

Exact results for gene-expression models with general waiting-time distributions

Jinqiang Zhang,¹ Aimin Chen², Huahai Qiu,³ Jiajun Zhang,^{1,4} Tianhai Tian⁵, and Tianshou Zhou^{1,4,*}

¹*School of Mathematics, Sun Yat-Sen University, Guangzhou 510275, People's Republic of China*

²*School of Mathematics and Statistics, Henan University, Kaifeng 475004, China*

³*School of Mathematics and Computers, Wuhan Textile University, Wuhan 430200, People's Republic of China*

⁴*Key Laboratory of Computational Mathematics, Guangdong Province, Guangzhou 510275, People's Republic of China*

⁵*School of Mathematics, Monash University, Clayton 3800, Australia*



(Received 10 July 2023; accepted 19 January 2024; published 20 February 2024; corrected 28 February 2024)

Complex molecular details of transcriptional regulation can be coarse-grained by assuming that reaction waiting times for promoter-state transitions, the mRNA synthesis, and the mRNA degradation follow general distributions. However, how such a generalized two-state model is analytically solved is a long-standing issue. Here we first present analytical formulas of burst-size distributions for this model. Then, we derive an iterative equation for the mRNA moment-generating function, by which mRNA raw and binomial moments of any order can be conveniently calculated. The analytical results obtained in the special cases of phase-type waiting-time distributions not only provide insights into the mechanisms of complex transcriptional regulations but also bring conveniences for experimental data-based statistical inferences.

DOI: [10.1103/PhysRevE.109.024119](https://doi.org/10.1103/PhysRevE.109.024119)

I. INTRODUCTION

mRNA molecules observed in experiments are a consequence of a series of biochemical reactions. And they are stochastically produced due to the discreteness of the systems and the low copy numbers of the reactants. This stochasticity is thought to be an important source of phenotypic variation across a genetically identical population of cells and can affect cell functioning and even cell fate decisions [1–6].

Transcription is regulated by a multitude of factors that cooperatively induce genes to switch between transcriptionally active (ON) and inactive (OFF) states. Prokaryotic transcription depends on transcription factors (TFs), and in some cases, on DNA looping. In contrast, eukaryotic transcription is more complex, involving a number of complexes that sequentially assemble on chromatin under the influence of TFs and the dynamic state of chromatin. On the other hand, most genes are transcribed in a bursty fashion [7–10]. Single-cell measurements have provided evidence for transcriptional bursting both in bacteria [8] and in eukaryotic cells [10,11].

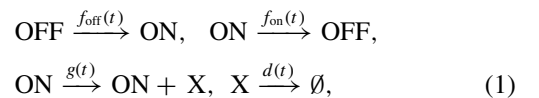
To understand transcriptional burst kinetics, many mathematical models have been proposed, such as extensively studied two-state models [12–17], models of promoter progression [16,18], and multistate models [19]. We note that almost all these models assume that the underlying reactions occur in a Markovian or memoryless manner, implying that the reaction waiting times follow exponential distributions. For gene expression, however, Markov is exceptional and non-Markov is more general [20–22]. Molecular processes such as transitions from OFF to ON states and vice versa, the mRNA synthesis, and degradation processes are usually all multistep, creating memories between molecular events. For example,

the complex control process of gene expression can generate nonexponential time intervals between transcription windows [20]; inactive phases of the promoter involving the prolactin gene in a mammalian cell are differently distributed, showing strong memory [23].

In this paper, we introduce a generalized model of gene expression, which considers general waiting-time distributions, including those between promoter activity states as well as for the synthesis and degradation of mRNA. This model includes most existing models as its special cases. Importantly, we derive the analytical formulas for calculating moments and the distribution of mRNA. The analytical results not only provide insight into the roles of transcriptional regulation and molecular memory in tuning mRNA expression levels but can also be used in the inference of bursting kinetics based on experimental data.

II. MODEL DESCRIPTION

To reveal the effects of molecular memory, we coarse-grain complex molecular details of transcriptional regulation by assuming that waiting times for promoter-state transitions, mRNA synthesis, and mRNA degradation all follow general distributions. Specifically, we assume that the biochemical reactions of the underlying gene-expression system are



where $f_{\text{off}}(t)$, $f_{\text{on}}(t)$, $g(t)$, and $d(t)$ are four arbitrary distribution functions, and X represents the gene product (without loss of generality, we assume that it is mRNA). We point out that $g(t)$ can model the process of transcription initiation involving pre-initiation-complex formation, open-complex formation, promoter escape, etc. We further point out that there are models that consider special forms of the function $g(t)$ [24–28], and in particular, there are experimental measurements that

* Author to whom correspondence should be addressed: mcszhtsh@mail.sysu.edu.cn

support the nonexponential $g(t)$ [29–31], but it is unclear how a general $g(t)$ affects the expression level of mRNA. Function $f_{\text{on}}(t)$ can model a deactivation process that is, e.g., due to the spontaneous unbinding of one single TF (activator), and $f_{\text{off}}(t)$ can mimic a complex activation process due to, e.g., chromatin opening and TF recruitment. Hereafter quantities with subscript “on” refer to the process of leaving the active state and vice versa for “off.” The question of how this generalized two-state model is analytically solved is a long-standing issue.

We point out that special cases of the above queuing model have been studied and some analytical results on statistical quantities of X have also been derived [20,22,32–34]. In particular, Szavits-Nossan and Grima [35] recently provided a tutorial review of an alternative approach to stochastic gene-expression models based on queuing theory. The models studied by them included some that could generate a very wide class of distributions of waiting times; and depending on the number of gene states included and on the values of the rate constants, the distributions of the ON and OFF times could be matched to a very wide variety of experimental distributions. In spite of these, the existing models did not consider that the waiting-time distribution from nascent RNA to mature RNA, i.e., the function $g(t)$ in Eq. (1), is general. It seems to us that no one considered that $f_{\text{on}}(t)$, $f_{\text{off}}(t)$, $g(t)$, and $d(t)$ are simultaneously general, and no analytical results were reported in this general case, either. We will focus on the derivation of analytical results for Eq. (1).

III. ANALYTICAL RESULTS

A. Moment-generating functions

For clarity, we distinguish the following two cases to derive the moment-generating functions (MGFs) of burst sizes.

Case 1. Neither gene inactivation nor mRNA degradation are considered. Let T_{on} represent the time that the gene dwells at the ON state. Then, the probability that the gene produces at least b bursts up to moment t is calculated via $P_{\text{burst}}\{B \geq b | T_{\text{on}} = t\} = \int_0^t g_b(\tau) d\tau$, where function $g_b(\tau) = \underbrace{g(\tau) * \dots * g(\tau)}_b$ represents the k th convolution of function $g(\tau)$ and B the mRNA copy number. The probability that the gene produces exactly b bursts at moment, called instantaneous burst-size distribution, is then expressed as

$$P_{\text{burst}}\{B = b | T_{\text{on}} = t\} = \int_0^t g_b(\tau) d\tau - \int_0^t g_{b+1}(\tau) d\tau. \quad (2)$$

Further, the burst-size distribution during the entire ON period is given by

$$P_{\text{burst}}\{B = b\} = \int_0^{+\infty} P_{\text{burst}}\{B = b | T_{\text{on}} = t\} f_{\text{on}}(t) dt. \quad (3)$$

If we define $M_{\text{burst}}(z, t) = \sum_b e^{bz} P_{\text{burst}}\{B = b | T_{\text{on}} = t\}$, and denote by $BS_k(t)$ the k th-order instantaneous moment of burst size at time t , then

$$\begin{aligned} BS_k(t) &= \partial_z^k M_{\text{burst}}(z, t)|_{z=0} \\ &= \sum_b b^k P_{\text{burst}}\{B = b | T_{\text{on}} = t\}, \quad k = 1, 2, \dots, \end{aligned} \quad (3a)$$

where symbol “ ∂_z^k ” represents the k th-order derivative with regard to z . Note that $M_{\text{burst}}(0, t) = 1$ due to the conservative condition of probability. Thus, the expectation $\langle B \rangle$ and the variance σ_{burst} of burst size during the entire ON period are calculated according to

$$\begin{aligned} \langle B \rangle &= \int_0^{+\infty} BS_1(t) f_{\text{on}}(t) dt, \\ \sigma_{\text{burst}} &= \int_0^{+\infty} BS_2(t) f_{\text{on}}(t) dt - \langle B \rangle^2. \end{aligned} \quad (3b)$$

Reference [36] gave another method for calculating the first- and second-order moments of burst size, expressed in a manner of the Laplace transform, e.g., the instantaneous burst size is given by $BS_1(t) = L^{-1}(\tilde{g}(s)/[1-\tilde{g}(s)])$, where L^{-1} is the inverse of Laplace transform operator L , and $\tilde{g}(s)$ is the Laplace transform of function $g(t)$.

