Roles of factorial noise in inducing bimodal gene expression

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Some gene regulatory systems can exhibit bimodal distributions of mRNA or protein although the deterministic counterparts are monostable. This noise-induced bimodality is an interesting phenomenon and has important biological implications, but it is unclear how different sources of expression noise (each source creates so-called factorial noise that is defined as a component of the total noise) contribute separately to this stochastic bimodality. Here we consider a minimal model of gene regulation, which is monostable in the deterministic case. Although simple, this system contains factorial noise of two main kinds: promoter noise due to switching between gene states and transcriptional (or translational) noise due to synthesis and degradation of mRNA (or protein). To better trace the roles of factorial noise in inducing bimodality, we also analyze two limit models, continuous and adiabatic approximations, apart from the exact model. We show that in the case of slow gene switching, the continuous model where only promoter noise is considered can exhibit bimodality; in the case of fast switching, the adiabatic model where only transcriptional or translational noise is considered can also exhibit bimodality but the exact model cannot; and in other cases, both promoter noise and transcriptional or translational noise can cooperatively induce bimodality. Since slow gene switching and large protein copy numbers are characteristics of eukaryotic cells, whereas fast gene switching and small protein copy numbers are characteristics of prokaryotic cells, we infer that eukaryotic stochastic bimodality is induced mainly by promoter noise, whereas prokaryotic stochastic bimodality is induced primarily by transcriptional or translational noise.

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I. INTRODUCTION

Gene expression is a complex biochemical process, involving gene-state switching (i.e., transitions between promoter activity states), transcription, translation, regulation, etc. [1–4]. Stochastic fluctuations generated in each of these biochemical subprocesses can affect the expression level, leading to variations (or factorial noise) in mRNA or protein abundance. Here, by factorial noise we mean that it is a component of the total noise. The resulting expression noise consisting of factorial noises can carry out some important biological functions. In unicellular organisms, noise improves fitness by inducing phenotypic differences within a clonal population of cells, thus enabling a rapid response to a fluctuating environment [5,6]. In multicellular organisms, noise plays an important role in development, e.g., allowing identical progenitor cells to acquire distinct phenotypes for better survival [7,8]. Because of the functional importance of noise, an important task in the post-genome era is to understand how different mechanisms of noise control variations in mRNA and protein levels across a population of genetically identical cells.

Diverse sources of noise in gene expression may complicate its mechanistic modeling, e.g., for an isolated genetic system inside a cell, possible origins of noise in protein include promoter noise due to stochastic switching between gene states, and transcriptional and translational noise due to the synthesis and degradation of mRNA and protein, respectively. In spite of this complexity, sources of noise can be in general classified as intrinsic or extrinsic [9,10]. Intrinsic noise results from the stochasticity of chemical kinetics, whereas extrinsic noise originates from other reactions or from fluctuations in rate constants, and is often the dominant source of variability in the underlying system [9,11]. The former can be described by the probability master equation (PME), and in essence represents the deviation of known reactions with known rates from their results predicted by classical chemical kinetics [12]. In contrast, the latter may result from any process not represented in the network model itself and therefore may be more complex. Several techniques are available to separate intracellular noise from extracellular noise [9,13], but experimental methods to identify different sources of intracellular noise are far less developed [14] (in fact, the experimental identification is very difficult). Therefore, it would be of particular interest to use stochastic models of gene expression to identify different sources of noise and elucidate their roles in controlling phenotypic switching.

Expression noise in prokaryotic and eukaryotic cells can exhibit different characters, which would lay foundations for efficiently approximating some relevant PMEs [15]. In prokaryotes, transcriptional or translational noise is in general large since the mRNA or protein number is very small [16,17]. An experiment quantifying the mean expression of more than 1000 *Escherichia coli* genes showed that the most frequent average protein number in a prokaryotic cell is of order of 10, while the most frequent average mRNA number is even of the order of 1 [18]. Because of no nucleus existing in prokaryotic cells, gene switching is thought to be very fast, implying that promoter noise is negligible but transcriptional or translational noise is important. Based on this, Hornos *et al.* [19] proposed a so-called adiabatic model in which only transcriptional or translational noise is considered (also see Refs. [20,21]). In contrast, promoter noise in eukaryotic cells is often more important [22] since gene switching between on and off states is in general slow. It is believed that in eukaryotic cells, promoter DNA wrapped around nucleosomes is very

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stable [23] and has a typical lifetime that is longer than the time scale of transcription. Lots of eukaryotic experiments have verified that mRNA is synthesized in bursts [24]. In addition, the mean number of mRNAs or proteins is much larger in eukaryotes than in prokaryotes. All these indicate that transcriptional or translational noise in eukaryotic cells may be neglected, and the corresponding gene models can be approximated by continuous models [25]. Min *et al.* [26] analyzed an enzymatic reaction for which they assumed that the dissociation of substrate is much faster than its catalysis. This assumption implies that the dissociation can be treated as a deterministic process, whereas the catalysis can be treated as a stochastic process. Additionally, cell-cycle transcriptional regulator gene SWI6 in yeast is an example where expression noise originates almost only from gene switching, while transcriptional or translational noise is negligible [27]. We will adopt two approximate models (i.e., continuous and adiabatic models) to trace sources of noise in a two-state model of gene expression with autoregulation and elucidate the roles of promoter noise and translational noise in inducing bimodality.

On the other hand, bimodality of gene expression, as a mechanism contributing to phenotypic diversity, can enhance the probability that cells survive in fluctuating environments. For a genetic system with deterministic bistability, the stochastic trajectories exhibit random jumps between different steady states, thus diverging qualitatively from the deterministic trajectories [28]. Correspondingly, the mRNA or protein distribution exhibits two distinct peaks. It has been shown that to produce deterministic bistability, a genetic system needs a nonlinear positive feedback, a mutual suppressing negative feedback, or a multiple feedback with or without cooperative binding of transcription factors [29–32]. However, the noncooperative binding of transcription factors can also give rise to bimodality in an open-loop system with only one deterministic stable state, e.g., noise can induce a bimodal response in a genetic system where the gene is positively regulated via the noncooperative binding of transcription factors on its promoter [33]. A biological example with this property is the developmental decision pathway of bacterial phage λ [34]. Some experimental studies have confirmed this functional effect of molecular noise [35]. In particular, some theoretical studies have shown that the noncooperation of transcriptional factors can induce bimodality in genetic systems with only one deterministic stable state [36]. In spite of these, it is unclear how sources of noise in gene regulatory networks, which may be complex due to diverse regulation mechanisms, contribute to the appearance of bimodality. We address this issue by analyzing a minimal model of gene regulation.

To clearly elucidate the mechanism of how expression noise induces bimodality and to better trace the effects of factorial noise on bimodality, we first assume that the gene product (in fact, protein) as a transcription factor regulates gene expression in an noncooperative way, i.e., we consider only linear self-feedback, so that the corresponding deterministic system has only one stable state (i.e., the system is monostable) and analytical results can be derived. Then, we assume that the gene has only one active (on) state and one inactive (off) state, although it is highly possible that a gene has many activity states, particularly in eukaryotic cells [37]. Finally, we assume that the gene produces proteins directly [19,20]. This assumption is reasonable since the half-life of mRNA is in general much shorter than that of protein. Thus, there are only two kinds of noises in our model: promoter noise and translational noise. We show that in the case of slow switching, the promoter noise in the continuous model can induce bimodality, whereas in the case of fast switching, the translational noise in the adiabatic model can also induce bimodality but the total noise (consisting of promoter noise and translational noise) in the exact model cannot induce bimodality. In other cases, both factorial noises in the exact model can cooperatively induce bimodality. These results indicate that different factorial noises (i.e., promoter noise and translational noise) play different roles in inducing bimodal expressions. Since transcriptional or translational noise is in general important in prokaryotic cells [16,17], whereas promoter noise is often dominant in eukaryotic cells [38], our results imply an interesting yet important biological fact; that is, eukaryotic stochastic bimodality is induced mainly by promoter noise, whereas prokaryotic bimodality primarily by transcriptional or translational noise.

II. MODEL AND HYPOTHESIS

First, we simply describe our biological model and state relevant hypotheses. Then, we establish a PME for the underlying network of biochemical reactions.

Assume that a gene has two activity states: "on," where transcription from DNA to mRNA is permissive and highly efficient; and "off," where transcription is also permissive but less efficient (this case is called promoter leakage [39]). In principle, the mRNAs transcribed from DNA are further translated into proteins, but for analysis convenience and to derive nice analytical distributions, we integrate transcription and translation into a single-step process. This simplification, which has been extensively made in previous studies [1,19,20,40–42], is reasonable as long as the half-life of protein is much longer than that of mRNA. In fact, Shahrezaei and Swain [20] did a survey of $\sim$2000 genes in budding yeast and showed that most genes indeed satisfy this condition. Additionally, we assume that there are stochastic transitions between on and off states, which results in promoter noise. In spite of these assumptions, the corresponding gene model still captures important events taking place in gene expression and therefore has been extensively used.

