



Lecture 6: Tissue Simulation Frameworks

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Introduction

Morphogenetic Modelling and Simulation

Morphogenesis = morphe (shape) + genesis (creation)

- Signalling
- Tissue
- Coupling

Causalities?

- Biochemical pre-patterning controls morphogenesis
- Mechanical cues control morphogenesis and signalling
- Mechano-chemical interactions control morphogenesis

Morphogenetic Modelling and Simulation

Signalling models:

- Molecular Dynamics
- Continuous:
 - deterministic or stochastic
 - reaction-advection-diffusion

Tissue models:

- Continuum mechanics
 - Solid mechanics (elastic & plastic)
 - Visco-elastic materials
 - Fluid mechanics
- Discrete Tissue Models
 - Subcellular elements
 - Cellular elements
 - Coarse-grained discrete models

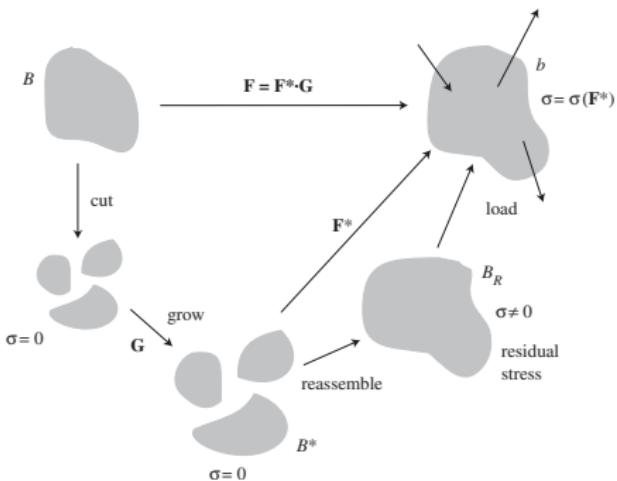
Continuous Tissue Models

Continuum theory for morphomechanics

Embryonic development involves

- growth (change in volume)
- remodelling (change in material properties)
- morphogenesis (change in shape)

Volumetric Growth Theory



Taber LA, Towards a unified theory for morphomechanics,
Phil. Trans. R. Soc. A, 2009

- Stress-free reference configuration B , growth does not cause stress \rightarrow stress-free state B^*
- (Active) growth tensor G
- (Passive) elastic deformation gradient tensor F^*
- Total deformation gradient tensor $F = F^* \cdot G$
- Incompressibility: $\det F = 1$ or $\det F^* = 1$
- Growth/Shrinkage $\det G > / < 1$
- Quasi-static: $\nabla \cdot \sigma = 0$ (σ stress tensor, ∇ defined in state b)

Mechanical constitutive relations

In this setup, stress is associated only with the elastic deformation given by \mathbf{F}^* for the deformation of b relative to the stress-free state B^* .

Constitutive relation for the Cauchy stress tensor

$$\boldsymbol{\sigma} = -p\mathbf{I} + \mathbf{F}^* \cdot \frac{\partial W}{\partial \mathbf{E}^*} \cdot \mathbf{F}^{*T}$$

- p Lagrange multiplier to enforce incompressibility
- \mathbf{I} identity tensor
- $W(\mathbf{E}^*)$ strain-energy density function, i.e.
 - $W = C(I_1^* - 3)$ neo-Hookean strain-energy density function
 - C material constant
 - $I_1^* = \text{tr } \mathbf{C}^*$ first invariant of the right Cauchy-Green deformation tensor defined by $\mathbf{C}^* = \mathbf{F}^{*T} \cdot \mathbf{F}^*$
- $\mathbf{E}^* = \frac{1}{2} (\mathbf{F}^{*T} \cdot \mathbf{F}^* - \mathbf{I})$ Lagrangian strain tensor for elastic deformation

Simplified equations in principal coordinates

If the directions of stress and strain align with the principal material directions, described by the mutually orthogonal unit vectors \mathbf{N}_i ,

$$\mathbf{F} = \lambda_1 \mathbf{N}_1 \mathbf{N}_1 + \lambda_2 \mathbf{N}_2 \mathbf{N}_2 + \lambda_3 \mathbf{N}_3 \mathbf{N}_3,$$

$$\mathbf{F}^* = \lambda_1^* \mathbf{N}_1 \mathbf{N}_1 + \lambda_2^* \mathbf{N}_2 \mathbf{N}_2 + \lambda_3^* \mathbf{N}_3 \mathbf{N}_3,$$

$$\boldsymbol{\sigma} = \sigma_1 \mathbf{N}_1 \mathbf{N}_1 + \sigma_2 \mathbf{N}_2 \mathbf{N}_2 + \sigma_3 \mathbf{N}_3 \mathbf{N}_3.$$

with the λ 's being stretch ratios. The stress invariant then becomes

$$I_1^* = \lambda_1^{*2} + \lambda_2^{*2} + \lambda_3^{*2}.$$

relative to the zero-stress state.

Morphomechanical laws

Growth is a tensor quantity \mathbf{G} defined as the change between the stress-free reference configuration B and the stress-free state B^* .

We assume that growth occurs locally along orthogonal directions, the mutually orthogonal unit vectors \mathbf{N}_i , which we take as principal material directions in B , or for isotropic materials, the principal components of stress such that

$$\mathbf{G} = G_1 \mathbf{N}_1 \mathbf{N}_1 + G_2 \mathbf{N}_2 \mathbf{N}_2 + G_3 \mathbf{N}_3 \mathbf{N}_3.$$

Morphomechanical laws

We then define the rate-of-growth tensor

$$\mathbf{dG} = \frac{1}{2} (\dot{\mathbf{GG}}^{-1} + (\dot{\mathbf{GG}}^{-1})^T)$$

where the dot denotes differentiation with respect to time.