As applications of the above analysis, we first consider the simplest case: $g(t) = \lambda e^{-\lambda t}$ and $f_{\text{on}}(t) = k_{\text{on}} e^{-k_{\text{on}} t}$, where λ and k_{on} are the mean generating rate for mRNA and the mean transition rate from ON to OFF states, respectively. According to Eq. (3), we can show

$$P_{\text{burst}}\{B = b\} = \frac{k_{\text{on}}}{\lambda + k_{\text{on}}} \left(1 - \frac{k_{\text{on}}}{\lambda + k_{\text{on}}}\right)^b, \quad (4)$$

indicating that the burst size follows a geometric distribution as assumed in previous studies [12,18,19,37]. Alternatively, the MGF for the burst size, denoted by $M_{\text{burst}}(z)$, is given by

$$M_{\text{burst}}(z) = \frac{k_{\text{on}}}{k_{\text{on}} - \lambda(e^z - 1)}. \quad (4a)$$

Then, we consider another example: $f_{\text{on}}(t) = k_{\text{on}} e^{-k_{\text{on}} t}$ and $g(t) = \lambda^\ell t^{\ell-1} e^{-\lambda t} / \Gamma(\ell)$ (Erlang or phase-type distribution [38]) (note, in this case, the mRNA production is considered a multistep process with equal rates), where $\Gamma(\ell)$ is a gamma function and ℓ is a positive integer, modeling the number of reaction steps, and called memory index [22]. Note that $\ell = 1$ corresponds to the Markovian case and $\ell \neq 1$ to the non-Markovian case. According to Appendix A of this paper, we can show that $P_{\text{burst}}\{B = b | T_{\text{on}} = t\}$ is given by

$$P_{\text{burst}}\{B = b | T_{\text{on}} = t\} = 1 - e^{-\lambda t} \sum_{i=b\ell}^{(b+1)\ell-1} \frac{(\lambda t)^i}{i!}, \quad (5b)$$

and the MGF for mRNA at time t by

$$M_{\text{burst}}(z, t) = \exp[-\bar{\lambda}(1 - e^{\ell z})(1 - e^{-k_d t})] \sum_{i=1}^{\ell} e^{(i-1)z}, \quad (5c)$$

where $\bar{\lambda} = \lambda/k_d$, and we have made use of the fact that the convolution of exponential distributions is an Erlang distribution [38].

Case 2. Both gene inactivation and mRNA degradation are considered. For a general waiting-time distribution $g(t)$, the burst-size distribution has not been derived so far even if mRNAs degrade in an exponential manner. The main difficulty is that bursts are produced not in a constant manner but in a time-dependent manner in this case. Here we develop a method to derive burst-size distributions for any $g(t)$. Note that for

exponentially distributed lifetimes of mRNA described by distribution $d(t) = k_d e^{-k_d t}$, integral $D(t) = \int_t^{+\infty} d(s) ds = e^{-k_d t}$ represents the probability that the degradation does not occur in the interval $(0, t)$ and $\int_0^t D(s) ds$ is the cumulant probability. For a general waiting-time distribution, $d(t)$, we have a similar interpretation. When one calculates the burst-size distribution at any time point using Eq. (2), t should then be replaced with $\bar{t} = \int_0^t D(s) ds$. For example, for $g(t) = \lambda e^{-\lambda t}$, Eq. (2) should be modified as

$$P_{\text{burst}}\{B = b | T_{\text{on}} = \bar{t}\} = 1 - \frac{(\lambda \bar{t})^b e^{-\lambda \bar{t}}}{\Gamma(b+1)}. \quad (5)$$

The distribution obtained in such a manner is called an effective burst-size distribution. The MGF for the corresponding burst size is given by

$$\begin{aligned} M_{\text{burst}}(z, t) &= \sum_{b=0}^{+\infty} \exp(bz) P_{\text{burst}}\{B = b | T_{\text{on}} = \bar{t}\} \\ &= \exp[\lambda \bar{t}(e^z - 1)]. \end{aligned} \quad (5a)$$

These results will be verified in the analysis of the following special cases.

B. An iterating equation for initial raw moments

Here we establish an integral equation for the MGF of initial (i.e., time $t = 0$) raw mRNA moments by using the fact that the MGF at the beginning of the OFF state equals that at the end of the ON state during one transcription period.

For simplicity but without loss of generality, we always assume $d(\tau) = k_d e^{-k_d \tau}$ in the following analysis. Let $M(z, t)$ be the MGF for the number of mRNA molecules at time t with $0 \leq t \leq \tau_{\text{on}} + \tau_{\text{off}}$, where τ_{on} and τ_{off} represent the times dwelling at the ON and OFF states, respectively, each changing between 0 and infinity. The following condition must be satisfied [39]:

$$\begin{aligned} M_{\text{ini}}(z) &\equiv M(z, 0) = M(z, \tau_{\text{on}} + \tau_{\text{off}}) \\ &= \int_{\tau=0}^{+\infty} \int_{t=\tau}^{+\infty} M(z, t) f_{\text{off}}(t - \tau) f_{\text{on}}(\tau) dt d\tau, \end{aligned} \quad (6)$$

$$M'_{\text{ini}}(0) = \frac{\int_{s=0}^{+\infty} a(t) f_{\text{on}}(t) dt}{1 - \tilde{f}_{\text{off}}(k_d) \tilde{f}_{\text{on}}(k_d)}, \quad (9a)$$

$$M''_{\text{ini}}(0) = \frac{2M'_{\text{ini}}(0) \tilde{f}_{\text{off}}(k_d) \int_{u=0}^{+\infty} e^{-k_d u} a(t) f_{\text{on}}(t) dt}{1 - \tilde{f}_{\text{off}}(2k_d) \tilde{f}_{\text{on}}(2k_d)} + \frac{M'_{\text{ini}}(0) [\tilde{f}_{\text{off}}(k_d) \tilde{f}_{\text{on}}(k_d) - \tilde{f}_{\text{off}}(2k_d) \tilde{f}_{\text{on}}(2k_d)] + \int_{u=0}^{+\infty} b(t) f_{\text{on}}(t) dt}{1 - \tilde{f}_{\text{off}}(2k_d) \tilde{f}_{\text{on}}(2k_d)}. \quad (9b)$$

Hereafter for convenience, we denote $a(t) = BS_1(t)$ and $b(t) = BS_2(t)$, which are given by Eq. (3a), and $\tilde{g}(s)$ is the Laplace transform of function $g(t)$.

C. Calculation of mRNA raw moments

After having obtained initial raw moments of mRNA, we can now calculate the raw moment of any order for the total mRNA copy number. This only needs to average over all ON-state and OFF-state times according to their distributions:

$$\langle m^k \rangle = \frac{1}{\langle \tau_{\text{on}} \rangle + \langle \tau_{\text{off}} \rangle} \left(\int_0^{+\infty} \langle m^k \rangle_{\text{off}} F_{\text{off}}(\tau) d\tau + \int_0^{+\infty} \langle m^k \rangle_{\text{on}} F_{\text{on}}(t) dt \right), \quad (10)$$

where $M_{\text{ini}}(z)$ is the MGF of the initial mRNA moment. Owing to the assumption of $d(\tau) = k_d e^{-k_d \tau}$, the probability that one molecule is still present after time τ is a Bernoulli random variable with the MGF denoted by $\xi(z, \tau)$. Moreover, we have $\xi(z, \tau) = 1 + e^{-k_d \tau}(e^z - 1)$. Starting with the MGF of the initial raw moment and considering only the mRNA degradation, we have

$$M(z, \tau) = M_{\text{ini}}[\ln \xi(z, \tau)], \quad (7)$$

where $0 \leq \tau \leq \tau_{\text{off}}$. The MGF at the end of the OFF state, $M(z, \tau_{\text{off}})$, should be the integral of $M(z, t)$ over time t from 0 to infinity.

Now, we consider an ON period. During this period, the degradation of the mRNA molecules that have been present at the beginning of the burst continues through function $\xi(z, t)$ with $M_{\text{deg}}(z, t) = M_{\text{ini}}(\ln [\xi(z, t)])$, where $\tau_{\text{off}} \leq t \leq \tau_{\text{off}} + \tau_{\text{on}}$. Then, the MGF of the mRNA number distribution is given by the convolution of the distributions of those molecules that are still present from previous bursts and the burst sizes with regard to the time during the OFF period, i.e.,

$$M(z, t) = M_{\text{burst}}(z, t) \int_{\tau=0}^{+\infty} M_{\text{ini}}(\ln [\xi(z, \tau + t)]) f_{\text{off}}(\tau) d\tau, \quad (8)$$

where $M_{\text{burst}}(z, t) = \sum_b e^{bz} P\{B=b | T_{\text{on}}=\bar{t}\}$ with $\bar{t}=(1 - e^{-k_d t})/k_d$, which is unrelated to variable s . By Eq. (6), we can arrive at the following closed form:

$$\begin{aligned} M_{\text{ini}}(z) &= \int_{t=0}^{+\infty} \int_{\tau=0}^{+\infty} M_{\text{ini}}(\ln [\xi(z, \tau + t)]) \\ &\quad \times M_{\text{burst}}(z, t) f_{\text{off}}(\tau) f_{\text{on}}(t) d\tau dt. \end{aligned} \quad (9)$$

This equation is actually an iterative system with $M_{\text{ini}}(0) = 1$ and can hence determine all raw moments for mRNA at time $t = 0$. For example, we can show that the first- and second-order initial raw moments of mRNA are respectively given by (see Appendix B for derivations)

where $\langle m^k \rangle_{\text{off}}$ represents the k th-order moment of mRNA during the OFF period and is calculated according to Eq. (7):

$$\langle m^k \rangle_{\text{off}} = \frac{\partial^k}{\partial z^k} M_{\text{ini}}[\ln \xi(z, \tau)]|_{z=0}, \quad (10a)$$

whereas $\langle m^k \rangle_{\text{on}}$ represents the k th-order moment of mRNA during the ON period and is calculated according to Eq. (8):

$$\langle m^k \rangle_{\text{on}} = \frac{\partial^k}{\partial z^k} \int_{\tau=0}^{+\infty} M_{\text{ini}}[\ln \xi(z, \tau + t)] \times M_{\text{burst}}(z, t) f_{\text{off}}(\tau) d\tau|_{z=0}. \quad (10b)$$

