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

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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?

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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, occupying 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.
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.
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.
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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 ≈ the wanted “true” physics (consistency), then the numerical solution → the true solution (convergence) IFF the numerical physics is stable*
Notation

Local physics, e.g. in a single voxel

-State $X \in \mathbb{Z}^D_+$, counting the number of each of $D$ species/agents/compartments.
-Events/reactions are transitions between these states,

$$X \xrightarrow{w_r(X)} X - N_r, \quad N \in \mathbb{Z}^{D \times R} \text{ (stoichiometric matrix)}$$

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

- Poisson representation

\[ X(t) = X(0) - \sum_r N_r \Pi_r \left( \int_0^t w_r(X(s)) \, ds \right), \]

each $\Pi_r$ a unit-rate Poisson process.
Notation
Spatial physics

Total volume $\Omega$ subdivided into small enough voxels $\Omega_j$ such that the local physics is an accurate model.

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

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

$$\mathbf{X}_{ij}(t) = \mathbf{X}_{ij}(0) - \sum_r N_{ri} N_{rj} \left( \int_0^t w_{rj}(\mathbf{X}_{.,j}(s)) \, ds \right),$$

for $i = 1, \ldots, D$ species.
Transport mechanism
Across voxels (e.g. diffusion)

Linear model (convection/diffusion): transport from one voxel $\Omega_j$ to another voxel $\Omega_k$ according to

$$X_{ij} \xrightarrow{q_{ijk}X_{ij}} X_{ik},$$

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

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

RDME

Combining reactions with transport events we arrive at

\[
\begin{align*}
X_{ij}(t) &= X_{ij}(0) - \sum_r N_{ri} \Pi_{rj} \left( \int_0^t w_{rj}(X_{.,j}(s)) \, ds \right) \\
- \sum_k \Pi'_{ijk} \left( \int_0^t q_{ijk} X_{ij}(s) \, ds \right) &+ \sum_k \Pi'_{ikj} \left( \int_0^t q_{ikj} X_{ik}(s) \, ds \right).
\end{align*}
\]
Assumptions

Local physics first...

Recall: CTMC $X(t) \in \mathbb{Z}^D_+$ governed by transitions

$$X \xrightarrow{w_r(X)} X - \mathbb{N}_r, \quad r = 1 \ldots R, \quad \mathbb{N} \in \mathbb{Z}^{D \times R},$$

or, to get some ODE-feeling, “$X'(t) = -\mathbb{N}w(X)$”.

The “blue assumptions”.

(Uppsala University)
Assumptions

Local physics first...

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

$$X \xrightarrow{w_r(X)} X - \mathbb{N}_r, \quad r = 1\ldots R, \quad \mathbb{N} \in \mathbb{Z}^{D \times R},$$

or, to get some ODE-feeling, \( \frac{dX}{dt}(t) = -\mathbb{N}w(X) \).

Norm \( \|x\|_I := I^T x, \ x \in \mathbb{Z}_+^D \).

Assumptions: \( x, y \in \mathbb{Z}_+^D \),

(i) \(-I^T \mathbb{N}w(x) \leq A + \alpha \|x\|_I \) \quad \text{\( ("I\)-outward bound")}

(ii) \(-I^T \mathbb{N})^2 w(x)/2 \leq B + \beta_1 \|x\|_I + \beta_2 \|x\|_I^2 \) \quad \text{\( ("I\)-outward absolute bound")}

(iii) \(|w_r(x) - w_r(y)| \leq L_r(P)\|x - y\|, \ r = 1, \ldots, R, \) and \( \|x\|_I \vee \|y\|_I \leq P \)

The "blue assumptions".
Assumptions

...then add space

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

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

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

$$
v_t = -\mathbb{N}u(v) + Qv, \quad \text{e.g. } \approx \nabla \cdot \Sigma \nabla
$$

where $v_{ik} \sim \mathbb{E}[X_{ik}\Omega_k^{-1}]$. 
Assumptions

...then add space

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

$$
X_{.,k} \xrightarrow{w_{rk}(X_{.,k})} X_{.,k} - N_r, \quad X_{ij} \xrightarrow{q_{ijk}X_{ij}} X_{ik},
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$k = 1...K$ voxels, $i = 1...D$ species, $r = 1...R$ reactions. To get “PDE-feeling”,

$$
v_t = -\text{div}(u) + Q v,
$$

where $v_{ik} \sim \mathbb{E}[X_{ik} \Omega_k^{-1}]$.

Assumptions:

(iv) $w_{rk}(x) = \Omega_k u_r(\Omega_k^{-1} x)$, “density dependent”
A priori

Norms: $\|X\|_{1,1} \equiv \sum_{j=1}^{K} \|X_{.,k}\|_1 = I^T X 1$, $\|X\|^2 \equiv \sum_{i,j} X_{ij}^2$.

With suitable initial data...

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

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

Norms: $\|X\|_{l,1} \equiv \sum_{j=1}^{K} \|X_{.,k}\|_{l} = I^{T}X1$, $\|X\|^{2} \equiv \sum_{i,j} X_{ij}^{2}$.

With suitable initial data...

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

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

-Actually, if both $X$ and $Y$ are bounded, then

$$E[\|X(t) - Y(t)\|^{2}] = O(\delta).$$
Analysis: Multiscale variable splitting

Set-up: $\epsilon, h$

Consider the separation of scales:

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

$\implies$ rescaled variable $\bar{X}(t) = \bar{X}_{ij}(t) \sim 1$. 
Analysis: Multiscale variable splitting

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$\implies$ rescaled variable $\bar{X}(t) = \bar{X}_{ij}(t) \sim 1.$

Multiscale splitting methods:

“Hybrid”, $\bar{Y}(t)$ all Poisson processes driving an abundant species are replaced with mean drift terms, $\Pi(t) \approx t$, so a “deterministic-stochastic hybrid”

“Numerical”, $\bar{Y}^{(h)}(t)$ 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,

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

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

**Multiscale error**

Under the (Assumptions) above,

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

**Time-discretization error**

Under the (Assumptions) above, then *if the processes are bounded*,

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

\[\begin{align*}
A + B & \xrightarrow{k_{AB}} C + B & A & \xrightarrow{\epsilon d_A} \emptyset \\
C + D & \xrightarrow{k_{CD}} A + D & B & \xrightarrow{d_B A} \emptyset \\
B + B & \xrightarrow{k_B (B-1)} D
\end{align*}\]

\[\text{RMS error} \propto \epsilon^{1/2}\]

\[\text{RMS error} \propto h\]
### Modeling framework

**RDME & DLCM**

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Where \( \langle \text{model} \rangle \) is one of \{ ODE, SDE, RDME \}.

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Work still to be done: analyze the DLCM following the outlined RDME theory.
Modeling framework

RDME & DLCM

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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


![Diagram of Delta-Notch signaling](image)

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
Non-trivial dynamics in tumour

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

- Finding (emergent behavior): increasing the surface means increasing oxygen intake \(\Rightarrow\) 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

![Images of cell protrusions](image)
Protrusions model


(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...
- “How to think”: realistic & useful models, through flexible/understandable/generalizable
Summary

- 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!