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MONOTONIC DYNAMICS OF MRNA DEGRADATION BY TWO PATHWAYS*

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Abstract mRNA degradation plays an important role in gene regulation. However, a defect in mRNA decay is expected to result in an increase in mRNA levels. In this paper, we will first establish a model of mRNA regulation by two pathways denoted by $5' \to 3'$ and $3' \to 5'$ for short, where there are two degradation rates δ_1, δ_2 on $5' \to 3'$ pathway and the degradation rate on $3' \to 5'$ pathway is δ_3. The advantage of this model is that it captures fundamental biochemical reactions in the gene expression process in eukaryotic cells. Then we obtain several basic principles on the monotonicity of the mean level of newly accumulated mRNAs. It is proved that (1) the newly mean level is strictly increasing in p and κ, but is strictly decreasing in γ, where p, κ and γ are the initial activation frequency, the activation rate, and the inactivation rate, respectively; (2) the newly mean level is strictly decreasing in both δ_2 and δ_3, remarkably, is strictly increasing in δ_1 when $\delta_2 < \delta_3$ and decreasing when $\delta_2 > \delta_3$ and; (3) the newly mean level is strictly increasing in time t when $p < \kappa/(\kappa + \gamma)$. These conclusions not only provide a better understanding on gene expression dynamics but also would be helpful to design reasonable gene expression modules.

Keywords Monotonic dynamics, mRNA degradation, model, two pathways.

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1. Introduction

Gene expression is a complex probabilistic process, which involves numerous components and biochemical processes. It includes two important steps. One is the transcription that the genetic information stored in DNA is converted into the production of messenger RNA, and the other is the translation that proteins are generated from mRNAs. Transcription is inherently a biochemical and dynamical process, which contains the binding of transcription factors to the promoter, the production and degradation of mRNAs, etc. Especially, mRNA degradation plays a crucial role in the gene regulation. The balance between mRNA synthesis and decay is a key aspect in the regulation of gene expression. Variation and randomness in

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these events would bring the dynamic behavior of transcripts even in the hypothetically identical cellular environment. Some results(see, for example, [21,22,29,31]) tell us that randomness in the transcription process comes from random switching between "gene on" and "gene off ", which seems like a bulb located between active and inactive states. Some results obtained in [5,11,32] also analysed the dynamic behavior of transcripts by establishing mathematical models. These elegant studies based on the simple birth and death model might predict a Poissonian nature of transcript bursts and the geometrical distribution of proteins. This prediction was confirmed through the development of real time direct detection techniques in the 2000s [8,13]. Moreover, a "three states model" [23,41,42] and a "cross-talking pathway activated transcription model " [39,44] were proposed to investigate the dynamics of the mean levels of mRNAs and proteins. In a recent work [26], the modulation of first-passage time for burst gene expression was studied.

In almost all experimental studies in gene transcription, after transcription is completely blocked by the incorporation of rifampicin or other means that inhibit the initiation or elongation of RNA polymerases, it has been conventionally assumed that mRNA degradation follows an exponential decay (see, for example, [23,39,41,42,44]). If mRNA is degraded in exponential way, the log scale curve of the population size would fit a straight line. However, in many experiments in different organisms it was found that large amounts of the decay patterns are not exponential. One convincing experiment made on S. cerevisiae (a yeast model organism) [36] shows that only 11 out of 424 (selected) mRNAs obey an exponential decay. Similarly in E. coli only 11 out of 103 and in the marine cyanobacterium Prochlorococcus 117 out of 1102 genes resemble an exponential decay [35]. It is therefore clear that this simple exponential decay kinetic model does not sufficiently describe the experimental situation in detail. Moreover, the assumption of a single and constant rate contradicts the detailed knowledge of the degradation process. Hence, a series of modifications are required for degradation so that each process contributes with its specific decay rate. The assumption of a single rate implies that either all reaction rates are the same (hence also the concentrations of all participating enzymes and their time scales of catalytic activity) or one rate dominates strongly over all other rates (i.e. it is much smaller than all other rates). Hence, a description with a single constant rate seems inappropriate in light of the knowledge of the degradation mechanisms. In previous studies, the interpretation of these mRNA decay experiments relied on a simple theoretical description based on an exponential decay. However, this does not account for the complexity of the corresponding mechanisms and, as a consequence, the exponential decay is often not in agreement with the experimental decay patterns. Reducing the gap between observed decay patterns and degradation pathway is one of the main challenges facing scientists. The most difficult issue is the fact that intermediate states of the degradation pathway are still unknown or difficult to quantify.

In this paper, a more detailed model of mRNA degradation is presented. Based on a large number of theoretical results and experimental data [1,3,12,17,24,43], it is certain that there are two important mRNA degradation pathways in eukaryotic cells, from $5' \to 3'$ by the XRN1 exoribonuclease after $5' - 7-$ methylguanosine cap being removed and from $3' \to 5'$ by the complex exosome. It's assumed that there are two consecutive decaying rates on one path but the decaying rate on the other path is unique. Accordingly, we get some conclusions on the kinetics of the mean of newly accumulated transcripts. The mean newly accumulated mRNAs increases

in the initial activation frequency p and the activation rate κ, however, decreases in the inactivation rate γ. Surprisingly, it doesn't always decrease in their degradation rates. With the help of experiments and theoretics, we hope that our findings can provide a better understanding of the dynamics of mRNA degradation.

