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Tau leaping of stiff stochastic chemical systems via local central limit approximation

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ABSTRACT

Stiffness manifests in stochastic dynamic systems in a more complex manner than in deterministic systems; it is not only important for a time-stepping method to remain stable but it is also important for the method to capture the asymptotic variances accurately. In the context of stochastic chemical systems, time stepping methods are known as *tau leaping*. Well known existing tau leaping methods have shortcomings in this regard. The implicit tau method is far more stable than the trapezoidal tau method but underestimates the asymptotic variance. On the other hand, the trapezoidal tau method which estimates the asymptotic variance exactly for linear systems suffers from the fact that the transients of the method do not decay fast enough in the context of very stiff systems. We propose a tau leaping method that possesses the same stability properties as the implicit method while it also captures the asymptotic variance with reasonable accuracy at least for the test system $S_1 \leftrightarrow S_2$. The proposed method uses a central limit approximation (CLA) locally over the tau leaping interval and is referred to as the LCLA-τ. The CLA predicts the mean and covariance as solutions of certain differential equations (ODEs) and for efficiency we solve these using a single time step of a suitable low order method. We perform a mean/covariance stability analysis of various possible low order schemes to determine the best scheme. Numerical experiments presented show that LCLA-τ performs favorably for stiff systems and that the LCLA-τ is also able to capture bimodal distributions unlike the CLA itself. The proposed LCLA-τ method uses a split implicit step to compute the mean update. We also prove that any tau leaping method employing a split implicit step converges in the fluid limit to the implicit Euler method as applied to the fluid limit differential equation.

1. Introduction

Intracellular processes are best described by the discrete and stochastic model of well stirred chemical systems where the vector of molecular copy numbers $X(t)$ is a Markov process with nonnegative integer state space $\mathbb{Z}_+^N$. Probabilistically exact simulation of the sample paths of $X(t)$ via the well known *stochastic simulation algorithm* (SSA) is relatively straightforward [1,2]. However in many practical systems of importance the SSA is exceedingly slow in the presence of vastly different time scales and/or large molecular copy numbers. The tau leaping methods were devised to provide an approximate but efficient way to simulate sample trajectories of such systems and the first tau method was proposed in [3].

The basic idea of a tau leaping method is to approximate the random number of firings of various reactions over a preselected time step by a reasonable criterion. Tau leaping methods can be regarded as the discrete and stochastic counterparts of the time stepping methods for ordinary differential equations (ODEs). Chemical reaction systems are well known for

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possessing vastly different time scales and hence the resulting systems are almost always stiff. The implicit tau leaping method was developed to deal with stiff systems, but it was realized that stiffness manifests in stochastic systems in a more complex manner than in deterministic systems [4]: it was not only important for a tau method to remain stable but it was also important for the method to capture the asymptotic variances correctly. See [5] where the asymptotic behavior of the explicit tau, the implicit tau as well as the trapezoidal tau methods are analyzed. Additionally when molecular copy numbers of some species are small, it was realized that while dealing with stiffness, preserving the integrality and nonnegativity of the states was also an important issue. The methods proposed in [6,7] address stiffness in the presence of small molecular copy numbers.

For non-stiff systems nonnegativity issues are addressed in [8–11]. A higher order method for moderately large copy number non-stiff systems is presented in [12]. In [13], the authors proposed a tau leaping method based on a splitting scheme and provided some error analysis. Step size selection for the explicit tau method is addressed in [14] and references therein. Error and convergence analysis of some tau leaping methods can be found in [15–17].

The stability analysis in [5] shows that while the implicit tau is stable, it underestimates the variance and that the trapezoidal tau captures the asymptotic variance exactly (in the case of linear propensity systems). Nevertheless the trapezoidal tau is undesirable in stiff systems due to the fact that the transients of the fast dynamics of the method decay much slower than those of the true system [7]. Additionally implicit tau and trapezoidal tau methods are only suited for moderately large molecular copy numbers as they produce non-integer states (without rounding).

In this article we present a new tau leaping method which also applies to stiff stochastic chemical systems with moderately large molecular copy numbers where integrality of the states is not an issue. The proposed new method overcomes the shortcomings of both the implicit tau and the trapezoidal tau methods and is based on a local approximation of the evolution of the mean and the covariance of the reaction count vector which holds for moderately large molecular copy numbers. More specifically, this method uses the *central limit approximation* (CLA) derived in [18] (Chapter 11, Section 2), locally over the tau leaping interval (conditioned on the initial random state at the beginning of the leaping interval). This approximation is recomputed for each successive tau leaping interval. We refer to our method as tau leaping via *local central limit approximation* (LCLA) and use the abbreviation LCLA-τ.

For sake of efficiency, we propose to solve the ODEs resulting from the CLA by applying one time step (of the same size as the tau leap) of a low order numerical scheme. We analyze the stability of mean and covariance of the resulting tau leaping methods to decide the best possible discretization of these ODEs. The stability analysis presented here clearly demonstrates one of the schemes as superior to the others in terms of performance in stiff systems, leading us to incorporate this scheme as part of the proposed method. What is remarkable about this scheme is that while it is as stable as the implicit tau method, it also captures the asymptotic variances very accurately at least in the case of the linear test system $S_1 \leftrightarrow S_2$ as revealed by our stability analysis. We refer to the resulting method as the LCLA-τ.

The proposed LCLA-τ uses a *split implicit step* to update the mean, a strategy also employed in [7]. We prove a theorem in the appendix showing that under modest assumptions any tau leaping method employing the split implicit step converges in the fluid limit to the implicit Euler method as applied to the resulting fluid limit RRE. In this fluid limit analysis we fix $\tau > 0$ and let $V \to \infty$. To our knowledge fluid limit (with $\tau > 0$ fixed and $V \to \infty$) of a tau leaping method has not been rigorously proven before.

Finally we like to remark that the basic idea of the LCLA-τ can be applied to stiff stochastic differential equations driven by Brownian motion with a "small" diffusion term as the CLA can be effectively applied to such equations. In that case the stability analysis provided in this paper will need to be generalized to such systems.

The outline of the paper is as follows. Section 2 provides an overview of stochastic chemical kinetics, the fluid limit, the central limit approximation (CLA) as well as tau leaping methods. Section 3 introduces the LCLA-τ method and discusses various choices of potential numerical schemes for computing the covariance. Section 4 provides the absolute stability analysis which helps to identify the best numerical scheme to use in computing the covariance. In Section 5, we compare LCLA-τ with SSA, and other tau leaping methods showing a favorable performance by LCLA-τ in the moderately large copy number regime. We also show that unlike CLA, the LCLA-τ can capture bimodal distributions. Finally Section 6 provides some concluding remarks. Additionally in Appendix A we prove under modest assumptions that any tau leaping method employing the split implicit step converges in the fluid limit to the implicit Euler method applied to the fluid limit RRE.

2. Overview of stochastic chemical systems, central limit approximation and tau leaping methods

2.1. Stochastic chemical systems and SSA

Stochastic chemical reaction systems involved with small number of molecules have a discrete and stochastic dynamic behavior. The standard well-stirred chemical model in [19,20] can be described by a Markov process in continuous time with nonnegative integer state space $\mathbb{Z}_+^N$.

The model is based on a well-stirred mixture of N molecular species $\{S_1, \ldots, S_N\}$ interacting through M chemical reaction channels $\{R_1, \ldots, R_M\}$. The state of the system is described by the molecular population vector $X(t) = (X_1(t), \ldots, X_N(t))$, where $X_i(t)$ is the number of molecules S_i at time t for each $i = 1, \ldots, N$. For each $j = 1, \ldots, M$, the *propensity function* $a_j(x)$ is defined by the condition that given $X(t) = x$, the probability that reaction R_j will occur during $(t, t+h]$ is $a_j(x)h + o(h)$ as $h \to 0+$.

Vector v_j for $j = 1, \ldots, M$ is the *stoichiometric vector*, whose ith component v_{ij} is the change in the number of S_i molecules due to one occurrence of reaction R_j. We often denote by v an $N \times M$ matrix with column vectors v_j, and denote by $a(x)$ the propensity vector with components $a_j(x)$, for $j = 1, \ldots, M$.

It also follows that the probability distribution as a function of time satisfies the *chemical master equation* (CME) [19] given by

$$\frac{\partial}{\partial t} p(x, t|x_0, t_0) = \sum_{j=1}^{M} [a_j(x - v_j) p(x - v_j, t|x_0, t_0) - a_j(x) p(x, t|x_0, t_0)],$$

where $p(x, t|x_0, t_0)$ denotes the probability that $X(t) = x$ given $X(t_0) = x_0$. The CME completely determines the dynamics of chemical systems. But computing probabilities via the CME is prohibitive due to the fact that the number of possible states grows exponentially with the number of distinct molecular species.

Probabilistically correct realizations of sample paths of such systems can be generated by the *stochastic simulation algorithm* (SSA) [1,2]. The SSA is based on the *next-reaction density function* $p(\tau, j|x, t)$ which is defined such that $p(\tau, j|x, t)dt$ is the probability, that given $X(t) = x$, the next reaction in the system will occur in the infinitesimal time interval $(t + \tau, t + \tau + dt]$ and will be an R_j reaction. It generates an elapsed time τ and the index of the next reaction j following

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

where $a_0(x) = \sum_{j=1}^{M} a_j(x)$. Then it advances the system according to

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

Since the SSA tracks every reaction event each time, it is very time consuming for systems with multiple time or population scales.

We shall denote by $R(t) = (R_1(t), R_2(t), \ldots, R_M(t))^T$ the *reaction count vector* where $R_j(t)$ is the number of times the jth reaction channel fires during $(0, t]$. Thus

$$X(t) = X(0) + vR(t), \tag{2}$$

where v is the $N \times M$ matrix whose jth column is v_j.

Finally, if one knows the initial state $X(0)$ and the reaction count vector $R(t)$ for a given $t \in [0, T]$ then one can recover $X(t)$. However, knowing $X(t)$ for a given $t \in [0, T]$ does not allow one to reconstruct $R(t)$ unless v is one-to-one. For this reason, in tau leaping approximations it is desirable to have approximations of $R(t)$ rather than $X(t)$.

2.2. Fluid limit

The stochastic behavior of the model described is typically prominent only when some species are present in small or moderately large copy numbers. When all the molecular species are present in large numbers and under certain additional assumptions on the propensity functions, the chemical system is well approximated by a deterministic ODE model known as the *reaction rate equation* (RRE). The RRE can be regarded as the limiting behavior that ensues when the system volume V approaches ∞ with the initial number of species $X(0)$ also growing proportional to V so that the concentration $X(0)/V$ is fixed [21,18]. This limit is known as the *thermodynamic limit* in chemical literature and is also known as the *fluid limit* in queueing theory.

The fluid limit can be described in mathematical terms [18] as follows. For a system with initial state $X(0) = x_0 \in \mathbb{Z}_+^N$ and volume V_0, let us denote by $z_0 = x_0/V_0$ the initial concentration. Consider a family of related systems with different volumes V and initial states $X_V(0) = Vz_0 = \frac{V}{V_0} x_0$, so that they have the same initial concentration. Denote by $X_V(t)$ the trajectory for the system with volume V. Note that our original system has a trajectory $X(t) = X_{V_0}(t)$. Thus the concentrations are $Z_V(t) = \frac{X_V(t)}{V}$. Additionally we assume that the propensities $a_j(x)$ depend on volume V such that

$$\lim_{V \to \infty} \frac{a_j(x, V)}{V} = \bar{a}_j(x), \tag{3}$$

which is true in the standard model of stochastic chemical kinetics (see [21]). See Appendix A where this is discussed in more detail. It is shown in [18] that (under a suitable coupling of all the systems with different V values) for each fixed $t \geqslant 0$, Z_V converges with probability 1 to the deterministic trajectory $\bar{Z}(t)$ uniformly on each bounded interval $[0, t]$ (for $t \geqslant 0$) where $\bar{Z}(t)$ is the unique solution of the reaction rate equation (RRE)

$$\frac{d\bar{Z}(t)}{dt} = \sum_{j=1}^{M} v_j \bar{a}_j(\bar{Z}(t)), \tag{4}$$

with initial condition $\bar{Z}(0) = z_0$.

Usually the large V limit is valid when molecular copy numbers of each species is very large and then (3) and (4) justify the following ODE approximation $\hat{X}(t)$ for the molecular population vector $X(t)$:

$$\frac{d\hat{X}(t)}{dt} = \sum_{j=1}^{M} v_j a_j(\hat{X}(t)).$$

2.3. Central limit approximation of stochastic chemical systems

The ODE approximation obtained via system size expansion described in the previous section is valid only when molecular copy numbers are very large (when system volume V is very large) as it ignores the random fluctuations. However, when the population count is only moderately large, the central limit approximation (CLA) [18] provides an improved asymptotic approximation in which the mean of $X(t)$ is given by the above ODE model while the deviation from the mean satisfies a simple stochastic differential equation (SDE). When the system has linear propensities, it can be shown that this approximation yields the exact mean and covariance for $X(t)$ while the distribution of $X(t)$ need not be accurate unless molecular copy numbers are moderately large.

More specifically, according to CLA, the process $X(t)$ is approximated by $\hat{X}(t)$ where $E(\hat{X}(t)) = m_{\hat{X}}(t)$ which is the solution of the RRE:

$$\frac{dm_{\hat{X}}(t)}{dt} = va(m_{\hat{X}}(t)), \quad m_{\hat{X}}(0) = x_0, \tag{5}$$

and the deviation $\xi(t) = \hat{X}(t) - E(\hat{X}(t))$ from the mean value, is given by the solution of the following stochastic differential equation (SDE):

$$d\xi(t) = A_{\hat{X}}(t)\xi(t)dt + \sum_{j=1}^{M} b_j(t)dB_j(t), \quad \xi(0) = 0, \tag{6}$$

where $B_1, \ldots, B_M$ are independent standard Brownian motions,

$$A_{\hat{X}}(t) = v\frac{\partial a}{\partial x}(m_{\hat{X}}(t)), \tag{7}$$

and

$$b_j(t) = v_j\sqrt{a_j(m_{\hat{X}}(t))}, \quad j = 1, \ldots, M. \tag{8}$$

It can be shown that $\xi(t)$ is Gaussian distributed for all $t \geqslant 0$. Thus the CLA $\hat{X}(t)$ is Gaussian with mean $m_{\hat{X}}(t)$ and covariance $C_{\hat{X}}(t)$, where $C_{\hat{X}}(t)$ satisfies the matrix ODE:

$$\frac{dC_{\hat{X}}(t)}{dt} = C_{\hat{X}}(t)A_{\hat{X}}^T(t) + A_{\hat{X}}(t)C_{\hat{X}}(t) + E_{\hat{X}}(t), \quad C_{\hat{X}}(0) = 0. \tag{9}$$

Here

$$E_{\hat{X}}(t) = \sum_{j=1}^{M} v_j v_j^T a_j(m_{\hat{X}}(t)).$$

For a rigorous derivation of CLA based on the *random time change representation*, the law of large numbers and the central limit theorem [18] (Chapter 11.2).

