CONVERGENCE OF MOMENTS OF TAU LEAPING SCHEMES FOR UNBOUNDED MARKOV PROCESSES ON INTEGER LATTICES

MURUHAN RATHINAM*

Abstract. Tau leap schemes were originally designed for the efficient time stepping of discrete state and continuous in time Markov processes arising in stochastic chemical kinetics. Previous convergence results on tau leaping schemes have been restricted to systems that remain in a bounded subdomain (which may depend on the initial condition) or satisfy global Lipschitz conditions on propensities. This paper extends the convergence results to fairly general tau leap schemes applied to unbounded systems that possess certain moment growth bounds. Specifically, we prove a weak convergence result, which shows order q convergence of all moments under certain form of moment growth bound assumptions on the stochastic chemical system and the tau leap method, as well as polynomial bound assumption on the propensity functions. The results are stated for a general class of Markov processes with $\mathbb{Z}^N$ as their state space.

Key words. Stochastic chemical kinetics, tau leaping, error analysis.

AMS subject classifications. 60H35, 65C30.

1. Introduction. The well stirred model of a chemical system as a continuous time Markov process with state space $\mathbb{Z}_+^N$ has been known for several decades [11, 12, 14]. Exact simulation of sample paths of such processes is very simple and is commonly known as the SSA (abbreviation for Stochastic Simulation Algorithm) or the Gillespie algorithm [12]. Stochastic chemical models have become important in applications in intracellular mechanisms and these models often possess some species in small molecular copy numbers as well as a range of time scales in addition to nonlinear propensity functions. Hence approximations of the whole system by ordinary differential equations (ODEs) or even stochastic differential equations (SDEs) driven by Brownian motion is often not valid. On the other hand the SSA is often prohibitively expensive. Tau leaping methods were proposed as efficient but approximate alternatives to the SSA simulations.

While the exact simulation (SSA) accounts for reaction events one at a time, the tau leap methods take a predetermined time step and then provide an approximation of the random state at the end of the time step using some criterion. Thus tau leap simulation of sample paths are akin to time stepping methods for ordinary differential equations (ODEs) and stochastic differential equations (SDEs) driven by Brownian motion. The first tau leap method was proposed by Gillespie [13] and is now known as the explicit tau leap method. This is in spirit the same as the explicit Euler method for ODEs. The implicit tau leap method was introduced in [20] and the trapezoidal tau leap method may be found in [5]. Several other tau leap methods have been proposed in the literature since then, see [27] for instance and references therein.

1.1. Previous error analyses of tau leap methods. As tau leap methods are analogous to the time stepping methods for SDEs (driven by Brownian motion) and ODEs, the question of convergence is a natural one, where convergence is studied for a fixed time interval $[0, T]$ with mesh size $\max(t_{j+1} - t_j) \to 0$ where $0 = t_0 < t_1 < \cdots < t_n = T$ is the mesh used by the time stepping method. However, unlike the case of ODEs and SDEs, exact simulation is possible in the case of discrete state

* Mathematics and Statistics, University of Maryland Baltimore County, 1000 Hilltop Circle, Baltimore, MD 21250, muruhan@umbc.edu, Ph 410-455-2423, Fax 410-455-1066. This research was supported in part by grant NSF DMS-0610013.

(continuous in time) Markov processes because the state of the process changes via discrete events happening in continuous time. This means that if the step size of the tau leap method is very small one may expect on average no more than one event to occur during a time step, and hence the tau leap will no longer be more efficient than the exact simulation method! This fact has lead to interesting discussions and analyses.

It was first shown in [18] that both the explicit and the implicit tau methods are first order convergent in all moments for systems that remain in a bounded region (which may depend on the initial condition) of the state space under the assumption of linear propensity functions. It was later proven in [23] that under the same bounded domain assumption but for general (nonlinear) propensity functions that the explicit tau method is first order convergent in moments as well as order $1/2$ convergent in a strong sense. Weak error analysis of explicit tau leap method with a "Poisson bridge" interpolation was provided in [2].

It must be noted that in the literature on numerical methods for stochastic dynamical systems the terms *strong error* and *weak error* are used in a slightly different sense from that of functional analysis. Strong error refers to the error $\hat{X}(t) - X(t)$ between the numerical approximation $\hat{X}$ of the process X usually measured in the $L_1(\Omega, \mathcal{F}, \mathrm{Prob}))$ or $L_2(\Omega, \mathcal{F}, \mathrm{Prob})$ sense where $(\Omega, \mathcal{F}, \mathrm{Prob})$ is the common probability space which carries both the process X as well as its approximation $\hat{X}$. In the context of continuous time Markov processes on $\mathbb{Z}^N$ it is not always easy to find a good coupling of X and $\hat{X}$ (unless one derives the method $\hat{X}$ starting from a stochastic equation for instance with the aid of the random time change representation [10] or with the aid of *Poisson random measures* [23]) and there may be different ways to couple X and $\hat{X}$ leading to potentially different strong errors. Often one is interested in the error between the distribution of $X(t)$ and $\hat{X}(t)$. In particular for a function $f : \mathbb{Z}^N \to \mathbb{R}$ one considers the error $E(f(\hat{X}(t))) - E(f(X(t)))$. This form of error analysis is termed *weak error* analysis. Usually f is taken to be a bounded function on $\mathbb{Z}^N$ following the standard notion of *weak convergence* of probability measures [10]. When the process X as well as the numerical scheme $\hat{X}$ remain in a bounded subset of $\mathbb{Z}^N$ no assumption on f is needed. However, it must be noted that when the process X is not bounded and f is taken to be a polynomial of degree higher than 2, strong L_2 convergence will require additional regularity conditions in order to imply the convergence of $E(f(\hat{X}(t)))$ to $E(f(X(t)))$.

When the molecular copy numbers are large, the stochastic chemical model may be well approximated by the reaction rate ODEs [13]. This behavior is known as the *thermodynamic limit* in the applied sciences literature where one considers starting with the initial number of molecular copy numbers and the corresponding system volume, and then envisages a sequence of systems obtained by multiplying the initial copy numbers as well as the system volume by an integer N and considering the behavior as $N \to \infty$. In order to obtain a limit, one must rescale the process by N and additionally a specific form of dependence of the propensities (probabilistic form of reaction rates) on the system volume is critical for this limiting behavior to occur. This specific form of volume dependence or more abstractly "system size" dependence occurs commonly in many real world systems including stochastic chemical kinetics and is referred to as *density dependence* in the works of T.G. Kurtz where a rigorous proof of the limit is also provided, see [10] for instance.

A natural question is how does a tau leap method behave when the system size becomes large. Some tau leap methods resemble higher order numerical schemes for

ODEs while the other tau leap methods resemble lower order schemes. This has motivated researchers to incorporate system size into the error analysis of tau leap methods. The first such analysis appeared in [7] where the analysis investigates the explicit tau method as well as the midpoint tau method. In particular the error analysis is carried out under the setting where the step size τ is related to system size V in the form of $\tau = V^{-\beta}$. This analysis is able to explain why when system size is sufficiently large the midpoint tau method performs better than the explicit tau method. This analysis is also able to explain why tau leap methods are effective while still leaping over several reaction events, when system size is sufficiently large. A system size dependent weak error analysis also appears in [24] where a rooted directed graph representation is developed for weak Taylor expansions. A weak error analysis under more general form of scaling with system size for general tau leap methods is presented in [8]. A related result shows that a large class of split step implicit tau leap methods limit to the implicit Euler scheme in the large volume limit while step size τ is fixed [26].

All convergence results for tau leap methods mentioned above [18, 23, 2, 7, 8, 24] effectively apply only to systems that remain in a bounded domain. In particular the Lipschitz or bounded derivative assumptions on propensity functions are only valid for either systems with linear propensity functions or systems that remain in a bounded domain. While closed chemical systems satisfy the boundedness assumption due to conservation of atoms, in practice the assumption of a closed system is restrictive. Several models of biochemical systems have production of chemical species captured by reactions that may be described abstractly in the form $S \to S + A$.

Related but different error analyses of time stepping methods for stochastic processes with jumps may be found in [9, 19, 1] to mention a few. These articles are concerned with stochastic equations driven by Brownian motion and Poisson random measures. The first two works [9, 19] consider fairly general jump processes but assume coefficient functions to be globally Lipschitz or possess bounded derivatives. The work in [1] proves convergence of moments under the less restrictive one-sided Lipschitz condition on the drift coefficient but nevertheless assumes global Lipschitz condition on the coefficients corresponding to the Brownian and Poisson processes. Moreover the Poisson process considered has fixed intensity. None of these results are applicable to the chemical kinetic models with nonlinear propensities when the system is unbounded.

1.2. Error analysis in this work. The important feature of the weak convergence result proved in this paper is that it does not assume boundedness of the system and moreover in the error $E(f(\hat{X}(t))) - E(f(X(t)))$ the function f need not be bounded, but is assumed to satisfy a polynomial growth bound. A form of moment growth bound (as a function of time) is assumed on the process X and one may find sufficient conditions in [16, 22, 3] that ensure such bounds. The result applies to any tau leap method provided that it yields integer valued states, satisfies similar moment growth bound conditions as the chemical system, possesses pointwise local error of order $q+1$ and in addition satisfies certain bounds on the time derivative of moments. The analysis technique does not differentiate between explicit or implicit methods and applies to both provided they satisfy above conditions. The convergence proof does not apply to the (unrounded) implicit tau for instance since it yields noninteger states. However, it applies to split step implicit methods such as those in [27].

The proof technique involves establishing consistency and uniform boundedness (or zero stability) of the method in a certain family of norms and related metrics in

the space of probability measures on a finite dimensional integer lattice which possess finite moments of all orders. Thus the proof is more in the spirit of the proof technique for ODEs though the spaces are infinite dimensional. It must be noted that the notion of *zero stability* (see [4] for instance) of a numerical scheme is an important concept. Essentially any sensible numerical scheme closely approximates the exact process over one time step τ which is sufficiently small. But as $\tau \to 0$, the number of steps over a finite interval $[0, T]$ increases to ∞, and zero-stability requires that the numerical scheme is well behaved (uniformly bounded) under this situation.

The analysis in this paper does not consider scaling with system size into account as is done in [7, 8]. For the analysis in this paper, the system size V is fixed while step size τ approaches zero. There has been some debate about which type of analysis is better or even "correct". In other words, whether the step size τ should be taken as a function of system size parameter V, typically in the form of $\tau = V^{-\beta}$, and study the limiting behavior as $V \to \infty$, or following the more conventional analysis (where V is fixed), study the limiting behavior as $\tau \to 0$. While the system size analysis provides valuable insights, a serious criticism of taking step size τ as a function $\tau = V^{-\beta}$ of V is that the quantity V is a given and not under the control of the user, while the step size τ is. Thus halving the step size τ to "check for convergence" will not be captured by this type of analysis. A good discussion highlighting the benefits of both types of analysis may be found in [24] and we agree with the sentiments expressed there in that both types of analysis are relevant.

Regarding the importance of fixed V analysis, it must be emphasized that if a tau leap method is not zero stable or not convergent then the user is potentially operating on a shaky ground. To put this another way, when using a zero stable method a practitioner only needs to worry about whether τ is small enough when it comes to accuracy issues. On the other hand if the practitioner uses a method that is not zero stable (s)he has to worry about whether τ is large enough as well as small enough, a very unsettling situation! Thus we believe that this form of convergence (or at least zero stability) is necessary and that the analysis represents an important improvement over previous results in that it accommodates unbounded systems with nonlinear propensities.

