# Feedback-induced counterintuitive correlations of gene expression noise with bursting kinetics

Lifang Huang, Zhanjiang Yuan, Peijiang Liu, and Tianshou Zhou*

*Guangdong Province Key Laboratory of Computational Science, School of Mathematics and Computational Science, Sun Yat-Sen University, Guangzhou 510275, Peoples' Republic of China*

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Previous studies showed that a higher frequency of bursting results in lower expression noise whereas a larger size of bursting leads to higher expression noise. Here, we show counterintuitive correlations of expression noise with bursting kinetics due to the effect of feedback. Specifically, in the case of increasing the negative feedback strength but keeping the mean expression fixed, both the mean burst frequency and the mean burst size are invariant if the off-switching rate decreases, but expression noise is reduced; or the mean burst frequency is invariant and the burst size decreases if the transcription rate increases, but expression noise is amplified. Similarly, in the case of increasing the positive feedback strength but keeping the mean expression fixed, both the mean burst frequency and the mean burst size are invariant if the on-switching rate decreases; or the mean burst frequency increases and the mean burst size is invariant if the leakage rate decreases, but expression noise is amplified. In addition, we find that the previous conclusion that a larger burst size results in the lower noise in burst size needs to be modified in the case of feedback. Our results not only clarify the confusing relationship between feedback and expression noise but also imply that the mRNA or protein noise is no longer a simple sum of the internal noise and the promoter noise as shown in the case of no feedback.

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## I. INTRODUCTION

Gene expression involves complex biochemical processes, such as transcription, translation, degradation, transitioning between promoter activity states, and recruitment of transcription factors and polymerases [1–6]. These biochemical processes are essentially single-molecule events and thus stochastic, resulting in fluctuations in mRNA and protein levels. This inherent stochasticity of gene expression is essential for many cell functions. In fact, it has been shown that the molecular noise can have not only a negative effect on, e.g., the functioning of a synthetic genetic oscillator [7], but also a positive effect on, e.g., stochastic focusing in a signaling system [8] and noise-induced cellular communication through stochastic synchronization in a multicell system [9]. In addition, gene expression noise has been identified as a major source underlying the observed phenotypic heterogeneity of genetically identical cells in homogeneous environments [10,11]. An important task in the post–genome era is to understand how different regulatory mechanisms of gene expression control variations in mRNA and protein levels across a population of cells. Quantifying the contributions of different sources of noise using stochastic models of gene expression is an important step towards understanding fundamental intracellular processes as well as cell-to-cell variability critical for cellular survival.

There have been two kinds of gene models: the so-called single-state gene model where mRNAs or proteins are synthesized in stochastic and uncorrelated events [12,13] and the so-called two-state gene model [14–17] where mRNAs or proteins are generated in a manner of high activity followed by a long refractory period [18–20]. In this article, we consider only the latter. For this model, it has been shown that the higher the burst frequency is, the lower is the gene expression noise, whereas the larger the burst size is, the higher is the noise [21–23]. On the other hand, feedback, as a ubiquitous mechanism of controlling signals, has been identified in various regulatory systems in prokaryotic or eukaryotic cells. For example, over 40% of *E. coli* transcription factors negatively regulate their own gene transcription [24]. Theories and experiments have verified that feedback has important influences on gene expression, but there has also existed conflicting evidence over the relationship between expression noise and feedback. Paulsson showed by analyzing a two-component system that positive feedback amplifies noise whereas negative feedback reduces noise [25]. Subsequently, Hornung and Barkai demonstrated that negative feedback in fact amplifies rather than reduces noise when system parameters are chosen to preserve system sensitivity, while positive feedback reduces noise when susceptibility (i.e., steady-state sensitivity) is controlled [26]. In contrast, we [17] found that when system sensitivity is maintained, either there exists a biologically feasible feedback strength such that the output noise intensity reaches the minimum, or the output noise intensity is a monotonic function of feedback strength bounded by biological and dynamical constraints. Several elegant studies showed that in the case that the mean protein level is not fixed, increasing the negative feedback strength can lead to the protein noise decreasing [27], increasing [26,28], or appearing at a U-shaped structure [17,21]. In the case that the mean protein level is fixed, however, increasing the negative feedback strength leads to the protein noise decreasing [16,25,29,30] or increasing [31]. In addition, there are some studies focusing on the relationship between positive feedback and expression noise but different assumption conditions result in different results [26,27]. Giving this conflicting evidence, it is not clear which relationship between feedback and noise is reasonable or just a highlighted exception.

All the above-mentioned feedback-noise relationships are obtained under the condition that promoter kinetics is fast.

*mcszhtsh@mail.sysu.edu.cn

 

However, the rates of transition between the states of promoter occupancy and accessibility (implying slow promoter kinetics) are critical in determining the magnitude of gene expression, and have been implicated as a cause of gene expression variability (see Ref. [32] wherein an extensive review is provided). Indeed, a series of experimental works [33–35] have suggested that variation in the rates of transition between different states of promoter activity may play an important role in determining the level of stochasticity in gene expression in *S. cerevisiae*. A variety of factors including self-regulation are important in mediating rates of transition between active and inactive promoter complexes, many of which are promoter specific [36]. Of these factors, the TATA box-binding protein is the most critical one, as it is highly conserved among eukaryotes and may be required for transcription of almost yeast genes [37–39]. When both self-regulation and slow promoter kinetics are considered simultaneously, several issues naturally arise: Do the previously obtained results on the noise-feedback relationship still hold? What is the exact relationship between noise and feedback? How is the mRNA or protein noise correlated with burst frequency, burst size, or burst size noise? In what manner does the promoter noise arising from stochastic switching between the promoter activity states contribute to expression noise? This paper will address these questions.

Here, we systematically analyze a gene autoregulatory model, where the promoter is assumed to have one active state and one inactive state and there are bidirectional transitions between them with constant transition rates. For simplicity and without loss of generality, we integrate both transcription and translation as a single step [21]. Different from previous studies, our model also considers the effect of promoter leakage (meaning that gene inactivity is not absolutely inactive but there is a small transcription rate compared with the one at the active state) [1,40,41]. First, we derive the analytical distribution for the number of gene products, which in turn can be used to analyze effects of feedback on expression noise as well as on bursting kinetics. Second, we find that there are only four possible kinds of qualitative relationships between feedback and noise, depending on transition rates between promoter activity states as well as on transcriptional rates. Third, in each kind of relationship, burst frequency, burst size, and burst size noise may exhibit different characteristics mainly due to the effect of feedback. Fourth, the mean burst size impacts the burst size noise not in a monotonic manner (i.e., the greater the burst size is, the lower is the burst size noise) but in a multimode manner, depending on the size of feedback strength. Fifth, expression noise is no longer a simple sum of the internal noise and the promoter noise as shown in the case of no feedback. Our results clarify confusing relationships between feedback and noise as well as vague correlations of expression noise with bursting kinetics.

## II. METHOD

We introduce a simple model of gene expression to investigate effects of feedback on expression noise and bursting kinetics, where by expression noise we mean that it is quantified by the ratio of the variance over the square of the mean of a gene product of interest (i.e., mRNA or protein). Assume that the gene promoter has two activity states:

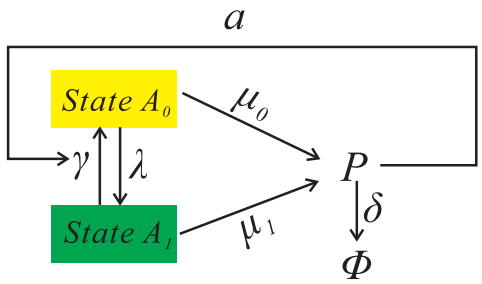


FIG. 1. (Color online) Schematic diagram for a two-state gene model with self-regulation: the promoter transitions between the on state where the transcription efficiency is very high and the off state where the transcription efficiency is very low, and the gene product self-represses or activates the expression level as a regulator.

one active (on) state where transcription is very efficient and one inactive (off) state where transcription is inefficient (more precisely, the transcription efficiency at the off state is much lower than that at the on state), implying that the promoter has a leakage [1,40]). There are bidirectional transitions between on and off states. Also, we assume that the gene product self-represses or activates the gene activity as a regulator, forming a negative or positive feedback loop. Refer to Fig. 1. The reasons for introducing such a gene model are as follows: (1) This genetic circuit is a motif of more complex gene regulatory networks in prokaryotic and eukaryotic cells; (2) the effect of promoter leakage has not been considered in previous studies; (3) analytical results are easily derived to well interpret how the interaction between feedback and promoter leakage impacts expression noise and bursting kinetics; (4) the results can clarify the confusing noise-feedback relationships and the vague correlations of expression noise with burst kinetics.

