

Reducing the master equations for noisy chemical reactions

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A reduced description for noisy chemical reactions in small systems is presented. By applying the projection operator formalism to the chemical master equation, we show that even when the number of molecules of an intermediate chemical species is small, its elimination from the description is possible provided that its characteristic time scale is short. The resulting master equation of the reduced system includes additional terms of a diffusive kind. The characteristic time of the eliminated chemical species contributes toward the fluctuations of the downstream chemical species, as well as the dispersion of the eliminated component does. © 2003 American Institute of Physics. [DOI: 10.1063/1.1603738]

I. INTRODUCTION

The chemical master equations, which give the time evolution of the probability of having a given number of molecules, provide the starting point to study the stochastic dynamical process of chemical species in a well stirred reactor.¹ However, there is no procedure to solve the master equation analytically. Therefore, a lot of effort must be necessary to understand stochastic behaviors of complicated reaction systems. Such complicated reaction systems could be found as cascades and networks of chemical reactions in systems such as chemical plants and biological systems.

If one could eliminate some intermediate reactions from the description, it could be helpful to study such complicated systems. If the size of the system is large enough, the elimination of the intermediate reactions could be possible if its time scale is fast. Since the evolution of the concentrations of chemical components could be well described by a Fokker–Planck equation, adiabatic elimination methods for Fokker–Planck equations can be used (for instance, see Refs. 2–4). However, if the size of the system is small such as a cell, since the fluctuation in the number could be large, it might not be clear if the elimination could be done. An adiabatic elimination method of the fast variable in a master equation was discussed briefly by Haken.³

The stochasticity of biochemical reactions in cells has been given much attention recently (for review, see Ref. 5). Stochasticity of gene expression is a particular example. Various kinds of processes are involved in the gene expression processes. Among them, Kepler and Elston have studied stochasticity of transcriptional regulation⁶ (see Sec. IV). For this process, they obtained an approximate chemical master equation, which includes additional terms of a diffusive kind. (Their derivation was similar to that by Haken, though the possibility of having such a term was not mentioned.³)

Intuitively, even in cases where the molecular number is small, if the fluctuation of it is rapid, the contribution of the fluctuation to the stochastic behaviors of the downstream re-

actions could be small. Recently, the author has shown that the temporal coarse-grain is applicable to eliminating an intermediate reaction with a fast but noisy concentration variable, i.e., chemical species whose concentration is small but fluctuating rapidly.⁷ The resulting effective chemical reaction has a reaction rate which fluctuates in time (*fluctuating reaction rate*). The master equation for this effective chemical reaction has been derived.⁷ The equation includes additional terms of a diffusive kind, yielding a contribution towards fluctuations from the eliminated chemical species.

In the present publication, the effective master equation for chemical reactions with a fast but noisy variable is derived by adopting the projection operator formalism.^{8–10} In Sec. II, we study a set of reactions, which involve two chemical species. The characteristic time scales in the numbers of these molecules are different. The faster one is synthesized from the slower one. First, the master equation for the reactions is given. Then the projection operator technique is applied in order to derive the effective master equation, which includes a kind of diffusion term. The coefficient for the term is explicitly given. In Sec. III, we show the Fokker–Planck equation and the Langevin equation corresponding to the effective master equation. In Sec. IV, the study of transcriptional regulation by Kepler and Elston⁶ is reformulated by applying the result of Sec. II to it and then in Sec. 4, brief concluding remarks are offered.

II. DERIVATION OF EFFECTIVE MASTER EQUATION FOR NOISY CHEMICAL REACTIONS

In this section, we study a set of chemical reactions, which consist of two chemical species with different characteristic time scales. The chemical species with a slower time scale is generated from the other one with a faster time scale. The number of molecules with the faster characteristic time scale is not necessarily large, i.e., it can be small. The evolution of the chemical reaction is described by the chemical master equation. In order to eliminate the fast variable, the projection operator formalism^{8,9} (see also Ref. 10) is applied to the chemical master equation. Then, we obtain the effec-

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tive master equation, which includes additional terms of a diffusive kind. This diffusion term is the contribution from the fluctuation of the eliminated variable.

A. Chemical reaction

Consider chemical reactions consisting of two chemical species X and Y . X is synthesized from Y , i.e., $Y \rightarrow X$. For Y , some other synthesis and degradation or depletion reactions, which we do not specify here, are supposed. Thus, the number of Y is also time-dependent. We postulate that the characteristic time scale of Y is much faster than that of X . This also suggests that the chemical reaction of synthesizing X , i.e., $Y \rightarrow X$, does not significantly affect the evolution of the number of molecule Y .