Central limit approximation can also be applied to the reaction count vector $R(t)$. Let $\hat{R}(t)$ denote the CLA for $R(t)$. Then $\hat{R}(t)$ is Gaussian with mean $m_{\hat{R}}(t)$ and covariance $C_{\hat{R}}(t)$, where $m_{\hat{R}}(t)$ and $C_{\hat{R}}(t)$ satisfy

$$\frac{dm_{\hat{R}}(t)}{dt} = a(x + vm_{\hat{R}}(t)), \quad m_{\hat{R}}(0) = 0, \tag{10}$$

and

$$\frac{dC_{\hat{R}}(t)}{dt} = C_{\hat{R}}(t)A_{\hat{R}}^T(t) + A_{\hat{R}}(t)C_{\hat{R}}(t) + E_{\hat{R}}(t), \quad C_{\hat{R}}(0) = 0, \tag{11}$$

where

$$A_{\hat{R}}(t) = \frac{\partial a}{\partial x}(x + vm_{\hat{R}}(t))v, \tag{12}$$

and

$$E_{\hat{R}}(t) = \sum_{j=1}^{M} e_j e_j^T a_j(x + vm_{\hat{R}}(t)). \tag{13}$$

Here e_j is a vector whose jth element is one and others are zeros.

Note that the CLA for $R(t)$ and $X(t)$ are consistent with the relation (2):

$$\hat{X}(t) = \hat{X}(0) + \nu\hat{R}(t).$$

2.4. Tau leaping methods

Tau leaping methods proceed as follows. First a time step τ is chosen. Given the current state $X(t) = x$, define $R_j(x,\tau)$ to be the (random) number of times that jth reaction channel will fire during the time interval $(t, t+\tau]$, for $j = 1,\ldots,M$. Then

$$X(t+\tau) = x + \sum_{j=1}^{M} \nu_j R_j(x,\tau). \tag{14}$$

In general, the distribution of $R_j(x,\tau)$ is not known. In a tau leaping method, an approximation $K_j(x,\tau)$ of $R_j(x,\tau)$ is computed.

We review the three most basic tau leaping methods here. The *explicit tau* method (see [3]) chooses $K_j(x,\tau)$ for $j = 1,\ldots,M$ to be independent Poisson random variables with mean $a_j(x)\tau$, i.e., $K_j^{(et)}(x,\tau) \sim \mathscr{P}(a_j(x)\tau)$. Here we denote by $\mathscr{P}(\lambda)$ a Poisson random variable with mean λ.

The *implicit tau* method (see [4]) computes $X^{(it)}(t+\tau)$ from

$$X^{(it)}(t+\tau) = x + \sum_{j=1}^{M} \nu_j \{P_j - a_j(x)\tau + a_j(X^{(it)}(t+\tau))\tau\}, \tag{15}$$

where $P_j \sim \mathscr{P}(a_j(x)\tau)$ for $j = 1,\ldots,M$ are independent. Thus $R_j(x,\tau)$ is approximated by

$$K_j^{(it)}(x,\tau) = P_j - a_j(x)\tau + a_j(X^{(it)}(t+\tau))\tau.$$

The *trapezoidal implicit tau* method (see [5]) generates the update equation by

$$X^{(tr)}(t+\tau) = x + \sum_{j=1}^{M} \nu_j \Big(P_j - \frac{\tau}{2} a_j(x) + \frac{\tau}{2} a_j(X^{(tr)}(t+\tau))\Big), \tag{16}$$

where $P_j \sim \mathscr{P}_j(a_j(x)\tau)$ are independent. Thus $R_j(x,\tau)$ is approximated by

$$K_j^{(tr)}(x,\tau) = P_j - \frac{\tau}{2} a_j(x) + \frac{\tau}{2} a_j(X^{(tr)}(t+\tau)).$$

We introduce a new tau method in this paper which is well suited for stiff systems with moderately large molecular copy numbers. This method combines the advantages of the implicit tau and the trapezoidal tau methods. Specifically it has the same stability characteristics as the implicit tau (i.e. very stable) while nearly preserving the asymptotic covariance (at least for the linear test system $S_1 \leftrightarrow S_2$). We note that even though the trapezoidal tau method computes the covariance exactly for linear propensity systems, it is unsuitable in very stiff systems due to the fact that the transients of the fast dynamics of the trapezoidal tau method decay much slower than those of the true system [7].

In order to ensure stability we use a *split implicit step* to compute the mean update. Thus at each time step, we first compute an intermediate deterministic state X' by applying the implicit Euler method to the underlying RRE: given current state x and step size τ, we compute X' that satisfies

$$X' = x + \sum_{j=1}^{M} \nu_j a_j(X')\tau. \tag{17}$$

Then we choose a random vector $K = (K_1,\ldots,K_M)$ such that $E(K_j) = a_j(X')\tau$. We obtain the population state X at $t+\tau$ by

$$X = x + \sum_{j=1}^{M} \nu_j K_j.$$

Heuristically, in the fluid limit, since K_j will be nearly deterministic, $K_j \approx E(K_j)$ and the updated state $X \approx X'$. In Appendix A we prove under suitable assumptions that any tau method employing the split implicit step has a fluid limit which is the implicit Euler applied to the fluid limit RRE.

The split implicit step scheme dictates only the expected values $E(K_j)$. The question of how to choose an appropriate joint distribution for $K = (K_1,\ldots,K_M)^T$ needs to be addressed. In [7] two variants of a split implicit step tau leaping method were proposed where the Minkowski–Weyl decomposition was used to determine the joint distributions of K_j. These methods, termed the implicit Minkowski–Weyl tau (IMW-τ) were shown to perform better than the implicit tau, trapezoidal implicit tau and the REMM-τ methods when applied to stiff systems with small number of molecular copy numbers. The key decision criterion governing the choice of distributions for K_j in the IMW-τ methods was based on satisfying the nonnegativity and integrality conditions on the updated state. For the tau method introduced in this paper, we propose an alternative criterion to choose the joint distribution for the K_js. Having decided on the mean of K_j via the split implicit step, it is natural to focus

on obtaining a good approximation for the covariance of K, and then to choose a joint distribution for K satisfying the mean and covariances. In order to obtain an approximation for the covariance we shall use the *central limit approximation* (CLA) described in the previous subsection. This leads to the tau leaping method proposed in this paper which is described in Section 3. Since the central limit approximation is only valid in moderately large molecular copy numbers we expect the method to work well only when the species counts are moderately large.

3. Tau leaping method via local central limit approximation

Given $X(t) = x$, we let $R(\tau)$ denote the vector of reaction counts during $(t, t+\tau]$. Then the number of species $X(t+\tau) = X$ at time $t+\tau$ is given by

$$X = x + vR(\tau).$$

Noting that $\mathrm{Cov}(X) = v\mathrm{Cov}(R(\tau))v^T$, we shall attempt to approximate $\mathrm{Cov}(R(\tau))$. When the population count is moderately large, the central limit approximation (CLA) described in Section 2.3 can be applied. In general, even with moderately large population count, CLA may not be accurate over a large time interval. Note that the CLA predicts the species counts as well as reaction counts to be Gaussians over arbitrary time intervals. This may not be accurate on several instances, especially in examples with bistability.

We may expect a better performance if CLA is applied over a relatively small time interval $(t, t+\tau]$ (which shall be the tau leaping interval for us), the population state updated according to a sample from the distribution computed by CLA, and then the CLA is recalculated for the next interval $(t+\tau, t+2\tau]$ based on the updated state corresponding to time $t+\tau$. This forms the basis of the tau leaping method introduced in this paper.

3.1. Local central limit approximation and the LCLA-τ method

If CLA is used to compute the distribution at some final time $t = T$ for a chemical system then one may simply solve the ODEs for $m_{\hat{X}}(t)$ and $C_{\hat{X}}(t)$ using highly accurate ODE solvers to obtain the parameters for the Gaussian distribution at $t = T$. However, if sample paths of $\hat{X}(t)$ are required then one needs to generate sample paths of the SDE (6) which requires more computational effort. Given this fact, it may very well be desirable to recompute the CLA *based on the random updated state* after each time step. This incurs little extra cost but results in better accuracy. Thus the method we propose *recomputes CLA during each time step* based on the current state and updates the state according to a Gaussian sample computed using CLA. Since CLA is recomputed at each time step, we shall name this approach *local central limit approximation* (LCLA), and refer to the resulting tau leaping method as LCLA-τ in short. We note that the LCLA-τ method proposed produces updated states that are Gaussian when conditioned on the state at the previous time step, but the unconditional distribution of the states needs not be Gaussian. We shall describe this idea in more details below.

Let $X(t) = x$ be given. Consider a time interval $(t, t+\tau]$. With slight inconsistency in notation let us denote by $R(\tau)$ the number of times that reactions fire during $(t, t+\tau]$. Let $X = X(t+\tau)$. Then

$$X = x + vR(\tau).$$

Let $E(R(\tau)) = m_R(\tau)$, and $\mathrm{Cov}(R(\tau)) = C_R(\tau)$. Then according to CLA, $m_R(\tau)$ and $C_R(\tau)$ are approximated by $m_{\hat{R}}(\tau)$ and $C_{\hat{R}}(\tau)$ which are given by (10) and (11). We need to use a suitable numerical scheme to approximately solve the ODEs (10) and (11). We denote the resulting numerical solutions by $m_K(\tau)$ and $C_K(\tau)$. The tau leaping approximation $K(\tau)$ of $R(\tau)$ is then chosen to be Gaussian with $E(K(\tau)) = m_K(\tau)$, and $\mathrm{Cov}(K(\tau)) = C_K(\tau)$. Then the state is updated to obtain

$$Y = x + vK(\tau).$$

Thus the framework of the proposed method is summarized in Table 1 which is described for constant step size $\tau > 0$ with initial state x_0 and time interval $[0, T]$.

We note that the important step is Step 2 which involves efficient numerical approximation of the ODEs (10) and (11) and this is considered in detail in Section 3.3.

Table 1
Basic framework of LCLA-τ algorithm.

(1)	Initialize $x \leftarrow x_0$ and $t \leftarrow 0$. Set $\tau > 0$
(2)	Compute $m_K(\tau)$ and $C_K(\tau)$ by approximate solutions of (10) and (11)
(3)	Compute Cholesky factor $B_K(\tau)$ such that $C_K(\tau) = B_K(\tau)B_K(\tau)^T$
(4)	Generate Gaussian random M-vector $G \sim \mathcal{N}(0, I)$
(5)	Set $K(\tau) \leftarrow B_K(\tau)G + m_K(\tau)$
(6)	Compute updated state $Y = x + vK(\tau)$
(7)	Set $x \leftarrow Y$ and $t \leftarrow t + \tau$
(8)	If $t \leqslant T$ go to step 2

3.2. Relationship to the chemical Langevin equation

At this point it is worth mentioning the *chemical Langevin equation* (CLE) and the relationship of the proposed LCLA-τ method to the CLE. The CLE for a chemical system with propensities a_j and stoichiometric vectors v_j is an Ito stochastic differential equation (SDE) for the state vector $X(t)$ driven by independent Brownian motions B_j of the form:

$$dX_i(t) = \sum_{j=1}^{M} v_{ij} a_j(X(t))dt + \sum_{j=1}^{N} v_{ij}\sqrt{a_j(X(t))}dB_j(t). \tag{18}$$

See [22,18] for instance. When the molecular copy numbers of a chemical system are moderately large, the CLE provides a reasonable approximation to the exact system governed by CME (or equivalently the SSA). In some literature this is referred to as the *diffusion approximation* [18]. It must be noted that unlike CLA, the approximation provided by CLE does not predict $X(t)$ to be Gaussian. In general the CLE has been numerically observed to provide a better approximation to CME than the CLA. A recent work [23] provides an analytical justification for this.

However, the computation of CLA solution is relatively easy compared to the solution of the CLE. Samples paths of the CLE may be generated using discrete time methods for SDEs such as the explicit Euler or the implicit Euler [24]. These methods involve generating random updates that are Gaussian conditioned on the previous state. In the limit as step size approaches zero with number of steps going to infinity, these methods are shown to converge to the exact solution of the SDE [24]. In this $\tau \to 0$ limit, the LCLA-τ updates which are Gaussian (along with the implicit Euler updates of the CLE) will approach the updates of the explicit Euler for CLE, and hence may be expected to converge in a similar manner to the exact solution of the CLE and not to the exact solution of the CME. In this regard, the LCLA-τ method may be regarded as a discrete time method for solving the CLE. The key advantage of the LCLA-τ method over the more familiar updating methods is that while it enjoys the same stability as the implicit method it better captures the asymptotic distribution as will be demonstrated analytically and numerically.

To see why the LCLA-τ update approaches that of the explicit Euler update in the $\tau \to 0$ limit, we simply note first that since (see (10))

$$\frac{dm_{\hat{R}}(0)}{dt} = a(x),$$

the mean $m_{\hat{R}}(\tau) \approx a(x)\tau$ and since (see (11))

$$\frac{dC_{\hat{R}}(0)}{dt} = E_{\hat{R}}(0) = \sum_{j=1}^{M} e_j e_j^T a_j(x),$$

the covariance matrix $C_{\hat{R}}(\tau)$ is diagonal (up to $O(\tau)$) with jth entry being $a_j(x)\tau$. Since the LCLA-τ is a discrete time approximation that agrees with the above ODE solutions for the mean and covariance up to $O(\tau)$, this leads to an update of the reaction count vector with independent Gaussian entrees with mean and variance $a_j(x)\tau$ for the jth entry. This is exactly the explicit Euler update of the CLE.

Of course in the case of stiff systems, step size τ is only small compared to the slow time scales but potentially very large compared to the fast time scales and thus the LCLA-τ method differs significantly from the explicit Euler in practice.

3.3. Numerical schemes for computing $m_K(\tau)$ and $C_K(\tau)$

In this section, we describe in detail the numerical schemes for obtaining $m_K(\tau)$ and $C_K(\tau)$ which we shall simply denote by $m(\tau)$ and $C(\tau)$ from hereafter.

Given the fact that CLA is only an approximation of the true stochastic system, it is not clear whether it is worth the computational effort to use higher order implicit methods or multiple time steps of the ODE solver over a given tau leaping interval. Additionally the use of higher order methods and/or multiple ODE solver time steps over a given tau leaping interval require extra computational effort. Thus we shall only investigate low order Euler type methods applied with *one time step of the same size as the tau leaping step size* τ.

To obtain $m(\tau)$ we shall use the implicit Euler approximation of (5) since among the low order schemes the implicit Euler is best suited for stiffness. Thus we first solve an intermediate step X' from implicit Euler solutions of the RRE given by

$$X' = x + va(X')\tau, \tag{19}$$

and then set

$$m(\tau) = a(X')\tau. \tag{20}$$

Note that the above setup is equivalent to applying the implicit Euler to solve (10) given by

$$m(\tau) = a(x + vm(\tau))\tau, \quad m(0) = 0,$$

since $X' = x + vm(\tau)$, and $a(X')\tau = a(x + vm(\tau))\tau$.

There are several possibilities for a low order numerical approximation of (11). We investigate two types of numerical schemes that one could consider when solving for $C(\tau)$. The first type is the approximation of an exact integral representation of $C_{\hat{R}}(\tau)$, and the second type is via low order Euler approximations of (11).

Type 1: Approximations of the integral representation.

The analytical solution of (11) can be written as

$$C_{\hat{R}}(t) = \int_0^t \phi(t,s) E_{\hat{R}}(s) \phi^T(t,s) ds, \tag{21}$$

where $\phi(t,s)$ is the fundamental solution of

$$\frac{\partial}{\partial t}\phi(t,s) = A_{\hat{R}}(t)\phi(t,s), \quad \text{with } \phi(s,s) = I. \tag{22}$$

Thus, within a step size τ, $C_{\hat{R}}(\tau)$ is given by

$$C_{\hat{R}}(\tau) = \int_0^\tau \phi(\tau,s) E_{\hat{R}}(s) \phi^T(\tau,s) ds. \tag{23}$$

We discuss the approximations for $C_{\hat{R}}(\tau)$ from three aspects.

