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Investigating the Gap between Discrete and Continuous Models of Chemically Reacting Systems

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The aim of this paper is to investigate the discrete nature of chemically reacting systems. In order to achieve our purpose we propose a systematic method to compare the discrete stochastic model of chemically reacting systems with the continuous stochastic model. We adopt the chemical master equation (CME) as the discrete stochastic model and the chemical Fokker-Planck equation (CFPE) as the continuous stochastic model. By making use of the well-known idea of approximating diffusion processes by birth-death processes, we construct a family of master equations parameterized by the degree of discreteness. This family of master equations bridges CME and CFPE. With full degree of discreteness we obtain CME and as decreasing discreteness the family of master equations converges to CFPE. Our strategy is not to study CME directly but to distinguish the properties of CME by putting CME into the family of master equations bridging CME and CFPE. We examine the usefulness of our construction by two simple examples.

Keywords: Chemical master equation, Chemical Fokker-Planck equation, Chemical Langevin equation, Discreteness

1 Introduction

Molecular discreteness would be important in intracellular chemical reactions since the number of copies of molecules included in the reactions is small compared to *in vitro* situations [1–5]. Recently an experimental evidence for the significance of the molecular discreteness was found [6]. For a theoretical study, Togashi and Kaneko [3] reported a new transition phenomenon in a small autocatalytic system by a discrete stochastic simulation of the system. It cannot be observed in a model based on the classical reaction rate equation. However, Ohkubo et al. [7] found that the transition phenomenon reported by Togashi and Kaneko [3] originated not from the discreteness but the large fluctuation due to the small number of copies of molecules by analyzing a simpler autocatalytic system. They showed that the same transition phenomenon can be observed in a model based on the Fokker-Planck Equation in which the numbers of molecules are represented by continuous variables.

It is convenient if there is a systematic method to discriminate the effects of discreteness from the effects of the fluctuation resulting from the small number of copies of molecules. One intuitively acceptable approach would be to compare the discrete stochastic model with the continuous stochastic model. As the discrete stochastic model, we here consider chemically reacting systems whose time evolutions are governed by the chemical master equation (CME) [8–10]. The chemical Langevin equation (CLE) (or corresponding chemical Fokker-Planck equation (CFPE)) [9,10] is adopted as the continuous stochastic model. Gillespie [9] derived CLE as an approximation for CME under an appropriate condition. However, we use CLE as a reference model in order to investigate the discrete nature of chemically reacting systems

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regardless of the condition considered by Gillespie [9]. In other words, we do not study the properties of CME directly but distinguish them by comparing CME and CFPE.

In this paper we construct a family of master equations bridging CME and CFPE. We introduce a parameter ε that can be considered as the degree of discreteness. We will show that the family of master equations converges to CFPE as $\varepsilon \to 0$ and $\varepsilon = 1$ gives CME. The idea of our construction is not new. It is given in the well-known Gardiner's textbook [11]. There the general one-variable diffusion process is approximated by birth-death master equations. What are new in this paper are as follows. First we construct the family of master equations for general many-variable chemically reacting systems. Second we construct the family of master equations so that $\varepsilon = 1$ gives CME. In particular, the latter is out of interests in the Gardiner′s textbook [11].

This paper is organized as follows. Section 2 reviews both CME and CLE (or CFPE). In section 3 we describe our construction of master equations bridging CME and CFPE. In section 4 we analyze two simple examples by applying our construction to them. In section 5 we give conclusions.

2 The Chemical Master Equation and the Chemical Langevin Equation

In this section we review the approximation of the chemical master equation by the chemical Langevin equation by Gillespie [9,10].

Let us consider a well-stirred chemically reacting system consisting of N molecular species and M chemical reactions with constant volume and constant temperature. We denote the molecular species by $X_1, \cdots, X_N$ and the chemical reactions by $R_1, \cdots, R_M$. We specify the state of the system at time t by a vector $\mathbf{X}(t) = (X_1(t), \cdots, X_N(t))$, where $X_i(t)$ is the number of X_i molecules in the system at time t, a non-negative integer ($i = 1, \cdots, N$). We use the same symbol to represent both the molecular species and the number of its molecules since there is no fear of confusions. Let $a_j(\mathbf{X})$ be the probability per unit time that one reaction R_j occurs when the state of the system is $\mathbf{X}$. The change in the number of X_i molecules by one reaction R_j is denoted by v_{ij}. We also introduce the vector for state change $\boldsymbol{v}_j = (v_{1j}, \cdots, v_{Nj})$ for each reaction R_j. Let $P(\mathbf{X},t)$ be the probability that $\mathbf{X}(t) = \mathbf{X}$ given a certain initial condition $\mathbf{X}(t_0) = \mathbf{X}_0$. The time evolution equation for $P(\mathbf{X},t)$ can be written as

$$\partial_t P(\mathbf{X},t) = \sum_{j=1}^{M} \left[a_j(\mathbf{X}-\nu_j) P(\mathbf{X}-\nu_j,t) - a_j(\mathbf{X}) P(\mathbf{X},t) \right]. \tag{1}$$

Equation (1) is called the chemical master equation (CME) [8–10]. Gillespie proposed an exact stochastic simulation algorithm (the Gillespie algorithm) to generate a sample path for CME about thirty yeas ago [8]. The Gillespie algorithm is now widely used to simulate chemically reacting systems with small number of molecules [10].

