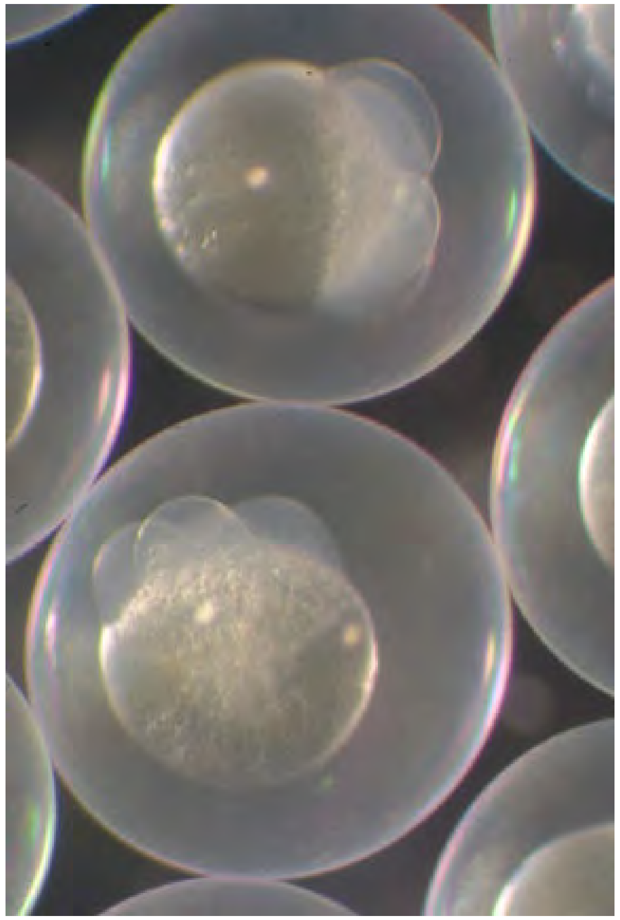

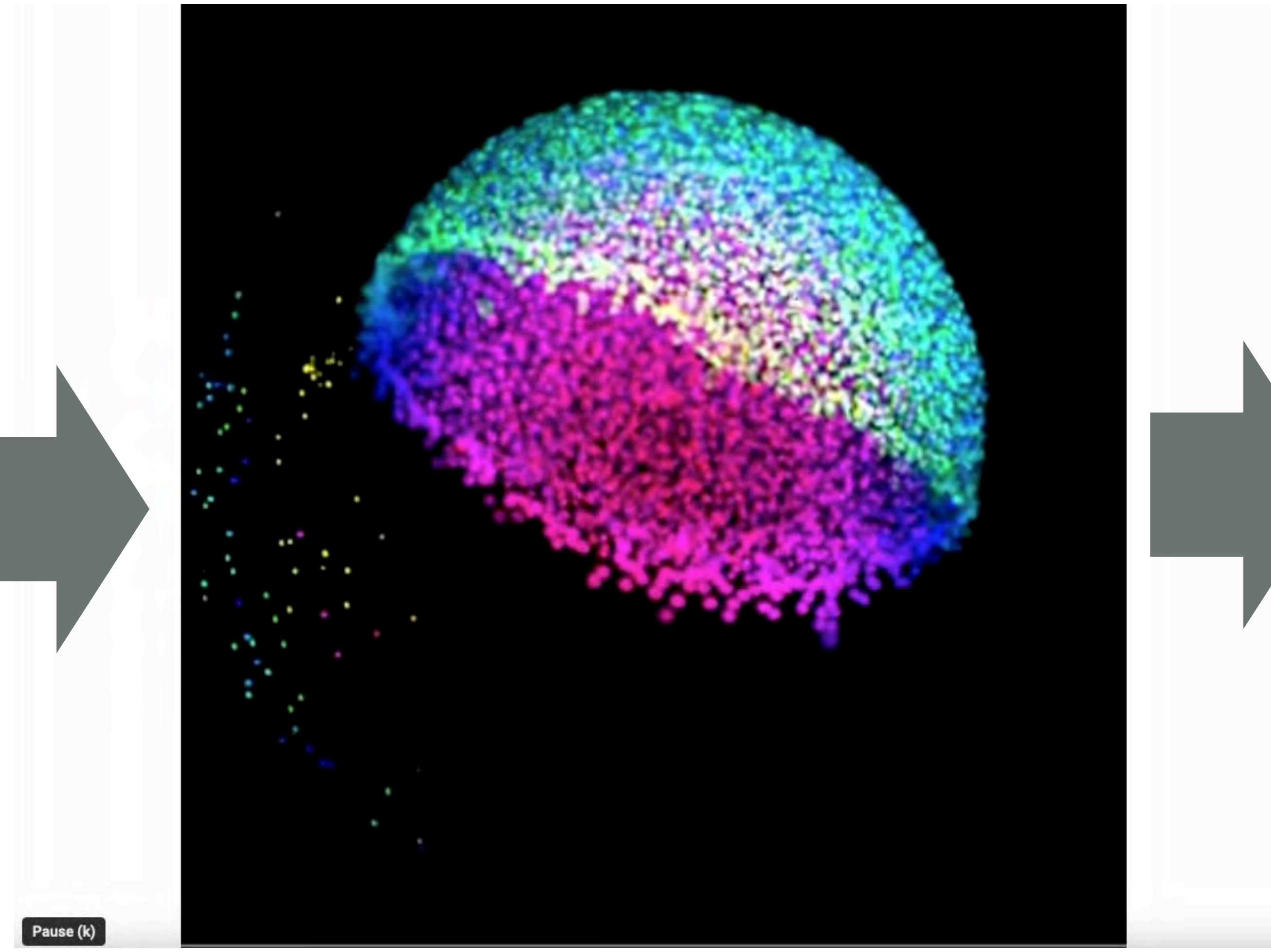

Gopi Shah, Max Planck Institute

Emergent mechanical properties of biological tissues

Boulder Summer School 2024
Self-organizing matter
Lecture 1
July 15th 2024

M. Lisa Manning
Syracuse University
BioInspired Institute
Department of Physics

Thanks to my group and collaborators!

Manning group
Tyler Hain
Sadjad Arzash
Ojan Damavandi -> Intel
Varda Hagh -> UIUC
Raj Kumar Manna
Somiealo Azote
Adil Ghaznavi
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Julia Ann Giannini -> Northwestern
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Dapeng Max Bi -> Northeastern
Michael Czajkowski -> GA Tech
Preeti Sahu -> IST Austria
Ethan Stanifer -> Michigan
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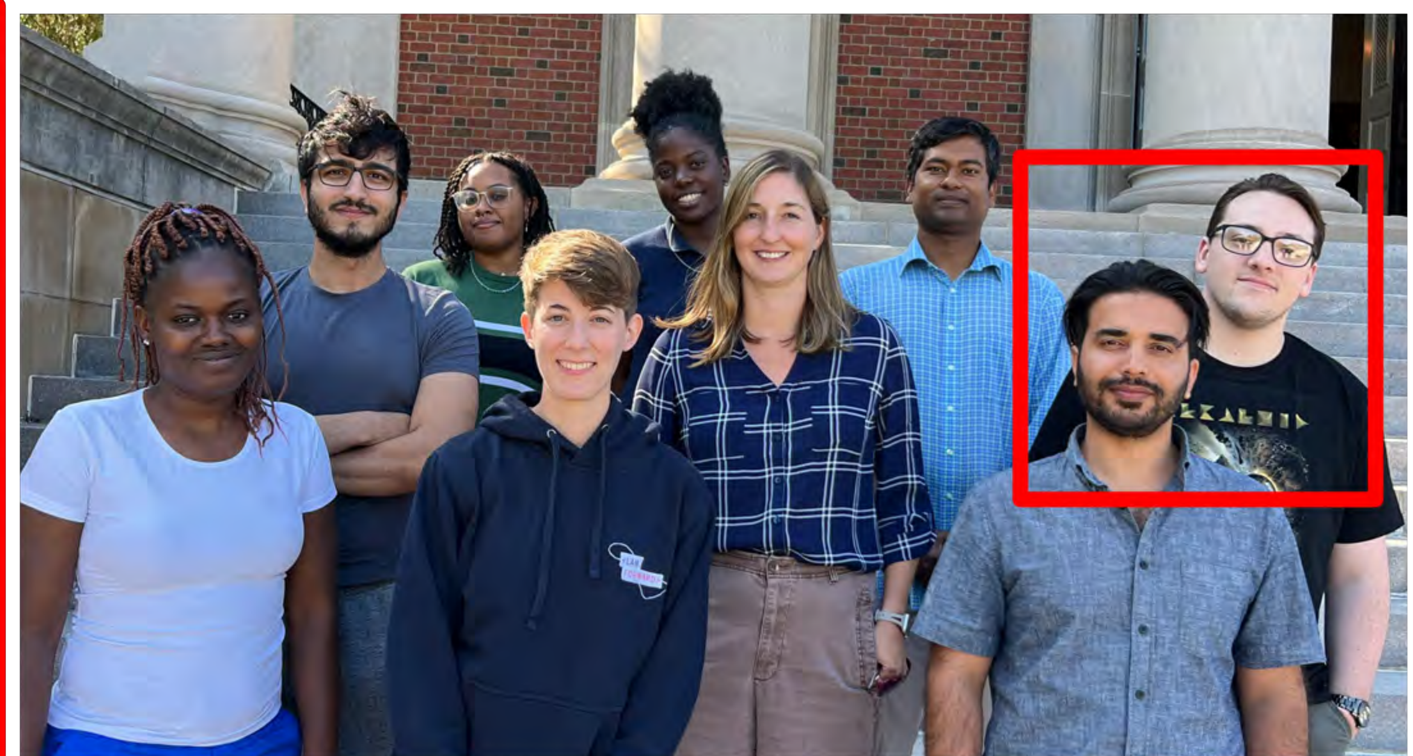
Amanda Parker -> Symbiosys
Paula Sanematsu -> Harvard Research Computing

Syracuse faculty collaborators
Chris Santangelo (SU)
Jennifer Schwarz (SU)
Heidi Hehnly (SU)

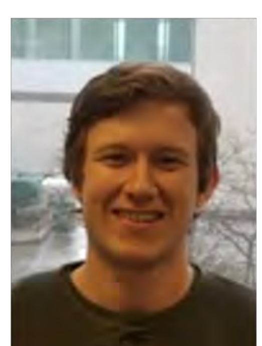


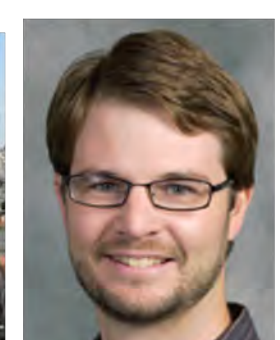








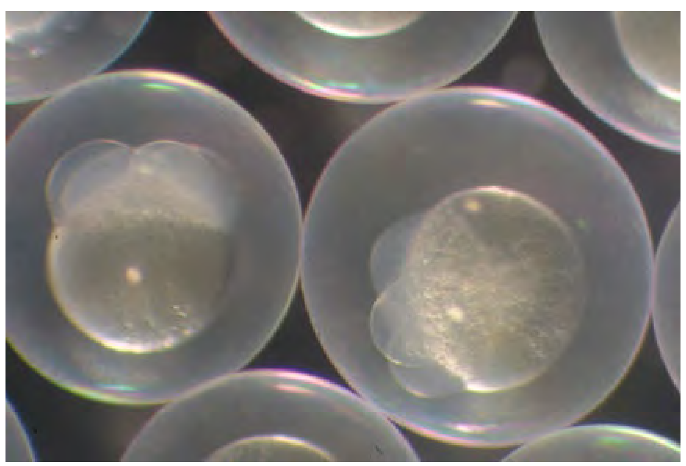



Collaborators:
Indrajit Tah (CSIR-CGCRI) & Andrea Liu (Upenn)
Brian Tighe & Karsten Baumgarten (TU Delft)
Margaret Gardel & John Devany (U Chicago)
Jeff Amack (SUNY Upstate Medical University)
Karen Kasza and Xun Wang (Columbia)
Ryan Hayward (CU Boulder)

How do you turn a blob of material into something that's the shape of a fish?

blob



zfin.org

development

Karlstrom et al, Development (1996)

fish

zfin.org

How do you turn a blob of material into something that's the shape of a fish?

glass blob

coursehorse.com

glass blower

Smithsonian Magazine

complex, stable, reproducible morphology

How do you turn a blob of material into something that's the shape of a fish?

Smithsonian Magazine

mandrel rod

applies localized forces:

pressures

shear stresses

focus on this first

heat

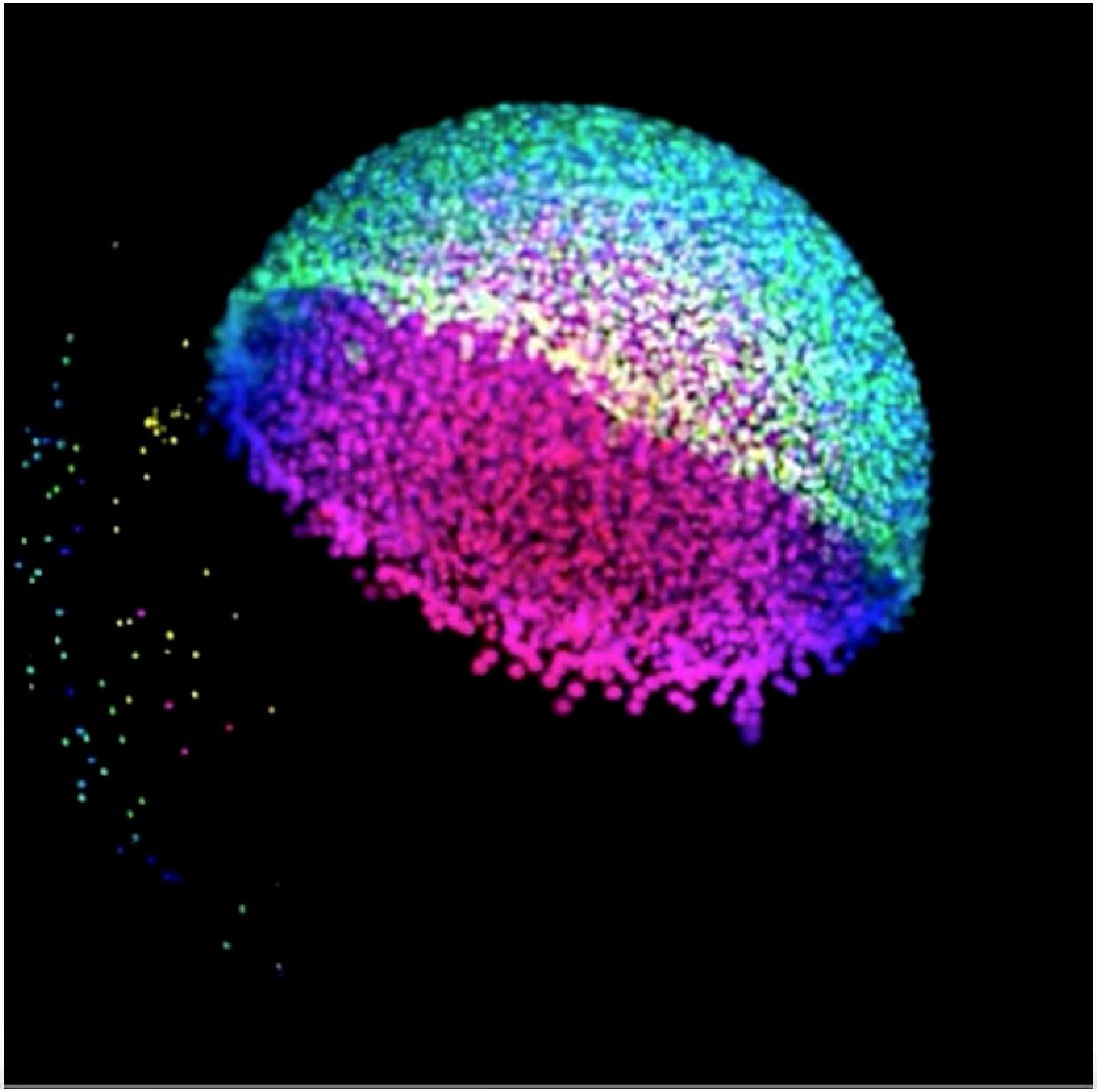
alters the local material properties:

elastic modulus

fluidity/viscosity

goes through a "glass transition"

solid → fluid → solid



are the local material properties changing?

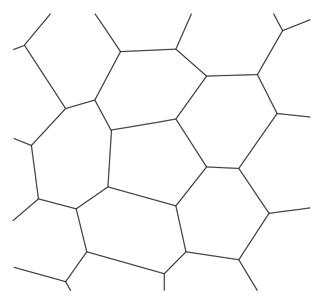
Gopi Shah, Max Planck Institute, Royal Microscopical Society Imaging Competition 2015
https://www.youtube.com/watch?v=V8xvGgcsqAQ

Recent biology experiments: tissues do change their fluidity during development

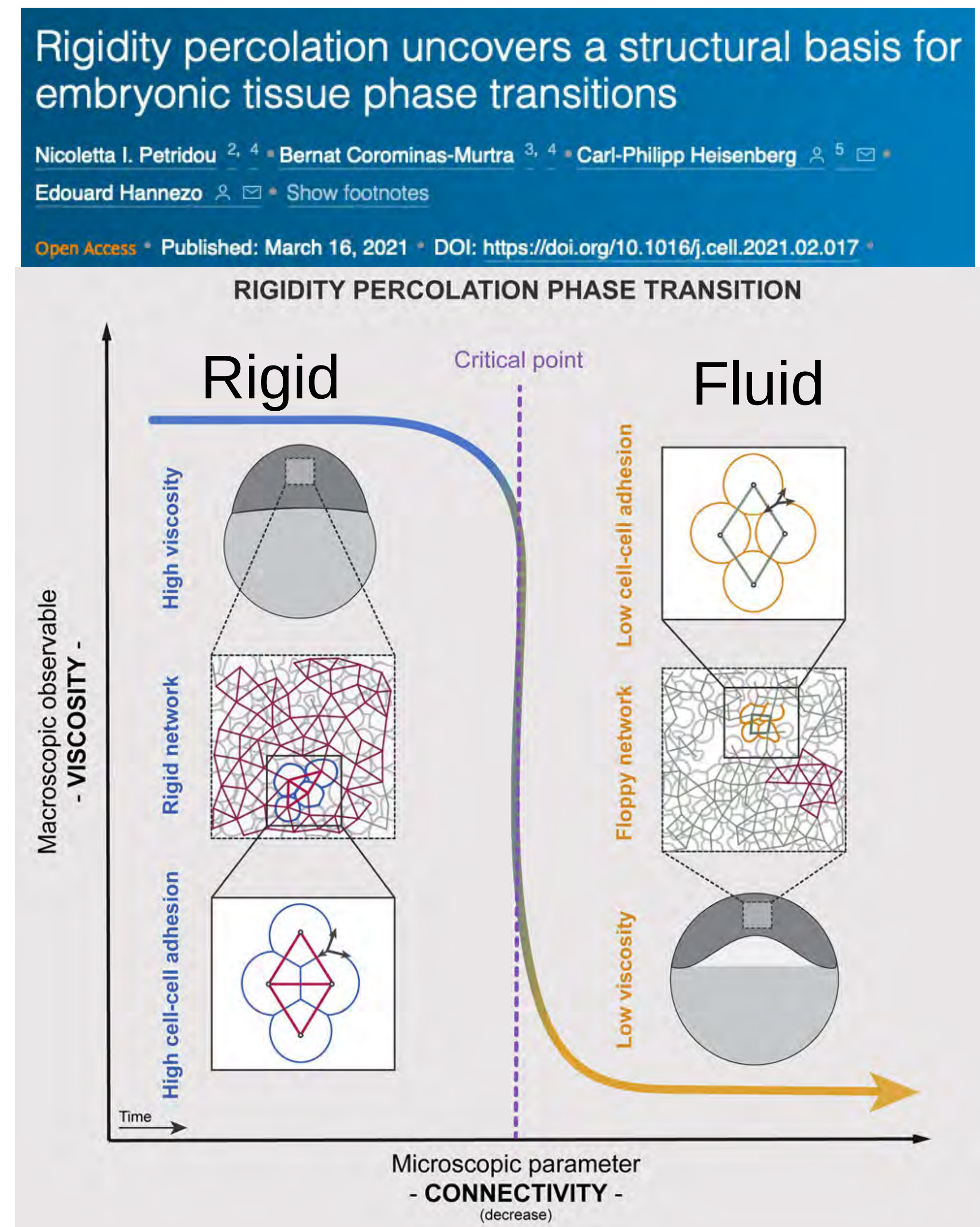
A fluid-to-solid jamming transition underlies vertebrate body axis elongation

Alessandro Mongera[1,2,7], Payam Rowghanian[1,2], Hannah J. Gustafson[1,2,3], Elijah Shelton[1,2], David A. Kealhofer[4], Emmet K. Carn[1], Friedhelm Serwane[1,2,8], Adam A. Lucio[1,2], James Giammona[2,4] & Otger Campàs[1,2,5,6]*

Rigid



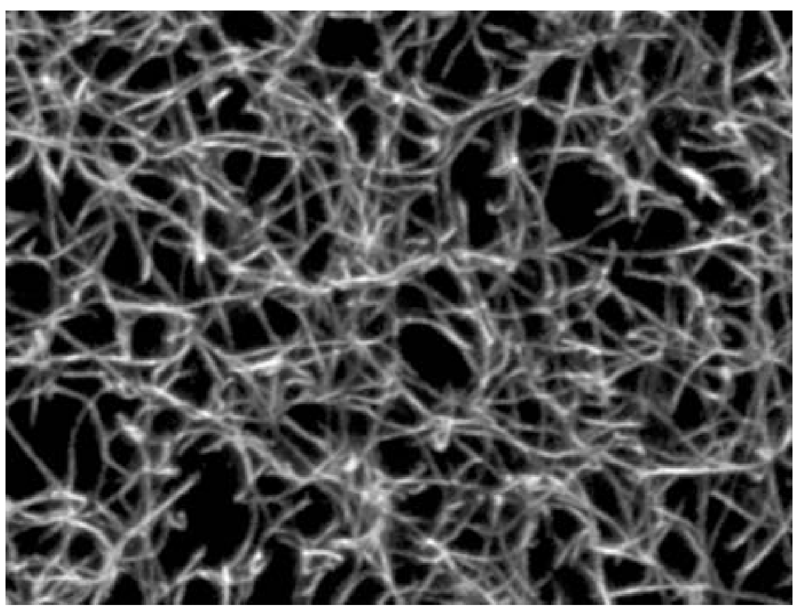
Fluid



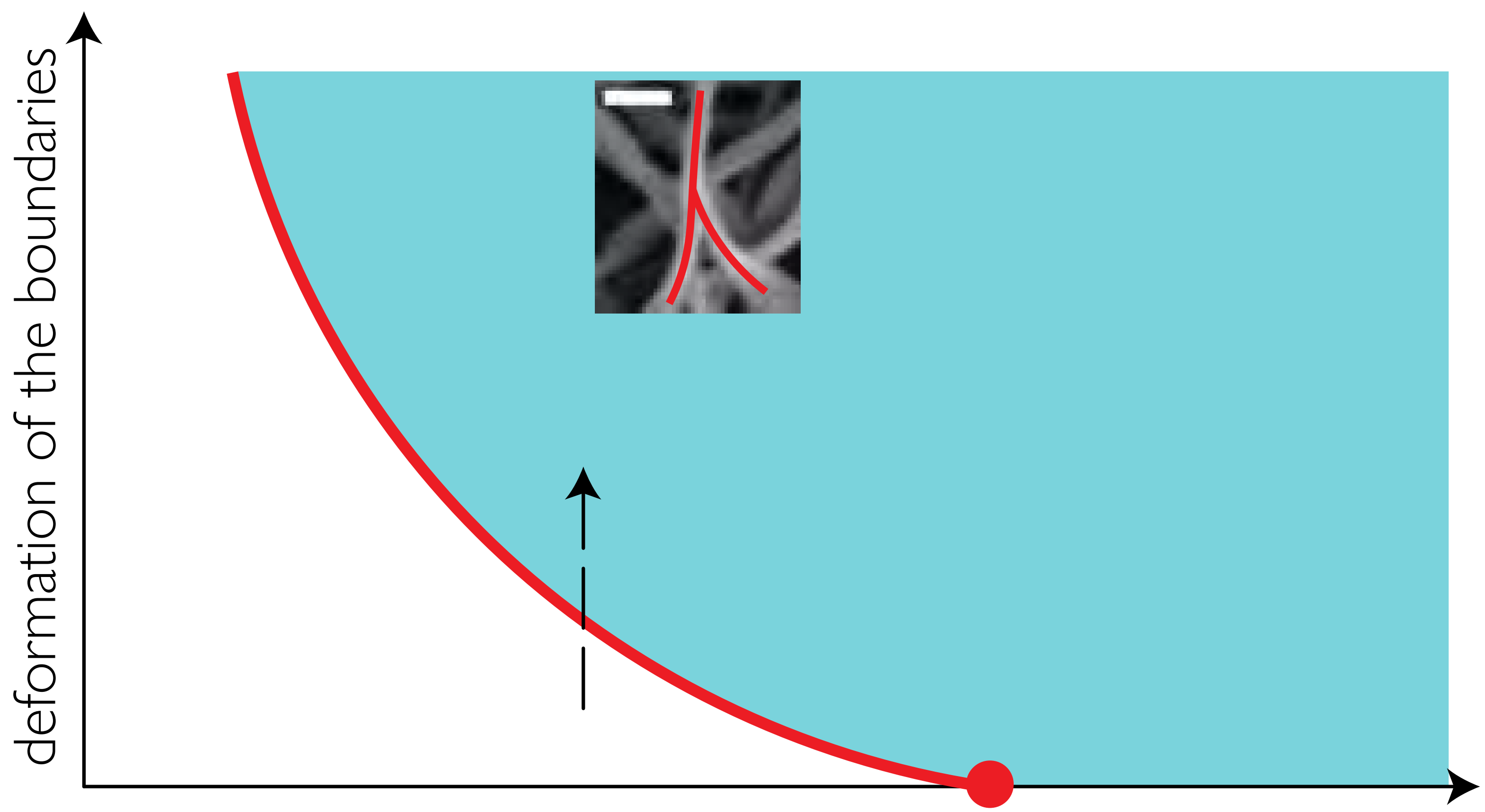
Mongera et al, Nature, 2018

Petridou et al, Cell 2021

Biology experiments: not just cells… tissues also composed of extracellular matrix (ECM), which often exists in disordered networks that **also** transition from floppy to stiff



Lindström et al., *PRE* (2010).