Gene expression inevitably involves regulation, e.g., due to the recruitment of transcription factors. In particular, gene self-regulation is a very common element of many gene regulatory networks, e.g., almost 40% of *E.coli* transcription factors regulate the expression of their own genes [43]. In fact, gene autoregulatory circuits are fundamental building blocks of more complex gene regulatory networks [44]. In addition, there is strong experimental evidence to support that for some genetic systems, transcription factors do not affect transcription rates but may increase the probability that protein is at high levels [45]. Here, we assume that a transcription factor regulates the switching rate from off to on states. Our interest is mainly in how factorial noise induces or contributes to stochastic bimodality, so we consider only linear feedback.

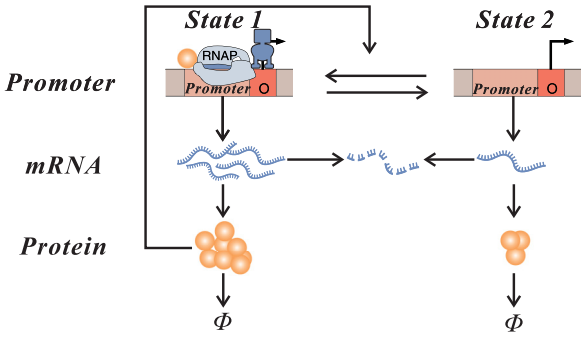

FIG. 1. (Color online) Schematic representation of a two-stage model of gene expression with positive autoregulation, where the promoter is assumed to stochastically switch between state 1 (on) and state 2 (off). It is also assumed that the switching rate from state 2 to state 1 is regulated by the transcription factor (protein). Note that the greater the amount of protein, the faster the switching.

More precisely, we assume that proteins as transcription factors regulate only the transiting rate from off to on states in a noncooperative manner (a similar assumption was also made in Refs. [46,47]), so that the corresponding deterministic system is monostable.

Schematic Fig. 1 integrates all the above considerations including assumptions. In this figure, state 1 represents the on state, whereas state 2 represents the off state. For convenience, let I and A denote these two states, respectively, and X represent protein. Then, our gene model can be described by the following set of biochemical reactions:

$$\begin{aligned} &I \underset{f}{\overset{\lambda}{\rightleftarrows}} A, \quad A \xrightarrow{k_1} A + X, \\ &I \xrightarrow{k_2} I + X, \quad I + X \xrightarrow{h} A + X, \quad X \xrightarrow{\gamma} \phi, \end{aligned} \tag{1}$$

where k_1 and k_2 are the transcription rates of protein at A and I, respectively. Parameter γ is the decay rate, which is practically a compound parameter consisting of both the net protein degradation rate and the cell division rate. Parameter λ is a rate describing the process of protein binding to DNA, whereas parameter f is another rate describing the release of protein from the bound DNA. Parameter h describes the regulatory effect of the transcription factor, and actually represents feedback strength. In general, h may be a function of the copy number of proteins taken as transcription factors [48], but here we assume that it is a constant, implying that our feedback regulation is linear. Note that the larger the protein copy number, the stronger the feedback.

Next, we introduce a PME based on the above reactions to trace the time evolution of the probability of the protein copy number. For this, we let $P_1(n,t)$ and $P_2(n,t)$ represent the probability of having n proteins at time t at A and I states, respectively (each called a factorial probability). Then, the PME for the full reaction network takes the following form:

$$\begin{aligned} \frac{\partial P_1(n,t)}{\partial t} =& -f P_1(n,t) + \lambda P_2(n,t) + k_1[P_1(n-1,t) \\ &- P_1(n,t)] + hn P_2(n,t) \\ &+ \gamma[(n+1)P_1(n+1,t) - n P_1(n,t)], \end{aligned}$$

$$\begin{aligned} \frac{\partial P_2(n,t)}{\partial t} =& f P_1(n,t) - \lambda P_2(n,t) + k_2[P_2(n-1,t) \\ &- P_2(n,t)] - hn P_2(n,t) \\ &+ \gamma[(n+1)P_2(n+1,t) - n P_2(n,t)]. \end{aligned} \tag{2}$$

On the right-hand side of the equation of $P_1(n,t)$, the first two terms describe the transition between active and inactive states [see the reversible reaction in Eq. (1) from top to bottom], the third term describes the synthesis of protein (the second reaction), the fourth term describes regulation (the fourth reaction), and the final term describes the degradation of protein (the final reaction). Similar interpretations are for the equation of $P_2(n,t)$. For convenience, Eq. (2) will be called the exact model throughout this paper. Note that this model contains two different sources of noise (or two different factorial noises): promoter noise due to stochastic switching between gene states and translational noise due to random birth and death of proteins.

We point out that similar models were also introduced and analyzed in previous studies [46,47,49,50]. There are similarities and differences between this study and the previous studies. A similarity is that our model is a special case of the models in Refs. [46,47] and is very similar to the models in Refs. [49,50], and that analytical distributions are derived for all the models. A difference is that we take a different method to derive analytical distributions. A bigger difference is that a main interest of the previous studies is in how analytical distributions are derived, whereas the focus of this paper is on how promoter noise and translational noise contribute separately to the appearance of bimodal expression, a previously unexplored question.

III. ANALYTICAL RESULTS

First, we derive the analytical expression for the steady-state distribution of protein. Then, we introduce three approximations to the PME, which are respectively used to show that the deterministic system is monostable and how the promoter noise and the transcriptional noise can separately induce bimodality.

A. Exact steady-state distribution

In order to solve Eq. (2) at steady state, we introduce two factorial probability-generating functions

$$G_i(z) = \sum_{n=0}^{\infty} P_i(n) z^n, \tag{3}$$

where $i = 1,2$. Thus, Eq. (2) can be transformed into the following coupled ordinary differential equations:

$$\begin{aligned} &\begin{pmatrix} z-1 & -hz \\ hz & z-1 \end{pmatrix} \begin{pmatrix} G_1' \\ G_2' \end{pmatrix} \\ &= \begin{pmatrix} k_1(z-1) - f & \lambda \\ f & k_2(z-1) - \lambda \end{pmatrix} \begin{pmatrix} G_1 \\ G_2 \end{pmatrix}, \end{aligned} \tag{4}$$

where all the parameters have been normalized by the protein decay rate γ, i.e., $\frac{f}{\gamma} \to f, \frac{\lambda}{\gamma} \to \lambda, \frac{h}{\gamma} \to h, \frac{k_1}{\gamma} \to k_1, \frac{k_2}{\gamma} \to k_2$. Without loss of generality, we can set $\gamma = 1$.

To solve Eq. (4), we introduce two transformations of functions $G_1(z)$ and $G_2(z)$, i.e., $G_1(z) = e^{(k_1-k)z}W(\omega)$ and $G_2(z) = e^{(k_2-k)z}\tilde{W}(\omega)$ with $\omega = [(h+1)z-1]\frac{k-hk_2}{(h+1)^2}$ and $k = k_1 - k_2$. Then, it follows from Eq. (4) that function $W(\omega)$ satisfies the following confluent hypergeometric equation of the standard form [51]:

$$\omega W''(\omega) + (\beta - \omega)W'(\omega) - \alpha W(\omega) = 0, \tag{5}$$

where $\alpha = 1 + (k\lambda)/R$, $\beta = 1 + [(k+f+\lambda)/(h+1)] - R/(h+1)^2$ with $R = k - hk_2$, which are all constants depending on reaction rates. This equation is solvable and its solution can be expressed using confluent hypergeometric functions. With the analytical solution combined with the conditions that $P_1(n) \to 0$ for $n \to \infty$ as well as with the fact that the mean number of protein molecules must be finite, we can reach the following analytical expressions for two factorial probability-generating functions $G_1(z)$ and $G_2(z)$:

$$\begin{aligned} G_1(z) &= Ae^{k_2 z}\,{}_1F_1\left(\alpha,\beta;[(h+1)z-1]\frac{k-hk_2}{(h+1)^2}\right), \\ G_2(z) &= Ae^{k_2 z}[C\,{}_1F_1(\alpha-1,\beta-1;hB) - {}_1F_1(\alpha,\beta;hB)], \end{aligned} \tag{6}$$

where $C = \frac{k+f+\lambda}{\lambda} - \frac{R}{\lambda(h+1)}$, $B = \frac{k-hk_2}{(h+1)^2}$, A is a normalization constant given by $A = e^{-k_2}[C\,{}_1F_1(\alpha-1;\beta-1;hB)]^{-1}$, and ${}_1F_1(\alpha,\beta;z)$ is a confluent hypergeometric function defined as ${}_1F_1(\alpha,\beta;z) = \sum_{k=0}^{\infty}\frac{(\alpha)_k}{(\beta)_k}\frac{z^k}{k!}$ with $(a)_n$ being the Pochhammer symbol defined as $(a)_n = \Gamma(a+n)/\Gamma(a)$.

