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A Moment Closure Method for Stochastic Chemical Reaction Networks with General Kinetics

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Abstract

The moment closure method is an approximation method for describing the stochastic dynamics of chemical reaction networks. In this paper we develop a moment closure method for stochastically modeled chemical reaction networks with general reaction rate laws including mass action, rational and fractional rate laws. Based on the Taylor formula of the reaction rate functions and truncation at a certain order of moment, we find a closed system of equations for the moments. We show the accuracy and efficiency of the method by comparing the simulation results of motivating examples obtained by the moment closure method and the stochastic simulation algorithm.

1 Introduction

Stochastic models are used for analyzing and computing the evolution of systems with small number of chemically reacting species. If there are s species and r reactions, one can write the governing equation, so-called the chemical master equation by

$$\frac{\partial}{\partial t}p(\mathbf{x},t) = \sum_{k=1}^{r} [a_k(\mathbf{x}-V_k)p(\mathbf{x}-V_k,t) - a_k(\mathbf{x})p(\mathbf{x},t)], \tag{1}$$

where $\mathbf{x}$ denotes the s-dimensional random vector of the numbers of molecules of species, $p(\mathbf{x}, t)$ the probability that there are $\mathbf{x}$ molecules in the network at time t, each $a_k, i = 1, ..., r$, the propensity that is the probability that the k^{th} reaction occurs per unit time, and V_k the k^{th} column vector of the stoichiometric matrix V [1,2]. If the system consists of a simple class of reactions and species, the analytic solution of (1) can be found explicitly [3]. For complex chemical reaction networks, it is difficult or impossible to find the solution of (1) mainly because there are a large number of possible states. Thus, researchers use the stochastic simulation algorithm(SSA) to simulate the solution trajectories and find the important statistical quantities such as mean and variance instead of finding probability solution of (1) [4]. However, the SSA requires heavy computational loads especially if there are fast reactions or relatively large number of molecules in the network. To overcome the difficulties, researchers have implemented approximation methods. One of the methods is so-called the moment closure method(MCM). The system of moment equations is not closed if there are second or higher order reactions, which are very common in chemical reaction networks. That is, if one writes the system of all equations for moments, one will have an infinite dimensional system of differential equations, of which exact solution can not be found analytically and numerically. Thus, in this case, one has to approximate the exact solution by truncating at a certain order of moment and obtaining a finite dimensional solvable system of equations of moments. The moment closure methods have been used in the area of population biology and stochastic chemical kinetics with mass action or polynomial rate laws [5–11]. Recently, a moment closure method for the chemical reaction networks with rational rate laws has been proposed with utilization of moment generating functions [12] and the author showed that the method works well for examples with Michaelis-Menten kinetics and Hill kinetics.

In a complex reaction mechanism, the reaction often has fractional order, i.e the order of the reaction is fractional such as $1/2, 3/2$ [13, 14]. For example, ethanal is decomposed into methane and carbon monoxide by the pyrolysis with rate of the order of $3/2$ [13]. In this paper, we propose a moment closure method that can be applied to reaction networks with general reaction rate laws of differentiable functions including fractional and mixed order reaction rate laws as well as mass action and rational rate laws. The method is the general extension of the result [10] with employment of Taylor expansion. To the author's knowledge, a moment closure method for reaction networks with general reaction rate laws has not been reported yet.

The organization of the paper is as follows. Section 2 contains the development of the moment closure method with general reaction rate laws. Section 3 contains four applications to illustrate the accuracy of the method. Throughout the paper, we use the bold letters to denote the vectors.

2 Moment closure method with general reaction kinetics

We consider a stochastically modeled chemical reaction network with s species and r reactions described by the master equation

$$\frac{\partial}{\partial t}p(\mathbf{x},t)=\sum_{k=1}^{r}\left[a_k(\mathbf{x}-V_k)p(\mathbf{x}-V_k,t)-a_k(\mathbf{x})p(\mathbf{x},t)\right]. \tag{2}$$

For general kinetics including mass action, rational (such as Michaelis-Menten and Hill kinetics), fractional and any mixed order kinetics, the propensity functions a_k are infinitely differentiable[1]. For such functions a_k, we apply the multivariable Taylor formula and derive moment equations for general kinetics. We first introduce the standard multi-index notation before the derivation; For any s-dimensional vectors $\boldsymbol{\alpha}=(\alpha_1,\dots,\alpha_s)$ and $\mathbf{x}=(x_1,\dots,x_s)$, let us denote

$$\boldsymbol{\alpha}!=\alpha_1!\cdots\alpha_s!,\quad \mathbf{x}^{\boldsymbol{\alpha}}=x_1^{\alpha_1}\cdots x_s^{\alpha_s}, |\boldsymbol{\alpha}|=\sum_{i=1}^{s}\alpha_i,\quad \text{and}\quad D^{\boldsymbol{\alpha}}f(\mathbf{x})=\frac{\partial^{|\boldsymbol{\alpha}|}f(\mathbf{x})}{\partial x_1^{\alpha_1}\cdots\partial x_s^{\alpha_s}}.$$

We denote the expected value of the vector $\mathbf{x}$ of molecular numbers by $E[\mathbf{x}]=\boldsymbol{\mu}$, where $\boldsymbol{\mu}=(\mu_1,\cdots,\mu_s)$ and $\mu_i=E[x_i], i=1,\dots,s$. Using the above notations, we write the multivariable Taylor formula at $\boldsymbol{\mu}$

$$a_k(\mathbf{x}) \;=\; \sum_{|\boldsymbol{\alpha}|=0}^{n}\frac{D^{\boldsymbol{\alpha}}a_k(\boldsymbol{\mu})}{\boldsymbol{\alpha}!}(\mathbf{x}-\boldsymbol{\mu})^{\boldsymbol{\alpha}}+S_{n+1},$$

where S_{n+1} is the remainder term. More explicitly, we can write the formula as

$$\begin{aligned}a_k(\mathbf{x}) &= a_k(\boldsymbol{\mu})+\sum_{l}\frac{\partial a_k(\boldsymbol{\mu})}{\partial x_l}(x_l-\mu_l)+\frac{1}{2!}\sum_{i_1,i_2}\frac{\partial^2 a_k(\boldsymbol{\mu})}{\partial x_{i_1}\partial x_{i_2}}(x_{i_1}-\mu_{i_1})(x_{i_2}-\mu_{i_2})+\cdots\\ &+\frac{1}{n!}\sum_{i_1,i_2,\dots,i_n}\frac{\partial^n a_k(\boldsymbol{\mu})}{\partial x_{i_1}\partial x_{i_2}\cdots\partial x_{i_n}}(x_{i_1}-\mu_{i_1})(x_{i_2}-\mu_{i_2})\cdots(x_{i_n}-\mu_{i_n})+S_{n+1},\end{aligned} \tag{3}$$

