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THE DYNAMICS OF GENE TRANSCRIPTION INDUCED BY VARIATION IN TRANSCRIPTION KINETICS*

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Abstract In single cells, the process of gene transcription generally demonstrates complicated and stochastic behaviors. The stochasticity of transcription brings about large variations in the number of mRNA molecules, even in a homogeneous intracellular environment. Randomly switching between periods of active and inactive gene expression is considered to be the main cause of the high variation of the mRNA distributions. Many studies have revealed that the transcription system will enter a steady state after several transcription cycles in the last three decades. Changes in the intracellular or intercellular environment give rise to changes in transcription parameters, resulting in perturbations of a homeostatic state. In this paper, we mainly studied the dynamic behaviors of the mean mRNA level and the noise following the occurrence of the variation in transcription kinetics. We defined three quantities that are used to determine the monotonicity of the average transcription level. When the mean level is not monotonous, the value may reach the potential thresholds, thereby changing the fate of cells. This is extremely significant for researching gene expression regulation.

Keywords Gene transcription, dynamic behavior, stochastic model, variation in transcription kinetics.

MSC(2010) 92C40, 92C37, 60J20, 37H10.

1. Introduction

Gene transcription is intrinsically a stochastic and complex biochemical reaction process [21, 24, 34, 43]. It produces an RNA chain identical in sequence with the coding strand from each allele. Almost all critical life evolution processes, such as cell proliferation, growth, and differentiation, are inseparable from gene transcription. In eukaryotic cells, differences in the expression of encoding protein genes are the main cause responsible for the phenotypic differences of the cells. During gene expression, frequent regulation is required in several stages. Transcription is the first stage in gene expression and is the step at which it is regulated most often [7, 10, 24, 31].

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Increasing experiments suggest that cells possess the ability to respond to diverse types of stimuli and intra- or extracellular environmental changes by sensing certain molecules [12, 26, 28, 38]. Take as rapid cell growth in an embryo or the motion of bacteria in response to chemical stimuli for instance. In mouse embryonic stem cells, Skinner et al [35] observed that the mean OFF duration in the transcription for *Oct4* boosts from 108 min before DNA duplication to 173 min after the duplication. In yeast cells, Trcek et al [40] found that mRNA degradation for both *SWI*5 and *CLB*2 is accelerated to a higher rate of 30-fold during prometaphase/metaphase. Changes in nuclear size, resource and architecture could impact gene transcription via regulating burst size or frequency [5, 27, 32].

The transcription reaction process can be divided into three stages: initiation, elongation, and termination. In the stage of initiation, the promoter is recognized, and a stable transcription factor-DNA complex is formed. When it enters elongation, the RNA polymerase moves along the DNA as the transcript is synthesized. Then the RNA transcript is released and the bubble closes. Ko [22] presented a stochastic model by assuming that a gene switches randomly between active and inactive states three decades ago. This telegraph or two-state model has been broadly employed in the literature to study the stochasticity of gene transcription and is generally quoted to explain the observed single-cell variability in mRNA numbers [6, 8, 9, 38]. The stochasticity and bursting fashion of transcription were widely studied both in experiments and theoretical researches in the last two decades to explore the intrinsic regulation mechanism [4, 14–16, 33, 42]. However, how the variation in transcription kinetics affects the dynamics of transcription remains unclear. A number of literature has paid attention to the regulation of transcription caused by such variation, but they mainly considered the regulation in a steady state [19, 32, 41, 46, 47] or assumed that the gene is in the inactive state at the initial moment and only counted the newly produced transcripts [23, 31, 44, 46].

We employ a two-state model to dig into changes in transcription behavior induced by variations in transcription parameters. In this model, we hypothesize that the transcription system is in an equilibrium state. The equilibrium state is broken due to the variation of the parameters, and the level as well as distribution of transcripts change accordingly. The transcription outputs and stochasticity have often been quantified by the mean, the noise, and the noise strength [1, 23, 30, 37, 38]. For a random variable X, $\mathrm{E}[X]$ denotes the mean value, and the noise is defined by

$$\eta^2[X] = \frac{\mathrm{Var}[X]}{[\mathrm{E}[X]]^2} \quad \text{and} \quad \mathrm{Var}[X] = \mu[X] - [\mathrm{E}[X]]^2, \tag{1.1}$$

where $\mu[X]$ denotes the second moment of X.