In Eq. (10), $F_{\text{on}}(t) = \int_t^{+\infty} f_{\text{on}}(\tau) d\tau$ and $F_{\text{off}}(s) = \int_s^{+\infty} f_{\text{off}}(\tau) d\tau$, and $\langle \tau_{\text{on}} \rangle = \int_0^{+\infty} \tau f_{\text{on}}(\tau) d\tau$ and $\langle \tau_{\text{off}} \rangle = \int_0^{+\infty} \tau f_{\text{off}}(\tau) d\tau$ are the mean times dwelling at ON and OFF states. The most frequently used moments are the first two raw ones. According to Eq. (10), the mRNA expectation is given by

$$\langle m \rangle = \frac{M'_{\text{ini}}(0)}{\langle \tau_{\text{on}} \rangle + \langle \tau_{\text{off}} \rangle} [\tilde{F}_{\text{off}}(k_d) + \tilde{f}_{\text{off}}(k_d) \tilde{F}_{\text{on}}(k_d)] + \frac{1}{\langle \tau_{\text{on}} \rangle + \langle \tau_{\text{off}} \rangle} \int_0^{+\infty} b(t) F_{\text{on}}(t) dt, \quad (11a)$$

and the second-order mRNA raw moment by

$$\begin{aligned} \langle m^2 \rangle = & \frac{1}{\langle \tau_{\text{on}} \rangle + \langle \tau_{\text{off}} \rangle} \{ M'_{\text{ini}}(0) \tilde{F}_{\text{off}}(k_d) + [M''_{\text{ini}}(0) - M'_{\text{ini}}(0)] \tilde{F}_{\text{off}}(2k_d) \} \\ & + \frac{M'_{\text{ini}}(0)}{\langle \tau_{\text{on}} \rangle + \langle \tau_{\text{off}} \rangle} \left[\tilde{f}_{\text{off}}(k_d) \tilde{F}_{\text{on}}(k_d) - \tilde{f}_{\text{off}}(2k_d) \tilde{F}_{\text{on}}(2k_d) + 2 \tilde{f}_{\text{off}}(k_d) \int_0^{+\infty} e^{-k_d t} a(t) F_{\text{on}}(t) dt \right] \\ & + \frac{1}{\langle \tau_{\text{on}} \rangle + \langle \tau_{\text{off}} \rangle} \left[M''_{\text{ini}}(0) \tilde{f}_{\text{off}}(2k_d) \tilde{F}_{\text{on}}(2k_d) + \int_0^{+\infty} b(t) F_{\text{on}}(t) dt \right], \end{aligned} \quad (11b)$$

where $M'_{\text{ini}}(0)$ and $M''_{\text{ini}}(0)$ are given by Eqs. (9a) and (9b), respectively.

To check whether the above general results are correct, we consider two special cases. The first case is $g(t) = \lambda e^{-\lambda t}$, $f_{\text{on}}(t) = k_{\text{on}} e^{-k_{\text{on}} t}$, and $f_{\text{off}}(t) = k_{\text{off}} e^{-k_{\text{off}} t}$, which corresponds to the common two-state model [12,14,16]. In this case, we can show that the mean mRNA and the second-order moment are given by $\langle m \rangle = \frac{\lambda \langle \tau_{\text{on}} \rangle}{\langle \tau_{\text{on}} \rangle + \langle \tau_{\text{off}} \rangle}$ and $\langle m^2 \rangle = \langle m \rangle \left[\frac{1}{k_{\text{on}}} + \frac{\lambda(k_{\text{off}} + k_d)}{k_{\text{on}} + k_{\text{off}} + k_d} \right]$; see Appendix C for the derivations based on Eqs. (11a) and (11b). Since these results are all known [18,19], here we do not plan to give discussions on the effects of model parameters on mRNA levels.

The second case is $g(t) = \frac{\lambda^n t^{n-1} e^{-\lambda t}}{\Gamma(n)}$, $f_{\text{on}}(t) = k_{\text{on}} e^{-k_{\text{on}} t}$, and $f_{\text{off}}(t) = k_{\text{off}} e^{-k_{\text{off}} t}$. In this case, we can show that the mean mRNA $\langle m \rangle$ is given by

$$\langle m \rangle = \frac{n k_{\text{on}} k_{\text{off}}}{k_{\text{on}} + k_{\text{off}}} \left[\frac{n-1}{2} \frac{k_{\text{on}} + k_d}{k_d k_{\text{on}}} + \frac{n \bar{\lambda}}{k_{\text{on}}} \right], \quad (12a)$$

which is apparently an extension of Eq. (12a). It is easy to show that $\langle m \rangle$ is a monotonically increasing function of n , implying that the number of reaction steps associated with the mRNA synthesis increases the mRNA mean level. Note that the switching rate k_{off} corresponds to the dissociation rate of the TF from its promoter. In the limit of large k_{off} , mRNA bursts are effectively produced constitutively with rate k_{on} . In this case, the mean mRNA can be approximated as $\langle m \rangle \approx n \left(\frac{n-1}{2} \frac{k_{\text{on}} + k_d}{k_d} + n \bar{\lambda} \right)$. Similarly, we can show that the second-order raw moments are

$$\langle m^2 \rangle = \langle m \rangle + \frac{c_1 + c_2 \bar{\lambda} + c_3 \bar{\lambda}^2}{\langle \tau_{\text{on}} \rangle + \langle \tau_{\text{off}} \rangle}, \quad (12b)$$

where c_i ($1 \leq i \leq 3$) are constants depending on model parameters (see Appendix D for details). In particular, if $n = 1$, then $c_1 = c_2 = 0$, and Eqs. (12a) and (12b) reproduce the

results in the Markovian case. If the Fano factor FF is defined as the ratio of the variance over the mean, then

$$\text{FF} = 1 + \frac{c_1 + c_2 \bar{\lambda} + c_3 \bar{\lambda}^2}{h_1}, \quad (12c)$$

where $h_1 = \frac{n(n-1)}{2} \frac{k_{\text{on}} + k_d}{k_d k_{\text{on}}} + \frac{n^2 \bar{\lambda}}{k_{\text{on}}}$. Note that if $n \geq 1$, then c_i ($1 \leq i \leq 3$) are all positive, implying that the mRNA number follows a super-Poissonian distribution (i.e., $\text{FF} > 1$ [40]). If $n < 1$, then $\text{FF} < 1$, implying that the mRNA number follows a sub-Poissonian distribution. In particular, if $n = 1$, then FF reduces to the Fano factor for the common two-state model.

D. Reconstruction of mRNA distribution

If the distribution of mRNA is denoted by $P(m)$, the k th-order binomial moment b_k is defined as $b_k = \sum_{m \geq k} \binom{m}{k} P(m)$, where symbol $\binom{m}{k}$ represents a combination number. Apparently, the binomial moments defined in such a manner are a linear combination of raw moments. If all the raw moments of $P(m)$ are known, all the binomial moments are also known. In turn, given all the binomial moments of a distribution, we can reconstruct this distribution [41] by the reconstruction formula

$$P(m) = \sum_{k \geq m} (-1)^{k-m} \binom{k}{m} b_k, \quad m = 0, 1, 2, \dots, \quad (13)$$

where $b_0 = 1$ due to the conservative condition of probability. By Eq. (10), we can calculate all mRNA raw moments, implying that the mRNA distribution can be reconstructed. In practical applications, we may use an approximate method to obtain an mRNA distribution [41].

It is worth pointing out that we can develop a statistical inference method based on the above theoretical results. Roughly speaking, we can calculate an “empirical” mRNA distribution, given a set of experimental data (e.g., single-cell RNA sequencing data of primary mouse fibroblasts). On the

other hand, by selecting model (1) as a candidate mechanism revealing transcriptional burst kinetics, we can obtain a “theoretical” mRNA distribution depending on model parameters. Further, e.g., by the maximum likelihood estimation, we can determine the values of the model parameters including memory indices. In a word, our results can be used not only for parameter inference but also for model selection in the sense of choosing switching-time distributions from the space of all possible distributions and thus determining an appropriate model that would generate them. Detailed results will be published elsewhere, but one may refer to [42,43]: in Ref. [42], a statistical inference framework was developed to infer both transcriptional bursting kinetics and the type of feedback regulation from single-cell RNA sequencing data on a genome-wide scale, but a (universal) question arising in inference is that selecting a different model would lead to different inferred results; and in Ref. [43], the authors used a dual driven approach of model and data to show the nonlinear control of transcriptional bursting by enhancer-promoter communications, but how the interactions between enhancers and promoters quantitatively impact bursting kinetics remains unclear.

Finally in this section, we point out that the above inference method is in theory feasible, but the inferred results would be approximate since it seems impossible to obtain all the binomial moments and further, the exact mRNA distribution.

IV. CONCLUDING REMARKS

In this paper, we have studied a generalized two-state model with arbitrary waiting-time distributions, and derived both analytical formulas of burst-size distributions and an iterative equation for the mRNA moment-generating function by which we can conveniently calculate mRNA raw and binomial moments of any orders. In particular, the analytical results obtained in the cases of phase-type waiting-time distributions not only provide insights into the mechanisms of complex transcription regulations but also link theoretical studies to experimental data by providing new inference possibilities. Thus, the development of analytical approaches, as outlined in this work, is an important ingredient for accurate quantitative modeling of complex cellular processes.

ACKNOWLEDGMENTS

This work was supported by Grants No. 62373384, No. 11931019, No. 12271416, No. 12171494, and No. 12371500 from the National Nature Science Foundation of People’s Republic of China and by Grant No. 2021YFA1302500 from the National Key R & D Program of China.

APPENDIX A: DERIVATION OF MOMENT-GENERATING FUNCTIONS

For clarity, we consider the following two cases separately.

