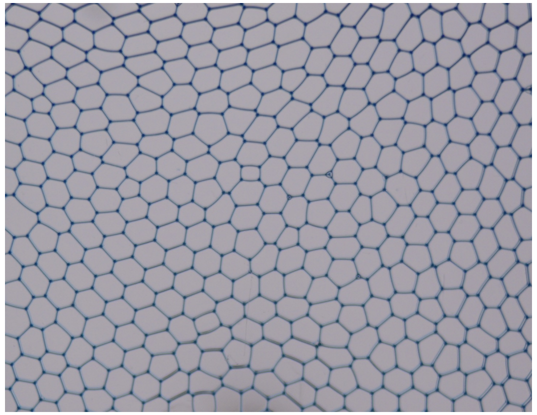
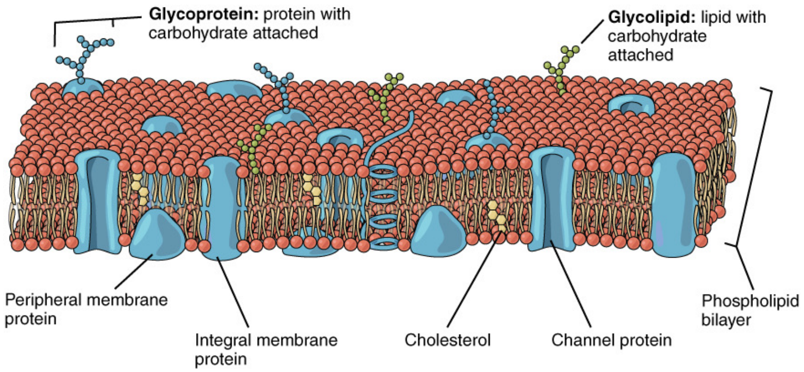
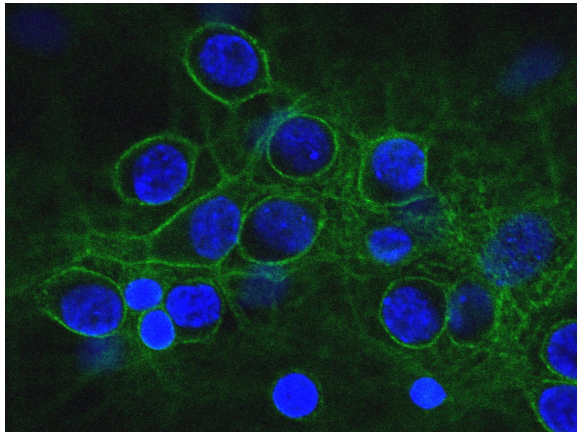
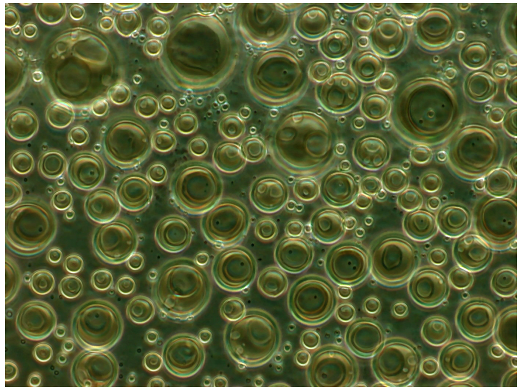
ME470: Mechanics of Soft and Biological Matter
Lecture13: Modeling of Multicellular Systems









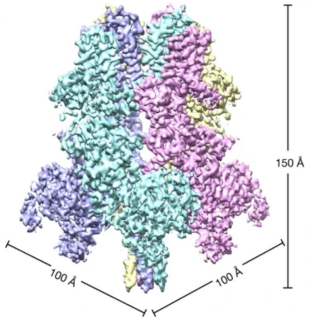
Red Blood Cells

Sangwoo Kim

MESOBIO – IGM – STI – EPFL

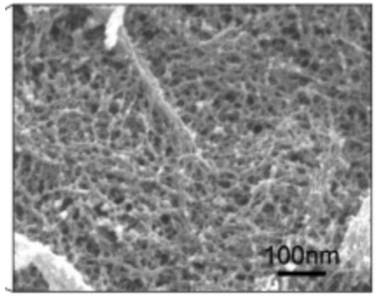
Biological Tissues: Hierarchical Materials

Protein structure



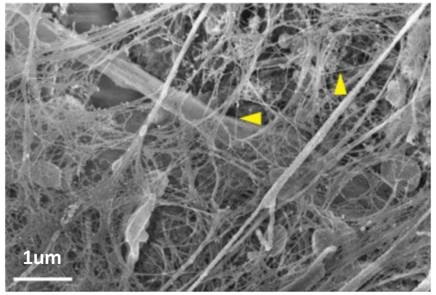
Guo et al. Nature (2017)

Cell cortex



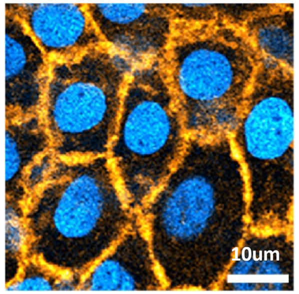
Kelkar et al. Curr. Opin. Cell Biol. (2020)

ECM



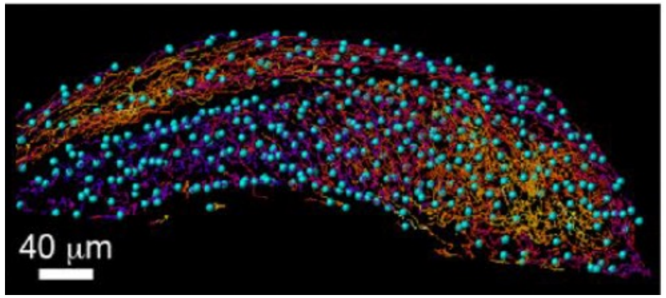
Lansky et al. J Struct. Biol. X (2019)

Zebrafish tail skin



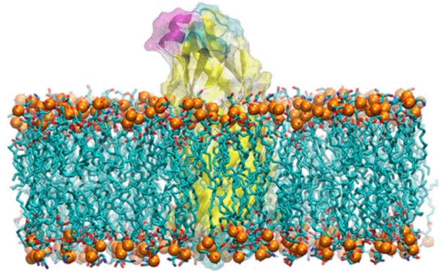
Campàs group: Rana Amini

Zebrafish tailbud



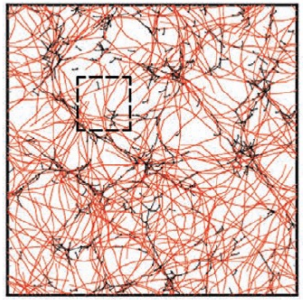
Banavar et al. Sci. Rep. (2021)

MD simulation



Goossens et al. J. Chem. Inf. Model (2018)

Active network simulation

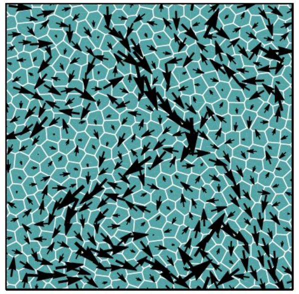


Tabatabai et al. Adv. Funct. Mater (2020)

Phase field model

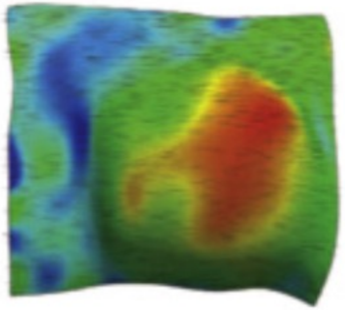
Kuang et al. arXiv (2022)

Self-Propelled Voronoi model



Bi et al. PRX (2018)

Continuum description



Lee et al. J. Mech. Behav. Biomed Mat. (2018)

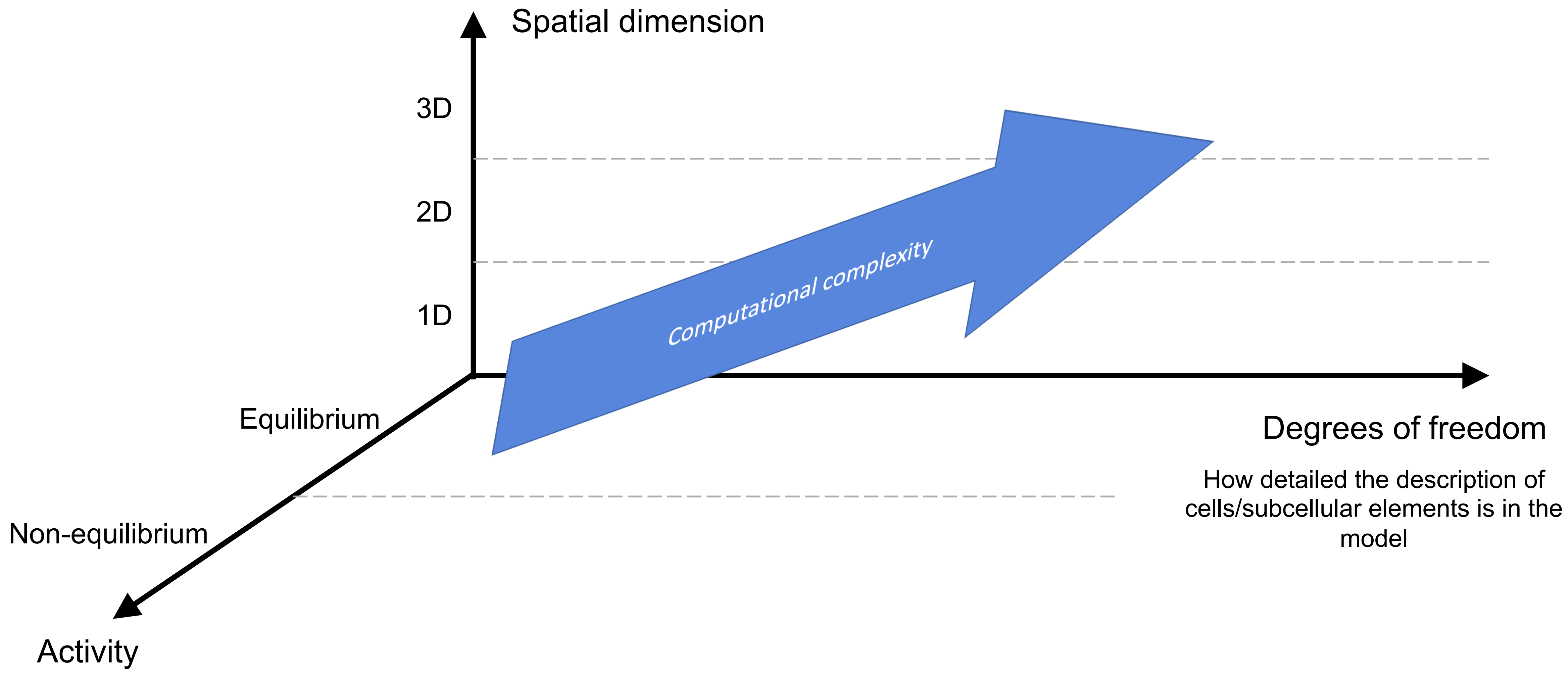
~nm ~μm ~mm **Length scale**

Interactions between characteristic structures within a length scale as well as across length scales determine emergent tissue properties!

Discrete Modeling for Multicellular Systems

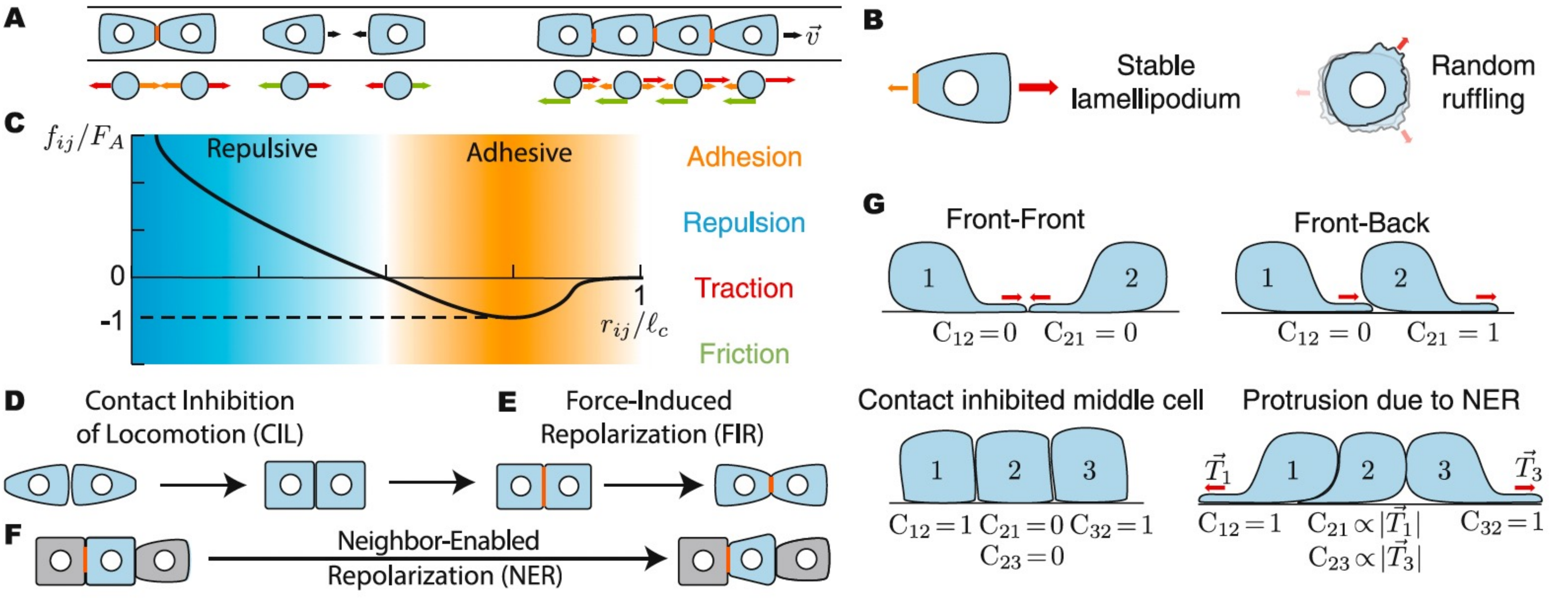
- Particle-based model
- Voronoi model
- Cellular Potts model
- Vertex Model
- Multiphase field model