The chemical Langevin equation (CLE), which is a continuous approximation for CME, is derived by Gillespie as follows [9]. Let $K_j(\mathbf{X}(t),\tau)$ be the number of occurrence for reaction R_j in a duration τ. By the definition of $K_j(\mathbf{X}(t),\tau)$, we can write

$$X_i(t+\tau) = X_i(t) + \sum_{j=1}^{M} \nu_{ij} K_j(\mathbf{X}(t),\tau). \tag{2}$$

Gillespie [9] considers the following two conditions (i) and (ii) for the duration τ.

(i) τ is sufficiently small so that the following holds:

$a_j(X(t')) \approx a_j(X(t))$ for all $t' \in [t, t+\tau],\ j = 1, \cdots, M$.

(ii) τ is sufficiently large so that the following holds:

$a_j(\mathbf{X}(t))\tau >> 1,\ j = 1, \cdots, M$.

If the above two conditions (i) and (ii) hold then $K_j(\mathbf{X}(t),\tau)$ can be approximated by a normal stochastic variable $N_j(a_j(\mathbf{X}(t))\tau, a_j(\mathbf{X}(t))\tau)$, where $N(m,\sigma^2)$ is a normal stochastic variable with mean m and variance σ^2. Since we have

$$N(m, \sigma^2) = m + \sigma N(0,1), \tag{3}$$

we obtain

$$X_i(t+\tau) = \\ X_i(t) + \sum_{j=1}^{M} \nu_{ij} a_j(\mathbf{X}(t))\tau + \sum_{j=1}^{M} \nu_{ij} a_j(\mathbf{X}(t))^{1/2} N_j(t) \tau^{1/2}, \tag{4}$$

where $N_j(t)$ is a normal stochastic variable with mean 0 and variance 1. If $j \neq j'$ or $t \neq t'$ then $N_j(t)$ and $N_j(t')$ are independent. Equation (4) is called the chemical Langevin equation (CLE) [9,10]. Now the state variable $X_i(t)$ in CLE is a non-negative real number, a continuous variable. The corresponding time evolution equation for the probability distribution is

$$\partial_t P(\mathbf{X},t) = \\ -\sum_{i=1}^{N} \partial_{X_i} \left[A_i(\mathbf{X}) P(\mathbf{X},t) \right] + \frac{1}{2} \sum_{i,i'=1}^{N} \partial_{X_i} \partial_{X_{i'}} \left[B_{ii'}(\mathbf{X}) P(\mathbf{X},t) \right], \tag{5}$$

where

$$A_i(\mathbf{X}) = \sum_{j=1}^{M} \nu_{ij} a_j(\mathbf{X}),\ B_{ii'}(\mathbf{X}) = \sum_{j=1}^{M} \nu_{ij} \nu_{i'j} a_j(\mathbf{X}) \text{ for } i = 1, \cdots, N.$$

Equation (5) is called the chemical Fokker-Planck equation (CFPE) [9,10].

The two conditions (i) and (ii) means that the approximation of CME by CLE is justified if there is a certain time scale satisfying both (i) and (ii). In particular, if each chemical species has a sufficiently large number of molecules then the required time scale is expected to exist. If there is no such time scale then the validity of the approximation is not guaranteed. However, we can write down CLE (or CFPE) just as a stochastic differential equation (or a partial differential equation) for a given chemically reacting system. In the following we will use them as a reference to study the discrete nature of chemical reactions.

3 Construction of a Family of Master Equations Bridging CME and CFPE

In this section we present our construction of a family of master equations bridging CME and CFPE. As mentioned in the introduction, it is well-known that general one-variable Fokker-Planck equations can be approximated by master equations as written in Gardiner's textbook [11]. By making use of the idea of the approximation method, we construct a family of master equations that bridges CME and CFPE.

We introduce a parameter $0 < \varepsilon \leq 1$. For each ε we define a master equation M_ε. We will construct a family of master equations such that M_1 = CME and $\mathrm{M}_\varepsilon \to$ CFPE as $\varepsilon \to 0$.

For each reaction R_j we prepare two reactions R_j^+ and R_j^-. The probabilities per unit time for the occurrence of reaction R_j^+ and R_j^- are given by

$$f_j^+(\mathbf{X},\varepsilon) = \frac{a_j(\mathbf{X},\varepsilon)}{2\varepsilon} + \frac{a_j(\mathbf{X},\varepsilon)}{2\varepsilon^2} \tag{6}$$

and

$$f_j^-(\mathbf{X},\varepsilon) = \frac{-a_j(\mathbf{X},\varepsilon)}{2\varepsilon} + \frac{a_j(\mathbf{X},\varepsilon)}{2\varepsilon^2}\ , \tag{7}$$

respectively. Here $a_j(\mathbf{X}, \varepsilon)$ is defined as follows. If there is an expression of the form $(X_i - c)$, which denotes the number of molecules, in $a_j(\mathbf{X})$ then we replace it by $(X_i - c\varepsilon)$. For example, consider a reaction $R_1 : 2X_1 \to X_1 + X_2$ and assume that $a_1(\mathbf{X}) = c_1 X_1 (X_1 - 1)/2$, where c_1 is a constant. Then we have $a_1(\mathbf{X}, \varepsilon) = c_1 X_1 (X_1 - \varepsilon)/2$. The state change vectors for R_j^+ and R_j^- are defined by $\varepsilon \boldsymbol{v}_j$ and $-\varepsilon \boldsymbol{v}_j$, respectively. Thus ε is the possible smallest change in the number of molecules. Hence it can be considered as the degree of discreteness.

