2017 Summer School in Condensed Matter Physics

Lecture notes

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Models for understanding glassy behavior in Biological tissues

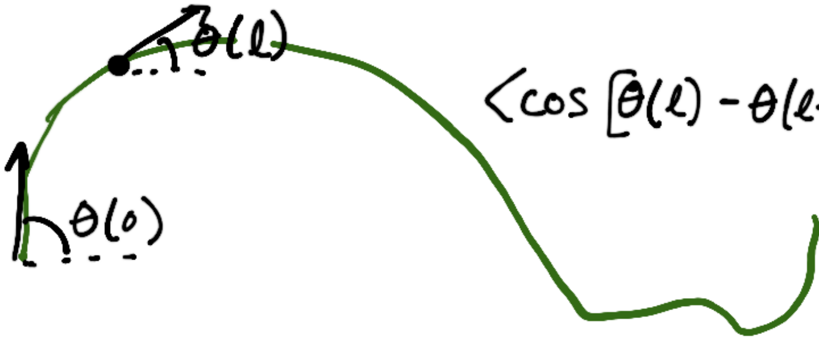
A. Glassy dynamics have been observed in experiments on biological tissues

B. How to model?

Must include two components:

1. interactions between cells
   - cells do not usually overlap (steric repulsion)
   - cells adhere to one another
   - cells may polarize (have a front + back)
     ↳ could align

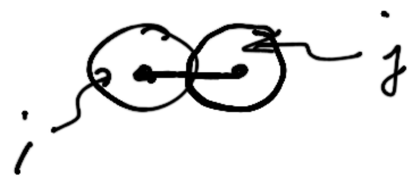
2. activity
   - cells locomote
     → crawl on each other or on a substrate
     → typically polarized, so they have a persistence length L
   - cells may change shape, tensions, etc



$$\langle \cos[\theta(\ell) - \theta(\ell+\ell')] \rangle \equiv e^{-(\ell'/L)}$$

C. Self-propelled particle models:

1. Interactions like in Ludo's talk:



$$V_{ij} = V(|\vec{r}_i - \vec{r}_j|) \equiv V(r_{ij})$$

Example: $V(r_{ij}) = 4\varepsilon\left[\left(\frac{\sigma}{r_{ij}}\right)^{12} - \left(\frac{\sigma}{r_{ij}}\right)^{6}\right]$

or

$$V(r_{ij}) = \begin{cases} \epsilon\left[1 - \frac{r_{ij}}{\sigma}\right]^{\alpha} & r_{ij} < \sigma \\ 0 & \text{o.w.} \end{cases}$$

2. Activity:

$$\cancel{m\frac{dv_i}{dt}} = F_{int} + F_{propelled} + F_{drag} + \cancel{F_{noise}}$$

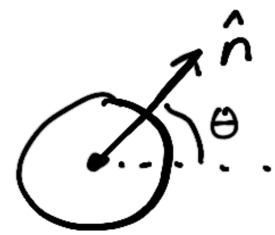
$$0 \qquad \sum_j -\frac{\partial V(r_{ij})}{\partial r_i} + F_0\hat{n}_i - bV_i \qquad 0$$

"over damped limit"
inertial effects negligible compared to drag

$$\Rightarrow \frac{dr_i}{dt} = \frac{F_0}{b}\hat{n}_i - \frac{1}{b}\sum_j \nabla_i V(r_{ij})$$

$$\boxed{\dot{r}_i = v_0\hat{n} - \mu\sum_j \nabla_i V(r_{ij})}$$

$\hat{n}_i$ is a vector that rotates:



$$\hat{n}_i = \cos\theta_i \hat{x} + \sin\theta_i \hat{y}$$

$$\dot{\theta}_i = \eta_i \quad \text{← white noise:}$$

$$\boxed{\text{For non-interacting system} \quad Pe = \frac{v_0}{2RD_r} = \frac{L}{2R}}$$

$$\langle \eta_i(t) \rangle = 0 \qquad \langle \eta_i(t)\, \eta_j(t') \rangle = 2D_r\, \delta_{ij}\, \delta(t-t')$$

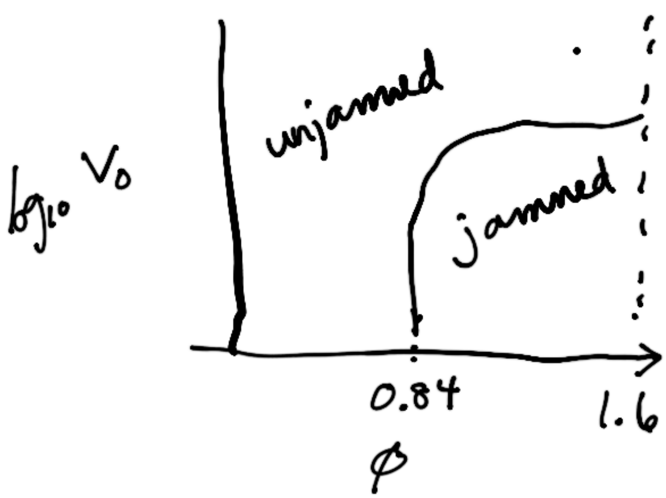
3. Lots of interesting stuff happens in these models.

