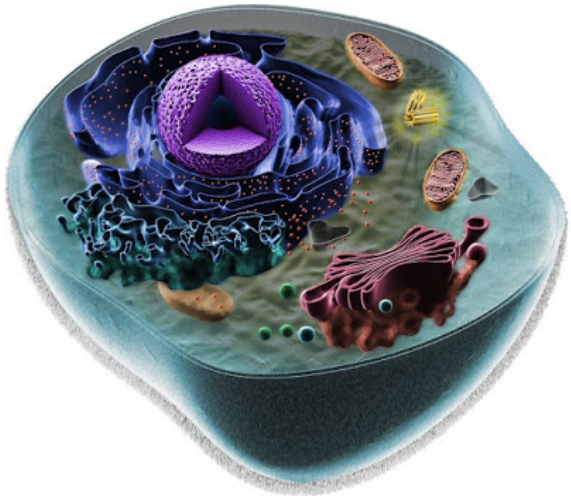
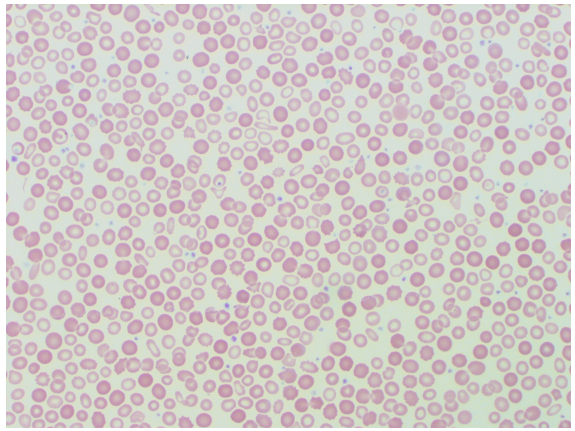
From the bottom and up: bridging the single cell with the cell population





Stefan Engblom

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

Centro di Ricerca Matematica Ennio De Giorgio, Pisa, Italy, October 1st, 2018

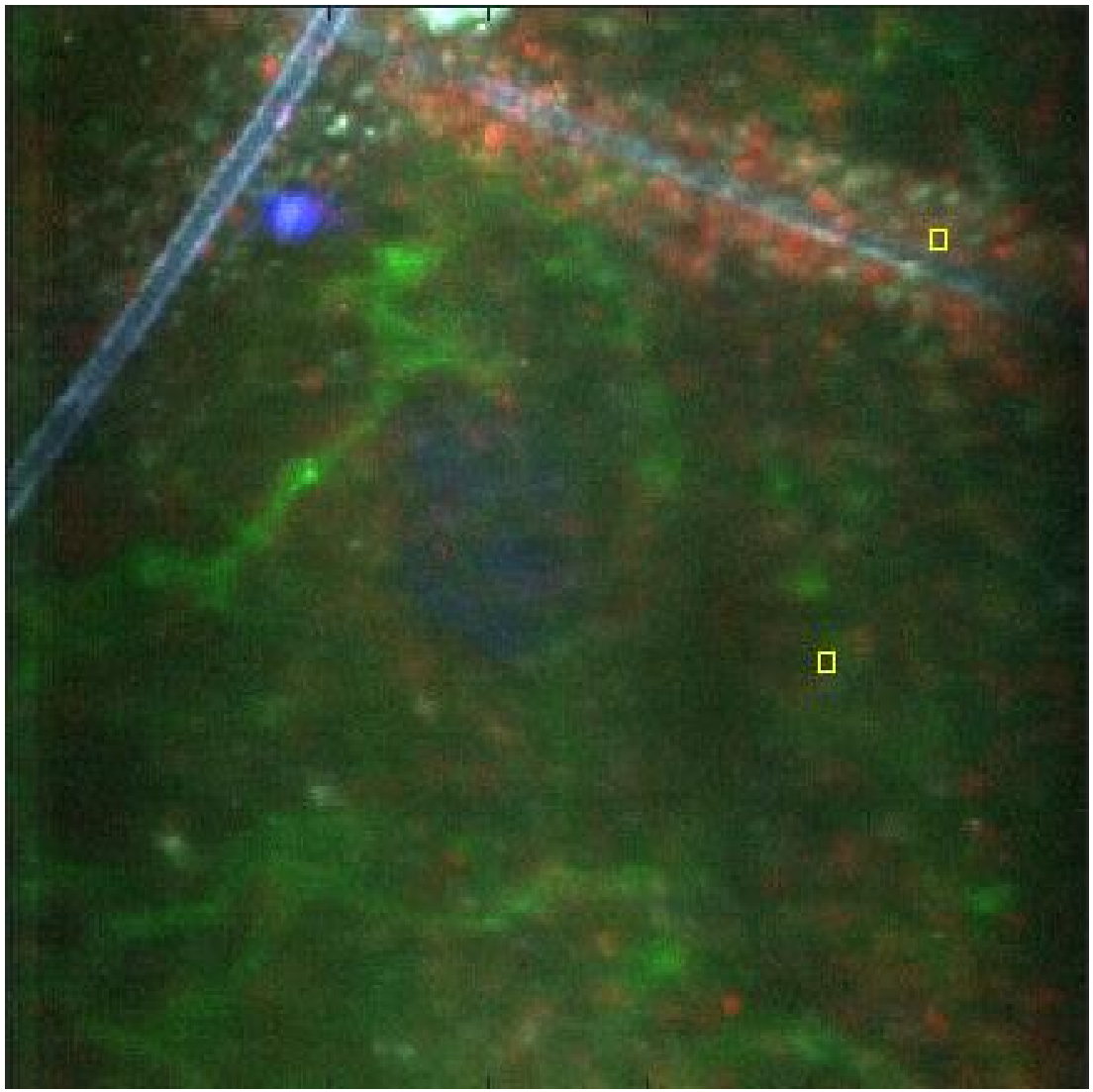
Outline

Joint work with and/or input from:

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

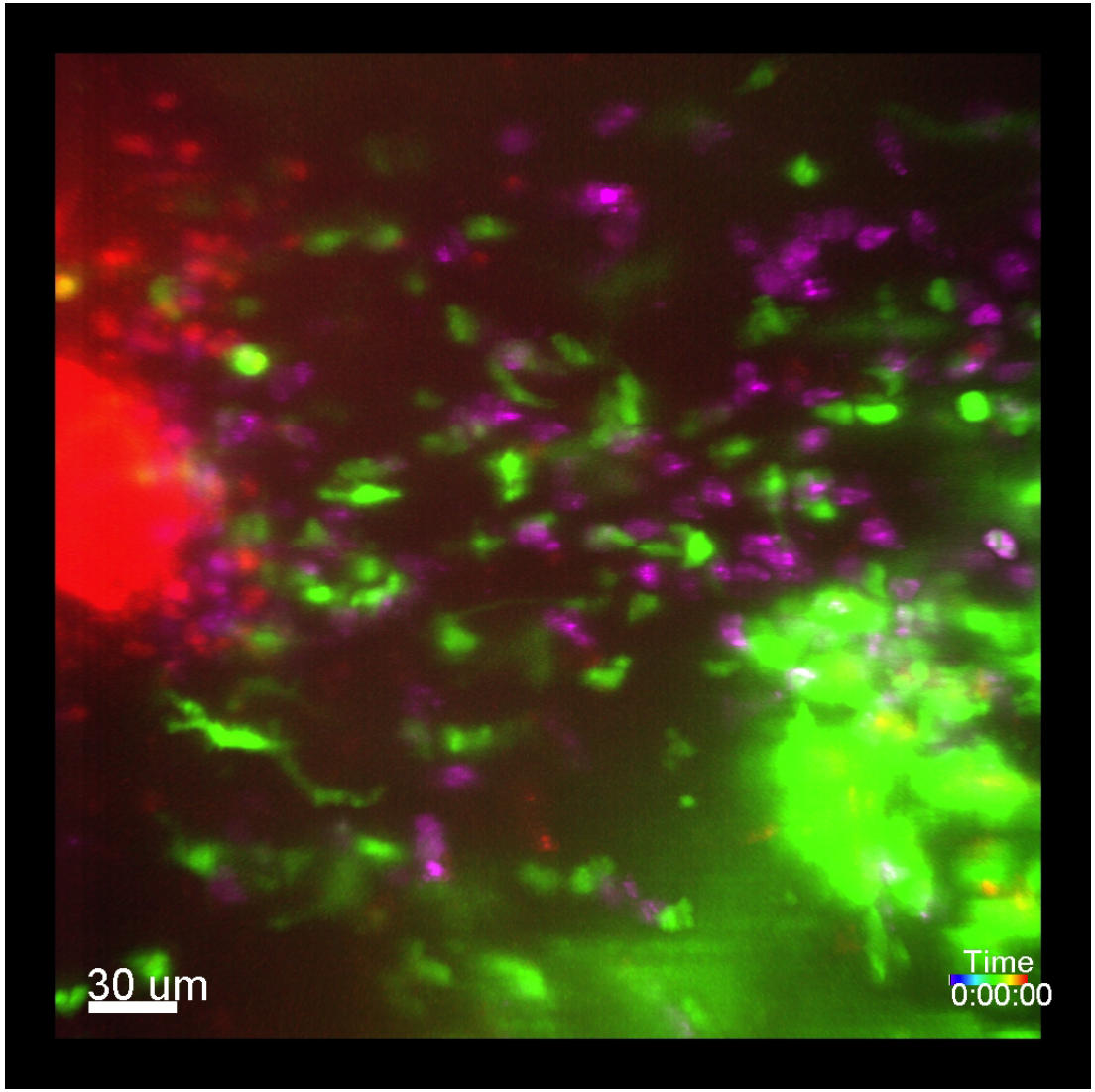
Wound healing around transplant

Recruitment of white blood-cells



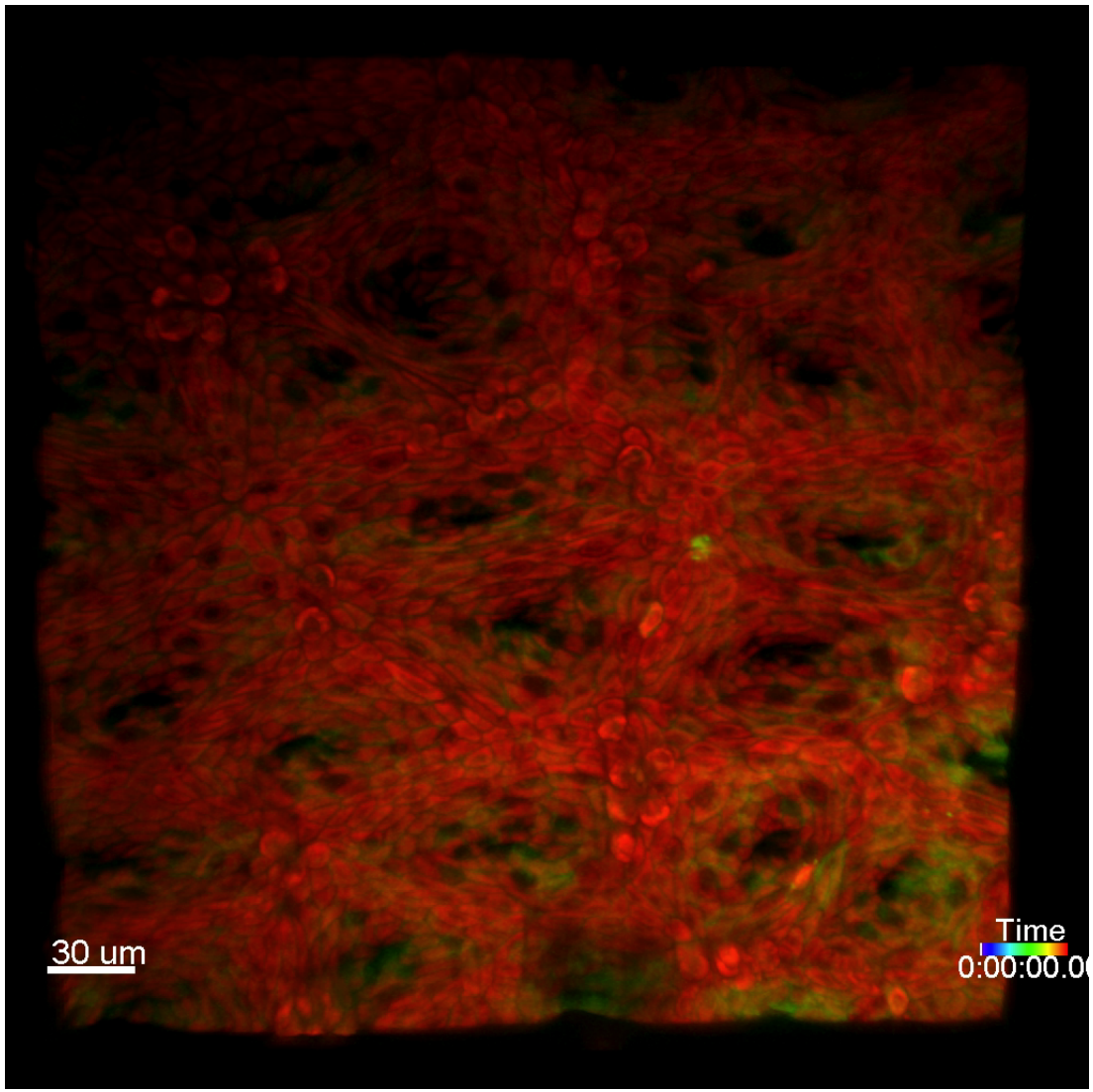
Migrating cells

Gradient sensing



Colon crypts

Stem cells



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.

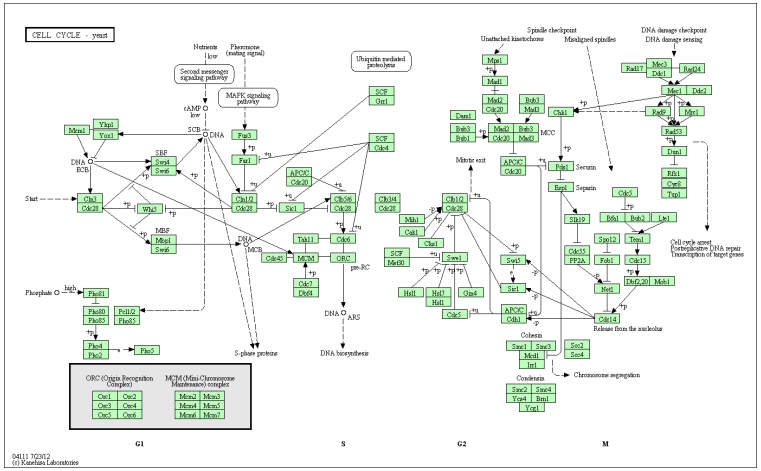
"Realistic" flexible and understandable (= analyzable) numerical models, that in perspective can incorporate all relevant processes

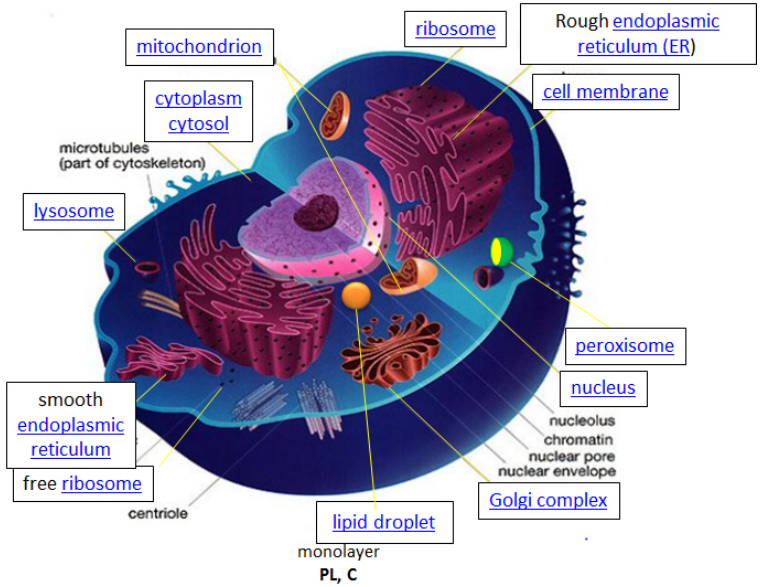
"Useful" (1) fully explanatory (support emergent behavior), (2) test hypotheses, (3) predictive value, (4) help to build an argument in cases where many factors are unknown

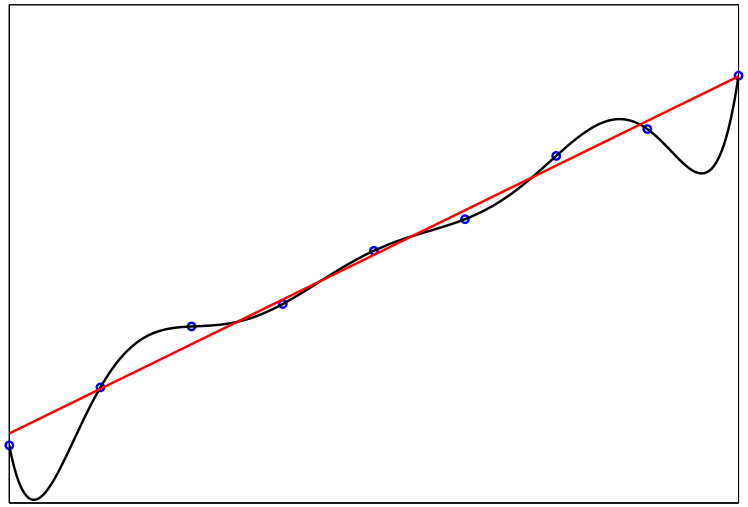
(1) is about modeling consistency (-power), (2)+(3)+(4) about being able to incorporate data *and* about simulation performance

Risk of over-modeling

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







Caution:

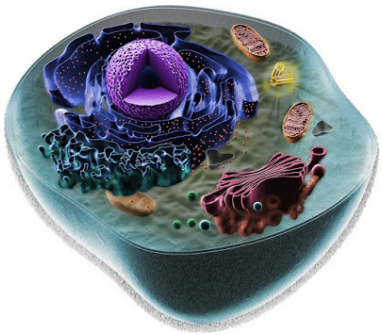
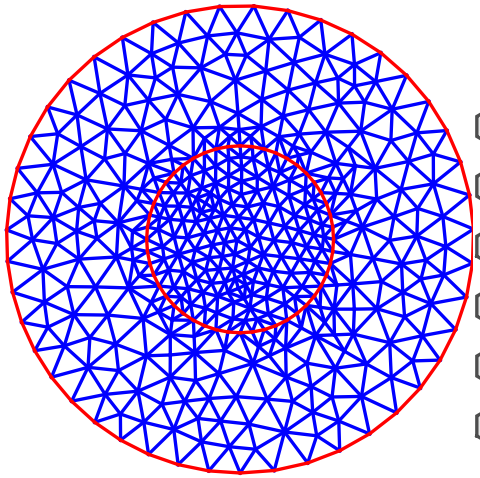
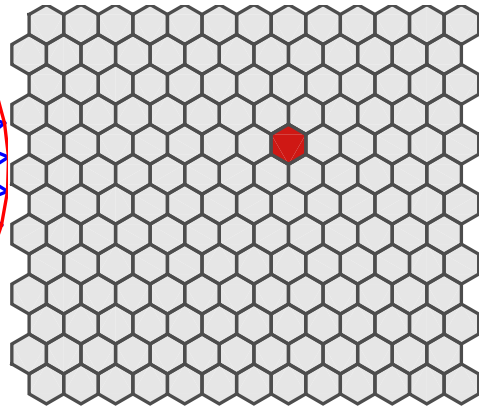
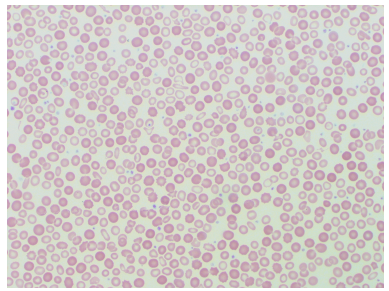
- *really* detailed, or,
- *imaginary* accuracy, or,
- just a plain overfit?