1. Approximating $E_{\hat{R}}(s)$.
2. Approximating $\phi(\tau,s)$.
3. Approximating the integral given by (23).

For computational efficiency, we want to approximate $E_{\hat{R}}(s)$ and $\phi(\tau,s)$ by their values at $s=0$ and/or $s=\tau$.

To approximate $E_{\hat{R}}(s)$, we may use $E(0)$, $E(\tau)$, or $(E(0)+E(\tau))/2$, where $E(0)$ and $E(\tau)$ are given by

$$E(0) = \sum_{j=1}^{M} e_j e_j^T a_j(x),$$

and

$$E(\tau) = \sum_{j=1}^{M} e_j e_j^T a_j(x + vm(\tau)),$$

where $m(\tau)$ is already solved. Note that $E(0)$ and $E(\tau)$ are diagonal matrices with diagonal elements being $a_j(x)$ and $a_j(x+vm(\tau))$, respectively.

For most values of s in the interval $[0,\tau]$, we note that $\phi(\tau,s)$ is very close to $\phi(\tau,0)$ in the case of stiff systems. To see this, for simplicity consider a linear propensity system so that $A(t)=A$ is a constant matrix and $\phi(\tau,s) = e^{A(\tau-s)}$ where $s \in [0,\tau]$. For a stiff system, the fast time scales correspond to the eigenvalues λ of A that have large negative real parts, and typically τ is much bigger than $|1/\Re(\lambda)|$ so that $e^{\Re(\lambda)(\tau-s)}$ decays fast with s and is close to $e^{\Re(\lambda)\tau}$ for most values of $s, s \in [0,\tau]$. On the other hand for the eigenvalues corresponding to the slow time scales, τ is smaller than $|1/\lambda|$ and hence evaluating $e^{\lambda(\tau-s)}$ at either endpoints $s=0$ or $s=\tau$ results in equal errors. Hence, for stiff systems, for most of the values of $s \in [0,\tau]$, $e^{A(\tau-s)}$ is closer to $e^{A\tau}$, and not to $e^{A(\tau-\tau)} = I$. Therefore, we shall approximate $\phi(\tau,s)$ by $\phi(\tau,0)$.

Now we consider how to approximately compute $\phi(\tau,0)$. Experience suggests that explicit Euler is not a good method for stiff systems. We shall investigate two choices, the implicit Euler and the trapezoidal Euler applied in (22) to approximate $\phi(\tau,0)$. We denote the resulting approximations by $\hat{\phi}(\tau,0)^{(im)}$ and $\hat{\phi}(\tau,0)^{(tr)}$. These are given by

$$\hat{\phi}(\tau,0)^{(im)} = (I - \tau A(\tau))^{-1},$$

and

$$\hat{\phi}(\tau,0)^{(tr)} = \left(I - \frac{\tau}{2}A(\tau)\right)^{-1}\left(I + \frac{\tau}{2}A(0)\right),$$

where $A(0)$ and $A(\tau)$ are given by

$$A(0) = \frac{\partial a}{\partial x}(x)v, \quad \text{and} \quad A(\tau) = \frac{\partial a}{\partial x}(x + vm(\tau))v.$$

Finally, we approximate the integral (21) by

$$C(\tau) = \tau \hat{\phi} \hat{E} \hat{\phi}^T,$$

where $\hat{\phi}$ is chosen to be either $\hat{\phi}(\tau,0)^{(im)}$ or $\hat{\phi}(\tau,0)^{(tr)}$, and $\hat{E}$ is chosen to be $E(0)$, $E(\tau)$, or $(E(0)+E(\tau))/2$. This leads to six numerical schemes in different combinations.

Type 2: Euler approximations of the ODE. Another numerical approach to solve for (11) is to use Euler approximation methods, i.e., the explicit Euler, implicit Euler and trapezoidal Euler methods. Given $C(0) = 0$, we consider applying Euler methods in one step.

The solution of the explicit Euler method of (11) is

$$C(\tau)^{(ex)} = E(0)\tau,$$

where $E(0)$ is the same as defined before.

Note that $C(\tau)^{(ex)}$ is a diagonal matrix since $E(0)$ is diagonal. Thus it cannot capture the correlations between different reactions since the covariances are zero for off-diagonal terms. Therefore, we do not consider the explicit Euler approximation for $C(\tau)$.

Applying the implicit Euler to solve for (11), we obtain

$$C(\tau)^{(im)} = C(\tau)^{(im)}A(\tau)^T\tau + A(\tau)C(\tau)^{(im)}\tau + E(\tau)\tau,$$

which is equivalent to the following *Lyapunov equation*

$$C(\tau)^{(im)}\left(A(\tau)\tau - \frac{I}{2}\right)^T + \left(A(\tau)\tau - \frac{I}{2}\right)C(\tau)^{(im)} + E(\tau)\tau = 0. \tag{24}$$

Similarly, the trapezoidal Euler approximating method gives

$$C(\tau)^{(tr)}(A(\tau)\tau - I)^T + (A(\tau)\tau - I)C(\tau)^{(tr)} + (E(0) + E(\tau))\tau = 0. \tag{25}$$

Here $A(\tau), E(0)$, and $E(\tau)$ are same as before.

Cholesky factorization and positive semi-definiteness of $C(\tau)$: Table 1 provides a scheme for generating $K(\tau)$ that are Gaussian with mean $m(\tau)$ and covariance $C(\tau)$. Note that $C(\tau)$ should be symmetric and positive semi-definite. For type 1 numerical scheme, $C(\tau)$ is given by $C(\tau) = \tau\hat{\phi}\hat{E}\hat{\phi}^T$, where $\hat{E}$ is a diagonal matrix. Hence $C(\tau)$ is always positive semi-definite and the Cholesky decomposition of $C(\tau)$ is given by

$$B(\tau) = \sqrt{\tau}\hat{\phi}\hat{E}_s(\tau), \tag{26}$$

where $\hat{E}_s(\tau)$ is the square root of the nonnegative diagonal matrix $\hat{E}(\tau)$. Hence the advantage of type 1 approximation is that the numerical computation of the Cholesky decomposition is not required.

For Type 2 schemes, i.e., the implicit Euler and trapezoidal Euler approximating methods, one needs to solve for the Lyapunov equation (24) or (25) to obtain $C(\tau)$, then obtain $B(\tau)$ by numerical computation of the Cholesky decomposition of $C(\tau)$.

We present a lemma which follows from a theorem in [25] to obtain sufficient conditions for the positive semidefiniteness of $C(\tau)$.

Lemma 3.1. *Let Q, R and W be $M \times M$ matrices, where W is symmetric and positive semidefinite. Suppose that all eigenvalues of R have negative real parts. Then the Lyapunov equation*

$$QR^T + RQ + W = 0, \tag{27}$$

has a unique symmetric solution Q, and Q is positive semidefinite.

The following lemma presents sufficient conditions for the positive semidefiniteness of $C(\tau)$.

Lemma 3.2. *If $A(\tau)$ has eigenvalues with real part less than $1/(2\tau)$, then $C(\tau)^{(im)}$ is symmetric positive semidefinite. If $A(\tau)$ has eigenvalues with real part less than $1/\tau$, then $C(\tau)^{(tr)}$ is symmetric positive semidefinite.*

Proof. Follows from (24) and (25), Lemma 3.1 and the fact that $E(\tau)$ and $E(0)$ are positive semidefinite. □

We note that the conditions that the real part of the eigenvalues of $A(\tau)$ be less than $1/(2\tau)$ or $1/\tau$ are not restrictive for stiff systems where the fast time scales all have negative real parts.

Thus we have described eight different possible numerical schemes for computing $C_K(\tau)$. In Section 4 we present the stability analysis of these schemes. This stability analysis shows that the type 2 method with the implicit Euler solution of (11) (which leads to (24)) provides the best scheme in terms of preserving the asymptotic covariance.

Table 2
Step 2 of the LCLA-τ algorithm: computing $m(\tau)$ and $C(\tau)$.

(i)	Compute X' from $X' = x + va(X')\tau$ (Newton's method).
(ii)	Set $m(\tau) \leftarrow a(X')\tau$.
(iii)	Set $A(\tau) \leftarrow \frac{\partial a}{\partial x}(x + m(\tau))v$ and $E(\tau) \leftarrow \sum_{j=1}^{M} e_j e_j^T a_j(x + vm(\tau))$.
(iv)	Solve $C(\tau)$ from $C(\tau)(A(\tau)\tau - I/2)^T + (A(\tau)\tau - I/2)C(\tau) + E(\tau)\tau = 0$.

We note that the type 2 schemes are more costly than the type 1 schemes due to the numerical solution of Lyapunov equations and Cholesky decompositions. Nevertheless the type 2 scheme with implicit Euler allows one to take step sizes much larger than the fast (and stable) time scales without compromising the accuracy of the asymptotic covariance. Hence the type 2 scheme with the implicit Euler shall be our choice for Step 2 of the basic framework of LCLA-τ algorithm shown in Table 1. Table 2 describes the details of Step 2 of Table 1.

4. Absolute stability analysis

We study the absolute stability of the LCLA-τ method with the various numerical schemes for computing $C(\tau)$ as described in Section 3.3. In absolute stability analysis we fix τ and let the number of time steps $n \to \infty$ and investigate the asymptotic mean and covariance.

First we study the test example $S_1 \leftrightarrow S_2$ in Section 4.1. Then in Section 4.2 we extend the study to general linear systems with the aid of numerics. Our analysis shows that the type 2 method of approximating (11) via implicit Euler provides the closest asymptotic covariance to the true one.

We state an important lemma (see [26] for the scalar version) which shall form the backbone of our analysis.

Lemma 4.1. *For (vector valued) random variables G and H,*

$$E(G) = E(E(G|H)), \quad \mathrm{Cov}(G) = E(\mathrm{Cov}(G|H)) + \mathrm{Cov}(E(G|H)).$$

4.1. Stability analysis with $S_1 \leftrightarrow S_2$

In this section, we study the absolute stability of the LCLA-τ method by applying it to the test problem

$$S_1 \xrightarrow{c_1} S_2, \quad S_2 \xrightarrow{c_2} S_1. \tag{28}$$

We denote by Y_1^n and Y_2^n, the tau leaping approximations of $X_1(n\tau)$ and $X_2(n\tau)$ respectively (assuming constant time step τ). Since the system has a conserved quantity $X_1(t) + X_2(t) = X_1(0) + X_2(0) = x_T$, it follows that $Y_2^n = x_T - Y_1^n$ and it is adequate to study the behavior of Y_1^n. We will derive propagation equations for the mean and variance of Y_1^n by applying Lemma 4.1. Note that it is not necessary to derive $\mathrm{Cov}(Y_1^n, Y_2^n)$ since this is equal to $\mathrm{Cov}(Y_1^n, x_T - Y_1^n) = -\mathrm{Var}(Y_1^n)$.

Let X^* be a random variable with a distribution which is the same as the asymptotic distribution of the true process $X_1(t)$ as $t \to \infty$. For $\lambda = c_1 + c_2, E(X^*) = c_2 x_T/\lambda$ and $\mathrm{Var}(X^*) = c_1 c_2 x_T/\lambda^2$ (see [27]). With modest abuse of notation, we shall use $E(Y_1^\infty)$ and $\mathrm{Var}(Y_1^\infty)$ to denote respectively the limits $\lim_{n\to\infty} E(Y_1^n)$ and $\lim_{n\to\infty} \mathrm{Var}(Y_1^n)$ when they exist.

We first compute Y_1' from the implicit Euler step

$$Y_1' = Y_1^n - c_1\tau Y_1' + c_2\tau(x_T - Y_1'), \tag{29}$$

and obtain

$$Y_1' = \frac{Y_1^n}{1+\lambda\tau} + \frac{c_2\tau}{1+\lambda\tau} x_T.$$

According to the LCLA-τ scheme, random variables $K^n = (K_1^n, K_2^n)$ are chosen to be Gaussians with mean $E(K^n) = (c_1 Y_1'\tau, c_2(x_T - Y_1')\tau)$. Since

$$Y_1^{n+1} = Y_1^n + K_2^n - K_1^n,$$

by conditioning on Y_1^n, we obtain

$$E(Y_1^{n+1}|Y_1^n) = \frac{1}{1+\lambda\tau} Y_1^n + \frac{c_2\tau x_T}{1+\lambda\tau}.$$

Applying the first formula from Lemma 4.1, we obtain that

$$E(Y_1^{n+1}) = \frac{1}{1+\lambda\tau} E(Y_1^n) + \frac{c_2\tau x_T}{1+\lambda\tau}.$$

Letting $n \to \infty$, and solving for $E(Y_1^\infty)$, we obtain that

$$E(Y_1^\infty) = E(X^*).$$

We note that the stability condition for the mean

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

is satisfied for all $\lambda\tau > 0$.

We show the details only for the implicit Euler approximation method of type 2 described in Section 3.3 in obtaining the propagation equation for the variance. Let $C_Y = \mathrm{Cov}(Y^{n+1}|Y^n)$ be the implicit Euler solution of (9). It follows that C_Y is the solution of the Lyapunov equation given by

$$C_Y\left(A_Y\tau - \frac{I}{2}\right)^T + \left(A_Y\tau - \frac{I}{2}\right)C_Y + E_Y\tau = 0.$$

Here

$$A_Y = \begin{pmatrix} -c_1 & c_2 \\ c_1 & -c_2 \end{pmatrix},$$

and

$$E_Y = \begin{pmatrix} a_0 & -a_0 \\ -a_0 & a_0 \end{pmatrix},$$

where

$$a_0 = \frac{(c_1 - c_2)Y_1^n}{1+\lambda\tau} + \frac{c_2 x_T}{1+\lambda\tau} + \frac{2c_1c_2x_T\tau}{1+\lambda\tau}.$$

A formula in [28] gives the analytic form of the solution C_Y for a 2×2 system of the Lyapunov equation to be

$$C_Y = \begin{pmatrix} \tau/(1+2\lambda\tau) & -\tau/(1+2\lambda\tau) \\ -\tau/(1+2\lambda\tau) & \tau/(1+2\lambda\tau) \end{pmatrix} a_0.$$

Therefore,

$$\mathrm{Var}(Y_1^{n+1}|Y_1^n) = \frac{(c_1-c_2)\tau Y_1^n}{(1+2\lambda\tau)(1+\lambda\tau)} + \frac{c_2x_T\tau}{(1+2\lambda\tau)(1+\lambda\tau)} + \frac{2c_1c_2x_T\tau^2}{(1+2\lambda\tau)(1+\lambda\tau)}.$$

Thus we obtain

$$\begin{aligned}\mathrm{Var}(Y_1^{n+1}) &= E(\mathrm{Var}(Y_1^{n+1}|Y_1^n)) + \mathrm{Var}(E(Y_1^{n+1}|Y_1^n)) \\ &= \frac{1}{(1+\lambda\tau)^2}\mathrm{Var}(Y_1^n) + \frac{(c_1-c_2)\tau E(Y_1^n)}{(1+2\lambda\tau)(1+\lambda\tau)} + \frac{c_2x_T\tau}{(1+2\lambda\tau)(1+\lambda\tau)} + \frac{2c_1c_2x_T\tau}{(1+2\lambda\tau)(1+\lambda\tau)}.\end{aligned}$$

Hence the stability condition for the variance is the same as (30) and the variance is stable for all $\lambda\tau > 0$. Letting $n\to\infty$, and solving for $\mathrm{Var}(Y_1^\infty)$ we obtain

$$\mathrm{Var}(Y_1^\infty) = \frac{2(1+\lambda\tau)^2}{(1+2\lambda\tau)(2+\lambda\tau)}\mathrm{Var}(X^*).$$

We define the *variance quotient* VQ of a tau leaping method as the ratio of the asymptotic variance $\mathrm{Var}(Y_1^\infty)$ of the method to the true asymptotic variance $\mathrm{Var}(X^*)$ for the test problem $S_1 \leftrightarrow S_2$. Note that VQ is typically a function of $\lambda\tau$ and ideally VQ is the constant function 1.

