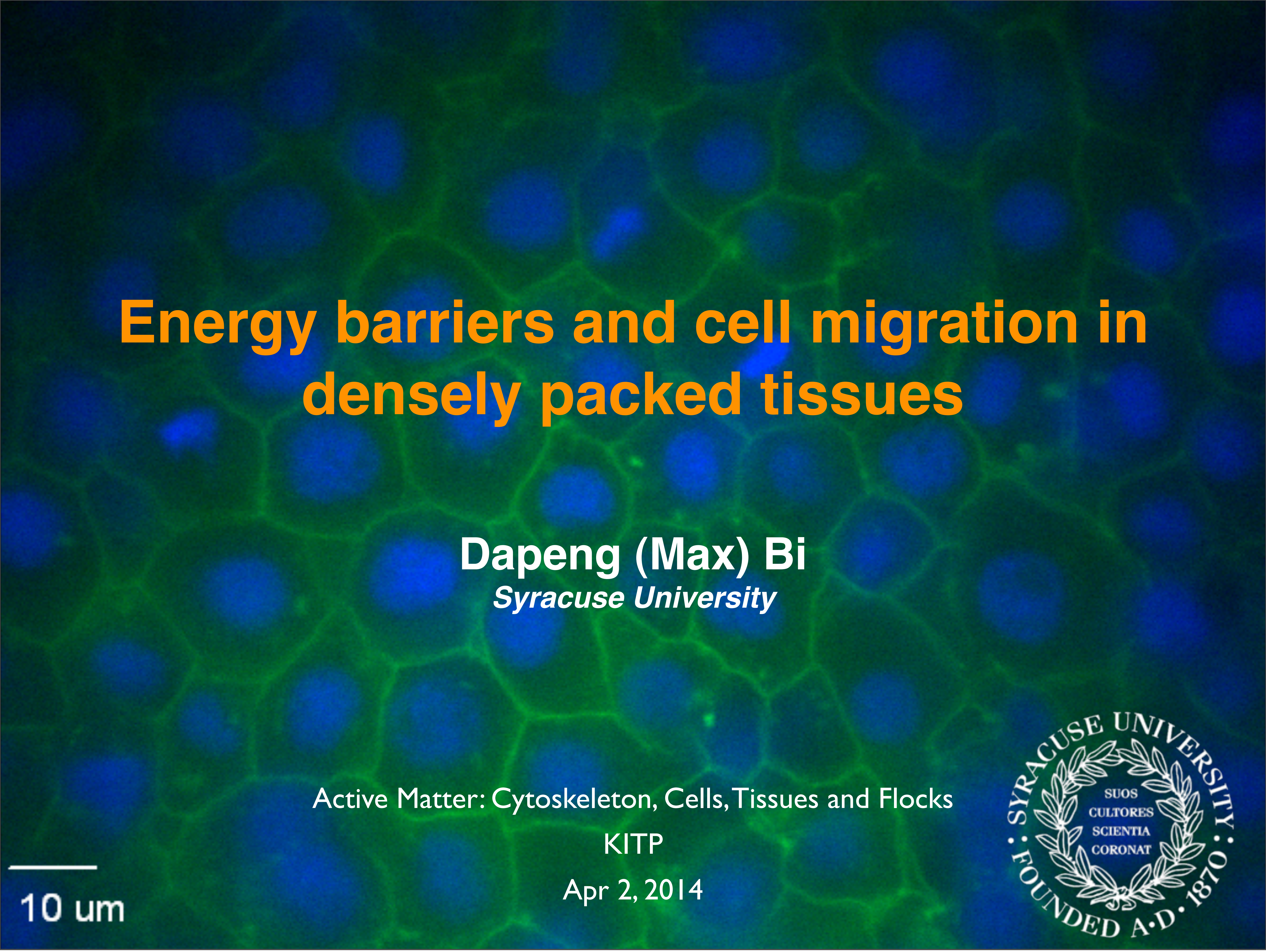
Energy barriers and cell migration in densely packed tissues



Dapeng (Max) Bi
Syracuse University

Active Matter: Cytoskeleton, Cells, Tissues and Flocks

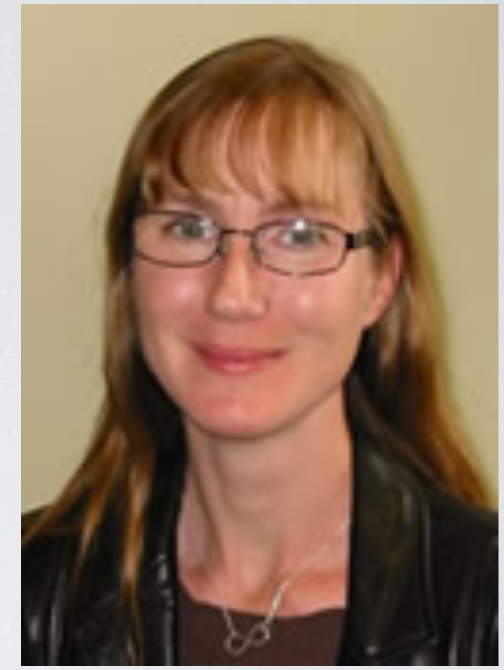
KITP

Apr 2, 2014

Collaborators

M. Lisa Manning

Jorge Lopez



Jen Schwarz

Syracuse University Chancellor Fund
NSF-DMR-0645373

bdpmax@gmail.com

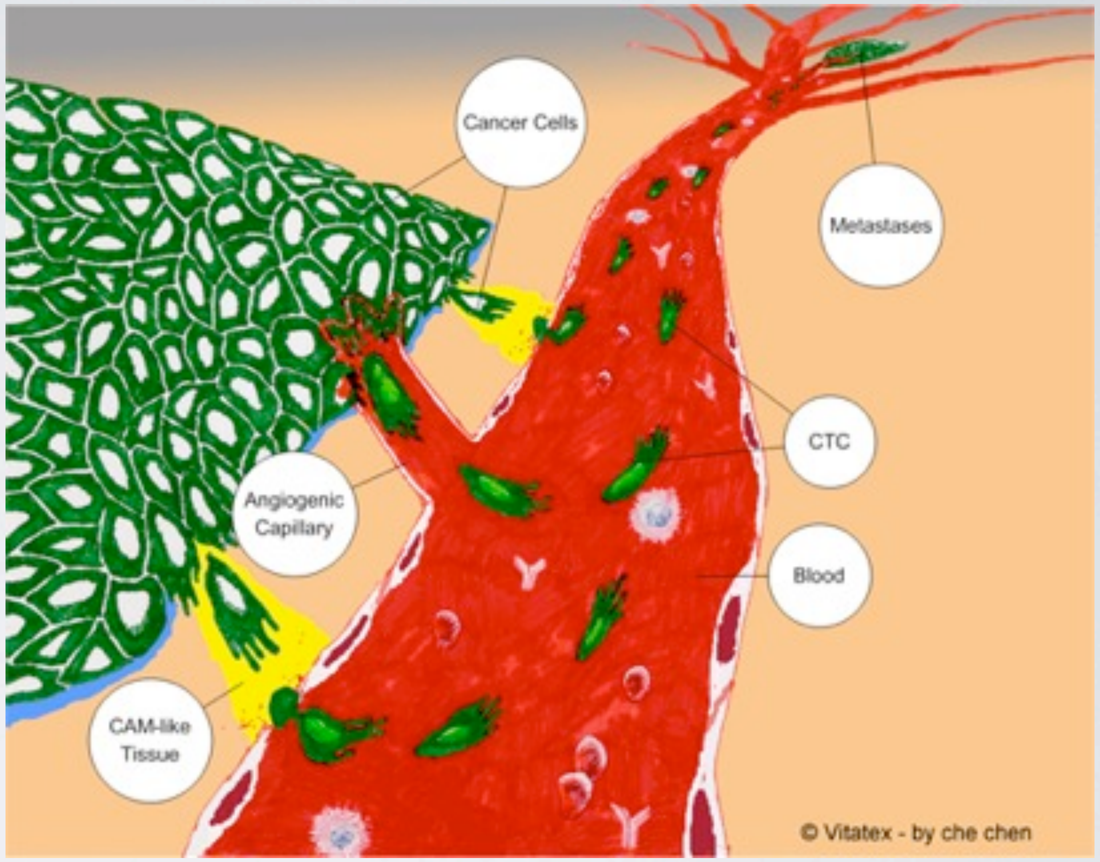
WWW.DAPENGBI.COM

Why study cell migration in dense tissues?

Wound healing assay

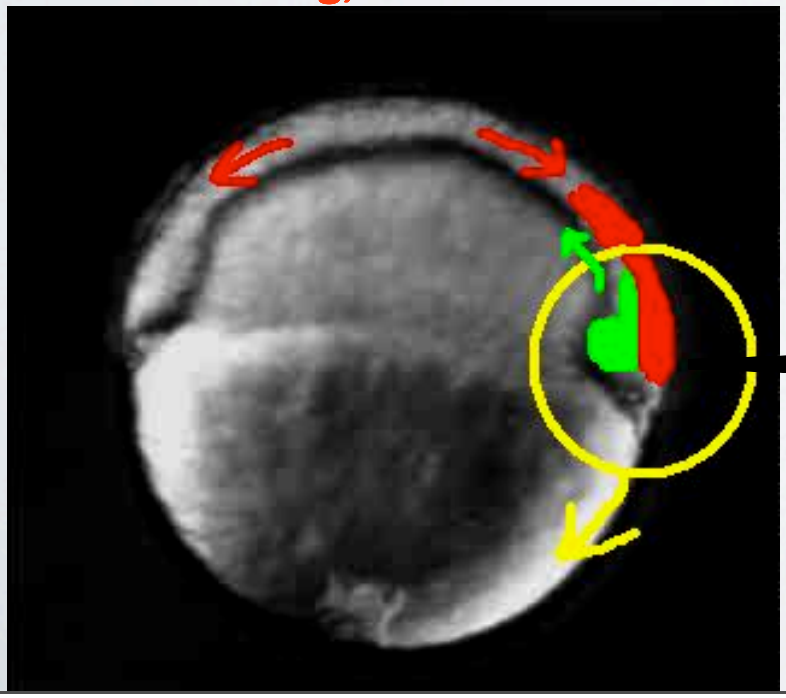
youtube.com/watch?v=v9xq_GiRXeE

Tumor cell migration



During development of embryo

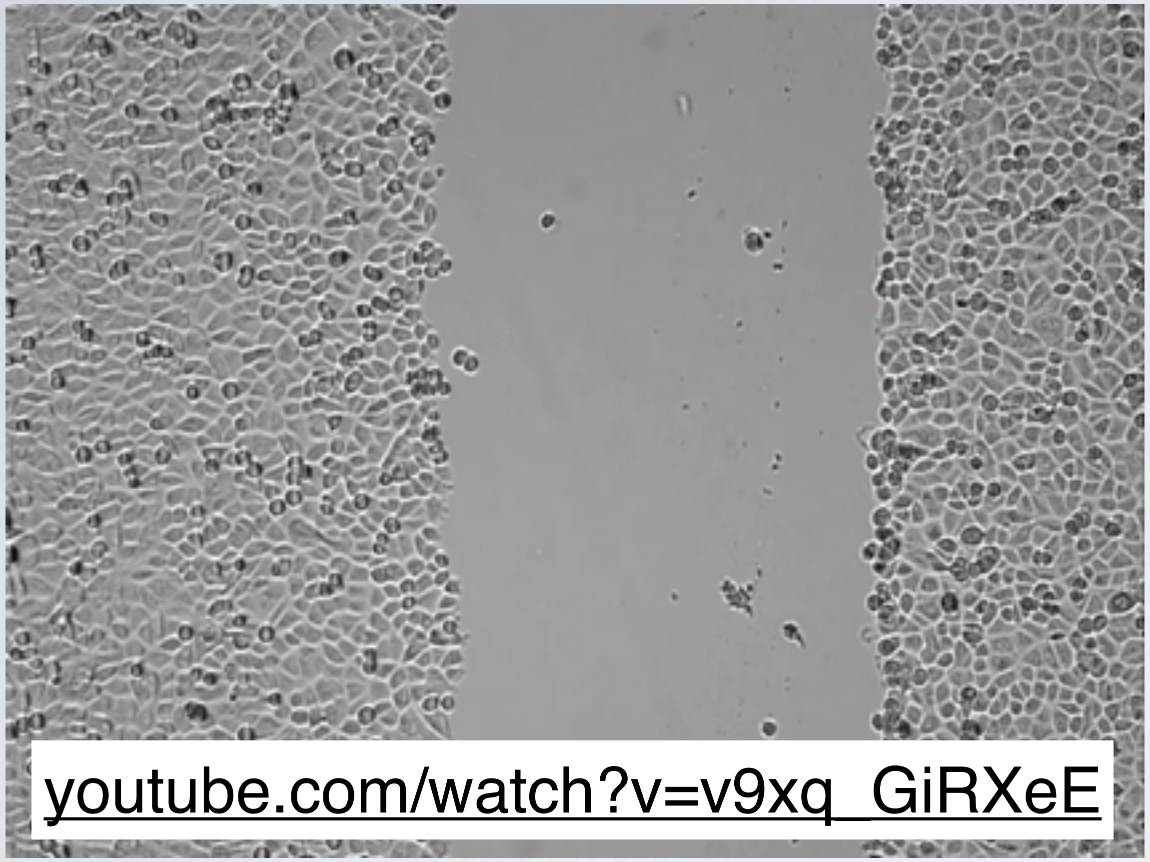
Differential Adhesion Hypothesis: Steinberg, Science 1962



E-M. Schöetz Thesis 2008

Why study cell migration in dense tissues?

Wound healing assay



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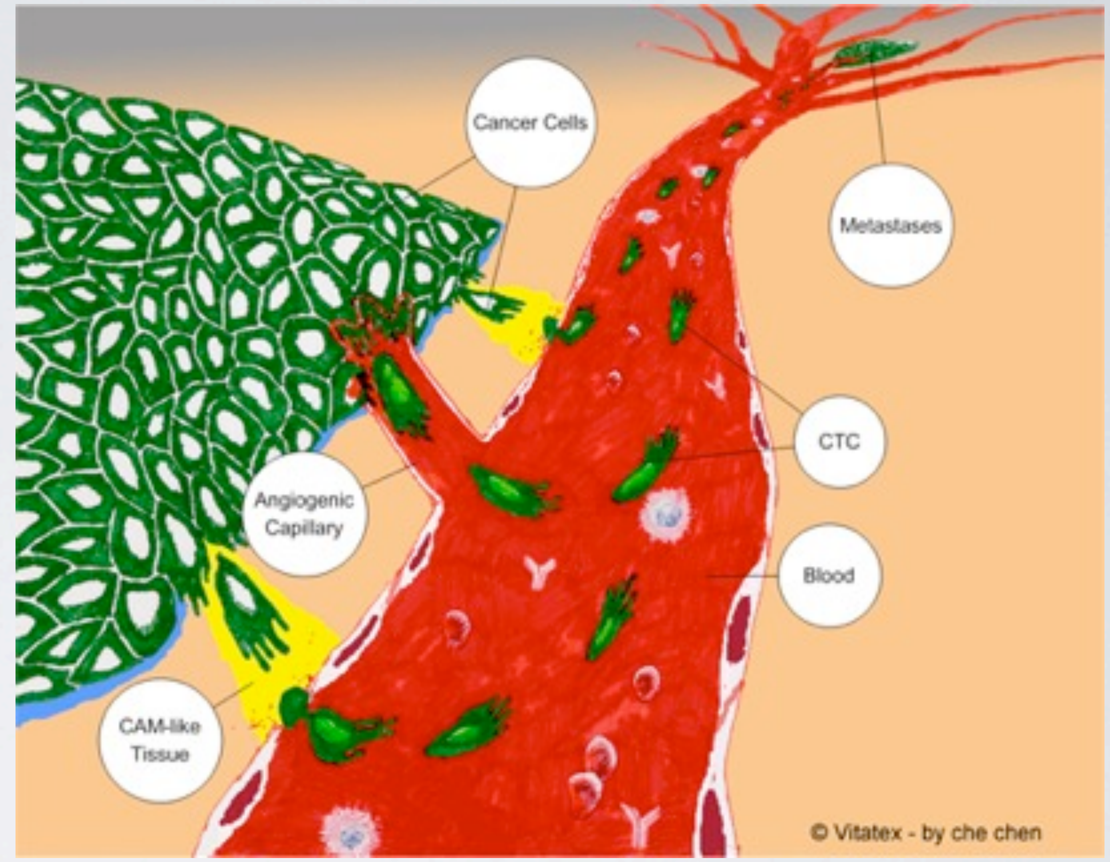

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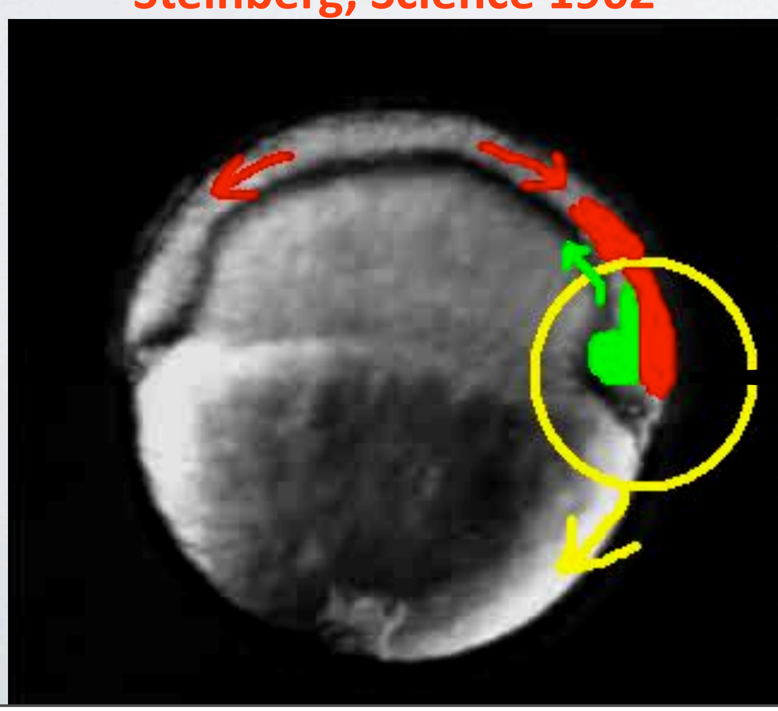
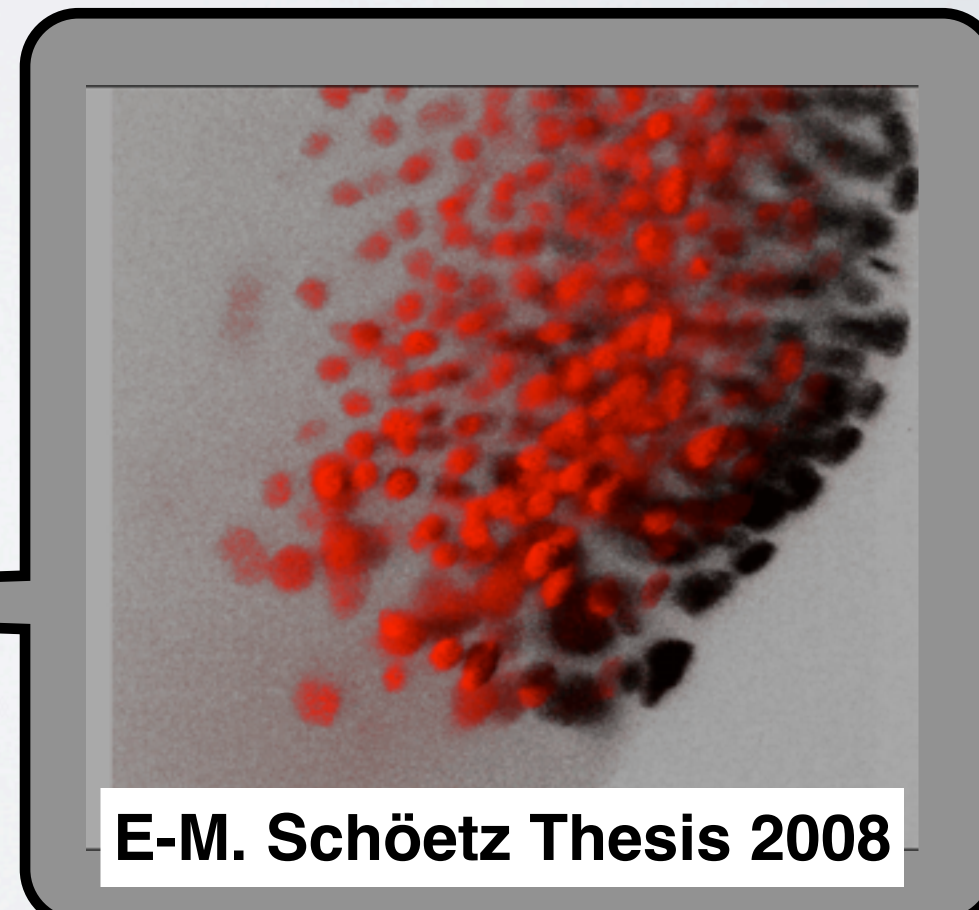




How do cells move?

