# Glassy behavior in biological tissues

Complexity in Mechanics
KITP conference
UC Santa Barbara
October 22, 2014

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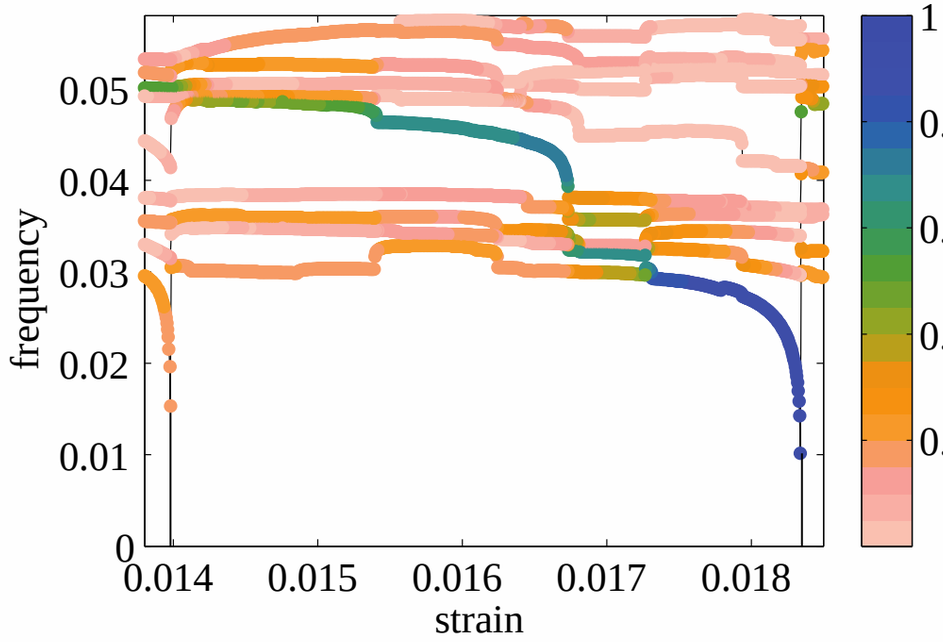
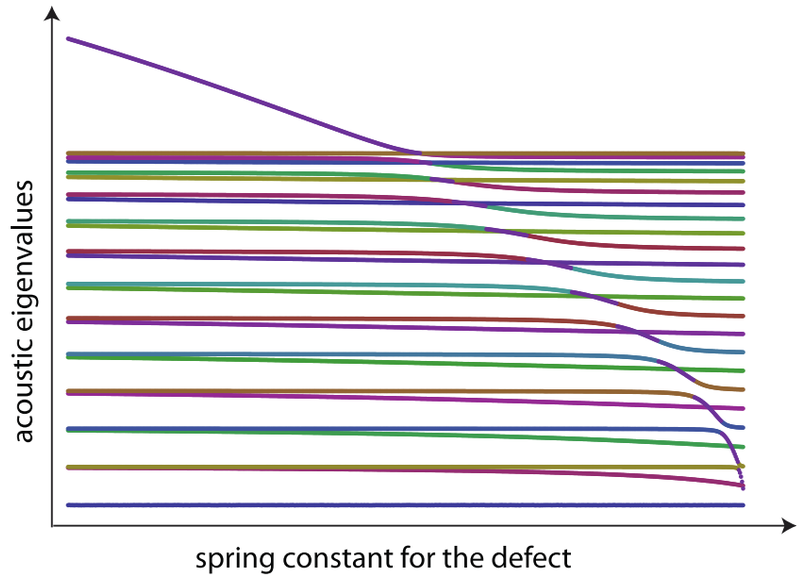
10 um

# Defects and vibrational modes in disordered solids

- Eigenfuctions are not as useful away from instability
- Instead, find “flow defects” or “soft spots” or “STZs”
- A new and improved algorithm for identifying truly localized soft spots and energy barriers
  - long-ranged elastic tails generate lower energy barriers
- A random matrix definition of the boson peak




Recorded KITP talk on this stuff http://online.kitp.ucsb.edu Avalanches (Oct 10th)

# Thanks, Jim!

Manning group

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SU Soft Matter

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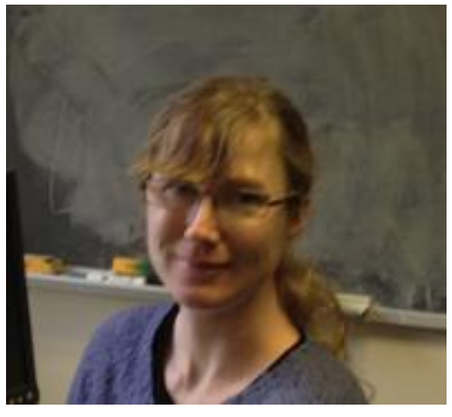
Jennifer Schwartz

Cristina Marchetti

Xingbo Yang



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Marcus Lanio (Princeton)

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Henderson Group (Syracuse Biomaterials Institute)

Jay Henderson

Megan Brasch

Richard Baker

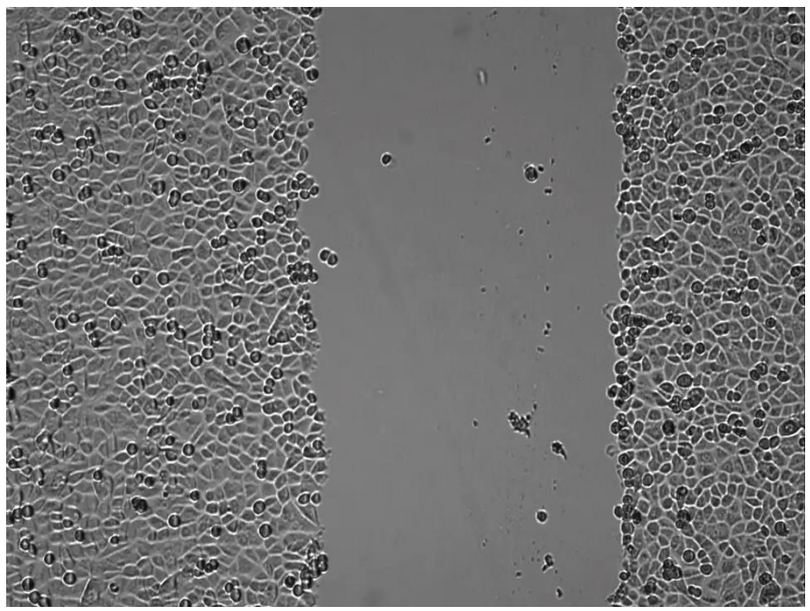
Turner Group(SUNY Upstate)

Chris Turner

Nick Deakin

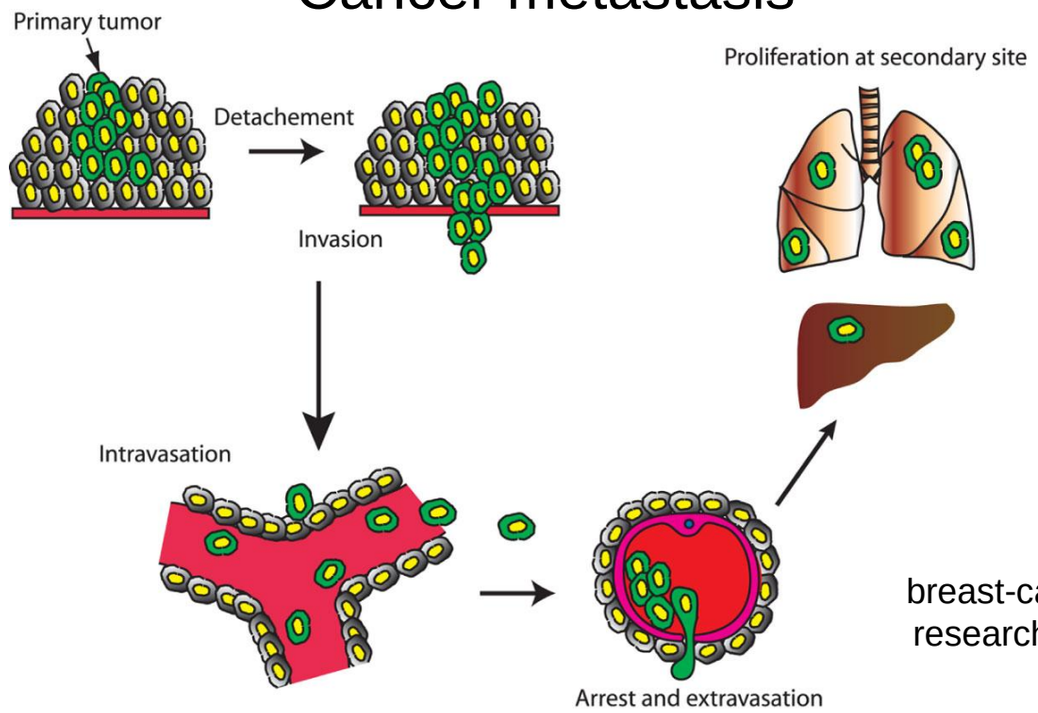
# Complexity in mechanics….

## Wound healing



youtube.com/watch?v=v9xq_GiRXeE

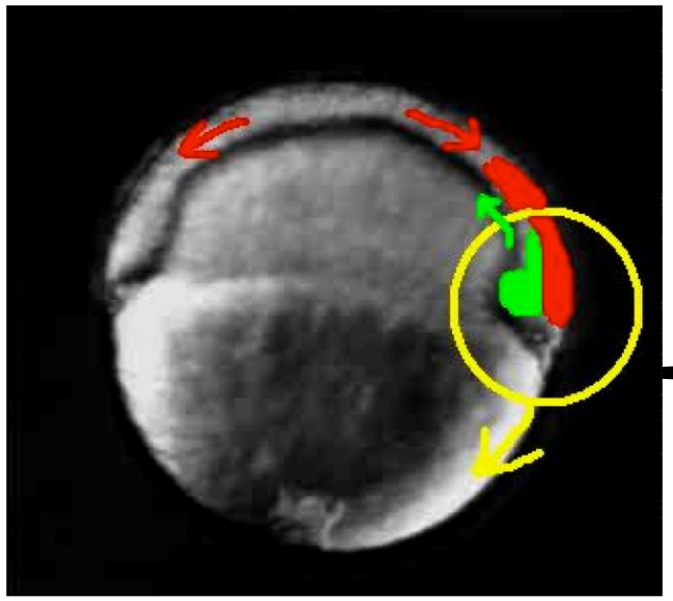
## Cancer metastasis



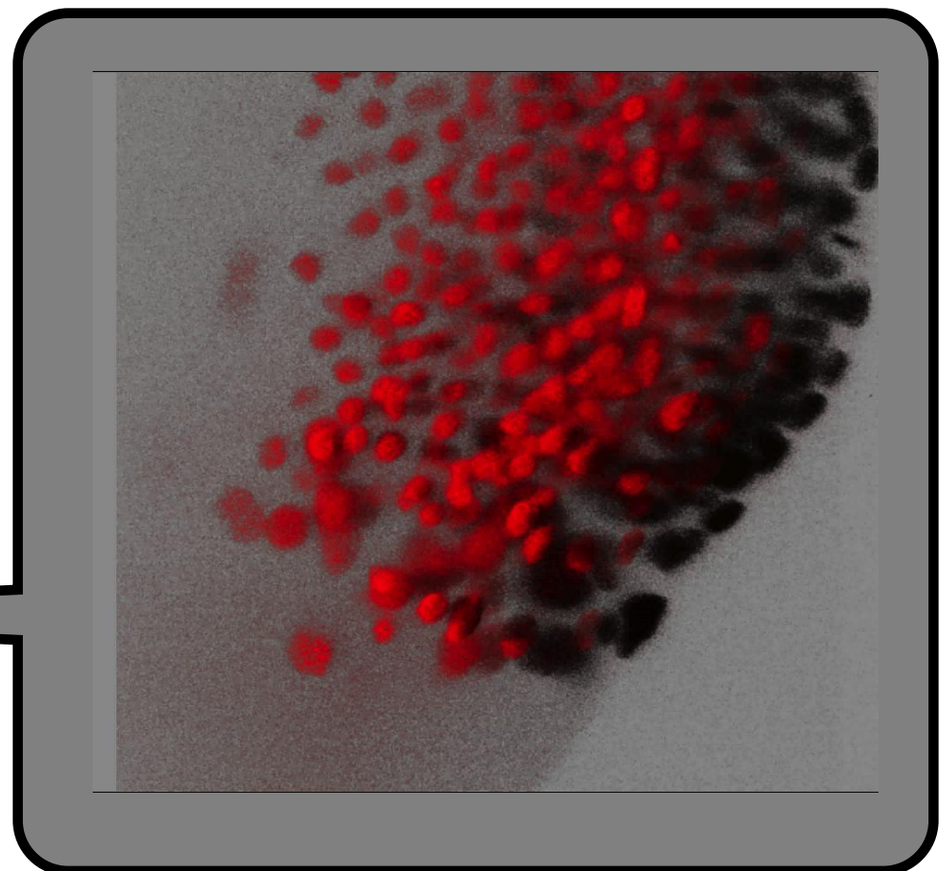

breast-cancer-research.com

## Embryonic development

Differential Adhesion Hypothesis:
Steinberg, Science 1962

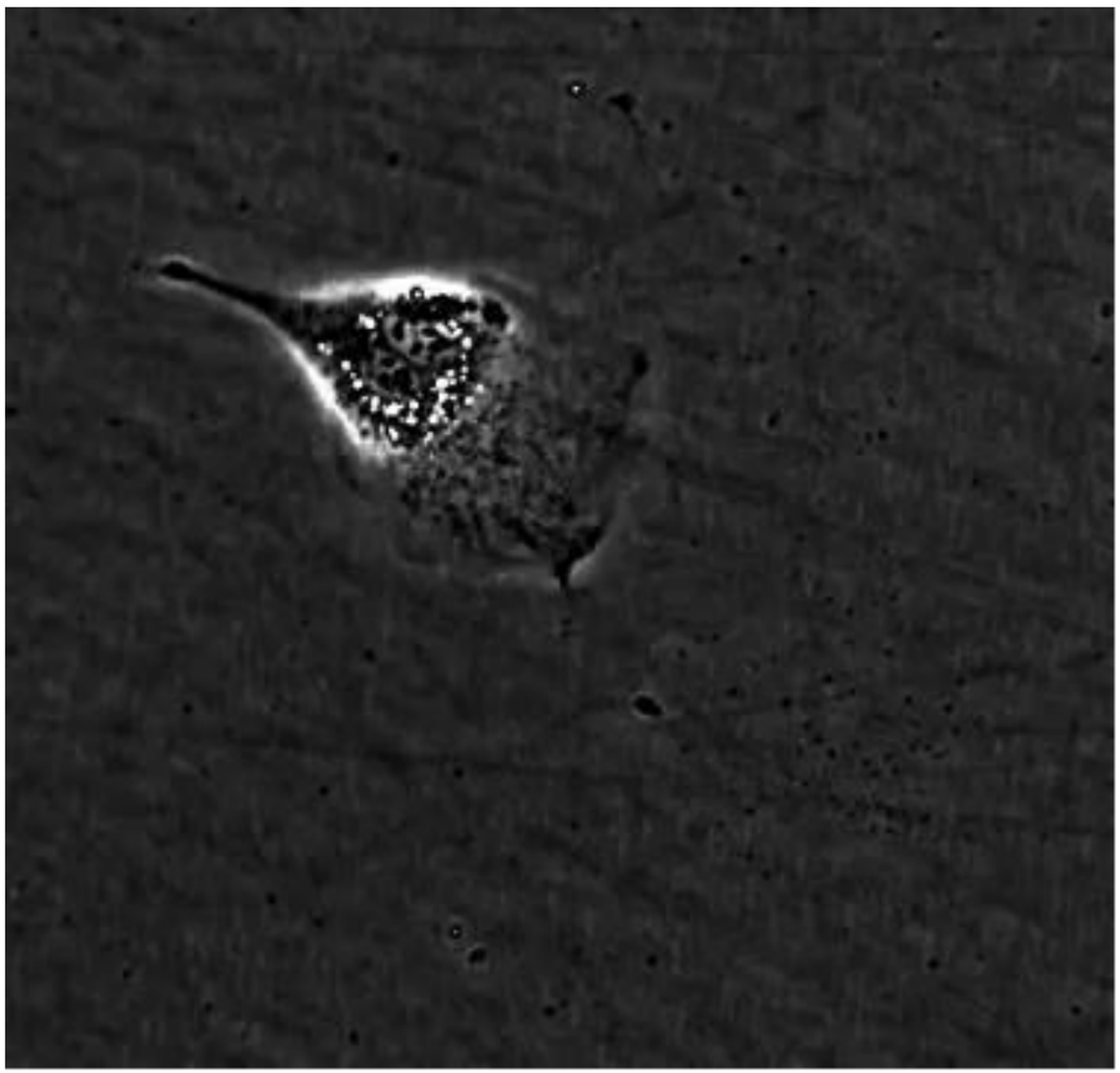


Schoetz 2008



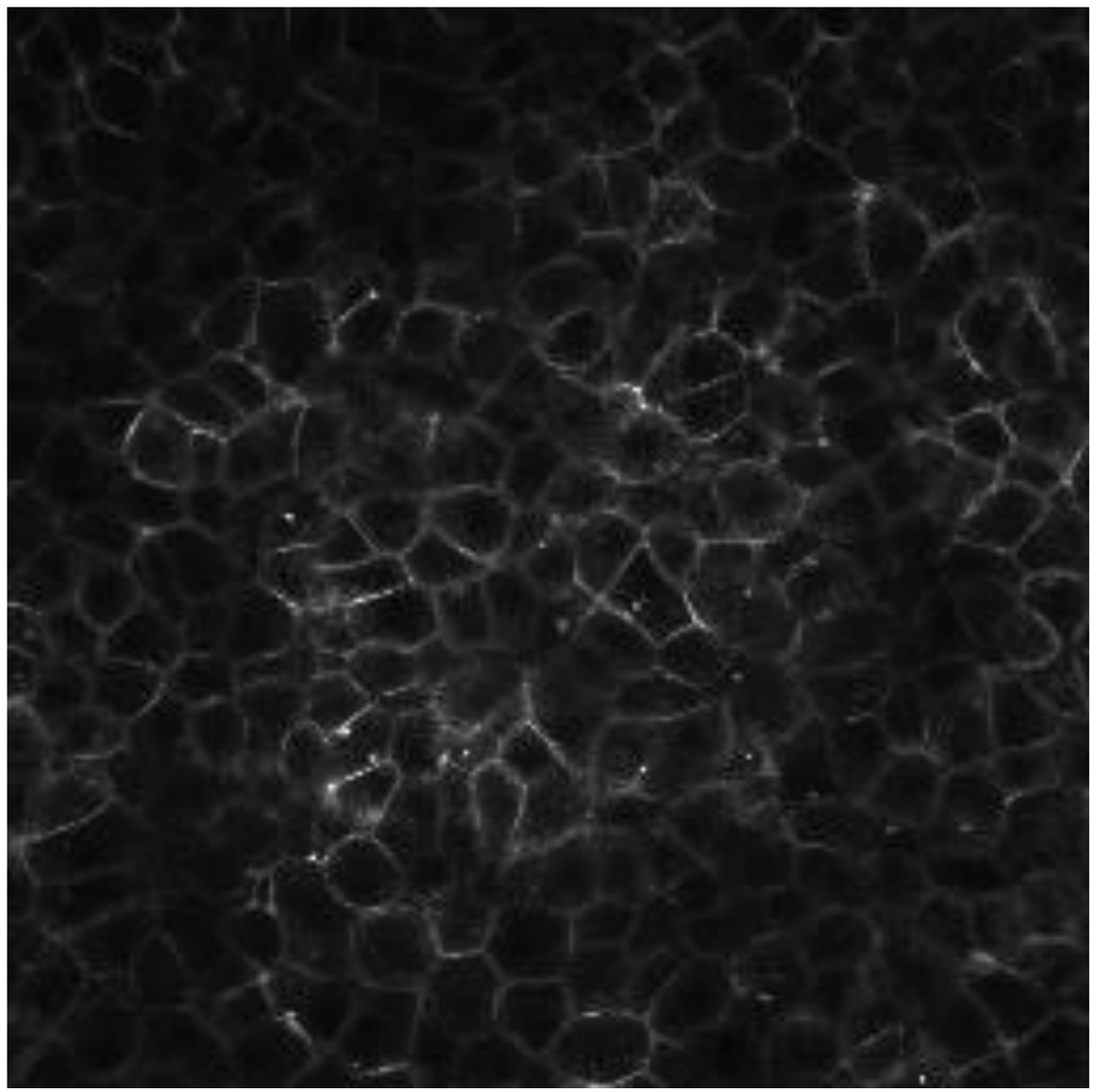
# How do cells move?

