Construction and accuracy of partial differential equation approximations to the chemical master equation

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The mesoscopic description of chemical kinetics, the chemical master equation, can be exactly solved in only a few simple cases. The analytical intractability stems from the discrete character of the equation, and hence considerable effort has been invested in the development of Fokker-Planck equations, second-order partial differential equation approximations to the master equation. We here consider two different types of higher-order partial differential approximations, one derived from the system-size expansion and the other from the Kramers-Moyal expansion, and derive the accuracy of their predictions for chemical reactive networks composed of arbitrary numbers of unimolecular and bimolecular reactions. In particular, we show that the partial differential equation approximation of order Q from the Kramers-Moyal expansion leads to estimates of the mean number of molecules accurate to order $\Omega^{-(2Q-3)/2}$, of the variance of the fluctuations in the number of molecules accurate to order $\Omega^{-(2Q-5)/2}$, and of skewness accurate to order $\Omega^{-(Q-2)}$. We also show that for large Q, the accuracy in the estimates can be matched only by a partial differential equation approximation from the system-size expansion of approximate order $2Q$. Hence, we conclude that partial differential approximations based on the Kramers-Moyal expansion generally lead to considerably more accurate estimates in the mean, variance, and skewness than approximations of the same order derived from the system-size expansion.

I. INTRODUCTION

Recent years have seen a surge of interest in chemical kinetics on mesoscopic length scales, such as those inside cells and in nanoreactors (see, for example, [1–7]). The accepted quantitative description in such scenarios and under well-mixed conditions is the chemical master equation (CME) [8–11]. This equation can be solved exactly for only a few simple cases [8,12,13]. Hence, one of the major thrusts in this field has been the development of approximate numerical and analytical methods to deal with the CME description of chemical reaction systems of arbitrary complexity.

The difficulties in handling CMEs stem from their discrete character. The logical alternative to circumventing these problems is to construct a partial differential equation approximation of the CME. These approximations can be handled much better than differential-difference equations such as the CME, particularly since there already exists a vast literature on their analytical and numerical solution in the physical sciences. There are two such partial differential equation approximations in popular usage: the linear and nonlinear Fokker-Planck equations. Both are second-order partial differential equations. Note that in this context, the linearity or nonlinearity refers to the dependence of the drift vector and the diffusion matrices in the Fokker-Planck equations on the continuous variables. The two equations are the lowest order truncations of two different expansions of the CME. The linear Fokker-Planck equation is obtained from the system-size expansion (SSE) [1,10,14], while the nonlinear Fokker-Planck equation is obtained from the Kramers-Moyal expansion (KME) [11,15,16]. Both expansions hold the promise of constructing partial differential equations of ever-increasing accuracy by including more terms in the truncated forms. However, to date, the general form and accuracy of the SSE-derived partial differential equation approximation of arbitrary order is unknown. The KME-derived partial differential equation approximation of arbitrary order is known, but its accuracy is unknown. These are important gaps in the literature to fill, since currently it is not clear how to construct partial differential approximations of the CME which can estimate quantities to some prescribed accuracy.

The article is organized as follows. In Sec. II, we obtain the general form and accuracy of the SSE-derived partial differential equation approximations of the CME for a chemical reactive system of arbitrary complexity. In Sec. III, the accuracy of the KME-derived approximations is obtained by means of a graphical representation of the SSE and KME. In Sec. IV, the SSE- and KME-derived partial differential equation approximations are contrasted and compared. In particular, we show that generally the KME-derived partial differential equation approximation of a given order produces estimates which are considerably more accurate than the SSE-derived approximation of the same order.

II. CONTINUOUS APPROXIMATIONS OF THE CME USING THE SSE

Consider a general chemical system consisting of a number V of distinct chemical species interacting via R elementary chemical reactions of the type

$$s_{1j}X_1 + \cdots + s_{Vj}X_V \xrightarrow{k_j} r_{1j}X_1 + \cdots + r_{Vj}X_V. \quad (1)$$
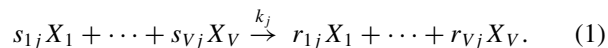
Here j is an index running from 1 to R, X_i denotes chemical species i, s_{ij} and r_{ij} are the stoichiometric coefficients, and k_j is the macroscopic rate of reaction. Note that each reaction is elementary, meaning unimolecular or bimolecular. Since such reactions involve the simultaneous interaction of at most two molecules of two different species, then it follows that most of the stoichiometric coefficients in reaction scheme (1) will be zero. Elementary termolecular interactions, that is, those

involving the simultaneous interaction of three molecules, are rare for reactions between molecules [17,18] but important for recombination and collision-induced reactions between atoms or diatoms [18–20]. In this article, we are interested in only molecular interactions (e.g., intracellular biochemical reactions involving the interaction of proteins, enzymes, etc.) and hence we can safely assume that any complex reaction mechanism of interest can be broken down into a sequence of elementary unimolecular and bimolecular reactions of the form of reaction scheme (1).

If this system is well mixed, then its macroscopic description is given by a set of rate equations (REs):

$$\frac{\partial \phi_i}{\partial t} = \sum_{j=1}^{R} S_{ij} f_j(\vec{\phi}), \qquad (2)$$

where $\vec{\phi} = (\phi_1, \ldots, \phi_V)^T$ is the vector of macroscopic concentrations, $S_{ij} = r_{ij} - s_{ij}$ is the (i,j) element of the stoichiometric matrix, and f_j is the macroscopic rate function of the jth reaction, which has the general mass-action form, $f_j(\vec{\phi}) = k_j \prod_{m=1}^{V} \phi_m^{s_{mj}}$. In contrast, on mesoscopic length scales, the description of the system is given by the CME [10,11]:

$$\frac{\partial P(\vec{n},t)}{\partial t} = \Omega \sum_{j=1}^{R} \left(\prod_{i=1}^{V} E_i^{-S_{ij}} - 1 \right) \hat{f}_j(\vec{n},\Omega) P(\vec{n},t). \qquad (3)$$

This equation is a time-evolution equation for the probability $P(\vec{n},t)$ of the system being in a particular mesoscopic state $\vec{n} = (n_1, \ldots, n_V)^T$, where n_i is the discrete number of molecules of the ith species. The reactions are assumed to occur in a compartment of volume Ω. The CME form is made considerably compact by the use of the step operator $E_i^{-S_{ij}}$, which is defined by its action on a general function g of the absolute number of molecules:

$$E_i^{-S_{ij}} g(n_1, \ldots, n_i, \ldots, n_V) = g(n_1, \ldots, n_i - S_{ij}, \ldots, n_V). \qquad (4)$$

The chemical reaction details are encapsulated in the stoichiometric matrix $S_{ij} = r_{ij} - s_{ij}$ and in the microscopic rate functions $\hat{f}_j(\vec{n},\Omega)$. The probability that the jth reaction occurs in the time interval $[t, t+dt)$ is given by $\Omega \hat{f}_j(\vec{n},\Omega)dt$. For elementary reactions, the microscopic rate function takes one of four different forms, depending on the order of the jth reaction (for the exact forms and the relationship between the microscopic and macroscopic rate functions, refer to [21]).

