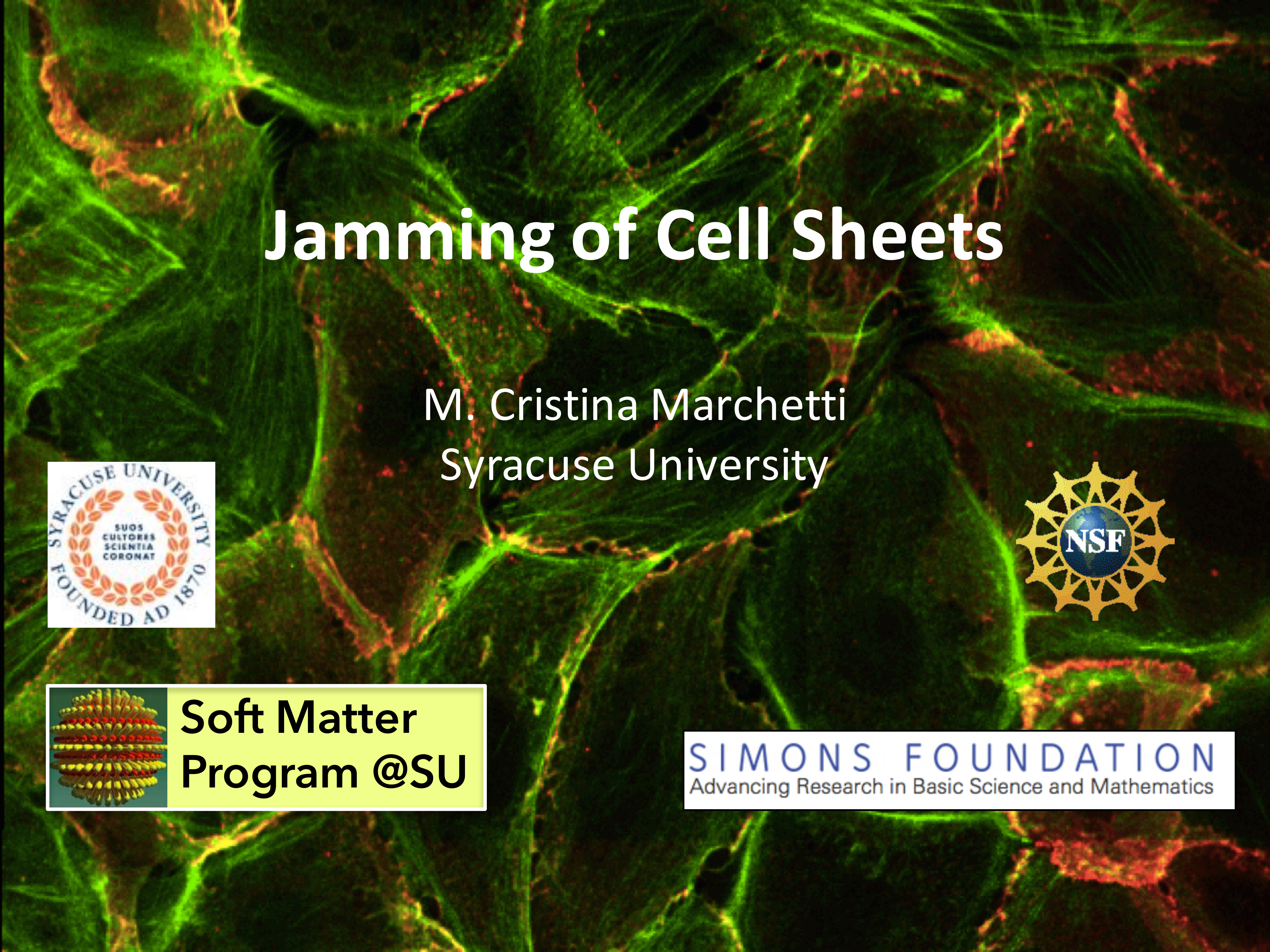

Jamming of Cell Sheets

M. Cristina Marchetti
Syracuse University

Soft Matter
Program @SU

NSF

SIMONS FOUNDATION
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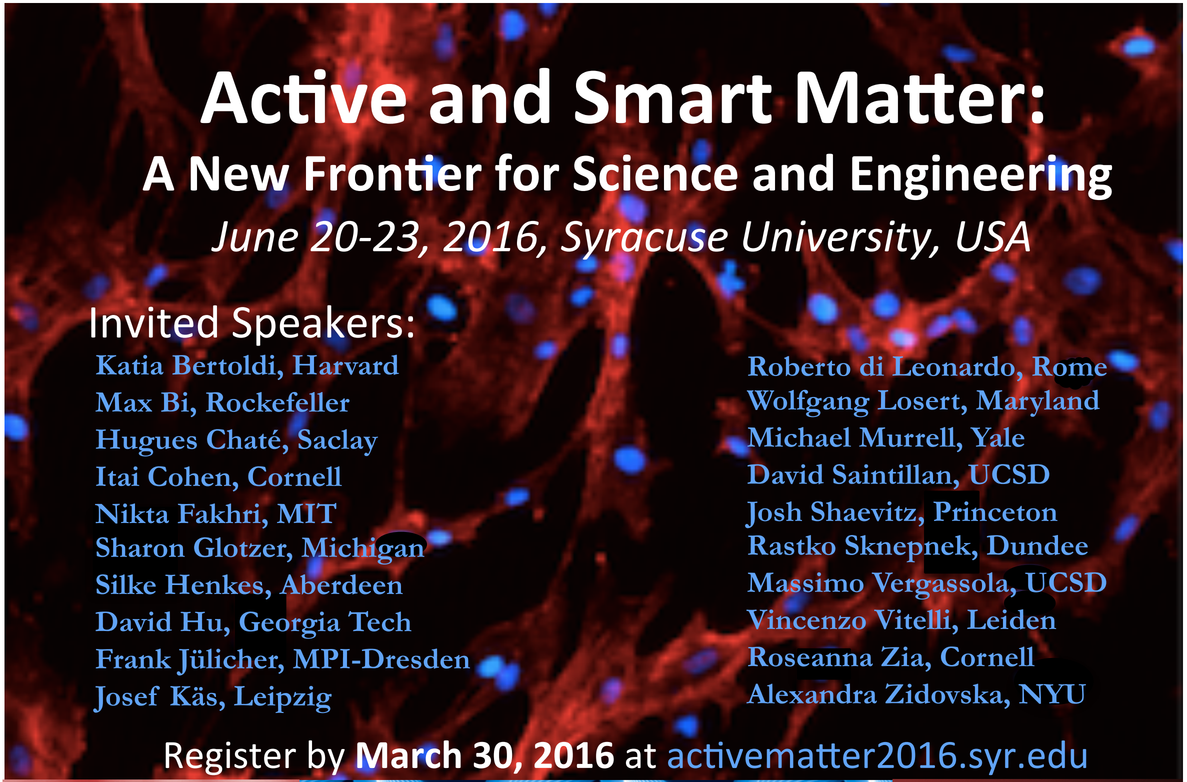


Active and Smart Matter:

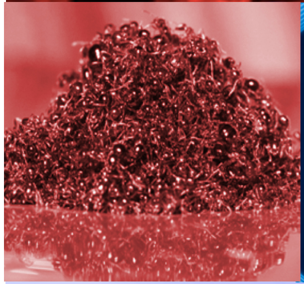
A New Frontier for Science and Engineering

June 20-23, 2016, Syracuse University, USA

Invited Speakers:

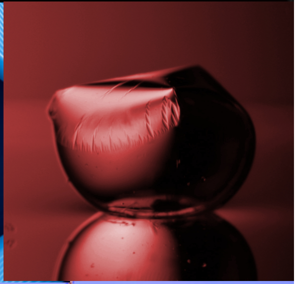
- Katia Bertoldi, Harvard
- Max Bi, Rockefeller
- Hugues Chaté, Saclay
- Itai Cohen, Cornell
- Nikta Fakhri, MIT
- Sharon Glotzer, Michigan
- Silke Henkes, Aberdeen
- David Hu, Georgia Tech
- Frank Jülicher, MPI-Dresden
- Josef Käs, Leipzig
- Roberto di Leonardo, Rome
- Wolfgang Losert, Maryland
- Michael Murrell, Yale
- David Saintillan, UCSD
- Josh Shaevitz, Princeton
- Rastko Sknepnek, Dundee
- Massimo Vergassola, UCSD
- Vincenzo Vitelli, Leiden
- Roseanna Zia, Cornell
- Alexandra Zidovska, NYU

Register by **March 30, 2016** at activematter2016.syr.edu



Organizers:

Jay Henderson
M. Cristina Marchetti
Joseph Paulsen
Ashok Sangani
J. M. Schwarz



ICAM-I2CAM Institute for Complex Adaptive Matter

SYRACUSE UNIVERSITY SUOS CULTORES SCIENTIA CORONAT FOUNDED AD 1870

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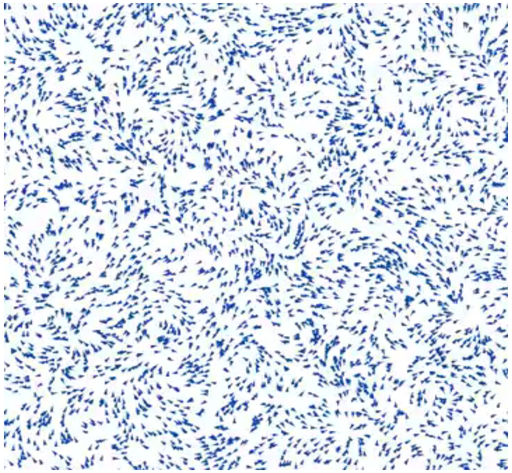
ACTIVE & SMART MATTER SU2016

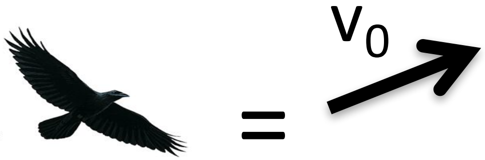
Active Matter

Models of self-propelled **point particle** with a minimal set of interaction rules describe complex patterns seen in nature on many scales

Review: MCM et al RMP **85**, 1143 (2013)

Vicsek et al PRL **76** 6 (1995)



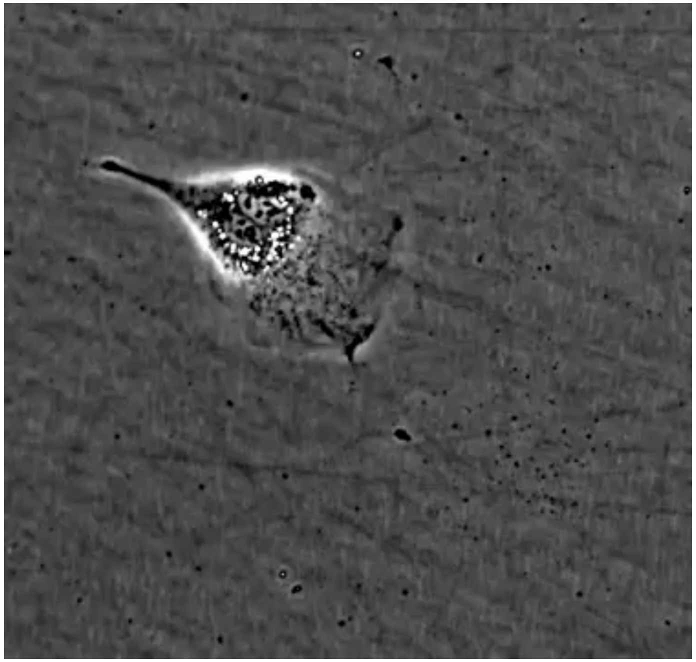


Flocking

- **point** particles
- **fixed speed** v_0
- **align** with neighbors with **noisy** rules

