

Article

Skewness and Kurtosis of mRNA Distributions in Stochastic Gene Transcription with Promoter Switching

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Abstract

Gene transcription is inherently stochastic, and promoter-switching-induced transcriptional bursting generates substantial cell-to-cell variability in mRNA abundance. Such variability is commonly characterized by the mean and variance; however, these low-order statistics fail to capture the geometric features of mRNA copy number distributions and may obscure mechanistic differences in promoter dynamics. In this work, we analyze a two-state stochastic gene transcription model and derive explicit analytical expressions for higher-order moments of mRNA abundance. We show that skewness and kurtosis provide mechanistically informative signatures of transcriptional bursting, explicitly depending on promoter switching kinetics and burst size. Our results demonstrate that distinct promoter dynamics can produce identical mean expression levels and variances while exhibiting markedly different skewness and kurtosis. The explicit analytical expressions derived here reveal how higher-order moments encode mechanistically informative signatures of transcriptional bursting through distributional asymmetry and heavy-tailed behavior. These results demonstrate that higher-order moments encode mechanistic information beyond mean–variance statistics and provide a powerful framework for distinguishing between different promoter-switching mechanisms in stochastic gene transcription.

Keywords: stochastic gene expression; promoter switching; transcriptional bursting; skewness and kurtosis; higher-order moments

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1. Introduction

Gene transcription is inherently stochastic, arising from the small copy numbers of transcription factors and RNA polymerases, as well as their random binding to gene regulatory sites [1–3]. Early theoretical and experimental studies established that intrinsic molecular fluctuations can produce pronounced cell-to-cell variability, even in genetically identical populations under homogeneous environmental conditions [3–6]. Beyond their fundamental stochasticity, gene regulatory programs are tightly linked to phenotypes and disease and are shaped by multiple regulatory layers, from genetic variation and epigenetic states to enhancer-mediated regulatory networks [7–11]. With the advent of single-cell and single-molecule experimental techniques, such variability has been directly observed at the mRNA level, revealing substantial heterogeneity in transcriptional output across individual cells [1,12,13]. Recent studies have further highlighted the importance of transcriptional

variability and its implications for gene regulation and disease [11,14]. Quantifying and interpreting this variability has therefore become a central challenge in systems biology and mathematical biology.

Variance and the Fano factor are among the most widely used statistical measures for characterizing transcriptional noise. These quantities effectively describe the overall dispersion of gene expression levels and have played an important role in elucidating the relationship between mean expression and noise [15–18]. However, variance-based measures provide only limited information about the geometric structure of the underlying mRNA copy-number distributions. In particular, they are insensitive to distributional asymmetry and tail behavior, which naturally arise from transcriptional bursting driven by stochastic promoter-switching dynamics [19–22]. A detailed understanding of the shape of mRNA distributions is therefore essential for uncovering the molecular mechanisms governing gene regulation and for accurately interpreting experimental data.

In principle, the full probability mass function of mRNA copy numbers contains complete information about distributional geometry. For simple stochastic gene transcription models, exact or approximate stationary distributions can sometimes be obtained [22–24]. However, for biologically realistic models with explicit promoter switching, feedback regulation, or time-dependent synthesis rates, analytical expressions for the full distribution are often unavailable or mathematically intractable [25,26]. Even when closed-form solutions exist, they do not necessarily provide intuitive or easily comparable summaries for experimental analysis. This motivates introducing reduced statistical descriptors that capture essential geometric features of the distribution while remaining analytically tractable and experimentally accessible.

In this work, we focus on two higher-order statistical measures, *skewness* and *kurtosis*, defined as the third and fourth standardized moments, respectively. Skewness quantifies the asymmetry of the mRNA distribution and indicates whether transcriptional fluctuations are biased toward rare high-expression events or toward low-expression states. Kurtosis characterizes the sharpness of the distribution peak and the heaviness of its tails relative to a Gaussian distribution, thereby reflecting the prevalence of extreme transcriptional events. By construction, both quantities are dimensionless and thus enable direct comparisons across genes, experimental conditions, and modeling frameworks. Recent studies have shown that these higher-order moments serve as sensitive indicators of transcriptional bursting and gene expression heterogeneity, particularly in large single-cell datasets [13,15].

In contrast to most existing studies that focus primarily on mean expression levels, variance, or the Fano factor, we derive closed-form expressions for skewness and excess kurtosis and systematically analyze their dependence on promoter-switching kinetics and burst size. We show that distinct promoter dynamics can produce identical mean expression levels and variances while exhibiting markedly different skewness and kurtosis. These higher-order moments provide additional geometric information about the mRNA distribution. In particular, skewness and kurtosis enable discrimination between different promoter-switching mechanisms that may be indistinguishable at the level of mean and variance alone.

The remainder of this article is organized as follows. In Section 2, we introduce a two-state stochastic gene transcription model with explicit promoter switching and present its mathematical formulation, followed by the derivation of higher-order moments of the mRNA distribution. In Section 3, we analyze several promoter-switching regimes, including the fast-switching, slow-switching, and bursty transcription regimes. In Section 4, we perform numerical simulations to investigate how skewness, kurtosis, and the coefficient of variation depend on key kinetic parameters.

2. The Model and Expressions of Skewness and Kurtosis

2.1. Two-State Gene Transcription Model

We consider a stochastic two-state gene transcription model, which has been widely used to characterize promoter-mediated transcriptional bursting and has also been adopted in our previous studies [17,27]. A schematic representation of the model is shown in Figure 1. In this framework, the promoter of a gene stochastically switches between two discrete states: inactive (OFF) and active (ON). To describe our model more clearly, we make the following assumptions:

- (i) The promoter switching dynamics between the OFF and ON states follow a continuous-time Markov process with constant transition rates λ and γ , implying exponentially distributed residence times in each state.
- (ii) Transcription occurs only when the promoter is in the ON state, with mRNA synthesis events modeled as a Poisson process with constant rate ν .
- (iii) mRNA molecules degrade independently according to a first-order reaction with a constant rate δ .
- (iv) All stochastic processes are assumed to be memoryless and time-homogeneous.
- (v) A unique stationary distribution exists provided that all kinetic parameters are positive.

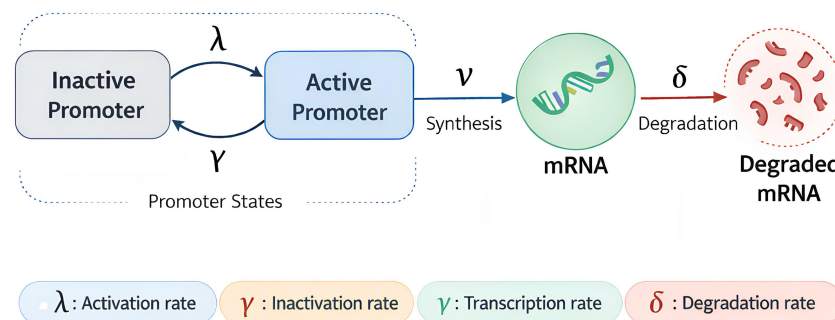


Figure 1. Schematic diagram of stochastic gene transcription with promoter switching. The gene promoter randomly switches between inactive and active states with rates λ and γ , respectively. Transcription occurs only when the promoter is active, producing mRNA molecules at rate ν . mRNA molecules are degraded independently at rate δ .

Let $M(t)$ denote the total number of mRNA transcripts present in a cell at time t , where $M(t)$ takes values in the set of non-negative integers. We introduce an indicator variable $I(t)$ to represent the promoter state at time t , with $I(t) = 0$ corresponding to the gene OFF state and $I(t) = 1$ corresponding to the gene ON state. The joint probability distributions are defined as

$$P_0(m, t) = \text{Prob}\{M(t) = m, I(t) = 0\},$$

$$P_1(m, t) = \text{Prob}\{M(t) = m, I(t) = 1\}.$$

The time evolution of the joint probabilities $P_0(m, t)$ and $P_1(m, t)$ is governed by the following system of chemical master equations (CMEs):

$$\frac{dP_0(m, t)}{dt} = \gamma P_1(m, t) - \lambda P_0(m, t) + \delta[(m+1)P_0(m+1, t) - mP_0(m, t)], \quad (1)$$

$$\begin{aligned} \frac{dP_1(m, t)}{dt} = & \lambda P_0(m, t) - \gamma P_1(m, t) + \delta[(m+1)P_1(m+1, t) - mP_1(m, t)] \\ & + \nu[P_1(m-1, t) - P_1(m, t)], \end{aligned} \quad (2)$$

for $m \geq 0$, with the convention that $P_1(-1, t) = 0$. The terms in Equations (1) and (2) account for stochastic switching of the promoter state, mRNA synthesis in the active state, and first-order degradation of mRNA molecules. This coupled system of master equations fully characterizes the stochastic dynamics of the two-state transcription process.

