Fluctuating reaction rates and their application to problems of gene expression

Tatsuo Shibata*

Department of Mathematical and Life Sciences, University of Hiroshima, 1-3-1, Kagamiyama, Higashi-Hiroshima, 739-8526, Japan and Department of Physical Chemistry, Fritz-Haber-Institut der Max-Planck-Gesellschaft, Faradayweg 4-6, 14195 Berlin (Dahlem), Germany

(Received 18 March 2003; published 20 June 2003)

A reduced description is presented for noisy chemical reactions in small systems, such as cells. We show that, even when the number of molecules of a chemical species is small, its elimination from the description is possible provided that its characteristic time scale is short. The resulting effective chemical reaction has a reaction rate which fluctuates in time. The strength of the fluctuations depends on the time scale of the eliminated species as well as its variance. We derive the master equation of the reduced system, which includes additional terms of a diffusive kind, yielding a contribution towards fluctuations from the eliminated species. The stochastic kinetic equation for the reduced system is also derived. Finally, these results are applied to some problems of gene expression.

DOI: 10.1103/PhysRevE.67.061906 PACS number(s): 82.39.Rt, 82.20.Uv

I. INTRODUCTION

A large number of chemical species coexist in a cell, and many chemical reactions are involved even in individual cell events. Their characteristics are quite heterogeneous. The numbers of molecules of each type are subject to strong variation and distributed from just a few to tens of thousands. The characteristic time scales of the changes in the concentration of each species are also strongly heterogeneous and vary from seconds to several hours. When some molecules are present in small amounts, this implies stochastic evolution for such molecules. Stochastic aspects of cell reactions have recently attracted much attention [1–3]. As an example, the reactions of gene expression have been studied [1,4–11]. Here, transcription of a single gene gives rise to a few copies of mRNA which in turn may produce, via the translation process, only tens of specific protein molecules. In such situations, the classical kinetic description becomes deficient and fluctuations due to the discrete stochastic nature of the considered reactions must be taken into account.

The full stochastic description is provided by a master equation that specifies the evolution of the joint probability distribution for discrete numbers of all the reacting molecules. However, for a cellular system involving a great variety of reactions, such a description is not efficient and may be impossible. A coarse-grained description is necessary for such systems. For master equations, coarse-graining with respect to volume size is well known [12]. However, this technique is not applicable to small systems. Thus, coarse-graining with respect to *time* is necessary. Coarse-graining of master equations with respect to time has been studied in detail by Gillespie [13]. He showed that temporal coarse-graining is essential for the derivation of stochastic kinetic equations (chemical Langevin equations) from master equations.

The problem that we want to address in this publication is how to eliminate a fast intermediate reaction even when the molecule number is small. In Sec. II, we develop a reduction technique by studying a set of reactions that is often observed in biological systems. Temporal coarse-graining is essential for the reduction. A fast reaction variable can be eliminated even though the average number of molecules involved is small. The resulting effective chemical reaction has a reaction rate which fluctuates in time. The strength of the fluctuations is proportional to the time scale of the eliminated variable as well as to its dispersion. In Sec. III, we derive a master equation for the reduced system, which includes additional terms of a diffusive kind, yielding a contribution toward fluctuations from the eliminated species. The corresponding stochastic kinetic equation for the reduced system is also derived.

In Sec. IV, these general results are applied to a model genetic system. The model describes the expression of a single gene in the absence of any regulation, but explicitly resolving both the transcription and translation stages. Since the characteristic time scale of the number of molecules of a given type of mRNA is much faster than that of the protein products, it is further eliminated, even though the mRNA molecule number is small. We find the approximate effective master equation of the reduced system and compare its predictions with the exact solutions which are available for this simple model. In Sec. V, brief concluding remarks are offered.

II. ELIMINATION OF A FAST BUT NOISY CHEMICAL VARIABLE AND THE FLUCTUATING REACTION RATE

In this section, we study a set of chemical reactions consisting of two chemical species with different characteristic time scales. The chemical species with the slower time scale is generated from the other one. The number of molecules with the faster characteristic time scale can be small. Thus, the concentration of this component can be noisy. Even in such a case, we show that the fast chemical component can be eliminated. As a result, a ''fluctuating reaction rate,''

*Electronic address: shibata@hiroshima-u.ac.jp

which is a reaction rate fluctuating in time, enters into the description.

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

Many kinds of biological reactions in a cell can be included in this type of reaction. Below, the three examples of gene expression, transcriptional regulation, and enzymatic reaction are considered.

(1) Gene expression can be described by the transcription process $G \rightarrow M+G$, $M \rightarrow$, and the translation process $M \rightarrow P+M$, $P \rightarrow$, in which G stands for a gene, M stands for its mRNA transcript, and P stands for its protein product [6]. The characteristic time scale of mRNA is much faster than that of the protein product. Thus, mRNA corresponds to the fast component Y, and the protein product corresponds to X.

(2) Transcriptional regulation is described by the regulation process $G_i \leftrightarrow R+G_a$, and the transcription process $G_a \rightarrow M+G_a$, $M \rightarrow$, in which G_a and G_i are the active and inactive states of the gene, and R is a repressor protein which inactivates the gene by binding to its operator region. When the characteristic time scale of the transition between two gene states is faster than that of mRNA, the transcription process is included in the present type of reaction. In this case, the active states of the gene and mRNA correspond to Y and X, respectively.