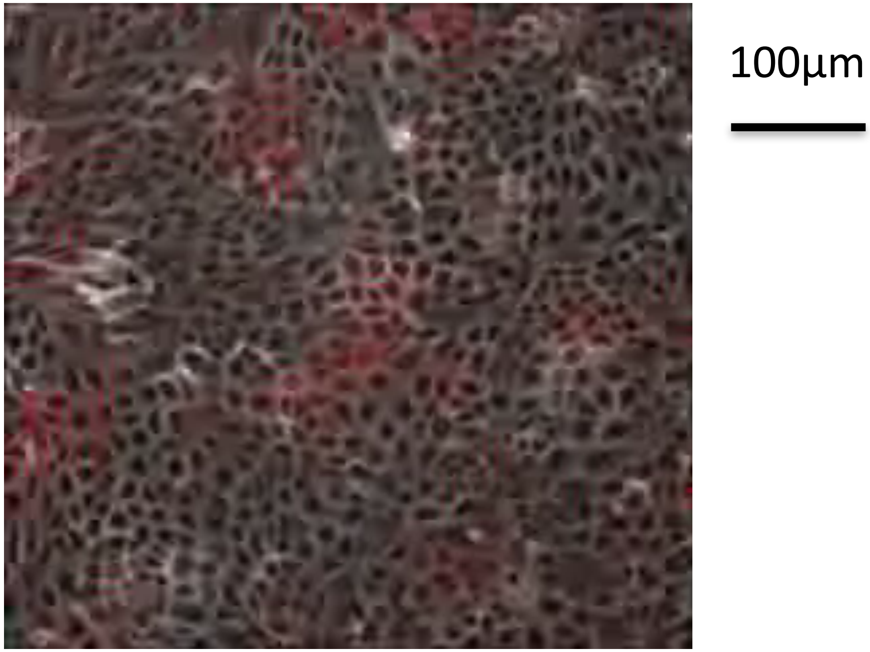
Living cells are motile active entities

One cell



Human bone cancer cell on fibronectin

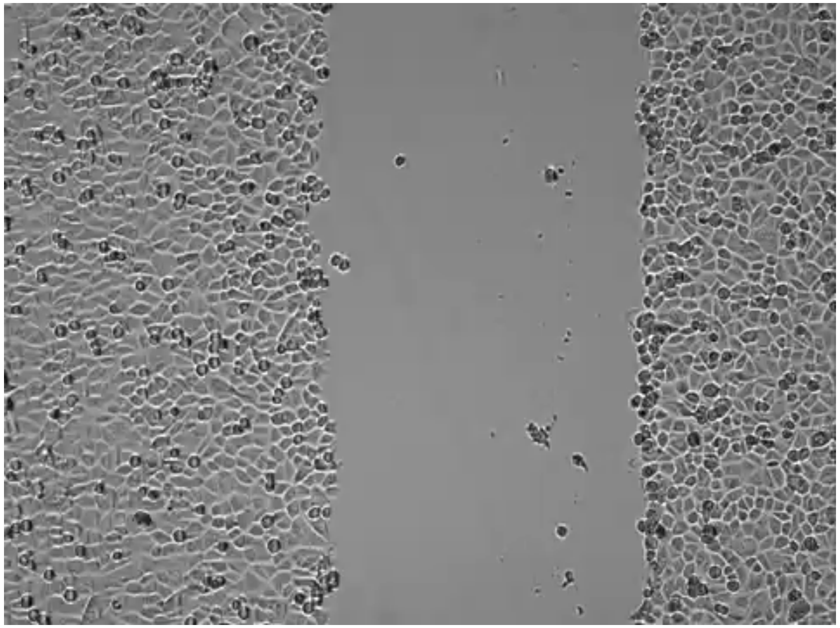
Many cells



Monolayer of epithelial MDCK cells (Weitz lab)

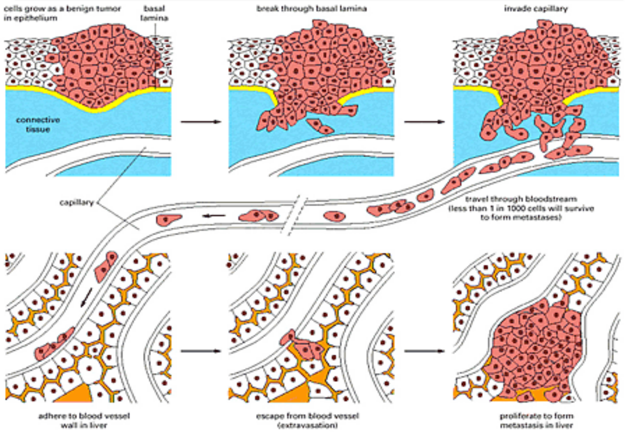
Coordinated cell migration in many developmental processes

Wound healing

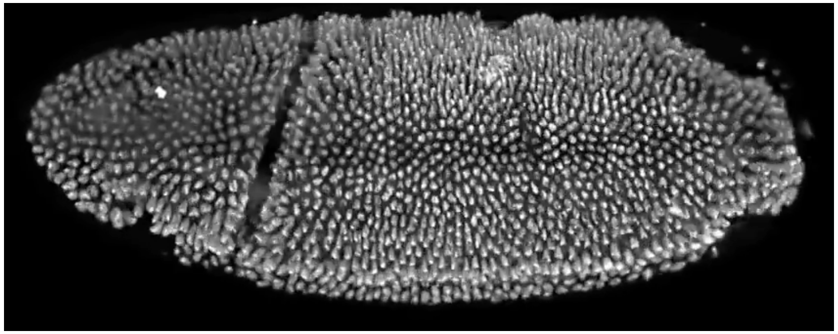


youtube.com/watch?v=v9xq_GiRXeE

Cancer metastasis

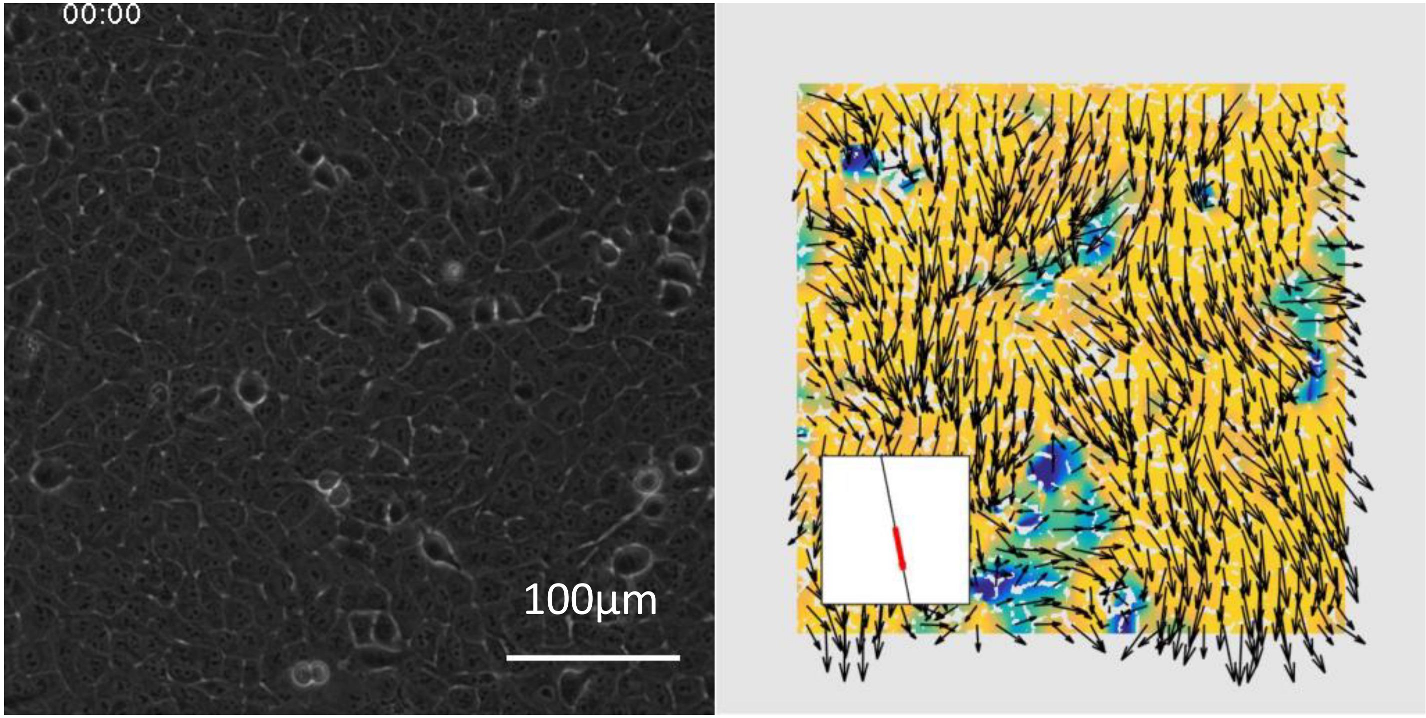


Embryonic development



youtube.com/watch?v=FChS4KU5jDM

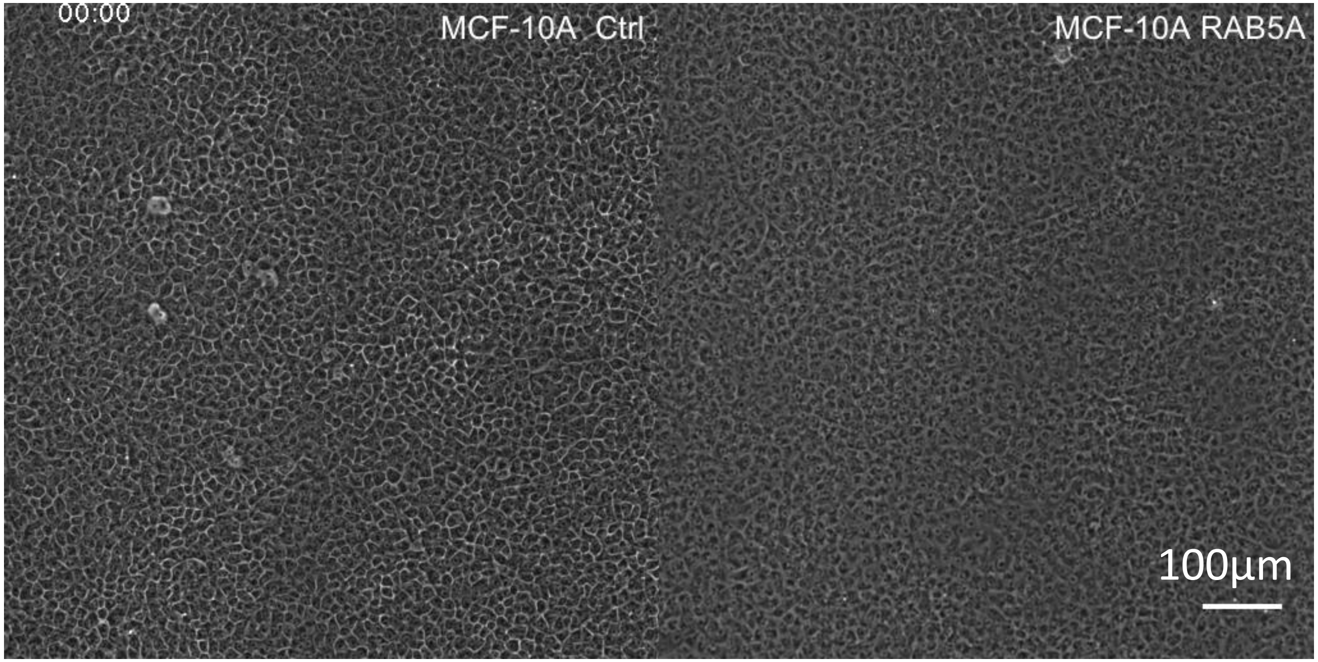
Role of crowding: epithelial cell monolayers jam over time



See also:
Angelini *et al.*, PRL 2010, PNAS 2011
Puliafito *et al.*, PNAS 2012
Nnetu *et al.*, New J Phys 2012
Garcia *et al.*, PNAS 2015

Epithelial breast cells MCF 10A jam over time (96h)
G. Scita & R. Cerbino, Universita’ di Milano

… and can be fluidified by suitable perturbations



A jammed confluent layer of MCF 10A unjams upon addition of Rab5a – over 24h

G. Scita & R. Cerbino, Universita' di Milano

Tissues as active materials with liquid-like and solid-like phases

Glass-like dynamics of collective cell migration

Thomas E. Angelini[a], Edouard Hannezo[b], Xavier Trepat[c], Manuel Marquez[d], Jeffrey J. Fredberg[e], and David A. Weitz[f,1]

PNAS 108, 4714 (2011)