Discrete Models: Overview



Combination of soft matter physics, statistical mechanics, continuum mechanics and computational geometry

Discrete Models: 1D Particle Model



(George17)

Single cell: $\xi\vec{v} = \vec{T} + \vec{F}_{ext}$

Viscous friction — Traction force — External force

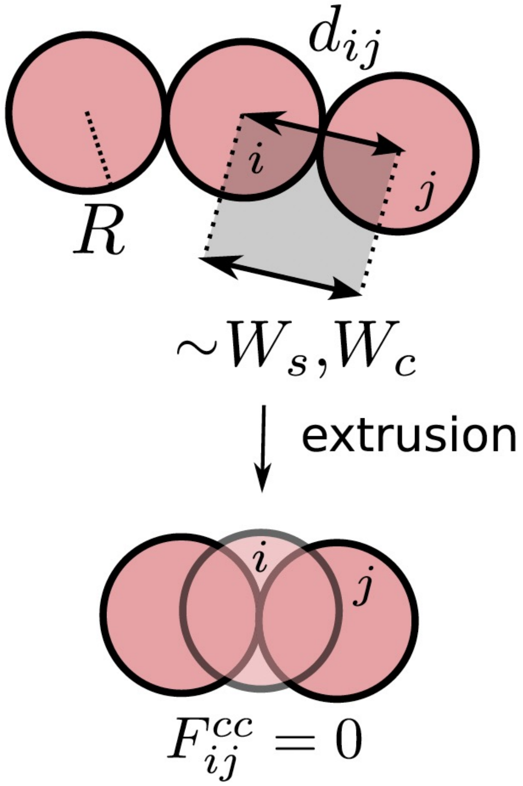
Multiple cells: $\xi\vec{v}_i = \vec{T}_i + \sum_{j\neq i} \vec{F}_{ji}$

Viscous friction — Traction force — Interaction force

Discrete Models: Agent-Based Model (2D Particle)

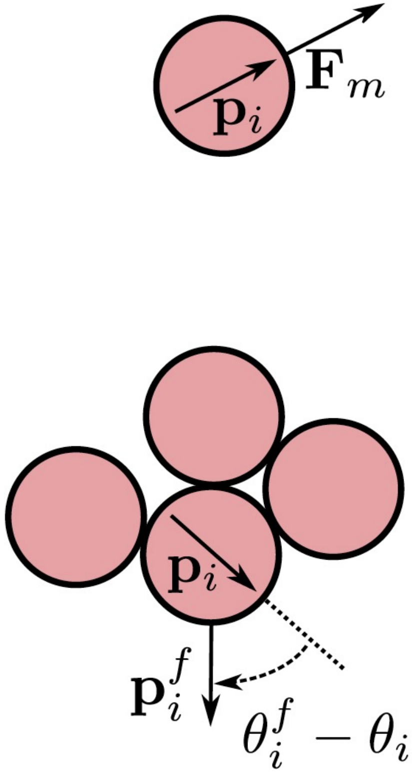
B

Cell extrusion

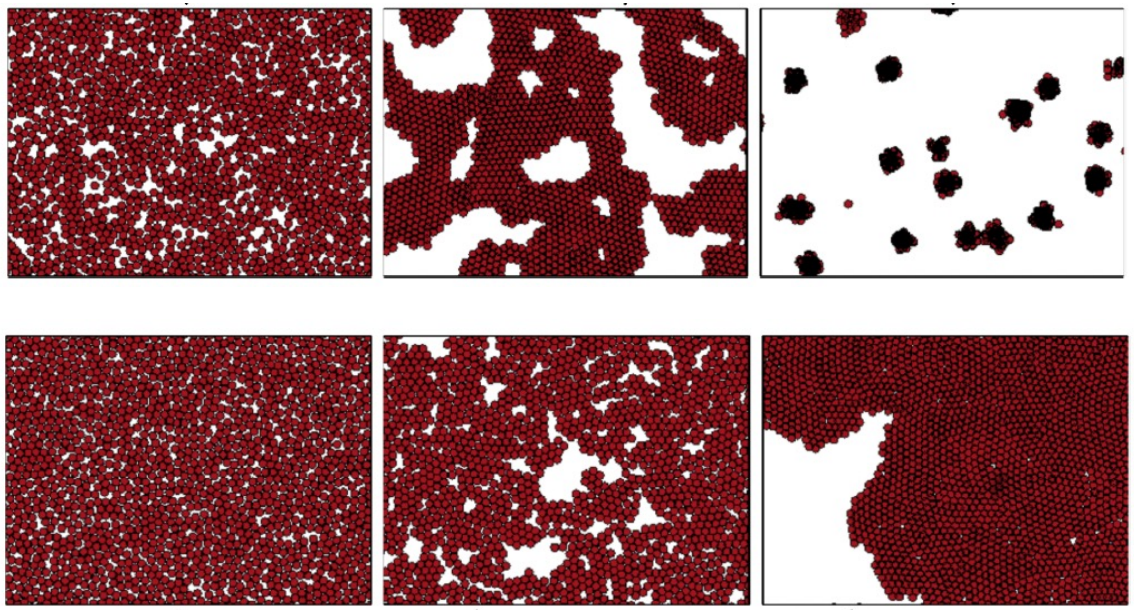


C

Contact inhibition of locomotion



Different tissue structure



(Smeets16)

$$F_m \vec{p}_i = \gamma_s \dot{\vec{x}}_i + \sum_{j}^{nn} \left[F_{ij}^{cc} \hat{n}_{ij} + \gamma\left(\dot{\vec{x}}_i - \dot{\vec{x}}_j\right) \right]$$

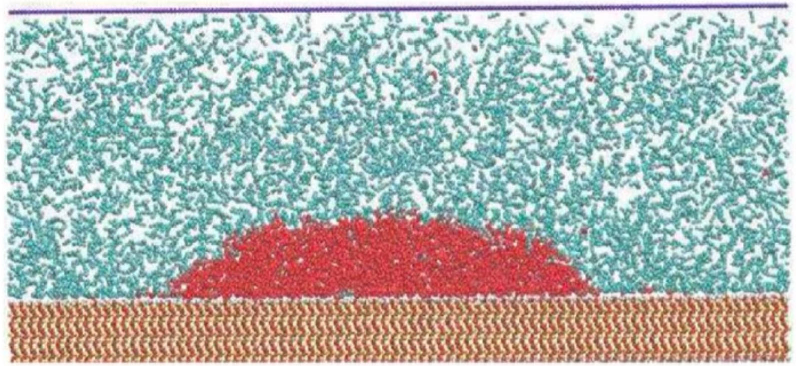
Self propulsion	Cell-substrate friction	Cell-cell interaction	Cell-cell friction

From Where: Particle Models

MD simulation: isotropic atoms
Agent-based model
Soft particle model
Self-propelled particle model
Active Brownian particle model

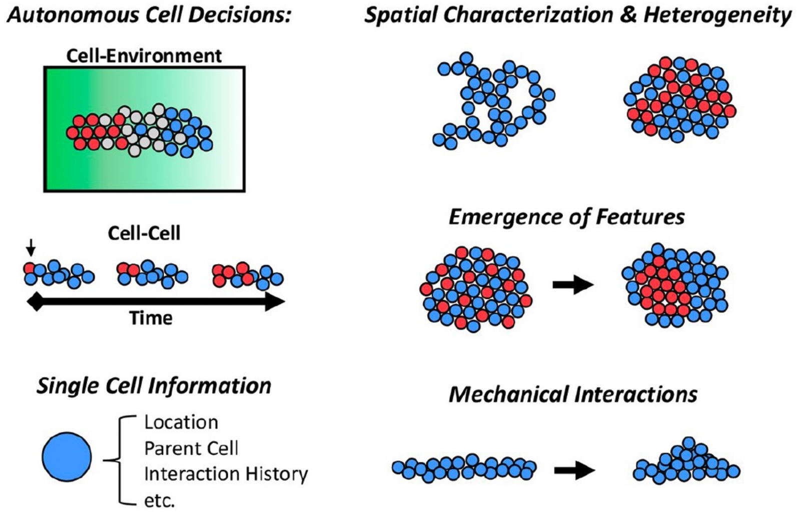
Tissue morphogenesis based on cell-cell interaction or cell-substrate interaction

MD simulation



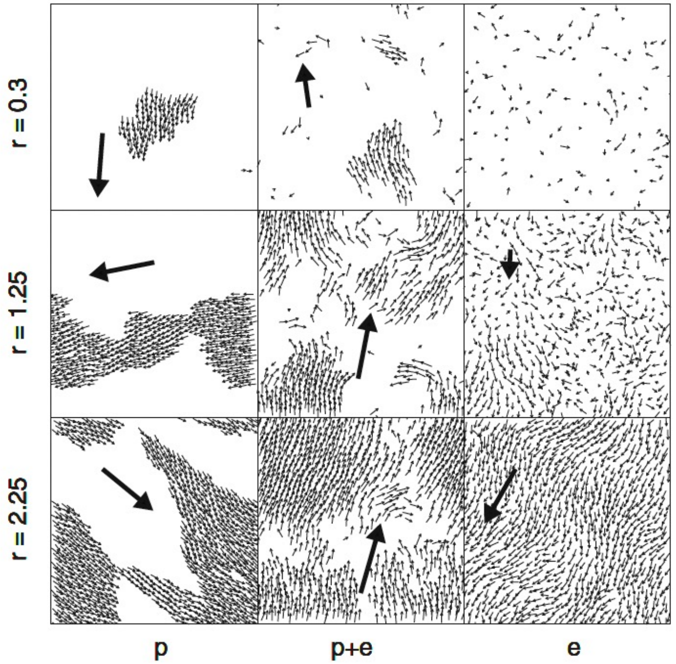
(*Sethi et al.* 2021)

Agent-based model



(Glenn *et al.* 2019)

Active Brownian particle model

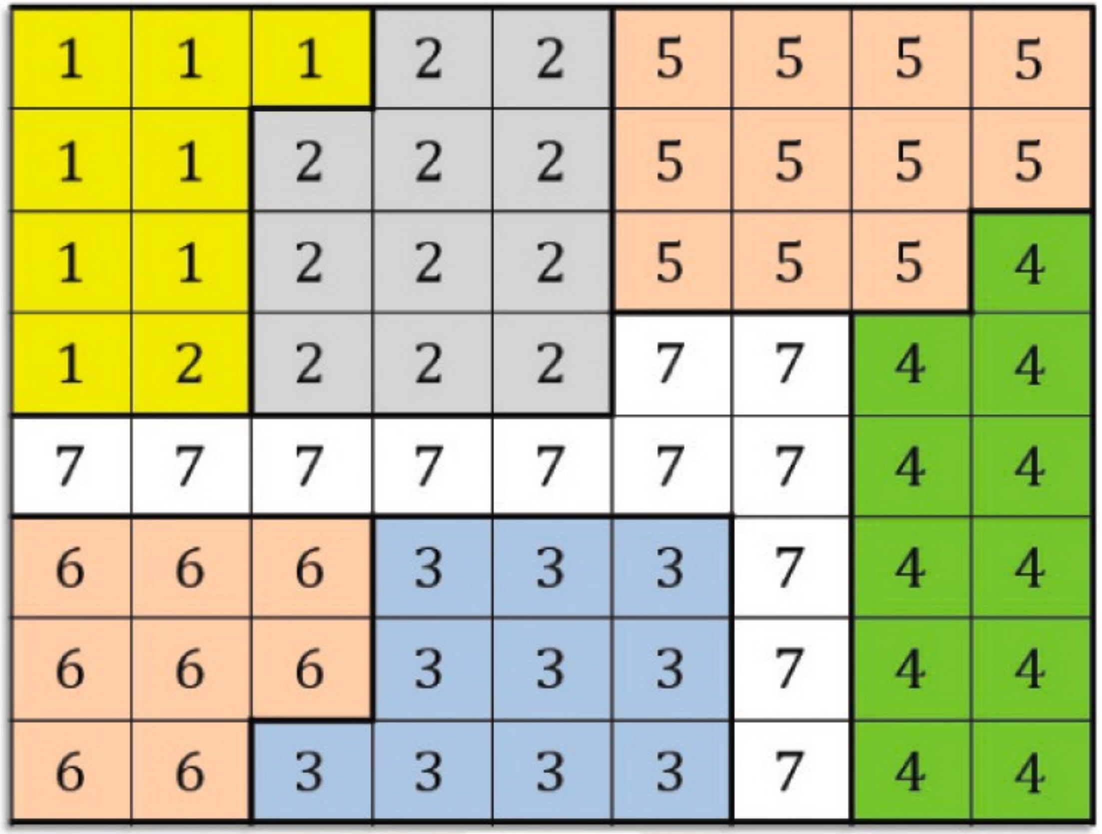


(Romanczuk *et al.* 2012)

- Flexibility to implement different types of interactions
- Computational efficient
- Unable to study role of shape changes in biological tissues

Discrete Models: 2D Cellular Potts Model

Typical 2D rectangular CPM lattice



(Scianna12)

- Lattice based model
- Each cell is a subset of connected lattice sites that shares the same cell ID
- Lattice sites that are not occupied by cells are extracellular spaces
- The dynamics are governed by an energy functional, Hamiltonian (H)
- Update of sites using Monte-Carlo simulation algorithm with Metropolis criterion
  - Randomly choose site i
  - Switch the cell ID of site i to the cell ID of site j that is randomly chosen site among neighboring sites of site i
  - Compare energy before and after the change
  - If an energy is lower, accept a new configuration. If not, accept a new configuration with a probability of $e^{-\Delta H/T}$

From Where: Cellular Potts Model

Cellular Potts model is a special version of Potts model in statistical physics, that is a generalization of Ising model

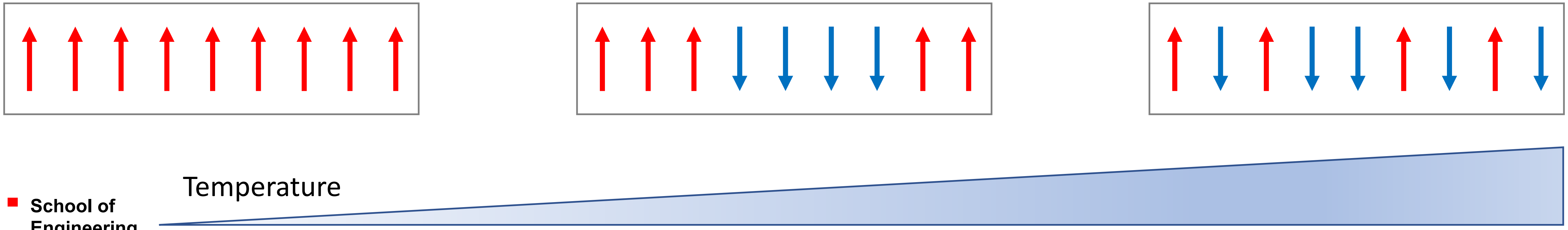
What is Ising model?

