EPFL

Week 8: Modeling of Cell Clusters - Structure, Dynamics, and Emergent Mechanics

November 8

ME 480 – Mechanobiology: how mechanics regulate life

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- Discrete vs Continuum
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What is the Scientific Modeling?

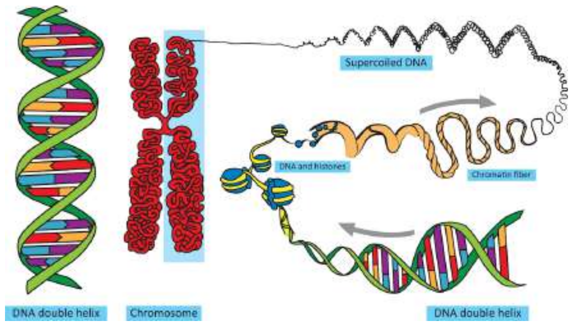
(Wikipedia)

The sciences do not try to explain, they hardly even try to interpret, they mainly make models. By a model is meant a mathematical construct which, with the addition of certain verbal interpretations, describes observed phenomena. The justification of such a mathematical construct is solely and precisely that it is expected to work.

John von Neumann

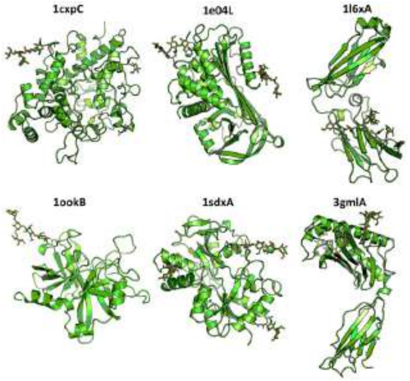
Observed Phenomena in Biological Tissues

DNA packaging



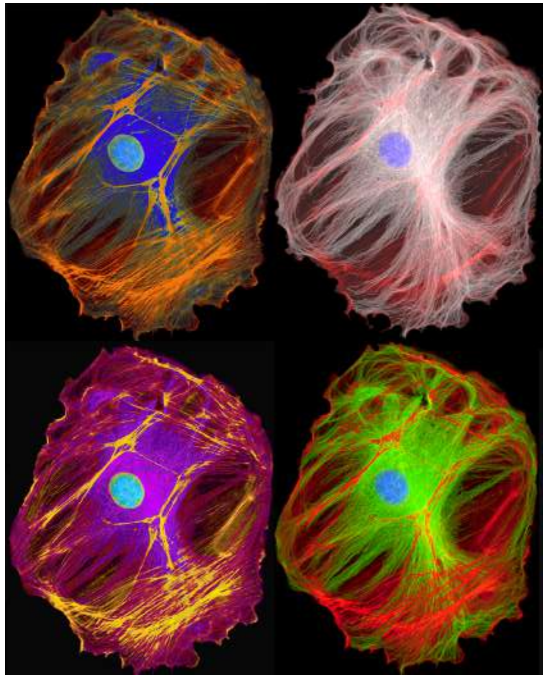
(EreborMountain/Shutterstock.com.)

Protein structure



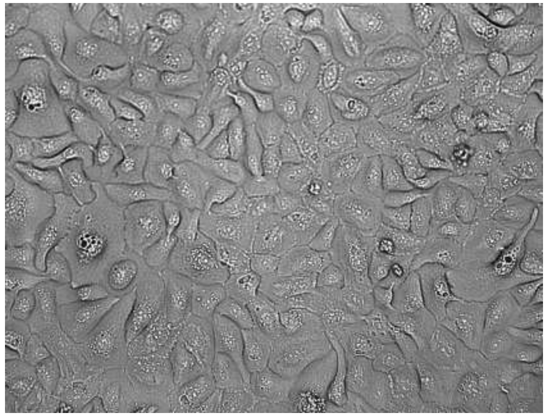
(Lee et al. Sci Rep 2015)

Cytoskeleton
Single cell migration

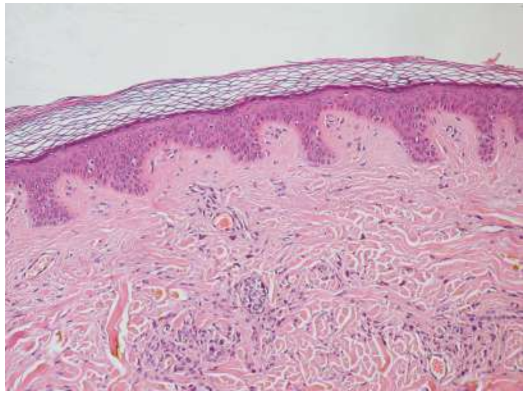


(https://sitn.hms.harvard.edu/art/2015/actin-four-ways/)

Animal tissues

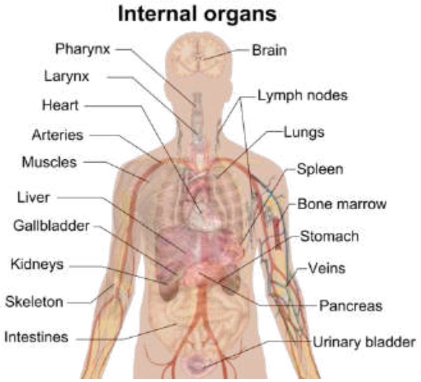


(Thomas et al. Journal of Allergy and Clinical Immunology, 2017)



(Wikipedia: loose connective tissue)

Organs



(Wikipedia: Organ)

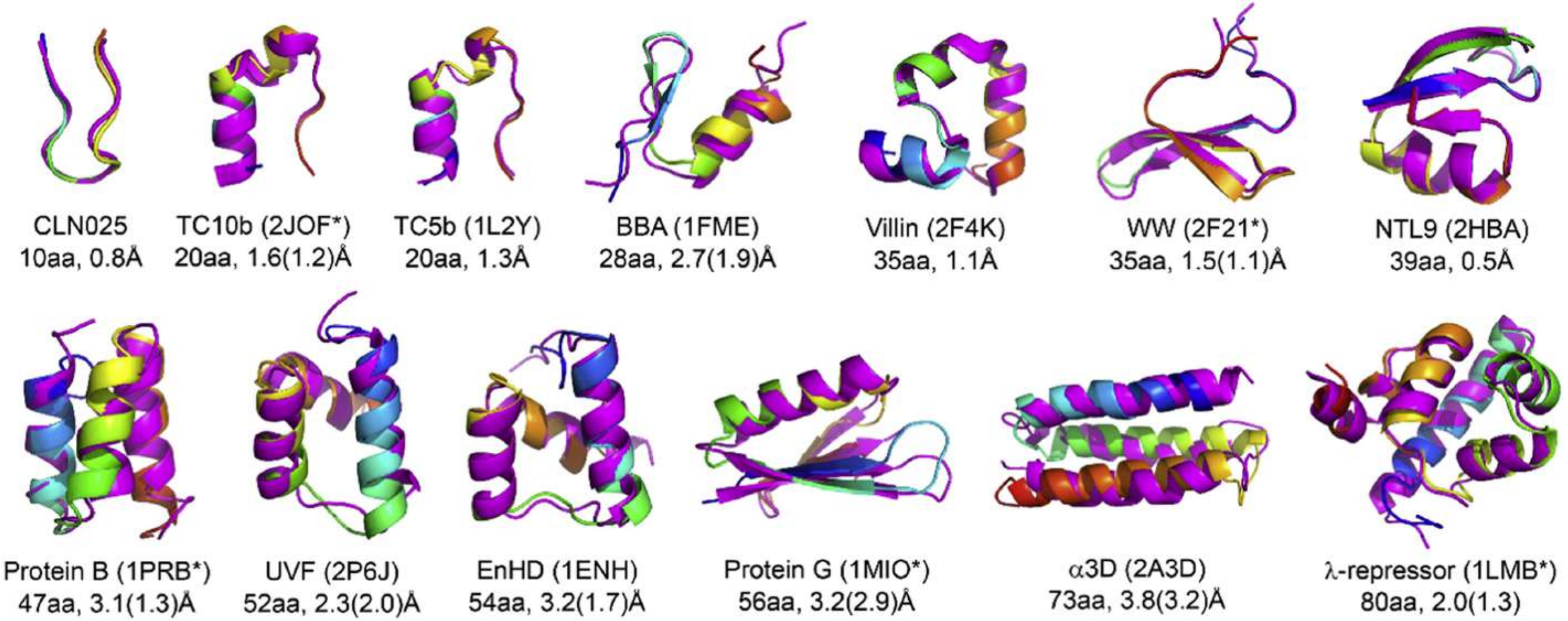
Bone

(Wikipedia: bone)

nm um mm

Length scale

Modeling of Protein Structure: MD Simulations

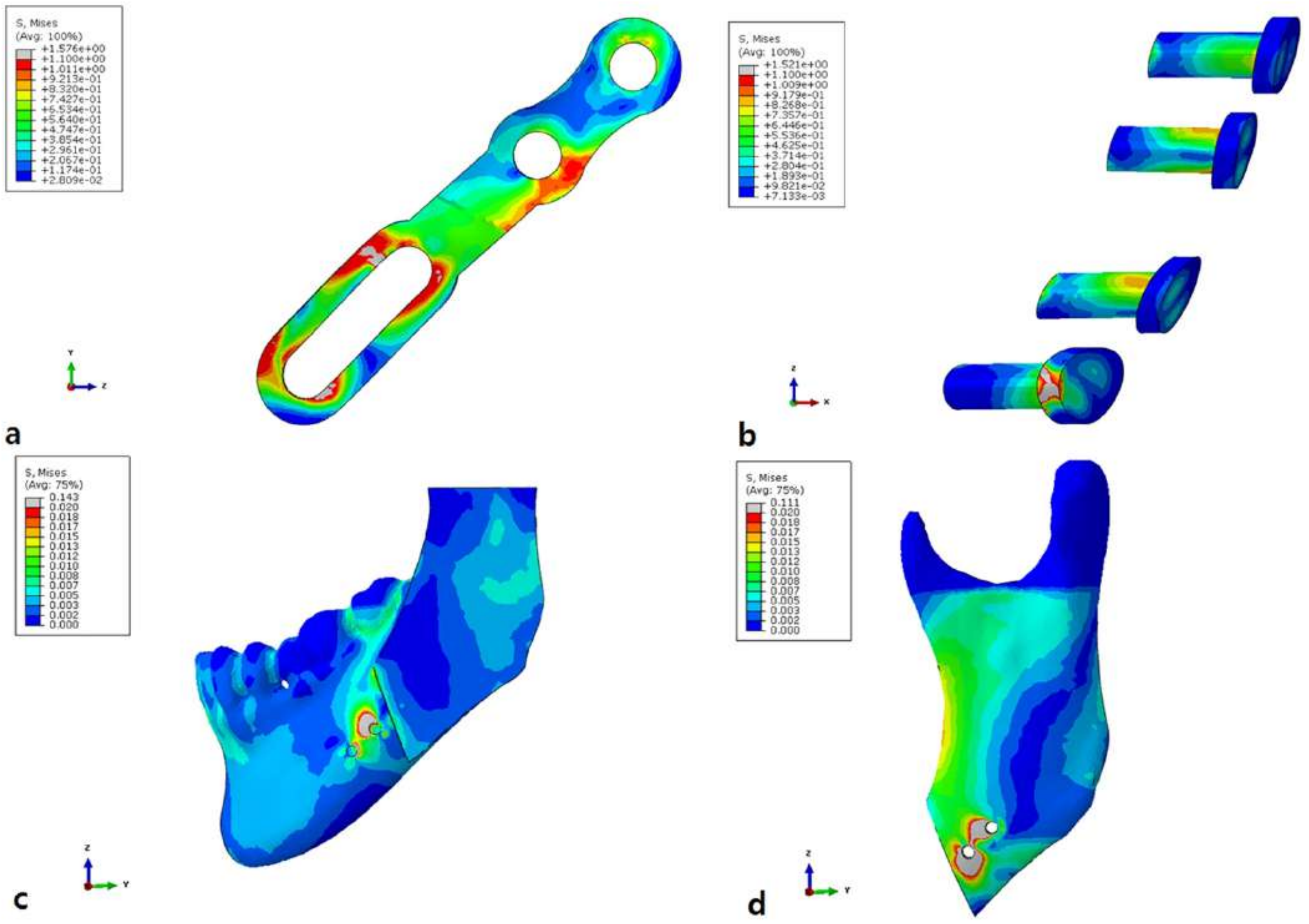


(Geng et al. Computational and Structural Biotechnology Journal, 2019)

- Discrete modeling approach
- Degrees of freedom as positions /orientations of atoms
- Compute forces/moments acting on each atom of protein
- Forces/moments are computed from a molecular mechanics force field
- Apply Newton’s laws of motion to predict the spatial position/orientation
- Large-scale Atomic /Molecular Massively Parallel Simulator (LAMMPS)

Keyword: MD simulations for protein conformation

Modeling at Macroscopic Scale: Continuum Mechanics



(Kim et al. Sci Rep, 2018)

- Continuum mechanics modeling (FEM)
- Based on fundamental mechanical principles
  - mass conservation
  - linear momentum conservation
  - angular momentum conservation
  - energy conservation
- Constitutive equations
  - Elastic vs Plastic
  - Newtonian vs Non-Newtonian
  - Viscoelastic
  - Viscoplastic
  - Hyperelastic
- Abaqus, Comsol Multiphysics

Keyword: Continuum mechanics for biological tissues

Discrete vs Continuum for Cell Clusters

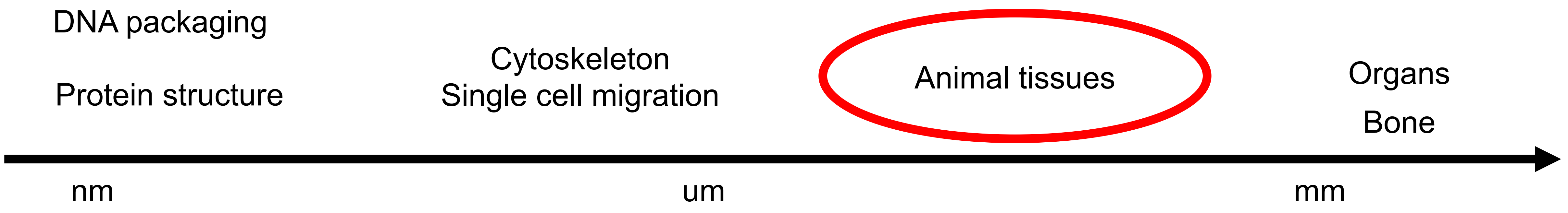
Discrete Modeling

- Resolution at cellular scale (or even subcellular scale)
- How to represent individual cells?
- What is dominant interaction between cells?
- Computationally challenging to study tissues with a large number of cells

Continuum Modeling

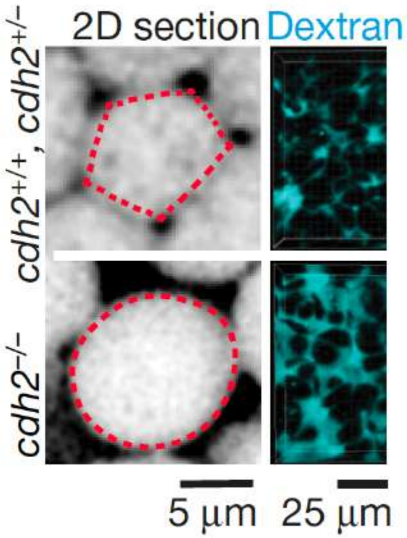
- Computationally efficient to study large system
- Study of a large system for a long time
- Local events cannot be predicted
- How to derive constitutive equations?

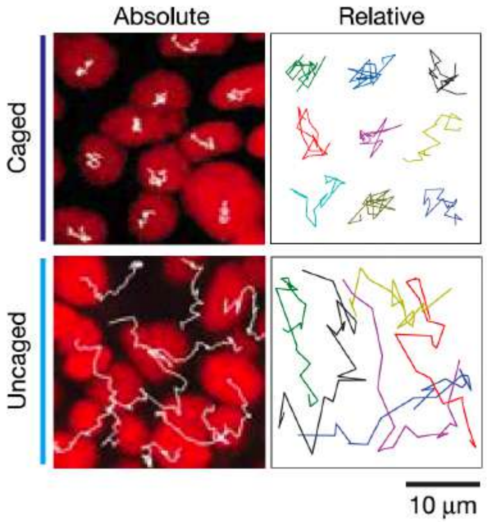
Discrete vs Continuum??

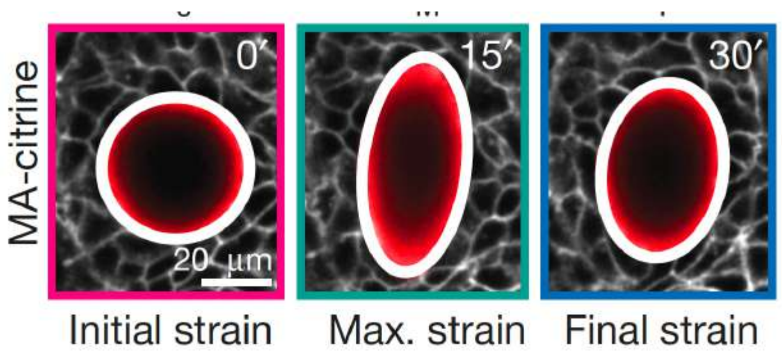


We will mainly discuss about discrete modeling approaches today

Observable Measures in Cell Clusters







(Mongera18)

Structure

- Measures from shapes of cells and subcellular elements
  - Cell size
  - Cell shape
  - Cell orientation
- Image analysis for a fixed time point

Dynamics

- Time-lapse movies of experimental data
- Image analysis over a period of time
- MSD, neighbor exchange event, etc

Mechanical properties

- Mechanical testing is required
- Macroscopic properties vs cellular/subcellular properties
- AFM, optical tweezer, micropipette, microbeads, droplets, etc
- Rheological test

How can we explain these observed measures in cell clusters based on models?

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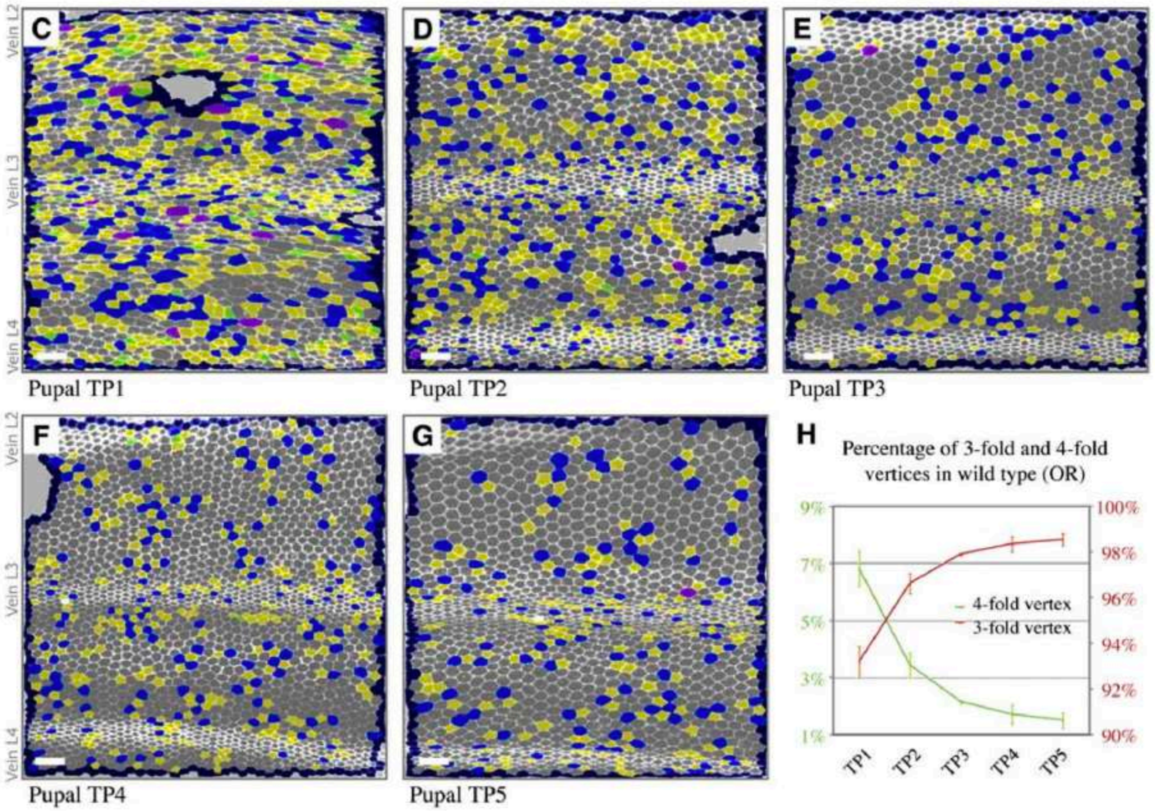
Mathematical Model: Granocentric Model

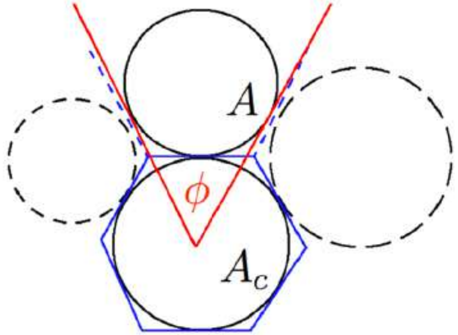
Can mathematical modeling explains observed phenomena in cell clusters?