Now our stated aim is to find a continuous approximation of the CME; in other words, we would like to write down a partial differential equation for the time evolution of a probability density function of a continuous variable. The method which naturally fits the task at hand is the system-size expansion of van Kampen [10], in which one writes the absolute number of molecules of species i as

$$\frac{n_i}{\Omega} = \phi_i + \Omega^{-1/2} \epsilon_i, \qquad (5)$$

where ϕ_i is the macroscopic concentration of species i as determined by the REs and ϵ_i is a new random variable. Note that while n_i is a discrete random variable, the ansatz Eq. (5) necessarily implies that ϵ_i is a continuous random variable

since the macroscopic concentration is always a positive real number. The change of variables causes the probability distribution of molecular populations, $P(\vec{n},t)$, to be replaced by the probability distribution of fluctuations, $\Pi(\vec{\epsilon},t)$, where $\vec{\epsilon} = (\epsilon_1, \ldots, \epsilon_V)^T$. The time derivative, the step operator, and the microscopic rate function in the CME read in the new variables:

$$\frac{\partial P(\vec{n},t)}{\partial t} = \frac{\partial \Pi(\vec{\epsilon},t)}{\partial t} - \Omega^{1/2} \sum_{i=1}^{V} \frac{\partial \phi_i}{\partial t} \frac{\partial \Pi(\vec{\epsilon},t)}{\partial \epsilon_i}, \qquad (6)$$

$$\prod_{i=1}^{V} E_i^{-S_{ij}} - 1 = \sum_{k=1}^{\infty} -1^k \Omega^{-k/2} a_j^k, \qquad (7)$$

$$\hat{f}_j = \sum_{m=0}^{2} \Omega^{-m/2} b_j^m + c_j^2 \Omega^{-1} + c_j^3 \Omega^{-3/2}, \qquad (8)$$

where

$$a_j^k = \frac{1}{k!} \left(\sum_{i=1}^{V} S_{ij} \frac{\partial}{\partial \epsilon_i} \right)^k, \qquad (9)$$

$$b_j^k = \frac{1}{k!} \left(\sum_{w=1}^{V} \epsilon_w \frac{\partial}{\partial \phi_w} \right)^k f_j(\vec{\phi}), \qquad (10)$$

$$c_j^2 = -\frac{1}{2} \sum_{w=1}^{V} \phi_w \frac{\partial^2 f_j(\vec{\phi})}{\partial \phi_w^2}, \qquad (11)$$

$$c_j^3 = -\frac{1}{2} \sum_{w=1}^{V} \epsilon_w \frac{\partial^2 f_j(\vec{\phi})}{\partial \phi_w^2}. \qquad (12)$$

Note that the upper limit of the sum in Eq. (8) is 2 because all reactions involve at most the interaction of two molecules and hence b_j^k equals zero for $k > 2$. Details of the derivations leading to Eqs. (6)–(12) can be found in [21]. Substituting these equations in the CME, Eq. (3), leads to

$$\frac{\partial \Pi(\vec{\epsilon},t)}{\partial t} - \Omega^{1/2} \sum_{i=1}^{V} \frac{\partial \phi_i}{\partial t} \frac{\partial \Pi(\vec{\epsilon},t)}{\partial \epsilon_i}$$
$$= \sum_{j=1}^{R} \sum_{k=1}^{\infty} (-1)^k a_j^k \Omega^{-k/2} \left(\sum_{m=0}^{2} b_j^m \Omega^{1-m/2} + c_j^2 + c_j^3 \Omega^{-1/2} \right)$$
$$\times \Pi(\vec{\epsilon},t). \qquad (13)$$

This equation is further simplified by substituting Eq. (2) in Eq. (13), which leads to terms of order $\Omega^{1/2}$ on both sides of Eq. (13) to cancel out and the equation to reduce to

$$\frac{\partial \Pi(\vec{\epsilon},t)}{\partial t} = \sum_{j=1}^{R} \sum_{k=1}^{\infty} (-1)^k a_j^k \Omega^{-k/2} \Bigg((1 - \delta_{k,1} \delta_{m,0})$$
$$\times \sum_{m=0}^{2} b_j^m \Omega^{1-m/2} + \left(c_j^2 + c_j^3 \Omega^{-1/2} \right) \Bigg) \Pi(\vec{\epsilon},t). \qquad (14)$$

Note that Eq. (14) is a time-evolution equation for the probability distribution of a continuous variable which is exactly equal to the CME, Eq. (3). Despite that the system-size expansion was developed fifty years ago [14], this is the

first time to our knowledge that it has been derived in a completely general form, that is, applicable to chemical reaction networks of arbitrary complexity and valid to the order of any power of the inverse square root of the volume. Elf and Ehrenberg [1] had previously derived the multivariate expansion to $O(\Omega^0)$ (the linear-noise approximation), while Grima and collaborators have derived and used the multivariate expansion up to order $O(\Omega^{-3/2})$ [4,21–23].

We can now use Eq. (14) to generate continuous approximations to the CME. Clearly the only way to do this is to keep a finite number of terms on the right-hand side of Eq. (14) since this will naturally lead to a partial differential equation of finite order. Of course, there are infinitely many ways in which one can accomplish this, each of which will lead to a different approximation of the CME. Of all these, the only mathematically rigorous approach is to truncate the right-hand side of Eq. (14) such that one keeps only terms whose order is at most $\Omega^{-T/2}$. It can be deduced from Eq. (14) that the resulting partial differential equation will be of order $Q = T + 2$. We shall call this equation the Q-SSE. The solution of this approximative equation leads to a probability density function accurate to order $\Omega^{-(Q-2)/2}$ and of course moments of the ϵ variables accurate to the same order. We will now find time-evolution equations for the moments and also devise a corresponding graphical representation. This representation provides a "visual summary" of the calculations implicit in the SSE method; furthermore, as we shall see in the next section,

its use bypasses lengthy calculations to obtain the accuracy of the KME-derived partial differential approximations.