Furthermore, using the relationship between probability distribution and generating function, i.e., $P_i(n) = (1/n!)[\partial^n G_i(z)/\partial z^n]|_{z=0}$, we obtain the following analytical expressions for two steady-state factorial distributions $P_1(n)$ and $P_2(n)$:

$$\begin{aligned} P_1(n) &= \frac{A}{n!}\sum_{m=0}^{n}\binom{n}{m}k_2^{n-m}[(h+1)B]^m \\ &\quad\times\frac{(\alpha)_m}{(\beta)_m}\,{}_1F_1(\alpha+m,\beta+m;-B), \\ P_2(n) &= \frac{A}{n!}\sum_{m=0}^{n}\binom{n}{m}k_2^{n-m}[(h+1)B]^m \\ &\quad\times\left[C\frac{(\alpha-1)_m}{(\beta-1)_m}\,{}_1F_1(\alpha+m-1,\beta+m-1;-B)\right. \\ &\quad\left.-\frac{(\alpha)_m}{(\beta)_m}\,{}_1F_1(\alpha+m,\beta+m;-B)\right], \end{aligned} \tag{7}$$

where $\binom{n}{m}$ is the common binomial coefficient. Thus, we finally obtain the analytical expression for the total probability distribution defined as $P(n) = P_1(n) + P_2(n)$ that corresponds to the total generating function $G(z) = G_1(z) + G_2(z)$,

$$\begin{aligned} P(n) &= \frac{AC}{n!}\sum_{m=0}^{n}\binom{n}{m}k_2^{n-m}[(h+1)B]^m\frac{(\alpha-1)_m}{(\beta-1)_m}\,{}_1F_1 \\ &\quad\times(\alpha+m-1,\beta+m-1;-B). \end{aligned} \tag{8}$$

This result can reproduce distributions of gene products in simplified cases, e.g., without promoter leakage [19,20], without regulation [52,53].

Although complex in form, the above analytical results provide, in principle, the complete information on stochastic properties of the underlying gene regulatory system, including the information on sources of noise. For example, the mean and variance of protein can be easily calculated by $\langle n\rangle = G'(1)$ and $\sigma_n^2 = G''(1) + G'(1) - [G'(1)]^2$, respectively, and in particular, the expression noise intensity defined as the ratio of variance over mean square is given by

$$\eta_n^2 = \{G''(1) + G'(1) - [G'(1)]^2\}/[G'(1)]^2, \tag{9}$$

where

$$\begin{aligned} G'(1) &= Ae^{k_2}[Ck_2\,{}_1F_1(\alpha-1,\beta-1;hB) + k\,{}_1F_1(\alpha,\beta;hB)], \\ G''(1) &= Ae^{k_2}[Ck_2\,{}_1F_1(\alpha-1,\beta-1;hB) \\ &\quad + 2kk_2\,{}_1F_1(\alpha,\beta;hB) + D\,{}_1F_1(\alpha+1,\beta+1;hB)] \end{aligned} \tag{10}$$

with $D = [k(k\lambda+R)(h+1)]/[(h+1)(k+\lambda+f+h+1) - R]$. Similarly, Eq. (9) can reproduce a previous formula for the noise strength in the case that promoter leakage is not considered [39].

In particular, the analytical distribution can be used to explicitly trace the sources of expression noise. For example, if there are neither regulation (i.e., $h = 0$) nor promoter leakage (i.e., $k_2 = 0$), then the intensity of the expression noise can be analytically expressed as

$$\begin{aligned} \eta_n^2 &= \frac{\gamma(\lambda+f)}{\lambda k_1}(\text{translational noise}) \\ &\quad + \frac{\gamma^2 f}{\lambda(\gamma\lambda+\gamma f+\lambda f)}(\text{promoter noise}), \end{aligned} \tag{11}$$

where all the original parameters have been recovered. The first term on the right-hand side of Eq. (11) describes translational noise, whereas the second term describes promoter noise. Equation (11) indicates that the noise in protein is the sum of promoter noise and translational noise. For a more general case, we also have a similar decomposition. The analytical decomposition is omitted because of complex form.

B. Deterministic approximation

To derive the deterministic model, one needs to make some assumptions. If both the switching between gene states and the evolution of the copy number of proteins are extremely rapid, then the gene states are in a rapid preequilibrium and a rescaled protein dynamics follows the mean-field rate equations in terms of a continuous variable x defined as the ratio of the protein copy number over the typical protein number (given by $M = k_1/\gamma$) at the fully induced state. Owing to linear feedback, this rescaled protein level x obeys the following ordinary differential equation:

$$\frac{dx}{dt} = G(x) - \gamma x \quad \text{with} \quad G(x) = \frac{k_1(\lambda+hx)+k_2 f}{\lambda+hx+f}. \tag{12}$$

At steady state, the corresponding algebraic equation has only one positive root given by

$$\tilde{x} = \frac{(k_1 h - \lambda\gamma - f\gamma) + \sqrt{(k_1 h - \lambda\gamma - f\gamma)^2 + 4\gamma h(k_1\lambda + k_2 f)}}{2\gamma h}. \tag{13}$$

This implies that the deterministic system is monostable in the biologically feasible range of system parameters.

In the following, however, we will show that molecular noise can induce bimodality. In particular, to better trace distinct sources of this functional noise, we will introduce two different kinds of approximations to the above PME. Each approximate model is derived based on dominant promoter noise (or switching noise) or based on dominant translational noise.

C. Continuous approximation: In the limit of fast translation

If the fluctuations in the protein copy number are nearly negligible compared to those generated from stochastic switching between promoter states (e.g., in eukaryotic cells), then the full PME given by Eq. (2) can be reduced to a simpler model (called the continuous model). In this simplified model, dynamics of the protein copy number at each gene state follows a deterministic law of mass action but the protein synthesis rate is still fluctuating due to stochastic switching between gene states. Using a similar model, switching noise was analyzed previously [54]. If the characteristic number of proteins is very large, as that in the deterministic case (i.e., $M = k_1/\gamma \gg 1$), then the ratio (or concentration) $x = n/M$ may be considered as a continuous variable, which follows equations

$$\begin{aligned} \frac{dx}{dt} &= k_1/M - \gamma x \quad \text{(State 1)}, \\ \frac{dx}{dt} &= k_2/M - \gamma x \quad \text{(State 2)}. \end{aligned} \tag{14}$$

This will define a time continuous piecewise Markov process. Two factorial discrete probabilities $P_1(n,t)$ and $P_2(n,t)$ are now replaced by two factorial continuous functions $P_1(x,t)$ and $P_2(x,t)$, which satisfy the following differential equations [25,55]:

$$\begin{aligned} &\frac{\partial}{\partial x}[(k_1/M - \gamma x)P_1(x,t)] \\ &\quad = -f P_1(x,t) + \lambda P_2(x,t) + \tilde{h} x P_2(x,t), \\ &\frac{\partial}{\partial x}[(k_2/M - \gamma x)P_2(x,t)] \\ &\quad = f P_1(x,t) - \lambda P_2(x,t) - \tilde{h} x P_2(x,t), \end{aligned} \tag{15}$$

where $\tilde{h} = hM$. Equation (15) will be called the continuous model throughout this paper. By solving Eq. (15), we find that the total steady-state probability given by $P(x) = P_1(x) + P_2(x)$ can be analytically expressed as [56]

$$\begin{aligned} P(x) = C \exp\left(\frac{\tilde{h}x}{\gamma}\right)(1-x)^{(f/\gamma)-1} \\ \times (x - k_2/k_1)^{[(\tilde{h}k_2 + \lambda k_1)/\gamma k_1]-1}, \end{aligned} \tag{16}$$

where C is a constant determined by $\int_0^1 P(x) = 1$.

Note that in this continuous approximation, the only noise existing in the gene network is caused by stochastic switching between gene states. It is interesting that if two gene switching rates satisfy the constraint, both $f/\gamma < 1$ and $\lambda/\gamma < 1$ (i.e., slow switching), then the underlying genetic network can exhibit binary or graded responses to the change of feedback strength (referring to Figs. 3 and 4). On the contrary, if both $f/\gamma > 1$ and $\lambda/\gamma > 1$ (i.e., fast switching) hold, then the system exhibits only a graded response to the change of feedback strength (referring to Figs. 5 and 6). In fact, we can analytically verify that in the case of slow switching, feedback can lead to a transition from bimodality to unimodality, whereas in the case of fast switching, the protein distribution is always unimodal.

D. Adiabatic approximation: In the limit of fast gene switching

Once the protein copy-number fluctuations become significant compared to those from switching between promoter activity states (e.g., in prokaryotic cells), the full PME (2) can be reduced to another simpler model, where all the gene states are simply integrated by fast equilibrium. In this simplified model, the dominant noise is the translational noise, which is generated due to the stochastic birth and death of protein. Moreover, the probability of protein copy number $P(n,t)$ evolves according to the following differential equations:

$$\begin{aligned} \frac{\partial p(n,t)}{\partial t} &= k(n-1)p(n-1,t) - k(n)p(n,t) \\ &\quad + \widetilde{\gamma}(n+1)p(n+1,t) - \widetilde{\gamma}(n)p(n,t), \\ \frac{\partial p(0,t)}{\partial t} &= -k(0)p(0,t) + \widetilde{\gamma}(1)p(1,t), \end{aligned} \tag{17}$$

where $k(n) = [(hn+\lambda)k_1 + fk_2]/(hn + f + \lambda)$ is the fast-equilibrated protein synthesis rate, and $\widetilde{\gamma}(n) = n\gamma$ is the fast-equilibrated protein decay rate. Equation (17) will be called the adiabatic model throughout this paper.