1.3. Outline of the paper. The rest of the paper is organized as follows. Section 2 deals with mathematical preliminaries and proves some results which are relevant for the convergence proof. Section 3 presents the convergence proof. Section 4 provides some results on the verification of the assumptions that underly the convergence proof. Second part of Section 4 specifically considers tau leap methods using Poisson and binomial updates which are common to most tau leap methods. Section 5 provides some concluding remarks.

2. Mathematical setup and preliminaries.

2.1. Chemical process and tau leap approximation. We shall be concerned with continuous time Markov chains that take values on the state space $\mathbb{Z}^N$ that have certain specific structure. The origin of this structure comes from stochastic models of chemical kinetics where N different molecular species undergo M different reaction channels, and hence our rationale for the term *chemical process*. The state of a stochastic chemical process is an N dimensional (nonnegative) integer vector such that the ith component of the vector stands for total the number of molecules of the ith species. The specific structure dictates that for any given state $x \in \mathbb{Z}_+^N$ there are at most M other states that the process can jump to and the possible jump sizes are

independent of the state x and time t. These jump sizes are *stoichiometric vectors* $\nu_1, \ldots, \nu_M \in \mathbb{Z}^N$ which correspond to the M different reaction channels. Associated with each stoichiometric vector ν_j there is a jump rate or *propensity* (in the chemical kinetics terminology) $a_j(x)$ which in general is a function of the state x. We define $a_0(x)$ by $a_0(x) = \sum_{j=1}^{M} a_j(x)$. In our general result in Section 3 we consider the slightly more general (than the chemical kinetic systems) case where the state space is $\mathbb{Z}^N$. In Section 4 we mostly specialize to the case of non-negative state space.

Given $N, M \in \mathbb{N}$, *stoichiometric vectors* $\nu_1, \ldots, \nu_M \in \mathbb{Z}^N$, and *propensity functions* $a_j : \mathbb{Z}^N \to \mathbb{R}$ for $j = 1, \ldots, M$, we define the associated *chemical process* $X(t)$ for $t \in [0, \infty)$ to be a $\mathbb{Z}^N$ valued Markov process which only admits jump sizes $\nu_1, \ldots, \nu_M \in \mathbb{Z}^N$ with corresponding intensities $a_j(x)$ for $j = 1, \ldots, M$. This means that given $X(t) = x$, the waiting time for the next jump event is exponentially distributed with rate $a_0(x)$ and the probability that the next jump is of size ν_j is $a_j(x)/a_0(x)$. We shall consider the version of $X(t)$ that has right continuous paths with left hand limits (known as *cadlag*). We shall only be concerned with chemical processes that are *non-explosive*, i.e. do not have infinitely many jumps in any finite time interval.

Given a chemical process $X(t)$ with N species and M reaction channels, we may define the transition probabilities $P : [0, \infty) \times \mathbb{Z}^N \times \mathbb{Z}^N \to \mathbb{R}$ by

$$P(\tau, x, x') = \text{Prob}\{X(t + \tau) = x' \,|\, X(t) = x\}. \tag{2.1}$$

By the non-explosivity assumption, it follows that for each $\tau \geq 0$, we have

$$\sum_{x' \in \mathbb{Z}^N} P(\tau, x, x') = 1.$$

For each $\tau \geq 0$, $P(\tau, x, x')$ is an infinite matrix indexed by $x, x' \in \mathbb{Z}^N$.

Throughout this paper we shall be concerned with infinite matrices indexed by $\mathbb{Z}^N$, i.e. functions $\psi : \mathbb{Z}^N \times \mathbb{Z}^N \to \mathbb{R}$. Such a matrix ψ may be naturally regarded also as a linear operator ψ from a subspace of $\mathbb{R}^{(\mathbb{Z}^N)}$ into $\mathbb{R}^{(\mathbb{Z}^N)}$ by the prescription that given $g \in \mathbb{R}^{(\mathbb{Z}^N)}$ we define $\psi\, g \in \mathbb{R}^{(\mathbb{Z}^N)}$ by the matrix vector multiplication (in reverse order)

$$(\psi\, g)(y) = \sum_{x \in \mathbb{Z}^N} \psi(x, y) g(x),$$

provided the sum converges absolutely. Given two operators (matrices) ψ_1, ψ_2 the "product" notation $\psi_1 \psi_2$ shall mean the composition $\psi_1 \circ \psi_2$ of operators which is also given by the matrix multiplication in *reverse order*

$$(\psi_1 \psi_2)(x, x') = \sum_{y \in \mathbb{Z}^N} \psi_1(y, x') \psi_2(x, y),$$

again when the sum above converges absolutely. Given such an operator ψ we denote by $|\psi|$ the function $(x, x') \mapsto |\psi(x, x')|$ and like wise given a function $g \in \mathbb{R}^{(\mathbb{Z}^N)}$ we denote by $|g|$ the function $x \mapsto |g(x)|$.

Since there are only finitely many jumps out of each state, the time evolution of $P(\tau)$ satisfies the Kolmogorov's forward equation

$$P^{(1)}(\tau, x, x') = \sum_{j=1}^{M} \left(P(\tau, x, x' - \nu_j) a_j(x' - \nu_j) - P(\tau, x, x') a_j(x') \right). \tag{2.2}$$

Let us define $Q : \mathbb{Z}^N \times \mathbb{Z}^N \to \mathbb{R}$ by

$$\begin{aligned} Q(x,x') &= a_j(x), \quad \text{if } x' = x + \nu_j, \\ Q(x,x') &= -a_0(x), \quad \text{if } x' = x, \\ Q(x,x') &= 0, \quad \text{otherwise.} \end{aligned} \tag{2.3}$$

Thus we may write (2.2) as

$$P^{(1)}(\tau, x, x') = \sum_{y \in \mathbb{Z}^N} Q(y, x') P(\tau, x, y),$$

and this may be compactly written in operator notation as

$$P^{(1)}(\tau) = Q\, P(\tau). \tag{2.4}$$

When regarded as an operator on $l_1(\mathbb{Z}^N; \mathbb{R})$, Q is known as the *generator* of the semigroup $P(\tau)$. It must be noted that Q is an unbounded operator and its domain is not all of $l_1(\mathbb{Z}^N; \mathbb{R})$. The above operator equation holds on the domain of both sides. Since the sum on the righthand side of (2.2) involves finitely many terms, we may differentiate it arbitrary number of times. In operator notation we obtain that for $q \in \mathbb{Z}_+$,

$$P^{(q)}(\tau) = Q^q\, P(\tau). \tag{2.5}$$

We note that Q^q is well defined as a function on $\mathbb{Z}^N \times \mathbb{Z}^N$ or an infinite matrix since any given row or column of Q has only finitely many nonzero entries and hence q-fold multiplication of Q is well defined.

Given a chemical process X let $R(t) \in \mathbb{Z}_+^M$ denote the vector of reaction counts during $(0, t]$; in other words, for $j = 1, \ldots, M$, $R_j(t)$ is the number of times reaction channel j fires during $(0, t]$. If $X(t) = x$ then $X(t + \tau) = x + \nu(R(t + \tau) - R(t))$. For given x and τ, the conditional distribution (conditioned on $X(t) = x$) of the random variable $R(t+\tau) - R(t)$ (which depends only on x and τ) is in general not known and hence it is difficult to generate a sample from. A tau leap method typically provides an approximation of the conditional distribution of $R(t + \tau) - R(t)$ given $X(t) = x$ by an easily computable random variable K whose distribution depends on x and τ and thus also provides an approximation for the distribution of $X(t + \tau)$ by that of $x + \nu K$.

In a very general sense, given (current) state $x \in \mathbb{Z}^N$ and a time step $\tau > 0$ a *tau leap method* assigns an (approximate) probability mass function for the state x' after elapsed time τ. Thus we take the view point that a tau leap method is uniquely characterized by a map $\phi : [0, \infty) \times \mathbb{Z}^N \times \mathbb{Z}^N \to \mathbb{R}$ where $\phi(\tau, x, x')$ is the probability assigned to state x'.

We shall define a *mesh* Π on $[0, T]$ to be a finite length sequence $\Pi = (t_0, \ldots, t_n)$ that satisfies $0 = t_0 < t_1 < \cdots < t_{n-1} < t_n = T$. We shall define step sizes associated with Π to be $\tau_j = t_j - t_{j-1}$ for $j = 1, \ldots, n$ and we shall denote the maximum step size $\max\{\tau_1, \ldots, \tau_n\}$ by $|\Pi|$. Given a tau leap method ϕ and a mesh $\Pi = (t_0, \ldots, t_n)$ on $[0, T]$ the *tau leap solution* $Y_\Pi(t)$ for $t \in [0, T]$ corresponding to initial condition $x_0 \in \mathbb{Z}^N$ is defined to be the stochastic process which is constant on $[t_{j-1}, t_j)$ for $j = 1, \ldots, n$ (thus jumps at $t_1, \ldots, t_n$), satisfies $Y_\Pi(0) = x_0$ and also satisfies

$$\phi(\tau_j, x, x') = \text{Prob}\{Y_\Pi(t_j) = x' \,|\, Y_\Pi(t_{j-1}) = x\}, \quad j = 1, \ldots, n. \tag{2.6}$$

Note that the tau leap solution $Y_\Pi(t)$ on any given mesh Π is also a Markov process, but it is not time homogeneous since the family $\phi(\tau)$ does not possess the semigroup property with respect to the time parameter τ.

We note that elements of $l_1(\mathbb{Z}^N;\mathbb{R})$ may be regarded as signed finite measures on $\mathbb{Z}^N$ and denote by $\mathcal{P}$ the set of all probability measures on $\mathbb{Z}^N$. We finally note that for each $\tau \geq 0$, the operators (or infinite matrices) $P(\tau)$ and $\phi(\tau)$ (which we call the *transition functions* of the process and the tau leap method respectively) have induced norm equal to 1 (on $l_1(\mathbb{Z}^N;\mathbb{R})$) and moreover they leave $\mathcal{P}$ invariant, i.e. map probabilities to probabilities.

2.2. Total variation, moment variation, spaces $\mathcal{M}$ and $\mathcal{C}$. In this section we define some spaces that shall play an important role in our convergence study. We remark up front that the spaces defined here are weighted l_1 spaces and their duals. Related but different spaces (weighted l_2 and related discrete Sobolev spaces) were developed in [21] for the spectral approximation of the solution of equation (2.2).

First we recall the *total variation* norm. Given two signed finite measures g_1 and g_2 on $\mathbb{Z}^N$ the total variation between g_1 and g_2 is given by the 1-norm distance

$$\|g_1 - g_2\|_1 = \sum_{x\in\mathbb{Z}^N} |g_1(x) - g_2(x)|.$$

Throughout this paper we shall use $|.|$ to denote a norm on $\mathbb{R}^N$. For each $r \in \mathbb{Z}_+$ we shall define the rth *moment variation* $|.|_r$ on $l_1(\mathbb{Z}^N;\mathbb{R})$ by

$$|g|_r = \sum_{x\in\mathbb{Z}^N} \frac{1}{2}\,(1+|x|^r)|g(x)| \leq \infty, \tag{2.7}$$

for all $g \in l_1(\mathbb{Z}^N;\mathbb{R})$. We define the subspaces $\mathcal{M}_r \subset l_1(\mathbb{Z}^N;\mathbb{R})$ for $r \in \mathbb{Z}_+$ by

$$\mathcal{M}_r = \{g \in l_1(\mathbb{Z}^N;\mathbb{R}) \mid \ |g|_r < \infty\} \tag{2.8}$$

and $\mathcal{M}$ by $\mathcal{M} = \bigcap_{r\in\mathbb{Z}_+} \mathcal{M}_r$. It follows that $|.|_r$ is a norm on $\mathcal{M}_r$ for each $r \in \mathbb{N}$ and when $r = 0$, $|.|_0$ is the total variation norm or equivalently the 1-norm ($\mathcal{M}_0 = l_1(\mathbb{Z}^N;\mathbb{R})$). We note that $\mathcal{M}_r$ equipped with $|.|_r$ norm is a Banach space isometrically isomorphic to l_1, the space of summable sequences. To see this let $\xi : \mathbb{N} \to \mathbb{Z}^N$ be a bijection. Define $\eta : \mathcal{M}_r \to l_1$ by

$$\eta(g)(n) = g(\xi(n))(1+|\xi(n)|^r)/2.$$

It is straightforward to verify that η is an isometric isomorphism.