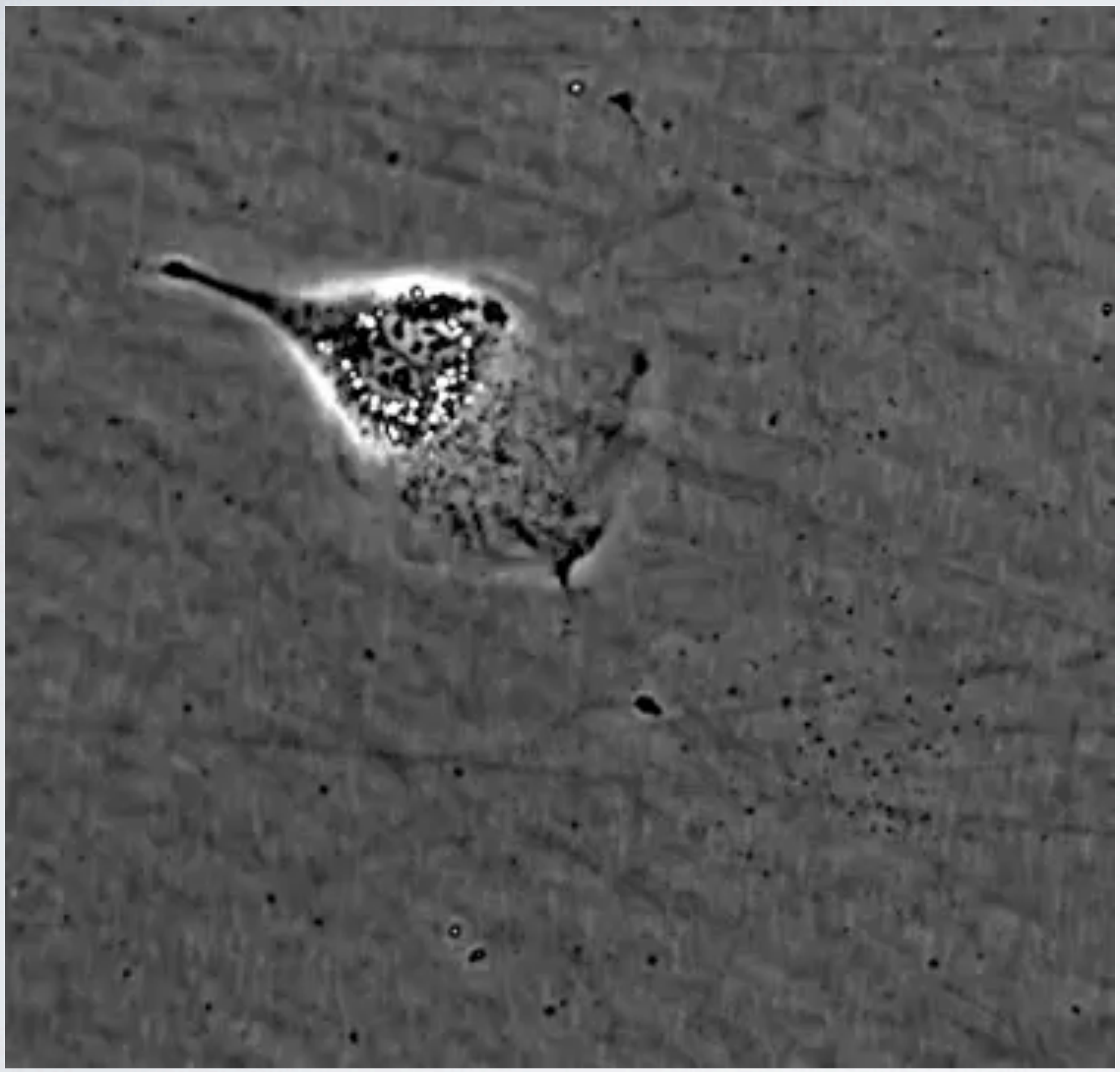
In isolation vs. inside dense tissue

Human bone cancer cell on fibronectin

Zebrafish embryo Schöetz Lab, UCSD

How do cells move?

In isolation vs. inside dense tissue



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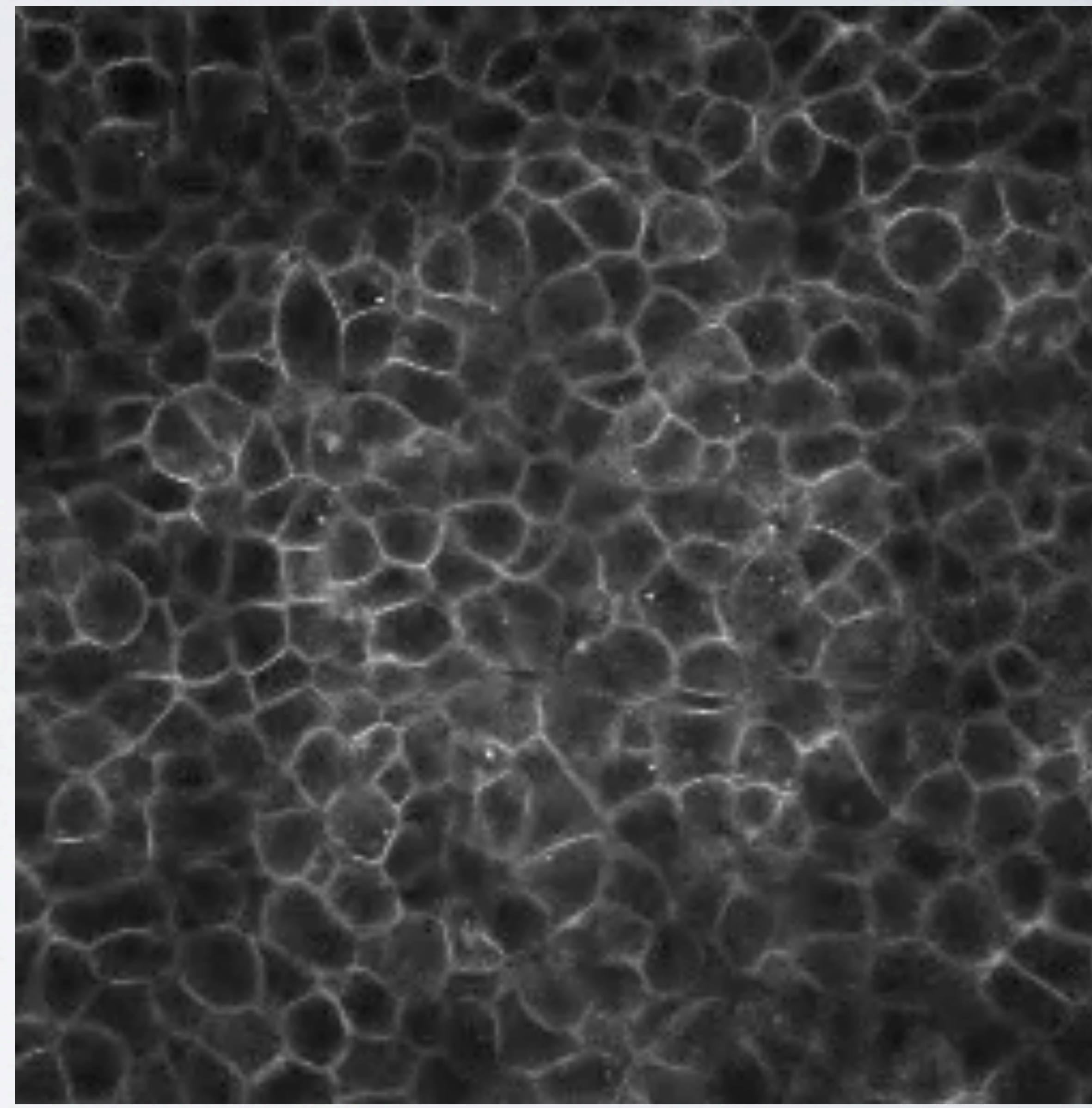
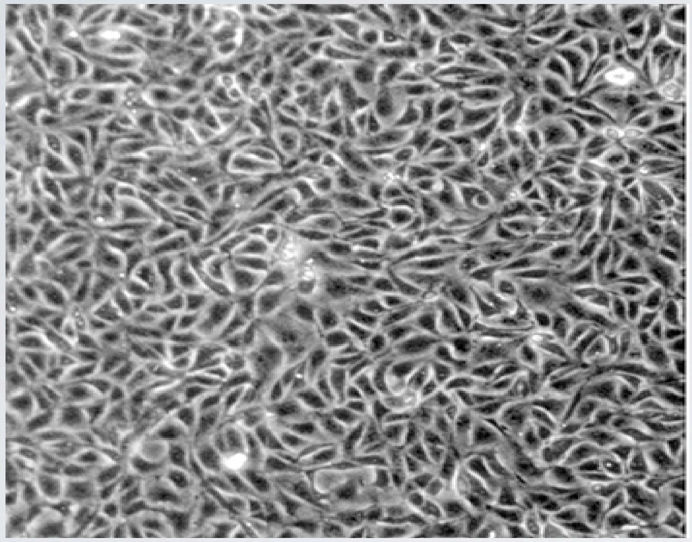


Zebrafish embryo Schöetz Lab, UCSD

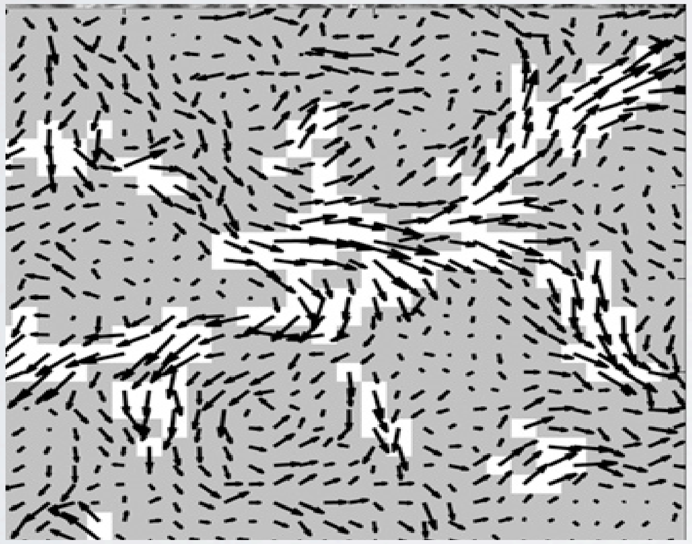
Similarity to glassy materials

Living and Active

Energy injection by cell



Madin-Darby canine kidney (MDCK) cells forming a 2-d confluent layer.



Velocity profile of cells show the spatially heterogeneous pattern in MDCK tissue.

Angelini et al PNAS 2010

Similarity to glassy materials

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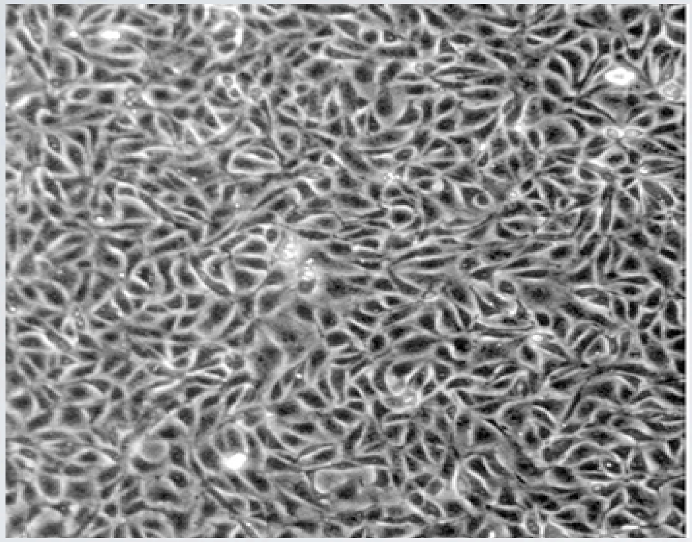

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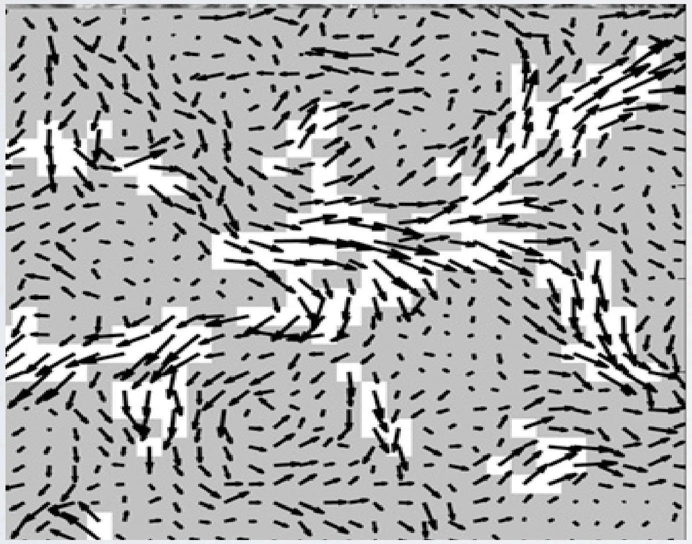
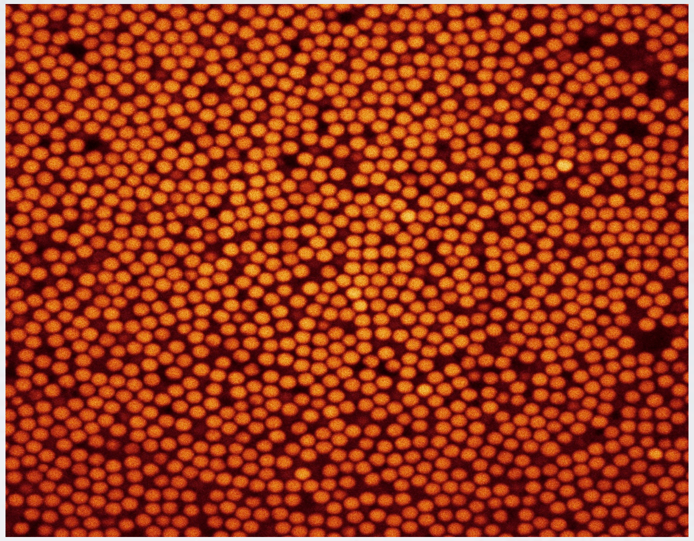


Velocity profile of cells show the spatially heterogeneous pattern in MDCK tissue.

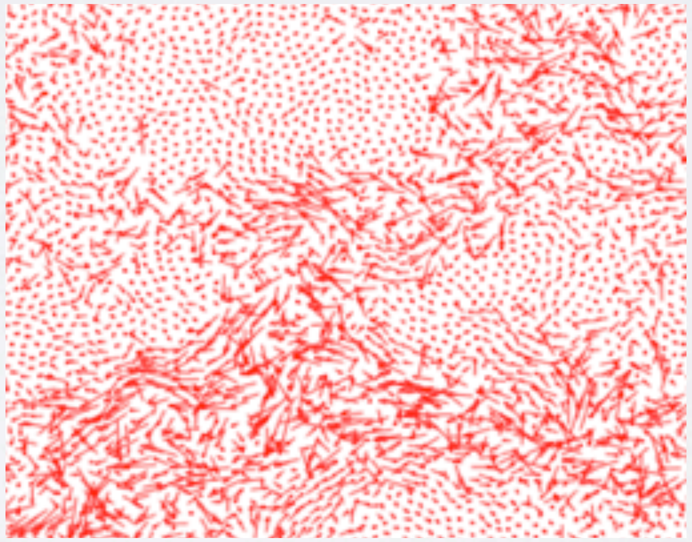
Angelini et al PNAS 2010

Non-living

Thermal



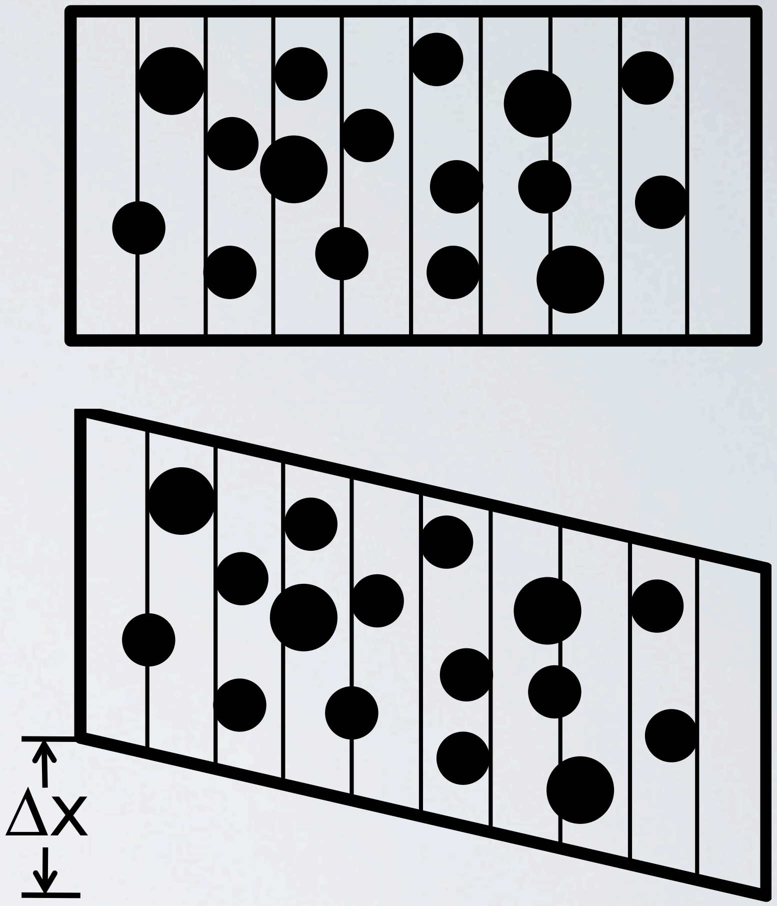
A colloidal glass.

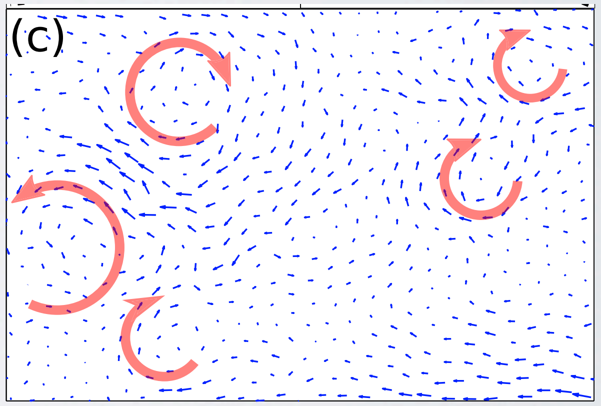


Displacement profile in simulation of a 2-d glass former.

Berthier PRL 2011

Boundary Driven





Sheared granular material

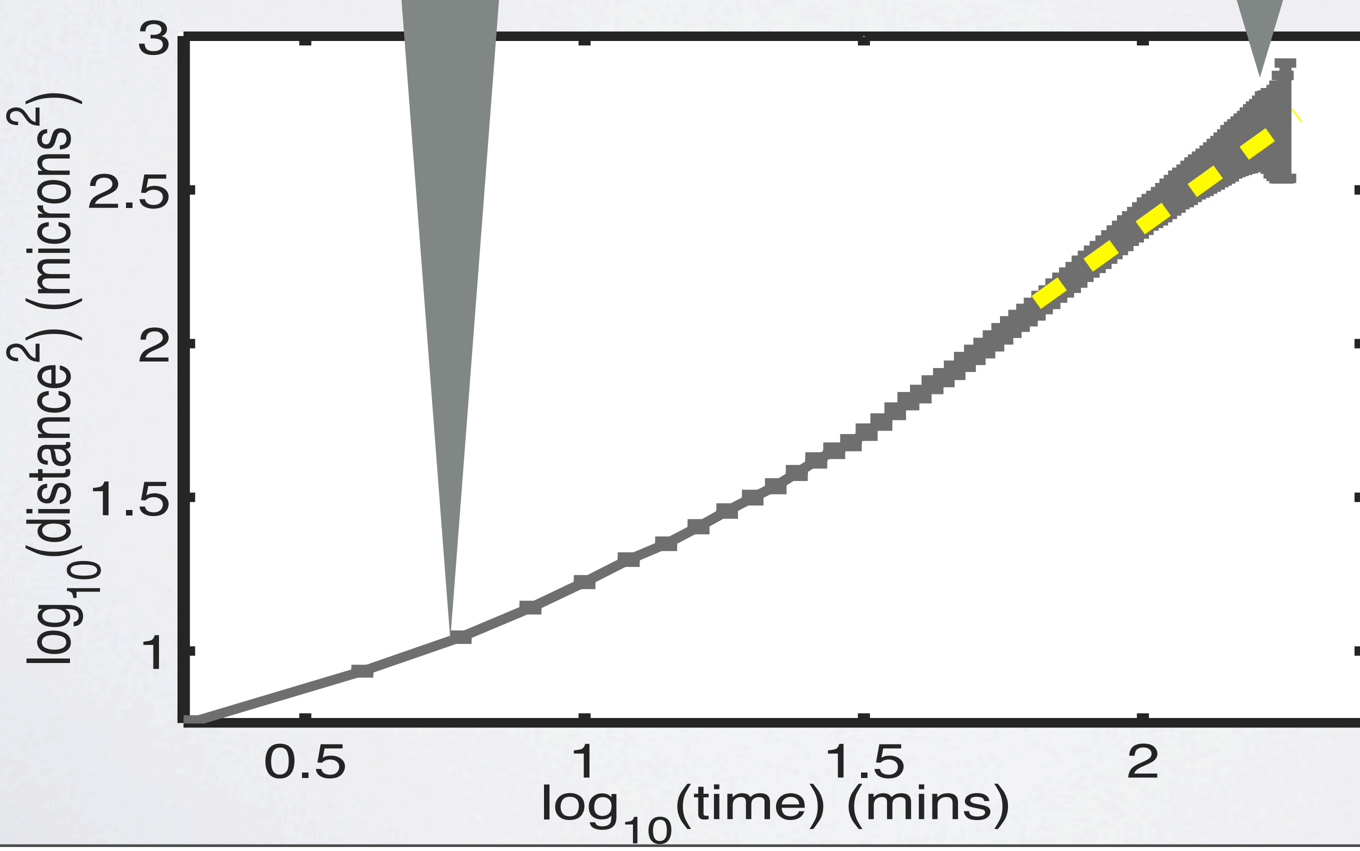
Jie Ren thesis 2013, Duke Univ.

