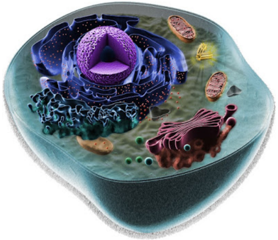
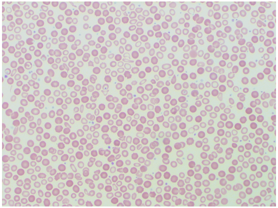
Stochastic modeling for the single cell and the cell population: considerations for data-driven methodologies





Stefan Engblom

Div of Scientific Computing, Dept of Information Technology, Uppsala University

Systems Biology Seminar, Stuttgart, Germany, November 7th, 2019

Outline

Intro: data for inspiration & the modeling challenge

1. Computational modeling...

2. ...numerical analysis

3. Worked examples

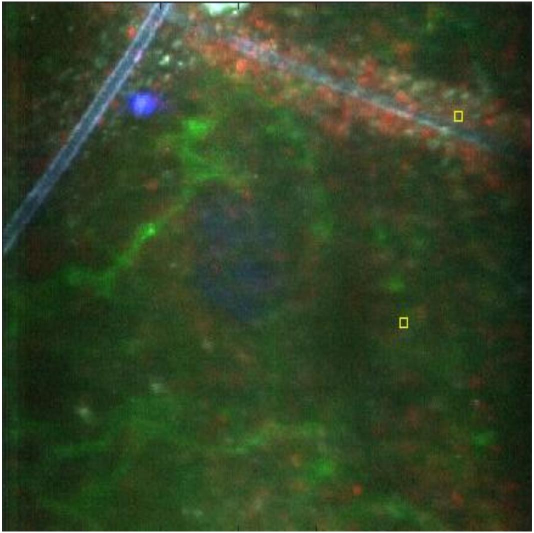
Summary

Joint work with and/or input from:

- **Mia Phillipson**, **Gustaf Christoffersson**, **Femke Heindryckx** @ Medical Cell Biology, Uppsala university
- **Ruth Baker**, **Dan Wilson** @ Math Institute, University of Oxford
- **Augustin Chevallier** @ ENS Cachan/INRIA Sophia Antipolis
  Jonas R. Umaras @ Scientific computing, Uppsala university

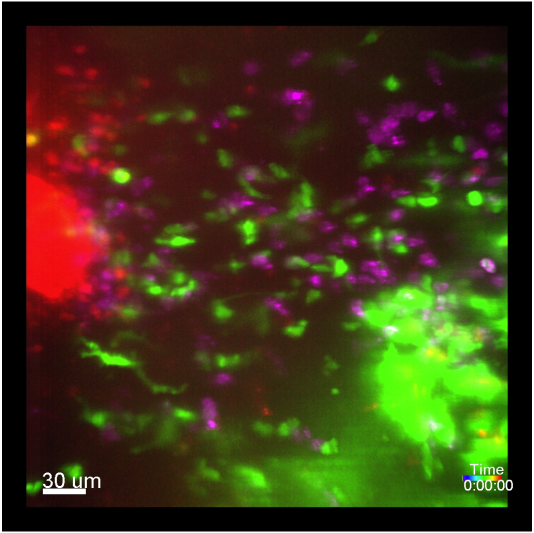
Wound healing around transplant

Recruitment and coordination of white blood-cells



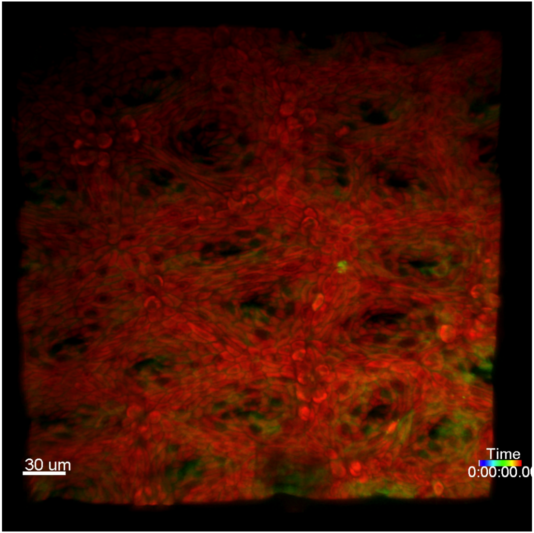
Migrating cells

Sensing gradients (lactic acid)



Colon crypts

Stem cells coordination in a noisy environment



Quorum sensing

Synthetic circuit *in vivo* from Danino, *et al.*, Nature 463, 2010

The modeling challenge

"How to think"

Aim: **realistic** and **useful** computational models of populations of living cells.

