ANALYTICAL FORMULA AND DYNAMIC PROFILE OF MRNA DISTRIBUTION

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Abstract. The stochasticity of transcription can be quantified by mRNA distribution \(P_m(t)\), the probability that there are \(m\) mRNA molecules for the gene at time \(t\) in one cell. However, it still lacks of a standard method to calculate \(P_m(t)\) in a transparent formula. Here, we employ an infinite series method to express \(P_m(t)\) based on the classical two-state model. Intriguingly, we observe that a unimodal distribution of mRNA numbers at steady-state could be transformed from a dynamical bimodal distribution. This indicates that “bet hedging” strategy can be still achieved for the gene that generates phenotypic homogeneity of the cell population. Moreover, the formation and duration of such bimodality are tightly correlated with mRNA synthesis rate, reinforcing the modulation scenario of some inducible genes that manipulates mRNA synthesis rate in response to environmental change. More generally, the method presented here may be implemented to the other stochastic transcription models with constant rates.

1. Introduction. Gene transcription in single cells is a stochastic process. In virtually all genomic loci, mRNA molecules are synthesized in pulsatile bursts that each episode of transcriptional activity is interrupted by a gene off period [7, 15, 19, 3]. A conventional method for quantifying the randomness of gene transcription is depicting the histogram of mRNA copy numbers [21, 13]. It sets a statistical basis for approximating the mass function \(P_m(t)\), the probability that there are exactly \(m\) mRNA molecules for the gene in a typical cell at time \(t\) [15, 25]. In mathematics, analytical formula of \(P_m(t)\) can be expressed in terms of system parameters in the model, and has been widely used to provide a good fitting to mRNA distribution measured in bacteria [29], yeast [37], and mammalian cells [25]. It helped biologists
analyze their data in a panoramic view to signify a phenotypic trend of the cell population. A decaying or unimodal distribution suggests a phenotypic homogeneity, while a bimodal distribution supports a binary process that steers cells into two sub-populations with distinct cell identities [21, 13, 27, 10].

Our main purpose in this work is to introduce a theoretical method to calculate $P_m(t)$ from stochastic transcription models with constant parameter rates. To make the presentation easier to follow, we illustrate the basic idea by implementing the method to the classical two-state model [3, 21, 11].

\begin{equation}
\text{off } \underset{\lambda}{\longrightarrow} \text{ on } \underset{v}{\longrightarrow} \text{ mRNA } \underset{\delta}{\longrightarrow} \emptyset. \tag{1.1}
\end{equation}

In the two-state model (1.1), gene transcription is modeled by first order kinetics with a constant activation rate $\lambda > 0$ and an inactivation rate $\gamma > 0$. When the gene is active, RNA polymerase (RNAP) binds to its promoter (often with other transcription factors) and traverses the template DNA strand to synthesize mRNA molecules, and its waiting time for birth and the lifetime before degradation are independently and exponentially distributed with rates $\varphi > 0$ and $\delta > 0$, respectively.

The conventional method for extracting analytical form of $P_m(t)$ from the two-state model (1.1) has endeavored to solve the generating function

\begin{equation}
V(z, t) = \sum_{m=0}^{\infty} (1 + z)^m P_m(t), \tag{1.2}
\end{equation}

and $P_m(t)$ is then calculated through the conversion formula

\begin{equation}
P_m(t) = \frac{1}{m!} \frac{\partial^m V(z, t)}{\partial z^m} \bigg|_{z=-1}. \tag{1.3}
\end{equation}

This procedure has been widely implemented to the transcription system at steady-state, namely, when the time $t \to \infty$. In such case, the steady-state mass function $P_m = \lim_{t \to \infty} P_m(t)$ can be expressed in form of confluent hypergeometric function [25, 23] or Poisson-beta distribution [11, 31] with three rescaled parameters

\begin{equation}
\tilde{\lambda} = \frac{\lambda}{\delta}, \quad \tilde{\gamma} = \frac{\gamma}{\delta}, \quad \text{and} \quad \tilde{\varphi} = \frac{\varphi}{\delta}. \tag{1.4}
\end{equation}

Both quantitative and qualitative analysis of $P_m$ help represent the commonly observed three mRNA distribution modes in experiments [21, 25], and also decompose the system parameter space into simply connected regions, each of which corresponds to exactly one of those three distribution modes [11, 9] (Fig. 3).

Nevertheless, it still lacks a standard method for calculating the dynamical expression of $P_m(t)$ although some numerical methods [6, 20] or limiting cases [28, 33] have been discussed for this purpose. One of the theoretical breakthrough [9] for computing $P_m(t)$ has expressed the generating function (1.2) in an elegant form consisting of four confluent hypergeometric functions, and $P_m(t)$ is computed by the relation (1.3). However, the intrinsic complexity of hypergeometric function does not permit an elementary inversion through (1.3) to yield a transparent expression of $P_m(t)$. It is still possible to express $P_m(t)$ in simple elementary functions and their single integrations under the special regime $\lambda = \delta$ or $\gamma = \delta$ [12]. Such simplicity helps analyze in mathematical detail the rich dynamic transition among different mRNA distribution modes.

In this paper, we are interested in further exploring distribution dynamics within the whole range of system parameters. We shall present an analytical formula of
ANALYTICAL FORMULA OF MRNA DISTRIBUTION 243

Figure 1. The three modes of the steady-state mRNA distribution.
(a) When $\bar{v} = v/\delta$ is fixed, the $\lambda$-$\gamma$ plane can be divided into three connected regions, and the values of $(\lambda, \gamma)$ in each region generate a corresponding steady-state distribution mode [11]: (b) The decaying distribution that $P_m$ decreases in $m$ for $m = 0, 1, 2, \cdots$; (c) The unimodal distribution that $P_m$ takes exactly one peak at some $m > 0$; (d) The bimodal distribution that $P_m$ takes exactly two peaks with the first one at $m = 0$, and the other one at some $m > 0$.

the mass function $P_m(t)$ in Section 2, and then characterize the dynamics of the distribution profile by three patterns in Section 3.

2. Analytical formulas of the mass function $P_m(t)$. In this section, we first express $P_m(t)$ in the form of a uniformly convergent series and then determine the exact forms of its general terms. We shall illustrate these two steps in more detail in the following two subsections.