Temporal behavior: viscoelasticity

timescale ~ minutes

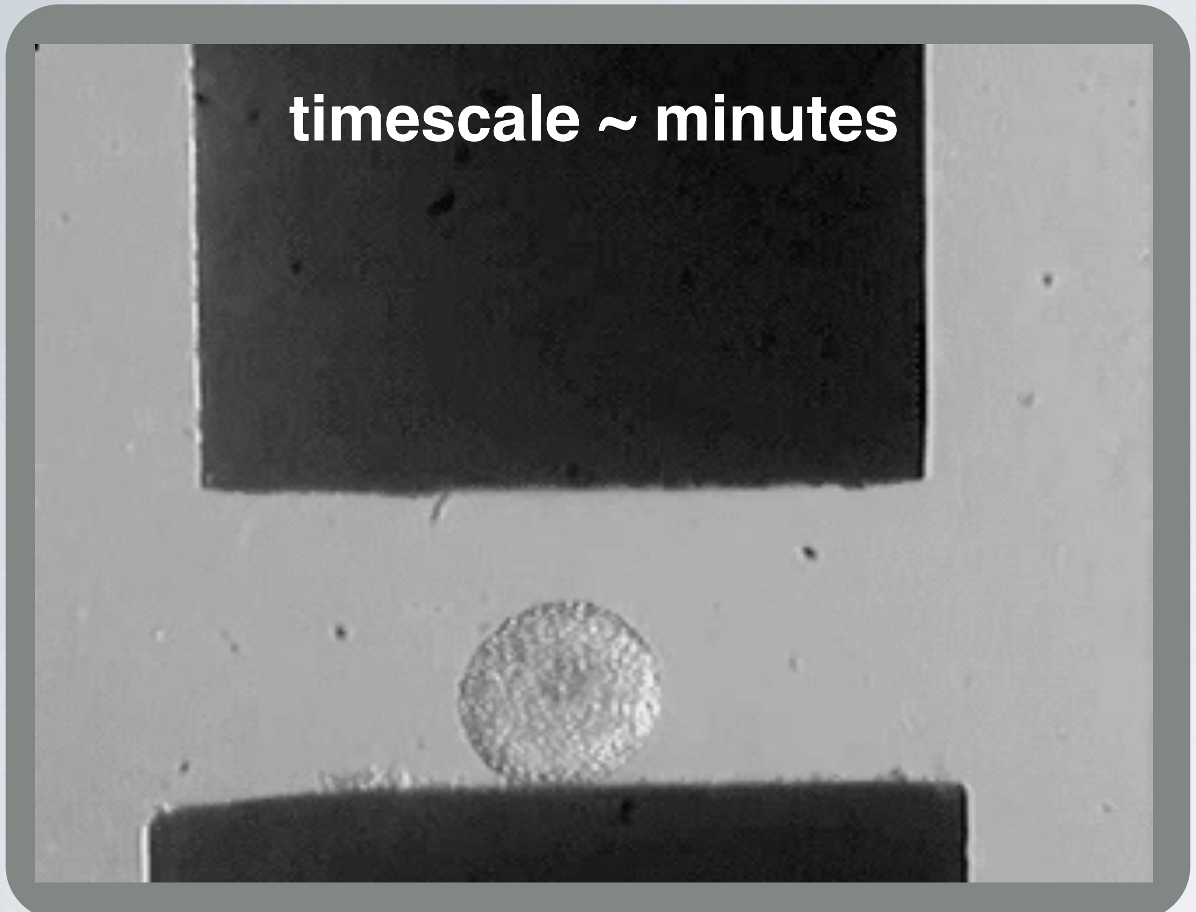
about 5000 cells

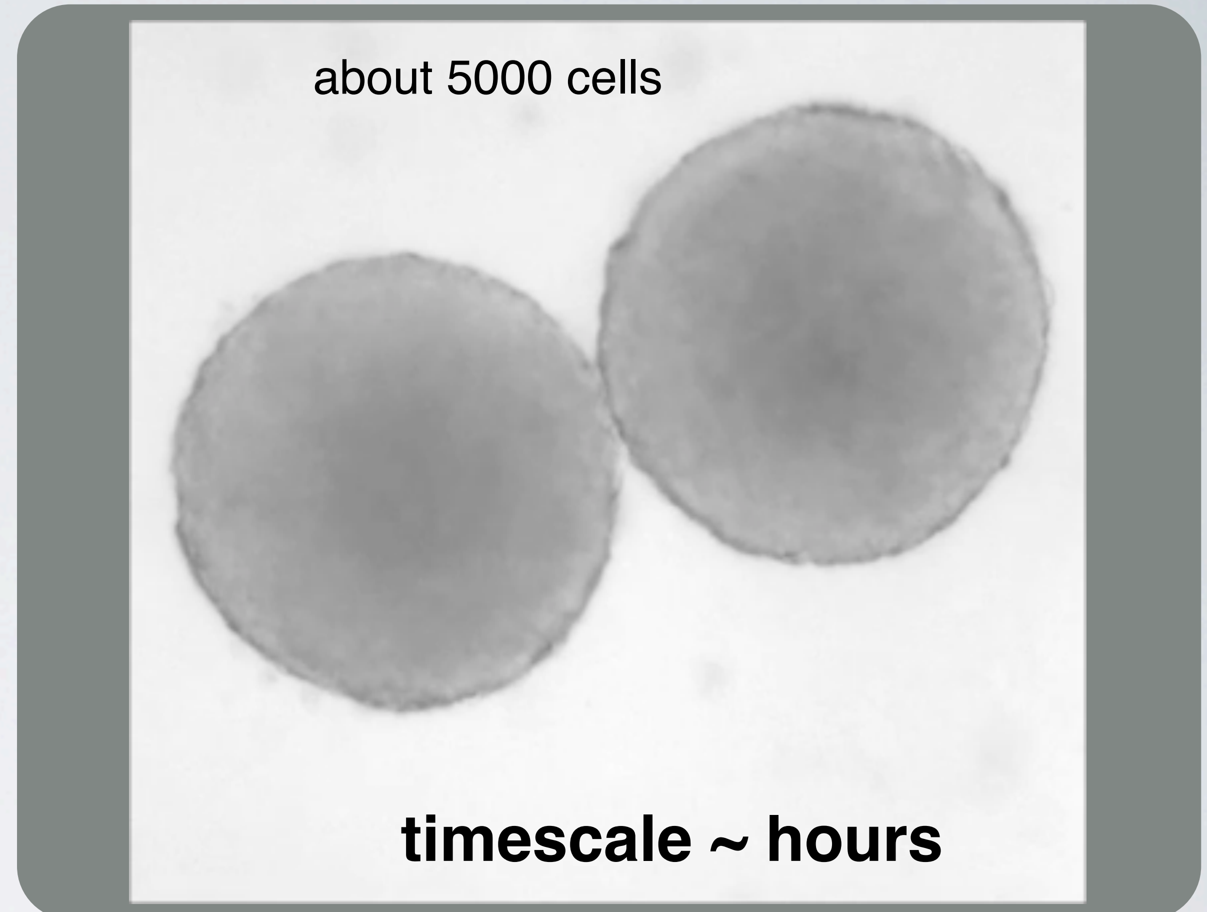
timescale ~ hours

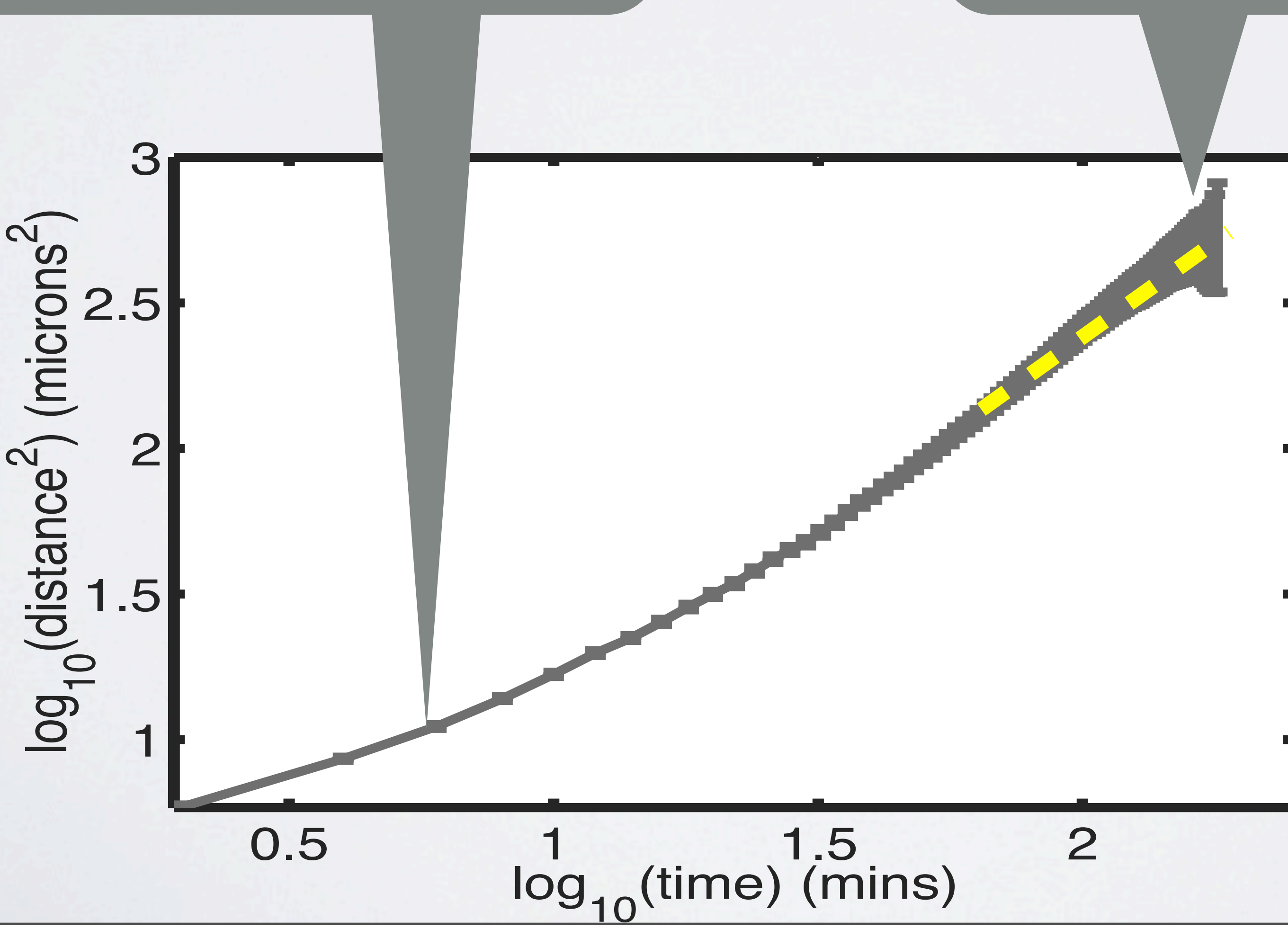


Schöetz et al
J. R. Soc. Interface 2013

Temporal behavior: viscoelasticity







Schöetz et al
J. R. Soc. Interface 2013

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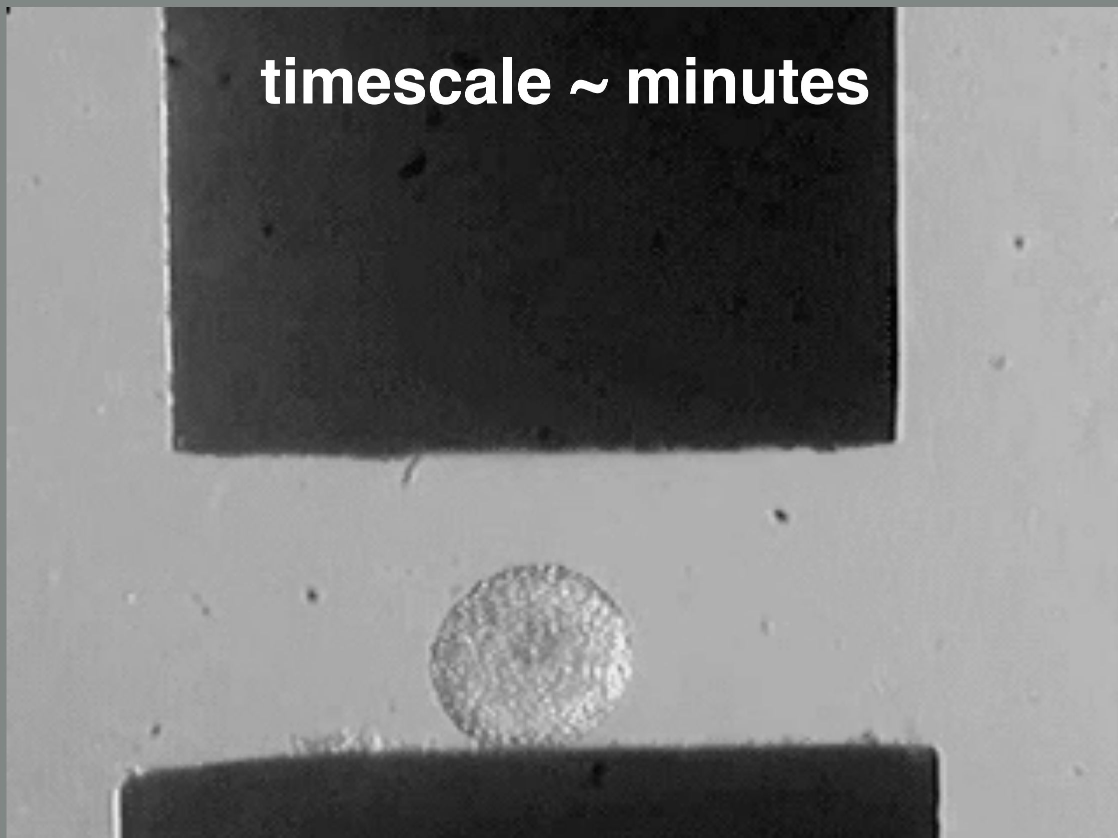
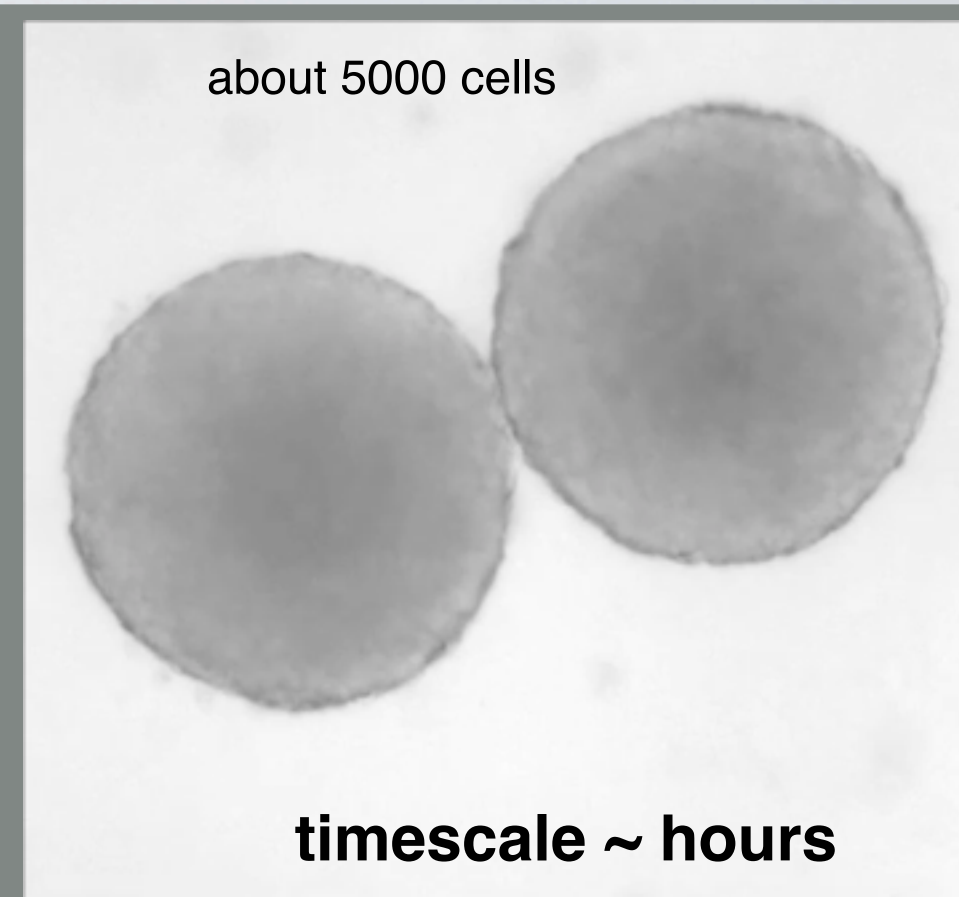
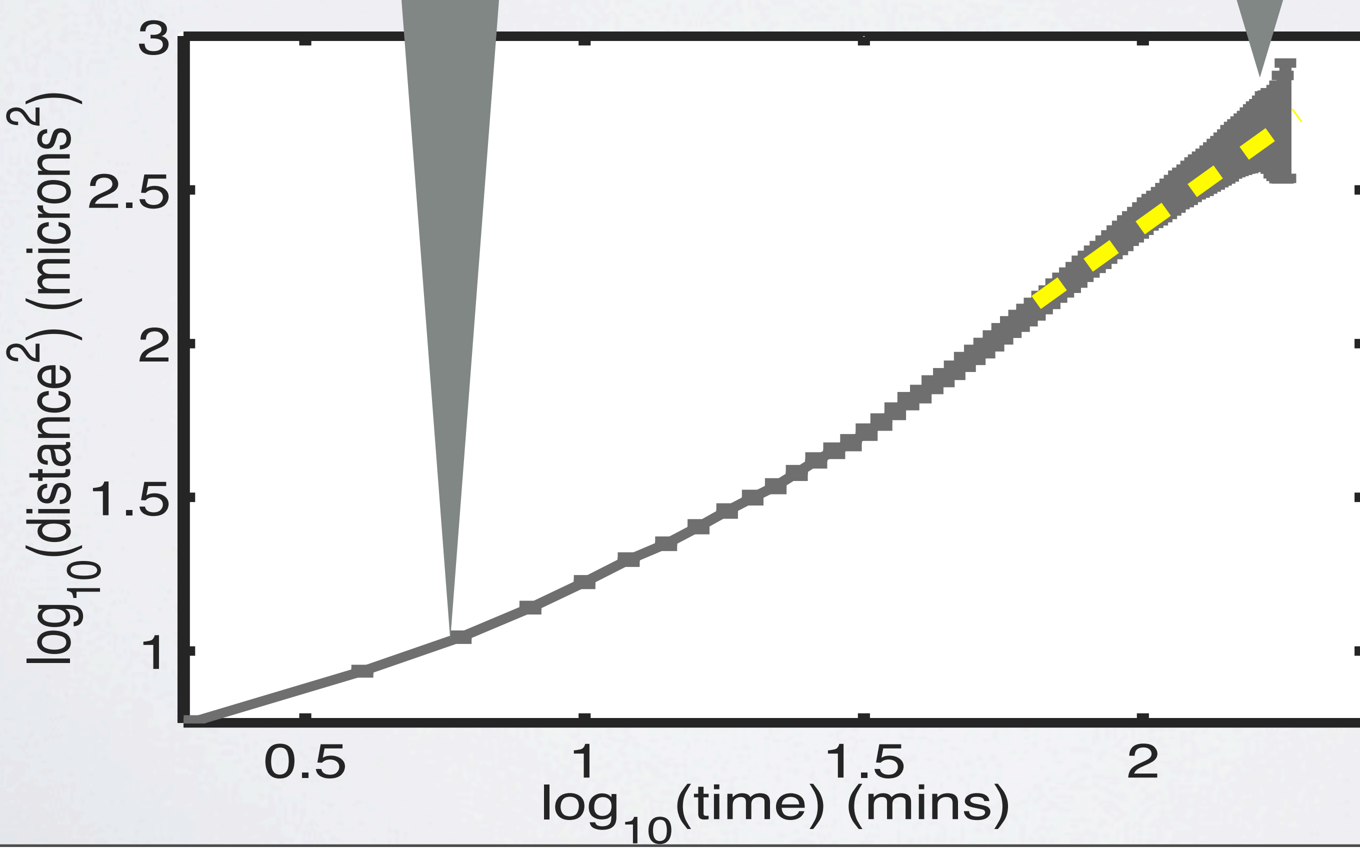
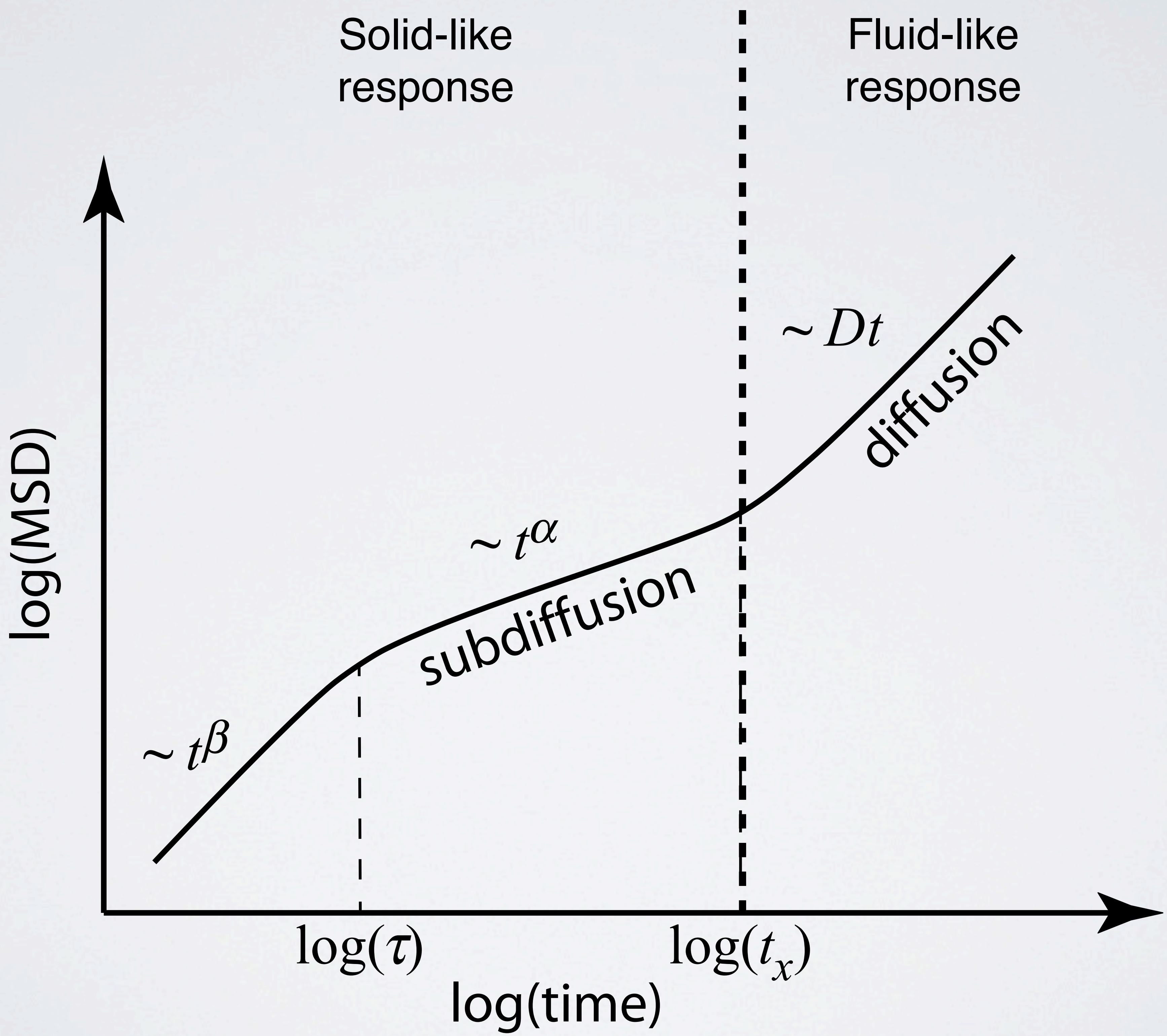






