Modeling tissues: numerical simulations and continuum mechanics

Part II - Numerical Simulations

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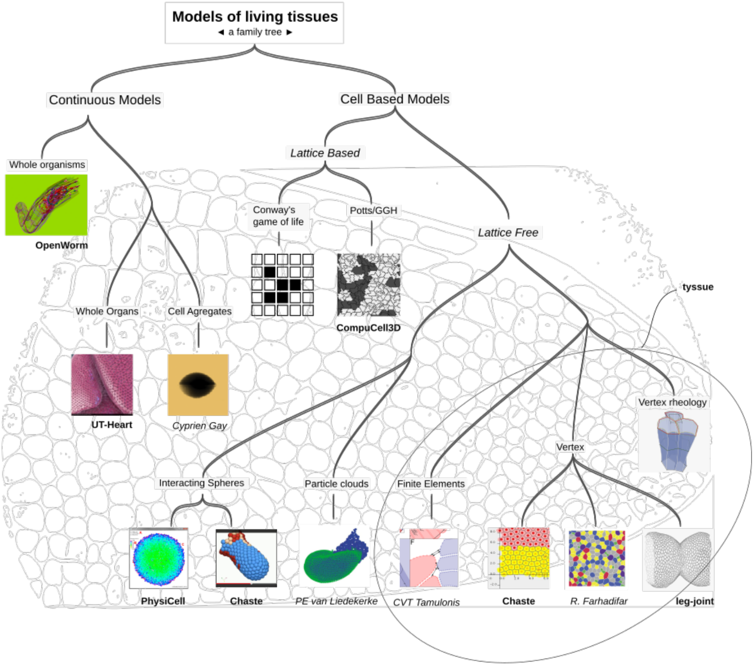
A rough taxonomy of tissue models

A rough taxonomy of tissue models

This courses relies a lot on Carlos Tamulonis' PhD Thesis (2013)



Models of living tissues
◄ a family tree ►
Continuous Models
Cell Based Models
Whole organisms
OpenWorm
Lattice Based
Conway's game of life
Potts/GGH
Lattice Free
CompuCell3D
tyssue
Whole Organs
Cell Agregates
UT-Heart
Cyprien Gay
Vertex rheology
Vertex
Interacting Spheres
Particle clouds
Finite Elements
PhysiCell
Chaste
PE van Liedekerke
CVT Tamulonis
Chaste
R. Farhadifar
leg-joint

Population dynamics

Population dynamics

- Only concerned with $N(t)$
- Focus on **signaling** and growth / death rates
- Main use is **mathematical oncology**: predict cancer growth in response to treatment

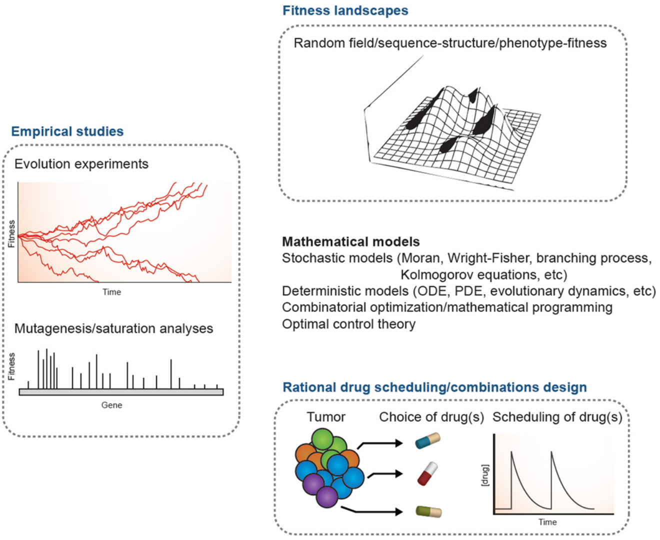


Figure 2: (Zhao, Hemann, and Lauffenburger 2016)

Agent based modelling

Agent based modelling

- Cells are **agents**: they *act*
- Follow each cell behavior
- Broad range of problems:
  - cancer
  - morphogenesis