⇒ Broad overview: *Hydrodynamics of soft active matter.* Marchetti et al Rev. Mod. Phys 85 1143 (2013)

⇒ Motility Induced Phase separation
Cates and Tailleur. ARCMP 6 219 (2015)

⇒ Glassy dynamics

2D { Henkes et al PRE 84 (2011)
Berthier PRL 112 (2014)



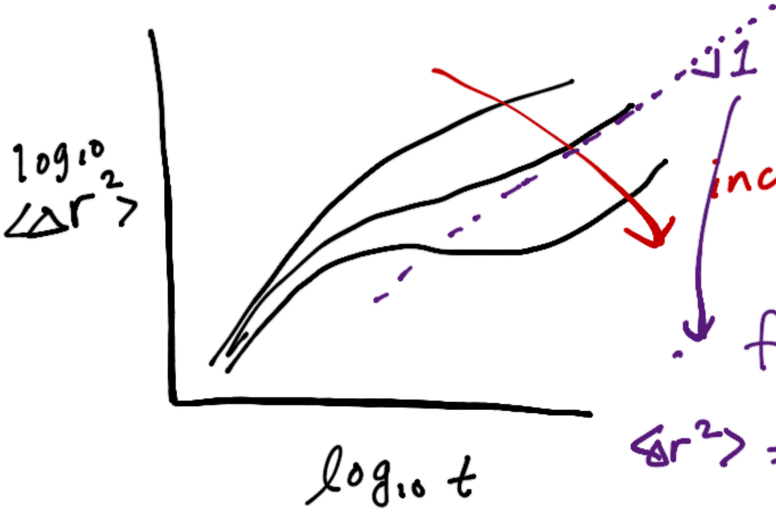
<u>Control parameters:</u>

v_0 (energy scale)

D_r (rotational diffusion)

$$\phi = \sum_i \frac{\pi \sigma_i^2}{R^2}$$

packing fraction → ϕ; box area → R^2; repulsive disk area → $\pi\sigma_i^2$



increasing ϕ

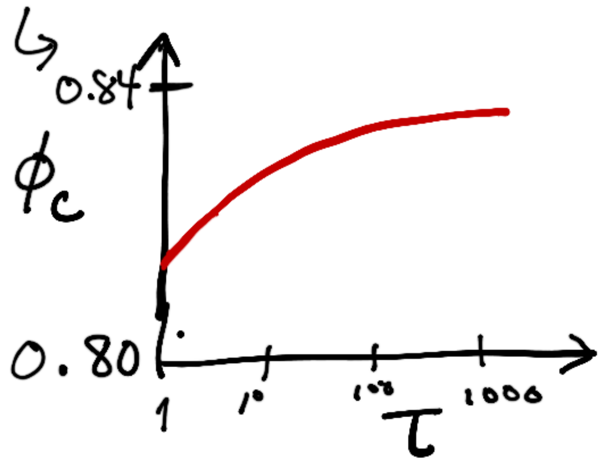
$\tau \sim \frac{1}{D_r}$

fit the long-time behavior to

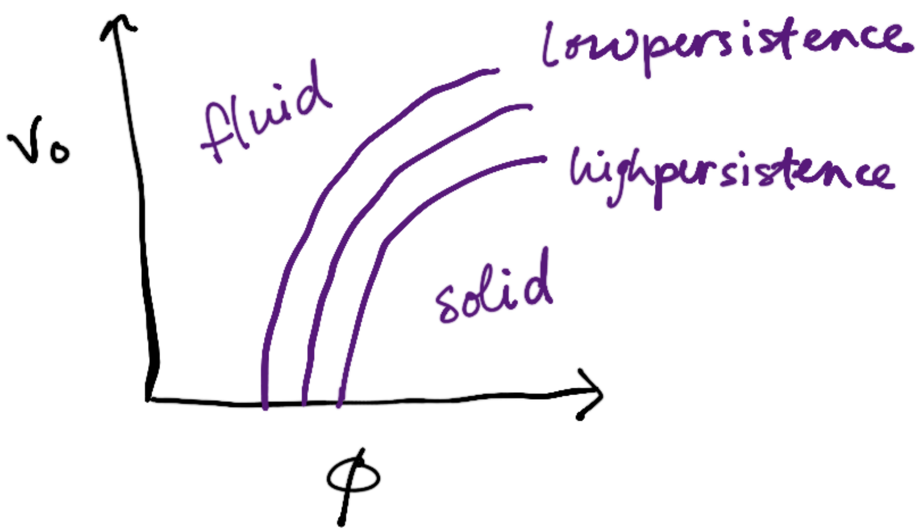
$\langle \Delta r^2 \rangle = 4 D_s(\tau, \phi)\, t$

long-time diffusion of particle.

