DISTRIBUTION PROFILES IN GENE TRANSCRIPTION ACTIVATED BY THE CROSS-TALKING PATHWAY

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ABSTRACT. Gene transcription is a stochastic process, manifested by the heterogeneous mRNA distribution in an isogenic cell population. Bimodal distribution has been observed in the transcription of stress responsive genes which have evolved to be easily turned on and easily turned off. This is against the conclusion in the classical two-state model that bimodality occurs only when the gene is hardly turned on and hardly turned off. In this paper, we extend the gene activation process in the two-state model by introducing the cross-talking pathway that involves the random selection between a spontaneous weak basal pathway and a stress-induced strong signaling pathway. By deriving exact forms of mRNA distribution at steady-state, we find that the cross-talking pathway is much more likely to trigger the bimodal distribution. Our further analysis reveals an observed transition among the decaying, bimodal and unimodal mRNA distribution for stress gene upon enhanced stimulations. Especially, the bimodality occurs when the stress-induced signalling pathway is more frequently selected, reinforcing the assertion that bimodal transcription is a general feature of stress genes in response to environmental change.

1. Introduction. Gene transcription is fundamentally a stochastic process, manifested by the fluctuation of mRNA copy number in a population of isogenic cell [7, 25, 16]. The advanced technique has helped biologists estimate rather precisely the mRNA copy number of a given gene in single cells. By combining with statistical method, they have obtained a large data set on histogram of mRNA copy numbers under various cellular conditions [16, 10, 23]. This sets a statistical basis for approximating the mass function $P_m$, the probability that there are exactly $m$ mRNA molecules of the gene in a typical cell [6, 4, 33].

The mass function $P_m$ depicts a complete characterization for the statistics of random gene transcription. The most common observed modes for $P_m$ have been one of the following three types:

\begin{itemize}
  \item Type I: $P_m \propto \frac{1}{m!}$
  \item Type II: $P_m \propto \frac{1}{m^2}$
  \item Type III: $P_m \propto \frac{1}{m^{3/2}}$
\end{itemize}

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Decaying distribution (Fig. 1a), as shown in tetO promoter in mammalian cells [23], for which 

$$P_{m+1} \leq P_m$$ for all \( m = 0, 1, \cdots \); 

Unimodal distribution (Fig. 1b), as shown by housekeeping genes in yeast [32], for which 

$$P_0 \leq P_1 \leq \cdots \leq P_m \leq \cdots$$ and 

$$P_m \geq P_{m+1} \geq \cdots$$; 

Bimodal distribution (Fig. 1c), as shown by P_{lac/ara} promoter in E. coli [3], for which 

$$P_m$$ takes exactly two peaks with the first one at \( m = 0 \) and the second at some \( m > 0 \).

Figure 1. Three modes of mRNA distribution generated by the two-state model. (a) The decaying distribution for which \( P_m \) deceases in \( m \) for \( m = 0, 1, 2, \cdots \). (b) The unimodal distribution for which \( P_m \) takes exactly one peak at some \( m > 0 \). (c) The bimodal distribution for which \( P_m \) takes exactly two peaks with the first one at \( m = 0 \), and the other one at some \( m > 0 \). The parameter sets \((k_{on}, k_{off}, k_b, k_d)\) in (a), (b), and (c) are chosen as \((0.5, 1.5, 20, 1)\), \((2, 2, 10, 1)\), and \((0.1, 0.2, 15, 1)\), respectively.

The experimental data on those three modes of mRNA distribution have been widely fitted by the two-state model [16, 10, 23, 2]

$$\begin{align*}
\text{gene off} & \xrightarrow[k_{on}]{k_{off}} \text{gene on} \xrightarrow{k_b} \text{mRNA} \xrightarrow{k_d} \emptyset.
\end{align*}$$

In the two-state model (1.1), the durations in the gene on (active) and gene off (inactive) states, the waiting time for producing one mRNA molecule in active genes, and the time for degrading one mRNA molecule are all assumed to follow exponential distributions, with the activation rate \( k_{on} \), the inactivation rate \( k_{off} \), the production rate \( k_b \), and the degradation rate \( k_d \). In our previous work [5], we proved that the two-state model (1.1) can generate, and generate only, the decaying, unimodal, or bimodal distribution \( P_m \) at steady-state. Especially, separately denote by \( T_{off} \) and \( T_{on} \) the dimensionless mean durations of gene off and on states. Then bimodal distribution occurs only in the “conservative” transcription system for which off states can hardly be turned on \((T_{off} = k_d/k_{on} > 1)\) and on states can hardly be turned off \((T_{on} = k_d/k_{off} > 1)\).

