UiO : University of Oslo

Modeling and simulation of multicellular and multiscale systems using the cellular Potts model

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Plan for week 45

Monday 2 Nov (Zoom only)

10:15 - 12:00, **Lecture**: Modelling multicellular systems using the cellular Potts model.

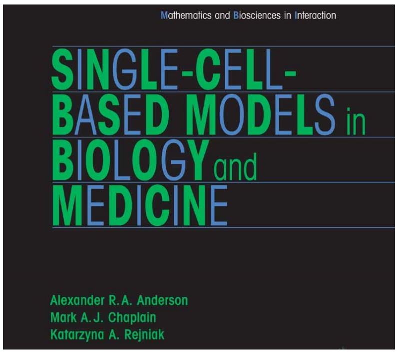
Tuesday 3 Nov (FV414 + Zoom)

12:00 - 13:20, **Hands-on 1**: Getting started with the software Morpheus.

13:40 - 15:00, **Hands-on 2**: Simulation and analysis of simple models.

Pre-assignments

Reading



II.1 Magnetization to Morphogenesis: A Brief History of the Glazier–Graner–Hogeweg Model

James A. Glazier, Ariel Balter and Nikodem J. Popławski

Abstract. This chapter discusses the history and development of what we propose to rename the Glazier–Graner–Hogeweg model (*GGH model*), starting with its ancestors, simple models of magnetism, and concluding with its current state as a powerful, cell-oriented method for simulating biological development and tissue physiology. We will discuss some of the choices and accidents of this development and some of the positive and negative consequences of the model's pedigree.

Installing

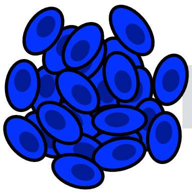
Morpheus

Python
+
Jupyter
Notebooks

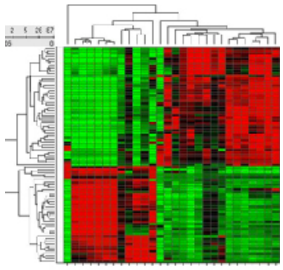
Modeling multicellular systems using the cellular Potts model

Systems biology

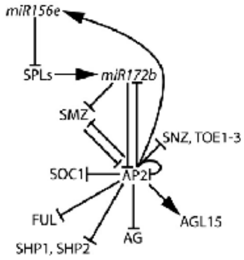
Tissue



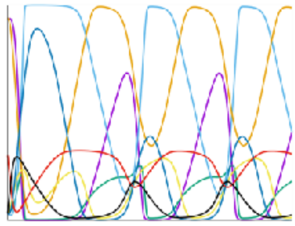
Bulk or single-cell data



Intracellular interactions

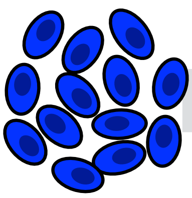


Intracellular simulation

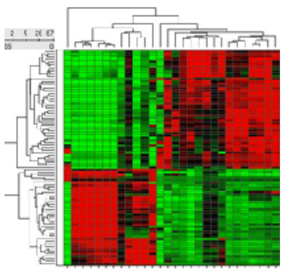


Multicellular systems biology

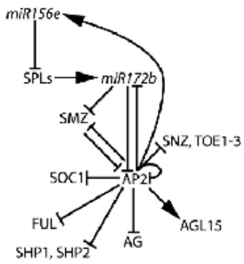
Tissue



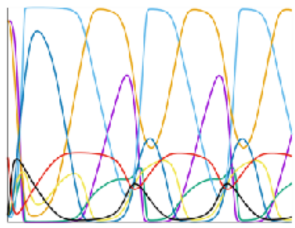
Bulk or single-cell data



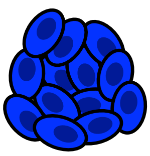
Intracellular interactions



Intracellular simulation

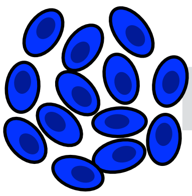


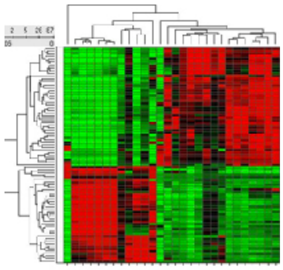
Tissue

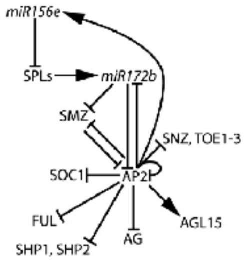


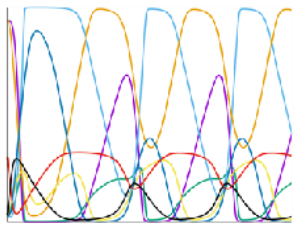
Multicellular systems biology

Tissue | Bulk or single-cell data | Intracellular interactions | Intracellular simulation

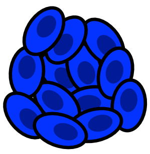


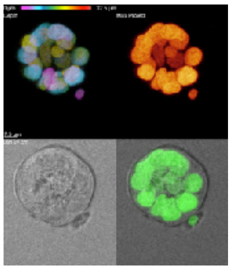






Tissue | Image data

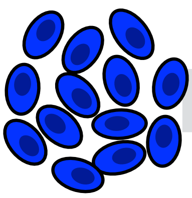


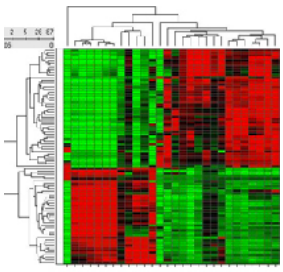


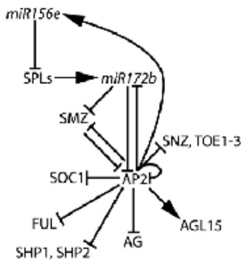
Drost et al, Nature 2015

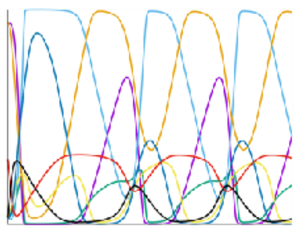
Multicellular systems biology

Tissue | Bulk or single-cell data | Intracellular interactions | Intracellular simulation

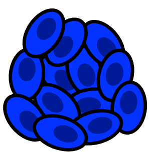


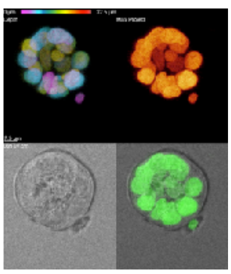




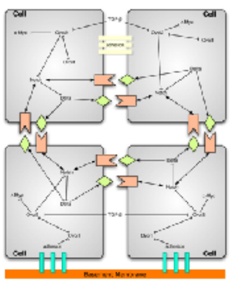


Tissue | Image data | Intercellular interactions



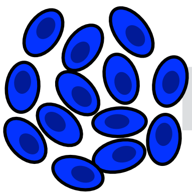


Drost et al, Nature 2015

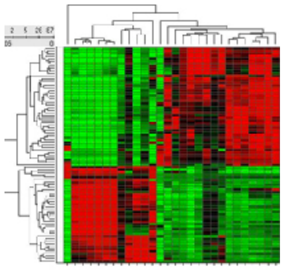


Multicellular Systems biology

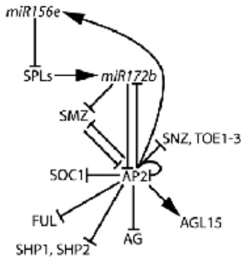
Tissue



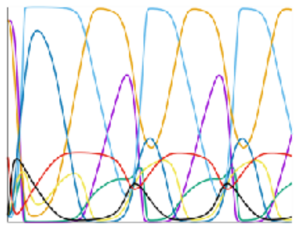
Bulk or single-cell data



Intracellular interactions



Intracellular simulation



Tissue

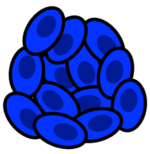
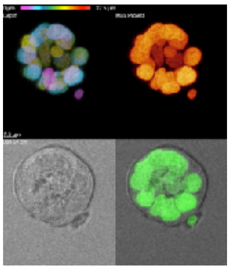
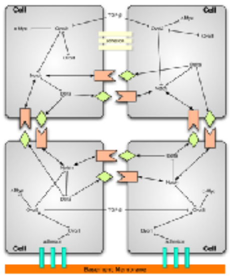


