The numerical stability of leaping methods for stochastic simulation of chemically reacting systems

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Tau-leaping methods have recently been proposed for the acceleration of discrete stochastic simulation of chemically reacting systems. This paper considers the numerical stability of these methods. The concept of stochastic absolute stability is defined, discussed, and applied to the following leaping methods: the explicit tau, implicit tau, and trapezoidal tau. © *2004 American Institute of Physics.* [DOI: 10.1063/1.1823412]

I. INTRODUCTION

Biochemical systems involving small numbers of molecules of certain species exhibit randomness which may account for the cell to cell variation and play critical roles in biological processes.[1–4] Simulation by means of the deterministic reaction rate equations (RREs) cannot capture the stochastic behavior inherent in these systems. Stochastic simulation methods for chemically reacting systems have therefore attracted much recent interest.[3–11] The stochastic simulation algorithm (SSA) (Refs. 5 and 6) has been a standard method to simulate the time evolution of a well-stirred chemically reacting system. It takes proper account of the randomness which is inherent in these systems. A well-known difficulty of SSA is the computational cost. The computing time tends to be prohibitively long if some of the reactions fire very frequently and/or if the molecular populations of some of the reactant species are very large. There are two main reasons for this, both arising from the multiscale nature of the underlying problem. The first is *stiffness*. Some reactions are much faster than others and quickly reach a stable state. The dynamics of the system is driven by the slow reactions. The SSA simulates every reaction and thus puts a great deal of effort into the more frequently firing fast reactions, even though they do not contribute much to the dynamics and stochasticity of the system. In the deterministic regime, this multiscale problem in time is known as stiffness.[12] We emphasize that most chemical systems, whether considered at a scale appropriate to stochastic or to deterministic simulation, involve several widely varying time scales, so such systems are *nearly always stiff*. The second reason for the slowness of SSA has to do with the multiscale population. Some species are present in relatively small quantities and should be modeled by a discrete stochastic process, whereas other species are present in larger quantities and are more efficiently modeled by a deterministic ordinary differential equation (or at some scale in between). SSA treats all of the species as discrete stochastic processes.

Several techniques have been proposed to simulate biochemical systems more efficiently. One set of techniques involves hybrid methods,[8,9] which combine the traditional deterministic ordinary differential equation (ODE) (or the chemical Langevin equation) and SSA. The idea is to split the system into two regimes: the continuous regime and the discrete regime. ODEs or algebraic equations are used to describe the fast reactions between species with large populations. SSA is used for slow reactions or species with small populations. The multiscale SSA method[10,11] generalizes this idea to the case in which species with small population are involved in fast reactions. The hybrid methods are efficient, but so far there is no theoretically justifiable method for automatically partitioning the system.

Another idea involves the use of leaping methods. Gillespie[7] first proposed the tau-leaping method, which we call the explicit tau method in this paper. By means of a Poisson approximation, the tau-leaping method can ''*leap over*'' many reactions. For many problems, the tau-leaping method can approximate the stochastic behavior of the system very well. The tau-leaping method connects the SSA in the discrete stochastic regime to the explicit Euler method for the chemical Langevin equation in the continuous stochastic regime and the RRE in the continuous deterministic regime. It reduces to SSA for sufficiently small τ and to the Euler method for the chemical Langevin equation (CLE) when τ is large but still satisfies the ''*leap condition.*'' When τ is allowed to be sufficiently large, the CLE tends smoothly to the deterministic RRE and the tau-leaping method reduces to the explicit Euler formula for the RRE.[7] Gillespie's original tau-leaping method offers a promising direction toward efficient multiscale stochastic simulation methods. But it is

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very inefficient for stiff stochastic problems, just as the explicit Euler method is very inefficient for stiff ODE systems. The implicit tau-leaping method, which tends to the implicit Euler method in the deterministic regime, was proposed recently in Ref. 13 for simulating stiff stochastic chemically reacting systems. It was demonstrated on some numerical examples that for stiff stochastic problems, the stepsize of the explicit tau method is limited by the stiffness, whereas the implicit tau method can use a much larger stepsize. It was also observed that the implicit tau method exhibits a damping effect in the sense that the variance of the solution given by the implicit tau method is much smaller than that given by SSA simulation. The variance can be restored by the downshifting method proposed in Ref. 13.

Convergence of the explicit tau and implicit tau methods has been shown in Ref. 14. Both methods are convergent of order 1 in the mean and the variance. Recently, we have also studied a trapezoidal tau method.[15] This method is consistent of order 2 for the mean and order 1 for the other moments. In this paper we will show that it also has numerical stability properties that may be advantageous. In this paper, we study the numerical stability of the three leaping methods, based on a test problem which has been carefully chosen to reveal the numerical stability properties. Such a test problem has been traditionally used to study the numerical stability in the deterministic regime, where

$$\dot{y}=\lambda y, \tag{1}$$

with λ being a complex constant, is used as the test problem. The numerical stability analysis in the deterministic regime studies two questions. The first question is: When the stepsize $h\to 0$, will the numerical solution for Eq. (1) be stable? This property is known as 0-stability. We have studied it recently[14] with respect to the leaping methods. The second question is: For a fixed stepsize h, when $t_n=nh$ tends to infinity, will the numerical solution of Eq. (1) be stable? The answer to this question yields the property known as absolute stability.

A detailed study of absolute stability of accelerated discrete stochastic methods such as tau leaping is necessary and helpful for our understanding of numerical stability and stiffness in this regime. The corresponding stochastic model for Eq. (1) is the decay process

$$S\to 0, \tag{2}$$

where the propensity function is $a(x)=\lambda x$. This simple model is not of much interest in the stochastic regime because all of the moments of X vanish to zero when n tends to infinity. Thus we need to consider a nonvanishing model. Such a model is given by the reversible isomerization process

$$S_1 \underset{c_2}{\overset{c_1}{\rightleftharpoons}} S_2, \tag{3}$$

where the propensity functions are given by $a_1(x)=c_1x_1$ and $a_2(x)=c_2x_2$. The reversible isomerization process has been well studied in the literature.[16] This system has a stationary state. There is an analytic solution for the distribution of the stationary state. Thus this model is well suited to serve as a test problem.