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



https://www.youtube.com/watch?v=FUlDCfFCTto

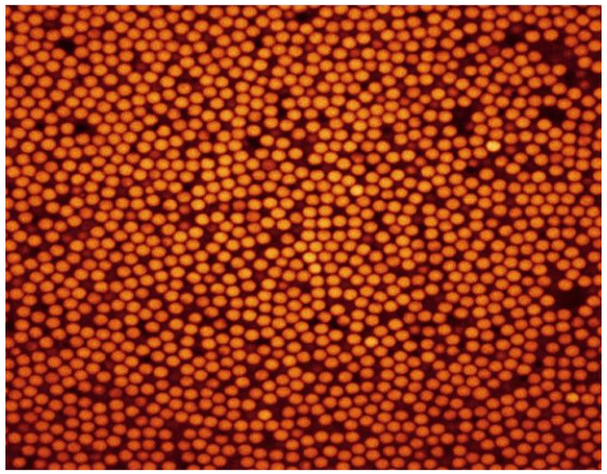
**Human bone cancer cell on fibronectin**



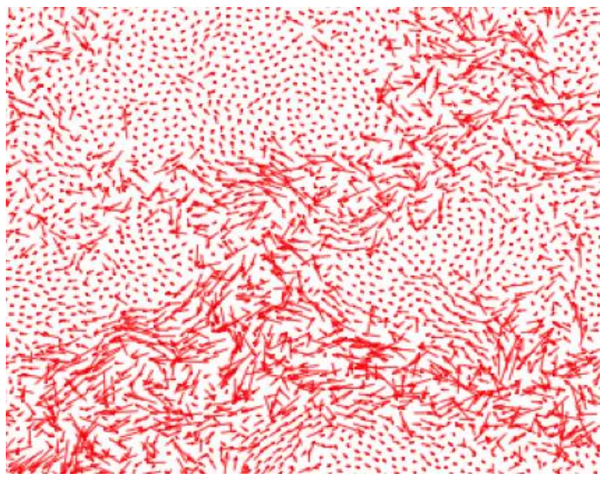
**Zebrafish embryo Schoetz Lab, UCSD**

# Dense (non-active) materials

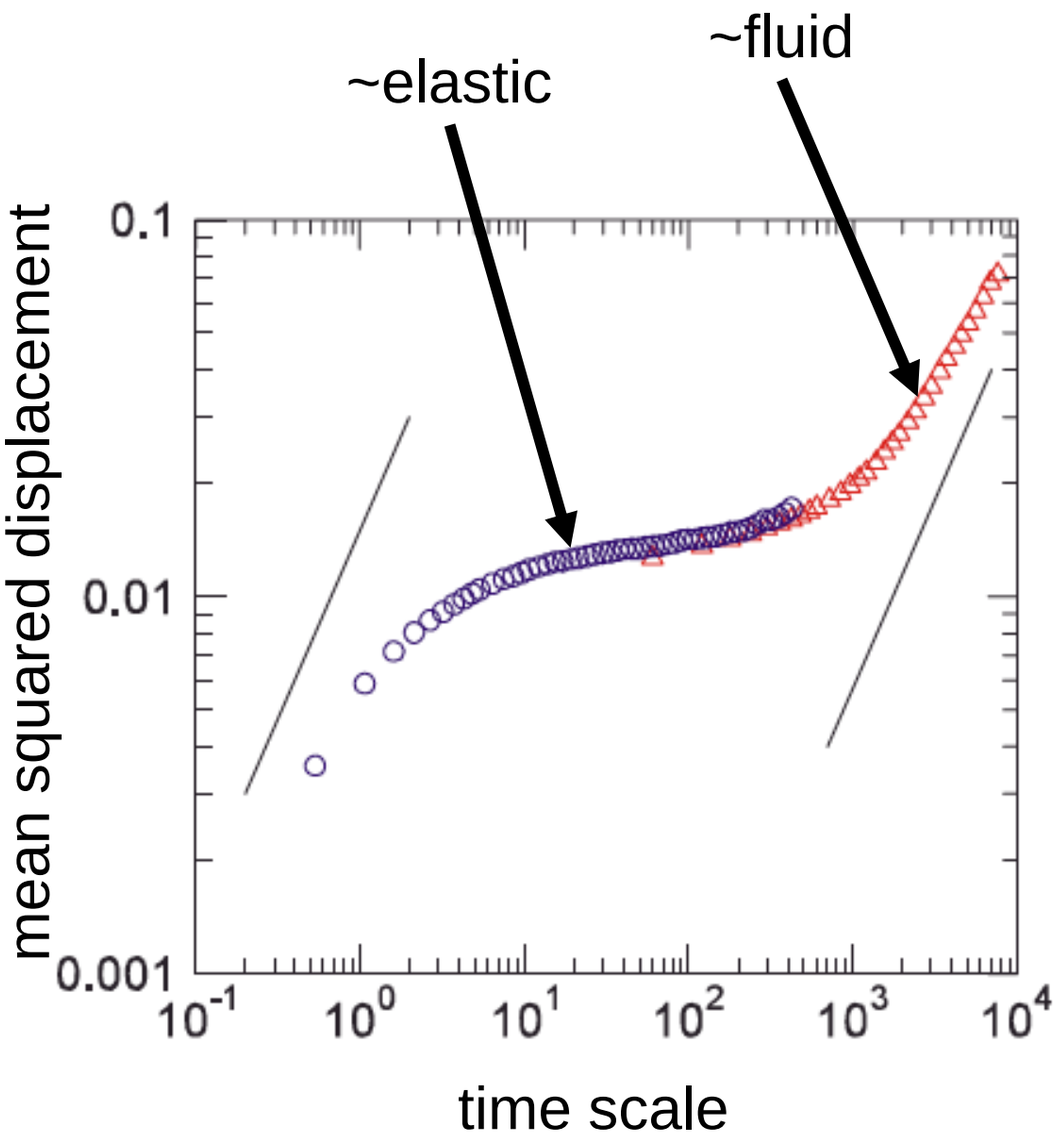
## Thermal



A colloidal glass.

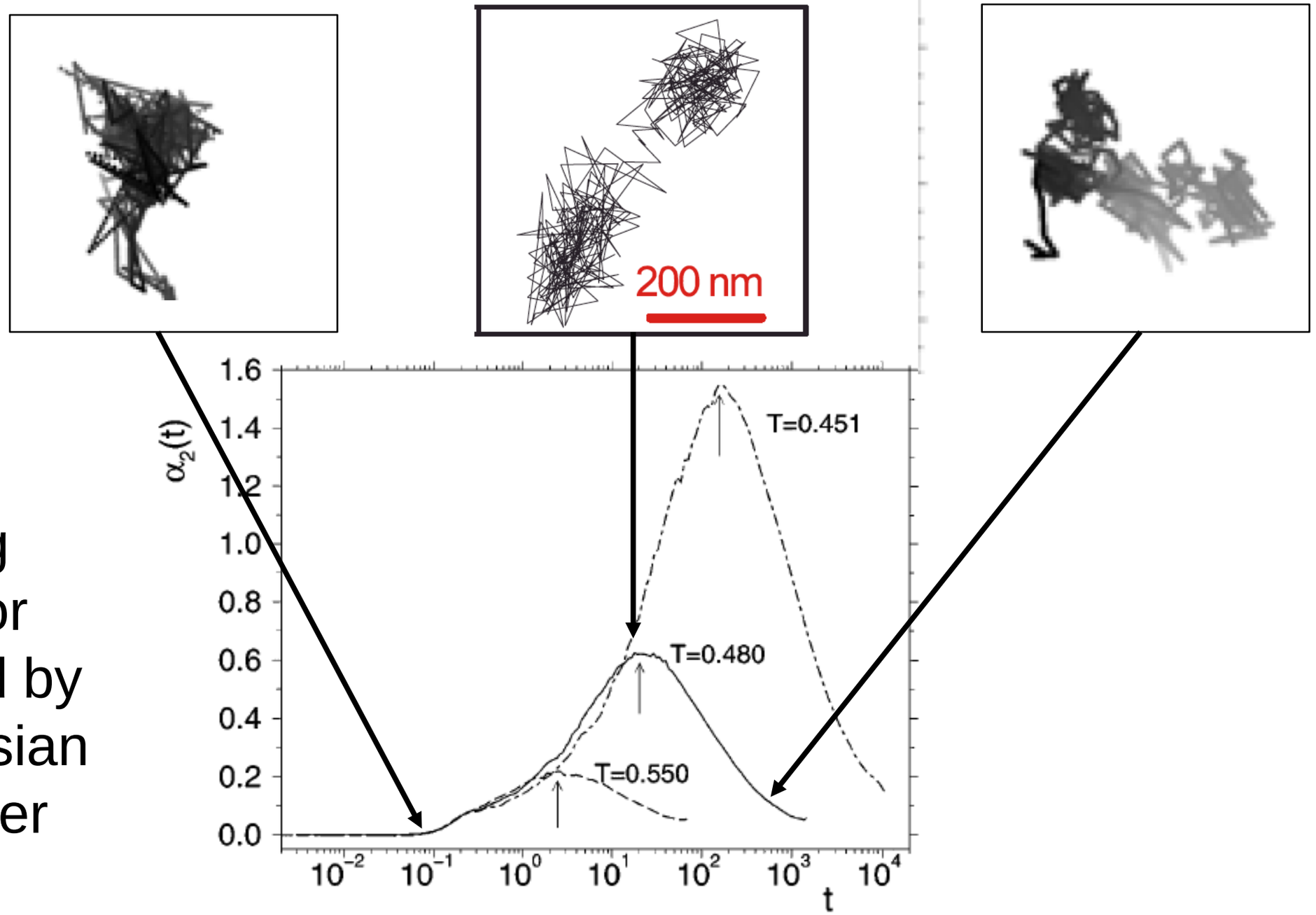


Displacement profile in simulation of a 2-d glass former.
**Berthier PRL 2011**



# Why do mechanical properties change with timescale?
# *non-active* materials

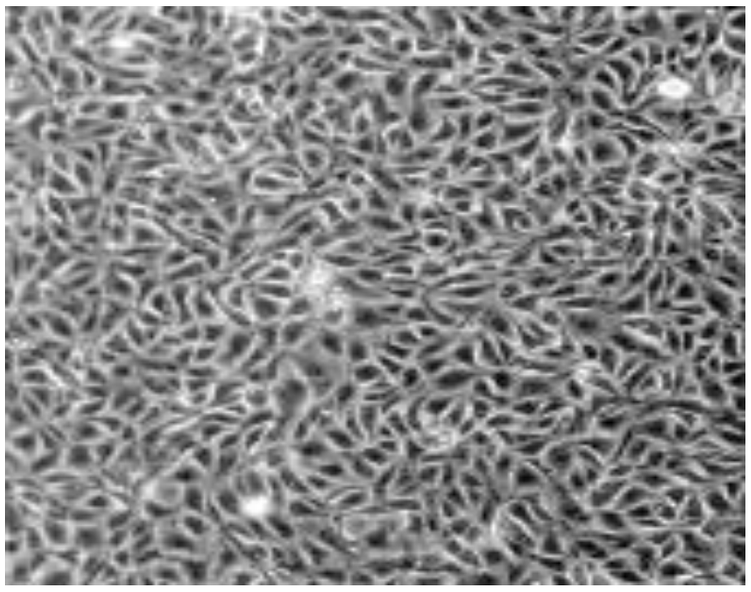
Weeks, Crocker, Weitz (2004)



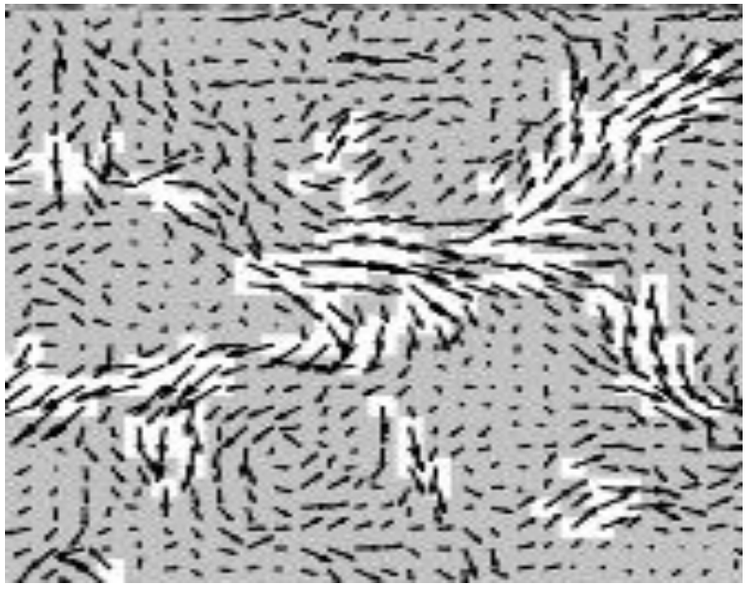

Caging behavior measured by non-gaussian parameter

Kob et al, PRL 79 15 2827 (1997)

# Dense biological tissues show the same features

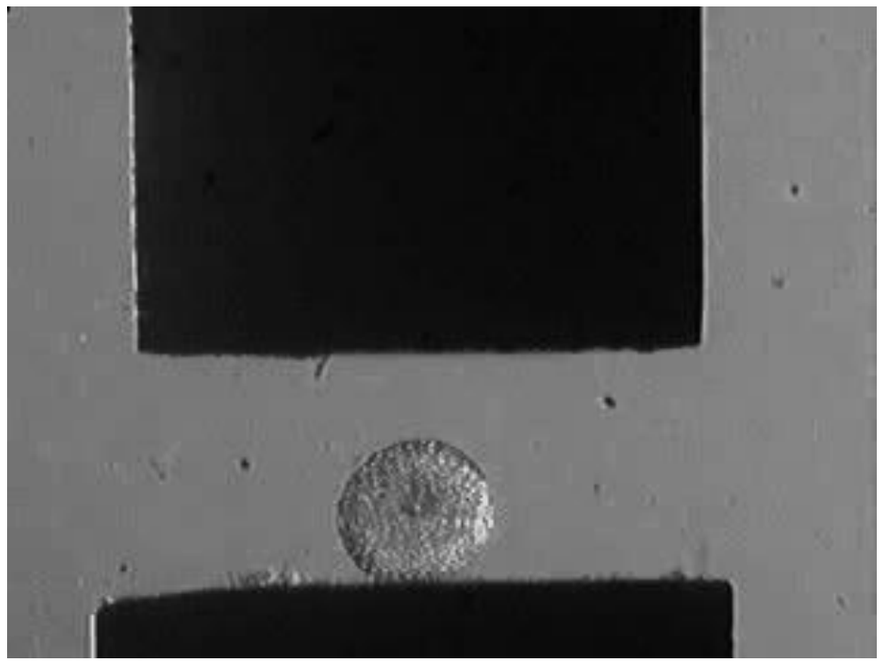


Madin-Darby canine kidney (MDCK) cells forming a 2-d confluent layer.
**Angelini et al PNAS 2010**

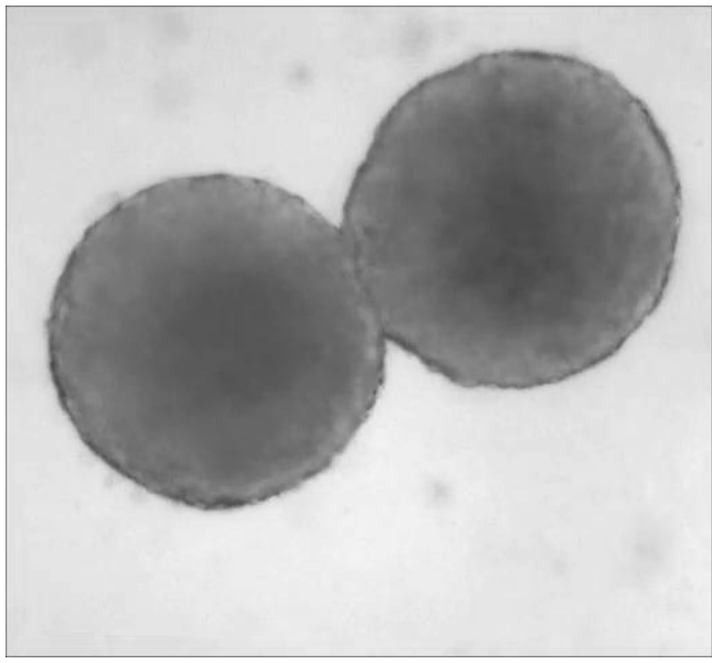


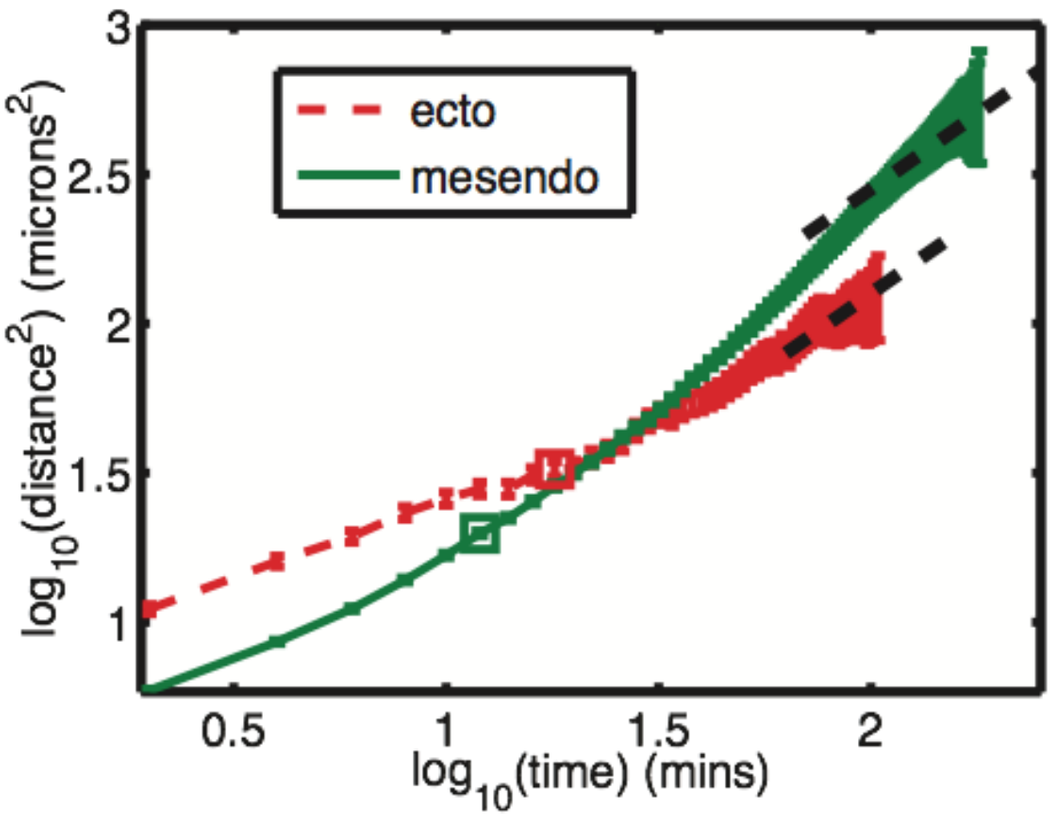
Velocity profile of cells show the spatially heterogeneous pattern in MDCK tissue.

timescale ~ seconds



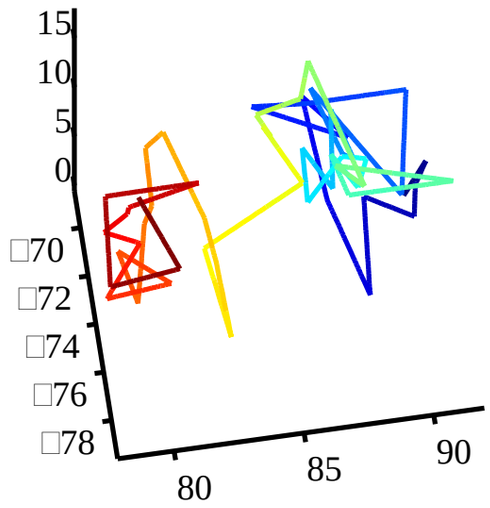
timescale ~ hours

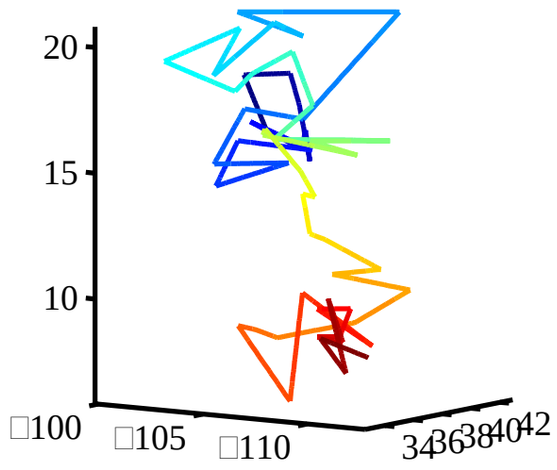


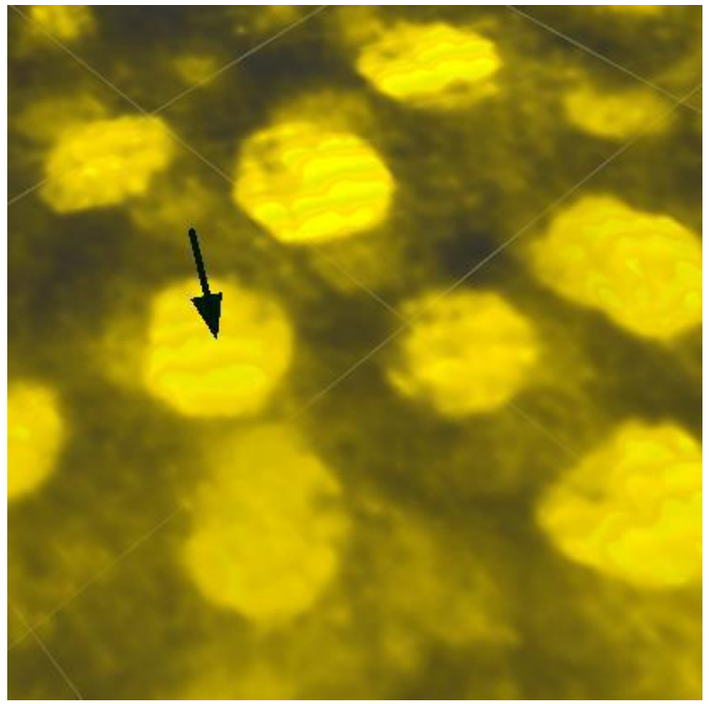


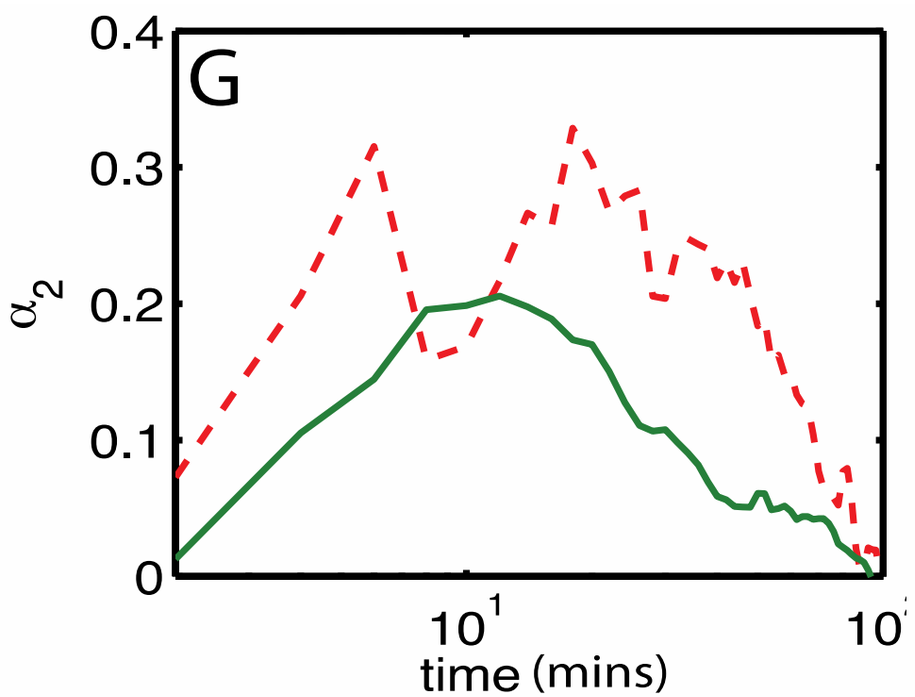

Schoetz, Lanio, Talbot, MLM J. R. Soc. Interface **10(89)**, 20130726 (2013)

