Improved leap-size selection for accelerated stochastic simulation

Daniel T. Gillespie[a)]
Dan T. Gillespie Consulting, Castaic, California 91384

Linda R. Petzold[b)]
Department of Computer Science, University of California, Santa Barbara, California 93106

(Received 8 May 2003; accepted 1 August 2003)

In numerically simulating the time evolution of a well-stirred chemically reacting system, the recently introduced ''tau-leaping'' procedure attempts to accelerate the exact stochastic simulation algorithm by using a special Poisson approximation to leap over sequences of noncritical reaction events. Presented here is an improved procedure for determining the maximum leap size for a specified degree of accuracy. © *2003 American Institute of Physics.* [DOI: 10.1063/1.1613254]

I. INTRODUCTION

In a well-stirred chemically reacting system, the state vector $\mathbf{X}(t)=(X_1(t),\ldots,X_N(t))$, where $X_i(t)$ is the number of molecules of species S_i in the system at time t, evolves stochastically because of the inherent randomness of thermal molecular motion. Random molecular collisions give rise to random chemical transmutations in accordance with some specified set of reaction channels $\{R_1,\ldots,R_M\}$. The dynamics of reaction channel R_j are mathematically defined by a *propensity function* a_j together with a *state-change vector* $\boldsymbol{\nu}_j=(\nu_{1j},\ldots,\nu_{Nj})$: $a_j(\mathbf{x})dt$ gives the probability that one R_j reaction will occur in state $\mathbf{x}$ during the next infinitesimal time interval dt, and ν_{ij} gives the change in the S_i molecular population produced by one R_j reaction.[1]

For numerically simulating the stochastic evolution of $\mathbf{X}(t)$, there exist several exact procedures that actualize every molecular reaction event.[2,3] But efforts to model the complex reactions inside living cells, where small molecular populations of some key reactants can set the stage for major stochastic effects,[4–6] have revealed the need for faster, possibly less meticulous stochastic simulation strategies.

The recently proposed ''leaping'' methodology[7] attempts to sacrifice some exactness for greater speed, and to do so in a way that segues as the system size becomes infinite to standard solution methods for the conventional deterministic reaction rate equation. The ''τ-leap method,'' for instance, tries to leap down the history axis of the system by some chosen time τ that encompasses many reaction events. But theoretical considerations demand that the size of τ be constrained by a *leap condition*, which says that the state change in any leap should be small enough that no propensity function will experience a macroscopically significant change in its value.

The mathematical rationale for the τ-leap method[7] is the fact that, to the extent that the leap condition is satisfied, then given $\mathbf{X}(t)=\mathbf{x}$, the number of times $K_j(\tau;\mathbf{x})$ that reaction channel R_j will fire in $(t,t+\tau)$ can be approximated by a *Poisson* random variable:

$$K_j(\tau;\mathbf{x})\approx\mathcal{P}_j(a_j(\mathbf{x}),\tau). \tag{1}$$

This is so because the generic Poisson random variable $\mathcal{P}(a,\tau)$ can be defined as the number of events that will occur in time τ, given that the probability for an event to occur in the next infinitesimal time dt is $a\,dt$, where a can be any non-negative *constant*. This last requirement is the rationale for the leap condition, and the consequent approximation (1) allows us to estimate the state change in the leap,

$$\mathbf{X}(t+\tau)-\mathbf{x}\equiv\boldsymbol{\Lambda}(\tau;\mathbf{x})=\sum_{j=1}^{M}K_j(\tau;\mathbf{x})\,\boldsymbol{\nu}_j, \tag{2}$$

by simple Poisson sampling.[8] But for this approach to be practicable, we need a reliable, expeditious, and preferably automatic way of determining the *largest* value of τ that is compatible with the leap condition.

In Ref. 7, it was suggested that a plausible mathematical framing of the leap condition would be to require the leap time τ to be such that

$$|a_j(\mathbf{x}+\boldsymbol{\Lambda}(\tau;\mathbf{x}))-a_j(\mathbf{x})|\leqslant\varepsilon a_0(\mathbf{x}),\quad\forall j=1,\ldots,M, \tag{3}$$

where ε is a prespecified *error control parameter* ($0<\varepsilon\ll 1$), and $a_0(\mathbf{x})\equiv\Sigma_l a_l(\mathbf{x})$ is the sum of all the propensity functions. It might seem more appropriate to use on the right-hand side of (3) $a_j(\mathbf{x})$ instead of $a_0(\mathbf{x})$; however, that leads to problems if $a_j(\mathbf{x})$ approaches zero during a simulation, as will happen if the population of any R_j reactant species approaches zero. A reasonable alternative to $a_0(\mathbf{x})$ in (3) would be $\max_{j'\in[1,M]}(a_{j'}(\mathbf{x}))$. With either choice, smaller values of ε ensure smaller changes in the propensity functions during a leap, and that in turn leads to greater accuracy in the approximation (1). But, of course, smaller values of ε also imply shorter leaps, and therefore longer simulation times.