The fact that the right-hand side of Eq. (14) is a series in powers of the inverse square root of the volume suggests that the most straightforward manner of solving this equation is by applying the standard power series method of solving differential equations. The method starts by expressing the solution of Eq. (14), $\Pi(\vec{\epsilon},t)$, as a series in powers of the inverse square root of the volume:

$$\Pi(\vec{\epsilon},t) = \sum_{j=0}^{\infty} \Pi_j(\vec{\epsilon},t)\Omega^{-j/2}. \tag{15}$$

By the normalization condition, we have $\int \Pi(\vec{\epsilon},t)d\vec{\epsilon} = 1 = \sum_{j=0}^{\infty} \int \Pi_j(\vec{\epsilon},t)\Omega^{-j/2}d\vec{\epsilon}$. By equating powers of the volume, one obtains $\int \Pi_0 d\vec{\epsilon} = 1$, $\int \Pi_j d\vec{\epsilon} = 0, \forall j \geqslant 1$. Hence, it follows that only Π_0 is a true probability density function and that the quantities $\Pi_1, \Pi_2, \ldots$ can take both positive and negative values. It also follows that any partial differential equation approximation which estimates the probability density function to an accuracy higher than order Ω^0, that is, the Q-SSE with $Q > 2$, will necessarily have a solution which is not strictly positive. This statement agrees with Pawula's theorem [24]. We will return to a discussion of Pawula's theorem in the context of our results in Section V.

Upon substituting Eq. (15) in Eq. (14) and equating powers of Ω on both sides of the equation, we find

$$\frac{\partial \Pi_n(\vec{\epsilon},t)}{\partial t} = \sum_{j=1}^{R}\left(\sum_{p=0}^{n}\left[(-1)^{n-p+1}a_j^{n-p+1}b_j^1 + (-1)^{n-p+2}a_j^{n-p+2}b_j^0\right]\Pi_p(\vec{\epsilon},t)\right.$$
$$\left. + \sum_{p=0}^{n-1}(-1)^{n-p}a_j^{n-p}\left(b_j^2+c_j^2\right)\Pi_p(\vec{\epsilon},t) + \sum_{p=0}^{n-2}(-1)^{n-p-1}a_j^{n-p-1}c_j^3\Pi_p(\vec{\epsilon},t)\right). \tag{16}$$

Note that if we had to start from the Q-SSE, we would get the same equation as Eq. (16) for all $\Pi_n(\vec{\epsilon},t)$ such that $n \leqslant Q - 2$.

We want to now find the corresponding time-evolution equations for the moments. By multiplying Eq. (15) by $\epsilon_k\epsilon_m \ldots \epsilon_r$ and integrating over $\vec{\epsilon}$, we get

$$\langle\epsilon_k\epsilon_m \ldots \epsilon_r\rangle = \sum_{j=0}^{\infty}[\epsilon_k\epsilon_m \ldots \epsilon_r]_j\Omega^{-j/2}, \tag{17}$$

where $[\epsilon_k\epsilon_m \ldots \epsilon_r]_j$ is the pseudomoment of perturbation order j defined as $[\epsilon_k\epsilon_m \ldots \epsilon_r]_j = \int \epsilon_k\epsilon_m \ldots \epsilon_r\ \Pi_j(\vec{\epsilon},t)d\vec{\epsilon}$. Note that we refer to this quantity as a pseudomoment of perturbation order j because $\Pi_j(\vec{\epsilon},t)$ is, as already shown, not a probability distribution except for the case $j = 0$. Time-evolution equations for the pseudomoment $[\epsilon_k\epsilon_m \ldots \epsilon_r]_n$ can in principle be obtained by multiplying Eq. (16) by $\epsilon_k\epsilon_m \ldots \epsilon_r$ and integrating over $\vec{\epsilon}$. In practice, this leads to considerably complicated expressions which can barely fit on a page of paper. Instead, we task ourselves to deduce only the general functional form of these equations, as this will be sufficient for our purposes in this paper.

Consider the time-evolution equation for the rth pseudomoment of perturbation order n, that is, for $[\epsilon_{\alpha_1}\epsilon_{\alpha_2} \ldots \epsilon_{\alpha_r}]_n$ where the subscript α_i can take any discrete positive value between 1 and V. Both sides of Eq. (16) are multiplied by $\epsilon_{\alpha_1}\epsilon_{\alpha_2} \ldots \epsilon_{\alpha_r}$ and the integral is taken over $\vec{\epsilon}$. The left-hand side leads to $\partial_t[\epsilon_{\alpha_1}\epsilon_{\alpha_2} \ldots \epsilon_{\alpha_r}]_n$. The right-hand side will have a contribution from each of the five sums over p on the right-hand side of Eq. (16). The contributions will be denoted as T_i, where i varies from 1 to 5. The first of these, T_1, is given by the expression

$$T_1 = \int \sum_{j=1}^{R}\sum_{p=0}^{n}\epsilon_{\alpha_1}\epsilon_{\alpha_2} \ldots \epsilon_{\alpha_r}(-1)^{n-p+1}a_j^{n-p+1}b_j^1\Pi_p(\vec{\epsilon},t)d\vec{\epsilon}$$
$$= \sum_{j=1}^{R}\sum_{p=0}^{n}\sum_{w=1}^{N}\sum_{\lambda_1}^{N} \cdots \sum_{\lambda_{n-p+1}=1}^{N}\frac{(-1)^{n-p+1}}{(n-p+1)!}$$
$$\times S_{\lambda_1,j} \ldots S_{\lambda_{n-p+1},j}\frac{\partial f_j(\vec{\phi})}{\partial \phi_w}I_{1,p}, \tag{18}$$

where the integrals $I_{1,p}$ are given by

$$I_{1,p} = \int \epsilon_{\alpha_1} \ldots \epsilon_{\alpha_r} \frac{\partial}{\partial \epsilon_{\lambda_1}} \ldots \frac{\partial}{\partial \epsilon_{\lambda_{n-p+1}}} \epsilon_w \Pi_p(\vec{\epsilon},t)d\vec{\epsilon}. \quad (19)$$

Clearly the functional form of T_1 will be solely dictated by the integrals $I_{1,p}$. If $p = n$, then integration by parts of Eq. (19) leads to an rth pseudomoment of order n. If $p = n - 1$, then integration by parts of Eq. (19) leads to an $(r - 1)$th pseudomoment of order $n - 1$ and so on. Note that if $n - p + 1 > r$, then the integral in Eq. (19) evaluates to zero, implying that only values of p greater than or equal to $n - r + 1$ will contribute to T_1. Hence if we denote an rth pseudomoment of perturbation order n as M_n^r we have the following functional form for T_1:

$$T_1 = f_1\left(M_n^r, M_{n-1}^{r-1}, M_{n-2}^{r-2}, \ldots, M_{n+1-r}^1\right). \quad (20)$$

Note that generally there are a large number of distinct rth pseudomoments of perturbation order n. The notation M_n^r simply means any one of these pseudomoments without specifying which one it is. As we shall see, this will be sufficient to answer the questions that we are interested in.