To study the numerical stability in the stochastic regime, we ask similar questions as in the deterministic regime. In this paper we will focus on absolute stability. Note that the numerical solutions are random. Thus we are more concerned with the distribution than with a single trajectory. But the distribution is hard to study. Instead, we will focus on the moments. The question we are concerned with is: For a fixed stepsize, will all the moments of the numerical solution be stable when n tends to ∞? The answer to this question yields a concept of absolute stability in the stochastic regime. We will show that the absolute stability region, as defined in this manner, is similar to the corresponding ones in the deterministic regime. But an important difference is that, although the moments of a given numerical method may converge, they may not converge to the corresponding moments of the theoretical solution. Thus a further question is: Will the moments of the numerical solution converge to the corresponding moments of the theoretical distribution of the stationary state? This paper provides answers to these two questions and presents a stochastic absolute stability theory.

The outline of this paper is as follows: In Sec. II we review the background of the SSA, the leaping methods, and the theoretical distribution for the stationary state of the reversible isomerization model. In Sec. III we define the concept of stochastic absolute stability and present results for the three methods. Finally, in Sec. IV we provide some numerical experiments illustrating the results.

II. BACKGROUND

A. SSA

Suppose we have N species $\{S_1,\ldots,S_N\}$ and M reaction channels $\{R_1,\ldots,R_M\}$. The dynamical state of the system is denoted by $X=[X_1(t),\ldots,X_N(t)]$, where $X_i(t)$ is the number of S_i molecules at time t. For each $j=1,\ldots,M$, $a_j(x)$ is the *propensity function* defined by the condition that

$$a_j(x)dt = \text{the probability, given } X(t)=x, \text{ that one } R_j \text{ reaction will occur in the next infinitesimal time interval } [t,t+dt). \tag{4}$$

The vectors $\nu_j, j=1,\ldots,M$ are the *state change vectors*, whose ith component is defined by

$$\nu_{ij} = \text{the change in the number of } S_i \text{ molecules produced by one } R_j \text{ reaction.} \tag{5}$$

The dynamics of the system obeys the *chemical master equation* (CME)

$$\frac{\partial P(x,t|x_0,t_0)}{\partial t}=\sum_{j=1}^{M}\left[a_j(x-\nu_j)P(x-\nu_j,t|x_0,t_0) - a_j(x)P(x,t|x_0,t_0)\right], \tag{6}$$

where the function $P(x,t|x_0,t_0)$ denotes the probability that $X(t)$ will be x given that $X(t_0)=x_0$. The CME is hard to solve both theoretically and numerically. An equivalent simulation method is the SSA,[5,6] which produce realizations of $X(t)$.

The SSA (Refs. 5 and 6) is based on the *next-reaction density function* $p(\tau,j|x,t)$ which is defined as the probability, given $X(t)=x$, that the next reaction in the system will occur in the infinitesimal time interval $[t+\tau,t+\tau+dt)$ and will be a R_j reaction. It follows from Eqs. (4) and (5) that

$$p(\tau,j|x,t)=a_j(x)\exp[-a_0(x)\tau] \quad (\tau\geqslant 0;j=1,\ldots,M), \quad (7)$$

where $a_0(x)=\Sigma_{j=1}^{M}a_j(x)$. The SSA generates τ and j according to Eq. (7) and then advances the system according to

$$X(t+\tau)=X(t)+\nu_j.$$

Four different (but mathematically equivalent) ways can be used to generate τ and j from Eq. (7). Details can be found in Refs. 5, 6, 17, and 18.

The SSA is exact in the sense that it generates the same distribution as described by the CME, but it can also be very time consuming because the simulation proceeds one reaction at a time.

B. Tau-leaping methods

The tau-leaping method[7] tries to accelerate the simulation by asking a different question: How many times does each reaction channel fire in each subinterval? In each step, the tau-leaping method can proceed with many reactions. This is achieved at the cost of some accuracy. Define

$$K_j(\tau;x,t)=\text{the number of times, given } X(t)=x, \text{ that reaction channel } R_j \text{ will fire in the time interval } [t,t+\tau) \quad (j=1,\ldots,M). \quad (8)$$

The tau-leaping method assumes the leap condition: *Require τ to be small enough that the change in the state during $[t,t+\tau)$ will be so small that no propensity function will suffer an appreciable change in its value.* $K_j(\tau;x,t)$ is approximated by the Poisson random variable $P[a_j(x),\tau]$ where $P(a,\tau)$ denotes the Poisson random variable with mean and variance $a\tau$. The basic tau-leaping method is the following: Choose a value for τ that satisfies the leap condition. Given $X(t)=x$, generate for each $j=1,\ldots,M$ a sample value of the Poisson random variable $P[a_j(x),\tau]$ and update the state

$$X^{(et)}(t+\tau)=x+\sum_{j=1}^{M}\nu_j P[a_j(x),\tau]. \quad (9)$$

The tau-leaping method tends to the explicit Euler method for the CLE whenever it is also true that $a_j(x)\tau\gg 1$ for all $j=1,\ldots,M$.[19] Numerical experiments[7] have shown that the tau-leaping method can achieve a very substantial speedup over SSA for some systems. But because it is explicit, it must take a very small τ for stiff problems. The implicit tau method.[13] has been proposed for discrete stochastic simulation of stiff problems. The formula is given by

$$X^{(it)}(t+\tau)=x+\sum_{j=1}^{M}\nu_j\{P[a_j(x),\tau]-a_j(x)\tau+a_j[X^{(it)}(t+\tau)]\tau\}. \quad (10)$$

Newton's method is used to solve Eq. (10). Note that here $X^{(it)}(t+\tau)$ are floating point values. In the simulation, we change them to integers by rounding the quantity in brackets on the right side of Eq. (10) to the nearest integer. But to simplify the analysis, here we will use Eq. (10) as written. It has been demonstrated[13] that the implicit tau method allows much larger stepsizes than the explicit tau method when applied to stiff problems. Convergence proofs for the explicit and implicit tau leaping methods are given in Ref. 14. Here we use the word ''leaping methods'' to represent a class of tau-leaping-like methods.

