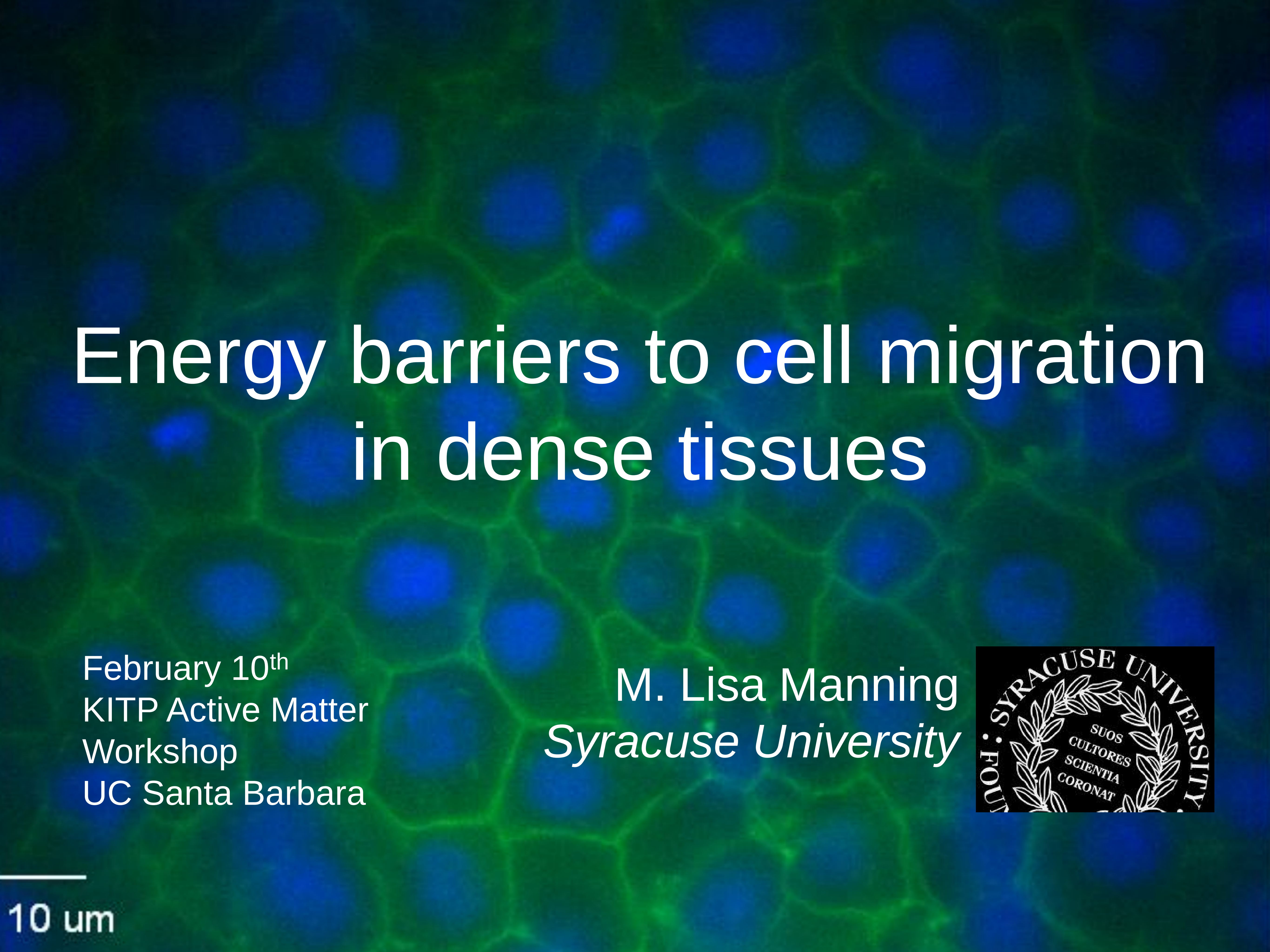

Energy barriers to cell migration in dense tissues

February 10th
KITP Active Matter Workshop
UC Santa Barbara

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Syracuse University

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Giuseppe Passucci
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Jared Talbot
Ramsey Foty
Mal Steinberg

Henderson Group

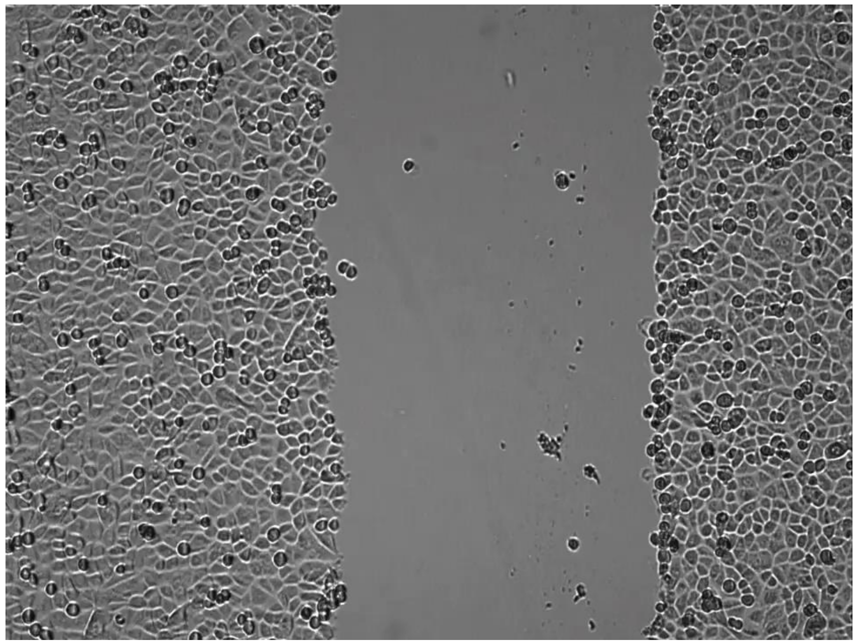
Jay Henderson
Megan Brasch
Richard Baker

Turner Group

Chris Turner
Nick Deakin

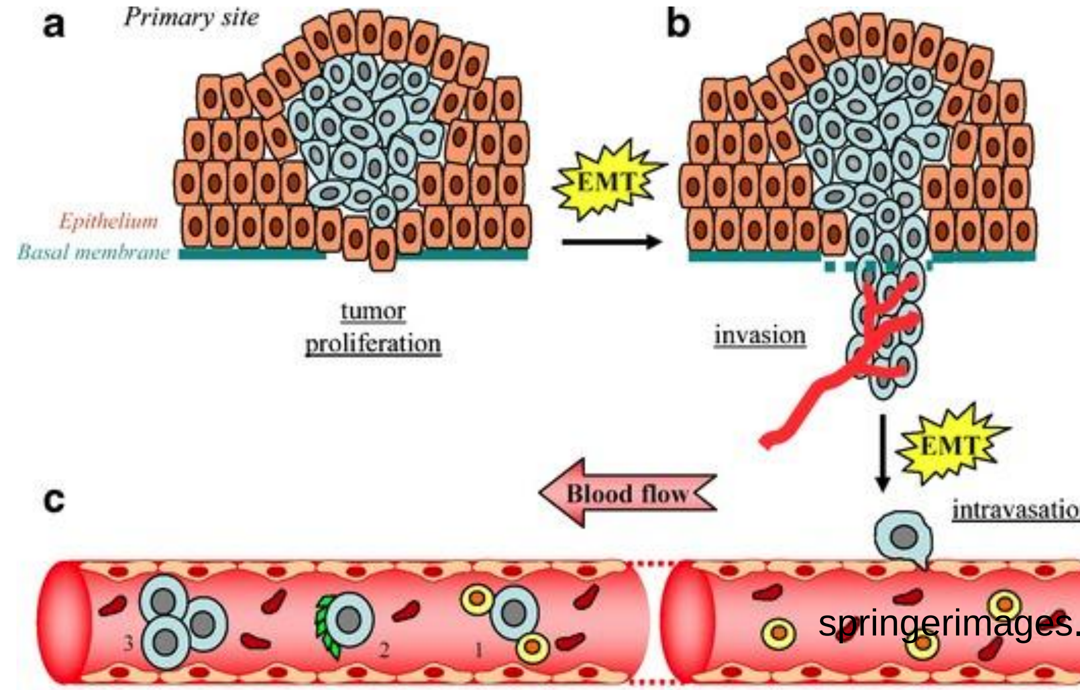
Why study cell migration in dense tissues?