The marginal probability mass function of the mRNA copy number is then given by

$$P(m, t) = P_0(m, t) + P_1(m, t),$$

which represents the probability that m mRNA molecules are present in the cell at time t . In principle, the probability mass function $P(m, t)$ provides a complete description of the distribution of mRNA copy numbers across a cell population. However, for transcription models of even moderate complexity, obtaining explicit analytical expressions for $P(m, t)$ is often intractable. Even for the two-state model considered here, closed-form solutions are available only under restrictive assumptions and are typically expressed in terms of integrals or special functions. Consequently, rather than relying exclusively on the full probability mass function, we focus on higher-order statistical descriptors, such as skewness and kurtosis, to characterize the geometric features of the mRNA copy-number distribution. These quantities provide tractable and informative measures of transcriptional variability when explicit distributional forms are unavailable.

2.2. Moments, Skewness, and Kurtosis of Transcript Distributions

Let $\mu_k(t)$ denote the k th moment of the mRNA transcript number at time t . By definition,

$$\mu_k(t) = \mathbb{E}[M^k(t)] = \sum_{m=0}^{\infty} m^k P(m, t),$$

where $P(m, t)$ is the marginal probability mass function of the mRNA copy number.

The first moment $\mu_1(t)$ corresponds to the mean mRNA copy number and characterizes the average transcription level across the cell population. The second central moment defines the variance,

$$\sigma^2(t) = \mathbb{E}[(M(t) - \mu_1(t))^2] = \mu_2(t) - \mu_1^2(t),$$

which quantifies the magnitude of transcriptional fluctuations around the mean.

To further characterize the geometric properties of the transcript number distribution, we consider higher-order standardized moments. The skewness is defined as

$$\text{Skew}(t) = \frac{\mathbb{E}[(M(t) - \mu_1(t))^3]}{\sigma^3(t)}, \quad (3)$$

which measures the degree of asymmetry of the distribution. The excess kurtosis is defined by

$$\text{Kurt}(t) = \frac{\mathbb{E}[(M(t) - \mu_1(t))^4]}{\sigma^4(t)} - 3, \quad (4)$$

and quantifies the heaviness of the distribution tails relative to a Gaussian distribution. Equations (3) and (4) show that both skewness and kurtosis are fully determined by the first four moments of the transcript number distribution. Consequently, analyzing the dynamics of these moments provides direct insight into the temporal evolution of the shape of mRNA distributions arising from stochastic gene transcription.

2.3. Moment Expressions and Higher-Order Statistics

The derivation proceeds in three main steps: (i) derive closed systems of ordinary differential equations for the promoter-state-resolved moments from CMEs; (ii) solve these equations at steady state to obtain explicit expressions for the moments μ_1, μ_2, μ_3 , and μ_4 ; (iii) compute the corresponding central moments and standardize them to obtain skewness and kurtosis. The full algebraic details are provided in Appendix A.

We now derive explicit expressions for the moments of the transcript number distribution. In the following analysis, we count only newly synthesized mRNA molecules and assume that the promoter initially resides in the gene OFF state at time $t = 0$. Accordingly, the initial condition is

$$M(0) = 0, \quad I(0) = 0. \quad (5)$$

Condition (5) implies

$$P_0(0,0) = 1, \quad P_0(m,0) = 0 \text{ for } m \geq 1, \quad P_1(m,0) = 0 \text{ for } m \geq 0.$$

Consequently, all moments vanish at the initial time,

$$\mu_k(0) = 0, \quad k \geq 1.$$

Using calculations analogous to those in previous studies, the time-dependent mean mRNA copy number is obtained as

$$\mu_1(t) = \frac{\nu\lambda}{\delta(\lambda + \gamma)} - \frac{\nu\lambda}{\delta(\lambda + \gamma - \delta)}e^{-\delta t} + \frac{\nu\lambda}{(\lambda + \gamma)(\lambda + \gamma - \delta)}e^{-(\lambda + \gamma)t}. \quad (6)$$

The last two terms in (6) exponentially decay to zero as $t \rightarrow \infty$. Hence, as $t \rightarrow \infty$, the mean mRNA copy number converges to the steady-state value

$$\mu_1 = \frac{\nu\lambda}{\delta(\lambda + \gamma)}.$$

In fact, under Assumption (v) that all kinetic parameters are strictly positive, the Markov process defined by Equations (1) and (2) is ergodic and admits a unique stationary distribution. Although time-dependent expressions for the moments can be derived, all biological interpretations and numerical results in this study concern steady-state behavior. Therefore, we focus primarily on steady-state quantities, while transient expressions are included only briefly to demonstrate convergence toward equilibrium.

Similarly, the second moment of transcripts at steady state is given by

$$\mu_2 = \mu_1 \left[1 + \frac{\nu(\delta + \lambda)}{\delta(\delta + \lambda + \gamma)} \right].$$

The variance in the transcript number distribution then follows as

$$\sigma^2 = \mu_2 - \mu_1^2 = \mu_1 \left[1 + \frac{\nu\gamma}{(\lambda + \gamma)(\delta + \lambda + \gamma)} \right],$$

where σ denotes the standard deviation.

The squared coefficient of variation and the Fano factor are therefore given by

$$\text{CV}^2 = \frac{\sigma^2}{\mu_1^2} = \frac{1}{\mu_1} + \frac{\delta\gamma}{\lambda(\delta + \lambda + \gamma)}, \quad \Phi = \frac{\sigma^2}{\mu_1} = 1 + \frac{\nu\gamma}{(\lambda + \gamma)(\delta + \lambda + \gamma)}.$$

These quantities characterize the dispersion of transcript numbers across single cells but do not fully describe the shape of the underlying distribution.

To further elucidate the distributional geometry of mRNA copy numbers, we consider the skewness and kurtosis. By definition,

$$\text{Skew} = \frac{\mu_3 - 3\mu_1\mu_2 + 2\mu_1^3}{\sigma^3},$$

$$\text{Kurt} = \frac{\mu_4 - 4\mu_1\mu_3 + 6\mu_1^2\mu_2 - 3\mu_1^4}{\sigma^4} - 3,$$

where μ_3 and μ_4 denote the third and fourth moments of the transcript number distribution, respectively. Using the moment equations derived from CMEs and solving the resulting algebraic systems at steady state, we obtain the following closed-form expressions for the higher-order moments:

$$\mu_3 = \mu_1 \left[1 + \frac{3\nu(\delta + \lambda)}{\delta(\delta + \lambda + \gamma)} + \frac{\nu^2(\delta + \lambda)(2\delta + \lambda)}{\delta^2(\delta + \lambda + \gamma)(2\delta + \lambda + \gamma)} \right],$$

$$\mu_4 = \mu_1 \left[1 + \frac{7\nu(\delta + \lambda)}{\delta(\delta + \lambda + \gamma)} + \frac{6\nu^2(\delta + \lambda)(2\delta + \lambda)}{\delta^2(\delta + \lambda + \gamma)(2\delta + \lambda + \gamma)} + \frac{\nu^3(\delta + \lambda)(2\delta + \lambda)(3\delta + \lambda)}{\delta^3(\delta + \lambda + \gamma)(2\delta + \lambda + \gamma)(3\delta + \lambda + \gamma)} \right].$$

These expressions explicitly reveal how skewness and kurtosis depend on transcriptional kinetics, promoter switching dynamics, and mRNA degradation rates.

Skewness and kurtosis provide biologically meaningful information about the shape of the mRNA copy number distribution beyond what is captured by the mean and variance. A positive value of Skew indicates a pronounced right tail, corresponding to rare cells exhibiting exceptionally high transcript abundance. Such asymmetry is a characteristic feature of stochastic gene expression and is commonly associated with transcriptional bursting.

Kurtosis quantifies the weight of the distribution tails relative to a Gaussian distribution. A large positive value of kurtosis implies an elevated probability of extreme transcriptional events, reflecting strong cell-to-cell heterogeneity. Together, skewness and kurtosis offer intuitive and quantitative measures of how transcriptional noise manifests at the population level and how strongly the mRNA distribution deviates from symmetric, light-tailed behavior.

3. Asymptotic Analysis

The explicit moment expressions derived above enable a systematic asymptotic analysis of the skewness and kurtosis in biologically relevant limits. In this section, we summarize the leading-order behavior of these higher-order statistics in three canonical parameter regimes that are commonly encountered in stochastic gene expression models. All kinetic parameters are nondimensionalized by the mRNA degradation rate δ .