We can define another interesting leaping method, namely, the trapezoidal tau method[15]

$$X^{(tr)}(t+\tau)=x+\sum_{j=1}^{M}\nu_j\left\{P[a_j(x),\tau]-\frac{1}{2}a_j(x)\tau+\frac{1}{2}a_j[X^{(tr)}(t+\tau)]\tau\right\}. \quad (11)$$

The trapezoidal tau method tends to the trapezoidal method in the deterministic regime. Although it looks similar to the implicit tau method, it is one order of accuracy higher for the mean of the solution. We will show in this paper that it also has numerical stability properties that may be advantageous for some problems.

C. The reversible isomerization

Recall the reversible isomerization reaction is

$$S_1 \underset{c_2}{\overset{c_1}{\rightleftharpoons}} S_2. \quad (12)$$

Since the species satisfy the conservation law

$$X_1(t)+X_2(t)=x_T, \quad (13)$$

where x_T is a constant, the problem is really a one-variable problem:

$$X_1(t)=X(t), \quad X_2(t)=x_T-X(t). \quad (14)$$

The system (12) has a stationary state,[16] as $t\to\infty$, which follows the *binomial distribution*

$$P(X^*=x)=\frac{x_T!}{x!(x_T-x)!}q^x(1-q)^{x_T-x}, \quad (15)$$

where $X^*=X(\infty)=X_1(\infty)$, $q=c_2/(c_1+c_2)$. The mean and variance of X^* are therefore given by the standard binomial formulas

$$E(X^*)=x_T q=\frac{c_2 x_T}{c_1+c_2}, \quad (16)$$

$$\mathrm{Var}(X^*)=x_T q(1-q)=\frac{c_1 c_2 x_T}{(c_1+c_2)^2}. \quad (17)$$

III. ABSOLUTE STABILITY AND STIFFNESS

To study the effects of stiffness on the test problem (12), we apply each formula analytically to the test problem to generate the propagation equation for the moments. It will be shown that each moment evolves in discrete time n according to a difference equation and that there is a propagation coefficient that essentially determines whether the moment grows unboundedly with n or not. For absolute stability, it is required that the absolute value of the propagation coefficient be no larger than 1. But even if this numerical stability condition is satisfied, it does not guarantee that the moments will converge to that of the theoretical solution.

In the study of absolute stability, we fix τ and let n tend to infinity. We denote $X_n = X(t_0 + n\tau)$. Here we will first focus on the stability of the mean and variance. We give detailed analysis for all three methods. Then we will show that the absolute stability region for higher moments is the same as that of the mean.

In our derivation, we will need the following results about the conditional probability. We first state a lemma on conditional expectation and conditional variance, see Ref. 20 for proof.

Lemma 3.1. If X and Y are random variables, then

$$E(Y) = E\{E(Y|X)\},$$

$$\mathrm{Var}(Y) = E\{\mathrm{Var}(Y|X)\} + \mathrm{Var}\{E(Y|X)\}.$$

A. Explicit tau method

Applying the explicit tau method (9) with a fixed stepsize τ to the test problem (12) we have

$$X_{n+1}^{(et)} = X_n^{(et)} + P[c_2(x_T - X_n^{(et)}), \tau] - P(c_1 X_n^{(et)}, \tau). \quad (18)$$

Conditioning on $X_n^{(et)}$ and applying first part of Lemma 3.1. we obtain

$$E(X_{n+1}^{(et)}) = (1 - \lambda\tau) E(X_n^{(et)}) + c_2 \tau x_T, \quad (19)$$

where $\lambda = c_1 + c_2$. The propagation coefficient is $(1 - \lambda\tau)$ and if $|1 - \lambda\tau| > 1$, the solution will blow up when $n \to \infty$. Thus to ensure the stability, τ must be chosen to satisfy

$$|1 - \lambda\tau| \leqslant 1. \quad (20)$$

Noting that Eq. (20) is similar to the absolute stability condition in the classic theory of numerical solution of ODEs, we call it the *absolute stability condition* of the explicit tau method. The set of $\lambda\tau$ for which Eq. (20) holds will be called the *region of absolute stability* of the explicit tau method.

Solving Eq. (20) we obtain

$$\tau < 2/\lambda. \quad (21)$$

Letting $n \to \infty$ and solving for $E[X^{(et)}(\infty)]$ in Eq. (19), we obtain

$$E[X^{(et)}(\infty)] = \frac{c_2}{c_1 + c_2} x_T = E(X^*). \quad (22)$$

Thus if Eq. (21) is satisfied, the mean value given by the explicit tau method converges to the theoretical mean value.

Next let us consider the evolution of the variance. Again conditioning on $X_n^{(et)}$ and using Lemma 3.1. we obtain

$$\begin{aligned}
\mathrm{Var}(X_{n+1}^{(et)}) &= E\{\mathrm{Var}(X_{n+1}^{(et)}|X_n^{(et)})\} + \mathrm{Var}\{E(X_{n+1}^{(et)}|X_n^{(et)})\} \\
&= E[c_2\tau(x_T - X_n^{(et)}) + c_1\tau X_n^{(et)}] \\
&\quad + \mathrm{Var}\{[1 - (c_1 + c_2)\tau] X_n^{(et)}\} \\
&= (1 - \lambda\tau)^2 \mathrm{Var}(X_n^{(et)}) \\
&\quad + c_2\tau x_T + (c_1 - c_2)\tau E(X_n^{(et)}). \quad (23)
\end{aligned}$$

Note that the propagation coefficient is given by $(1 - \lambda\tau)^2$. Thus the stability region for the variance is also given by Eq. (20). Letting $n \to \infty$ in Eq. (23) and applying Eq. (22), we obtain

$$\begin{aligned}
\mathrm{Var}[X^{(et)}(\infty)] &= [1 - (c_1 + c_2)\tau]^2 \mathrm{Var}[X^{(et)}(\infty)] + c_2\tau x_T \\
&\quad + \frac{(c_1 - c_2)c_2}{c_1 + c_2} \tau x_T. \quad (24)
\end{aligned}$$

Solving Eq. (24) for $\mathrm{Var}[X^{(et)}(\infty)]$, we obtain

$$\mathrm{Var}[X^{(et)}(\infty)] = \frac{2}{2 - \lambda\tau} \frac{c_1 c_2 x_T}{(c_1 + c_2)^2} = \frac{2}{2 - \lambda\tau} \mathrm{Var}(X^*). \quad (25)$$

Thus the variance given by the explicit tau method does not converge to the theoretical value, even if the stability condition is satisfied. If Eq. (21) is satisfied, $\mathrm{Var}[X^{et}(\infty)]$ is larger than $\mathrm{Var}(X^*)$.

