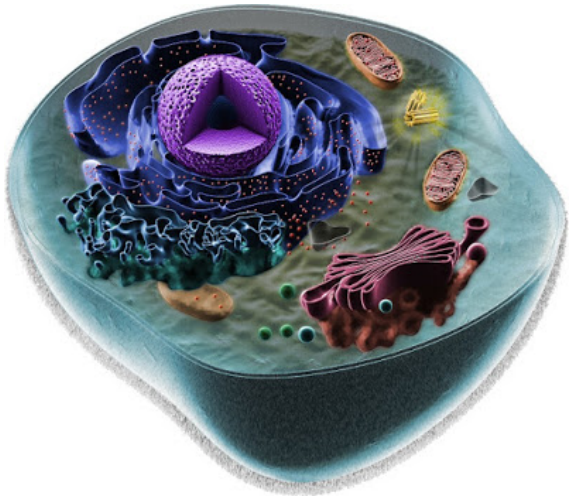
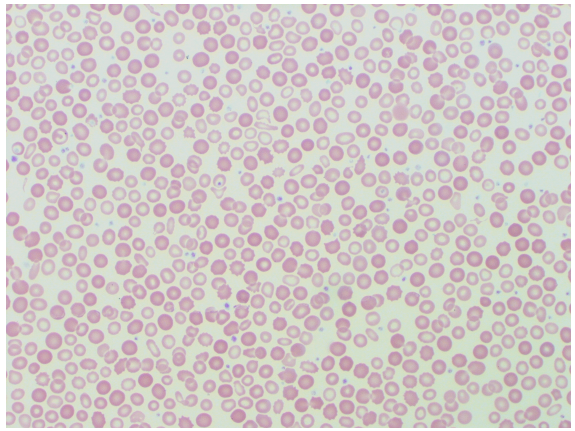
Bridging the scales between the single cell and the cell population - computational considerations





Stefan Engblom

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IPAM/UCLA, Los Angeles, CA, November 13th, 2017

Outline

Intro: data for inspiration & the modeling challenge

1. Computational modeling...
2. ...numerical analysis
3. Worked examples

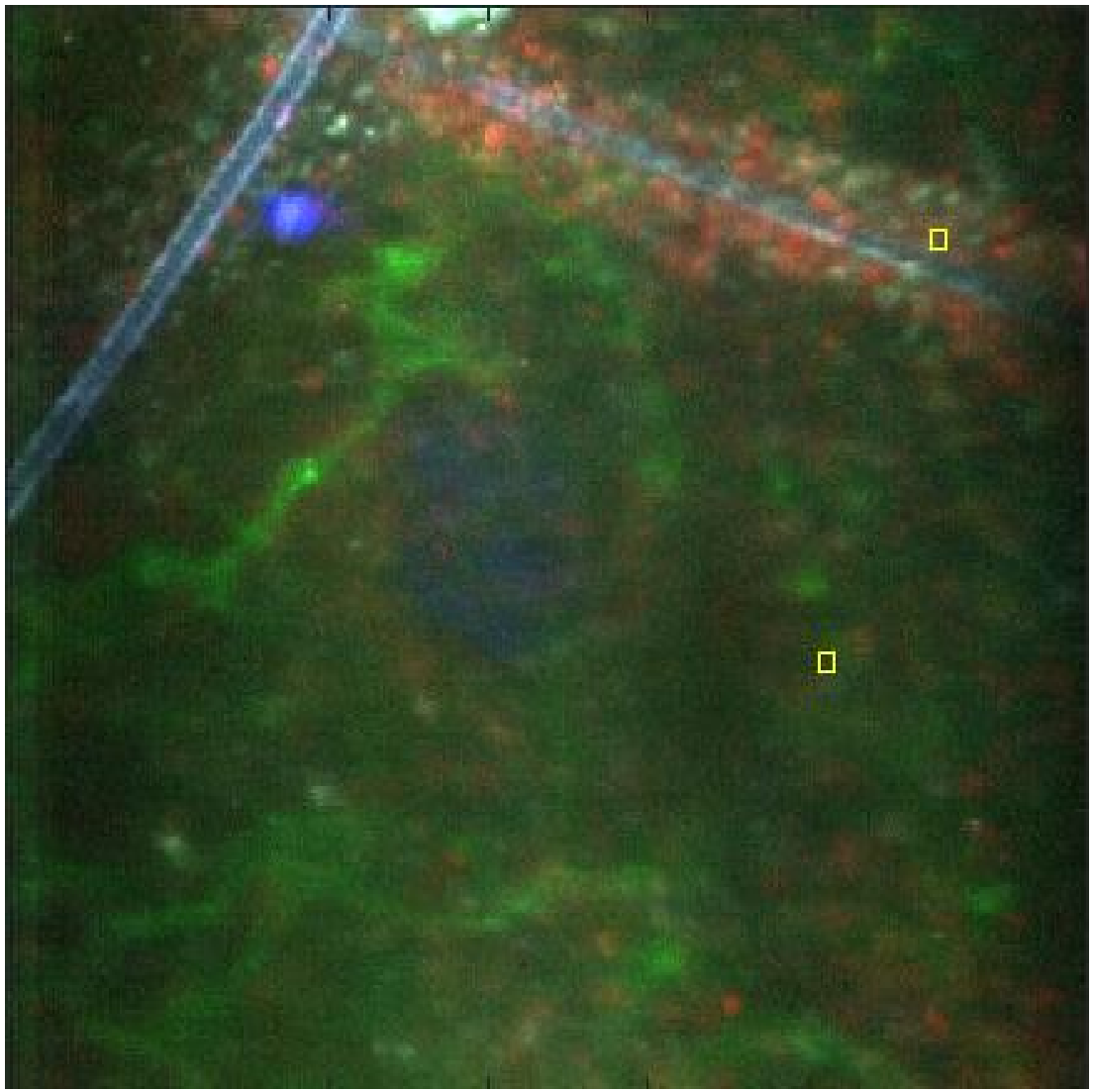
Summary

Joint work with and/or input from:

- **Mia Phillipson**, **Gustaf Christoffersson** @ 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