2. The model and the master equation

2.1. The two-pathway degradation model

The $5' - 7-$methylguanosine cap and the $3'-$poly(A) tail are two key parts of the integral stability determinants of mRNAs in eukaryotic cells [3, 17]. These two structures interact with cytoplasmic proteins eIF4E and the poly(A)-binding protein (PABP), respectively, to protect the transcript from exonucleases and to enhance translation initiation. To initiate mRNA decay, either one of these two structures must be compromised or mRNA must be cleaved internally by endonucleolytic attack. Nevertheless, once mRNAs are degraded, one of the two routes must be taken. Within the commoner degradation pathway, the $5'-$cap is removed by a process known as decapping which takes place in the small cytoplasmic processing Body (P-body) [2, 6], involving many intracellular factors and complexes such as Dcp1, Dcp2 [4], Pat1p, Rap55 [40] and so on. Hence, this process allows the mRNA body to be degraded in the $5' \to 3'$ direction by the XRN1 exoribonuclease. Before the decapping of mRNA, the poly(A) tail is deadenylated to an oligo(A). The deadenylation is a crucial step, in making mRNAs susceptible for decapping. The next pathway is that mRNAs can be degraded from the unprotected $3'$ end by a complex called exosome, which takes advantage of different co-factors.

The two-state model has been a primary mathematical formalism of stochastic gene transcription [10, 14, 16, 18, 19, 25, 28, 30, 33, 34, 37, 38]. In the model, it is postulated that a gene transits between active (noted as gene on) and inactive (noted as gene off) states, with an activation rate κ and an inactivation rate γ, respectively. When the gene is active, a new mRNA molecule is produced with a rate ν. The degradation of mRNAs follows a single exponential decay with a rate δ. The model has been widely used in fitting experimental data from single cell measurements in bacteria , yeast [7], and mammalian cells [10] to elucidate the intricate relation between the stochasticity of gene transcription and the regulatory mechanisms [9, 10, 28, 34].

We are interested in analyzing a modified version of the classical two-state model where mRNA is regulated by two different paths, involving two states gene on and gene off. This model captures fundamental biochemical reaction steps in the mRNA degradation process of the eukaryotic cells. One pathway is that mRNA is indirectly degraded from $5' \to 3'$ by the XRN1 exoribonuclease after its $5' - 7-$methylguanosine cap is removed, where the decapping rate is δ_1, and the death rate is δ_2; the other pathway is that mRNA is directly decayed from $3' \to 5'$ by the complex exosome with the death rate is δ_3. See Fig.1 a.

2.2. The master equation

Let the state space of the model be

$$\Omega = \{(k, m, n)\ ,\ k \in \{0, 1\}, m, n \in \mathbb{N}\}\,.$$

In any state (k, m, n), the first coordinate denotes the status of the gene. We define $k = 0$ when the gene is in off-state and $k = 1$ when the gene is in on-state. Let $M(t)$ and $N(t)$ be the random processes counting the numbers of mRNA with the cap (denoted by the capped mRNA) and mRNA without the cap (denoted by the decapped mRNA), respectively. Set the primary probability

$$P_{i,\,m,\,n}(t) = \text{Prob}\,\{k = i,\, M(t) = m,\, N(t) = n\}\,. \tag{2.1}$$

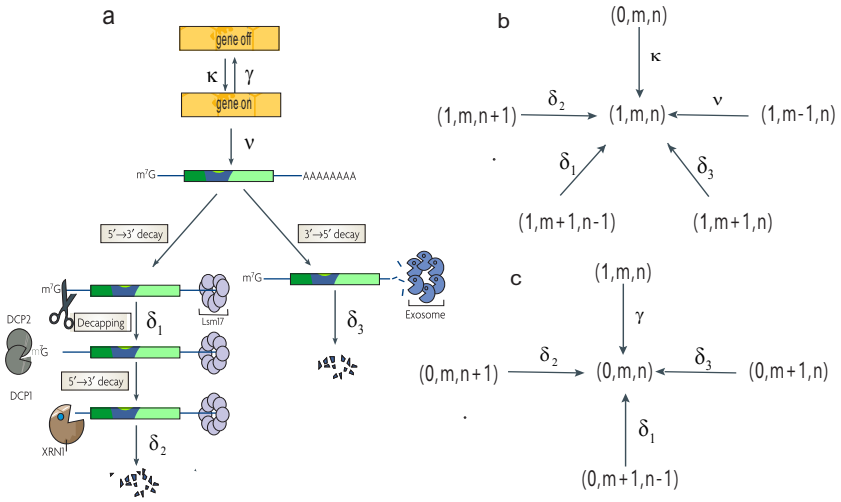

Figure 1. a. The model of gene transcription: a gene switches between on-state and off-state, where the activation rate is κ and the inactivation rate is γ. When the gene is active, a new mRNA molecule is produced with a rate ν. mRNA degradation is regulated by two different pathways. One is that mRNA is indirectly degraded from $5' \to 3'$ by the XRN1 exoribonuclease after its $5' - 7-$methylguanosine cap is removed, where the decapping rate is denoted by δ_1 and the death rate is denoted by δ_2; the other is that mRNA is directly decayed from $3' \to 5'$ by the complex exosome, where the death rate is denoted by δ_3 . b. and c.: The absorbing state transitions of the gene regulation.

The following hypotheses are needed to get the stochastic equation of $P_{k,m,n}(t)$.
(H_1): transitions in gene states, mRNA generation, mRNA decapping and mRNA degradation are mutually independent random events.
(H_2): for an infinitesimal time increment $h > 0$, the probability that two or more than two random events occur at one time is a higher order infinitesimal of h, denoted as $o(h)$.

With the help of Fig.1 a. and b., a detailed calculation for $P'_{1,m,n}(t)$ is given by using the total probability formula.

1. The system switches to state $(1, m, n)$ during the time interval $(t, t + h)$ from the state $(0, m, n)$ at time t, and no other event is happening at the same time. This event has a probability $\kappa P_{0,m,n}(t)h + o(h)$.
2. The exactly one decapped mRNA is dagraded during the time interval $(t, t+h)$ when the system is in the state $(1, m, n + 1)$ at time t, and no other event is happening at the same time. This event has a probability $C^1_{n+1}(\delta_2 h)(1 - \delta_2 h)^n P_{1,m,n+1}(t) + o(h)$.
3. The exactly one capped mRNA is turned into decapped mRNA during the time interval $(t, t + h)$ when the system is in $(1, m + 1, n - 1)$ at time t, and

no other event is happening at the same time. The probability of the event is $C^1_{m+1}(\delta_1 h)(1-\delta_1 h)^m P_{1,m+1,n-1}(t)+o(h)$.