Wound healing assay



youtube.com/watch?v=v9xq_GiRXeE

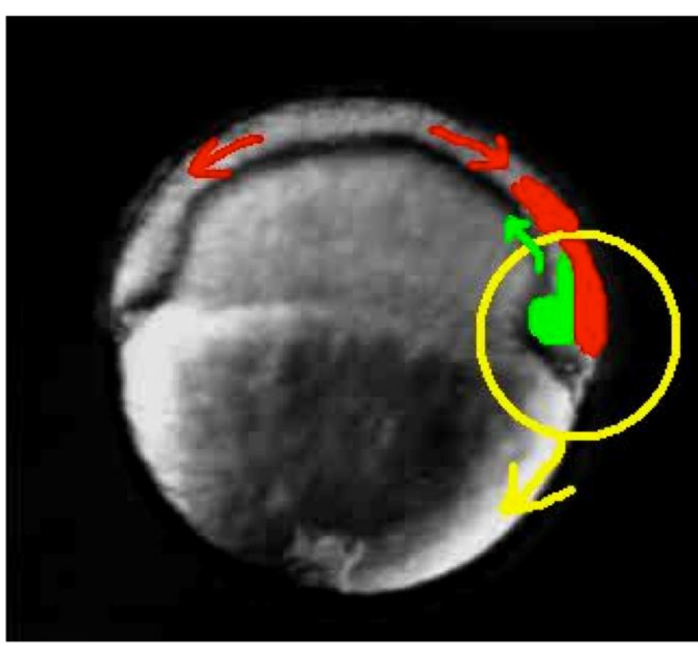
Tumor metastasis



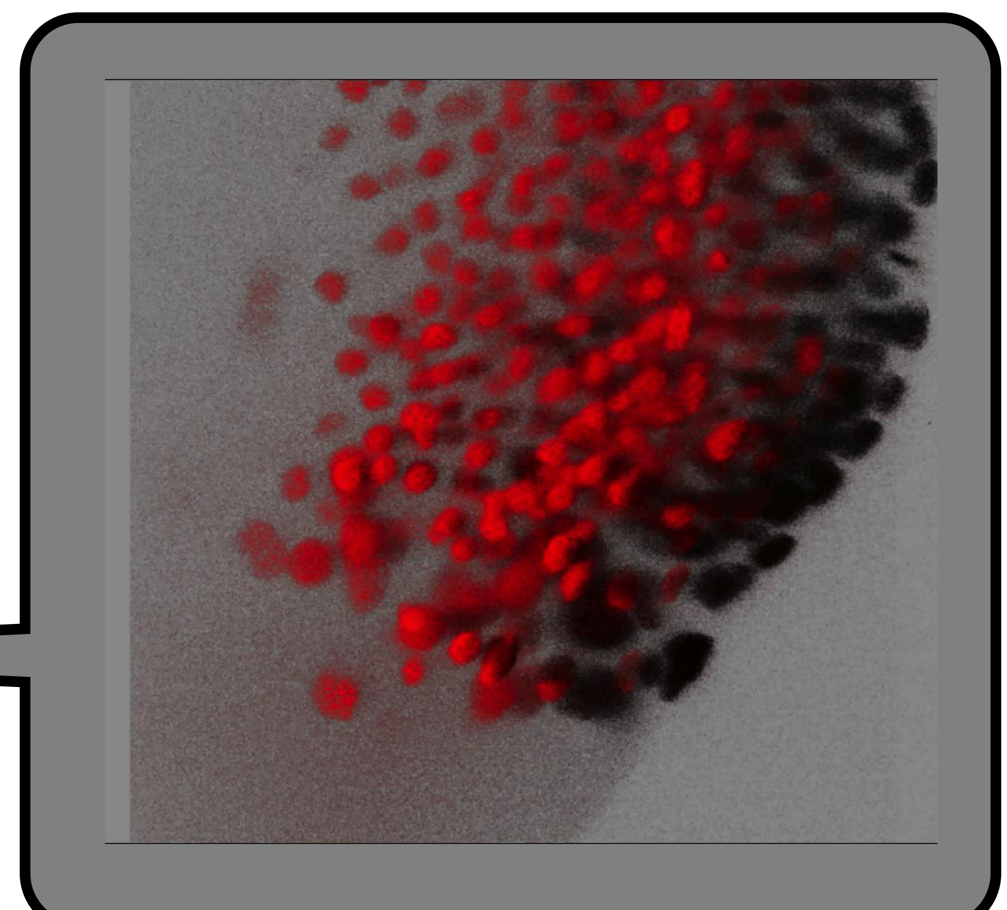
springerimages.com

During development of embryo

Differential Adhesion Hypothesis: Steinberg, Science 1962

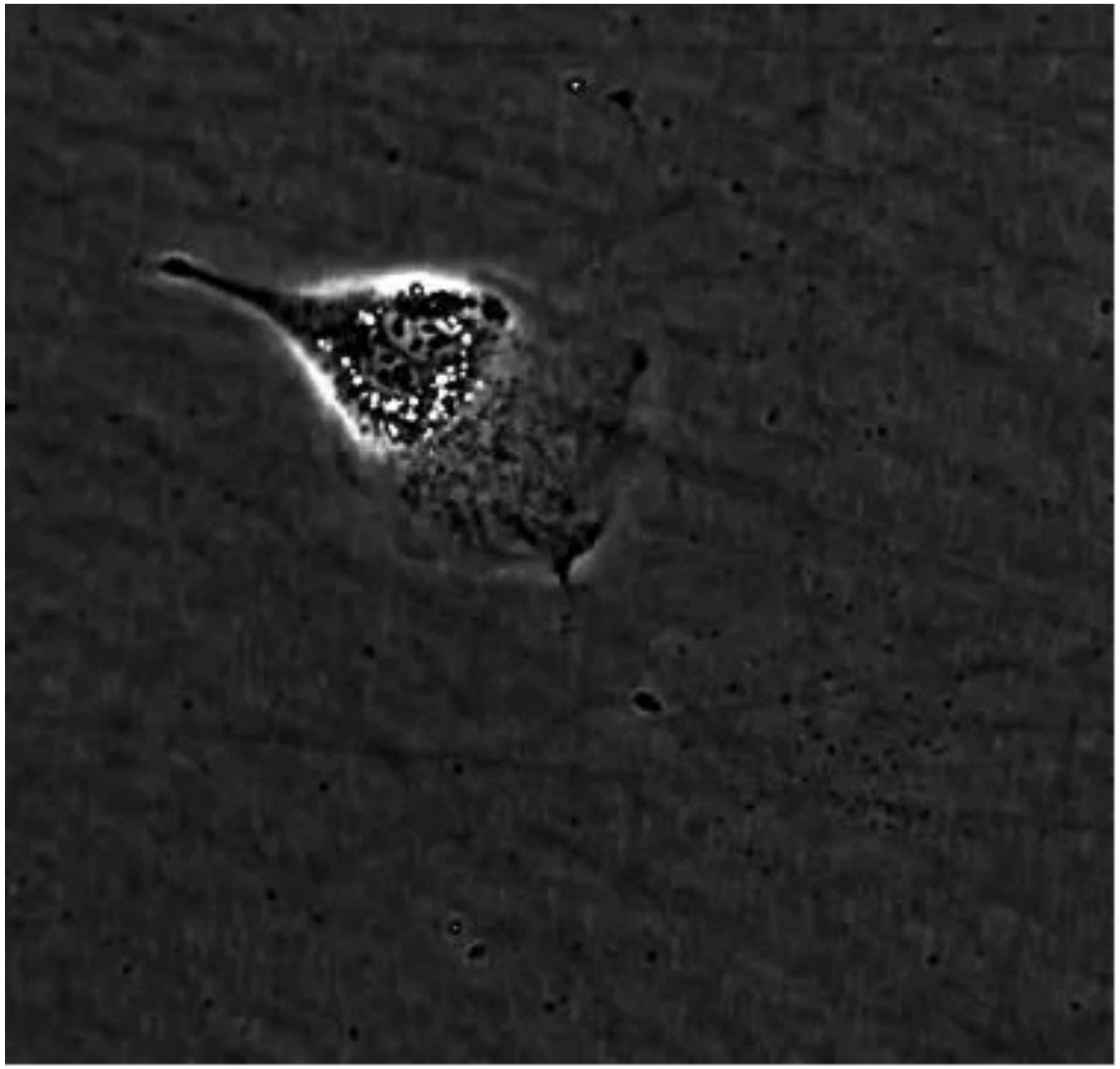


Schoetz Ph D thesis, 2008

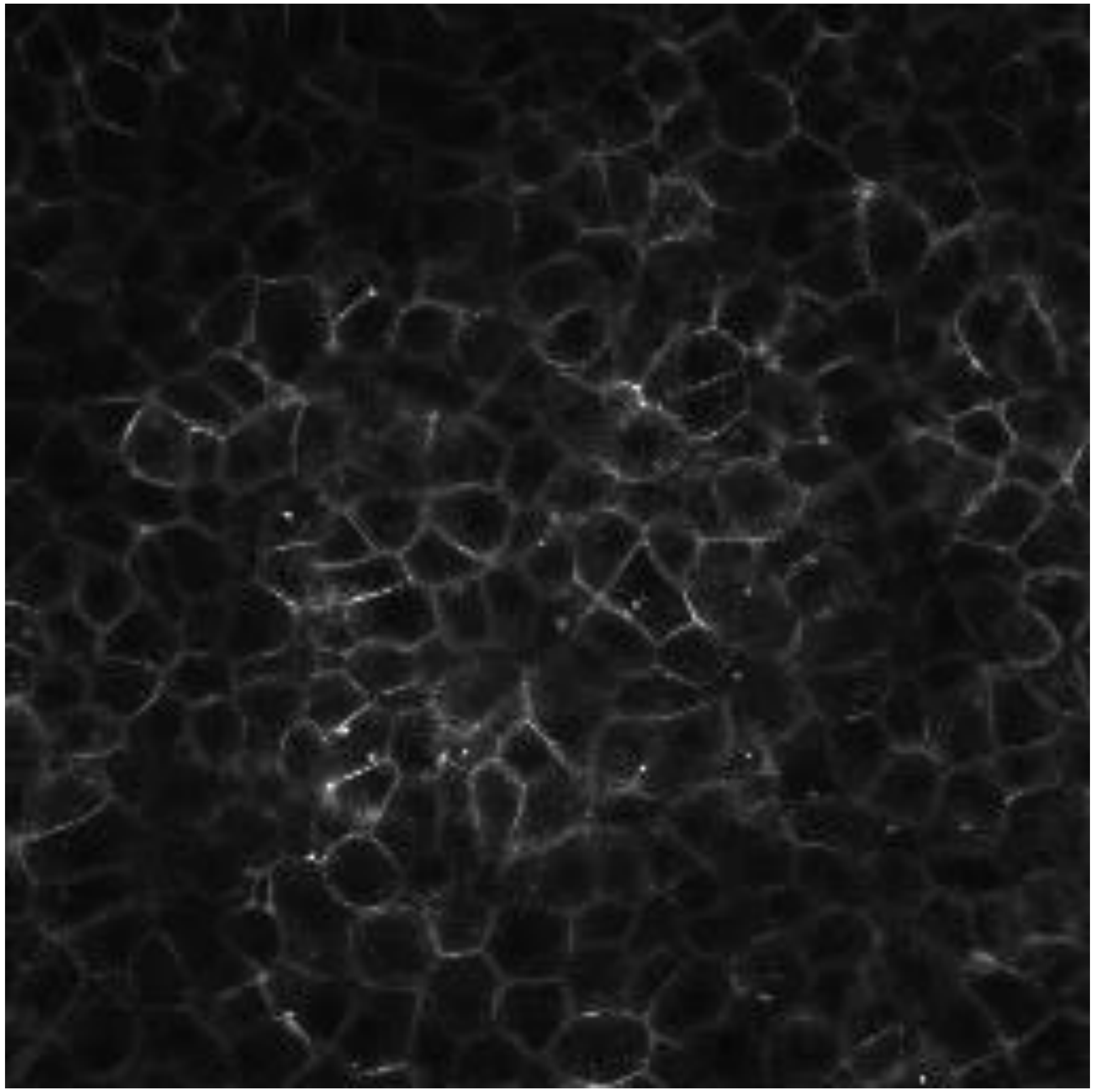


How do cells move?

In isolation **vs.** **in dense tissue**



Human bone cancer cell on fibronectin

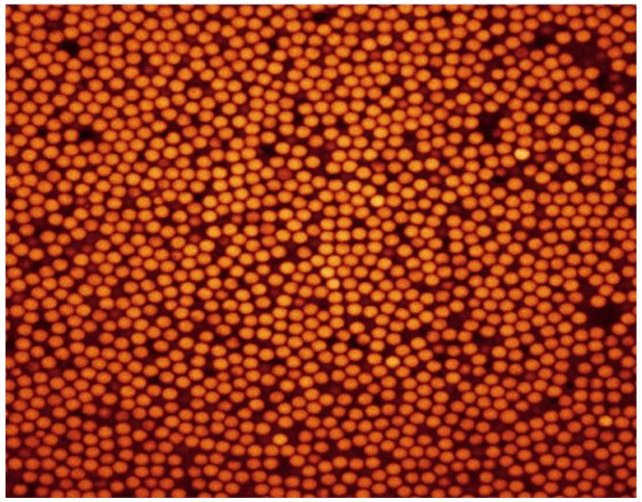


Zebrafish embryo Schoetz Lab, UCSD

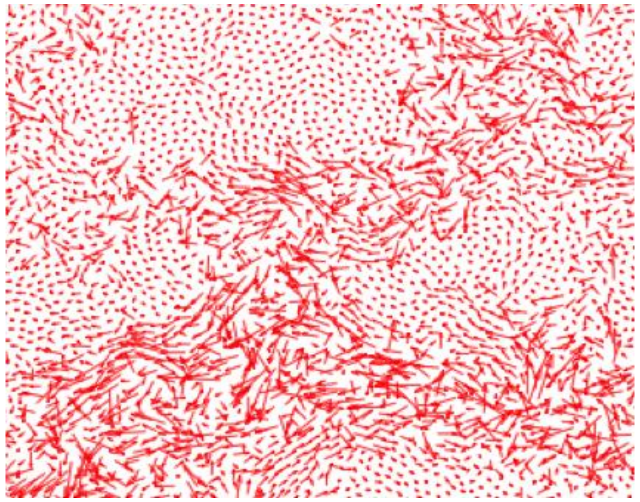
Dense (non-active) materials near a glass transition

Global energy injection

Thermal

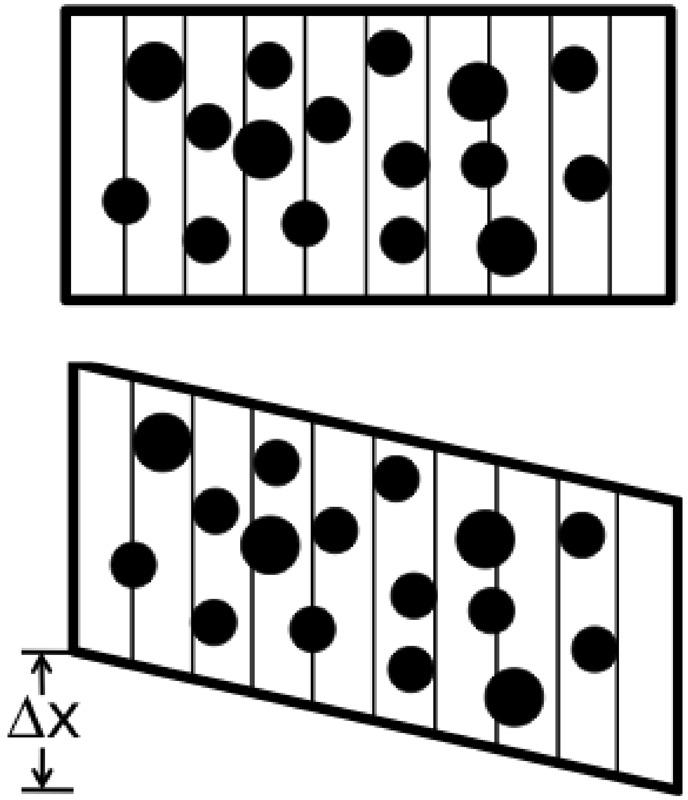


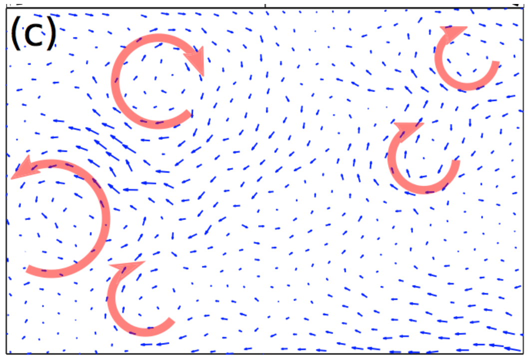
A colloidal glass.



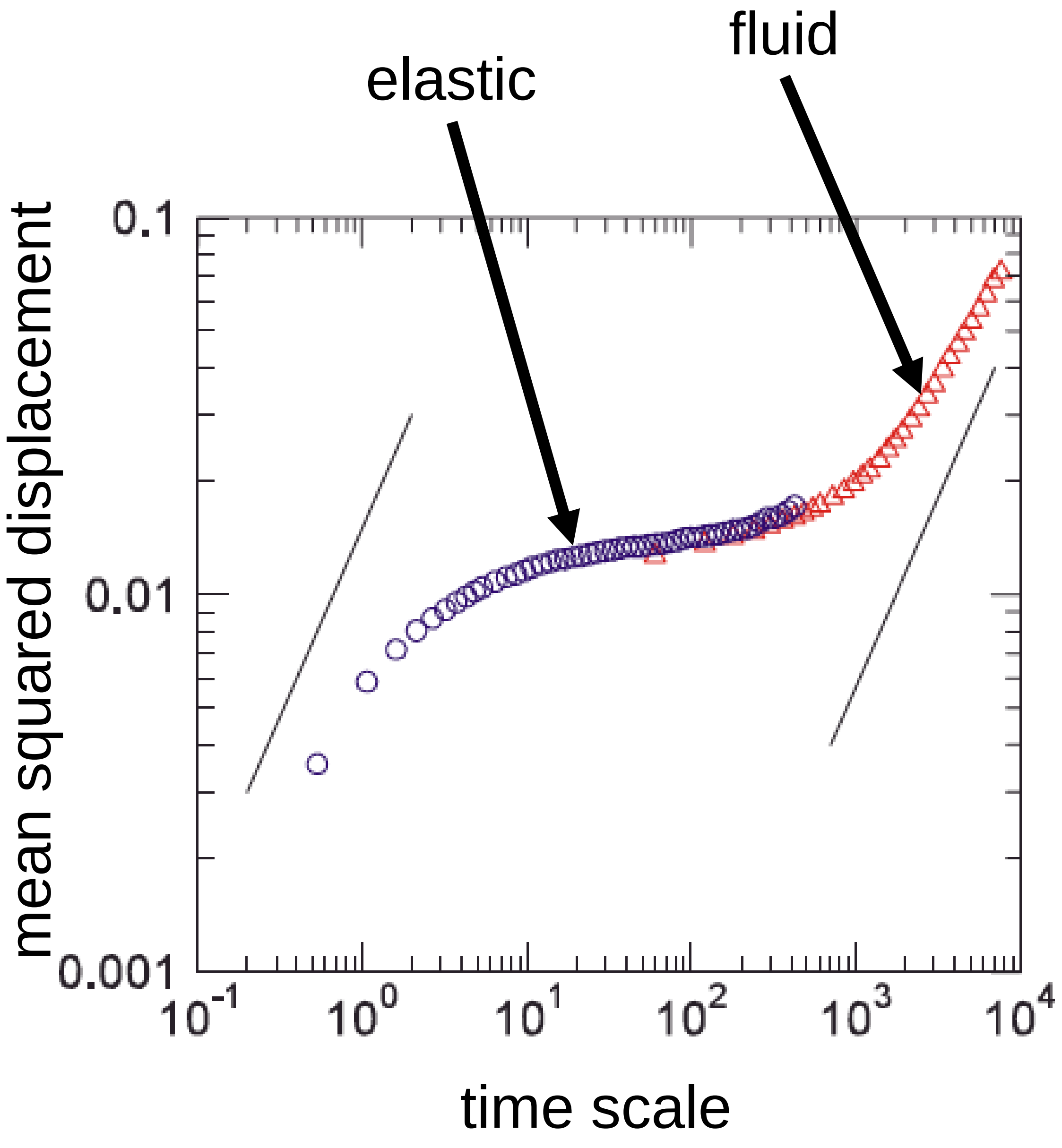
Displacement profile in simulation of a 2-d glass former.
Berthier PRL 2011

Boundary Driven

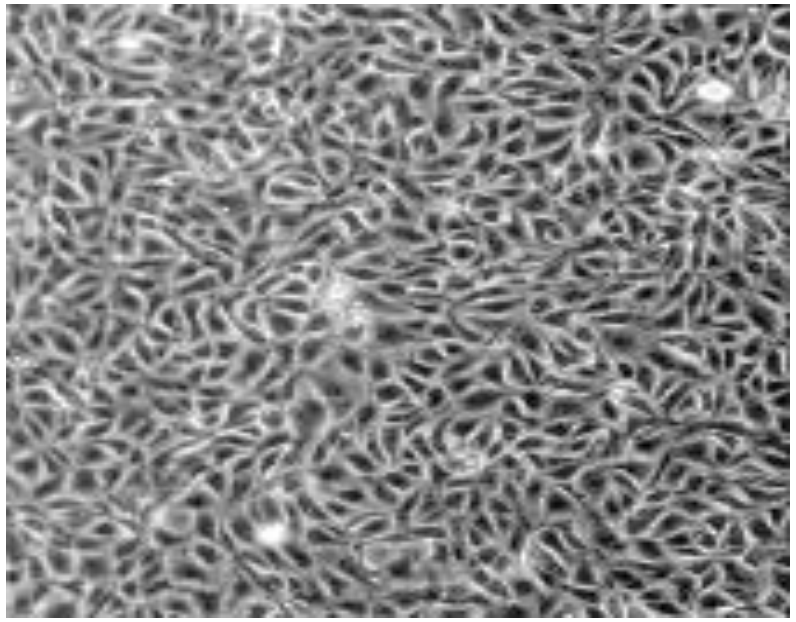




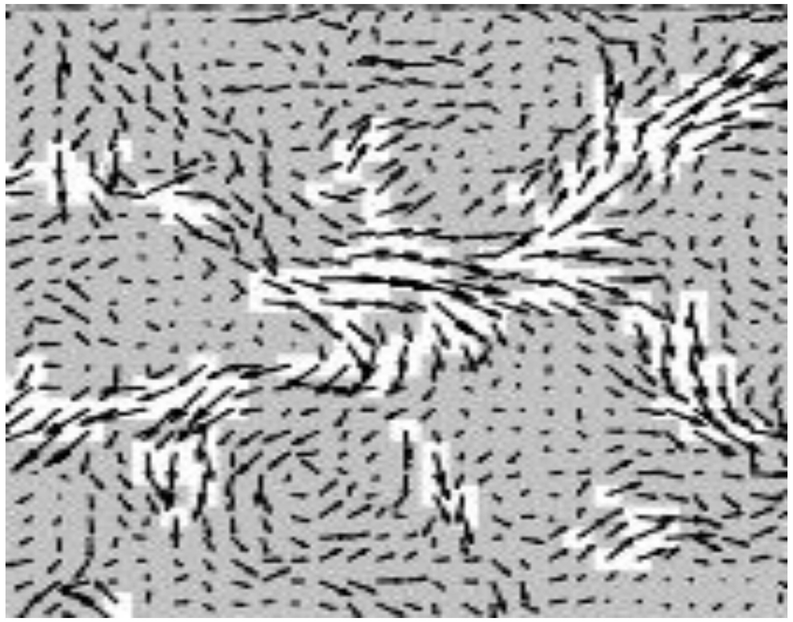
Sheared granular material
Jie Ren thesis 2013



Many tissues seem to be close to a glass transition

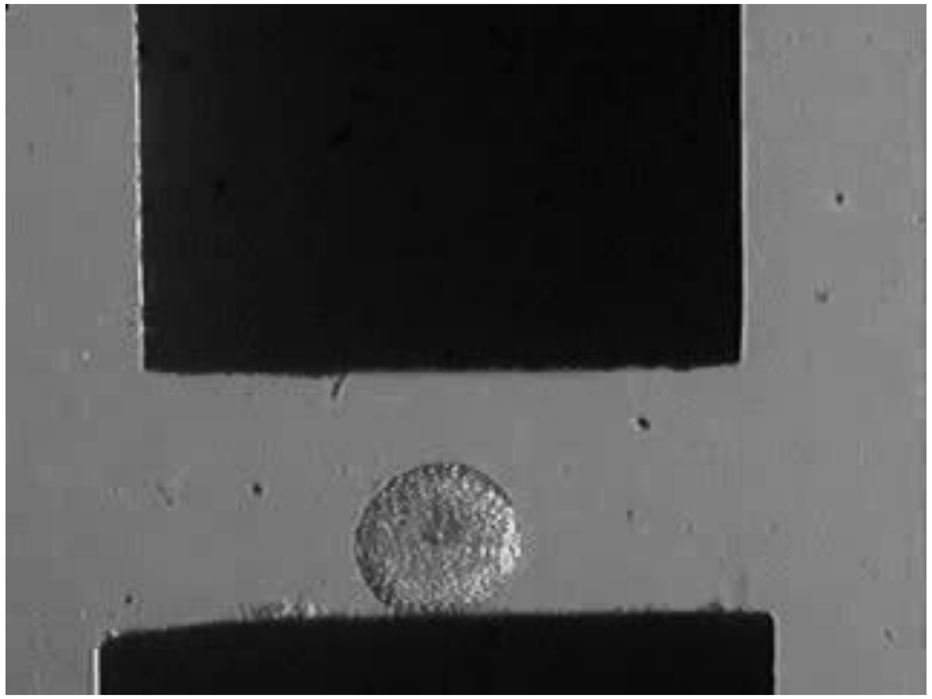


Madin-Darby canine kidney (MDCK) cells forming a 2-d confluent layer.
Angelini et al PNAS 2010