It must also be noted that $\mathcal{M}_r$ includes all probability measures which have a finite rth moment and $\mathcal{M}$ includes all probability measures that have finite moments of all orders.

REMARK 2.1. *Due to the equivalence of norms on $\mathbb{R}^N$, two different norms $|.|_r$ arising from two different norms on $\mathbb{R}^N$ are equivalent.*

We state the following lemma which will be used frequently throughout this paper.

LEMMA 2.2. *For $0 < r_1 < r_2$ there exists α such that*

$$|g|_{r_1} \leq \alpha |g|_{r_2},$$

for all $g \in \mathcal{M}$.

Proof. The set of $x \in \mathbb{Z}^N$ for which $|x| < 1$ is finite. Thus there exists α such that $|x|^{r_1} \le \alpha |x|^{r_2}$ for all $x \in \mathbb{Z}^N$. □

COROLLARY 2.3. *For $r \in \mathbb{Z}_+$, $\mathcal{M}_{r+1} \subset \mathcal{M}_r$.*

The main convergence results in this paper are obtained under the assumption that the propensity functions are at most of polynomial growth. We define classes $\mathcal{C}_r$ and $\mathcal{C}$ to make this concept precise and prove some important results concerning the generator Q under the polynomial growth assumption on propensities. In particular we show that under polynomial growth assumption on propensities, Q maps $\mathcal{M}$ into $\mathcal{M}$.

For each $r \in \mathbb{Z}_+$ the class $\mathcal{C}_r$ of functions $f : \mathbb{Z}^N \to \mathbb{R}$ that are said to be of *polynomial growth* of degree r are defined by the condition that $f \in \mathcal{C}_r$ if and only if there exists $\alpha > 0$ such that

$$|f(x)| \le \alpha(|x|^r + 1), \quad \forall x \in \mathbb{Z}^N.$$

We define the class $\mathcal{C}$ by $\mathcal{C} = \cup_{r \in \mathbb{Z}_+} \mathcal{C}_r$.

It is easy to see that for each $r \in \mathbb{Z}_+$, $\mathcal{C}_r$ is a Banach space when equipped with the norm that is given by

$$\|f\| = \sup\{2f(x)/(1 + |x|^r) \,|\, x \in \mathbb{Z}^N\},$$

for $f \in \mathcal{C}_r$. Moreover, $\mathcal{C}_r$ can be naturally identified with the dual $\mathcal{M}_r^*$ of $\mathcal{M}_r$ with the pairing given by

$$\langle f, g \rangle = \sum_{x \in \mathbb{Z}^N} f(x) g(x),$$

where $f \in \mathcal{C}_r$ and $g \in \mathcal{M}_r$.

LEMMA 2.4. *Suppose $f : \mathbb{Z}^N \to \mathbb{R}$ is given by a polynomial in $|x|$ of degree r. Then $f \in \mathcal{C}_r$.*

Proof. We note that if $0 \le r_1 < r_2$ then there exists $\alpha > 0$ such that $|x|^{r_1} \le \alpha(|x|^{r_2} + 1)$ for all $x \in \mathbb{Z}^N$. This follows because the set of $x \in \mathbb{Z}^N$ such that $|x| < 1$ is finite regardless of the norm used. □

The following corollary is immediate.

COROLLARY 2.5. *A (multivariate) polynomial $f : \mathbb{Z}^N \to \mathbb{R}$ belongs to $\mathcal{C}$.* Also note that the definitions of $\mathcal{C}_r$ and $\mathcal{C}$ are independent of the norm used in $\mathbb{R}^N$.

The following lemma plays an important role in our convergence analysis.

LEMMA 2.6. *Let Q as defined in (2.3) correspond to a chemical system whose propensity functions are of class $\mathcal{C}_s$ for some $s \in \mathbb{Z}_+$. Then for each $r \in \mathbb{Z}_+$, there exists $B_r > 0$ such that*

$$|Q\, g|_r = \big||Q\, g|\big|_r \le \big||Q|\, |g|\big|_r \le B_r |g|_{s+r},$$

for each $g \in \mathcal{M}$. Hence $Q\,\mathcal{M} \subset \mathcal{M}$ and $|Q|\,\mathcal{M} \subset \mathcal{M}$. In particular the domain of the generator Q contains $\mathcal{M}$. (See Section 2.1 for definition of absolute value $|Q|$).

Proof.

$$\begin{aligned}
\big||Q|\, |g|\big|_r &= \frac{1}{2} \sum_{x' \in \mathbb{Z}^N} (1 + |x'|^r) \Big| \sum_{x \in \mathbb{Z}^N} |Q(x, x')||g(x)| \Big| \\
&= \frac{1}{2} \sum_{x \in \mathbb{Z}^N} \sum_{j=1}^{M} (1 + |x + \nu_j|^r) a_j(x) |g(x)| + \frac{1}{2} \sum_{x \in \mathbb{Z}^N} (1 + |x'|^r) a_0(x) |g(x)|,
\end{aligned}$$

where we have used (2.3). Since a_j are of class $\mathcal{C}_s$, there exists α independent of x such that

$$a_j(x) \leq a_0(x) \leq \alpha(|x|^s + 1),$$

for all x. Additionally we have

$$1 + |x + \nu_j|^r \leq 1 + (|x| + |\nu_j|)^r \leq 2^r(|x|^r + |\nu_j|^r) + 1 \leq \beta(|x|^r + 1),$$

for some β independent of x. Thus we obtain that for some constants $\tilde{B}_r$ and B_r the following holds for all g:

$$\begin{aligned} \big||Q|\,|g|\big|_r &\leq \frac{1}{2} \sum_{x \in \mathbb{Z}^N} \tilde{B}_r(|x|^s + 1)(|x|^r + 1)|g(x)|, \\ &\leq B_r\,|g|_{r+s} \end{aligned}$$

Note that we have used Lemma 2.4. □

Finally we provide a lemma which shows that convergence in the moment variation norm $|.|$ is equivalent to convergence of $E(f(X_n))$ to $E(f(X))$ for all $f \in \mathcal{C}_r$.

LEMMA 2.7. *For $n \in \mathbb{N}$, let $p_n, p \in \mathcal{M}_r$ be probability measures. The following are equivalent:*

1. $\lim_{n\to\infty} |p_n - p|_r = 0$.
2. *For every function $f : \mathbb{Z}^N \to \mathbb{R}$ that is of class $\mathcal{C}_r$ we have*

$$\sum_{x \in \mathbb{Z}^N} f(x)p_n(x) \to \sum_{x \in \mathbb{Z}^N} f(x)p(x).$$

Proof. We note that the first statement is that of strong convergence of p_n to p in $\mathcal{M}_r$ (equipped with $|.|_r$) and the second is that of weak convergence of p_n to p in $\mathcal{M}_r$. Since l_1 possesses the *Schur property* which states that "a weakly convergent sequence is also strongly convergent"[6], and $\mathcal{M}_r$ is isometrically isomorphic to l_1, the result follows. □

3. Convergence analysis. Given the same initial condition $p_0 \in \mathcal{M} \cap \mathcal{P}$ (an initial probability measure on $\mathbb{Z}^N$ with finite moments of all orders) and a mesh $\Pi = (t_0, \ldots, t_n)$ on $[0, T]$, let the $p(t)$ and $\hat{p}_\Pi(t)$ describe the probability mass functions of the chemical process $X(t)$ and its tau leap approximation $Y_\Pi(t)$ both of which satisfy $p(0) = \hat{p}(0) = p_0$. We shall prove the convergence of $\hat{p}_\Pi(t)$ to $p(t)$ for $t = t_i$ in the rth moment variation norm under suitable assumptions. In this section $P(\tau)$ stands for the transition function of the chemical process, $\phi(\tau)$ stands for the transition function of the tau leap method as defined in Section 2.1. In what follows we shall use $\hat{p}(t)$ suppressing the subscript Π for brevity.

We state a few assumptions about the chemical process $X(t)$ and its tau leap approximation that may be needed in the convergence results presented in this section. We note that Section 4 addresses the question of verification of these assumptions. Assumption 1 holds in all stochastic chemical models we have encountered in the literature and results in [16, 3, 22] provide conditions under which Assumption 2 holds and Theorem 4.4 of Section 4 restates a special case of a result proved in [16] regarding Assumption 2. Theorems 4.1, 4.3 and 4.5 of Section 4 provide some general conditions under which Assumptions 5, 3 and 6 hold respectively and Theorem 4.11, Corollary 4.12 and Theorem 4.15 provide more specific conditions for tau leap

methods where reaction counts are approximated by (conditioned on current state) independent Poisson and/or binomial random variables.

Assumption 1: Polynomial growth bound on propensities All propensity functions of the chemical process are in class $\mathcal{C}_{s^*}$ for some $s^* \geq 0$.

Assumption 2: Exponential moment growth bound for P. For all $r \in \mathbb{Z}_+$ there exist $\lambda_r > 0$ such that for all $\tau > 0$ and all $x \in \mathbb{Z}^N$ the following holds:

$$\sum_{x' \in \mathbb{Z}^N} (1 + |x'|^r)\, P(\tau, x, x') \leq (1 + |x|^r)\, e^{\lambda_r \tau}. \tag{3.1}$$

We may state (3.1) equivalently as

$$|P(\tau) g|_r \leq |g|_r\, e^{\lambda_r \tau}, \quad \forall g \in \mathcal{M} \tag{3.2}$$

Yet another equivalent way to state Assumption 2 is

$$E(1 + |X(t+\tau)|^r \,|X(t) = x) \leq (1 + |x|^r)\, e^{\lambda_r \tau}. \tag{3.3}$$

Assumption 3: Pointwise consistency of order q. For each $x \in \mathbb{Z}^N$ and $x' \in \mathbb{Z}^N$, $\phi(\tau, x, x')$ is $q+1$ times continuously differentiable in τ and the following hold:

$$\phi^{(i)}(0, x, x') = P^{(i)}(0, x, x'), \quad i = 1, \ldots, q. \tag{3.4}$$

Note that it follows from the finite sum on the right hand side of the Kolmogorov's forward equations (2.2) that P is infinitely differentiable in τ, so we do not need the differentiability assumption for P.

Assumption 4: Derivative bound on ϕ in total variation norm. There exist $H_0 > 0$, $s_0 > 0$, $\delta_0 > 0$ and $\gamma_0 > 0$ such that for all $\tau \in [0, \delta_0)$

$$\sum_{x' \in \mathbb{Z}^N} |\phi^{(q+1)}(\tau, x, x')| \leq \frac{H_0}{2}(|x|^{s_0} + 1)\, e^{\gamma_0 \tau}, \tag{3.5}$$

where q is as in Assumption 3. Equation (3.5) may be equivalently stated as

$$\big||\phi^{(q+1)}(\tau)|g\big|_0 \leq H_0\, |g|_{s_0}\, e^{\gamma_0 \tau}, \quad \forall g \in \mathcal{M}. \tag{3.6}$$

Assumption 5: Derivative bound on ϕ in moment variation norms. For each $r \in \mathbb{Z}_+$ there exist $H_r > 0$, $s_r > 0$, $\delta_r > 0$ and $\gamma_r > 0$ such that for all $\tau \in [0, \delta_r)$

$$\sum_{x' \in \mathbb{Z}^N} (1 + |x'|^r)\, |\phi^{(q+1)}(\tau, x, x')| \leq H_r(|x|^{s_r} + 1)\, e^{\gamma_r \tau}, \tag{3.7}$$

where q is as in Assumption 3. Equation (3.7) may be equivalently stated as

$$\big||\phi^{(q+1)}(\tau)|g\big|_r \leq H_r\, |g|_{s_r}\, e^{\gamma_r \tau}, \quad \forall g \in \mathcal{M}. \tag{3.8}$$

Note that Assumption 5 implies Assumption 4.