Similar analysis can be carried out for the other numerical schemes, and for sake of brevity, we shall not provide all the details. We note that since all these schemes involve linear low order methods applied to the ODE (9) which depends linearly on current state x, it follows that for all these schemes $\mathrm{Var}(Y_1^{n+1}|Y_1^n)$ is linear in Y_1^n and as a result the coefficient of propagation in the difference equation for $\mathrm{Var}(Y_1^n)$ is always $1/(1+\lambda\tau)^2$. Hence for all these schemes the variance (in addition to the mean) is stable provided $\lambda\tau > 0$. However, the asymptotic variances, and hence the variance quotients VQ differ.

Table 3 summarizes the VQ for the various LCLA-τ schemes discussed in Section 3.3. None of the LCLA-τ numerical schemes provide a constant value of 1. Nevertheless, one may look for a VQ($\lambda\tau$) that remains bounded away from 0 and ∞ and preferably close to 1 for $\lambda\tau \in [0,\infty)$.

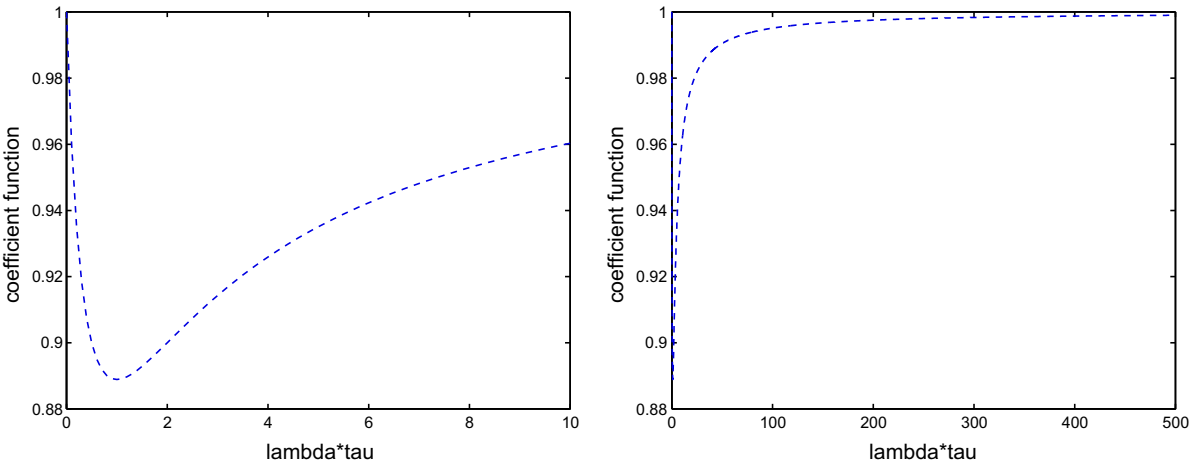
The variance quotient of an LCLA type 1 numerical scheme is independent of the approximation $\hat{E}$. When $\lambda\tau\to\infty$, VQ either approaches ∞ (for $\hat{\phi}(\tau,0)^{(tr)}$) or 0 (for $\hat{\phi}(\tau,0)^{(im)}$). Of the type 2 numerical schemes, if explicit Euler is used to solve (11), the resulting scheme has a variance quotient that approaches ∞ as $\lambda\tau\to\infty$.

Only two schemes, namely the type 2 with implicit Euler and type 2 with trapezoidal Euler have VQ that is bounded away from 0 and ∞. But as $\lambda\tau\to\infty$ for the type 2 with implicit Euler VQ approaches 1 while for the type 2 with Trapezoidal Euler VQ approaches 2. Thus we conclude that the best scheme as judged by the variance quotient is the type 2 implicit Euler scheme. Fig. 1 illustrates the dependence of VQ on $\lambda\tau$ for this scheme and we note that VQ is always between approximately 0.88 and 1, a very desirable feature indeed.

Table 3 also shows the VQ of the basic tau methods for the purpose of comparison which were derived in [5]. For the Trapezoidal tau method VQ = 1 identically for all $\lambda\tau > 0$. Nevertheless as discussed and illustrated in [7], the problem with the trapezoidal tau method is that in stiff systems the fast dynamics of the method decay much slower than those of the true

Table 3
Test example $S_1 \leftrightarrow S_2$: variance quotients for LCLA-τ with type 1, type 2 numerical schemes, and comparison with the basic tau leaping methods.

$\hat{\phi}(\tau,0)$	$\hat{E}$		
	$E(0)$	$E(\tau)$	$\frac{E(0)+E(\tau)}{2}$
LCLA-τ Type 1 (approximations of the integral representation)			
$\hat{\phi}(\tau,0)^{(im)}$	$\frac{2}{2+\lambda\tau}$	$\frac{2}{2+\lambda\tau}$	$\frac{2}{2+\lambda\tau}$
$\hat{\phi}(\tau,0)^{(tr)}$	$\frac{2(2-\lambda\tau)^2(1+\lambda\tau)^2}{(2+\lambda\tau)^3}$	$\frac{2(2-\lambda\tau)^2(1+\lambda\tau)^2}{(2+\lambda\tau)^3}$	$\frac{2(2-\lambda\tau)^2(1+\lambda\tau)^2}{(2+\lambda\tau)^3}$
LCLA-τ Type 2 (Euler approximations of the ODE)			
	Exp. Euler	Imp. Euler	Trap. Euler
Lyapunov	$\frac{2(1+\lambda\tau)^2}{2+\lambda\tau}$	$\frac{2(1+\lambda\tau)^2}{(1+2\lambda\tau)(2+\lambda\tau)}$	$\frac{2(1+\lambda\tau)}{(2+\lambda\tau)}$
Basic tau leaping methods			
	Exp. tau	Imp. tau	Trap. tau
	$\frac{2}{2-\lambda\tau}$	$\frac{2}{2+\lambda\tau}$	1



(a) VQ $= \frac{2(1+\lambda\tau)^2}{(1+2\lambda\tau)(2+\lambda\tau)}$ vs. $\lambda\tau$ for $\lambda\tau \in [0,10]$ (b) VQ $= \frac{2(1+\lambda\tau)^2}{(1+2\lambda\tau)(2+\lambda\tau)}$ vs. $\lambda\tau$ for $\lambda\tau \in [0,500]$

Fig. 1. VQ($\lambda\tau$) vs. $\lambda\tau$ for the LCLA-τ Type 2 implicit Euler (test example $S_1 \leftrightarrow S_2$).

system. Thus for a very stiff system the LCLA-τ method (with the Type 2, implicit Euler scheme) will outperform the Trapezoidal tau method.

4.2. Numerical studies of stability with linear propensity systems

In this section, we expand the stability analysis to general linear systems. Consider chemical systems with linear propensities, where the LCLA-τ solutions at the nth time step are given by $Y^n = (Y_1^n, Y_2^n, \ldots, Y_N^n)$. Here we will derive the propagation equations for $E(Y^n)$ and $\mathrm{Cov}(Y^n)$. Note that linear propensities have a general form $a(x) = Px + d$.

First step of LCLA-τ involves solving for the intermediate state X' from

$$X' = Y^n + \tau v a(X') = Y^n + \tau v(PX' + d),$$

and we obtain that

$$X' = (I - \tau vP)^{-1}(Y^n + \tau vd).$$

Thus

$$E(Y^{n+1}|Y^n) = X' = (I - \tau vP)^{-1}(Y^n + \tau vd). \tag{31}$$

Moreover,

$$\mathrm{Cov}(Y^{n+1}|Y^n) = v\mathrm{Cov}(K^n|Y^n)v^T = vC_K v^T, \tag{32}$$

where $C_K = \mathrm{Cov}(K^n|Y^n)$. By Lemma 4.1 we obtain the following propagation equations from (31) and (32):

$$E(Y^{n+1}) = (I - \tau\nu P)^{-1}(E(Y^n) + \tau\nu d), \tag{33}$$

$$\mathrm{Cov}(Y^{n+1}) = \nu C_K \nu^T + (I - \tau\nu P)^{-1}\mathrm{Cov}(Y^n)((I - \tau\nu P)^{-1})^T. \tag{34}$$

We note that C_K depends on which one of the numerical schemes of Section 3.3 is used. For the type 1 schemes we may obtain an analytical form for C_K. For the type 2 implicit Euler and trapezoidal Euler schemes an analytical form for C_K is not available as C_K is given by the solution of a Lyapunov equation. For instance for type 2 implicit Euler scheme C_K is the same as $C(\tau)^{(im)}$ given by (24). Nevertheless we may compute C_K numerically using the `lyap` command in MATLAB.

Noting that $\mathrm{Cov}(Y^0) = 0$, we obtain $\mathrm{Cov}(Y^n)$ according to (34) numerically where the computation of C_K varies according to the numerical scheme. The comparison of the trajectories of $\mathrm{Cov}(Y^n)$ (against n) for various numerical schemes is illustrated through a linear test example (35) shown below.

A linear test example:

$$\begin{aligned} &(1)\ S_1 \xrightarrow{c_1} S_2, \quad (2)\ S_2 \xrightarrow{c_2} S_1, \\ &(3)\ S_1 \xrightarrow{c_3} S_3, \quad (4)\ S_3 \xrightarrow{c_4} S_1. \end{aligned} \tag{35}$$

We chose the initial value to be $X(0) = (20, 20, 20)^T$. The system has a conserved quantity $X_1(t) + X_2(t) + X_3(t) = X_1(0) + X_2(0) + X_3(0) = x_T$, where $x_T = 60$. We set $c_1 = 0.5$, $c_2 = 0.3$, $c_3 = 1000$ and $c_4 = 500$. The eigenvalues of the Jacobian matrix corresponding to the RRE are $(-1500, 0, -0.5)^T$ with the slowest time scale $1/0.5 = 2$, and the fastest time scale $1/1500 \approx 0.0007$. We chose final time $T = 20$, and step size $\tau = 0.2$. Because $X_3 = x_T - X_1 - X_2$, it is adequate to study the variance and covariance of species X_1 and X_2, namely, $\mathrm{Var}(X_1)$, $\mathrm{Var}(X_2)$ and $\mathrm{Cov}(X_1, X_2)$. We also used the MATLAB ODE solver `ode15s` to solve the evolution equation for $\mathrm{Var}(X_1)$, $\mathrm{Var}(X_2)$ and $\mathrm{Cov}(X_1, X_2)$ to use as a benchmark for comparison of the different schemes.

The comparison of the evolutions of the variances and the covariance for all the type 1 and type 2 schemes are shown in Figs. 2–4. It is shown that the type 2 implicit Euler method is the most accurate. Type 1 with $\hat{\phi}(\tau, 0)^{(im)}$ underestimates the

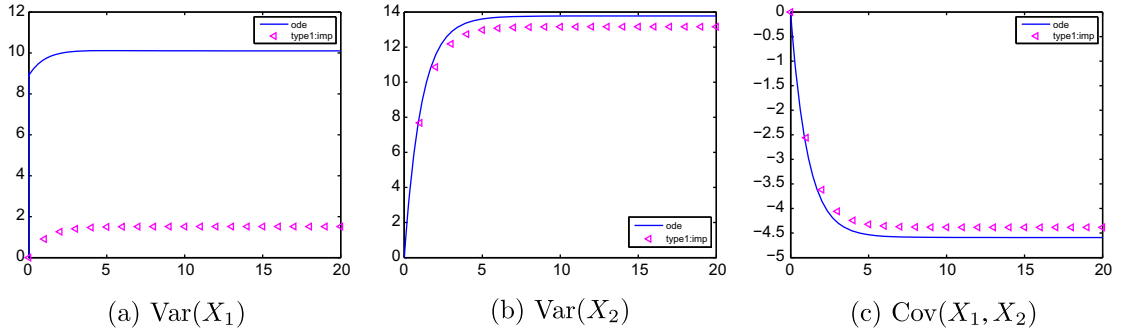


Fig. 2. Stability analysis of (35): trajectories of $\mathrm{Var}(X_1)$, $\mathrm{Var}(X_2)$ and $\mathrm{Cov}(X_1, X_2)$ obtained by ODE solver (MATLAB: `ode15s`, solid line), and type 1 numerical schemes with $\phi^{(im)}$ (triangle). Three choices of $\hat{E}$ lead to same asymptotic trajectories.

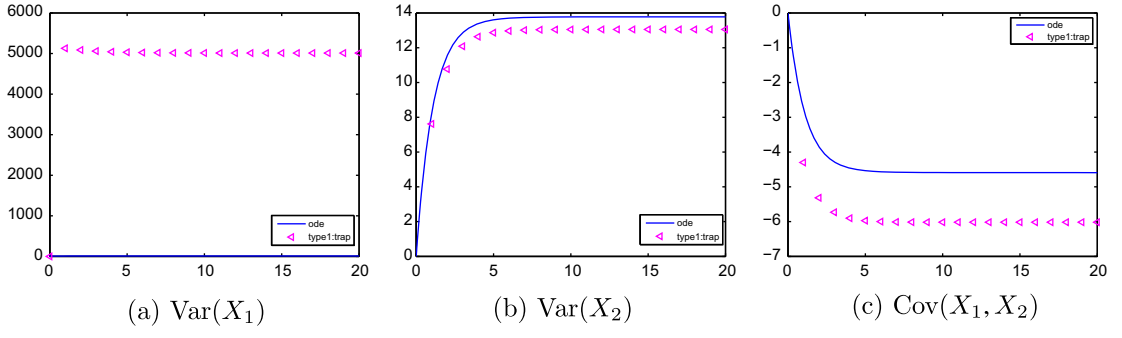


Fig. 3. Stability analysis of (35): trajectories of $\mathrm{Var}(X_1)$, $\mathrm{Var}(X_2)$ and $\mathrm{Cov}(X_1, X_2)$ by ODE solver (MATLAB: `ode15s`, solid line), and type 1 numerical schemes with $\phi^{(tr)}$ (triangle). Three choices of $\hat{E}$ lead to same asymptotic trajectories.

