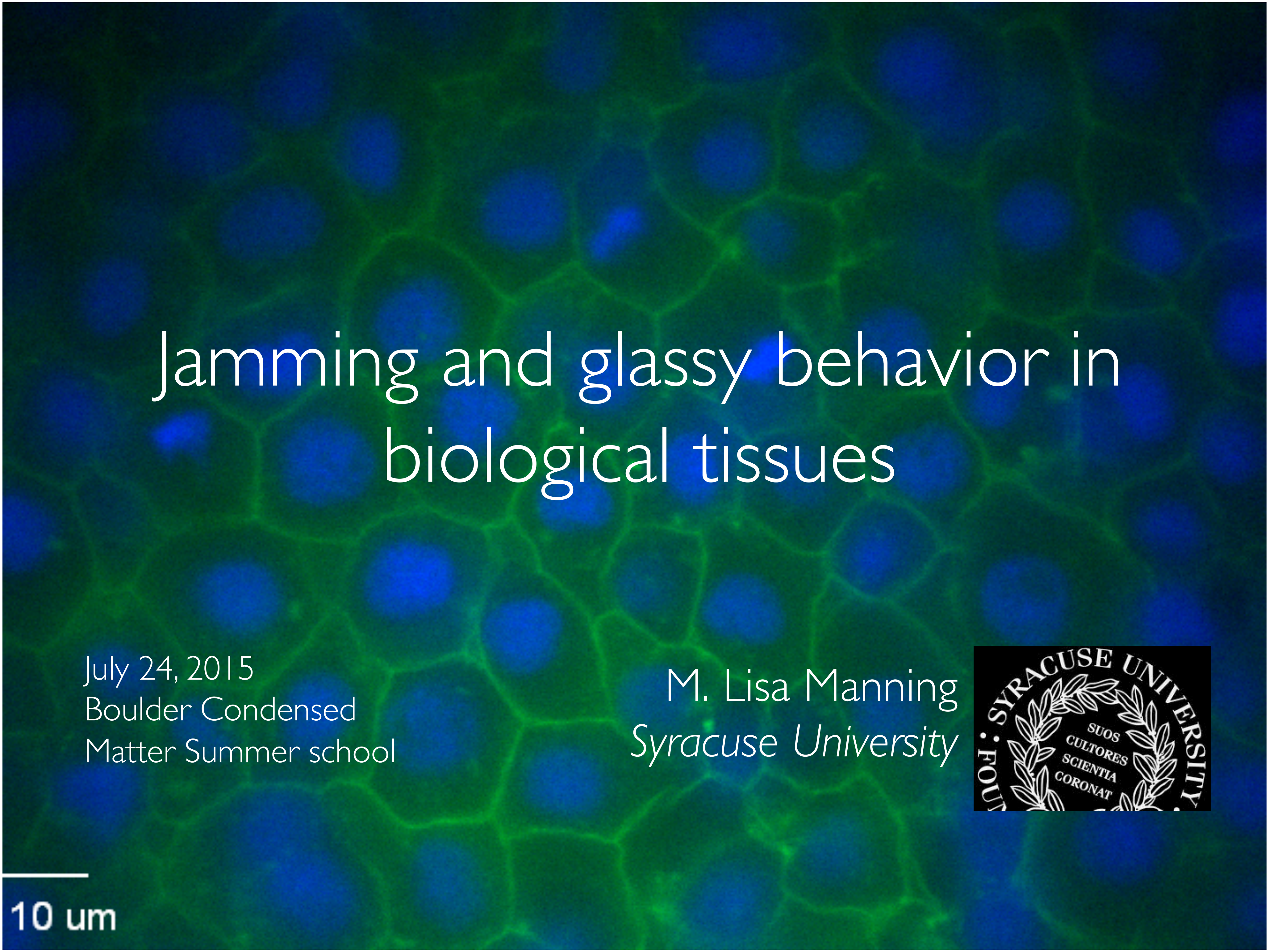
Jamming and glassy behavior in biological tissues

M. Lisa Manning
Syracuse University

July 24, 2015
Boulder Condensed Matter Summer school



Boulder School 2006: Physics of Soft Matter: Complex Fluids and Biological Materials

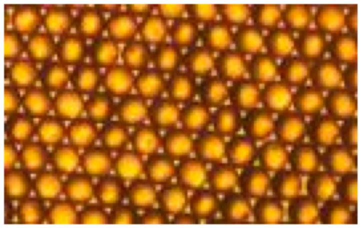
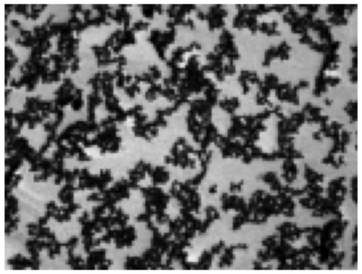
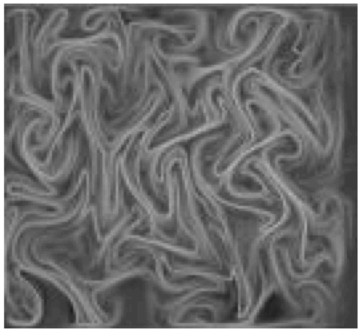
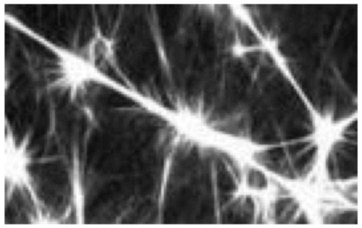
June 26-July 21, 2006

Scientific Coordinators:

Corey O'Hern (Yale), Eric R. Dufresne (Yale), Thomas R. Powers (Brown), Anthony Dinsmore (UMass)

Site Coordinator: Leo Radzihovsky

Thanks, Leo!

Also: Doing biophysics and work-life balance

Manning group and collaborators

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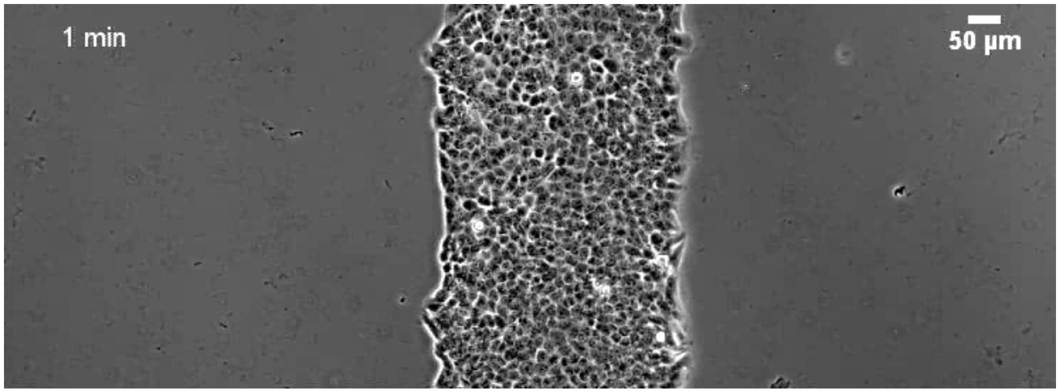
Henderson Group (Syracuse Biomaterials Institute)
Turner Group (SUNY Upstate Medical)

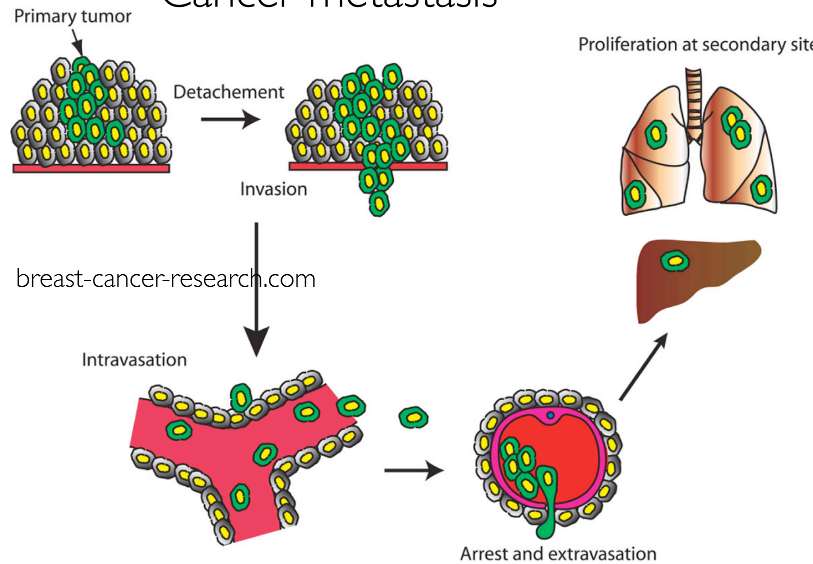
Why study cell motion in dense tissues?

Wound healing



Silberzan lab

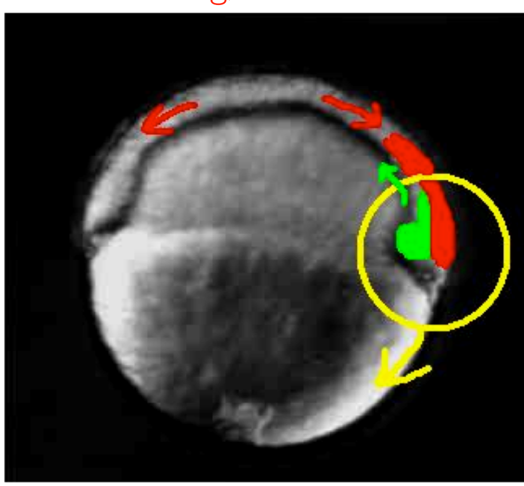
Cancer metastasis



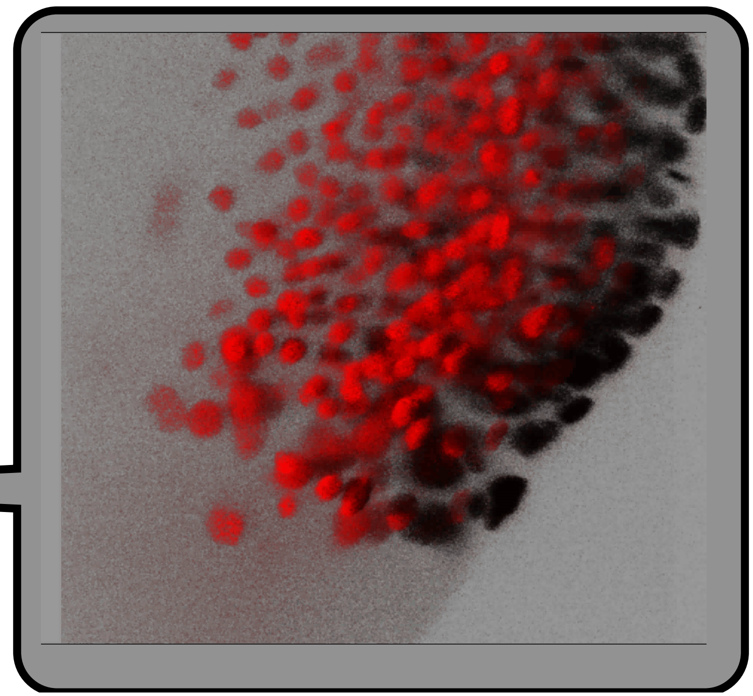
breast-cancer-research.com

Embryonic development

Differential Adhesion Hypothesis:
Steinberg, Science 1962

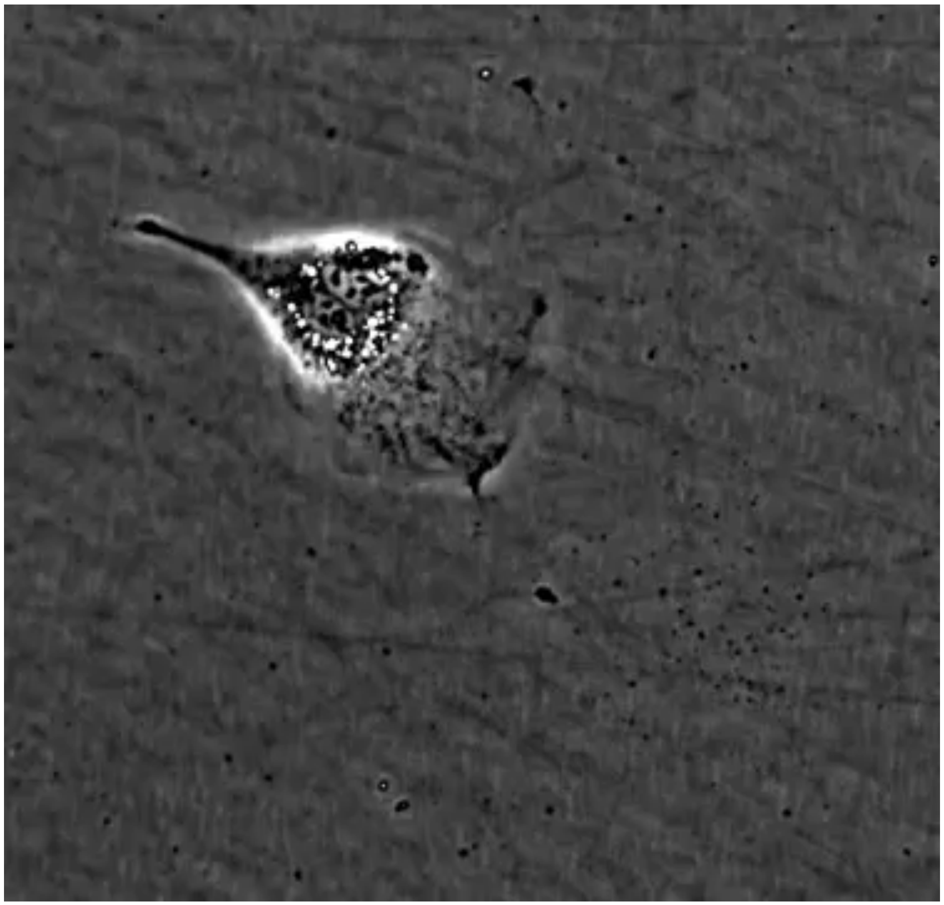


Schoetz 2008



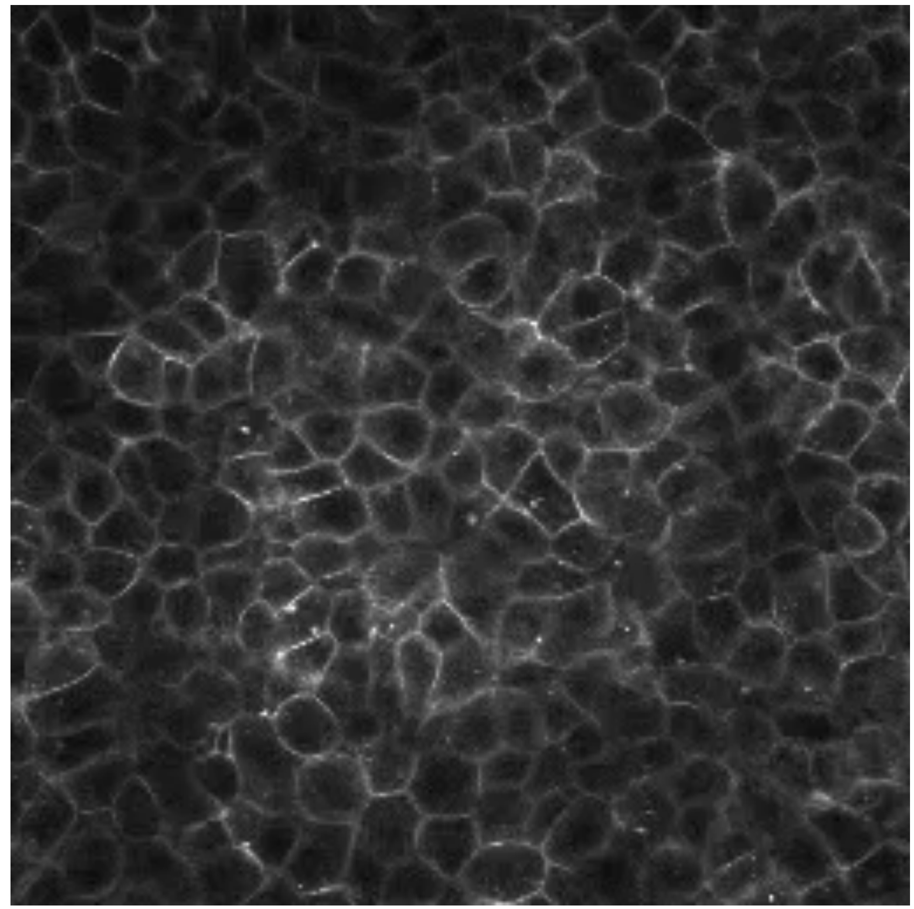
How do cells move?

In isolation vs. in dense tissue



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

Human bone cancer cell on fibronectin



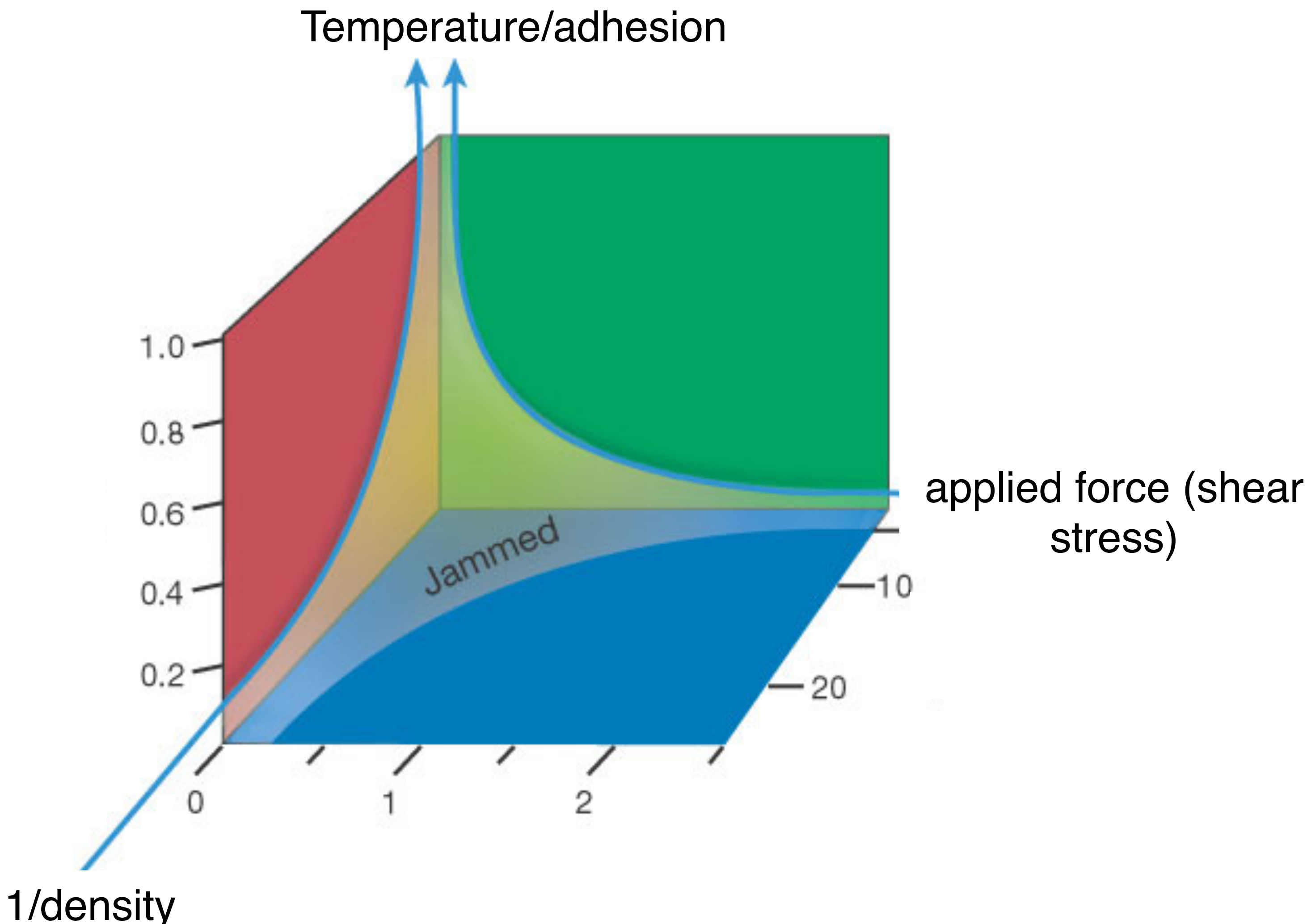
Zebrafish embryo
Schoetz Lab, UCSD

Perhaps some features of cell motion in tissues are a simple consequence of being crowded together

How do we quantify this?

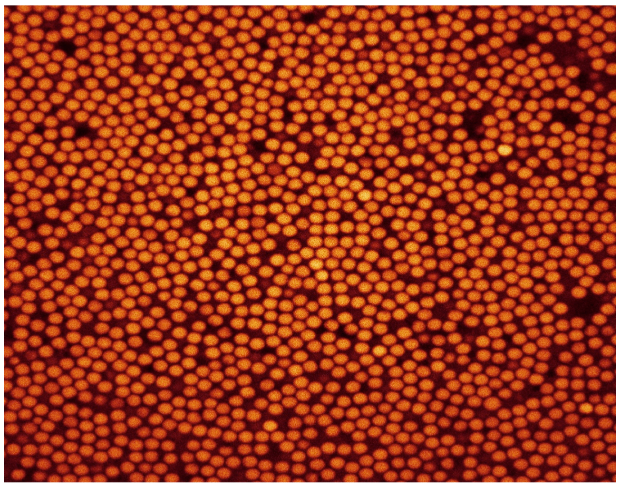
Use tools from jamming and the glass transition

Jamming phase diagram for inert matter

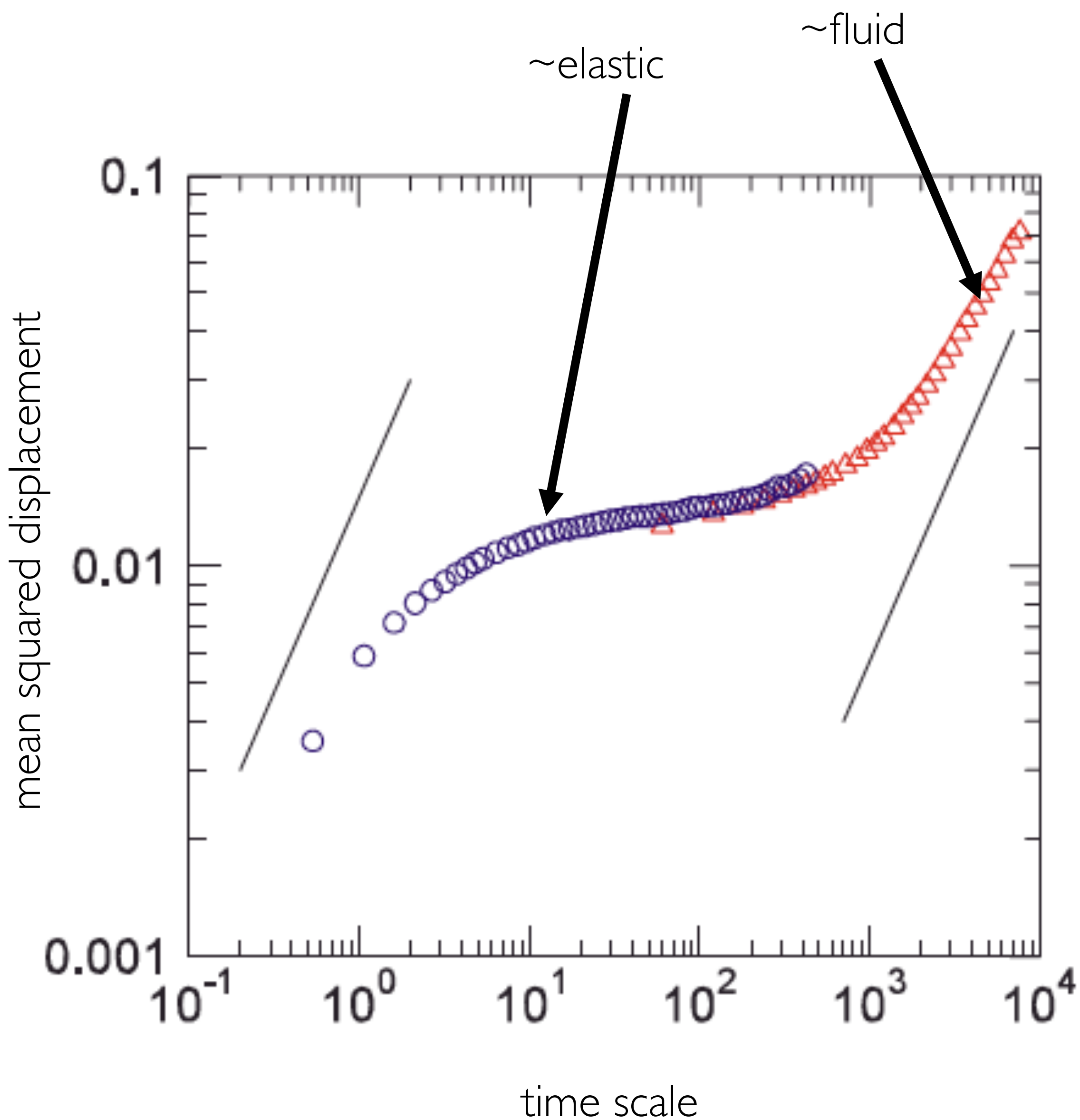


Trappe et al, *Nature* **411**, 772-775 (2001)

two-point correlation function: mean squared displacement

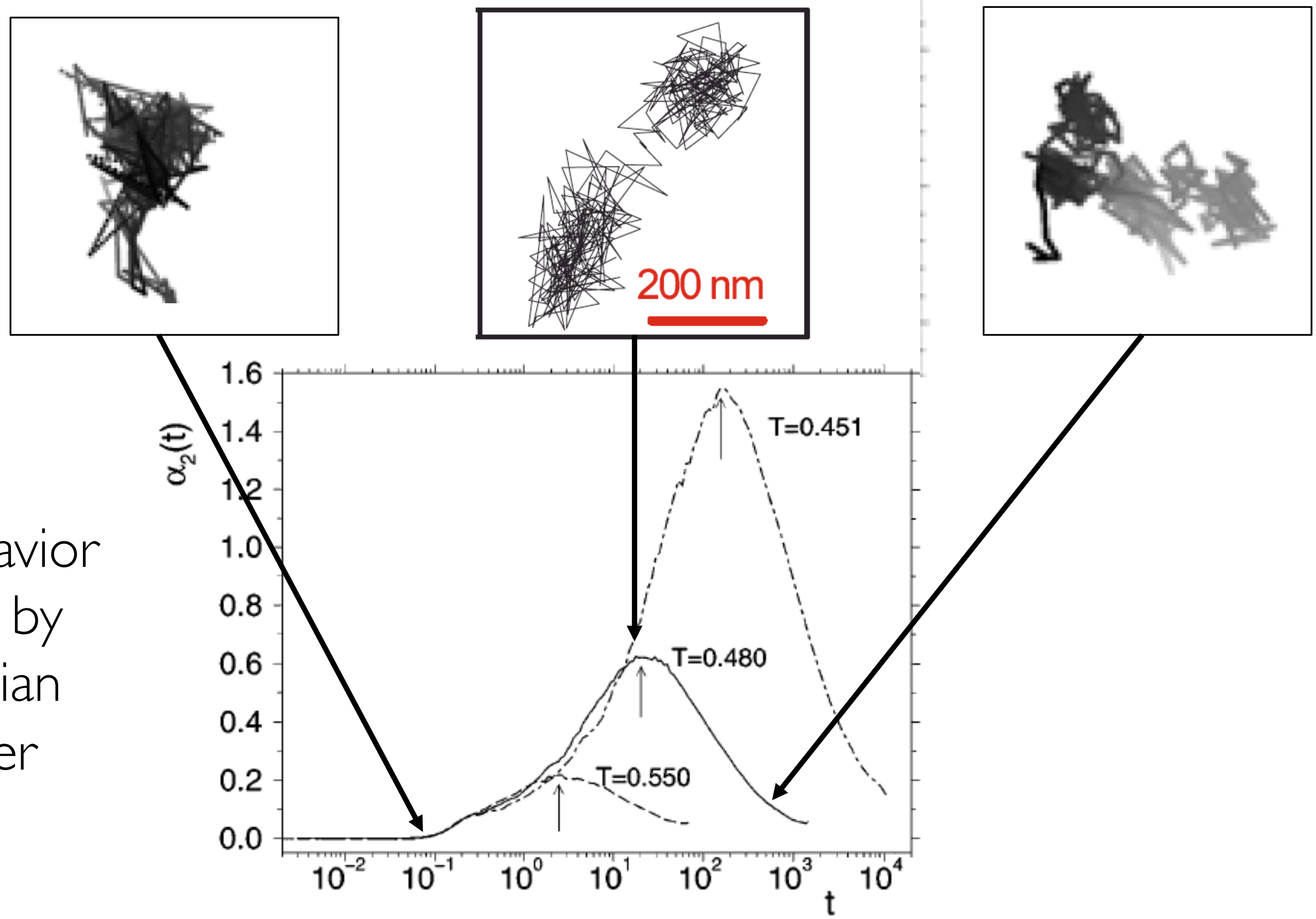


A colloidal glass.



Non-gaussian parameter

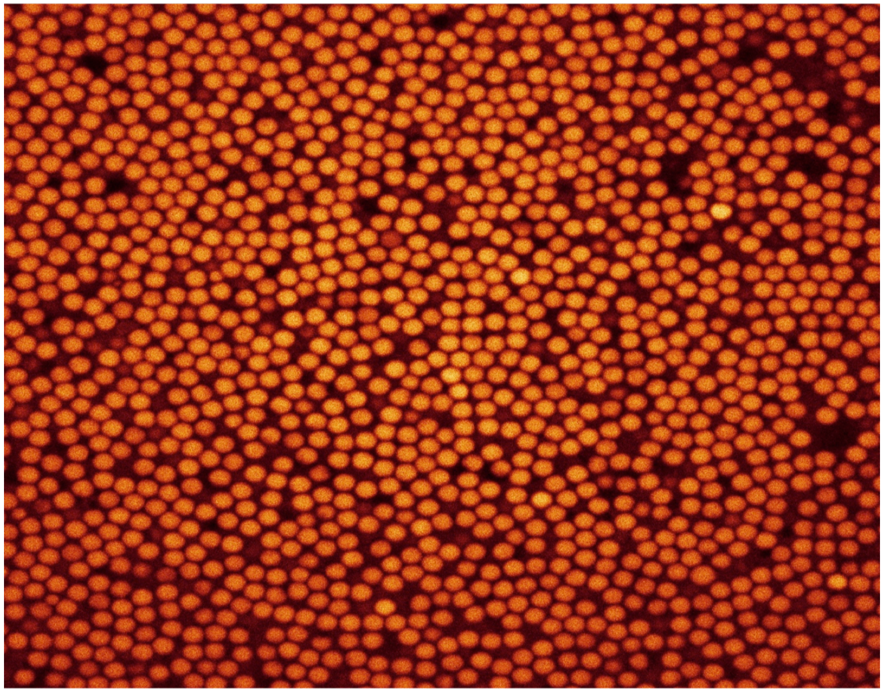
Weeks, Crocker, Weitz (2004)



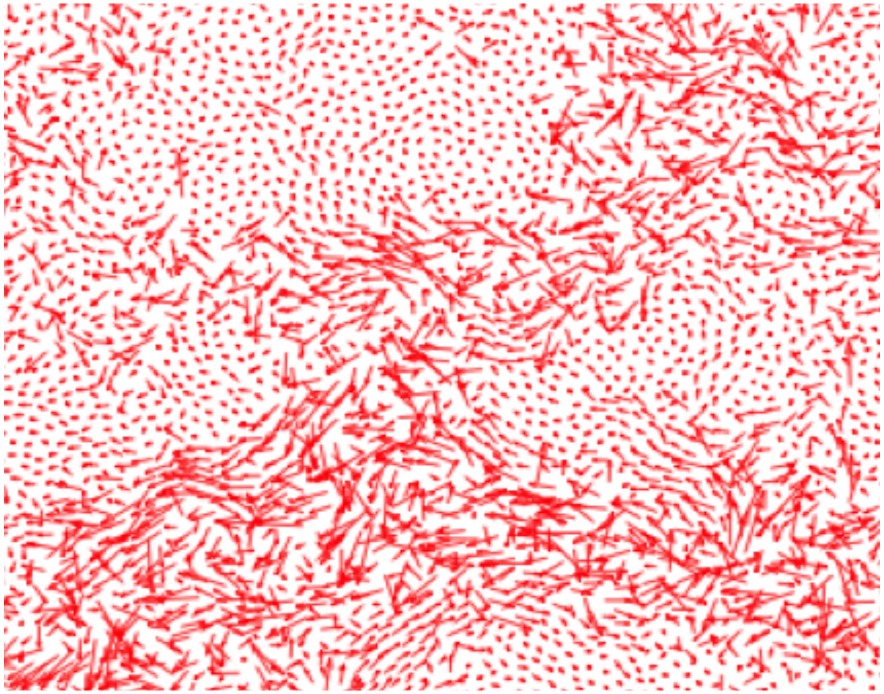
Caging behavior measured by non-gaussian parameter

Kob et al, PRL 79 15 2827 (1997)

Dynamical heterogeneities



A colloidal glass.

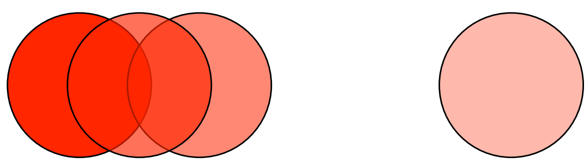


Displacement profile in simulation of a 2-d glass former.
Berthier PRL 2011

Four point correlation functions: captures "swirls" or "dynamical heterogeneities"

$$G_4((r-r');(t-t')) \;=< \rho(r',t')\rho(r',t)\rho(r,t')\rho(r,t) >$$

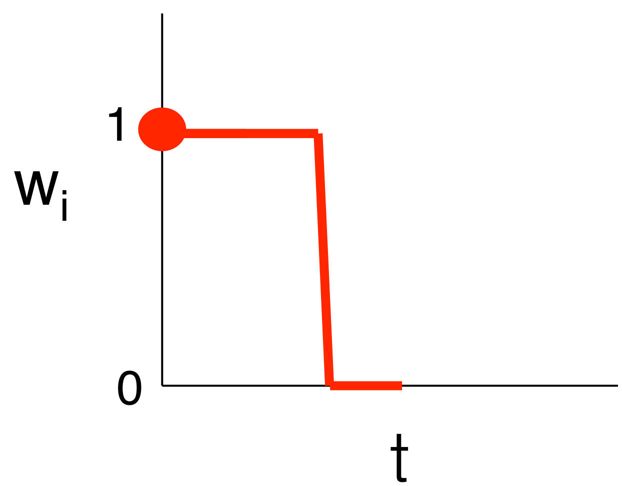
$$Q_t(l,\tau) = \frac{1}{N}\sum_{i=1}^{N} w_i, \quad w_i = \begin{cases} 1, & overlap > l \\ 0, & overlap < l \end{cases}$$



t t + t1 t + t2 t + t3

$w_i = 1$ $w_i = 1$ $w_i = 0$

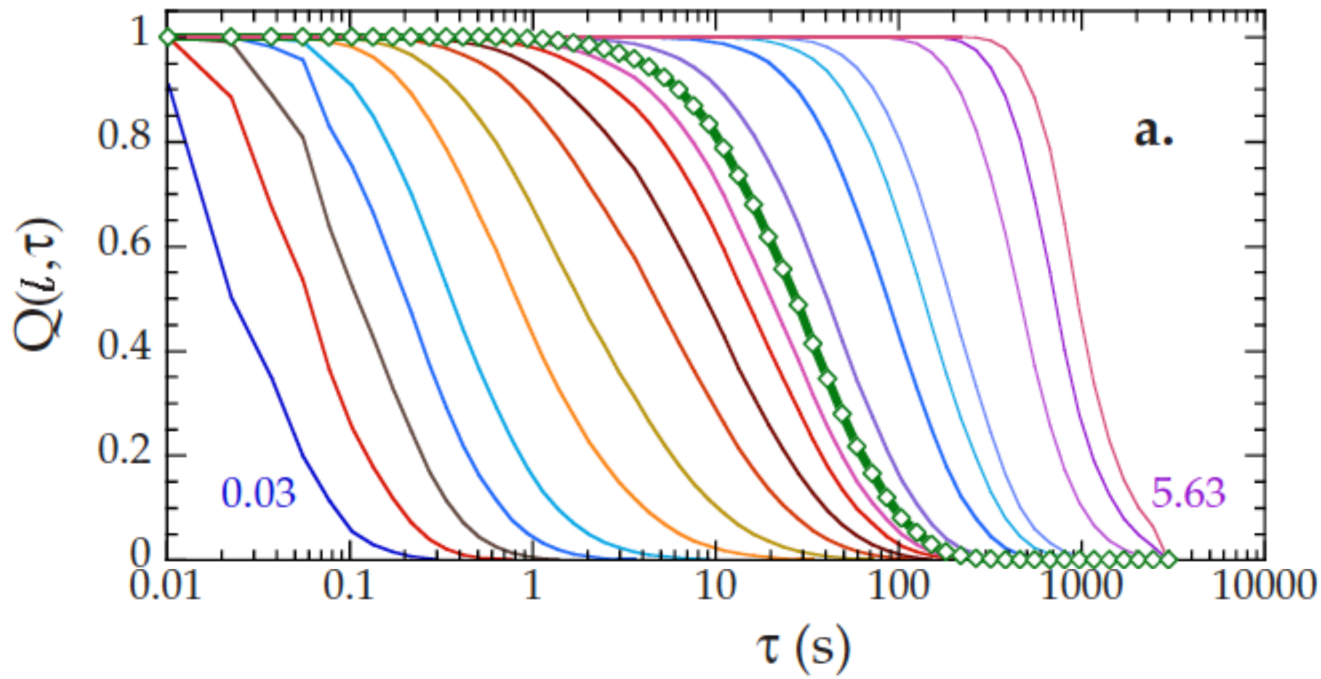
l = ½ d

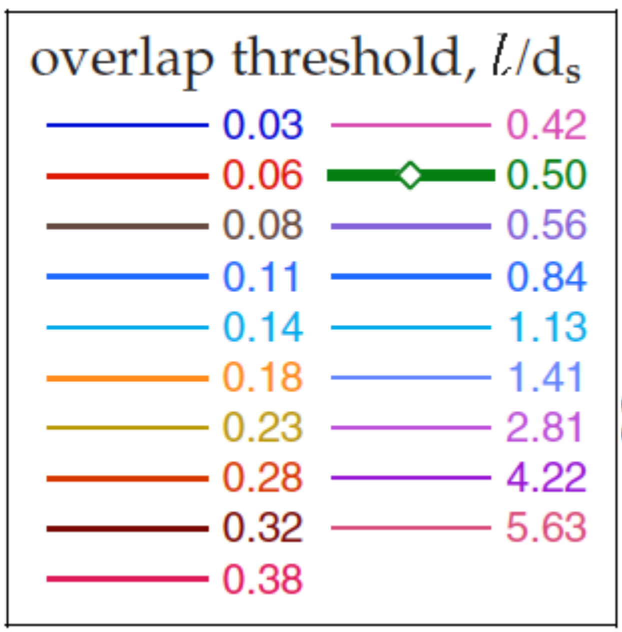


Four point correlation functions

$$Q_t(l,\tau) = \frac{1}{N}\sum_{i=1}^{N} w_i,$$

$$Q(l,\tau) = \langle Q_t(l,\tau)\rangle,$$

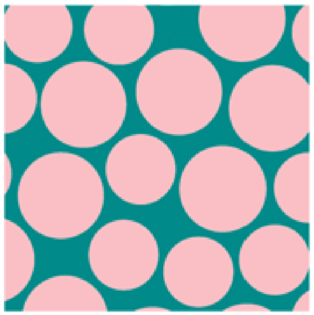


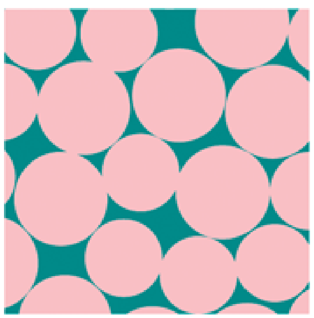


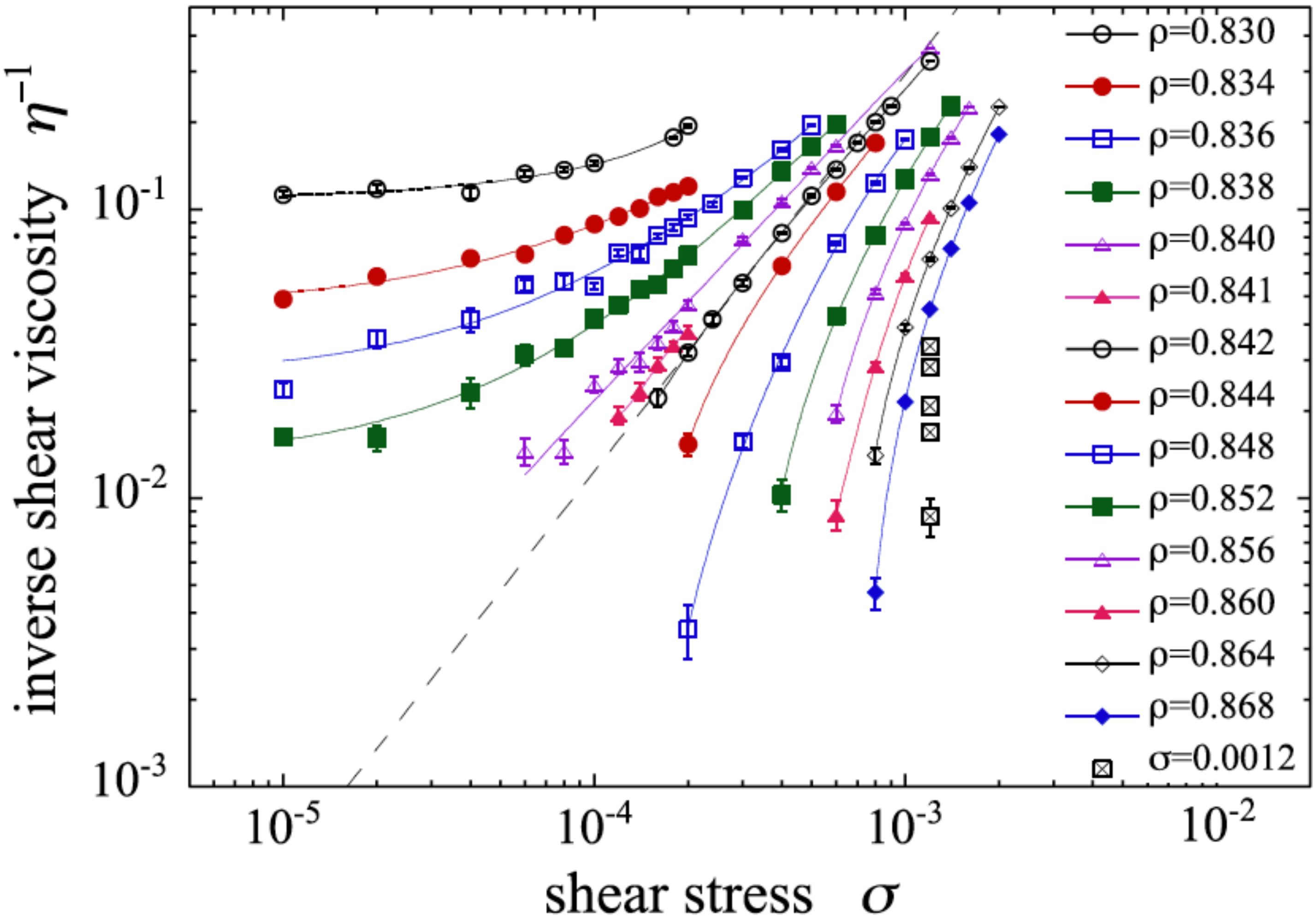
$\chi_4($ … $\rangle^2]$

Abate and Durian PRE 2007

What type of transition? 1st order? 2nd order?





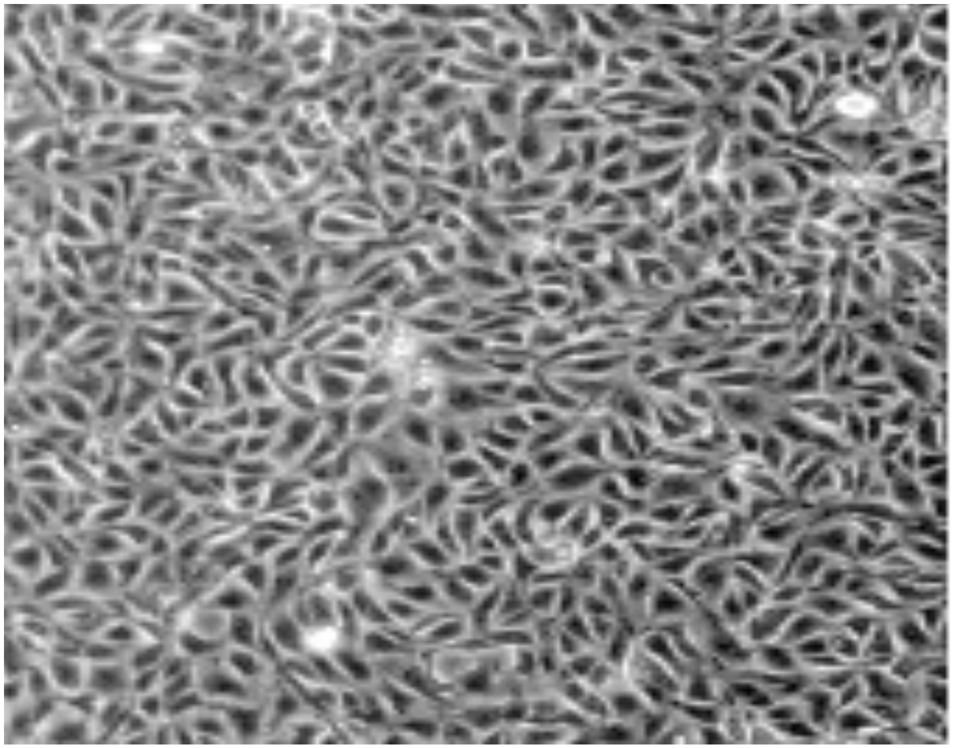


Olsson and Teitel, PRL 99, 178001 (2007)

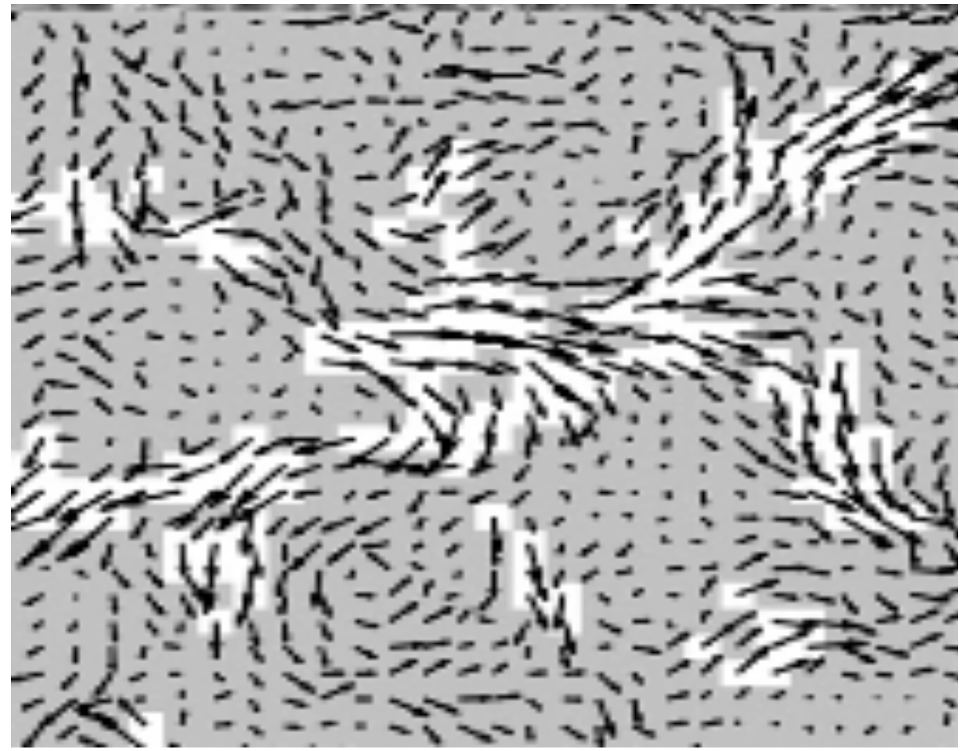
The onset of jamming is controlled by the **area density**: $(r-r_c)$

What happens in dense tissues?

Epithelial sheets show collective "swirls": dynamical heterogeneity



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

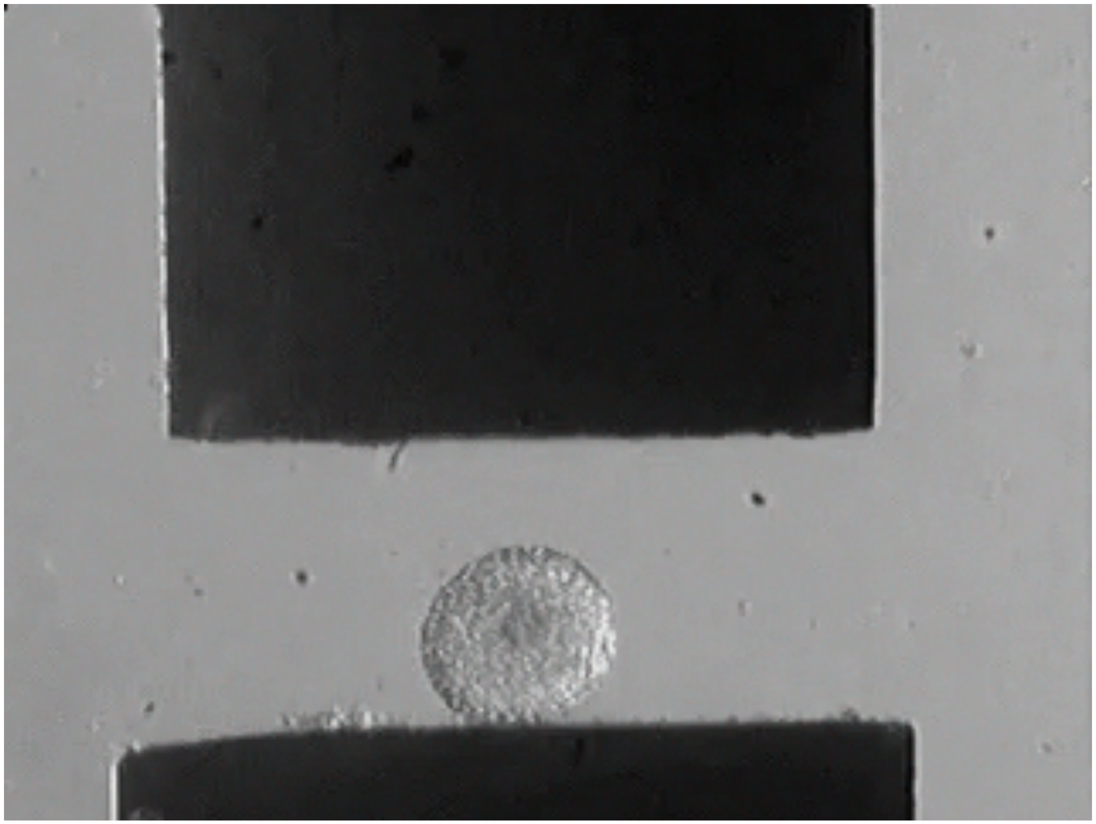


Velocity profile of cells show the spatially heterogeneous pattern in MDCK tissue.

