STREAMLINED FORMULATION OF ADAPTIVE EXPLICIT-IMPLICIT TAU-LEAPING WITH AUTOMATIC TAU SELECTION

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ABSTRACT

The adaptive explicit-implicit tau-leaping method with automatic tau selection is a flexible algorithm for accelerated stochastic simulation of chemically reacting systems. It combines the advantages of different simulation schemes and is particularly useful when a system changes its dynamical behavior over time in the sense that it behaves well in some time periods but possesses stiffness in other time periods. However, the ingredients necessary to fully understand and implement the algorithm are spread over several papers, not always consistent in terminology and notation, which considerably hampers and possibly even prevents accessibility and widespread practical use. We present a streamlined description of the algorithm using a unified terminology and notation and introduce significantly simplified versions of two major ingredients, namely the step size selection and the switching mechanism between the sub-algorithms.

1 INTRODUCTION AND BACKGROUND

Stochastic modeling of chemically reacting systems has become prevalent in physics, chemistry and biology since the stochastic nature of such systems has been more and more often demonstrated (Arkin et al. 1998, Blake et al. 2003, Fedoroff and Fontana 2002, McAdams and Arkin 1997, McAdams and Arkin 1999, Srivastava et al. 2002, van Kampen 1992). It is evident that the system dynamics are well represented by continuous-time Markov chains (CTMCs) governed by the chemical master equation (CME). System analysis is frequently performed by stochastic simulation, either by stochastically exact methods such as Gillespie's (Gillespie 1976, Gillespie 1977) stochastic simulation algorithm (SSA) or by approximate accelerated simulation algorithms such as tau-leaping, which exists in diverse versions (Anderson 2008, Cao et al. 2007, Cao and Petzold 2005, Cao and Petzold 2008, Chatterjee et al. 2005, Gillespie 2001, Gillespie and Petzold 2003, Harris and Clancy 2006, Pettigrew and Resat 2007, Rathinam et al. 2003, Rathinam and El Samad 2007, Tian and Burrage 2004, Xu and Cai 2008).
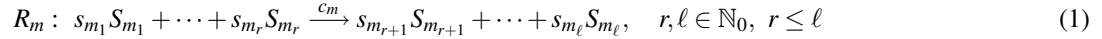
The adaptive explicit-implicit tau-leaping method with automatic tau selection (Cao et al. 2007), which is considered in this paper, combines the SSA with (Poisson) explicit tau-leaping (Gillespie 2001), implicit tau-leaping (Rathinam et al. 2003), and recent improvements in the step size selection procedure for the tau-leaping methods (Cao et al. 2006, Cao and Petzold 2005). The goal is to exploit the advantages and at the same time to overcome major drawbacks of either method with systems that possess stiffness only in some time periods as a main application in mind.

In order to facilitate accessibility, implementation and practical application of the algorithm, we present it in a unified manner. We provide a streamlined formulation and clarify important ingredients of the algorithm. Significantly simplified versions are presented for the step size (tau) selection procedure and the switching mechanism that dynamically chooses either SSA, explicit, or implicit tau-leaping in the course of simulation. This should be greatly helpful for researchers not yet familiar with but interested in tau-leaping methods as well as for practitioners in actually implementing and applying the method.

The organization of the paper is as follows. In the remainder of the present section, we provide the mathematical background of stochastic chemical kinetics, the CME, and stochastic simulation. In Section 2, the general principles and an algorithmic framework for multi-step simulation approaches is given, followed by brief descriptions of explicit and implicit tau-leaping. Section 3 addresses the tau selection and contains our unified version, which basically integrates the tau selection for the explicit and the implicit version in such a way that both can be taken as special cases of a more general formula. In Section 4, a concise algorithmic description of the complete adaptive scheme is given, including our simplification of the switching mechanism. Finally, Section 5 concludes the paper discusses topics of further research.