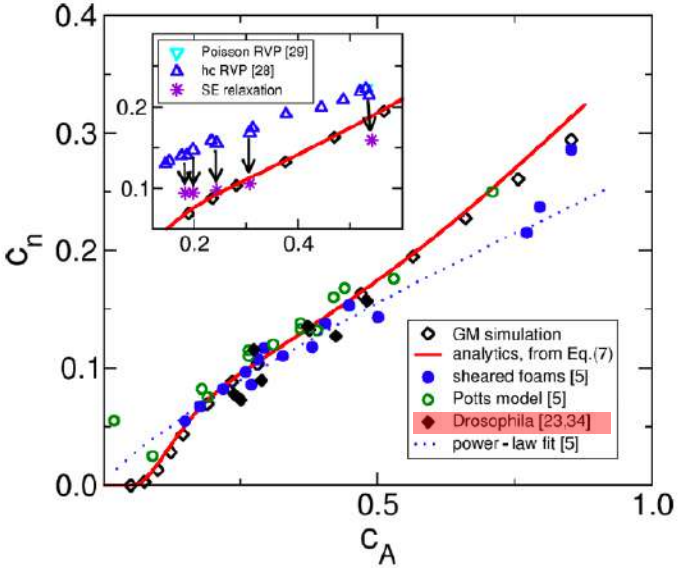
(Classen05)

Structural ordering of wing epithelium of Drosophila embryo

Size distribution →



→ Topology distribution



(Miklius12)

Universal relation between size and topology

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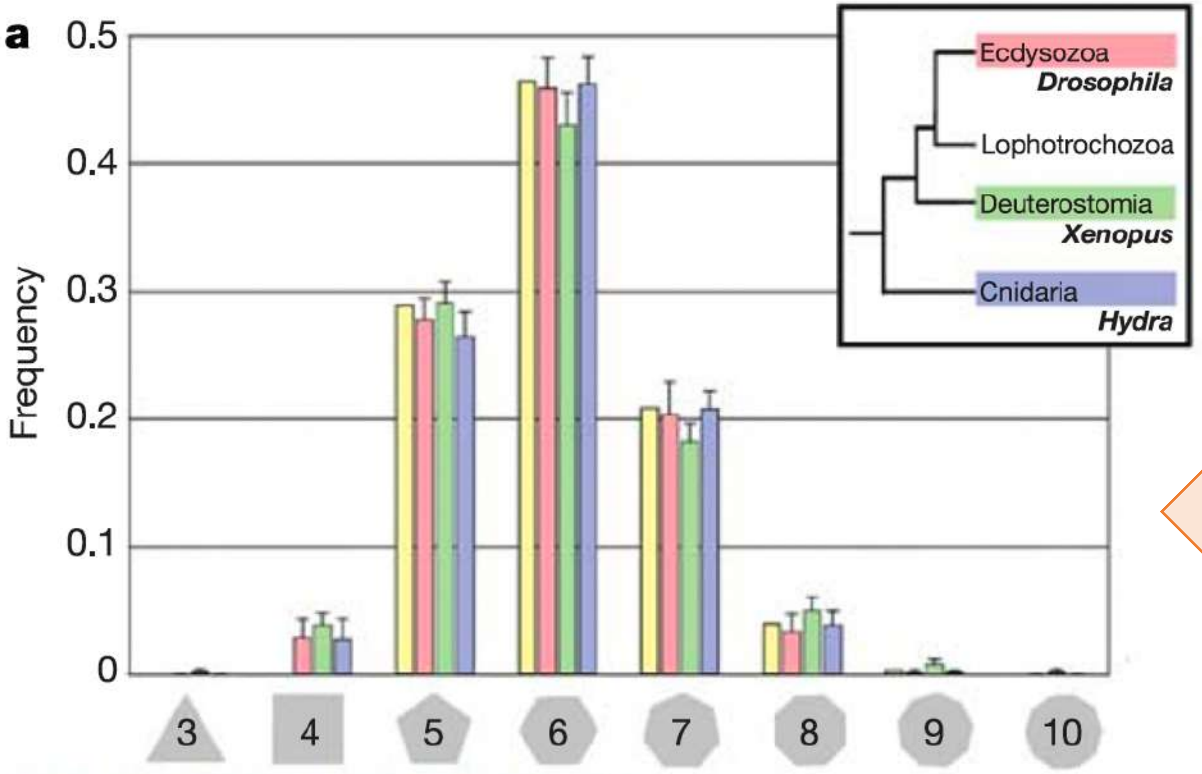
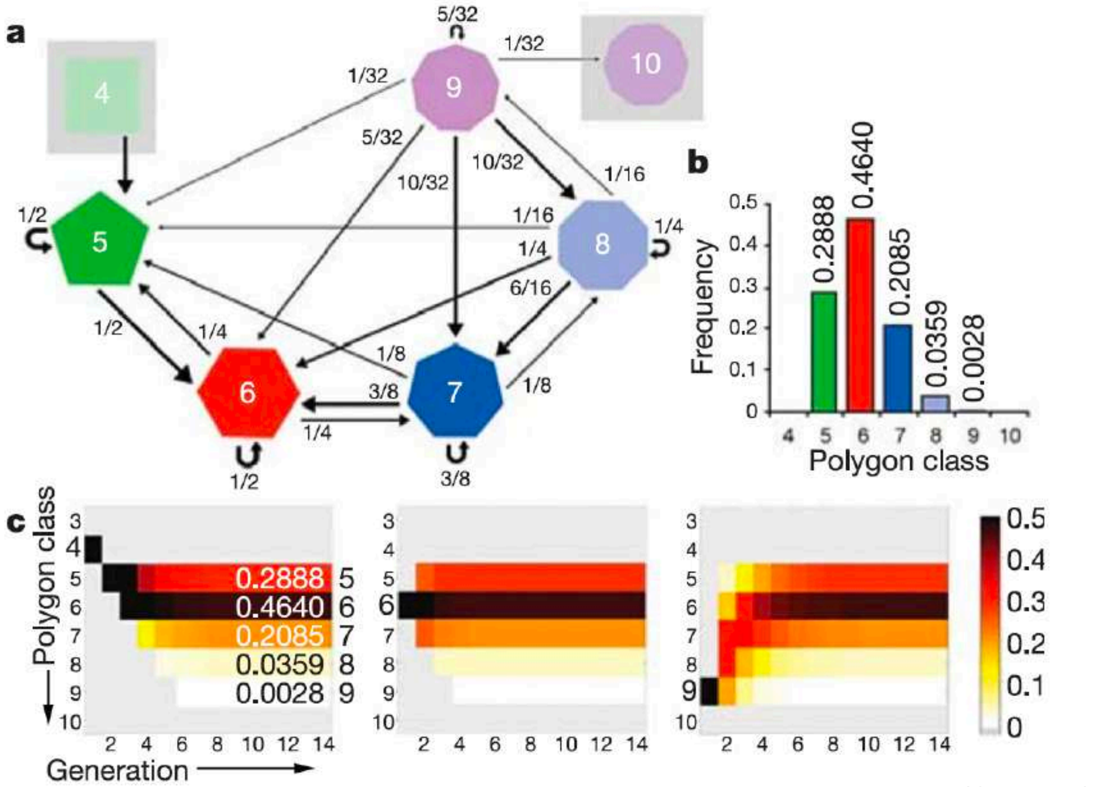
Mathematical Model: Markov Chain for Cell Division

Markov chain: stochastic model describing a sequence of possible events in which the probability of each event depends only on the state attained in the previous event

Random division plane +
neighbor addition by adjacent diving cells



Universal topology distributions
within proliferating epithelia

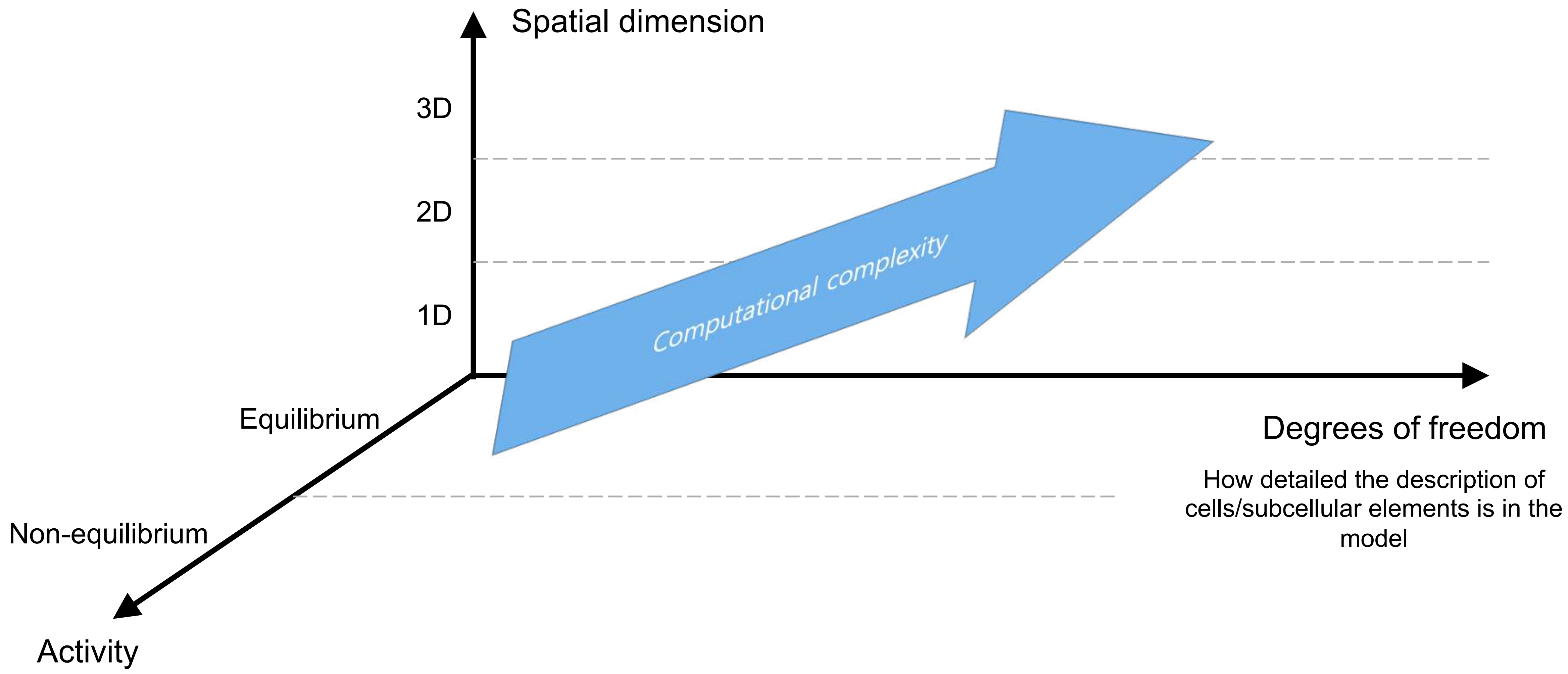


(Gibson06)

A robust equilibrium topology distribution
can be derived from a Markov chain model

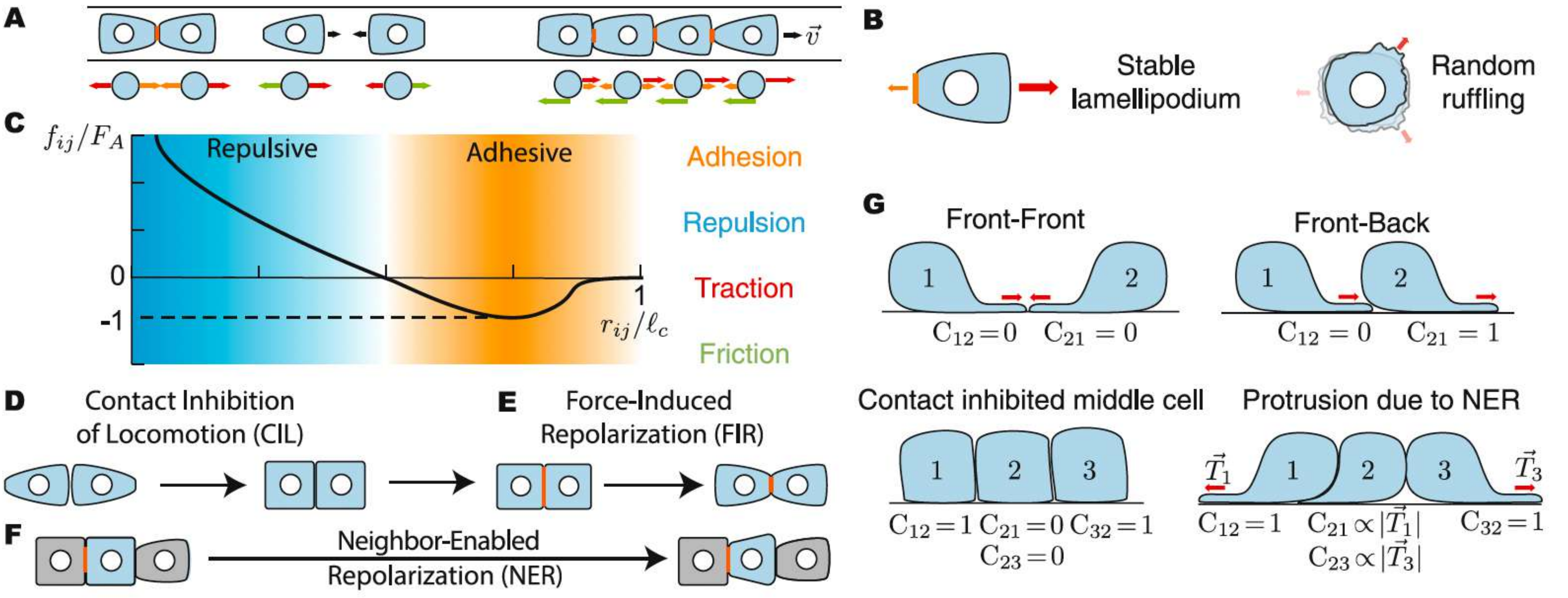
School of
Engineering

Discrete Models: Overview



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

Discrete Models: 1D Particle Model



(George17)

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

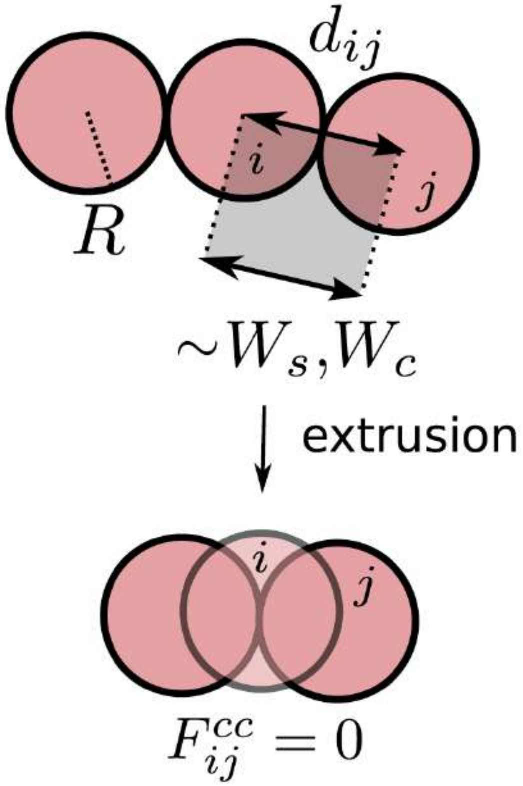
Viscous friction — Traction force — External force

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

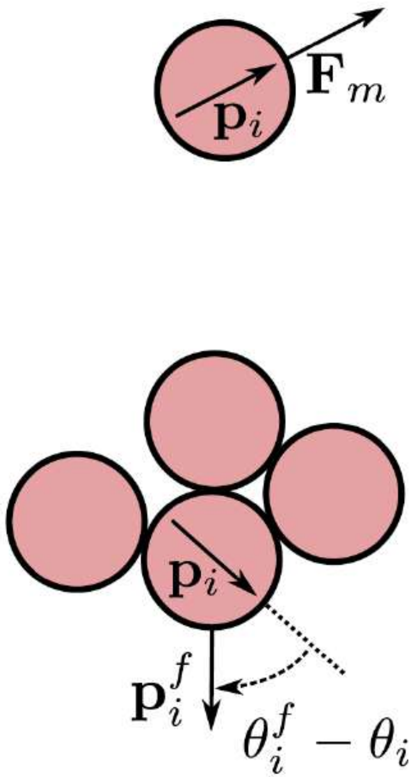
Viscous friction — Traction force — Interaction force

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

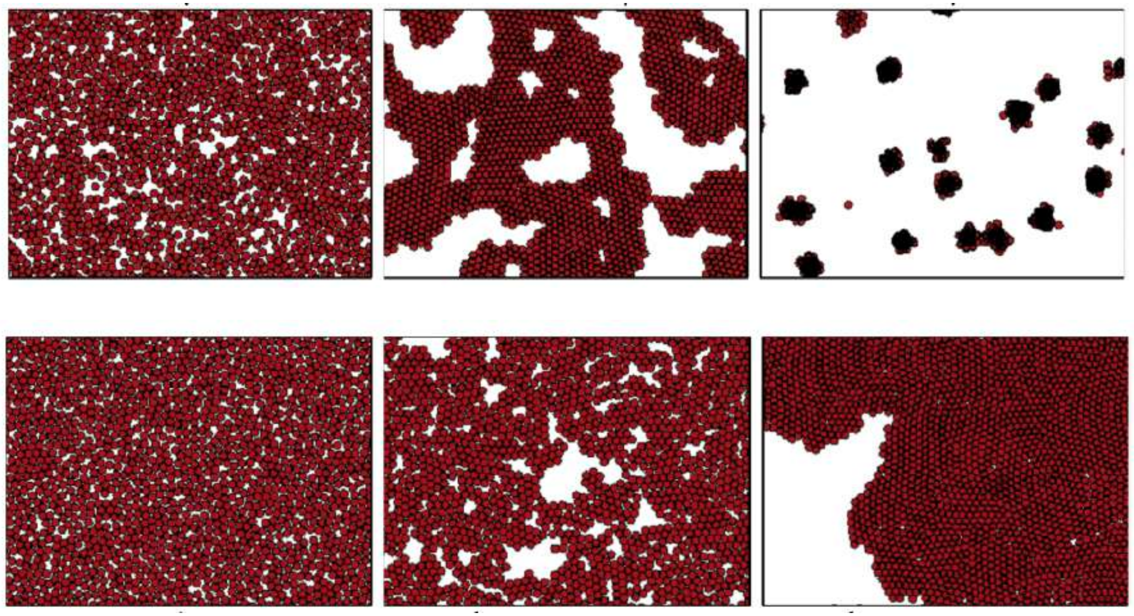
B Cell extrusion



C Contact inhibition of locomotion



Different tissue structure



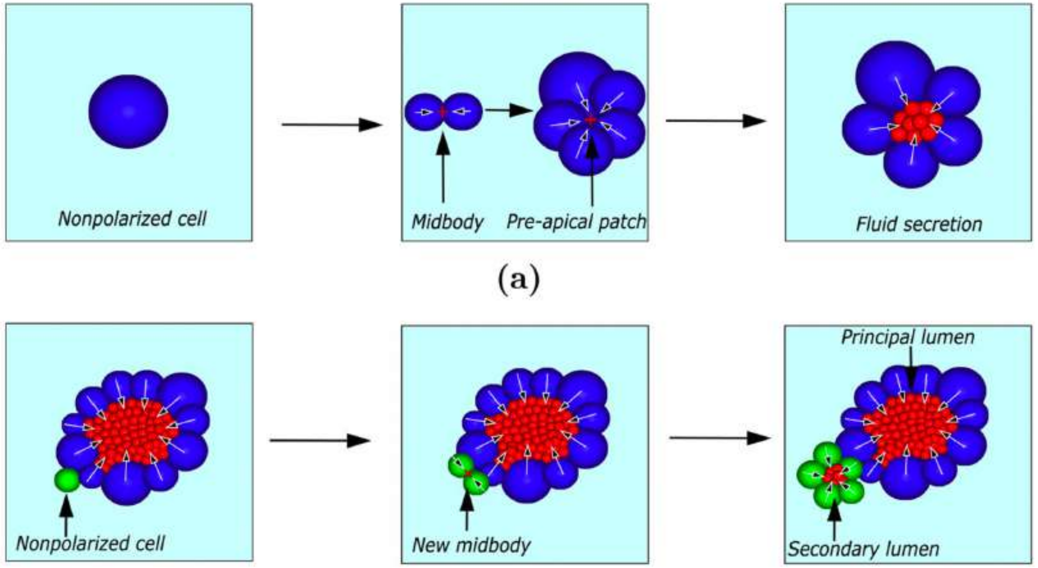
(Smeets16)