The asymptotic structure of the skewness and kurtosis is primarily governed by the relative timescales of promoter switching and mRNA degradation. Qualitatively distinct transcriptional behaviors can emerge depending on whether promoter switching is fast or slow compared to transcript turnover, each associated with characteristic distributional signatures [28–31]. Accordingly, we classify the asymptotic regimes into fast promoter switching, slow promoter switching, and a bursty transcription limit, and for each regime, we derive the leading-order asymptotic expressions for skewness and kurtosis and interpret their implications for transcriptional variability and distributional shape.

Slow-promoter-switching regime. Assume

$$\lambda, \gamma \ll 1,$$

so that mRNA degradation occurs much faster than promoter switching [32,33]. In this regime, transcription proceeds in well-separated episodes, leading to pronounced cell-to-cell heterogeneity. Introducing the ratio $\alpha = \gamma/\lambda$, the asymptotic expressions for the steady-state moments are

$$\begin{aligned}\mu_2 &\approx \mu_1[1 + \mu_1(1 + \alpha)], \\ \mu_3 &\approx \mu_1[1 + 3\mu_1(1 + \alpha) + \mu_1^2(1 + \alpha)^2], \\ \mu_4 &\approx \mu_1[1 + 7\mu_1(1 + \alpha) + 6\mu_1^2(1 + \alpha)^2 + \mu_1^3(1 + \alpha)^3].\end{aligned}$$

Consequently, the skewness and excess kurtosis, respectively, admit the asymptotic forms

$$\begin{aligned}\text{Skew} &\approx \frac{\mu_1^3\alpha^2 - \mu_1^3\alpha + 3\mu_1^2\alpha + \mu_1}{(\mu_1 + \mu_1^2\alpha)^{3/2}}, \\ \text{Kurt} &\approx \frac{\mu_1^4(\alpha^3 - 4\alpha^2 + \alpha) + 6\mu_1^3(\alpha^2 - \alpha) + 7\mu_1^2\alpha + \mu_1}{\mu_1^2(1 + \mu_1\alpha)^2} - 3.\end{aligned}$$

Both quantities increase with the ratio α , reflecting strong distributional asymmetry and heavy-tailed behavior induced by long inactive periods and rare promoter activation events. Although the mRNA distribution may exhibit bimodality in this regime, the large excess kurtosis primarily originates from intermittent transcriptional bursts interspersed with long OFF periods, which generate strong deviations from Poisson-like statistics.

Two representative limits, corresponding to simplified expressions for the variance, skewness, and kurtosis, are summarized in Table 1. To make the asymptotic results precise, we consider the steady-state moments in the slow-promoter-switching regime. Here μ_1 denotes the exact steady-state mean and $\alpha = \gamma/\lambda$. The results are derived under the assumption that μ_1 is sufficiently large, and we examine two representative limits: (i) $\mu_1\alpha \gg 1$ with $\alpha \gg 1$, and (ii) $\mu_1 \gg 1$ with $\alpha \approx 1$. In each case, the asymptotic regime and the corresponding scaling relation between μ_1 and α are held fixed, and the expressions reported in Table 1 correspond to leading-order approximations obtained from the exact steady-state formulas of the moments, skewness, and excess kurtosis.

Table 1. Asymptotic expressions for steady-state mRNA statistics in the slow-promoter-switching regime under different parameter limits.

Condition	Variance	CV ²	Skewness	Kurtosis
$\mu_1\alpha \gg 1, \alpha \gg 1$	$\alpha\mu_1^2$	α	$\sqrt{\alpha}$	$\alpha - 3$
$\mu_1 \gg 1, \alpha \approx 1$	μ_1^2	1	$3/\mu_1$	−2

The entries in Table 1 are obtained by substituting the slow-switching asymptotic expansions of μ_2 , μ_3 , and μ_4 into the exact steady-state definitions of the variance, skewness, and excess kurtosis, and retaining the leading-order terms under each scaling assumption. Detailed derivations are provided in Appendix B.

Fast-promoter-switching regime. Assume

$$\lambda, \gamma \gg 1,$$

so that promoter switching is much faster than mRNA degradation [34]. In this limit, the promoter rapidly equilibrates on the timescale of mRNA dynamics, and the system effectively reduces to a single birth–death process with mean

$$\mu_1 = \frac{\nu\lambda}{\lambda + \gamma}.$$

Expanding the higher-order moments yields

$$\begin{aligned}\mu_2 &\approx \mu_1^2 + \mu_1, \\ \mu_3 &\approx \mu_1^3 + 3\mu_1^2 + \mu_1, \\ \mu_4 &\approx \mu_1^4 + 6\mu_1^3 + 7\mu_1^2 + \mu_1.\end{aligned}$$

Accordingly, the skewness and excess kurtosis scale asymptotically as

$$\text{Skew} \approx \frac{1}{\sqrt{\mu_1}}, \quad \text{Kurt} \approx \frac{1}{\mu_1}.$$

Thus, both skewness and excess kurtosis decrease with increasing mean expression level, and the mRNA copy-number distribution approaches a Poisson-like form characterized by weak asymmetry and light tails.

Bursty transcription regime. Assume

$$\gamma \gg \max\{1, \lambda\}, \quad \nu \gg 1,$$

while keeping the burst size

$$B = \frac{\nu}{\gamma}$$

finite [35,36]. In this limit, transcription occurs in rare but intense bursts separated by long inactive periods. The mean mRNA copy number is given by

$$\mu_1 = \lambda B.$$

The higher-order moments admit the asymptotic expressions

$$\begin{aligned}\mu_2 &\approx \mu_1(1 + B + \mu_1), \\ \mu_3 &\approx \mu_1[1 + 3(B + \mu_1) + (B + \mu_1)(2B + \mu_1)], \\ \mu_4 &\approx \mu_1[1 + 7(B + \mu_1) + 6(B + \mu_1)(2B + \mu_1) + (B + \mu_1)(2B + \mu_1)(3B + \mu_1)].\end{aligned}$$

From these expressions, the skewness and excess kurtosis scale as

$$\begin{aligned}\text{Skew} &\approx \frac{1 + 2B}{\sqrt{(1 + B)\mu_1}}, \\ \text{Kurt} &\approx \frac{1 + 6B + 6B^2}{(1 + B)\mu_1}.\end{aligned}$$

These results show that increasing the burst size amplifies both skewness and excess kurtosis, even when the mean expression level is held fixed, providing a natural mechanism for generating highly asymmetric, heavy-tailed mRNA distributions.

In the bursty transcription limit, the steady-state mRNA copy number distribution converges to a negative binomial distribution with mean μ_1 and variance

$$\sigma^2 = \mu_1(1 + B),$$

where B denotes the burst size [37,38]. The probability mass function of the negative binomial distribution is

$$P(m) = \binom{m+r-1}{m} p^r (1-p)^m,$$

with parameters

$$r = \frac{\mu_1^2}{\sigma^2 - \mu_1} = \frac{\mu_1}{B}, \quad p = \frac{\mu_1}{\sigma^2} = \frac{1}{1+B}.$$

For a random variable $X \sim NB(r, p)$, direct calculation of the moments yields

$$\mathbb{E}(X) = \mu_1,$$

$$\mathbb{E}(X^2) = \mu_1(1+B+\mu_1),$$

which implies the variance $\sigma^2 = \mu_1(1+B)$. Similarly, the skewness and excess kurtosis are given by

$$\text{Skew} = \frac{1+2B}{\sqrt{(1+B)\mu_1}},$$

$$\text{Kurt} = \frac{1+6B+6B^2}{(1+B)\mu_1}.$$

Our calculations show that, in the bursty transcription limit, the negative binomial distribution matches the first four moments of the exact mRNA distribution in the strict asymptotic regime. For finite parameter values, however, small deviations may arise due to higher-order corrections beyond the asymptotic approximation.

The relative timescales of promoter switching and mRNA degradation critically shape transcriptional variability and distributional form. In the fast-switching regime, rapid equilibration between active and inactive promoter states leads to transcription at an effectively averaged rate [29,39], resulting in weak bursting and near-Poisson statistics. In contrast, slow promoter switching produces long inactive periods punctuated by rare activation events that generate intense transcriptional bursts [1,21,40]. This temporal clustering yields highly asymmetric and heavy-tailed mRNA distributions, characterized by large positive skewness and elevated kurtosis [41]. Importantly, these higher-order statistical features persist even when mean expression levels are fixed, demonstrating that promoter switching kinetics encode mechanistic information beyond that captured by mean–variance statistics alone.