4. The exactly one capped mRNA is directly degraded during the time interval $(t,t+h)$ when the system is in $(1,m+1,n)$ at time t, and no other event is happening at the same time. The probability of this event is $C^1_{m+1}(\delta_3 h)(1-\delta_3 h)^m P_{1,m+1,n}(t)+o(h)$.
5. The exactly one capped mRNA is produced during the time interval $(t,t+h)$ when the system is in $(1,m-1,n)$ at time t, and no other event is happening at the same time. The probability of the event is $(\nu h)P_{1,m-1,n}(t)+o(h)$.
6. There are no generation, degradation, transition or decapping during the time interval $(t,t+h)$ on the state $(1,m,n)$ at time t. This event has a probability $P_{1,m,n}(t)(1-\nu h)(1-\delta_2 h)^n(1-\delta_3 h)^m(1-\gamma h)(1-\delta_1 h)^m$.
7. At least two events among transition, generation, decapping and degradation during the time interval $(t,t+h)$ are occurring simultaneously. The probability of this event is $o(h)$.

Adding all the above seven terms gives

$$\begin{aligned}P_{1,m,n}(t+h)=\ &\kappa P_{0,m,n}(t)h+C^1_{n+1}(\delta_2 h)(1-\delta_2 h)^n P_{1,m,n+1}(t)+(\nu h)P_{1,m-1,n}(t)\\ &+C^1_{m+1}(\delta_1 h)(1-\delta_1 h)^m P_{1,m+1,n-1}(t)\\ &+C^1_{m+1}(\delta_3 h)(1-\delta_3 h)^m P_{1,m+1,n}(t)\\ &+P_{1,m,n}(t)(1-\gamma h)(1-\delta_1 h)^m(1-\delta_2 h)^n(1-\delta_3 h)^m(1-\nu h)+o(h).\end{aligned}$$

This yields by taking limit as $h\to 0$

$$\begin{aligned}P'_{1,m,n}(t)=\ &\kappa P_{0,m,n}(t)+\delta_2(n+1)P_{1,m,n+1}(t)+\delta_1(m+1)P_{1,m+1,n-1}(t)\\ &+\delta_3(m+1)P_{1,m+1,n}(t)+\nu P_{1,m-1,n}(t)-\gamma P_{1,m,n}(t)-\delta_2 nP_{1,m,n}(t)\\ &-\delta_1 mP_{1,m,n}(t)-\delta_3 mP_{1,m,n}(t)-\nu P_{1,m,n}(t).\end{aligned}\tag{2.2}$$

Similarly, we can obtain the following equation based on Fig.1.c.,

$$\begin{aligned}P'_{0,m,n}(t)=\ &\gamma P_{1,m,n}(t)+\delta_2(n+1)P_{0,m,n+1}(t)+\delta_1(m+1)P_{0,m+1,n-1}(t)-\kappa P_{0,m,n}(t)\\ &+\delta_3(m+1)P_{0,m+1,n}(t)-\delta_2 nP_{0,m,n}(t)-\delta_1 mP_{0,m,n}(t)-\delta_3 mP_{0,m,n}(t).\end{aligned}$$

We define

$$P_1(t)=\sum_{m=0}^{\infty}\sum_{m=0}^{\infty}P_{1,m,n}(t)\quad\text{and}\quad P_0(t)=\sum_{m=0}^{\infty}\sum_{m=0}^{\infty}P_{0,m,n}(t).\tag{2.3}$$

Then $P_1(t)$ and $P_0(t)$ mean the probabilities that the system is in on-state and off-state, respectively. From (2.2), we immediately have

$$\begin{aligned}P'_1(t)=\sum_{m,n=0}^{\infty}P'_{1,m,n}(t)=\ &\kappa\sum_{m,n=0}^{\infty}P_{0,m,n}(t)+\delta_2\sum_{m,n=0}^{\infty}(n+1)P_{1,m,n+1}(t)\\ &+\delta_1\sum_{m,n=0}^{\infty}(m+1)P_{1,m+1,n-1}(t)+\delta_3\sum_{m,n=0}^{\infty}(m+1)P_{1,m+1,n}(t)\end{aligned}$$

$$
\begin{aligned}
&-\gamma \sum_{m,n=0}^{\infty} P_{1,m,n}(t) - \delta_2 \sum_{m,n=0}^{\infty} nP_{1,m,n}(t) - \delta_1 \sum_{m,n=0}^{\infty} mP_{1,m,n}(t) \\
&-\delta_3 \sum_{m,n=0}^{\infty} mP_{1,m,n}(t) - \nu \sum_{m,n=0}^{\infty} P_{1,m,n}(t) + \nu \sum_{m,n=0}^{\infty} P_{1,m-1,n}(t) \\
&= \kappa P_0(t) - \gamma P_1(t). \qquad (2.4)
\end{aligned}
$$

Similarly, we can obtain

$$P_0'(t) = -\kappa P_0(t) + \gamma P_1(t). \qquad (2.5)$$

Solving (2.4) and (2.5) with the initial condition $P_1(0) = p \in [0,1]$, we get

$$P_1(t) = p^* + (p - p^*)e^{-(\kappa+\gamma)\,t}, \quad p^* = \frac{\kappa}{\kappa+\gamma}, \qquad (2.6)$$

where p^* is the stationary probability of the on-state. Clearly, we see that $P_1(t)$ monotonically increases to p^* if the initial probability $p < p^*$ and monotonically decreases to p^* if $p > p^*$.