Let $P(n)$ denote the steady-state probability. Then, the net probability flow between two neighboring states n and $n+1$ at steady state is equal to zero, i.e.,

$$P(n)k(n) - P(n+1)\widetilde{\gamma}(n+1) = 0 \tag{18}$$

from which we can obtain the analytical expression of $P(n)$ in the form

$$P(n) = P(0)\prod_{i=0}^{n-1}\frac{k(i)}{\widetilde{\gamma}(i+1)}, \tag{19}$$

where $P(0)$ is determined by the normalization condition $\sum_{n=0}^{\infty} P(n) = 1$. Numerical calculation verifies that with the above adiabatic approximation, the protein probability distribution is always unimodal if the promoter switching rates are less than 1 but may be bimodal if the switching rates are larger than 1 (referring to Figs. 3–5).

IV. NUMERICAL RESULTS

Before presenting the main results of this paper, let us simply introduce our numerical method. First, as is pointed out above, the total noise in protein (or the expression noise) in the exact gene model contains two components (or sources): promoter noise and translational noise. To clearly show how these factorial noises induce and/or affect bimodality in the exact model, we introduce an index, which will be called the noise ratio and is defined as the ratio of the strength (or level) of promoter noise over that of translational noise. That is,

$$\text{Ratio} = \frac{\text{promoter noise level}}{\text{translational noise level}}. \tag{20}$$

Apparently, promoter noise is dominant if Ratio $\gg 1$, whereas translational noise is dominant if Ratio $\ll 1$. Thus, the former corresponds to the continuous approximation, whereas the latter to the adiabatic approximation. Then, for three PMEs corresponding, respectively, to the full PME [Eq. (2)], the continuous model [Eq. (15)], and the adiabatic model [Eq. (17)], we will adopt the Gillespie stochastic simulation algorithm [57] or directly use the analytical distributions above, to perform numerical calculations.

Before presenting the roles of factorial noise in inducing bimodal expression, let us give a reasonable explanation of how bimodality can appear in the exact model but cannot appear in the deterministic model. For this, we work out, based on Ref. [58], a phase diagram describing the appearance of the bimodality by plotting the extrema of the probability density, referring to Fig. 2. From this figure, we observe that the deterministic system is always monostable whenever switching is fast or slow. However, the stochastic system can exhibit two stable states (high and low), one of which is induced by noise or stochasticity. Moreover, the system can switch between these two states due to noise driving (see the following contents). Note that this switching behavior never takes place in the deterministic case [34,35].

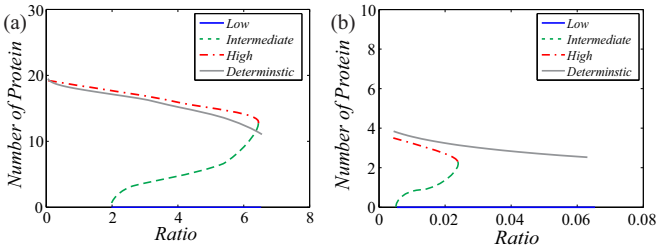

FIG. 2. (Color online) Phase diagrams describing the generation of stochastic bimodality: (a) slow switching, where $f = 0.5$, $\lambda = 0.5$; (b) fast switching, where $f = 20$, $\lambda = 2$. In (a) and (b), the gray curve represents the monostable state given by Eq. (13) in the deterministic case, and blue, dashed green, and dot-dashed red curves each representing the noise-induced stable state in the stochastic case correspond, respectively, to the high state where the protein number is large, the middle state where the protein number is moderate (corresponding to the valley between two peaks of the distribution), and the low state where the protein number is small.

A. The continuous model can exhibit bimodality: The case of slow switching

Here, we use the above continuous model to show how promoter noise or switching noise contributes to bimodality in the case of slow switching. For this, we change the feedback strength while keeping the other parameters fixed. This will change the noise "Ratio" defined by Eq. (20) since this ratio is a function of feedback strength. We compare numerical results obtained using three models: the exact model (2), the continuous model (15), and the adiabatic model (17). The numerical results are shown in Fig. 3, where the first column corresponds to the exact model, the second column to the continuous model, and the third column to the adiabatic model. Note that by slow switching we mean that the relative switching rates f/γ and λ/γ are small. In numerical simulation, they are set as less than 1 but γ is fixed at $\gamma = 1$.

From Fig. 3, we observe that the total noise in the exact model and the factorial noise (i.e., promoter noise) in the continuous model can all induce bimodality for a large noise ratio, referring to the first and the second columns in Fig. 3, but the factorial noise (i.e., translational noise) in the adiabatic model cannot induce bimodality for any noise ratio, referring to the third column in Fig. 3. The leftmost diagram of the first row in Fig. 3 shows a three-dimensional pseudodiagram for probability distribution in the exact model, where the horizontal axis represents the protein number, the vertical axis represents the noise ratio defined by Eq. (20), and different colors represent the change of probability distribution (see color bar on the right). This subfigure along with four subfigures below it (these subfigures correspond, respectively, to four different feedback strengths 0, 0.1, 0.3 to 1 from top to bottom or, respectively, to different noise ratios 5, 3.2, 0.4 to 0.03, also from top to bottom) clearly shows how the total noise can induce bimodality in the case of slow yet symmetric switching. More precisely, for a pair of small relative switching rates (e.g., $f/\gamma = 0.5$ and $\lambda/\gamma = 0.5$), the total protein noise consisting of both promoter noise and translational noise and the promoter noise each can induce bimodality for a large noise ratio (e.g., Ratio $= 5.0$ or 3.2) but only the translational noise cannot solely induce bimodality for any noise ratio. Moreover, the bimodality will disappear with the increase of feedback strength (e.g., from 0.3 to 1) or with the decrease of the noise ratio in this case (e.g., from 0.4 to 0.03).

We also observe, by comparing three diagrams from bottom to top in the first and second columns of Fig. 3, that the total noise can induce bimodality but the promoter noise cannot for the same feedback strength (orange line in Fig. 3). This implies that only when the feedback strength is below a certain threshold, can the promoter noise induce bimodality. Moreover, the threshold of feedback strength for the total noise-induced bimodality is different from that for the promoter noise-induced bimodality. More precisely, the former is larger than the latter, which is in accord with our intuition since the total noise is always higher than the promoter noise. The difference between them can be offset by the feedback strength. In addition, we can show that in the case of symmetric yet slow switching, the smaller the feedback strength, the larger the noise ratio (data are not shown). This point can be partially seen from the setting of parameter values used in Fig. 3.