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"Useful" (1) explanatory (incl. emergent behavior), (2) test hypotheses, (3) predictive value, (4) help to build an argument in cases where many factors are unknown

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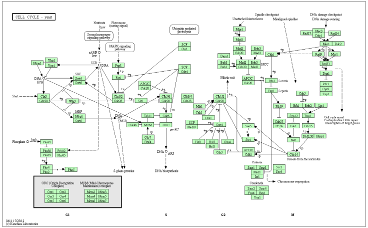
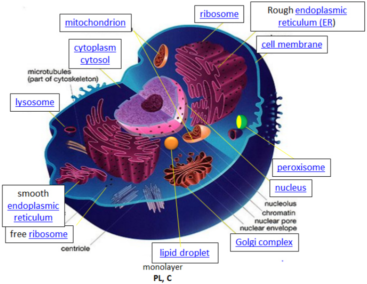
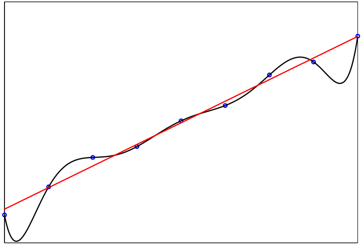
(1) is about modeling consistency & power, (2)+(3)+(4) mainly about being able to incorporate data *and* about simulation performance

Risk of over-modeling

"...help to build an argument in cases where many factors are unknown..."







Caution:

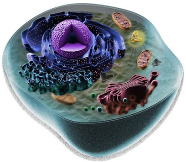
- *really* detailed, or,
- *imaginary* accuracy, or,
- just a plain overfit?

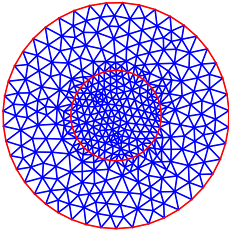
Rest of the talk

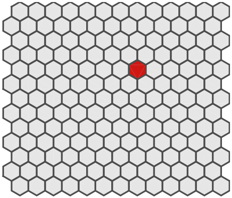
1. Computational modeling: aim for a single scalable framework
2. Analysis in that framework: propagation of uncertainties & errors
3. Illustrations

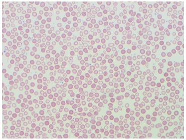
Computational modeling

inner-outer idea





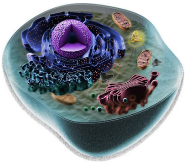
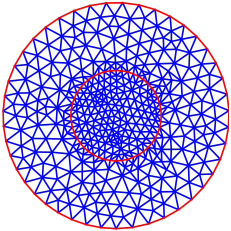
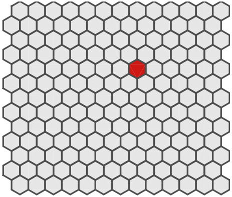
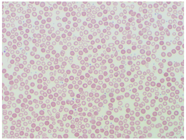




Immediate idea: one type of model describing an individual cell ("inner scale"), coupled together with a population level model ("outer scale").

Computational modeling

inner-outer idea

Immediate idea: one type of model describing an individual cell ("inner scale"), coupled together with a population level model ("outer scale").

Challenge: the aim is a single (analyzable) framework. So: {inner workings of singel cells, sensatory input/output, extracellular space, population mechanics, ...} — also *fast*!

A single framework

Properties

Real-world property	Model implication
"noisy"	stochastic
species discreteness	discrete state
spatial inhomogeneous	grid-based

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The RDME

-A spatial continuous-time Markov chain stand out as a promising alternative. This is the Reaction-Diffusion Master Equation, (a kind of "discretized SPDE").

