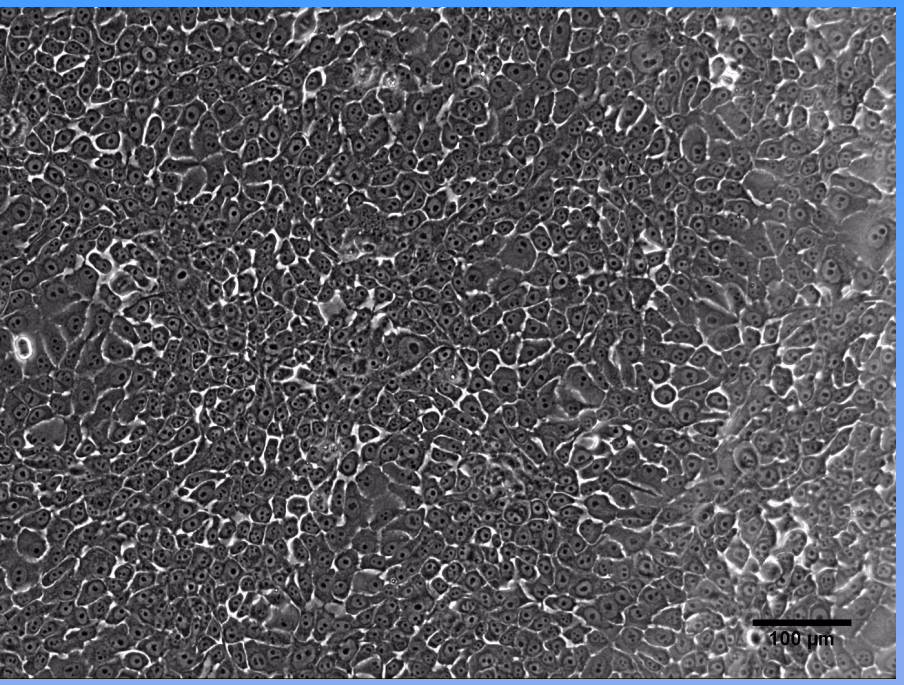
Physics of Cancer



Wolfgang Losert
Director, Cancer Technology Partnership
Director, Biophysics Program
University of Maryland

University of Maryland – National Cancer Institute

PARTNERSHIP FOR CANCER TECHNOLOGY

Research Team & Collaborators

Grad Students & Postdocs

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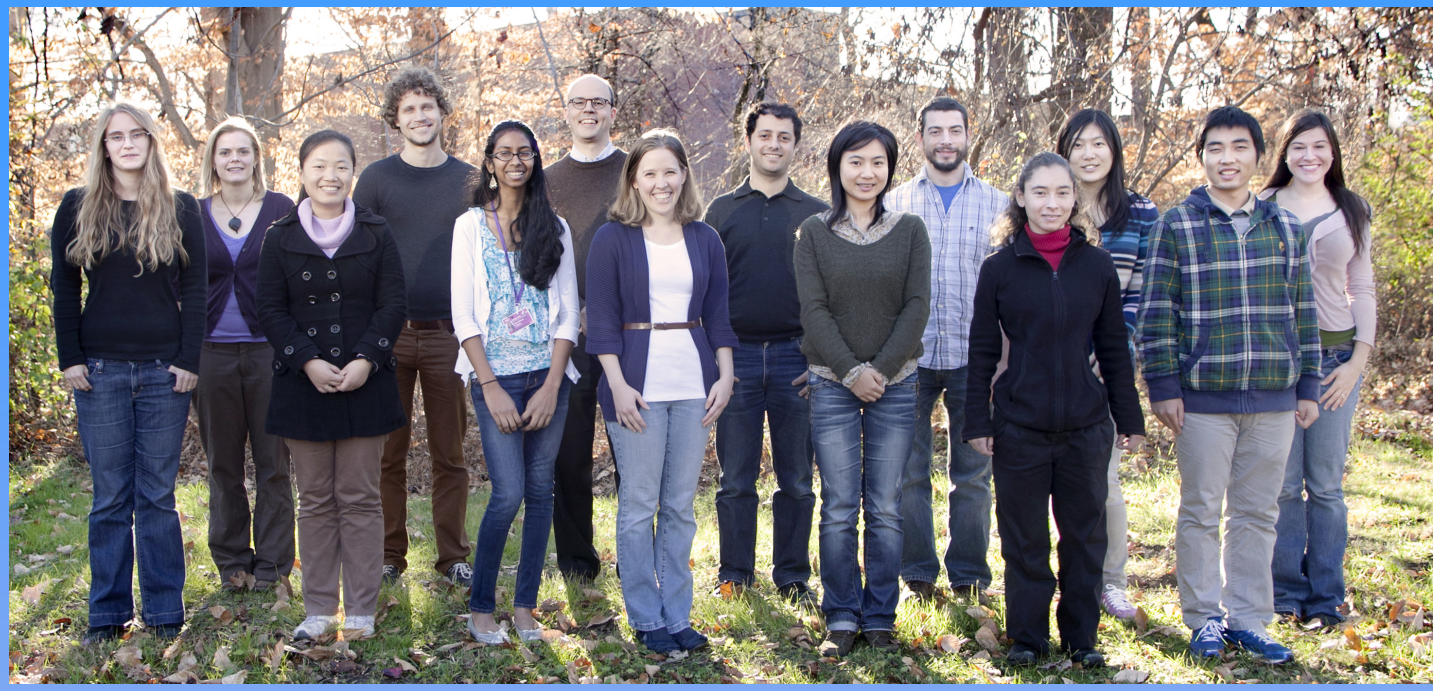
Deb. Hemingway
Rachel Lee
Kerstin Nordstrom
Eleanor Ory
Joshua Parker
Yang Shen
Xiaoyu Sun
Chenlu Wang



Undergraduates

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Andrew Shaw
Ryan Shute
Zeshan Tariq
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Anders Carlsson *(WashU)*
Jack Douglas *(NIST)*
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SK Gupta
Josef Kaes *(Leipzig)*
Amos Maritan *(Padua)*
Stuart Martin *(Med School)*
Alex Morozov *(Rutgers)*
Bob Nussenblatt *(NIH)*
Ed Ott
Joe Redish
Kandice Tanner *(NCI)*

Physics in Cancer Research!

Initiated by National Cancer Institute in 2008:
Physical Sciences Oncology Centers
http://physics.cancer.org

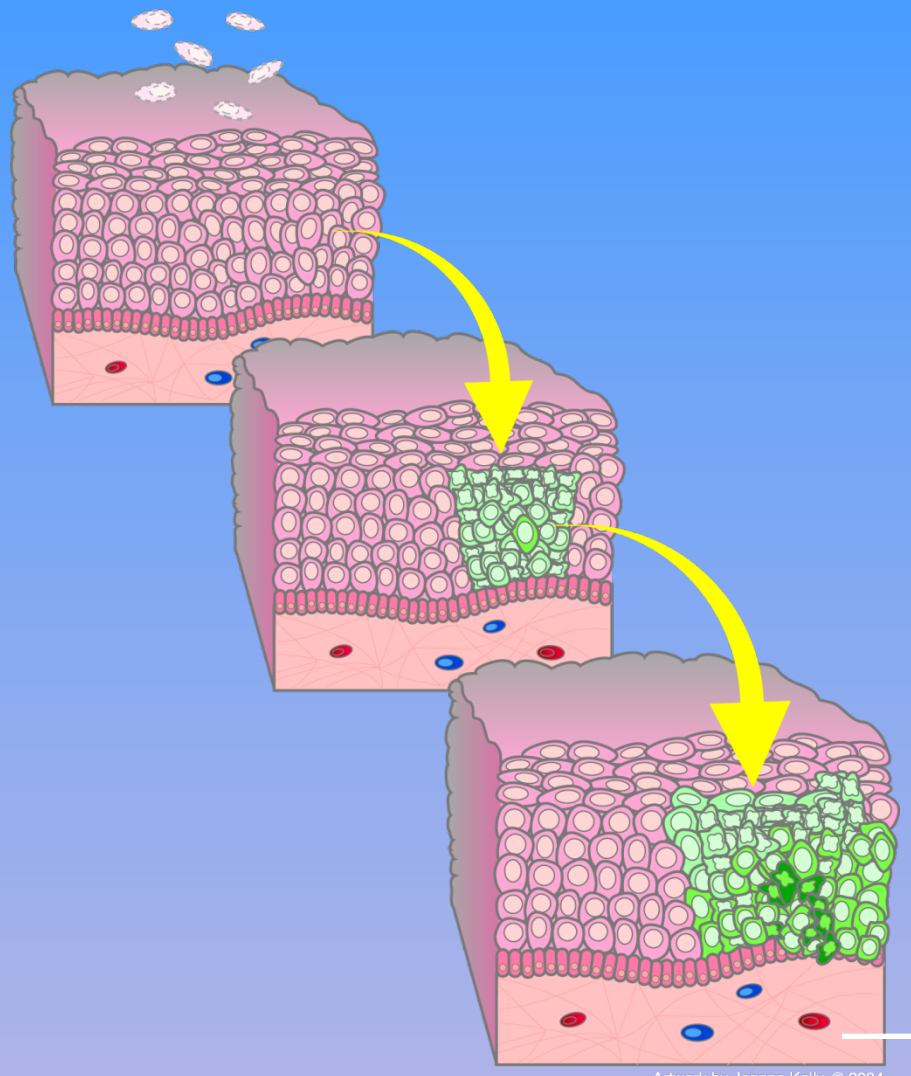
John Niederhuber, Director (2006-2010), National Cancer Institute: *"it is the NCI's hope that physics, physical chemistry, mathematics, and engineering can help to solve some of the most difficult and complex problems in cancer biology today"*

What can Physics contribute to Cancer Research?

What is Cancer?
(a physicist's perspective)

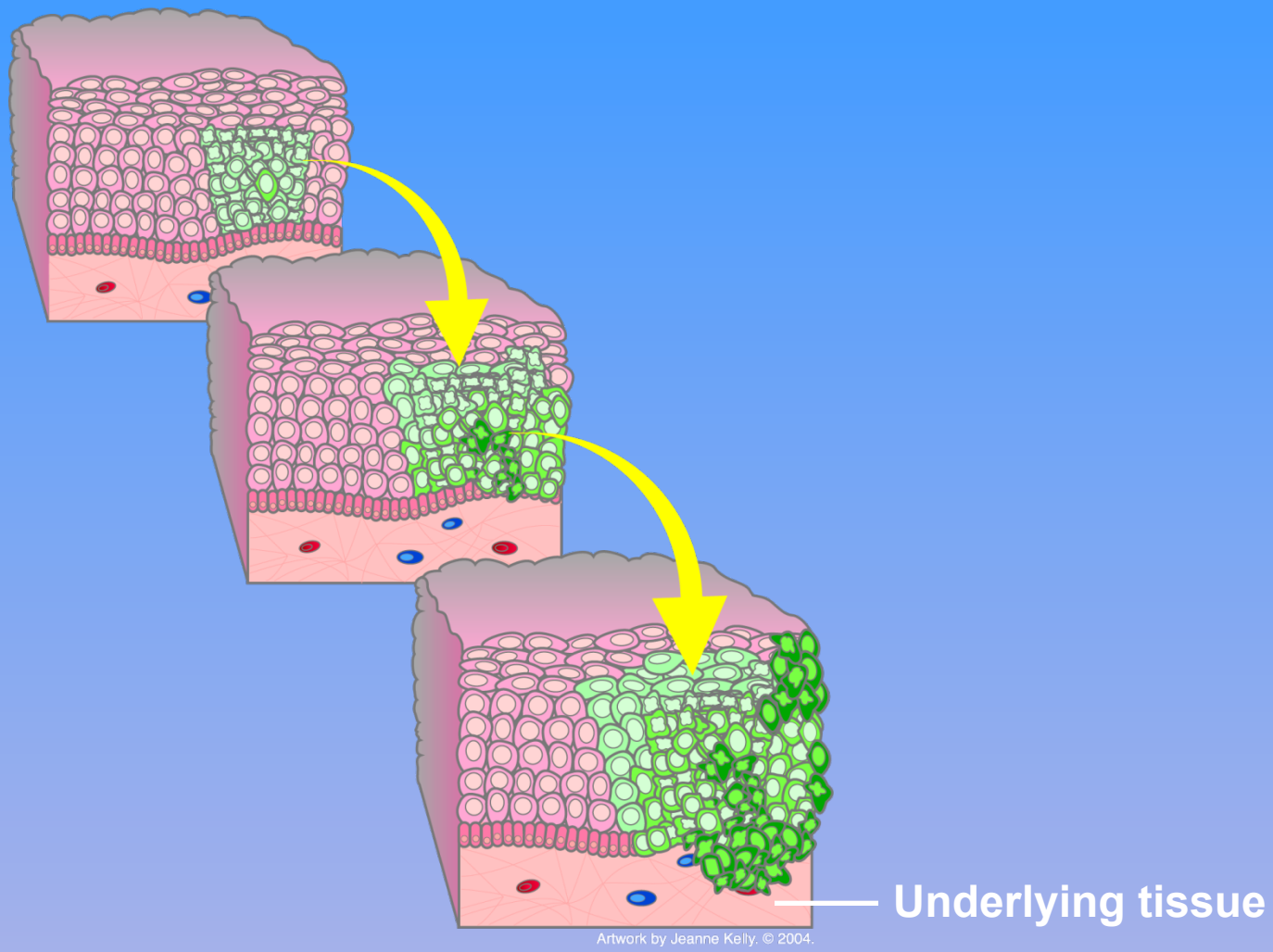
The Beginning of Cancerous Growth

(from National Cancer Institute– "Understanding Cancer" Series)



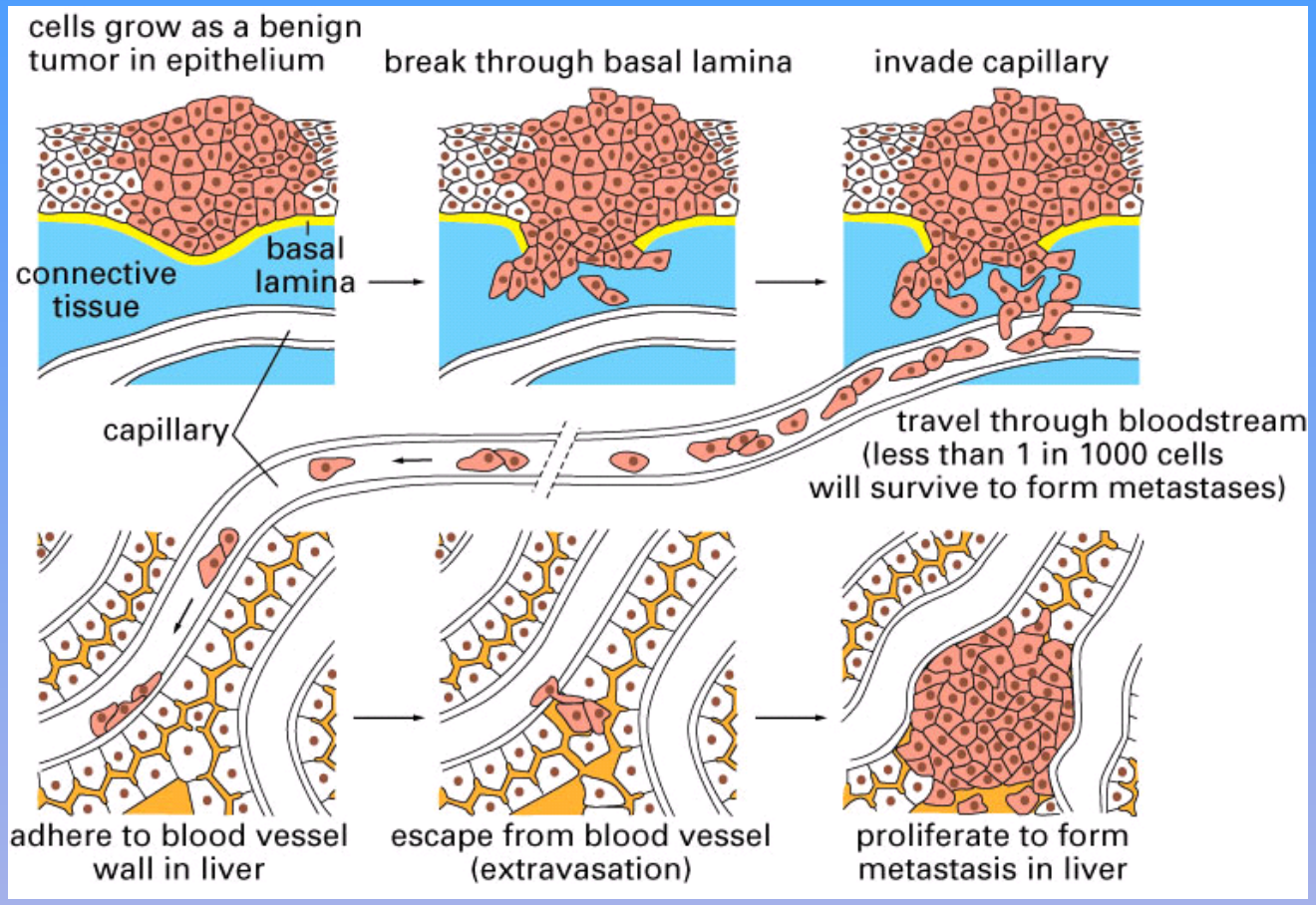
Artwork by Jeanne Kelly. © 2004.

Tumors Spread Into Surrounding Tissue



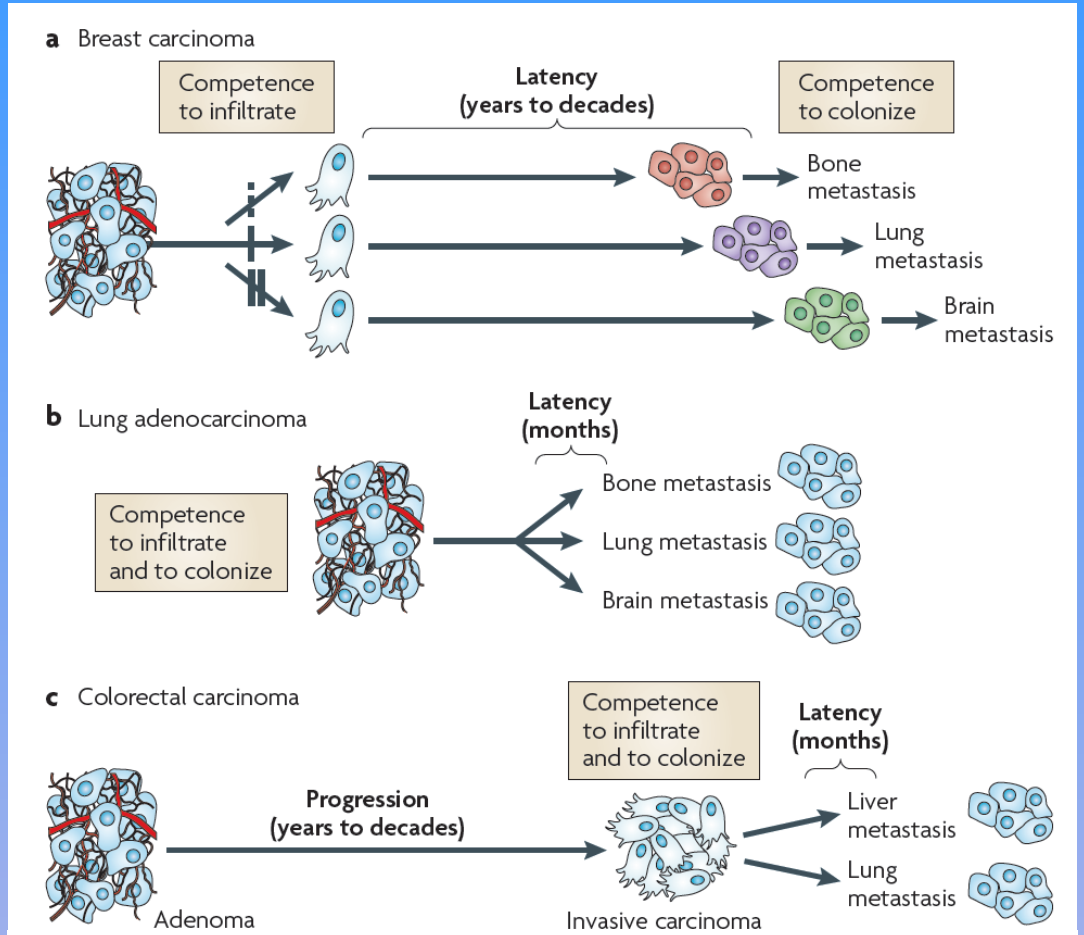
from the NCI – Understanding Cancer Series

Tumor invades into the bloodstream and develops metastasis at new location



Alberts, B. et al. Molecular Biology of the Cell p. 1325 (2002)

Metastatic tumors are localized in specific organs and grow after a long delay

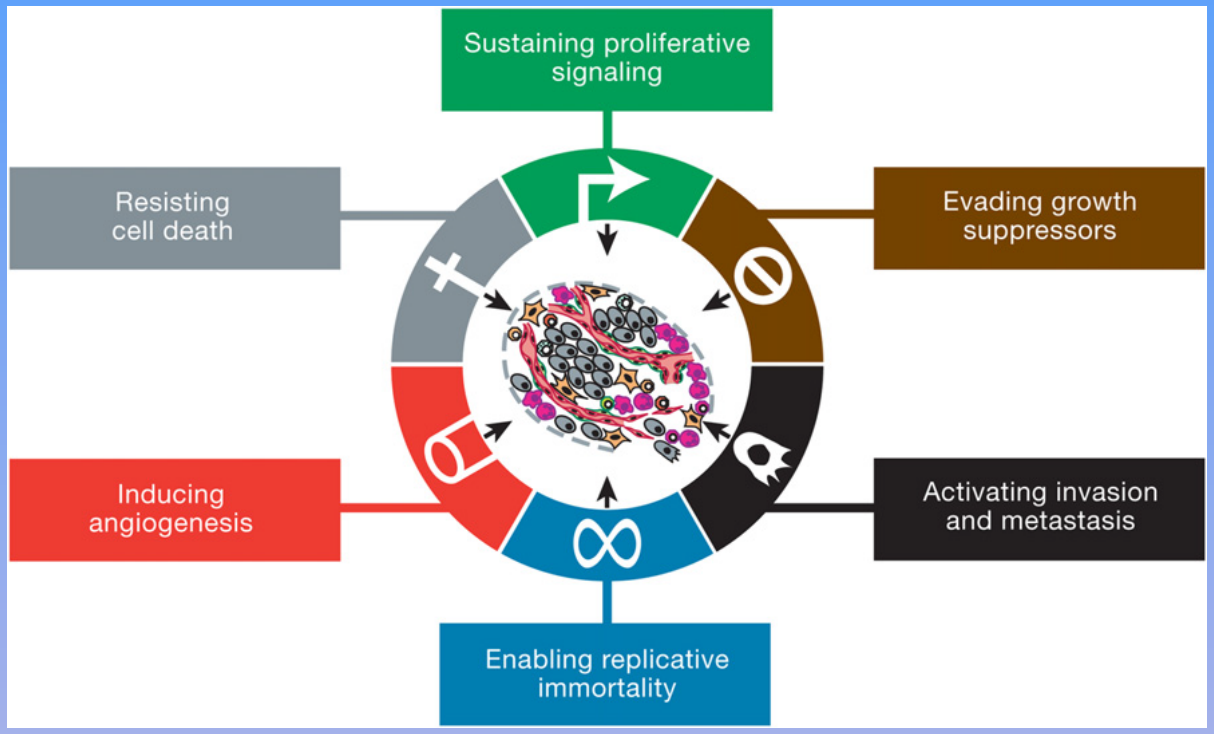


Metastasis: from dissemination to organ-specific colonization

Don X. Nguyen, Paula D. Bos* and Joan Massagué*‡*

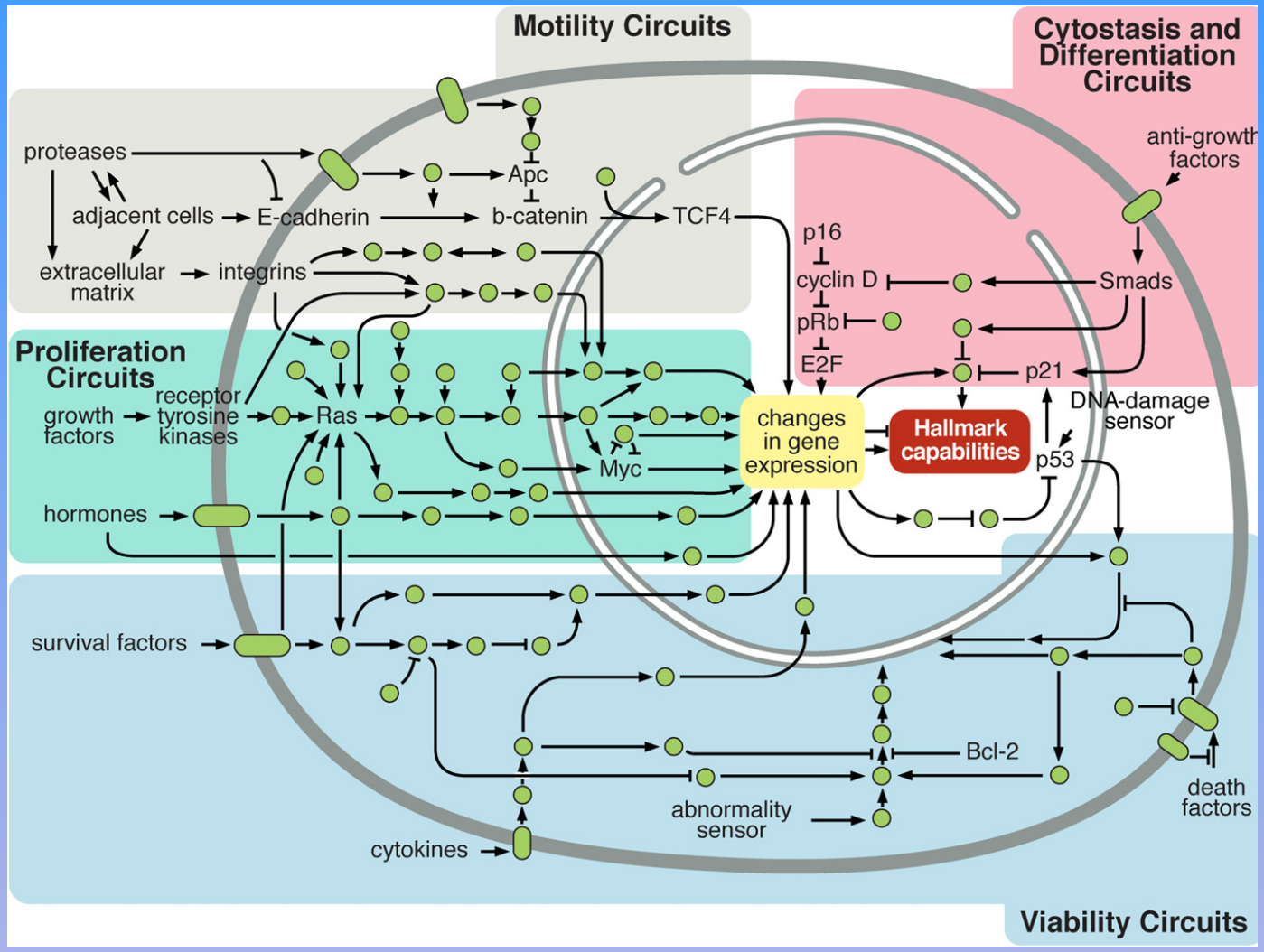
What changes in cell behavior are associated with Cancer?

The Hallmarks of Cancer: Key capabilities of Cancer Cells



Hanahan and Weinberg 2000

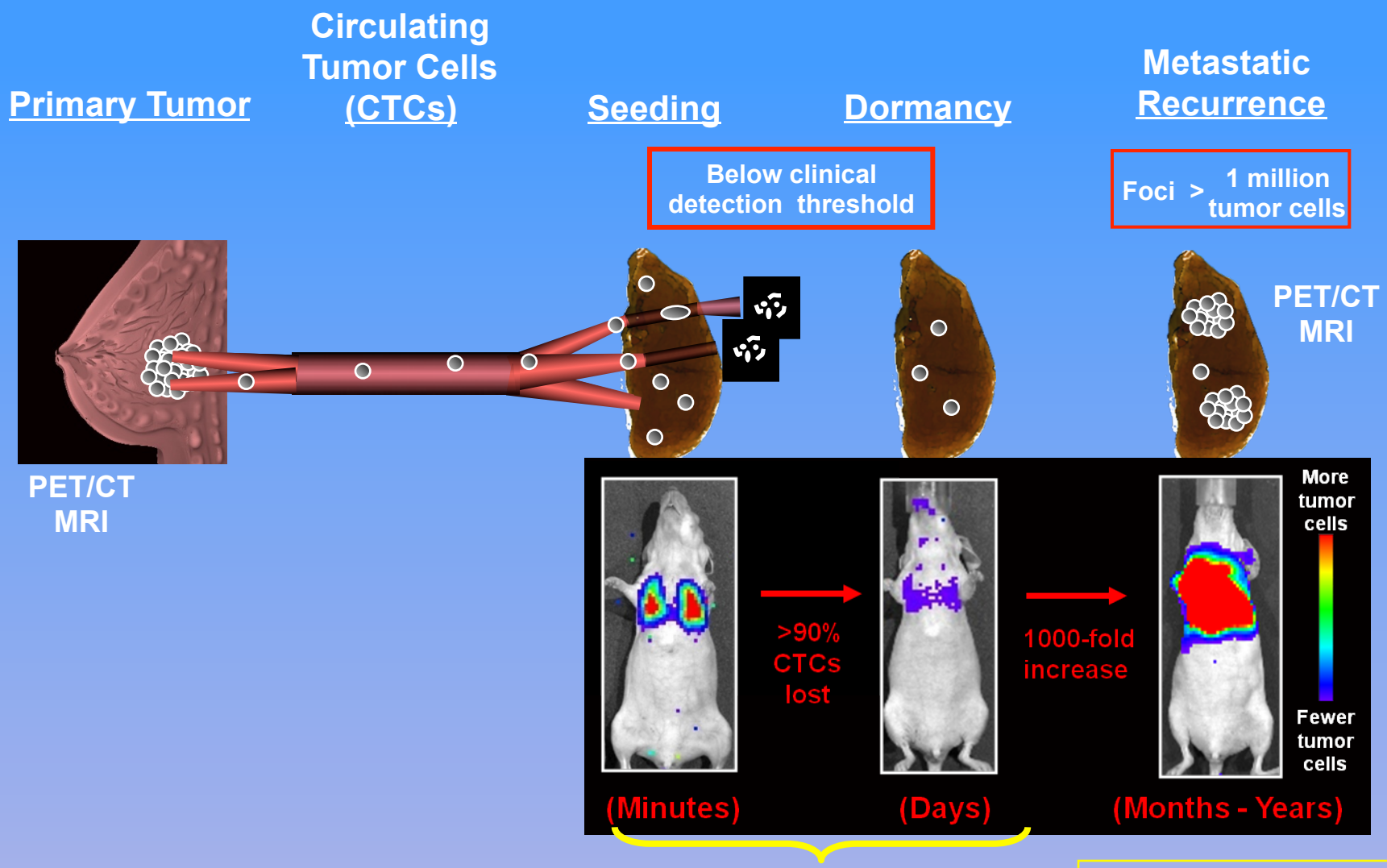
Hallmark capabilities are driven by complex Circuits



Hanahan and Weinberg, Cell 2010

Some of the many Challenges in Cancer Research

How to detect cancer early?