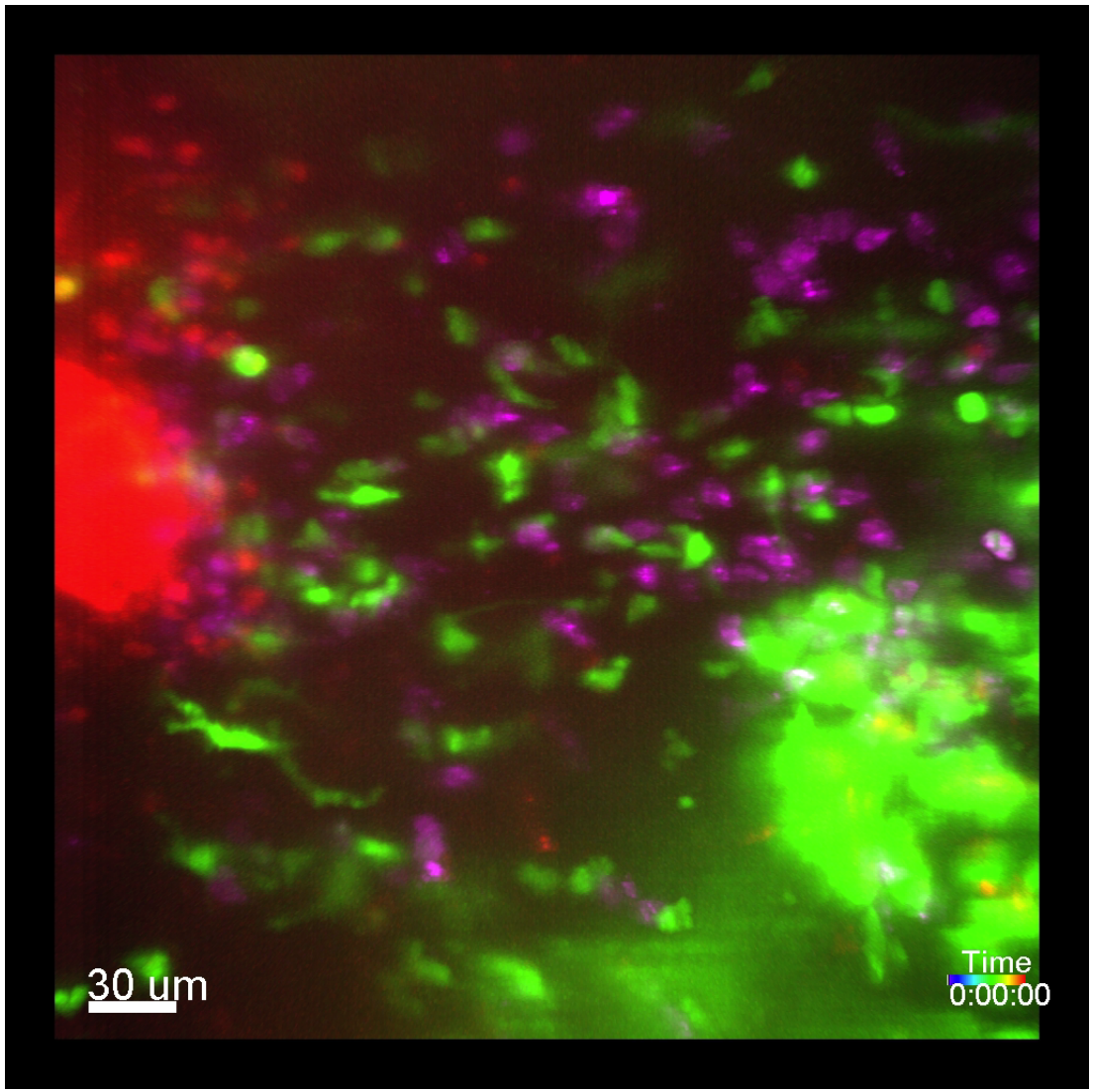
Wound healing around transplant

Recruitment of white blood-cells



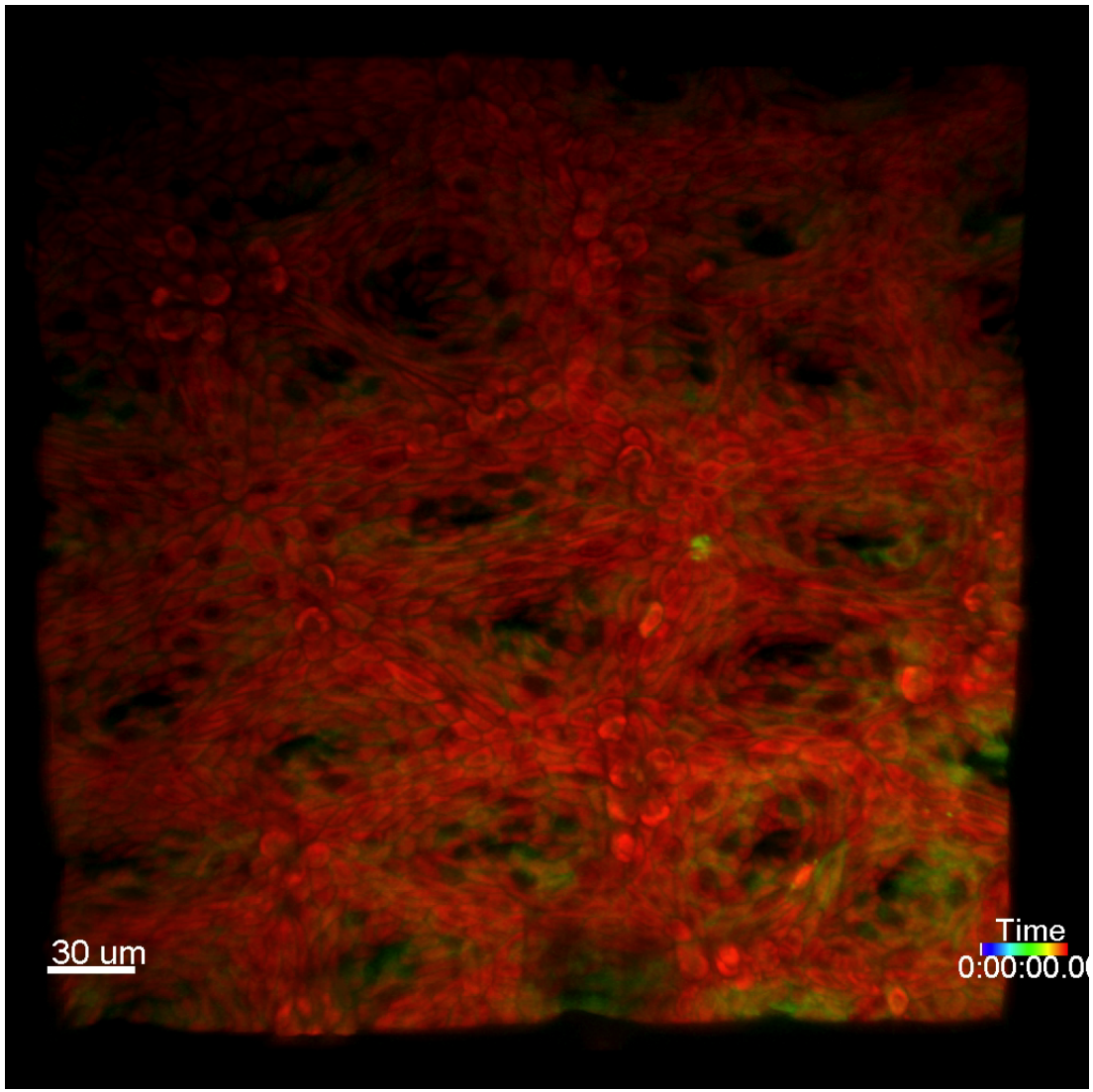
Migrating cells

Gradient sensing



Colon crypts

Stem cells



The modeling challenge

"How to think"

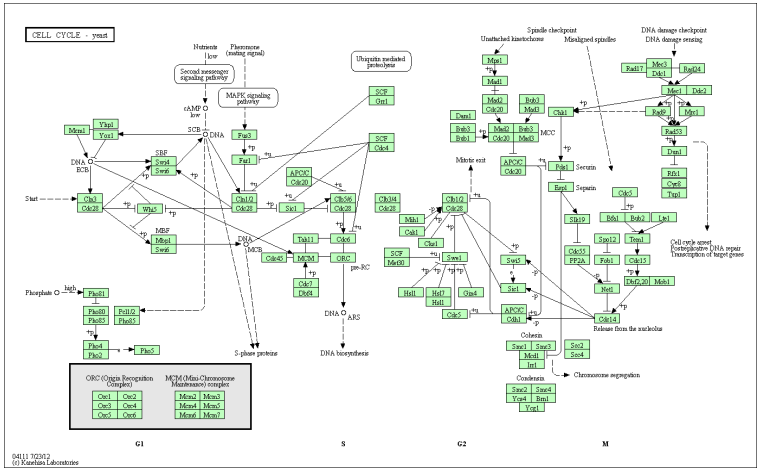
Aim: to develop **realistic** and **useful** computational models of populations of living cells.

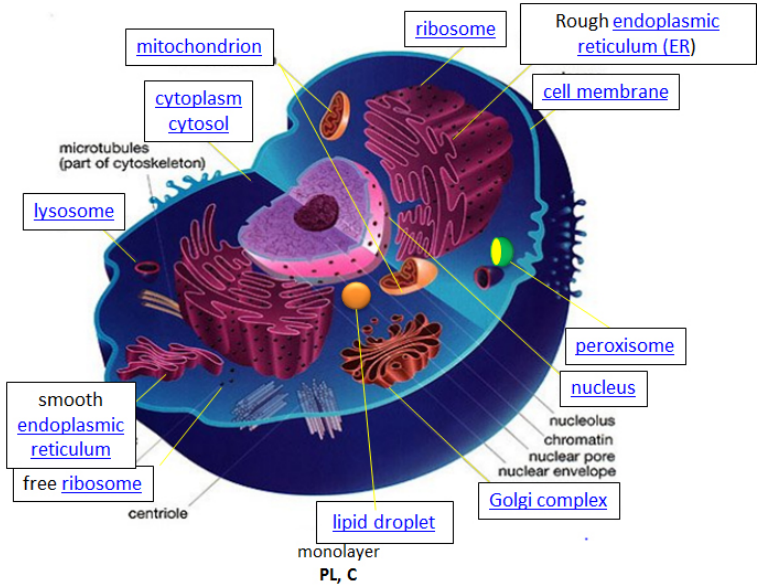
"Realistic" flexible and understandable (= analyzable) numerical models, that in the longer perspective can incorporate all conceivable relevant processes

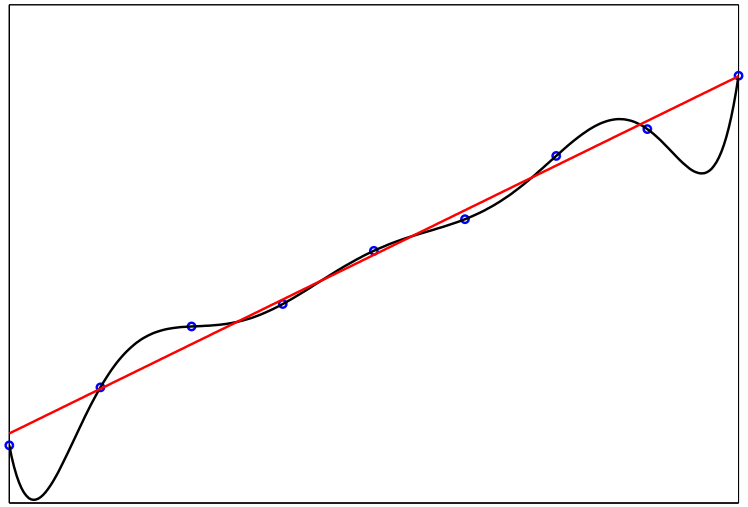
"Useful" (1) fully explanatory (including emergent behavior), (2) test hypotheses, (3) predictive value, (4) help to build an argument in cases where many factors are unknown

Risk of over-modeling

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







Caution:

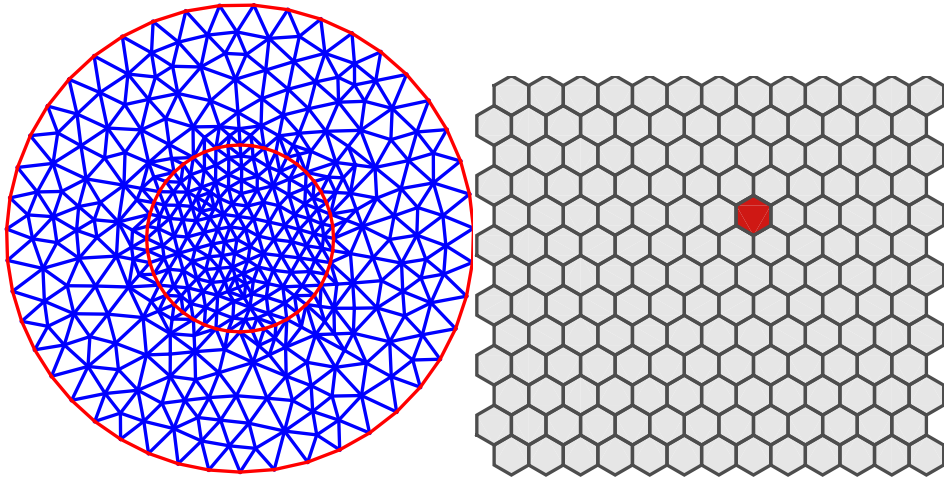
- *really* detailed, or,
- *imaginary* accuracy, or,
- just a plain overfit?