Ansatz: $D_s(\tau, \phi) = |\phi_c(\tau) - \phi|^{\gamma(\tau)}$



$\Rightarrow$ ϕ_c changes as a function of $\tau \sim \frac{1}{D_r}$!



one can take a formerly solid state into a fluid state just by changing D_r.

D. Vertex models

Note: I am skipping some other really nice models for tissues, including subcellular element models, cellular potts models, finite element models...

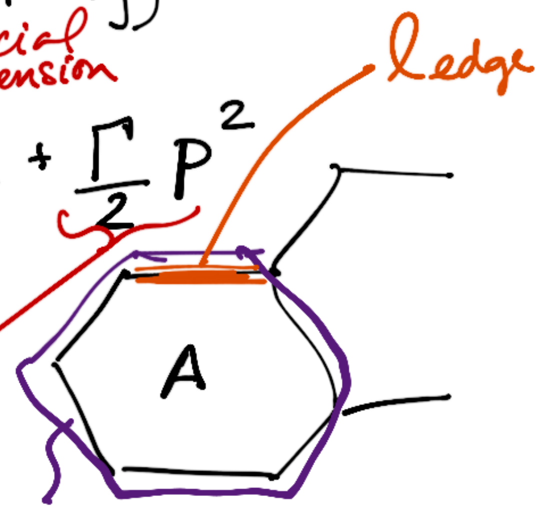
1. Zero-motility limit (no activity)

interfacial tension

a. $$E_{cell} = \underbrace{\frac{K_A}{2}(A-A_0)^2}_{} + \sum_{edges} \overbrace{\frac{\Lambda}{2}}^{} l_{edge} + \underbrace{\frac{\Gamma}{2}}_{} P^2$$

$$P \equiv \sum_{edges} l_{edge}.$$

3D incompressibility + height fluctuations



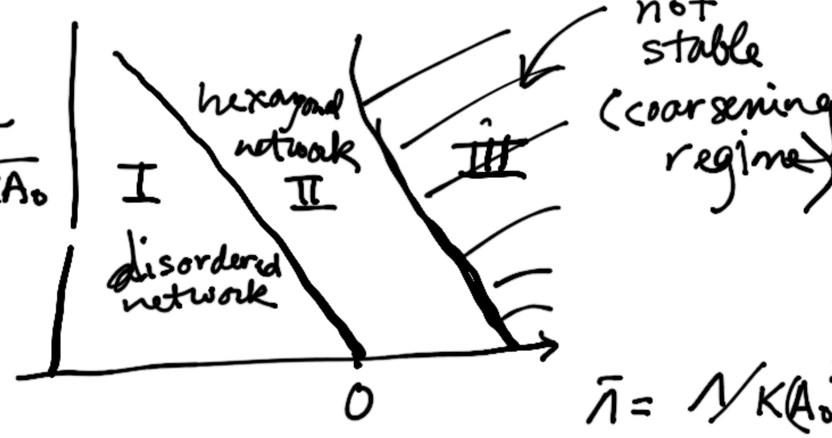
"contractility" or "limited adhesion molecules"

Farhadifar et al Current Biology 17 2007

Note: lots of others before this. Honda, Hufnagel

b. Ground states:

$\bar{\Gamma} = \frac{\Gamma}{KA_0}$



$\bar{\Lambda} = \Lambda / K(A_0)^{3/2}$

c. For physicists, it is much easier in case where all Λ's are the same and so we can rewrite this as

$$E_{cell} = K_A (A - A_0)^2 + K_P (P - P_0)^2$$

where $P_0 = -\frac{\Lambda}{2\Gamma}$ and $K_A = \frac{K_A}{2}$

$K_P = \frac{\Gamma}{2}$

$$\mathcal{E}_{tot} = \frac{1}{K_A A_0^2} \sum_1^N E_i = \sum_1^N \left[(a_i - 1)^2 + \frac{1}{r} (p_i - p_0)^2 \right]$$

with $\underbrace{r = \frac{K_A A_0}{K_P}}_{\text{stiffness ratio}}$ and $p_0 = \frac{P_0}{\sqrt{A_0}}$. ← shape index

Homework Exercise:

calculate the algebraic expressions for the lines shown in the phase diagram for the ground states.

Hint: In phase I $p_i = p_0$, $a_i = 1$ $\forall i$

In phase II p_i can be related to a_i $\forall i$

In phase III $p_i = 0$ $a_i = 0$

d. This is a good model for confluent tissues.

also really fun system for exploring disordered solidification in a system that is very different from sphere packings

e. Beyond ground states

→ biological tissues very rarely look ordered.