Image data

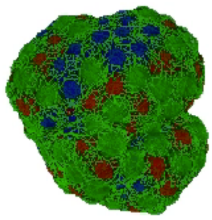


Drost et al, Nature 2015

Intercellular network



Multicellular simulation



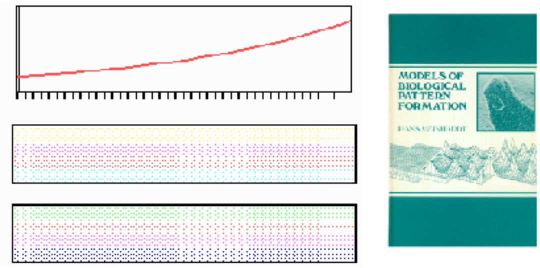
Buske et al., FEBS J 2012

Approaches

for tissue and multicellular modeling

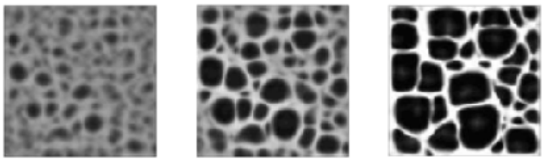
Tissue modeling: continuous approach

Drosophila segmentation



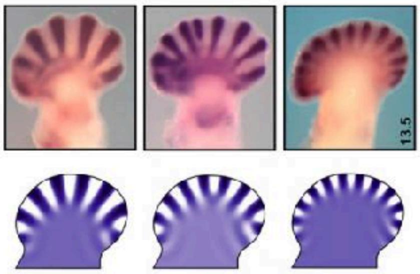
Hans Meinhardt, Models of Biological Pattern Formation 1982
The Algorithmic Beauty of Sea Shells 1998

Vascular patterning



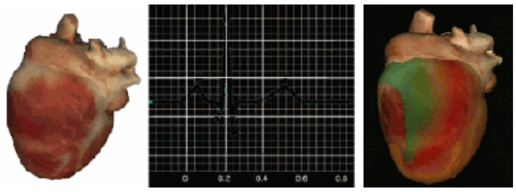
Manoussaki et al., Acta biotheoretica 1996

Limb morphogenesis



Sheth et al., Science 2012

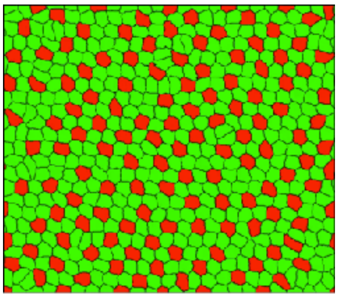
Cardiac physiology



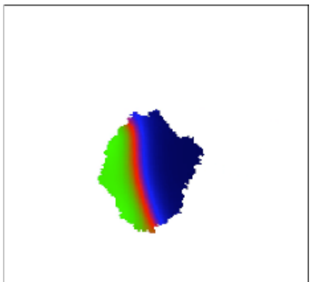
Fenton et al., Scholarpedia 2008

Tissue modeling: discrete / cell-based approach

Lateral inhibition

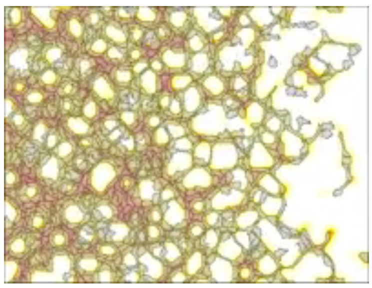


Single cell migration



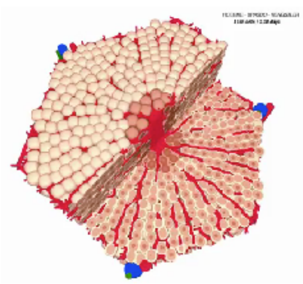
After Maree et al., 2012

Vascular Patterning



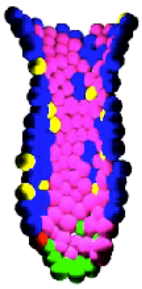
Köhn-Luque et al., 2013

Liver regeneration



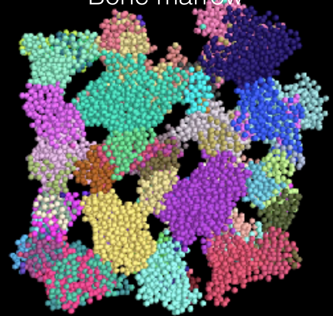
Hoehme et al., PNAS 2010

Intestinal crypt



Buske et al., 2011

Bone marrow



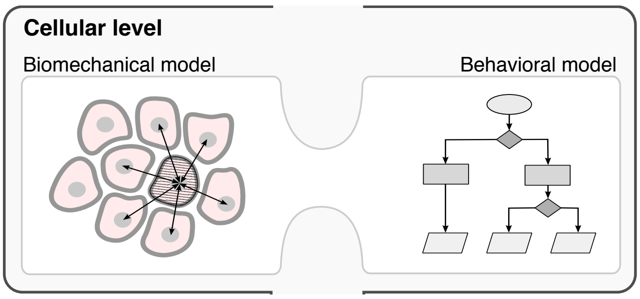
de Back, 2017 (unpublished)

Tissue modeling: discrete approach

- Tissue organization at cellular level
  - spatial structure
  - dynamic changes
- Cellular behavior
  - cell motility
  - cell division
  - cell adhesion
  - cell shape
  - etc.
- Multi-scale coupling
  - intracellular processes
  - extracellular gradients

Cell-based modeling

- Tissue organization at cellular level
  - spatial structure
  - dynamic changes
- Cellular behavior
  - cell motility
  - cell division
  - cell adhesion
  - cell shape
  - etc.
- Multi-scale coupling
  - intracellular processes
  - extracellular gradients



Multi-scale cell-based modeling

- Tissue organization at cellular level
  - spatial structure
  - dynamic changes
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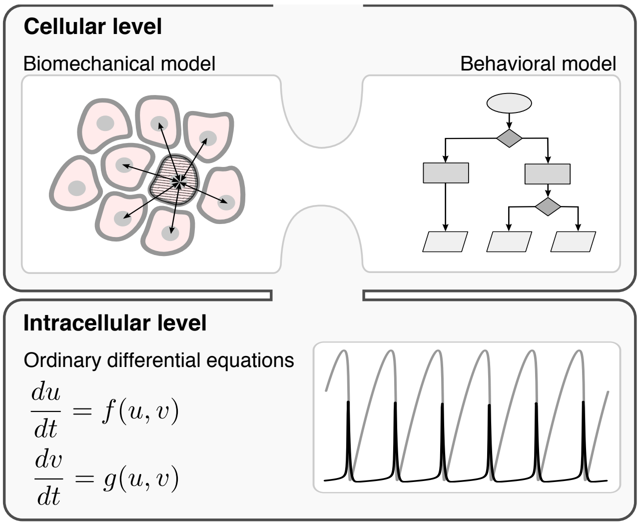

Multi-scale cell-based modeling

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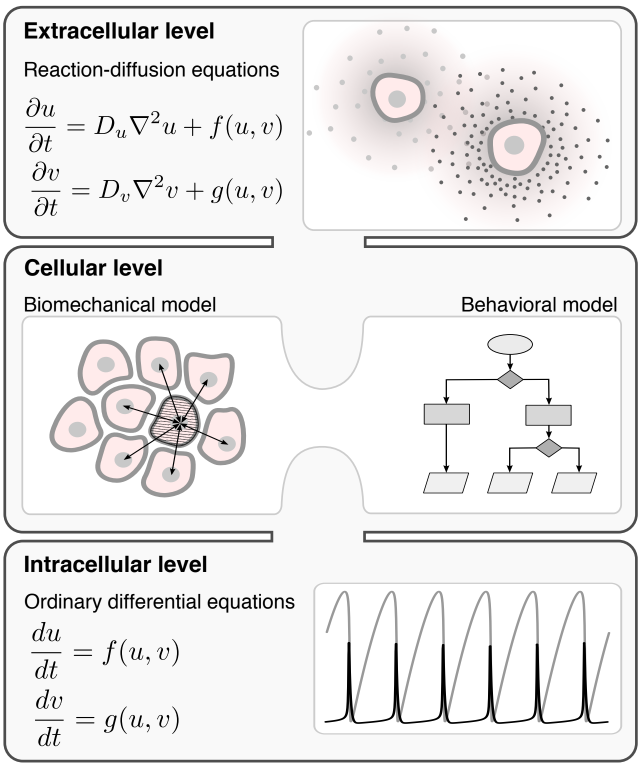
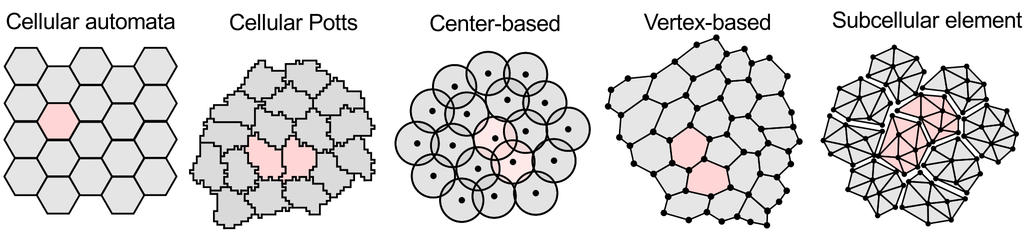