3. The dynamics of transcript

Let $P_{1,m}(t)$ and $P_{0,m}(t)$ be the probabilities that the system is in the on-state and off-state with m copies of the capped mRNAs at time t, respectively. Let $m_1(t)$ and $m_0(t)$ denote the mean number of capped mRNAs under the on-state and off-state, respectively. Then

$$m_1(t) = \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} mP_{1,m,n}(t) \quad \text{and} \quad m_0(t) = \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} mP_{0,m,n}(t).$$

From (2.2), we obtain

$$
\begin{aligned}
m_1'(t) \;&= \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} mP_{1,m,n}'(t) = \delta_1 \sum_{m,n=0}^{\infty} m(m+1)P_{1,m+1,n-1}(t) \\
&+\kappa \sum_{m,n=0}^{\infty} mP_{0,m,n}(t) + \delta_2 \sum_{m,n=0}^{\infty} m(n+1)P_{1,m,n+1}(t) - \nu \sum_{m,n=0}^{\infty} mP_{1,m,n}(t) \\
&+\delta_3 \sum_{m,n=0}^{\infty} m(m+1)P_{1,m+1,n}(t) + \nu \sum_{m,n=0}^{\infty} mP_{1,m-1,n}(t) - \gamma \sum_{m,n=0}^{\infty} mP_{1,m,n}(t) \\
&-\delta_2 \sum_{m,n=0}^{\infty} mnP_{1,m,n}(t) - \delta_1 \sum_{m,n=0}^{\infty} m^2P_{1,m,n}(t) - \delta_3 \sum_{m,n=0}^{\infty} m^2P_{1,m,n}(t) \\
&= \kappa m_0(t) - (\gamma + \delta_1 + \delta_3)m_1(t) + \nu P_1(t). \qquad (3.1)
\end{aligned}
$$

Similarly, we obtain by using (2.3)

$$m_0'(t) = -(\kappa + \delta_1 + \delta_3)m_0(t) + \gamma m_1(t). \qquad (3.2)$$

Let $m(t)$ and $n(t)$ be the mean number of capped mRNAs and decapped mRNAs, respectively. In terms of (3.1) and (3.2), we have

$$m'(t) = -(\delta_1 + \delta_3)m(t) + vP_1(t). \qquad (3.3)$$

To simplify $m(t)$ and $n(t)$, we introduce

$$\begin{aligned}\delta_{13\kappa\gamma} &= (\delta_1+\delta_3)-(\kappa+\gamma), \quad \delta_{2\kappa\gamma} = \delta_2-(\kappa+\gamma),\\ \delta_{12\kappa\gamma} &= (\delta_1+\delta_2)-(\kappa+\gamma), \quad \delta_{2,13} = \delta_2-(\delta_1+\delta_3).\end{aligned} \tag{3.4}$$

From (3.3), we can get

$$\begin{aligned}m(t) = &\frac{p^*\nu}{\delta_1+\delta_3}+m_0e^{-(\delta_1+\delta_3)t}\\ &-[p^*\frac{\nu}{\delta_1+\delta_3}+(p-p^*)\frac{\nu}{\delta_{13\kappa\gamma}}]e^{-(\delta_1+\delta_3)t}\\ &+(p-p^*)\frac{\nu}{\delta_{13\kappa\gamma}}e^{-(\kappa+\gamma)t}\end{aligned} \tag{3.5}$$

where $m_0 := m(0)$. Similarly, from (2.2) and (2.3), we get

$$n'(t) = -\delta_2 n(t)+\delta_1 m(t). \tag{3.6}$$

From (3.5) and (3.6) , we conclude

$$\begin{aligned}n(t) = &\frac{p^*\nu}{\delta_1+\delta_3}\frac{\delta_1}{\delta_2}+n_0e^{-\delta_2 t}+m_0\frac{\delta_1}{\delta_{2,13}}[e^{-(\delta_1+\delta_3)t-e^{-\delta_2 t}}]\\ &+[\frac{p^*\nu}{\delta_1+\delta_3}+(p-p^*)\frac{\nu}{\delta_{13\kappa\gamma}}]\frac{\delta_1}{\delta_{2,13}}[e^{-\delta_2 t}-e^{-(\delta_1+\delta_3)t}]\\ &-(p-p^*)\frac{\nu}{\delta_{13\kappa\gamma}}\frac{\delta_1}{\delta_{2\kappa\gamma}}[e^{-\delta_2 t}-e^{-(\kappa+\gamma)t}]-\frac{\kappa}{\kappa+\gamma}\frac{\nu}{\delta_1+\delta_3}\frac{\delta_1}{\delta_2}e^{-\delta_2 t},\end{aligned} \tag{3.7}$$

where $n_0 := n(0)$.

In order to further study the dynamics of the mean level of newly accumulated mRNAs, we suppose that the production of mRNA is inhibited by the rifampicin. Under this condition, the model of biochemical reaction (Fig.1) is simplified to the following model.

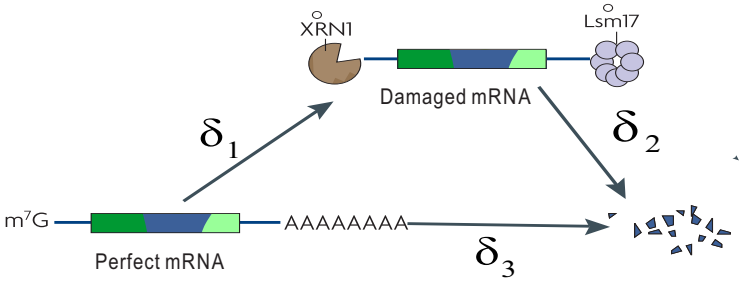

Figure 2. The model of gene degradation: when the generation of mRNA is terminated, mRNAs degradation is regulated by two different pathways. One is that the mRNA is indirectly degraded from $5' \to 3'$ by the XRN1 exoribonuclease after its $5'-7-$methylguanosine cap is removed, where the decapping rate is denoted by δ_1 and the death rate is denoted by δ_2. The other pathway is that mRNA directly decayes from $3' \to 5'$ by the complex exosome where the death rate is denoted by δ_3.