The jump probability per unit time from $\mathbf{X}$ to $\mathbf{X}'$ is given by

$$\begin{aligned} W_\varepsilon(\mathbf{X}'\,|\,\mathbf{X}) = &\sum_{j=1}^{M}\left[f_j^+(\mathbf{X},\varepsilon)\delta(\mathbf{X}' - (\mathbf{X}+\varepsilon\nu_j))\right] \\ &+ \sum_{j=1}^{M}\left[f_j^-(\mathbf{X},\varepsilon)\delta(\mathbf{X}' - (\mathbf{X}-\varepsilon\nu_j))\right], \end{aligned} \tag{8}$$

where δ is the Dirac's delta function. The master equation M_ε for the chemically reacting systems with the above jump probability per unit time is

$$\partial_t P(\mathbf{X},t) = \int d\mathbf{X}'\left[W_\varepsilon(\mathbf{X}\,|\,\mathbf{X}')P(\mathbf{X}',t) - W_\varepsilon(\mathbf{X}'\,|\,\mathbf{X})P(\mathbf{X},t)\right]. \tag{9}$$

It is easy to see that M_1 = CME since $f_j^+(\mathbf{X},1) = a_j(\mathbf{X})$ and $f_j^-(\mathbf{X},1) = 0$. One can show that M_ε converges to a Fokker-Planck equation as $\varepsilon \to 0$ by using the following relations for jump moments:

$$\int d\mathbf{X}'(X_i' - X_i)W_\varepsilon(\mathbf{X}'\,|\,\mathbf{X}) = \sum_{j=1}^{M}\nu_{ij}a_j(\mathbf{X},\varepsilon), \tag{10}$$

$$\int d\mathbf{X}'(X_i' - X_i)(X_{i'}' - X_{i'})W_\varepsilon(\mathbf{X}'\,|\,\mathbf{X}) = \sum_{j=1}^{M}\nu_{ij}\nu_{i'j}a_j(\mathbf{X},\varepsilon). \tag{11}$$

The proof of convergence can be done by just imitating the derivation of the differential Chapman-Kolmogorov equation [11]. We call the proposed approximation scheme the ε-approximation. The obtained Fokker-Planck equation is exactly the same as the original CFPE if all $a_j(\mathbf{X})$ have no expression of the form $(X_i - c)$ with $c > 0$, which denotes the number of molecules. Otherwise, the difference between the obtained Fokker-Planck equation and the original CFPE would be the order of $1/V$ if we change the variables from the numbers of molecules to the concentrations, where V is the volume of the system. Hence we can disregard the difference in the large volume limit. However, when the numbers of molecules can become small as typically in the case of a small value of the volume, it is crucial that the original CFPE cannot be defined for $0 \leq X_i <$ c if $a_j(\mathbf{X})$ has an expression of the form $(X_i - c)$ for some reaction R_j. In such case, it is convenient to use the obtained Fokker-Planck equation instead of the original CFPE. In the following, we also call the obtained Fokker-Planck equation CFPE.

What are the advantages of the ε-approximation? It is not useful to study the properties of CME directly. But our aim of using the ε-approximation is to distinguish CME in a family of master equations converging to CFPE as $\varepsilon \to 0$. By decreasing the value of ε from 1 to 0, we can study the "response" of a chemically reacting system to the loss of the discreteness. We could obtain some insights into the discreteness of chemically reacting systems by solving M_ε numerically or analytically.

We can expect that M_ε is a good approximation for CFPE for sufficiently small ε. Since M_ε is a master equation whose state variables take discrete values, it is easier to implement its boundary conditions than CFPE. The time evolution of M_ε can be readily simulated by the Gillespie algorithm. Thus we have no worry about the numerical implementation of boundary conditions. This is also an advantage of our approximation scheme. However, it should be noted that a long time simulation of M_ε by the Gillespie algorithm becomes harder as $\varepsilon \to 0$ since $f_j^+(\mathbf{X},\varepsilon)$ grows in the order of ε^{-2}.

Let us consider the meaning of our construction. The first terms and the second terms in $f_j^+(\mathbf{X},\varepsilon)$ and $f_j^-(\mathbf{X},\varepsilon)$ correspond to the drift term and the diffusion term in CFPE, respectively. When ε is 1, we have the perfect balance between the "drift" and the "diffusion" as $f_j^-(\mathbf{X},1)=0$. If ε is smaller than 1 then the balance is broken. The broken balance can be visible as an inhomogeneous term in the generating function equation for M_ε (but we do not show it explicitly here).