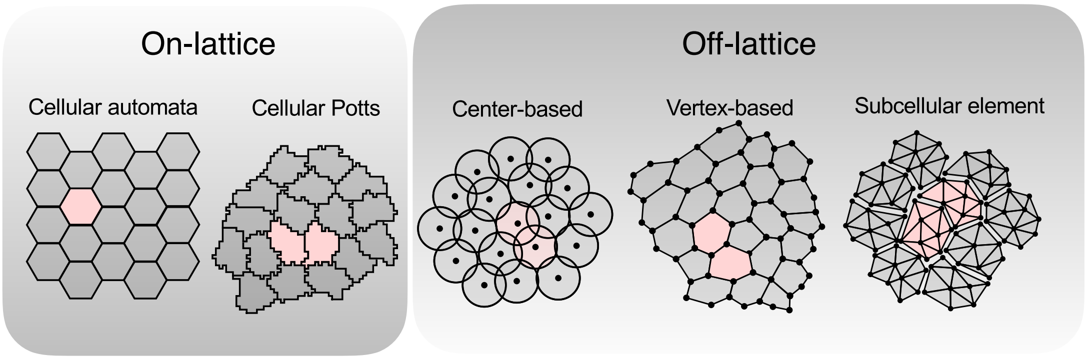
Mathematical and Computational Models

for cell-based modeling

Different cell-based modeling approaches



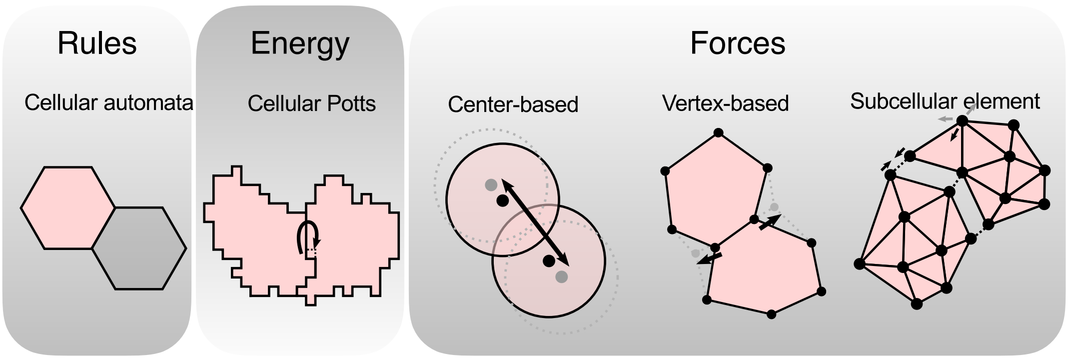
Different cell-based modeling approaches



How are cell spatially represented?

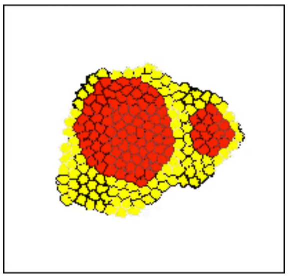
On-lattice   Off-lattice

Different cell-based modeling approaches

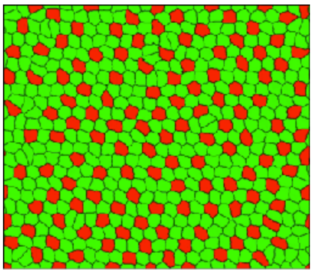


How is cell dynamics modelled?

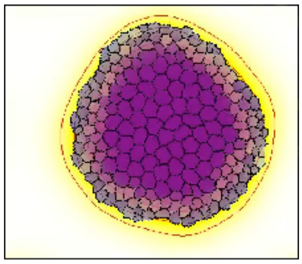
Rule-based   Energy-based   Force-based cell sorting



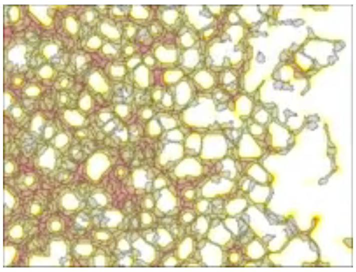
lateral inhibition



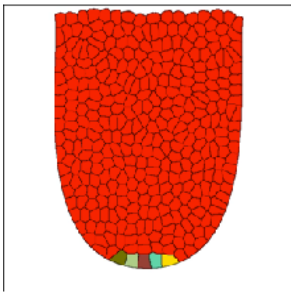
tissue growth



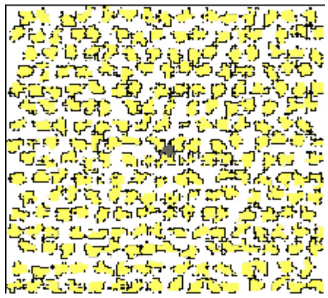
Cellular Potts model



vascular patterning



Stem cells in the intestinal crypt



Social life of Dictoystelium Discoideum

CPM: From Magnetization to Morphogenesis

Ising Model

−	−	+	−	+	−
−	−	−	+	+	−
+	+	−	−	−	+
+	−	+	+	+	−
+	+	−	−	−	−
+	+	−	−	+	−

2 states

$$\mathcal{H}_{\text{Ising}} = -\frac{J}{2} \sum_{(\vec{i},\vec{j})\ \text{neighbors}} \sigma(\vec{i})\sigma(\vec{j})$$

static equilibrium statistics

random initial conditions

Potts Model

1	1	2	2	3	3
1	1	1	2	2	3
3	1	2	3	3	2
3	2	1	1	2	2
2	2	2	3	3	1
1	2	1	1	2	3

q states

$$\mathcal{H}_{\text{Potts}} = J \sum_{(\vec{i},\vec{j})\ \text{neighbors}} (1-\delta(\sigma(\vec{i}),\sigma(\vec{j}))) + \lambda \sum_{\sigma} (v(\sigma) - V_t(\sigma))^2$$

static equilibrium statistics

physically-motivated initial conditions and domain properties

Cellular Potts Model

1	1	1	1	1	2	2	2	2
1	1	1	1	1	2	2	2	2
3	1	1	4	4	4	2	2	2
3	3	4	4	4	4	4	2	2
3	3	4	4	4	4	4	2	2
3	3	4	4	4	4	4	6	2
3	5	5	4	4	4	6	6	6
5	5	5	5	4	6	6	6	6
5	5	5	5	5	6	6	6	6

q states (unique per domain)

$$\mathcal{H}_{\text{CPM}} = \sum_{(\vec{i},\vec{j})\ \text{neighbors}} J(\tau(\sigma(\vec{i})),\tau(\sigma(\vec{j})))(1-\delta(\sigma(\vec{i}),\sigma(\vec{j}))) + \sum_{\sigma} \lambda_{\text{Vol}}(\tau)(v(\sigma) - V_t(\tau(\sigma)))^2$$

kinetics

biologically-motivated initial conditions and domain properties

Glazier et al. Birkhäuser 2007 (chapter II.1)

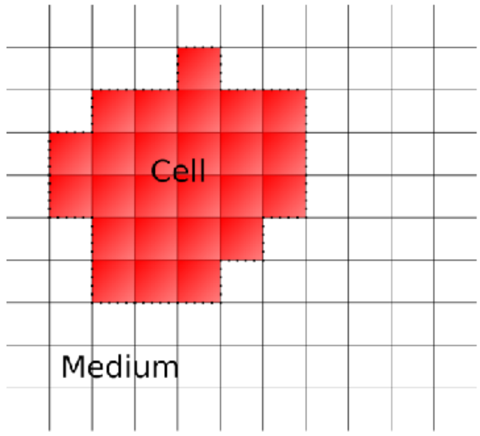
Cellular Potts model - cell size

Cell represented as a lattice domain

energy — actual area

$$H = \sum_{\sigma>0} (a_\sigma - A_\sigma)^2$$

sum over cells — target area



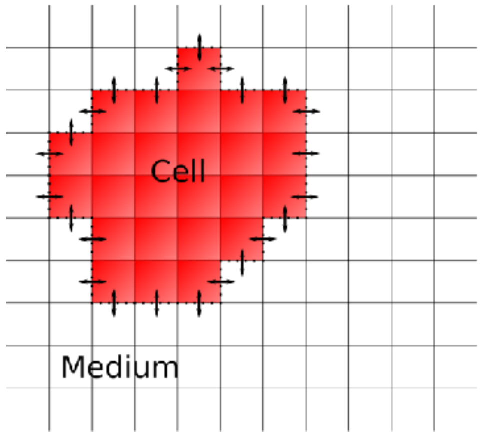
Cellular Potts model - contact energy

energy — contact energy

$$H = \sum_{interfaces} J_{x,y}(1 - \delta_{x,y})$$

sum over interfaces — between domains

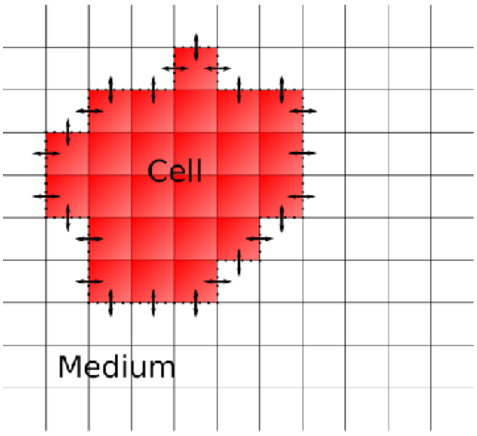
Contact	Cell	Medium
Cell	J_{CC}	J_{CM}
Medium	J_{CM}	—



Cellular Potts model - energy function

energy — adhesion — area constraint

$$H = \sum_{interfaces} J_{x,y}(1-\delta_{x,y}) + \sum_{cells} \lambda_A (a_\sigma - A_\sigma)^2$$