Component-wise we thus have

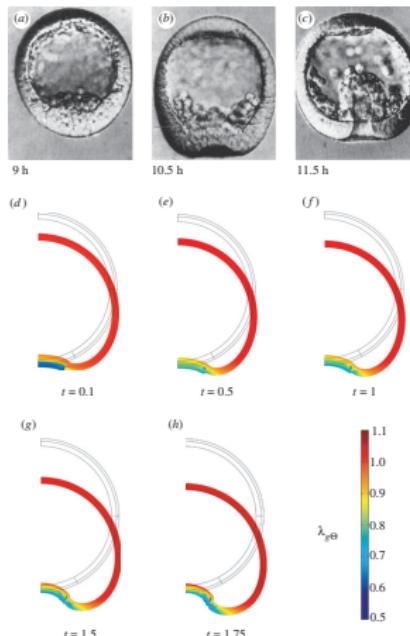
$$\mathbf{dG} = dG_1 \mathbf{N}_1 \mathbf{N}_1 + dG_2 \mathbf{N}_2 \mathbf{N}_2 + dG_3 \mathbf{N}_3 \mathbf{N}_3$$

With $\dot{\mathbf{G}}$ written in the same form, these equations give

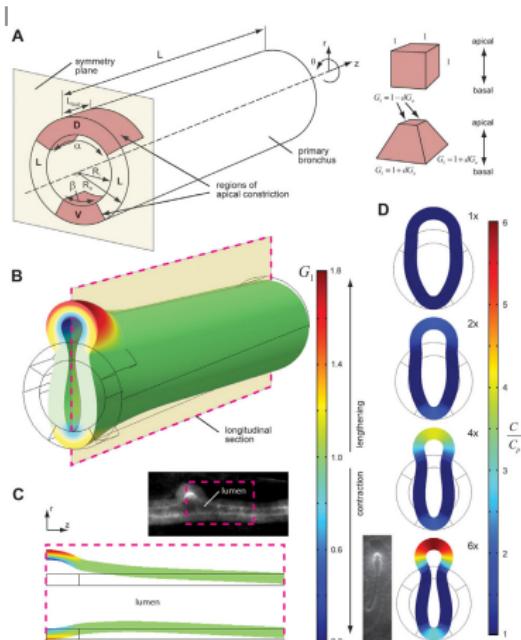
$$dG_i = \dot{G}_i / G_i,$$

the rate of change in length (due to growth) per unit length of an infinitesimal element in the current zero-stress state.

Volumetric Growth Theory: Applications



Taber LA, Towards a unified theory for morphomechanics,
Phil. Trans. R. Soc. A, 2009



Kim et al., Apical constriction initiates new bud formation during monopodial branching of the embryonic chicken lung, Development, 2013

Continuum theory for morphomechanics

How to solve $\nabla \cdot \sigma = 0$ or similar mechanical equations to simulate tissue growth and deformation?

A suitable method should:

- be efficient enough to simulate problems on the tissue scale
- allow for anisotropic and nonlinear material behavior
- work for complicated geometries

The Finite Element Method (FEM) offers all of this in many cases.

Introduction to the Finite Element Method

Find a function $u : \Omega \rightarrow \mathbb{R}^n$ that solves a boundary value problem of the form

$$Lu(x) = f(x) \text{ in } \Omega$$

$$Bu(x) = g(x) \text{ on (a part of) the boundary } \partial\Omega$$

where L and B are differential operators (Laplacian, divergence, partial derivative, etc.)

Example: Steady-state diffusion of a morphogen concentration $u(x)$ in a tissue Ω :

$$-D\Delta u(x) = f(x) \text{ in } \Omega$$

$$u(x) = 0 \text{ on } \partial\Omega$$

Introduction to the Finite Element Method

This is called the **strong form** of the problem:

$$\begin{aligned}-D\Delta u(x) &= f(x) \text{ in } \Omega \\ u(x) &= 0 \text{ on } \partial\Omega\end{aligned}$$

Idea no. 1: Multiply the differential equation by a test function $v(x)$ and integrate over the entire tissue domain:

$$-D \int_{\Omega} v \Delta u \, dx = \int_{\Omega} vf \, dx$$

This is called the **weak form**. If u solves strong form, then it also solves the weak form for any v that is compliant with the boundary conditions. And vice versa!

Introduction to the Finite Element Method

Weak form:

$$-D \int_{\Omega} v \Delta u \, dx = \int_{\Omega} vf \, dx$$

Idea no. 2: Reduce the differential operator by one order by partial integration:

$$-D \int_{\Omega} \nabla v \cdot \nabla u \, dx - \int_{\partial\Omega} v n \cdot \nabla u \, dS = \int_{\Omega} vf \, dx$$

The boundary integral is zero, because we can choose v such that $v(\partial\Omega) = 0$:

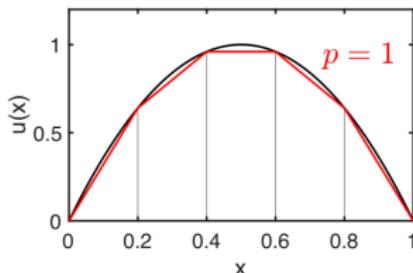
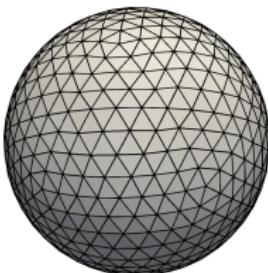
$$-D \int_{\Omega} \nabla v \cdot \nabla u \, dx = \int_{\Omega} vf \, dx$$

Introduction to the Finite Element Method

$$-D \int_{\Omega} \nabla v \cdot \nabla u \, dx = \int_{\Omega} vf \, dx$$

Problem: The space of possible solutions $u(x)$ is infinite-dimensional.
The computer is a finite state machine \Rightarrow we need to restrict the search for $u(x)$ to a finite set of functions.

Idea no. 3: Subdivide Ω into **finite elements** Ω_i , and approximate $u(x)$ by a finite-dimensional function $\tilde{u}(x)$ (e.g., piecewise polynomials of degree p) in each element.