Eradicate these cells → Delay or Eliminate Recurrence

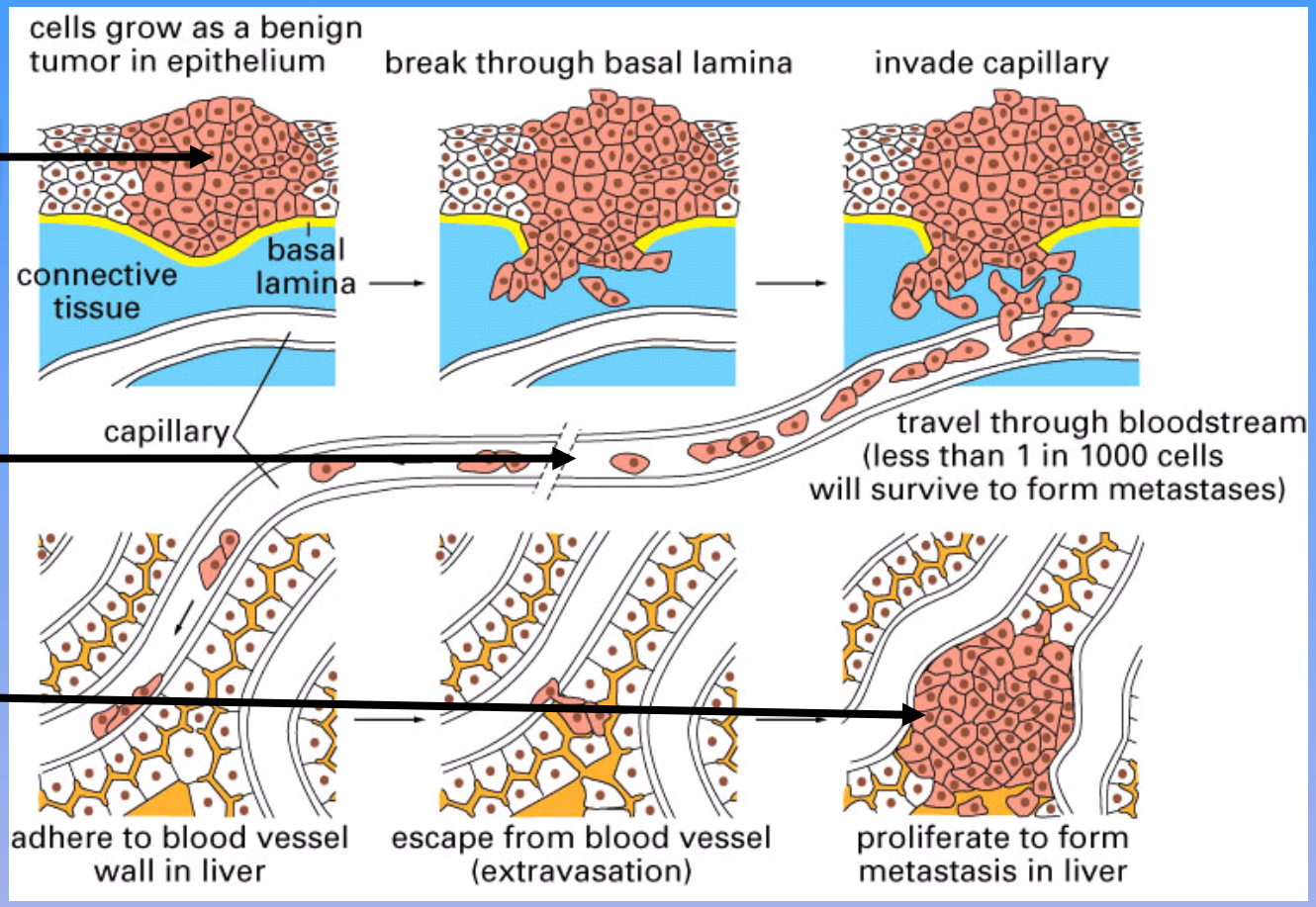
Stuart Martin, University of Maryland Medical School

How to target cancer cell subpopulations?

Primary Tumor

Circulating Tumor Cells

Metastasis



Source:

What can Physics contribute to Cancer Research?

What can Physics contribute to Cancer Research?

Experimental Tools for Diagnosis and Therapy

- MRI for high resolution imaging
- X-ray tomography

Experimental Tools for Studies of Living Systems

- Superresolution imaging (Betzig)
- NextGeneration Gene Sequencing (Quake)

Physics Approaches: Quantitative Approaches to Complexity & Information

Physical Principles: Forces and Motion

(stochastic system far from equilibrium)

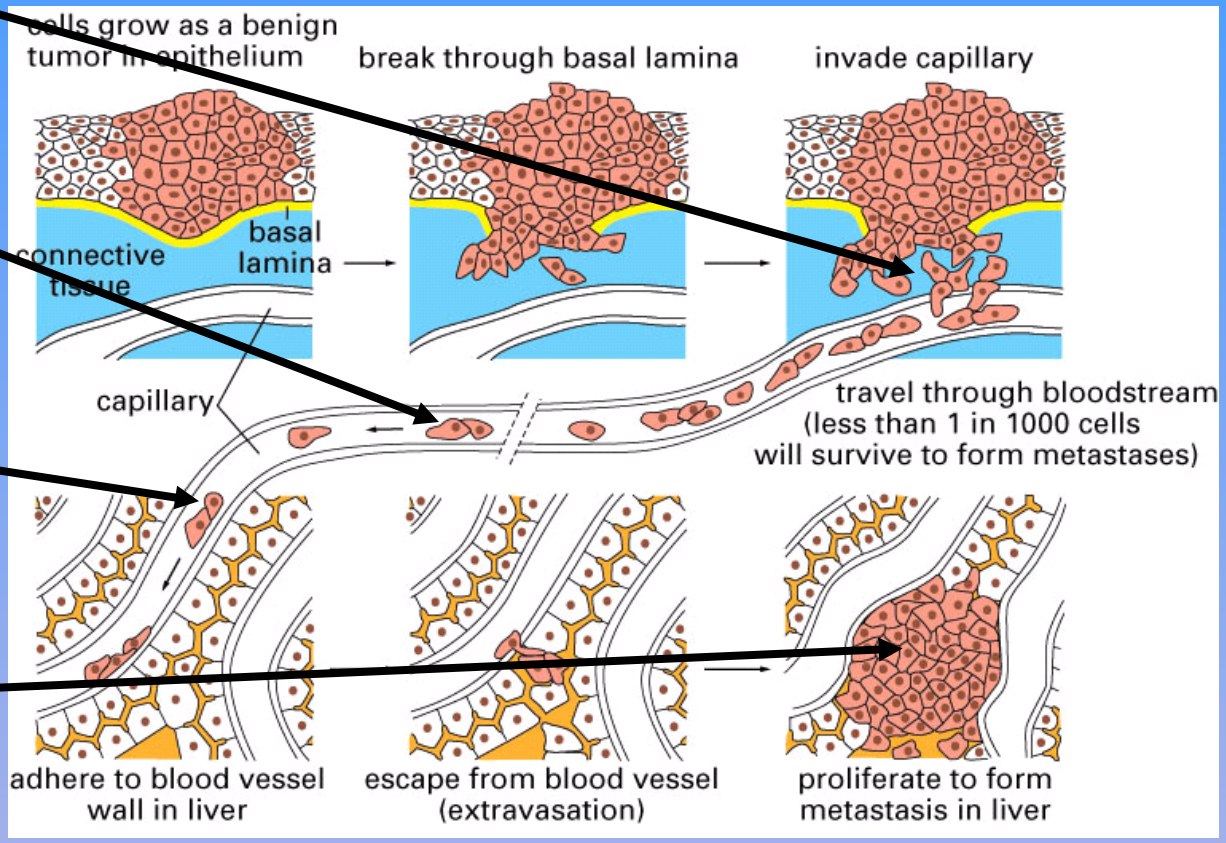
Constraints on Forces & Motion for Cancer Metastasis

Cancer cells generate forces & migrate

Cells are deformed by fluid forces

Cells adhere to blood vessel walls

Cells grow in tissue with different stiffness



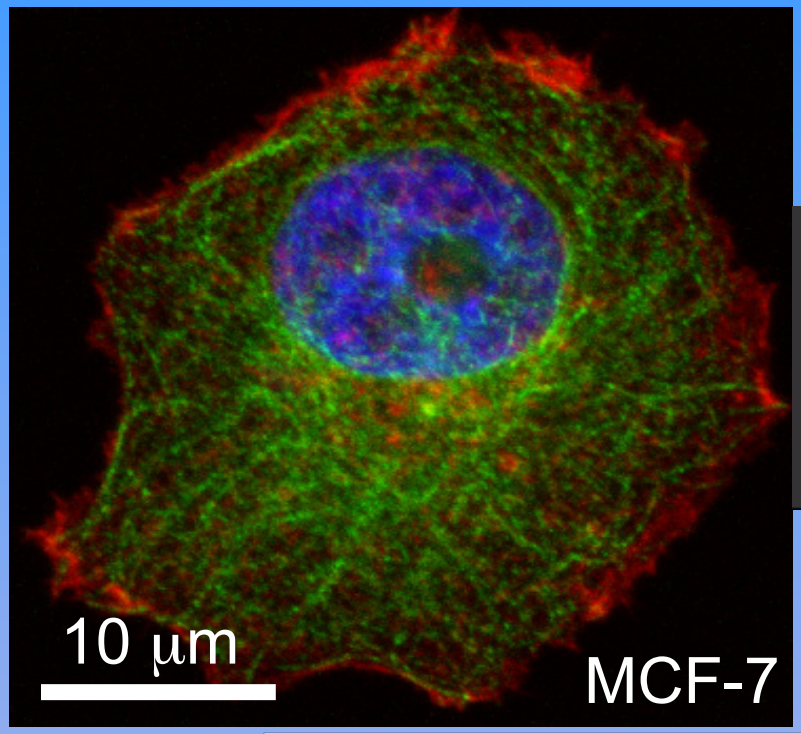
Alberts, B. et al. Molecular Biology of the Cell p. 1325 (2002)

Mechanics of the Cell

a complementary perspective on cancer

Proteins Actively Control Forces and Motion

Structural Elements



Eleanor Ory

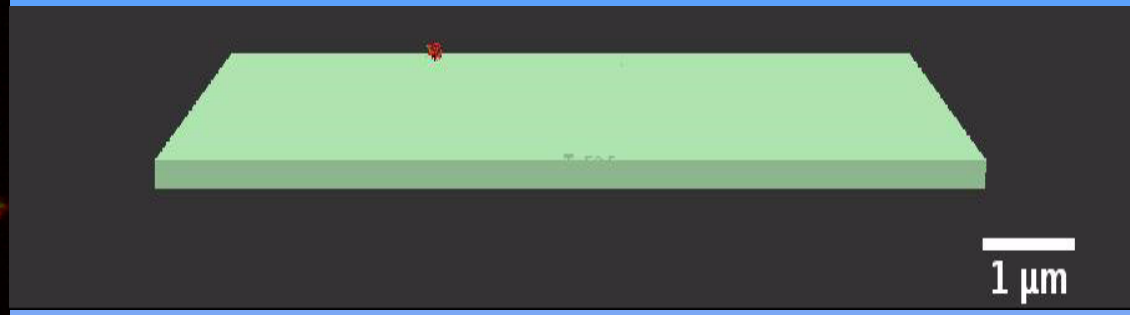
Scaffolding of

- **Actin,**
- **Microtubules,**
- Intermediate Filaments

Active Elements

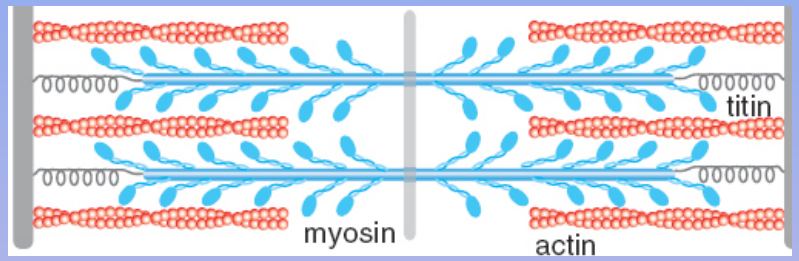
Joshua Parker

Nucleation, growth and crosslinking of scaffolding



Simulations of Actin Waves w/ Carlsson (WashU)

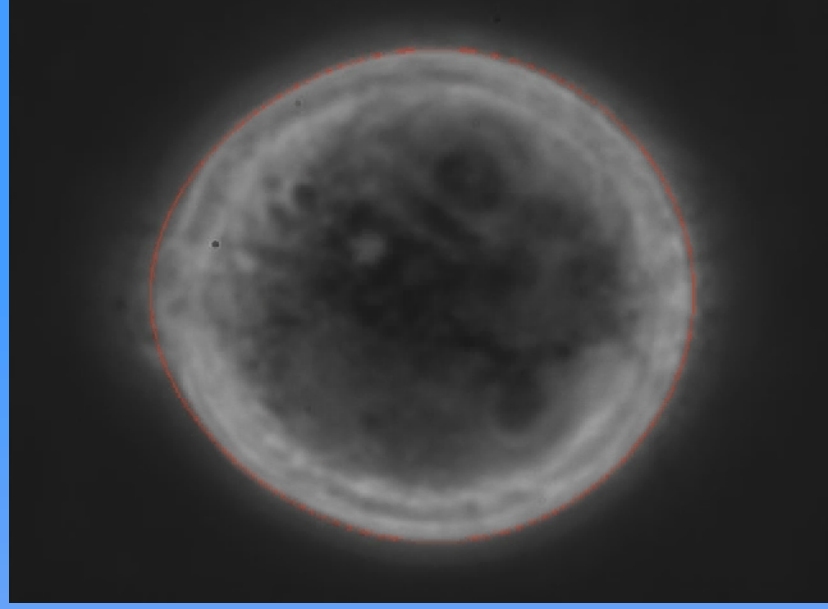
Pulling on Scaffolding (e.g.myosin motors)



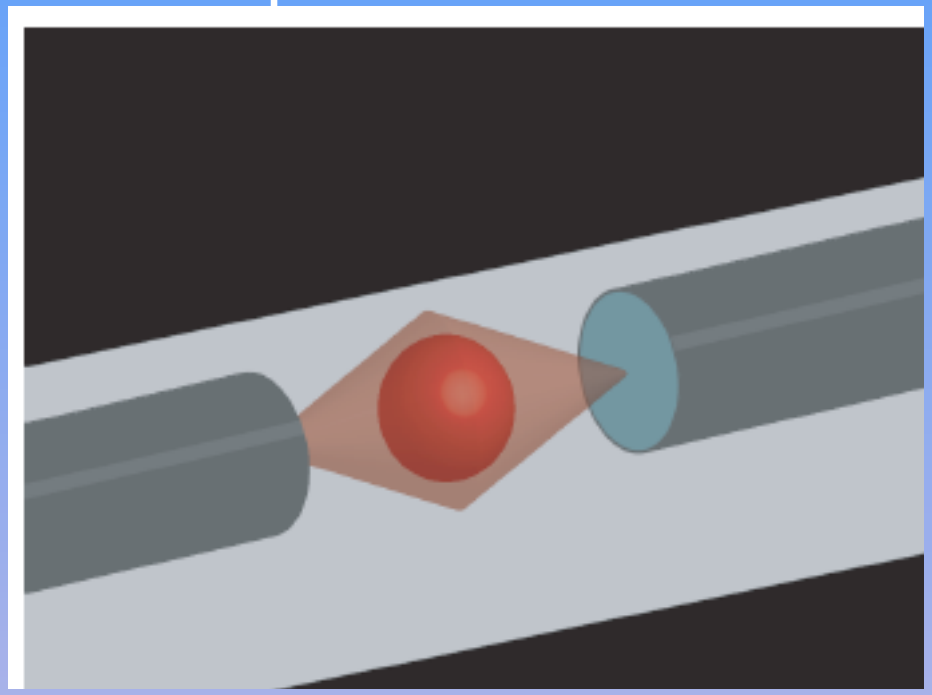
Günther and Kruse, NJ Phys. (2007)

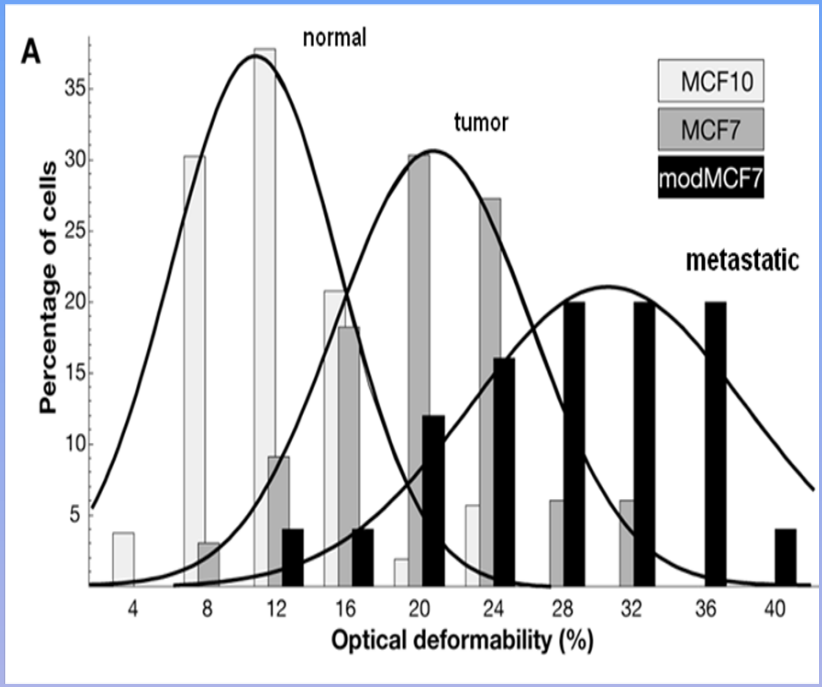
Genes Proteins → Forces

Cells cultured from tumorous or metastatic tissue are usually softer than normal cells.



Optical Stretcher



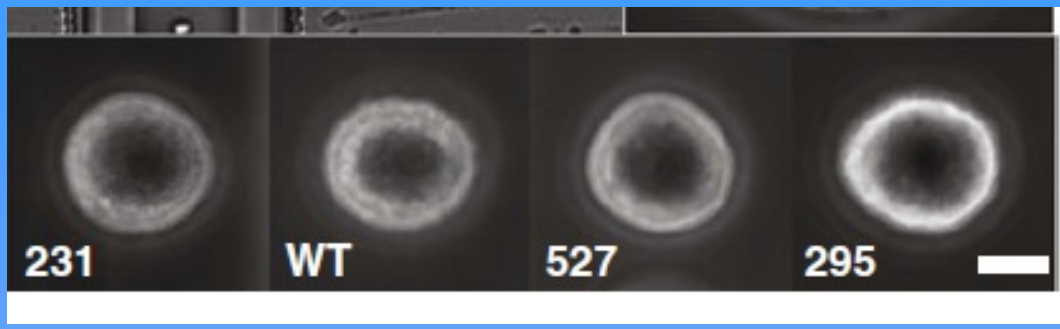


Käs Lab, Leipzig

Activation of Cancer related genes increase softness

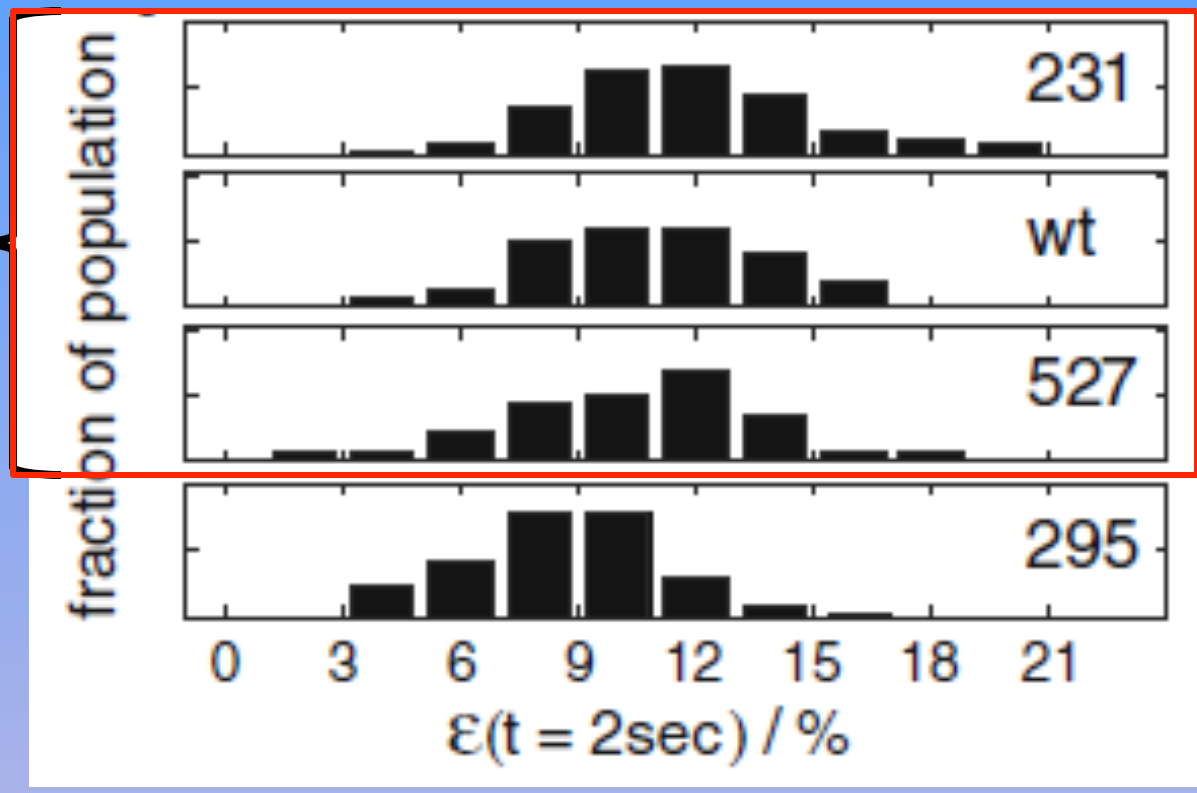
231: Breast Cancer Cell line

c-src:
Proto-Oncogene
On in 50% of cancers



src ON

src OFF

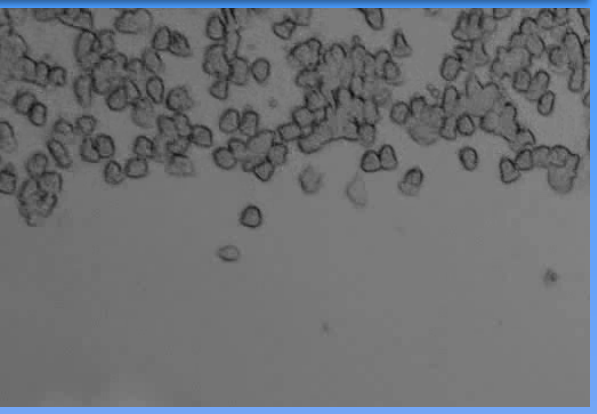


Kiessling, Herrera, Nnetu, Balzer, Girvan, Fritsch, Martin, Kaes, and WL, *Euro. Biophys. J* (2013)

Physics of Cell Migration

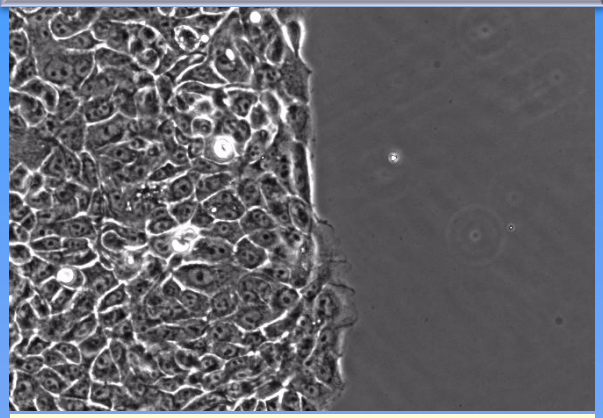
What is Cell Migration?

Immune Response
(white blood cells)



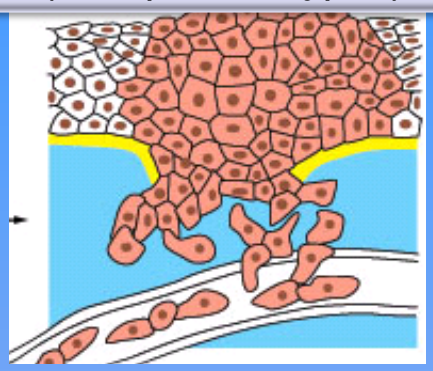
L. Liu, S. Das, W. Losert, & CA. Parent *Dev. Cell* (2010)

Wound Healing
(epithelial cells)



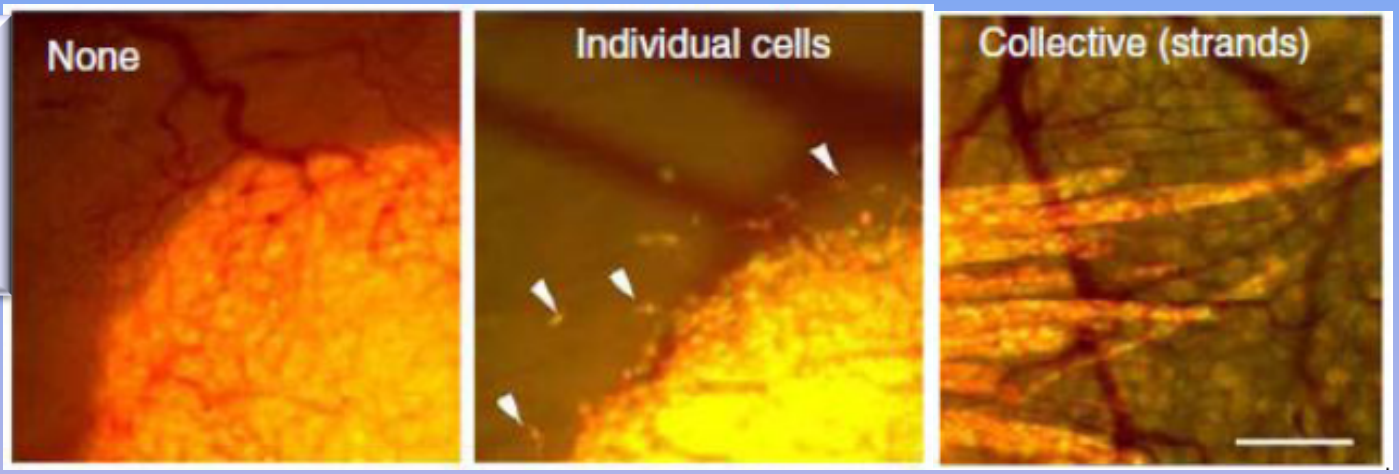
MC. Weiger, …W.Losert, & CA Parent, *PLOS ONE* (2013).

Cancer Cell Migration
(multiple cell types)



Alberts, B. et al. (2002)

In-Situ Imaging of Tumor Growth and Spreading in a Living Mouse



Alexander, Koehl, et al. Histochemistry and Cell Biology(2008).

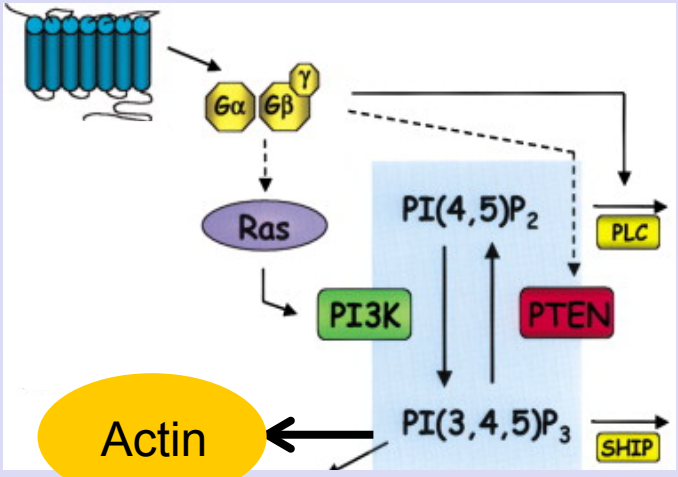
Signaling Pathways Control Cell Migration

Genes
Proteins

↓

Forces

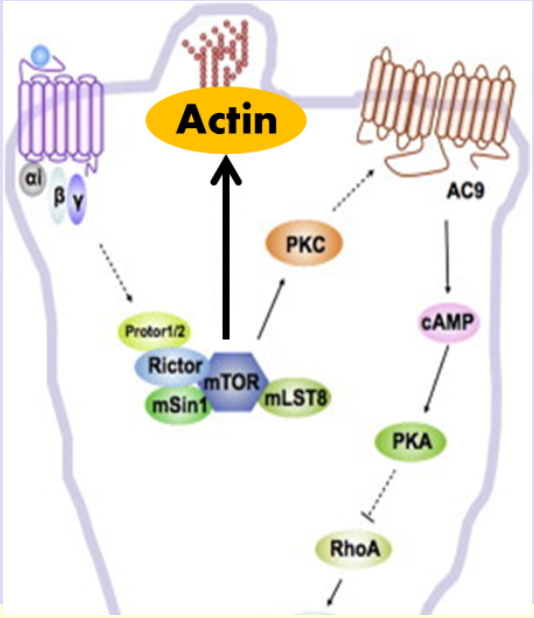
Dictyostelium



F Comer & CA Parent *Cell* (2002).