Here, we are interested in a reduced description for the reaction of the end product X . As we shall see, the fast chemical component Y can be eliminated from the reaction scheme, and then we obtain a reduced description. Here, we start with the chemical reaction among X and Y , given by



in which k and λ are the rate constants, and m and n are the numbers of X and Y molecules, respectively. We assume that some synthesis and degradation or depletion reactions for Y are present, which are not specified here. Thus, the number of Y is also time-dependent. For the synthesis reaction, it is enough to consider the situation in which the properties of the number of Y molecules are not influenced by the reaction of synthesizing X . Here, for simplicity we choose the chemical reactions that do not change the number of Y molecules. Thus, any statistical and dynamical properties of the number of Y molecules are not affected by this reaction.

B. Master equation and operators

First consider the master equation which describes chemical reaction (1) with some synthetic and degradation reaction for Y . Let $f(m, n, t)$ give the distribution function of m and n at time t . Then, the master equation of the reactions is written as

$$\frac{df}{dt} = \Gamma f = (\Gamma_1 + \Gamma_0)f. \quad (2)$$

Here Γ_1 is the operator for f , which describes the chemical reaction (1), given by

$$\begin{aligned} \Gamma_1 f = & kn[f(m-1, n, t) - f(m, n, t)] \\ & + \lambda[(m+1)f(m+1, n, t) - mf(m, n, t)]. \end{aligned} \quad (3)$$

The synthetic and depletion reactions for Y , which are not specified here, are described by the operator Γ_0 . Thus, Γ_0 gives the evolution rule of n .

C. Probability conservation and stationary distribution function for Y

The probability distribution function $f(m, n, t)$ satisfies $\sum_{m,n} f(m, n, t) = 1$ and $f(m, n, t) \leq 1$. Since $\sum_{m,n} f(m, n, t) = 1$ must be satisfied for any t , operator Γ_0 must satisfy

$$\sum_{n=0}^{\infty} \Gamma_0 h(m, n, t) = 0. \quad (4)$$

Let $\varphi_0(n)$ give the stationary distribution of n . Then $\varphi_0(n)$ follows

$$\Gamma_0 \varphi_0(n) = 0. \quad (5)$$

D. Projection operators

We consider a projection of the distribution function $f(m, n, t)$. For the function $f(m, n, t)$, the projection operator \mathcal{P} is defined by

$$\mathcal{P}f(m, n, t) = \varphi_0(n) \sum_{n=0}^{\infty} f(m, n, t). \quad (6)$$

The function $\mathcal{P}f$ is essentially described by a function of m . Therefore, we introduce the distribution function $g(m, t)$ defined as

$$\mathcal{P}f = \varphi_0(n) \sum_{n=0}^{\infty} f(m, n, t) = \varphi_0(n) g(m, t). \quad (7)$$

The definition of \mathcal{P} leads to

$$\Gamma_0 \mathcal{P}f = \Gamma_0 \varphi_0(n) \sum_{n=0}^{\infty} f(m, n, t) = 0 \quad (8)$$

and

$$\mathcal{P}\Gamma_0 f = \varphi_0(n) \sum_{n=0}^{\infty} \Gamma_0 f(m, n, t) = 0. \quad (9)$$

Here, Eqs. (4) and (5) are used.

We also define a projection operator $\mathcal{P}' = 1 - \mathcal{P}$ as

$$\mathcal{P}'f(m, n, t) = f(m, n, t) - \mathcal{P}f(m, n, t). \quad (10)$$

It is expected that the evolution of $\mathcal{P}f$ contains only slow changes. Then, the evolution of $\mathcal{P}'f$ describes the fast changes of the reactions.