A: a mathematical model of ferromagnetism (a collection of atomic spins aligns in the same direction, yielding a net magnetic moment in macroscopic scale)

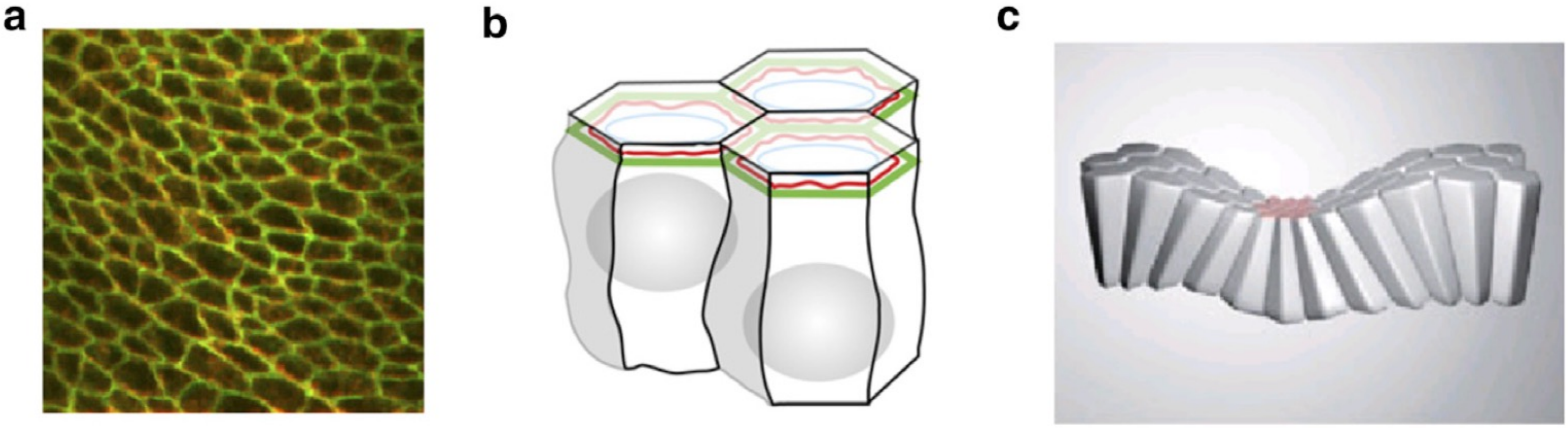
$$H_{Ising} = -J \sum_{<ij>} \sigma_i \sigma_j - h \sum_i \sigma_i$$

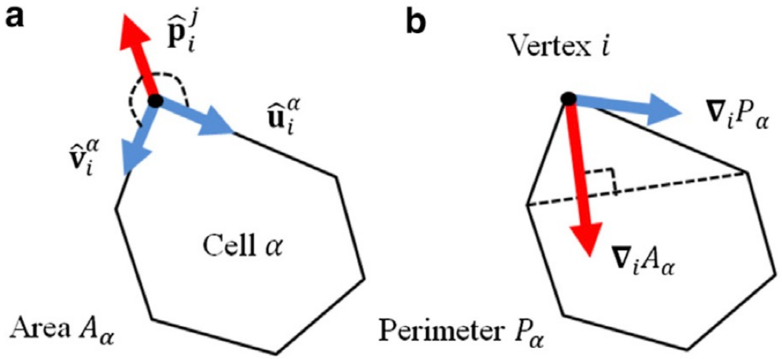
Interaction between neighboring sites

Energy contribution from external field



Discrete Models: 2D Vertex Model





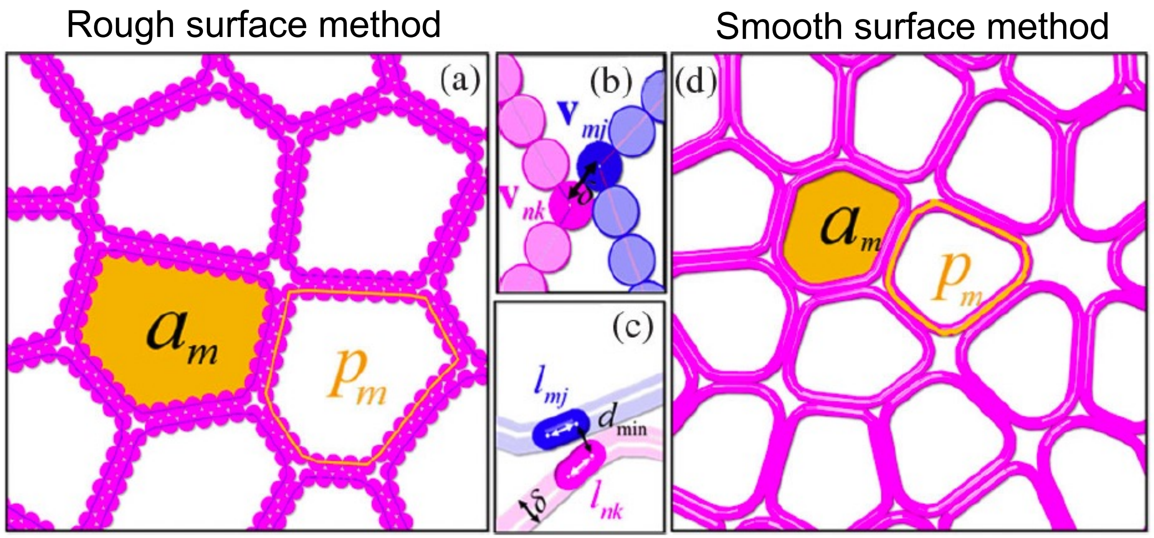
(Fletcher14)

- Confluent epithelial layer can be simplified as 2D polygonal packings
- Cell shape is described by positions of vertices at the tricellular junctions
- The dynamics is governed by an energy functional

$$E = \sum_i K_A(A_i - A_{i,0})^2 + K_P(P_i - P_{i,0})^2$$

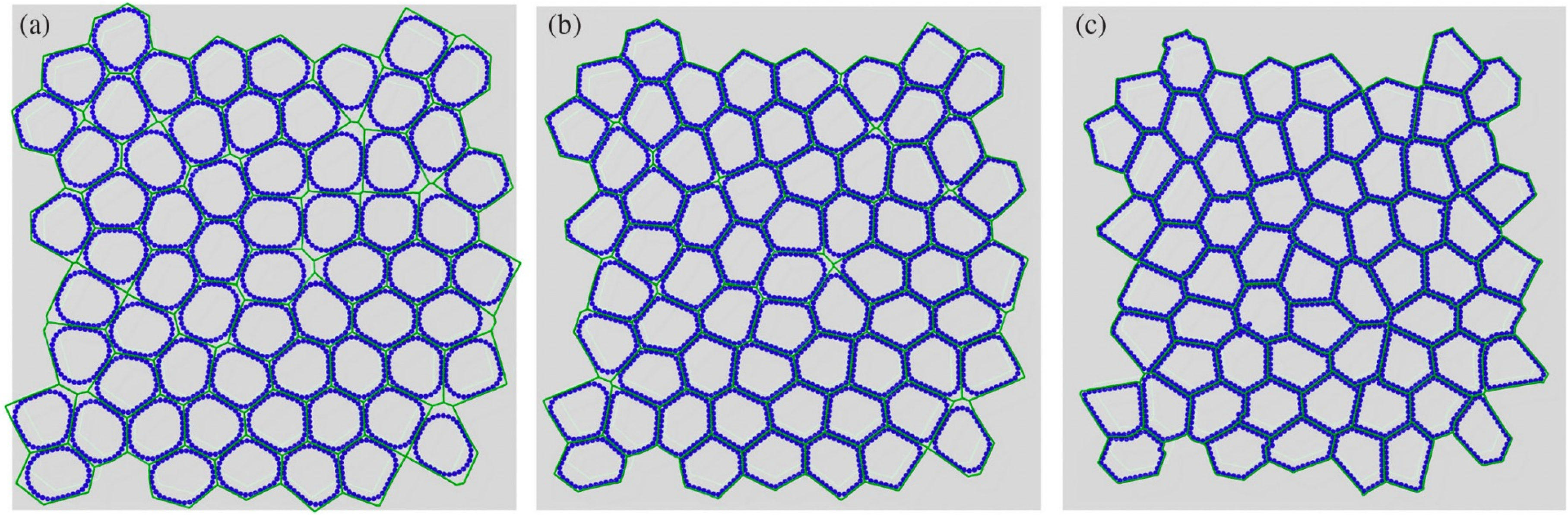
Area elasticity — Perimeter elasticity

Discrete Models: Deformable Particle Model

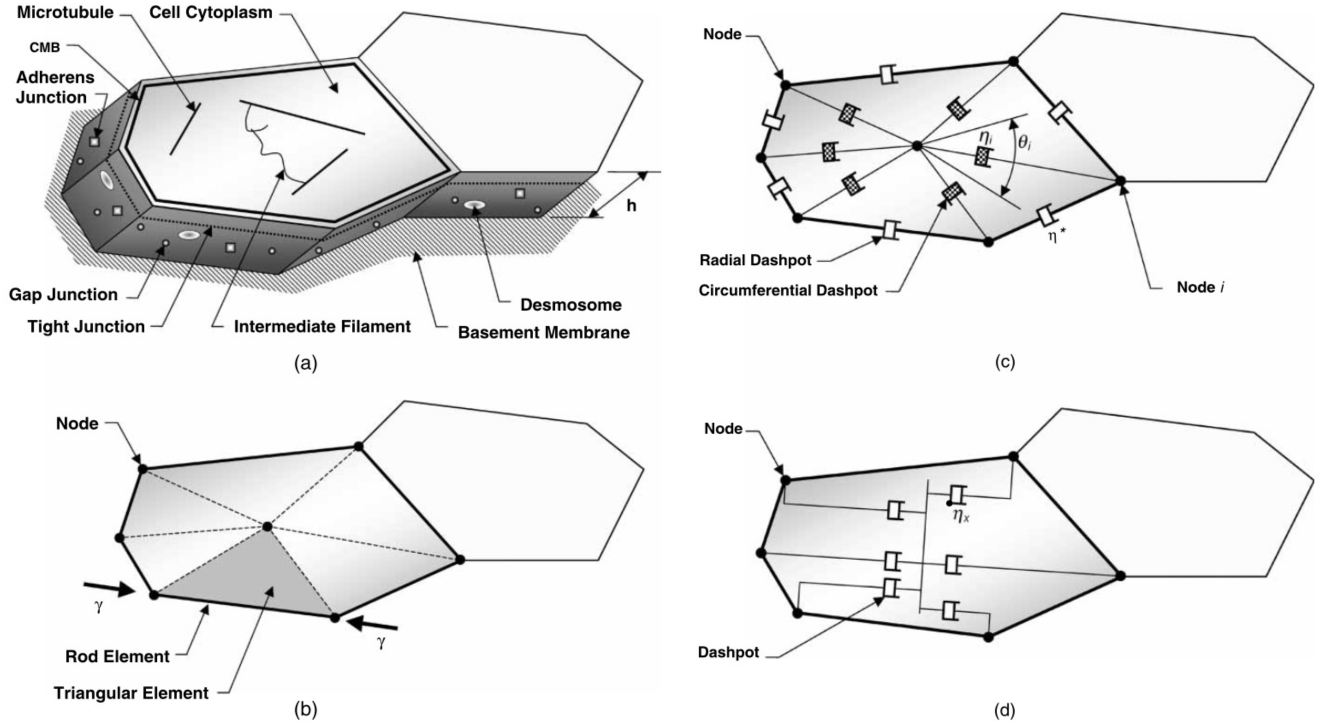


(Boromand18)

- Energy = junction contractility + area elasticity + line tension + junction bending + repulsive interaction
- Two different methods to deal with cell boundary
- More detailed description of cell shape compared to vertex model
- Double interface for cell-cell junction, (a single interface for the conventional vertex model)
- Able to simulate non-confluent systems



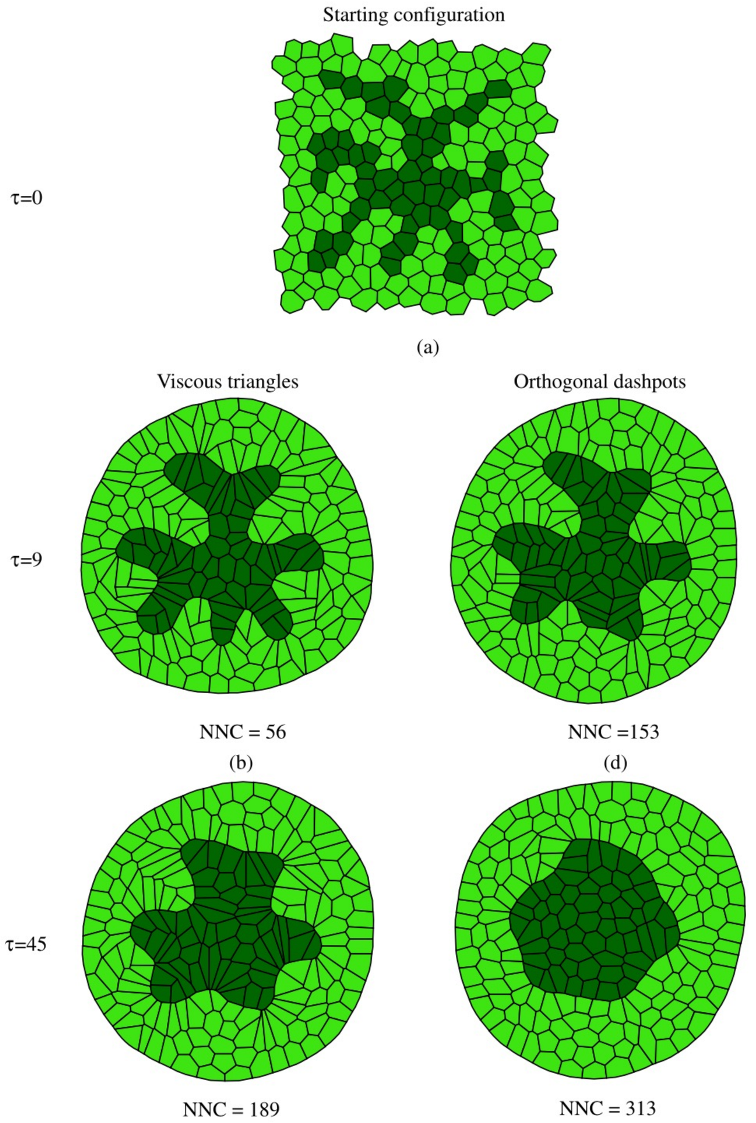
Discrete Models: FEM Vertex Model



(Brodland07)