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[1] More generally, all derivations in this section are true if $(n+1)^{st}$ partial derivatives of a_k are continuous. Here n can be chosen for accuracy control of the moment closure method.

where S_{n+1} is the reminder term

$$\frac{1}{(n+1)!}\sum_{i_1,\cdots,i_{n+1}}\frac{\partial a_k^{n+1}(\mathbf{c})}{\partial x_{i_1}\partial x_{i_2}\cdots\partial x_{i_n}\partial x_{i_{n+1}}}(x_{i_1}-\mu_{i_1})(x_{i_2}-\mu_{i_2})\cdots(x_{i_{n+1}}-\mu_{i_{n+1}}), \tag{4}$$

where $\mathbf{c}$ is a point between $\boldsymbol{\mu}$ and $\mathbf{x}$ and

$$|\frac{\partial a_k^{n+1}(\mathbf{c})}{\partial x_{i_1}\partial x_{i_2}\cdots\partial x_{i_n}\partial x_{i_{n+1}}}|\leq\frac{K}{(n+1)!}, \tag{5}$$

where

$$K=\max_{|\boldsymbol{\alpha}|=n+1}\max_{\mathbf{y}\in B}|D^{\boldsymbol{\alpha}}a_k(\mathbf{y})|$$

and B is a compact set that includes $\mathbf{c}$ [15]. In Equation (3), the summation $\sum\limits_{i_1,i_2,\ldots,i_n}$ means adding any n^{th} partial derivative terms

$$\frac{\partial^n a_k(\boldsymbol{\mu})}{\partial x_{i_1}\partial x_{i_2}\cdots\partial x_{i_n}}(x_{i_1}-\mu_{i_1})(x_{i_2}-\mu_{i_2})\cdots(x_{i_n}-\mu_{i_n})$$

over all possible indices $i_1,\ldots,i_n$.

Especially, the Taylor formulas of first and second orders at $\boldsymbol{\mu}$ are written, respectively, as

$$a_k(\mathbf{x}) = a_k(\boldsymbol{\mu})+\sum_l\frac{\partial a_k(\boldsymbol{\mu})}{\partial x_l}(x_l-\mu_l)+S_2, \tag{6}$$

$$\begin{aligned} a_k(\mathbf{x}) &= a_k(\boldsymbol{\mu})+\sum_l\frac{\partial a_k(\boldsymbol{\mu})}{\partial x_l}(x_l-\mu_l) \\ &\quad+\frac{1}{2!}\sum_{l,m}\frac{\partial^2 a_k(\boldsymbol{\mu})}{\partial x_l\partial x_m}(x_l-\mu_l)(x_m-\mu_m)+S_3, \end{aligned} \tag{7}$$

where

$$S_2=\frac{1}{2!}\sum_{i_1,i_2}\frac{\partial a_k^2(\mathbf{d})}{\partial x_{i_1}\partial x_{i_2}}(x_{i_1}-\mu_{i_1})(x_{i_2}-\mu_{i_2}),$$

and

$$S_3=\frac{1}{3!}\sum_{i_1,i_2,i_3}\frac{\partial a_k^3(\mathbf{e})}{\partial x_{i_1}\partial x_{i_2}\partial x_{i_3}}(x_{i_1}-\mu_{i_1})(x_{i_2}-\mu_{i_2})(x_{i_3}-\mu_{i_3}),$$

where $\mathbf{d}$ and $\mathbf{e}$ are points between $\boldsymbol{\mu}$ and $\mathbf{x}$ that satisfy the condition (5) for $n=1,2$, respectively. Since the expected value $E[x_l-\mu_l]=E[x_l]-\mu_l=0$ for each l, taking the expected value of Equation (7) leads to

$$E[a_k(\mathbf{x})] = a_k(\boldsymbol{\mu})+\frac{1}{2}\sum_{l,m}\frac{\partial^2 a_k(\boldsymbol{\mu})}{\partial x_l\partial x_m}E[(x_l-\mu_l)(x_m-\mu_m)]+R_3, \tag{8}$$

where

$$R_3 = E[S_3] = \frac{1}{3!}\sum_{i_1,i_2,i_3} \frac{\partial a_k^3(\mathbf{e})}{\partial x_{i_1}\partial x_{i_2}\partial x_{i_3}} E\Big[(x_{i_1}-\mu_{i_1})(x_{i_2}-\mu_{i_2})(x_{i_3}-\mu_{i_3})\Big].$$

Multiplying (6) by $(x_i - \mu_i), i = 1, \ldots, s$, we obtain

$$a_k(\mathbf{x})(x_i-\mu_i) = a_k(\boldsymbol{\mu})(x_i-\mu_i) + \sum_l \frac{\partial a_k(\boldsymbol{\mu})}{\partial x_l}(x_l-\mu_l)(x_i-\mu_i) + S_2(x_i-\mu_i). \tag{9}$$

Taking the expected value of (9) gives

$$E[a_k(\mathbf{x})(x_i-\mu_i)] = \sum_l \frac{\partial a_k(\boldsymbol{\mu})}{\partial x_l} E[(x_i-\mu_i)(x_l-\mu_l)] + \bar{R}_3, \tag{10}$$

where

$$\bar{R}_3 = E[S_2(x_i-\mu_i)] = \frac{1}{2!}\sum_{i_1,i_2} \frac{\partial a_k^2(\mathbf{d})}{\partial x_{i_1}\partial x_{i_2}} E\Big[(x_{i_1}-\mu_{i_1})(x_{i_2}-\mu_{i_2})(x_i-\mu_i)\Big].$$

Referring to the results (A1) and (A2) of Appendix in Lee et al. [10], we have

$$\begin{aligned} \frac{dE[x_i]}{dt} &= \sum_k V_{k,i} E[a_k(\mathbf{x})] && (11) \\ \frac{dE[(x_i-\mu_i)(x_j-\mu_j)]}{dt} &= \sum_k \Big(V_{k,i}E[(x_j-\mu_j)a_k(\mathbf{x})] + V_{k,j}E[(x_i-\mu_i)a_k(\mathbf{x})] \\ &+ V_{k,i}V_{k,j}E[a_k(\mathbf{x})]\Big), && (12) \end{aligned}$$

where $i, j = 1, \ldots, s$ and $V_{k,i}$ denotes the i^{th} entry of the k^{th} column V_k of V. We substitute (8) into (11) and obtain

$$\frac{dE[x_i]}{dt} = \sum_k V_{k,i}\Big(a_k(\boldsymbol{\mu}) + \frac{1}{2}\sum_{l,m}\frac{\partial^2 a_k(\boldsymbol{\mu})}{\partial x_l \partial x_m}E[(x_l-\mu_l)(x_m-\mu_m)] + R_3\Big). \tag{13}$$