Rest of the talk

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

Computational modeling

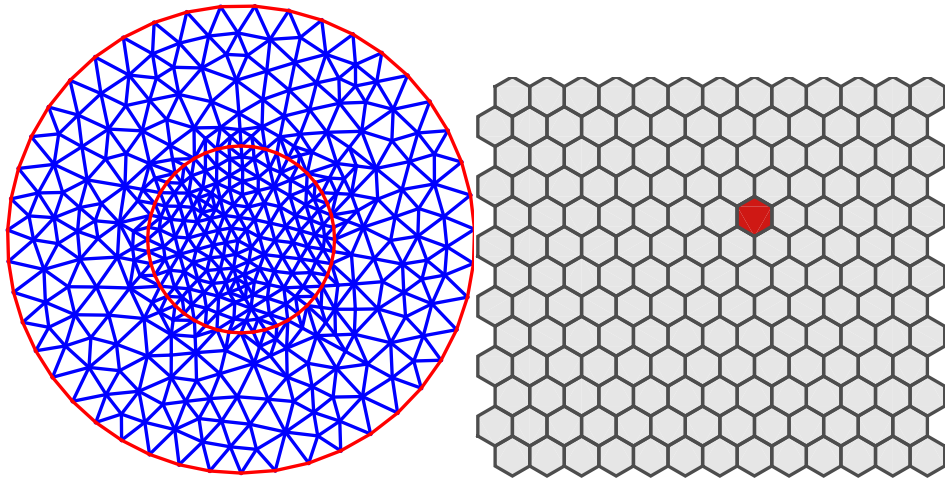
inner-outer idea



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

Computational modeling

inner-outer idea



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

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

One model to rule them all?

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

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"noisy"	stochastic
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The RDME

-A spatial continuous-time Markov chain stand out as a promising alternative. This is usually called 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.

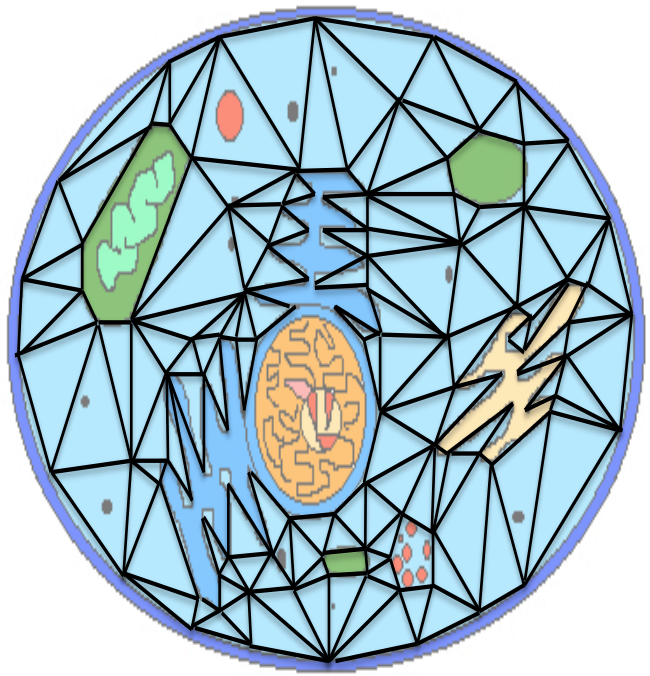
repeat

pick a random number

sample what happens and when

execute this event

until done



www.urdme.org

One model to rule them all?

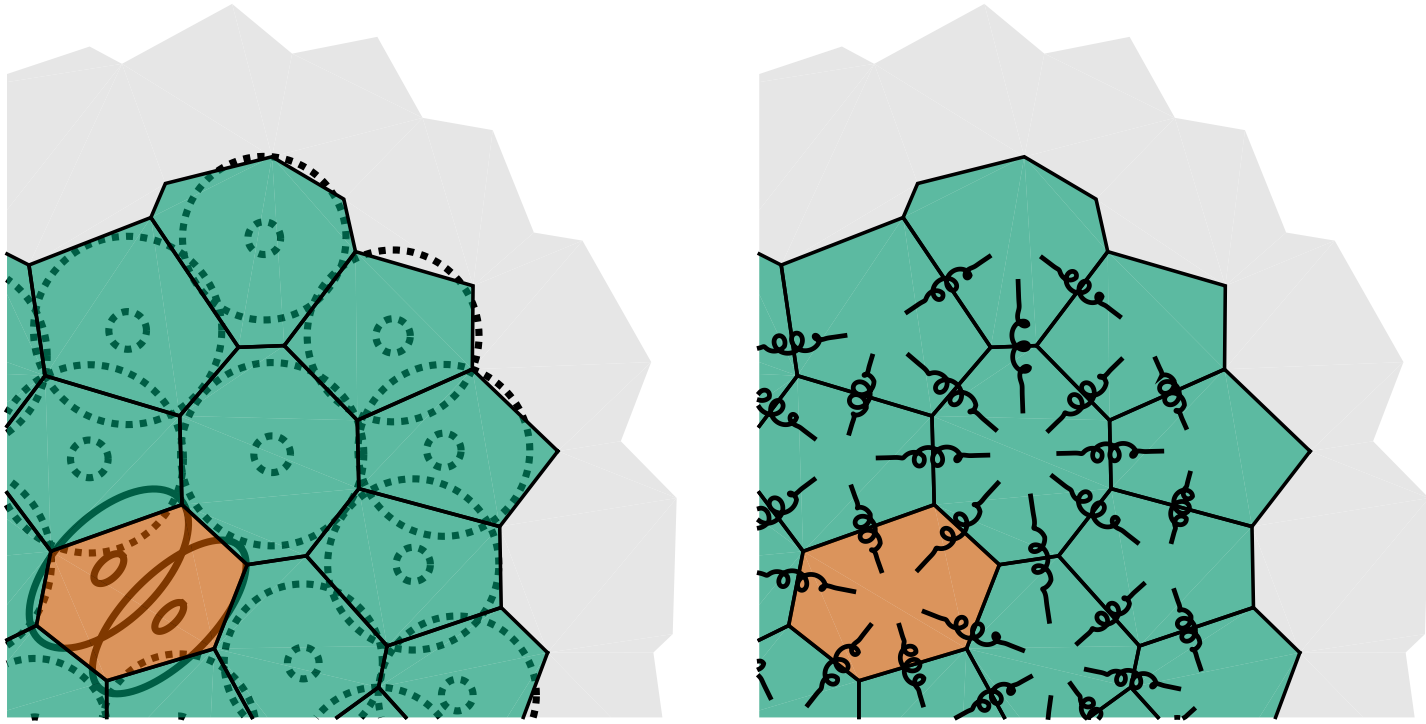
(cont)

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

-A difference is that cells move due to (1) mechanics/pushing, (2) active movements/crawling.

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).

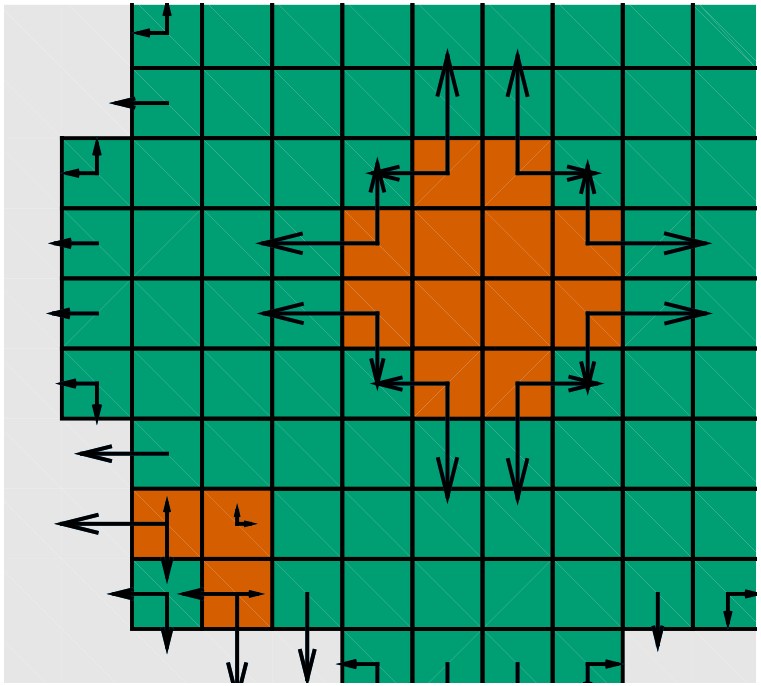
The idea 2

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.

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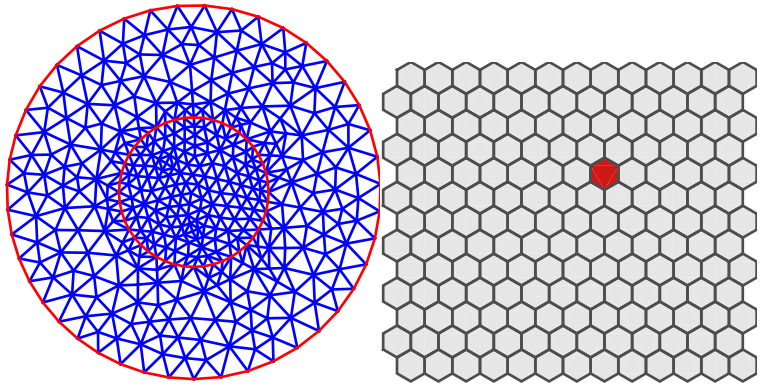
Observation #1: since both the inner scale and the outer scale are formed in continuous time, there is *one and only one* way of correctly coupling them together.