Lattice based models

Lattice based models

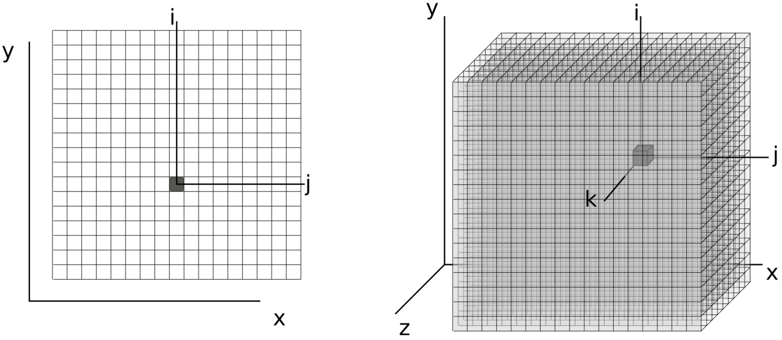


Figure 3: Discrete space in 2 and 3D

Game of life

Game of life

(James Conway)

- Not really cells, but Cellular Automata
- Classical 'emergent behavior' system

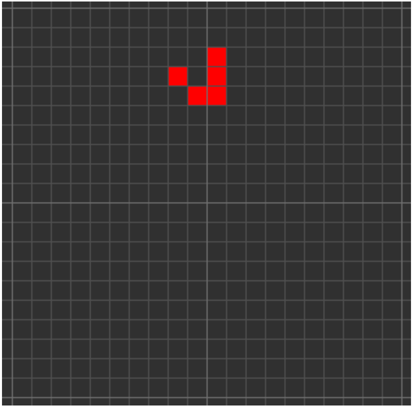


Figure 4: Game of life

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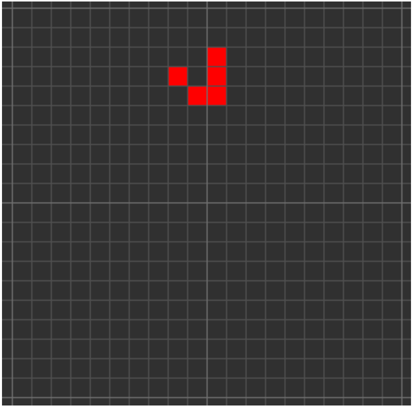

Figure 4: Game of life

Follow this link for a fun example of cellular automata

The Graner Glazier Hogeweg model

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- The world is a fixed grid
- Each cell α occupies a set of pixels
- Pixels at the interface can swap cells

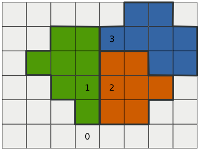

Figure 5: step n

The Modified Metropolis Algorithm

The behavior is governed by the definition of a **Hamiltonian** H governing the energy of the cells

Changes follow a simple local algorithm:

1. Choose randomly a site (i, j)

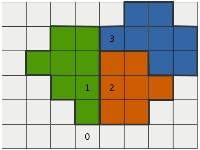

Figure 6: step n

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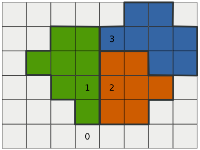

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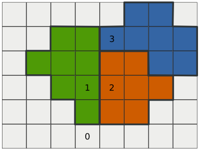

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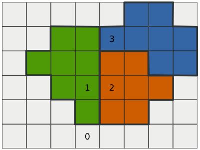

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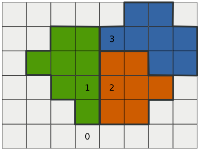

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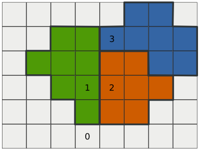

Figure 6: step n

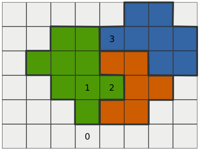

Figure 7: step n+1

Cellular Potts Model Hamiltonian

The game is now to define the Hamiltonian to better reflect our problem!