How can we find the largest value of τ that is consistent with (3) for a specified value of ε? This would be a reasonably straightforward problem were it not for the fact that the left-hand side of (3) is a *random variable* [since $\boldsymbol{\Lambda}(\tau;\mathbf{x})$ is a random variable]. In any case, we would like to make our determination of τ without performing repeated ''trial'' leaps, checking after each one to see if condition (3) is satisfied and

a)Electronic mail: GillespieDT@mailaps.org
b)Electronic mail: petzold@engineering.ucsb.edu

 © 2003 American Institute of Physics

Downloaded 24 Oct 2003 to 131.120.105.24. Redistribution subject to AIP license or copyright, see http://ojps.aip.org/jcpo/jcpcr.jsp

adjusting τ accordingly; such a post-leap procedure not only would consume much time and many random numbers, but it might also discriminate against statistically rare but nonetheless legitimate large changes in the system's state.

A specific pre-leap τ-selection procedure was proposed in Ref. 7; however, it was subsequently realized that that procedure does not always adequately ensure condition (3). In this paper we present a new τ-selection procedure that should be more robust. We shall first describe the procedure operationally, then outline its theoretical justification, and finally give a numerical example that illustrates its improved performance.

II. THE NEW TAU-SELECTION PROCEDURE

The new τ-selection procedure requires us to determine in advance first the M^2 functions,

$$f_{jj'}(\mathbf{x}) \triangleq \sum_{i=1}^{N} \frac{\partial a_j(\mathbf{x})}{\partial x_i} \nu_{ij'} \quad (j,j'=1,...,M), \tag{4}$$

and then the $2M$ functions,

$$\mu_j(\mathbf{x}) \triangleq \sum_{j'=1}^{M} f_{jj'}(\mathbf{x}) a_{j'}(\mathbf{x}) \quad (j=1,...,M), \tag{5a}$$

$$\sigma_j^2(\mathbf{x}) \triangleq \sum_{j'=1}^{M} f_{jj'}^2(\mathbf{x}) a_{j'}(\mathbf{x}) \quad (j=1,...,M). \tag{5b}$$

This obviously represents some computational overhead, but the task is not quite as daunting as it might at first appear: The functional dependence of a_j on x_i will typically be very simple—often constant, sometimes linear, but rarely more than quadratic. Furthermore, for large systems the matrix ν_{ij} will typically be sparse. In any case, with the functions (4) and (5) determined, then given a current state $\mathbf{X}(t)=\mathbf{x}$, the largest τ that is compatible with the leap condition (3) is taken to be

$$\tau = \min_{j\in[1,M]} \left\{ \frac{\varepsilon a_0(\mathbf{x})}{|\mu_j(\mathbf{x})|}, \frac{\varepsilon^2 a_0^2(\mathbf{x})}{\sigma_j^2(\mathbf{x})} \right\}. \tag{6}$$

Acceptance of this τ value is, however, subject to the *proviso* that if it is less than a few multiples of $1/a_0(\mathbf{x})$, which is the mean time step for the exact stochastic simulation algorithm (SSA),[2] then it would be better to forego leaping and instead use the SSA.

As will be discussed later, the essential difference between the τ-selection procedure described above and the one proposed in Ref. 7 is that *the earlier procedure lacks the second argument in the minimization braces of (6)*. The major extra effort involved in using this new τ-selection procedure is thus the repeated evaluation of the $\sigma_j^2(\mathbf{x})$ quantities in Eq. (5b). Ameliorating that effort is the fact that the quantities $f_{jj'}(\mathbf{x})$ and $a_{j'}(\mathbf{x})$ needed for the $\sigma_j^2(\mathbf{x})$ computations are already at hand from the $\mu_j(\mathbf{x})$ computations in Eq. (5a).

III. DERIVATION

To derive Eq. (6), we begin by approximating the leap-induced propensity function change on the left-hand side of Eq. (3) by a first-order Taylor expansion:

$$\begin{aligned}\Delta a_j(\tau;\mathbf{x}) &\triangleq a_j(\mathbf{x}+\mathbf{\Lambda}(\tau;\mathbf{x})) - a_j(\mathbf{x}) \\ &\approx \mathbf{\Lambda}(\tau;\mathbf{x})\cdot\nabla a_j(\mathbf{x}) \\ &= \sum_{i=1}^{N} \Lambda_i(\tau;\mathbf{x}) \frac{\partial a_j(\mathbf{x})}{\partial x_i}. \end{aligned} \tag{7}$$

From Eqs. (1) and (2) we have the approximation

$$\Lambda_i(\tau;\mathbf{x}) \approx \sum_{j'=1}^{M} \mathcal{P}_{j'}(a_{j'}(\mathbf{x}),\tau)\nu_{ij'}. \tag{8}$$

Substituting this into Eq. (7), interchanging the order of the two summations, and then invoking the definition (4), we obtain

$$\Delta a_j(\tau;\mathbf{x}) \approx \sum_{j'=1}^{M} f_{jj'}(\mathbf{x}) \mathcal{P}_{j'}(a_{j'}(\mathbf{x}),\tau). \tag{9}$$