R. Skupsky, C. McCann, R. Nossal, & W. Losert, *J. Theor. Biol.* (2007).

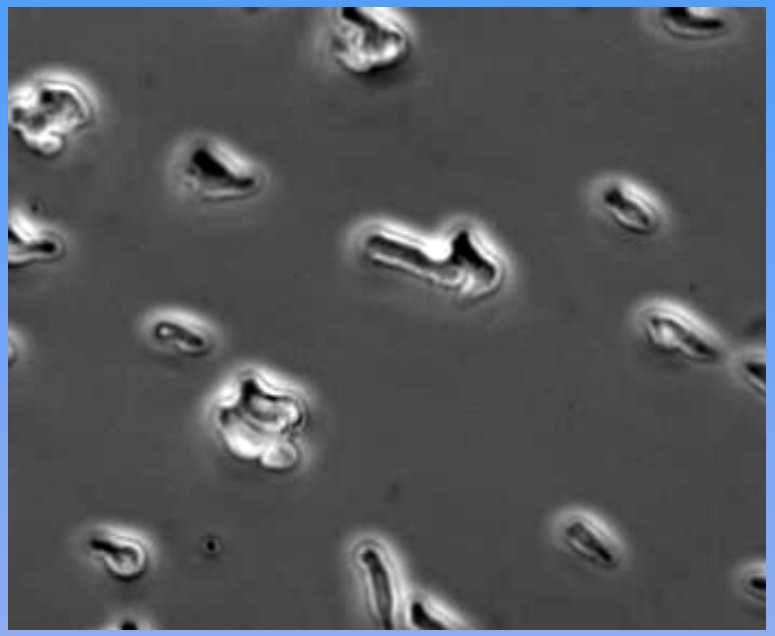
White Blood Cells



L. Liu, S. Das, W. Losert, & C.A. Parent *Developmental Cell* (2010).

A physical model of Cell Migration

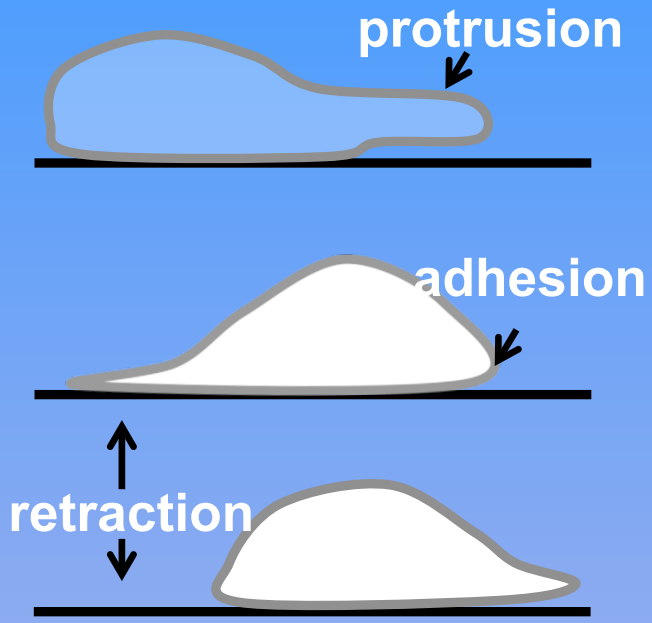
Model Organism for Migration
Dictyostelium discoideum



(top view, data)

- Amoeboid type migration
- Weak adhesion to surface
  (no focal adhesion complexes)

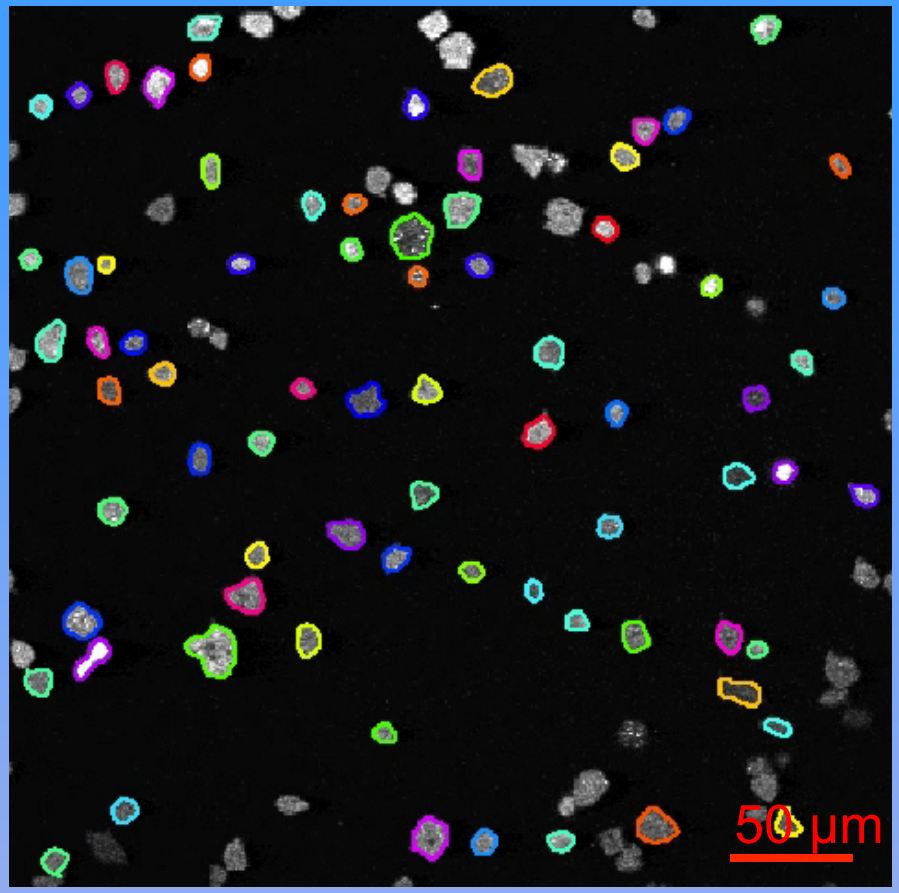
Model of the Physical Process:

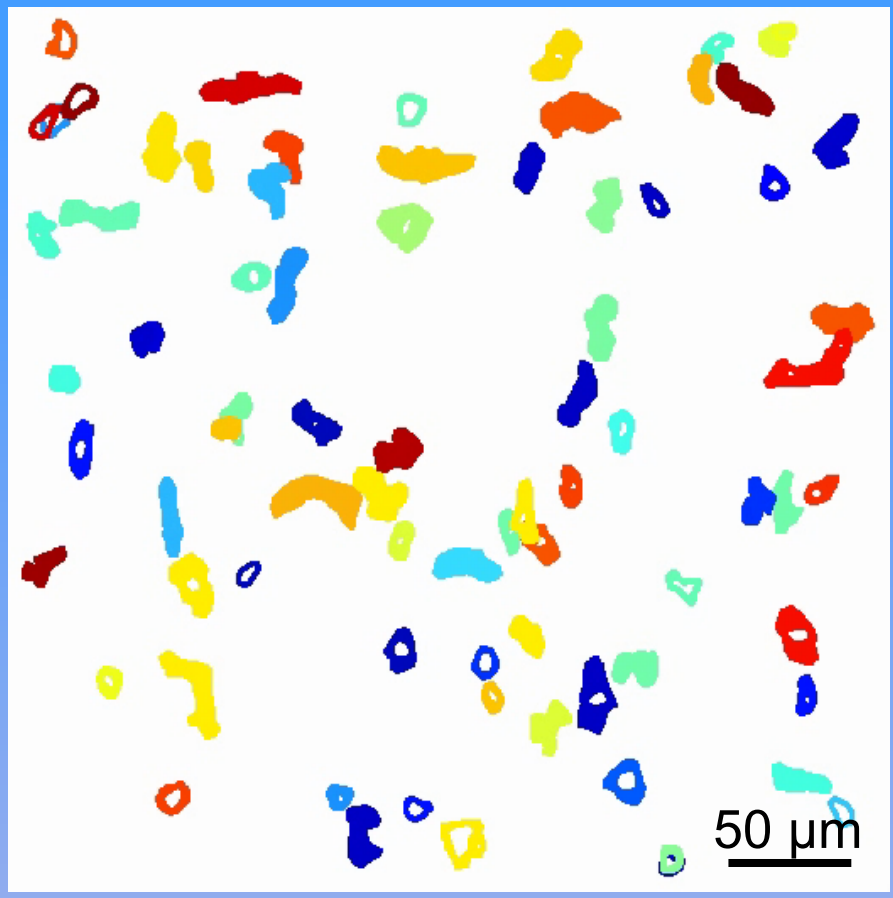


(side view, schematic)

- Protrusion of front
- Adhesion of front
- Retraction of back

Systematic Analysis of Shape Dynamics





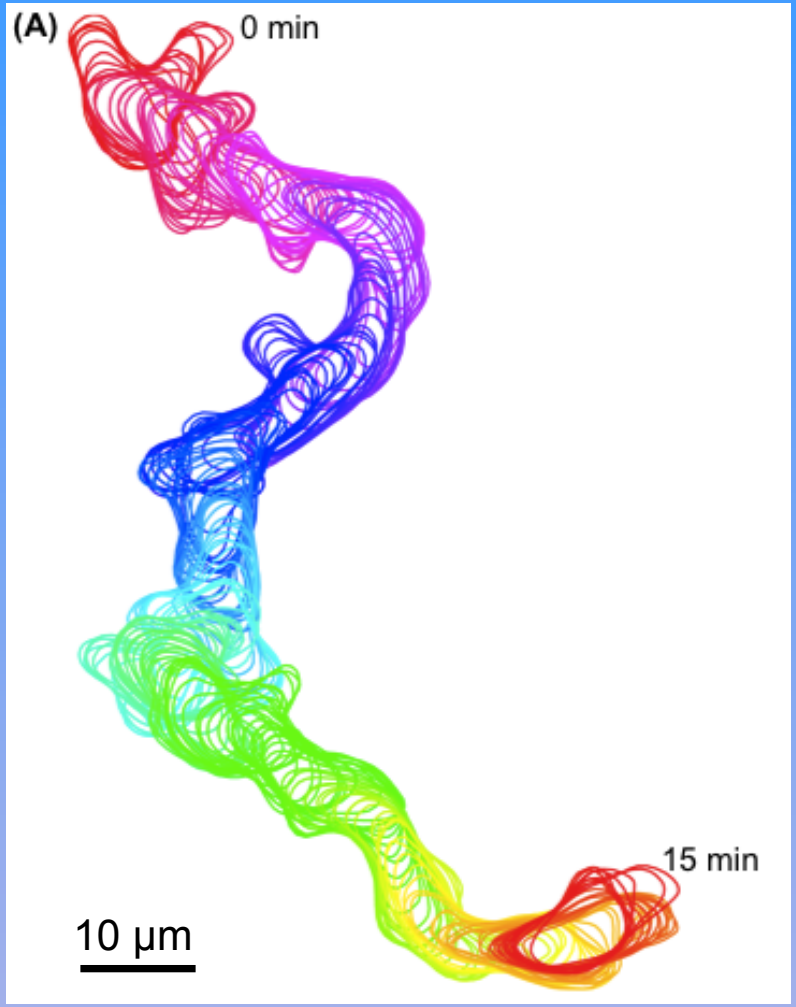
Meghan Driscoll

100 frames; 6.7 minutes

One Movie: 71,700 shapes in 922 tracks
(1200 frames; 80 minutes)

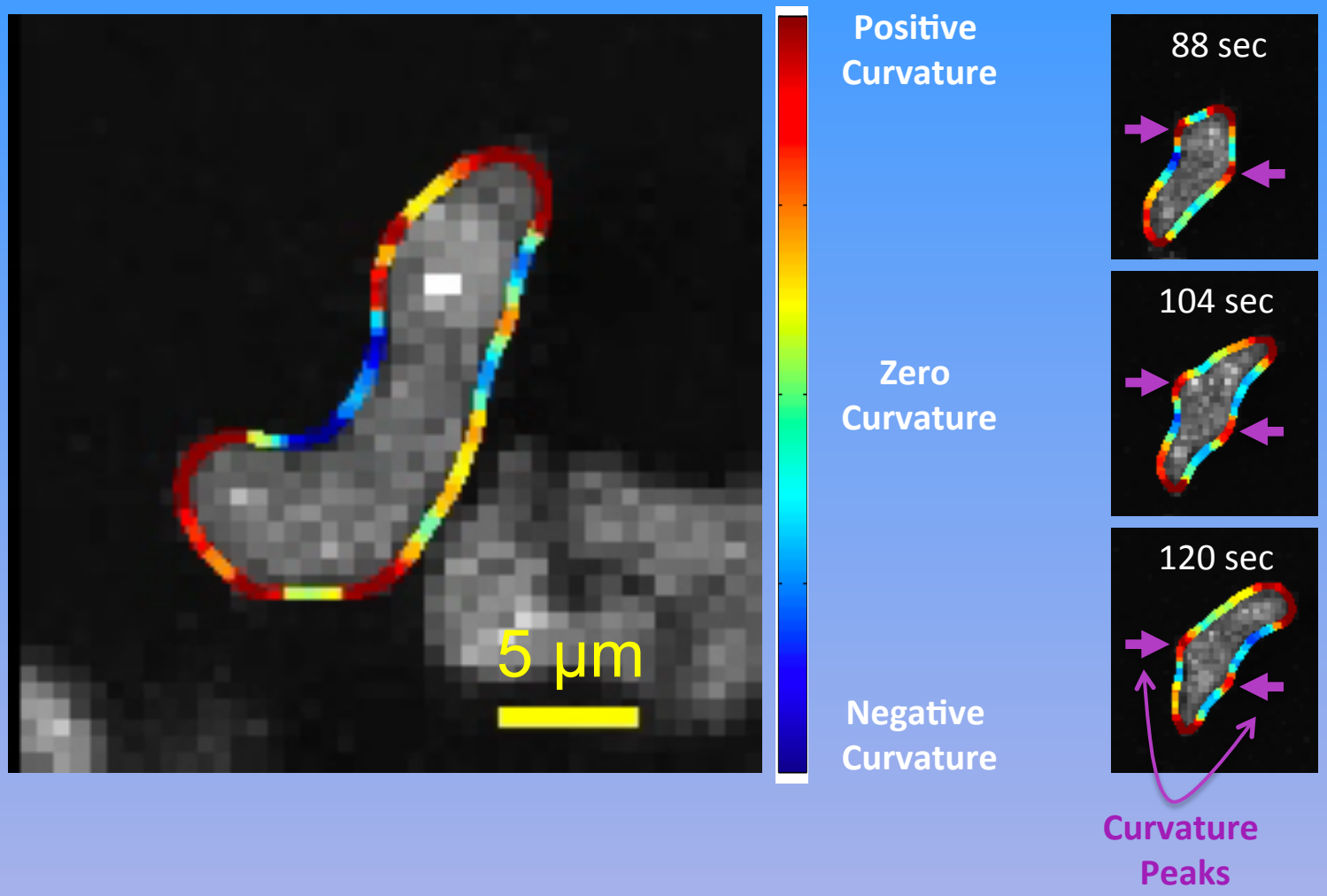
Driscoll et al., *PLOS Comp. Biol.* (2012)

Analyzing Shapes and Shape Dynamics



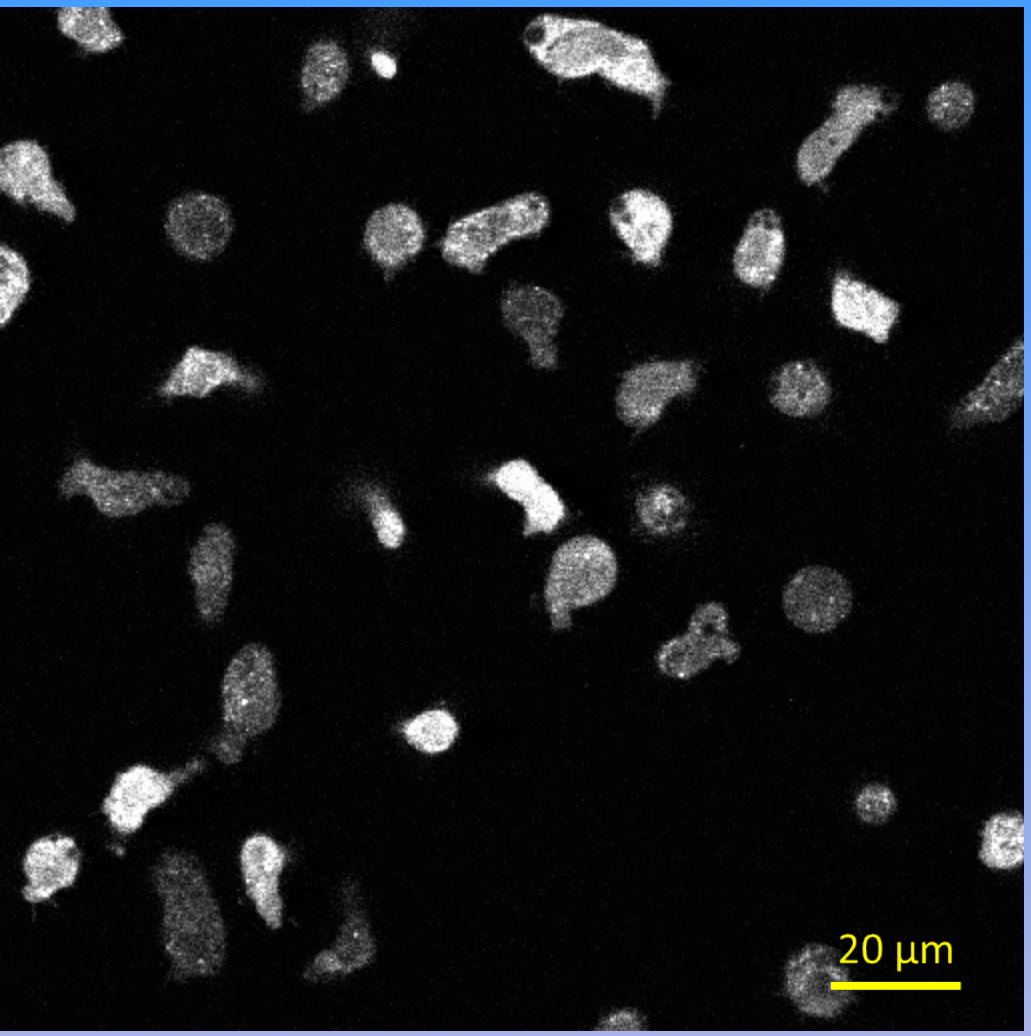
Driscoll, Fourkas and Losert, *Physical Biology* (2011)

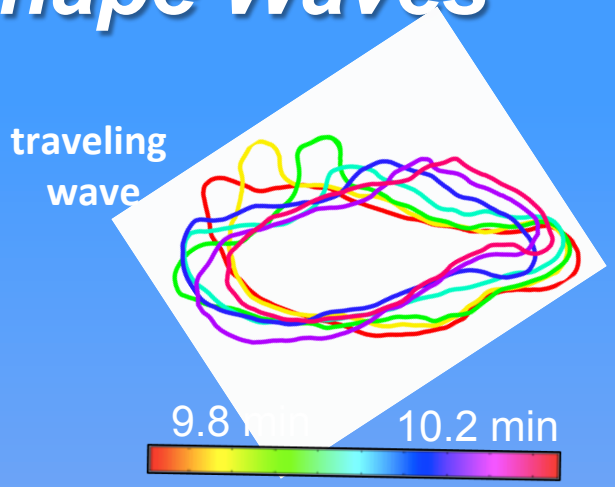
Local Shape Reveals Traveling Protrusions

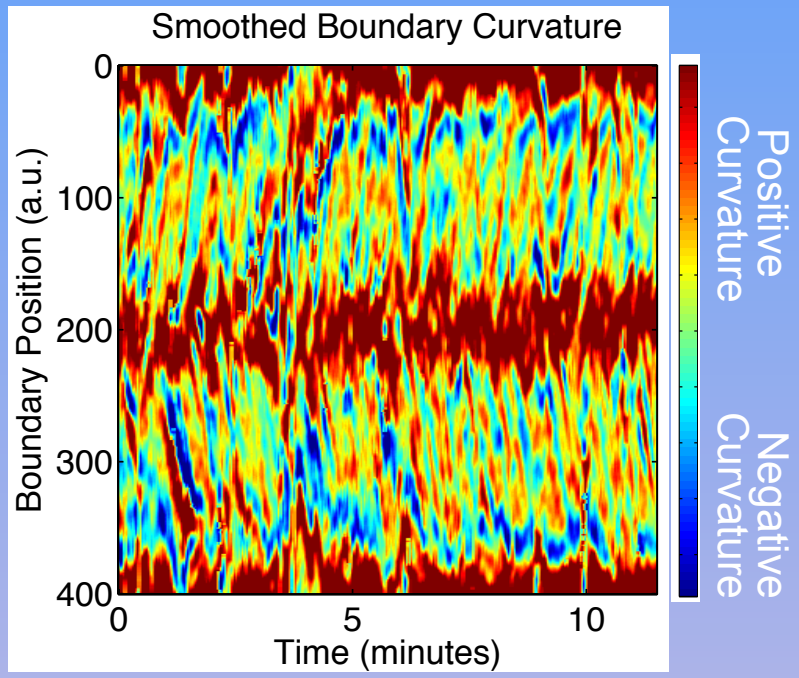


Driscoll, Fourkas and Losert, *Physical Biology* (2011)

Inhibiting Cell-Surface Adhesion Enhances Visibility of Shape Waves



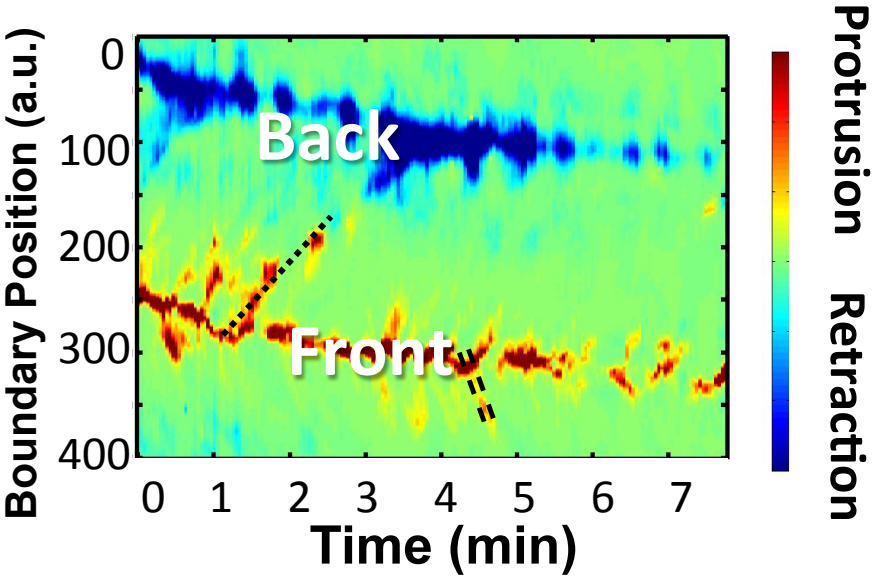




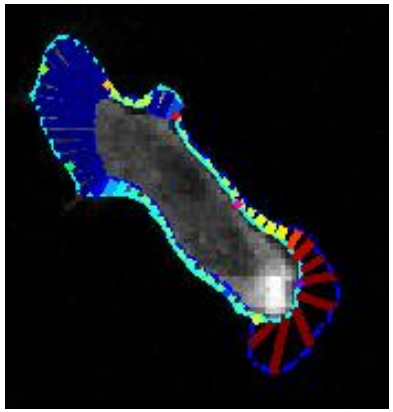
Driscoll et al *PLOS Comp Biol* (2012)

Protrusions Correlate with Actin Waves

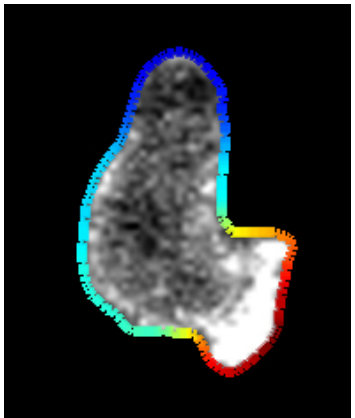
Actin Waves

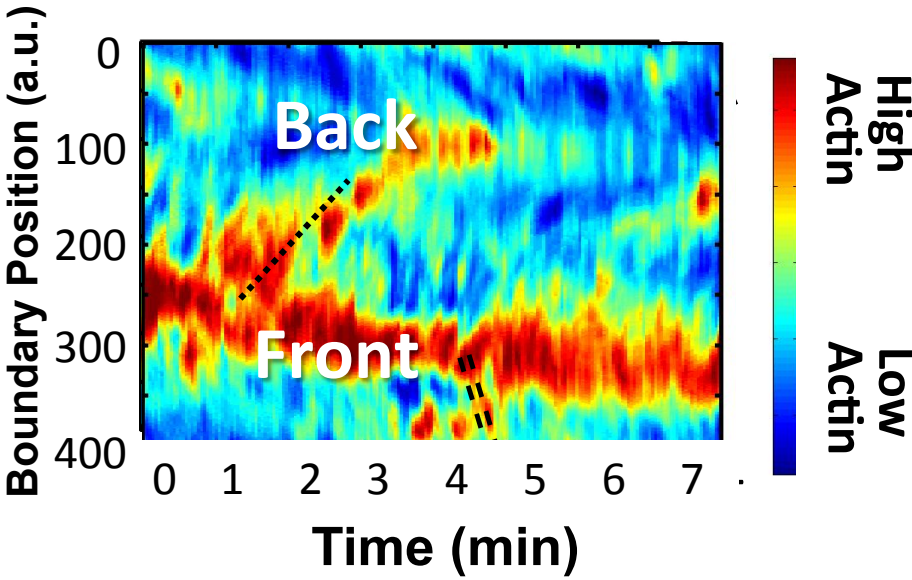


Protrusions

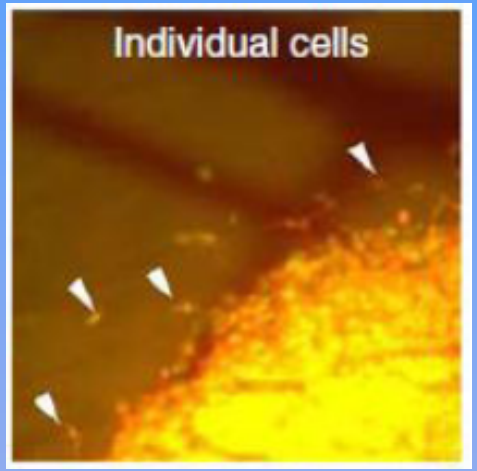


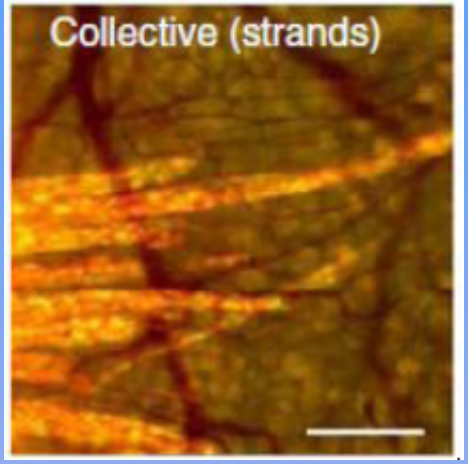
Actin





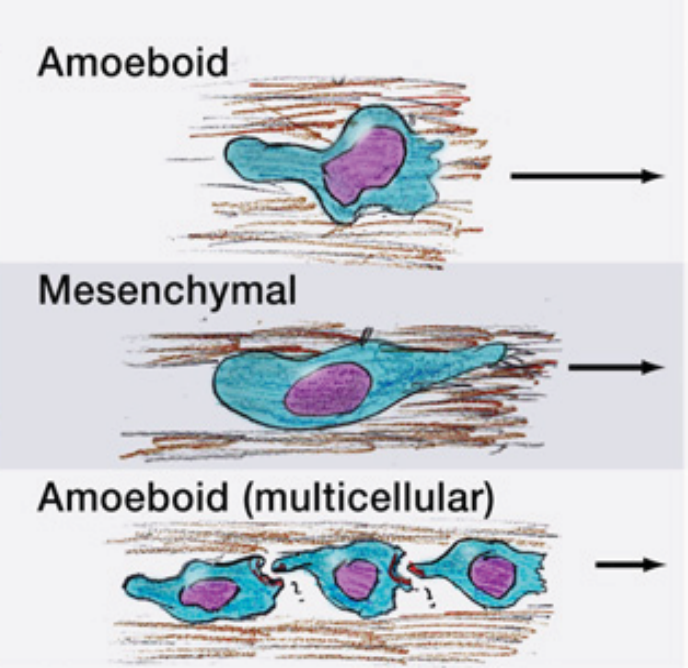
Does the wave-like nature of Cell Migration provide a new perspective on Cancer?





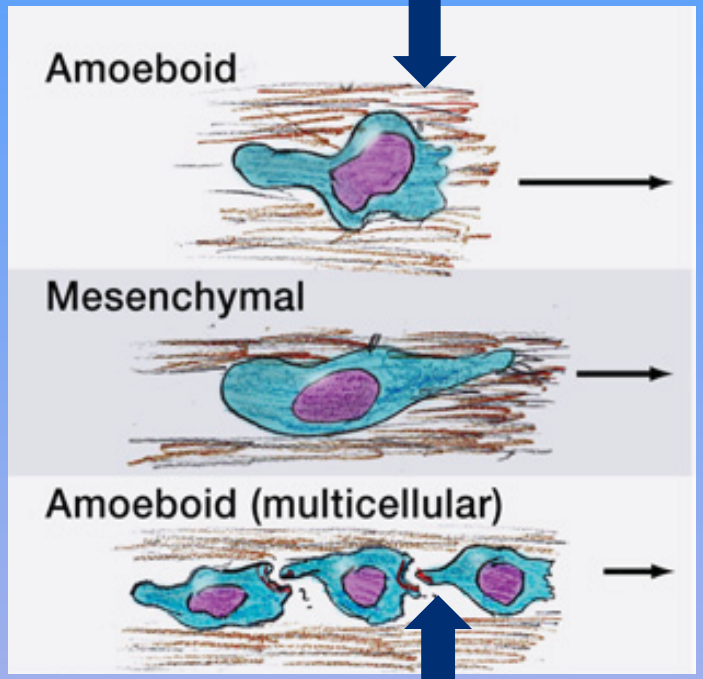
Alexander, Koehl, et al. Histochemistry and Cell Biology(2008).