2.1. Infinite series expansion for $P_m(t)$. At time $t \geq 0$, let $X(t) = q$ when the gene is inactive, and $X(t) = e$ when the gene is active. Let $M(t)$ denote the copy number of the mRNA and define

$$P_{m,i}(t) = \text{Prob}\{M(t) = m, X(t) = i\}, \ m = 0, 1, 2, \cdots.$$ 

Then $P_m(t) = P_{m,q}(t) + P_{m,e}(t)$, and the calculation of $P_m(t)$, $m \geq 0$, is transformed to solve the system of master equations [23, 9, 12]:

$$\frac{dP_{m,q}(t)}{dt} = \gamma P_{m,q}(t) - (m\delta + \lambda)P_{m,q}(t) + (m+1)\delta P_{m+1,q}(t), \tag{2.1}$$

$$\frac{dP_{m,e}(t)}{dt} = \lambda P_{m,q}(t) - (v + m\delta + \gamma)P_{m,e}(t) + (m+1)\delta P_{m+1,e}(t)$$

$$+ v P_{m-1,e}(t), \tag{2.2}$$

$$P_{0,q}(0) = 1, \ P_{0,e}(0) = 0, \text{ and } P_{m,q}(0) = P_{m,e}(0) = 0 \text{ for } m \geq 1, \tag{2.3}$$

where by convention $P_{-1,e}(t) = 0$ and the initial values in (2.3) assume that the gene is inactive and the number of transcripts is zero at $t = 0$. By introducing
Theorem 1. In the two-state model \((1 + z)^{n}P_{m,q}(t)\), we can multiply the system \((1 + z)^{m}P_{m,e}(t)\), we can multiply the system \((1 + z)^{m}\) and summing them up. This leads to a system of partial differential equations \([23, 9, 12]\):

\[
\begin{align*}
\frac{\partial V_{q}}{\partial t}(z, t) &= -\lambda V_{q}(z, t) + \gamma V_{e}(z, t) - \delta z \frac{\partial V_{q}}{\partial z}(z, t), \\
\frac{\partial V_{e}}{\partial t}(z, t) &= \lambda V_{q}(z, t) - \gamma V_{e}(z, t) + v_{z}V_{e}(z, t) - \delta z \frac{\partial V_{e}}{\partial z}(z, t),
\end{align*}
\]

\(V_{q}(z, 0) = 1, \quad V_{e}(z, 0) = 0,\)

\(V_{q}(0, t) = \frac{\gamma}{\lambda + \gamma} + \frac{\lambda e^{-(\lambda + \gamma) t}}{\lambda + \gamma}\) and \(V_{e}(0, t) = \frac{\lambda}{\lambda + \gamma}(1 - e^{-(\lambda + \gamma) t}).\) (2.7)

Then \(P_{m}(t)\) can be obtained by the solution of (2.4)-(2.7) via the conversion formula (1.3) with

\[V(z, t) = V_{q}(z, t) + V_{e}(z, t).\]

**Theorem 1.** In the two-state model (1.1), the probability mass function \(P_{m}(t)\), \(m \geq 0\) can be expressed as a uniformly convergent infinite series

\[P_{m}(t) = \sum_{n=m}^{\infty} (-1)^{n-m} C_{n}^{m} a_{n}(t), \text{ for } C_{n}^{m} = \frac{n!}{(n-m)!m!}.\] (2.8)

Here, the coefficients \(a_{n}(t)\) are found to be

\[a_{0}(t) = 1, \quad a_{n}(t) = v e^{-n \delta t} \int_{0}^{t} e^{n \delta s} a_{n-1}(s) ds, \quad n \geq 1,\] (2.9)

and \(a_{n,e}(t)\) are calculated by the following iteration relation

\[
\begin{align*}
a_{0,e}(t) &= \frac{\lambda}{\lambda + \gamma}(1 - e^{-(\lambda + \gamma) t}), \\
a_{n,e}(t) &= v e^{-n \delta t} \int_{0}^{t} e^{n \delta s} a_{n-1,e}(s) \left( \frac{\lambda + \gamma e^{(\lambda + \gamma)(s-t)}}{\lambda + \gamma} \right) ds, \quad n \geq 1.
\end{align*}
\] (2.10)

**Proof.** We first express empirically generating functions as power series in \(z\):

\[V(z, t) = \sum_{n=0}^{\infty} a_{n}(t) z^{n}, \quad V_{x}(z, t) = \sum_{n=0}^{\infty} a_{n,x}(t) z^{n}, \quad x = q, e.\] (2.11)

Then the substitution of this into (1.3) gives (2.8) immediately. Moreover, the values of \(a_{0}(t)\) and \(a_{0,e}(t)\) claimed in (2.9) and (2.10) can be easily verified by letting \(z = 0\) in (2.11), and then (2.7) gives

\[a_{0}(t) = V(0, t) = 1 \quad \text{and} \quad a_{0,e}(t) = V_{e}(0, t) = \frac{\lambda}{\lambda + \gamma}(1 - e^{-(\lambda + \gamma) t}).\]

We next calculate \(a_{n}(t)\) for \(n \geq 1\) in (2.9). Summing (2.4) and (2.5) gives

\[
\frac{\partial V}{\partial t}(z, t) = v_{z}V_{e}(z, t) - \delta z \frac{\partial V}{\partial z}(z, t).
\]
Then the substitution of (2.11) leads to
\[\sum_{n=0}^{\infty} a'_n(t)z^n + \sum_{n=0}^{\infty} n\delta a_n(t)z^n = \sum_{n=0}^{\infty} va_{n,e}(t)z^{n+1}.\]

Since \(a_0(t) \equiv 1\), we have \(a'_0(t) = 0\), and the above identity can be rewritten as
\[\sum_{n=1}^{\infty} [a'_n(t) + n\delta a_n(t)]z^n = \sum_{n=1}^{\infty} va_{n-1,e}(t)z^n,\]
which gives
\[a'_n(t) + n\delta a_n(t) = va_{n-1,e}(t), \quad n \geq 1. \tag{2.12}\]

To determine initial values \(a_n(0), n \geq 1\) for the differential equations (2.12), we first notice that (2.11) indicates
\[a_n(t) = \frac{1}{n!} \left. \frac{\partial^n V(z,t)}{\partial z^n} \right|_{z=0}. \tag{2.13}\]

We then utilize (1.2) to take partial derivatives of \(V(z,t)\) with respect to \(z\). It gives
\[\frac{\partial^n V(z,t)}{\partial z^n} = \sum_{m=0}^{\infty} m(m-1)\cdots(m-n+1)(1+z)^{(m-n)}P_m(t), \quad n \geq 1.\]

The substitution of this into (2.13) correlates \(a_n(t)\) with \(P_m(t)\):
\[a_n(t) = \frac{1}{n!} \sum_{m=0}^{\infty} m(m-1)\cdots(m-n+1)P_m(t)
= \frac{1}{n!} \sum_{m=n}^{\infty} m(m-1)\cdots(m-n+1)P_m(t) \geq 0, \quad n \geq 1, \tag{2.14}\]
which indicates \(a_n(0) = 0\) for \(n \geq 1\) as \(P_m(0) = 0\) for \(m \geq 1\). Then (2.9) is obtained by applying the method of variation of constant to the differential equation (2.12) with initial value condition \(a_n(0) = 0, n \geq 1\) [12, 8].