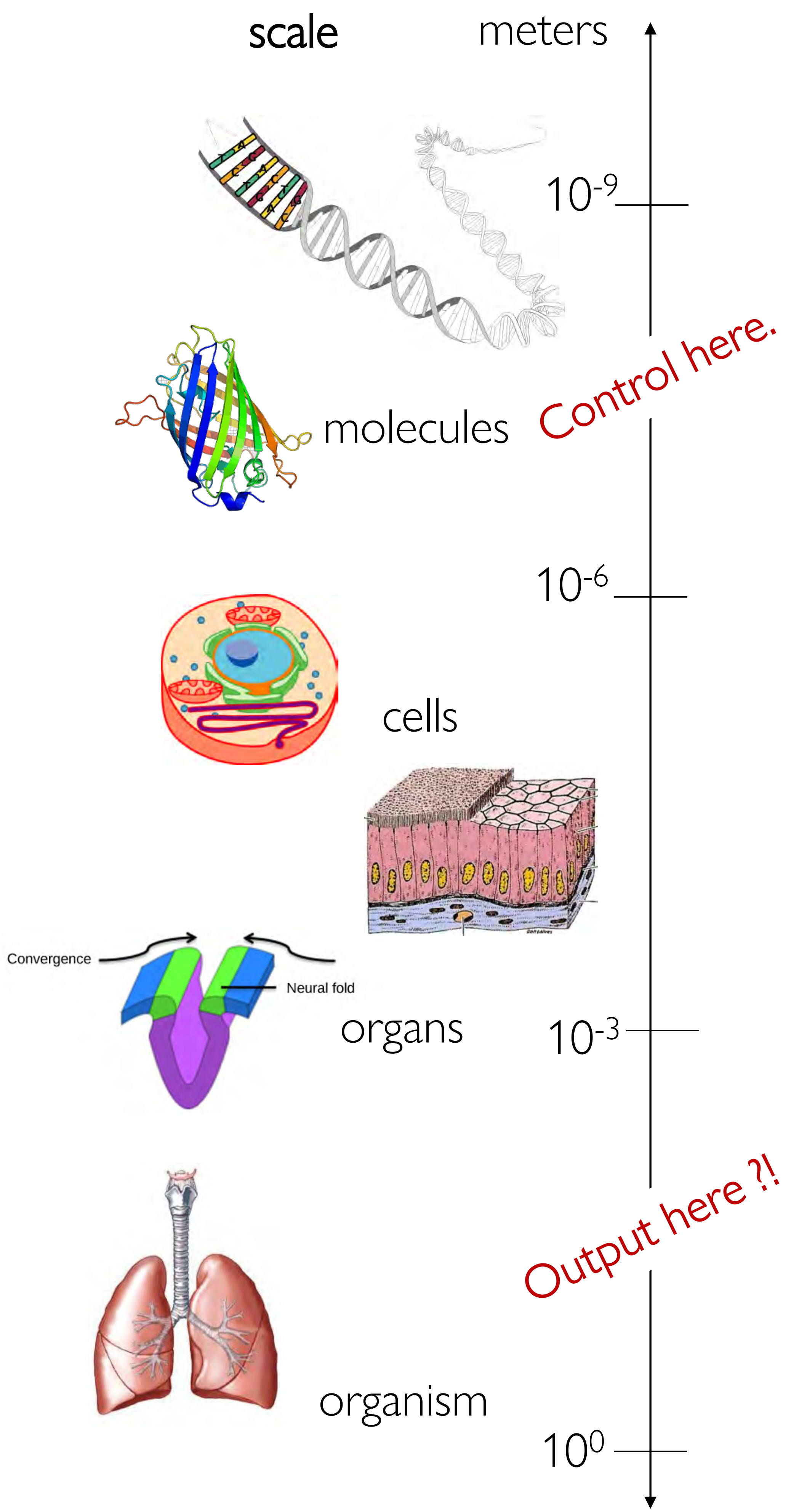
Sharma et al., *Nature Physics* (2016).
Jansen et al., *Biophysical Journal* (2018).

Rigidity transitions occur in other systems and at different scales, too:

- Possible rigidification of condensates in liquid-liquid phase separation, implications for plaques and disease

- cytoskeleton inside a cell can tune its rigidity

    - active gel (c.f. Ulrich Schwarz's awesome lectures)



Also biology experiments: all the control systems are encoded and evolve at the scale of molecules

biologists, biophysicists:
how does it do that?

materials scientists:
we'd like to do that, too!

why it is difficult:

challenge 1) emergent rigidity is difficult

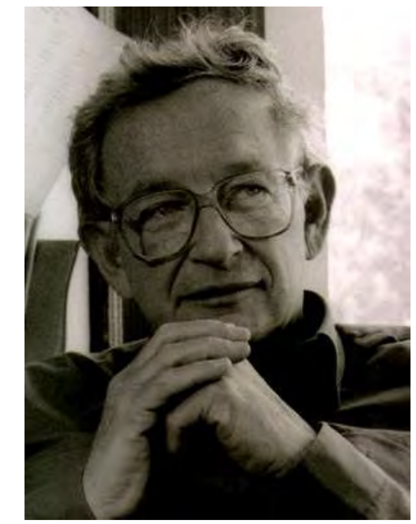
challenge 2) there are many tunable parameters, tuning parameters are at a much smaller scale than emergent behavior. how to control? (cf talks by Andrea Liu next week)

challenge 1) emergent rigidity is difficult

"We are so accustomed to the rigidity of solid bodies – the idea for instance that when move one end of ruler the other end same distance …

. . . that we don't … ost miraculous nature, **that i… ergent property'** not contain… law of physics, although it is a … of them."

Let's work on challenge 1!



P. W. Anderson

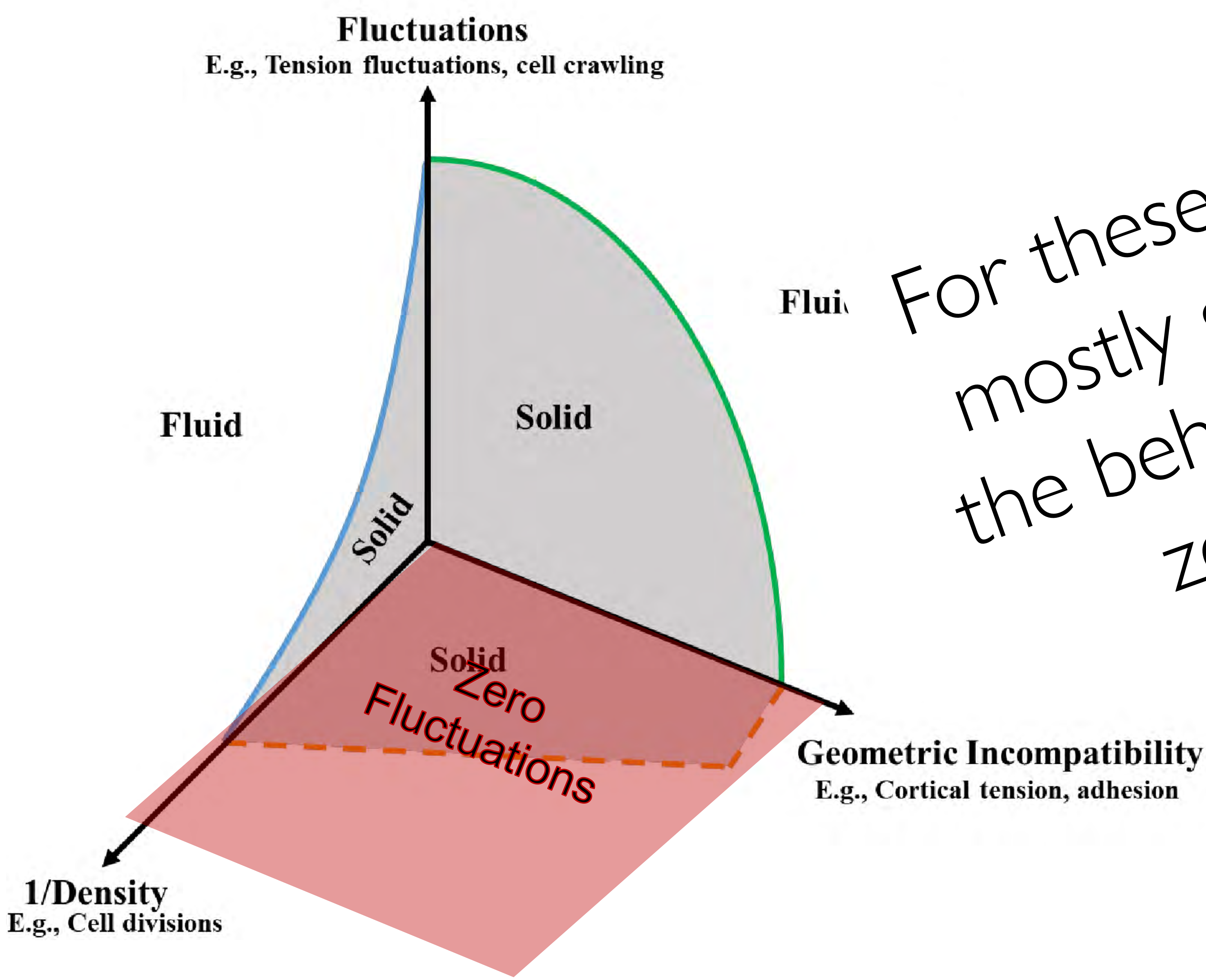
"The deepest and most interesting unsolved problem in solid state theory is probably the theory of the nature of glass and the glass transition." (1995)

Moumita Das gave a fantastic introduction to this topic in the first week, focused on:

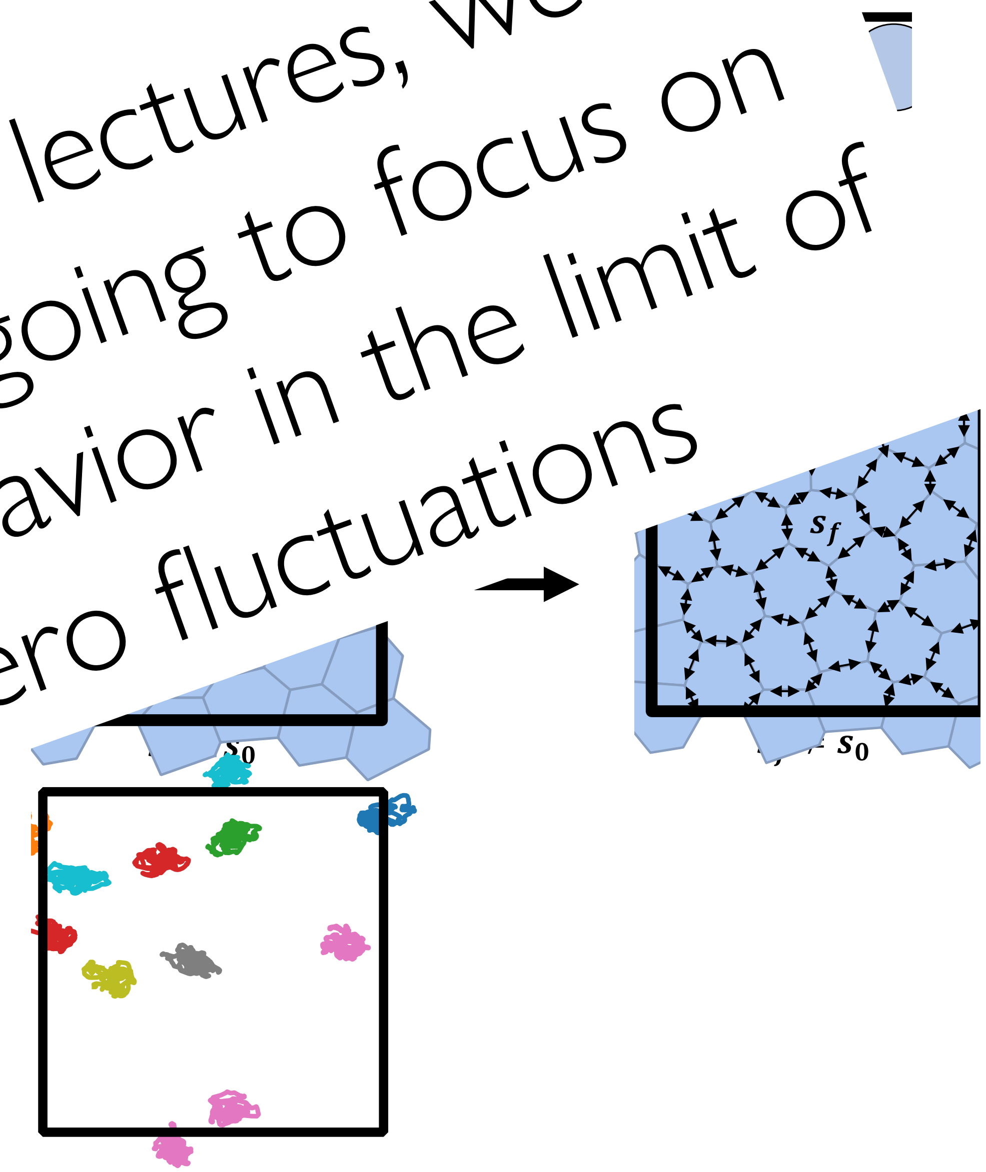
- semi-flexible networks
- effective medium theory
- composite networks

here, we will be extending some of those ideas in different ways

Answer to challenge 1: there are multiple physical mechanisms that can drive rigidity/fluidity in tissues:



For these lectures, we are mostly going to focus on the behavior in the limit of zero fluctuations



Lawson-Keister++, Current Opinions in Cell Biology (2021)
adapted from Kim++ Nature Physics (2021) and Bi++ PRX 2016

Today's lecture: 1/density axis

- theory: revisit the Dynamical Matrix, shear modulus
- canonical example for 1/density axis: jamming transition for spheres
- theory: First-order rigidity
- a few examples in biology

Tomorrow's lecture: geometric incompatibility axis

- theory: Second-order rigidity
- canonical examples for geometric incompatibility
  - underconstrained spring networks
  - vertex models
- how does this show up in biology experiments?
- (if time) a tiny bit of finite temperature + dense active matter

Wednesday's lecture: critical manifolds and programming/control

- universality
    - shear modulus
    - shape parameter/incompatible length scales
    - finite frequency response
- how to pick the right degrees of freedom for a model – does it matter?
- Can we think of how to design or evolve specific emergent mechanics?
    - theory for second-order rigid systems: parameterization of the critical manifold

A fluid-to-solid jamming transition underlies vertebrate body axis elongation

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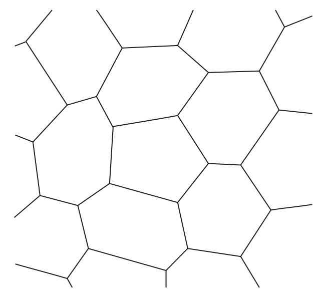
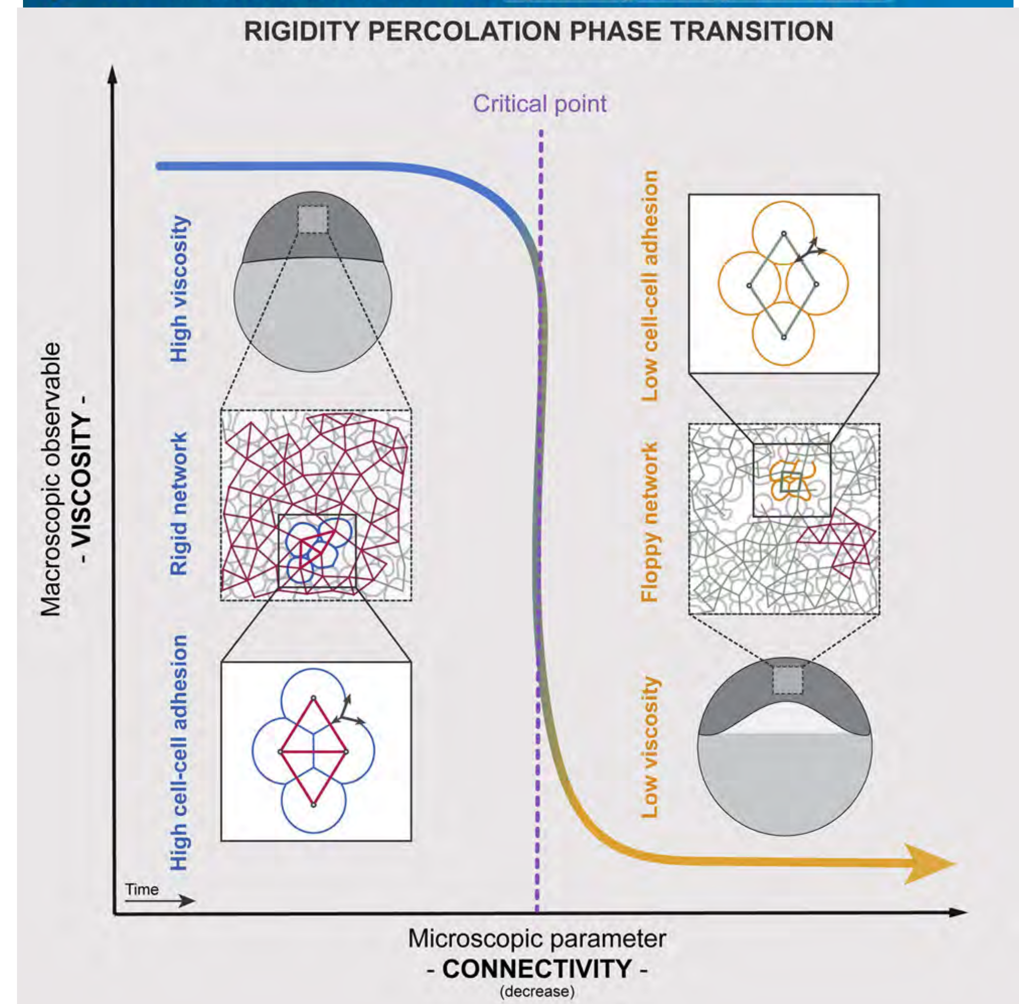


Rigidity percolation uncovers a structural basis for embryonic tissue phase transitions

Nicoletta I. Petridou [2, 4] • Bernat Corominas-Murtra [3, 4] • Carl-Philipp Heisenberg [5] • Edouard Hannezo • Show footnotes

Open Access • Published: March 16, 2021 • DOI: https://doi.org/10.1016/j.cell.2021.02.017



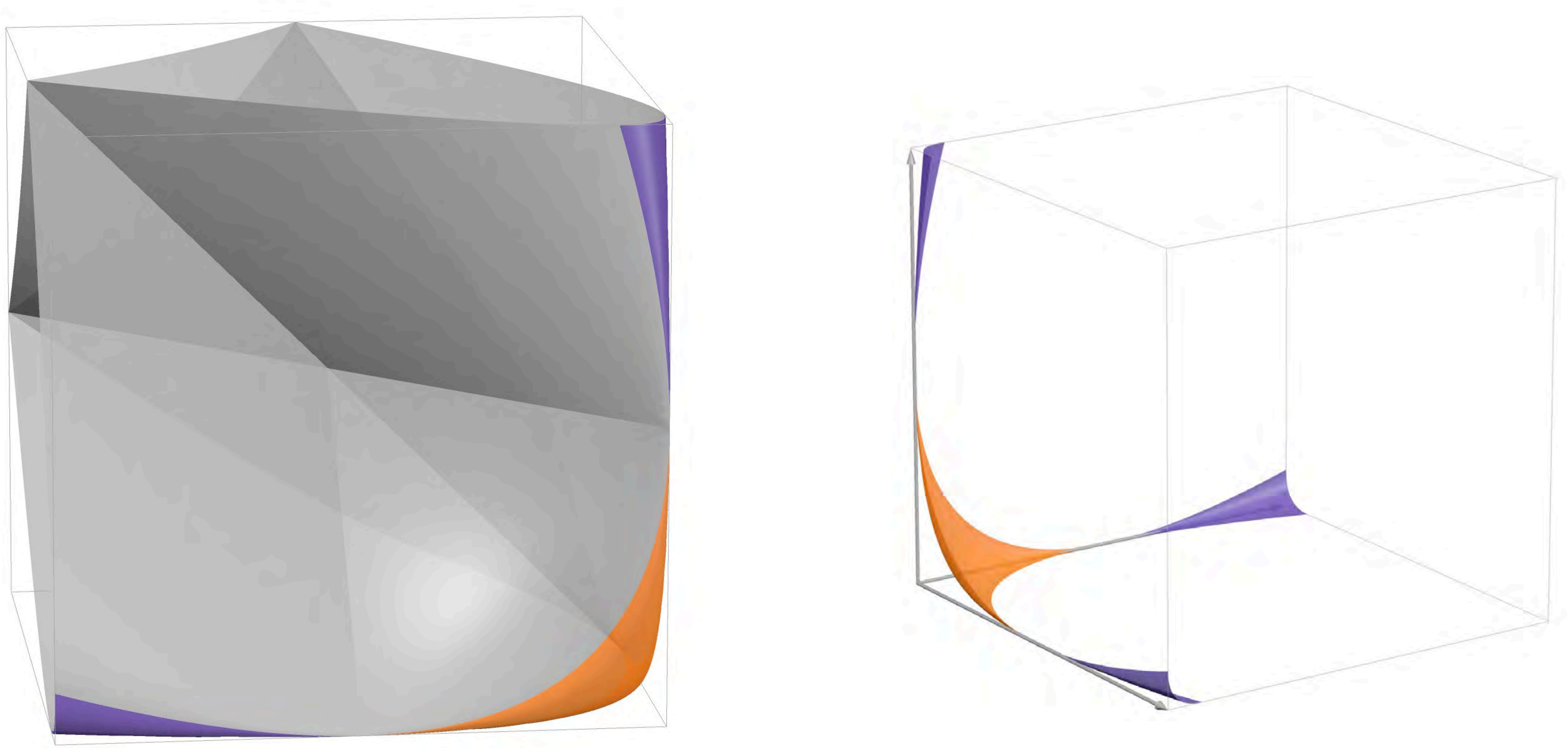
Mongera et al, Nature, 2018

Petridou et al, Cell 2021

Beautiful data and modeling: in these cases, fluidization caused by changes to density and number of contacts

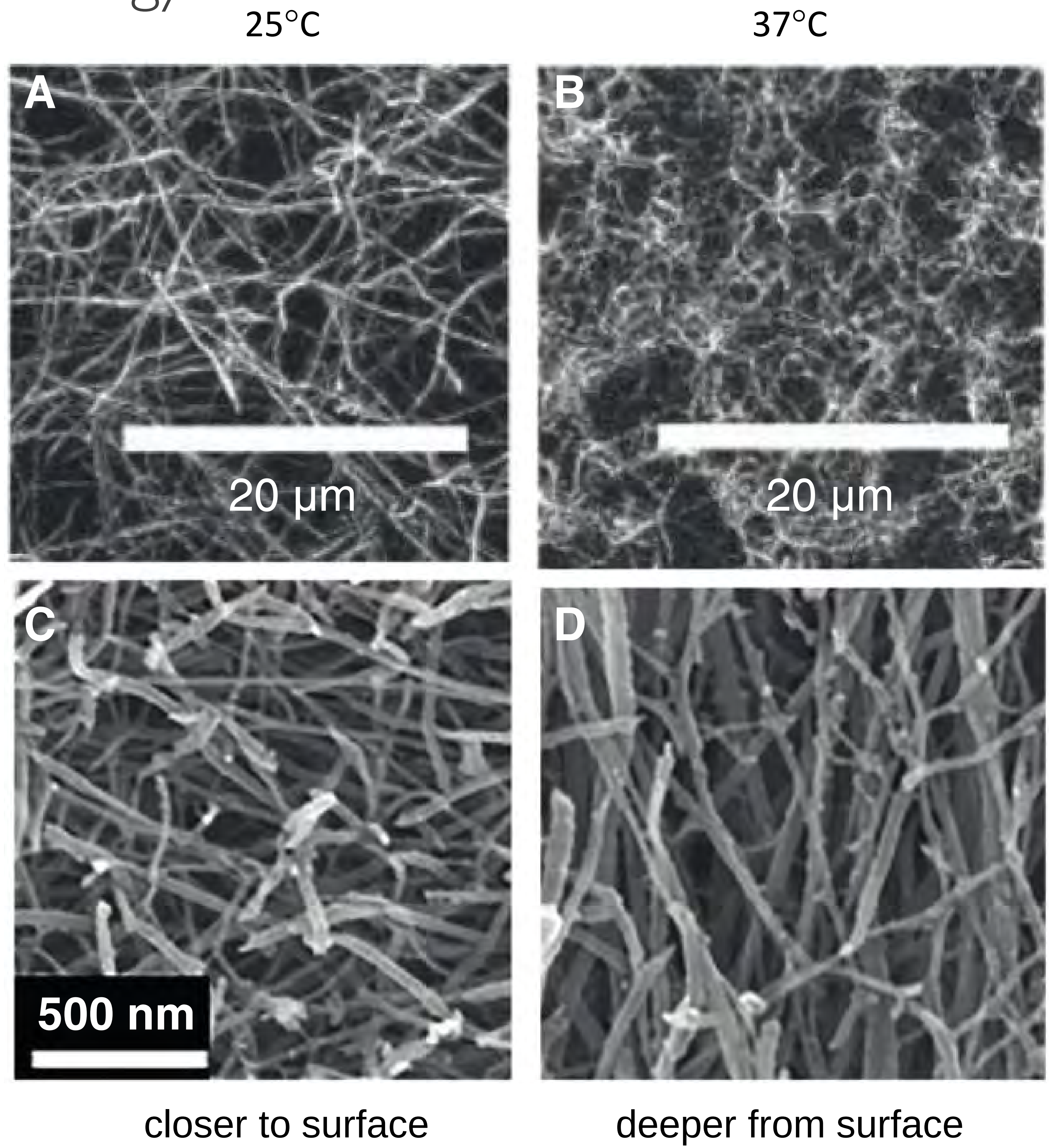
Cells as squishy spheres is a good model for such systems!