Vertex model geometric description + Constant-force rod elements for cell-cell contact & viscous triangular elements for cytoplasm

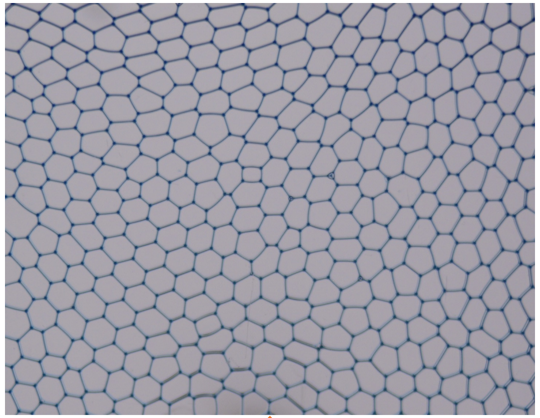
Cell sorting behavior



EPFL

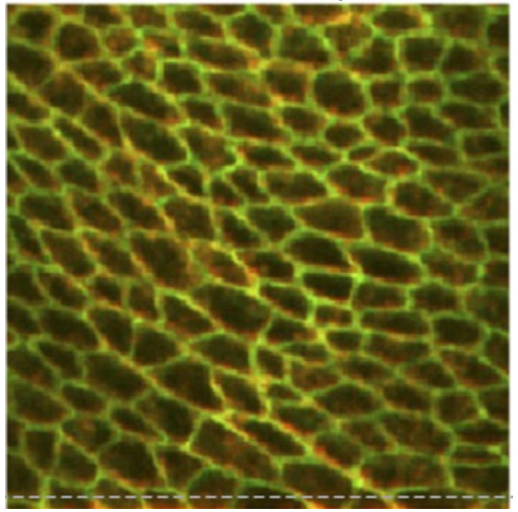
From Where: Vertex Model

Liquid foam



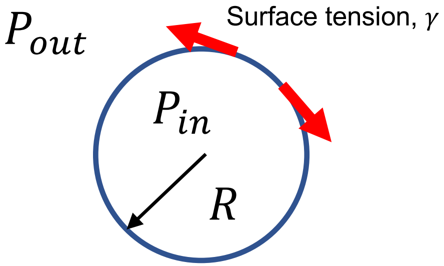
(Hilgenfeldt group)

Epithelial layer



(Fletcher et al. 2014)

Governing mechanics:

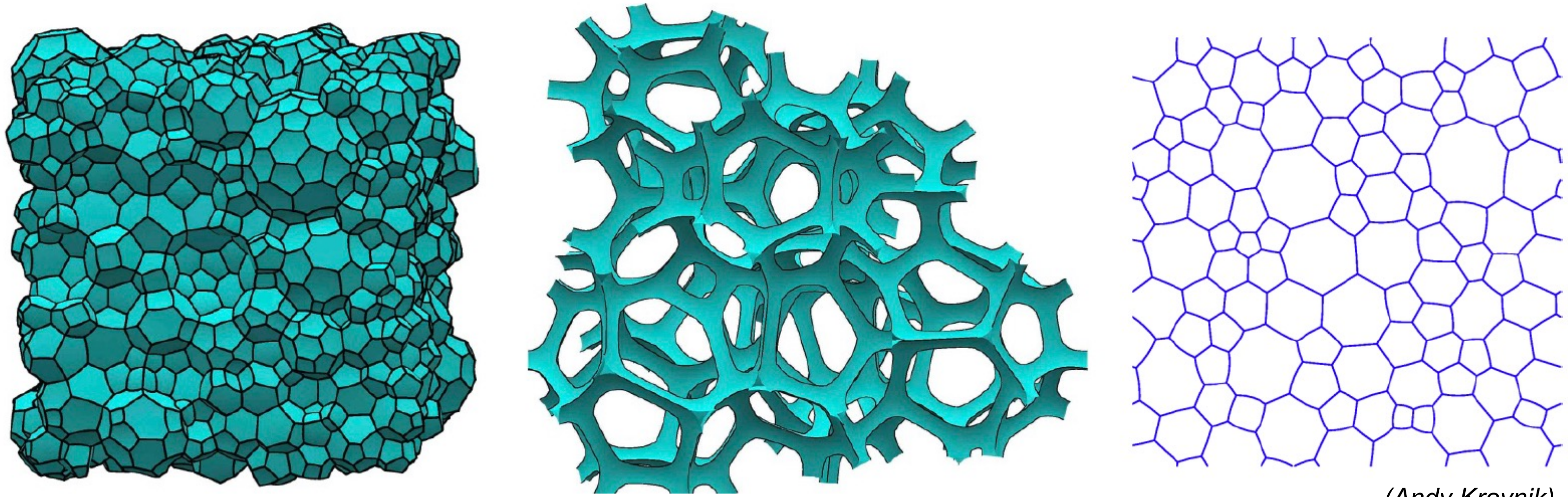


$$P_{in} - P_{out} = \frac{\gamma}{R}$$

- Short timescale: minimizing interfacial area (length in 2D)
- Long timescale: coarsening

$$E = \gamma \sum L_{ij}$$

Dry foam simulations



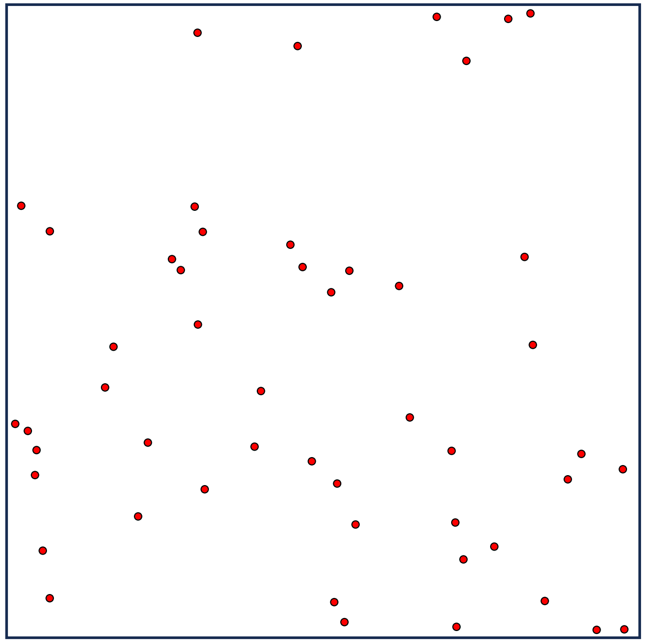
(Andy Kraynik)

Simulation software: Surface Evolver

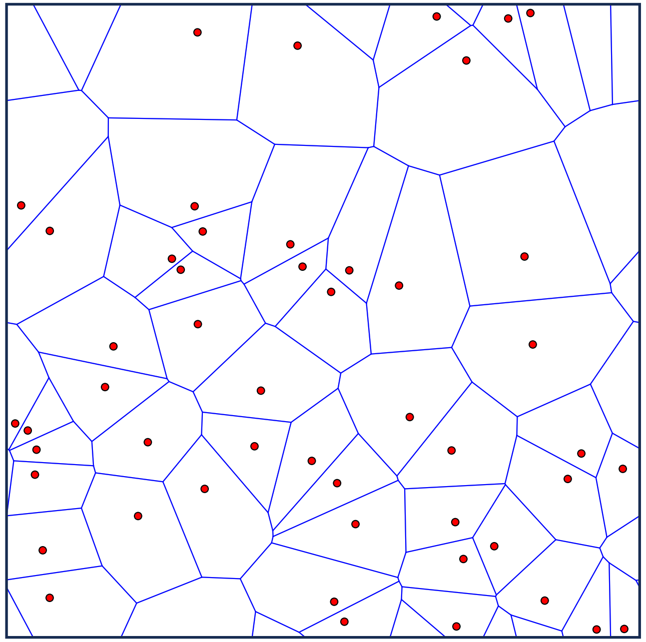
Discrete Models: Voronoi Model

Voronoi model: hybrid between the particle model and the vertex model

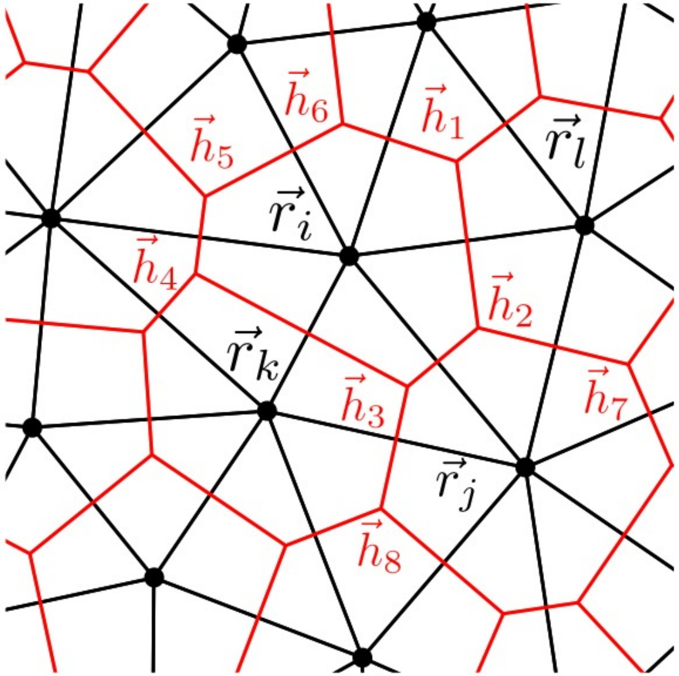
Cell dynamics: $$\frac{d\vec{r}_i}{dt} = \mu\vec{F}_i + v_0\hat{n}_i$$



Point pattern in space



Space partitioning: a Voronoi cell for a given point includes all points that are closest to the given point



(Bi16)