B. Implicit tau method

Applying the implicit tau method (10) with a fixed stepsize τ to the test problem (12), we have

$$\begin{aligned}
X_{n+1}^{(it)} &= X_n^{(it)} + P[c_2(x_T - X_n^{(it)}), \tau] - P(c_1 X_n^{(it)}, \tau) \\
&\quad + c_2\tau(x_T - X_{n+1}^{(it)}) - c_1\tau X_{n+1}^{(it)} - c_2\tau(x_T - X_n^{(it)}) \\
&\quad + c_1\tau X_n^{(it)}. \quad (26)
\end{aligned}$$

Simplifying Eq. (26), we obtain

$$\begin{aligned}
X_{n+1}^{(it)} &= X_n^{(it)} + \frac{1}{1 + (c_1 + c_2)\tau} \{P[c_2(x_T - X_n^{(it)}), \tau] \\
&\quad - P(c_1 X_n^{(it)}, \tau)\}. \quad (27)
\end{aligned}$$

Applying Lemma 3.1. as before, we obtain

$$\begin{aligned}
E(X_{n+1}^{(it)}) &= E(X_n^{(it)}) + \frac{1}{1 + (c_1 + c_2)\tau} \{c_2\tau[x_T - E(X_n^{(it)})] \\
&\quad - c_1\tau E(X_n^{(it)})\}. \quad (28)
\end{aligned}$$

Thus

$$E(X_{n+1}^{(it)}) = \frac{1}{1 + (c_1 + c_2)\tau} E(X_n^{(it)}) + \frac{c_2\tau x_T}{1 + (c_1 + c_2)\tau}. \quad (29)$$

The propagation coefficient is $1/(1 + \lambda\tau)$, thus the stability condition for the implicit tau method is

$$\left|\frac{1}{1+\lambda\tau}\right|<1. \tag{30}$$

In contrast to the situation for the explicit tau method, Eq. (30) is satisfied for large $|\lambda\tau|$. Thus the implicit tau method is stable for stiff problems. Letting $n\to\infty$ in Eq. (28), we obtain the converged mean value given by the implicit tau method,

$$E[X^{(it)}(\infty)]=\frac{c_2}{c_1+c_2}x_T=E(X^*). \tag{31}$$

For the variance,

$$\begin{aligned}\mathrm{Var}(X_{n+1}^{(it)})&=E[\mathrm{Var}(X_{n+1}^{(it)}|X_n^{(it)})]+\mathrm{Var}[E(X_{n+1}^{(it)}|X_n^{(it)})]\\&=E\left(\frac{1}{[1+(c_1+c_2)\tau]^2}c_2\tau(x_T-X_n^{(it)})+c_1\tau X_n^{(it)}\right)\\&\quad+\mathrm{Var}\left(\frac{1}{1+[c_1+c_2]\tau}X_n^{(it)}\right)\\&=\frac{1}{[1+(c_1+c_2)\tau]^2}\mathrm{Var}(X_n)+\frac{1}{[1+(c_1+c_2)\tau]^2}\\&\quad\times[c_2\tau x_T+(c_1-c_2)\tau E(X_n^{(it)})].\end{aligned} \tag{32}$$

Thus the stability condition for variance is the same as Eq. (30). Letting $n\to\infty$ in Eq. (32) and applying Eq. (31), we obtain

$$\mathrm{Var}[X^{(it)}(\infty)]=\frac{2}{2+\lambda\tau}\mathrm{Var}(X^*). \tag{33}$$

Thus the variance given by the implicit tau method does not converge to the theoretical value. $\mathrm{Var}[X^{(it)}(\infty)]$ is smaller than $\mathrm{Var}(X^*)$. This explains the damping effect of the implicit tau method, which was reported in Rathinam *et al.*[13]

C. Trapezoidal tau method

Applying the trapezoidal tau method (11) with a fixed stepsize τ to the test problem (12), we have

$$\begin{aligned}X_{n+1}^{(tr)}&=X_n^{(tr)}+P[c_2(x_T-X_n^{(tr)}),\tau]-P(c_1X_n^{(tr)},\tau)\\&\quad+\tfrac{1}{2}[c_2\tau(X_n^{(tr)}-X_{n+1}^{(tr)})-c_1(\tau X_{n+1}^{(tr)}-X_n^{(tr)})].\end{aligned} \tag{34}$$

Simplifying Eq. (34), we obtain

$$\begin{aligned}X_{n+1}^{(tr)}&=X_n^{(tr)}+\frac{1}{1+\frac{(c_1+c_2)\tau}{2}}\{P[c_2(x_T-X_n^{(tr)}),\tau]\\&\quad-P(c_1X_n^{(tr)},\tau)\}.\end{aligned} \tag{35}$$

Taking expectation we obtain

$$\begin{aligned}E(X_{n+1}^{(tr)})&=E(X_n^{(tr)})+\frac{1}{1+\frac{(c_1+c_2)\tau}{2}}\\&\quad\times\{c_2\tau[x_T-E(X_n^{(tr)})]-c_1\tau E(X_n^{(tr)})\}.\end{aligned} \tag{36}$$

Thus

$$E(X_{n+1}^{(tr)})=\frac{2-(c_1+c_2)\tau}{2+(c_1+c_2)\tau}E(X_n^{(tr)})+\frac{c_2\tau x_T}{1+\frac{(c_1+c_2)\tau}{2}}. \tag{37}$$

