Modeling tissues: numerical simulations and continuum mechanics

Part II - Numerical Simulations

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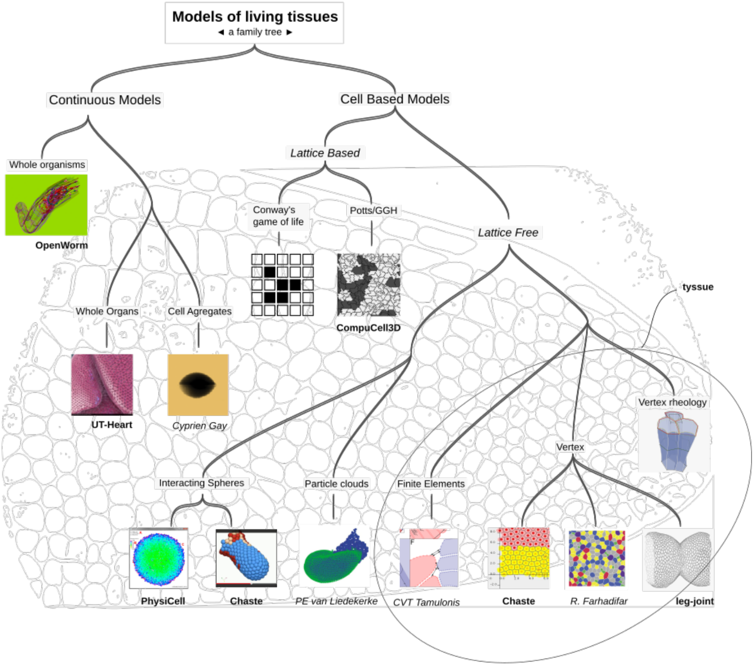
A rough taxonomy of tissue models

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
CompuCell3D
Lattice Free
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

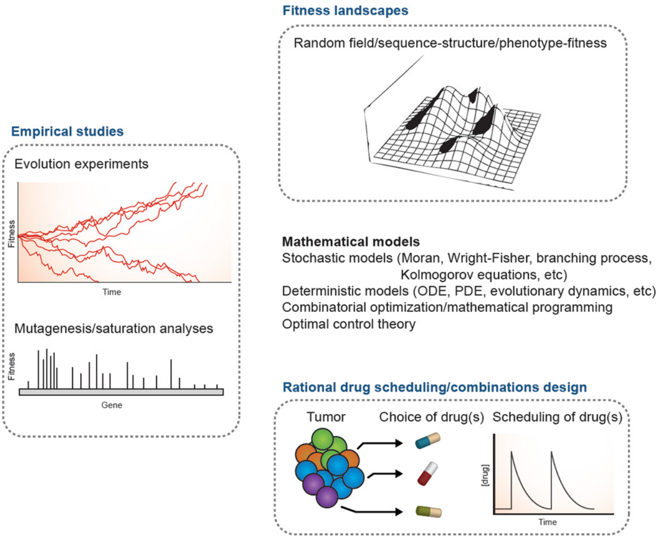


Figure 2: (Zhao, Hemann, and Lauffenburger 2016)

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

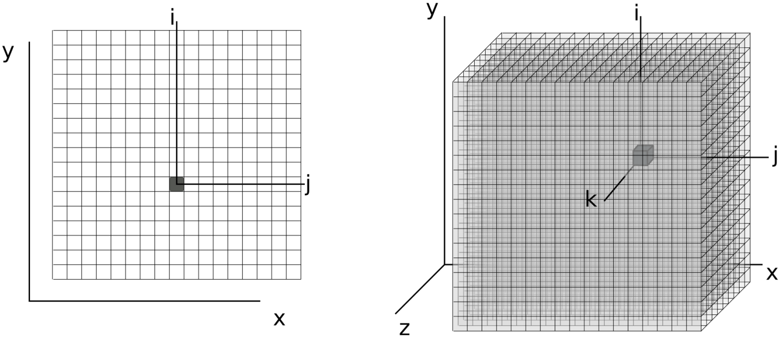


Figure 3: Discrete space in 2 and 3D

Game of life

Game of life

(James Conway)

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

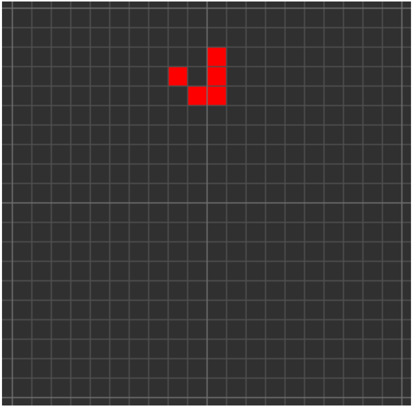


Figure 4: Game of life

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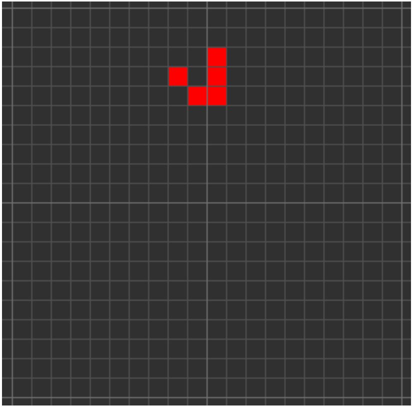