1.1 Stochastic Chemical Kinetics

Consider a well-stirred mixture of $d \in \mathbb{N}_+$ molecular species $S_1, \ldots, S_d$ interacting through $M \in \mathbb{N}_+$ chemical reaction channels $R_1, \ldots, R_M$ in a thermally equilibrated system of fixed volume, where each reaction channel is defined by a corresponding stoichiometric equation

$$R_m : \quad s_{m_1} S_{m_1} + \cdots + s_{m_r} S_{m_r} \xrightarrow{c_m} s_{m_{r+1}} S_{m_{r+1}} + \cdots + s_{m_\ell} S_{m_\ell}, \quad r, \ell \in \mathbb{N}_0, \; r \leq \ell \tag{1}$$

with an associated stochastic rate constant c_m. Mathematically, the stoichiometry is described by the state change vector $v_m = (v_{m1}, \ldots, v_{md})$, where v_{mk} is the change of molecules of species S_k due to R_m. At any time $t \geq 0$ the system state is given by a discrete d-dimensional random vector $X(t) = (X_1(t), \ldots, X_d(t))$, where a discrete random variable $X_k(t)$ describes the number of molecules of species S_k present at time t. The system's state space is the set $\mathcal{X} \subseteq \mathbb{N}_0^d$ of all possible system states and the conditional transient (time dependent) probability that the system is in state $x \in \mathcal{X}$ at time t, given that the system starts in an initial state $x_0 \in \mathcal{X}$ at time t_0, is denoted by

$$p^{(t)}(x) := p^{(t)}(x|x_0, t_0) = P(X(t) = x \mid X(t_0) = x_0). \tag{2}$$

The reaction rate for each R_m is given by a state dependent *propensity function* α_m, where $\alpha_m(x)dt$ is the conditional probability that a reaction of type R_m occurs in the time interval $[t, t+dt)$, given that the system is in state x at time t. That is

$$\alpha_m(x)dt = P(R_m \text{ occurs in } [t, t+dt) \mid X(t) = x). \tag{3}$$

The propensity function is simply given by c_m times the number of possible combinations of the required reactants and thus computes as

$$\alpha_m(x) = c_m \cdot \prod_{j=1}^{m_r} \binom{x_{m_j}}{s_{m_j}}, \tag{4}$$

where x_{m_j} is the number of molecules of species S_{m_j} present in state x, and s_{m_j} is the stoichiometric coefficient of S_{m_j} according to (1). Because at any time the system's future evolution only depends on the current state, $(X(t))_{t \geq 0}$ is a time-homogeneous CTMC. Therefore, given that the system starts in an initial state $x_0 \in \mathcal{X}$ at time t_0, the system dynamics in terms of the state probabilities' time derivatives are described by the CME

$$\frac{\partial p^{(t)}(x)}{\partial t} = \sum_{m=1}^{M} \left(\alpha_m(x - v_m) p^{(t)}(x - v_m) - \alpha_m(x) p^{(t)}(x) \right), \tag{5}$$

well known as the Kolmogorov differential equations in the general theory of Markov processes. Stochastic chemical kinetics via Markov chains governed by the CME can be traced back to the work by Delbrück (Delbrück 1940) in the early 1940s and subsequent work by Singer (Singer 1953) and Bartholomay (Bartholomay 1957), see, e.g., (Bharucha-Reid 1960, McQuarrie 1967, van Kampen 1992) for historical surveys.

   It is important to note that the CME provides differential equations for the state probabilities rather than for molecular concentrations as in classical mass action kinetics and that the Markovian approach is a generalization of the traditional deterministic approach rather than an alternative. In fact, the deterministic ODEs based on the law of mass action (LMA) are the special case of the CME in the thermodynamic limit, when the number of molecules and the volume approach infinity but the concentrations remain finite (Kurtz 1972, Oppenheim et al. 1969). In general, the accordance of the CME with the theory of thermodynamics has been formally shown by Gillespie (Gillespie 1976, Gillespie 1977, Gillespie 1992). For small numbers of molecules, deterministic models are inappropriate and Markovian modeling is inevitable in order to properly capture the stochastic nature of the system. However, the corresponding rate constants for the CME and LMA models, respectively, are closely related as they can be easily converted by considering the system's volume and the Avogadro number (Gillespie 1976, Wolkenhauer et al. 2004).