(3) Many enzymatic and signal transduction reactions are described by the Michaelis-Menten scheme $S+E \rightarrow ES \rightarrow E+P$. Suppose that synthesis and the degradation or depletion reactions are present for the substrate S. Thus, the number of molecules of S is time dependent. In such a case, the fluctuations of S can affect the generation of product molecules [14]. If a reaction of the Michaelis-Menten type does not affect the dynamics of the number of substrate molecules, S corresponds to Y.

Here we are interested in a reduced description of the reaction for the end product X. As we shall see, the fast chemical components can be eliminated from the reaction scheme, and then we obtain the reduced description. In order to acquire the reduction method, we consider the chemical reactions between X and Y,

$$Y \overset{k}{\rightarrow} X+Y, \quad X \overset{\lambda}{\rightarrow}, \tag{1}$$

in which k and λ are rate constants. We assume that some synthesis and degradation or depletion reactions for Y are present, which are not specified in this section. Thus, the number of Y molecules is also time dependent. For the synthesis reaction, it is enough to consider the situation in which the variation of the number of Y molecules is not influenced by the synthesis reaction of the molecules of X. Here, for simplicity we choose 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.

Let $X(t)$ and $Y(t)$ be the numbers of X and Y molecules, respectively. The evolution equation of $X(t)$ is given by

$$\dot{X}(t) = \eta(kY(t),t) - \eta(\lambda X(t),t). \tag{2}$$

Here, $\eta(\kappa(t),t)$ is a shot noise representing a random series of pulses. Whenever a reaction event takes place, a pulse appears in the evolution equation. This shot noise process is a nonhomogeneous Poisson process, in which the probability of having a pulse per unit time is $\kappa(t)$. Mathematically, $\eta(\kappa(t),t)$ is a series of δ functions that are distributed with frequency $\kappa(t)$, and the time of occurrence of the δ function is statistically independent. If a reaction occurs at time t_i ($i=1,2,\ldots$), then $\eta(\kappa(t),t)=\Sigma_{i=1}\delta(t-t_i)$. The number of reaction events taking place within an interval $[t,t+\tau]$ is a Poisson random variable. If n stands for this number, the probability distribution of n is given by

$$\text{prob}\left\{ \int_t^{t+\tau} \kappa(t')dt' = n \right\} = \frac{\left[\int_t^{t+\tau} \kappa(t')dt' \right]^n}{n!} \exp\left(- \int_t^{t+\tau} \kappa(t')dt' \right), \tag{3}$$

which depends on the function $\kappa(t)$.

Next, we consider the situation in which the characteristic time scale τ_c of $Y(t)$ is much shorter than the characteristic time scale τ_X of $X(t)$, i.e., $\tau_X \gg \tau_c$. We do not impose any condition on the concentration of Y. Thus, the concentration of Y can be small. Even in this case, it is possible to eliminate the variable $Y(t)$ from Eq. (2).

(a) Eliminating the fast chemical component. One of the ways to eliminate the variable $Y(t)$ is to solve the evolution equation for $Y(t)$ within a short time interval and then use the short interval solution of $Y(t)$ for the evolution of $X(t)$. Within the short time interval, if $Y(t)$ changes frequently and $X(t)$ does not change so much, the detailed behavior of $Y(t)$ cannot much influence the behavior of $X(t)$.

In this case, we choose a time scale τ that satisfies the following conditions (similar to the arguments by Gillespie [13]). The time scale τ is small enough so that $X(t)$ and other time dependent parameters change only slightly. On the other hand, τ must be so large that $Y(t)$ is stationary. Within such a time interval τ, we replace the evolution equation for $Y(t)$ by the stationary-state properties of $Y(t)$, such as the mean value, the variance, and the characteristic time scale of Y. Then we have an evolution equation for $X(t)$ that does not include the detailed behavior of $Y(t)$. The evolution equation obtained describes the temporally coarse-grained behavior of $X(t)$.

We first consider the synthesis reaction of X in reaction (1). The number of reaction events occurring within a time interval $[t,t+\tau]$ is then given by

$$n=\int_t^{t+\tau}\eta(kY(t'),t')dt'. \tag{4}$$

This process is a nonhomogeneous Poisson process, in which the probability that a reaction event takes place depends on time, i.e., the probability that a reaction event takes place per unit time is given by $kY(t)$. Then, in terms of the integral of $Y(t)$, the probability distribution of n for a particular realization of $Y(t)$ is given by

$$\begin{aligned}\text{prob}\left\{\int_t^{t+\tau}\eta(kY(t'),t')dt'=n\,\middle|\,Y(t)\right\}&\\ =\frac{\left[k\int_t^{t+\tau}Y(t')dt'\right]^n}{n!}\exp\left(-k\int_t^{t+\tau}Y(t')dt'\right).&\end{aligned} \tag{5}$$

Let $y(t)$ be the short time average of $Y(t)$,

$$y(t)=\frac{1}{\tau}\int_t^{t+\tau}Y(t')dt', \tag{6}$$

and $\mathcal{P}_{n|y}$ be the probability distribution of n for a given y. Substituting $y(t)$ into Eq. (5), we find that

$$\mathcal{P}_{n|y}=\frac{[ky(t)\tau]^n}{n!}e^{-ky(t)\tau}. \tag{7}$$

Suppose that $\mathcal{Q}_n$ is the probability distribution of the number n of reaction events occurring within the interval $[t,t+\tau]$. The distribution $\mathcal{Q}_n$ is obtained by integrating $\mathcal{P}_{n|y}$ over all possible realization of y. Thus, it is given by

$$\mathcal{Q}_n=\int\mathcal{P}_{n|y}\mathcal{R}(y)dy \tag{8}$$

where $\mathcal{R}(y)$ is the probability distribution of y in the interval $[t,t+\tau]$.