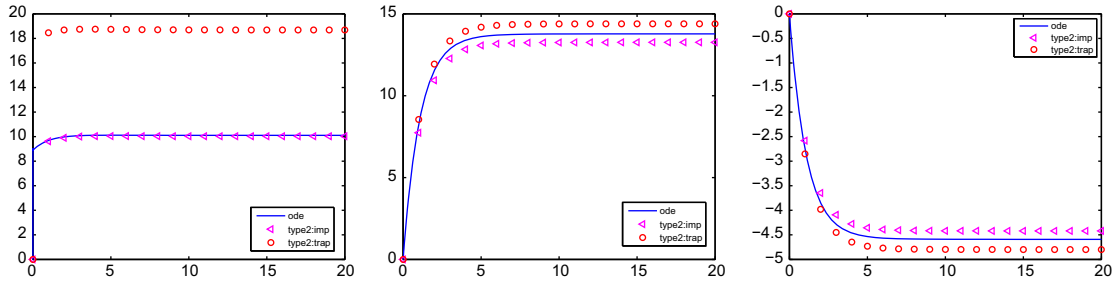


Fig. 4. Stability analysis of (35): trajectories of Var(X_1), Var(X_2) and Cov(X_1,X_2) by ODE solver (MATLAB: `ode15s`, solid line), type 2 with implicit Euler (triangle), and trapezoidal Euler (circle) methods.

variance for Var(X_1), and type 1 with $\hat{\phi}(\tau,0)^{(tr)}$ overestimates the variance for Var(X_1). We also confirm that for type 1 schemes, the asymptotic numerical behaviors depend only on the choices of approximations for $\hat{\phi}$ and not on the choices of $\hat{E}$. These numerical results agree with the analysis of the example $S_1 \leftrightarrow S_2$ shown in Table 3.

5. Numerical examples

In this section we will illustrate LCLA-τ through several numerical examples and compare with other tau leaping methods. By LCLA-τ we shall mean the LCLA-τ with type 2 implicit Euler scheme as outlined in Tables 1 and 2.

All tau leaping simulations were run on MATLAB. Since the SSA simulations were prohibitively slow on MATLAB, they were run on a C platform. For the purpose of reasonable comparison of computational effort, we ran few SSA trajectories on MATLAB to estimate the average running time (physical time) of a trajectory on the MATLAB platform (using `tic toc` command). Tables 4, 5, 7, and 9 show running time comparison.

The time scales of the chemical systems were estimated from the RRE by the eigenvalues of the Jacobian matrix evaluated at the final time. We chose both stiff and non-stiff systems. For stiff systems, we selected the time step τ to be small when compared with the slowest time scale, but much larger than the fastest time scale. We compared LCLA-τ with SSA, trapezoidal tau, the implicit Minkowski–Weyl tau methods including IMW-S and IMW-P. We chose chemical systems with number of molecules for each species ranging from small to large. We note that for the LCLA-τ method we applied rounding of the final state for ease of comparison of probability distributions.

5.1. Linear test example: $S_2 \leftrightarrow S_1 \leftrightarrow S_3$

We used the example (35), with the same parameter settings described before. We chose three initial values: $X(0) = (2,2,2)^T$, $X(0) = (20,20,20)^T$, and $X(0) = (200,200,200)^T$. We chose the final time $T = 2$. The step size was $\tau = 0.2$.

The comparison of the probability distributions in a simulation of 10,000 trajectories for SSA, LCLA-τ, IMW-S, and trapezoidal tau methods are shown in Figs. 5–7. The IMW-S performed better than LCLA-τ and the trapezoidal tau methods for small number of molecules ($x_T = 6$). For large x_T such as $x_T = 60$ and $x_T = 600$, LCLA-τ performed better in capturing probability distributions. The trapezoidal tau did not capture the mean correctly due to its poor performance for very stiff systems which was discussed in [7].

Table 4
Linear test example: comparison of estimated mean execution time for one trajectory (in s) between the SSA and LCLA methods on MATLAB platform.

	$x_T = 6$	$x_T = 60$	$x_T = 600$
SSA	0.18	1.9	19.9
LCLA	0.0049	0.0051	0.0048

Table 5
Genetic loop example: comparison of estimated mean execution time for one trajectory (in s) between the SSA and LCLA methods on MATLAB platform.

SSA	744
LCLA	0.034

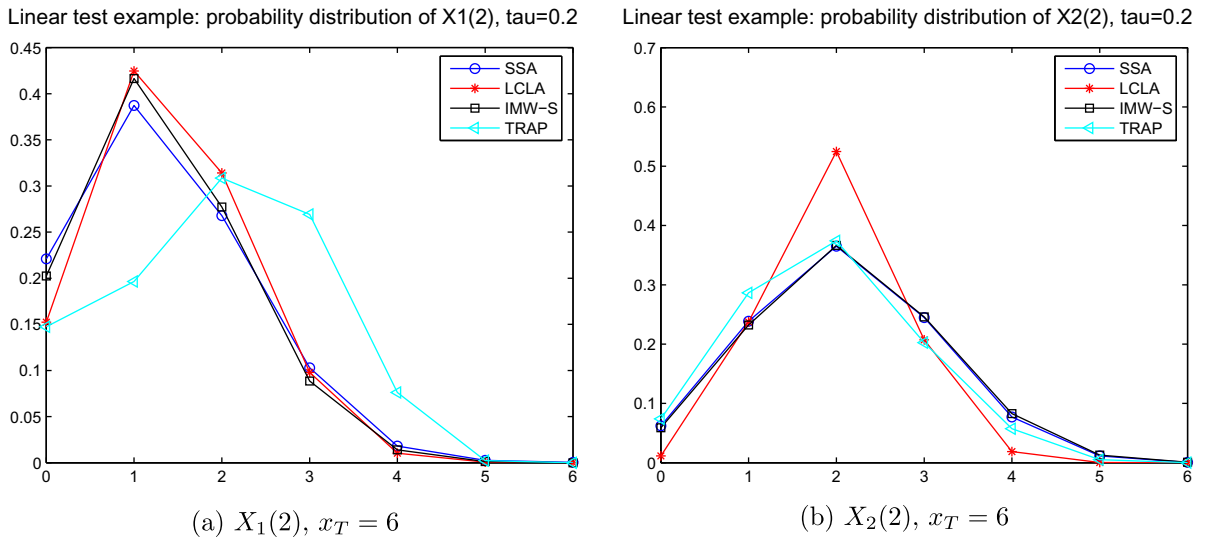


Fig. 5. Linear test example: comparison of probability distributions (10,000 sample trajectories) of $X_1(2)$ and $X_2(2)$ obtained by the SSA (circle), LCLA (star), IMW-S (square), and trapezoidal tau (triangle). Here $\tau = 0.2$, $T = 2$, and $x_T = 6$.

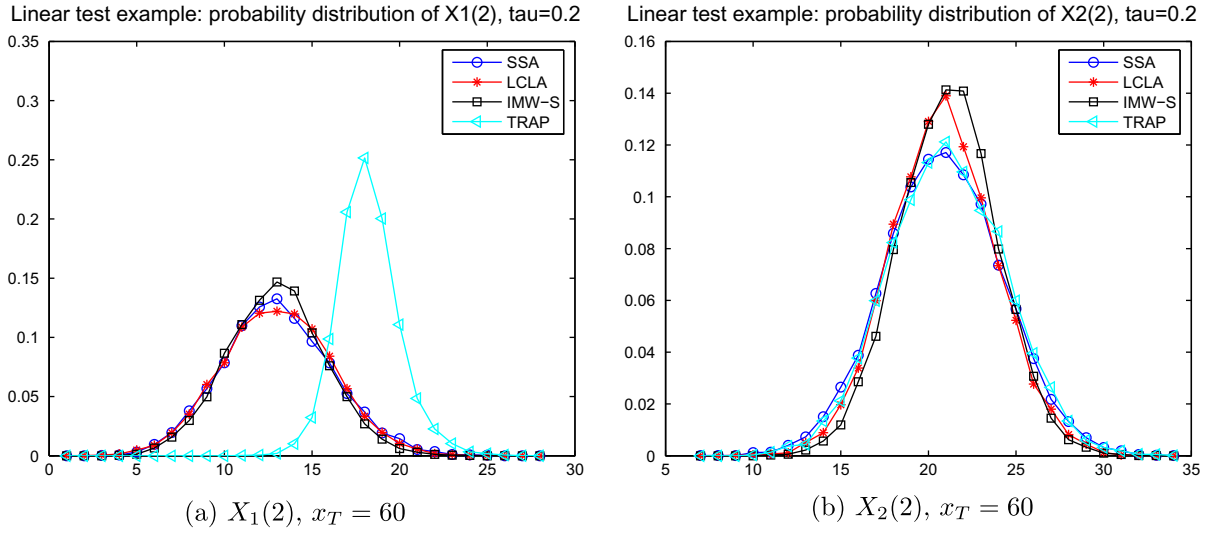
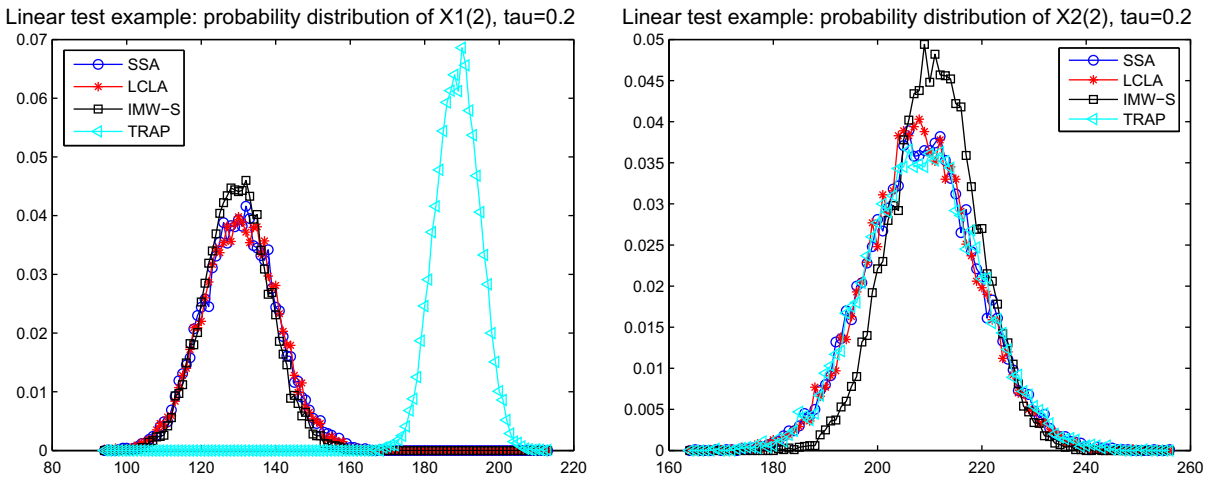


Fig. 6. Linear test example: comparison of probability distributions (10,000 sample trajectories) of $X_1(2)$ and $X_2(2)$ obtained by the SSA (circle), LCLA (star), IMW-S (square), and trapezoidal tau (triangle). Here $\tau = 0.2$, $T = 2$, and $x_T = 60$.

5.2. Genetic positive feedback loop

We considered the example (36) with large and small species counts. It describes a genetic transcription model with important biological significance (see [29]). Here x is the protein monomer, y is the protein dimer, d_0 is the regulatory site unbounded to protein dimer, d_r is the regulatory site bounded to protein dimer, and m is the mRNA. Reactions (1) and (2) correspond to reversible reactions involving the dimerization of the protein x. Reactions (3) and (4) describe the binding and unbinding processes of the dimer y to the regulatory site. Reactions (5) and (6) are the processes of transcription, and reaction (7) is the process of translation. Reactions (8) and (9) are the decays of the protein monomers x and the mRNA m. Here reactions (1)–(4) occur more frequently than reactions (5)–(9).

$$\begin{aligned}
&(1)\ x + x \xrightarrow{\kappa_+} y, \quad (2)\ y \xrightarrow{\kappa_-} x + x, \quad (3)\ y + d_0 \xrightarrow{k_+} d_r,\\
&(4)\ d_r \xrightarrow{k_-} y + d_0, \quad (5)\ d_0 \xrightarrow{\alpha} d_0 + m, \quad (6)\ d_r \xrightarrow{\beta} d_r + m,\\
&(7)\ m \xrightarrow{\sigma} m + x, \quad (8)\ x \xrightarrow{\gamma_p} 0, \quad (9)\ m \xrightarrow{\gamma_m} 0.
\end{aligned} \tag{36}$$



(a) $X_1(2)$, $x_T = 600$ (b) $X_2(2)$, $x_T = 600$

Fig. 7. Linear test example: comparison of probability distributions (10,000 sample trajectories) of $X_1(2)$ and $X_2(2)$ obtained by the SSA (circle), LCLA (star), IMW-S (square), and trapezoidal tau (triangle). Here $\tau = 0.2$, $T = 2$, and $x_T = 600$.

Let $X_1 = \#x$, $X_2 = \#y$, $X_3 = \#d_0$, $X_4 = \#d_r$, $X_5 = \#m$. The initial value chosen was $X(0) = (10, 0, 20, 0, 0)^T$, and we note that $X_3(t) + X_4(t) = 20$ is a conserved quantity. The reaction parameter values used were $\kappa_+ = 50$, $\kappa_- = 1000$, $k_+ = 50$, $k_- = 1000$, $\alpha = 1$, $\beta = 10$, $\sigma = 3$, $\gamma_p = 1$, $\gamma_m = 6$ and we chose $T = 50$. The eigenvalues of the Jacobian corresponding to RRE at $T = 50$ are $(-9979, -11382, -0.083, -6.02, 0)^T$. The fastest and the slowest time scales are $1/11{,}382 \approx 10^{-5}$ and $1/0.083 \approx 12$, respectively. We chose $\tau = 1$.

The histograms are shown in Fig. 8 with the comparisons of SSA, LCLA-τ, IMW-P and trapezoidal tau methods. It can be seen that for the species with small number of molecules, such as S_3, the IMW-P is better than the LCLA. For species with large molecule numbers such as S_1, S_2 and S_5, LCLA performs better than the IMW-P. We also note that the trapezoidal tau shows a bimodal distribution for $X_1(50)$ which is because of the oscillatory transient which does not decay fast enough. This is seen by the fact that the amplification factor (for the mean) for trapezoidal method is $(2 + \lambda\tau)/(2 - \lambda\tau)$ for an eigenvalue λ. For the fastest time scale $\lambda = -11382$ and since $\tau = 1$ the amplification factor is -0.9996. Over 50 time steps $(-0.9996)^{50} \approx 0.9826$ which shows the oscillatory transient of the method does not decay.

5.3. Examples with bistability

In this section, we emphasize the advantage of the LCLA-τ over a direct application of CLA. We chose two examples with bistability which leads to a bimodal distribution. For comparison we show the result of simply approximating the final state via CLA which predicts Gaussians with mean $m_R(T)$ and $C_R(T)$ which we obtain by solving (10) and (11) with high order ODE solvers.