Case 1. $g(t) = \lambda e^{-\lambda t}$, $f_{\text{on}}(t) = k_{\text{on}} e^{-k_{\text{on}} t}$, and $f_{\text{off}}(t) = k_{\text{off}} e^{-k_{\text{off}} t}$.

Note that the multiple convolution of an exponential distribution is an Erlang distribution. Using this fact and con-

sidering $g(t) = \lambda e^{-\lambda t}$, we can have

$$\begin{aligned} P_{\text{burst}}\{B = b | T_{\text{on}} = \bar{t}\} &= P_{\text{burst}}\{B \geq b | T_{\text{on}} = \bar{t}\} - P_{\text{burst}}\{B \geq b+1 | T_{\text{on}} = \bar{t}\} \\ &= \int_0^{\bar{t}} \underbrace{g(t) * \dots * g(t)}_b dt - \int_0^{\bar{t}} \underbrace{g(t) * \dots * g(t)}_{b+1} dt \\ &= \int_0^{\bar{t}} \frac{\lambda^b t^{b-1} e^{-\lambda t}}{\Gamma(b)} dt - \int_0^{\bar{t}} \frac{\lambda^{b+1} t^b e^{-\lambda t}}{\Gamma(b+1)} dt \\ &= 1 - \sum_{i=0}^{b-1} \frac{(\lambda \bar{t})^i e^{-\lambda \bar{t}}}{i!} - \left[1 - \sum_{i=0}^b \frac{(\lambda \bar{t})^i e^{-\lambda \bar{t}}}{i!} \right]. \end{aligned}$$

Therefore,

$$P_{\text{burst}}\{B = b | T_{\text{on}} = \bar{t}\} = \frac{(\lambda \bar{t})^b e^{-\lambda \bar{t}}}{\Gamma(b+1)}, \quad (\text{A1})$$

where $\bar{t} = \int_0^t D(s) ds = \frac{1}{k_d} (1 - e^{-k_d t})$. By $M_{\text{burst}}(z, \bar{t}) = \sum_{b=0}^{+\infty} e^{bz} P_{\text{burst}}\{B = b | T_{\text{on}} = \bar{t}\}$, the instantaneous moment-generating function at time \bar{t} is given by Eq. (4b) in the main text. Moreover, $M_{\text{burst}}(0, \bar{t}) = 1$, $\partial_z M_{\text{burst}}(z, \bar{t})|_{z=0} = \lambda \bar{t}$, and $\partial_z^2 M_{\text{burst}}(z, \bar{t})|_{z=0} = \lambda \bar{t} + (\lambda \bar{t})^2$.

Case 2. $g(t) = \frac{\lambda^k t^{k-1} e^{-\lambda t}}{\Gamma(k)}$, $f_{\text{on}}(t) = k_{\text{on}} e^{-k_{\text{on}} t}$, $f_{\text{off}}(t) = k_{\text{off}} e^{-k_{\text{off}} t}$.

Note that the Laplace transform of function $g(t)$ is

$$\begin{aligned} \tilde{g}(s) &= \int_0^{+\infty} g(t) e^{-st} dt = \frac{\lambda^k}{\Gamma(k)} \int_0^{+\infty} t^{k-1} e^{-(\lambda+s)t} dt \\ &= \left(\frac{\lambda}{s + \lambda} \right)^k. \end{aligned} \quad (\text{A2})$$

If we define $G(t) = \underbrace{g(t) * \dots * g(t)}_b$, the Laplace transform of $G(t)$ is

$$\tilde{G}(s) = \underbrace{\tilde{g}(s) \times \dots \times \tilde{g}(s)}_b = \left(\frac{\lambda}{s + \lambda} \right)^{bk}. \quad (\text{A3})$$

Using the inverse of the Laplace transform, we know that function $G(t)$ can be analytically expressed as the following Erlang distribution:

$$G(t) = L^{-1}[\tilde{G}(s)] = \frac{\lambda^{bk} t^{bk-1} e^{-\lambda t}}{\Gamma(bk)}. \quad (\text{A4})$$

Since $\int_0^{\bar{t}} \frac{\lambda^{bk} t^{bk-1} e^{-\lambda t}}{\Gamma(bk)} dt = 1 - e^{-\lambda \bar{t}} \sum_{i=0}^{bk-1} \frac{(\lambda \bar{t})^i}{i!}$, the instantaneous burst-size distribution at time \bar{t} is given by

$$\begin{aligned} P_{\text{burst}}\{B = b | T_{\text{on}} = \bar{t}\} &= \int_0^{\bar{t}} \underbrace{g(t) * \dots * g(t)}_b dt - \int_0^{\bar{t}} \underbrace{g(t) * \dots * g(t)}_{b+1} dt \\ &= 1 - e^{-\lambda \bar{t}} \sum_{i=0}^{bk-1} \frac{(\lambda \bar{t})^i}{i!} - 1 + e^{-\lambda \bar{t}} \sum_{i=0}^{(b+1)k-1} \frac{(\lambda \bar{t})^i}{i!} \\ &= e^{-\lambda \bar{t}} \sum_{i=bk}^{bk+k-1} \frac{(\lambda \bar{t})^i}{i!}. \end{aligned} \quad (\text{A5})$$

Therefore, according to the definition of moment-generating function, we can show Eq. (4c) in the main text. Moreover, $M_{\text{burst}}(0, \bar{t}) = 1$, and derivatives are $\partial_z M_{\text{burst}}(z, \bar{t})|_{z=0} = \frac{k(k-1)}{2} + k^2 \lambda \bar{t}$ and $\partial_z^2 M_{\text{burst}}(z, \bar{t})|_{z=0} = \frac{k(k-1)(2k-1)}{6} + k^2(2k-1)\lambda \bar{t} + k^3(\lambda \bar{t})^2$, where $\bar{t} = \frac{1}{k_d}(1 - e^{-k_d t})$.

APPENDIX B: DERIVATION OF THE FIRST TWO INITIAL RAW MOMENTS

For convenience, we denote $A(z, t) = \frac{\partial}{\partial z} M_{\text{burst}}(z, t)$, $B(z, t) = \frac{\partial^2}{\partial z^2} M_{\text{burst}}(z, t)$, $a(t) = A(0, t)$, and $b(t) = B(0, t)$. According to Eq. (9) in the main text, the first-order derivative of function $M_{\text{ini}}(z)$ with regard to z is

$$\begin{aligned} \frac{d}{dz} M_{\text{ini}}(z) &= \int_{t=0}^{+\infty} \int_{\tau=0}^{+\infty} \frac{e^{z-k_d(\tau+t)}}{1 + e^{-k_d \tau} (e^z - 1)} M'_{\text{ini}}[\ln \xi(z, \tau + t)] M_{\text{burst}}(z, t) f_{\text{off}}(\tau) f_{\text{on}}(t) d\tau dt \\ &+ \int_{t=0}^{+\infty} \int_{\tau=0}^{+\infty} M_{\text{ini}}(\ln [\xi(z, \tau + t)]) A(z, t) f_{\text{off}}(\tau) f_{\text{on}}(t) d\tau dt. \end{aligned}$$

Therefore,

$$M'_{\text{ini}}(0) = \int_{t=0}^{+\infty} \int_{\tau=0}^{+\infty} e^{-k_d(\tau+t)} M'_{\text{ini}}(0) f_{\text{off}}(\tau) f_{\text{on}}(t) d\tau dt + \int_{t=0}^{+\infty} \int_{\tau=0}^{+\infty} a(t) f_{\text{off}}(\tau) f_{\text{on}}(t) d\tau dt,$$

which yields Eq. (9a) in the main text. Similarly, the second-order derivative of function $M_{\text{ini}}(z)$ with regard to z at point $z = 0$ is

$$\begin{aligned} M''_{\text{ini}}(0) &= M'_{\text{ini}}(0) \int_{t=0}^{+\infty} \int_{\tau=0}^{+\infty} e^{-k_d(\tau+t)} (1 - e^{-k_d(\tau+t)}) f_{\text{off}}(\tau) f_{\text{on}}(t) d\tau dt \\ &+ \int_{t=0}^{+\infty} \int_{\tau=0}^{+\infty} b(t) f_{\text{off}}(\tau) f_{\text{on}}(t) d\tau dt + M''_{\text{ini}}(0) \int_{t=0}^{+\infty} \int_{\tau=0}^{+\infty} e^{-2k_d(\tau+t)} f_{\text{off}}(\tau) f_{\text{on}}(t) d\tau dt \\ &+ 2M'_{\text{ini}}(0) \int_{t=0}^{+\infty} \int_{\tau=0}^{+\infty} e^{-k_d(\tau+t)} a(t) f_{\text{off}}(\tau) f_{\text{on}}(t) d\tau dt, \end{aligned}$$

which yields Eq. (9b) in the main text.