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

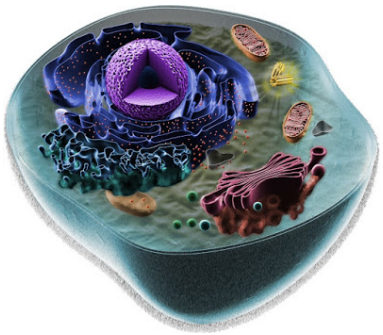
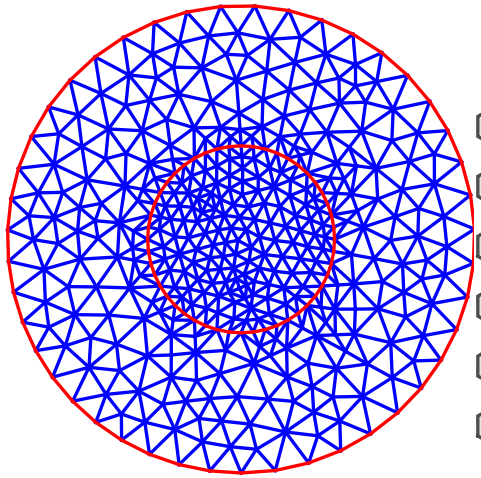
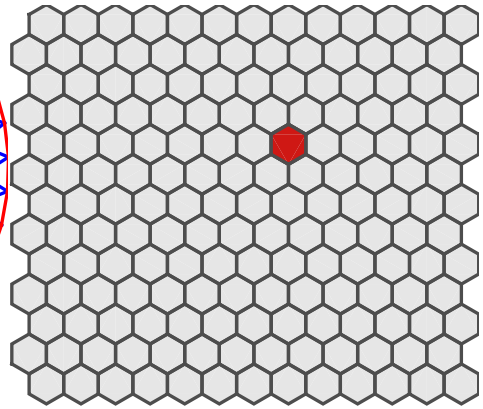
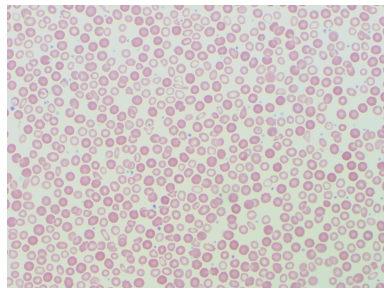
inner-outer idea

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*!

One model to rule them all?

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

The RDME

-A spatial continuous-time Markov chain stand out as a promising alternative. This is the "Reaction-Diffusion Master Equation".

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.

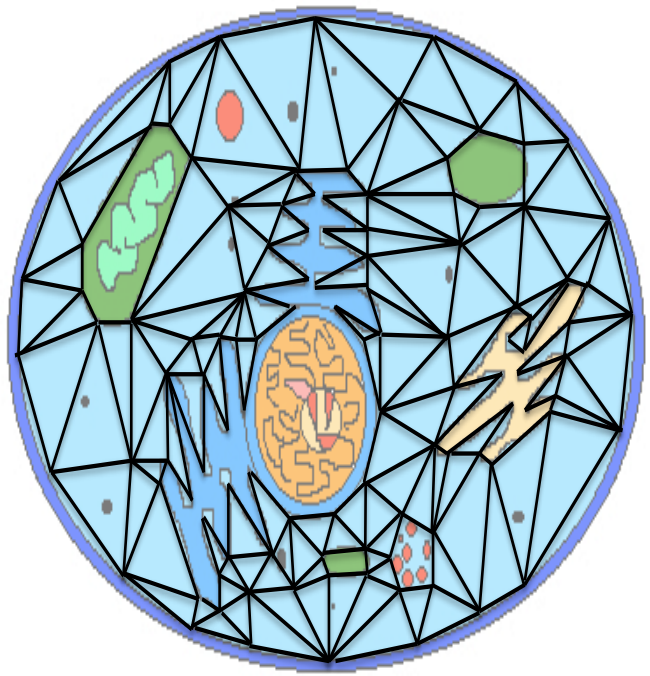
repeat

pick a random number

sample what happens and when

execute this event

until done



www.urdme.org

One model to rule them all?

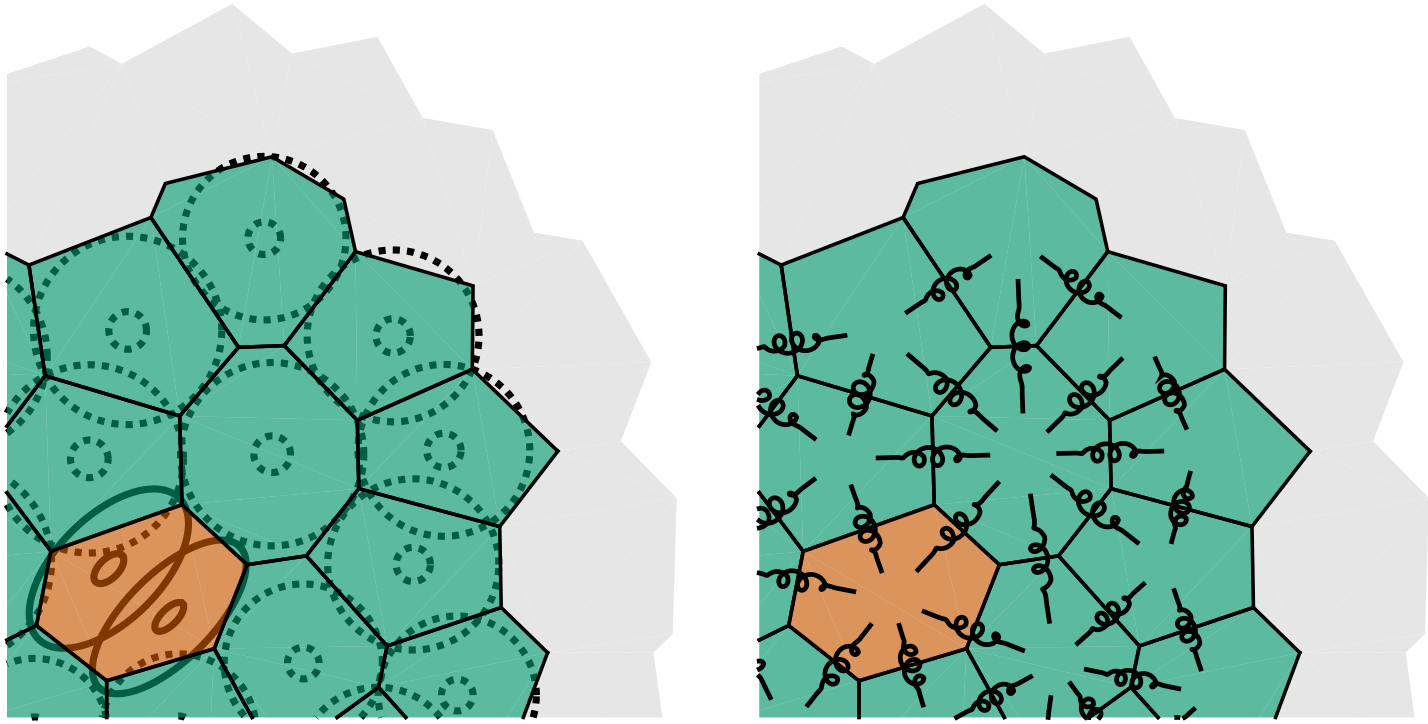
(cont)

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

-Differences include: that 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).

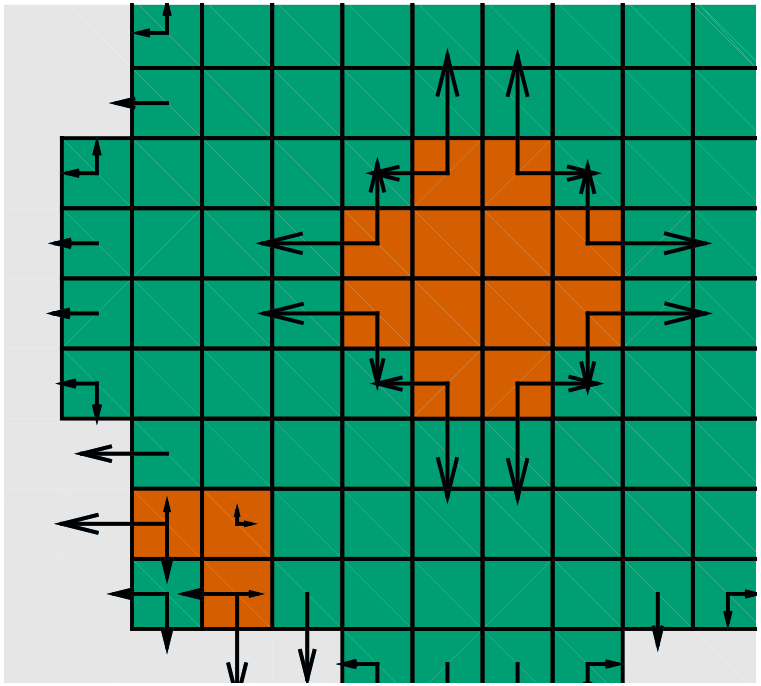
The idea 2

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.



"Discrete Laplacian Cell Mechanics" (DLCM).

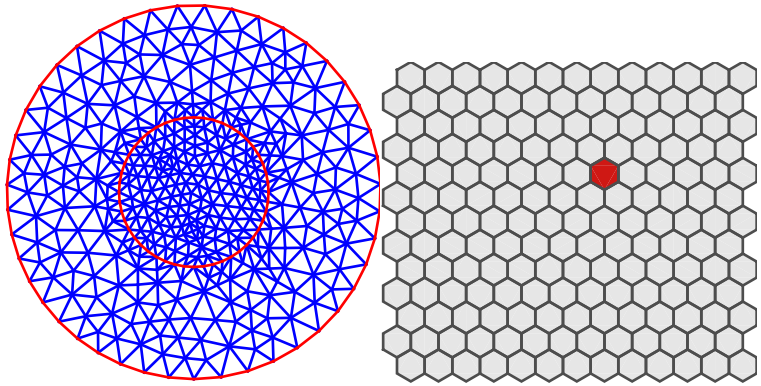
Coupling of scales

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.