→ need to generate an ensemble of higher energy states

→ numerically, can do an "infinite temperature quench", take a voronoi tessellation of uniformly distributed points, and find nearest minimum using gradient or conjugate gradient descent

$$\mu \dot{\underbrace{r_i}_{\text{vertex position } i}} = -\nabla_i \varepsilon$$

→ Program ~~es~~ "Surface Evolver" has built in functions to do this, or you can write your own

f. Linear Response

- Calculate the shear modulus around a minimum energy state

- For simple shear, describe deformation of the box γ

- $\varepsilon = \varepsilon(\{\vec{r}_i\}, \gamma)$

$$\mathcal{E}_{min}(\gamma) = \min_{\{r_i\}} \mathcal{E}(\{r_i\}, \gamma)$$

$$g \equiv \frac{1}{V} \frac{d^2 \mathcal{E}_{min}(\gamma)}{d\gamma^2}$$

vertex index $(1 \ldots N)$

$$g = \frac{1}{V}\left(\frac{\partial^2 \mathcal{E}}{\partial \gamma^2} + \sum_{k,\beta} \frac{\partial^2 \mathcal{E}}{\partial r_k^\beta \partial \gamma} \dot{r}_k^{min,\beta}\right) \qquad \dot{r}_k^{min,\beta} = \frac{dr_k^{min,\beta}}{d\gamma} \qquad (\star)$$

dimension index (x, y)

→ Want to re-write this in terms of the dynamical matrix introduced by Ludo:

labels dimensions

$$D_{j\alpha, k\beta} \equiv \frac{\partial^2 \mathcal{E}}{\partial r_j^\alpha \partial r_k^\beta}$$

labels vertices

eigenvalues ≥ 0

$$= \sum_m \omega_m^2 \, u_{j\alpha}^m u_{k\beta}^m$$

$m = (1 \ldots Nd)$ eigenvectors

but force balance means

$$0 = \frac{\partial \mathcal{E}(r^{min}(\gamma), \gamma)}{\partial r_j^\alpha}$$

taking total derivative w.r.t γ:

$$0 = \sum_{k,\beta} D_{j\alpha, k\beta} \, \dot{r}_k^{min,\beta} + \frac{\partial^2 \mathcal{E}}{\partial r_j^\alpha \partial \gamma} \qquad (\star\star)$$

Let $\bar{D}_{pq} = \frac{\partial^2 \mathcal{E}}{\partial z_p \partial z_q}$ where $z_p = \underbrace{(\vec{r}_1 \cdots \vec{r}_N, \gamma)}_{3N+1\text{ - dimensional}}$

$$\bar{D}_{pq} = \sum_m \bar{\omega}_m^2 \, \bar{u}_p^m \, \bar{u}_q^m$$

and $\dot{z}^{min} \equiv (\dot{r}_1^{min} \ldots \dot{r}_{Nd}^{min}, 1)$.

Note that using ✪✪, we can re-write ✪ as:

$$V g \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ \vdots \\ 1 \end{bmatrix} = \begin{bmatrix} & D_{j\alpha,k\beta} & & \frac{\partial^2 \mathcal{E}}{\partial \gamma \partial r_1} \\ & & & \vdots \\ \frac{\partial^2 \mathcal{E}}{\partial r_1 \partial \gamma} & \cdots & & \frac{\partial^2 \mathcal{E}}{\partial \gamma^2} \end{bmatrix} \begin{bmatrix} \dot{r}_1^{min} \\ \vdots \\ \dot{r}_{Nd}^{min} \\ 1 \end{bmatrix}$$

OR

$$V g \, \delta_{\gamma p} = \bar{D}_{pq} \, \dot{z}_q^{min}$$

Take scalar product with $\bar{u}_p^m$:

$$V g \, \bar{u}_\gamma^m = \bar{\omega}_m^2 \sum_q u_q^m \, \dot{z}_q^{min} \quad \forall m \quad ✪✪✪$$

Comment 1: if $\exists$ a zero mode $\tilde{m}$ with $u_\gamma^{\tilde{m}} \neq 0$ (e.g. non-zero overlap with shear DOF)

then $g = 0$.

Comment 2: otherwise, all zero modes have vanishing overlap with the shear degree of freedom so the shear must be the sum over remaining e-vectors:

m non-zero

$$\delta_{\gamma q} = \sum_{\substack{m \text{ with} \\ \text{nonzero } \omega_m}} \bar{u}^m_\gamma \bar{u}^m_q \quad \Rightarrow \quad 1 = \sum_{m,q} \bar{u}^m_\gamma \bar{u}^m_q \dot{z}^{\overline{min}}_q$$

(because $\dot{z}^{min}_\gamma = 1$)

Define $\{\tilde{m}\}$ as m s.t. $\omega_m \neq 0$.