Note that

$$\langle m \rangle_{\text{off}} = e^{-k_d s} M'_{\text{ini}}(0), \quad \langle m \rangle_{\text{on}} = a(t) + \tilde{f}_{\text{off}}(k_d) M'_{\text{ini}}(0) e^{-k_d t}. \quad (\text{B1})$$

According to Eq. (10) in the main text, the first-order mRNA raw moment is given by

$$\langle m \rangle = \frac{M'_{\text{ini}}(0)}{\langle \tau_{\text{on}} \rangle + \langle \tau_{\text{off}} \rangle} \left[\int_0^{+\infty} e^{-k_d s} F_{\text{off}}(\tau) d\tau + \tilde{f}_{\text{off}}(k_d) \int_0^{+\infty} e^{-k_d t} F_{\text{on}}(t) dt \right] + \frac{1}{\langle \tau_{\text{on}} \rangle + \langle \tau_{\text{off}} \rangle} \int_0^{+\infty} a(t) F_{\text{on}}(t) dt. \quad (\text{B2})$$

Next, we consider the second-order raw moment of mRNA. Note that

$$\begin{aligned} \frac{\partial}{\partial z} M_{\text{ini}}[\ln \xi(z, \tau)] &= \frac{e^{z-k_d \tau}}{1 + e^{-k_d \tau} (e^z - 1)} M'_{\text{ini}}[\ln \xi(z, \tau)], \\ \frac{\partial^2}{\partial z^2} M_{\text{ini}}[\ln \xi(z, \tau)] &= \frac{e^{z-k_d \tau} (1 - e^{-k_d s})}{[1 + e^{-k_d \tau} (e^z - 1)]^2} M'_{\text{ini}}[\ln \xi(z, \tau)] + \frac{e^{2z-2k_d \tau}}{[1 + e^{-k_d \tau} (e^z - 1)]^2} M''_{\text{ini}}[\ln \xi(z, \tau)]. \end{aligned}$$

Therefore,

$$\langle m^2 \rangle_{\text{off}} = e^{-k_d \tau} (1 - e^{-k_d \tau}) M'_{\text{ini}}(0) + e^{-2k_d \tau} M''_{\text{ini}}(0). \quad (\text{B3})$$

Since the derivatives of $M_{\text{burst}}(z, t)$ with regard to z are unrelated to s , we have

$$\begin{aligned} \frac{\partial^2}{\partial z^2} \int_{\tau=0}^{+\infty} M_{\text{ini}}(\ln [\xi(z, \tau + t)]) M_{\text{burst}}(z, t) f_{\text{off}}(\tau) d\tau &= \int_{\tau=0}^{+\infty} \frac{\partial^2 M_{\text{ini}}(\ln \xi)}{\partial z^2} M_{\text{burst}}(z, t) f_{\text{off}}(\tau) d\tau \\ &+ 2 \frac{\partial^2}{\partial z^2} \int_{\tau=0}^{+\infty} \frac{\partial M_{\text{ini}}(\ln \xi)}{\partial z} A(z, t) f_{\text{off}}(\tau) d\tau + \int_{\tau=0}^{+\infty} M_{\text{ini}}(\ln \xi) B(z, t) f_{\text{off}}(\tau) d\tau. \end{aligned}$$

That is,

$$\begin{aligned} \frac{\partial^2}{\partial z^2} \int_{\tau=0}^{+\infty} M_{\text{ini}}(\ln [\xi(z, \tau + t)]) M_{\text{burst}}(z, t) f_{\text{off}}(\tau) d\tau &= \int_{\tau=0}^{+\infty} \left\{ \frac{e^{z-k_d(\tau+t)} (1 - e^{-k_d(\tau+t)}) M'_{\text{ini}}(\ln \xi)}{[1 + e^{-k_d(\tau+t)} (e^z - 1)]^2} + \frac{e^{2z-2k_d(\tau+t)} M''_{\text{ini}}(\ln \xi)}{[1 + e^{-k_d(\tau+t)} (e^z - 1)]^2} \right\} M_{\text{burst}}(z, t) f_{\text{off}}(\tau) d\tau \\ &+ 2 \int_{\tau=0}^{+\infty} \frac{e^{z-k_d(\tau+t)}}{1 + e^{-k_d(\tau+t)} (e^z - 1)} M'_{\text{ini}}(\ln \xi) A(z, t) f_{\text{off}}(\tau) d\tau + \int_{\tau=0}^{+\infty} M_{\text{ini}}(\ln \xi) B(z, t) f_{\text{off}}(\tau) d\tau. \end{aligned}$$

Therefore, we obtain

$$\langle m^2 \rangle_{\text{on}} = M'_{\text{ini}}(0)[\tilde{f}_{\text{off}}(k_d)e^{-k_d t} - \tilde{f}_{\text{off}}(2k_d)e^{-2k_d t} + 2\tilde{f}_{\text{off}}(k_d)e^{-k_d t}a(t)] + M''_{\text{ini}}(0)\tilde{f}_{\text{off}}(2k_d)e^{-2k_d t} + b(t). \quad (\text{B4})$$

According to Eq. (10) in the main text, the second-order mRNA raw moment is given by Eq. (11b) in the main text.

APPENDIX C: REPRODUCTION OF KNOWN RESULTS

To check whether the method in the main text is correct, here we reproduce known analytical results for the common two-state model of gene expression. This model corresponds to the case of $g(t) = \lambda e^{-\lambda t}$, $f_{\text{on}}(t) = k_{\text{on}}e^{-k_{\text{on}}t}$, and $f_{\text{off}}(t) = k_{\text{off}}e^{-k_{\text{off}}t}$. According to Eqs. (9a) and (9b) in the main text and by complex calculations, we can show

$$\begin{aligned} M'_{\text{ini}}(0) &= \frac{\bar{\mu}(k_{\text{off}} + k_d)}{k_{\text{on}} + k_{\text{off}} + k_d}, \\ M''_{\text{ini}}(0) &= \frac{\bar{\lambda}(k_{\text{off}} + k_d)}{k_{\text{on}} + k_{\text{off}} + k_d} + \frac{\bar{\lambda}^2(k_{\text{off}} + k_d)(k_{\text{off}} + 2k_d)}{(k_{\text{on}} + k_{\text{off}} + k_d)(k_{\text{on}} + k_{\text{off}} + 2k_d)}. \end{aligned} \quad (\text{C1})$$

Then, by combining Eq. (11a) in the main text with $a(t) = \bar{\lambda}(1 - e^{-k_d t})$ and substituting the Laplace transforms of these three distribution functions into Eq. (11a), we have

$$\langle m \rangle = \frac{M'_{\text{ini}}(0)}{\langle \tau_{\text{on}} \rangle + \langle \tau_{\text{off}} \rangle} \left[\frac{1}{k_{\text{off}} + k_d} + \frac{k_{\text{off}}}{k_{\text{off}} + k_d} \frac{1}{k_{\text{on}} + k_d} \right] + \frac{\bar{\lambda}}{\langle \tau_{\text{on}} \rangle + \langle \tau_{\text{off}} \rangle} \int_0^{+\infty} (1 - e^{-k_d t}) e^{-k_{\text{on}} t} dt,$$

i.e.,

$$\langle m \rangle = \frac{\bar{\lambda}}{\langle \tau_{\text{on}} \rangle + \langle \tau_{\text{off}} \rangle} \frac{1}{k_{\text{on}} + k_d} + \frac{\bar{\lambda}}{\langle \tau_{\text{on}} \rangle + \langle \tau_{\text{off}} \rangle} \frac{k_d}{k_{\text{on}}} \frac{1}{k_{\text{on}} + k_d}. \quad (\text{C2})$$

Thus, the first-order raw moment of mRNA is given by Eq. (12a) in the main text. Similarly, by noting the expressions of $a(t) = \bar{\lambda}(1 - e^{-k_d t})$ and $b(t) = \bar{\lambda}[1 - e^{-k_d t} + \bar{\lambda}(1 - 2e^{-k_d t} + e^{-2k_d t})]$, Eq. (11b) in the main text becomes

$$\begin{aligned} \langle m^2 \rangle &= \frac{\bar{\lambda}}{\langle \tau_{\text{on}} \rangle + \langle \tau_{\text{off}} \rangle} \frac{1}{k_{\text{on}} + k_d} \frac{k_d}{k_{\text{on}}} + \frac{M''_{\text{ini}}(0)}{\langle \tau_{\text{on}} \rangle + \langle \tau_{\text{off}} \rangle} \left(\frac{1}{k_{\text{on}} + 2k_d} \frac{k_{\text{off}}}{k_{\text{off}} + 2k_d} + \frac{1}{k_{\text{off}} + 2k_d} \right) \\ &+ \frac{M'_{\text{ini}}(0)}{\langle \tau_{\text{on}} \rangle + \langle \tau_{\text{off}} \rangle} \left[\frac{1}{k_{\text{on}} + k_d} \frac{k_{\text{off}}}{k_{\text{off}} + k_d} - \frac{1}{k_{\text{on}} + 2k_d} \frac{k_{\text{off}}}{k_{\text{off}} + 2k_d} + \frac{k_d}{(k_{\text{off}} + k_d)(k_{\text{off}} + 2k_d)} \right] \\ &+ \frac{2\bar{\lambda}M'_{\text{ini}}(0)}{\langle \tau_{\text{on}} \rangle + \langle \tau_{\text{off}} \rangle} \frac{k_{\text{off}}}{k_{\text{off}} + k_d} \frac{k_d}{k_{\text{on}} + k_d} \frac{1}{k_{\text{on}} + 2k_d} + \frac{\bar{\lambda}^2}{\langle \tau_{\text{on}} \rangle + \langle \tau_{\text{off}} \rangle} \frac{2k_d^2}{k_{\text{on}}(k_{\text{on}} + k_d)(k_{\text{on}} + 2k_d)}. \end{aligned}$$