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.

Perhaps the main 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!* Hence the model itself is likely sensitive to perturbations in anyone of these.

Perhaps the main 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!* Hence the model itself is likely sensitive to perturbations in anyone of these.

Designing/understanding numerical methods: either we do

- An analysis by analogy/fingerspitzengefühl...
- Or, using the **Lax principle**: *if the numerical physics* $\approx$ *the wanted "true" physics (consistency), then the numerical solution* $\rightarrow$ *the true solution (convergence) IFF the numerical physics is stable*

Notation

Local physics, e.g. in a single voxel

-State $X \in \mathbf{Z}_+^D$, counting the number of each of D species/agents/compartments.

-Events/reactions are transitions between these states,

$$X \xrightarrow{w_r(X)} X - \mathbb{N}_r, \qquad \mathbb{N} \in \mathbf{Z}^{D \times R} \text{ (\textit{stoichiometric matrix})}$$

with *propensity* $w_r : \mathbf{Z}_+^D \to \mathbf{R}_+$, $r = 1...R$.

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-Poisson representation

$$X(t) = X(0) - \sum_r \mathbb{N}_r \Pi_r \left(\int_0^t w_r(X(s))\, ds \right),$$

each Π_r a unit-rate Poisson process.

Notation

Spatial physics

Total volume Ω subdivided into small enough voxels Ω_j such that the local physics is an accurate model.

- The state of the system is now an array $\mathbb{X}$ with $D \times K$ elements; D species $\mathbb{X}_{ij}$, $i = 1, \ldots, D$, counted separately in K voxels, $j = 1, \ldots, K$.
- This state is changed by local physics events (vertically in $\mathbb{X}$) *and* by transport into adjacent voxels (horizontally in $\mathbb{X}$).

Local physics

Per voxel (e.g. reactions)

Same model in K voxels, $j = 1, \ldots, K$,

$$\mathbb{X}_{ij}(t) = \mathbb{X}_{ij}(0) - \sum_r \mathbb{N}_{ri} \Pi_{rj} \left(\int_0^t w_{rj}(\mathbb{X}_{\cdot,j}(s))\, ds \right),$$

for $i = 1, \ldots, D$ species.

Transport mechanism

Across voxels (e.g. diffusion)

Linear model (convection/diffusion): transport from one voxel Ω_j to another voxel Ω_k according to

$$\mathbb{X}_{ij} \xrightarrow{q_{ijk}\mathbb{X}_{ij}} \mathbb{X}_{ik},$$

where q_{ijk} is non-zero only for connected voxels.

$$\mathbb{X}_{ij}(t) = \mathbb{X}_{ij}(0) - \sum_k \Pi'_{ijk} \left(\int_0^t q_{ijk}\mathbb{X}_{ij}(s)\, ds \right) + \sum_k \Pi'_{ikj} \left(\int_0^t q_{ikj}\mathbb{X}_{ik}(s)\, ds \right).$$

Computational framework

RDME

Combining reactions with transport events we arrive at

$$\begin{aligned}\mathbb{X}_{ij}(t) =& \mathbb{X}_{ij}(0) - \sum_r \mathbb{N}_{ri}\Pi_{rj}\left(\int_0^t w_{rj}(\mathbb{X}_{\cdot,j}(s))\,ds\right) \\ &- \sum_k \Pi'_{ijk}\left(\int_0^t q_{ijk}\mathbb{X}_{ij}(s)\,ds\right) + \sum_k \Pi'_{ikj}\left(\int_0^t q_{ikj}\mathbb{X}_{ik}(s)\,ds\right).\end{aligned}$$

Assumptions

Local physics first...

Recall: CTMC $X(t) \in \mathbf{Z}_+^D$ governed by transitions

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Norm $\|x\|_{\boldsymbol{I}} := \boldsymbol{I}^T x$, $x \in \mathbf{Z}_+^D$.

Assumptions: $x, y \in \mathbf{Z}_+^D$,

(i) $-\boldsymbol{I}^T \mathbb{N} w(x) \le A + \alpha \|x\|_{\boldsymbol{I}}$ ("$\boldsymbol{I}$-outward bound")

(ii) $(-\boldsymbol{I}^T \mathbb{N})^2 w(x)/2 \le B + \beta_1 \|x\|_{\boldsymbol{I}} + \beta_2 \|x\|_{\boldsymbol{I}}^2$ ("$\boldsymbol{I}$-outward absolute bound")

(iii) $|w_r(x) - w_r(y)| \le L_r(P)\|x - y\|$, $r = 1, \dots, R$, and $\|x\|_{\boldsymbol{I}} \vee \|y\|_{\boldsymbol{I}} \le P$

The "blue assumptions".

Assumptions

...then add space

Recall: CTMC $\mathbb{X}(t) \in \mathbf{Z}_+^{D\times K}$ with transitions

$$\mathbb{X}_{\cdot,k} \xrightarrow{w_{rk}(\mathbb{X}_{\cdot,k})} \mathbb{X}_{\cdot,k} - \mathbb{N}_r, \quad \mathbb{X}_{ij} \xrightarrow{q_{ijk}\mathbb{X}_{ij}} \mathbb{X}_{ik},$$

$k = 1...K$ voxels, $i = 1...D$ species, $r = 1...R$ reactions. To get "PDE-feeling",

$$\mathbf{v}_t = -\mathbb{N}u(\mathbf{v}) + \underbrace{Q}_{\text{e.g. } \approx\nabla\cdot\Sigma\nabla}\mathbf{v},$$

where $\mathbf{v}_{ik} \sim \mathbb{E}[\mathbb{X}_{ik}\Omega_k^{-1}]$.

Assumptions

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Assumptions:

(iv) $w_{rk}(x) = \Omega_k u_r(\Omega_k^{-1}x)$, "density dependent"

A priori

Norms: $\|\mathbb{X}\|_{\boldsymbol{I},1} \equiv \sum_{j=1}^{K} \|\mathbb{X}_{\cdot,k}\|_{\boldsymbol{I}} = \boldsymbol{I}^T \mathbb{X} \mathbf{1}$, $\|\mathbb{X}\|^2 \equiv \sum_{i,j} \mathbb{X}_{ij}^2$.

With suitable initial data...

- $\mathbb{E}[\sup_{s\in[0,t]} \|\mathbb{X}(s)\|_{\boldsymbol{I},1}^p]$ 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 transition intensities ($w_r \to (1 \pm \delta) w_r$), then

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

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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 the 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 $\bar{\mathbb{X}}(t) = \bar{\mathbb{X}}_{ij}(t) \sim 1$.

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Multiscale splitting methods:

"Hybrid", $\bar{\mathbb{Y}}(t)$ all Poisson processes driving an abundant species are replaced with mean drift terms, $\Pi(t) \approx t$, so 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 the (Assumptions) above,

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

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Time-discretization error

Under the (Assumptions) above, 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