Lecture 2



Rigidity manifold for the 3-bar linkage

Fiber networks in biology



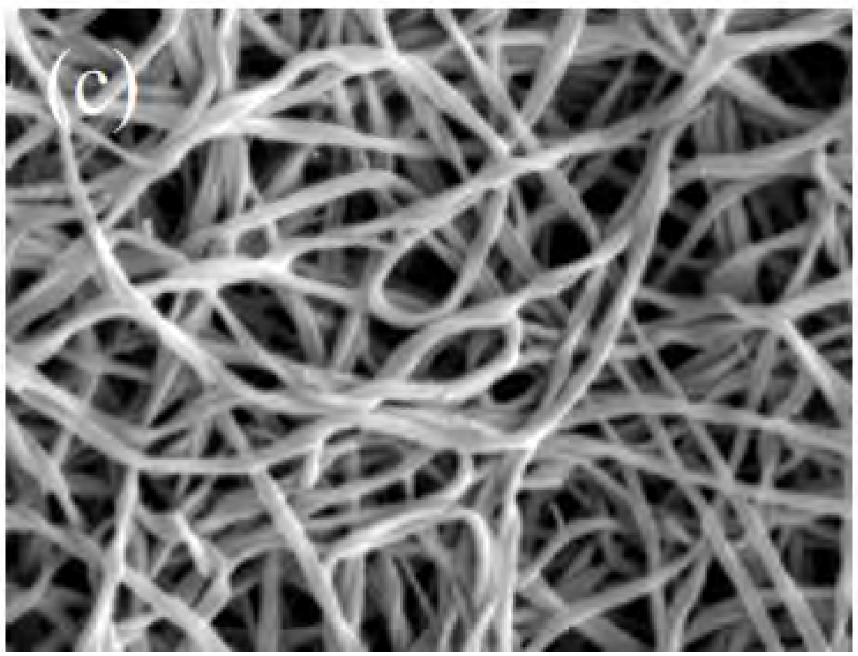
in vitro
(reconstituted collagen network)

Licup, A.J., et al PNAS (2015).

in vivo
(bovine knee cartilage)

Brown et al Clinical Biomechanics (2020)

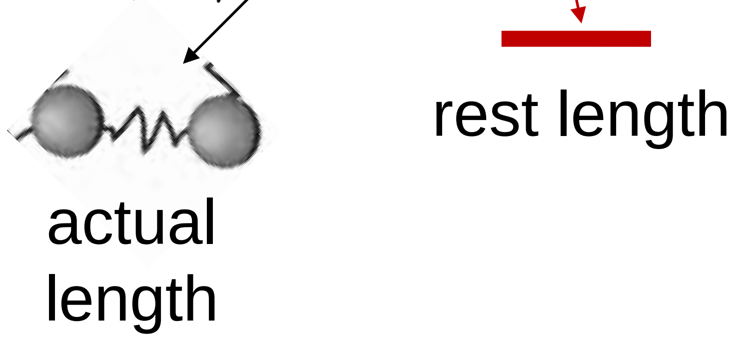
Fiber networks in biology are often under-constrained

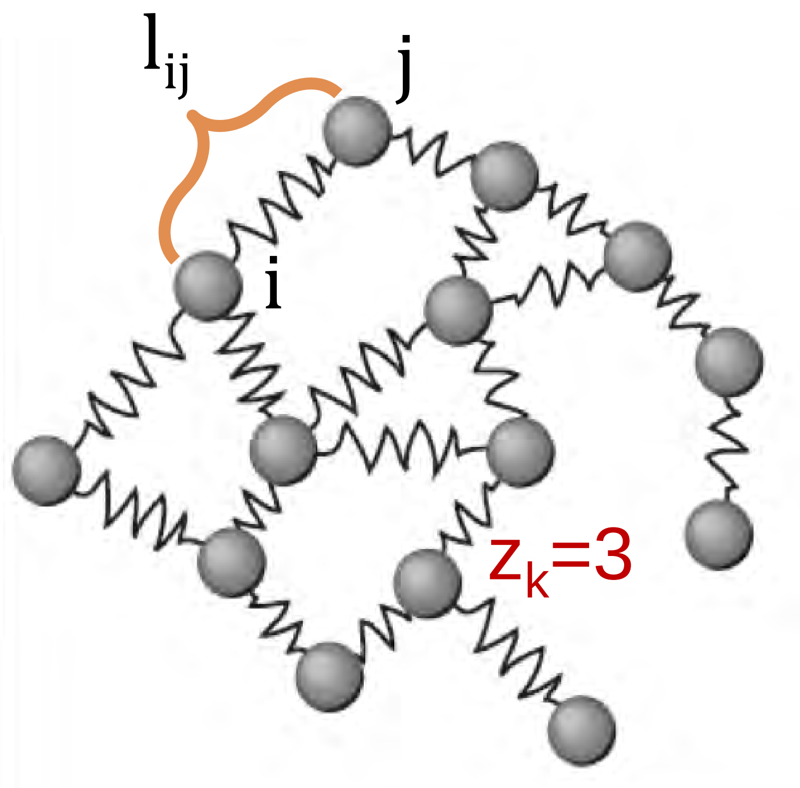


Sharma et al. Nature Phys. 2016.

can be approximated as a network of springs

$$e_{network} = k_{spring} \sum_{\langle ij \rangle} (l_{ij} - l_0)^2$$



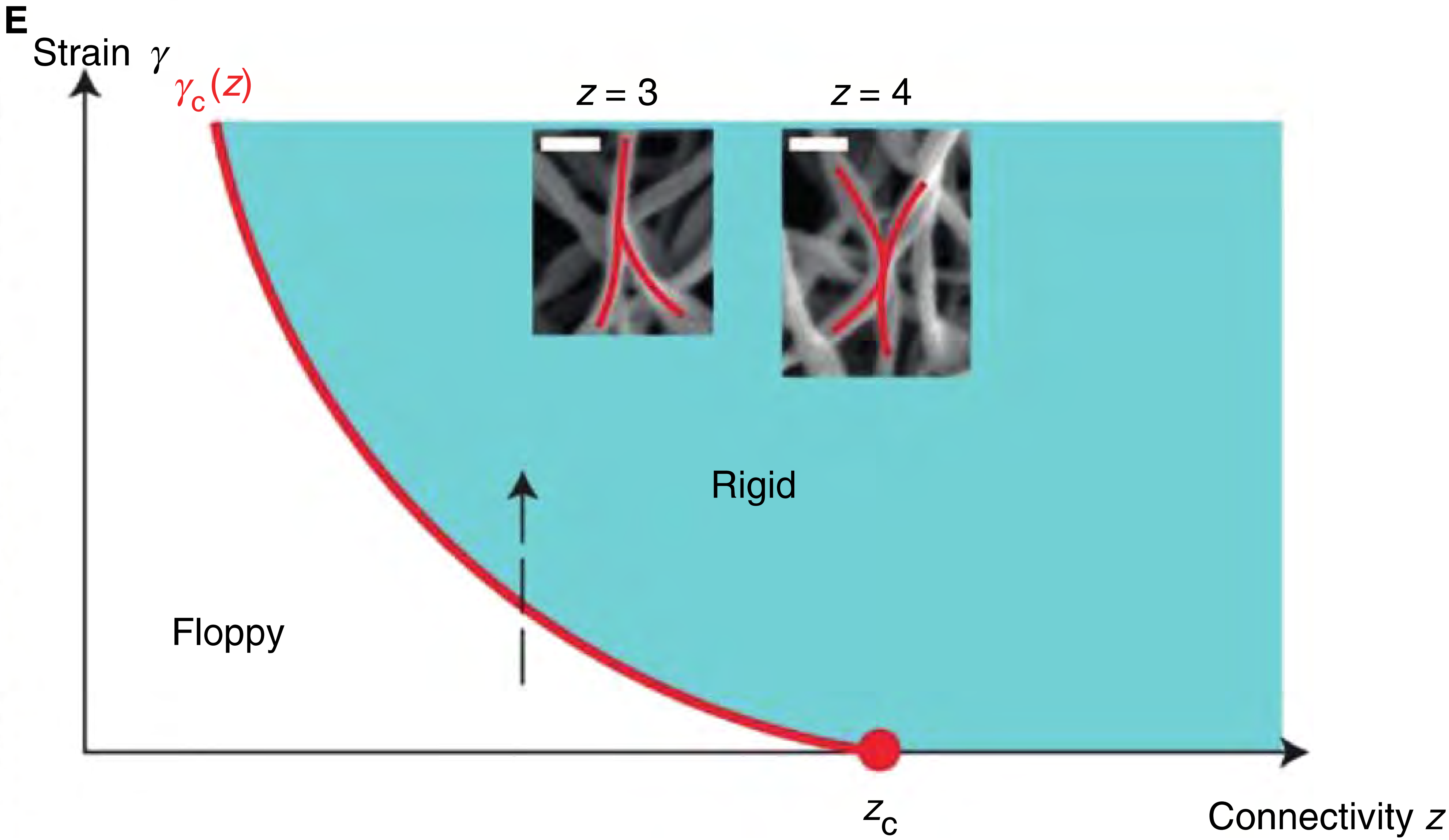


in biological tissues networks like collagen are almost always under-constrained:

network coordination

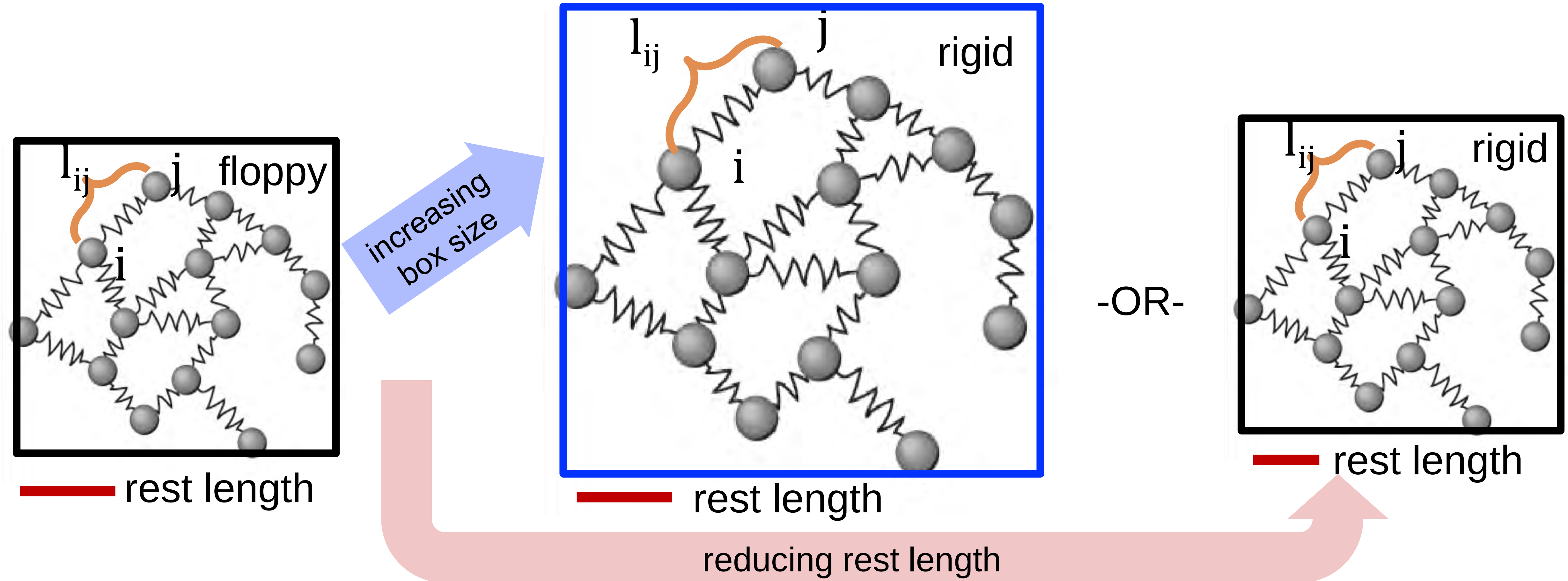
$z < z_c = 2d$

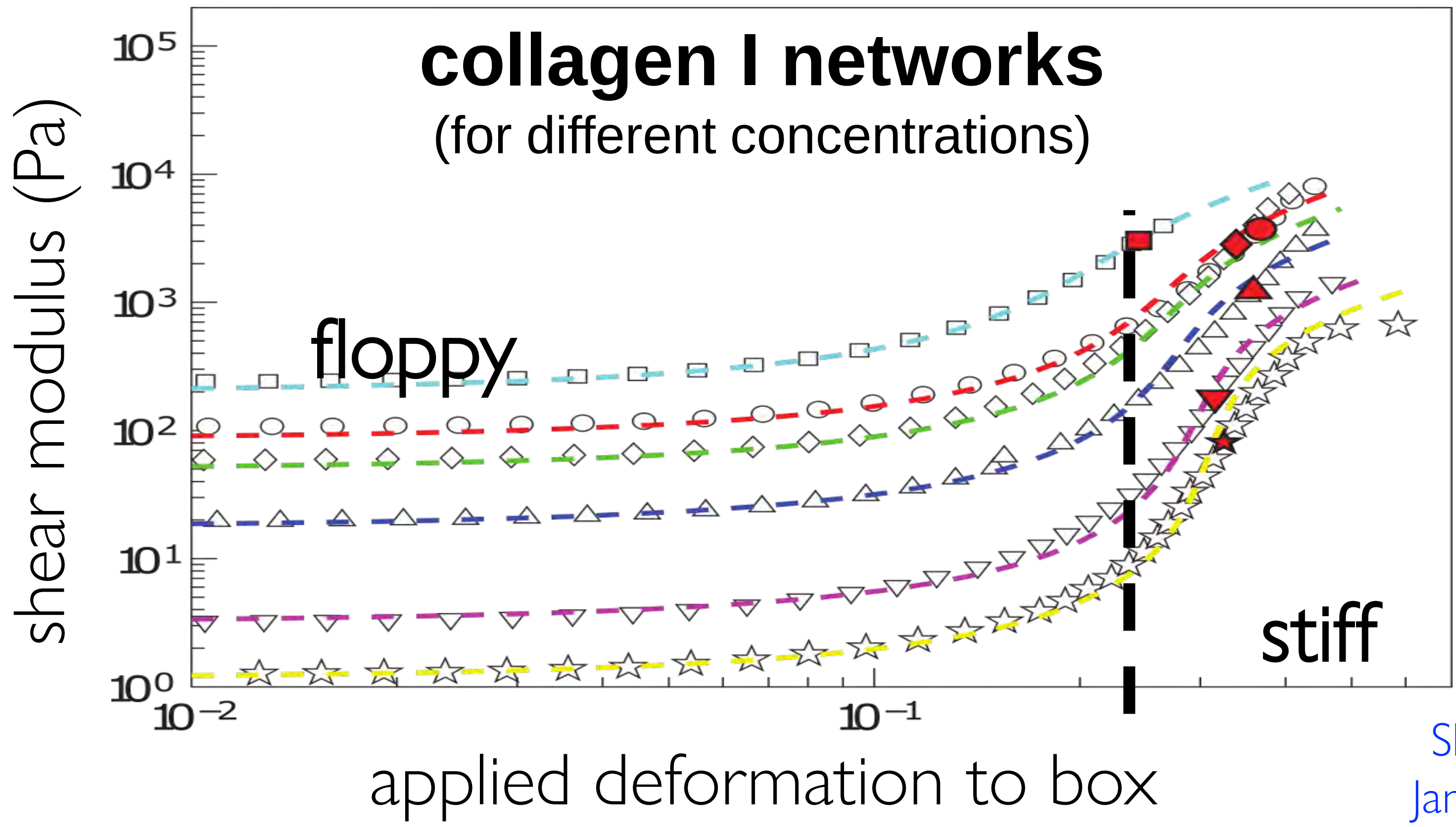
Sharma et al., *Nature Physics* (2016).
Jansen et al., *Biophysical Journal* (2018).



Sharma et al., Nature Physics (2016).

Fiber networks can rigidify via changing box size or spring rest length





Sharma et al., *Nature Physics* (2016).
Jansen et al., *Biophysical Journal* (2018).

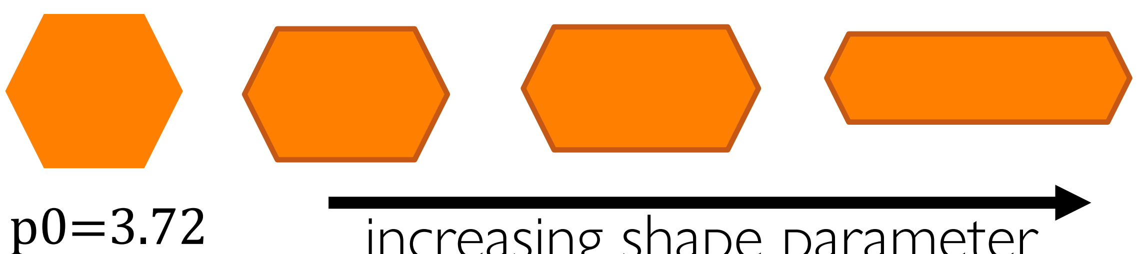
Lecture 3

Outline for Lecture 3

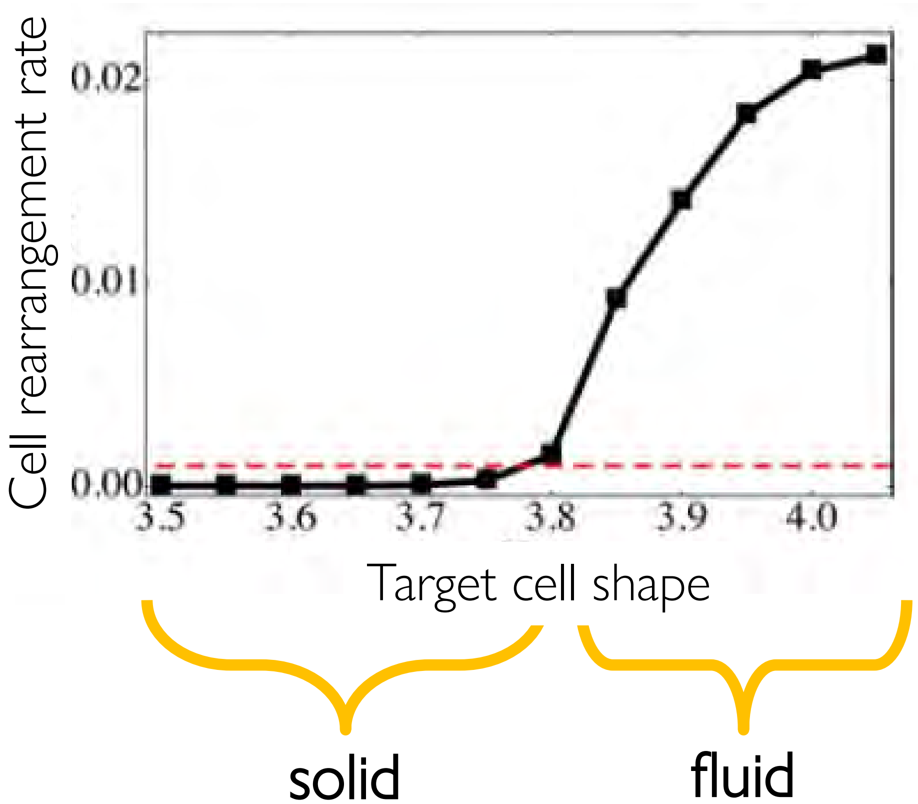
- more about vertex models
- universality of vertex models
    - shear modulus/shape parameter/incompatible length scales
    - finite frequency response
- how to pick the right degrees of freedom for a model – does it matter?
- Can we think of how to design or evolve specific emergent mechanics?
    - theory for second-order rigid systems: parameterization of the critical manifold

experiments: confluent tissues rigidify by tuning cell shape

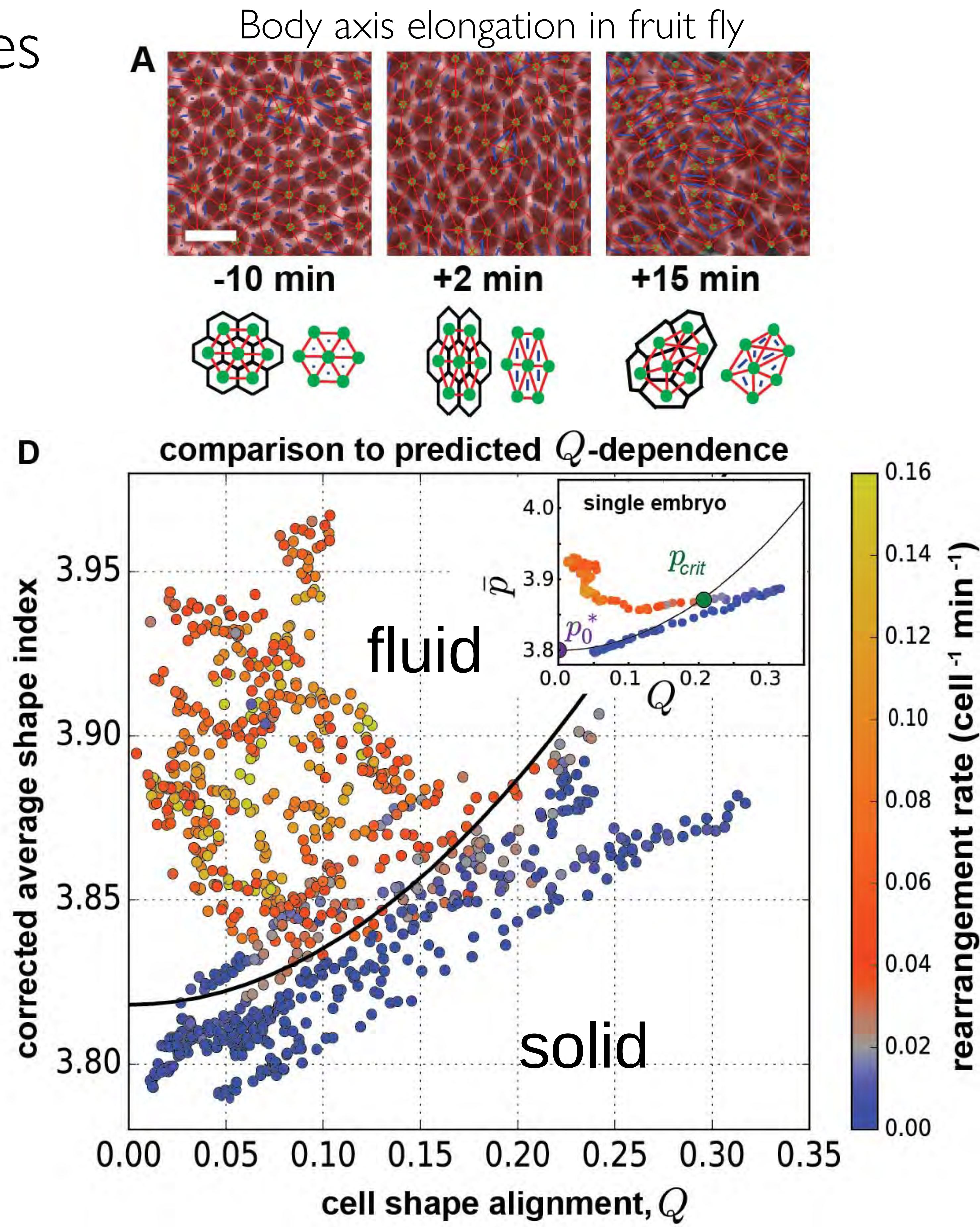
shape index: perimeter / $\sqrt{\text{area}}$



Model for confluent tissue



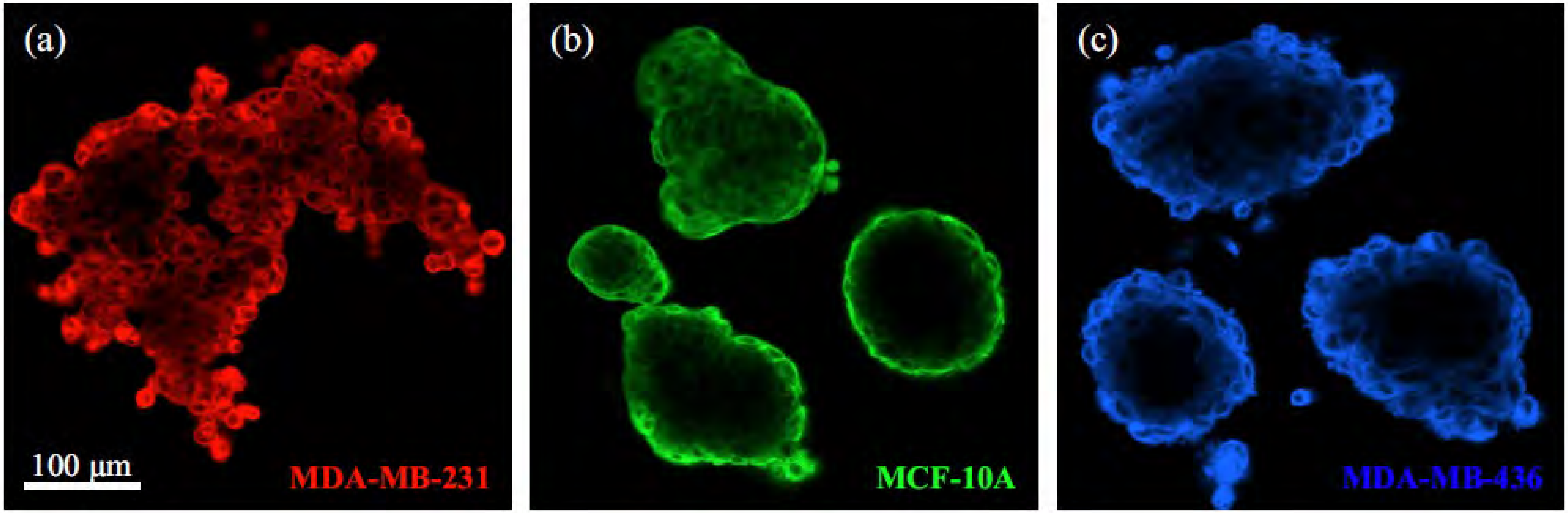
Bi++(2016)

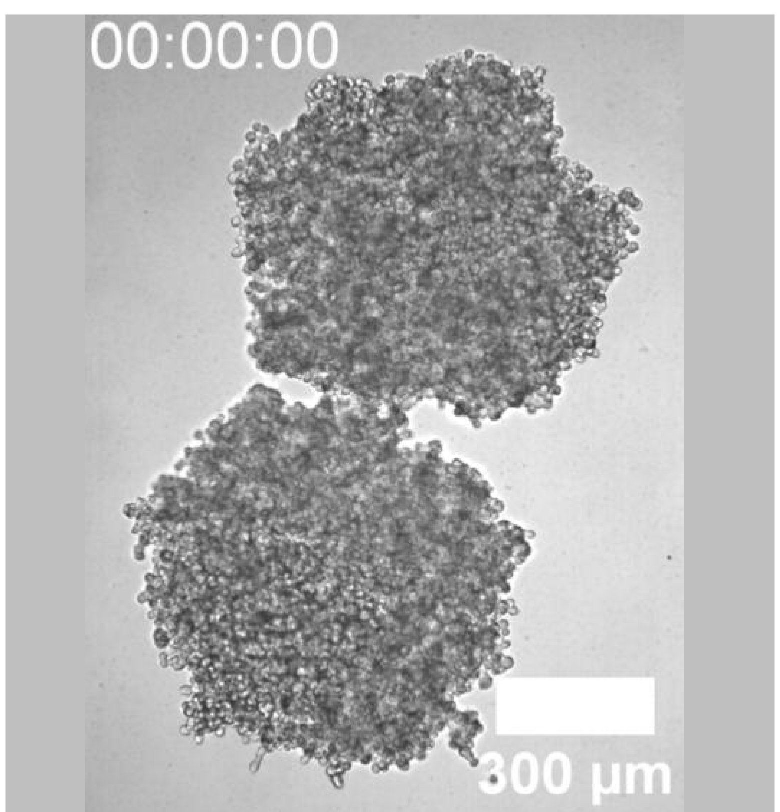


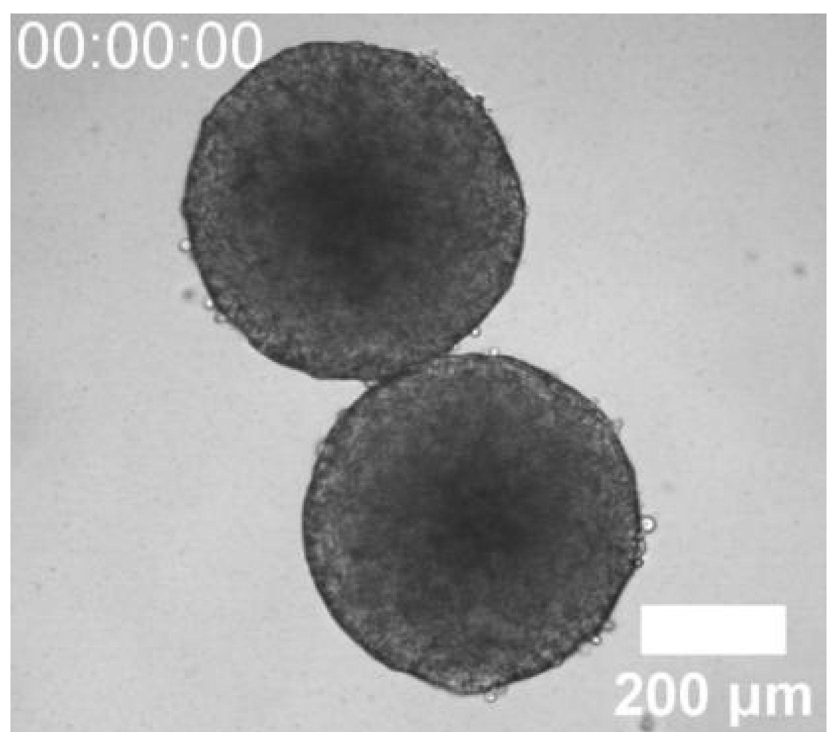
Wang++ PNAS (2020)

