

Integral tau methods for stochastic chemical systems

Yushu Yang, Muruhan Rathinam and Jinglai Shen

Department of Mathematics and Statistics
University of Maryland, Baltimore County (UMBC)
Baltimore, MD, 21250
USA

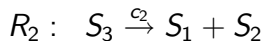
Sep. 25th, 2010

Outline

- ▶ Introduction to stochastic chemical systems.
- ▶ Existing tau leaping methods for simulating chemical systems.
- ▶ Motivations and ideas for the new tau methods.
- ▶ Examples.

Chemically reacting system

- ▶ An example of the chemically reacting system

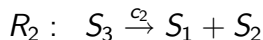


General case:

- ▶ N molecular species $\{S_1, S_2, \dots, S_N\}$. S_i
- ▶ M chemical reaction channels $\{R_1, R_2, \dots, R_M\}$. R_j
- ▶ Molecular population vector
 $X(t) = (X_1(t), X_2(t), \dots, X_N(t))'$.
 $X_i(t)$ = the number of S_i molecules at time t .
- ▶ Modeled by a continuous time Markov process $X(t)$ with state space \mathbb{Z}_+^N .

Chemically reacting system (cont.)

- ▶ $a_j(x)\tau + o(\tau)$: the probability, given $X(t) = x$, that reaction R_j will occur in $(t, t + \tau]$.
 $a_j(x)$ is the **propensity** (also known as **intensity** or **rate**) for reaction R_j .
- ▶ ν_{ji} = the change in the number of S_i molecules produced by one reaction R_j .
 ν_j is the **stoichiometric vector**.
- ▶ In this example



$$a_1(x) = c_1 x_1 x_2, \quad a_2(x) = c_2 x_3.$$

$$\nu_1 = (-1, -1, 1)', \quad \nu_2 = (1, 1, -1)'.$$

Fluid limit

- ▶ Suppose the system has a volume V_0 . Define $z_0 = \frac{x_0}{V_0}$ to be the initial concentration. Let us consider a family of related systems with different volumes V such that the initial state is $X^V(0) = Vz_0 = \frac{V}{V_0}x_0$. Let the solution trajectory be denoted by $X^V(t)$. Note that the original system has a trajectory $X(t) = X^{V_0}(t)$. Define the concentrations $z^V(t) = \frac{X^V(t)}{V}$.
- ▶ **Reaction rate** function $\bar{a}_j(z) = \lim_{V \rightarrow \infty} a_j(zV, V)/V$.

Fluid limit (cont.)

- ▶ (Kurtz) For each fixed $t \geq 0$, $z^V(t)$ converges (almost surely) to the deterministic quantity $\bar{z}(t)$ where $\bar{z}(t)$ is the unique solution of the **reaction rate equation** (RRE):
$$\dot{\bar{z}}(t) = \sum_{j=1}^M \nu_j \bar{a}_j(\bar{z}(t)),$$
 with initial condition $\bar{z}(0) = z_0$.
- ▶ $\bar{z}(t)$ is the **fluid limit** of $z^V(t)$ as $V \rightarrow \infty$.

Stochastic Simulation Algorithm (SSA)

- ▶ $p(\tau, j|x, t) = p_1(\tau|x, t)p_2(j|x, t)$ where
 - ▶ $p_1(\tau|x, t) = a_0(x)\exp(-a_0(x)\tau)$
 - ▶ $p_2(j|x, t) = \frac{a_j(x)}{a_0(x)}$
 - ▶ $a_0(x) = \sum_{j=1}^M a_j(x)$
- ▶ Generate τ and j according to $p(\tau, j|x, t)$
- ▶ $X(t + \tau) = X(t) + \nu_j$

Tau leaping methods

Basic idea

- ▶ **Tau leaping** methods: define $K_j(x, \tau)$ to approximate the number of times, given $X(t) = x$, that j th reaction channel will fire in the time interval $(t, t + \tau]$.
Update next state: $X(t + \tau) = x + \sum_{j=1}^M \nu_j K_j$.
- ▶ **Explicit tau** Choose K_j to be independent Poisson random variables with mean $a_j(x)\tau$

$$K_j \sim \mathcal{P}(a_j(x)\tau).$$

- ▶ **Implicit tau** Choose $K'_j \sim \mathcal{P}(a_j(x)\tau)$ independent, and then solve for $X(t + \tau)$ in

$$X(t + \tau) = x + \sum_{j=1}^M \nu_j a_j(X(t + \tau))\tau + \sum_{j=1}^M \nu_j (K'_j - a_j(x)\tau).$$