Cellular Potts model - dynamics

Stochastic minimization of energy

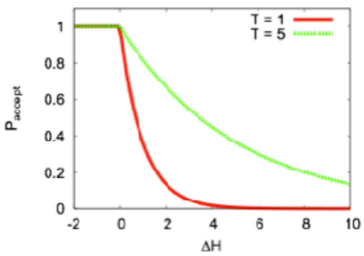
Modified Metropolis algorithm:

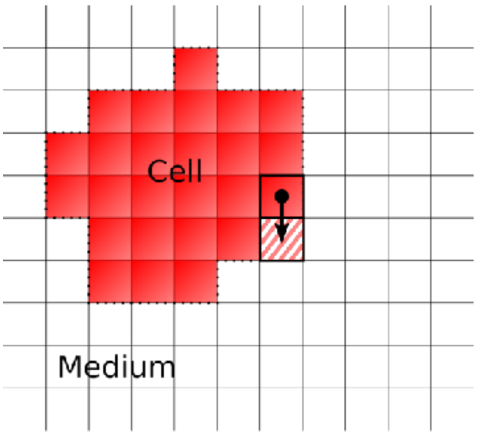
- Pick a random node
- Pick a second random node in neighborhood
- Compute energy difference ΔH is spin is copied:

$$\Delta H = H_{after} - H_{before}$$

- Probabillty to accept copy depends on ΔH:

$$P(\Delta H) = \begin{cases} 1 & \text{if } \Delta H \leq 0 \\ e^{-\frac{\Delta H}{T}} & \text{otherwise} \end{cases}$$





Cellular Potts model - dynamics

Stochastic minimization of energy

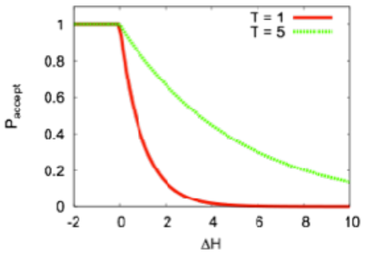
Modified Metropolis algorithm:

- Pick a random node
- Pick a second random node in neighborhood
- Compute energy difference ΔH is spin is copied:

$$\Delta H = H_{after} - H_{before}$$

- Probabillty to accept copy depends on ΔH:

$$P(\Delta H) = \begin{cases} 1 & \text{if } \Delta H \le 0 \\ e^{-\frac{\Delta H}{T}} & \text{otherwise} \end{cases}$$



Cellular Potts model - cell sorting

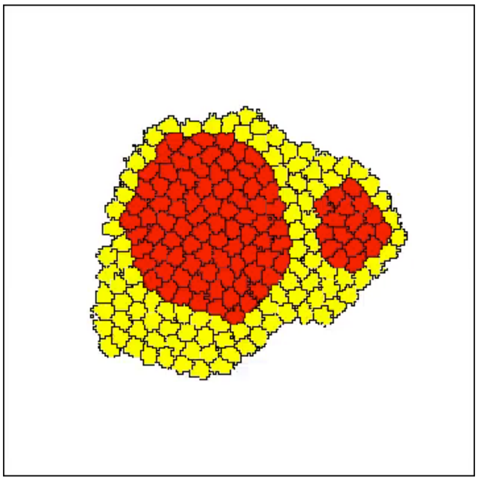
Energy function (Hamiltonian):

energy | adhesion | area constraint

$$H = \sum_{interfaces} J_{x,y}(1 - \delta_{x,y}) + \sum_{cells} \lambda_A (a_\sigma - A_\sigma)^2$$

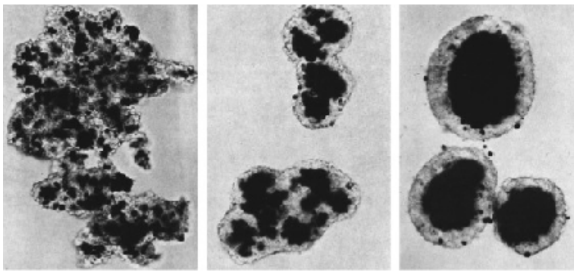
Energy minimization:

$$P(\Delta H) = \begin{cases} 1 & \text{if } \Delta H \le 0 \\ e^{-\frac{\Delta H}{T}} & \text{otherwise} \end{cases}$$



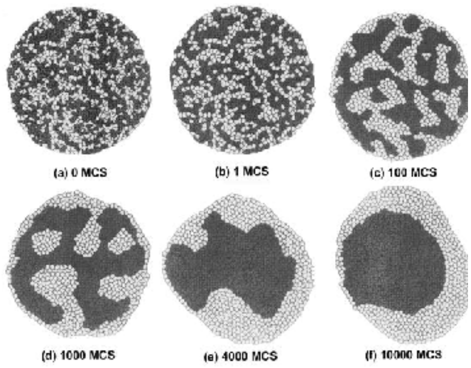
CPM: Modeling Cell Sorting

Experimental Observation



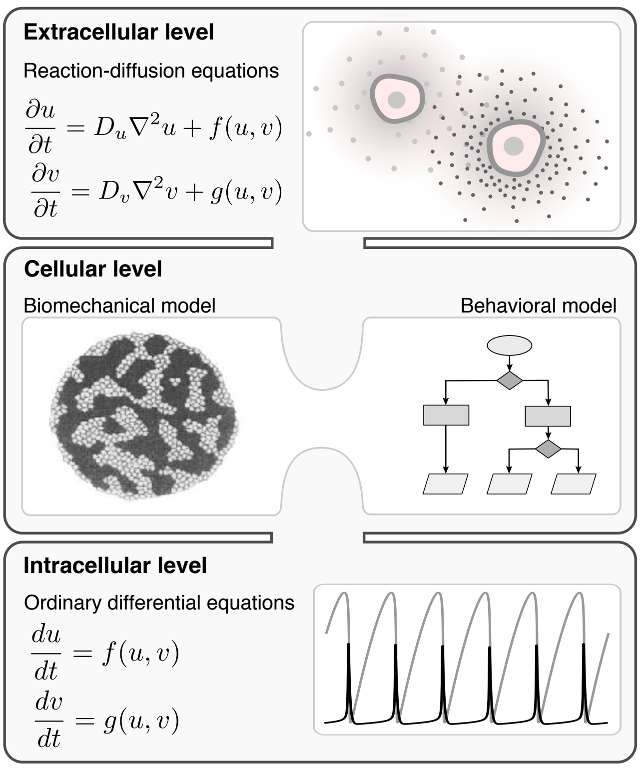
Differential adhesion hypothesis
(Steinberg 1963, Science)

Simulations

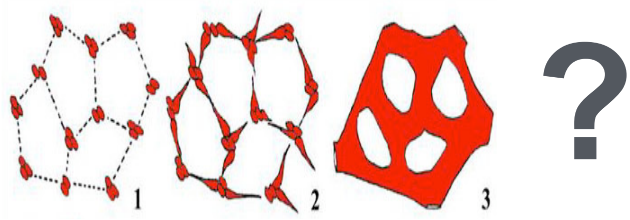


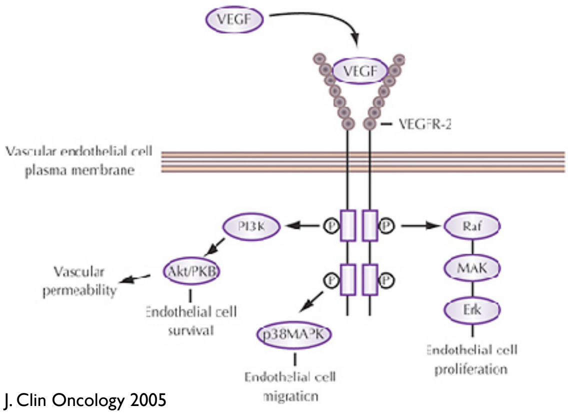
Cell sorting is an activated process
requiring membrane fluctuations
(Graner & Glazier 1992, Phys Rev Lett)

Multi-scale cell-based modeling using CPM

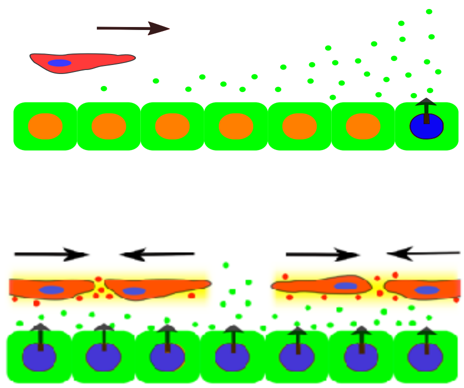


Proposed Mechanism of Vascular Patterning

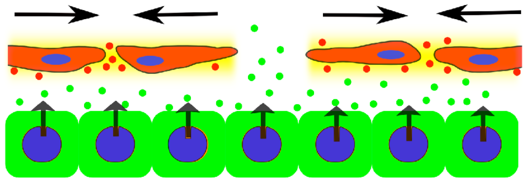




J. Clin Oncology 2005



A hybrid cellular Potts model for vascular patterning



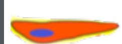
PDE

$$\frac{\partial u}{\partial t} = D_u \Delta u - k_{on} us + k_{off} b - \tau u$$
$$\frac{\partial s}{\partial t} = \gamma - k_{on} us + k_{off} b$$
$$\frac{\partial b}{\partial t} = k_{on} us - k_{off} b,$$