The amount of mRNA molecules, commonly in the form of positive integer, is a random variable in a single cell. In this paper, we primarily examine the average expression level of the transcripts and employ the noise to depict the fluctuation of the transcripts in a cell population. In Section 2, we introduce the model with more details and present the time evolution of the mean and the noise. When the parameters of the transcription system are altered, the original equilibrium state will be demolished, causing the mean level and the fluctuation of the transcripts in the cell population to change accordingly. In Section 3, we will provide the analytical expressions of the mean transcription level and the noise, and then analyze the dynamic behavior of the mean level. We carry out some simulations to exhibit the dynamic behavior of transcription induced by some variations in Section 4.

2. The model

2.1. Description of the transcription model

In the past three decades, the two-state model has been widely employed to characterize stochastic gene transcription in single cells. In the model, as depicted in Figure 1, the promoter of the gene shifts randomly between two basic states: the active state and the inactive state. RNA synthesis is catalyzed by the enzyme RNA polymerase, which creates the transcription bubble when it binds to a promoter. The active state is considered to be the instant when the first RNA polymerase binds to the promoter. In this state, RNA polymerase synthesizes RNA transcripts while moving along the template. The inactive state is described by the lack of specific bindings of transcription factors and RNA polymerase to the promoter. The duration that the promoter resides at the active state is assumed to have an exponential distribution with a constant parameter γ, which is called the activation rate. Likewise, the duration that the promoter resides at the inactive state has an exponential distribution with a constant parameter λ, which is called the inactivation rate. The mRNA molecules are produced with a synthesis rate ν only when the promoter is active, and are degraded at a rate of δ in either state.

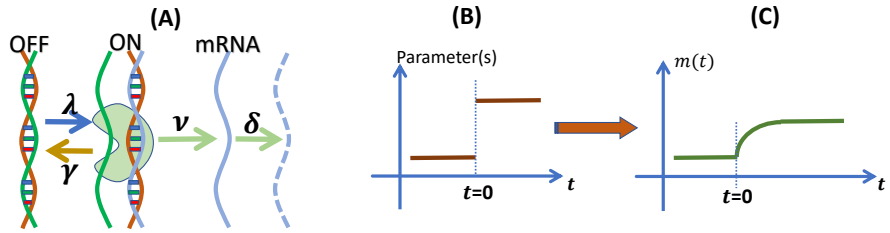

Figure 1. Stochastic gene transcription induced by parameter changes. (A) The promoter is activated by binding transcription factors to the regulation region, and transcription starts when RNA polymerase binds to a promoter, and then moves along the template and produces an RNA chain. (B) Transcription is regulated frequently by RNA polymerase and other regulatory factors, leading to variations in transcription kinetics. (C) The variation in parameters enables the transcription system to deviate from the original equilibrium state.

For a deeper insight of the dynamic behavior of transcription resulting from the variation in transcription kinetics, the two-state bursting model with an occurrence of variation in parameters is studied. A few assumptions are as follows to complete the description of the model:

(1) The transcription system is in a steady state before variation occurs.

(2) The variation in transcription kinetics is completed instantaneously.

(3) The transition between ON and OFF is also completed instantaneously.

We will maintain these assumptions when analyzing dynamic behavior of transcription from a steady state after variation occurs. In order to demonstrate a clearer picture of the model, we assume that the variation in transcription kinetics occurs at some time point, denoted by $t = 0$. The transcription is described by a two-state model, but the parameter set switches instantaneously from $\nu_0, \delta_0, \lambda_0$, and γ_0 for $t \leq 0$ to $\nu_1, \delta_1, \lambda_1$, and γ_1 for $t > 0$.

