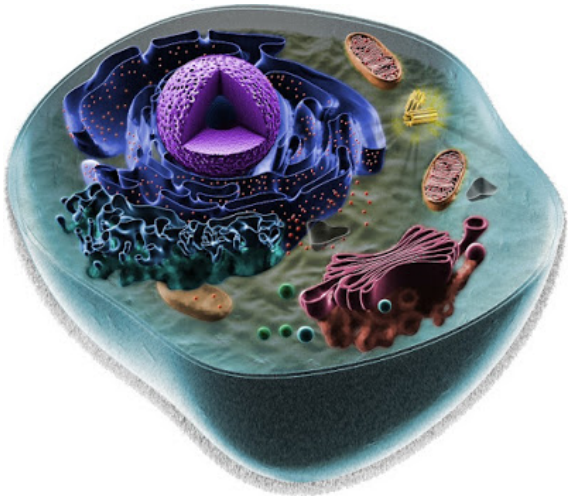
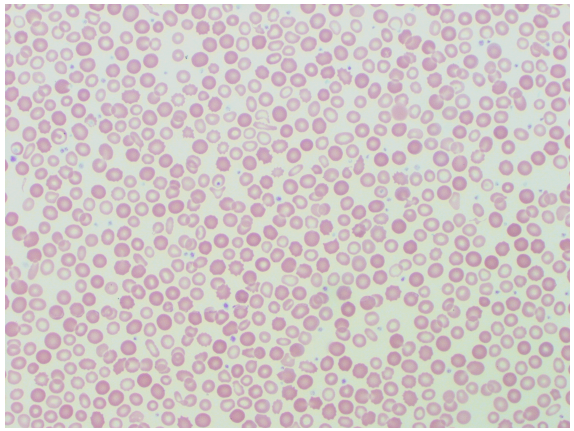
Bridging the single cell with the cell population: opening up for data-driven methodologies





Stefan Engblom

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Egmond aan Zee, The Netherlands, September 30th, 2019

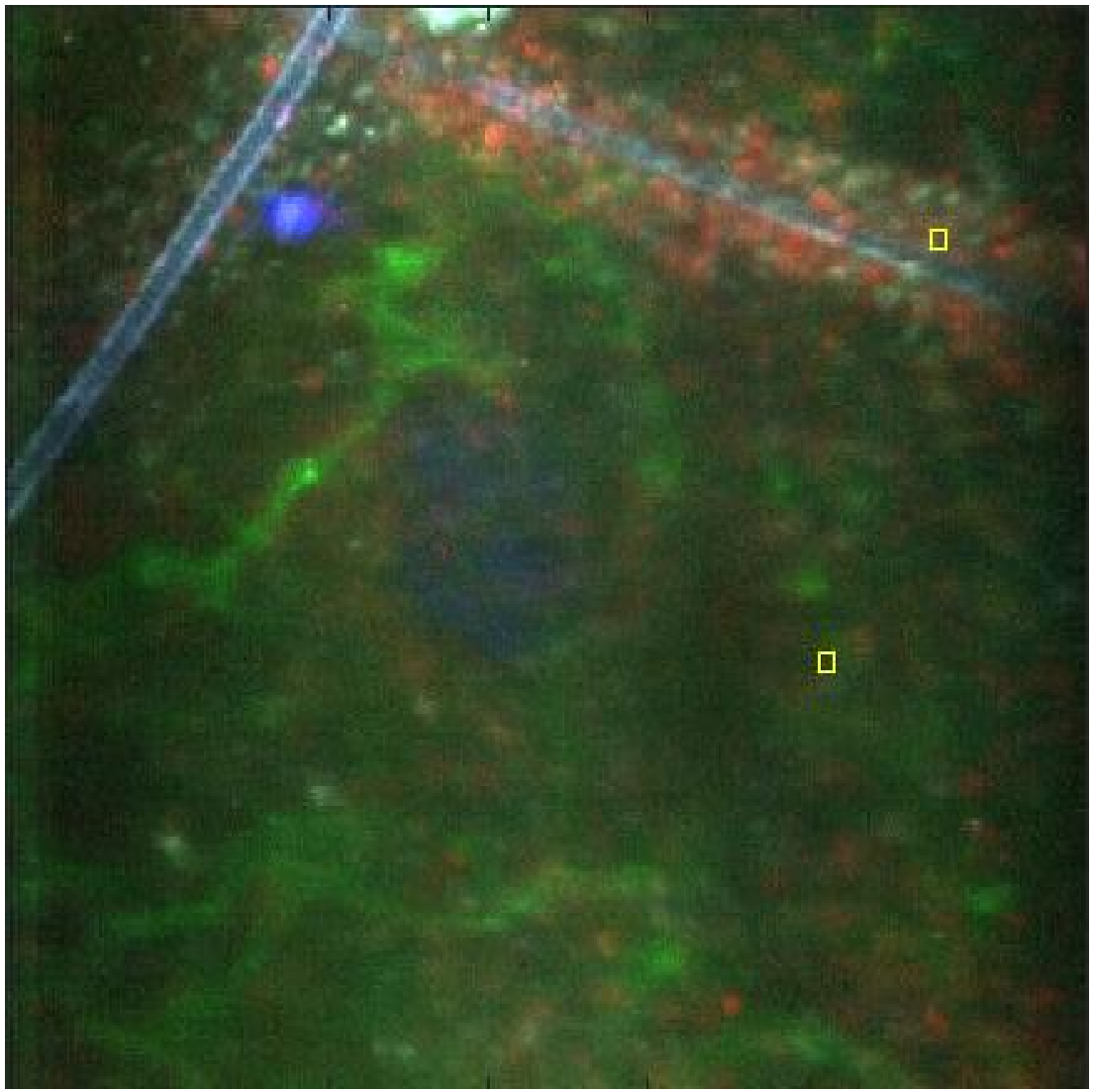
Outline

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 of white blood-cells (gradient sensing)



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.