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

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

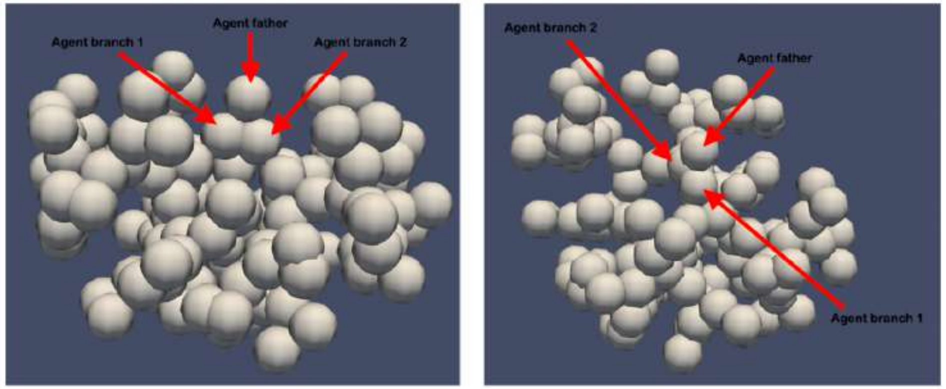
Discrete Models: Agent-Based Model (3D Particle)

Lumen morphogenesis



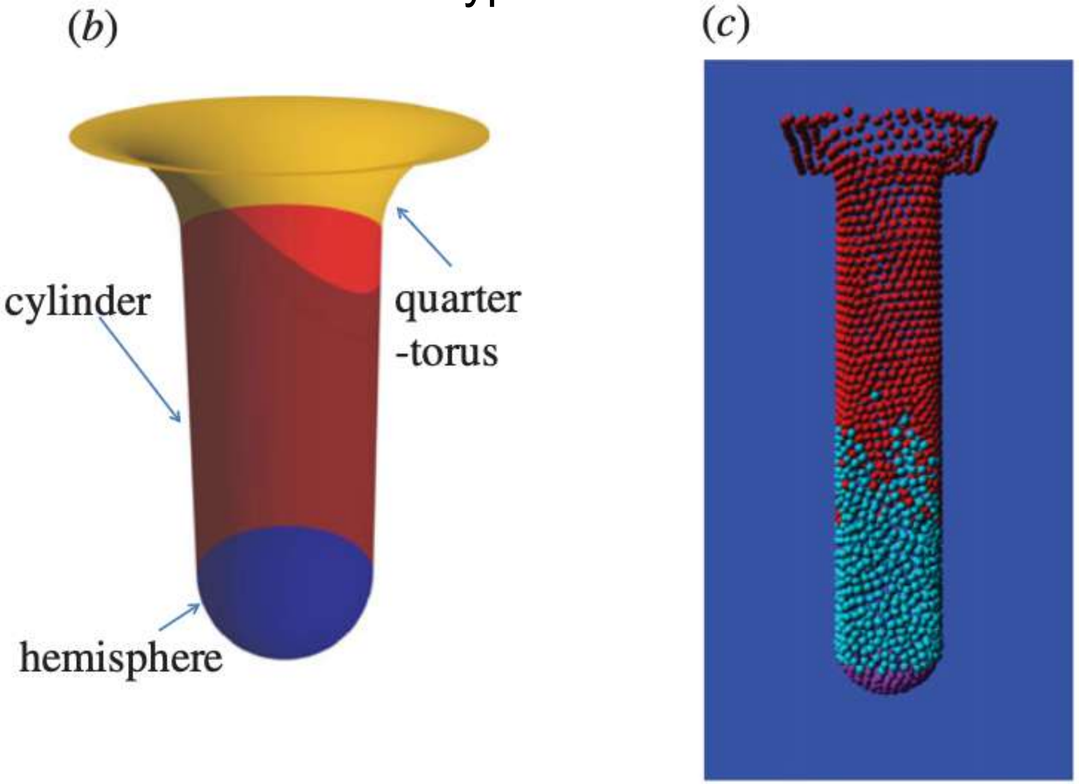
(Gomez et al. Engineering with Computers, 2022)

Lung fibrosis



(Cogno et al. Symmetry, 2022)

Crypt simulations



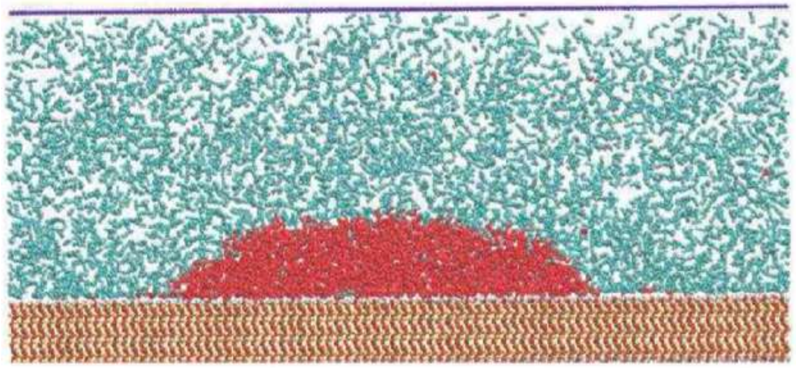
(Dempster et al. R Soc Open Sci, 2017)

From Where: Particle Models

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

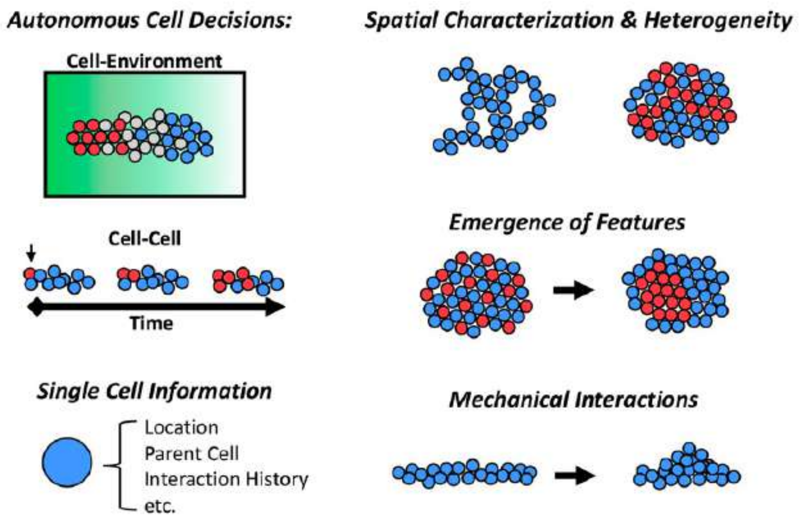
⇨ Tissue morphogenesis based on cell-cell interaction or cell-substrate interaction

MD simulation



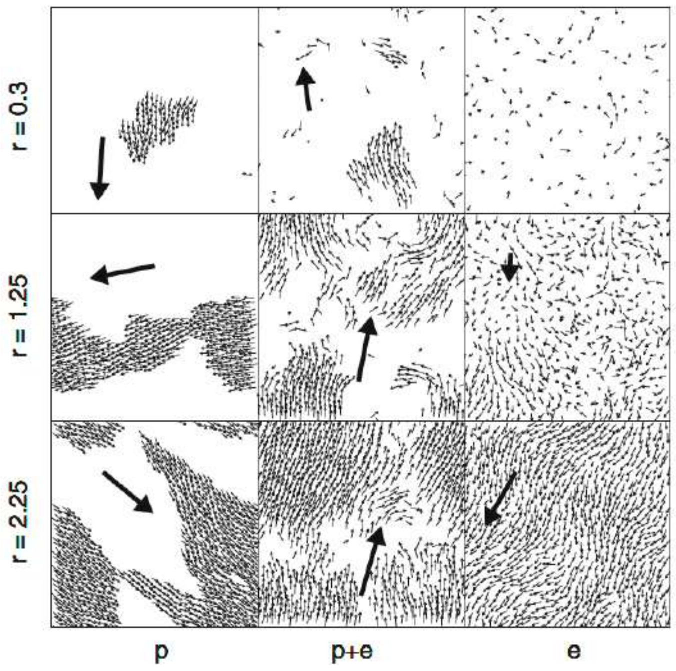
(Sethi et al. 2021)

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

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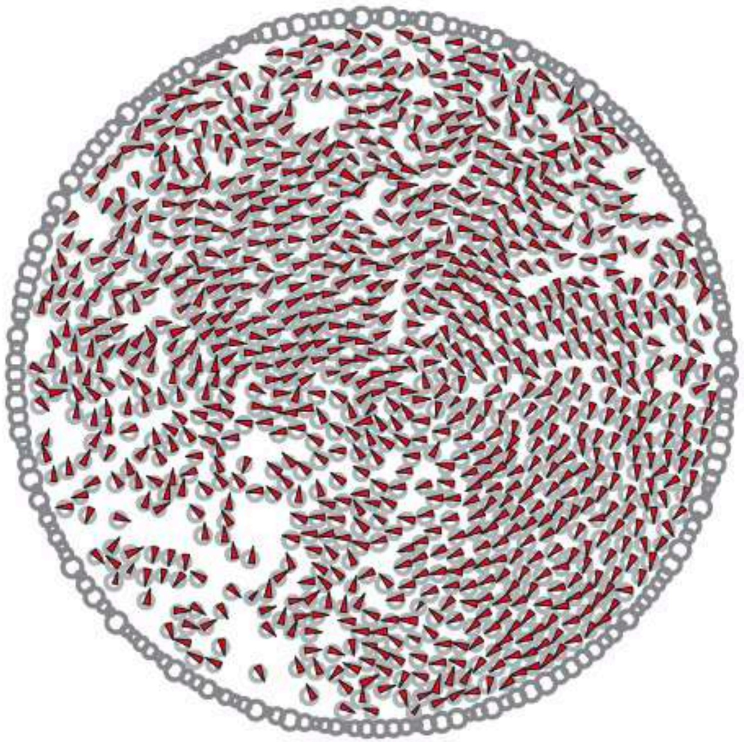
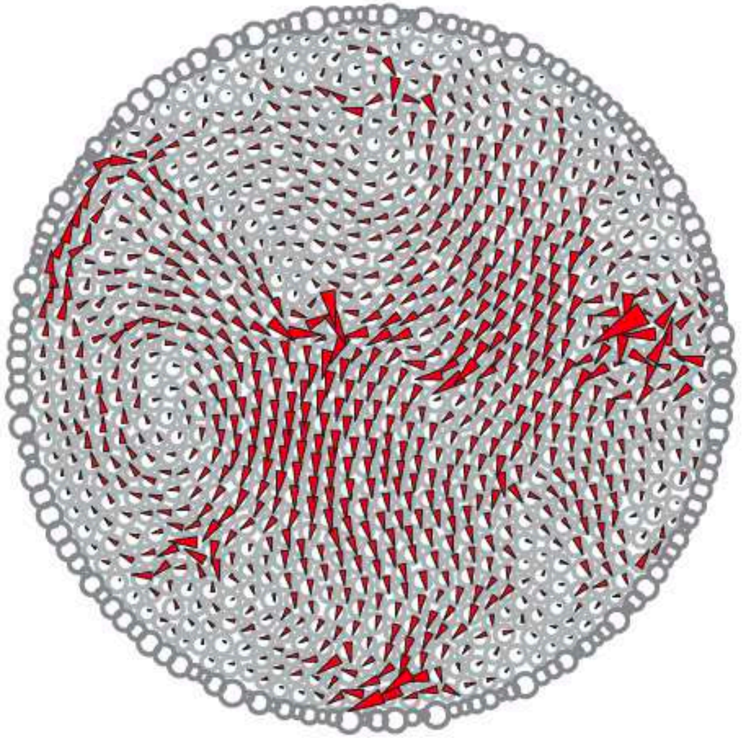
Discrete Models: Jamming Transition

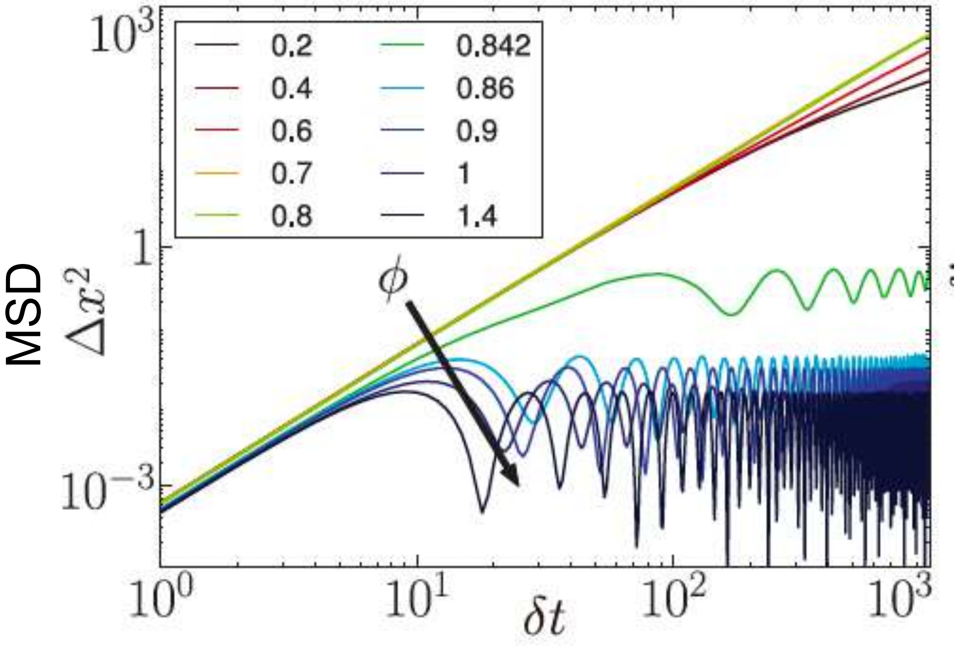


$\phi = 0.6$



$\phi = 0.95$

(Henkes11)

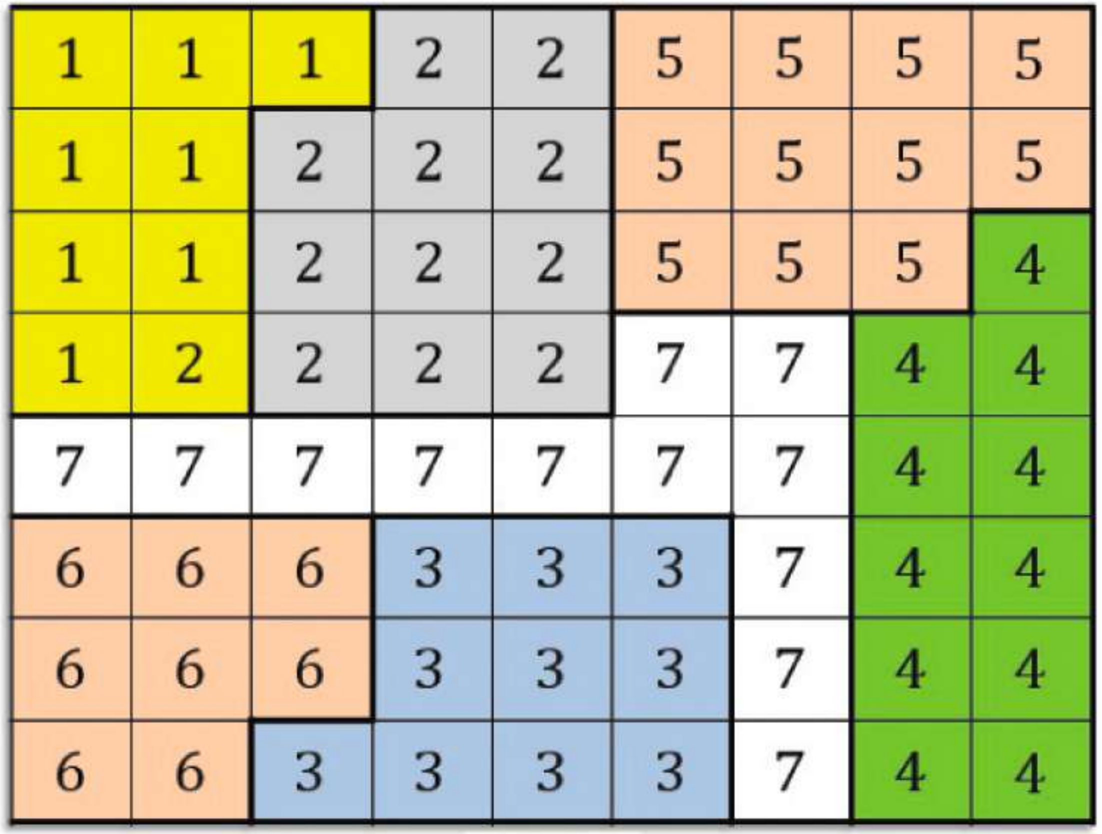


$$\dot{\vec{r}}_i = v_0 \hat{n}_i + \mu \sum_{j=1}^{z_i} \vec{F}_{ij}$$

Cell velocity | Self propulsion | Cell-cell interaction

Discrete Models: 2D Cellular Potts Model

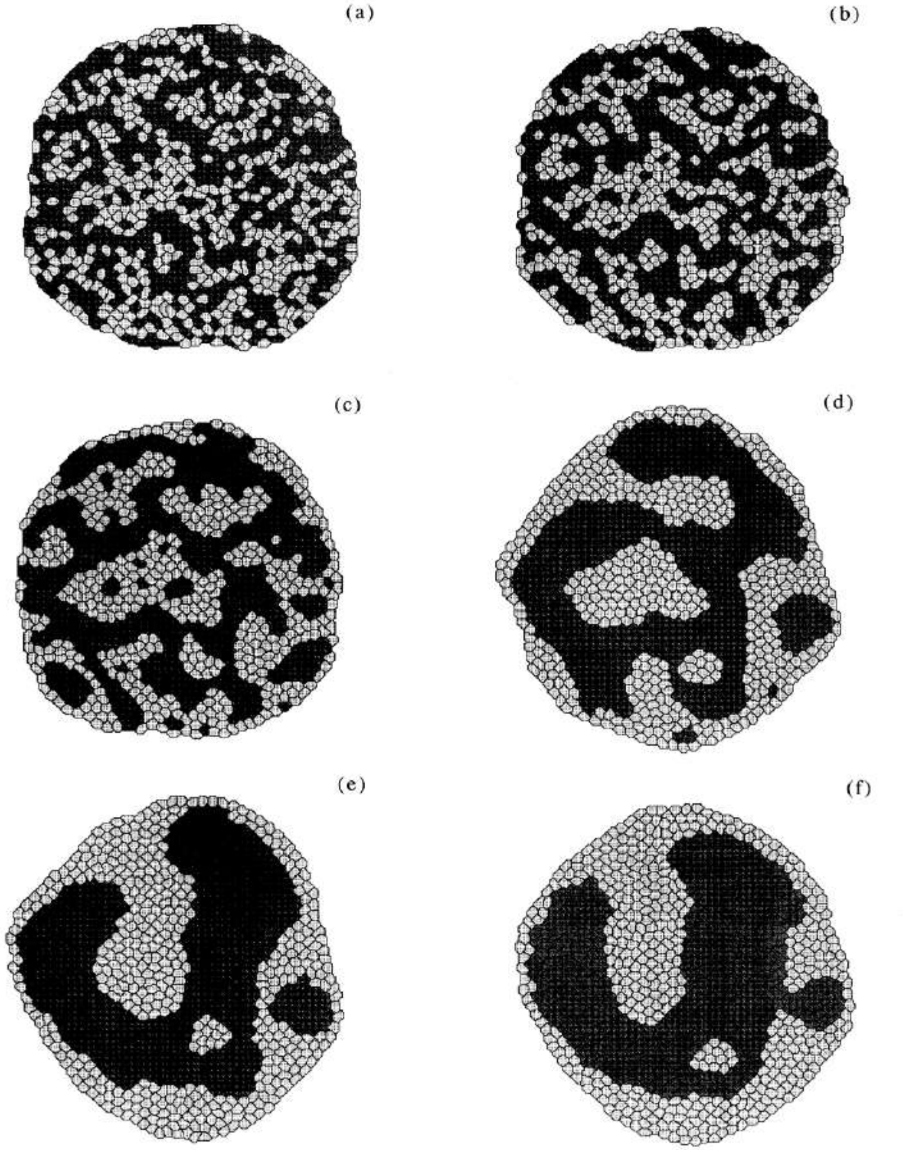
Typical 2D rectangular CPM lattice



(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 $e^{-\Delta H/T}$

Discrete Models: Cell Sorting



(Glazier93)

$$H_{Potts} = \sum_{\substack{(i,j)(k,l)\\ neighbors}} J(\tau(\sigma(i,j)),\tau(\sigma(k,l)))(1-\delta_{\sigma(i,j)\sigma(k,l)}) + \lambda\sum_{\sigma}\left(a(\sigma)-A_{\tau(\sigma)}\right)^2$$

Energy = surface energy + area elasticity

τ : type of cells

σ : cell ID

J : surface tension

- Cell sorting behavior depending on relations of distinct surface tensions
- Differential adhesion hypothesis (differential interfacial tension hypothesis)

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

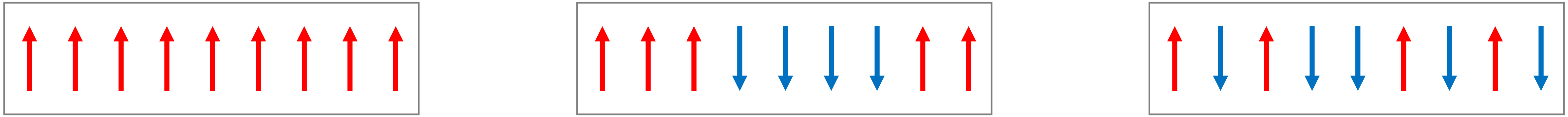
What is Ising model?

