Stochastic multi-scale models of biomolecular networks

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...joint work with A. Ganguly and D. Altintan
(SIAM Multiscale Modeling and Simulation, in press, 2015/arxiv)
Our research

- Statistical inference (ML) methods
- Stochastic analysis of systems
- Single-cell experiments
- Microfluidic chips
Example: osmotic stress response

- High-osmolarity induced gene expression in yeast (PNAS’12)
Motivation: Cell biology is multi-scale (…and multi-level)

- System-level understanding requires coupling of cellular processes.
- Cross-regulation between signaling, gene expression, metabolism.
- Different time-scales results in computational bottleneck.
- On top of that: spatial effects (e.g., membrane trafficking) often significant - additional scale of resolution.

Karr et al, Cell’12
Population models (aka Petri nets)

\[ R_k : \nu_k^- S_1 + \nu_k^- S_2 + \ldots + \nu_k^- S_m \xrightarrow{c_k} \nu_k^+ S_1 + \nu_k^+ S_2 + \ldots + \nu_k^+ S_m \]

\[ \nu_k = (\nu_k^+ - \nu_k^-, \nu_k^+ - \nu_k^-, \ldots, \nu_k^+ - \nu_k^-)^T \] Stoichiometric change vector

\[ X(t) = (X_1(t), X_2(t), \ldots, X_m(t))^T \] State vector, \( c_k \in \mathbb{R}_+ \): Rate constant

\[ X(t) = X(t-) + \nu_k \] occurrence of \( R_k \) updates the state vector

- **Jump process formulation (CTMC)**
  Continuous time, countable states - stochastic simulation or chemical master equation.

- **Diffusion approximation**
  Continuous time, continuous state - stochastic differential equation, Fokker-Planck equation.

- **Mean-field approximation - thermodynamic limit**
  Continuous time, continuous state - ordinary differential equation (RRE).
Introduction and motivation

Multi-scale models

Combine different model description to exploit multi-scale nature.

Addressed questions:

1. How do we partition a given CTMC model into discrete and approximate, continuous parts?
2. How can we bound the error for a certain partition?
3. How can we simulate such a multi-scale model?
Introduction and motivation

Research agenda

- Propose partitioning according to Poisson approximation.
- Perform path-wise, strong error analysis.
- Design dynamic partitioning algorithm to simulate multi-scale systems efficiently.
Random time-change representation

\[ R_k : \nu_1^- S_1 + \nu_2^- S_2 + \ldots + \nu_m^- S_m \xrightarrow{c_k} \nu_1^+ S_1 + \nu_2^+ S_2 + \ldots + \nu_m^+ S_m \]

Propensity function example: \( a_k(x) = c_k \prod_{i=1}^{m} \left( \frac{x_i}{\nu_{ki}} \right) \), \( k = 1, \ldots, r \)

e.g. \( R_k : S_1 + S_2 \xrightarrow{c_k} *, \quad a_k(X) = c_k X_1 X_2 \) or \( S_1 \xrightarrow{c_k} *, \quad a_k(X) = c_k X_1 \)

With \( a_k(x)dt \equiv \) the probability of reaction \( R_k \) to occur in time interval \( (t, t + dt] \).

A path-wise representation of the CTMC is as follows

\[ X(t) = X(0) + \sum_{k=1}^{r} \xi_k \left( \int_{0}^{t} a_k(X(s))ds \right) \nu_k, \]

where \( \xi_k \)'s are independent Poisson processes.
Scaling

The abundance of species and time-scales of reactions can vary over different orders of magnitude. We introduce additional scaling variables to make that explicit (other variables are $O(1)$).

$$
\begin{align*}
\bar{X}_i^N &= X_i / N^{\alpha_i}, \quad \bar{X}_i^N = O(1), \\
d_k &= c_k / N^{\beta_k}, \quad d_k = O(1), \\
\text{Example} \quad a_k(X) &= c_k X_i = N^{\beta_k} d_k N^{\alpha_i} \bar{X}_i^N \equiv N^{\beta_k + \alpha_i} \lambda(\bar{X}_i^N) \\
a_k(X) &= N^{\beta_k + \nu_k^- \cdot \alpha} \lambda_k(\bar{X}^N), \quad \implies \lambda_k(\cdot) = O(1), \\
t &\rightarrow t N^\gamma, \\
X^N(t) &= \bar{X}^N(t N^\gamma).
\end{align*}
$$

We obtain random time-change model for normalized variables

$$
X^N(t) = X^N(0) + \sum_{k=1}^{R} \xi_k \left( N^{\rho_k} \int_0^t \lambda_k(X^N(s))ds \right) \nu_k^N,
$$

where we define $\rho_k = \gamma + \beta_k + \nu_k^- \cdot \alpha$ and $\nu_k^N = \nu_{ki} / N^{\alpha_i}$. 
Idea

- High intensity Poisson process can well be approximated by Brownian motion (plus drift), i.e. $\xi(t) \approx t + W(t)$.

**Theorem (Kolmos, Major, Tusnady)**

*There exists a Brownian motion $W(t)$ on the same probability space as $\xi(t)$ such that*

$$\Gamma = \sup_t \frac{\tilde{\xi}(t) - W(t)}{\log(2 \lor t)} < \infty \quad (a.s.),$$

where $\tilde{\xi}(t) = \xi(t) - t$ is the centered Poisson process.

- That is

$$\left[ \frac{1}{\sqrt{n}} \tilde{\xi}(nt) - \frac{1}{\sqrt{n}} W(nt) \right] \leq \frac{\log(2 \lor nt)}{\sqrt{n}} \Gamma,$$

where $\frac{1}{\sqrt{n}} W(nt)$ is a standard Brownian motion $W(t)$.