# Why do mechanical properties change with timescale?
# biological tissues



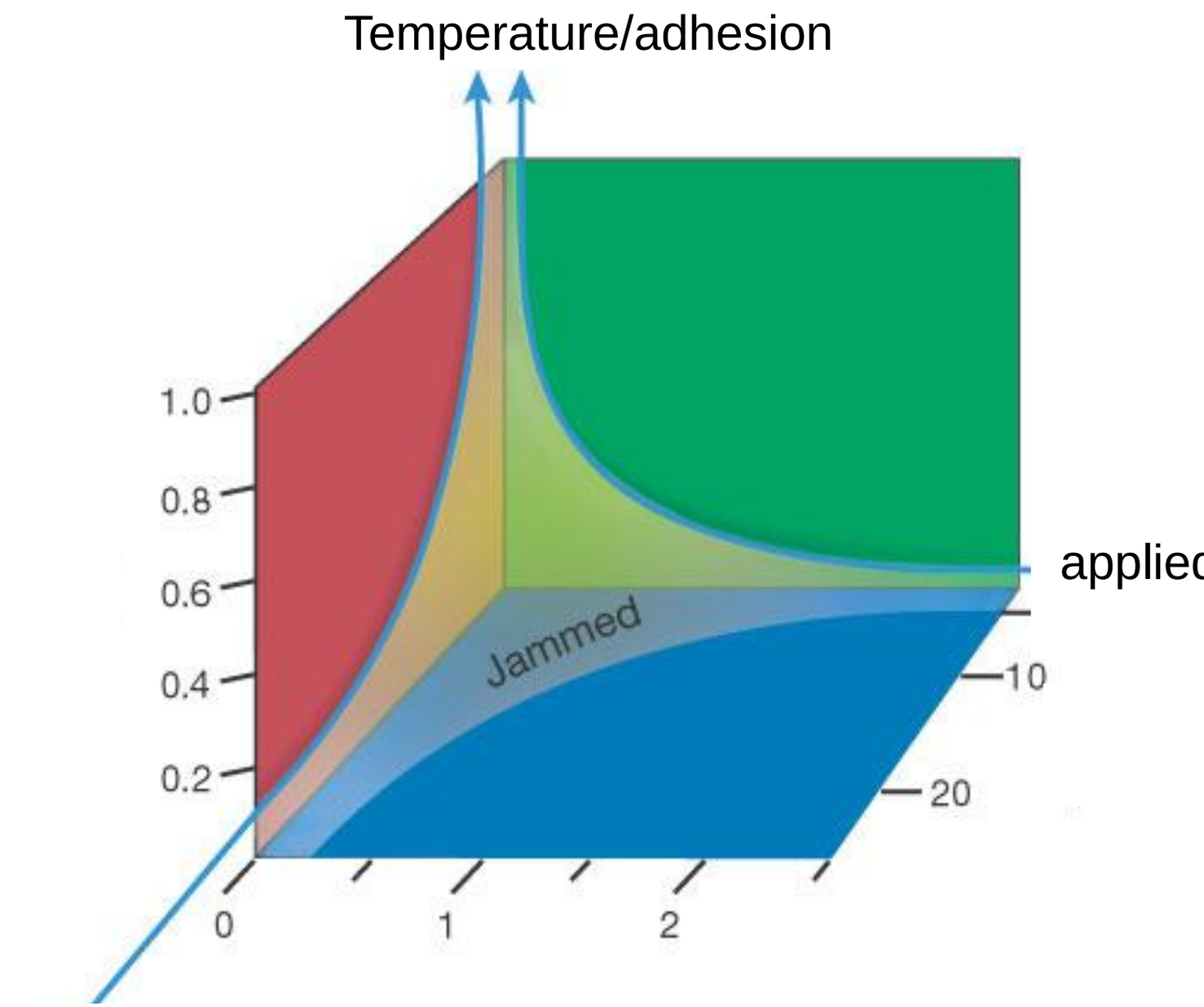





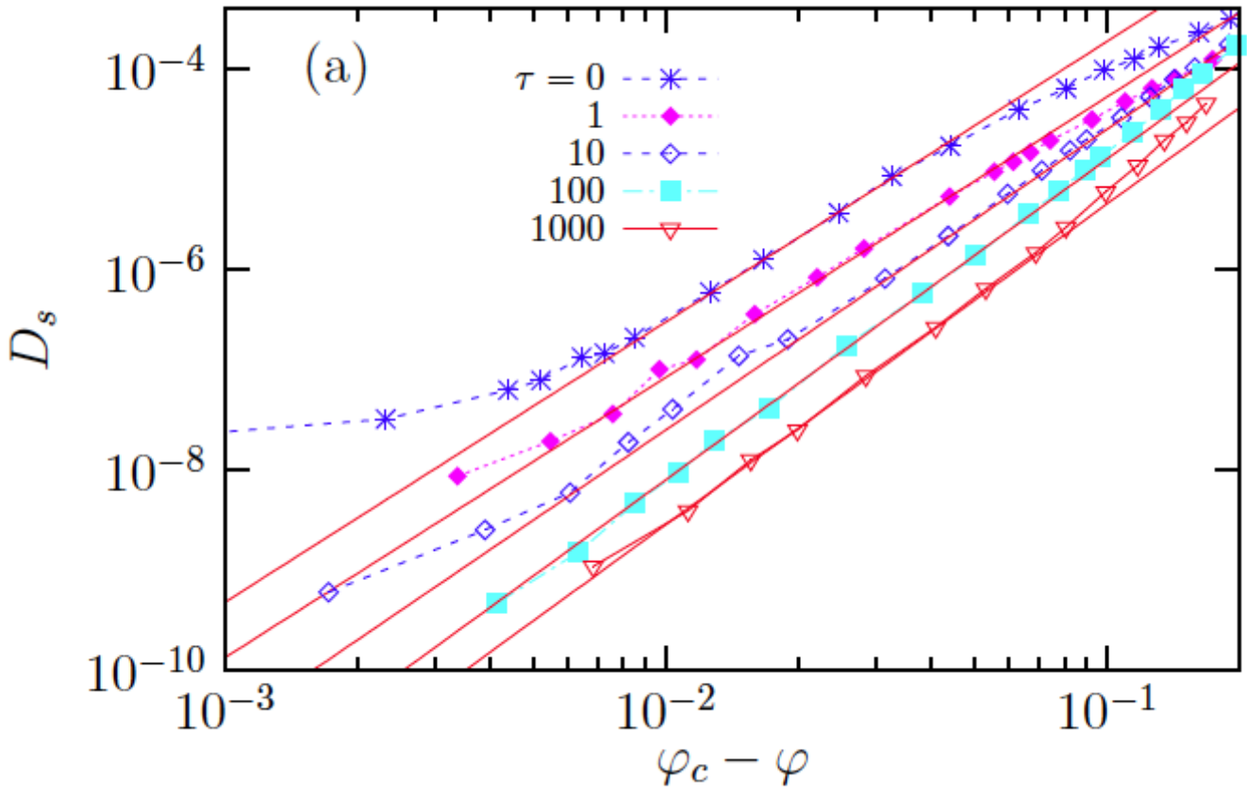

Schoetz, Lanio, Talbot, MLM J. R. Soc. Interface **10(89)**, 20130726 (2013)

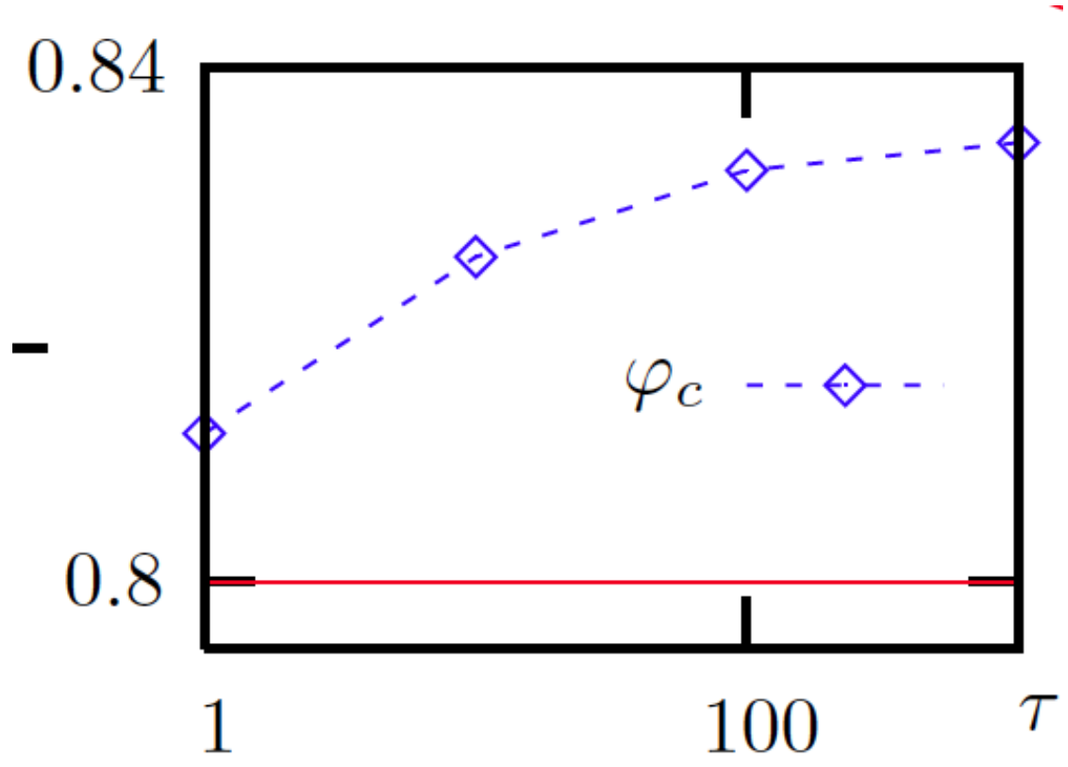
# Jamming phase diagram for inert matter




Trappe et al, *Nature* **411**, 772-775 (2001)

# Glass transition in self-propelled particle models is identical to adhesive colloids*

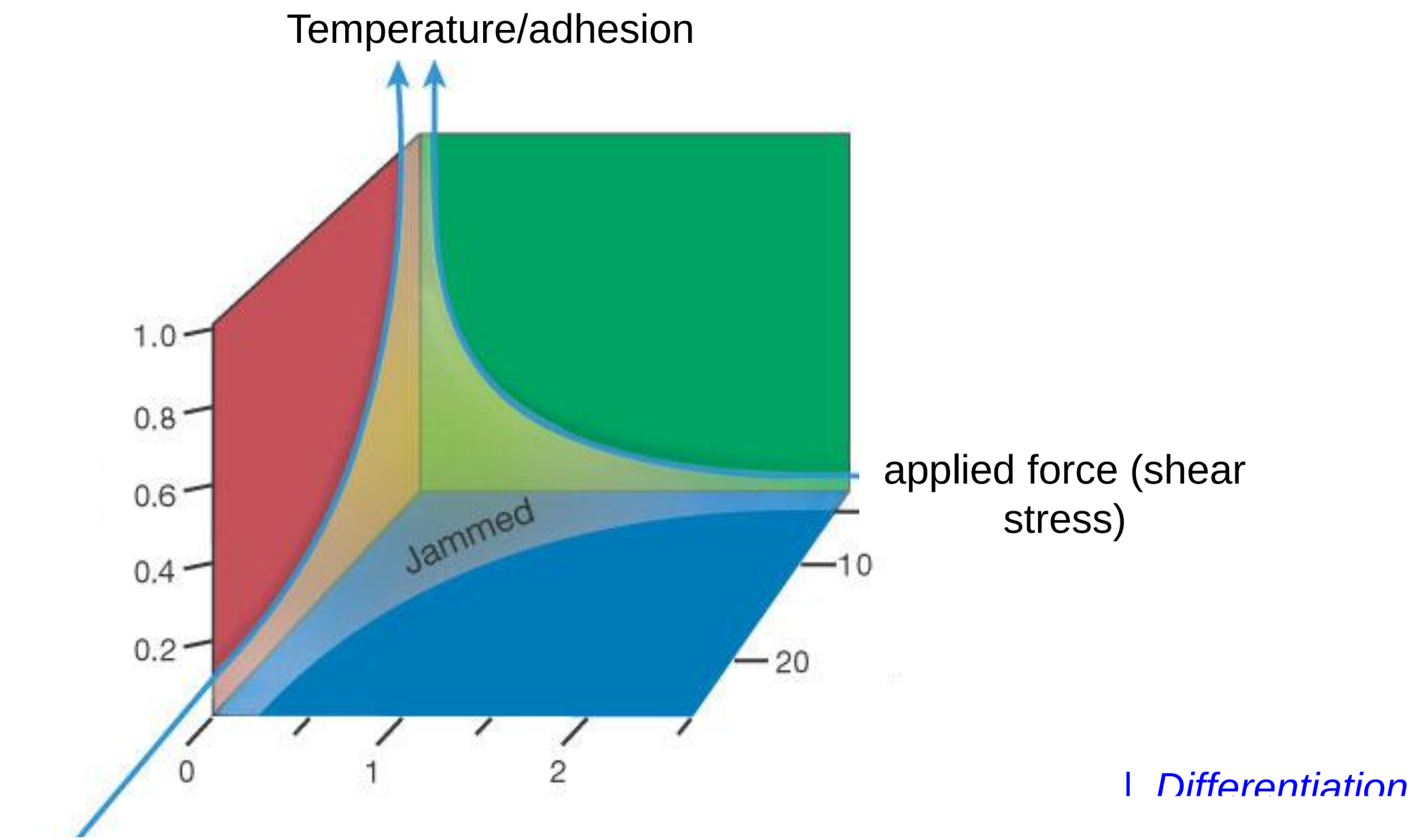



Berthier, PRL 112, 220602 (2014)

*almost: The critical packing fraction changes with the persistence time of the self propelled particles, because the activity generates an effective adhesion

# Jamming phase diagram for biological tissues




Trappe et al, *Nature* **411**, 772-775 (2001)

**Vector**
near jamming transition

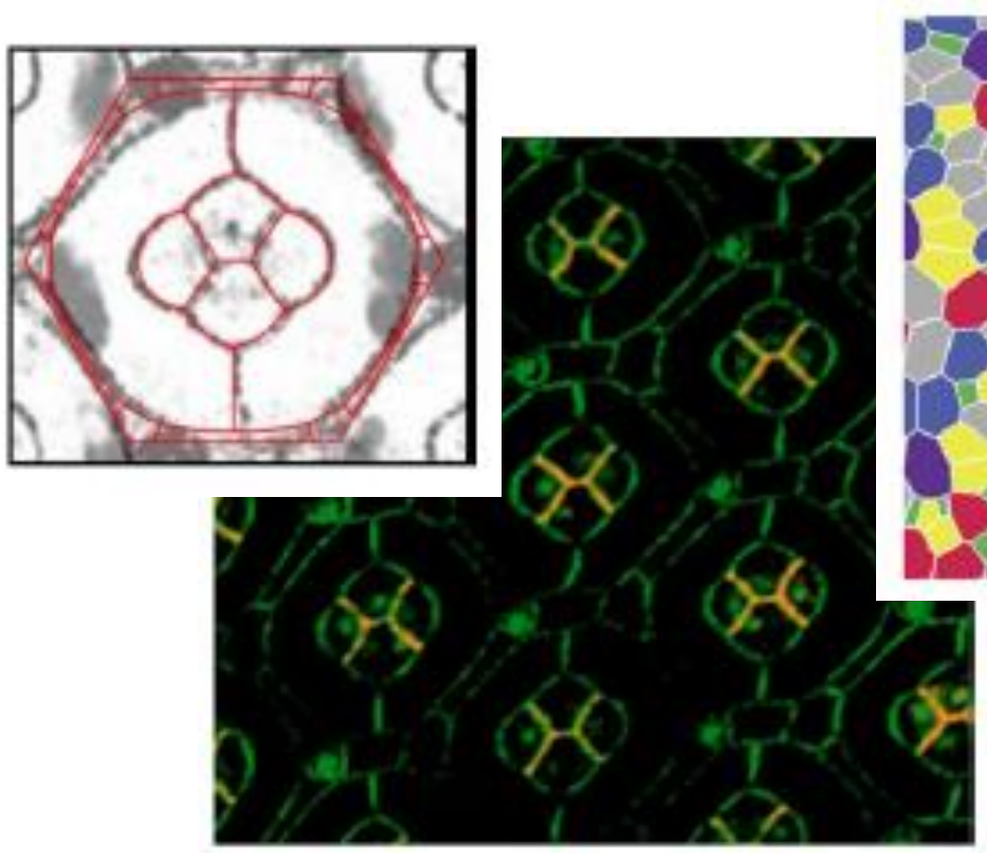
# In many tissues, a density-driven transition is impossible

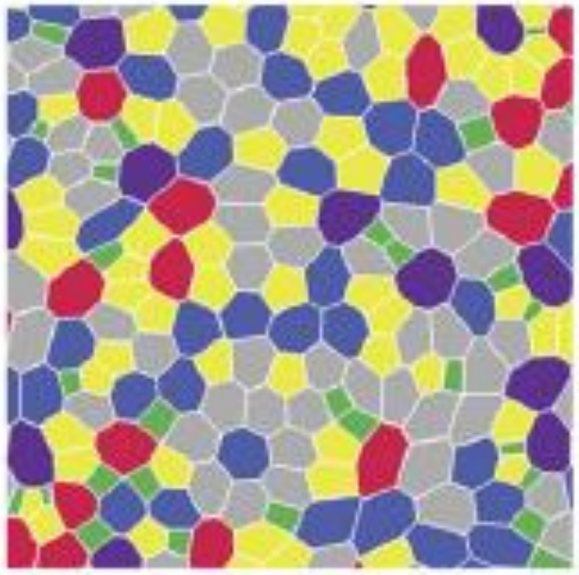
e.g. confluent tissues where there are no gaps between cells and the packing fraction is one

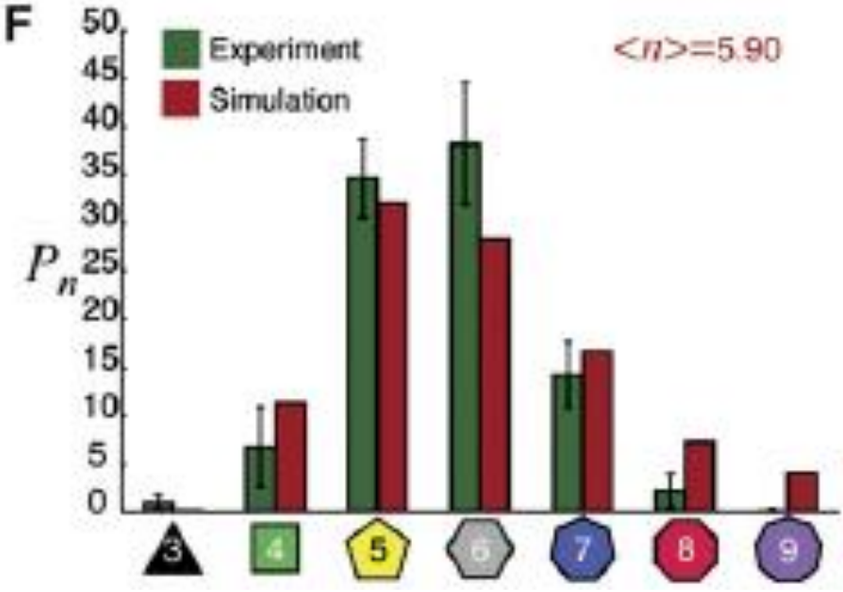
# Is there some analogue to the jamming transition for confluent tissues?