Let $A_1$ and $A_0$ represent two activity states of the gene promoter and $P$ represent a repressor or an activator. The transcription process is in general much faster than the translation process [15], so we can integrate these two processes into a single-step process. In the following, we always view the gene product as protein. Thus, chemical kinetics of the protein in the gene model schematized in Fig. 1 can be described by the following biochemical reactions:

$$\begin{aligned} &A_0 \xrightarrow{\lambda} A_1, \quad A_1 \xrightarrow{\gamma} A_0, \quad A_1 + P \xrightarrow{a} A_0 + P, \\ &A_1 \xrightarrow{\mu_1} A_1 + P, \quad A_0 \xrightarrow{\mu_0} A_0 + P, \quad P \xrightarrow{\delta} \emptyset, \end{aligned} \tag{1}$$

where $\lambda$ and $\gamma$ are transition rates between the promoter activity states; $a$ represents the regulation strength; $\delta$ is the degradation rate; $\mu_1$ and $\mu_0$ represent transcription rates. Note that in the case of negative feedback, $A_1$ represents the on state whereas $A_0$ represents the off state; in the case of positive feedback, $A_0$ represents the on state whereas $A_1$ represents the off state. Thus, we can analyze the gene autoactivating and autorepressing models in a unified framework. In addition, it is reasonably assumed that $\mu_1 \gg \mu_0$ in the case of negative feedback whereas $\mu_1 \ll \mu_0$ in the case of positive feedback. We point that this gene model is an extended version of not only the common on-off model where the effect of promoter leakage is not considered [14–17] but also the gene self-regulatory model where the effect of promoter leakage is neglected [17,22,26]. In our model, transcriptional regulation is modeled

by a single reaction of the form $A_1 + P \xrightarrow{a} A_0 + P$. Such simplification was also made in a previous study [42].

In order to better trace the time evolution of the probability distribution for reactive species P, we introduce two factorial probability distributions, $P_0(n,t)$ and $P_1(n,t)$, which represent that this species has $n$ molecules at time $t$ when the gene is at the $A_0$ and $A_1$ states, respectively. Then, the chemical master equation corresponding to the reaction network described by Eq. (1) takes the form

$$\begin{aligned}\frac{\partial P_0(n,t)}{\partial t} &= -\lambda P_0(n,t) + \gamma P_1(n,t) + anP_1(n,t)\\ &\quad + \mu_0[P_0(n-1,t) - P_0(n,t)]\\ &\quad + \delta[(n+1)P_0(n+1,t) - nP_0(n,t)],\\ \frac{\partial P_1(n,t)}{\partial t} &= \lambda P_0(n,t) - \gamma P_1(n,t) - anP_1(n,t)\\ &\quad + \mu_1[P_1(n-1,t) - P_1(n,t)]\\ &\quad + \delta[(n+1)P_1(n+1,t) - nP_1(n,t)].\end{aligned} \tag{2}$$

In general, solving a probability master equation like Eq. (2) is not easy. In this paper, we will take the probability-generating function method to solve Eq. (2). In this method, it is needed to introduce two factorial probability-generating functions for factorial probabilities $P_0(n,t)$ and $P_1(n,t)$: $G_i(z) = \sum_{n=0}^{\infty} P_i(n) z^n$ with $i = 0,\ 1$. Thus, Eq. (2) can be transformed into the following partial differential equations:

$$\begin{aligned}\frac{\partial}{\partial t}G_0 &= -\lambda G_0 + \gamma G_1 + az\frac{\partial}{\partial z}G_1\\ &\quad + \mu_0(z-1)G_0 - (z-1)\frac{\partial}{\partial z}G_0,\\ \frac{\partial}{\partial t}G_0 &= \lambda G_0 - \gamma G_1 - az\frac{\partial}{\partial z}G_1\\ &\quad + \mu_1(z-1)G_1 - (z-1)\frac{\partial}{\partial z}G_1.\end{aligned} \tag{3}$$

If the solution of Eq. (3) is analytically found, then the total probability function $P = P_0 + P_1$ is also analytically given. The next section will give the main steps for solving Eq. (3) and the Appendix of this paper will provide more details.

To quantify the noise in the protein P, we introduce an index called the noise intensity, which is defined as the ratio of the variance over the square of the mean. Using the total probability-generating function $G = G_0 + G_1$, we can give the formal formulas for calculating the mean ($\langle n\rangle$) and the variance ($\sigma_n^2$) as well as the noise intensity ($\eta_n^2$) for P. That is,

$$\langle n\rangle = G'(1), \quad \sigma_n^2 = G''(1) + G'(1) - [G'(1)]^2, \tag{4}$$

$$\eta_n^2 = \frac{\sigma_n^2}{\langle n\rangle^2} = \frac{G''(1) + G'(1) - [G'(1)]^2}{[G'(1)]^2}, \tag{5}$$

where the derivatives are with respect to $z$. These formulas are exact if the total generating function $G$ is exactly found. In the next section, we will give the analytical expression of this function.

Note that burst kinetics are quantified often by burst size and burst frequency. Since both the burst size and burst frequency are stochastic variables, we can calculate the statistical quantities in light of the above definitions. By the burst size noise we mean that it is quantified by the ratio of the variance over the square of the mean of the burst size. In addition, the mean burst frequency and the mean burst size are calculated according, respectively, to [19]

$$\langle \mathrm{BF}\rangle = \frac{1}{\tau_{\mathrm{OFF}}}, \quad \langle \mathrm{BS}\rangle = k_{\mathrm{transcription}}\tau_{\mathrm{ON}}, \tag{6}$$

where $\tau_{\mathrm{OFF}}$ and $\tau_{\mathrm{ON}}$ represent the mean times that the gene dwells at off and on states (i.e., the mean off time and the mean on time), respectively, and $k_{\mathrm{transcription}}$ represents the mean transcription rate when the gene is at the on state.

The above equations and explicit formulas provide methodology for analyzing effects of the interaction of feedback and promoter leakage on both expression noise and bursting kinetics.

## III. RESULTS

Stochastic transitions between promoter activity states can result in the bursty generation of mRNA or protein. In general, the bursting kinetics are characterized by the frequency and the size of bursting as well as the burst size noise. Previous studies showed that in the case of no feedback, a larger burst frequency results in the lower expression noise whereas a larger burst size leads to the higher expression noise. Here, we will show that feedback can induce counterintuitive correlations of expression noise with bursting kinetics. Specifically, in the case of negative feedback, increasing the negative feedback strength can lead to (1) the invariance of the mean burst frequency and the reduction of both the mean burst size and the burst size noise, but the increase of the expression noise due to the change of one transcription rate; (2) the invariance of both the mean burst frequency and the mean burst size as well as the reduction of the burst size noise, but the decrease of the expression noise due to the change of one transition rate. See the shadowed part in Table I. Similarly, increasing the positive feedback strength can lead to (1) the increase of the mean burst frequency and the invariance of both the mean burst size and its noise, but the increase of the expression noise due to the change of one transcription rate; (2) the invariance of the mean burst frequency, the mean burst size, and the burst size noise, but the increase of the expression noise due to the change of one transition rate. See the shadowed part in Table III. In addition, we will derive an analytical steady-state distribution for the protein [see Eq. (13) in Sec. III A] and give two modified formulas for the effects of feedback on the burst size noise [see Eq. (19) in Sec. III B] and on the expression noise [see Eq. (20) in Sec. III B], respectively.

### A. Analytical steady-state distribution

To find the analytical distribution for reactive species $P$, we mainly solve Eq. (3) at steady state. Note that this steady-state equation can be rewritten as the following ordinary differential equations (ODEs):

$$\begin{aligned}-\lambda G_0 + \gamma G_1 + azG_1' + \mu_0(z-1)G_0 - (z-1)G_0' = 0,\\ \lambda G_0 - \gamma G_1 - azG_1' + \mu_1(z-1)G_1 - (z-1)G_1' = 0,\end{aligned} \tag{7}$$

where all parameters have been normalized by $\delta$, that is, $\lambda/\delta \to \lambda, \gamma/\delta \to \gamma, a/\delta \to a, \mu_0/\delta \to \mu_0, \mu_1/\delta \to \mu_1$, and

thus they are all dimensionless. With loss of generality, we set $\delta = 1$.