Introduction to the Finite Element Method

This way, the weak form

$$-D \int_{\Omega} \nabla v \cdot \nabla u \, dx = \int_{\Omega} vf \, dx$$

becomes

$$-D \sum_i \int_{\Omega_i} \nabla \tilde{v} \cdot \nabla \tilde{u} \, dx = \sum_i \int_{\Omega_i} \tilde{v} f \, dx.$$

These integrals of known functions over finite elements can be calculated analytically or using numerical quadrature rules. One obtains a system of equations that can be written as

$$\mathbf{A}\mathbf{u} = \mathbf{f}$$

Often, this is a linear system of equations that can be solved with standard methods. In mechanics ($\nabla \cdot \boldsymbol{\sigma} = 0$) with large deformations, the stiffness matrix \mathbf{A} depends on the displacement u itself, making the system nonlinear and harder to solve.

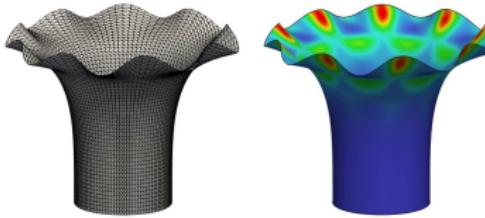
Volumetric Growth with the FEM



Torn plastic sheet and beet leave. Sharon et al.,
Buckling cascades in free sheets,
Nature 2002



Myrsine australis, <http://plant-photography.blogspot.com>



Vetter et al., Simulating thin sheets: buckling, wrinkling,
folding and growth, J. Phys.: Conf. Ser. 2014

Finite element simulation
of elastic thin shell with
growth tensor

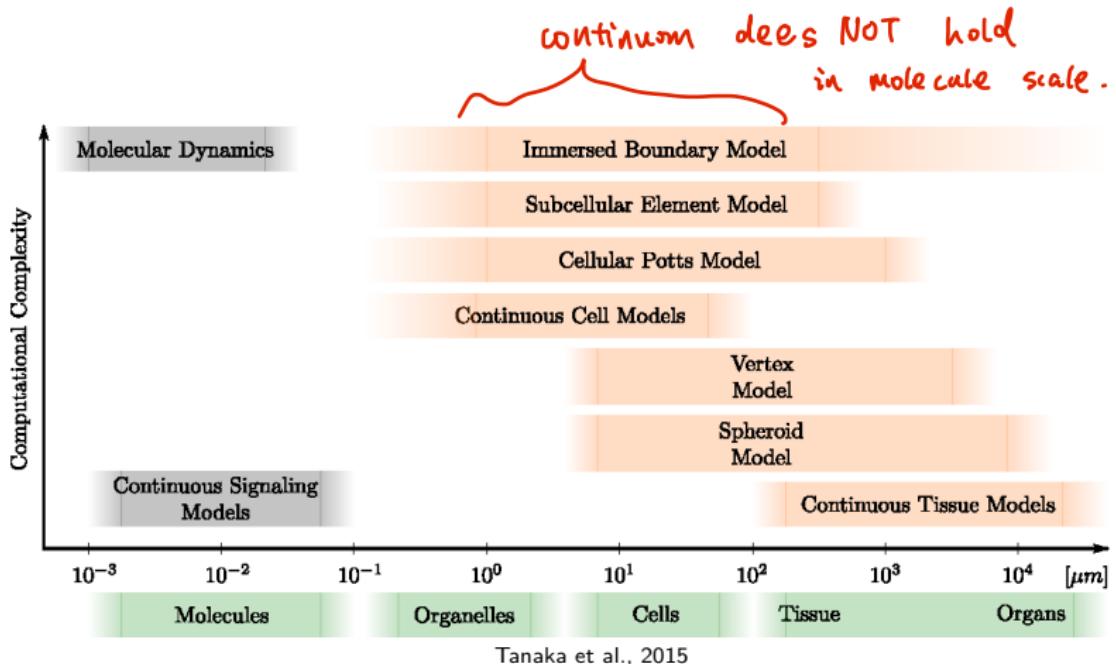
$$\mathbf{G}(t) = \begin{bmatrix} \frac{1}{1+y/L(t)} & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}$$

Finite Element Method: Discussion

- widely used, well-studied and mature
- very mathematical and difficult to implement
- extremely flexible and powerful
- tunable precision & performance (adaptive mesh size control)
- no information below the tissue scale (cells, molecules, etc.)
- assumption of a continuum is sometimes inaccurate for tissues
- software: COMSOL, Abaqus, ANSYS, libMesh, deal.II, etc.

Cell-Based Tissue Models

Cell-based Simulation Frameworks

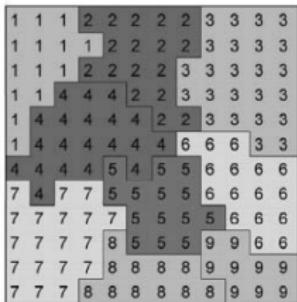


Why cell-based modeling?

Representation of:

- cell division (directed and undirected)
- cell migration
- cell adhesion
- cell differentiation
- cell polarity
- cell proliferation/cell death

Cellular Potts Model



Glazier et al., 2007

- originates from the Ising model
- generalization: Potts model
- spin: $\sigma(x) \in \mathbb{Z}^{+} \cup \{0\}$ 12^+ 10 10 4
- spin value = cell identity

Cellular Potts Model: Hamiltonian

Energy function describing how it evolves over time.

Typical Hamiltonian H is composed of two contributions, a volume constriction term H_v and a cell-cell adhesion term H_a :

$$H = H_v + H_a = \sum_{\sigma} \lambda_v (V_{\sigma} - V_{\sigma}^T)^2 + \sum_{(x,x')} J(\sigma(x), \sigma(x')) \cdot (1 - \delta(\sigma(x), \sigma(x')))$$

control volume growth .
cell type
over all cells
of 1, diff.
0, same

where V_{σ} and V_{σ}^T are the actual and target volume of cell σ , respectively. The coefficient λ_v controls the energy penalization. The term $J(\sigma, \sigma')$ is the surface energy between two cell types σ and σ' . Here, $\sigma(x)$ denotes the type of the cell at position x . The inverse Kronecker delta $1 - \delta(\cdot, \cdot)$ equals one if $\sigma \neq \sigma'$, which is true if the two neighbouring lattice sites are of different cell type. The summation $\sum_{(x,x')}$ runs over all lattice sites x and its neighbouring lattice sites x' .