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.

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 either one of

- stochasticity
- species discreteness
- spatial inhomogeneities

make a difference. *Or else an ODE would work just as well!* The model itself is therefore likely going to be sensitive to perturbations in any of these.

Analysis message

Terms & conditions

Want to use these models when either one of

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make a difference. *Or else an ODE would work just as well!* The model itself is therefore likely going to be sensitive to perturbations in any of these.

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

A priori

Long story, but short

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

With suitable initial data and assumptions...

- $\mathbb{E}[\sup_{s\in[0,t]} \|\mathbb{X}(s)\|^p]$ 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

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

A priori

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

-Actually, if both $\mathbb{X}$ and $\mathbb{Y}$ are bounded, then

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

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

Analysis: Multiscale variable splitting

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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

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

Multiscale error

Under certain assumptions,

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

Analysis of errors

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

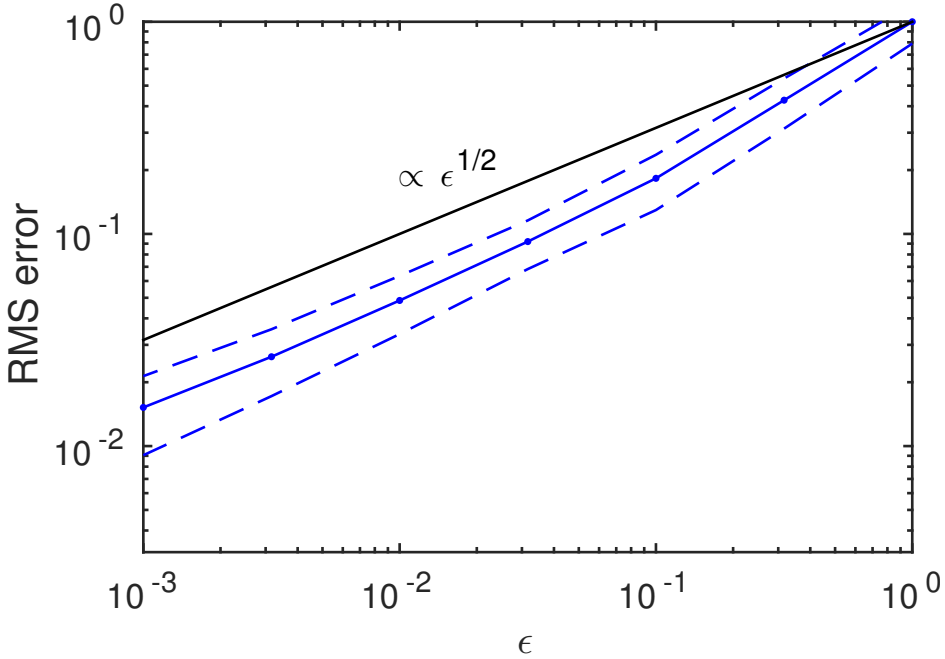
"Stress test" of theory

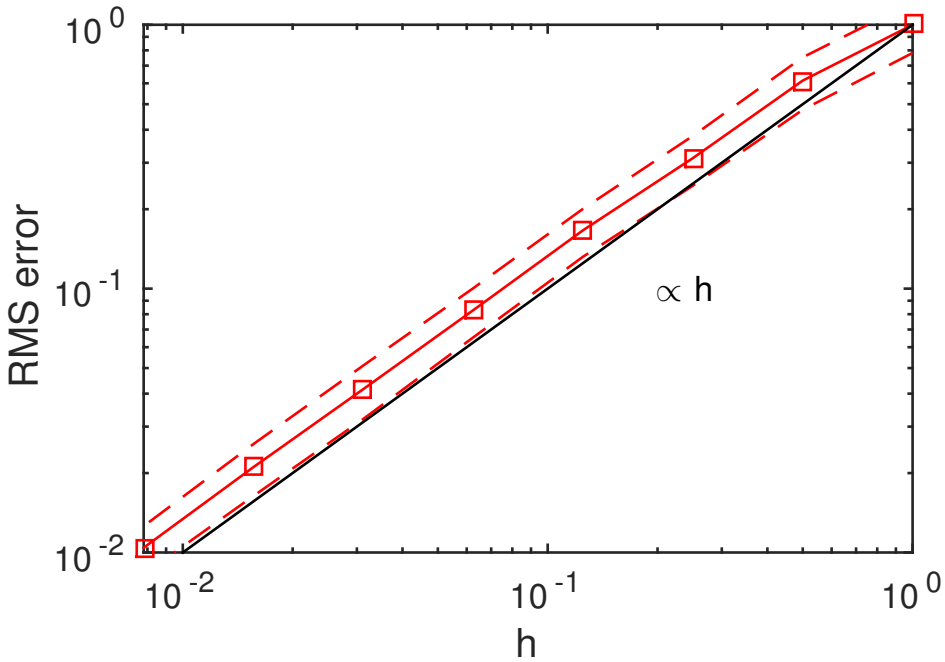
$(A, C) \sim \epsilon^{-1}$, $(B, D) \sim 1$, $\text{diffusion}_{A,C} \sim \epsilon$, $\text{diffusion}_{B,D} \sim 1$.

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

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

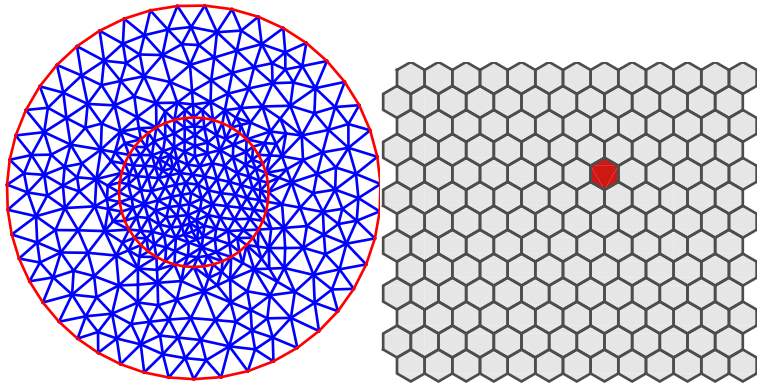
$$B + B \underset{k_d D}{\overset{k_b B(B-1)}{\rightleftharpoons}} D$$





Modeling framework

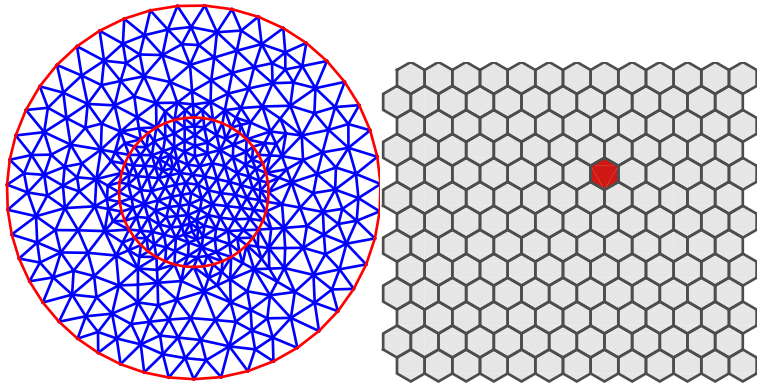
RDME & DLCM



	units	inner scale	outer scale
RDME	#molecules	reactions in a voxel	diffusion between voxels

Modeling framework

RDME & DLCM



	units	inner scale	outer scale
RDME	#molecules	reactions in a voxel	diffusion between voxels
DLCM	#cells	⟨model⟩	pressure-driven movement

Where ⟨model⟩ is one of {ODE, SDE, RDME}.

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

Cellular communication: delta-notch

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

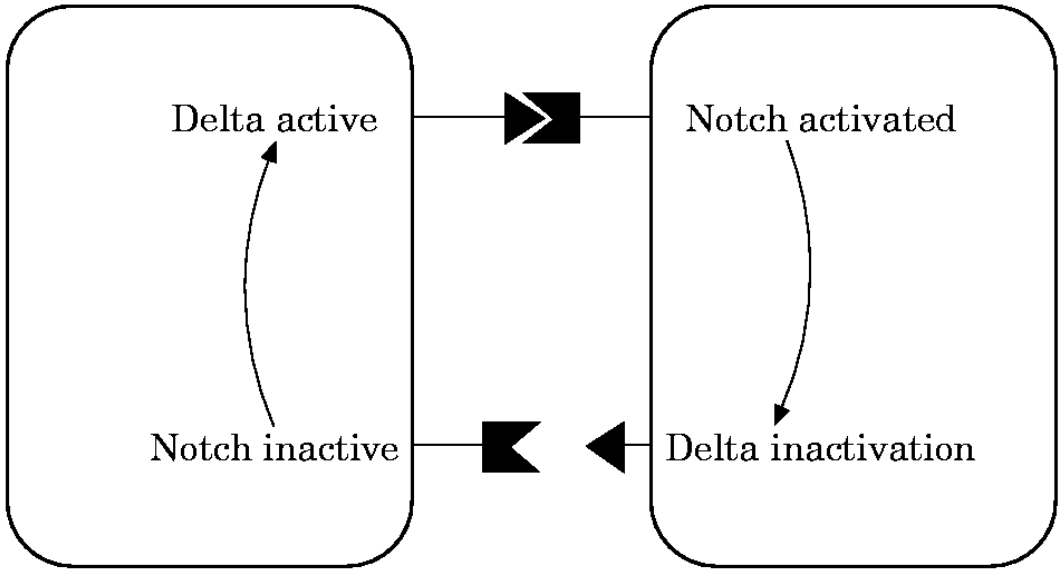
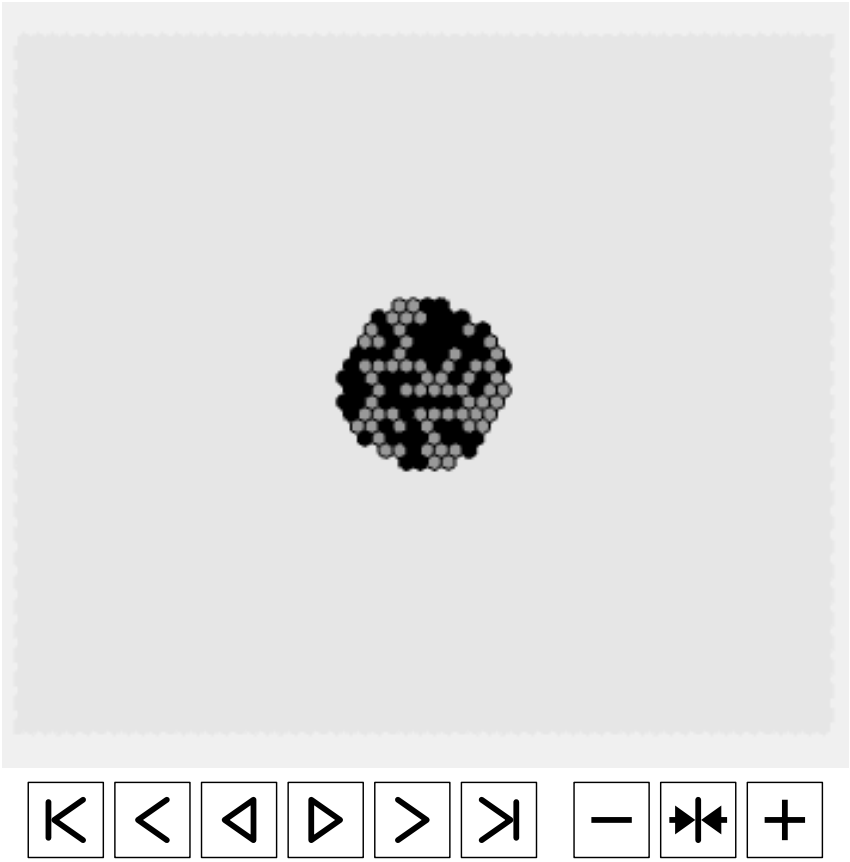