Schöetz et al
J. R. Soc. Interface 2013

Similarity to glassy materials



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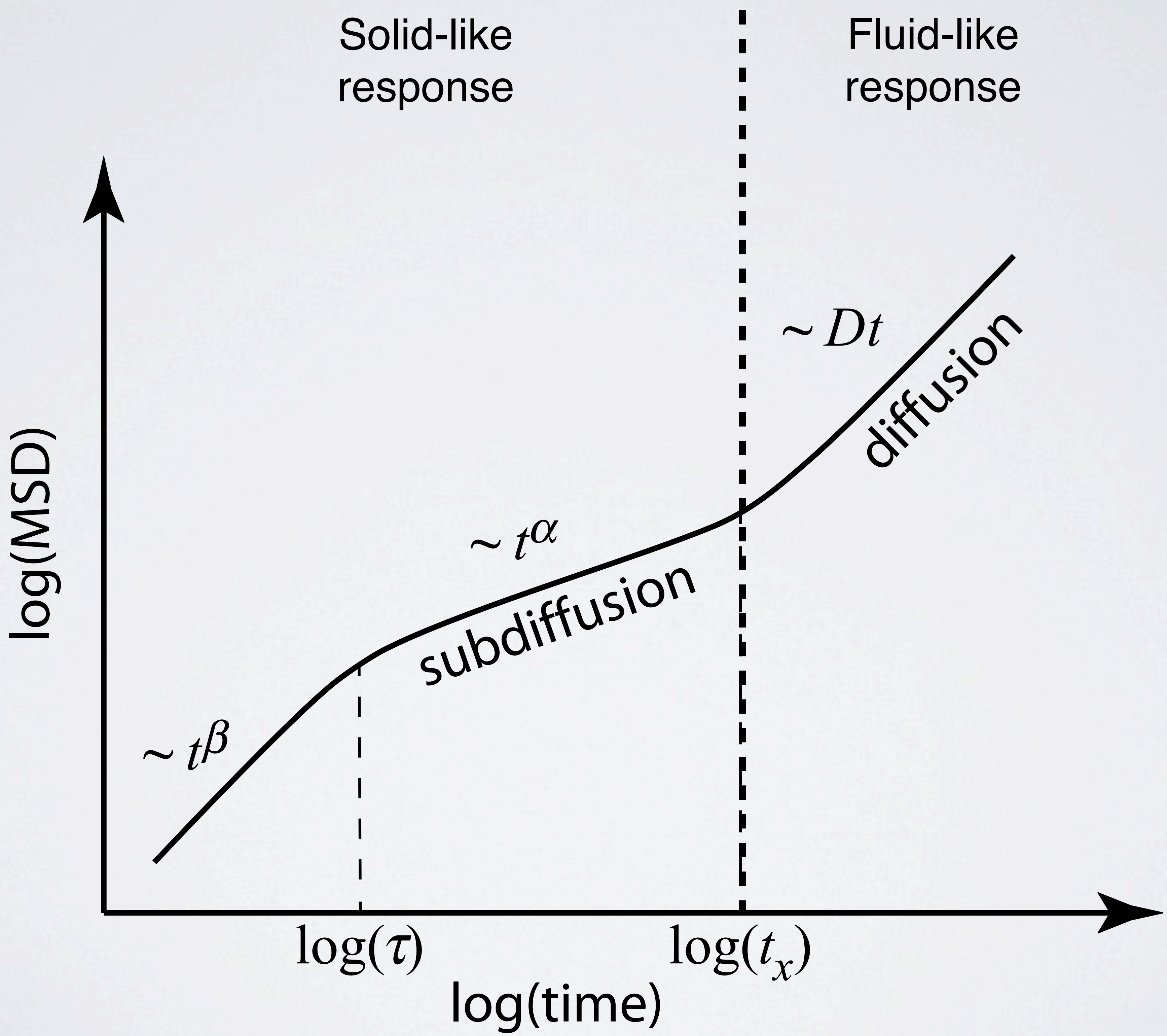
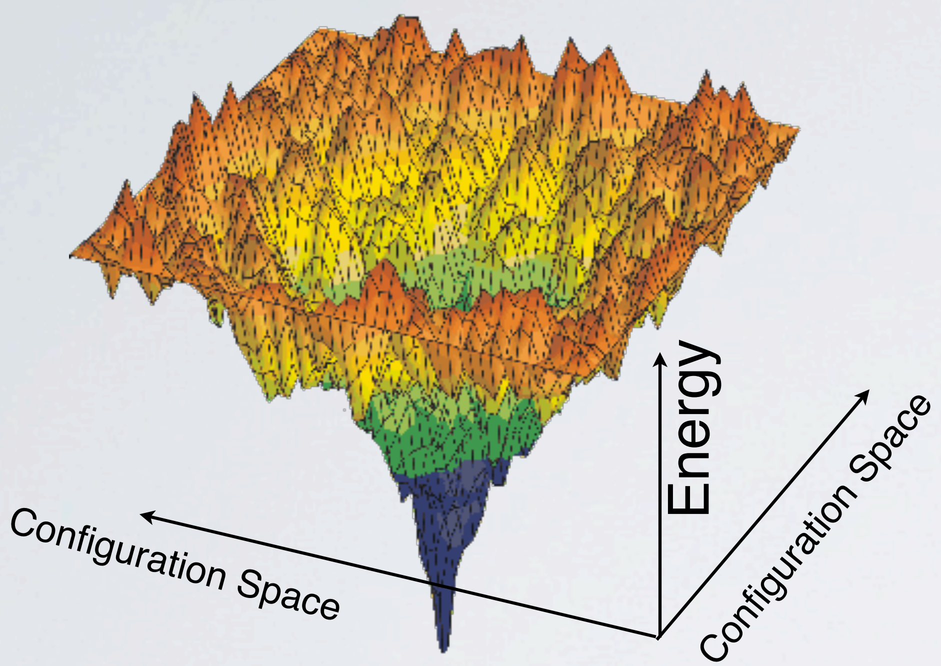


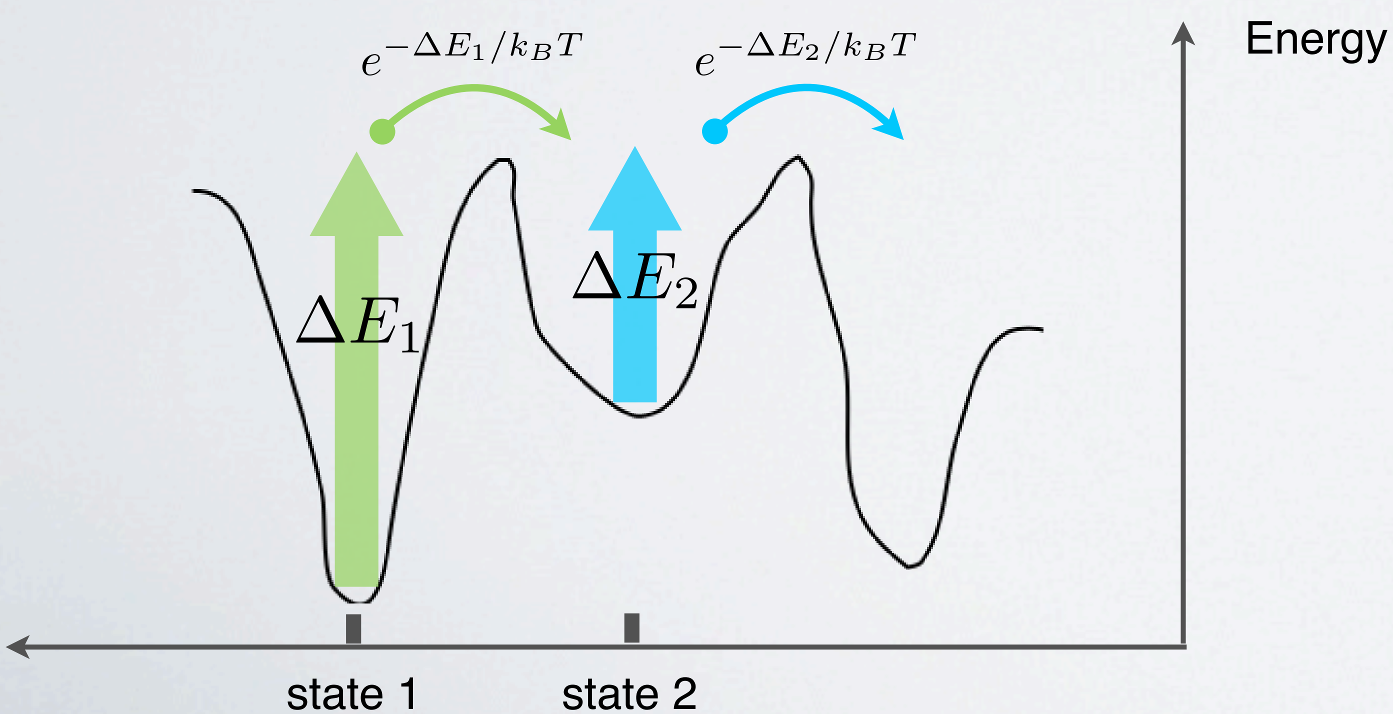
Why might tissues generically be close to a glass transition?

- For wound healing, embryonic development, cancer invasion:
  - ✴ Initially need large scale flows (i.e. fluid-like rheology)
  - ✴ Subsequently need to support forces and shear stresses (i.e. a solid-like rheology)

What is the microscopic origin of glassy behavior in ***non-active*** materials?



- ✳ The existence of a complex potential energy landscape
- ✳ System close to energy landscape surface
- ✳ System is trapped in metastable states, needs energy fluctuations to escape



Trap Model for glassy dynamics

C. Monthus & J.-P Bouchaud
J. Phys. A 29 3847 (1996)

Soft Glassy Rheology

P. Sollich et al
PRL 78 2020 (1997)

Exploring the Potential Energy Landscape

Cells in tissues

Sheared foam

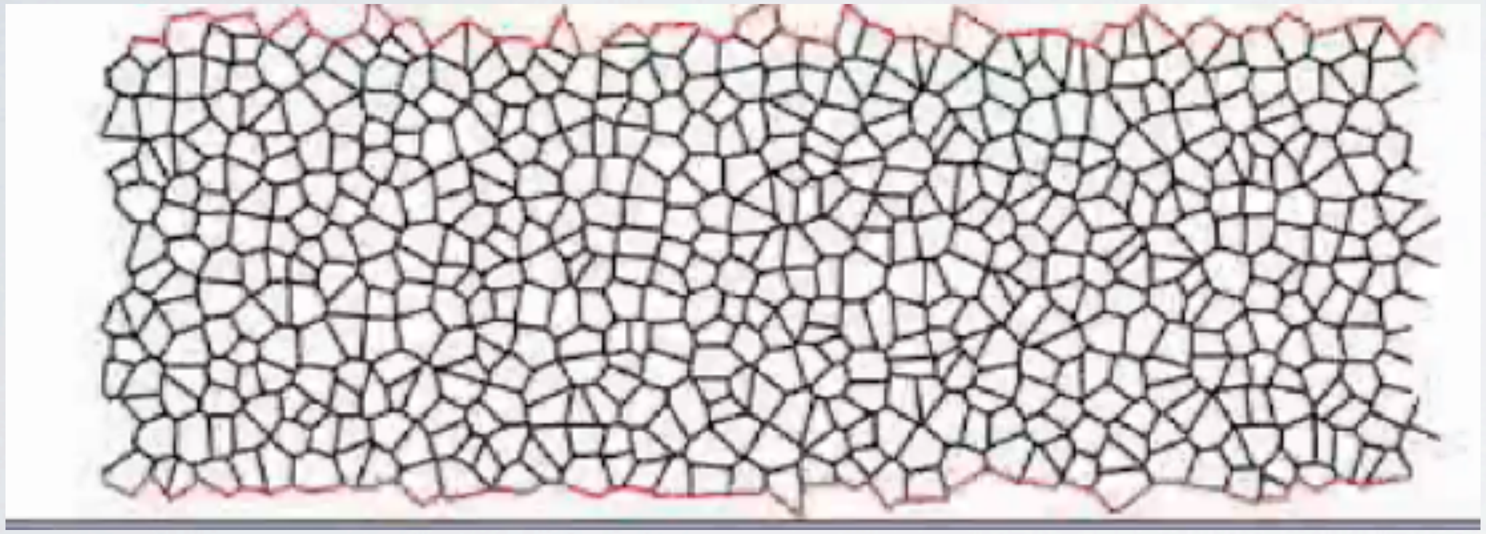
Alexandre J Kabla

Global injection of energy

Energy injection by cell

Exploring the Potential Energy Landscape

Sheared foam



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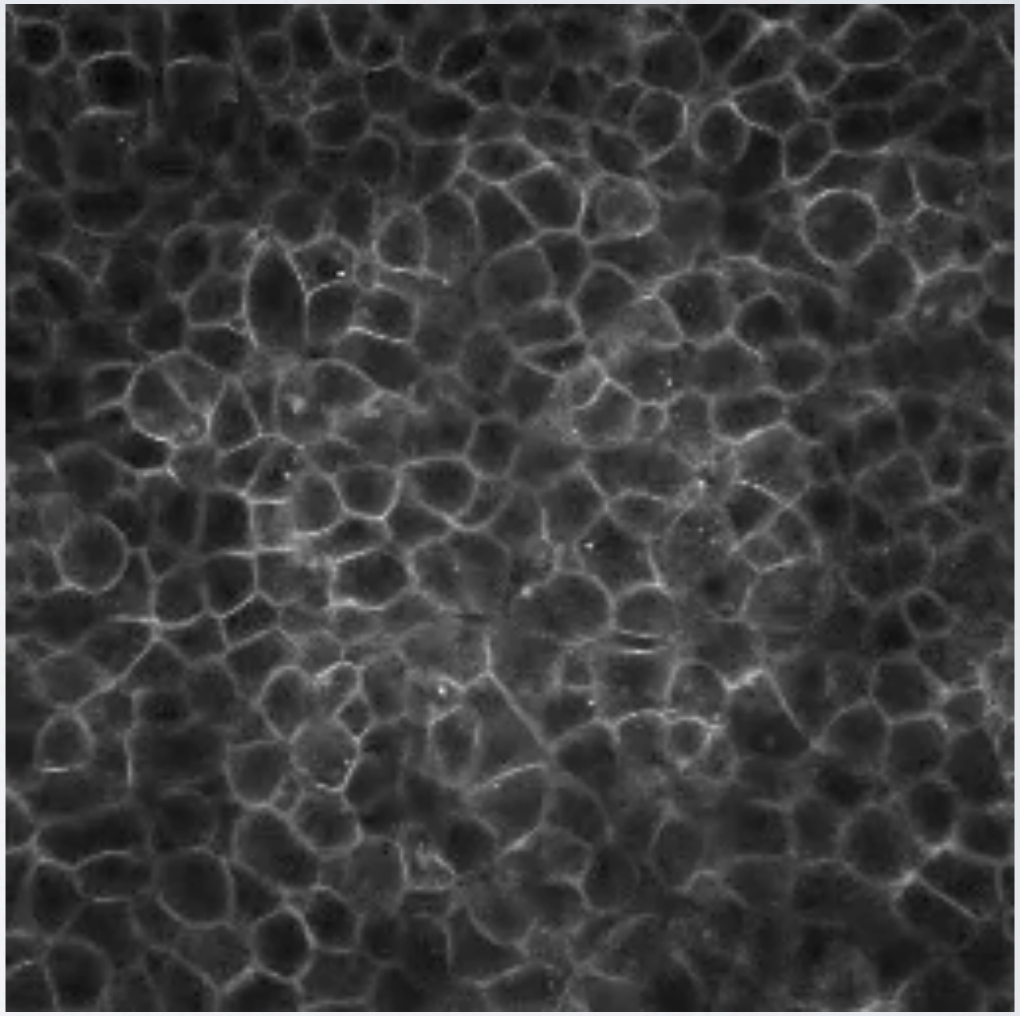
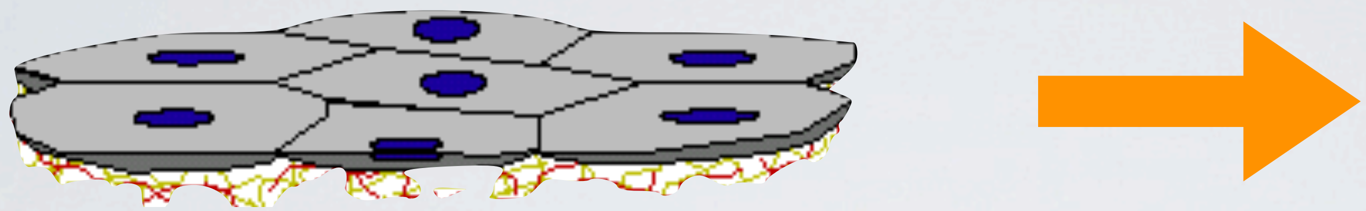
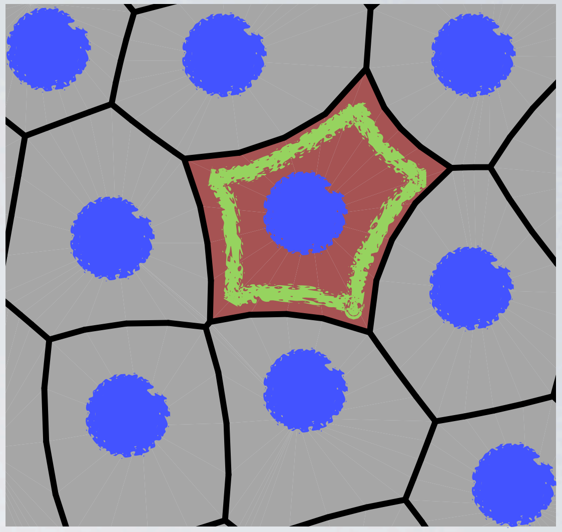


