Pathwise analysis for split-step methods and multiscale variable splitting in spatial stochastic kinetics

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1. Framework
   The model: stochastic R & D from the bottom and up
   The framework: event-based mesoscopic R & D top down

2. Analysis
   Assumptions and \textit{a priori} results
   Split-step methods
   Multiscale variable splitting methods

3. Applications
   Multiscale neuronal model
   National-scale epidemics

Summary
Brownian motion

*Example:* Particle diffusing in a fluid.

(micro) → (stoch) The stochastic model is simpler but random (*error:* microscale effects in a statistical sense only).

(stoch) → (meso) Discrete space approximation (*error:* finite $h > 0$).

The mesoscopic stochastic model is a continuous-time Markov chain.
Chemical reactions

Example: Bimolecular reaction \( X + Y \rightarrow Z \).

-Required: a model of physics in the zoomed in situation.
Chemical reactions

Example: Bimolecular reaction $X + Y \rightarrow Z$.

- Required: a model of physics in the zoomed in situation.
- Assuming locally well-stirred, what is the probability $P(1X$ and $1Y$ reacts in $[0, \Delta t])$ in a volume $V$?
Chemical reactions

(Locally) well-stirred

*Example:* Bimolecular reaction $X + Y \rightarrow Z$.

$-P(1X \text{ and } 1Y \text{ reacts in } [0, \Delta t])$ in a volume $V$...

Well-stirred, then

- $P \propto n_X$ ("number of $X$-molecules")
- $P \propto n_Y$
- $P \propto 1/V$
- $P \propto \Delta t$

$\implies P(X + Y \rightarrow Z \text{ in } [0, \Delta t]) = \text{const} \cdot n_X n_Y \Delta t / V$.

As $\Delta t \rightarrow 0$ we recover again a continuous-time Markov chain.
Back to the details...

Mesoscopic well-stirred kinetics

**Assuming** a homogeneous probability of finding a molecule throughout the *local* volume.

- State $X \in \mathbb{Z}^D$, counting the number of molecules of each of $D$ species.
- Reactions are transitions between these states,

$$X \xrightarrow{w_r(X)} X - \mathbb{N}_r,$$  
where the *propensity* $w_r : \mathbb{Z}^D_+ \rightarrow \mathbb{R}_+$, $r = 1 \ldots R$, is the probability of reacting per unit of time.

Jump SDE formulation: 

$$dX_t = - \mathbb{N}_r \mu(dt),$$

(where $E[\mu_r(w_r(X); dt)] = E[w_r(X)] dt$),

Poisson representation: 

$$X_t = X_0 - \mathbb{N}_r \Pi(\int_0^t w(X_s) \, ds),$$

($\Pi_r$ a unit-rate Poisson process).
Back to the details...

Mesoscopic spatial kinetics

Assuming that the domain $\Omega$ has been subdivided into small enough computational cells $\Omega_j$ such that diffusion suffices to make each cell well-stirred.

- The state of the system is now an array $\mathbf{X}$ with $D \times K$ elements; $D$ chemically active species $\mathbf{X}_{ij}$, $i = 1, \ldots, D$, counted separately in $K$ cells, $j = 1, \ldots, K$.

- This state is changed by chemical reactions occurring between the molecules in the same cell (vertically in $\mathbf{X}$) and by diffusion/transport where molecules move to adjacent cells (horizontally in $\mathbf{X}$).
Reactions

By assumption, each cell is well-stirred and consequently the jump SDE is valid as a description of reactions,

\[ d\mathbf{X}_t = -\mathbf{N}\mu(dt), \]

where \( \mu \) is now \( R \)-by-\( K \); \( E[\mu_{rj}]dt^{-1} \) = propensity of the \( r \)th reaction in the \( j \)th cell.
Diffusion
(as an important example of transport)

A natural model of diffusion from one cell $\Omega_k$ to another cell $\Omega_j$ is

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

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

For a certain array multiplication $\otimes (\ldots)$,

$$dX_t = S \otimes (-\nu^T + \nu)(dt),$$

where $S$ is 1-by-$K$ of all 1’s, and $\nu$ is $K$-by-$K$-by-$D$; $E[\nu_{kji}]dt^{-1} =$ diffusion rate of the $i$th species from cell $\Omega_k$ to cell $\Omega_j$. 
The reaction-diffusion jump SDE
“RDME”

Combining reactions with diffusions we arrive at

\[ dX_t = -N\mu(dt) + S \otimes (-\nu^T + \nu)(dt). \]

- An approximation, valid when

\[ \rho^2 \ll h^2 \ll \sigma^2 \tau_\Delta, \]

\( \rho \) the molecular radius, \( \tau_\Delta \) average molecular survival time.
Outlook

Event-based mesoscopic framework

Figure: Primal mesh (thin), dual mesh (blue). The nodal dofs are the # of molecules in each dual cell.