"Realistic" flexible and understandable (= analyzable) numerical models, that in perspective can incorporate all relevant processes

"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

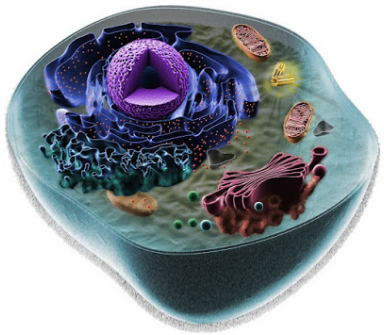
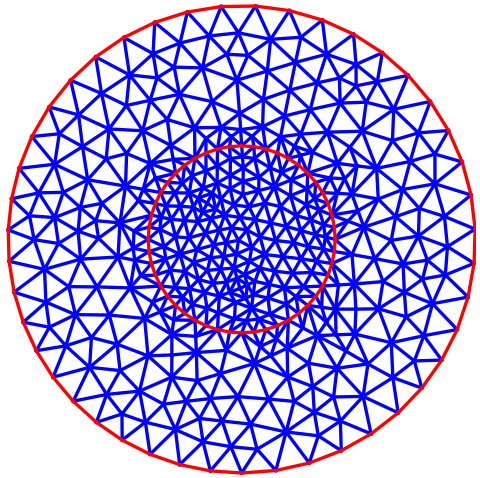
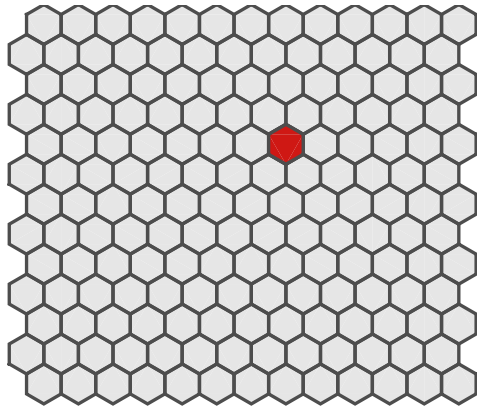
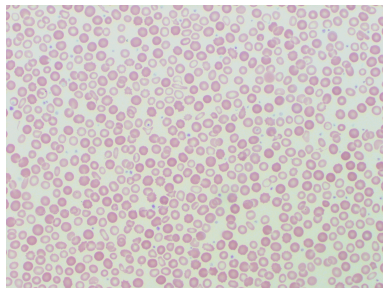
(1) is about modeling consistency & power, (2)+(3)+(4) mainly about being able to incorporate data *and* about simulation performance

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").

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

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.

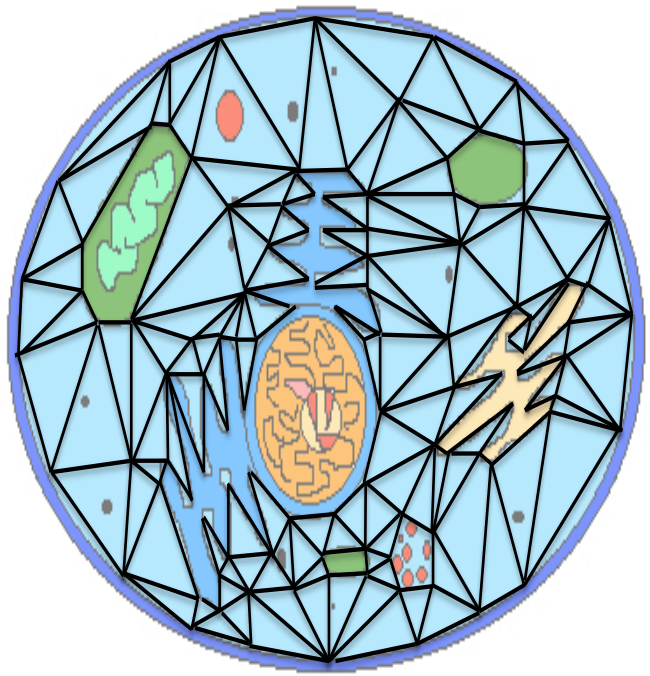
repeat

pick a random number

sample what happens and when

execute this event

until done



www.urdme.org

One model to rule them all?