Assumption 6: Exponential moment growth bound for ϕ. For each $r \in \mathbb{Z}_+$ there exist $\lambda_r > 0$ and $\delta_r > 0$ such that for all $\tau \in [0, \delta_r)$ and all $x \in \mathbb{Z}^N$ the following holds:

$$\sum_{x' \in \mathbb{Z}^N} (1 + |x'|^r)\, \phi(\tau, x, x') \leq (1 + |x|^r)\, e^{\lambda_r \tau}. \tag{3.9}$$

We may state (3.9) equivalently as

$$|\phi(\tau)g|_r \le |g|_r \, e^{\lambda_r \tau}, \quad \forall g \in \mathcal{M} \tag{3.10}$$

Note that for convenience we have chosen without loss of generality λ_r to be the same as in (3.1) of Assumption 2.

REMARK 3.1. *We note that when these assumptions are used, it is assumed that there exists a common norm on $\mathbb{R}^N$ such that Assumptions 1 through 6 hold (in that same norm). Assumptions 1 and 3 are independent of the norm used on $\mathbb{R}^N$. Under suitable sufficient conditions Assumption 2 may be shown to hold in any norm on $\mathbb{R}^N$ with constants λ_r depending on the norm [16]. It is straight forward to show that Assumptions 4 and 5 are independent of the norm as long as norm dependent constants H_r are allowed.*

REMARK 3.2. *If deterministic initial condition is assumed then convergence results can be obtained under slightly relaxed versions of the above assumptions. For instance in Assumption 2 the constant λ_r will be required to be independent of x only within the set of states reachable from the initial condition and not independent of all $x \in \mathbb{Z}_+^N$. We shall not pursue this line of inquiry for sake of brevity.*

An equation similar to (3.7) follows for $P(\tau)$ under Assumptions 1 and 2, which we state as a lemma.

LEMMA 3.3. *For each $r \in \mathbb{Z}_+$ there exist $H_r > 0$, $s_r > 0$ and $\gamma_r > 0$ such that for all $\tau > 0$,*

$$\sum_{x' \in \mathbb{Z}^N} (1 + |x'|^r) \, |P^{(q+1)}(\tau, x, x')| \le H_r(|x|^{s_r} + 1) \, e^{\gamma_r \tau} \tag{3.11}$$

which may be equivalently stated as

$$\left| |P^{(q+1)}(\tau)|g \right|_r \le H_r \, |g|_{s_r} \, e^{\gamma_r \tau}, \quad \forall g \in \mathcal{M}. \tag{3.12}$$

Note that without loss of generality we may take γ_r, s_r, and H_r to be the same in equations (3.5), (3.7) and (3.11).

Proof.

$$\begin{aligned}
\left| |P^{(q+1)}(\tau)| \, g \right|_r &\le \left| |P^{(q+1)}(\tau)| \, |g| \right|_r = \left| |Q^{q+1} \, P(\tau)| \, |g| \right|_r \le \left| |Q|^{q+1} \, P(\tau) \, |g| \right|_r \\
&\le B_r B_{r+s^*} B_{r+2s^*} \cdots B_{r+qs^*} \left| P(\tau)|g| \right|_{(q+1)s^*+r} \\
&\le B_r B_{r+s^*} \cdots B_{r+qs^*} \, |g|_{(q+1)s^*+r} e^{\lambda_{(q+1)s^*+r} \tau} \\
&\le H_r \, |g|_{s_r} \, e^{\gamma_r \tau},
\end{aligned}$$

where H_r, s_r and γ_r are suitably large, and we have used Lemma 2.6 repeatedly and Assumptions 1 and 2. □

The following consistency result follows from Assumptions 1 through 5 and Lemma 3.3.

LEMMA 3.4. **Order q Consistency in moment variation.** *Suppose for a common norm on $\mathbb{R}^N$ the Assumptions 1 through 5 hold. (For $r = 0$ case only Assumptions 1 through 4 are needed). For each $r \in \mathbb{Z}_+$ let s_r, δ_r and γ_r be as in* (3.7) *and* (3.11). *Then for each $r \in \mathbb{Z}_+$ there exist $C_r > 0$ such that for all $\tau \in [0, \delta_r)$ and $g \in \mathcal{M}$,*

$$|(\phi(\tau) - P(\tau))g|_r \le C_r \, |g|_{s_r + r} \, \tau^{q+1} \, e^{\gamma_r \tau} \tag{3.13}$$

Proof. From (3.7) and (3.11) we obtain using triangle inequality that

$$\sum_{x'\in\mathbb{Z}^N} (1+|x'|^r)\,|\phi^{(q+1)}(\tau,x,x') - P^{(q+1)}(\tau,x,x')| \le 2H_r(1+|x|^{s_r})\,e^{\gamma_r\tau},$$

for all $\tau > 0$. From Taylor's theorem we have that for each $x, x' \in \mathbb{Z}^N$, and for each $\tau > 0$,

$$\phi(\tau,x,x') - P(\tau,x,x') = \int_0^\tau \frac{1}{q!}\left(\phi^{(q+1)}(s,x,x') - P^{(q+1)}(s,x,x')\right)(\tau-s)^q ds.$$

Hence

$$\begin{aligned}
&\sum_{x'\in\mathbb{Z}^N} (1+|x'|)^r\,|\phi(\tau,x,x') - P(\tau,x,x')| \\
&= \frac{1}{q!}\sum_{x'\in\mathbb{Z}^N}\left|\int_0^\tau (1+|x'|^r)\left(\phi^{(q+1)}(s,x,x') - P^{(q+1)}(s,x,x')\right)(\tau-s)^q ds\right| \\
&\le \frac{1}{q!}\sum_{x'\in\mathbb{Z}^N}\int_0^\tau (1+|x'|^r)\left|\phi^{(q+1)}(s,x,x') - P^{(q+1)}(s,x,x')\right|(\tau-s)^q ds \\
&= \frac{1}{q!}\int_0^\tau\left(\sum_{x'\in\mathbb{Z}^N}(1+|x'|^r)\left|\phi^{(q+1)}(s,x,x') - P^{(q+1)}(s,x,x')\right|\right)(\tau-s)^q ds \\
&\le \int_0^\tau 2\frac{(\tau-s)^q}{q!}\,H_r\,(|x|^{s_r}+1)\,e^{\gamma_r s} ds \;\le 2\frac{\tau^{q+1}}{q!}\,H_r\,(|x|^{s_r}+1)\,e^{\gamma_r\tau} \\
&\le \frac{2H_r}{q!}(|x|^{s_r}+1)\,\tau^{q+1}\,e^{\gamma_r\tau},
\end{aligned}$$

where we have used the dominated convergence theorem to swap the sum and the integral. Thus, given $g \in \mathcal{M}$ we obtain

$$\begin{aligned}
|(\phi(\tau)-P(\tau))g|_r &\le \sum_{x\in\mathbb{Z}^N}\sum_{x'\in\mathbb{Z}^N}\frac{1}{2}(1+|x|^r)\,|\phi(\tau,x,x') - P(\tau,x,x')|\,|g(x)| \\
&\le \sum_{x\in\mathbb{Z}^N}\frac{C_r}{2}(1+|x|^{s_r+r})\,|g(x)|\,\tau^{q+1}\,e^{\gamma_r\tau} \\
&= C_r\,|g|_{s_r+r}\,\tau^{q+1}\,e^{\gamma_r\tau}
\end{aligned}$$

where C_r is a suitably large constant. □

The following theorem establishes the order q convergence in total variation of a tau leap method that is pointwise order q consistent under the Assumptions 1 through 4.

THEOREM 3.5. **Order q convergence in total variation** *Let $\Pi = (t_0,\ldots,t_n)$ be a mesh on $[0,T]$. Let $p(t)$ and $\hat{p}_\Pi(t)$ for $t\in[0,T]$ be the probability mass functions corresponding to the stochastic chemical process and its tau leap approximation on mesh Π both started with initial distribution $p_0 \in \mathcal{M}\cap\mathcal{P}$. Let $\tau = |\Pi|$ be the maximum step size. Suppose for a common norm on $\mathbb{R}^N$ the Assumptions 1 through 4 hold and s_0, δ_0 and γ_0 be as in (3.7) and (3.11) and let C_0 be as in Lemma 3.4 for the case $r=0$ and let $\mu_0 = \max\{\lambda_{s_0},\gamma_0\}$. Then for each $i = 0,1,\ldots,n$ and for $\tau\in(0,\delta_r)$ the following holds :*

$$|\hat{p}_\Pi(t_i) - p(t_i)|_0 \le C_0\,|p_0|_{s_0}\,t_i\,e^{\mu_0 t_i}\,\tau^q \le C_0\,|p_0|_{s_0}\,T\,e^{\mu_0 T}\,\tau^q. \tag{3.14}$$

Proof. For $i = 1, \ldots, n$ we may write the error $\hat{p}(t_i) - p(t_i)$ as

$$\hat{p}(t_i) - p(t_i) = \phi(\tau_i)\,(\hat{p}(t_{i-1}) - p(t_{i-1})) + (\phi(\tau_i) - P(\tau_i))\,p(t_{i-1}).$$

Repeated application of the above leads to the telescoping sum

$$\hat{p}(t_i) - p(t_i) = \sum_{j=1}^{i} \phi(\tau_i)\,\phi(\tau_{i-1})\,\ldots\,\phi(\tau_{j+1})\,(\phi(\tau_j) - P(\tau_j))\,p(t_{j-1}) \tag{3.15}$$

where we have used the fact that $\hat{p}(0) = p(0) = p_0$. From (3.13)

$$|(\phi(\tau_j) - P(\tau_j))\,p(t_{j-1})|_0 \le C_0\,|p(t_{j-1})|_{s_0}\,\tau_j^{q+1}\,e^{\gamma_0\tau_j},$$

since $|p(t_{j-1})|_0 = 1$. From (3.2) we obtain

$$|p(t_{j-1})|_{s_0} = |P(t_{j-1})p_0|_{s_0} \le |p_0|_{s_0}\,e^{\lambda_{s_0}t_{j-1}}.$$

Hence with $\mu_0 = \max\{\lambda_{s_0}, \gamma_0\}$ we obtain

$$|(\phi(\tau_j) - P(\tau_j))\,p(t_{j-1})|_0 \le C_0\,|p_0|_{s_0}\,\tau^q\,\tau_j e^{\mu_0 t_j}. \tag{3.16}$$

The equation (3.16) is a statement of order q *uniform consistency* in total variation norm on the interval $[0, T]$. Using the fact that $|\phi(\tau_i)|_0 = 1$ for all i, we obtain from (3.15) the estimate

$$|\hat{p}_\Pi(t_i) - p(t_i)|_0 \le \sum_{j=1}^{i} C_0\,|p_0|_{s_0}\,\tau^q\,\tau_j\,e^{\mu_0 t_j} \le C_0\,|p_0|_{s_0}\,t_i\,e^{\mu_0 t_i}\,\tau^q.$$

This completes the proof. □

Now we have the following 0-stability or uniform boundedness result for the tau leap method which follows directly from Assumption 6.