Local physics within each small voxel, connected through transport mechanisms (diffusion).
Motivation...
...for the effort with stating assumptions and \textit{a priori} results

Scalar ODE+Euler forward,

\[ y' = f(y), \]
\[ y_{n+1} = y_n + hf(y_n), \quad y_n \approx y(t_n) = y(n \cdot h). \]

Assume:

1. \( f \) is (locally) Lipschitz, \( |f(x) - f(y)| \leq L_Y |x - y| \) whenever \( |x| \vee |y| \leq Y \),
2. \textit{a priori} stability, \( |y| \vee |y_n| \leq Y \)

Then, straightforwardly, \( e_n = |y_n - y(t_n)| \) is \( O(h) \).

\textbf{Problem}: assumptions and analysis are both incomplete without a verification of the 2nd assumption above.

-Additional complications in the stochastic setting (…).
Assumptions & *a priori*: well-stirred case

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

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

or, to get some ODE-feeling, “\( X'(t) = -Nw(X) \)“.

**Norm** \( \|x\|_I := I^T x, \ x \in \mathbb{Z}_+^D, \) for min; \( I_i = 1 \).
Assumptions & a priori: well-stirred case

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

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

or, to get some ODE-feeling, “$X'(t) = -NW(X)$”.

Norm $\|x\|_I := I^{T}x$, $x \in \mathbb{Z}_+^D$, for $\min_i l_i = 1$.

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

(i) $-I^{T}NW(x) \leq A + \alpha \|x\|_I$, 
(ii) $(-I^{T}N)^2w(x)/2 \leq B + \beta_1 \|x\|_I + \beta_2 \|x\|_I^2$, 
(iii) $|w_r(x) - w_r(y)| \leq L_r(P)\|x - y\|$, $r = 1, \ldots, R$, and $\|x\|_I \vee \|y\|_I \leq P$. 

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Consistent & Efficient R-D simulations
Assumptions & \textit{a priori}: well-stirred case

Results

With suitable initial data...

\begin{itemize}
\item $E \sup_{s \in [0,t]} \|X_s\|_p^p$ bounded, any $p \geq 1$
\item if $X_0 = Y_0$ almost surely, then $E\|X_t - Y_t\|^2 = 0$
\item if $\alpha + \beta_2(p - 1) < 0$, then $E \|X_t\|^p$ bounded as $t \to \infty$
\end{itemize}

-Can also elaborate on continuity wrt parameter perturbations (...)


2. Analysis

Split-step methods

Split-step method

Set-up

Split into two sets of reaction pathways

\[
\mathbb{N} = \begin{bmatrix} \mathbb{N}^{(1)} & \mathbb{N}^{(2)} \end{bmatrix}, \quad w(x) = \begin{bmatrix} w^{(1)}(x) ; w^{(2)}(x) \end{bmatrix},
\]

where \( \mathbb{N}^{(i)} \) is \( D \)-by-\( R_i \), \( i \in \{1, 2\} \), \( R_1 + R_2 = R \).

Method:

\[
Y_{t+h/2} = Y_t - \sum_{r \in \mathcal{R}_1} \mathbb{N}_r \Pi_r \left( \int_{t}^{t+h/2} 2w_r(Y_s^-) \, ds \right)
\]

\[
Y_{t+h} = Y_{t+h/2} - \sum_{r \in \mathcal{R}_2} \mathbb{N}_r \Pi_r \left( \int_{t+h/2}^{t+h} 2w_r(Y_s^-) \, ds \right).
\]
Split-step method

Results

Assume the (Assumptions) hold for both sub-systems. Then

- \( E \sup_{s \in [0,t]} \| Y_s \|_p^p \) bounded, any \( p \geq 1 \)
- \( E \| Y_t - X_t \|^2 = O(h) \), any finite \( t \)
Assumptions & a priori: R&D case

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

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

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

$$
\mathbf{u}_t = -\mathbb{N}u + \mathbf{Q}u,
$$

$$
\approx \nabla \cdot \Sigma \nabla
$$
Assumptions & a priori: R&D case

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

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

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

$$
\mathbf{u}_t = -\mathbb{N} \mathbf{u}(\mathbf{u}) + \mathbf{Q} \mathbf{u}.
\approx \nabla \cdot \Sigma \nabla
$$

Assumptions:

- on the mesh, some natural and quite weak assumptions (…)
- reactions, as before, plus
  (iv) $w_{rk}(x) = \Omega_k u_r(\Omega_k^{-1} x)$, “density dependent”
- diffusion:
  (i) $(x^{p-1} \odot \Omega)^T Q x \leq R_p \|x\|_p^p, \ p \geq 1, \ x \in \mathbb{R}_+^K$, consistency with $p$-norm decay of diffusion
Assumptions & a priori: R&D case

Results

\[ \text{Norm } \| \mathbf{X} \|_{I,p}^p \equiv \sum_{k=1}^{K} \| \mathbf{X}_k \|_{I}^p \Omega_{k}^{1-p} \approx \int_{V} \| \mathbf{u} \|_{I}^p \, dV. \]

With suitable initial data...

- only reactions: as before
- pure diffusion: \( E \| \mathbf{X}_t \|_{I,p}^p \) bounded in finite time, or even grows very slowly for \( R_p \leq 0 \)
- full R&D: \( E \sup_{s \in [0,t]} \| \mathbf{X}_s \|_{I,p}^p \) bounded, any \( p \geq 1 \)
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- and diffusion constants are either fast $\sim 1$, or slow $\epsilon$ (per reaction/per species)

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

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$\Rightarrow$ 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”, $\bar{Y}_t^{(h)}$ 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 $[t, t+h)$
Multiscale variable splitting

Results

Under the \textit{a priori} conditions above and under similar (Assumptions) for the splitted system \( \bar{Y}^{(h)}_t \) (...), then

\begin{itemize}
  \item \( E \sup_{s \in [0,t]} \| \bar{Y}_s \|_{l,p}^p \) bounded, any \( p \geq 1 \)
  \item \( E \| \bar{Y}_t - \bar{X}_t \|^2 = O(\epsilon) \), any finite \( t \)
  \item \( E \sup_{s \in [0,t]} \| \bar{Y}^{(h)}_s \|_{l,p}^p \) bounded, any \( p \geq 1 \)
  \item \( E \| \bar{Y}^{(h)}_t - \bar{Y}_t \|^2 = O(h) \), any finite \( t \)
\end{itemize}

- Additional conditions for this concerns the reaction topology: effectively fast reactions must not affect low copy number species (…)

Application: multiscale neuronal model

- Ion Channel Gating (CTMC)
- Membrane dynamics (ODE)
- Local Field Potential (PDE)
- Morphological Information
- Ion Channel kinetics

$V_m$, $N_{channels}$, $I_m$
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

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

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"):

\[
X_{t+\tau} = X_t - \int_t^{t+\tau} \mathbb{N} \mu(V_m(t), w(X_{s-}); ds).
\]
Middle level

Membrane dynamics

Cable equation circuit.
Morphological information extracted using the Trees toolbox

System of current-balance and cable equations is solved for each time step $\tau$

\[ I_m = c_m \frac{dV_m}{dt} + \sum_{i \in C_v} \gamma_i N_3^i(t)[V_m(t) - E_i] \]
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 → humans) of great public health interest, causing enteroheamorrhagic 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)
Events

(Note: Germany:Sweden, pop. density ~ 10:1, area ~ 7:9)
Epidemic model

“Locally well-stirred” ($SIS_E$)

Model states: **Susceptible**, **Infected**, in $\sim40,000$ holdings and in 3 age categories \{*calves*, *youngstock*, *adults*\}.

**Environmental infectious pressure**

\[
\frac{d\varphi_i}{dt} = \frac{\alpha \sum_j l_{i,j}(t)}{\sum_j S_{i,j}(t) + l_{i,j}(t)} - \beta(t)\varphi_i(t)
\]

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

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

Rate $S_{i,j} \rightarrow I_{i,j} = \gamma_j \varphi_i(t) S_{i,j}(t)$

Rate $I_{i,j} \rightarrow S_{i,j} = \frac{l_{i,j}(t)}{\delta_j}$
Sample simulation

http://user.it.uu.se/~stefane/animations/collection/siminf/siminf_sample.gif
Summary

- Mesoscopic stochastic R & D, **event-based computational framework**: fairly intuitive modeling, coupling and up/down-scaling, simulation algorithms

- **Terms & conditions**. If used when required: accurately capturing a stochastic nonlinear phenomenon is a very hard constraint for method’s development!

- Well-posedness, stability, convergence... of simple numerical methods

- Multiscale neuronal application solved in **URDME** (GitHub): coupling different types of models

- Epidemiological national-scale model solved in **SimInf** (GitHub): data-driven simulation
Acknowledgments

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