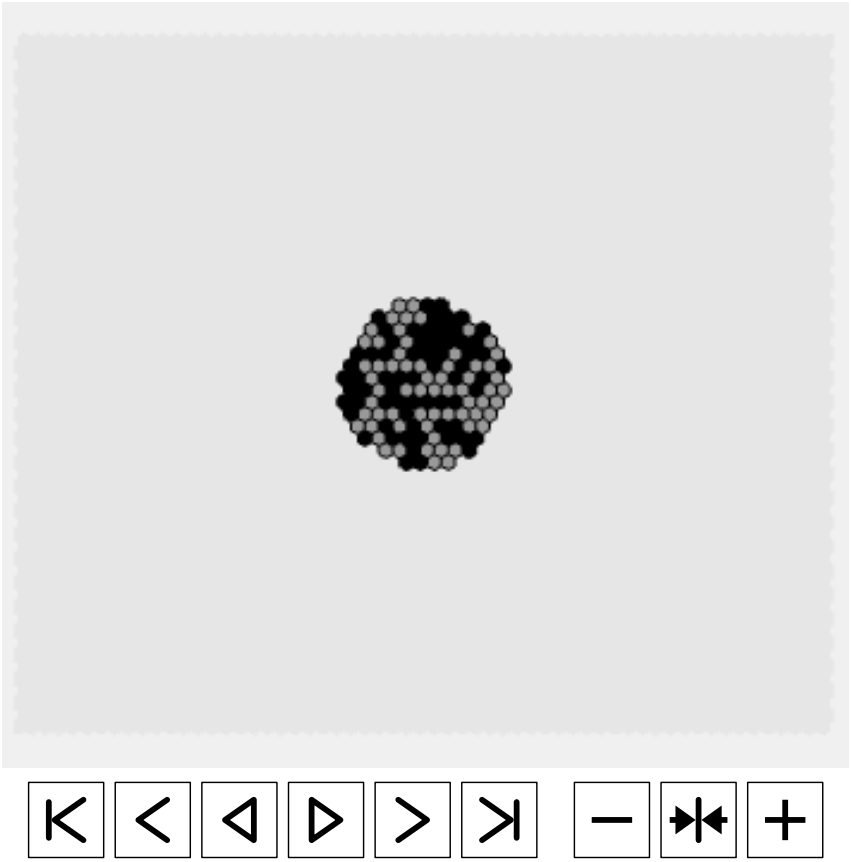
FIG. 1. Diagrammatic representation of the effective feedback loop between Notch and Delta in neighbouring cells. Details of the Notch signalling pathway are omitted for clarity. *Key*: ▶ Delta; ⚑ Notch.

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

Cellular communication: delta-notch

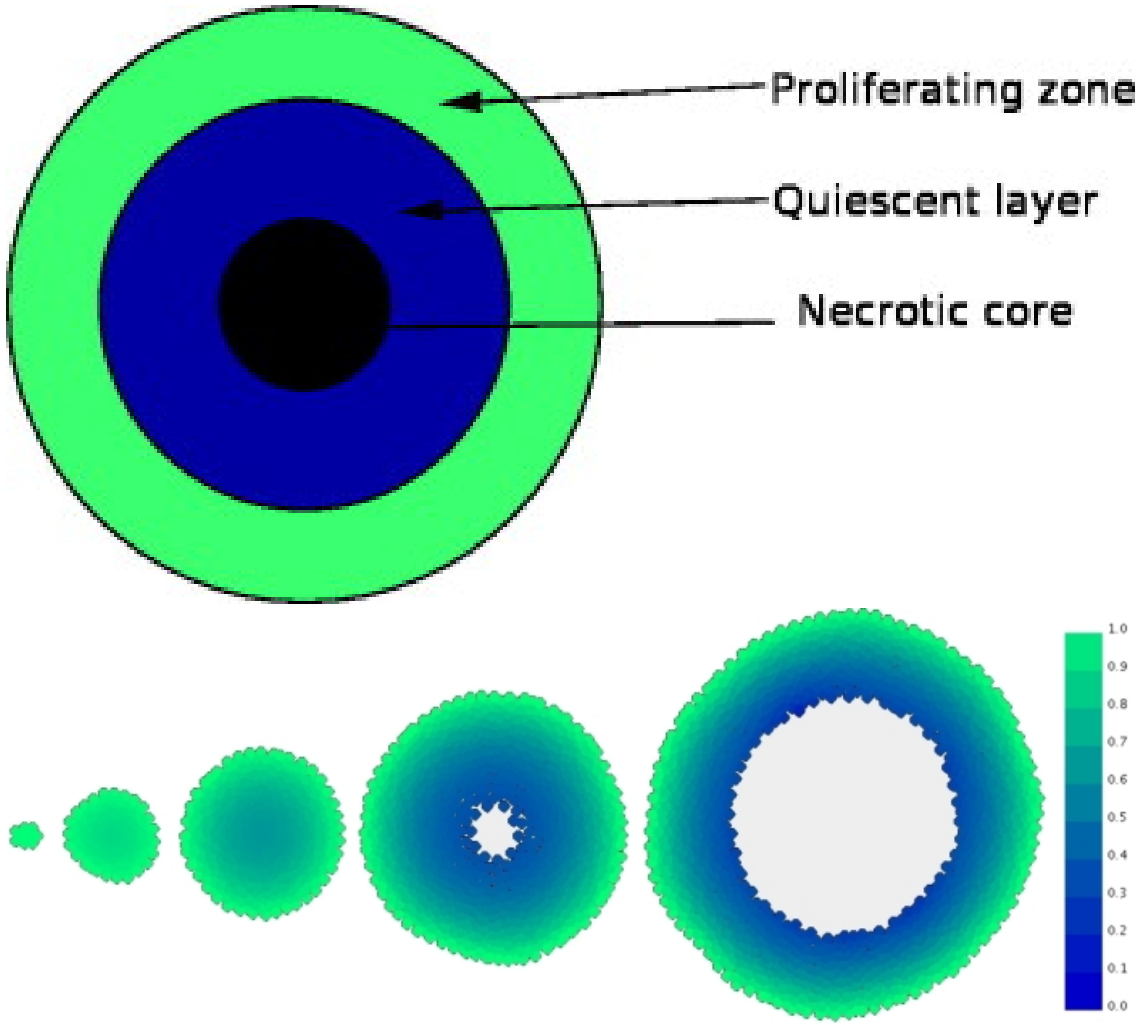
Inner scale: ODE, outer scale: spatial stochastic