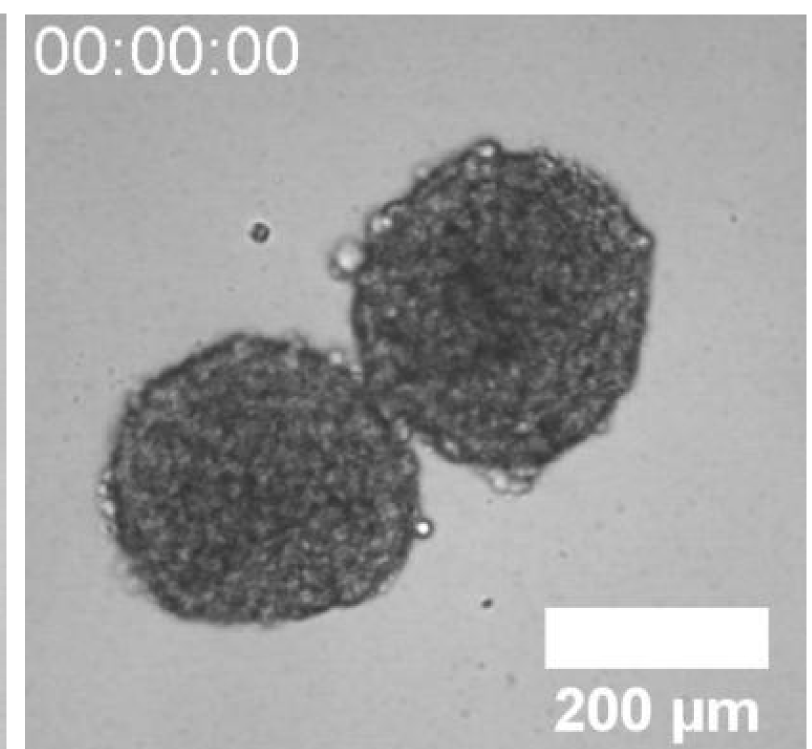
Also in breast cancer cell lines

model for **metastatic** breast cancer cells | model for **normal** breast cells | model for **malignant** breast cancer cells



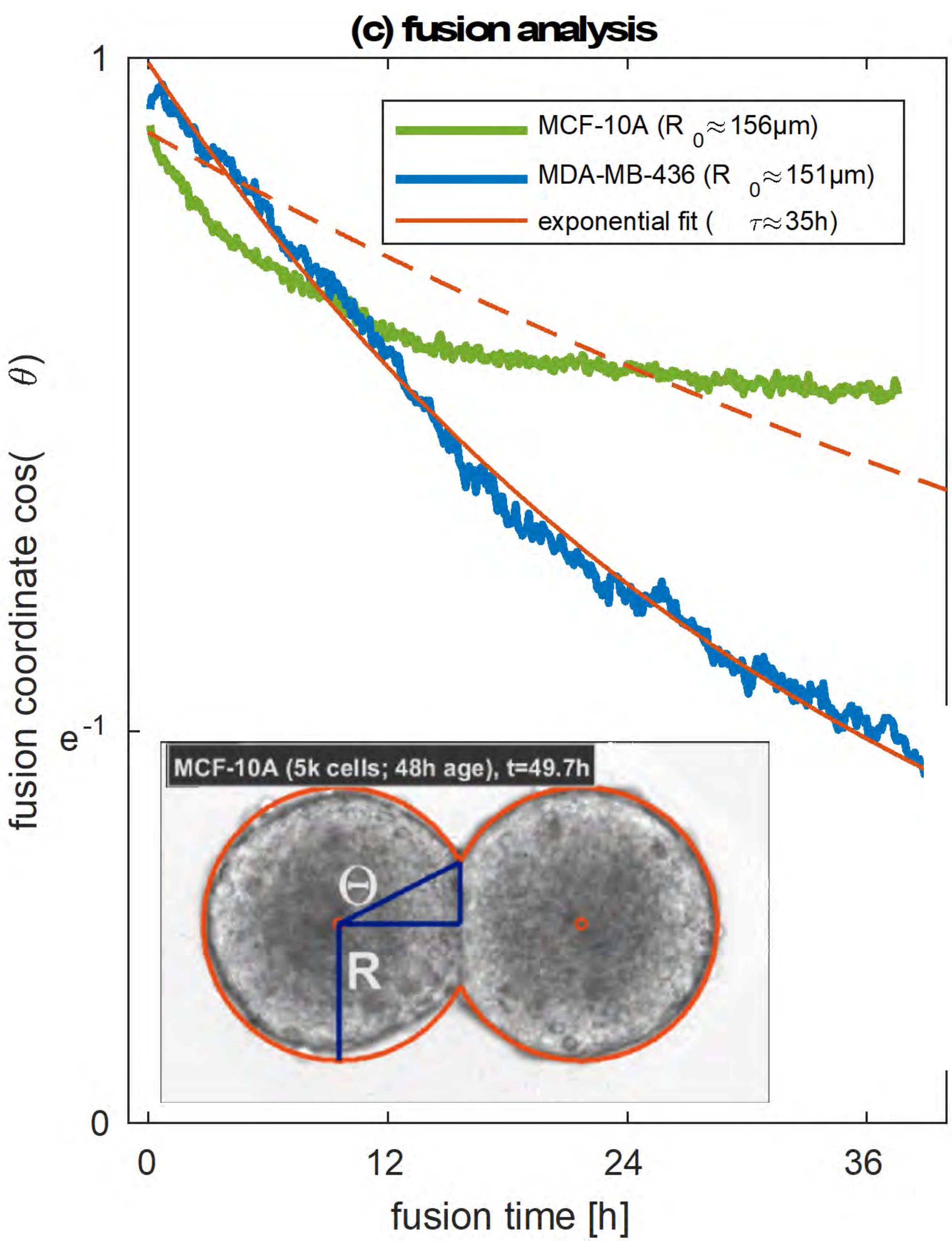


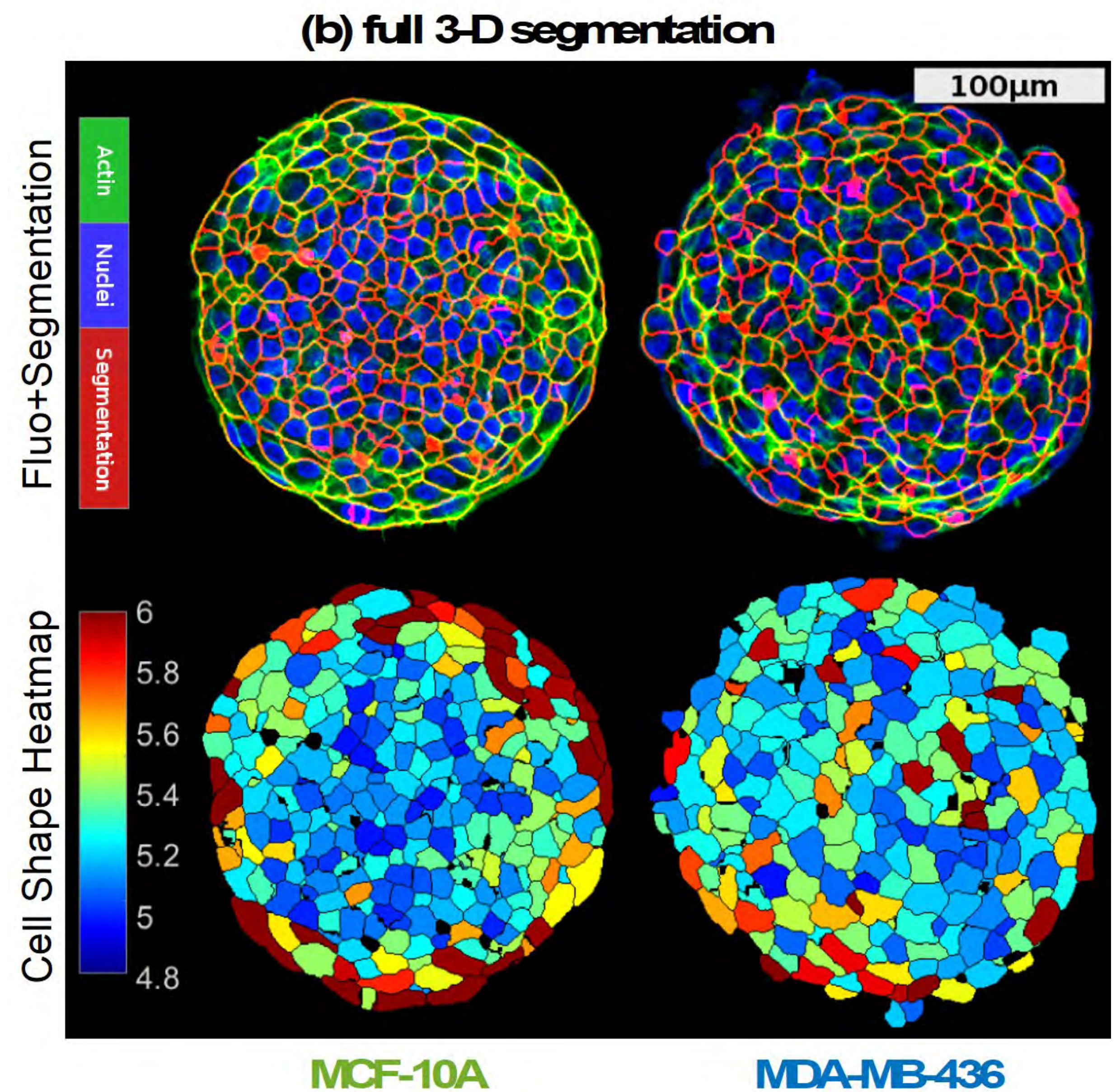


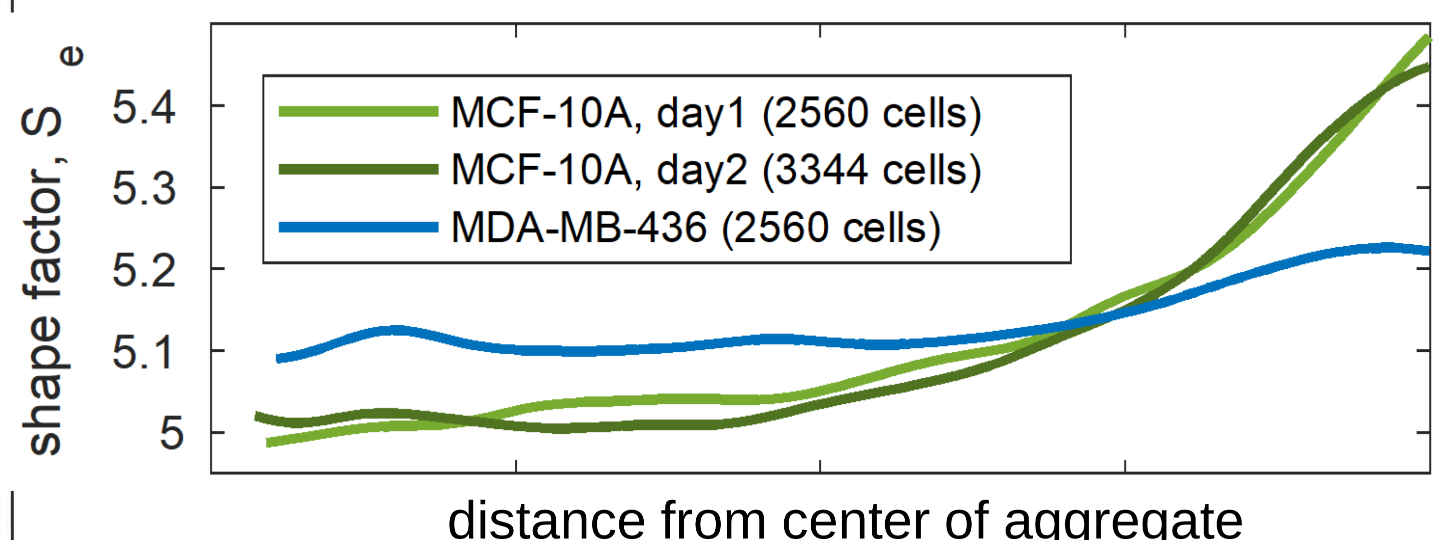


Käs lab, Leipzig University

Testing predictions in breast cancer cell lines







Steffen Grosser, Jürgen Lippoldt, Josef Käs, Matthias Merkel, +++

Ojan
Damavandi

Sadjad
Arzash

Elizabeth
Lawson-Keister

Why do vertex models work at all?

Possible answer: this rigidity transition is universal across a large class of models

Damavandi et al BioRXiv 2022 (update coming this week!)

Let's investigate changes to FUNCTIONAL FORM of U:

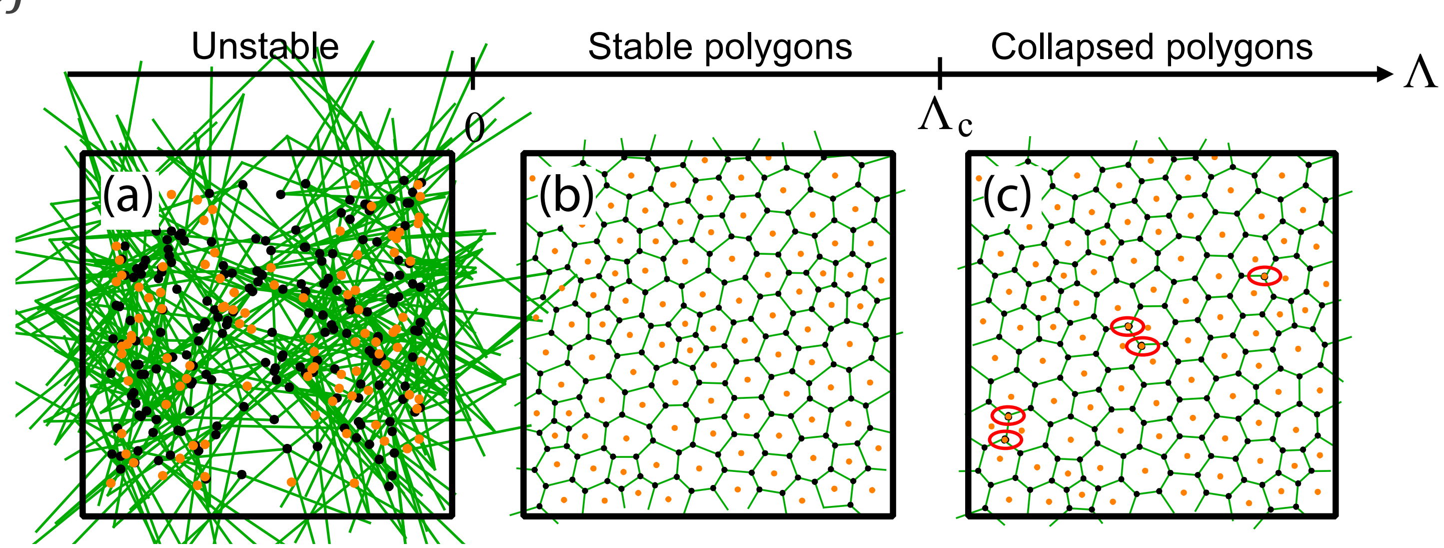
$$E_{cell} = k_A(A - A_0)^2 + k_P(P - P_0)^2$$

Standard vertex model
Farhadifar et al 2007

$$E_{cell} = K_{Af}(A_f - A_f^0)^2 + \sum_{<ij>} \gamma_{ij}\, l_{ij} + \Gamma_\propto P_\propto^2$$

Foam model
c.f Campas, Shraiman

$$E_{cell} = K_{Af}(A_f - A_f^0)^2 + \Lambda \sum_{<ij>} l_{ij}$$

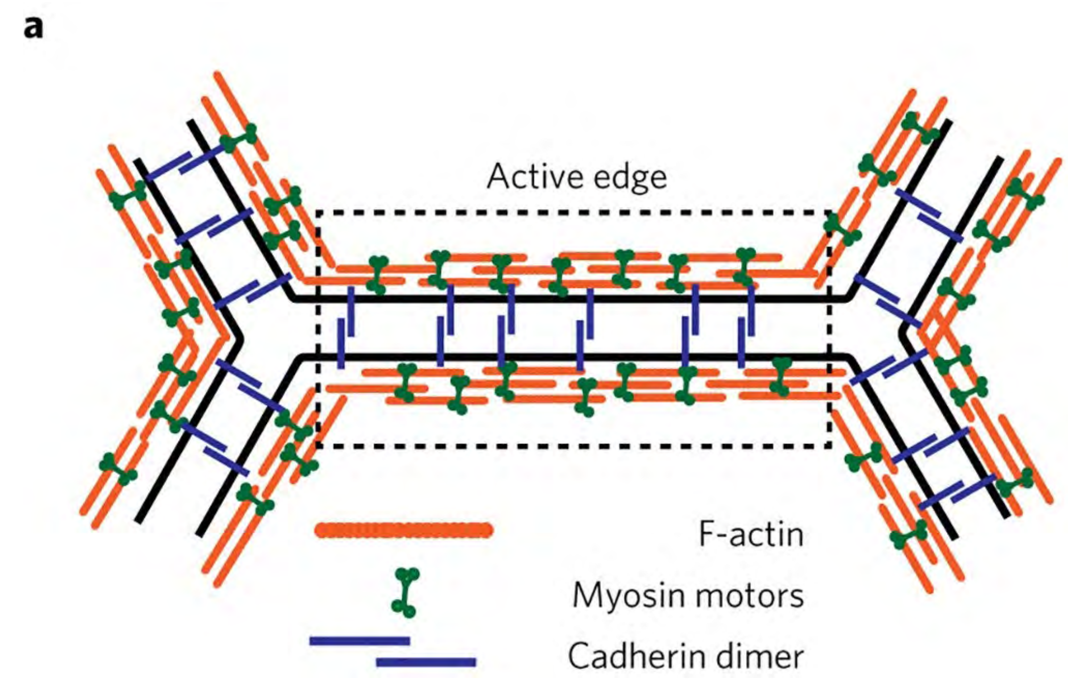


No fluid phase: system becomes numerically unstable instead.

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

Spring-edge model + extensions (big change to model!)

$$E_{cell} = K_A(A_f - A_f^0)^2 + \sum_{<ij>} k_{ij}\,(l_{ij} - l_{ij}^0)^2$$



Plus, can add dynamics on l_{ij}^0 to mimic myosin recruitment

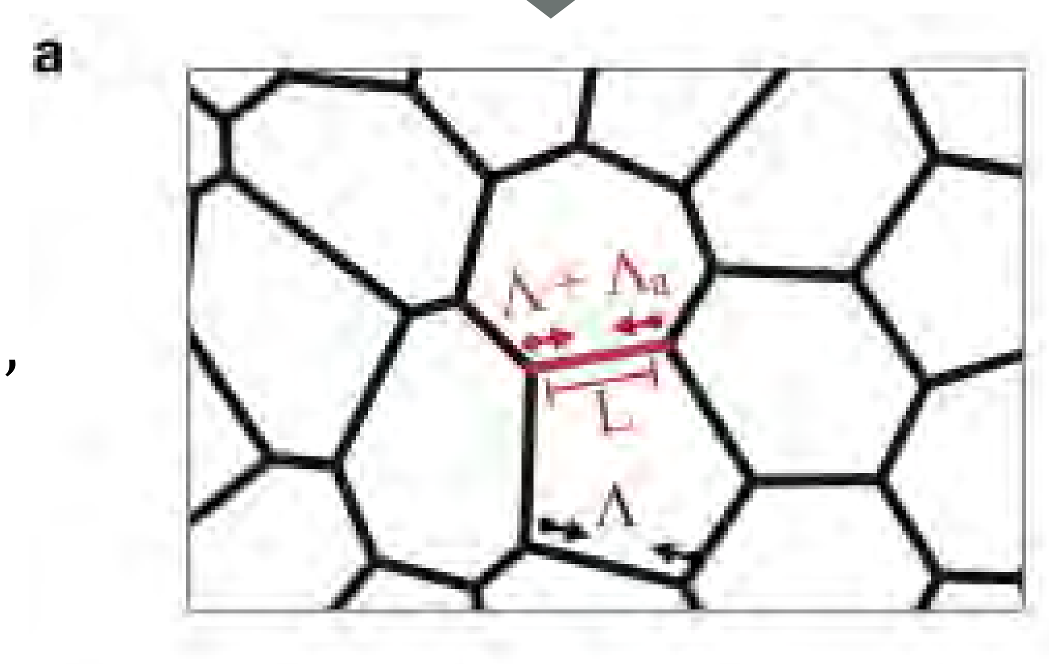
e.g. active spring edge
Staddon et al Biophys J 2019

e.g. active tension model
Noll 2017

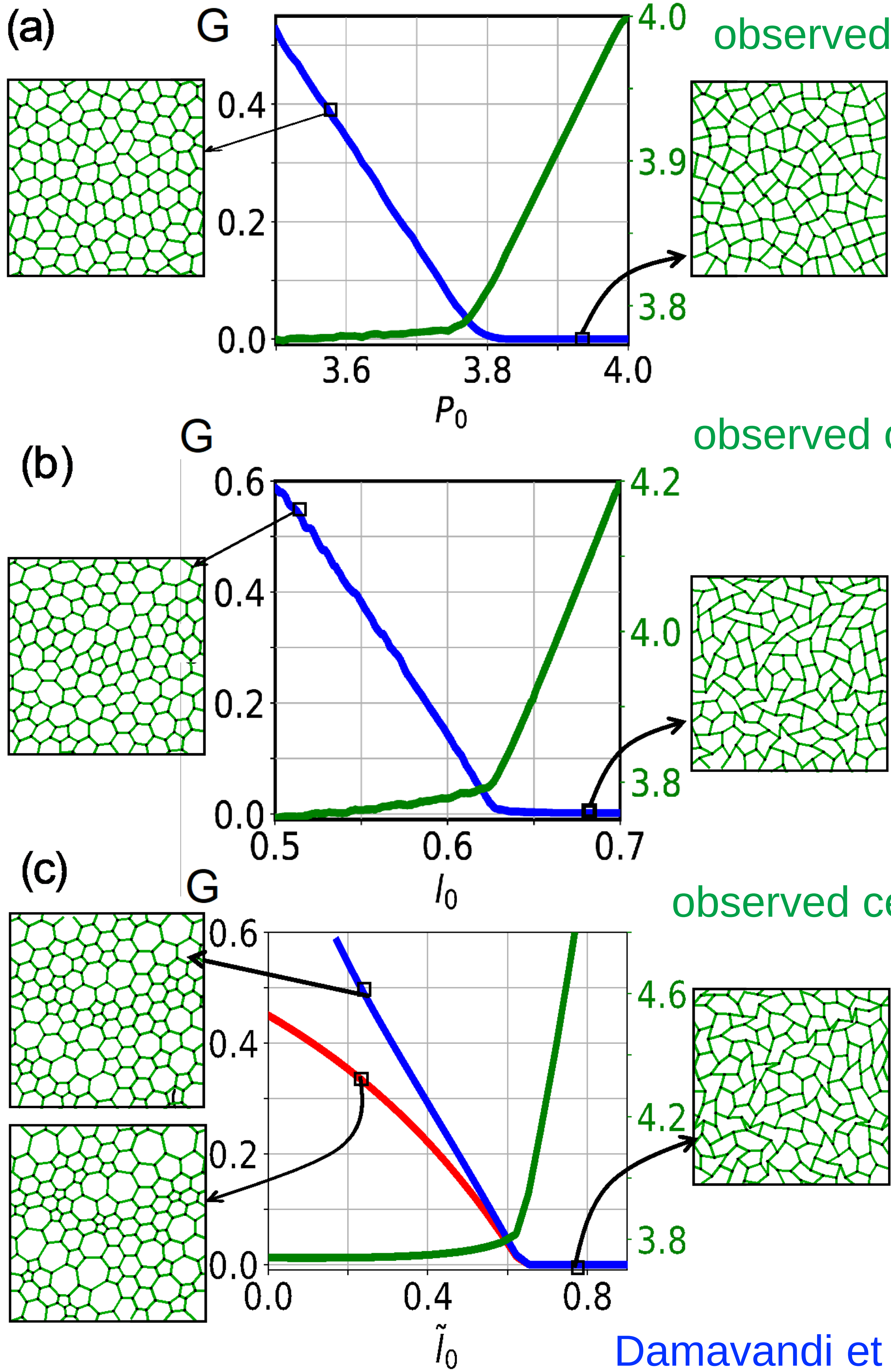
$$l^0{}_{ij}^{-1}\frac{dl_{ij}^0}{dt} = \tau_l^{-1} W\left[\frac{T_{ij}}{m_{ij}}\right] \approx \tau_l^{-1}\left(\frac{T_{ij} - m_{ij}}{m_{ij}}\right),$$

$$W[1] = 0$$

$$m_{ij}^{-1}\frac{dm_{ij}}{dt} = \alpha l^0{}_{ij}^{-1}\frac{dl_{ij}^0}{dt}$$



α myosin recruitment rate



Standard vertex model

Farhadifar et al 2007

Spring edge model

Sadhukan eLife 2022

Staddon et al Biophys J 2019

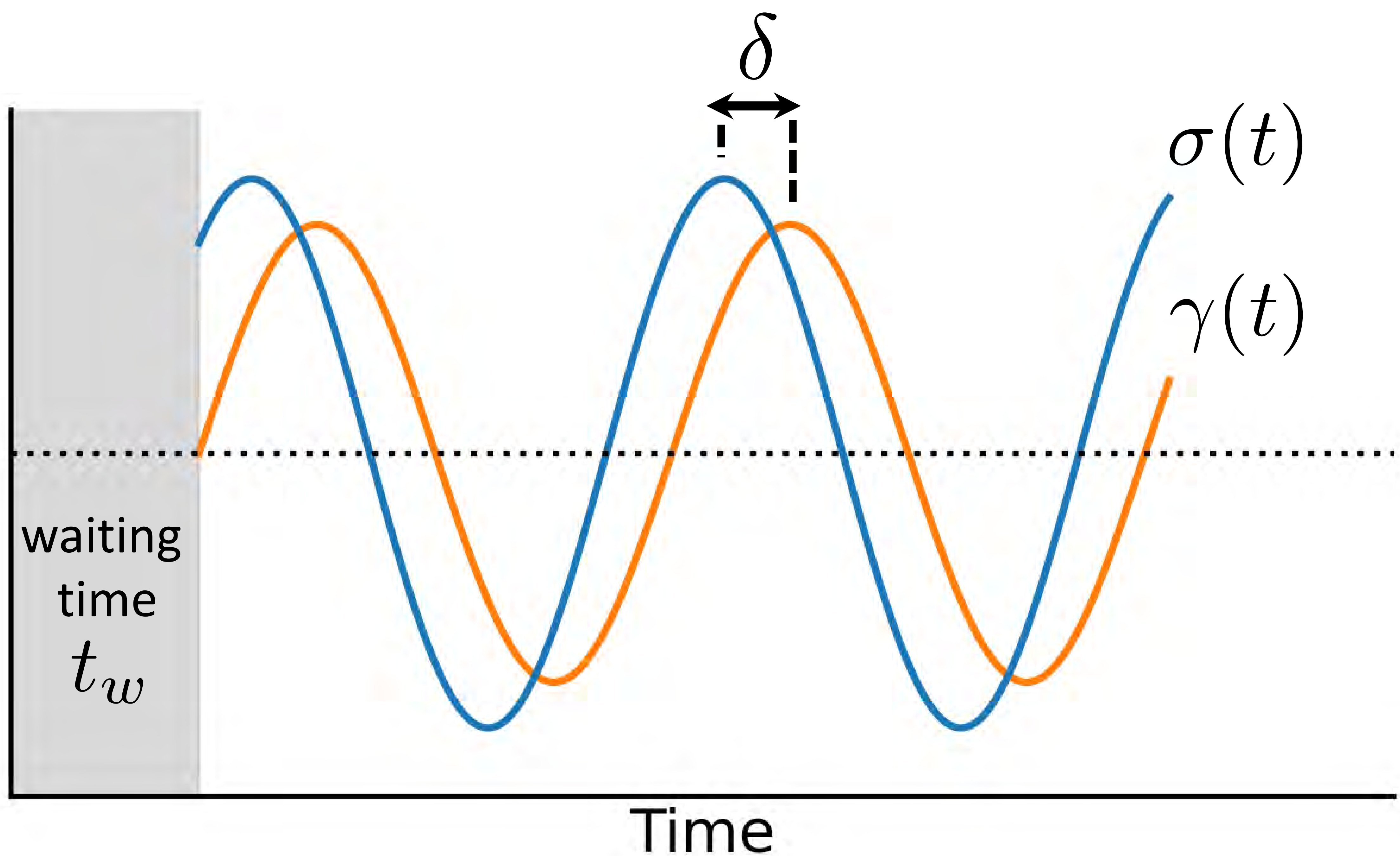
Active tension model

Noll 2017

changing α myosin recruitment rate

Damavandi et al BioRXiv 2022 (update coming this week!)