E. Evolution of projected functions

We start with the well-known operator identity,^{9,10} given by

$$\begin{aligned} \frac{\partial}{\partial t} \mathcal{P}f = & \mathcal{P}\Gamma \mathcal{P}f + \mathcal{P}\Gamma \int_0^t e^{(t-s)\mathcal{P}'\Gamma} \mathcal{P}'\Gamma \mathcal{P}f ds \\ & + \mathcal{P}\Gamma e^{t\mathcal{P}'\Gamma} \mathcal{P}'f_0, \end{aligned} \quad (11)$$

in which f_0 is the initial distribution at $t=0$, i.e., $f_0 = f(m, n, 0)$. Noticing the condition given by Eq. (8), we have an identity for the distribution function $g(m, t)$, given by

$$\begin{aligned} \frac{\partial}{\partial t} g(m,t) = & \sum_{n=0}^{\infty} \Gamma_1 \mathcal{P}f \\ & + \sum_{n=0}^{\infty} \Gamma_1 \int_0^t e^{(t-s)\mathcal{P}'\Gamma} \mathcal{P}'\Gamma_1 \mathcal{P}f(m,n,s) ds \\ & + \sum_{n=0}^{\infty} \Gamma_1 e^{t\mathcal{P}'\Gamma} \mathcal{P}'f_0(m,n). \end{aligned} \quad (12)$$

The first term on the right-hand side in Eq. (12) is

$$\sum_{n=0}^{\infty} \Gamma_1 \mathcal{P}f = \sum_{n=0}^{\infty} \Gamma_1 \varphi_0(n) g(m,t) = \langle \Gamma_1 \rangle g(m,t) \quad (13)$$

in which $\langle \Gamma_1 \rangle$ is defined for $g(m,t)$ as

$$\begin{aligned} \langle \Gamma_1 \rangle g(m,t) = & k \langle n \rangle [g(m-1,t) - g(m,t)] \\ & + \lambda [(m+1)g(m+1,t) - mg(m,t)]. \end{aligned} \quad (14)$$

Here, the angular brackets $\langle \cdot \rangle$ indicate the ensemble average with respect to the stationary distribution $\varphi_0(n)$.

Equation (14) is considered to describe the chemical reaction of synthesizing X without the effect of the fluctuation in the number of Y molecules. Thus, Eq. (14) describes the evolution of the chemical reactions given by



If the fluctuation in the number of Y is not significant, this term, Eq. (14), could be enough to describe the evolution of the number of molecule X.

For the second term on the right-hand side in Eq. (12), substituting Eq. (13) into the second term, the term is rewritten as

$$\sum_{n=0}^{\infty} \Gamma_1 \int_0^t e^{(t-s)\mathcal{P}'\Gamma} (\Gamma_1 - \langle \Gamma_1 \rangle) \varphi_0(n) g(m,s) ds. \quad (16)$$

Since $\mathcal{P}'\Gamma$ determines the rapid evolution, $\mathcal{P}'\Gamma$ determines the evolution of the fast variable n . Notice, however, that $\mathcal{P}'\Gamma$ still contains the rapid evolution of m due to the rapid change of n . To see this, let us rewrite $\mathcal{P}'\Gamma$ as

$$\mathcal{P}'\Gamma = \mathcal{P}'\Gamma_1 + \Gamma_0 = (1 - \mathcal{P})\Gamma_1 + \Gamma_0. \quad (17)$$

Here we use Eq. (9). Whereas the second term on the right-hand side describes the evolution of n , the first term on the right-hand side gives the contribution from the rapid change of m . If the characteristic time scale of n is much faster than m , we expect that the contribution of the first term is much smaller than the second term. Then we can adopt the approximation

$$e^{(t-s)\mathcal{P}'\Gamma} \rightarrow e^{(t-s)\Gamma_0}. \quad (18)$$

Substituting Eqs. (3) and (14) into Eq. (16), the second term on the right-hand side in Eq. (12) is rewritten as

$$\begin{aligned} & \sum_{n=0}^{\infty} \Gamma_1 \int_0^t e^{(t-s)\Gamma_0} k(n - \langle n \rangle) \varphi_0(n) \\ & \quad \times [g(m-1,s) - g(m,s)] ds \\ = & k \int_0^t \left(\sum_{n=0}^{\infty} \Gamma_1 e^{(t-s)\Gamma_0} n \varphi_0(n) - \langle n \rangle \langle \Gamma_1 \rangle \right) \\ & \quad \times [g(m-1,s) - g(m,s)] ds \\ = & k^2 \int_0^t \left(\sum_{n=0}^{\infty} n e^{(t-s)\Gamma_0} n \varphi_0(n) - \langle n \rangle^2 \right) \\ & \quad \times [g(m,s) - 2g(m-1,s) + g(m-2,s)] ds. \end{aligned} \quad (19)$$

Let $\phi(t)$ give the correlation function of n , defined as

$$\phi(t) = \frac{\langle n(t)n(0) \rangle - \langle n \rangle^2}{\langle n^2 \rangle - \langle n \rangle^2}. \quad (20)$$