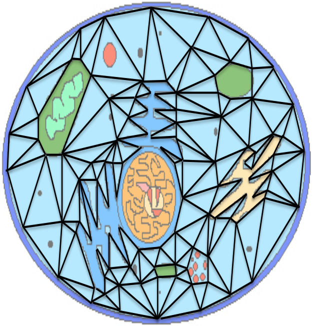
The idea 1

inner scale: RDME

Inside a cell, reactions and diffusion of various molecules take place.

The rates for these events determines *what* happens and *when* in a stochastic, event-driven simulation.

repeat
  pick a random number
  sample what happens and when
  execute this event
until done



www.urdme.org

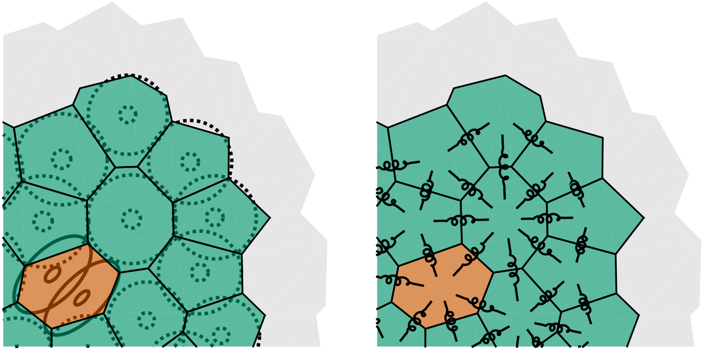
A single framework?

-Cells are also discrete noisy objects, occuping space. Is there a "cell-population RDME"?

-Differences: cells move due to (1) mechanics/pushing, (2) active movements/crawling, and (3) experience adhesion.

The idea 2

outer scale



Cellular pressure, propagated by a connecting spring model. The “flow” of cells is driven by a gradient in this pressure (Darcy’s law).

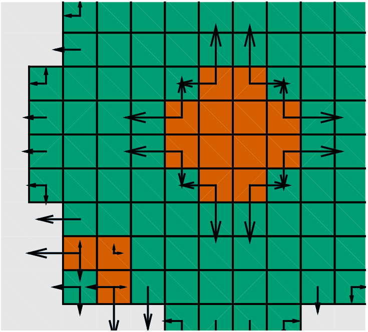
The idea 2

outer scale: DLCM

From three basic assumptions:

1. thermal movements are ignored
2. rapid equilibrium of pressure
3. movements only into less crowded voxels

one derives a (discrete) Laplacian with certain BCs and source terms. Hence rates... hence events in continuous time.



"Discrete Laplacian Cell Mechanics" (DLCM).
"Darcy's Law Cell Mechanics"...

Coupling of scales

Observation #1: since both the inner scale and the outer scale are formed in continuous time, there is *one and only one* way of correctly coupling them together.

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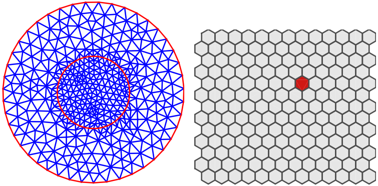
Observation #2: the two types of models can be expected to take place at different temporal scales. *Approximation:* evolve the inner scales one step in time (e.g., in parallel), then connect at the outer scale.



-*In fact*, one can think of all sorts of computational tricks like this. Often: accept a small(?) error for computational efficiency.

Analysis message

Terms & conditions

Want to use these models when any combination of

- stochasticity
- nonlinearity
- species discreteness
- spatial inhomogeneities

makes a difference. The model itself is therefore likely going to be sensitive to perturbations in any of the above.

$\Longrightarrow$ A computational framework should allow for error estimates of useful approximations.

A priori

Long story, but short

Notation: $\mathbb{X}_{ij}$ =#molecules of species i in voxel j (RDME, but a similar notation for the DLCM works too), $\|\mathbb{X}\|^2 \equiv \sum_{i,j} \mathbb{X}_{ij}^2$.

A priori

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$\Longrightarrow$ *a priori*: with suitable initial data and under certain assumptions on the model formulation and the rates, one can show that the problem is strongly well-posed, i.e., $\mathbb{X}$ exists and behaves well.

