Stability and strong convergence in multiscale methods for spatial stochastic kinetics

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Spatially Distributed Stochastic Dynamical Systems in Biology
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Outline

1. The computational framework
   Stochastic reaction-transport modeling
   A reminder: why?

2. Analysis
   Assumptions and a priori results
   (Multiscale) variable splitting methods

3. Applications
   Multiscale neuronal model
   National-scale epidemics

Summary
Local physics + transport mechanism

= Event-based mesoscopic & stochastic computational framework

Figure: Primal mesh (thin), dual mesh (blue). The state is the number of agents (e.g., molecules) in each dual voxel.

Local physics within each voxel, connected through transport mechanisms (e.g., diffusion).

Like PDEs, but better!
“Local physics” first...

Well-stirred kinetics

*Example*: Bimolecular reaction $X + Y \rightarrow Z$. Or infection spread $S + I \rightarrow 2I$. Or...

-When counting individual species/agents, a **continuous-time Markov chain** is the most immediate model of the physics in the zoomed in situation.
...“transport physics” next

Space-discrete, time-continuous model of moving particle

*Example*: Brownian motion.

\[(\text{micro}) \rightarrow (\text{stoch})\] The stochastic model is *simpler* but random (*error*: microscale effects in a statistical sense only).

\[(\text{stoch}) \rightarrow (\text{meso})\] Discrete space approximation (*error*: finite \( h > 0 \)).
Why stochastic? Why discrete? Why space?

SE ’06 “The situation is clearly different when biological systems inside living cells are considered. [—] It is intuitively clear that under such circumstances the inherent stochasticity of the system plays a vital role”

SE & others ’09 “Intrinsic noise in biochemical networks can have a large impact [—] The extremely complex ... microscopic behavior paired with the fact that the copy number is a small nonnegative integer make a discrete, stochastic description of the system necessary”

SE & others ’15 “...spatial stochastic models based on a Markov process formalism are popular due to their high level of biological realism compared to [PDEs], with only a moderate increase in computational complexity…”

-And a great many similar remarks have been made by several many others...! (everybody “knows”)

S. Engblom (Uppsala University) Stability & Convergence in spatial stochastic k...
The main message

Just to rub it in...

Terms & conditions. Want to use these models when either one of

- stochasticity
- nonlinearities
- species discreteness
- spatial inhomogeneities

make a big, or at least an interesting difference. Hence the physical model itself is *sensitive to perturbations* in anyone of these.
The main message

Just to rub it in...

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▶ nonlinearities
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make a big, or at least an interesting difference. Hence the physical model itself is *sensitive to perturbations* in anyone of these.

Designing/understanding computational models: 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

-State \( X \in \mathbb{Z}_+^D \), counting the number of each of \( D \) species/agents/compartment.

-Events/reactions are transitions between these states,

\[
\begin{align*}
X & \xrightarrow{w_r(X)} X - N_r, \\
N & \in \mathbb{Z}^{D \times R} \text{ (stoichiometric matrix)}
\end{align*}
\]

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.
2. Analysis

Notation (cont)

Mesoscopic spatial kinetics

Total volume $\Omega$ subdivided into small enough computational cells $\Omega_j$ 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 $K$ cells, $j = 1, \ldots, K$.
- This state is changed by local physics events (vertically in $X$) and by transport into adjacent cells (horizontally in $X$).
Local physics
(eg. reactions)

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

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

for $i = 1, \ldots, D$ species.
Transport mechanism
(eg. diffusion)

Linear model (convection/diffusion, but also crowding): transport from one cell $\Omega_j$ to another cell $\Omega_k$ according to

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

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

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

“RDME”

Combining reactions with transport events we arrive at

\[ X_{ij}(t) = X_{ij}(0) - \sum_r N_{ri} \Pi_{rj} \left( \int_0^t w_{rj}(X_{..j}(s)) \, ds \right) \]

\[ - \sum_k \Pi'_{ijk} \left( \int_0^t q_{ijk} X_{ij}(s) \, ds \right) + \sum_k \Pi'_{ikj} \left( \int_0^t q_{ikj} X_{ik}(s) \, ds \right). \]

-Formulated in already discrete space! The limit when the cell size \( \to 0 \) is not straightforward.
Assumptions & a priori: well-stirred case

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, “$X'(t) = -\mathbb{N} w(X)$”.

Norm $\|x\|_I := I^T x$, $x \in \mathbb{Z}_+^D$, normalized so $\min_i I_i = 1$. 
Assumptions & \textit{a priori}: well-stirred case

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Norm \( \|x\|_I := I^T x, \ x \in \mathbb{Z}_+^D \), normalized so \( \min_i I_i = 1 \).

