Stochastic Simulation Algorithms for Chemical Reactions

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Motivation

- Why do we use stochastic simulation methods in biochemical modeling?
  - In chemical systems, the small number of molecules of a few reactant species can result in dynamic behavior that is discrete and stochastic, rather than continuous and deterministic
- Stochastic simulation algorithm (SSA) using Monte Carlo methods is a stochastic method to simulate chemical systems, but the SSA is often slow because it simulates every reaction.
- One remarkable attempt to improve the computational efficiency is the tau-leaping method.
- QSSA and tQSSA are for stiff systems.
- This paper compares computational efficiency and exactness between SSA, tau-leaping, implicit tau-leaping, QSSA, and tQSSA based on numerical experiments with simple chemical reactions and stiff systems.

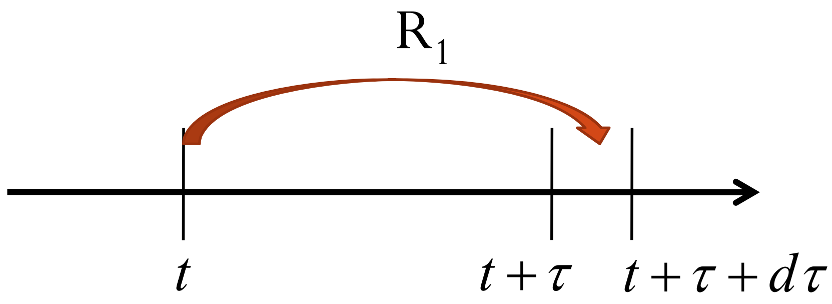
Assumptions

- A well-stirred system at constant volume and temperature.
- N species $\{S_1,\ldots,S_N\}$. System state $X(t) = (X_1(t),\ldots,X_N(t))$,
- $X_i(t)$ = number of S_i molecules at time t .
- M reactions $\{R_1,\ldots,R_M\}$. Propensity functions $a_1,\ldots,a_M$,
- $a_j(x)dt$ = probability, given $X(t) = x$, that R_j will fire in next dt.
- When R_j fires, the system's state changes from x to $x + \nu_j$,
- $v_j = (\nu_{1j},\ldots,\nu_{Nj})$, $\{\nu_{ij}\}$ is the "stoichiometric matrix"

Idea of Stochastic Simulation Algorithm

When will the next reaction occur?

What kind of reaction will it be?



R_1: A + B -> C

	t	$t+\tau$
A	3	2
B	4	3
C	2	3

System state X

Stochastic Simulation Algorithm

- $p(\tau, j \mid x, t)d\tau$ = probability that, given the system state *x* at time *t*, the next reaction will occur in the infitesimal time interval $[t+\tau, t+\tau+d\tau)$, and will be an R_j reaction.
- We call this $p(\tau, j \mid x, t)$ as "reaction probability density function" because it is joint probability function of the two random variables.
  - τ = "time to the next reaction"
  - j = "index of the next reaction"

Stochastic Simulation Algorithm

- Draw two independent samples r_1 and r_2 from $U(0,1)$

  and take $$\tau = \frac{1}{a_0(X)} 1n\left(\frac{1}{r_1}\right)$$

  $j =$ the smallest integer satisfying $$\sum_{j'=1}^{j} a_{j'}(x) > r_2 a_0(x)$$

- Update X $$X \leftarrow X + \upsilon_j$$

Tau-leaping Method

- Idea – Many reactions can be simulated at each step with a preselected time τ
- τ must be small enough to satisfy the "leap condition": The expected state change induced by the leap must be sufficiently small that propensity functions remain nearly constant during the time step τ

Tau-leaping Method: Some Details

- Agrees with SSA in the small step size limit
- Equivalent to forward Euler in the SDE and ODE regimes

$$\Delta X = \nu P(a(x), \tau)$$

where

ΔX	Change of state
x	Current state
τ	Time step
$P(a, \tau)$	Poisson variable with parameters a and τ
$a_j(x)$	Propensity functions
ν_{ij}	Change in species i due to reaction j

Stiff Systems

- Exhibit **slow** and **fast** time scales. The fast scales are stable.
- **Fast** reactions almost **cancel each other** while **slow** reactions determine the trend.
- **Explicit methods** require unreasonably small time steps in order to maintain stability.
- **Implicit methods** in general do not have step size limitations due to stability. Accuracy concerns alone determine the step size.