Global injection of energy

Energy injection by cell

The Shape Equilibrium Model / Vertex Model





$$E_{cell} = k_A(A - A_0)^2 + k_P(P - P_0)^2$$
$$= k_A(A - A_0)^2 + k_P(P^2 - 2P_0P + P_0^2)$$

Bulk elasticity term

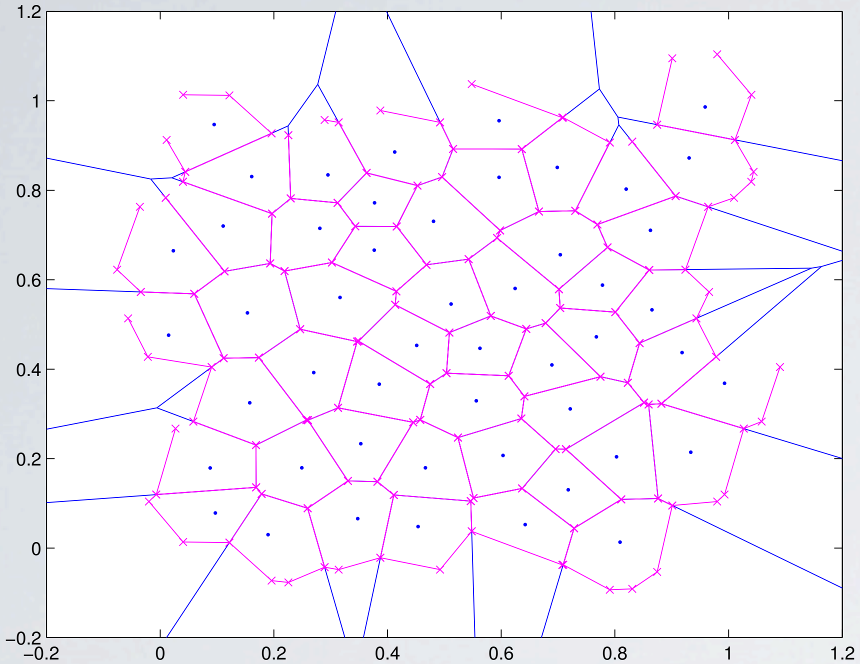
Contractility

Line tension and Adhesion

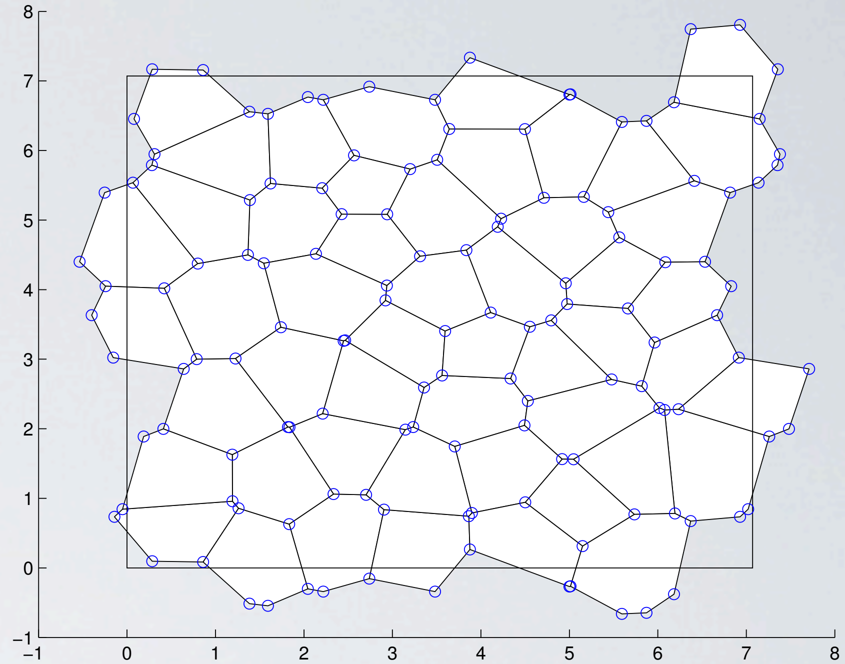
- Developed more than 10 years ago and well-studied
- Generalization of a foam model
- Reasonably good agreement with experimentally observed cell shapes

Nagai & Honda Phil. Mag. B vol. 81 (7) (2001)
Hufnagel et al, PNAS vol. 104 (10) pp. 3835 (2007)
Farhadifar et al, Current Biology (2007)
Jülicher et al Phys. Rep. (2007)
Manning et al, PNAS (2010)
Staple et al EPJE 33 (2) 117 (2010)
Chiou et al PLOS Comp Bio 8 (5) e1002512 (2012)

Simulating a cellular structure



Voronoi tessellation of
a random point pattern

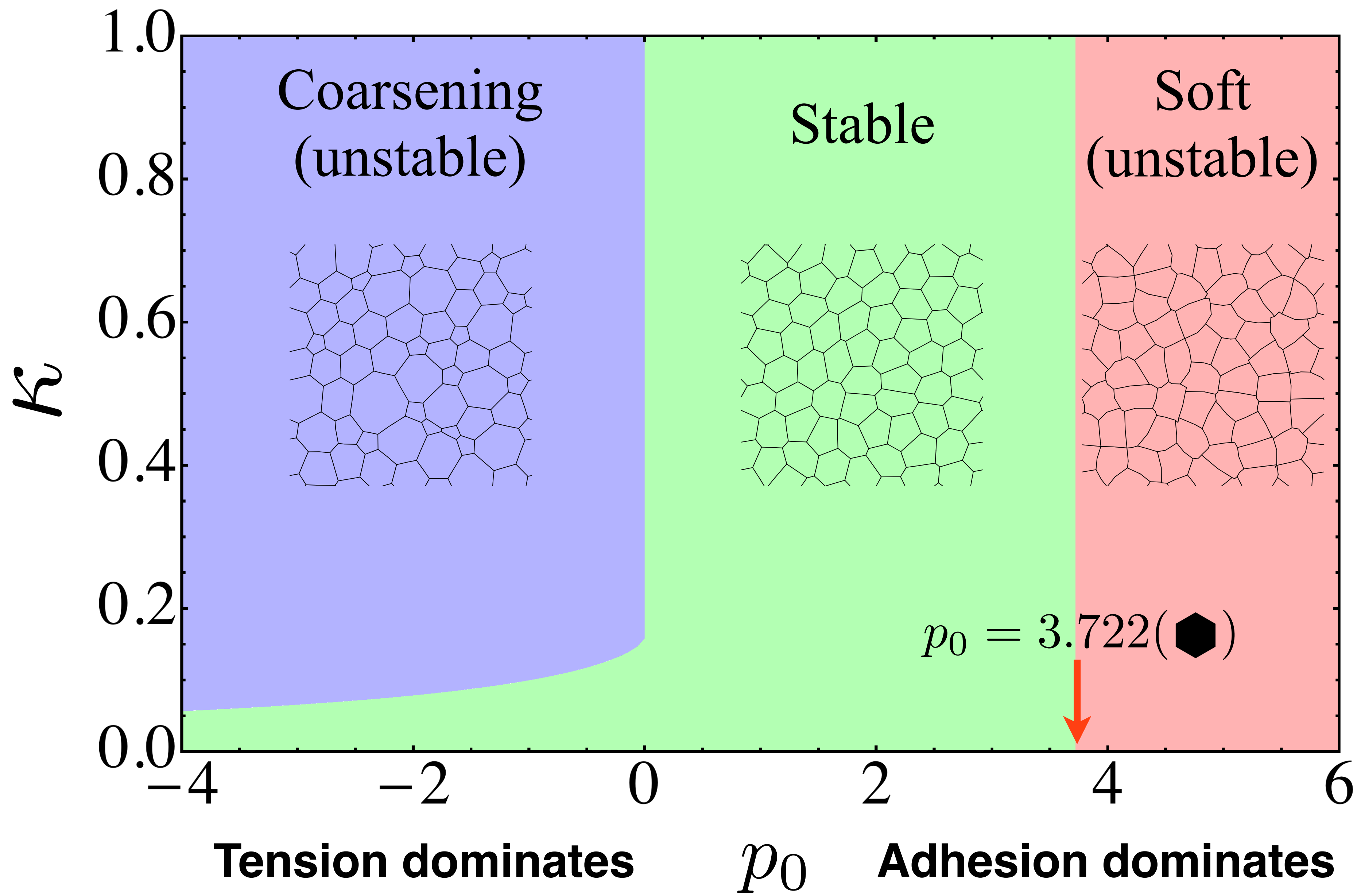


✴ Modeling tissues using **Surface Evolver**

- Using refined polygon tiling to represent 2-d confluent monolayer
- Configurations obtained by minimizing $E_{tot} = \sum_{cell} E_{cell}$

Phase space of disordered metastable states

$$u_{tissue} = \sum_i u_i; \quad u_i = \kappa p_i^2 - 2\kappa p_0 p_i + (a_i - 1)^2$$

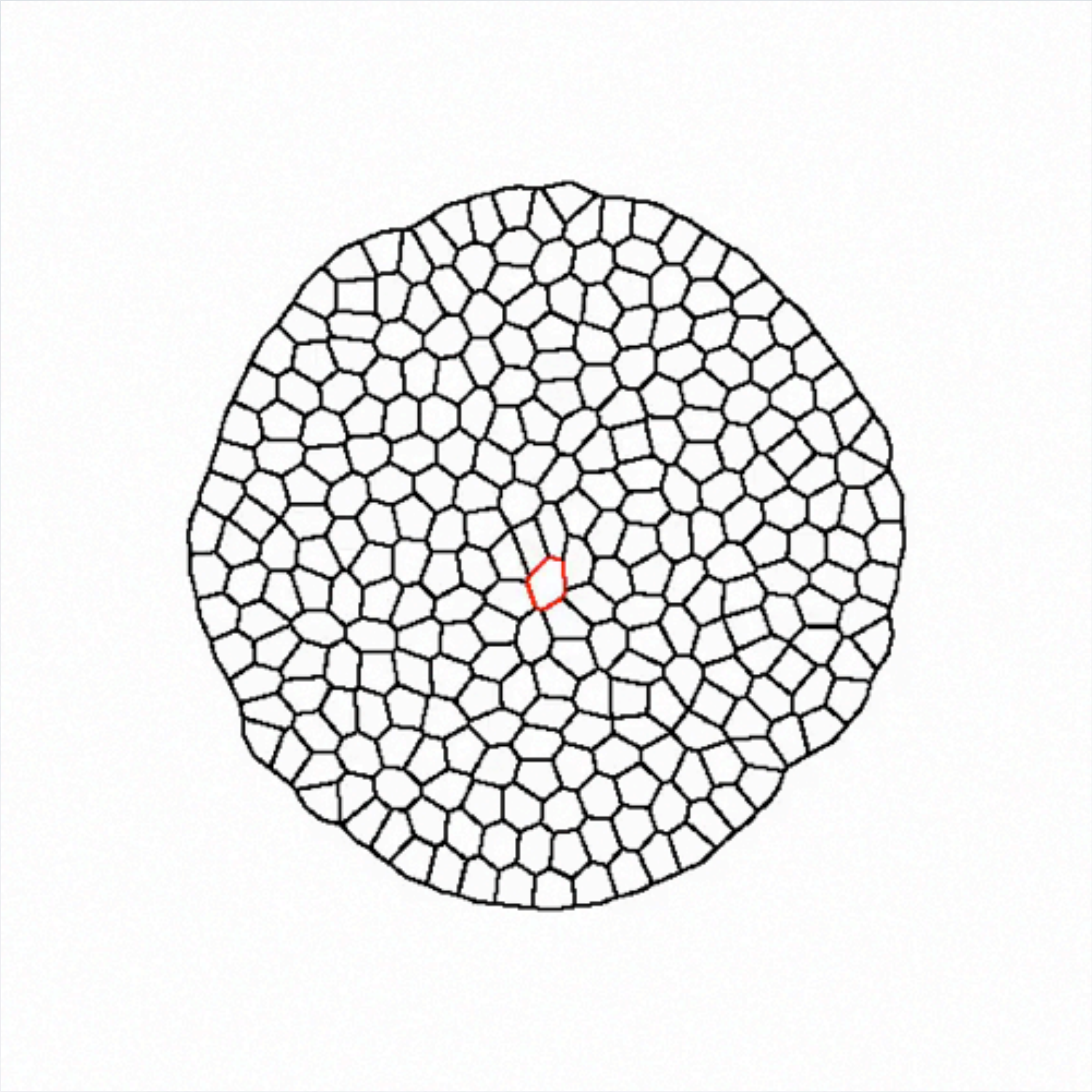


Tension dominates **Adhesion dominates**

Ground states first studied by
Staple et al, EPJ-E 33(2) 117 (2010)

D. Bi et al, unpublished

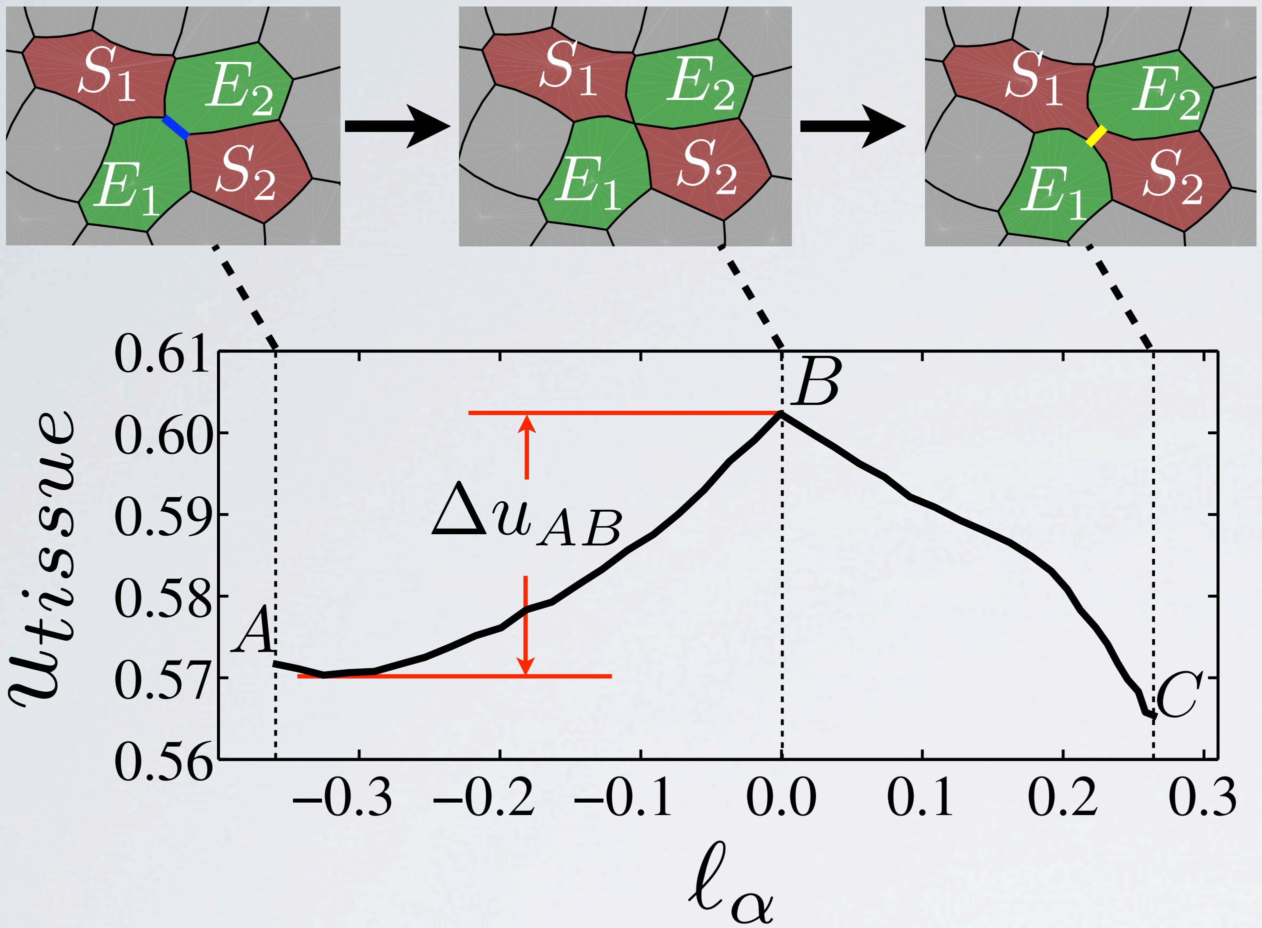
Migration in 2D happens via T-1 transitions



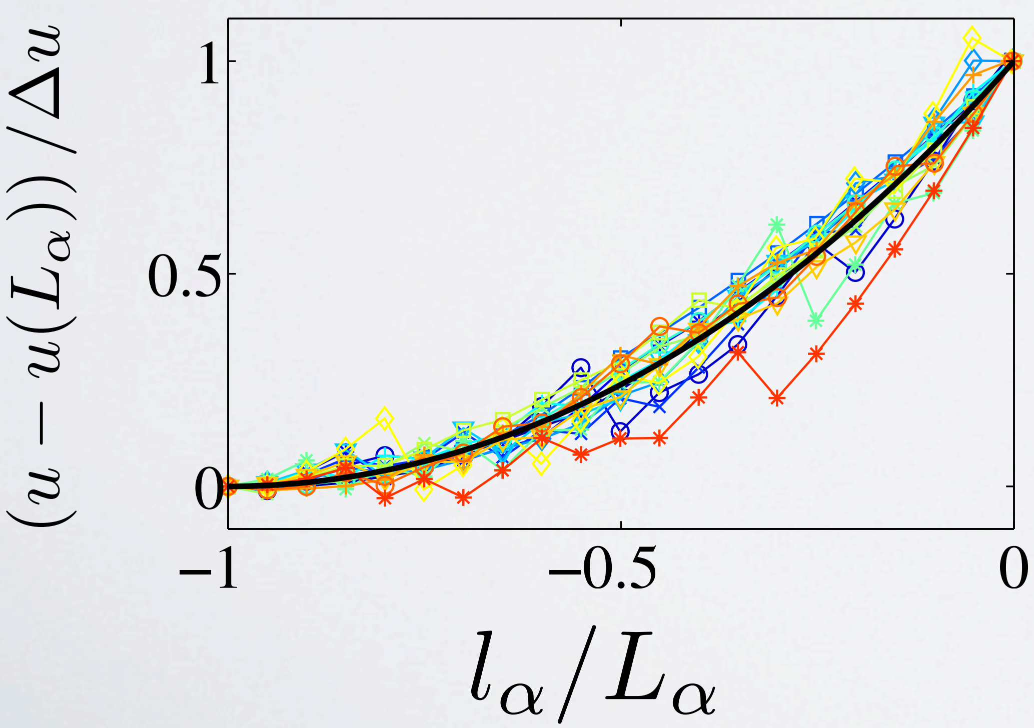
Cell divisions also and cell death (T2) also cause migrations, but it is not necessary for fluid behavior