For the uniqueness of $f_j^+(\mathbf{X},\varepsilon)$ and $f_j^-(\mathbf{X},\varepsilon)$, we have the following result. Define

$$
\begin{aligned}
W_{\varepsilon,j}(\mathbf{X}'\,|\,\mathbf{X}) &= f_j^+(\mathbf{X},\varepsilon)\delta(\mathbf{X}'-(\mathbf{X}+\varepsilon v_j)) \\
&\quad + f_j^-(\mathbf{X},\varepsilon)\delta(\mathbf{X}'-(\mathbf{X}-\varepsilon v_j)).
\end{aligned} \tag{12}
$$

Let us require that

$$
\int d\mathbf{X}'(X_i'-X_i)W_{\varepsilon,j}(\mathbf{X}'\,|\,\mathbf{X}) = v_{ij}a_j(\mathbf{X},\varepsilon) \tag{13}
$$

and

$$
\int d\mathbf{X}'(X_i'-X_i)(X_{i'}'-X_{i'})W_{\varepsilon,j}(\mathbf{X}'\,|\,\mathbf{X}) = v_{ij}v_{i'j}a_j(\mathbf{X},\varepsilon) \tag{14}
$$

for $i = 1,\cdots,N$ and $j = 1,\cdots,M$. Further we assume that there is a chemical species X_i such that $v_{ij} \neq 0$ for each reaction R_j. That is, at least one molecular species changes its number of molecules in each reaction R_j. By our requirement, we have

$$
\begin{cases}
(f_j^+(\mathbf{X},\varepsilon) - f_j^-(\mathbf{X},\varepsilon))\varepsilon = a_j(\mathbf{X},\varepsilon) \\
(f_j^+(\mathbf{X},\varepsilon) + f_j^-(\mathbf{X},\varepsilon))\varepsilon^2 = a_j(\mathbf{X},\varepsilon)
\end{cases} \tag{15}
$$

for each $j = 1,\cdots,M$. Hence we obtain

$$
f_j^+(\mathbf{X},\varepsilon) = \frac{a_j(\mathbf{X},\varepsilon)}{2\varepsilon} + \frac{a_j(\mathbf{X},\varepsilon)}{2\varepsilon^2} \tag{16}
$$

and

$$
f_j^-(\mathbf{X},\varepsilon) = \frac{-a_j(\mathbf{X},\varepsilon)}{2\varepsilon} + \frac{a_j(\mathbf{X},\varepsilon)}{2\varepsilon^2}. \tag{17}
$$

4 Examples

In this section we examine the usefulness of our ε-approximation by two simple examples. First consider the following set of chemical reactions:

$$
R_1 : \phi \to X_1,\ R_2 : X_1 \to \phi,\ R_3 : \phi \to X_2,\ R_4 : X_2 \to \phi,
$$
$$
R_5 : X_1 + X_2 \to X_1.
$$

We set

$$
a_1(\mathbf{X}) = k_1 V,\ a_2(\mathbf{X}) = k_2 X_1,\ a_3(\mathbf{X}) = DsV,\ a_4(\mathbf{X}) = DX_2
$$
and $a_5(\mathbf{X}) = \dfrac{k_3}{V} X_1 X_2$.

V is the volume of the container in which the above set of chemical reactions occur. X_1 is generated and degraded within the container at reaction rate constants k_1 and k_2, respectively. Sufficiently large number of molecules of X_2 exists outside of the container with concentration s. X_2 molecules can diffuse from the inside to the outside of the container with diffusion rate D and vice versa. X_1 molecules can degrade X_2 molecules with reaction rate constant k_3. We also assume that all the other molecular species that are needed to maintain the above set of chemical reactions exist in the container with sufficiently large numbers of molecules. We consider the same assumption for the following second example. Here we set the parameters as follows: $k_1 = k_2 = 0.01$, $k_3 = 1$, $D = 1$, $s = 1000$ and $V = 1$. Both generation and degradation of X_1 molecules are set to be very slow compared to the other reactions. On the other hand, reactions involving X_2 molecules are expected to occur rapidly

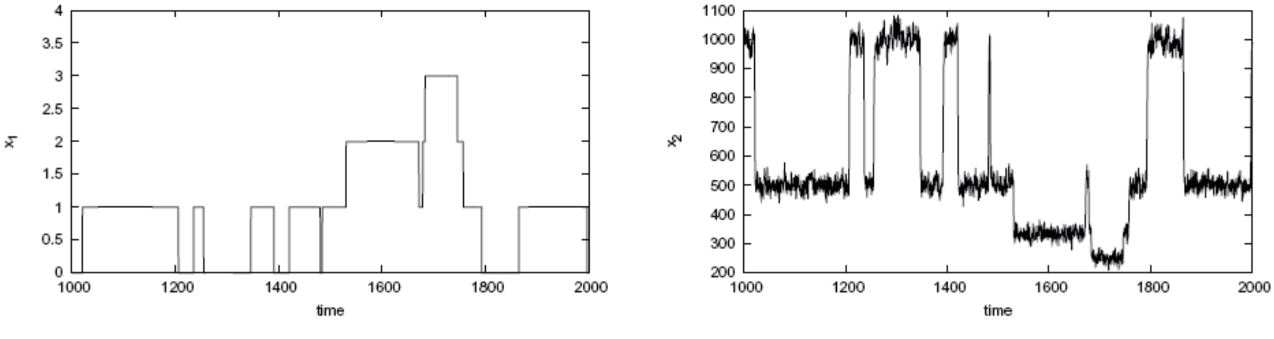

Figure 1. A time evolution of the number of X_1 molecules (left hand side) and X_2 molecules (right hand side) based on CME in the first example. The time series are produced by Gillespie algorithm.