Inserting eq ~~***~~ we find

$$1 = \sum_{\tilde{m}} \bar{u}^m_\gamma \underbrace{\sum_q u^m_q \dot{z}^{min}_q}_{\frac{V g\, u^m_\gamma}{\bar{\omega}_m^2}} \Rightarrow 1 = Vg \sum_{\tilde{m}} \frac{\bar{u}^m_\gamma}{\bar{\omega}_m^2}$$

$$\Rightarrow \boxed{g = \frac{1}{V}\left[\sum_{\tilde{m}} \frac{(\bar{u}^m_\gamma)^2}{\omega_m^2}\right]^{-1}}$$

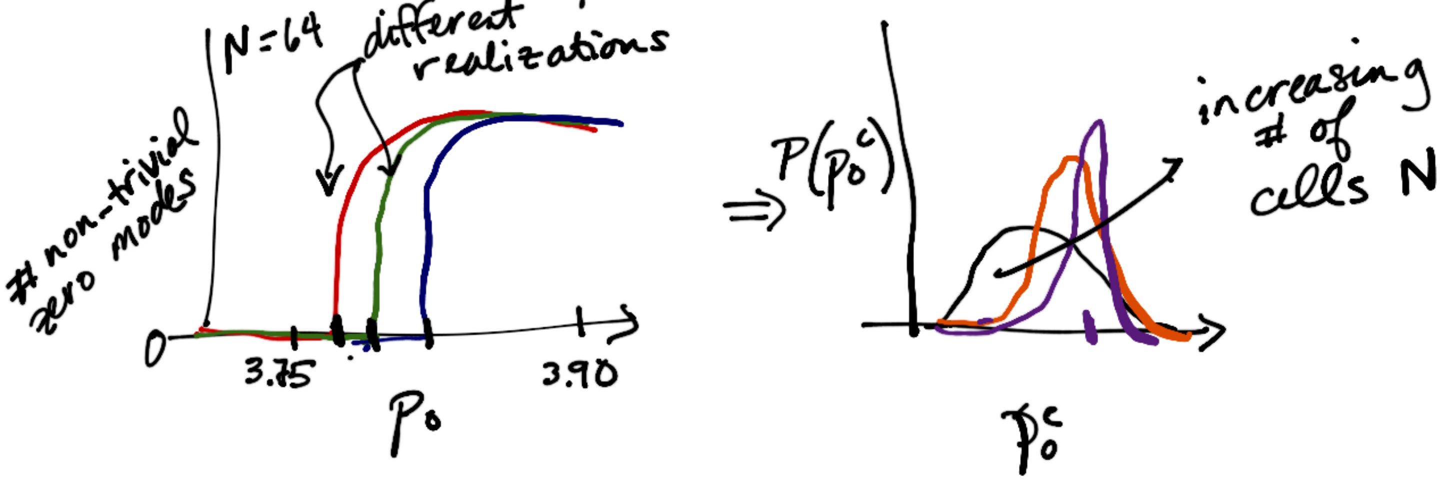
if no non-trivial zero modes.

Result

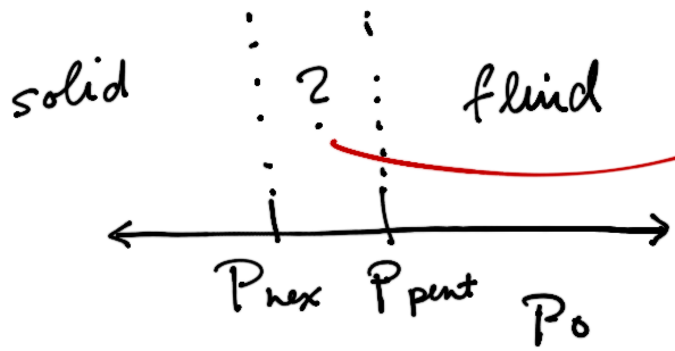
$$g = \begin{cases} 0 \text{ if } \exists \text{ a nontrivial zero mode} \\ \text{otherwise, its a weighted sum of overlaps of eigenvectors with shear D.O.F} \end{cases}$$

Easiest to quantify the number of non-trivial zero modes: for <u>ordered</u> ground states, Staple et al EPJE 2010 demonstate that the system is linearly stable below $p_0 = p_{hex} \cong 3.72$

For disordered states, we can numerically calculate the number of zero modes as a function of p_0 for different realizations of the disorder:



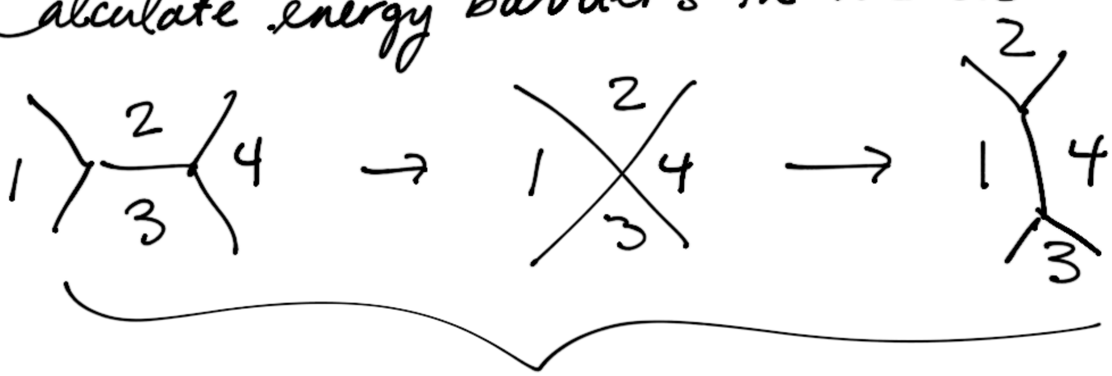
extrapolate and find $\lim_{N\to\infty} \overline{p_0^c} = p_0^* \cong 3.81 \cong p_0^{pent}$



hexagons linearly unstable
but disordered states linearly stable

g. Nonlinear response:

Calculate energy barriers for localized rearrangements

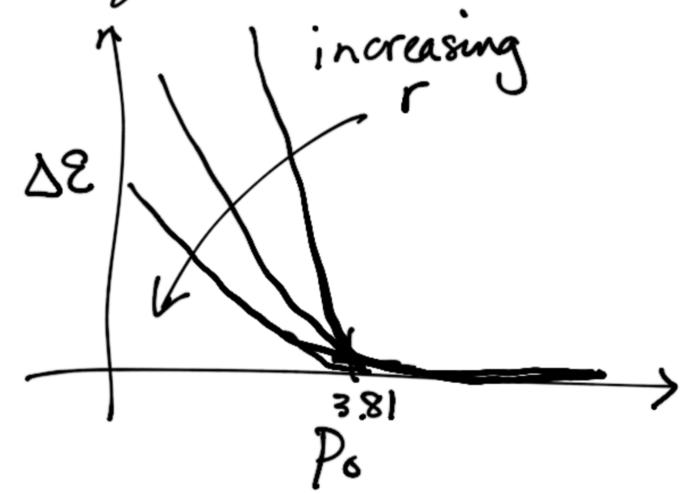


T_1 transition

→ execute T_1 transition by shortening 1 edge + extending in other direction (other transition paths possible)

→ minimize global energy (allowing passive T_1 transitions elsewhere)

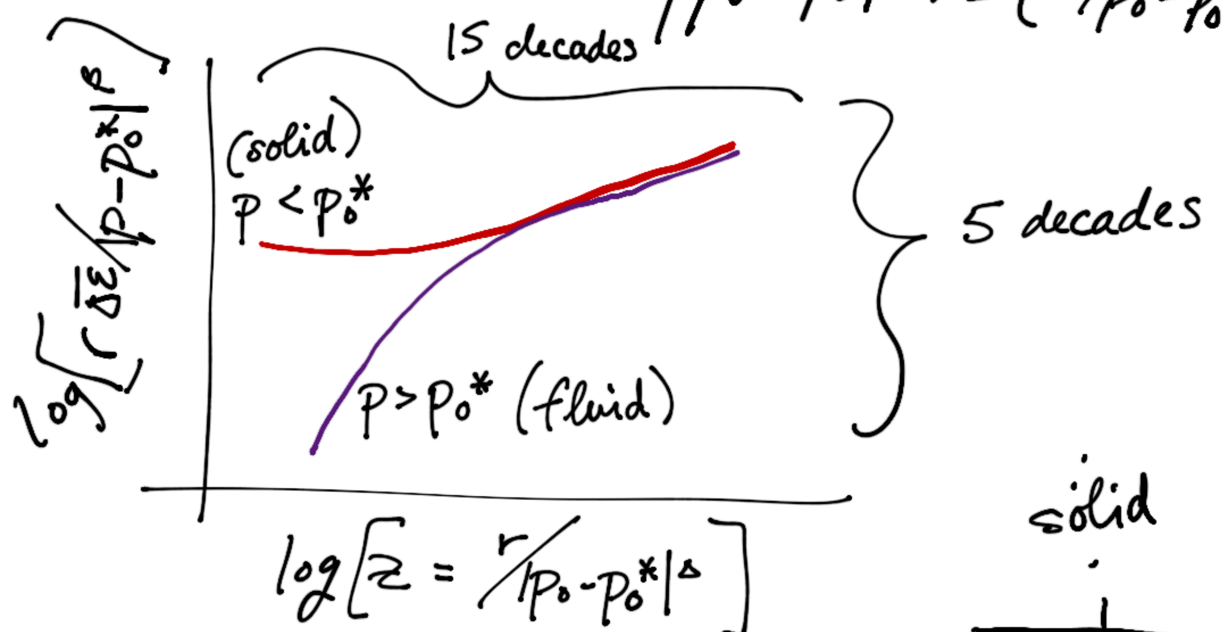
Result

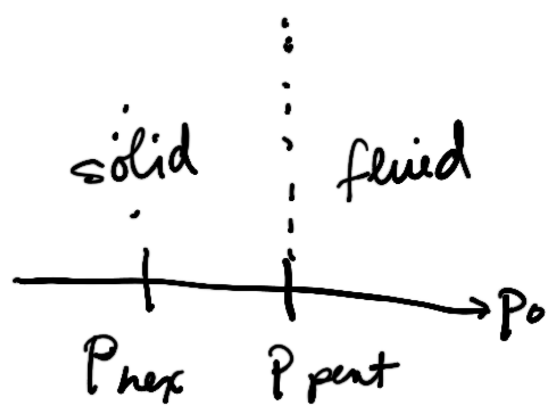


Scaling ansatz: just like $(m, h, T-T_c)$ in Ising model

$(r\overline{\Delta\varepsilon}, r, p_0 - p_0^*)$ here ⇒

$$r\,\overline{\Delta\varepsilon} = |p_0 - p_0^*|^\beta f_\pm\left(\frac{r}{|p_0 - p_0^*|^\Delta}\right)$$