1.2 Stochastic Simulation

In principle, the CME may be solved numerically via ODE solvers but standard ODE solvers fail due to the systems' complexity and/or stiffness. Nevertheless, numerical solution of the CME is not always intractable and it can be a very valuable approach. In recent years, there has been significant progress, often by adapting clever Markov chain solution techniques from other domains, such that today quite large biochemical models, say involving 20-30 species can be solved and many promising efforts are further ongoing, see, e.g., (Busch et al. 2006, MacNamara et al. 2008, MacNamara et al. 2008, Sandmann and Wolf 2008).

However, despite the considerable progress in advanced numerical techniques, there are still many situations where the underlying system is too complex and the CME is intractable by such approaches. Stochastic simulation constitutes an alternative – often the only viable – approach and is in widespread use for more than three decades. Algorithms for stochastically exact trajectory generation of the underlying continuous-time Markov chain were proposed by Bortz et. al. (Bortz et al. 1975) and similarly by Gillespie (Gillespie 1976, Gillespie 1977) who formulated it in the context of stochastic chemical kinetics and the CME. It is today famous, often referred to as the stochastic simulation algorithm (SSA) and works as follows:

Init $t := t_0$, $x := x_0$ and t_{end}
while $t < t_{end}$

1. Compute all $\alpha_m(x)$ and $\alpha_0(x) := \alpha_1(x) + \cdots + \alpha_M(x)$;

2. Generate two random numbers u_1, u_2, uniformly distributed on $(0,1)$;

3. Generate time τ to next reaction, exp. distributed with mean $1/\alpha_0(x)$:
$\tau := -\ln(u_1)/\alpha_0(x)$;

4. Determine reaction channel R_m:
$m := \min\{k : \alpha_1(x) + \cdots + \alpha_k(x) > u_2 \alpha_0(x)\}$;

5. Set $t := t + \tau$; $x := x + v_m$.

Hence, one such simulation run generates a realization of a Markov chain trajectory and repeated runs provide a statistical sample from which properties such as means, variances or higher moments of the numbers of all molecular species at any time and even complete probability distributions, all along with confidence intervals, can be obtained by statistical analysis. The SSA is particularly appealing for its simplicity as well as for the feature of stochastic exactness. Unfortunately, the latter one is also one of the major drawbacks. In particular, since it simulates every single reaction, the SSA is highly inefficient for stiff systems and accelerated stochastic simulation algorithms become desirable. One such approach is tau-leaping which aims at advancing the simulation by larger time steps and performs a corresponding approximate trajectory generation based on combining stochastic simulation with some ODE solver principles.

2 TAU-LEAPING

For $m = 1, \ldots, M$ denote by K_m the random variable describing the number of times that a reaction of type R_m occurs in the time interval interval $[t, t + \tau)$. Then

$$X(t + \tau) = X(t) + \sum_{m=1}^{M} v_m K_m. \tag{6}$$

Accordingly, a general algorithmic framework for approximate trajectory generation where the simulation is advanced by pre-defined time steps instead of simulating every single reaction is as follows:

Init $t := t_0$, $x := x_0$ and t_{end};
while $t < t_{end}$

1. Compute all $\alpha_m(x)$ and $\alpha_0(x) := \alpha_1(x) + \cdots + \alpha_M(x)$;

2. Choose a step size τ according to some appropriate rule;

3. Compute suitable estimates $\hat{k}_1, \ldots, \hat{k}_M$ for $K_1, \ldots, K_M$;

4. Set $t := t + \tau$ and update the system state x according to (6).

If $X(t) = x$ and all propensity functions are constant in the time interval $[t, t+\tau)$, the random variable K_m is Poisson distributed with mean $\tau\alpha_m(x)$, that is for $k \in \mathbb{N}_0$:

$$P(K_m = k) = \frac{(\tau\alpha_m(x))^k \exp(-\tau\alpha_m(x))}{k!}, \qquad m = 1, \ldots, M. \tag{7}$$

With tau-leaping, it is assumed that all propensity functions are approximately constant in $[t, t+\tau)$, referred to as the *leap condition* that needs to be formally specified. Handling all propensity functions as if they were indeed constant gives an appropriate rule for Step 2 of the above algorithm. An essential difference between explicit and implicit tau-leaping lies in computing the estimates $\hat{k}_1, \ldots, \hat{k}_M$. Besides, the choice of the step size τ differs.