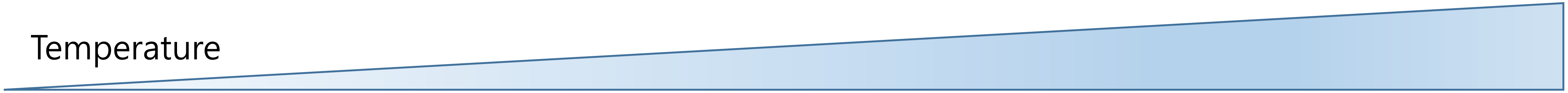
A: a mathematical model of ferromagnetism (a collection of atomic spins aligns in the same direction, yielding a net magnetic moment in macroscopic scale)

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

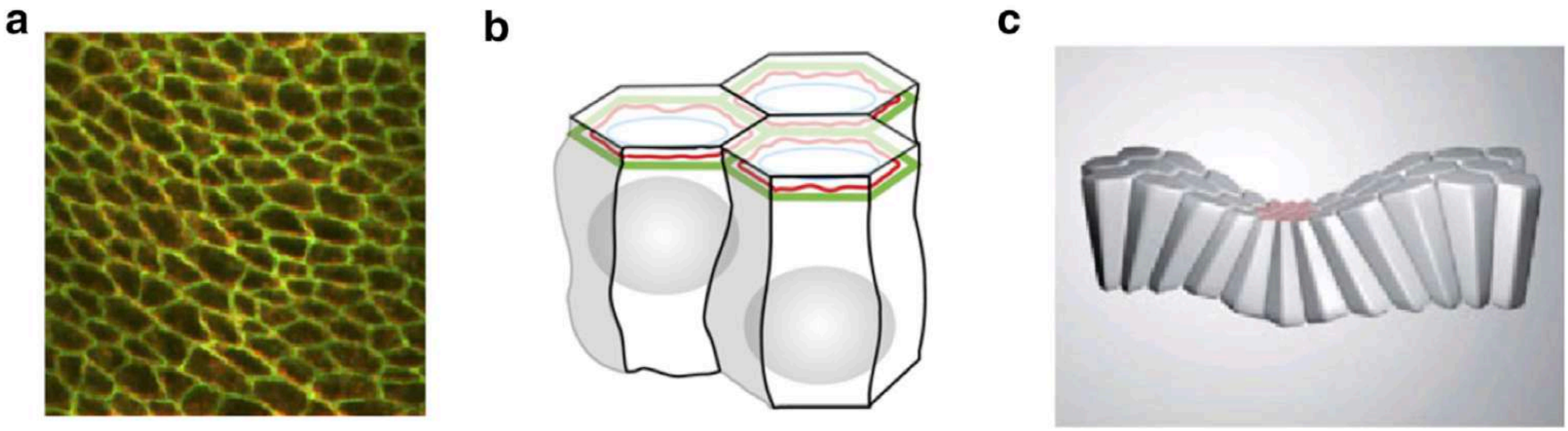
Interaction between neighboring sites

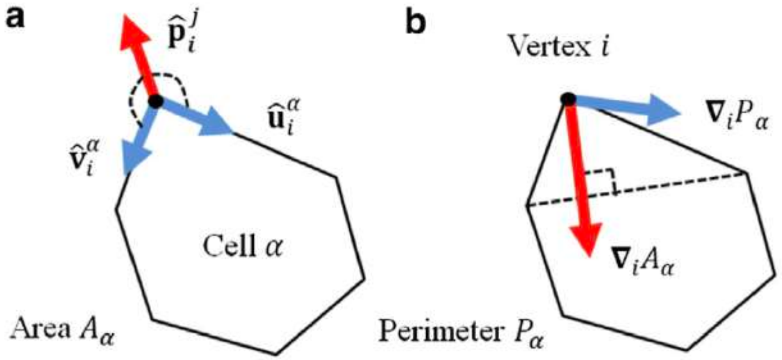
Energy contribution from external field





Discrete Models: 2D Vertex Model





(Fletcher14)

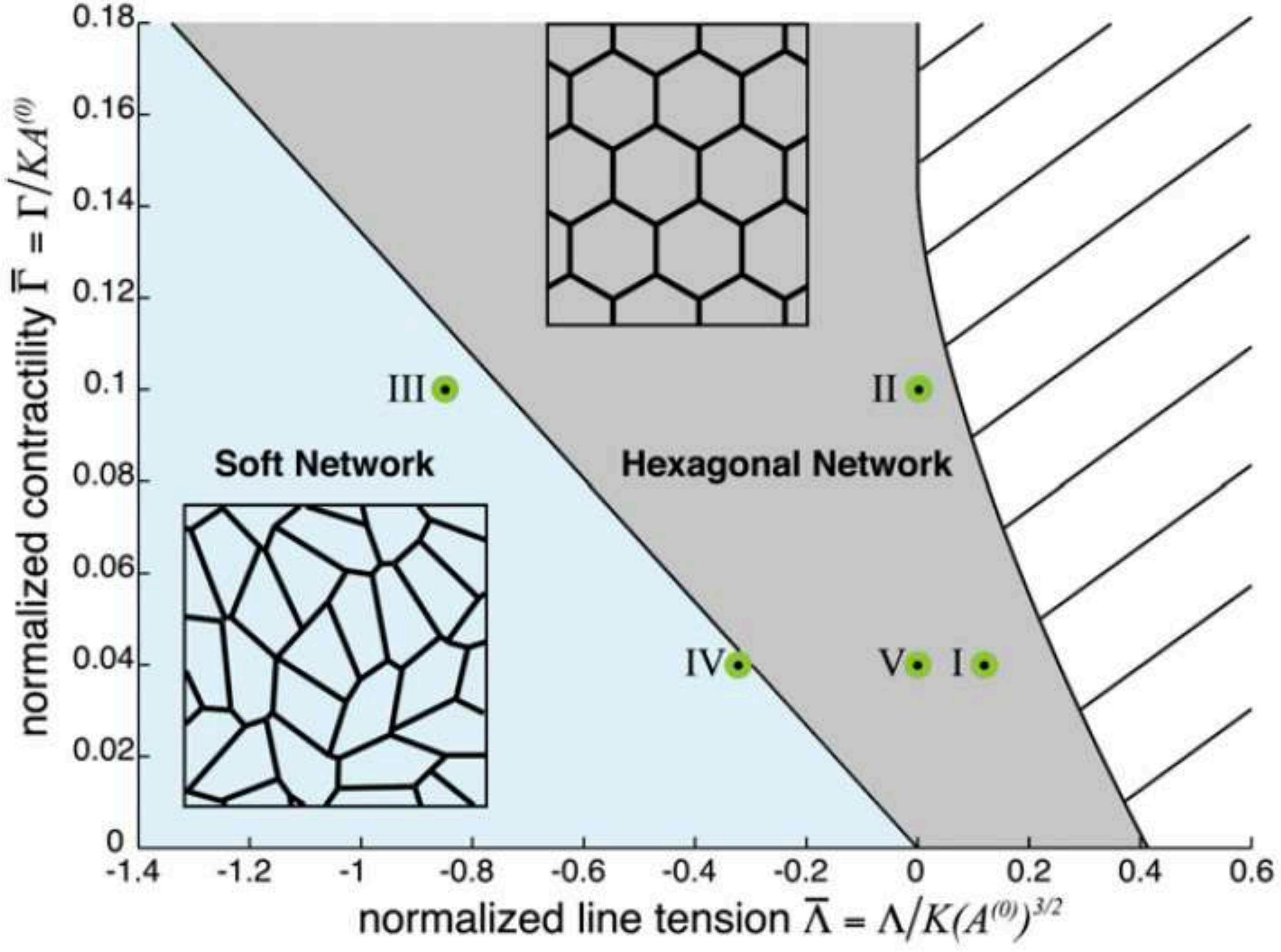
- Confluent epithelial layer can be simplified as 2D polygonal packings
- Cell shape is described by positions of vertices at the tricellular junctions
- The dynamics is governed by an energy functional

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

Area elasticity | Perimeter elasticity

Discrete Models: Ground States

Phase diagram of ground states

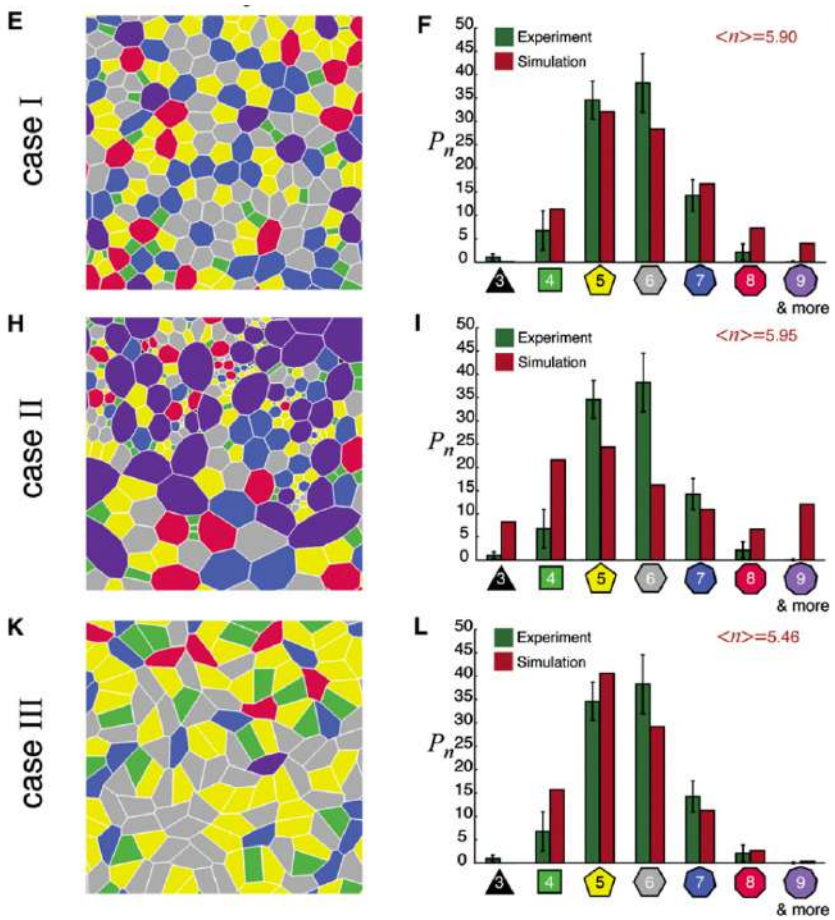


(Farhadifar07)

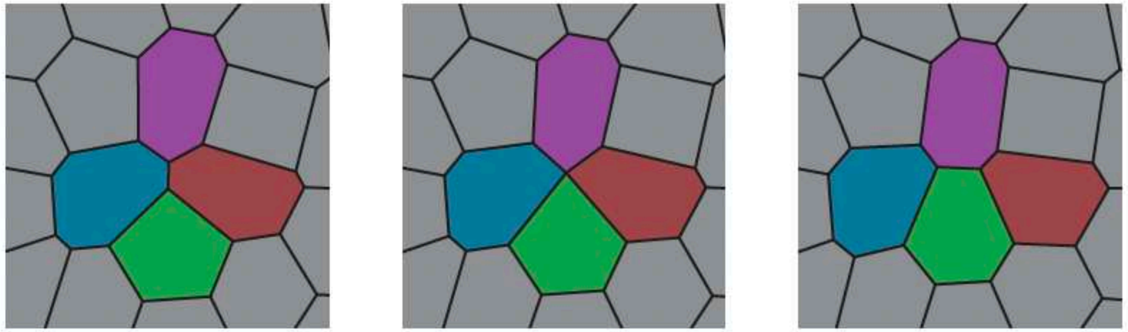
$$E = \sum_i \frac{K_A}{2}(A_i - A_{i,0})^2 + \frac{\Gamma_\alpha}{2} P_i^{\,2} + \sum_{<ij>} \Lambda L_{ij}$$

Area elasticity | Perimeter contractility | Line tension

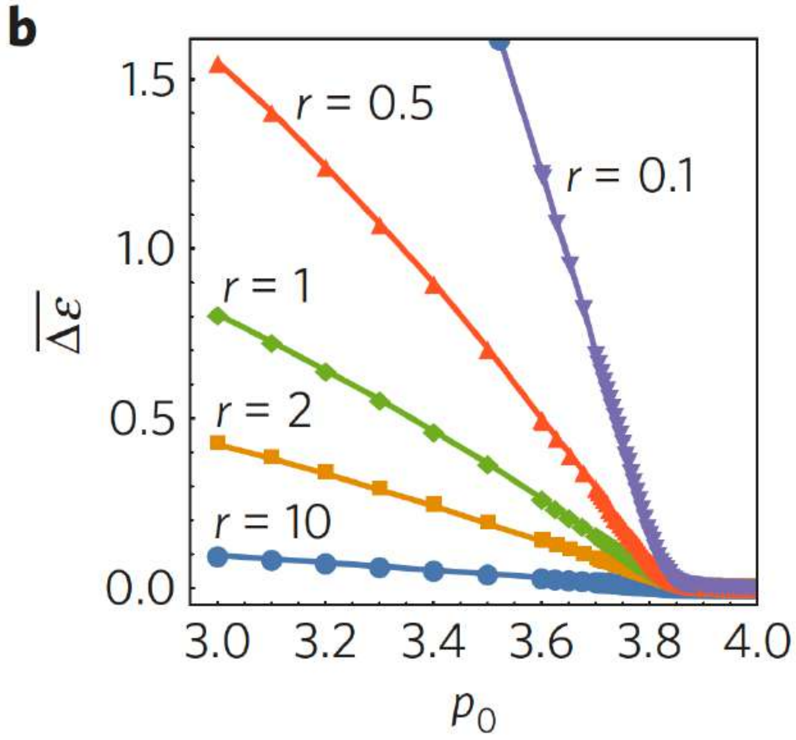
Different tissue structures can be realized depending on cellular parameters



Discrete Models: Density-Independent Transition



Energy barrier for cell rearrangement vanishes



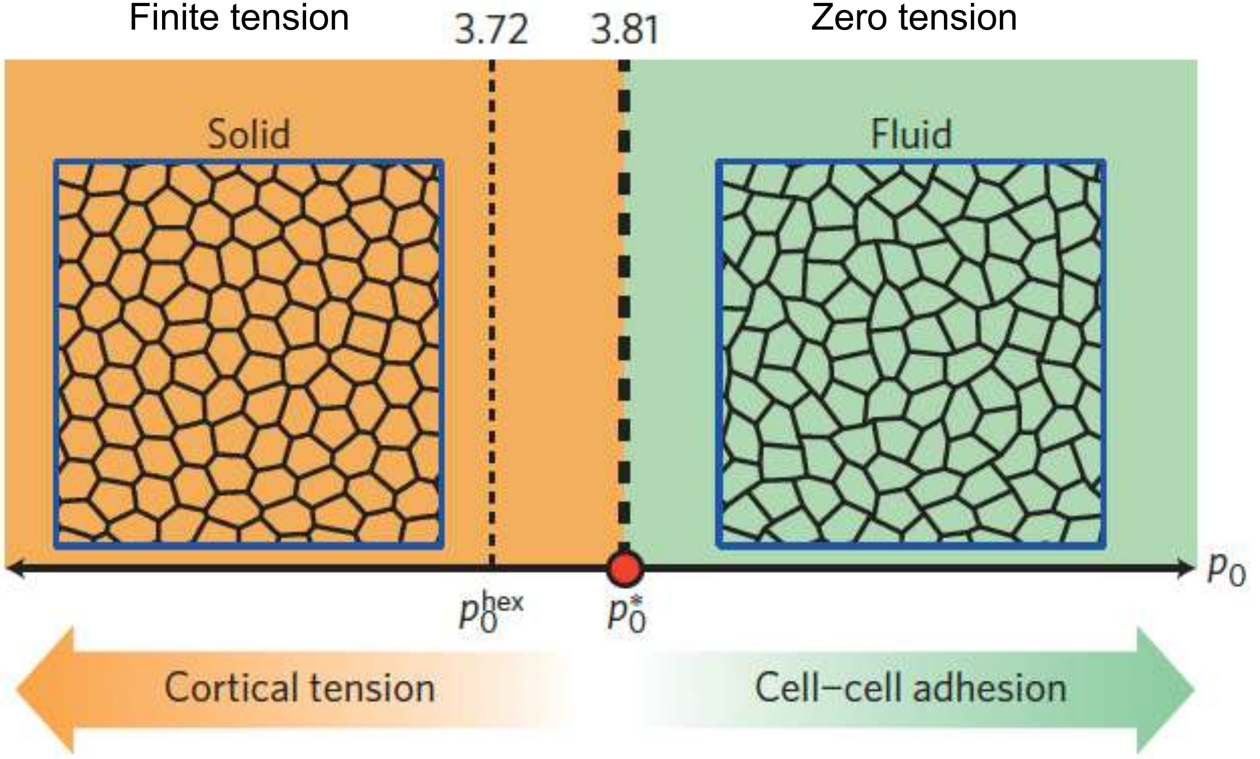
$$\varepsilon = \sum_i (a_i - 1)^2 + \frac{(p_i - p_0)^2}{r}$$

Area elasticity

Perimeter elasticity

Isotropic cell shape
Finite tension

Anisotropic cell shape
Zero tension



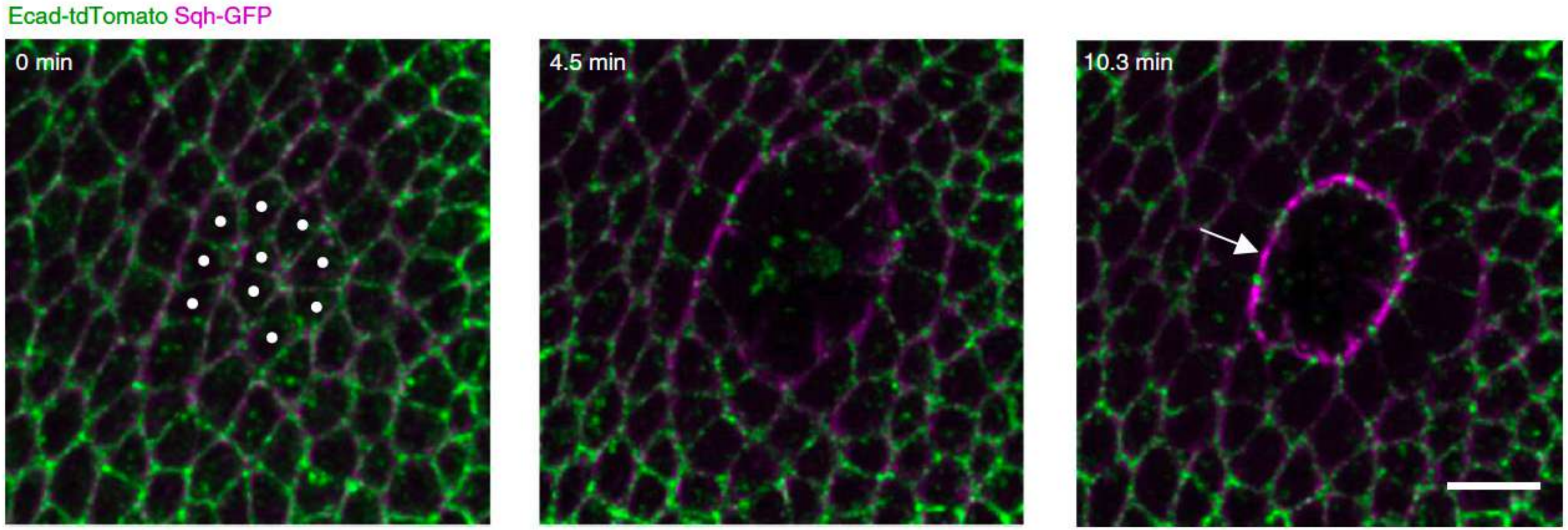
Effective tension: $\Gamma_{ij} = \frac{2}{r}[(p_i - p_0) + (p_j - p_0)]$

(Bi15)

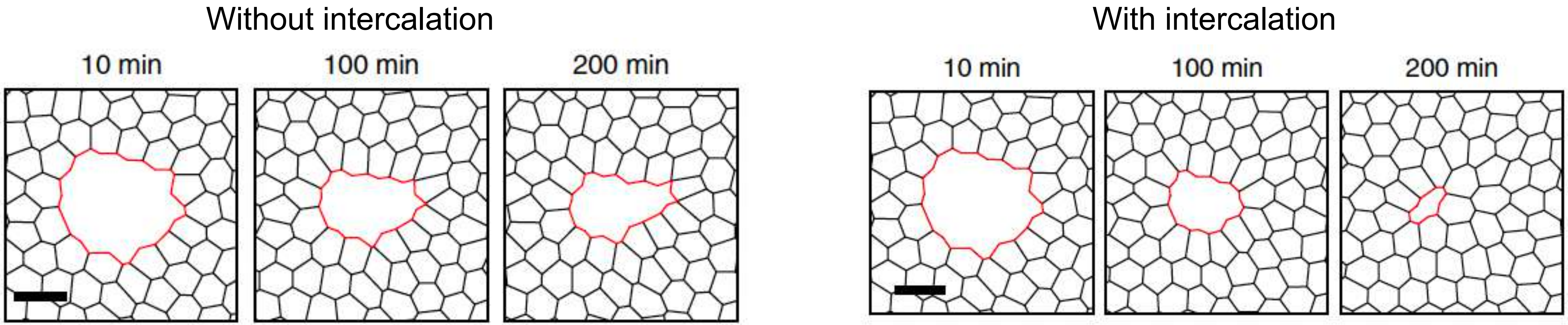
Discrete Models: Wound healing

Laser ablation of epithelial layer in Drosophila wing imaginal disc

Accumulation of myosin to form pulse ring at the wound boundary



(Tetley19)