Figure 4: Game of life

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

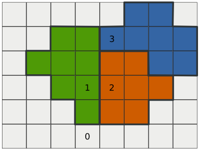

Figure 5: step n

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)

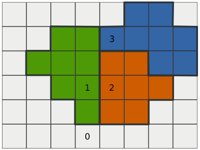

Figure 6: step n

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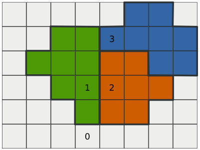

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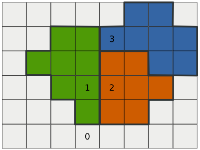

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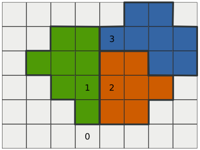

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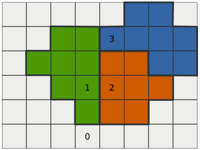

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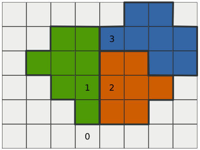

Figure 6: step n

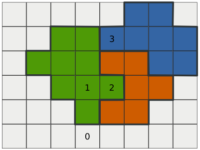

Figure 7: step n+1

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:

$$H = H_V + H_i$$

$$H_V = \frac{\lambda}{2}\sum_{\alpha}(V_\alpha - V_0)^2$$

$$H_i = \sum_{ij,i'j'} J(\tau(ij), \tau(i'j'))$$

$\tau(ij)$ 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

$$\begin{aligned}
J(1,1) &= 0 \\
J(1,1) &= 1 \\
J(2,2) &= 8 \\
J(2,1) &= 16 \\
J(1,0) &= J(2,0) = 32
\end{aligned}$$

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Contact prefered between same type, 1 more so than 2

What happens?

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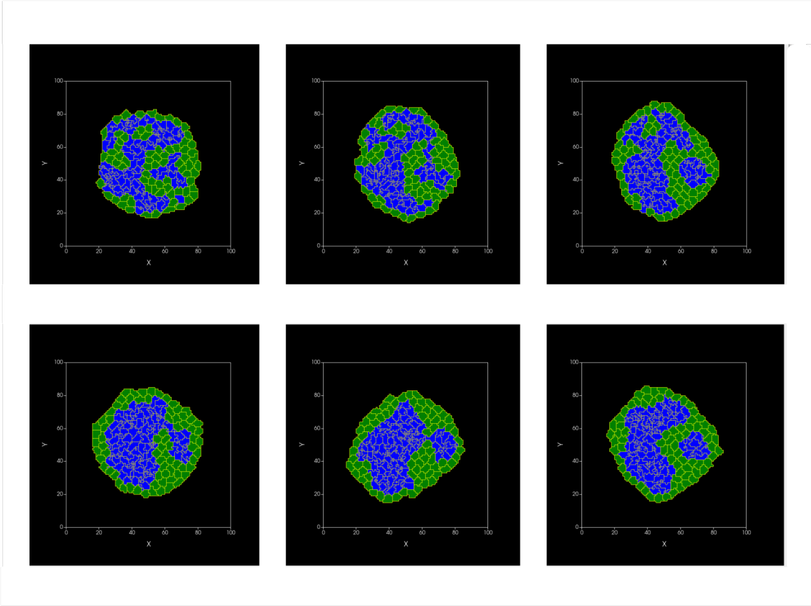

Chemotaxis

Add a term for chemotaxis:

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

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

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

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Figure 9: Dictyostelium Aggregation

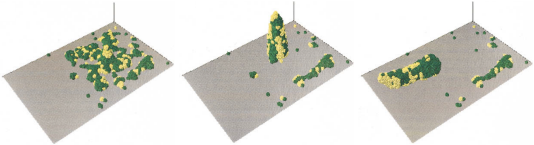

Figure 10: (Savill and Hogeweg 1997)

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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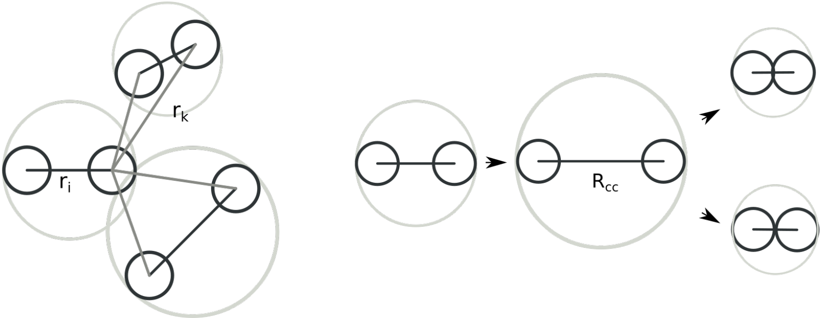