Friedl and Alexander Cell (2011).



Our observations of mechanical waves raise two new questions about cancer related cell migration

1) How does topography of surrounding affect waves?

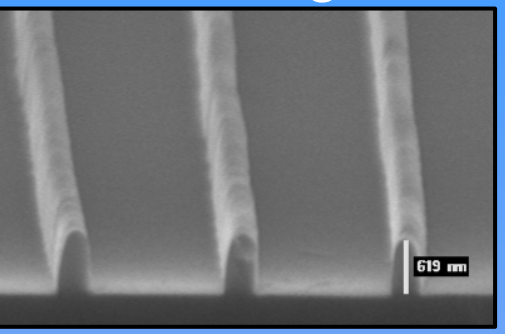


Friedl and Alexander Cell (2011).

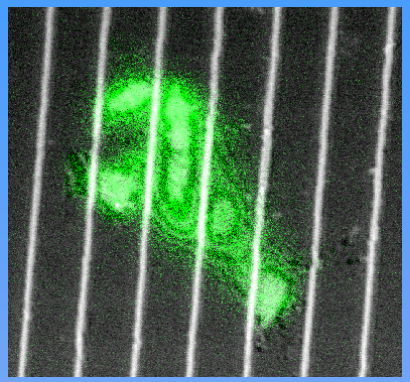
2) How do waves cooperate in cell groups?

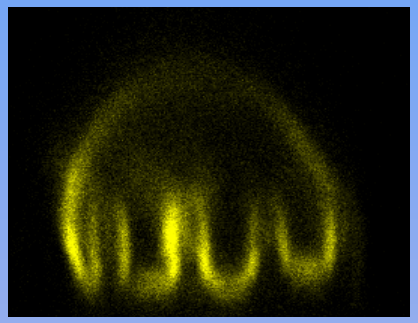
Dictyostelium Cells Follow Ridges on Surface

Nano-Ridges



500 nm

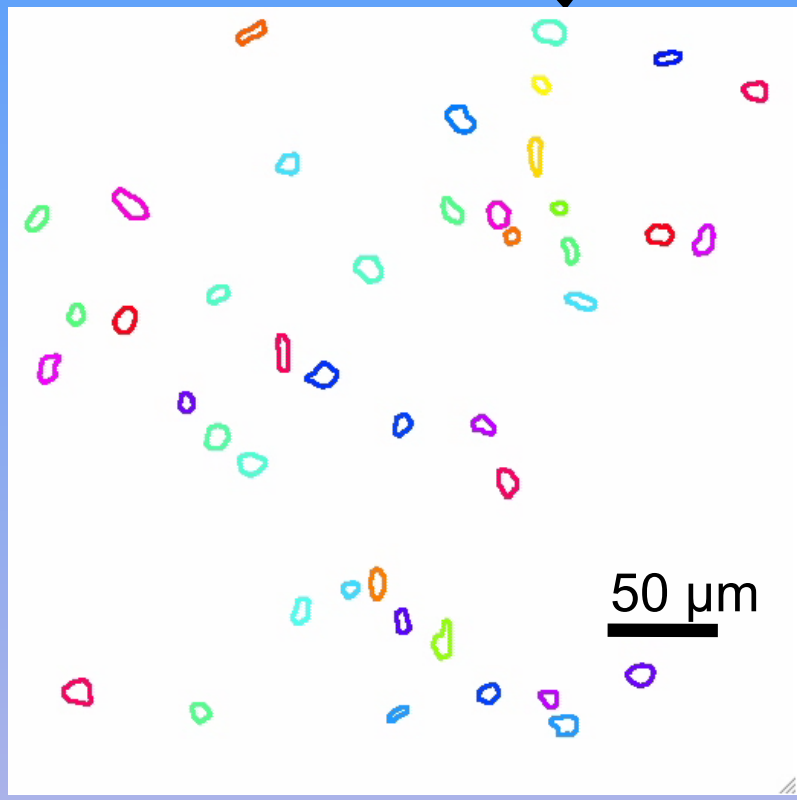




Xiaoyu Sun

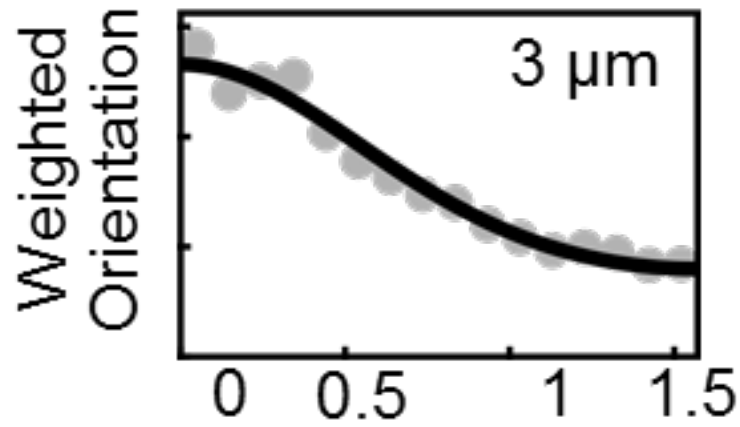
Meghan Driscoll

Ridge Orientation



Optimal Ridge Spacing for Contact Guidance

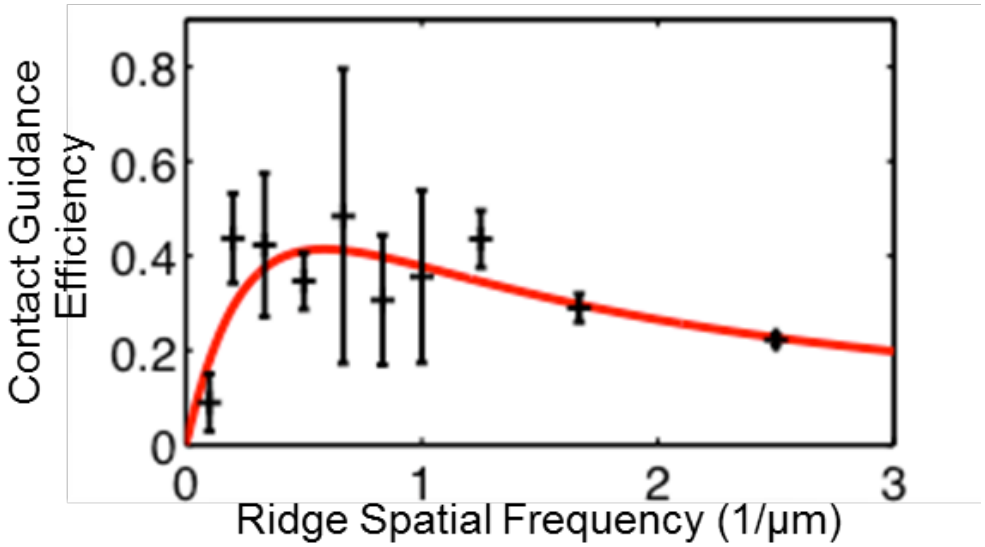
Fit to Circular Normal Distribution



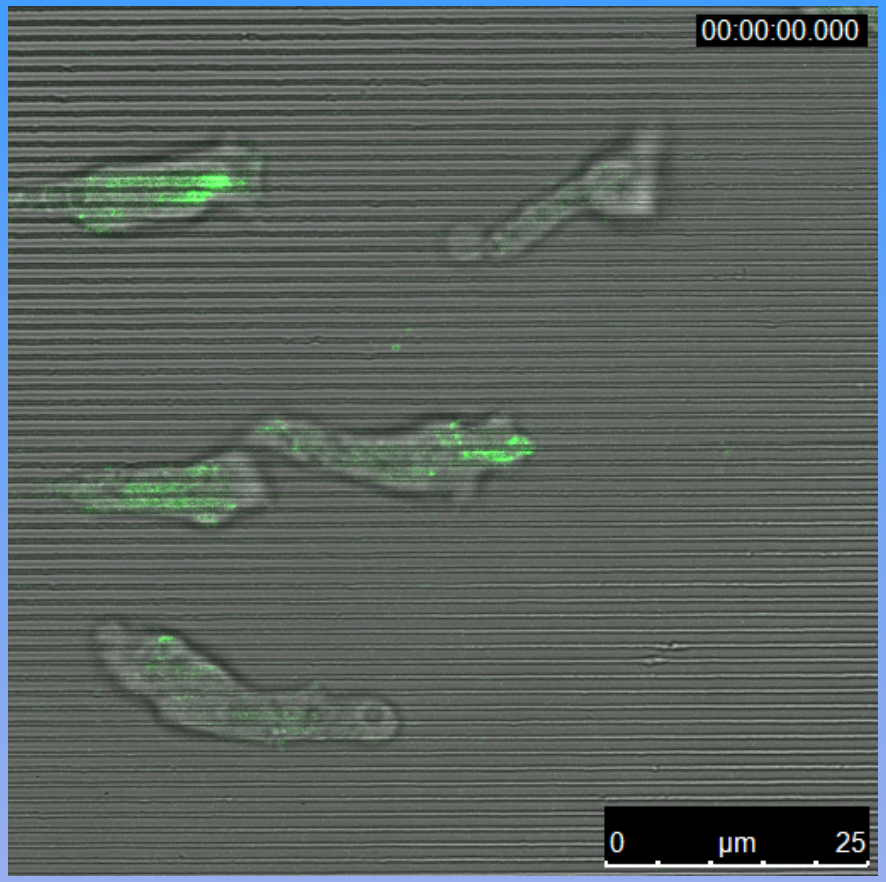
Can Guven

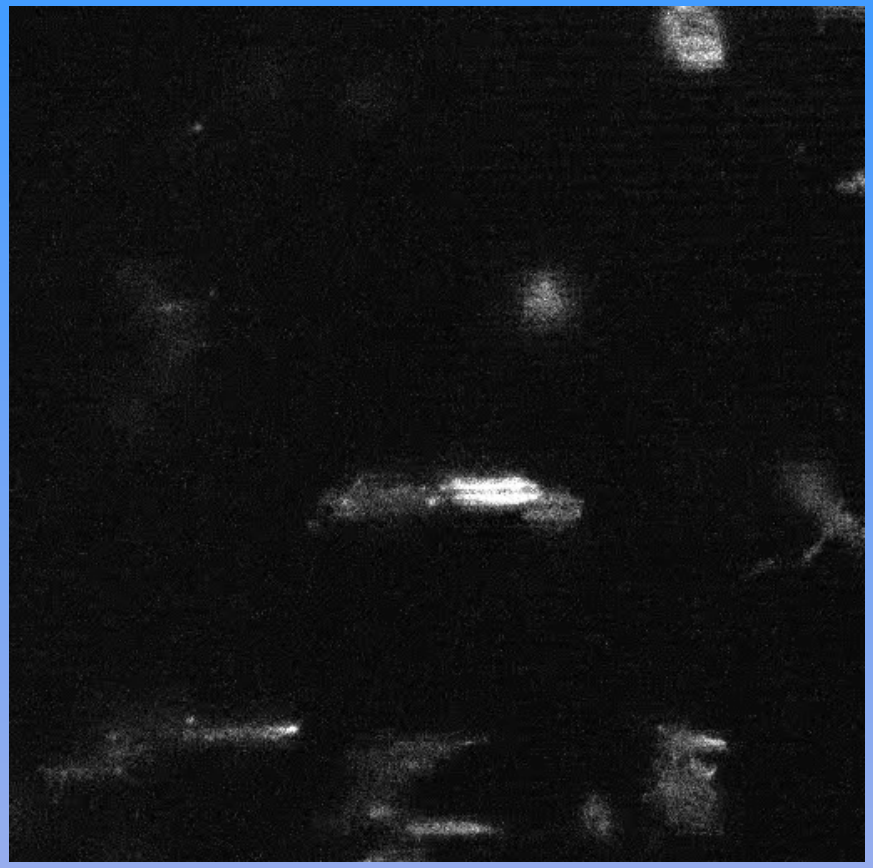
Stochastically driven damped harmonic oscillator?

$$\frac{< P >}{a' v_0} = \frac{a' L}{1 + L\beta' + (L\omega_0')^2}$$



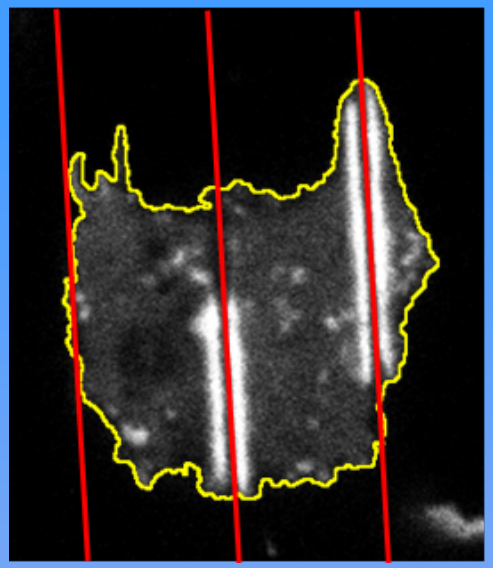
Actin Waves Travel Along Ridges



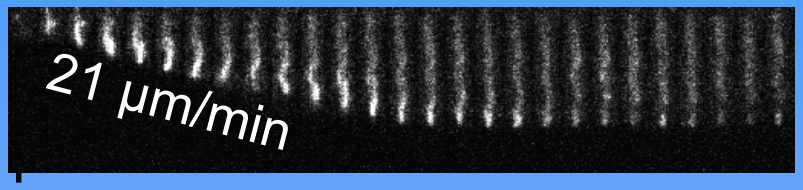


Quantifying Waves of Actin Polymerization

5 μm ridges



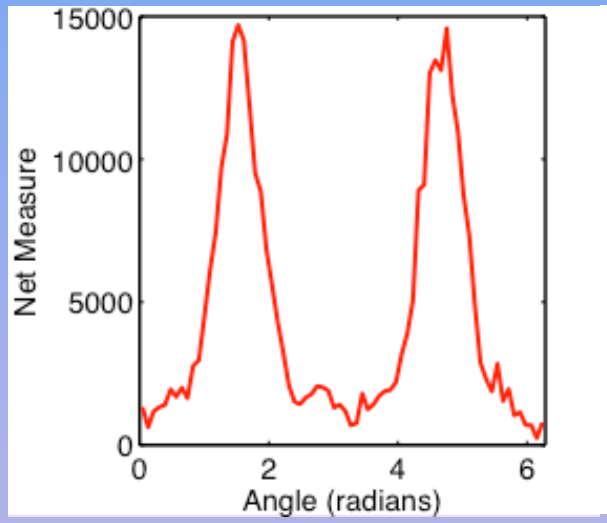
kymograph – actin waves
(vertical scale 16.3 μm)



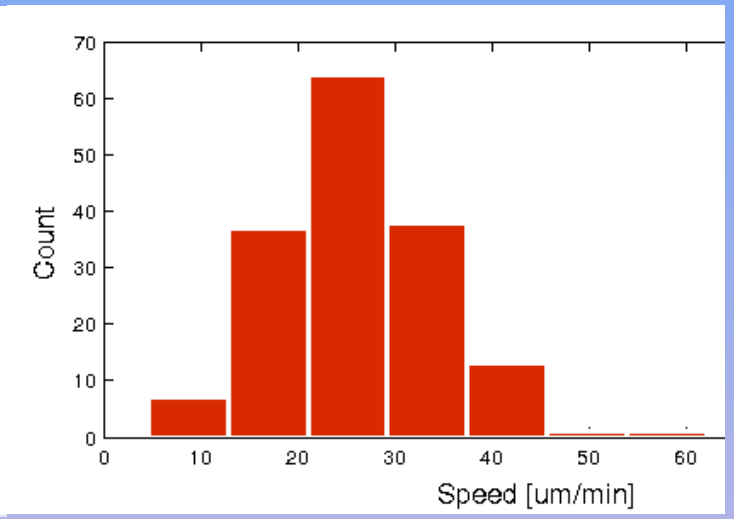
time →

Tracking Waves

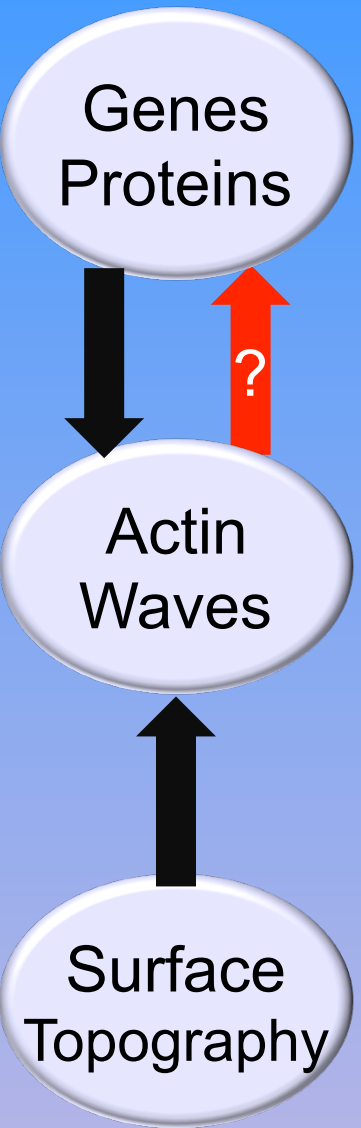
Wave Direction



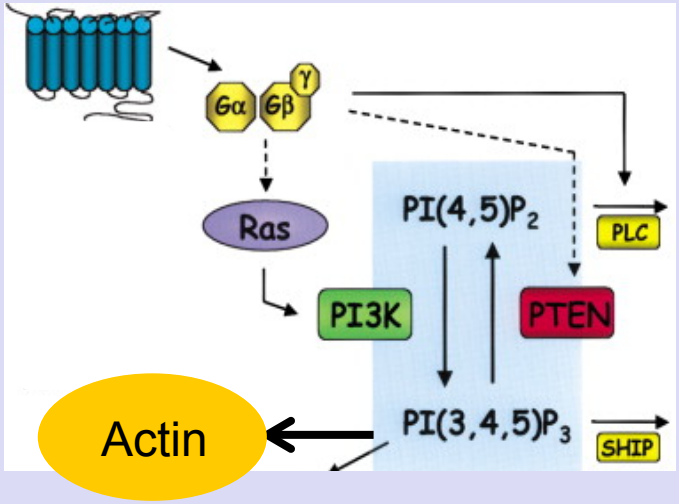
Wave Speed



Can Actin Waves Affect Signaling Pathways?



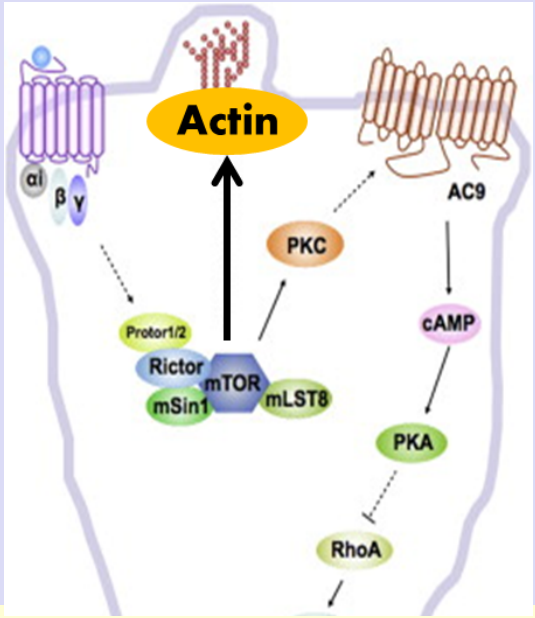
Dictyostelium



F Comer & CA Parent *Cell* (2002).

R. Skupsky, C. McCann, R. Nossal, & W. Losert, *J. Theor. Biol.* (2007).

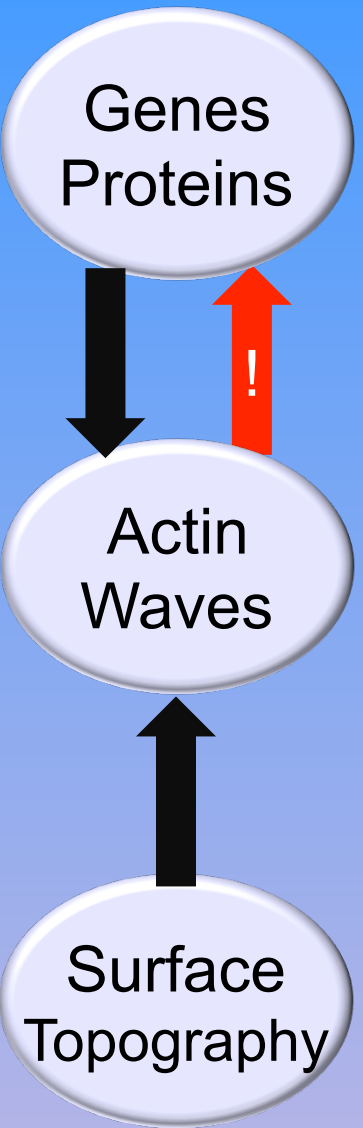
White Blood Cells

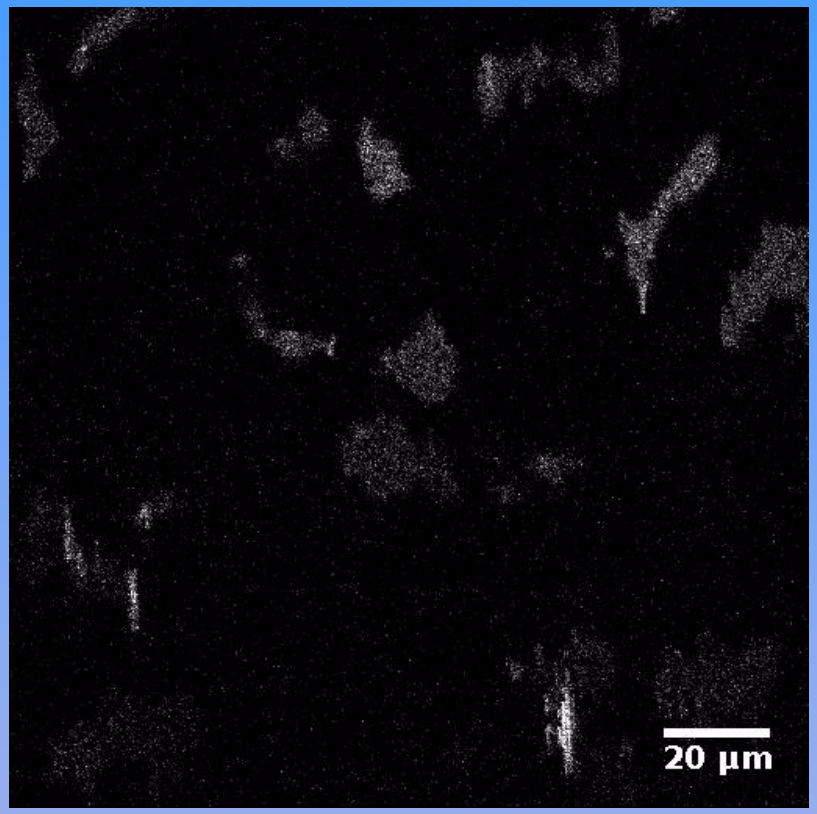


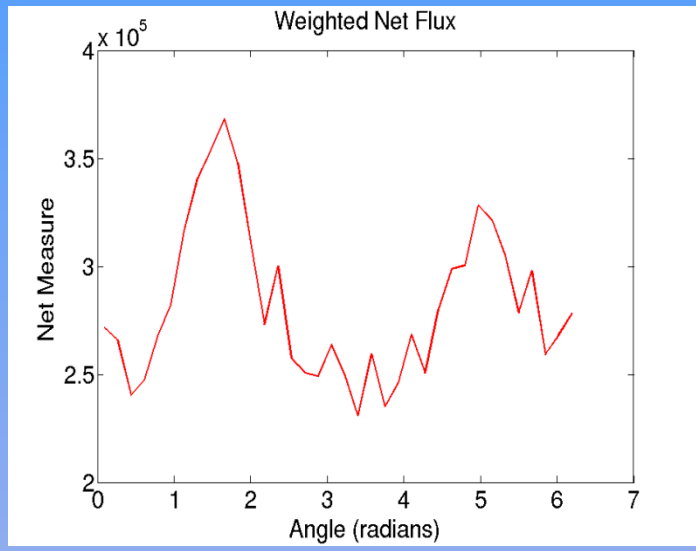
L. Liu, S. Das, W. Losert, & C.A. Parent *Developmental Cell* (2010).

Actin Waves Guide PIP3 Signals

Can Guven





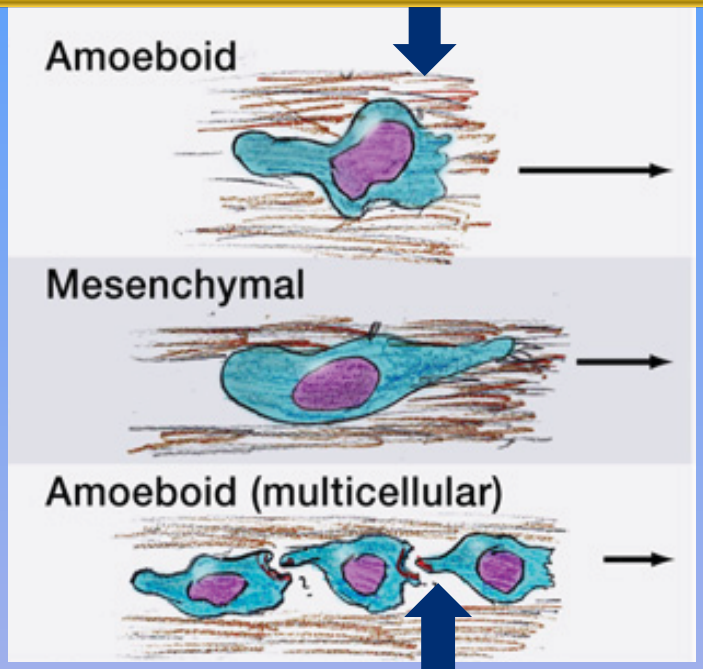


PIP3 Flux

Our observations of mechanical waves raise two new questions about cancer related cell migration

1) How does topography of surrounding affect waves?

Actin waves and cell migration are guided by nanotopography

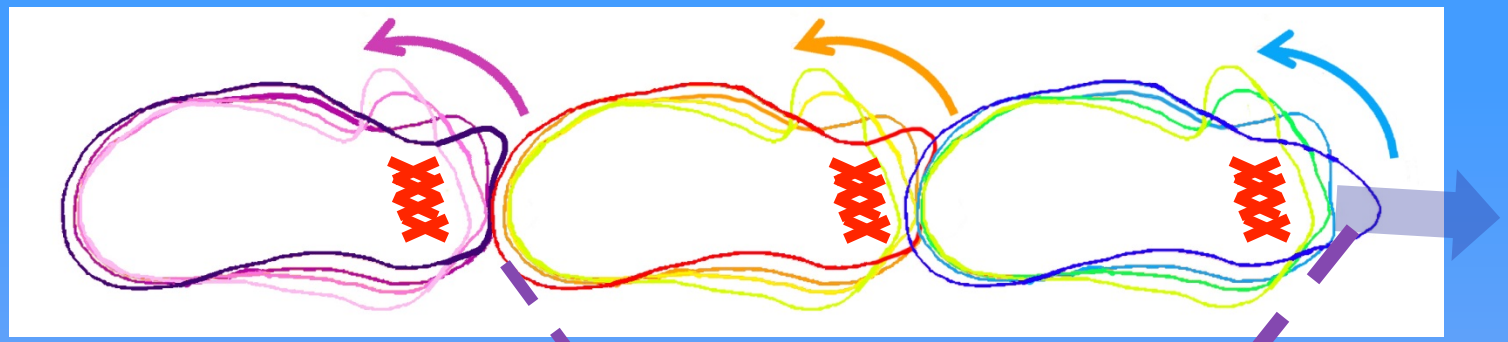


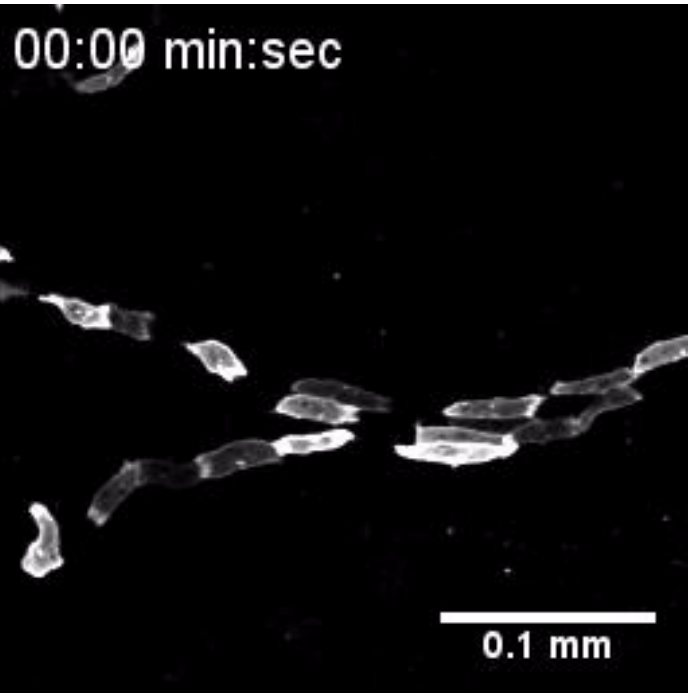
Friedl and Alexander Cell (2011).