Equation (9) evidently expresses the random variable $\Delta a_j(\tau;\mathbf{x})$ as a *linear combination* of statistically independent Poisson random variables. It follows from a general result in statistics that the mean and variance of $\Delta a_j(\tau;\mathbf{x})$ can then be computed as

$$\langle \Delta a_j(\tau;\mathbf{x})\rangle \approx \sum_{j'=1}^{M} f_{jj'}(\mathbf{x}) \langle \mathcal{P}_{j'}(a_{j'}(\mathbf{x}),\tau)\rangle, \tag{10a}$$

$$\mathrm{var}\{\Delta a_j(\tau;\mathbf{x})\} \approx \sum_{j'=1}^{M} f_{jj'}^2(\mathbf{x}) \mathrm{var}\{\mathcal{P}_{j'}(a_{j'}(\mathbf{x}),\tau)\}. \tag{10b}$$

Since $\langle \mathcal{P}(a,\tau)\rangle = \mathrm{var}\{\mathcal{P}(a,\tau)\} = a\tau$, this gives, using the definitions (5),

$$\langle \Delta a_j(\tau;\mathbf{x})\rangle \approx \sum_{j'=1}^{M} f_{jj'}(\mathbf{x}) (a_{j'}(\mathbf{x})\tau) \equiv \mu_j(\mathbf{x})\tau, \tag{11a}$$

$$\mathrm{var}\{\Delta a_j(\tau;\mathbf{x})\} \approx \sum_{j'=1}^{M} f_{jj'}^2(\mathbf{x}) (a_{j'}(\mathbf{x})\tau) \equiv \sigma_j^2(\mathbf{x})\tau. \tag{11b}$$

Now, the leap condition (3) requires that each random variable $\Delta a_j(\tau;\mathbf{x})$ be bounded in absolute value by $\varepsilon a_0(\mathbf{x})$. Leaving aside the question of whether the multiplier of ε in this bound ought to be $a_0(\mathbf{x})$ or $\max_{j'\in[1,M]}(a_{j'}(\mathbf{x}))$ or perhaps something else, we are faced here with the interesting question of how we should go about ensuring an inequality condition on a *random variable*. We shall take the position that the inequality should be enforced only in some approximate statistical sense.

Since we expect $\Delta a_j(\tau;\mathbf{x})$ to be "small," then to a first approximation we should be able to write it as

$$\Delta a_j(\tau;\mathbf{x}) \approx \langle \Delta a_j(\tau;\mathbf{x})\rangle \pm \mathrm{sdev}\{\Delta a_j(\tau;\mathbf{x})\}. \tag{12}$$

The first term on the right here can be positive, negative, or zero, while the standard deviation (the square root of the variance) is always positive [becoming zero if and only if $\Delta a_j(\tau;\mathbf{x})$ becomes a *sure* variable]. The problem with the approximation (12) is that we have to allow for *both signs* on the right-hand side. A conservative maximal estimate of the above approximation would be $|\langle \Delta a_j(\tau;\mathbf{x})\rangle| + \mathrm{sdev}\{\Delta a_j(\tau;\mathbf{x})\}$, and if we required that quantity to be bounded by $\varepsilon a_0(\mathbf{x})$ for each j, we could use Eq. (11) to

Downloaded 24 Oct 2003 to 131.120.105.24. Redistribution subject to AIP license or copyright, see http://ojps.aip.org/jcpo/jcpcr.jsp

obtain a computable formula for the largest τ. But it would be easier, and in the final analysis probably just as reasonable, to require *each* of the two terms on the right-hand side of (12) to be absolutely bounded by $\varepsilon a_0(\mathbf{x})$. If we impose that requirement, and then invoke the approximations (11), we obtain

$$|\mu_j(\mathbf{x})\tau| \leqslant \varepsilon a_0(\mathbf{x}) \quad \text{and} \quad \sigma_j(\mathbf{x})\tau^{1/2} \leqslant \varepsilon a_0(\mathbf{x}), \quad \forall j = 1,...,M. \tag{13}$$

Of course, the two alternative bounding procedures just described are not equivalent to each other for a given value of ε; however, owing to the intrinsic arbitrariness in choosing a value for ε in the first place, both procedures achieve essentially the same end. And since neither procedure is obviously ''more correct'' than the other, it seems reasonable to go with the computationally simpler one.

Accepting, then, conditions (13) as a reasonable quantification of the leap condition (3), it is easy to see that this condition is secured by choosing τ according to Eq. (6).

IV. k_α-LEAPING

A variation of the τ-leaping strategy is ''k_α-leaping,'' [7] in which we leap down the history axis of the system by a specified number k_α of firings of some chosen reaction channel R_α. Whereas in τ leaping we are faced with the task of finding the largest value of τ that is compatible with the leap condition, in k_α leaping we are faced with the task of finding the largest value of k_α that is compatible with the leap condition.

One way to solve the k_α selection problem is to observe that, when the leap condition is satisfied, the *average*, number of firings of channel R_α in a time τ will be

$$\langle K_\alpha(\tau;\mathbf{x})\rangle \approx \langle \mathcal{P}_\alpha(a_\alpha(\mathbf{x}),\tau)\rangle = a_\alpha(\mathbf{x})\tau. \tag{14}$$

So a leap by time τ is, *on average* equivalent to a leap by

$$k_\alpha = [a_\alpha(\mathbf{x})\tau], \tag{15}$$

R_α events, where $[z]$ denotes ''the greatest integer in z.''