Comparison of the existing tau leaping methods

- ▶ **Trapezoidal tau** solve for $X(t + \tau)$ in

$$X(t + \tau) = x + \sum_{j=1}^M \nu_j (K'_j - \frac{\tau}{2} a_j(x) + \frac{\tau}{2} a_j(X^{(tr)}(t + \tau)))$$

Methods	Fluid limit	Integer	Nonnegativity
Explicit- τ	Explicit Euler	YES	NO
Implicit- τ	Implicit Euler	NO	NO
Trapezoidal- τ	Trapezoidal Euler	NO	NO

Key issues

- ▶ Consistency.
- ▶ Stiffness - The presence of vastly different time scales.
- ▶ Integer valued and nonnegative states.
- ▶ Correct behavior in fluid limit.

Challenges

- ▶ Implicit methods are good for stiffness but yield non-integer states without rounding.
- ▶ Nonnegativity of states imposes restrictions on $K_j(x, \tau)$.

Main idea of the IMW- τ (Implicit Minkowski-Weyl tau) method

Deal with challenges by

- ▶ Use a split-step-implicit method to compute only the mean values $\lambda_j = E(K_j)$:
 1. Compute X' from $X' = x + \sum_{j=1}^M \nu_j a_j(X')\tau$.
 2. Set $\lambda_j = a_j(X')\tau$.
- ▶ Use integer valued distributions for K_j with mean λ_j .
- ▶ To ensure nonnegativity of updated state $X = x + \nu K$, the K_j can not be independent. They must satisfy the inequality conditions $x + \nu K \geq 0$.
- ▶ The set \mathcal{P} of feasible values of K can be parameterized by the *Minkowski-Weyl decomposition*.
- ▶ Fluid limit of the method is the implicit Euler.

Main idea of the IMW- τ method (cont.)

- ▶ Minkowski-Weyl decomposition (Nonnegativity):
 $K = B\alpha + D\beta$ where $\alpha \geq 0$, $\mathbf{1}^T \alpha \leq 1$, $\beta \geq 0$,
Extreme points $B = [v_1, \dots, v_s]$ ($M \times s$),
Extreme directions $D = [d_1, \dots, d_\ell]$ ($M \times \ell$).
- ▶ Generate random variables α and β and let
 $K = B\alpha + D\beta$, where $\alpha \geq 0$, $\mathbf{1}^T \alpha \leq 1$, $\beta \geq 0$.
- ▶ B and D are easy to compute when the dimension is 1 or 2 ($K \in \mathbb{R}$ or $K \in \mathbb{R}^2$).
- ▶ Partition the set of reactions into groups that consist of a single reaction or reversible pairs.

Examples in one dimension

▶ $S_1 \xrightarrow{c} S_2$

1. Compute $X' = x_1 - a_1(X')\tau$, and $\lambda = a(X')\tau = cX'\tau$.
2. $x_1 - K \geq 0$, $x_2 + K \geq 0$.
3. $0 \leq K \leq x_1$.
4. Generate Binomial random variable $K \sim \mathcal{B}(x_1, p)$ where $p = \frac{\lambda}{x_1}$.

▶ $0 \xrightarrow{c} S_1$

Generate Poisson random variable $K \sim \mathcal{P}(c\tau)$.

▶ $S_1 + S_2 \xrightarrow{c} S_3$

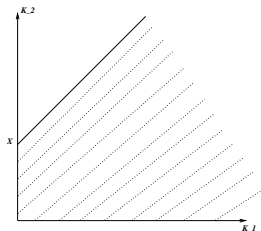
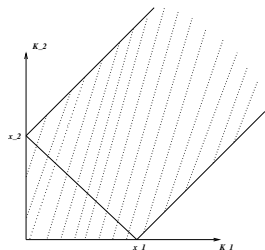
Generate Binomial random variable $K \sim \mathcal{B}(\min(x_1, x_2), p)$.