- Strategy: Replace reaction count process of high scaling factor $N^{\rho_k}$ by an diffusion approximation.
Multi-scale approximation

- **Jump-Diffusion Approximating process (first reaction replaced)**

\[
Y^N(t) = X^N(0) + N^{\rho_1} \int_0^t \lambda_1(Y^N(s)) ds \nu_1^N + W_1 \left( N^{\rho_1} \int_0^t \lambda_1(Y^N(s)) ds \right) \nu_1^N \\
+ \sum_{k>1} \xi_k \left( N^{\rho_k} \int_0^t \lambda_k(Y^N(s)) ds \right) \nu_k^N
\]

- **Piece-wise deterministic Markov process (Jump-ODE)**

\[
Y^N(t) = X^N(0) + N^{\rho_1} \int_0^t \lambda_1(Y^N(s)) ds \nu_1^N \\
+ \sum_{k>1} \xi_k \left( N^{\rho_k} \int_0^t \lambda_k(Y^N(s)) ds \right) \nu_k^N
\]

- Between two jumps overall system state \( Y^N(t) \) evolves deterministically.
Bounding the error

- Compute bound on path-wise error for some $T \geq 0$

$$\sup_{t \leq T} E|X^N(t) - Y^N(t)| = \sup_{t \leq T} \sum_{i=1}^{m} E|X^N_i(t) - Y^N_i(t)|$$

for different reactions replaced by an approximation.

**Theorem**

Let $X^N(t)$ be the exact jump process and $Y^N(t)$ its jump-diffusion approximation with reaction $k = 1$ replaced then for $T \geq 0$

$$\sup_{t \leq T} E|X^N(t) - Y^N(t)| \leq C_T (C' \log N^\rho_1 / N^{m_1} + K'' / N^{2\rho_1 + m_1})$$

where $|\nu^N_k| = O(N^{-m_k}) = O(\sum_{i \in R_k} N^{-\alpha_i})$ with $R_k = \{i \in \mathbb{N} | v_{ki} \neq 0\}$ and with the reaction non-specific constant $C_T = \exp \left(2 \sum_{k=1}^{r} N^\rho_k |\nu^N_k| L_k T \right)$
Convert reaction-specific error terms involving scaling variables back to states and propensities

$$\delta_k = \log \frac{N^{\rho_k}}{N^{m_k}} + \frac{1}{N^{2\rho_k + m_k}}$$

Fix time horizon $\Delta = O(N^\gamma)$ and recall that $a_k(X)\Delta = O(N^{\rho_k})$ and $(N^{-m_k}) = O(\sum_{i \in R_k} N^{-\alpha_i}) = O(\sum_{i \in R_k} 1/X_i)$

Then the jump-diffusion error criterion is

$$\delta_k(\Delta) = \sum_{i \in R_k} \frac{\log(a_k(X)\Delta)}{X_i} + \frac{1}{(a_k(X)\Delta)^2 X_i}$$

Fix approximation accuracy $\epsilon$ and check at every $\Delta$ for each reaction $k$ whether the incurred error of approximating it by diffusion is below $\epsilon$. 
Consider the single species $S$

$$\emptyset \xrightarrow{c_1} 10S, \quad S \xrightarrow{c_2} \emptyset.$$  

(1)

with the number of molecules of $S$ at time $t$ is denoted by $X(t)$. we use

$$X(0) = 0, \quad \Delta = 0.1, \quad \varepsilon = 0.09, \quad P = 50.$$  

Reaction constants of $R_1, R_2$ are given as $c_1 = 1 \text{molec s}^{-1}, \quad c_2 = 1\text{s}^{-1}$. Death process is expected to be approximated by diffusion.
Simulation studies

Dynamic partitioning
Simulation studies

Weak error analysis by simulation
Let $S_1$ and $S_2$ denote the prey and the predator, respectively. The corresponding Lotka-Volterra prey-predator model can be depicted as

$$
S_1 \xrightarrow{c_1} 2S_1, \quad S_1 + S_2 \xrightarrow{c_2} 2S_2 \quad S_2 \xrightarrow{c_3} \emptyset.
$$

(2)

Let $X_1(t)$ and $X_2(t)$ denote the number of the prey and the predator at time $t > 0$, respectively, then, the state of the system is defined by $X(t) = (X_1(t), X_2(t))^T \in \mathbb{N}^2_{\geq 0}$. We use

$$
X(0) = (900, 800)^T, \quad c_1 = 2s^{-1}, \quad c_2 = 0.002\text{molec}^{-1}s^{-1}, \quad c_3 = 2s^{-1}.
$$

$$
\Delta = 0.5, \quad \varepsilon = 0.03, \quad P = 50, \quad t \in (0, 50)
$$
Simulation studies

Dynamic partitioning

![Graph showing dynamic partitioning with copy numbers and time in seconds. The graph compares continuous and discrete states, with different lines representing different entities labeled as S1 and S2.](attachment:graph.png)
Weak error analysis by simulation
EGFR signaling and gene expression

- Rate constants and abundances based on Schoeberl et al., Science Sci’09
- 30 signaling reactions, 6 gene expression reactions
- Runge-Kutta strong order 2 SDE integrator
Conclusions

- Multi-scale models essential for systems biology.
- Traditional hybrid models often involve ad-hoc partitioning of species.
- Reaction partitioning leveraging existing approximation results for point processes.
- Generally, every state becomes a jump-diffusion process (i.e. no species partitioning).
- Explicit bound for finite-time error for approximating specific reaction channels.
- Real gain requires higher-order integration schemes for SDEs.
- Bounds for ODE-Jump and ODE-SDE-Jump.