Therefore, a plausible way to choose a suitable value for k_α would be to first compute the τ value in Eq. (6), and then use it to compute k_α according to Eq. (15). That done, the τ value computed from Eq. (6) should be *discarded*, since (as is explained more fully in Ref. 7) the time increment τ associated with the *preselected* value k_α should be obtained by sampling the *gamma* random variable $\Gamma(a_\alpha(x),k_\alpha)$. [8] Using *that* τ value as the leap time, the numbers of firings of all the other reaction channels $R_{j\neq\alpha}$ are then generated according to formula (1).

If the value of k_α found using the above procedure turns out to be zero, one would want to rethink the wisdom a making a k_α leap. But, in practice, k_α-leaping is more likely to be used in situations where one wants to *avoid* leaping over the occurrences of some *pivotally important* reaction R_α—e.g., when one would like to leap *precisely* to the next R_α event. (For instance, R_α might be a reaction that initiates some critical genetic transcription or translation sequence inside a cell.) In that case, if the selection rule (15) produces any positive value for k_α, one could safely assume that leaping with $k_\alpha = 1$ would not violate the leap condition.

V. A NUMERICAL EXAMPLE

In Ref. 7, the tau-leaping methodology was demonstrated on the model reaction set,

$$S_1 \xrightarrow{c_1} 0, \quad S_1 + S_1 \underset{c_3}{\overset{c_2}{\rightleftharpoons}} S_2, \quad S_2 \xrightarrow{c_4} S_3. \tag{16}$$

In these reactions, a decay-prone monomer S_1 reversibly dimerizes to an unstable form S_2, which can convert to a stable form S_3. For the parameter values

$$c_1 = 1, \quad c_2 = 0.002, \quad c_3 = 0.5, \quad c_4 = 0.04, \tag{17}$$

and the initial conditions $X_1(0) = 10^5$, $X_2(0) = X_3(0) = 0$, numerical simulations were performed in Ref. 7 using both the exact stochastic simulation algorithm (SSA) and the tau-leaping algorithm, the latter using a τ-selection scheme that is equivalent to (6) but *without* the σ_j^2 test. For $\varepsilon = 0.03$, the tau-leaping method produced results that agreed reasonably well with the SSA results (see Ref. 7, Figs. 4 and 5); however, the tau-leaping trajectory showed a high degree of *unevenness* in the sizes of the leaps. That tau-leaping trajectory is recreated in Fig. 1, and the unevenness in the step sizes for $t > 0.2$ is apparent.

In Fig. 2 we show a tau-leaping simulation made with the new τ-selection scheme (6), using the same value of ε. It is apparent that the sizes of the time leaps in Fig. 2 are much more uniform than they are in Fig. 1. A detailed monitoring of the Fig. 2 run revealed that, between times $t = 2$ and $t = 20$, a total of 143 leaps occurred, and in 59 of those leaps (roughly 40%) the limiting constraint on τ was imposed by the σ_j^2 requirement in (6). This suggests, in light of our analysis in Sec. III, that the simulation run in Fig. 1 was frequently taking leaps that were larger than warranted by the leap condition (3) for the chosen value of ε. Although it might be argued that those larger leaps simply correspond to larger values of the somewhat arbitrary parameter ε, it is clearly an inefficient strategy to allow the accuracy of a single leap to vary randomly and uncontrollably during a simulation run.

But the important question is the following: do the larger-than-warranted leaps in Fig. 1 materially affect the accuracy of the overall simulation? To answer this question, we made a series of *repeated* simulations to examine the statistics of the trajectories between times $t = 2$ and $t = 12$. More precisely, using the parameter values (17), we started each simulation run with the initial condition

$$X_1(0) = 4150, \quad X_2(0) = 39565, \quad X_3(0) = 3445, \tag{18}$$

and we ran to $t = 10$, at which time we recorded the populations of the three species. We made 10 000 such simulation runs *each* using (i) the exact SSA, (ii) the tau-leaping method with $\varepsilon = 0.03$ using the *new* τ-selection scheme, and (iii) the tau-leaping method with $\varepsilon = 0.03$ using the *old* τ-selection scheme. Figure 3 shows the resulting population histograms (normalized and smoothed) at time $t = 10$.

In Fig. 3(a) we see that both τ-selection procedures accurately reproduce the mean of $X_1(10)$, but they give standard deviations for $X_1(10)$ that are too large according to the SSA histogram (*solid* curve), by a factor of 1.5 for the new

Downloaded 24 Oct 2003 to 131.120.105.24. Redistribution subject to AIP license or copyright, see http://ojps.aip.org/jcpo/jcpcr.jsp