The bimodal transcription distribution has been observed for some inducible genes in response to acute stresses [22, 17, 18]. Signal transduction of those stress genes is often rapid to ensure the cellular adaption of transient environmental changes. For instance, most osmostress-responsive genes, such as STL1, GRE2 or GPD1, are induced within 1 to 3 minutes in yeast [22, 17]. Also, some intrinsic regulatory mechanisms have developed to suppress stress genes under normal growth condition to avoid the over-exuberant expression. For instance, RNA Pol II usually initiates transcription into only the first 20-40 nucleotides of heat-responsive...
gene in *Drosophila melanogaster* [17]. These observations suggest that stress genes have evolved to be easily turned off and easily turned on, in which case the two-state modal is unable to generate the bimodal distribution [5].

Stress genes have to fulfill two requirements. First, the spontaneous basal pathway with weak activation strength is presented when cells are under normal growth conditions [22, 14]. In this case, most cells are off, giving rise to the decaying mRNA distribution. Second, when cells are challenged by acute stresses, the transcription of stress genes is induced by specific signal transduction pathways with strong strength [12, 24]. For instance, upon osmotic stress, the osmostress-responsive genes in *S. cerevisiae* are activated by the MAPK HOG pathway [22]. This gives rise to the bimodal transcription pattern that increases fitness to face a large range of stress.

To characterize the transcription of stress genes stimulated by environmental signals, we integrate the cross-talking pathway into the activation process in the two-state model (1.1). As depicted in Fig. 2, the gene activation is induced by two parallel pathways from gene off state (denoted by $O$) to gene on state (denoted by $E$) [31, 26, 27]. The residence times in two pathways are independent and exponentially distributed, with the induction strengths $k_{on1}$ for the weak basal pathway and $k_{on2}$ for the strong signaling pathway, satisfying

$$0 < k_{on1} < k_{on2} < \infty.$$  

Let $O_1$ denote the gene off state in which the transition from state $O$ to state $E$ is induced by the weak pathway, and $O_2$ otherwise. The individual pathways are selected with probabilities $q_i = \text{Prob}(O = O_i), \ i = 1, 2,$ with

$$0 < q_1, q_2 < 1 \text{ and } q_1 + q_2 = 1.$$  

The residence times for the active state $E$ and the production of a new transcript are controlled by the same mechanisms in the two-state model (1.1).  

![Figure 2. Gene transcription modulated by the cross-talking pathway [31].](image)

We normalize the system parameters by the degradation rate $k_d$, and obtain dimensionless rates

$$\lambda_1 = \frac{k_{on1}}{k_d}, \ \lambda_2 = \frac{k_{on2}}{k_d}, \ \gamma = \frac{k_{off}}{k_d}, \ v = \frac{k_b}{k_d}. \quad (1.2)$$

We introduce two symbols

$$\alpha = A + \sqrt{A^2 - B}, \ \beta = A - \sqrt{A^2 - B}, \quad (1.3)$$
where $A$ and $B$ are the simple mathematical formulas of the rate constants

$$A = \frac{\lambda_1 + \lambda_2 + \gamma}{2} \quad \text{and} \quad B = \lambda_1\lambda_2 + q_1\lambda_2\gamma + q_2\lambda_1\gamma.$$  

(1.4)

It is easy to verify that

$$A^2 > B \quad \text{and} \quad \lambda_1 < \beta < \lambda_2 < \alpha.$$  

(1.5)

We first calculate the analytical forms of $P_m$. To simplify the expressions, we denote by $I_m(a_1, a_2, b_1, b_2, c, m = 0, 1, \ldots)$, the double integral:

$$I_m(a_1, a_2, b_1, b_2, c) = \int_0^1 \int_0^1 s^{a_1+m-1}(1-s)^{b_1-a_1-1} \times [e^{-cs\sigma}\sigma^{a_2+m-1}(1-\sigma)^{b_2-a_2-1}d\sigma]ds,$$  