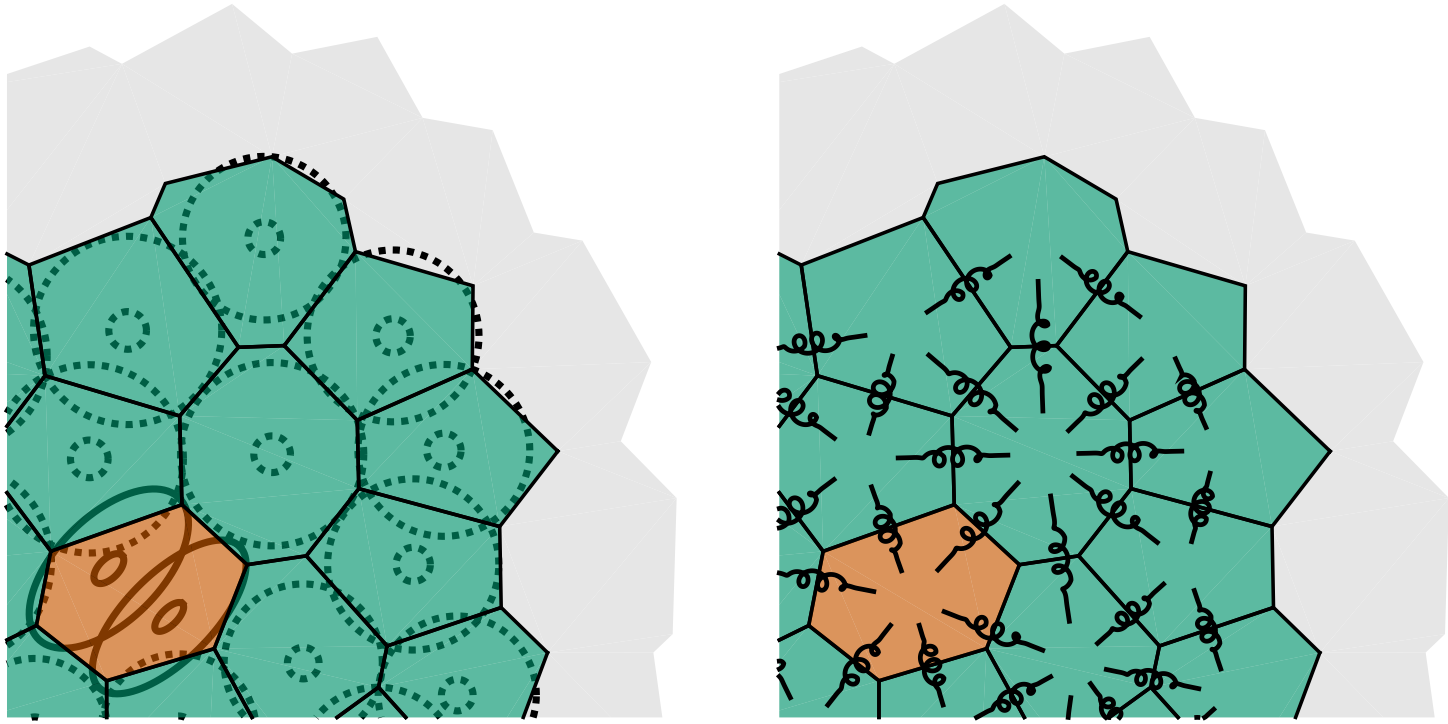
(cont)

-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).

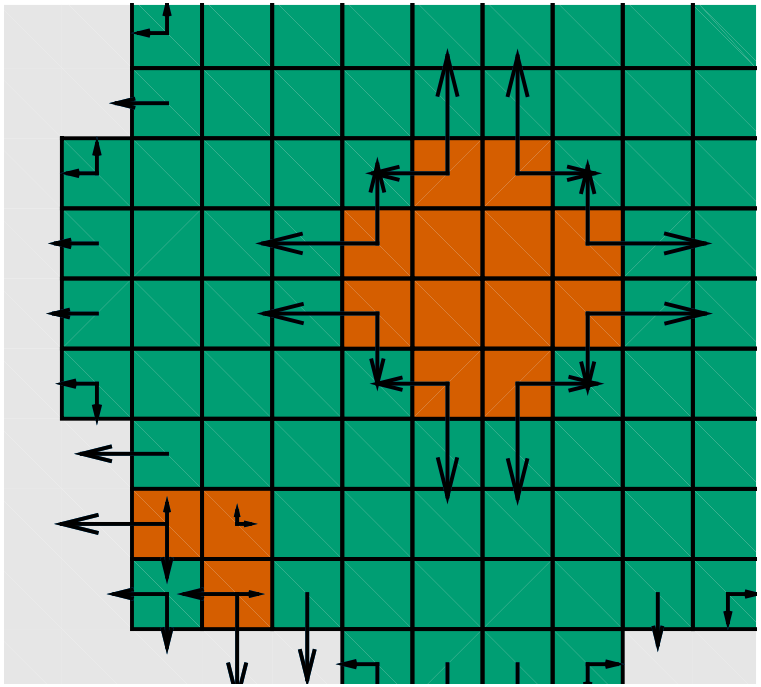
The idea 2

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.



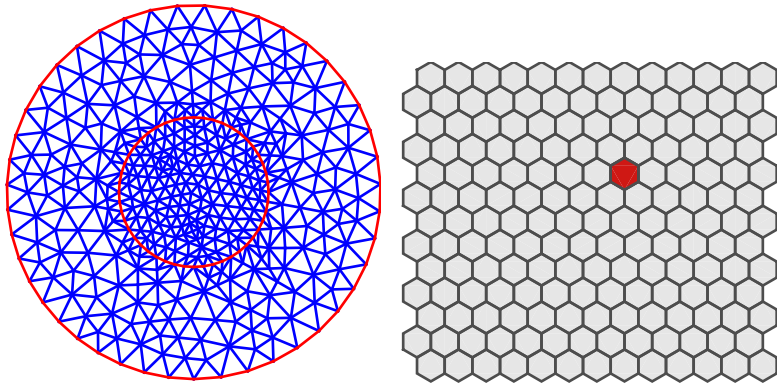
"Discrete Laplacian Cell Mechanics" (DLCM).

"Darcy's Law Cell Mechanics"...

Coupling of scales

Observation #1: whenever 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.

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: *a priori*

Long story, but short

-Useful computational frameworks should allow for error estimates of various approximations.

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

$\Longrightarrow$ *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.