Now we consider an approximation of the probability distribution $\mathcal{R}(y)$. Note that the properties of $\mathcal{R}(y)$ depend on τ. For instance, the variance of the time average y decreases as τ increases. As we discussed above, since τ is much larger than the characteristic time scale of $Y(t)$, τ_c, a large number of reaction events of synthesis and degradation or depletion of Y are occurring within the interval. This implies that the central limit theorem is applicable for the temporal average y, even though the mean concentration $y(t)$ itself can be small. Thus, the time average y is described by the mean value and the fluctuation about it and the probability distribution $\mathcal{R}(y)$ is well described by a Gaussian distribution. Note that τ is still much shorter than the time scale of $X(t)$. Hence, in this interval τ, $X(t)$ is far from a stationary state. Since y is the concentration, y cannot be negative. The condition for this is discussed later.

The variance $\langle\delta y(t)^2\rangle$ of y is given by

$$\langle\delta y(t)^2\rangle=\frac{1}{\tau^2}\int_t^{t+\tau}\int_t^{t+\tau}C(t',t'')dt'dt'', \tag{9}$$

where $C(t',t'')$ is the time correlation function of $Y(t)$, defined as

$$C(t',t'')=\langle[Y(t')-\langle Y(t')\rangle][Y(t'')-\langle Y(t'')\rangle]\rangle. \tag{10}$$

Note that $\langle\delta y(t)^2\rangle$ depends on the time scale of Y. The variance $\langle\delta y(t)^2\rangle$ can be expanded as a series of the powers of $1/\tau$ for large τ, and the leading term is proportional to $1/\tau$. Let $\beta(t)^2$ be the coefficient of the leading term of the variance of $y(t)$, i.e., $\langle\delta y(t)^2\rangle=\beta(t)^2/\tau+\mathcal{O}(1/\tau^2)$. For large τ, the higher-order terms can be neglected. Therefore, using $\alpha(t)=\langle y(t)\rangle$ and $\beta(t)^2$, the probability distribution of $y(t)$ is written as

$$\mathcal{R}(y)=\frac{1}{\sqrt{2\pi\beta(t)^2/\tau}}\exp\left(-\frac{[y-\alpha(t)]^2}{2\beta(t)^2/\tau}\right). \tag{11}$$

Instead of considering Y explicitly, this $\mathcal{R}(y)$ is used for calculating $\mathcal{Q}_n$. We should notice that $\beta(t)^2$ depends on the time scale of $Y(t)$ as well as on the variance of $Y(t)$. As the time scale of Y increases, the fluctuations become stronger.

(b) Reduced evolution equation and the fluctuating reaction rate. The probability that X is generated per unit time is $kY(t)$. If the interval $[t,t+\tau]$ is much shorter than the characteristic time scale of $X(t)$, this probability is well approximated by a short time average of $kY(t)$. Thus, within such an interval, the probability is given by $ky(t)$. Therefore, instead of Eq. (2), the evolution equation for $X(t)$ is given by

$$\dot{X}(t)=\eta(ky(t),t)-\eta(\lambda X(t),t). \tag{12}$$

On the other hand, since the interval $[t,t+\tau]$ is much longer than the characteristic time scale of Y, a large number of reaction events to change Y have occurred in the interval. Therefore, the distribution of the time average y is well approximated by the Gaussian distribution, as we have discussed. Then, using $\mathcal{R}(y)$ given by Eq. (11), $y(t)$ is expressed as

$$y(t)=\alpha(t)+\beta(t)\frac{1}{\sqrt{\tau}}\mathcal{N}, \tag{13}$$

where $\mathcal{N}$ denotes a statistically independent random variable which follows a normal distribution with zero mean and unit variance. This implies that $y(t)$ can be rewritten as

$$y(t)=\alpha(t)+\beta(t)\xi(t), \tag{14}$$

where $\xi(t)$ is the Gaussian random variable with $\langle\xi(t)\rangle=0$ and $\langle\xi(t')\xi(t'')\rangle=\delta(t'-t'')$. Hence, we have the evolution equation for $X(t)$ given by

$$\dot{X}(t)=\eta(k[\alpha(t)+\beta(t)\xi(t)],t)-\eta(\lambda X(t),t), \tag{15}$$

where the evolution of $Y(t)$ does not explicitly appear, and thus $Y(t)$ is eliminated.

This evolution equation implies that the chemical reaction is rewritten as

$$\overset{k[\alpha(t)+\beta(t)\xi(t)]}{\rightarrow} \mathsf{X}, \quad \mathsf{X} \overset{\lambda}{\rightarrow}, \tag{16}$$

where the reaction probability per unit time is given by $ky(t)=k[\alpha(t)+\beta(t)\xi(t)]$. Here, the reaction probability per unit time is not a constant but fluctuates in time. In this way, chemical reactions that involve a fast but noisy chemical concentration can be described by a ''fluctuating reaction rate.''