Moreover, substitution of (8) and (10) into (12) leads to

$$\begin{aligned} &\frac{dE[(x_i-\mu_i)(x_j-\mu_j)]}{dt} \\ = \ &\Big[\sum_k V_{k,i}\Big(\sum_l \frac{\partial a_k(\boldsymbol{\mu})}{\partial x_l}E[(x_j-\mu_j)(x_l-\mu_l)] + \bar{R}_3\Big) && (14) \\ + \ &V_{k,j}\Big(\sum_l \frac{\partial a_k(\boldsymbol{\mu})}{\partial x_l}E[(x_i-\mu_i)(x_l-\mu_l)] + \bar{R}_3\Big) \\ + \ &V_{k,i}V_{k,j}\Big(a_k(\boldsymbol{\mu}) + \frac{1}{2}\sum_{l,m}\frac{\partial^2 a_k(\boldsymbol{\mu})}{\partial x_l\partial x_m}E[(x_l-\mu_l)(x_m-\mu_m)] + R_3\Big)\Big]. \end{aligned}$$

If we denote $\sigma_{ij} = E[(x_i - \mu_i)(x_j - \mu_j)]$, we can rewrite (13) and (14) as

$$\begin{aligned}
\frac{d\mu_i}{dt} &= \sum_k V_{k,i}\Big(a_k(\boldsymbol{\mu}) + \frac{1}{2}\sum_{l,m}\frac{\partial^2 a_k(\boldsymbol{\mu})}{\partial x_l \partial x_m}\sigma_{lm} + R_3\Big), && (15)\\
\frac{d\sigma_{ij}}{dt} &= \sum_k \Big[V_{k,i}\Big(\sum_l \frac{\partial a_k(\boldsymbol{\mu})}{\partial x_l}\sigma_{jl} + \bar{R}_3\Big) + V_{k,j}\Big(\sum_l \frac{\partial a_k(\boldsymbol{\mu})}{\partial x_l}\sigma_{il} + \bar{R}_3\Big) && (16)\\
&+ V_{k,i}V_{k,j}\Big(a_k(\boldsymbol{\mu}) + \frac{1}{2}\sum_{l,m}\frac{\partial^2 a_k(\boldsymbol{\mu})}{\partial x_l \partial x_m}\sigma_{lm} + R_3\Big).
\end{aligned}$$

Now we derive an equation for general moments. We use the s-dimensional vector $\mathbf{i} = (i_1, \ldots, i_s)$ that denotes indices of moments, and we denote the central moment $\sigma_{\mathbf{l}} = \sigma_{l_1,\ldots,l_s} = E\Big[(x_1 - \mu_1)^{l_1} \cdots (x_s - \mu_s)^{l_s}\Big]$ for $\mathbf{l} = (l_1, \ldots, l_s)$. Note that if $|\mathbf{l}| = l_1 + \cdots + l_s = 0$, $\sigma_{\mathbf{l}} = 1$, and if $|\mathbf{l}| = 1$, $\sigma_{\mathbf{l}} = 0$. Also, let us denote $\sigma_{\mathbf{i+j}} = \sigma_{i_1+j_1,\ldots,i_s+j_s}$. Then for $|\mathbf{i}| = m \geq 3$, we compute the equation for the m^{th} moment

$$\begin{aligned}
&\frac{d\sigma_{i_1,i_2,\ldots,i_s}}{dt} = \frac{d}{dt}E\Big[(x_1 - \mu_1)^{i_1} \cdots (x_s - \mu_s)^{i_s}\Big]\\
=\ & \sum_{\mathbf{x}} (x_1 - \mu_1)^{i_1} \cdots (x_s - \mu_s)^{i_s} \frac{dp(\mathbf{x},t)}{dt}\\
-\ & \sum_{\mathbf{x}} \sum_{j=1}^{s} i_j \mu_j' (x_1 - \mu_1)^{i_1} \cdots (x_j - \mu_j)^{i_j - 1} \cdots (x_s - \mu_s)^{i_s} p(\mathbf{x},t)\\
=\ & \sum_k \sum_{\mathbf{x}} \Big[(x_1 - \mu_1 + V_{k,1})^{i_1} \cdots (x_s - \mu_s + V_{k,s})^{i_s} - (x_1 - \mu_1)^{i_1} \cdots (x_s - \mu_s)^{i_s}\Big]\\
\times\ & a_k(\mathbf{x}) p(\mathbf{x},t) - \sum_{j=1}^{s} i_j \mu_j' \sigma_{i_1,\ldots,i_j - 1,\ldots,i_s}\\
=\ & \sum_k \sum_{\mathbf{x}} \Big[\sum_{l_1=0}^{i_1} \binom{i_1}{l_1} (x_1 - \mu_1)^{l_1} (V_{k,1})^{i_1 - l_1} \cdots \sum_{l_s=0}^{i_s} \binom{i_s}{l_s} (x_s - \mu_s)^{l_s} (V_{k,s})^{i_s - l_s}\\
-\ & (x_1 - \mu_1)^{i_1} \cdots (x_s - \mu_s)^{i_s}\Big]\\
& \Big[a_k(\boldsymbol{\mu}) + \sum_{i_1} \frac{\partial a_k(\boldsymbol{\mu})}{\partial x_{i_1}} (x_{i_1} - \mu_{i_1}) + \frac{1}{2} \sum_{i_1,i_2} \frac{\partial^2 a_k(\boldsymbol{\mu})}{\partial x_{i_1} \partial x_{i_2}} (x_{i_1} - \mu_{i_1})(x_{i_2} - \mu_{i_2}) + \cdots\\
+\ & \frac{1}{n!} \sum_{i_1,i_2,\ldots,i_n} \frac{\partial^n a_k(\boldsymbol{\mu})}{\partial x_{i_1} \partial x_{i_2} \cdots \partial x_{i_n}} (x_{i_1} - \mu_{i_1})(x_{i_2} - \mu_{i_2}) \cdots (x_{i_n} - \mu_{i_n}) + S_{n+1}\Big] p(\mathbf{x},t)\\
-\ & \sum_{j=1}^{s} i_j \mu_j' \sigma_{i_1,\ldots,i_j - 1,\ldots,i_s}
\end{aligned}$$