Cellular Potts Model: Time Evolution

Metropolis algorithm:

The probability of converting the spin $\sigma(x)$ of the lattice site x into the spin value $\sigma(x')$ is:

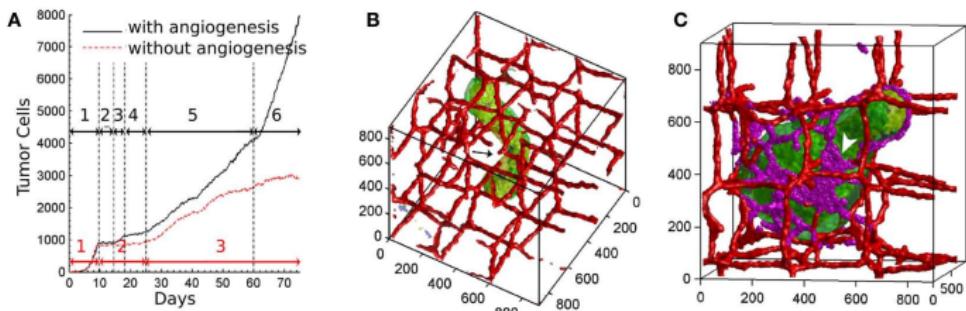
$$p(\sigma(x) \rightarrow \sigma(x')) = \begin{cases} 1 & \text{if } \Delta H(\sigma(x) \rightarrow \sigma(x')) < 0 \\ \exp\left[\frac{-\Delta H(\sigma(x) \rightarrow \sigma(x'))}{k_B T}\right] & \text{otherwise} \end{cases}$$

energy

Problems:

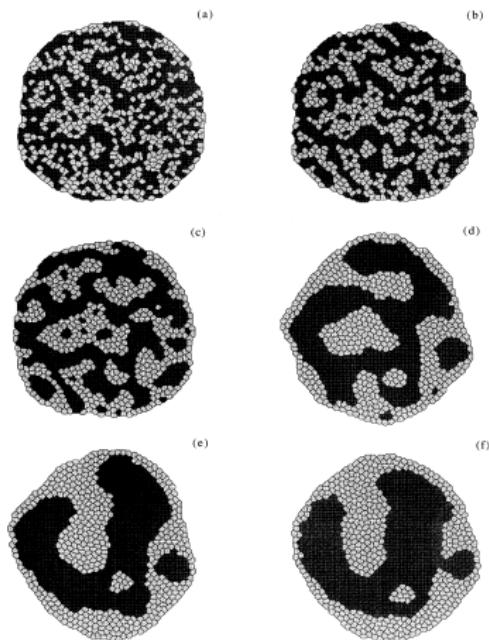
- What is the time step?
- What is the “temperature” T ?

Cellular Potts Model: Applications

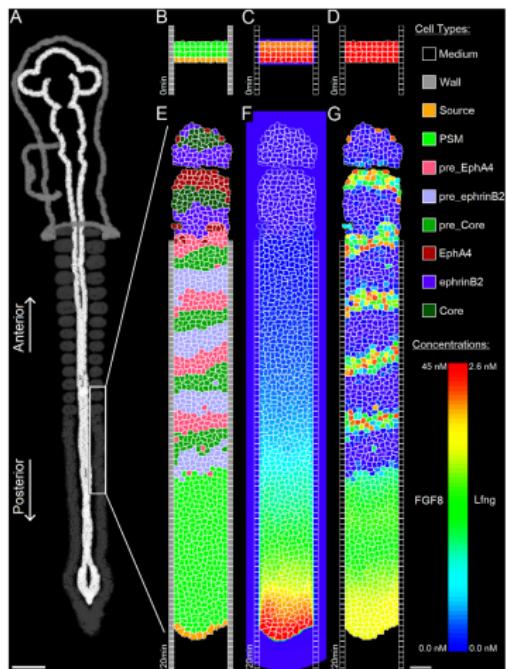


Szabo et al., Cellular potts modeling of tumor growth, tumor invasion, and tumor evolution, Frontiers in Oncology, 2013

Cellular Potts Model: Applications



Glazier et al., 1993

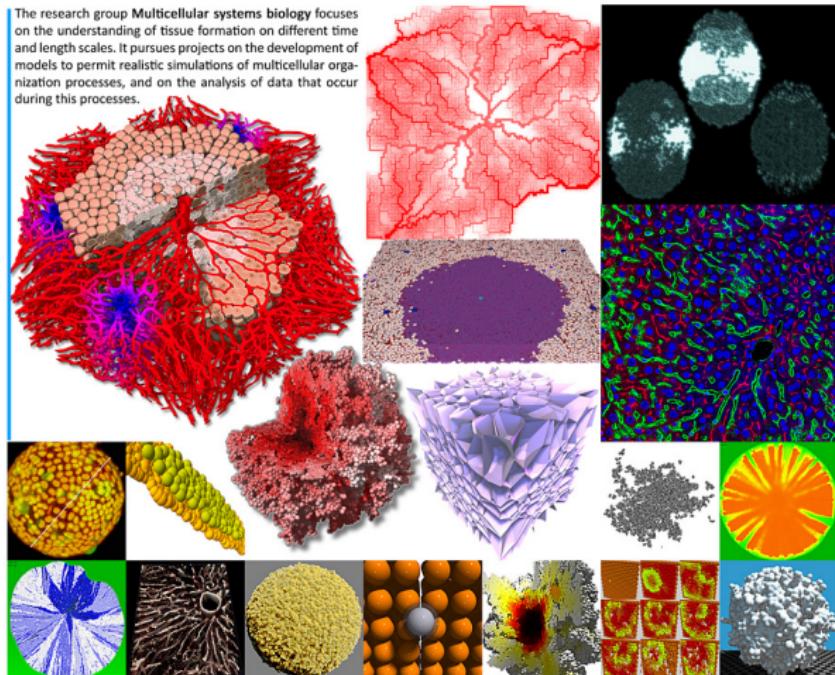


Lattice init. {
 ◦ by direct random
 ◦ taking values from real
 images.