LEMMA 3.6. **Uniform boundedness or zero stability of tau leap method in rth moment variation.** *For each $r \in \mathbb{Z}_+$, $T > 0$ $g \in \mathcal{M}$, and for all meshes $\Pi = (t_0, \ldots, t_n)$ on $[0, T]$ satisfying $|\Pi| < \delta_r$ and for any indices i, j with $0 \le j < i \le n$ the following holds:*

$$|\phi(\tau_i)\phi(\tau_{i-1})\ldots\phi(\tau_{j+1})g|_r \le |g|_r e^{\lambda_r(\tau_{j+1}+\cdots+\tau_i)} \le |g|_r e^{\lambda_r T}. \tag{3.17}$$

The following theorem establishes the order q convergence in rth moment variation of a tau leap method that is order q consistent under the Assumptions 1 through 6.

THEOREM 3.7. **Order q convergence in moment variation** *Let $\Pi = (t_0, \ldots, t_n)$ be a mesh on $[0, T]$. Let $p(t)$ and $\hat{p}_\Pi(t)$ for $t \in [0, T]$ be the probability mass functions corresponding to the stochastic chemical process and its tau leap approximation on mesh Π both started with initial distribution $p_0 \in \mathcal{M} \cap \mathcal{P}$. Let $\tau = |\Pi|$ be the maximum step size. Suppose for some common norm on $\mathbb{R}^N$ the Assumptions 1 through 6 hold. Given any $r \in \mathbb{Z}_+$ let s_r and γ_r be as in (3.7) and (3.11), let C_r be as in Lemma 3.4 and let $\mu_r = \max\{\lambda_{s_r+r}, \gamma_r\}$.*

Then for each $r \geq 0$ and for each $i = 0, 1, \ldots, n$ and $\tau \in (0, \delta_r)$ the following holds :

$$|\hat{p}_\Pi(t_i) - p(t_i)|_r \leq C_r |p_0|_{s_r+r}\, t_i\, e^{\mu_r t_i}\, \tau^q \leq C_r |p_0|_{s_r+r}\, T\, e^{\mu_r T}\, \tau^q. \tag{3.18}$$

Proof. From (3.13)

$$|(\phi(\tau_j) - P(\tau_j))\, p(t_{j-1})|_r \leq C_r |p(t_{j-1})|_{s_r+r}\, \tau_j^{q+1}\, e^{\gamma_r \tau_j}.$$

From (3.2) we obtain

$$|p(t_{j-1})|_{s_r+r} = |P(t_{j-1})\, p_0|_{s_r+r} \leq |p_0|_{s_r+r}\, e^{\lambda_{s_r+r} t_{j-1}}.$$

With $\mu_r = \max\{\lambda_{s_r+r}, \gamma_r\}$ we obtain

$$|(\phi(\tau_j) - P(\tau_j))\, p(t_{j-1})|_r \leq C_r |p_0|_{s_r+r}\, \tau_j^{q+1}\, e^{\mu_r t_j}. \tag{3.19}$$

which is a statement of *uniform consistency*. In Lemma 3.6 for $i > j$ taking $g = (\phi(\tau_j) - P(\tau_j))\, p(t_{j-1})$ and using (3.19) we obtain the estimate

$$\begin{aligned} &|\phi(\tau_i)\phi(\tau_{i-1}) \ldots \phi(\tau_{j+1})(\phi(\tau_j) - P(\tau_j))\, p(t_{j-1})|_r \\ &\leq C_r |p_0|_{s_r+r}\, \tau_j^{q+1} e^{\mu_r t_j} e^{\lambda_r(\tau_{j+1} + \cdots + \tau_i)} \leq C_r |p_0|_{s_r+r}\, \tau_j^{q+1} e^{\mu_r t_i}. \end{aligned}$$

Thus we obtain from (3.15) the estimate

$$\begin{aligned} |\hat{p}_\Pi(t_i) - p(t_i)|_r &\leq \sum_{j=1}^{i} C_r |p_0|_{s_r+r}\, \tau^q\, \tau_j\, e^{\mu_r t_i} \\ &\leq C_r |p_0|_{s_r+r}\, t_i\, e^{\mu_r t_i}\, \tau^q \leq C_r |p_0|_{s_r+r}\, T\, e^{\mu_r T}\, \tau^q \end{aligned}$$

This completes the proof. □

The following corollary affirming the order q convergence of moments is immediate.

COROLLARY 3.8. **Order q convergence of moments** *Let the assumptions of Theorem 3.7 hold. Then the error in the rth moment satisfies*

$$|E(|Y_\Pi(T)|^r) - E(|X(T)|^r)| \leq 2\, C_r E(|X(0)|^{s_r+r})\, T\, e^{\mu_r T}\, \tau^q. \tag{3.20}$$

Proof.

$$|E(|Y_\Pi(T)|^r) - E(|X(T)|^r)| = \Big| \sum_{x \in \mathbb{Z}^N} |x|^r \hat{p}_\Pi(T, x) - \sum_{x \in \mathbb{Z}^N} |x|^r p(T, x) \Big|$$

$$\leq \sum_{x \in \mathbb{Z}^N} (1 + |x|^r)\, |\hat{p}_\Pi(T, x) - p(T, x)| = 2\, |\hat{p}_\Pi(T) - p(T)|_r \leq 2\, C_r |p_0|_{s_r+r}\, T\, e^{\mu_r T}\, \tau^q.$$

□

REMARK 3.9. *For convenience of exposition our convergence analysis and the Assumptions 2, 4 and 6 dealt with the situation where moments of all orders exist. However it is clear from our analysis that our Assumptions 2, 4 and 6 along with the*

assumption $p_0 \in \mathcal{P} \cap \mathcal{M}$ can be weakened to the case where moments exist only up to some order r_0.

REMARK 3.10. *We note that using Assumption 2 it is straightforward to extend the convergence results to obtain a first order supremum error bound of the form*

$$\sup_{t\in[0,T]} |E(|Y_\Pi(t)|^r) - E(|X(t)|^r)| \leq \tilde{C}_r |p_0|_{s_r+r} T e^{\tilde{\mu}_r T} \tau, \tag{3.21}$$

where per our convention the tau leap approximation $Y_\Pi(t)$ is constant on $[t_{j-1}, t_j)$.

4. Verification of the conditions of the convergence theorem. In this section we provide some results on the verification of Assumptions 1 through 6. All forms for propensity functions proposed in the literature that we have encountered satisfy the polynomial growth bound of Assumption 1 and thus it is not restrictive. It is also straightforward to verify.

4.1. General results on verification of Assumption 2 through 6. Firstly it must be noted that from (2.5) we have $P^{(i)}(0) = Q^i$ for $i = 1, 2, \ldots$ since $P(0)$ is the identity. This gives explicit expressions for $P^{(i)}(0, x, x')$. The pointwise consistency (Assumption 3) requires $\phi^{(i)}(0, x, x')$ to agree with $P^{(i)}(0, x, x')$ for $i = 1, \ldots, q$. So checking Assumption 3 relies on evaluating $\phi^{(i)}(0, x, x')$. If direct expressions are available for $\phi(\tau, x, x')$ this is easy to do. However, in practice the expressions for $\phi(\tau, x, x')$ may involve infinite sums. To see this, recall that one may write the change in the chemical process $X(t)$ as

$$X(t+\tau) = x + \sum_{j=1}^{M} \nu_j [R_j(t+\tau) - R_j(t)], \tag{4.1}$$

where $X(t) = x$ and $R_j(t)$ are processes that count the number of reactions that occurred during $(0, t]$. Most tau leap methods are of the form

$$Y(t+\tau) = x + \sum_{j=1}^{M} \nu_j K_j \tag{4.2}$$

where $Y(t) = x$ and K_j are random variables whose distribution depends on x and τ and are approximations of $R_j(t+\tau) - R_j(t)$. Let us define the conditional probabilities

$$\begin{aligned} \tilde{\phi}(\tau, x; k) &= \text{Prob}(K = k \,|\, Y(t) = x), \\ \tilde{p}(\tau, x; k) &= \text{Prob}(R(t+\tau) - R(t) = k \,|\, X(t) = x). \end{aligned} \tag{4.3}$$

In order to see the relationship between P and $\tilde{p}$ as well as ϕ and $\tilde{\phi}$, given a a pair of states $x, x' \in \mathbb{Z}^N$, we define the associated set $S(x, x') \subset \mathbb{Z}_+^M$ to be the set of all reaction counts $k \in \mathbb{Z}_+^M$ that would take the system from state x to state x':

$$S(x, x') = \{k \in \mathbb{Z}_+^M \,|\, x' - x = \nu\, k\}. \tag{4.4}$$

Then we have that for $x, x' \in \mathbb{Z}^N$,

$$\begin{aligned} P(\tau, x, x') &= \sum_{k \in S(x,x')} \tilde{p}(\tau, x; k), \\ \phi(\tau, x, x') &= \sum_{k \in S(x,x')} \tilde{\phi}(\tau, x; k). \end{aligned} \tag{4.5}$$

Since expressions for $\tilde{\phi}$ are more readily available than for ϕ, we shall seek pointwise consistency of $\tilde{\phi}$ with $\tilde{p}$. In order to go from pointwise consistency of $\tilde{\phi}$ with $\tilde{p}$ to that of ϕ with P, term by term differentiation needs to be justified as $S(x, x')$ may be infinite.

In order to derive pointwise consistency conditions for $\tilde{\phi}(\tau, x; k)$ in comparison with $\tilde{p}(\tau, x; k)$ we first note that given $X(t) = x$, the reaction count process $R(t+\tau) - R(t)$ is a Markov process and hence we obtain the following Kolmogorov's forward equation:

$$\tilde{p}^{(1)}(\tau, x; k) = \sum_{j=1}^{M} \tilde{p}(\tau, x; k - e_j) a_j(x + \nu(k - e_j)) - \sum_{j=1}^{M} \tilde{p}(\tau, x; k) a_j(x + \nu k), \quad (4.6)$$

with initial probability $\tilde{p}(0, x; 0) = 1$ and $\tilde{p}(0, x; k) = 0$ for $k \neq 0$. Here e_j is the vector with all zeros except a one on the jth entry. Defining the infinite matrix $\tilde{Q}(x)$ that depends on state x by

$$\begin{aligned} \tilde{Q}(x; k', k) &= a_j(x + \nu k'), \quad k = k' + \nu_j, \\ &= -a_0(x + \nu k'), \quad k = k', \\ &= 0, \quad \text{else}, \end{aligned} \quad (4.7)$$

we note that

$$\tilde{p}^{(i)}(0, x; k) = \tilde{Q}^i(x; 0, k), \ \forall k \in \mathbb{Z}_+^M, \quad (4.8)$$

where $\tilde{Q}^i$ is the ith power of $\tilde{Q}$. Thus pointwise consistency of order q for $\tilde{\phi}(\tau, x; k)$ is given by

$$\tilde{\phi}^{(i)}(0, x; k) = \tilde{Q}^i(x; 0, k), \ \forall k \in \mathbb{Z}_+^M, \ i = 1, \ldots, q. \quad (4.9)$$

We note that for $q = 1$, (4.9) yields that $\tilde{\phi}^{(1)}(0, x; k) = a_j(x)$ if $k = e_j$, $\tilde{\phi}^{(1)}(0, x; 0) = -a_0(x)$ and $\tilde{\phi}^{(1)}(0, x; k) = 0$ for all other k.