Then, the correlation function $\phi(t)$ is formally written as

$$\phi(t) = \frac{1}{\langle \delta n^2 \rangle} \left(\sum_{m,n} n e^{\Gamma_0 t} n \varphi_0(n) - \langle n \rangle^2 \right). \quad (21)$$

Substituting Eq. (21) into Eq. (19), the second term on the right-hand side of Eq. (12) is rewritten by

$$k^2 \langle \delta n^2 \rangle \int_0^t \phi(t-s) [g(m,s) - 2g(m-1,s) + g(m-2,s)] ds. \quad (22)$$

Let τ_c be the characteristic time scale of n . τ_c is estimated at

$$\tau_c = \int_0^{\infty} \phi(s) ds. \quad (23)$$

Since the reaction for n is faster than m , the time interval $[0,t]$ is larger than τ_c . In the interval, the correlation function $\phi(t)$ decays to zero, while g does not change so much, i.e.,

$$\left| \frac{\partial g(m,t)}{\partial t} \tau_c \right| \ll 1. \quad (24)$$

In such a situation, we take $g(m,s)$ in Eq. (22) out of the integral. Thus we replace it as

$$g(m,s) \rightarrow g(m,t). \quad (25)$$

Then, the second term on the right-hand side of Eq. (12) is rewritten by

$$k^2 \langle \delta n^2 \rangle \tau_c [g(m,t) - 2g(m-1,t) + g(m-2,t)]. \quad (26)$$

This term is a kind of diffusion term due to the fluctuation in the number of Y molecule. We should notice that not only the dispersion of n , δn^2 but also the time scale τ_c determines the contribution toward the fluctuation of m .

Finally, the third term on the right-hand side of Eq. (12) is

$$\begin{aligned} \sum_{n=0}^{\infty} \Gamma_1 e^{t\Gamma_0} \mathcal{P}' f_0(m, n) &= \sum_{n=0}^{\infty} \Gamma_1 e^{t\Gamma_0} (f_0 - \mathcal{P} f_0) \\ &= \sum_{n=0}^{\infty} \Gamma_1 (f(m, n, t) - e^{t\Gamma_0} \mathcal{P} f_0). \end{aligned} \quad (27)$$

Here we use the approximation given by Eq. (18). Thus, in the interval $t \gg \tau_c$, the third term disappears quickly. Hence, we can neglect this term.

F. Reduced master equation

In this way, we have derived the effective master equation for the probability distribution of the number of X molecules. Under the condition that the time scale of n is much faster than that of m , the evolution of the distribution function $g(m, t)$ is effectively described by the master equation given by

$$\begin{aligned} \frac{\partial}{\partial t} g(m, t) &= k \langle n \rangle [g(m-1, t) - g(m, t)] \\ &\quad + \lambda [(m+1)g(m+1, t) - mg(m, t)] \\ &\quad \times D [g(m, t) - 2g(m-1, t) + g(m-2, t)], \end{aligned} \quad (28)$$

with

$$D = k^2 \langle \delta n^2 \rangle \tau_c. \quad (29)$$

The third term is the contribution from the fluctuation of $n(t)$ toward the stochastic behavior of $m(t)$. The coefficient of this term is given by $k^2 \langle \delta n^2 \rangle \tau_c$. Hence, the time scale τ_c does contribute to the stochasticity of m as well as the dispersion of n .

G. Remarks

Here, we study the effect of the third term on the behavior of X. If the third term could be neglected, this equation describes the simple chemical reactions of synthesis of X with constant rate $k \langle n \rangle$ and degradation of X with the rate λm . This corresponds to the case in which the concentration of Y is so large that its fluctuation can be neglected. In the present case, even if the diffusive kind term is included, the mean value is equivalent to the case without the term. When the number of X at time $t=0$ is $m(0)$, the mean number of X at time t is given by

$$\langle m(t) \rangle = m(0) e^{-\lambda t} - \frac{k}{\lambda} (e^{-\lambda t} - 1). \quad (30)$$

Thus, the diffusive term does not affect the mean number. This number must be equivalent to the mean value calculated from the original master equation, Eq. (2).