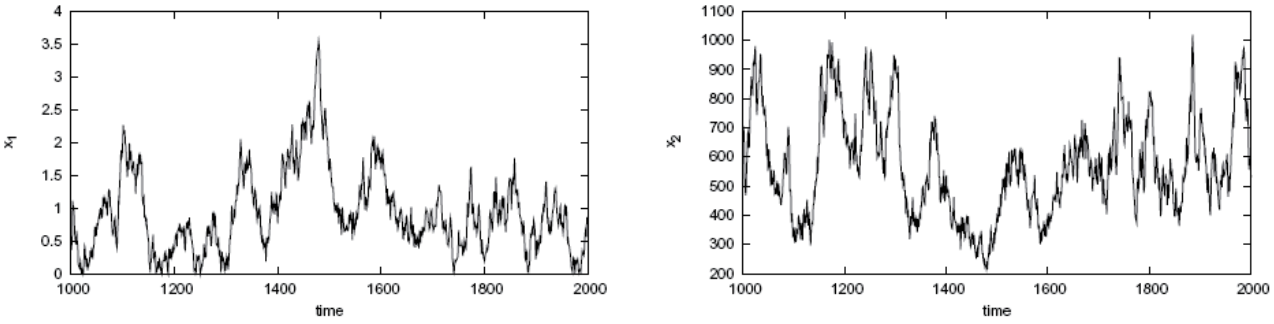

Figure 2. A time evolution of the number of X_1 molecules (left hand side) and X_2 molecules (right hand side) based on CLE in the first example. The time series are produced by directly integrating CLE with $\tau = 0.01$.

since X_2 molecules exist in large excess outside the container.

Figure 1 shows a time evolution of the number of X_1 and X_2 molecules simulated by the Gillespie algorithm [8]. We can see a clear discreteness effect. The number of X_2 molecules rapidly responds to one-by-one changes in the number of X_1 molecules. On the other hand, Figure 2 shows a time evolution of the numbers of X_1 and X_2 molecules by numerically integrating the CLE with $\tau = 0.01$. Although the stationary solution of CLE for X_1 molecules has the same mean and variance as those for CME, they have qualitatively different features in their time evolutions. The probability distributions of the number of X_2 molecules for CME, $M_\varepsilon(\varepsilon = 1/2, 1/4, 1/8, 1/16)$ and CLE are shown in Figure 3. One can see that the probability distribution for M_ε converges to that for CLE as $\varepsilon \to 0$. There are peaks in the probability distributions corresponding to quasi-steady states due to the slow change in the number of X_1 molecules. For example, the peaks around $X_2 = 1000$ correspond to $X_1 = 0$, the peaks around $X_2 = 500$ correspond to $X_1 = 1$, and so on. In general, there are peaks around $X_2 = 1000/(1+X_1)$ for CME and M_ε with large ε. Since more states are available in M_ε for smaller ε, at first the number of peaks for M_ε increases as ε becomes small. However, if ε is small enough then the newly appeared peaks begin to merge. Indeed, one can estimate when the probability distribution of the number of X_2 molecules becomes unimodal. The average time τ_1 for the occurrence of one of the reactions in which the number of X_1 molecules changes is the reciprocal of $\sum_{j=1}^{2} f_j^{+}(\mathbf{X},\varepsilon)+f_j^{-}(\mathbf{X},\varepsilon)=(k_1V+k_2N)\varepsilon^{-2}$ given the present number of X_1 molecules is N. On the other hand, the time scale that the number of X_2 molecules reaches the quasi-steady state is $\tau_2 = (k_3N + DV)V^{-1}$. If τ_1 is sufficiently smaller than τ_2 for all values of N then the probability distribution of the number of X_2 molecules would be unimodal. Thus we consider the condition $\tau_1 << \tau_2$, from which we obtain $\varepsilon^2 << \min\{k_1/D, k_2/k_3\}V$. For the present set of values of the parameters, we have $\varepsilon^2 << 0.01$, which is consistent with the numerical result in Figure 3.