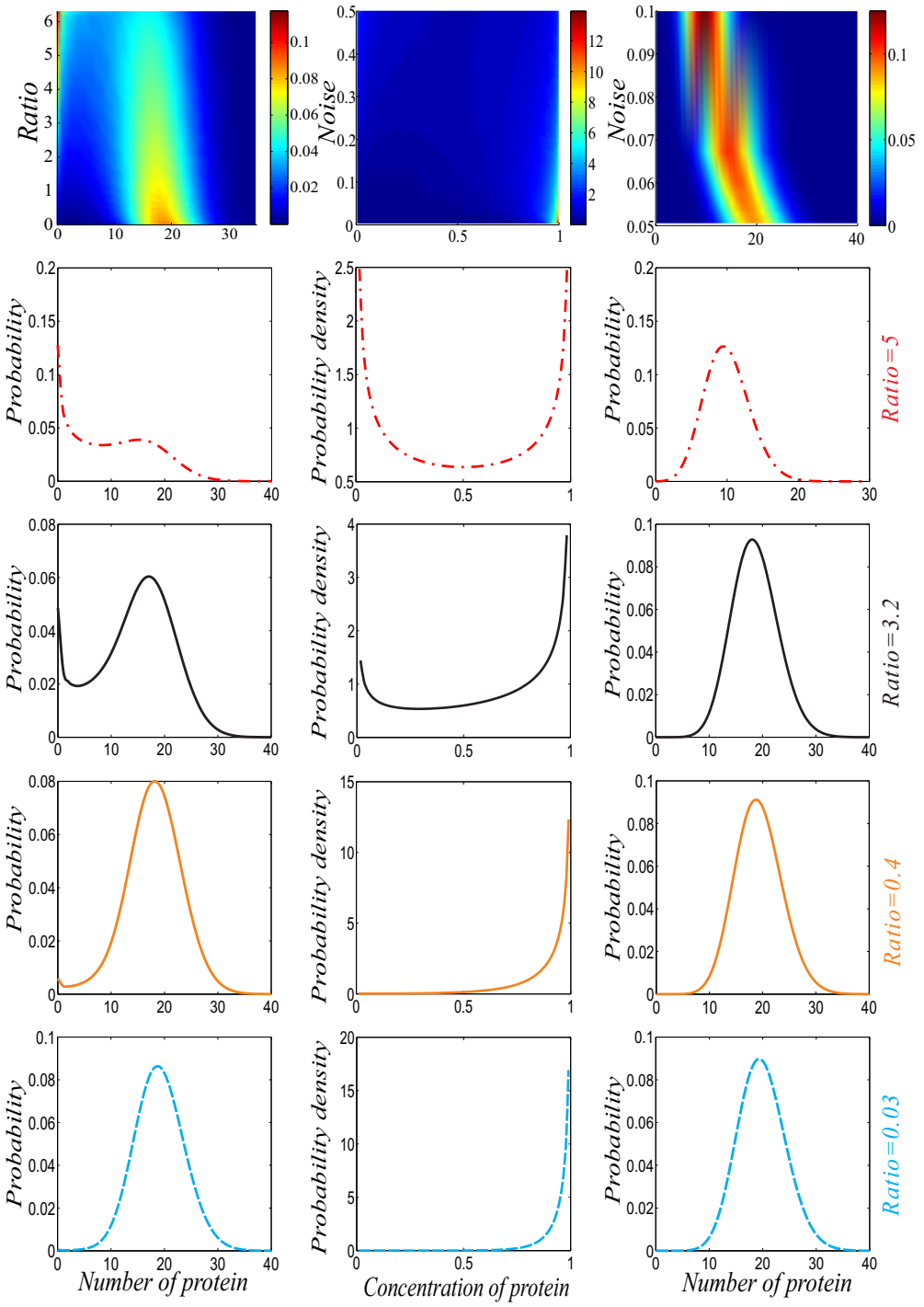

FIG. 3. (Color online) The total noise and the promoter noise can separately induce bimodality in the case of slow and symmetric switching, where the first column corresponds to the exact model, the second column to the continuous model, and the third column to the adiabatic model from left to right. Two switching rates are set as $f = \lambda = 0.5$, the protein's synthesis rates at on and off states as $k_1 = 20$ and $k_2 = 0$, respectively, and the decay rate as $\gamma = 1$. The top subfigures of each column are pseudodiagrams for distribution, probability density, and distribution from left to right. Four subfigures of each column below the first row, which show four particular distributions, correspond, respectively, to feedback strengths 0, 0.1, 0.3, and 1 from top to bottom. Note that the size of "Ratio" is determined uniquely by feedback strength if the other parameters are fixed, so if the feedback strength changes from 0, 0.1, 0.3, and 1, then the "Ratio" changes from 5, 3.2, 0.4 to 0.03.

Note that the results shown in Fig. 3 actually correspond to the case of symmetric switching due to the specific setting of parameter values. Next, we consider the case of asymmetric switching. The numerical results are shown in Fig. 4, where two switching rates are set as $f = 0.9$ and $\lambda = 0.5$, which are not equal, meaning that switching is asymmetric. In addition, we observe from the first column of Fig. 4 that only when the noise ratio is in a certain range or equally only when the

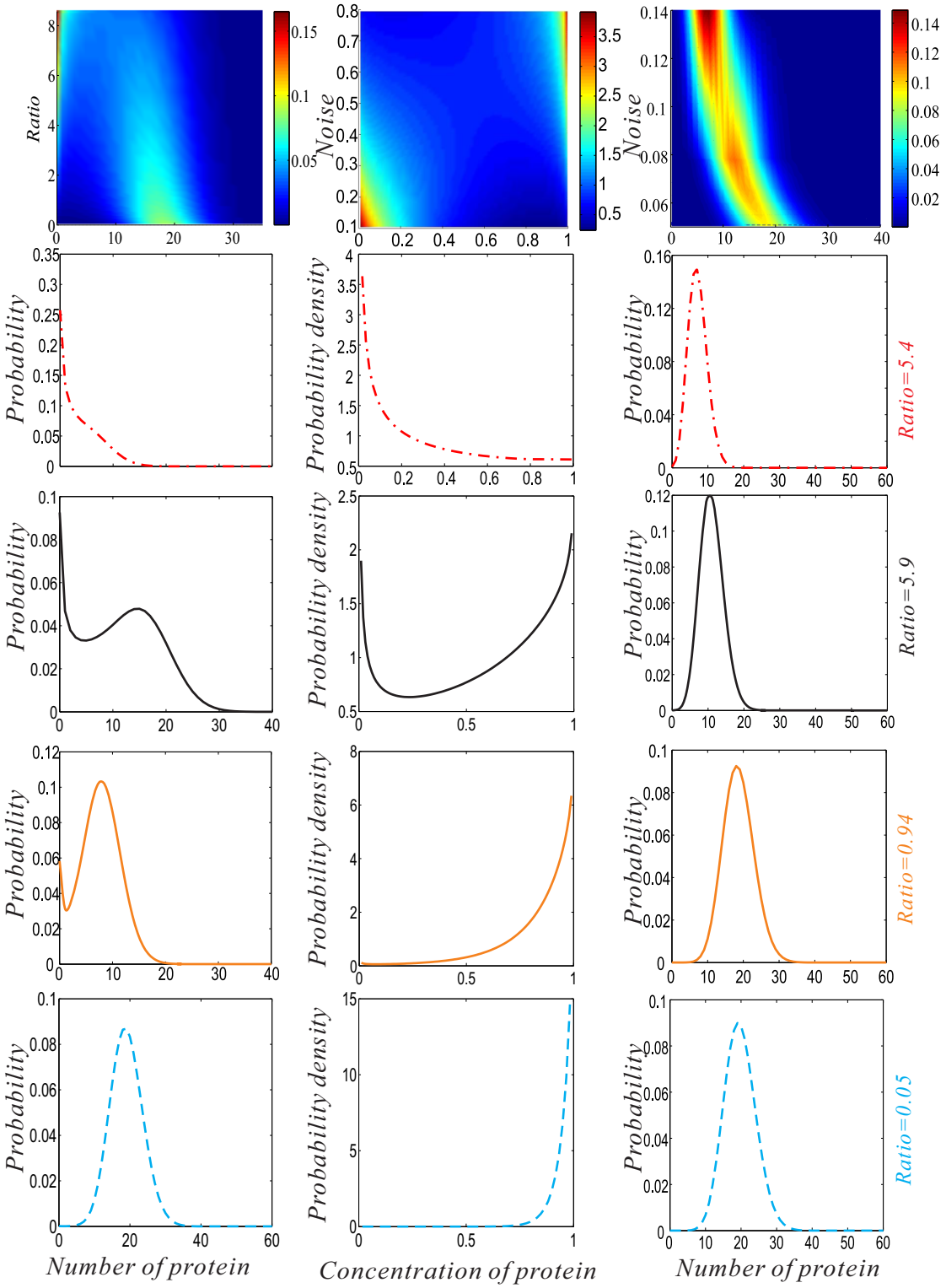

FIG. 4. (Color online) The total noise and the promoter noise both can induce bimodality in the case of slow yet asymmetric switching, where the first column corresponds to the exact model, the second column to the continuous model, and the third column to the adiabatic model from left to right. Two asymmetric switching rates are set as $f = 0.9$ and $\lambda = 0.5$, the protein synthesis rates as $k_1 = 20$ and $k_2 = 0$, and the protein degradation rate as $\gamma = 1$. The top subfigures of each column are pseudodiagrams for distribution, probability density, and distribution from left to right. Four subfigures of each column below the first row, which show four particular distributions, correspond, respectively, to feedback strengths 0, 0.1, 0.3, and 1 from top to bottom. Correspondingly, the noise ratio is 5.4, 5.9, 0.94, and 0.05, respectively.

feedback strength is in a certain range, can the total noise induce bimodality. In other words, to guarantee that the total noise can induce bimodality, feedback strength cannot be too large or too small.

In addition, we observe from the first diagram of the first column (from top to bottom) in Fig. 4 that bimodality exists only in the case that the positive feedback strength is within the interval of 0.1 and 1. If the feedback strength is larger than 1, however, the protein distribution will become unimodal for all the three models (data are not shown). Note that a small noise ratio corresponds to a large feedback strength or vice versa if the other parameters are fixed. With the increase of the feedback strength, the promoter noise becomes quickly decreasing and the translational noise becomes dominant. In this case, the shape of the exact protein probability (see the cyan curve in the first column of Fig. 4) is almost the same as that of the protein distribution in the adiabatic model (see the dashed cyan curve in the third column of Fig. 4). Thus, we conclude that if the translational noise is much larger than the promoter noise, then the appearance of unimodal distribution in the exact model is mainly due to the stochastic birth and death of protein.

Then, let us observe characteristics of the diagrams in the second column of Fig. 4 (corresponding to the continuous model). The first subfigure of this column beginning at the top is a pseudodiagram for probability density function, where the horizontal axis represents the normalized protein concentration, the vertical axis represents the noise intensity, and the color bar shows the change of probability density function. This subfigure clearly shows that the promoter noise can solely induce bimodality but the feedback strength must be in a suitable range (neither too large nor too small). Note that the probability distribution in the exact model is unimodal in the absence of feedback (see the dot-dashed red line in Fig. 4). In this case, we can see from the change of the noise ratio that promoter switching is the main source of expression noise. Moreover, the shape of probability distribution in the exact model is similar to that of probability distribution in the continuous model.

Next, let us turn to analyzing the diagrams in the third column of Fig. 4, which corresponds to the adiabatic approximation (or the adiabatic model). The first subfigure of the third column beginning at the top is a pseudodiagram for probability, where the horizontal axis represents the protein number, the vertical axis represents the noise intensity, and the color bar shows changes in the probability size. This subfigure clearly shows that translational noise cannot induce bimodality for any feedback strength in the case of slow yet asymmetric switching. Note that if the feedback strength is larger than 0.5, then the shape of unimodal probability distribution in the exact model is almost the same as that of probability distribution in the adiabatic model (cyan line in Fig. 4).