Hence, the diffusive kind term affects the behavior of the fluctuation in the number of X rather than the mean number. Here, we study the correlation function of the number of X. The correlation function is calculated at

$$\langle m(\tau) m(0) \rangle - \langle m \rangle^2 = \langle \delta m^2 \rangle e^{-\lambda \tau}, \quad (31)$$

with

$$\langle \delta m^2 \rangle = \frac{k}{\lambda} + \frac{D}{\lambda}. \quad (32)$$

Whereas the characteristic time of the number of X is the same as the case without the diffusion kind term, the variance in the number of X increases as the coefficient of the diffusive kind term augments. The fluctuations of the eliminated chemical species Y is the source of this increase in the stochasticity of the number of X.

III. APPROXIMATION OF THE MASTER EQUATION BY FOKKER-PLANCK EQUATION

If the mean number of X molecules is much larger than unity, the description can be further reduced. This condition enables us to approximate a discrete molecular number by a continuous molecular concentration. Thus, the behavior of the concentration is described by a Fokker-Planck equation and the corresponding Langevin equation. In this section, the Fokker-Planck equation and the Langevin equation corresponding to the master equation, Eq. (28), are shown. For the derivation of a Fokker-Planck equation from a master equation, temporal coarse-graining can be adopted.¹¹ Then, the continuous molecular concentration is interpreted as a short interval average of the discrete molecular number. Recently, Gillespie discussed that the coarse-graining of a chemical master equation with respect to *time* is deeply connected with the Kramers-Moyal expansion.¹¹ Following his discussion, here the Kramers-Moyal expansion is adopted.

Let $P(x, t)$ give the probability distribution function for the concentration of X, x . Here, the concentration x should be interpreted as a short time average of the number of X.^{7,11} By applying the Kramers-Moyal expansion to Eq. (28) and taking the terms up to the second-order derivatives, we have the Fokker-Planck equation

$$\begin{aligned} \frac{\partial P(x, t)}{\partial t} &= - \frac{\partial}{\partial x} \left(k \langle n \rangle - \lambda x - \frac{1}{2} \frac{\partial}{\partial x} [k \langle n \rangle + \lambda x \right. \\ &\quad \left. + 2D] \right) P(x, t). \end{aligned} \quad (33)$$

For this approximation, x must be much larger than unity. The corresponding stochastic kinetic equation of chemical Langevin equation is given by

$$\frac{dx}{dt} = k \langle n \rangle - \lambda x + \sqrt{k \langle n \rangle + \lambda x + 2D} \xi(t) \quad (34)$$

in which $\xi(t)$ is the Gaussian random variable with $\langle \xi(t) \rangle = 0$ and $\langle \xi(t) \xi(t') \rangle = \delta(t - t')$.

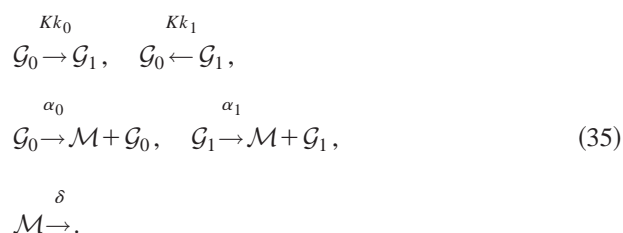
The effect of the diffusive kind term of the master equation, Eq. (28), is clearly seen in Eq. (34). Without taking account the diffusive kind term of Eq. (28) or $D=0$, Eq. (34) is reduced to the well-known chemical Langevin equation. The diffusive kind term contributes to increasing the strength of the additive noise in the Langevin equation.

IV. TRANSCRIPTIONAL REGULATION IN GENE EXPRESSION

In this section, we study the stochastic behavior of transcriptional regulation in gene expression, reformulating the study by Kepler and Elston.⁶ In the process of transcriptional regulation, a particular type of regulatory protein can bind the operator region of a gene to control its activity. The operator region on DNA is located around the promoter region on DNA where RNA polymerase binds to initiate RNA polymerizations (transcription). Binding of the regulatory proteins to the operator region enhances or inhibits the binding of RNA polymerase to the promoter.

The association and dissociation of the regulatory protein are stochastic processes. The number of the state of the gene is two, association state and dissociation state. Thus, the fluctuation of the gene activity measured by the standard deviation is comparable to the mean activity. This strong fluctuation could contribute toward the stochasticity of the gene expression. However, if the association and dissociation process are fast processes, the state fluctuates rapidly. In such a case, the contribution from this noise to the downstream could be effectively averaged out.