5.3.1. The Schlögl model

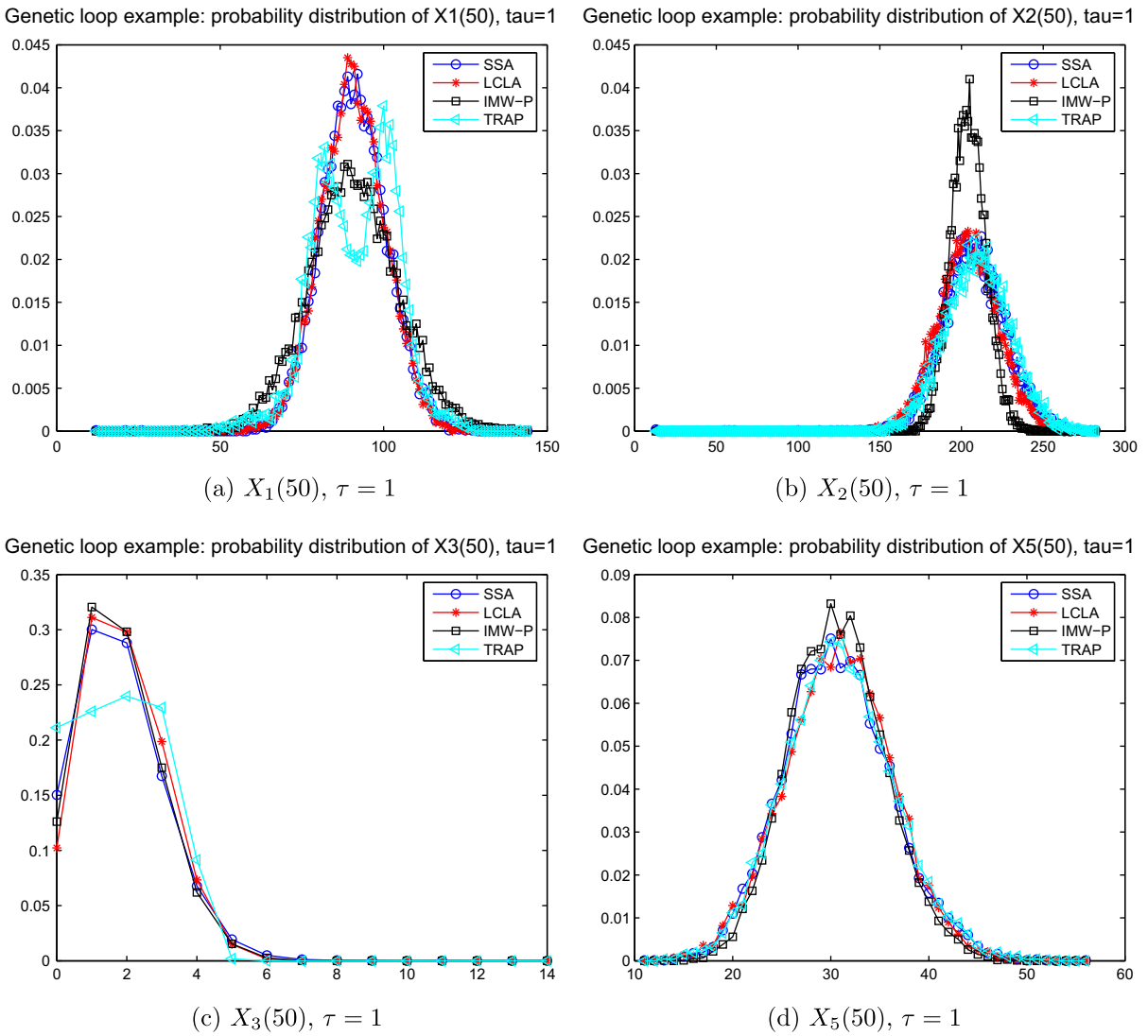
The first example is the Schlögl model in [21] involving three species and four reactions. Suppose the number of molecules for S is given by $X(t)$, where $X(0) = 250$. We denote by X_A and X_B the number of species for A and B, and these numbers are fixed. Here $X_A = 10^5, X_B = 2 \times 10^5$, and $c_1 = 3 \times 10^{-7}$, $c_2 = 10^{-4}$, $c_3 = 10^{-3}$, $c_4 = 3.5$. Schlögl reactions are given by

$$\begin{aligned} &(1)\ A + 2S \xrightarrow{c_1} 3S, \quad (2)\ 3S \xrightarrow{c_2} A + 2S, \\ &(3)\ B \xrightarrow{c_3} S, \qquad\quad (4)\ S \xrightarrow{c_4} B. \end{aligned} \tag{37}$$

The propensities for each reaction are

$$\begin{aligned} a_1(X) &= 0.03X(X-1)/2, \\ a_2(X) &= 10^{-4}X(X-1)(X-2)/6, \\ a_3(X) &= 200, \\ a_4(X) &= 3.5X. \end{aligned} \tag{38}$$

It can be shown that the ODE system has two stable stationary states, and one unstable state. We first observe that the range of eigenvalue of the Jacobian λ is from -9.1 to 1.1 as the species counts $X(t)$ varies from 80 to 750. Therefore, for $\lambda \geqslant 0$, one needs to choose $\tau \leqslant 2/(2 \times 2.2)$ to ensure the positive semidefiniteness of $C(\tau)$ as stated in Lemma 3.2 in Section 3.3. Therefore, we chose $\tau = 0.4$.



(a) $X_1(50)$, $\tau = 1$ (b) $X_2(50)$, $\tau = 1$

(c) $X_3(50)$, $\tau = 1$ (d) $X_5(50)$, $\tau = 1$

Fig. 8. Genetic loop example: comparison of probability distributions (10,000 sample trajectories) of $X_i(50)$ ($i = 1, 2, 3, 5$) obtained by the SSA (circle), LCLA (star), IMW-P (square), trapezoidal tau (triangle). Here $\tau = 1$ and $T = 50$.

We chose two different final times $T = 4$ and $T = 20$. The probability distributions obtained by the LCLA-τ and the CLA methods are shown in Fig. 9(a) and (b) for $T = 4$, and in Fig. 9(c) and (d) for $T = 20$. We note that the LCLA-τ method performs well in capturing the bimodal probability distribution. Table 6 shows that CLA also fails to compute the variance correctly while LCLA-τ performs better.

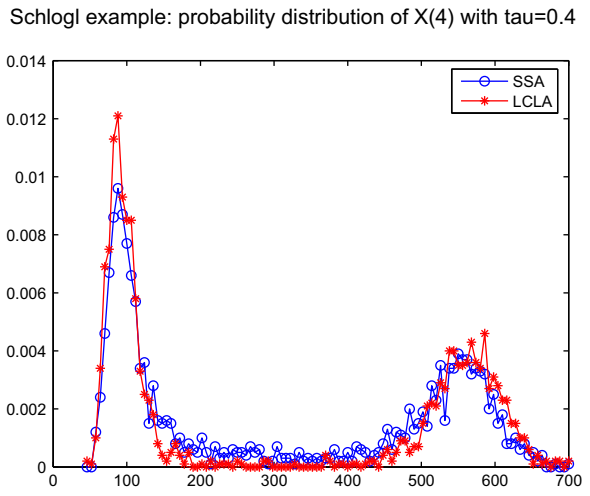
5.3.2. Toggle switch example

We consider the toggle switch model (39) proposed by Gardner et al. [30]. It consists of two proteins S and R and switches between two states. One state has large population for S and small population for R while the other has small population for S and large population for R.

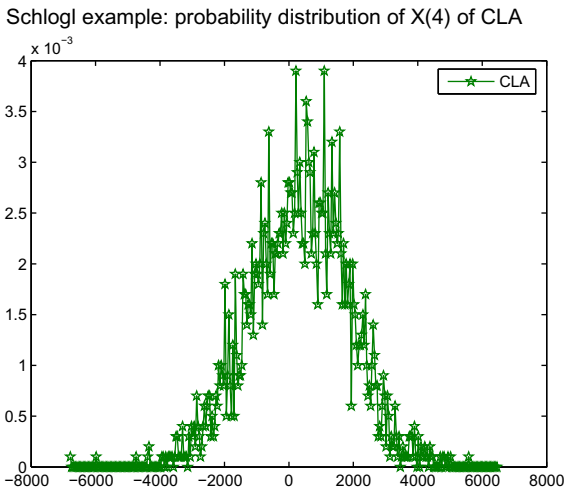
$$\begin{aligned} &(1)\ 0 \to R, \quad (2)\ R \to 0, \\ &(3)\ 0 \to S, \quad (4)\ S \to 0. \end{aligned} \tag{39}$$

The populations of R and S are denoted by X_1 and X_2 respectively. Thus the state is $X = (X_1, X_2)^T$. The system has Hill function like propensities, given by

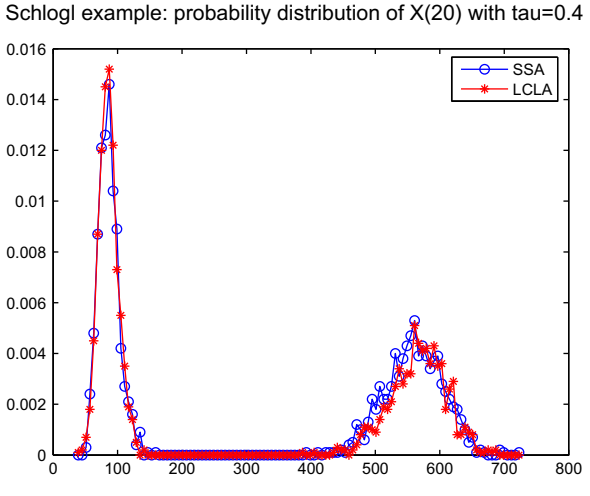
$$a_1(X) = \frac{\alpha_1}{1 + \frac{X_2^{2.5}}{200^{2.5}}}, \quad a_2(X) = X_1, \quad a_3(X) = \frac{\alpha_2}{1 + \frac{X_1}{200}}, \quad a_4 = X_2.$$



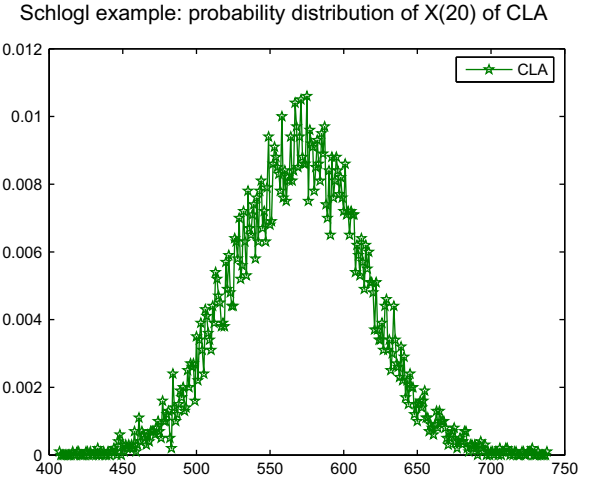
(a) $\tau = 0.4$, $T = 4$, LCLA



(b) $T = 4$, CLA



(c) $\tau = 0.4$, $T = 20$, LCLA



(d) $T = 20$, CLA

Fig. 9. Schlögl reactions: comparison of probability distributions (10,000 sample trajectories) of X obtained by SSA (circle), LCLA (star) and CLA (pentagram) methods. Here (a) is SSA and LCLA for $T = 4$, (b) is CLA for $T = 4$, (c) is SSA and LCLA for $T = 20$, and (d) is CLA for $T = 20$. Here $\tau = 0.4$ for all plots.

Table 6
Schlögl reactions: comparison of the variances computed from SSA, LCLA and CLA for $T = 4$ and $T = 20$.

Covariance	Methods		
	SSA	LCLA	CLA
$\mathrm{Var}(X)$, $T = 4$	4.7014×10^4	5.4323×10^4	2.3476×10^6
$\mathrm{Var}(X)$, $T = 20$	5.6602×10^4	5.8193×10^4	1.9499×10^3

Table 7
Schlögl reactions: comparison of estimated mean execution time for one trajectory (in s) between the SSA and LCLA methods on MATLAB platform.

	$T = 4$	$T = 20$
SSA	0.56	3.65
LCLA	0.0461	0.22

We chose $\alpha_1 = 10^4$, $\alpha_2 = 3200$, $X(0) = (200, 200)^T$, $T = 20$, and $\tau = 0.05$. The eigenvalues of the system at final time are given by $(-0.6353, -1.3647)^T$. We define the switch being in the OFF state when X_1 has a small population, and X_2 has a large population. Correspondingly for ON state, X_1 has a large population, and X_2 has a small population.

We compare the probability distribution for $X_1(20)$ and $X_2(20)$ in Fig. 10 with SSA, LCLA, and CLA methods. We observed that the copy numbers of X_1 widely range from 0 to 10,000 at $T = 20$. For the purpose of clarity, we show the OFF state and ON state for X_1 separately in plots (a) and (b). It can be seen from Fig. 10 that LCLA method is good in capturing both oscillating population states for X_1 and X_2, where as CLA only exhibits one of the oscillating states.

Table 8 shows that LCLA-τ is far more accurate in capturing the variances and the covariance than CLA.

We like to mention that it has been shown that the CLE does not always provide a good approximation to bimodal asymptotic distributions [31]. While we expect the LCLA-τ to be no more accurate than the CLE, in these two examples considered the agreement with SSA (CME) is quite good.

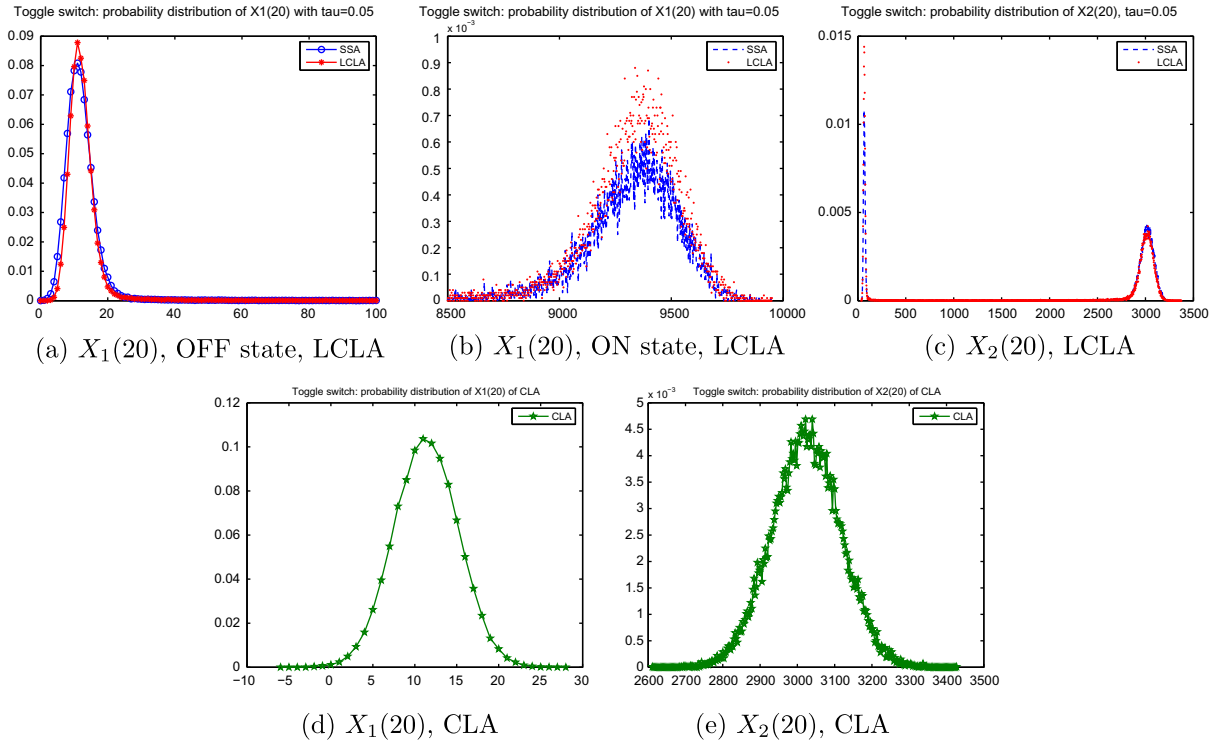


Fig. 10. Toggle switch example: comparison of probability distributions (10^5 sample trajectories) obtained by SSA (circle/dashed line), LCLA (star/dot), and CLA (pentagram). Here (a)–(b) are the distributions of OFF and ON states for X_1 obtained from LCLA, (c) is the distribution for X_2 obtained from LCLA, and (d)–(e) are distributions for X_1 and X_2 obtained from CLA. Here $X(0) = (200, 200)^T$, $T = 20$, and $\tau = 0.05$.