For clarity and understanding, here we provide a brief summary for the above analysis. The promoter noise in the continuous model can induce bimodality in the case of slow switching. The threshold of feedback strength corresponding to this functional noise is in general different from than that of the feedback strength for the total noise-induced bimodality. In the case that feedback strength is not very large, the shape of the distribution induced by the total noise in the case of asymmetric switching is similar to that of the distribution induced by the promoter noise in the case of asymmetric switching, and the change trends in the shape of distribution with feedback in the two cases are the same (i.e., from unimodality to bimodality and finally back to unimodality). Moreover, this change tendency is determined mainly by promoter noise that can be regulated by feedback. The shape of distribution in the adiabatic model is almost kept invariant (more prcisely, independent of feedback). In addition, the noise ratio is not a monotonic function of feedback strength in the case of asymmetric switching but first increases and then decreases as the feedback strength increases from 0 to 1.

Finally in this section, we give a simple biological interpretation and simply discuss the biological implications of our results. As is well known, promoter noise is important in eukaryotic cells [38,59–61], where transitions between on and off states are much less frequent. An analysis of gene expression in mammalian cells showed that mRNAs are often produced in bursts during periods of time when the gene is transcriptionally active [52]. The characteristic number of mRNAs or proteins is in general much larger in eukaryotic cells than in prokaryotic cells, so transcriptional or translational noise in eukaryotic cells may be neglected in many cases [25,55], or considered in a diffusion approximation [33,62]. A biological example is the cell-cycle transcriptional regulator gene SWI6 in yeast, where expression noise originates almost only from gene switching but transcriptional noise is negligible [27]. According to these facts, combined with our analysis, we can infer that stochastic bimodality in eukaryotic cells is induced mainly by promoter noise.

B. An adiabatic model can exhibit bimodality: The case of fast switching

Here, we show how translational noise can induce bimodality in the case of fast switching. Similar to the case of slow switching, we change the feedback strength while keeping the other parameter fixed. This will change the noise "Ratio" defined by Eq. (20). We also compare numerical results obtained using three models: the exact model (2), the continuous model (15), and the adiabatic model (17). Note that by fast switching we mean that the relative transition rates f/γ and λ/γ are larger than 1. In prokaryotic cells, gene activation and deactivation are thought to be very fast due to small volume, implying that transcription factors more easily contact and more frequently bind to gene promoters. In most cases, the transition rates between on and off states are not equal (asymmetric). In fact, the rate switching from on to off is much larger than that from off to on [23]. Therefore, we set f/γ and λ/γ all more than 1 but unequal in numerical simulation. In addition, we can set $\gamma = 1$ without loss of generality. We point out that in the case of fast switching, numerical simulation verifies that if the switching rates are equal or if the switching rate from off to on is larger than that from on to off, then the probability distributions in the three models are all unimodal (data are not shown).

We show numerical results by distinguishing two cases: both strong feedback and fast switching; both weak feedback and fast switching. The results for the former are shown in

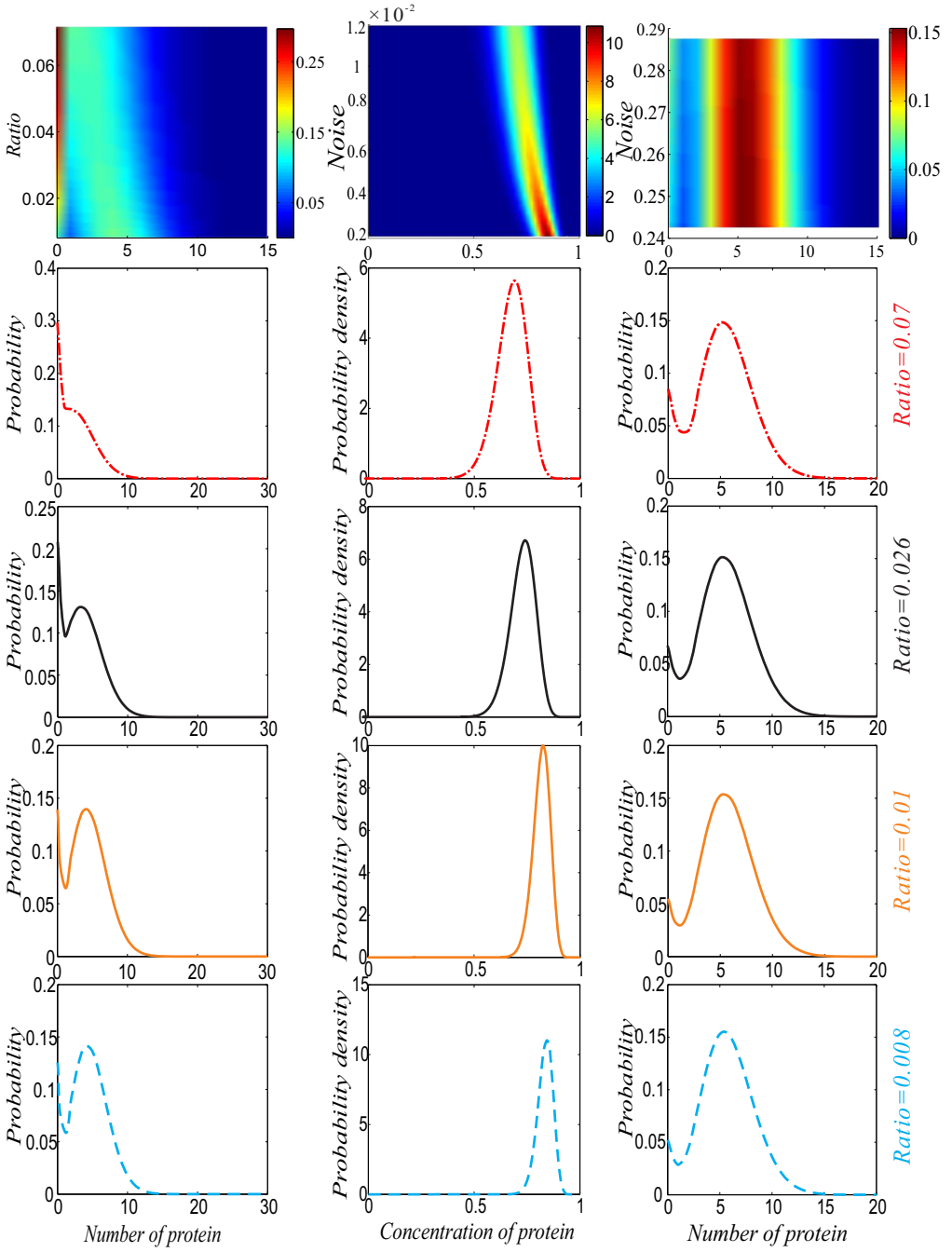

FIG. 5. (Color online) The total noise and the translational noise both can induce bimodality in the case of both strong feedback and fast switching, where the first column corresponds to the exact model, the second column to the continuous model, and the third column to the adiabatic model from left to right. Two asymmetric switching rates are set as $f = 20$ and $\lambda = 2$, the protein synthesis rates as $k_1 = 5$ and $k_2 = 0$, and the protein degradation rate as $\gamma = 1$. The top subfigures of each column are pseudodiagrams for distribution, probability density, and distribution from left to right. Four subfigures of each column below the first row, which show four particular distributions, correspond, respectively, to feedback strengths 8, 12, 18, and 20 from top to bottom. Correspondingly, the promoter noise strength in the second column is 0.029, 0.007, 0.0025, and 0.0019, respectively, and the translational noise strength in the third column is 0.3, 0.27, 0.247, and 0.242, respectively, so the noise ratio is 0.07, 0.026, 0.01, and 0.008, respectively.

Fig. 5, whereas the results for the latter are shown in Fig. 6. In the case of both strong feedback and fast switching, the total noise and the translational noise both can induce bimodality. In the case of both weak feedback and fast switching, however, only the translational noise can induce bimodality (but the total noise cannot).

Specifically, when the promoter switching rates are larger than 1, the probability distribution in the continuous model is always unimodal no matter how the other parameter values are selected (second column in Fig. 5). However, the probability distribution in the adiabatic model is always bimodal in spite of the change of feedback strength (the third column in