Implicit Tau-leaping

$$\Delta X = \nu\tau a(x+\Delta X) + \nu P(a(x),\tau) - \nu\tau a(x)$$

- Based on the (explicit) tau method
- Only the **mean** part is implicit
- Tends to the backward Euler scheme as populations get larger
- Better suited for **stiff** problems

Quasi-Steady Sate Assumption

- System in stiff.
- In deterministic kinetics, the net rate of formation is zero when the fast reacting species are in a quasi-steady state.

Example for Michaelis-Menten kinetics

$$E + S \Leftrightarrow E:S \rightarrow P + E$$

$$\frac{d[E:S]}{dt} = 0$$

→

$$\hat{S} \rightarrow P,$$

$$a(s) = \frac{k_2 E_T [\hat{S}]}{K_M + [\hat{S}]}$$

Total Quasi-Steady Sate Assumption

- QSSA eliminates fastest reacting variable under some assumptions.
- In Michalis-Menten kinetics, the necessary condition for the QSSA is $S_0 >> E_T$.
- In a protein interaction network, however, the enzymes and substrates often swap their roles. Therefore QSSA assumption is not correct some models.
- The proper slow time scale is $[\hat{S}] = [S] + [E:S]$.

SSA vs. Tau-leaping

- Irreversible Isomerization $S_1 \xrightarrow{c_1} 0$

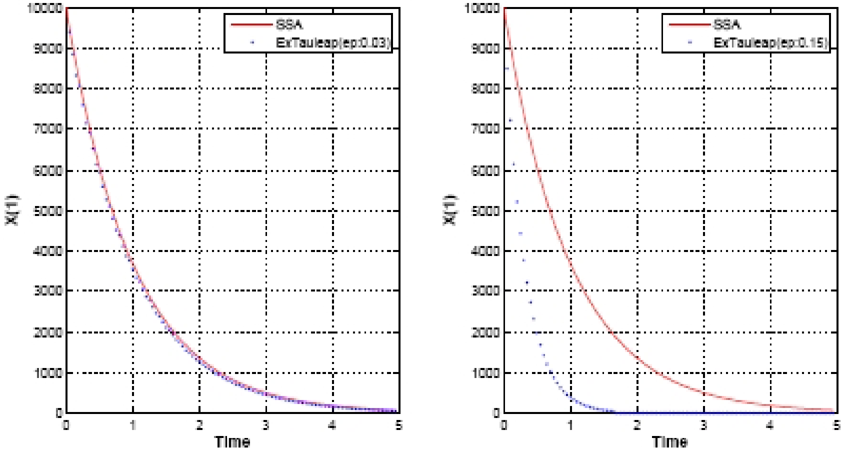


Fig. 1. The SSA simulation (solid lines) and the explicit tau-leaping simulation (dotted lines) for the irreversible isomerization. The error control parameter ϵ is 0.03 (left) and 0.15 (right).

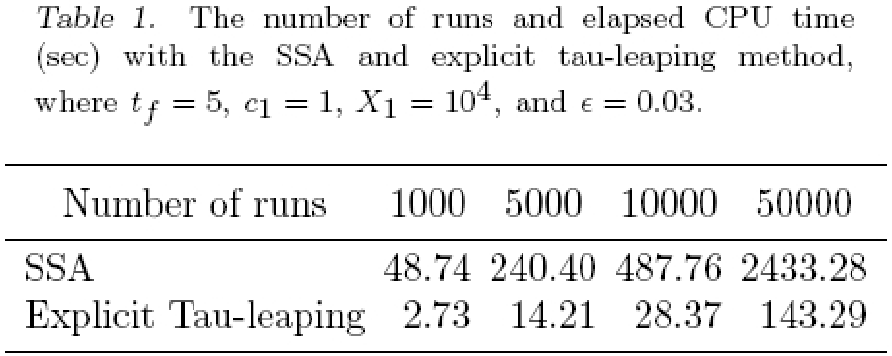


Table 1. The number of runs and elapsed CPU time (sec) with the SSA and explicit tau-leaping method, where $t_f = 5$, $c_1 = 1$, $X_1 = 10^4$, and $\epsilon = 0.03$.