To proceed, we verify the second term in (2.10). By substituting \(V_q\) and \(V_e\) given in the second term of (2.11) into (2.4) and (2.5), and following the similar procedure that derives (2.12) and its initial values \(a_n(0) = 0, n \geq 1\), we arrive at a system of ordinary differential equations
\[a'_n,q(t) = \gamma a_{n,e}(t) - (\lambda + n\delta)a_{n,q}(t), \quad n \geq 1, \tag{2.15}\]
\[a'_n,e(t) = \lambda a_{n,q}(t) - (\gamma + n\delta)a_{n,e}(t) + va_{n-1,e}(t), \quad n \geq 1, \tag{2.16}\]
\[a_{n,q}(0) = a_{n,e}(0) = 0, \quad n \geq 1. \tag{2.17}\]

The system (2.15)-(2.17) can be solved by standard techniques in the theory of linear ordinary differential equations [8] and (2.10) follows.

Our final task is to show the convergence of \(P_m(t)\) defined by (2.8)-(2.10). We can use ratio test [2] to distinguish whether the infinite series is uniform convergence or not, namely, for any fixed \(m = 0, 1, \cdots\) and \(t \in [0, \infty)\), we only need to see if
\[\lim_{n \to \infty} \frac{|(-1)^{n+1-m}C_m^{m+1}a_{n+1}(t)|}{|(-1)^{-m}C_m^m a_n(t)|} = \lim_{n \to \infty} \frac{C_m^{m+1}a_{n+1}(t)}{C_m^m a_n(t)} < 1. \tag{2.18}\]

We first show that \(a_{n,e}(t)\) increases in \(t\). The first term of (2.10) indicates that \(a_{0,e}(t)\) increases in \(t\) on \([0, \infty)\). Therefore, under the assumption that \(a_{n-1,e}(t)\)
increases in \( t \), we only need to show that \( a_{n,e}(t) \) increases in \( t \). By taking derivative on both side of (2.10) we obtain

\[
a'_{n,e}(t) = v a_{n-1,e}(t) - \frac{v \lambda n \delta}{\lambda + \gamma} \int_0^t e^{n \delta (s-t)} a_{n-1,e}(s) \, ds
\]

\[\quad - \frac{v \gamma (n \delta + \lambda + \gamma)}{\lambda + \gamma} \int_0^t e^{(n \delta + \lambda + \gamma)(s-t)} a_{n-1,e}(s) \, ds.
\]

Due to the assumption that \( a_{n-1,e}(s) \) increases in \( s \) on \([0, t]\), we can replace \( a_{n-1,e}(s) \) in integrals by \( a_{n-1,e}(t) \) and “\( = \)” by “\( \geq \)”. This gives

\[
a'_{n,e}(t) \geq v a_{n-1,e}(t) - \frac{v \lambda}{\lambda + \gamma} a_{n-1,e}(t)(1 - e^{-n \delta t})
\]

\[\quad - \frac{v \gamma}{\lambda + \gamma} a_{n-1,e}(t)(1 - e^{-(n \delta + \lambda + \gamma)t})
\]

\[= \frac{v}{\lambda + \gamma} [\lambda e^{-n \delta t} + \gamma e^{-(n \delta + \lambda + \gamma)t}] a_{n-1,e}(t) \geq 0,
\]

implying that \( a_{n,e}(t) \) increases in \( t \) on \([0, \infty)\).

Together with (2.9), the increasing monotonicity of \( a_{n,e}(t) \) further gives the following estimation

\[
a_{n+1}(t) = v e^{-(n+1) \delta t} \int_0^t e^{(n+1) \delta s} a_{n,e}(s) \, ds
\]

\[\leq v a_{n,e}(t) e^{-(n+1) \delta t} \int_0^t e^{(n+1) \delta s} \, ds
\]

\[= \frac{v a_{n,e}(t)}{(n+1) \delta} (1 - e^{-(n+1) \delta t})
\]

\[\leq \frac{v}{(n+1) \delta} a_{n,e}(t).
\]

(2.19)

Note that (2.9) and (2.10) indicate \( a_{n,e}(t) \leq a_{n}(t) \). Then (2.19) gives

\[
a_{n+1}(t) \leq \frac{v}{(n+1) \delta} a_{n,e}(t) \leq \frac{v}{(n+1) \delta} a_{n}(t) \Rightarrow \frac{a_{n+1}(t)}{a_{n}(t)} \leq \frac{v}{(n+1) \delta}.
\]

Such relation allows us to easily verify \( C_{n+1}^m a_{n+1}(t) < C^n_m a_{n}(t) \) for \( n > m - 1 + v/\delta \), and thus (2.18) holds. The proof is completed.

2.2. **Exact form of general terms for** \( P_n(t) \). Our next move is to calculate \( a_n(t) \) defined by (2.9) and (2.10). However, one can be easily convinced that the complexity of the expression of \( a_n(t) \) increases dramatically with \( n \). To calculate \( a_n(t) \), we can take advantage of the hypergeometric function \(_1 F_1\), defined as

\[
_1 F_1(a, b, z) = \sum_{k=0}^{\infty} \frac{1}{k!} \binom{a}{b} \frac{1}{k} \frac{z^k}{k},
\]

where \( \binom{a}{b} \) is the shifted factorial defined by

\[
\binom{a}{b} = \begin{cases} 1, & \text{if } a = b = 0, \\ \frac{a + 1}{b + 1} \cdots \frac{a + k - 1}{b + k - 1}, & \text{for } k = 1, 2, \ldots. \end{cases}
\]

We have
Theorem 2. The coefficients $a_n(t)$ of $P_m(t)$ given in (2.8) can be expressed as:

$$a_0(t) = 1 \text{ and } a_n(t) = \bar{v}^n \left[ \sum_{i=0}^{n} a_{i,n} e^{-i\delta t} + \sum_{i=0}^{n-1} \bar{a}_{i,n} e^{-(i\delta + \lambda + \bar{\gamma})t} \right], \quad n = 1, 2, \cdots, \quad (2.22)$$

where

$$a_{i,n} = \frac{(-1)^i}{i! (n - i)!} \left( \frac{-\bar{\lambda}}{1 - \lambda - \bar{\gamma}} \right)^{i} \left( \frac{\bar{\lambda}}{\lambda + \bar{\gamma}} \right)^{n-i}, \quad (2.23)$$

and

$$\bar{a}_{i,n} = \frac{(-1)^{i+1}\bar{\lambda}}{i! (n - 1 - i)! (\lambda + \bar{\gamma})(1 - \lambda - \bar{\gamma})} \left( \frac{\bar{\gamma}}{1 + \lambda + \bar{\gamma}} \right)^{i} \left( \frac{1 - \bar{\gamma}}{2 - \lambda - \bar{\gamma}} \right)^{n-1-i}, \quad (2.24)$$

with three dimensionless parameters $\bar{v}, \bar{\lambda}$ and $\bar{\gamma}$ given in (1.4).