$$= \sum_k \sum_{\mathbf{x}} \sum_{\substack{l_1,l_2,\ldots,l_s \\ 0\le|\mathbf{l}|\le m-1}} \binom{i_1}{l_1} \cdots \binom{i_s}{l_s} (V_{k,1})^{i_1-l_1} \cdots (V_{k,s})^{i_s-l_s} (x_1-\mu_1)^{l_1} \cdots (x_s-\mu_s)^{l_s}$$

$$\Big[a_k(\boldsymbol{\mu}) + \sum_{i_1} \frac{\partial a_k(\boldsymbol{\mu})}{\partial x_{i_1}}(x_{i_1}-\mu_{i_1}) + \frac{1}{2}\sum_{i_1,i_2} \frac{\partial^2 a_k(\boldsymbol{\mu})}{\partial x_{i_1}\partial x_{i_2}}(x_{i_1}-\mu_{i_1})(x_{i_2}-\mu_{i_2}) + \cdots$$

$$+ \frac{1}{n!}\sum_{i_1,i_2,\ldots,i_n} \frac{\partial^n a_k(\boldsymbol{\mu})}{\partial x_{i_1}\partial x_{i_2}\cdots\partial x_{i_n}}(x_{i_1}-\mu_{i_1})(x_{i_2}-\mu_{i_2})\cdots(x_{i_n}-\mu_{i_n}) + S_{n+1}\Big] p(\mathbf{x},t)$$

$$- \sum_{j=1}^{s} i_j \mu'_j \sigma_{i_1,\ldots,i_j-1,\ldots,i_s}$$

Thus, we obtain

$$\frac{d\sigma_{i_1,i_2,\ldots,i_s}}{dt}$$

$$= \sum_k \sum_{|\mathbf{l}|=0}^{m-1} \Big[\sum_{l_1,l_2,\ldots,l_s} \binom{i_1}{l_1} \cdots \binom{i_s}{l_s} (V_{k,1})^{i_1-l_1} \cdots (V_{k,s})^{i_s-l_s} \sum_{|\boldsymbol{\alpha}|=0}^{m-|\mathbf{l}|} \frac{D^{\boldsymbol{\alpha}} a_k(\boldsymbol{\mu})}{\boldsymbol{\alpha}!} \sigma_{\mathbf{l}+\boldsymbol{\alpha}} \tag{17}$$

$$+ E[S_{m-|\mathbf{l}|+1}]\Big] - \sum_{j=1}^{s} i_j \mu'_j \sigma_{i_1,\ldots,i_j-1,\ldots,i_s},$$

where $\sum_{\mathbf{x}}$ is the sum over all possible values of $x_1,\ldots,x_s$, and $E[S_{m-|\mathbf{l}|+1}]$ is the expected value of the remainder term $S_{m-|\mathbf{l}|+1}$ that can be written in the form (4). Note that $E[S_{m-|\mathbf{l}|+1}]$ includes the $(m+1)^{st}$ moment terms as the highest moment. Thus, we can write Equations (15), (16), (17) in the form

$$\frac{d\boldsymbol{\mu}}{dt} = \mathbf{G}_1(\boldsymbol{\mu}) + \mathbf{C}_2\boldsymbol{\sigma}_2 \tag{18}$$

$$\frac{d\boldsymbol{\sigma}_k}{dt} = \mathbf{G}_k(\boldsymbol{\mu},\boldsymbol{\mu}',\boldsymbol{\sigma}_2,\ldots,\boldsymbol{\sigma}_k) + \mathbf{C}_{k+1}\boldsymbol{\sigma}_{k+1}, \quad k=2,\ldots,m \tag{19}$$

where $\boldsymbol{\mu}$ and $\boldsymbol{\sigma}_k$ denote the vectors of all means and k^{th} central moments, respectively, and $\mathbf{G}_k, k\ge 1$ and $\mathbf{C}_k, k\ge 2$ are the vectors of functions and constant matrices which are obtained from (15),(16) and (17), respectively.

The above system is not a closed system because the m^{th} moment equation includes the $(m+1)^{st}$ moment term $E[S_{m-|\mathbf{l}|+1}]$ and thus one cannot find the exact solution of the moment equations analytically and numerically. However, by truncating the system at the $(m+1)^{st}$ moments, i.e. setting $\boldsymbol{\sigma}_{m+1}=0$, one can obtain a closed system of moments up to m^{th} moments as

$$\frac{d\boldsymbol{\mu}}{dt} = \mathbf{G}_1(\boldsymbol{\mu}) + \mathbf{C}_2\boldsymbol{\sigma}_2 \tag{20}$$

$$\frac{d\boldsymbol{\sigma}_i}{dt} = \mathbf{G}_i(\boldsymbol{\mu}, \boldsymbol{\mu}', \boldsymbol{\sigma}_2, \ldots, \boldsymbol{\sigma}_i) + \mathbf{C}_{i+1}\boldsymbol{\sigma}_{i+1}, \quad \text{for } i = 2, \cdots, m-1 \tag{21}$$

$$\frac{d\boldsymbol{\sigma}_m}{dt} = \mathbf{G}_m(\boldsymbol{\mu}, \boldsymbol{\mu}', \boldsymbol{\sigma}_2, \ldots, \boldsymbol{\sigma}_m). \tag{22}$$

One can solve the above closed system with conventional numerical schemes such as Runge-Kutta method and also improve the accuracy of numerical solutions by raising the order of the truncations. The formal error estimation and numerical consistency of approximate solution obtained from the truncation at a certain order are justified by the following Theorem [10]. For the proof, refer to Lee et al [10].

Theorem 1. *Suppose that we truncate the system (18) and (19) by letting* $(m+1)^{st}$ *central moment* $\boldsymbol{\sigma}_{m+1}(t) = 0$ *at any* t *in a time interval* $[0, h]$. *Then the error between the exact mean and the approximated mean obtained from the truncated equations is* $O(h^m)$ *and the error in second central moments* $\boldsymbol{\sigma}_2(t)$ *is* $O(h^{m-1})$, *for any* $t \in [0, h]$.