The following theorem provides a set of sufficient conditions that guarantee the validity of the term by term differentiation for the sums involving $\tilde{\phi}$ and also guarantee that the Assumption 5 (on the derivative bounds) holds.

THEOREM 4.1. *Suppose there exists $\delta > 0$, such that $\tilde{\phi}(\tau, x; k)$ are continuously differentiable (in τ) $q + 1$ times for $\tau \in [0, \delta]$ and for each x, k, and suppose that for each k and $i = 0, 1, \ldots, q + 1$ there exist $\mu_{k,i}(x)$ such that*

$$|\tilde{\phi}^{(i)}(\tau, x; k)| \leq \mu_{k,i}(x),$$

and that for each $r \in \mathbb{Z}_+$ there exist $\eta_{r,i}$ and $\sigma_{r,i}$ such that

$$\sum_{k \in \mathbb{Z}_+^M} |k|^r \mu_{k,i}(x) \leq \eta_{r,i}(1 + |x|^{\sigma_{r,i}}).$$

Then Assumption 5 holds with $\delta_r = \delta$, $\gamma_r = 0$, and some s_r for all $r \in \mathbb{Z}_+$.

Proof. First we note that using Weierstrass test, for $i = 0, 1, \ldots, q + 1$ and all $r \in \mathbb{Z}_+$, the series

$$\sum_{k \in \mathbb{Z}_+^M} |k|^r \tilde{\phi}^{(i)}(\tau, x; k),$$

converges uniformly for $\tau \in [0, \delta]$ and that the commutation

$$\left(\sum_{k \in \mathbb{Z}_+^M} |k|^r \tilde{\phi}(\tau, x; k) \right)^{(i)} = \sum_{k \in \mathbb{Z}_+^M} |k|^r \tilde{\phi}^{(i)}(\tau, x; k)$$

holds. It is also then clear that (4.5) may be differentiated term by term $q+1$ times:

$$\phi^{(i)}(\tau, x, x') = \sum_{k \in S(x, x')} \tilde{\phi}^{(i)}(\tau, x; k).$$

This leads to the estimate

$$\begin{aligned}
&\sum_{x' \in \mathbb{Z}^N} |x'|^r |\phi^{(q+1)}(\tau, x, x')| \leq \sum_{k \in \mathbb{Z}_+^M} |x + \nu k|^r |\tilde{\phi}^{(q+1)}(\tau, x; k)| \\
&\leq \sum_{l=0}^{r} \frac{r!}{l!(r-l)!} |x|^{r-l} \|\nu\|^l \left(\sum_{k \in \mathbb{Z}_+^M} |k|^l |\tilde{\phi}^{(q+1)}(\tau, x; k)| \right) \\
&\leq \tilde{\eta}_r (1 + |x|^{s_r}),
\end{aligned}$$

where $\tilde{\eta}_r$ is a suitably large constant and s_r is the maximum of $r - l + \sigma_{l,q+1}$ over $l = 0, 1, \ldots, r$. Assumption 5 follows with a suitably large H_r and $\gamma_r = 0$. □

COROLLARY 4.2. *Suppose the conditions of Theorem 4.1 and Assumption 1 hold. Then* (4.5) *may be term by term differentiated $q+1$ times.*

Proof. The result for ϕ follows from the proof of Theorem 4.1. Under Assumption 1, because of (4.6) it can be shown that $\tilde{p}$ satisfies conditions similar to those required on $\tilde{\phi}$ by Theorem 4.1. So the term by term differentiation for P also follows. □

The following theorem is immediate.

THEOREM 4.3. *Suppose the conditions of Theorem 4.1 hold and additionally that Assumption 1 and* (4.9) *hold. Then Assumption 3 holds.*

The Assumption 2 involves the moment growth bound condition on the chemical process. Verifying these conditions may not be trivial. Some sufficient conditions for Assumption 2 may be found in [16, 22, 3]. We provide one result which follows from Theorem 3.6 of [16].

We shall say that a reaction channel j is *linearly bounded* if there exists a constant H such that

$$a_j(x) \leq H(1 + |x|), \quad \forall x \in \mathbb{Z}_+^N.$$

If a reaction channel is not linearly bounded we refer to it as *superlinear*. Let us denote by M_s the number of superlinear reactions. In what follows we assume without loss of generality that the reactions are ordered such that the first M_s are superlinear.

While our convergence analysis of Section 3 did not assume that the non-negative lattice $\mathbb{Z}_+^N$ was invariant for the process, the sufficient condition we provide here for Assumption 2 will only apply to systems that remain in $\mathbb{Z}_+^N$ when started in $\mathbb{Z}_+^N$. Such a process is said to be *conservative* with respect to $\mathbb{Z}_+^N$. Any realistic model of chemical kinetics as well as other population processes must have this property. It is easy to see that the process X is conservative with respect to $\mathbb{Z}_+^N$ if and only if for every $x \in \mathbb{Z}_+^N$ if $x + \nu_j \notin \mathbb{Z}_+^N$ then $a_j(x) = 0$.

THEOREM 4.4. *Suppose that X is conservative with respect to $\mathbb{Z}_+^N$, Assumption 1 is satisfied and that there exists $\alpha \in \mathbb{Z}_+^N$ such that $\alpha > 0$ and $\alpha^T \nu_j \leq 0$ for $j =$*

$1, \ldots, M_s$. *Assume* $X(0) \in \mathbb{Z}_+^N$ *with probability* 1. *Then for each* $r \in \mathbb{N}$ *there exists* λ_r *such that the following holds for all* $t \geq 0$ *and in any norm* $|.|$ *on* $\mathbb{R}^N$*:*

$$E(|X(t)|^r) \leq E(|X(0)|^r)e^{\lambda_r t} + e^{\lambda_r t} - 1.$$

Proof. This is implied by the proof of Theorem 3.6 of [16]. □

For $x \in \mathbb{Z}_+^N$, $l \in \mathbb{Z}_+$ and $\tau > 0$ let us define $m_l(x, \tau)$ to be the lth moment of the vector copy number of the linearly bounded reactions over a time step τ starting with state x according to the tau leap method:

$$m_l(x, \tau) = \sum_k |k^{(2)}|^l \tilde{\phi}(\tau, x; k). \tag{4.10}$$

Here vector copy number of reaction counts k is written as $k = (k^{(1)}, k^{(2)}) \in \mathbb{Z}_+^{M_s} \times \mathbb{Z}_+^{M-M_s}$ where $k^{(1)}$ is the vector copy number of superlinear reactions and $k^{(2)}$ is that of linearly bounded ones. We note that $m_0 = 1$.

The following theorem provides sufficient conditions that guarantee Assumption 6.

THEOREM 4.5. *Suppose that there exists* α *satisfying the hypotheses of Theorem 4.4. Suppose further that for each* $l \in \mathbb{N}$ *there exist* $\beta_l > 0, \tilde{\delta}_l > 0$ *such that for all* $x \in \mathbb{Z}_+^N$ *and* $\tau \in [0, \tilde{\delta}_l]$*,*

$$m_l \leq \beta_l(1 + |x|^l)\tau, \tag{4.11}$$

and for $x \notin \mathbb{Z}_+^N$ *suppose that* $\tilde{\phi}(\tau, x; 0) = 1$ *(i.e.* $K = 0$ *with probability* 1*) which means that if the tau leap scheme leaves* $\mathbb{Z}_+^N$ *it is stopped. Furthermore suppose that if* $x \in \mathbb{Z}_+^N$ *and for* $k = (k^{(1)}, k^{(2)})$ *if* $x + \nu^{(1)}k^{(1)} \notin \mathbb{Z}_+^N$ *then* $\tilde{\phi}(\tau, x; k) = 0$*. (This means if* $x \in \mathbb{Z}_+^N$ *then the tau update of the superlinear reactions alone will still result in a state in* $\mathbb{Z}_+^N$ *with probability* 1*). Then Assumption 6 holds in a particular norm. If in addition the conditions of Theorem 4.1 hold then Assumption 6 holds in any norm.*

Proof. Define the norm on $\mathbb{R}^N$ by $|x| = \sum_{i=1}^N \alpha_i |x|_i$. Then $|x + \nu_j| \leq |x|$ if $x \in \mathbb{Z}_+^N$ and $x + \nu_j \in \mathbb{Z}_+^N$ for $j = 1, \ldots, M_s$. We denote by $\nu^{(1)}$ the $N \times M_s$ sub-matrix consisting of superlinear reactions and by $\nu^{(2)}$ the $N \times (M - M_s)$ sub-matrix consisting of linearly bounded reactions. Then we have that for $\tilde{\phi}(\tau, x; k) \neq 0$ with $k = (k^{(1)}, k^{(2)})$,

$$|x + \nu k| = |x + \nu^{(1)}k^{(1)} + \nu^{(2)}k^{(2)}| \leq |x + \nu^{(1)}k^{(1)}| + |\nu^{(2)}k^{(2)}| \leq |x| + \|\nu^{(2)}\||k^{(2)}|,$$

where $\|\nu^{(2)}\|$ is the induced norm of $\nu^{(2)}$. Using this we get

$$\begin{aligned}
&\sum_{x'} |x'|^r \phi(\tau, x, x') = \sum_k |x + \nu k|^r \tilde{\phi}(\tau, x; k) \\
&\leq \sum_k \left(|x| + \|\nu^{(2)}\||k^{(2)}|\right)^r \tilde{\phi}(\tau, x; k) \leq \sum_{l=0}^r \frac{r!}{l!(r-l)!} |x|^{r-l} \|\nu^{(2)}\|^l m_l(x, \tau).
\end{aligned}$$

Using the bounds on m_l we obtain that for suitably large λ_r and suitably small $\delta_r > 0$ we have

$$\sum_{x'} (1 + |x'|^r)\phi(\tau, x, x') \leq (1 + |x|^r)(1 + \lambda_r \tau) \leq (1 + |x|^r)e^{\lambda_r \tau},$$

for all $\tau \in [0, \delta_r]$. This shows that Assumption 6 holds in the particular norm defined above.

If in addition the conditions of Theorem 4.1 hold then

$$\sum_{x'}(1 + |x'|^r)\phi(\tau, x, x')$$

is differentiable in τ and by Lemma 3.5 of [16] the Assumption 6 holds in any norm. □

REMARK 4.6. *We note that proof of Theorem 4.5 uses an approach similar to that of Theorem 4.4 (see [16]) in that it is required that the reactions that have superlinear propensities are expected to decrease the norm of the state (in some norm). Since the original process remains non-negative the existence of $\alpha \in \mathbb{Z}_+^N$ such that $\alpha > 0$ and $\alpha^T \nu_j \leq 0$ for $j = 1, \ldots, M_s$ is adequate to ensure this. However in the case of a tau leap method we directly require that the superlinear reactions alone shall not result in a non-negative state in order to accomplish this. Thus it will be advisable to use bounded random variables such as Binomials for superlinear reactions to ensure non-negativity.*

4.2. Tau leap methods with Poisson and binomial updates. Most tau leap methods use Poisson or binomial random variables for the K_j. In this subsection we present further results that apply specifically to tau leap methods that use Poisson and binomial random variables.

We first state some lemmas related to Poisson and binomial random variables.