Table 8
Toggle switch example: comparison of the variances and covariances computed from SSA, LCLA and CLA for $T = 20$.

Covariance	Methods		
	SSA	LCLA	CLA
$\mathrm{Var}(X_1)$	1.5610×10^7	1.8489×10^7	0.0144×10^3
$\mathrm{Var}(X_2)$	0.1607×10^7	0.1866×10^7	8.5099×10^3
$\mathrm{Cov}(X_1, X_2)$	-0.4931×10^7	-0.5799×10^7	-0.2904×10^3

Table 9
Toggle switch example: comparison of estimated mean execution time for one trajectory (in s) between the SSA and LCLA methods on MATLAB platform.

SSA	4.82
LCLA	0.21

6. Conclusion

In this paper, we introduced a new tau leaping method called the LCLA-τ for the efficient simulation of stiff stochastic chemical systems with moderate molecular copy numbers. The method uses a *local central limit approximation* over each tau leaping step. A *split implicit step* is used to compute the mean update, a strategy which ensures that in the fluid limit the method behaves like the implicit Euler as applied to the fluid limit reaction rate equation (RRE). We provided (in Appendix A) a rigorous proof of this fluid limit which holds under certain reasonable assumptions for any tau leaping method that employs the split implicit step.

The local central limit approximations result in an ODE to be solved for the covariance. For numerical efficiency, we proposed to solve this ODE by the application of one time step (same as the tau leaping step) of a suitable low order scheme. We investigated several possible numerical schemes to compute this covariance and performed an absolute stability analysis of all the possible variants of the resulting LCLA-τ method. Based on this stability analysis one scheme emerged as the most suitable for stiff systems. Thus we adopted this scheme as part of our proposed LCLA-τ method.

We illustrated the resulting LCLA-τ method through several numerical examples and compared it with the SSA, IMW-τ and the trapezoidal tau methods. We demonstrated that LCLA-τ achieves better performance than these existing tau leaping methods for stiff systems with species in moderately large population numbers. In addition, for chemical systems with bistability the LCLA-τ was able to capture the resulting bimodal distribution, whereas a straightforward implementation of the central limit approximation always predicts a unimodal Gaussian distribution.

We also remark that the basic idea of the LCLA-τ can be applied to stiff stochastic differential equations driven by Brownian motion with a "small" diffusion term as the CLA can be effectively applied to such equations. For that purpose the stability analysis provided in this paper will need to be generalized to such systems.

Acknowledgements

We like to thank the anonymous reviewer for the comments that helped improve this manuscript.

Appendix A. Fluid limit of tau methods employing the split implicit step

The fluid limit described in Section 2.2 provides a good approximation when all molecular copy numbers are very large. The parameter V that is interpreted as the volume plays a critical role in the study of this limit. In practice, in many stochastic systems some species behave closer to the fluid limit (because of large molecular copy numbers) while other species exhibit behavior far from fluid limit. This *multiregime* behavior should be contrasted with the more familiar *multiscale* behavior in the form of stiffness that is often present in both ODE systems as well as stochastic systems.

When a tau leaping method is applied to a stochastic system a natural question that arises is whether the tau leaping method is effective in a multiregime and/or stiff situation. One may formulate the multiregime situation as follows. Given a family of suitably scaled systems $Z_V(t)$ indexed by V with propensities $a_j(x,V)$, denote the corresponding tau leaping solution with step size τ by $Z_V^\tau(t)$ over a time interval $[0,T]$. An ideal condition that ensures that the tau leaping method is effective uniformly across all regimes (characterized by V values) is that the error at the final time $Z_V^\tau(T) - Z_V(T)$ (measured in some suitable sense) is of order $O(\tau)$ *uniformly in* V.

Establishing such a uniform error bound is much harder than investigating the following related question: for the tau leaping solution, do the limits as $V \to \infty$ and $\tau \to 0$ commute? In other words does the following hold:

$$\lim_{V\to\infty} \lim_{\tau\to 0} Z_V^\tau(T) = \lim_{\tau\to 0} \lim_{V\to\infty} Z_V^\tau(T),$$

where the limits are taken in some suitable sense? If we assume the convergence of the tau leaping method (for each V) to the true solution $Z_V(T)$ then the above question is equivalent to asking whether the fluid limit $\lim_{V\to\infty} Z_V^\tau(T) = Z^\tau(T)$ of the tau leaping method corresponds to a convergent time stepping method for the fluid limit ODE.

For a nonstiff system an intuitive argument is presented in [3] which essentially asserts that in the large V limit the explicit tau behaves like explicit Euler applied to the fluid limit ODE. A similar intuitive reasoning has been used by Rathinam et al. [4] to assert that the implicit tau method in the fluid limit behaves like implicit Euler. However, a rigorous proof of these assertions has not been provided. In this appendix, we focus on the fluid limit of tau leaping methods that employ the split implicit step. Examples of such methods include the IMW-τ proposed in [7] and the LCLA-τ proposed in this paper.

In this appendix, we shall show that under suitable assumptions the fluid limit (τ fixed, $V \to \infty$) of any tau leaping method employing the split implicit step scheme is the implicit Euler method applied to the fluid limit RRE. We like to note that in contrast the analysis in [17] considers a limit where $V \to \infty$ while $\tau = V^{-\beta}$ scales inversely with V when applied to two specific explicit leaping methods.

Let us suppose a stochastic chemical system has M reaction channels and N molecular species. For each reaction channel j, we define nonnegative vectors $\mu_j', \mu_j \in \mathbb{Z}_+^N$, where μ_j is the vector whose ith component counts the number of molecules of ith species appearing as reactants in the reaction while μ_j' is the vector whose ith component counts the number of molecules of ith species appearing as products in the reaction. As an example, consider a two species system with a reaction channel j

given by $S_1 + S_1 \to S_1 + S_2$. Then $\mu_j = (2,0)^T$ and $\mu_j' = (1,1)^T$. We define $v_j = \mu_j' - \mu_j$ to be the stoichiometric vectors. Let us define the "combinations" function $k : \mathbb{Z}_+ \times \mathbb{Z}_+ \to \mathbb{Z}_+$ by

$$\begin{aligned} k(x,y) &= \frac{x!}{y!(x-y)!}, \quad y \leqslant x, \\ k(x,y) &= 0, \quad y > x. \end{aligned} \tag{40}$$

Thus $k(x,y)$ is the number of distinct ways to choose y items from x items. Note that $k(x,0) = 1$.

Volume dependence of propensity function

The key to the fluid limit is the form of volume dependence of the propensity functions. Denote the system volume by V. Let μ be the matrix with jth column μ_j. Then the *propensity function* a_j of reaction j is given by (see [19])

$$a_j(x,V) = c_j \frac{1}{V^{|\mu_j|-1}} \prod_{i=1}^{N} k(x_i, \mu_{ij}), \tag{41}$$

where $|\mu_j| = \mu_{1j} + \cdots + \mu_{Nj}$. Thus we obtain

$$a_j(x,V) = c_j \frac{1}{V^{|\mu_j|-1}} \prod_{i=1}^{N} \frac{x_i(x_i-1)\cdots(x_i-\mu_{ij}+1)}{\mu_{ij}!}. \tag{42}$$

Note that the derivation in [19] does not consider zero order reactions (i.e. reactions that involve no reactants) of the form $0 \to S_1$. But we assume that (42) also holds for zero order reactions. For such reactions $|\mu_j| = 0$ and above equation yields

$$a_j(x,V) = c_j V.$$

We define the concentration $Z(t) = \frac{X(t)}{V} \in \mathbb{R}_+^{\mathbb{N}}$ to be the number of species per volume. Introducing the change of variable $z = x/V$ in (42) and keeping z fixed and letting $V \to \infty$ (such that Vz remains integer), yields the asymptotic form

$$a_j(Vz,V) \sim V c_j \prod_{i=1}^{N} \frac{z_i^{\mu_{ij}}}{\mu_{ij}!}. \tag{43}$$

We define the *reaction rate* function $\bar{a}_j$ of reaction j by

$$\bar{a}_j(z) = \kappa_j \prod_{i=1}^{N} z_i^{\mu_{ij}} \tag{44}$$

where the *reaction rate* constant κ_j is related to the reaction propensity constant c_j by

$$\kappa_j = \frac{c_j}{\prod_{i=1}^{N} \mu_{ij}!}. \tag{45}$$

Now we state a Lemma that describes the asymptotic behavior of propensities and their derivatives.

Lemma 6.1. *For each fixed $V \geqslant 0$, let $z_V \in \mathbb{R}_+^N$, and suppose $z_V \to z \in \mathbb{R}_+^N$ as $V \to \infty$. We obtain that, as $V \to \infty$*

$$\frac{a_j(Vz_V, V)}{V} \to \bar{a}_j(z). \tag{46}$$

Moreover, as $V \to \infty$,

$$\frac{\partial a_j}{\partial x}(Vz_V, V) \to \frac{\partial \bar{a}_j}{\partial z}(z). \tag{47}$$

Proof. The results follow from (42) which shows a polynomial dependence of a_j on x. □

The fluid limit

Having established the $V \to \infty$ limit properties of the propensity functions, we are ready to study the fluid limit of the tau leaping method. Fix a step size $\tau > 0$, let us consider the application of L steps of step size τ of the split implicit step tau method starting with an initial state $x_0 = z_0 V$ for a system of volume $V \geqslant V_0$. Here V_0 is some given volume and z_0 is a fixed concentration. Let K_V^l for $l = 1, \ldots, L$ denote the reaction count vector updates at successive time steps. Let X_V^l for $l = 0, \ldots, L$ denote the successive states reached by the tau leaping method. Thus $X_V^l = X_V^{l-1} + vK_V^l$ for $l = 1, \ldots, L$ with $X_V^0 = z_0 V$. Let Z_V^l for $l = 0, \ldots, L$ denote the corresponding concentrations given by $Z_V^l = X_V^l / V$, noting that $Z_V^0 = z_0$ is independent of V. We shall show that under suitable assumptions, $Z_V^l \to \overline{Z}^l$ in L^2 for $l = 1, \ldots, L$, where $\overline{Z}^l$ for $l = 0, \ldots, L$ denote the implicit Euler solution of the RRE (4) with step size τ for the initial condition $\overline{Z}^0 = z_0$. Thus

$$\overline{Z}^l = \overline{Z}^{l-1} + v\bar{a}(\overline{Z}^l)\tau, \quad l = 1, \ldots, L.$$

We note that since $\overline{Z}^l$ are constants (nonrandom), the L^2 convergence of Z_V^l to $\overline{Z}^l$ is well-defined even if Z_V^l for different V are not defined on the same sample space. In what follows, we assume that for each V, there is a probability space $(\Omega_V, \mathscr{F}_V, P_V)$ on which X_V^l, Z_V^l and K_V^l are defined.

To aid the analysis of the implicit equation solved during the application of the implicit Euler step we define $g_V : \mathbb{R}^N \to \mathbb{R}^N$, where $\tau > 0$ is the fixed step size,

$$g_V(y) = y - \frac{va(yV, V)\tau}{V}, \tag{48}$$

and define $g : \mathbb{R}^N \to \mathbb{R}^N$ where

$$g(y) = y - v\bar{a}(y)\tau. \tag{49}$$

We make the following assumptions.

Assumption 1. Suppose V_0 is the volume of the given system. Suppose there exists a compact and convex set $U \subset \mathbb{R}^N$ such that for any $V \geqslant V_0$, the following holds:

1. g and g_V have unique inverse functions f and f_V on U.
2. $f(U) \subset U$ and $f_V(U) \subset U$.
3. f and f_V are C^1 on U.

We note that f_V and f are characterized implicitly by

$$f_V(y) = y + \frac{va(f_V(y)V, V)\tau}{V},$$

and

$$f(y) = y + v\bar{a}(f(y))\tau.$$

Thus the functions f_V and f describe the implicit Euler solution. Hence according to the split implicit step scheme Z_V^l and K_V^l satisfy the following relations:

$$E(K_V^l | Z_V^{l-1}) = a(f_V(Z_V^{l-1})V, V)\tau, \quad l = 1, 2, \ldots, L, \tag{50}$$

in addition to the update formula $Z_V^l = Z_V^{l-1} + v\frac{K_V^l}{V}$. Therefore it follows that

$$E(Z_V^l | Z_V^{l-1}) = f_V(Z_V^{l-1}), \quad l = 1, 2, \ldots, L. \tag{51}$$

Also $\overline{Z}^l$ satisfy the relations

$$\overline{Z}^l = f(\overline{Z}^{l-1}), \quad l = 1, 2, \ldots, L.$$

We state a Lemma that relates f_V to f.

Lemma 6.2. *For any $y \in U, f_V(y) \to f(y)$ as $V \to \infty$.*

Proof. The proof follows from standard arguments. Let V_n be an increasing sequence such that $V_n \to \infty$. For any $y \in U$, let $Y_{V_n} = f_{V_n}(y)$, and $\overline{Y} = f(y)$. By Assumption 1, Y_{V_n} has a convergent subsequence $Y_{V_{n_k}}$. Suppose $Y_{V_{n_k}} \to \widetilde{Y}$. Then $\widetilde{Y} \in U$. By Lemma 6.1, it follows that

$$\frac{a(V_{n_k} Y_{V_{n_k}}, V_{n_k})}{V_{n_k}} \to \bar{a}(\widetilde{Y}).$$

Since

$$Y_{V_{n_k}} = y + \frac{va(Y_{V_{n_k}} V_{n_k}, V_{n_k})\tau}{V_{n_k}},$$

it follows that $\widetilde{Y} = y + \tau v\bar{a}(\widetilde{Y})$. Hence by Assumption 1, we conclude that $\widetilde{Y} = \overline{Y}$.

Also by the same argument, it follows that every subsequence of Y_{V_n} has a subsequence that converges to $\overline{Y}$. By the "subsubsequence Lemma" it follows that Y_{V_n} converges to $\overline{Y}$. Thus we conclude that $\lim_{V_n \to \infty} Y_{V_n} = \overline{Y}$, namely, for any $y \in U, \lim_{V \to \infty} f_V(y) = f(y)$. □

Lemma 6.3. *The family $f_V : U \to U$, for $V \geqslant V_0$, is uniformly Lipschitz on U. In other words, there exists a finite constant $C > 0$ such that for all $V \geqslant V_0$, and all $y_1, y_2 \in U$,*

$$\|f_V(y_1) - f_V(y_2)\| \leqslant C\|y_1 - y_2\|.$$

Proof. For $y \in U$ and $V \in [V_0, \infty]$, we define $Q(V,y)$ by

$$\begin{aligned} Q(V,y) &= \left(\frac{\partial g_V(y)}{\partial y}\right)^T \frac{\partial g_V(y)}{\partial y}, \quad V \in [V_0, \infty), \\ Q(V,y) &= \left(\frac{\partial g(y)}{\partial y}\right)^T \frac{\partial g(y)}{\partial y}, \quad V = \infty. \end{aligned} \tag{52}$$

We note that $Q(V,y)$ is symmetric positive definite for $(V,y) \in [V_0,\infty] \times U$. Moreover $Q(V,y)$ is continuous on $[V_0,\infty] \times U$. This follows from the form of the propensity functions and by virtue of Lemma 6.1.