(1.6)

with the relation of real numbers

$$b_1 > a_1 > 0, \ b_2 > a_2 > 0 \ \text{and} \ c > 0$$

(1.7)

that guarantees the existence of the integral in (1.6). For each integer $n \geq 0$, let $G(n)$ be the constant consisting of four Gamma functions:

$$G(n) = \Gamma(\beta + n)\Gamma(\alpha + n)\Gamma(\lambda_1 + n)\Gamma(\lambda_2 + n), \ n = 0, 1, \ldots.$$  

(1.8)

Theorem 1. The mass function $P_m$ at steady-state can be expressed as

$$P_m = \frac{v^m}{m! G(m)} G(0) \frac{\Gamma(\alpha - \lambda_2)\Gamma(\beta - \lambda_1)}{\Gamma(\lambda_1 + \alpha + m)\Gamma(\lambda_2 + \beta + m)} I_m(\lambda_1, \lambda_2, \beta, \alpha, v)$$

(1.9)

$$= \frac{v^m}{m! G(m)} G(0) 2F_2(\lambda_1 + m, \lambda_2 + m; \beta + m, \alpha + m, -v),$$  

(1.10)

where $I_m$ and $G(\cdot)$ are given by (1.6) and (1.8), and $2F_2$ is the generalized hypergeometric function$[1]$

$$2F_2(\lambda_1 + m, \lambda_2 + m; \beta + m, \alpha + m; x) = \sum_{k=0}^{\infty} \frac{(\lambda_1 + m)_k (\lambda_2 + m)_k}{(\beta + m)_k (\alpha + m)_k} x^k,$$  

(1.11)

with $(a)_k$ being the shifted factorial:

$$(a)_0 = 1, \quad (a)_k = a (a + 1) \cdots (a + k - 1) \quad \text{for} \quad k = 1, 2, \ldots.$$  

By taking advantage of exact forms (1.9) and (1.10), we are able to analyze in detail how the cross-talking pathway modulates mRNA distribution profiles. Compared to the two-state model (1.1), there is no more new types of mRNA distribution except for the decaying, unimodal and bimodal distributions. However, the cross-talking pathway is much more likely to generate the bimodal distribution. Especially, we see the clear bimodality even if the gene is hardly turned on (T_{off} < 1) and easily turned off (T_{on} < 1), extending the assertion that the bimodal distribution happens only when the gene is hardly turned on (T_{off} > 1) and hardly turned off (T_{on} > 1)$[16, 8]. Also, it is reported that the multi-pathway tends to enhance transcription noise$[31, 13, 30]$, while the single pathway tends to suppress noise$[33, 9]$. A bimodal distribution with a large noise supports a binary process that steers cells into sub-populations with distinct cell identities$[16]$. Therefore, for stress genes, the cross-talking pathway would generate a phenotypic variability in response to unpredictable environmental changes.
When the stress gene is induced by acute stresses with enhanced intensity, we successfully simulate the typical transcriptional transition from the decaying to the unimodal distribution undergoing the intermediate bimodality [22, 17, 18]. Interestingly, the bimodal distribution occurs when the stress-induced strong signaling pathway is more frequently selected. This explains why the bimodal expression is so general for stress genes upon osmotic, heat and oxidative stimulations [22], and indicates an evolution strategy of the stress-induced pathway: The transcription of stress genes is dominated by the single weak pathway to maintain the basal transcription at lower stress levels, but modulated by the cross-talking pathway to generate bimodal distribution that has a better fitness benefit as stress level increases [22].

2. Exact forms of mRNA distribution at steady-state. We prove Theorem 1 in this section. Let \( P_{m,j}(t), j = 1, 2, e, \) be the respective probabilities that the gene is residing in states \( O_1, O_2 \) and \( E \) at time \( t \), and \( m \) mRNA molecules are produced. Then the total probability mass function

\[
P_m(t) = P_{m,1}(t) + P_{m,2}(t) + P_{m,e}(t)
\]

quantifies the probability of \( m \) mRNA molecules at time \( t \). By the standard steps in the theory of stochastic processes [33, 28, 11, 29], the calculation of \( P_m(t) \) determined in the cross-talking pathway model (Fig. 2) can be transformed into solving the system of the following master equations:

\[
\frac{1}{k_d} \frac{d}{dt} P_{m,1}(t) = q_1 \gamma P_{m,e}(t) - (m + \lambda_1)P_{m,1}(t) + (m + 1)P_{m+1,1}(t), \tag{2.1}
\]

\[
\frac{1}{k_d} \frac{d}{dt} P_{m,2}(t) = q_2 \gamma P_{m,e}(t) - (m + \lambda_2)P_{m,2}(t) + (m + 1)P_{m+1,2}(t), \tag{2.2}
\]

\[
\frac{1}{k_d} \frac{d}{dt} P_{m,e}(t) = (m + 1)P_{m+1,e}(t) + vP_{m-1,e}(t), \tag{2.3}
\]

where by convention \( P_{-1,e}(t) = 0 \). Without loss of generality, we assume that the gene is inactive and the number of transcripts is zero at \( t = 0 \):

\[
P_{0,1}(0) = q_1, \quad P_{0,2}(0) = q_2 \quad \text{and} \quad P_{0,e}(0) = P_{m,i}(0) = 0, \quad i = 1, 2, e, \quad m \geq 1. \tag{2.4}
\]

To move on, the standard procedure is to introduce the probability generating functions

\[
V_i(z,t) = \sum_{m=0}^{\infty} (z+1)^m P_{m,i}(t), \quad i = 1, 2, e, \tag{2.5}
\]

which transform (2.1)-(2.4) into the system of first order partial differential equations:

\[
\frac{1}{k_d} \frac{\partial V_1(z,t)}{\partial t} = -\lambda_1 V_1(z,t) + q_1 \gamma V_e(z,t) - z \frac{\partial V_1(z,t)}{\partial z}, \tag{2.6}
\]

\[
\frac{1}{k_d} \frac{\partial V_2(z,t)}{\partial t} = -\lambda_2 V_2(z,t) + q_2 \gamma V_e(z,t) - z \frac{\partial V_2(z,t)}{\partial z}, \tag{2.7}
\]

\[
\frac{1}{k_d} \frac{\partial V_e(z,t)}{\partial t} = \lambda_1 V_1(z,t) + \lambda_2 V_2(z,t) + (vz - \gamma) V_e(z,t) - z \frac{\partial V_e(z,t)}{\partial z}, \tag{2.8}
\]

\[
V_1(z,0) = q_1, \quad V_2(z,0) = q_2 \quad \text{and} \quad V_e(z,0) = 0. \tag{2.9}
\]
Then $P_m(t)$ can be obtained by the solutions of (2.6)-(2.9) through the conversion relation

$$P_m(t) = \left. \frac{1}{m!} \frac{\partial^m V(z,t)}{\partial z^m} \right|_{z=-1}, \text{ where } V(z,t) = V_1(z,t) + V_2(z,t) + V_e(z,t), \ m \geq 0. \quad (2.10)$$

**Proof of Theorem 1.** Let $t \to \infty$ in (2.5) and denote by

$$V_i(z) = V_i(z, \infty), \ i = 1, 2, \text{ and } V(z) = V_1(z) + V_2(z) + V_e(z)$$

the probability generating functions at steady-state. Let

$$W_i(x) = V_i(z), \ i = 1, 2, \text{ and } W(x) = V(z), \text{ with } x = vz.$$  

By using the chain rule, we find $dV_i(z)/dz = v dW_i(x)/dx$ for $i = 1, 2, e$. Letting $t \to \infty$ in Eqs.(2.6)-(2.9), and using $\lim_{t \to \infty} \partial V_i(z,t)/\partial t = 0$ [20], we arrive at the initial value problem of the system of first order ordinary differential equations:

$$\begin{align*}
xW'_1(x) &= -\lambda_1 W_1(x) + q_1 \gamma W_e(x), \quad (2.11) \\
xW'_2(x) &= -\lambda_2 W_2(x) + q_2 \gamma W_e(x), \quad (2.12) \\
xW'_e(x) &= \lambda_1 W_1(x) + \lambda_2 W_2(x) - \gamma W_e(x) + xW_e(x), \quad (2.13) \\
W_1(0) &= \frac{q_1 \lambda_2 \gamma}{\alpha \beta}, \quad W_2(0) = \frac{q_2 \lambda_1 \gamma}{\alpha \beta} \text{ and } W_e(0) = \frac{\lambda_1 \lambda_2}{\alpha \beta}, \quad (2.14)
\end{align*}$$

where the initial values (2.14) follow from the fact that $W_i(0) = V_i(0)$ are the respective probabilities that the gene is residing in $O_1, O_2$ and $E$ states at steady-state [31].