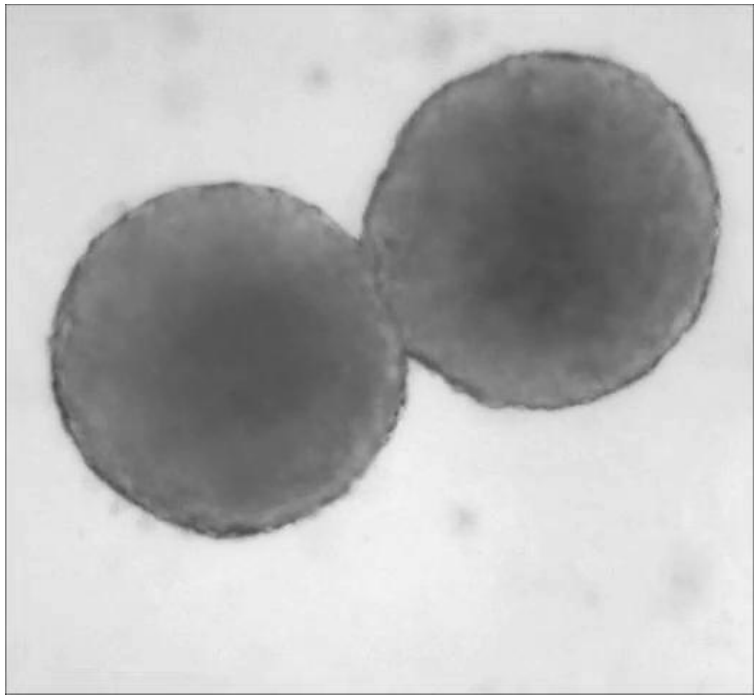


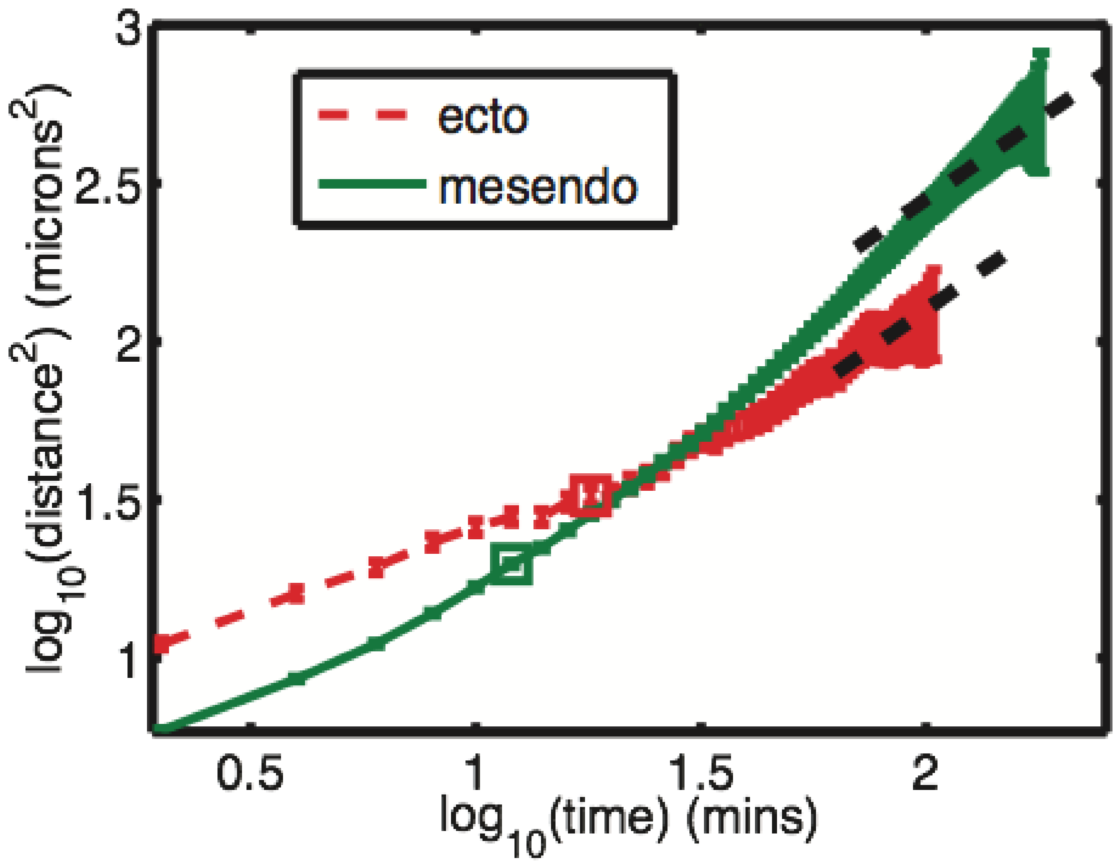
Velocity profile of cells show the spatially heterogeneous pattern in MDCK tissue.

timescale ~ seconds



timescale ~ hours





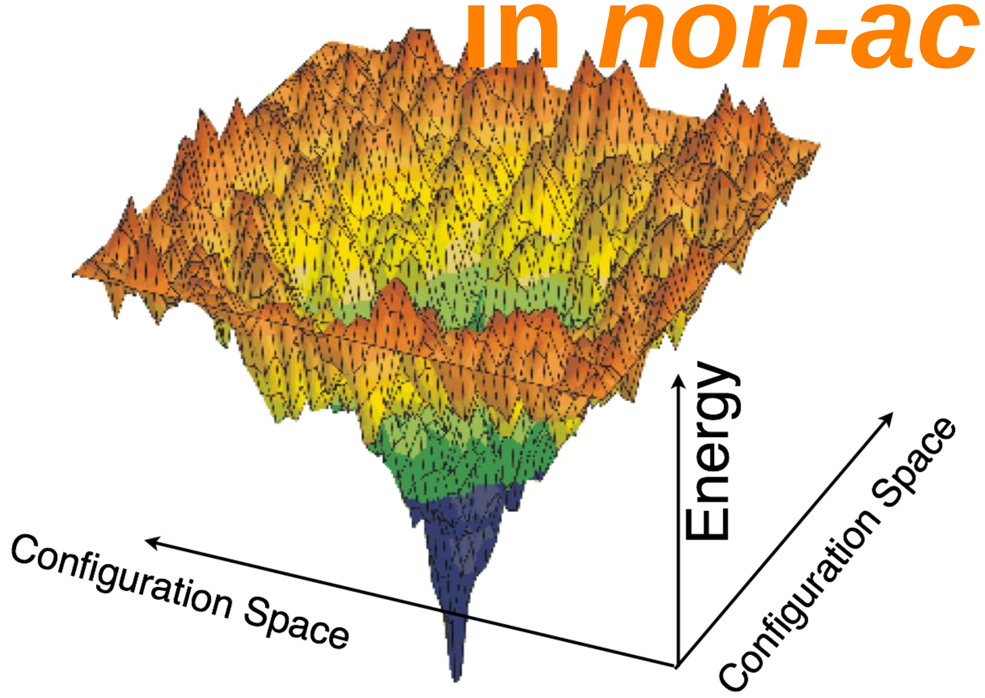
Schoetz et al
J. R. Soc.
Interface **10(89)**,
20130726
(2013)

why might tissues generically be close to a glass transition?

For wound healing, embryonic development, cancer invasion:

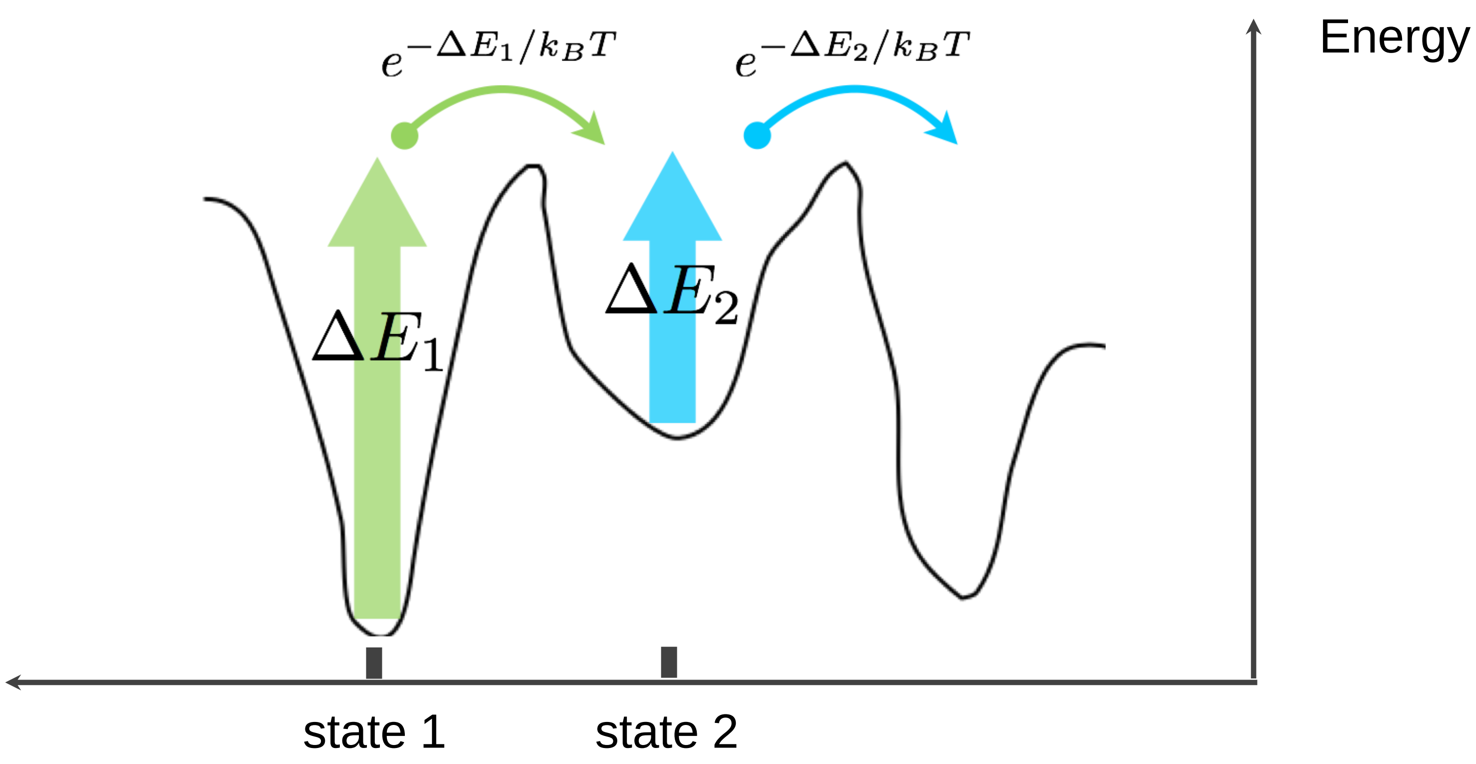
- initially need large scale flows (i.e. a fluid-like rheology)
- subsequently need to support forces and shear stresses (i.e. a solid-like rheology)

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



Complex potential energy landscape
+
system close to energy landscape surface

System is "trapped" in a metastable state until a rare fluctuation allows it to escape:

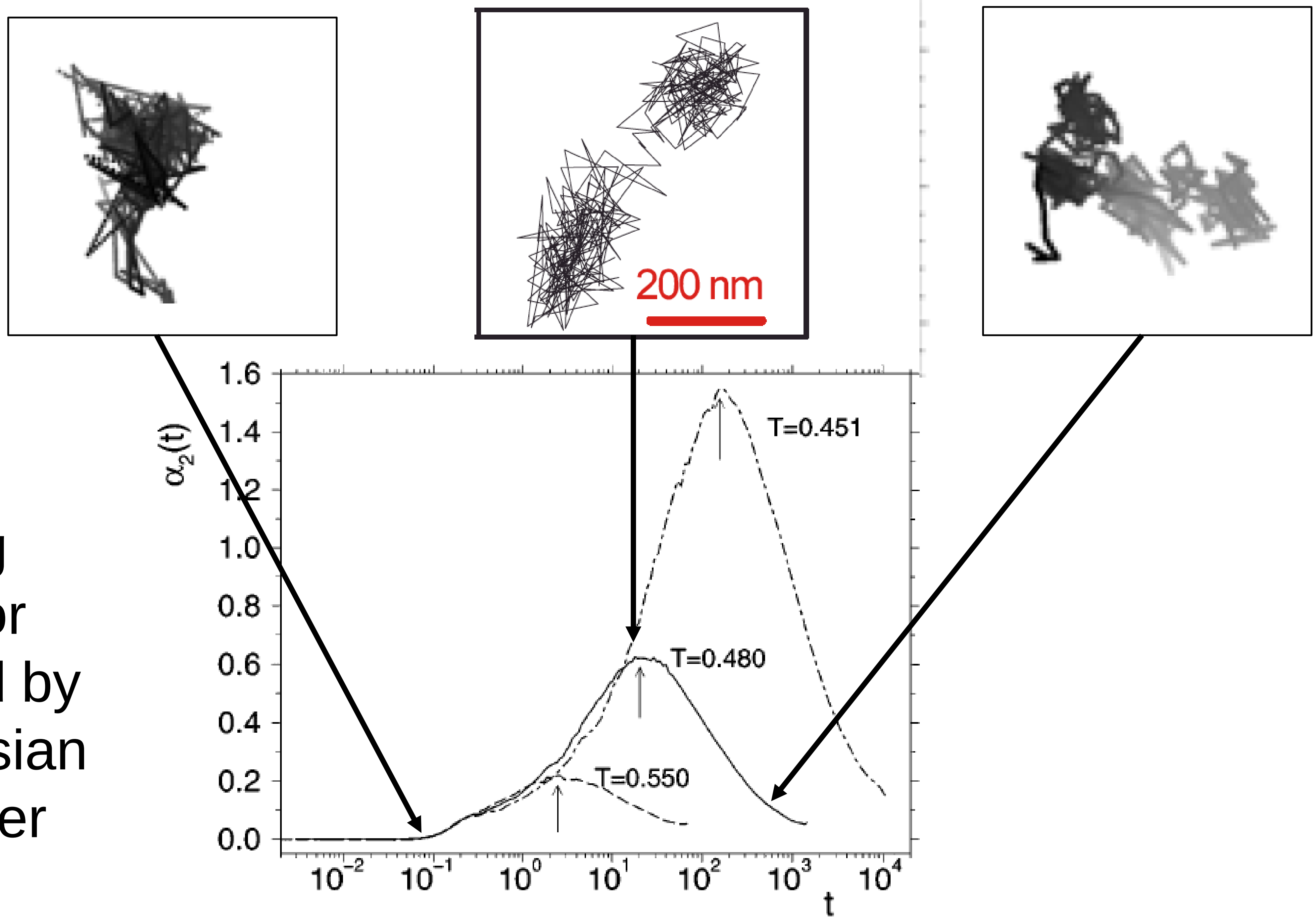


trap model **C. Monthus and J.-P. Bouchaud, J. Phys. A 29, 3847 (1996)**

soft glassy rheology
Sollich et al, PRL 78 2020 (1997)

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

Weeks, Crocker, Weitz (2004)

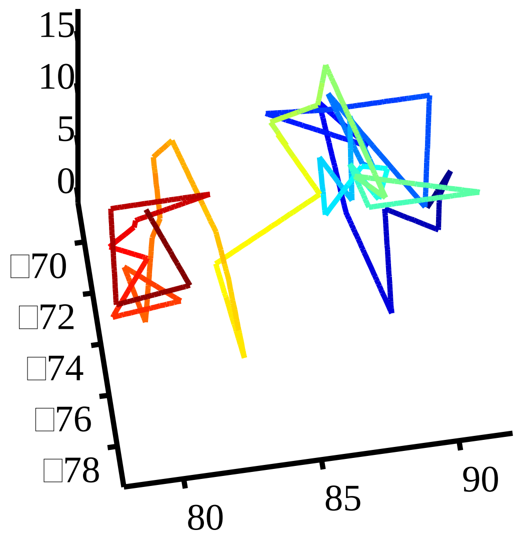


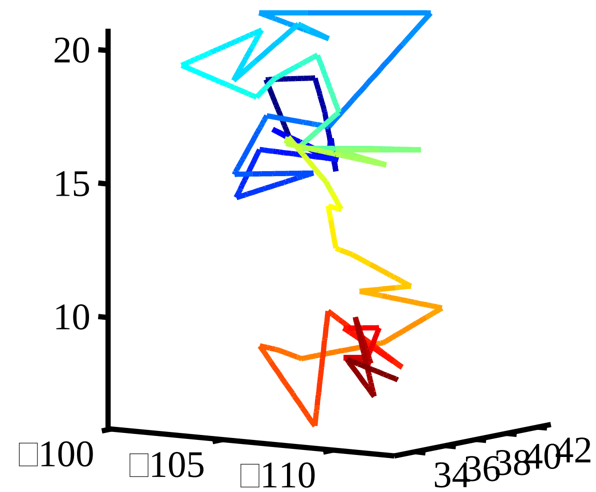
Caging behavior measured by non-gaussian parameter