4. Numerical Simulations

In this section, all parameters are nondimensionalized by the mRNA degradation rate. This normalization does not affect the values or qualitative properties of the mean, skewness, or kurtosis of the mRNA distribution. All numerical simulations were performed using MATLAB R2023a, and the corresponding codes are provided as Supplementary Materials to ensure reproducibility. We note that higher-order moments, such as skewness and kurtosis, are sensitive to sampling variability and tail behavior; therefore, sufficiently large sample sizes are required to obtain reliable estimates.

To identify the dominant regulatory factors underlying the skewness and kurtosis of mRNA copy number distributions, we examined their joint dependence on the promoter activation rate λ and inactivation rate γ using three-dimensional representations. In Figure 2, the three-dimensional surfaces display the values of the skewness (A) and kurtosis (B) of the steady-state mRNA distribution as functions of λ and γ , both varying within the range $[0.05, 5]$. Red dots mark the locations of the minimum values on each surface. Fast promoter activation or inactivation, corresponding to small λ or γ , gives rise

to large skewness and kurtosis due to pronounced transcriptional bursting, whereas slow switching reduces higher-order variability. Interestingly, when λ and γ are comparable in magnitude and both are small, a global minimum of both skewness and kurtosis is observed. These surfaces provide a clear visualization of how promoter kinetics shape mRNA variability across a biologically relevant parameter space.

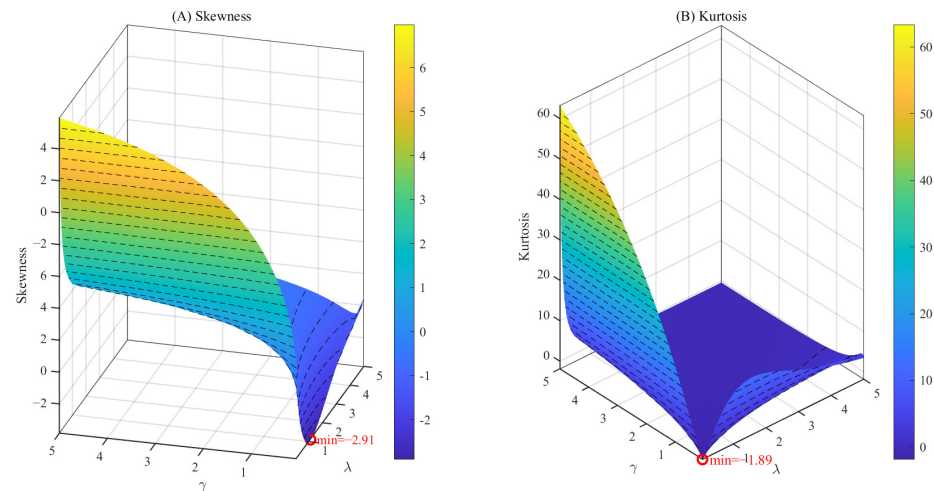


Figure 2. Skewness and kurtosis of the steady-state mRNA distribution as functions of the promoter switching rates λ and γ . Red dots indicate the local minimum values on each surface.

To further assess the impact of promoter activation dynamics, we compare two representative regimes, a slow- ($\lambda = \gamma = 0.05$) and fast-switching promoter ($\lambda = \gamma = 20$), while keeping all other parameters fixed. Figure 3 shows distributions of mRNA copy numbers obtained from exact Gillespie simulations of the two-state gene transcription model. For the slow-promoter-switching regime (Figure 3A), the gene spends long periods in the inactive state, interrupted by activation events. During each active period, mRNA molecules are produced rapidly, giving rise to pronounced transcriptional bursts. As a consequence, the distribution is strongly right-skewed (0.03). Moreover, the coexistence of low- and high-expression subpopulations may lead to a bimodal structure, in which probability mass is distributed between two modes rather than concentrated in extreme tails, resulting in a comparatively reduced kurtosis relative to strongly burst-dominated, heavy-tailed regimes (-1.89). In contrast, for the fast-promoter-switching regime (Figure 3B), frequent switching between the active and inactive states effectively averages transcriptional activity over time. This suppresses burstiness and yields a narrower and more symmetric mRNA distribution with increased skewness (0.13) and kurtosis (-0.05). In both regimes, the vertical lines denote the mean mRNA copy number. Analytical predictions derived from the exact expressions of the first four moments are in quantitative agreement with the simulation results, validating the theoretical analysis of mean expression levels and higher-order fluctuations.

To evaluate the validity of the negative binomial approximation in the bursty regime, we compared the mRNA distribution of the two-state transcription model with its negative binomial counterpart (Figure 4). The parameters $\nu = 200$, $\lambda = 0.05$, and $\gamma = 5$ correspond to slow promoter activation and large burst size ($B = \nu/\gamma = 40$), a regime in which the negative binomial approximation ($r = \mu_1/B$, $p = 1/(1+B)$) is expected to be accurate. As shown in Figure 4(left), the exact distribution obtained from CMEs is visually indistinguishable from the negative binomial distribution over most of the support, and the Pearson correlation coefficient is nearly unity ($R = 0.999999$). This confirms that the negative binomial provides an excellent global approximation of the distributional shape in the bursty transcription limit. However, a closer inspection of higher-order statistics

(Figure 4, right) reveals systematic deviations. While the mean and variance are well captured, the negative binomial approximation slightly overestimates the skewness and, more prominently, the excess kurtosis. In particular, the excess kurtosis differs by more than 15%, indicating that the negative binomial distribution predicts heavier tails than the mRNA distribution. It is worth noting that the agreement between the negative binomial distribution and the exact mRNA distribution, including the first four moments, holds strictly in the asymptotic bursty limit. In the numerical computation, however, the mRNA distribution is obtained from the truncated chemical master equation with a finite cutoff on the maximum mRNA copy number. This truncation introduces small deviations in the tail probabilities. Since higher-order moments, particularly skewness and kurtosis, are highly sensitive to tail behavior, these small discrepancies can lead to noticeable differences in their values. In particular, the negative binomial distribution exhibits a slightly heavier tail compared to the truncated distribution, resulting in an overestimation of kurtosis. This observation underscores that higher-order moments provide sensitive probes of tail behavior and can distinguish between distributions that are otherwise similar at the level of mean and variance.

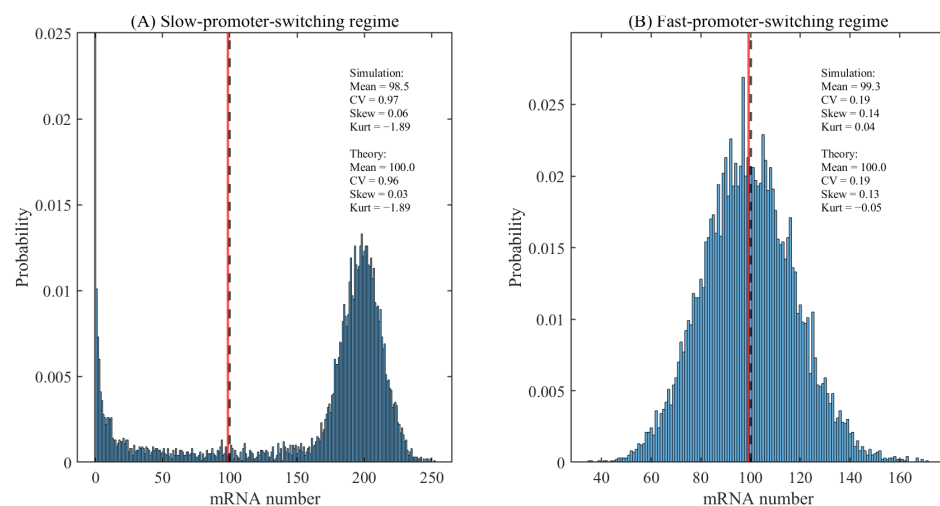


Figure 3. Steady-state mRNA distributions for different promoter switching regimes. (A) Slow- ($\lambda = \gamma = 0.05$) and (B) fast-promoter-switching regimes ($\lambda = \gamma = 20$).

The promoter switching parameters λ and γ play distinct and complementary roles in shaping the asymmetry and tail behavior of mRNA distributions. A small activation rate λ implies long inactive periods punctuated by rare transcriptional bursts, leading to pronounced right-skewness. Conversely, a large inactivation rate γ shortens active periods and concentrates transcriptional output into brief episodes, increasing the probability of extreme mRNA counts and thereby enhancing heavy-tailed behavior. As a result, skewness and kurtosis increase with the ratio γ/λ , providing a direct quantitative link between promoter switching kinetics and distributional geometry.