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The simplest model: volume conservation and adhesion:

$$
\begin{aligned}
H &= H_V + H_i \\
H_V &= \frac{\lambda}{2}\sum_{\alpha}(V_\alpha - V_0)^2 \\
H_i &= \sum_{ij,i'j'} J(\tau(ij), \tau(i'j'))
\end{aligned}
$$

$\tau(ij)$ type of cell at ij

$J(\tau(ij), \tau(i'j'))$: bond energy

Cell sorting

A classical problem:
2 cell types $(1,2)$ — 0 is the medium

$$\begin{aligned}
J(1,1) &= 0 \\
J(1,1) &= 1 \\
J(2,2) &= 8 \\
J(2,1) &= 16 \\
J(1,0) &= J(2,0) = 32
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Contact prefered between same type, 1 more so than 2

What happens?

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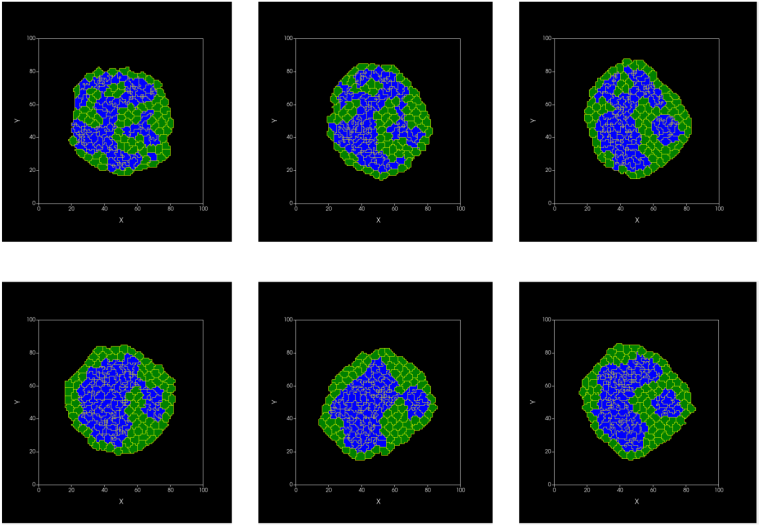

Chemotaxis

Add a term for chemotaxis:

- chemoatractant distribution on the grid ($C(ij)$)
- Favor switch for increasing C:

$$H' = H - \mu\left(C(ij) - C(i'j')\right)$$

- The chemoatractant can be *produced* by the cells (cAMP)

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Figure 9: Dictyostelium Aggregation

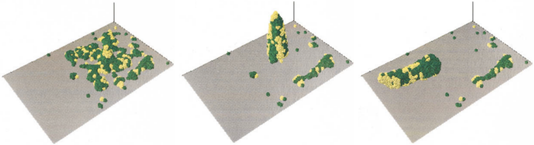

Figure 10: (Savill and Hogeweg 1997)

Existing Software

- Chaste
- CompuCell3D
- Morpheus

Cells as spheres

Cells as spheres

Figure 11: A ball pit

- Cells are defined by their position in free space
- Movement goverened by Newton:

Mechanical impact of cell dynamics

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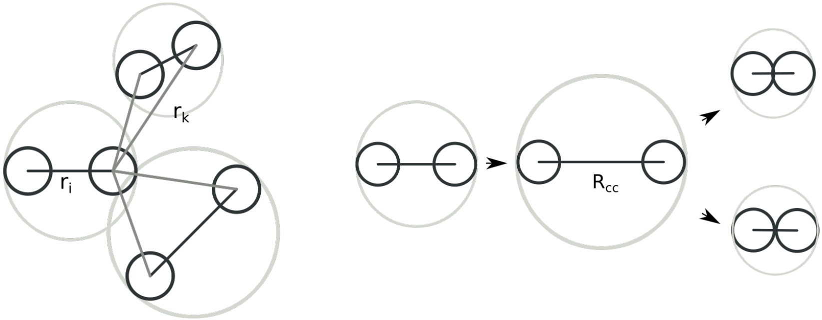

Figure 12: Cells as dipoles Ranft et al. (2010)

- Cell-cell interactions:

$$V^{CC}(r) = \begin{cases} \frac{f_0 R_{pp}^5}{4 r_k^4} + (f_0 + f_1) r_k - (1.25 f_0 + f_1) & r_k \leq R_{pp} \\ 0 & r_k > R_{pp} \end{cases}$$

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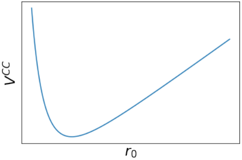