To verify (1.9) and (1.10), we first extract a third order linear equation for $W = W_1 + W_2 + W_e$ from (2.11)-(2.14). Let $a$, $b$, $c$ and $d$ be real constants, and $f = f(x)$ be a smooth function of $x$. We introduce the linear operator

$$\mathcal{L}_{a,b}^c(f) = x^2 f''(x) + x(1 - x + c + d)f'(x) + (cd - x(a + b + 1))f(x) - abf(x).$$

We claim that $W(x)$ is the unique solution of the initial value problem

$$\begin{cases}
\mathcal{L}_{a,b}^c(W) = 0, \\
W(0) = 1, \ W'(0) = \frac{\lambda_1 \lambda_2}{\alpha \beta} \text{ and } W''(0) = \frac{\lambda_1 \lambda_2 (\lambda_1 + 1)(\lambda_2 + 1)}{\alpha \beta (\alpha + 1)(\beta + 1)}. \quad (2.15)
\end{cases}$$

To verify this, summing (2.11)-(2.13) leads to $W'(x) = W_e(x)$, by which the verification of the initial values $W(0)$ and $W'(0)$ becomes trivial. To calculate $W''(0)$, we first take derivatives of (2.11) and (2.12), and then substitute $x = 0$. It gives

$$W'_1(0) = \frac{q_1 \gamma}{1 + \lambda_1} W_e(0) \quad \text{and} \quad W'_2(0) = \frac{q_2 \gamma}{1 + \lambda_2} W_e(0). \quad (2.16)$$

By taking derivative of (2.13) and then substituting $x = 0$, (2.14) and (2.16), we derive

$$W'_e(0) = \left( \frac{q_1 \lambda_1 \gamma}{1 + \lambda_1} + \frac{q_2 \lambda_2 \gamma}{1 + \lambda_2} - \gamma \right) W_e(0) + \frac{\lambda_1 \lambda_2}{\alpha \beta}.$$  

Then replacing $W_e'(0)$ by $W_e''(0)$ gives the value of $W''(0)$ in (2.15).

To confirm $\mathcal{L}_{a,b}^c(\lambda W) = 0$, we first transform (2.13) to

$$\lambda_1(W_1(x) + W_2(x)) = xW'_e(x) + \gamma W_e(x) - xW_e(x) - (\lambda_2 - \lambda_1)W_2(x).$$
Substituting this equality and \( W_e = W' \) into \( W = W_1 + W_2 + W_e \) gives
\[
\lambda_1 W(x) = xW''(x) + \gamma W_e(x) - xW_e(x) - (\lambda_2 - \lambda_1)W_2(x) + \lambda_1 W_e = xW''(x) + \gamma W'(x) - xW'(x) - (\lambda_2 - \lambda_1)W_2(x) + \lambda_1 W'(x),
\]
which indicates
\[
(\lambda_2 - \lambda_1)W_2(x) = xW''(x) + (\gamma + \lambda_1 - x)W'(x) - \lambda_1 W(x).
\]
We multiply it by \( x^{\lambda_2} \) and then take derivative. It gives
\[
(\lambda_2 - \lambda_1)x^{\lambda_2-1}[xW_2'(x) + \lambda_2 W_2(x)] = x^{\lambda_2+1}W'''(x) + (1 + \lambda_2)x^{\lambda_2}W''(x) + x^{\lambda_2}(\gamma + \lambda_1 - x)W''(x) + \lambda_2 x^{\lambda_2-1}(\gamma + \lambda_1 - x)W'(x) - x^{\lambda_2}W'(x) - \lambda_1 x^{\lambda_2}W'(x) - \lambda_1 \lambda_2 x^{\lambda_2-1}W(x).
\]
The substitution of Eq.(2.12) and \( W_e = W' \) into the left hand side of the above identity leads to
\[
x^2W'''(x) + x(1 - x + \lambda_1 + \lambda_2 + \gamma)W''(x)
\]
\[
+ [\lambda_1 \lambda_2 + \lambda_2 \gamma - (\lambda_2 - \lambda_1)q_2 \gamma - x(\lambda_1 + \lambda_2 + 1)]W'(x) = \lambda_1 \lambda_2 W(x), \quad (2.17)
\]
Noticing that \( q_1 + q_2 = 1 \), we can rewrite the over-braced terms as \( \lambda_1 \lambda_2 + q_1 \lambda_2 \gamma + q_2 \lambda_1 \gamma \). Then, the substitution of the definition (1.4) into (2.17) simplifies the identity to
\[
x^2W'''(x) + x(1 - x + 2A)W''(x) + [B - x(\lambda_1 + \lambda_2 + 1)]W'(x) = \lambda_1 \lambda_2 W(x), \quad (2.18)
\]
Recognizing the definitions of \( \alpha \) and \( \beta \) given in (1.3) imply \( 2A = \alpha + \beta \) and \( B = \alpha \beta \) in (2.18), it follows immediately that \( \mathcal{L}_{\alpha,\beta}^\lambda(W) = 0 \).