Figure 12: Cells as dipoles Ranft et al. (2010)

- 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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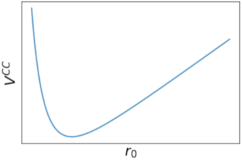

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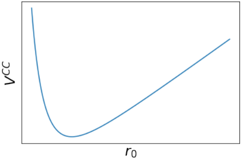

- Self-interaction (growth):

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

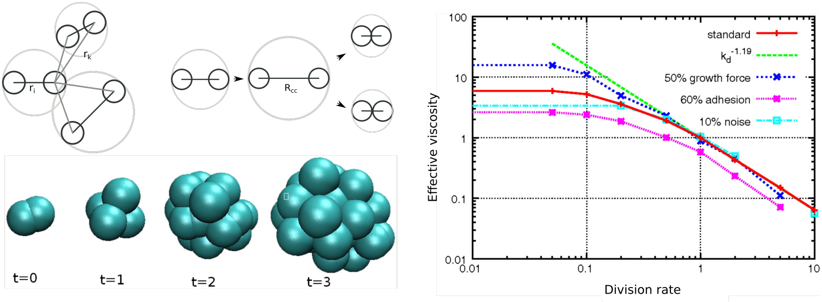

Figure 13: Fluidization (Ranft et al. 2010)

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

Modeling tumors

Modeling tumors

- Spheres with adhesion and repulsion

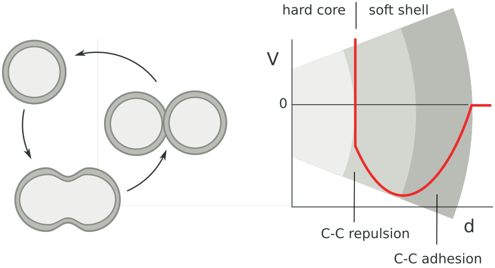

Figure 14: (Drasdo and Höhme 2005)

- 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

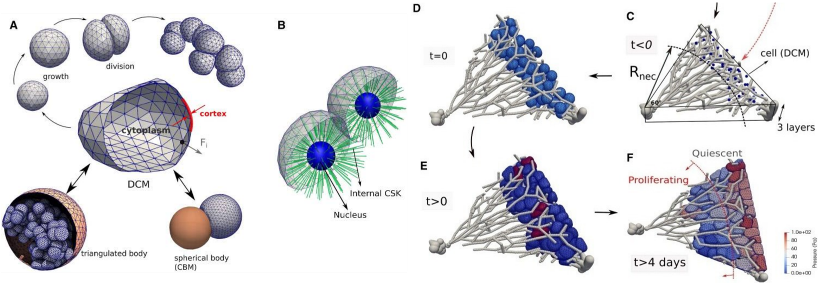

Figure 15: (Van Liedekerke et al. 2020)

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

PhysiCell (Mathematical Oncology)

Cells as polygons

Topology of epithelium

Voronoï tessalation (Honda et al.)

Topology changes in 2D & 3D

Active vertex model

Rosettes

Mechanical Model formulations

Work by Farhadifar et al.

Work by Lisa Manning et al.

Towards rheological models

Existing implementations

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.

Ranft, Jonas, Markus Basan, Jens Elgeti, Jean-François Joanny, Jacques Prost, and Frank Jülicher. 2010. "Fluidization of Tissues by Cell Division and Apoptosis." *Proc Natl Acad Sci U S A* 107 (49): 20863–68. https://doi.org/10.1073/pnas.1011086107.

Savill, Nicholas J., and Paulien Hogeweg. 1997. "Modelling Morphogenesis: From Single Cells to Crawling Slugs." *Journal of Theoretical Biology* 184 (3): 229–35. https://doi.org/10.1006/jtbi.1996.0237.

Van Liedekerke, Paul, Johannes Neitsch, Tim Johann, Enrico Warmt, Ismael Gonzàlez-Valverde, Stefan Hoehme, Steffen Grosser, Josef Kaes, and Dirk Drasdo. 2020. "A Quantitative High-Resolution Computational Mechanics Cell Model for Growing and Regenerating Tissues." *Biomech Model Mechanobiol* 19 (1): 189–220. https://doi.org/10.1007/s10237-019-01204-7.

Zhao, Boyang, Michael T. Hemann, and Douglas A. Lauffenburger. 2016. "Modeling Tumor Clonal Evolution for Drug Combinations Design."