These results demonstrate that low-order moments such as the mean and variance do not uniquely characterize stochastic gene expression models with promoter switching. Distinct kinetic parameter sets may yield identical mean expression levels and noise magnitudes while exhibiting fundamentally different distributional shapes, as revealed by skewness and kurtosis. This highlights intrinsic limitations of inference strategies relying solely on second-order statistics.

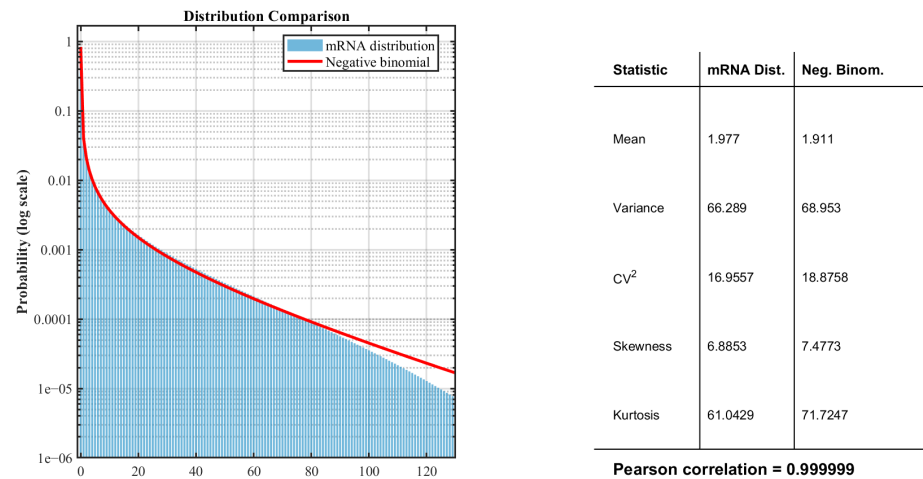


Figure 4. Comparison between the mRNA distribution and its negative binomial approximation. **Left** panel: The exact distribution obtained from the truncated CMEs (blue bars, logarithmic scale) is compared with the negative binomial distribution (red solid line). **Right** panel: Quantitative comparison of statistical measures, including mean, variance, coefficient of variation squared (CV^2), skewness, and excess kurtosis, together with the Pearson correlation coefficient between the two distributions.

In practice, skewness and kurtosis can be estimated from finite single-cell transcriptomic datasets using standard sample moment estimators. Because higher-order moments are more sensitive to rare events and tail fluctuations, their estimation is generally more susceptible to sampling noise than that of the mean or variance. Reliable estimation therefore typically requires larger sample sizes, particularly in regimes characterized by strong transcriptional bursting or heavy-tailed distributions. Nevertheless, the increasing availability of high-throughput single-cell RNA sequencing datasets, often comprising thousands to tens of thousands of cells, makes the practical estimation of higher-order moments increasingly feasible. In this context, our analytical results provide a valuable theoretical benchmark for interpreting experimentally measured skewness and kurtosis and for assessing their robustness against sampling noise.

While heavy-tailed distributions with positive kurtosis are typically associated with large burst sizes and rare extreme expression events within a single mode, negative kurtosis emerges when the distribution becomes flatter or bimodal. In slow promoter-switching regimes, intermittent activation can generate two subpopulations corresponding to low- and high-expression states, leading to a redistribution of probability mass away from the tails. As a result, kurtosis is reduced and may become negative. This distinction highlights that heavy-tailed behavior reflects burst intensity, whereas bimodality arises from stochastic switching between transcriptional states, and underscores the complementary roles of skewness and kurtosis in characterizing transcriptional variability. This provides a clear statistical signature for distinguishing between burst-dominated and switching-dominated transcriptional regimes.

5. Conclusions

Classical two-state promoter models have been extensively studied in the context of stochastic gene expression, with analytical results primarily focusing on the probability mass function, the mean expression level, variance, or noise measures such as the Fano factor. While these quantities effectively characterize the overall magnitude of transcriptional variability, they do not uniquely determine the geometric shape of the underlying mRNA copy number distribution. By contrast, in the present work, we extend classical moment-based analyses by providing explicit closed-form expressions for higher-order

moments and their standardized counterparts, namely skewness and excess kurtosis. These higher-order statistics capture distributional asymmetry and tail behavior that are inherently inaccessible through mean–variance analysis alone, even within the same two-state promoter framework.

Indeed, it has long been recognized that low-order statistics are insufficient in fully describing mRNA distributions generated by promoter switching and transcriptional bursting [5,18]. Here, we demonstrate that skewness provides essential information about distributional asymmetry that cannot be inferred from variance alone, thereby revealing mechanistic features of transcriptional regulation that are hidden at the level of second-order statistics.

Positive skewness emerges naturally from bursty transcription dynamics, in which rare promoter activation events give rise to intense transcriptional episodes [1,21,40]. Our analytical results show that the skewness Skew depends explicitly on promoter switching kinetics and burst size, increasing with the ratio γ/λ and with the burst size $B = \nu/\gamma$, even when the mean expression level is held fixed. This establishes skewness as a mechanistically informative statistic that reflects the underlying regulatory architecture rather than merely the overall noise magnitude. From a biological perspective, skewness quantifies the contribution of rare, high-expression cells within a population. Such cells can play a disproportionate role in downstream regulatory processes, including threshold-dependent responses, stress adaptation, and phenotypic diversification [33,42]. Variance-based measures treat fluctuations symmetrically around the mean and therefore obscure the statistical weight of these rare transcriptional events, whereas skewness directly captures the asymmetry induced by transcriptional bursting and slow promoter switching.

Beyond skewness, kurtosis further characterizes the sharpness and tail heaviness of mRNA distributions. Our results indicate that low-mRNA-abundance regimes are associated with elevated skewness and kurtosis, reflecting highly asymmetric and heavy-tailed distributions dominated by rare transcriptional bursts. This behavior is consistent with effective averaging over many transcription events and aligns with previous theoretical analyses of noise–mean relationships in gene expression models [15,43].

Finally, our analysis provides a theoretical foundation for extending negative binomial-based analyses of single-cell transcriptomic data beyond conventional mean–variance fitting [13]. Distinct promoter dynamics may generate identical mean expression levels and variances while exhibiting markedly different skewness and kurtosis, a limitation that has been highlighted in recent studies on model identifiability and model reduction [39,44]. Incorporating higher-order statistics therefore offers a principled route toward improved discrimination between competing transcriptional mechanisms and establishes a tighter quantitative link between statistical inference and the underlying molecular regulation of gene expression. Future work may extend this framework to multi-state promoter models, feedback regulation, and spatially resolved enhancer–promoter interactions.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/math14061074/s1>, MATLAB codes for generating Figures in the main text.

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Appendix A. Derivation of Moments

In this appendix, we give a step-by-step derivation of the mean, variance, skewness, and excess kurtosis of mRNA distributions in the two-state transcription model. The derivation proceeds from CMEs (1) and (2) for the OFF/ON states.

The frequency of elongation. Summing over all transcript numbers m , we define

$$P_0(t) = \sum_{m=0}^{\infty} P_0(m, t), \quad P_1(t) = \sum_{m=0}^{\infty} P_1(m, t),$$

which represent the probabilities that the promoter resides in the OFF and ON states at time t , respectively. As these two states form a complete set, we have

$$P_0(t) + P_1(t) = 1, \quad \forall t \geq 0.$$

Differentiating $P_0(t)$ and $P_1(t)$ with respect to t and using Equations (1) and (2), we obtain a closed system

$$P_0'(t) = \gamma P_1(t) - \lambda P_0(t), \quad P_1'(t) = \lambda P_0(t) - \gamma P_1(t).$$

Solving this system with the initial conditions $P_0(0) = 1$ and $P_1(0) = 0$ yields

$$P_0(t) = \frac{\gamma}{\lambda + \gamma} + \frac{\lambda}{\lambda + \gamma} e^{-(\lambda + \gamma)t},$$

$$P_1(t) = \frac{\lambda}{\lambda + \gamma} - \frac{\lambda}{\lambda + \gamma} e^{-(\lambda + \gamma)t},$$

where $P_1(t)$ represents the frequency of elongation. The steady-state promoter occupancy probabilities are therefore given by

$$P_0 = \frac{\gamma}{\lambda + \gamma}, \quad P_1 = \frac{\lambda}{\lambda + \gamma}.$$

More generally, for initial conditions $P_0(0) = p_0$ and $P_1(0) = p_1$ satisfying $p_0 + p_1 = 1$, the solution can be written as

$$P_0(t) = \frac{\gamma}{\lambda + \gamma} + \left(p_0 - \frac{\gamma}{\lambda + \gamma}\right) e^{-(\lambda + \gamma)t}, \quad P_1(t) = \frac{\lambda}{\lambda + \gamma} + \left(p_1 - \frac{\lambda}{\lambda + \gamma}\right) e^{-(\lambda + \gamma)t}.$$

The exponential decay of $p_0 e^{-(\lambda + \gamma)t}$ and $p_1 e^{-(\lambda + \gamma)t}$ indicates that the promoter dynamics rapidly forget their initial state, and the system relaxes to a unique steady-state distribution determined solely by the switching rates λ and γ .