Let $x_1(t)$ and $x_2(t)$ denote the mean numbers of capped mRNA and decapped mRNA at time t under the condition that mRNA formation is inhabited, respec-

tively. Then by the biochemical reaction principle [27], we have

$$\begin{cases} x_1'(t) = -(\delta_1 + \delta_3)x_1(t) \\ x_2'(t) = \delta_1 x_1(t) - \delta_2 x_2(t). \end{cases} \tag{3.8}$$

It follows that

$$x_1(t) + x_2(t) = m_0 e^{-(\delta_1+\delta_3)t} + n_0 e^{-\delta_2 t} + m_0 \frac{\delta_1}{\delta_{2,13}}[e^{-(\delta_1+\delta_3)t} - e^{-\delta_2 t}]. \tag{3.9}$$

When mRNA molecules are regulated by two different pathways, we find that the logarithm of the average copy numbers are either concave up or concave down. That is, mRNA is degraded in non-exponential way.

Over a period of time [0, t], let $x(t, p)$ denote the mean number of newly accumulated mRNA, where p is the initial activation frequency. Then we have

$$x(t, p) = [m(t) + n(t)] - [x_1(t) + x_2(t)].$$

In terms of (3.5), (3.7) and (3.9), we have

$$\begin{aligned} x(t,p) = {} & p^*\nu \frac{\delta_1 + \delta_2}{\delta_2(\delta_1 + \delta_3)} + \frac{(p - p^*)\delta_{12\gamma\kappa}\nu}{\delta_{13\kappa\gamma}\delta_{2\kappa\gamma}} e^{-(\gamma+\kappa)t} \\ & - \frac{(\delta_2 - \delta_3)[p(\delta_1 + \delta_3) - \kappa]\nu}{(\delta_1 + \delta_3)\delta_{2,13}\delta_{13\kappa\gamma}} e^{-(\delta_1+\delta_3)t} + \frac{\delta_1(p\delta_2 - \kappa)\nu}{\delta_2\delta_{2\kappa\gamma}\delta_{2,13}} e^{-\delta_2 t}. \end{aligned} \tag{3.10}$$

The following theorem provides some monotonic dynamical behaviors on the mean level of newly accumulated mRNAs. For the convenience, we rewrite $x(t, p)$ by $x(t)$.

Theorem 3.1. *The following two conclusions hold.*

(i) $x(t)$ increases in p, the initial activation frequency.

(ii) $x(t)$ increases in t when $p < p^*$.

Remark. When $p \geq p^*$, the monotonicity of $x(t)$ would be much more complicated. This will be discussed in our future works.

Proof. (i) Taking partial derivative in (3.10) with respect to p gives

$$\frac{\partial x(t)}{\partial p} = \frac{\delta_{12\kappa\gamma}\nu}{\delta_{13\kappa\gamma}\delta_{2\kappa\gamma}} e^{-(\gamma+\kappa)t} - \frac{(\delta_2 - \delta_3)\nu}{\delta_{2,13}\delta_{13\kappa\gamma}} e^{-(\delta_1+\delta_3)t} + \frac{\delta_1\nu}{\delta_{2\kappa\gamma}\delta_{2,13}} e^{-\delta_2 t}. \tag{3.11}$$

Let $r(t) = x(t) - (p - p^*)\partial x(t)/\partial p$. Then we obtain

$$r(t) = p^*\nu \frac{\delta_1 + \delta_2}{\delta_2(\delta_1 + \delta_3)} - p^*\nu \frac{(\delta_2 - \delta_3)}{(\delta_1 + \delta_3)\delta_{2,13}} e^{-(\delta_1+\delta_3)t} + p^*\nu \frac{\delta_1}{\delta_2\delta_{2,13}} e^{-\delta_2 t}. \tag{3.12}$$

It is easy to see that $r(0) = 0$ and $x(0) = x(0, p) = 0$. Thus we get $\partial x(0)/\partial p = 0$. This means that the sum of all coefficients of the above exponential functions in (3.11) is equal to zero, and hence

$$\begin{aligned} \frac{\partial x(t)}{\partial p} &= \frac{\delta_2 - \delta_3}{[(\delta_1 + \delta_3) - \delta_2]\delta_{13\kappa\gamma}} \left(e^{-(\delta_1+\delta_3)t} - e^{-(\kappa+\gamma)\,t}\right) + \frac{\delta_1 \left(e^{-\delta_2 t} - e^{-(\kappa+\gamma)\,t}\right)}{[\delta_2 - (\delta_1 + \delta_3)]\delta_{2\kappa\gamma}} \\ &= \frac{1}{(\delta_1 + \delta_3) - \delta_2} \left((\delta_2 - \delta_3) \frac{e^{-(\delta_1+\delta_3)\,t} - e^{-(\kappa+\gamma)\,t}}{(\delta_1 + \delta_3) - (\kappa + \gamma)} - \delta_1 \frac{e^{-\delta_2\,t} - e^{-(\kappa+\gamma)\,t}}{\delta_2 - (\kappa + \gamma)} \right). \end{aligned}$$

Define

$$f_1(x) = \frac{e^{-x} - 1}{x}.$$

It's easy to see that $f_1(x)$ is negative and increases for $x \neq 0$. For the case where $\delta_1 + \delta_3 > \delta_2$, we have

$$f_1([\delta_1 + \delta_3 - (\kappa + \gamma)]t) > f_1([\delta_2 - (\kappa + \gamma)]t),$$

i.e.,

$$\frac{e^{-[(\delta_1+\delta_3)-(\kappa+\gamma)]t} - 1}{(\delta_1 + \delta_3) - (\kappa + \gamma)} > \frac{e^{-[\delta_2-(\kappa+\gamma)]t} - 1}{\delta_2 - (\kappa + \gamma)},$$

which yields

$$\frac{e^{-(\delta_1+\delta_3)t} - e^{-(\kappa+\gamma)t}}{(\delta_1 + \delta_3) - (\kappa + \gamma)} > \frac{e^{-\delta_2 t} - e^{-(\kappa+\gamma)t}}{\delta_2 - (\kappa + \gamma)}$$

and hence

$$(\delta_2 - \delta_3)\frac{e^{-(\delta_1+\delta_3)t} - e^{-(\kappa+\gamma)t}}{(\delta_1 + \delta_3) - (\kappa + \gamma)} > \delta_1 \frac{e^{-\delta_2 t} - e^{-(\kappa+\gamma)t}}{\delta_2 - (\kappa + \gamma)}.$$