By an analogous set of calculations, one finds the following integrals stemming from consideration of the four remaining terms on the right-hand side of Eq. (16):

$$I_{2,p} = \int \epsilon_{\alpha_1} \ldots \epsilon_{\alpha_r} \frac{\partial}{\partial \epsilon_{\lambda_1}} \ldots \frac{\partial}{\partial \epsilon_{\lambda_{n-p+2}}} \Pi_p(\vec{\epsilon},t)d\vec{\epsilon}, \quad (21)$$

$$I_{3,p} = \int \epsilon_{\alpha_1} \ldots \epsilon_{\alpha_r} \frac{\partial}{\partial \epsilon_{\lambda_1}} \ldots \frac{\partial}{\partial \epsilon_{\lambda_{n-p}}} \epsilon_w \epsilon_y \Pi_p(\vec{\epsilon},t)d\vec{\epsilon}, \quad (22)$$

$$I_{4,p} = \int \epsilon_{\alpha_1} \ldots \epsilon_{\alpha_r} \frac{\partial}{\partial \epsilon_{\lambda_1}} \ldots \frac{\partial}{\partial \epsilon_{\lambda_{n-p}}} \Pi_p(\vec{\epsilon},t)d\vec{\epsilon}, \quad (23)$$

$$I_{5,p} = \int \epsilon_{\alpha_1} \ldots \epsilon_{\alpha_r} \frac{\partial}{\partial \epsilon_{\lambda_1}} \ldots \frac{\partial}{\partial \epsilon_{\lambda_{n-p-1}}} \epsilon_w \Pi_p(\vec{\epsilon},t)d\vec{\epsilon}. \quad (24)$$

By reasoning similar to that for the first term, one can deduce that the above integrals imply the following dependence:

$$T_2 = f_2\left(M_n^{r-2}, M_{n-1}^{r-3}, \ldots, M_{n+3-r}^1\right), \quad (25)$$

$$T_3 = f_3\left(M_{n-1}^{r+1}, M_{n-2}^r, \ldots, M_{n-r}^2\right), \quad (26)$$

$$T_4 = f_4\left(M_{n-1}^{r-1}, M_{n-2}^{r-2}, \ldots, M_{n-r+1}^1\right), \quad (27)$$

$$T_5 = f_5\left(M_{n-2}^r, M_{n-3}^{r-1}, \ldots, M_{n-1-r}^1\right). \quad (28)$$

Hence the time-evolution equation for the rth pseudomoment of perturbation order n is generally given by

$$\partial_t M_n^r = T_1 + T_2 + T_3 + T_4 + T_5. \quad (29)$$

Note that the time-evolution equations for the pseudomoments of perturbation order zero ($n = 0$) are closed; that is, the determination of M_0^R requires that we know M_0^r such that $r < R$. Hence, one can obtain M_0^R by an iterative solution of Eq. (29). Now consider the time-evolution equations for the pseudomoments of perturbation order greater than zero. The functions T_1, T_2, T_4, and T_5 imply that the calculation of a pseudomoment M_N^R, where $N > 0$, requires pseudomoments M_n^r such that $r \leqslant R$ and $n \leqslant N$; the function T_3 implies a further dependence on M_{N-1}^{R+1}. The pseudomoments needed for the calculation of M_N^R are represented in a diagram of r versus
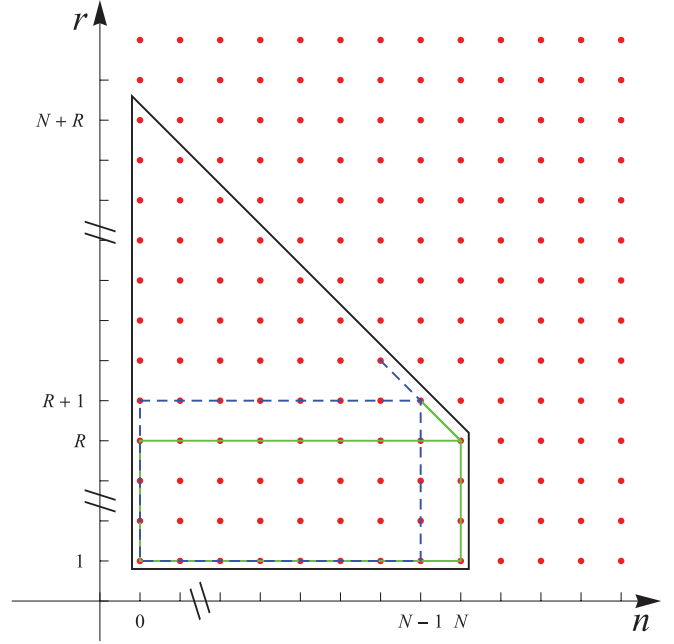

FIG. 1. (Color online) Graphical representation of the set of calculations inherent in obtaining an Rth pseudomoment of perturbation order N, denoted as M_N^R, using the system-size expansion (SSE). In $n - r$ space, a point with coordinates (x,y) represents the pseudomoment M_x^y. Points enclosed by the green (light gray) construct and on which it passes represent those pseudomoments which appear on the right-hand side of the time-evolution equation for M_N^R; i.e., Eq. (29) with $n = N$ and $r = R$. Similarly, points enclosed by the blue (dashed black) construct and on which it passes represent those pseudomoments which appear on the right-hand side of the time-evolution equation for M_{N-1}^{R+1}; i.e., Eq. (29) with $n = N - 1$ and $r = R + 1$. The time-evolution equation of M_N^R depends on the knowledge of M_{N-1}^{R+1}, the time-evolution equation of M_{N-1}^{R+1} depends on M_{N-2}^{R+2}, and so forth, implying that the iterative procedure of obtaining the final solution for M_N^R will generally involve the computation of pseudomoments enclosed by the black polygon.

n in Fig. 1 by the green (light gray) geometrical construct. The interpretation is that some of the pseudomoments in $n - r$ space (represented by the red dots) enclosed by the green (light gray) lines or through which the lines pass are required for the computation of M_N^R by Eq. (29). In other words, one needs to first solve for these other pseudomoments using Eq. (29) before one can arrive at the solution for M_N^R. One can convince oneself using Fig. 1 that this iterative procedure will generally involve the computation of pseudomoments enclosed by the black polygon. Note that the hierarchy of equations for the time evolution of the pseudomoments of perturbation order greater than zero ultimately depends on the knowledge of the pseudomoments of perturbation-order zero, which are all known as previously discussed. Hence, the hierarchy of equations for the time evolution of the pseudomoments closes automatically without requiring any ad hoc closure relations. Note that once the pseudomoments up to perturbation order N are known, one can easily calculate using Eq. (17) the moments of the ϵ variables accurate to order $\Omega^{-N/2}$. Subsequently the latter can be used to calculate the moments of the absolute

number of molecules using Eq. (5), which typically are the desired final output.