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

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,

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

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

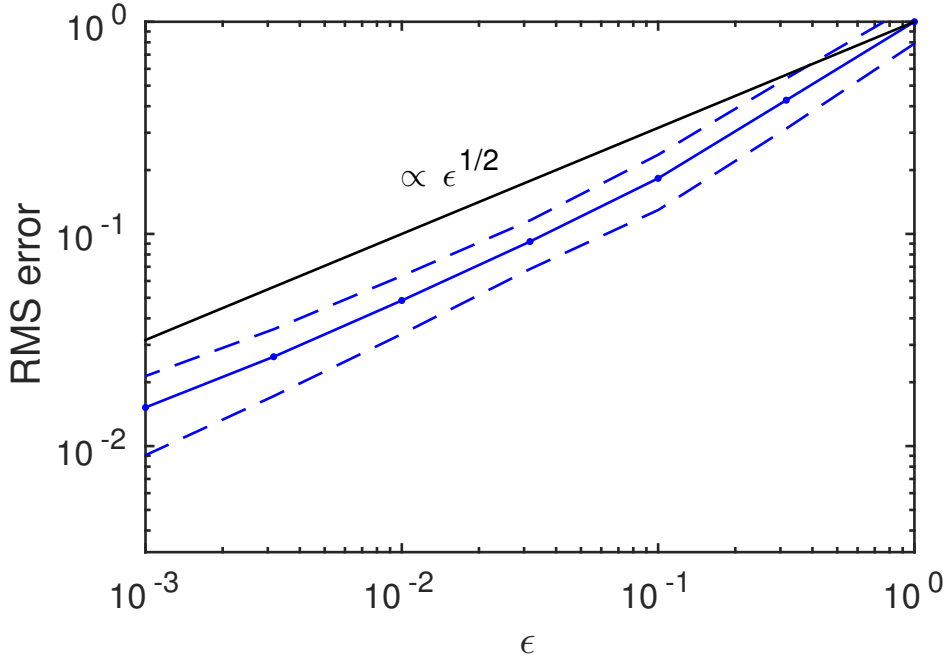
"Stress test" of theory

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

$$A + B \xrightarrow{kAB} C + B \qquad A \underset{b_a}{\overset{\epsilon d_a A}{\rightleftharpoons}} \emptyset$$

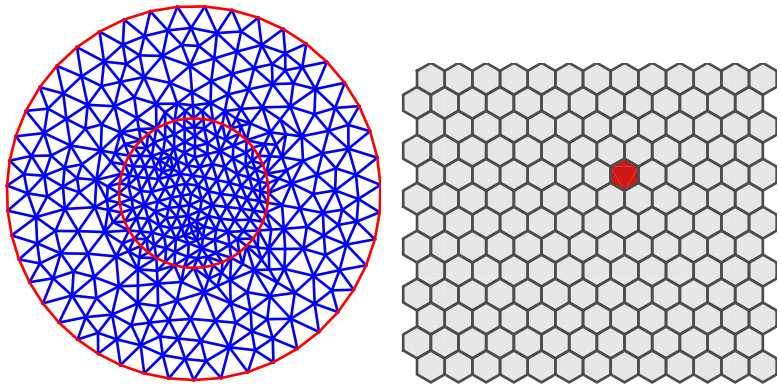
$$C + D \xrightarrow{kCD} A + D \qquad B \underset{b_b}{\overset{d_b AB}{\rightleftharpoons}} \emptyset$$

$$B + B \underset{k_d D}{\overset{k_b B(B-1)}{\rightleftharpoons}} D$$



Proposed modeling framework

RDME & DLCM



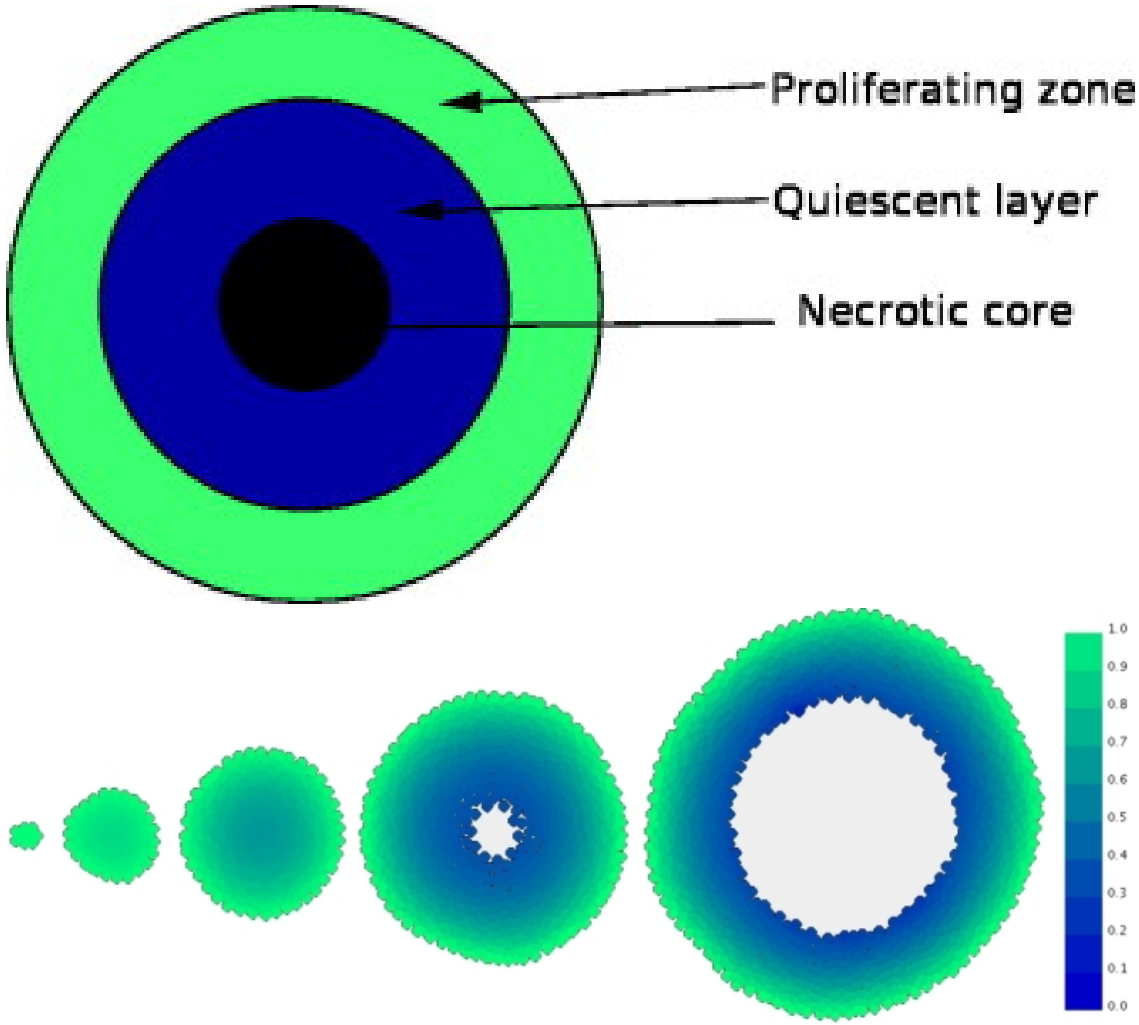
Outer scale DLCM, pressure-driven (passive) cellular movements