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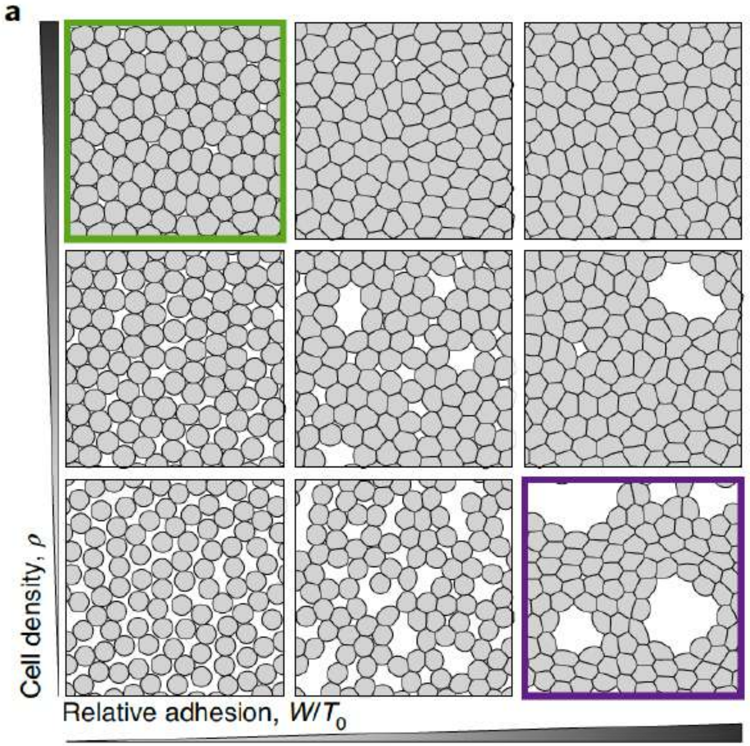
Discrete Models: Active Foam Model

Vertex dynamics: $$\eta_R \frac{d\vec{R}_\alpha}{dt} = \sum_{i,j \in F(\alpha)} \vec{T}_{ij} H(T_{ij}) + \vec{N}_{ij}$$

Viscous friction   Tangential force   Normal force

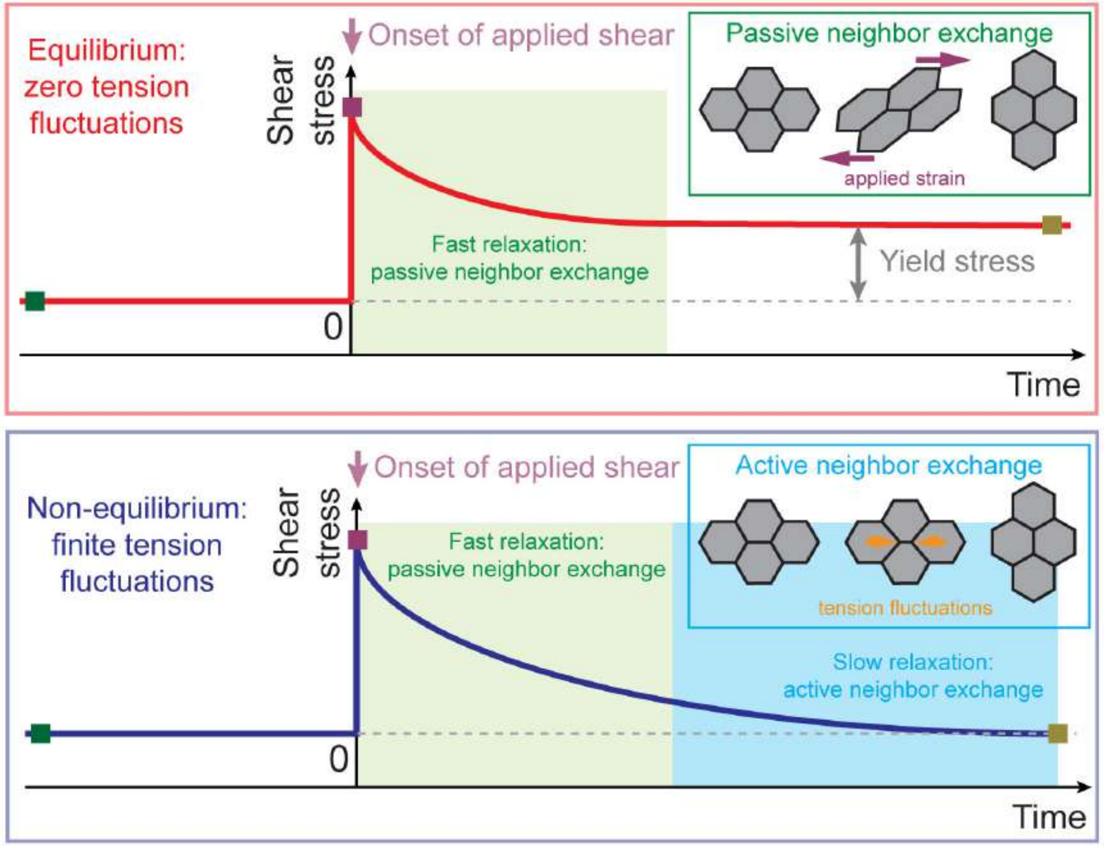
The model includes spaces between cells, complex cell shape and junctional tension dynamics

Structural transition from non-confluent state to confluent states



(Kim21)

Active fluctuation governs longtime stress relaxation and tissue fluidization



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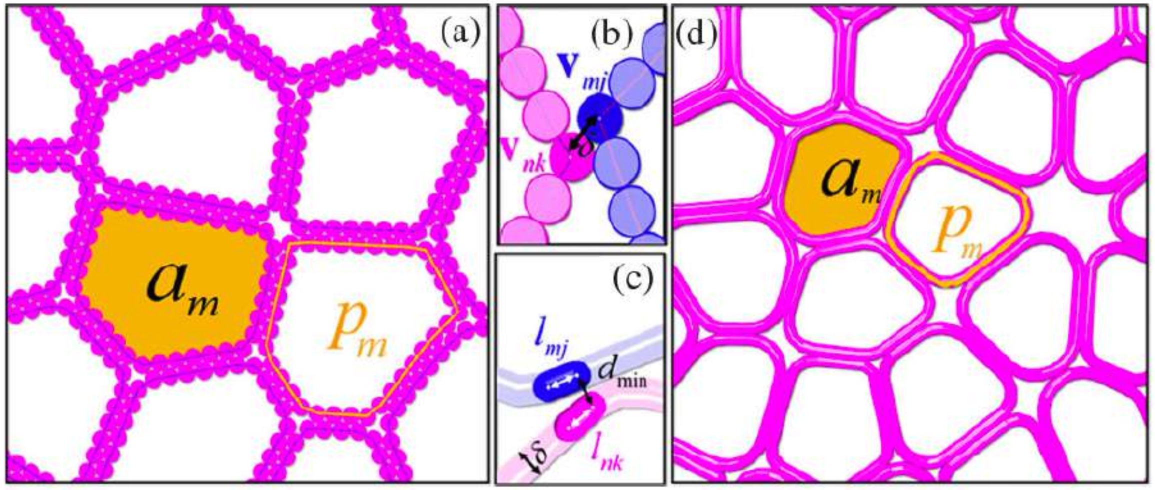
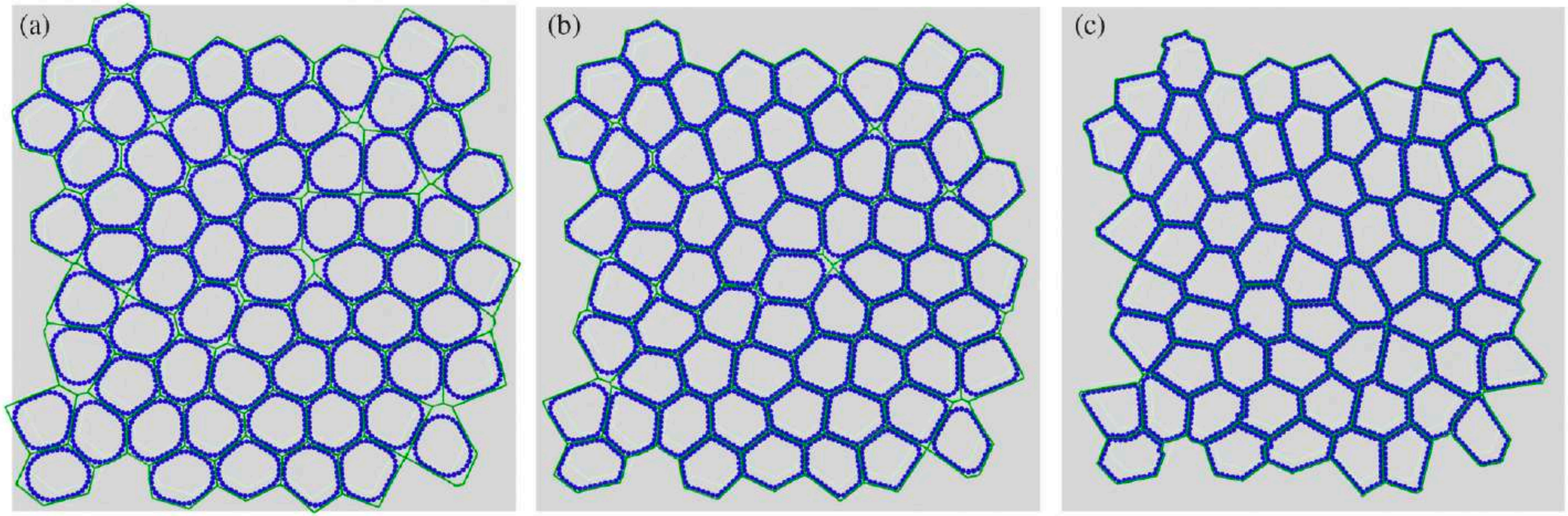
Discrete Models: Deformable Particle Model

Rough surface method | Smooth surface method

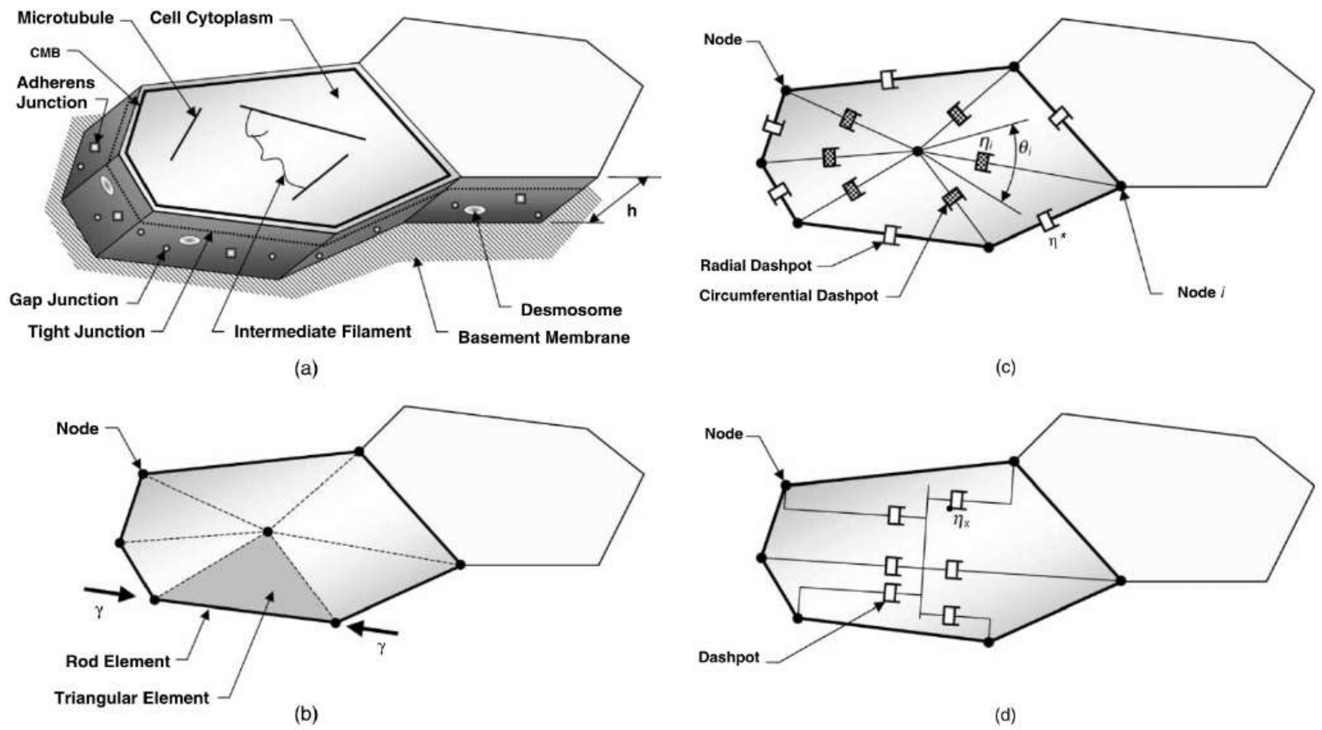


(Boromand18)

- 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

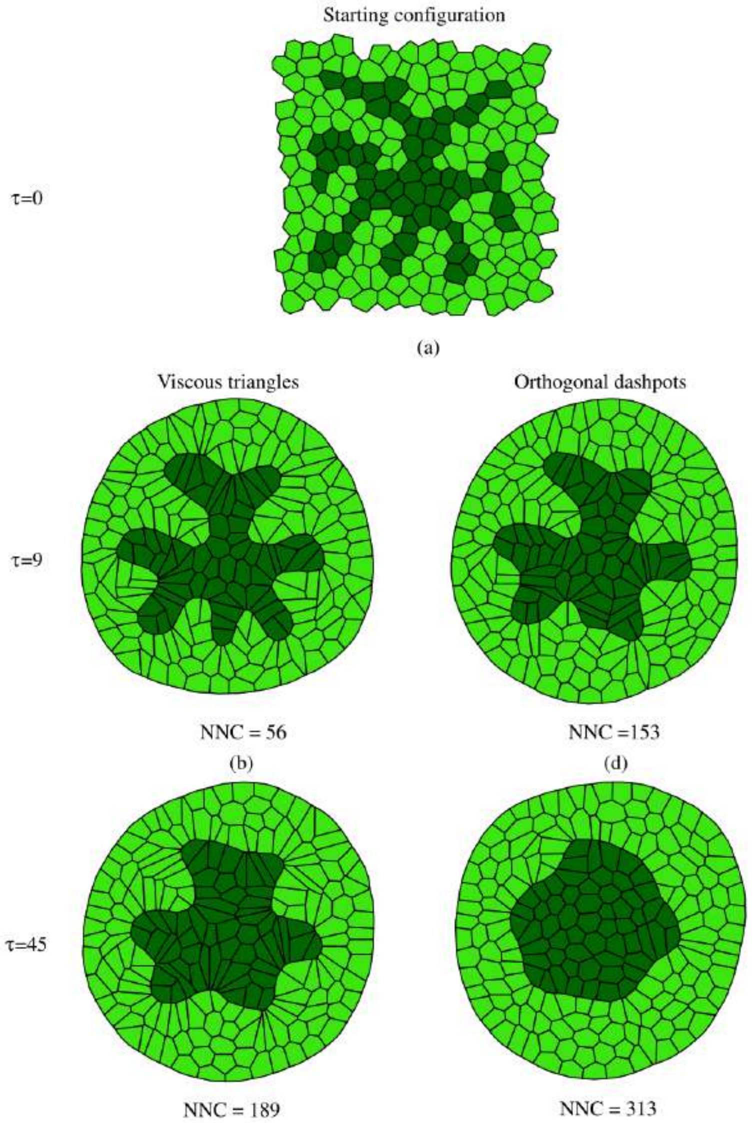


Discrete Models: FEM Vertex Model



(Brodland07)

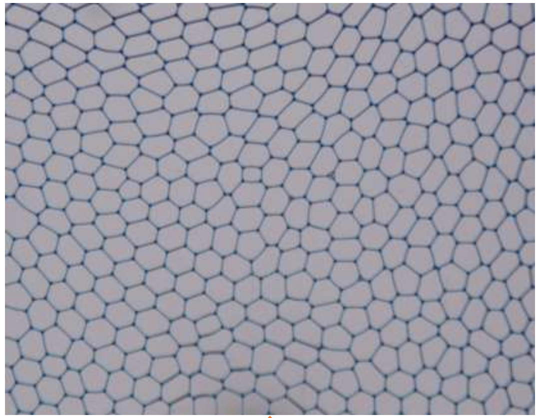
Cell sorting behavior



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

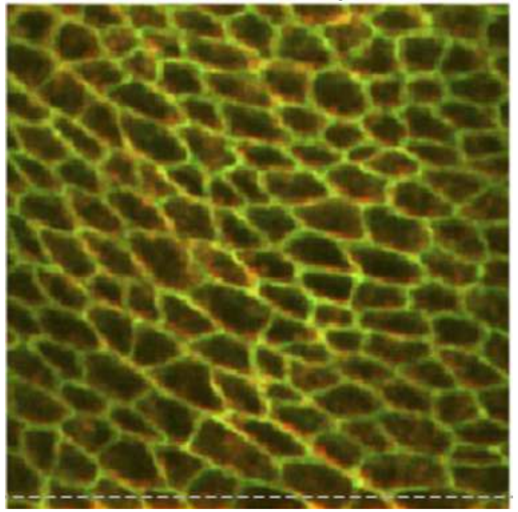
From Where: Vertex Model

Liquid foam



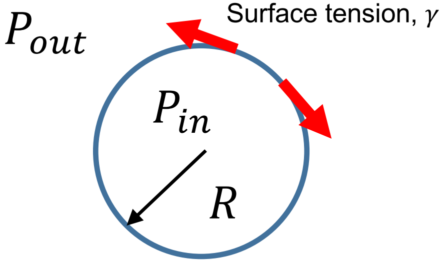
(Hilgenfeldt group)

Epithelial layer



(Fletcher et al. 2014)

Governing mechanics:

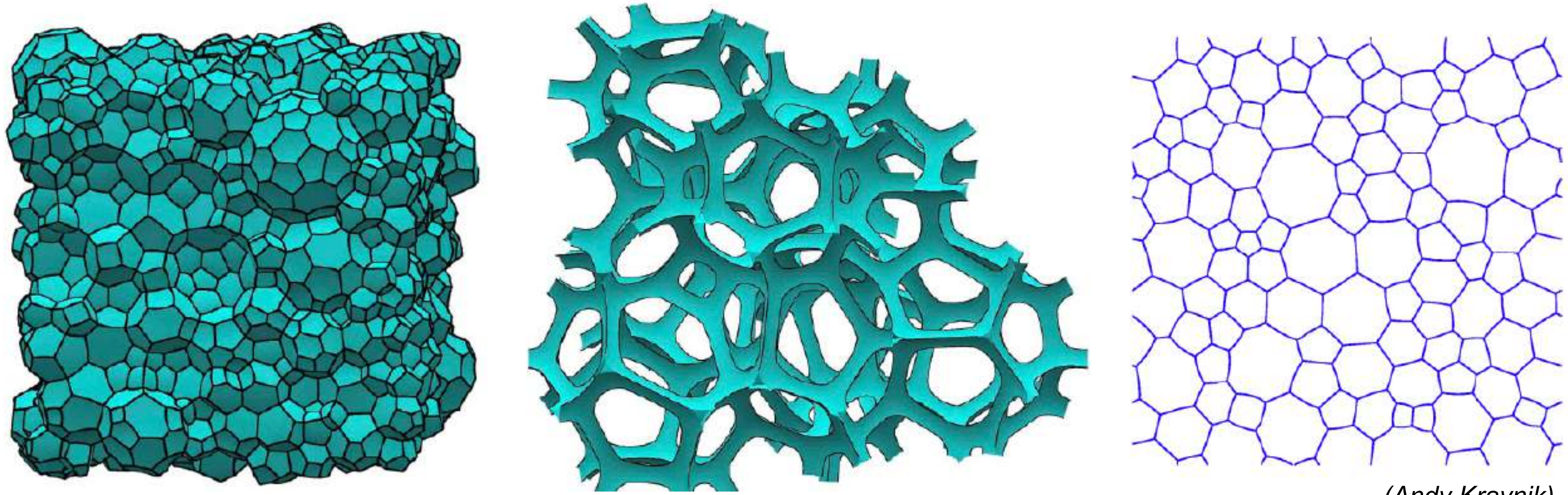


$$P_{in} - P_{out} = \frac{\gamma}{R}$$

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

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

Dry foam simulations



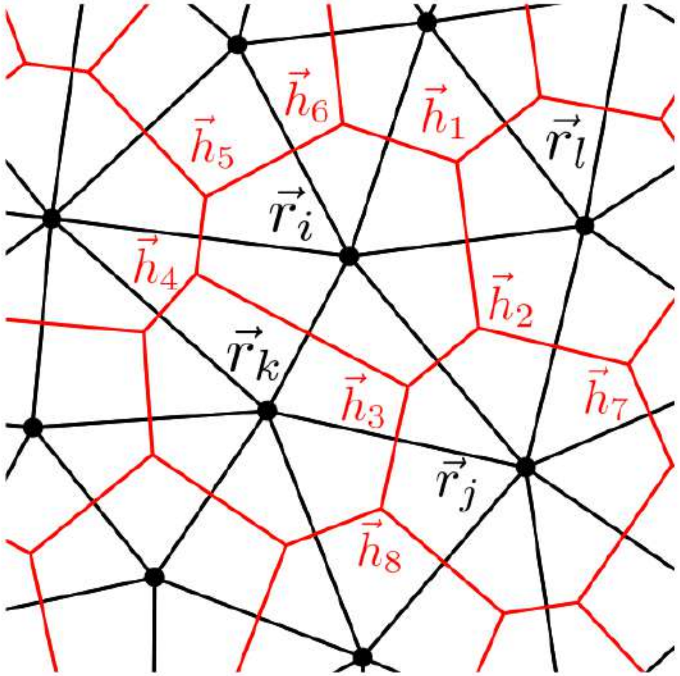
(Andy Kraynik)