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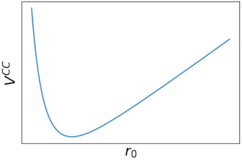
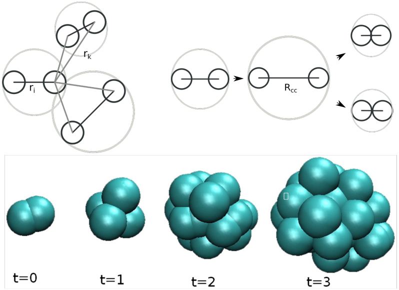


- Self-interaction (growth):

$$V^G(r) = \frac{B}{r_i + r_0}$$



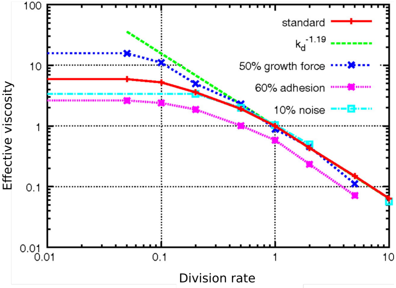


Figure 13: Fluidization (Ranft et al. 2010)

Due to proliferation and death, cell aggreagate behaces as a fluid

Modeling tumors

Modeling tumors

- Spheres with adhesion and repulsion

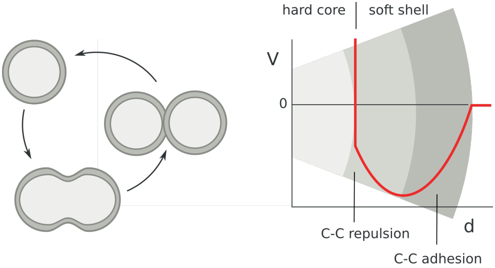


Figure 14: (Drasdo and Höhme 2005)

- Same Metropolis alorithm as GGH:

$$P(\delta r) = \min\{1, \exp \frac{-(V(t+dt) - V(t))}{F_T}\}$$

Mixed resolution models

Mixed resolution models

- Deformable cells at high resolution meshes mixed with cell-based model

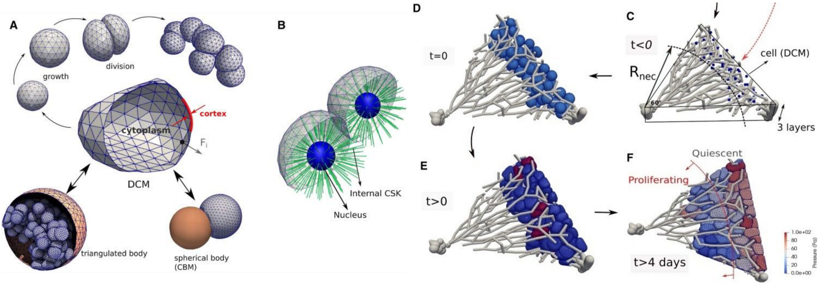


Figure 15: (Van Liedekerke et al. 2020)

- Complex continuous / fluid dynamics finite elements for cells
- Very "realistic" results
- High computational cost

PhysiCell (Mathematical Oncology)

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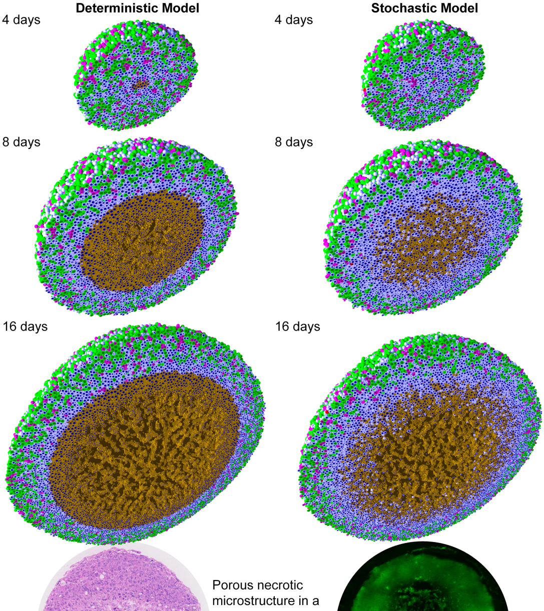
Physicell is a very powerfull simulation toolkit



- Friction and adhesion model
- Very multi-agent oriented
- Coupled with a powerfull reaction / diffusion solver, BioFMV

Cells as polygons

Cells as polygons

The apical junctions meshworks play a central role in many morphogenesis events (Lecuit and Lenne 2007) and are poorly rendered by cell center models.