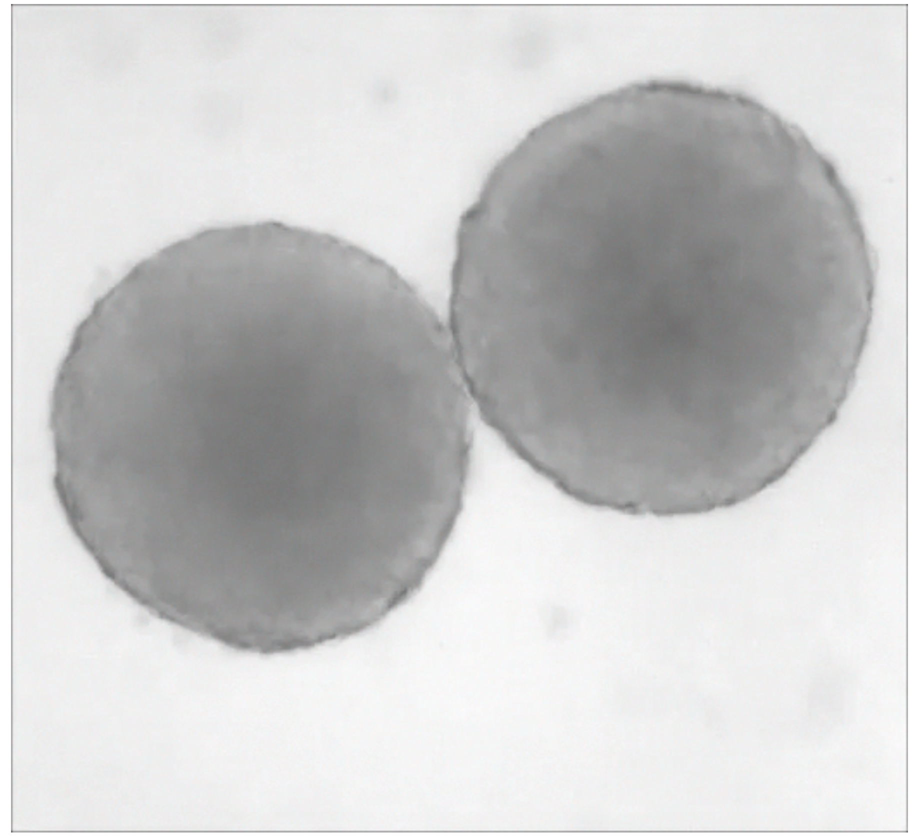
Angelini et al PNAS 2010

Early embryonic tissues are viscoelastic

timescale ~ seconds

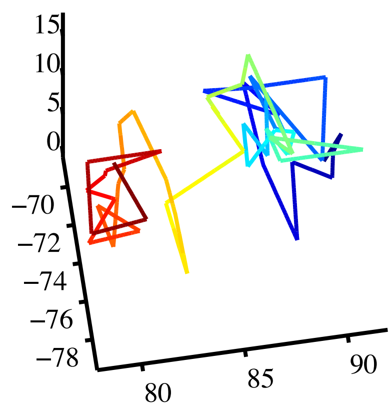


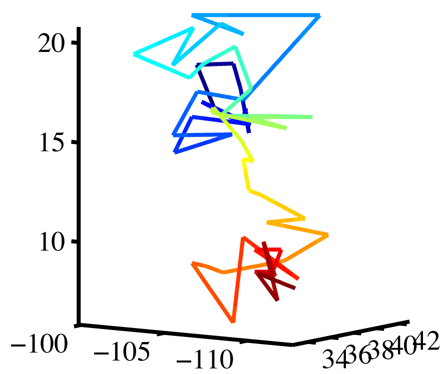
timescale ~ hours

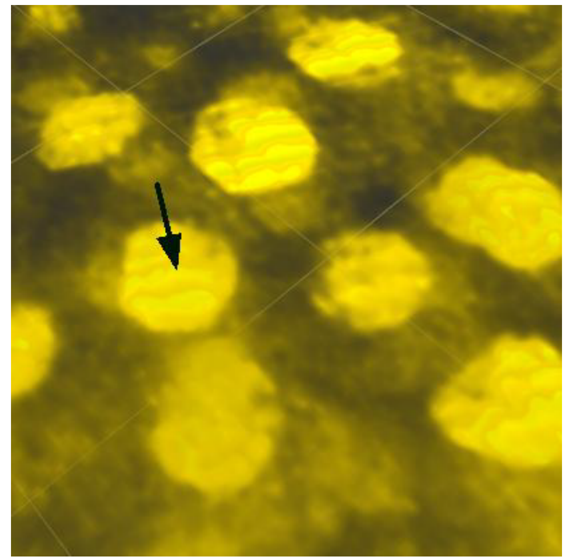


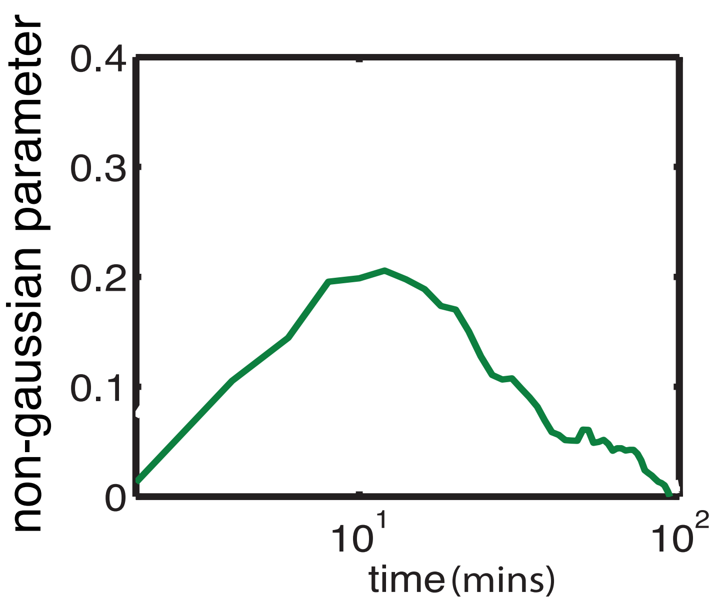
Schoetz, Lanio, Talbot, **MLM**
J. R. Soc. Interface (2013)

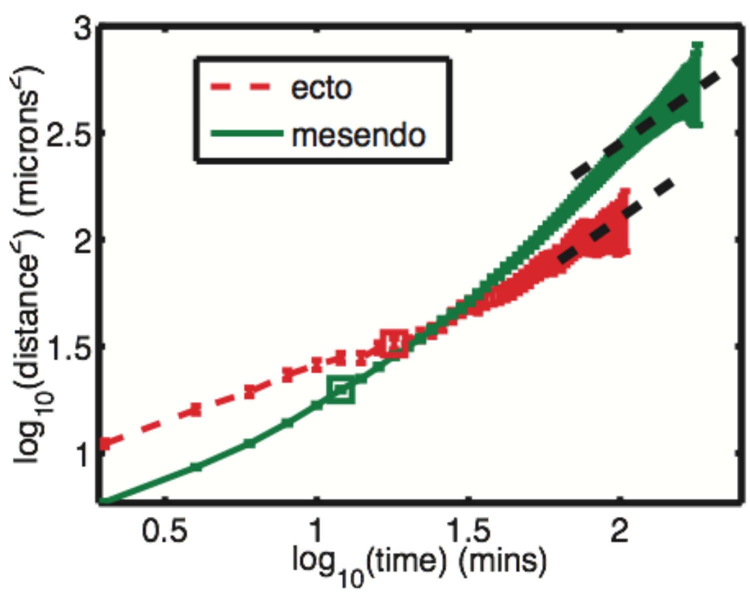
Caging behavior in tissues





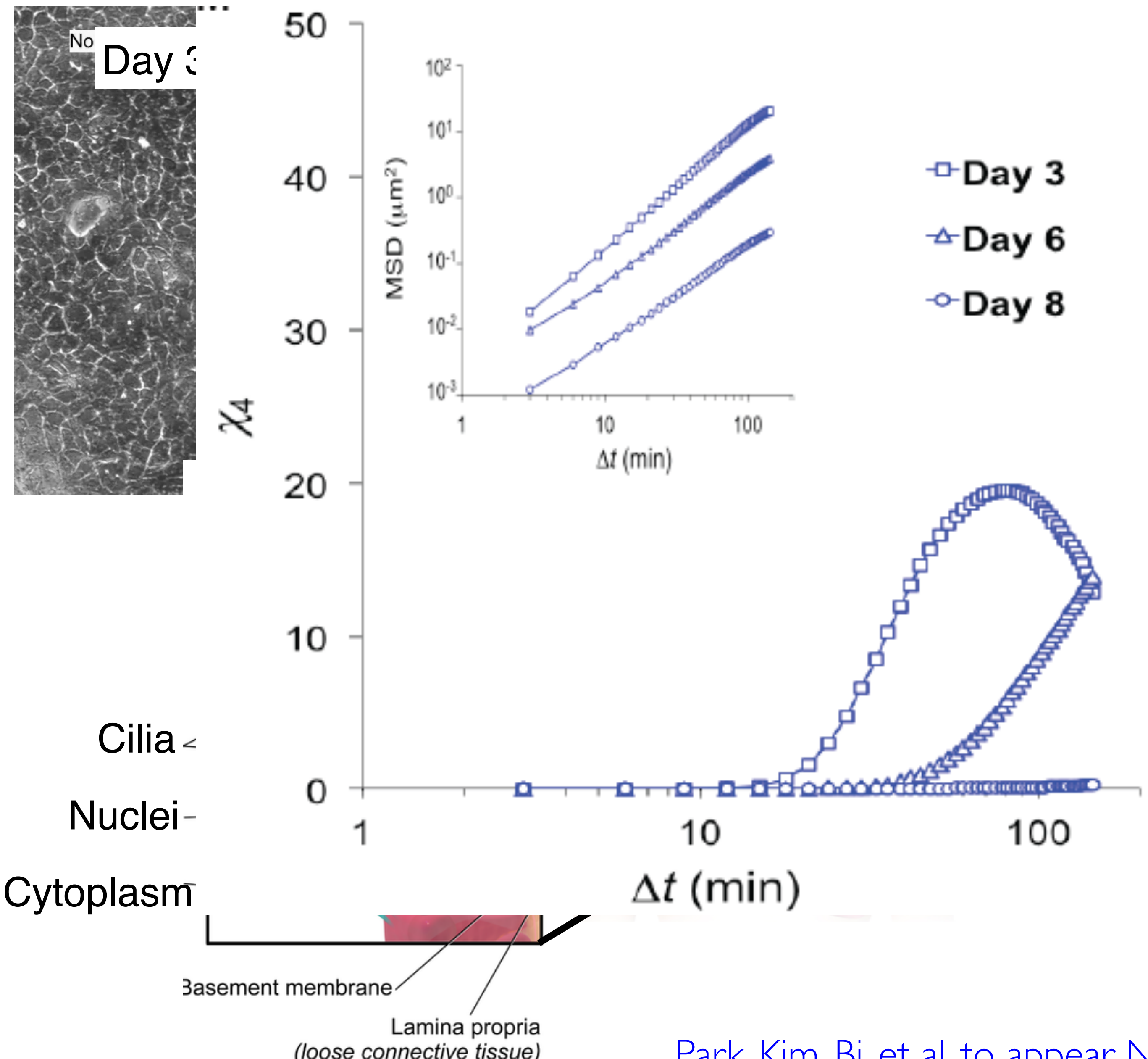


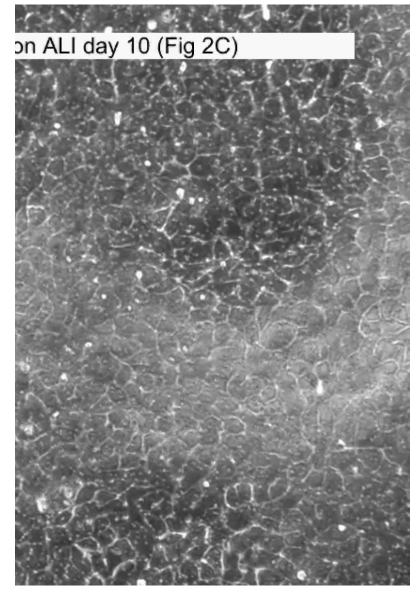




Schoetz, Lanio, Talbot, **MLM**
J. R. Soc. Interface
10(89), 20130726
(2013)

Four-point correlations





Primary Human
ıchial Epithelial Cells
(HBECs)
ɛxhibit dynamical
heterogeneties

Park, Kim, Bi, et al, to appear Nature Materials Aug 2015

What happens in models for dense tissues?

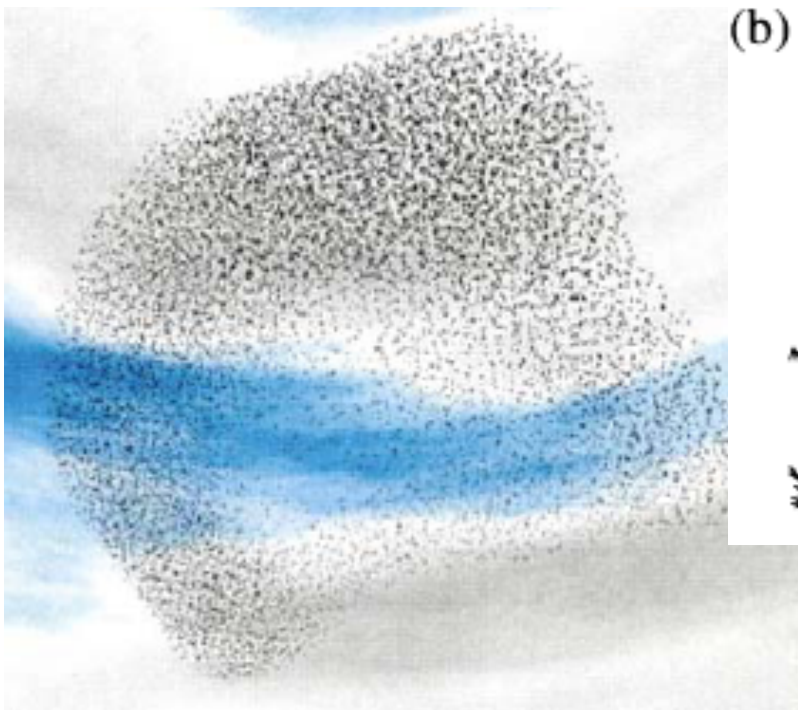
in other words, can we explain this?

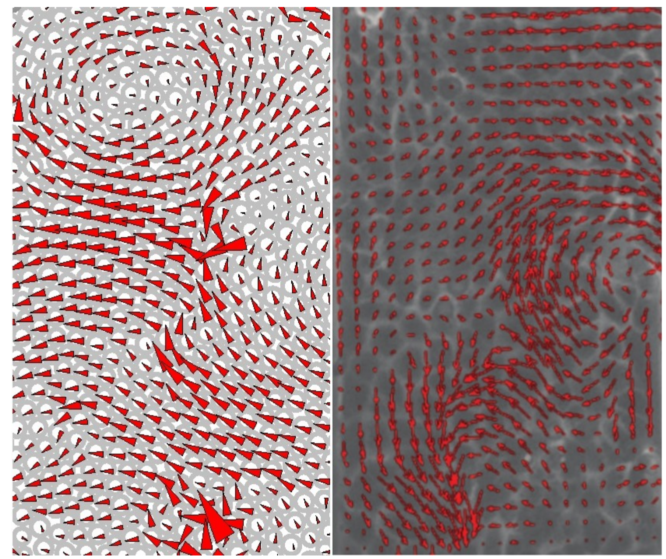
or

Let’s do physics!

Active particle models

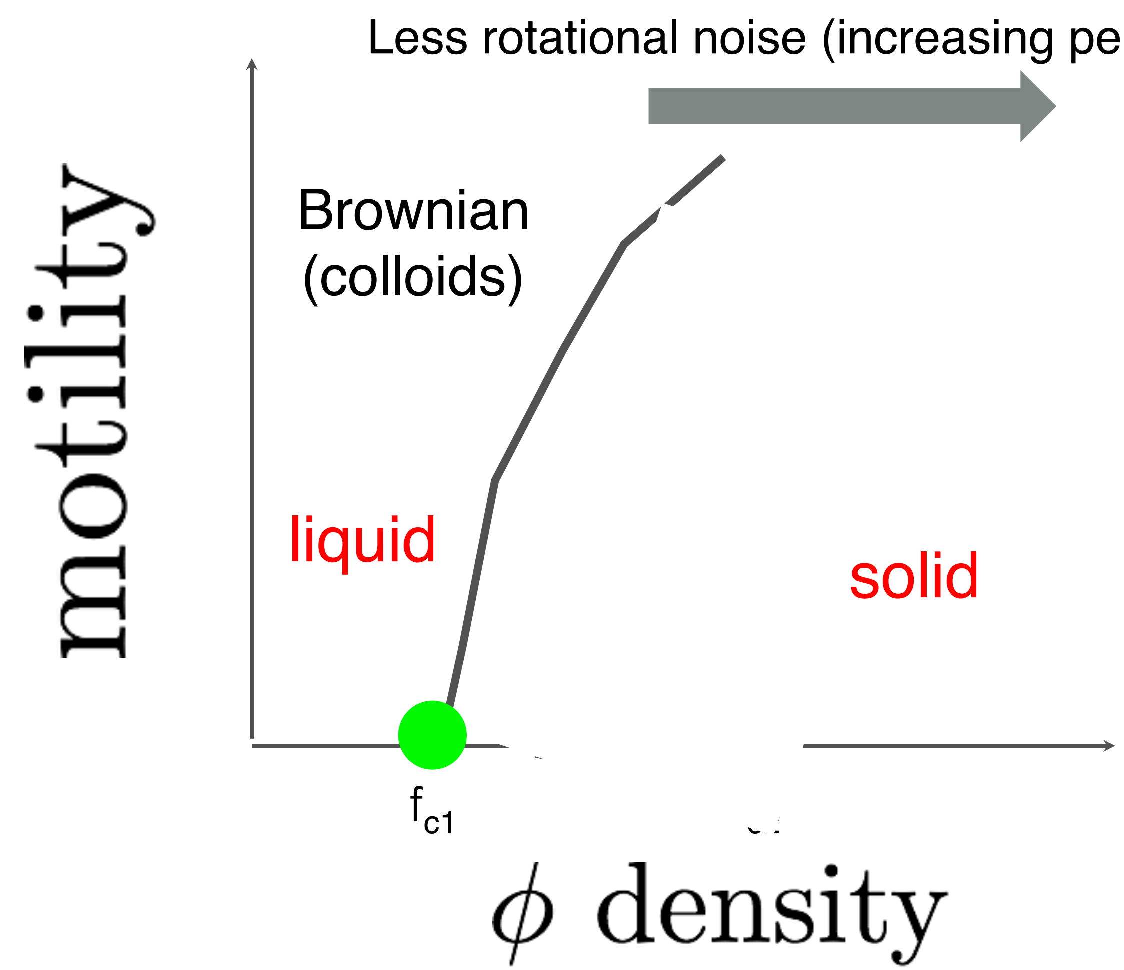
Talks this week and next by Marchetti, Dogic, etc.
Use "self propelled particle models", add short-range repulsive (and maybe attractive) interactions to mimic cells

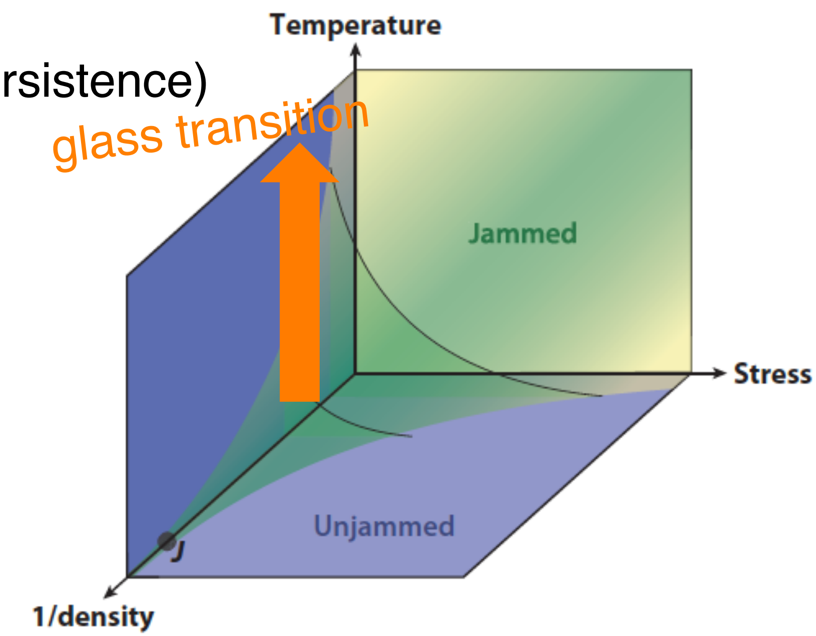




Vicsek et al PRL **76** 6 (1995), Chate et al EPJB **64**, 451–456 (2008), Henkes et al PRE **84**, (2011), Basan et al, HFSP **3** (4) 265 (2009), Ranft et al PNAS **107** (49) 20863 (2010), Schoetz, Lanio, Talbot, **MLM** J. R. Soc. Interface 10(89), 20130726 (2013), Yang, **MLM**, Marchetti Soft Matter(2014)

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

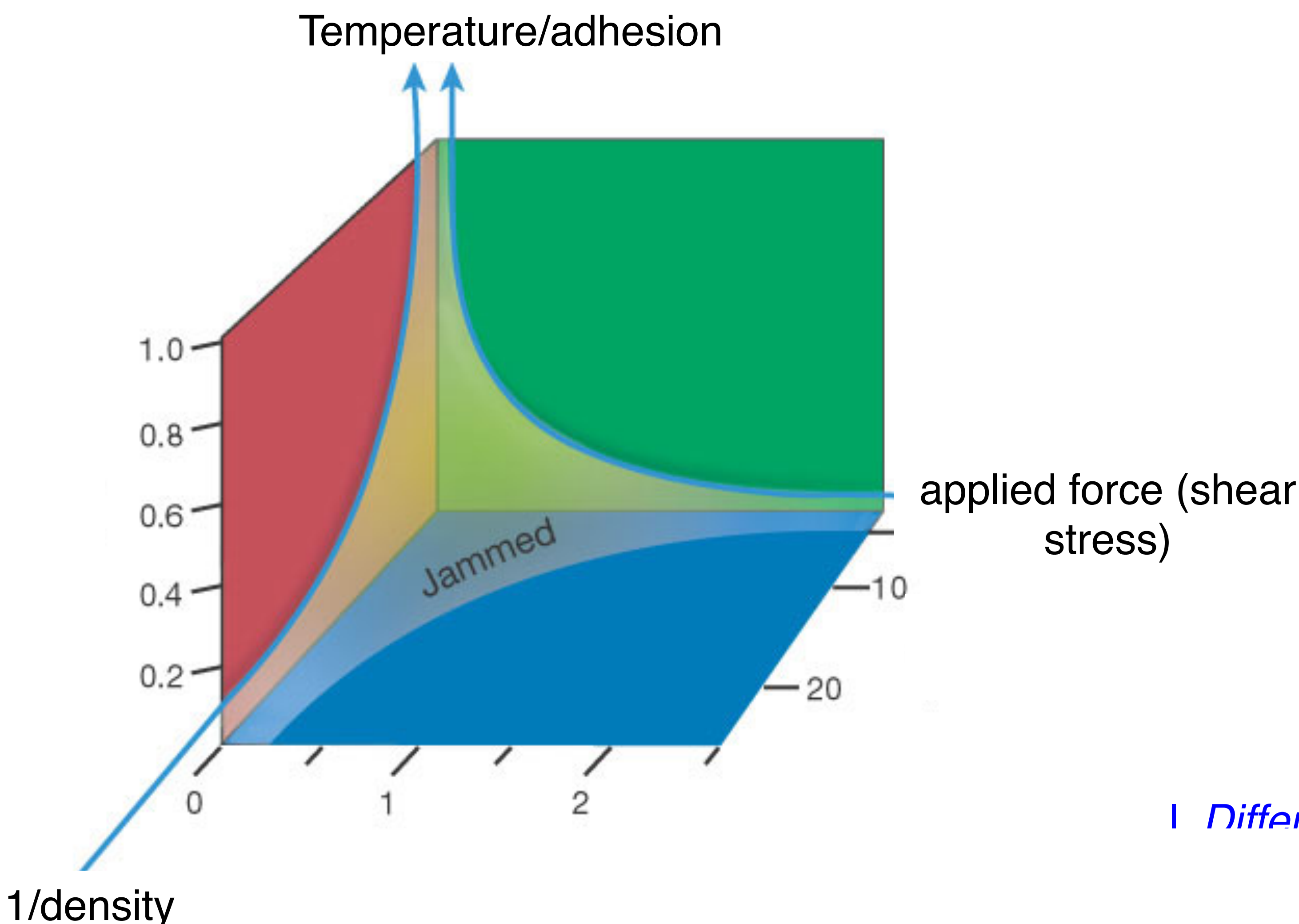




Berthier PRL 2014
Fily, Henkes & Marchetti Soft Matter 2014

*almost: f_c changes a little with the persistence time; the activity generates an effective adhesion

Jamming phase diagram for biological tissues



I *Differentiation*

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

Vector
near jamming transition

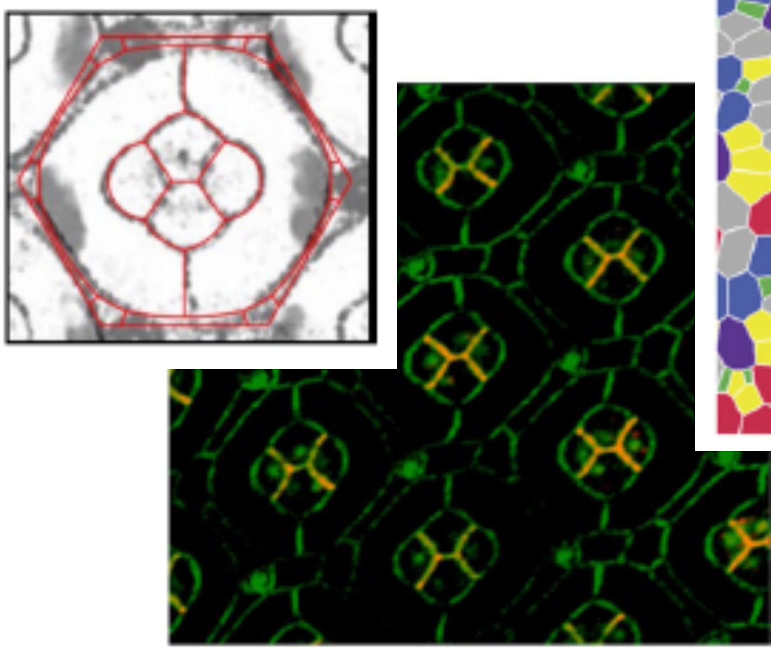
In many tissues, a density-driven transition is impossible

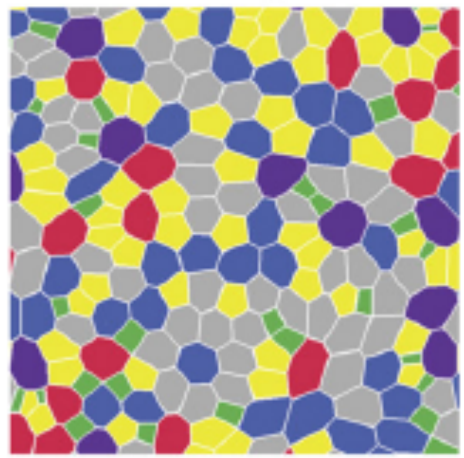
e.g. confluent tissues where there are no gaps between cells and the packing fraction is one

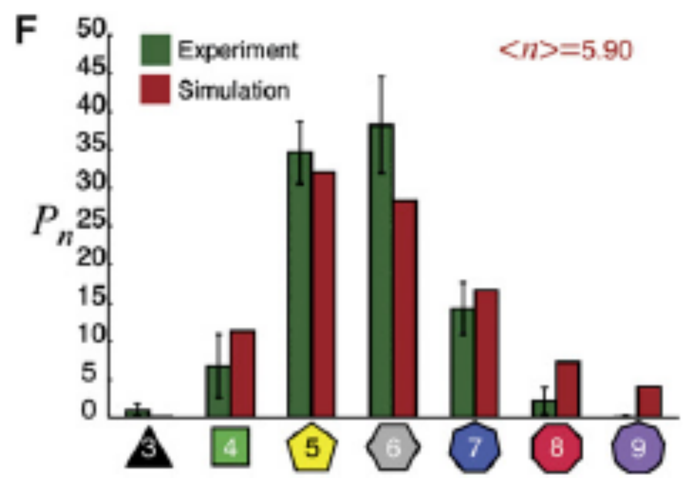
Is there some analogue to the jamming transition for confluent tissues?

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)

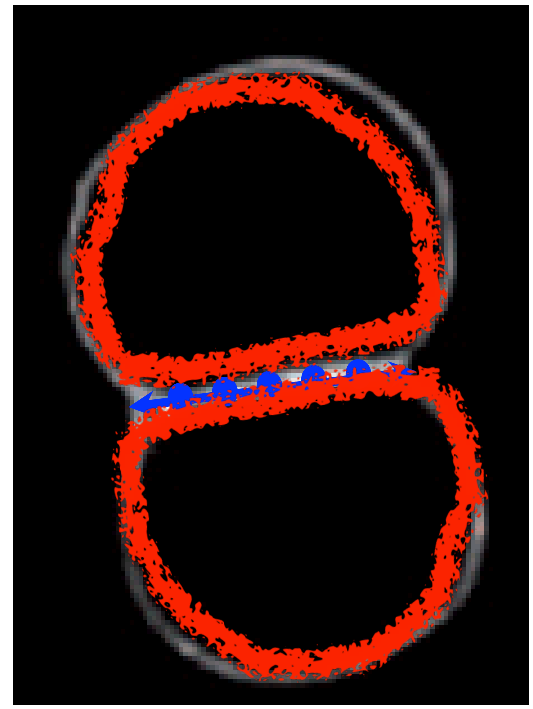
"Shape equilibrium" or "vertex" model: what mechanical forces act to generate cell shapes?

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

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

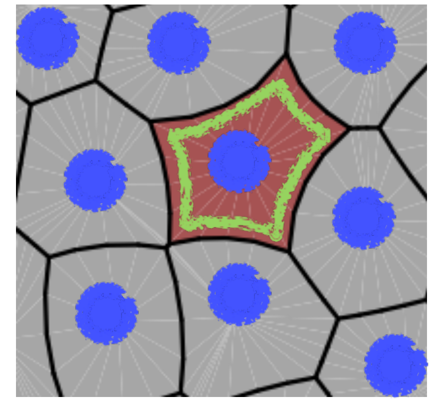
3. Bulk effects: fluid resists dialation/ compression, cytoskeleton resists shear

4. Cortical elasticity: cytoskeletal networks



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

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 fluctuations

acto-myosin contractilty

Interfacial tension: adhesion and cortical tension

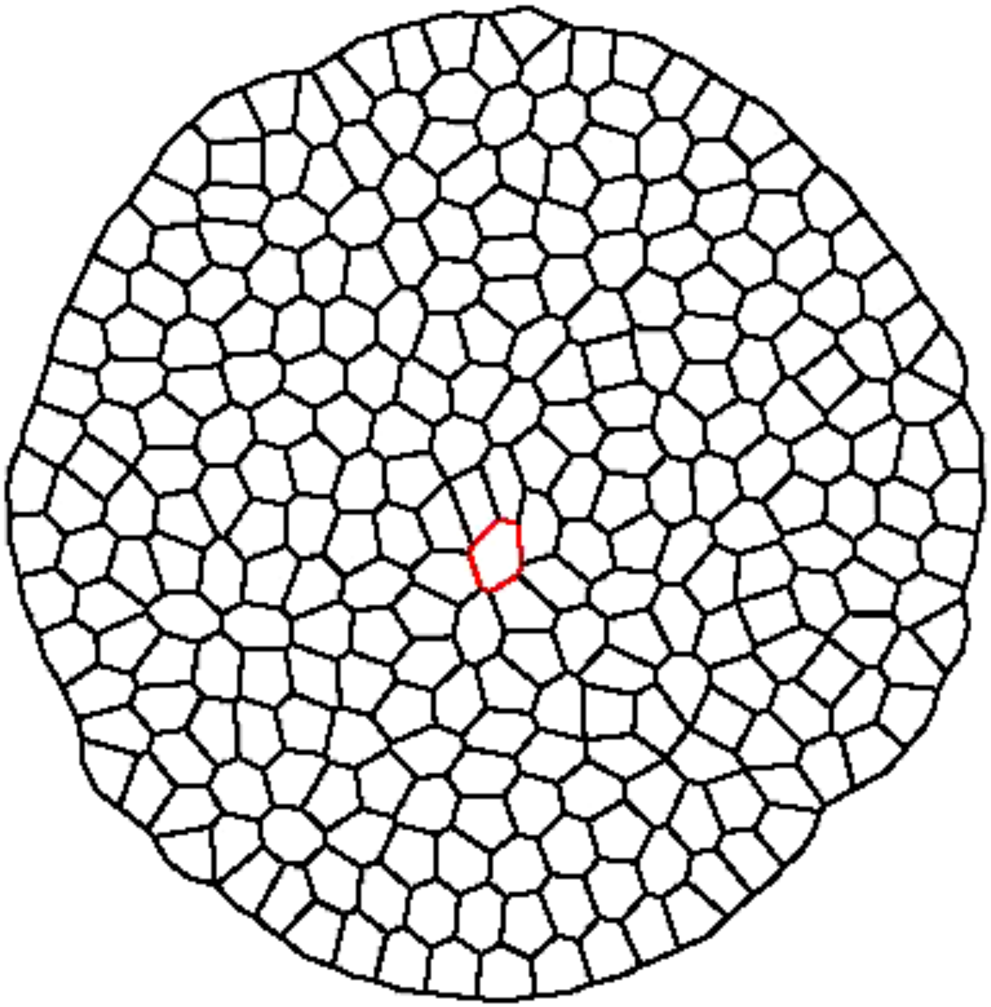
$$\varepsilon = \frac{1}{\beta A_0}\sum_i^N E_i = \sum_i \left[(a_i - 1)^2 + \frac{(p_i - p_0)^2}{r}\right]$$

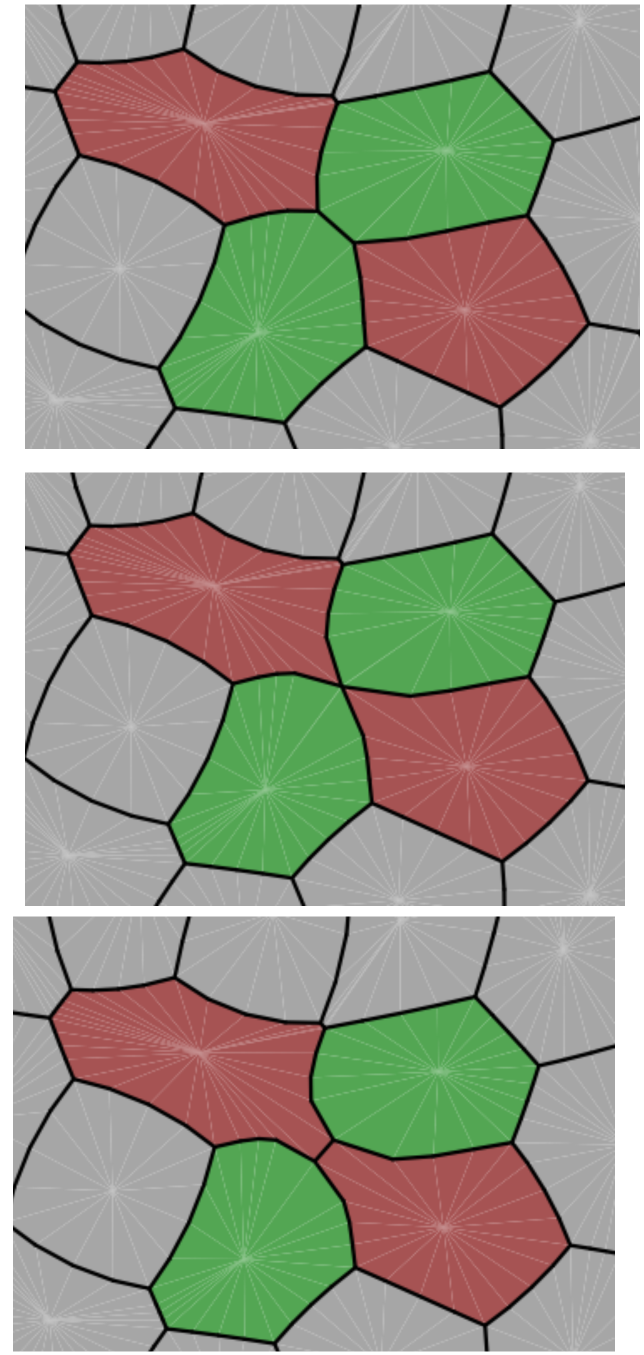
Non-dimensionalized mechanical energy

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

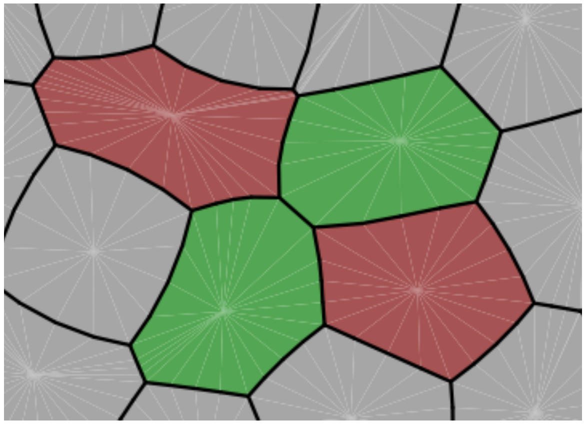




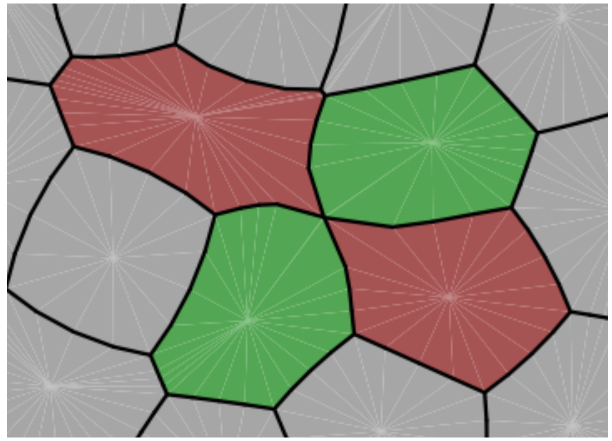
Bi, Lopez, Schwarz, **MLM** Soft Matter (2014)

Energy trace for T-1 transitions

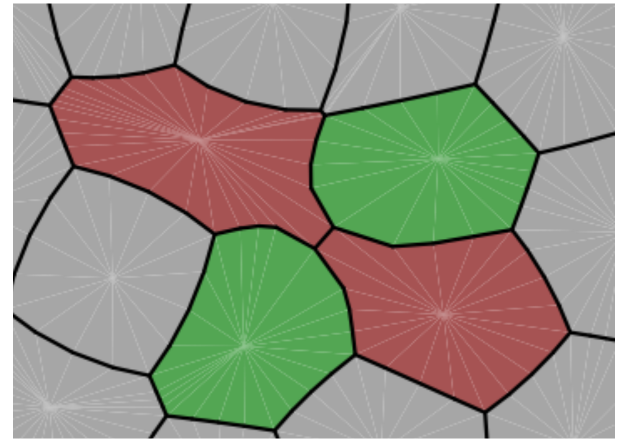
Shrink edge before T-1

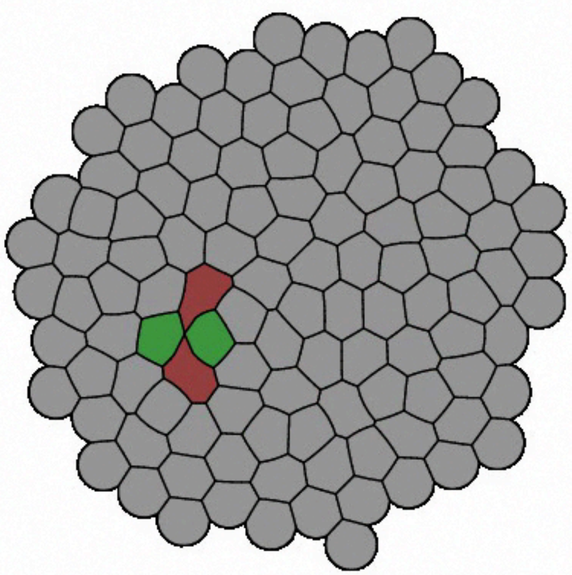


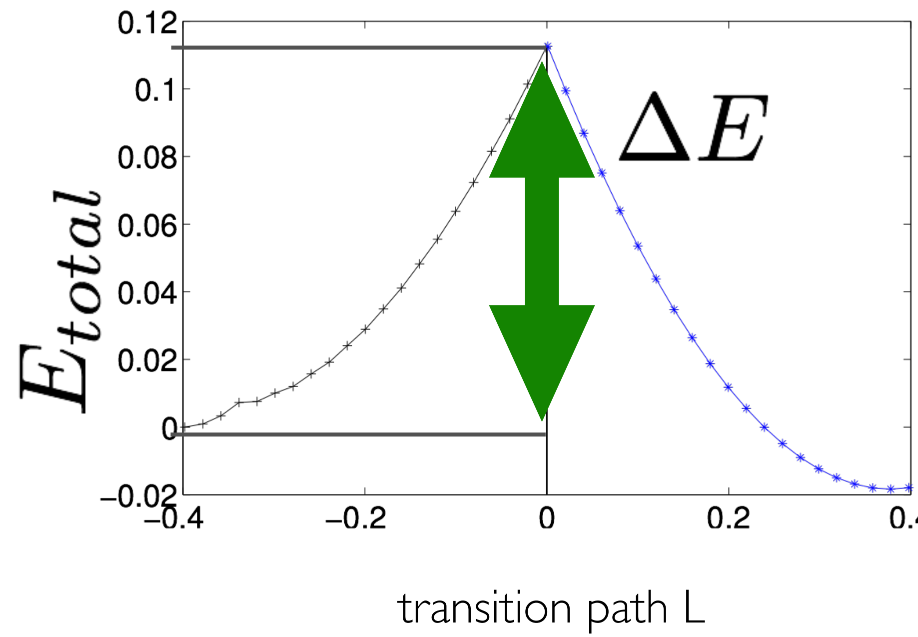
At T-1



Grow edge after T-1

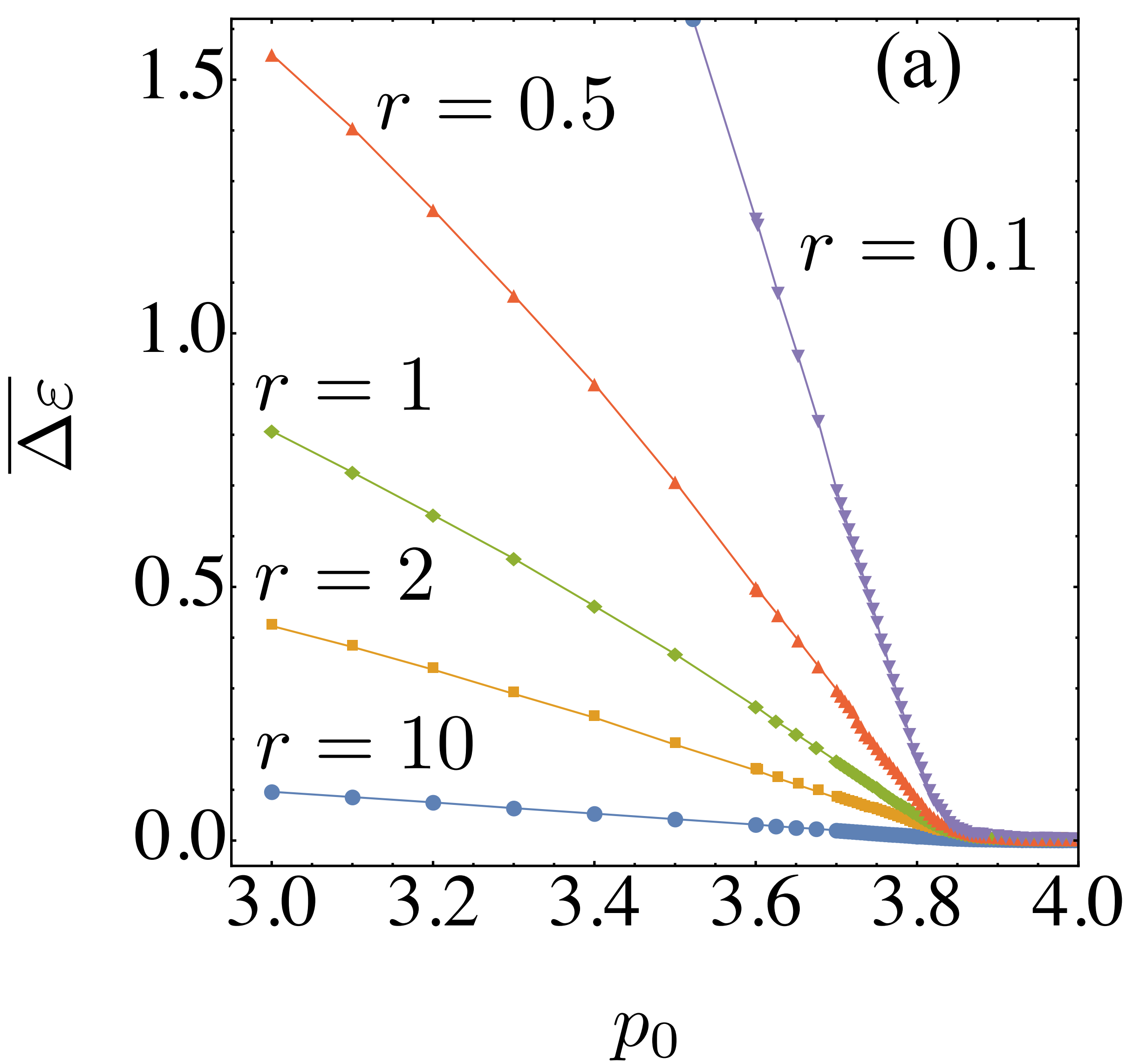




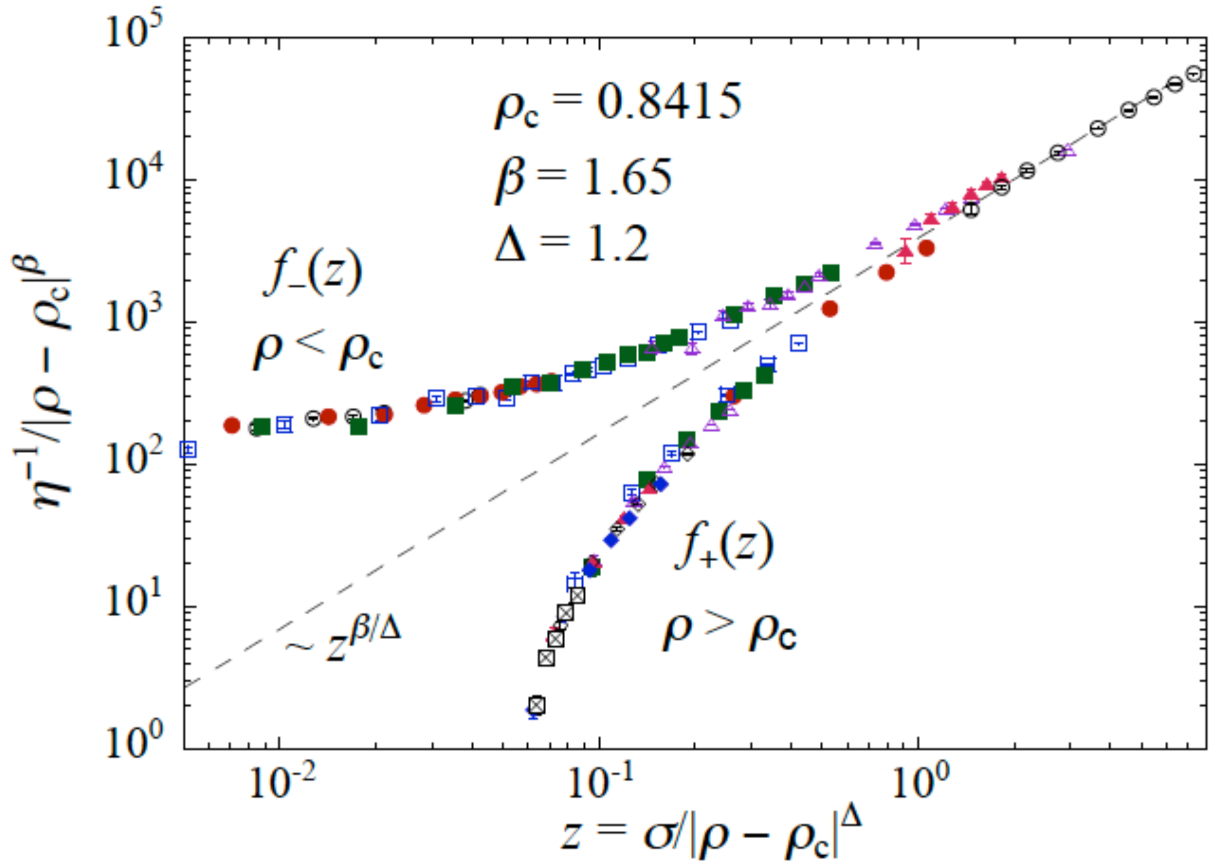


Bi, Lopez, Schwarz, **MLM** Soft Matter (2014)

Average energy barrier height vanishes at $p_0^* \sim 3.81$



Scaling collapse for jamming in inert matter:



Olsson and Teitel, PRL 99, 178001 (2007)