We next introduce the differential operator \( \Theta = x(d/dx) \). It can be verified directly that \( \mathcal{L}_{\alpha,\beta}^\lambda(W) = 0 \) is equivalent to a generalized confluent hypergeometric equation [33]
\[
\Theta(\Theta + \alpha - 1)(\Theta + \beta - 1)W(x) - x(\Theta + \lambda_1)(\Theta + \lambda_2)W(x) = 0,
\]
which possesses a solution \( W(x) = _2F_2(\lambda_1, \lambda_2; \beta, \alpha; x) \) [33]. Also, it satisfies the initial values in (2.15) according to (1.11), implying that \( W(x) = _2F_2(\lambda_1, \lambda_2; \beta, \alpha; x) \) is the unique solution of the initial value problem (2.15). Thus, by substituting \( x = vz \), we obtain
\[
V(z) = W(vz) = _2F_2(\lambda_1, \lambda_2; \beta, \alpha; vz). \quad (2.19)
\]
Let \( a_1, a_2, b_1, b_2 \) and \( c \) be real numbers that satisfy the relation (1.7). Then we have the integral representation of \( _2F_2 \) function [19]
\[
_2F_2(a_1, a_2; b_1, b_2; c) = \frac{\Gamma(b_1)\Gamma(b_2)}{(a_1)\Gamma(a_2)\Gamma(b_1 - a_1)\Gamma(b_2 - a_2)} I_0(a_1, a_2, b_1, b_2, -c), \quad (2.20)
\]
where \( I_0 \) is given by (1.6) with \( m = 0 \). Therefore, \( V(z) \) in (2.19) can be expressed in integral form by replacing \( a_1, a_2, b_1, b_2 \) and \( c \) in (2.20) by \( \lambda_1, \lambda_2, \beta, \alpha \) and \( vz \), respectively. We obtain
\[
V(z) = \frac{G(0)}{\Gamma(\beta - \lambda_1)\Gamma(\alpha - \lambda_2)} I_0(\lambda_1, \lambda_2, \beta, \alpha, -vz). \quad (2.21)
\]
We further extract $P_m$ through the conversion formula (2.10), and have
\[
\frac{\partial^m V(z)}{\partial z^m} = \frac{v^m G(0)}{\Gamma(\beta - \lambda_1) \Gamma(\alpha - \lambda_2)} I_m(\lambda_1, \lambda_2, \beta, \alpha, -vz).
\]

By substituting $z = -1$ into this expression and then dividing it by $m!$, we obtain (1.9).

To derive (1.10), we separately replace $a_1, a_2, b_1, b_2$ and $c$ in (2.20) by $\lambda_1 + m, \lambda_2 + m, \alpha + m$ and $-v$, and obtain
\[
I_m(\lambda_1, \lambda_2, \beta, \alpha, -v) = \frac{\Gamma(\beta - \lambda_1) \Gamma(\alpha - \lambda_2)}{G(m)} 2F_2(\lambda_1 + m, \lambda_2 + m; \beta + m, \alpha + m; -v).
\]

Along with (1.9), it leads to (1.10) immediately. The proof is completed.