Proof. We first express the generating function $V(z, t)$ in the form of hypergeometric function $\text{}_1 F_1$. Let $z_0$ be a parameter. Following the same procedure as in [12], we first introduce

$$w(x) = V(z_0 e^{\delta t}, t), \quad \text{with } x = \bar{v} z_0 e^{\delta t}$$

on the characteristic curve

$$z = z_0 e^{\delta t},$$

and then utilize the method of characteristics [4] to transform the system (2.4)-(2.7) to a initial value problem of the confluent hypergeometric equation (or Kummer equation) [1, 30].

$$xw''(x) + (\bar{\lambda} + \bar{\gamma} - x)w'(x) - \bar{\lambda}w(x) = 0, \quad w(\bar{v} z_0) = 1 \quad \text{and } w'(\bar{v} z_0) = 0. \quad (2.25)$$

Eq. (2.25) possesses two independent particular solutions given by

$$\text{}_1 F_1(\bar{\lambda}, \bar{\lambda} + \bar{\gamma}, x) \quad \text{and} \quad x^{1-\bar{\lambda} - \bar{\gamma}} \text{}_1 F_1(1 - \bar{\gamma}, 2 - \bar{\lambda} - \bar{\gamma}, x),$$

which indicates that Eq. (2.25) has a general solution in the form of

$$w(x) = C_1 \cdot \text{}_1 F_1(\bar{\lambda}, \bar{\lambda} + \bar{\gamma}, x) + C_2 \cdot x^{1-\bar{\lambda} - \bar{\gamma}} \text{}_1 F_1(1 - \bar{\gamma}, 2 - \bar{\lambda} - \bar{\gamma}, x), \quad (2.26)$$

with two undetermined coefficients $C_1$ and $C_2$. To determine $C_1$ and $C_2$, we can substitute the general solution (2.26) into initial values in (2.25), and utilize formulas [1]

$$\begin{align*}
\frac{d_1 F_1(a, b, z)}{dz} &= \frac{a}{b} F_1(a + 1, b + 1, z) \\
\frac{d_1 [z^{b-1} F_1(a, b, z)]}{dz} &= (b - 1) z^{b-2} F_1(a, b - 1, z)
\end{align*}$$

to obtain

$$\begin{align*}
\left\{ \begin{array}{c}
C_1 \cdot \text{}_1 F_1(\bar{\lambda}, \bar{\lambda} + \bar{\gamma}, \bar{v} z_0) + C_2 \cdot (\bar{v} z_0)^{1-\bar{\lambda} - \bar{\gamma}} F_1(1 - \bar{\gamma}, 2 - \bar{\lambda} - \bar{\gamma}, \bar{v} z_0) = 1, \\
\frac{C_1 \cdot \bar{\lambda}}{\lambda + \bar{\gamma}} \text{}_1 F_1(\bar{\lambda} + 1, \bar{\lambda} + \bar{\gamma} + 1, \bar{v} z_0) + \frac{C_2 \cdot (1 - \bar{\lambda} - \bar{\gamma})}{(\bar{v} z_0)^{\lambda + \bar{\gamma}}} F_1(1 - \bar{\gamma}, 1 - \bar{\lambda} - \bar{\gamma}, \bar{v} z_0) = 0.
\end{array} \right.
\end{align*}$$

Solving these algebra equations readily leads to $C_1$ and $C_2$. By applying Wronskian equality [9, 30]

$$e^z = \text{}_1 F_1(c - d + 1, 1 - d, z) F_1(c, d, z) - \frac{cz}{d(1 - d)} F_1(c - d + 1, 2 - d, z) F_1(c + 1, d + 1, z),$$
and Kummer transformation $e^{-z} {}_1 F_1(c, d, z) = {}_1 F_1(d - c, d, -z)$ [9, 30], we have

$$C_1 = {}_1 F_1(-\bar{\lambda}, 1 - \bar{\lambda} - \bar{\gamma}, -\bar{v}z_0) \text{ and } C_2 = \frac{-\bar{\lambda}(\bar{v}z_0)^{\lambda + \bar{\gamma}} {}_1 F_1(\bar{\gamma}, \bar{\lambda} + \bar{\gamma} + 1, -\bar{v}z_0)}{(1 - \lambda - \bar{\gamma})(\lambda + \bar{\gamma})}.$$  

The substitution of this into (2.26) with $x = \bar{v}z$ and $z_0 = z e^{-\delta t}$ gives the generating function

$$V(z, t) = -\frac{\bar{v}z \lambda e^{-(\lambda + \gamma)^t} {}_1 F_1(\bar{\gamma}; 1 + \bar{\lambda} + \bar{\gamma}; -\bar{v}ze^{-\delta t})}{(\lambda + \bar{\gamma})(1 - \lambda - \bar{\gamma})} {}_1 F_1(1 - \bar{\gamma}; 2 - \lambda - \bar{\gamma}; \bar{v}z) + {}_1 F_1(-\bar{\lambda}; 1 - \bar{\lambda} - \bar{\gamma}; -\bar{v}ze^{-\delta t}) {}_1 F_1(\bar{\lambda}; \bar{\lambda} + \bar{\gamma}; \bar{v}z). \quad (2.27)$$