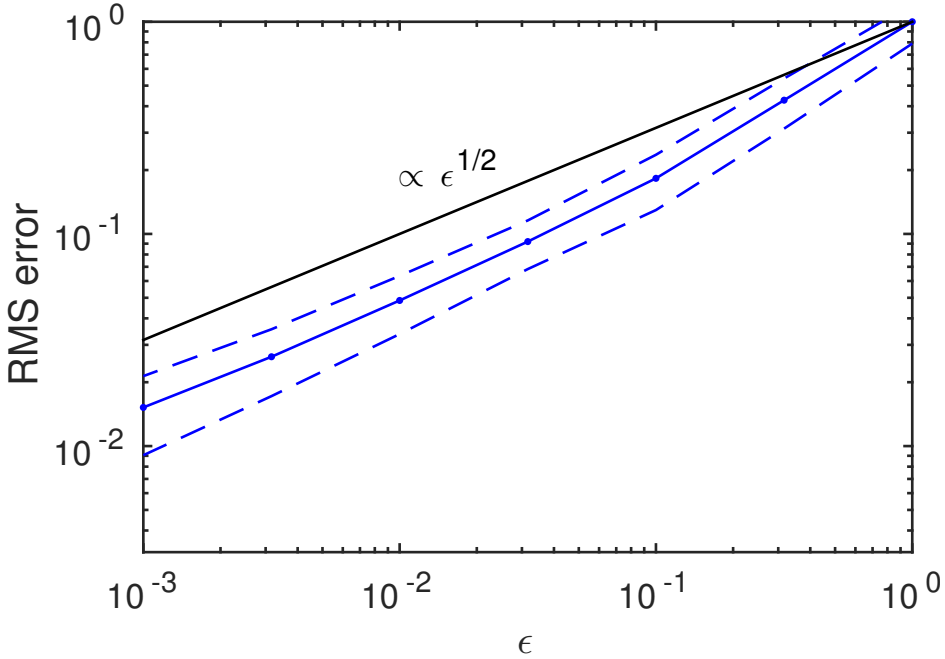
"Stress test" of theory

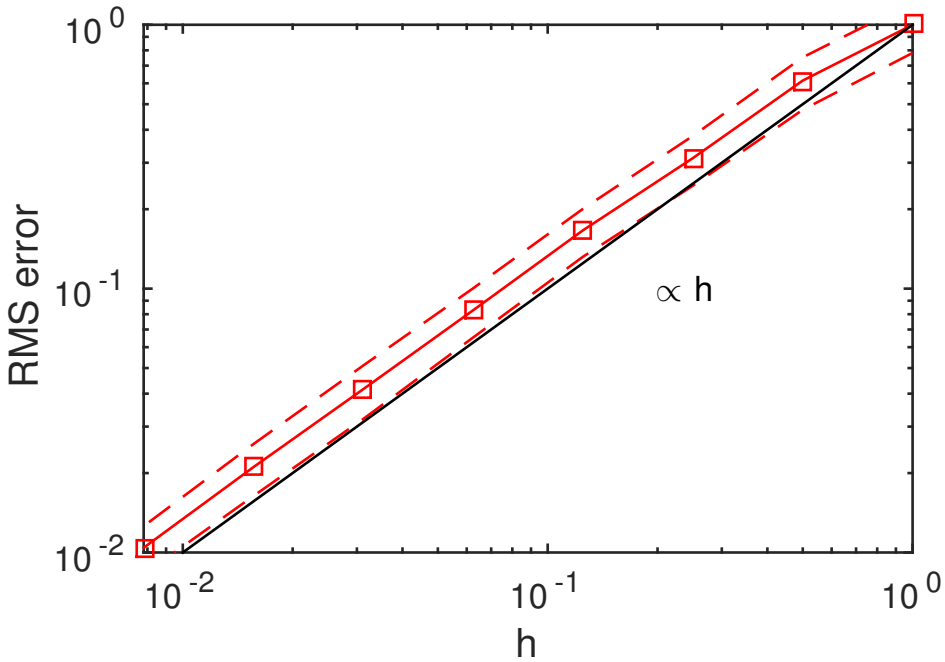
$(A, C) \sim \epsilon^{-1}$, $(B, D) \sim 1$, $\text{diffusion}_{A,C} \sim \epsilon$, $\text{diffusion}_{B,D} \sim 1$.

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

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

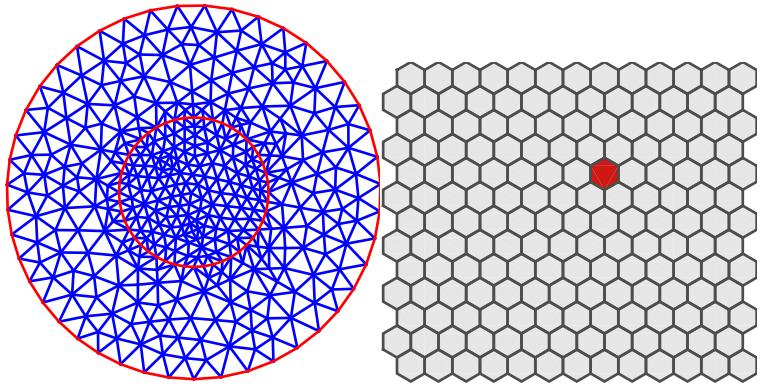
$$B + B \underset{k_d D}{\overset{k_b B(B-1)}{\rightleftharpoons}} D$$





Modeling framework

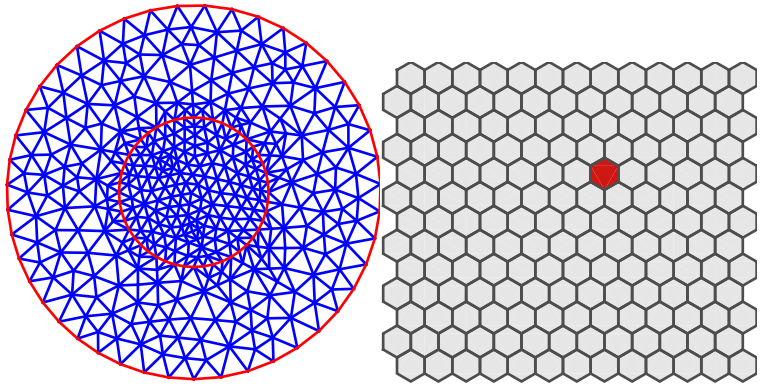
RDME & DLCM



	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}.

-*Work still to be done:* analyze the DLCM following the outlined RDME theory.

Cellular communication: delta-notch

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

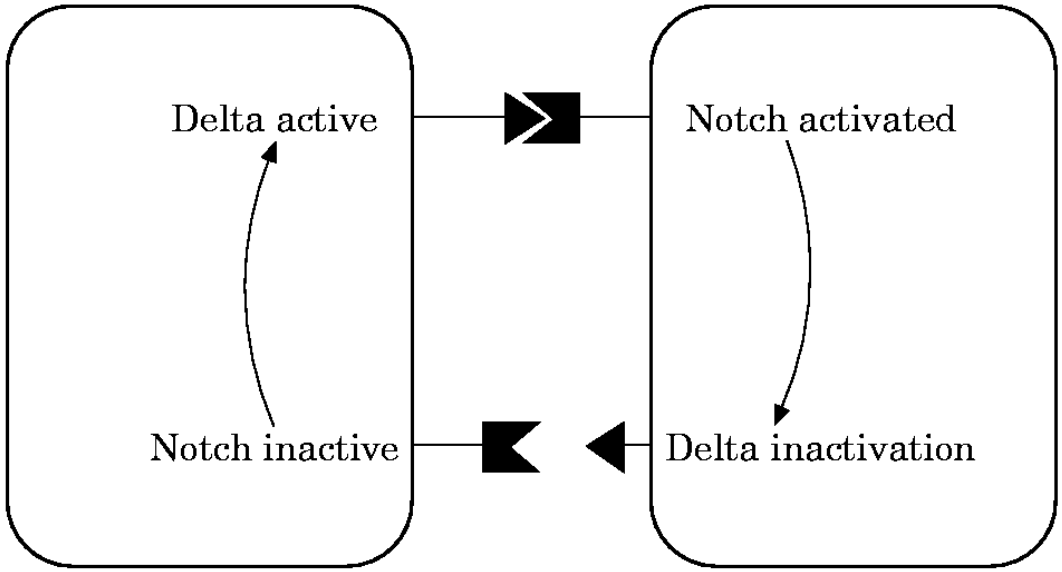
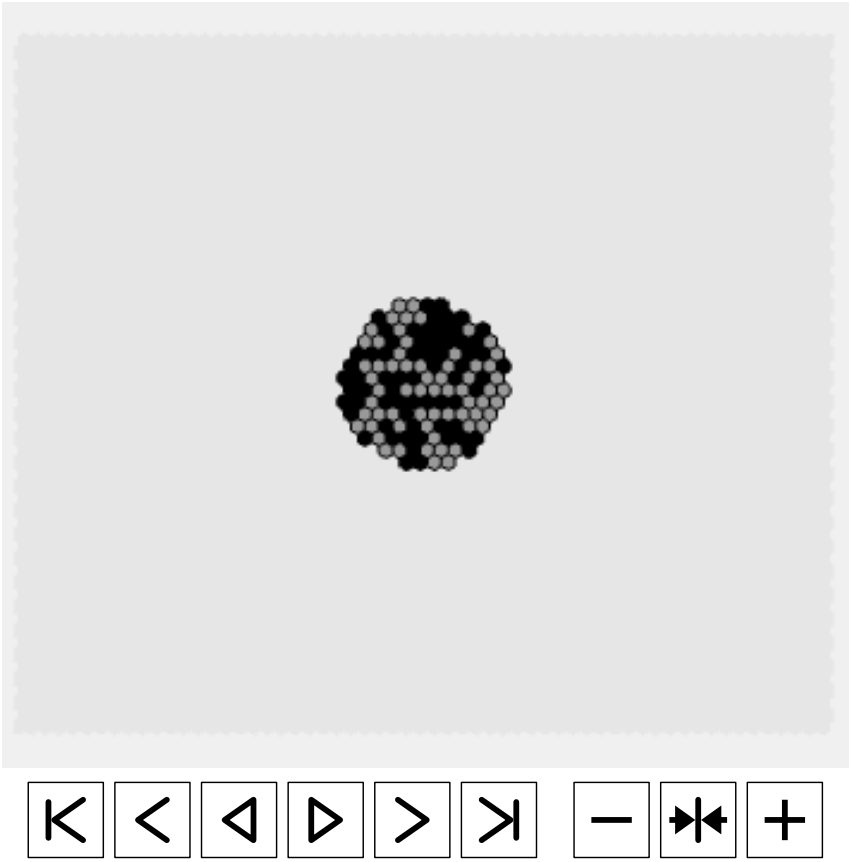


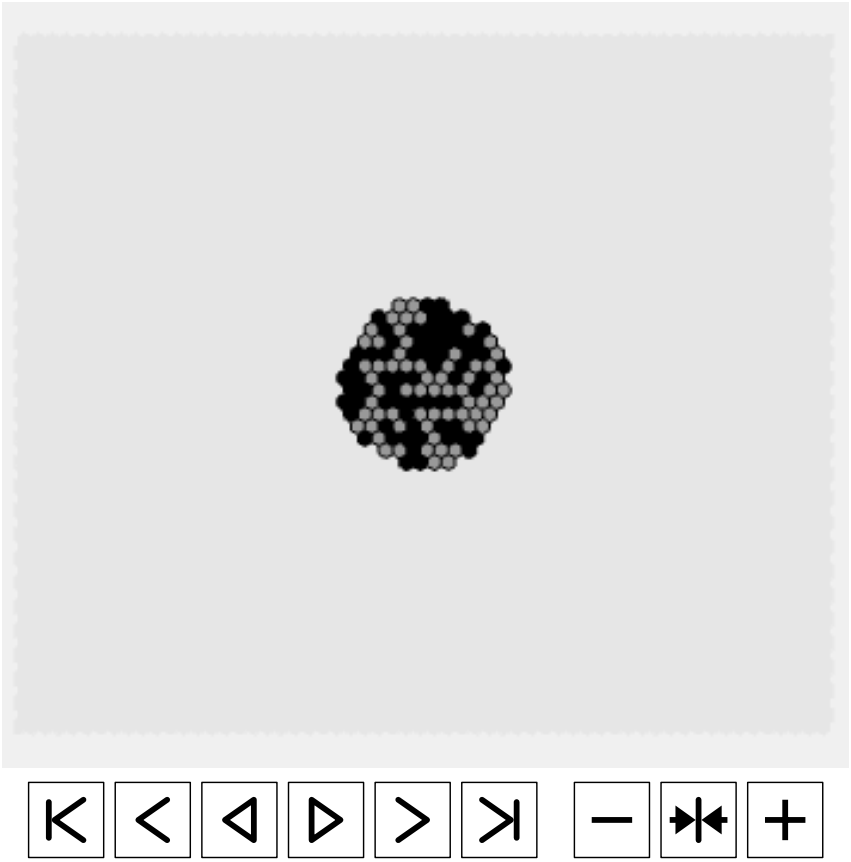
FIG. 1. Diagrammatic representation of the effective feedback loop between Notch and Delta in neighbouring cells. Details of the Notch signalling pathway are omitted for clarity. *Key*: ▶ Delta; ⊣ Notch.