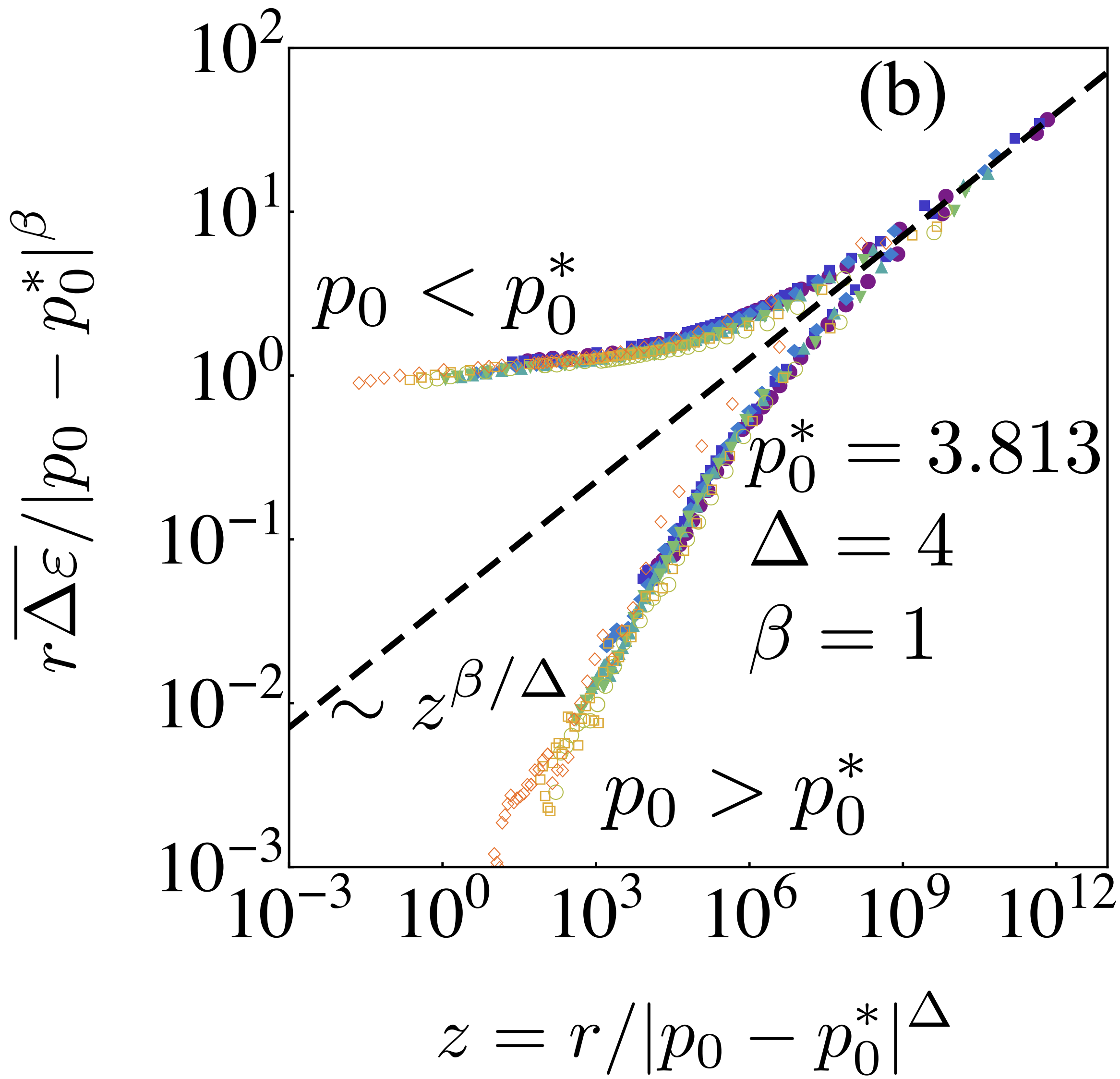
The onset of jamming is controlled by the **area density**: $(r-r_c)$ ~ pressure

A critical rigidity transition controlled by p_0:

CHEAT SHEET:
Average energy barrier height ~ yield stress

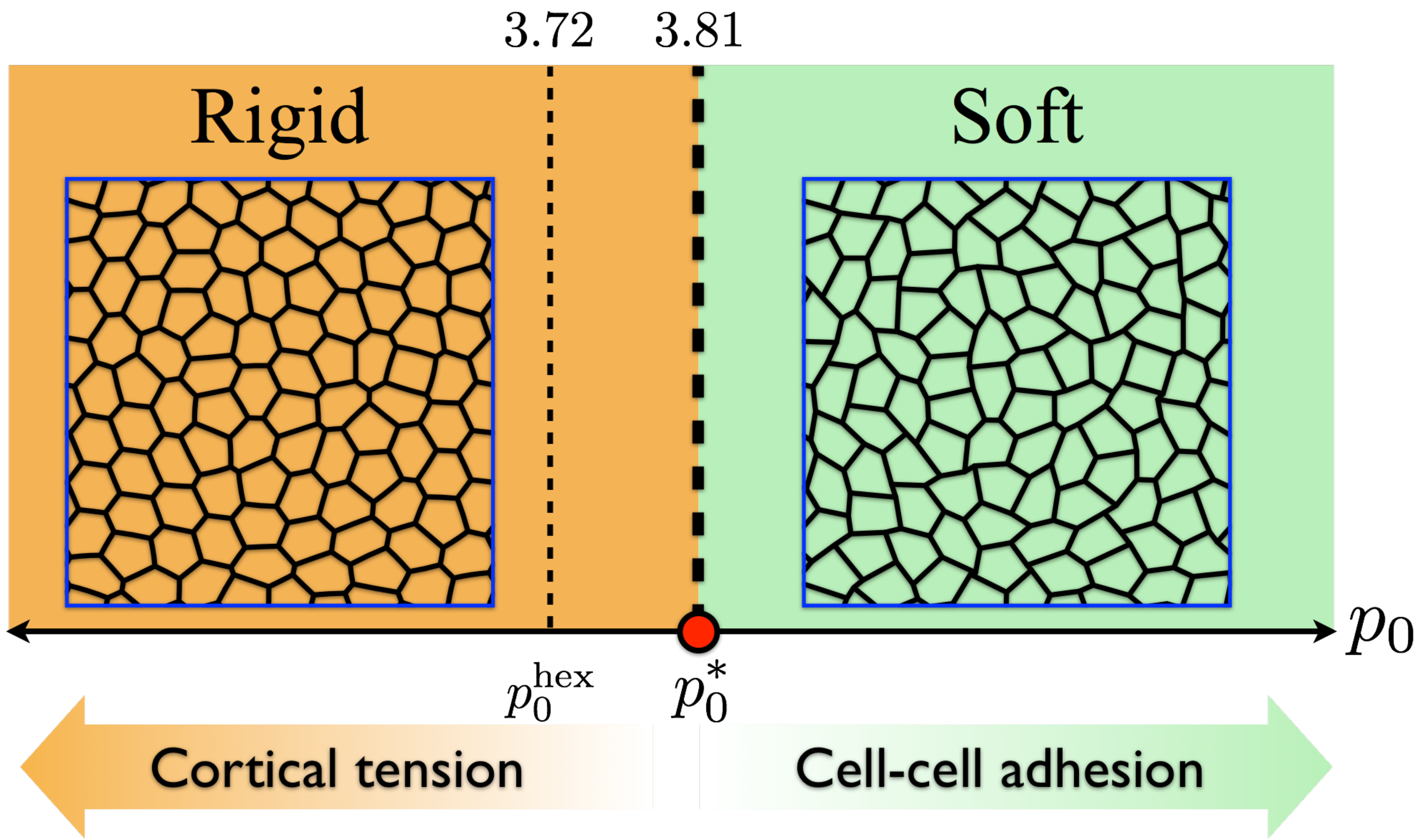
inverse perimeter modulus r ~ strain rate

preferred perimeter p_0 ~ density



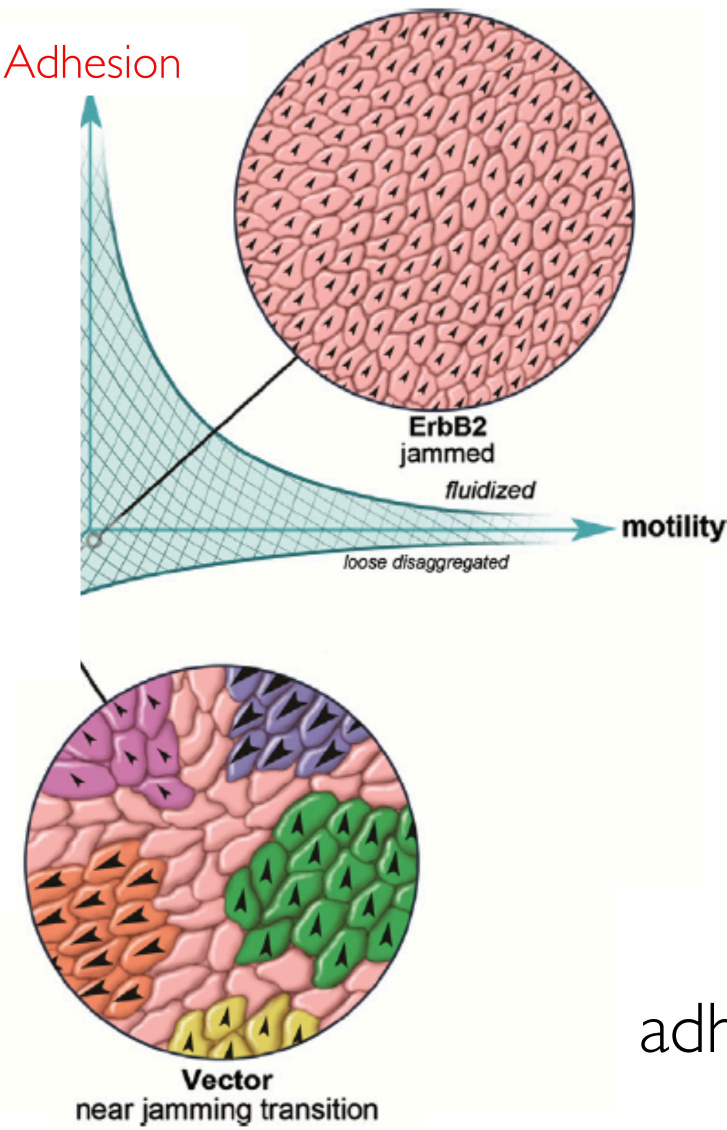
Bi, Lopez, Schwarz, **MLM** submitted (2015)

A critical rigidity transition at zero cell motility



New rigidity phase diagram for biological tissues

Opposite for confluent tissues!



Particulate matter: axis is 1/adhesion

more adhesion means more gelation means more solid-like

First prediction: more adhesion can actually lead to unjamming in a tissue

New order parameter: shape index

Recall: p_0 is a **model parameter**, which is the target perimeter-to-area ratio.

Define the observable shape index p:

$$p_i = \frac{P_i}{\sqrt{A_i}}; \quad \bar{p} = median\{p_i\}$$

Simulations of vertex model suggest $\bar{p}$ is an order parameter

Pre

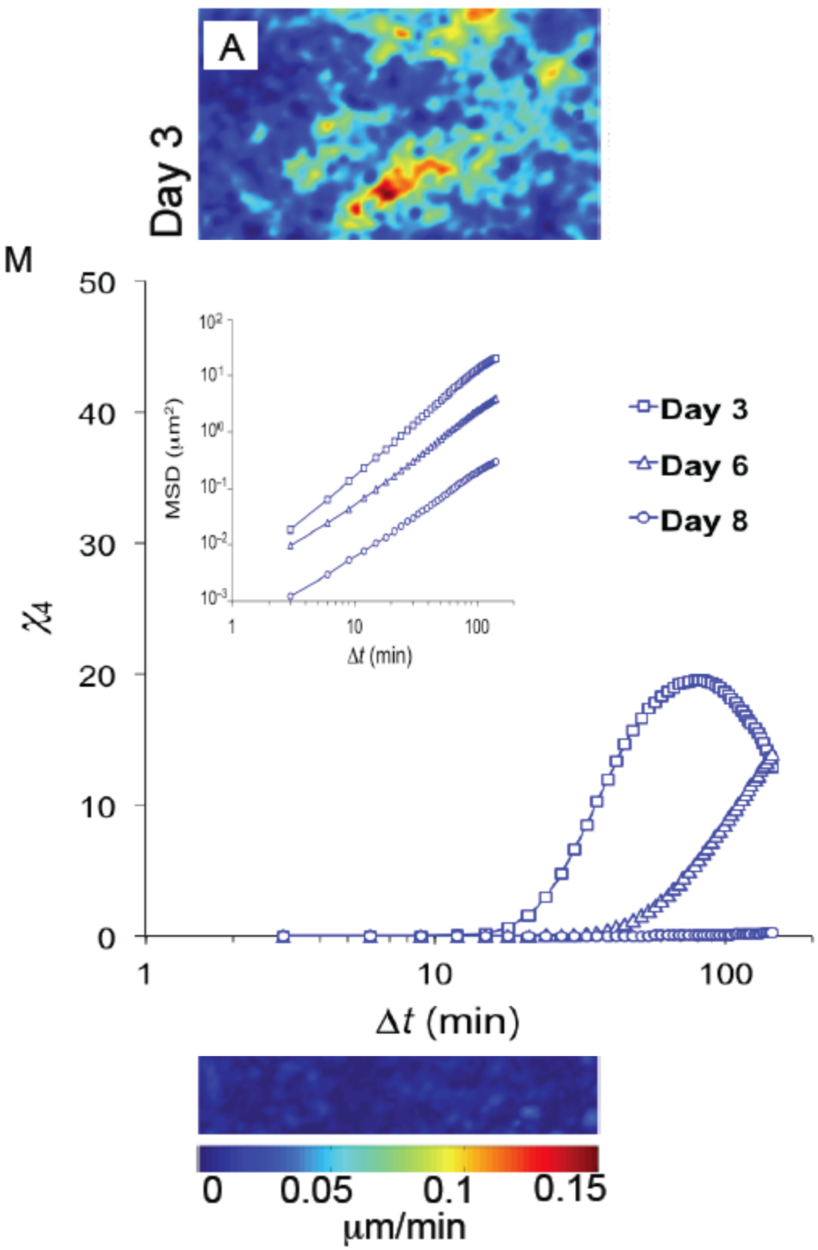
A jammed tissue should have a $\bar{p}$ that is precisely 3.81.

As a tissue becomes more unjammed, its $\bar{p}$ should increase above 3.81.

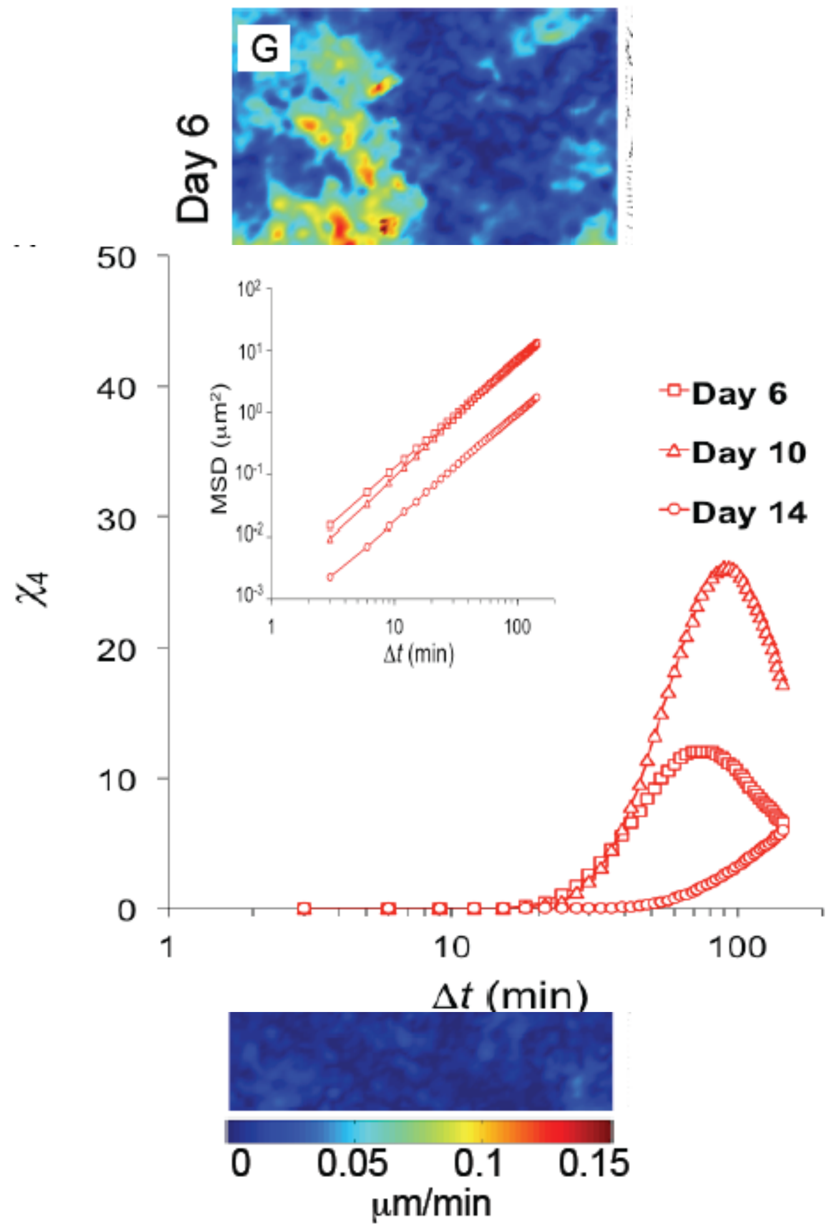
Park, Kim, Bi, et al, to appear in Nature Materials, August 2015

A jamming transition in primary human bronchial epithelial cells

Non-asthma

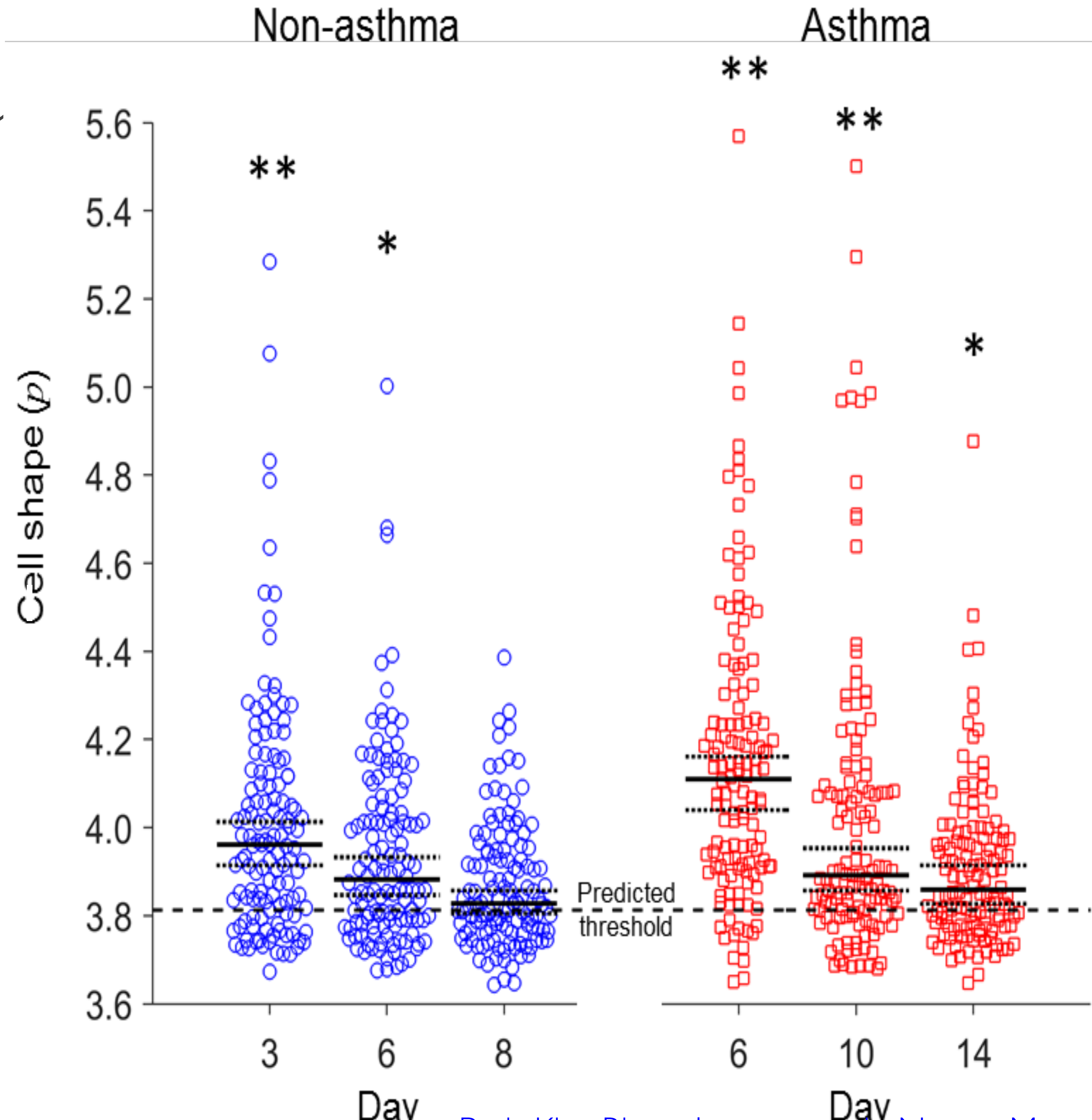


Asthma



Sha y the

Purely structural quantity!



Almost
ammed

Park, Kim, Bi, et al, to appear in Nature Materials, August 2015

Effect of finite cell motility?

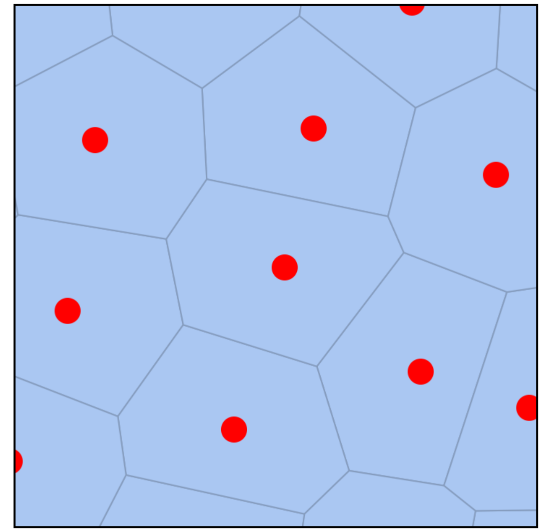
Add an equation for cell polarization with a finite velocity v_0 (like in Vicsek model introduced by Prof. Marchetti), called self-propelled voronoi (SPV)

$$E = \sum^{N} \left[K_A (A_i - A_0)^2 + K_P (P_i - P_0)^2 \right]$$

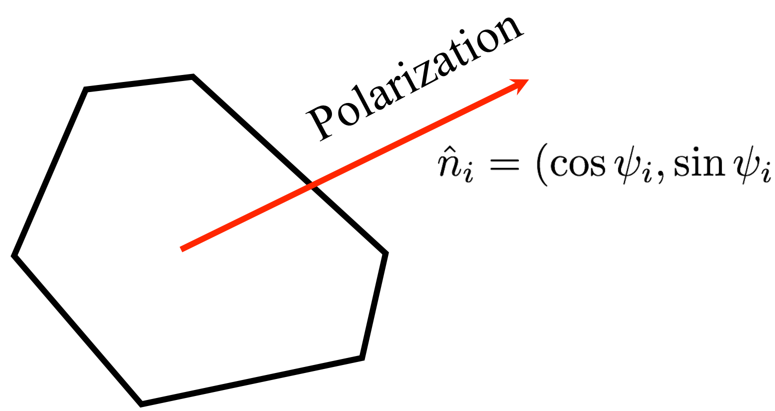
$$\frac{d\boldsymbol{r}_i}{dt} = \mu \boldsymbol{F}_i + v_0 \hat{\boldsymbol{n}}_i \qquad \boldsymbol{F}_i = -\boldsymbol{\nabla}_i E$$

$$\partial_t \theta_i = \eta_i(t)$$

$$\langle \eta_i(t) \eta_j(t') \rangle = 2 D_r \delta(t - t') \delta_{ij}$$

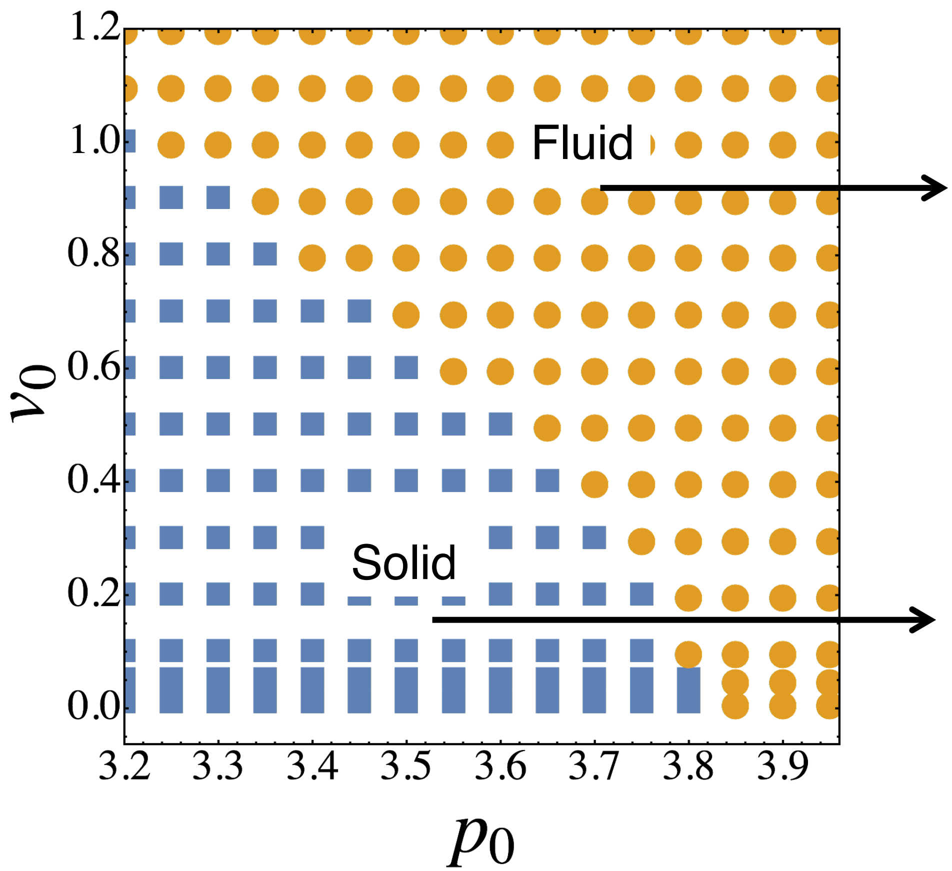


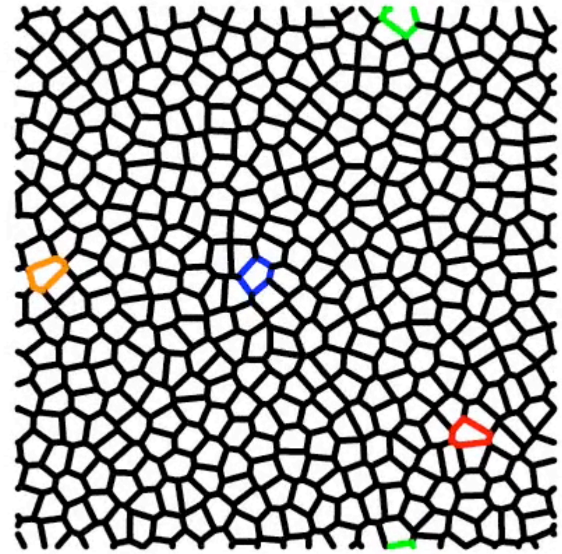
Two parameters:
v_0 and D_r.
Focus on changing $\mathbf{v_0}$ in limit $D_r \rightarrow \infty$

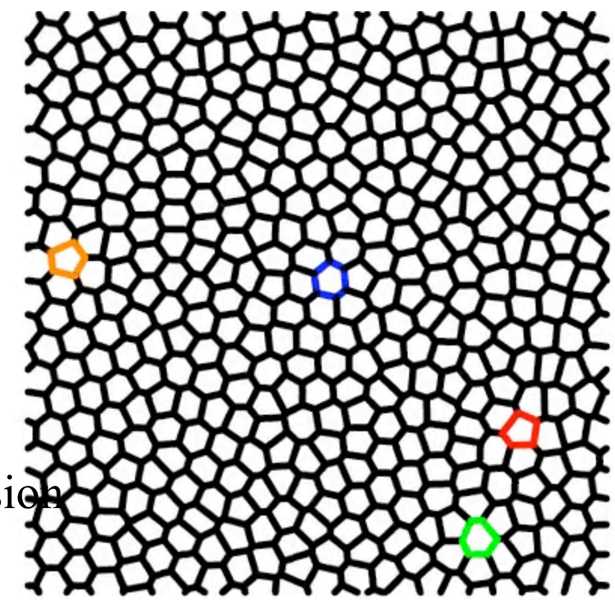


Bi, Yang, Marchetti, Manning, in preparation (2015)

Effect of finite c







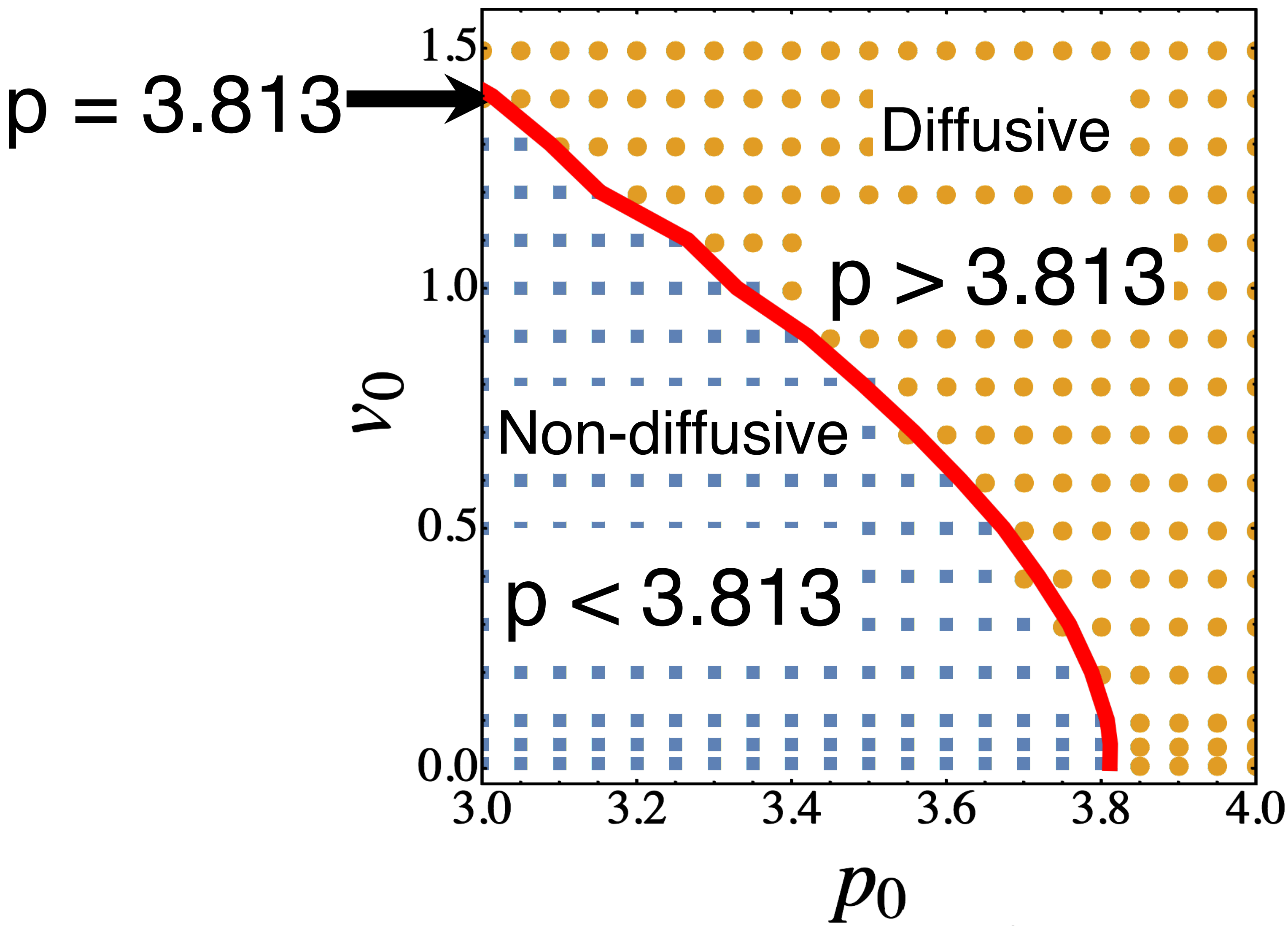
increasing cortical tension

increasing cell-cell adhesion

Solid/liquid phases determined by diffusion constant

Bi, Yang

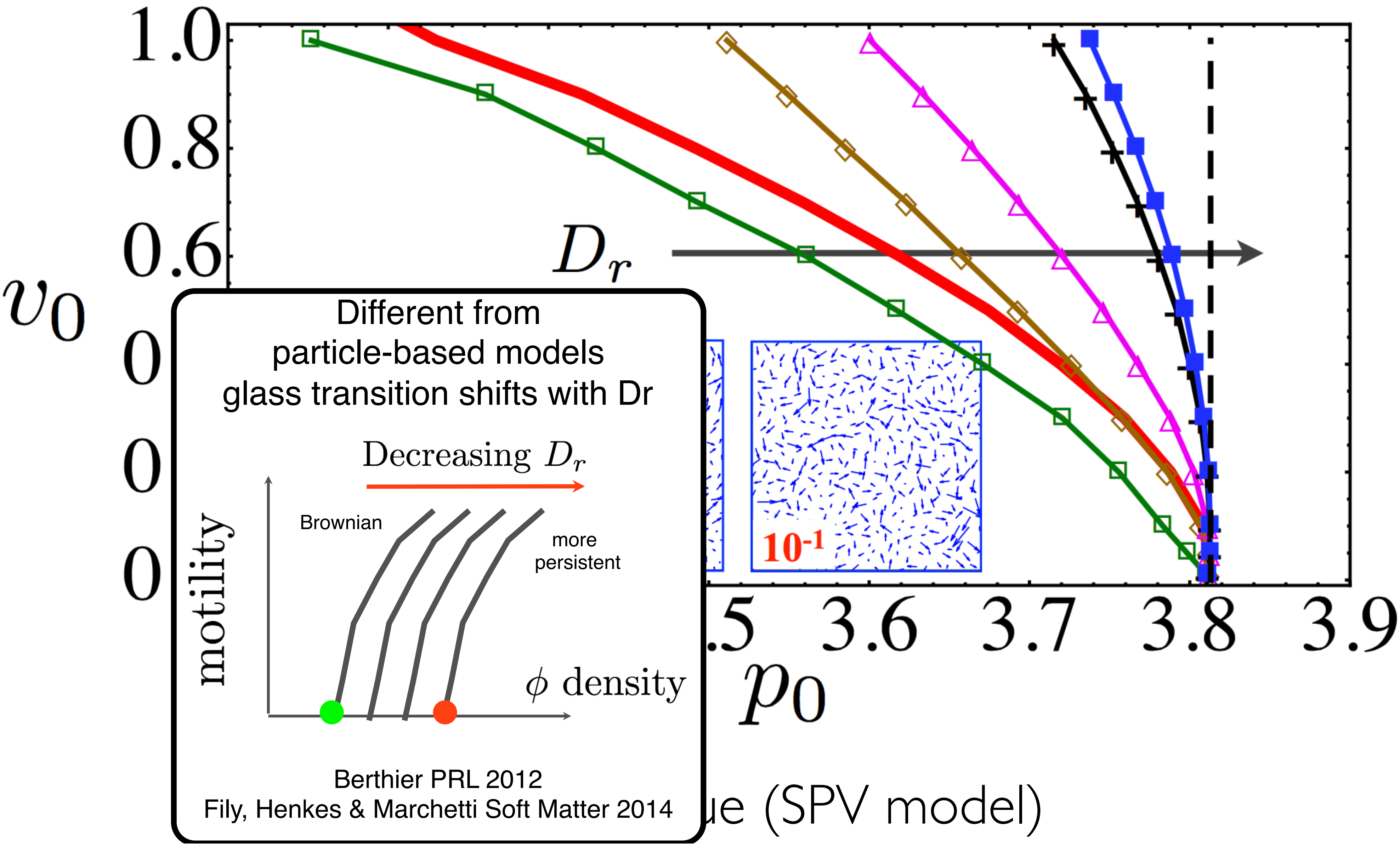
Does the shape index still indicate a fluid to solid transition?



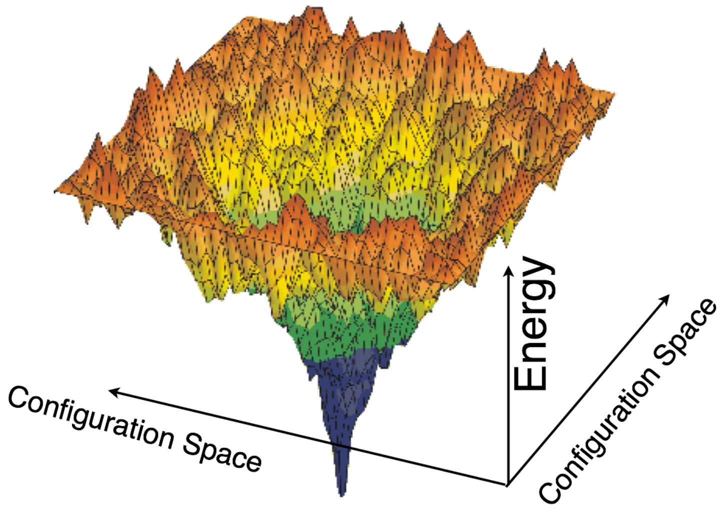
shape order parameter: $\mathrm{p} = \langle \mathrm{perimeter}/\sqrt{\mathrm{area}} \rangle$

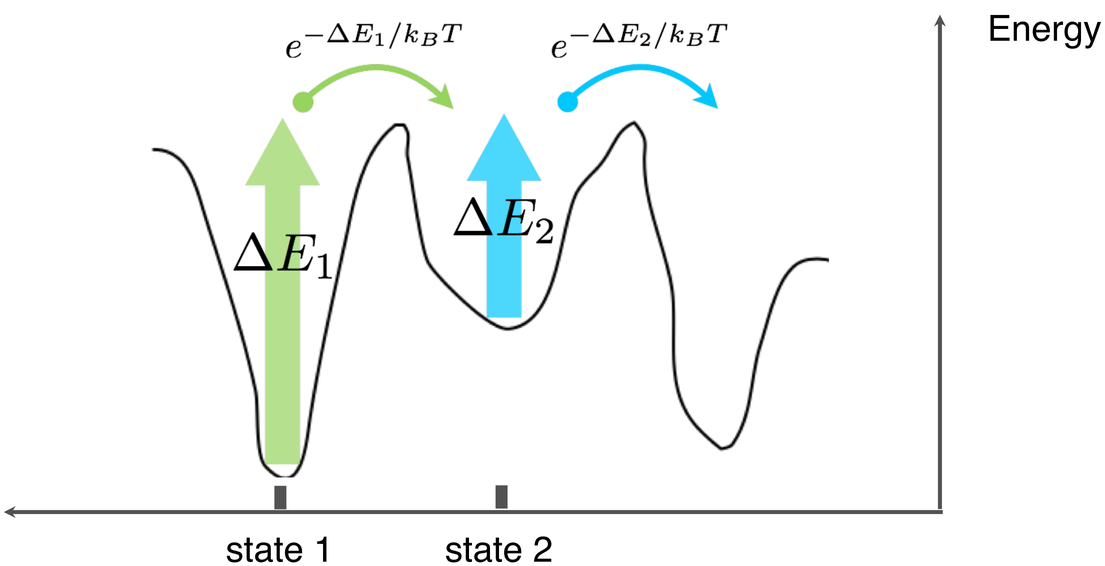
Yes!

Now, what happens if you change the rotational noise D_r?



Theories for glass transitions: effect of fluctuations





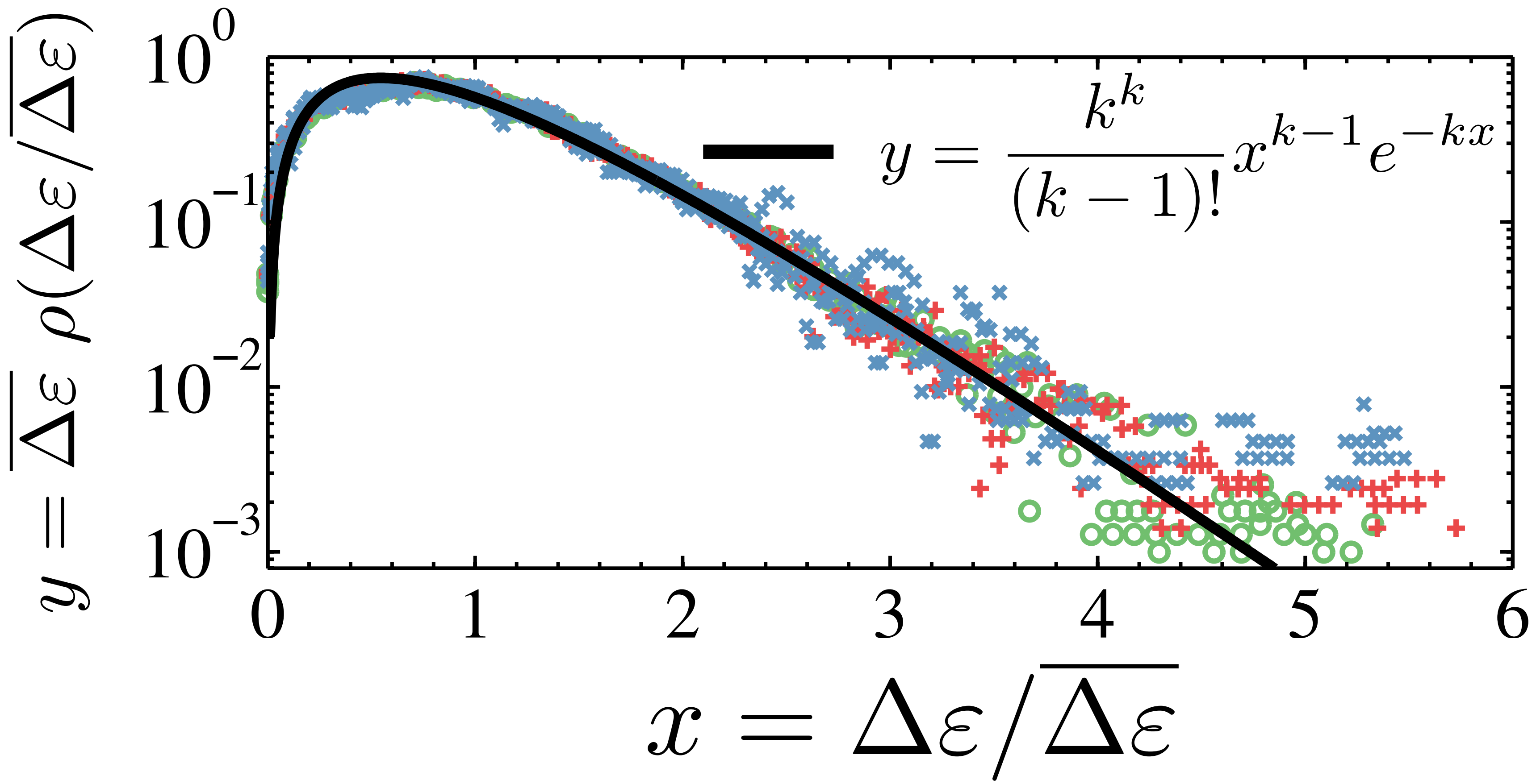
Complex potential energy landscape
+
system close to energy landscape surface

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)

System is glassy if and only if trap depths have exponential tail

Unlike many other models, we can enumerate and calculate distribution of trap depths



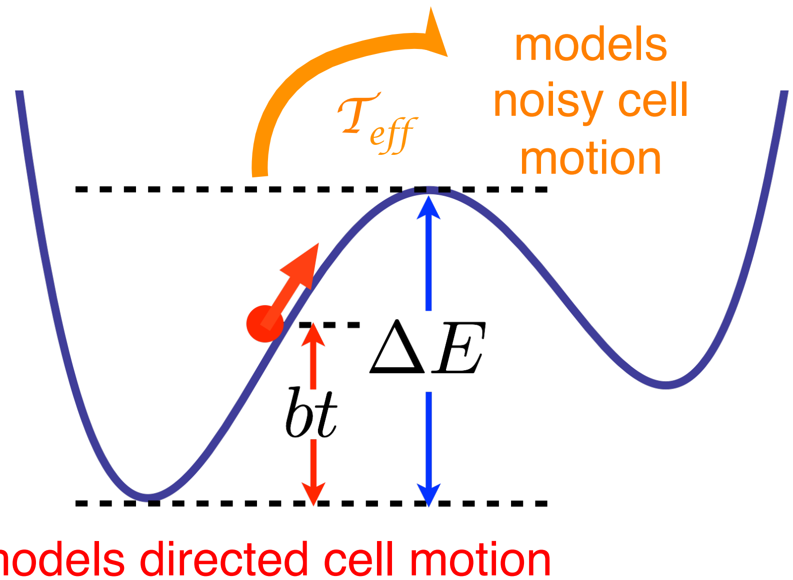
P(De) has a simple exponential tail

Modify SGR for biological systems:

noisy fluctuations: effective temperature T_{eff}

directed motion: cell motility b

$$R_{hopping} = R_0 exp\left[-(\Delta E - bt)/T_{eff}\right]$$



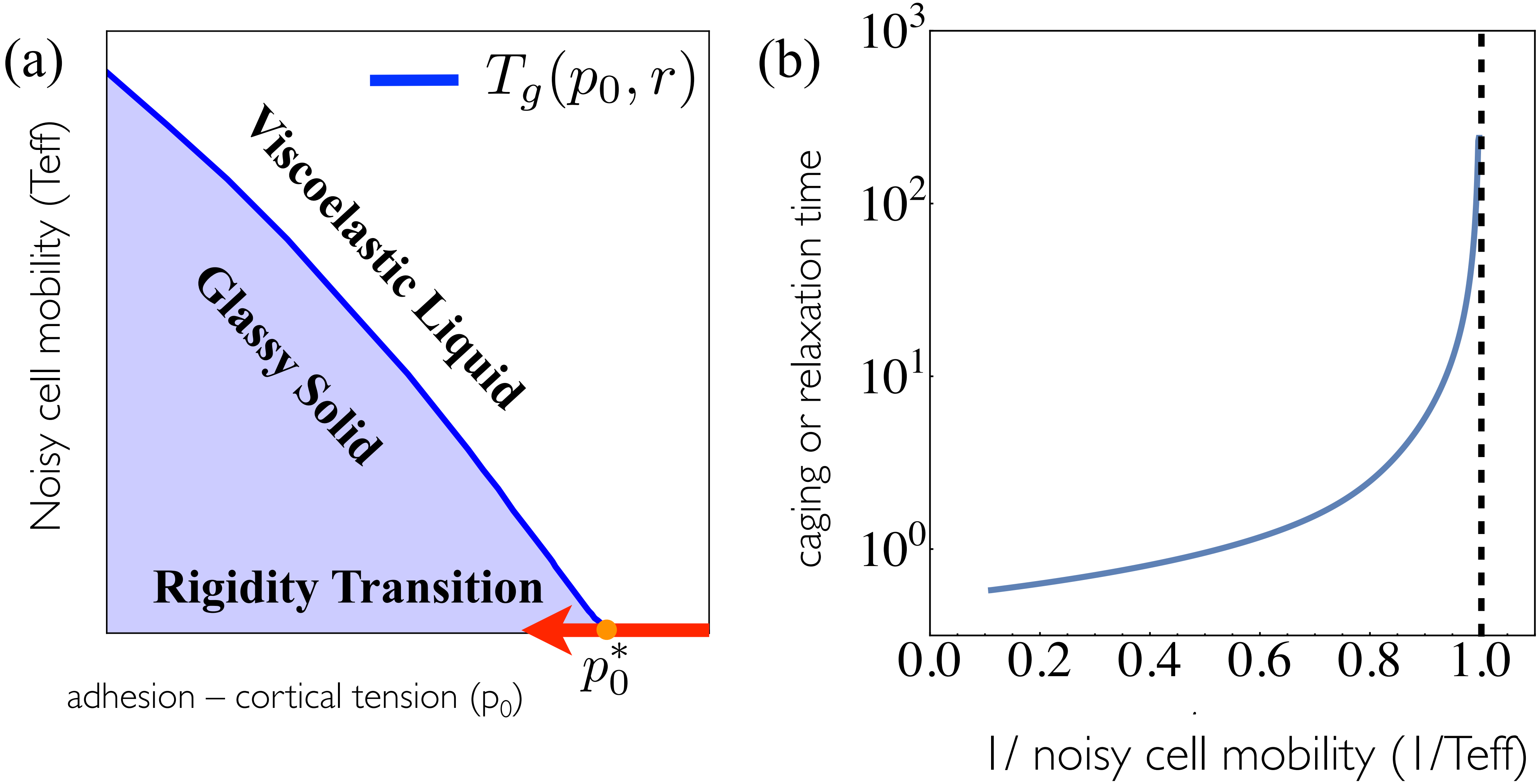
trap model: C. Monthus and J.-P. Bouchaud, J. Phys. A 29, 3847 (1996)

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

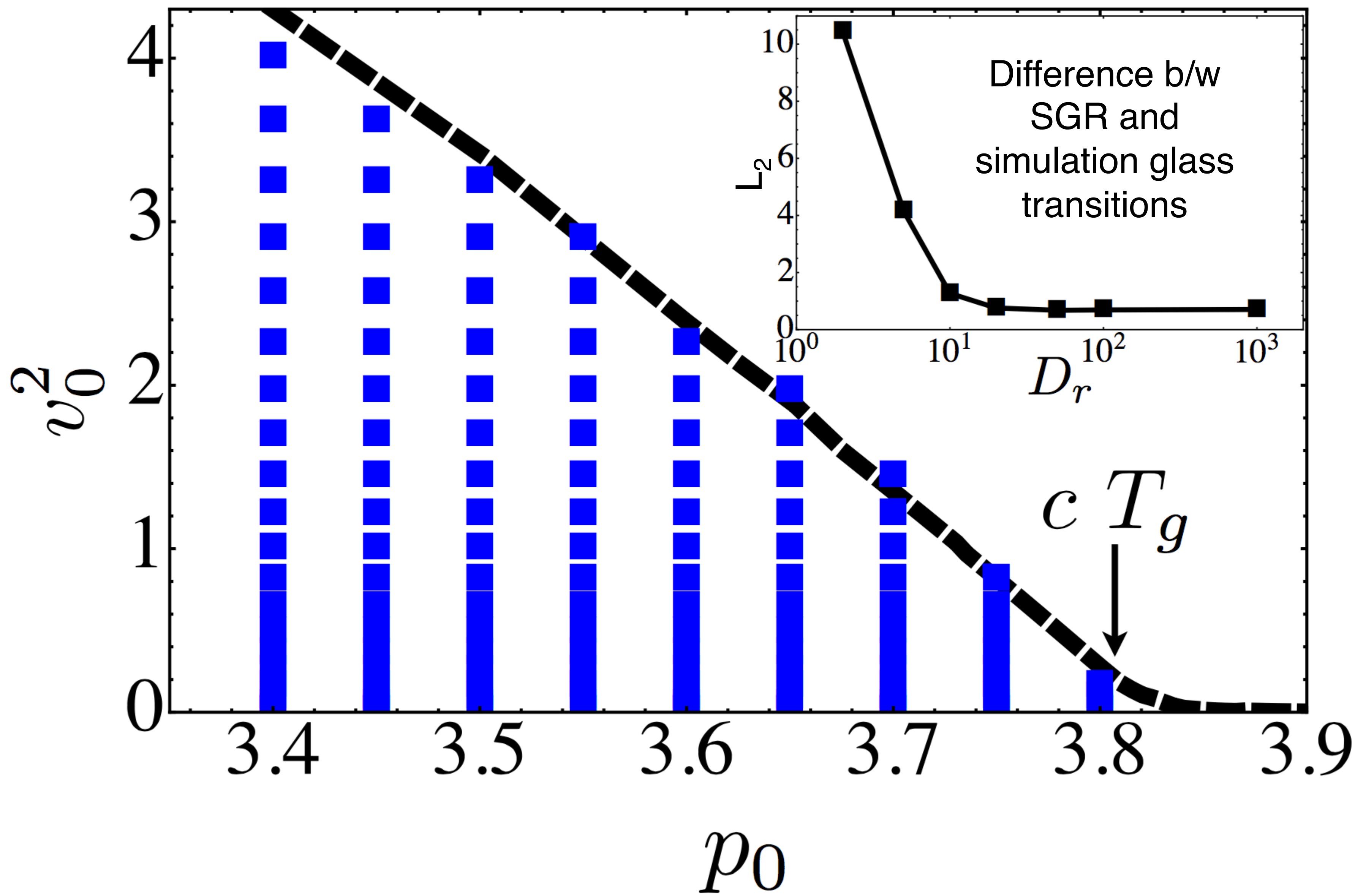
In the limit $\mathbf{D_r} \rightarrow \infty$, $T_{eff} \sim v_0^2$, $b = 0$

How does cell mobility alter the rigidity transition?

use a trap model to go from energy barriers to cell dynamics



SGR prediction matches simulation data in high D_r limit

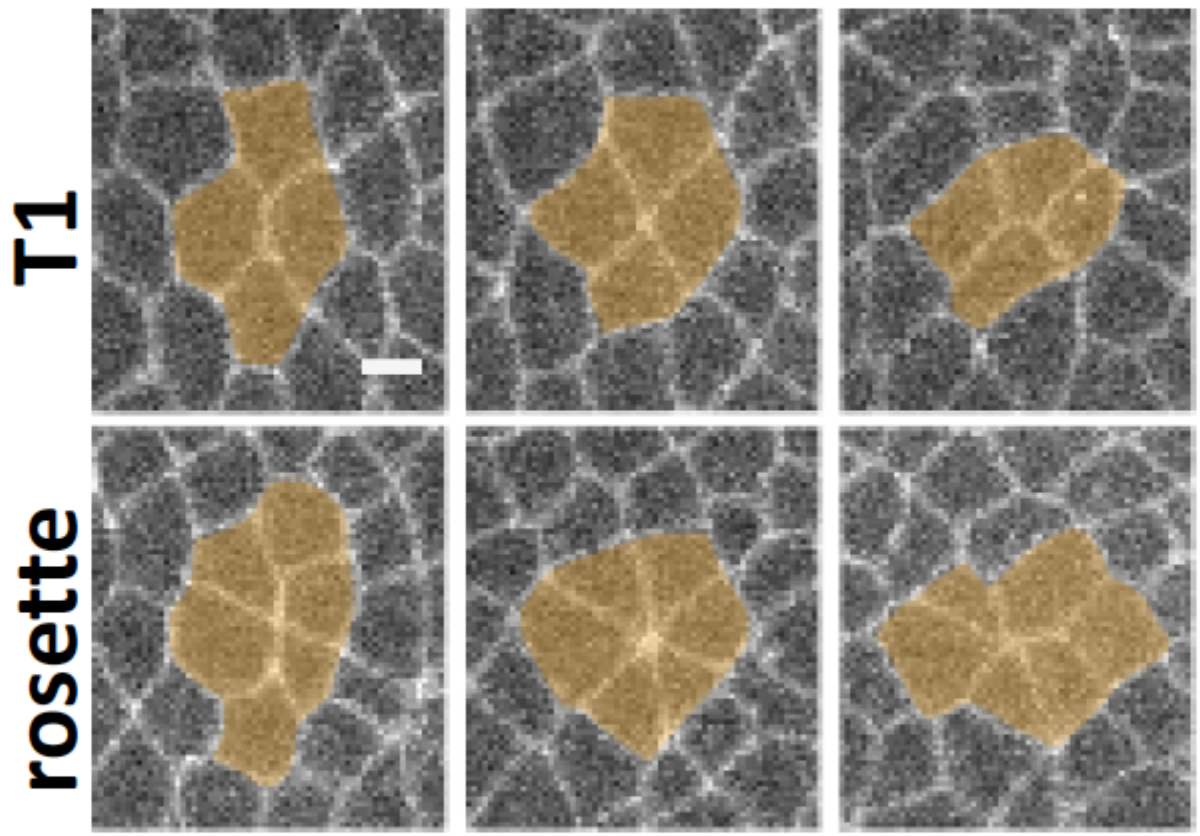


Bi, Yang, Marchetti, Manning, in preparation (2015)

What next?