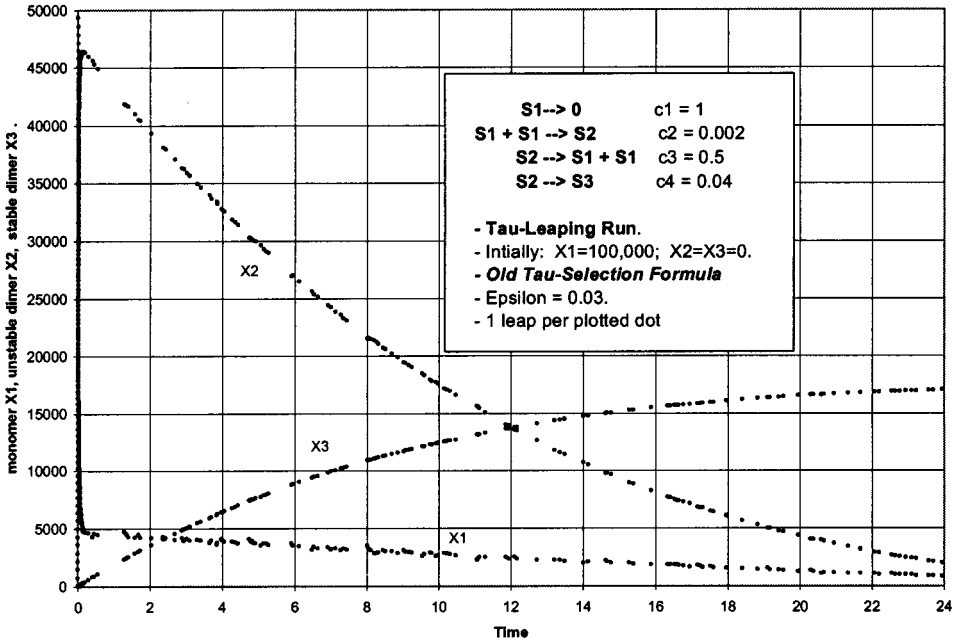

FIG. 1. A τ-leap simulation of reactions (16) using the parameter values (17), $\varepsilon = 0.03$, and the *old* τ-selection procedure of Ref. 7, which anticipates only the *average* change in each propensity function during a leap. Note the unevenness in the successive leap sizes.

τ-selection procedure (*dashed* curve), and by a factor of 2.2 for the old τ-selection procedure (*dotted* curve). For $X_2(10)$ and $X_3(10)$, there is much less broadening of the tau-leaping peaks; however, the means of those peaks are noticeably shifted relative to the SSA peak: The shift is *downward* for $X_2(10)$, by 0.9 standard deviations for the new τ-selection procedure and 2.5 standard deviations for the old, and *upward* for $X_3(10)$, by 0.6 standard deviations for the new τ-selection procedure and 1.5 standard deviations for the old. But in all cases, the new τ-selection procedure gives significantly more accurate results than the old τ-selection procedure; hence, we conclude that the erratic leap sizes in the simulation of Fig. 1 is indeed accompanied by a loss of simulation accuracy.

What prompts us to accept such tau-leaping errors? A monitoring of the *execution times* for the simulation runs used to obtain the plots in Fig. 3 revealed that both tau simulations are faster than the SSA simulation by over two orders of magnitude: Using Mathcad 11 on a 2 GHz processor running Windows XP, the 10 000 tau-leaping simulations took about 6 and 4 min, respectively, for the new and old τ-selection procedures, whereas the 10 000 exact SSA simulations took almost 32 h.

Figure 4 shows the results obtained in a repeat of the simulations made for Fig. 3 with the tau-leaping accuracy control parameter ε reduced from 0.03 to 0.02. As we should expect, the accuracy of both tau-leaping simulations is improved in every respect from the $\varepsilon = 0.03$ results in Fig. 3.

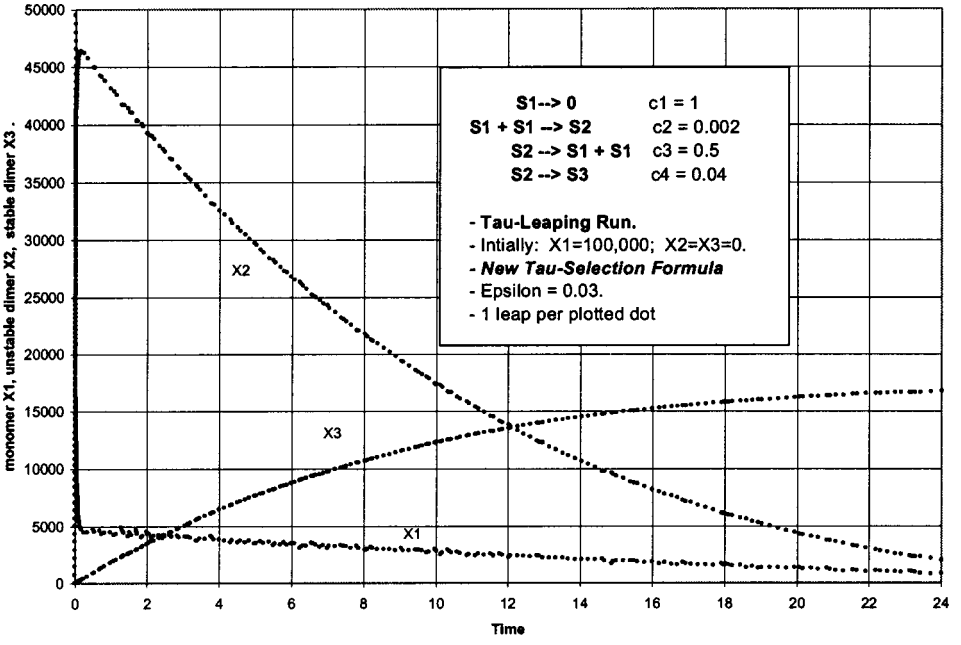

FIG. 2. A repeat of the simulations in Fig. 1 using the *new* τ-selection formula (6), which anticipates also the *fluctuations* in the propensity function changes by adding to the old procedure the $\sigma_j^2(\mathbf{x})$ argument in Eq. (6). The leap sizes here are evidently much more uniform than those in Fig. 1.