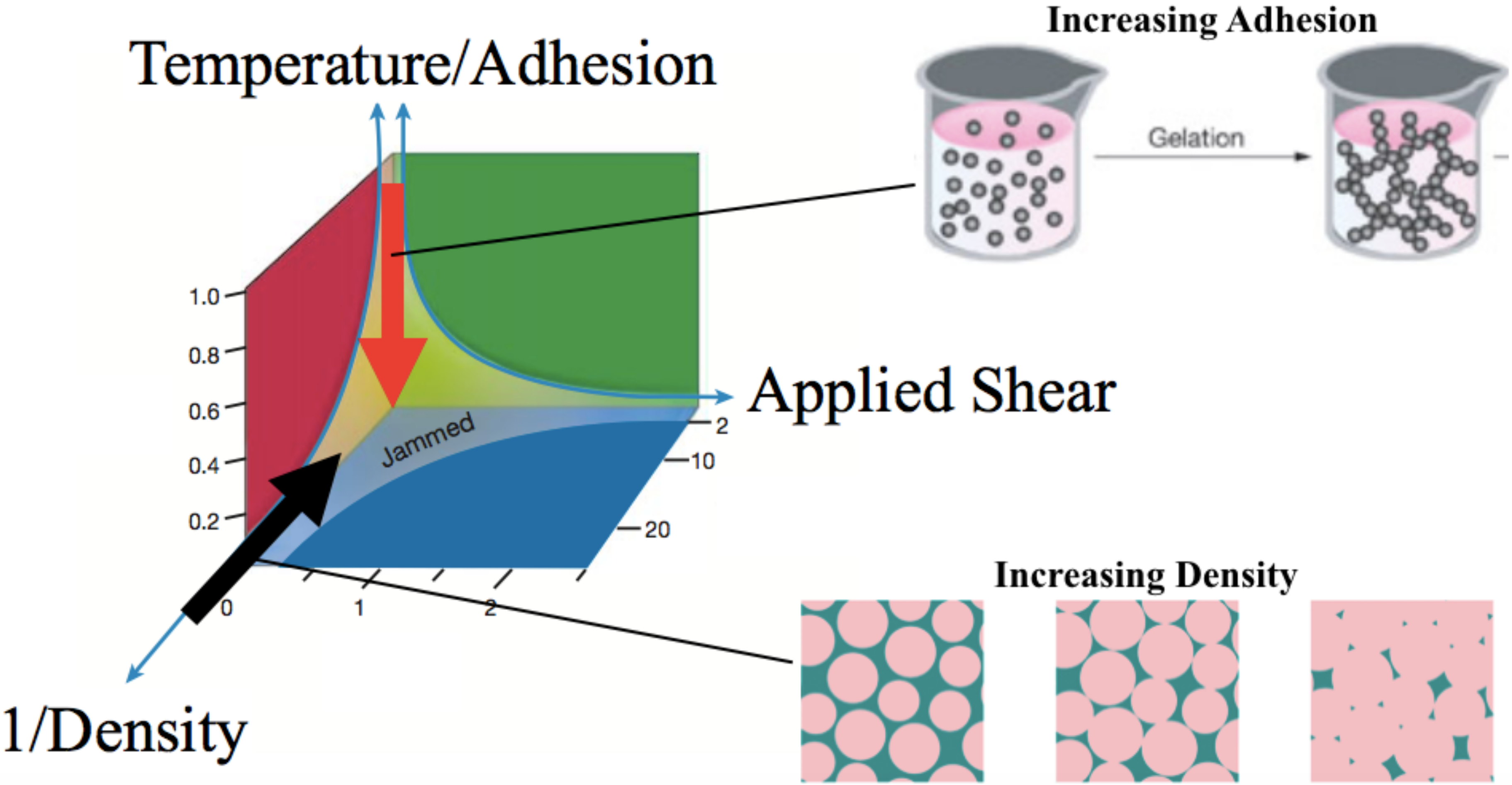
PHYSICAL REVIEW E **84**, 040301(R) (2011)

Active jamming: Self-propelled soft particles at high density

Silke Henkes,[1] Yaouen Fily,[1] and M. Cristina Marchetti[1,2]

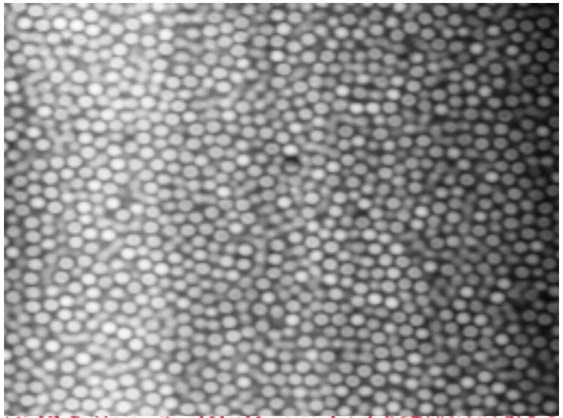
Jamming of attractive colloids

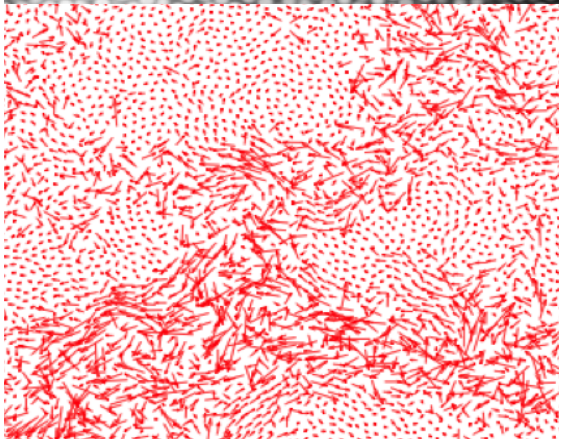
Trappe et al, *Nature* **411**, 772-775 (2001)



Glassy behavior: dynamical heterogeneities, caging & viscoelasticity

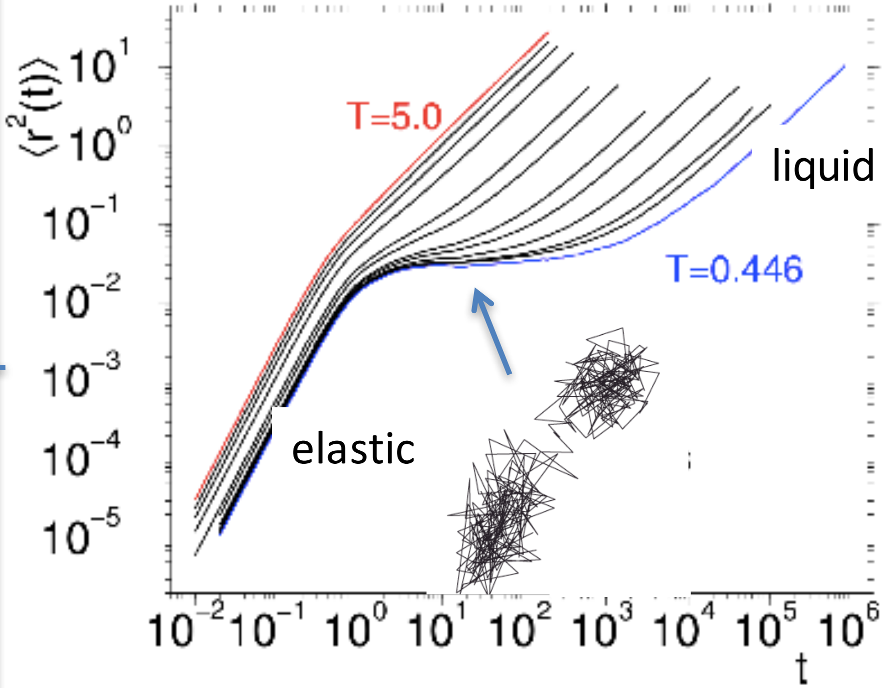
Colloidal glass of ~ 2µm PMMA – **Eric Weeks, Emory**





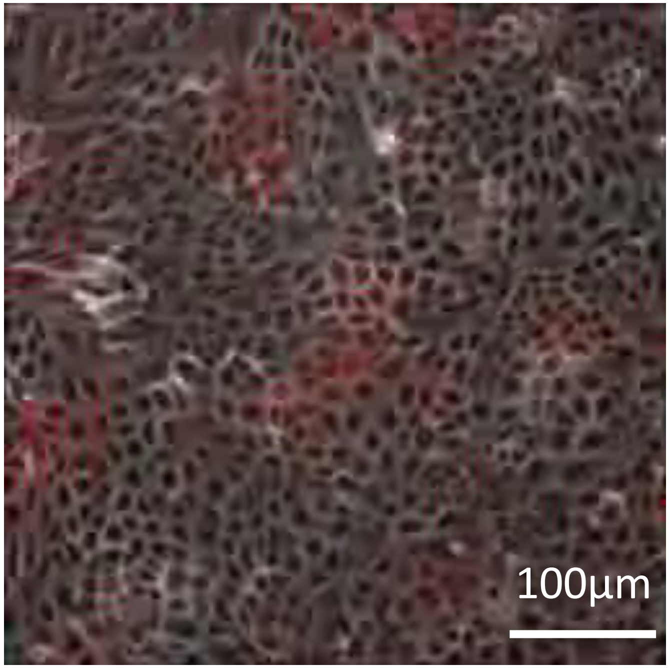
Displacements in simulation of a 2 glass former - **Berthier PRL 2011**

Slow relaxation and transient caging evident in Mean-Square Displacement → **viscoelasticity**

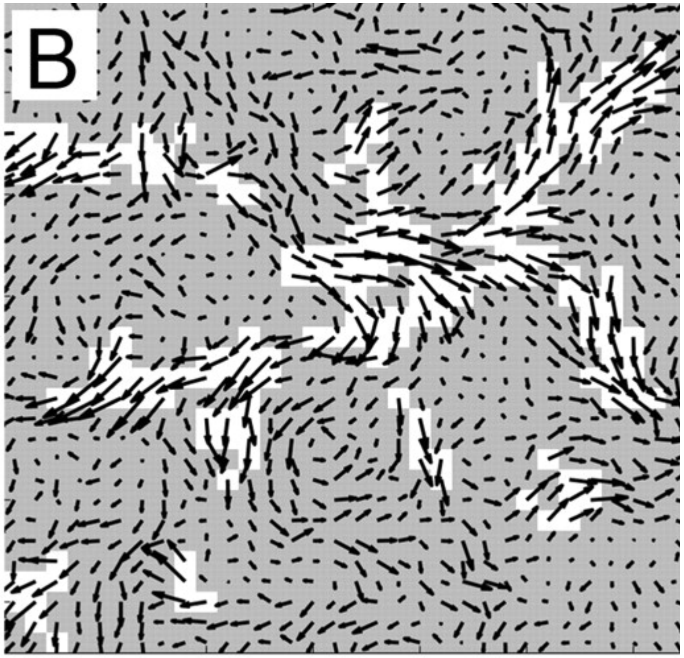


Kob PRE 2000

Dynamical heterogeneities in confluent cell layers



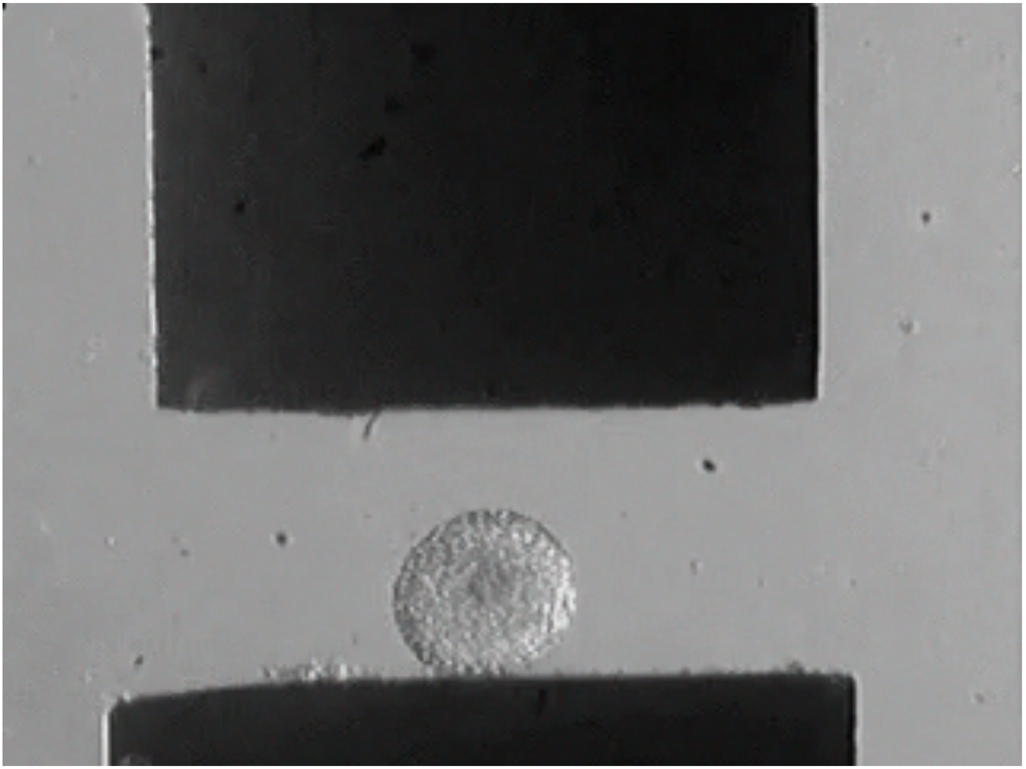
MDCK epithelial cells v_{avg} 35 µm/h
Angelini *et al*. 2011