Rosette formation

Drosophila (Fruit fly) embryonic epithelia during convergent extension

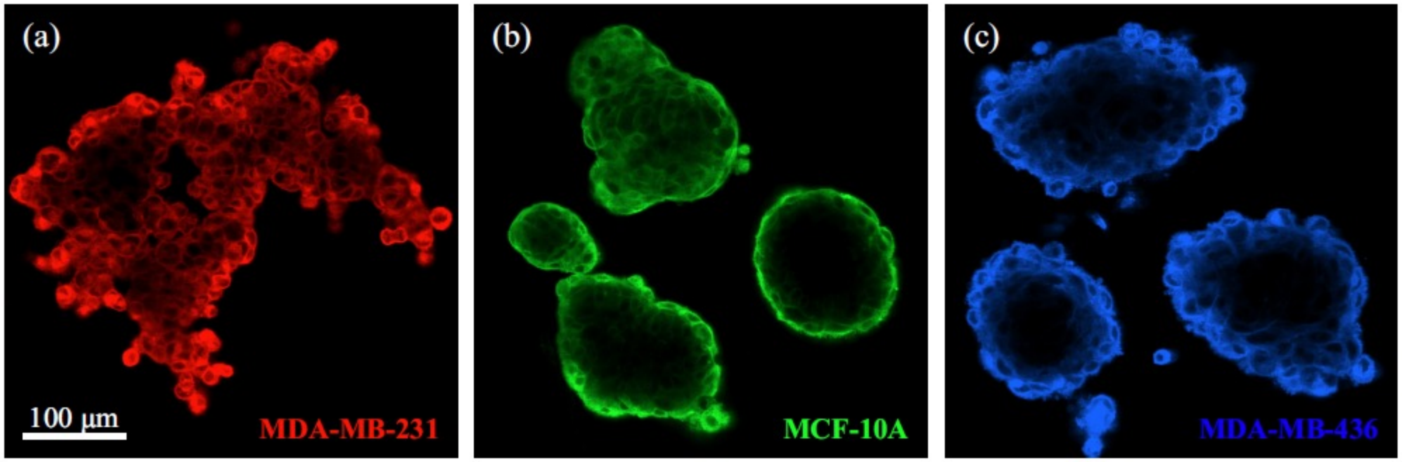


Kasza and Zallen, PNAS 2014

Existing vertex models: 3-fold coordinated vertices and 4-fold transition points

What about higher order transitions?

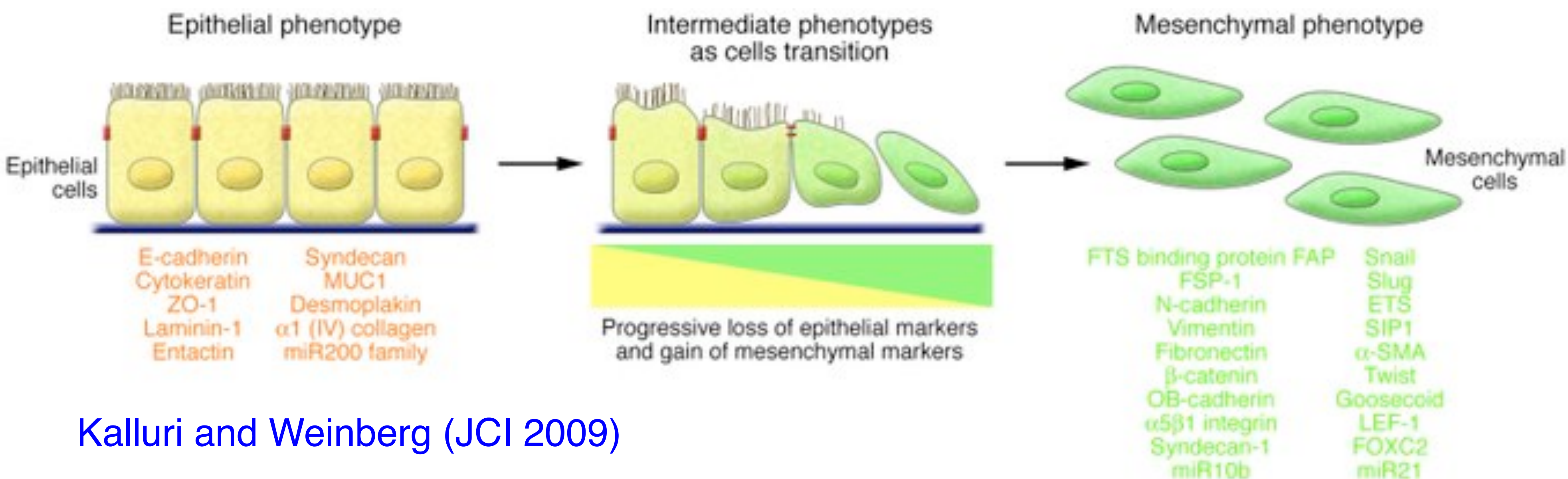
Cancer tumor boundaries and the EMT transition



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

Pawlizak … MLM, Kaes, to appear in New J. Phys (2015)

- 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 materials, with material properties that are important for biological function**
- **Many tissue types are apparently close to a glass transition**
  - migration rates are dominated by collective effects
- **The vertex model for confluent tissues exhibits a novel type of density-independent rigidity transition**
  - control parameter is p_0, which is proportional to single-cell adhesion or preferred cell perimeter
- **The predictions of this model are precisely realized in primary human bronchial epithelial cells**
  - perimeter-to-area ratio =3.813 indicates jamming threshold
  - asthmatic patients have a delayed jamming transition
- **A new SPV model predicts that the rigidity transition controls a line of glass transitions**
  - Again, different from particulate matter, matches SGR model
- **This is a rich framework with lots more to do (EMT?)**

Thanks so much for your attention!

Collaborators:

- Max Dapeng Bi, Xingbo Yang, Cristina Marchetti, Jen Schwarz, Jorge Lopez (SU)
- Eva-Mara Schoetz (UCSD), Marcus Lanio, Jared Talbot (Princeton)
- Jin-Ah Park, Jae Hun Kim, Jen Mitchell, Jeff Fredberg et al (Harvard School of Public Health)

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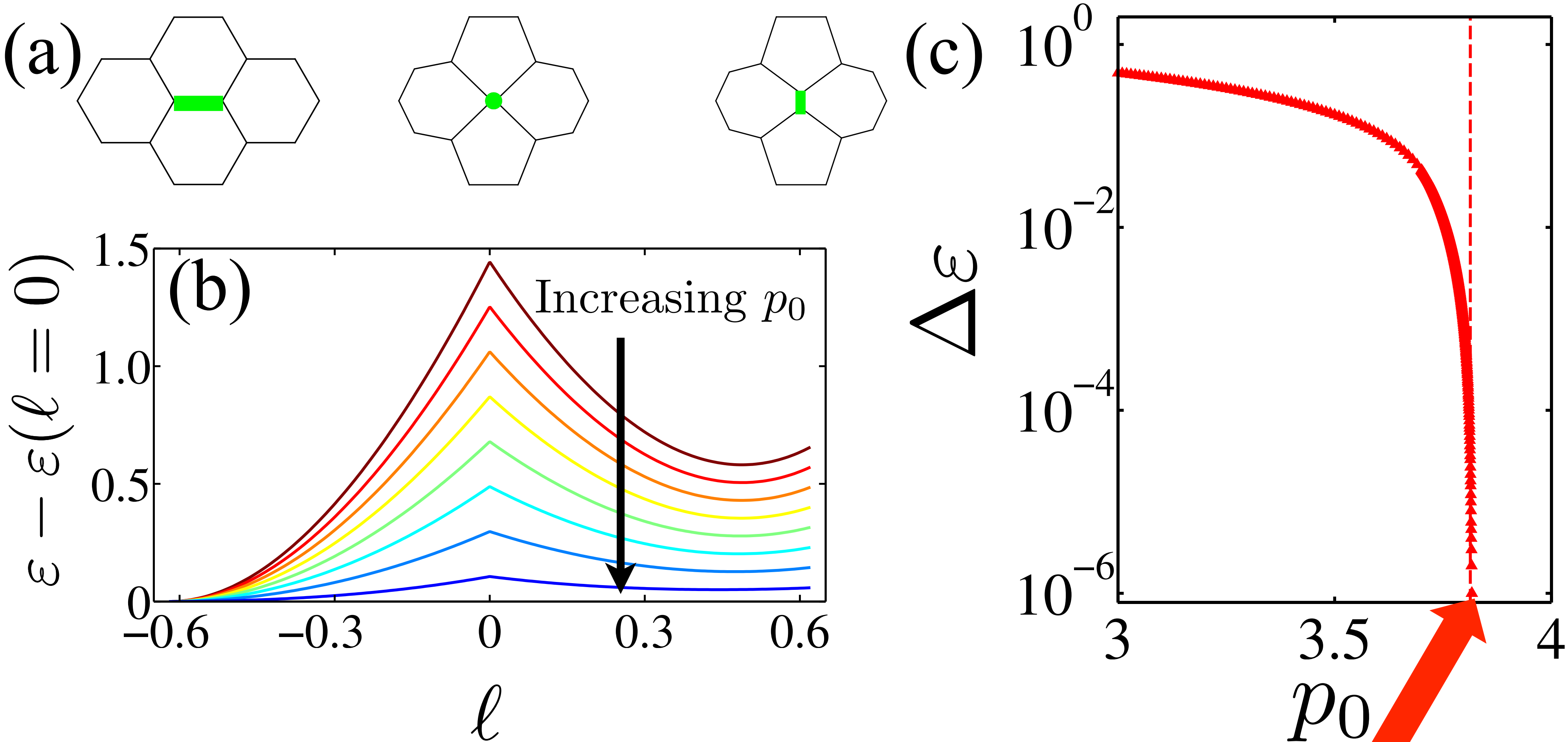
- Cottrell Scholarship
- Gordon and Betty Moore Foundation
- Soft Interfaces IGERT (DGE-1068780)

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

Fixed area, four cells

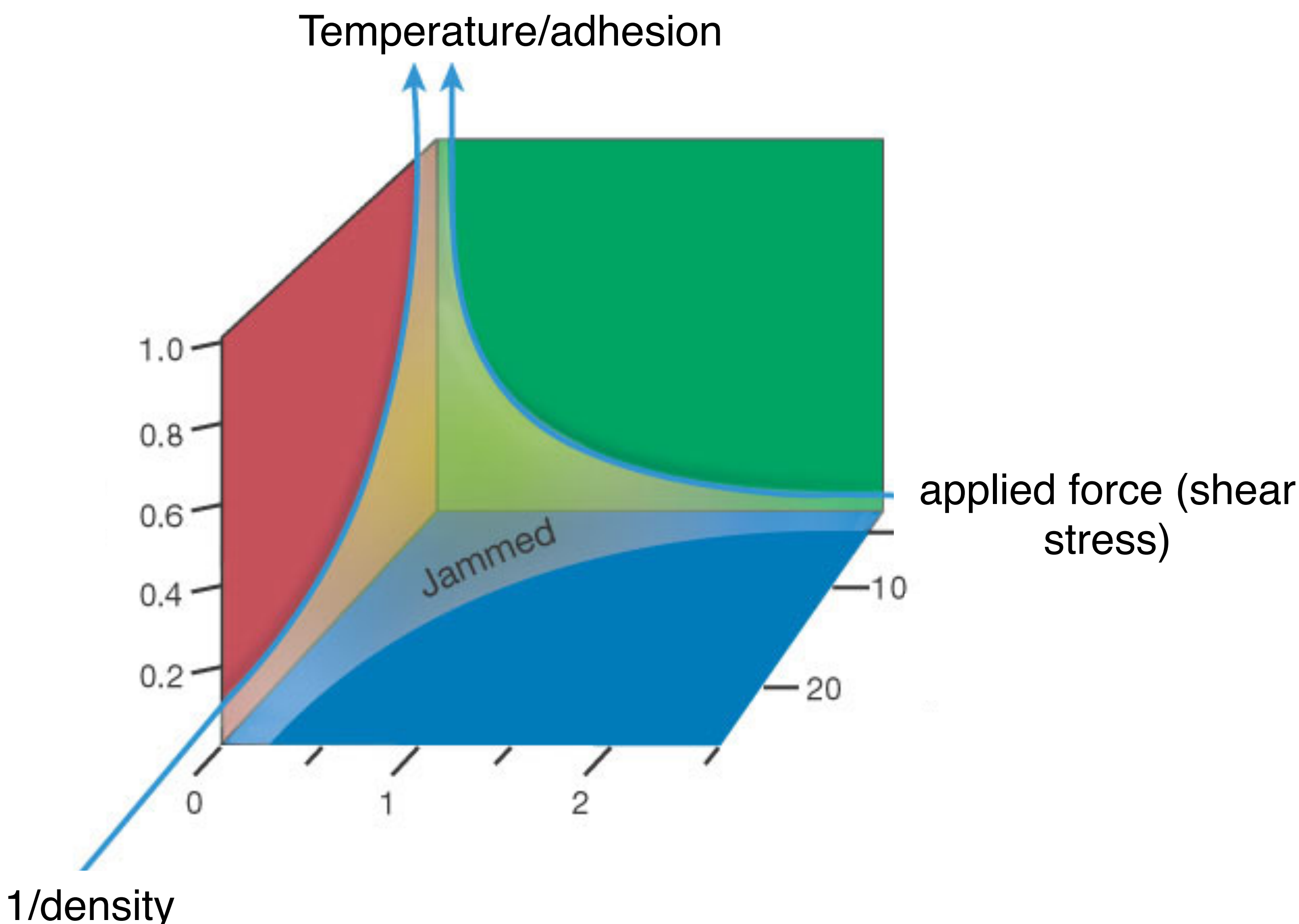
p_0 only control parameter



Bi, Lopez, Schwarz, **MLM** submitted(2015)

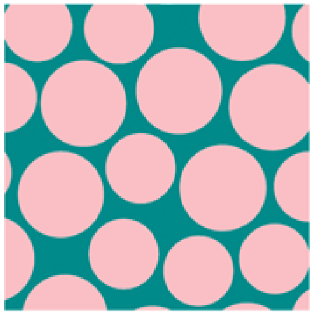
Transition point p_0^* =3.813 = perimeter of regular pentagon with unit area

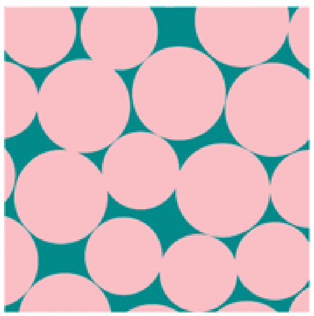
Jamming phase diagram for inert matter

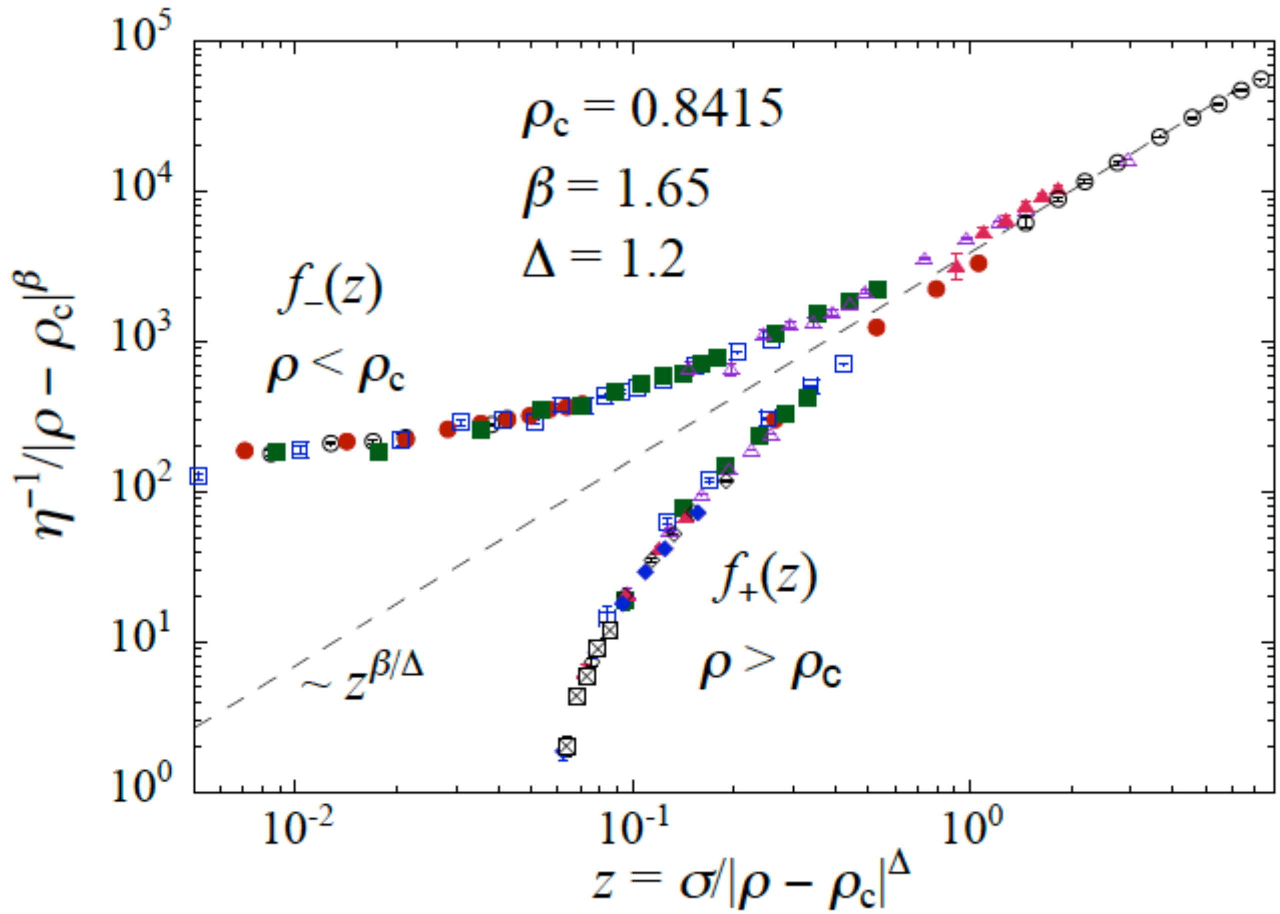


Trappe et al, *Nature* **411**, 772-775 (2001)

Proving the existence of a critical jamming transition



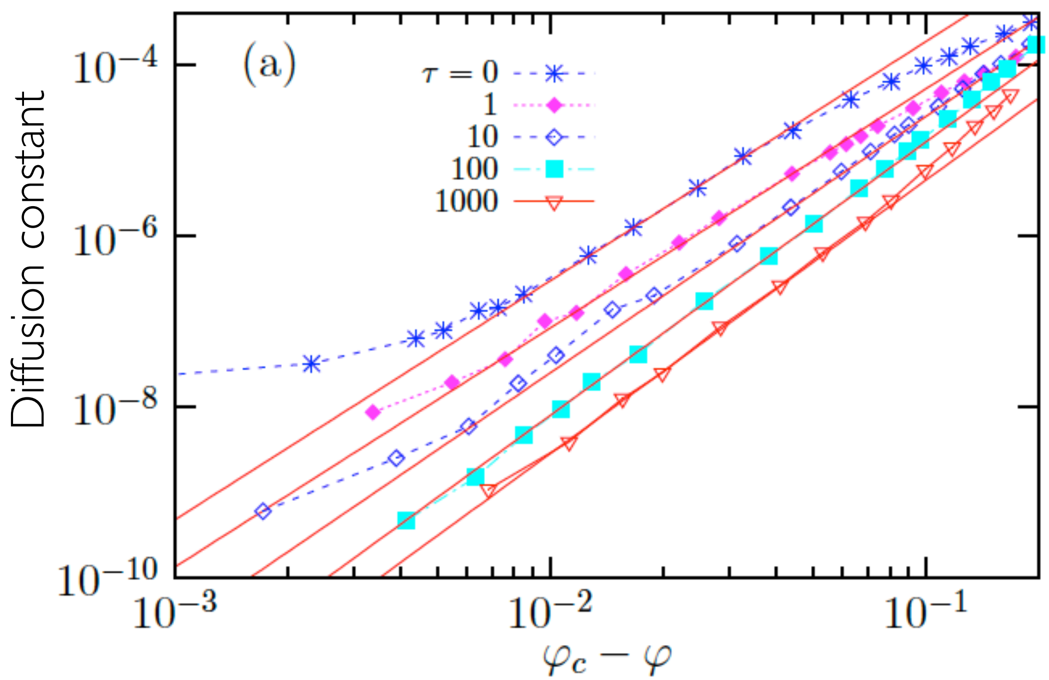


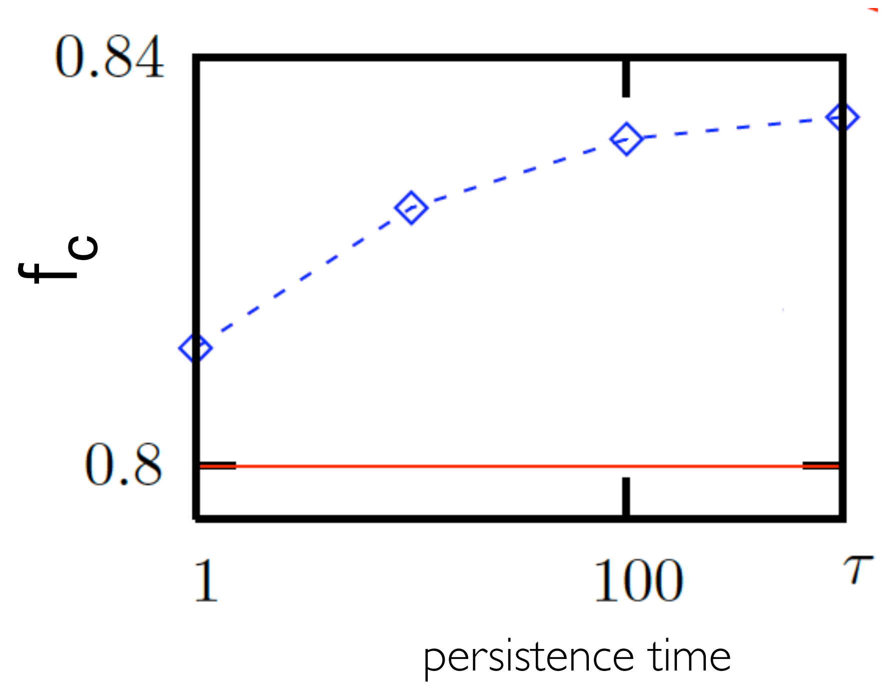


Olsson and Teitel, PRL 99, 178001 (2007)

The onset of jamming is controlled by the **area density**: $(r-r_c)$

Jamming and glass transitions in self-propelled particle models are identical to adhesive colloids*





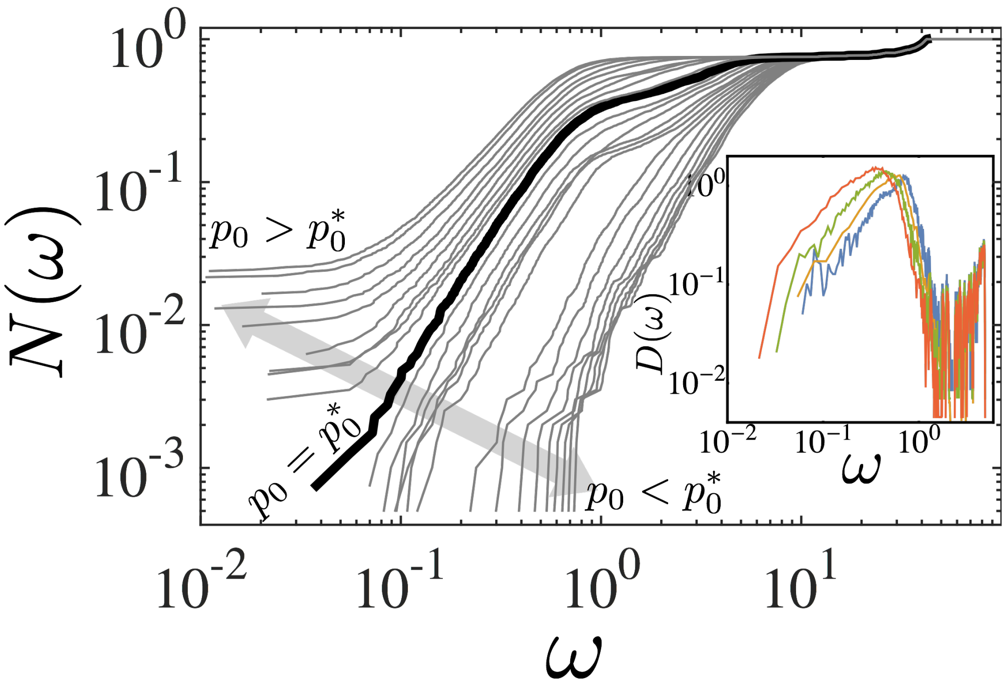
f_c is the critical density at which there is no diffusion

*almost: f_c changes with the persistence time;
the activity generates an effective adhesion

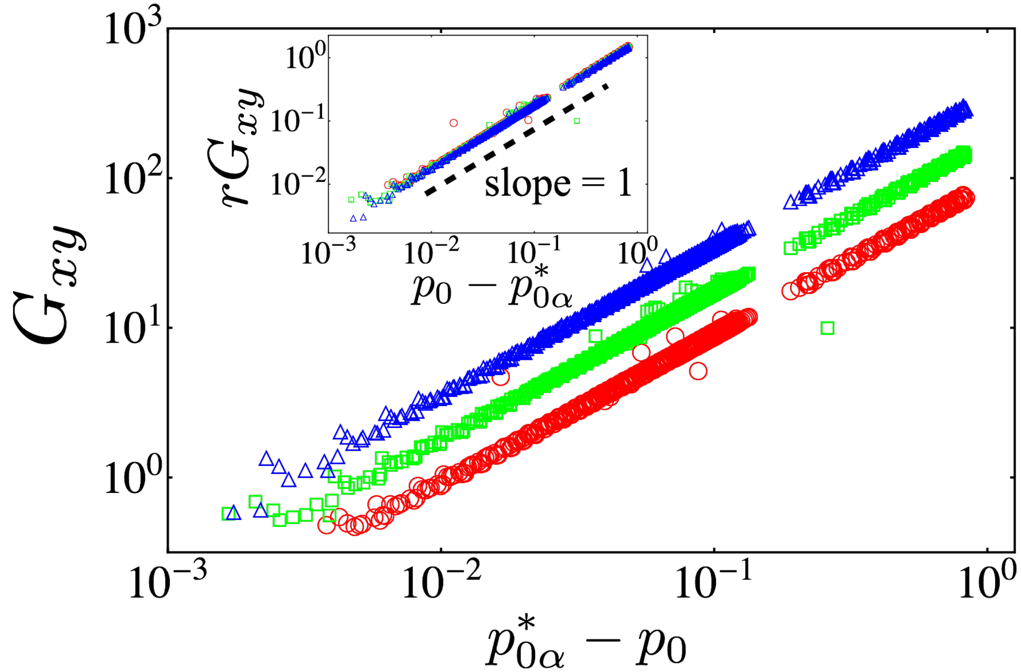
Berthier, PRL 112, 220602 (2014)

We can also look at linear mechanical response

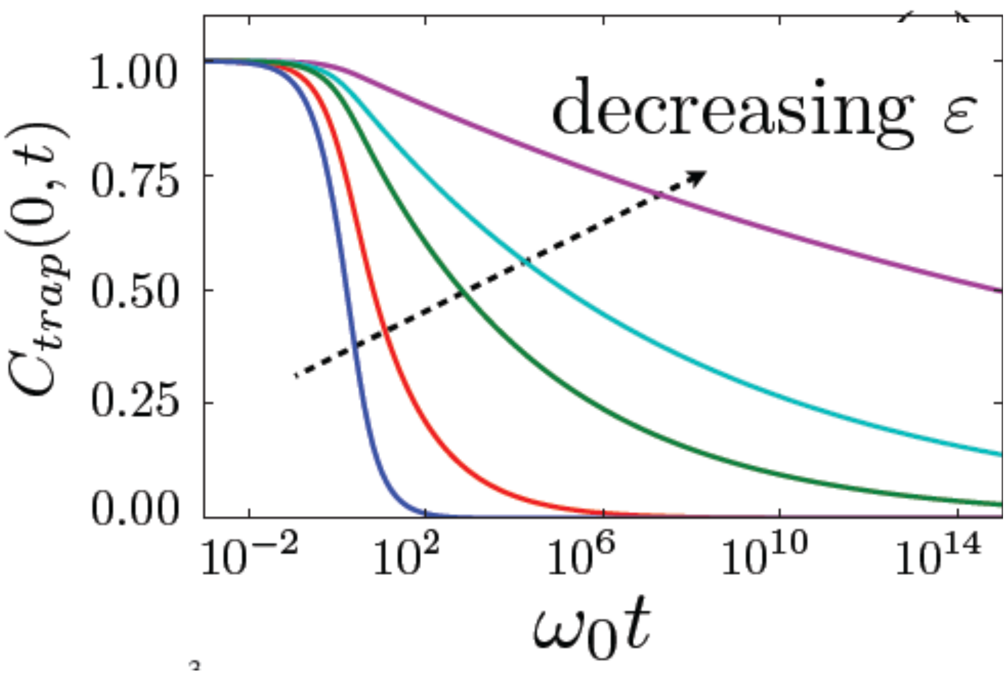
Emergence of linearly unstable modes at p_0^*



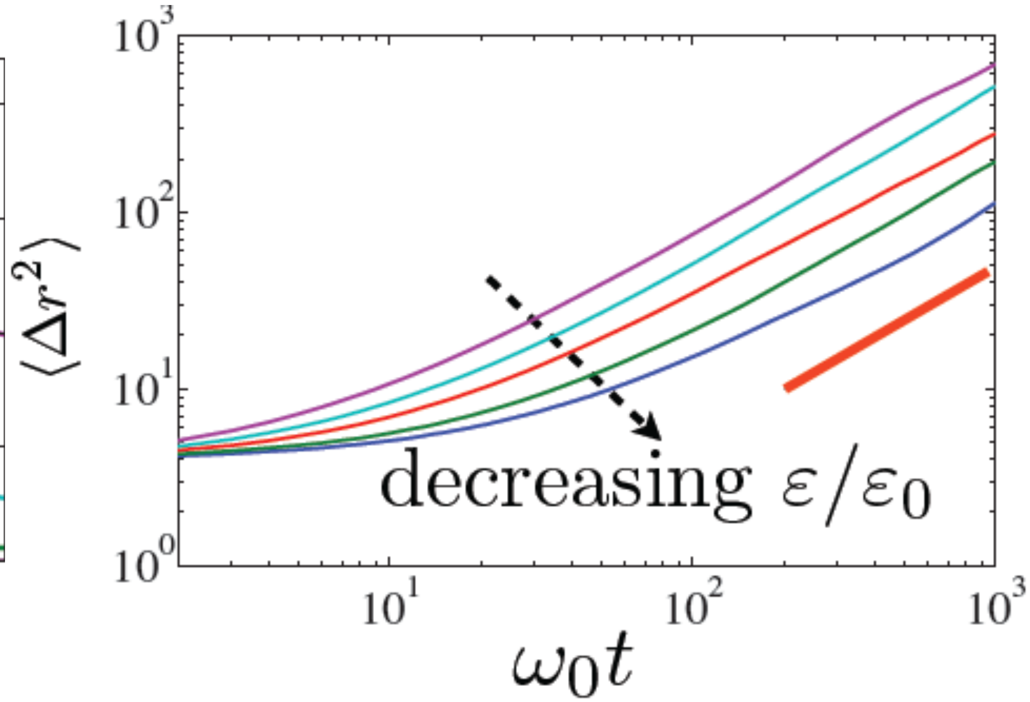
Vanishing shear modulus at p_0^*



From energy barriers to cell migration:



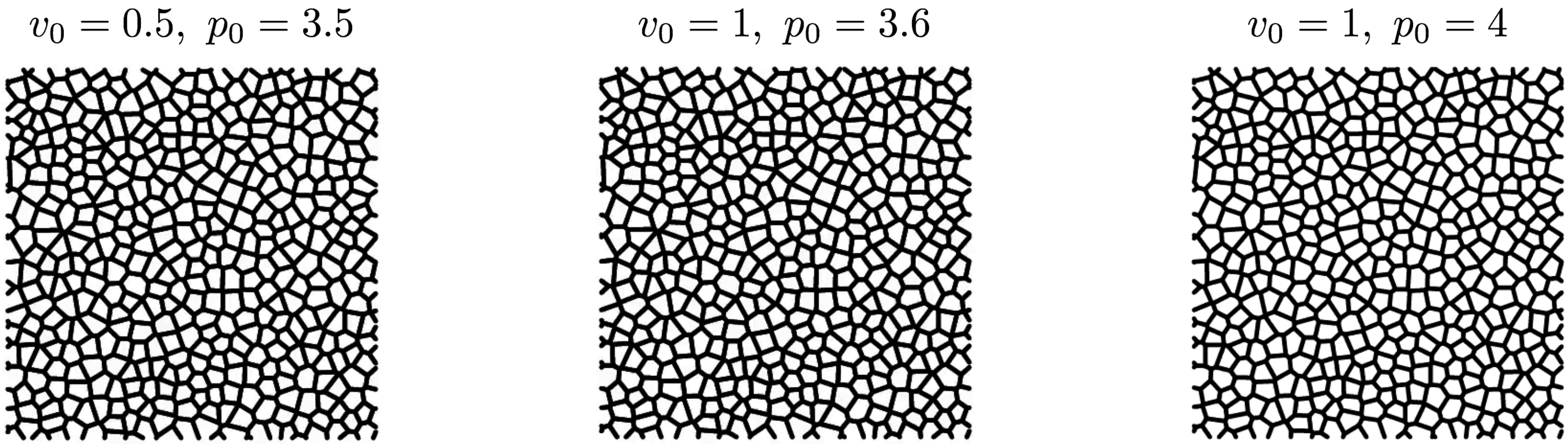
Analytic calculation



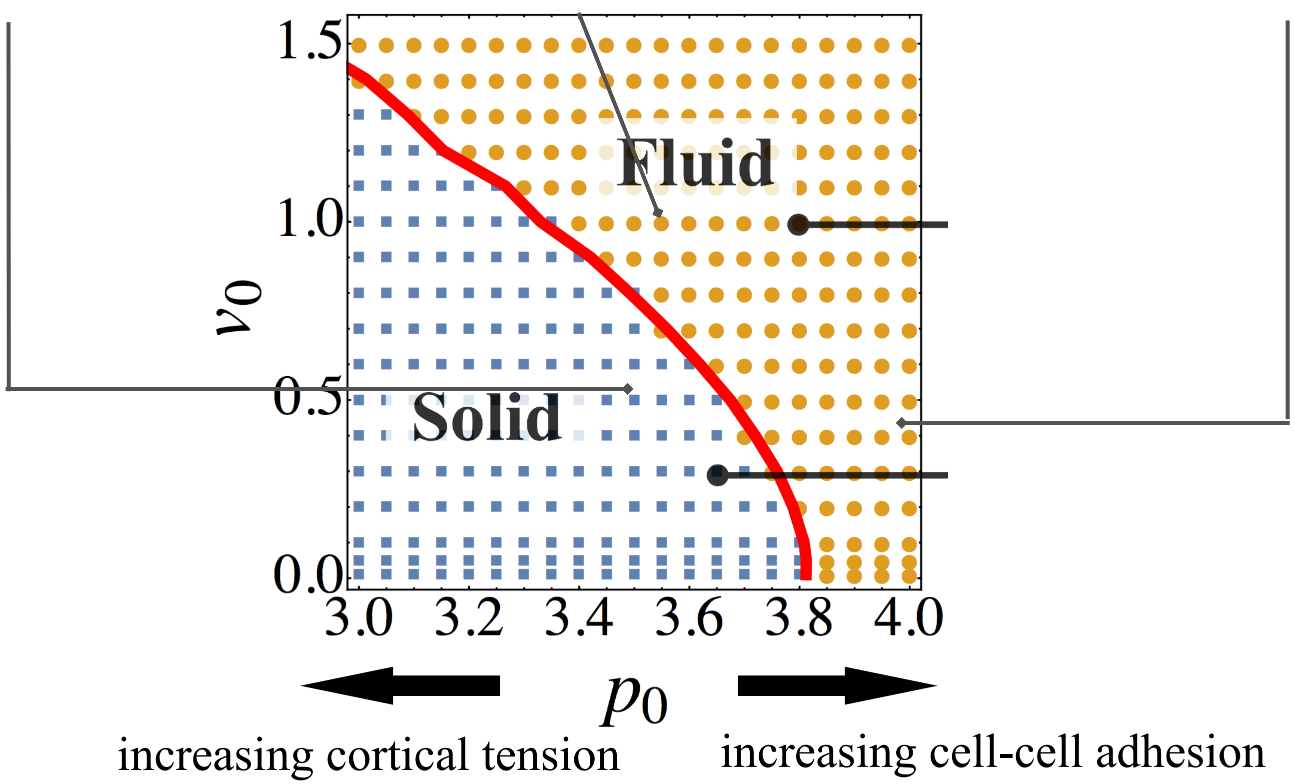
random walkers

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

Effect of finite cell motility?

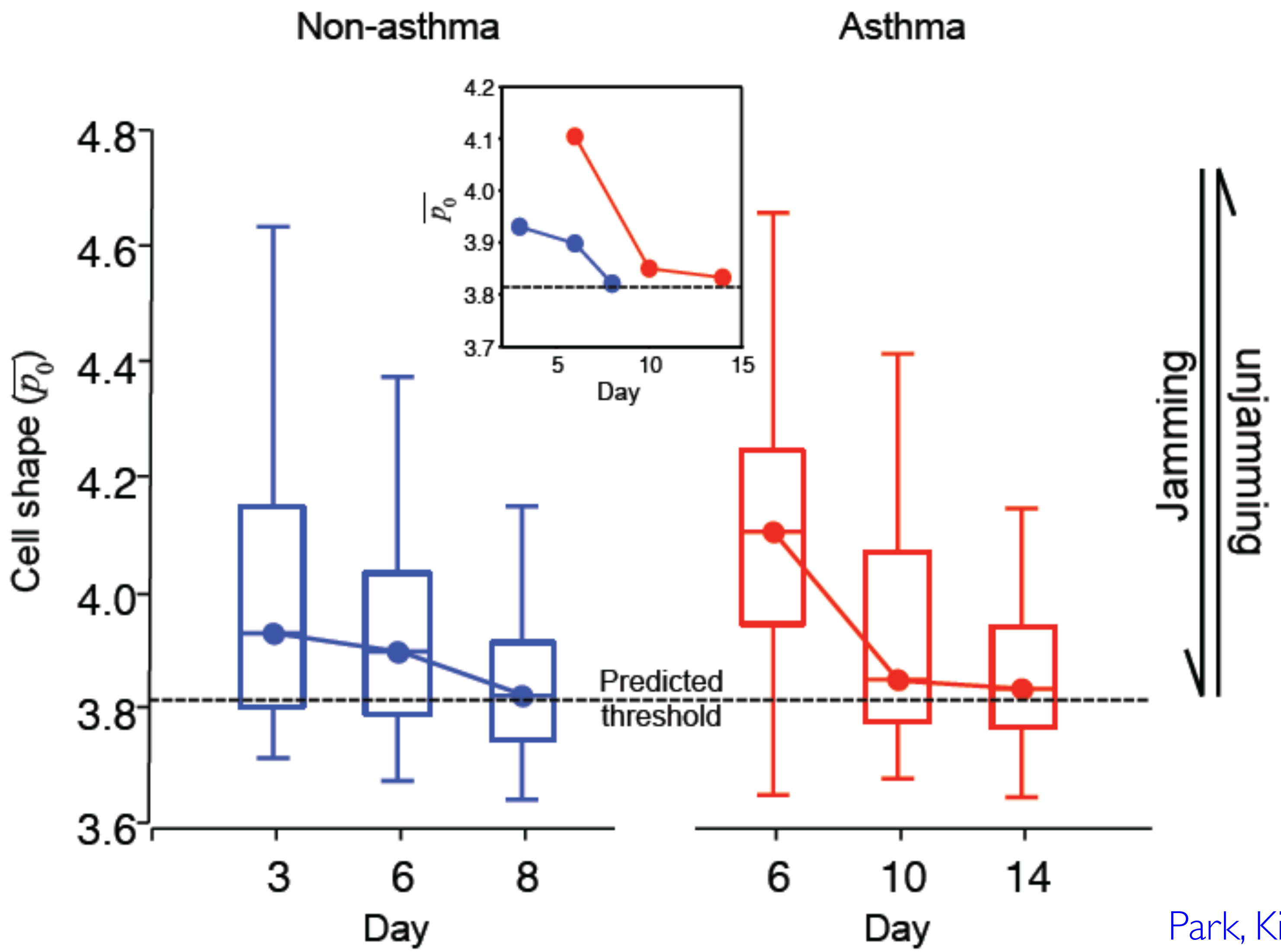


Add an equation for cell polarization with a finite velocity v_0 (like in self-propelled particle models)



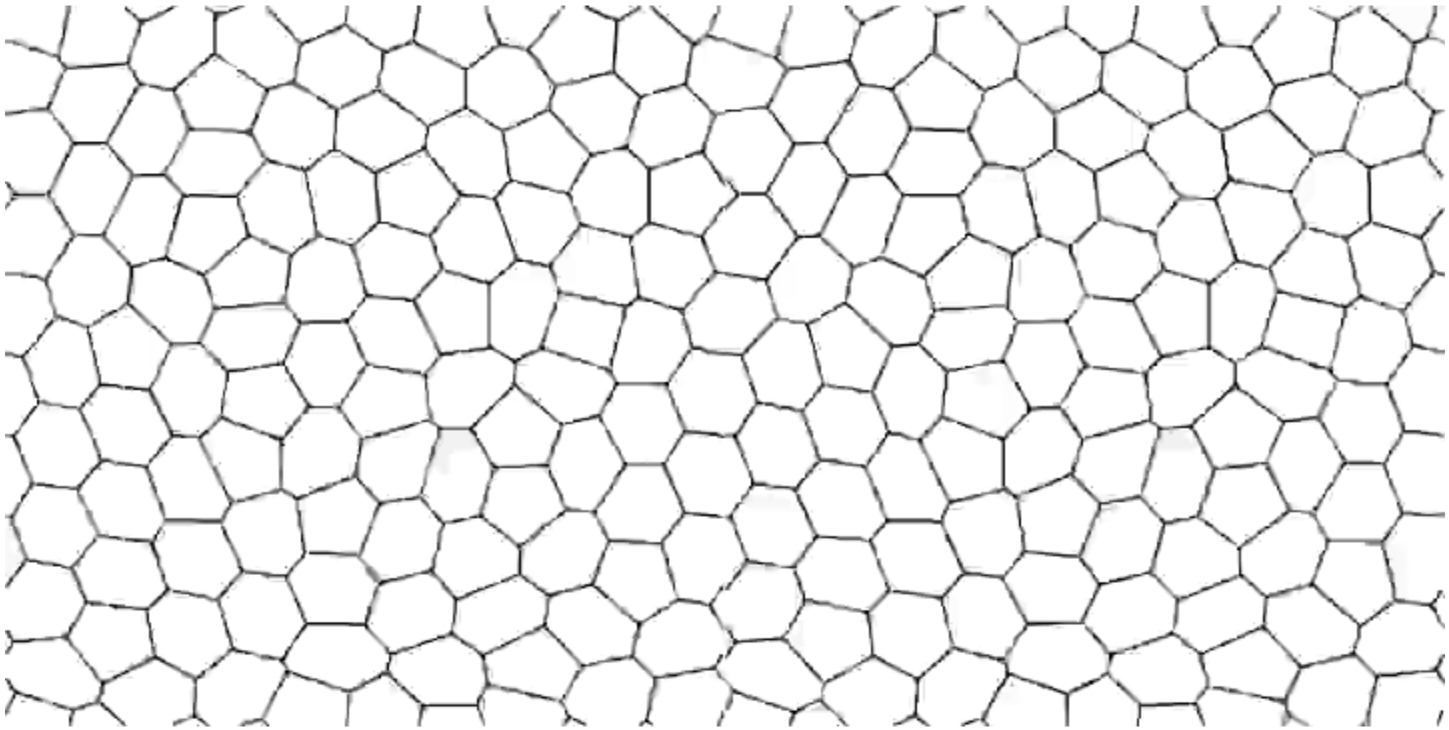
Bi, Yang, Marchetti, Manning, in preparation (2015)

Perimeter to area ratio approaches precisely the predicted value at jamming



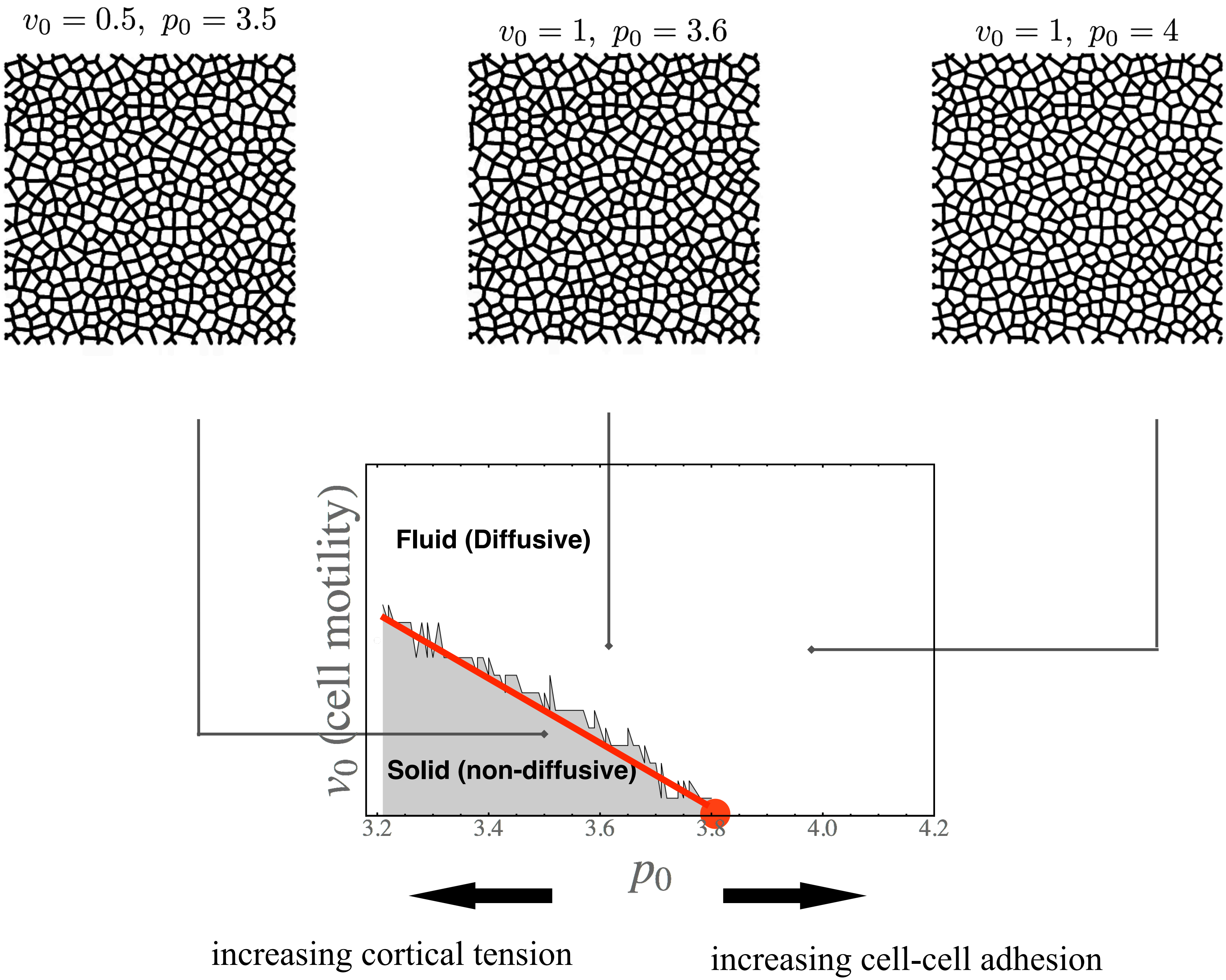
Park, Kim, Bi, et al, submitted (2014)

Effect of finite cell motility?