This shows $\partial x(t)/\partial p > 0$ for the case where $\delta_1 + \delta_3 > \delta_2$. Similarly, we can prove that $\partial x(t)/\partial p > 0$ for the case where $\delta_1 + \delta_3 < \delta_2$. This tells us that $x(t)$ increases in p. Hence, the proof of (i) is completed.

(ii) We divide the proof into four steps.

Step 1. We are going to show that the function $\partial x(t)/\partial p$ has at least one critical point. Since $\lim_{t\to+\infty} \partial x(t)/\partial p = 0$ and $\partial x(0)/\partial p = 0$, it is easy to see that this conclusion holds according to the mean value theorem. Denote one of the critical points by $t_0 \in (0, \infty)$.

Step 2. We prove that the function $\partial x(t)/\partial p$ has at most two critical points. To this end, assume for contradiction that $\partial x(t)/\partial p$ has three critical points. Then from (3.11), we have

$$\frac{\partial^2 x(t)}{\partial t \partial p} = -\frac{\delta_{12\kappa\gamma}(\gamma + \kappa)\nu}{\delta_{13\kappa\gamma}\delta_{2\kappa\gamma}} e^{-(\gamma+\kappa)t} + \frac{(\delta_2 - \delta_3)(\delta_1 + \delta_3)\nu}{\delta_{2,13}\delta_{13\kappa\gamma}} e^{-(\delta_1+\delta_3)t} - \frac{\delta_1\delta_2\nu}{\delta_{2\kappa\gamma}\delta_{2,13}} e^{-\delta_2 t}.$$

Hence the following equation

$$\frac{\delta_{12\kappa\gamma}(\gamma + \kappa)\nu}{\delta_{13\kappa\gamma}\delta_{2\kappa\gamma}} - \frac{(\delta_2 - \delta_3)(\delta_1 + \delta_3)\nu}{\delta_{2,13}\delta_{13\kappa\gamma}} e^{-\delta_{13\gamma\kappa} t} + \frac{\delta_1\delta_2\nu}{\delta_{2\kappa\gamma}\delta_{2,13}} e^{-\delta_{2\gamma\kappa} t} = 0 \quad (3.13)$$

has three roots. Naturally, the next equation

$$(\delta_2 - \delta_3)(\delta_1 + \delta_3)e^{-\delta_{13\gamma\kappa} t} + \delta_1\delta_2 e^{-[\delta_2-(\gamma+\kappa)]t} = 0 \quad (3.14)$$

has at least two roots. This is impossible and hence $\partial x(t)/\partial p$ has at most two critical points.

Step 3. We prove that $\partial x(t)/\partial p$ has a unique extremum. In fact, by a simple computation, we have

$$\frac{\partial^2}{\partial t^2}\left(\frac{\partial x(t)}{\partial p}\right) = \frac{\delta_{12\kappa\gamma}(\gamma + \kappa)^2\nu}{\delta_{13\kappa\gamma}\delta_{2\kappa\gamma}} e^{-(\gamma+\kappa)t} - \frac{(\delta_2 - \delta_3)(\delta_1 + \delta_3)^2\nu}{\delta_{2,13}\delta_{13\kappa\gamma}} e^{-(\delta_1+\delta_3)t} - \frac{\delta_1\delta_2^2\nu}{\delta_{2\kappa\gamma}\delta_{2,13}} e^{-\delta_2 t}. \quad (3.15)$$

Define

$$f_2(t) = -\delta_{2,13}[(\delta_2 - \delta_3)(\delta_1 + \delta_3) - \delta_1\delta_2 e^{-\delta_{2,13}t}].$$

Then in terms of (3.13), (3.15), and the monotonicity of function $f_2(x)$, we find

$$\begin{aligned}\frac{\partial^3 x(t_0)}{\partial t^2\partial p} &= \frac{\partial^3 x(t_0)}{\partial t^2\partial p} + (\kappa+\gamma)\frac{\partial^2 x(t_0)}{\partial t\partial p}\\ &= -\delta_{2,13}[(\delta_2 - \delta_3)(\delta_1 + \delta_3) - \delta_1\delta_2 e^{-\delta_{2,13}t_0}]e^{-(\delta_1+\delta_3)\,t_0} < 0, \quad (3.16)\end{aligned}$$

which means that $\partial^2 x(t)/\partial t\partial p$ is strictly decreasing for $t \in (0,\infty)$. Since $\partial^2 x(t_0)/\partial t\partial p = 0$, we find that $\partial^2 x(t)/\partial t\partial p > 0$ for $t \in (0, t_0)$ and $\partial^2 x(t)/\partial t\partial p < 0$ for $t \in (t_0,\infty)$. This shows that $\partial x(t)/\partial p > 0$ takes its maximum at t_0. Thus $\partial x(t)/\partial p$ has a unique extremum.