In order to solve Eq. (7), we introduce two new functions $H_0(z)$ and $H_1(z)$, which are associated, respectively, with two factorial probability-generating functions $G_0(z)$ and $G_1(z)$ by

$$G_0(z) = e^{\mu_0 z} H_0(z), \quad G_1(z) = e^{\mu_1 z} H_1(z). \tag{8}$$

It is not difficult to show that $H_1(z)$ satisfies the following second-order ODE (see the Appendix):

$$B(z) H_1''(z) + D(z) H_1'(z) + F(z) H_1(z) = 0, \tag{9}$$

where coefficients $B(z)=(a+1)z-1$, $D(z)=(a\Delta\mu+\Delta\mu+a\mu_1)z+\gamma+\lambda+a+1-\Delta\mu$, and $F(z)=(a\mu_1\Delta\mu)z+\gamma\Delta\mu+a\mu_1$ with $\Delta\mu=\mu_1-\mu_0$ are all linear functions of variable $z$. From the Appendix, we know that Eq. (9) has the solution of the following form:

$$H_1(z) = Ae^{-(\Delta\mu)z}{}_1F_1\left\{\alpha;\beta;[(a+1)z-1]\frac{\Delta\mu-a\mu_0}{(a+1)^2}\right\}, \tag{10}$$

where two parameters, $\alpha = 1+(\lambda\Delta\mu/R)$ and $\beta = 1+[(\Delta\mu+\gamma+\lambda)/(a+1)]-R/(a+1)^2$, with $R=\Delta\mu-a\mu_0$, are all constants depending only on the reaction rates, and ${}_1F_1(\alpha;\beta;w)$ is a confluent hypergeometric function [43]. Using Eq. (9) and the relationship between probability distribution and generating function, we thus obtain analytical expressions for two steady-state factorial probability distributions as

$$\begin{aligned} P_0(n) = {} & \frac{A}{n!}\sum_{m=0}^{n}\binom{n}{m}(\mu_0)^{n-m}[(a+1)Q]^m \\ & \times\left[C\frac{(\alpha-1)_m}{(\beta-1)_m}{}_1F_1(\alpha+m-1;\beta+m-1;-Q)\right. \\ & \left.-\frac{(\alpha)_m}{(\beta)_m}{}_1F_1(\alpha+m;\beta+m;-Q)\right], \end{aligned} \tag{11}$$

and

$$\begin{aligned} P_1(n) = {} & \frac{A}{n!}\sum_{m=0}^{n}\binom{n}{m}(\mu_0)^{n-m}[(a+1)Q]^m\frac{(\alpha)_m}{(\beta)_m}{}_1F_1 \\ & \times(\alpha+m;\beta+m;-Q), \end{aligned} \tag{12}$$

where three constants, $A=e^{-\mu_0}[C_1F_1(\alpha-1;\beta-1;aQ)]^{-1}$, $C=\frac{\Delta\mu+\gamma+\lambda}{\lambda}-\frac{R}{\lambda(a+1)}$, and $Q=\frac{\Delta\mu-a\mu_0}{(a+1)^2}$, all depend only on the reaction rates. Thus, the total steady-state probability distribution is analytically expressed as

$$\begin{aligned} P(n) = {} & \frac{AC}{n!}\sum_{m=0}^{n}\binom{n}{m}(\mu_0)^{n-m}[(a+1)Q]^m\frac{(\alpha-1)_m}{(\beta-1)_m}{}_1F_1 \\ & \times(\alpha+m-1;\beta+m-1;-Q). \end{aligned} \tag{13}$$

In Eqs. (11)–(13), $\binom{n}{m}$ represents the common binomial coefficient and $(c)_n$ is the Pochhammer symbol defined as $(c)_n=\Gamma(c+n)/\Gamma(c)$.

The above analytical results indicate that each of three distributions, $P_0(n)$, $P_1(n)$, and $P(n)$, is a linear combination of confluent hypergeometric functions. In particular, if $a=0$ (i.e., no feedback) and $\mu_0=0$ (i.e., no promoter leakage), which corresponds to the common two-state gene model, then the resulting Eq. (13) can reproduce previous distributions [20,44]. In fact, our numerical simulation has verified correctness of the above analytical distribution, referring to Fig. 3(e).

### B. Feedback-induced additional contributions to both expression noise and burst kinetics: Two modified formulas

First, we give an analytical, exact formula for the relationship between expression noise and feedback. Note that the square of the noise intensity for protein $P$ can be calculated according to formula (5), where

$$G'(1) = Ae^{\mu_0}[C\mu_{01}F_1(\alpha-1;\beta-1;aQ)+\mu_1F_1(\alpha;\beta;aQ)], \tag{14}$$

$$\begin{aligned} G''(1) = {} & Ae^{\mu_0}[C(\mu_0)^2{}_1F_1(\alpha-1;\beta-1;aQ) \\ & +2\mu_0\Delta\mu_1F_1(\alpha;\beta;aQ) \\ & +D_1F_1(\alpha+1;\beta+1;aQ)], \end{aligned} \tag{15}$$

with $D=[\Delta\mu(\Delta\mu\lambda+R)(a+1)]/[(a+1)(\Delta\mu+\lambda+\gamma+a+1)-R]$. One main advantage of this analytical expression is that it can help us show how feedback both quantitatively and qualitatively affects expression noise in the presence of promoter leakage. The detailed discussions are here omitted due to tedious mathematics but some numerical results based on the analytical formula will be later demonstrated. It should be pointed out that previous studies gave only approximate results for the relationship between expression noise and feedback [45,46]. In particular, if neither feedback nor promoter leakage is considered, i.e., $a=0$ and $\mu_0=0$, then the analytical formula for calculating the protein noise intensity is reduced to

$$\eta_n^2 = \frac{1}{\langle n\rangle}+\eta_{\text{promoter}}^2 \quad \text{with} \quad \eta_{\text{promoter}}^2 = \frac{\tau_{\text{OFF}}^2}{\tau_{\text{ON}}+\tau_{\text{OFF}}+\tau_{\text{ON}}\tau_{\text{OFF}}}, \tag{16}$$

where $\langle n\rangle = b/(\tau_{\text{OFF}}+\tau_{\text{ON}})$ with $\tau_{\text{OFF}}=1/\lambda$ (the mean time that the gene dwells at off state), $\tau_{\text{ON}}=1/\gamma$ (the mean time that the gene dwells at on state), and $b=k_{\text{transcription}}/\gamma=\mu_1/\gamma$ (the mean burst size). In Eq. (16), $\eta_{\text{promoter}}^2$ represents the size of relative fluctuations in the promoter (i.e., the promoter noise), $\eta_n^2$ represents the expression noise intensity, and $\langle n\rangle$ represents the mean expression level.

Then, we give approximate formulas for bursting kinetics and expression noise in the case of no feedback. Note that $\tau_{\text{OFF}}=1/k_{\text{ON}}$ and $\tau_{\text{ON}}=1/k_{\text{OFF}}$, where $k_{\text{ON}}$ and $k_{\text{OFF}}$ are transition rates from off to on states and from on to off states, respectively. For our model without feedback (i.e., $a=0$), if $\mu_1\gg\mu_0$, then we have the approximations $\langle\text{BF}\rangle=\lambda$ and $\langle\text{BS}\rangle=\mu_1/\gamma$ due to $k_{\text{ON}}=\lambda$, $k_{\text{OFF}}=\gamma$, and $k_{\text{transcription}}=\mu_1$. In addition, the burst size noise intensity is calculated according to the following approximate formula [47]:

$$\sigma_{\text{BS}}^2 \approx 1+\frac{1}{\langle\text{BS}\rangle} = 1+\frac{\gamma}{\mu_1}, \tag{17}$$

which implies that a larger mean burst size results in the lower burst size noise. At the same time, the protein noise intensity is calculated according to the following approximate formula [22]:

$$\eta_n^2 \approx \frac{1+\langle \mathrm{BS}\rangle}{\langle n\rangle} = \frac{1}{\langle n\rangle} + \frac{1}{\langle \mathrm{BF}\rangle} \quad \text{with} \quad \langle n\rangle \approx \langle \mathrm{BF}\rangle \langle \mathrm{BS}\rangle . \tag{18}$$

From Eq. (18), we see that a higher mean burst frequency results in the lower noise and a higher mean burst size leads to the higher noise if the mean expression level is fixed.

Third, we discuss how to calculate expression noise in the case of feedback. Note that in this case, $k_{\mathrm{ON}}$ or $k_{\mathrm{OFF}}$ (implying $\tau_{\mathrm{OFF}}$ or $\tau_{\mathrm{ON}}$) is no longer a constant but is a variable, depending on the type of feedback. Specifically, in the case of negative feedback, $k_{\mathrm{OFF}}$ (implying $\tau_{\mathrm{ON}}$) depends on the number of proteins but $k_{\mathrm{ON}}$ (implying $\tau_{\mathrm{OFF}}$) is still a constant. Thus, Eq. (16) no longer holds, and $\tau_{\mathrm{ON}}$ has no analytical expression but can be given by the Gillespie stochastic simulation algorithm [48]. Similarly in the case of positive feedback, $k_{\mathrm{ON}}$ (implying $\tau_{\mathrm{OFF}}$) depends on the number of proteins but $k_{\mathrm{OFF}}$ (implying $\tau_{\mathrm{ON}}$) is still a constant. In this case, Eq. (16) no longer holds, and $\tau_{\mathrm{OFF}}$ has no analytical expression but can be given only by the numerical method.