2.2. Differential equations and initial conditions

Since the transcription system can be described by a two-state model before and after parameter changes, we simply need to discuss the two-state transcription model governed by constant parameters ν, δ, λ, and γ, and then vary the parameters to the corresponding ones to derive the kinetic equations before and after the variation occurs. As usual, we denote by $M(t)$ the amount of mRNA molecules for the gene in a single cell with $M(t) \in \{0, 1, 2, \cdots\}$ and $I(t)$ denote the promoter state with $I(t) \in \{O, E\}$. $I(t) = O$ indicates that the promoter resides on the OFF state and $I(t) = E$ the ON state. We introduce $P_O(m, t)$ to represent the probability of the amount of m transcripts in the cell and the promoter is in the OFF state at time t, that is,

$$P_O(m, t) = \text{Prob}\{M(t) = m, I(t) = O\}, \ m = 0, 1, 2, \cdots. \tag{2.1}$$

Similarly,

$$P_E(m, t) = \text{Prob}\{M(t) = m, I(t) = E\}, \ m = 0, 1, 2, \cdots \tag{2.2}$$

is defined to indicate the probability of the amount of m transcripts in the cell and the promoter has already been ON. By employing a standard procedure in stochastic process [39, 44], we derive the time evolution of these two probabilities, that is,

$$P'_O(m, t) = \gamma P_E(m, t) + (m + 1)\delta P_O(m + 1, t) - (\lambda + m\delta)P_O(m, t), \tag{2.3}$$

$$\begin{aligned} P'_E(m, t) = {} & \lambda P_O(m, t) + (m + 1)\delta P_E(m + 1, t) - (\gamma + m\delta)P_E(m, t) \\ & \times \nu P_E(m - 1, t) - \nu P_E(m, t). \end{aligned} \tag{2.4}$$

By adding the joint probabilities $P_0(m, t)$ and $P_1(m, t)$ in (2.1) and (2.2) when m takes all natural numbers, we derive two other probabilities,

$$P_O(t) = \sum_{m=0}^{\infty} P_O(m, t) \ \text{ and } \ P_E(t) = \sum_{m=0}^{\infty} P_E(m, t).$$

These probabilities $P_O(t)$ and $P_E(t)$ describe the percentages of inactivated and activated cells in the cell population, respectively. By adding (2.3) and (2.4) in m, we obtain a system of $P_O(t)$ and $P_E(t)$, that is,

$$P'_O(t) = \gamma P_E(t) - \lambda P_O(t), \tag{2.5}$$

$$P'_E(t) = \lambda P_O(t) - \gamma P_E(t). \tag{2.6}$$

We use f^* to denote the equilibrium point of $f(t)$ before a variation occurs, and f^{**} to denote its new equilibrium point of $f(t)$ after the variation occurs. We will maintain these notations throughout the rest of this paper.

As is stated above in the assumptions, we can derive the steady state of (2.5) and (2.6) before the variation occurs, which is characterized by the equilibrium point,

$$P_O^* = \frac{\gamma_0}{\lambda_0 + \gamma_0} \quad \text{and} \quad P_E^* = \frac{\lambda_0}{\lambda_0 + \gamma_0}. \tag{2.7}$$

In fact, the dynamic behavior of transcription is determined by parameters $\nu_0, \delta_0, \lambda_0$ and γ_0. The equilibrium point of (2.5) and (2.6) can be derived by letting $\lim_{t\to\infty} P'_O(t) = \lim_{t\to\infty} P'_E(t) = 0$ and $P_O(t) + P_E(t) \equiv 1$.

The definition of the mean number of mRNA molecules is

$$m(t) = \mathbf{E}[M(t)] = \sum_{m=0}^{\infty} mP(m,t),$$

where $P(m,t)$ characterizes the probability that the cell has exactly m transcripts at the time t, that is,

$$P(m,t) = \text{Prob}\{M(t) = m\} = P_O(m,t) + P_E(m,t).$$

The probability mass function $P(m,t)$ is another widely used and important quantity to depict the randomness of mRNAs in cells, and many novel approaches were established to calculate the probability mass function [2, 3, 17, 20, 36, 45].