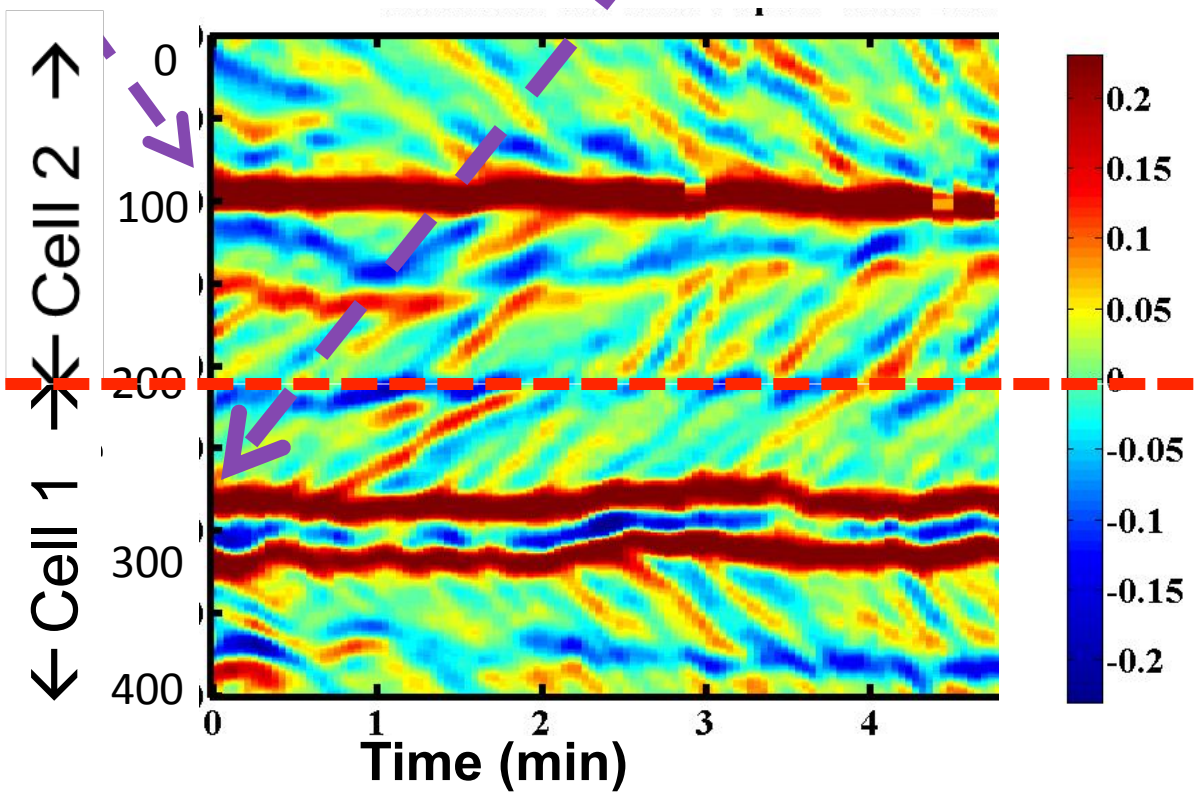
2) How do waves cooperate in cell groups?

Shape Waves can Couple Cell-to-Cell

Chenlu Wang



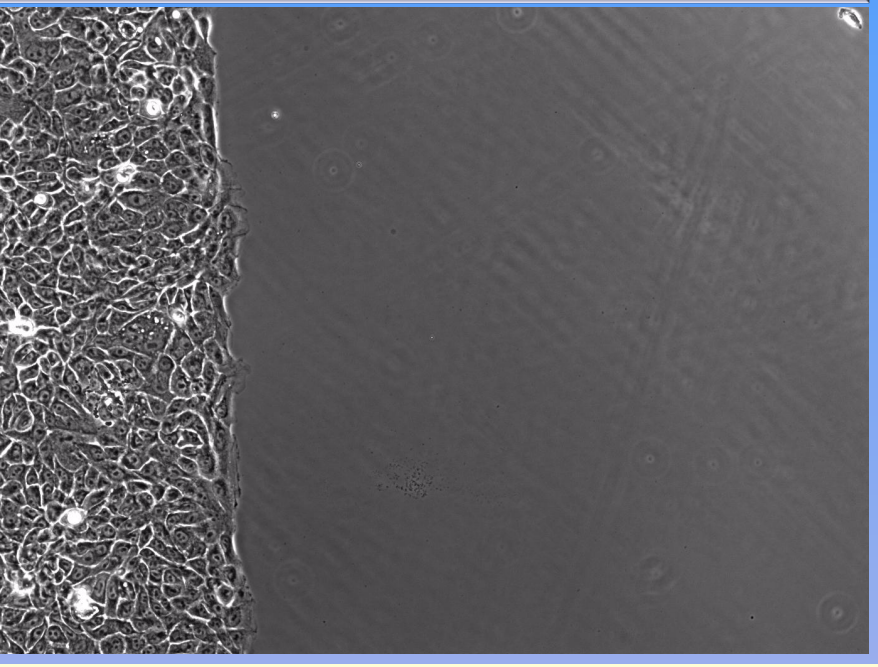




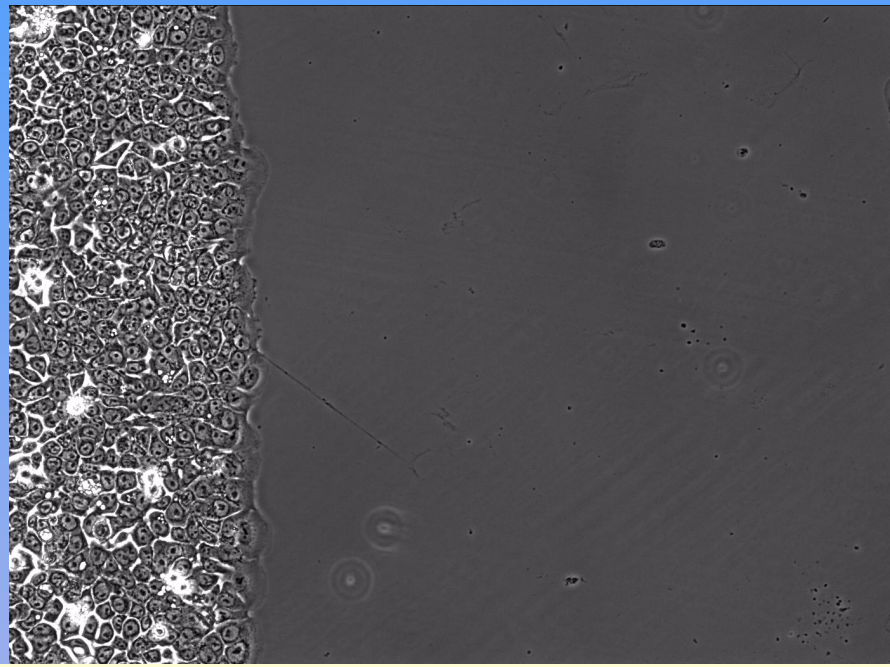
Physics of Collective Cell Migration

Models of Collective Cell Migration

Healthy **"wound healing"**
Mammary epithelial MCF10a



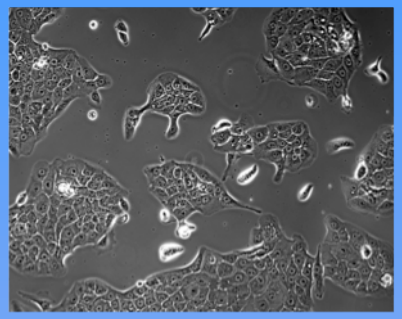
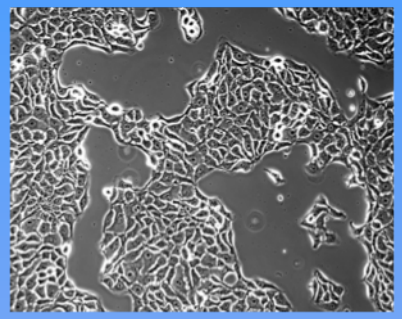
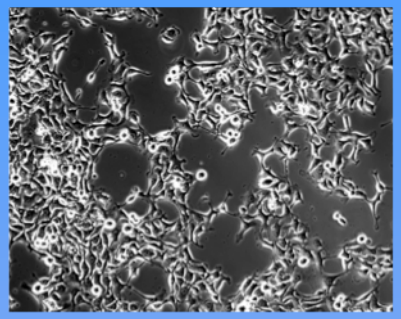
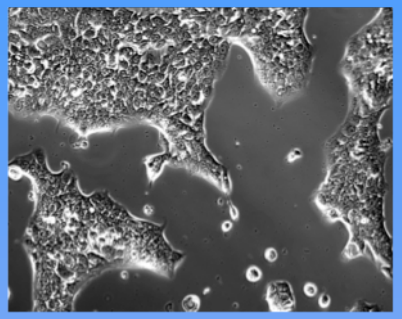
Perturbed **"wound healing"**
Ras activated, metastatic MCF10a



MC. Weiger, V. Vedham, CH. Stuelten,…W. Losert, & CA. Parent, *PLOS ONE* (2013).

Model system for breast cancer progression

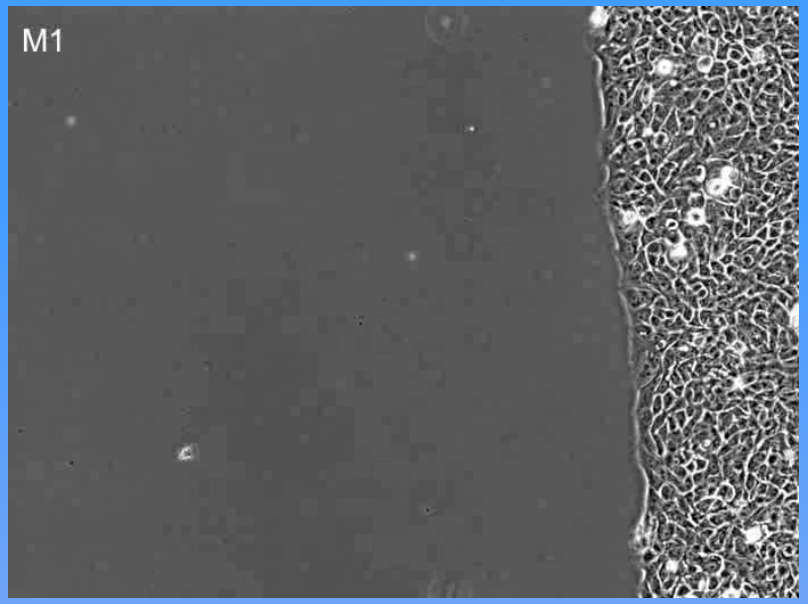
MCF-10A	MCF-10AT1k	MCF-10CA1h	MCF-10CA1a
Immortal line from non-malignant human breast	Ha-Ras transfectant	Line from MCF-10AT xenograft	Line from MCF-10AT xenograft

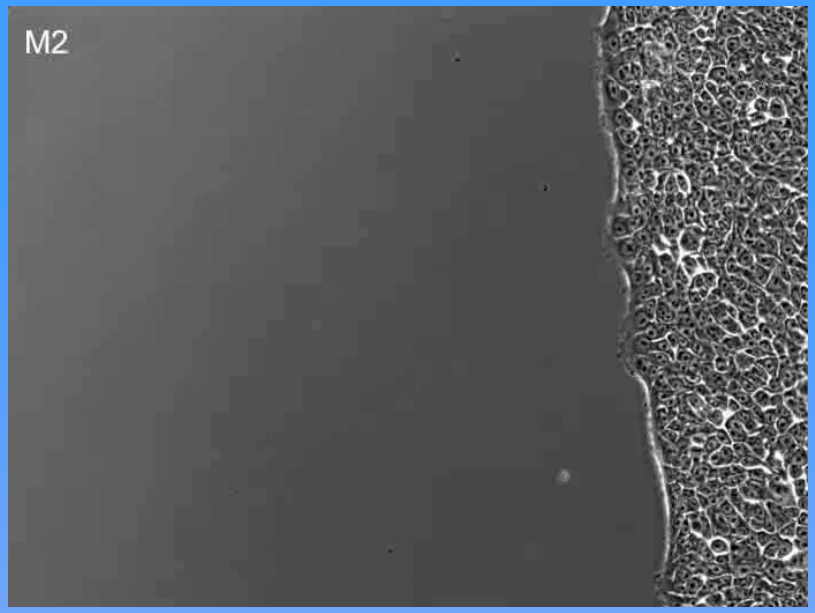





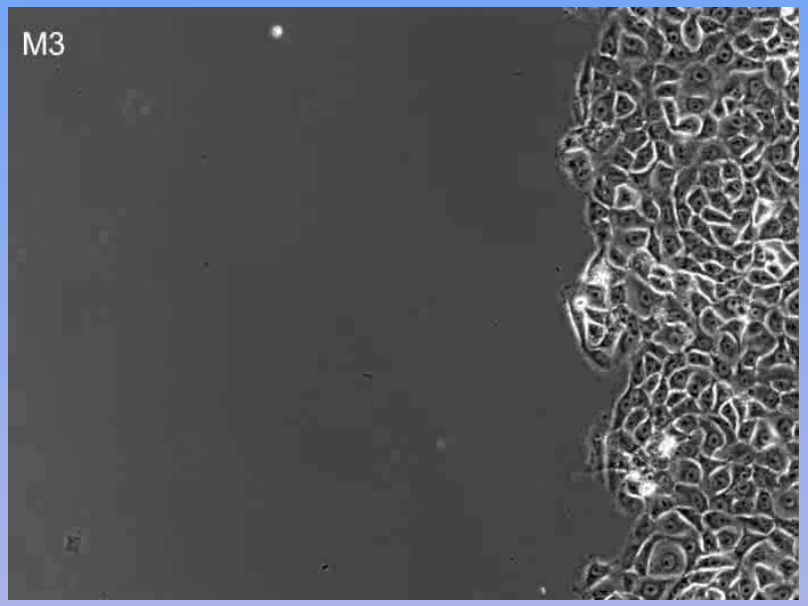
"Normal" M1	Pre-malignant M2	Tumorigenic M3	Metastatic M4

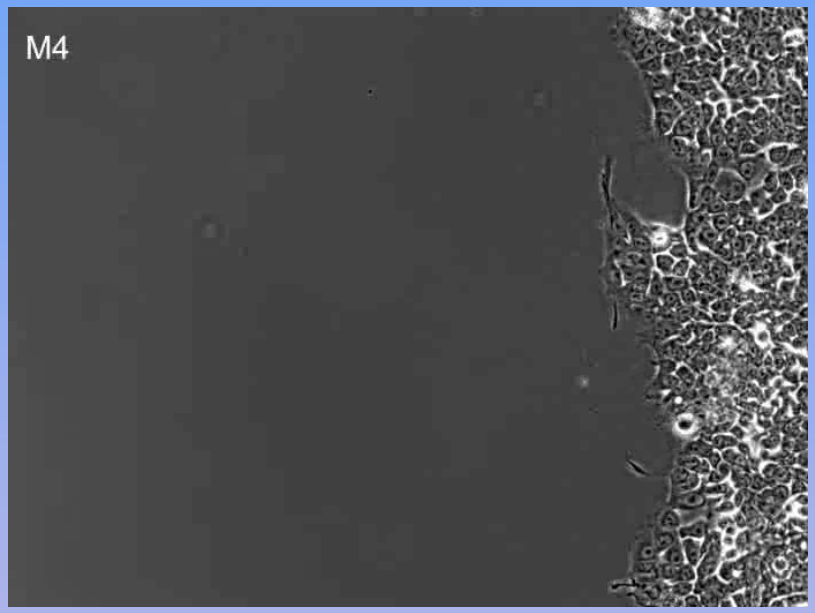
Tumorigenicity

Weiger et al PLOS One (2013)

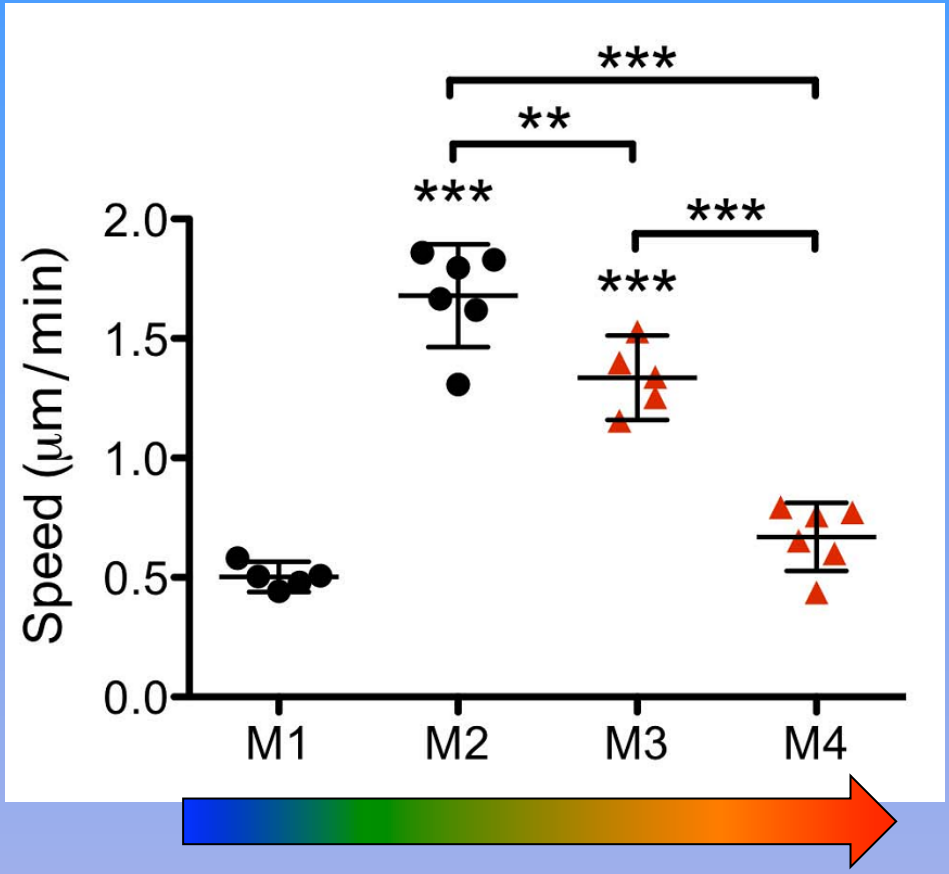

M1


M2


M3

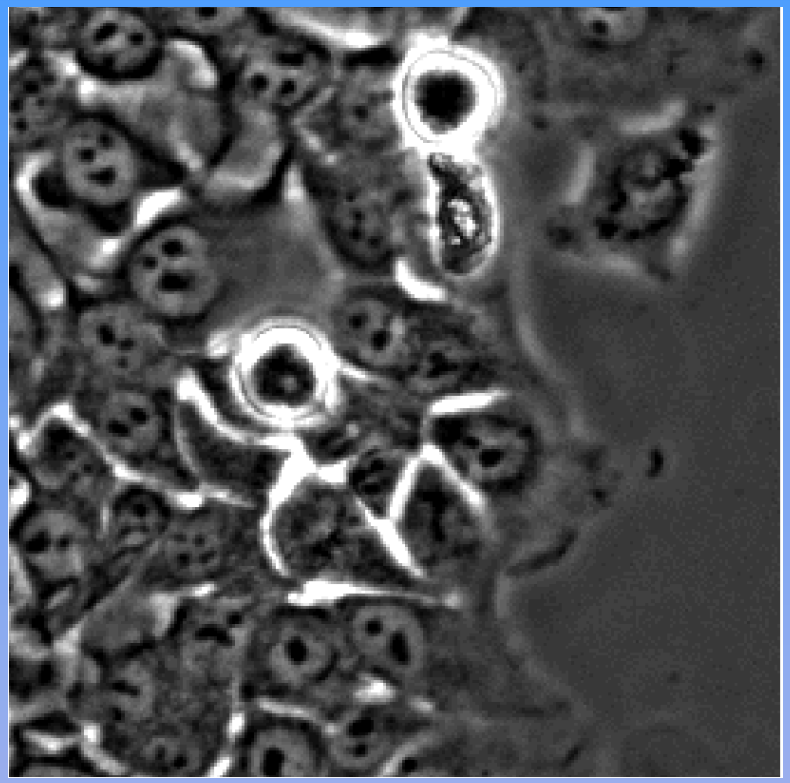

M4

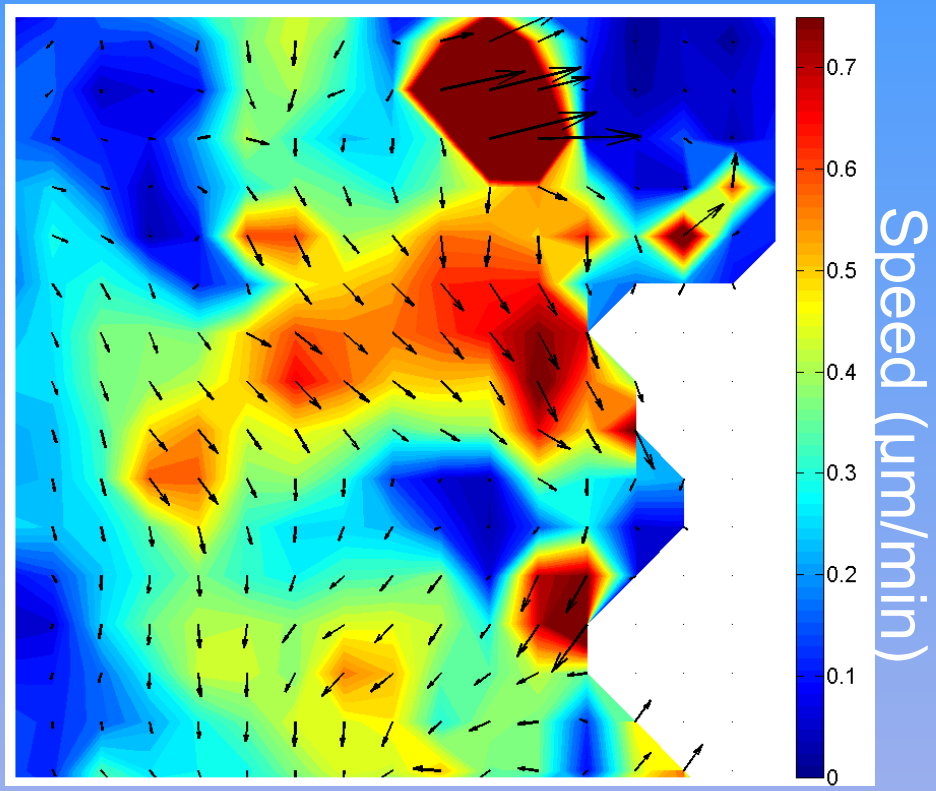
Speed is not an indicator of tumorigenicity



Weiger, M., et al. (2013). PLoS ONE

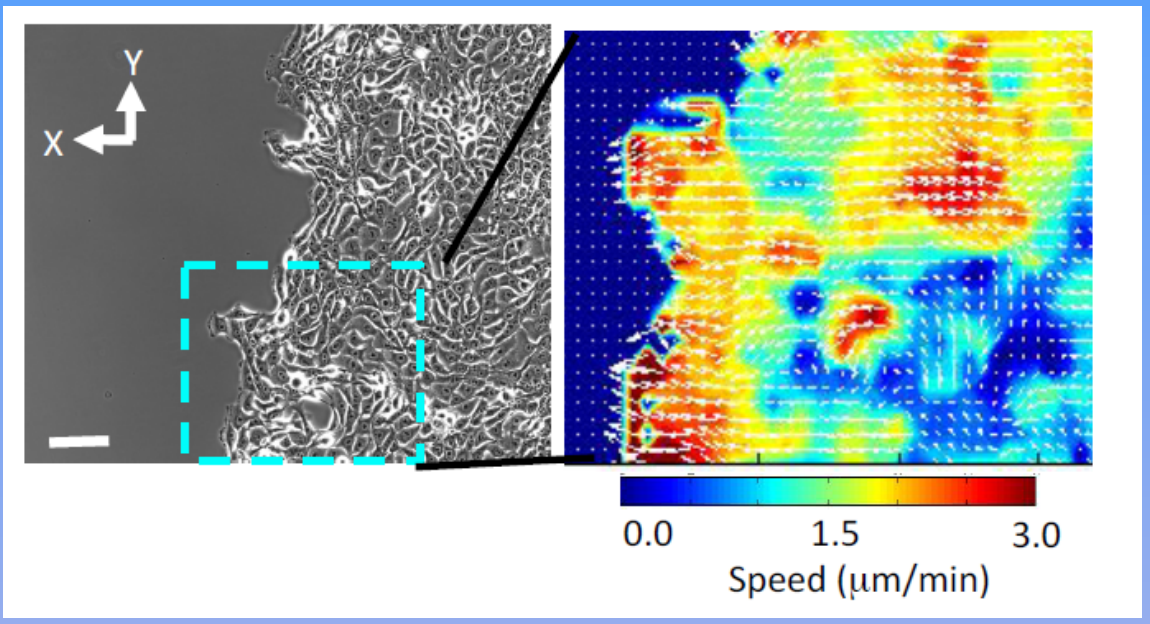
Extracting information from the movies: Particle Image Velocimetry



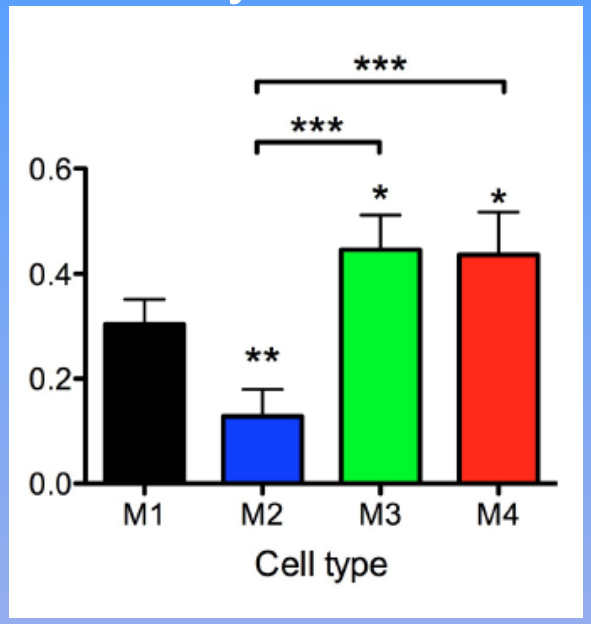


Cross Correlation

PIV Measurements

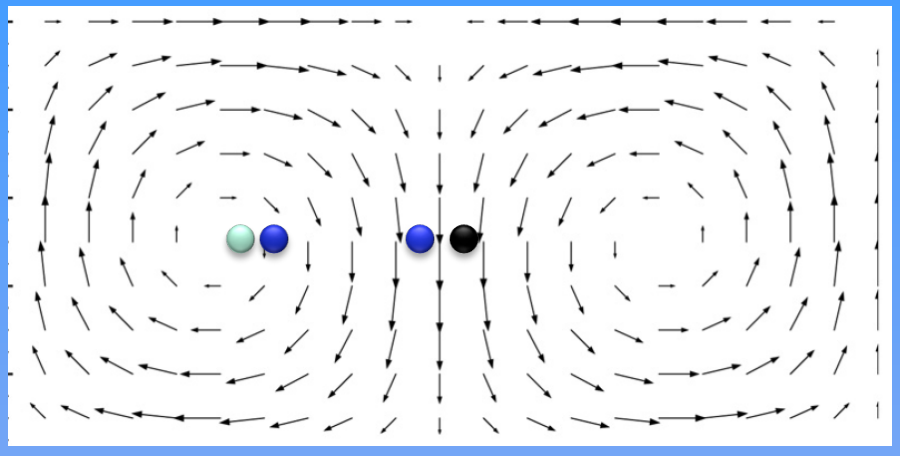


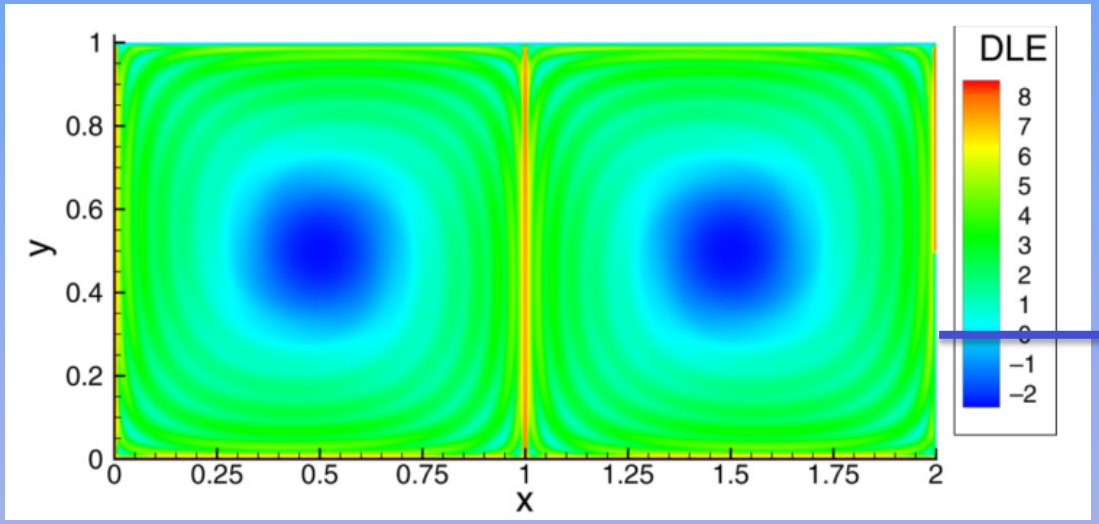
Variability in Direction



Weiger et al PLOS One (2013)