We are now to verify (2.22)-(2.24). As shown in (2.11), $V(z, t)$ can be expressed in the form of an infinite series with the general term $a_{n_i}(t)z^{n_i}$. This indicates that we can substitute the expression (2.20) of $a_{n_i}(t)$ into (2.27), and then expanding (2.27) in $z^n$ with its coefficients $a_{n_i}(t)$. For $n_i F_1(a, b, z) \times {}_1 F_1(c, d, z)$, if $n_i \geq 0$ and $0 \leq i \leq n$, then the multiplication of the $i$th term of the first $n_i$ and the $(n - i)$th term of the second $n_i$ can generate $z^n$. This finding helps expand the first formula of (2.27):

$$\sum_{n=0}^{\infty} \frac{(-\bar{v}z \lambda e^{-(\lambda + \gamma)^t} {}_1 F_1(\bar{\gamma}; 1 + \bar{\lambda} + \bar{\gamma}; -\bar{v}ze^{-\delta t})}{(\lambda + \bar{\gamma})(1 - \lambda - \bar{\gamma})} {}_1 F_1(1 - \bar{\gamma}; 2 - \lambda - \bar{\gamma}; \bar{v}z)$$

$$= \sum_{n=0}^{\infty} \sum_{i=0}^{n} -\frac{\bar{v}z \lambda e^{-(\lambda + \gamma)^t}}{(\lambda + \bar{\gamma})(1 - \lambda - \bar{\gamma})} (\bar{v}z)^n (\lambda + \bar{\gamma})^{-1} (1 + \bar{\lambda} + \bar{\gamma})^{-1} (1 - \bar{\gamma})^{-1} (2 - \lambda - \bar{\gamma})^{-1} z^{n-i}$$

$$= \sum_{n=0}^{\infty} \sum_{i=0}^{n} \sum_{j=0}^{n-i} a_{i,j} e^{-(\lambda + \gamma)^t} z^n,$$  

where $a_{i,j}$ is given by (2.24). Similarly, the second formula in (2.27) takes the form of

$$\sum_{n=0}^{\infty} \frac{\bar{v}z \lambda e^{-(\lambda + \gamma)^t} {}_1 F_1(\bar{\gamma}; 1 + \bar{\lambda} + \bar{\gamma}; -\bar{v}ze^{-\delta t})}{(\lambda + \bar{\gamma})(1 - \lambda - \bar{\gamma})} {}_1 F_1(1 - \bar{\gamma}; 2 - \lambda - \bar{\gamma}; \bar{v}z)$$

$$= \sum_{n=0}^{\infty} \sum_{i=0}^{n} \frac{1}{(1 - \lambda - \bar{\gamma})} (\bar{v}z)^n (\lambda + \bar{\gamma})^{-1} (1 + \bar{\lambda} + \bar{\gamma})^{-1} (1 - \bar{\gamma})^{-1} (2 - \lambda - \bar{\gamma})^{-1} z^{n-i}$$

$$= \sum_{n=0}^{\infty} \sum_{i=0}^{n} \sum_{j=0}^{n-i} a_{i,j} e^{-(\lambda + \gamma)^t} z^n,$$  

where $a_{i,j}$ is given by (2.23). Summing up (2.28) and (2.29) gives

$$V(z, t) = \sum_{n=0}^{\infty} a_n(t)z^n = 1 + \sum_{n=1}^{\infty} \bar{v}z^n \left[ \sum_{i=0}^{n} a_{i,n} e^{-i\delta t} + \sum_{i=0}^{n-1} a_{i,n} e^{-(i\delta + \lambda + \gamma)t} \right] z^n,$$  

which verifies (2.22) and the proof is completed. \qed
Therefore, the substitution of (2.22)-(2.24) gives

\[
m(t) = a_1(t) = \frac{\bar{v}\lambda}{\lambda + \gamma} + \frac{\bar{v}\lambda e^{-\delta t}}{1 - \lambda - \gamma} - \frac{\bar{v}\lambda}{(\lambda + \gamma)(1 - \lambda - \gamma)} e^{-(\lambda + \gamma)t}. \tag{2.30}
\]

and

\[
V(t) = a_1(t) - a_1^2(t) + \frac{\bar{v}^2\lambda(\lambda + 1)}{\lambda + \gamma + 1} e^{-(\lambda + \gamma)t} - \frac{\bar{v}^2\lambda(1 - \bar{\lambda})}{(1 - \lambda - \gamma)(2 - \lambda - \bar{\gamma})} e^{-2\delta t}.
\]

\[
- \frac{\bar{v}^2\lambda}{(\lambda + \gamma)(1 - \lambda - \gamma)} \left[ \frac{1 - \bar{\gamma}}{(2 - \lambda - \bar{\gamma})} e^{-(\lambda + \gamma)t} - \frac{\bar{\gamma}}{(1 + \lambda + \gamma)} e^{-(\delta + \lambda + \gamma)t} \right].
\]

Remark 2.2. For generic reason, we shall assume that \(\bar{\lambda} + \bar{\gamma}\) does not equal to positive integers otherwise there exist singular points in (2.23) and (2.24). This case can be treated by taking limits appropriately in the calculation. For example, by letting \(\bar{\lambda} + \bar{\gamma} \rightarrow 1\) in (2.30) and utilizing L’Hospital’s rule [2], we obtain

\[
\lim_{\bar{\lambda} + \bar{\gamma} \rightarrow 1} a_1(t) = \bar{v}\lambda + \bar{v}\lambda \lim_{\bar{\lambda} + \bar{\gamma} \rightarrow 1} \frac{e^{-\delta t} - e^{-(\lambda + \gamma)t}}{1 - \lambda - \gamma} = \bar{v}\lambda - \bar{v}\lambda \delta t e^{-\delta t} = \bar{v}\lambda(1 - \delta t e^{-\delta t}).
\]

Theorem 2 indicates that \(P_m(t)\) takes an alternative form.

Corollary 2.1. For each integer \(m \geq 0\), the mass function \(P_m(t)\) can be expressed by

\[
P_0(t) = 1 + \sum_{i=0}^{\infty} \left[ \sum_{n=\max\{1, i\}}^{\infty} b_{i,n} \right] e^{-i\delta t} + \sum_{i=0}^{\infty} \left[ \sum_{n=\max\{1, i+1\}}^{\infty} \bar{b}_{i,n} \right] e^{-(i\delta + \lambda + \gamma)t} \tag{2.31}
\]

and for \(m \geq 1\)

\[
P_m(t) = \sum_{i=0}^{\infty} \left[ \sum_{n=\max\{m, i\}}^{\infty} b_{i,n} \right] e^{-i\delta t} + \sum_{i=0}^{\infty} \left[ \sum_{n=\max\{m, i+1\}}^{\infty} \bar{b}_{i,n} \right] e^{-(i\delta + \lambda + \gamma)t}. \tag{2.32}
\]