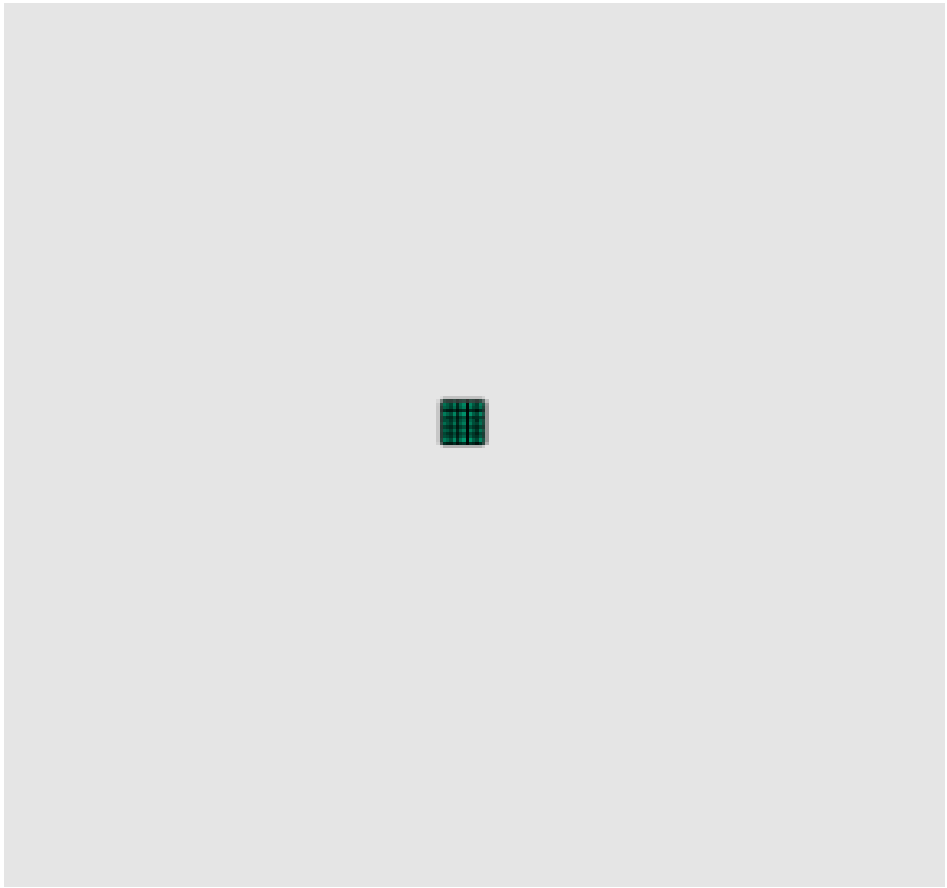
Non-trivial dynamics in tumour

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



Non-trivial dynamics in tumour

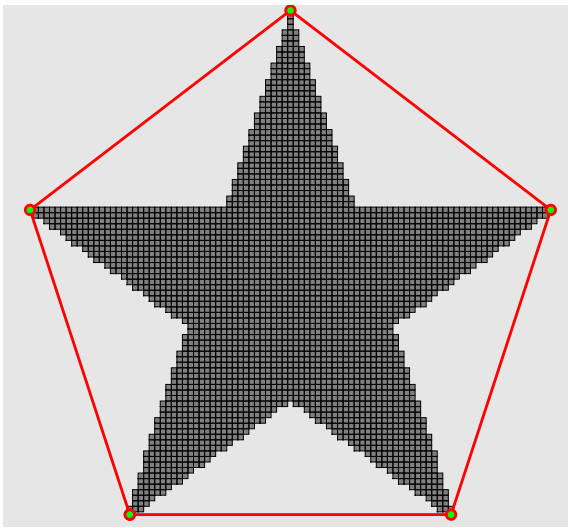
Inner scale: non-spatial stochastic, outer scale: spatial stochastic

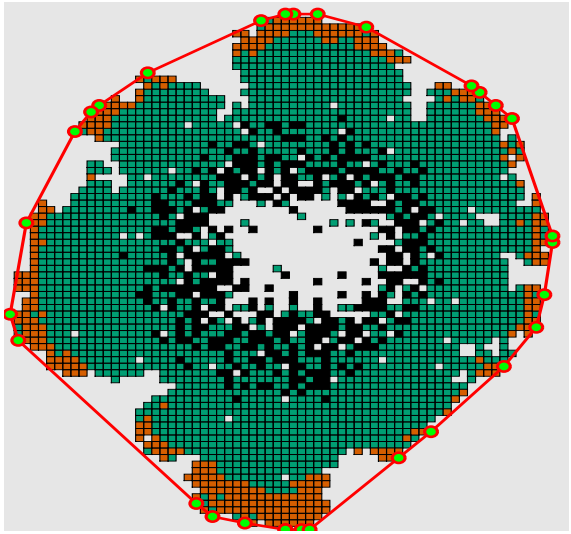


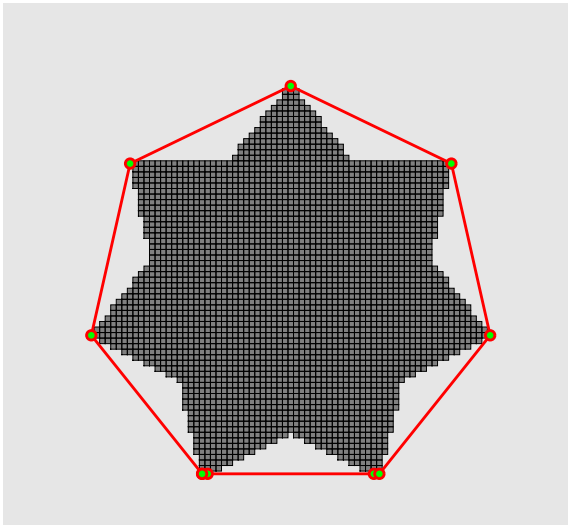
-Finding (emergent behavior): increasing the surface means increasing oxygen intake $\Longrightarrow$ steady-state is unstable.

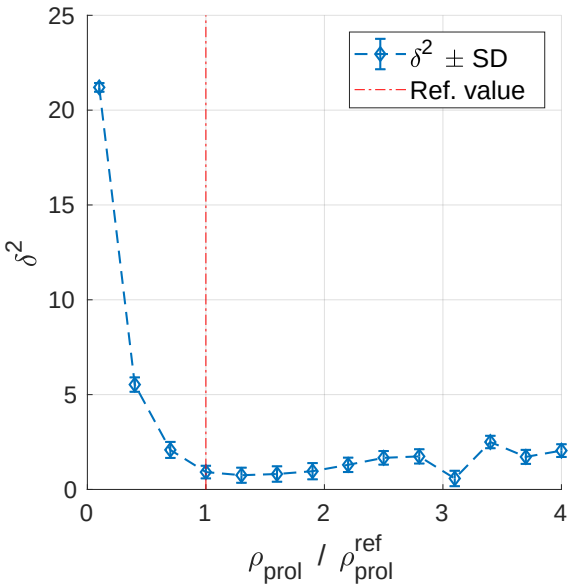
Ongoing work...