D. Bi et al, Soft Matter 2014

Energy trace for T-1 transitions



Testing all possible transition paths



D. Bi et al, Soft Matter 2014

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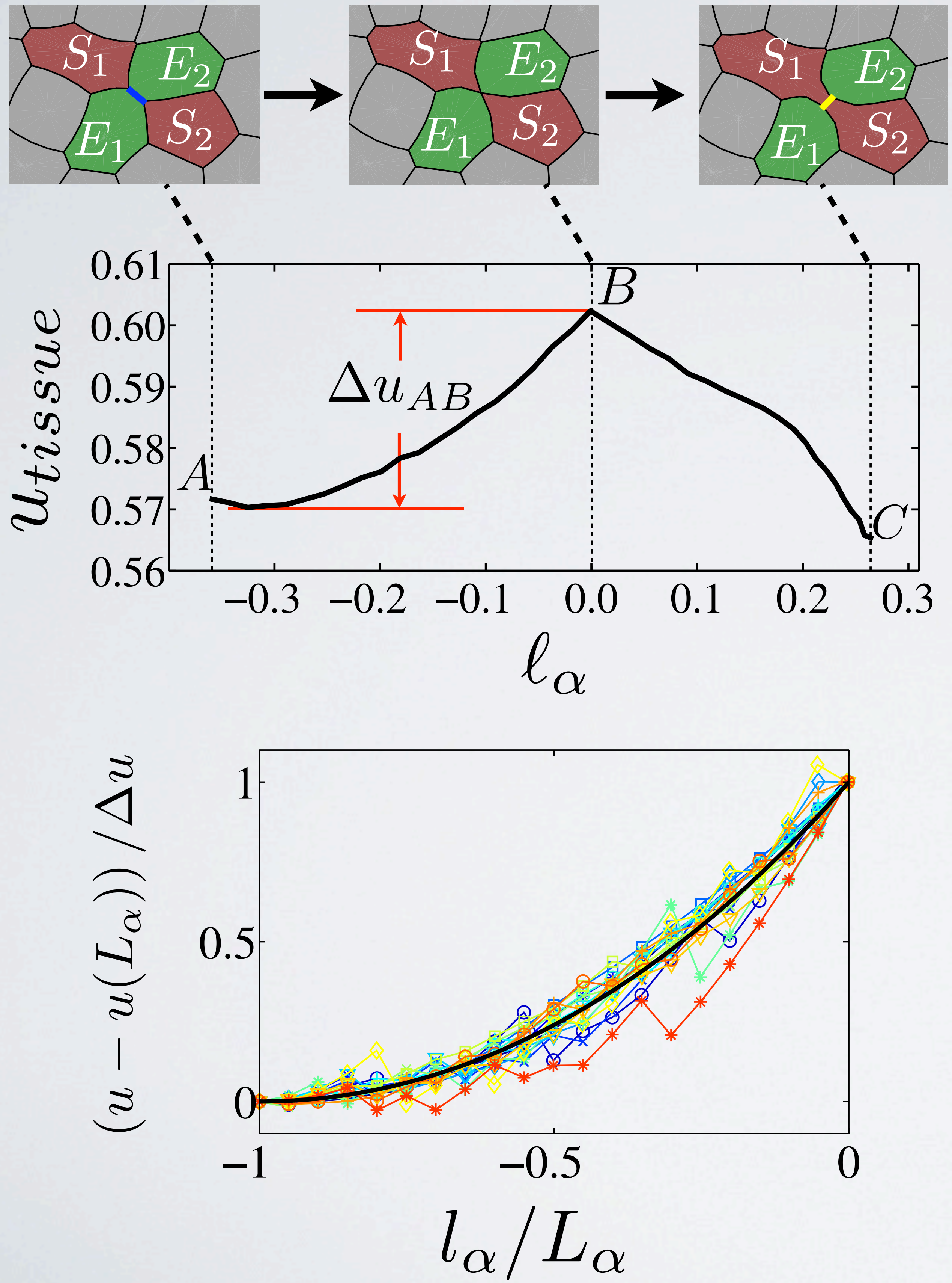

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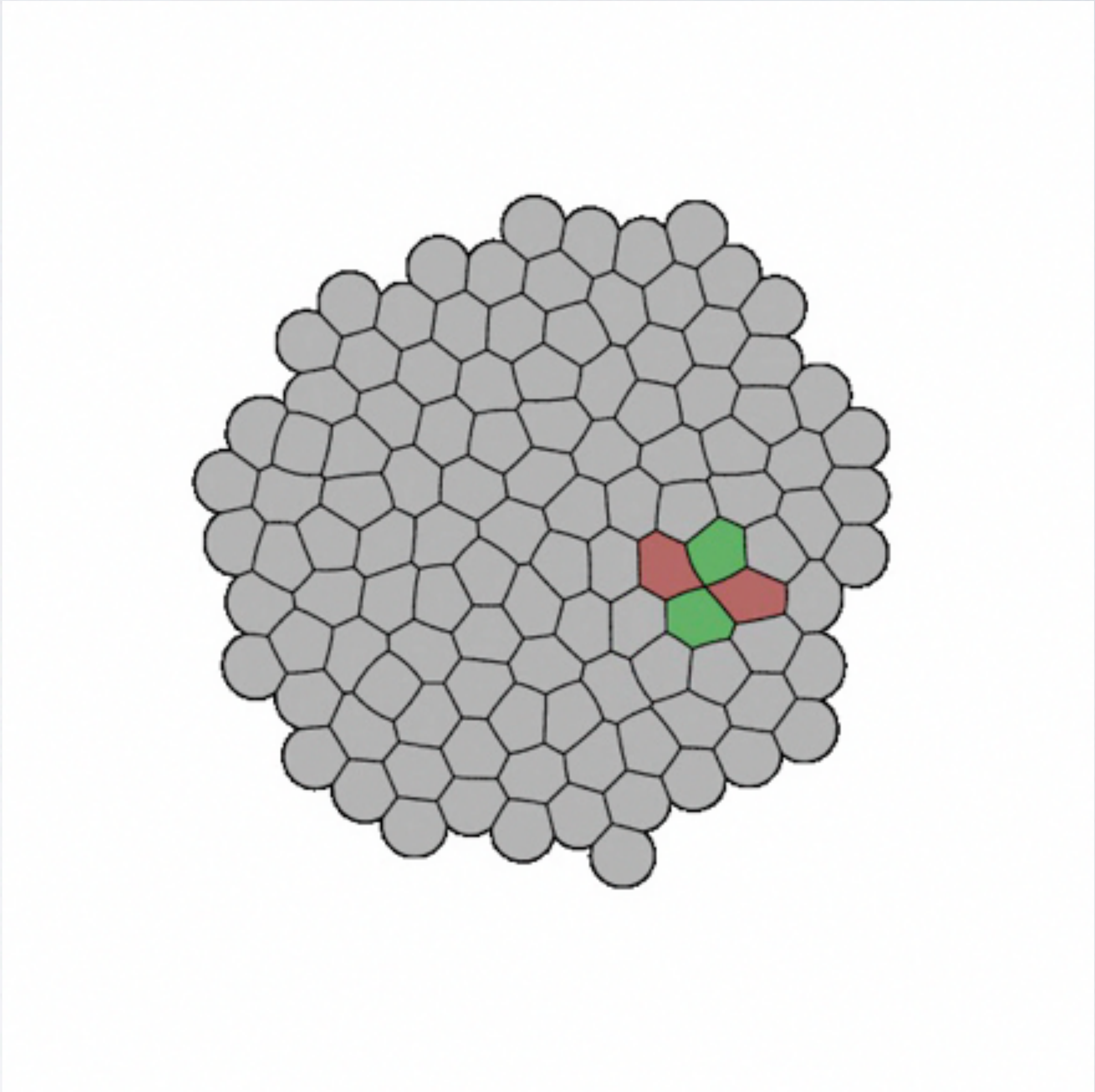
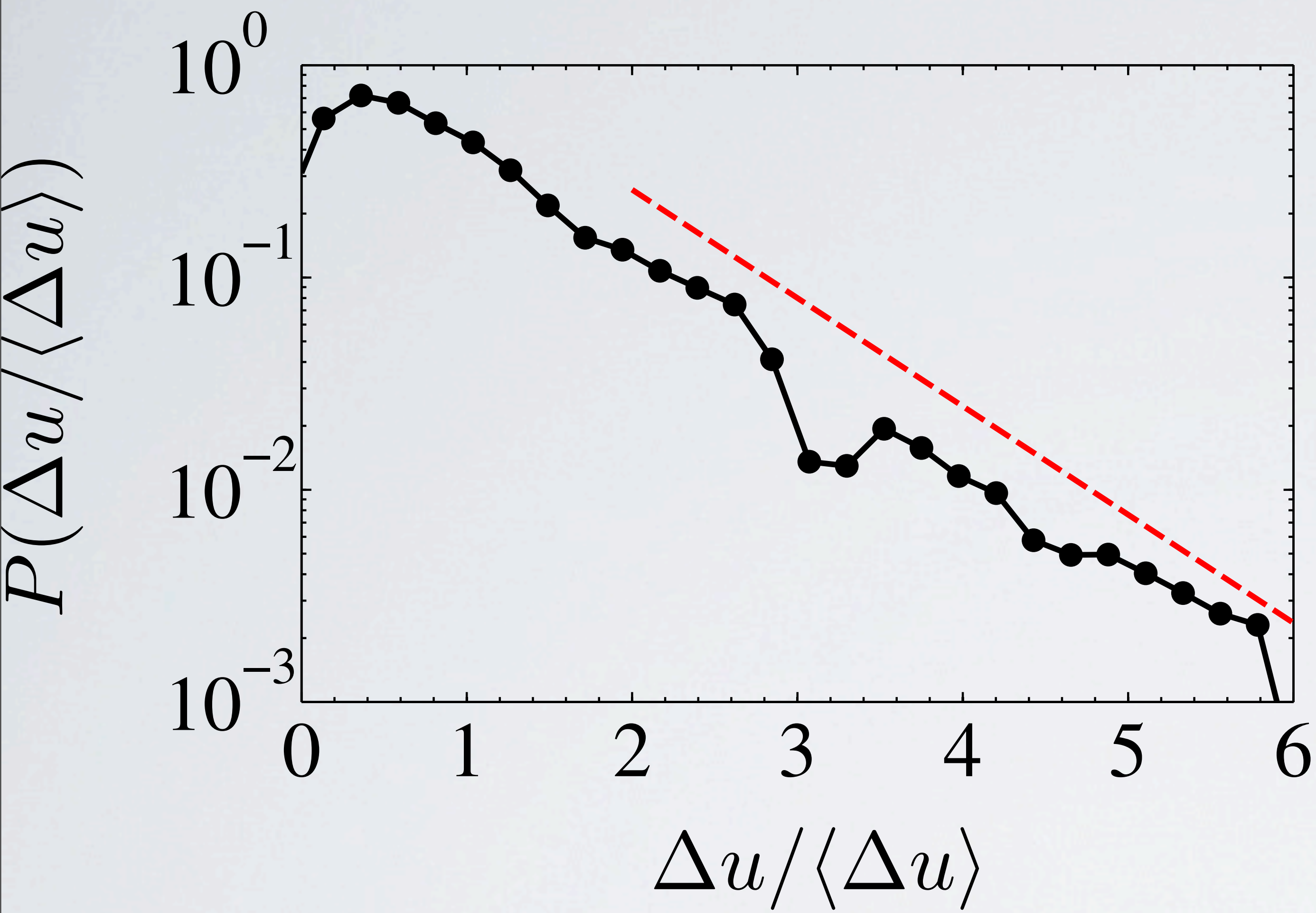


D. Bi et al, Soft Matter 2014

Energy barrier statistics

Tissues

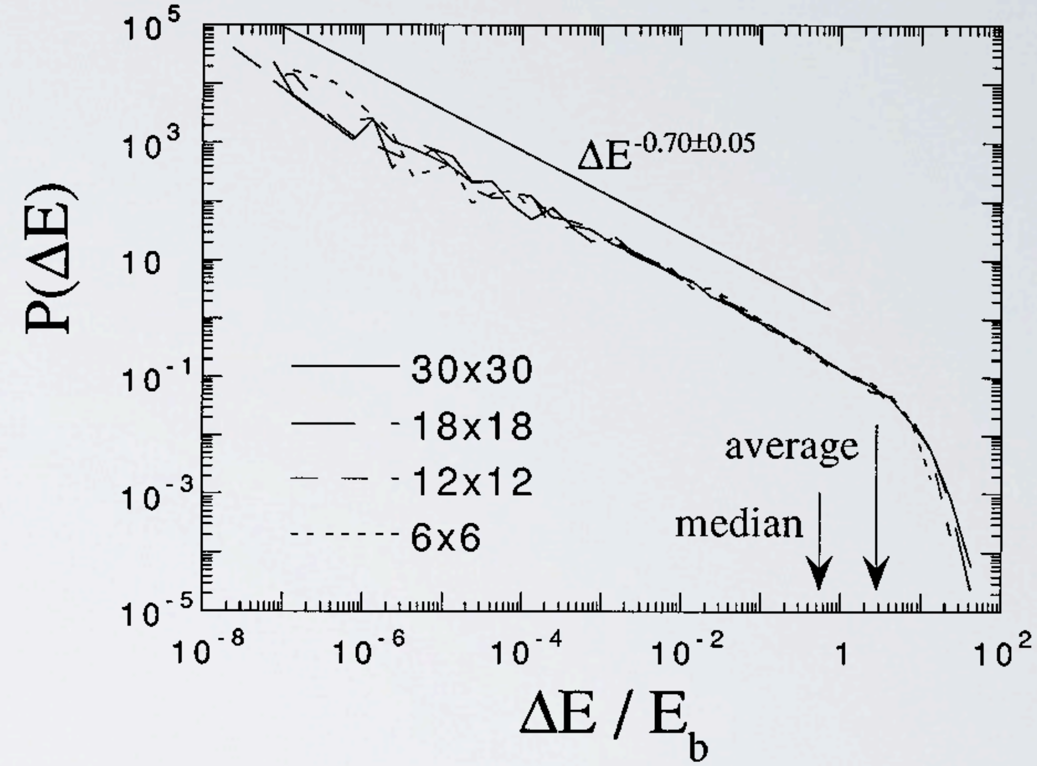


- ✳ Robust exponential tail
- ✳ Energy is injected locally, all sites are probed

D. Bi et al, Soft Matter 2014

Sheared foams, grains

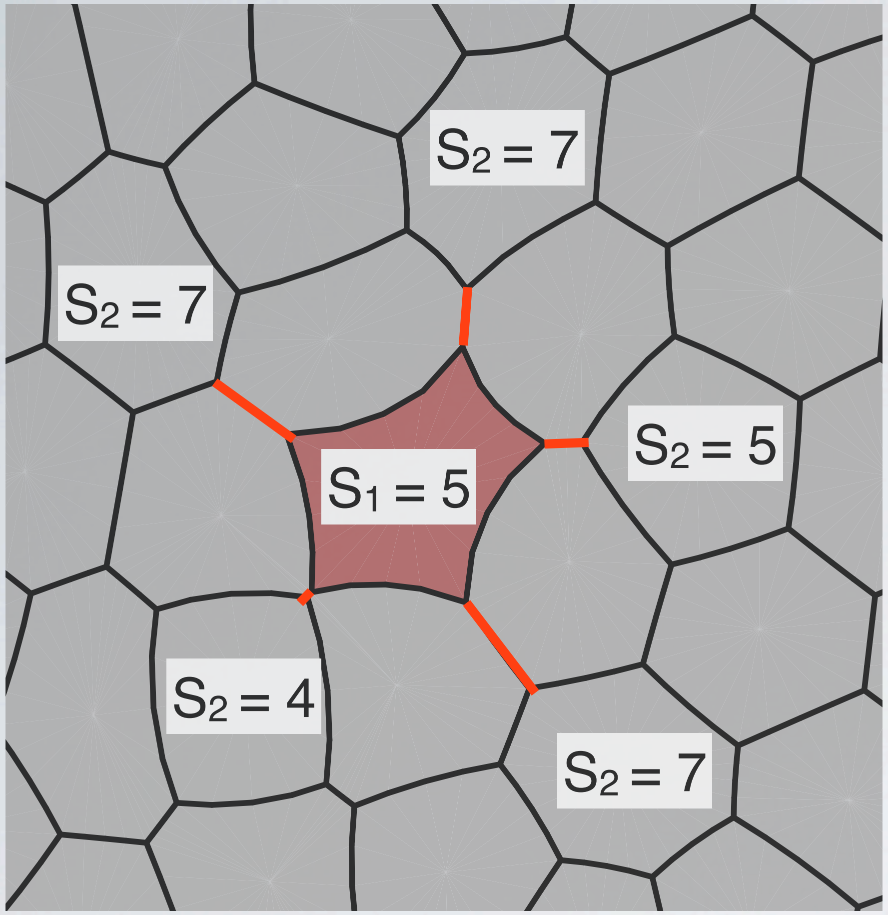
Durian PRE 1995



Also: Okuzono, Kawasaki and Ngai (1992)

- ✳ Power-law distributed, with exponential cut-off
- ✳ Energy is injected globally and failure occurs a special soft spots in a material that is tuned near a critical point

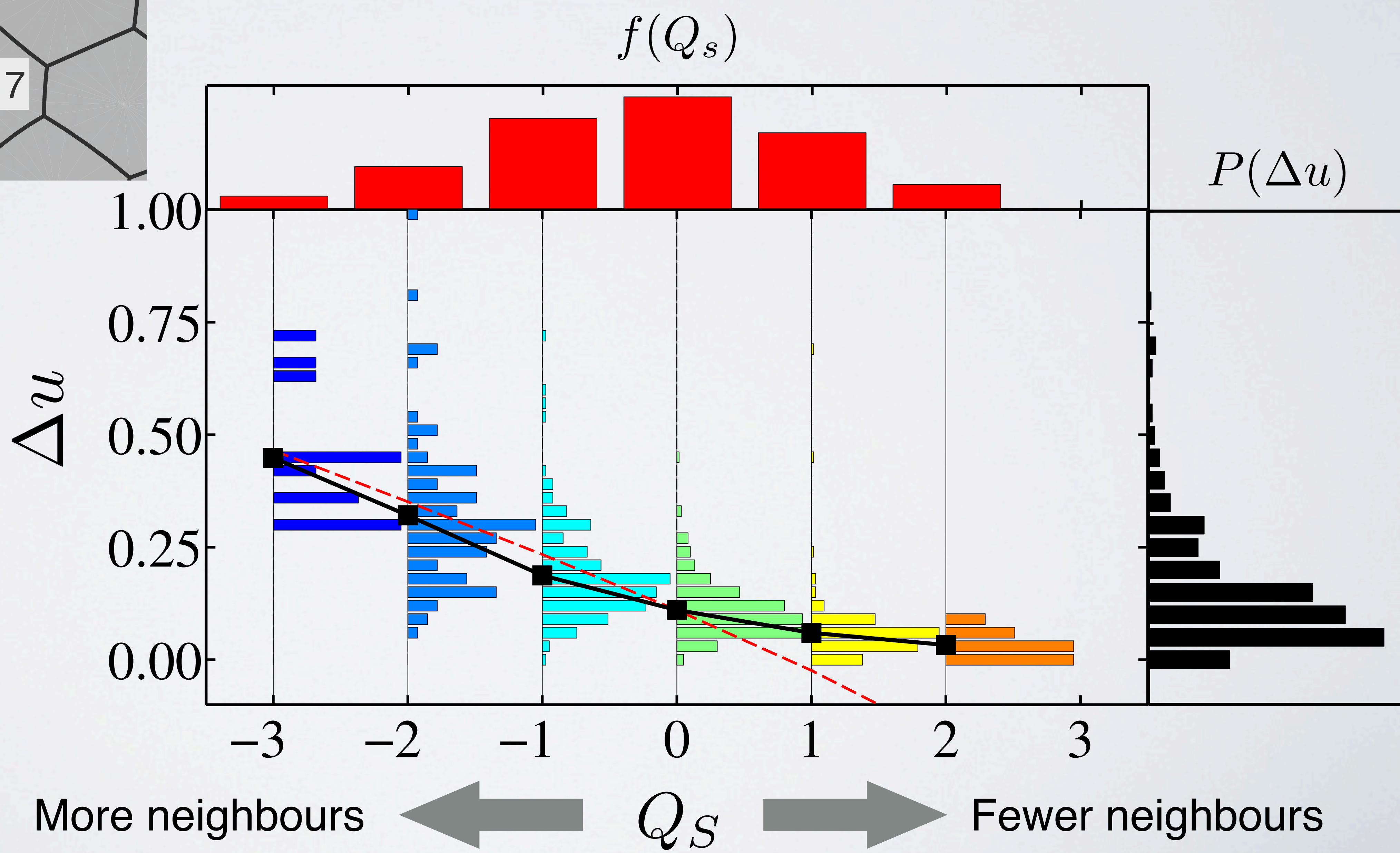
Energy barrier depend on cell topology



S_1 and S_2 are T-1 neigbours,
Define a topological measure:

$$Q_S = (6 - S_1) + (6 - S_2)$$

D. Bi et al, Soft Matter 2014



From energy barriers to cell migration

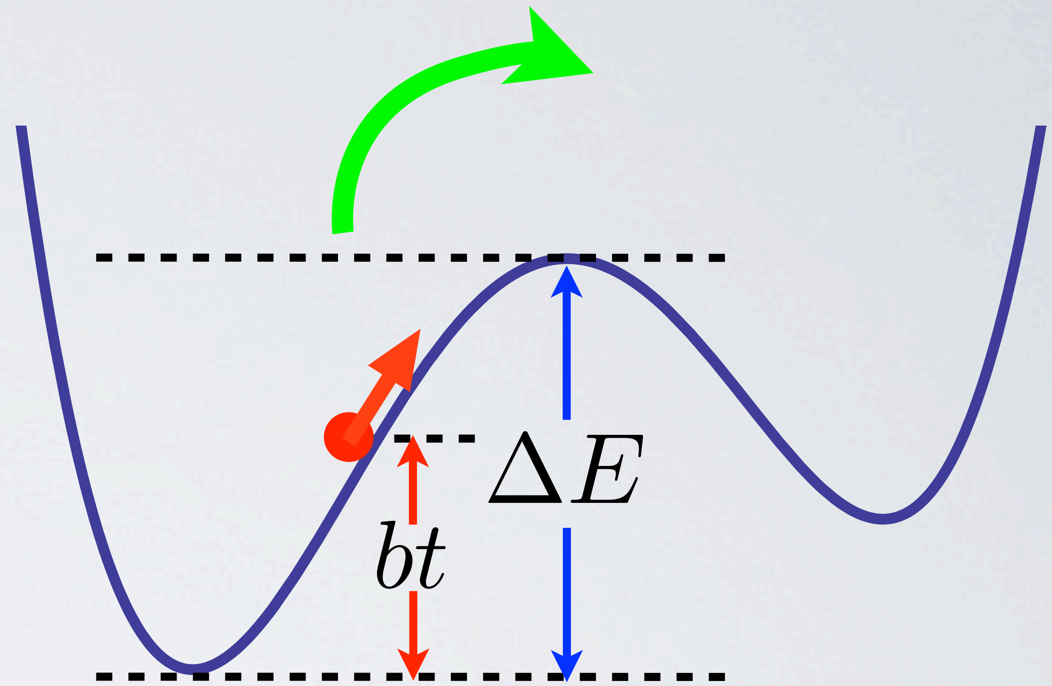
A very minimal model:

$$R = \omega_0 \exp\left[-(\Delta E - bt)/\varepsilon\right]$$

- ✳ A cell is 'caged' by its neighbors
- ✳ Can escape cage by:
  - ✓ Polarized cell motion **b**

    +

  - ✓ Active shape fluctuations ε
- ✳ Energy landscape has shape given by $\rho(\Delta E) = e^{-\Delta E/\varepsilon_0}$



Master equation for dynamics

$$\frac{\partial}{\partial t} P(\Delta E, t) = -\,\omega_0 e^{-[\Delta E - bt]/\varepsilon} P(\Delta E, t) + \varrho(\Delta E) \int d\Delta E' \omega_0 e^{-[\Delta E' - bt]/\varepsilon} P(\Delta E', t)$$

These are sufficient to lead to glassy dynamics!