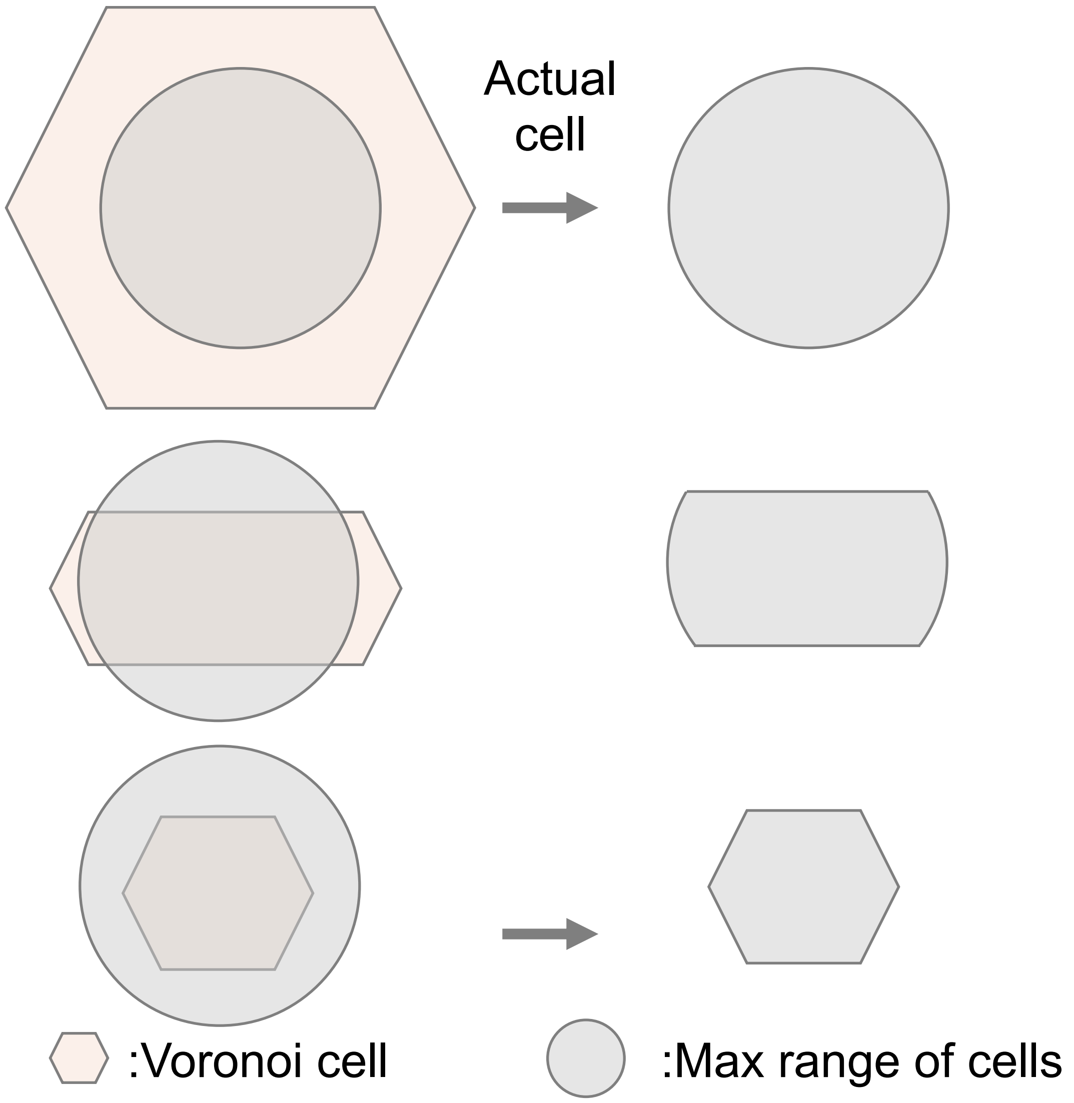
Degrees of freedom: particle position

Energy functional: depending on Voronoi tessellation properties

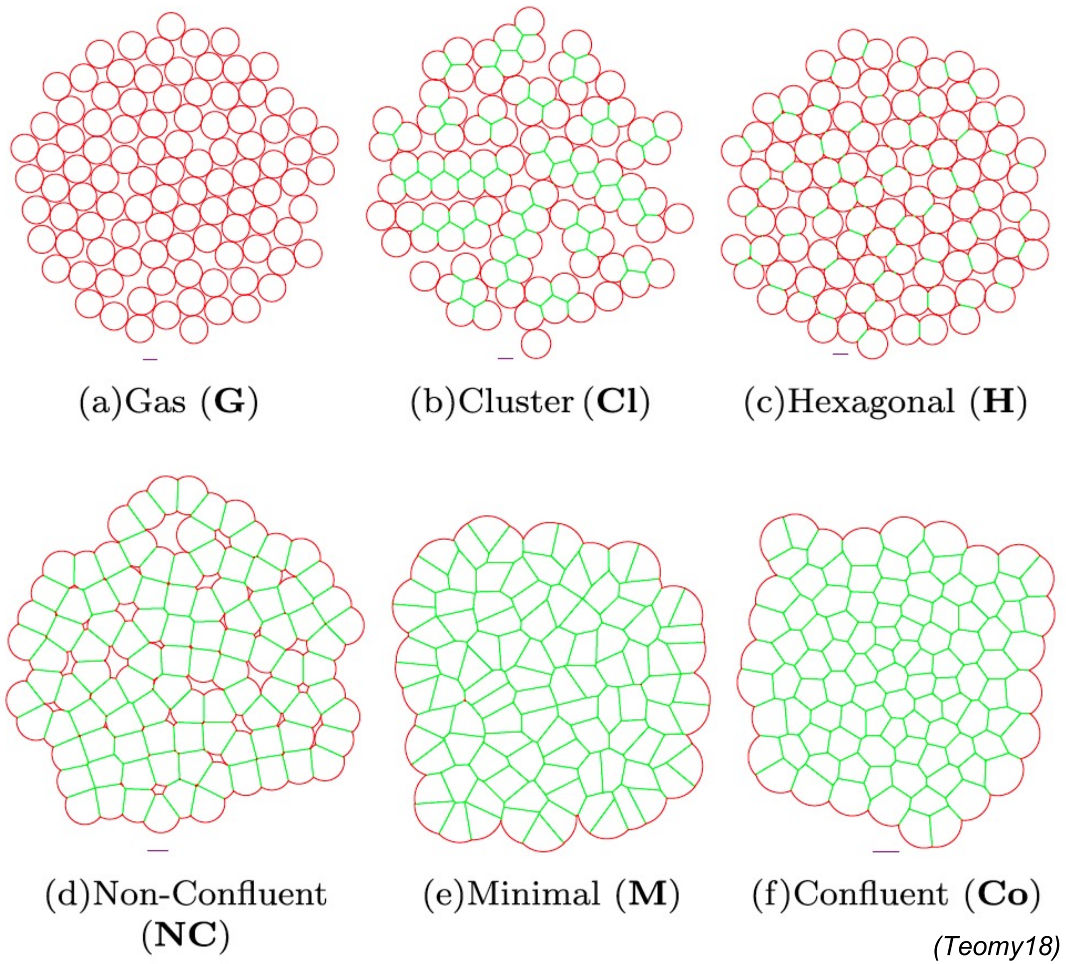
$$E = \sum_i K_A(A_i - A_{i,0})^2 + K_P(P_i - P_{i,0})^2$$

Discrete Models: Voronoi Model

Modified Voronoi model with a maximum cell radius → Can simulation non-confluent systems



Distinct classes of tissue structures

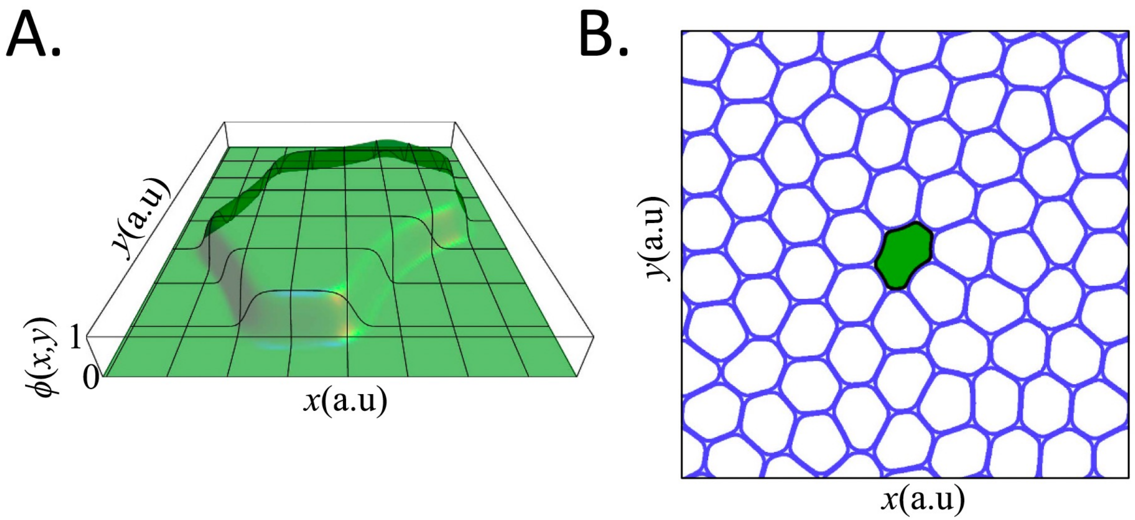


(Teomy18)

Discrete Models: Phase Field Model

Single cell phase field
1: cell interior
0: outside of cell
Rapid decrease from 1 to 0

Monolayer is constructed based on multiple fields



(Palmieri15)

- N scalar fields, $\{\phi_i\}$, describe cell shape
- Continuum limit of Cellular Potts model
- Extreme deformation is possible
- No need to deal with topological transition

Governing equation :

$$\frac{\partial \phi_n}{\partial t} + \vec{v}_n \cdot \nabla \phi_n = -\frac{1}{2}\frac{\delta F}{\delta \phi_n}$$

Time derivative of each field — Cell translational velocity — Functional derivative of free energy

Free energy: $F = F_0 + F_{int}$

Free energy of a single cell — Free energy from interactions

$$F_0 = \sum_n \left[\gamma_n \int dx \int dy \left((\nabla \phi_n)^2 + \frac{30}{\lambda^2} \phi_n^2 (1-\phi_n)^2 \right) + \frac{\mu_n}{\pi R^2} \left(\pi R^2 - \int dx \int dy\, \phi_n^2 \right)^2 \right]$$

Cell elasticity — Sharp boundary — Area constraints

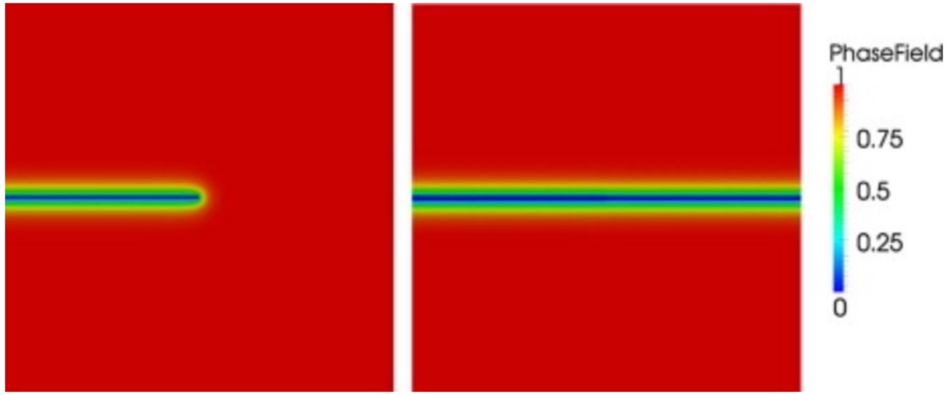
$$F_{int} = \frac{30\kappa}{\lambda^2} \int dx \int dy \sum_{n,m\neq n} \phi_n^2 \phi_m^2$$