If we truncate the system of moments at the third moments, i.e. we set the third moments to be zero in Equations (15) and (16), we obtain a closed system

$$\frac{d\mu_i}{dt} = \sum_k V_{k,i}\Big(a_k(\boldsymbol{\mu}) + \frac{1}{2}\sum_{l,m}\frac{\partial^2 a_k(\boldsymbol{\mu})}{\partial x_l \partial x_m}\sigma_{lm}\Big) \tag{23}$$

$$\begin{aligned} \frac{d\sigma_{ij}}{dt} &= \sum_k \Big[V_{k,i}\Big(\sum_l \frac{\partial a_k(\boldsymbol{\mu})}{\partial x_l}\sigma_{jl}\Big) + V_{k,j}\Big(\sum_l \frac{\partial a_k(\boldsymbol{\mu})}{\partial x_l}\sigma_{il}\Big) \\ &+ V_{k,i}V_{k,j}\Big(a_k(\boldsymbol{\mu}) + \frac{1}{2}\sum_{l,m}\frac{\partial^2 a_k(\boldsymbol{\mu})}{\partial x_l \partial x_m}\sigma_{lm}\Big)\Big]. \end{aligned} \tag{24}$$

The truncation at the third moments is practically more useful than the truncation at the higher moments, in that solving the resulted system of (23) and (24) gives a sufficiently good approximation to the exact solution of the first and second moments that show a decent description of the stochastic dynamics and also it is more efficient in numerical computation than the system resulted from the truncation at the higher moments. By that reason, we mainly use Equations (23) and (24) to compare the MCM and SSA and show the accuracy and efficiency of the MCM for four applications in Section 3.

3 Applications

3.1 Enzyme-substrate model

An enzyme-substrate model is described as

$$E + S \underset{k_1}{\overset{k_1}{\rightleftarrows}} ES \overset{k_2}{\to} E + P,$$

where E is an enzyme, S is a substrate, ES is an enzyme-substrate complex and P is a product. This model is reduced into a reaction model with Michaelis-Menten kinetics,

$$S \ \rightarrow \ P.$$

Let us denote the molecular numbers of S, P by x_1, x_2, respectively. The reaction propensity is $a(\mathbf{x}) = \frac{V_m x_1}{K_m + x_1}$ determined by Michaelis-Menten kinetics, where $K_m = \frac{k_{-1}+k_2}{k_1}$, $V_m = k_2 E_0$ and E_0 is the initial number of E. To obtain the moment equations, we first find the partial derivatives of $a(\mathbf{x})$

$$\frac{\partial a}{\partial x_1} = \frac{V_m K_m}{(K_m + x_1)^2}, \quad \frac{\partial^2 a}{\partial x_1^2} = \frac{-2V_m K_m}{(K_m + x_1)^3}$$

and using Equations (23) and (24), we obtain the closed system for $\mu_i, \ \sigma_{ij}, \ i, j = 1, 2$

$$\begin{aligned}
\frac{d\mu_1}{dt} &= -V_m\Big(\frac{\mu_1}{K_m + \mu_1} - \frac{K_m}{(K_m + \mu_1)^3}\sigma_{11}\Big) \\
\frac{d\mu_2}{dt} &= V_m\Big(\frac{\mu_1}{K_m + \mu_1} - \frac{K_m}{(K_m + \mu_1)^3}\sigma_{11}\Big) \\
\frac{d\sigma_{11}}{dt} &= -V_m\Big[-\frac{\mu_1}{K_m + \mu_1} + K_m\Big(\frac{1}{(K_m + \mu_1)^3} + \frac{2}{(K_m + \mu_1)^2}\Big)\sigma_{11}\Big] \\
\frac{d\sigma_{22}}{dt} &= V_m\Big[\frac{\mu_1}{(K_m + \mu_1)} + \frac{2K_m}{(K_m + \mu_1)^2}\sigma_{12} - \frac{K_m}{(K_m + \mu_1)^3}\sigma_{11}\Big] \\
\frac{d\sigma_{12}}{dt} &= -V_m\Big[\frac{\mu_1}{(K_m + \mu_1)} - \frac{K_m}{(K_m + \mu_1)^2}(\sigma_{11} - \sigma_{12}) - \frac{K_m}{(K_m + \mu_1)^3}\sigma_{11}\Big].
\end{aligned}$$

The simulation results for mean and mean ± standard deviation are shown in Figure 1. One can see that the results from SSA and MCM match well. For obtaining the result of MCM, it only takes less than one second.

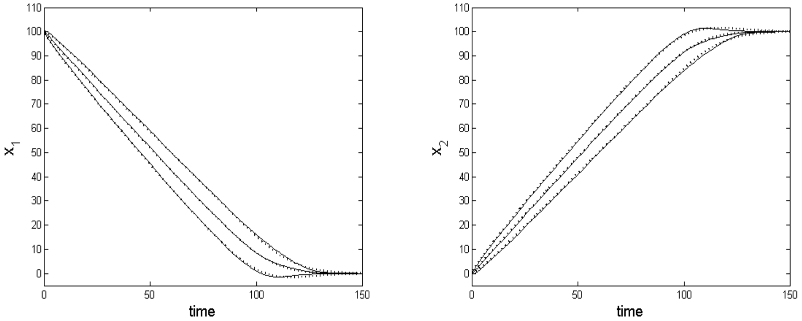

Figure 1: Under the initial condition $(x_1, x_2) = (100, 0)$ and the parameters $K_m = 3, V_m = 1$ in Example 1, comparison of the mean + standard deviation(upper curves), mean(middle curves) and mean − standard deviation(lower curves) from MCM(solid) and SSA(dotted). (a) x_1 (b) x_2. The results by SSA are based on 30,000 realizations.

3.2 Reaction with fractional rate law

We consider a reaction of methane with molecular chlorine [14]

$$CH_4 + Cl_2 \to CH_3Cl + HCl.$$

Let x_1, x_2, x_3, x_4 be the molecular numbers of CH_4, Cl_2, CH_3Cl and HCL, respectively. Due to the conserved quantities $x_1 + x_3$ and $x_2 + x_4$, we only consider two independent variables x_1, x_2. The propensity of the reaction has a fractional order $a(\mathbf{x}) = c_1 x_1 x_2^{\frac{1}{2}}$ [14]. After finding the partial derivatives of $a(\mathbf{x})$

$$\frac{\partial a}{\partial x_1} = c_1 x_2^{1/2}, \quad \frac{\partial a}{\partial x_2} = \frac{1}{2} c_1 x_1 x_2^{-1/2}$$