In order to derive the noise, we need to calculate two transcription levels, that is,

$$m_O(t) = \sum_{m=0}^{\infty} mP_O(m,t) \quad \text{and} \quad m_E(t) = \sum_{m=0}^{\infty} mP_E(m,t).$$

By definition of $m(t)$, it is easy to find that

$$m(t) = m_O(t) + m_E(t).$$

Multiplying (2.3) and (2.4) by m and taking the sum, we derive

$$m_O'(t) = \gamma m_E(t) - (\delta + \lambda)m_O(t), \tag{2.8}$$

$$m_E'(t) = \nu P_E(t) + \lambda m_O(t) - (\delta + \gamma)m_E(t). \tag{2.9}$$

The equilibrium point of (2.8) and (2.9) is

$$m_O^* = \frac{\nu_0\lambda_0\gamma_0}{\delta_0(\lambda_0+\gamma_0)(\delta_0+\lambda_0+\gamma_0)} \text{ and } m_E^* = \frac{\nu_0\lambda_0(\delta_0+\lambda_0)}{\delta_0(\lambda_0+\gamma_0)(\delta_0+\lambda_0+\gamma_0)}. \tag{2.10}$$

The derivative of $m(t)$ is given as

$$m'(t) = \nu P_E(t) - \delta m(t), \tag{2.11}$$

and its equilibrium point is

$$m^* = \frac{\nu_0\lambda_0}{\delta_0(\lambda_0+\gamma_0)}. \tag{2.12}$$

The noise of transcripts is defined as

$$\eta^2(t) = \frac{\sigma^2(t)}{m^2(t)} = \frac{\mu(t) - m^2(t)}{m^2(t)},$$

where $\mu(t)$ is the second moment of transcripts, that is,

$$\mu(t) = \mathbf{E}[M^2(t)] = \sum_{m=0}^{\infty} m^2 P(m,t). \tag{2.13}$$

Differentiating (2.13) and with the help of (2.3) and (2.4) again, we obtain its derivative of the second moment as

$$\mu'(t) = 2\nu m_E(t) + \nu P_E(t) + \delta m(t) - 2\delta\mu(t). \tag{2.14}$$

Before the variation of transcription kinetics occurs, the second moment is also in a steady state with a stationary value,

$$\mu^* = \frac{\nu_0\lambda_0}{\delta_0(\lambda_0+\gamma_0)} + \frac{\nu_0^2\lambda_0(\delta_0+\lambda_0)}{\delta_0^2(\lambda_0+\gamma_0)(\delta_0+\lambda_0+\gamma_0)}. \tag{2.15}$$

3. Results

3.1. The average transcription level

Increasing experimental and theoretical results demonstrate that highly variable mRNA distributions in bacterial, yeast, and mammalian cells are the result of randomly switching between active and inactive states, and also are largely driven by variations in transcription initiation and mRNA stability.

All eight system parameters are involved in this transcription system before and after the variation of parameters occurs. Solving (2.5) and (2.6) with the initial condition (2.7), we derive

$$P_O(t) = \frac{\gamma_1}{\lambda_1+\gamma_1} + \left(P_O^* - \frac{\gamma_1}{\lambda_1+\gamma_1}\right) e^{-(\lambda_1+\gamma_1)t}, \tag{3.1}$$

$$P_E(t) = \frac{\lambda_1}{\lambda_1+\gamma_1} + \left(P_E^* - \frac{\lambda_1}{\lambda_1+\gamma_1}\right) e^{-(\lambda_1+\gamma_1)t}. \tag{3.2}$$

The limits of them are

$$P_O^{**} = \lim_{t\to\infty} P_O(t) = \frac{\gamma_1}{\lambda_1+\gamma_1} \quad \text{and} \quad P_E^{**} = \lim_{t\to\infty} P_E(t) = \frac{\lambda_1}{\lambda_1+\gamma_1}.$$

Solving (2.11) with the initial condition (2.12) or solving (2.8) and (2.9) with initial condition (2.10), we derive the following theorem, which gives the mean transcription level $m(t)$.