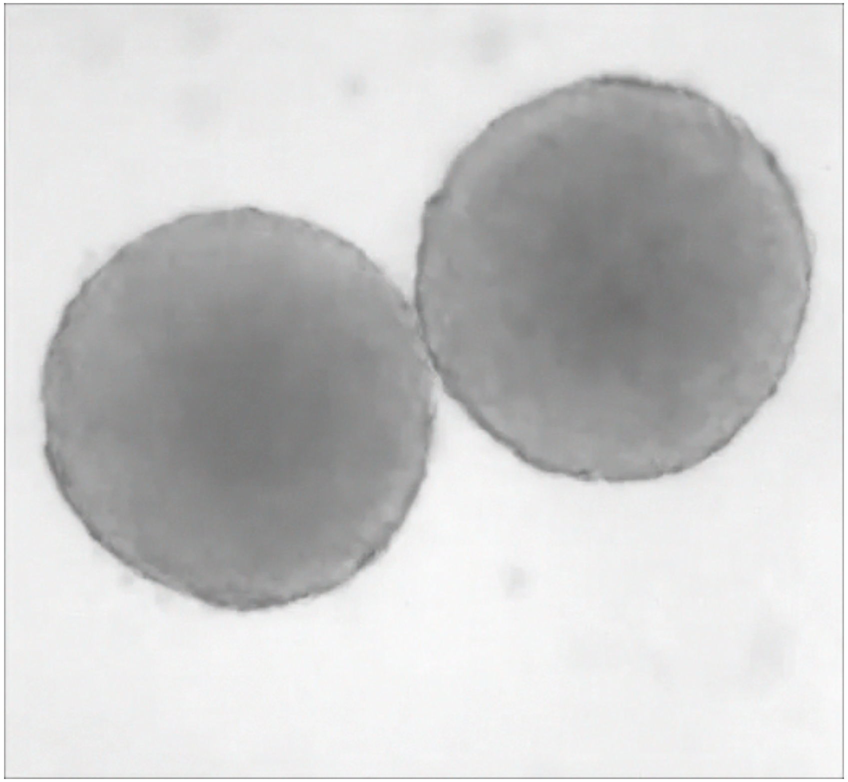
Dynamical heterogeneities probed by PIV

Tissues are viscoelastic materials

timescale ~ seconds



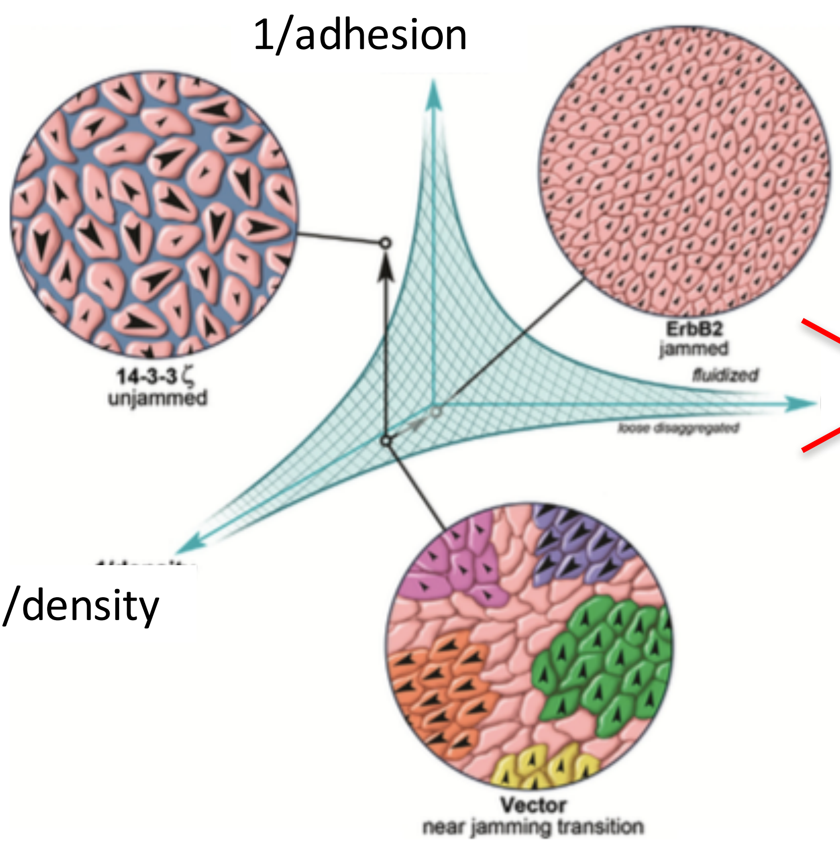
timescale ~ hours



Schoetz *et al.*J. R. Soc. Interface (2013)

Can the behavior of dense tissues be organized in a jamming phase diagram inspired by that of inert matter?

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



1/adhesion

~~external shear~~

cell motility

1/density

Can we use active matter models to quantify such a phase diagram?

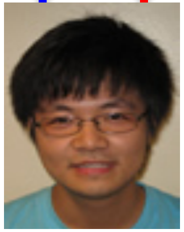
Motile cells as Self-Propelled Particles (**SPP**)

Silke Henkes
Aberdeen

Yaouen Fily
Brandeis

David
Yllanes

Adam
Patch



Xingbo Yang
Northwestern

Confluent cell layers as Self Propelled Voronoi (**SPV**)

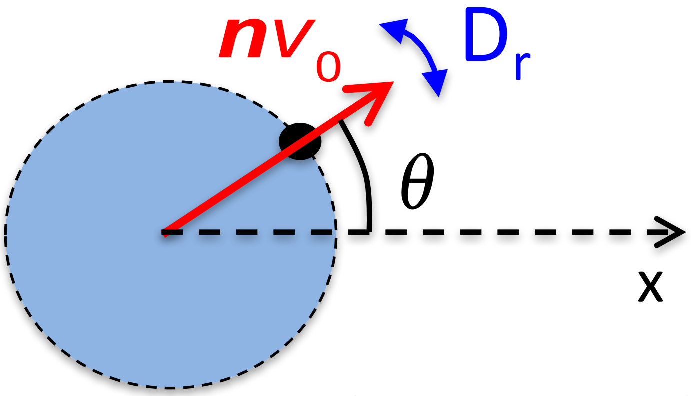
Max Bi
Rockefeller

Lisa
Manning

Michael
Czajkowski

One Self-Propelled Particle

- Overdamped dynamics
- Self-propulsion speed v_0 along axis **n**
- Rotational noise D_r



$$\boldsymbol{n} = \left(\cos\theta, \sin\theta\right)$$

$$\cancel{m\partial_t \vec{v}} = \zeta\left(\vec{v} - v_0\hat{n}\right) = 0$$
$$\dot{\theta} = \eta(t) \qquad \left\langle \eta(t)\eta(0)\right\rangle = 2D_r\delta(t)$$

Persistent random walk:

- Ballistic `runs' at speed v_0
- Change of direction at rate D_r

``persistence'' length $\ell_p = v_0/D_r$

$$\langle[\Delta\vec{x}(t)]^2\rangle = 4D_{sp}\left[t - \frac{1}{D_r}\left(e^{-D_r t} - 1\right)\right]$$

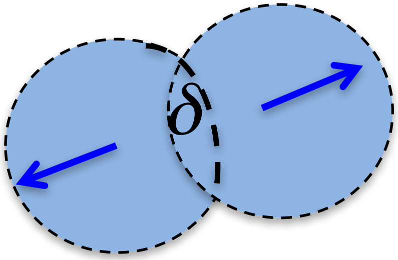
$$D_{sp} = \frac{v_0^2}{2D_r} \gg D = \frac{k_B T}{\zeta}$$

Many SPPs: activity & excluded volume

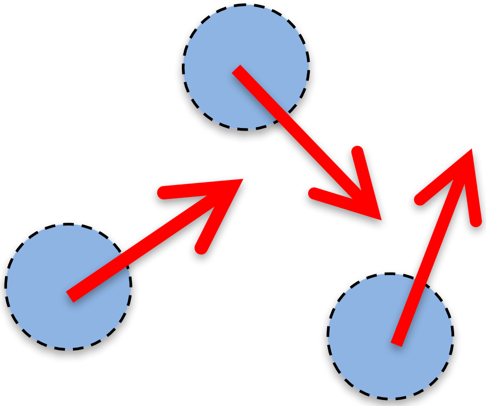
Fily & MCM PRL 2012
Fily, Henkes & MCM, Soft Matter 2014

$$\vec{v}_i = v_0 n_i + \mu \sum_{j\neq i} \vec{f}_{ij}$$

$$\dot{\theta}_i = \eta_i(t) \qquad \langle \eta_i(t)\eta_j(t') \rangle = 2D_R \delta_{ij} \delta(t-t')$$



$\vec{f}_{ij} \sim k\delta$: spring-like pair repulsive forces $\propto$ overlap δ



$$\phi = \frac{N\pi\bar{a}^2}{L^2}$$ packing fraction

$$Pe = \frac{v_0}{aD_r} = \frac{\ell_p}{a}$$ Peclet number

No alignment rule, no steric alignment
→ no flocking state at any density

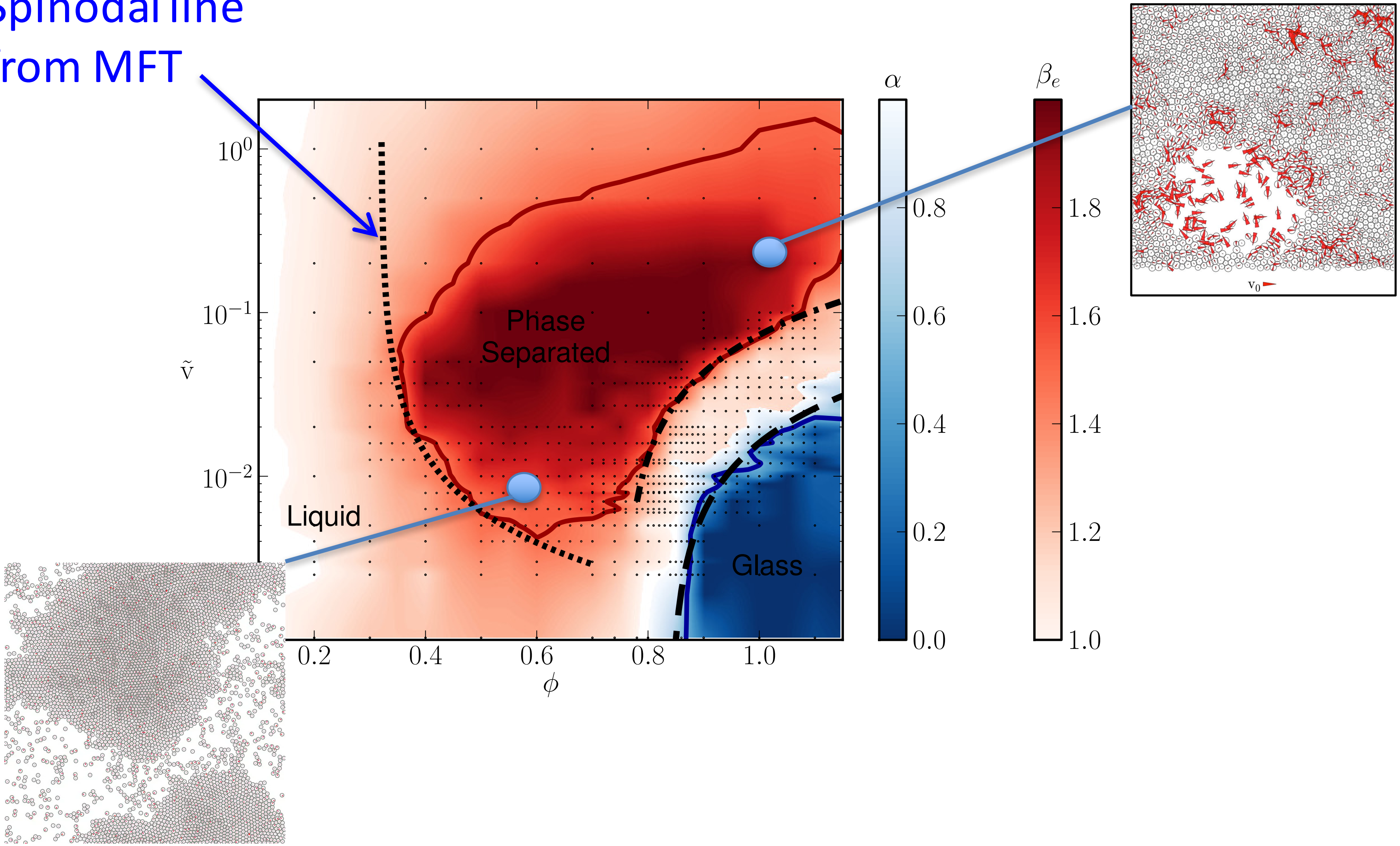
Polydispersity: passive limit is granular jamming

See also Bialké et al PRL 2012, Redner et al PRL 2013, …

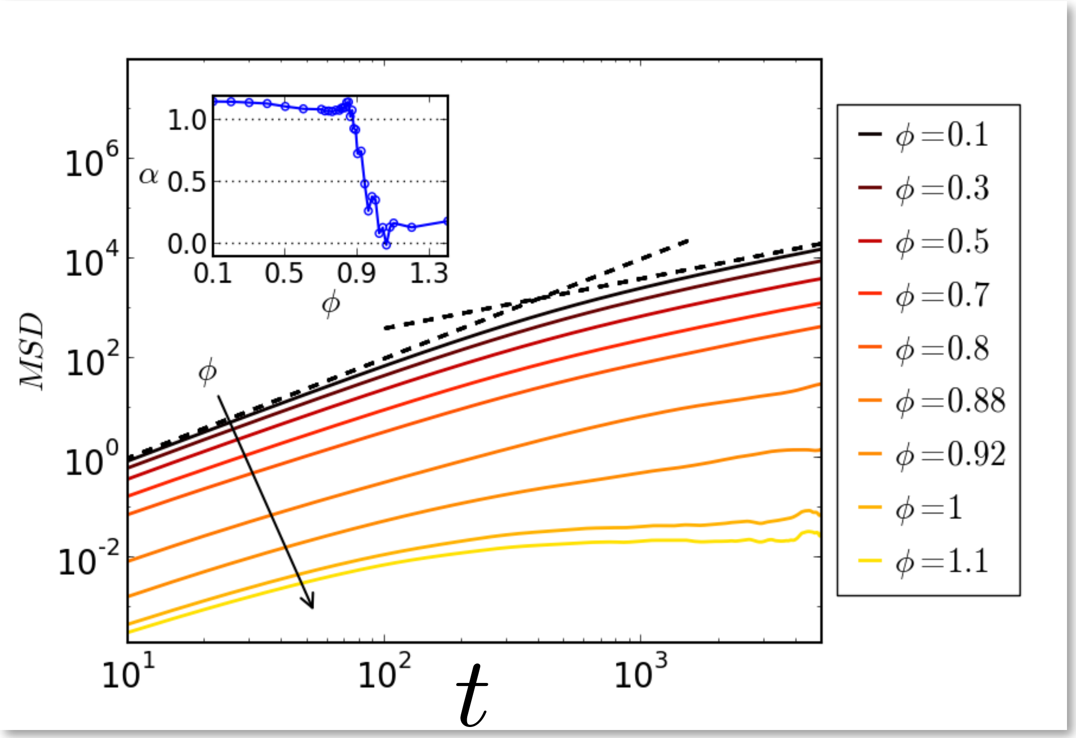
A Phase Diagram for repulsive SPP

Fily, Henkes & MCM, Soft Matter **10**, 2132 (2014)