The propagation coefficient is $(2-\lambda\tau)(2+\lambda\tau)$. Thus the stability condition for the trapezoidal tau method is

$$\left|\frac{2-\lambda\tau}{2+\lambda\tau}\right|<1. \tag{38}$$

Since Eq. (38) is satisfied for large $|\lambda\tau|$, the trapezoidal tau method is also a good candidate for the solution of stiff problems. Letting $n\to\infty$ in Eq. (36), we obtain the converged mean value:

$$E(X^{(tr)}(\infty))=\frac{c_2}{c_1+c_2}x_T=E(X^*). \tag{39}$$

For the variance,

$$\begin{aligned}&\mathrm{Var}(X_{n+1}^{(tr)})\\&=E[\mathrm{Var}(X_{n+1}^{(tr)}|X_n^{(tr)})]+\mathrm{Var}[E(X_{n+1}^{(tr)}|X_n^{(tr)})]\\&=E\left(\frac{1}{\left[1+\frac{(c_1+c_2)\tau}{2}\right]^2}c_2\tau(x_T-X_n^{(tr)})+c_1\tau X_n^{(tr)}\right)\\&\quad+\mathrm{Var}\left(\frac{1-\frac{(c_1+c_2)\tau}{2}}{1+\frac{(c_1+c_2)\tau}{2}}X_n^{(tr)}\right)\\&=\left(\frac{1-\frac{(c_1+c_2)\tau}{2}}{1+\frac{(c_1+c_2)\tau}{2}}\right)^2\mathrm{Var}(X_n^{(tr)})+\frac{1}{\left(1+\frac{(c_1+c_2)\tau}{2}\right)^2}\\&\quad\times[c_2\tau x_T+(c_1-c_2)\tau E(X_n^{(tr)})].\end{aligned} \tag{40}$$

Thus the stability condition for variance is the same as Eq. (38). Letting $n\to\infty$ in Eq. (40) and applying Eq. (39), we obtain the limit of the variance

$$\mathrm{Var}[X^{(tr)}(\infty)]=\mathrm{Var}(X^*). \tag{41}$$

Thus the variance given by the trapezoidal tau method converges to the theoretical value. This is an advantage of the trapezoidal tau method over the explicit and implicit tau methods.

D. Stability of higher moments

To study the stability region for higher moments, we need to calculate the propagation coefficient. We will show that for each of the above three leaping methods, the stability region for higher moments is the same as the stability region for the mean. Since the analysis is similar for all three methods, in the following we show only the analysis for the explicit tau method. First we need the following Lemma for the Poisson distribution which is easy to prove and we shall omit the proof.

Lemma 3.2. For the Poisson distribution $X=P(\lambda)$,

$$E(X^k)=\lambda^k+\sum_{j=0}^{k-1}\alpha_j\lambda^j, \tag{42}$$

where α_j are constants for fixed k.

Applying the explicit tau method to the test problem (12), we obtain Eq. (18). For convenience of presentation, we omit the superscript and rewrite Eq. (18) as

$$X_{n+1}=X_n+P[c_2(x_T-X_n),\tau]-P(c_1X_n,\tau). \tag{43}$$

For the kth moment, from Lemma 3.1. we have

$$E(X_{n+1}^k)=E[E(X_{n+1}^k|X_n)]. \tag{44}$$

Applying Eq. (44) to Eq. (43), we obtain

$$E(X_{n+1}^k)=E[E(\{X_n+P[c_2(x_T-X_n),\tau]-P(c_1X_n,\tau)\}^k|X_n)]. \tag{45}$$

Expanding $E(\{X_n+P[c_2(x_T-X_n),\tau]-P(c_1X_n,\tau)\}^k|X_n)$, we obtain

$$E(\{X_n+P[c_2(x_T-X_n),\tau]-P(c_1X_n,\tau)\}^k|X_n)$$
$$=\sum_{i+j+l=k}C_{ijl}X_n^iE(\{P[c_2(x_T-X_n),\tau]\}^j|X_n)\times E\{[-P(c_1X_n,\tau)]^l|X_n\}, \tag{46}$$

where $C_{ijl}=k!/i!j!l!$. Note that we have used the fact that conditioned on X_n the two Poisson numbers are independent. Taking expectation of Eq. (46) we may obtain an expression for $E(X_{n+1}^k)$ as a linear combination of moments $E(X_n^\alpha)$ where $\alpha=1,\ldots,k$. We are interested in the coefficient of $E(X_n^k)$, i.e., the propagation constant for the kth moment. For this we only need to count the coefficient for X_n^j in $E(\{P[c_2(x_T-X_n),\tau]\}^j|X_n)$ and the coefficient for X_n^l in $E\{[-P(c_1X_n,\tau)]^l|X_n\}$. Applying Eq. (42), we have

$$C_{ijl}X_n^iE(\{P[c_2(x_T-X_n),\tau]\}^j|X_n)E\{-[P(c_1X_n,\tau)]^l|X_n\}=C_{ijl}(-c_2\tau)^j(-c_1\tau)^lX_n^k+\sum_{r<k}B_{ijlr}X_n^r, \tag{47}$$

where B_{ijlr} are some constants that depend on τ. Substituting Eq. (47) into Eq. (46) and taking expectation we obtain

$$E(X_{n+1}^k)=[1-(c_1+c_2)\tau]^kE(X_n^k)+\sum_{j=0}^{k-1}C_j^k\tau^jE(X_n^j), \tag{48}$$

where C_j^k are constants. Note that we have used the fact that

$$\sum_{i+j+l=k}C_{ijl}(-c_2\tau)^j(-c_1\tau)^l=(1-c_1\tau-c_2\tau)^k.$$

Thus the propagation coefficient is $(1-\lambda\tau)^k$. The stability region is the set of $\lambda\tau$ such that

$$|1-\lambda\tau|\leqslant 1. \tag{49}$$

This is the same as the absolute stability region for the mean and for the variance.

A similar analysis can be applied to the implicit tau and trapezoidal tau methods. We know that the variance for the implicit tau does not converge to the variance of the stationary solution, while the variance for the trapezoidal tau method does. In the following section we shall show that not all of the higher moments of the trapezoidal method can converge to that of the stationary solution.

E. Convergence of higher moments for trapezoidal tau

Provided that the stability condition (38) is satisfied we know that all the moments of the trapezoidal tau converge. We have shown that the mean and variance actually converge to the mean and variance of the stationary distribution (15) of the reversible isomerization reaction. A natural question is whether all higher moments also converge to those of the stationary distribution. Unfortunately the answer is negative.