3. Discussion and implications in biology.

3.1. Distribution profiles. Let $T_{off}$ and $T_{on}$ be dimensionless average durations that the gene resides at off and on states, respectively. Our previous work proves that the two-state model (1.1) can generate bimodal distribution only when $T_{off} = k_d/k_{on} > 1$ and $T_{on} = k_d/k_{off} > 1$ [5]. Intriguingly, by taking advantage of the exact form (1.10), we find (i) The cross-talking pathway is capable of generating the bimodal distribution even if $T_{off} < 1$ and $T_{on} < 1$.

This phenomenon is displayed in Fig. 3a, where mRNA production rate is fixed as $v = 30$ to ensure a broad prototypical behavior of $P_m$ [4]. We take the weak and strong induction strengths $\lambda_1 = 0.6$ and $\lambda_2 = 6$, with the selection probability of the weak pathway $q_1 = 0.2$, and the inactivation rate $\gamma = 2$. Such parameter set generates relatively short gene off and on periods:
\[
T_{off} = \left( \frac{q_1}{\lambda_1} + \frac{q_2}{\lambda_2} \right) \approx 0.47 < 1, \quad \text{and} \quad T_{on} = \frac{1}{\gamma} = 0.5 < 1,
\]

and a clear bimodal distribution (Fig. 3a). Moreover, the bimodal distribution also occurs when $T_{off} < 1$ and $T_{on} > 1$ (Fig. 3b) or $T_{off} > 1$ and $T_{on} > 1$ (Fig. 3c).

Figure 3. Cross-talking pathway can generate bimodal distribution when the gene is (a) easily turned on ($T_{off} < 1$) and easily turned off ($T_{on} < 1$); (b) easily turned on ($T_{off} < 1$) but hardly turned off ($T_{on} > 1$); and (c) hardly turned on ($T_{off} < 1$) and hardly turned off ($T_{on} > 1$). mRNA synthesis rate $v = 30$ and the other parameters are set to be $(\lambda_1, \lambda_2, \gamma, q_1) = (0.6, 6, 2, 0.2)$ in (a), $(\lambda_1, \lambda_2, \gamma, q_1) = (0.2, 4, 0.2, 0.1)$ in (b), and $(\lambda_1, \lambda_2, \gamma, q_1) = (0.2, 4, 0.2, 0.2)$ in (c).

However, it is hard to see the bimodal distribution when $T_{off} > 1$ and $T_{on} < 1$. For instance, if the selection probability $q_1$ in Fig. 1(a) increases to $q_1 \geq \lambda_1 = 0.6$, etc.
then the bimodal distribution degenerates to the decaying distribution. In this case, it is easy to verify that the parameter set satisfies
\[ \lambda_1 \leq 1 \quad \text{and} \quad \beta - \lambda_1 \geq 1, \quad (3.1) \]
and we can prove

(ii) The cross-talking pathway is capable of generating the decaying distribution as long as (3.1) holds.