Substitution of Eq. (C1) into the general expression of $\langle m^2 \rangle$ yields

$$\langle m^2 \rangle = \frac{\bar{\lambda}I_1}{\langle \tau_{\text{on}} \rangle + \langle \tau_{\text{off}} \rangle} + \frac{\bar{\lambda}^2 I_2}{\langle \tau_{\text{on}} \rangle + \langle \tau_{\text{off}} \rangle}, \quad (\text{C3})$$

where

$$\begin{aligned} I_1 &= \frac{1}{k_{\text{on}} + k_d} \frac{k_d}{k_{\text{on}}} + \frac{1}{k_{\text{on}} + k_{\text{off}} + k_d} \left(\frac{k_{\text{off}}}{k_{\text{on}} + k_d} - \frac{k_{\text{off}} + k_d}{k_{\text{on}} + 2k_d} \frac{k_{\text{off}}}{k_{\text{off}} + 2k_d} + \frac{k_d}{k_{\text{off}} + 2k_d} \right) \\ &+ \frac{(k_{\text{off}} + k_d)}{k_{\text{on}} + k_{\text{off}} + k_d} \frac{1}{k_{\text{off}} + 2k_d} \frac{k_{\text{on}} + k_{\text{off}} + 2k_d}{k_{\text{on}} + 2k_d} \end{aligned}$$

and

$$\begin{aligned} I_2 &= \frac{1}{k_{\text{off}} + 2k_d} \frac{k_{\text{on}} + k_{\text{off}} + 2k_d}{k_{\text{on}} + 2k_d} \frac{(k_{\text{off}} + k_d)(k_{\text{off}} + 2k_d)}{(k_{\text{on}} + k_{\text{off}} + k_d)(k_{\text{on}} + k_{\text{off}} + 2k_d)} \\ &+ \frac{2k_d k_{\text{off}}}{k_{\text{on}} + k_{\text{off}} + k_d} \frac{1}{k_{\text{on}} + k_d} \frac{1}{k_{\text{on}} + 2k_d} + \frac{2k_d^2}{k_{\text{on}}(k_{\text{on}} + k_d)(k_{\text{on}} + 2k_d)}. \end{aligned}$$

Simple calculations show

$$I_1 = \frac{1}{k_{\text{on}} + k_d} \frac{k_d}{k_{\text{on}}} + \frac{1}{k_{\text{on}} + k_{\text{off}} + k_d} \frac{k_{\text{off}}}{k_{\text{on}} + k_d} + \frac{1}{k_{\text{on}} + k_{\text{off}} + k_d} = \frac{1}{k_{\text{on}}}$$

and

$$I_2 = \frac{(k_{\text{off}} + k_d)(k_{\text{on}} + k_d)(k_{\text{on}} + 2k_d)}{k_{\text{on}} + k_{\text{off}} + k_d} \frac{1}{k_{\text{on}} + 2k_d} \frac{1}{k_{\text{on}} + k_d} \frac{1}{k_{\text{on}}} = \frac{1}{k_{\text{on}}} \frac{k_{\text{off}} + k_d}{k_{\text{on}} + k_{\text{off}} + k_d}.$$

Thus, we obtain the analytical expression of the second-order raw moment, given by Eq. (12b) in the main text.

APPENDIX D: DERIVATION OF THE FIRST TWO RAW MOMENTS IN THE CASE THAT $g(t)$ IS A GAMMA DISTRIBUTION

Here we consider the case $f_{\text{on}}(t) = k_{\text{on}}e^{-k_{\text{on}}t}$, $f_{\text{off}}(t) = k_{\text{off}}e^{-k_{\text{off}}t}$, and $g(t) = \lambda^n t^{n-1} e^{-\lambda t} / \Gamma(n)$. In this case, if we denote $\bar{a}(t) = A(0, t)$ and $\bar{b}(t) = B(0, t)$, then $\bar{a}(t) = \frac{n(n-1)}{2} + n^2 a(t)$ with $a(t) = \bar{\lambda}(1 - e^{-k_d t})$, and $\bar{b}(t) = \frac{n(n-1)(2n-1)}{6} + n^2(2n-1)\bar{a}(t) + n^3[\bar{a}(t)]^2$ that can be rewritten as $\bar{b}(t) = -\frac{n(n-1)(n-2)}{3} + n^2(n-2)a(t) + \bar{a}(t) + n^3b(t)$ with $b(t) = a(t) + [a(t)]^2$. Note that in this case, the first-order raw moment denoted by $\langle \bar{m} \rangle$ and second-order raw moments denoted by $\langle \bar{m}^2 \rangle$ can be respectively expressed as

$$\langle \bar{m} \rangle = \frac{\bar{M}'_{\text{ini}}(0)}{\langle \tau_{\text{on}} \rangle + \langle \tau_{\text{off}} \rangle} \left[\frac{1}{k_{\text{off}} + k_d} + \frac{\tilde{f}_{\text{off}}(k_d)}{k_{\text{on}} + k_d} \right] + \frac{1}{\langle \tau_{\text{on}} \rangle + \langle \tau_{\text{off}} \rangle} \int_0^{+\infty} \bar{a}(t) e^{-k_{\text{on}}t} dt \quad (\text{D1})$$

and

$$\begin{aligned} \langle \bar{m}^2 \rangle &= \langle \bar{m} \rangle + \frac{1}{\langle \tau_{\text{on}} \rangle + \langle \tau_{\text{off}} \rangle} \int_0^{+\infty} \left[-\frac{n(n-1)(n-2)}{3} + n^2(n-2)a(t) + n^3b(t) \right] e^{-k_{\text{on}}t} dt \\ &+ \frac{\bar{M}''_{\text{ini}}(0) - \bar{M}'_{\text{ini}}(0)}{\langle \tau_{\text{on}} \rangle + \langle \tau_{\text{off}} \rangle} \frac{1}{k_{\text{off}} + 2k_d} + \frac{\bar{M}'_{\text{ini}}(0) - \bar{M}'_{\text{ini}}(0)}{\langle \tau_{\text{on}} \rangle + \langle \tau_{\text{off}} \rangle} \frac{\tilde{f}_{\text{off}}(2k_d)}{k_{\text{on}} + 2k_d} \\ &+ \frac{2\bar{M}'_{\text{ini}}(0)\tilde{f}_{\text{off}}(k_d)}{\langle \tau_{\text{on}} \rangle + \langle \tau_{\text{off}} \rangle} \int_0^{+\infty} e^{-k_d t} e^{-k_{\text{on}}t} \bar{a}(t) dt, \end{aligned} \quad (\text{D2})$$

where $\bar{M}'_{\text{ini}}(0)$ and $\bar{M}''_{\text{ini}}(0)$ are the initial first-order and second-order raw moments of burst size, respectively. We can easily show

$$\bar{M}'_{\text{ini}}(0) = \frac{n(n-1)}{4} \frac{(k_{\text{on}} + 2k_d)(k_{\text{off}} + 2k_d)}{k_d(k_{\text{on}} + k_{\text{off}} + 2k_d)} + \frac{\bar{\lambda}n^2(k_{\text{off}} + k_d)}{k_{\text{on}} + k_{\text{off}} + k_d}. \quad (\text{D3})$$

Thus, the first-order raw moment of mRNA is given by Eq. (12a) in the main text.

In order to derive the analytical expression of the second-order raw moment, the key is to derive $\bar{M}''_{\text{ini}}(0)$. Note that

$$\begin{aligned} \bar{M}''_{\text{ini}}(0) &= \frac{\int_0^{+\infty} \bar{b}(t) f_{\text{on}}(t) dt}{1 - \tilde{f}_{\text{off}}(2k_d)\tilde{f}_{\text{on}}(2k_d)} + \frac{2\bar{M}'_{\text{ini}}(0)\tilde{f}_{\text{off}}(k_d) \int_0^{+\infty} e^{-k_d t} \bar{a}(t) f_{\text{on}}(t) dt}{1 - \tilde{f}_{\text{off}}(2k_d)\tilde{f}_{\text{on}}(2k_d)} \\ &+ \frac{\bar{M}'_{\text{ini}}(0)[\tilde{f}_{\text{off}}(k_d)\tilde{f}_{\text{on}}(k_d) - \tilde{f}_{\text{off}}(2k_d)\tilde{f}_{\text{on}}(2k_d)]}{1 - \tilde{f}_{\text{off}}(2k_d)\tilde{f}_{\text{on}}(2k_d)}. \end{aligned} \quad (\text{D4})$$

Also note that

$$\begin{aligned} 2\bar{M}'_{\text{ini}}(0)\tilde{f}_{\text{off}}(k_d) \int_0^{+\infty} e^{-k_d t} \bar{a}(t) f_{\text{on}}(t) dt &= 2\bar{M}'_{\text{ini}}(0)\tilde{f}_{\text{off}}(k_d) \int_0^{+\infty} e^{-k_d t} \left[\frac{n(n-1)}{2} + k^2 a(t) \right] f_{\text{on}}(t) dt \\ &= n(n-1) \left[\frac{1}{2} \frac{n(n-1)}{1 - \tilde{f}_{\text{off}}(k_d)\tilde{f}_{\text{on}}(k_d)} + n^2 \bar{\lambda} \frac{1 - \tilde{f}_{\text{on}}(k_d)}{1 - \tilde{f}_{\text{off}}(k_d)\tilde{f}_{\text{on}}(k_d)} \right] \tilde{f}_{\text{off}}(k_d) \int_0^{+\infty} e^{-k_d t} f_{\text{on}}(t) dt \\ &+ 2n^2 \left[\frac{1}{2} \frac{n(n-1)}{1 - \tilde{f}_{\text{off}}(k_d)\tilde{f}_{\text{on}}(k_d)} + n^2 \bar{\lambda} \frac{1 - \tilde{f}_{\text{on}}(k_d)}{1 - \tilde{f}_{\text{off}}(k_d)\tilde{f}_{\text{on}}(k_d)} \right] \tilde{f}_{\text{off}}(k_d) \int_0^{+\infty} e^{-k_d t} a(t) f_{\text{on}}(t) dt. \end{aligned}$$