Spinodal line from MFT



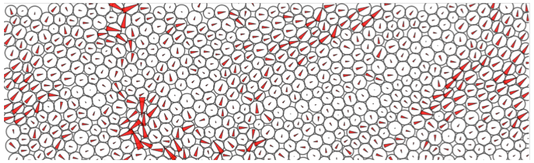
Quantify glass transition with MSD

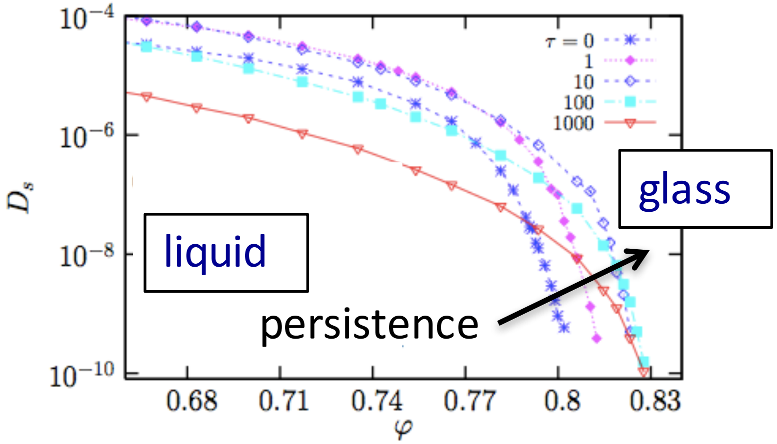


α=1 diffusion → liquid
α=0 glass

$$MSD = \langle [\Delta \vec{x}(t)]^2 \rangle \sim t^{\alpha}$$

Active Glass



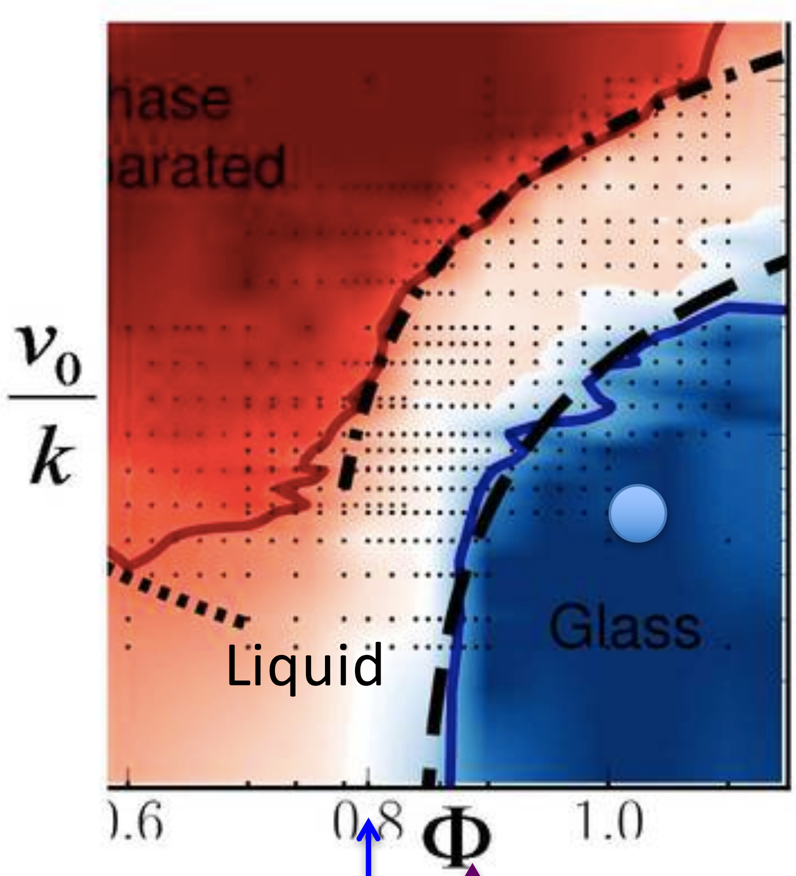


liquid

glass

persistence

Berthier, PRL **112**, 220602 (2014)



Liquid

thermal

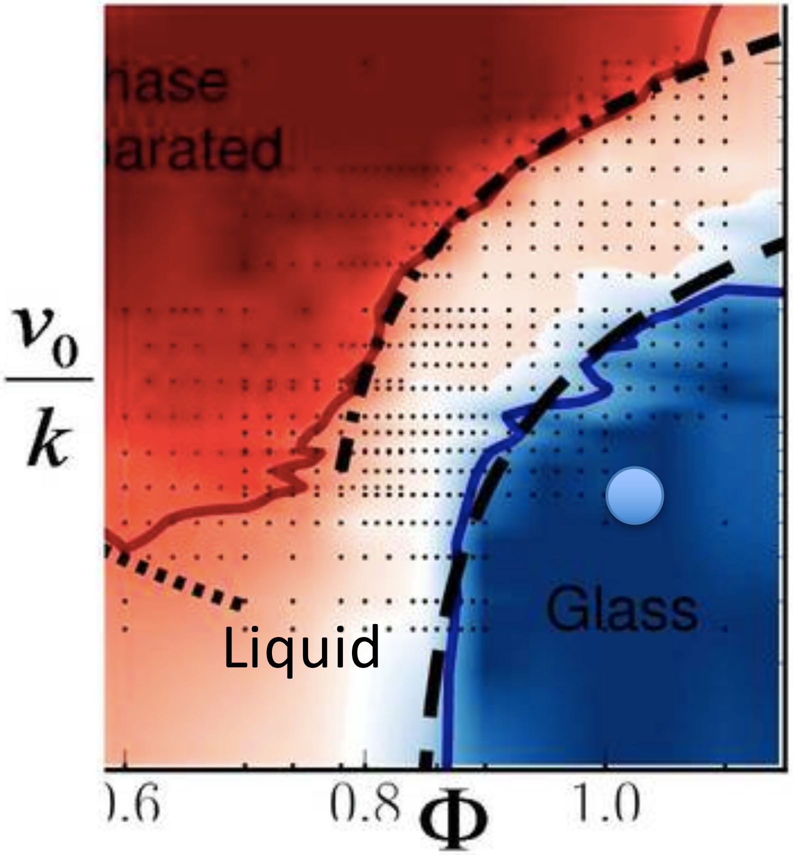
φ_G

$\varphi_{RCP}=0.842$

Activity provides new dynamical pathways and shifts φ_g to higher density.

Berthier 2014, Ni *et al* 2013 (hard disks)

Estimating glass transition at small v_0



Solid: passive pressure form jamming

$$p = p_0(\phi - \phi_J)$$

$$p_0 \sim 0.34k$$

Active fluid pushing against interface

$$p_a = (v_0/\mu)/2a$$

Pressure balance

$$v_0^* = u(\phi - \phi_J)$$

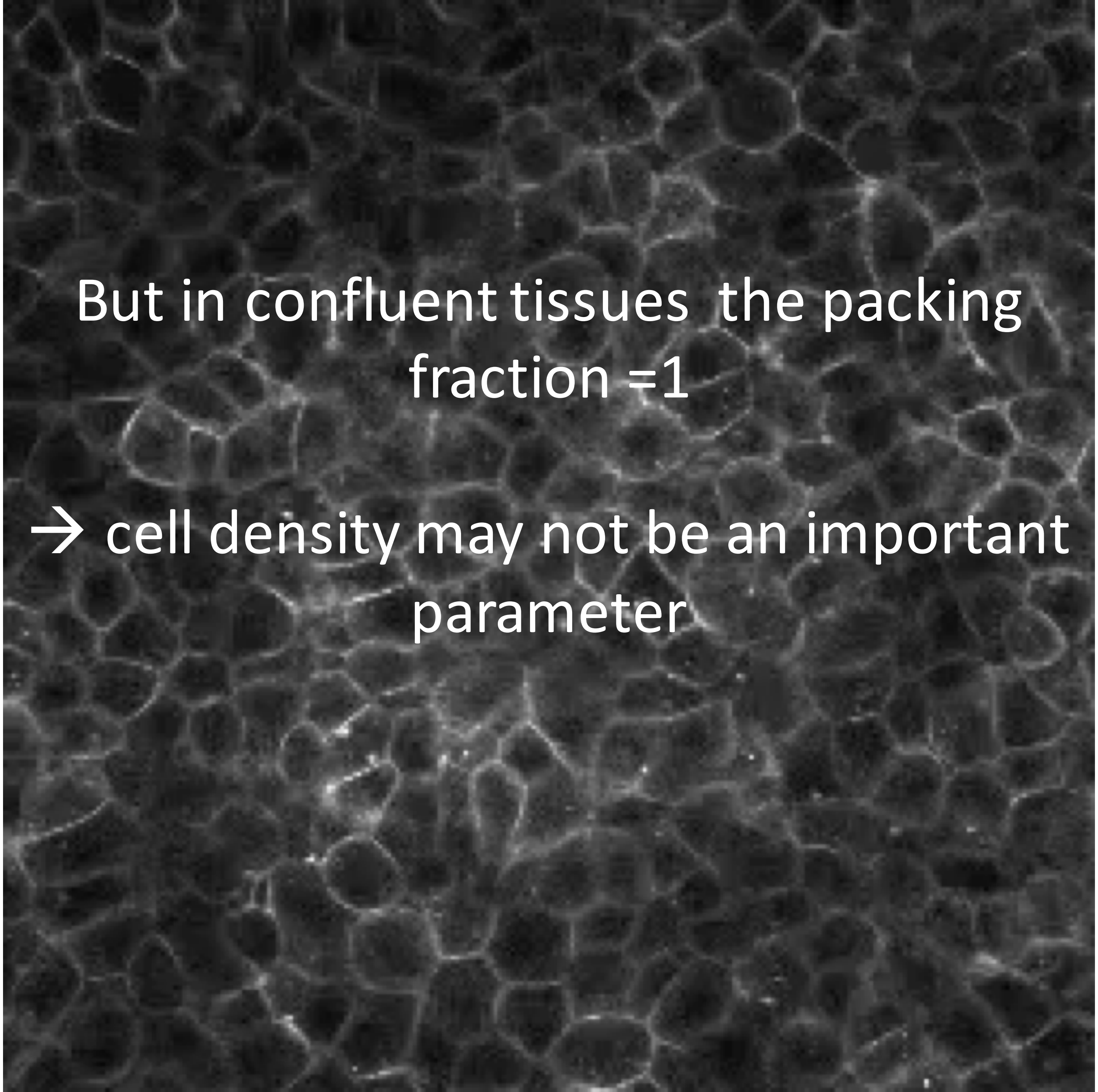
$$u = 0.68$$

Fit: u=0.07 - active particles squeeze through gaps between neighbors at 10% of the passive pressure due to persistent motion → **modes**

Density-driven glass transition of soft SPP

- SPP form glassy states with $D \rightarrow 0$ in spite of finite amplitude driving forces (motility) ≠ external shear
- $\boldsymbol{\varphi}_G$ shifts to higher values with increasing persistence because activity allows particles to explore new dynamical pathways
- Behavior consistent with notion that motility yields an effective attraction (see adhesive colloids)

Do dense cell sheets behave like 2d attractive soft colloids?