Here

\[
b_{i,n} = \frac{(-1)^{n-m+i} C_n C_{i,n} \bar{v}^n}{i!(n-i)!} \left( \frac{-\bar{\lambda}}{1 - \lambda - \bar{\gamma}} \right)_i \left( \frac{\bar{\lambda}}{\lambda + \bar{\gamma}} \right)_{n-i} \tag{2.33}
\]

and

\[
\bar{b}_{i,n} = \frac{(-1)^{n-m+i+1} C_n C_{i,n} \bar{v}^n \bar{\lambda}}{(\lambda + \bar{\gamma})(1 - \lambda - \bar{\gamma})i!(n - 1 - i)!} \left( \frac{\bar{\gamma}}{1 + \lambda + \bar{\gamma}} \right)_i \left( \frac{1 - \bar{\gamma}}{2 - \lambda - \bar{\gamma}} \right)_{n-1-i}. \tag{2.34}
\]
Proof. For the case $m \geq 1$, we first substitute $a_n(t), n \geq 1$ of (2.22) into (2.8) and obtain

$$P_m(t) = \sum_{n=m}^{\infty} (-1)^{n-m} c_n^m \bar{v}^n \left[ \sum_{i=0}^{n} a_{i,n} e^{-i\delta t} + \sum_{i=0}^{n-1} \bar{a}_{i,n} e^{-(i\delta + \lambda + \gamma)t} \right],$$

which gives

$$P_m(t) = \sum_{n=m}^{\infty} \sum_{i=0}^{n} (-1)^{n-m} c_n^m \bar{v}^n a_{i,n} e^{-i\delta t} + \sum_{n=m}^{\infty} \sum_{i=0}^{n-1} (-1)^{n-m} c_n^m \bar{v}^n \bar{a}_{i,n} e^{-(i\delta + \lambda + \gamma)t},$$

Then by reversing the order of summarization we further derive

$$P_m(t) = \sum_{i=0}^{\infty} \sum_{n=\max\{m,i\}}^{\infty} (-1)^{n-m} c_n^m \bar{v}^n a_{i,n} e^{-i\delta t} + \sum_{i=0}^{\infty} \sum_{n=\max\{m,i+1\}}^{\infty} (-1)^{n-m} c_n^m \bar{v}^n \bar{a}_{i,n} e^{-(i\delta + \lambda + \gamma)t},$$

and (2.32) is verified by the substitution of (2.23) and (2.24).

Similarly, for the case $m = 0$, we first express $P_0(t)$ as

$$P_0(t) = \sum_{n=0}^{\infty} (-1)^n c_n^0 a_n(t) = 1 + \sum_{n=1}^{\infty} (-1)^n a_n(t)$$

by virtue of (2.8) and (2.22). Then the substitution of (2.22) followed by the change of the summarization order lead to

$$P_0(t) = 1 + \sum_{i=0}^{\infty} \sum_{n=\max\{1,i\}}^{\infty} (-1)^n \bar{v}^n a_{i,n} e^{-i\delta t} + \sum_{i=0}^{\infty} \sum_{n=\max\{1,i+1\}}^{\infty} (-1)^n \bar{v}^n \bar{a}_{i,n} e^{-(i\delta + \lambda + \gamma)t},$$

and (2.31) is verified by substituting (2.23) and (2.24).

The ratio test (2.18) shows that the series (2.8) converges absolutely, and thus (2.31) and (2.32) are convergent due to Riemann rearrangement theorem [2]. We finally show the convergence of coefficients $\sum_{n=\max\{1,i\}}^{\infty} b_{i,n}$ and $\sum_{n=\max\{m,i+1\}}^{\infty} b_{i,n}$. It is sufficient to test if ratios satisfy [2]

$$\lim_{n \to \infty} \frac{b_{i,n+1}}{b_{i,n}} < 1 \text{ and } \lim_{n \to \infty} \frac{\bar{b}_{i,n+1}}{\bar{b}_{i,n}} < 1.$$

In fact, this can be readily verified by substituting (2.33) and (2.34)

$$\lim_{n \to \infty} \frac{b_{i,n+1}}{b_{i,n}} = \lim_{n \to \infty} \left| \frac{\bar{v}(n+1) (\bar{\lambda} + n - i)}{(n-m+1)(n+1-i)(\bar{\lambda} + \bar{\gamma} + n - i)} \right| = 0 < 1,$$

and

$$\lim_{n \to \infty} \frac{\bar{b}_{i,n+1}}{\bar{b}_{i,n}} = \lim_{n \to \infty} \left| \frac{\bar{v}(n+1) (1 - \bar{\gamma} + n - 1 - i)}{(n-m+1)(n-i)(2 - \bar{\lambda} - \bar{\gamma} + n - 1 - i)} \right| = 0 < 1.$$

The proof is completed. \qed
Corollary 2.2. If $\gamma = \delta$, then $P_m(t)$ can be simplified in the form of integrals

$$
P_m(t) = \frac{\pi^m}{m!} \left[ \lambda \int_0^1 e^{-\bar{z}(s-e^{-\delta t})} (s - e^{-\delta t})^m s^{\bar{\lambda}-1} ds ight. $$

$$
\left. - (-1)^m e^{-(\lambda+m\delta)t} \int_0^1 (m + \bar{v}e^{-\delta t}s) e^{\bar{v}e^{-\delta t}s} s^{m-1}(1-s)^{\bar{\lambda}} ds \right]. \tag{2.35}
$$

**Proof.** We first substitute $\bar{\gamma} = \gamma/\delta = 1$ into (2.27). This gives

$$
V(z, t) = _1F_1(-\bar{\lambda}; -\bar{v}e^{-\delta t}; \bar{\lambda} + 1; \bar{v}z) + \frac{\bar{v}e^{-\lambda e^{-\delta t}t} \Gamma(1_2 + \bar{\lambda}; -\bar{v}e^{-\delta t})}{1 + \lambda}.
$$

The definition (2.20) of $\Gamma(z)$ indicates $\Gamma(1) = e^z$ and $\Gamma(0, a, z) = 1$, and thus $V(z, t)$ can be simplified as

$$
V(z, t) = e^{-\bar{v}e^{-\delta t}} _1F_1(\bar{\lambda}; \bar{\lambda} + 1; \bar{v}z) + \frac{\bar{v}e^{-\lambda e^{-\delta t}t} \Gamma(1; 2 + \bar{\lambda}; -\bar{v}e^{-\delta t})}{1 + \lambda}. \tag{2.36}
$$

By the integral representation of $\Gamma(z)$

$$
_1F_1(a, b, z) = \frac{\Gamma(b)}{\Gamma(a)\Gamma(b-a)} \int_0^1 e^{zs} s^{a-1} (1-s)^{b-a-1} ds, \quad b > a > 0,
$$

with $\Gamma(z)$ being Gamma function, we further transform $V(z, t)$ to the integral form

$$
V(z, t) = e^{-\bar{v}e^{-\delta t}} \frac{\Gamma(\bar{\lambda} + 1)}{\Gamma(\bar{\lambda})} \int_0^1 e^{\bar{v}zs} \lambda^{\bar{\lambda} - 1} ds
$$

$$
+ \frac{\bar{v}e^{-\lambda e^{-\delta t}t} \Gamma(2 + \bar{\lambda})}{1 + \lambda} \int_0^1 e^{-\bar{v}e^{\delta t} - \delta t} (1-s)^{\bar{\lambda}} ds.
$$