Since the reaction probability and the averaged concentration y cannot be negative, the time scale should be carefully chosen. For this, the standard deviation of y must be smaller than the average value of y. This condition is always satisfied if τ is sufficiently large. Notice that the standard deviation of y is given by $\sqrt{\beta^2/\tau}$. Thus, if the time scale satisfies

$$\tau \gg \frac{\beta^2}{\alpha^2}, \tag{17}$$

this description is valid.

From the viewpoint of nonequilibrium statistical physics, the noise intensity β^2 is

$$\beta^2 = 2\langle \delta Y^2 \rangle \tau_c, \tag{18}$$

where τ_c is the characteristic time scale of Y,

$$\tau_c = \int_0^\infty \phi(s) ds, \tag{19}$$

and $\phi(t)$ is the time correlation function defined by

$$\phi(t) = \frac{\langle Y(t)Y(0)\rangle - \langle Y^2 \rangle}{\langle \delta Y^2 \rangle}. \tag{20}$$

The time scale τ determined from the number scale δn and the fluctuation strength β should be much larger than τ_c. Then it follows that

$$\tau \approx \frac{(\delta n)^2}{\beta^2} \gg \tau_c. \tag{21}$$

On this time scale, the time correlation of the reaction rate of synthesizing X is approximated by a δ function. This condition, given by Eq. (21), implies

$$\delta n \gg \sqrt{\langle \delta Y^2 \rangle}\, \tau_c. \tag{22}$$

This condition can be used to estimate the accuracy of the description.

III. EVOLUTION EQUATIONS FOR REACTIONS WITH FLUCTUATING REACTION RATES

In the previous section, we introduced a chemical reaction with a fluctuating reaction rate. In this section, we derive the evolution equations for such reactions. We first obtain the master equation for such reactions. Then we derive the stochastic kinetic equation and the Fokker-Planck equation. Thus, in this section we consider the chemical reaction

$$\overset{k[\alpha(t)+\beta(t)\xi(t)]}{\rightarrow} \mathsf{X}, \quad \mathsf{X} \overset{\lambda}{\rightarrow} \tag{23}$$

where the production rate of X fluctuates in time. Here, $\xi(t)$ is the Gaussian white noise with $\langle \xi(t) \rangle = 0$ and $\langle \xi(t')\xi(t'') \rangle = \delta(t'-t'')$. While we derive the fluctuating reaction rate from a particular reaction scheme, the notion of a fluctuating reaction rate is not restricted to this case. For instance, one may imagine the case in which the reaction rate of an enzymatic reaction depends on the internal dynamical state of the enzyme, and the internal state fluctuates in time according to some evolution rule. This has been discussed extensively from a different point of view [15].

A. Master equation

Here, we derive the master equation for the reaction (23). For simplicity, α and β are supposed to be time-independent constants.

First we consider only the synthesis process of X. For this process, let n be the number of chemical reaction events taking place within the interval $[t,t+\tau]$. Let $\mathcal{W}_n(t)$ be the probability distribution of n given by

$$\mathcal{W}_n(t) = \left\langle \frac{\lambda(t)^n}{n!} e^{-\lambda(t)} \right\rangle \tag{24}$$

with

$$\lambda(t) = \int_t^{t+\tau} k[\alpha + \beta\xi(s)] ds. \tag{25}$$

The distribution $\mathcal{W}_n$ can be calculated by considering the generating function $f(s)$ given by

$$f(s) = \sum_{n=0}^{\infty} s^n \mathcal{W}_n \tag{26}$$

$$= \exp\left[(s-1)k\alpha\tau + (s-1)^2 \frac{k^2\beta^2}{2}\tau \right]. \tag{27}$$

Using $f(s)$, the distribution $\mathcal{W}_n$ is obtained as

$$\mathcal{W}_n = \frac{1}{n!} \frac{d^n f(s)}{ds^n}\bigg|_{s=0}. \tag{28}$$

This probability distribution $\mathcal{W}_n$ gives the transition probability that the number of X molecules increases by n in the interval $[t,t+\tau]$. Let X give the number of X and $\mathcal{P}_X(t)$ give the probability distribution of X at time t. Then we have

$$\mathcal{P}_X(t+\tau)=\sum_{i=0}^{\infty}\mathcal{W}_i\mathcal{P}_{X-i}(t). \tag{29}$$

Expanding the right hand side of Eq. (29), it follows that

$$\mathcal{P}_X(t+\tau)=\left[1-\left(k\alpha-\frac{k^2\beta^2}{2}\right)\tau\right]\mathcal{P}_X(t)+(k\alpha-k^2\beta^2)\times\tau\mathcal{P}_{X-1}(t)+\frac{k^2\beta^2}{2}\tau\mathcal{P}_{X-2}(t)+\mathcal{O}(\tau^2). \tag{30}$$

This implies the master equation

$$\frac{d\mathcal{P}_X(t)}{dt}=k\alpha[\mathcal{P}_{X-1}(t)-\mathcal{P}_X(t)]+\frac{k^2\beta^2}{2}[\mathcal{P}_X(t)-2\mathcal{P}_{X-1}(t)+\mathcal{P}_{X-2}(t)], \tag{31}$$

where only the synthesis process is taken into account. Taking the degradation process into account also, we obtain the master equation for considered reaction (23) in the form

$$\frac{d\mathcal{P}_X(t)}{dt}=k\alpha[\mathcal{P}_{X-1}(t)-\mathcal{P}_X(t)]+\frac{k^2\beta^2}{2}[\mathcal{P}_X(t)-2\mathcal{P}_{X-1}(t)+\mathcal{P}_{X-2}(t)]+\lambda[(X+1)\mathcal{P}_{X+1}(t)-X\mathcal{P}_X(t)]. \tag{32}$$

Here the diffusion like term corresponds to the fluctuations of the reaction rate.