$u \equiv$ unbound VEGF
$s \equiv$ binding sites
$b \equiv$ bound VEGF

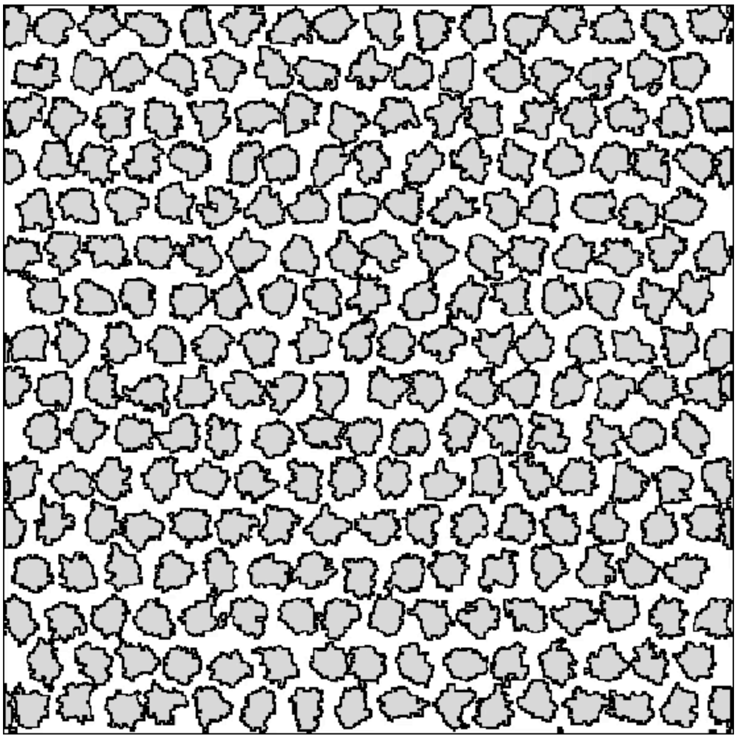
CPM

$$H = \sum_{\sigma > 0} (\lambda_a (a_\sigma - A)^2 + \lambda_p p_\sigma)$$
$$\Delta H_c = \Delta H + \mu(b_{\mathbf{x}} - b_{\mathbf{x}'})$$
$$P(\Delta H_c) = \begin{cases} 1 & \Delta H_c \leq 0 \\ e^{-\Delta H_c} & otherwise \end{cases}$$



Köhn-Luque et al PLoS One 2011
Köhn-Luque et al Phys Biol 2013

A hybrid cellular Potts model for vascular patterning

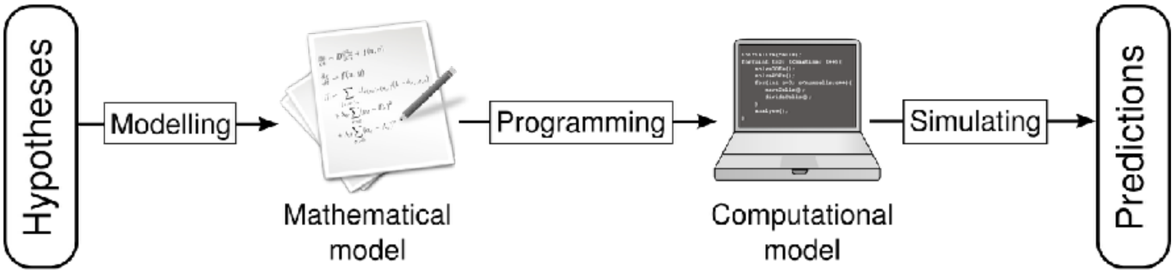


Morpheus
modeling environment for
multicellular systems biology

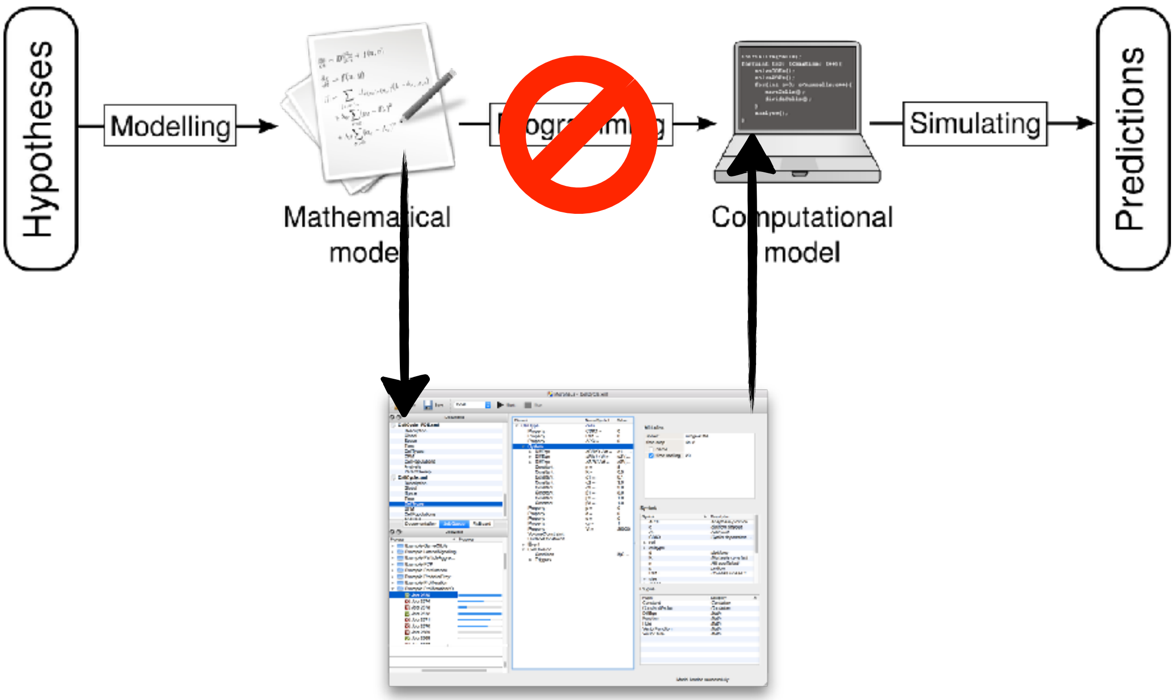
Walter de Back
ContextVision AB

Jörn Starruß
Center for High
Performance Computing

Computational modeling
Workflow



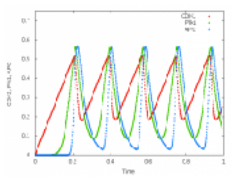
Computational modeling
Without the need for programming



Modeling features

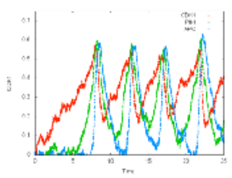
Differential equations

Gene regulatory and signaling networks



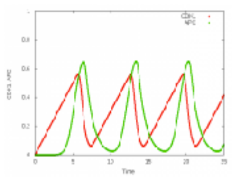
Ordinary differential equations

Euler, Heun, Runge-Kutta, adaptive time-step methods, stiff methods



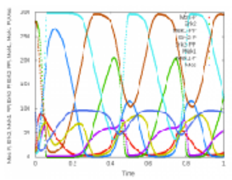
Stochastic differential equations

Heun-Maruyama



Delay differential equations

with constant delays

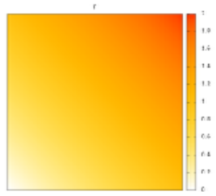


Import models in SBML format

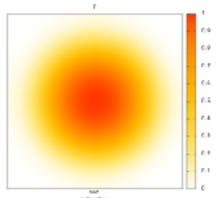
e.g. from BioModels database

Reaction-diffusion systems

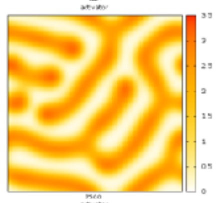
Morphogen gradients and intercellular signaling



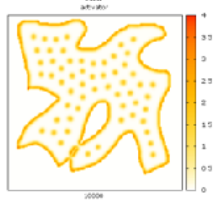
Static gradients
Scalar fields



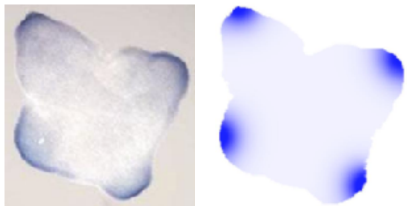
Diffusion
Finite volume method



Reaction-diffusion systems
Operator-splitting method



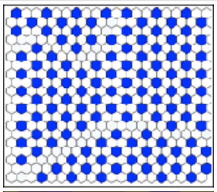
Import domains from images
TIFF format



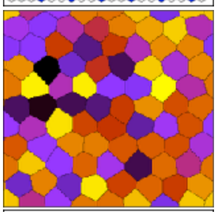
Brusch et al., *Curr Top Dev Biol*, 2014

Cell-based models

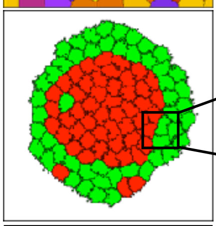
Cell shape, motility and surface mechanics