Therefore, we have

$$\begin{aligned} 2\bar{M}'_{\text{ini}}(0)\tilde{f}_{\text{off}}(k_d) \int_0^{+\infty} e^{-k_d t} \bar{a}(t) f_{\text{on}}(t) dt &= \frac{[n(n-1)]^2}{2} \frac{k_{\text{on}}k_{\text{off}}}{k_d(k_{\text{on}} + k_{\text{off}} + k_d)} + \bar{\lambda}n^3(n-1) \left(\frac{1}{k_{\text{on}} + k_d} + \frac{1}{k_{\text{on}} + 2k_d} \right) \frac{k_{\text{on}}k_{\text{off}}}{k_{\text{on}} + k_{\text{off}} + k_d} \\ &+ 2\bar{\lambda}^2 n^4 \frac{k_d}{(k_{\text{on}} + k_d)(k_{\text{on}} + 2k_d)} \frac{k_{\text{on}}k_{\text{off}}}{k_{\text{on}} + k_{\text{off}} + k_d}. \end{aligned}$$

Similarly, we can show

$$\begin{aligned} & \int_0^{+\infty} \bar{b}(t) f_{\text{on}}(t) dt + \bar{M}'_{\text{ini}}(0) [\tilde{f}_{\text{off}}(k_d) \tilde{f}_{\text{on}}(k_d) - \tilde{f}_{\text{off}}(2k_d) \tilde{f}_{\text{on}}(2k_d)] \\ &= \frac{n(n-1)(2n-1)}{6} + \frac{n(n-1)k_{\text{on}}k_{\text{off}}(k_{\text{on}} + k_{\text{off}} + 3k_d)}{2(k_{\text{on}} + k_{\text{off}} + k_d)(k_{\text{on}} + 2k_d)(k_{\text{off}} + 2k_d)} \\ &+ \frac{\bar{\lambda}n^2k_d}{k_{\text{on}} + k_d} \left[2n - 1 + \frac{k_d k_{\text{on}} k_{\text{off}} (k_{\text{on}} + k_{\text{off}} + 3k_d)}{(k_{\text{on}} + k_{\text{off}} + k_d)(k_{\text{on}} + 2k_d)(k_{\text{off}} + 2k_d)} \right] + \frac{2\bar{\lambda}^2 n^3 k_d^2}{(k_{\text{on}} + k_d)(k_{\text{on}} + 2k_d)}. \end{aligned}$$

Combining the above analysis, we finally arrive at

$$\bar{M}''_{\text{ini}}(0) = \xi_1 + \xi_2 \bar{\lambda} + \xi_3 \bar{\lambda}^2, \quad (56)$$

where

$$\begin{aligned} \xi_1 &= \frac{n(n-1)(2n-1)}{12} \frac{(k_{\text{on}} + 2k_d)(k_{\text{off}} + 2k_d)}{k_d(k_{\text{on}} + k_{\text{off}} + 2k_d)} + \frac{n(n-1)k_{\text{on}}k_{\text{off}}}{4k_d(k_{\text{on}} + k_{\text{off}} + k_d)} \frac{k_{\text{on}} + k_{\text{off}} + 3k_d}{k_{\text{on}} + k_{\text{off}} + 2k_d} \\ &+ \frac{[n(n-1)]^2 k_{\text{on}}k_{\text{off}}(k_{\text{on}} + 2k_d)(k_{\text{off}} + 2k_d)}{4k_d^2(k_{\text{on}} + k_{\text{off}} + k_d)(k_{\text{on}} + k_{\text{off}} + 2k_d)}, \end{aligned} \quad (D5a)$$

$$\begin{aligned} \xi_2 &= \frac{n^2(2n-1)(k_{\text{on}} + 2k_d)(k_{\text{off}} + 2k_d)}{4(k_{\text{on}} + k_d)(k_{\text{on}} + k_{\text{off}} + 2k_d)} + \frac{1}{2} \frac{n^2}{k_{\text{on}} + k_d} \frac{nk_{\text{on}}k_{\text{off}}}{k_{\text{on}} + k_{\text{off}} + k_d} \frac{k_{\text{on}} + k_{\text{off}} + 3k_d}{k_{\text{on}} + k_{\text{off}} + 2k_d} \\ &+ \frac{n^3(n-1)k_{\text{on}}k_{\text{off}}(2k_{\text{on}} + 3k_d)(k_{\text{off}} + 2k_d)}{2k_d(k_{\text{on}} + k_d)(k_{\text{on}} + k_{\text{off}} + k_d)(k_{\text{on}} + k_{\text{off}} + 2k_d)}, \end{aligned} \quad (D5b)$$

$$\xi_3 = \frac{n^3(k_{\text{off}} + 2k_d)}{(k_{\text{on}} + k_d)(k_{\text{on}} + k_{\text{off}} + 2k_d)} \left(\frac{nk_{\text{on}}k_{\text{off}}}{k_{\text{on}} + k_{\text{off}} + k_d} + k_d \right). \quad (D5c)$$

Apparently, Eq. (D6) reduces Eq. (C1) if $n = 1$.

Note that Eq. (D2) can be rewritten as

$$\langle \bar{m}^2 \rangle_k = \langle \bar{m} \rangle_k + \eta_1 - \eta_2 + \frac{\bar{M}''_{\text{ini}}(0)}{\langle \tau_{\text{on}} \rangle + \langle \tau_{\text{off}} \rangle} \left[\frac{1}{k_{\text{off}} + 2k_d} + \frac{\tilde{f}_{\text{off}}(2k_d)}{k_{\text{on}} + 2k_d} \right], \quad (D6)$$

where

$$\eta_1 = \frac{1}{\langle \tau_{\text{on}} \rangle + \langle \tau_{\text{off}} \rangle} \int_0^{+\infty} \left[-\frac{n(n-1)(n-2)}{3} + n^2(n-2)a(t) + k^3b(t) \right] e^{-k_{\text{on}}t} dt + \frac{2\bar{M}'_{\text{ini}}(0)\tilde{f}_{\text{off}}(k_d)}{\langle \tau_{\text{on}} \rangle + \langle \tau_{\text{off}} \rangle} \int_0^{+\infty} e^{-k_d t} e^{-k_{\text{on}}t} \bar{a}(t) dt \quad (D6a)$$

and

$$\eta_2 = \frac{\bar{M}'_{\text{ini}}(0)}{\langle \tau_{\text{on}} \rangle + \langle \tau_{\text{off}} \rangle} \left[\frac{1}{k_{\text{off}} + 2k_d} + \frac{\tilde{f}_{\text{off}}(2k_d)}{k_{\text{on}} + 2k_d} \right]. \quad (D6b)$$

By calculations, we can show

$$\begin{aligned} \eta_1 &= -\frac{1}{3} \frac{n(n-1)(n-2)}{\langle \tau_{\text{on}} \rangle + \langle \tau_{\text{off}} \rangle} \frac{1}{k_{\text{on}}} + \frac{1}{2} \frac{[n(n-1)]^2}{\langle \tau_{\text{on}} \rangle + \langle \tau_{\text{off}} \rangle} \frac{k_{\text{off}}}{k_d(k_{\text{on}} + k_{\text{off}} + k_d)} \\ &+ \frac{\bar{\lambda}n^2(n-1)}{\langle \tau_{\text{on}} \rangle + \langle \tau_{\text{off}} \rangle} \left[\frac{2k_d}{k_{\text{on}}(k_{\text{on}} + k_d)} + n \left(\frac{1}{k_{\text{on}} + k_d} + \frac{1}{k_{\text{on}} + 2k_d} \right) \frac{k_{\text{off}}}{k_{\text{on}} + k_{\text{off}} + k_d} \right] \\ &+ \frac{2\bar{\lambda}^2 n^3}{\langle \tau_{\text{on}} \rangle + \langle \tau_{\text{off}} \rangle} \left(\frac{k_d}{k_{\text{on}}} + \frac{nk_{\text{off}}}{k_{\text{on}} + k_{\text{off}} + k_d} \right) \frac{k_d}{(k_{\text{on}} + k_d)(k_{\text{on}} + 2k_d)} \end{aligned}$$

and

$$\begin{aligned} \eta_2 &= \frac{1}{2} \frac{n(n-1)}{\langle \tau_{\text{on}} \rangle + \langle \tau_{\text{off}} \rangle} \frac{(k_{\text{on}} + k_d)(k_{\text{off}} + k_d)}{k_d(k_{\text{on}} + k_{\text{off}} + k_d)} \frac{k_{\text{on}} + k_{\text{off}} + 2k_d}{k_{\text{on}} + 2k_d} \frac{1}{k_{\text{off}} + 2k_d} \\ &+ \frac{n^2\bar{\lambda}}{\langle \tau_{\text{on}} \rangle + \langle \tau_{\text{off}} \rangle} \frac{k_{\text{off}} + k_d}{k_{\text{on}} + k_{\text{off}} + k_d} \frac{k_{\text{on}} + k_{\text{off}} + 2k_d}{k_{\text{on}} + 2k_d} \frac{1}{k_{\text{off}} + 2k_d}. \end{aligned}$$

Substituting the expressions of I_1 , I_2 , and $\bar{M}_{\text{ini}}''(0)$ into Eq. (D6), we find that the second-order raw moments of mRNA are expressed as

$$\langle \bar{m}^2 \rangle = \langle \bar{m} \rangle + \frac{c_1 + c_2 \bar{\lambda} + c_3 \bar{\lambda}^2}{\langle \tau_{\text{on}} \rangle + \langle \tau_{\text{off}} \rangle}, \quad (\text{D7})$$

where c_i ($1 \leq i \leq 3$) are constants depending on model parameters, and

$$c_1 = \frac{n(n-1)(n-2)}{6} \frac{k_{\text{on}} + 2k_d}{k_d k_{\text{on}}} + \frac{[n(n-1)]^2}{4} \frac{k_{\text{off}}(k_{\text{on}} + 2k_d)}{k_d^2(k_{\text{on}} + k_{\text{off}} + k_d)}, \quad (\text{D7a})$$

$$c_2 = \frac{n^2(n-1)(k_{\text{on}} + 2k_d)}{k_{\text{on}}(k_{\text{on}} + k_d)} + \frac{n^2(n-1)k_{\text{off}}}{2(k_{\text{on}} + k_d)} \left[\frac{n(2k_{\text{on}} + 3k_d)}{k_d(k_{\text{on}} + k_{\text{off}} + k_d)} + \frac{k_{\text{on}}(k_{\text{on}} + k_{\text{off}} + 3k_d)}{(k_{\text{on}} + 2k_d)(k_{\text{off}} + 2k_d)} \right], \quad (\text{D7b})$$

$$c_3 = \frac{n^3}{k_{\text{on}} + k_d} \left(\frac{nk_{\text{off}}}{k_{\text{on}} + k_{\text{off}} + k_d} + \frac{k_d}{k_{\text{on}}} \right). \quad (\text{D7c})$$

Similarly, we can derive the analytical expressions of mRNA raw moments of higher orders.