Trap model for glassy dynamics

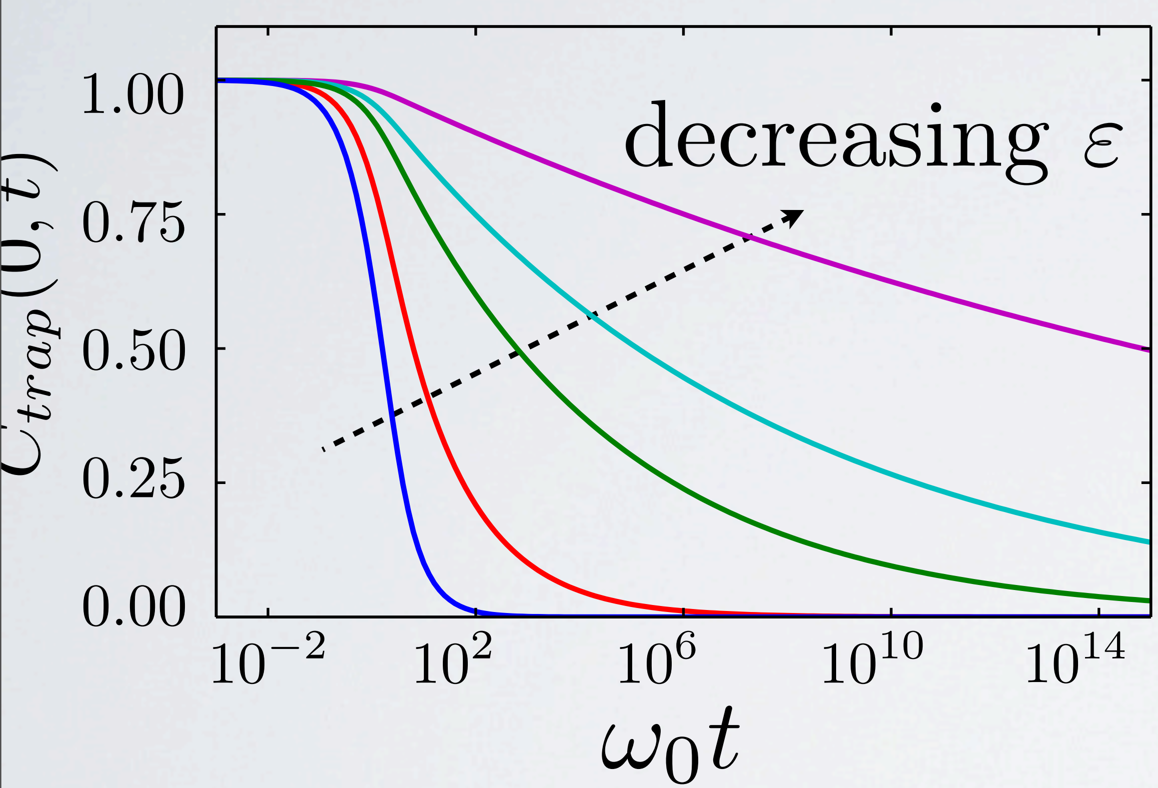
Monthus & Bouchaud(1996)

Soft Glassy Rheology

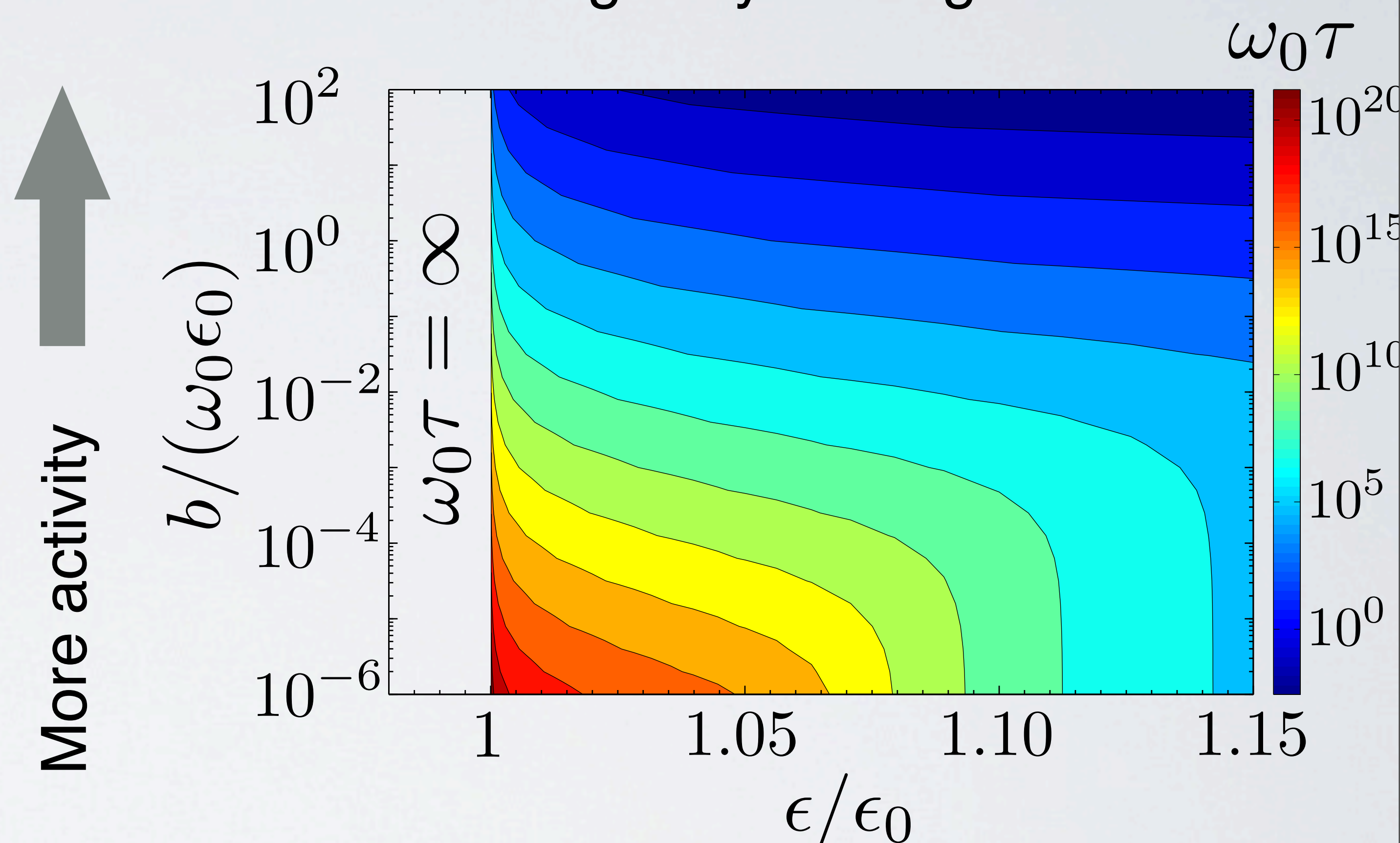
Sollich et al, PRL (1997)

From energy barriers to cell migration

Probability to remain in a ‘cage’

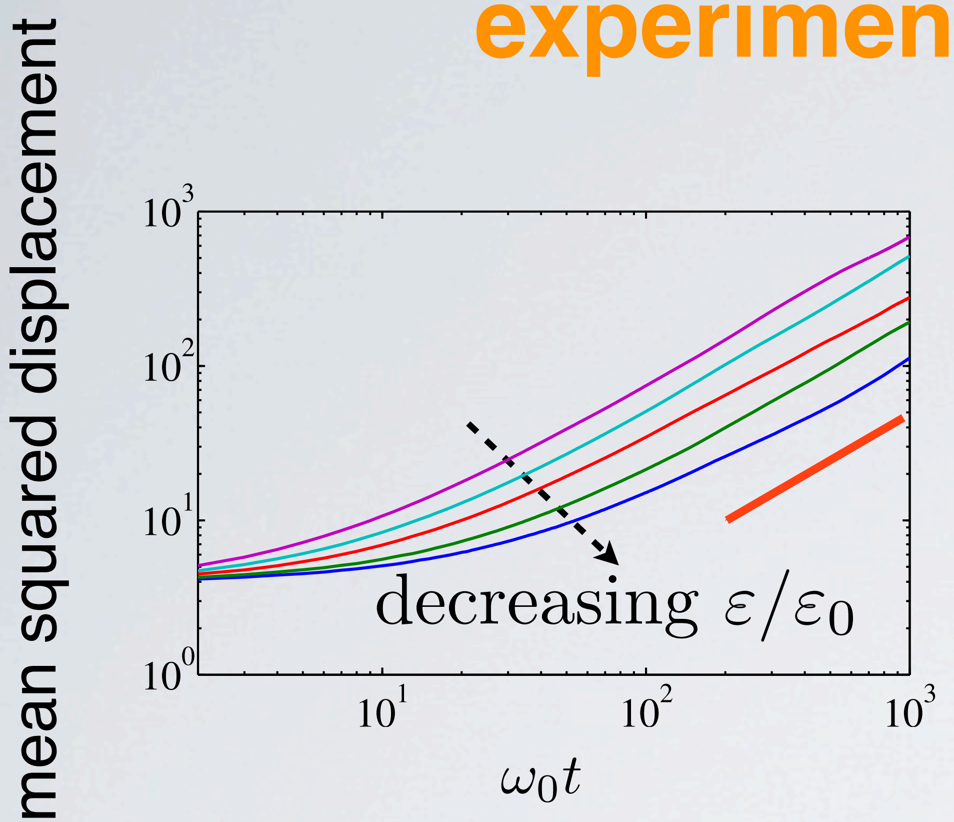


A glassy waiting time



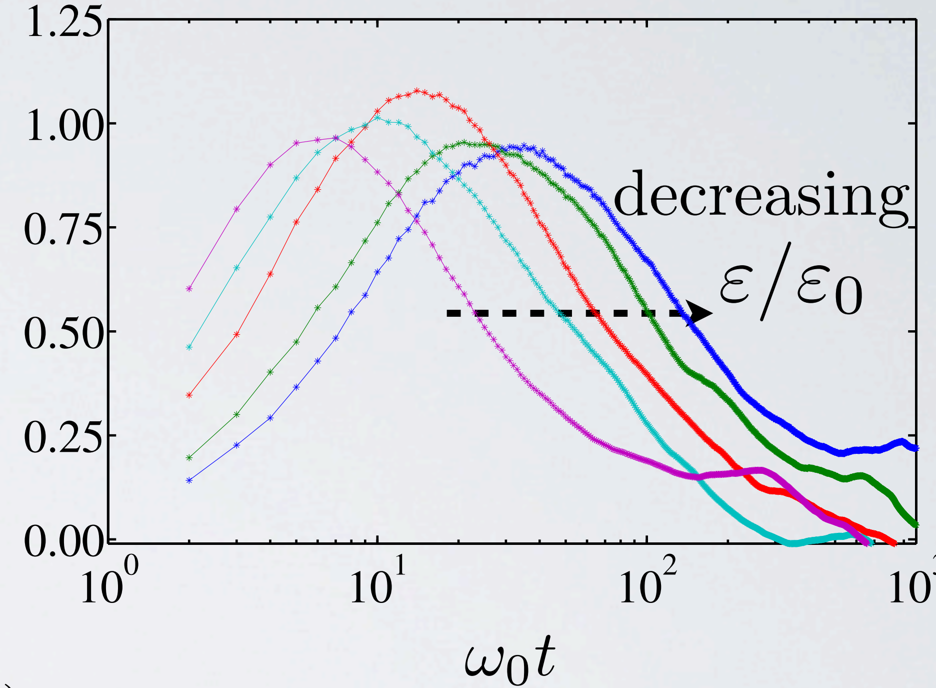
$$\varepsilon/\varepsilon_0 = \frac{\text{shape fluctuation energy scale}}{\text{characteristic energy scale landscape}}$$

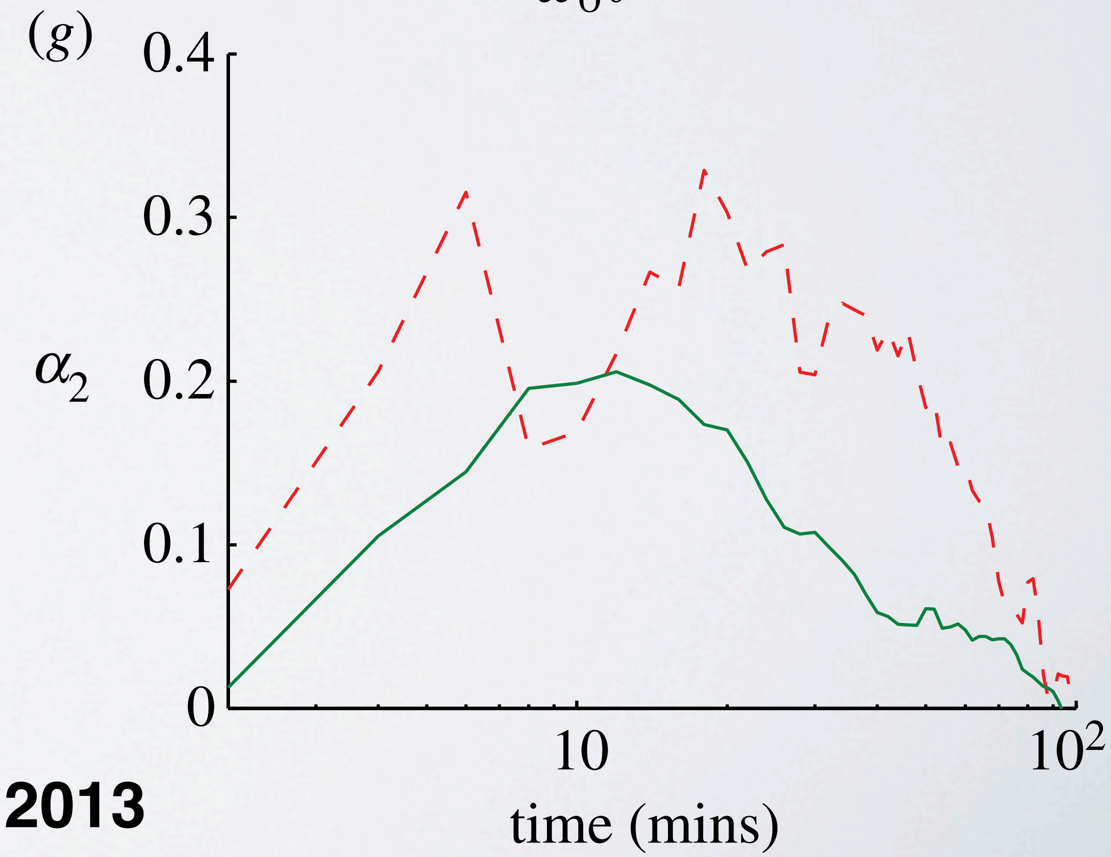
From energy barriers to cell migration: experimentally accessible predictions



α_2: non-gaussian parameter

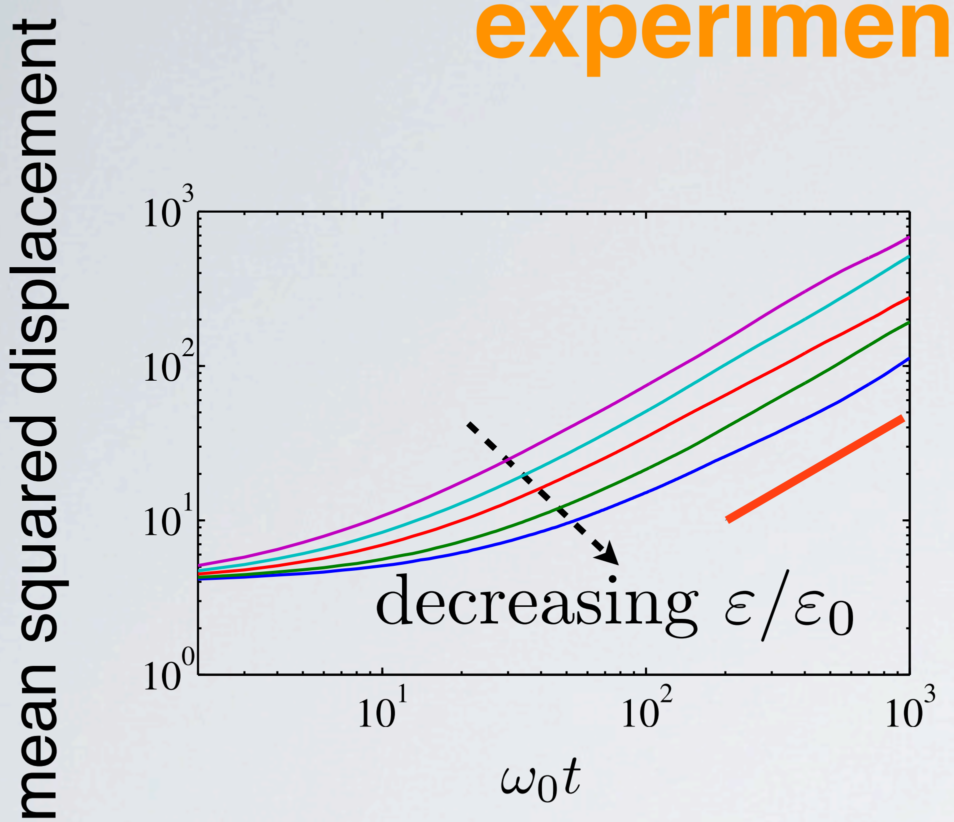
$\alpha_2 = 0$: Brownian motion $\qquad \alpha_2 \sim 1$: Cage breaking





Schöetz et al
J. R. Soc. Interface 2013

From energy barriers to cell migration: experimentally accessible predictions



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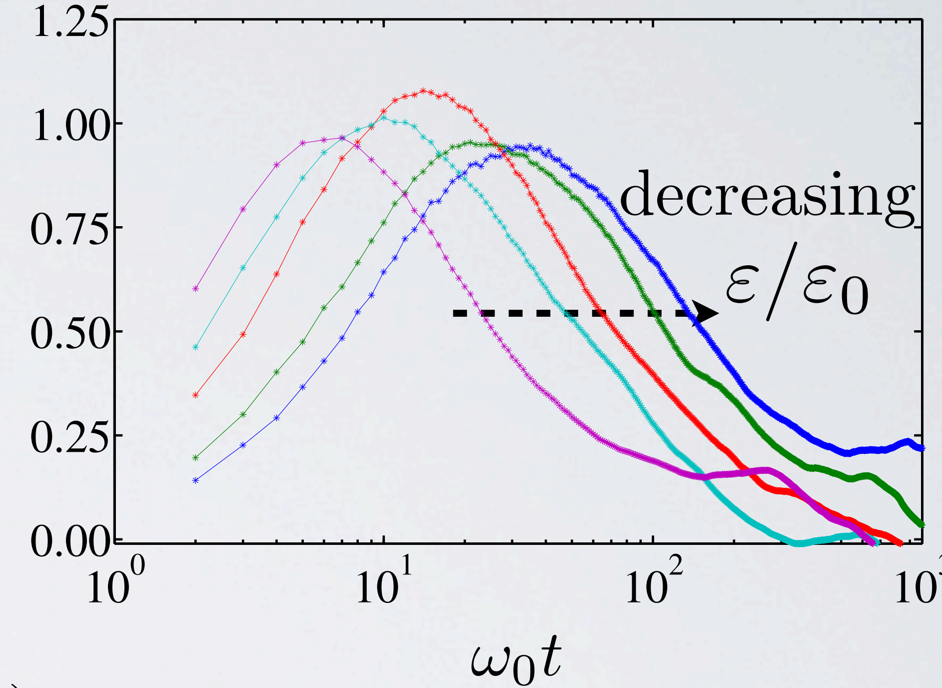