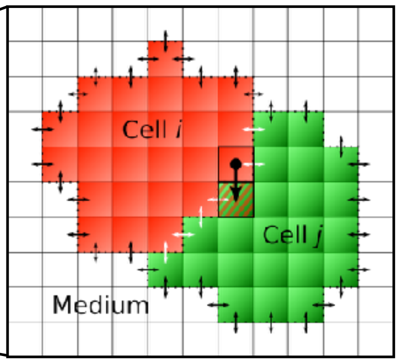
Discrete lattice
regular cell shape



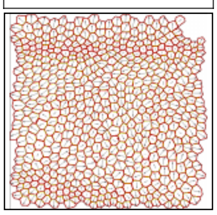
Voronoi tesselations
irregular cell shape



Cellular Potts model
cell shape and motility

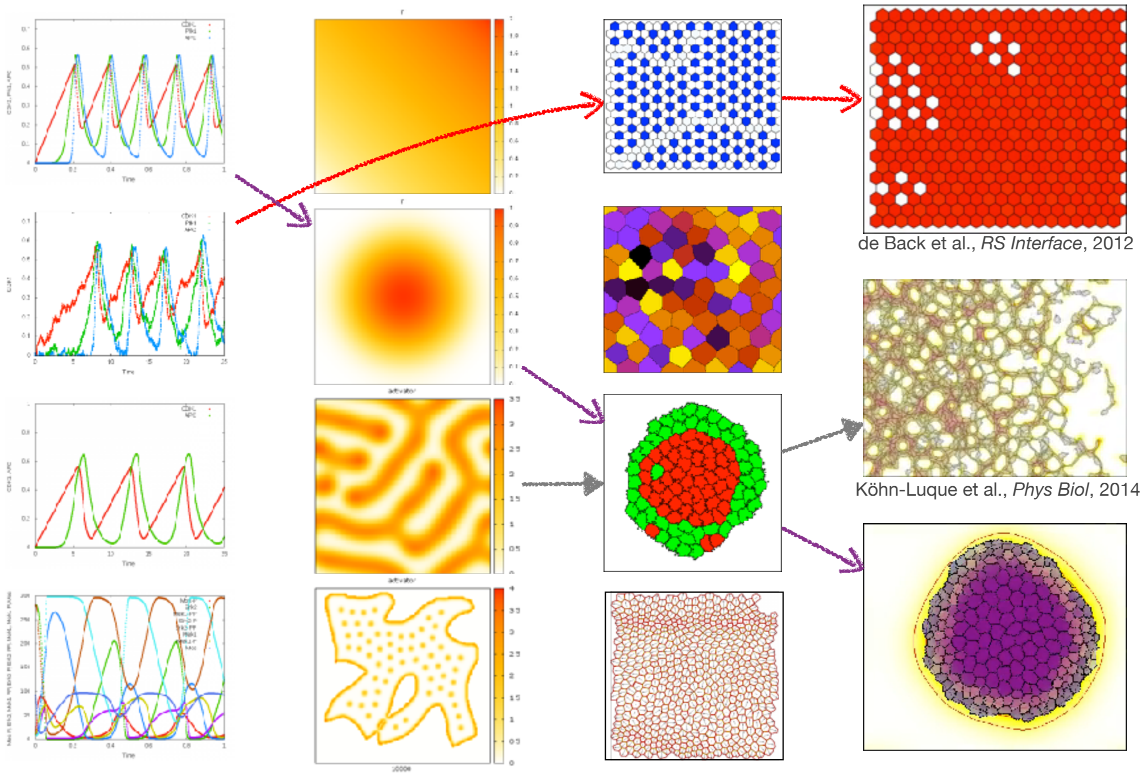


Graner and Glazier, PRL, 1992



Import microscopy images
realistic cell shape

Multi-scale models
Coupling model formalisms

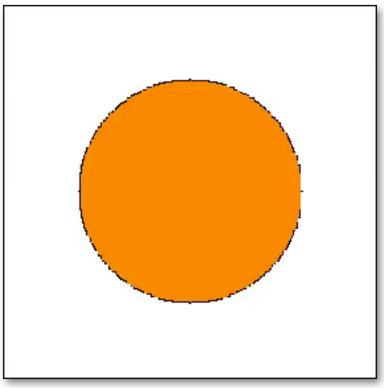


Multi-scale models
Cell cycle example

- Intracellular ODE model for cell cycle dynamics

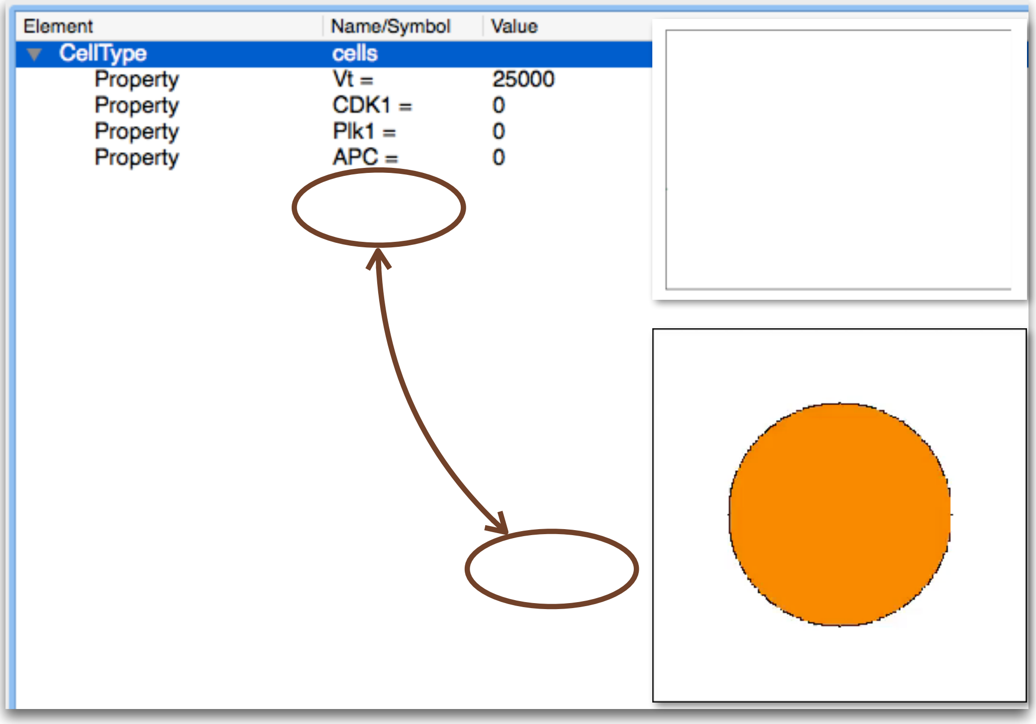
↓

- Cell-based Potts model cell surface mechanics and cell division

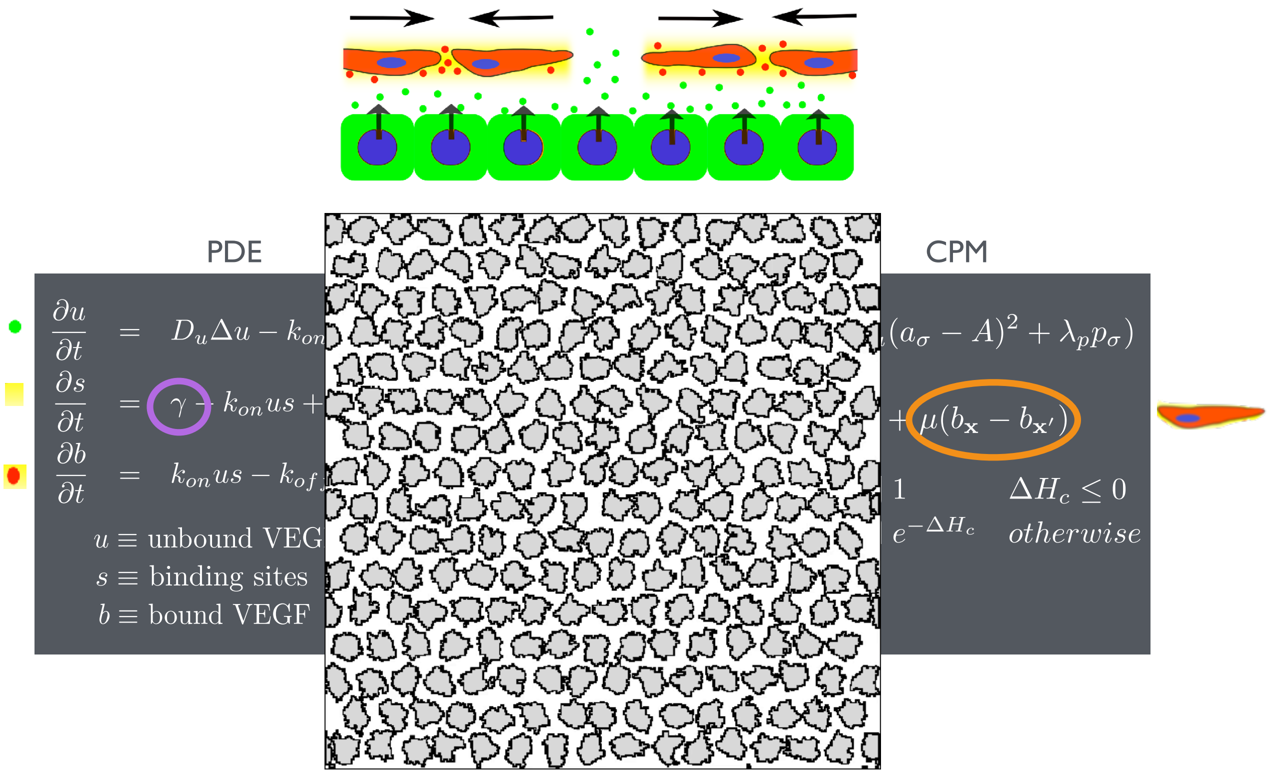


Multi-scale models

Cell cycle example



