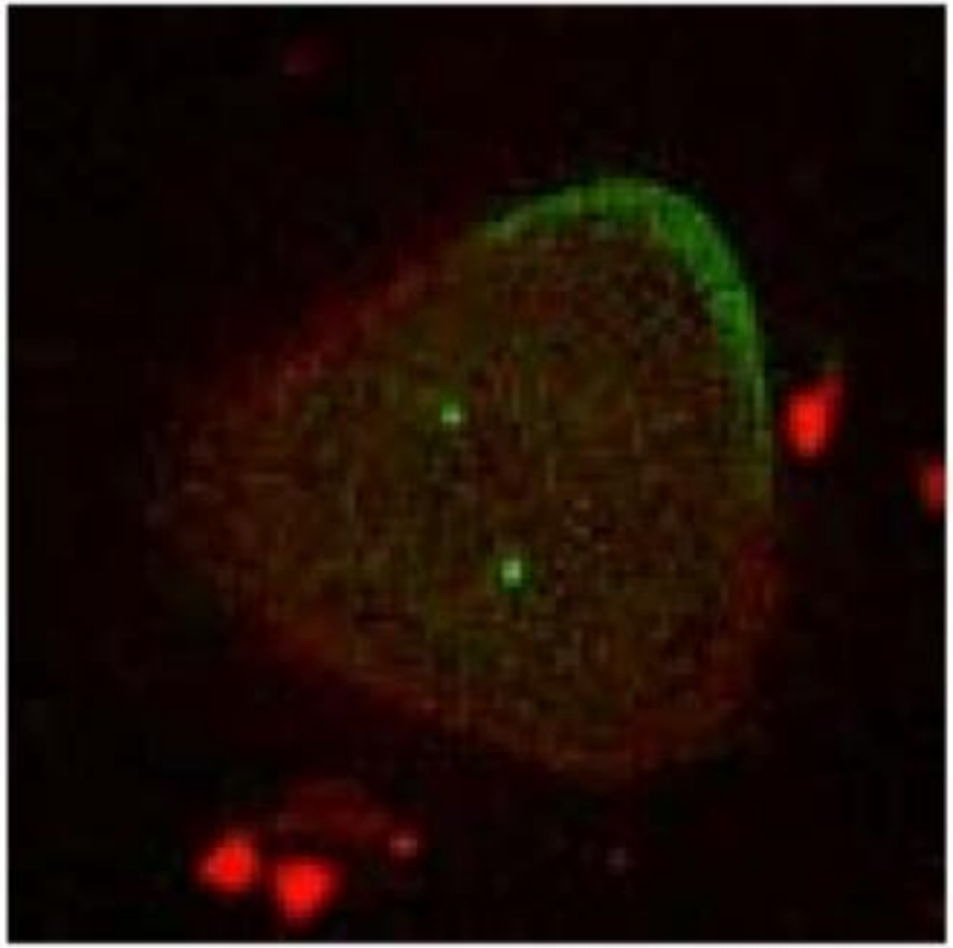


Caveats: far more to the PAR system than a single protein



π
3π/4
π/4
0
θ
θ_{final}
0
π/4
π/2
3π/4
π
$\theta_{initial}$





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Acknowledgments

Later work done with Amit Singh, Travis Leadbetter
Singh, Leadbetter, Camley arXiv:2111.08496 (2021)

Earlier work: Yanxiang Zhao, Bo Li, Herbert Levine, Wouter-Jan Rappel
Juliane Zimmermann
Camley*, Zhao*, et al. Phys. Rev. E 2017
Camley et al. Phys. Rev. Lett. 2016

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