Using $\Gamma(a + 1) = a\Gamma(a)$ we arrive at

$$
V(z, t) = \bar{\lambda} \int_0^1 e^{\bar{v}z(s-e^{-\delta t})} s^{\bar{\lambda} - 1} ds + \bar{v}e^{-\lambda e^{-\delta t}t} \int_0^1 e^{-\bar{v}zse^{-\delta t}} (1-s)^{\bar{\lambda}} ds. \tag{2.36}
$$

We extract $P_m(t)$ from (2.36) through the conversion formula (1.3). With the help of the elementary identity

$$
\partial^m (z^a) / \partial z^m = (m + az)^m = (m + az)^m e^{az},
$$

we find

$$
\frac{\partial^m V(z, t)}{\partial z^m} = \bar{\lambda} \int_0^1 e^{\bar{v}z(s-e^{-\delta t})} (s - e^{-\delta t})^m s^{\bar{\lambda} - 1} ds
$$

$$
+ (-1)^m e^{-(\lambda+m\delta)t} \int_0^1 (m - \bar{v}e^{-\delta t}s)e^{-\bar{v}e^{-\delta t}s} s^{m-1}(1-s)^{\bar{\lambda}} ds.
$$

By substituting $z = -1$ into this expression and then dividing it by $m!$, we obtain (2.35) and the proof is completed. \qed
3. Dynamic profile of mRNA distribution. In this section, we shall discuss how the profile of \( P_m(t) \) changes as time \( t \) develops. We first claim

**Theorem 3.** \( P_m(t) \) near \( t = 0 \) takes the following property

\[
\begin{cases}
    P_0(0) = 1, \\
    P_m(0) = P_m'(0) = \cdots = P_m^{(m)}(0) = 0 \quad \text{and} \quad P_m^{(m+1)}(0) = \lambda v^m, \ m \geq 1.
\end{cases}
\]  

(3.1)

**Proof.** To verify (3.1), we first consider the property of \( a_n(t) \) near \( t = 0 \). When \( n = 0 \), note that (2.11) indicates \( a_{0,e}(t) = V_e(0,t) \) and \( a_{0,q}(t) = V_q(0,t) \). Then letting \( t = 0 \) in (2.7) gives

\[
a_{0,q}(0) = 1, \ a_{0,e}(0) = 0, \ a_{0,q}'(0) = -\lambda \text{ and } a_{0,e}'(0) = \lambda. \tag{3.2}
\]

Let integer \( j \geq 0 \). We take \( j \)th derivatives on both sides of (2.15) and (2.16), and obtain

\[
a_{n,q}^{(j+1)}(t) = \gamma a_{n,e}^{(j)}(t) - (\lambda + n\delta) a_{n,q}^{(j)}(t), \ n \geq 1, \tag{3.3}
\]

\[
a_{n,e}^{(j+1)}(t) = \lambda a_{n,q}^{(j)}(t) - (\gamma + n\delta) a_{n,e}^{(j)}(t) + v a_{n-1,e}^{(j)}(t), \ n \geq 1. \tag{3.4}
\]

If \( n = 1 \), then together with (3.2) and initial values (2.17), Eqs. (3.3) and (3.4) with \( j = 0, 1 \) indicate

\[
a_{1,q}(0) = a_{1,q}(0) = a_{1,q}'(0) = 0, \ a_{1,e}'(0) = \lambda v. \tag{3.5}
\]

Similarly, if \( n = 2 \), then the substitution of (3.5) and (2.17) into Eqs. (3.3) and (3.4) with \( j = 0, 1, 2 \) lead to

\[
\begin{cases}
    a_{2,q}(0) = a_{2,q}(0) = a_{2,q}'(0) = 0, \ a_{2,e}'(0) = \lambda v, \\
    a_{2,e}''(0) = 0
\end{cases}
\]

Repeating the same procedure finally leads to

\[
a_{n,q}^{(j)}(0) = a_{n,e}^{(j)}(0) = a_{n,q}^{(n+1)}(0) = 0 \quad \text{and} \quad a_{n,e}^{(n+1)}(0) = \lambda v^n, \ j \leq n, \ n \geq 1.
\]

Due to \( a_n(t) = a_{n,q}(t) + a_{n,e}(t) \), this implies

\[
a_n^{(j)}(0) = 0 \quad \text{and} \quad a_n^{(n+1)}(0) = \lambda v^n, \ j \leq n, \ n \geq 1. \tag{3.6}
\]

We then take \( j \)th derivatives on both side of (2.8), and arrive at

\[
P_m^{(j)}(t) = \sum_{n=m}^{\infty} (-1)^{n-m} C_n^m a_n^{(j)}(t), \ 0 \leq j \leq m + 1.
\]

Together with (3.6) and \( a_0(0) = 1 \), this readily gives (3.1), and the proof is completed.

The property (3.1) indicates that \( P_0(t) > P_m(t) \) and \( P_m(t) \) increases faster than \( P_{m+1}(t) \) near the time \( t = 0 \) regime for \( m = 1, 2, \cdots \). Thus \( P_m(t) \) must has a decaying distribution within a short original time period. This is intuitive as most genes are still remained silent. As time develops, it is expected that the profile of \( P_m(t) \) may change constantly. Intriguingly, we observe three patterns for the dynamic transition among \( P_m(t) \) profile curves, which are tightly correlated with the three steady-state distribution modes: Decaying, unimodality and bimodality (Fig.3). To illustrate this, we fix the degradation rate \( \delta = 0.1 \text{ min}^{-1} \) and set two
synthesis rates \( v = 1 \text{ min}^{-1} \) and \( v = 0.5 \text{ min}^{-1} \). We separately choose the pair \((\lambda, \gamma) = (3\delta, 0.6\delta), (0.5\delta, 0.1\delta), (0.6\delta, 3\delta)\) in the three subregions of the \( \lambda-\gamma \) plane, each of which corresponds to a mode of the three steady-state distributions [11]; see Fig. 3(a). Then we substitute those parameter groups into the analytical expression of \( P_m(t) \) to exhibit the rich dynamics of its profile. It shows a uniform trend that \( P_0(t) \) is pushed down and the profile curve of \( P_m(t) \) shifts to the right as time develops (Fig. 2), indicating the increase of active genes and the accumulation of mRNA copy numbers. This feature is embedded in the three transition patterns of \( P_m(t) \) profile:

(I) If \( P_m = \lim_{t \to \infty} P_m(t) \) has a unimodal distribution, then there is a threshold value \( \bar{v}^* > 0 \), when the ratio \( \bar{v} = v/\delta > \bar{v}^* \), the profile of \( P_m(t) \) changes from the decaying distribution at the initial time, to the intermediate bimodal distribution, and ultimately arrives at the unimodal distribution (Fig. 2(a)); however, the intermediate bimodality disappears when \( \bar{v} \leq \bar{v}^* \) (Fig. 2(b));

(II) If \( P_m \) has a bimodal distribution, then \( P_m(t) \) transits from the decaying distribution to the bimodal distribution and remains bimodality in the long run as time develops (Fig. 2(c));

(III) If \( P_m \) has a decaying distribution, then \( P_m(t) \) maintains the decaying distribution during the whole time scale (Fig. 2(d)).