LEMMA 4.7. *Let K be Poisson distributed with parameter λ. Then for each $r \in \mathbb{Z}_+$ the moment $E(K^r)$ is a polynomial in λ of degree r.*

Proof. This follows via induction using the easy to establish recursion

$$E(K^r) = \lambda E((K + 1)^{r-1}).$$

□

LEMMA 4.8. *Let K be binomially distributed with parameters N and p. Then for each $r \in \mathbb{Z}_+$ the moment $E(K^r)$ is a polynomial of degree r separately in N and p.*

Proof. This follows via induction using the easy to establish recursive relation

$$E(K_N^r) = NpE((1 + K_{N-1})^{r-1}),$$

where K_N denotes a binomial random variable with parameters N and p. □

LEMMA 4.9. *Let K be Poisson distributed with parameter λ where $\lambda = \lambda(x, \tau)$ is a function of state $x \in \mathbb{Z}_+^N$ and step size $\tau \geq 0$. Denote $\psi(\lambda, k)$ the probability that $K = k$. Suppose that there exists $\delta > 0$ such that for all $x \in \mathbb{Z}_+^N$ and $\tau \in [0, \delta]$, λ is $q+1$ times continuously differentiable in τ, and the supremum of $\lambda, |\lambda^{(1)}|, \ldots, |\lambda^{(q+1)}|$ over $\tau \in [0, \delta]$ is bounded above by a polynomial in $|x|$. Then for each $r \in \mathbb{Z}_+$ and $i = 0, 1, \ldots, q + 1$, the supremum of*

$$\sum_k k^r |\psi^{(i)}(\lambda, k)|$$

over $\tau \in [0, \delta]$ is bounded above by a polynomial in $|x|$.

Proof. It is straight forward to verify the relation

$$\psi^{(1)}(\lambda, k) = \lambda^{(1)} \left(\psi(\lambda, k - 1) - \psi(\lambda, k)\right), \quad k \in \mathbb{Z}_+,$$

where the convention that $\psi(\lambda, k) = 0$ for $k < 0$ is used. By repeated application one can relate $\psi^{(i)}$ for $i = 2, \ldots, q+1$ also to ψ. This provides an upper bound for the quantities of interest in terms of the moments. Then the result follows by Lemma 4.7. □

LEMMA 4.10. *Let K be binomially distributed with parameters N_0 and p where $N_0 = N_0(x)$ is a function of state $x \in \mathbb{Z}_+^N$ and $p = p(x, \tau)$ is a function of state x and step size $\tau \geq 0$. Denote $\psi(N_0, p, k)$ the probability that $K = k$. Suppose that there exists $\delta > 0$ such that for all $x \in \mathbb{Z}_+^N$ and $\tau \in [0, \delta]$, p is $q+1$ times continuously differentiable in τ, and $N_0(x)$ as well as the supremum of $p, |p^{(1)}|, \ldots, |p^{(q+1)}|$ over $\tau \in [0, \delta]$ are bounded above by a polynomial in $|x|$. Then for each $r \in \mathbb{Z}_+$ and $i = 0, 1, \ldots, q+1$, the supremum of*

$$\sum_k k^r |\psi^{(i)}(N_0, p, k)|$$

over $\tau \in [0, \delta]$ is bounded above by a polynomial in $|x|$.

Proof. It is straight forward to verify the relation

$$\psi^{(1)}(N_0, p, k) = N_0 p^{(1)} \left(\psi(N_0 - 1, p, k-1) - \psi(N_0 - 1, p, k)\right), \quad k \in \{0, \ldots, N_0\},$$

where the convention that $\psi(N_0, p, k) = 0$ for $k \notin \{0, 1, \ldots, N_0\}$ is used. By repeated application one can relate $\psi^{(i)}$ for $i = 2, \ldots, q+1$ also to ψ. Then the result follows from Lemma 4.8. □

THEOREM 4.11. *Suppose the tau leap method generates K_j for $j = 1, \ldots, M$ to be independent conditioned on current state x and each K_j is either binomially or Poisson distributed with their distributions satisfying the assumptions of Lemmas 4.10 and 4.9. Then the hypotheses of Theorem 4.1 are satisfied and thus Assumption 5 holds.*

Proof. By the assumed independence of K_j it follows that $\tilde{\phi}$ has a product form

$$\tilde{\phi}(\tau, x; k) = \tilde{\phi}_1(\tau, x; k_1) \ldots \tilde{\phi}_M(\tau, x; k_M).$$

Then for $i = 0, 1, \ldots, q+1$ the ith derivative $\tilde{\phi}^{(i)}(\tau, x; k)$ is a linear combination of terms of the form

$$\tilde{\phi}_1^{(i_1)}(\tau, x; k_1) \ldots \tilde{\phi}_M^{(i_M)}(\tau, x; k_M),$$

where $i_j \in \{0, 1, \ldots, q+1\}$ for $j = 1, \ldots, M$. Noting that

$$\begin{aligned}\sum_k |k|^r |\tilde{\phi}^{(i)}| &= \sum_k (k_1 + \cdots + k_M)^r |\tilde{\phi}^{(i)}| \\ &\leq M^r \sum_{k_1} \sum_{k_2} \cdots \sum_{k_M} (k_1^r + \cdots + k_M^r) |\tilde{\phi}_1^{(i_1)}| \ldots |\tilde{\phi}_M^{(i_M)}|\end{aligned}$$

the result follows from using Lemmas 4.10 and 4.9. □

COROLLARY 4.12. *Suppose that the conditions of Theorem 4.11 and the extra conditions of 4.3 hold. Then Assumption 3 holds.*

Proof. The conditions of Theorem 4.1 are implied by conditions of Theorem 4.11. Given the extra conditions of Theorem 4.3 the conclusions of Theorem 4.3 follow. □

LEMMA 4.13. *Let K be Poisson distributed with parameter λ where $\lambda = \lambda(x, \tau)$ is a function of state $x \in \mathbb{Z}_+^N$ and step size $\tau \geq 0$. Suppose that there exists $\delta > 0$*

such that for all $x \in \mathbb{Z}_+^N$ and $\tau \in [0,\delta]$, λ is continuously differentiable in τ, and the supremum of $\lambda, |\lambda^{(1)}|$ over $\tau \in [0,\delta]$ is bounded above by a polynomial of degree s in $|x|$. Then for $\tau \in [0,\delta]$ and for each $r \in \mathbb{N}$ the supremum of $|dE(K^r)/d\tau|$ over $\tau \in [0,\delta]$ is bounded by a polynomial of degree rs in $|x|$.

Proof. For a fixed $x \in \mathbb{Z}_+^N$, the random variable $K(x,\tau)$ is a time non-homogeneous Poisson process in τ with rate (intensity) $\lambda^{(1)}(x,\tau)$. It follows that

$$dE(K^r)/d\tau = \lambda^{(1)} E\{(K+1)^r - K^r\}.$$

This together with Lemma 4.7 implies the desired result. □

LEMMA 4.14. *Let K be binomially distributed with parameters N_0 and p where $N_0 = N_0(x)$ is a function of state $x \in \mathbb{Z}_+^N$ and $p = p(x,\tau)$ is a function of state x and step size $\tau \geq 0$. Suppose that there exists $\delta > 0$ such that for all $x \in \mathbb{Z}_+^N$ and $\tau \in [0,\delta]$, p is continuously differentiable in τ, and the suprema of $|p^{(1)}|$ over $\tau \in [0,\delta]$ and $N_0(x)$ are bounded above by polynomials of degree s_1 and s_2 respectively in $|x|$. Then for $\tau \in [0,\delta]$ and for each $r \in \mathbb{N}$ the supremum of $|dE(K^r)/d\tau|$ over $\tau \in [0,\delta]$ is bounded by a polynomial of degree $s_1 + rs_2$ in $|x|$.*

Proof. We write $K = K_{N_0}$. Using the relationship mentioned in the proof of Lemma 4.10 we obtain that

$$dE(K_{N_0}^r)/d\tau = N_0 p^{(1)} E\left((K_{N_0-1}+1)^r - K_{N_0-1}^r\right).$$

This together with Lemma 4.8 implies the result. We note that since p lies in $[0,1]$ we only need to focus on dependence on N_0 and $p^{(1)}$. □

THEOREM 4.15. *Suppose that there exists $\alpha > 0$ satisfying the hypothesis of Theorem 4.4 and that the K_j for $j = M_s + 1, \ldots, M$ corresponding to the linearly bounded reactions are (conditioned on current state x) are each either binomially or Poisson distributed with their distributions satisfying the assumptions of Lemmas 4.14 with $s_1 = 0$ and $s_2 = 1$ or 4.13 with $s = 1$ respectively.*

Additionally suppose that for $x \in \mathbb{Z}_+^N$ and for $j = 1, \ldots, M$ that $x + \nu K^{(1)} \in \mathbb{Z}_+^N$ with probability 1 where $K^{(1)}$ is the M_s vector of the superlinear reaction counts per tau leap. Also suppose that for $x \notin \mathbb{Z}_+^N$ we have that $K_j = 0$ with probability 1 for all j. Then the hypotheses of Theorem 4.5 are satisfied and thus Assumption 6 holds.

Proof. These assumptions guarantee that with $K^{(2)} = (K_{M_s+1}, \ldots, K_M)$,

$$|dE(|K^{(2)}|^r)/d\tau| \leq \beta_r(1 + |x|^r),$$

for some β_r independent of $\tau \in [0,\delta]$ and x. Since for $\tau = 0$ we have $E(|K|^r) = 0$, using mean value theorem we obtain the bounds

$$E(|K^{(2)}|^r) = m_r \leq \beta_r(1 + |x|^r)\tau, \quad \tau \in [0,\delta].$$

Thus all the assumptions of Theorem 4.5 are satisfied and thus Assumption 6 holds. □

4.3. Example. We consider the example of the unbounded reaction system

$$S_1 + S_2 \to S_3, \;\; S_3 \to S_1 + S_2 \;\; S_2 \to 2S_2, \;\; S_2 \to 0, \tag{4.12}$$

where the propensities are assumed to be of the stochastic mass action form:

$$a_1(x) = c_1 x_1 x_2, \;\; a_2(x) = c_2 x_3, \;\; a_3(x) = c_3 x_1, \;\; a_4(x) = c_4 x_2. \tag{4.13}$$

We note that Assumption 1 is clearly satisfied.

The stoichiometric vectors are $\nu_1 = (-1,-1,1)^T$, $\nu_2 = (0,1,-1)^T$, $\nu_3 = (0,1,0)^T$ and $\nu_4 = (0,-1,0)^T$. It is easy to see that S_1 and S_3 are bounded (if initial conditions are bounded) as $(1,0,1)^T\nu_j \leq 0$ for all j implying that $X_1(t)+X_3(t) \leq X_1(0)+X_3(0)$. However S_2 is not bounded because of reaction 3 and thus the system is unbounded. However since $\alpha = (1,1,1)^T$ satisfies the hypothesis of Theorem 4.4 we see that Assumption 2 is satisfied.

Suppose we use a tau leap update following the REMM-τ method [17]:

$$X(t+\tau) = X(t) + \sum_{j=1}^{M} \nu_j K_j$$

where $K_1 \sim \text{Binomial}(N_1, p_1)$, $K_2 \sim \text{Binomial}(N_2, p_2)$, $K_3 \sim \text{Poisson}(\lambda_3)$ and $K_4 \sim \text{Binomial}(N_4, p_4)$, where K_j are all independent conditioned on $X(t) = x \in \mathbb{Z}_+^N$ and

$$\begin{aligned}
&N_1 = \min\{x_1, x_2\}, \;\; p_1 = \frac{\tilde{c}_1}{\tilde{c}_1 + c_2}(1 - e^{-(\tilde{c}_1+c_2)\tau}),\\
&N_2 = x_3, \;\; p_2 = \frac{c_2}{\tilde{c}_1 + c_2}(1 - e^{-(\tilde{c}_1+c_2)\tau}),\\
&\lambda_3 = \frac{c_3 x_2}{c_4}(1 - e^{-c_4\tau}),\\
&N_4 = x_2, \;\; p_4 = (1 - e^{-c_4\tau}),
\end{aligned}$$

where

$$\begin{aligned}
&\tilde{c}_1 = (\max\{x_1, x_2\} + 1)c_1 \text{ if } \min\{x_1, x_2\} = 0,\\
&\tilde{c}_1 = \max\{x_1, x_2\}c_1 \text{ else.}
\end{aligned}$$

If $X(t) = x \notin \mathbb{Z}_+^N$ then we set $K_j = 0$ for all j and the update is $X(t+\tau) = x$. We note that this particular step differs from the way negativity was handled in [17], but freezing the tau leap process once it leaves $\mathbb{Z}_+^N$ allows for easier verification of Assumption 6 as stated in Theorem 4.5.