-
- [1] M. I. Robson, A. R. Ringel, and S. Mundlos, Regulatory landscaping: How enhancer-promoter communication is sculpted in 3D, *Mol. Cell* **74**, 1110 (2019).
 - [2] M. A. Zabidi and A. Stark, Regulatory enhancer–core-promoter communication via transcription factors and cofactors, *Trends Genet.* **32**, 801 (2016).
 - [3] R. Stadhouders, G. J. Filion, and T. Graf, Transcription factors and 3D genome conformation in cell-fate decisions, *Nature (London)* **569**, 345 (2019).
 - [4] R. Andersson and A. Sandelin, Determinants of enhancer and promoter activities of regulatory elements, *Nat. Rev. Genet.* **21**, 71 (2020).
 - [5] S. Schoenfelder and P. Fraser, Long-range enhancer–promoter contacts in gene expression control, *Nat. Rev. Genet.* **20**, 437 (2019).
 - [6] V. Haberle and A. Stark, Eukaryotic core promoters and the functional basis of transcription initiation, *Nat. Rev. Mol. Cell Biol.* **19**, 621 (2018).
 - [7] S. Yunger, L. Rosenfeld, Y. Garini, and Y. Shav-Tal, Single-allele analysis of transcription kinetics in living mammalian cells, *Nat. Methods* **7**, 631 (2010).
 - [8] I. Golding, J. Paulsson, S. M. Zawilski, and E. C. Cox, Real-time kinetics of gene activity in individual bacteria, *Cell* **123**, 1025 (2005).
 - [9] T. Muramoto, D. Cannon, M. Gierliński, A. Corrigan, G. J. Barton, and J. R. Chubb, Live imaging of nascent RNA dynamics reveals distinct types of transcriptional pulse regulation, *Proc. Natl. Acad. Sci. USA* **109**, 7350 (2012).
 - [10] A. Raj, C. S. Peskin, D. Tranchina, D. Y. Vargas, and S. Tyagi, Stochastic mRNA synthesis in mammalian cells, *PLoS Biol.* **4**, e309 (2006).
 - [11] J. R. Chubb, T. Treck, S. M. Shenoy, and R. H. Singer, Transcriptional pulsing of a developmental gene, *Curr. Biol.* **16**, 1018 (2006).
 - [12] J. Paulsson, Models of stochastic gene expression, *Phys. Life Rev.* **2**, 157 (2005).
 - [13] J. Peccoud and B. Ycart, Markovian modelling of gene product synthesis, *Theor. Popul. Biol.* **48**, 222 (1995).
 - [14] V. Shahrezaei and P. S. Swain, Analytical distributions for stochastic gene expression, *Proc. Natl. Acad. Sci. USA* **105**, 17256 (2008).
 - [15] T. B. Kepler and T. C. Elston, Stochasticity in transcriptional regulation: Origins, consequences, and mathematical representations, *Biophys. J.* **81**, 3116 (2001).
 - [16] D. R. Larson, What do expression dynamics tell us about the mechanism of transcription?, *Curr. Opin. Genet. Dev.* **21**, 591 (2011).
 - [17] N. Friedman, L. Cai, and X. S. Xie, Linking stochastic dynamics to population distribution: An analytical framework of gene expression, *Phys. Rev. Lett.* **97**, 168302 (2006).
 - [18] J. J. Zhang, L. N. Chen, and T. S. Zhou, Analytical distribution and tunability of noise in a model of promoter progress, *Biophys. J.* **102**, 1247(2012).
 - [19] J. J. Zhang and T. S. Zhou, Promoter-mediated transcriptional dynamics, *Biophys. J.* **106**, 479 (2014).
 - [20] J. M. Pedraza and J. Paulsson, Effects of molecular memory and bursting on fluctuations in gene expression, *Science* **319**, 339 (2008).
 - [21] T. Guérin, N. Levernier, O. Bénichou, and R. Voituriez, Mean first-passage times of non-Markovian random walkers in confinement, *Nature (London)* **534**, 356(2016).
 - [22] J. J. Zhang and T. S. Zhou, Markovian approaches to modeling intracellular reaction processes with molecular memory, *Proc. Natl. Acad. Sci. USA* **116**, 23542(2019).
 - [23] C. V. Harper, B. Finkenzstädt, D. J. Woodcock *et al.*, Dynamic analysis of stochastic transcription cycles, *PLoS Biol.* **9**, e1000607 (2011).
 - [24] M. R. Roussel and R. Zhu, Stochastic kinetics description of a simple transcription model, *Bull. Math. Biol.* **68**, 1681 (2006).
 - [25] M. Voliotis, N. Cohen, C. Molina-Paris, and T. B. Liverpool, Fluctuations, pauses, and backtracking in DNA transcription, *Biophys. J.* **94**, 334 (2008).
 - [26] G. Bel, B. Munsky, and I. Nemenman, The simplicity of completion time distributions for common complex biochemical processes, *Phys. Biol.* **7**, 016003 (2010).
 - [27] J. Makela, J. Lloyd-Price, O. Yli-Harja, and A. S. Ribeiro, Stochastic sequence-level model of coupled transcription and translation in prokaryotes, *BMC Bioinf.* **12**, 121 (2011).
 - [28] R. Roussel, On the distribution of transcription times, *Biomath.* **2**, 1307247 (2013).

- [29] M. Kandhavelu, A. Hakkinen, O. Yli-Harja, and A. S. Ribeiro, Single-molecule dynamics of transcription of the *lar* promoter, *Phys. Biol.* **9**, 026004 (2012).
 - [30] M. Kandhavelu, J. Lloyd-Price, A. Gupta, A. B. Muthukrishnan, O. Yli-Harja, and A. S. Ribeiro, Regulation of mean and noise of the in vivo kinetics of transcription under the control of the *lacIara-1* promoter, *FEBS Lett.* **586**, 3870 (2012).
 - [31] B. Choi, Y. Y. Cheng, S. Cinar, W. Ott, M. R. Bennett, K. Josic, and J. K. Kim, Bayesian inference of distributed time delay in transcriptional and translational regulation, *Bioinformatics* **36**, 586 (2020).
 - [32] T. Jia and R. V. Kulkarni, Intrinsic noise in stochastic models of gene expression with molecular memory and bursting, *Phys. Rev. Lett.* **106**, 058102 (2011).
 - [33] N. Kumar, A. Singh, and R. V. Kulkarni, Transcriptional bursting in gene expression: Analytical results for general stochastic models, *PLoS Comput. Biol.* **11**, e1004292 (2015).
 - [34] C. H. Shi, X. Y. Yang, J. J. Zhang, and T. S. Zhou, Stochastic modeling of the mRNA life process: A generalized master equation, *Biophys. J.* **122**, 4023(2023).
 - [35] J. Szavits-Nossan and R. Grima, Charting the landscape of stochastic gene expression models using queueing theory, [arXiv:2307.03253v1](https://arxiv.org/abs/2307.03253).
 - [36] E. Parzen, *Stochastic Processes* (Holden-Day, San Francisco, 1962); D. Heyman and M. Sobel, *Stochastic Models in Operations Research* (McGraw-Hill, New York, 1982).
 - [37] N. Kumar, T. Platini, and R. V. Kulkarni, Exact distributions for stochastic gene expression models with bursting and feedback, *Phys. Rev. Lett.* **113**, 268105 (2014).
 - [38] B. C. Arnold, Majorization: Here, there and everywhere, *Statist. Sci.* **22**, 407 (2007).
 - [39] A. Schwabe, K. N. Rybakova, and F. J. Bruggeman, Transcription stochasticity of complex gene regulation models, *Biophys. J.* **103**, 1152 (2012).
 - [40] Y. He and E. Barkai, Super- and sub-Poissonian photon statistics for single molecule spectroscopy, *J. Chem. Phys.* **122**, 184703 (2005).
 - [41] J. J. Zhang, Q. Nie, and T. S. Zhou, A moment-convergence method for stochastic analysis of biochemical reaction networks, *J. Chem. Phys.* **144**, 018620 (2016).
 - [42] S. H. Luo, Z. H. Wang, Z. Q. Zhang, T. S. Zhou, and J. J. Zhang, Genome-wide inference reveals that feedback regulations constrain promoter-dependent transcriptional burst kinetics, *Nucl. Acids Res.* **51**, 68 (2023).
 - [43] J. Zuin *et al.*, Nonlinear control of transcription through enhancer-promoter interactions, *Nature (London)* **604**, 571 (2022).
- Correction:* Incorrect information was used for the affiliation of the fifth author. A new affiliation and affiliation indicator have been inserted.