Cellular Potts Model: Discussion

- widely used, well-studied and mature
- "simple" mechanism
- computationally intensive: lattice, time step
- level of abstraction relatively high
- software: CompuCell3D

Spheroid Model

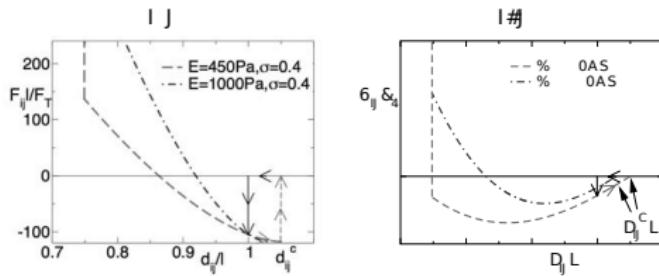


Instead of fixed lattice points.

Spheroid Model

Representation of cells:

- particle-like cells
- spherical, isotropic shape represented by a soft sphere
- interaction potentials: Johnson-Kendall-Roberts (adhesive spheres), Hertz (elastic), harmonic potentials, ...



Drasdo et al., 2007

Spheroid Model - Evolution in time

- 1 Solving eq of motion **deterministically**:

$$\eta \frac{\partial \mathbf{x}}{\partial t} = \sum \underline{\mathbf{f}} \quad \text{sum of all forces.}$$

with η being a viscosity coefficient.

- 2 Solving **stochastic** eqs of motion (Langevin):

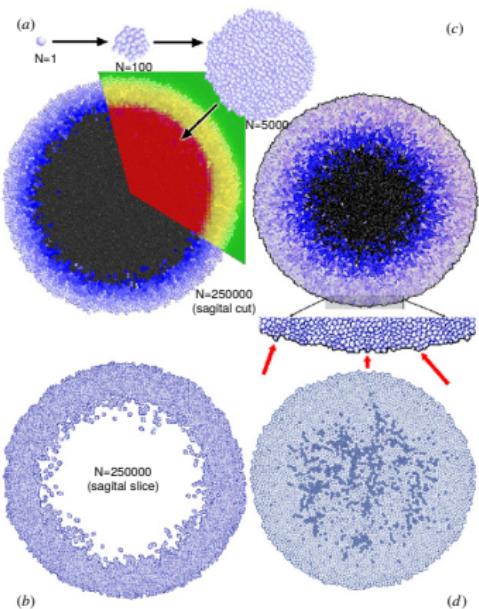
$$(\gamma + \boldsymbol{\Gamma}_{is}^f) \dot{\mathbf{x}}^i + \sum_{j \neq i} \boldsymbol{\Gamma}_{ij}^f (\mathbf{x}^i - \mathbf{x}^j) = \sum_{j=0}^N \boldsymbol{F}^{ij} + \boldsymbol{\eta}^i(t)$$

where γ is an effective friction coefficient. The tensor

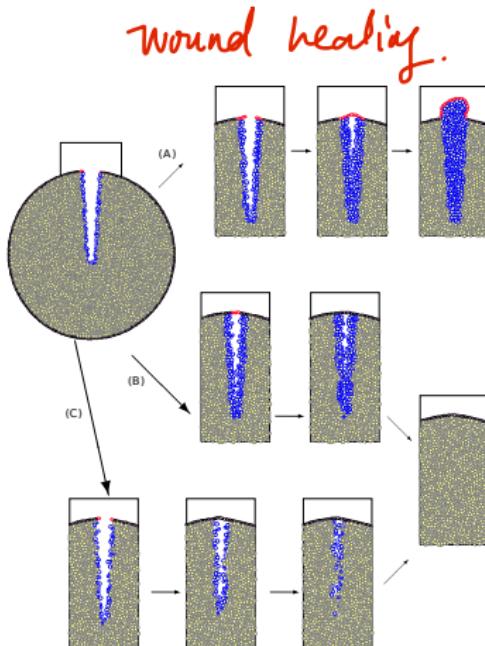
$$\boldsymbol{\Gamma}_{iy}^f = \gamma_{\parallel}^{(iy)} \mathbf{n}_{iy} \otimes \mathbf{n}_{iy} + \gamma_{\perp}^{(iy)} (\mathbf{I} - \mathbf{n}_{iy} \otimes \mathbf{n}_{iy})$$

(with $y = s$ for substrate- and $y = j$ for cell-cell interactions) is composed of a parallel and perpendicular contribution with friction coefficients $\gamma_{\parallel}^{(ij)}$ and $\gamma_{\perp}^{(ij)}$, respectively.

Spheroid Model: Applications



Drasdo et al., 2005



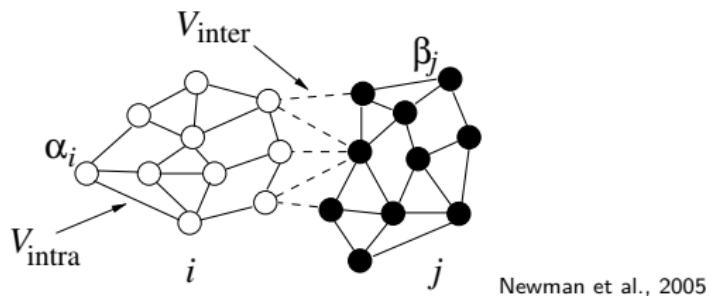
Drasdo et al., 2007

3.1 Spheroid Model: Discussion

- simple representation:
 - cheap → large number of cells
 - 3D as simple as 2D
 - no cellular details
- coupling to signaling restricted
- software: CellSys

Subcellular Model

Representation of cells:



Newman et al., 2005

- one cell = many subcellular elements
- similar to spheroid model: forces derived from interaction potentials between elements (often Morse potential used)