- $\mathbb{E}[\sup_{s \in [0,t]} \|\mathbb{X}(s)\|^p]$ bounded, any $p \geq 1$
- if $\mathbb{X}(0) = \mathbb{Y}(0)$ a.s., and if $\mathbb{Y}(t)$ is obtained by δ-perturbing the rate intensities ($r \to (1 \pm \delta)r$), then

$$\lim_{\delta \to 0} \mathbb{E}[\|\mathbb{X}(t) - \mathbb{Y}(t)\|^2] = 0.$$

Analysis: Multiscale variable splitting

Set-up: ϵ, h

Consider a separation of scales:

- species are either abundant $\sim \epsilon^{-1}$, or appear in low copy numbers ~ 1
- rate constants are either fast ~ 1, or slow ϵ

$\Longrightarrow$ rescaled variable $\bar{\mathbb{X}}(t) \sim 1$.

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Multiscale splitting methods:

"Hybrid", $\bar{\mathbb{Y}}(t)$ all stochastic processes driving an abundant species are replaced with mean drift terms, a "deterministic-stochastic hybrid"

"Numerical", $\bar{\mathbb{Y}}^{(h)}(t)$ discrete step h; low copy number variables are first simulated in $[t, t+h)$ letting abundant species be frozen at time t, next abundant species are integrated in $[t, t+h)$

Analysis of errors

Results

For certain explicit exponents (u, v)...

Multiscale error

Under certain assumptions,

- $\mathbb{E}[\|\bar{\mathbb{Y}}(t) - \bar{\mathbb{X}}(t)\|^2] = O(\epsilon^{1+v} + \epsilon^{1/2+v/2+u})$

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Time-discretization error

Under the same assumptions, then if the processes are bounded,

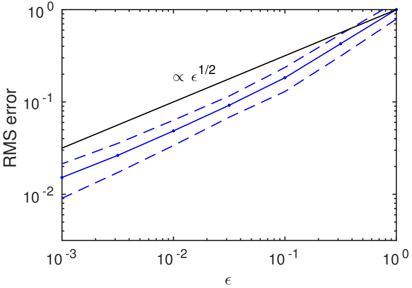
- $\mathbb{E}[\|\bar{\mathbb{Y}}^{(h)}(t) - \bar{\mathbb{Y}}(t)\|^2] = O\left(h(\epsilon^{2u} + \epsilon^{u+v})\right) + O\left(h^2\epsilon^{2v}\right)$

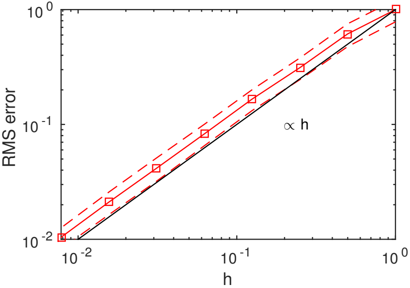
Example: catalytic process

"Stress test" of theory

$(A, C) \sim \epsilon^{-1}$, $(B, D) \sim 1$, diffusion$_{A,C} \sim \epsilon$, diffusion$_{B,D} \sim 1$.

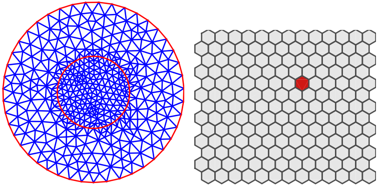
$$\begin{array}{lcl}
A + B \xrightarrow{kAB} C + B & \qquad & A \underset{b_a}{\overset{\epsilon d_a A}{\rightleftharpoons}} \emptyset \\
C + D \xrightarrow{kCD} A + D & \qquad & B \underset{b_b}{\overset{d_b AB}{\rightleftharpoons}} \emptyset \\
B + B \underset{k_d D}{\overset{k_b B(B-1)}{\rightleftharpoons}} D & &
\end{array}$$





Proposed modeling framework

RDME & DLCM



Outer scale DLCM, pressure-driven (passive) cellular movements

Inner scale ODEs, SDEs, or the RDME for the highest resolution

-*Clearly doable:* analyze an inner/outer RDME/DLCM split-step method following the outlined RDME theory.