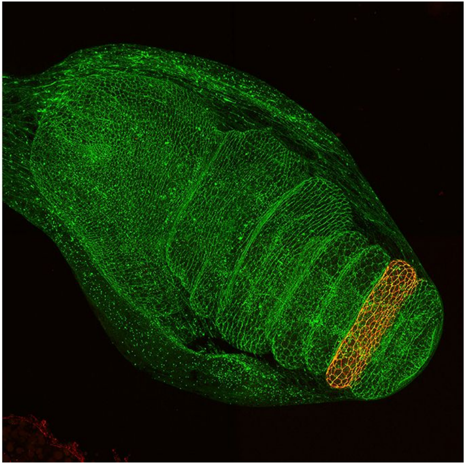
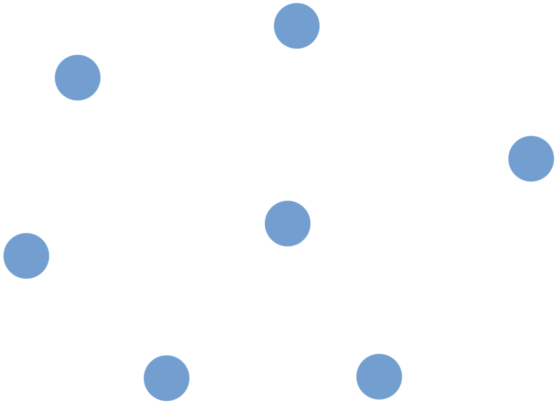


Figure 17: Apical junctions in Drosophila leg disk

Topology of epithelium

Voronoï tessalation (Honda, Tanemura, and Nagai 2004)

Instead of focusing on the cell centers, we now look at the contact between junctions



- Solution 1 : The active vertex model : Consider the Delaunay triangulation instead of it's dual (Barton et al. 2016), and compute it at every step.

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- Solution 2 : Allow for more than 3 way vertices! (Finegan et al. 2019)

3D topology

Topology gets trickier in 3D

- (Okuda et al. 2013) defines rules for stable deformations
- Can we generalize Dapeng Bi et al. solution?

Mechanical Model formulations

2D Models

- (Farhadifar et al. 2007)
- (Bi et al. 2015)

3D Models

- (Bielmeier et al. 2016) Extrapolate to 3D the 2D formulation
- Sophisticated expression for the friction: (Okuda, Inoue, and Adachi 2015)

2.5D

- Only the apical mesh (Martin et al. 2021)
- Potential expression like the 2D one + some volume conservation

Towards rheological models

Existing implementations

- Chaste
- Tyssue

Barton, Daniel L., Silke Henkes, Cornelis J. Weijer, and Rastko Sknepnek. 2016. "Active Vertex Model for Cell-Resolution Description of Epithelial Tissue Mechanics." *bioRxiv*, December, 095133. https://doi.org/10.1101/095133.

Bi, Dapeng, J. H. Lopez, J. M. Schwarz, and M. Lisa Manning. 2015. "A Density-Independent Rigidity Transition in Biological Tissues." *Nature Physics* 11 (September): 1074. https://doi.org/10.1038/nphys3471.

Bielmeier, Christina, Silvanus Alt, Weichselberger Vanessa, Marco La Fortezza, Hartmann Harz, Frank Jülicher, Guillaume Salbreux, and Ann-Kathrin Classen. 2016. "Interface Contractility Between Differently Fated Cells Drives Cell Elimination and Cyst Formation." *Current Biology* 26: 563–74. https://doi.org/10.1016/j.cub.2015.12.063.

Drasdo, Dirk, and Stefan Höhme. 2005. "A Single-Cell-Based Model of Tumor Growthin Vitro: Monolayers and Spheroids." *Phys. Biol.* 2 (3): 133–47. https://doi.org/10.1088/1478-3975/2/3/001.