Finite Time Lyapunov Exponents

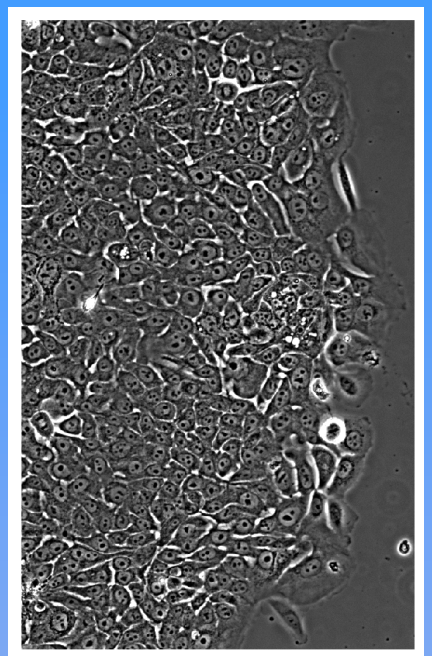


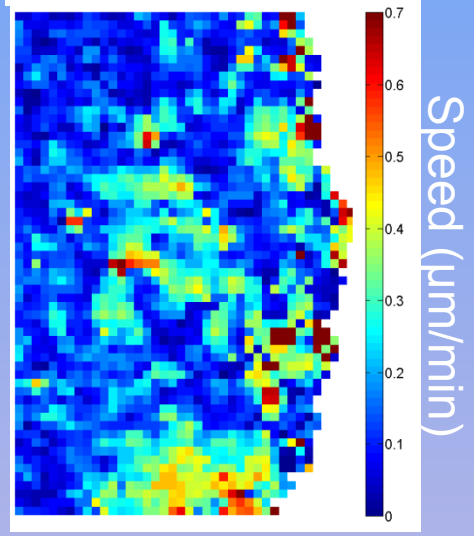


Chaos

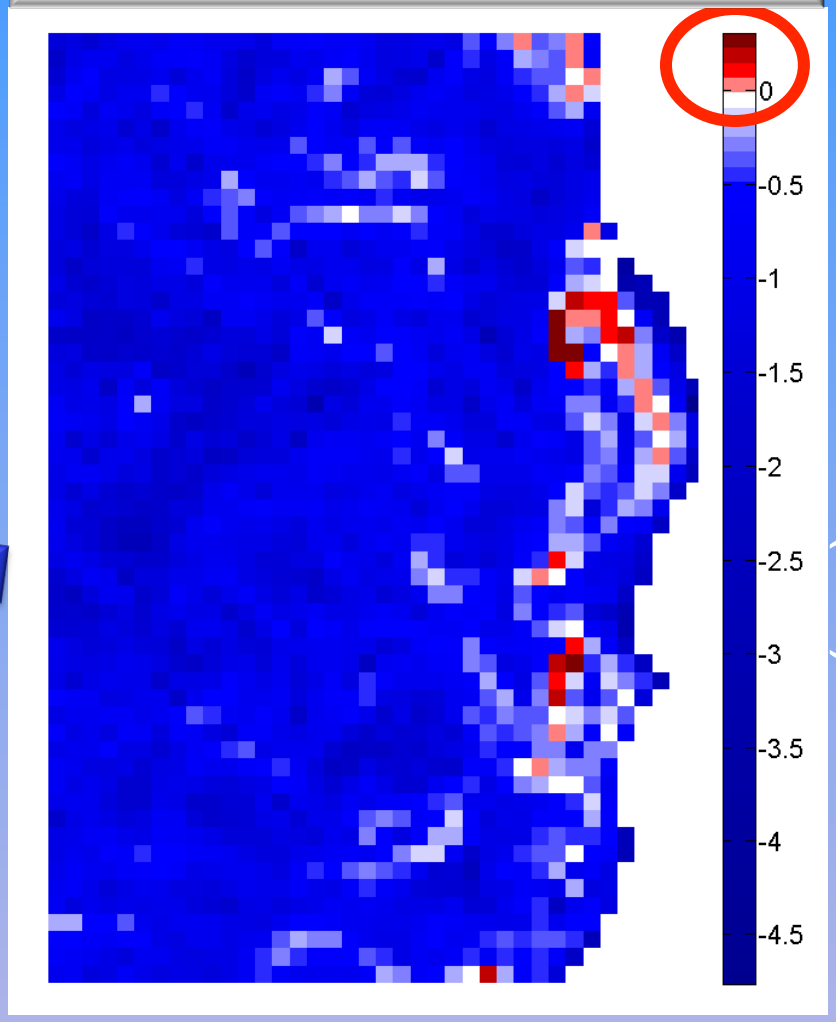
Shadden S., et al. (2005). Physica D: Nonlinear Phenomena

FTLE Analysis of non-malignant cells





RED: Cells move away from their neighbors

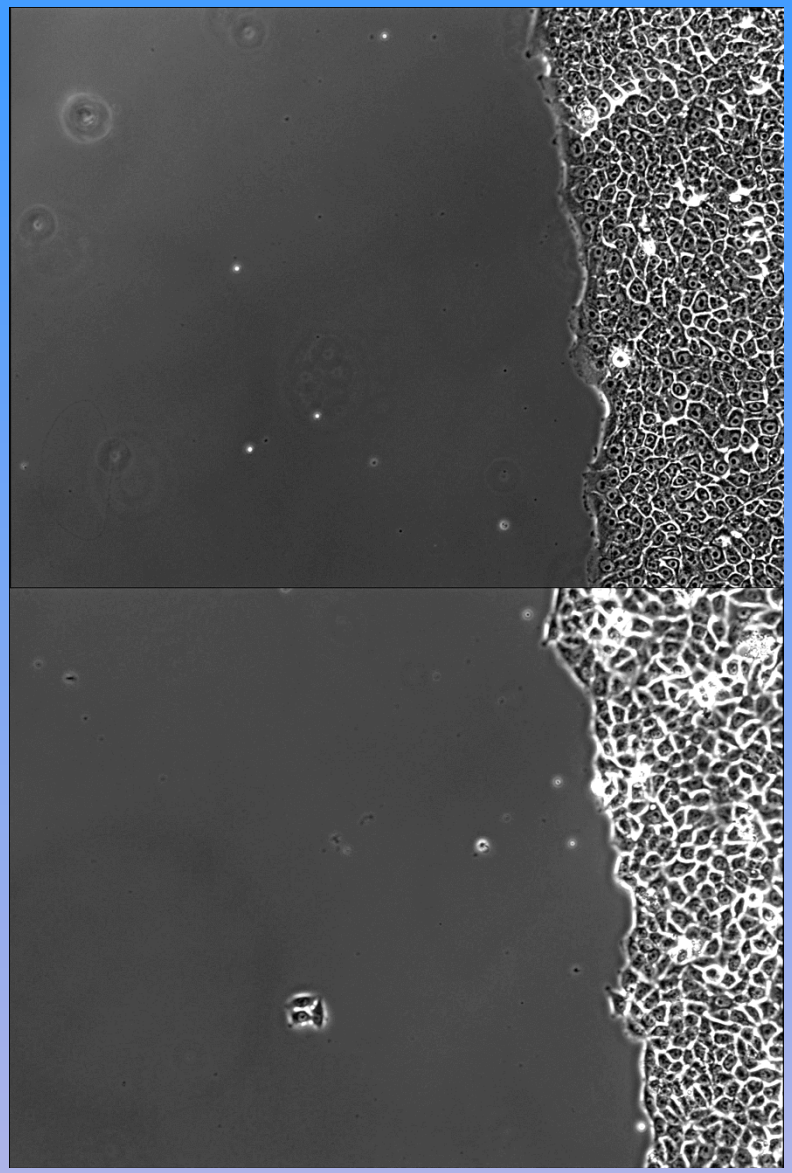


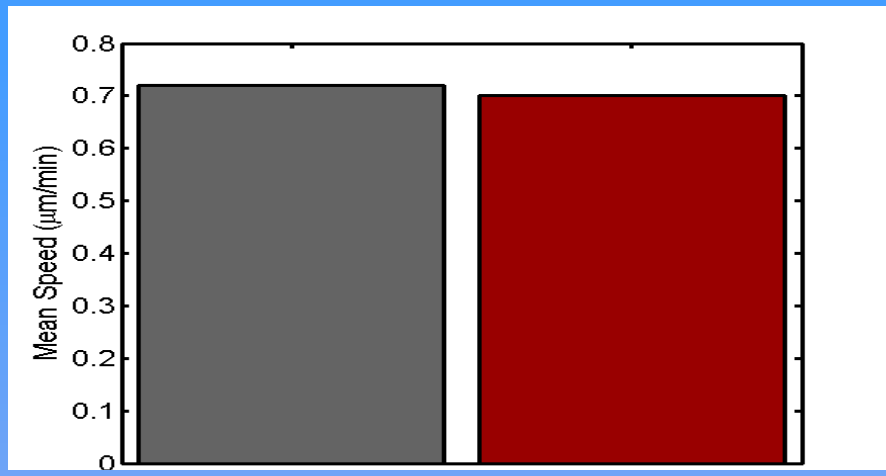
Lee R, et al. (2013). *New Journal of Physics*

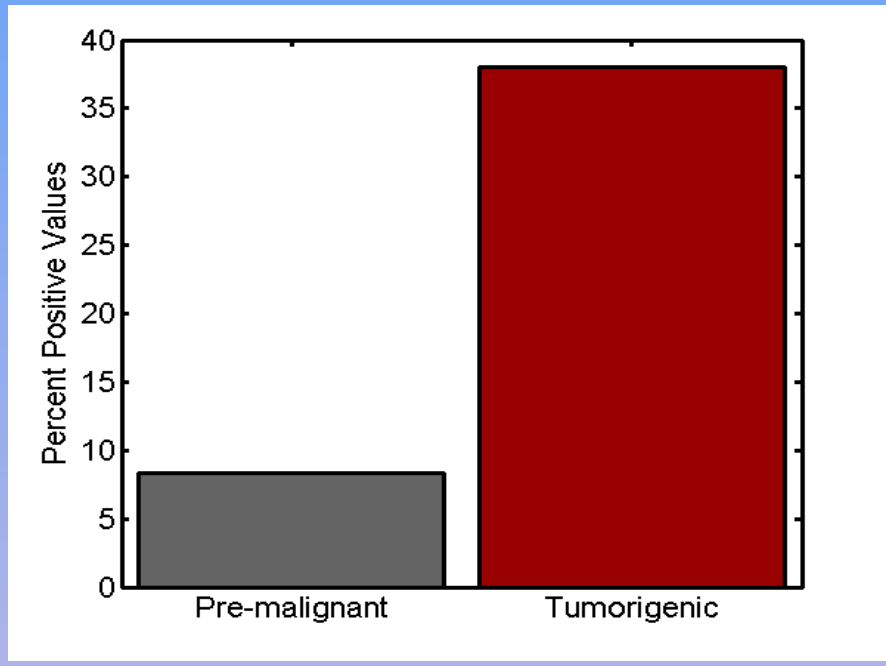
FTLE Analysis distinguishes pre-malignant and tumorigenic

Pre-malignant (M2)

Tumorigenic (M3)







Summary

- The physics perspective provides new insights into Cell migration, a key process of cancer metastasis.
  - Observed and measured the wave-like nature of cell migration (amoeboid cells)
  - Waves play a role in Contact Guidance and Streaming

- Physical properties may be suitable for phenotyping of Cancer (as a complement to other indicators)
  - Cancer cells tend to be softer as measured by optical stretching
  - Cancer cell groups move in a more chaotic manner as measured via FTLE

Research Team & Collaborators

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Alex Morozov *(Rutgers)*
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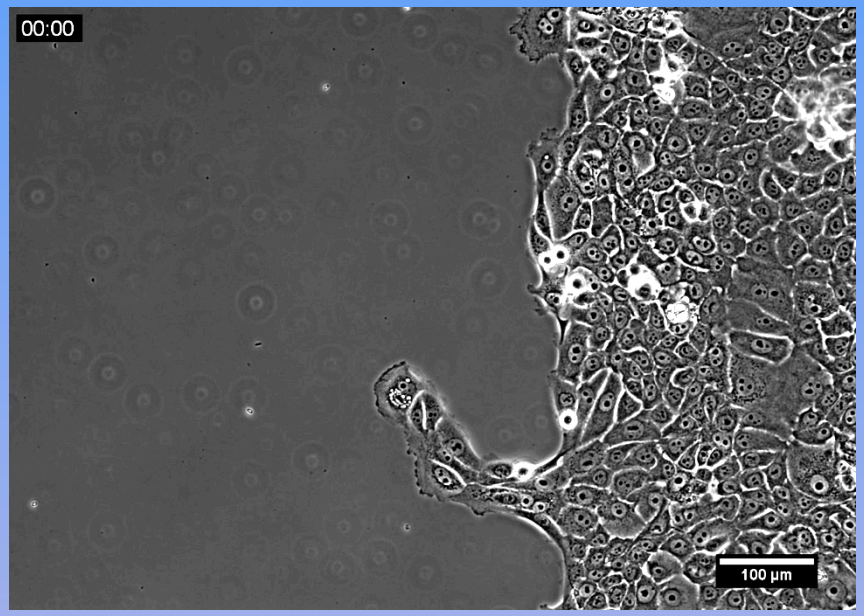
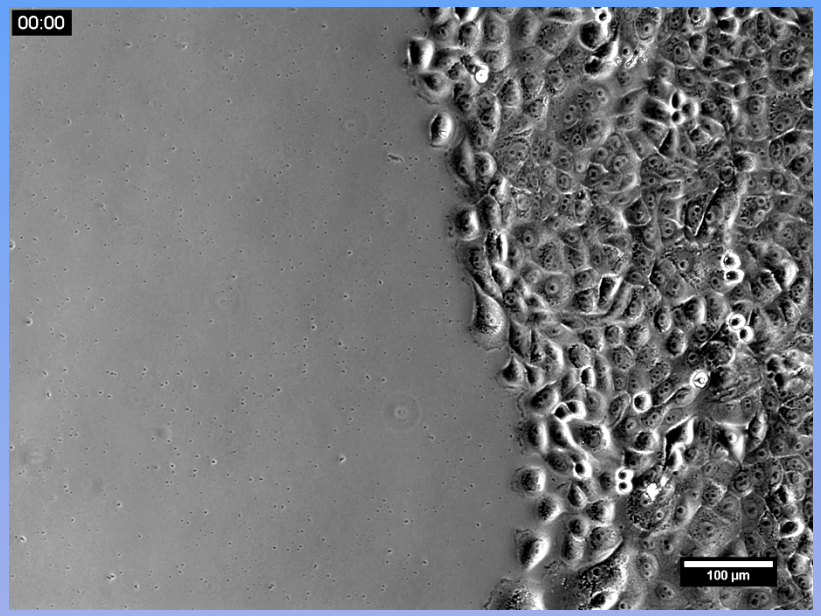
Ed Ott
Joe Redish
Kandice Tanner *(NCI)*

Stimulation Changes Collective Character of Migration

1% Horse Serum

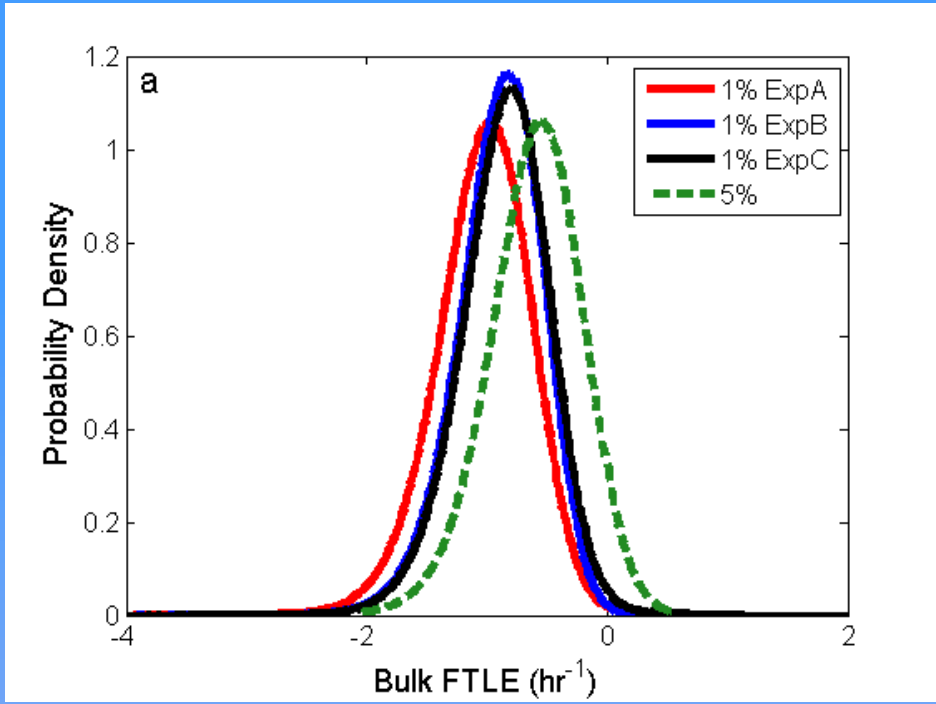


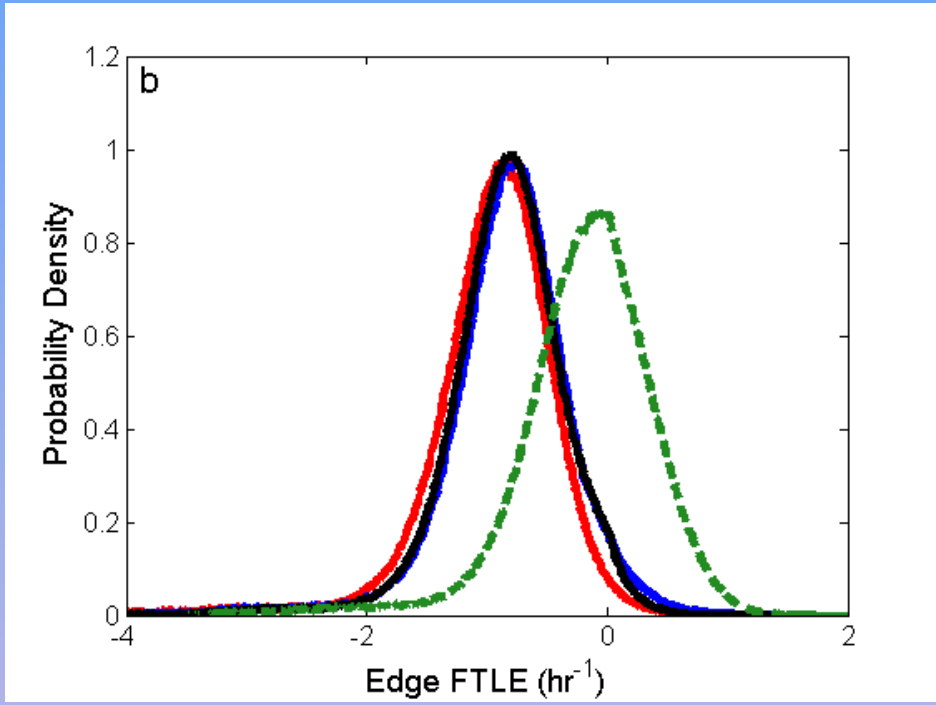
5% Horse Serum

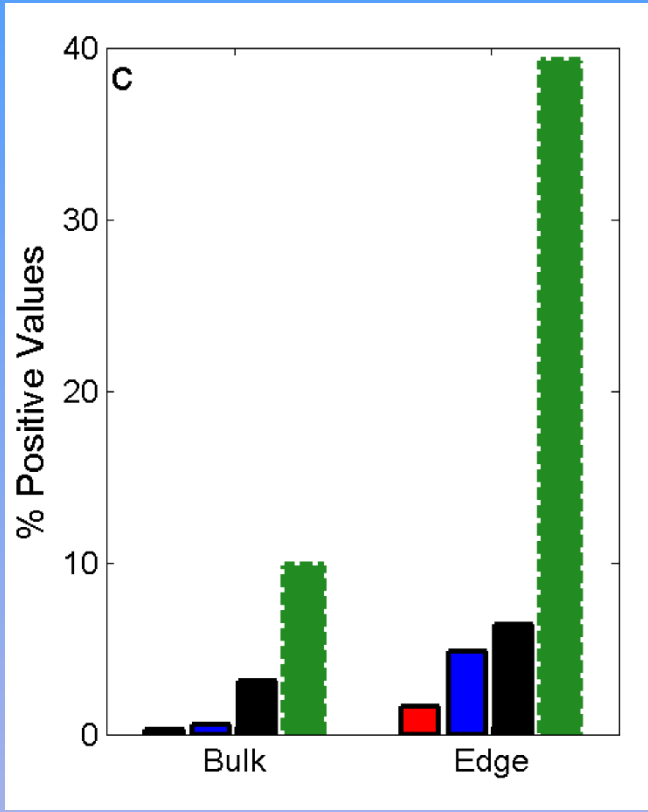


Lee R, et al. (2013). *New Journal of Physics*

Measuring **Chaotic Motion** via **Lyapunov Exponents**







Lee R, et al. (2013). *New Journal of Physics*

Outline

1. What is cancer?
2. Physics Perspectives on Cancer
   - Defining the Physics Perspective
   - Cell Mechanics and Migration
   - Physics of Collective Behavior
3. **How to contribute to the Convergence of Physics and Biology**

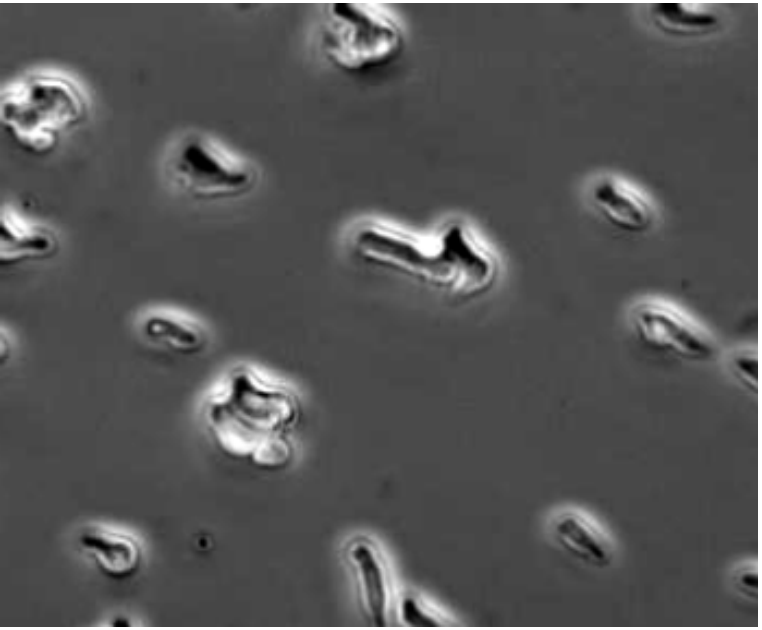
How to contribute to the Convergence of Physics and Cancer Research

1. Learn the basics of Biology
2. Build an intuition for the Physics of Living Systems
3. Remember, it may not be known what physical processes are important for specific biological observations.

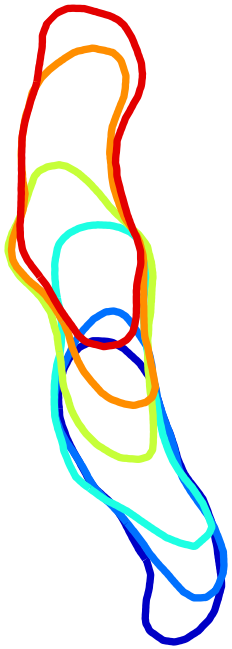
GOAL: Bring a Physics Perspective to Cancer Research

Physics of Amoeboid migration

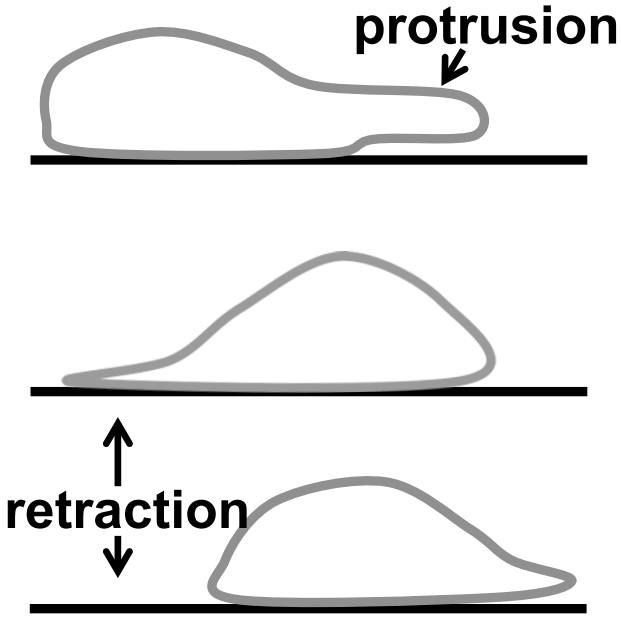
Dictyostelium discoideum



Physics: Protrusion and retraction

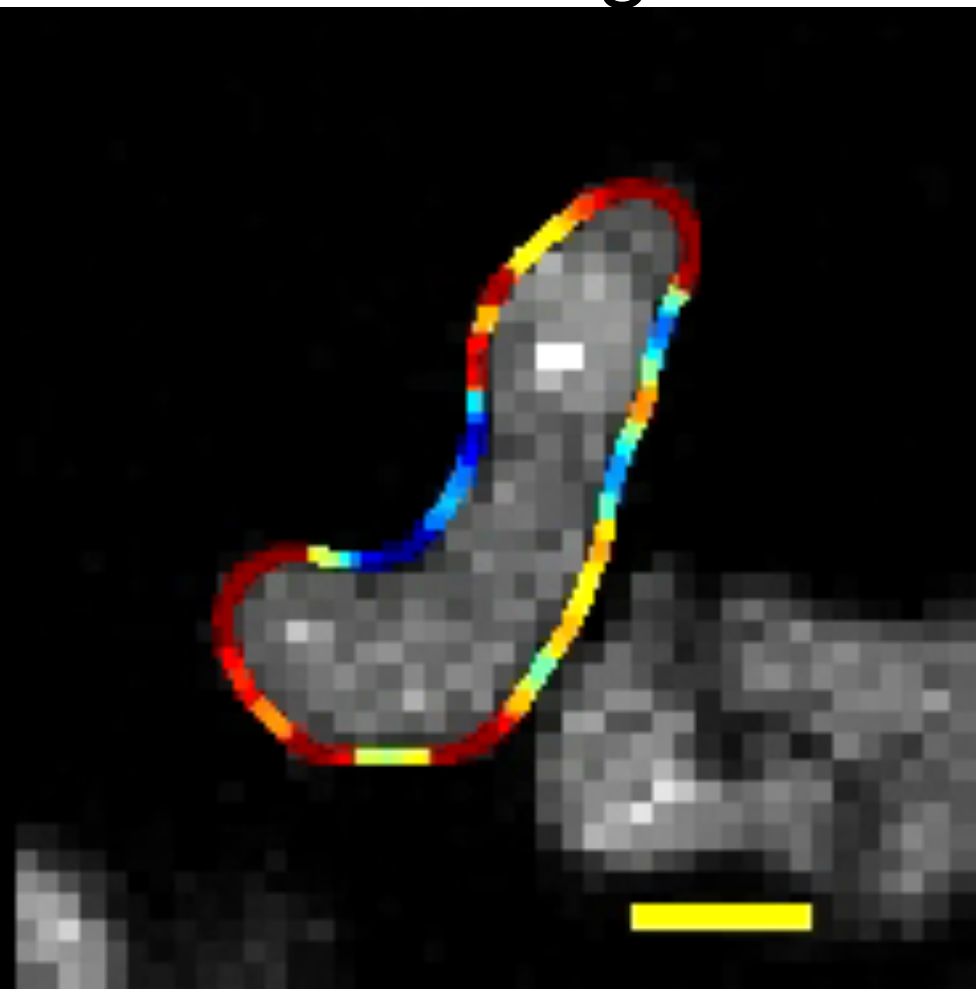


(top view, data)



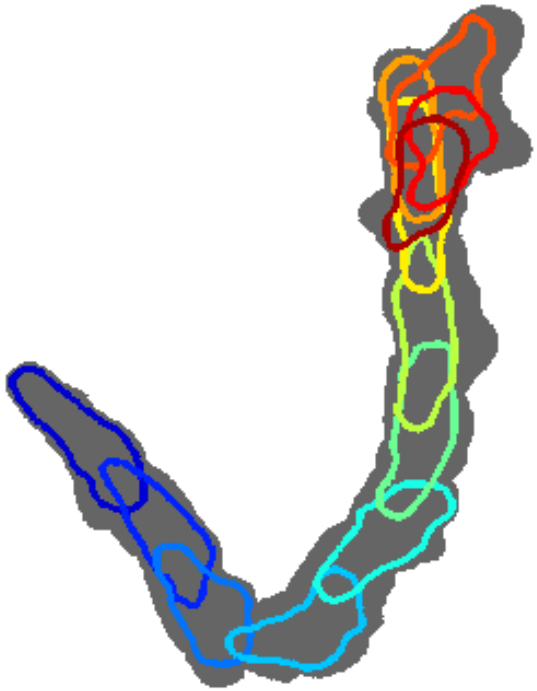
(side view, schematic)

Measuring protrusion dynamics by tracking cell shape dynamics



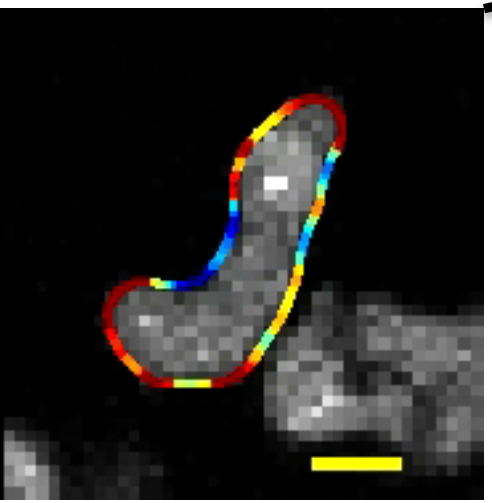
Active contour with 400 equidistant boundary points

Modified from snake program by Xu and Prince



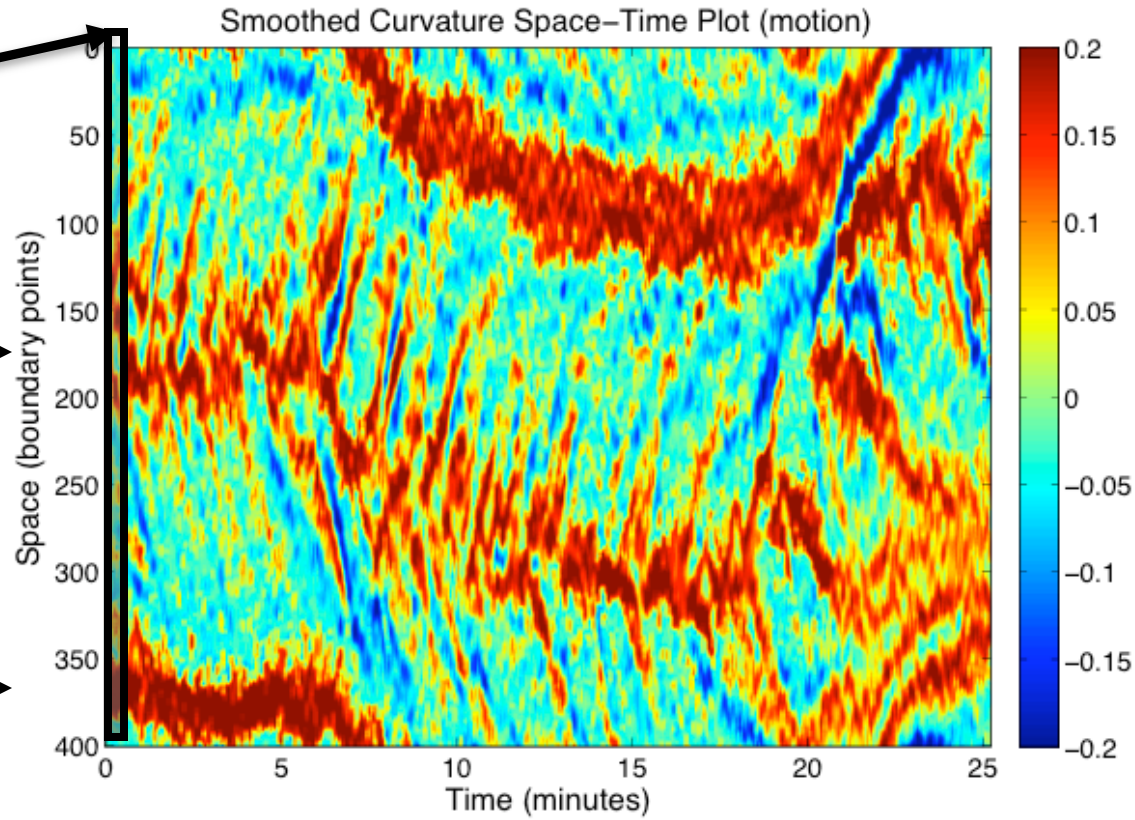
Color based on local curvature
-> highlights protrusions