For $i = 1,\ldots,N$, let $\lambda^i(V,y)$ be the ith largest eigenvalue of $Q(V,y)$. Then $\lambda^i(V,y)$ is continuous on $[V_0,\infty] \times U$ for each i, by virtue of the eigenvalue perturbation theory in [32] (p. 551). Hence $\lambda^i(V,y)$ has a minimum value on $[V_0,\infty] \times U$ for each i, and this minimum value is strictly positive. In particular,

$$\gamma = \min\{\underset{\sim}{\lambda}(V,y) \,|\, (V,y) \in [V_0,\infty] \times U\} > 0,$$

where $\underset{\sim}{\lambda}(V,y)$ is the smallest eigenvalue of $Q(V,y)$.

For $y \in U$, $\frac{\partial f_V(y)}{\partial y} = \left(\frac{\partial g_V(y')}{\partial y}\right)^{-1}$, where $y' = f_V(y) \in U$. Hence

$$\left\| \frac{\partial f_V(y)}{\partial y} \right\|_2 = \left\| \left(\frac{\partial g_V(y')}{\partial y}\right)^{-1} \right\|_2 = \frac{1}{\sqrt{\underset{\sim}{\lambda}_V(y')}}.$$

Letting $C = 1/\sqrt{\gamma}$ and using the Mean Value Theorem we obtain the result. □

The following lemma is related to the application of one time step of the split implicit step scheme. In the lemma z_V and $\bar{z}$ may be thought of as the states at the beginning of the time step corresponding to the (stochastic) system with volume V and the fluid limit system respectively. Likewise Z_V and $\overline{Z}$ may be thought of as the updated states.

Lemma 6.4. *For $V \geqslant V_0$, let z_V and Z_V be $\mathbb{R}^N$ valued random variables carried by $(\Omega_V, \mathscr{F}_V, P_V)$. Further suppose z_V for $V \geqslant V_0$ take values in U and suppose as $V \to \infty$, $z_V \to \bar{z} \in U$ in L^2, where $\bar{z}$ is nonrandom. Let $\overline{Z} = f(\bar{z})$. Also suppose Z_V for $V \geqslant V_0$ satisfy the following:*

1. *$E(Z_V|z_V) - f_V(z_V) \to 0$ in L^2 as $V \to \infty$.*
2. *For each $i,j \in \{1,\ldots,N\}$, $\mathrm{Cov}(Z_V|z_V)_{i,j} \to 0$ in L^1 as $V \to \infty$.Then $Z_V \to \overline{Z}$ in L^2.*

Proof. First we shall show that $f_V(z_V) \to \overline{Z} = f(\bar{z})$ in L^2. Let $Z'_V = f_V(z_V)$. Then we may write,

$$(Z'_{Vi} - \overline{Z}_i)^2 = (f_V(z_V)_i - f(\bar{z})_i)^2 \leqslant 2(f_V(z_V)_i - f_V(\bar{z})_i)^2 + 2(f_V(\bar{z})_i - f(\bar{z})_i)^2 \leqslant 2C^2(z_{Vi} - \bar{z}_i)^2 + 2(f_V(\bar{z})_i - f(\bar{z})_i)^2, \quad \text{a.s.},$$

where subscript i stands for the ith component of a vector and C is the uniform Lipschitz constant from Lemma 6.3. Taking the expected value of the above inequality, we obtain

$$E((Z'_{Vi} - \overline{Z}_i)^2) \leqslant 2C^2E((z_{Vi} - \bar{z}_i)^2) + 2(f_V(\bar{z})_i - f(\bar{z})_i)^2.$$

As $V \to \infty$, $E((z_{Vi} - \bar{z}_i)^2) \to 0$ by assumption, and $f_V(\bar{z})_i - f(\bar{z})_i \to 0$ by Lemma 6.2. Thus $E((Z'_{Vi} - \overline{Z}_i)^2) \to 0$.

We define $w_V = E(Z_V|z_V) - f_V(z_V)$ and note that by our assumption $E((w_V)_i^2) \to 0$ as $V \to \infty$. By the definition of the conditional variance $\mathrm{Var}(Z_V - \overline{Z}|z_V)$, for $V \geqslant V_0$, it follows that

$$\begin{aligned} E((Z_{Vi} - \overline{Z}_i)^2|z_V) &= \mathrm{Var}(Z_{Vi} - \overline{Z}_i|z_V) + (E(Z_{Vi} - \overline{Z}_i|z_V))^2 = \mathrm{Var}(Z_{Vi}|z_V) + (Z'_{Vi} - \overline{Z}_i + w_{Vi})^2 \\ &\leqslant \mathrm{Var}(Z_{Vi}|z_V) + 2(Z'_{Vi} - \overline{Z}_i)^2 + 2(w_{Vi})^2, \quad \text{a.s.}. \end{aligned}$$

Taking expectation we obtain

$$E((Z_{Vi} - \overline{Z}_i)^2) \leqslant E(\mathrm{Var}(Z_{Vi}|z_V)) + 2E((Z'_{Vi} - \overline{Z}_i)^2) + 2E(w_{Vi})^2 \to 0, \quad \text{as } V \to \infty. \qquad \square$$

Finally we have the desired fluid limit in the following theorem.

Theorem 6.5. *Suppose L steps of a split implicit step tau method with fixed step size $\tau > 0$ is applied to a system with initial concentration $z_0 \in U$. Suppose that for each $l = 1,\ldots,L$, $Z_V^l \in U$ with probability 1 for all $V \geqslant V_0$. Further suppose that the following conditions hold for $l = 1,\ldots,L$:*

1. $E\left(\frac{K_V^l}{V}\middle|Z_V^{l-1}\right) - \frac{a(f_V(Z_V^{l-1})V,V)\tau}{V} \to 0$ *in* L^2 *as* $V \to \infty$.
2. *For each* $i,j \in \{1,\dots,M\}$, $\mathrm{Cov}\left(\frac{K_V^l}{V}\middle|Z_V^{l-1}\right)_{i,j} \to 0$ *in* L^1 *as* $V \to \infty$.*Then for* $l = 1,\dots,L$, $Z_V^l \to \overline{Z}^l$ *in* L^2 *as* $V \to \infty$.

Proof. The result follows from Lemma 6.4 using mathematical induction and the relationship $Z_V^l = Z_V^{l-1} + \frac{\nu K_V^l}{V}$. □

We like to remark that in Theorem 6.5 the assumption that $E\left(\frac{K_V^l}{V}\middle|Z_V^{l-1}\right) - \frac{a(f_V(Z_V^{l-1})V,V)\tau}{V} \to 0$ in L^2 is a relaxation of the relation in (50). This relaxation compensates for the restrictive assumption that for all l, Z_V^l takes values in U with probability 1. Assuming that the state Z_V^{l-1} at the beginning of the lth step is in U, one needs a mechanism to guarantee that the updated Z_V^l is in U with probability 1. One way to accomplish this is to bound K_V^l by an upper bound $\overline{K}_V$ which may be chosen based on the initial (deterministic) state $z_0 \in U$ as follows. Let R be the radius of the largest ball centered at z_0 and contained in U. Then set $\overline{K}_V = \frac{RV}{L\|\nu\|}$. Thus $\left\|K_V^l\right\| \leqslant \overline{K}_V$ implies that $\left\|Z_V^l - z_0\right\| \leqslant R$ for $l = 1,\dots,L$.

Fluid limit of the LCLA-τ

In this section we shall show that the LCLA-τ method described in Tables 1 and 2 in combination with the bounding procedure described below indeed satisfies the conditions 1 and 2 of Theorem 6.5 on the fluid limit.

Bounding procedure: At each time step l, generate tentative reaction count vectors H_V^l according to the LCLA-τ prescription. Then set actual reaction count vectors K_V^l as follows:

$$\begin{aligned} K_{Vj}^l &= -\overline{K}_V, \quad \text{if } H_{Vj}^l < -\overline{K}_V, \\ K_{Vj}^l &= H_{Vj}^l \quad \text{if } |H_{Vj}^l| \leqslant \overline{K}_V, \\ K_{Vj}^l &= \overline{K}_V, \quad \text{if } H_{Vj}^l > \overline{K}_V, \end{aligned} \tag{53}$$

where $l = 1,\dots,L$, $j = 1,\dots,M$ and $\overline{K}_V = \frac{RV}{L\|\nu\|}$ as mentioned before.

First we shall show that the conditional covariance $\widetilde{C}(V,z) = \mathrm{Cov}(H_V^l | Z_V^{l-1} = z)$ is $O(V)$ as $V \to \infty$. Recall that $\widetilde{C}(V,z)$ satisfies

$$\widetilde{C}(V,z)\left(A(V,z) - \frac{I}{2}\right)^T + \left(A(V,z) - \frac{I}{2}\right)\widetilde{C}(V,z) = -E(V,z), \tag{54}$$

where

$$A(V,z) = \frac{\partial a}{\partial x}(Vf_V(z),V)\nu\tau, \quad E(V,z) = \sum_{j=1}^{M} e_j e_j^T a_j(Vf_V(z),V)\tau.$$

Now from Lemmas 6.1 and 6.2 it follows that $A(V,z) \to \frac{\partial a}{\partial x}(f(z))\nu\tau = \overline{A}(z)$ and $E(V,z)/V \to \sum_{j=1}^{M} e_j e_j^T \bar{a}_j(f(z))\tau = \overline{E}(z)$.

Let us consider the following equation obtained as a limiting form of (54).

$$\overline{C}(z)\left(\overline{A}(z) - \frac{I}{2}\right)^T + \left(\overline{A}(z) - \frac{I}{2}\right)\overline{C}(z) = -\overline{E}(z). \tag{55}$$

Assumption 2. We shall assume that for all $z \in U$ and $V \geqslant V_0$ all eigenvalues of the matrix $A(V,z)$ as well the eigenvalues of $\overline{A}(z)$ have real part less than $1/2$.

From Assumption 2 and Lemma 3.2 it follows that $\widetilde{C}(V,z)$ and $\overline{C}(z)$ are uniquely defined. Furthermore since $\widetilde{C}(V,z)$ is uniquely defined implicitly via a linear equation, it follows that $\widetilde{C}(V,z)/V \to \overline{C}(z)$.

Now we shall verify both conditions 1 and 2 of Theorem 6.5.

Condition 1: Let us fix l. For $V \geqslant V_0$ and $z \in U$, let $G_j(V,z)$ be defined by

$$G_j(V,z) = E((K_{Vj}^l - H_{Vj}^l)^2 | Z_V^{l-1} = z).$$

Then one may write

$$G_j(V,z) = \int_{-\infty}^{-\overline{K}_V} (u + \overline{K}_V)^2 \frac{1}{\sqrt{2\pi v}} e^{-\frac{(u-m)^2}{2v}} du + \int_{\overline{K}_V}^{\infty} (u - \overline{K}_V)^2 \frac{1}{\sqrt{2\pi v}} e^{-\frac{(u-m)^2}{2v}} du,$$

where $m = a_j(Vf_V(z),V)\tau$ and $v = \widetilde{C}(V,z)_{j,j}$. Using the limiting properties of m and v one can establish that for each fixed z, $G_j(V,z)/V^2 \to 0$ as $V \to \infty$. Additionally $G_j(V,z)/V^2$ is continuous for $(V,z) \in [V_0,\infty] \times U$ and thus it is bounded on that set. Since $Z_V^{l-1} \in U$ with probability 1, it follows from dominated convergence that $G_j(V,Z_V^{l-1})/V^2 \to 0$ in L^1 as $V \to \infty$.

We may write

$$\left(E\left(\frac{K_{Vj}^l}{V}\middle|Z_V^{l-1}\right) - \frac{a_j(Vf_V(Z_V^{l-1}),V)\tau}{V}\right)^2 = \left(E\left(\frac{K_{Vj}^l}{V}\middle|Z_V^{l-1}\right) - E\left(\frac{H_{Vj}^l}{V}\middle|Z_V^{l-1}\right)\right)^2 \leqslant \frac{1}{V^2}E((K_{Vj}^l - H_{Vj}^l)^2 | Z_V^{l-1}) = G_j(V,Z_V^{l-1})/V^2.$$

From this condition 1 follows.

Condition 2: It follows from the preceding discussions that

$$\mathrm{Cov}\left(\frac{H_V^l}{V}|Z_V^{l-1}=z\right)=\frac{\tilde{C}(V,z)}{V^2}\to 0,\quad \text{as } V\to\infty.$$

Using basic inequalities we may obtain

$$\left|\frac{K_{Vj}^l}{V}-E\left(\frac{K_{Vj}^l}{V}\middle|Z_V^{l-1}=z\right)\right|^2\leqslant 3\left|\frac{K_{Vj}^l}{V}-\frac{H_{Vj}^l}{V}\right|^2+3\left|\frac{H_{Vj}^l}{V}-E\left(\frac{H_{Vj}^l}{V}\middle|Z_V^{l-1}=z\right)\right|^2+3\left|E\left(\frac{H_{Vj}^l}{V}\middle|Z_V^{l-1}=z\right)-E\left(\frac{K_{Vj}^l}{V}\middle|Z_V^{l-1}=z\right)\right|^2.$$

Taking conditional expectation of both sides by conditioning on $Z_V^{l-1}=z$ we see that the terms on the right hand side tend to zero as $V\to\infty$ for each $z\in U$ and hence so does the term on the left. Thus for each $z\in U$, $\mathrm{Var}\left(\frac{K_{Vj}^l}{V}\middle|Z_V^{l-1}=z\right)\to 0$ as $V\to\infty$. As before using the continuity of $\mathrm{Var}\left(\frac{K_{Vj}^l}{V}\middle|Z_V^{l-1}=z\right)$ in (V,z) we can establish that it is bounded as a function of $(V,z)\in[V_0,\infty]\times U$. Since $Z_V^{l-1}\in U$ with probability 1, by dominated convergence it follows that $\mathrm{Var}\left(\frac{K_{Vj}^l}{V}\middle|Z_V^{l-1}\right)\to 0$ in L^1.

When $i\neq j$, it follows that,

$$E\left|\mathrm{Cov}\left(\frac{K_V^l}{V}\middle|Z_V^{l-1}\right)_{ij}\right|\leqslant E\left(\sqrt{\mathrm{Var}\left(\frac{K_{Vi}^l}{V}\middle|Z_V^{l-1}\right)\mathrm{Var}\left(\frac{K_{Vj}^l}{V}\middle|Z_V^{l-1}\right)}\right)\leqslant\left\{E\left(\mathrm{Var}\left(\frac{K_{Vi}^l}{V}\middle|Z_V^{l-1}\right)\right)\right\}^{\frac{1}{2}}\left\{E\left(\mathrm{Var}\left(\frac{K_{Vj}^l}{V}\middle|Z_V^{l-1}\right)\right)\right\}^{\frac{1}{2}}\to 0.$$

Therefore condition 2 holds.

We remark that the bounding procedure described above was not used in our numerical simulations. It merely serves as a conceptual tool in establishing the fluid limit. We also remark that to our knowledge a rigorous demonstration that a tau leaping method converges to some suitable discretization of the fluid limit RRE of the stochastic model has not appeared before. While the result seems intuitive, the proof in the case of implicit methods is nontrivial as we have seen here.

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