Suppose two chemical species, \mathcal{G} and \mathcal{M} , which correspond to the gene and the transcript, respectively. \mathcal{G} takes one of the two states \mathcal{G}_0 and \mathcal{G}_1 , among which stochastic transitions happen. The transition rate from \mathcal{G}_0 to \mathcal{G}_1 and its reverse are given by Kk_0 and Kk_1 , respectively. Note that $k_0 + k_1 = 1$. From each of these states, \mathcal{M} is generated with the rates α_0 and α_1 , respectively. (Here we follow the notation adopted in Ref. 6.) Then the reaction scheme is written as

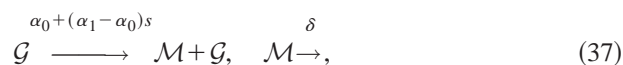


Let p_m^0 and p_m^1 give the probability distribution of having m molecules when the states of the gene are \mathcal{G}_0 and \mathcal{G}_1 , respectively. Then the master equation for the transcriptional regulation process (35) is given by

$$\begin{aligned} \frac{dp_m^s}{dt} = & \alpha_s(p_{m-1}^s - p_m^s) + \delta[(m+1)p_{m+1}^s - mp_m^s] \\ & + K(k_s p_m^{\hat{s}} - k_s p_m^s) \end{aligned} \tag{36}$$

in which $s = \{0, 1\}$ and $\hat{s} = 1 - s$. In Ref. 6, it was supposed that the difference $\xi_m = k_0 p_m^0 - k_1 p_m^1$ reaches a rapid quasi-equilibrium for any value of p_m . Therefore, the authors set the time derivative of ξ_m equal to zero, i.e., $d\xi_m/dt = 0$. Then, they obtained the approximate master equation for the probability $p_m = p_m^0 + p_m^1$, given by Eq. (38) below.

Here, we derive the effective master equation according to the result in Sec. II. Let $\mathcal{G}_{s(t)}$ with $s(t) = \{0, 1\}$ give the state of \mathcal{G} at time t . Then, the reaction rate of synthesizing \mathcal{M} at time t is given by $\alpha_0(1 - s(t)) + \alpha_1 s(t)$. Thus, the reaction scheme is rewritten as



with the stochastic transition between \mathcal{G}_0 and \mathcal{G}_1 . The mean value, the variance, and the characteristic time scale of $s(t)$ are calculated at $\langle s \rangle = k_0$, $\langle \delta s^2 \rangle = k_0 k_1$, and $\tau_c = 1/K$, respectively. Hence, according to the result in Sec. II, we have the master equation that the probability $p_m(t)$ of having m molecule at time t follows is given by

$$\begin{aligned} \frac{dp_m(t)}{dt} = & \alpha_0(p_{m-1} - p_m) + \delta[(m+1)p_{m+1} - mp_m] \\ & + (\alpha_1 - \alpha_0)k_0(p_{m-1} - p_m) + (\alpha_1 - \alpha_0)^2 k_0 k_1 \\ & \times \frac{1}{K}(p_m - 2p_{m-1} - p_{m-2}). \end{aligned} \tag{38}$$

The fourth term is the contribution from the fluctuation in the state of \mathcal{G} toward the stochasticity in the number of \mathcal{M} . This effective master equation is the same as Eq. (21) given in Ref. 6.

V. CONCLUDING REMARKS

In the present paper, we apply the projection operator formalism^{9,10} to a chemical master equation, which describes chemical reactions among two chemical species with fast and slow characteristic time scales, respectively. The chemical species with the slow characteristic time scale is synthesized from the other chemical species with the fast characteristic time scale. Then, the fast chemical species can be eliminated. Notice that the concentration of them can be small. The resulting reduced master equation given by Eq. (28) includes a diffusive kind term. The time scale of the eliminated variable does contribute toward the fluctuations of the downstream chemical species as well as the dispersion of the eliminated variable. The corresponding Fokker-Planck equation and the chemical Langevin equation have also been shown.

The diffusion term is interpreted to mean that the reaction rate of synthesizing the product is fluctuating in time.⁷ Hence, the chemical reaction (1) is effectively rewritten as



with $\alpha = \langle n \rangle$ and $\beta^2 = 2 \langle \delta n^2 \rangle \tau_c$. Here, $\xi(t)$ is the Gaussian random variable with $\langle \xi(t) \rangle = 0$ and $\langle \xi(t) \xi(t') \rangle = \delta(t - t')$.

In the present paper, as an application of the result, we have studied transcriptional regulation process. However, the application is not restricted to that case. A variety of systems could be found for the application. In particular, a variety of the application could be found in biochemical reactions in cells.

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