III. CONTINUOUS APPROXIMATIONS OF THE CME USING THE KME

In this section, we will derive the accuracy of continuous approximations to the CME using the KME. The KME is obtained by a Taylor expansion of the step operator in the CME, Eq. (3). Starting from the definition of the step operator, one obtains

$$\prod_{i=1}^{V} E_i^{-S_{ij}} g(n_1,\ldots,n_i,\ldots,n_V)$$
$$= g(n_1 - S_{1j},\ldots,n_i - S_{ij},\ldots,n_V - S_{Vj}). \quad (30)$$

By Taylor expanding the right-hand side about the point $(n_1,\ldots,n_i,\ldots,n_V)$, one obtains

$$\prod_{i=1}^{V} E_i^{-S_{ij}} - 1 = \sum_{k=1}^{\infty} \frac{-1^k}{k!} \left(\sum_{i=1}^{V} S_{ij} \frac{\partial}{\partial n_i} \right)^k. \quad (31)$$

By substituting the above equation in Eq. (3), one obtains the KME of the CME:

$$\frac{\partial P(\vec{n},t)}{\partial t} = \Omega \sum_{j=1}^{R} \sum_{k=1}^{\infty} \frac{-1^k}{k!} \left(\sum_{i=1}^{V} S_{ij} \frac{\partial}{\partial n_i} \right)^k \hat{f}_j(\vec{n},\Omega) P(\vec{n},t). \quad (32)$$

This equation is formally equivalent to the CME, as was Eq. (14). Both Eqs. (14) and (32) have an infinite number of terms on their right-hand sides, and hence a truncation to some finite number of terms is necessary to generate a continuous approximation to the CME. Now as regards Eq. (14), it was straightforward to deduce from the form of the equation that the only meaningful truncation involves keeping terms up to some desired order in the power of the inverse square root of the volume. Unfortunately, the same guiding principle cannot be used for Eq. (32) because it is not clear from the form of the equation what small parameter is being considered [11]. Hence, the only reasonable means to truncate Eq. (32) to a finite number of terms and to obtain a continuous approximation to the CME involves its arbitrary truncation to include at most derivatives of order Q, leading to what we shall refer to as the Q-KME:

$$\frac{\partial P(\vec{n},t)}{\partial t} = \Omega \sum_{j=1}^{R} \sum_{k=1}^{Q} \frac{-1^k}{k!} \left(\sum_{i=1}^{V} S_{ij} \frac{\partial}{\partial n_i} \right)^k \hat{f}_j(\vec{n},\Omega) P(\vec{n},t). \quad (33)$$

Note that the Q-KME is a partial differential equation of order Q. The case $Q = 2$ is the celebrated nonlinear Fokker-Planck equation [10,11,25], the most frequently used form of the truncated KME. The problem with the above partial differential equation is that we cannot tell the accuracy of its estimates since we have no idea of the size of each term. This problem can be rectified by applying the change of variables given by Eq. (5) to Eq. (33). The time derivative on the left-hand side of Eq. (33) and the microscopic rate function on its right-hand side transform as Eqs. (6) and (8) respectively.

The derivative with respect to n_i on the right-hand side of Eq. (33) transforms as $\partial/\partial n_i \rightarrow \Omega^{-1/2}\partial/\partial \epsilon_i$. The probability distribution of molecular populations, $P(\vec{n},t)$, transforms to the probability distribution of fluctuations, $\hat{\Pi}(\vec{\epsilon},t)$, where the hat is to distinguish this distribution from that obtained from the SSE. Hence, the Q-KME can be written as

$$\frac{\partial \hat{\Pi}(\vec{\epsilon},t)}{\partial t} = \sum_{j=1}^{R} \sum_{k=1}^{Q} (-1)^k a_j^k \Omega^{-k/2} \Bigg((1 - \delta_{k,1}\delta_{m,0})$$
$$\times \sum_{m=0}^{2} b_j^m \Omega^{1-m/2} + \left(c_j^2 + c_j^3 \Omega^{-1/2} \right) \Bigg) \hat{\Pi}(\vec{\epsilon},t). \quad (34)$$

The same result can be obtained by applying the small noise expansion method developed by Gardiner [11] for Fokker-Planck equations.

The solution of this equation proceeds as before, by substituting $\hat{\Pi}(\vec{\epsilon},t) = \sum_{j=0}^{\infty} \hat{\Pi}_j(\vec{\epsilon},t)\Omega^{-j/2}$ in Eq. (34) and finding time-evolution equations for $\hat{\Pi}_n$. Note that Eq. (34) has the same precise form as Eq. (14) but with the upper limit of the sum over k being Q rather than infinity. Hence, it can be immediately stated that the time-evolution equations for $\hat{\Pi}_n(\vec{\epsilon},t)$ have the same form as those for $\Pi_n(\vec{\epsilon},t)$ given by Eq. (16) with the additional constraint that the superscript index k of a_j^k takes a maximum value of Q. It then follows that in the calculation of the time evolution of the pseudomoments according to the KME, we will obtain integrals of the same form as Eq. (19) and Eqs. (21)–(24) with the additional constraint that $n - p + 1 \leqslant Q$ in Eq. (19), $n - p + 2 \leqslant Q$ in Eq. (21), $n - p \leqslant Q$ in Eqs. (22) and (23), and $n - p - 1 \leqslant Q$ in Eq. (24). Since the minimum value of p is 0, it follows that if $n \leqslant Q - 2$, then all these constraints are automatically satisfied. Hence, we can state

$$\partial_t M_{n,\text{QKM}}^r \stackrel{f}{=} \partial_t M_n^r, \quad n \leqslant Q - 2, \quad (35)$$

where $M_{n,\text{QKM}}^r$ is the rth pseudomoment of perturbation order n as determined by the Q-KME. Note that the symbol $\stackrel{f}{=}$ in Eq. (35) means that the time-evolution equation for an rth pseudomoment of perturbation order n using the Q-KME has the same functional dependence as the time-evolution equation for the same pseudomoment determined using the SSE.