Number of runs	1000	5000	10000	50000
SSA	48.74	240.40	487.76	2433.28
Explicit Tau-leaping	2.73	14.21	28.37	143.29

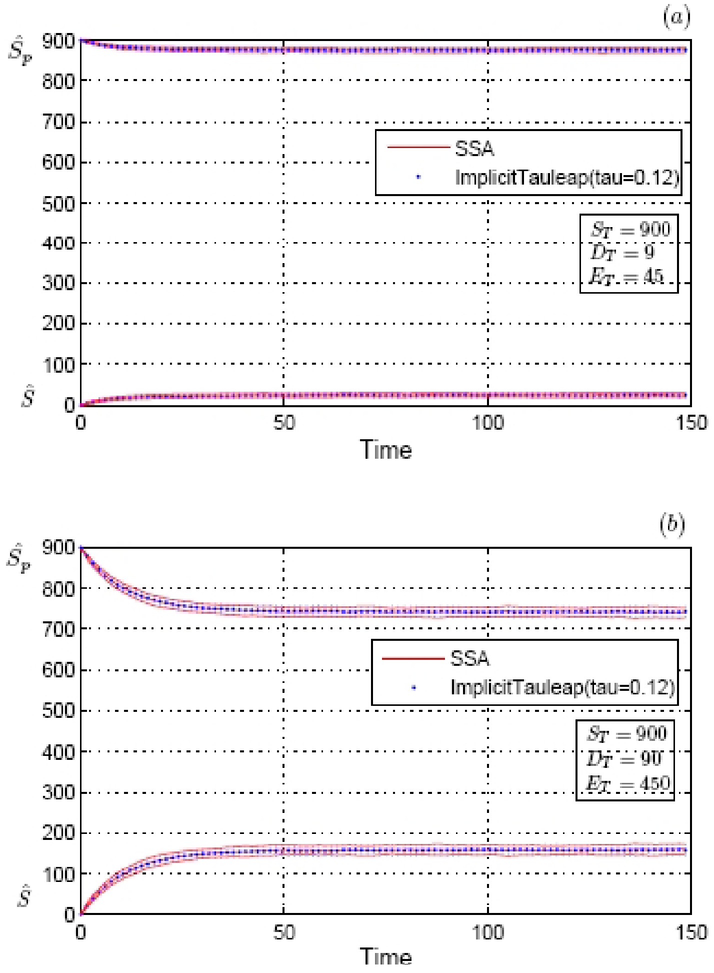
Goldbeter-Koshland switch

$$D + S_p \underset{k_{-1d}}{\overset{k_{1d}}{\rightleftharpoons}} D : S_p \xrightarrow{k_{2d}} S + D,$$

$$E + S \underset{k_{-1e}}{\overset{k_{1e}}{\rightleftharpoons}} E : S \xrightarrow{k_{2e}} S_p + E.$$

Table 2. The number of runs and elapsed CPU time (sec) for the SSA, explicit tau-leaping, implicit tau-leaping, QSSA, and tQSSA algorithms.

Number of runs	1000	5000	10000	50000
SSA	44.57	216.77	434.10	2175.45
Explicit Tau-leaping	4.75	18.23	46.57	181.31
Implicit Tau-leaping	18.43	89.13	181.29	887.44
QSSA	2.63	13.23	26.33	132.47
tQSSA	2.67	13.33	26.79	133.68



Results So Far

- SSA is slow, but exact.
- The explicit tau-leaping method improves computational efficiency for nonstiff systems, but can be unstable on stiff systems.
- The implicit tau-leaping is stable, but much slower than the explicit tau-leaping with appropriate correctness.
- In terms of CPU time, QSSA and tQSSA algorithms are the fastest approximate algorithms. But QSSA has conditional assumption. Therefore, tQSSA is better.

Under Development

- Comparing stochastic and deterministic results with budding yeast model in JigCell project.
- Hybrid method with automatic partition(slow and fast reactions) estimator.

Question?