Steric repulsion between cells

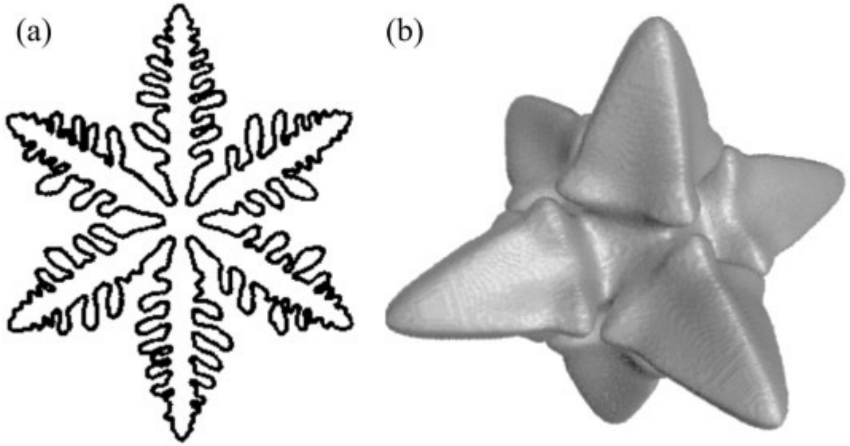
From Where: Phase Field Model

An efficient method for problems on materials modeling

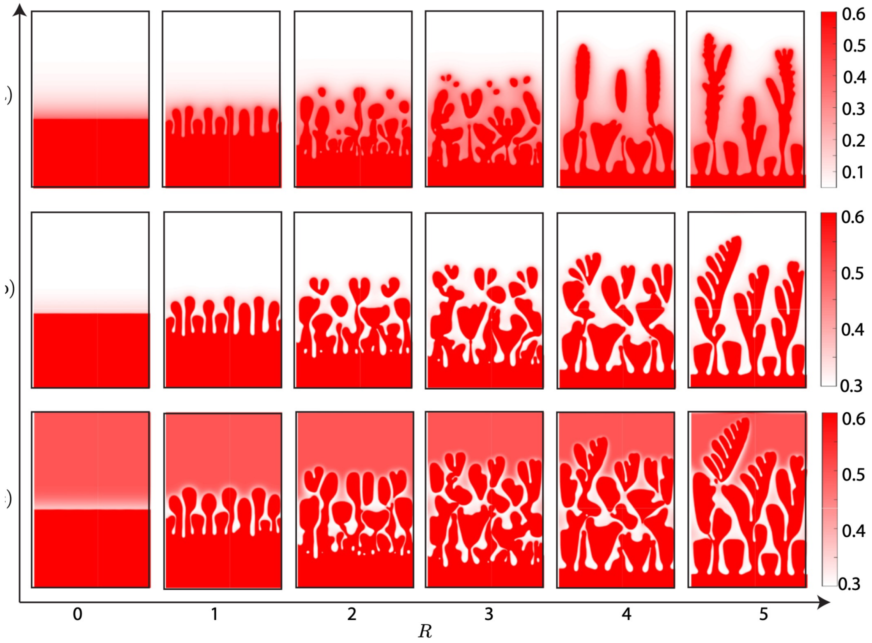
fracture



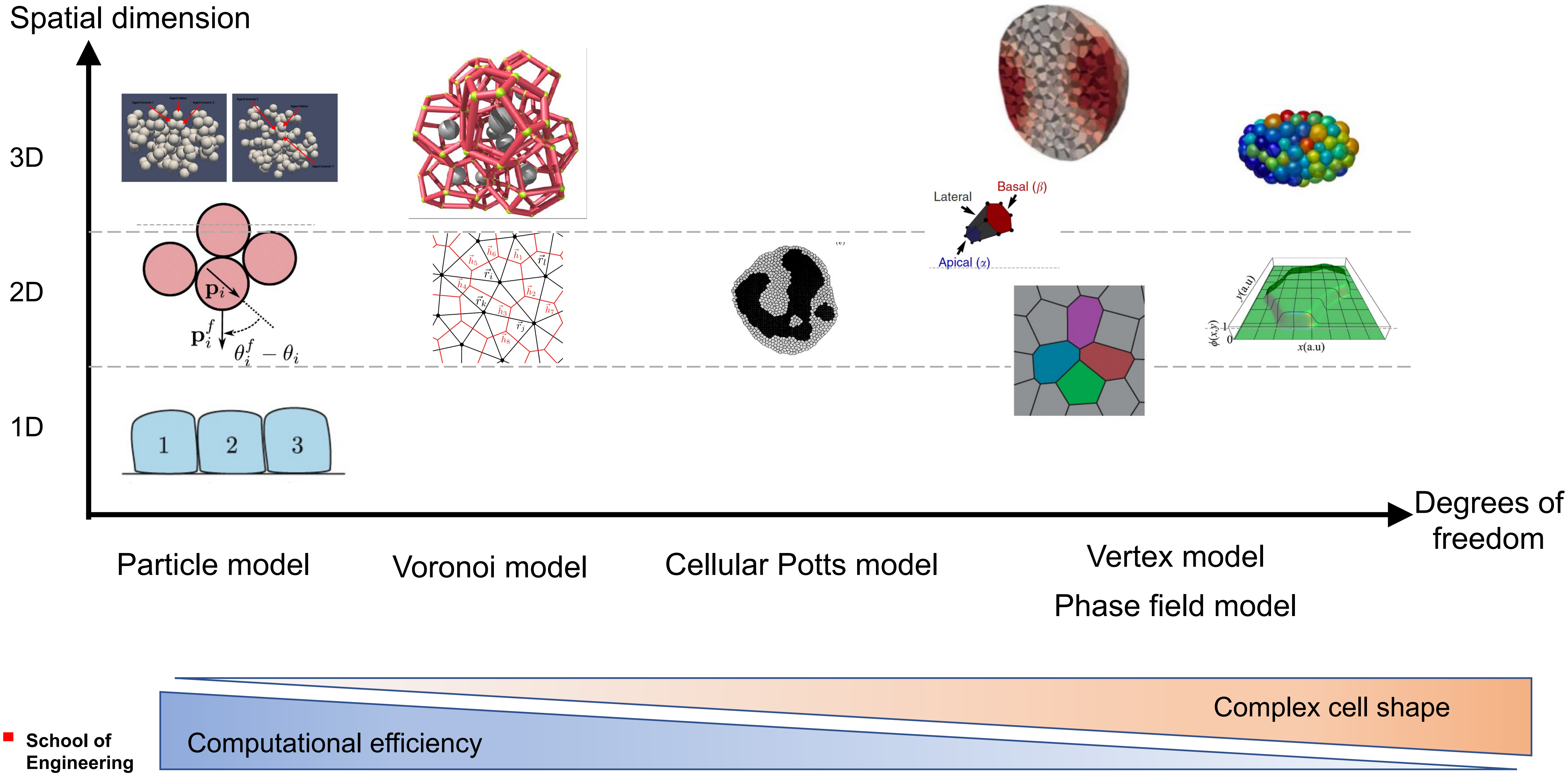
Solidification: dendritic growth



Viscous fingering



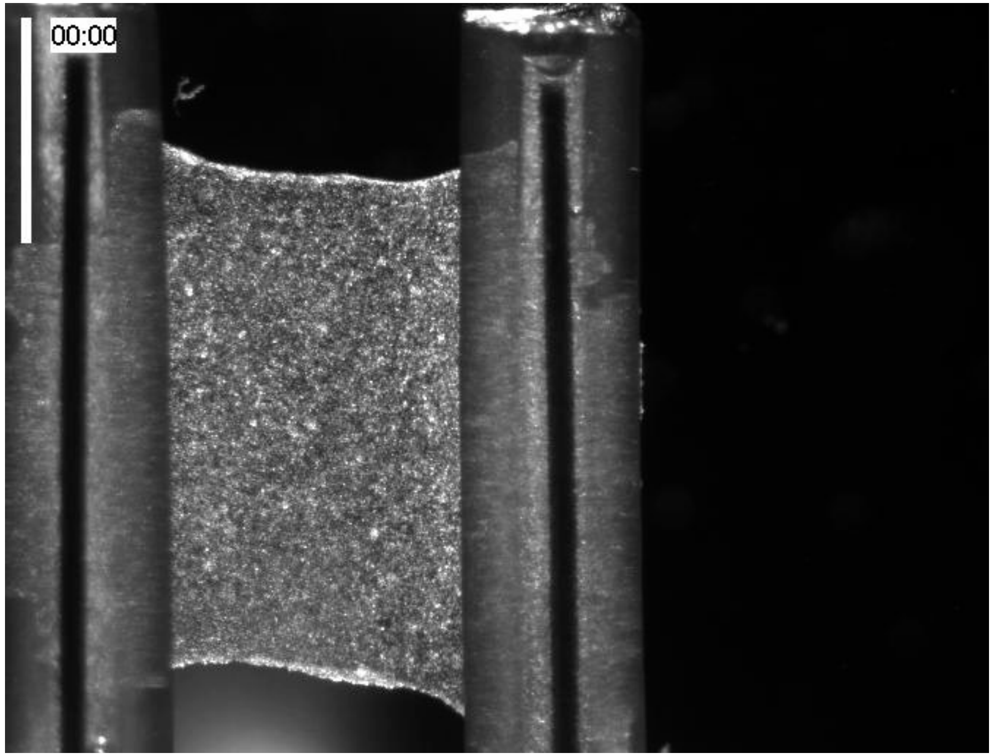
Summary


Spatial dimension
3D
2D
1D
Lateral
Basal (β)
Apical (α)
1
2
3
x(a.u)
y(a.u)
Degrees of freedom
Particle model
Voronoi model
Cellular Potts model
Vertex model
Phase field model
Complex cell shape
Computational efficiency

Solid-like and Fluid-like States

Does biological tissue act like a solid or a fluid?

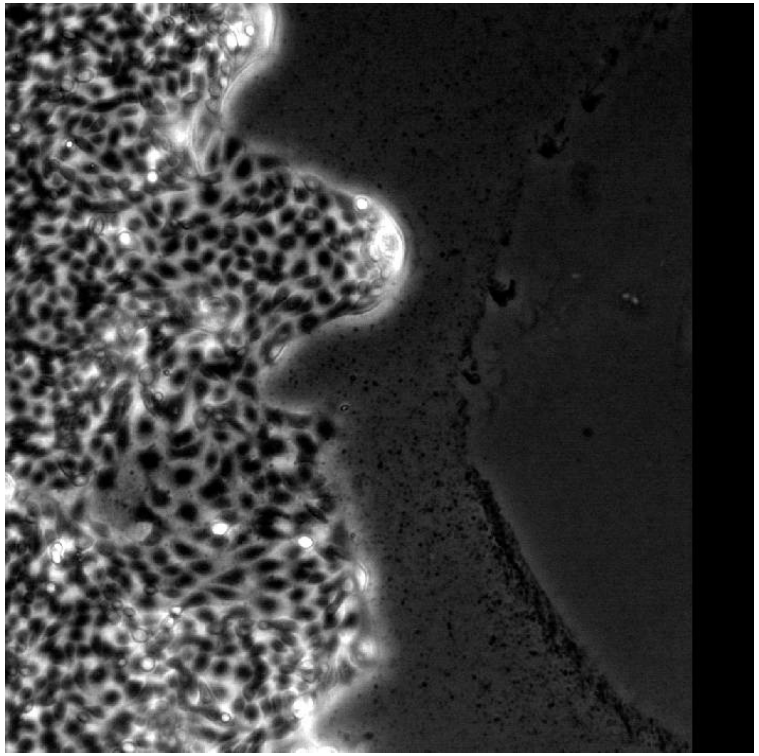
Solid-like for tissue integrity



Harris et al. PNAS, 2012

Fracture of epithelial layer

Fluid-like for development and growth



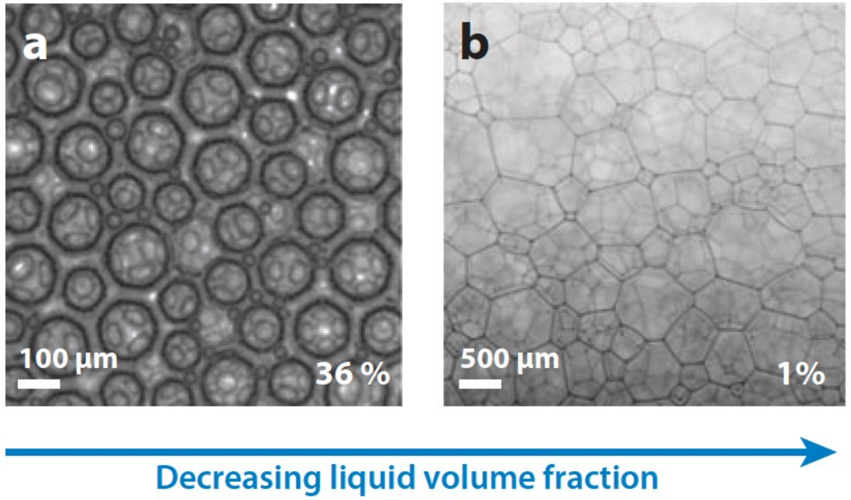
Kim et al. Nature Materials, 2013

Collective migration of epithelial monolayer

Phase transitions!!

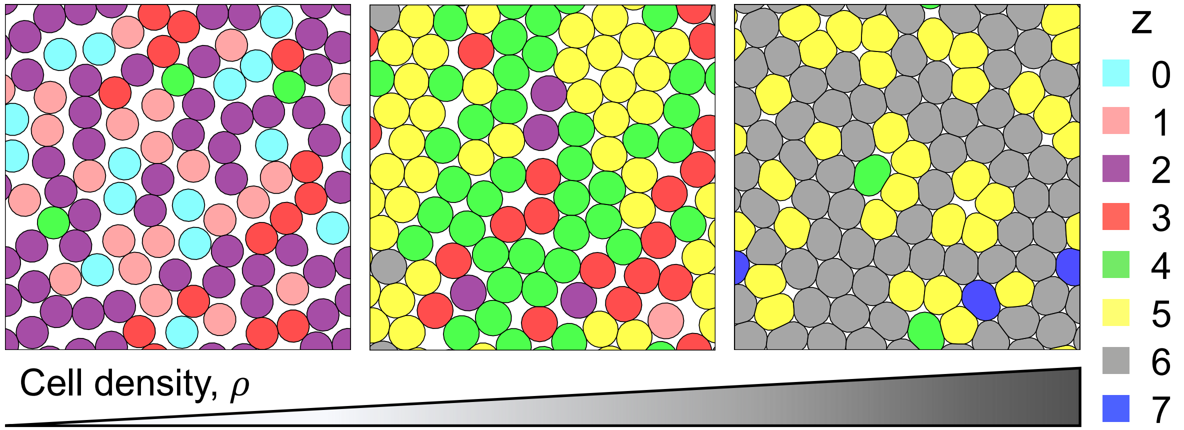
Jamming Transition: No adhesion

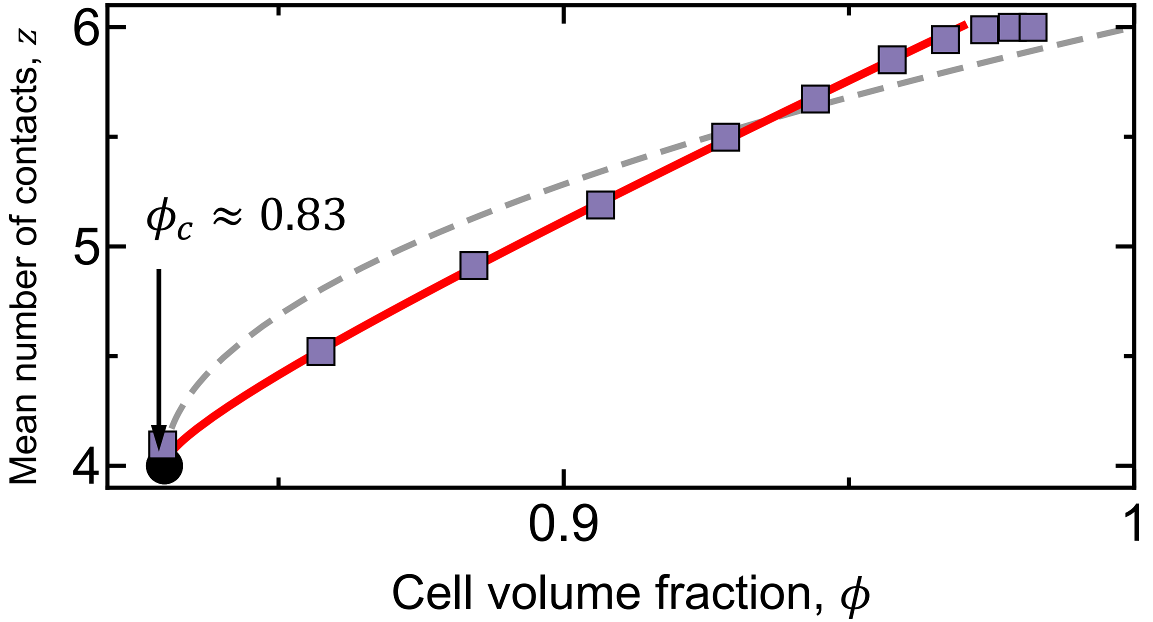
Liquid Foam



(Cohen-Addad et al. Annu. Rev. Fluid Mech., 2013)

Active Foam Model





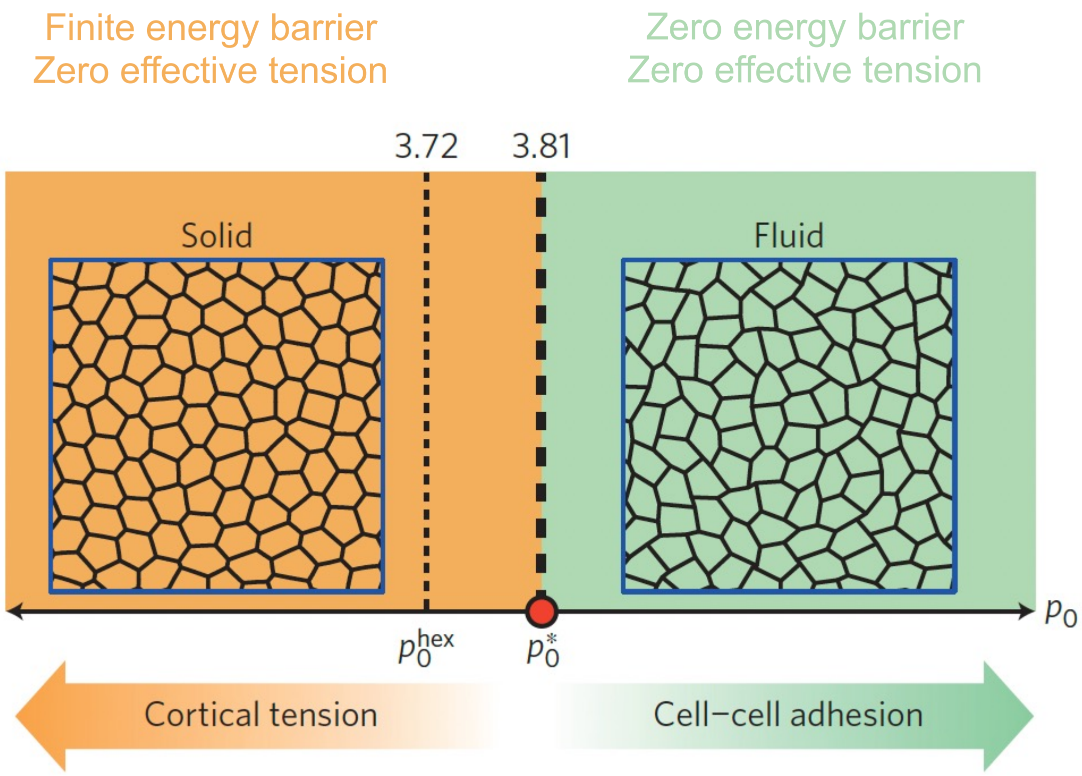
$$\phi - \phi_c = a_{1/2}(z - z_c)^{1/2}$$

$$\phi - \phi_c = a_{1/2}(z - z_c)^{1/2} + a_1(z - z_c)^1$$

Active Foam Model recovers the critical jamming volume fraction as well as the scaling relation close to the critical point!