Subcellular Model

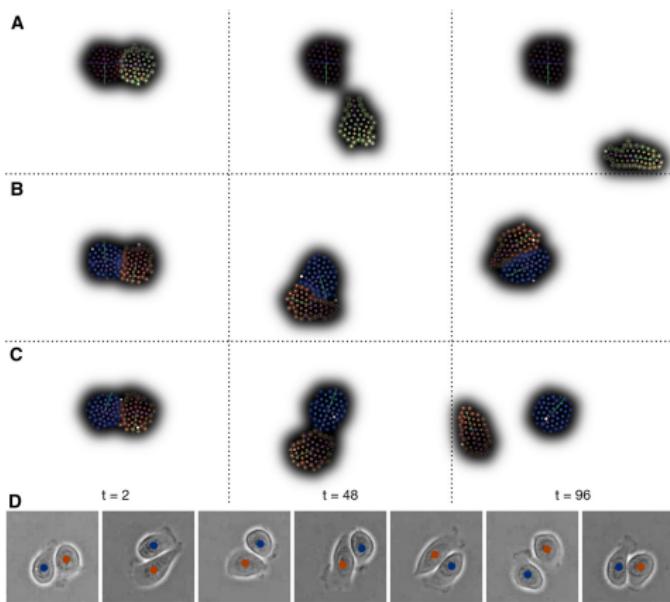
Equation of motion for position \mathbf{y}_{α_i} of a subcellular element α_i of cell i :

$$\eta \frac{\partial \mathbf{y}_{\alpha_i}}{\partial t} = \zeta_{\alpha_i} - \nabla_{\alpha_i} \sum_{\beta_i \neq \alpha_i} V_{intra}(|\mathbf{y}_{\alpha_i} - \mathbf{y}_{\beta_i}|) - \nabla_{\alpha_i} \sum_{j \neq i} \sum_{\beta_j} V_{inter}(|\mathbf{y}_{\alpha_i} - \mathbf{y}_{\beta_j}|)$$

where ζ_{α_i} is Gaussian noise.

- term 1: intra-cellular interactions, summation runs over all remaining elements β_i of cell i
- term 2: inter-cellular interaction, pair-interactions between the elements β_j of other cells j and the elements α_i of cell i
- Morse Potential: $V(r) = U_0 \exp(-r/\xi_1) - V_0 \exp(-r/\xi_2)$, with U_0, V_0 being energy scales and ξ_1, ξ_2 being length scale constants.

Subcellular Model: Applications



Milde et al., 2014

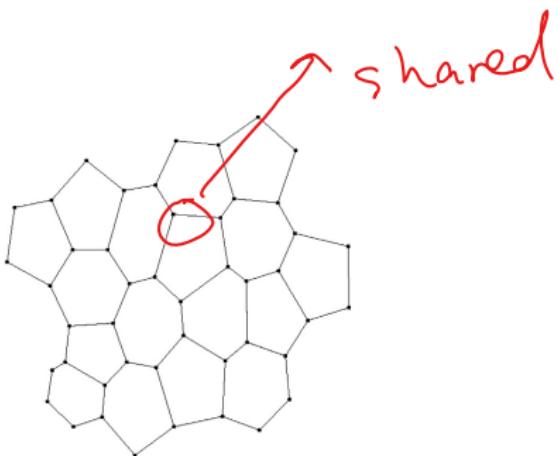
2D simulation of one migrating cell initially located to the right (a: white, b&c: orange) interacting with a second cell via cell-cell adhesion compared to experiments (d). The cell to the left is quiescent (a: red) or actively remodelling its cytoskeleton from regions of low to regions of high density as defined by d_{a_i} (b: blue) or $d_{a_i}^{int}$ (c: blue). The last row shows an experimental observation of two living cells circling around each other (d).

Subcellular Model: Discussion

- explicit, detailed resolution of shape
- 3D implementation straightforward
- however, computationally expensive

→ Exercise: subcellular model

Vertex Model



Fletcher et al., Implementing vertex dynamics models of cell populations in biology within a consistent computational framework, Progr. Biophys. Mol. Biol., 2013

- Cells bound by polygons
- Neighboring cells share edges
- Forces derived from potentials:
 $\mathbf{F}_i = \frac{\partial E}{\partial \mathbf{R}_i}$ with \mathbf{R}_i being a junctional direction of vertex i .
- Equation of motion: $\eta \frac{d\mathbf{x}_i}{dt} = \mathbf{F}_i$

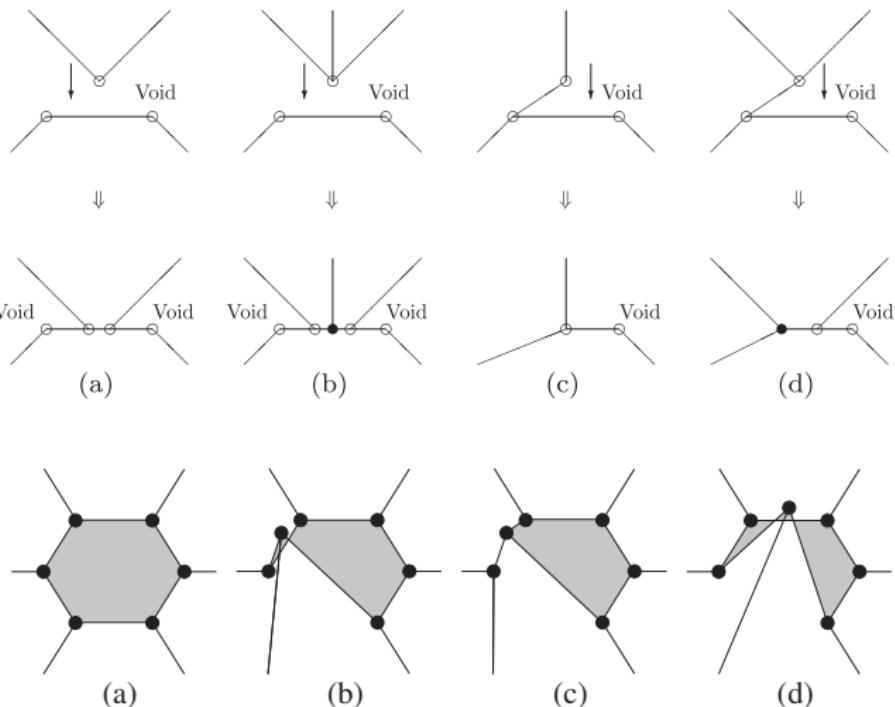
Vertex Model

A typical energy function includes area elasticity, line tension and contractility of the cell perimeter