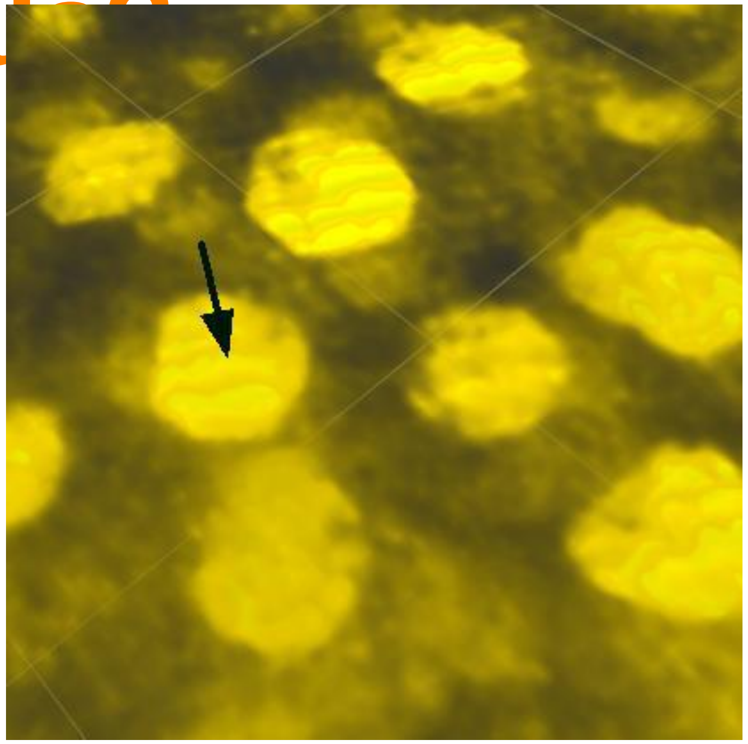
Kob et al, PRL 79 15 2827 (1997)

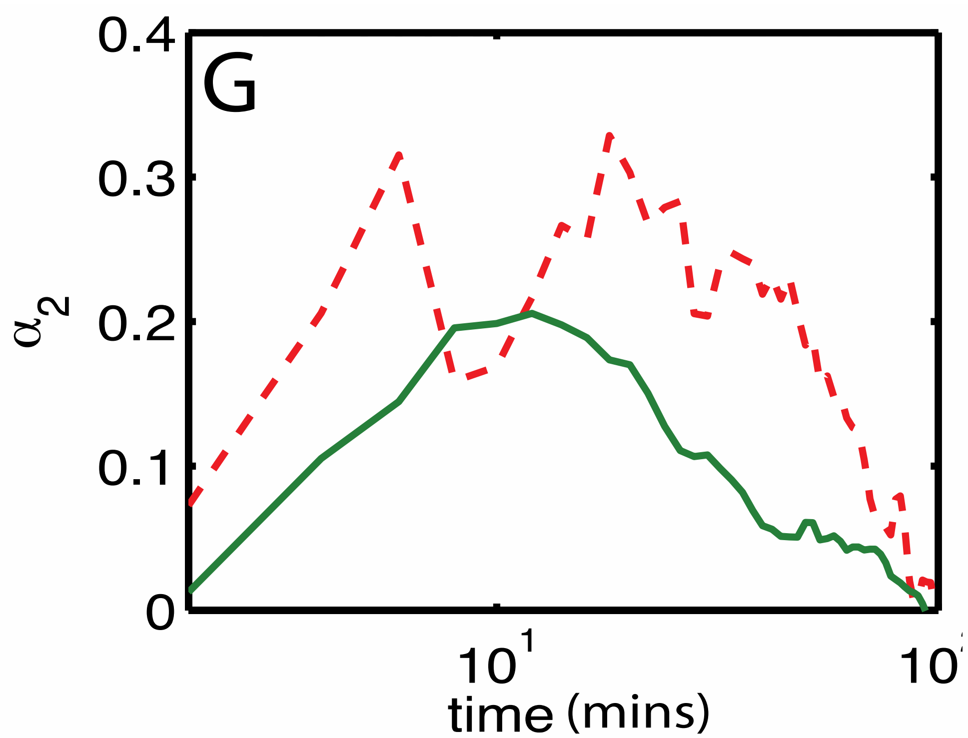
What is the microscopic origin of this glassy behavior
in *active* materials?

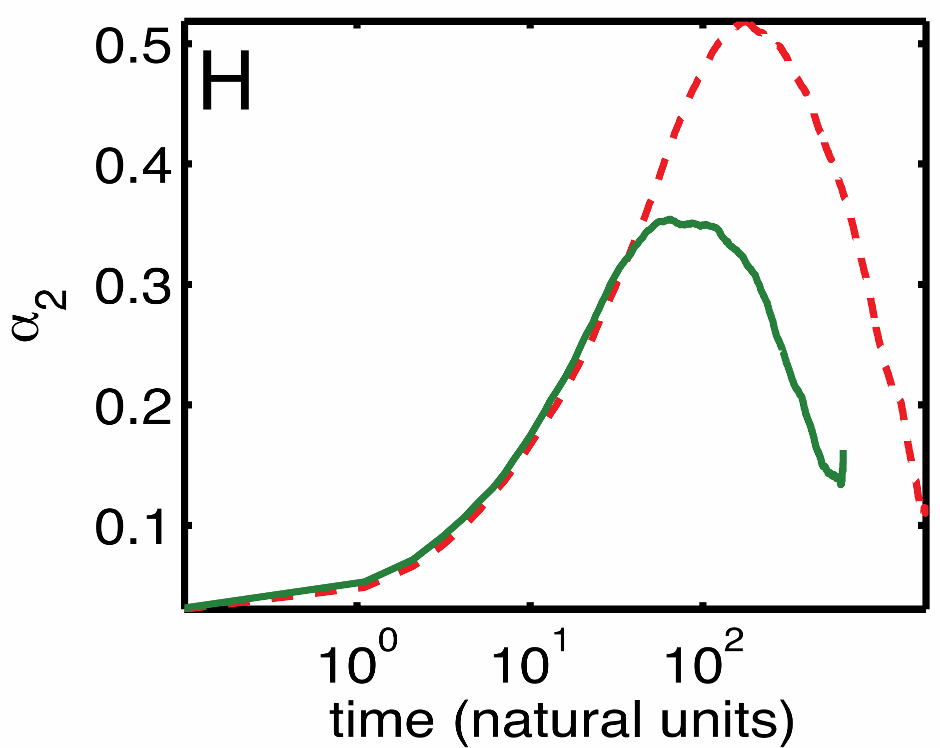
Local Energy injection by cells









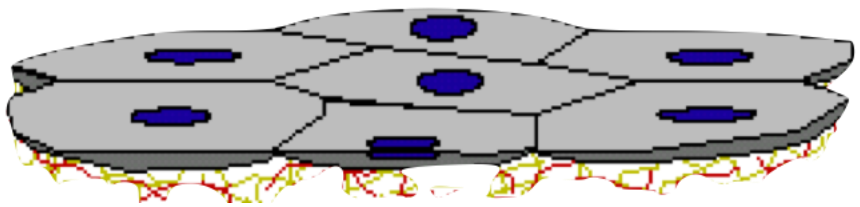


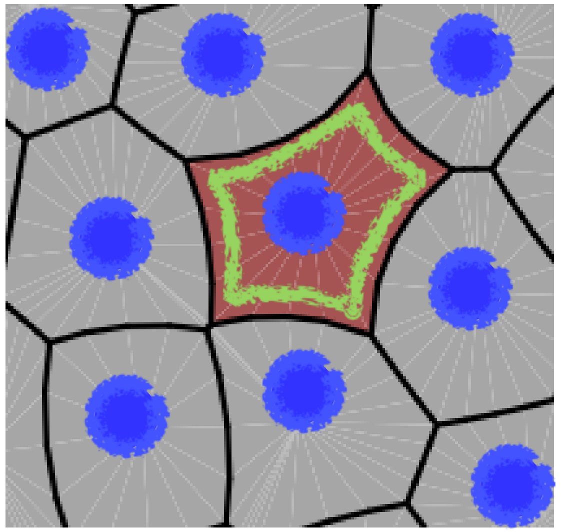
Schoetz et al
J. R. Soc.
Interface **10(89)**,
20130726
(2013)

must understand landscape (and energy barriers) for dense tissues!

The Shape Equilibrium Model

- Developed almost 10 years ago and well-studied
- Reasonably good agreement with experimentally observed cell shapes
- Generalization of a foam model
- “Vertex model”



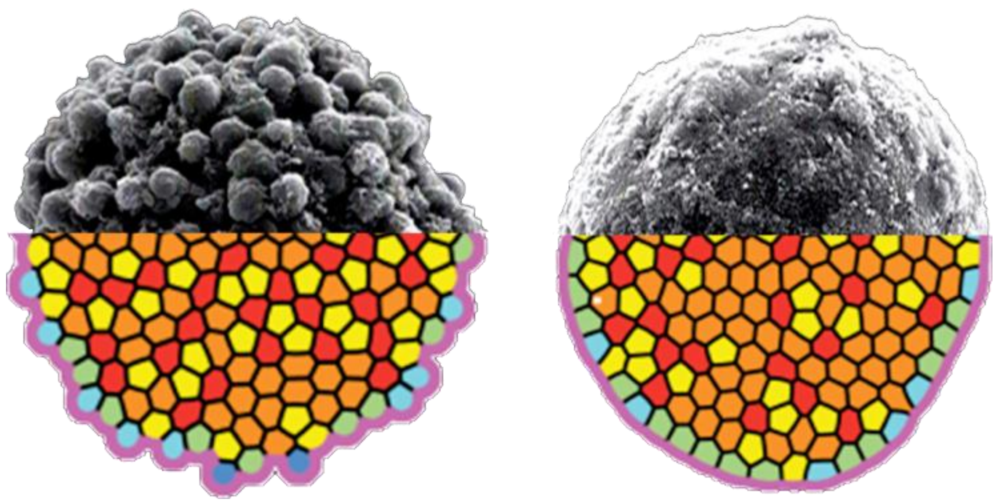


$$E_{cell} = k_A(A - A_0)^2 + k_P(P - P_0)^2$$
$$= k_A(A - A_0)^2 + k_P(P^2 - 2P_0P + P_0^2)$$

Bulk elasticity term

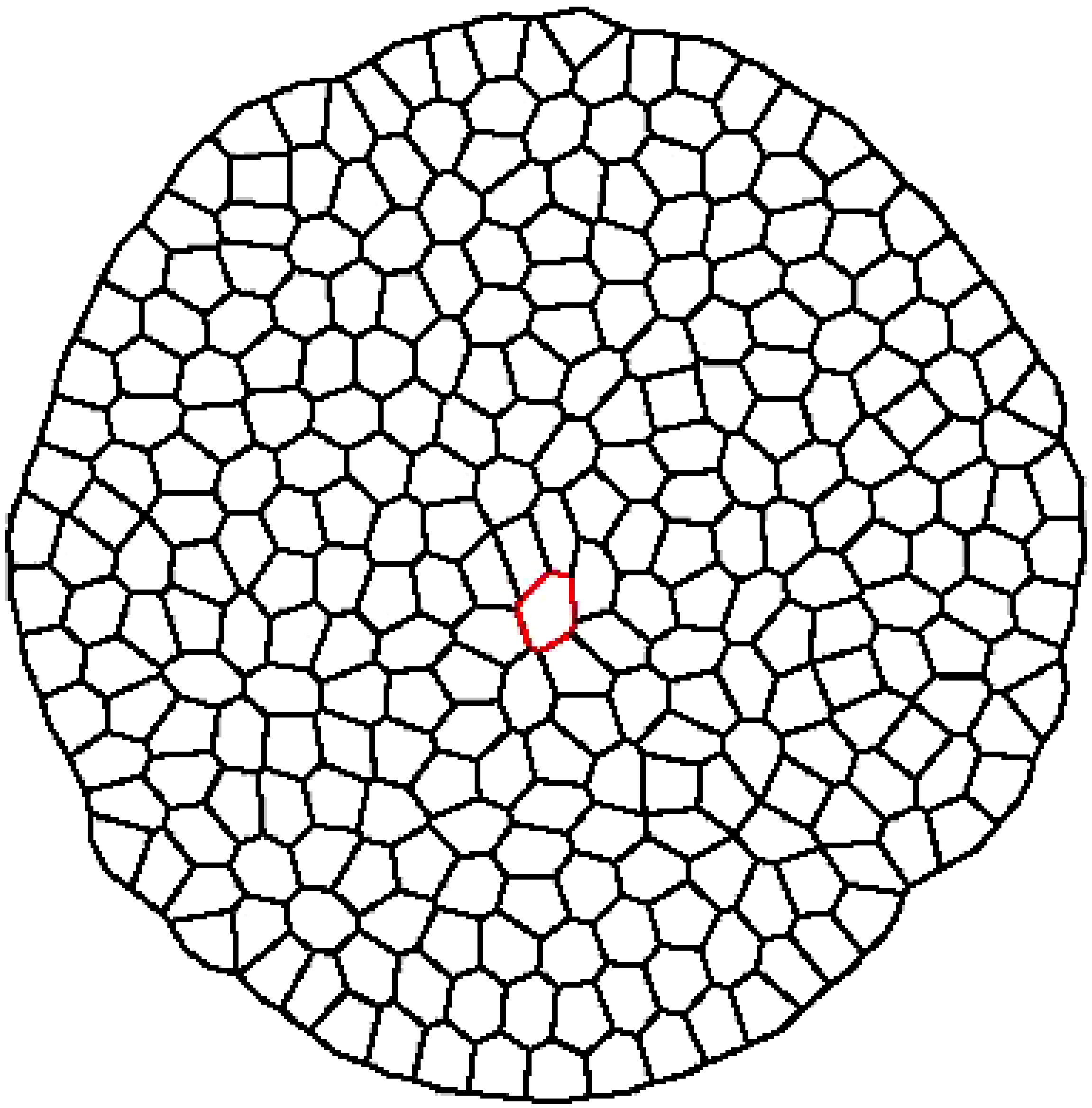
Line tension

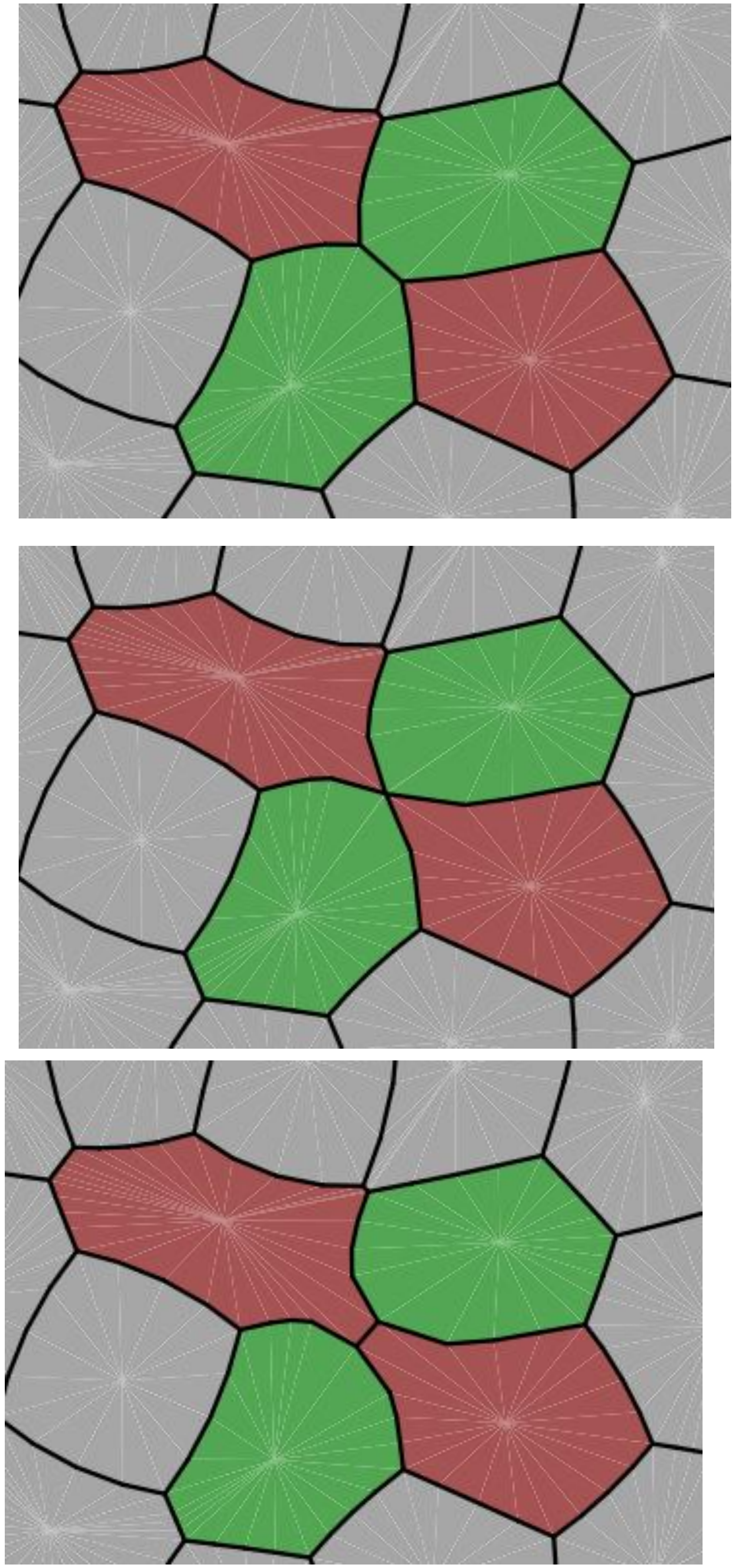
Contractility



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)