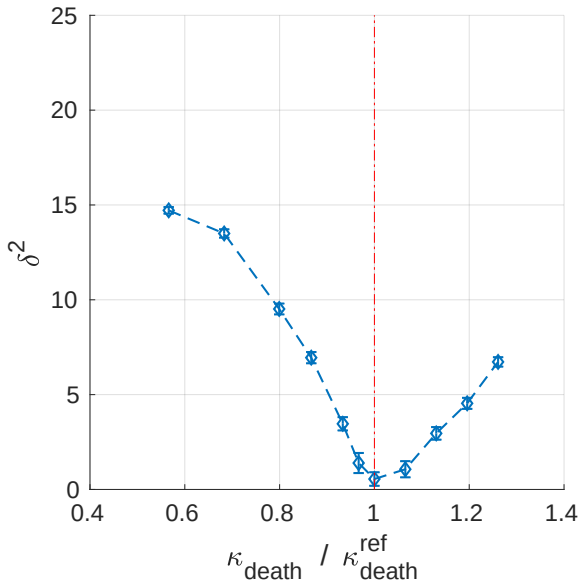
ABC parameter inversion of tumour model







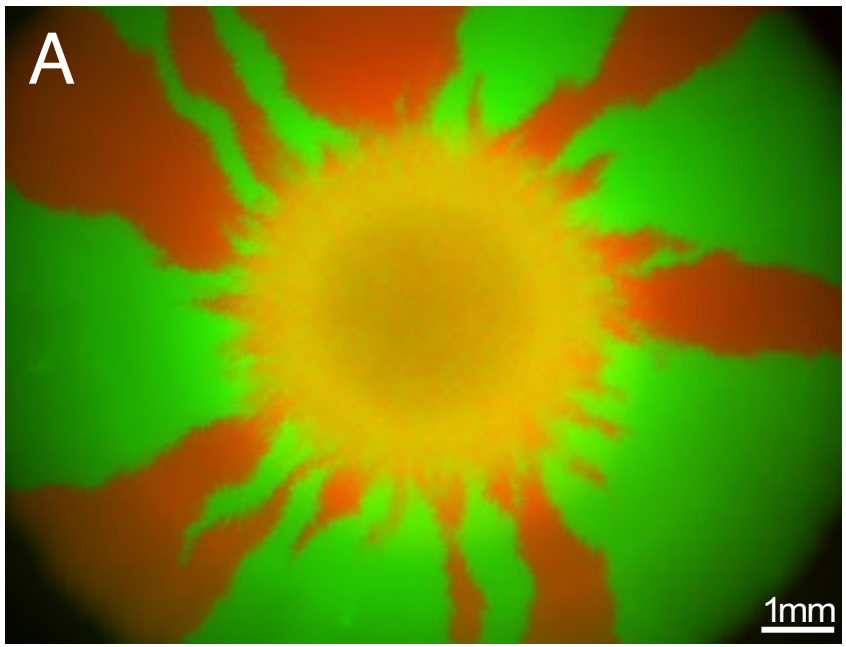




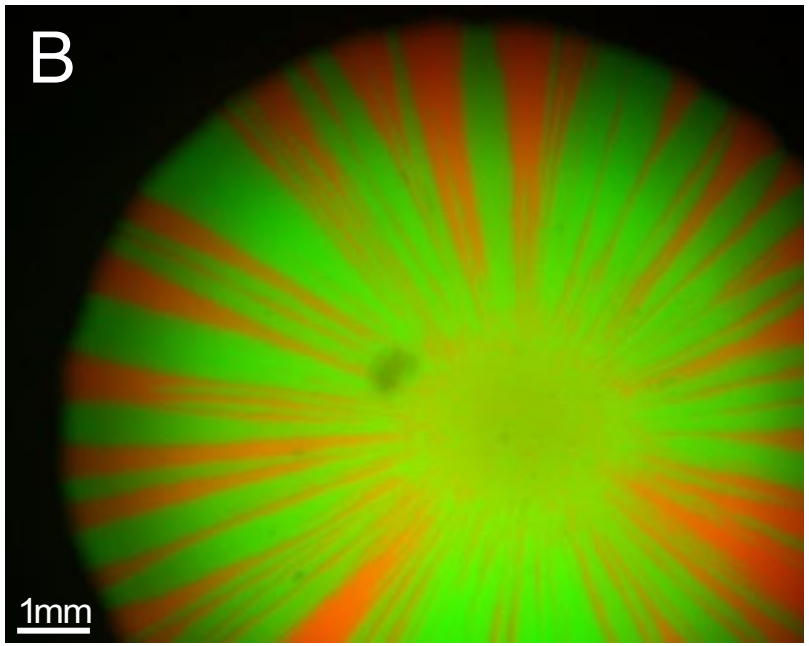
Pattern formation 1: colonization

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

E. coli



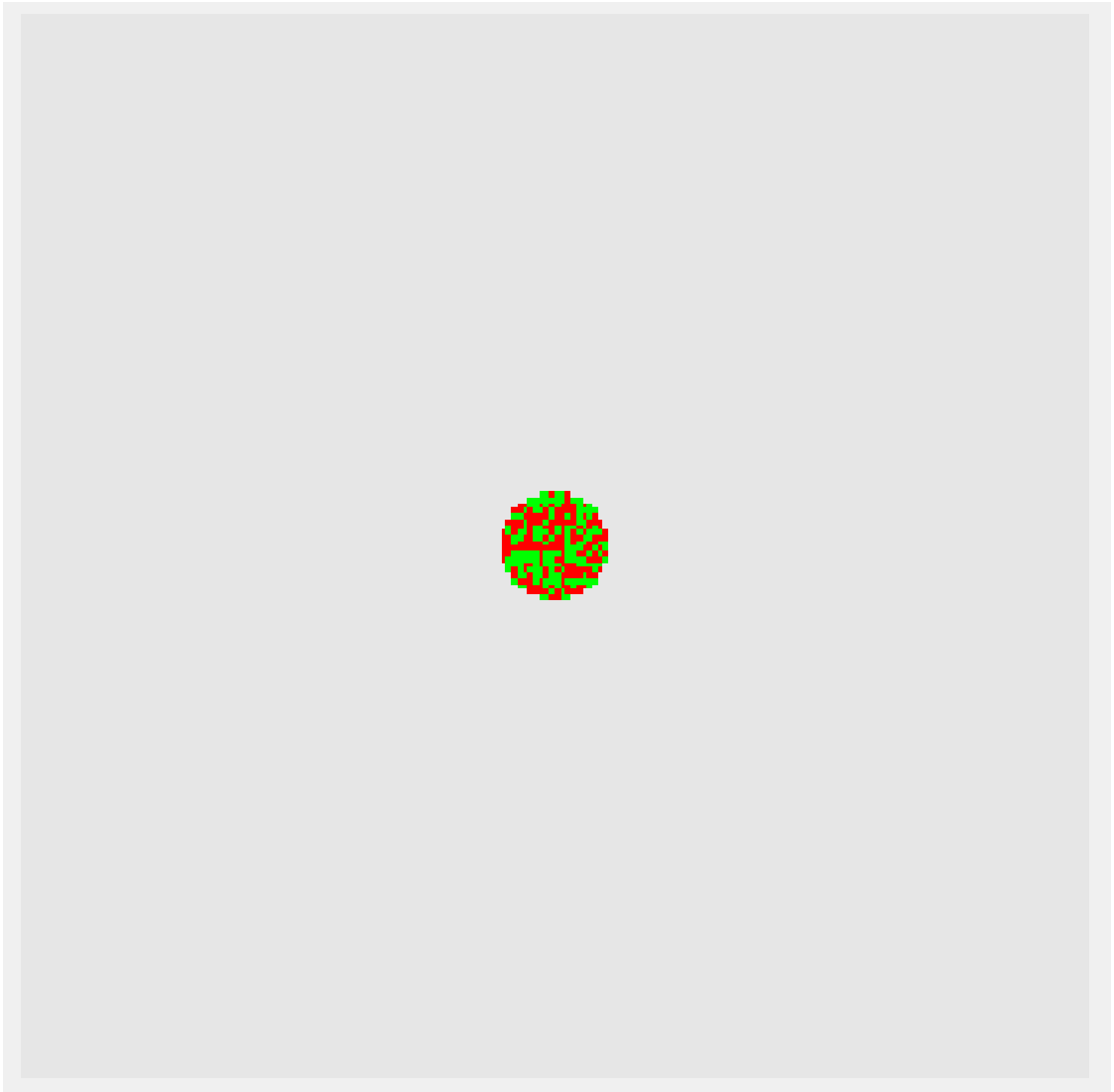
S. cerevisiae



-Through colonization the red/green gene wins.

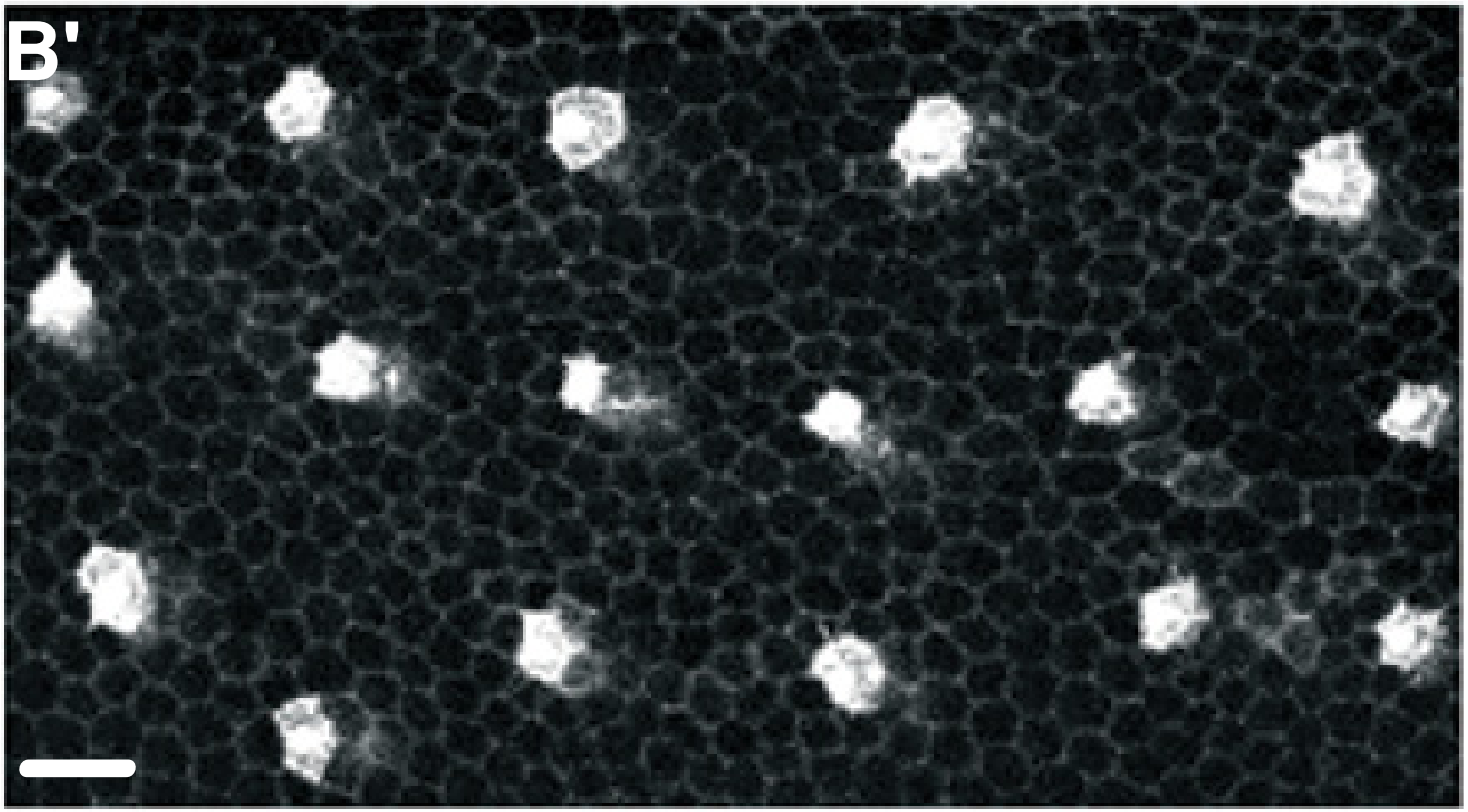
In silico colonization

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

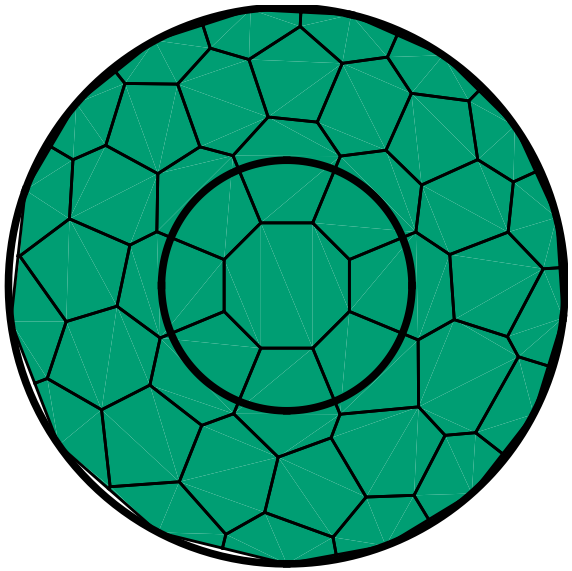
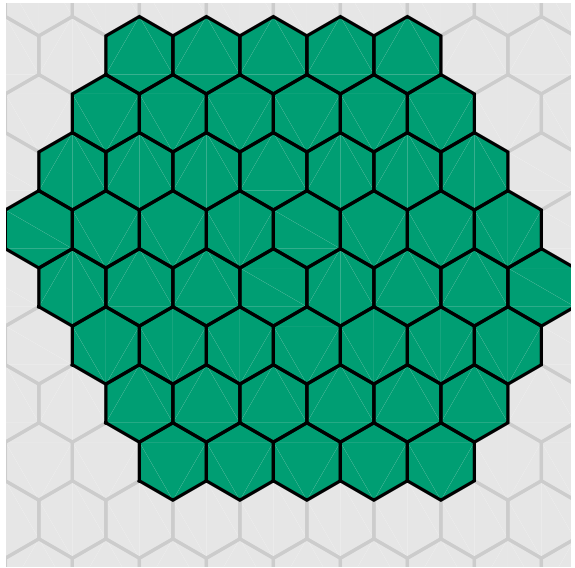
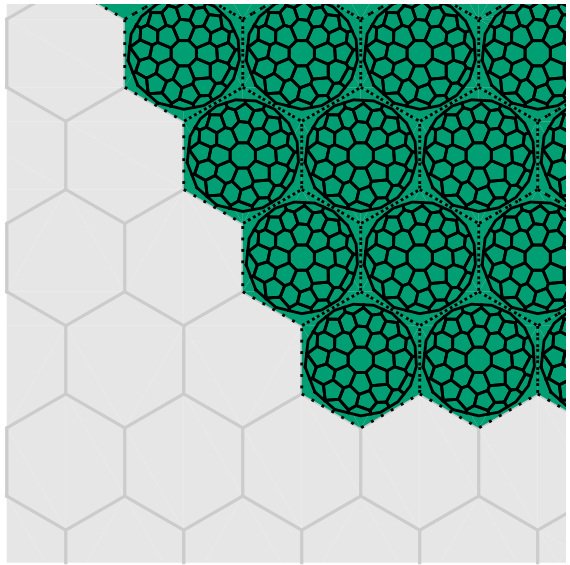