Cellular communication: Notch Delta

Classical model from Coller *et al.* J. theor. Biol. 183, 1996

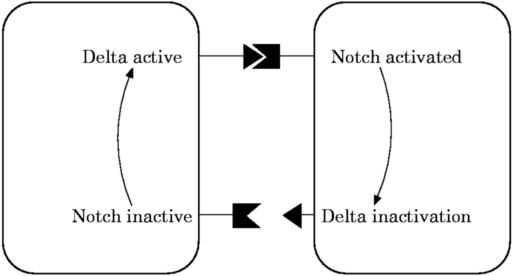
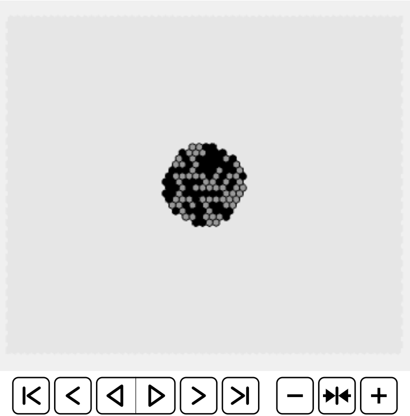


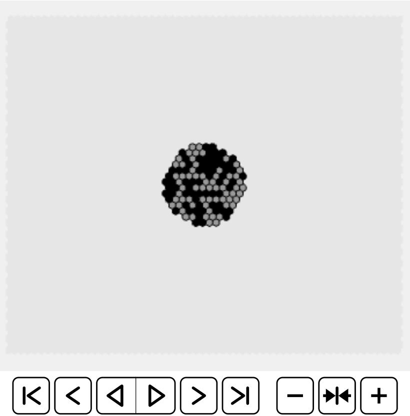
FIG. 1. Diagrammatic representation of the effective feedback loop between Notch and Delta in neighbouring cells. Details of the Notch signalling pathway are omitted for clarity. *Key*: Delta; Notch.

-One cell develops high Notch, the other low Notch (black/white patterning).

Cellular communication: Notch Delta

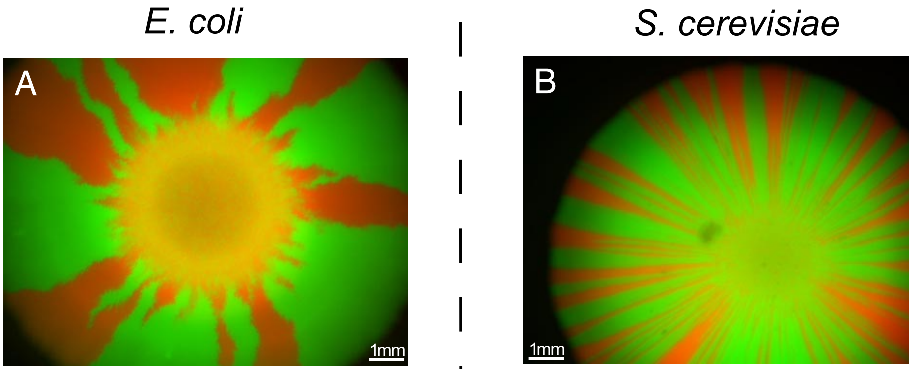
Inner scale: ODE, outer scale: spatial stochastic





Pattern formation 1: colonization

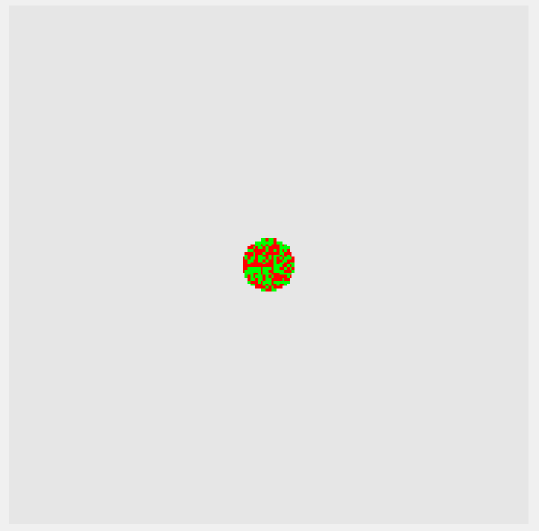
In vitro results from Hallatschek, *et al.*, PNAS 104, 2007



-Through colonization the red/green gene wins.