Example in two dimension: $S_1 + S_2 \leftrightarrow S_3$

- ▶ Compute X' from $X' = x + \sum_{j=1}^2 \nu_j a_j(X')\tau$.
- ▶ The feasible values for $K = (K_1, K_2)^T$ satisfy $-x_3 \leq K_1 - K_2 \leq \min\{x_1, x_2\}$,
- ▶ $E(K_j) = a_j(X')\tau = \lambda_j, j = 1, 2$.
- ▶ The Minkowski-Weyl decomposition gives
$$\begin{pmatrix} K_1 \\ K_2 \end{pmatrix} = \begin{pmatrix} x_1 & 0 \\ 0 & x_2 \end{pmatrix} \begin{pmatrix} \alpha_1 \\ \alpha_2 \end{pmatrix} + \begin{pmatrix} 1 \\ 1 \end{pmatrix} \beta.$$
$$\begin{pmatrix} \lambda_1 \\ \lambda_2 \end{pmatrix} = \begin{pmatrix} x_1 & 0 \\ 0 & x_2 \end{pmatrix} \begin{pmatrix} p_1 \\ p_2 \end{pmatrix} + \begin{pmatrix} 1 \\ 1 \end{pmatrix} q,$$
- ▶ $E(\alpha_i) = p_i, E(\beta) = q, i = 1, 2$.
- ▶ Solve p_i, q from λ_1, λ_2 .
- ▶ Generate Binomial random variables $x_i \alpha_i \sim \mathcal{B}(x_i, p_i)$ and Poisson random variable $\beta \sim \mathcal{P}(q)$.

Feasible regions in 2D: Two prototypes

- ▶ Type 1: applicable to $S_1 + S_2 \leftrightarrow S_3$, $S_1 \leftrightarrow S_2$, etc.
- ▶ Type 2: applicable to $0 \leftrightarrow S_1$, $S_1 \leftrightarrow S_1 + S_2$, etc.



(a) Feasible region of Type 1 (b) Feasible region of Type 2

Two updating schemes: sequential and parallel

- ▶ Both approaches partition the reaction set into groups: $\{J_1, J_2, \dots, J_L\}$.
- ▶ Sequential update: Update the reaction groups in order J_1, J_2, \dots, J_L .
 - ▶ Nonnegativity is ensured.
 - ▶ The fluid limit is the sequential implicit Euler.
 - ▶ IMW-S: Implicit Minkowski-Weyl sequential method.
- ▶ Parallel update: Update the reaction groups simultaneously and independently.
 - ▶ Nonnegativity is not ensured, and a bounding procedure is required.
 - ▶ The fluid limit is the implicit Euler.
 - ▶ IMW-PB: Implicit Minkowski-Weyl parallel bounded method.

Fluid limits: Sequential vs. regular implicit Euler

- ▶ Sequential implicit Euler:

$$\begin{aligned} Y_{n+1}^{(0)} &= Y_n, \\ Y_{n+1}^{(l)} &= Y_n^{(l-1)} + \nu^{(l)} \bar{a}^{(l)}(Y_{n+1}^{(l)}) \tau, \quad \text{for } l = 1, \dots, L, \\ Y_{n+1} &= Y_{n+1}^{(L)}. \end{aligned}$$

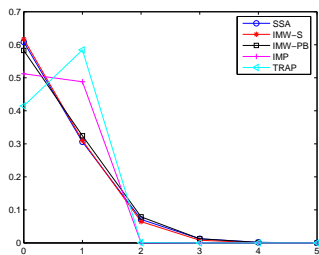
- ▶ Regular implicit Euler:

$$Y_{n+1} = Y_n + \nu \bar{a}(Y_{n+1}) \tau.$$

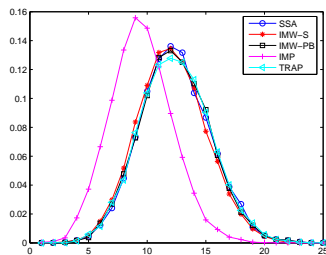
- ▶ The drawbacks of the sequential implicit Euler:
 - ▶ It does not always preserve the fixed points.
 - ▶ It is slower during the transient than the actual system.
- ▶ The implicit Euler does not have the above shortcomings.

Example 1: $0 \leftrightarrow S_1 \rightarrow S_2 \rightarrow S_3 \rightarrow 0$

1. Four groups: $0 \leftrightarrow S_1$, $S_1 \rightarrow S_2$, $S_2 \rightarrow S_3$ and $S_3 \rightarrow 0$.
2. Eigenvalues: $(-1, -100, -10100)^T$.
3. Choose $T = 1$, $\tau = 0.01$.