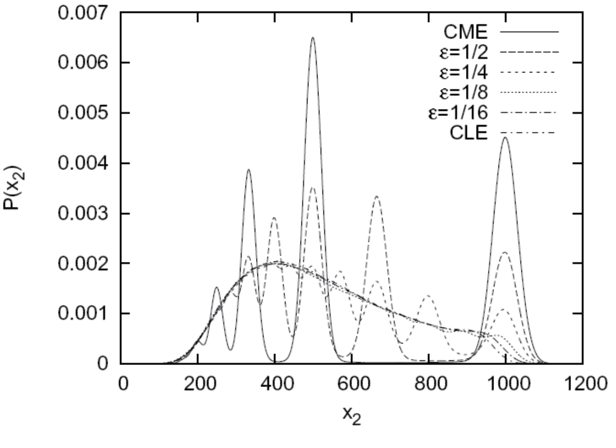

Figure 3. Probability distribution functions of the number of X_2 molecules for CME, $M_\varepsilon(\varepsilon = 1/2, 1/4, 1/8, 1/16)$ and CLE in the first example.

The second example consists of the following set of chemical reactions:

$$R_1 : X_1 + X_2 \to 2X_1,\ R_2 : X_1 \to X_2,\ R_3 : X_2 \to X_1.$$

We set

$$a_1(\mathbf{X}) = \frac{k_1}{V} X_1X_2,\ a_2(\mathbf{X}) = k_2X_1$$

and $a_2(\mathbf{X}) = k_3X_2$, where k_1, k_2 and k_3 are reaction rate constants. This set of chemical reactions has a remarkable property. The sum of the numbers of all chemical species is conserved. If we assume $X_1(0)+X_2(0)=nV$ for a constant n then we have $X_1(t) + X_2(t) = nV$ for all $t \geq 0$. Substituting $X_2 = nV - X_1$ into $a_j(\mathbf{X})$ for $j = 1, 2, 3$, we obtain CME, M_ε and CFPE

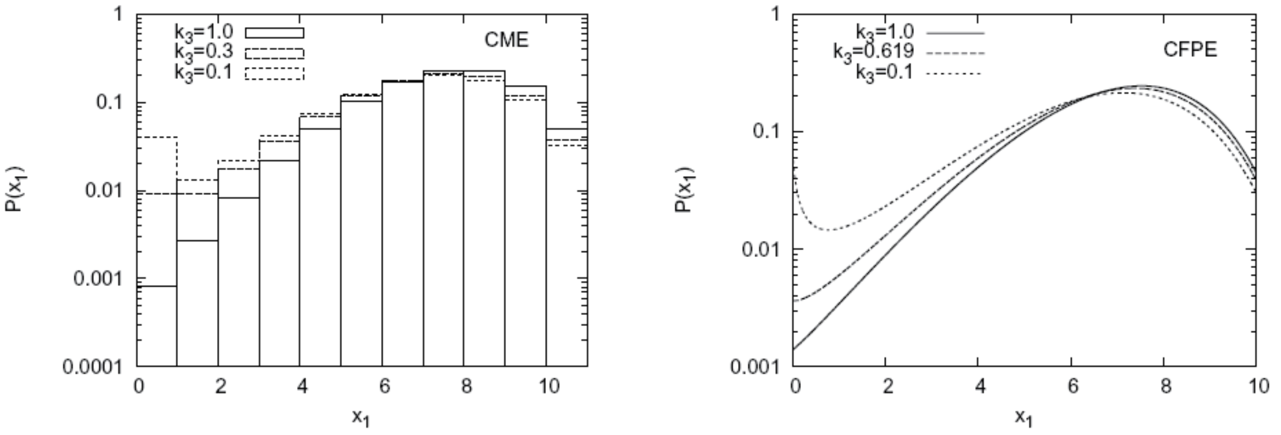

Figure 4. Stationary solutions for CME (left hand side) and CFPE (right hand side) in the second example.

with one state variable $0 \leq X_1 \leq nV$. In particular, for any $0 < \varepsilon \leq 1$ we can treat the master equation M_ε as a finite-dimensional linear ordinary differential equation: $\partial_1 \mathbf{P}(t) = \mathbf{W}_\varepsilon \mathbf{P}(t)$, where $\mathbf{P}(t) = (P(0,t), P(\varepsilon,t), P(2\varepsilon,t), \cdots, P(nV,t))$ and $\mathbf{W}_\varepsilon$ is a matrix with its components

$$(\mathbf{W}_\varepsilon)_{ii'} = W_\varepsilon(\varepsilon i \mid \varepsilon i') - \delta_{ii'} \sum_{i''} W_\varepsilon(\varepsilon i'' \mid \varepsilon i). \tag{18}$$

We here assume that nV/ε is a positive integer. δ is the Kronecker's delta. 0 is a non-degenerated eigenvalue of $\mathbf{W}_\varepsilon$ corresponding to the unique stationary solution $\mathbf{P}^S$ satisfying the detailed balance condition

$$(\mathbf{W}_\varepsilon)_{ii'} (\mathbf{P}^s)_{i'} = (\mathbf{W}_\varepsilon)_{i'i} (\mathbf{P}^s)_{i}. \tag{19}$$

In such case, it is well-known that all the other eigenvalues are negative real numbers [12]. If $\mathbf{W}_\varepsilon \mathbf{\Phi}_\lambda = -\lambda \mathbf{\Phi}_\lambda$ then the solution is

$$\mathbf{P}(t) = \mathbf{P}^s + \sum_{\lambda > 0} c_\lambda \mathbf{\Phi}_\lambda \exp(-\lambda t) \tag{20}$$

where c_λ are constants. In the following we investigate how the stationary solutions and characteristics of the relaxation to the stationary solutions are different between CME and CFPE by using the ε-approximation for the second example.