$p0 < p0^*$ $p0 > p0^*$

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

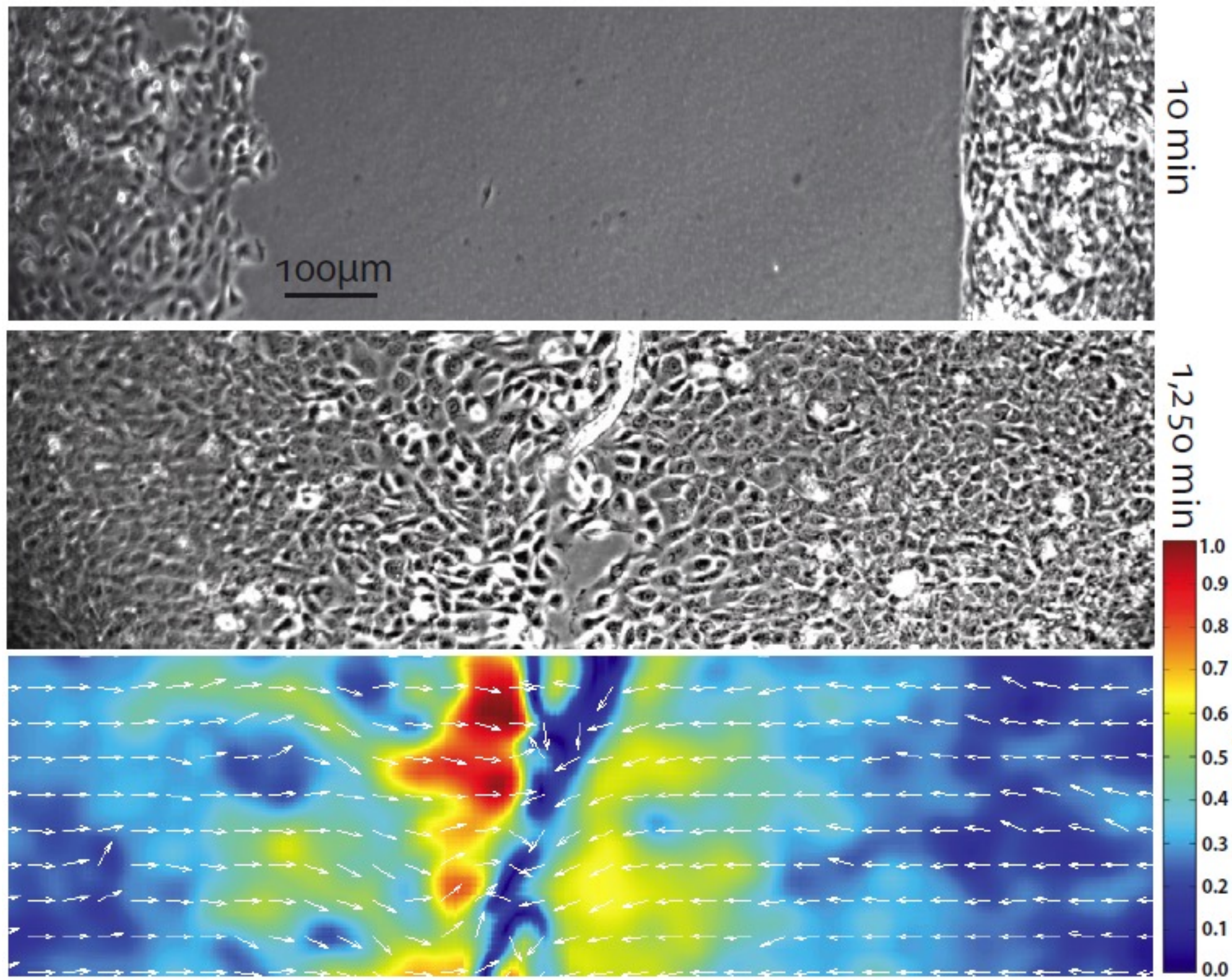


$v_0 = 0.5,\ p_0 = 3.5$
$v_0 = 1,\ p_0 = 3.6$
$v_0 = 1,\ p_0 = 4$
v_0 (cell motility)
Fluid (Diffusive)
Solid (non-diffusive)
3.2
3.4
3.6
3.8
4.0
4.2
p_0
increasing cortical tension
increasing cell-cell adhesion

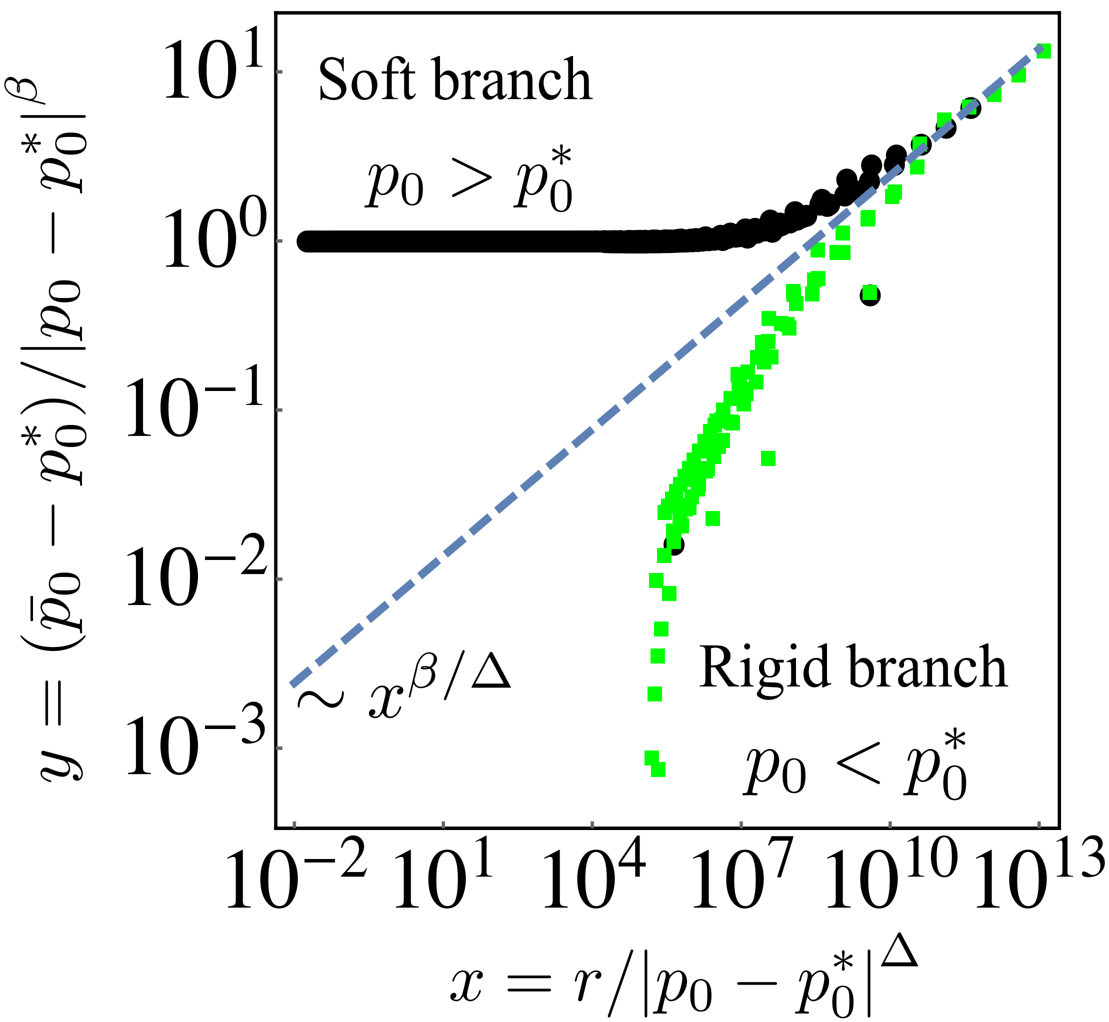
Jamming in transformed (cancer-like) cell lines generates **boundaries**

MCF-10A cell monolayer

Nnetu et al NJP 2012



What else does this predict for experiments?



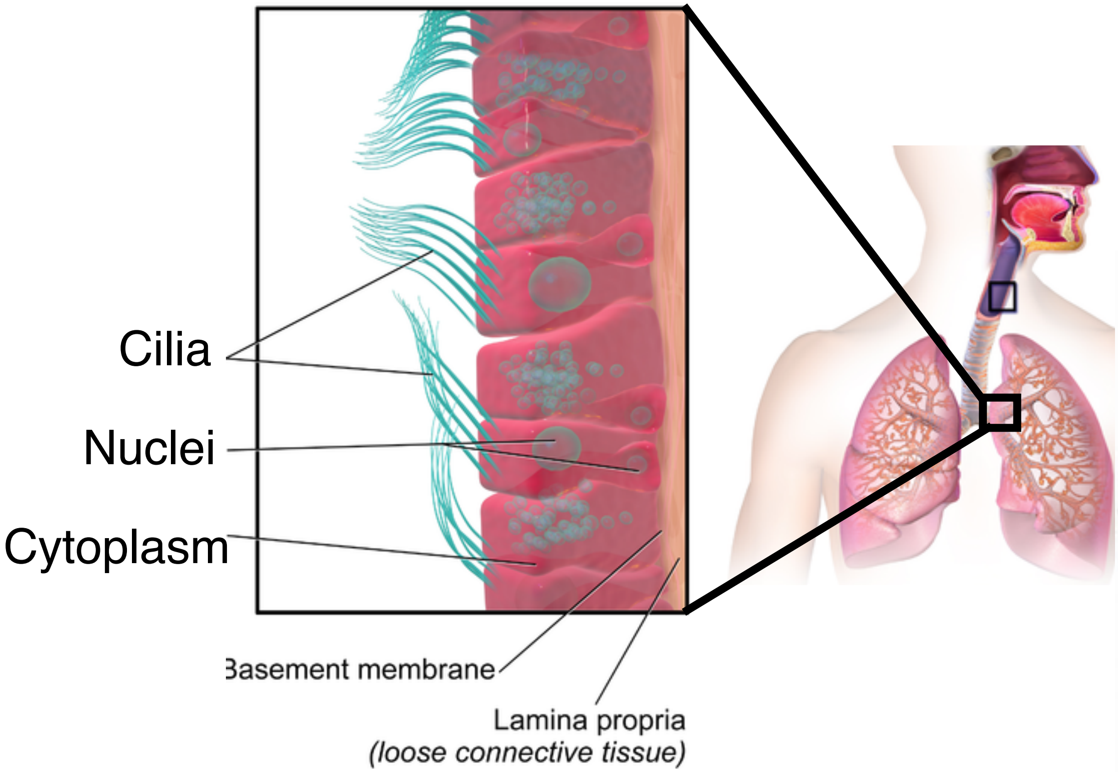
$$\bar{p}_0 = \langle p \rangle / \sqrt{\langle a \rangle}$$

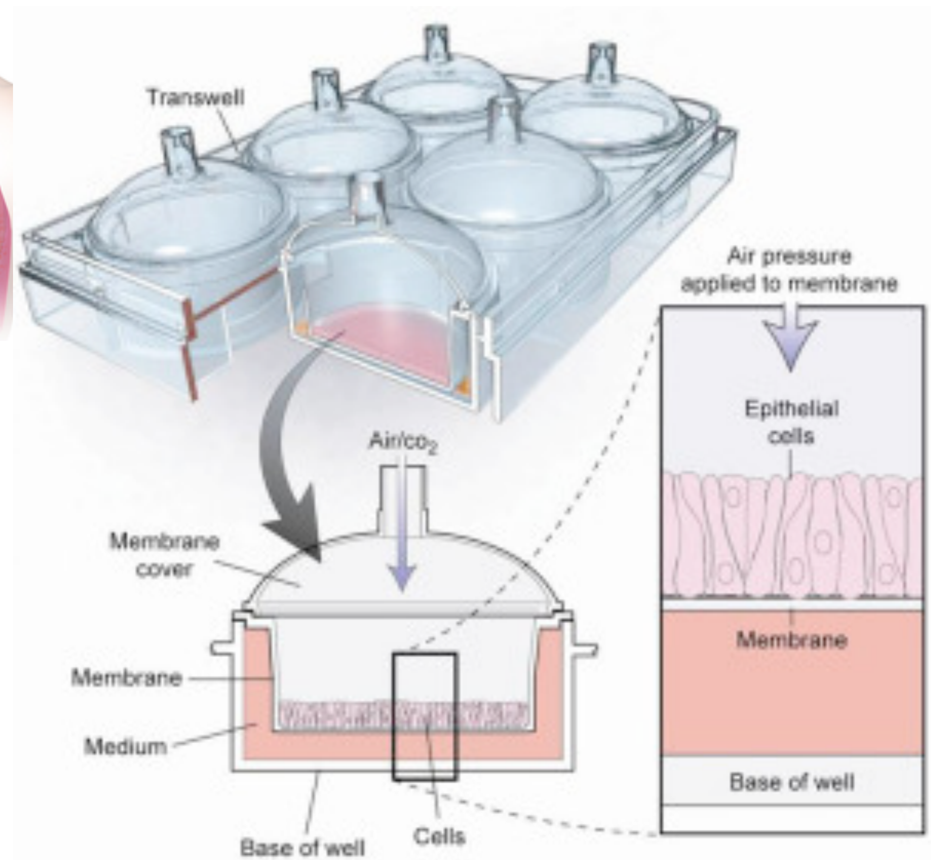
This also has a critical scaling!

Experiments in primary human bronchial epithelial cells (HBECs)

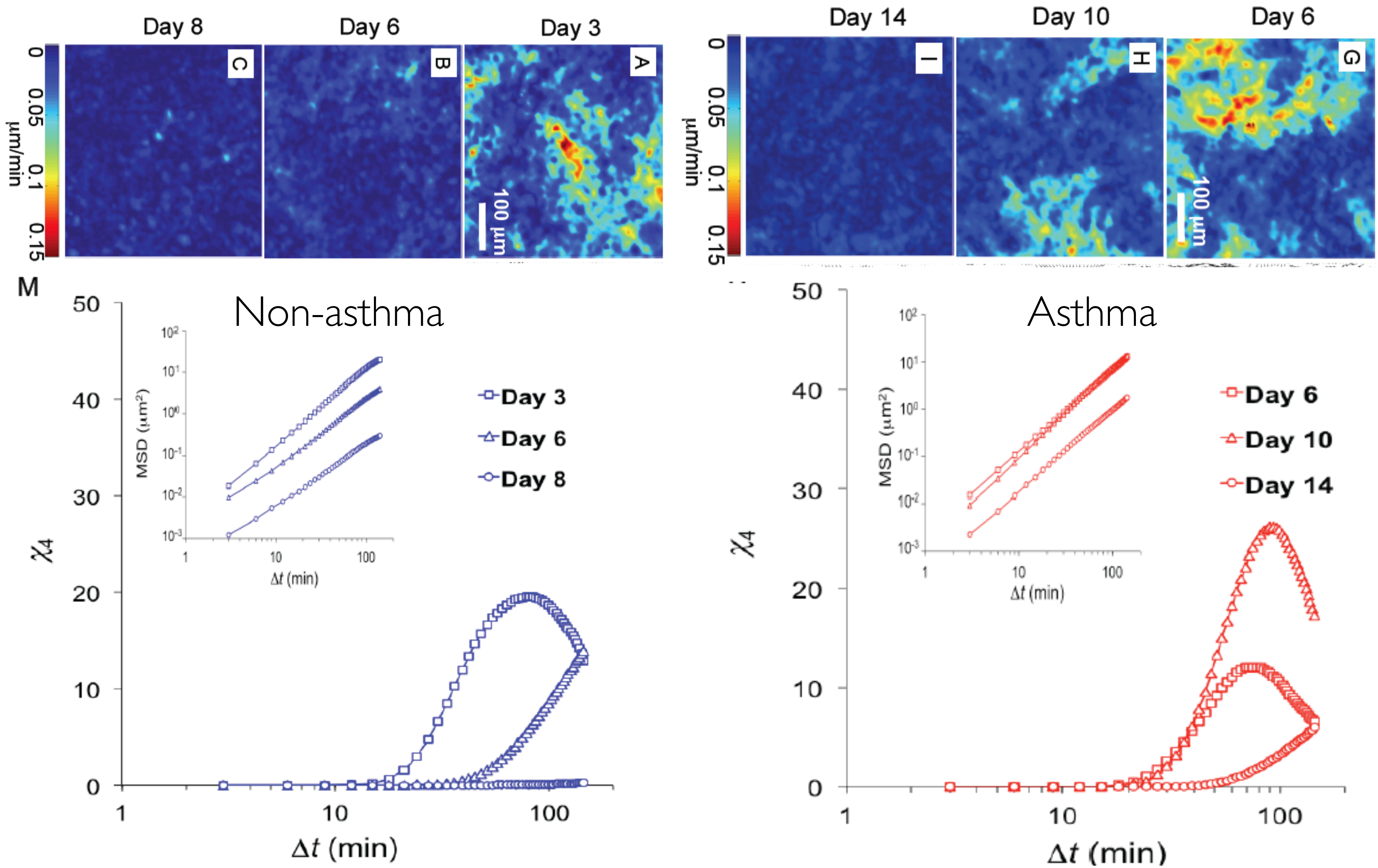
with Fredberg group, Harvard School of Public Health

Jin-Ah Park
Jae Hun Kim
Jennifer Mitchel

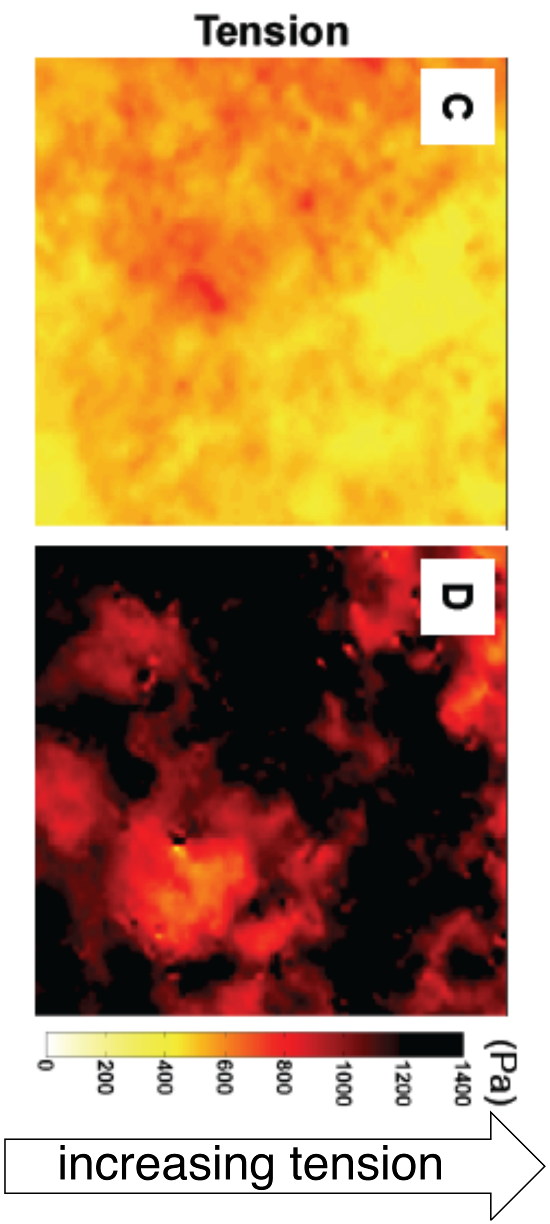


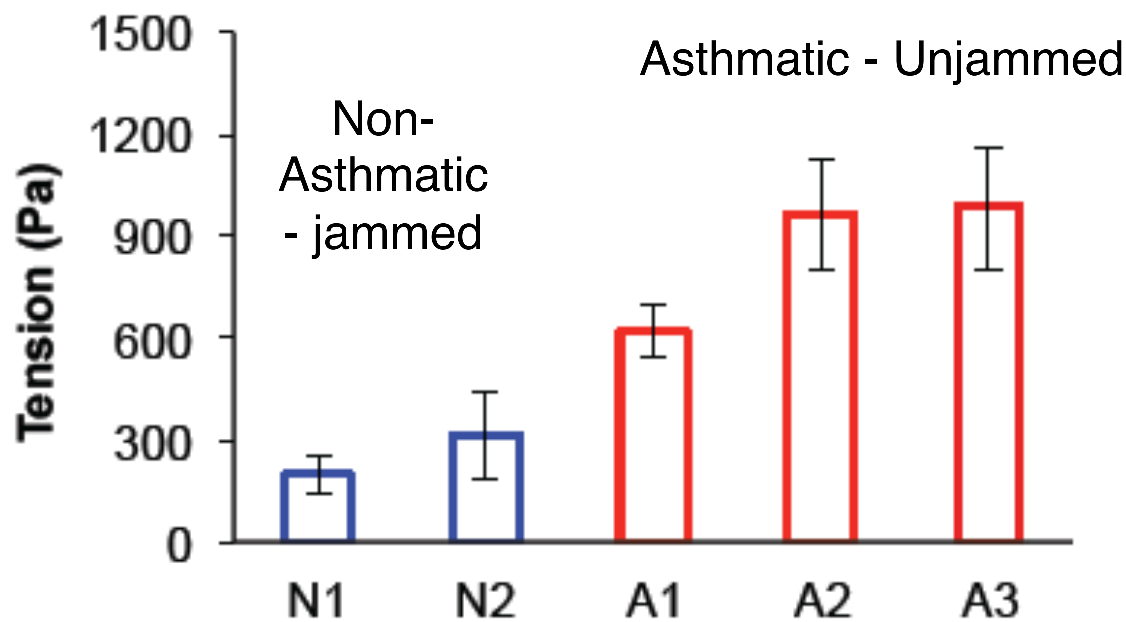


A jamming transition in primary human cell culture



Intra-tissue tension higher in asthmatic tissues

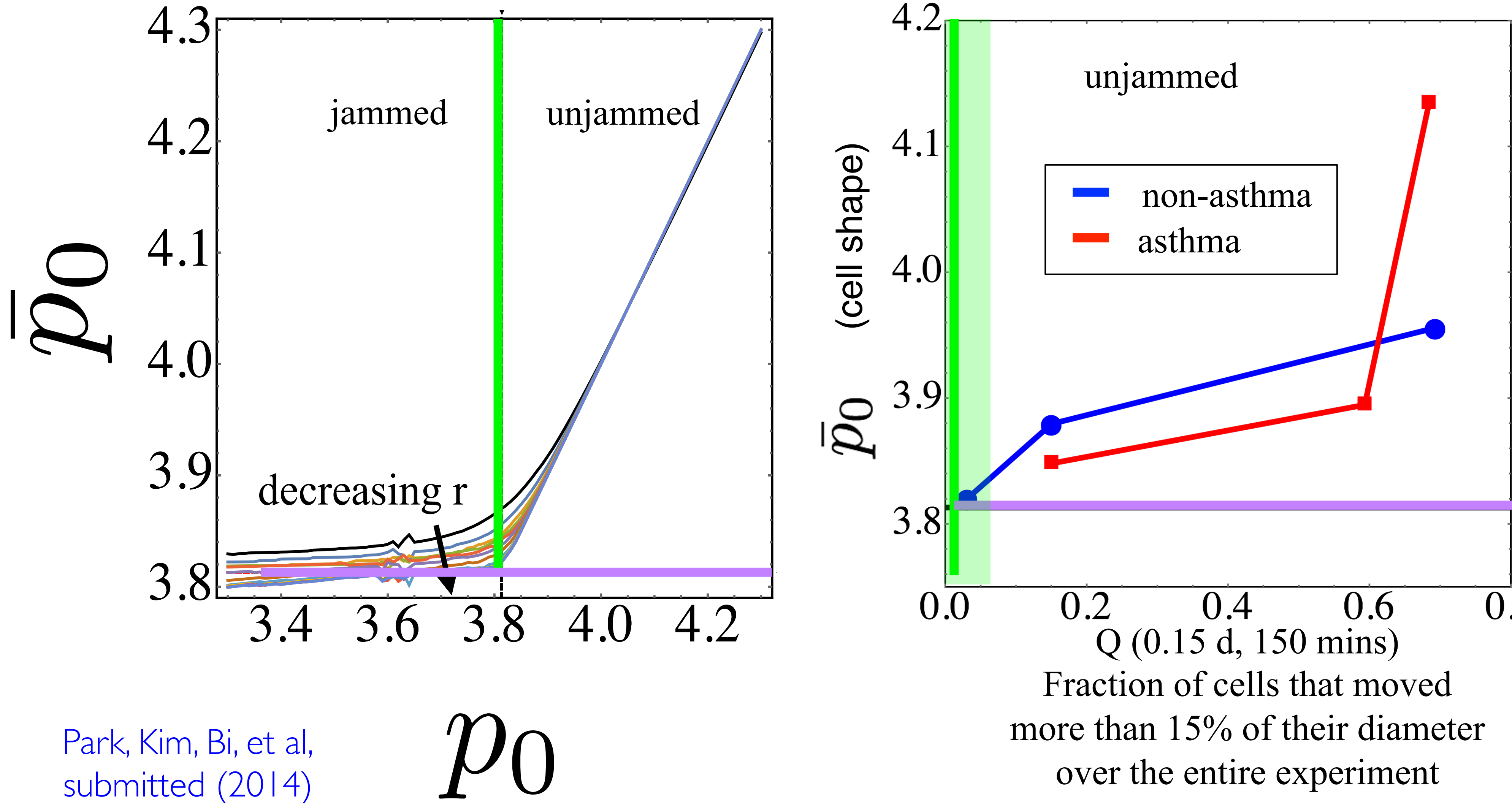




Unjammed tissues support higher tensile stresses (not less)

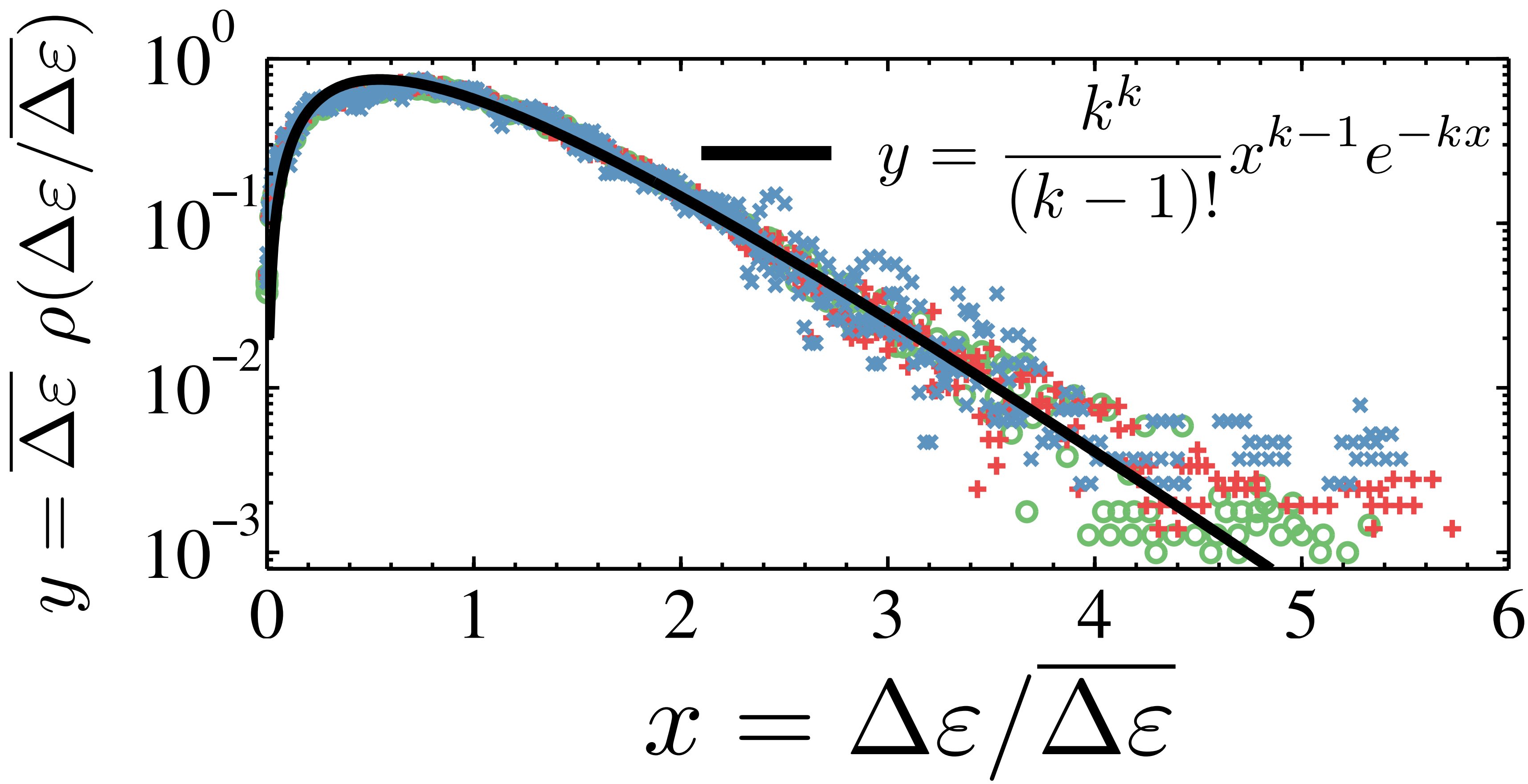
Consistent with idea that adhesive interactions are stronger in the unjammed tissues

Perimeter to area ratio approaches precisely the predicted value at jamming



Park, Kim, Bi, et al, submitted (2014)

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



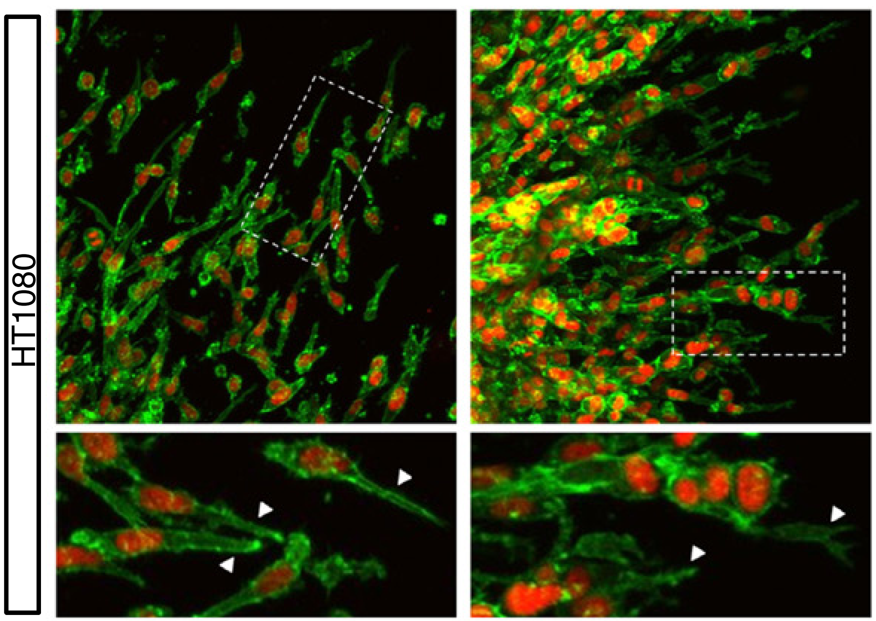
k-gamma distribution with one fit parameter: k=2.2± 0.2
(found in many cellular systems e.g. Aste & Matteo, PRE 2008)

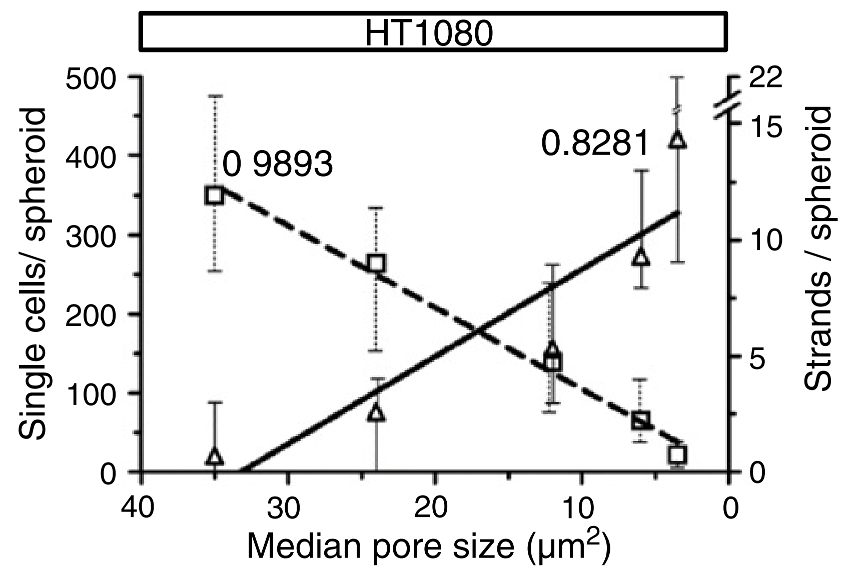
Cancer cells change invasion strategies depending on confinement

Cell jamming: Collective invasion of mesenchymal tumor cells imposed by tissue confinement☆

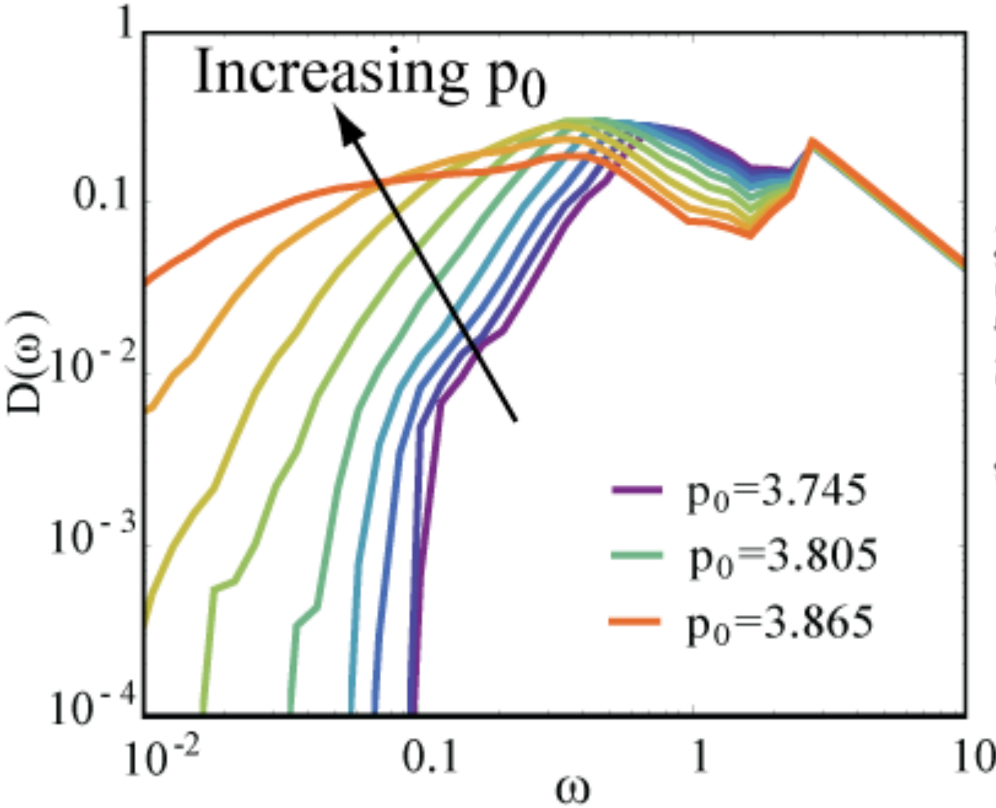
Anna Haeger[a,1], Marina Krause[a,1], Katarina Wolf[a,1], Peter Friedl[a,b,c,*,1]

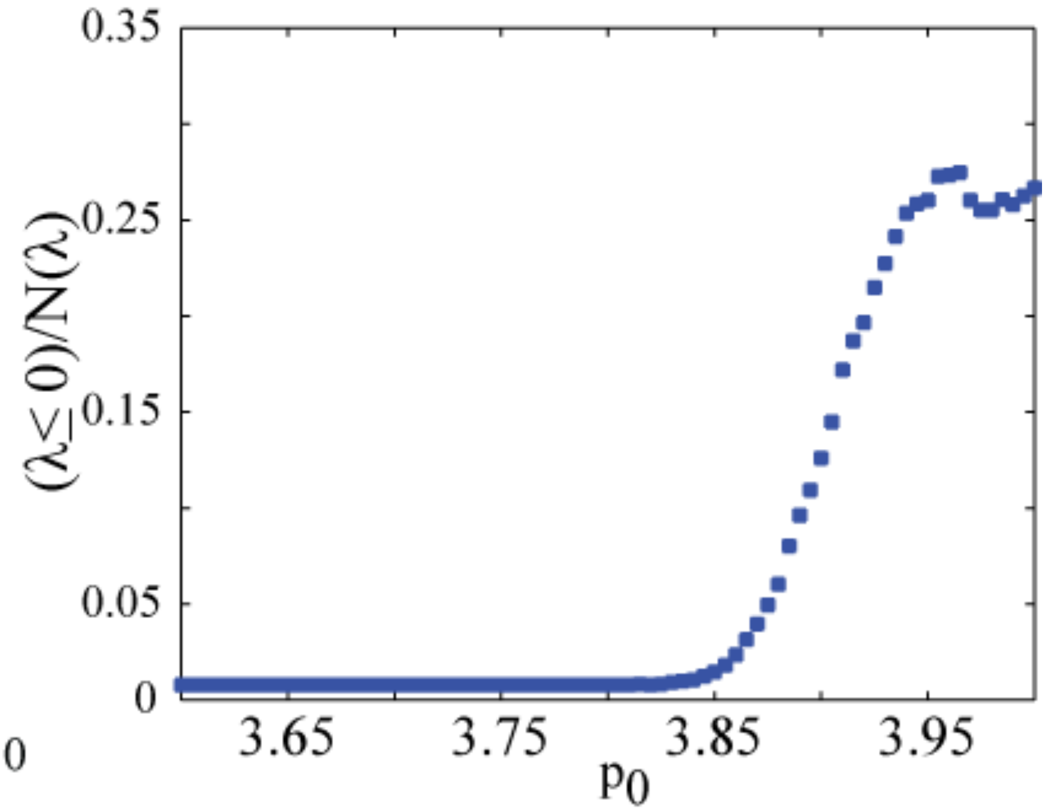
Biochimica et Biophysica Acta 1840 (2014) 2386–2395



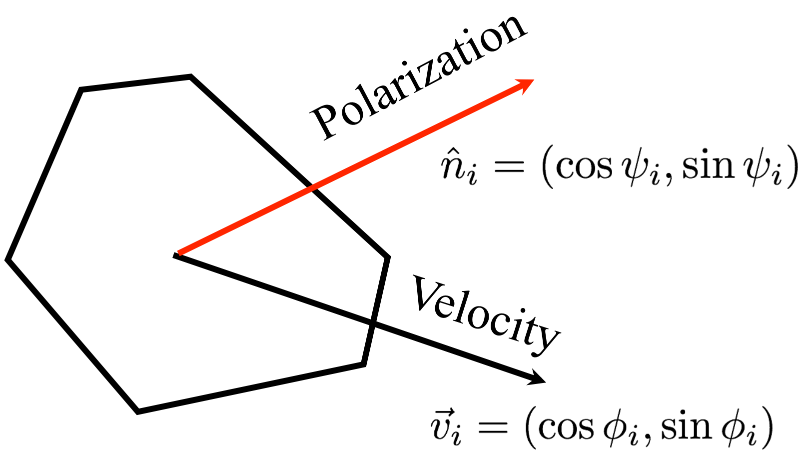


What about normal modes? Collective behavior? Is it okay to study localized T1s?





From rigidity transition to glass transition
"Active Vertex Model" (ongoing work)



At each vertex, simulate the overdamped equation of motion:

$$b\frac{d\vec{r}_\nu}{dt} = -\frac{\partial\varepsilon}{\partial\vec{r}_\nu} + v_0\sum_{i\leftrightarrow\nu}\hat{n}_i$$

Forces depend on shape of cell

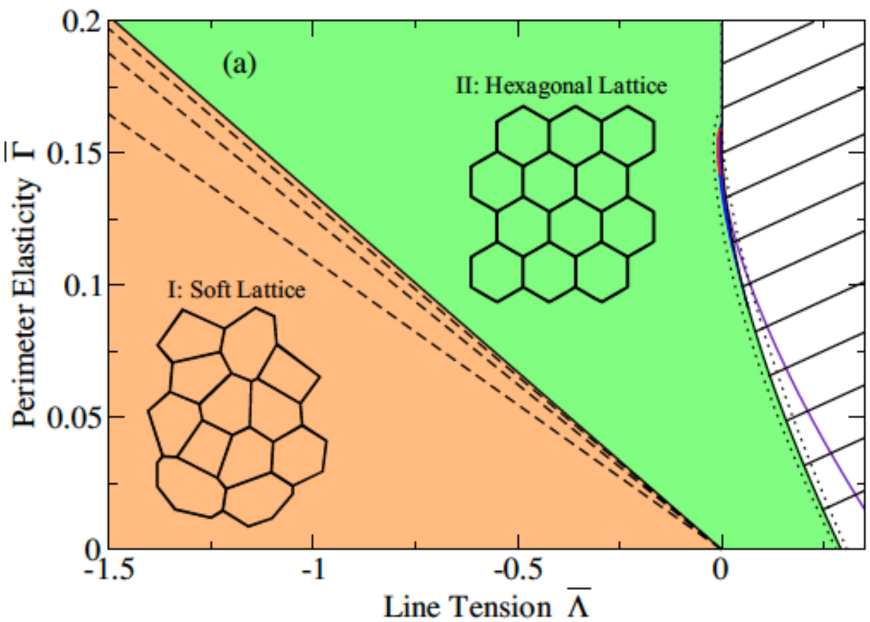
Cell Motility Force

Polarization Dynamics:
Polarization vector tends to align with cell velocity

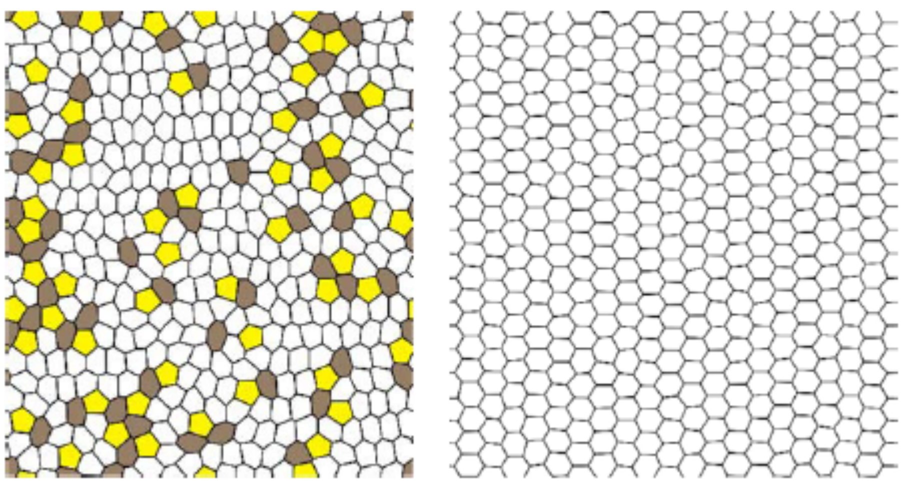
$$\frac{d\psi_i}{dt} = -\frac{\psi_i - \phi_i}{\tau} + \eta_i$$

$$\langle\eta_i\eta_j\rangle = \sigma^2\delta_{ij}\delta(t-t')$$

Previous results on ground states:



Staple et al EPJE 33 (2010)

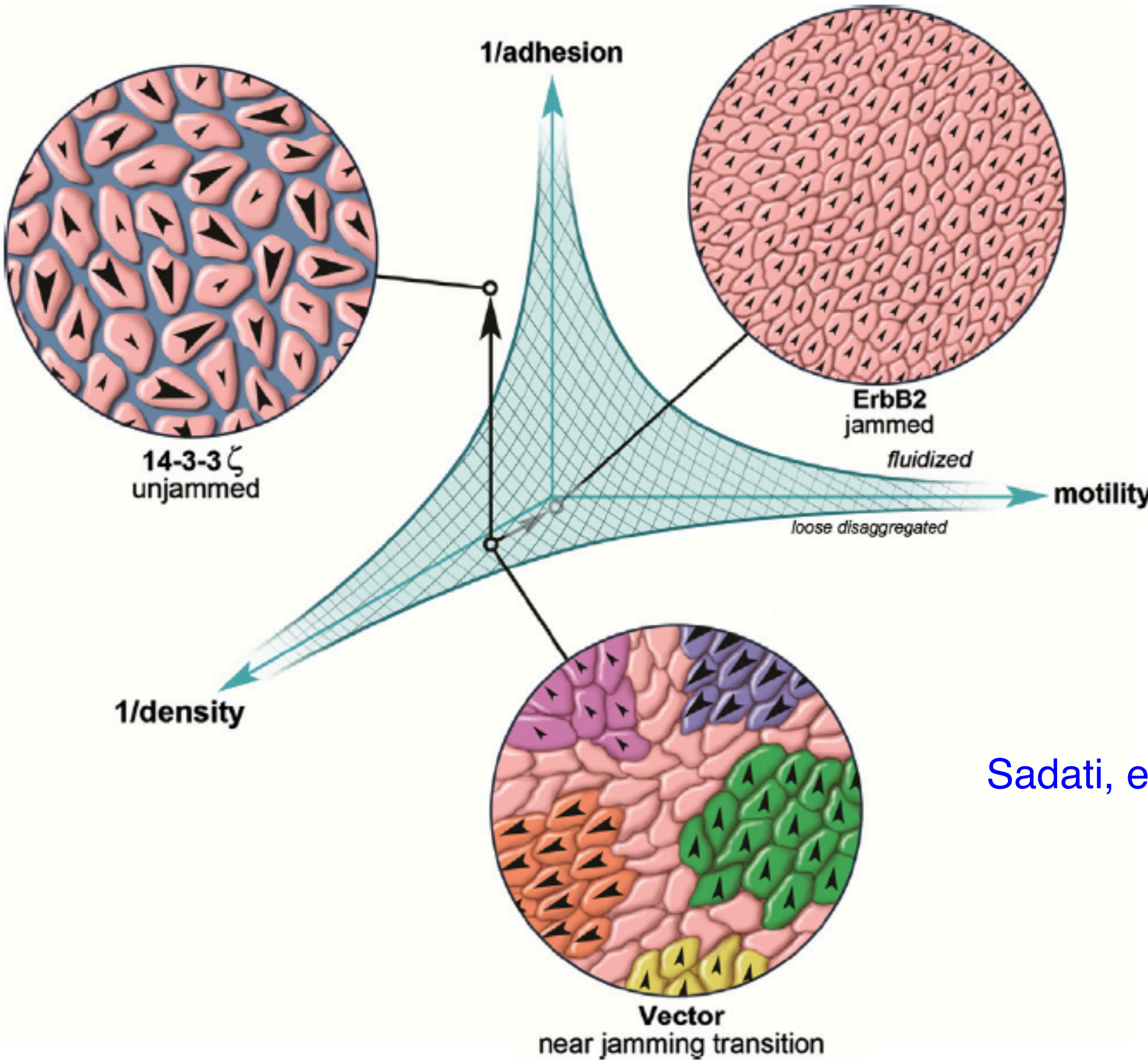


a = 0.86 a = 0.90

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

Hocevar and Ziherl PRE 80 11904 (2009)

Jamming phase diagram for biological tissues



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

why might tissues generically be close to a glass transition?

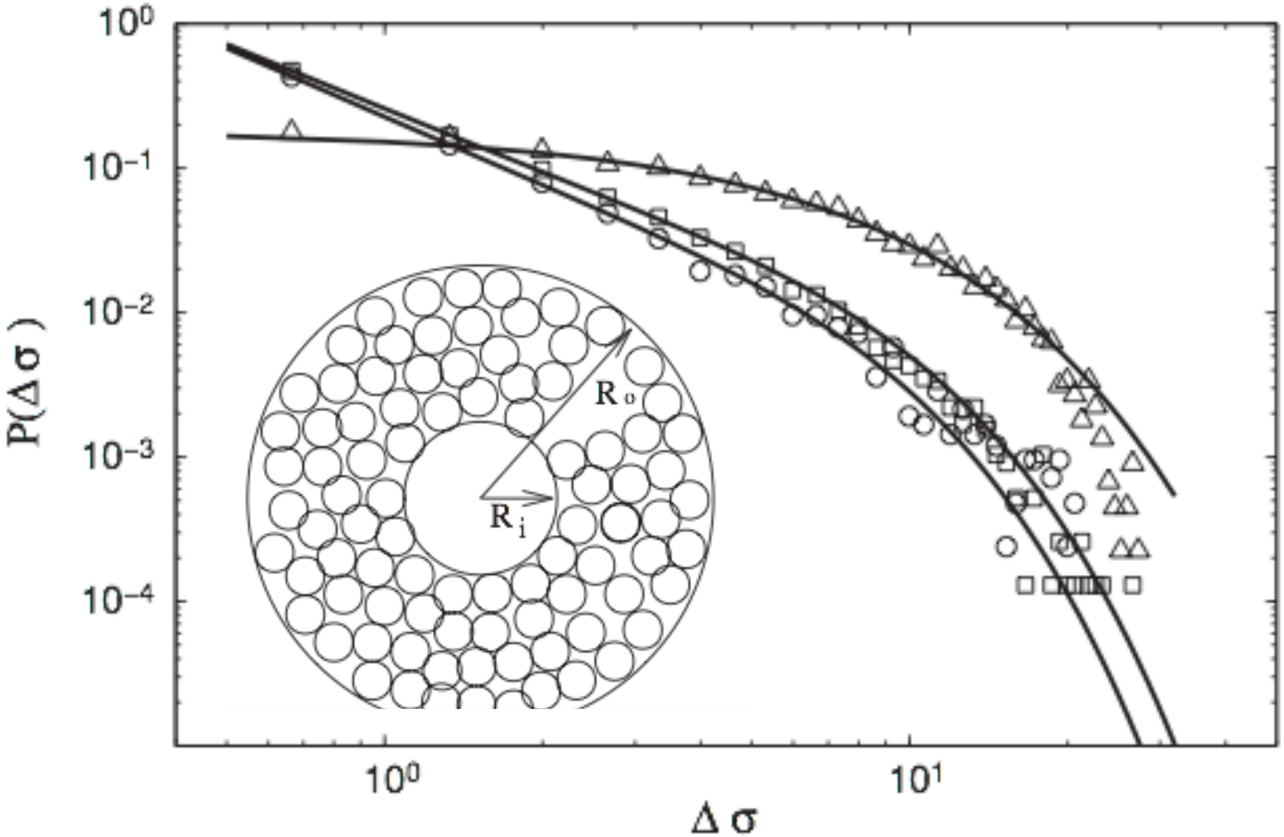
For wound healing, embryonic development, cancer invasion:

- 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 evidence for this idea?