We emphasize that the above formulas (16)–(18) are efficient only in the case of no feedback. A natural question is whether they still hold in the case of feedback. The answer is negative. In fact, numerical results shown in Fig. 2 indicate that feedback can induce additional contributions to the protein noise and the burst size noise. Therefore, formulas (16)–(18) need to be modified. Specifically, formula Eq. (17) should be modified as

$$\tilde{\sigma}_{\mathrm{BS}}^2 = \sigma_{\mathrm{BS}}^2 + f_{\mathrm{correction}}, \tag{19}$$

where $\sigma_{\mathrm{BS}}^2$ is calculated by Eq. (17), and $f_{\mathrm{correction}}$ represents a corrected term due to the effect of feedback, which may be positive and negative, depending on the type of feedback (positive or negative). Note that in general, $f_{\mathrm{correction}}$ is a function of both feedback strength $a$ and mean burst size $\langle \mathrm{BS}\rangle$, and is not equal to zero unless $a = 0$. Similarly, Eq. (16) or (18) should be modified as

$$\eta_{\mathrm{exact}}^2 = \eta_{\mathrm{classic}}^2 + g_{\mathrm{correction}}, \tag{20}$$

where the function $g_{\mathrm{correction}}$ represents the feedback-induced correlation between the internal noise in the gene product and the promoter noise, and is equal to zero if $a = 0$ (i.e., no feedback). In Eq. (20), $\eta_{\mathrm{classic}}^2 = \eta_{\mathrm{internal}}^2 + \eta_{\mathrm{promoter}}^2$, where $\eta_{\mathrm{internal}}^2$ representing the internal noise is calculated by $\eta_{\mathrm{internal}}^2 = 1/\langle n\rangle$, and $\eta_{\mathrm{promoter}}^2$ representing the promoter noise is calculated by the second formula in Eq. (16).

Formula (20) indicates that the expression noise is not a simple sum of the internal noise of the gene product (mRNA or protein) and the promoter noise as in the case of no feedback but needs to add an extra, nonzero term generated from the correlation between the internal noise and the promoter noise. Moreover, the sign of this additional term depends on the type of feedback. Figure 2 justifies formula (20), where Figs. 2(a) and 2(b) correspond to negative feedback whereas Figs. 2(c) and 2(d) correspond to positive feedback. The sign of function $g_{\mathrm{correction}}$ is clearly indicated in the shadowed parts of this figure. In the next two sections we will give more explanations for Fig. 2 and analyze the mechanism of how these additional terms are generated.

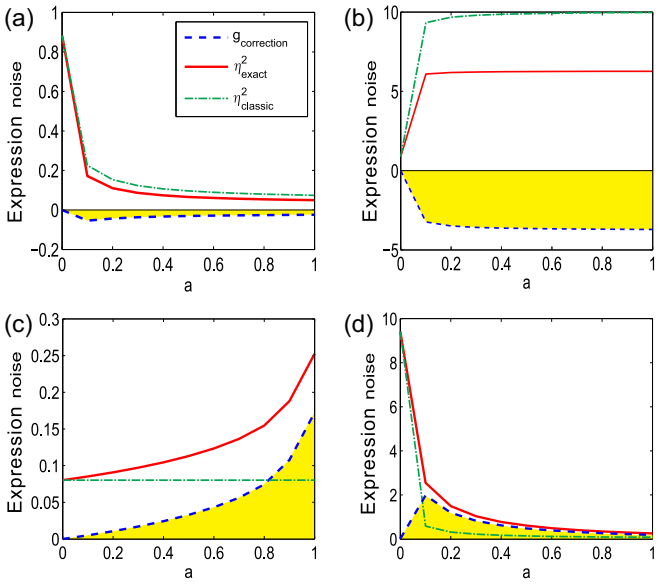


FIG. 2. (Color online) Feedback-induced additional contributions to gene expression noise: (a), (b) negative feedback; (c), (d) positive feedback. The solid line represents the exact noise calculated by Eq. (5) with Eqs. (14) and (15), the dash-dotted line represents the noise calculated by Eq. (16), the dashed line represents the additional noise induced by feedback, and the shadowed areas represent the area bounded by the curve $g_{\mathrm{correction}}$ and by two coordinate axes. (a) and (b) are plotted using the parameter values corresponding to the first and second subfigures of Fig. 3(a) from left to right, respectively; (c) and (d) are plotted using the parameter values corresponding to the third and fourth subfigures of Fig. 5(a) from left to right, respectively.

### C. Negative feedback can induce counterintuitive correlations of expression noise with bursting kinetics

To make comparisons with previous results, we always keep the mean expression level fixed. Similar assumptions were previously made, in particular when analyzing design principles of nature systems [16,29–31]. Some authors studied influences of transition rates between promoter activity states on expression noise [33–35,44] and other authors investigated effects of mRNA synthesis rate on expression levels [49]. Here, we are interested mainly in the effects of five system parameters: $\lambda$, $\gamma$, $a$, $\mu_1$, and $\mu_0$, on both bursting kinetics and expression noise. Note that if the negative feedback strength increases, then this will lead to only one of the following four cases taking place: (1) increasing $\lambda$, (2) decreasing $\gamma$, (3) increasing $\mu_1$, and (4) increasing $\mu_0$, due to the assumption that the mean expression level is fixed. Here, the other parameters must be fixed in each case.

First, we use Table I to conclude our qualitative results, which do not depend on the choice of system parameter values. This table shows that there are actually four distinct kinds of relationships between negative feedback and expression noise in terms of bursting kinetics: case 1 and case 4 correspond

TABLE I. Qualitative effects of negative feedback on both bursting kinetics and expression noise in the case that the mean expression level is fixed, where the shadowed part represents that feedback induces counterintuitive correlations of expression noise with bursting kinetics.

| Negative feedback | Some parameters | Mean burst frequency | Mean burst size | Burst size noise | Expression noise |
|---|---|---|---|---|---|
| Increasing $a$ | (1) Increasing $\lambda$ | Increase | Decrease | Increase | Decrease |
| | (2) Increasing $\mu_1$ | No change | Decrease | Decrease | Increase |
| | (3) Decreasing $\gamma$ | No change | No change | Decrease | Decrease |
| | (4) Increasing $\mu_0$ | No change | Decrease | Increase | Decrease |

to the results obtained in the common gene model without feedback (i.e., a higher mean burst frequency or a smaller mean burst size results in the lower expression noise), and the other two cases (i.e., case 2 and case 3) indicate that negative feedback induces counterintuitive correlations of expression noise with bursting kinetics. Interestingly, we find that there are three same cases where increasing the negative feedback strength leads to reduction of the expression noise, but bursting kinetics exhibits different characteristics in each case. In the next two subsections, we will elucidate the mechanism of how negative feedback induces counterintuitive correlations.

Then, we use Fig. 3 to demonstrate detailed numerical results, where some parameter values are listed in Table II. From Fig. 3(a), we observe that negative feedback may amplify or reduce the expression noise, depending on the change of one of the four parameters $\lambda$, $\gamma$, $\mu_1$, and $\mu_0$. This subfigure implies that the influence of negative feedback on expression noise does not take a single mode as shown in previous studies. For several representative points in Fig. 3(a), Figs. 3(b)–3(e) demonstrate the main characteristics of promoter-state activity, the time evolution of the gene product number, burst size, and probability distribution, respectively. All these subfigures can be used to verify the correctness of the qualitative results concluded in Table I. The next two subsections will give more interpretations for the numerical results shown in Fig. 3, including analyzing the mechanisms of how negative feedback induces the counterintuitive correlation of expression noise with bursting kinetics.

#### 1. *Effects of negative feedback on expression noise*

Note that if the negative feedback strength increases and the mean expression level is kept at a fixed value (we set $\langle n \rangle = 20$ in simulation), then one of the following four cases will take place: (1) increasing the transition rate from off to on states ($\lambda$); (2) increasing the transcription rate ($\mu_1$); (3) decreasing the transition rate from on to off states ($\gamma$); and (4) increasing the promoter leakage rate ($\mu_0$). Here, the other parameter values must be fixed in each case (see Table II). Also note that in the case of negative feedback (i.e., $a \neq 0$), the mean off time is still equal to $1/\lambda$ but the mean on time $\tau_{\mathrm{ON}}$ is no longer equal to $1/\gamma$. In spite of this, the mean on time can be numerically given.

TABLE II. Parameter values corresponding to several particular points indicated in Fig. 3(a) (see arrows).

| Parameter | Description | Point 1 | Point 2 | Point 3 |
|---|---|---|---|---|
| $a$ | Negative feedback strength | 0 | 1 | 1 |
| $\lambda$ | On-switching rate | 0.1 | 20.1 | 0.1 |
| $\gamma$ | Off-switching rate | 0.1 | 0.1 | 0.1 |
| $\mu_1$ | Transcription rate | 40 | 40 | 28904 |
| $\mu_0$ | Leakage rate | 0 | 0 | 0 |

The quantitative results on the relationship between expression noise and negative feedback strength are shown in Fig. 3(a), where circles represent numerical results obtained by the Gillespie stochastic simulation algorithm [48] and the solid lines represent theoretical results obtained by the above analytical formulas [e.g., Eq. (5) combined with Eqs. (14) and (15)]. We observe that if the transition rate from off to on states increases, or if the transition rate from on to off states decreases, or if the leakage rate increases, then increasing the negative feedback strength will reduce the expression noise. If the transcription rate at the on state increases, then increasing the negative feedback strength will amplify the expression noise. Figure 3(b) shows that the promoter activity exhibits different dynamic characteristics including different burst frequencies in three cases: no feedback [i.e., point 1 indicated in Fig. 3(a)], strong feedback with a large transition rate from off to on [i.e., point 2 indicated in Fig. 3(a)], and strong feedback with a large transcription rate at the on state [i.e., point 3 indicated in Fig. 3(a)]. From this subfigure, we further observe that the resident time at the on or off state is also different in each case. Similarly, Fig. 3(c) shows the time evolution of the protein number with different characteristics. Finally, we observe from Fig. 3(e) that the $P$ probability distribution is bimodal in the case of no feedback ($a = 0$) [corresponding to point 1 in Fig. 3(a)], but unimodal in cases of strong feedback ($a = 1$) [corresponding to points 2 and 3 in Fig. 3(a)], where the peak exhibits different characteristics in each case. These indicate that negative feedback has important influences on the probability distribution of the gene product.