Recall that for a given function $g(t)$, its Laplace transform is given by

$$G(s) = \mathcal{L}\left(g(t)\right) = \int_0^\infty e^{-st} g(t)dt.$$

And for a given function $G(s)$, its inverse Laplace transform is given by

$$g(t) = \mathcal{L}^{-1}\left(G(s)\right) \quad \Longleftrightarrow \quad G(s) = \mathcal{L}\left(g(t)\right).$$

Theorem 3.1. *Assume that the transcription is maintained homeostasis. Transcription kinetics alter at time $t = 0$, then the expected value $m(t) = \mathrm{E}[M(t)]$ of its mRNA copy number $M(t)$ is given by*

$$\begin{aligned} m(t) = {} & \frac{\nu_1\lambda_1}{\delta_1(\lambda_1+\gamma_1)} - \frac{\nu_1[\lambda_1 - (\lambda_1+\gamma_1)P_E^*]}{(\lambda_1+\gamma_1)(\delta_1-\lambda_1-\gamma_1)} e^{-(\lambda_1+\gamma_1)t} \\ & + \left[m^* + \frac{\nu_1(\lambda_1 - \delta_1 P_E^*)}{\delta_1(\delta_1-\lambda_1-\gamma_1)}\right] e^{-\delta_1 t}. \end{aligned} \tag{3.3}$$

When the time $t \to \infty$, $m(t)$ approaches a constant value,

$$m^{**} = \lim_{t\to\infty} m(t) = \frac{\nu_1\lambda_1}{\delta_1(\lambda_1+\gamma_1)}. \tag{3.4}$$

Proof. We will derive the mean transcription level (3.3) by solving (2.8) and (2.9) with initial condition (2.10) through the Laplace transform and the inverse Laplace transform.

To begin with, by applying the Laplace transform to (2.5)-(2.6) and noticing that the initial condition (2.7) holds, we transform the two equations into a closed system of algebraic equations,

$$\begin{cases} (s+\lambda_1)\mathcal{L}(P_O) - \gamma_1\mathcal{L}(P_E) = P_O^*, \\ (s+\gamma_1)\mathcal{L}(P_E) - \lambda_1\mathcal{L}(P_O) = P_E^*. \end{cases}$$

Solving the system, we have the Laplace transforms of $P_O(t)$ and $P_E(t)$ as

$$\mathcal{L}(P_O) = \frac{sP_O^* + \gamma_1}{s(s+\lambda_1+\gamma_1)} \quad \text{and} \quad \mathcal{L}(P_E) = \frac{sP_E^* + \lambda_1}{s(s+\lambda_1+\gamma_1)}, \tag{3.5}$$

which can be rewritten as

$$\begin{aligned} \mathcal{L}(P_O) &= \frac{\gamma_1}{\lambda_1+\gamma_1}\cdot\frac{1}{s} + \left(P_O^* - \frac{\gamma_1}{\lambda_1+\gamma_1}\right)\cdot\frac{1}{s+\lambda+\gamma_1}, \\ \mathcal{L}(P_E) &= \frac{\lambda_1}{\lambda_1+\gamma_1}\cdot\frac{1}{s} + \left(P_E^* - \frac{\lambda_1}{\lambda_1+\gamma_1}\right)\cdot\frac{1}{s+\lambda_1+\gamma_1}. \end{aligned}$$

Then by applying the inverse Laplace transform to them, we derive analytical formulas of $P_O(t)$ and $P_E(t)$ as given in (3.1) and (3.2).

Next, we calculate the exact forms of $m_O(t)$ and $m_E(t)$ under a similar discussion above. By applying the Laplace transform to the two equations to (2.8) and (2.9), we obtain another closed system

$$\begin{cases} s\mathcal{L}(m_O) - m_O^* = \gamma_1\mathcal{L}(m_E) - (\delta_1+\lambda_1)\mathcal{L}(m_O), \\ s\mathcal{L}(m_E) - m_E^* = \nu_1\mathcal{L}(P_E) + \lambda_1\mathcal{L}(m_O) - (\delta_1+\gamma_1)\mathcal{L}(m_E). \end{cases}$$