2.1 Explicit Tau-Leaping

Explicit tau-leaping proceeds by simply computing the estimates $\hat{k}_1, \ldots, \hat{k}_M$ as realizations of the corresponding Poisson random variables. Obviously, (6) then becomes an explicit deterministic expression for $X(t+\tau)$ as a function of x and obeys similarities to the explicit (forward) Euler method for solving systems of deterministic ODEs. More specifically, if the number of molecules of each species is large and the Poisson random variates are approximated by their means, (6) becomes the explicit Euler formula for the deterministic reaction rate equations. However, explicit ODEs solvers become instable for stiff ODE systems, and the same holds for explicit tau-leaping in the case of stiff Markovian systems.

2.2 Implicit Tau-Leaping

Implicit tau-leaping is inspired by the implicit (backward) Euler method which is known to be well suited for stiff ODE systems. Unfortunately, a completely implicit version of tau-leaping would require to generate random variates according to the Poisson distribution with means $\tau\alpha_m(X(t+\tau)), m = 1, \ldots, M$, which depend on the unknown random state $X(t+\tau)$. Instead, a partially implicit version is considered. Rewriting the random variables K_m as $K_m - \tau\alpha_m(X(t)) + \tau\alpha_m(X(t))$ and evaluating all propensity functions in the last term at $X(t+\tau)$ instead of $X(t)$ yields

$$X(t+\tau) = X(t) + \sum_{m=1}^{M} v_m \Big(K_m - \tau\alpha_m(X(t)) + \tau\alpha_m(X(t+\tau)) \Big). \tag{8}$$

Then, in a first step, all K_m are approximated by computing realizations of Poisson distributed random variables as with explicit tau-leaping. Once these realizations, denoted by $k_1, \ldots, k_M$, have been generated and given $X(t) = x$, (8) becomes an implicit deterministic equation that is solved by, e.g., Newton iteration. Typically, the resulting estimate $\hat{x}(t+\tau)$ for $X(t+\tau)$ is not integer-valued. Therefore, in practice, the estimates to be used for the updating in Step 4 of the above algorithm are obtained by rounding the corresponding term in (8) to the nearest integer. That is

$$\hat{k}_m = \text{round}\Big(k_m - \tau\alpha_m(x) + \tau\alpha_m(\hat{x}(t+\tau)) \Big). \tag{9}$$

It has been empirically demonstrated that implicit tau-leaping significantly speeds up the simulation of *some* stiff systems. As an alternative to (8), motivated by the properties of the trapezoidal rule for solving systems of deterministic ODEs, (Cao and Petzold 2005) proposed to substitute (8) by the *trapezoidal tau-leaping formula*

$$X(t+\tau) = X(t) + \sum_{m=1}^{M} v_m \Big(K_m - \frac{\tau}{2}\alpha_m(X(t)) + \frac{\tau}{2}\alpha_m(X(t+\tau)) \Big), \tag{10}$$

which sometimes yields higher accuracy. However, it depends on the specific problem at hand whether (8) or (10) should be preferred.

3 TAU SELECTION

As the accuracy of both explicit and implicit tau-leaping relies on the leap condition of approximately constant propensity functions in the time interval $[t, t+\tau)$, it is important to select an appropriate step size τ. First of all, the leap condition

must be formally specified, that is, it must be mathematically defined what is meant by approximately constant propensity functions. Accordingly, a selection procedure must be developed providing a step size τ preferably much larger than with the SSA and efficiently computed such that the computational overhead is small and does not spoil the potential simulation acceleration compared to the SSA. Besides, it is obviously possible that the updating step taken without care can yield a negative number of molecules because certain critical reactions may exhaust one or more of its reactants. Such a tentative updating step must be rejected and in order to be efficient such rejections should be rare.