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

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

(ii) \( (-I^T \mathbb{N})^2 w(x)/2 \leq B + \beta_1 \|x\|_I + \beta_2 \|x\|_I^2 \) (\textit{"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 & *a priori*: local physics

Summary of results

With suitable initial data...

- This $\mathbb{E}[\sup_{s \in [0,t]} \|X(s)\|_p^p]$ bounded, any $p \geq 1$
- if $X(0) = Y(0)$ almost surely, then $\mathbb{E}[\|X(t) - Y(t)\|^2] = 0$
- if $\alpha + \beta_2(p - 1) < 0$, then $\mathbb{E}[\|X(t)\|_p^p]$ bounded as $t \to \infty$
Assumptions & a priori: local physics

Summary of results

With suitable initial data...

- This $\mathbb{E}[\sup_{s \in [0,t]} \|X(s)\|^p] \text{ bounded, any } p \geq 1$;
- If $X(0) = Y(0)$ almost surely, then $\mathbb{E}[\|X(t) - Y(t)\|^2] = 0$;
- If $\alpha + \beta_2(p - 1) < 0$, then $\mathbb{E}[\|X(t)\|^p] \text{ bounded as } t \to \infty$.

In fact, if $X(0) = Y(0)$ almost surely, and if $Y(t)$ is obtained by $\delta$-perturbing the transition intensities ($w_r \to (1 \pm \delta)w_r$), then $\lim_{\delta \to 0} \mathbb{E}[\|X(t) - Y(t)\|^2] = 0$.

Actually, if both $X$ and $Y$ are bounded, then $\mathbb{E}[\|X(t) - Y(t)\|^2] = O(\delta)$. 
Assumptions & *a priori*: spatial case

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

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

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

$$
\mathbf{v}_t = -\mathbb{N}u(\mathbf{v}) + Q\mathbf{v}.
$$

eg. $\approx \nabla \cdot \Sigma \nabla$
Assumptions & *a priori*: spatial case

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

\[
\mathbb{X}_{.,k} \xrightarrow{w_{rk}(\mathbb{X}_{.,k})} \mathbb{X}_{.,k} - N_r, \quad \mathbb{X}_{ij} \xrightarrow{q_{ijk}X_{ij}} X_{ik},
\]

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

\[
\mathbf{v}_t = -\nabla u(\mathbf{v}) + \nabla \cdot \Sigma \nabla \mathbf{v}.
\]

eq \text{eg.} \approx \nabla \cdot \Sigma \nabla

Assumptions:

- on the mesh, some natural and quite weak assumptions (...)
- reactions, as before, *plus*
  \[(iv) \quad w_{rk}(x) = \Omega_k u_r(\Omega_k^{-1}x), \text{ “density dependent”}\]
Assumptions & \textit{a priori}: spatial case

Summary of results

\begin{align*}
\text{Norm } \| \mathbf{X} \|_{I,1} & \equiv \sum_{k=1}^{K} \| \mathbf{X}_k \|_I = \mathbf{I}^T \mathbf{X} \mathbf{1}.
\end{align*}

With suitable initial data...

- only reactions: as before
- pure transport: \( \| \mathbf{X}(t) \|_{I,1} = \| \mathbf{X}(0) \|_{I,1} \), so bounded by initial data
- coupled spatial model: \( \mathbb{E} \left[ \sup_{s \in [0,t]} \| \mathbf{X}(s) \|_{I,1}^p \right] \) bounded, any \( p \geq 1 \)
- (strong) continuous dependence on parameters as before
Application: 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 $\sim 1$ (*on a per voxel basis*)
- rate constants are either fast $\sim 1$, or slow $\epsilon$ (...)

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

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- rate constants are either fast $\sim 1$, or slow $\epsilon$ (...)

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

**Multiscale splitting methods:**

- "Exact", $\bar{Y}(t)$: all Poisson processes driving an abundant species are replaced with mean drift terms, $\Pi(t) \approx t$
- "Numerical", $\bar{Y}(h)(t)$: discrete steps $h$; 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 $[t, t + h)$
Scale separation

Details

**Scale vector** $S \in \mathbb{R}^D$

$$\bar{X}_i,(t) = S_i \bar{X}_i,(t), \quad S_i = 1 \text{ or } \epsilon^{-1}.$$

The rates are assumed to obey the scaling laws

$$q_{ijk}x = \epsilon^{-\mu_i} \bar{q}_{ijk} S^{-1} x,$$
$$u_r(x) = \epsilon^{-\nu r} \bar{u}_r(S^{-1} x).$$