Step 4. We show that $x(t)$ is strictly increasing for the case where $p < p^*$. In fact, from (3.12), we have

$$r'(t) = \frac{p^*\nu}{[\delta_2 - (\delta_1+\delta_3)]}[(\delta_2 - \delta_3)\,e^{-(\delta_1+\delta_3)\,t} - \delta_1\,e^{-\delta_2\,t}]. \quad (3.17)$$

Now we prove that $r'(t) > 0$ for $t \in (0,\infty)$. If $\delta_1 + \delta_3 < \delta_2$, we have

$$e^{-(\delta_1+\delta_3)} > e^{-\delta_2\,t} > 0 \quad \text{and} \quad \delta_2 - \delta_3 > \delta_1,$$

which imply

$$(\delta_2 - \delta_3)e^{-(\delta_1+\delta_3)} > \delta_1 e^{-\delta_2\,t} > 0$$

and hence

$$r'(t) = \frac{p^*\nu}{[\delta_2 - (\delta_1+\delta_3)]}[(\delta_2 - \delta_3)\,e^{-(\delta_1+\delta_3)\,t} - \delta_1\,e^{-\delta_2\,t}] > 0.$$

The proof for the case where $\delta_1 + \delta_3 > \delta_2$ is exactly similar and will be omitted here. In summary, we have shown that $r'(t) > 0$ for all $t \in (0,\infty)$.

From (3.13) and (3.15), we have

$$\begin{aligned}&r'(t) - p^*\frac{\partial^2 x(t)}{\partial t\partial p}\\ =\ &(\kappa+\gamma)[-\frac{\delta_{12\kappa\gamma}(\gamma+\kappa)\nu}{\delta_{13\kappa\gamma}\delta_{2\kappa\gamma}}e^{-(\gamma+\kappa)t} + \frac{(\delta_2-\delta_3)(\delta_1+\delta_3)\nu}{\delta_{2,13}\delta_{13\kappa\gamma}}e^{-(\delta_1+\delta_3)t} - \frac{\delta_1\delta_2\nu}{\delta_{2\kappa\gamma}\delta_{2,13}}e^{-\delta_2 t}]\\ =\ &(\kappa+\gamma)\frac{\partial x(t)}{\partial p}. \quad (3.18)\end{aligned}$$

Since $p < p^*$, we find from (3.18) that, for $t \in (0, t_0)$,

$$\frac{\partial x(t)}{\partial t} = r'(t) + (p-p^*)\frac{\partial^2 x(t)}{\partial t\partial p} \geq r'(t) - p^*\frac{\partial^2 x(t)}{\partial t\partial p} = (\kappa+\gamma)\frac{\partial x(t)}{\partial p} > 0$$

and for $t \in (t_0,\infty)$,

$$\frac{\partial x(t)}{\partial t} = r'(t) + (p-p^*)\frac{\partial^2 x(t,p)}{\partial t\partial p} \geq r'(t) > 0.$$

Therefore, Conclusion (ii) is true. The proof is completed. □

The following result provides some monotonic dynamics of $x(t)$ in parameters $\kappa, \gamma, \delta_1, \delta_2$ and δ_3 .

Theorem 3.2. *The following two conclusions hold.*

(i) $x(t)$ increases in κ, decreases in γ, δ_2 and δ_3.

(ii) $x(t)$ increases in δ_1 when $\delta_2 < \delta_3$ and decreases in δ_1 when $\delta_2 > \delta_3$.

Proof. (i) In order to verify the monotonicity of $x(t)$ in κ, γ, δ_2, δ_3 and δ_1 , we need to take its partial derivative with respect to each parameter. From (2.6), we have

$$\begin{aligned}\frac{\partial P_1(t)}{\partial \kappa} &= \frac{\gamma}{(\kappa+\gamma)^2}\left(1-e^{-(\kappa+\gamma)\,t}\right) - (p-p^*)te^{-(\kappa+\gamma)\,t}\\ &\geq \frac{\gamma}{(\kappa+\gamma)^2}\left(1-e^{-(\kappa+\gamma)\,t}\right) - (1-p^*)te^{-(\kappa+\gamma)\,t}\\ &= \frac{\gamma}{(\kappa+\gamma)^2}\left[1-(1+(\kappa+\gamma)t)e^{-(\kappa+\gamma)\,t}\right] > 0.\end{aligned}$$

Since $[1+(\kappa+\gamma)t]\exp(-(\kappa+\gamma)\,t)$ is strictly decreasing for $t>0$, we see by (3.3) that

$$\frac{\partial^2 m(t)}{\partial\kappa\partial t} + (\delta_1+\delta_3)\frac{\partial m(t)}{\partial\kappa} = \nu\frac{\partial P_1(t)}{\partial\kappa} > 0$$

and hence

$$\frac{\partial}{\partial t}\left(e^{(\delta_1+\delta_3)t}\frac{\partial m(t)}{\partial\kappa}\right) > 0.$$

Since $\partial m(0)/\partial\kappa = 0$. It follows that $\partial m(t)/\partial\kappa > 0$ for all $t>0$, and so $m(t)$ is strictly increasing in κ. By using the same method, we can show by (3.6) that $n(t)$ is also strictly increasing in κ. Consequently, $m(t)+n(t)$ is strictly increasing in κ. Since $x_1(t)+x_2(t)$ is independent of κ, it verifies the monotonicity of $x(t)$ in κ.

Similarly, we have from (2.6) that

$$\begin{aligned}\frac{\partial P_1(t)}{\partial \gamma} &= -\frac{\kappa}{(\kappa+\gamma)^2}\left(1-e^{-(\kappa+\gamma)\,t}\right) - (p-p^*)te^{-(\kappa+\gamma)\,t}\\ &\leq -\frac{\kappa}{(\kappa+\gamma)^2}\left(1-e^{-(\kappa+\gamma)\,t}\right) + p^*te^{-(\kappa+\gamma)\,t}\\ &= -\frac{\kappa}{(\kappa+\gamma)^2}\left[1-(1+(\kappa+\gamma)t)e^{-(\kappa+\gamma)\,t}\right] < 0.\end{aligned}$$

By repeating the same argument above in the discussion of the partial derivative with respect to κ, we can show that $x(t)$ is strictly decreasing in γ.