But in confluent tissues the packing fraction =1

→ cell density may not be an important parameter

A well-established model: Vertex Model

Nagai et al 2001; Hufnagel et al 2007; Farhadifar et al 2007;
Jülicher et al 2007; ….

$$E = \sum_i \left[\underline{k_A(A_i - A_0)^2} + \underline{k_P P_i^2} \underline{- \gamma P_i} \right]$$

A = area
P = perimeter

3D Incompressibility
+ resistance to
height fluctuations

Contractility

Interfacial tension:

- **adhesion γ>0**
- **cortical tension γ<0**

Nondimensionalize → two model parameters: *r*, *p₀*

$$r = \frac{k_P}{k_A A_0}$$

$$E = \sum_i \left[(a_i - 1)^2 + r(p_i - p_0)^2 \right]$$

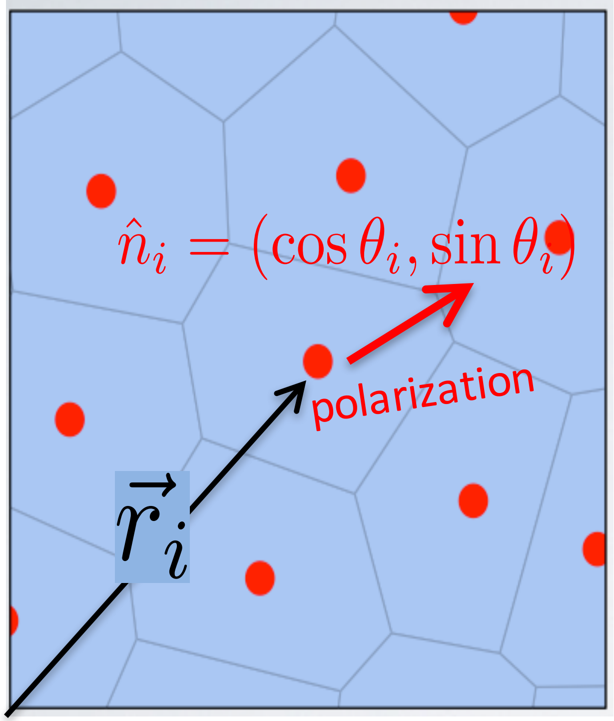
$$p_0 = \frac{P_0}{\sqrt{A_0}}$$

Shape parameter

Vertex + SPP Model → Self-Propelled Voronoi

Bi, Yang, MCM, Manning arXiv 1509.06578

A = area
P = perimeter



- Voronoi tesselation and shape energy:

$$E_{tissue} = \sum_i \left[(a_i - 1)^2 + r(p_i - p_0)^2\right]$$

- Add motility and persistence:

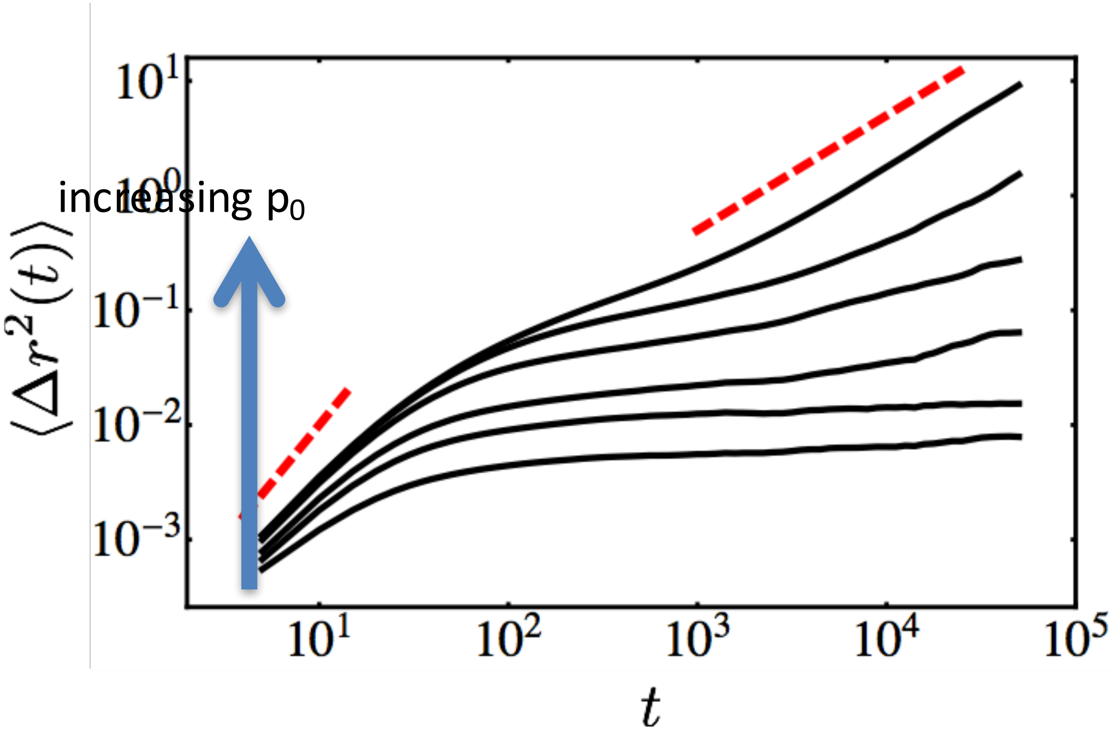
$$\frac{d\vec{r}_i}{dt} = v_0 \hat{n}_i \boxed{- \frac{\partial E_{tissue}}{\partial \vec{r}_i}}$$

$$\frac{d\theta_i}{dt} = \sqrt{2 D_r}\,\eta_i(t) \qquad \langle \eta_i(t)\eta_j(t')\rangle = \delta_{ij}\delta(t - t')$$

Force between cell is multicellular and cannot be expressed as a pairwise interaction

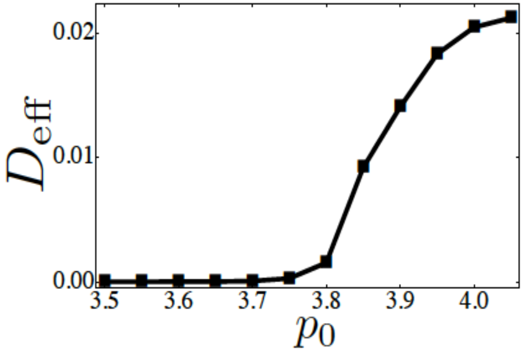
Li & Sun Biophys. J. 2014

Quantifying the dynamics: MSD at fixed motility v_0



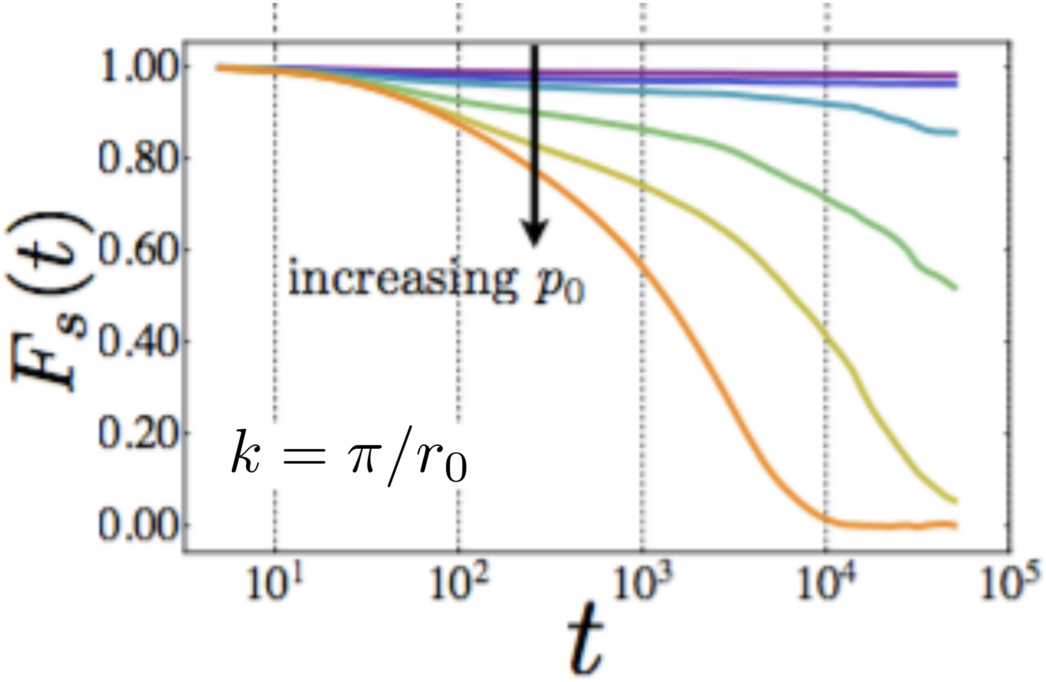
Diffusivity as order parameter:

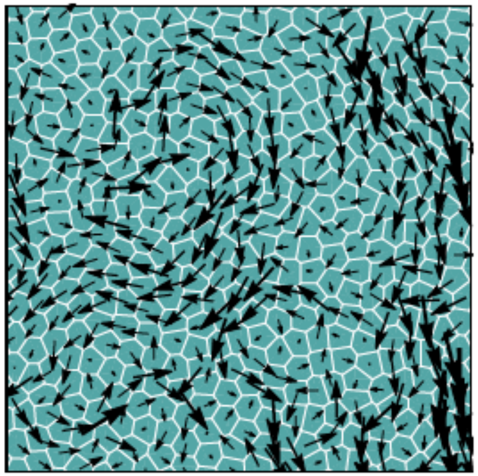
$$D_{eff} = \lim_{t\to\infty} \frac{\langle \Delta \mathbf{r}(t)^2 \rangle}{4t}$$



Intermediate scattering function

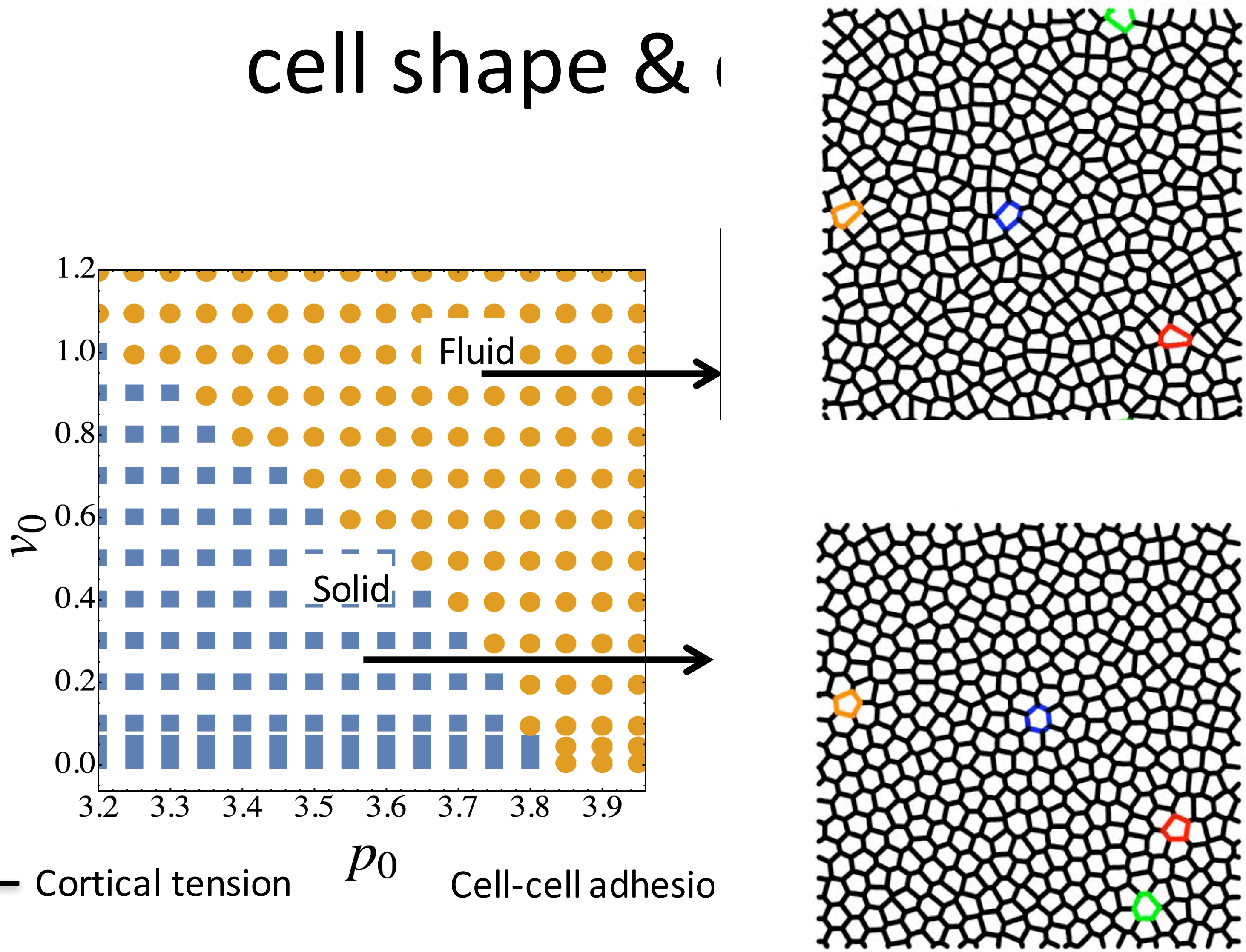
$$F_s(k,t) = \langle e^{i\mathbf{k}\cdot\Delta\mathbf{r}(t)} \rangle$$