Also, we compute fano factor \( \phi(t) = V(t)/m(t) \) using the exact expression for dynamical mean transcription level \( m(t) \) and its variance \( V(t) \) in Remark 2.1 [18, 34]. For those three patterns, \( \phi(t) \) versus time \( t \) exhibits the similar profile that \( \phi(t) \) first increases in \( t \) to its peak and then decreases to the steady-state value (Fig. 2 (Inset)), reinforcing the stochastic modulation during the intermediate transcription process.

To illustrate the formation of the intermediate bimodality in Pattern (I), we vary the synthesis rate \( v \) and utilize the data from the connective tissue growth factor (ctgf) gene in response to increasing TGF-1 levels [19]: \( \delta \equiv 0.01 \text{ min}^{-1}, \lambda \equiv 2.3 \text{ min}^{-1}, \gamma \equiv 2.9 \text{ min}^{-1}, \) and \( v \) increases from 0.05 min\(^{-1}\) to 0.15 min\(^{-1}\) to up-regulate the transcription. For small \( v = 0.05 \text{ min}^{-1} \), the bimodality does not form, and the distribution mode changes directly from decaying to unimodality at the time point \( t = 190 \text{ min} \) (Fig. 3(a)). When \( v \) is enhanced across the threshold value and reaches \( v = 0.1 \text{ min}^{-1} \), the bimodality appears but lasts for only 20 minutes (Fig. 3(b)). As \( v \) increases further to \( v = 0.15 \text{ min}^{-1} \), the bimodality becomes much more significant and its duration prolongs for more than 3 folds (Fig. 3(c)).

4. **Conclusion.** In this paper, we divide the calculation of mass function \( P_m(t) \) into two steps. The first step provides a theoretical support for the method (Theorem 1). It proves that \( P_m(t) \) can be expanded in the form of a uniformly convergent infinite series

\[
P_m(t) = \sum_{n=m}^{\infty} (-1)^{n-m} C_n^m a_n(t), \quad \text{with } \frac{C_{n+1}^{m+1} a_{n+1}(t)}{C_n^m a_n(t)} \leq \bar{v} \frac{1}{(n+1-m)}, \quad n \geq m.
\]

The next step is to determine the coefficients \( a_n(t) \) (Theorem 2). This depends on solving the generating function \( V(z,t) \) from an initial value problem of a hypergeometric equation. We have derived
Figure 2. Dynamic transitions among three mRNA distribution modes. (a,b) Pattern (I): If $P_m(t)$ takes a unimodal distribution at steady-state, then for sufficient large synthesis rate $v = 10\delta$, its profile develops from the original decaying to the intermediate bimodality, and finally switches to the unimodality. However, when $v$ decreases below the threshold value $v = 5\delta$, the intermediate bimodality disappears. (c) Pattern (II): If $P_m(t)$ takes a bimodal distribution at steady-state, then its profile transits from the decaying to the bimodality at some time points, and maintains the bimodality in a long run. (d) Pattern (III): If $P_m(t)$ takes a decaying distribution at steady-state, then it maintains the same distribution mode within the whole time regime. (Inset) Fano factor versus time for the three patterns.

\[ a_0(t) = 1, \]

\[
a_n(t) = \sum_{i=0}^{n} (-1)^i \tilde{v}^i e^{-\delta t} \left( \frac{-\tilde{\lambda}}{1 - \tilde{\lambda} - \tilde{\gamma}} \right)_i \left( \frac{\tilde{\lambda}}{\tilde{\lambda} + \tilde{\gamma}} \right)^{n-i} + \sum_{i=0}^{n-1} \frac{(-1)^{i+1} \tilde{v}^{i+1}}{i!(n-1-i)!(\lambda + \gamma)(1 - \lambda - \gamma)} \left( \frac{\gamma}{1 + \lambda + \gamma} \right)_i \left( \frac{1 - \gamma}{2 - \lambda - \gamma} \right)^{n-i}, \quad n \geq 1,
\]

with the shifted factorial $(\cdot)_k$ defined by (2.21). More generally, the two steps presented here may be implemented to the other stochastic transcription models with constant rates [14, 35, 36]. However, this method can not be directly applied when system rates are time-dependent [16, 17, 26] as ordinary equations (2.15)-(2.17) and (2.25) with variable coefficients are hard to be solved.
Figure 3. Increasing mRNA synthesis rate $v$ improves the formation of the intermediate bimodal distribution. (a) The mRNA distribution does not form bimodality when $v$ is relatively small. (b) The intermediate bimodality appears when $v$ increases across the threshold value. (c) As $v$ increases further, the duration of the bimodality prolongs with its second peak moving to the right.

The exact expression of $P_m(t)$ helps us characterize the dynamics of its profile by three patterns, each of which separately corresponds to one of the three distribution mode at steady-state (Fig. 3(a)). Intriguingly, for the gene that generates a unimodal steady-state distribution, the profile of $P_m(t)$ may go through the bimodality during an intermediate time regime (Fig. 2(a)). Such transition pattern has been observed for inducible genes in yeast and mammalian cells under high stress levels [24, 22, 5]. The bimodal distribution has been widely suggested to allow cellular probabilistic “bet hedging” in face of external stresses, and is often generated by “conservative” gene that can hardly be turned active and hardly be turned inactive [15, 13, 12, 24]. However, the intermediate bimodality indicates that the “bet hedging” strategy is still able to be achieved even for the active gene that would generate phenotypic homogenous expressing cell population at steady-state.

Moreover, we show that such bimodality does not form until the mRNA synthesis rate $v$ exceeds a threshold value and its duration can be prolonged significantly by increasing $v$. This finding may shed light on illustrating the fitness benefit for the observed regulation scenario in mammalian ctf4 gene that up-regulates $v$ in response to increasing physiological stimuli [19].

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