# Vertex models for tissues

- Developed about 15 years ago
- Good agreement with experimentally observed cell shapes
- Explain/predict mechanically stable cell shapes and statistical properties



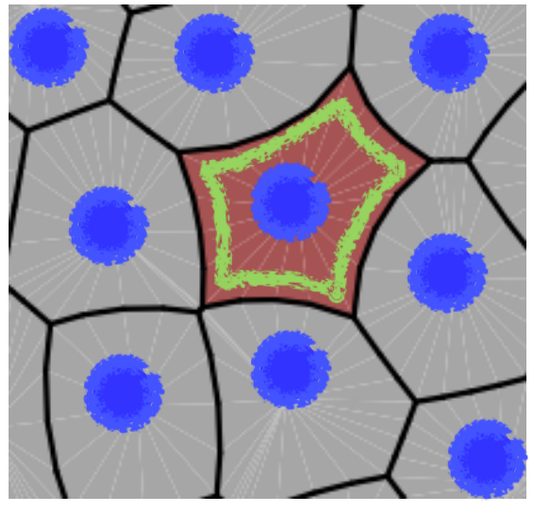






T. Nagai, H. Honda, Philos. Mag. B 81, 699 (2001)
Hufnagel et al, PNAS vol. 104 (10) pp. 3835 (2007)
Farhadifar et al, Current Biology (2007)
Jülicher et al Phys. Rep. (2007)
Hilgenfeldt et al, PNAS 105 3 907–911 (2008)
MLM et al, PNAS (2010)
Staple et al EPJE 33 (2) 117 (2010)
Chiou et al PLOS Comp Bio 8 (5) e1002512 (2012)

# Vertex model equations



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

A = area, P = perimeter

3D

**Incompressibility + resistance to height**

**acto-myosin contractilty**

**Interfacial tension: adhesion and cortical tension**

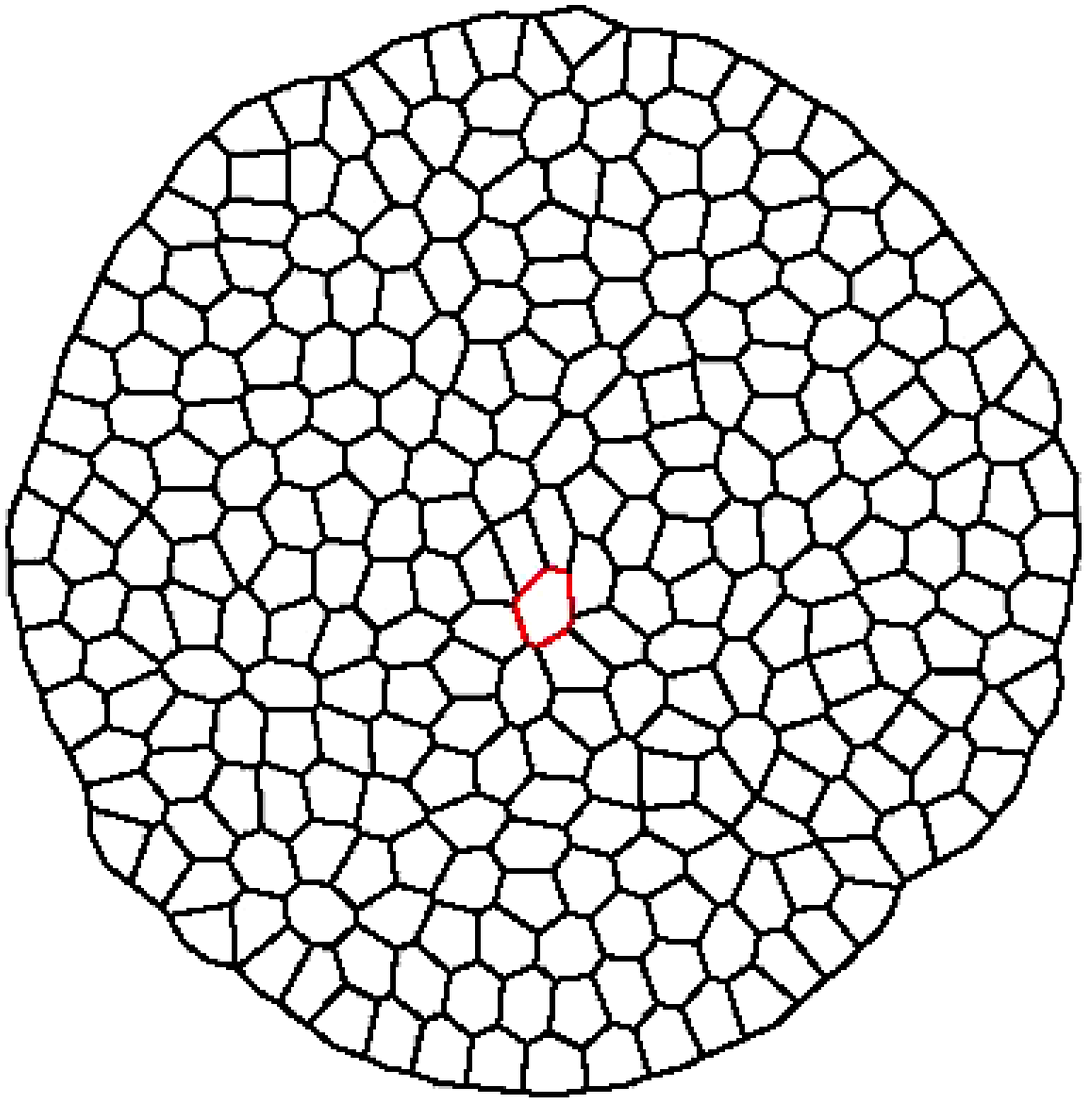
$$\varepsilon = \frac{1}{\beta A_0}\sum_i^N E_i = \sum_i \left[(a_i - 1)^2 + \frac{(p_i - p_0)^2}{r}\right]$$

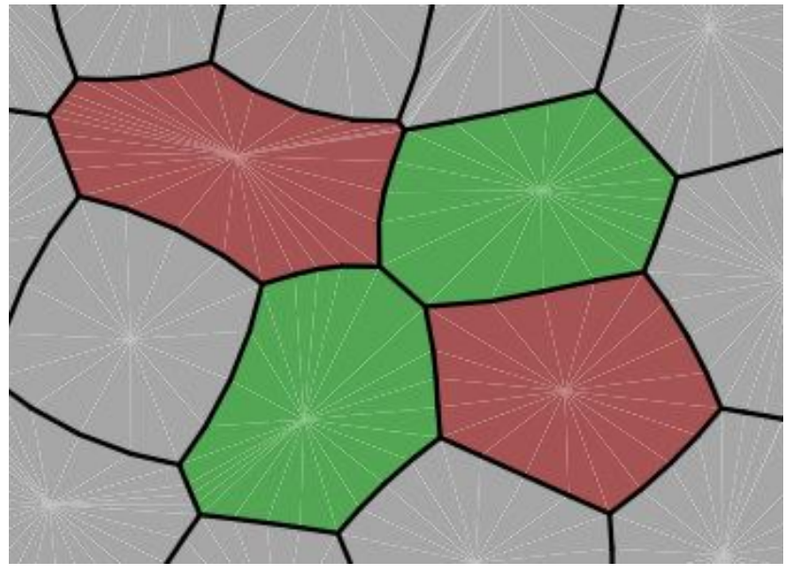
Non-dimensionalized mechanical energy

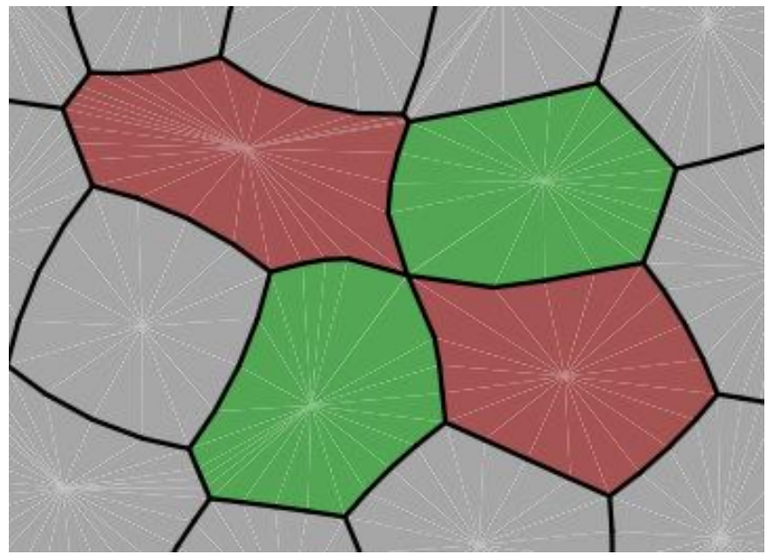
Our model has two parameters:

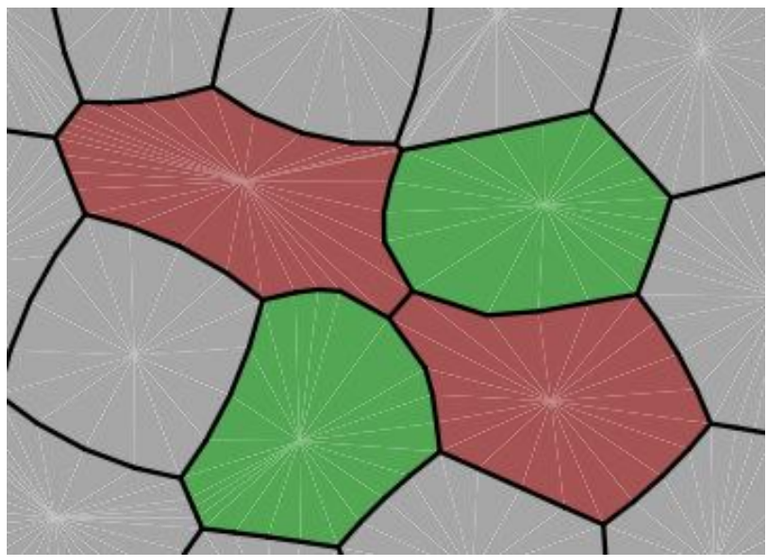
- $p_0$ = preferred perimeter: interfacial tension generated by adhesion and cortical tension
- r = inverse perimeter modulus: resistance to height fluctuations normalized by perimeter contractility OR ratio between bulk stiffness and interface stiffness

# Rearrangements and migration in tissues via T-1 transitions



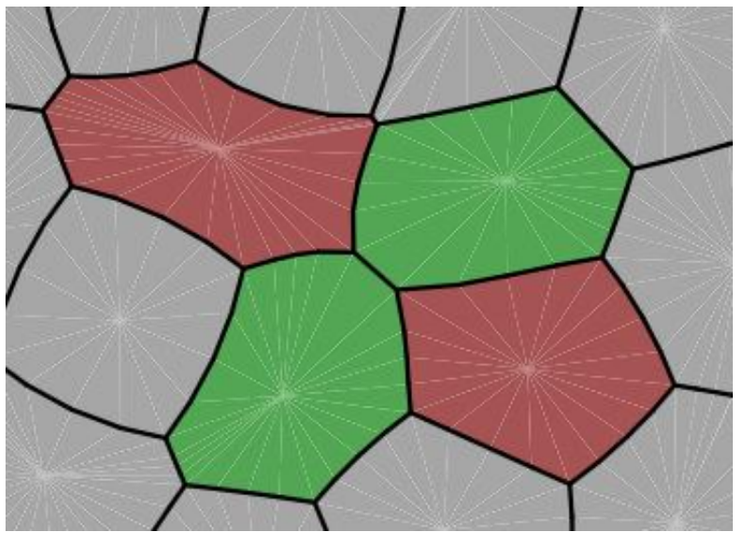




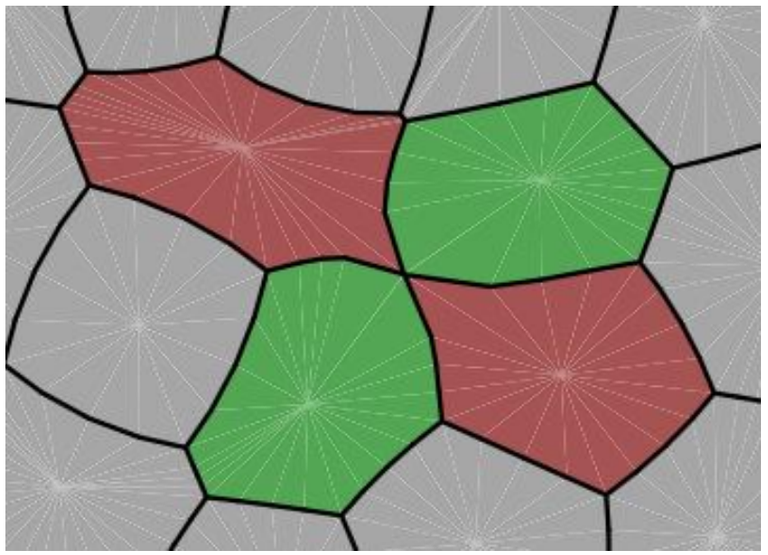


# Energy trace for T-1 transitions

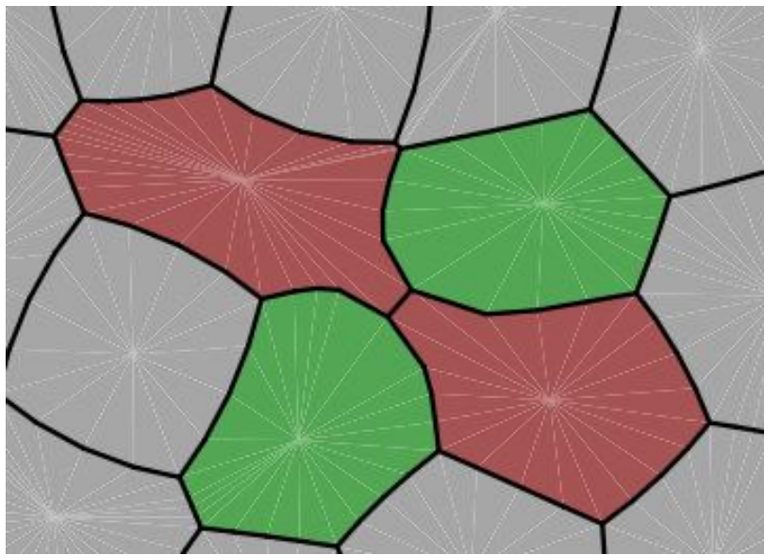
Shrink edge before T-1

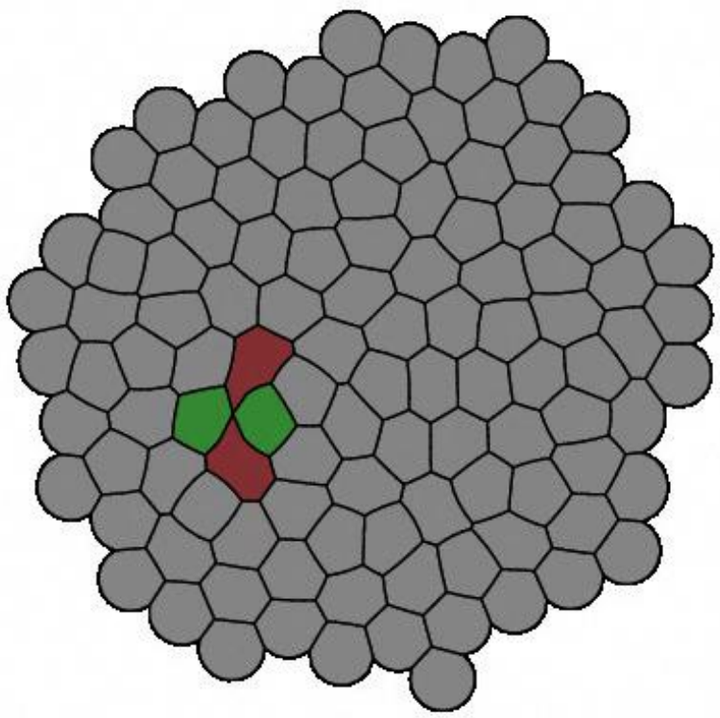


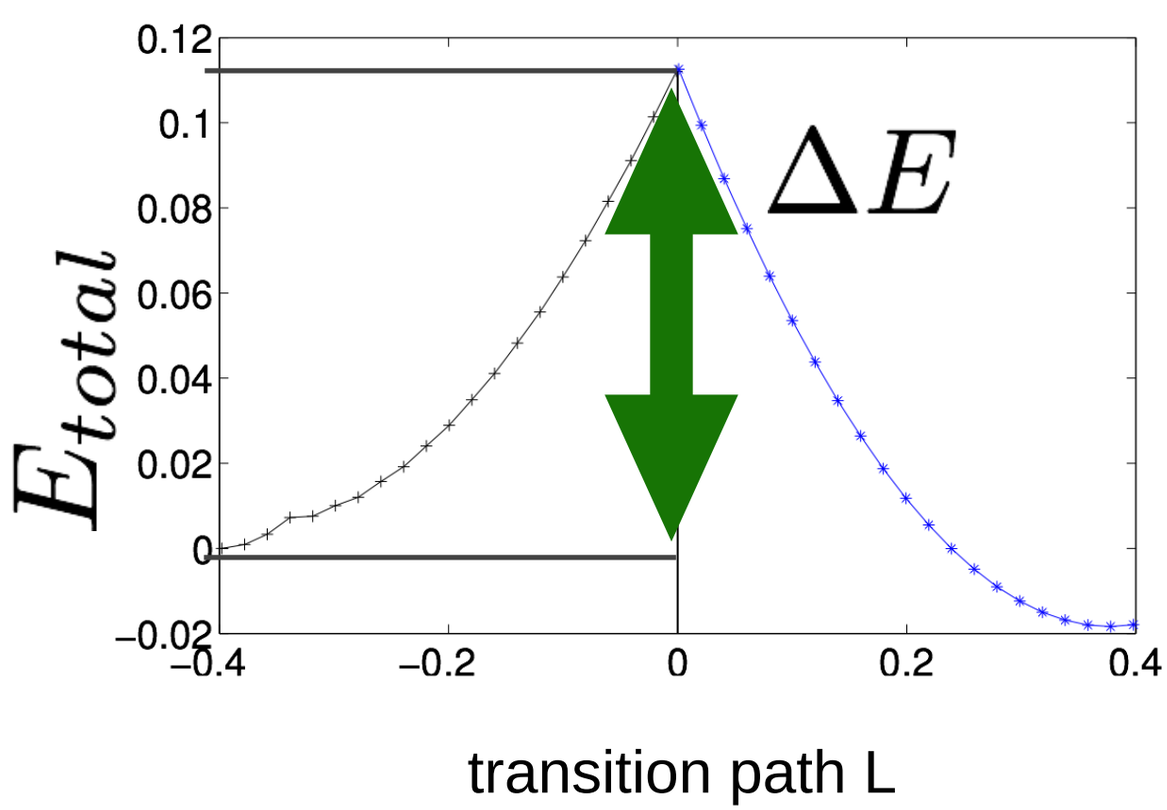
At T-1



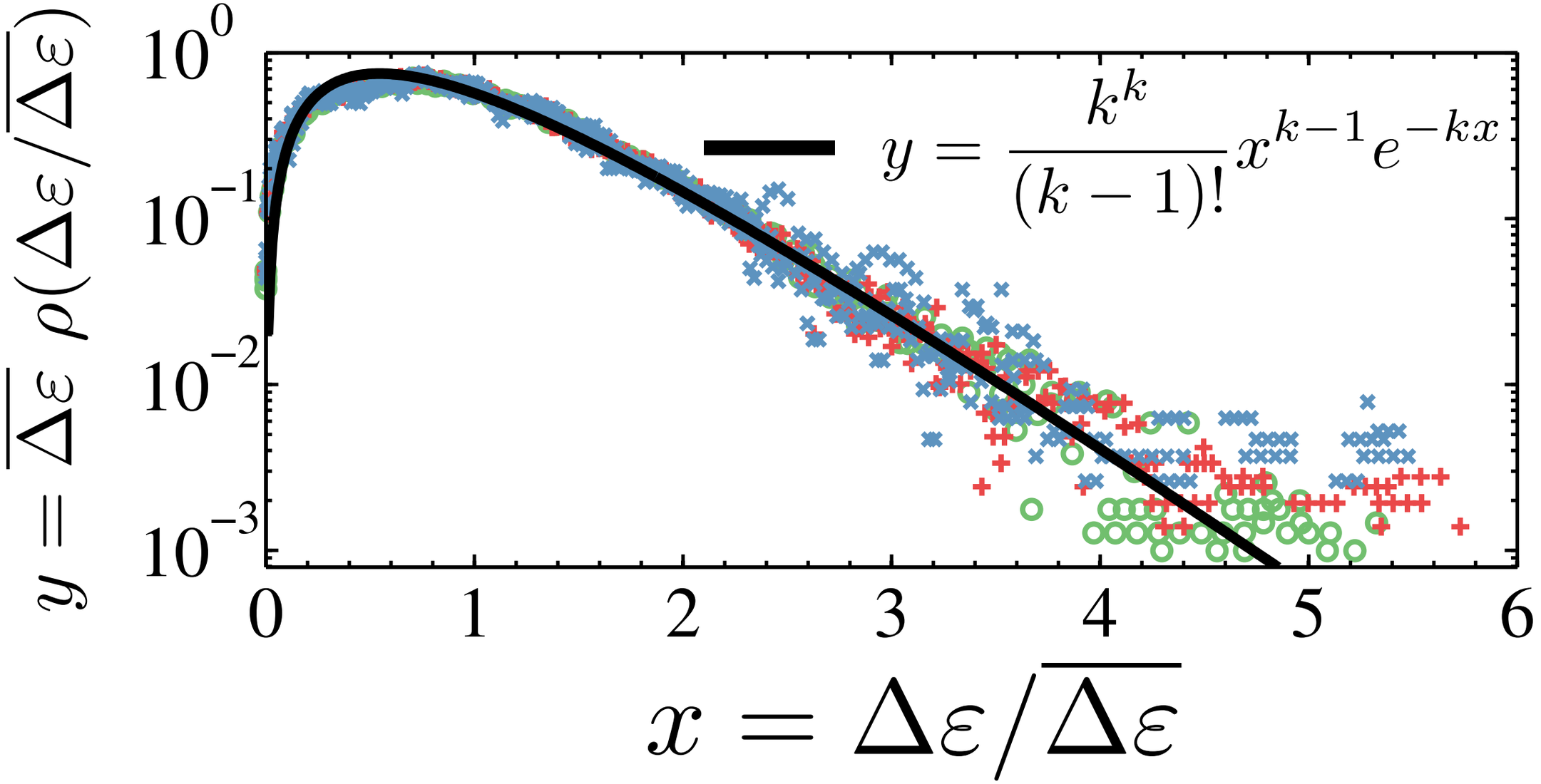
Grow edge after T-1







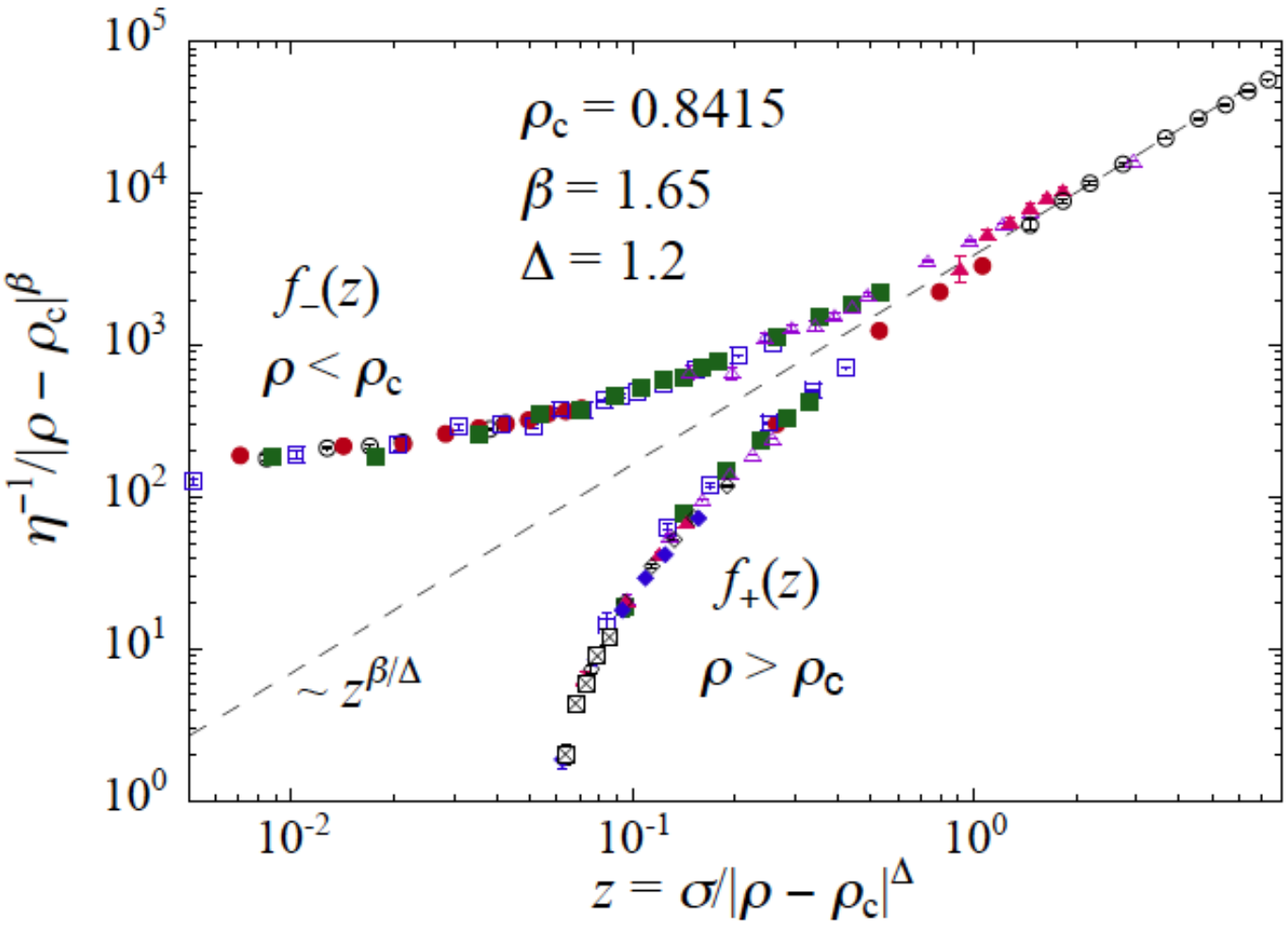
# Large tissues: energy barrier statistics determined entirely by the mean energy barrier height