First moment (mean). Decomposing the moments according to the promoter state, we write

$$\mu_k(t) = \mu_{k0}(t) + \mu_{k1}(t), \quad \mu_{k0}(t) = \sum_{m=0}^{\infty} m^k P_0(m, t), \quad \mu_{k1}(t) = \sum_{m=0}^{\infty} m^k P_1(m, t).$$

The initial condition implies that $\mu_k(0) = \mu_{k0}(0) = \mu_{k1}(0) = 0$.

For $k = 1$ (the mean), differentiating $\mu_{10}(t)$ yields

$$\begin{aligned}\frac{d\mu_{10}(t)}{dt} &= \frac{d}{dt} \sum_{m=0}^{\infty} mP_0(m, t) = \sum_{m=0}^{\infty} m \frac{dP_0(m, t)}{dt} \\ &= \sum_{m=0}^{\infty} m \left[\gamma P_1(m, t) - \lambda P_0(m, t) + \delta \left((m+1)P_0(m+1, t) - mP_0(m, t) \right) \right] \\ &= \gamma\mu_{11}(t) - \lambda\mu_{10}(t) + \delta \sum_{m=0}^{\infty} \left[m(m+1)P_0(m+1, t) - m^2P_0(m, t) \right].\end{aligned}$$

It remains to compute the last summation term. We have

$$\begin{aligned}&\sum_{m=0}^{\infty} \left[m(m+1)P_0(m+1, t) - m^2P_0(m, t) \right] \\ &= \sum_{m=0}^{\infty} \left[(m+1-1)(m+1)P_0(m+1, t) - m^2P_0(m, t) \right] \\ &= \sum_{m=0}^{\infty} (m+1)^2P_0(m+1, t) - \sum_{m=0}^{\infty} m^2P_0(m, t) - \sum_{m=0}^{\infty} (m+1)P_0(m+1, t) \\ &= -\mu_{10}(t),\end{aligned}$$

where we used the index shift identities

$$\begin{aligned}\sum_{m=0}^{\infty} (m+1)^2P_0(m+1, t) &= \sum_{m=0}^{\infty} m^2P_0(m, t), \\ \sum_{m=0}^{\infty} (m+1)P_0(m+1, t) &= \sum_{m=0}^{\infty} mP_0(m, t) = \mu_{10}(t).\end{aligned}$$

Therefore,

$$\frac{d\mu_{10}(t)}{dt} = \gamma\mu_{11}(t) - (\lambda + \delta)\mu_{10}(t).$$

Similarly, differentiating $\mu_{11}(t)$ gives

$$\begin{aligned}\frac{d\mu_{11}(t)}{dt} &= \frac{d}{dt} \sum_{m=0}^{\infty} mP_1(m, t) = \sum_{m=0}^{\infty} m \frac{dP_1(m, t)}{dt} \\ &= \sum_{m=0}^{\infty} m \left[\lambda P_0(m, t) - \gamma P_1(m, t) + \delta \left((m+1)P_1(m+1, t) - mP_1(m, t) \right) \right. \\ &\quad \left. + \nu \left(P_1(m-1, t) - P_1(m, t) \right) \right] \\ &= \lambda\mu_{10}(t) - (\gamma + \delta)\mu_{11}(t) + \nu \sum_{m=0}^{\infty} \left[mP_1(m-1, t) - mP_1(m, t) \right].\end{aligned}$$

For the production term, using $P_1(-1, t) = 0$ and shifting indices, we obtain

$$\begin{aligned}\sum_{m=0}^{\infty} \left[mP_1(m-1, t) - mP_1(m, t) \right] &= \sum_{m=1}^{\infty} mP_1(m-1, t) - \sum_{m=0}^{\infty} mP_1(m, t) \\ &= \sum_{n=0}^{\infty} (n+1)P_1(n, t) - \sum_{n=0}^{\infty} nP_1(n, t) \\ &= \sum_{n=0}^{\infty} P_1(n, t) = P_1(t).\end{aligned}$$

Hence,

$$\frac{d\mu_{11}(t)}{dt} = \nu P_1(t) + \lambda \mu_{10}(t) - (\gamma + \delta) \mu_{11}(t).$$

Taking the above two equations together, we obtain a closed system of first-order differential equations:

$$\frac{d\mu_{10}(t)}{dt} = \gamma \mu_{11}(t) - (\lambda + \delta) \mu_{10}(t), \quad (\text{A1})$$

$$\frac{d\mu_{11}(t)}{dt} = \nu P_1(t) + \lambda \mu_{10}(t) - (\gamma + \delta) \mu_{11}(t). \quad (\text{A2})$$

As $P_1(t)$ has been obtained explicitly and $P_1(t) - P_1$ decays exponentially as $t \rightarrow \infty$, the system (A1) and (A2) admits a unique equilibrium and converges to it exponentially. Moreover, solving (A1) and (A2) directly with $\mu_{10}(0) = \mu_{11}(0) = 0$ yields

$$\mu_{10}(t) = \frac{\nu\lambda}{\delta(\lambda + \gamma)} \left[\frac{\gamma - \gamma e^{-(\lambda + \gamma + \delta)t}}{\lambda + \gamma + \delta} + \frac{\gamma e^{-(\lambda + \gamma)t} - \gamma e^{-\delta t}}{\lambda + \gamma - \delta} \right], \quad (\text{A3})$$

$$\mu_{11}(t) = \frac{\nu\lambda}{\delta(\lambda + \gamma)} \left[\frac{(\delta + \lambda) + \gamma e^{-(\delta + \lambda + \gamma)t}}{\lambda + \gamma + \delta} + \frac{(\delta - \gamma)e^{-(\lambda + \gamma)t} - \lambda e^{-\delta t}}{\lambda + \gamma - \delta} \right]. \quad (\text{A4})$$

Summing $\mu_{10}(t)$ and $\mu_{11}(t)$ gives the mean mRNA copy number

$$\mu_1(t) = \mu_{10}(t) + \mu_{11}(t) = \frac{\nu\lambda}{\delta(\lambda + \gamma)} \left[1 + \frac{\delta e^{-(\lambda + \gamma)t} - (\lambda + \gamma)e^{-\delta t}}{\lambda + \gamma - \delta} \right].$$

Setting derivatives to zero, the equilibrium moments are

$$\mu_{10} = \frac{\nu\lambda\gamma}{\delta(\lambda + \gamma)(\delta + \lambda + \gamma)}, \quad \mu_{11} = \frac{\nu\lambda(\delta + \lambda)}{\delta(\lambda + \gamma)(\delta + \lambda + \gamma)}.$$

The total mean is

$$\mu_1 = \mu_{10} + \mu_{11} = \frac{\nu\lambda}{\delta(\lambda + \gamma)}.$$

Remark (resonant case). If $\delta = \lambda + \gamma$, the terms with $(\lambda + \gamma - \delta)^{-1}$ in (A3) and (A4) should be replaced by the corresponding limit, producing terms proportional to $\gamma t e^{-(\lambda + \gamma)t}$ or $(\lambda t + 1)e^{-(\lambda + \gamma)t}$.