(Kim et al. Nature Physics, 2021)

Density-Independent Transition: Zero Tension

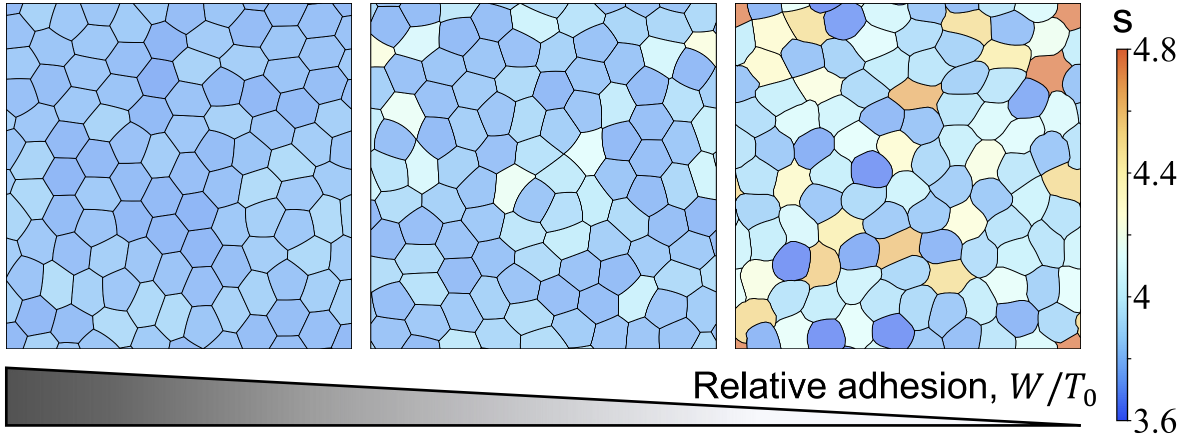


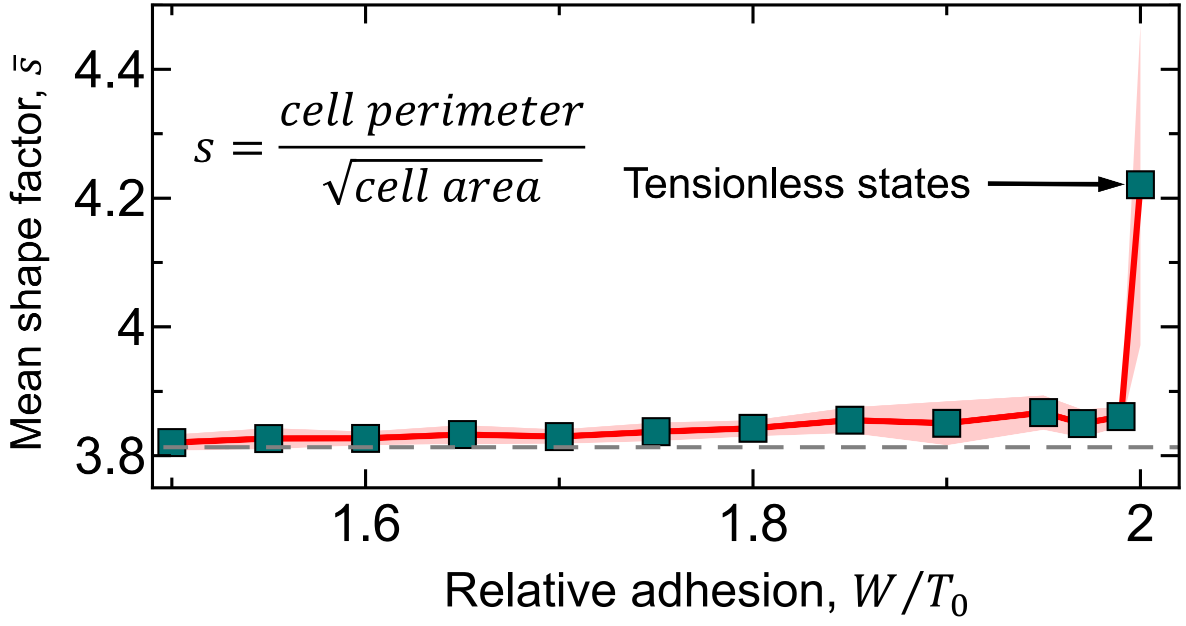
(Bi et al. Nature Physics, 2015)

$$E = \sum K_A(A_i - A_0)^2 + K_P(P_i - P_0)^2$$

Target area — Target perimeter

Target shape index: $p_0 = \frac{P_0}{\sqrt{A_0}}$

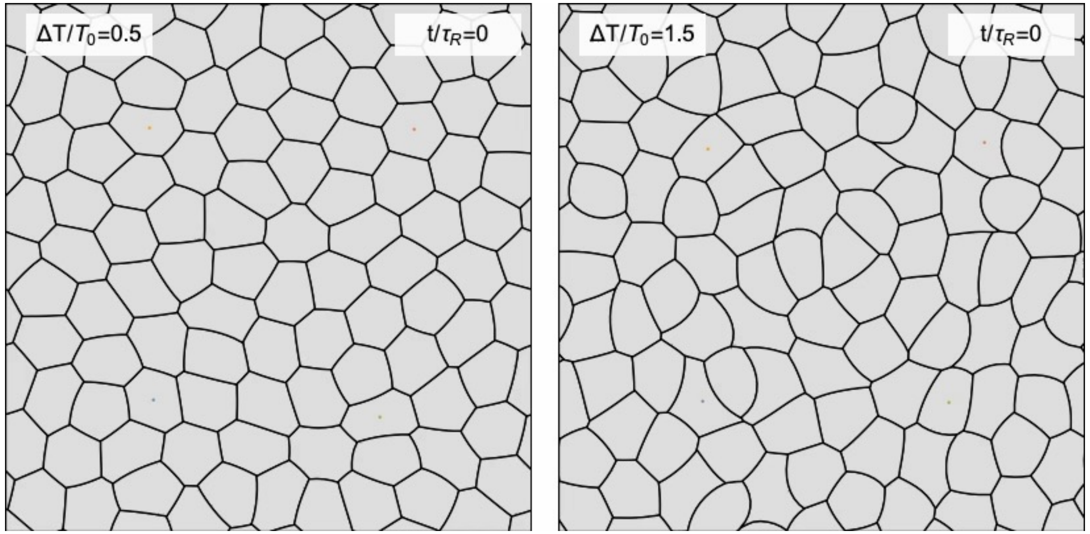


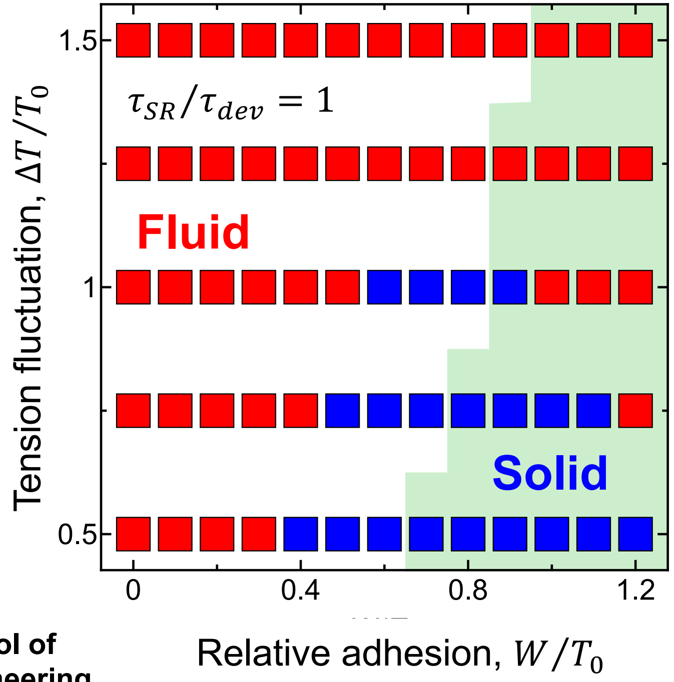


$T_{ij,0} = 2T_0 - W$ ⇒ $T_{ij,0} = 0$ for $W/T_0 = 2$

(Kim et al. Nature Physics, 2021)

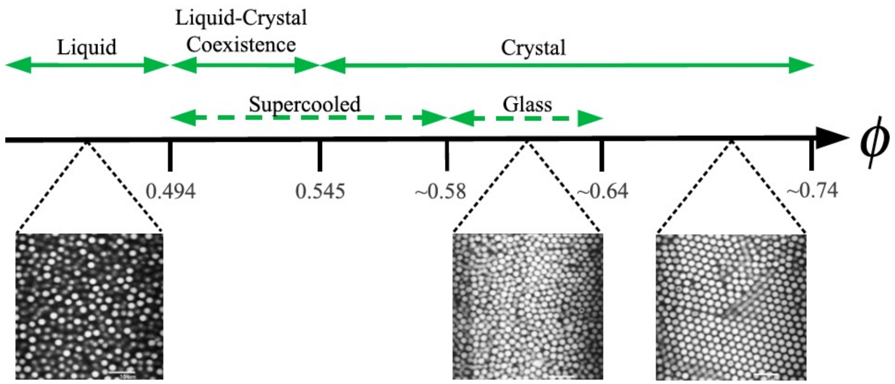
Activity-induced Transition in Embryonic Tissues





Increasing **active fluctuations** fluidize tissues

Colloidal glass transition



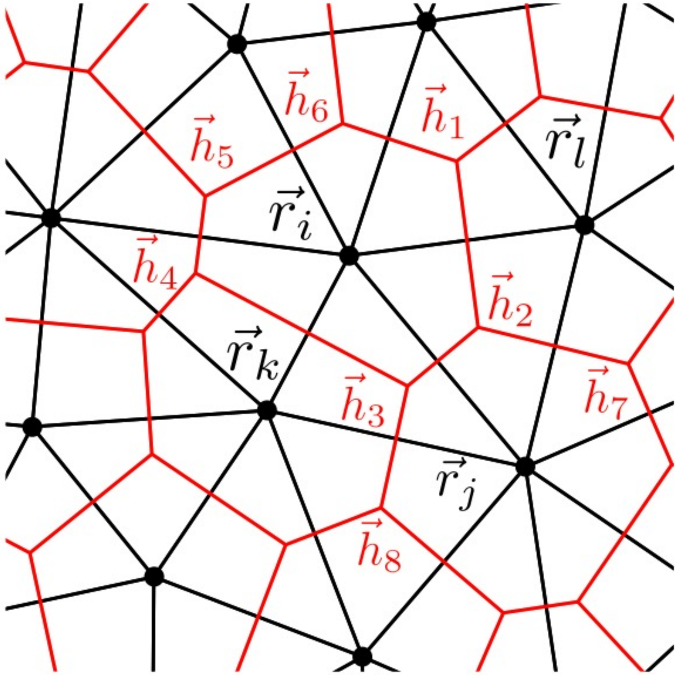
Similarity
- Diverging a relaxation time scale near the transition point.
- Dynamic slowdown and caging behavior for glassy states

Difference
- Control parameter: temperature vs active tension fluctuations

Kim et al. Nature Physics, 2021

Motility-induced transition

Voronoi model: hybrid between the particle model and the vertex model



(Bi16)

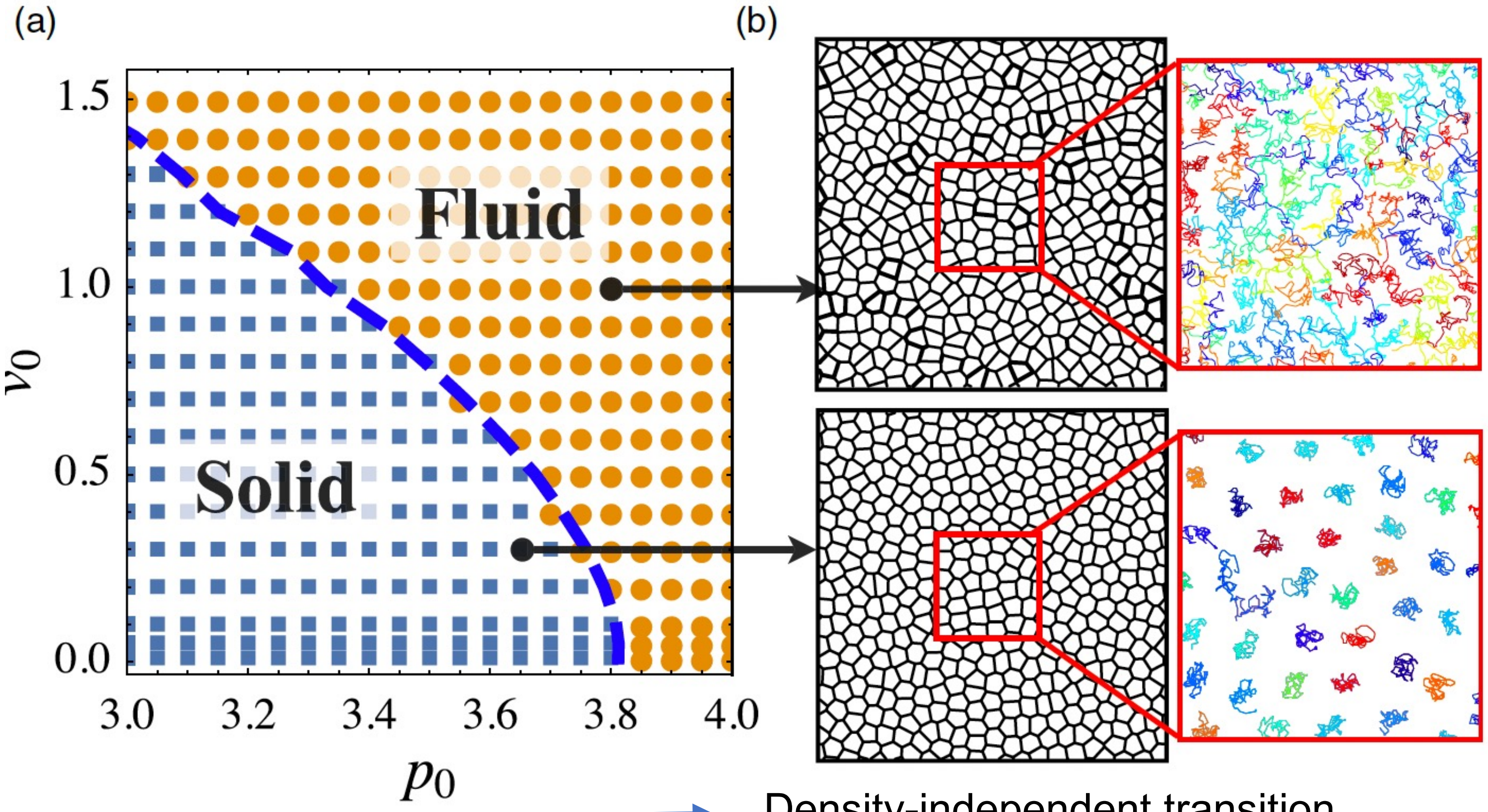
Degrees of freedom: particle position
Energy functional: depending on Voronoi tessellation properties