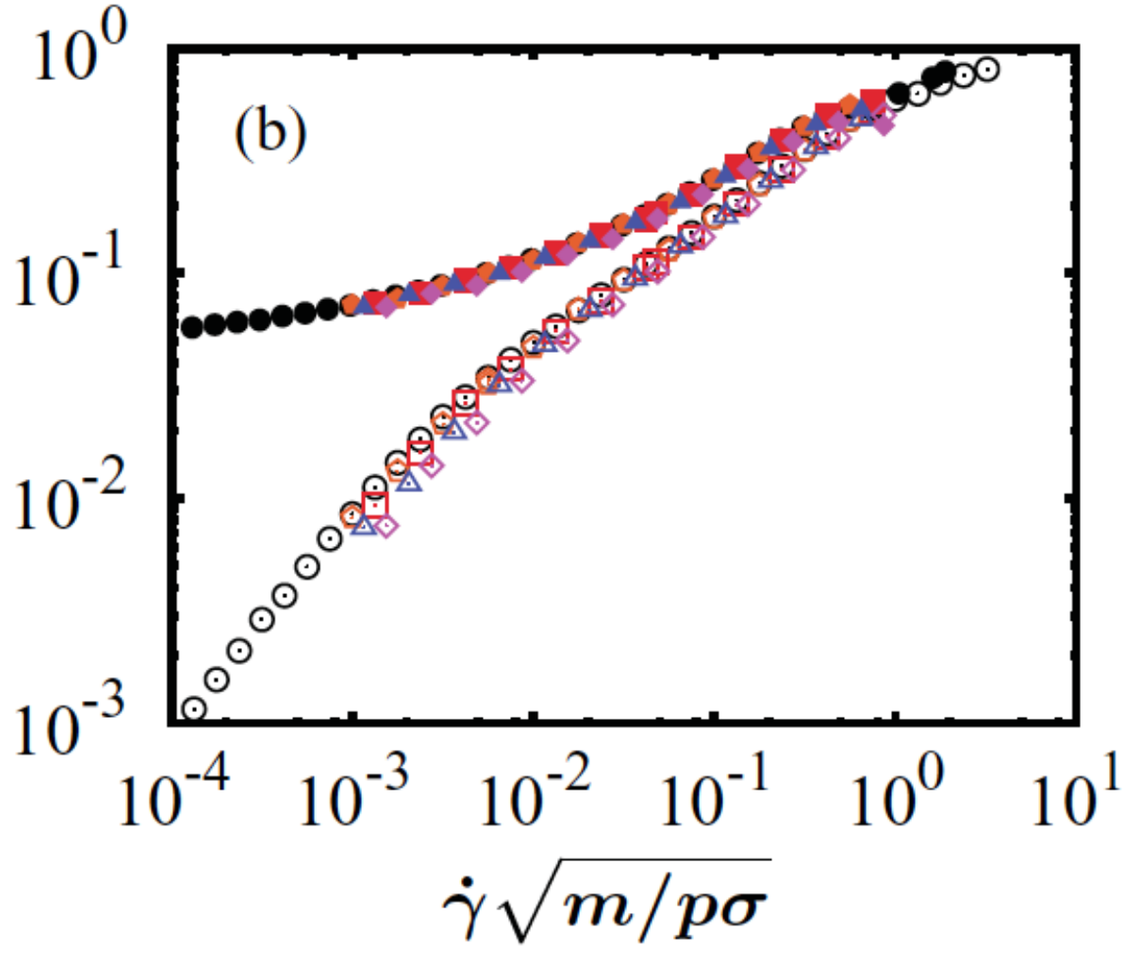

k-gamma distribution with one fit parameter: k=2.2± 0.2
(found in many cellular systems)

Aste & Matteo, PRE 77 21309 (2008)

# Proving the existence of a critical “jamming” transition in inert matter:




Olsson and Teitel, PRL 99, 178001 (2007)




Haxton et al PRE **83**, 031503 (2011)

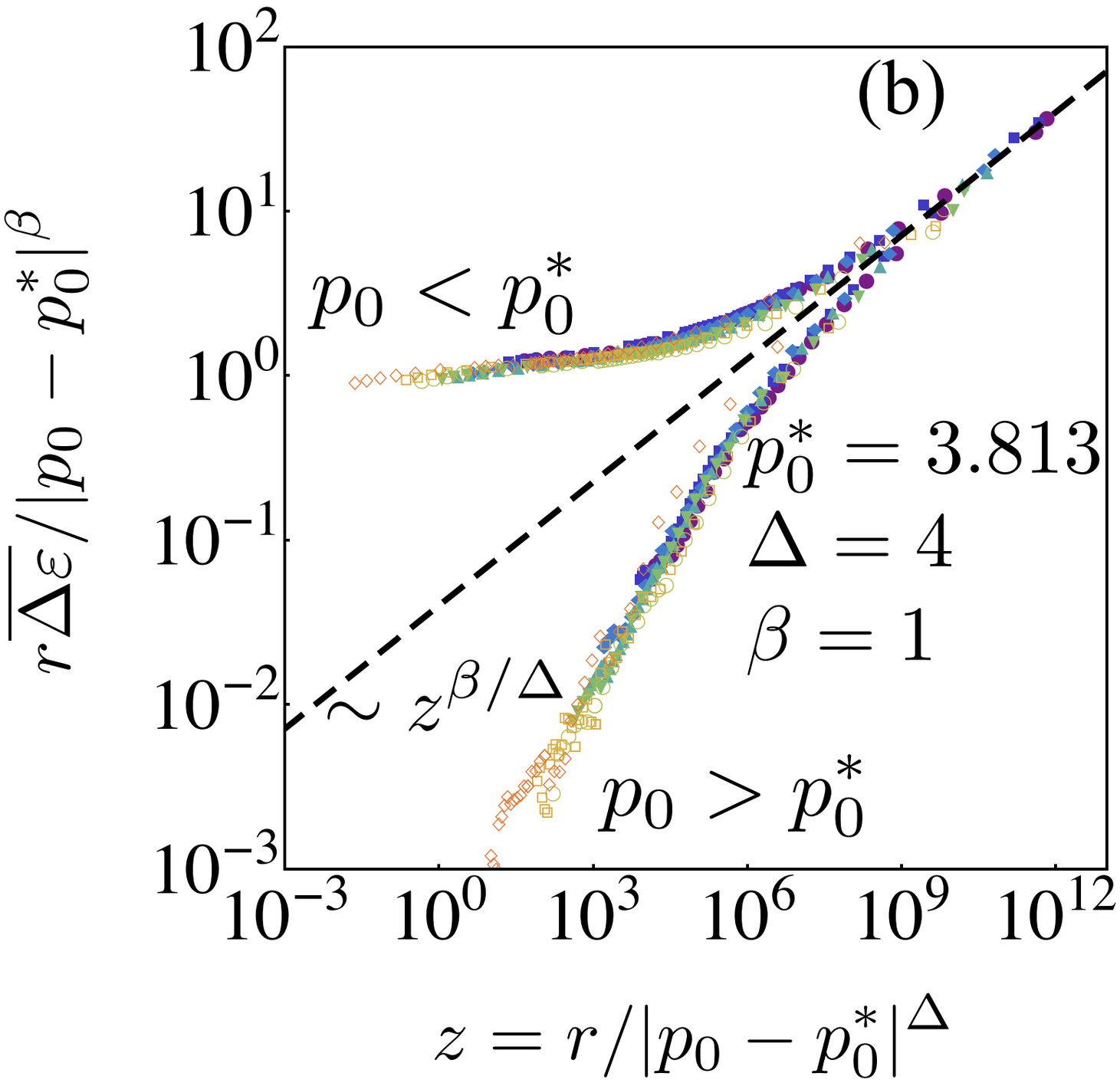
The onset of jamming is controlled by the **density**: ($\rho$-$\rho_c$) ~ pressure

# A critical rigidity transition controlled by $p_0$:

CHEAT SHEET:
Average energy barrier height ~ yield stress

inverse perimeter modulus r ~ strain rate

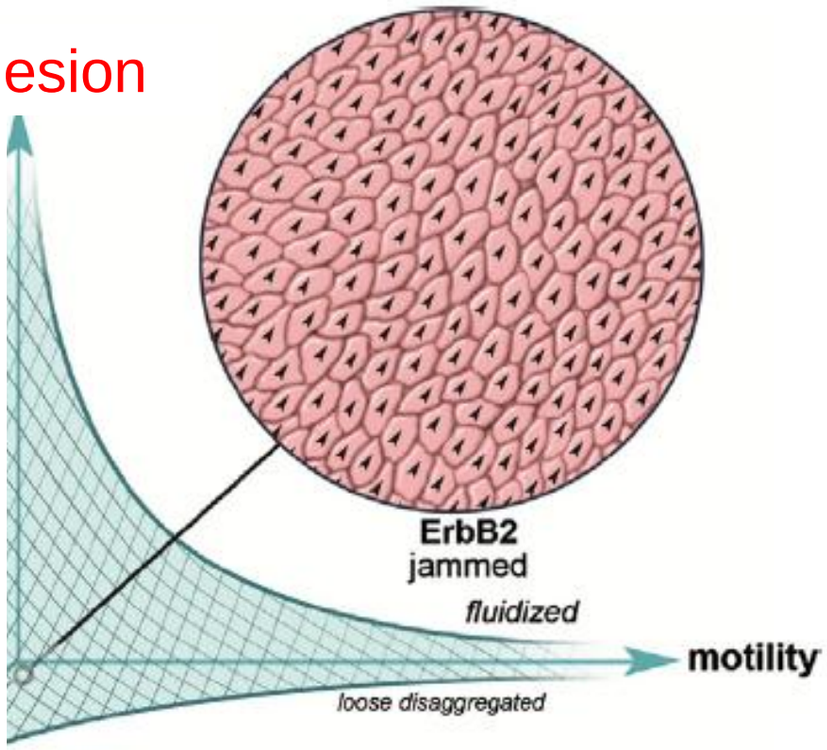
preferred perimeter $p_0$ ~ density




Bi, Lopez, Schwarz, MLM submitted (2014)

# new rigidity phase diagram for biological tissues

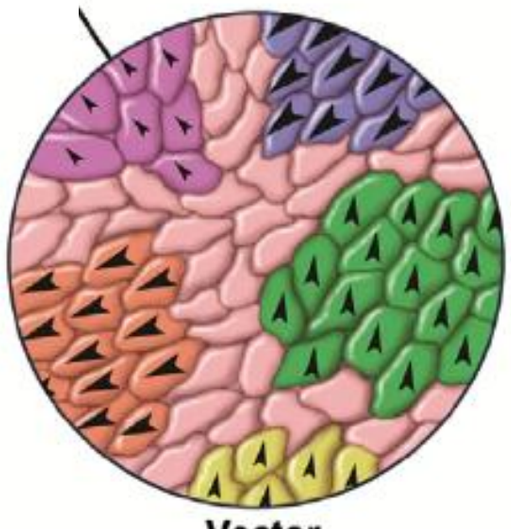
Adhesion




Opposite for confluent tissues!

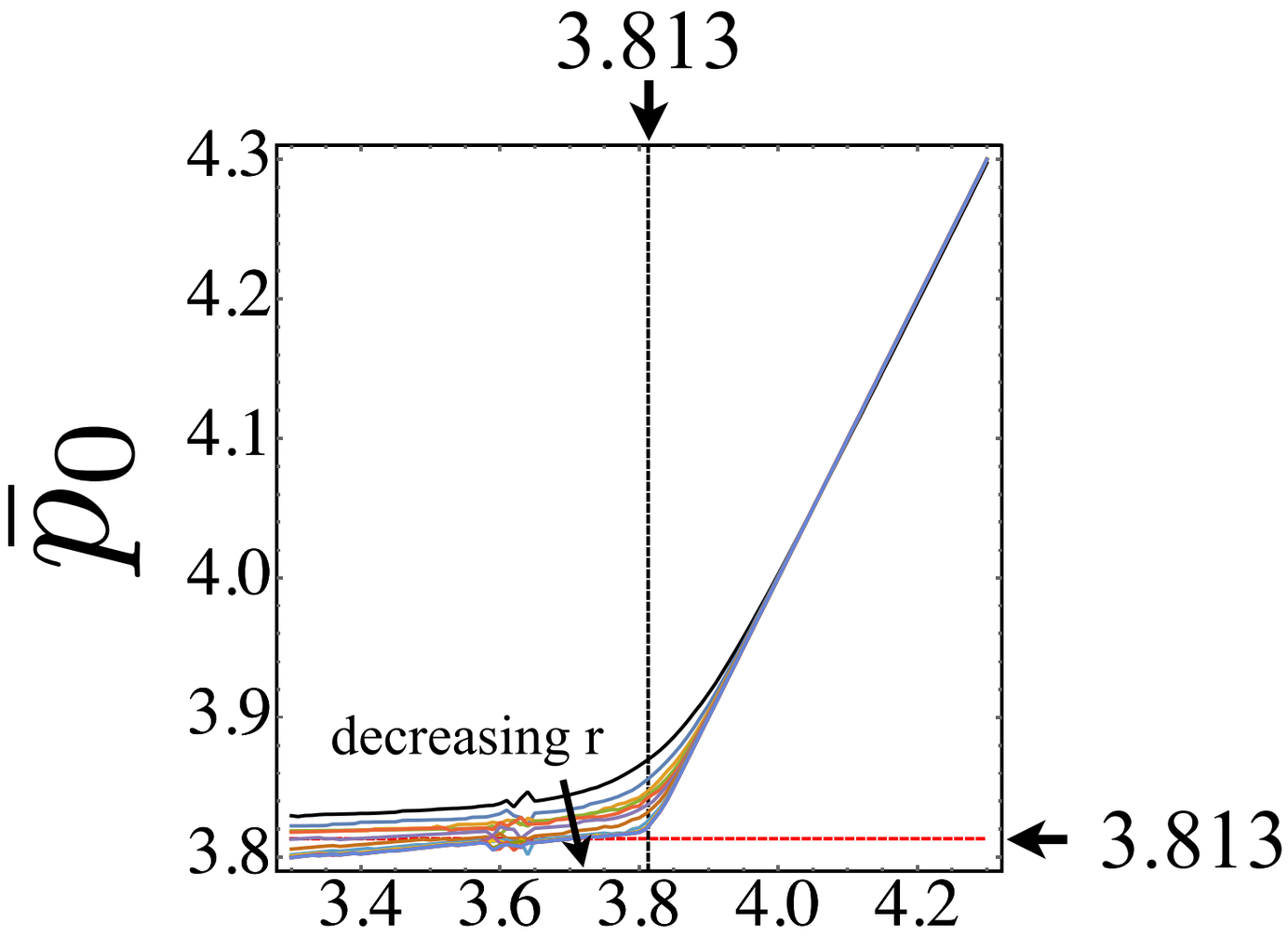
Particulate matter: axis is 1/adhesion

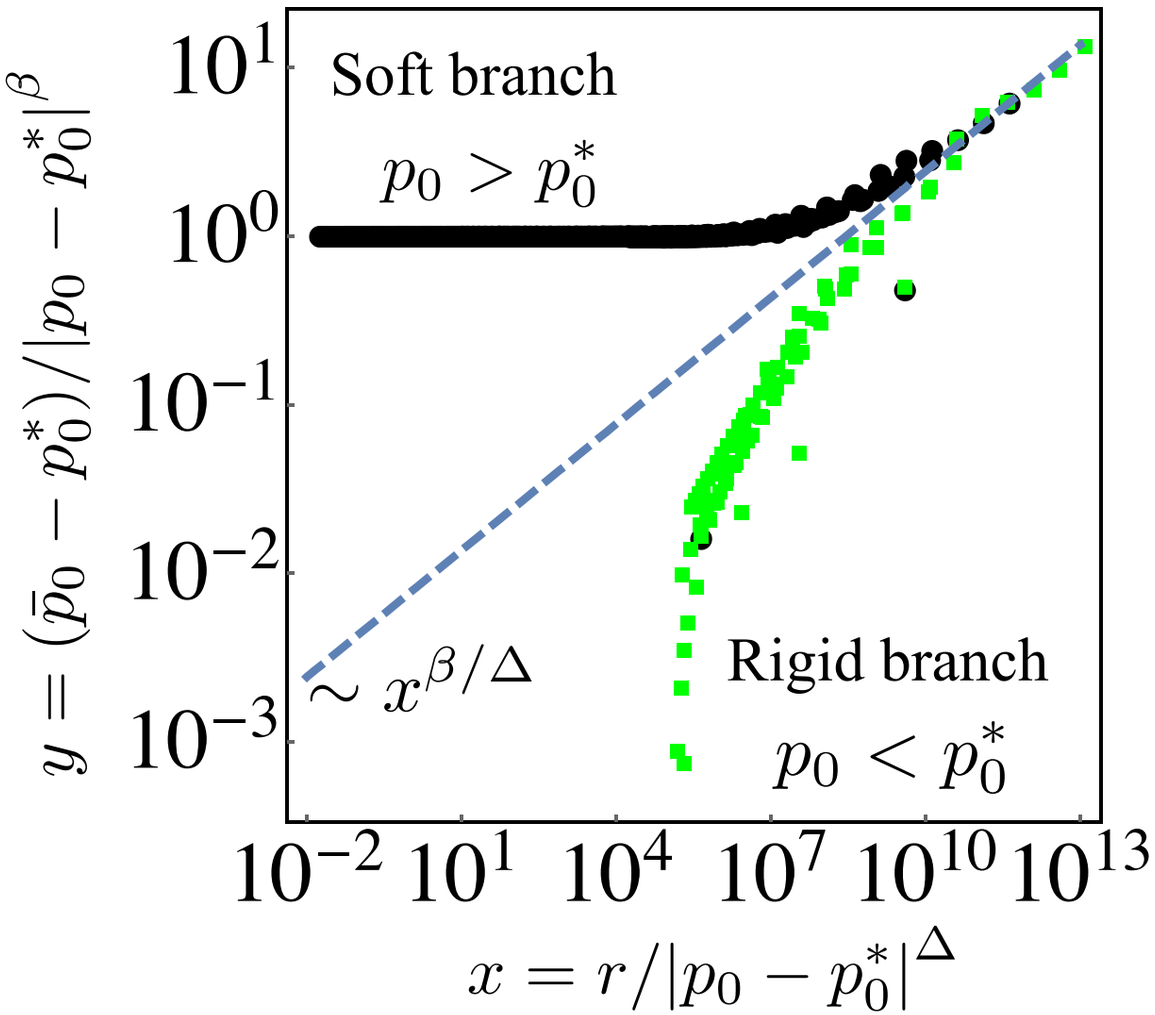
more adhesion means more gelation means more solid-like




Sadati, et al. *Differentiation 86* (2013)

# Experimental prediction



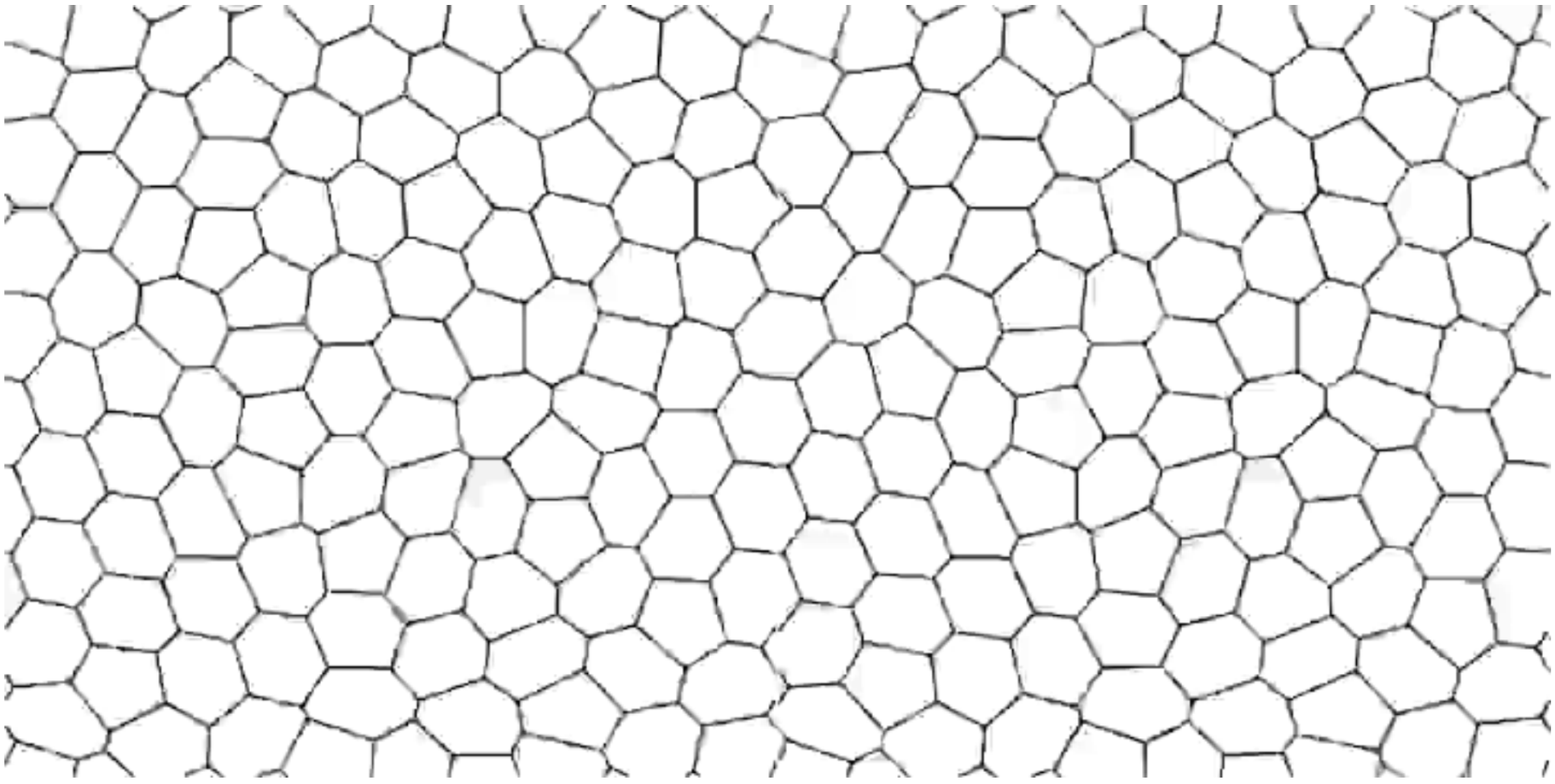




$\bar{p}_0$

p0 is the average OBSERVED perimeter-to-area ratio:

$$\bar{p}_0 = \langle p \rangle / \sqrt{\langle a \rangle}$$

# Effect of finite cell motility?

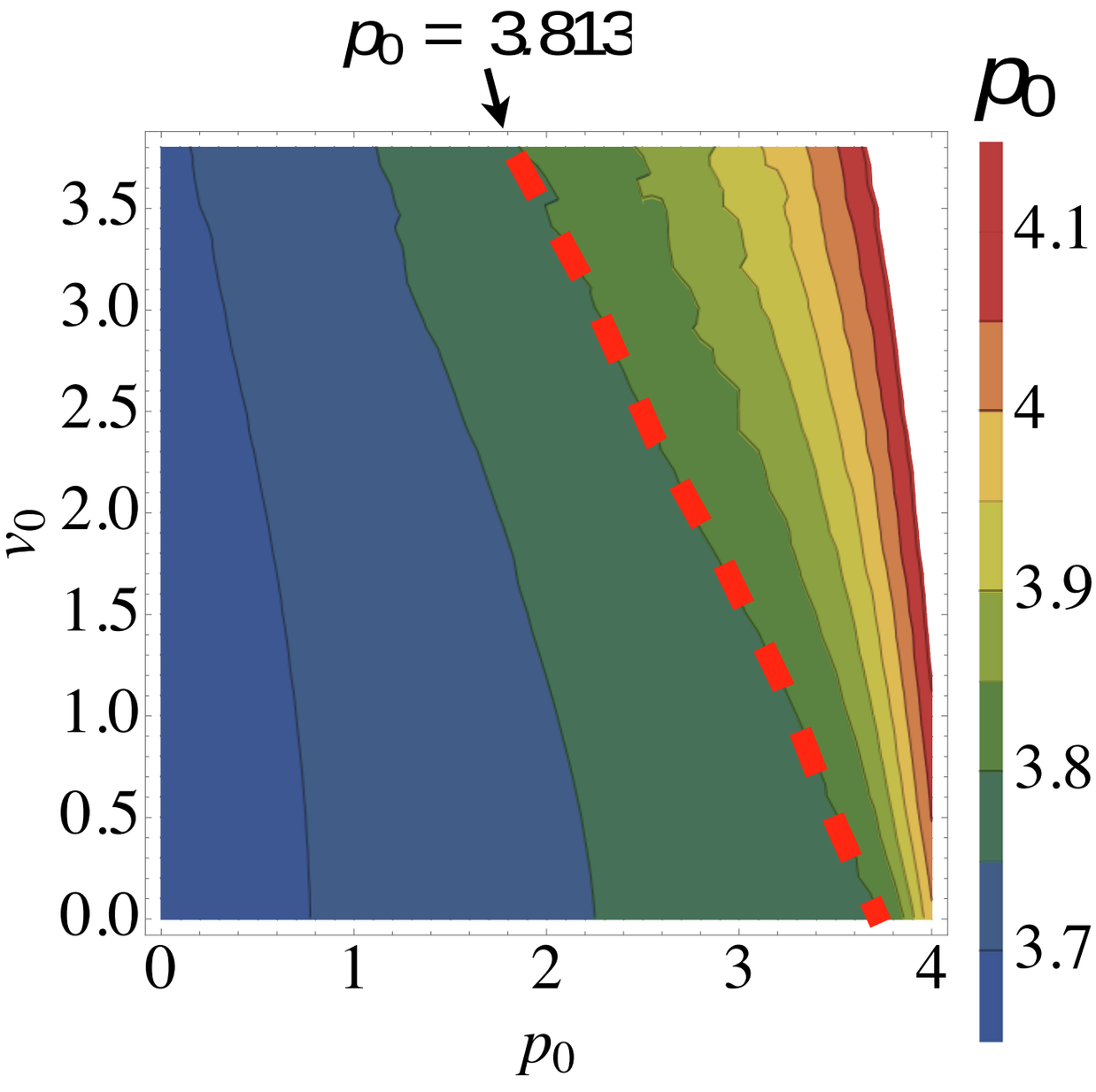


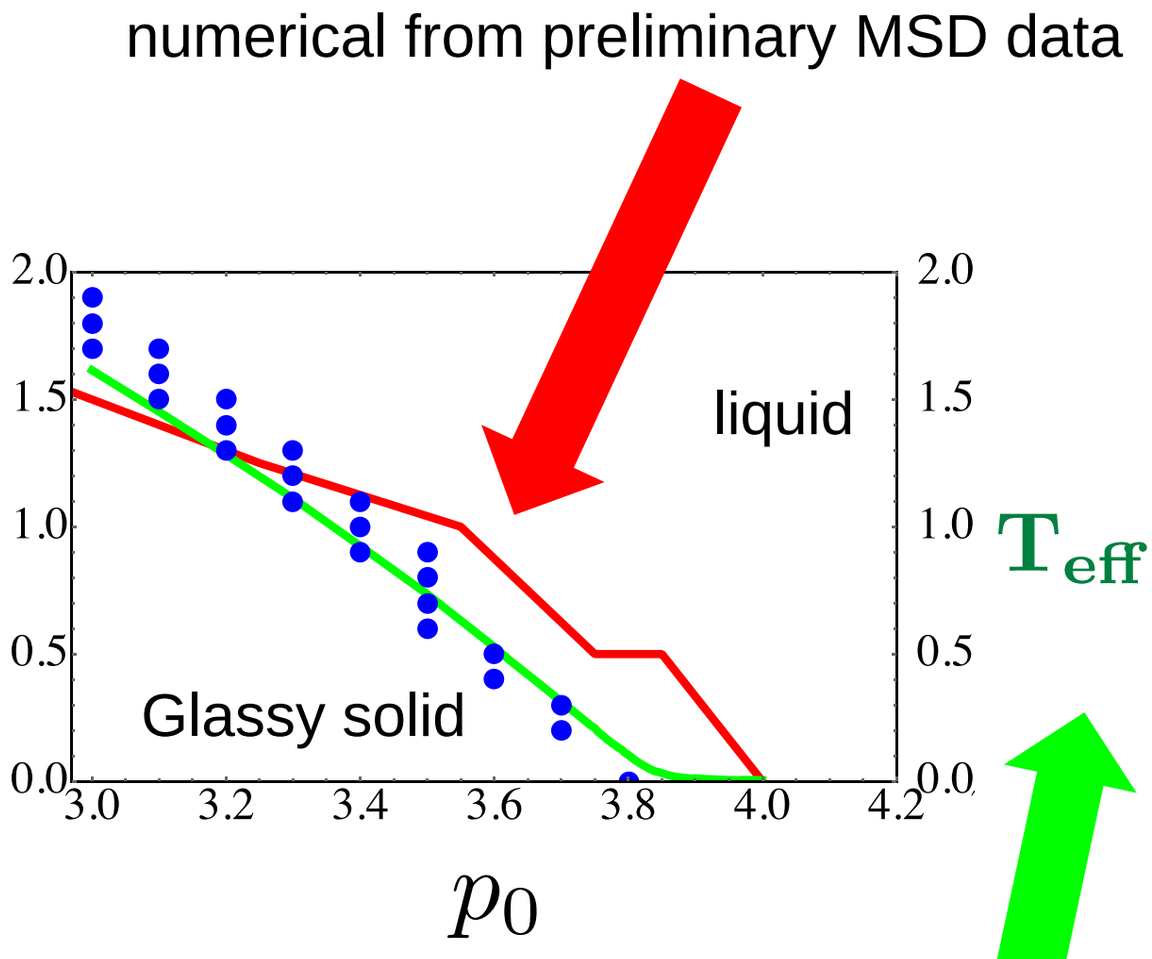
p0 < p0*

p0 > p0*

Add an equation for cell polarization (like in self-propelled particle or Vicsek models)

# Observed cell perimeter-to-area ratio **robust** to cell motility

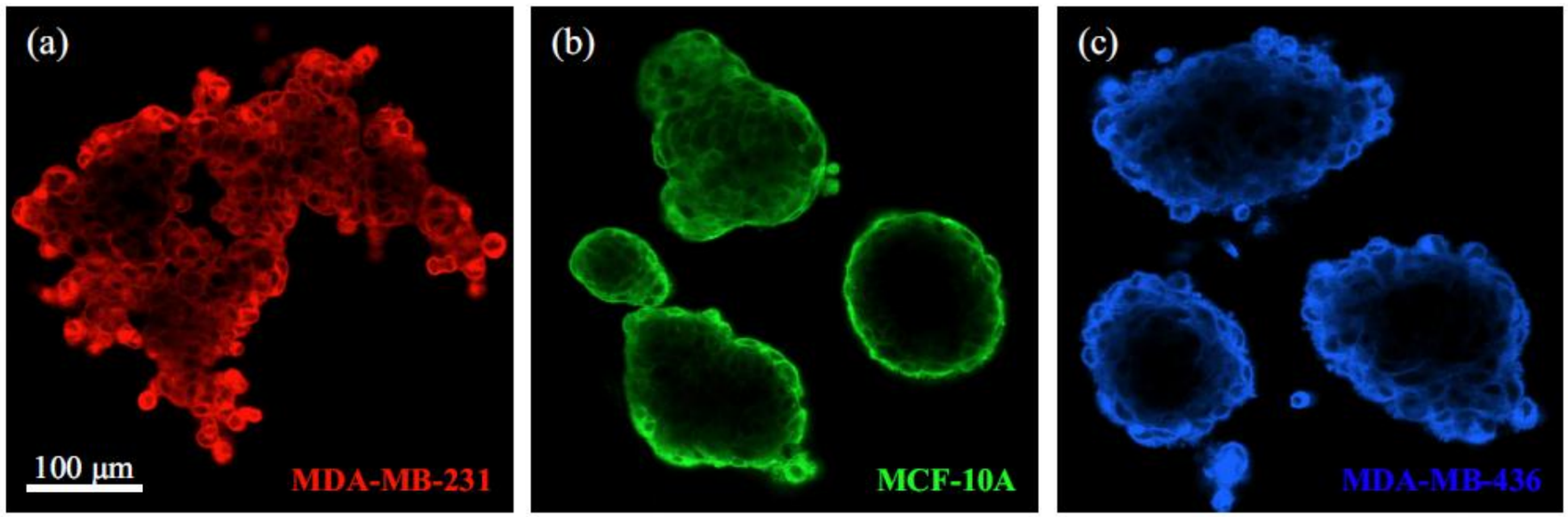



numerical: from an active vertex model simulation

Analytic: from an extended SGR/trap model

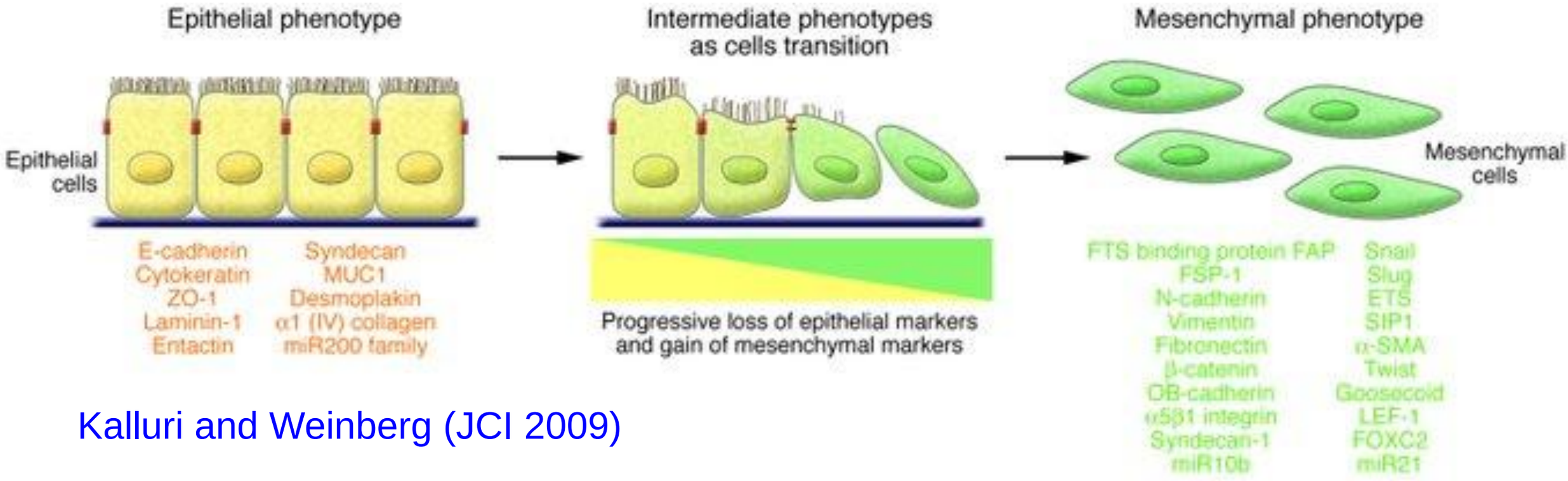
# Cancer tumor boundaries and the EMT transition




Cancer cell sorting not driven by differential adhesion/ tissue surface tension!

Pawlizak … MLM …Kaes, in preparation (2014)

- Could the EMT transition be thought of as a change in $p_0$ – the ratio between the cell area and perimeter?
- If so, mesenchymal cells metastisize easily because they are on liquid side of rigidity transition?




Kalluri and Weinberg (JCI 2009)

# Conclusions

- Biological tissues are complex materials, with mechanical properties that are important for biological function
- Many tissue types are apparently close to a glass transition
- The vertex model for confluent tissues exhibits a novel type of density-independent rigidity transition
  - excellent scaling collapse
  - control parameter is $p_0$, which is proportional to single-cell adhesion or preferred cell perimeter
  - this is opposite of what you'd expect from particulate matter
- This is a rich framework with lots more to do:
  - cancer cell migration
  - EMT transitions
  - collective modes
  - effect of cell motility

# Thanks so much for your attention!

Collaborators:

- Max Dapeng Bi (SU)
- Jen Schwarz (SU), Jorge Lopez (SU), Eva-Mara Schoetz (UCSD), Marcus Lanio(Princeton), Jared Talbot(Princeton)
- Jeff Amack (Upstate), Guliang Wang (Upstate)

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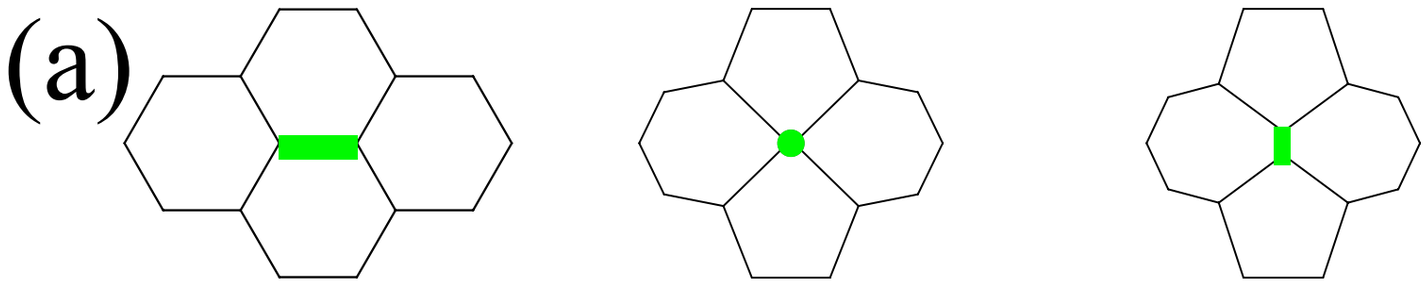
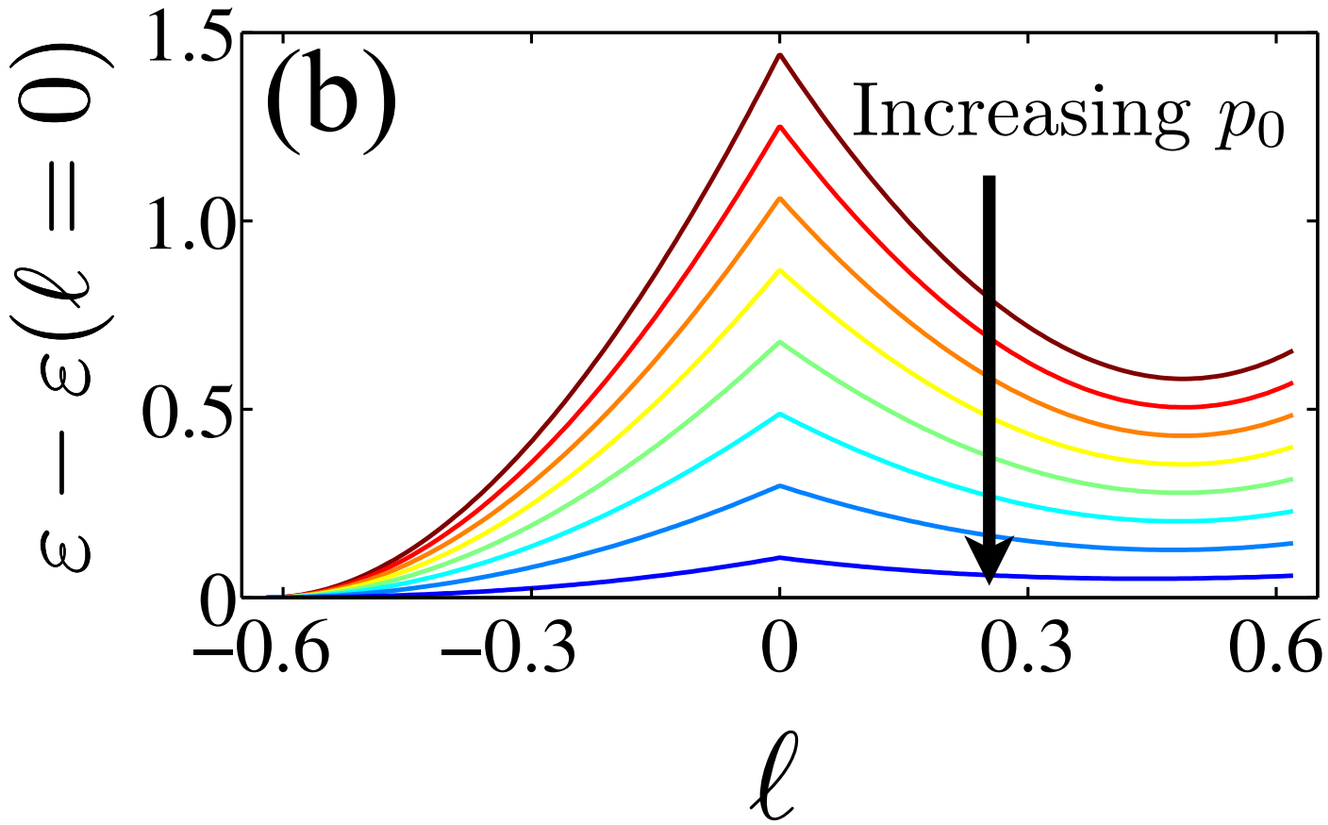
- Alfred P. Sloan Foundation
- Soft Interfaces IGERT (DGE-1068780)