In addition, we observe from Figs. 2(a) and 2(b) that the noise intensity calculated by the classic formula, i.e., Eq. (16), is always larger than the exact noise calculated by Eq. (5) with Eqs. (14) and (15) in the case of negative feedback, indicating that the corrected term in Eq. (20), $g_{\mathrm{correction}}$, is always negative [referring to the shadowed area in Figs. 2(a) and 2(b)]. This implies that for a fixed negative feedback strength, the classic method [i.e., Eq. (16)] overestimates the expression noise.

Table I shows the qualitative relationship between expression noise and negative feedback. We see that increasing the negative strength can not only amplify but also reduce the expression noise. However, this amplification or reduction is mainly because of the change in feedback-induced bursting kinetics.

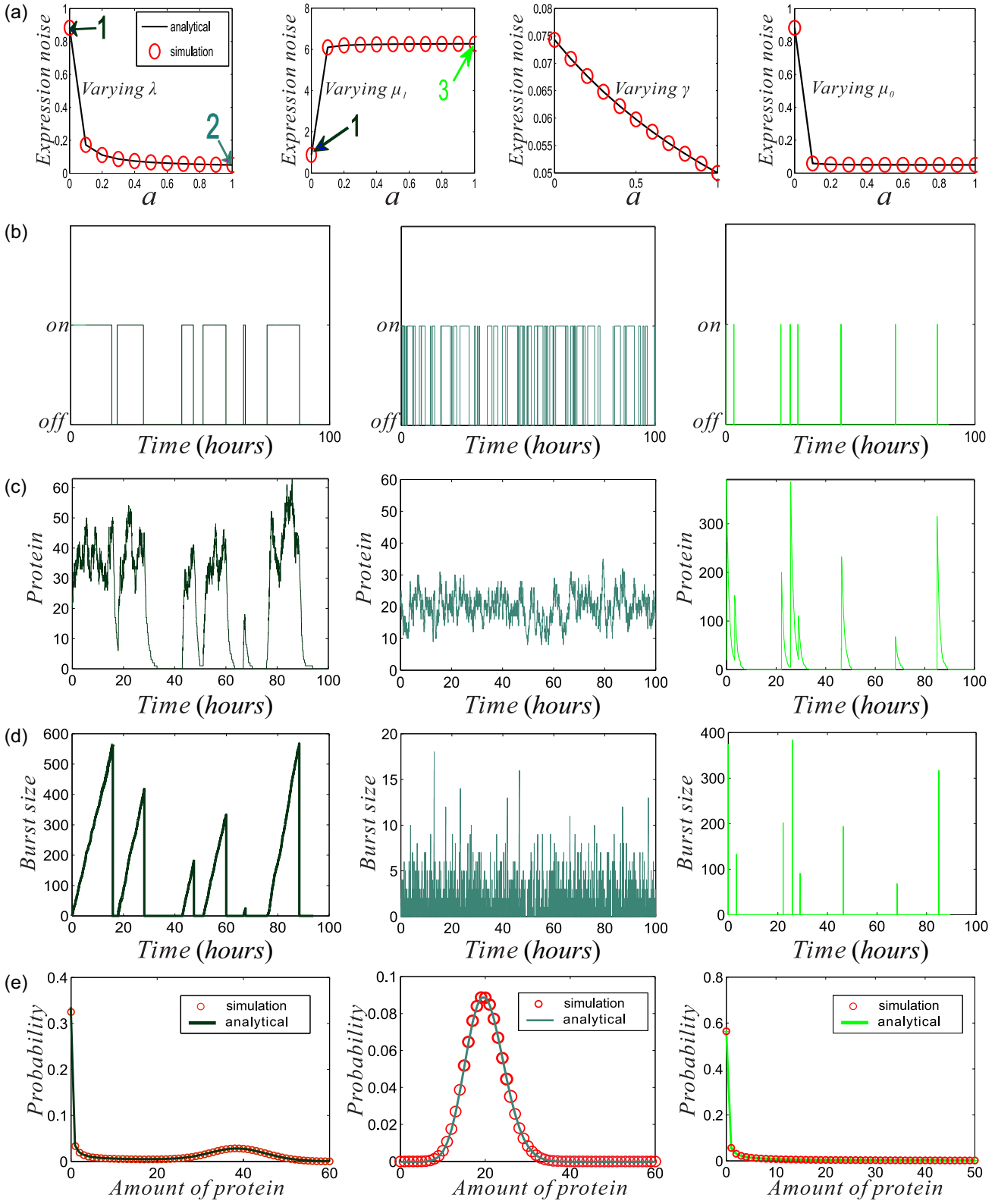


FIG. 3. (Color online) Quantitative influences of negative feedback on expression noise and bursting kinetics, where the mean protein number is fixed at $\langle n \rangle = 20$: (a) the relationship between feedback and noise, where "analytical" represents the exact noise calculated by Eq. (5) with Eqs. (14) and (15), and from left to right corresponds to changes of transition rate from off to on ($\lambda$), transcription rate at on state ($\mu_1$), transition rate from on to off ($\gamma$), and transcription rate at off state ($\mu_0$), respectively. Three representative points are indicated by symbols 1, 2, and 3 with arrows; (b)–(d) time evolutions of promoter activity, the protein number, and burst size, where from left to right corresponds, respectively, to three representative points 1, 2, and 3 indicated in (a); and (e) protein distribution, where from left to right corresponds, respectively, to three points indicated in (a) and "analytical" represents the exact distribution calculated by Eq. (13). The parameter values are listed in Table II and all the variables are dimensionless.