$$\frac{\partial^2 a}{\partial x_1^2} = 0, \quad \frac{\partial^2 a}{\partial x_2^2} = -\frac{1}{4} c_1 x_1 x_2^{-3/2}, \quad \frac{\partial^2 a}{\partial x_1 \partial x_2} = \frac{1}{2} c_1 x_2^{-1/2},$$

and substituting the partial derivatives into Equations (23) and (24), we find the equations for the first and second moments

$$\begin{aligned}
\frac{d\mu_1}{dt} &= -c_1 \mu_1 \mu_2^{\frac{1}{2}} - \frac{1}{2} c_1 \mu_2^{-\frac{1}{2}} \sigma_{12} + \frac{1}{8} c_1 \mu_1 \mu_2^{-\frac{3}{2}} \sigma_{22} \\
\frac{d\mu_2}{dt} &= -c_1 \mu_1 \mu_2^{\frac{1}{2}} - \frac{1}{2} c_1 \mu_2^{-\frac{1}{2}} \sigma_{12} + \frac{1}{8} c_1 \mu_1 \mu_2^{-\frac{3}{2}} \sigma_{22} \\
\frac{d\sigma_{11}}{dt} &= c_1 \mu_1 \mu_2^{\frac{1}{2}} - 2 c_1 \mu_2^{\frac{1}{2}} \sigma_{11} + (\frac{1}{2} c_1 \mu_2^{-\frac{1}{2}} - c_1 \mu_1 \mu_2^{-\frac{1}{2}}) \sigma_{12} - \frac{1}{8} c_1 \mu_1 \mu_2^{-\frac{3}{2}} \sigma_{22}
\end{aligned}$$

$$
\begin{aligned}
\frac{d\sigma_{22}}{dt} &= c_1\mu_1\mu_2^{\frac{1}{2}} + (\frac{1}{2}c_1\mu_2^{-\frac{1}{2}} - 2c_1\mu_2^{\frac{1}{2}})\sigma_{12} + (-c_1\mu_1\mu_2^{-\frac{1}{2}} - \frac{1}{8}c_1\mu_1\mu_2^{-\frac{3}{2}})\sigma_{22} \\
\frac{d\sigma_{12}}{dt} &= c_1\mu_1\mu_2^{\frac{1}{2}} - c_1\mu_2^{\frac{1}{2}}\sigma_{11} + (\frac{1}{2}c_1\mu_2^{-\frac{1}{2}} - c_1\mu_2^{\frac{1}{2}} - \frac{1}{2}c_1\mu_1\mu_2^{-\frac{1}{2}})\sigma_{12} \\
&+ (-\frac{1}{2}c_1\mu_1\mu_2^{-\frac{1}{2}} - \frac{1}{8}c_1\mu_1\mu_2^{-\frac{3}{2}})\sigma_{22}
\end{aligned}
$$

The simulation results for mean and mean ± standard deviation are shown in Figure 2. One can see that the results from the SSA and MCM are in good agreement.

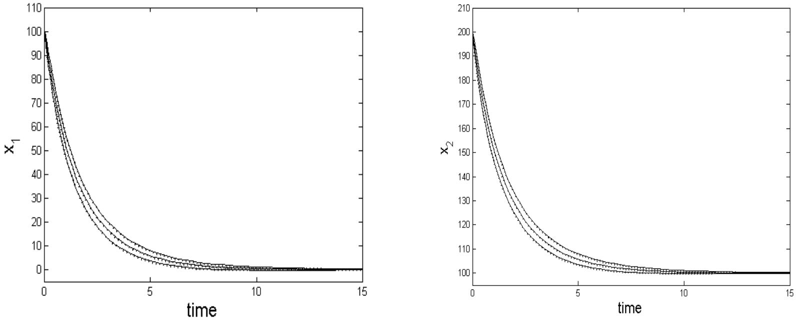

Figure 2: Under the initial condition $(x_1, x_2) = (100, 200)$ and the parameter $c_1 = 0.05$, in Example 2, comparison of the mean + standard deviation(upper curves), mean(middle curves) and mean − standard deviation(lower curves) from MCM(solid) and SSA(dotted). (a) x_1 (b) x_2. The results by SSA are based on 30,000 realizations.

3.3 Reversible reaction with Michaelis-Menten rate law

We consider a model

$$A \xrightarrow{k_1} B, \quad B \xrightarrow{k_2} A.$$

Let x_1, x_2 be the molecular numbers of A, B, respectively. Then the propensity functions are

$$a_1(\mathbf{x}) = \frac{k_1x_1}{c_1 + x_1 + c_2x_2}, \; a_2(\mathbf{x}) = \frac{k_2x_2}{c_1 + x_1 + c_2x_2},$$

where k_1, k_2, c_1, c_2 are constant determined by Michaelis-Menten rate law. One can find the partial derivatives of a_1, a_2

$$\frac{\partial a_1}{\partial x_1} = \frac{k_1(c_1 + c_2x_2)}{(c_1 + x_1 + c_2x_2)^2}, \quad \frac{\partial a_1}{\partial x_2} = \frac{-k_1c_2x_1}{(c_1 + x_1 + c_2x_2)^2}, \quad \frac{\partial^2 a_1}{\partial x_1^2} = \frac{-2k_1(c_1 + c_2x_2)}{(c_1 + x_1 + c_2x_2)^3},$$

$$\frac{\partial^2 a_1}{\partial x_2^2} = \frac{2k_1c_2^2x_1}{(c_1+x_1+c_2x_2)^3}, \frac{\partial^2 a_1}{\partial x_1 \partial x_2} = \frac{k_1(-c_1c_2+c_2x_1-c_2^2x_2)}{(c_1+x_1+c_2x_2)^3},$$

$$\frac{\partial a_2}{\partial x_1} = \frac{-k_2x_2}{(c_1+x_1+c_2x_2)^2}, \quad \frac{\partial a_2}{\partial x_2} = \frac{k_2(c_1+x_1)}{(c_1+x_1+c_2x_2)^2}, \quad \frac{\partial^2 a_2}{\partial x_1^2} = \frac{2k_2x_2}{(c_1+x_1+c_2x_2)^3},$$

$$\frac{\partial^2 a_2}{\partial x_2^2} = \frac{-2k_2c_2(c_1+x_1)}{(c_1+x_1+c_2x_2)^3}, \quad \frac{\partial^2 a_2}{\partial x_1 \partial x_2} = \frac{k_2(-c_1-x_1+c_2x_2)}{(c_1+x_1+c_2x_2)^3} \ .$$