First we recall the notions of distribution functions and weak convergence. Given a random variable X, its distribution function F (also known as cumulative distribution function) is defined by

$$F(x)=\text{Prob}\{X\leqslant x\},\quad x\in\mathbb{R}.$$

A sequence of distributions F_n is said to *converge weakly* to a distribution F (as $n\to\infty$) if

$$\lim_{n\to\infty}F_n(x)=F(x)$$

for each $x\in\mathbb{R}$ at which F is continuous.

Our argument comes down to two facts. One is that the trapezoidal tau cannot converge weakly to the stationary distribution described by Eq. (15). This is because the Poisson scheme gives unboundedly large possible values. The other is that since the stationary distribution (15) is uniquely characterized by its moments, convergence of moments implies weak convergence of the distributions.

Lemma 3.3. The binomial distribution is uniquely characterized by its moments. In other words given the moments μ_k, $k\in\mathbb{N}$ of a binomial distribution, if another distribution has the same moments then it is the same binomial distribution.

Proof. We will use Proposition 8.49 of Ref. 21 which states that if $\mu_k\in\mathbb{R}$, $k\in\mathbb{N}$ satisfy

$$\limsup_k\frac{|\mu_k|^{1/k}}{k}<\infty$$

then there exists *at most* one distribution with moments μ_k.

The stationary distribution of the reversible isomerization is binomial with parameter $N=x_T$. This means $P(X^*>x_T)=0$, where X^* is a random variable distributed according to the stationary distribution. Hence it follows that

$$\mu_k=E[(X^*)^k]\leqslant x_T^k$$

and thus

$$\frac{|\mu_k|^{1/k}}{k}\leqslant\frac{x_T}{k}\to 0,$$

as $k\to\infty$. Proposition 8.49 of Ref. 21 stated above completes the proof. ■

Lemma 3.4. The stationary binomial distribution (15) cannot be a stationary distribution for the trapezoidal tau method. Thus the trapezoidal tau can not converge weakly to the distribution given by Eq. (15).

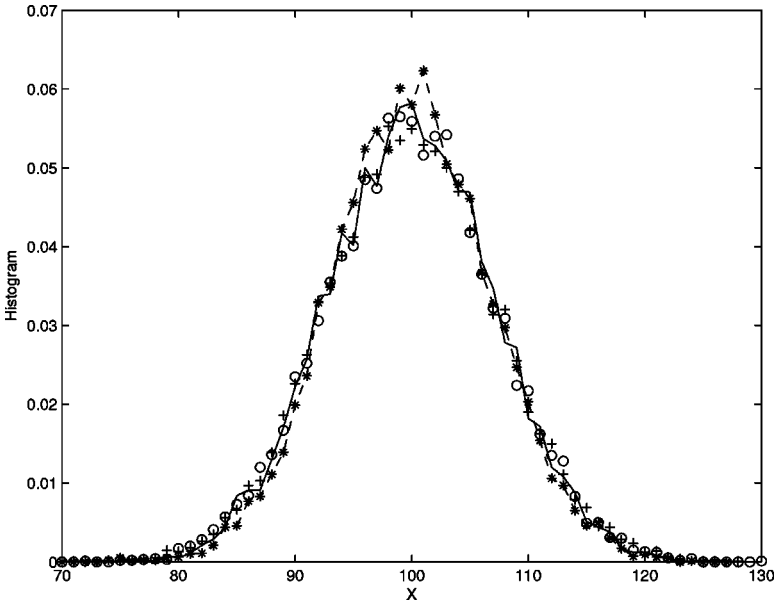

FIG. 1. Histogram (10 000 samples) of X_1 solved by the SSA method (solid line), explicit tau (plot with "+"), implicit tau (plot with "*"), and trapezoidal tau (plot with "o") for test problem (12) with $\tau=0.01$.

Proof. Suppose $X^{(tr)}(t)$ has the same distribution as X^* given in Eq. (15). Then it follows from Eq. (35) that

$$\text{Prob}\{X^{(tr)}(t+\tau)>x_T\}>0.$$

Thus $X^{(tr)}(t+\tau)$ does not have the same distribution (15) attributed to $X^{(tr)}(t)$. Hence the distribution (15) cannot be a stationary distribution for the trapezoidal tau method. ■

Lemma 3.5. Not all moments of the trapezoidal tau method converge to the corresponding moments of the stationary distribution given by Eq. (15).

Proof. We will use Theorem 8.48 of Ref. 21. This theorem states that if a sequence of probability distributions F_n, $n\in\mathbb{N}$, have convergent moments, i.e.,

$$\mu_k=\lim_{n\to\infty}\int x^k dF_n(x)$$

exist and are finite, and if there is *at most* one distribution function F such that

$$\int x^k dF(x)=\mu_k,$$

then the sequence F_n converges weakly to F. Thus if all the moments of the trapezoidal tau converge to those of the stationary distribution (15) then using Lemma 3.3 we may conclude that the trapezoidal tau must converge weakly to the stationary distribution (15). But this contradicts Lemma 3.4. ■

IV. NUMERICAL COMPARISON

In this section we apply the three methods: explicit tau, implicit tau and trapezoidal tau to solve two chemically re-

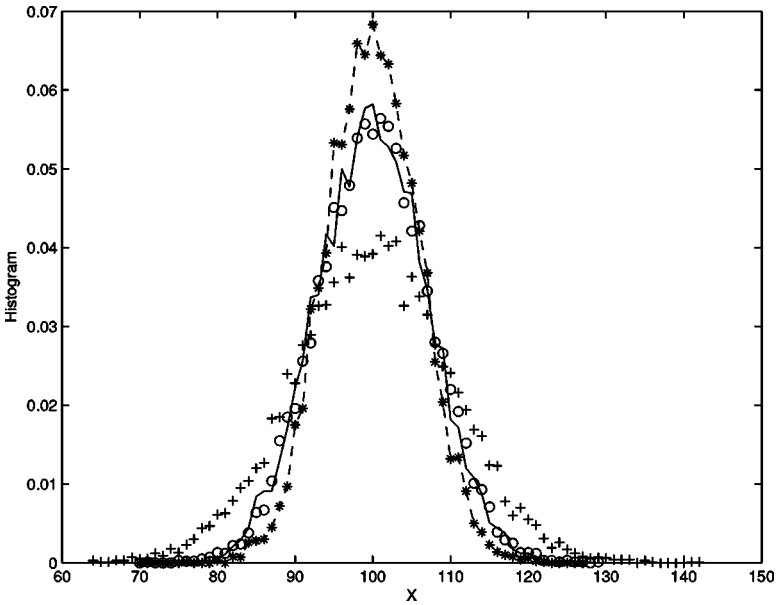

FIG. 2. Histogram (10 000 samples) of X_1 solved by the SSA method (solid line), explicit tau (plot with "+"), implicit tau (plot with "*"), and trapezoidal tau (plot with "o") for test problem (12) with $\tau=0.05$.