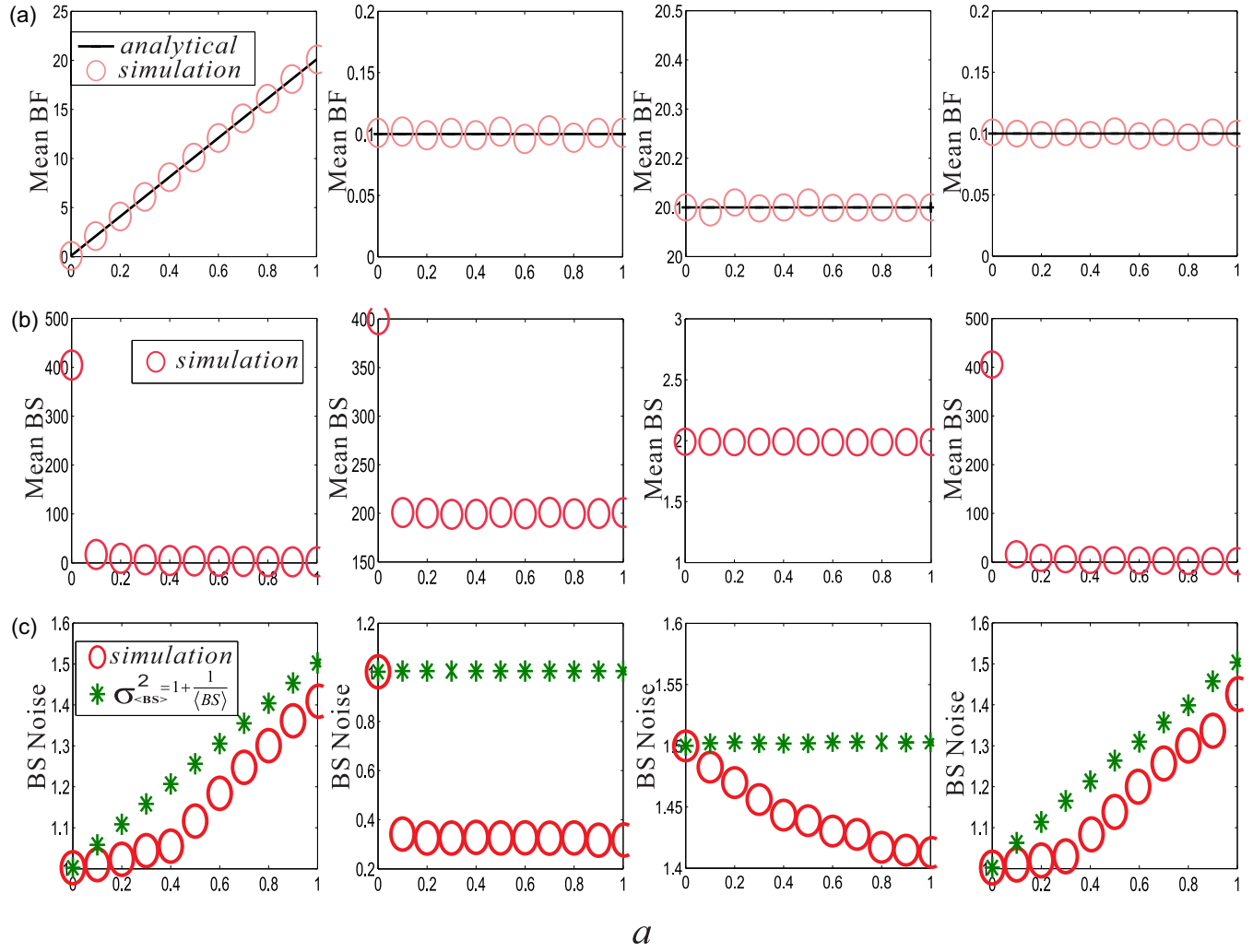


FIG. 4. (Color online) Quantitative effects of negative feedback strength on mean burst frequency, mean burst size, and burst size noise, where four subfigures in each of (a)–(c) correspond, respectively, to four subfigures in Fig. 3(a) from left to right, and "analytical" represents the exact mean burst frequency calculated by BF = λ Parameter values are the same as those used in Fig. 3(a) and all the variables are dimensionless.

### 2. *Effects of negative feedback on bursting kinetics*

The qualitative results are concluded in Table I whereas the quantitative results are demonstrated in Fig. 3. Here, we will focus on some interpretations for Table I.

We numerically find that the change trend of burst size or expression noise with negative feedback strength in case (1) and case (4) of Table I is fundamentally in accord with the prediction of the approximate formula (17) or (18), indicating that the negative feedback-induced additional effect is not remarkable in these two cases. This would be determined by bursting kinetics of gene expression itself. The numerical results shown in the first and fourth columns of Fig. 4 further verify this change trend.

In the following, we will focus on case (2) and case (3) in Table I, both showing the negative feedback-induced counterintuitive correlation of expression noise with bursting kinetics, and give some explanations of how this counterintuitive phenomenon is generated.

First, consider case (2) in Table I. Note that increasing the negative feedback strength will decrease the time that the gene dwells at the on state (i.e., the on time), thus increasing the transcription rate at the on state due to the fixed mean expression level. Also note that the decrease of the on time will make burst size decrease. On the other hand, both the decrease of the on time and a large transcription at the on state will make the gene be expressed in a more remarkably bursty mode [referring to the third subfigure in Fig. 3(d)], leading to the expression noise appearing at an amplification trend. Our numerical result also verifies this point, referring to the second column in Fig. 4. A similar mechanism was also elucidated in Ref. [50].

Then, consider case (3) in Table I. Note that increasing the negative feedback strength can decrease the transition rate ($\gamma$) from on to off states if the mean expression level is kept at a fixed value. In this case, we can obtain that both the burst size noise and the total noise are reduced. To give a reasonable explanation for this conclusion, we borrow an important result obtained in Ref. [51]: Negative feedback can result in the negative correlation of the dwelling time interval between on states, thus reducing the noise in the on time. Therefore,

the promoter noise propagating to the downstream mRNA or protein is reduced, leading to both the burst size and expression noise decreasing. Refer to numerical results shown in the third column of Fig. 4.

Next, we give a simple analysis for the phenomena displayed in Fig. 4(c). For this, note that there are two factors impacting the burst size noise: One is transcription or translation, and the other is the on time. In general, the transcription or translation process is Poissonian, so it has so small a contribution to the burst size noise that it is neglectable. Thus, the burst size noise is determined mainly by the on time noise. However, the authors in Ref. [51] pointed out that a negative correlation between interspikes can reduce noise. In other words, the negative correlation between two switchings can result in the decrease of the on time noise. On the other hand, negative feedback always gives rise to such a negative correlation. Therefore, negative feedback always plays a role of attenuating the burst size noise, implying that the function $f_{\text{correction}}$ is always negative.

According to the above analysis, we make the following brief summary: In the case of negative feedback, (1) there are four modes of the relationship between feedback and expression noise, depending on transition rates between promoter activity states as well as on transcription rates (see Table I). This classification is based on different characteristics of bursting kinetics in each mode; (2) one previous qualitative conclusion (i.e., a higher mean burst frequency results in the lower expression noise) and another previous qualitative conclusion (i.e., a larger mean burst size leads to the higher expression noise) both no longer hold in the case of negative feedback. Negative feedback can induce counterintuitive correlations of expression noise with bursting kinetics (see the shadowed part in Table I); (3) the analytical formulas for burst size noise and expression noise in the common on-off model need to be modified [referring to Eqs. (19) and (20), where $f_{\text{correction}}$ and $g_{\text{correction}}$ are always negative].

### D. Effects of positive feedback on bursting kinetics and expression noise

Note that, similar to the case of negative feedback, if the positive feedback strength increases and the mean expression is fixed, then only the one of the following four cases will take place: (1) increasing the transition rate from on to off states ($\lambda$); (2) decreasing the transcription rate ($\mu_0$); (3) decreasing the transition rate from off to on states ($\gamma$); and (4) decreasing the promoter leakage rate ($\mu_1$). Here, the other parameters must be fixed in each case.

Also similar to the case of negative feedback, we can analyze effects of positive feedback on mean burst frequency, mean burst size, burst size noise, and expression noise for each of the above four cases. We emphasize that in this analysis, the mean expression level is always kept at a fixed value. The qualitative results are summarized in Table III, which show how positive feedback impacts bursting kinetics and expression noise.

From Table III, we observe that when positive feedback intensity increases, the expression noise is sensitive to four parameters: transition rate from on to off states ($\lambda$), promoter leakage rate ($\mu_1$), transition rate from off to on states ($\gamma$), and transcription rate ($\mu_0$); the mean burst frequency is sensitive to three parameters: $\lambda$, $\mu_1$, and $\mu_0$, but is irrelative to $\gamma$; both the mean burst size and its noise are sensitive to $\lambda$ and $\mu_0$, but are irrelative to $\mu_1$ and $\gamma$. Similar to the case of negative feedback, positive feedback-induced counterintuitive correlations of expression noise with bursting kinetics take place at cases of decreasing $\mu_1$ and $\gamma$. Different from the case of negative feedback, however, bursting kinetics exhibits different characteristics in terms of mean burst frequency, mean burst size, and burst size noise.

Next, we take several particular sets of parameter values and keep the mean expression level fixed at 20, to perform numerical calculation. The numerical results are shown in Fig. 5. We observe from Fig. 5(a) that if the promoter leakage rate ($\mu_1$) or the transition rate from off to on states ($\gamma$) decreases, then increasing the positive feedback strength will amplify the expression noise; if the transcription rate at the on state ($\mu_0$) decreases or the transition rate from on to off states ($\lambda$) increases, then increasing the positive feedback strength will reduce the expression noise. Figure 5(b) shows that promoter activity exhibits different characteristics in terms of bursting kinetics in the three cases of feedback indicated in Fig. 5(a) (i.e., points 1, 2, and 3, which represent no feedback, strong positive feedback with a large transition rate from on to off, and no feedback with a large transcription rate at the on state, respectively). From this figure, we observe that the on time or the off time is also different in each case. Similarly, the time evolutions of both the protein number and the burst size also exhibit different characteristics, referring to Figs. 5(c) and 5(d), respectively. Finally, with the feedback strength at point 2 ($a = 1$) indicated in Fig. 5(a), the protein distribution is basically bimodal whereas with the feedback strength at points 1 and 3 ($a = 0$) indicated in Fig. 5(a), the distribution is unimodal but the peak exhibits different characteristics. Refer to Fig. 5(e).

To verify correctness of qualitative results in Table III, we also plot Fig. 6, where four subfigures in each row correspond, respectively, to four subfigures of Fig. 5(a) from left to right. Note that in the case of positive feedback (i.e., $a \neq 0$), the mean on time is still equal to $1/\gamma$, so, the exact mean burst size solution is calculated by $\langle \text{BS} \rangle = \mu_0/\lambda$, but the mean off time $\tau_{\text{OFF}}$ is no longer equal to $1/\lambda$. In spite of this, the mean burst frequency can be numerically given [see Fig. 6(a)].

From Fig. 6(c), we observe that positive feedback has little influence on the burst size noise [Fig. 6(c)]. In particular, we find the above approximate formulas (19) are fundamentally efficient by comparing lines with circles in Fig. 6(c).