The scaled rates $\{\bar{q}_{ijk}, \bar{u}_r(\cdot)\}$ are understood to be $O(1)$ with respect to $\epsilon$. 
Scale separation

Existence

If the following scaled assumptions hold,

\[ -l^T S^{-1} \mathbb{N} u(x) \leq A + \alpha \| S^{-1} x \|_I \]  
\[ (-l^T S^{-1} \mathbb{N})^2 u(x)/2 \leq B + \beta_1 \| S^{-1} x \|_I + \beta_2 \| S^{-1} x \|_I^2 \]  
\[ |\bar{u}_r(x) - \bar{u}_r(y)| \leq L_r(P) \| x - y \|, \quad r = 1 \ldots R, \text{ and } \| x \|_I \vee \| y \|_I \leq P \]

for \( \{l, A, \alpha, B, \beta_1, \beta_2, L\} \) all independent of \( \epsilon \).

Then in an \( O(1) \) interval of time, with \( O(1) \) initial data,
\[ \mathbb{E}[\sup_{s \in [0,t]} \| \vec{X}(s) \|^p_{I,1}] \] is also \( O(1) \).
Scale separation

Existence (cont)

1. Replace (2) with

\[
\left(-I_1^T N^{(1)}\right)^2 u(x)/2 \leq B + \beta_1 \left\| S^{-1} x \right\|_I + \beta_2 \left\| S^{-1} x \right\|^2_I
\]

(I-outward absolute bound for stochastic part only)

\[\implies\] Then \(\bar{Y}(t)\) is also \(O(1)\).

2. Additionally replace (1) with

\[
\max \left(-I_1^T N^{(1)} u(x), -I_2^T \epsilon N^{(2)} u(x)\right) \leq A + \alpha \left\| S^{-1} x \right\|_I
\]

(I-outward bound for deterministic/stochastic parts individually)

\[\implies\] Then \(\bar{Y}^{(h)}(t)\) is also \(O(1)\).
Multiscale split

Terms & conditions

Species in low numbers $i \in G_1$, in large numbers $i \in G_2$. Put

$$R(G_1) := \{ r ; \text{ transition } r \text{ affects a species } i \in G_1 \}$$

(and same for $R(G_2)$).

Define also

$$u := \min_{r \in R(G_1)} -\nu_r \land \min_{i \in G_1} -\mu_i \ ('\text{worst'} \ \epsilon\text{-scaling of transition affecting } G_1)$$

$$v := 1 + \min_{r \in R(G_2)} -\nu_r \land \min_{i \in G_2} -\mu_i \ ('\text{worst'} \ \epsilon\text{-scaling of transition affecting } G_2 \plus 1)$$
Errors

Convergence results

Under the (Assumptions) above, then

- \( \mathbb{E}[\|\tilde{Y}(t) - \tilde{X}(t)\|^2] = O(\epsilon^{1+\nu} + \epsilon^{1/2+\nu/2+u}) \)
- Bounded/unbounded case: *almost* the same result...

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

- \( \mathbb{E}[\|\tilde{Y}^{(h)}(t) - \tilde{Y}(t)\|^2] = O(h(\epsilon^{2u} + \epsilon^{u+\nu})) + O(h^2\epsilon^{2\nu}) \)
- Unbounded case: only convergence as \( h \to 0 \) remains...
Example: catalytic process

“Stress test” of theory

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

\[
\begin{align*}
A + B & \xrightarrow{k_{AB}} C + B & A & \xleftrightarrow{\epsilon d_{aA}} \emptyset \\
C + D & \xrightarrow{k_{CD}} A + D & B & \xleftrightarrow{d_{bAB}} \emptyset \\
B + B & \xrightarrow{k_{bB(B-1)}} D & & \text{RMS error}
\end{align*}
\]

\[
\begin{align*}
\text{RMS error} & \propto \epsilon^{1/2} \\
\text{RMS error} & \propto h
\end{align*}
\]
Application: multiscale neuronal model

- Ion Channel Gating (CTMC)
- Membrane dynamics (ODE)
- Local Field Potential (PDE)
- V_m
- N_channels
- I_m

Ion Channel kinetics
Morphological Information
Bottom level
Ion channel gating

Gating process: sodium channels.
Bottom level

Ion channel gating

The gating process of ion channels can be mesoscopically described as

\[ \begin{align*}
N_0 & \xrightleftharpoons{3\alpha_m(V_m)N_0}{\beta_m(V_m)N_1} N_1 \\
N_1 & \xrightleftharpoons{2\alpha_m(V_m)N_1}{2\beta_m(V_m)N_2} N_2 \\
N_2 & \xrightleftharpoons{\alpha_m(V_m)N_2}{3\beta_m(V_m)N_3} N_3,
\end{align*} \]

again a continuous-time Markov chain. Output: \( N_3 \), the number of open gates.