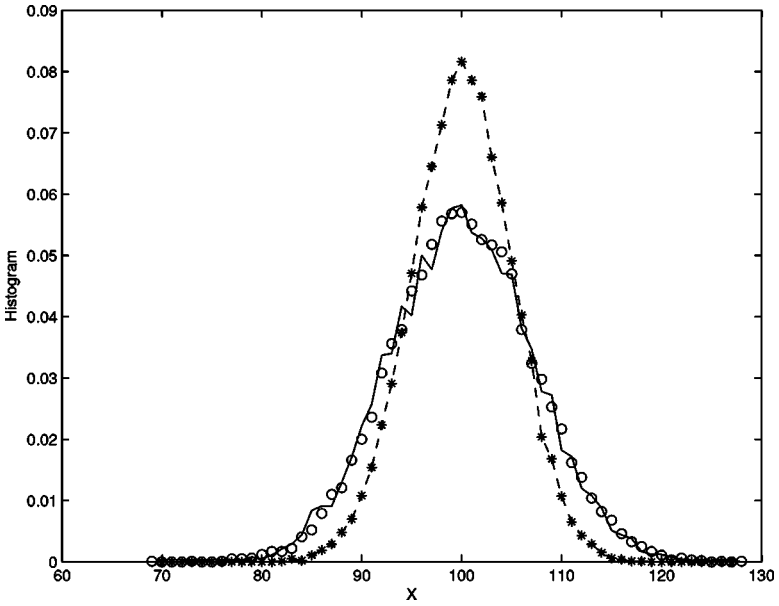

FIG. 3. Histogram (10 000 samples) of X_1 solved by the SSA method (solid line), implicit tau (plot with "*"), and trapezoidal tau (plot with "o") for test problem (12) with $\tau=0.1$. Explicit tau is unstable for this stepsize.

acting systems. The first is the test problem (12). The corresponding parameters were chosen as $c_1=c_2=10$, $x_1(0)=x_2(0)=100$ $(x_T=200)$. Histograms were plotted from 10 000 realizations from each method at final time $T=10$. Figures 1–4 show the corresponding histograms of the $X_1(T)$ obtained with different numerical methods and different stepsizes τ. When τ is small, all three methods generate histograms close to that of the SSA method. As τ increases, as predicted by the analysis, the histogram generating from the explicit tau method is too broad and the histogram given by the implicit tau is too narrow, while the trapezoidal tau method generates a histogram very close to the SSA method. Note that when $\tau \geqslant 0.1$, the explicit tau method is unstable. Thus there is no plot for the explicit tau method in the corresponding figures.

The second example is the Schlögl reaction. This reaction is famous for its bistable distribution. The reactions are given by

$$\begin{aligned} &B_1+2X \underset{c_2}{\overset{c_1}{\rightleftharpoons}} 3X, \\ &B_2 \underset{c_4}{\overset{c_3}{\rightleftharpoons}} X, \end{aligned} \tag{50}$$

where B_1 and B_2 denote buffered species whose respective molecular populations N_1 and N_2 are assumed to remain essentially constant over the time interval of interest. Let

$$x(t)=\text{number of } X \text{ molecules in the system at time } t. \tag{51}$$

The state change vectors are $\nu_1=\nu_3=1$, $\nu_2=\nu_4=-1$. The propensity functions are

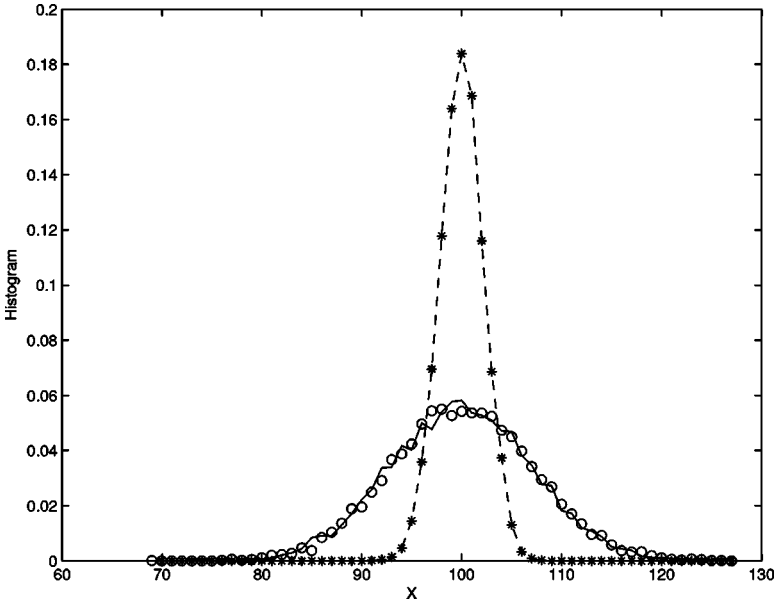

FIG. 4. Histogram (10 000 samples) of X_1 solved by the SSA method (solid line), implicit tau (plot with "*"), and trapezoidal tau (plot with "o") for test problem (12) with $\tau=1$. Explicit tau is unstable for this stepsize.