Where did it come from?

Energy barrier statistics, foams and grains

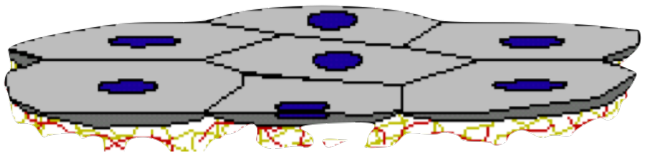


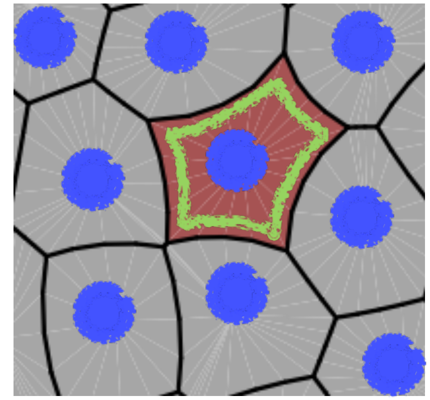
Behringer et al PRL 101 268301 (2008)

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

Why? conjecture: energy is injected globally and failure occurs at special soft spots in materials that are tuned near a critical point

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 fluctuations

acto-myosin contractilty

Interfacial tension: adhesion and cortical tension

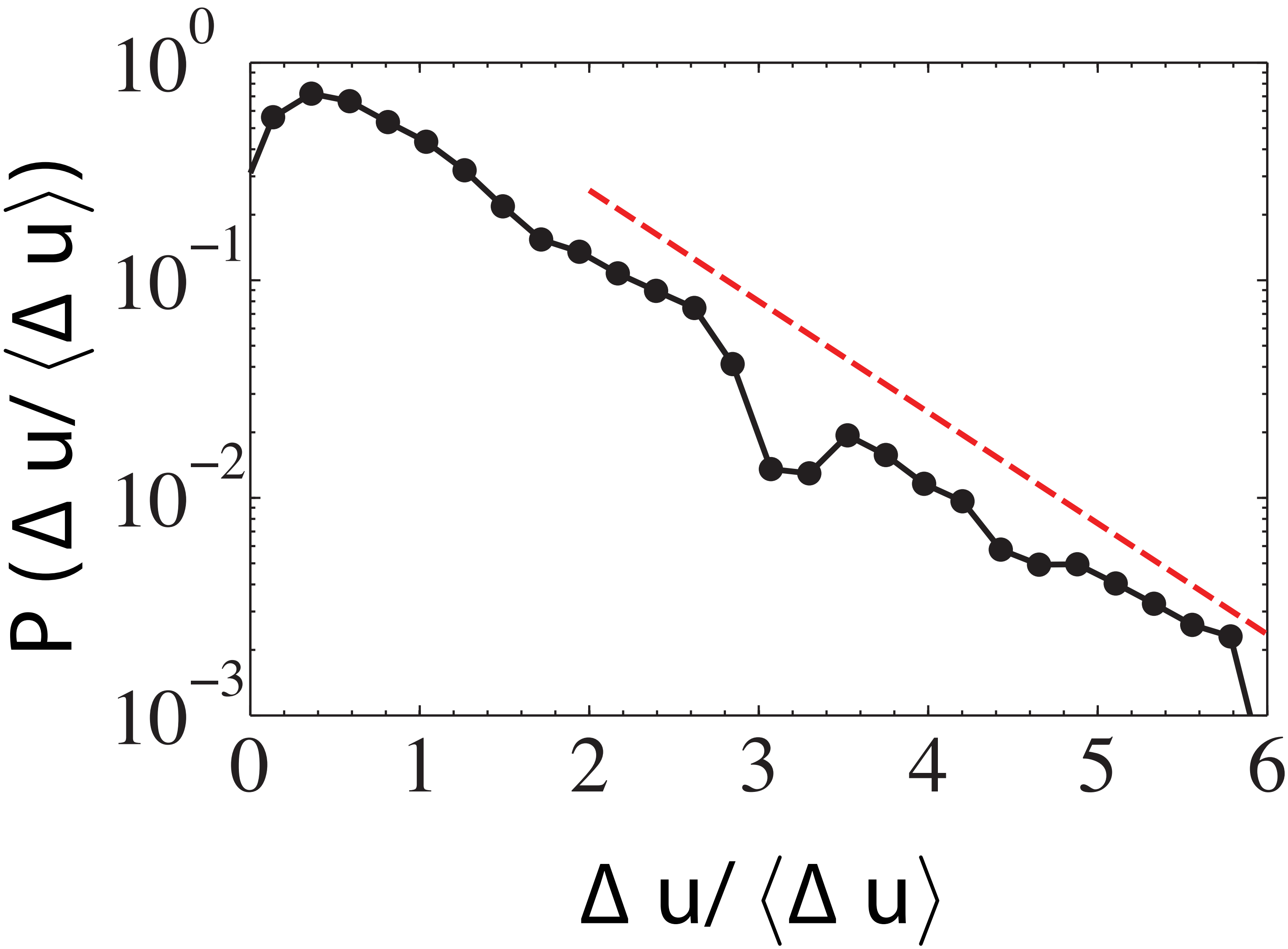
$$\varepsilon = \frac{1}{\beta A_0}\sum_i^N E_i = \sum_i \left[(a_i - 1)^2 + \frac{(p_i - p_0)^2}{r}\right]$$

Non-dimensionalized mechanical energy

but that was all for one set of parameter values!

what is the phase diagram for the vertex model?

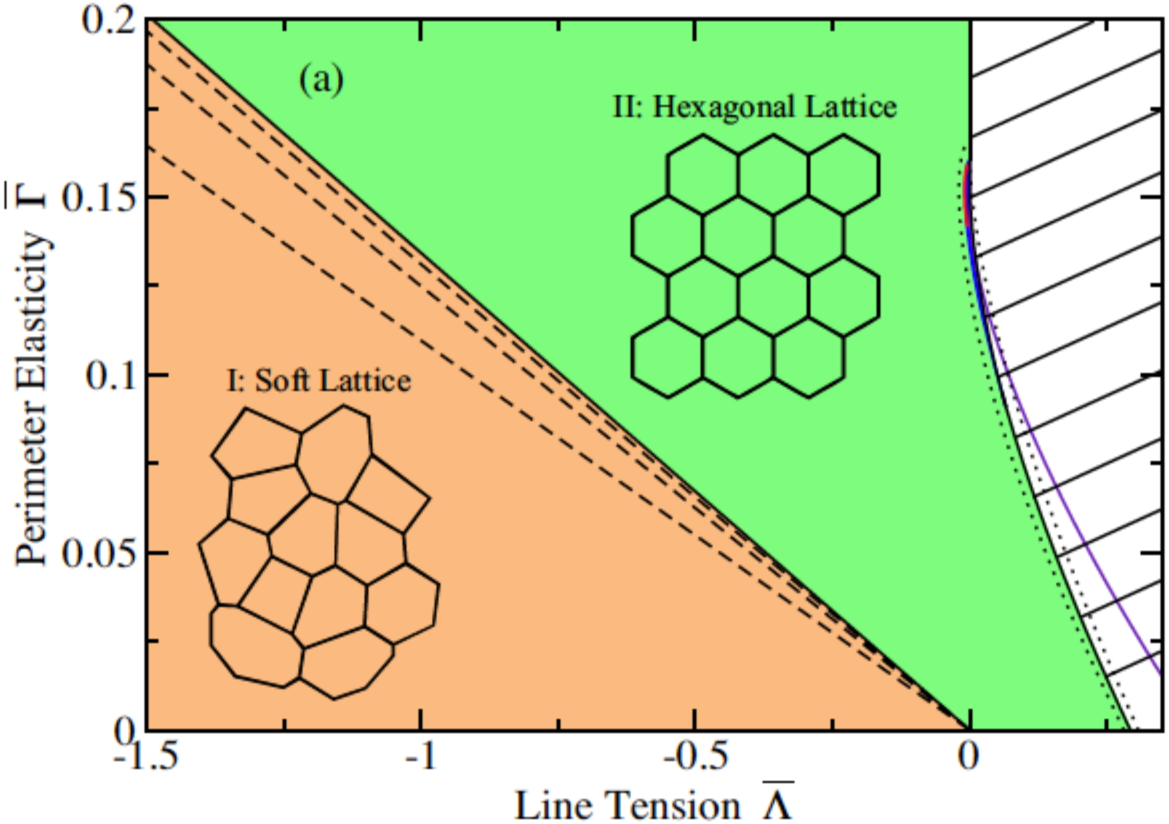
Energy barrier statistics, tissue simulation



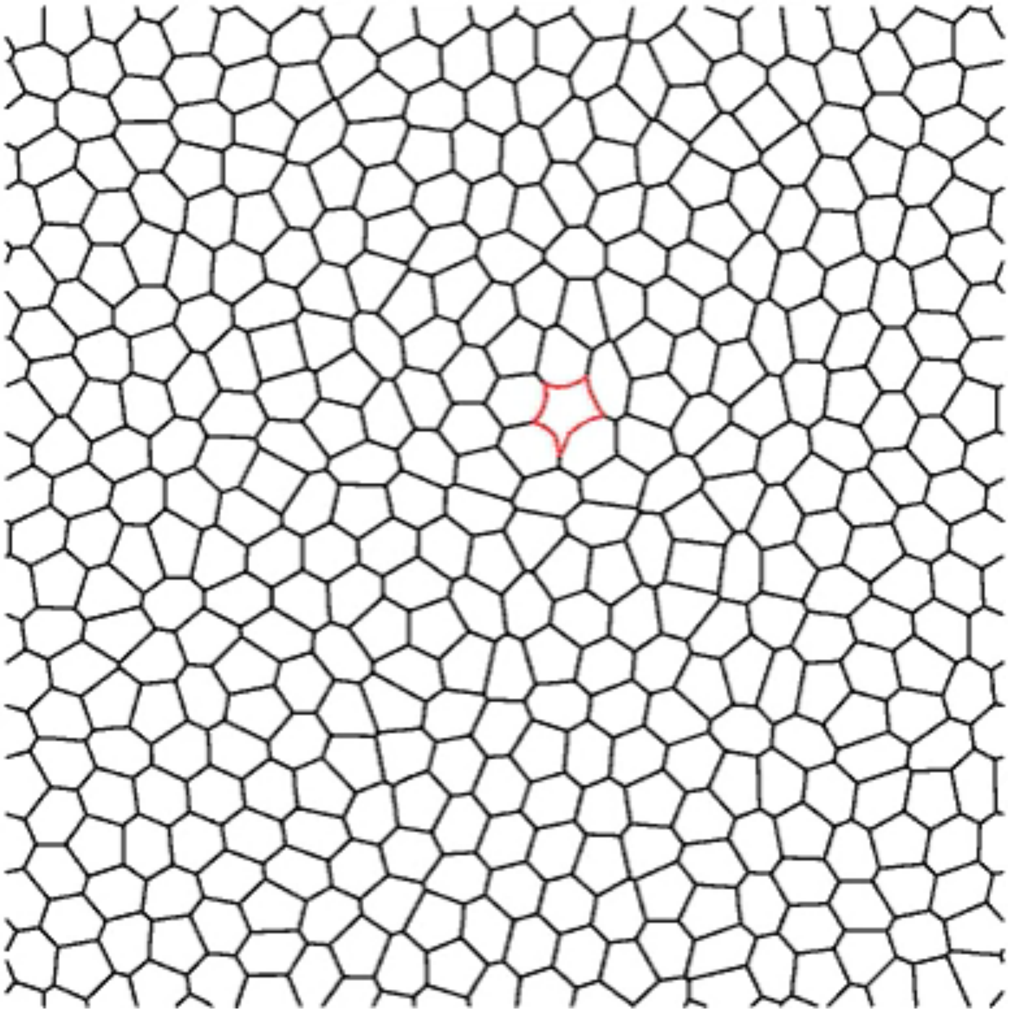
Energy barriers are exponentially distributed!

Energy is injected locally, all sites are probed

Ordered vs. disordered branches, linear vs. nonlinear response



Work in progress

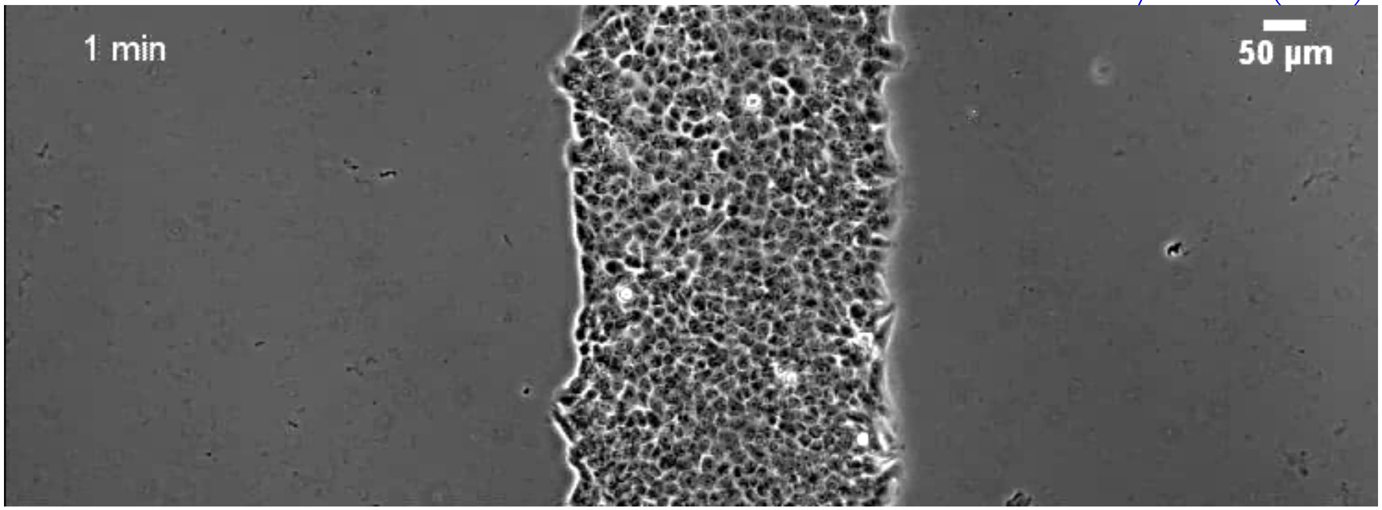


"Abnormal" cancer-like cell embedded in normal cells

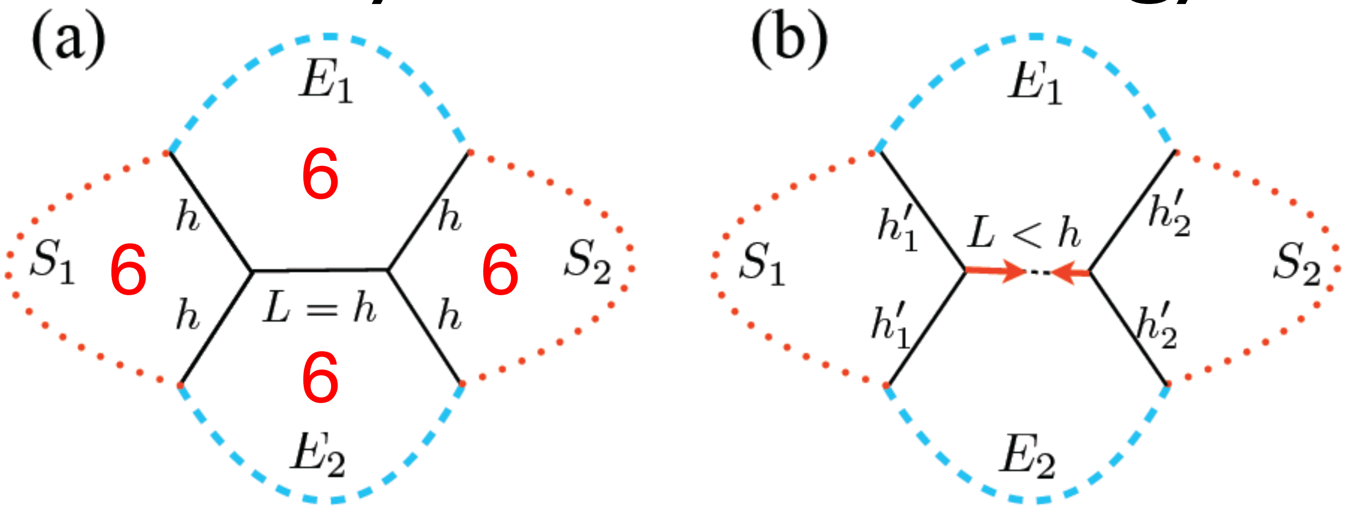
Work in progress

adding cell divisions and cell polarization to shape equilibrium model for full dynamics

Serra-Picamal et al Nature Phys. 8 628 (2012)

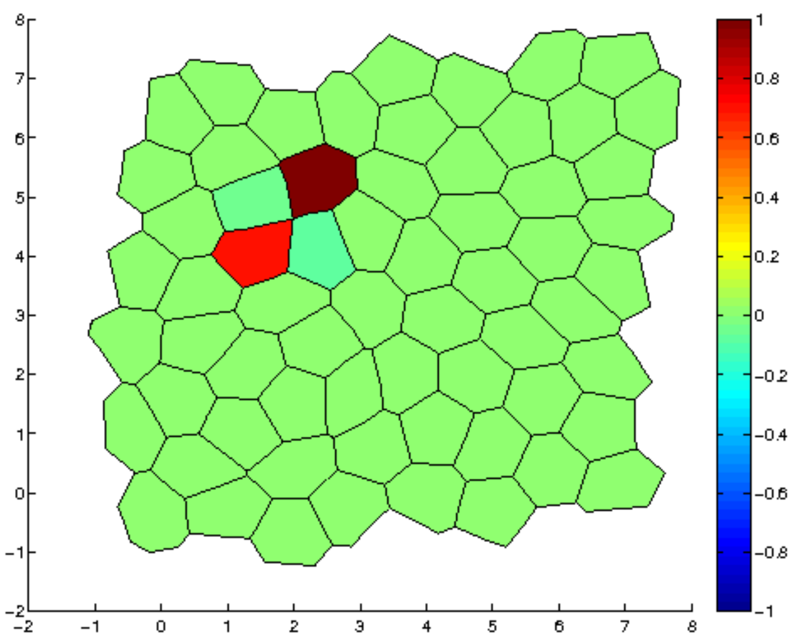


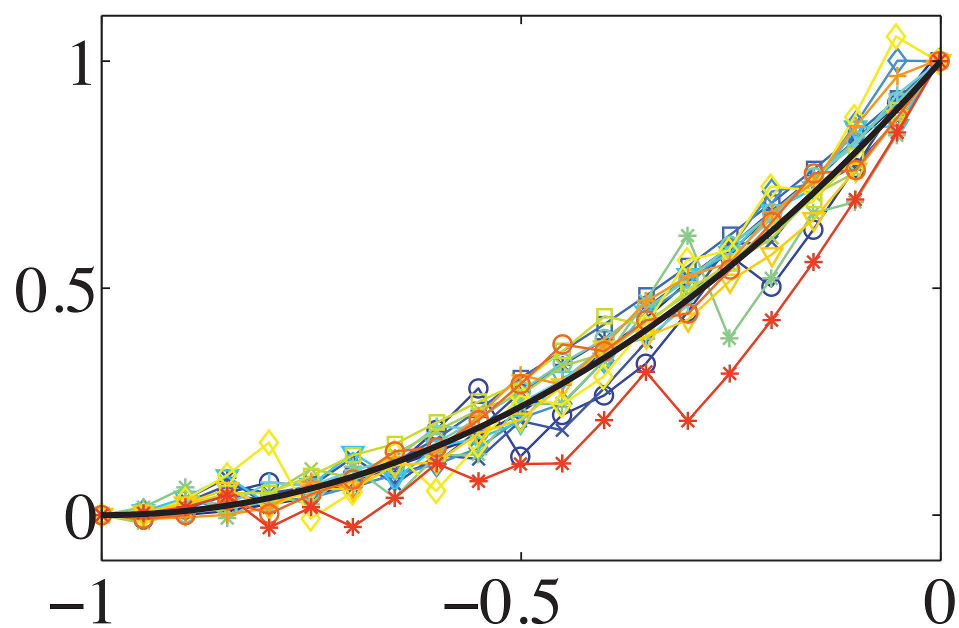
Analytic results: energy barrier shape



Mean field model:

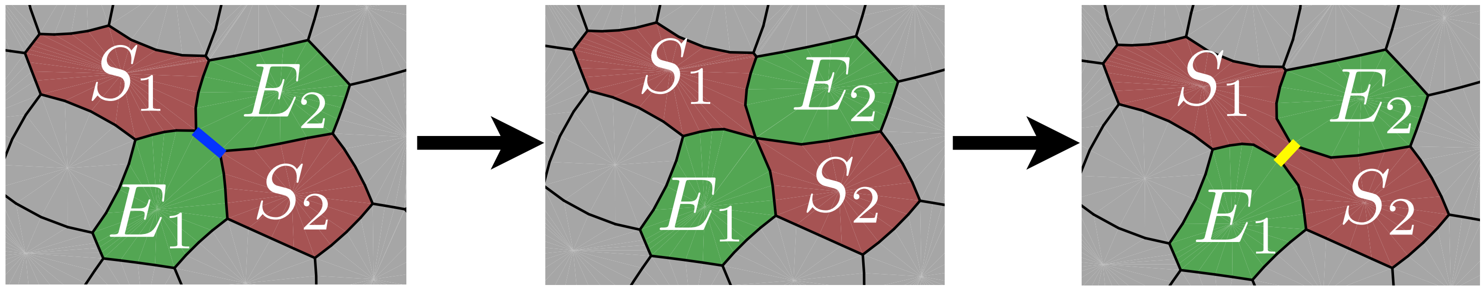
- energy change is localized to 4 cells
- all cells have 6 sides (on average, required by Gauss-Bonnet Theorem)

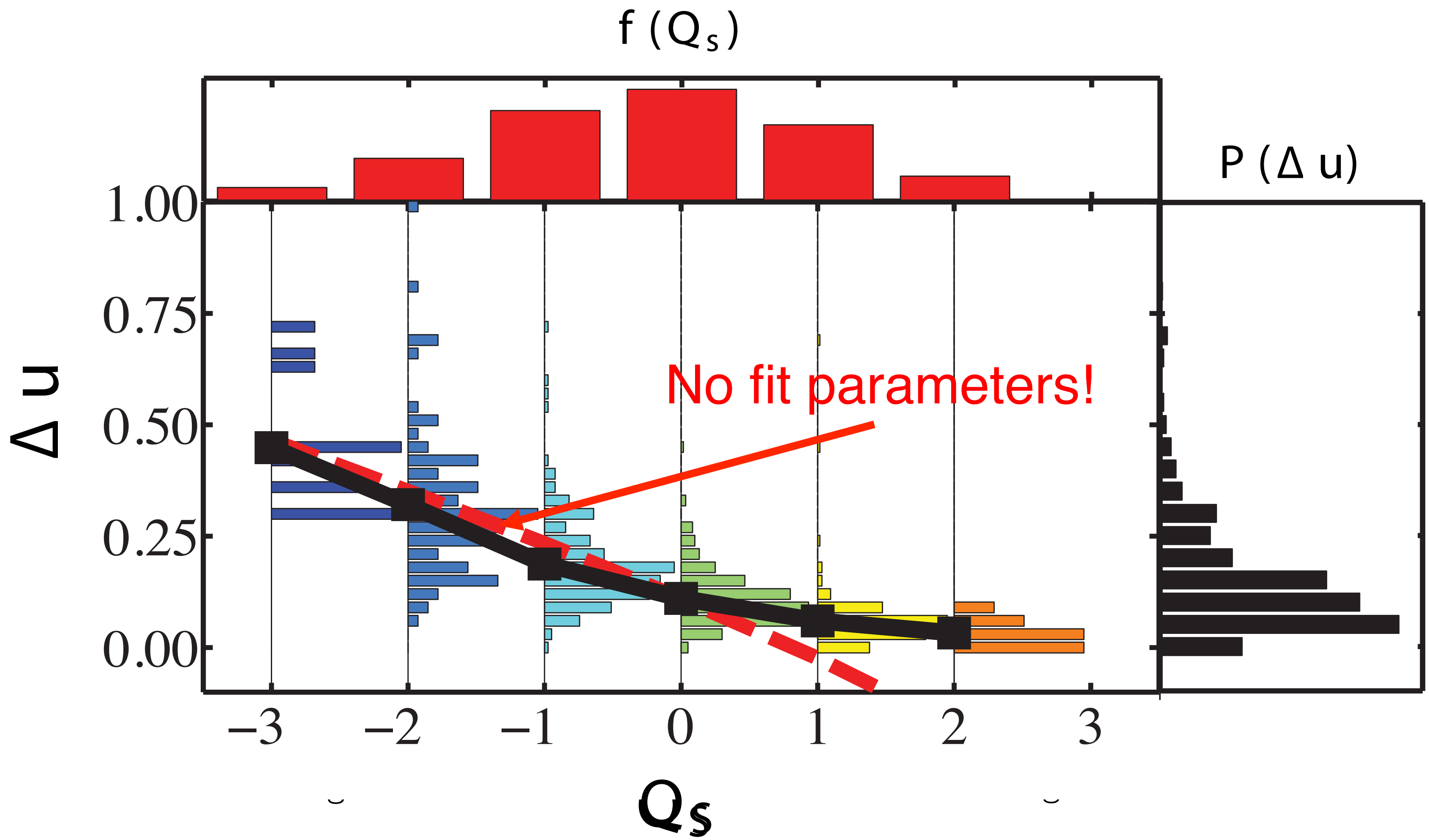




Bi, Lopez, Schwarz, MLM, Soft Matter 10 (2014)

Energy barrier depends on a cell's number of neighbors

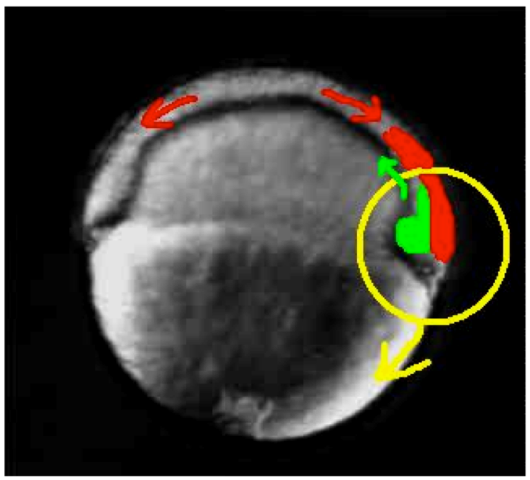


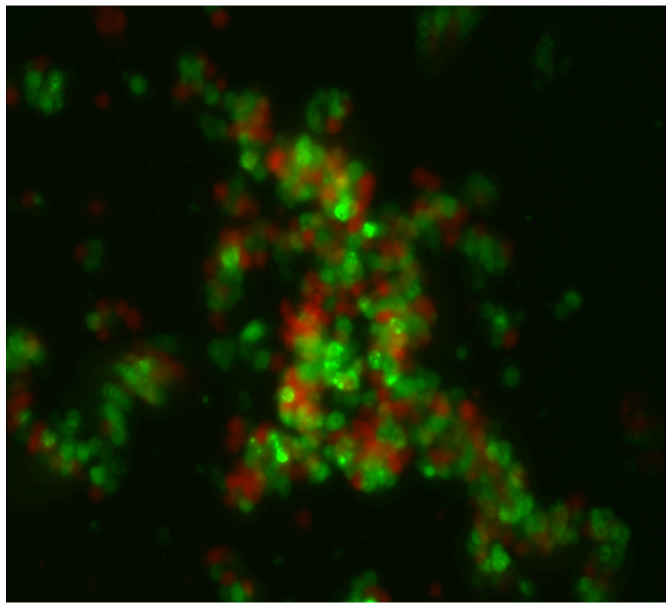


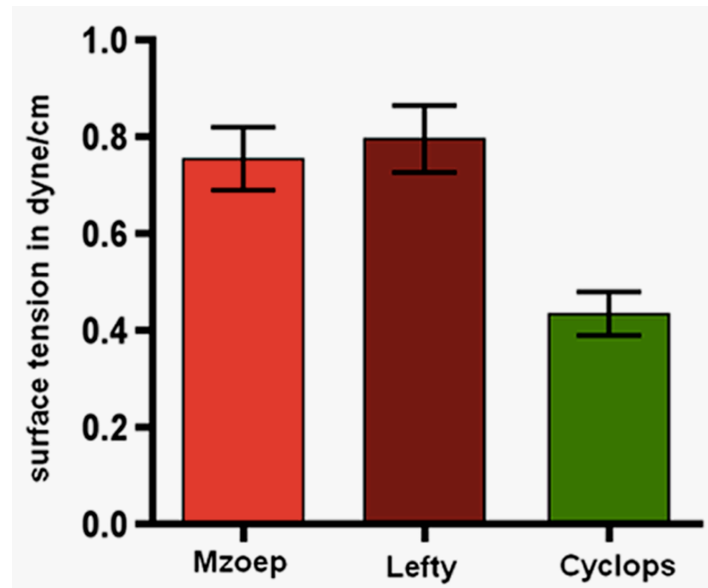
successful predictions based on mechanically stable states

Tissue surface tension governs motion in early embryos

Schoetz, 2008

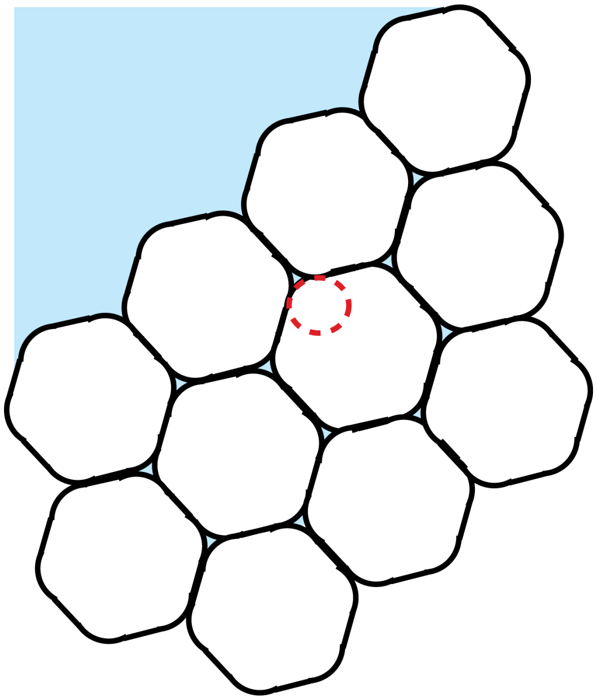


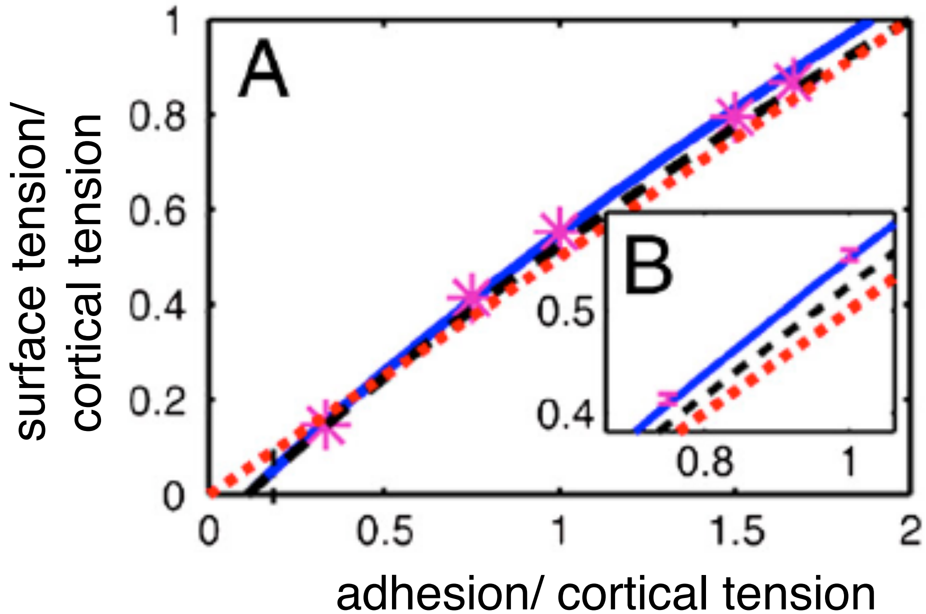


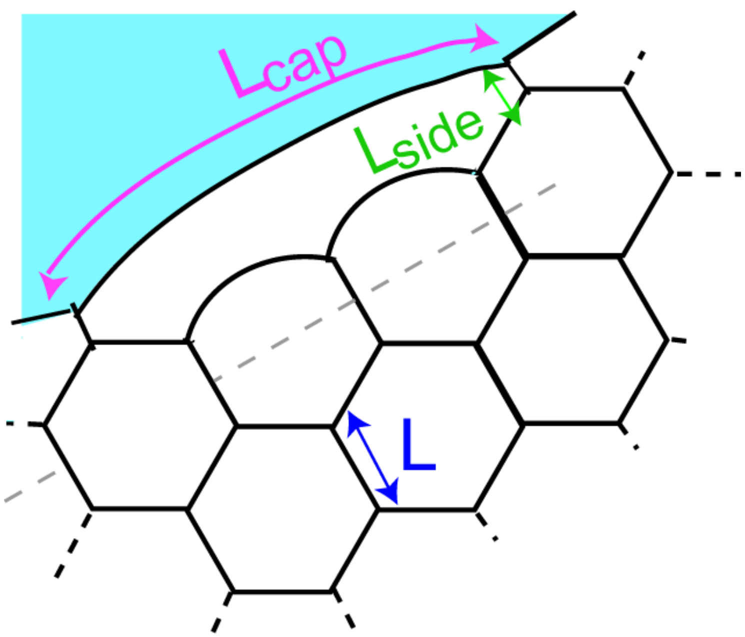


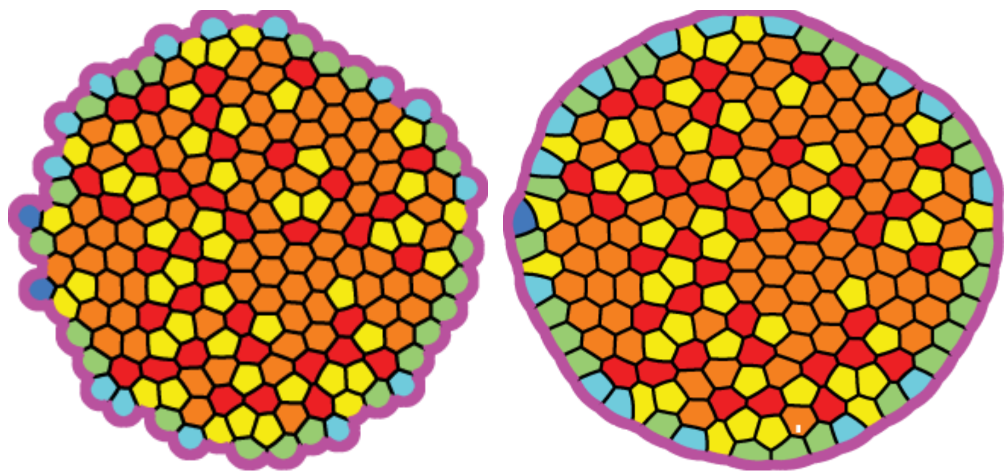
Differential Adhesion Hypothesis: Steinberg, Science 1962

Surface tension in tissues:



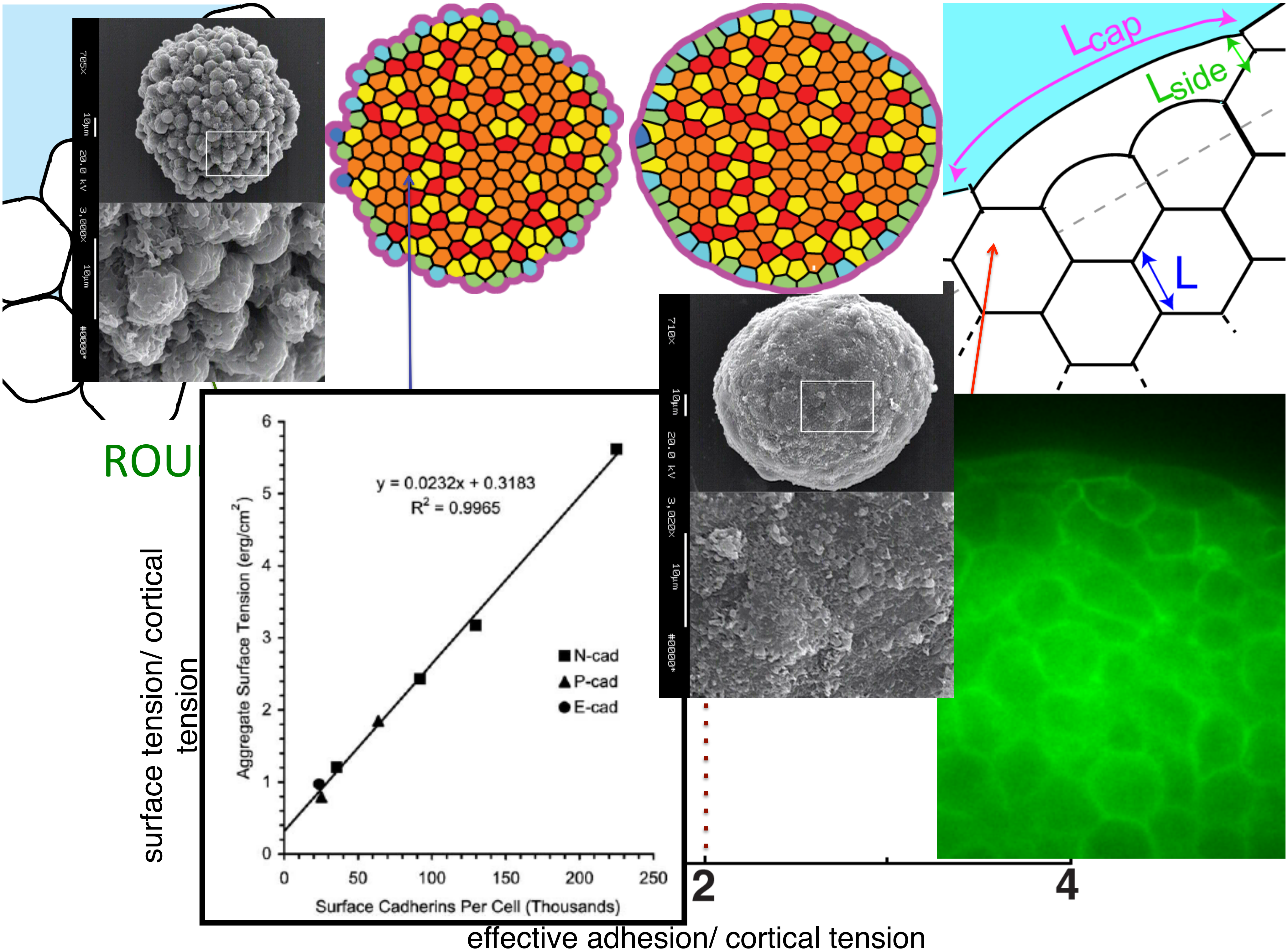






MLM, Foty, Steinberg and Schoetz. PNAS **107, 28 12517-12522** (2010)

Amack, **MLM**, Science 338 (2012)

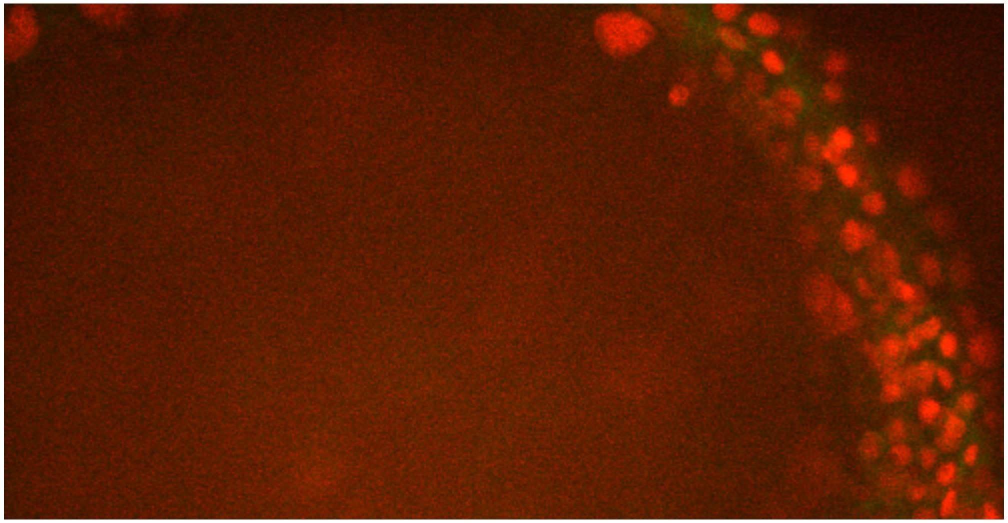


ROU
Lcap
Lside
L
y = 0.0232x + 0.3183
R^2 = 0.9965
Aggregate Surface Tension (erg/cm^2)
Surface Cadherins Per Cell (Thousands)
N-cad
P-cad
E-cad
0
1
2
3
4
5
6
0
50
100
150
200
250
surface tension/ cortical tension
effective adhesion/ cortical tension
2
4
705x
10μm
20.0 kV
3,000x
#0000*
710x
3,020x

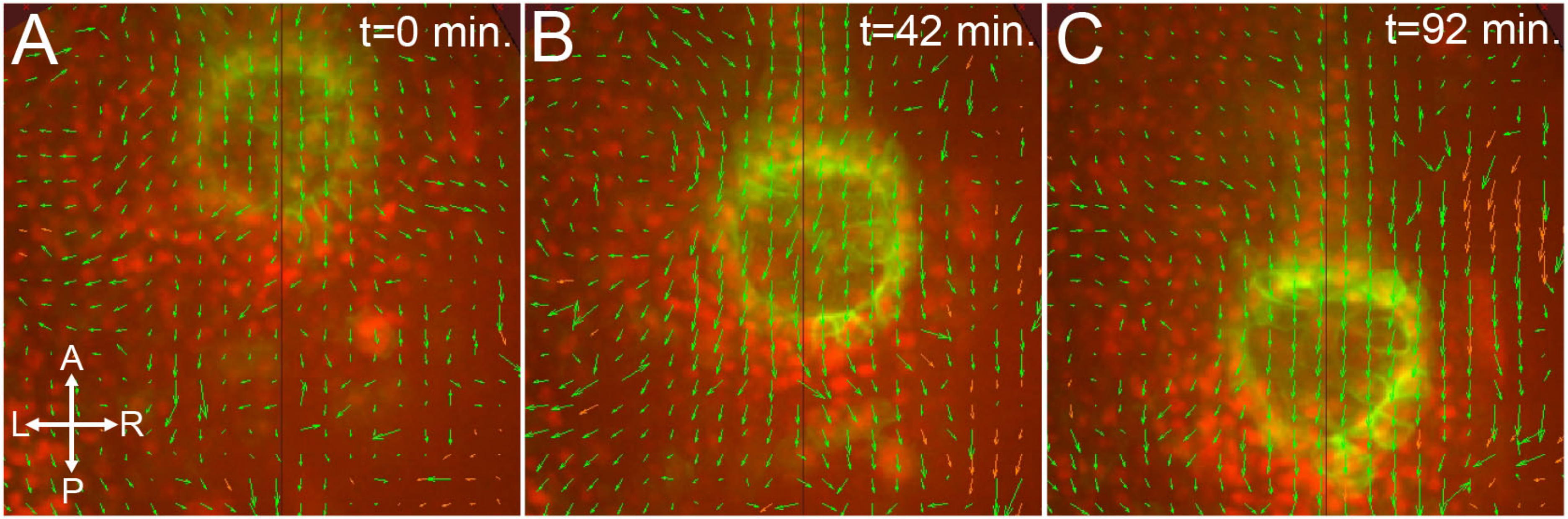
But what about the dynamics of cell rearrangements?

Can the tissues explore metastable states or do they get stuck? What sets the rate at which cells can move through tissues?

Future work

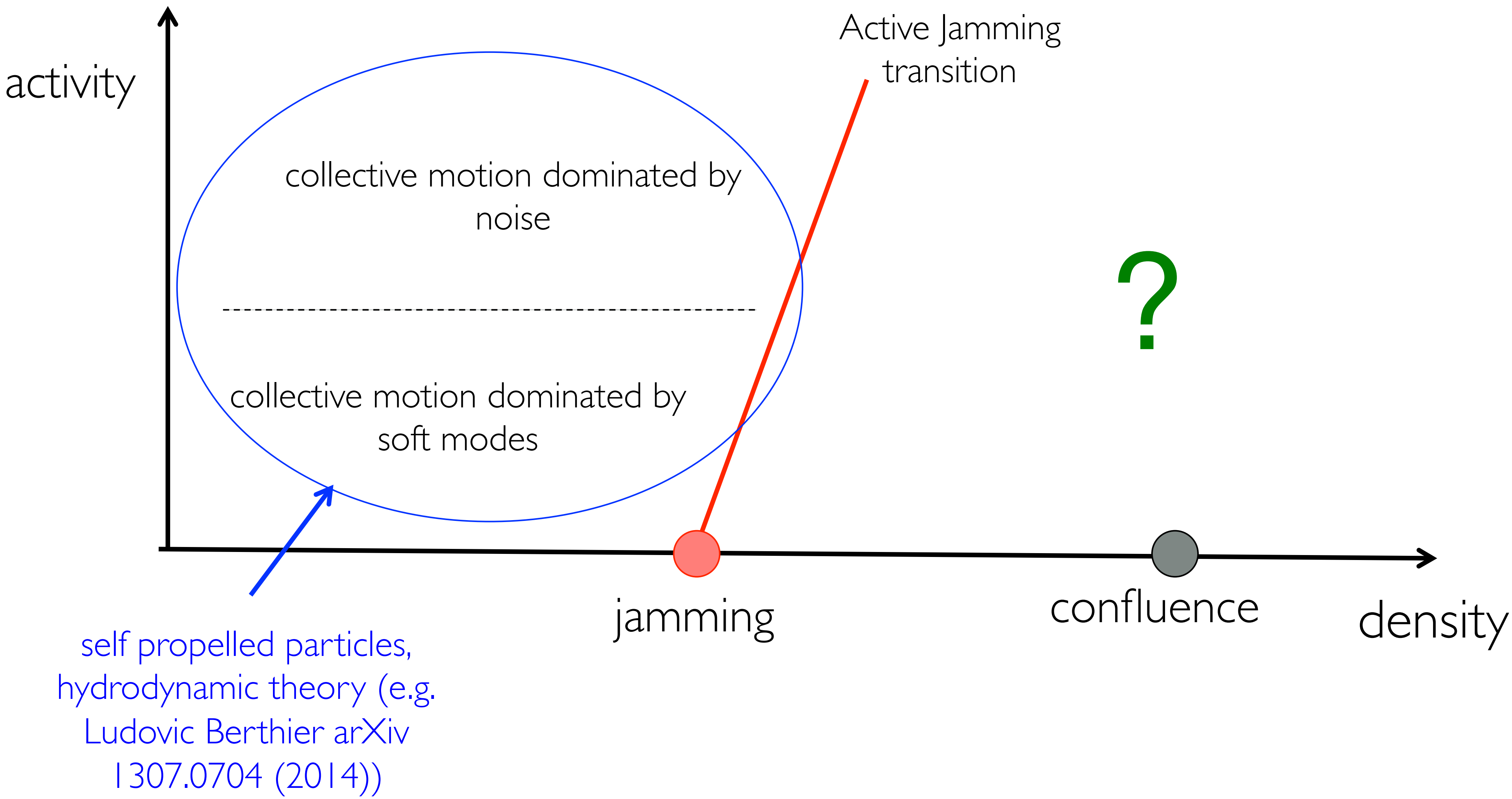


studying the motion of the KV through surrounding tissue



Future work

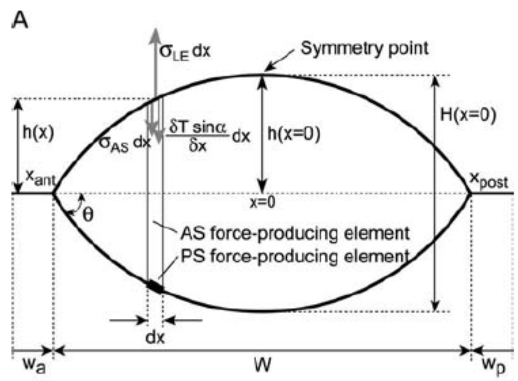
What do we really mean by glass transition in confluent tissues?