But maybe the zero-strain rate limit isn't relevant for tissues: what about finite frequency?



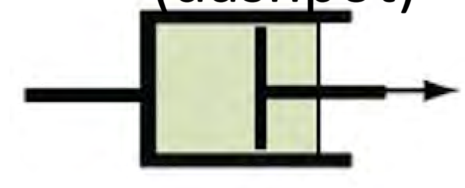
Phenomenological models in rheology

Elastic element
(spring)

$$\sigma = k\epsilon$$

Mimicking the
instantaneous bond
deformations

Viscous element
(dashpot)



$$\sigma = \eta\dot{\epsilon}$$

Mimicking the
entropic uncoiling
processes

Phenomenological models in rheology: an example

$$\sigma = \sigma_s = \sigma_d$$

$$\epsilon = \epsilon_s + \epsilon_d$$

$$\dot{\epsilon} = \dot{\epsilon_s} + \dot{\epsilon_d} = \frac{\dot{\sigma}}{k} + \frac{\sigma}{\eta}$$

Maxwell material

$$\boxed{k\dot{\epsilon} = \dot{\sigma} + \frac{1}{\tau}\sigma}$$

$$\tau = \eta/k$$

→ In stress relaxation, strain rate is zero →

$$\sigma(t) = \sigma_0 \exp(-t/\tau)$$

Dynamic loading

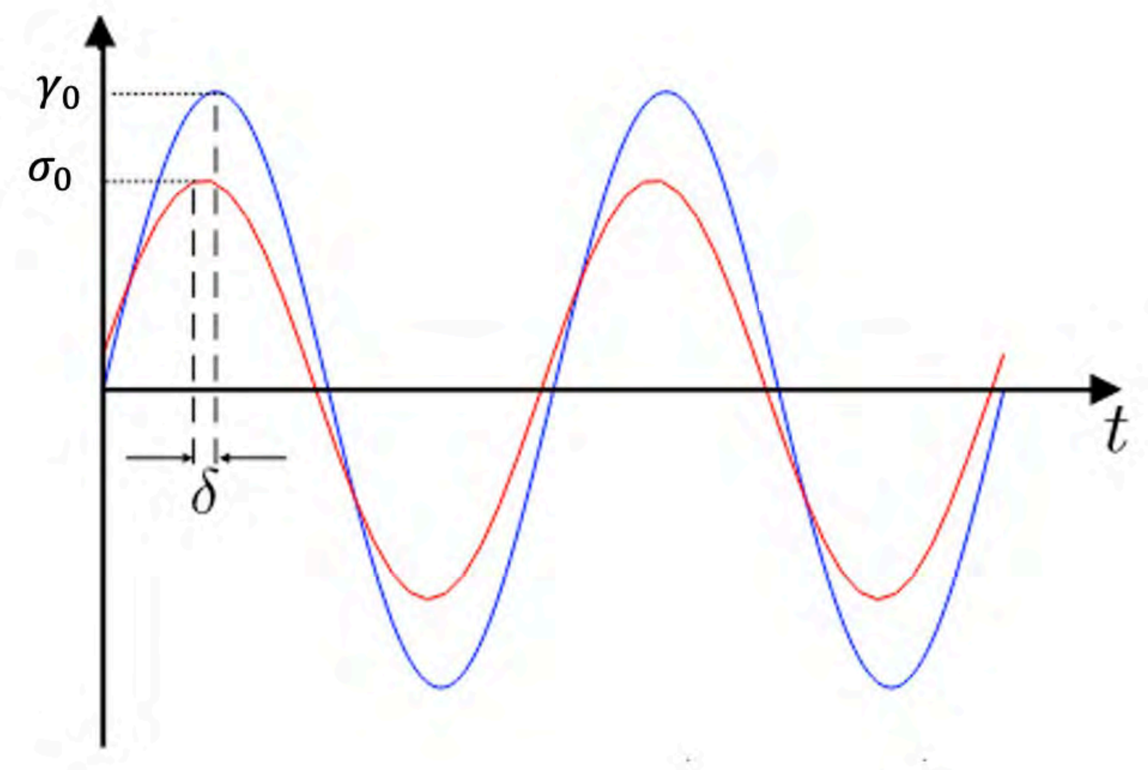
$$\gamma(t) = \gamma_0 \sin(\omega_0 t)$$

$$\sigma(t) = \sigma_0 \sin(\omega_0 t + \delta) = \overbrace{\sigma_0 \cos(\delta)}^{\sigma_0'} \sin(\omega_0 t) + \overbrace{\sigma_0 \sin(\delta)}^{\sigma_0''} \cos(\omega_0 t)$$

$G' = \dfrac{\sigma_0'}{\gamma_0}$ in-phase or storage modulus

$G'' = \dfrac{\sigma_0''}{\gamma_0}$ out-of-phase or loss modulus

$$\tan(\delta) = \frac{G''}{G'}$$

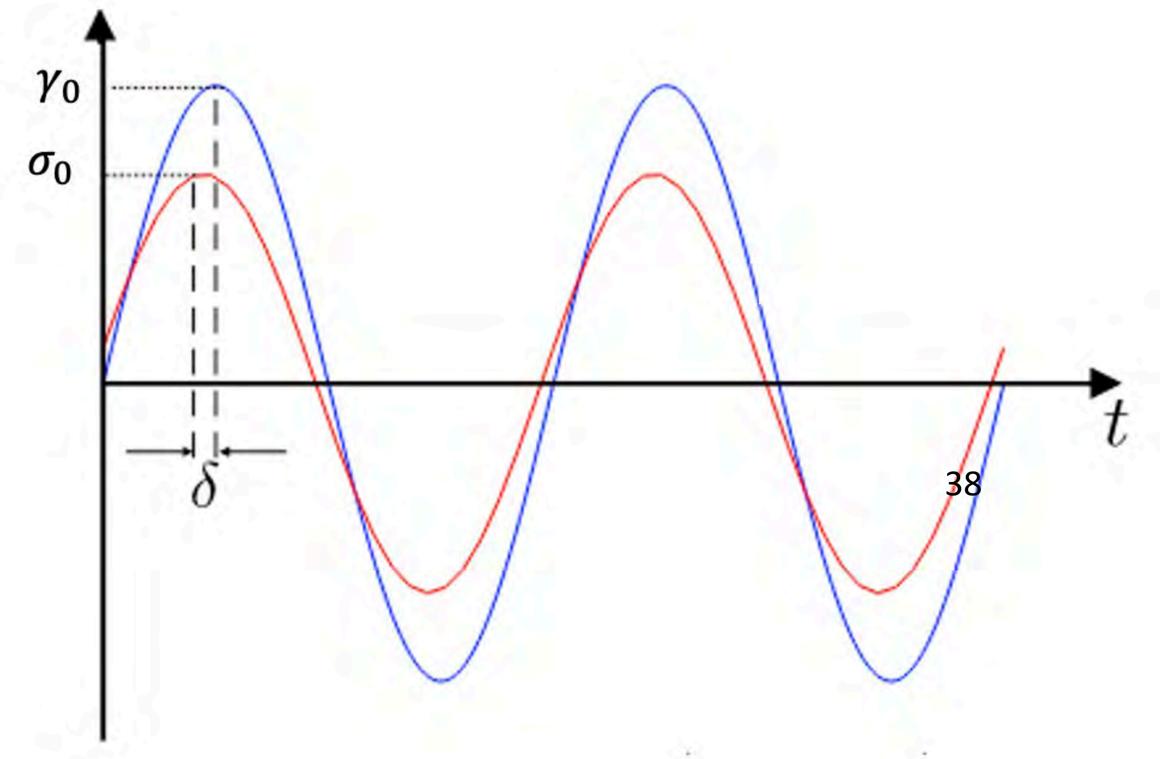


Dynamic loading

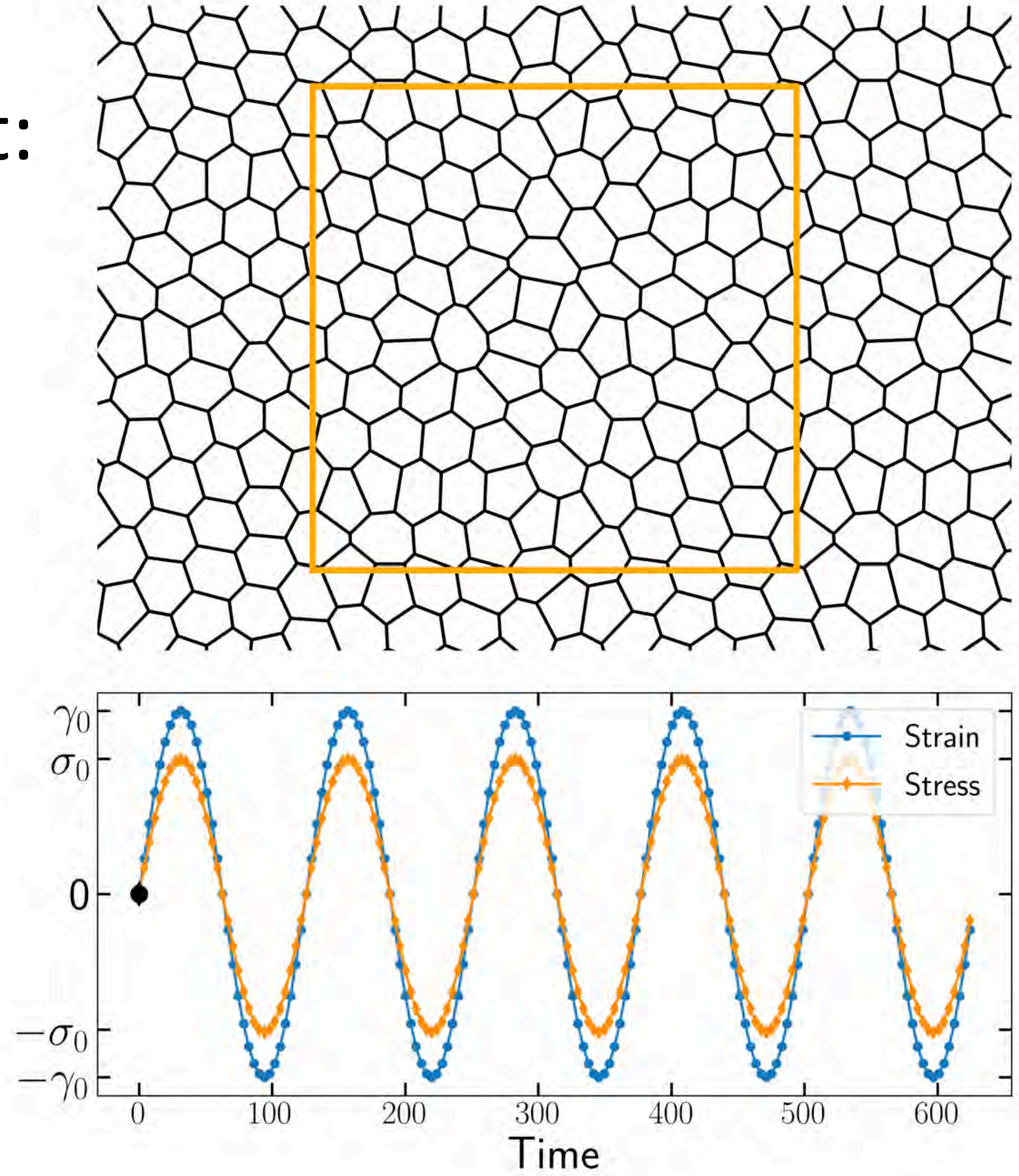
$$\gamma(t) = \gamma_0 \sin(\omega_0 t)$$

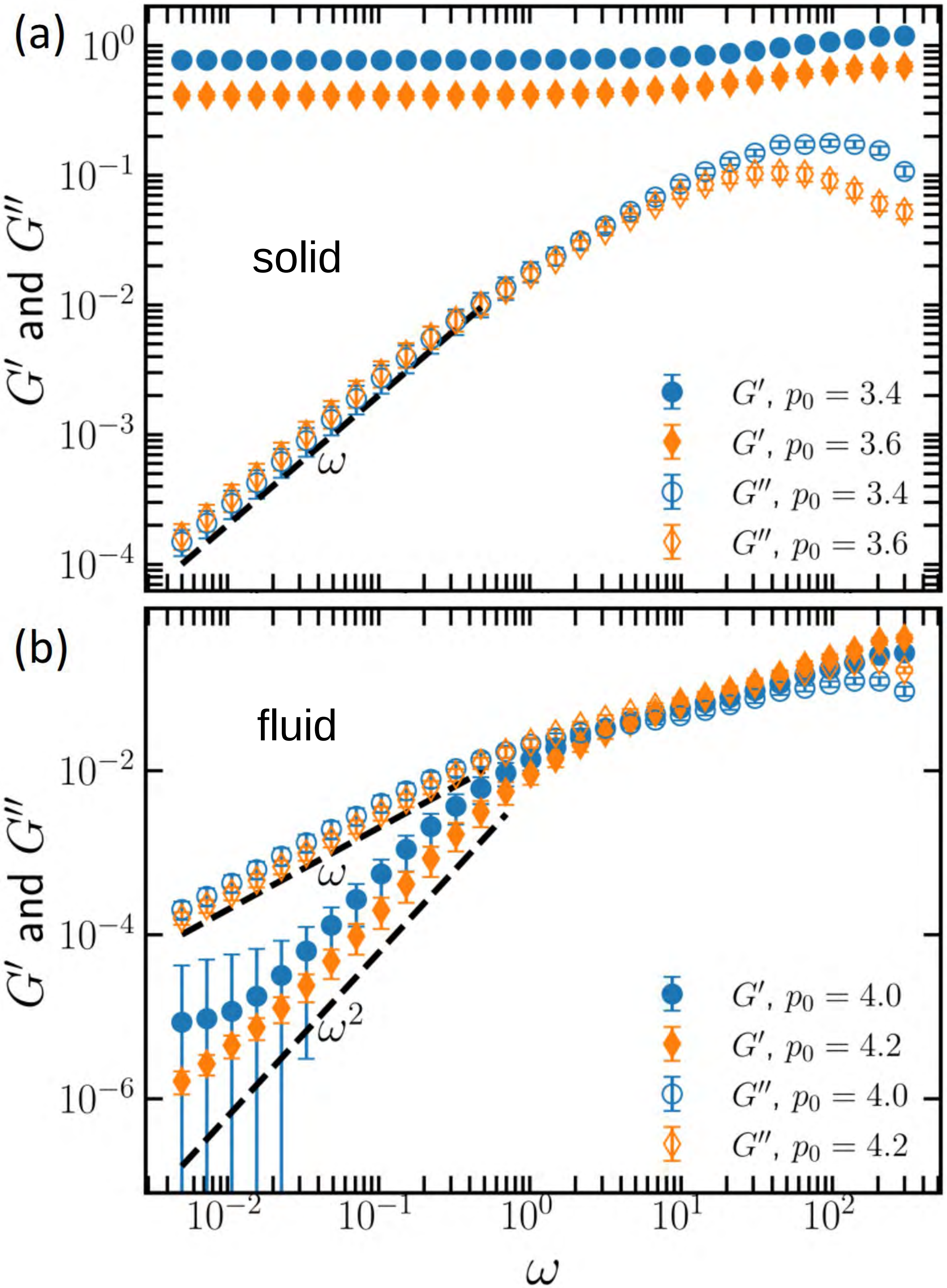
$$\sigma(t) = \sigma_0 \sin(\omega_0 t + \delta) = \overbrace{\sigma_0 \cos(\delta)}^{\sigma_0'} \sin(\omega_0 t) + \overbrace{\sigma_0 \sin(\delta)}^{\sigma_0''} \cos(\omega_0 t)$$

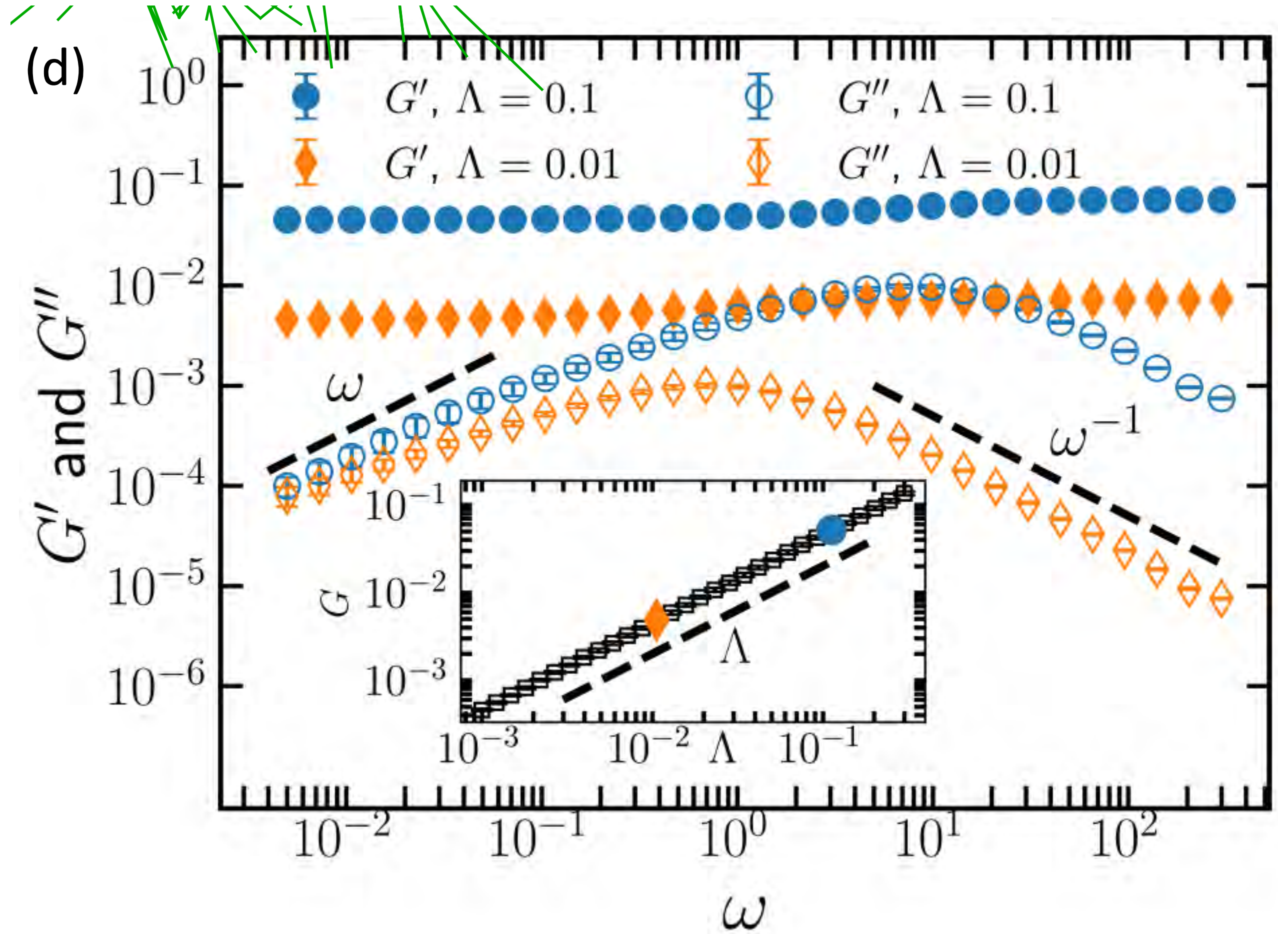
$$\sigma(t) = \gamma_0 \left\lfloor G' \sin(\omega_0 t) + G'' \cos(\omega_0 t) \right\rfloor$$



How do we do it:





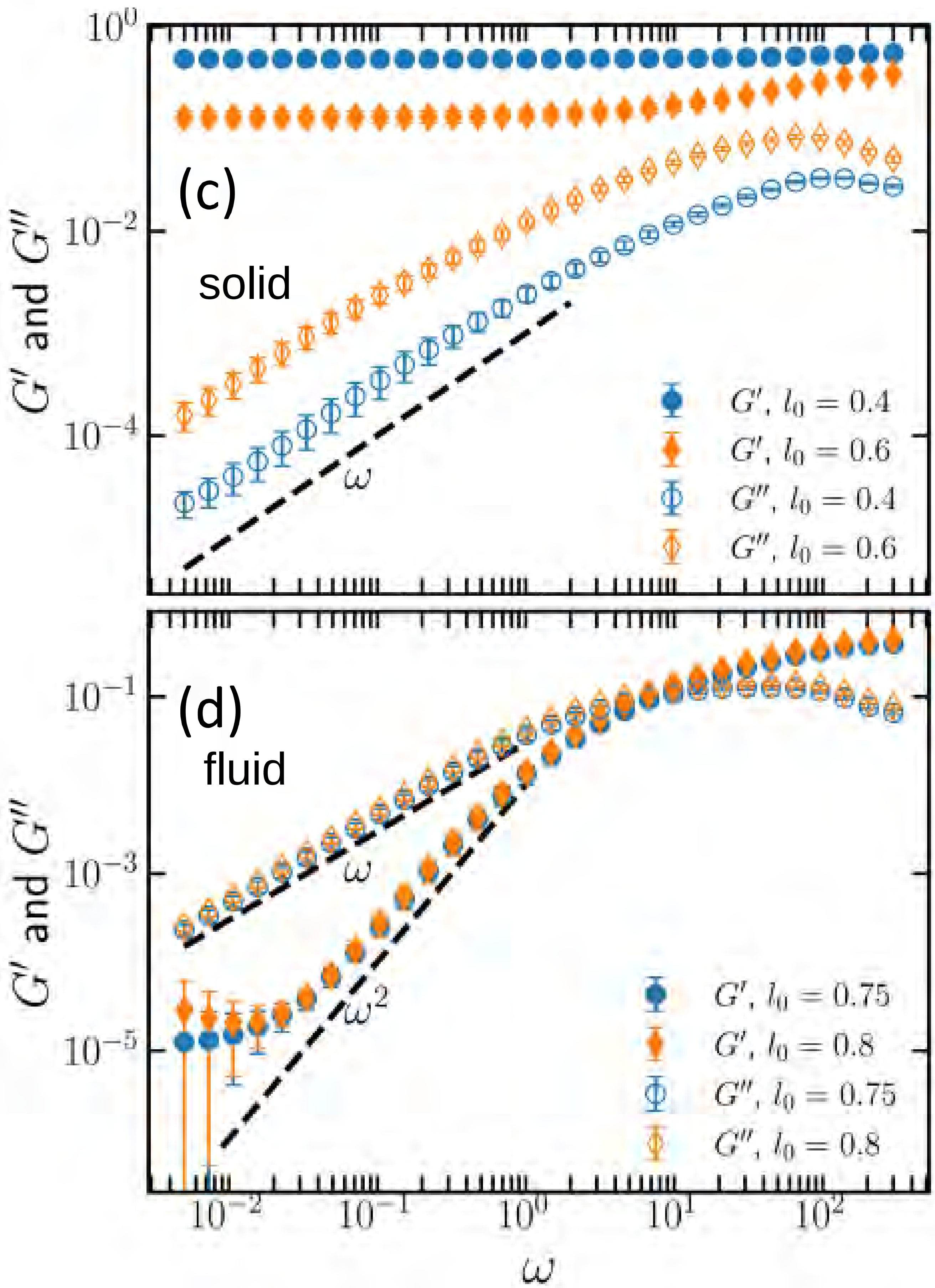


Foam model (no fluid phase)

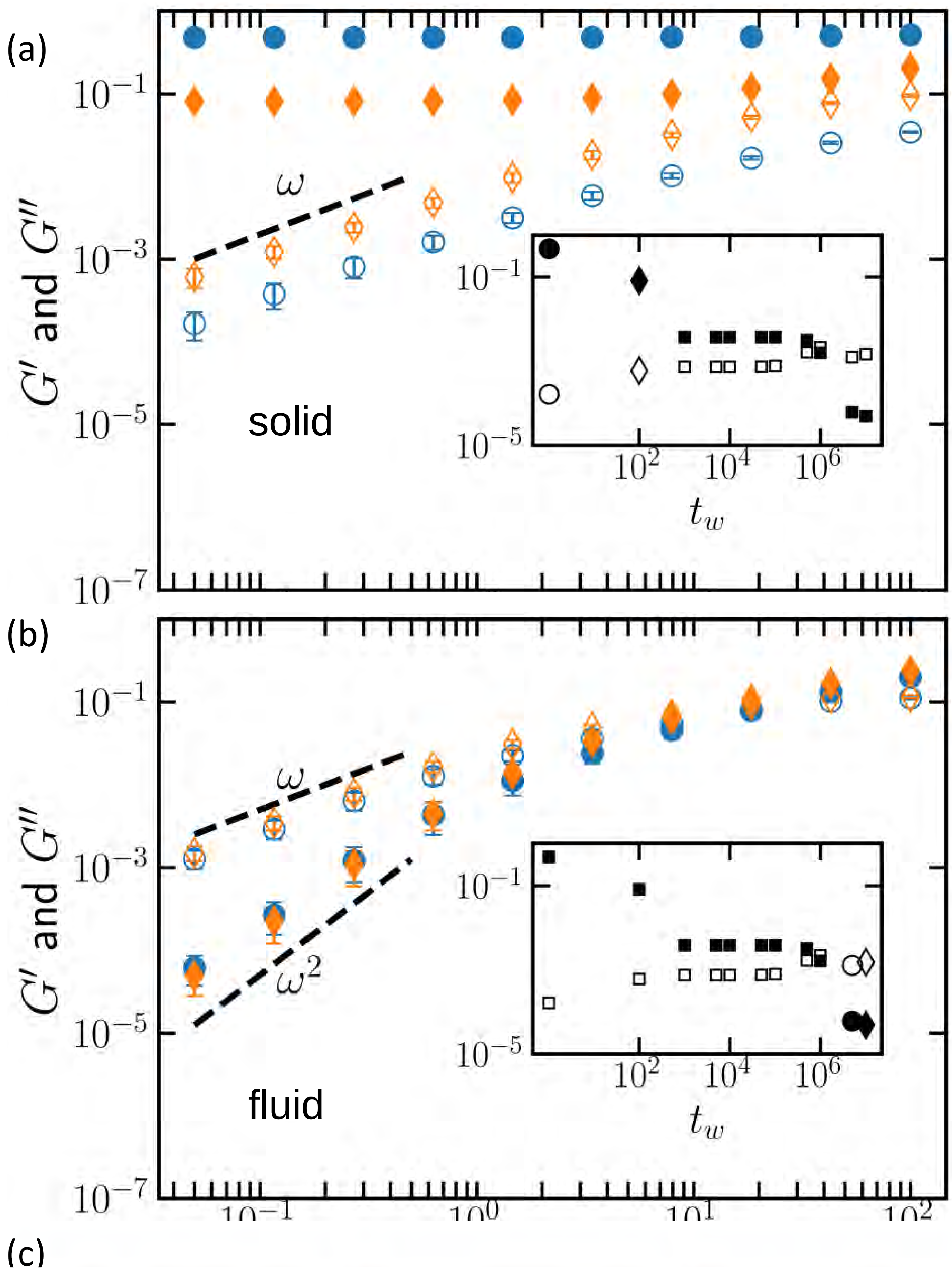
c.f Campas, Shraiman

Standard vertex model

c.f. Tong PLOS Comp Bio 2022



Spring-edge model



Active spring-edge model

Conclusion: Yes, there is universal rigidity transition across many models, predicted by the shape parameter, in both in zero-frequency and finite frequency response.