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.

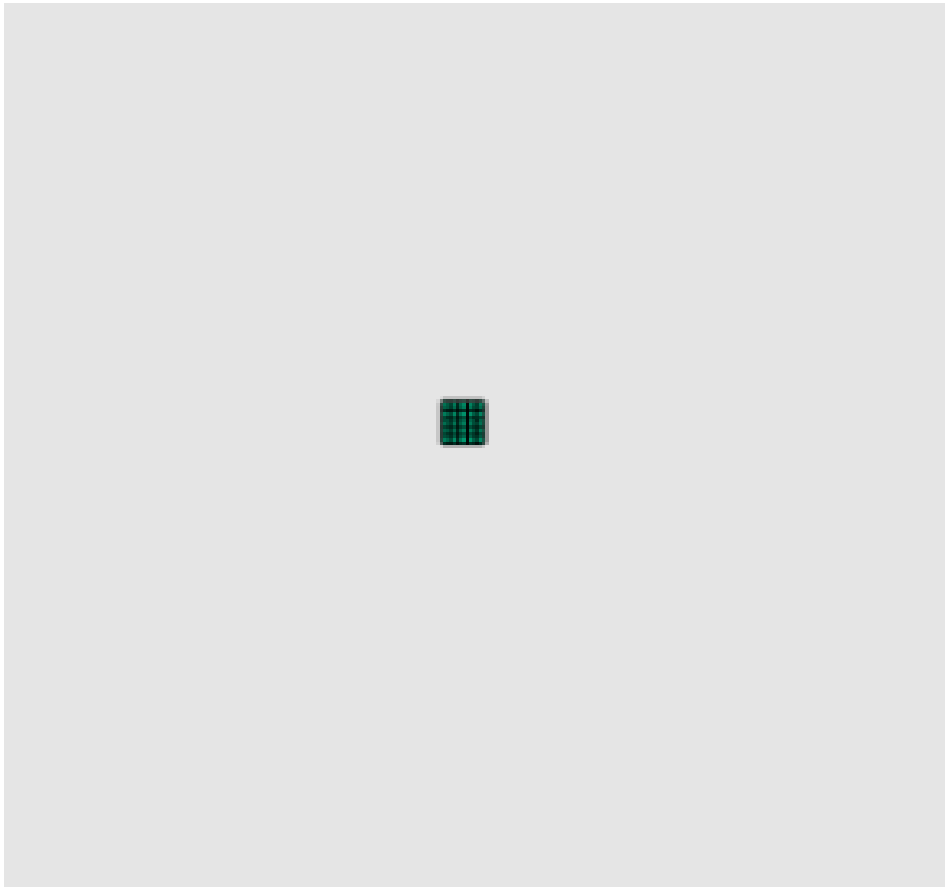
Non-trivial dynamics in tumour

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



Non-trivial dynamics in tumour

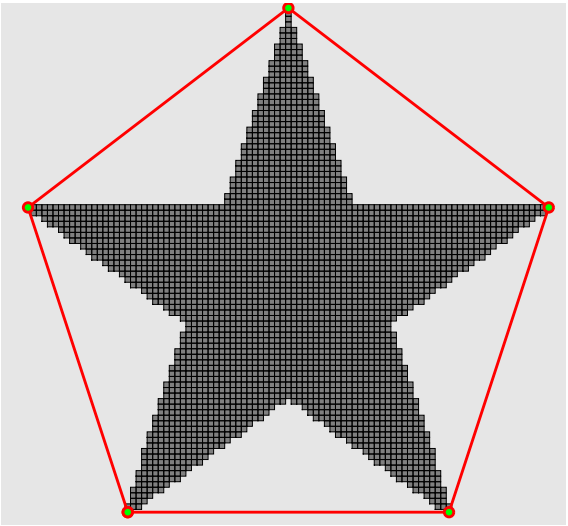
Inner scale: non-spatial stochastic, outer scale: spatial stochastic