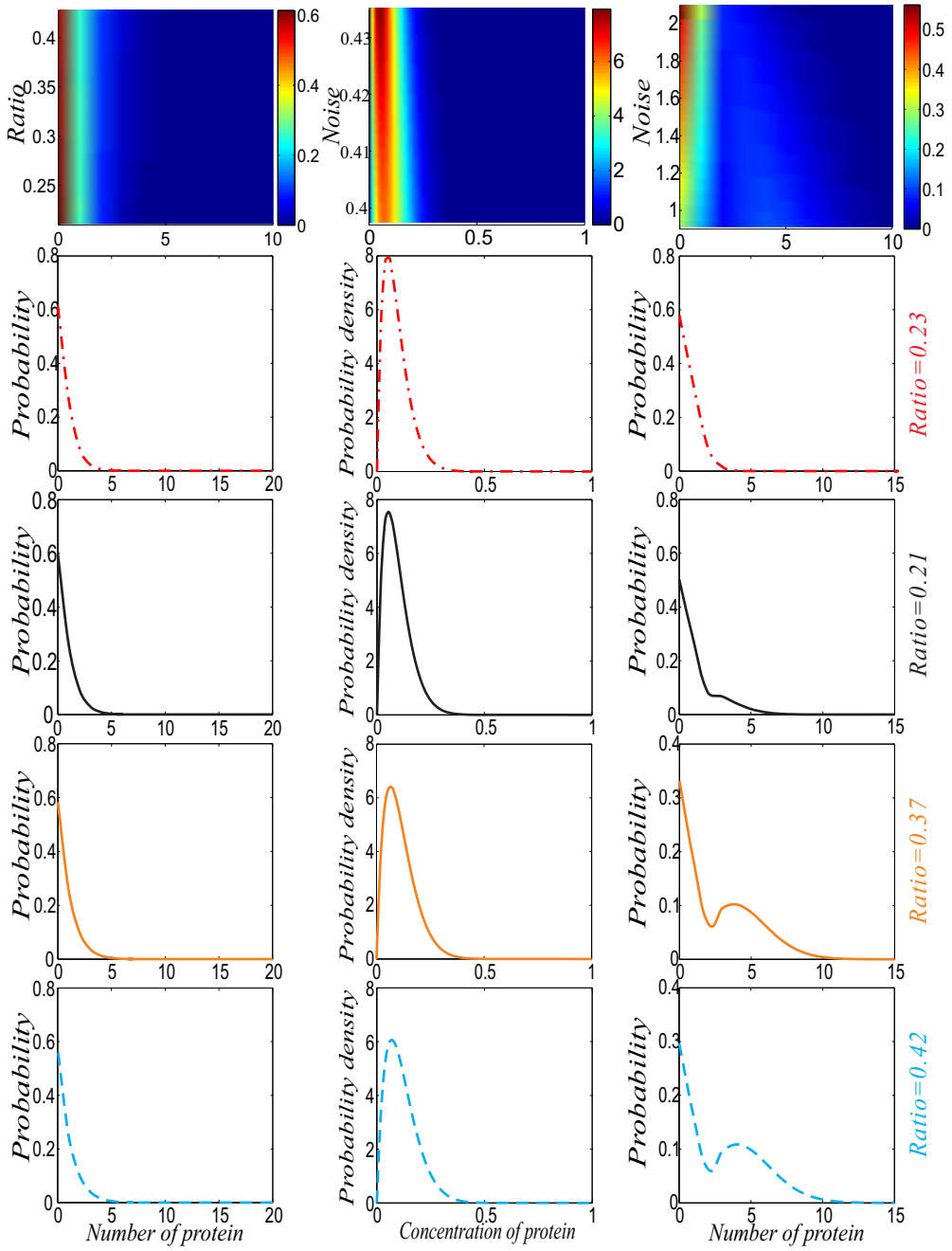

FIG. 6. (Color online) The translational noise can induce bimodality but the total noise cannot in the case of both weak feedback and fast switching, where the first column corresponds to the exact model, the second column to the continuous model, and the third column to the adiabatic model from left to right. Two asymmetric switching rates are set as $f = 20$ and $\lambda = 2$, the protein synthesis rates as $k_1 = 5$ and $k_2 = 0$, and the protein degradation rate as $\gamma = 1$. The top subfigures of each column are pseudodiagrams for distribution, probability density, and distribution from left to right. Four subfigures of each column below the first row, which show four particular distributions, correspond, respectively, to feedback strengths 0, 0.2, 0.8, and 1 from top to bottom. Correspondingly, the promoter noise strength in the second column is 0.435, 0.429, 0.406, and 0.397, respectively, and the translational noise strength in the third column is 1.83, 1.98, 1.08, and 0.94 respectively, so the noise ratio is 0.23, 0.211, 0.37, and 0.42, respectively.

Fig. 5). Similarly, the probability distribution in the exact model is always bimodal as feedback strength increases (the first column in Fig. 5). Moreover, the shape of distribution in the adiabatic model is fundamentally similar to that in the exact model (comparing the first and the third columns in Fig. 5). How noise (including the total noise and the translational noise) induces bimodality can be also seen clearly from three subfigures in the first row of Fig. 5, where the first and third subfigures from left to right are two pseudodiagrams for probability, whereas the second subfigure is a pseudodiagram for probability density function.

As is well known, the noise caused by stochastic gene switching is typically low since promoter switching rates are relatively large in prokaryotic cells. Due to the small number of

mRNAs or proteins, gene expression noise in prokaryotic cells originates mostly from transcription or translation events [18]. Thus, we can infer from Fig. 4 that in prokaryotic cells, the appearance of bimodality in the exact model is determined mainly by the noise from the random birth and death of protein (i.e., translational noise), implying that promoter noise has hardly any contribution to noise-induced bimodality in the case of strong feedback.

Next, we turn to the case of both weak feedback and fast switching. We have seen that in the case of slow gene switching, if two switching rates are equal or if the switching rate from off to on is smaller than that from on to off, then bimodality can appear not only in the exact model but also in the continuous model. Therefore, to present reasons why noise-induced bimodality can appear in a two-stage gene model, we consider only the case that the gene switching rates are asymmetric, i.e., the promoter inactive rate is much larger than the active rate. In this case, we find an interesting fact, that is, the translational noise can induce bimodality but the total noise cannot, referring to Fig. 6. This result implies that only in the case that the noise ratio is small enough, can the role of translational noise in inducing bimodality be apparent. Note that this role of translational noise cannot appear in the case of weak feedback. In fact, for weak feedback, translational noise cannot be small but promoter noise may be very large, leading to the fact that the noise ratio is not small.

Now, we describe some details. From Fig. 6, we observe that in the case of asymmetric and fast switching (two switching rates are set as $f = 20$ and $\lambda = 2$ in simulation), translational noise cannot induce bimodality if the feedback strength is very small (e.g., less than 0.2) but can if the feedback strength is beyond a threshold (larger than 0.2). In all the cases, neither the total noise nor the promoter noise can induce bimodality. Three subfigures in the first row of Fig. 6 show panoramas of how noise influences probability or probability density function in three models with only the feedback strength parameter changing.

In particular, we can give, based on Figs. 5 and 6, conditions under which the noise can induce a bimodal distribution in the exact model. If the two-stage model neglects translational noise, then the protein distribution is always unimodal (see the second column in Fig. 5). If the noise ratio is small enough (e.g., less than 0.07), then the bimodal distribution can appear (see the red dot-dashed curve in the first column of Fig. 5). If the feedback strength is smaller than 0.8, then the protein distribution is always unimodal in the exact model but bimodal in the adiabatic model (the orange line and the dashed cyan line in Fig. 6). On the other hand, bimodality can still be sustained whenever the feedback strength continues to increase (Fig. 6). This is in full accordance with the pattern of probability distribution in the adiabatic model (see black, orange, and dashed cyan lines in the first and third columns of Fig. 5).

In addition, we find in the case of fast switching, only when the production rate of protein is small enough (e.g., less than 10), can the exact and adiabatic models exhibit a bimodal distribution simultaneously. In other words, only when the translational noise is so large that the noise ratio is very small, can the bimodality appear in both models. Moreover, the shape of two distributions is similar in the case of strong feedback. In this case, the effect of promoter noise is negligible and the synthesis and decay of protein is a main source of noise that induces bimodality.

Similar to the case of slow switching, here we also provide a brief summary for the above analysis. If gene switching is fast, then the translational noise can solely induce bimodality but the promoter noise cannot. In the case of translational noise-induced bimodality, the total noise may or may not induce bimodality, depending on either its level or on feedback strength. More specifically, in the case of strong feedback, the translational noise and the total noise can all induce bimodality and the shape of both bimodal distributions is similar, but the promoter noise cannot induce bimodality; in the case of weak feedback, the translation noise can still induce bimodality but neither the total noise nor the promoter noise can. Note that the conclusion obtained in the case of both weak feedback and fast switching is different from that obtained in the case of both strong feedback and fast switching.

Finally in this section, we give a simple biological interpretation and simply discuss the biological implications of our results. As is well known, transcriptional or translational noise is characteristic of prokaryotic cells in which the mRNA or protein number is in general very small [16,17,63]. Recently, Taniguchi *et al.* [18] showed that the most frequent average protein number is of the order of 10, whereas the most frequent average mRNA number is even of the order of 1. The gene switching in prokaryotic cells is thought to be very fast and gene regulation is frequently considered as an adiabatic process [19] where only mRNA transcription or protein translation, or both, is important [10,20,21]. According to these facts combined with our analysis, we can infer that stochastic bimodality in prokaryotic cells is induced mainly by transcriptional or translation noise.

C. Promoter noise and translational noise can cooperatively induce bimodality: A general case of switching

In the previous two sections, we have discussed the effects of noise on the expression spectrum in the two limit cases, fast switching and slow switching, and have shown that promoter noise and translational noise can solely induce bimodality. Here we consider a general case of gene switching, i.e., we consider that the levels of promoter noise and translational noise are of almost the same order of magnitude. The numerical results are shown in Fig. 7, where the first column corresponds to the exact model, the second column to the continuous model, and the third column to the adiabatic model.