Since $m(t)$ is independent of δ_2, we see that $\partial^2 m(t)/\partial\delta_2\partial t = 0$ for all $t>0$.

Let $y(t) = m(t)+n(t)$. Then from (3.3) and (3.6), we obtain

$$y'(t) = -\delta_2 y(t) + (\delta_2-\delta_3)m(t) + \nu P_1(t).$$

It follows that

$$\frac{\partial^2 y(t)}{\partial\delta_2\partial t} = -\delta_2\frac{\partial y(t)}{\partial\delta_2} - y(t) + m(t),$$

which implies

$$\frac{\partial}{\partial t}\left(e^{\delta_2 t}\frac{\partial y(t)}{\partial\delta_2}\right) = -e^{\delta_2 t}n(t) < 0$$

and therefore $\partial y(t)/\partial\delta_2 < 0$ for all $t>0$. Note that our calculation here does not use any initial conditions on $m(0)$ and $n(0)$. Hence $\partial x(t)/\partial\delta_2 < 0$ holds when $m(0)=n(0)=0$, for which $x(t)=y(t)$ and $x(t)$ is strictly decreasing in δ_2.

Now, in terms of (3.3), we have

$$\frac{\partial^2 m(t)}{\partial \delta_3 \partial t} = -m(t) - (\delta_1 + \delta_3)\frac{\partial m(t)}{\partial \delta_3}$$

which means

$$\frac{\partial}{\partial t}\left(e^{(\delta_1+\delta_3)t}\frac{\partial m(t)}{\partial \delta_3}\right) = -m(t)e^{(\delta_1+\delta_3)t} < 0$$

and hence $\partial m(t)/\partial \delta_3 < 0$ for all $t > 0$.

Similarly, from (3.6), we have

$$\frac{\partial^2 n(t)}{\partial \delta_3 \partial t} + \delta_2 \frac{\partial n(t)}{\partial \delta_3} = \delta_1 \frac{\partial m(t)}{\partial \delta_3}.$$

It yields

$$\frac{\partial}{\partial t}\left(e^{\delta_2 t}\frac{\partial n(t)}{\partial \delta_3}\right) = \delta_1 e^{\delta_2 t}\frac{\partial m(t)}{\partial \delta_3} < 0$$

and hence $\partial n(t)/\partial \delta_3 < 0$ for all $t > 0$. It follows that $\partial y(t)/\partial \delta_3 < 0$ for all $t > 0$. Note that any initial values $m(0)$ and $n(0)$ has not been involved in our calculation above. Hence $\partial x(t)/\partial \delta_3 < 0$ holds and, $x(t)$ is strictly decreasing in δ_3.

Next, by (3.3), we have

$$\frac{\partial^2 m(t)}{\partial \delta_1 \partial t} = -m(t) - (\delta_1 + \delta_3)\frac{\partial m(t)}{\partial \delta_1},$$

which implies

$$\frac{\partial}{\partial t}\left(e^{(\delta_1+\delta_3)t}\frac{\partial m(t)}{\partial \delta_1}\right) = -m(t)e^{(\delta_1+\delta_3)t} < 0$$

and hence $\partial m(t)/\partial \delta_1 < 0$ for all $t > 0$. By (3.3) and (3.6), we obtain

$$y'(t) = -\delta_2 y(t) + (\delta_2 - \delta_3)m(t) + \nu P_1(t).$$

It follows that

$$\frac{\partial^2 y(t)}{\partial \delta_1 \partial t} = -\delta_2 \frac{\partial y(t)}{\partial \delta_1} + (\delta_2 - \delta_3)\frac{\partial m(t)}{\partial \delta_1} + 0$$

and we get

$$\frac{\partial}{\partial t}\left(e^{\delta_2 t}\frac{\partial y(t)}{\partial \delta_1}\right) = (\delta_2 - \delta_3)e^{\delta_2 t}\frac{\partial m(t)}{\partial \delta_1}.$$

Again note that not any initial values $m(0)$ and $n(0)$ has been used in the above calculation. It follows that $\partial y(t)/\partial \delta_1 > (<)0$ holds when $\delta_2 < (>)\delta_3$. Therefore, $x(t)$ is strictly increasing in δ_1 when $\delta_2 < \delta_3$ and strictly decreasing in δ_1 when $\delta_2 > \delta_3$. The proof is finished. □

4. conclusion and discussion

Gene transcription is inherently a random and dynamical process. The stochasticity of transcription produces complicated dynamics on the mean number of transcripts. Usually, the intermediate states of the mRNA degradation are unknown or difficult to qualify. In this paper, we establish an mRNA degradation model with two

pathways, coupling with the process of two states transitions, to examine how the signal parameters contribute to the transcripts. This model is different from other existed ones. The stationary mean of transcripts in the model is less than that in the two-state model with two consecutive decaying steps in one degradation path, which implies that more than one degradation path can accelerate the degradation of mRNA. Moreover, it is more than that of the two-state model with one degradation path and one decaying rate δ_3 in [42] under the condition $\delta_2 > \delta_3$ and vice versa. When the mRNA mortality rates in two paths are the same, the number of newly accumulated transcripts is independent of the decapping rate δ_1. We also get some conclusions on the kinetics of the mean of newly accumulated transcripts. The mean of newly accumulated mRNAs increases in the activation rate κ, however, decreases in the inactivation rate γ. It is surprising find that it increases in δ_1 when $\delta_2 < \delta_3$ and decreases in δ_1 when $\delta_2 > \delta_3$. The mean of newly accumulated transcripts increases in the initial activation frequency p and decreases in time t when $p < \kappa/(\kappa+\gamma)$. The heterogeneity of transcript distribution has typically been quantified by noise, the variance normalized by the square of the mean. The noise has been thought to arise from random switching between "gene on" and "gene off " states. But what underlies the random transition among these states remains largely unknown. It is our next job to make use of the model in this paper to examine how the pathways contribute to the gene transcription noise.

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