Consider now the case $n = Q - 1$. The constraints on Eqs. (19), (22), (23), and (24) are satisfied for all allowable values of p but the constraint on Eq. (21) is not possible to uphold when $p = 0$. In other words, the time-evolution equations for the SSE have a contribution from the integral Eq. (21) with $n = Q - 1$ and $p = 0$ while the time-evolution equations for the Q-KME do not. The question now is whether this extra integral evaluates to a nonzero value. Clearly if $n - p + 2 = Q + 1 > r$, then the integral gives no contribution to the SSE time-evolution equation of an rth pseudomoment. Hence, we can further state

$$\partial_t M_{Q-1,\text{QKM}}^r \stackrel{f}{=} \partial_t M_{Q-1}^r, \quad r \leqslant Q. \quad (36)$$

One can generalize the arguments leading to Eq. (36) for $n \geqslant Q - 1$ leading to

$$\partial_t M_{n,\text{QKM}}^r \stackrel{f}{=} \partial_t M_n^r, \quad n \geqslant Q - 1, \quad r \leqslant Q. \quad (37)$$
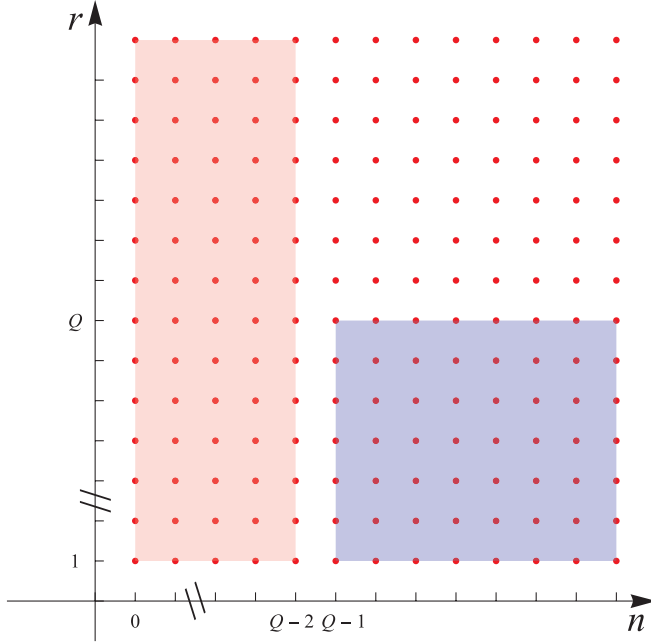
FIG. 2. (Color online) Illustration of the regions in $n-r$ space where the time-evolution equations for the pseudomoments of the Q-KME (the partial differential approximation of order Q obtained from the Kramers-Moyal expansion) have the same functional dependence on other pseudomoments as those from the SSE. In this space, a point with coordinates (x,y) represents a yth pseudomoment of perturbation order x, denoted as M_x^y. The red (light gray) and blue (dark gray) regions correspond to Eqs. (35) and (37) respectively.

The regions in $n-r$ space where the time-evolution equations of the Q-KME have the same functional dependence on other pseudomoments as those from the SSE are illustrated in Fig. 2, where the red (light gray) and blue (dark gray) regions correspond to Eqs. (35) and (37) respectively.

Now we will use Figs. 1 and 2 to deduce the accuracy of the pseudomoments as predicted by the Q-KME. Say that we are interested in determining whether $M_{N,\text{QKM}}^R = M_N^R$, that is, whether the Q-KME prediction of the Rth moment is accurate to order $\Omega^{-N/2}$. To obtain this quantity from the SSE, we have to solve time-evolution equations for the pseudomoments enclosed by the black polygon in Fig. 1. Now if the time-evolution equations for the pseudomoments from the Q-KME have the same functional dependence as those from the SSE in the region of $n-r$ space enclosed by the black polygon, then it immediately follows that that $M_{N,\text{QKM}}^R = M_N^R$. Of course, if $N \leqslant Q-2$ then $M_{N,\text{QKM}}^R = M_N^R$ for all R by Eq. (35). However, when $N \geqslant Q-1$, the situation is more complex. This case is illustrated in Fig. 3, which shows a superposition of Figs. 1 and 2 for three different subcases: (a) $Q > N - Q + R + 1$, (b) $Q = N - Q + R + 1$, and (c) $Q < N - Q + R + 1$. Note that in subcases (a) and (b) the blue (dark gray) and red (light gray) regions cover all the points in $n-r$ space enclosed by the black polygon, whereas in (c) this is not the case. Hence, we can now state the following general results:

$$M_{n,\text{QKM}}^r = M_n^r, \quad n \leqslant Q-2, \quad \forall r, \tag{38}$$

$$M_{n,\text{QKM}}^r = M_n^r, \quad Q-1 \leqslant n \leqslant 2Q-r-1, \quad r \leqslant Q. \tag{39}$$

It is interesting to compare these with those obtained from the Q-SSE. As remarked in Sec. II after Eq. (16), the Q-SSE time-evolution equations for an rth pseudomoment of perturbation order n agree with those of the SSE for all r provided $n \leqslant Q-2$. This statement is the equivalent of Eq. (38) for the Q-KME. However, the Q-SSE has no equivalent of Eq. (39). As we shall see in the next section, the lack of this equivalent implies that Q-SSE estimates are generally less accurate than those of the Q-KME, even though the two partial differential approximations have the same order Q.

IV. ACCURACY OF THE MEAN, VARIANCE, AND SKEWNESS ESTIMATED BY THE CONTINUUM APPROXIMATIONS

Typically what we are after is not an approximation to the full probability distribution of the CME but instead some useful statistical measures such as the mean, variance, Fano factors, coefficients of variation, and the skewness. We will now use the results derived in previous sections to deduce the accuracy of the Q-KME and Q-SSE predictions for these various statistical measures.

We start by noting that since $Q \geqslant 2$ (the lowest order Q-KME is the nonlinear Fokker-Plance equation with $Q = 2$), it follows from Eqs. (17), (38), and (39) that the 1st moments, $\langle \epsilon_i \rangle$, and the 2nd moments, $\langle \epsilon_i \epsilon_j \rangle$, determined from the Q-KME, are accurate to order $\Omega^{-(Q-1)}$ and order $\Omega^{-(2Q-3)/2}$ respectively. Similarly, it can also be shown that the 3rd moments, $\langle \epsilon_i \epsilon_j \epsilon_k \rangle$, are accurate to order $\Omega^{-(Q-2)}$. Using this information, we can now deduce the order of accuracy of some common and useful statistical quantities as estimated by the Q-KME:

$$\langle n_i \rangle = \Omega \phi_i + \Omega^{1/2} \langle \epsilon_i \rangle \sim O(\Omega^{-(2Q-3)/2}), \tag{40}$$

$$\sigma_i^2 = \langle n_i^2 \rangle - \langle n_i \rangle^2 = \Omega(\langle \epsilon_i^2 \rangle - \langle \epsilon_i \rangle^2) \sim O(\Omega^{-(2Q-5)/2}), \tag{41}$$

$$F_i = \frac{\sigma_i^2}{\langle n_i \rangle} \sim O(\Omega^{-(2Q-5)/2}), \tag{42}$$

$$C_i^2 = \frac{\sigma_i^2}{\langle n_i \rangle^2} \sim O(\Omega^{-(2Q-5)/2}), \tag{43}$$