Second Moment. For $k = 2$, differentiating $\mu_{20}(t)$ yields

$$\begin{aligned} \frac{d\mu_{20}(t)}{dt} &= \frac{d}{dt} \sum_{m=0}^{\infty} m^2 P_0(m, t) = \sum_{m=0}^{\infty} m^2 \frac{dP_0(m, t)}{dt} \\ &= \sum_{m=0}^{\infty} m^2 \left[\gamma P_1(m, t) - \lambda P_0(m, t) + \delta \left((m+1)P_0(m+1, t) - mP_0(m, t) \right) \right] \\ &= \gamma \mu_{21}(t) - \lambda \mu_{20}(t) + \delta \sum_{m=0}^{\infty} \left[m^2(m+1)P_0(m+1, t) - m^3P_0(m, t) \right]. \end{aligned}$$

It remains to compute the last summation term. We have

$$\begin{aligned}
 & \sum_{m=0}^{\infty} \left[m^2(m+1)P_0(m+1, t) - m^3P_0(m, t) \right] \\
 &= \sum_{m=0}^{\infty} \left[(m+1-1)^2(m+1)P_0(m+1, t) - m^3P_0(m, t) \right] \\
 &= \sum_{m=0}^{\infty} (m+1)^3P_0(m+1, t) - \sum_{m=0}^{\infty} m^3P_0(m, t) \\
 &\quad - 2 \sum_{m=0}^{\infty} (m+1)^2P_0(m+1, t) + \sum_{m=0}^{\infty} (m+1)P_0(m+1, t) \\
 &= -2\mu_{20}(t) + \mu_{10}(t).
 \end{aligned}$$

Therefore,

$$\mu'_{20}(t) = \gamma\mu_{21}(t) - (\lambda + 2\delta)\mu_{20}(t) + \delta\mu_{10}(t).$$

Similarly, differentiating $\mu_{21}(t)$ gives

$$\begin{aligned}
 \frac{d\mu_{21}(t)}{dt} &= \frac{d}{dt} \sum_{m=0}^{\infty} m^2P_1(m, t) = \sum_{m=0}^{\infty} m^2 \frac{dP_1(m, t)}{dt} \\
 &= \sum_{m=0}^{\infty} m^2 \left[\lambda P_0(m, t) - \gamma P_1(m, t) + \delta \left((m+1)P_1(m+1, t) - mP_1(m, t) \right) \right. \\
 &\quad \left. + \nu (P_1(m-1, t) - P_1(m, t)) \right] \\
 &= \lambda\mu_{20}(t) - (\gamma + 2\delta)\mu_{21}(t) + \delta\mu_{11}(t) + \nu \sum_{m=0}^{\infty} \left[m^2P_1(m-1, t) - m^2P_1(m, t) \right].
 \end{aligned}$$

For the production term, using $P_1(-1, t) = 0$ and shifting indices, we obtain

$$\begin{aligned}
 & \sum_{m=0}^{\infty} \left[m^2P_1(m-1, t) - m^2P_1(m, t) \right] \\
 &= \sum_{m=1}^{\infty} m^2P_1(m-1, t) - \sum_{m=0}^{\infty} m^2P_1(m, t) \\
 &= \sum_{m=0}^{\infty} (m-1+1)^1P_1(m-1, t) - \sum_{m=0}^{\infty} m^2P_1(m, t) \\
 &= 2\mu_{11}(t) + P_1(t).
 \end{aligned}$$

Hence,

$$\mu'_{21}(t) = \nu P_1(t) + (2\nu + \delta)\mu_{11}(t) + \lambda\mu_{20}(t) - (\gamma + 2\delta)\mu_{21}(t).$$

Taking the above two equations together, we obtain a closed system of first-order differential equations:

$$\begin{aligned}
 \mu'_{20}(t) &= \delta\mu_{10}(t) + \gamma\mu_{21}(t) - (\lambda + 2\delta)\mu_{20}(t), \\
 \mu'_{21}(t) &= \nu P_1(t) + (2\nu + \delta)\mu_{11}(t) + \lambda\mu_{20}(t) - (\gamma + 2\delta)\mu_{21}(t).
 \end{aligned}$$

Setting derivatives to zero,

$$\begin{aligned}\mu_{20} &= \frac{\nu\lambda\gamma[\nu(\delta+\lambda)+\delta(2\delta+\lambda+\gamma)]}{\delta^2(\lambda+\gamma)(\delta+\lambda+\gamma)(2\delta+\lambda+\gamma)} = \mu_{10} \left[1 + \frac{\nu(\delta+\lambda)}{\delta(2\delta+\lambda+\gamma)} \right], \\ \mu_{21} &= \frac{\nu\lambda(\delta+\lambda)[\nu(2\delta+\lambda)+\delta(2\delta+\lambda+\gamma)]}{\delta^2(\lambda+\gamma)(\delta+\lambda+\gamma)(2\delta+\lambda+\gamma)} = \mu_{11} \left[1 + \frac{\nu(2\delta+\lambda)}{\delta(2\delta+\lambda+\gamma)} \right].\end{aligned}$$

The total second moment is

$$\mu_2 = \mu_{20} + \mu_{21} = \frac{\nu\lambda[\nu(\delta+\lambda)+\delta(\delta+\lambda+\gamma)]}{\delta^2(\lambda+\gamma)(\delta+\lambda+\gamma)} = \mu_1 \left[1 + \frac{\nu(\delta+\lambda)}{\delta(\delta+\lambda+\gamma)} \right].$$

In addition, the variance is

$$\sigma^2 = \mu_2 - \mu_1^2 = \mu_1 \left[1 + \frac{\nu\gamma}{(\lambda+\gamma)(\delta+\lambda+\gamma)} \right].$$

Third moment. Differentiating $\mu_{30}(t)$ gives

$$\begin{aligned}\frac{d\mu_{30}(t)}{dt} &= \sum_{m=0}^{\infty} m^3 \frac{P_0(m+1, t)}{dt} \\ &= \sum_{m=0}^{\infty} m^3 \left[\gamma P_1(m, t) - \lambda P_0(m, t) + \delta \left((m+1)P_0(m+1, t) - mP_0(m, t) \right) \right] \\ &= \gamma\mu_{31}(t) - \lambda\mu_{30}(t) + \delta \sum_{m=0}^{\infty} \left[m^3(m+1)P_0(m+1, t) - m^4P_0(m, t) \right].\end{aligned}$$

The last term is

$$\sum_{m=0}^{\infty} \left[m^3(m+1)P_0(m+1, t) - m^4P_0(m, t) \right] = -3\mu_{30}(t) + 3\mu_{20}(t) - \mu_{10}(t).$$

The derivative of $\mu_{30}(t)$ is

$$\frac{d\mu_{30}(t)}{dt} = \gamma\mu_{31}(t) - \delta\mu_{10}(t) + 3\delta\mu_{20}(t) - (3\delta+\lambda)\mu_{30}(t). \quad (\text{A5})$$

Similarly, the derivative of $\mu_{31}(t)$ is

$$\frac{d\mu_{31}(t)}{dt} = \nu[P_1(t) + 3\mu_{11}(t) + 3\mu_{21}(t)] + \lambda\mu_{30}(t) - \delta\mu_{11}(t) + 3\delta\mu_{21}(t) - (3\delta+\gamma)\mu_{31}(t). \quad (\text{A6})$$

Equations (A5) and (A6) have only one equilibrium point, which is

$$\begin{aligned}\mu_{30} &= \frac{\nu\lambda\gamma[\nu^2(\delta+\lambda)(2\delta+\lambda) + 3\nu\delta(\delta+\lambda)(3\delta+\lambda+\gamma) + \delta^2(2\delta+\lambda+\gamma)(3\delta+\lambda+\gamma)]}{\delta^3(\lambda+\gamma)(\delta+\lambda+\gamma)(2\delta+\lambda+\gamma)(3\delta+\lambda+\gamma)} \\ &= \mu_{10} \left[1 + \frac{3\nu(\delta+\lambda)}{\delta(2\delta+\lambda+\gamma)} + \frac{\nu^2(\delta+\lambda)(2\delta+\lambda)}{\delta^2(2\delta+\lambda+\gamma)(3\delta+\lambda+\gamma)} \right], \\ \mu_{31} &= \frac{\nu\lambda(\delta+\lambda)[\nu^2(2\delta+\lambda)(3\delta+\lambda) + 3\nu\delta(2\delta+\lambda)(3\delta+\lambda+\gamma) + \delta^2(2\delta+\lambda+\gamma)(3\delta+\lambda+\gamma)]}{\delta^3(\lambda+\gamma)(\delta+\lambda+\gamma)(2\delta+\lambda+\gamma)(3\delta+\lambda+\gamma)} \\ &= \mu_{11} \left[1 + \frac{3\nu(2\delta+\lambda)}{\delta(2\delta+\lambda+\gamma)} + \frac{\nu^2(2\delta+\lambda)(3\delta+\lambda)}{\delta^2(2\delta+\lambda+\gamma)(3\delta+\lambda+\gamma)} \right],\end{aligned}$$

and the third moment is

$$\begin{aligned}\mu_3 &= \frac{\nu\lambda[\nu^2(\delta+\lambda)(2\delta+\lambda) + 3\nu\delta(\delta+\lambda)(2\delta+\lambda+\gamma) + \delta^2(\delta+\lambda+\gamma)(2\delta+\lambda+\gamma)]}{\delta^3(\lambda+\gamma)(\delta+\lambda+\gamma)(2\delta+\lambda+\gamma)} \\ &= \mu_1 \left[1 + \frac{3\nu(\delta+\lambda)}{\delta(\delta+\lambda+\gamma)} + \frac{\nu^2(\delta+\lambda)(2\delta+\lambda)}{\delta^2(\delta+\lambda+\gamma)(2\delta+\lambda+\gamma)} \right].\end{aligned}$$