By rescaling time and redefining the reaction rate constants k_2, k_3 we can set $k_1 = 1$ without loss of generality. Put $t^+(X_1) = X_1(nV - X_1)/V + k_3(nV - X_1)$ and $t^-(X_1) = k_2 X_1$.

We define

$$t_\varepsilon^+(X_1) = \begin{cases} \frac{1}{2}(\varepsilon^{-1} + \varepsilon^{-2}) t^+(X_1) + \frac{1}{2}(-\varepsilon^{-1} + \varepsilon^{-2}) t^-(X_1), & (0 \leq X_1 \leq nV - \varepsilon) \\ 0, \ (X_1 = nV) \end{cases} \tag{21}$$

and

$$t_\varepsilon^-(X_1) = \begin{cases} \frac{1}{2}(\varepsilon^{-1} + \varepsilon^{-2}) t^-(X_1) + \frac{1}{2}(-\varepsilon^{-1} + \varepsilon^{-2}) t^+(X_1), & (\varepsilon \leq X_1 \leq nV) \\ 0, \ (X_1 = 0). \end{cases} \tag{22}$$

The master equation M_ε $(0 < \varepsilon \leq 1)$ consists of

$$\partial_t P(X_1,t) =$$
$$t_\varepsilon^+(X_1 - \varepsilon) P(X_1 - \varepsilon, t) + t_\varepsilon^-(X_1 + \varepsilon) P(X_1 + \varepsilon, t) - (t_\varepsilon^+(X_1) + t_\varepsilon^-(X_1)) P(X_1, t) \tag{23}$$

for $\varepsilon \leq X_1 \leq nV - \varepsilon$,

$$\partial_t P(0,t) = t_\varepsilon^-(\varepsilon) P(\varepsilon,t) - t_\varepsilon^+(0) P(0,t) \tag{24}$$

and

$$\partial_t P(nV,t) = t_\varepsilon^+(nV - \varepsilon) P(nV - \varepsilon, t) - t_\varepsilon^-(nV) P(nV,t). \tag{25}$$

CFPE is given by

$$\partial_t P(X_1,t) = -\partial_{X_1}[A(X_1) P(X_1,t)] + \frac{1}{2} \partial_{X_1} \partial_{X_1} [B(X_1) P(X_1,t)] \tag{26}$$

where

$$A(X_1) = t^+(X_1) - t^-(X_1) \text{ and } B(X_1) = t^+(X_1) + t^-(X_1).$$

Using the detailed balance condition

$$t_\varepsilon^-(i\varepsilon) P(i\varepsilon) = t_\varepsilon^+((i-1)\varepsilon) P((i-1)\varepsilon)\,, \tag{27}$$

we obtain the stationary solution of the master equation [11,12]

$$P(i\varepsilon) = P(0) \prod_{i'=1}^{i} \frac{t_\varepsilon^+((i'-1)\varepsilon)}{t_\varepsilon^-(i'\varepsilon)} \tag{28}$$

for $i = 1, \cdots, nV/\varepsilon$, which converges to the stationary solution of CFPE $P(X_1) \propto \frac{1}{B(X_1)} \exp\left(2\int^{X_1} \frac{A(X)}{B(X)} dX\right)$ as $\varepsilon \to 0$ [11].