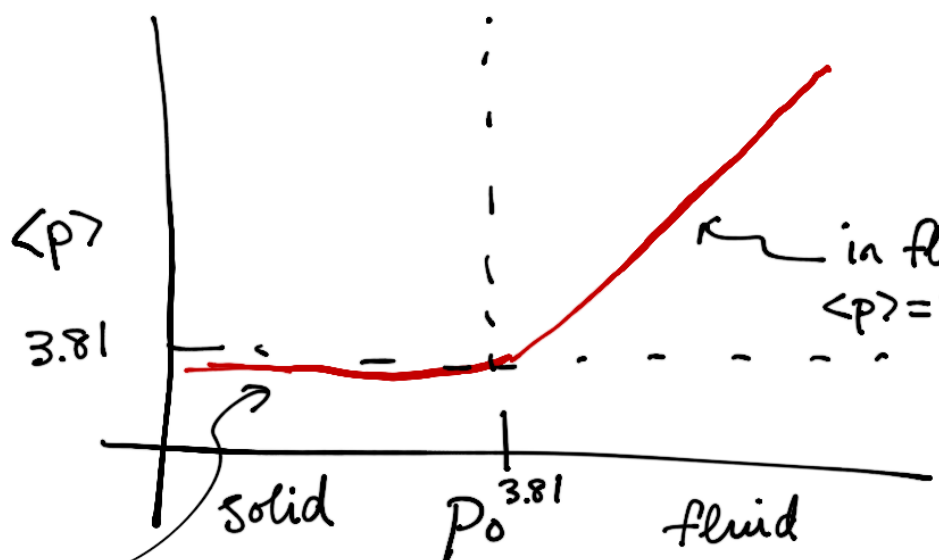


Interesting: energy barriers seem to go to zero
at same location as shear modulus goes to zero.

h. Structural Order parameter:

Unlike particulate matter, vertex models have a **structural order parameter** for the transition:

$\langle p \rangle$ = observed perimeter-to-area ratio



in fluid $\langle p \rangle = p_0$ and $E = 0$

In solid
$p \neq p_0$
$E > 0$

Idea: perhaps rigidity occurs because system cannot minimize its perimeter below some value (e.g a minimal surface)

This idea seems to be precisely true in 3D.
(more later.)

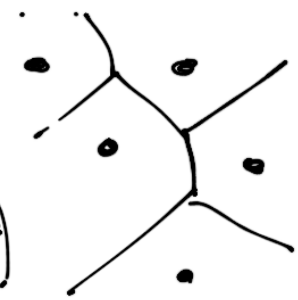
2. Adding activity
   → work in progress
   → developed voronoi models to simplify activity

E. Voronoi models:

1. Model description.

DOF are cell centers: $\vec{r}_i$

cell shapes are given by a voronoi tessellation (Wigner-Seitz cell)



- interactions are driven by cell shapes according to usual energy functional:

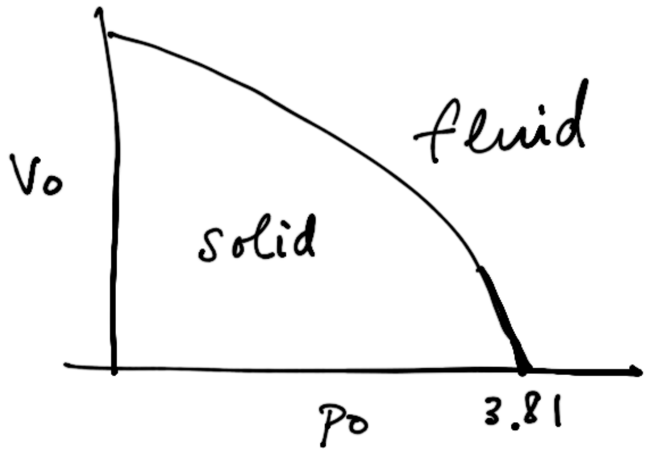
$$E = \sum_i^N \left[K_A (A - A_0)^2 + K_P (P - P_0)^2 \right]$$