Kymograph representation of shape dynamics



Front →

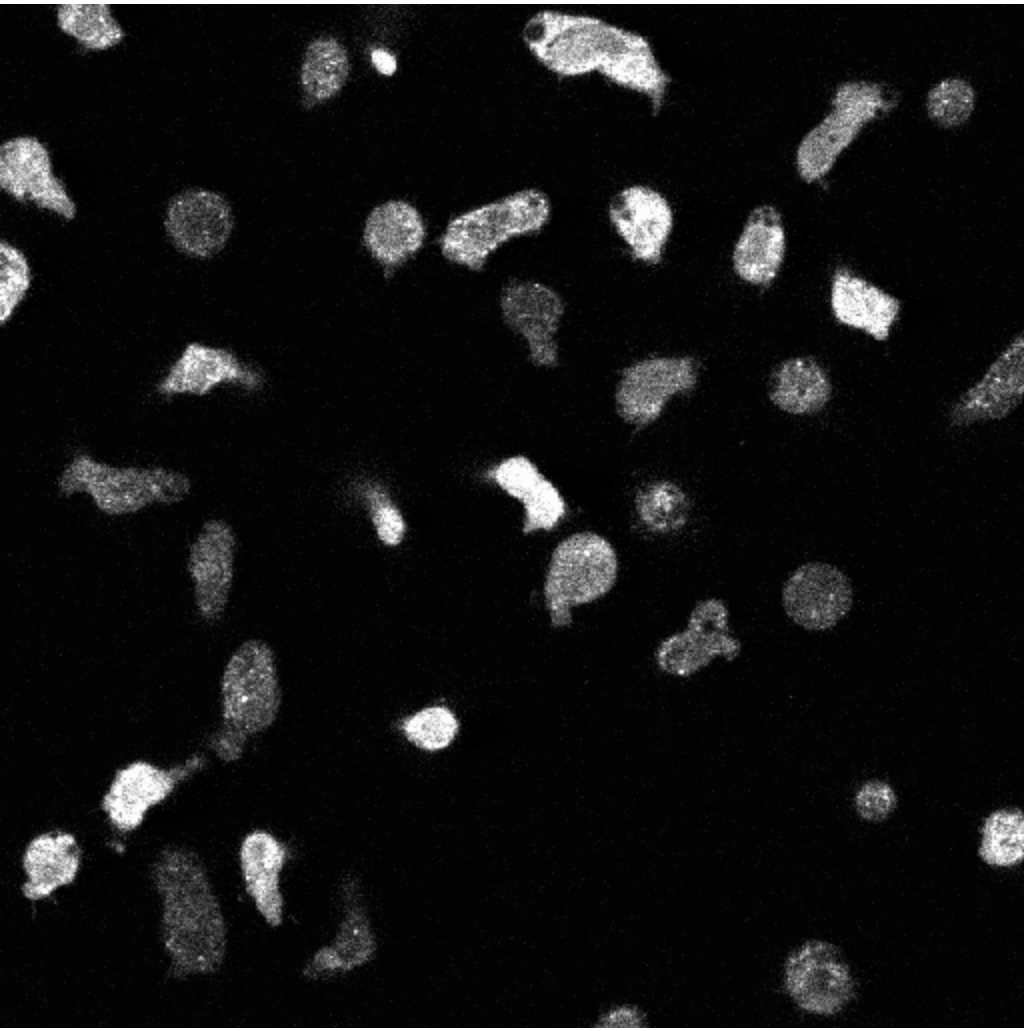
Back →

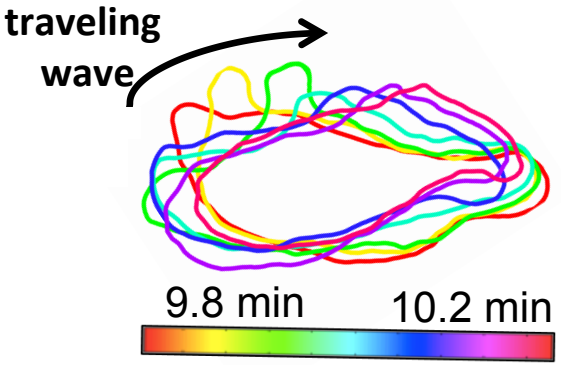


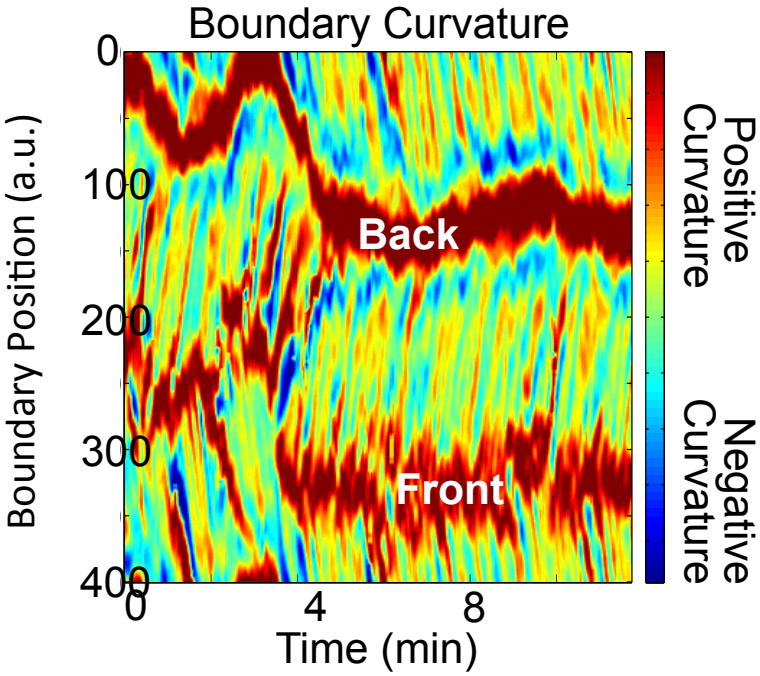
Protrusions travel from front toward back

Driscoll, Fourkas and Losert, *Physical Biology* (2011)

Suspended *Dictyostelium* highlight traveling protrusions



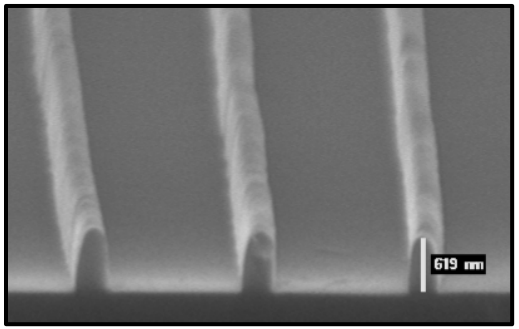




Driscoll, McCann, Fourkas, Parent, and Losert *PLOS Comp Biol* (2012).

Dictyostelium cells follow ridges on surface

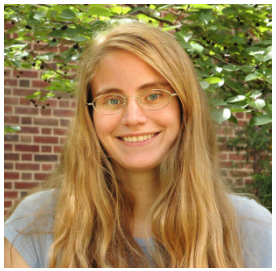
Nano-Ridges



~500 nm

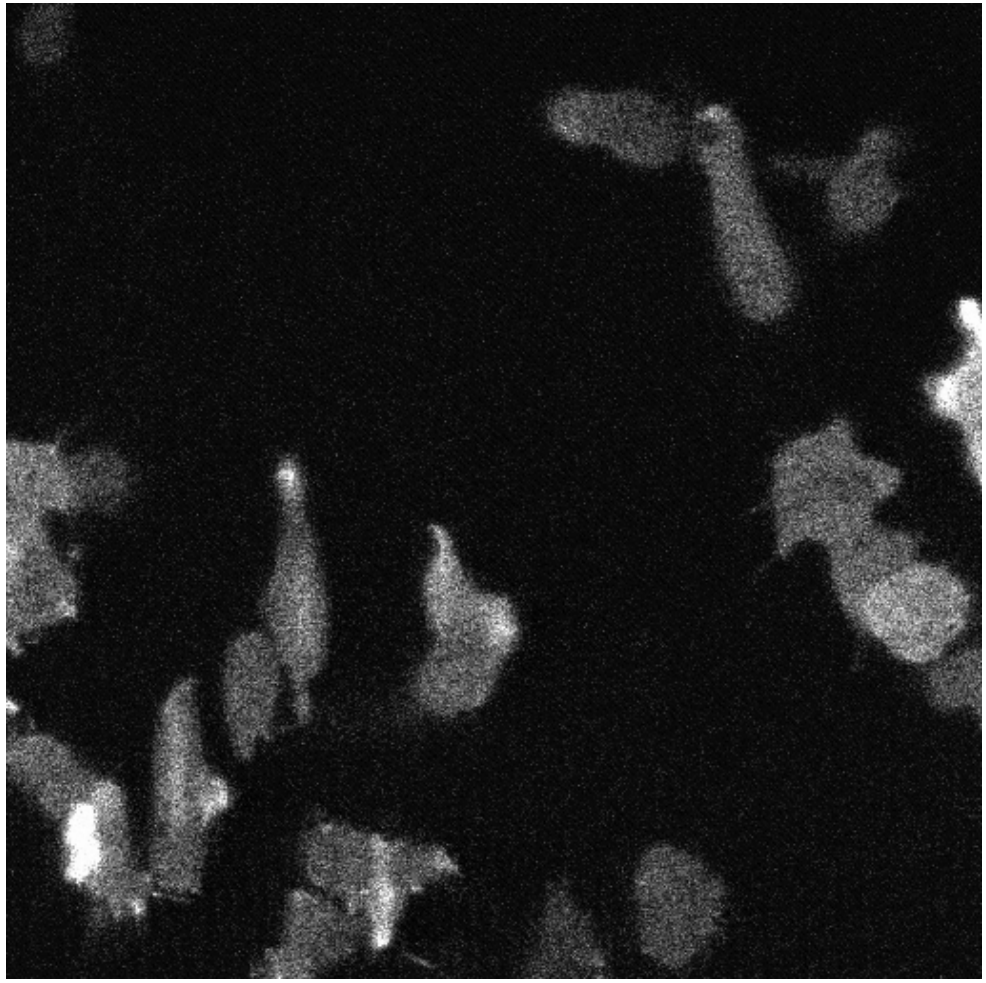
Ridge Orientation

Xiaoyu Sun



Meghan Driscoll

Actin polymerization in guided cells

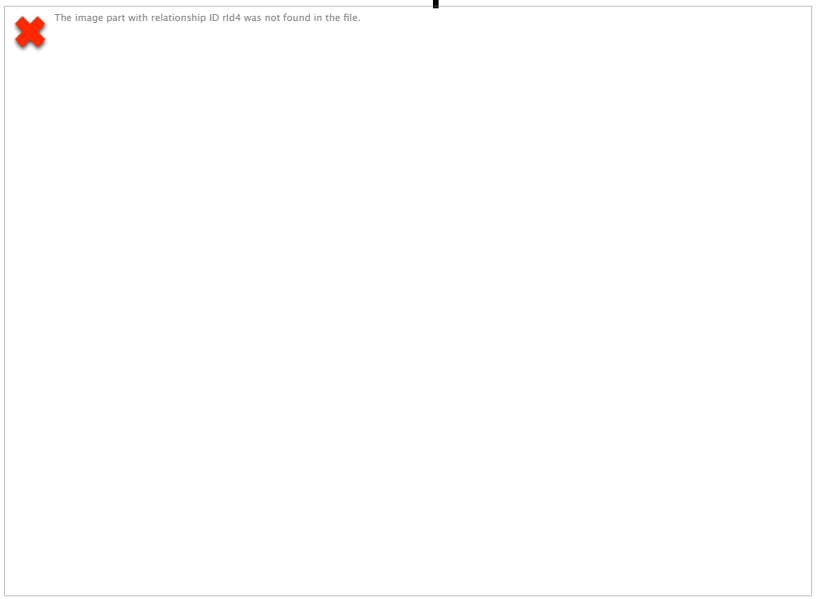


Ridge Orientation

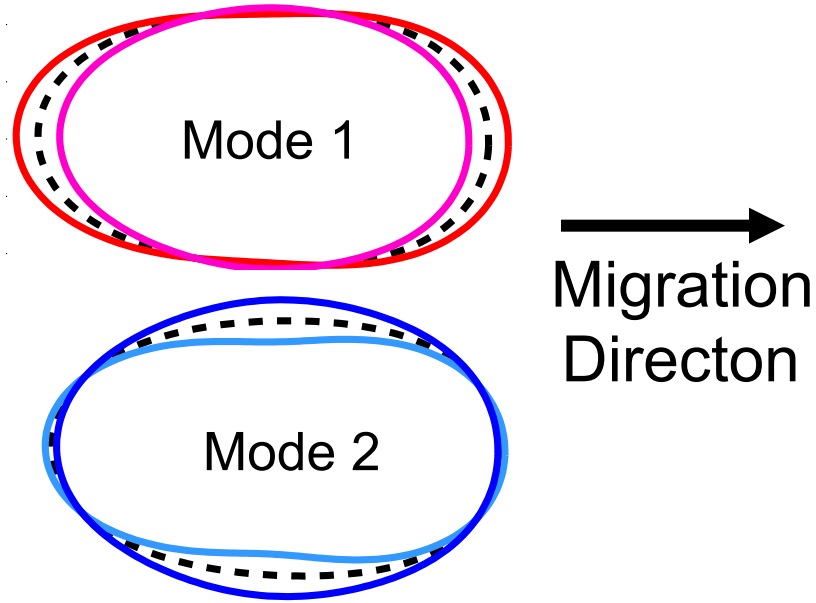
Speed of actin patches comparable to wave-like protrusion speed (~30 μm/min)

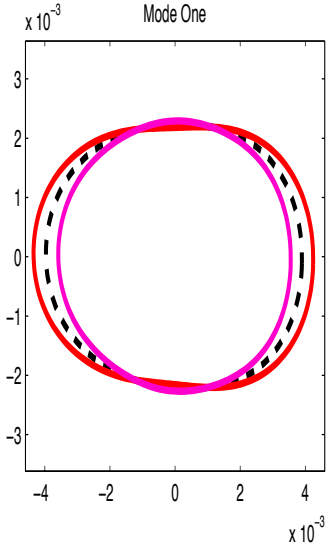
Principal Component Analysis of Global Shape

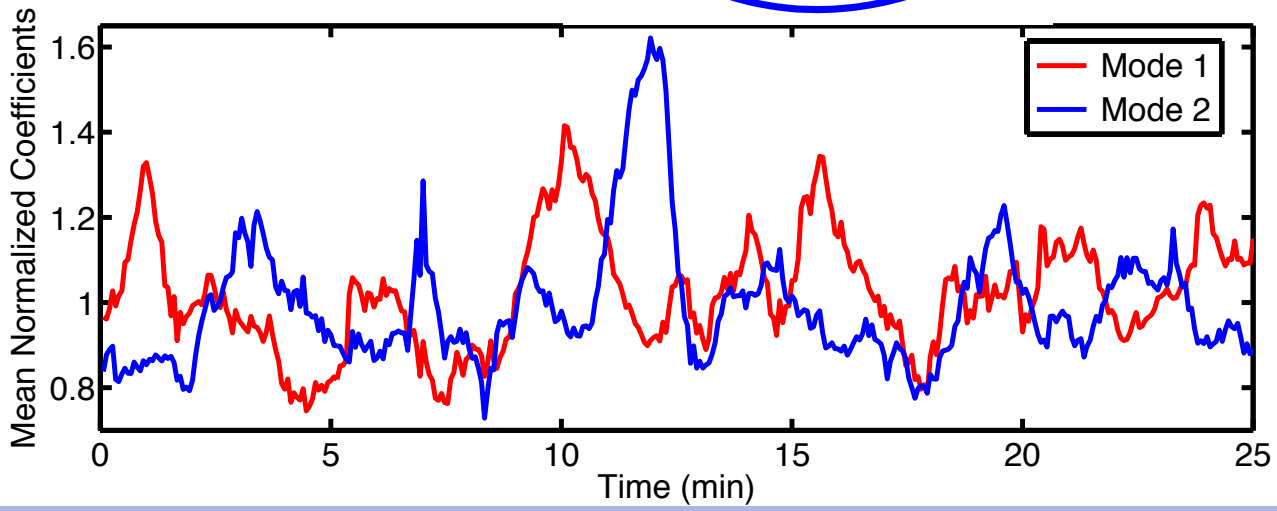
All Shapes



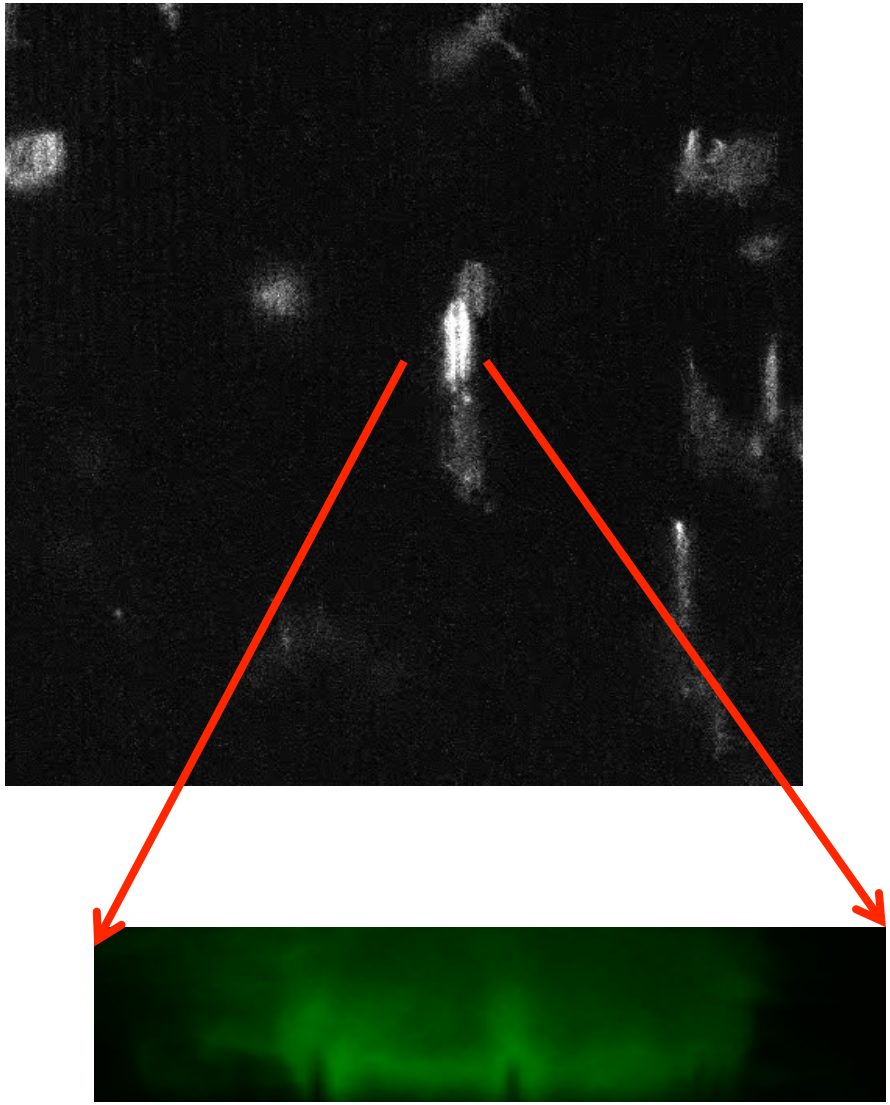
$$\hat{S} = C_1\hat{M}_1 + C_2\hat{M}_2 + \ldots$$







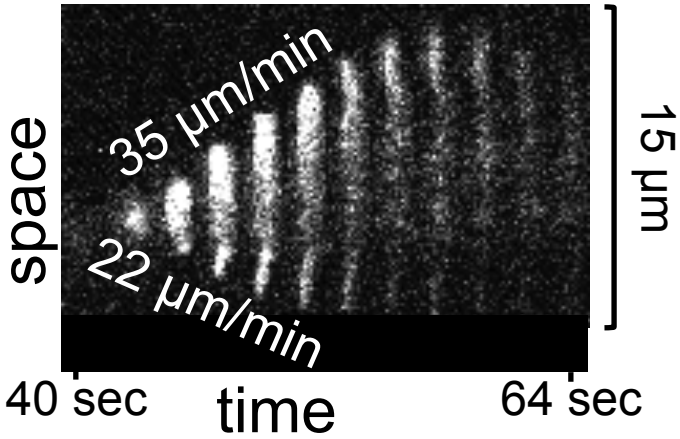
At surface, actin waves move along ridges



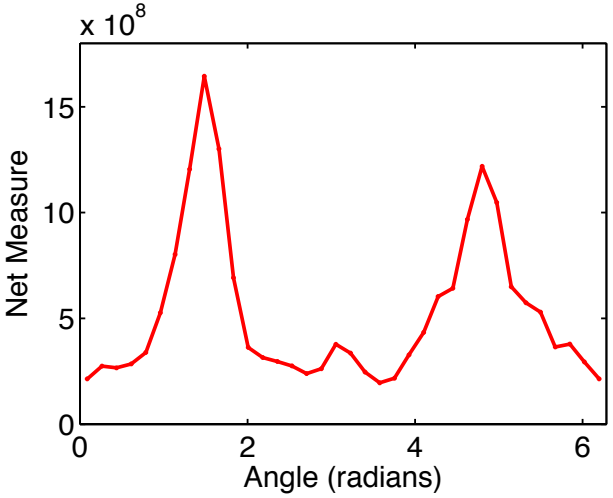
Side View

kymograph

actin waves along ridges

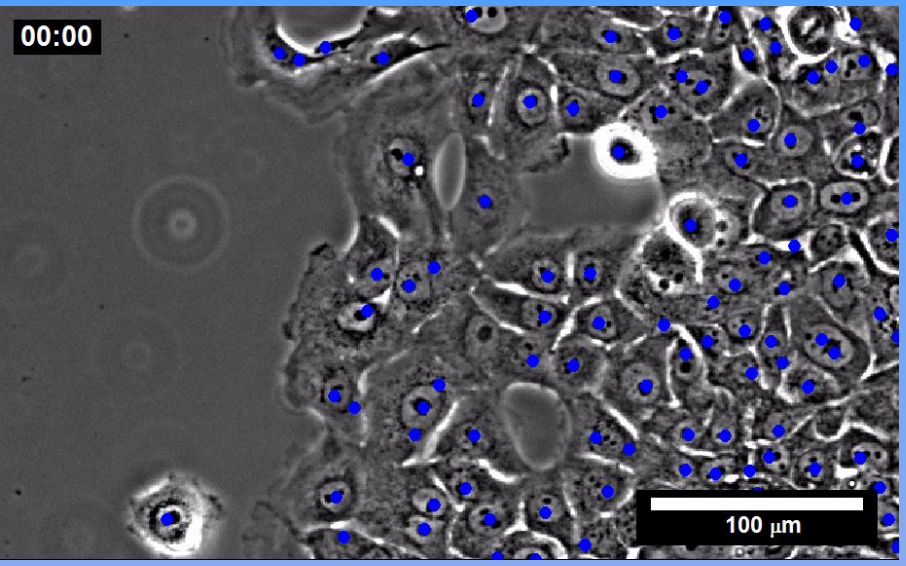


Direction of actin “flow”



Where do our Findings Lead Us

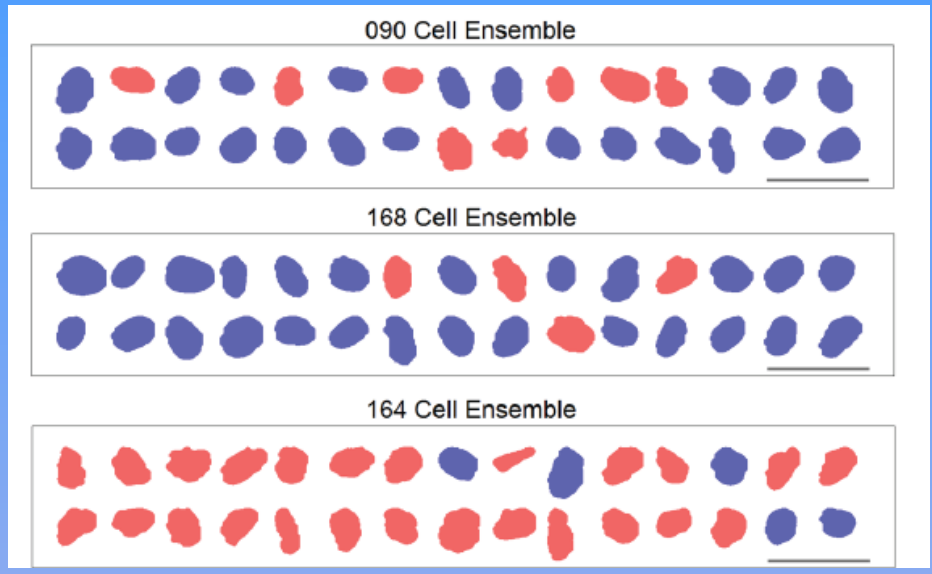
Understanding Collective Cell Migration *(with NCI)*



RM. Lee…NT. Ouellette,& W. Losert, *New J. of Physics* (2013).

C. Guven, …E. Ott, & W. Losert, *PLOS Comp. Biol.* (2013).

Shape Based Phenotyping *(with NIST, NIH & UM Med School)*



M.K. Driscoll, …W. Losert, & K. Cao, *Aging* (2012).

J. Candia, …& W. Losert, *PLOS Comp. Biol.* (2013).

Thanks

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Colin McCann

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John Fourkas *(Chemistry)*
Tobias Kiessling *(Leipzig)*
Josef Kaes *(Leipzig)*
Stuart Martin *(UM Medical School)*

DOD Era of Hope Award
(to Stuart Martin)

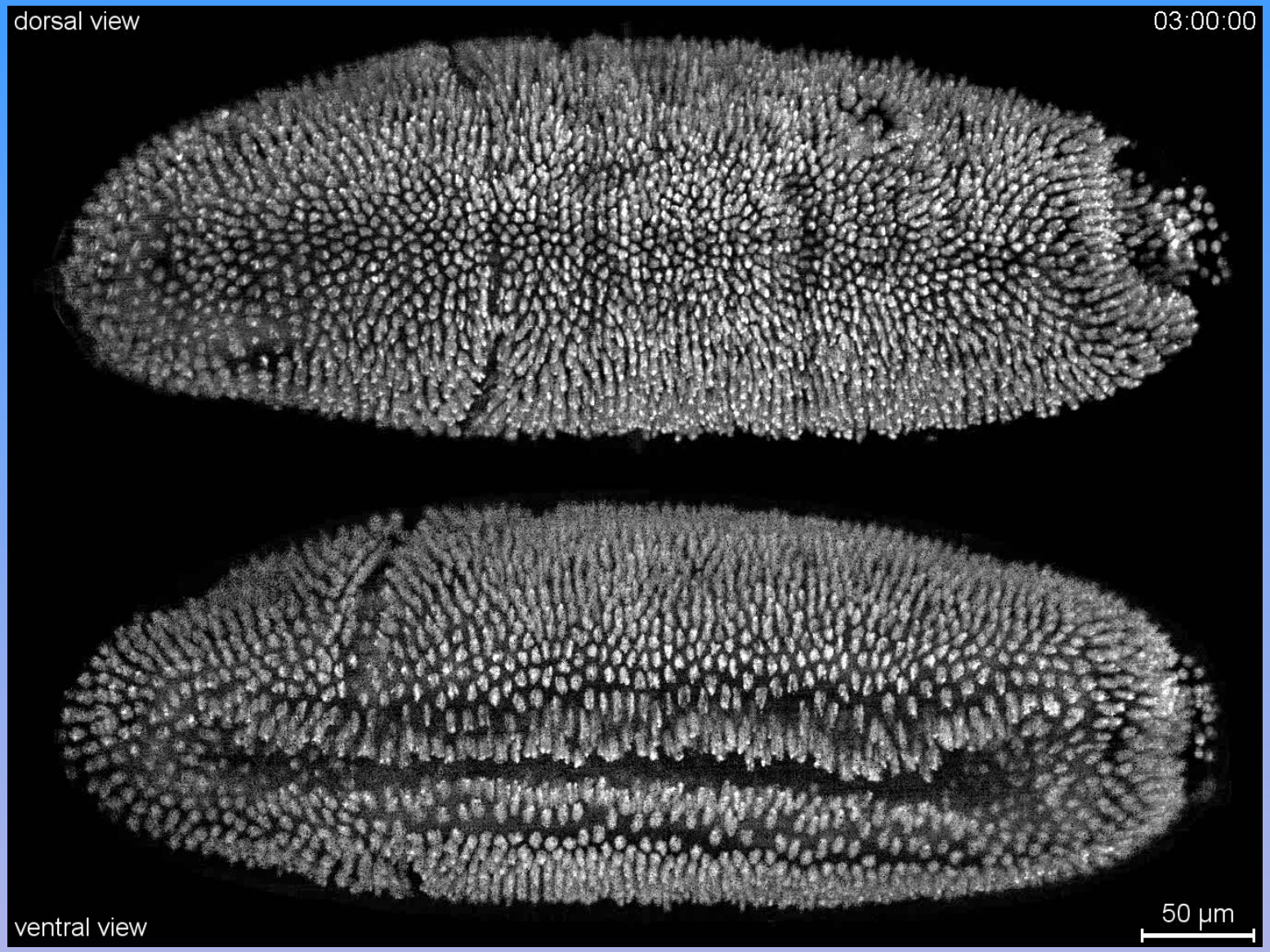
NSF Physics of Living Systems

NIH Nanotechnology

Univ. of Maryland – National Cancer Institute
Partnership for Cancer Technology
Open for Visiting Scientists

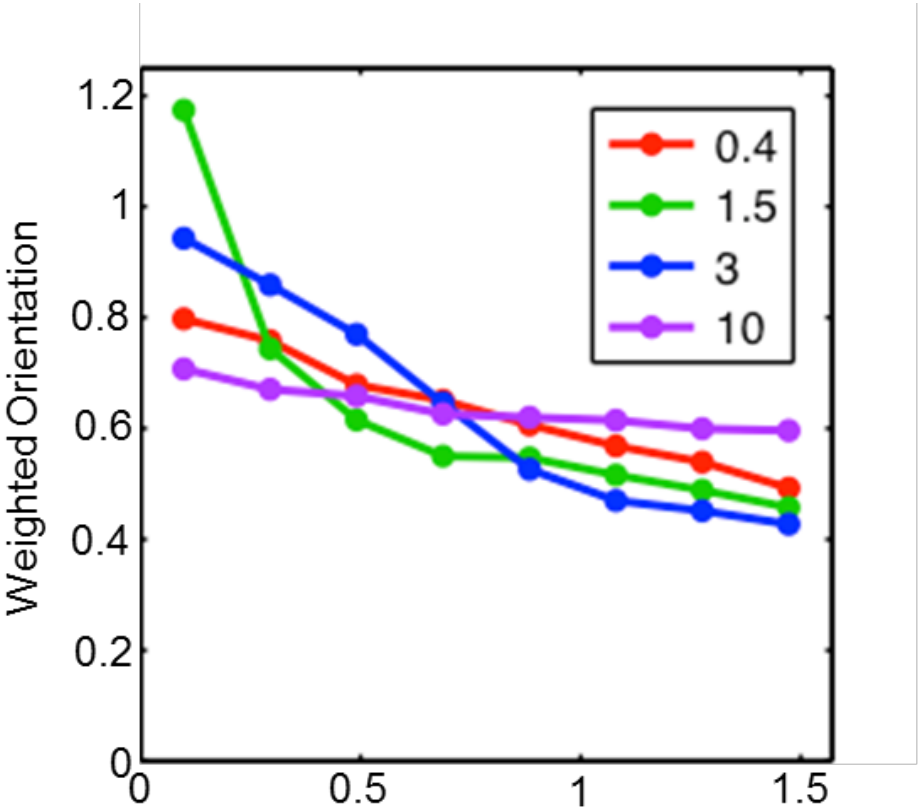
wlosert@umd.edu

Is this motion random?
Is this motion elastic?