$$S_i = \left\langle \left(\frac{n - \langle n_i \rangle}{\sigma_i} \right)^3 \right\rangle = \frac{\langle \epsilon_i^3 \rangle - 3 \langle \epsilon_i \rangle \langle \epsilon_i^2 \rangle + 2 \langle \epsilon_i \rangle^3}{\left[\langle \epsilon_i^2 \rangle - \langle \epsilon_i \rangle^2 \right]^{3/2}}$$
$$\sim O(\Omega^{-(Q-2)}), \tag{44}$$

where $\langle n_i \rangle$ is the mean number of molecules of species i, σ_i^2 is the variance in the fluctuations, F_i is the Fano factor, C_i is the coefficient of variation, and S_i is the skewness. Note that in all the above equations we used Eq. (5) to relate the moments of the ϵ variables to those of the absolute number of molecules. From Eqs. (40) and (41), it follows that for the case $Q = 2$, the mean concentration $\langle n_i \rangle / \Omega$ and the variance of the fluctuations in the concentration $\sigma_i^2 \Omega^{-2}$ are both accurate to order $O(\Omega^{-3/2})$, which agrees with a recent detailed study of the nonlinear Fokker-Planck equation (or chemical Fokker-Planck equation) [22].
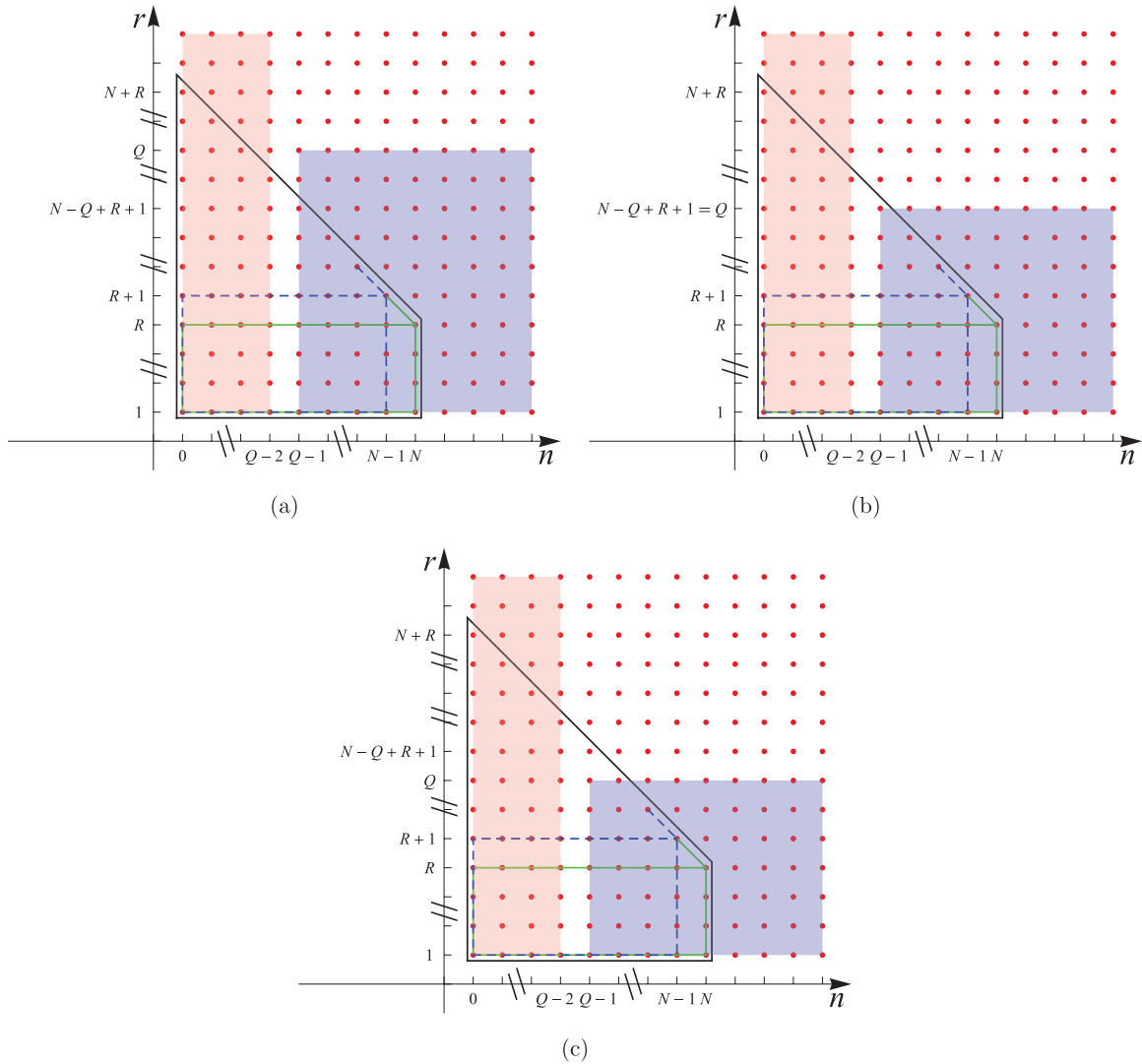
FIG. 3. (Color online) Illustration of the method used to deduce the accuracy of the pseudomoments as predicted by the Q-KME. These figures are superpositions of Figs. 1 and 2 when $N \geqslant Q - 1$ and for the conditions (a) $Q > N - Q + R + 1$, (b) $Q = N - Q + R + 1$, and (c) $Q < N - Q + R + 1$. Note that in cases (a) and (b), the blue (dark gray) and red (light gray) regions cover all the points in $n - r$ space enclosed by the black polygon, whereas in (c) this is not the case. These results imply Eq. (39). See the text for discussion and details.

In contrast, the moments of the ϵ variables estimated using the Q-SSE are all accurate to order $\Omega^{-(Q-2)/2}$, as already determined in Sec. II. This implies the mean absolute number of molecules is accurate to $\Omega^{-(Q-3)/2}$, the variance and Fano factors are accurate to order $\Omega^{-(Q-4)/2}$, and the skewness is accurate to $\Omega^{-(Q-2)/2}$. By comparing these accuracies to those for the Q-KME, Eqs. (40)–(44), we can now firmly state that the Q-KME estimates are generally more accurate than the Q-SSE estimates.