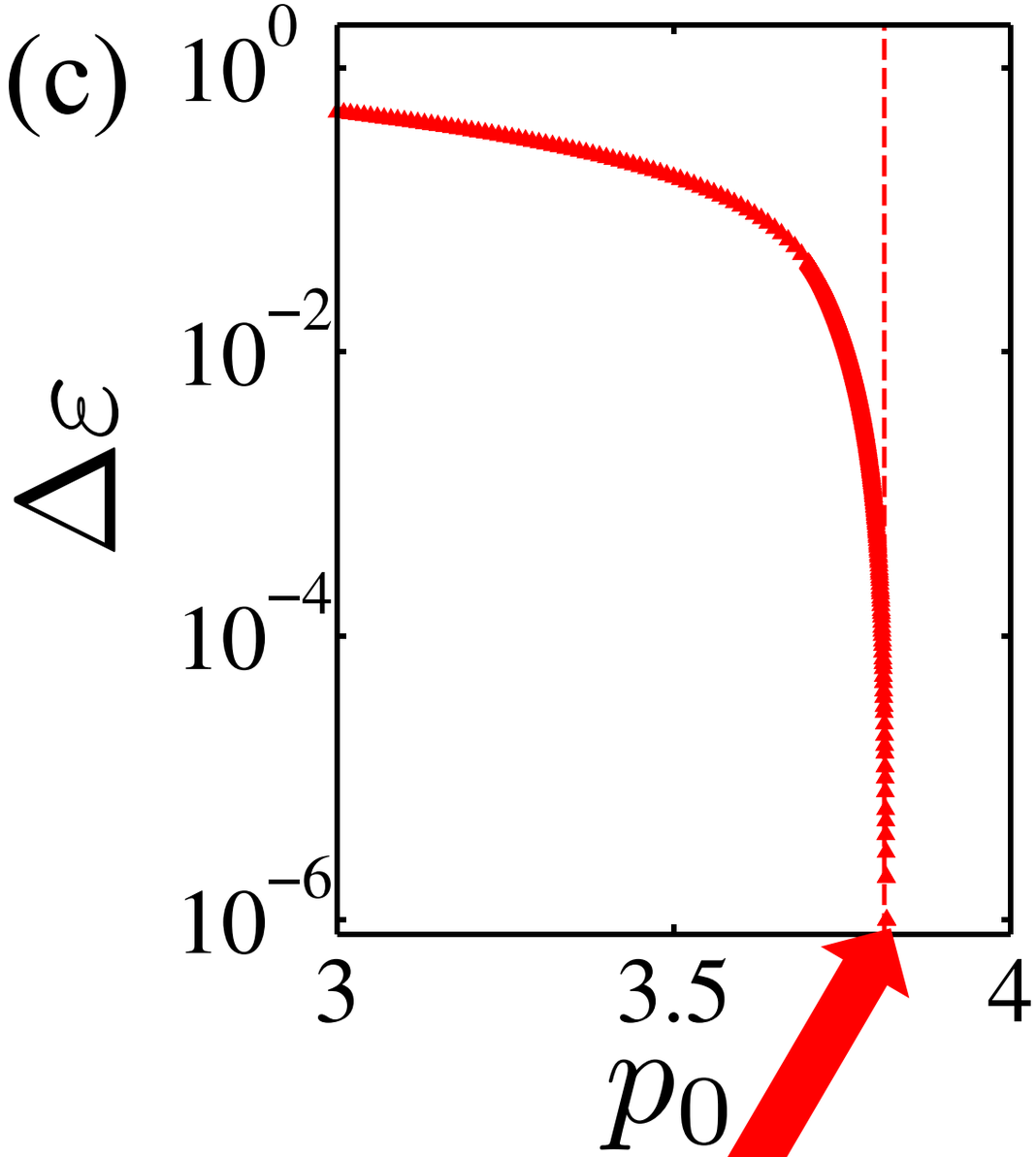
http://www.phy.syr.edu/~mmanning/

# Fixed area, four cells

## $p_0$ only control parameter



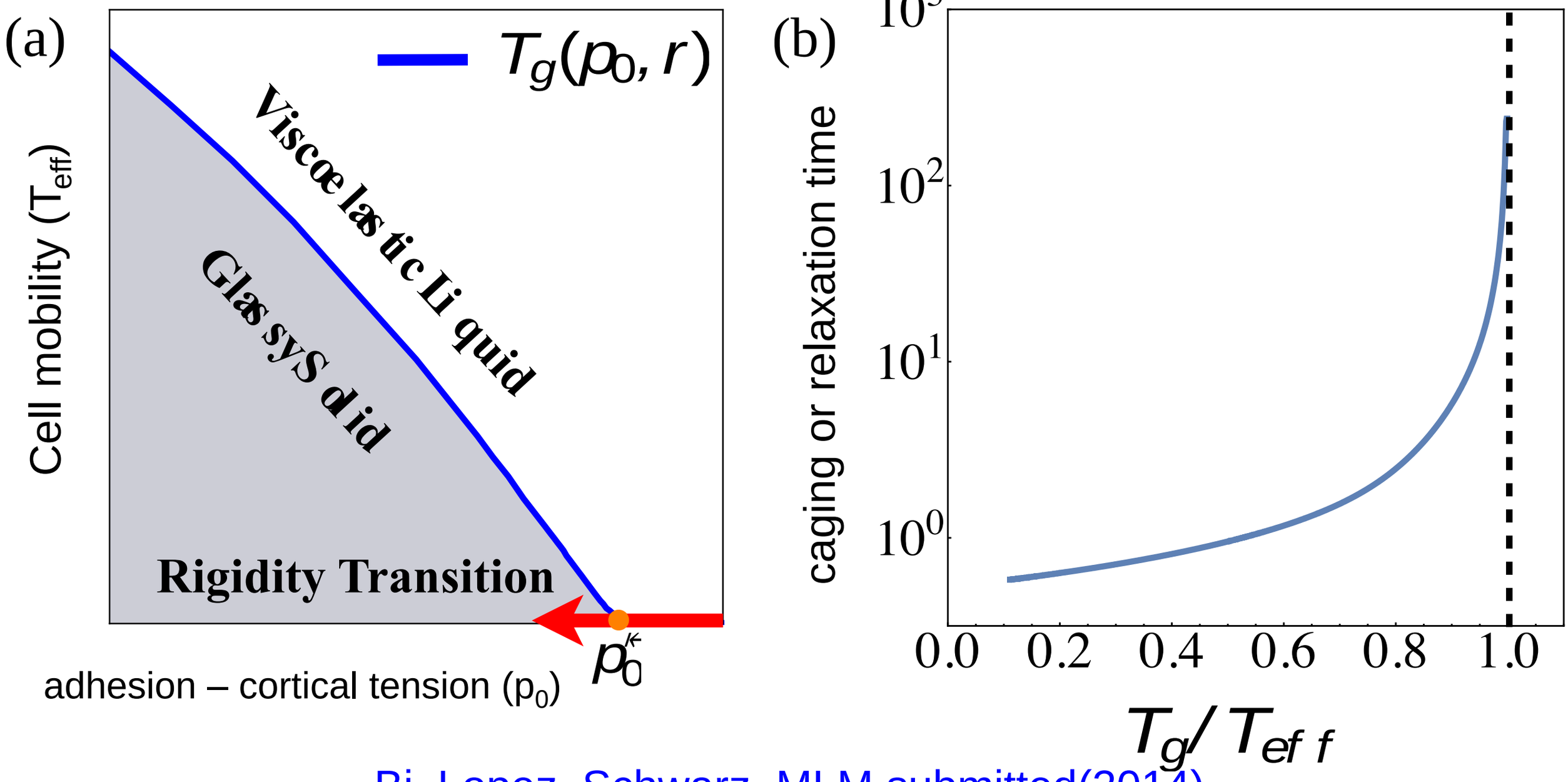




Bi, Lopez, Schwarz, MLM submitted(2014)

Transition point $p_0^* = 3.813$
= perimeter of regular
pentagon with unit area

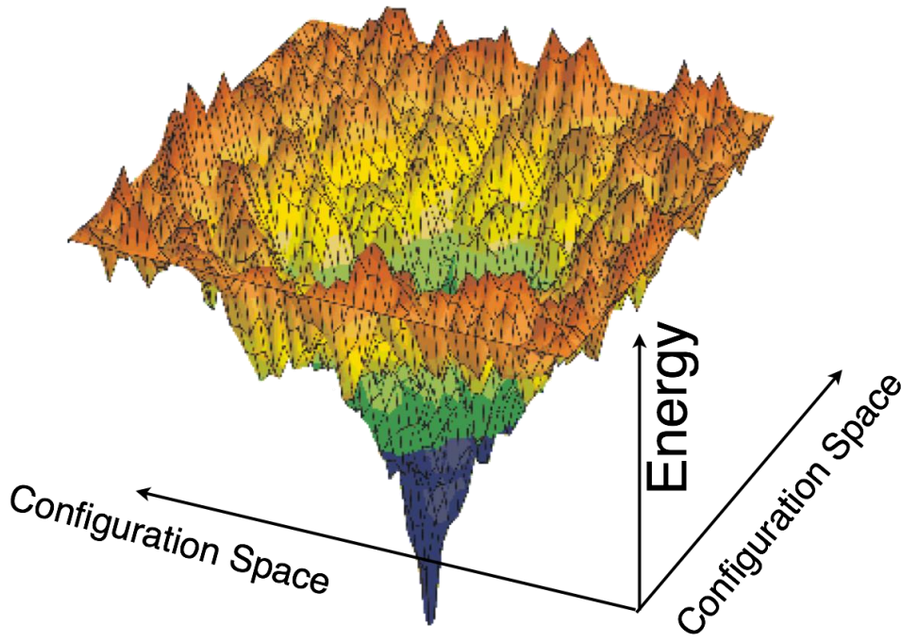
# What happens when you include a finite cell activity or mobility?

# Using a trap or SGR model to go from energy barriers to cell dynamics




Bi, Lopez, Schwarz, MLM submitted(2014)

# When cells are actively fluctuating and moving, how does this change the transition?

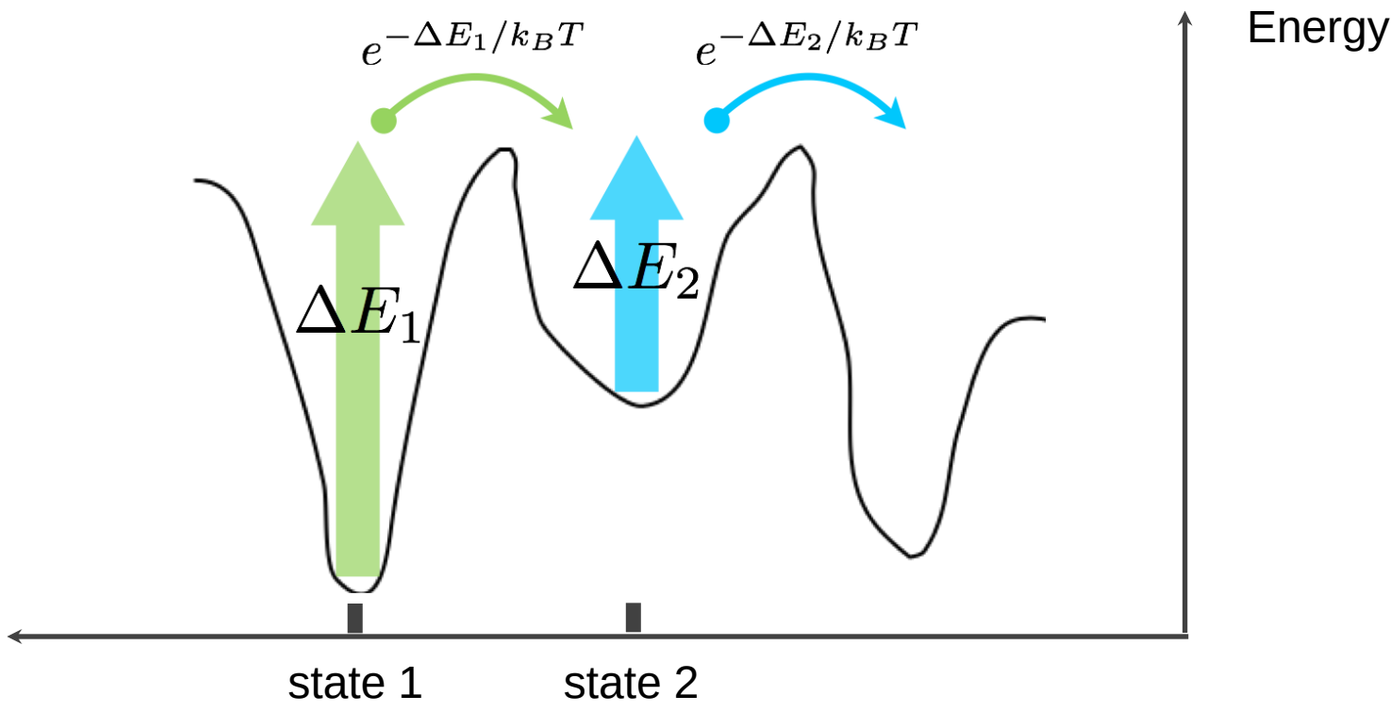



**Complex potential energy landscape**

**+**

**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)**

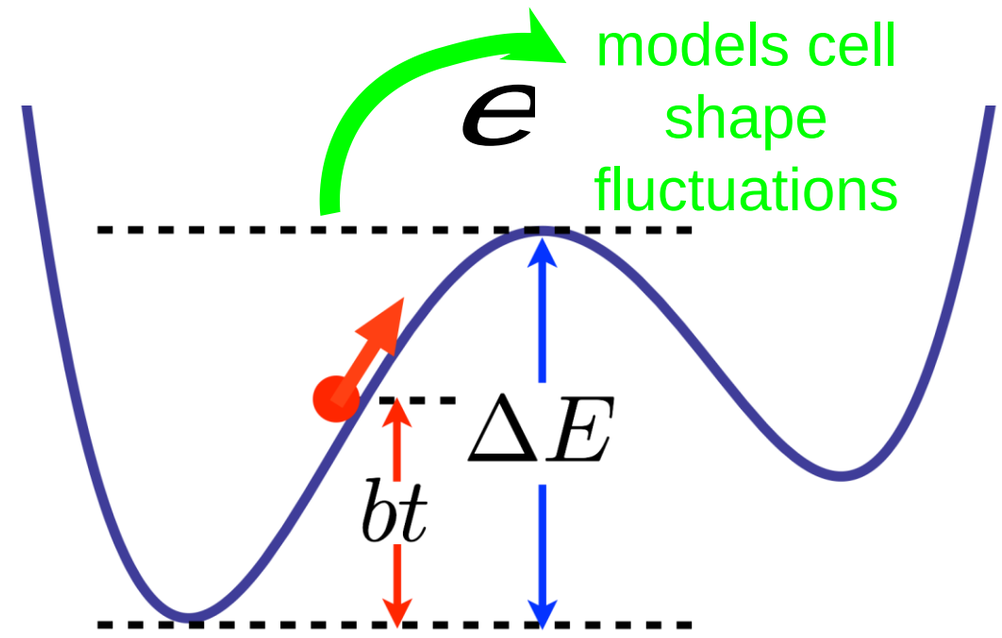
soft glassy rheology Sollich et al, PRL 78 2020 (1997)

# From energy barriers to cell migration:

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

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

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

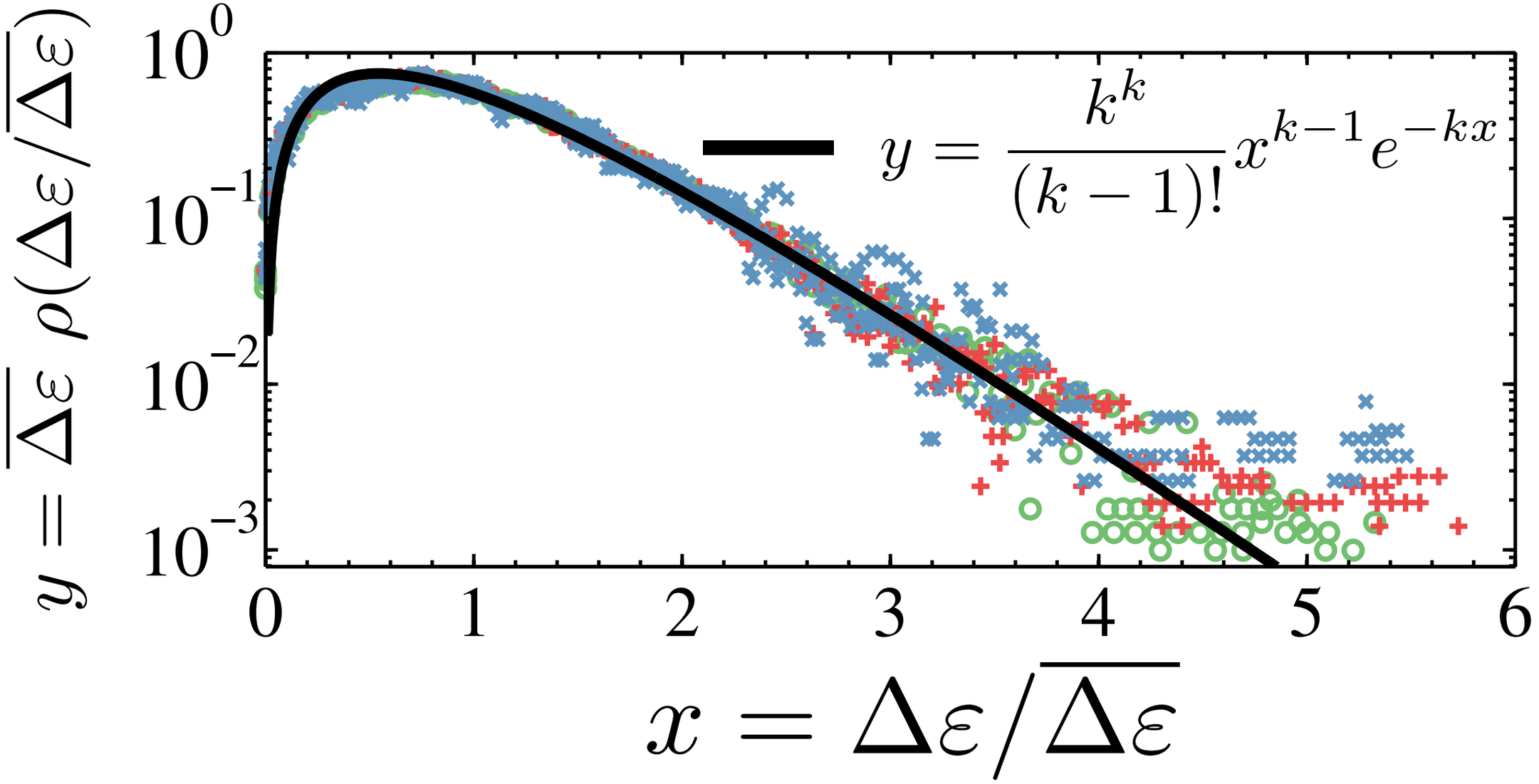



models polarized cell motion

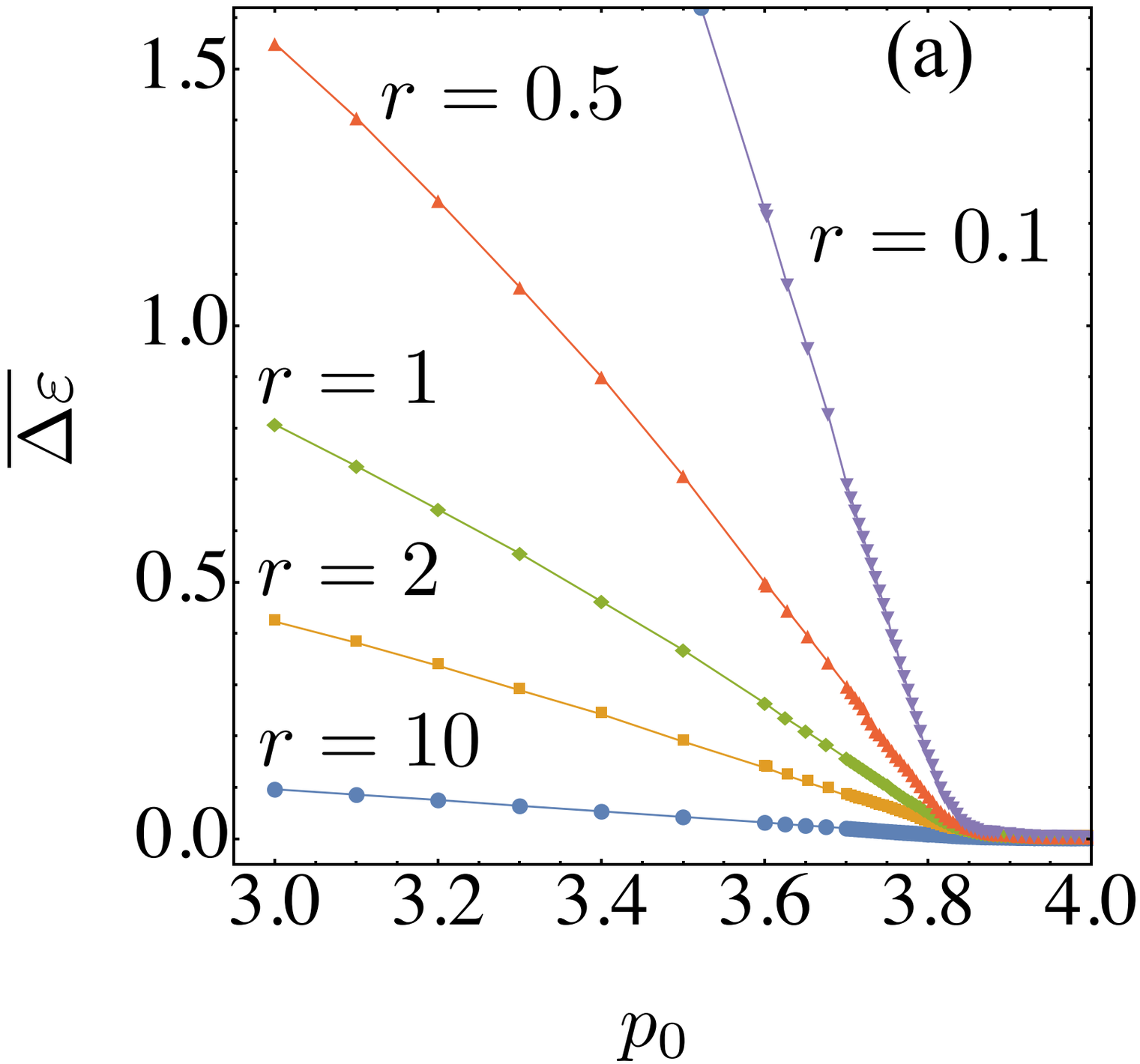
$$\frac{\partial}{\partial t}P(\Delta E,t) = -\omega_0 e^{-[\Delta E - bt]/\varepsilon}P(\Delta E,t)$$

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

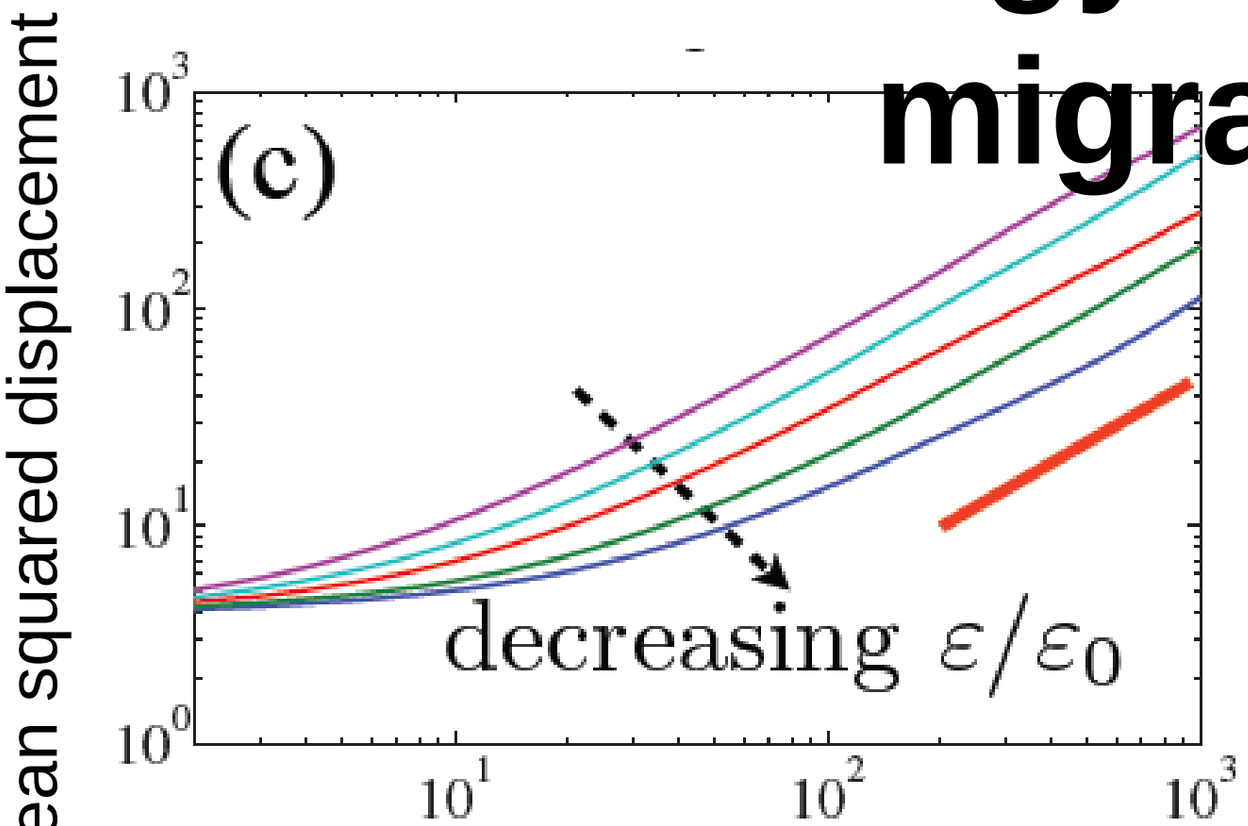
# Exponential tail + trap model = glassy dynamics