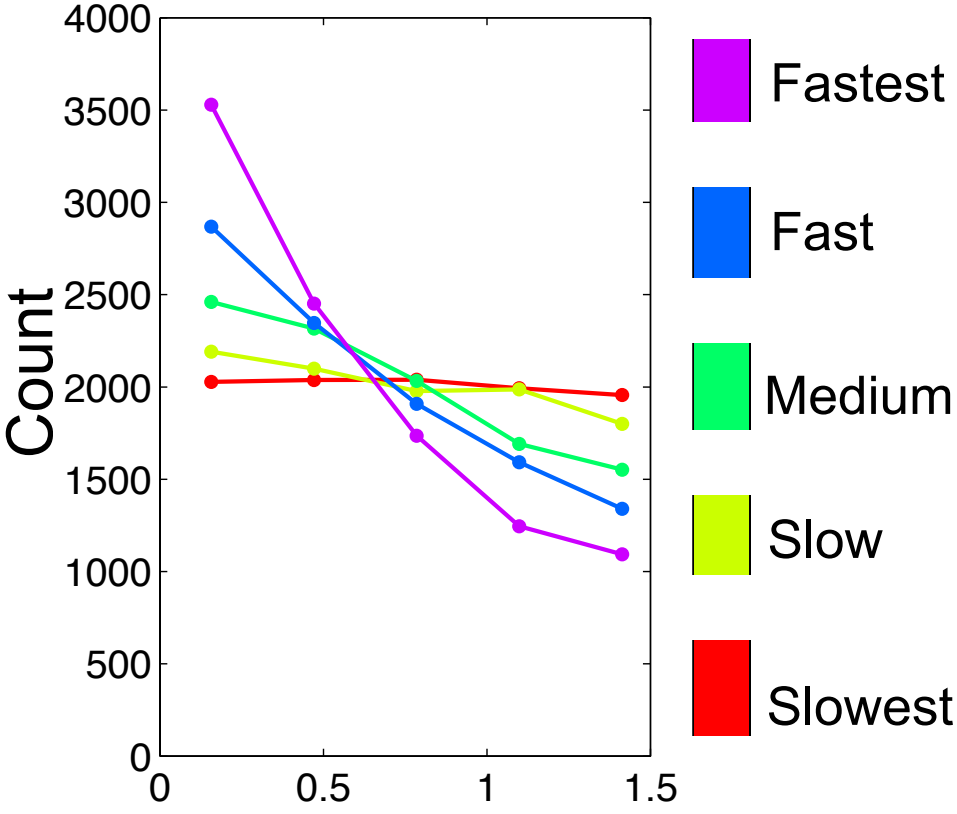
Contact Guidance depends on ridge spacing and cell speed

Optimal guidance efficiency: 1.5 μm ridge spacing



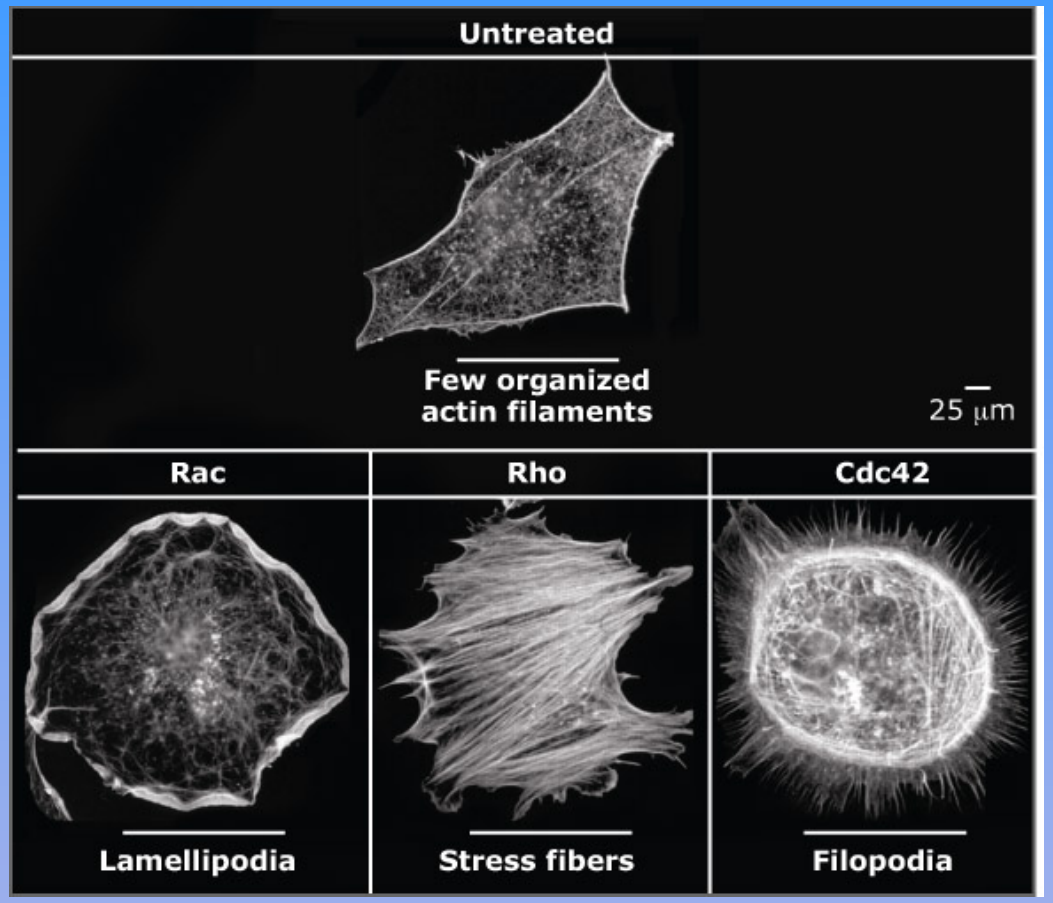
Cell orientation with respect to ridges

Faster Cells are guided better



Direction of Cell motion with respect to ridges

Actin Polymerization into fibers is controlled by Actin Binding Proteins (ABP)



Rac, Rho and Cdc42 regulate actin organization.

Reproduced from A. Hall, Science 279 (1998): 509-514
Levin's Cell, Chapter 12, Fig 12.23

Physics Approaches continued

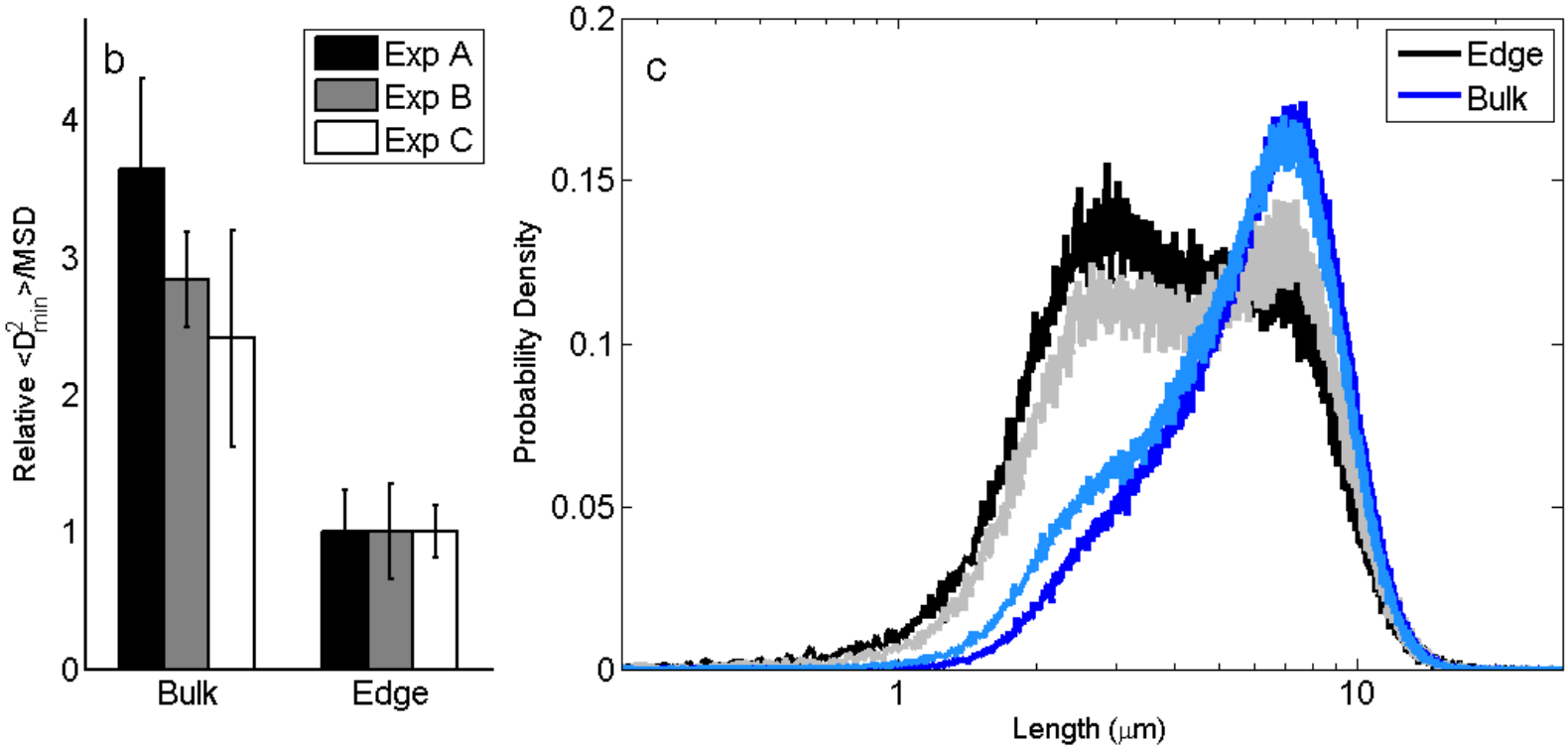
Can the concepts of entropy and information theory be applied to model cancer?

Differential network entropy reveals cancer system hallmarks

James West[1,2,3], Ginestra Bianconi[4], Simone Severini[2,3] & Andrew E. Teschendorff[1,3]

Nature, 2012

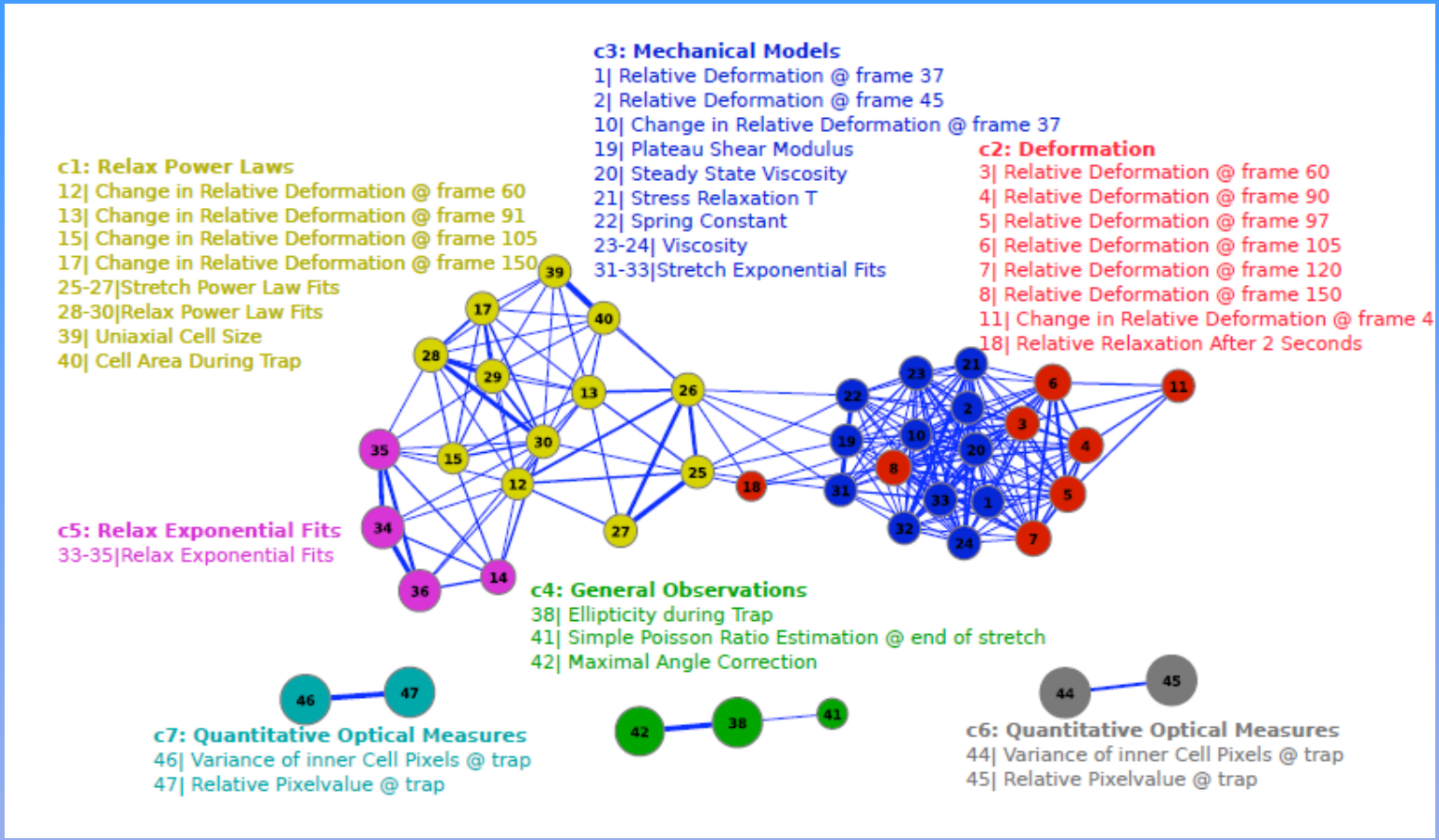
Collective Motion is different bulk vs edge



Lee, R., et al. *New Journal of Physics* (2013)

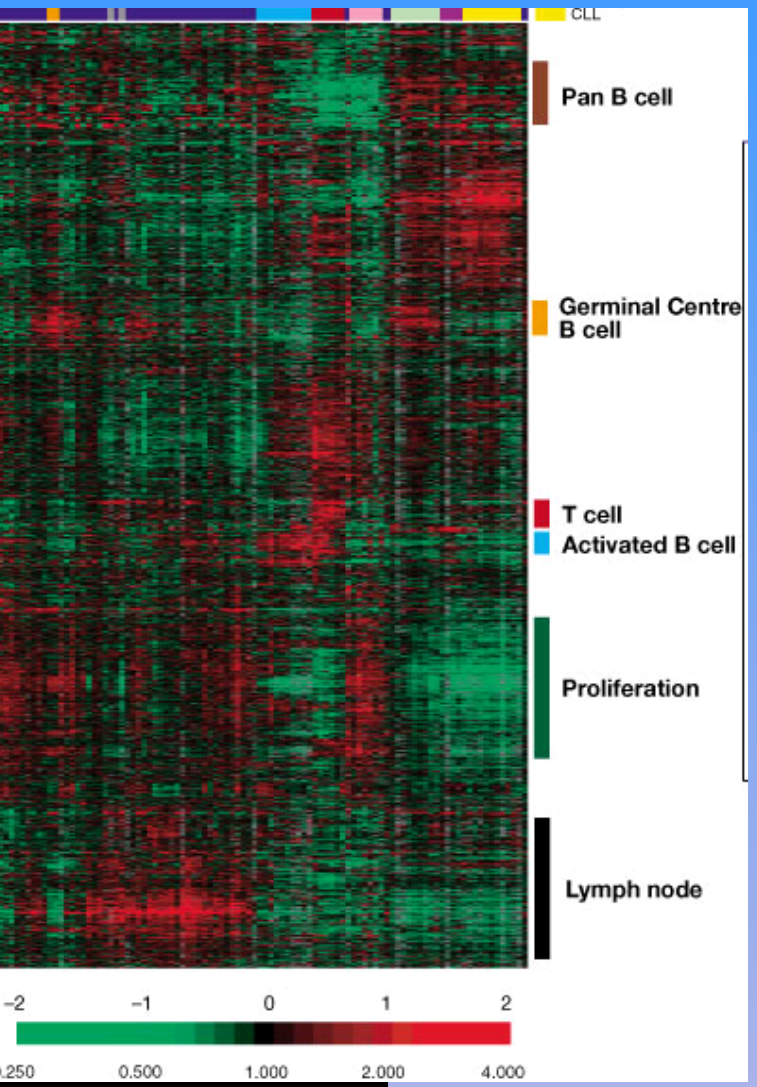
- Bulk has a higher non-affine motion than bulk.
- Bulk predominately rearranges on a longer length scale

Network Analysis reveals the potential of multiple mechanical modules



T. Kiessling, M. Herrera, D. Nnetu, E. Balzer, M. Girvan, S. Martin, J. Kaes, W. Losert, European Journal of Physics (2013)

How to classify cancer?
No unique genetic signature in many cancers

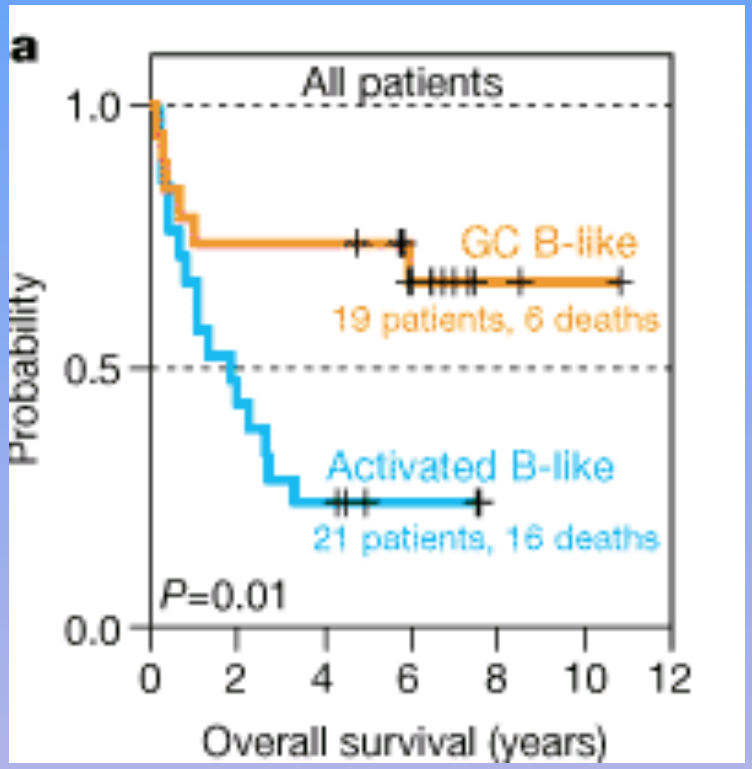


400 patients

20,000 genes

Lymphoma: Gene Expressions show a variety of genetic phenotypes "one cancer, many diseases"

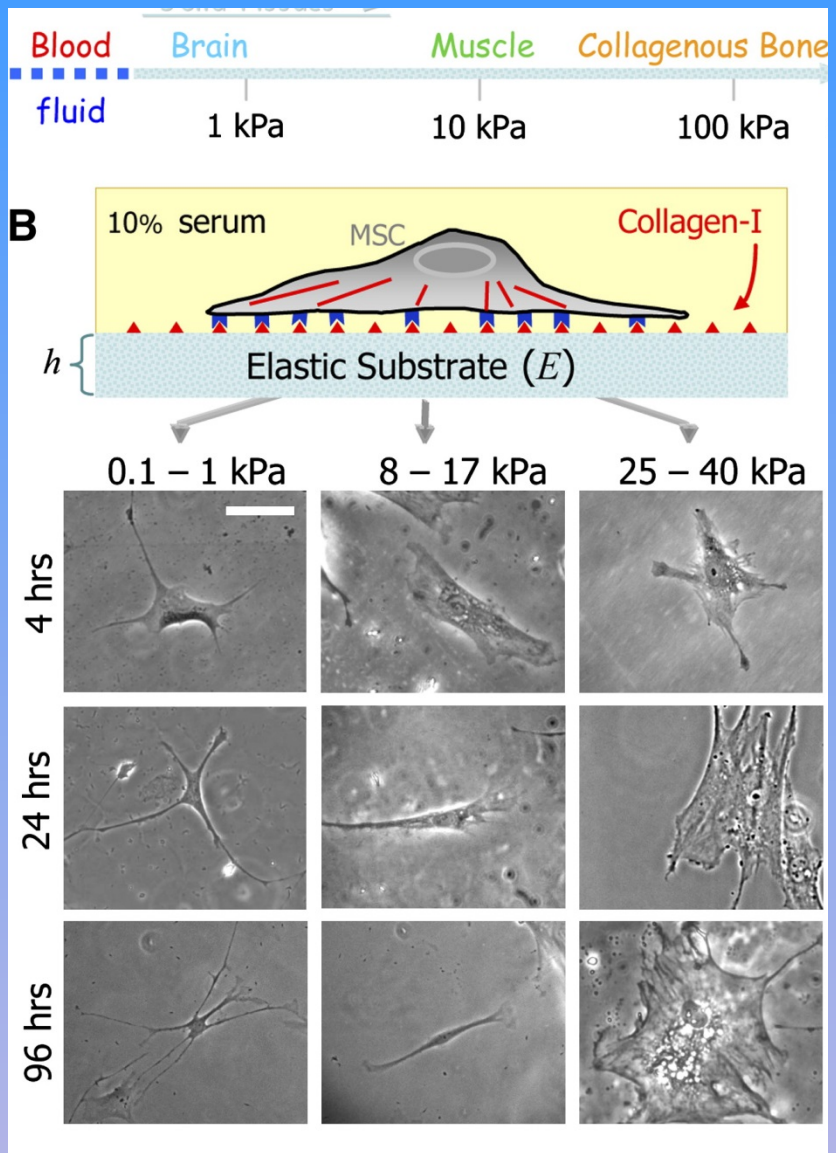
(L. Staudt, NCI, Nature 2000)

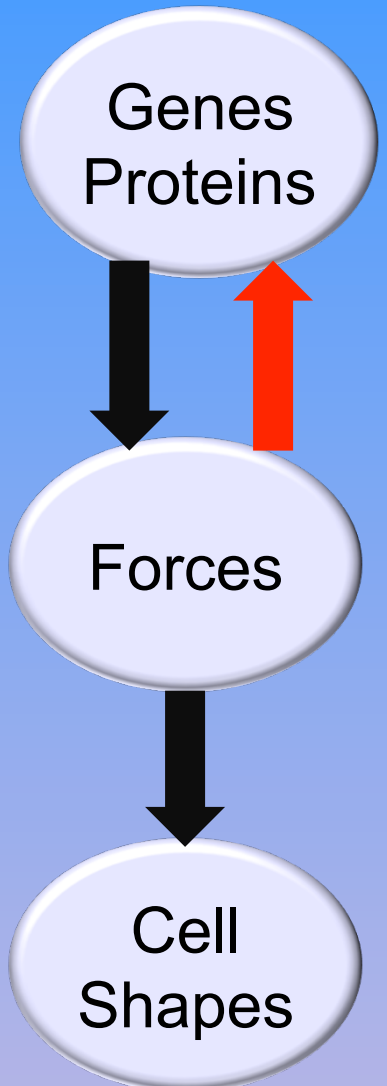


Forces can Trigger Protein Production

Matrix Elasticity Directs Stem Cell Lineage Specification

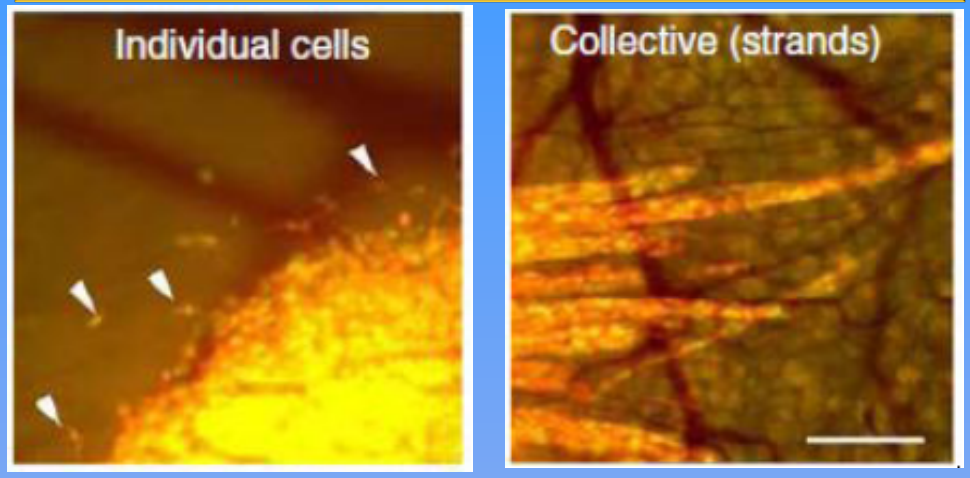
Disher Group, *Cell* 2006



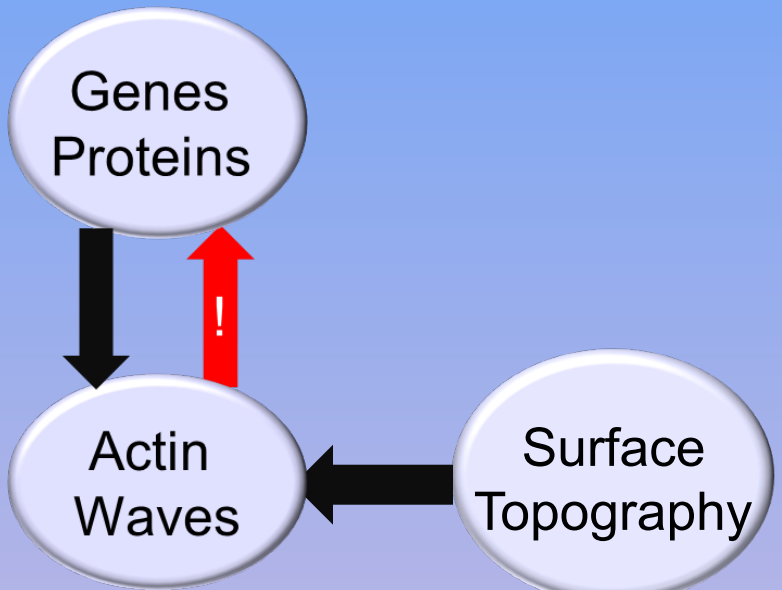


Summary

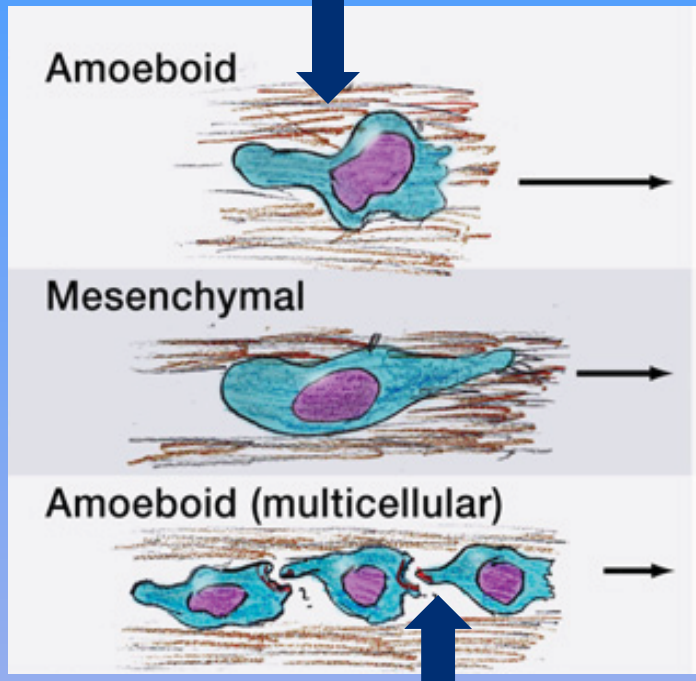
Demonstrated the wave-like character of single cell migration



Alexander, Koehl, et al. Histochemistry and Cell Biology(2008).



Actin waves and cell migration are guided by nanotopography



Friedl and Alexander Cell (2011).

Shape waves can couple in cell groups. *Synchronization?*