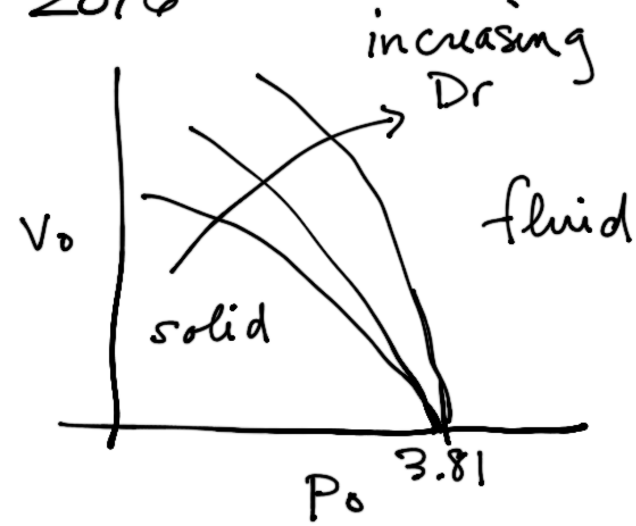
- cells move according to overdamped dynamics + self-propelled part:

$$\frac{d\vec{r}_i}{dt} = \mu \vec{F}_i + v_0 \hat{n}_i$$

$$\vec{F}_i = -\vec{\nabla}_i E \qquad \partial_t \theta_i = \text{white noise with strength } D_r.$$

2. 2D Results: Bi et al PRX 2016





Comment 1: It appears that lim $v_0 \to 0$ $p_0^* = 3.81$
e.g. glass transition in SPV and jamming transition in vertex model occur at same p_0^*.
but, lots of ongoing work on this. May just be close.

Comment 2: Dr doesn't appear to change p_0^*, unlike SPP results where Dr changes ϕ_G.

Comment 3: Structural order parameter still works.

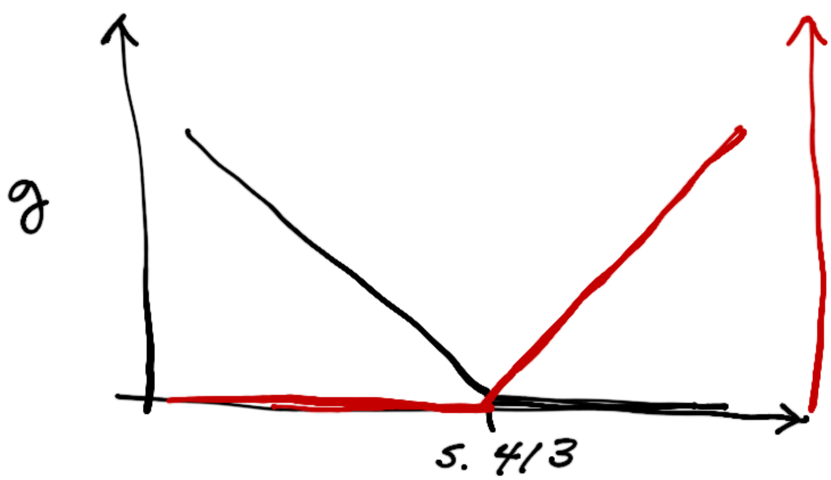
MSD (dynamical data)
matches
shape index $\langle p \rangle$

3. 3D Results : Merkel + Manning, ArXiv 2017

'zero temperature' $\to$ $v_0 = 0$

$$E = \sum_i \left[K_V (V_i - V_0)^2 + K_S (S_i - S_0)^2 \right]$$

$$s_0 = \frac{S_0}{\langle V \rangle^{2/3}} = \text{3D shape index} \quad \Big| \quad \langle S \rangle = \frac{\langle S_i \rangle}{\langle V \rangle^{2/3}}$$



Same as in 2D $\Rightarrow$

$\langle S \rangle$ structural order parameter.

= average observed shape index

s_0

4. Rigidity in these systems different from jamming.

When do the number of constraints = number DOF ?

not exactly correct $\to$?

$$2N \left(\begin{matrix} 1 \text{ volume constraint} \\ 1 \text{ surface constraint} \end{matrix} \text{ per cell} \right) = \underset{\text{SPV in 3D}}{3N}$$

underconstrained?

Better :

$$\bar{D}_{pq} = 2 \sum_i \Bigg[\underbrace{\frac{\partial s_i}{\partial z_p} \frac{\partial s_i}{\partial z_q} + K_V \frac{\partial v_i}{\partial z_p} \frac{\partial v_i}{\partial z_q}}_{\text{spring terms}} + \underbrace{\underbrace{(s_i - s_0)}_{\text{surface tension}} \frac{\partial^2 s_i}{\partial z_p \partial z_q} + \underbrace{K_V (V_i - 1)}_{\text{pressure}} \frac{\partial^2 V_i}{\partial z_p \partial z_q}}_{\text{residual stresses}} \Bigg]$$

Numerical observation: residual stresses "turn on" precisely at the rigidity transition.

$\Rightarrow$ spring terms remain constant across transition.

Observation: $\left.\begin{matrix} s = s_0 \\ v = 1 \end{matrix}\right\}$ for all cells in fluid

so variances $\langle \sigma_s \rangle, \langle \sigma_v \rangle = 0$.

Since energy functional drives residual stresses to zero, non-zero stresses suggest there is no possible state where $s = s_0$, $v = 1$ reachable by steepest descent.

Conjecture: s_0^* corresponds to a minimum in the average surface area subject to the constraint that $\sigma_s = \sigma_v = 0$.

F: Open questions:

1. Anisotropy?
2. Gardner transition?
3. Continuum approximation?
4. Ordered transition?
5. Many more...