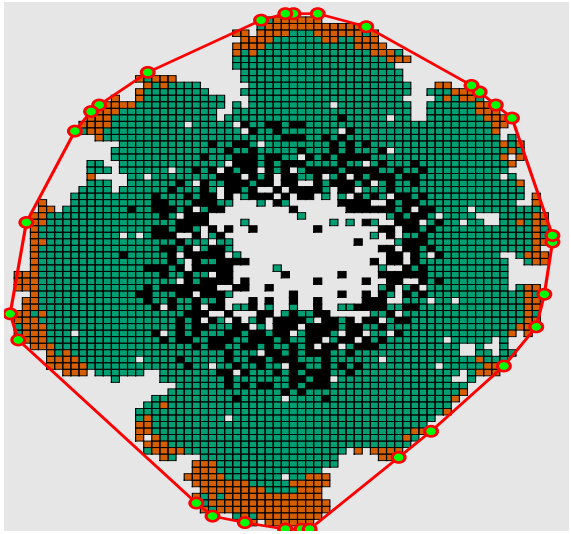


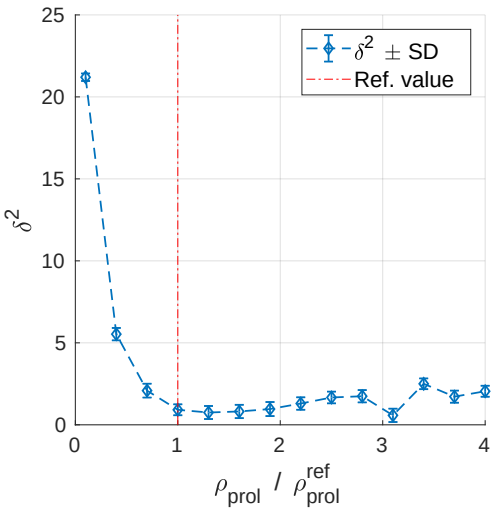
-Finding (emergent behavior): increasing the surface means increasing oxygen intake $\Longrightarrow$ steady-state is unstable.

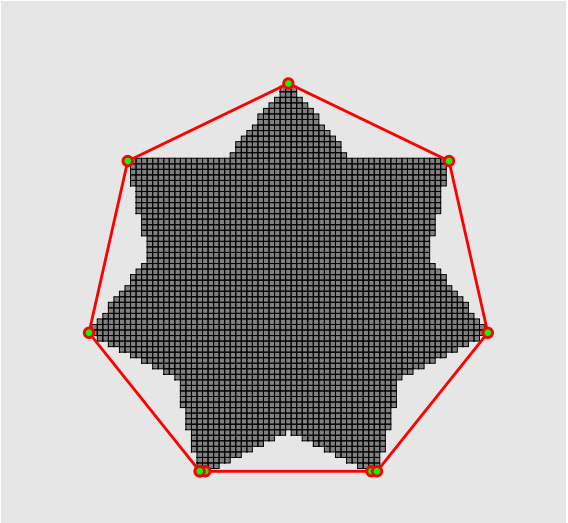
Ongoing work...