Simulation software: Surface Evolver

EPFL

Discrete Models: Voronoi Model

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

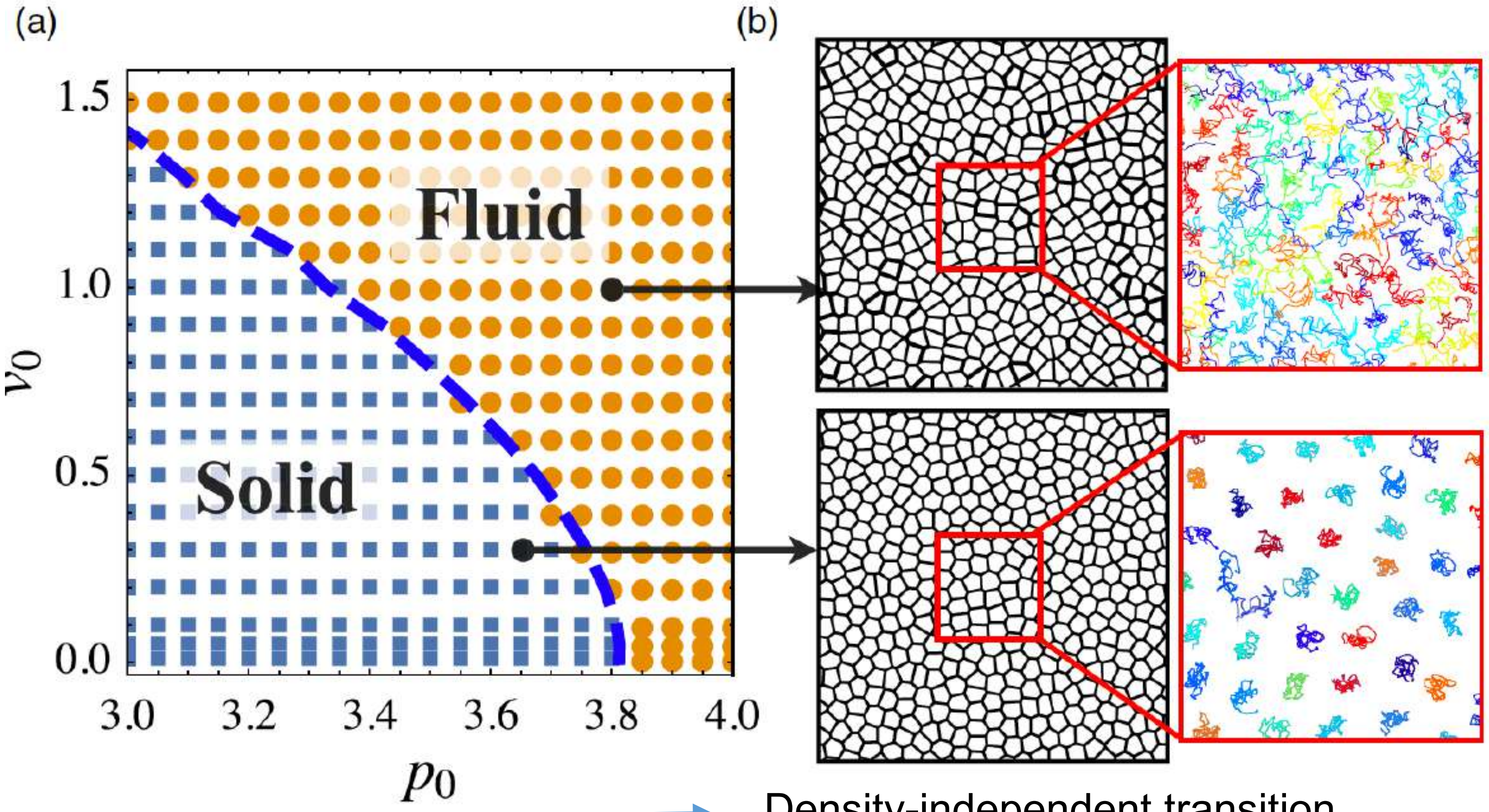


(Bi16)

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



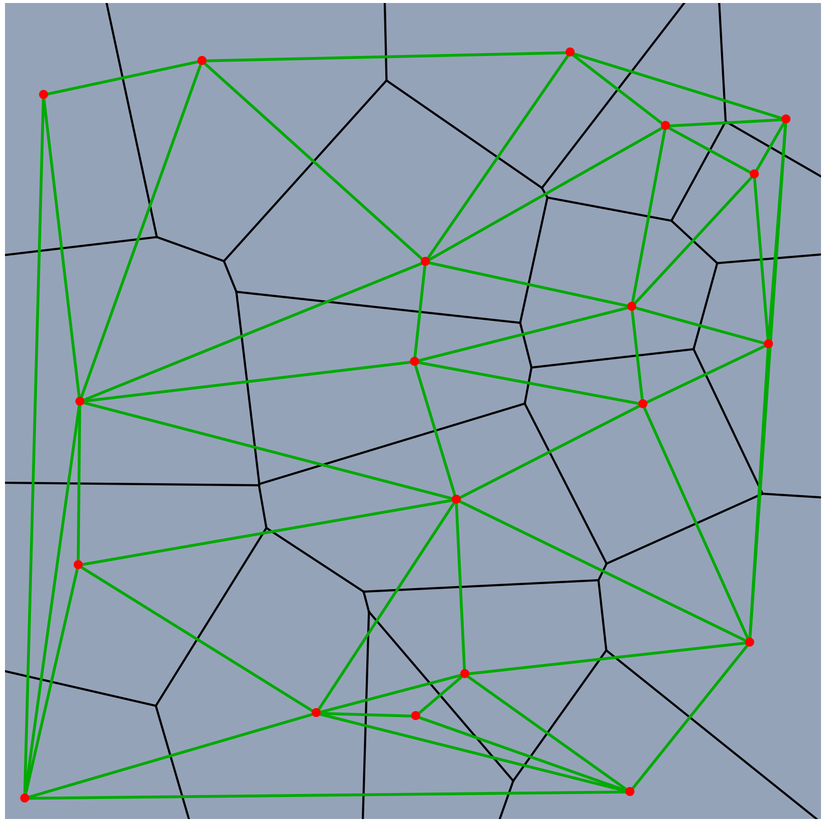
Density-independent transition

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

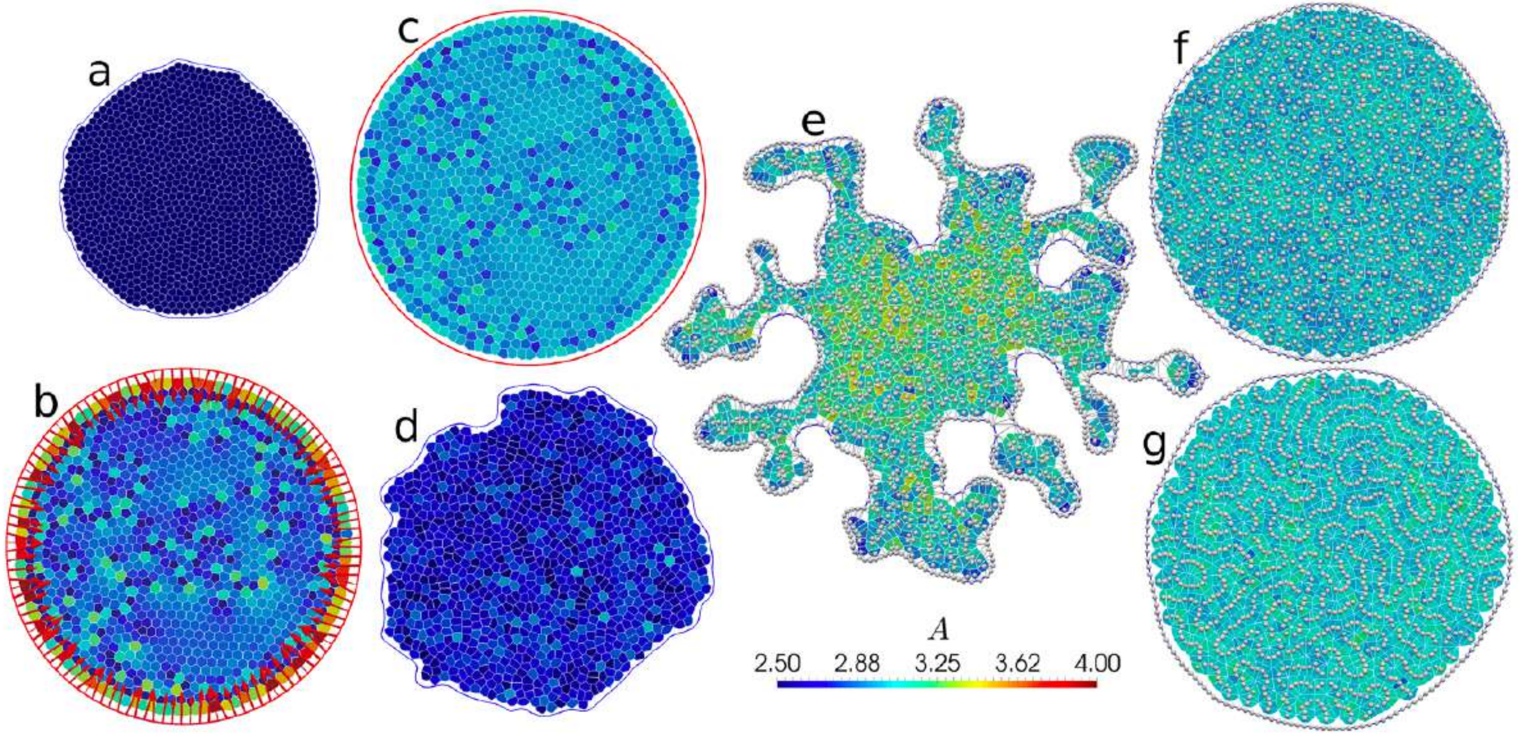
$$E = \sum_i K_A(A_i - A_{i,0})^2 + K_P(P_i - P_{i,0})^2$$

Discrete Models: Active Vertex Model

- Generalized version of Voronoi model: Use Delaunay triangulation for computational efficiency
- Voronoi tessellation and Delaunay triangulation is dual graph



Examples of Voronoi tessellation and Delaunay triangulation

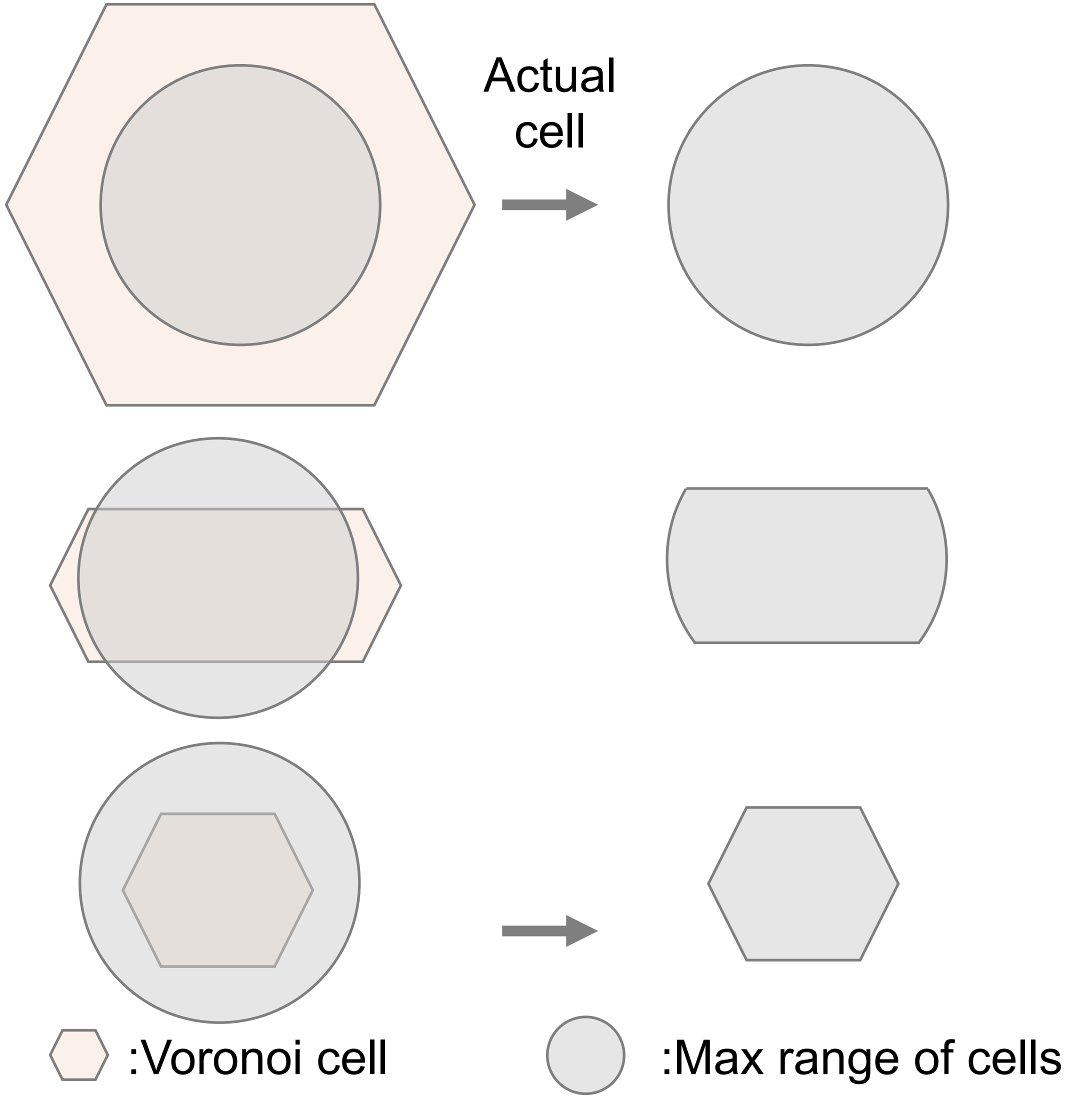


(Barton17)

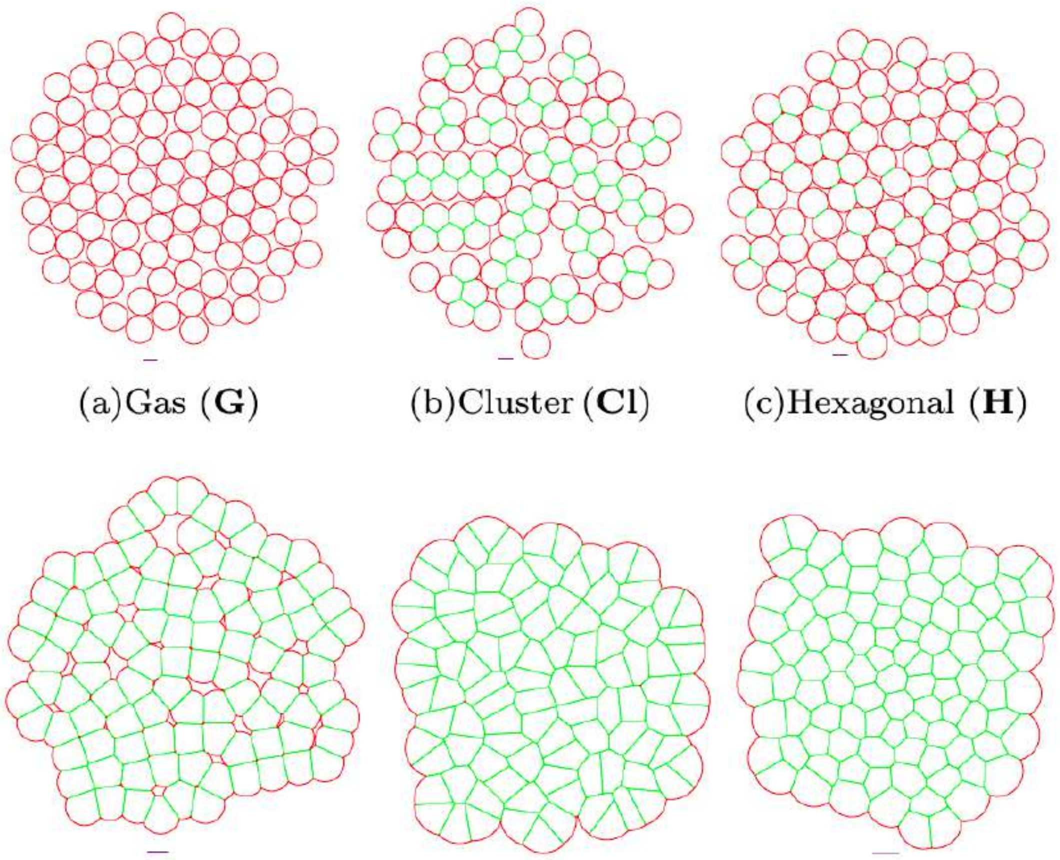
- Add cell division, cell alignment, etc.

Discrete Models: Voronoi Model

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



Distinct classes of tissue structures



(a)Gas (**G**) (b)Cluster (**Cl**) (c)Hexagonal (**H**)

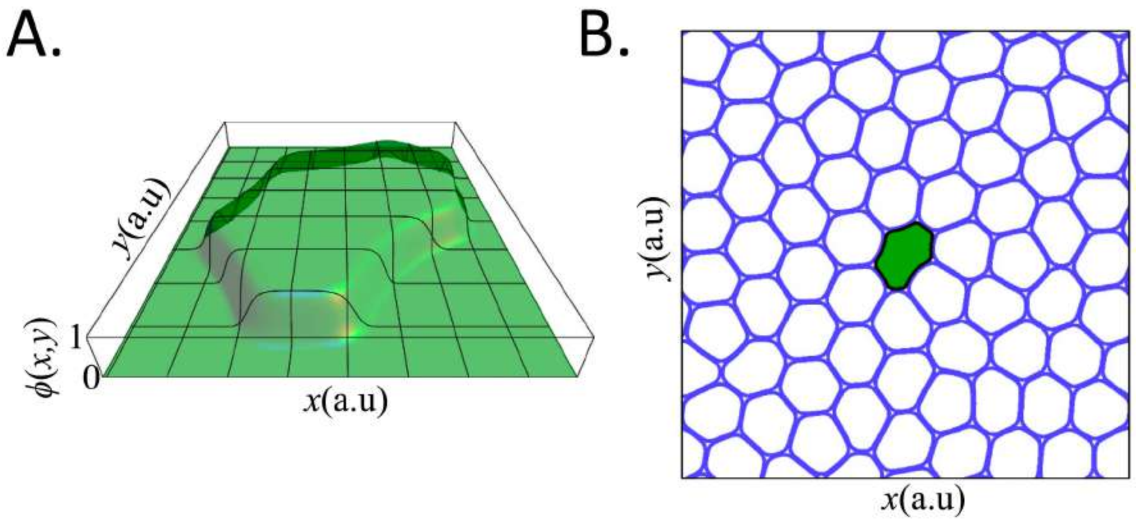
(d)Non-Confluent (**NC**) (e)Minimal (**M**) (f)Confluent (**Co**)