To verify the conclusion in (ii), we express (1.9) as
\[ P_m = \frac{M v^m}{(m + \lambda_1)m!} \int_0^1 s^{\lambda_2+m-1}(1-s)^{\alpha-\lambda_2-1} \left[ \int_0^1 e^{-vs\sigma} (1-\sigma)^{\beta-\lambda_1-1} d\sigma \right] \lambda_1+m ds, \]
If \( \beta - \lambda_1 > 1 \), through the integration by parts, we reformulate \( P_m \), \( m \geq 0 \) as
\[ P_m = \frac{M v^{m+1}}{(m + \lambda_1)m!} \int_0^1 \int_0^1 s^{\lambda_2+m}(1-s)^{\alpha-\lambda_2-1}[e^{-vs\sigma}\sigma^{\lambda_1+m}(1-\sigma)^{\beta-\lambda_1-1} d\sigma] ds 
+ \frac{M v^m(\beta - \lambda_1 - 1)}{(m + \lambda_1)m!} H_m, \quad (3.2) \]
where \( H_m \) is defined by
\[ H_m = \int_0^1 \int_0^1 s^{\lambda_2+m-1}(1-s)^{\alpha-\lambda_2-1}[e^{-vs\sigma}\sigma^{\lambda_1+m}(1-\sigma)^{\beta-\lambda_1-2} d\sigma] ds > 0. \]
Recognizing that the last second term in (3.2) is exactly \( (m + 1)P_{m+1}/(m + \lambda_1) \), and the assumption \( \beta - \lambda_1 > 1 \) guarantees the existence of \( H_m \), we arrive at
\[ P_m - P_{m+1} = \frac{1 - \lambda_1}{\lambda_1 + 1} P_{m+1} + \frac{M v^m(\beta - \lambda_1 - 1)}{(m + \lambda_1)m!} H_m > 0 \quad \text{for} \quad \lambda_1 \leq 1. \]
Similarly, if \( \beta - \lambda_1 = 1 \), we obtain
\[ P_m = \frac{M v^m}{(m + \lambda_1)m!} \int_0^1 s^{\lambda_2+m-1}(1-s)^{\alpha-\lambda_2-1} \left[ \int_0^1 e^{-vs\sigma} d\sigma \right] \lambda_1+m ds \]
\[ = \frac{M v^{m+1}}{(m + \lambda_1)m!} \int_0^1 \int_0^1 s^{\lambda_2+m}(1-s)^{\alpha-\lambda_2-1}[e^{-vs\sigma}\sigma^{\lambda_1+m} ds] ds 
+ \frac{M v^m}{(m + \lambda_1)m!} \int_0^1 s^{\lambda_2+m-1}(1-s)^{\alpha-\lambda_2-1} e^{-vs} ds. \]
Since the last second term is exactly \( (m + 1)P_{m+1}/(m + \lambda_1) \), for \( \lambda_1 \leq 1 \), we further arrive at
\[ P_m - P_{m+1} = \frac{1 - \lambda_1}{\lambda_1 + 1} P_{m+1} + \frac{M v^m}{(m + \lambda_1)m!} \int_0^1 s^{\lambda_2+m-1}(1-s)^{\alpha-\lambda_2-1} e^{-vs} ds > 0. \]
Consequently, \( P_m \) has a decaying distribution as long as (3.1) is satisfied.

3.2. Transcriptional transition pattern of stress-responsive genes. The external osmotic shock triggers MAPK HOG pathway in \( S. cerevisiae \), and leads to the rapid Hog1 nuclear translocation to activate the transcription of osmostress-responsive genes. In the interesting study [22], Pelet et al. have observed the bimodal transcription of osmostress-responsive genes in mild stress condition (0.05-0.15 M NaCl solution), manifested by two distinct cell sub-populations representing silent cells and highly expressed cells. No expression was detected at low NaCl concentration (below 0.05 M) referred to as the decaying distribution. Moreover,
cells are fully expressed at the highest NaCl concentration (above 0.15 M) referred to as the unimodal distribution. The similar phenomenon has also been observed in *S. cerevisiae* upon oxidative or heat stresses [22, 17] and pheromone gradients [18]. We demonstrate that the cross-talking pathway can generate such transition among the three mRNA distribution modes. Most mRNA half-lives in *S. cerevisiae* range around a median of 11 min [15], so we fix $k_d = \ln(2)/11 \approx 0.063 \text{ min}^{-1}$. Also, we choose $k_b = 2 \text{ min}^{-1}$, the upper bound of transcription rate for more than 4,600 genes in *S. cerevisiae* [21], and hence $v = k_b/k_d \approx 32$. Under normal growth conditions, the activity of basal pathway modulates the transcription, and the most stress genes are silenced [22, 14]. Thus we set relatively low weak induction strength $\lambda_1 = 0.6$ and high inactivation rate $\gamma = 3$. Most typical osmostress-responsive genes, such as *STL1, GRE2* or *GPD1*, are induced within 3 minutes in response to stimuli in yeast [22, 17], and thus we set the strong induction strength $k_{on2} = 1/2 \text{ min}^{-1}$, and $\lambda_2 = k_{on2}/k_d \approx 8$.

The increase of NaCl concentration gradually enhances the Hog1 nuclear accumulation both in magnitude and retention time [22], resulting in the increased selection probability $q_2$ of the stress-induced strong pathway. We set $q_2 = 0.1, 0.9$ and 0.99 that separately correspond to lower, intermediate and the highest stress levels. When $q_2 = 0.1$, the weak basal pathway is frequently selected and therefore most cells are off, giving rise to the decaying distribution (Fig. 4a). As $q_2$ increases, the strong HOG pathway is more frequently selected, giving rise to the bimodal distributions with clear on and off cell sub-populations (Fig. 4b). Finally, when $q_2$ approaches 1, most cells are turned on, resulting in the unimodal distribution (Fig. 4c).

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