We solve the system and derive

$$\mathcal{L}(m_O) = \frac{\nu_1\gamma_1\mathcal{L}(P_E) + \gamma_1 m_E^* + (s+\delta_1+\gamma_1)m_O^*}{(s+\delta_1)(s+\delta_1+\lambda_1+\gamma_1)}, \tag{3.6}$$

$$\mathcal{L}(m_E) = \frac{\nu_1(s+\delta_1+\lambda_1)\mathcal{L}(P_E) + (s+\delta_1+\lambda_1)m_E^* + \lambda_1 m_O^*}{(s+\delta_1)(s+\delta_1+\lambda_1+\gamma_1)}. \tag{3.7}$$

Noting that the Laplace form of $P_E(t)$ has been given in (3.5), substituting it into (3.6) and (3.7), and applying the inverse Laplace transform, we gain the analytical expressions of $m_O(t)$ and $m_E(t)$, that is,

$$\begin{aligned} m_O(t) = {} & \frac{\nu_1\lambda_1\gamma_1}{\delta_1(\lambda_1+\gamma_1)(\delta_1+\lambda_1+\gamma_1)} - \frac{\nu_1\gamma_1[\lambda_1-(\lambda_1+\gamma_1)P_E^*]}{\delta_1(\lambda_1+\gamma_1)(\delta_1-\lambda_1-\gamma_1)}e^{-(\lambda_1+\gamma_1)t} \\ & + \frac{\delta_1\gamma_1(\lambda_1+\gamma_1-\delta_1)m^* - \nu_1\gamma_1(\lambda_1-\delta_1P_E^*)}{\delta_1(\lambda_1+\gamma_1)(\lambda_1+\gamma_1-\delta_1)}e^{-\delta_1 t} \\ & - \frac{\nu_1\lambda_1\gamma_1 + (\delta_1+\lambda_1+\gamma_1)[\delta_1\gamma_1 m_E^* - \delta_1\lambda_1 m_O^* - \nu_1\gamma_1 P_E^*]}{\delta_1(\lambda_1+\gamma_1)(\delta_1+\lambda_1+\gamma_1)}e^{-(\delta_1+\lambda_1+\gamma_1)t}, \\ m_E(t) = {} & \frac{\nu_1\lambda_1(\delta_1+\lambda_1)}{\delta_1(\lambda_1+\gamma_1)(\delta_1+\lambda_1+\gamma_1)} - \frac{\nu_1(\delta_1-\gamma_1)[\lambda_1-(\lambda_1+\gamma_1)P_E^*]}{\delta_1(\lambda_1+\gamma_1)(\delta_1-\lambda_1-\gamma_1)}e^{-(\lambda_1+\gamma_1)t} \\ & + \frac{\delta_1\lambda_1(\lambda_1+\gamma_1-\delta_1)m^* - \nu_1\lambda_1(\lambda_1-\delta_1P_E^*)}{\delta_1(\lambda_1+\gamma_1-\delta_1)(\lambda_1+\gamma_1)}e^{-\delta_1 t} \end{aligned}$$

$$+\frac{\nu_1\lambda_1\gamma_1+(\delta_1+\lambda_1+\gamma_1)[\delta_1\gamma_1 m_E^*-\delta_1\lambda_1 m_O^*-\nu_1\gamma_1 P_E^*]}{\delta_1(\lambda_1+\gamma_1)(\delta_1+\lambda_1+\gamma_1)}e^{-(\delta_1+\lambda_1+\gamma_1)t}.$$

Adding up $m_O(t)$ and $m_E(t)$, we derive the average transcription level $m(t)$ as shown in (3.3). Taking the limit to $m(t)$ as $t\to\infty$, we obtain its limit value. This establishes the theorem. □

Since $\exp(-(\lambda_1+\gamma_1)t)$ and $\exp(-\delta_1 t)$ in (3.3) exponentially decay, the mean transcription level $m(t)$ will stay close to the steady state after a short time. During such a short time, the level displays several different behaviors caused by variations in transcription kinetics, as shown in the following proposition. To display the proposition, we give three notations denoted by

$$\Delta=\frac{\nu_1}{\delta_1}-\frac{\nu_0}{\delta_0},\ \Theta=\frac{\lambda_1}{\lambda_1+\gamma_1}-\frac{\lambda_0}{\lambda_0+\gamma_0},\ \Lambda=(\lambda_1+\gamma_1)(m^{**}-m^*)-\delta_1 P_E^*\cdot\Delta.$$