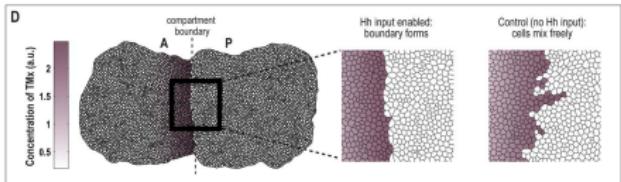
$$E(\mathbf{R}_i) = \sum_{\alpha} \frac{K_{\alpha}}{2} \left(A_{\alpha} - A_{\alpha}^0 \right)^2 + \sum_{<i,j>} \Lambda_{ij} l_{ij} + \sum_{\alpha} \frac{\Gamma_{\alpha}}{2} L_{\alpha}^2$$

The first term on the right hand side describes the area elasticity, with K_{α} being the area elasticity coefficient, A_{α} the current area and A_{α}^0 the resting area. The second term denotes line tension, which, for vertex i , considers all neighbouring vertices j . Λ_{ij} is the line tension coefficient, and l_{ij} the edge length, and $< i, j >$ denotes the summation over all edges. The last term represents the perimeter contractility, with Γ_{α} being the cell perimeter contractility coefficient and L_{α} the cell's perimeter.

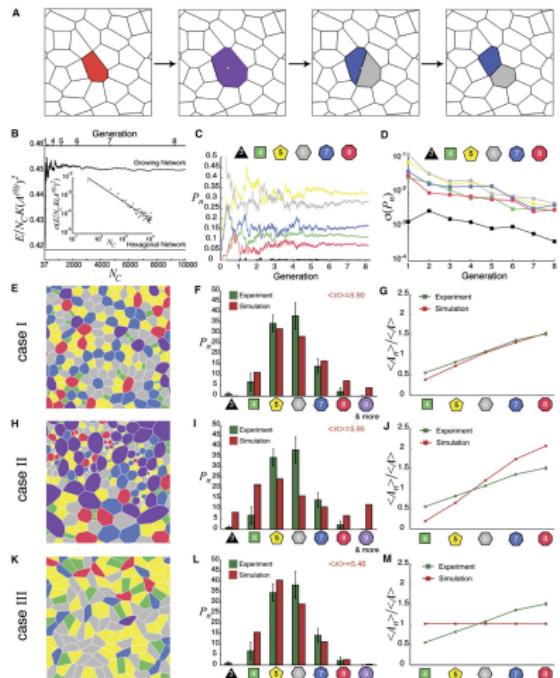
Vertex Model: Topological Operations



Vertex Model: 2D Application

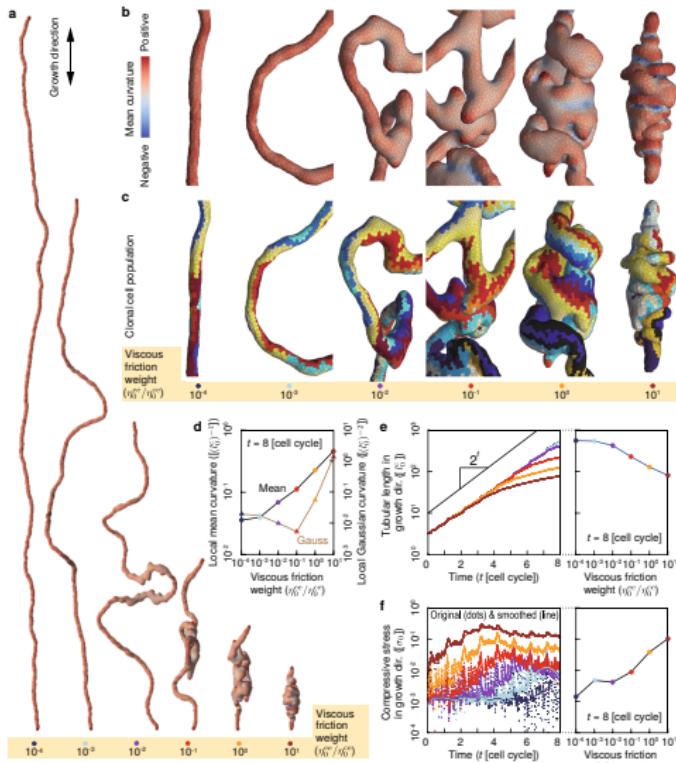


Schilling et al., Cell-sorting at the A/P boundary in the Drosophila wing primordium: a computational model to consolidate observed non-local effects of Hh signaling, PLoS Comp. Biol., 2011



Farhadifar et al., The influence of cell mechanics, cell-cell interactions, and proliferation on epithelial packing, Curr. Biol., 2007

Vertex Model: 3D Application

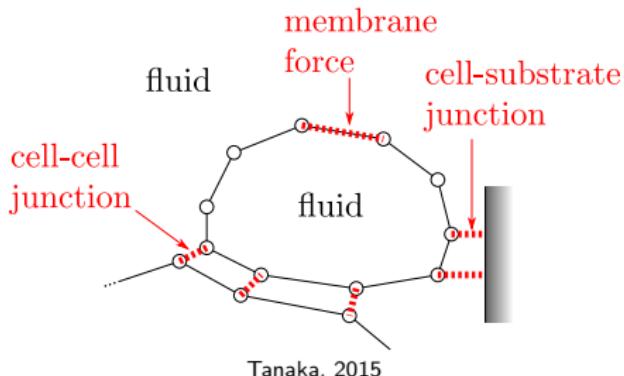


Okuda et al., Vertex dynamics simulations of viscosity-dependent deformation during tissue morphogenesis, Biomech. Model. Mechanobiol., 2014

Vertex Model: Discussion

- Still relatively efficient
- Explicit cell shapes allow relatively high level of detail
- However, cell-cell junction dynamics, rearrangements etc. require high level of abstraction
- 3D is a current research topic (can be complicated)
- No curved cell membranes