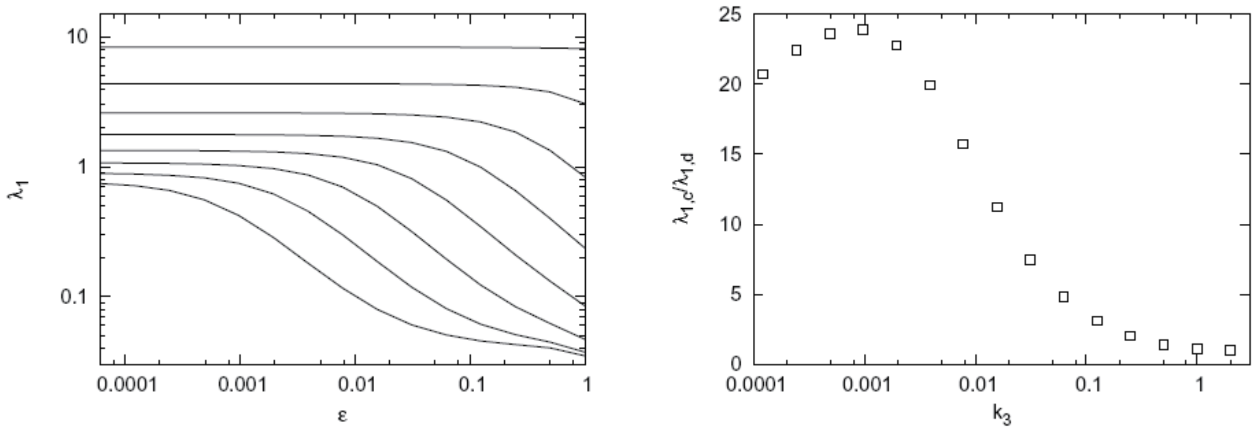

Figure 5. In the left hand side, the absolute value of the largest non-zero eigenvalue $-\lambda_1$ for $\mathbf{W}_\varepsilon$ in the second example is plotted as a function of ε for each value of k_3. The values of k_3 are 2, 1/2, 1/8, 1/32, 1/128, 1/512, 1/2048 and 1/8192 from the top of the figure. In the right hand side, the ratio between λ_1 for CME ($\lambda_{1,d}$) and λ_1 for CFPE ($\lambda_{1,c}$) is plotted as a function of k_3. $\lambda_{1,c}$ is estimated by $\mathbf{W}_\varepsilon$ with $\varepsilon = 10^{-4}$. The values of parameters except k_3 are the same as in figure 4.

In Figure 4 we plot the stationary solutions of CME (left hand side) and CFPE (right hand side) for $k_2 = 3$, $V = 1$ and $n = 10$. We can see the emergence of a new peak around $X_1 = 0$ for both CME and CFPE as the value of k_3 decreases. This is due to the depletion of X_1 molecules. One can estimate the critical value for the emergence of a new peak by considering the detailed balance between $X_1 = 0$ and $X_1 = \varepsilon$. Let us define the emergence of a new peak by $P(0) > P(\varepsilon)$, which is equivalent to $t_\varepsilon^+(0) < t_\varepsilon^-(\varepsilon)$ if the detailed balance condition holds. Thus we obtain the condition

$$k_3 < \frac{k_2 + n + (k_2 - n - 1/V)\varepsilon + (1/V)\varepsilon^2}{2nV + 1 - \varepsilon} \qquad (29)$$

for the emergence of a new peak. This becomes $k_3 < \frac{k_2}{nV}$ for $\varepsilon = 1$ and $k_3 < \frac{k_2 + n}{2nV + 1}$ in the limit $\varepsilon \to 0$. The latter can also be obtained by $P'(0) < 0$ for the stationary solution of CFPE. For the set of parameters in Figure 4 we get $k_3 < 0.3$ for CME and $k_3 < 0.6190\cdots$ for CFPE. Although the critical values for the emergence of a new peak are different, CME and CFPE exhibit the same transition phenomenon in their stationary solutions.

The time scale of the relaxation to the stationary solution is determined by the largest nonzero eigenvalue $-\lambda_1$ of $\mathbf{W}_\varepsilon$ (it is the reciprocal of λ_1). In the left hand side of Figure 5 we plot λ_1 as a function of ε for each k_3. The values of k_3 are 2, 1/2, 1/8, 1/32, 1/128, 1/512, 1/2048 and 1/8192 from the top of the figure. λ_1 seems to converge to a certain value as $\varepsilon \to 0$ for each value of k_3. Hence we adopt $-\lambda_1$ for sufficiently small ε as an approximation for the largest nonzero eigenvalue for CFPE (*i.e.*, the largest nonzero eigenvalue of the linear operator $L(P) = -\partial_{X_1}[A(X_1)P] + \frac{1}{2}\partial_{X_1}\partial_{X_1}[B(X_1)P]$). As the value of k_3 decreases the relaxation to the stationary solution becomes slower in each M_ε. For small values of k_3 the relaxation to the stationary solution is much slower in the discrete model (CME) than in the continuous model (CFPE). When does the difference between them become maximized? The ratio between λ_1 for CME ($\lambda_{1,d}$) and λ_1 for CFPE ($\lambda_{1,c}$, estimated by $\mathbf{W}_\varepsilon$ with $\varepsilon = 10^{-4}$) is maximized at a certain value of k_3 (Figure 5, right hand side). At the critical value of k_3 the relaxation to the stationary solution in CME is about 25 times slower than that in CFPE. We can see that the situation is not so simple that the difference between the discrete model and the continuous model becomes large as the degree of depletion of X_1 molecules increases.

5 Conclusions

In this paper we constructed a family of master equations bridging CME and CFPE by making use of the well-known idea to approximate diffusion processes by birth-death processes. We called the method ε-approximation. CME is obtained by setting $\varepsilon = 1$. We get CFPE by taking the limit $\varepsilon \to 0$.

Our strategy to understand the discreteness of chemically reacting systems is not just studying CME in detail. We attempted to distinguish CME by putting it in the family of master equations converging to CFPE as the discreteness is lost.

We studied two simple chemically reacting systems in order to examine how the ε-approximation works. We can numerically investigate the difference between the discrete stochastic model (CME) and the continuous stochastic model (CLE or CFPE) by the ε-approximation if the total number of molecules is relatively small. In particular, it would be a powerful analytical and numerical tool to study the effect of discreteness in chemically reacting systems in which the total number of molecules is conserved. In this case, the master equation for any ε can be treated as a finite-dimensional linear ordinary differential equation. The more detailed analysis of the time fluctuation based on the large deviation theory [13,14] would enhance the usefulness of the ε-approximation. This is now under ongoing study and will be presented elsewhere.

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