We derive this master equation in a formal way. However, as we pointed out in the previous section, this description is not valid on a short time scale. Thus, one should choose the appropriate time scale carefully (see the discussion in the previous section). Actually, the transition probability $\mathcal{W}_n$ might be negative if one ignored the condition. Note that a similar diffusionlike term was obtained in a different way by Kepler and Elston in Ref. [7] in a special case of transcriptional regulation of gene expression.

B. Stochastic kinetic equation and the Fokker-Planck equation

If the number of X molecules is much larger than unity, the description can be further reduced. In this case, it is possible to choose a short interval $[t,t+\tau]$ satisfying the following conditions. The interval τ is short enough that $\alpha(t)$ and $\beta(t)$ are considered as constants inside the interval, and the change in the number of X is so slight that the reaction rate of degradation is replaced by its average value within this interval, i.e., by $\lambda x(t)$ where $x(t)$ is the time average of $X(t)$ in the considered interval. At the same time, τ also satisfies the condition that it is long enough that the number of reactions taking place within the interval is much larger than unity, i.e., $k\alpha(t)\tau\gg 1$ and $\lambda x(t)\gg 1$. (See the discussion in Ref. [13].)

We first consider the synthesis reaction of X. Let $n(t)$ give the number of chemical reactions taking place in the interval $[t,t+\tau]$. The probability distribution of n is given by Eq. (8) with Eqs. (7) and (11). As we mentioned above, the number of reaction events taking place inside the interval is much larger than unity. Thus, $k\alpha(t)\tau\gg 1$. In this case, the probability distribution of n is approximated by a Gaussian distribution. The mean value and the variance of $n(t)$ are calculated from Eq. (8). The mean value $\langle n(t)\rangle$ and the variance $\langle \delta n^2\rangle$ are given by

$$\langle n(t)\rangle=k\alpha(t)\tau \quad \text{and} \quad \langle \delta n(t)^2\rangle=k\alpha(t)\tau+k^2\beta(t)^2\tau. \tag{33}$$

Therefore, the probability distribution function $\mathcal{Q}_n$ is

$$\mathcal{Q}_n=\frac{1}{\sqrt{2\pi[k\alpha(t)\tau+k^2\beta(t)^2\tau]}}\times\exp\left(-\frac{[n-k\alpha(t)\tau]^2}{2[k\alpha(t)\tau+k^2\beta(t)^2\tau]}\right). \tag{34}$$

Here, n is a continuous number written as

$$n(t)=k\alpha(t)\tau+\sqrt{k\alpha(t)+k^2\beta(t)^2}\mathcal{N}/\sqrt{\tau}, \tag{35}$$

where $\mathcal{N}$ is a statistically independent random variable obeying a normal distribution with the mean being zero and the variance being unity.

For the degradation process, we repeat a similar discussion. The number of degradation reaction events occurring inside the interval $[t,t+\tau]$ is given by

$$n=\int_t^{t+\tau}\eta(\lambda X(t'))dt'. \tag{36}$$

As we have discussed, the interval $[t,t+\tau]$ is so short that the change in the number $X(t)$ is slight. This condition is explicitly given by $\lambda\int_t^{t+\tau}X(t')dt'\ll X(t)$, or by $\tau\ll 1/\lambda$. Since the change in $X(t)$ is small, $X(t)$ in Eq. (36) is well approximated by the time average of $X(t)$, given by $x(t)=(1/\tau)\int_t^{t+\tau}X(t')dt'$. Then the number of reactions is

$$n=\int_t^{t+\tau}\eta(\lambda x(t))dt'. \tag{37}$$

The interval $[t,t+\tau]$ also satisfies the condition that it is so long that the number of reaction events occurring within this interval is much larger than unity, i.e., $\lambda x(t)\tau\gg 1$. Then the distribution of n is approximated by a Gaussian distribution. Therefore, n is given by

$$n=\lambda x(t)\tau+\sqrt{\lambda x(t)}\mathcal{N}\sqrt{\tau}, \tag{38}$$

where $\mathcal{N}$ is a statistically independent random variable obeying a normal distribution with the mean being zero and the variance being unity.

Therefore, the number of X molecules at time $t+\tau$ is

$$x(t+\tau)=x(t)+k\alpha(t)\tau-\lambda x\tau+\sqrt{k\alpha(t)+k^2\beta(t)^2+\lambda x}\mathcal{N}\sqrt{\tau}, \tag{39}$$

where $\mathcal{N}$ is a statistically independent random variable obeying a normal distribution with the mean being zero and the variance being unity. This equation then implies the stochastic kinetic equation

$$\frac{dx}{dt} = k\alpha(t) - \lambda x + \sqrt{k\alpha(t) + k^2\beta(t)^2 + \lambda x}\,\xi(t), \quad (40)$$

where $\xi(t)$ is a Gaussian white noise with $\langle \xi(t) \rangle = 0$ and $\langle \xi(t)\xi(t') \rangle = \delta(t-t')$.