Migration happens via T-1 transitions

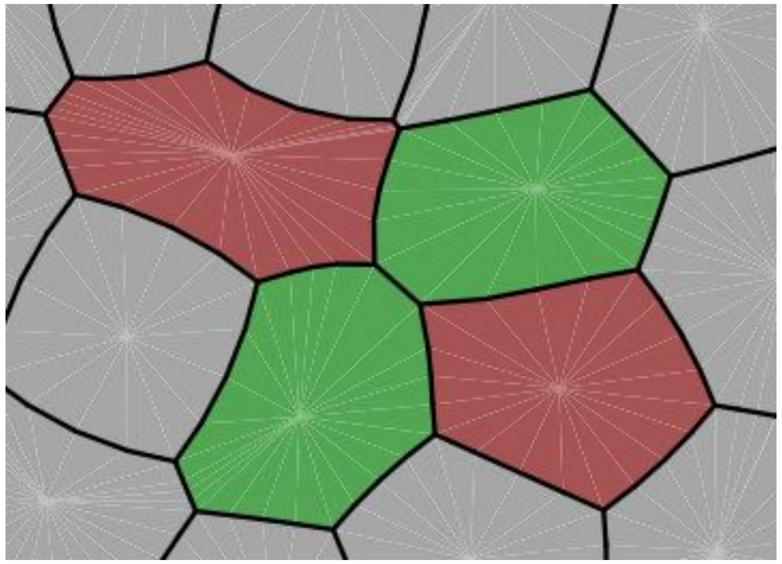




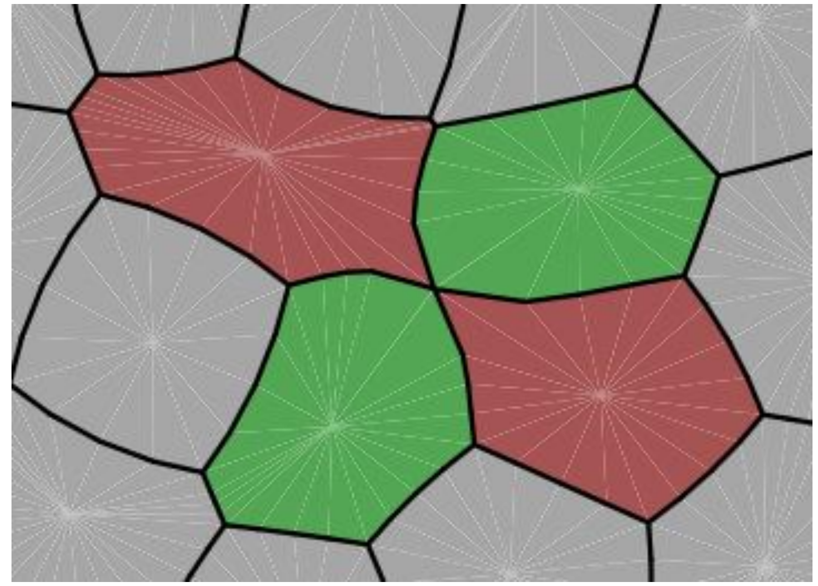
In absence of cell divisions – not needed for fluid behavior

Energy trace for T-1 transitions

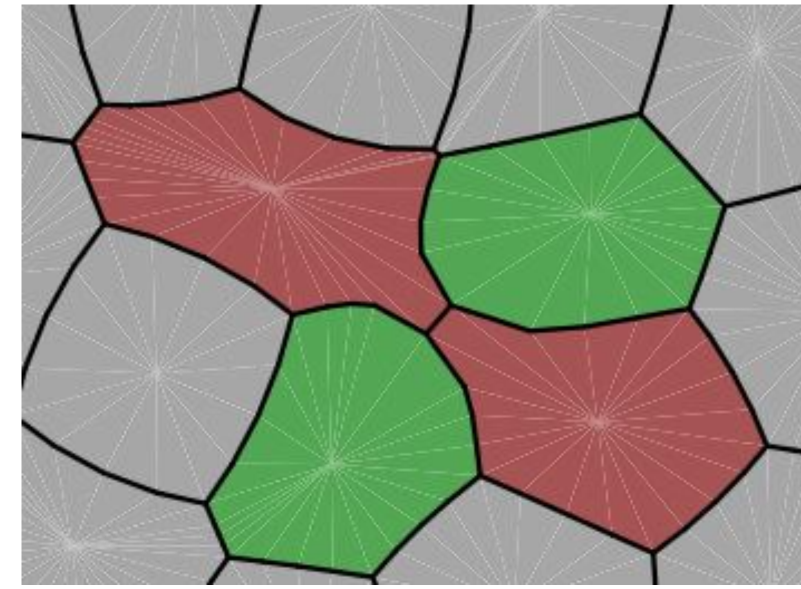
Shrink edge before T-1

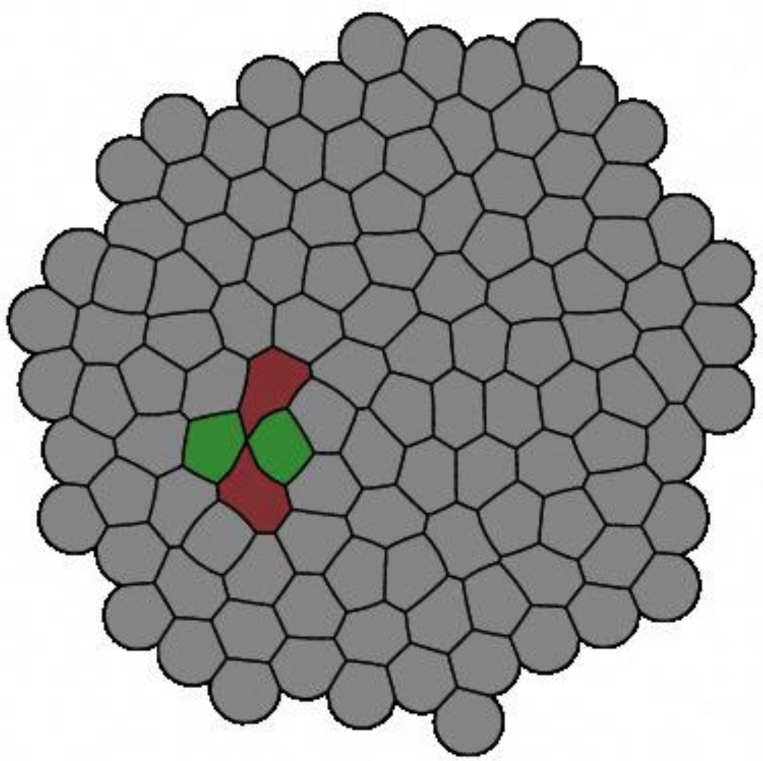


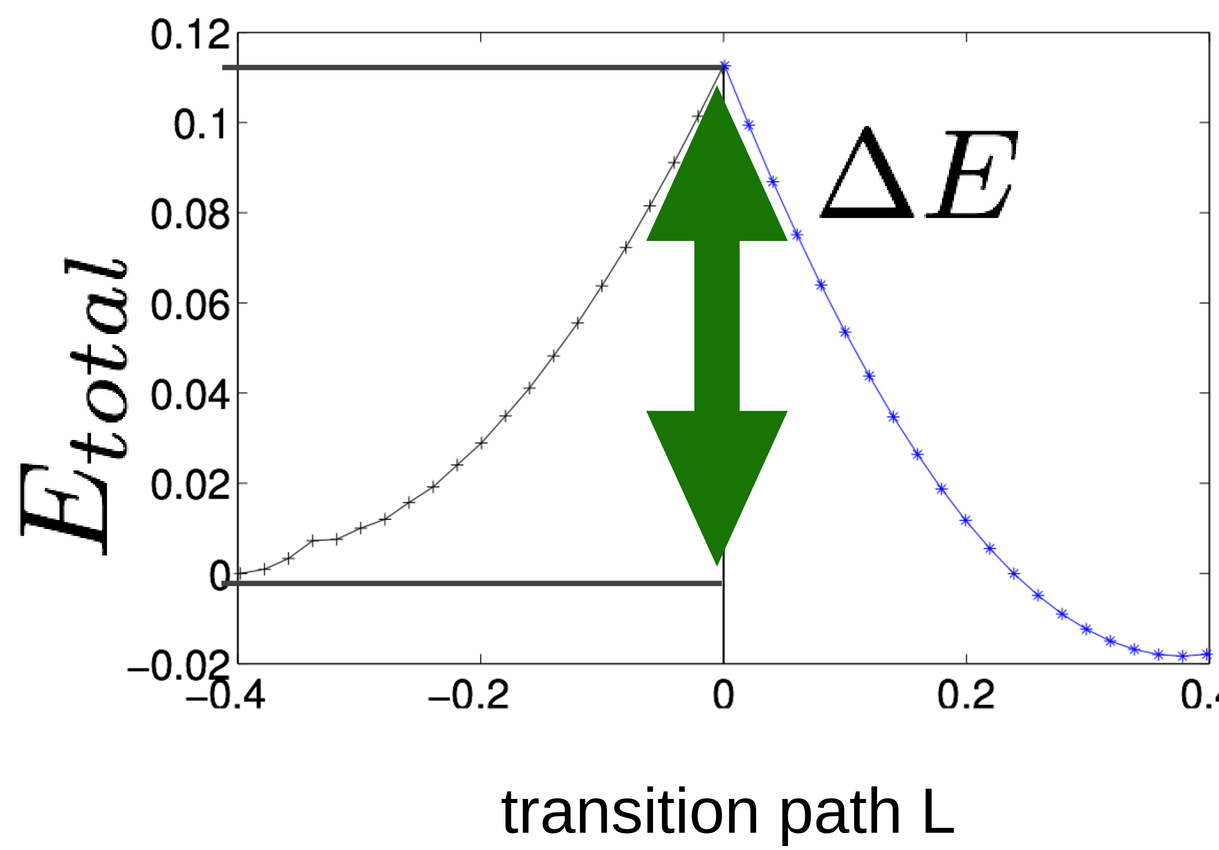
At T-1



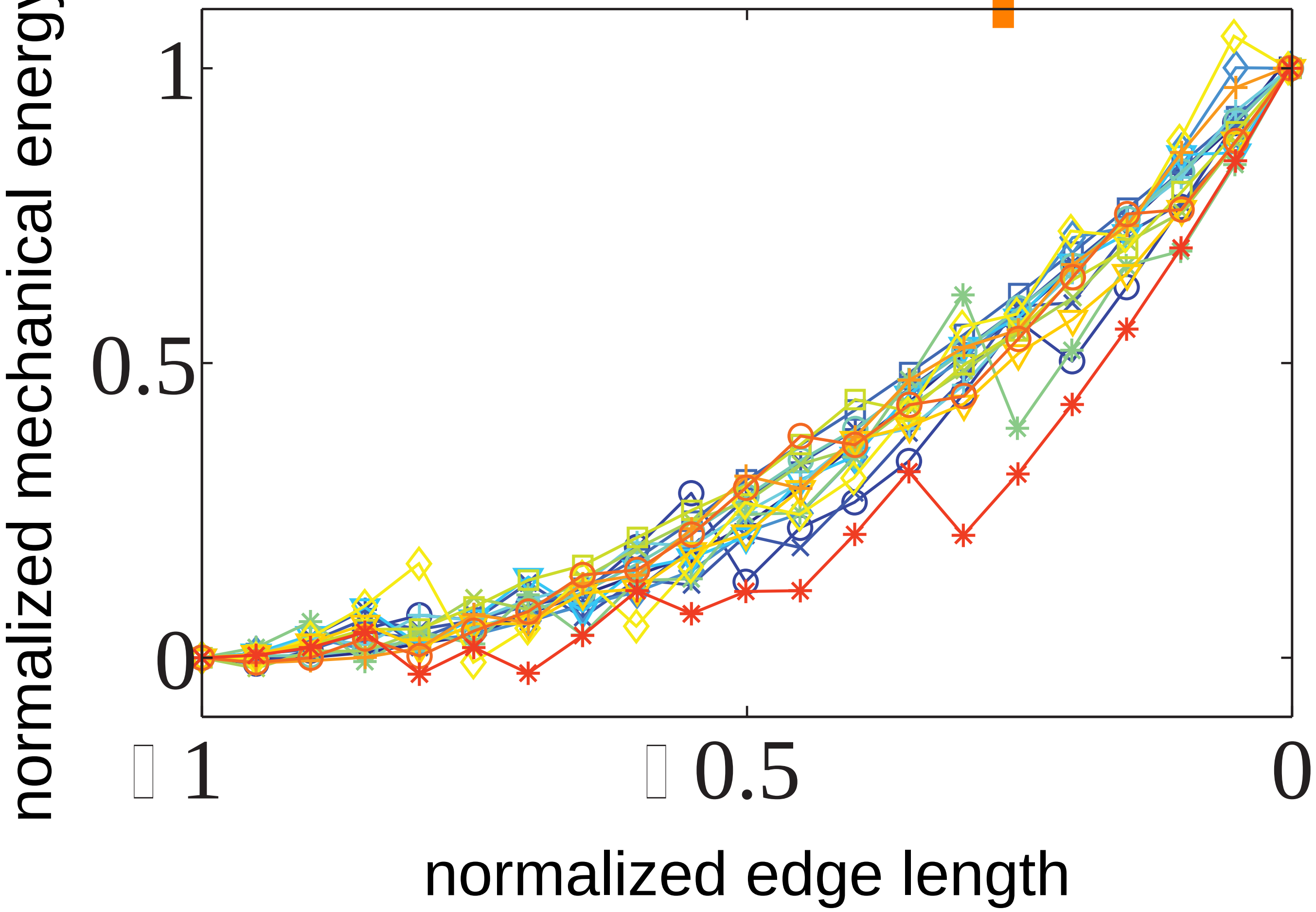
Grow edge after T-1



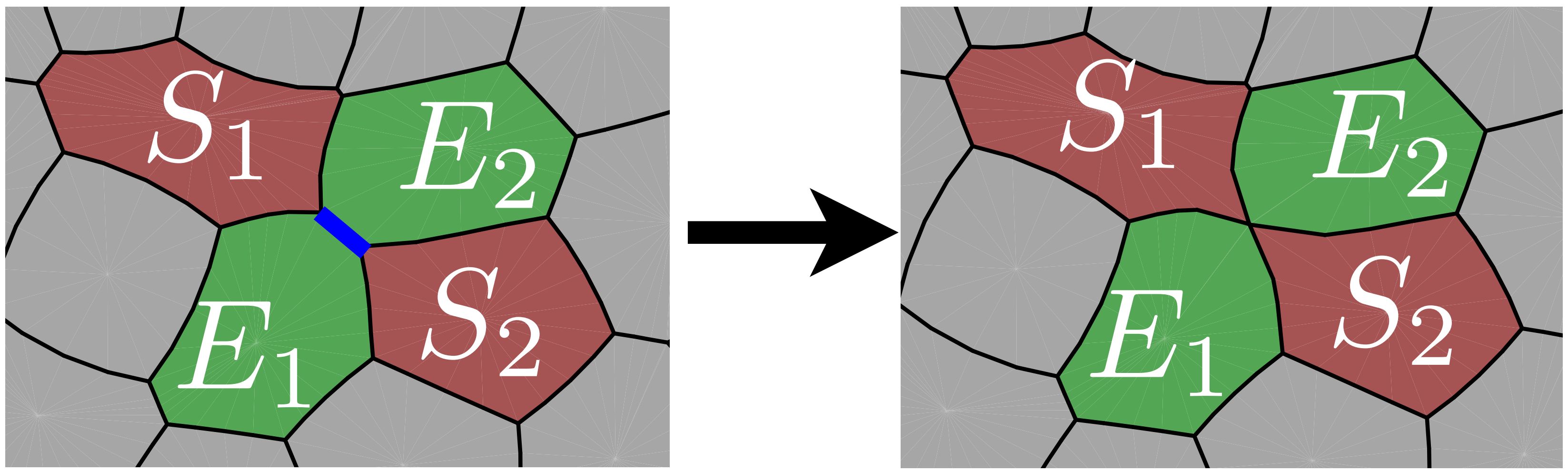




Simulation results: energy barrier shape

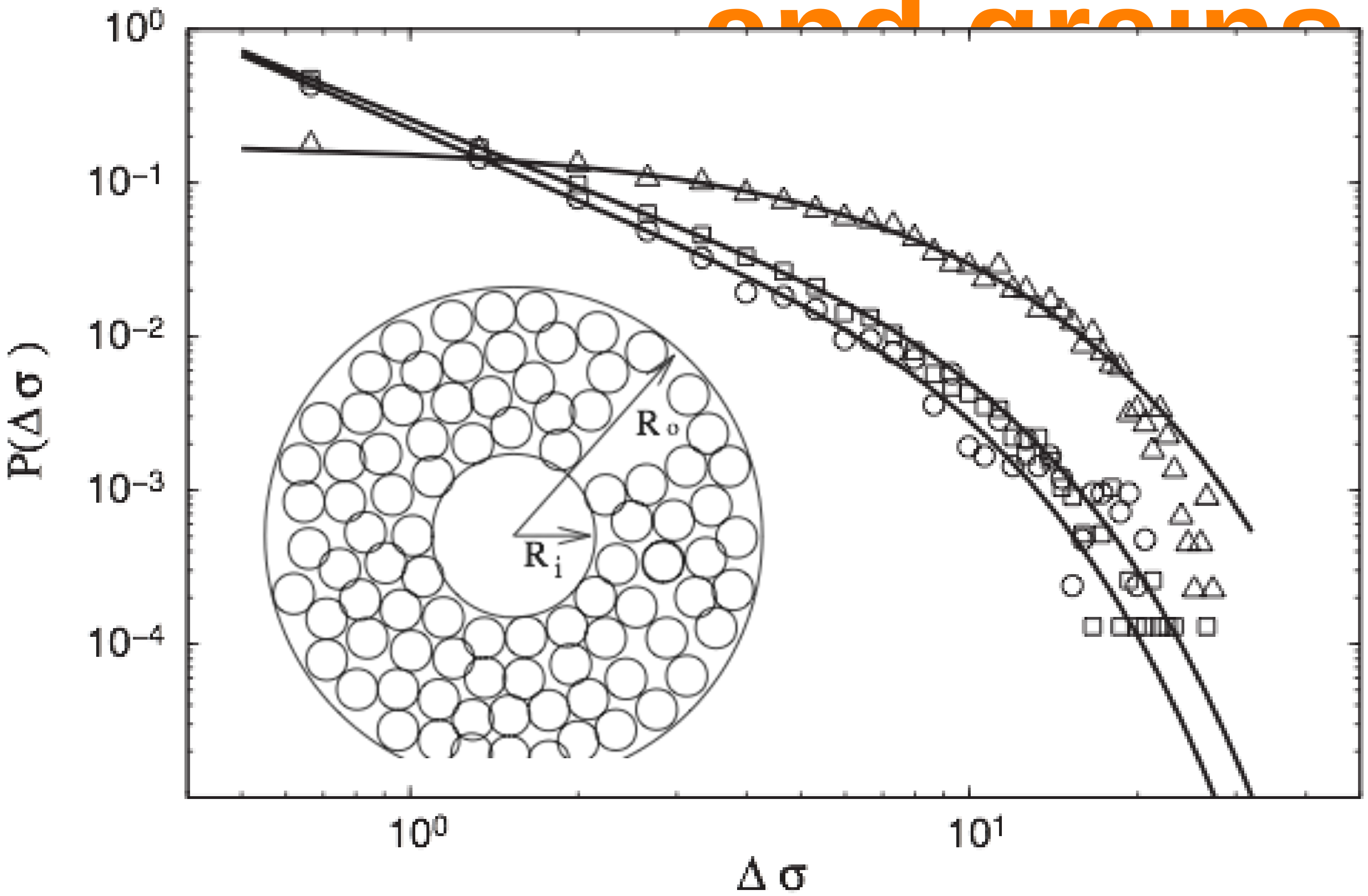


Energy barriers exhibit positive curvature



Bi et al, to appear in Soft Matter [Arxiv:1308.3891 (2014)]