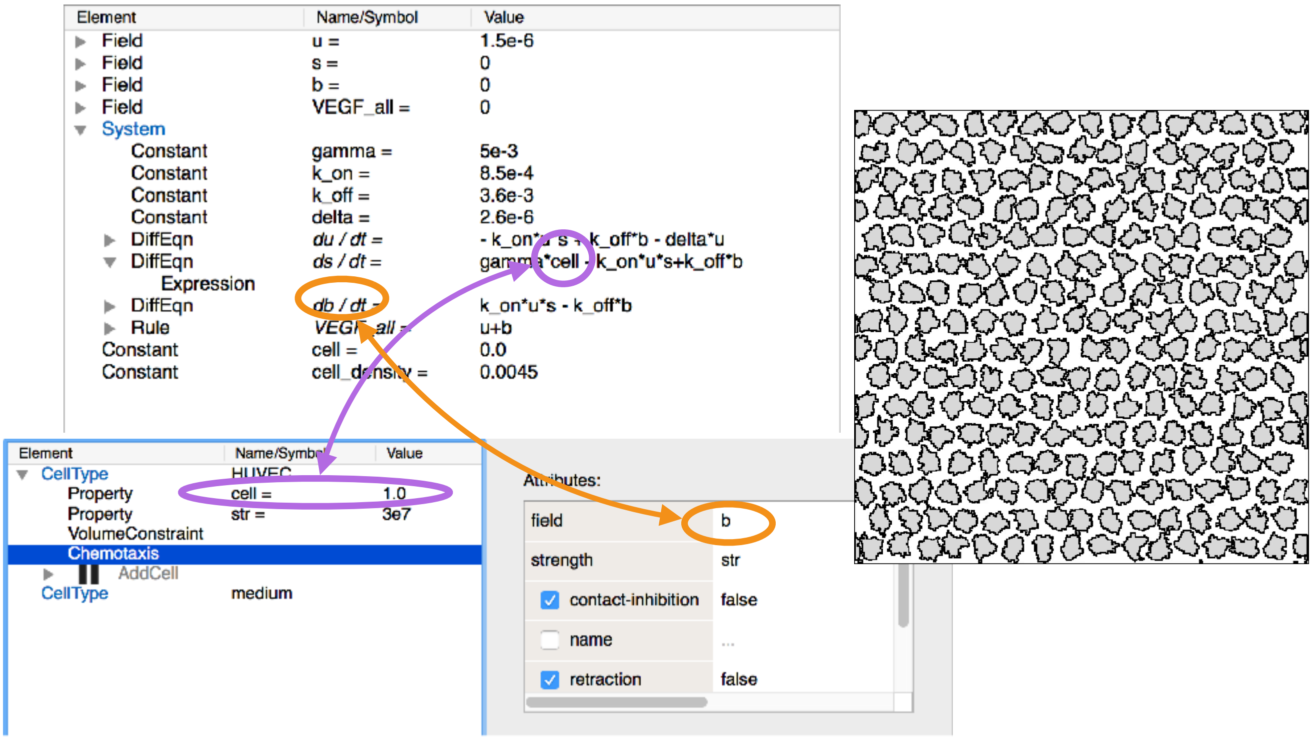
A hybrid cellular Potts model for vascular patterning



Köhn-Luque et al PLoS One 2011

Multi-scale models

Vascular patterning example



Multi-scale models

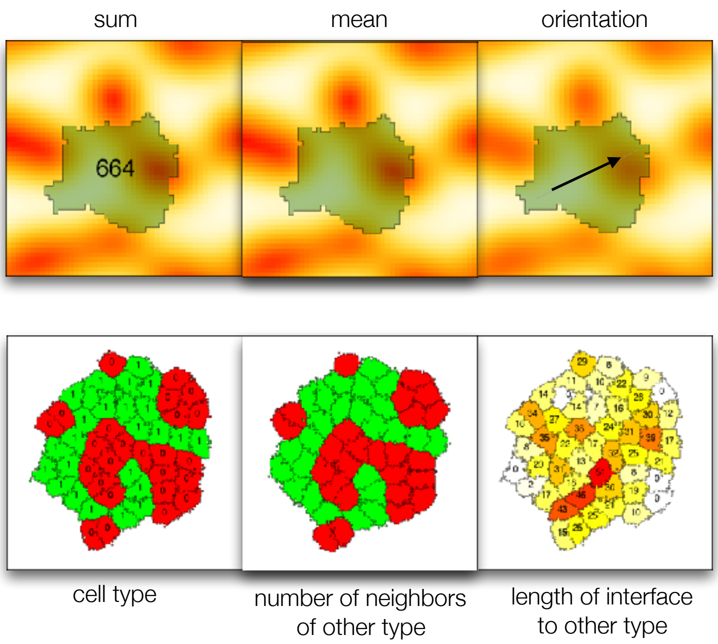
Mapping between different spatial contexts

CellReporter

Collect data within cellular domain

NeighborhoodReporter

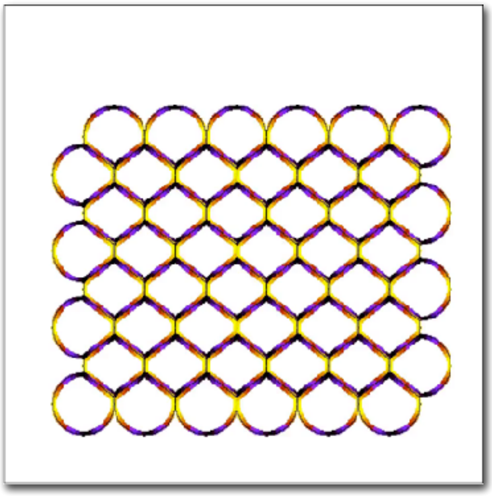
Collect data about cell's microenvironment



Multi-scale models
Mapping data to cell membranes

MembraneProperties

- Scalar field on cell membrane
- Couple to biomechanical properties



Ouchi et al., 2006

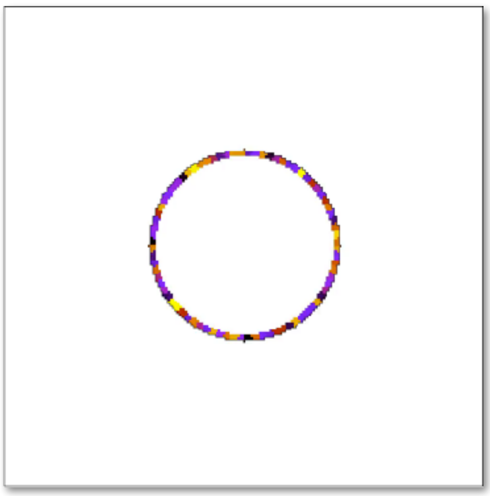
Multi-scale models
Mapping data to cell membranes