From Fig. 7, we observe that the promoter noise and the translational noise cannot induce bimodality separately but the total noise can. The first subfigure from the left of the first row clearly shows how the total noise in the exact model can induce bimodality, where the horizontal axis shows the protein number and the vertical axis shows the ratio of the promoter noise level over the translational noise level, which is only a function of feedback strength under the hypothesis that the other reaction rates are fixed and is therefore determined uniquely by feedback strength. Four diagrams below this subfigure show the images of four particular distributions, which correspond, respectively, to feedback strengths 3, 4, 5, and 9 from top to bottom. We see that noise-induced

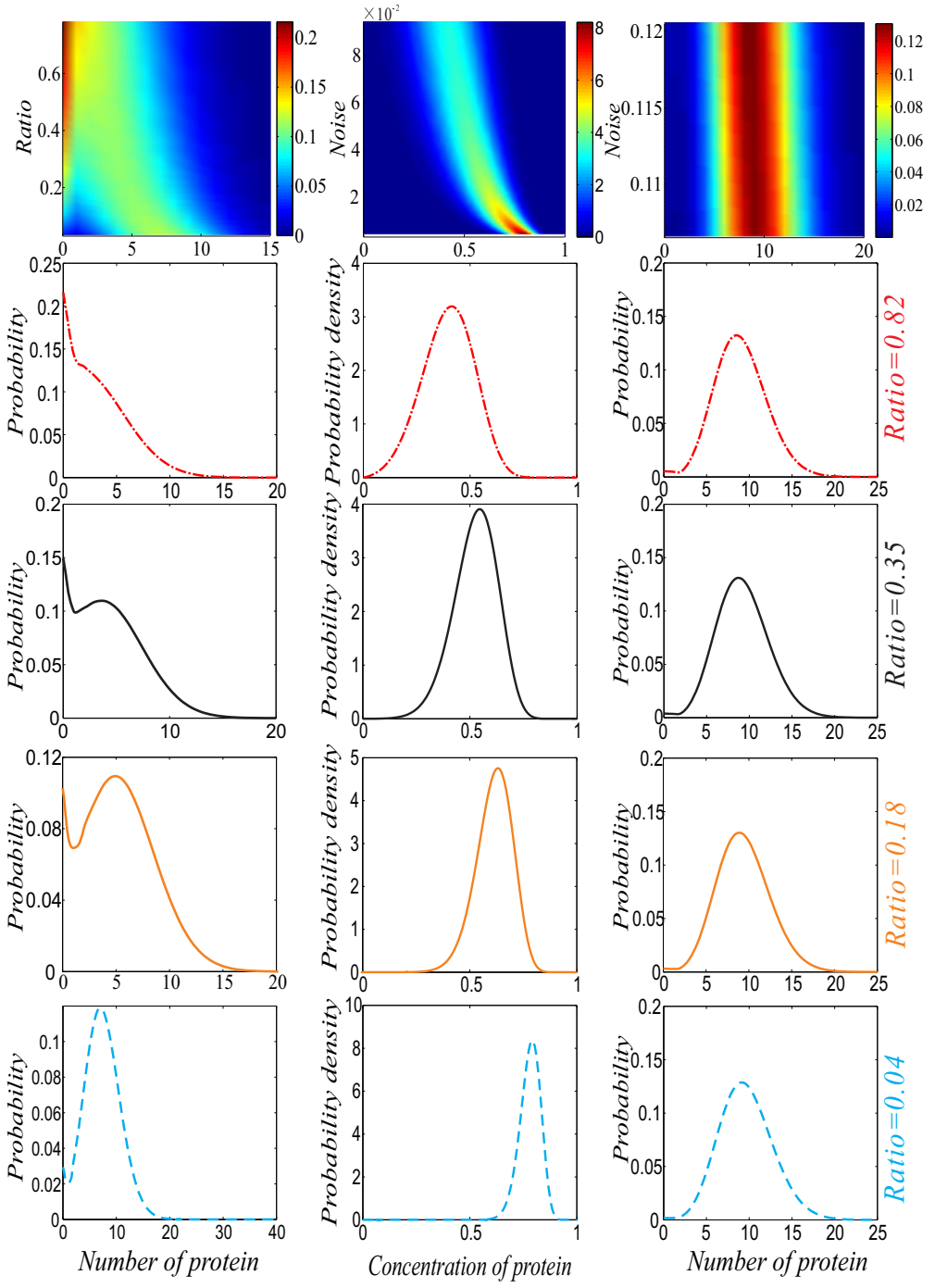

FIG. 7. (Color online) Both promoter noise and translational noise (i.e., the total noise) can cooperatively induce bimodality but the single factorial noise cannot, where the first column corresponds to the exact model, the second column to the continuous model, and the third column to the adiabatic model from left to right. Two switching rates are set as $f = 20$ and $\lambda = 2$, the protein synthesis rates as $k_1 = 10$ and $k_2 = 0$, and the protein degradation rate as $\gamma = 1$. The top subfigures of each column are pseudodiagrams for distribution, probability density, and distribution from left to right. Four subfigures of each column below the first row, which show four particular distributions, correspond, respectively, to feedback strengths 3, 4, 5, and 9 from top to bottom. Correspondingly, the noise ratio is 0.82, 0.35, 0.18, and 0.04, respectively.

bimodality can appear only in the cases of moderate feedback strengths. The latter two subfigures in the first row clearly show that promoter noise and translational noise cannot induce bimodality separately. The combination of all these subfigures indicates that only the cooperation of promoter noise and translational noise can induce bimodality. In addition, we observe that increasing the feedback strength can shift the peak of distribution in the continuous model and takes it away from the origin (see the second column) but cannot impact the shape and the peak location of distribution in the adiabatic model.

It should be pointed out that for a small feedback strength (e.g., less than 1), each of three kinds of noises (total noise, promoter noise, and translational noise) cannot induce

bimodality in the cases that two gene switching rates are moderate (data are not shown).

V. CONCLUSION AND DISCUSSION

That gene expression noise can induce bimodality is a known yet interesting fact [35,36], and this bimodality would be important for cellular survival in fluctuating environments [35]. On the other hand, complexity of gene expression would imply that expression noise is of multicomponents. Tracing different sources of noise and quantifying the effect of factorial noise on the expression spectrum is fundamentally important for understanding intracellular processes. Here, we have analyzed a representative gene model, the two-state model with autoregulation. This mode ignoring transcription, although simple, contains two representative sources of noise: gene switching and translation (i.e., birth and death of protein). We have shown that promoter noise and translational noise can play different roles in inducing bimodality. Specifically, only the promoter noise itself can induce bimodality in the case of slow switching; the translational noise can independently induce bimodality in the case of both fast switching and weak feedback; in the case of both fast switching and low protein synthesis, the appearance of bimodality is determined mainly by the translational noise if feedback is strong (Fig. 5), but if feedback is weak, then the adiabatic model can exhibit a bimodal distribution, whereas the exact model cannot (Fig. 6) (in other words, only for both a small mean protein number and strong feedback, does the translation noise play a decisive role in noise-induced bimodality); both the promoter noise and the translational noise can cooperatively induce bimodality in other cases. Our results indicate that factorial noise would be important and cannot be deliberately neglected.

For a probability master equation describing the stochastic behavior of the two-state gene model with autoregulation, we have proposed two simplified models to trace the effects of factorial noise—continuous and adiabatic models—and derived analytical distributions in these limit models. These approximations, which are effective under suitable hypotheses (see Sec. III), can be easily extended to other more complex cases. In particular, the continuous approximation is in general effective for eukaryotic cells, whereas the adiabatic approximation is generally effective for prokaryotic cells. This is because gene switching is slow and the protein copy number is large in a eukaryotic cell but the former is fast and the latter is small in a prokaryotic cell. Thus, we can infer an interesting fact, that is, eukaryotic stochastic bimodality is induced mainly by promoter noise, whereas prokaryotic stochastic bimodality is primarily induced by transcriptional or translational noise. This inference indicates that mathematical models are a strong tool for understanding complex biological phenomena.

Gene expression is a complex biochemical process. Except that several biochemical subprocesses such as switching between gene states and both synthesis and degradation of protein have been considered here, there would be many other biochemical subprocesses, such as RNA nuclear retention [64–66], alternative splicing [67,68], and more complex transition patterns among promoter states (i.e., a gene has many activity states) [37,69]. Each of these detailed processes may in principle lead to fluctuations in mRNA and protein, thus contributing to the resulting expression noise. Investigating how each factorial noise carries out its biological function as done in this paper would be interesting and is worth being further investigated. For a gene model with many on states or off states, or both, one can also use the continuous approximation proposed here to trace the effect of promoter noise due to stochastic transitions among gene activity states on expression level. In particular, for a gene model with the multi-on mechanism, which may produce multimodality [37], the promoter noise would modify this multimodality, e.g., it would make it become unimodal (data are not shown here), but for a multi-off gene model, we have previously shown that the multi-off mechanism always attenuates expression noise and can modulate the noise to the lowest level [53].

Deterministic bistability can occur in many systems with positive feedback loops [29,31,70]. A feedback loop may be formed by binding of transcription factors to DNA. This binding may be linear (e.g., the case that has been considered here) but also nonlinear [31,70]. In addition, some bistable systems can become monostable when the system parameters (i.e., reaction rates) are changed. In the case of nonlinear feedback, a similar conclusion to that obtained in this paper can be also obtained but new phenomena can take place (results will be published elsewhere).

Finally, it should be pointed out that the investigation in this study primarily gives us insight about the design principles of gene regulatory systems as well as about how the cooperative effect of gene switching and feedback impacts expression noise.

ACKNOWLEDGMENTS

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