$$E = \sum_i K_A (A_i - A_{i,0})^2 + K_P (P_i - P_{i,0})^2$$

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

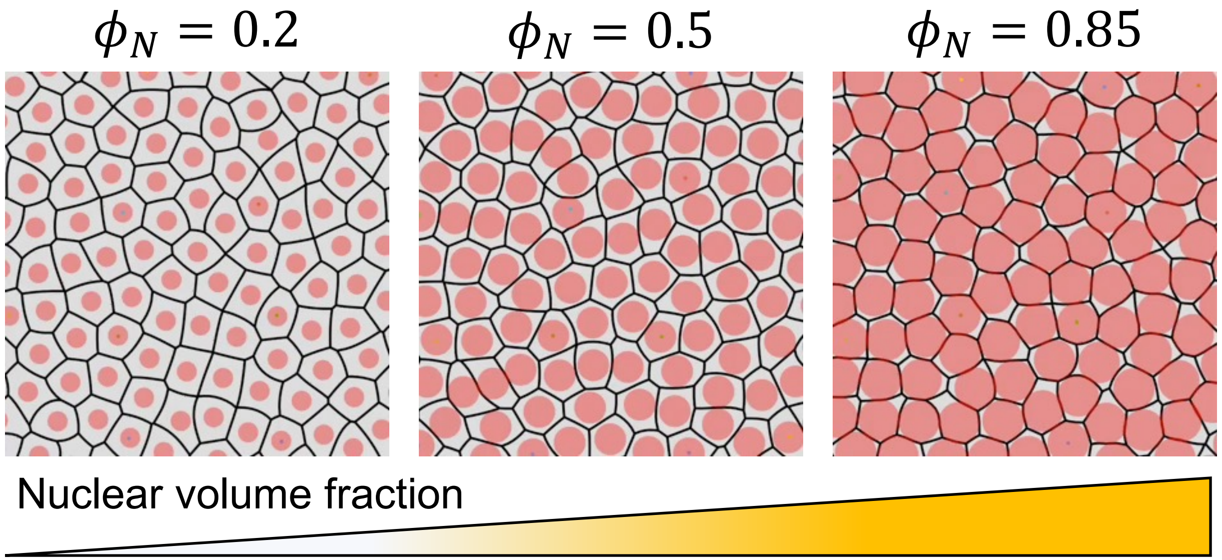
Solid/fluid phase is determined by effective diffusion coefficient

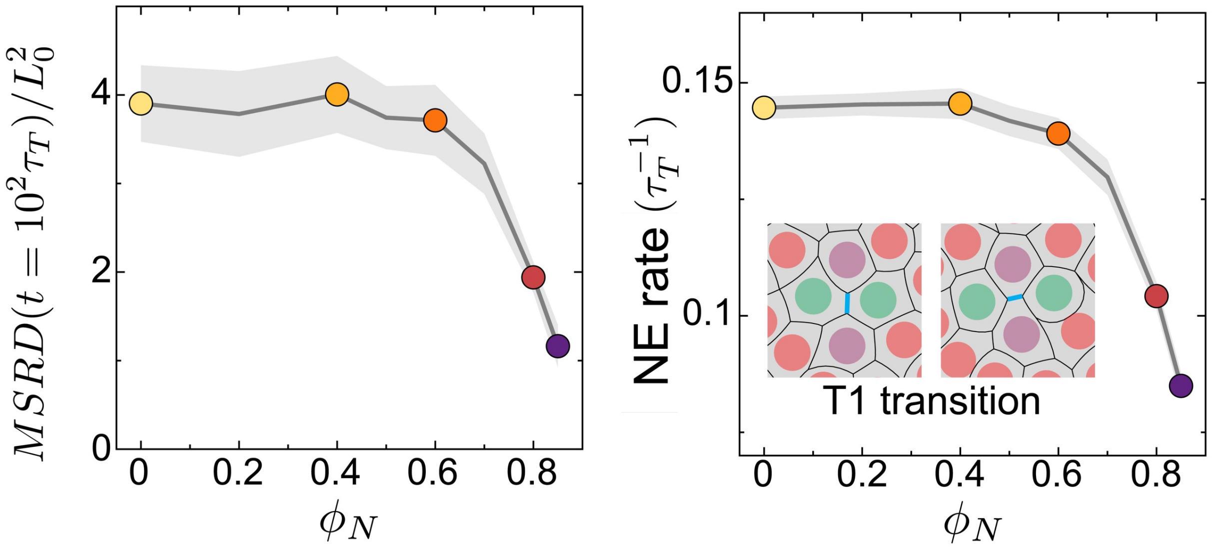
Motility induced transition

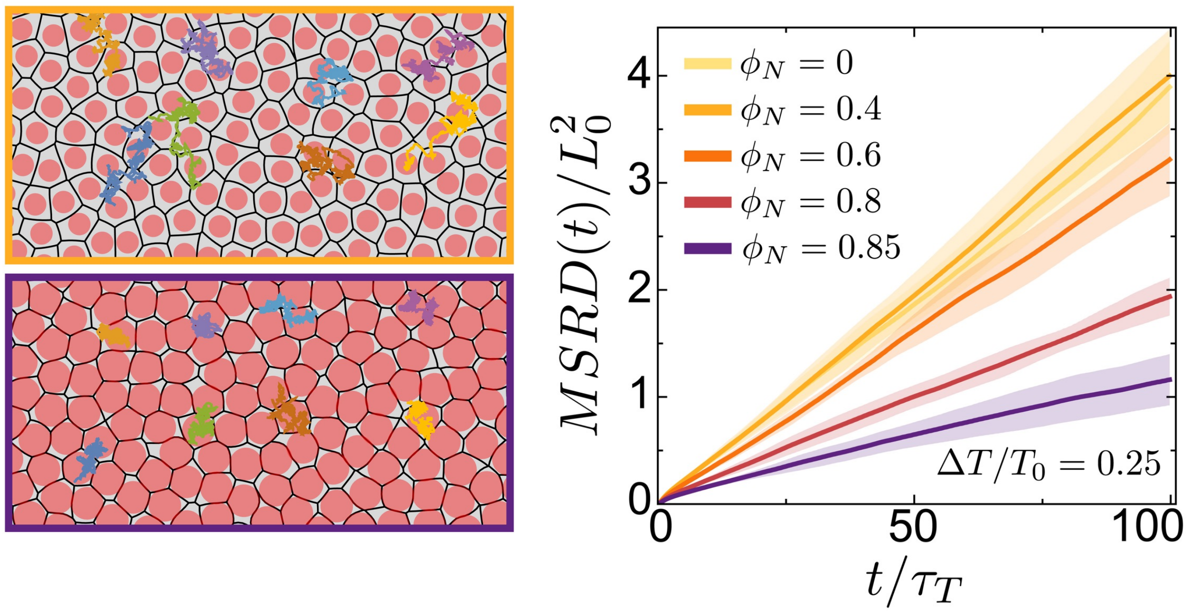


Density-independent transition

Nuclear Jamming Transition





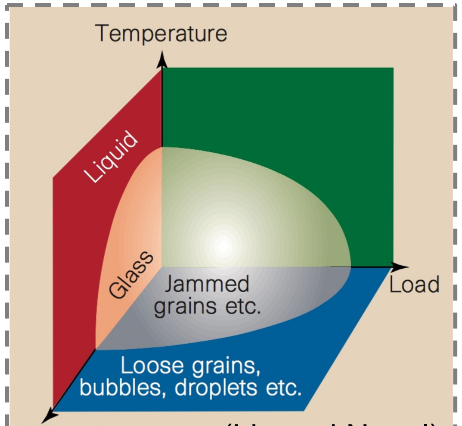


Cell movement as well as neighbor exchange rate progressively decrease for increasing nuclear volume fraction

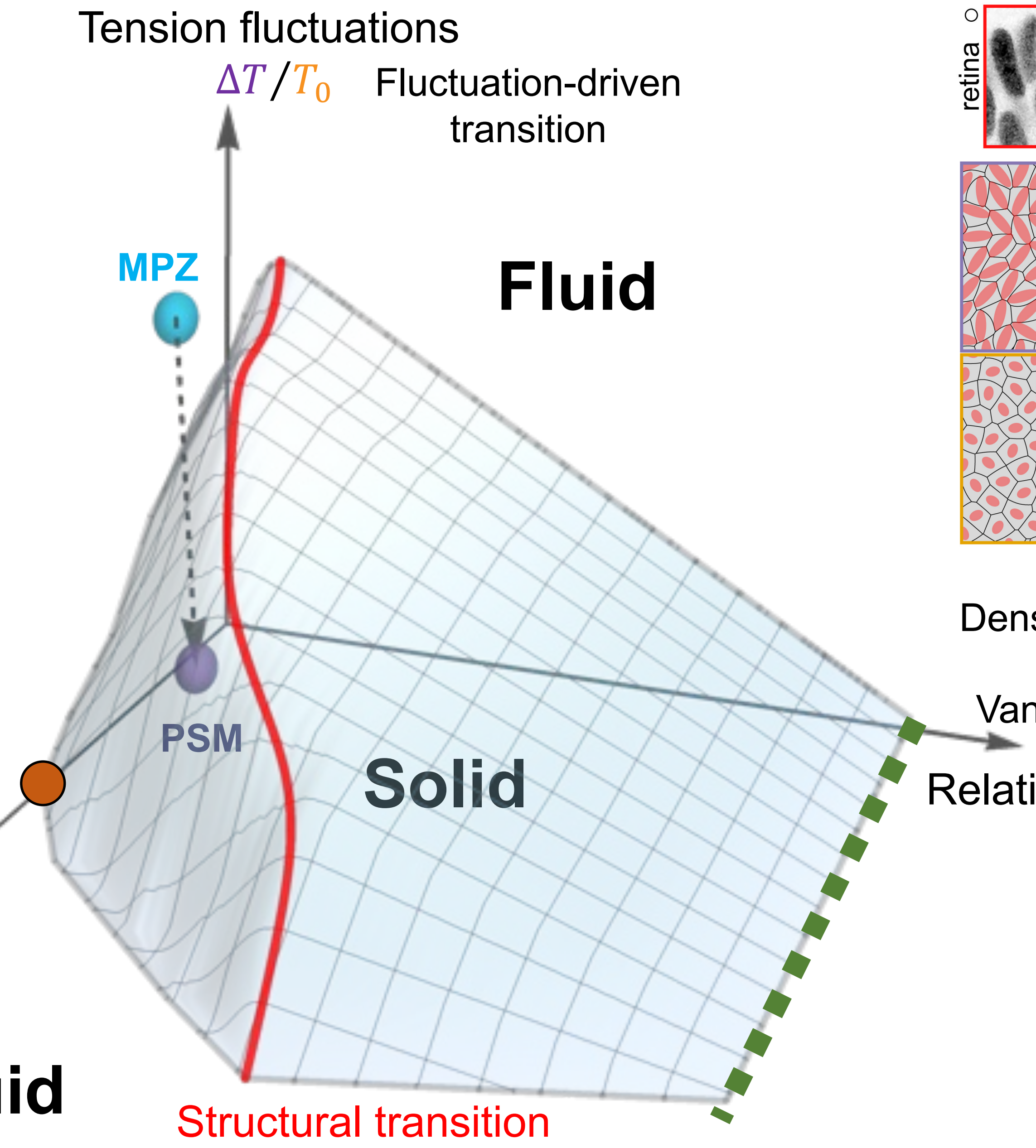
Kim et al. Nature Materials, 2024

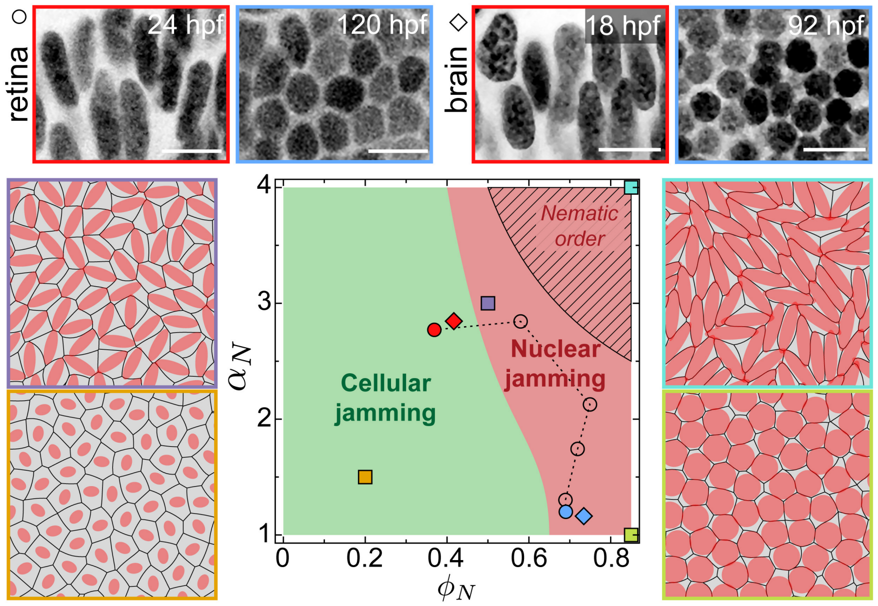
EPFL

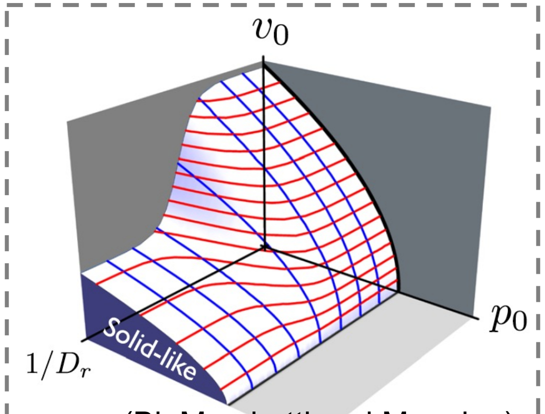
Phase Transitions in Biological Tissues



(Liu and Nagel)







(Bi, Marchetti and Manning)