MembraneProperties

- Scalar field on cell membrane

+ System

- Reaction-diffusion on membrane

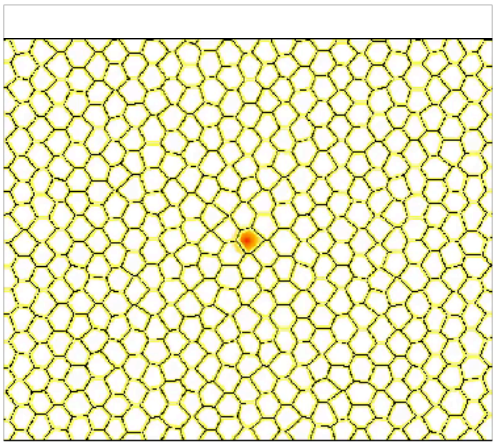


Multi-scale models
Mapping data to cell membranes

MembraneProperties
- Scalar field on cell membrane

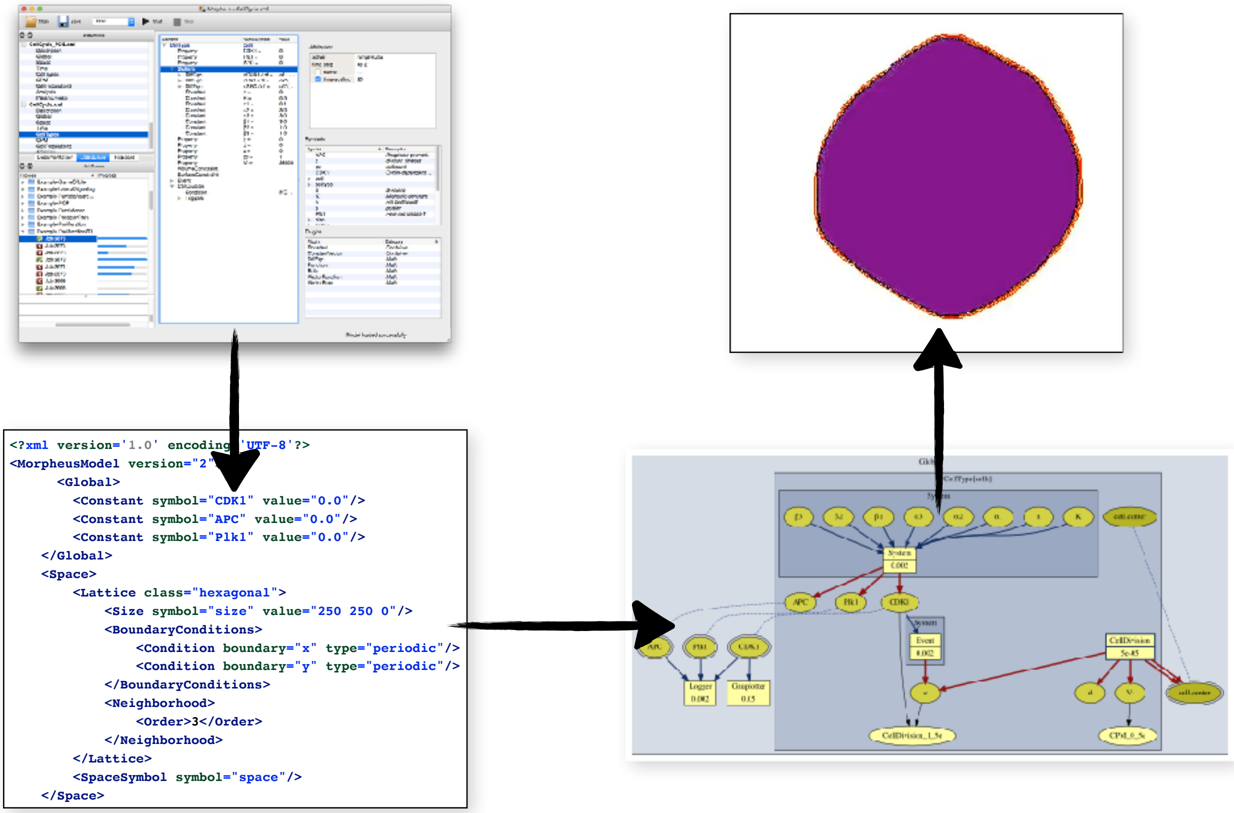
+ System
- Reaction-diffusion on membrane

+ NeighborhoodReporter
- Modeling cell-cell signaling via membrane-bound ligands/receptors

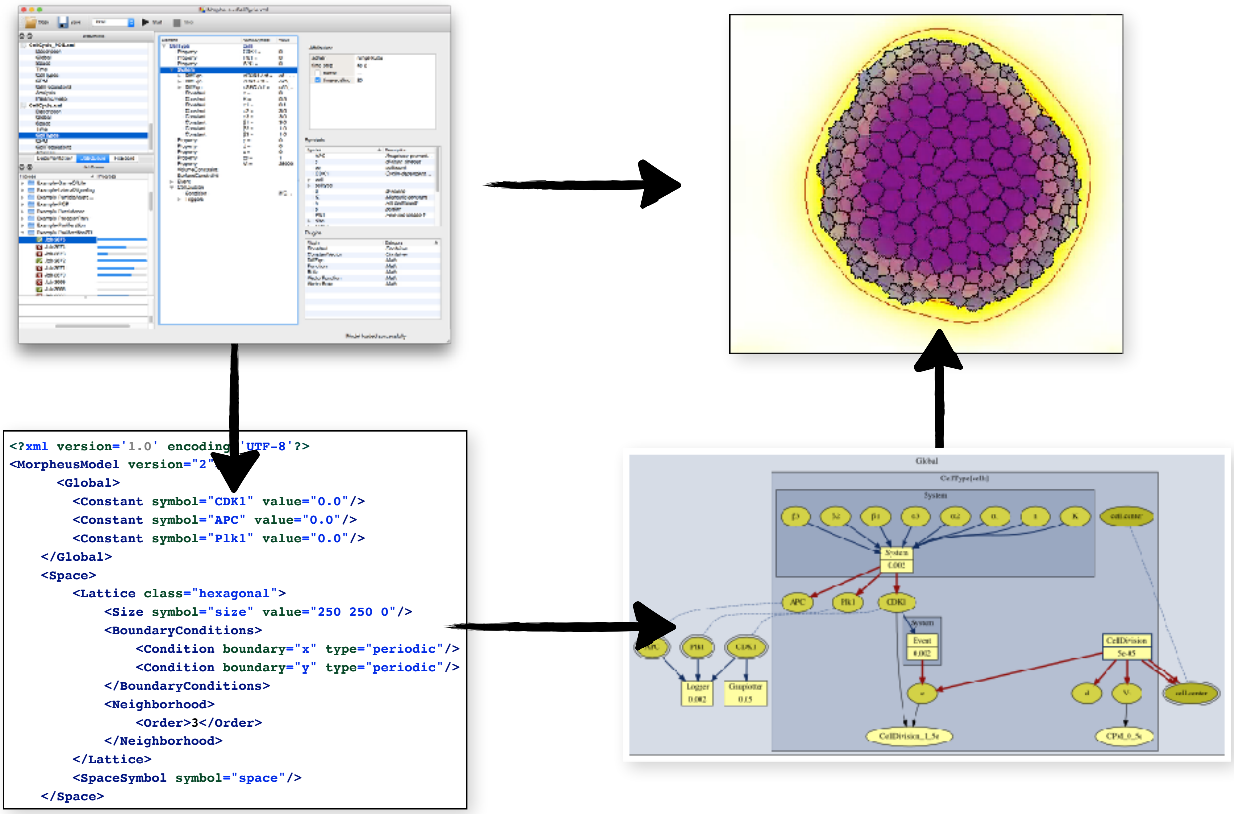


Automation and model integration

Convert mathematical models into simulations



Convert mathematical models into simulations



Plan for week 45

Monday 2 Nov

10:15 - 12:00, **Lecture**: Modelling multicellular systems using the cellular Potts model.

Tuesday 3 Nov

12:00 - 13:20, **Hands-on 1**: Getting started with the software Morpheus.

13:40 - 15:00, **Hands-on 2**: Simulation and analysis of simple models.

Cellular Potts model

Energy function (Hamiltonian):

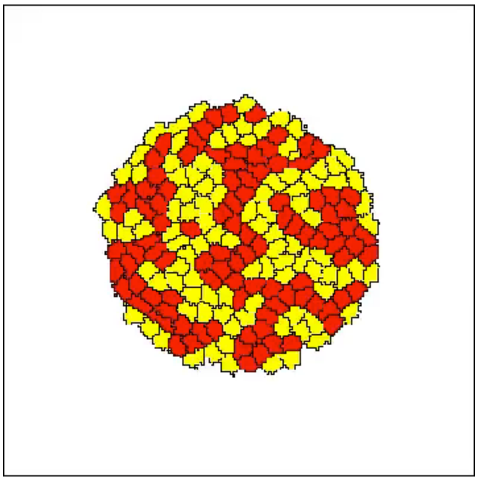
energy — adhesion — area constraint

$$\mathcal{H} = \sum_{ij}\sum_{i'j'} J_{\tau(\sigma_{ij}),\tau(\sigma_{i'j'})}\left(1-\delta_{\sigma_{ij},\sigma_{i'j'}}\right) + \sum_{\sigma}\lambda\left(a_\sigma - A_{\tau(\sigma)}\right)^2$$

Parameters: J_{yy}, J_{rr}, $J_{ry}=J_{yr}$, $J_{ym}=J_{my}$, $J_{rm}=J_{mr}$, λ, $A_y=A_r$

Modified Metropolis algorithm for energy minimization:

$$P(\Delta H) = \begin{cases} 1 & \text{if } \Delta H \leq 0 \\ e^{-\frac{\Delta H}{T}} & \text{otherwise} \end{cases}$$



UiO : University of Oslo

Hands-on session 1:
Getting started with Morpheus

Alvaro Köhn-Luque
alvaro.kohn-luque@medisin.uio.no
Twitter: *@AlvaroKohn*

Department of Biostatistics
Oslo Centre for Biostatistics and Epidemiology
Faculty of Medicine
University of Oslo

Goals for hands-on session 1

1. Check out the GUI and run example models
2. Understand and edit the main components of a model
3. Construct a simple ODE model, export and visualize the data
4. Build a simple CPM model and visualize cells
5. Combine these models to create a multi-scale model.

UiO : University of Oslo

Hands-on session 2:
Simulation and analysis of simple models

Alvaro Köhn-Luque
alvaro.kohn-luque@medisin.uio.no
Twitter: *@AlvaroKohn*

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Oslo Centre for Biostatistics and Epidemiology
Faculty of Medicine
University of Oslo

Goals for hands-on session 2

1. Select parameters for a parameter sweep analysis
2. Specify parameter ranges
3. Run a parameter sweep
4. Visualize sets of simulation results from a parameter sweep
5. Use a python notebook for further analysis