(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

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

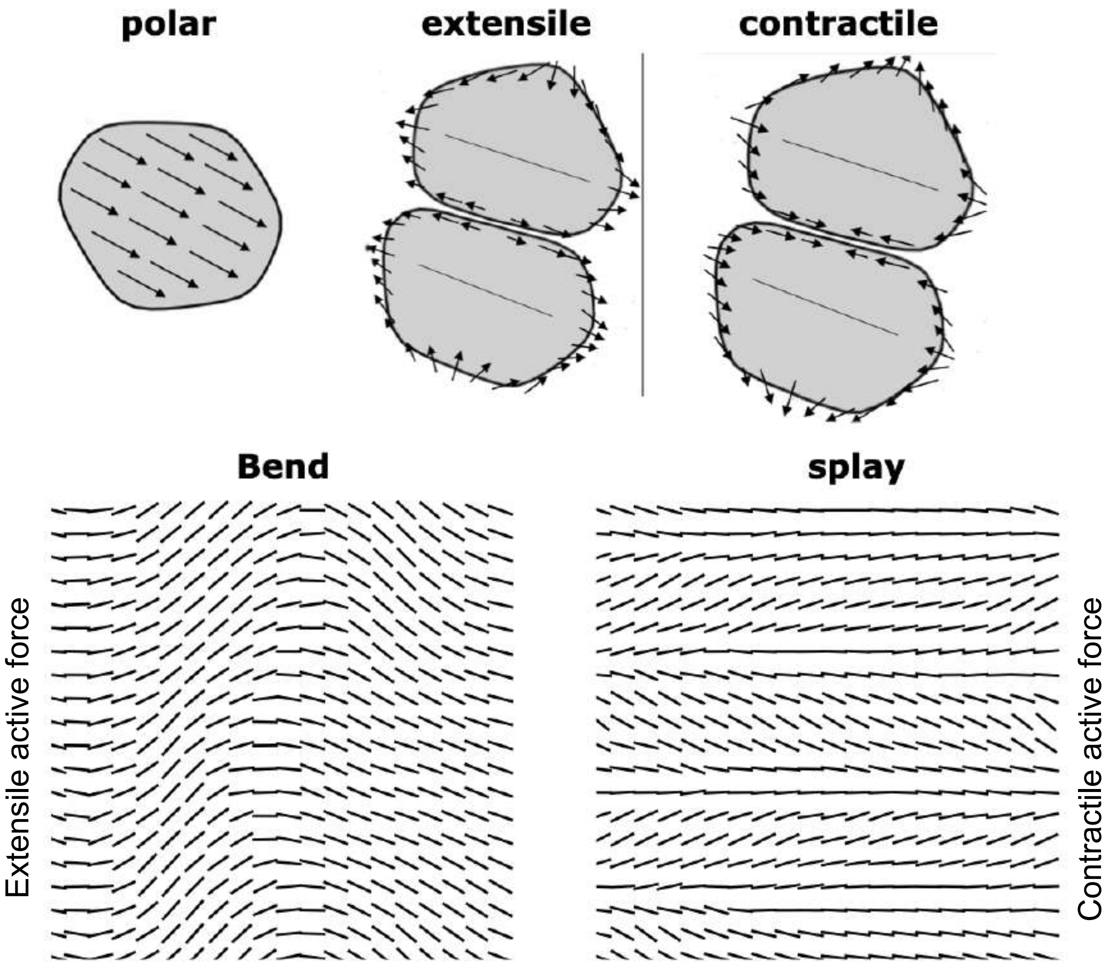
Cell elasticity; Sharp boundary; Area constraints

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

Steric repulsion between cells

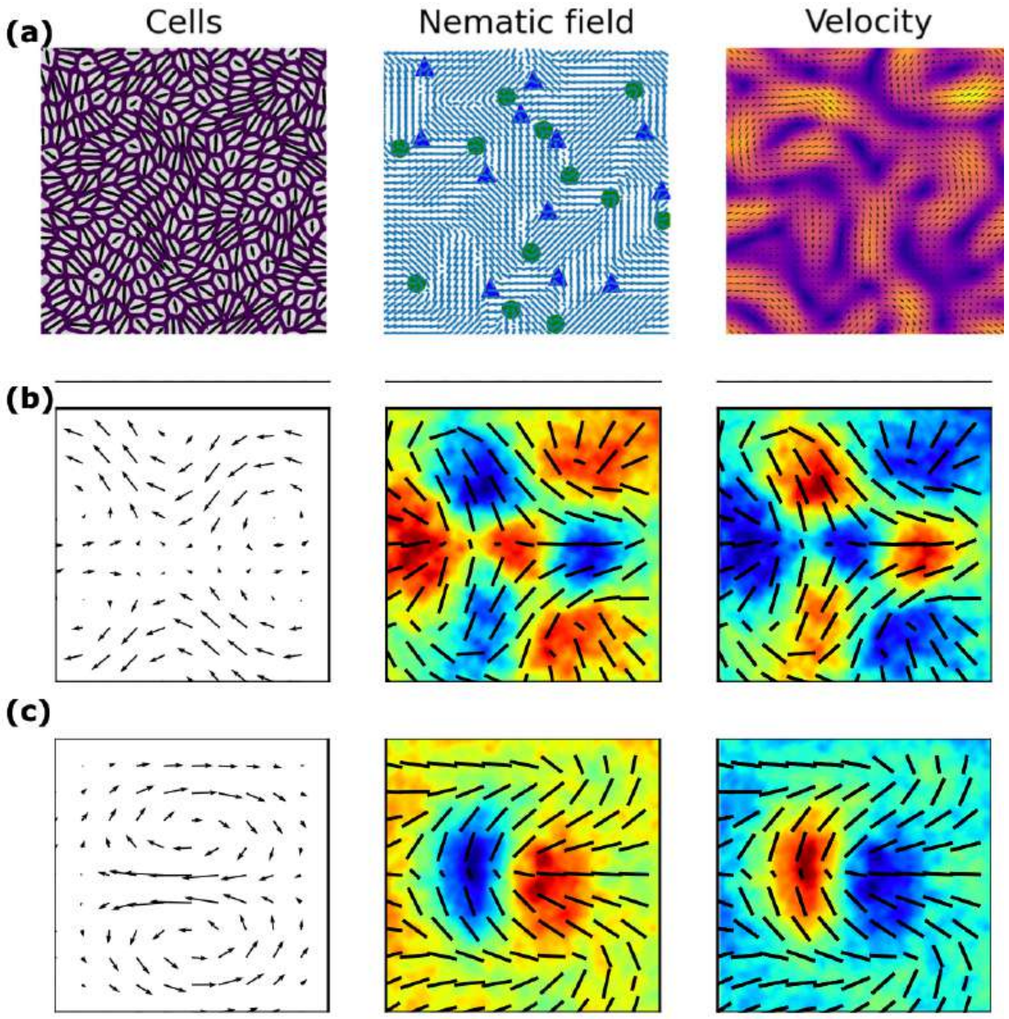
Discrete Models: Phase Field Model

Active force and instabilities in cell monolayer



(Mueller21)

Emergence of active turbulence and nematic field

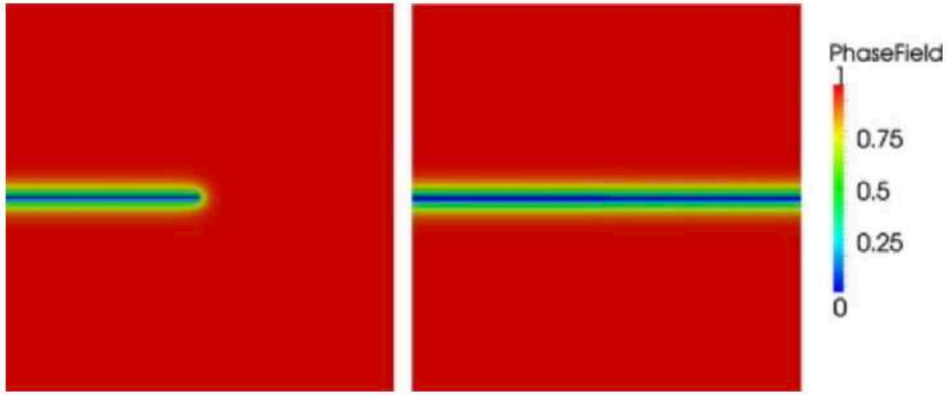


(Mueller21)

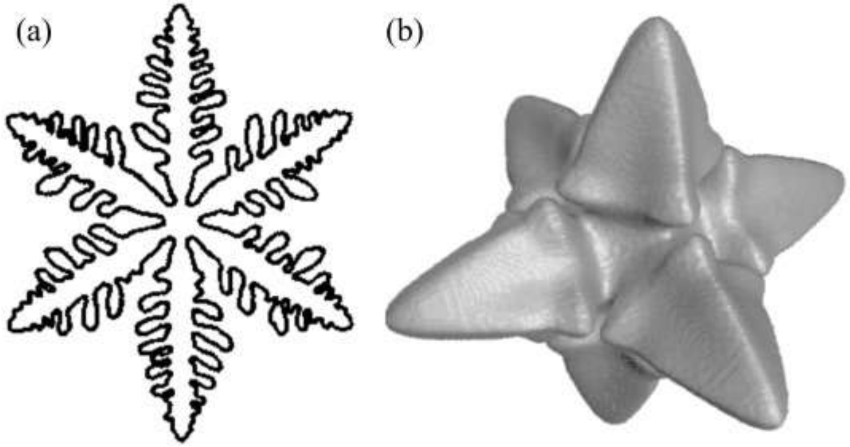
From Where: Phase Field Model

An efficient method for problems on materials modeling

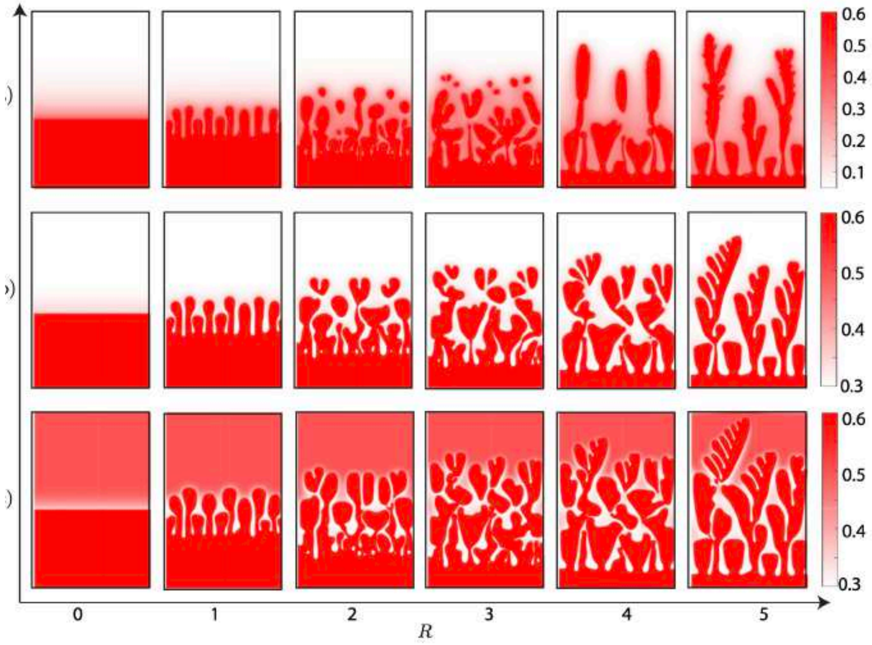
fracture



Solidification: dendritic growth

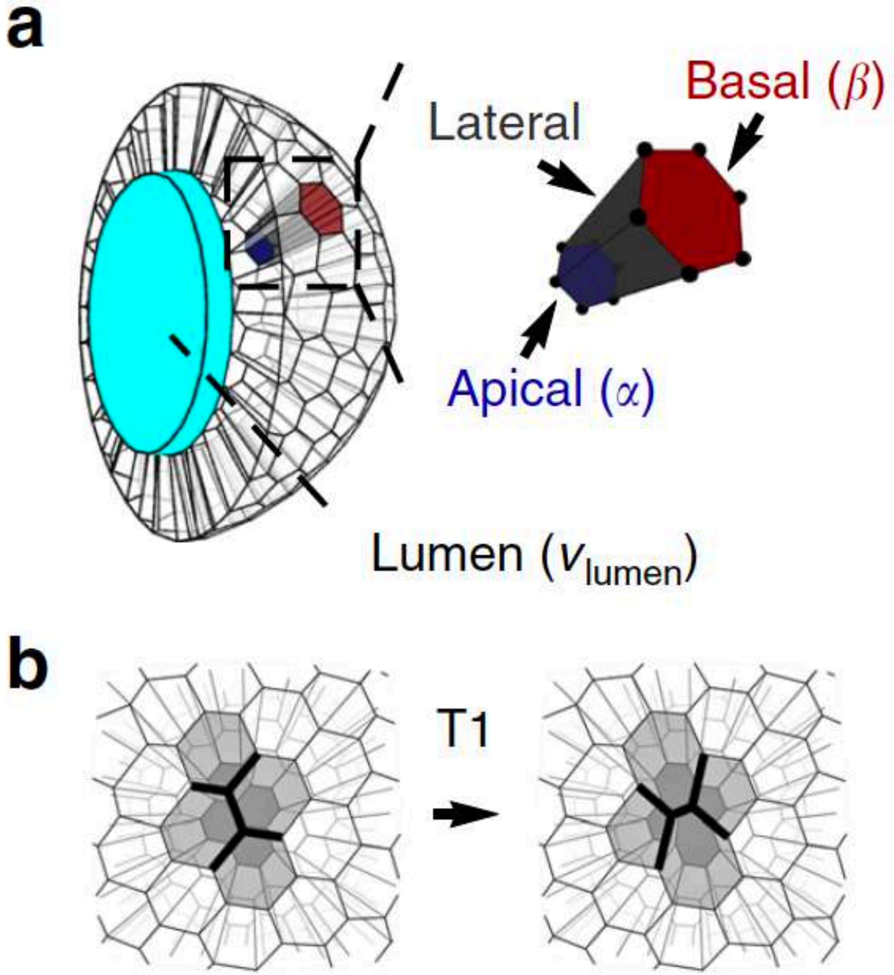


Viscous fingering



Discrete Models: 2.5D models

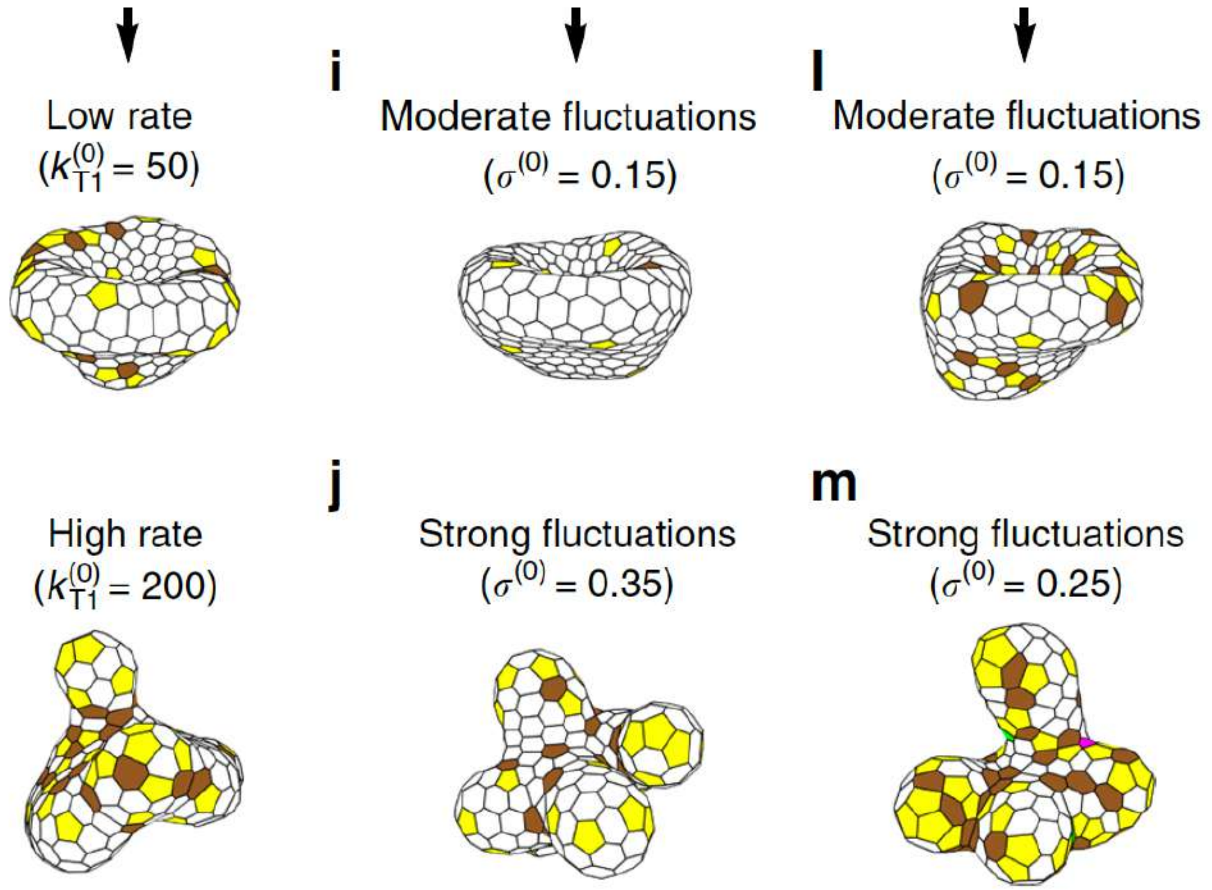
3D model for epithelial monolayer: apical and basal polarity



(Rozman20)

$$w = \sum_i \left[\alpha a_a^{(i)} + \beta a_b^{(i)} + \frac{1}{2} a_l^{(i)} \right]$$

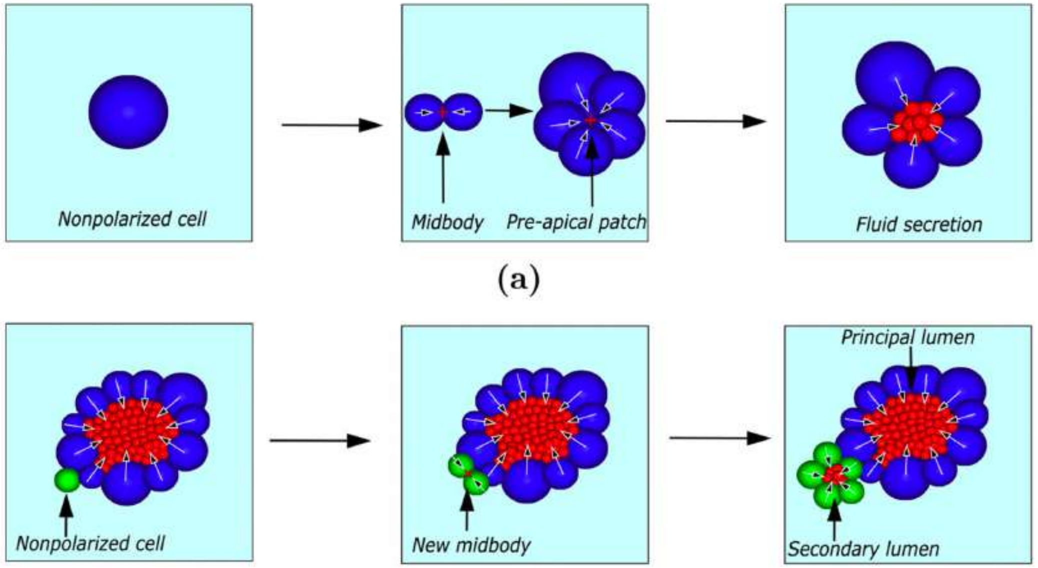
Apical tension Basal tension Lateral tension



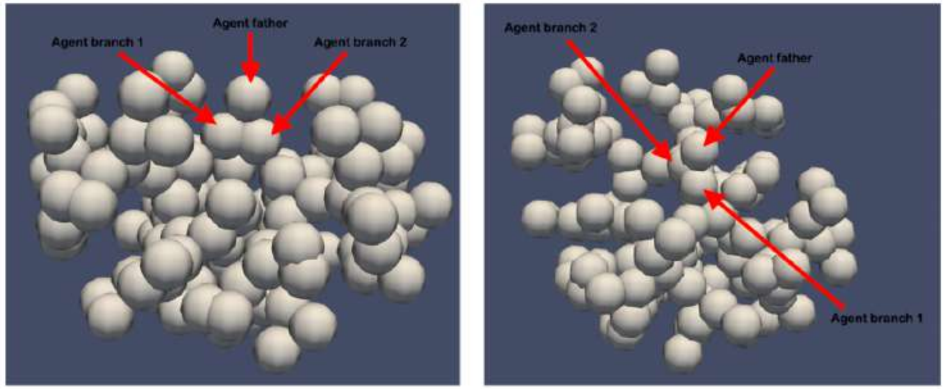
Different cellular properties lead to distinct budding morphology