For efficient model coupling we freeze the voltage dependency for a short time-step \( \tau \) ("split-step" or "1st order Strang split"):

\[ X(t + \tau) = X(t) - \mathbb{N} \Pi \left( \int_t^{t+\tau} w(X(s), V_m(t)) \, ds \right). \]
Middle level
Membrane dynamics

Cable equation circuit.
Middle level

Membrane dynamics

\[ I_m = c_m \frac{dV_m}{dt} + \sum_{i \in C_v} \gamma_i N^i(t)[V_m(t) - E_i] \]
Top level
Maxwell’s equations, potential form

Electric field intensity \( \mathbf{E} \) in terms of the electric scalar potential \( V \),

\[
\mathbf{E} = -\nabla V.
\]

Trans-membrane current \( I_m \) is scaled with the compartment surface area and coupled as a current source,

\[
-\nabla \cdot \left( \sigma \nabla V + \varepsilon_0 \varepsilon_r \frac{\partial}{\partial t} \nabla V \right) = \frac{1}{\Omega_c} I_m,
\]

with conductivity \( \sigma \) and permittivity \( \varepsilon \). The time dependent potential \( V \) is solved via finite element methods.
Sample simulation
Application: national-scale epidemics

- Modeling the spread of verotoxinogenic *E. coli* O157:H7 (VTEC O157:H7) in the Swedish cattle population
- Important *zoonotic pathogen* (animal $\rightarrow$ humans) of great public health interest, causing enteroheamorrhagic colitis (EHEC) in humans ($\sim 500$ cases annually in Sweden).
Application: national-scale epidemics

- Modeling the spread of verotoxinogenic *E. coli* O157:H7 (VTEC O157:H7) in the Swedish cattle population
- Important *zoonotic pathogen* (animal → humans) of great public health interest, causing enterohemorrhagic colitis (EHEC) in humans (∼500 cases annually in Sweden).
- In Germany during the summer 2011, a particularly aggressive variant emerged, with 3,816 reported cases and 54 deceased.
- *Infected animals show no signs of the disease!*
- Cattle is a main reservoir of the bacteria, ongoing research to better understand the epidemiology of VTEC O157:H7 in the cattle population
- Mixed event-based approach:
  - Data-driven simulation using all registered cattle events 2005-2013
  - Stochastic simulation of within-herd dynamics (i.e. *mesoscopic*)
Data-driven

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Total: 18 649 921 reports and 37 221 holdings

Events

- Exit \((n=1\,438\,506)\)
- Enter \((n=3\,479\,000)\)
- Internal transfer \((n=6\,593\,921)\)
- External transfer \((n=732\,292)\)
3. Applications
National-scale epidemics

Events
(Population UK:Sweden is $\sim 10:1$, area $\sim 5:9$)
Epidemic model

“Locally well-stirred” ($SIS_E$)

Model states: Susceptible, Infected, in $i = 1, \ldots, \sim 40,000$ holdings and in 3 age categories $j \in \{\text{calves}, \text{youngstock}, \text{adults}\}$.

**State transitions** at node $i$ in the $j$th age category,

\[
\begin{align*}
\text{Rate } & l_{ij} \rightarrow S_{ij} = \gamma_j l_{ij}(t) \\
\text{Rate } & S_{ij} \rightarrow l_{ij} = \nu_j S_{ij}(t)\varphi_i(t)
\end{align*}
\]

**Environmental infectious pressure**

\[
\frac{d\varphi_i}{dt} = \frac{\alpha \sum_j l_{ij}(t)}{\sum_j S_{ij}(t) + l_{ij}(t)} - \beta(t)\varphi_i(t) + \epsilon
\]
Epidemic model

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\[
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\]

**Finding #1**: $\beta = \beta(t)$ required in the Swedish climate.

**Finding #2**: finite-time extinction for $\epsilon = 0$, contrary to the corresponding ODE-model.
Sample simulation

Connected through \( \sim 9 \) years of actual transport data
Summary

- Mesoscopic stochastic reaction-transport, **event-based computational framework**: fairly intuitive modeling & coupling
- **Terms & conditions.** If used when required: accurately capturing a stochastic nonlinear phenomenon is a very hard constraint for method’s development!
- The **Lax principle** ⇒ Well-posedness, stability, consistency, convergence
- Analysis of simple numerical methods
- Multiscale neuronal application solved in **URDME** (GitHub): proof of concept for coupling different types of models
- Epidemiological national-scale model solved in **SimInf** (GitHub): data-driven simulation, some findings when attempting to fit parameters to data
Thanks

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