Finally, the probability distribution of x obeys the following Fokker-Planck equation:

$$\frac{\partial P(x,t)}{\partial t} = -\frac{\partial}{\partial x}\left(k\alpha(t) - \lambda - \frac{1}{2}\frac{\partial}{\partial x}[k\alpha(t) + k^2\beta(t)^2 + \lambda x] \right) P(x,t). \quad (41)$$

Note that this equation can also be obtained by applying the Kramers-Moyal expansion to the master equation given by Eq. (32).

IV. GENE EXPRESSION

In this section, we study the gene expression processes of a single gene as an application of the method developed in the previous sections. We show that the transcription reactions can be eliminated and introduce a ''fluctuating translation rate.'' Finally, we determine the intensity of the noise of gene expression. The result shows good agreement with microscopic models and experiments.

The number of mRNA molecules of a given type in a cell is typically less than ten copies. Under these conditions, because of the stochastic nature of chemical reactions, the number of protein product molecules is subject to stochastic time evolution. Several recent experiments on the noise of gene expression indicate the existence of strong noise [9,8]. The noise of gene expression has been studied theoretically [1,4,6,7], suggesting that this noise can be much stronger than Poissonian noise. McAdams and Arkin investigated the elementary gene expression process in detail and discussed the biological relevance of stochastic gene expression [1]. Thattai and van Oudenaarden studied the noise in the gene expression system using simple models and showed that the noise in gene expression is linearly proportional to the translation efficiency, that is, to the average number of protein products produced by one mRNA molecule [6]. This result was then experimentally verified by the same group [9].

Several models have been proposed for gene expression [1,6,11]. Even in the simplest case, a lot of processes are taking place, such as binding of RNA polymerase (RNAP) and initiation of transcription, transcription progression of RNAP, binding of ribosome and RNase on mRNA, and transcription progression of ribosomes [1]. We begin with the model proposed by Thattai and van Oudenaarden [6], where the state of gene expression is described by the numbers of mRNA and protein product molecules. Other processes included in gene expression could affect the behavior, but their contributions with respect to the noise of gene expression are minor. Then, a single gene expression is *effectively* written as

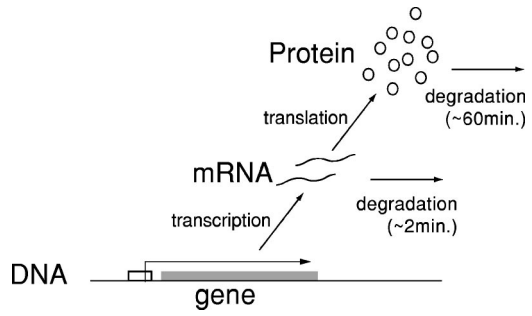

FIG. 1. A single gene expression in a procaryote. The typical time scales of degradation of mRNA and protein products are shown in the figure. The parameters are the transcription rate k_0, the translation rate k, the degradation rate of the protein products, λ, and the degradation rate of mRNA, λ_0.

$$\mathsf{G} \xrightarrow{k_0} \mathsf{M} + \mathsf{G}, \quad \mathsf{M} \xrightarrow{\lambda_0},$$

$$\mathsf{M} \xrightarrow{k} \mathsf{P} + \mathsf{M}, \quad \mathsf{P} \xrightarrow{\lambda}, \quad (42)$$

where G stands for the gene, M stands for its mRNA transcript, and P stands for its protein product (Fig. 1). The parameters are the transcription rate k_0, the translation rate k, the degradation rate λ of the protein products, and the degradation rate λ_0 of mRNA.

In the case of a procaryote, the half-life time of the mRNA transcript, given by $\log 2/\lambda_0$, is typically a few minutes, whereas the half-life time of the protein, given by $\log 2/\lambda$, is about one hour or a few hours. Therefore, for gene expression processes, we can consider a short time interval τ which is much longer than the half-life time of the mRNA transcript but much shorter than the half-life time of the protein product. This means that τ satisfies the conditions $1/\lambda \gg \tau \gg 1/\lambda_0$. Within the time interval τ, many events of synthesis and degradation of the mRNA transcript take place. Thus, the process of transcription is essentially in a stationary state, although the number of mRNA molecules could be a few within a cell, suggesting the existence of strong molecular noise. Thus, for gene expression processes, we expect to apply the method developed in the previous sections, and to eliminate the detailed description of the chemical reaction for mRNA.