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

Cellular communication: delta-notch

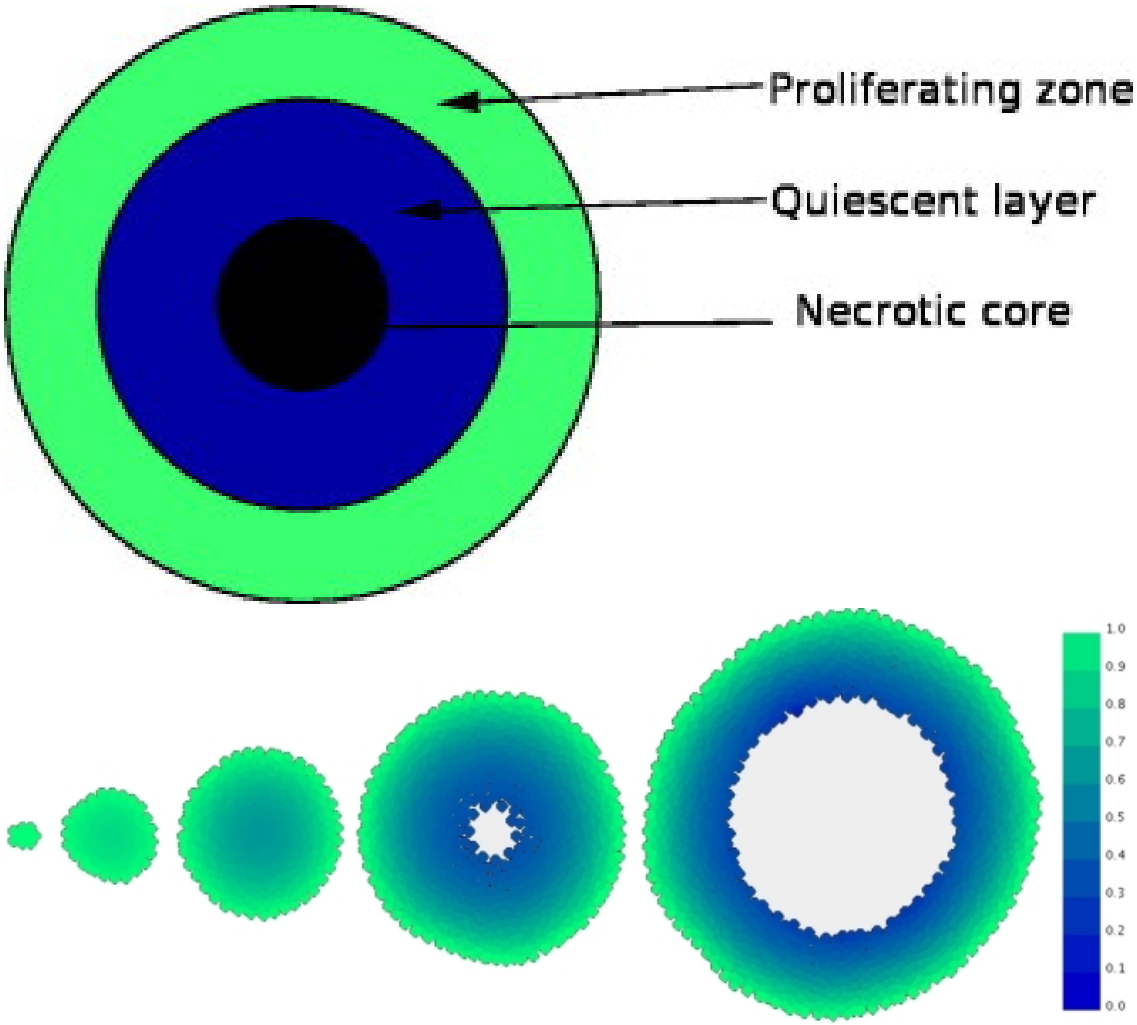
Inner scale: ODE, outer scale: spatial stochastic





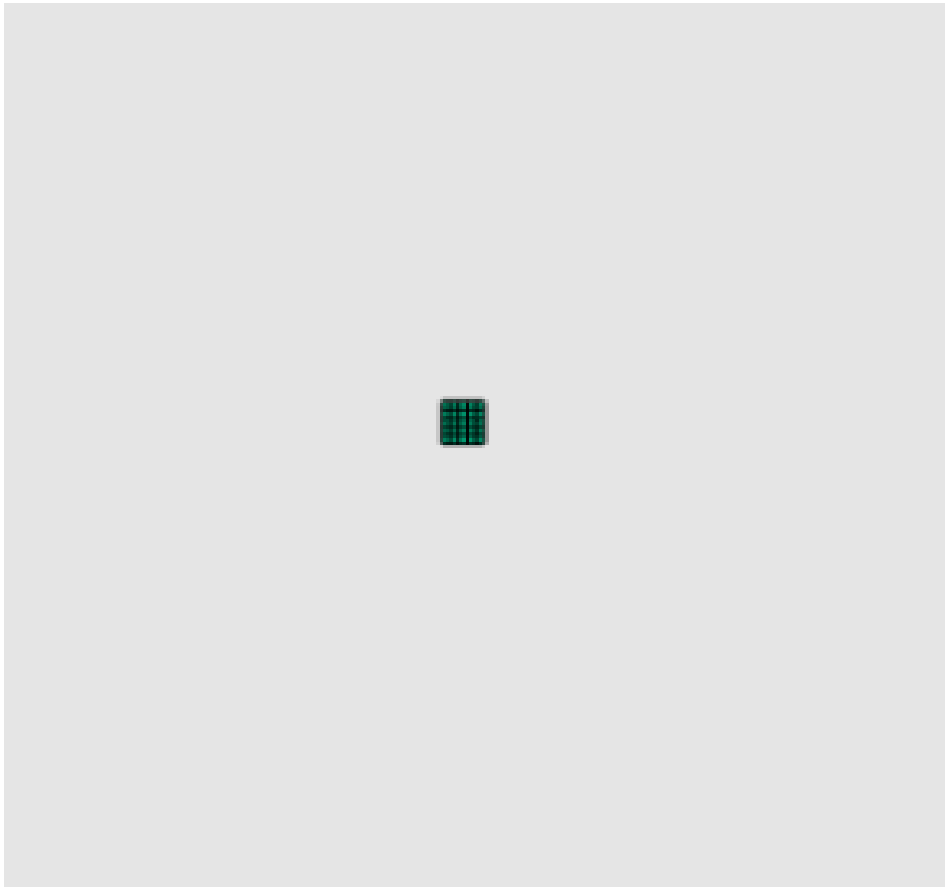
Non-trivial dynamics in tumour

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



Non-trivial dynamics in tumour

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

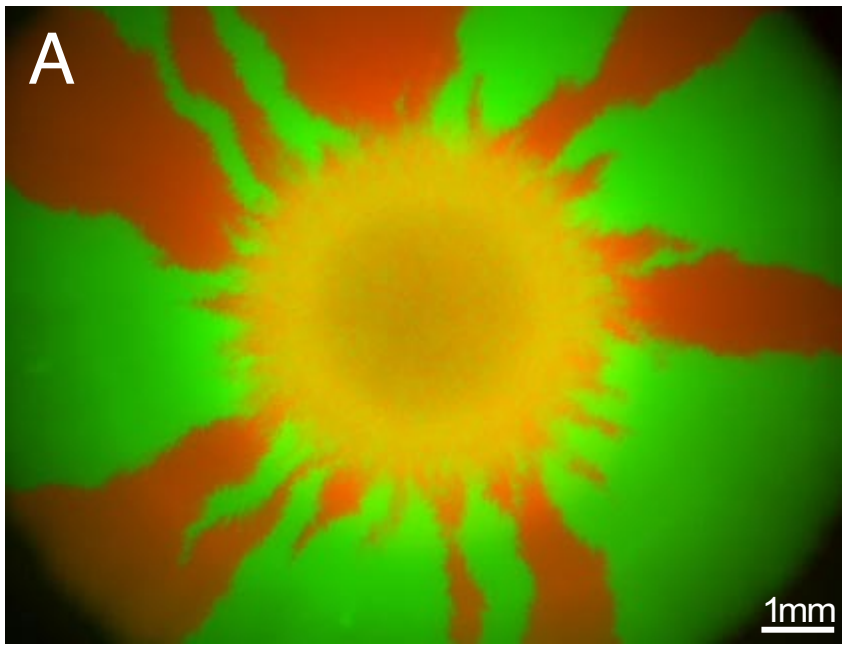


-Finding (emergent behavior): increasing the surface means increasing oxygen intake $\Longrightarrow$ steady-state is unstable.