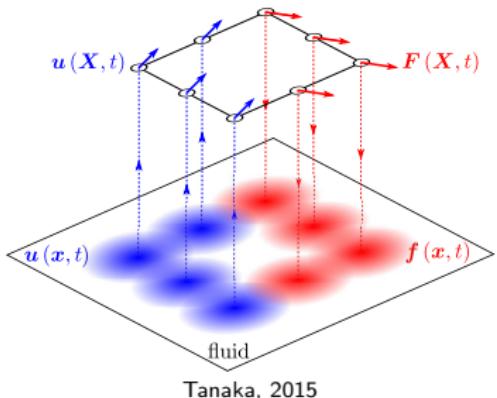
Immersed Boundary Cell Model



- membrane is discretized → polygons
- elastic cell membranes
- fluid inside and outside of the cells
- fluid-structure interaction
- cell-cell junctions
- cell division, growth, differentiation

Immersed Boundary Cell Model

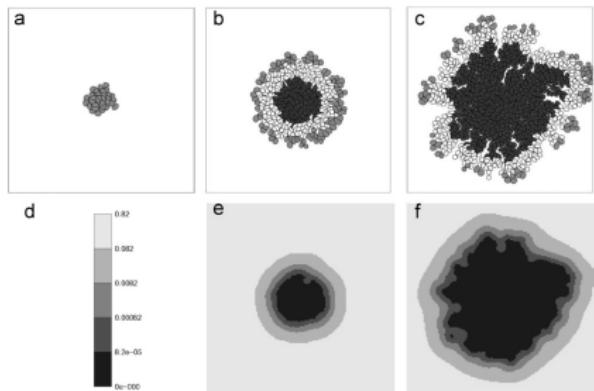
Immersed Boundary method:



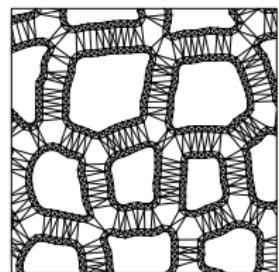
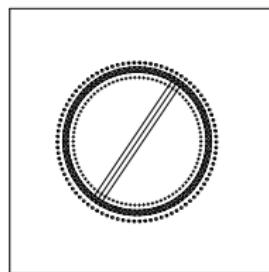
- force on vertex distributed to local fluid neighborhood: $\mathbf{f}(\mathbf{x}, t) = \int \mathbf{F}(q, r, s, t) \delta(\mathbf{x} - \mathbf{X}(q, r, s, t))$
- fluid equation solved
- velocity of vertex interpolated from local fluid neighborhood:

$$\frac{\partial \mathbf{X}}{\partial t}(q, r, s, t) = \mathbf{u}(\mathbf{X}(q, r, s, t), t) = \int \mathbf{u}(\mathbf{x}, t) \delta(\mathbf{x} - \mathbf{X}(q, r, s, t)) d\mathbf{x}$$
- iteration

Immersed Boundary Cell Model: Applications



Rejniak, 2007

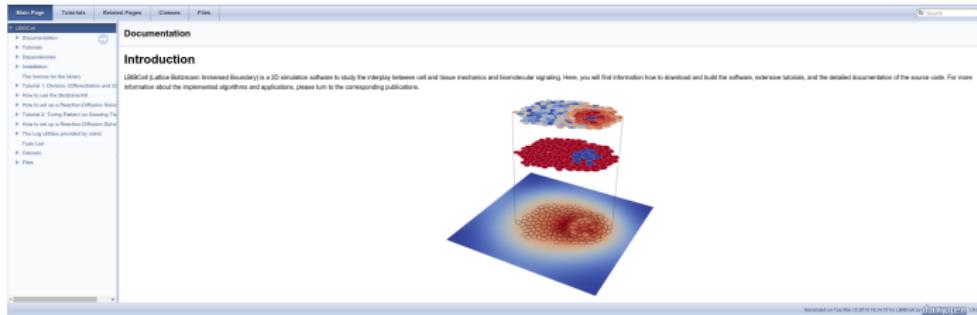


Dillon et al., 2008

Immersed Boundary Cell Model: Discussion

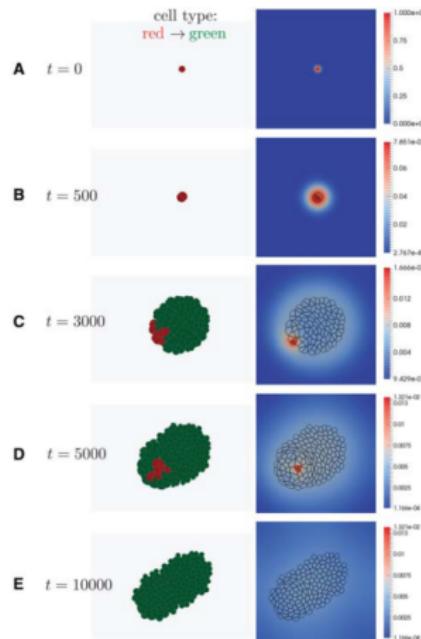
- currently only in 2D
- very high level of detail, down to individual cell-cell junctions
- physical representation of tissue mechanics
- computationally expensive
- software: LBIBCell

LBIBCell



- “*LBIBCell: A Cell-Based Simulation Environment for Morphogenetic Problems*”, Tanaka et al., Bioinformatics, 2015
- LBIB: Lattice Boltzmann - Immersed Boundary
- coupled modeling of signaling and tissue growth

LBIBCell



Tanaka et al., 2015

Summary: Discrete tissue mechanics

- tissue consists of cells
- cell dynamics considered
- simulation of small tissues / cell groups
- various models to represent the cells:
 - (sub-) cellular models
 - coarse grained discrete models
 - Immersed Boundary models

Outlook

- cell-based modelling techniques is an ongoing field of research
- models have to be implemented efficiently
- models have to be compared to each other and validated against experimental data
- more and more: (live) (3D) data with (sub-) cellular resolution

Thanks!!

Thanks for your attention!

Slides for this talk will be available at:

<https://www.bsse.ethz.ch/cobi/teaching>