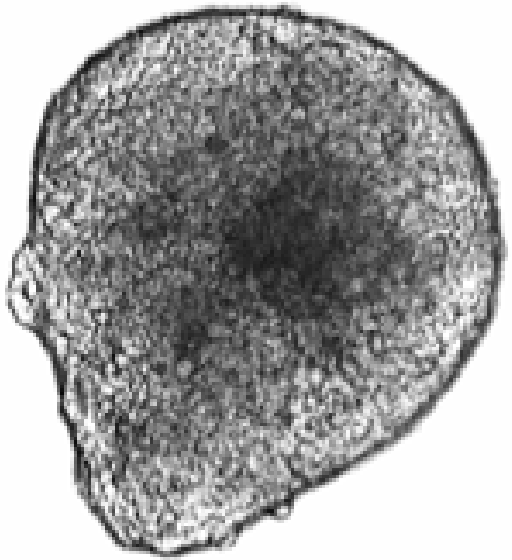
ABC parameter inversion of tumour model

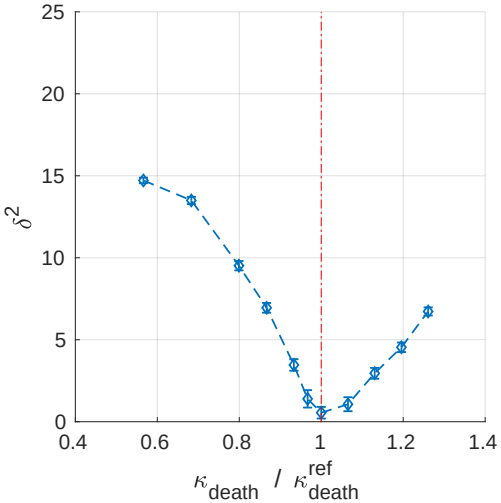






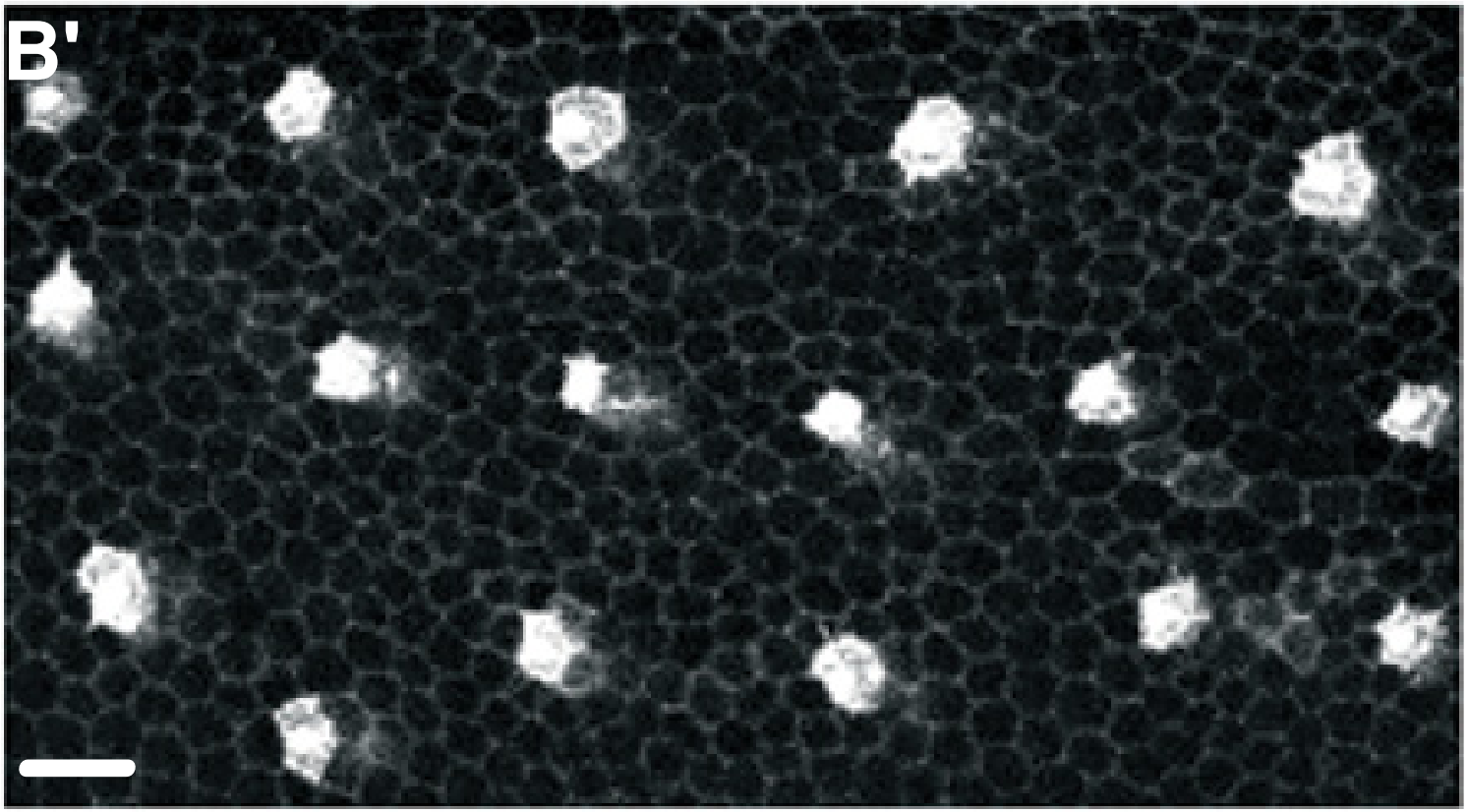






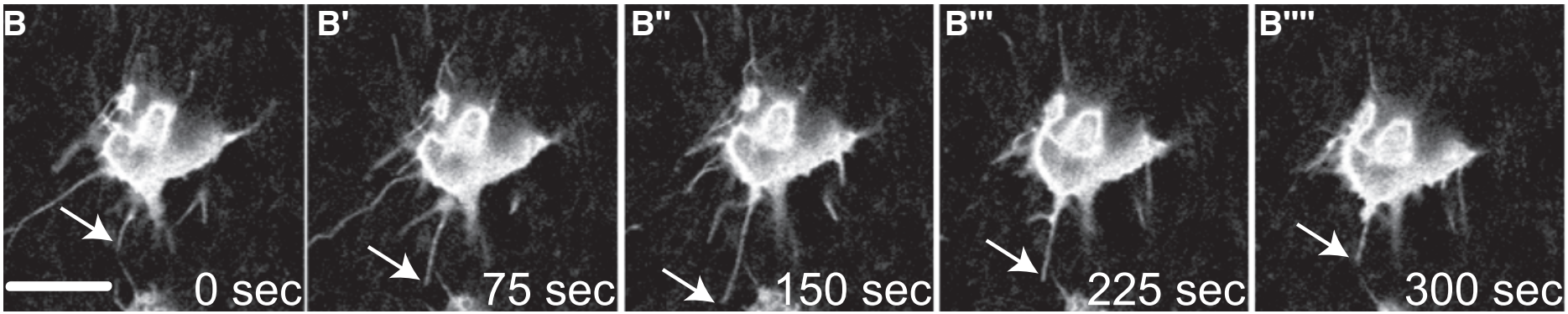
Pattern formation: Notch Delta

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



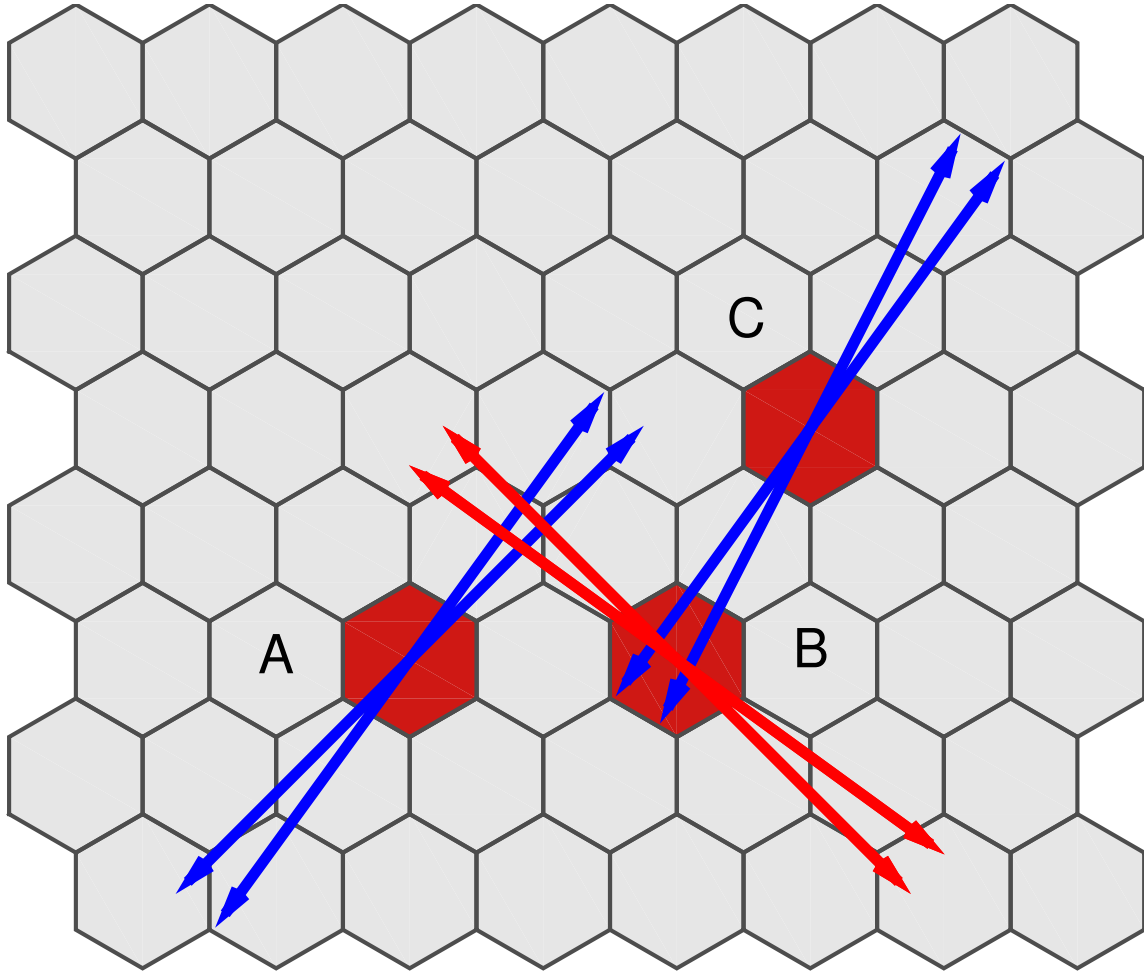
Protrusions

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



Protrusion interactions model

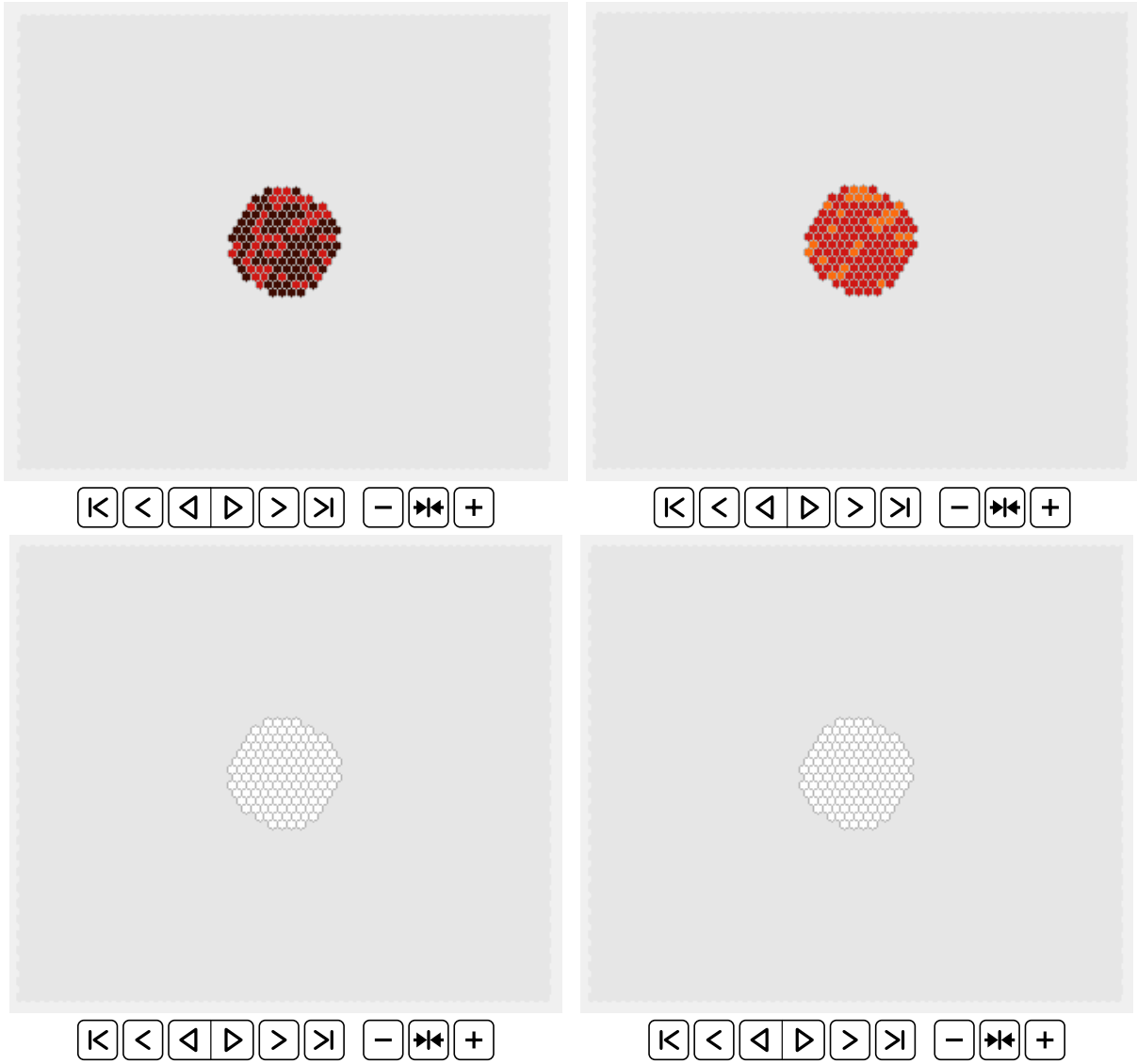
In silico model from Hadjivasiliou, *et al.*, J. R. Soc. Interface 13, 2016



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

Delta-notch: differential weighting of signals

Inner scale: spatial stochastic, outer scale: spatial stochastic



Summary

- Microscopy data, mostly for inspiration...
- "How to think": realistic & useful models, through flexible/understandable/generalizable
- 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!