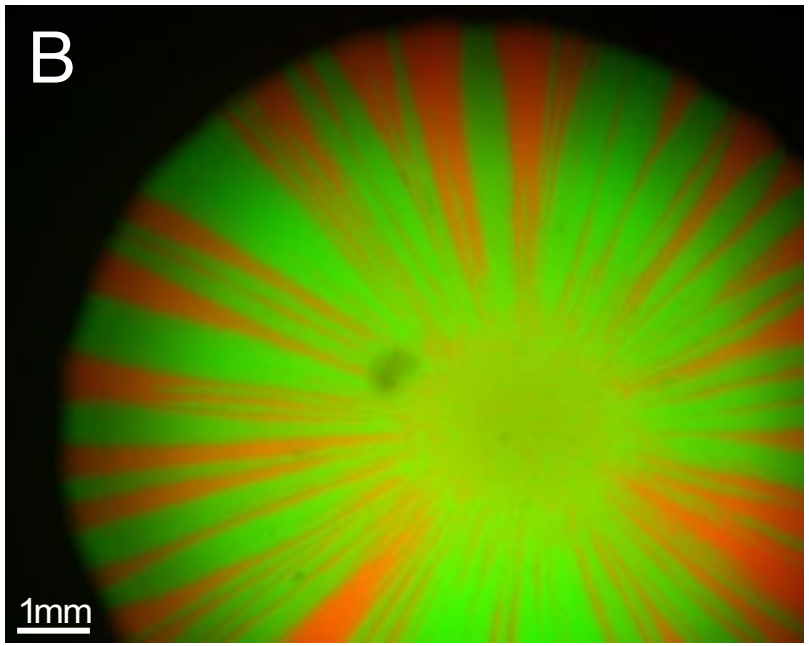
Pattern formation 1: colonization

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

E. coli



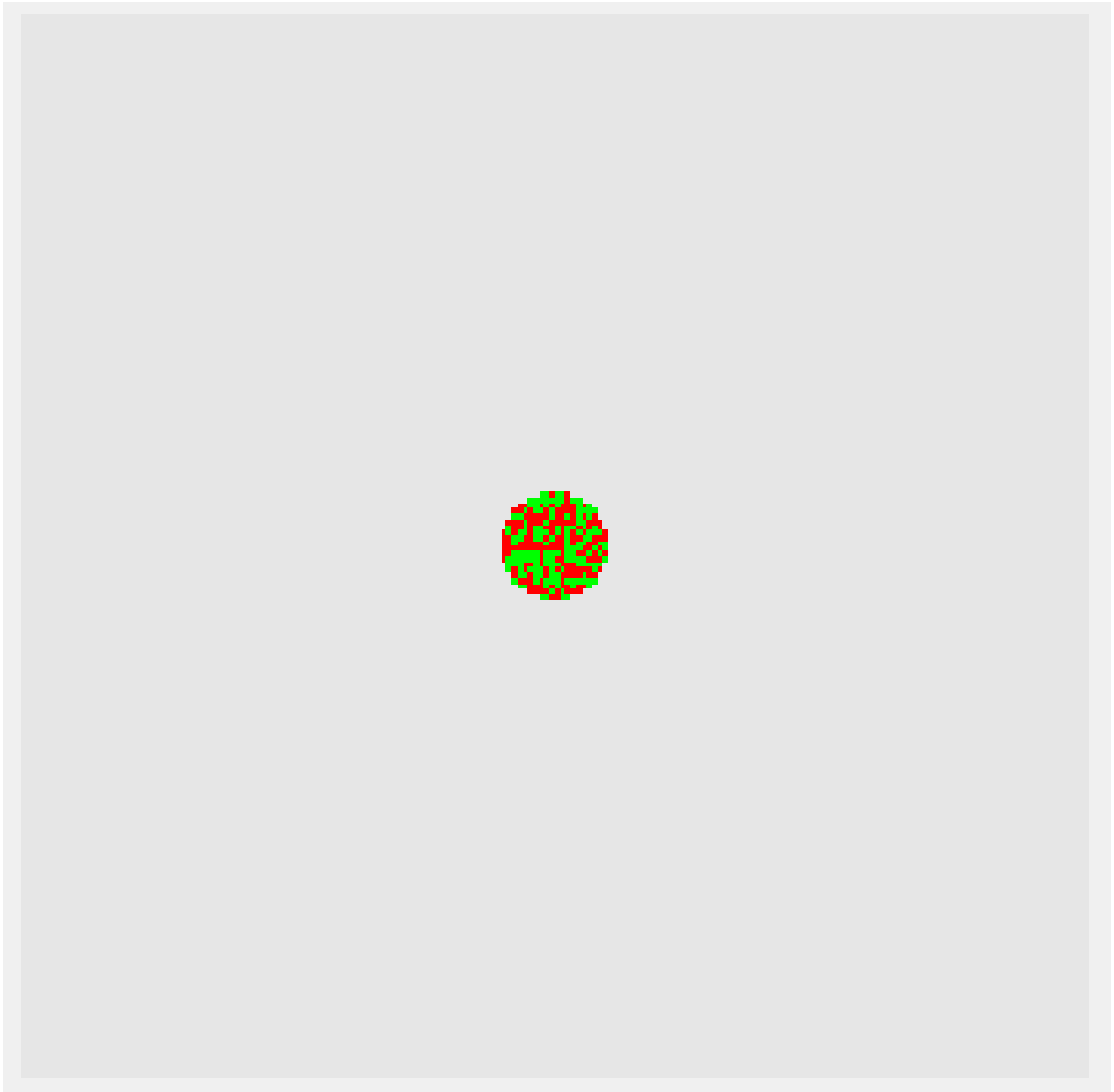
S. cerevisiae



-Through colonization the red/green gene wins.