In practice, this is handled by keeping the probabilities of critical reactions small. A reaction is taken as critical in state x if it exhausts at least one of its reactants when it occurs n_c times, where n_c is a threshold and constitutes a parameter that has to be specified in the algorithm implementation. Accordingly, we can define the set of indices of critical reactions:

$$\mathscr{C} := \left\{ m \in \{1,\ldots,M\} : \alpha_m(x) > 0 \wedge \min_{i:v_{im}<0} \left\lfloor \frac{x_i}{|v_{im}|} \right\rfloor < n_c \right\}. \tag{11}$$

The tau selection procedure has been successively improved over the years. In early versions the goal was to assure the leap condition by bounding for every reaction the expected change in its propensity function during a time step of size τ by $\varepsilon \alpha_0(x)$, hence by ε times the sum of all propensity functions evaluated at state x where $\varepsilon > 0$ is an error control parameter.

The original tau selection procedure in (Gillespie 2001) does not always yield an appropriate step size that satisfies this condition but according to (Gillespie and Petzold 2003) the largest value of τ that satisfies this condition can be obtained by bounding the mean and the standard deviation of the expected change in the propensity function of each reaction by $\varepsilon \alpha_0(x)$. It was also recognized that it is more appropriate to bound the change in the propensity function individually for every reaction R_m by $\varepsilon \alpha_m(x)$, which corresponds to bounding the relative changes in each propensity function by ε. Strictly applied, this implies that τ becomes zero and the simulation does not advance at all if any of the propensity functions evaluated at state x is very small. But, as noted in (Cao et al. 2006), if α_m changes, then according to (4) it changes by at least c_m such that a change of less than c_m does not make sense. Therefore, the change in α_m can be bounded by the maximum of $\varepsilon \alpha_m(x)$ and c_m. Furthermore, (Cao et al. 2006) presented a procedure that approximately enforces this bound, which is much faster than estimating the mean and the standard deviation according to (Gillespie and Petzold 2003).

Essentially, instead of directly considering propensity functions, the relative changes in populations of certain molecular species are bounded such that the relative changes in the propensity functions will be all approximately bounded by ε. The details of the derivation can be found in (Cao et al. 2006). With implicit tau-leaping for stiff systems the step size can be often chosen much larger than suggested by (Cao et al. 2006) when neglecting some of the species (Cao et al. 2007). In the following, we present this current state of the art in tau selection for explicit and implicit tau-leaping in an integrated manner and further streamline some ingredients, which results in a compact form that unifies and significantly simplifies the formulae in (Cao et al. 2006, Cao et al. 2007, Cao and Petzold 2005). In either case, it suffices to consider reactant species. Denote by $\mathscr{R}$ the set of indices of all reactant species and define for all $i \in \mathscr{R}$ and an arbitrary set $\mathscr{M}$ of indices of reactions

$$\hat{\mu}_{i,\mathscr{M}}(x) := \sum_{m \in \mathscr{M}} v_{mi}\alpha_m(x), \qquad \hat{\sigma}^2_{i,\mathscr{M}}(x) := \sum_{m \in \mathscr{M}} v^2_{mi}\alpha_m(x). \tag{12}$$