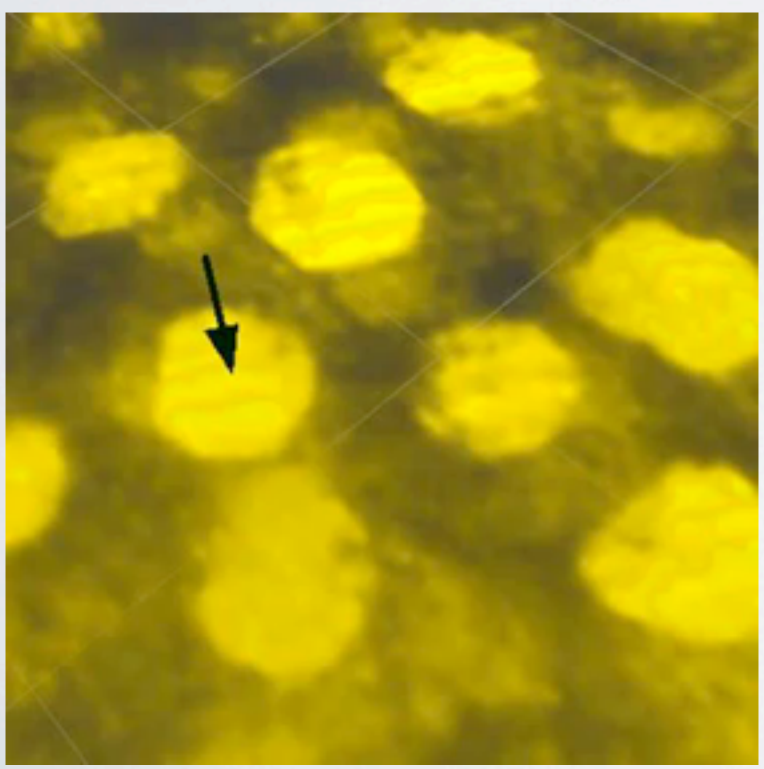

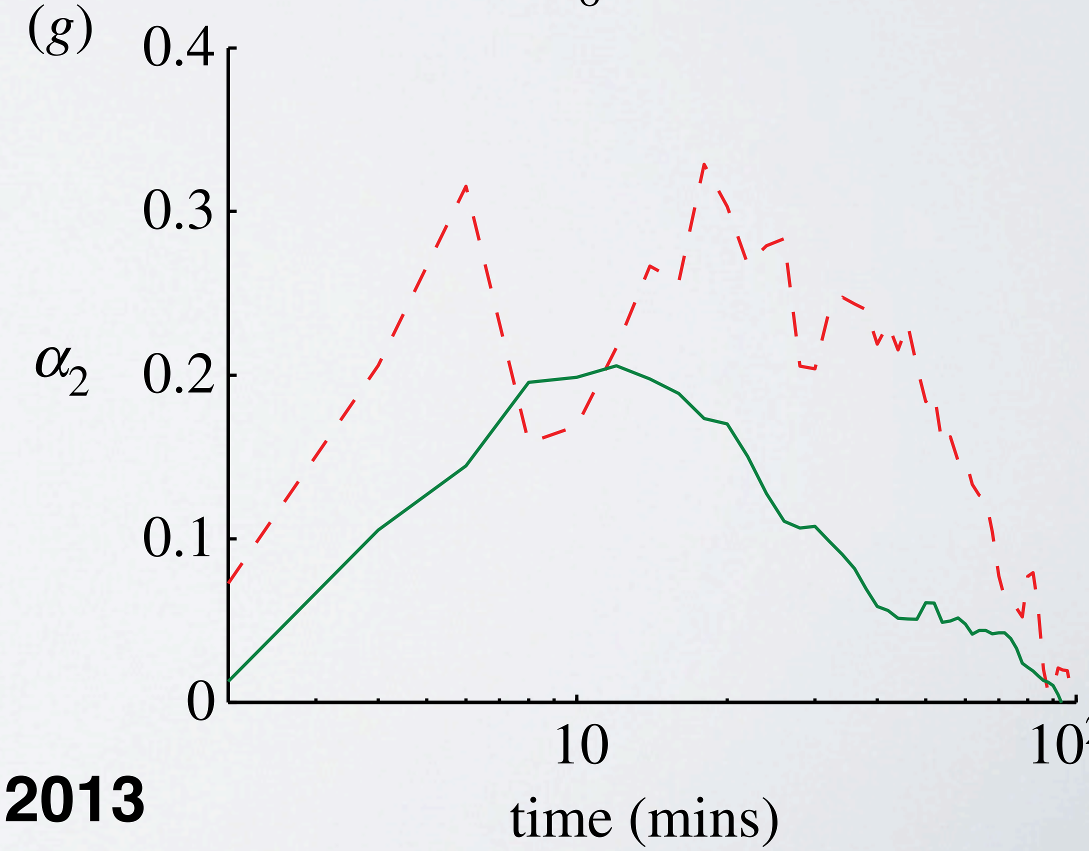

Schöetz et al
J. R. Soc. Interface 2013

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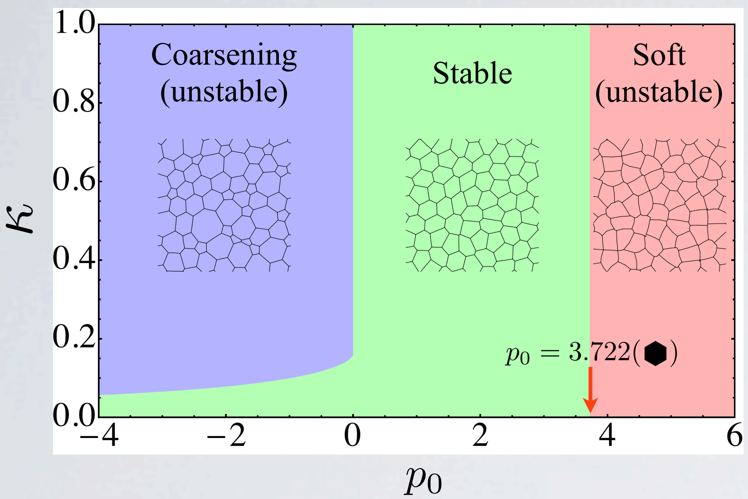

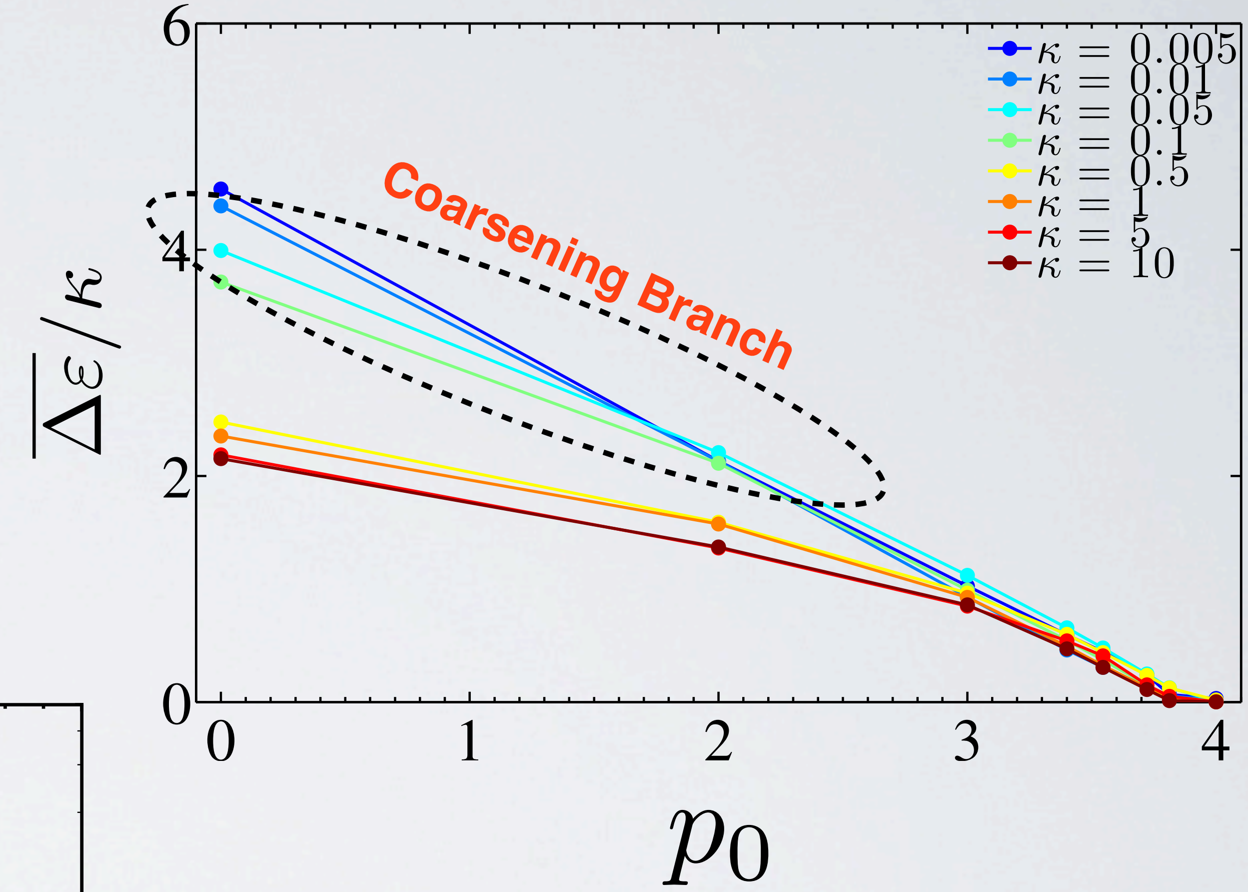

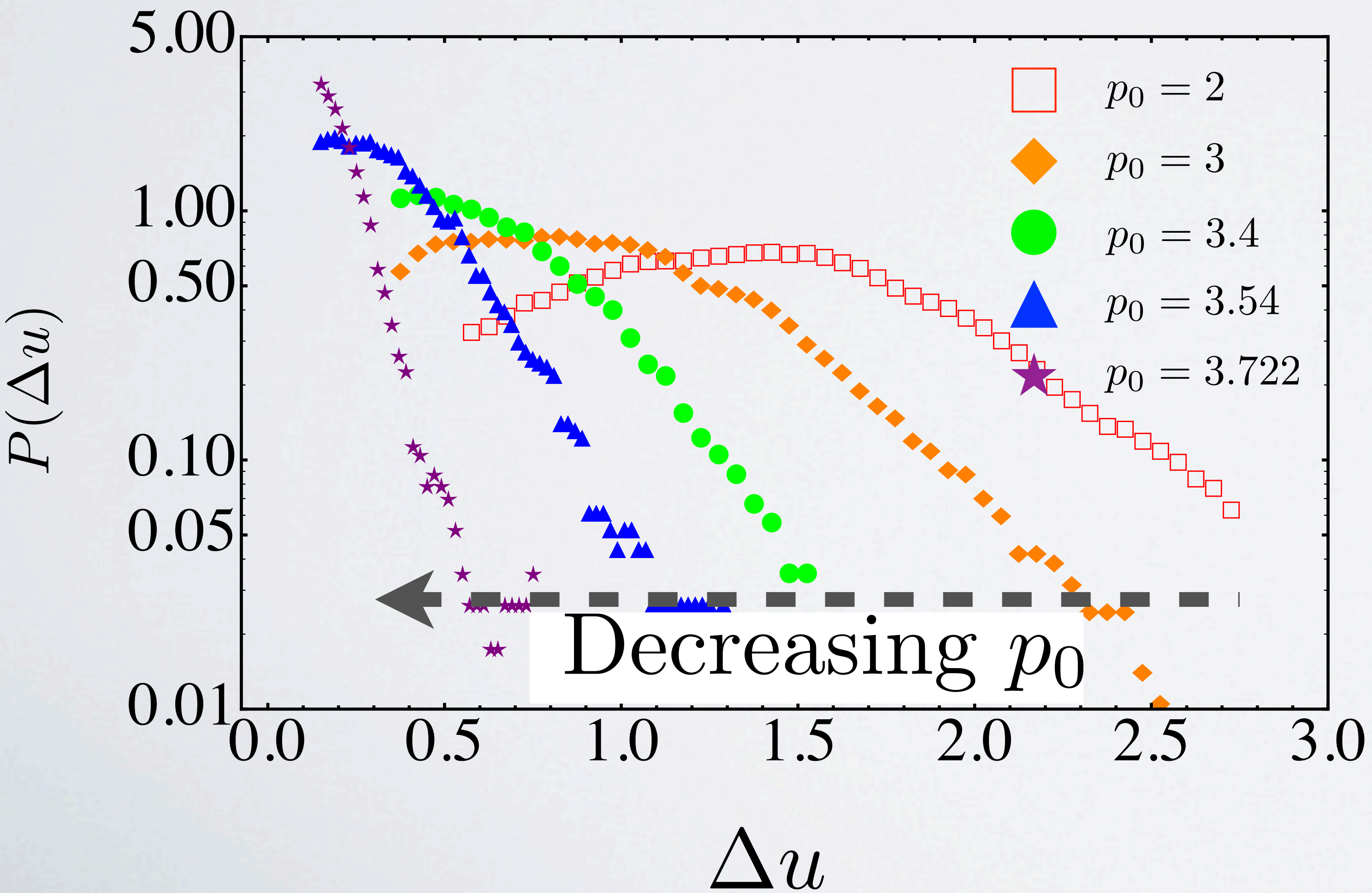

D. Bi et al, unpublished

Work in progress
Migration of ‘abnormal’ cells embedded in healthy cells

Work in progress
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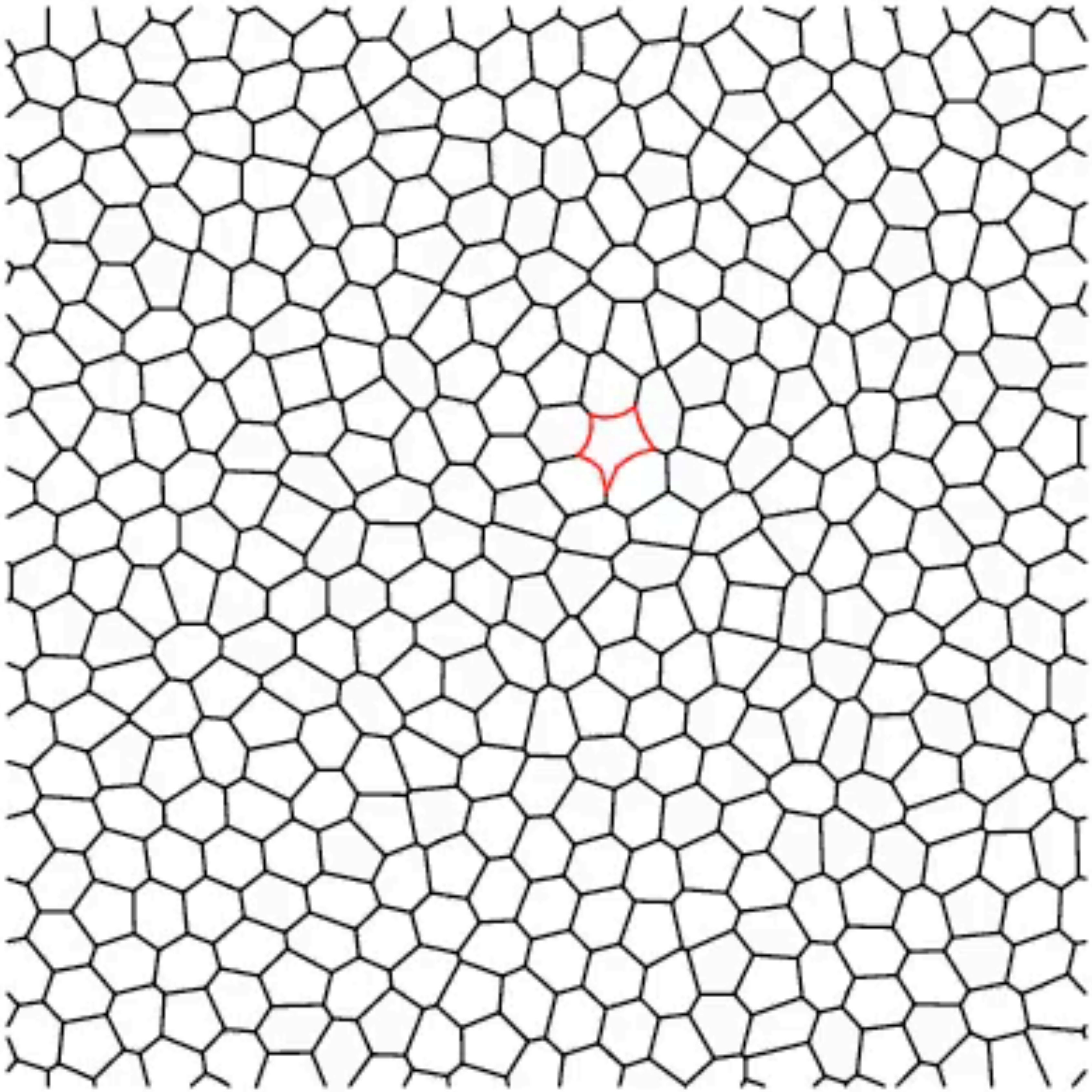
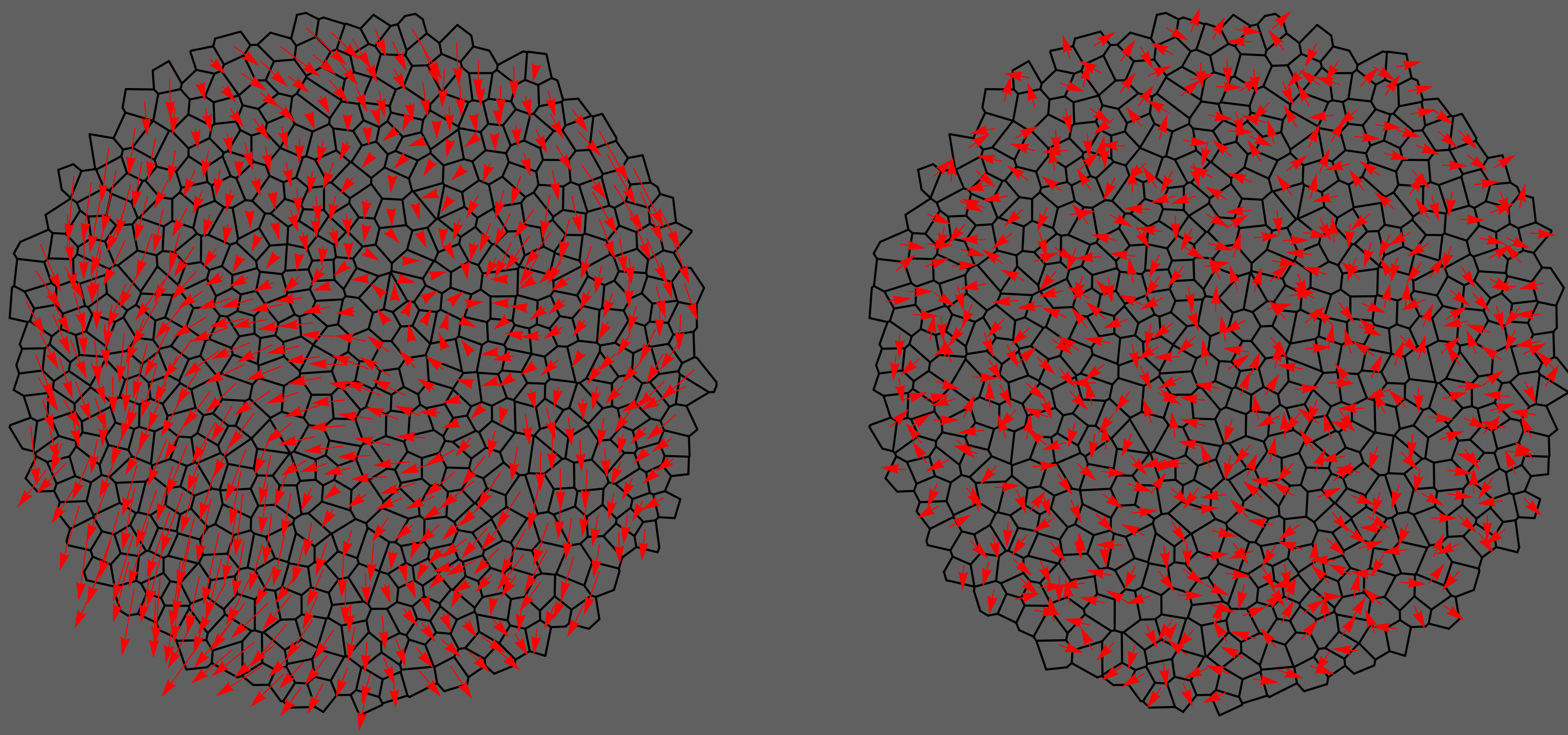


Work in progress

Dynamical simulation with active T-1 rearrangements



Conclusion

- Many tissue types show evidence of being close to a glass transition (wound healing, embryonic development)

- For confluent (density ~ 1) tissues, we have developed a framework for estimating energy barriers to cell rearrangements,
    - Self propelled particle models are perhaps less useful than shape equilibrium models at this density
    - energy barriers are exponentially distributed
    - energy barriers depend strongly on a cell's number of nearest neighbors (experimentally accessible predictions)

- Our model predicts how changing single-cell properties changes cell migration rates. Can apply cell sorting or cancer migration?

D. Bi et al, Soft Matter 2014,10, 1885-1890