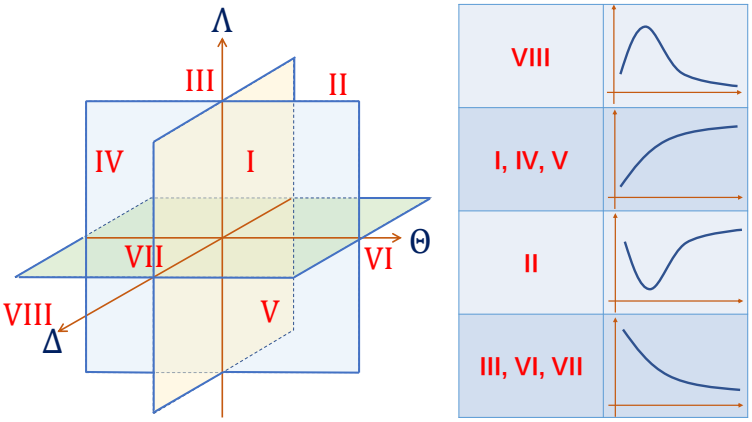

Figure 2. The planes $\Delta=0$, $\Theta=0$, and $\Lambda=0$ divide the space into eight octants. The monotonicity of $m(t)$ is determined by the octant that the point (Δ,Θ,Λ) lies in.

Proposition 3.1. *Under the basic Assumptions (1)-(3), we have the analytical behaviors of $m(t)$ after the variation of parameters occurs, that is,*

(a) When the condition $\Delta>0$ holds, the transcription level $m(t)$ increases at time $t=0$, and

(1) if $\Theta\geq 0$, the level $m(t)$ increases over $(0,+\infty)$,

(2) if $\Theta<0$, the level $m(t)$ increases over $(0,+\infty)$ when $\Lambda\geq 0$, and peaks at some time $t=t_p$ when $\Lambda<0$.

(b) When $\Delta=0$ and

(1) if $\Theta>0$, the level $m(t)$ increases over $(0,+\infty)$,

(2) if $\Theta=0$, the level $m(t)$ is maintained over $(0,+\infty)$,

(3) if $\Theta<0$, the level $m(t)$ decreases over $(0,+\infty)$.

(c) When $\Delta<0$, the transcription level $m(t)$ decreases at time $t=0$ and

(1) if $\Theta>0$, the level $m(t)$ decreases over $(0,+\infty)$ when $\Lambda\leq 0$, and bottoms out at some time $t=t_q$ when $\Lambda>0$.

(2) if $\Theta \le 0$, the level decreases over $(0, +\infty)$.

Proof. Differentiating the mean level $m(t)$ with respect to t, we obtain the derivative, that is,

$$m'(t) = e^{-\delta_1 t} \cdot \theta(t),$$

where

$$\theta(t) = \frac{\nu_1[\lambda_1 - (\lambda_1 + \gamma_1)P_E^*]}{\delta_1 - \lambda_1 - \gamma_1} e^{(\delta_1 - \lambda_1 - \gamma_1)t} - \frac{m^*\delta_1(\delta_1 - \lambda_1 - \gamma_1) + \nu_1(\lambda_1 - \delta_1 P_E^*)}{\delta_1 - \lambda_1 - \gamma_1}.$$

From this derivative, we find that

$$m'(0) = \left(\frac{\nu_1}{\delta_1} - \frac{\nu_0}{\delta_0}\right) \cdot \delta_1 P_E^*,$$

which implies that $m(t)$ increases at time $t = 0$ when $\Delta > 0$ or decreases when $\Delta < 0$. Then the monotonicity of $m(t)$ over $(0, +\infty)$ is determined by the existence of positive roots of $\theta(t) = 0$.