Pattern formation 2: protrusions

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



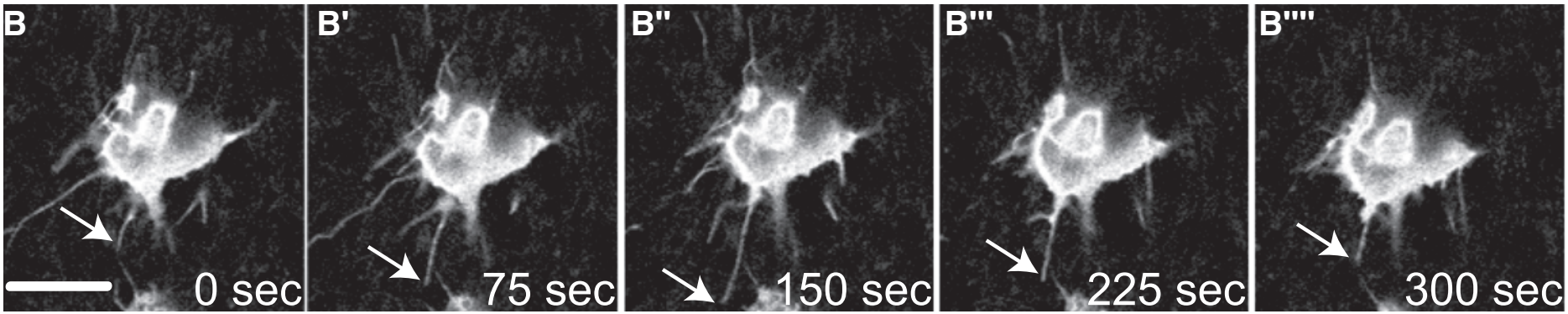
Spatial discretization

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

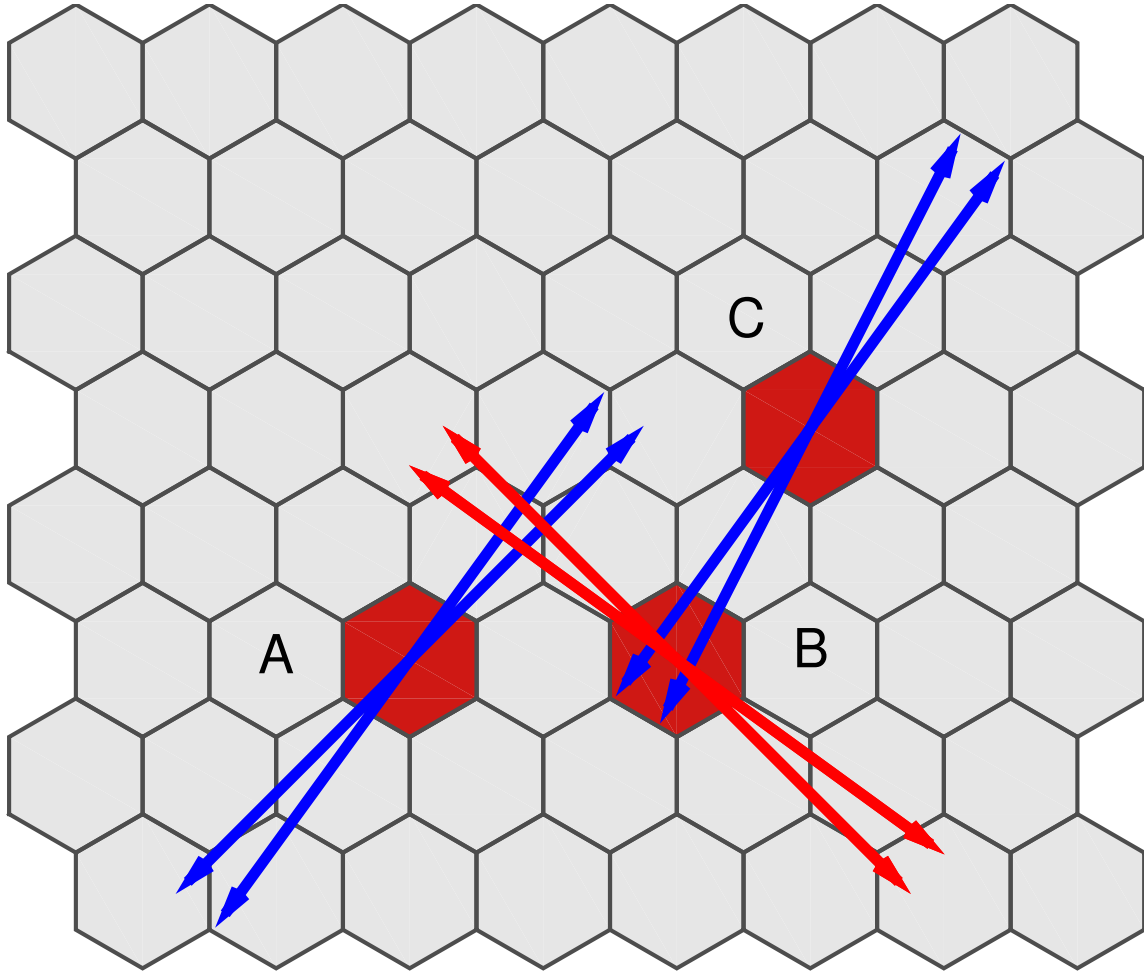
Protrusions

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



Protrusions model

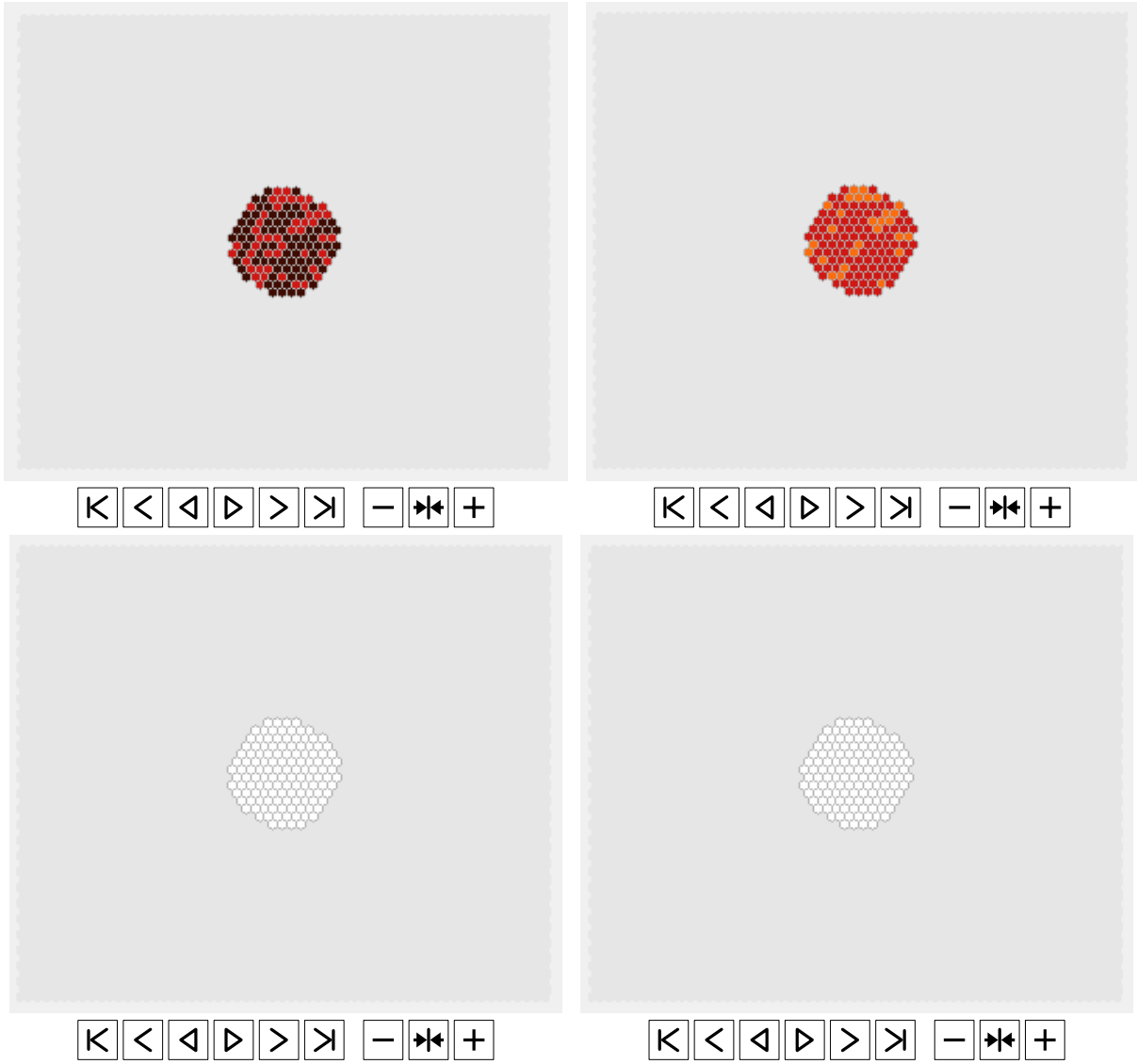
In silico model from Hadjivasiliou, *et al.*, J. R. Soc. Interface 13, 2016



(1) Direct, (2) protrusion mediated, and (3+4) non-symmetric protrusion-junctional.

Delta-notch: differential weighting of signals

Inner scale: spatial stochastic, outer scale: spatial stochastic



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- 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!