Similar to the case of negative feedback, we make the following brief summary for the above analysis. In the case of positive feedback, there are four modes of relationships between positive feedback and expression noise, depending on transition rates between promoter activity states as well as on transcription and leakage rates. This classification is based on different characteristics of bursting kinetics in each mode. Neither the qualitative conclusion that a higher mean burst frequency leads to the lower expression noise nor the qualitative conclusion that a larger mean burst size results in the higher expression noise no longer holds in the case of positive feedback. Positive feedback can induce counterintuitive correlations of expression noise with bursting

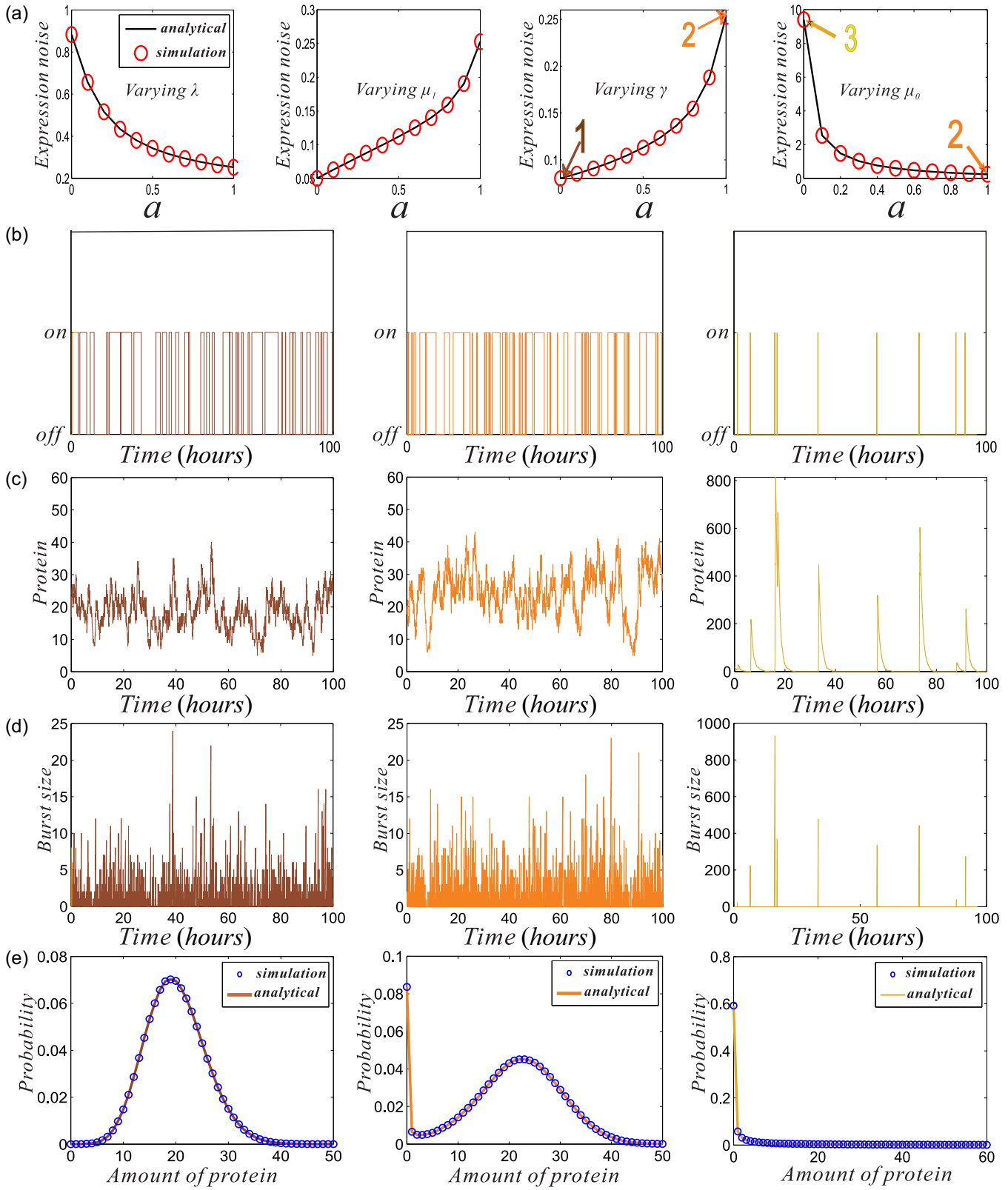


FIG. 5. (Color online) Quantitative influences of positive feedback on expression noise and bursting kinetics, where the mean protein number is kept at $\langle n \rangle = 20$: (A) the relationship between feedback and noise, where "analytical" represents the exact noise calculated by Eq. (5) with Eqs. (14) and (15), and from left to right corresponds to changes of transition rate from on to off ($\lambda$), promoter leakage rate ($\mu_1$), transition rate from off to on ($\gamma$), and transcription rate at on state ($\mu_0$), respectively; (b)–(d) time evolutions of promoter activity, the protein number, and burst size, where from left to right corresponds, respectively, to three representative points indicated in (a) (i.e., points 1, 2, and 3); (e) protein distribution, from left to right corresponds, respectively, to three points indicated in (a) (i.e., points 1, 2, and 3), and "analytical" represents the exact distribution calculated by Eq. (13). See Table IV for the parameter values used in simulation and all the variables are dimensionless.

TABLE III. Qualitative influences of positive feedback on bursting kinetics and expression noise in the case that the mean expression level is fixed, where the shadowed part represents that feedback induces counterintuitive correlations of expression noise with bursting kinetics.

| Positive feedback | Some parameters | Mean burst frequency | Mean burst size | Burst size noise | Expression noise |
|---|---|---|---|---|---|
| Increasing $a$ | (1) Increasing $\lambda$ | Increase | Decrease | Increase | Decrease |
| | (2) Decreasing $\mu_1$ | Increase | No change | No change | Increase |
| | (3) Decreasing $\gamma$ | No change | No change | No change | Increase |
| | (4) Decreasing $\mu_0$ | Increase | Decrease | Increase | Decrease |

kinetics (see the shadowed part in Table III). In addition, the analytical formulas for expression noise in the common on-off model need to be modified [refer to Eq. (20), where $g_{\text{correction}}$ is always positive. Refer to Figs. 2(c) and 2(d)]. Thus, we obtain a qualitative conclusion that in the case of positive feedback, the classic method [i.e., Eq. (20)] underestimates expression noise. However, since positive feedback does not affect mean burst size and burst size noise, Eq. (17) is still valid [i.e., $f_{\text{correction}} = 0$, referring to Fig. 6(c)]. In other words, positive feedback effect on burst frequency does not affect burst size nor burst size noise.

## IV. CONCLUSION AND DISCUSSION

Gene expression noise is a lasting topic and has attracted extensive attention. In this paper, we have analyzed a two-state gene autoregulatory model with a fixed mean expression level. In contrast to previous studies showing that in the case of no feedback, the higher the burst frequency is, the lower is the expression noise whereas the larger the burst size is, the higher the expression noise, we have shown different qualitative results depending on how feedback mediates burst frequency, burst size, and the noise in burst size. Specifically,