Then a step size dependent on $\mathscr{M}$ can be expressed by

$$\tau_{\mathscr{M}} = \min_{i \in \mathscr{R}} \left(\frac{\max(\varepsilon x_i/g_i(x), 1)}{|\hat{\mu}_{i,\mathscr{M}}(x)|}, \frac{\max(\varepsilon x_i/g_i(x), 1)^2}{|\hat{\sigma}^2_{i,\mathscr{M}}(x)|} \right) \tag{13}$$

where g_i is a function defined in order to guarantee that bounding the relative change of states is sufficient for bounding the relative change of propensity functions. This function g_i appears rather complicated in (Cao et al. 2006) as it involves case differentiations. We have reasonably simplified it and present it in a quite artless closed form. Denote by $h(i)$ the highest order of reactions in which species S_i appears as reactant and by $n(i)$ the maximum number of S_i molecules required by any of the highest-order reactions. Then

$$g_i(x) = h(i) + \frac{h(i)}{n(i)} \sum_{j=1}^{n(i)-1} \frac{j}{x_i - j}. \tag{14}$$

The step size depends on $\mathscr{M}$ only through $\hat{\mu}_{i,\mathscr{M}}(x)$ and $\hat{\sigma}^2_{i,\mathscr{M}}(x)$, and the only difference in the step size selection for explicit and implicit tau-leaping is in the choice of $\mathscr{M}$ which defines exactly those reactions that are considered in the step size

selection. For explicit tau-leaping, these are simply the non-critical reactions. Hence,

$$\tau^{(expl)} = \tau_{\{1,\dots,M\}\backslash\mathscr{C}}.$$ (15)

For implicit tau-leaping, the principle of the partial equilibrium assumption (see, e.g., (Ramshaw 1980, Ramshaw and Cloutman 1981, Rein 1992, Schauer and Heinrich 1979, Segel 1988, Segel and Slemrod 1989) for detailed descriptions) is exploited. As it is difficult to identify all reactions that are in partial equilibrium, only reversible reactions are checked for partial equilibrium, which means that their propensity functions evaluated at state x must be approximately equal. More specifically, (Cao et al. 2007) assume that two reactions R_{m_1}, R_{m_2} where R_{m_1} reverses R_{m_2} and vice versa are in partial equilibrium if the difference of their propensity functions, both evaluated at state x, is less than δ times the minimum of the propensity functions, where δ is a parameter to be specified in the algorithm implementation:

$$|\alpha_{m_1}(x) - \alpha_{m_2}(x)| \leq \delta \min(\alpha_{m_1}(x), \alpha_{m_2}(x)), \qquad \delta > 0.$$ (16)

Then in the step size selection for implicit tau-leaping only reactions that are neither critical nor in partial equilibrium (for reversible reactions) are considered. Hence, denoting by $\mathscr{E}$ the set of indices of (reversible) partially equilibrated reactions,

$$\tau^{(impl)} = \tau_{\{1,\dots,M\}\backslash\mathscr{C}\backslash\mathscr{E}}.$$ (17)

4 ADAPTIVE TAU-LEAPING

In practice, when a system has to be simulated it is not always clear in advance whether or not it possesses stiffness. Quite often, this even changes along the trajectory, i.e. in some time periods the system "behaves well" but in other periods it appears highly stiff. In some periods it might be even the case that neither explicit nor implicit tau-leaping provide an acceleration compared to SSA if the leap condition implies a step size τ that is so small that the computational overhead eliminates the speed-up. Then, of course, SSA should be executed. This reasoning motivates an adaptive stochastic simulation algorithm that switches between the methods depending on which of them is most efficient in the current region.

In state x, the expected time to the next reaction is $1/\alpha_0(x)$. Consequently, if a candidate step size is less than $n_a/\alpha_0(x)$ it is considered inefficient and n_b single reactions are simulated according to the standard direct method, where both n_a and n_b are parameters to be specified. With adaptive tau-leaping, at each updating step during the simulation either explicit or implicit tau-leaping is chosen dynamically. Hence, a decision rule is necessary. Adaptive tau-leaping applies the simple rule that the system is considered to be stiff if the tentative step size for explicit tau-leaping is more than n_d times smaller than the tentative step size for implicit tau-leaping, which introduces another parameter to be specified.

Now, we have all ingredients we need for formulating an algorithm that, given state x at time t and step size selection procedures for explicit and for implicit tau-leaping, dynamically chooses one of the two methods with an appropriate step size and resorts to SSA if both step sizes are too small to provide simulation acceleration. Our formulation here streamlines that in Section 4 of (Cao et al. 2007) and is much more concise but equivalent to it.