Substitution of the above partial derivatives into Equations (23) and (24) leads to the equations for the first moments

$$\begin{aligned}
\frac{d\mu_1}{dt} &= \frac{k_2\mu_2-k_1\mu_1}{c_1+\mu_1+c_2\mu_2} + \Big(\frac{k_2\mu_2+k_1(c_1+c_2\mu_2)}{(c_1+\mu_1+c_2\mu_2)^3}\Big)\sigma_{11} + \Big(\frac{-k_1c_2^2\mu_1-k_2c_2(c_1+\mu_1)}{(c_1+\mu_1+c_2\mu_2)^3}\Big)\sigma_{22} \\
&+ \Big(\frac{-k_1(c_2\mu_1-c_2^2\mu_2-c_1c_2)+k_2(c_2\mu_2-\mu_1-c_1)}{(c_1+\mu_1+c_2\mu_2)^3}\Big)\sigma_{12} \\
\frac{d\mu_2}{dt} &= -\frac{k_2\mu_2-k_1\mu_1}{c_1+\mu_1+c_2\mu_2} - \Big(\frac{k_2\mu_2+k_1(c_1+c_2\mu_2)}{(c_1+\mu_1+c_2\mu_2)^3}\Big)\sigma_{11} - \Big(\frac{-k_1c_2^2\mu_1-k_2c_2(c_1+\mu_1)}{(c_1+\mu_1+c_2\mu_2)^3}\Big)\sigma_{22} \\
&- \Big(\frac{-k_1(c_2\mu_1-c_2^2\mu_2-c_1c_2)+k_2(c_2\mu_2-\mu_1-c_1)}{(c_1+\mu_1+c_2\mu_2)^3}\Big)\sigma_{12},
\end{aligned}$$

and the equations for the second moments

$$\begin{aligned}
\frac{d\sigma_{11}}{dt} &= \frac{k_1\mu_1+k_2\mu_2}{c_1+\mu_1+c_2\mu_2} + \Big(\frac{-2\big(k_1(c_1+c_2\mu_2)+k_2\mu_2\big)}{(c_1+\mu_1+c_2\mu_2)^2} + \frac{k_2\mu_2-k_1(c_1+c_2\mu_2)}{(c_1+\mu_1+c_2\mu_2)^3}\Big)\sigma_{11} \\
&+ \Big(\frac{k_1c_2^2\mu_1-k_2c_2(c_1+\mu_1)}{(c_1+\mu_1+c_2\mu_2)^3}\Big)\sigma_{22} \\
&+ \Big(\frac{2\big(k_1c_2\mu_1+k_2(c_1+\mu_1)\big)}{(c_1+\mu_1+c_2\mu_2)^2} + \frac{k_1(c_2\mu_1-c_2^2\mu_2-c_1c_2)+k_2(c_2\mu_2-\mu_1-c_1)}{(c_1+\mu_1+c_2\mu_2)^3}\Big)\sigma_{12} \\
\frac{d\sigma_{22}}{dt} &= \frac{k_1\mu_1+k_2\mu_2}{c_1+\mu_1+c_2\mu_2} + \Big(\frac{k_2\mu_2-k_1(c_1+c_2\mu_2)}{(c_1+\mu_1+c_2\mu_2)^3}\Big)\sigma_{11} \\
&+ \Big(\frac{-2\big(k_1c_2\mu_1+k_2(c_1+\mu_1)\big)}{(c_1+\mu_1+c_2\mu_2)^2} + \frac{k_1c_2^2\mu_1-k_2c_2(c_1+\mu_1)}{(c_1+\mu_1+c_2\mu_2)^3}\Big)\sigma_{22} \\
&+ \Big(\frac{2\big(k_1(c_1+c_2\mu_2)+k_2\mu_2\big)}{(c_1+\mu_1+c_2\mu_2)^2} + \frac{k_1(c_2\mu_1-c_2^2\mu_2-c_1c_2)+k_2(c_2\mu_2-\mu_1-c_1)}{(c_1+\mu_1+c_2\mu_2)^3}\Big)\sigma_{12} \\
\frac{d\sigma_{12}}{dt} &= -\frac{k_1\mu_1+k_2\mu_2}{c_1+\mu_1+c_2\mu_2} + \Big(\frac{k_1(c_1+\mu_2)+k_2\mu_2}{(c_1+\mu_1+c_2\mu_2)^2} + \frac{k_1(c_1+c_2\mu_2)-k_2\mu_2}{(c_1+\mu_1+c_2\mu_2)^3}\Big)\sigma_{11} \\
&+ \Big(\frac{k_1c_2\mu_1+k_2(c_1+\mu_1)}{(c_1+\mu_1+c_2\mu_2)^2} + \frac{-k_1c_2^2\mu_1+k_2c_2(c_1+\mu_1)}{(c_1+\mu_1+c_2\mu_2)^3}\Big)\sigma_{22} \\
&+ \Big(\frac{-k_1(c_1+c_2\mu_2+c_2\mu_1)-k_2(c_1+\mu_1+\mu_2)}{(c_1+\mu_1+c_2\mu_2)^2} \\
&+ \frac{-k_1(c_2\mu_1-c_2^2\mu_2-c_1c_2)-k_2(c_2\mu_2-\mu_1-c_1)}{(c_1+\mu_1+c_2\mu_2)^3}\Big)\sigma_{12} \ .
\end{aligned}$$

The simulation results from MCM and SSA are compared in Figure 3, which shows that the results from the SSA and MCM are in good agreement.

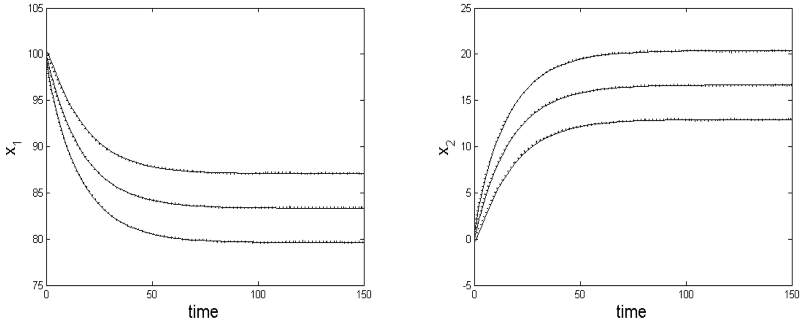

Figure 3: Under the initial condition $(x_1, x_2) = (100, 0)$ and $k_1 = 1, k_2 = 5, c_1 = 1, c_2 = 1$ in Example 3, comparison of the mean + standard deviation(upper curves), mean(middle curves) and mean − standard deviation(lower curves) from MCM(solid) and SSA(dotted). (a) x_1 (b) x_2. The results by SSA are based on 30,000 realizations.