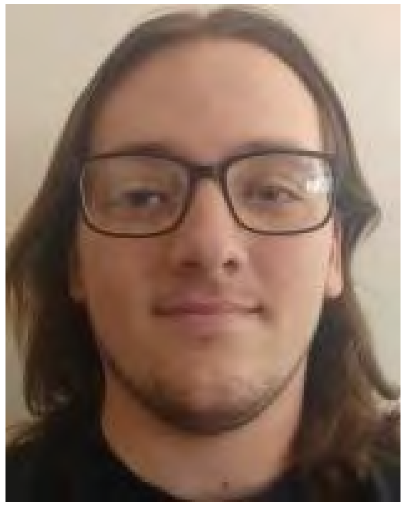
Why?

Second order rigidity: there are two length scales in the system:
1) the number of cells/vertices per unit area and
2) the characteristic distance between two cells or vertices defined by the energy functional (parameterized by the cell perimeter in vertex models or the rest length for edges in spring-edge models)

The second-order rigidity transition occurs at a special point in configuration space where states that are compatible with both the energy length scale and the density length scale disappear.

perhaps cell shape is a dimensionless comparison of these two lengthscales that generically describes the point at which these states disappear across models?

Chris Santangelo

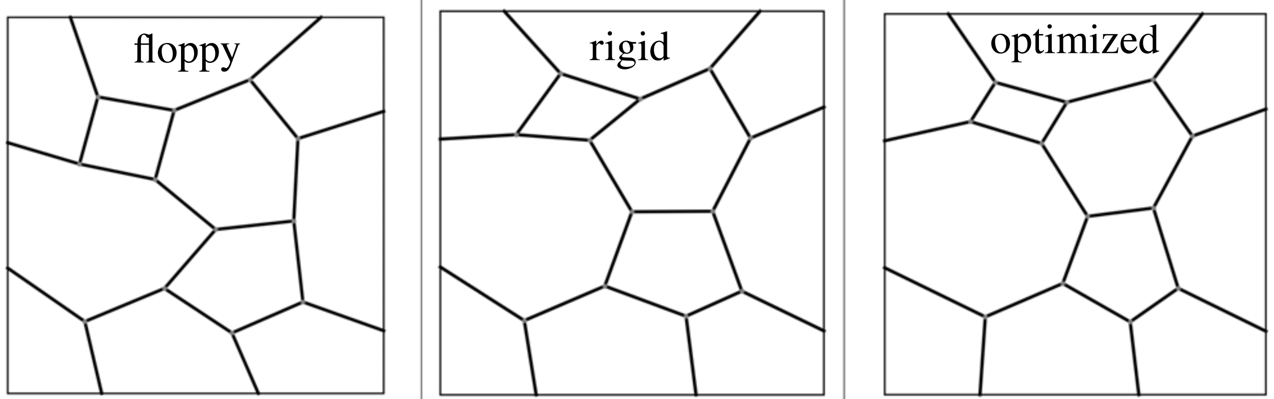


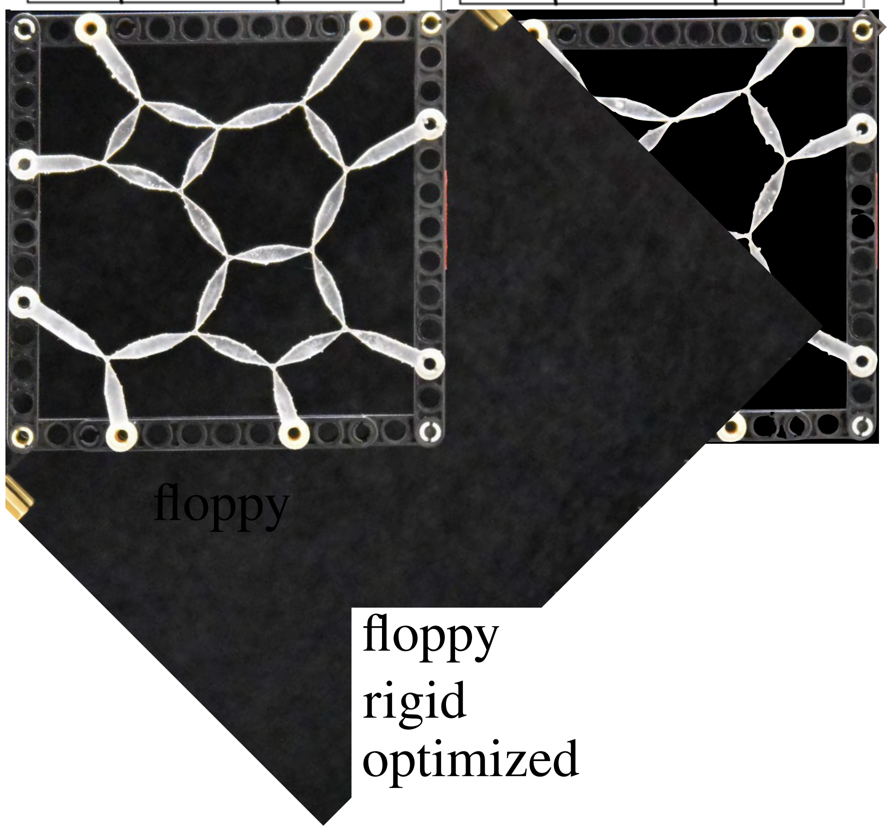
Tyler Hain

Designing mechanical metamaterials

Hain, Santangelo, Manning, to appear on arXiv this week!

optimized: maximum bulk stiffness / minimum shear stiffness





floppy

optimized

floppy
rigid
optimized

shear force

Joe Roback

Ryan Hayward

Preliminary: Examples of small designed networks

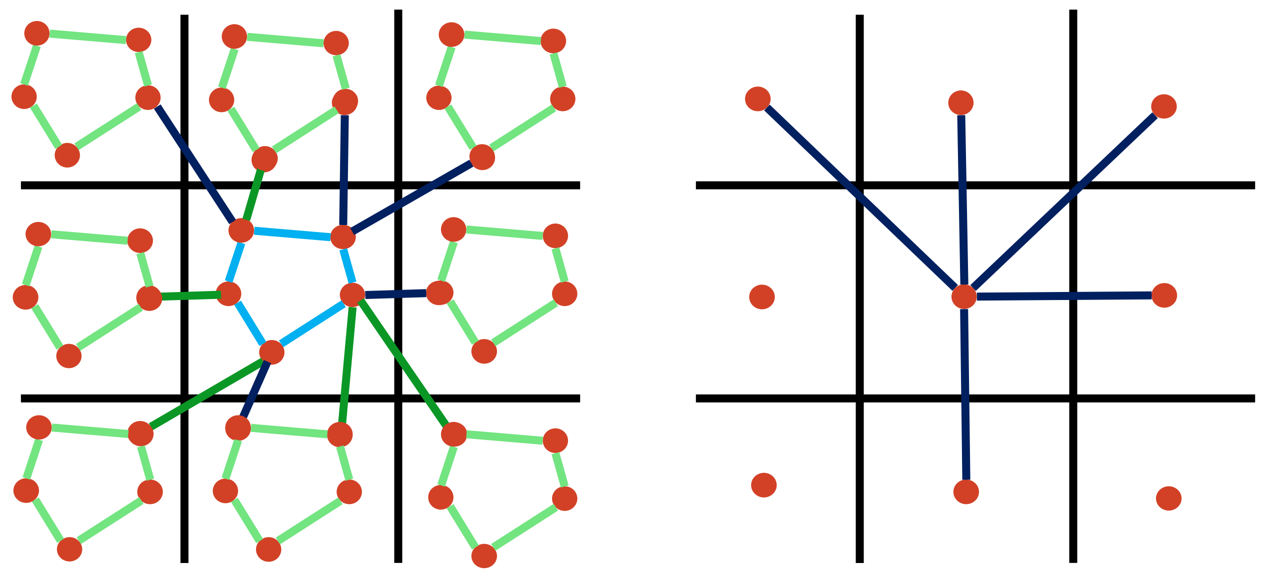
3D printed hydrogel

theory: representing a spring network

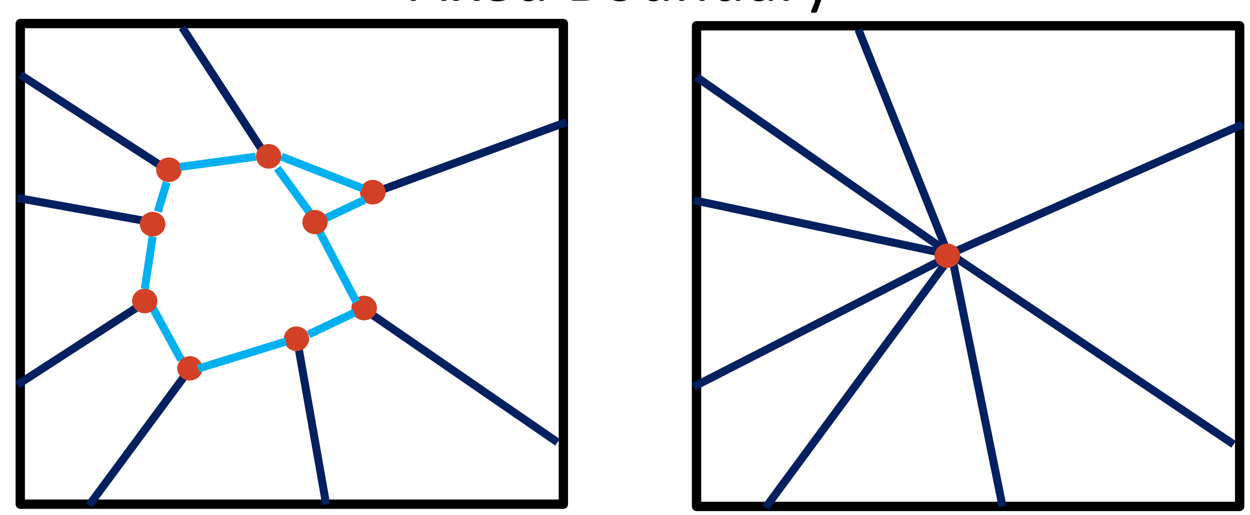
$$L_{\alpha\mu} = g_{\alpha i} x_{i\mu} + b_{\alpha\mu}$$

Encodes boundary conditions: which edges don't go to zero when all vertices are collapsed?

Periodic Boundary



Fixed Boundary



Can we make a new set of degrees of freedom that parameterizes the critical manifold?

The critical manifold contains all configurations that satisfy force balance while having internal stresses:

$$F(\sigma, x) = 0$$

Net forces on vertices → F

Generalized stresses → σ

Coordinates of vertices → x

Can we solve for the coordinates?

$$x(\sigma)$$

Describe internal stresses by coarse-graining the lowest level degrees of freedom (node coordinates) into higher geometric quantities (lengths, areas, etc)

$$F(\sigma, x) = \frac{\partial E}{\partial x_i} = \sum_\alpha \frac{\partial E}{\partial h_\alpha}\frac{\partial h_\alpha}{\partial x_i} = \sum_\alpha \sigma_\alpha \frac{\partial h_\alpha}{\partial x_i}$$

Geometric relationship

Generalized stress associated with h_α

If we instead choose $h_\alpha = L_\alpha^2/2$, the force balance equation is linear!

$$\sigma_\alpha = \frac{T_\alpha}{L_\alpha}$$

Tension on edge α

Length of edge α

Generalized stress is a force density

$$F(\sigma, x) = P\vec{x} + \vec{b} = 0$$

Prestress Matrix

Quantifies boundary conditions

$$P = \sigma_\alpha \frac{\partial^2 h_\alpha}{\partial x_{i\mu} \partial x_{j\nu}} = [\sigma_\alpha g_{\alpha i} g_{\alpha j}]\delta_{\mu\nu}$$

Schek, Comput. Methods Appl. Mech. Eng. (1974)

Yes, we can parameterize the critical manifold!

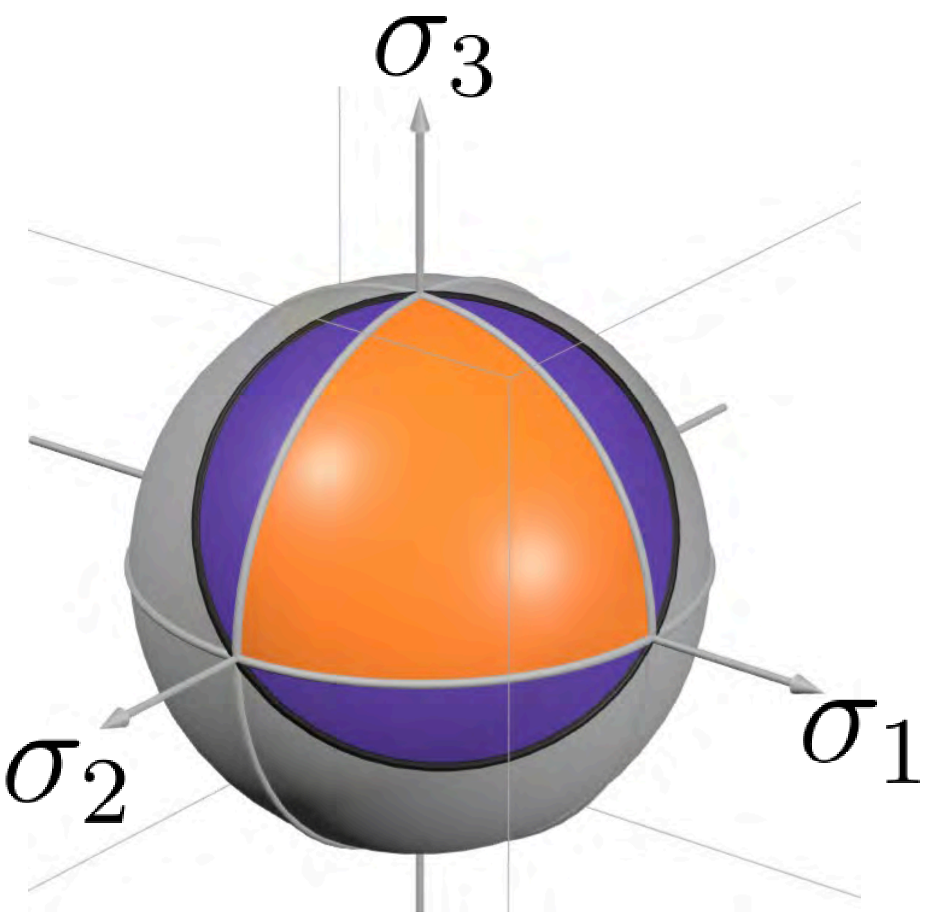
If you give me your favorite

- Network structure: g
- Boundary conditions: b
- Self-stress: σ

I can give you the coordinates of the corresponding critical configuration:

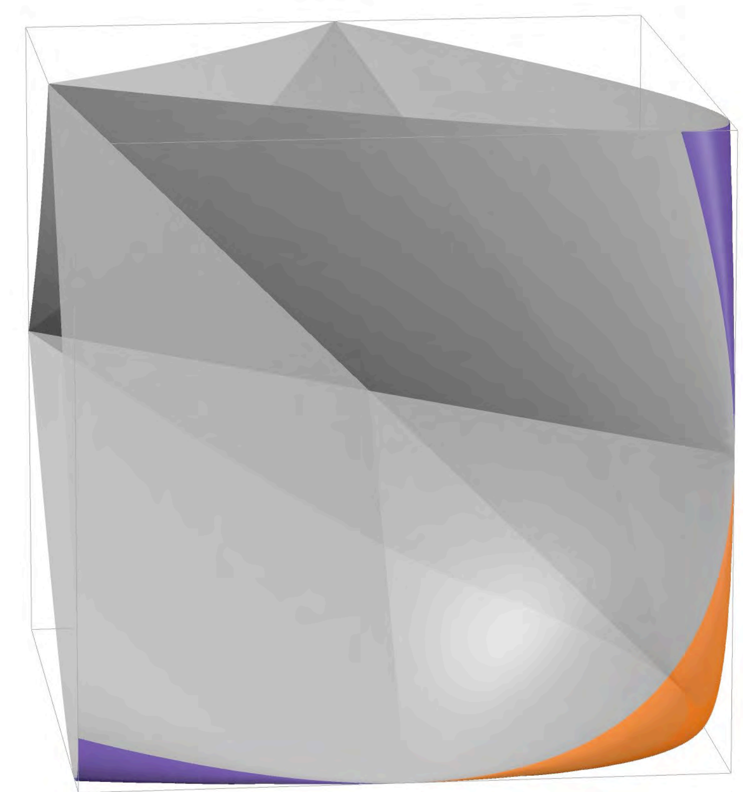
$$x_{i\mu}(\sigma) = -\sum_{\alpha j} P^{-1}_{ij} g_{\alpha j} \sigma_\alpha b_{\alpha\mu}$$

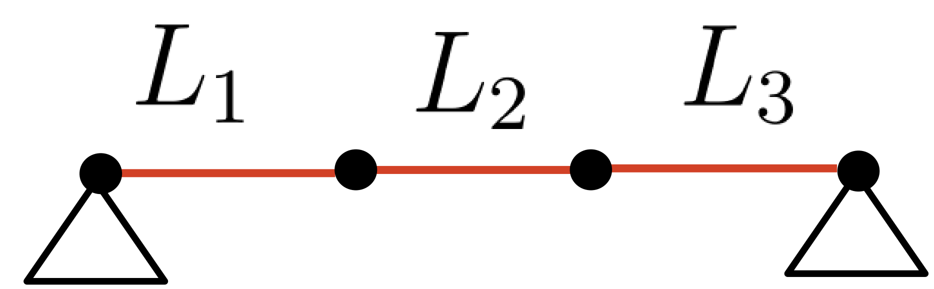
Critical Manifold of the 3-Bar Linkage



$$x_{i\mu}(\sigma)$$

$$P\vec{x} + \vec{b} = 0$$





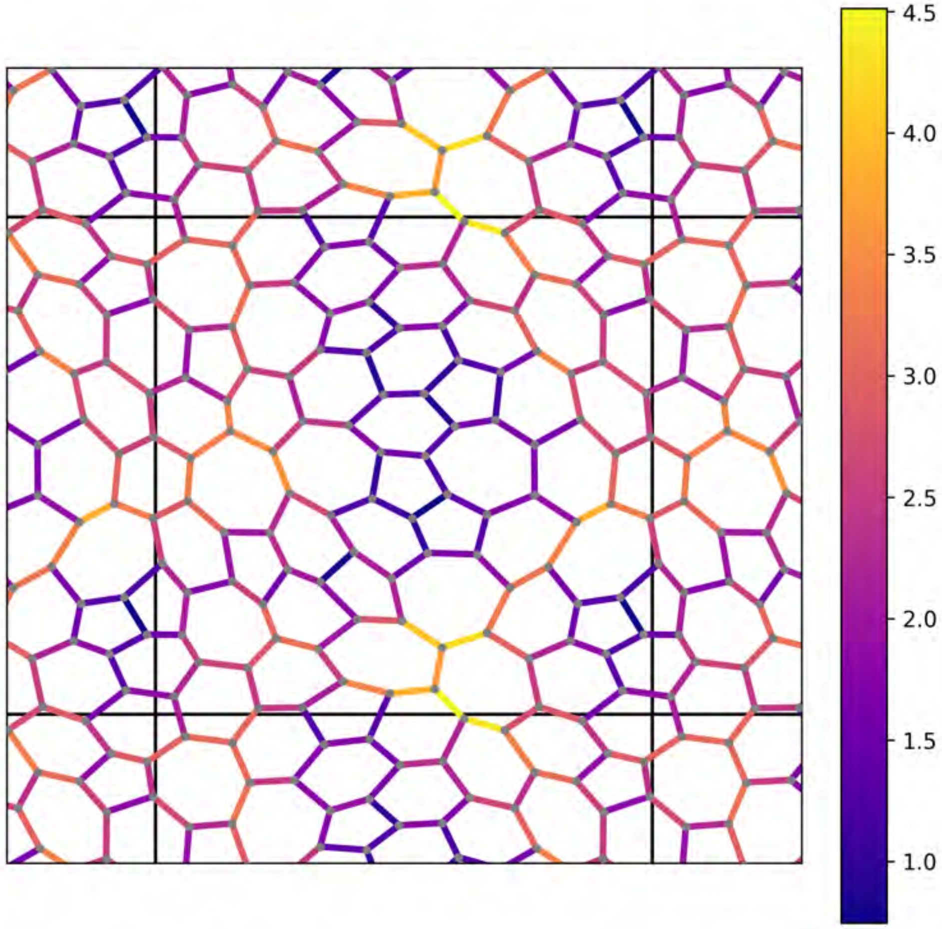
Space of Self-Stresses

With this self-stress parameterization, we can rationally search the critical manifold for special configurations

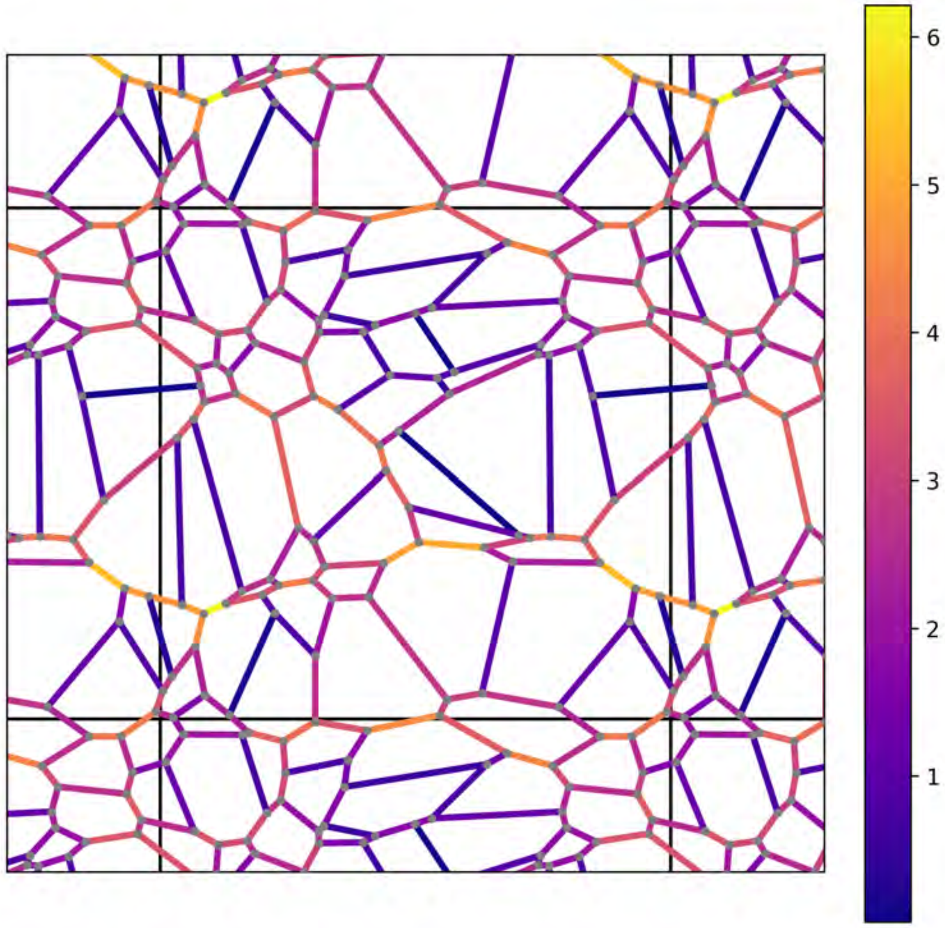
Can we compare these with configurations sampled randomly from the critical manifold?

Randomly generated configurations

Randomly assign rest lengths, strain to the critical manifold



Randomly assign self-stresses, use parameterization to get configuration

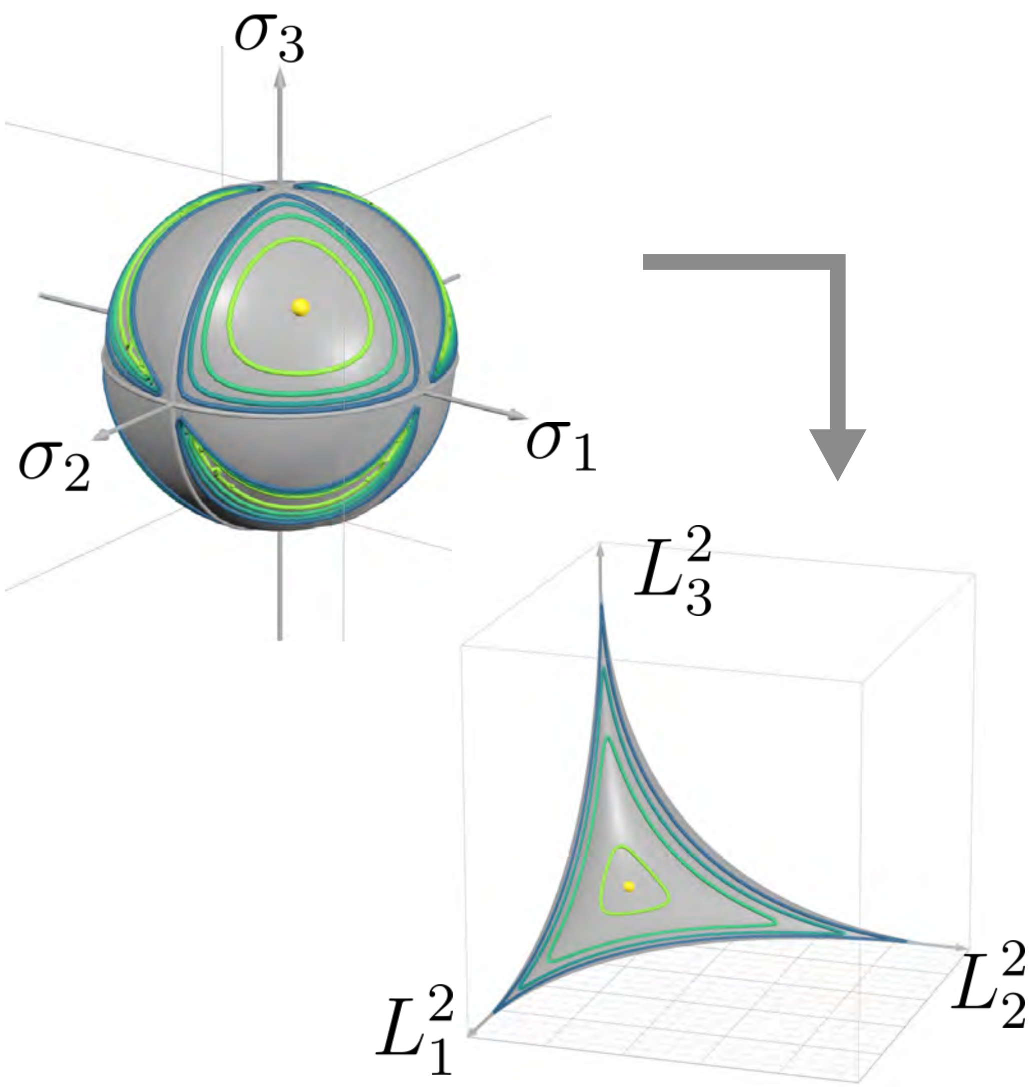


With this self-stress parameterization, we can rationally search the critical manifold for special configurations

Use gradient descent to traverse the space of self-stresses to optimize any objective function

$$\frac{\mathrm{d}\mathcal{O}}{\mathrm{d}\sigma_\alpha} = \frac{\partial \mathcal{O}}{\partial \sigma_\alpha} + \sum_{\beta\mu} \frac{\partial \mathcal{O}}{\partial L_{\beta\mu}} \frac{\partial L_{\beta\mu}}{\partial \sigma_\alpha}$$

Self-stress parameterization lets us take a total derivative!