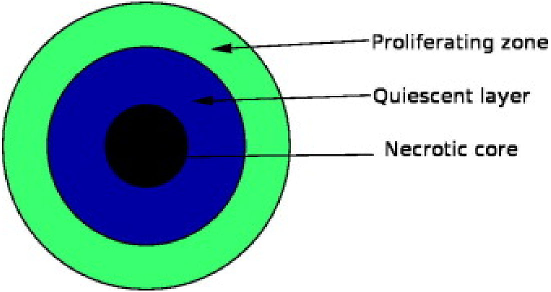
In silico colonization

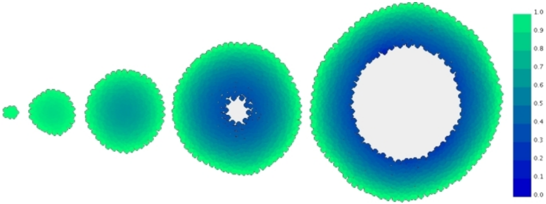
Inner scale: non-spatial stochastic, outer scale: spatial stochastic



Non-trivial dynamics in tumour

Mambili-Mamboundou *et al.*, Math. Bio. 249, 2014, & *Chaste*





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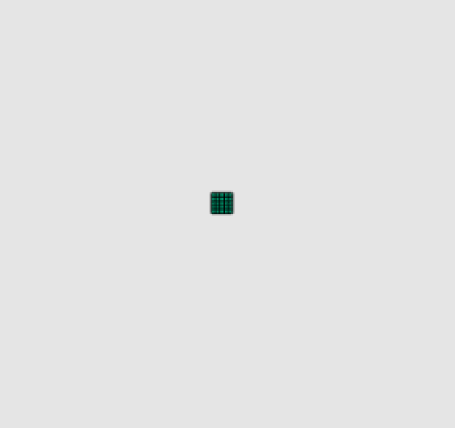
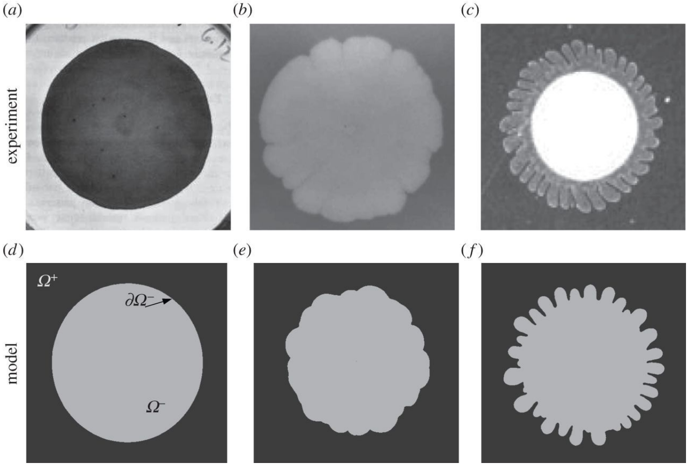


-Finding (emergent behavior): increasing the surface means increasing oxygen intake $\Longrightarrow$ steady-state is unstable.

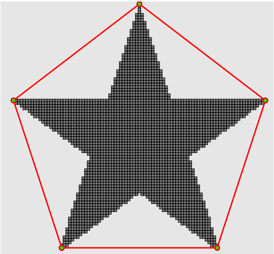
Sidenote: instability

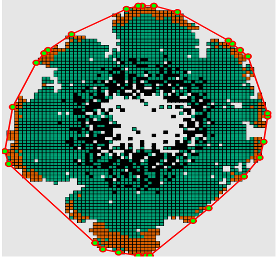
In vitro and *in silico* results from Giverso, *et al.*, J. R. Soc. Interface 12, 2015

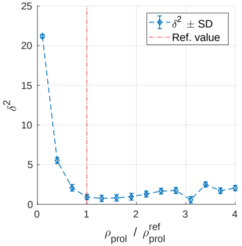


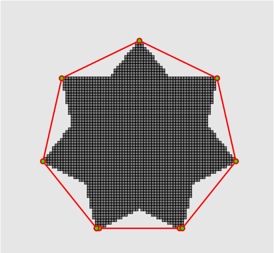
Ongoing work...