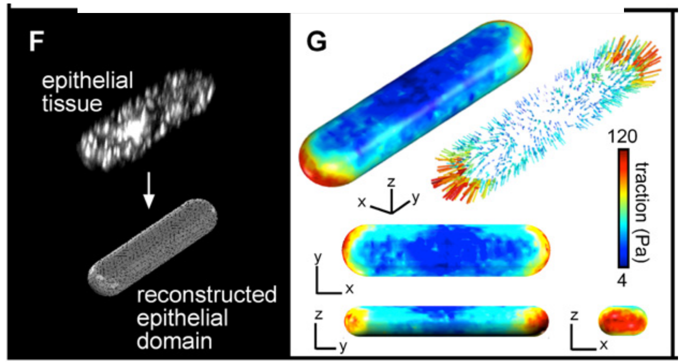


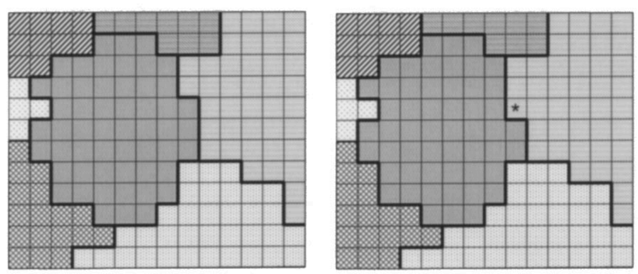
Models for the mechanics of tissues

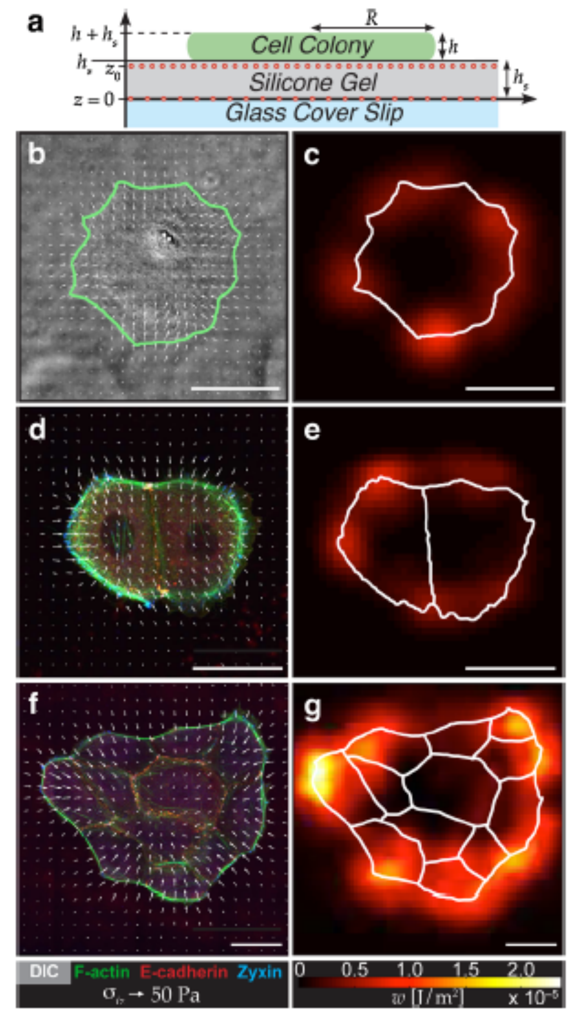
Many others:

- PDEs in confined geometries
- finite element code
- tensegrity models
- cellular potts models
- active elastic films



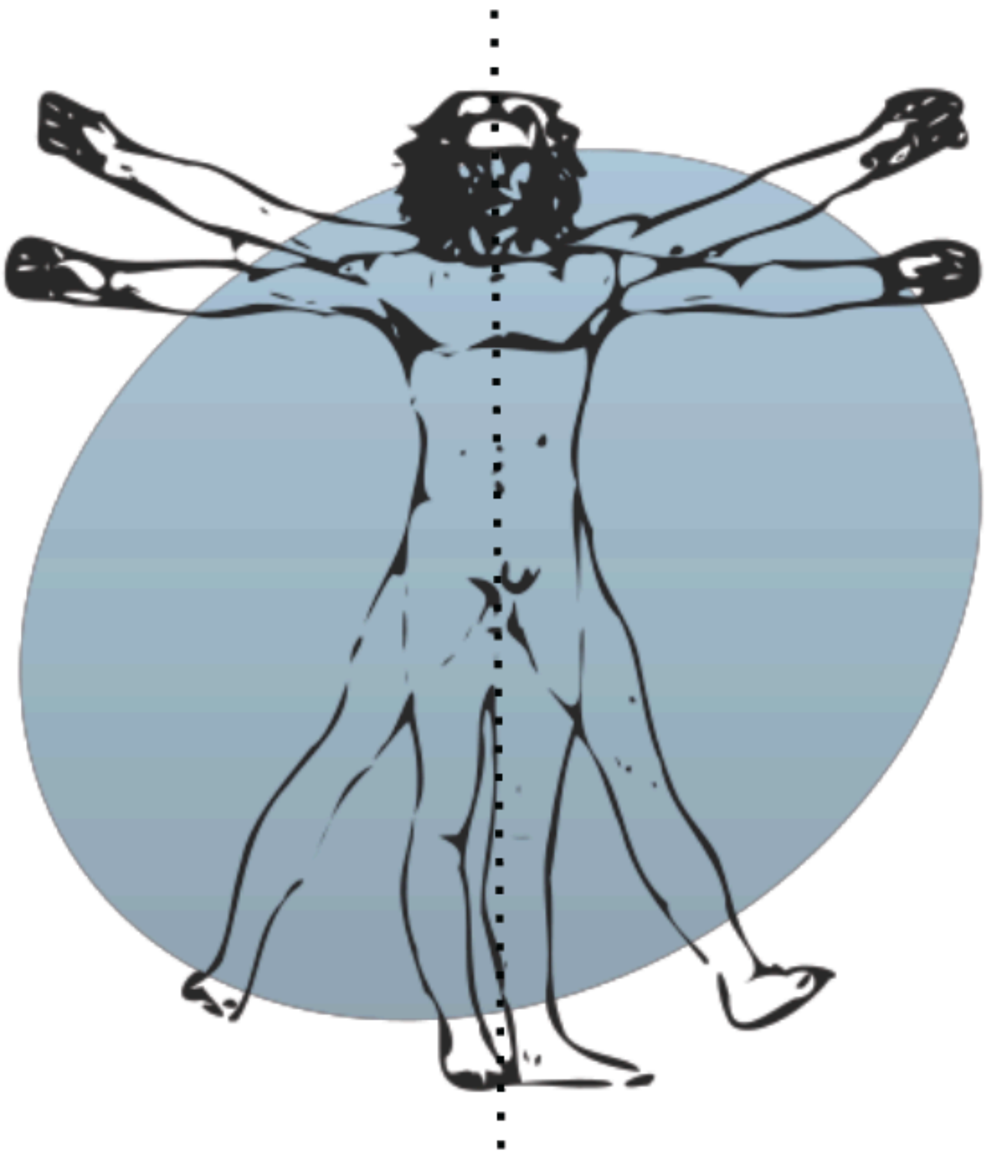


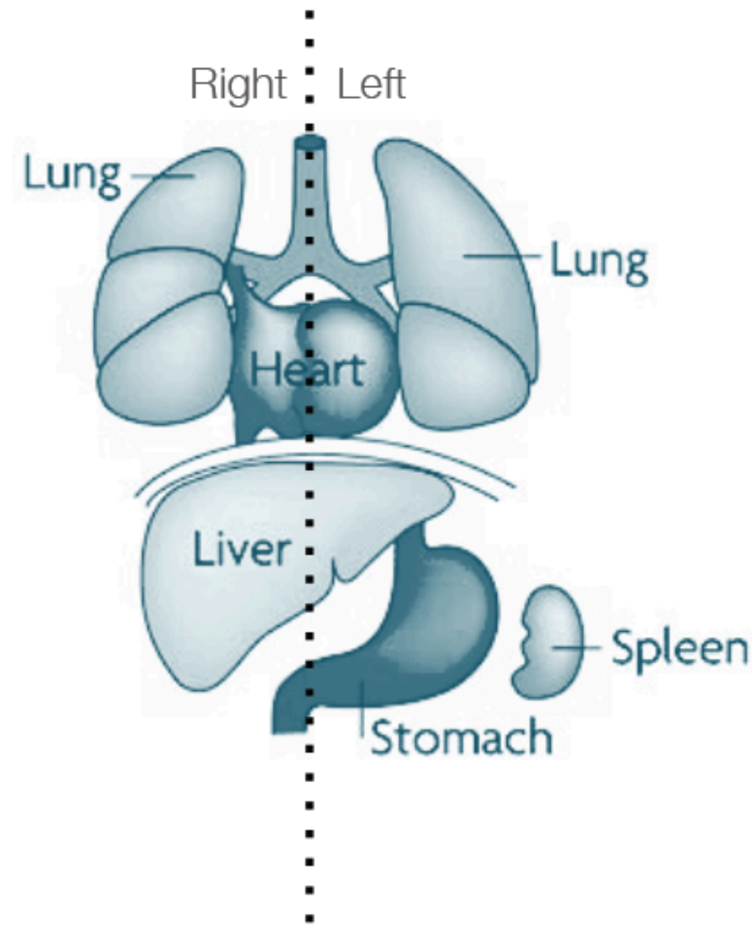




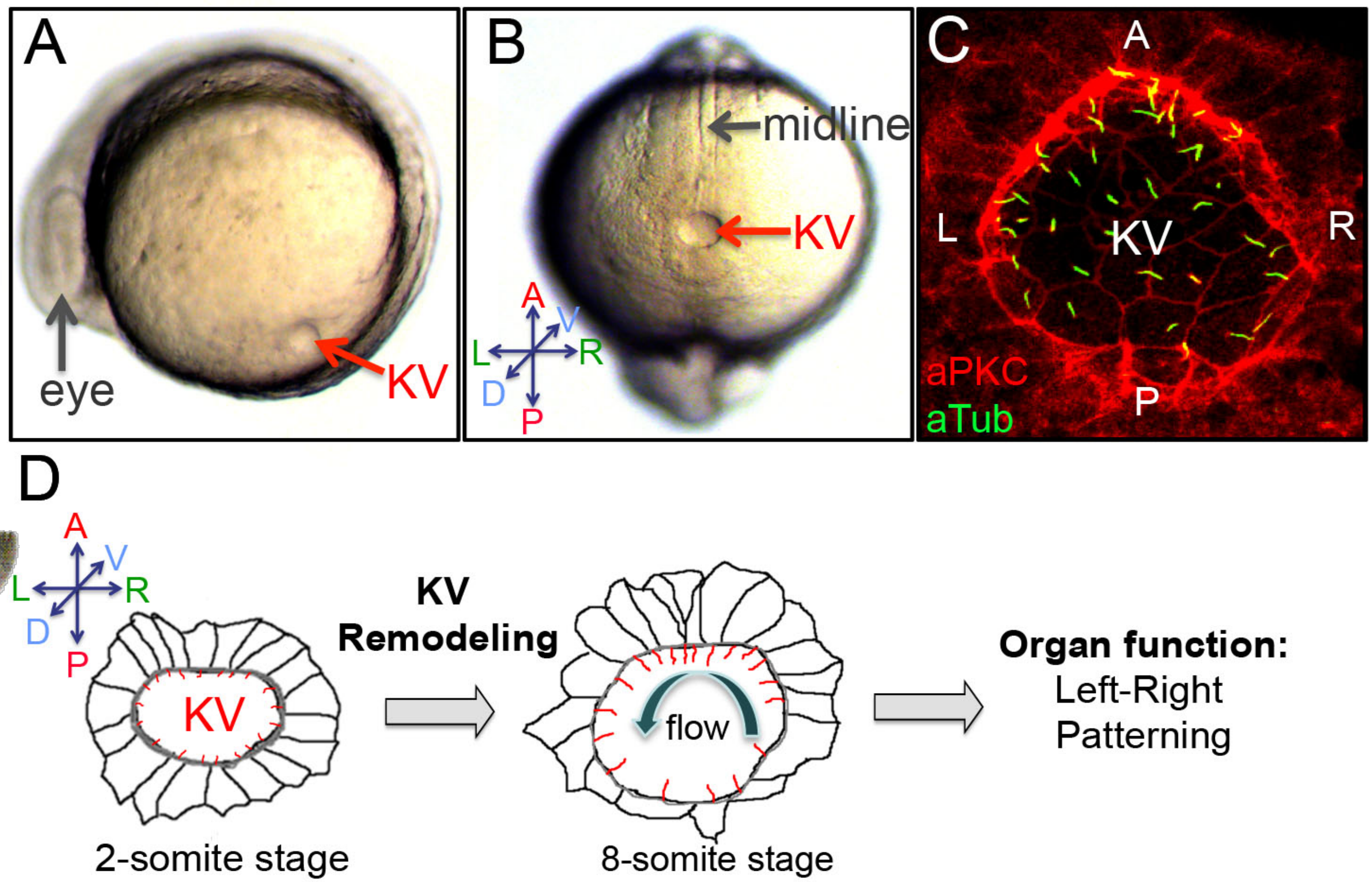
Layton et al, HFSP 3:6 (2009), Mertz et al, PRL 108 (2012), Brodland, Applied Mechanics Reviews (2004), Graner and Glazier, PRL 69 (1992), Ingber, D.E. J. Cell Sci. 116, (2003) Gjorevski N. & Nelson C.M. Biophys. J., 103 (2012)

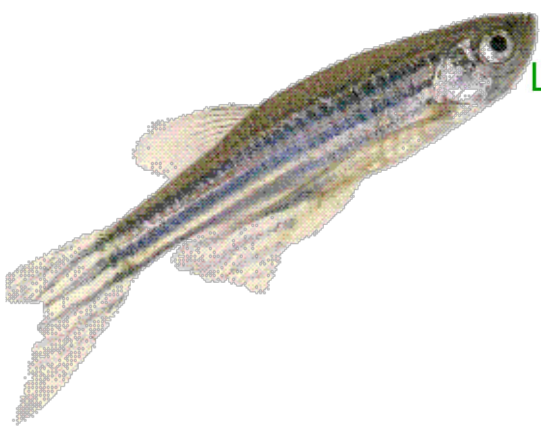
asymmetries along left-right axis in vertebrates





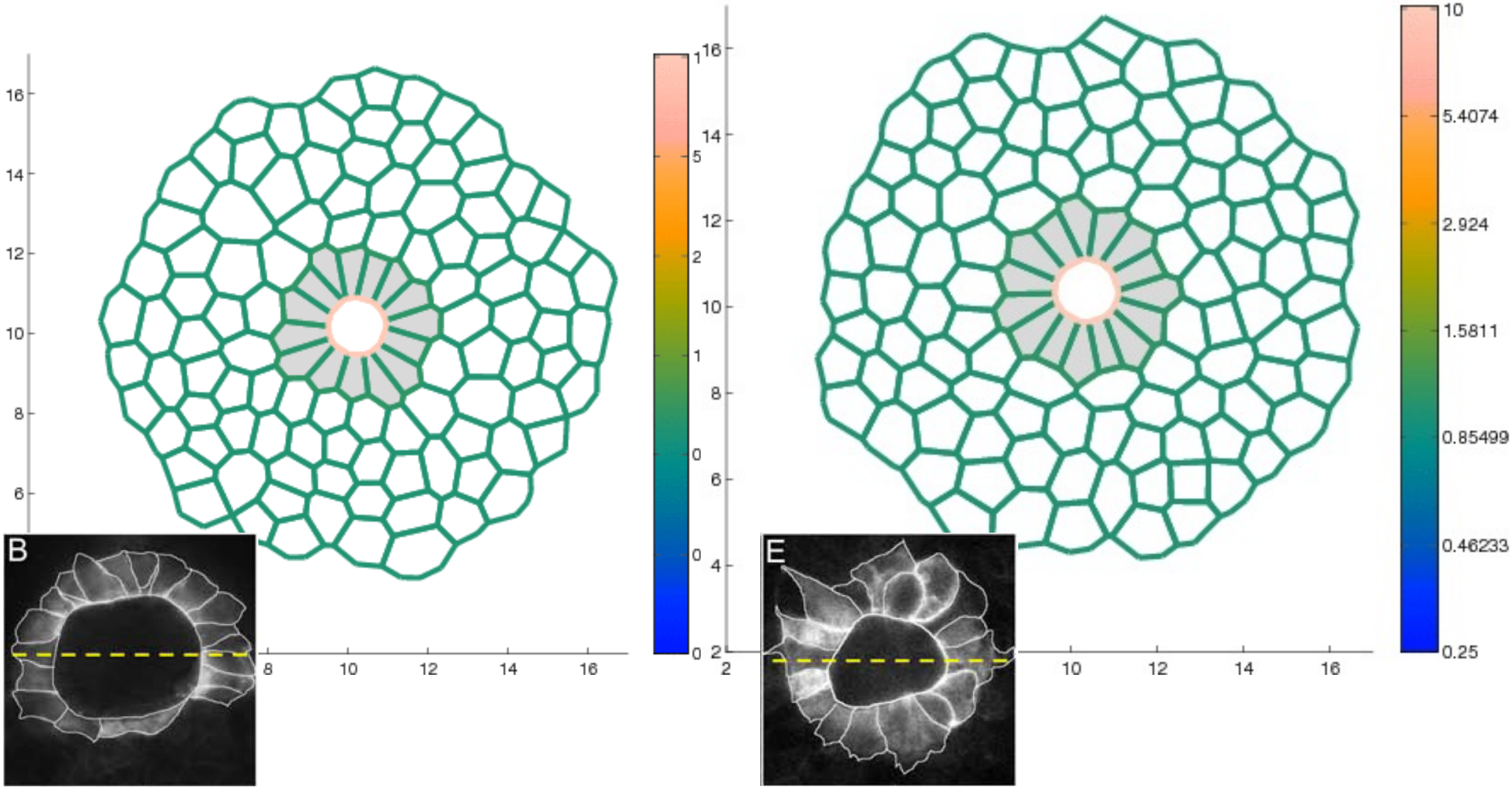
Kupffer's vesicle(KV): model for organogenesis and left-right symmetry breaking in zebrafish



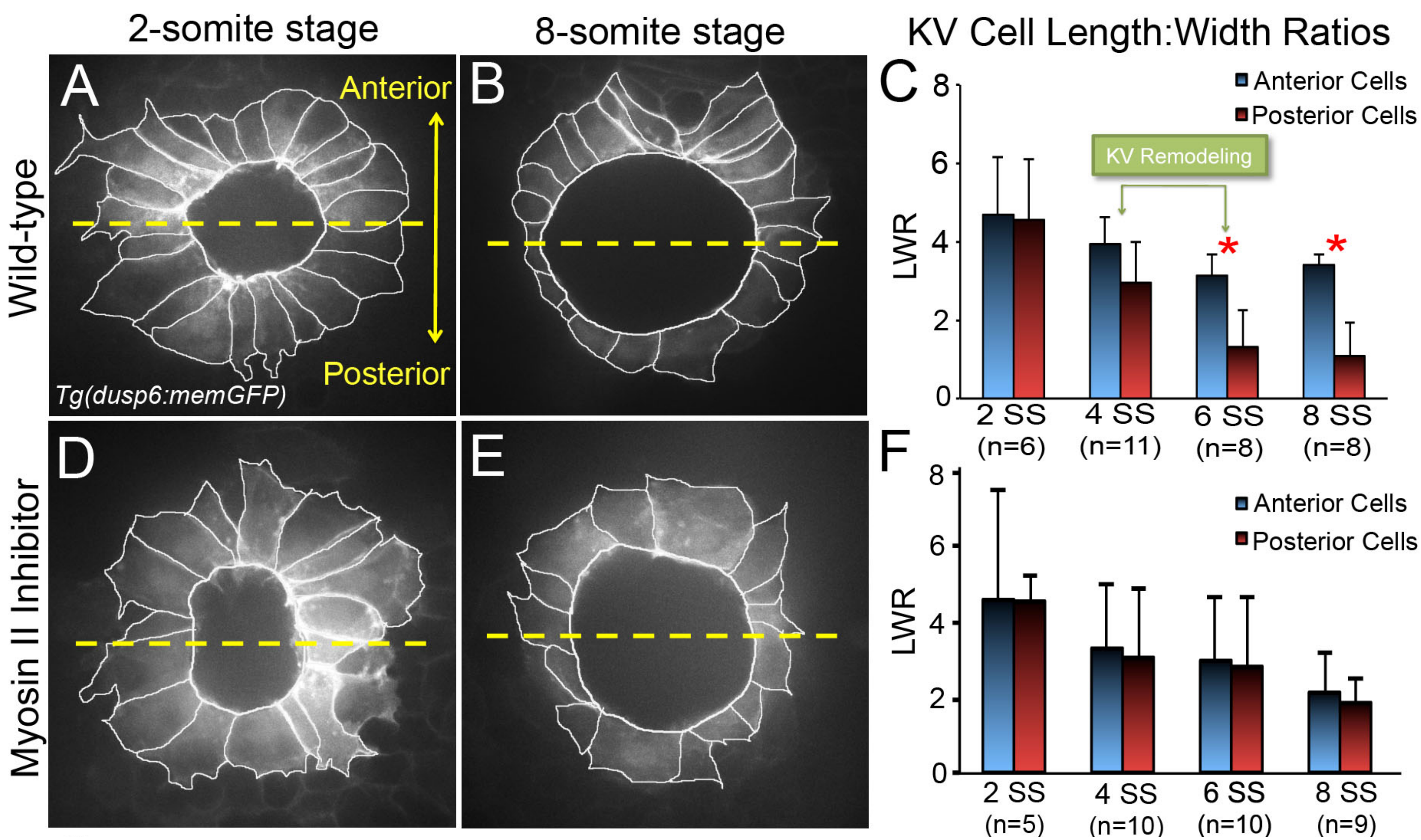


“Shape equilibrium” modeling of KV

Guangliang Wang, **MLM**, Jeffrey D Amack. Dev. Bio **370**, 1, 52–62 (2012).

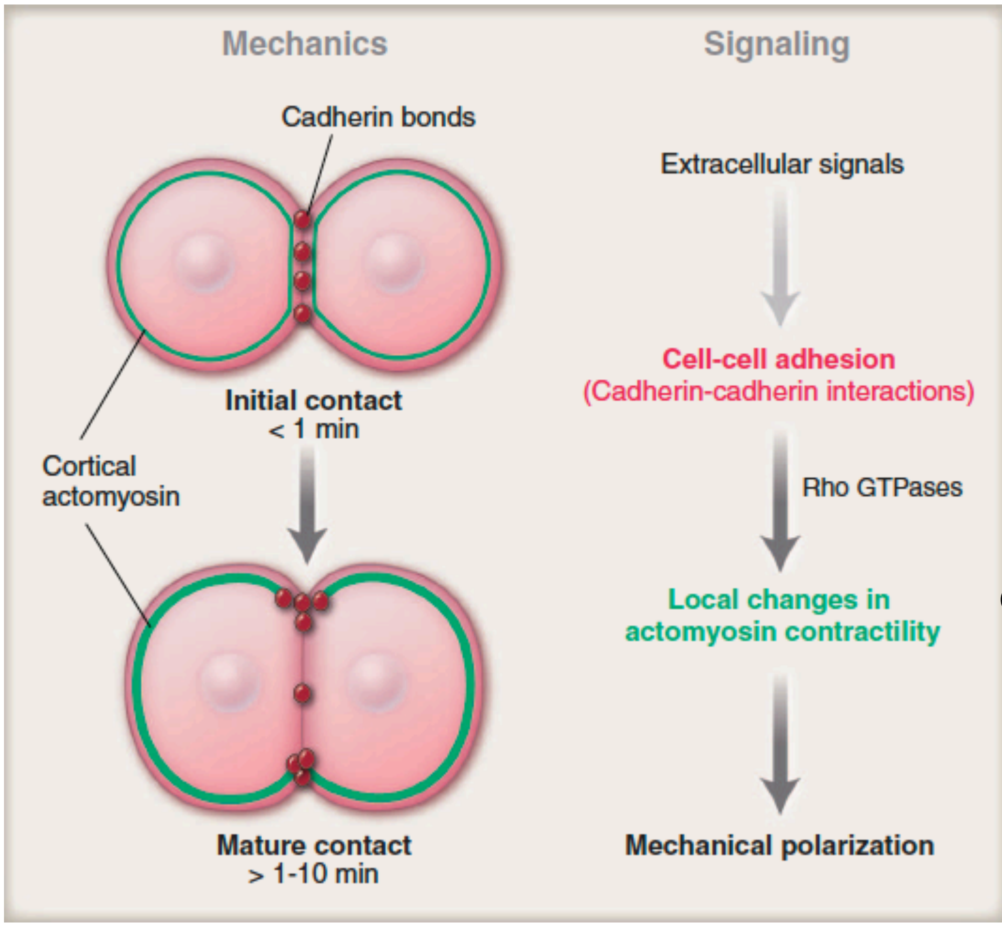


Experiment: reduce all interfacial tensions



Guangliang Wang, **MLM**, Jeffrey D Amack. Dev. Bio 370, 1, 52–62 (2012).

Resolves a paradox: adhesion 4 orders of magnitude too small to explain surface tension



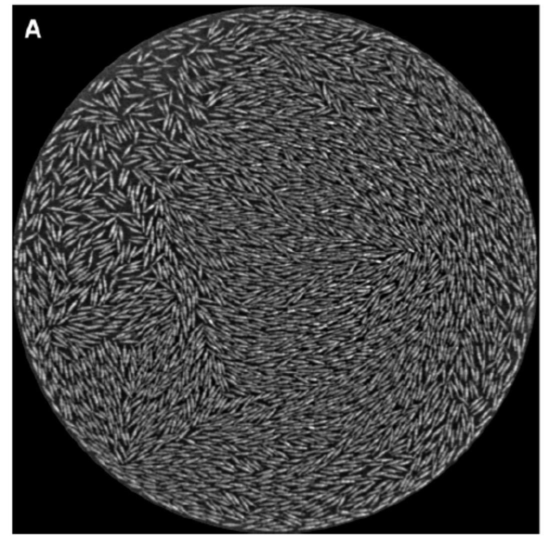
Amack, **MLM**, Science 338 (2012).

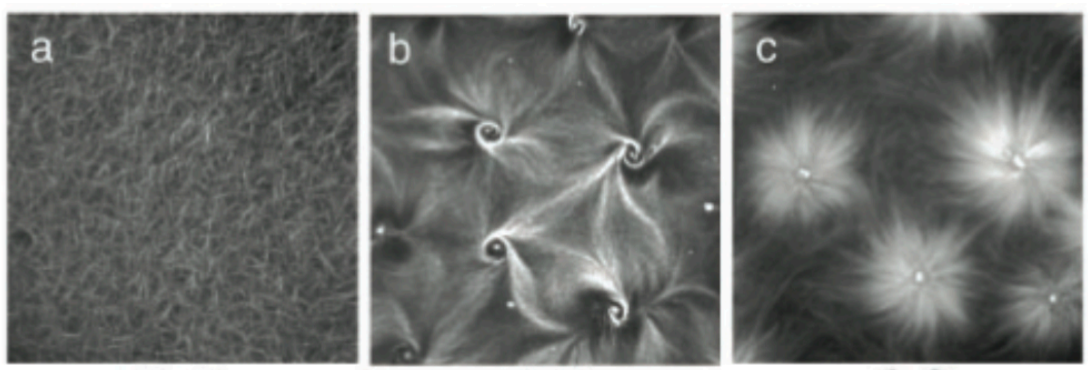
$$\gamma = \Gamma - 2\Delta\beta$$

- γ: effective adhesion
- Γ: free energy cadherin bonds per unit area
- $2\Delta\beta$: difference in cortical tension along contacting and non-contacting interfaces

Models for the mechanics of tissues

- Continuum or hydrodynamic active matter descriptions
- New physics:
  - flocking
  - giant number fluctuations
- Interesting phase transitions/ pattern formation

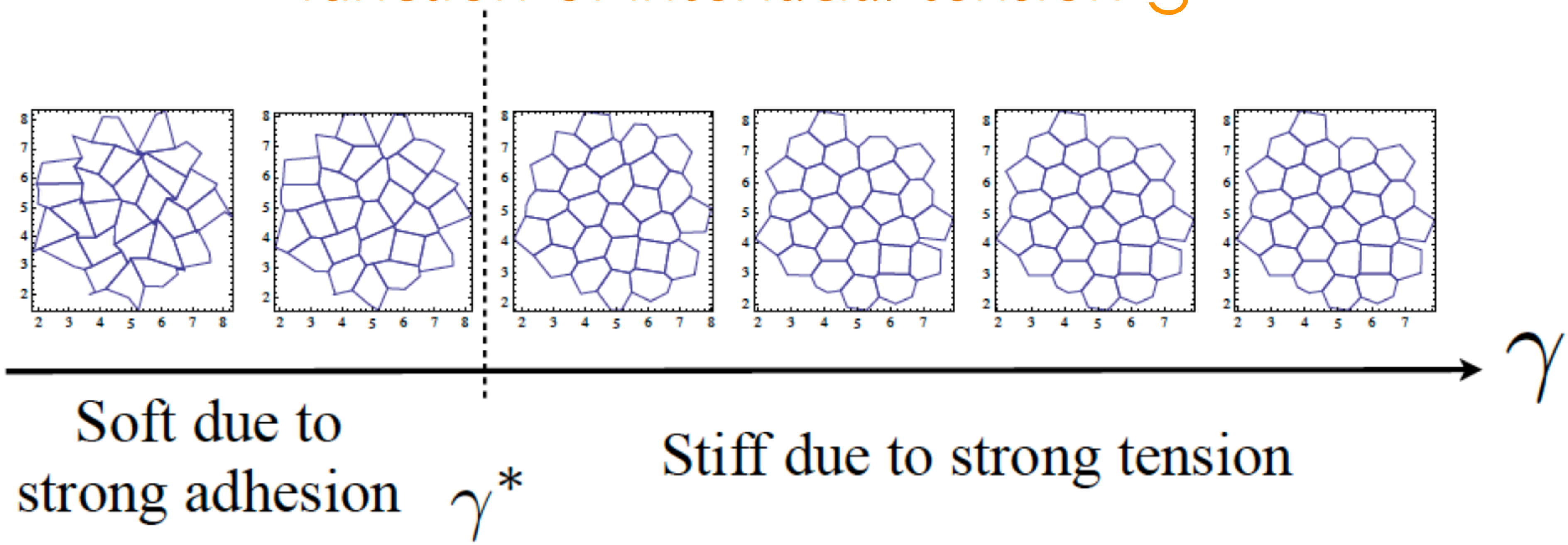




Toner and Tu PRL 75 (1995) , Surrey et al Science (2001), Narayan, et al. Science 317, 105 (2007), Marchetti et al. RMP 85 3 (2013)

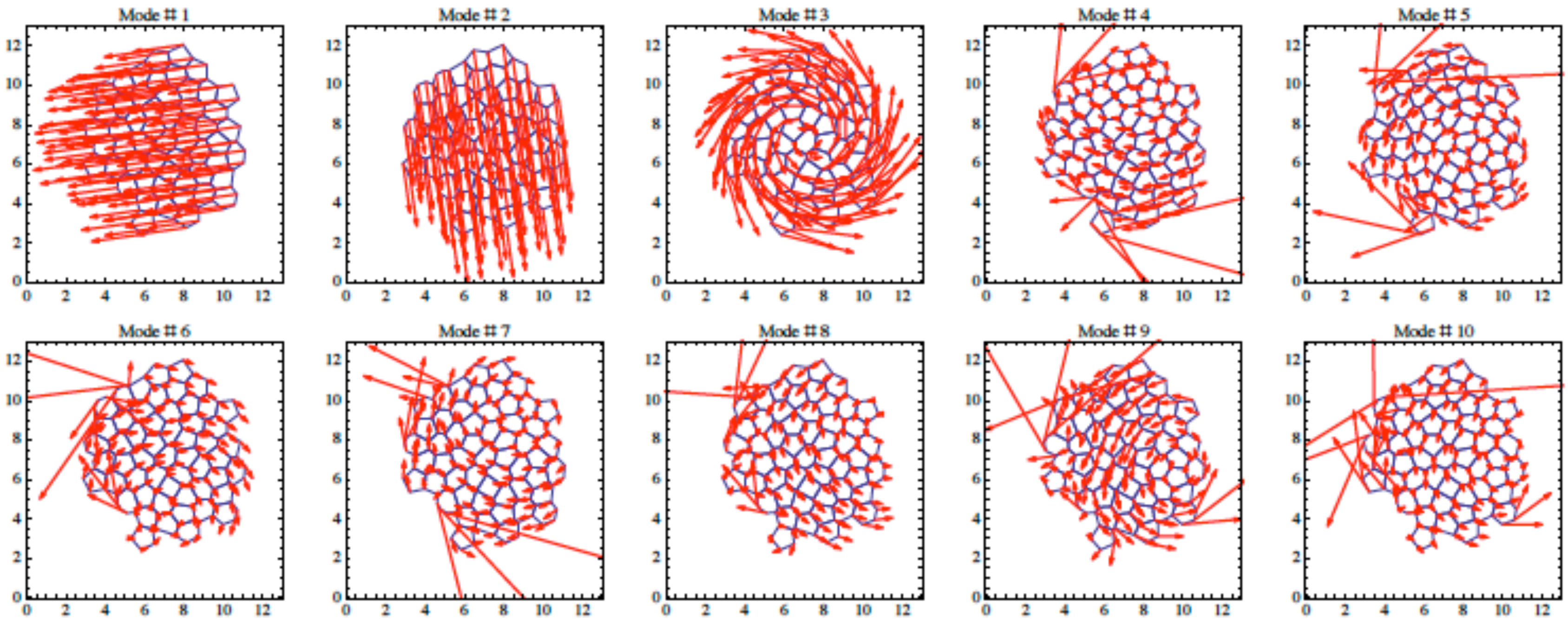
Work in progress

This CONFLUENT system has a thermodynamic order-disorder transition (and accompanying rigidity transition) as a function of interfacial tension g



New physics?

Work in progress



Soft modes in these models tend to be extended (not likely to have low energy barriers except at jamming transition)

Analytic results: energy barrier statistics

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

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

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

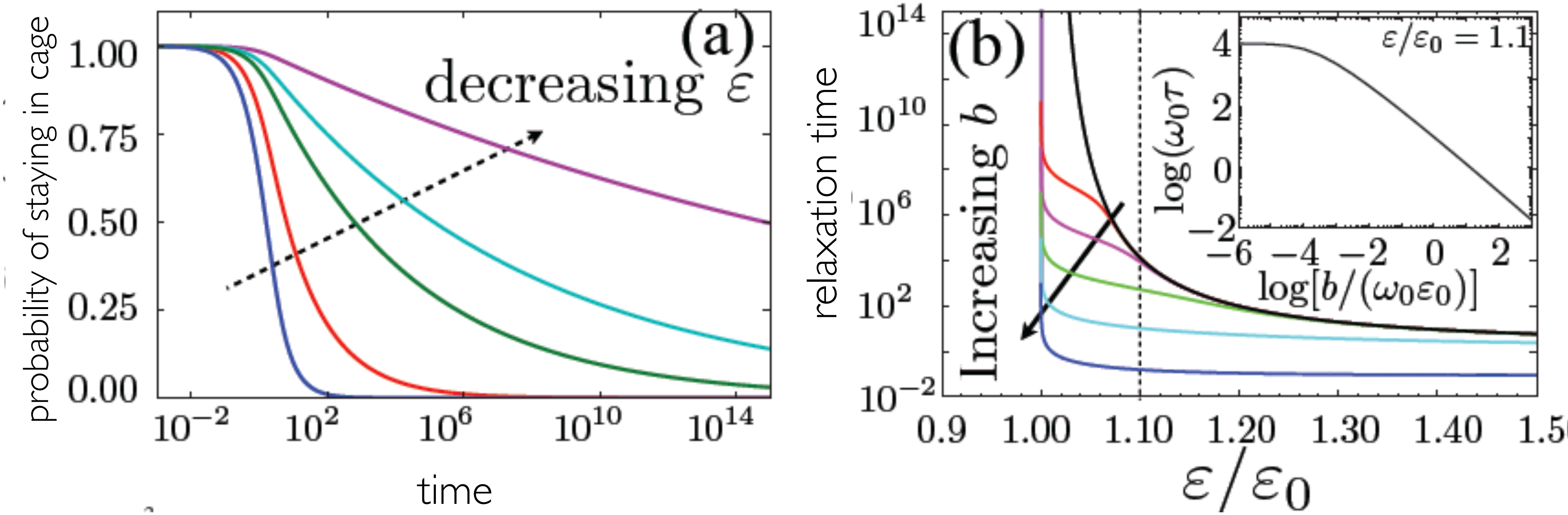
Metastable mechanical states have gaussian distribution of edge lengths (verified in simulations)

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

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

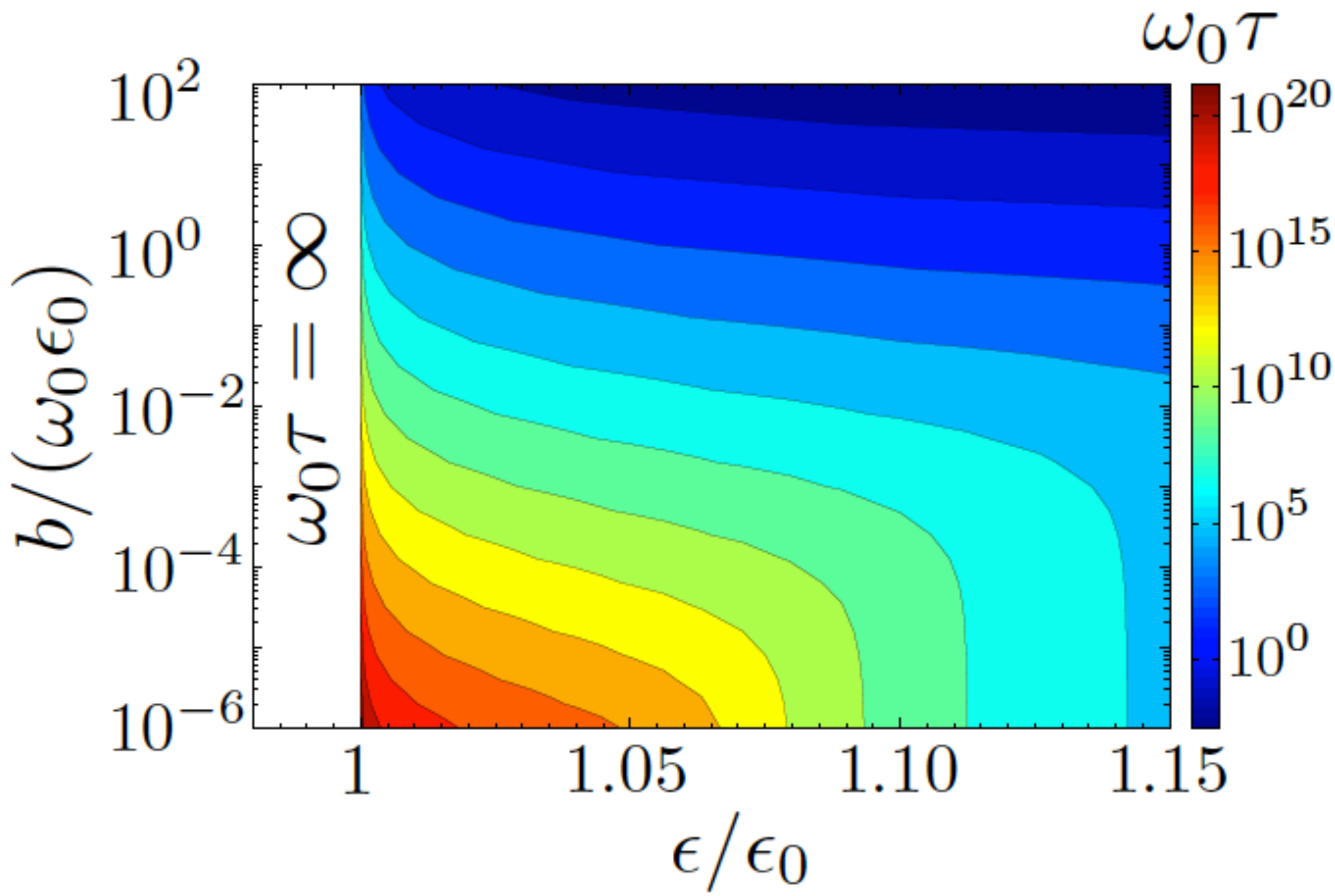
$$p(\Delta u) \propto \exp\left(\frac{-\Delta u}{u^*}\right)$$

From energy barriers to cell migration:

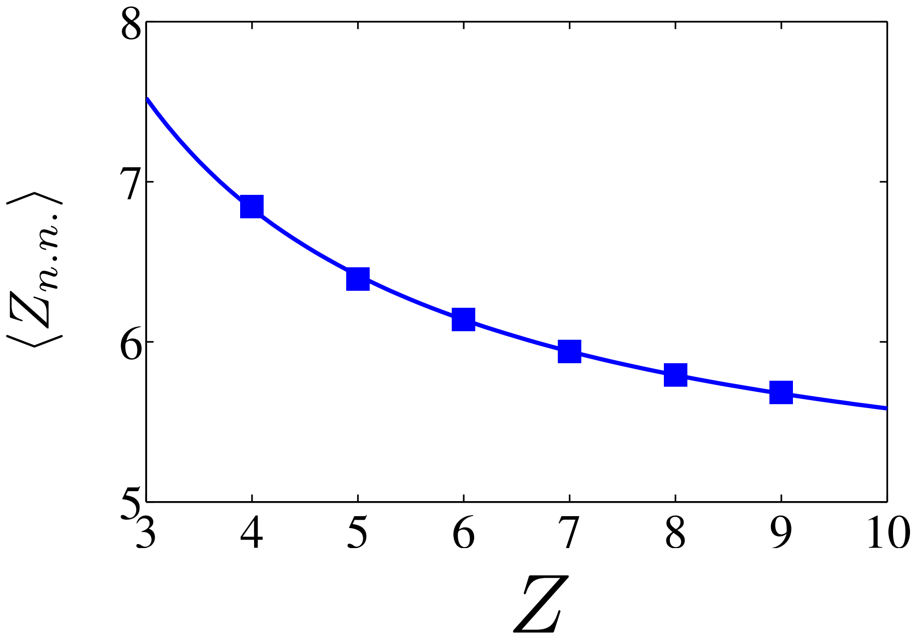


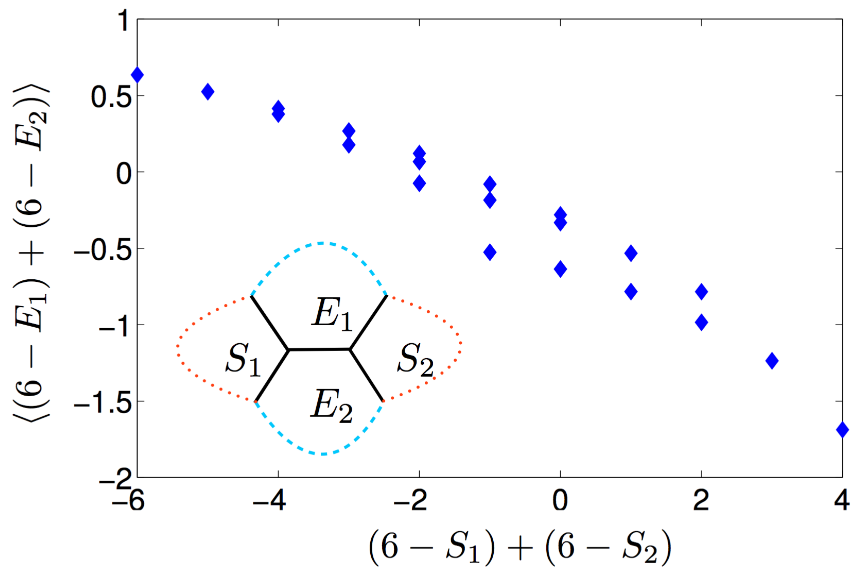
Bi et al, to appear in *Soft Matter*, Arxiv:1308.3891 (2014)

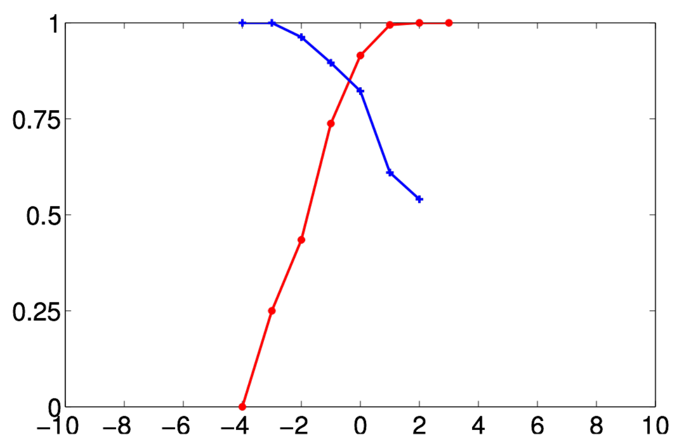
relaxation time phase diagram

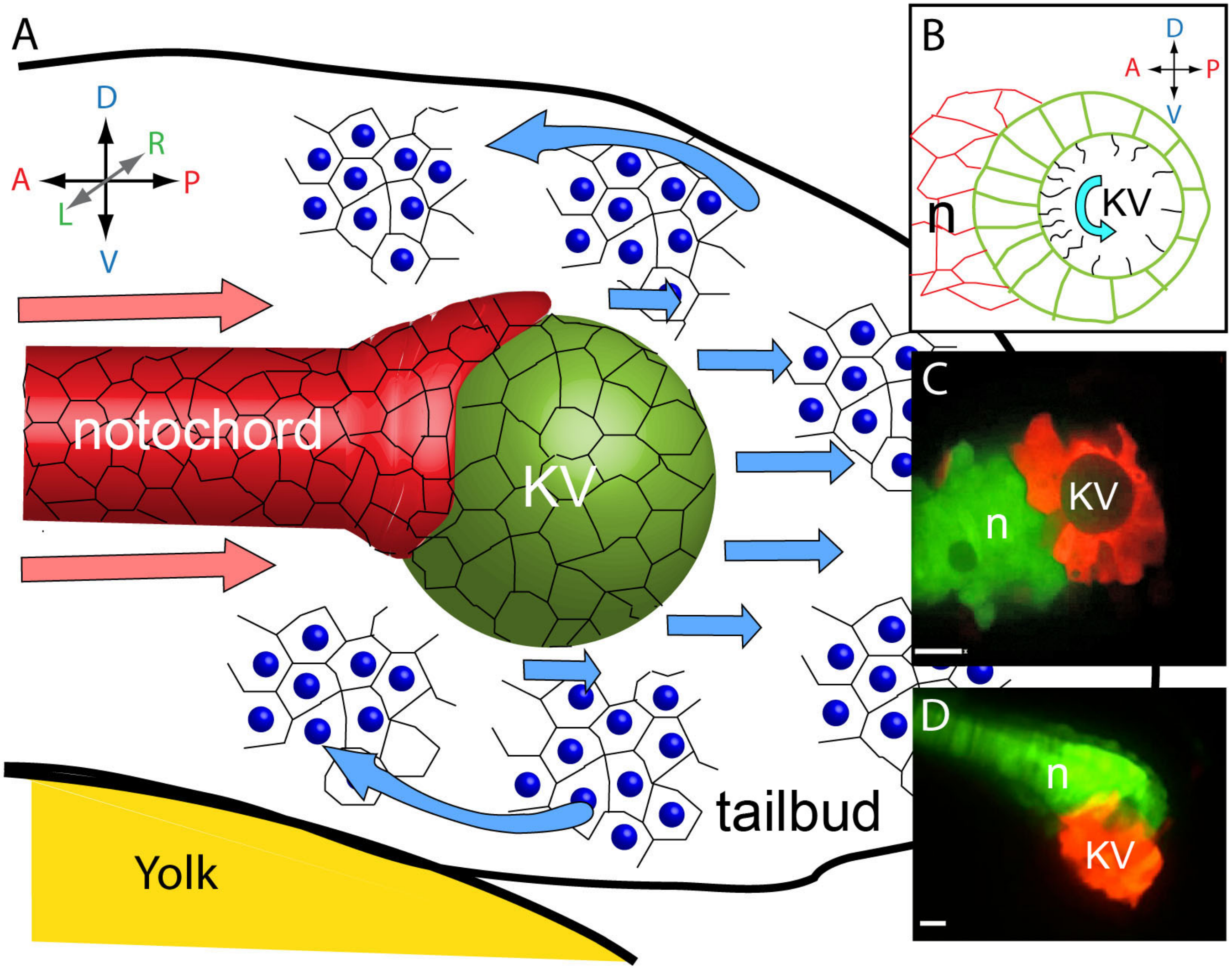


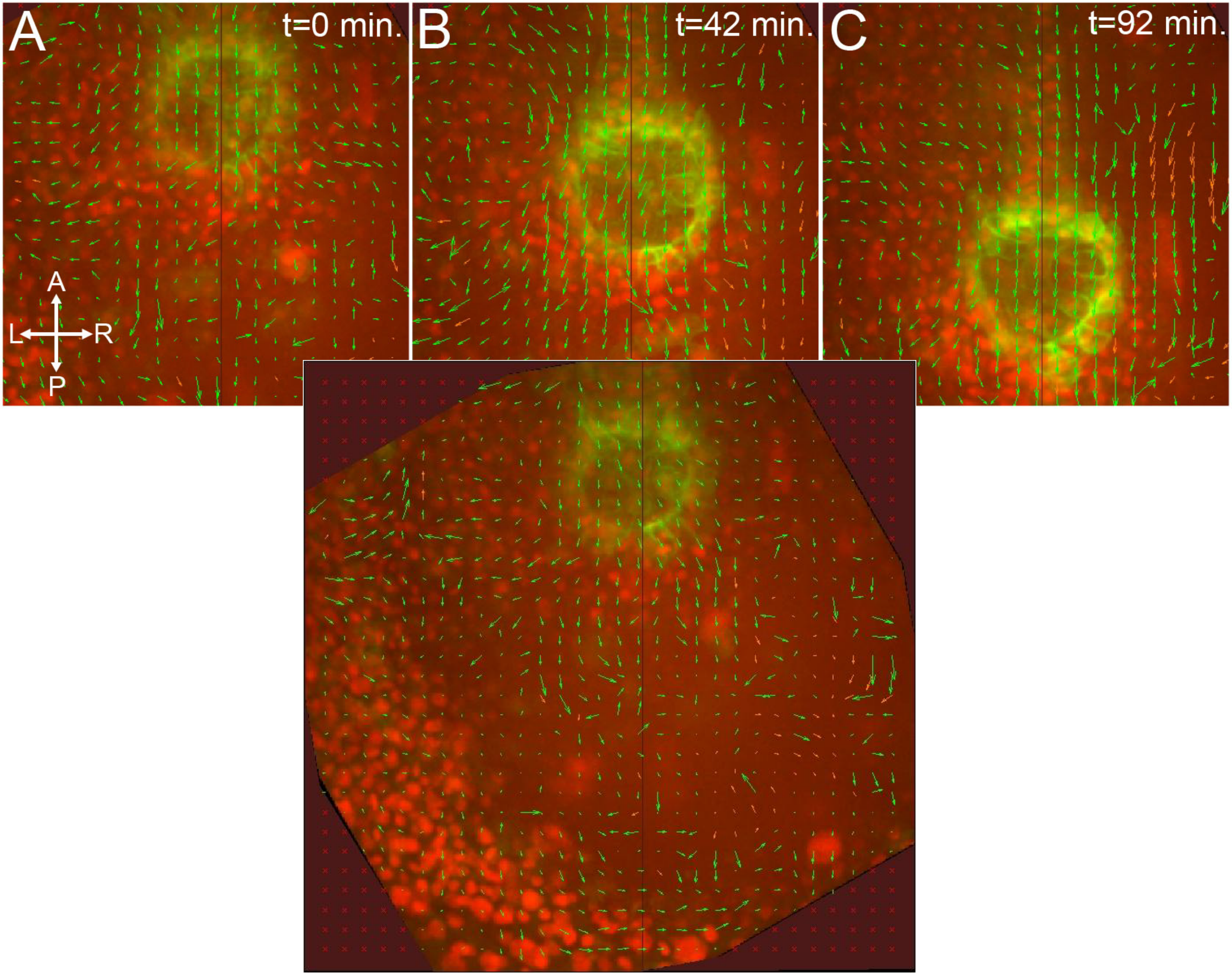
Aboav-Weaire law



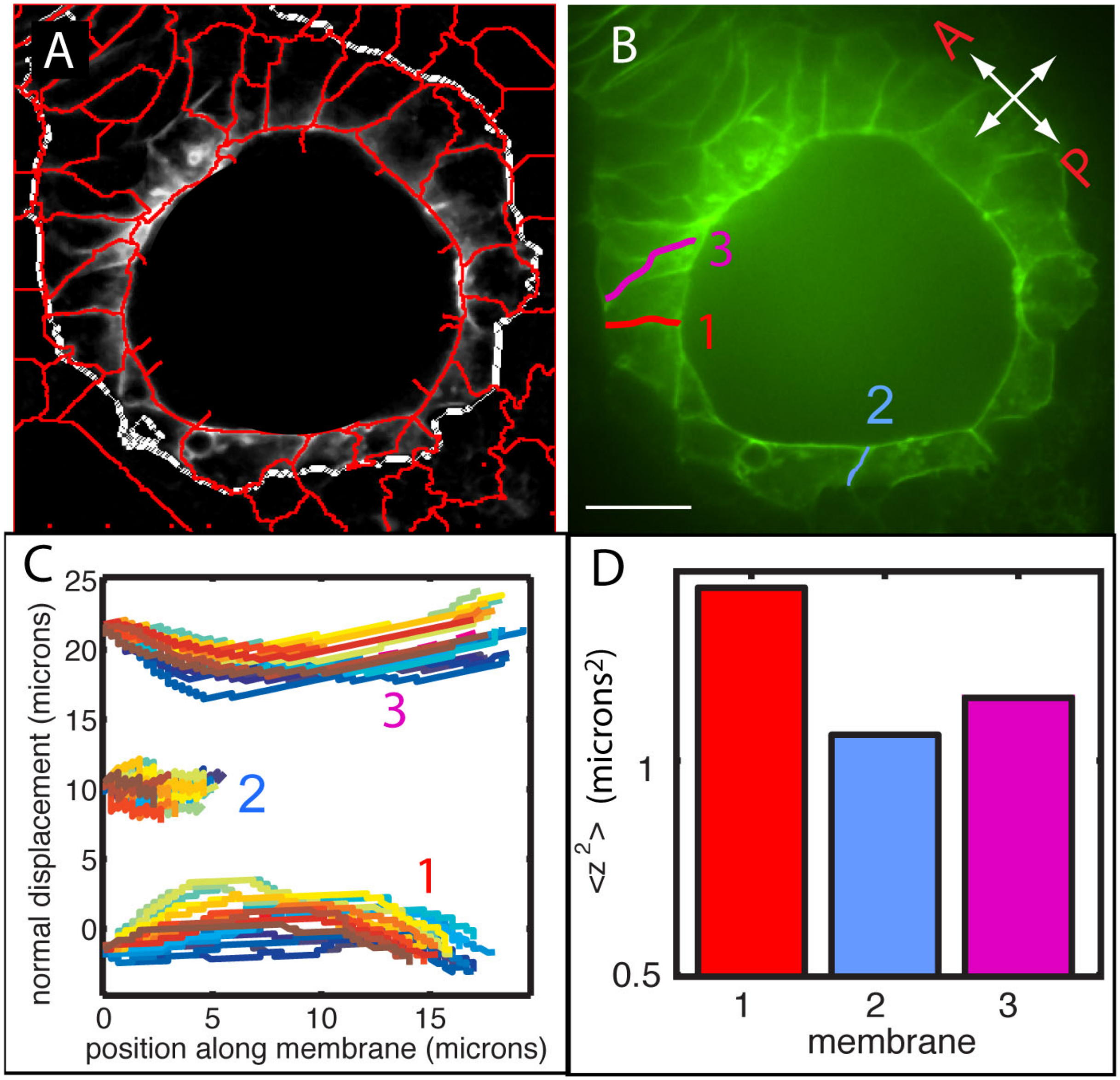





A
D
R
A
P
L
V
notochord
KV
tailbud
Yolk
B
D
A
P
V
n
KV
C
KV
n
D
n
KV

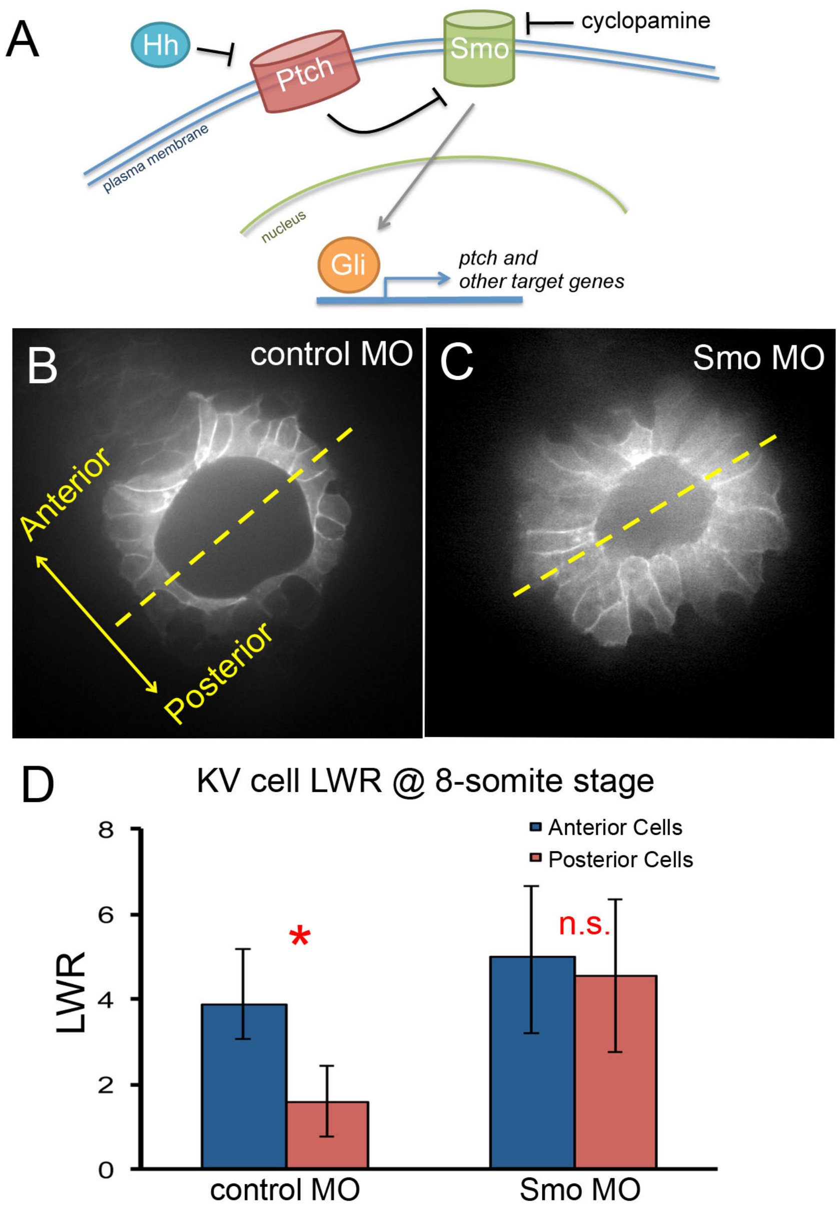


A
t=0 min.
B
t=42 min.
C
t=92 min.
A
L
R
P



Laser ablation experiments difficult this deep inside embryo

Perhaps we can estimate tensions from membrane fluctuations.