Downloaded 24 Oct 2003 to 131.120.105.24. Redistribution subject to AIP license or copyright, see http://ojps.aip.org/jcpo/jcpcr.jsp

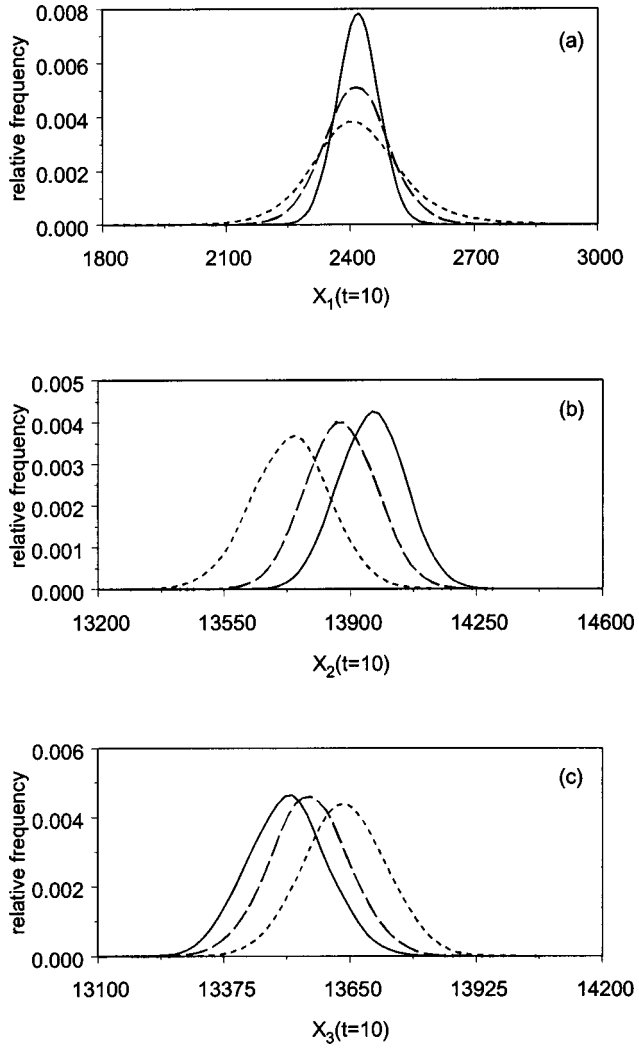

FIG. 3. Comparing the results obtained in three sets of simulation runs of reactions (16), using the parameter values (17). Each run starts at $t=0$ with the initial condition (18) (which approximates the $t=2$ state in Figs. 1 and 2) and ends at $t=10$. The three curves in (a) show the smoothed frequency histograms of the $X_1(10)$ values obtained in 10 000 simulation runs *each* using the exact SSA (*solid* curve), the tau-leaping method with $\varepsilon=0.03$ and the *new* τ-selection procedure (*dashed* curve), and the tau-leaping method with $\varepsilon=0.03$ and the *old* τ-selection procedure (*dotted* curve). The curves in (b) and (c) show, for the same runs, the smoothed frequency histograms of $X_2(10)$ and $X_3(10)$, respectively.