With this self-stress parameterization, we can rationally search the critical manifold for special configurations

Structure-Based Objective Functions:

Say we want to find rigid networks with regular structure: e.g. all edges have equal lengths or equal tensions

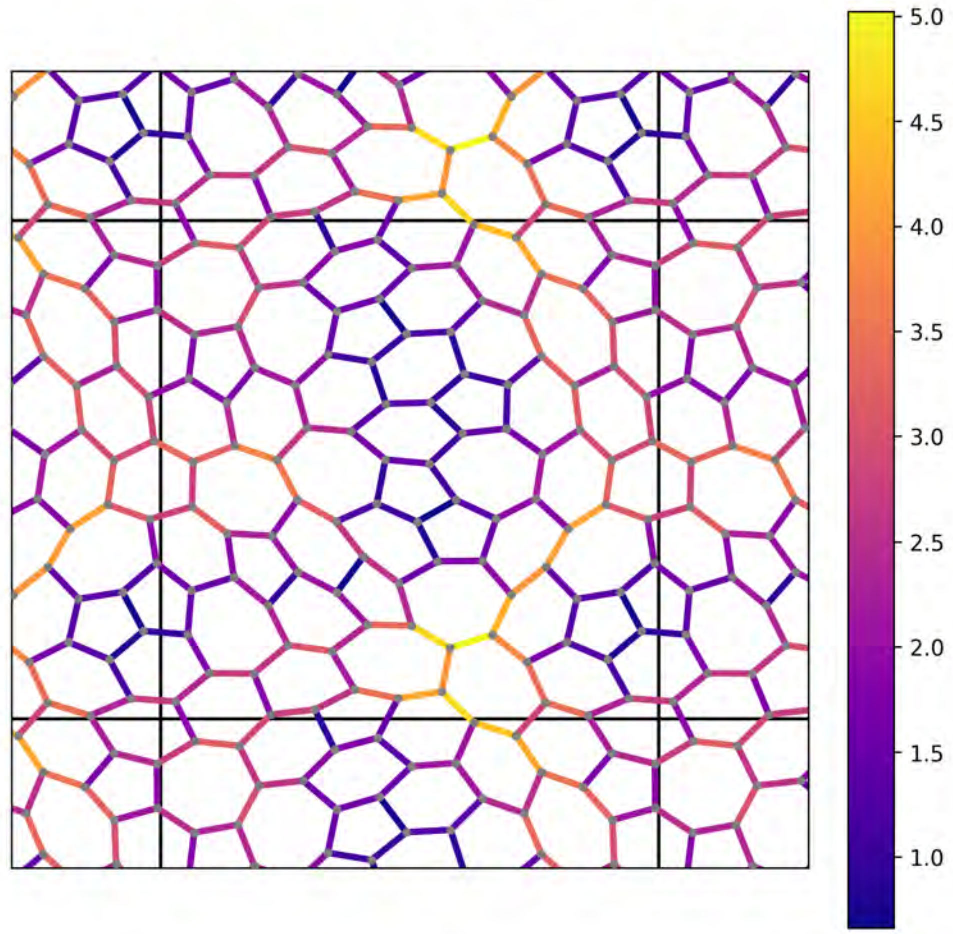
We can minimize the fluctuations of these quantities

$$V_L = \frac{\langle (L - \langle L \rangle)^2 \rangle}{\langle L \rangle^2}$$

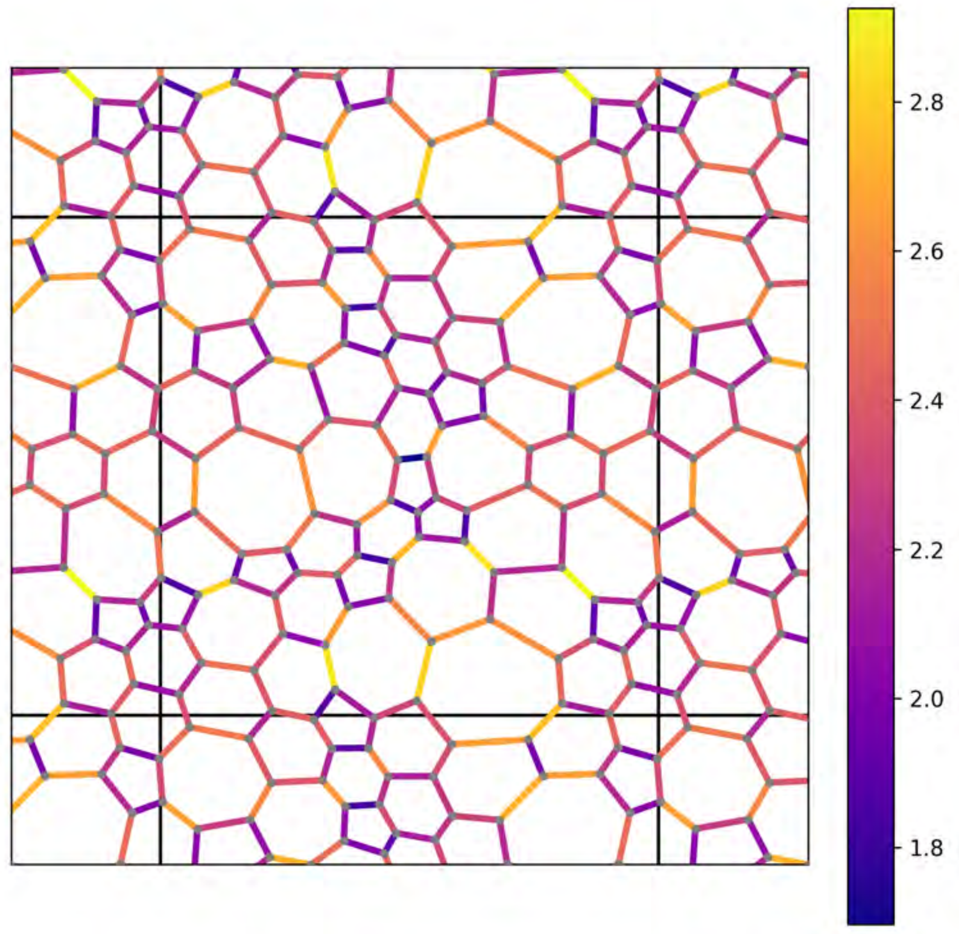
$$V_\tau = \frac{\langle (\tau - \langle \tau \rangle)^2 \rangle}{\langle \tau \rangle^2}$$

Structural Objective Functions

Minimized length fluctuations

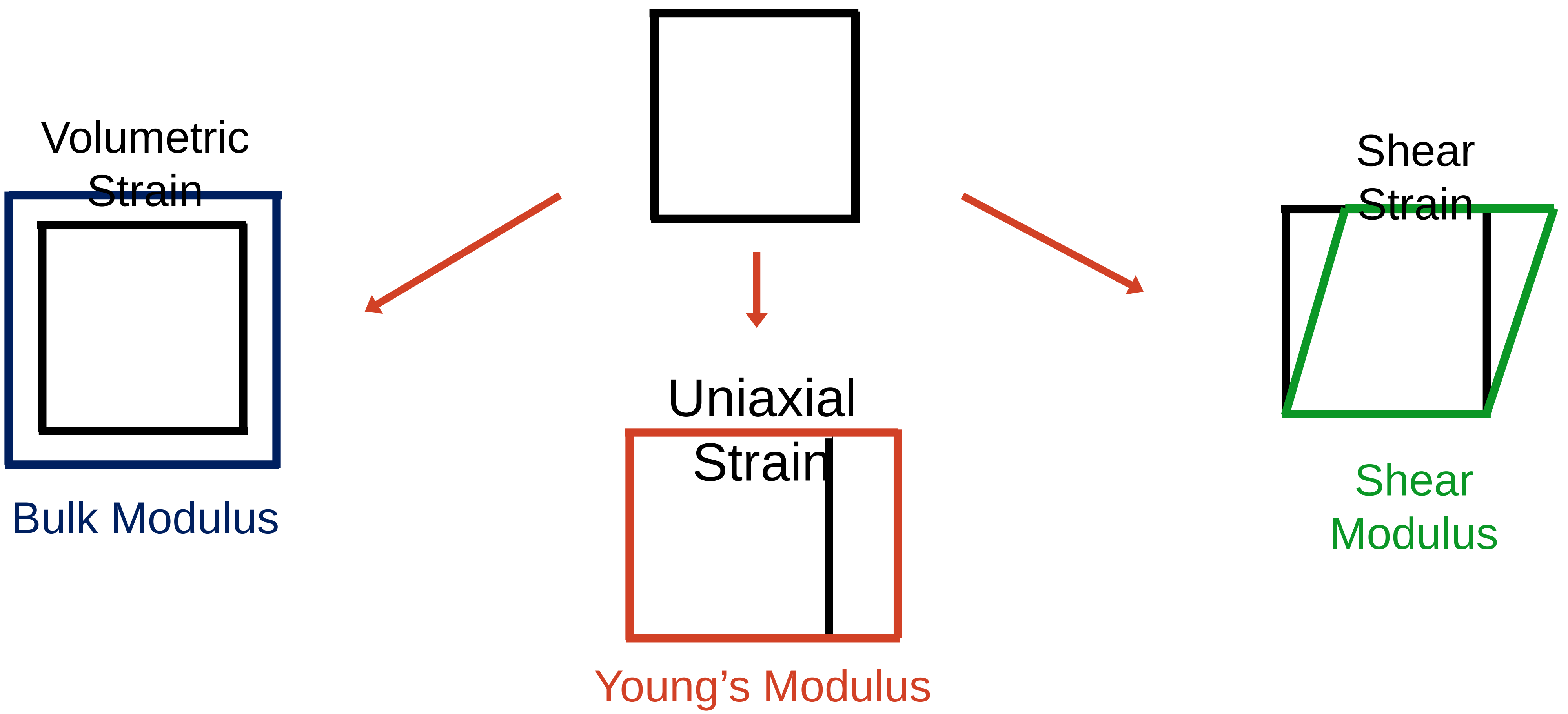


Minimized tension fluctuations

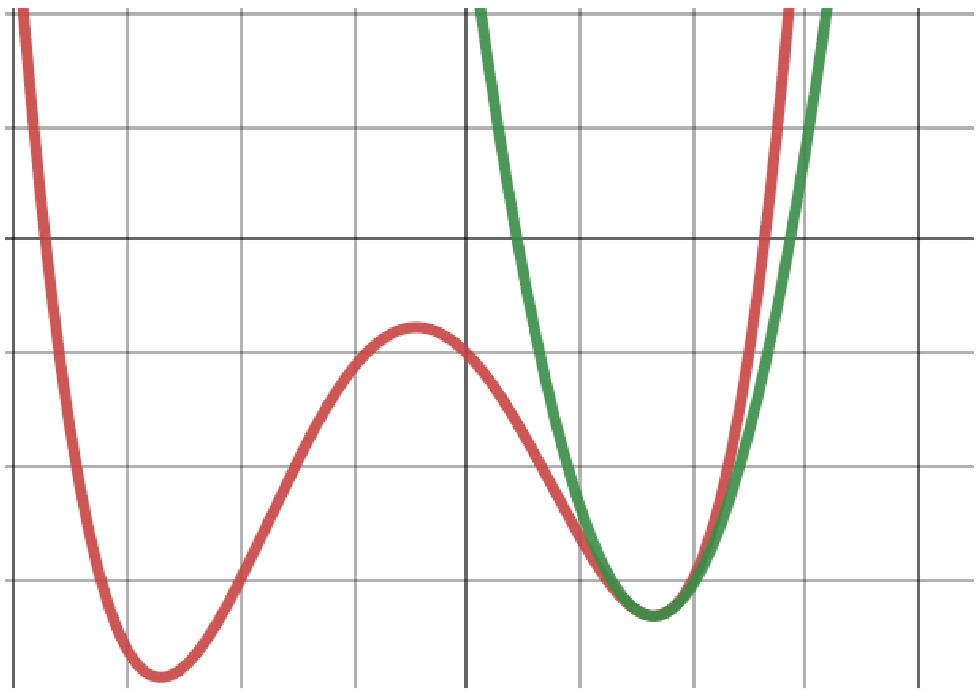


We can use the Hessian to calculate elastic moduli

- Hessian contains all microscopic details, but we often just care about the stiffness of a material under a bulk deformation



Linear Response is determined by the Hessian

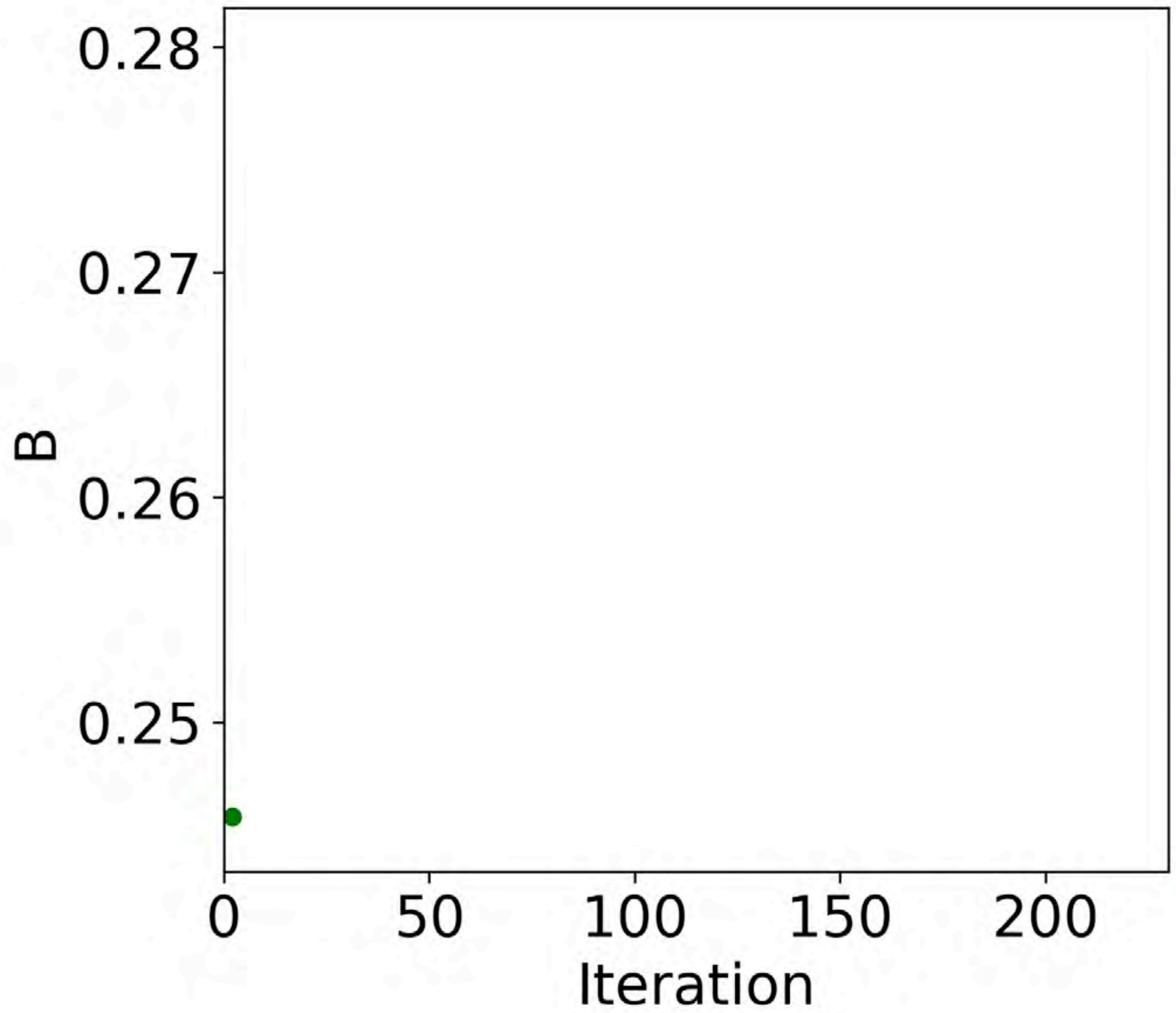


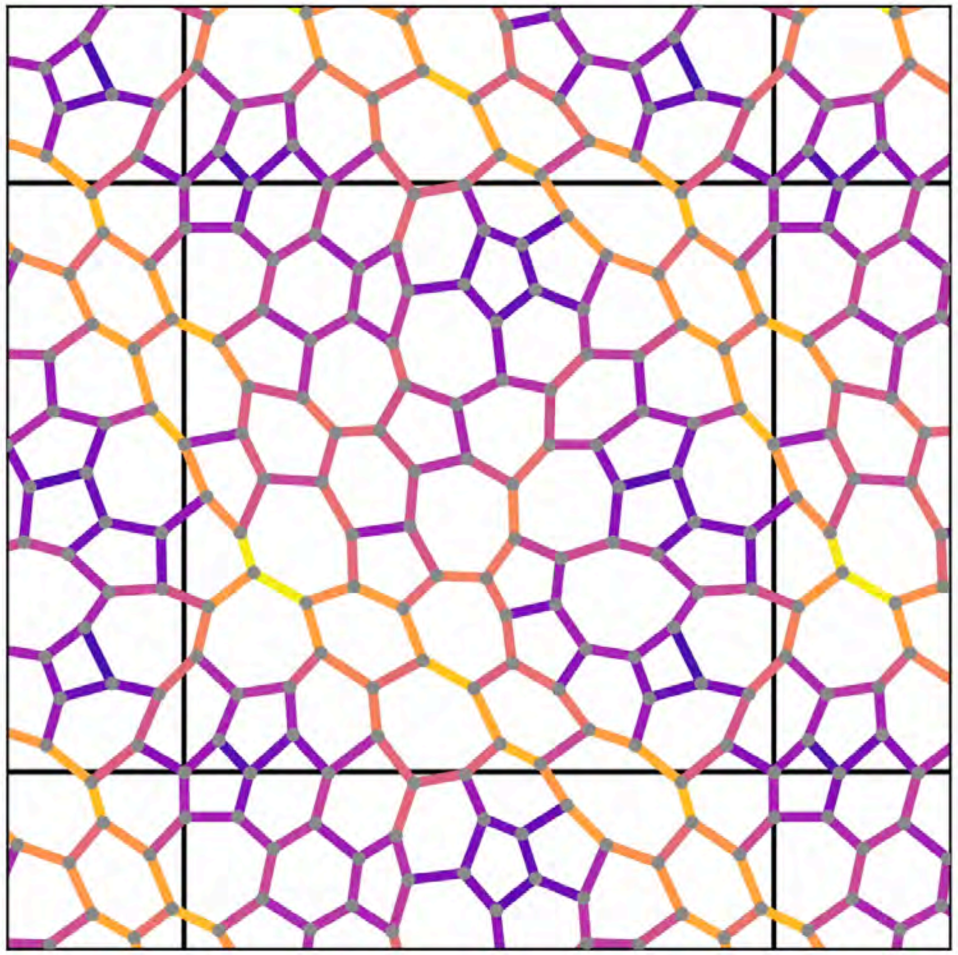
- Hessian describes the curvature of the energy landscape
- Lets us calculate the deformation due to an applied force

$$\delta E = \frac{\partial E}{\partial x_i}\delta x_i + \frac{1}{2}\boxed{\frac{\partial^2 E}{\partial x_i \partial x_j}}\delta x_i \delta x_j + \mathcal{O}(\delta x^3)$$

Maximize bulk modulus at the transition

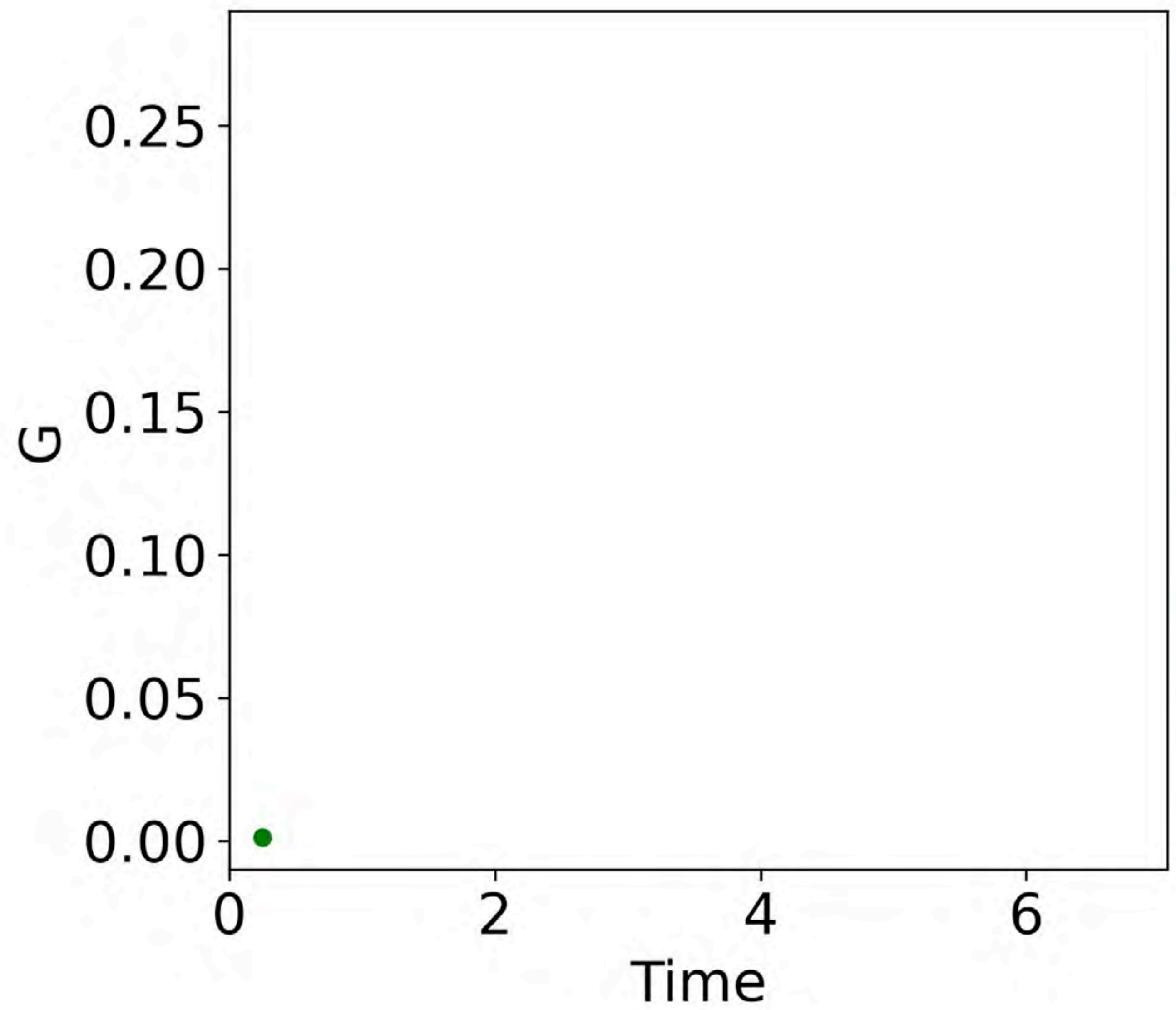
$$\dot{h}_\alpha = L_\alpha^2$$

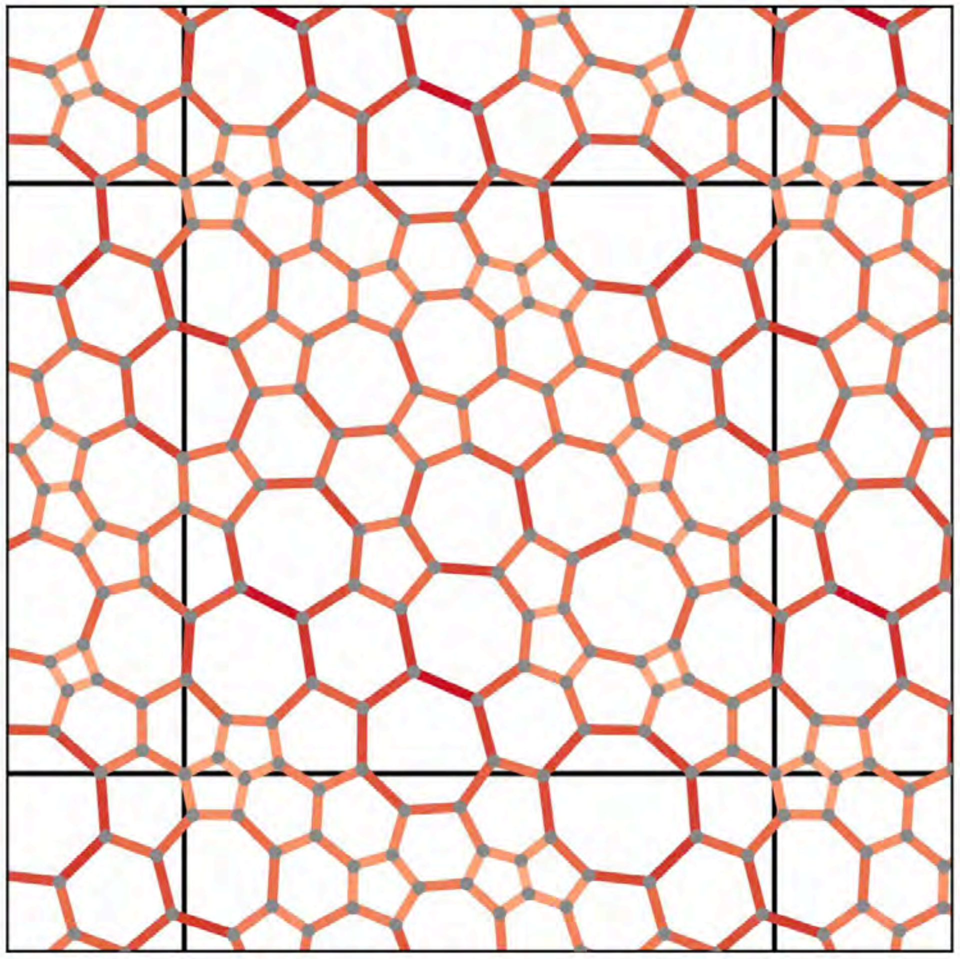




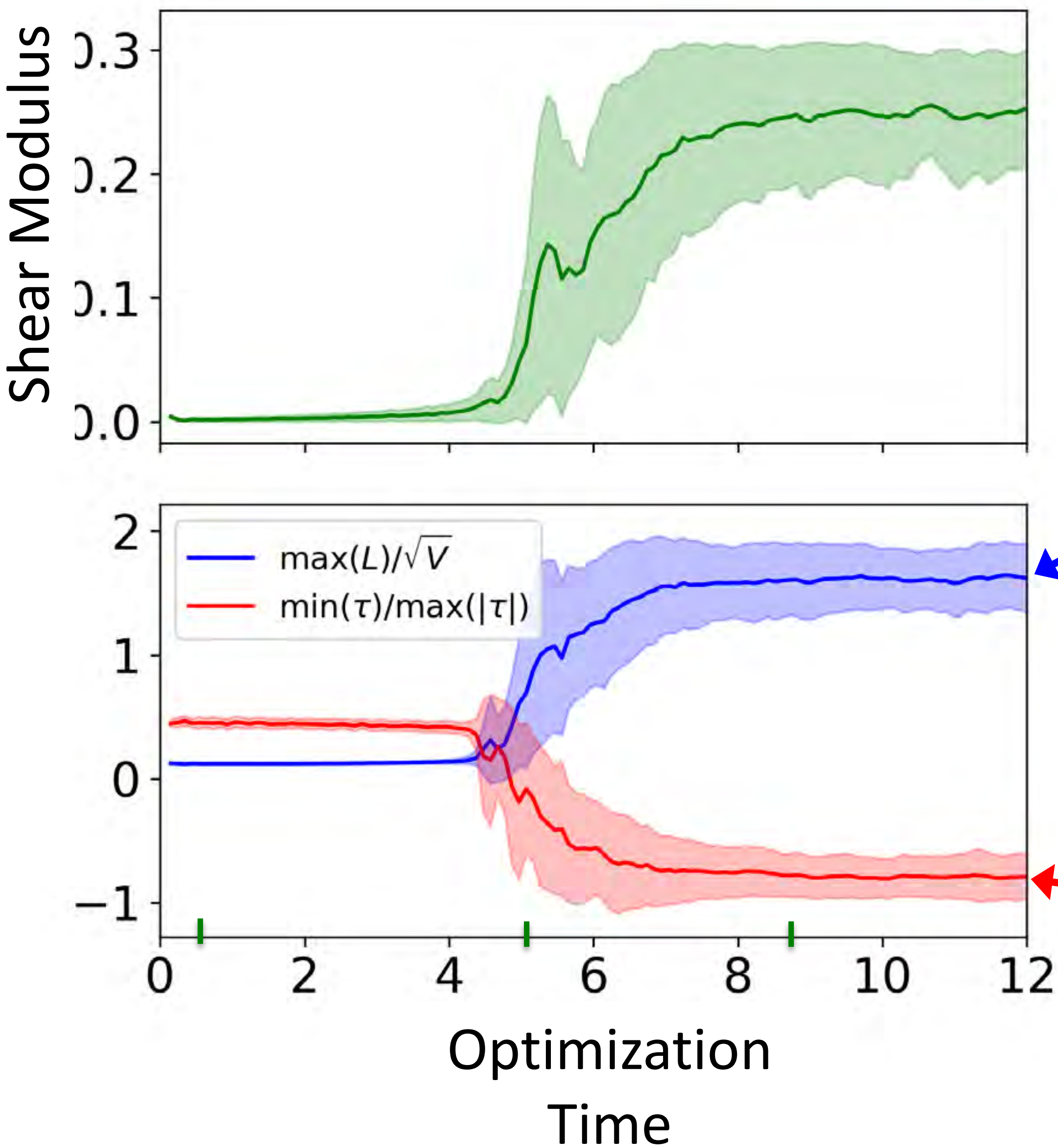
Maximize shear modulus at the transition