Time-averaged displacements very close to glass transition

Liquid-solid transit
cell shape &



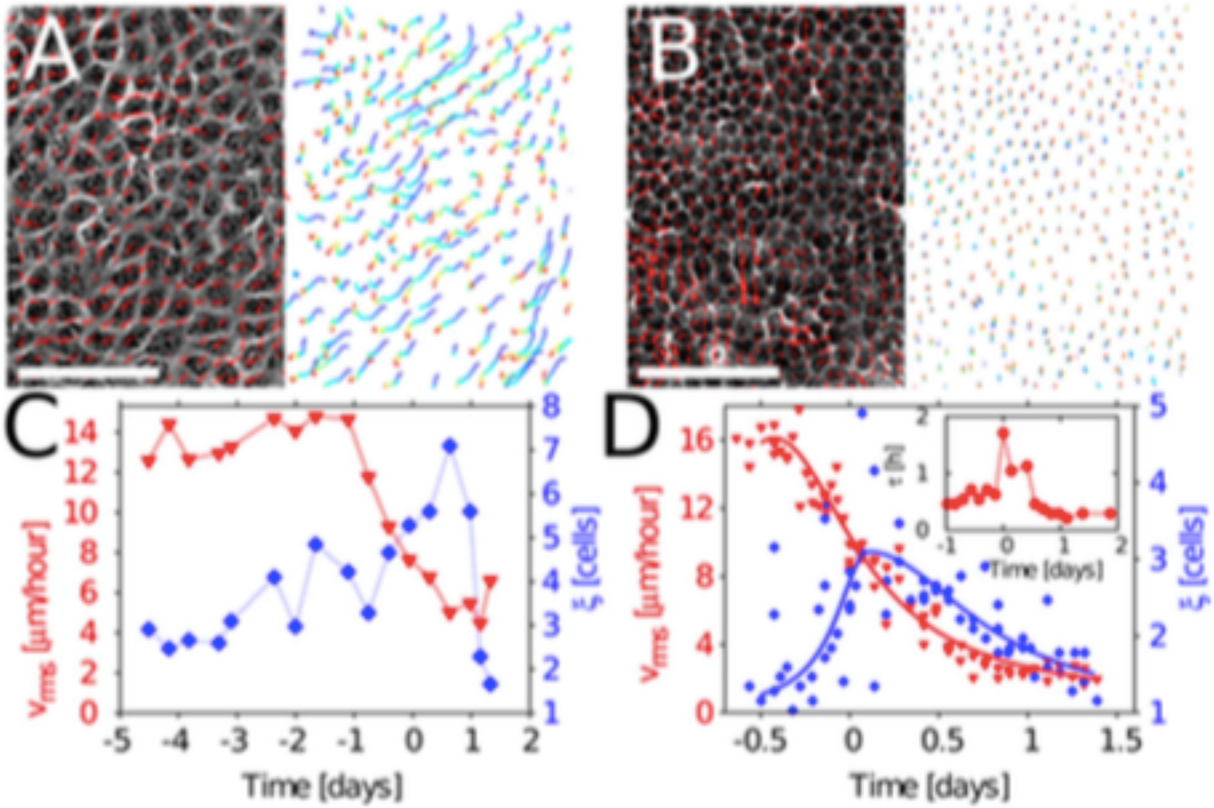
← Cortical tension

Cell-cell adhesio

B

578

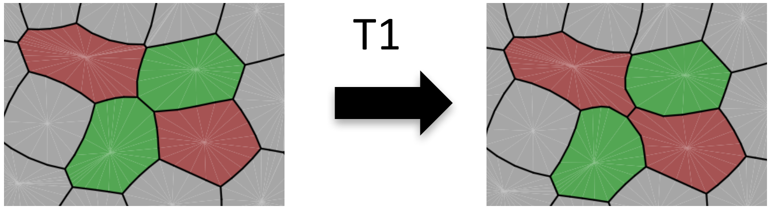
Quantitative correlation between cell motility and cell area in dividing MDCK cells. Puliafito, … Shraiman, PNAS 2012

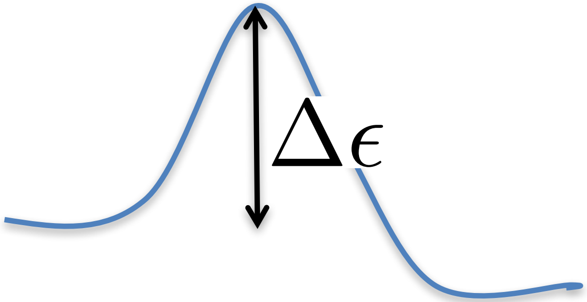


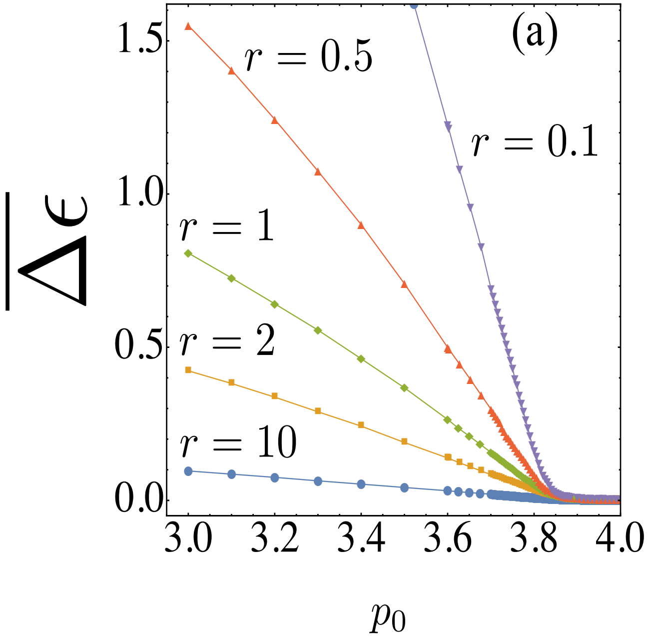
Equilibrium: minimize shape energy

$$\frac{\partial E}{\partial \mathbf{r}_{vertices}} = 0$$

Vanishing of average energy barriers for local rearrangements signals a fluid state

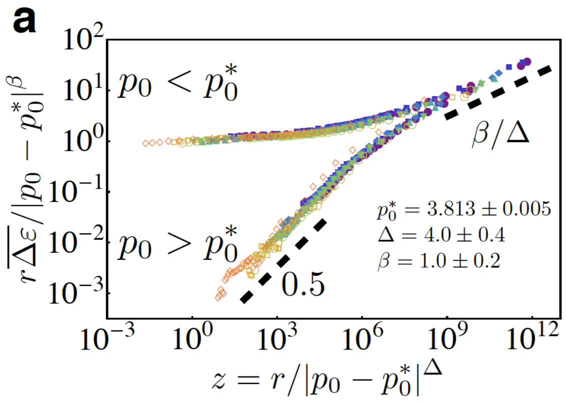


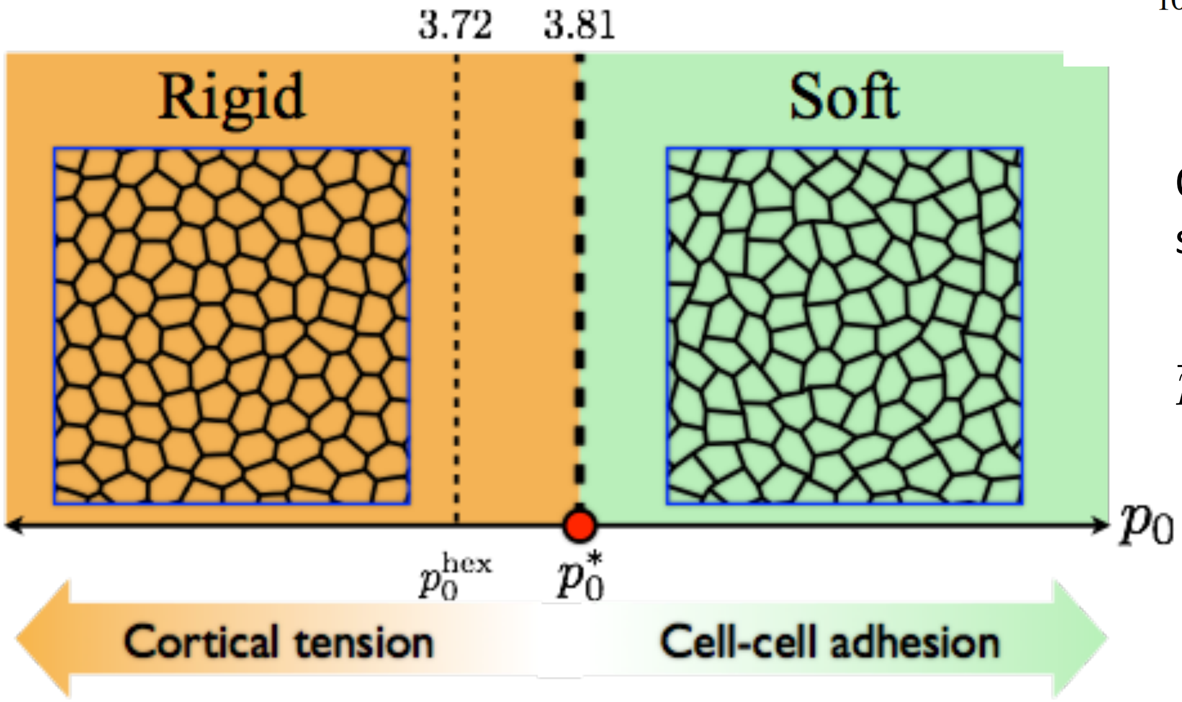




Bi, Lopez, Schwarz, Manning 2014
Park et al, 2015

Solid-liquid transition associated with cell shape anisotropy





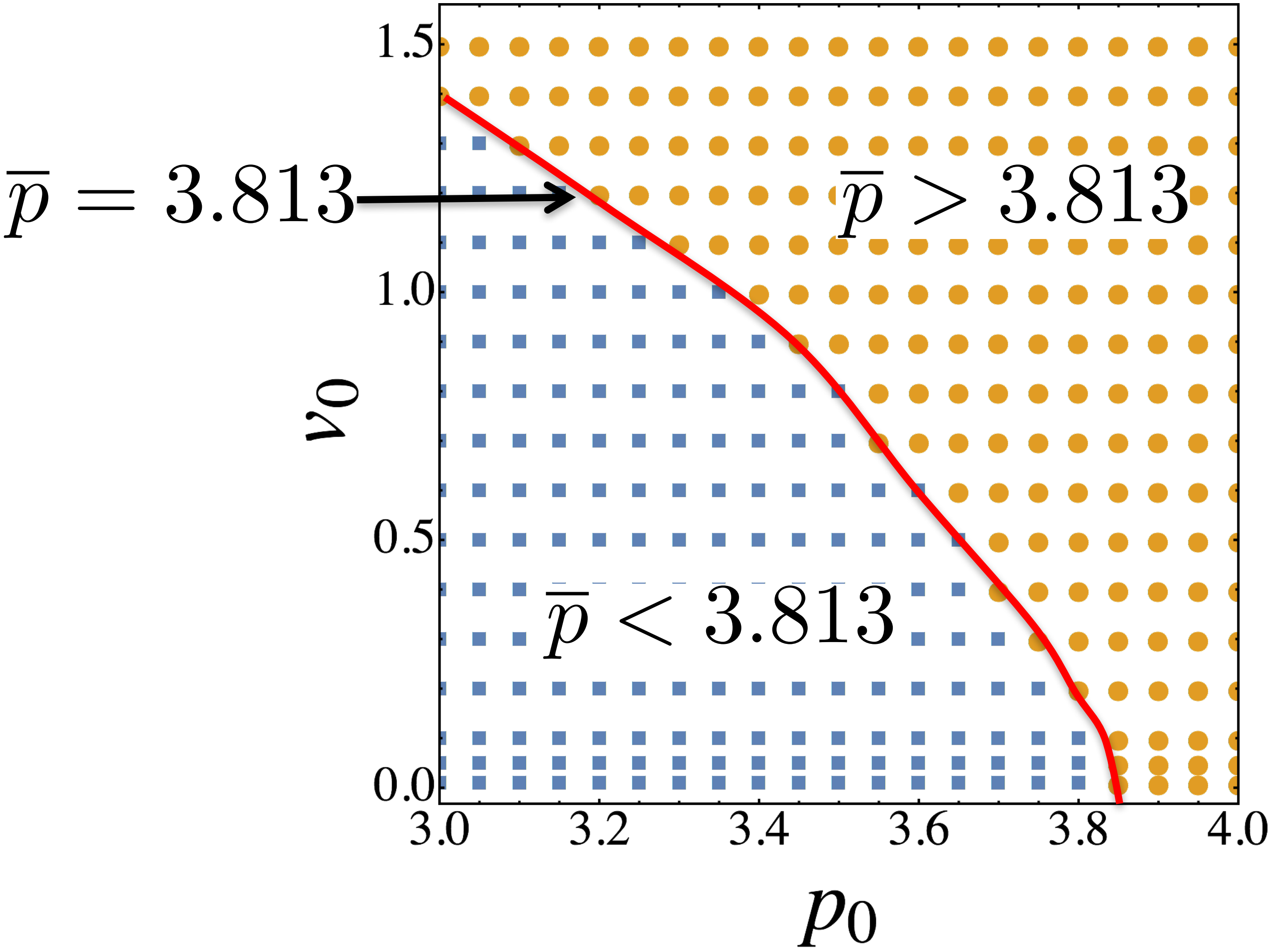
Order parameter:
shape index

$$\overline{p} = \text{median}\{\frac{P_i}{\sqrt{A_i}}\}$$

But this is equilibrium!