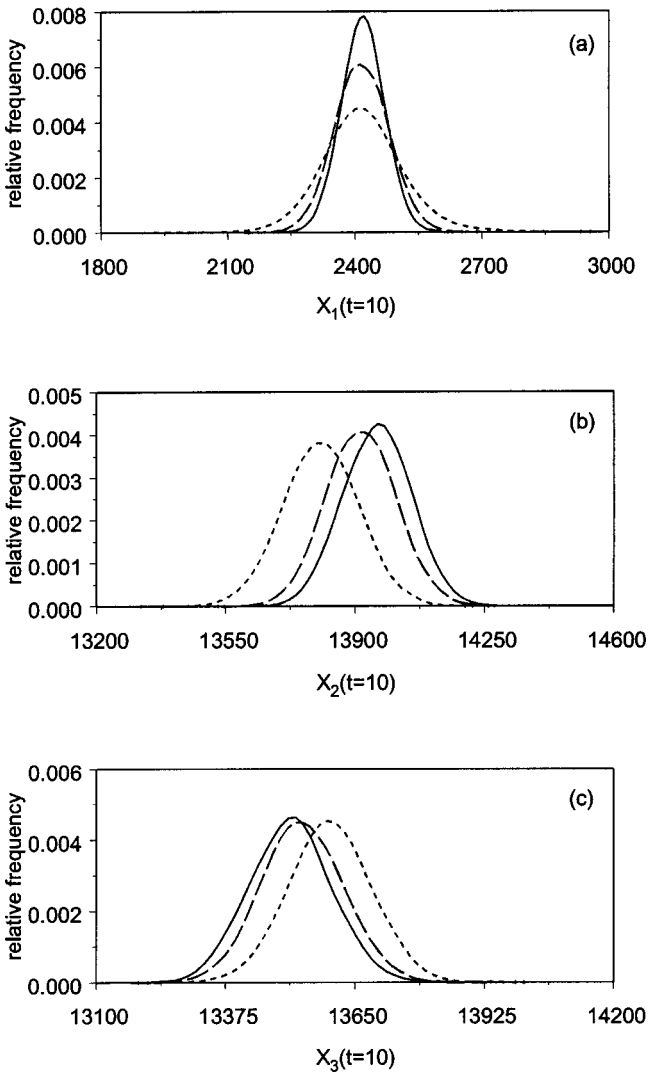

FIG. 4. A repeat of the simulation experiment in Fig. 3, but with the accuracy control parameter ε for the two tau-leaping sets of runs reduced from 0.03 to 0.02. As expected, all tau-leaping results here are more accurate than those in Fig. 3; furthermore, the $\varepsilon=0.02$ results for the old τ-selection procedure are not as accurate as the $\varepsilon=0.03$ results for the new τ-selection procedure. Both tau-leaping simulations here were over 100 times faster than the SSA simulations.

And although the run times for the two tau-simulation series were increased by a factor of about 50% over what they were with $\varepsilon=0.03$, both were still more than two orders of magnitude smaller than the run time for the SSA series. Note also that the new τ-selection procedure with $\varepsilon=0.03$ gave results that are significantly more accurate than the old τ-selection procedure results with $\varepsilon=0.02$.

VI. DISCUSSION

The τ-selection procedure used in Ref. 7 essentially approximates each leap component $\Lambda_i(\tau;\mathbf{x})$ by its *mean*. That approximation should be justified whenever the standard deviation of $\Lambda_i(\tau;\mathbf{x})$ is *small* compared to its mean. But in cases where $\mathrm{sdev}\{\Lambda_i(\tau;\mathbf{x})\}$ is *large* compared to $\langle\Lambda_i(\tau;\mathbf{x})\rangle$, a situation that typically arises when the system is in a slowly varying "quasiequilibrium" mode with $\langle\Lambda_i(\tau;\mathbf{x})\rangle \approx 0$, replacing $\Lambda_i(\tau;\mathbf{x})$ by $\langle\Lambda_i(\tau;\mathbf{x})\rangle$ could lead one to conclude that a large τ leap could be made without changing a_j very much, whereas, in fact, the natural fluctuations in $\Lambda_i(\tau;\mathbf{x})$ for that large τ could result in unacceptably large changes in a_j. Because our new τ-selection procedure approximates $\Lambda_i(\tau;\mathbf{x})$ in a way that retains the full random variable character of $\Lambda_i(\tau;\mathbf{x})$ [cf. Eq. (8)], the new procedure is able to anticipate fluctuation-induced changes in the propensity functions for a prospective τ leap, and thus make a more informed choice for τ.

We can see from Figs. 1 and 2 that both τ-selection procedures perform well in the early transient stage (up to about $t=0.2$), as reaction channel R_2 rapidly and determinedly brings the S_1 and S_2 populations to "quasiequilibrium" levels with respect to channels R_2 and R_3. Thereafter, the changes in the *means* of the species populations occur

Downloaded 24 Oct 2003 to 131.120.105.24. Redistribution subject to AIP license or copyright, see http://ojps.aip.org/jcpo/jcpcr.jsp

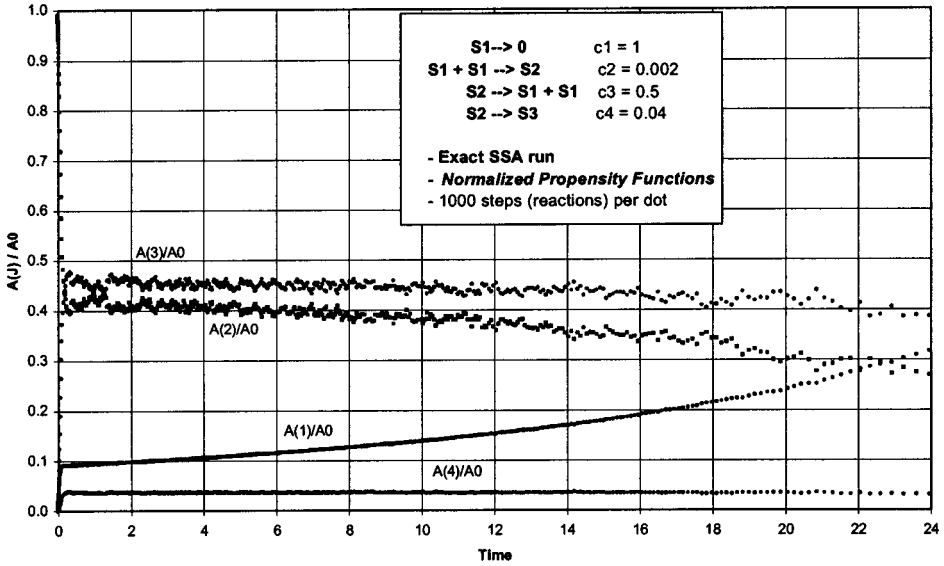

FIG. 5. An *exact* stochastic simulation of reactions (16), recorded at 1000 reactions per dot, showing the evolution of the normalized propensity functions $a_j(\mathbf{x})/a_0(\mathbf{x})$, a ratio that essentially measures the probability that the next reaction will be an R_j reaction. The surprisingly large fluctuations in this ratio for the two dominant channels R_2 and R_3 in the region after the initial transient show that stochasticity is present even at these relatively large population levels. These intrinsic fluctuations are no doubt a major contributor to the erratic performance of the old τ-selection procedure in Fig. 1.