3.4 Two metabolites model with mass action and rational rate laws

We consider a model that describes two metabolites coupled by a bimolecular reaction [16];

$$\phi \rightarrow A, \quad A \rightarrow \phi, \quad \phi \rightarrow B$$
$$B \rightarrow \phi, \quad A + B \rightarrow \phi$$

Let x_1, x_2 be the molecular numbers of A, B, respectively. Then the propensity functions are written as

$$a_1(\mathbf{x}) = \frac{c_1}{k_1 + x_1}, \; a_2(\mathbf{x}) = k_2 x_2, \; a_3(\mathbf{x}) = \frac{c_3}{k_3 + x_2},$$
$$a_4(\mathbf{x}) = k_4 x_2, a_5(\mathbf{x}) = k_5 x_1 x_2,$$

where $c_1, c_3, k_i = 1, \ldots, 5$ are constant. One can find the partial derivatives of a_1, a_2

$$\frac{\partial a_1}{\partial x_1} = \frac{-c_1}{(k_1 + x_1)^2}, \quad \frac{\partial^2 a_1}{\partial x_1^2} = \frac{2c_1}{(k_1 + x_1)^3}, \quad \frac{\partial a_2}{\partial x_1} = k_2,$$
$$\frac{\partial a_3}{\partial x_2} = \frac{-c_3}{(k_2 + x_2)^2}, \quad \frac{\partial^2 a_3}{\partial x_2^2} = \frac{2c_3}{(k_2 + x_2)^3}, \quad \frac{\partial a_4}{\partial x_2} = k_4,$$
$$\frac{\partial a_5}{\partial x_1} = k_5 x_2, \quad \frac{\partial a_5}{\partial x_2} = k_5 x_1, \quad \frac{\partial^2 a_5}{\partial x_1 \partial x_2} = k_5.$$

By the substitution of the above partial derivatives into Equations (23) and (24), we obtain the equations for the first moments

$$\begin{aligned}
\frac{d\mu_1}{dt} &= \frac{c_1}{k_1+\mu_1} - k_2\mu_1 - k_5\mu_1\mu_2 + \frac{c_1}{(k_1+\mu_1)^3}\sigma_{11} - k_5\sigma_{12} \\
\frac{d\mu_2}{dt} &= \frac{c_3}{k_3+\mu_2} - k_4\mu_2 - k_5\mu_1\mu_2 + \frac{c_3}{(k_3+\mu_2)^3}\sigma_{22} - k_5\sigma_{12}
\end{aligned}$$

and the equations for the second moments

$$\begin{aligned}
\frac{d\sigma_{11}}{dt} &= \frac{c_1}{k_1+\mu_1} + k_2\mu_1 + k_5\mu_1\mu_2 \\
&+ \sigma_{11}\Big(\frac{-2c_1}{(k_1+\mu_1)^2} + \frac{c_1}{(k_1+\mu_1)^3} - 2k_2 - 2k_5\mu_2\Big) + \sigma_{12}(-2k_5\mu_1 + k_5) \\
\frac{d\sigma_{22}}{dt} &= \frac{c_3}{k_3+\mu_2} + k_4\mu_2 + k_5\mu_1\mu_2 \\
&+ \sigma_{22}\Big(\frac{-2c_3}{(k_3+\mu_2)^2} + \frac{c_3}{(k_3+\mu_2)^3} - 2k_4 - 2k_5\mu_1\Big) + \sigma_{12}(-2k_5\mu_2 + k_5) \\
\frac{d\sigma_{12}}{dt} &= k_5\mu_1\mu_2 + \sigma_{11}(-k_5\mu_2) + \sigma_{22}(-k_5\mu_1) \\
&+ \sigma_{12}\Big(-\frac{c_1}{(k_1+\mu_1)^2} - k_2 - \frac{c_3}{(k_3+\mu_2)^2} - k_4 - k_5\mu_2 - k_5\mu_1 + k_5\Big)\ .
\end{aligned}$$

The simulation results are shown in Figure 4. One sees that the results from the SSA and MCM match well.

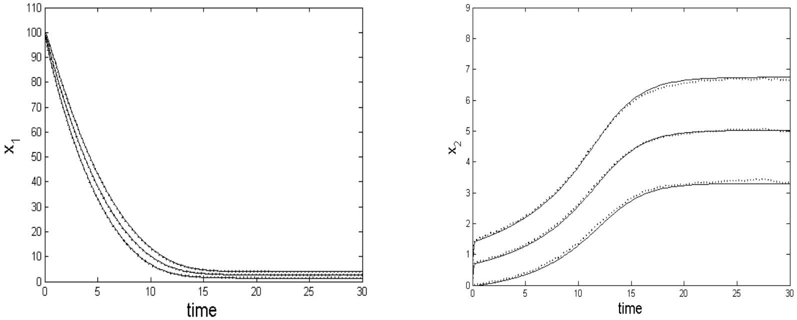

Figure 4: Under the initial condition $(x_1, x_2) = (100, 0)$ and $k_1 = 1, k_2 = 0.1, k_3 = 1, k_4 = k_5 = 0.1, c_1 = 5, c_3 = 10$ in Example 4, comparison of the mean + standard deviation(upper curves), mean(middle curves) and mean − standard deviation(lower curves) from MCM(solid) and SSA(dotted). (a) x_1 (b) x_2. The results by SSA are based on 30,000 realizations.

4 Conclusion

Moment closure approximation is a widely used method when one finds the moments of stochastically modeled chemical reaction networks. Especially if computation of reaction networks by the stochastic simulation algorithm is expensive, the moment closure methods are good alternative methods that approximate the solution efficiently and accurately. In this paper, we presented a moment closure method for chemical reaction networks with general kinetics, which can be applied to reaction networks with rational, fractional and mixed rate laws. It has not been known yet how to formulate the moment closure method for general kinetics including fractional rate laws before this work. We showed that the MCM captures the first and second moments accurately when it is compared to the SSA. Concerning computational efficiency, we observed that the MCM takes less than one second, but the SSA takes about ten minutes to more than one hour to obtain the results for the four applications, which implies that the MCM is more efficient than the SSA. The MCM obtained after the truncation at the third moment is practically useful, although the truncation at the higher moments can give more accurate approximate solution.

We expect that this method will be applied to stochastically modeled complex chemical reaction networks with any general kinetic models especially if the simulation by the SSA needs heavy computational loads.

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