1. Define the set $\mathscr{C}$ of indices of critical reactions according to (11);
2. Compute candidate step sizes $\tau^{(expl)}, \tau^{(impl)}$ for explicit and implicit tau-leaping;
3. If $\tau^{(expl)} < n_a/\alpha_0(x) \wedge \tau^{(impl)} < n_a/\alpha_0(x)$
   then simulate n_b single reactions, update t and x, and goto 1;
4. Compute candidate step size $\tilde{\tau}$ as expected time to next critical reaction:

$$\text{Generate } \tilde{\tau} \sim \text{Exponential}\left(\sum_{m\in\mathscr{C}} \alpha_m(x)\right);$$

5. If $\tau^{(expl)} > \min(\tau^{(impl)}/n_d; \tilde{\tau})$
   then use explicit tau-leaping with $\tau := \min(\tau^{(expl)}; \tilde{\tau})$;
   else use implicit tau-leaping with $\tau := \min(\tau^{(impl)}; \tilde{\tau})$;
6. If $x + \sum_m \hat{k}_m v_m$ has negative components
   then reduce $\tau^{(expl)}$ and $\tau^{(impl)}$, and goto 3.

Note that the last step is required because there is still a positive probability of generating negative population sizes though this probability should be small for appropriately chosen parameters. Hence, altogether the step size selection procedure can be interpreted as an acceptance-rejection method. The inventors more specifically reduce $\tau^{(expl)}$ and $\tau^{(impl)}$ by half, but this seems rather arbitrary and may be subject to changes. In any case, the reduction factor is one more parameter to be specified in the algorithm implementation.

5 CONCLUSION AND DISCUSSION

We have presented a unified description of the adaptive explicit-implicit tau-leaping method with automatic tau selection. Thereby, some inconsistencies in earlier papers have been clarified, and simplified versions of the definition of the function g_i which is central for the tau selection and of the switching mechanism for adaptively choosing either SSA, explicit or implicit tau-leaping have been provided. We believe that this contributes to the accessibility of the method by researchers and practitioners and facilitates practical implementation of the algorithm. Therefore, also some necessary theoretical background has been briefly addressed in order to make the description in some sense self-contained and the algorithm understandable without consulting too much other material.

A couple of issues for further investigation arise quite naturally, most of which are concerned with concrete implementation details or related practical as well as theoretical studies of the algorithm's efficiency and the robustness of corresponding estimators. In the inventing papers it has been empirically demonstrated that tau-leaping can significantly accelerate the simulation of chemically reacting systems. The consistency and stability is formally addressed in (Rathinam et al. 2005). However, in particular the choice of the many parameters calls for systematic studies. First of all, the choice of $\varepsilon, \delta, n_a, n_b, n_c, n_d$ is currently rather informal and they are specified heuristically. The inventors state that they take "normally" or "usually" ε in the range 0.03 to $0.05, n_a = 10, n_b = 10$, if the previous step uses implicit tau-leaping and $n_b = 100$ otherwise, $n_c = 10, n_d = 100$ and δ "around" 0.05. This seems to rely mainly on empirical comparisons of tau-leaping with SSA. Obviously, in practically relevant cases of huge models, such a comparison will not be feasible as the SSA does not provide accurate results in reasonable time. Similarly, the statistical accuracy of the estimates was most often only shown by comparison to SSA. The first formal approach given in (Cao and Petzold 2006) considers the Kolmogorov distance, the histogram distance and the newly introduced self distance for probability measures. Another issue of interest is how the probability of rejecting a candidate step size depends on the parameters mentioned above. As mentioned before, the reduction factor in the case of negative components of the tentative state vector is proposed as 2 to reduce the candidate time steps by half, but this should be also further investigated. In addition to and in support of these issues, it would be particularly desirable to see the algorithm in action, working on practically relevant models from, e.g., systems biology or neuroscience.

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