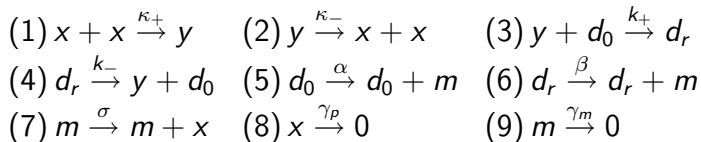
(a) $X_1(1)$



(b) $X_2(1)$

Example 2: The genetic loop

- ▶ The genetic positive feedback loop example:



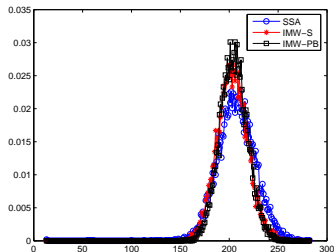
- ▶ Four groups:

$$\{(1), (2)\} \quad \{(3), (4)\} \quad \{(5), (6), (9)\} \quad \{(7), (8)\}$$

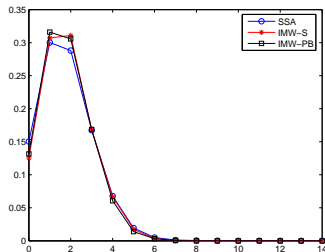
- ▶ Eigenvalues: $(-1011, -1165, -0.0822, -0.1662, 0)^T$ for $X(0) = (10, 0, 20, 0, 0)^T$.

The genetic loop example: Comparison of the probability distribution

Choose $T = 50$, $\tau = 0.05$.



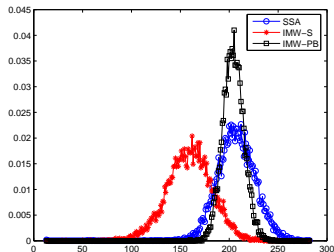
(a) $X_2(50)$



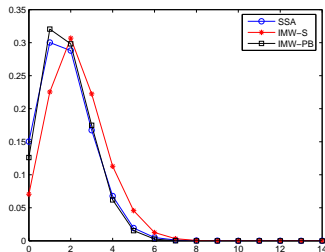
(b) $X_3(50)$

The genetic loop example: Comparison of the probability distribution (cont.)

Choose $T = 50$, $\tau = 1$.

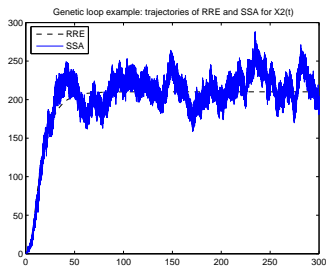


(a) $X_2(50)$

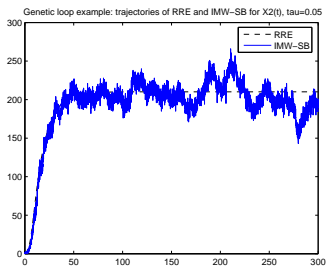


(b) $X_3(50)$

The genetic loop example: Comparison of the trajectories

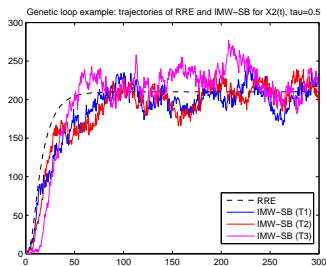


(a) SSA

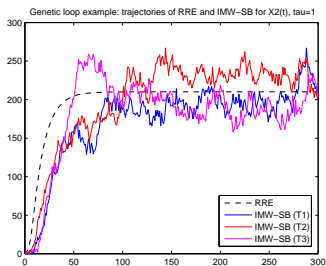


(b) IMW-S, $\tau = 0.05$

The genetic loop example: Comparison of the trajectories (cont.)

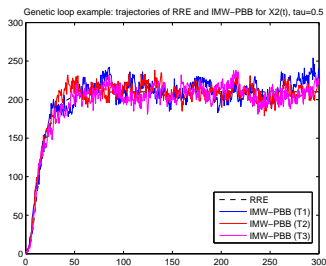


(c) IMW-S, $\tau = 0.5$

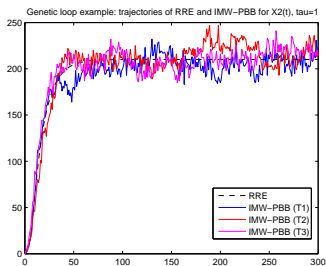


(d) IMW-S, $\tau = 1$

The genetic loop example: Comparison of the trajectories (cont.)



(e) IMW-PB, $\tau = 0.5$



(f) IMW-PB, $\tau = 1$

Conclusions

Methods	Fluid limit	Integer	Nonnegativity
IMW-S	Sequential-Implicit Euler	YES	YES
IMW-PB	Implicit Euler	YES	NO

Thank you!

Questions?