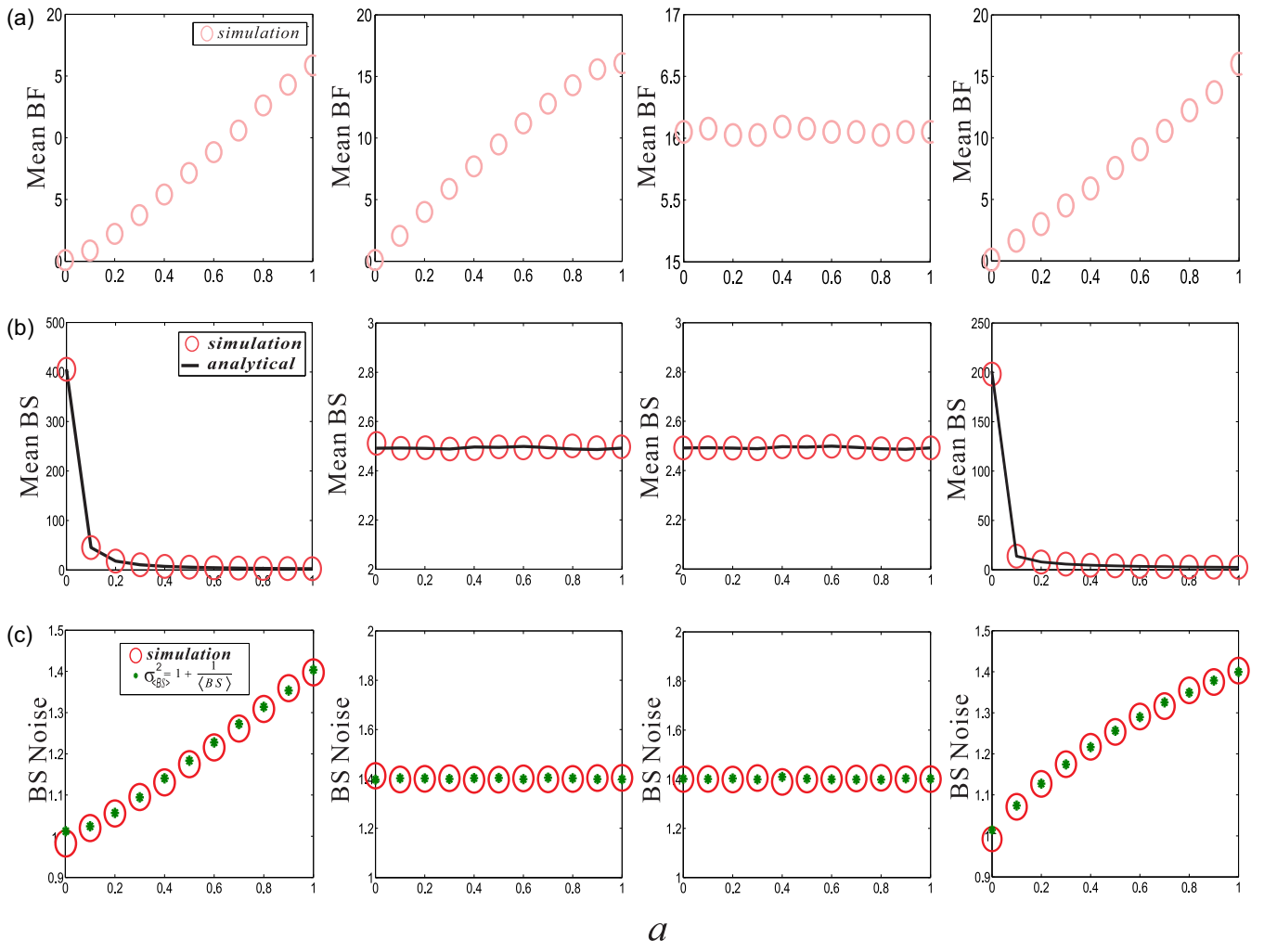


FIG. 6. (Color online) Quantitative effects of positive feedback strength on mean burst frequency, mean burst size, and burst size noise, where four subfigures in each of (a)–(c) correspond, respectively, to four subfigures in Fig. 5(a) from left to right, and "analytical" represents the exact mean burst size calculated by $\langle \text{BS} \rangle = \mu_0/\lambda$. Parameter values are the same as those used in Fig. 5(a) and all the variables are dimensionless.

TABLE IV. Parameter values corresponding to several particular points indicated in Fig. 5(a) (see arrows).

| Parameter | Description | Point 1 | Point 2 | Point 3 |
|---|---|---|---|---|
| $a$ | Positive feedback strength | 0 | 1 | 1 |
| $\lambda$ | Off-switching rate | 0.1 | 16.0457 | 16.0457 |
| $\gamma$ | On-switching rate | 0.1 | 0.1 | 0.1 |
| $\mu_1$ | Leakage rate | 0 | 0 | 19.8755 |
| $\mu_0$ | Transcription rate | 40 | 40 | 40 |

increasing the negative feedback strength does not impact both burst frequency and burst size if the transition rate from on to off states decreases, but reduces the expression noise; or increasing the negative feedback strength makes burst size decrease without impacting burst frequency if the transcription rate increases, but amplifies the expression noise. Refer to Table I. Increasing the positive feedback strength will make both burst frequency and burst size invariant if the transition rate from off to on decreases, or will make burst frequency increase and burst size invariant if the leakage rate decreases, but amplifies the expression noise, referring to Table III. In addition, we have also shown that the qualitative conclusion that the larger the burst size is, the lower is the burst size noise, no longer holds in the case of feedback but needs to be modified (refer to Tables II and IV). These results not only describe how feedback influences the expression noise as well as bursting kinetics but also imply that the expression noise is not a simple sum of the internal noise and the promoter noise (refer to Fig. 2), under the hypothesis that the mean expression level is fixed. Such plasticity of feedback-mediated bursting kinetics would be useful when protein is taken as an input signal of the downstream networks.

We point out that our results are obtained under the assumption that the gene promoter has one active and one inactive state. However, that the promoter has multiple activity states is not an exception but is ubiquitous in particular in eukaryotic cells [49,52]. For example, the PRM promoter of phage lambda in *E. coli* is regulated by two different transcription factorss binding to two sets of three operators that can be brought together by looping out the intervening DNA. As a result, the number of regulatory states of the PRM promoter is up to 128 [53]. In contrast, eukaryotic promoter structures may be more complex since they involve nucleosomes competing with or being removed by transcription factors [54]. Except for the conventional regulation by transcription factors, the eukaryotic promoters can be also epigenetically regulated via, e.g., histone modifications [55,56]. Such regulation may lead to very intricate promoter structures [57]. For a gene model with complex promoter structure, it remains to be fully explored how feedback impacts bursting kinetics and expression noise. In spite of this, we conjecture that qualitative results obtained here still hold but quantitative results would need to be modified.

Finally, our model did not consider effects of RNA nuclear retention and alternative splicing. In fact, alternative splicing is a fundamental process during gene expression and has been found to be ubiquitous in eukaryotes [58,59]; RNA nuclear retention is not an exceptional but is a ubiquitous phenomenon occurring during the process of gene expression [60,61]. However, it is unclear how these two processes impact gene expression levels in the case of feedback. Thus, our next task is to focus on investigating qualitative and quantitative effects of alternative splicing and RNA nuclear retention on bursting kinetics and expression noise.

## ACKNOWLEDGMENT

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## APPENDIX: DERIVATION OF MASTER EQUATIONS

Summing two equations in Eq. (7) in the main text yields the following relation:

$$\mu_0 G_0 - G_0' = -(\mu_1 G_1 - G_1'). \tag{A1}$$

Under transformations (8) in the main text, Eq. (A1) can be rewritten as

$$e^{\mu_1 z} H_1'(z) = -e^{\mu_0 z} H_0'(z). \tag{A2}$$

In addition, Eq. (7) in the main text can be rewritten as

$$\begin{aligned} &-\lambda e^{\mu_0 z} H_0(z) + \gamma e^{\mu_1 z} H_1(z) + az[\mu_1 e^{\mu_1 z} H_1(z) + e^{\mu_1 z} H_1'(z)] \\ &\quad -(z-1)e^{\mu_0 z} H_0'(z) = 0, \\ &\lambda e^{\mu_0 z} H_0(z) - \gamma e^{\mu_1 z} H_1(z) - az[\mu_1 e^{\mu_1 z} H_1(z) + e^{\mu_1 z} H_1'(z)] \\ &\quad -(z-1)e^{\mu_1 z} H_1'(z) = 0. \end{aligned} \tag{A3}$$

Multiplying $e^{-\mu_0 z}$ on both sides of the second equation in Eq. (A3), we have

$$\begin{aligned} &e^{(\mu_1-\mu_0)z}\left[(a+1)z-1\right] H_1'(z) + e^{(\mu_1-\mu_0)z}(az\mu_1+\gamma) H_1(z) \\ &\quad = \lambda H_0(z). \end{aligned} \tag{A4}$$

Substituting Eq. (A4) into the first equation of Eq. (A3) will yield Eq. (9) in the main text.

To solve Eq. (9) in the main text, we make another transformation

$$\begin{aligned} H_1(z) &= e^{-(\Delta\mu)z} f\left\{\left[(a+1)z-1\right]\frac{\Delta\mu - a\mu_0}{(a+1)^2}\right\} \\ &\equiv e^{-(\Delta\mu)z} f(w), \end{aligned} \tag{A5}$$

where the function $f$ will be determined by substituting Eq. (A5) into Eq. (9) in the main text. It is found that $f(w)$ satisfies the following standard confluent hypergeometric equation [43]:

$$w f''(w) + (\beta - w) f'(w) - \alpha f(w) = 0, \tag{A6}$$

where $\alpha$ and $\beta$ are given in the main text. From the viewpoint of mathematics, we know that Eq. (A6) admits two independent solutions: the confluent hypergeometric function ${}_1F_1(\alpha;\beta;w)$ [43] and the Tricomi function $U(\alpha;\beta;w)$ [43]. However, since the condition $P_1(n) \to 0$ for $n \to \infty$ is required and the mean number of the gene product must be finite, we know that $H_1(z)$ takes only the form of Eq. (10) in the main text. Thus, we obtain the analytical expression for the factorial

probability-generating function $G_1(z)$:

$$G_1(z) = e^{\mu_1 z} H_1(z) = A e^{\mu_0 z}\, {}_1F_1\left\{\alpha;\beta;[(a+1)z-1]\frac{\Delta\mu - a\mu_0}{(a+1)^2}\right\}. \tag{A7}$$

According to this expression and using the first relation in Eq. (8) in the main text, we further obtain the following analytical expression for $G_0(z)$:

$$G_0(z) = A e^{\mu_0 z}[C_1 F_1(\alpha-1;\beta-1;aQ) - {}_1F_1(\alpha;\beta;aQ)], \tag{A8}$$

where $\alpha$, $\beta$, $C$, $Q$, and $A$ are given in the main text. After having obtained the analytical expressions for $G_0(z)$ and $G_1(z)$, we easily give the analytical expressions for two factorial distributions $P_0(n)$ and $P_1(n)$ according to the relationship between probability distribution and generating function $P_i(n) = (1/n!)\partial^n G/\partial z^n|_{z=0}$ with $i = 0, 1$.


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