According to Sec. II, in order to eliminate the reactions of synthesis and degradation of mRNA, we consider the short time average of the number of mRNA molecules. In particular, we need the average and the variance of the short time average. Let Y be the number of mRNA molecules. The evolution equation for the distribution function $P(Y,t)$ of Y is

$$\frac{\partial P(Y,t)}{\partial t} = k_0[P(Y-1,t) - P(Y,t)] + \lambda_0[(Y+1)P(Y+1,t) - YP(Y,t)]. \quad (43)$$

Let $y(t)$ be the time average of $Y(t)$ during the time interval $[t,t+\tau]$,

$$y(t)=\frac{1}{\tau}\int_t^{t+\tau} Y(t')dt'. \tag{44}$$

By solving Eq. (43), the average of y is calculated as

$$\langle y\rangle=\frac{k_0}{\lambda_0} \tag{45}$$

for sufficiently large t such that $Y(t)$ is in a stationary state. The variance of y is given by

$$\langle \delta y^2\rangle=\frac{1}{\tau^2}\int_t^{t+\tau}\int_t^{t+\tau} C(t',t'')dt'dt'', \tag{46}$$

where $C(t',t'')$ is the time correlation function defined by

$$C(t',t'')=\langle Y(t')Y(t'')\rangle-\langle Y(t')\rangle\langle Y(t'')\rangle. \tag{47}$$

If $t'\geqslant t''\gg 0$, it follows that

$$C(t',t'')=\frac{k_0}{\lambda_0}e^{-\lambda_0(t'-t'')}.$$

Substituting this $C(t',t'')$ into Eq. (46), we have the variance of $y(t)$ for sufficiently large t given by

$$\langle \delta y^2\rangle=\frac{2k_0}{\lambda_0^2}\frac{1}{\tau}+\frac{k_0}{\lambda_0^2}(e^{-\lambda_0\tau}-1)\frac{1}{\tau^2}. \tag{48}$$

According to Sec. II, we calculate α and β defined there. As we have discussed, τ is large enough so that $Y(t)$ is in a stationary state. In the present case, this mean that τ is much larger than the decay time $1/\lambda_0$, i.e., $\tau\gg 1/\lambda_0$. Then we have

$$\alpha=\frac{k_0}{\lambda_0},\quad \text{and}\quad \beta^2=\frac{2k_0}{\lambda_0^2}. \tag{49}$$

Hence, the gene expression is effectively described by

$$\mathrm{G}\overset{k[\alpha+\beta\xi(t)]}{\longrightarrow}\mathrm{P}+\mathrm{G},\quad \mathrm{P}\overset{\lambda}{\longrightarrow} \tag{50}$$

with Eq. (49), where ξ is Gaussian white noise with $\langle\xi(t)\rangle=0$ and $\langle\xi(t)\xi(t')\rangle=\delta(t-t')$. In this way, a "fluctuating translation rate" is introduced for the gene expression process by eliminating the transcription process. Note that the strength of stochasticity in the fluctuating translation rate depends on the characteristic time scale of the change in the number of mRNA transcript molecules.

Let X denote the number of protein product molecules. Using the results of Sec. III, the master equation for reaction (50) is

$$\frac{d\mathcal{P}_X(t)}{dt}=\frac{k_0k}{\lambda_0}[\mathcal{P}_{X-1}(t)-\mathcal{P}_X(t)]+\lambda[(X+1)\mathcal{P}_{X+1}(t)-X\mathcal{P}_X(t)]+\frac{k_0k^2}{\lambda_0^2}[\mathcal{P}_X(t)-2\mathcal{P}_{X-1}(t)+\mathcal{P}_{X-2}(t)]. \tag{51}$$

If the number of protein product molecules is much larger than unity, i.e., $k_0k/\lambda_0\lambda\gg 1$, a stochastic kinetic equation describes the evolution of the number of protein product molecules. Let x be that number. As follows from Sec. III, this stochastic kinetic equation is

$$\dot{x}=k_0b-\lambda x+\sqrt{k_0b(1+2b)+\lambda x}\,\xi(t) \tag{52}$$

where b is the translation efficiency, i.e., the mean number of protein product molecules per a single transcript given by $b=k/\lambda_0$. Here $\xi(t)$ is the Gaussian white random noise with $\langle\xi(t)\rangle=0$ and $\langle\xi(t)\xi(t')\rangle=\delta(t-t')$. Since the number of mRNA molecules fluctuates in time, the noise intensity is larger than that corresponding to a simple Poisson process. The probability distribution function for $x(t)$ obeys the Fokker-Planck equation

$$\frac{\partial P(x,t)}{\partial t}=-\frac{\partial}{\partial x}\left(k_0b-\lambda x-\frac{1}{2}\frac{\partial}{\partial x}[k_0b(1+2b)+\lambda x]\right)P(x,t). \tag{53}$$

Now we solve this equation to study the evolution of the mean and of the variance of the number of protein product molecules. If $x=0$ at time $t=0$, the mean value of $x(t)$ is

$$\langle x(t)\rangle=\frac{k_0}{\lambda}b(1-e^{-\lambda t}) \tag{54}$$

while the variance of $x(t)$ is

$$\langle \delta x(t)^2\rangle=\langle x(t)^2\rangle-\langle x(t)\rangle^2=[1+b(1+e^{-\lambda t})]\langle x(t)\rangle. \tag{55}$$

The same expression can be obtained by directly solving the master equation, under the condition that the degradation rate of the protein is much smaller than that of mRNA [6]. In this case, the Fano factor, defined as the variance divided by the mean value, is given by

$$\nu=1+b(1+e^{-\lambda t}). \tag{56}$$

Hence, the molecular noise is stronger than that corresponding to a Poisson distribution. When t is sufficiently large, $\nu=1+b$. The solution obtained directly from the reaction scheme (42) is $\nu=1+k/(\lambda_0+\lambda)$ [6]. In the present case, $\lambda_0\gg\lambda$. Thus, the reaction scheme with the fluctuating reaction rate gives a good approximation of the original reaction scheme. The strength of the noise $\nu=1+b$ was experimentally confirmed by Ozbudak *et al.* [9].