Discrete Models: 3D models

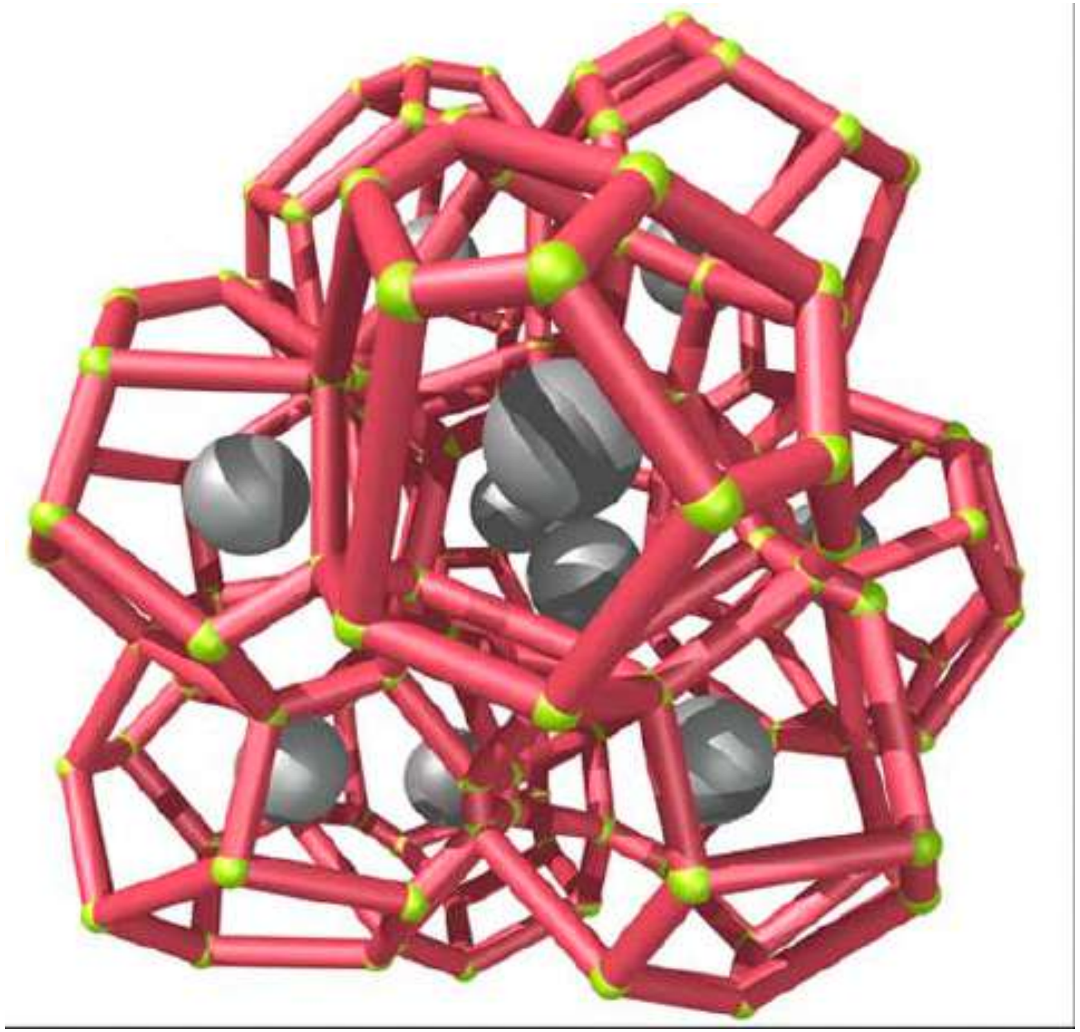
Lumen morphogenesis



Lung fibrosis

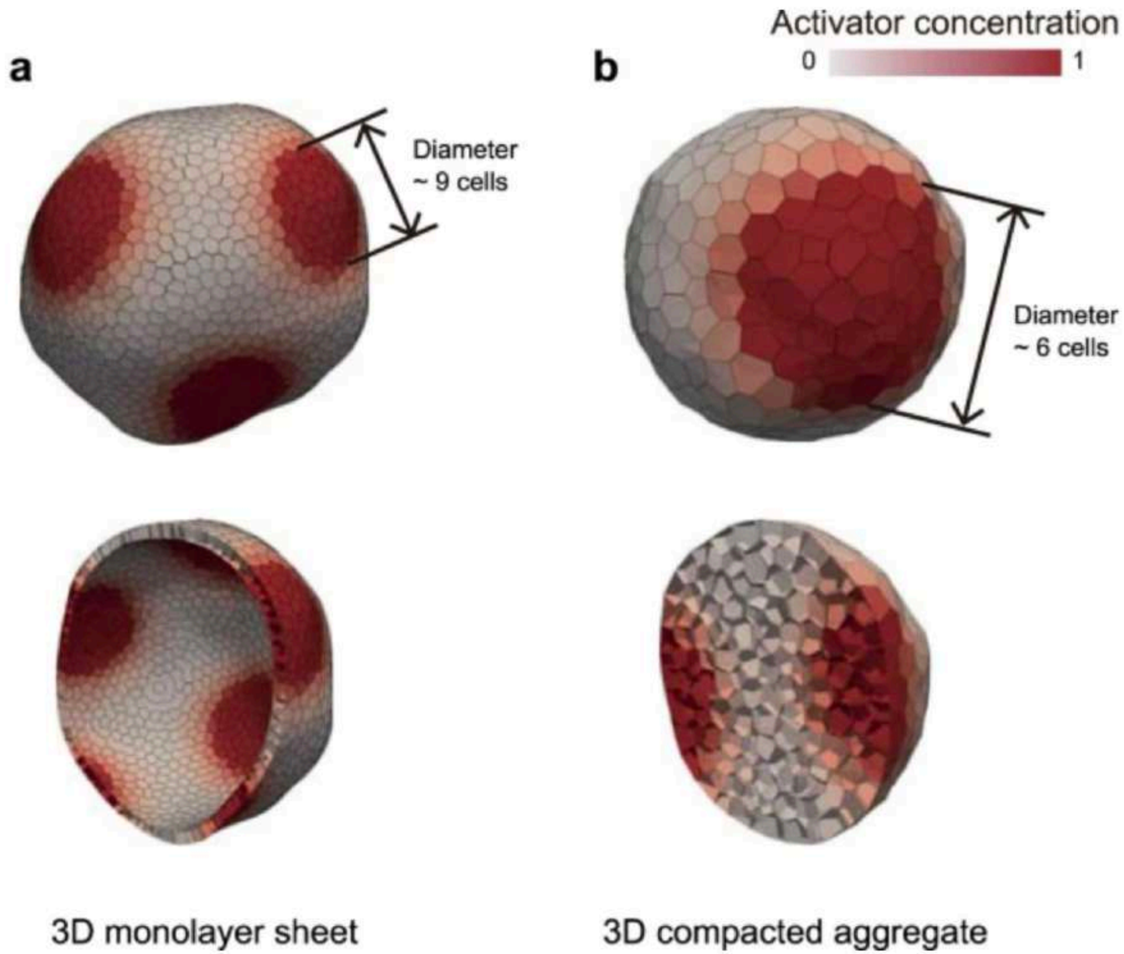


Self Propelled Voronoi Model



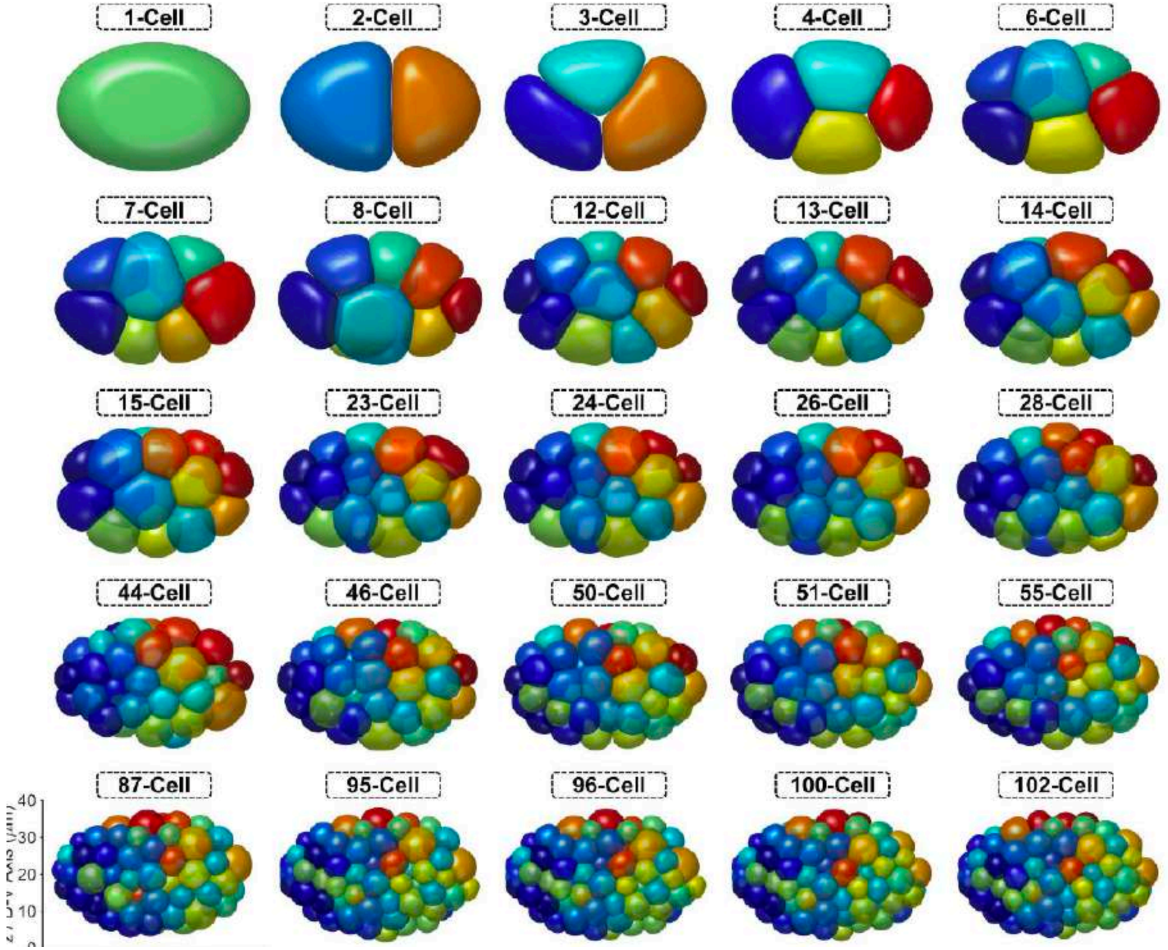
Discrete Models: 3D models

Vertex model



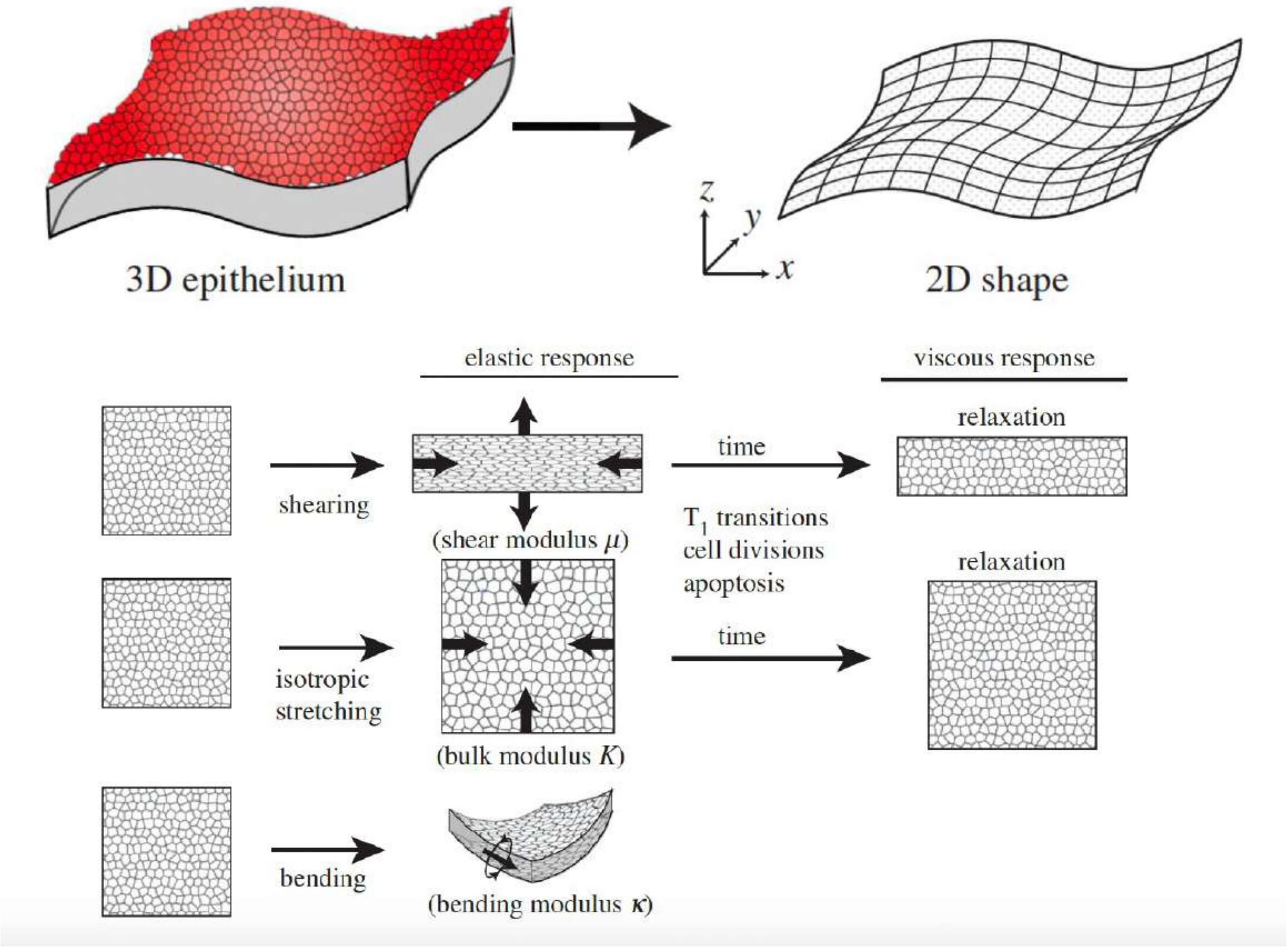
(Okuda18)

Phase field model



(Kuang22)

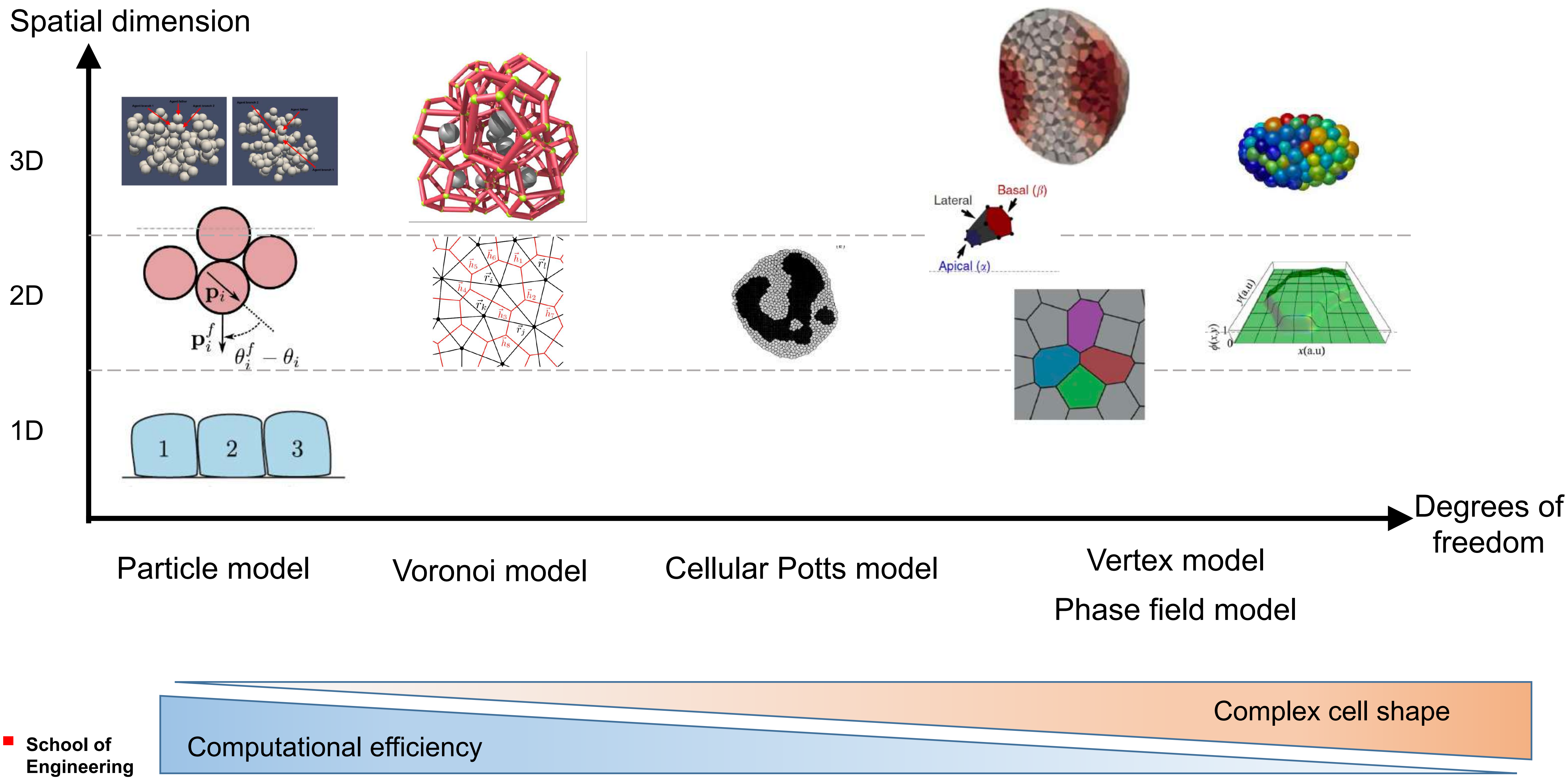
Discrete to Continuum



How one can derive constitutive equation from discrete simulations?

Viscoelastic?
Viscoplastic?
Hyperelastic?

Conclusion


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

EPFL

Reference

- Mongera18: A fluid-to-solid jamming transition underlies vertebrate body axis elongation
- Classen05: Hexagonal Packing of Drosophila Wing Epithelial Cells by the Planar Cell Polarity Pathway
- Miklius12: Analytical Results for Size-Topology Correlations in 2D Disk and Cellular Packings
- Gibson06: The emergence of geometric order in proliferating metazoan epithelia
- George17: Connecting individual to collective cell migration
- Smeets16: Emergent structures and dynamics of cell colonies by contact inhibition of locomotion
- Henkes11: Active jamming: Self-propelled soft particles at high density
- Scianna12: Multiscale developments of the Cellular Potts Model
- Glazier93: Simulation of the differential adhesion driven rearrangement of biological cells
- Fletcher14: Vertex Models of Epithelial Morphogenesis
- Farhadifar07: The Influence of Cell Mechanics, Cell-Cell Interactions, and Proliferation on Epithelial Packing
- Bi15: A density-independent rigidity transition in biological tissues
- Tetley19: Tissue fluidity promotes epithelial wound healing
- Kim21: Embryonic tissues as active foams
- Boromand18: Jamming of Deformable Polygons
- Brodland07:A new cell-based FE model for the mechanics of embryonic epithelia
- Bi16: Motility-Driven Glass and Jamming Transitions in Biological Tissues
- Barton17: Active Vertex Model for cell-resolution description of epithelial tissue mechanics
- Teomy18: Confluent and nonconfluent phases in a model of cell tissue
- Palmieri15: Multiple scale model for cell migration in monolayers: Elastic mismatch between cells enhances motility
- Mueller21: Phase field models of active matter
- Rozman20: Collective cell mechanics of epithelial shells with organoid-like morphologies
- Merkel17: A geometrically controlled rigidity transition in a model for confluent 3D tissues
- Okuda18: Combining Turing and 3D vertex models reproduces autonomous multicellular morphogenesis with undulation, tubulation, and branching
- Kuang22: MorphoSim: An efficient and scalable phase-field framework for accurately simulating multicellular morphologies

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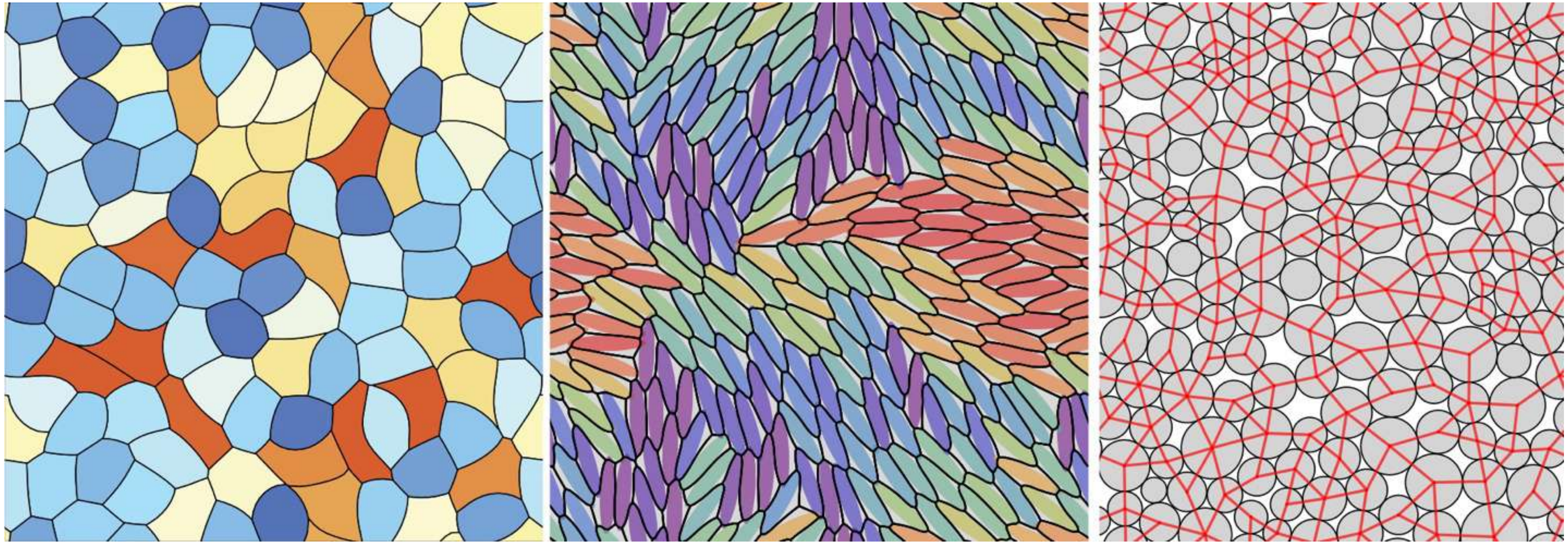

Anyone interested in modeling of biological/living systems and soft/active matter?
Contact me for potential research opportunities!!
sangwoo.kim@epfl.ch