much more slowly. But there are rapid fluctuations occurring in the system during this later period, some of which are larger than one might expect at these population levels. This is illustrated in Fig. 5, which shows for an exact SSA run how the normalized propensity functions $a_j(\mathbf{x})/a_0(\mathbf{x})$ for reaction channels R_2 and R_3 "fight" each other during this period with surprisingly large, anticorrelated fluctuations. Given such fluctuations, the need to consider more than just the mean of $\Delta a_j(\tau;\mathbf{x})$ becomes clear. The new τ-selection procedure attempts to meet this need through Eq. (11b). And the numerical experiments described in Sec. V demonstrate that this new procedure is indeed an improvement: it makes successive leap sizes less erratic, and the overall simulation more accurate.

But Figs. 3 and 4 also show that the new τ-selection procedure does *not* eliminate *all* inaccuracy. We believe that this residual inaccuracy is mainly a consequence of the "stiffness" of the dynamical system (16), and probably cannot be further reduced (apart from reducing the size of ε) as long as we use the simple leaping approximation (1). The system (16) is "stiff" because when it is on its "slow manifold" it evolves slowly, but when it is off that manifold it wants to move *very rapidly* toward the manifold. Stiffness is a common and computationally troublesome problem for many if not most real-world chemical systems. But it is important to recognize that many effects of stiffness, such as the earlier noted large fluctuations in the R_2 and R_3 propensity functions in the exact SSA run of Fig. 5, are *real physical effects*, so we must take care not to eliminate them in the process of trying to get around the computational difficulties associated with stiffness. The ramifications of stiffness in a stochastic context are addressed more fully in a concurrent paper,[9] which describes an "implicit" version of the "explicit" tau-leaping approximation (1).

Although the exact stochastic simulation algorithm (SSA) often takes a long time to execute, the simple mechanics of its application are the same for any system. By contrast, the general tau-leaping strategy of leaping over "unimportant" reaction events requires us to pay some attention to the specifics of the system—essentially so that we can decide which reaction events are "unimportant." The degree of such circumspection involved in using the new τ-selection procedure (6) is actually rather minimal, since it requires us only to decide on an "appropriate" value for ε. This procedure seems to work surprisingly well, though, for the model reactions (16); e.g., Figs. 2–4 show that the τ-selection algorithm (6) and the leaping formula (1) together are able to track with reasonable accuracy both the initial fast transient behavior ($t<0.2$) and the subsequent quasistationary behavior, *without* our having to pay special attention to the transition from the former region to the latter. But leaping simulation strategies are still in their infancy, and cannot yet be regarded as a robust tool that automatically and reliably handles all situations. We may hope that continuing efforts will lead to new τ-selection procedures and leaping formulas, which, by paying closer attention to the specifics of the given reaction set, will give simulations that are even faster and more accurate.

ACKNOWLEDGMENTS

The authors thank Muruhan Rathinam, Yang Cao, and John Doyle for helpful discussions and suggestions. This work was supported by the Air Force Office of Scientific Research and the California Institute of Technology under DARPA Award No. F30602-01-2-0558.

[1] As here defined, ν_{ij} is the ν_{ji} in earlier works of Gillespie (e.g., Ref. 7). This notational change makes ν_{ij} the conventional *stoichiometric matrix*.
[2] D. T. Gillespie, J. Comput. Phys. **22**, 403 (1976); J. Phys. Chem. **81**, 2340 (1977).
[3] M. A. Gibson and J. Bruck, J. Phys. Chem. A **104**, 1876 (2000).
[4] H. H. McAdams and A. P. Arkin, Proc. Natl. Acad. Sci. U.S.A. **94**, 814 (1997).
[5] A. P. Arkin, J. Ross, and H. H. McAdams, Genetics **149**, 1633 (1998).
[6] D. Endy and R. Brent, Nature (London) **409**, 391 (2001).
[7] D. T. Gillespie, J. Chem. Phys. **115**, 1716 (2001).
[8] W. Press, B. Flannery, S. Teukolsky, and W. Vetterling, *Numerical Recipes, The Art of Scientific Computing* (Cambridge University Press, New York, 1986).
[9] M. Rathinam, L. Petzold, Y. Cao, and D. Gillespie, J. Chem. Phys. (to be published).

Downloaded 24 Oct 2003 to 131.120.105.24. Redistribution subject to AIP license or copyright, see http://ojps.aip.org/jcpo/jcpcr.jsp