Energy barrier statistics, foams and grains

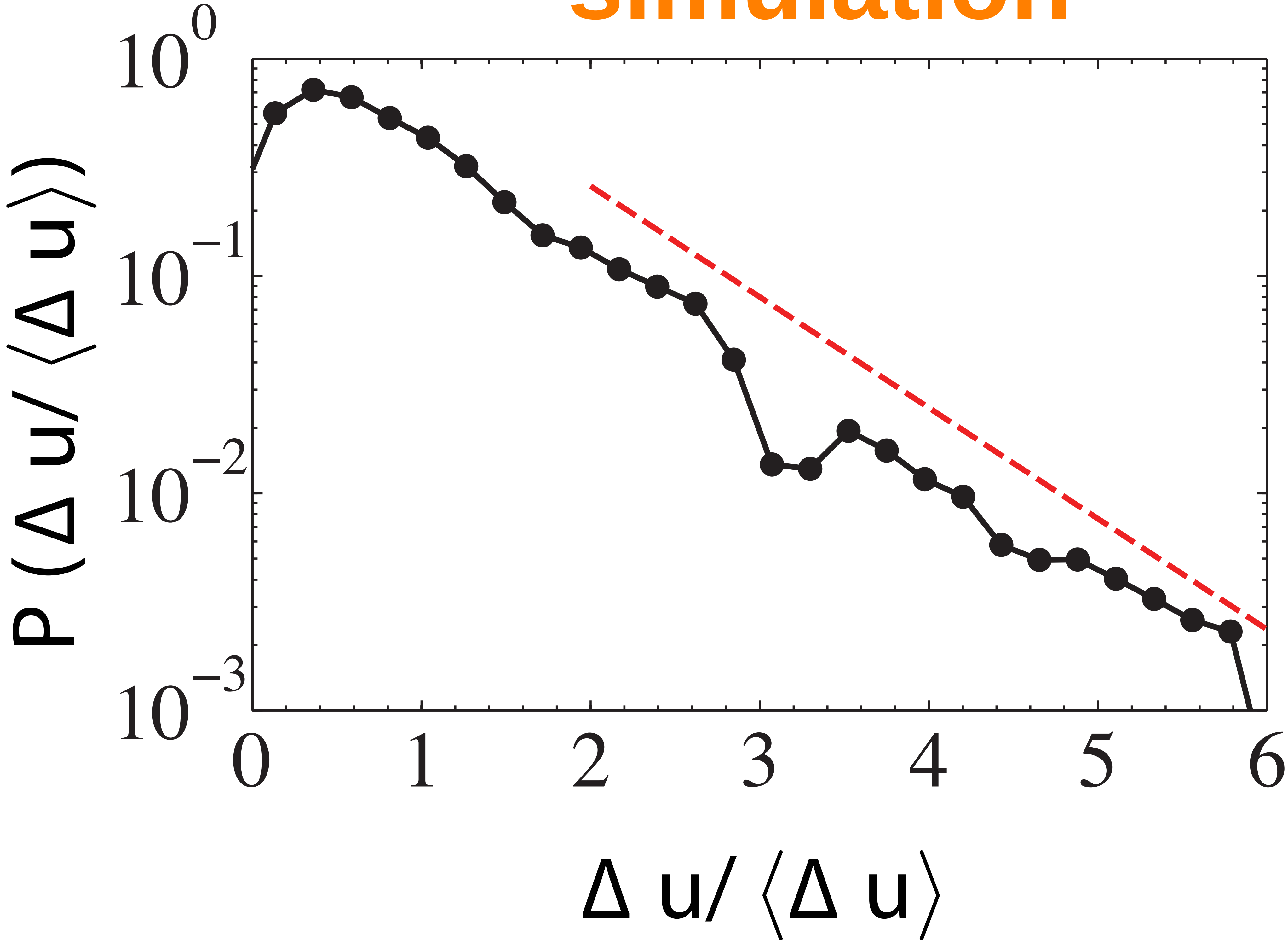


Behringer et al PRL **101** 268301 (2008)

Energy barriers are **power-law** distributed (with a cutoff)

Why? conjecture: energy is injected globally and failure occurs a special soft spots in a material that is tuned near a

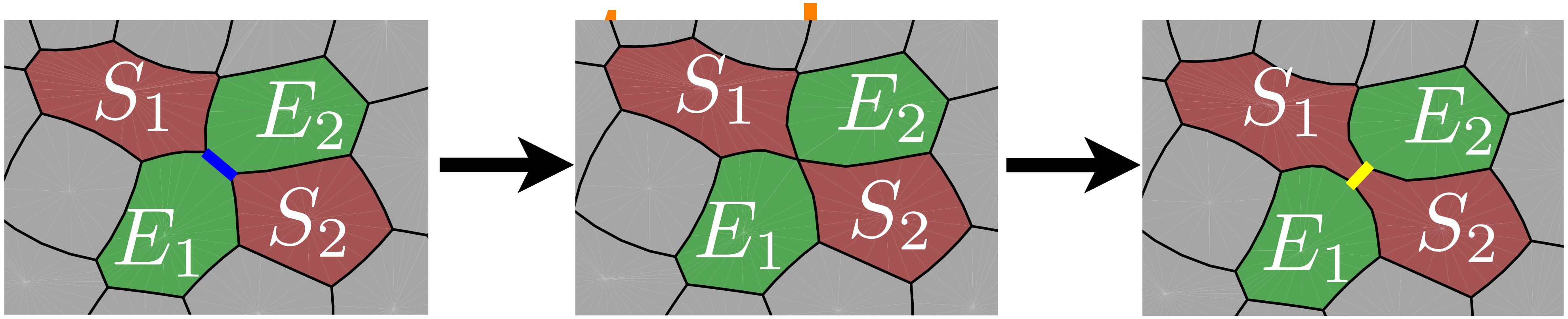
Energy barrier statistics, tissue simulation

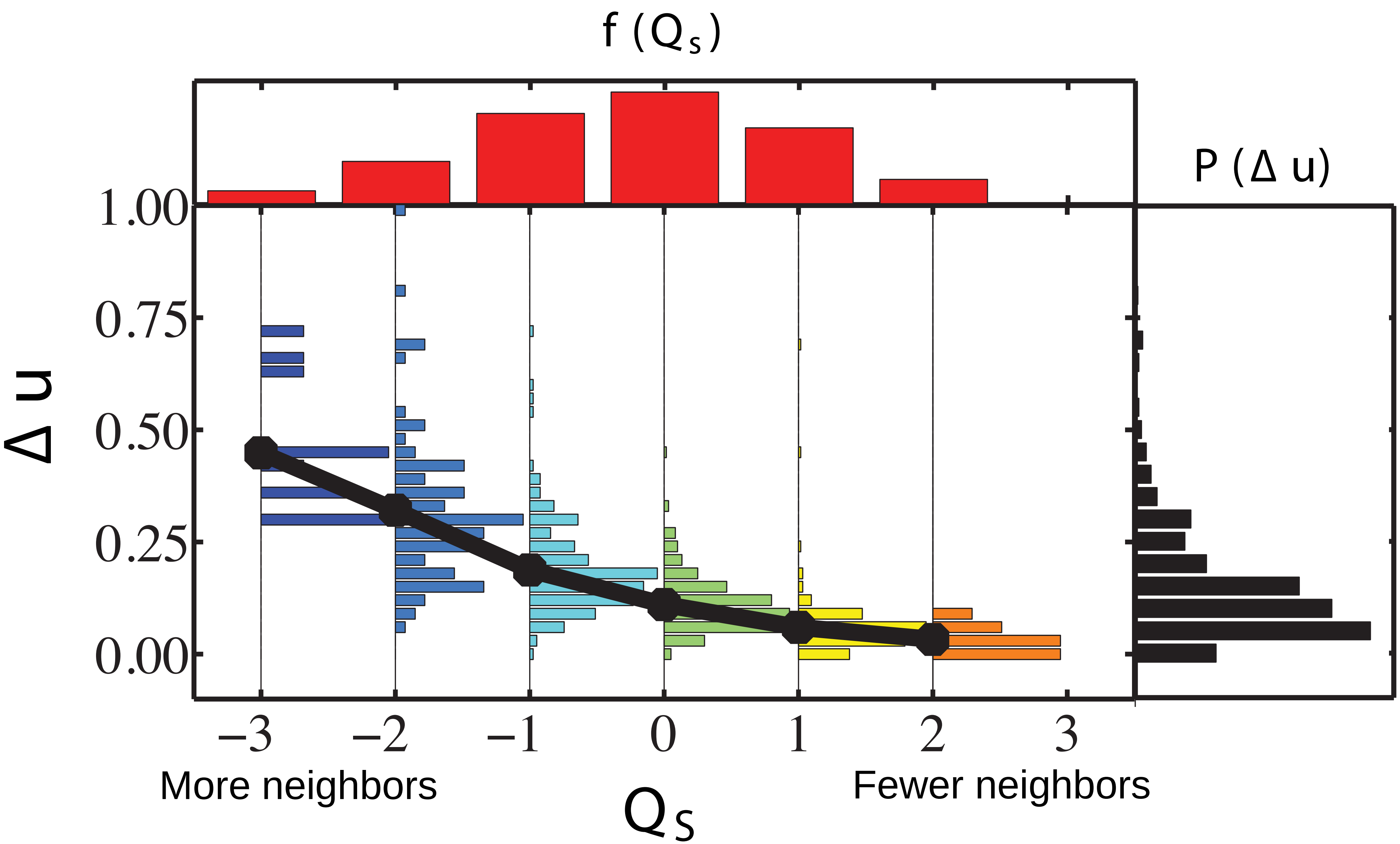


Energy barriers are exponentially distributed: surprising?

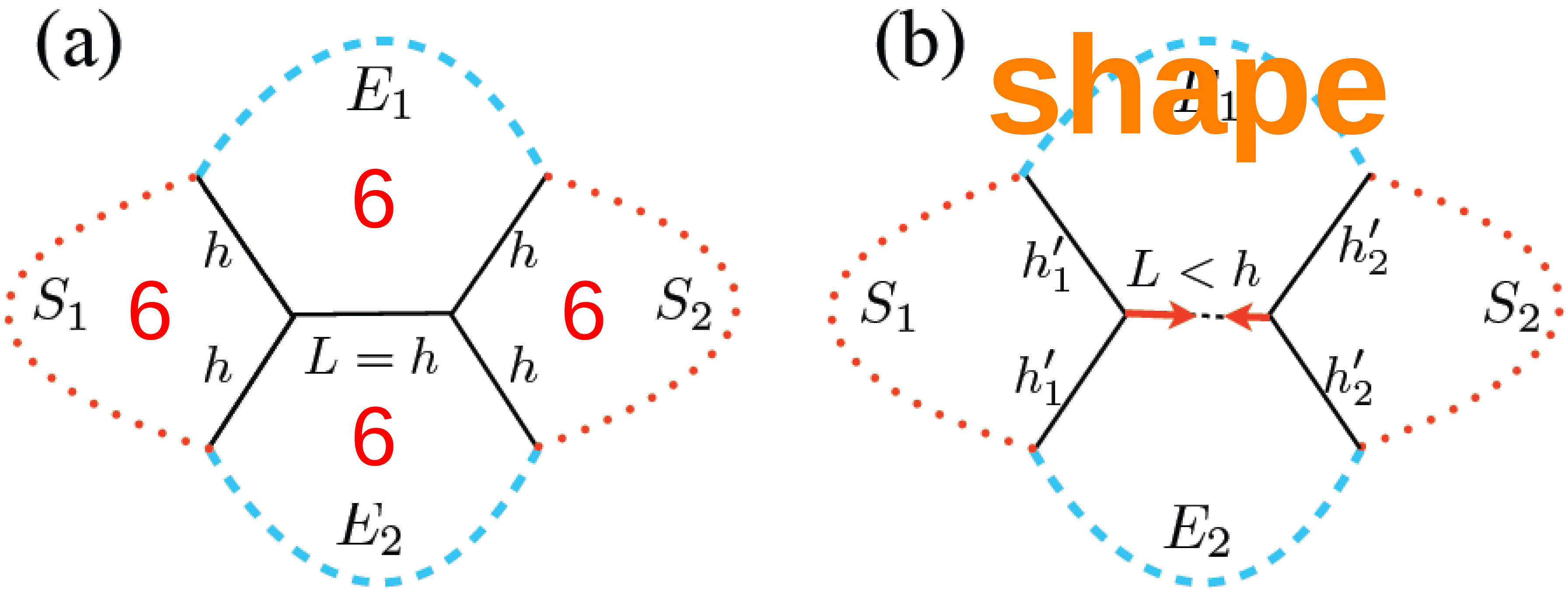
Energy is injected locally, all sites are probed