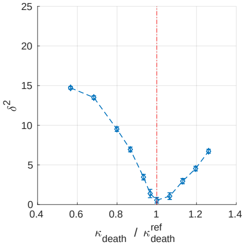
ABC parameter inversion of tumour model





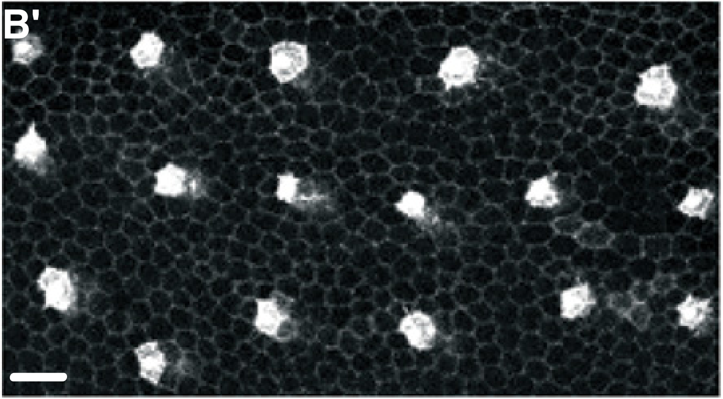






Pattern formation 2: Notch Delta & protrusions

In vivo results from Cohen, *et al.*, Cell 19, 2010



Protrusions

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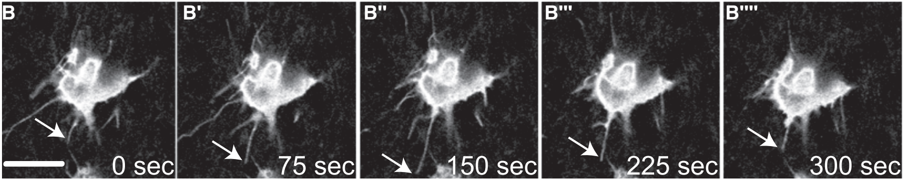
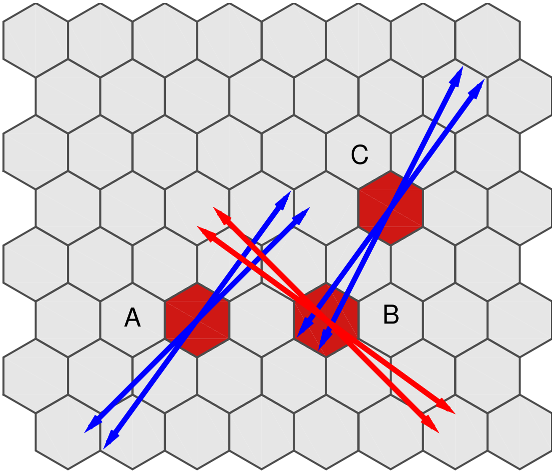


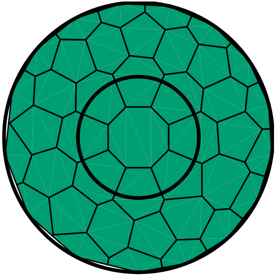
Protrusion interactions model

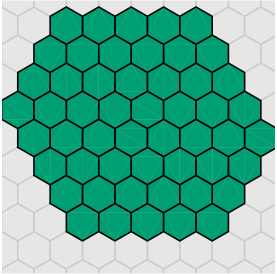
In silico model from Hadjivasiliou, *et al.*, J. R. Soc. Interface 13, 2016

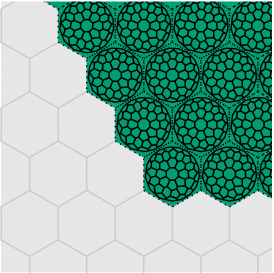


Direct (neighbor↔neighbor), via protrusions (A↔B), and non-symmetric (B↔C).

Spatial discretization







Left: single cell discretization, *middle:* cell population layer, *right:* grids combined.

Notch Delta: differential weighting of signals

Inner scale: spatial stochastic, outer scale: spatial stochastic

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- 1. Modeling: inner/outer scale, RDME/DLCM one suitable such combination, consistency through time-continuous coupling, **event-based computational framework** *(fast!)*
- 2. Analysis: the RDME framework, stability, analysis of basic numerical methods, *doable*: bring this to the RDME/DLCM combination.
- 3. Examples: flexible coupling cell-to-cell/cell-to-environment (solutions in URDME @ GitHub, `www.urdme.org`)

Thanks

Programs, Papers, and Preprints are available from my web-page.
Thank you for the attention!