It is clear that N_1, N_2 and N_4 are bounded by a polynomial in $|x|$. It is also clear that p_1, p_2, p_4 and λ_3 are infinitely differentiable and the maximum of their derivatives on any bounded interval $[0, \delta]$ of τ is also bounded by a polynomial in $|x|$. Thus the hypotheses of Theorem 4.11 are satisfied and hence Assumption 5 holds.

The REMM-τ method was designed to satisfy the conditions that

$$\begin{aligned}
&\tilde{\phi}^{(1)}(0, x; 0) = -a_0(x),\\
&\tilde{\phi}^{(1)}(0, x; e_j) = a_j(x), \;\; j = 1, \ldots, M,\\
&\tilde{\phi}^{(1)}(0, x; k) = 0, \;\; k \notin \{0, e_1, e_2, \cdots, e_M\},
\end{aligned}$$

which can be directly verified by differentiation the details of which we shall omit. Thus by Corollary 4.12 pointwise consistency Assumption 3 follows.

As Assumptions 1 through 5 hold, by Theorem 3.5 the method is first order ($O(\tau)$) convergent in total variation.

In order to verify Assumption 6 we shall verify the conditions of Theorem 4.15. Firstly we note that the only superlinear reaction is 1, and that as $0 \leq K_1 \leq \min\{x_1, x_2\}$ it is clear that starting from a state $x \in \mathbb{Z}_+^N$ the state reached after the update $x + \nu_1 K_1$ still remains in $\mathbb{Z}_+^N$.

We note that $|\lambda^{(1)}| \leq c_3 x_2$ and hence can take $s = 1$ in Lemma 4.13 regarding K_3. Also we note that $N_2(x) \leq |x|$ and $N_4(x) \leq |x|$ and $|p_2^{(1)}| \leq c_2$ and $|p_4^{(1)}| \leq c_4$. Thus we can take $s_1 = 0$ and $s_2 = 1$ regarding both K_2 and K_4 in Lemma 4.14. Hence all the conditions of Theorem 4.15 are satisfied and we can conclude that Assumption 6 holds and hence by Theorem 3.7 the method is first order convergent in rth moment variation for each $r \in \mathbb{N}$. This also implies the convergence of all moments.

5. Discussion of results and concluding remarks. For the purpose of this discussion we need to differentiate the type of convergence considered in this paper from the type of analysis which relates τ to system size V as $\tau = V^{-\beta}$ and studies convergence as $V \to \infty$. We shall refer to the former as *convergence in fixed system sense* and the latter as *convergence in large system limit*.

While our (fixed system sense) convergence results were stated for general order of convergence $O(\tau^q)$, we have not seen a practical tau leap method that is $O(\tau^2)$ convergent in general in the fixed system sense. The *weak trapezoidal method* mentioned in [25, 8] was shown to be 2nd order consistent under the restrictive assumption that $\xi_1 a_j(x + \nu_k) - \xi_1 a_j(x) \geq a_j(x)$ for all x, j and k where $\xi_1 \in [2, \infty)$ is a method parameter. This leads to the condition that $a_j(x+\nu_k) \geq a_j(x)(1-1/\xi_1)$ for all x, j, k. When x is on the boundary of $\mathbb{Z}_+^N$ this may not hold for most systems. However, if with probability close to 1 the system state is far away from the "bad" boundaries, then one expects this method to be more accurate and for this to be valid one expects the system size to be large. The *midpoint tau* method is shown to be $O(\tau^2)$ convergent when $V \to \infty$ with $\tau = V^{-\beta}$ [7]. However, midpoint method is only first order convergent in the fixed system sense. In practice, for modestly large molecular copy numbers one may expect higher accuracy for both these methods(than the explicit tau leap), while for low copy numbers one may still expect these methods to be well behaved because they are first order convergent in the fixed system sense.

As a general rule, if a tau leap method shows higher order accuracy in the large system limit and is first order convergent in the fixed system sense it will be expected to be more effective than the first order convergent explicit tau. On the other hand if a method is higher order convergent in the large system limit, but is non-convergent or (even worse) not zero stable in the fixed system sense then the method should not be used.

It is easy to come up with higher order accurate (in the fixed system sense) tau methods that may not be practical. For instance one may take the tau update probabilities $\tilde{\phi}(\tau, x; k) = \text{Prob}(K = k \,|\, Y(t) = x)$ to agree with exact probabilities $\tilde{p}(\tau, x; k)$ up to $O(\tau^q)$ for the case of $|k| = 1, \ldots, q$, set $\tilde{\phi}(\tau, x; k) = 0$ for $|k| \geq q + 1$ and set $\tilde{\phi}(\tau, x; 0)$ accordingly. (We note that $\tilde{p}(\tau, x; k) = O(\tau^{|k|})$, see [18] for instance). Such a naive approach will result in a $O(\tau^2)$ convergent method that will leap over at most two reaction events (q events for the case of order q), not to mention other practical issues that need to be dealt with such as truncated Taylor expansions being for probabilities being non-negative.

The analysis in this paper does not suggest new tau leap methods. However it does provide some guidance to ensure that a tau leap method is convergent and zero stable (in the fixed system sense) so that the user does not have to worry about the small step sizes resulting in large errors. The most delicate of the assumptions is Assumption 6 which implies zero stability of the tau leap method (in term of moments). Zero-stability may not be taken for granted. We refer to [15] for an example (in the case of SDEs driven by Brownian motion) showing lack of convergence (and lack of zero stability) of the moments of the Euler method. Theorem 4.5 provides sufficient

conditions under which Assumption 6 can be verified and suggests that it is best to use bounded random variables (such as Binomials) in the tau update of superlinear reactions (see Remark 4.6).

Finally we like to note that finding a tau leap method that is $O(\tau^2)$ convergent *uniformly in system size* V (after a suitable scaling by a power of V) might prove to be useful. The error estimates derived in [7, 25, 8] contain system size V and step size τ (under the bounded system condition and/or global Lipschitz condition on propensities). None of the methods presented there are $O(\tau^2)$ convergent uniformly in V. We believe that the analysis in this paper can be extended to include the dependence of the error in the moments of a tau leap method on V and τ for the case of unbounded systems with nonlinear but polynomial growth propensities. While this exercise will not automatically result in a "$O(\tau^2)$ convergent uniformly in V" method, it will help provide some insights towards the construction of such methods.

REFERENCES

[1] D.J. Higham, P.E. Kloeden, *Numerical methods for nonlinear stochastic differential equations with jumps*, Numerische Mathematik, 101 (2005), pp. 101–119.

[2] J. Karlsson, R. Tempone, *Towards automatic global error control: Computable weak error expansion for the tau-leap method*, Monte Carlo Methods and Applications, 17 (2011), pp. 233–278.

[3] A. Gupta, C. Briat, M. Khammash, *A scalable computational framework for establishing long-term behavior of stochastic reaction networks*, PLOS Comput. Biol., 10 (2014).

[4] U.M. Ascher and L.R. Petzold, *Computer Methods for Ordinary Differential Equations and Differential-Algebraic Equations*, SIAM, 1998.

[5] Y. Cao, L.R. Petzold, M. Rathinam, and D.T. Gillespie, *The numerical stability of leaping methods for stochastic simulation of chemically reacting systems*, J. Chem. Phys., 121 (2004), pp. 12169–78.

[6] J.B. Conway, *A course in functional analysis*, Springer-Verlag, 1990.

[7] D. Anderson, A. Ganguly, T. Kurtz , *Error analysis of tau-leap simulation methods*, Ann. App. Probability, 21 (2011), pp. 2226–2262.

[8] D. Anderson, M. Koyama , *Weak error analysis of numerical methods for stochastic models of population processes*, SIAM J. MMS., 10 (2012), pp. 1493–1524.

[9] E. Hausenblas, *Error analysis for approximation of stochastic differential equations driven by poisson random measures*, SIAM J. Numer. Anal., 40 (2002), pp. 87–113.

[10] Stewart N. Ethier and Thomas G. Kurtz, *Markov Processes: Characterization and Convergence*, Wiley Series in Probability and Statistics, Wiley, Mar. 1986.

[11] D. T. Gillespie, *A general method for numerically simulating the stochastic time evolution of coupled chemical reactions*, J. Comp. Phys., 22 (1976), pp. 403–434.

[12] ———, *Exact stochastic simulation of coupled chemical reactions*, J. Phys. Chem., 81 (1977), pp. 2340–2361.

[13] ———, *Approximate accelerated stochastic simulation of chemically reacting systems*, J. Chem. Phys., 115 (2001), pp. 1716–1733.

[14] N.G. Van Kampen, *Stochastic Processes in Physics and Chemistry*, Elsevier Science Publishing Company, 1992.

[15] M. Hutzenthaler, A. Jentzen, P.E. Kloeden, *Strong and weak divergence in finite time of euler's method for stochastic differential equations with non-globally lipschitz continuous coefficients*, Proc. R. Soc. A, 467 (2010), pp. 1563–1575.

[16] M. Rathinam, *Moment growth bounds on continuous time markov processes on non-negative integer lattices*. To appear in the Quarterly of Applied Mathematics. arXiv:1304.5169.

[17] M. Rathinam, H. El-Samad, *Reversible-equivalent-monomolecular tau: A leaping method for "small-number and stiff" stochastic chemical systems*, Journal of Computational Physics, 224 (2007), pp. 897–923.

[18] M. Rathinam, L. Petzold, Y. Cao, D. Gillespie, *Consistency and stability of tau leaping schemes for chemical reaction systems*, SIAM J. MMS., 4 (2005), pp. 867–895.

[19] P. Glasserman, N. Merener, *Convergence of a discretization scheme for jump-diffusion processes with state-dependent intensities*, Proc. R. Soc. Lond. A, 460 (2004), pp. 111–127.

[20] M. Rathinam, L.R. Petzold, Y. Cao, and D.T. Gillespie, *Stiffness in stochastic chemically*

reacting systems: The implicit tau-leaping method, J. Chem. Phys., 119 (2003), pp. 12784–94.

[21] S. Engblom, *Spectral approximation of solutions to the chemical master equation*, J. Comput. Appl. Math., 229 (2009), pp. 208–221.

[22] ———, *On the stability of stochastic jump kinetics*, Appl. Math., 5 (2014), pp. 3217–3239.

[23] T. Li, *Analysis of explicit tau-leaping schemes for simulating chemically reacting systems*, SIAM J. MMS., 6 (2007), pp. 417–436.

[24] Y. Hu, T. Li, B. Min, *The weak convergence analysis of tau-leaping methods: revisited*, Commun. Math. Sci., 9 (2011), pp. 965–996.

[25] ———, *A weak second order tau-leaping method for chemical kinetic systems*, J. Comp. Phys., 135 (2011), p. 024113.

[26] Y. Yang, M. Rathinam, *Tau leaping of stiff stochastic chemical systems via local central limit approximation*, Journal of Computational Physics, 242 (2013), pp. 581–606.

[27] Y. Yang, M. Rathinam, J. Shen, *Integral tau methods for stiff stochastic chemical systems*, Journal of Chemical Physics, 134 (2011), p. 044129.