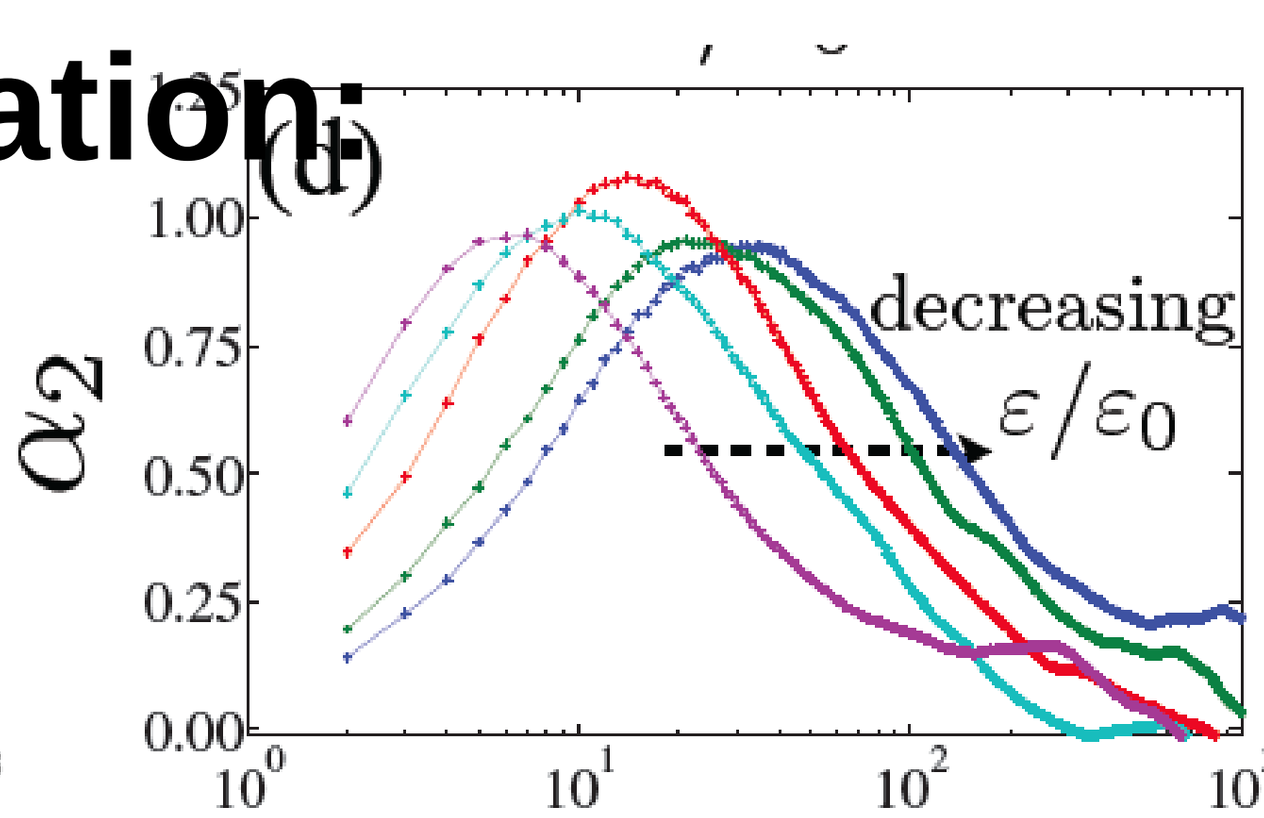


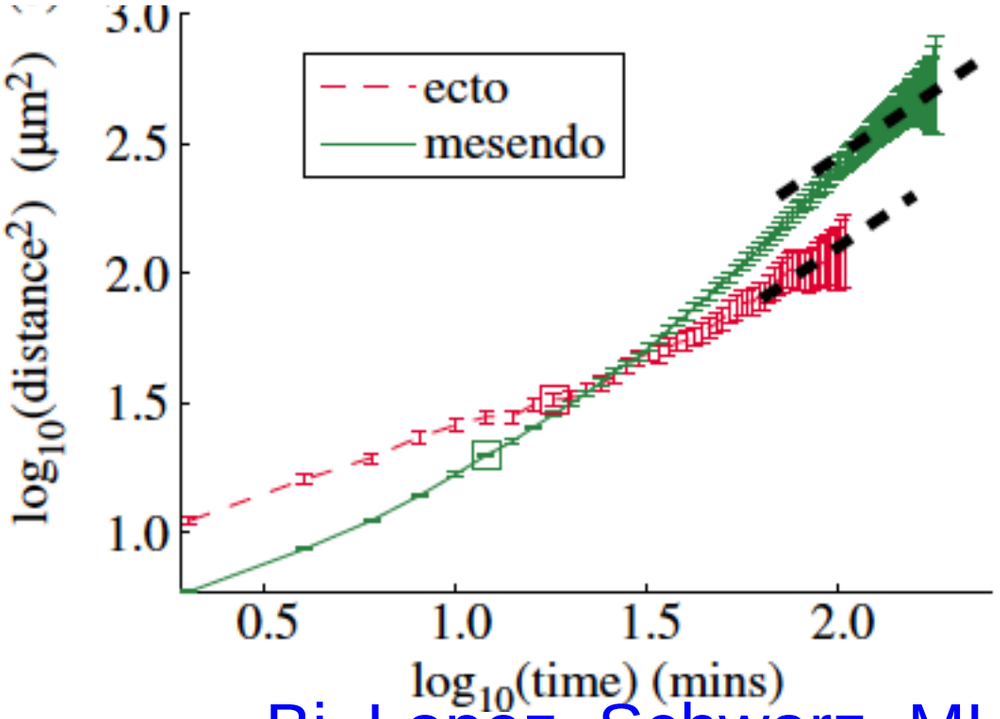
# Average energy barrier height vanishes at $p_0$*~3.813

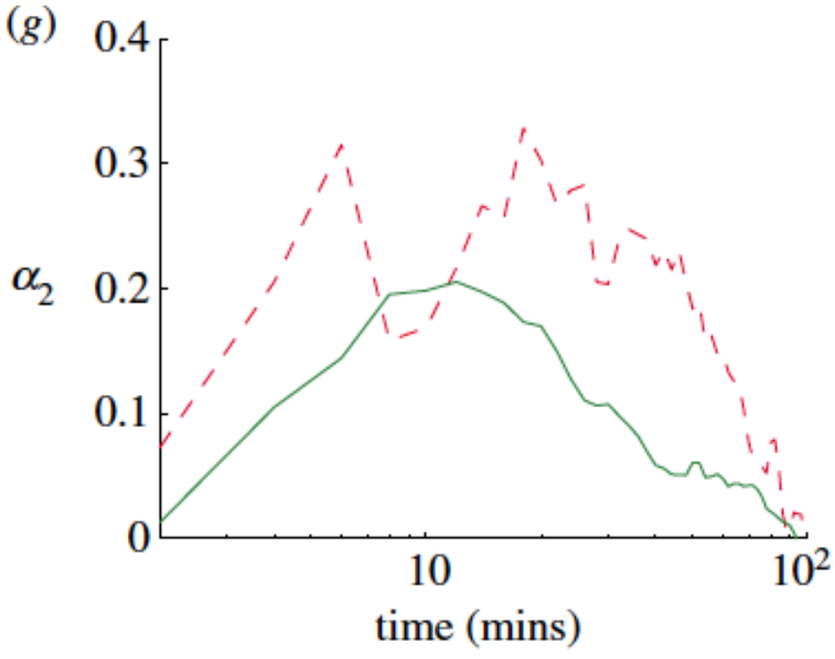


# From energy barriers to cell migration:



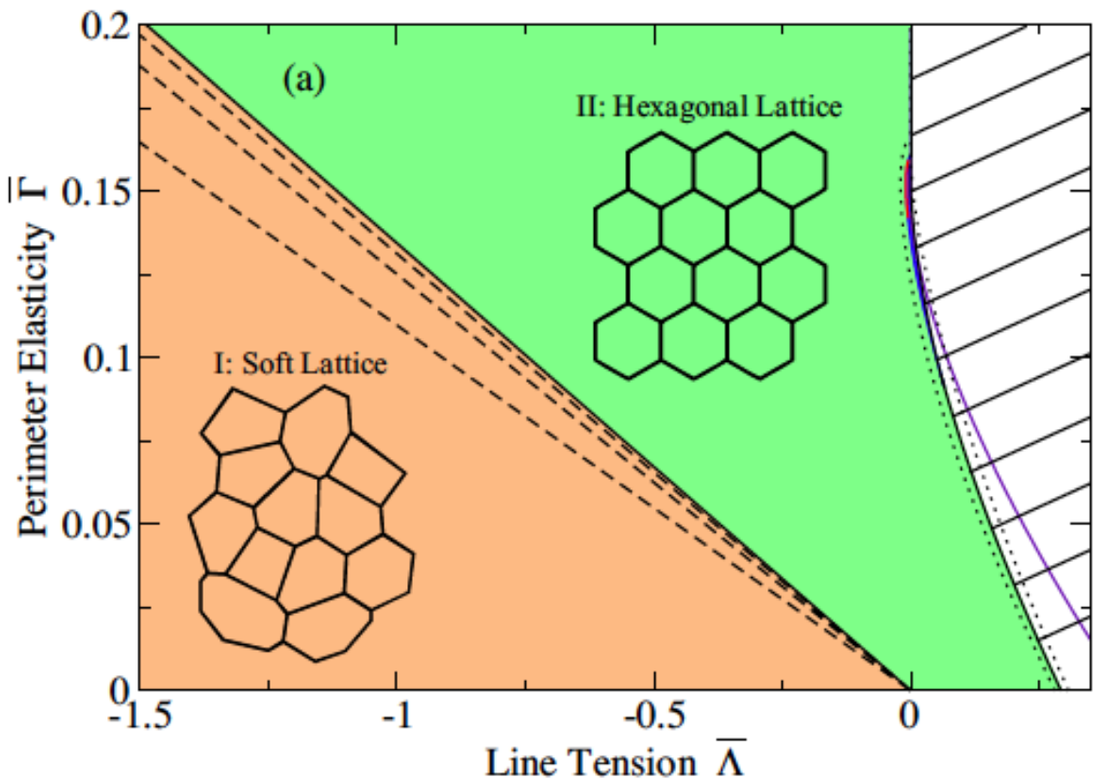



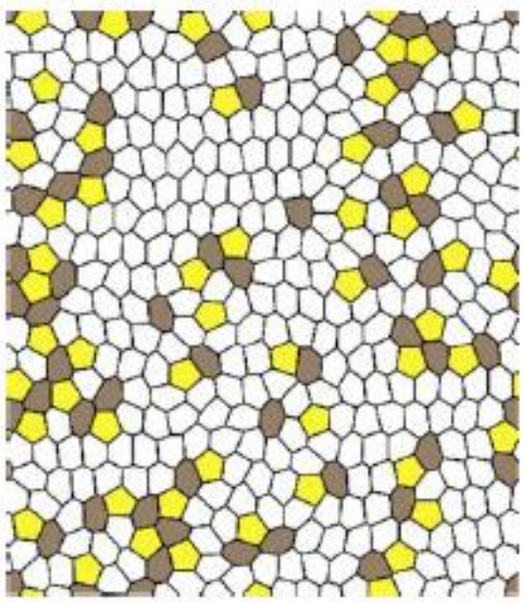




Bi, Lopez, Schwarz, MLM Soft Matter 10 (2014)

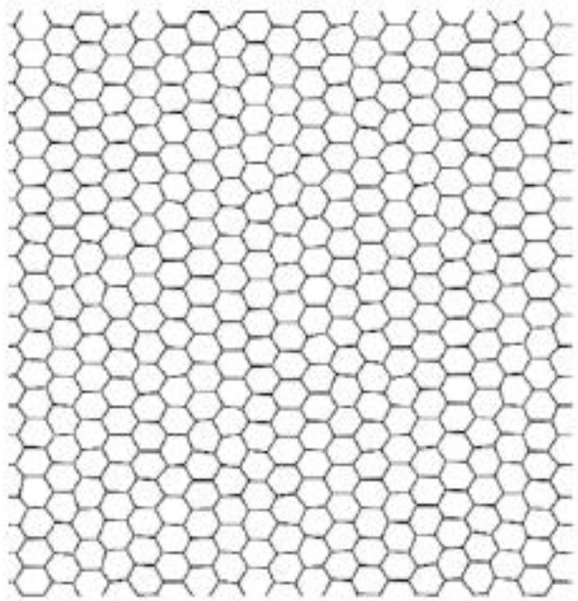
# Previous results on ground states:




Staple et al EPJE 33 (2010)



$a = 0.86$

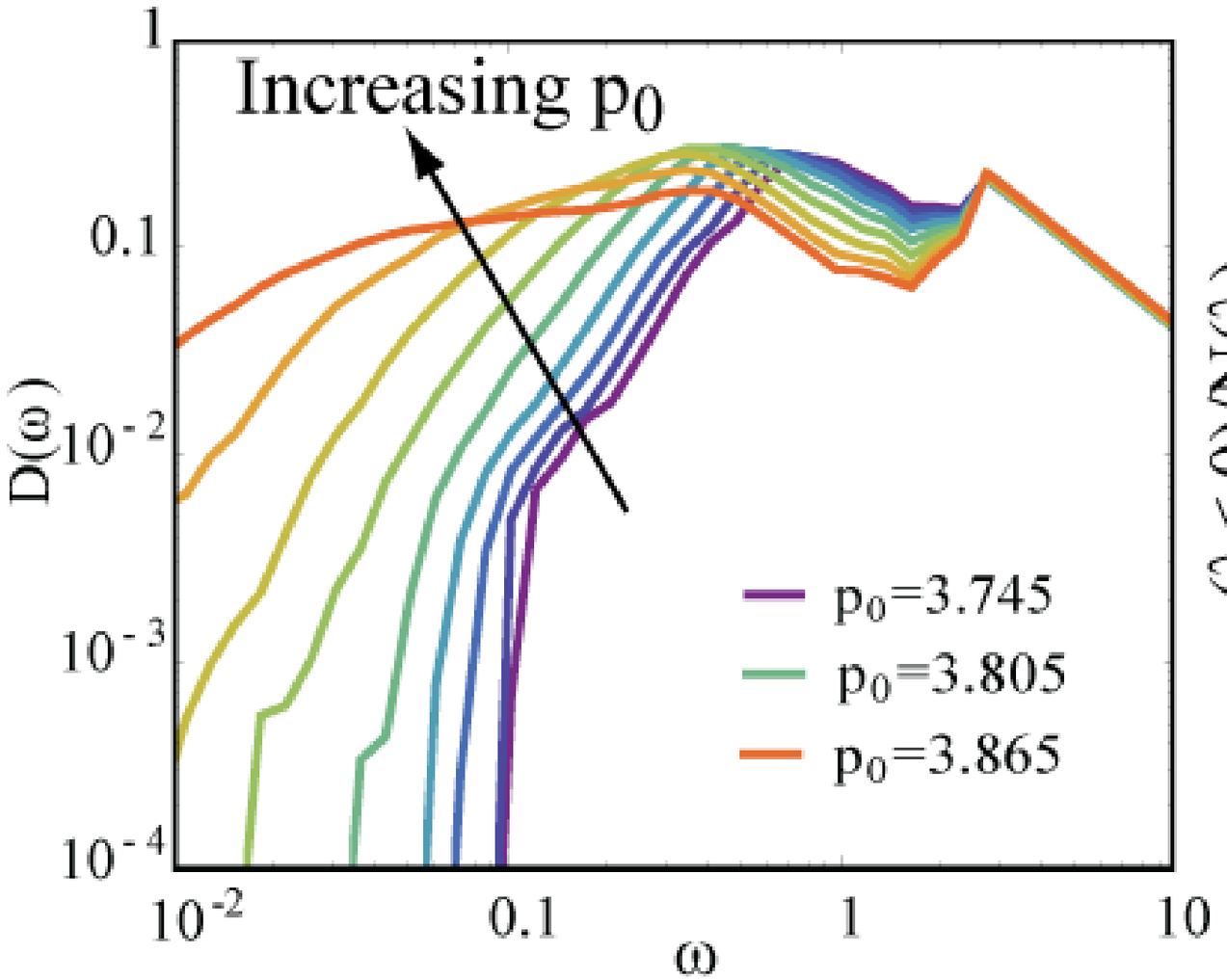


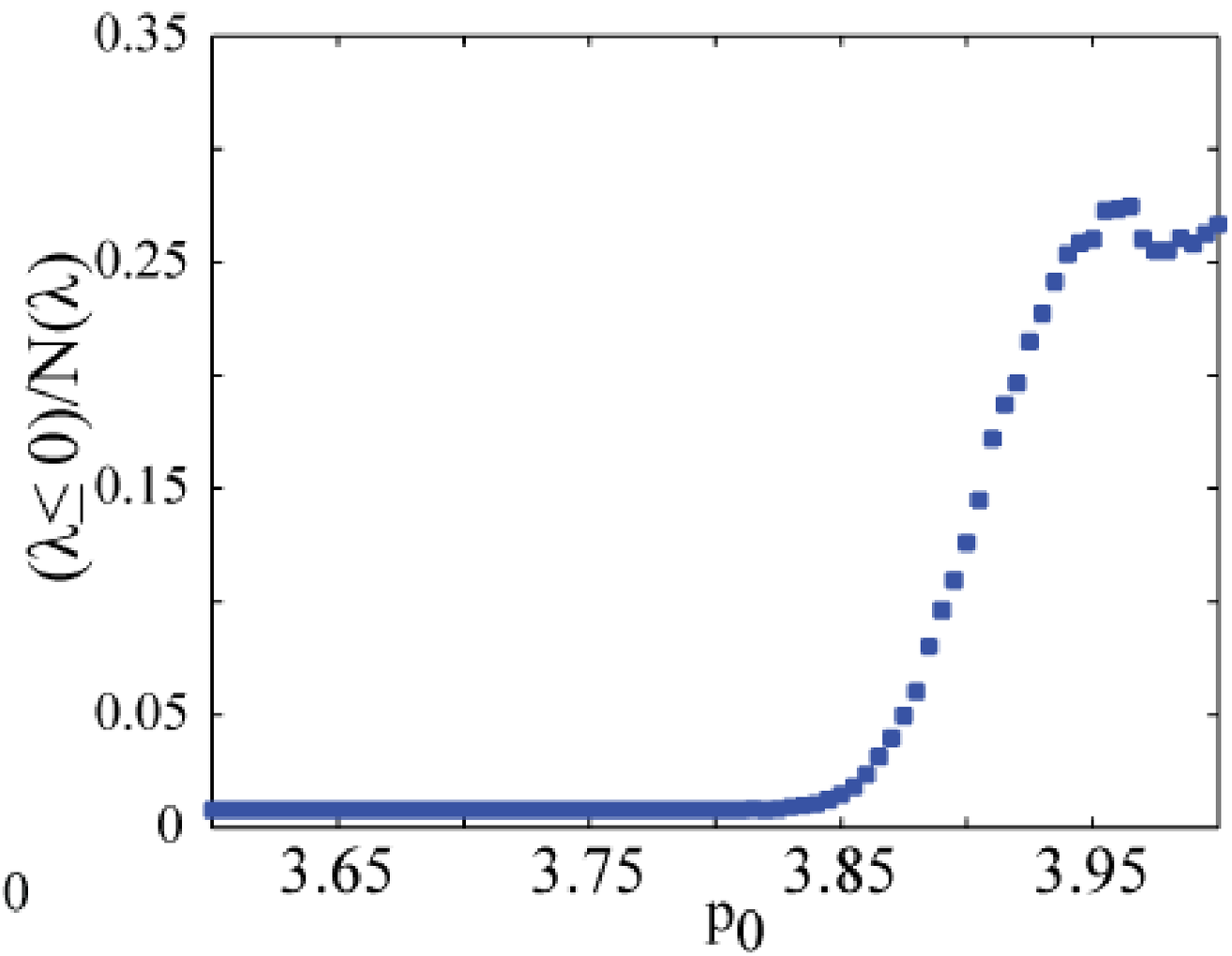
$a = 0.90$

$$a = \frac{4\pi A}{L^2}$$

Hocevar and Ziherl PRE 80 11904 (2009)

# What about normal modes? Collective behavior? Is it okay to study localized T1s?



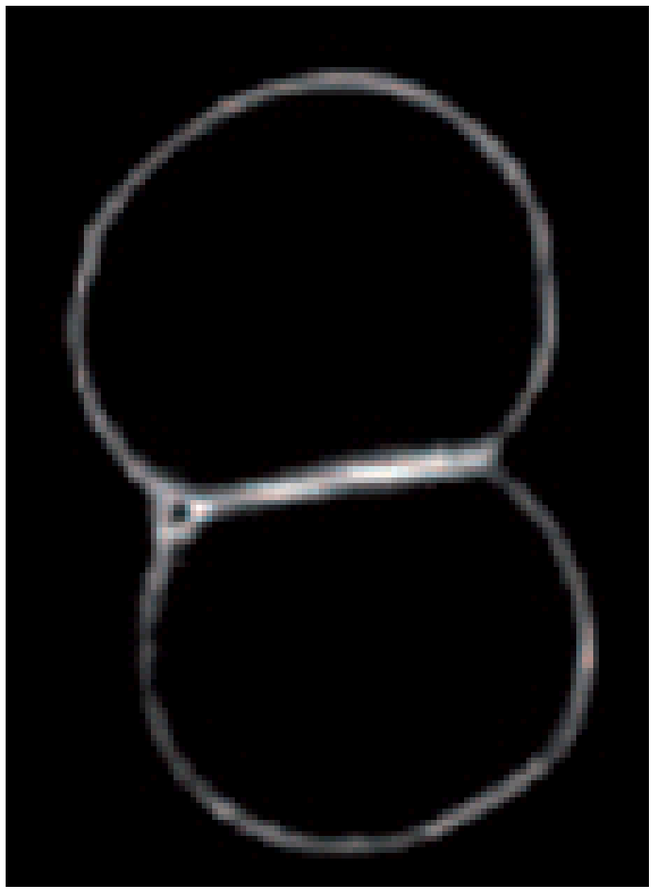
# “Shape equilibrium” or “vertex” model: what mechanical forces act to generate cell shapes?

1. Cell-cell adhesion: cadherins, alpha-catenin, beta catenin, etc.

2. Active cortical tension: myosin II, actin (Experiments: Evans, Theory: Joanny, Prost et al)

3. Bulk effects: fluid resists dialation/ compression, cytoskeleton resists shear

4. Cortical elasticity: cytoskeletal networks



Devries et al, Development **131**, 4435–4445 (2004)