Bi, Lopez, Schwarz, Manning 2014
Park et al, 2015

Shape index indicates transition

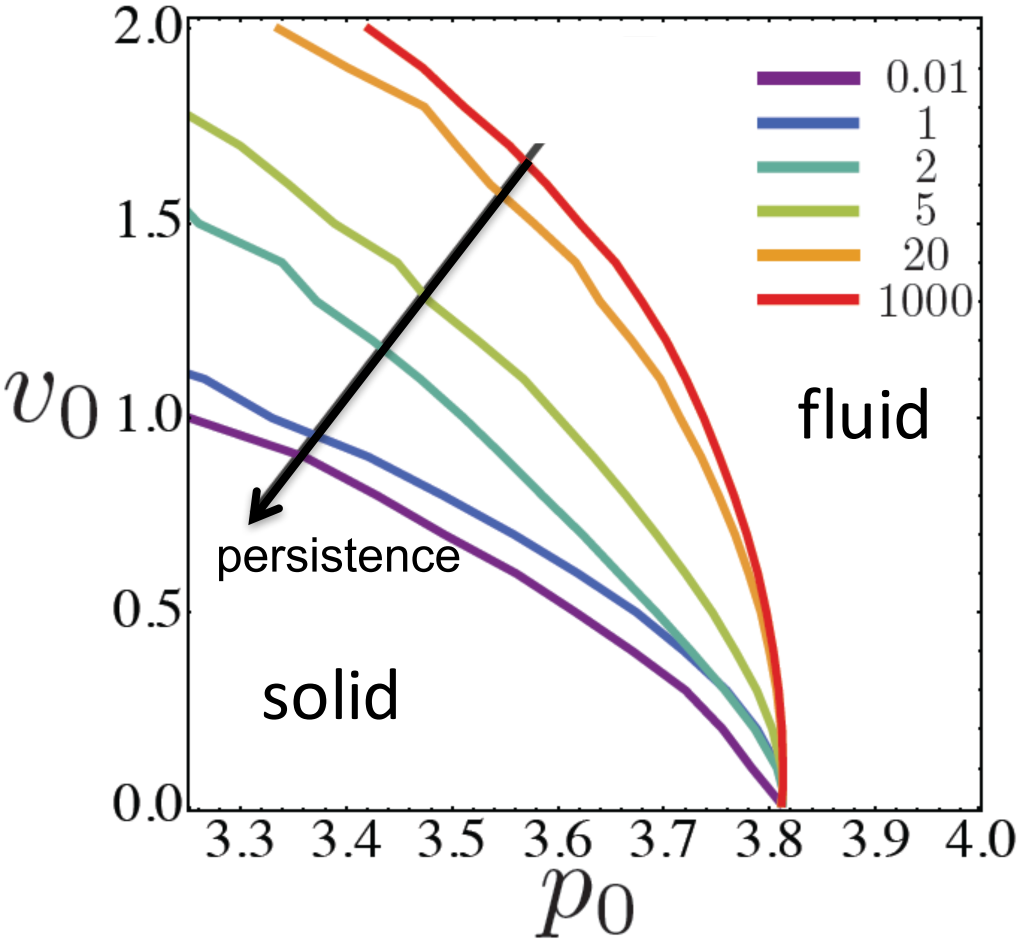


$\bar{p} = 3.813$

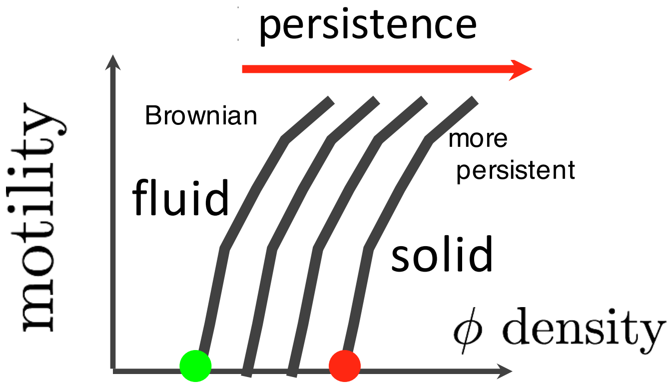
$\bar{p} > 3.813$

$\bar{p} < 3.813$

Changing noise D_r or persistence $1/D_r$



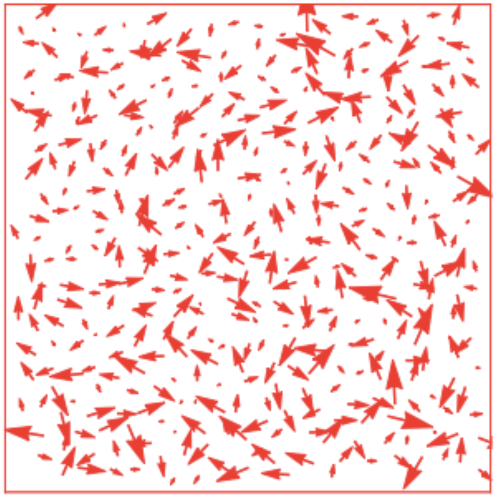
Different from
particle-based models
glass transition shifts with Dr



Berthier PRL 2013
Fily, Henkes & MCM Soft Matter 2014

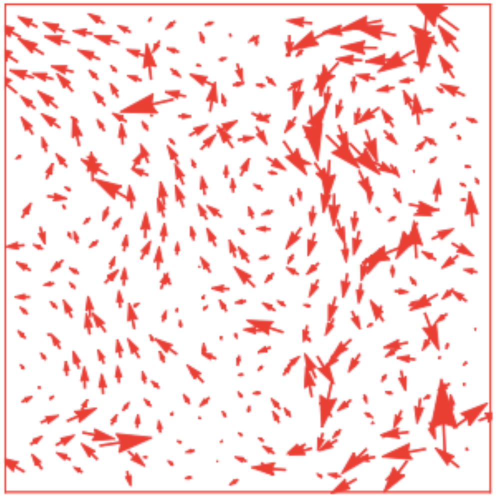
Rearrangements are more collective at small D_r

Instantaneous displacements at p_0=3.65 and v_0=0.5 $\ast$



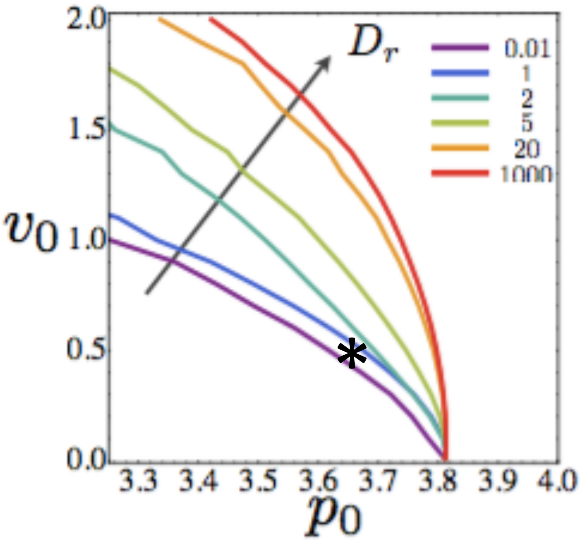
solid: D_r=1

Uncorrelated rattling about mean position



liquid: D_r=0.01

Collective displacements

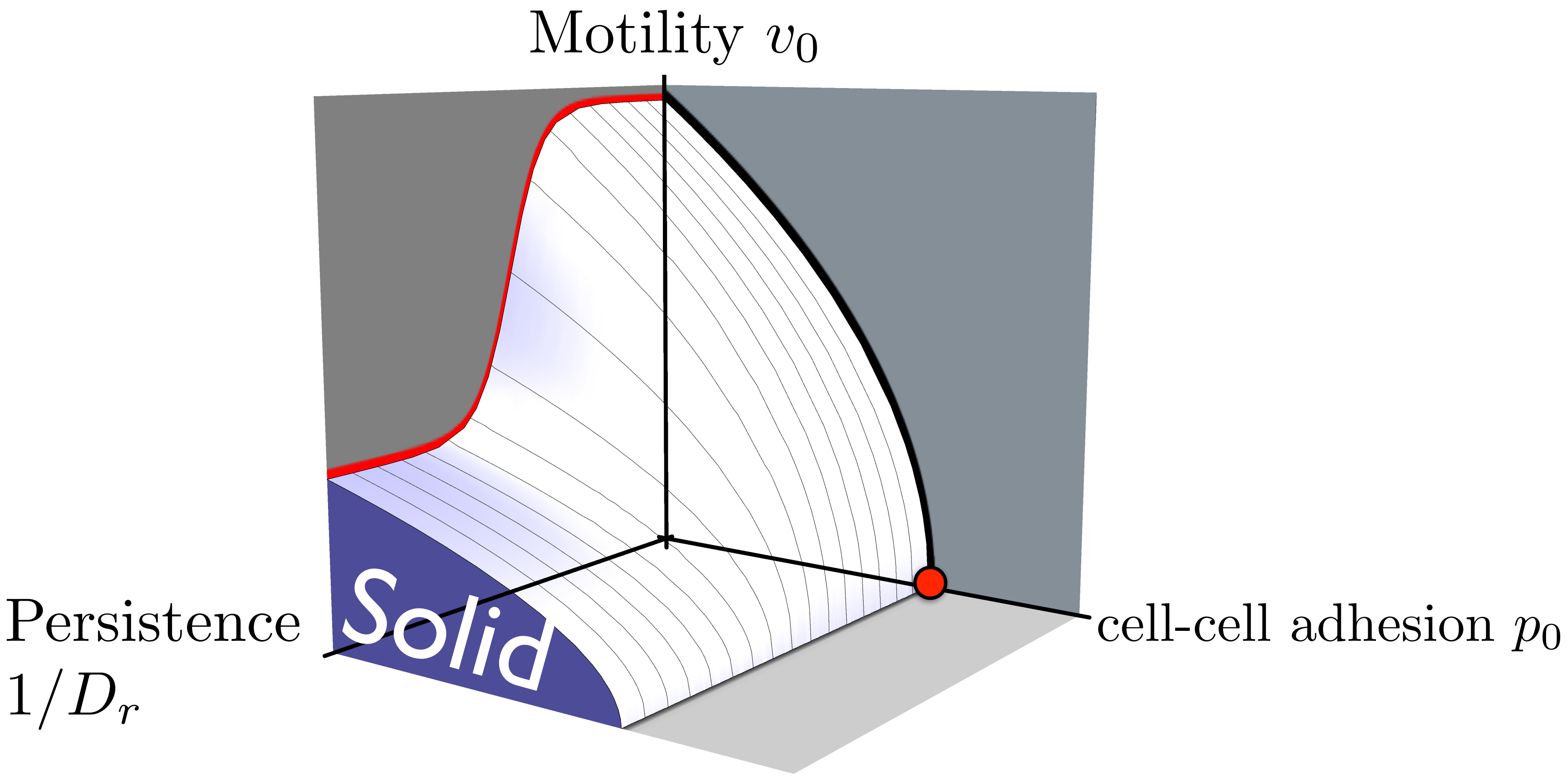


Persistence of cellular dynamics promotes collective rearrangements by providing dynamical pathways not available in equilibrium

Relating structure and mechanics

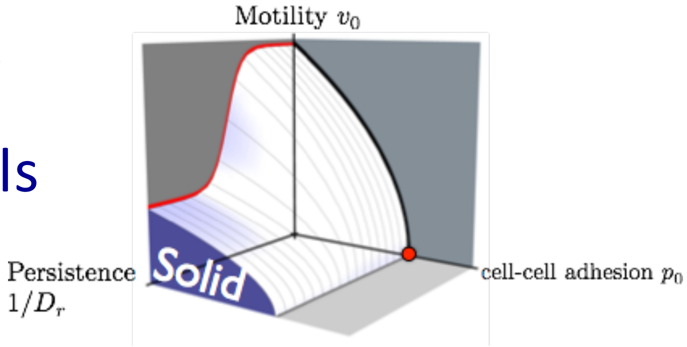
- Correlating dynamical and structural properties: mean shape anisotropy as an order parameter for liquid-solid transition in tissues.
- Cell proliferation and associated contact inhibition of locomotion decrease motility driving the system towards jamming
- Growing correlations (swirls) as transition is approached form the fluid side

Phase diagram for dense tissues



Conclusions & Questions

- SPV: a novel solid-liquid transition of confluent tissues controlled by motility, adhesion and persistence.
- Different from active glasses of SPP
- Role of cell division, heterogeneities, …
- Can the paradigm of tissues as materials help us organize biological data?



- What is the role of tissue rigidity/fluidity in cancer progression and metastatic escape?