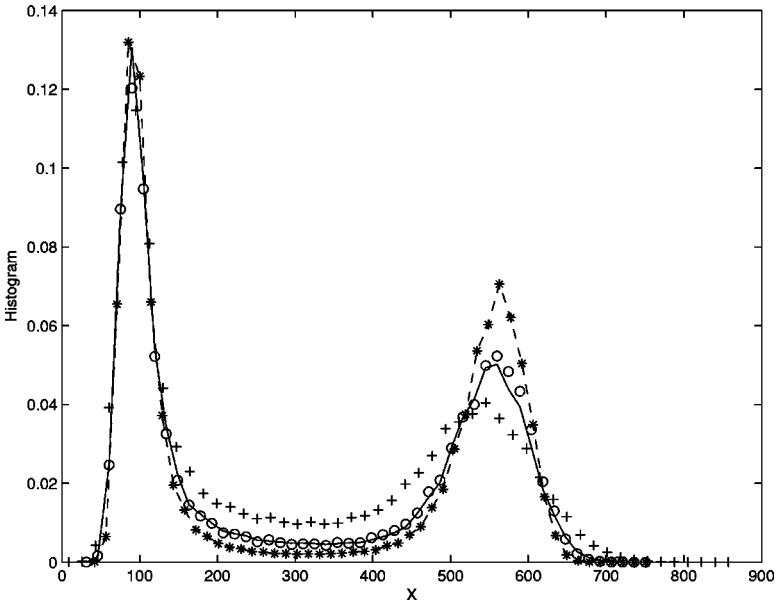

FIG. 5. Histogram (10 000 samples) of X_1 solved by the SSA method (solid line), explicit tau (plot with "+"), implicit tau (plot with "*"), and trapezoidal tau (plot with "o") for Schlögl reaction with $\tau=0.4$.

$$
\begin{aligned}
a_1(x) &= \frac{c_1}{2} N_1 x(x-1), \\
a_2(x) &= \frac{c_2}{6} x(x-1)(x-2), \\
a_3(x) &= c_3 N_2, \\
a_4(x) &= c_4 x.
\end{aligned}
\tag{52}
$$

For some parameter values, this model has two stable states. The parameter set that we used in our simulation has this property and was given by

$$
\begin{aligned}
&c_1 = 3\times 10^{-7}, \quad c_2 = 10^{-4}, \quad c_3 = 10^{-3}, \quad c_4 = 3.5, \\
&N_1 = 1\times 10^{5}, \quad N_2 = 2\times 10^{5}.
\end{aligned}
\tag{53}
$$

We ran the simulation from $t=0$, with initial state $x(0)=250$, to time $t=4$. The histograms generated from SSA, explicit tau, implicit tau, and trapezoidal tau with fixed step-sizes $\tau=0.4$ are shown in Fig. 5. The results are similar to those obtained for the first problem. The histogram produced by the trapezoidal tau is close to that produced by the SSA method, while the histogram produced by the explicit tau exhibits a broadening of the two peaks, and the histogram produced by the implicit tau exhibits a sharpening of the peaks.

V. CONCLUSION

We have presented an analysis of the absolute stability of the explicit, implicit, and trapezoidal tau methods applied to the simulation of the reversible isomerization reaction. The analysis reveals that the stability region for any moment is the same as the stability region for the first moment for each of these leaping methods. Further more these stability regions are the same as the stability regions of the explicit Euler, implicit Euler, and trapezoidal implicit methods applied to the ODE $\dot{y}=\lambda y$.

When the stability is maintained, the means of all three leaping methods converge to the mean of the stationary distribution of the reversible isomerization reaction. However, the asymptotic variance of explicit tau is larger than the variance of the stationary distribution, while that of implicit tau is smaller. These results agree with the intuition that explicit tau amplifies noise while implicit tau dampens it. The variance of trapezoidal tau converges to the variance of the stationary distribution. Furthermore, we showed that the higher order moments of trapezoidal tau in general do not converge to those of the stationary distribution.

We have provided two examples which appear to validate the theoretical results. The first is the reversible isomerization reaction. For this problem, explicit tau broadens the peak of the histogram and implicit tau sharpens the peak; trapezoidal tau captures the peak more accurately than the other two methods. The second example was the Schlögl reaction, which has a final state histogram with double peaks (as computed by SSA). Although our theory does not directly apply to this reaction, the qualitative effects seem to apply: explicit tau broadens both peaks, implicit tau sharpens both peaks, and trapezoidal tau captures the distribution the most accurately.

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[1] A. Arkin, J. Ross, and H. H. McAdams, Genetics **149**, 1633 (1998).
[2] N. Fedoroff and W. Fontana, Science **297**, 1129 (2002).
[3] H. H. McAdams and A. Arkin, Proc. Natl. Acad. Sci. U.S.A. **94**, 814 (1997).
[4] H. H. McAdams and A. Arkin, Trends Genet. **15**, 65 (1999).
[5] D. Gillespie, J. Comput. Phys. **22**, 403 (1976).
[6] D. Gillespie, J. Phys. Chem. **81**, 2340 (1977).
[7] D. Gillespie, J. Chem. Phys. **115**, 1716 (2001).
[8] E. Haseltine and J. Rawlings, J. Chem. Phys. **117**, 6959 (2002).
[9] T. Mattheyses and M. Simmons, Bioinformatics **20**, 316 (2004).
[10] Y. Cao, D. Gillespie, and L. Petzold, J. Chem. Phys. (to be published).
[11] Y. Cao, D. Gillespie, and L. Petzold (unpublished).
[12] K. E. Brenan, S. L. Campbell, and L. R. Petzold, *Numerical Solution of Initial-Value Problems in Differential-Algebraic Equations* (SIAM, Philadelphia, PA, 1996).
[13] M. Rathinam, L. Petzold, Y. Cao, and D. Gillespie, J. Chem. Phys. **119**, 12784 (2003).
[14] M. Rathinam, L. Petzold, Y. Cao, and D. Gillespie, J. Chem. Phys (to be published).
[15] Y. Cao and L. Petzold (unpublished).
[16] D. Gillespie, J. Phys. Chem. A **106**, 5063 (2002).
[17] M. Gibson and J. Bruck, J. Phys. Chem. A **104**, 1876 (2000).
[18] Y. Cao, H. Li, and L. Petzold, J. Chem. Phys. **121**, 4059 (2004).
[19] D. Gillespie, J. Chem. Phys. **113**, 297 (2000).
[20] S. Ross, *Introduction to Probability Models*, 8th ed. (Academic, New York, 2002).
[21] L. Breiman, *Probability* (SIAM, Philadelphia, PA, 1992).