Simulation results: energy barrier depends on



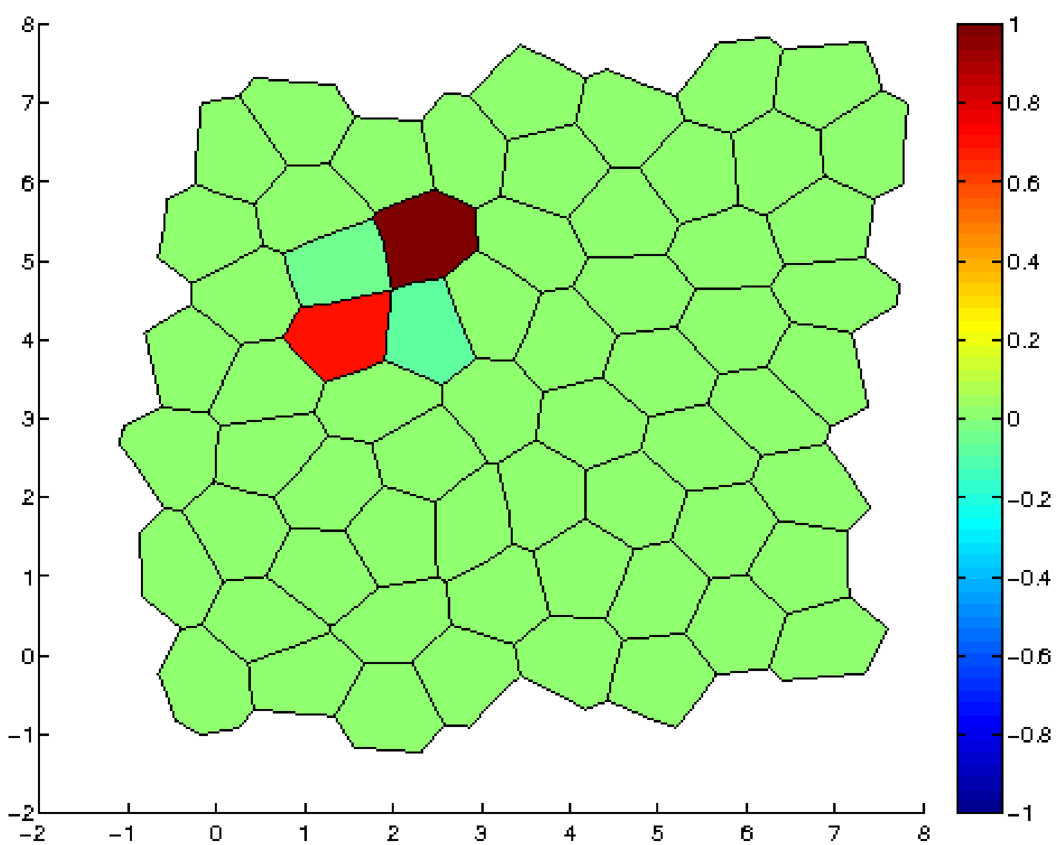


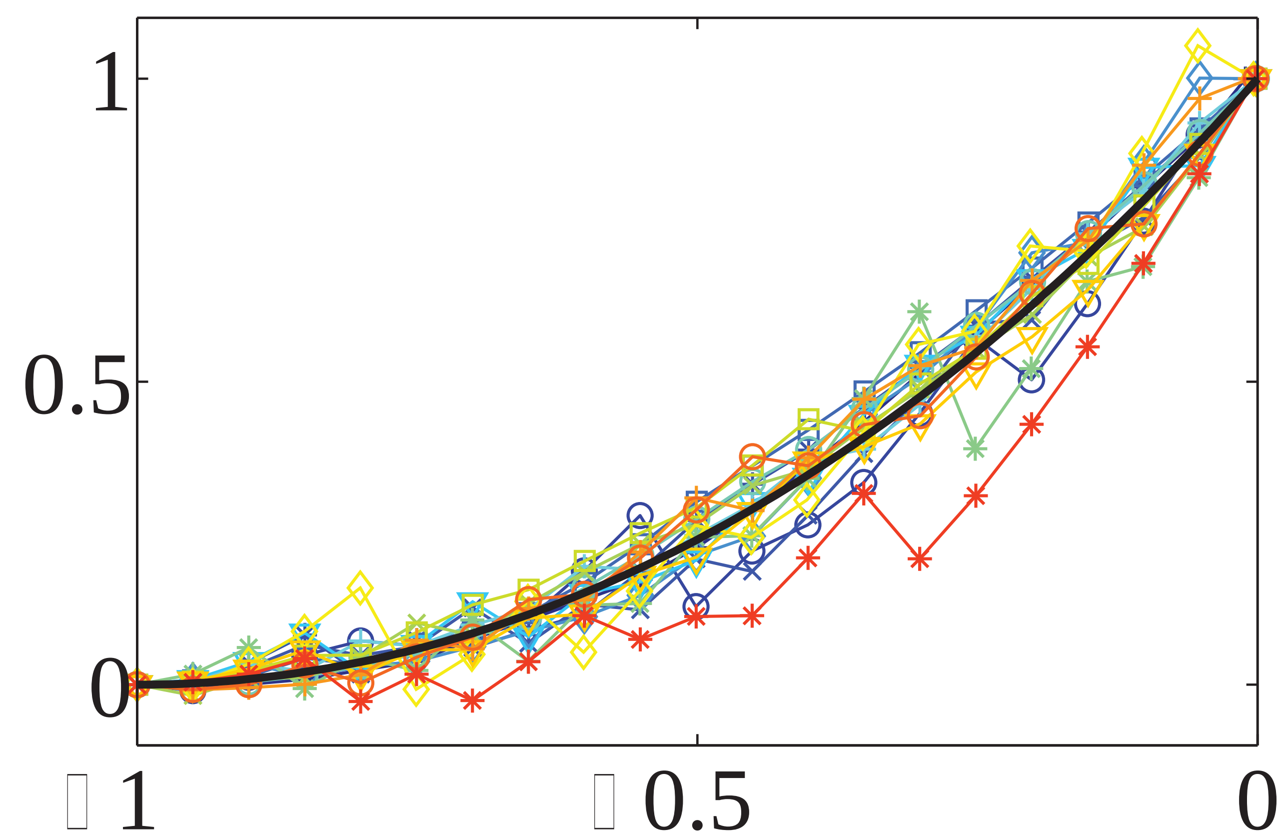
Analytic results: energy barrier shape



Mean field model:

- energy change is localized to 4 cells
- all cells have 6 sides (on average, required by Gauss-Bonnet Theorem)





Bi et al, to appear in Soft Matter Arxiv:1308.3891 (2014)

Analytic results: energy barrier statistics

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

Energy is quadratic in edge lengths or perimeters (verified in simulations)

$$\Delta u(L) \propto L^2$$

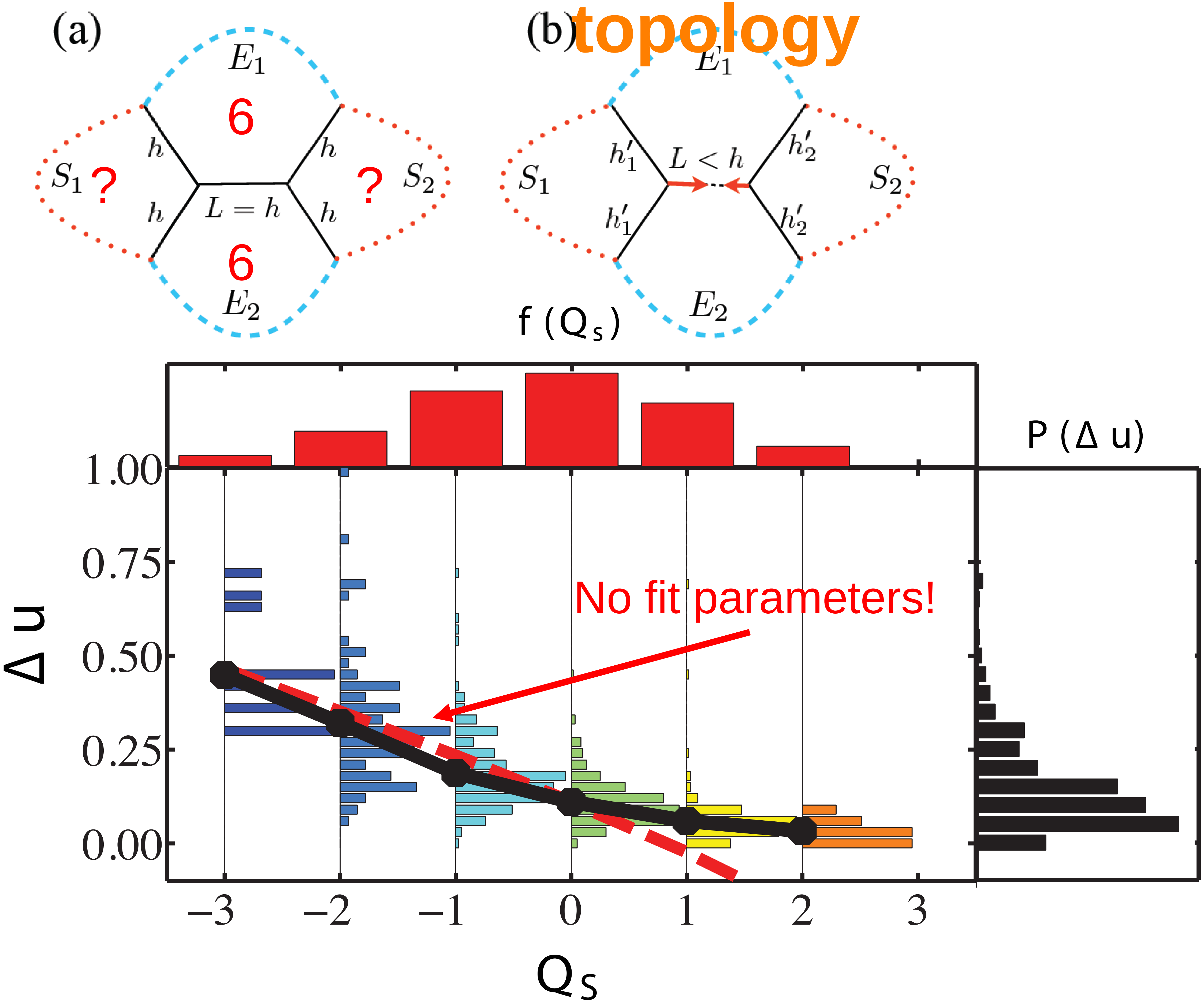
Metastable mechanical states have gaussian distribution of edge lengths (verified in simulations)

$$p(L) \propto \exp\left(\frac{(L - L_0)^2}{\sigma}\right)$$

Metastable mechanical states have gaussian distribution of edge lengths (verified in simulations)

$$p(\Delta u) \propto \exp\left(\frac{-\Delta u}{u^*}\right)$$

Analytic results: energy barrier depends on topology



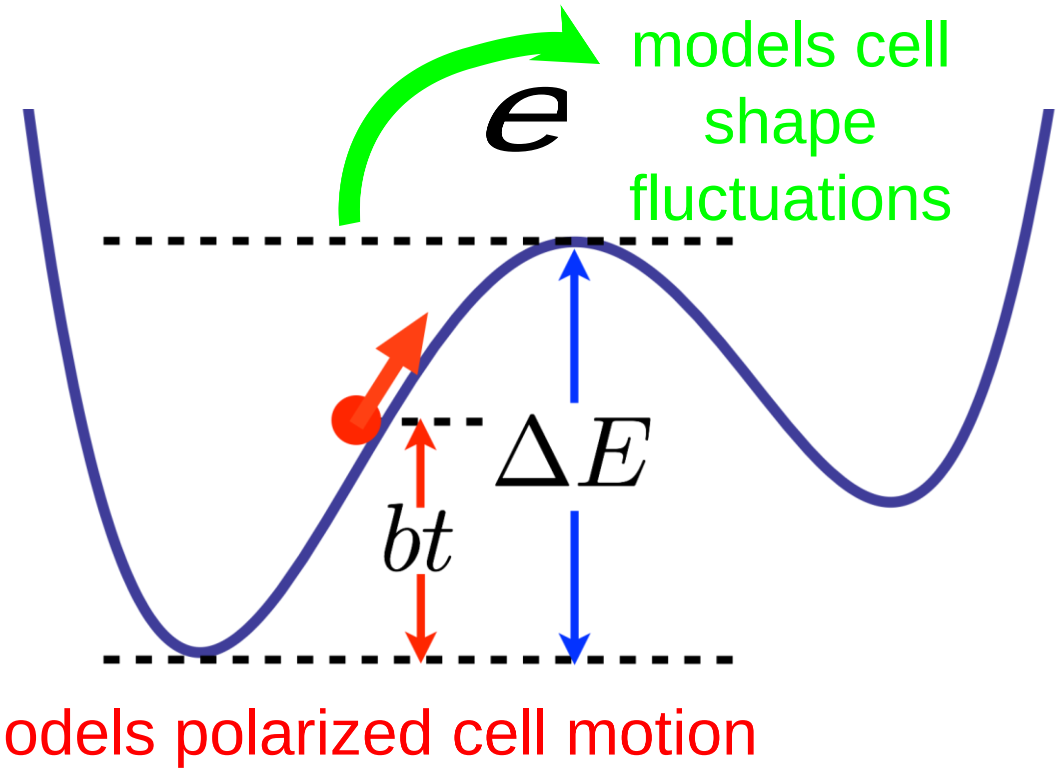
From energy barriers to cell migration:

Exponentially distributed energy landscape (with characteristic scale ε_0) can easily lead to glassy dynamics!

trap model: C. Monthus and J.-P. Bouchaud, J. Phys. A 29, 3847 (1996)

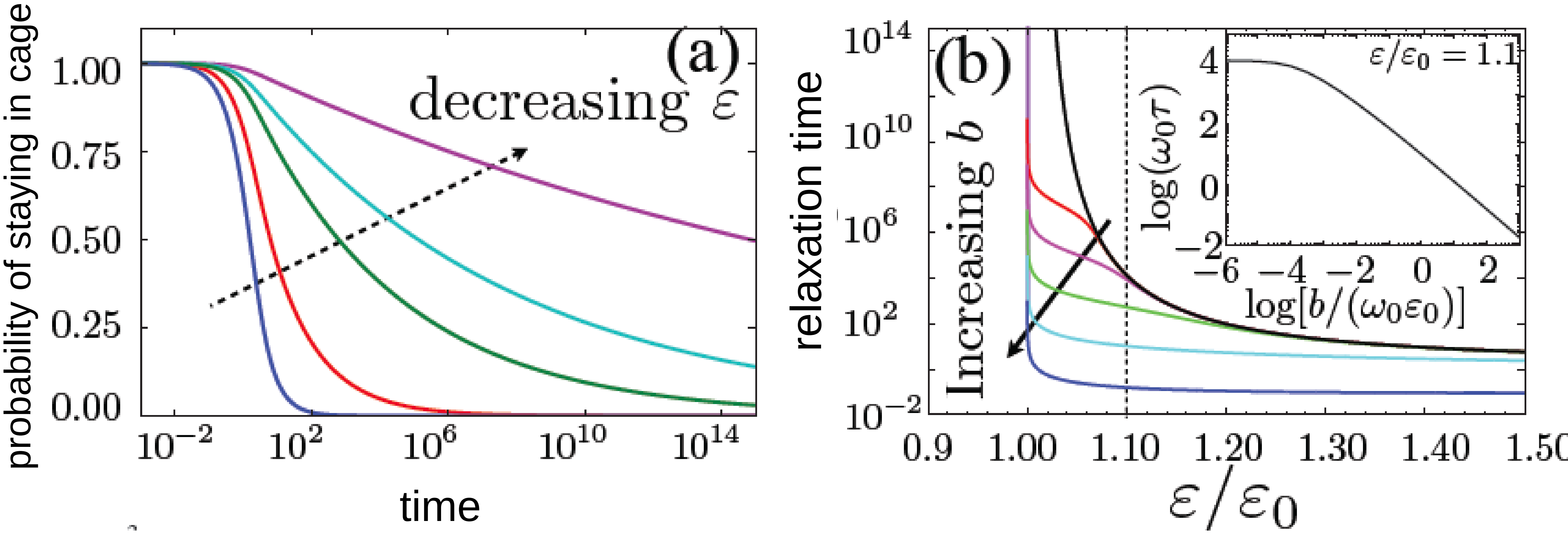
soft glassy rheology: Sollich et al, PRL 78 2020 (1997)

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



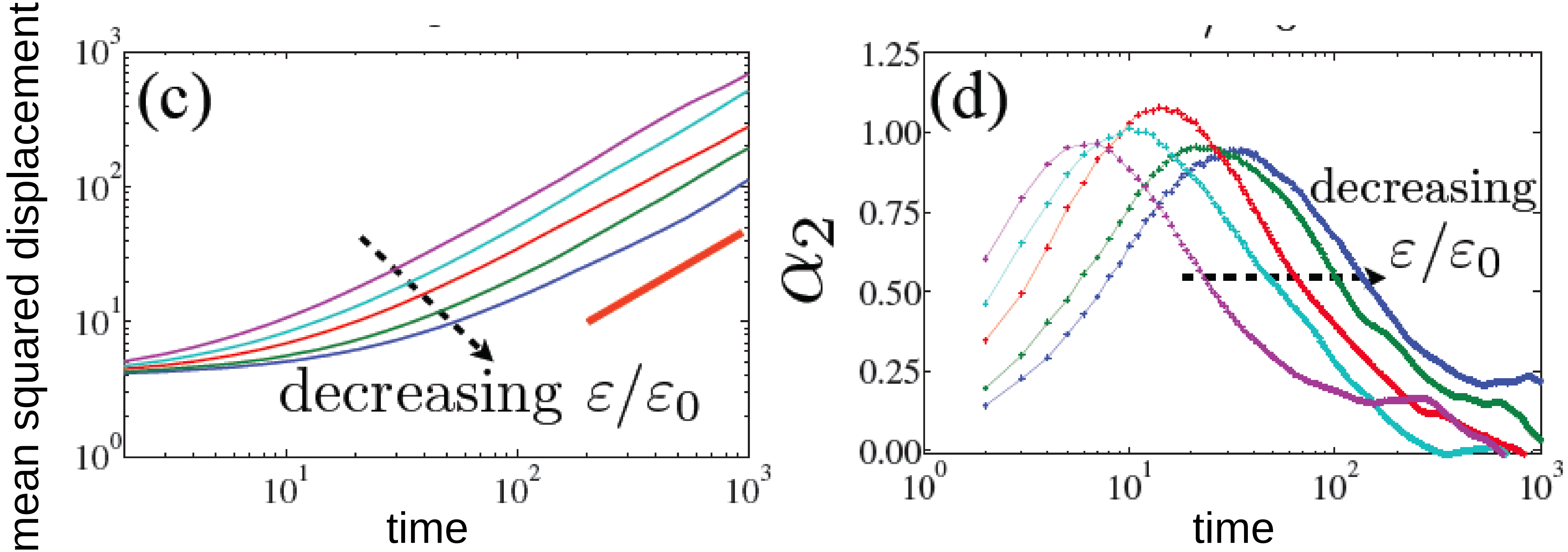
$$\frac{\partial}{\partial t} P(\Delta E, t) = -\omega_0 e^{-[\Delta E - bt]/\varepsilon} P(\Delta E, t) + \rho(\Delta E) \int d\Delta E' \omega_0 e^{-[\Delta E' - bt]/\varepsilon} P(\Delta E', t),$$

From energy barriers to cell migration:



Bi et al, to appear in *Soft Matter*, Arxiv:1308.3891 (2014)