Fourth moment. Differentiating $\mu_4(t)$ gives

$$\mu_4'(t) = \nu[P_1(t) + 4\mu_{11}(t) + 6\mu_{21}(t) + 4\mu_{31}(t)] + \delta[\mu_1(t) - 4\mu_2(t) + 6\mu_3(t) - 4\mu_4(t)].$$

The stationary fourth moment is

$$\begin{aligned}\mu_4 &= \mu_1 \left[1 + \frac{7\nu(\delta+\lambda)}{\delta(\delta+\lambda+\gamma)} + \frac{6\nu^2(\delta+\lambda)(2\delta+\lambda)}{\delta^2(\delta+\lambda+\gamma)(2\delta+\lambda+\gamma)} \right. \\ &\quad \left. + \frac{\nu^3(\delta+\lambda)(2\delta+\lambda)(3\delta+\lambda)}{\delta^3(\delta+\lambda+\gamma)(2\delta+\lambda+\gamma)(3\delta+\lambda+\gamma)} \right].\end{aligned}$$

Appendix B. Derivation of Asymptotic Formulas

In this Appendix, we detail the derivation of asymptotic expressions for the moments, skewness, and excess kurtosis under different transcriptional regimes, starting from the exact formulas for the first four moments obtained in Appendix A. As all kinetic parameters ν , λ , and γ have been nondimensionalized by the mRNA degradation rate δ , the second to the fourth moments, respectively, are given as

$$\begin{aligned}\mu_2 &= \mu_1 \left[1 + \frac{\nu(1+\lambda)}{1+\lambda+\gamma} \right], \\ \mu_3 &= \mu_1 \left[1 + \frac{3\nu(1+\lambda)}{1+\lambda+\gamma} + \frac{\nu^2(1+\lambda)(2+\lambda)}{(1+\lambda+\gamma)(2+\lambda+\gamma)} \right], \\ \mu_4 &= \mu_1 \left[1 + \frac{7\nu(1+\lambda)}{1+\lambda+\gamma} + \frac{6\nu^2(1+\lambda)(2+\lambda)}{(1+\lambda+\gamma)(2+\lambda+\gamma)} + \frac{\nu^3(1+\lambda)(2+\lambda)(3+\lambda)}{(1+\lambda+\gamma)(2+\lambda+\gamma)(3+\lambda+\gamma)} \right].\end{aligned}$$

Slow-promoter-switching regime. In the slow-switching limit, mRNA degradation is fast compared to promoter switching, such that

$$\lambda, \gamma \ll 1.$$

As the mean mRNA number is given by

$$\mu_1 = \frac{\nu\lambda}{\lambda+\gamma},$$

the transcription rate can be expressed as

$$\nu = \mu_1 \left(1 + \frac{\gamma}{\lambda} \right).$$

In the exact expressions for μ_2 , μ_3 , and μ_4 , terms such as $i + \lambda$ and $i + \lambda + \gamma$ with $i = 1, 2, 3$ can be approximated as

$$i + \lambda \approx i, \quad i + \lambda + \gamma \approx i.$$

The second moment becomes

$$\mu_2 \approx \mu_1(1 + \nu) = \mu_1[1 + \mu_1(1 + \alpha)],$$

where $\alpha = \gamma/\lambda$. The variance is therefore given by

$$\sigma^2 = \mu_2 - \mu_1^2 = \mu_1(1 + \mu_1\alpha).$$

Applying the same approximation procedure to higher-order moments yields

$$\begin{aligned}\mu_3 &\approx \mu_1 \left[1 + 3\mu_1(1 + \alpha) + \mu_1^2(1 + \alpha)^2 \right], \\ \mu_4 &\approx \mu_1 \left[1 + 7\mu_1(1 + \alpha) + 6\mu_1^2(1 + \alpha)^2 + \mu_1^3(1 + \alpha)^3 \right].\end{aligned}$$

Substituting them into the definitions of skewness and excess kurtosis, we have

$$\begin{aligned}\text{Skew} &\approx \frac{\mu_1^3\alpha^2 - \mu_1^3\alpha + 3\mu_1^2\alpha + \mu_1}{(\mu_1 + \mu_1^2\alpha)^{3/2}}, \\ \text{Kurt} &\approx \frac{\mu_1^4(\alpha^3 - 4\alpha^2 + \alpha) + 6\mu_1^3(\alpha^2 - \alpha) + 7\mu_1^2\alpha + \mu_1}{\mu_1^2(1 + \mu_1\alpha)^2} - 3.\end{aligned}$$

When $\mu_1, \alpha \gg 1$, the skewness and excess kurtosis can be approximated as

$$\text{Skew} \approx \sqrt{\alpha}, \quad \text{Kurt} \approx \alpha - 3.$$

If $\mu_1 \gg 1$ and $\alpha \approx 1$, the skewness and excess kurtosis reduce to

$$\text{Skew} \approx \frac{3}{\mu_1}, \quad \text{Kurt} \approx -2.$$

Fast-promoter-switching regime. In the fast-switching limit, the promoter switching rates are assumed to be much larger than the mRNA degradation rate,

$$\lambda, \gamma \gg 1. \quad (\text{A7})$$

Under this assumption, terms of the form $i + \lambda$ with $i = 1, 2, 3$ can be approximated as

$$i + \lambda \approx \lambda.$$

Using this approximation, the second moment can be simplified as

$$\mu_2 = \mu_1 \left[1 + \frac{\nu(1 + \lambda)}{1 + \lambda + \gamma} \right] \approx \mu_1 \left[1 + \frac{\nu\lambda}{\lambda + \gamma} \right] = \mu_1 + \mu_1^2.$$

Consequently, the variance reduces to

$$\sigma^2 \approx \mu_2 - \mu_1^2 = \mu_1.$$

Applying the same approximation procedure to higher-order moments, we further obtain

$$\begin{aligned}\mu_3 &\approx \mu_1^3 + 3\mu_1^2 + \mu_1, \\ \mu_4 &\approx \mu_1^4 + 6\mu_1^3 + 7\mu_1^2 + \mu_1.\end{aligned}$$

From the definitions of skewness and excess kurtosis, it follows that

$$\text{Skew} \approx \frac{1}{\sqrt{\mu_1}}, \quad \text{Kurt} \approx \frac{1}{\mu_1}. \quad (\text{A8})$$

Therefore, in the fast-switching regime, the mRNA distribution approaches a Poisson distribution, characterized by weak asymmetry and light tails.

Bursty transcription regime. The bursty limit corresponds to rare but intense transcription events,

$$\gamma \gg \max\{1, \lambda\} \quad \text{and} \quad \nu \gg 1,$$

while keeping the burst size

$$B = \frac{\nu}{\gamma} = \text{finite}.$$

In this limit, the mean and second moment reduce to

$$\begin{aligned} \mu_1 &= \frac{\nu\lambda}{\lambda + \gamma} = \lambda \cdot \frac{\nu}{\gamma} \cdot \frac{\gamma}{\lambda + \gamma} \approx \lambda B, \\ \mu_2 &= \mu_1 \left[1 + \frac{\nu(1 + \lambda)}{1 + \lambda + \gamma} \right] \approx \mu_1 \left[1 + \frac{\nu(1 + \lambda)}{\gamma} \right] = \mu_1(1 + B + \mu_1), \end{aligned}$$

and the variance reduces to $\sigma^2 \approx \mu_1(1 + B)$, which coincide with a negative binomial distribution.

Expanding the exact expressions of μ_3, μ_4 in powers of B gives

$$\begin{aligned} \mu_3 &\approx \mu_1[1 + 3(B + \mu_1) + (B + \mu_1)(2B + \mu_1)], \\ \mu_4 &\approx \mu_1[1 + 7(B + \mu_1) + 6(B + \mu_1)(2B + \mu_1) + (B + \mu_1)(2B + \mu_1)(3B + \mu_1)]. \end{aligned}$$

Substituting them into the skewness and excess kurtosis yields

$$\text{Skew} \approx \frac{1 + 2B}{\sqrt{(1 + B)\mu_1}}, \quad \text{Kurt} \approx \frac{1 + 6B + 6B^2}{(1 + B)\mu_1}.$$

The negative binomial PMF with parameters

$$r = \frac{\mu_1^2}{\sigma^2 - \mu_1} = \frac{\mu_1}{1 + B}, \quad p = \frac{\mu_1}{\sigma^2} = \frac{1}{1 + B}$$

reproduces the above skewness and excess kurtosis, confirming that bursty transcription naturally leads to overdispersed transcript count distributions.

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