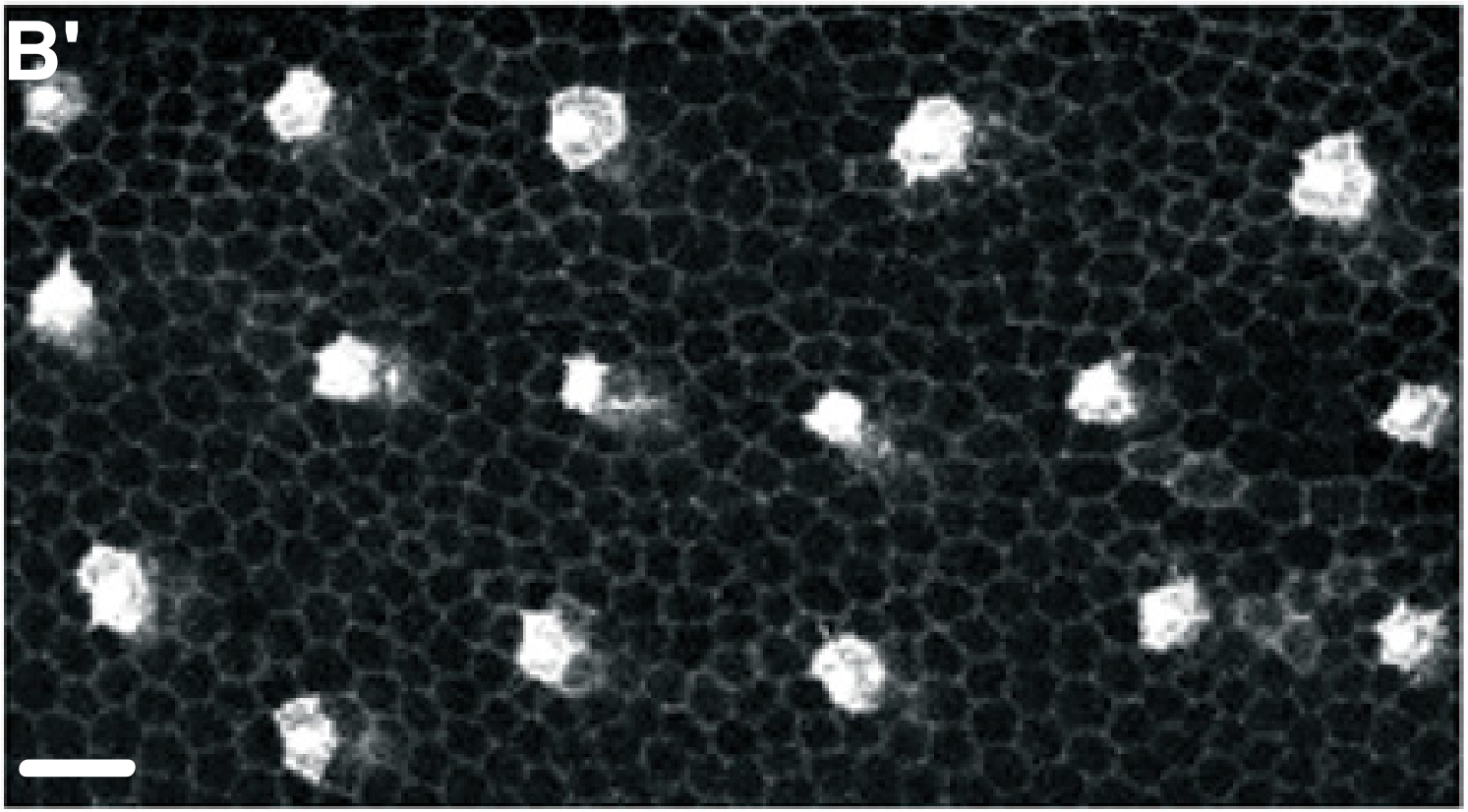
In silico colonization

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



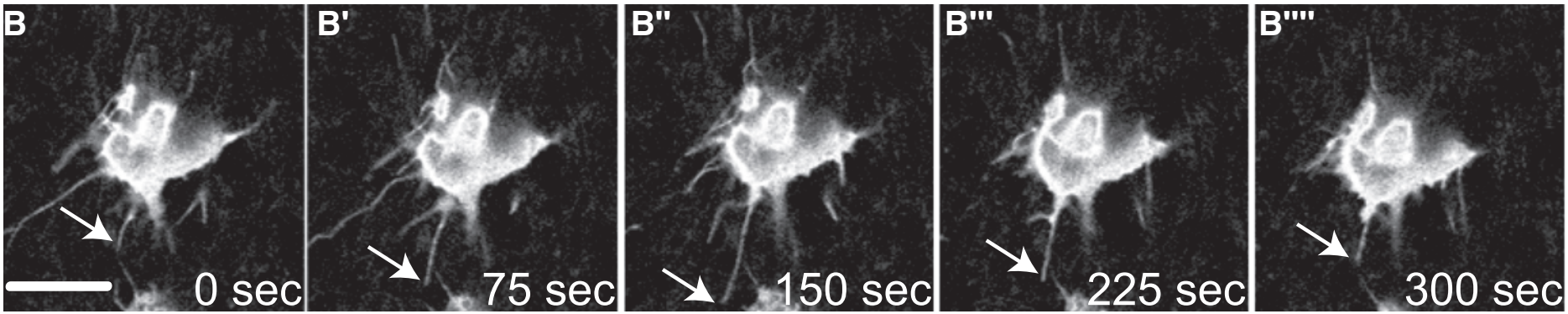
Pattern formation 2: protrusions

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



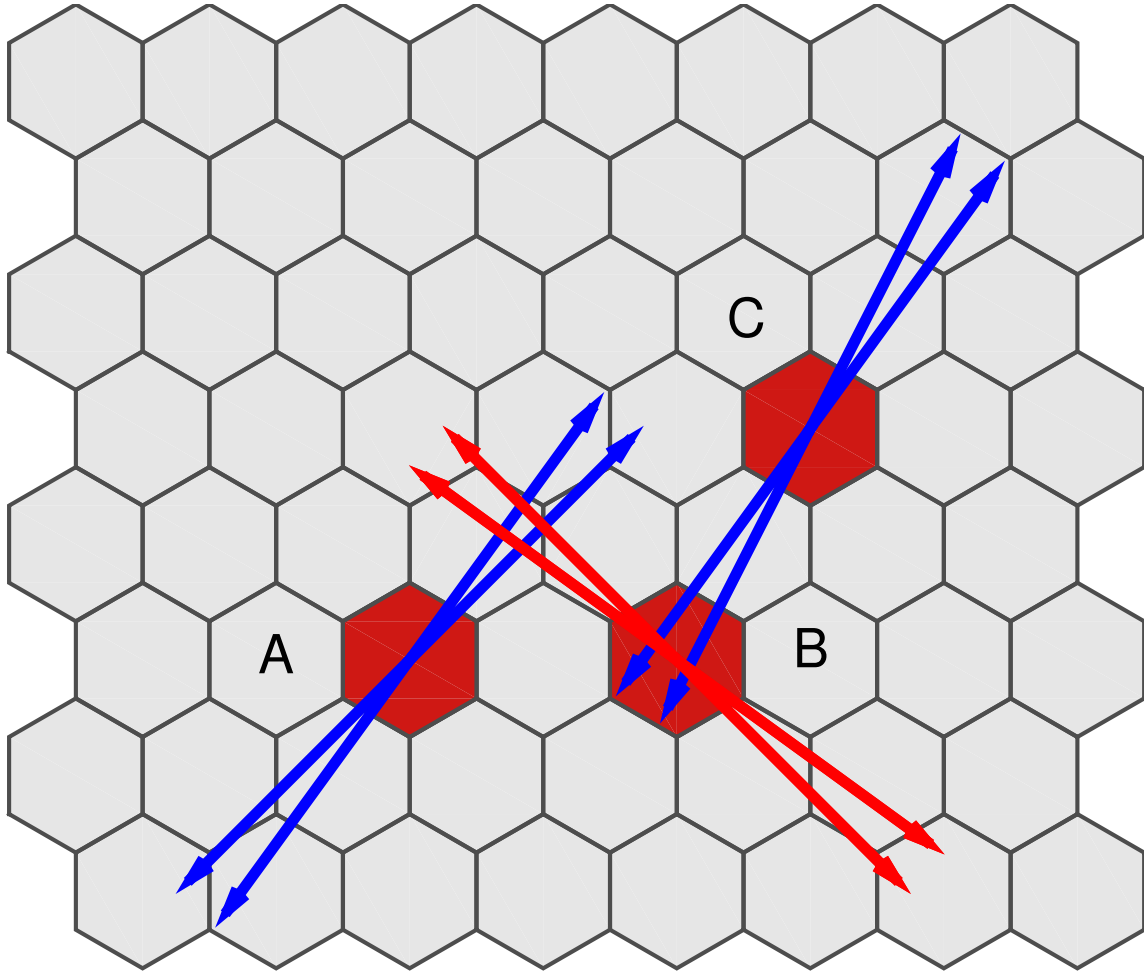
Protrusions

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



Protrusions model

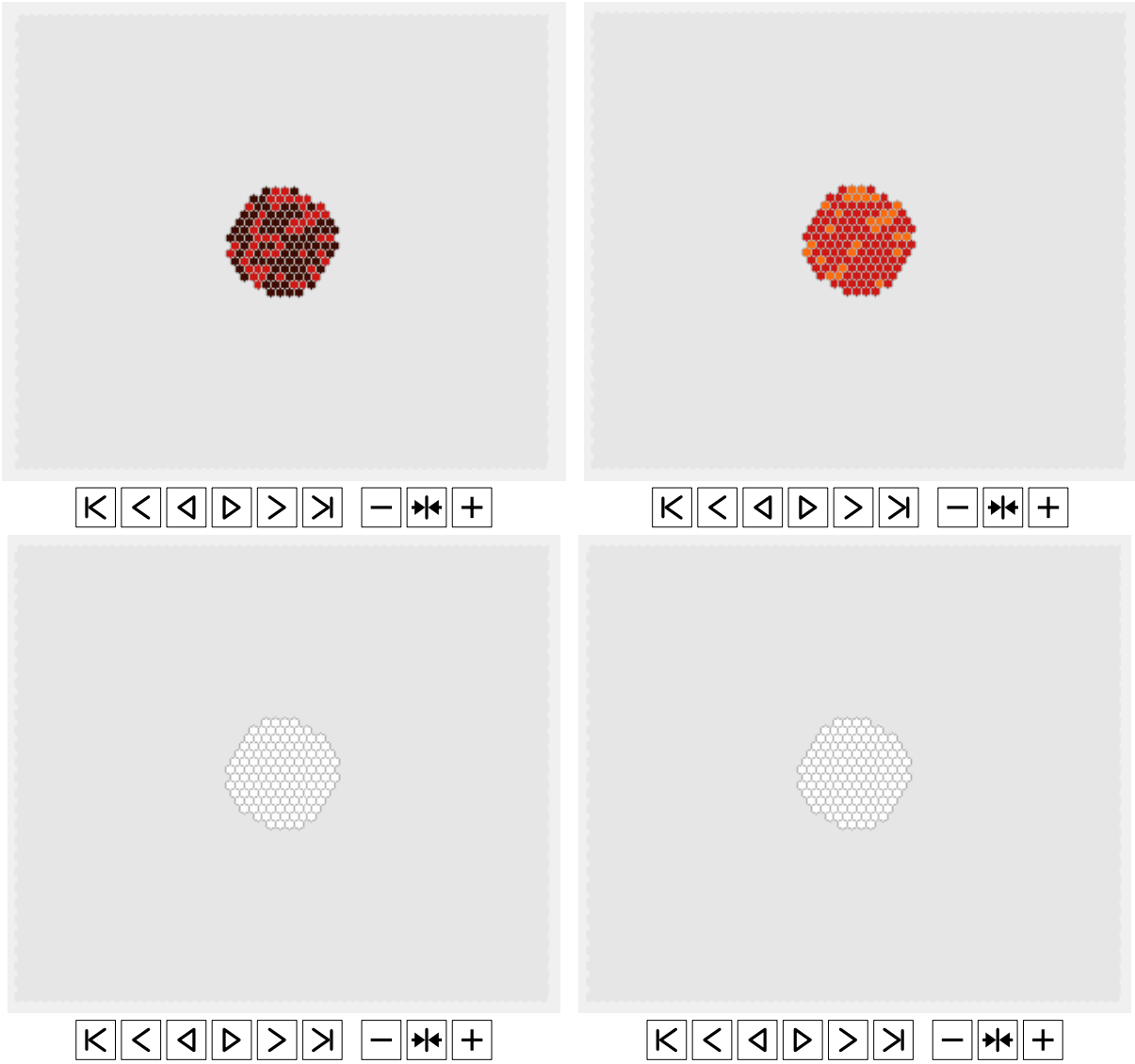
In silico model from Hadjivasiliou, *et al.*, J. R. Soc. Interface 13, 2016



(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



Summary

- Microscopy data, mostly for inspiration...
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- Microscopy data, mostly for inspiration...
- "How to think": realistic & useful models, through flexible/understandable/generalizable
- 1. Modeling: inner/outer scale with RDME/DLCM one suitable such combination, consistency through time-continuous coupling, **event-based computational framework**
- 2. Analysis: the RDME framework, stability, analysis of basic numerical methods
- 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!