What could be driving the asymmetric tension?

Possible mechanism: signaling molecules generated from the notochord cells (on Anterior side of KV)

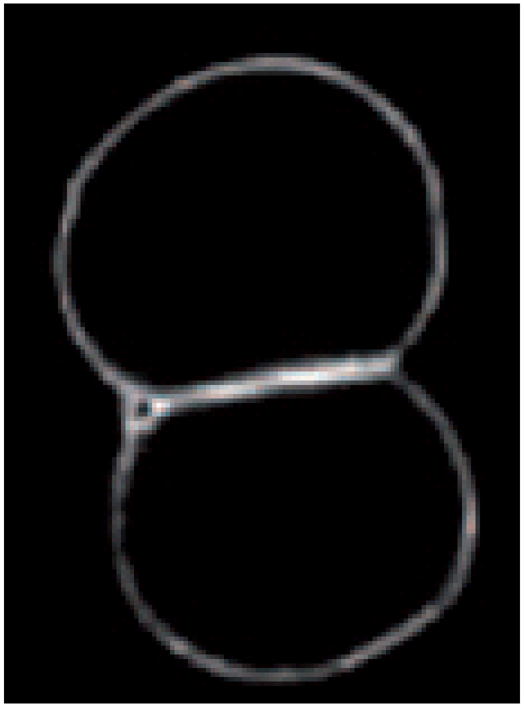
"Shape equilibrium" or "vertex" cell model: what mechanical forces act to generate steady state cell shapes?

1. Surface adhesion: cadherins

2. Active cortical tension: myosin motors
   (Joanny, Prost et al)

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

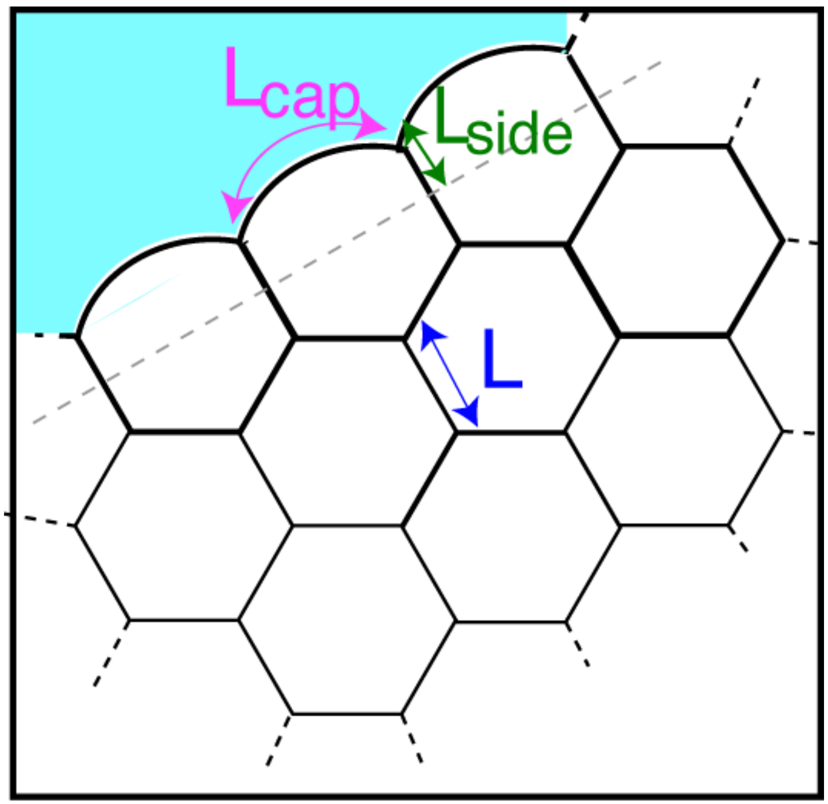
4. Cortical elasticity: cytoskeletal networks



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

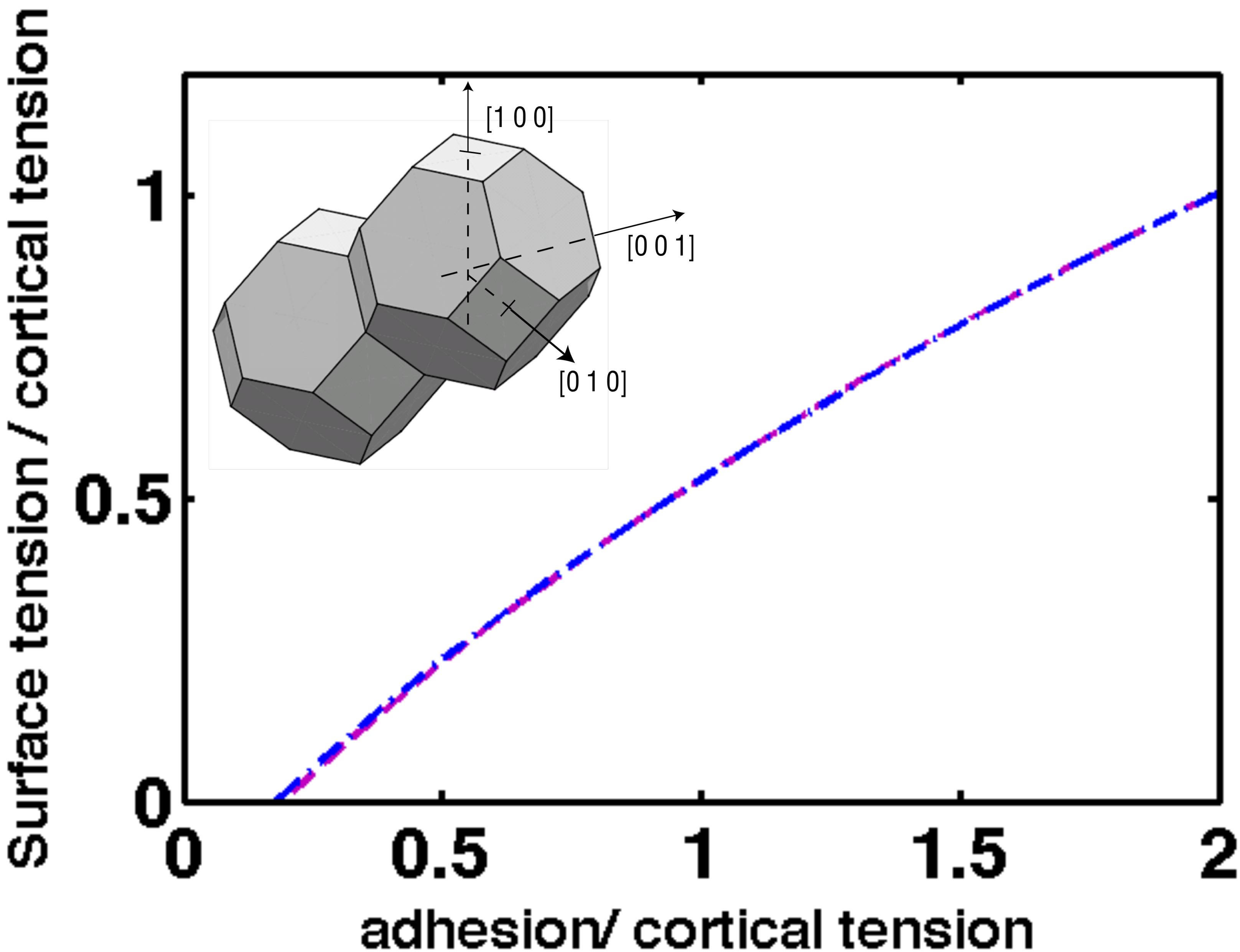
Goal: steady state cell shapes

Find the local minimum energy shapes for a collection of cells subject to constraints

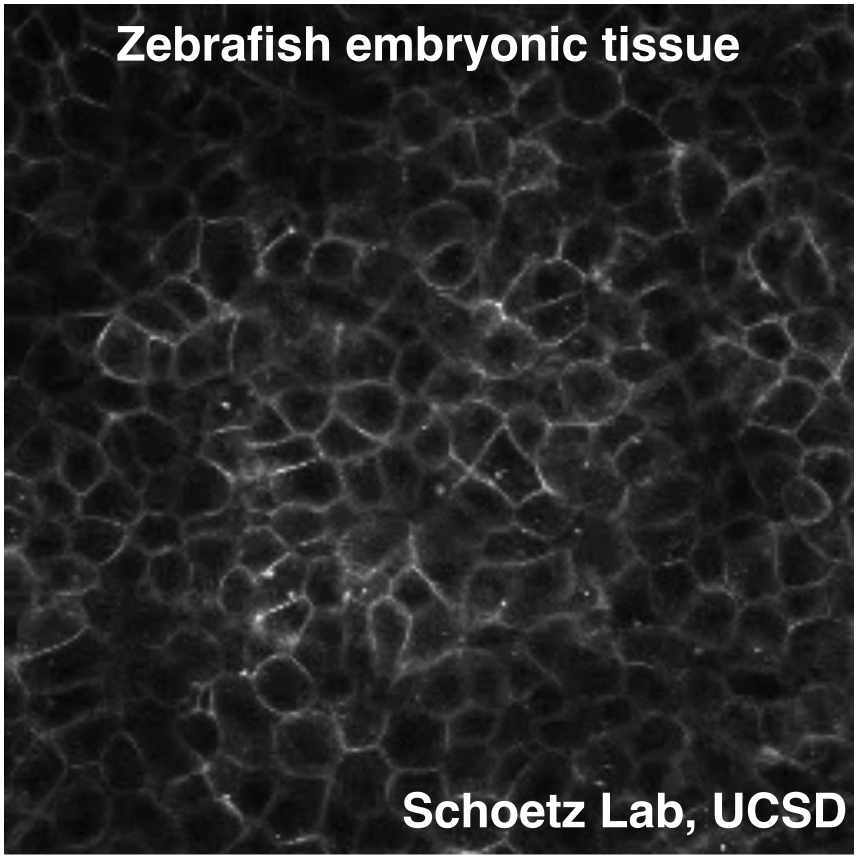


- difficult in general (functional shape derivatives)
- exact solution(!) for 2D ordered packing

3D- ordered solution



How do cells move within a tightly packed tissue?



Structure

- Nearly confluent
- Disordered

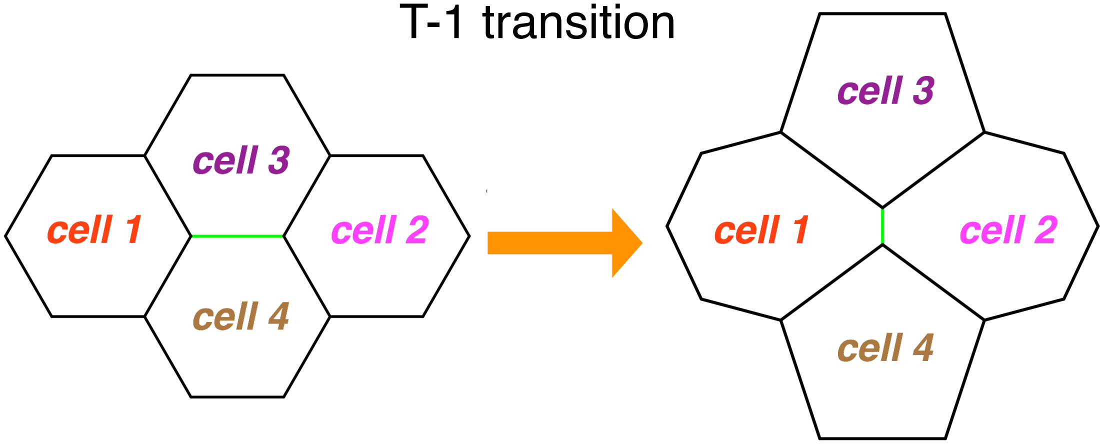
Dynamics

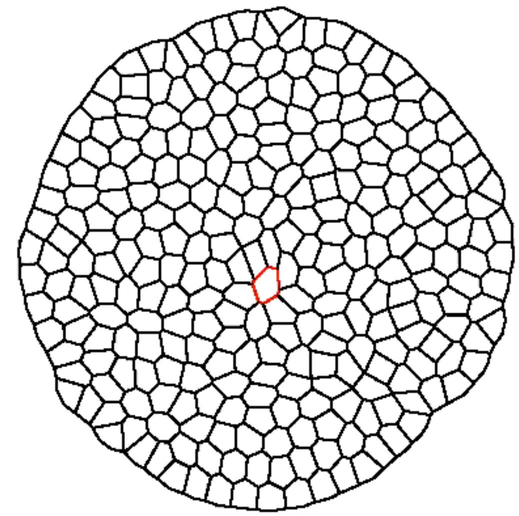
- Cell shape change through active processes
- Cells move past one another by developing protrusions and exerting tension on new contacts
- 'Jiggling' seen here is non-gaussianCell divisions do happen, but rare. Can have interesting behavior with just local rearrangements

Modeling Cell Migration

In a confluent tissues in 2-d, cells can rearrange via T-1 moves only (assuming no cell death):

T-1 transition





What are the energy barriers associated?

Existing models for modeling cells in tissues

"Active matter" models

- Model individual cells as particles
  - Active forcing on every particle
  - Short range interaction between particles
- Explain / predict dynamic properties, such as viscosity
- Explain / predict some collective properties, such as swarming, giant number fluctuations, etc.
- Does not taken into account cell shapes and shape changes

"Shape equilibrium" models

- Includes more microscopic details about single cell mechanics
- Write down a mechanical energy functional for the shapes
  - Explain / predict shape of cell by minimizing energy functional
  - Explain / predict collective statistics of cell topologies
- Dynamics can be hard to implement

Also: cellular Potts model, continuum, many more ......

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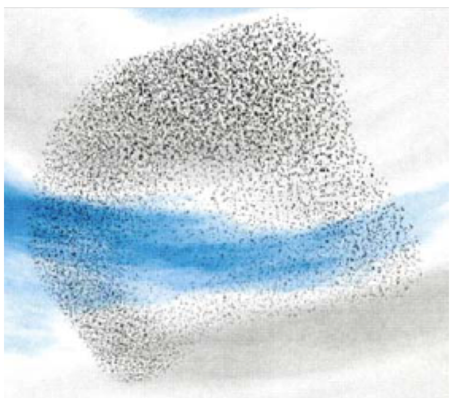
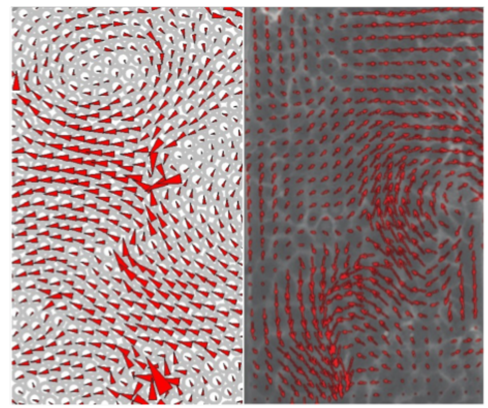
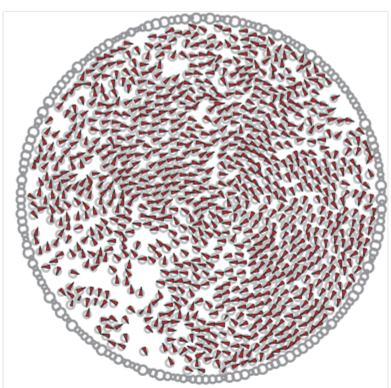
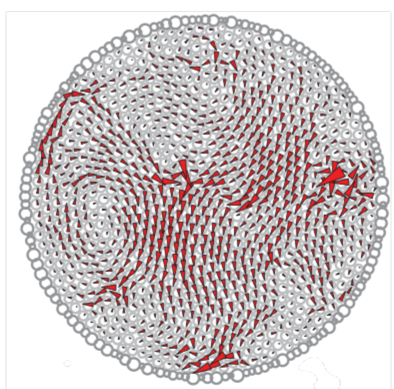


(b)





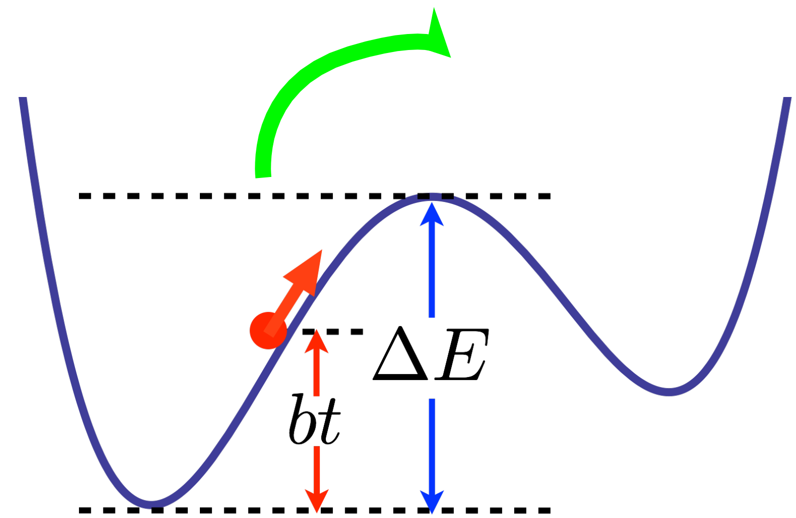


Vicsek et al PRL 76 6 (1995),
Chate et al EPJB 64, 451–456 (2008),
Henkes et al PRE 84, (2011),
Basan et al, HFSP 3 (4) 265 (2009),
Ranft et al PNAS 107 (49) 20863 (2010).....

Simple model for glassy behavior based on Soft Glassy Rheology

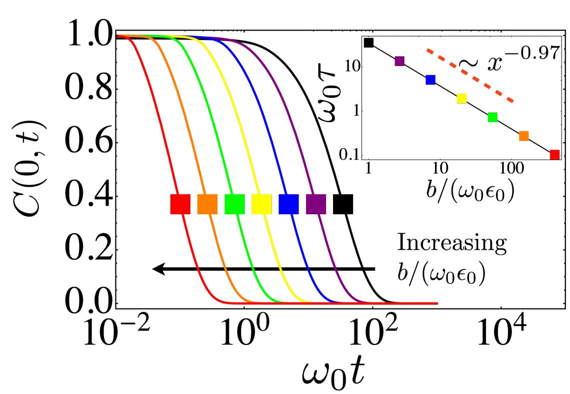
- Energy consumption due to single cell motility: b
- Active fluctuations in cell shape: ε
- Energy landscape 'shape' taken from simulations:

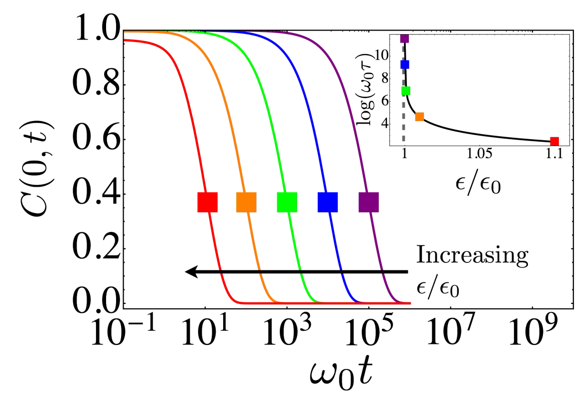
$$R = \omega_0 \exp\left[-(\Delta E - bt)/\varepsilon\right]$$



$$\rho(\Delta E) = e^{-\Delta E/\varepsilon_0}$$

★ Predict two-time correlation function:





Existing models for modeling cells in tissues

“Active matter” models

•Model individual cells as particles
—Active forcing on every particle
—Short range interaction between particles
•Explain / predict dynamic properties, such as viscosity
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“Shape equilibrium” models

•Includes more microscopic details about single cell mechanics
•Write down a mechanical energy functional for the shapes
—Explain / predict shape of cell by minimizing energy functional
—Explain / predict collective statistics of cell topologies
•Dynamics can be hard to implement

Also: cellular Potts model, continuum, many more ......

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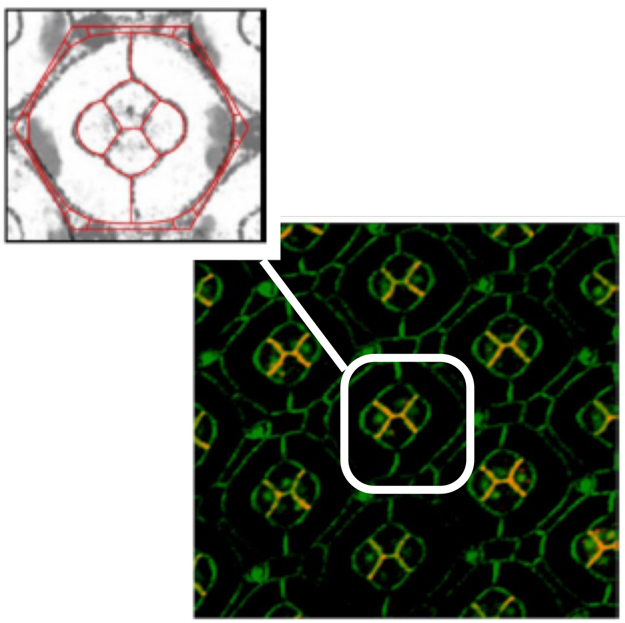
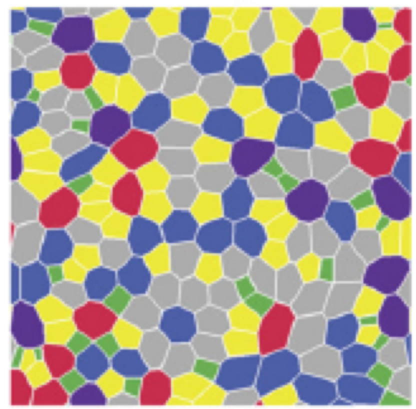
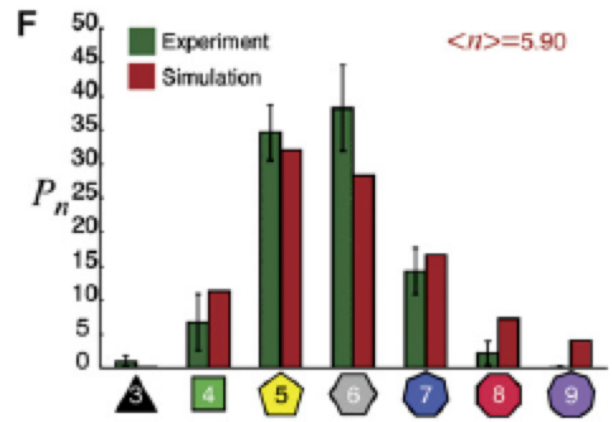
Fruit fly eye development







Hilgenfeldt et al, PNAS 105 3 907–911,
Farhadifar et al Curr. Bio 17 2095, 2007Hocevar & Ziherl Phys Rev E. (2009)

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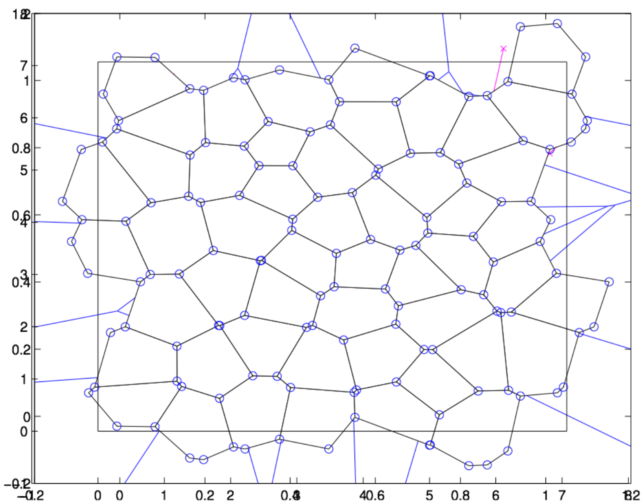
Numerical Modeling

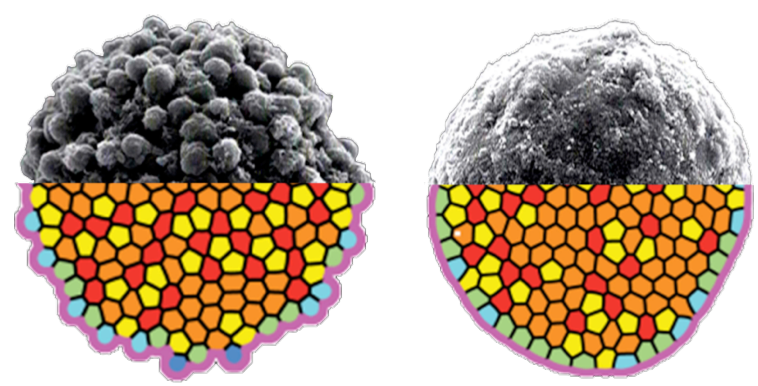
✳ Modeling tissues using **Surface Evolver**

- Using refined polygon tiling to represent 2-d confluent monolayer
- Configurations obtained by minimizing

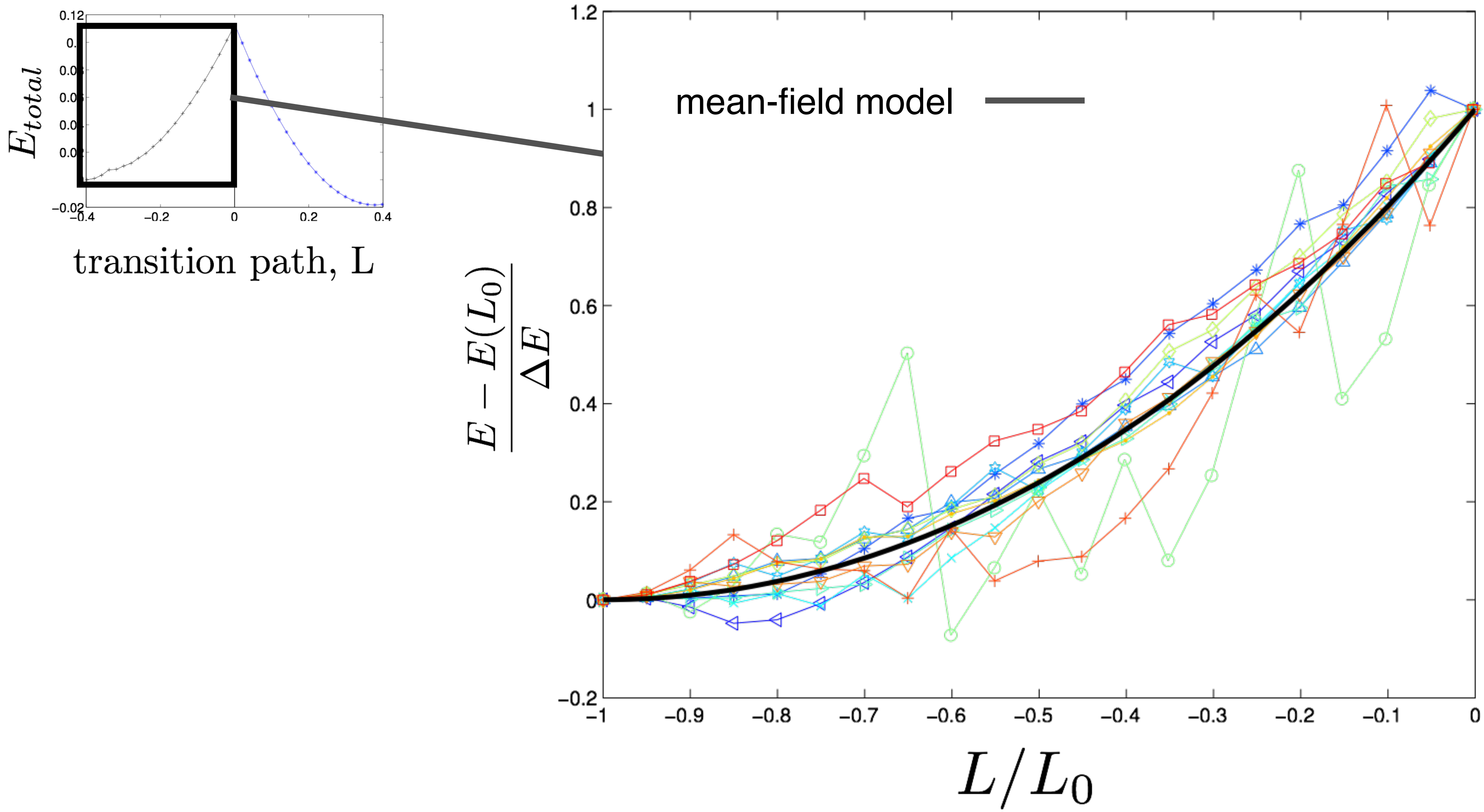
$$E_{tot} = \sum_{cell} E_{cell}$$

✳ The parameters A_0, P_0, k_A, k_P correspond to different cellular properties. Obtain from experiments.

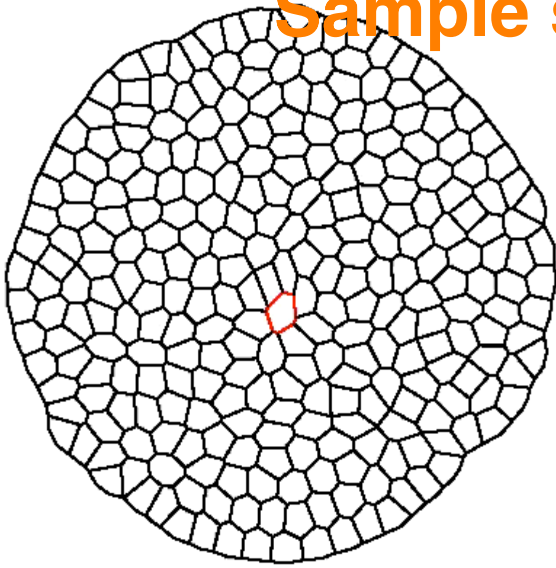




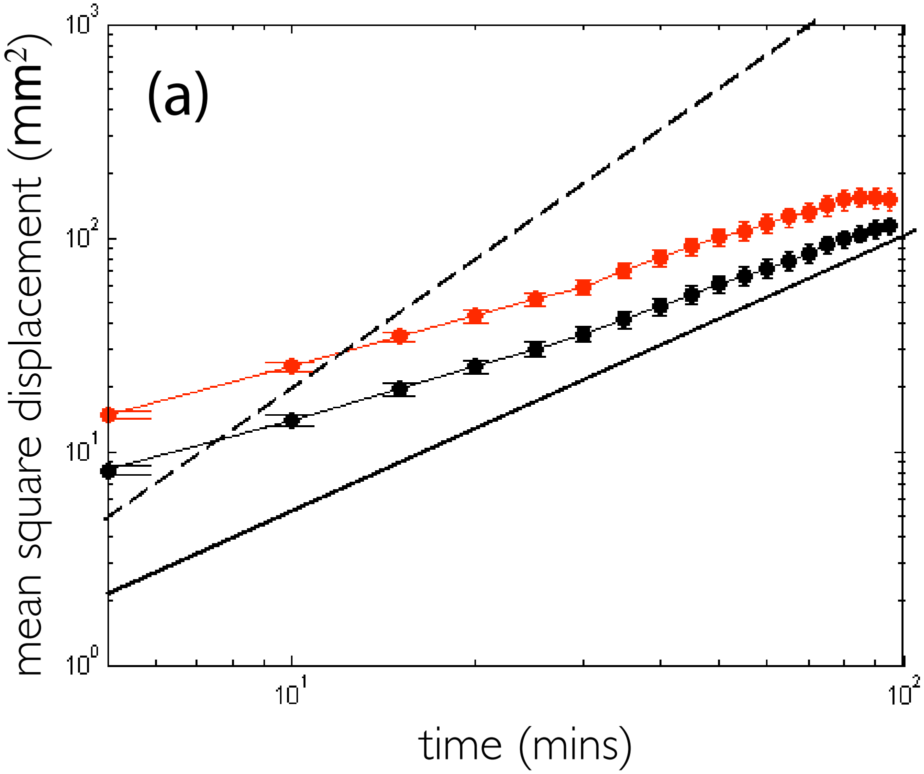
Shape of the energy barrier: universal?
prediction using mean-field model

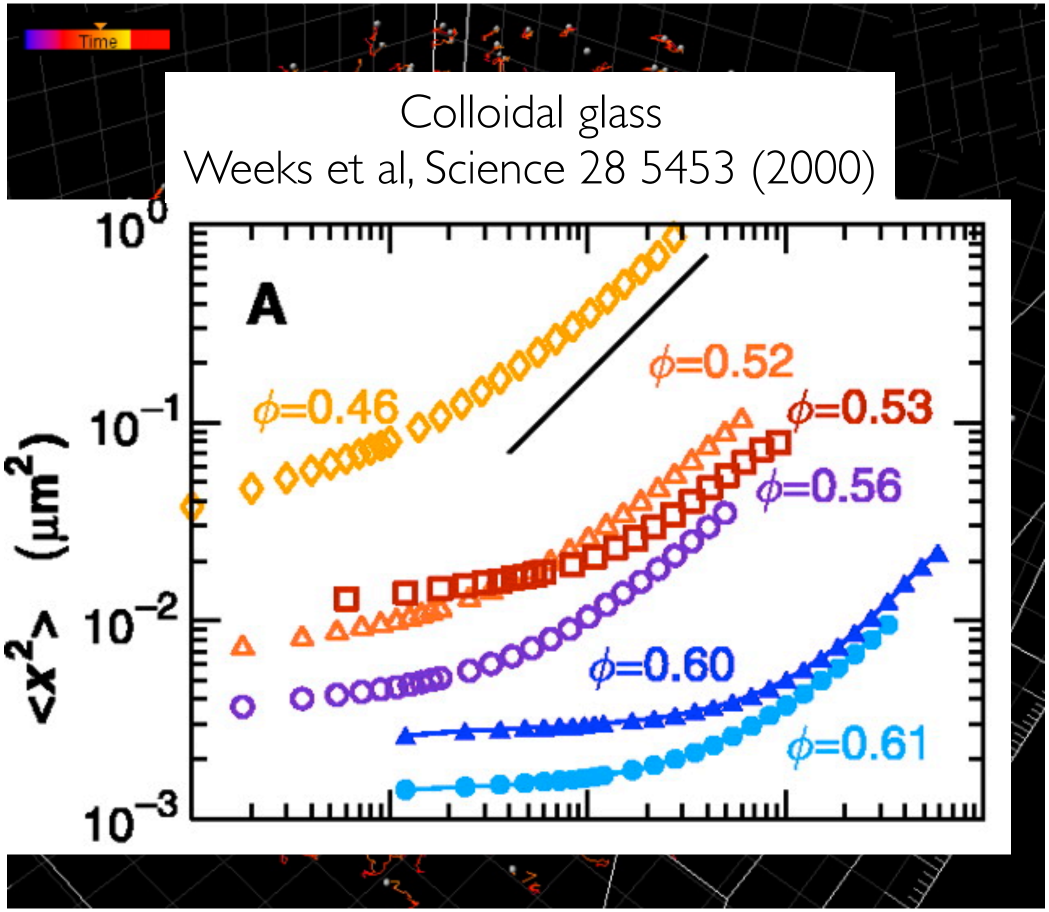


Sample single cell migration



Cell trajectories also change with timescale

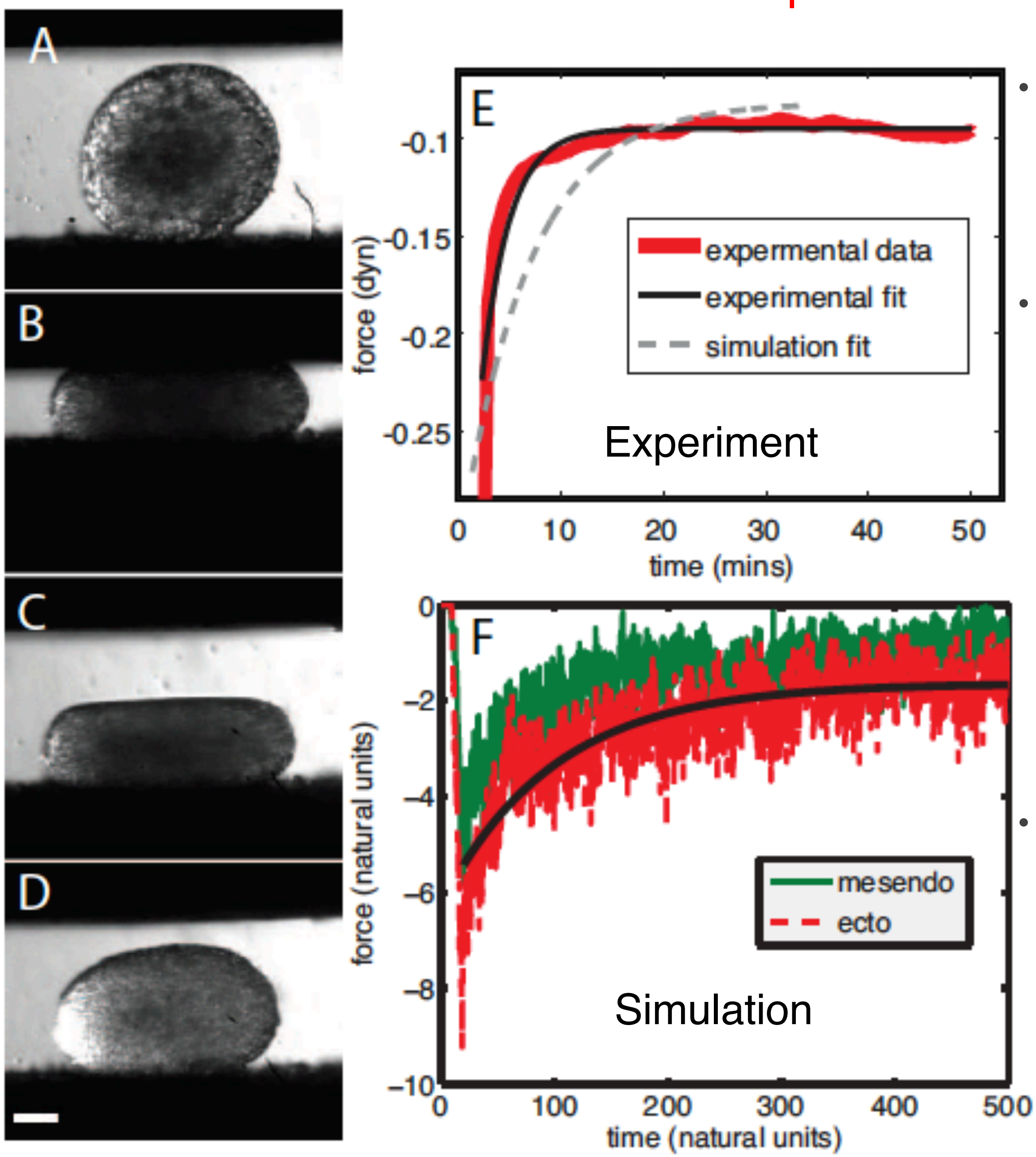




How is structure related to flow in tightly packed, disordered materials?

Prediction: Tissue compression

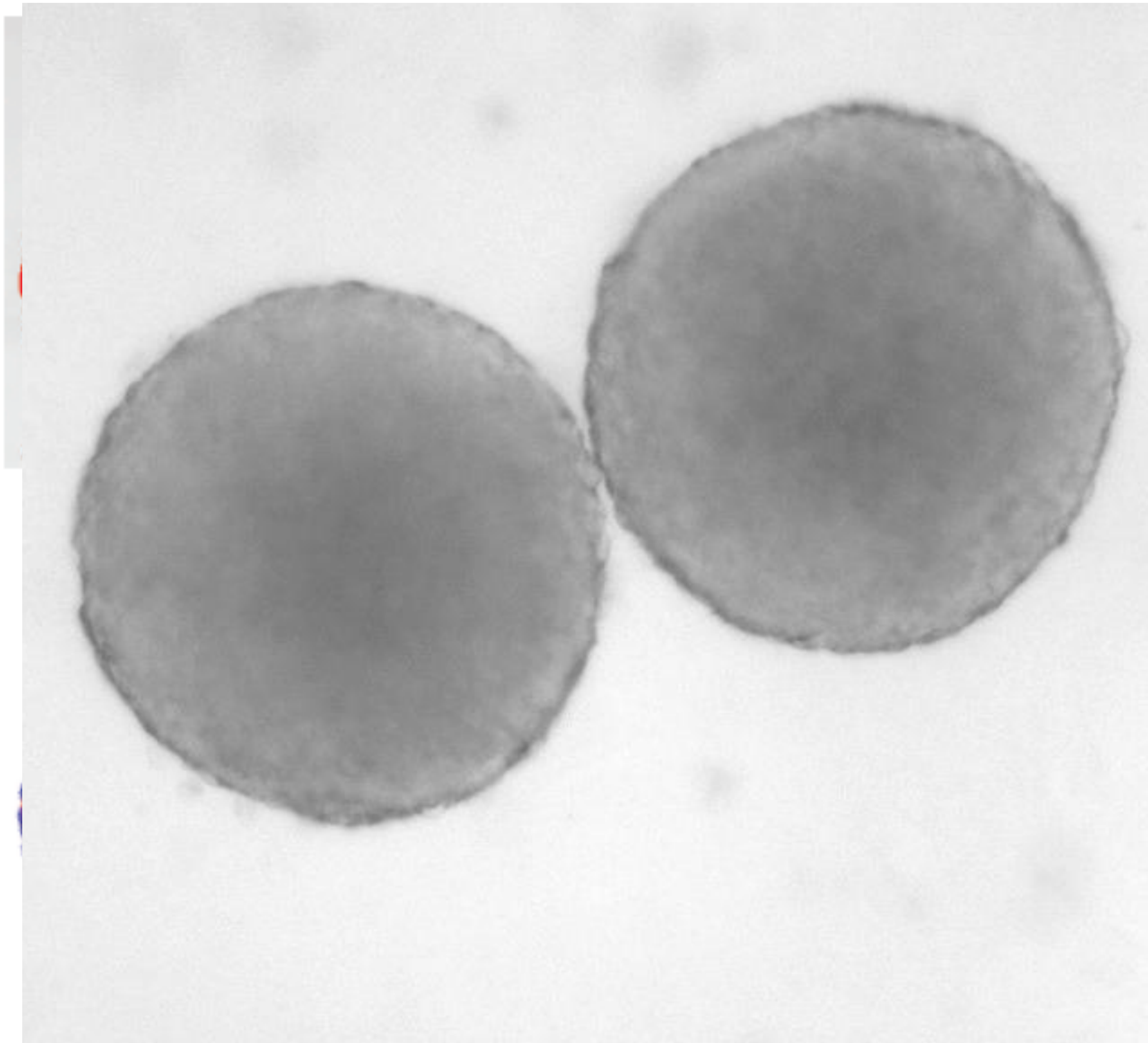
No fit parameters



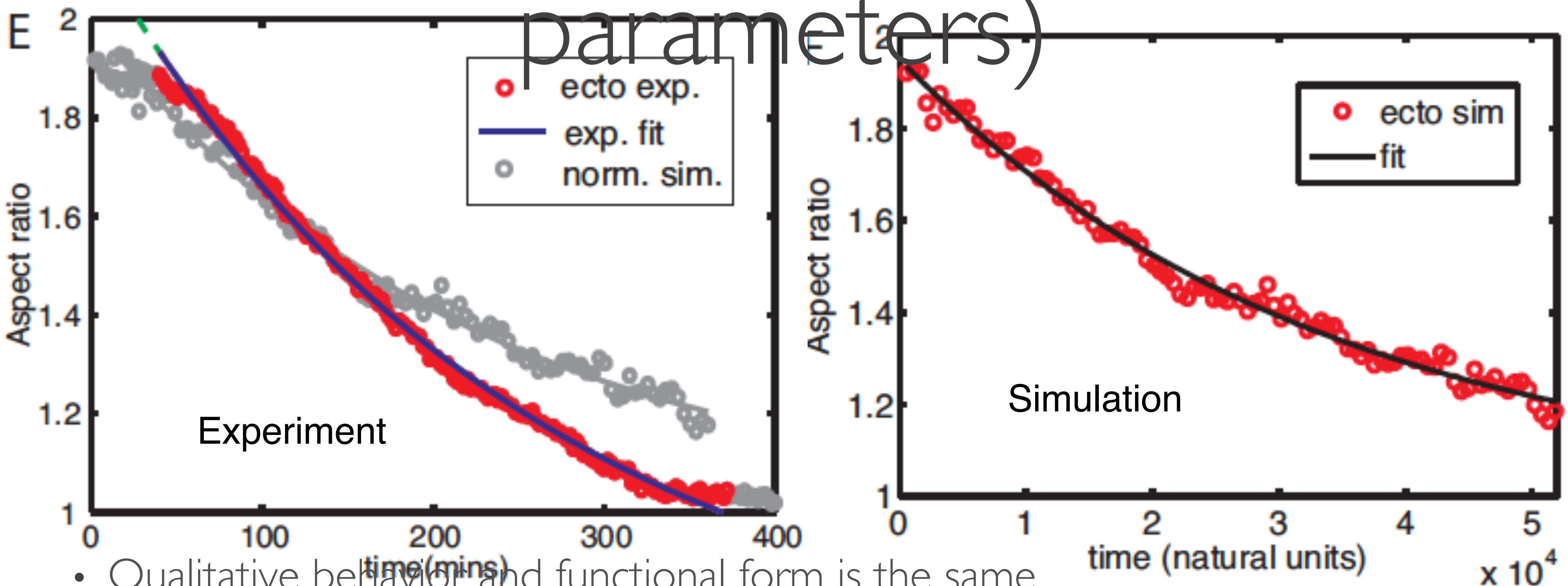
- Qualitative behavior identical (GOOD)
- viscous relaxation:
  - experiment: 8 min
  - simulation: 11 min
  - GOOD
- But surface tension off by a factor of 30!
  - BAD
  - We think this is due to a biologically driven feedback at the surface

Schoetz, Lanio, Talbot and Manning, submitted (2012)

Fusion measurement: convex hull



Prediction: Fusion assay (no fit parameters)



- Qualitative behavior and functional form is the same
- Accounting for difference in volume and surface tension (Young, 1939) with no fit parameters
  - relaxation time: experiment = 100 min, simulations = 160 min, GOOD

Schoetz, Lanio, Talbot and Manning, submitted (2012)