Note that thus far we have not mentioned anything about initial conditions. Deterministic initial conditions are the most common type of such conditions. The probability distribution of the CME is set to be a Dirac δ function centered on some state $\vec{n} = (n_1, \ldots, n_V)^T$; that is, the state of the system is precisely known at time $t = 0$ and hence is deterministic. Of course, the RE of the chemical system would have corresponding initial conditions $\vec{\phi} = (n_1/\Omega, \ldots, n_V/\Omega)^T$. Following the arguments in Sec. IV B of [22], it is not difficult to show

that for deterministic initial conditions, the mean number of molecules and the variance of the fluctuations about it, as predicted by the truncated forms of the SSE and KME, have expansions in powers of the inverse volume. In other words, terms of order $\Omega^{-r/2}$, where r is an odd number, vanish. This means that if the formulas given above for the accuracy of the mean number of molecules and the variance for the Q-KME and the Q-SSE result in an accuracy of order $\Omega^{-r/2}$, where r is an even number, then for deterministic initial conditions the accuracy is actually slightly higher, namely of order $\Omega^{-(r+1)/2}$.

The higher accuracy of the Q-KME can be seen from a different point of view. One can ask the following question: What is the order Y of the SSE-derived partial differential equation approximation (the M-SSE with $M = Y$) for which its estimates have the same accuracy as those of a KME-derived partial differential approximation of order Q (Q-KME)? By replacing Q with Y in the formulas for the accuracy of the

Q-SSE and comparing these accuracies with those of the Q-KME, Eqs. (40)–(44), we find

$$Y_{\text{mean}} = 2Q, \tag{45}$$

$$Y_{\text{var}} = 2Q - 1, \tag{46}$$

$$Y_{\text{skew}} = 2Q - 2, \tag{47}$$

where Y_{mean}, Y_{var}, and Y_{skew} are the orders of the SSE-derived partial differential equation approximation at which there is agreement with the Q-KME in the mean number of molecules, the variance of the fluctuations about the mean, and the skewness of the probability distribution, respectively. From the above equations, we can make the general conclusion that to match the accuracy of the Q-KME with $Q \gg 2$, one needs the order of the SSE-derived partial differential equation approximation to be approximately twice that of the Q-KME.

V. DISCUSSION AND CONCLUSION

In this paper, we have shown how one can construct partial differential equation approximations to the CME of any prescribed accuracy. We note that although the system-size and Kramers-Moyal expansions have been known for over half a century, a systematic investigation of the form and accuracy of the partial differential equation approximations of arbitrary order stemming from them has not been previously undertaken. Our study fills in this gap in the literature and also clarifies the general relationship between the partial differential equation approximations obtained from the two expansions.

As we noted in Sec. II, partial differential equation approximations of third or higher orders have a solution which is not strictly positive and which hence cannot be interpreted as a probability density function, in agreement with Pawula's theorem [24]. This fact appears to be one of the major reasons why studies have almost exclusively focused on Fokker-Planck equations, second-order partial differential equation approximations to the CME. The 1979 and 1987 studies by Risken and Vollmer [26,27] challenged the notion that higher-order approximations are useless by numerically showing that the accuracy of the moments of a Poisson process as predicted by the Q-KME generally increased with the order of the partial differential approximation, Q, even though the probability density function was not strictly positive for $Q > 2$. The theory developed in this paper supports their numerical observations; the formulas derived for the accuracy of the mean, variance, and skewness show that it increases with the order Q of the partial differential approximation stemming from the KME. Note that there is no discrepancy between this statement and Pawula's theorem. The higher-order partial differential equation approximations are simply approximate equations for the exact probability density function of the CME: A solution of these partial-differential approximations could agree very well with the exact distribution function for most values of $\vec{n}$ and yet be slightly negative for a few values of $\vec{n}$. We note that the use of higher-order partial differential approximations is particularly significant for the study of chemical systems with at least one bimolecular reaction since for systems with purely unimolecular reactions, the mean and variance as predicted by the lowest order truncations of the

expansions (i.e., the Q-KME and the Q-SSE with $Q = 2$) are exact [8,28].

Since we have derived the accuracies of moment predictions of the partial differential approximations of the CME, one maybe inclined to compare our results with those of Kurtz [11,29]. The error estimates in the latter work are for the supremum of the absolute difference between the full sample paths, that is, the trajectories, of the CME and of the nonlinear Fokker-Planck equation (the Q-KME with $Q = 2$) on a bounded time interval. In contrast, in our work we have obtained the differences between the moments of the two sample paths at points in time. The sample paths contain information about the whole probability distribution while the moments contain only partial information about the distribution, and hence the error estimates in the sample paths and the moments cannot be the same. For example, for a system of first-order reactions, the mean and variance as predicted by the Q-KME with $Q = 2$ agrees exactly with those of the CME (zero error in the first two moments for all volumes), but the higher moments are different, implying different full probability distributions and hence nonzero errors in the full sample paths. It follows that one would generally expect the errors derived for the sample paths to be larger than the errors on the moments. Our results predict that the mean concentration of the Q-KME with $Q = 2$ is accurate to order $\Omega^{-3/2}$ (see Sec. IV); that is, the difference between the mean concentrations of the CME and of the Q-KME with $Q = 2$ are proportional to Ω^{-2} (see Fig. 1 in [22] for numerical confirmation); Kurtz's results predict the difference between the sample paths divided by the volume to be of order $\log \Omega / \Omega$, which in the limit of large Ω is indeed larger than the difference of the first moments. Hence, there is no discrepancy between Kurtz's and our results. We furthermore note that Kurtz's theorems cannot be extended for $Q > 2$ because there are no corresponding sample paths for the Q-KME and Q-SSE. This is since, as discussed in the previous paragraph, these partial-differential approximations do not admit a probabilistic interpretation; that is, they do not correspond to stochastic processes.

We have also shown that the partial-differential equation approximations constructed from the KME are considerably more accurate than the same order approximations constructed using the SSE. This agrees with the results of a recent analytical and numerical study of the accuracy of the nonlinear Fokker-Planck equation [22], the second order approximation which can be obtained from the KME. Note that the results in this paper are generally valid for partial differential approximations of any order and the graphical method used to arrive to the results is also different than the method used in [22], which cannot be easily extended to higher-order approximations due to its algebraic complexity. The fact that the KME-derived approximations are more accurate than those based on the SSE may appear somewhat surprising given that the latter are obtained from a systematic method whereas the former arise out of an ad hoc truncation procedure. Indeed, van Kampen [10] criticized the use of the truncated KME because it is not clear from the form of the expansion what small parameter one is performing the expansion in and hence the accuracy of its estimates are also unknown. We have remedied this problem by expanding the Q-KME in powers of the inverse square root

of the volume; this enables us to estimate the size of the terms neglected by the Q-KME and hence to obtain the accuracy of its estimates.

We finish by noting that the higher accuracy of the Q-KME over the Q-SSE and the rapid increase in accuracy with Q suggest that the numerical solution of Q-KME with Q a little larger larger than 2 is a viable, highly accurate alternative to simulations based on the nonlin-

ear Fokker-Planck equation (Q-KME with $Q = 2$; see, for example, [30,31]).

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