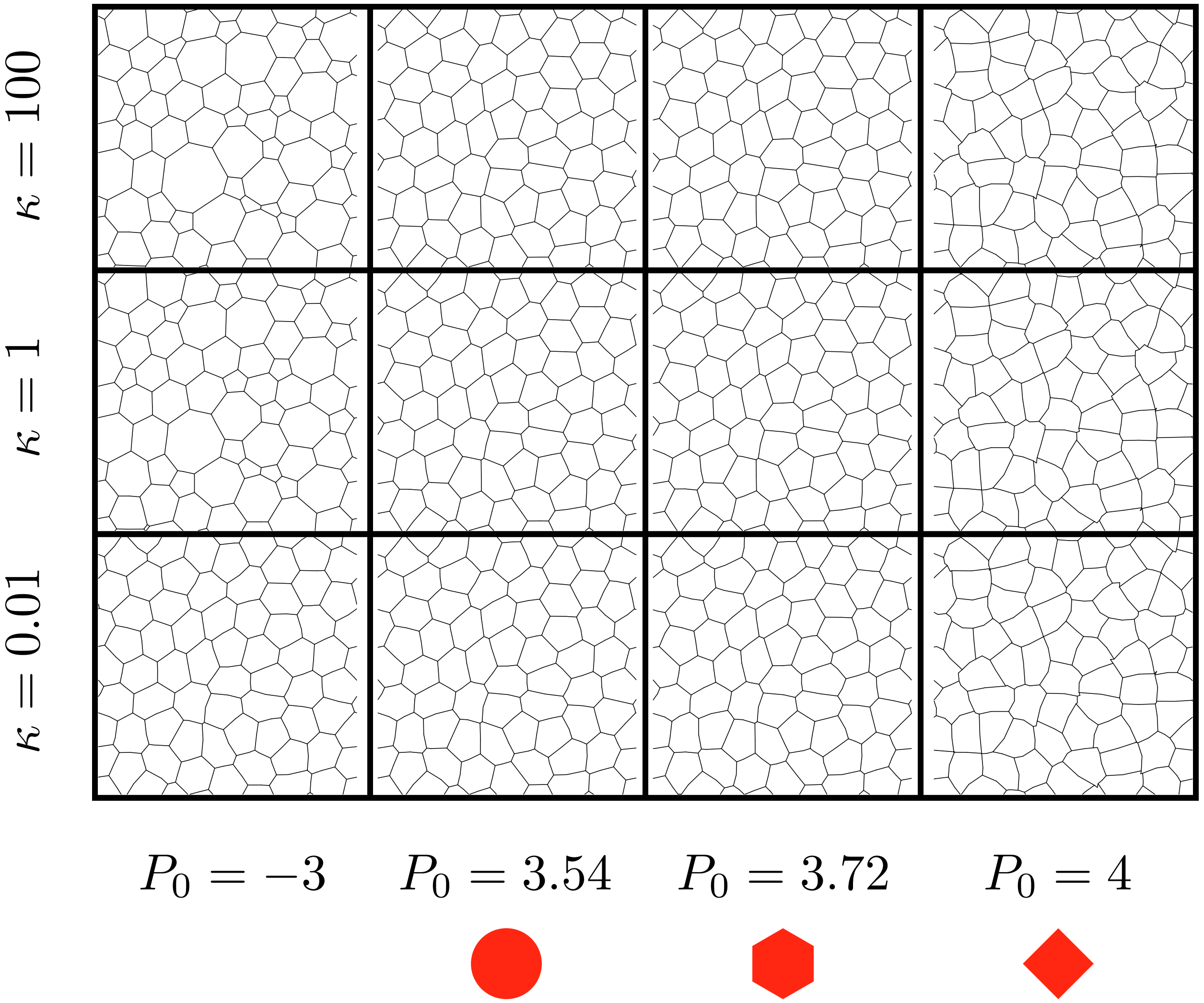
From energy barriers to cell migration:



Bi et al, to appear in *Soft Matter*, Arxiv:1308.3891 (2014)

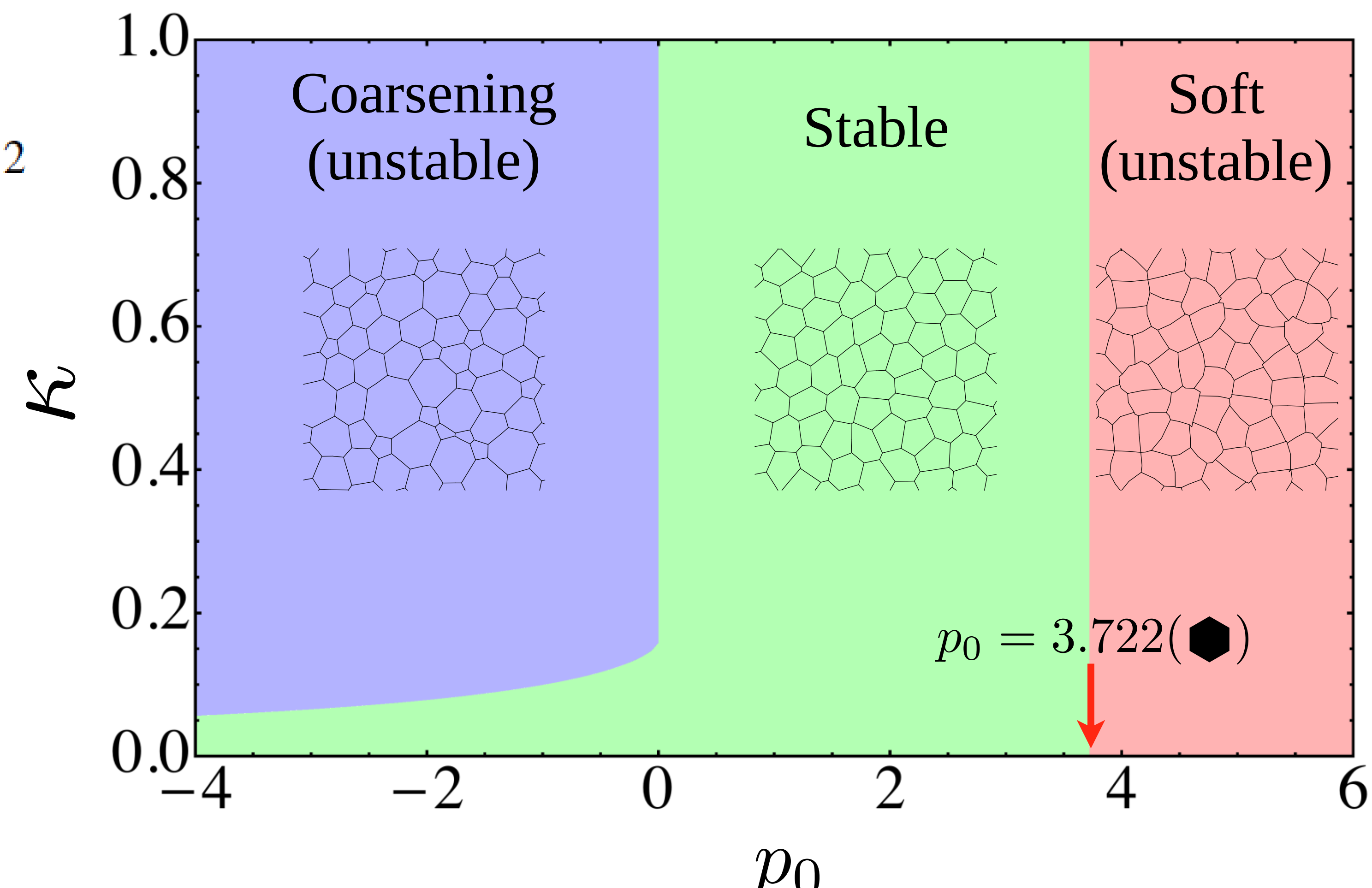
work in progress

Exploring the phase space of metastable states and energy barriers



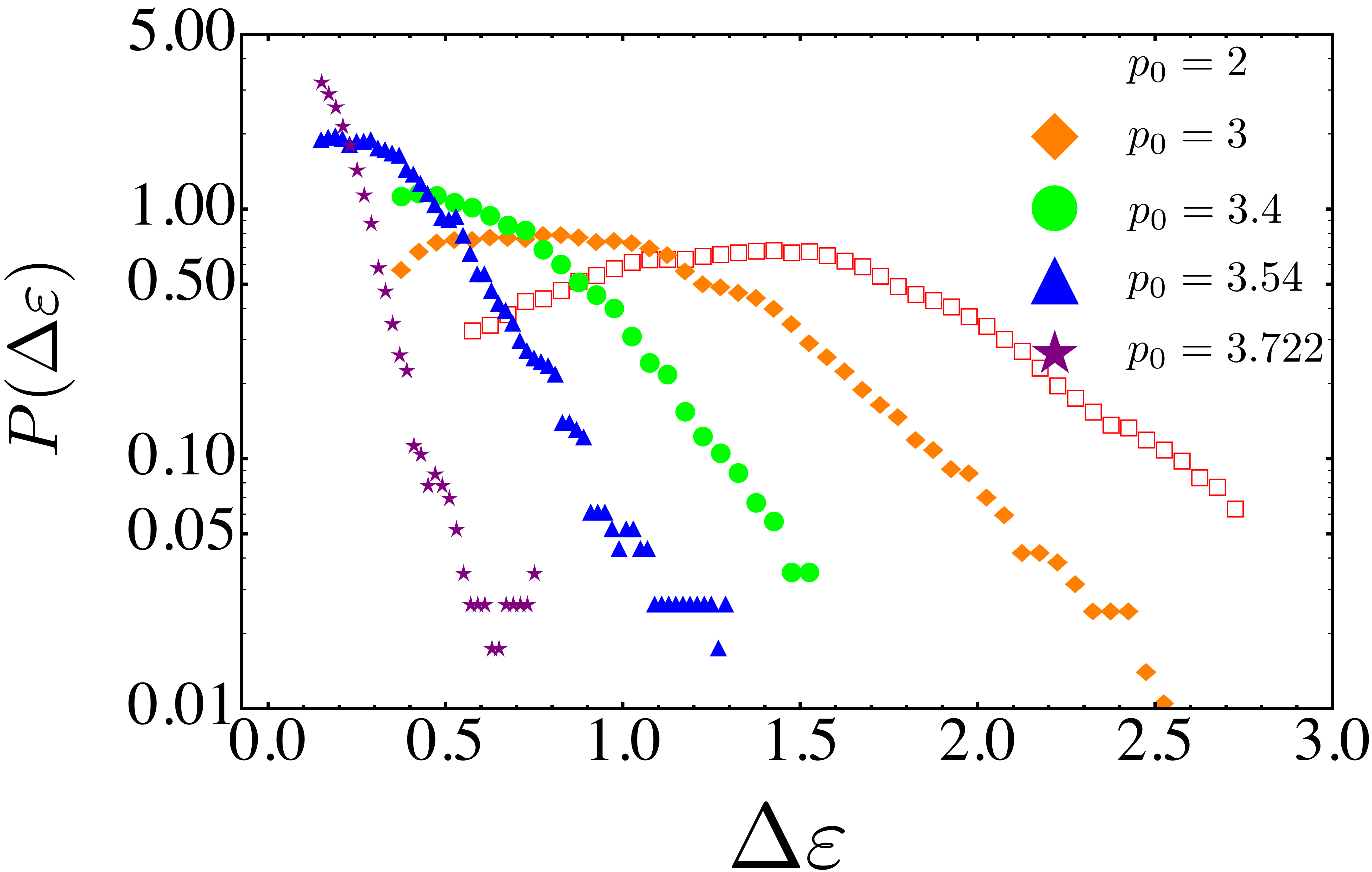
$$\varepsilon_{tot} = \frac{1}{\beta A_0}\sum_i^N E_i = \sum_i \left[(a_i - 1)^2 + \kappa(p_i - p_0)^2\right]$$

$$\kappa = \xi/(\beta A_0) \qquad p_0 = P_0/\sqrt{A_0}$$

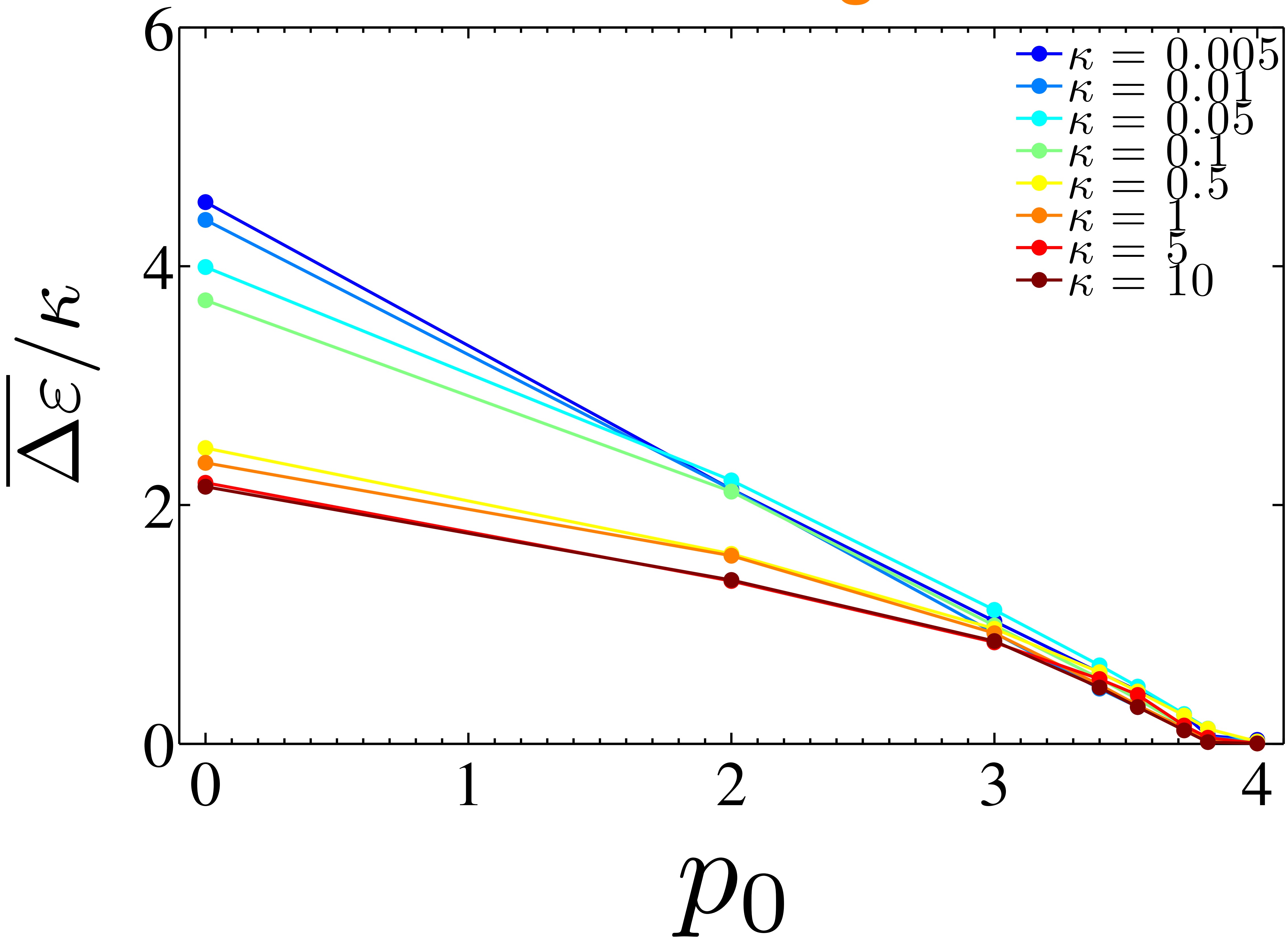


Ground states:
Staple et al EPJE 33 (2) 117 (2010)

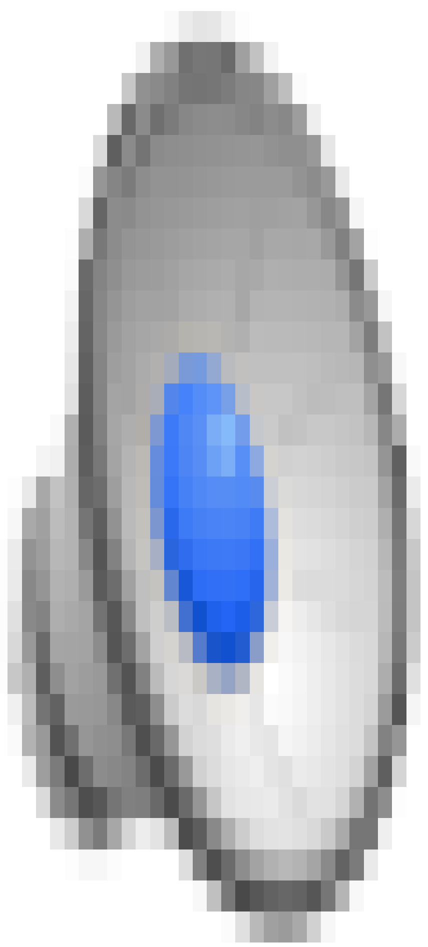
Exponential tail is robust



Scaling collapse of average energy barrier height



“Abnormal” cell embedded in normal cells



Conclusions

- Many tissue types show evidence of being close to a glass transition (wound healing, embryonic development)
- For dense (confluent) tissues, we have developed a framework for estimating energy barriers to cell rearrangements
  - self-propelled particle models are probably less useful at these densities
  - energy barriers are exponentially distributed
  - energy barriers depend strongly on a cell’s number of nearest neighbors (experimentally accessible predictions)
- We develop an SGR- or trap-like model to translate energy barriers into cell migration rates
- Our model predicts how changing single-cell properties changes cell migration rates

Schoetz et al J. Roy. Soc. Interface **10(89)**, 20130726 (2013)

Bi et al, to appear in *Soft Matter*, Arxiv:1308.3891 (2014)

Thanks so much for your attention!

Collaborators:

- Max Dapeng Bi (SU -- arriving at KITP in a month or so)
- Jen Schwarz (SU), Jorge Lopez (SU), Eva-Mara Schoetz (UCSD), Marcus Lanio(Princeton), Jared Talbot(Princeton)

Funding:

- NSF BMMB CMMI-1334611
- NSF DMR CMMT-1352184

Graduate fellowships available at Syracuse:

- IGERT program on soft interfaces (30K/year for first two years)
- Early engagement in interdisciplinary research

http://www.phy.syr.edu/~mmanning/