$$\dot{h}_\alpha = L_{\alpha x} L_{\alpha y}$$





Maximize shear modulus at the transition

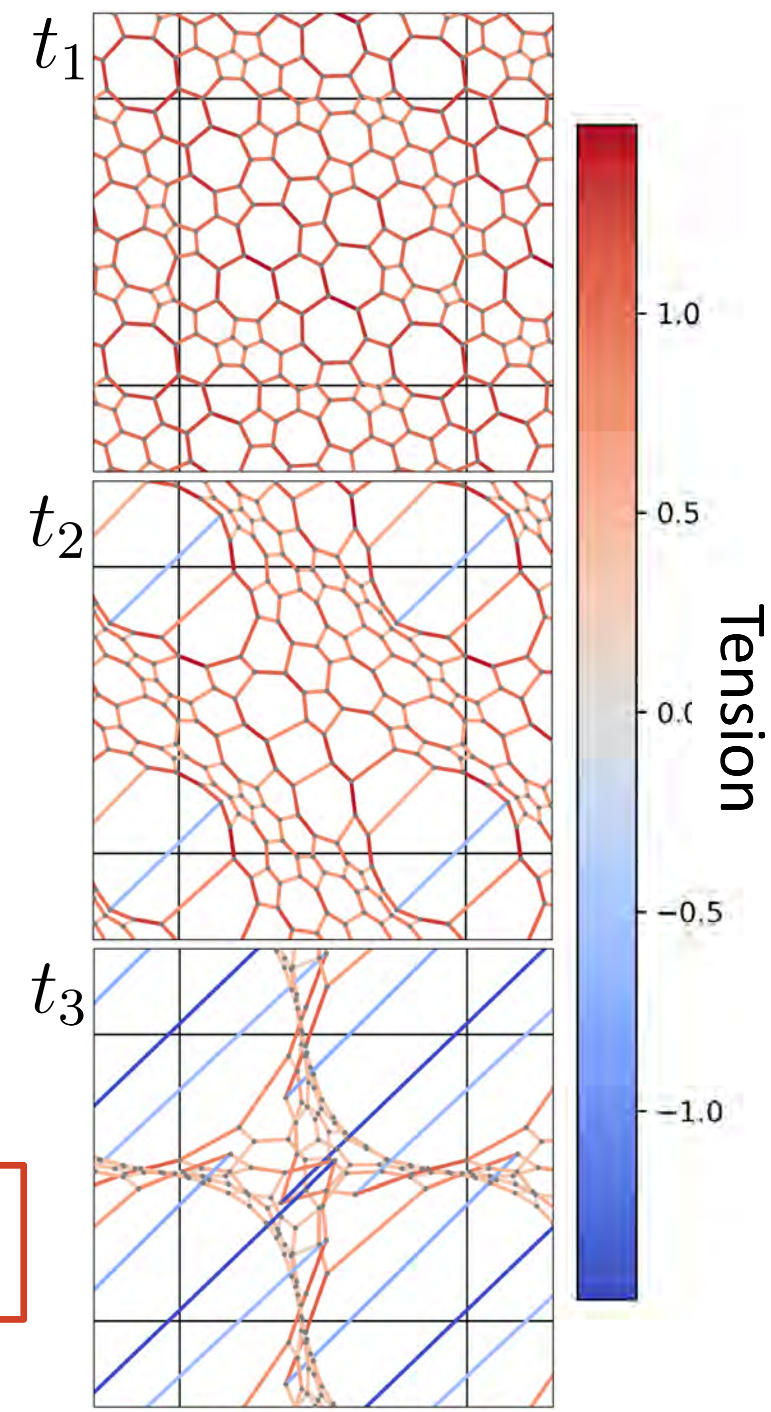


Optimization leads to weird configurations!

Increasing Time

Longest edge becomes larger than the box size

The edge with the most stress is under compression



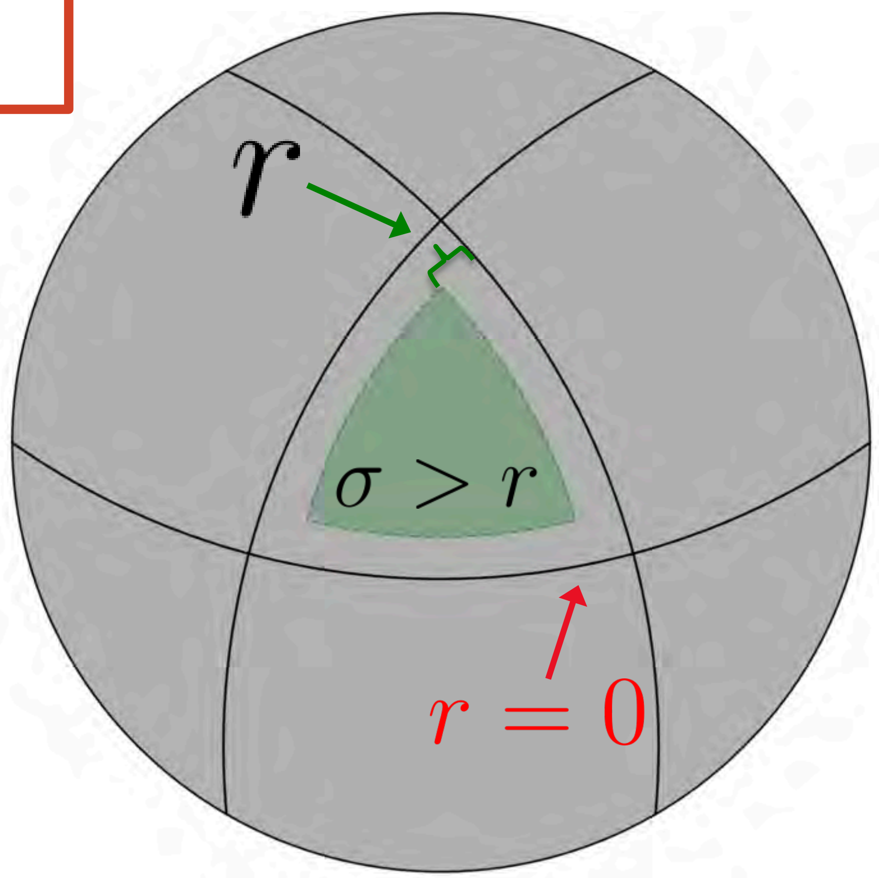
Maximize shear modulus at the transition

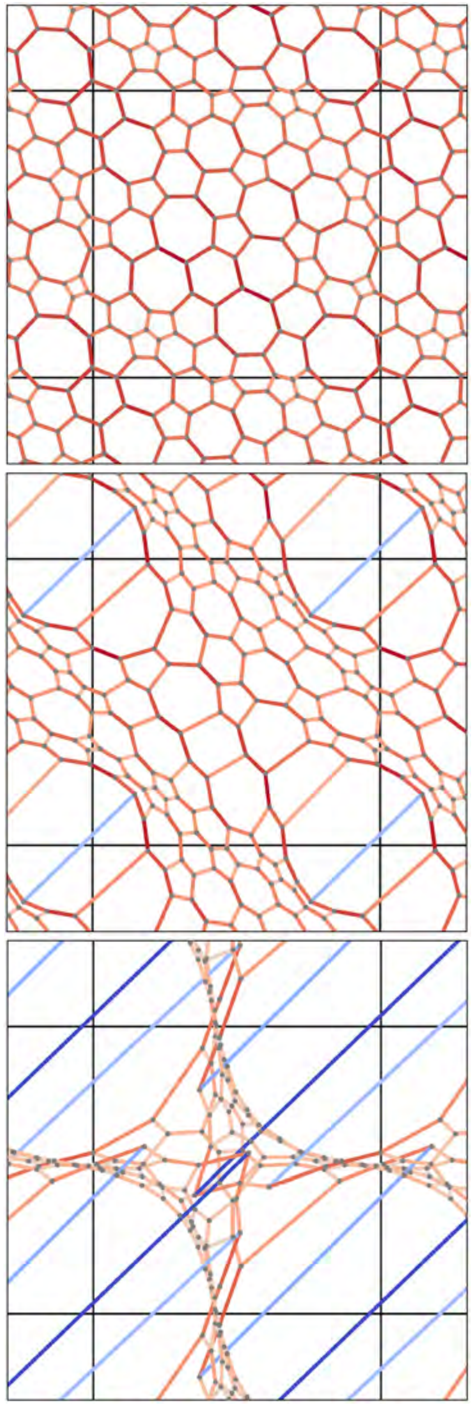
We can add additional constraints to keep the self-stress above a given threshold

$$\sigma > r$$

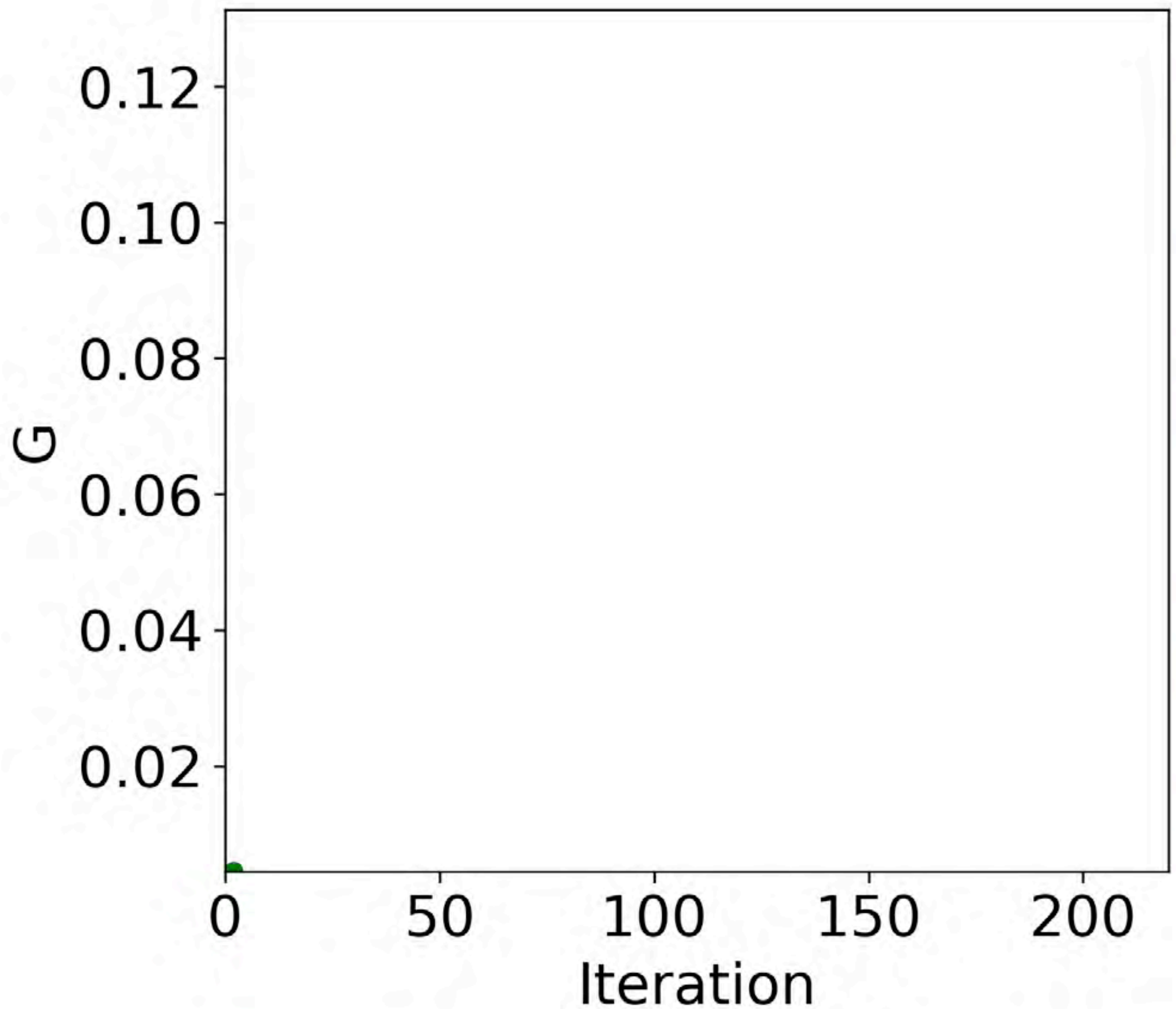
Optimize new objective function:

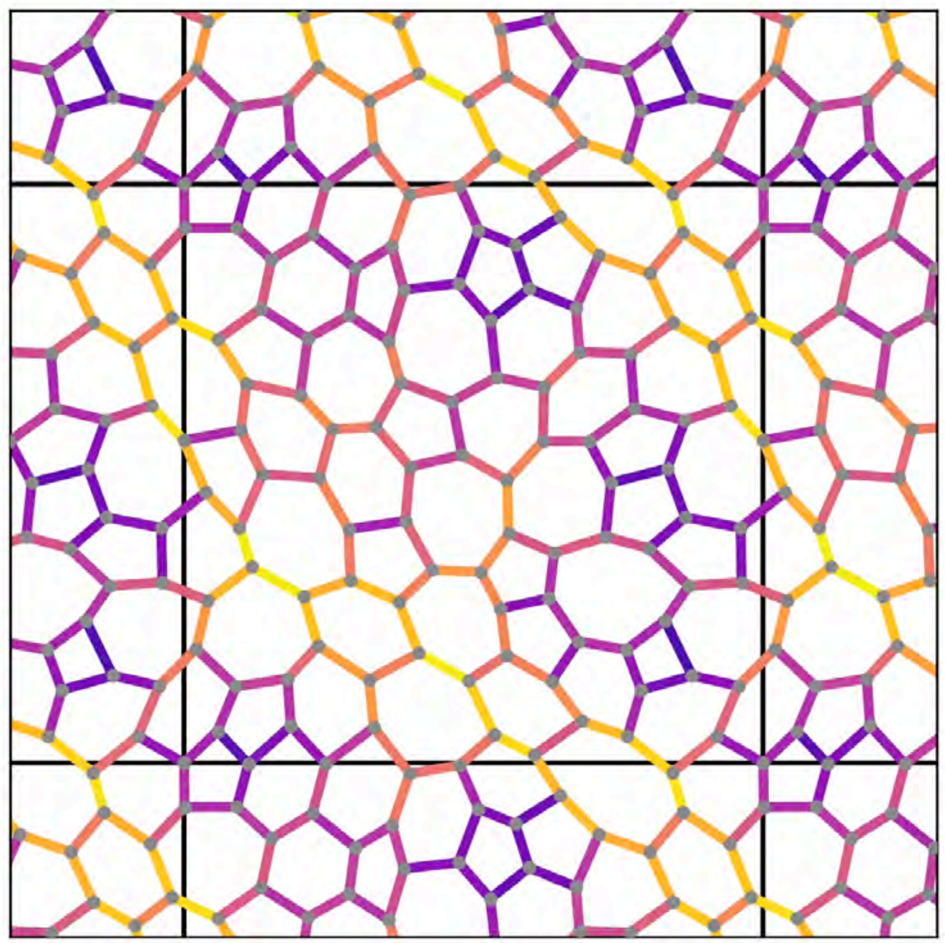
$$\mathcal{O}(\sigma, r) = G_0(\sigma) - \frac{1}{N_b}\sum_\alpha \left(\frac{\sigma_\alpha}{r}\right)^{-10}$$





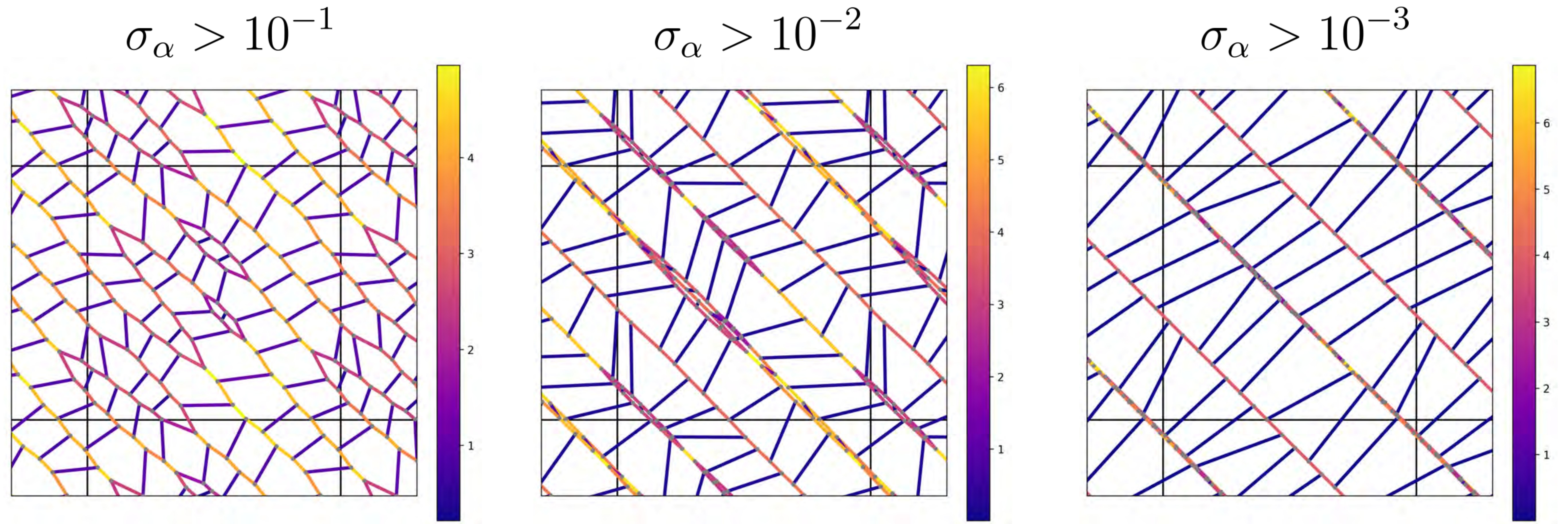
Maximize shear modulus at the transition (w/ constraint)

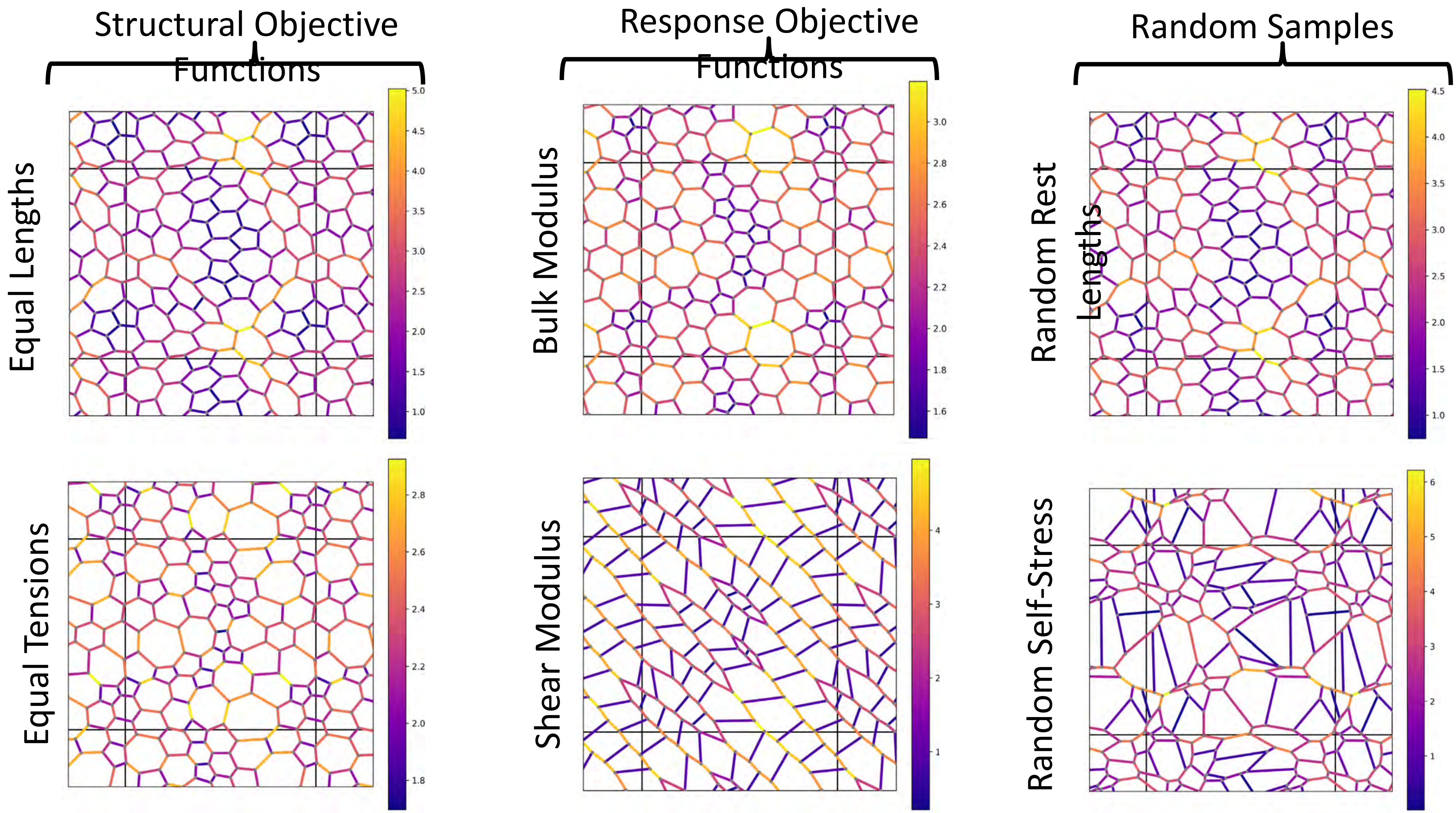




$\sigma_\alpha > 10^{-2}$

Lower threshold produces more aligned networks

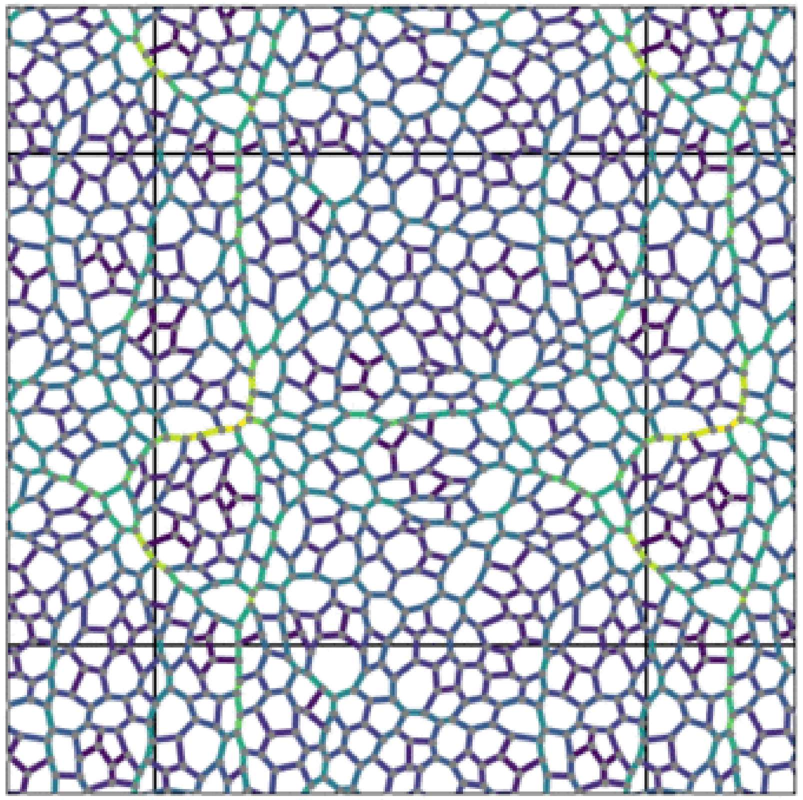



Structural Objective Functions
Response Objective Functions
Random Samples
Equal Lengths
Bulk Modulus
Random Rest Lengths
Equal Tensions
Shear Modulus
Random Self-Stress

Summary

What is the space of states at the transition?

There is a manifold of states at the critical point of any underconstrained network, which we can completely characterize with an analytic parameterization



Can we search this space to find configurations with specific desired properties?

Yes! We can find configurations that optimize a smooth objective function

End of lecture 3