In biology textbooks, it has been argued that the lifetime of mRNA in procaryotes is chosen in such a way that the

cells respond to environmental change as quickly as possible. But additionally the lifetime of mRNA should be constrained with respect to the strength of the noise of the gene product, i.e., the generated protein. If the lifetime of mRNA gets longer, the noise of the protein product becomes larger.

V. CONCLUDING REMARKS

In this paper, we have studied a reduction method to eliminate a fast intermediate chemical reaction. In order to develop such a method, it is essential to consider coarse-graining with respect to time. This method is particularly applicable to small systems, such as reactions in a cell. After applying this method, we obtained a reduced description in terms of an effective chemical reaction which has a fluctuating reaction rate. We derived the master equations for such reactions. This master equation has additional terms of a diffusive kind. The stochastic kinetic equation and the Fokker-Planck equation were also derived. As an application of our method, we studied a gene expression process. Similar ideas would be applicable for reducing the description of more complicated situations. In our future work, reduced descriptions of autoregulation, transcriptional regulation, and operons might be obtained, for example [16]. This is necessary for studying the stochastic behavior of large genetic networks [10,17].

Our results indicate that, even if the number of molecules is small, it is possible to eliminate a component from the reaction scheme if its characteristic time scale is shorter than that of the other components. Therefore, when modeling cell phenomena, the concentrations of slow chemical components should be used as the variables. For instance, when one studies a system including a genetic network, the protein concentrations should be used as the variables, and the mRNA numbers can be eliminated even if they are small. One should not adopt the concentration of mRNA as a variable instead of the protein concentrations [18].

As we discussed in Sec. II, the strength of the noise that affects the behavior of the downstream reaction is given by $\beta = 2\langle \delta Y^2 \rangle \tau_c$ [see Eq. (18)]. Since the relative variation of Y given by the standard deviation divided by the mean value is normally proportional to the inverse of the mean value, $\sqrt{\langle \delta Y^2 \rangle}/\langle Y \rangle \approx 1/\sqrt{\langle Y \rangle}$, the relative noise strength given by β/α is proportional to $\sqrt{\tau_c/\langle Y \rangle}$. This indicates that the increase of the mean value $\langle Y \rangle$ and the increase of the characteristic velocity of the change, $1/\tau_c$ (the decrease of the characteristic time scale τ_c), contribute *equally* to reducing the effects of noise on the downstream reaction. In a cell, reactions constitute cascades. In such a situation, it is important how the behavior of upstream chemical species affects the behavior of the downstream reactions. The small numbers themselves indicate strong noise in the concentrations. However, the characteristic time scale is essential as well to control the noise.

ACKNOWLEDGMENTS

The author is grateful to A. S. Mikhailov for stimulating discussions and critical reading of this manuscript. The author gratefully acknowledges support from the Alexander von Humboldt Foundation (Germany).

[1] H. H. McAdams and A. Arkin, Proc. Natl. Acad. Sci. U.S.A. **94**, 814 (1997).
[2] N. Barkai and S. Leibler, Nature (London) **403**, 267 (2000).
[3] V. R. Christopher, D. M. Wolf, and P. A. Arkin, Nature (London) **420**, 213 (2000).
[4] O. G. J. Berg, J. Theor. Biol. **71**, 587 (1978).
[5] A. Becskei and L. Serrano, Nature (London) **405**, 590 (2000).
[6] M. Thattai and A. van Oudenaarden, Proc. Natl. Acad. Sci. U.S.A. **98**, 8614 (2001).
[7] T. B. Kepler and T. C. Elston, Biophys. J. **81**, 3116 (2002).
[8] M. B. Elowitz, A. J. Levine, E. D. Siggia, and P. S. Swain, Science (Washington, DC, U.S.) **297**, 1183 (2002).
[9] E. M. Ozbudak, M. Thattai, I. Kurtser, A. D. Grossman, and A. van Oudenaarden, Nat. Genet. **31**, 69 (2002).
[10] E. Aurell and K. Sneppen, Phys. Rev. Lett. **88**, 048101 (2002).
[11] P. S. Swain, M. B. Elowitz, and E. D. Siggia, Proc. Natl. Acad. Sci. U.S.A. **99**, 12795 (2002).
[12] N. G. van Kampen, *Stochastic Processes in Chemistry and Physics* (North-Holland, Amsterdam, 1992).
[13] D. T. Gillespie, J. Chem. Phys. **113**, 297 (2000).
[14] J. Paulsson and M. Ehrenberg, Phys. Rev. Lett. **84**, 5447 (2000); J. Paulsson and M. Ehrenberg, Q. Rev. Biophys. **34**, 1 (2001).
[15] N. Agmon and J. J. Hopfield, J. Chem. Phys. **78**, 6947 (1983); J. Wang and P. Wolynes, Phys. Rev. Lett. **74**, 4317 (1995).
[16] T. Shibata (unpublished).
[17] C. C. Guet, M. B. Elowitz, W. H. Hsing, and S. Leibler, Science (Washington, DC, U.S.) **296**, 1466 (2002).
[18] J. M. Vilar, H. Y. Kueh, N. Barkai, and S. Leibler, Proc. Natl. Acad. Sci. U.S.A. **99**, 5988 (2002).