(a) We consider the first case that $\Delta > 0$, which means that $m(t)$ increases at time $t = 0$. If the condition $\Theta \ge 0$ holds, we have

$$\theta'(t) = \nu_1\big[\lambda_1 - (\lambda_1 + \gamma_1)P_E^*\big] e^{(\delta_1 - \lambda_1 - \gamma_1)t} \ge 0,$$

which implies that

$$\theta(t) \ge \theta(0) = \delta_1 P_E^* \cdot \Delta > 0.$$

There is no positive time t such that $\theta(t) = 0$. Thus $m(t)$ is increasing on the interval $(0, +\infty)$.

When $\Theta < 0$, by using a similar discussion as above, we have $\theta'(t) < 0$ and $\theta(0) > 0$. If $\delta_1 - \lambda_1 - \gamma_1 > 0$, the limit of $\theta(t)$ when $t \to +\infty$ is

$$\theta(+\infty) = \lim_{t \to +\infty} \theta(t) = -\infty.$$

The Intermediate Value Theorem says there is a zero of $\theta(t)$ on $(0, +\infty)$. At this moment, we claim that $\Lambda < 0$. In fact, from $\theta(0) > 0$ we get

$$\delta_1 \Lambda = m^*\delta_1(\delta_1 - \lambda_1 - \gamma_1) + \nu_1(\lambda_1 - \delta_1 P_E^*) < \nu_1\big[\lambda_1 - (\lambda_1 + \gamma_1)P_E^*\big] < 0.$$

If $\delta_1 - \lambda_1 - \gamma_1 < 0$, the limit of $\theta(t)$ when $t \to +\infty$ is

$$\theta(+\infty) = \lim_{t \to +\infty} \theta(t) = -\frac{m^*\delta_1(\delta_1 - \lambda_1 - \gamma_1) + \nu_1(\lambda_1 - \delta_1 P_E^*)}{\delta_1 - \lambda_1 - \gamma_1} = -\frac{\delta_1}{\delta_1 - \lambda_1 - \gamma_1}\Lambda.$$

Thus, $\theta(+\infty) < 0$ when $\Lambda < 0$ and there is a positive root of $\theta(t) = 0$ on $(0, +\infty)$, $\theta(+\infty) > 0$ when $\Lambda > 0$ and there is no positive root on $(0, +\infty)$.

(b) We consider the second case $\Delta = 0$. At this moment, we find $\theta(0) = 0$ and

$$\theta'(t) = \nu_1\big[\lambda_1 - (\lambda_1 + \gamma_1)P_E^*\big] e^{(\delta_1 - \lambda_1 - \gamma_1)t} \begin{cases} > 0, \Theta > 0, \\ \equiv 0, \Theta = 0, \\ < 0, \Theta < 0. \end{cases}$$

The monotonicity of $m(t)$ can be derived.

(c) The last case $\Delta < 0$ can be discussed similarly as in (a), we omit the detailed discussion. □

A three-dimensional space can be established by using vector $(\Delta, \Theta, \Lambda)$. The $\Theta\Lambda$-plane ($\Delta = 0$), $\Delta\Lambda$-plane ($\Theta = 0$) and $\Delta\Theta$-plane ($\Lambda = 0$) divide the space into eight octants as shown in Figure 2. The Proposition 3.1 tells the monotonicity of $m(t)$ in detail. For instance, when $\Delta > 0$, $\Theta > 0$ and $\Lambda > 0$, the point $(\Delta, \Theta, \Lambda)$ lies in the first octant and the mean transcription level $m(t)$ increases over the whole time interval $(0, +\infty)$. Similarly, the monotonicity of $m(t)$ is determined by the plane that the point $(\Delta, \Theta, \Lambda)$ lies in. When $\Lambda = 0$, the point $(\Delta, \Theta, \Lambda)$ will lie in $\Delta\Theta$-plane. We find that $m(t)$ increases when $\Delta > 0$ and decreases when $\Delta < 0$, as shown in Figure 3. We also find that there is no point $(\Delta, \Theta, \Lambda)$ will lie in Λ-axis. In fact, when $\Delta = 0$ and $\Theta = 0$, the value of Λ must be zero.

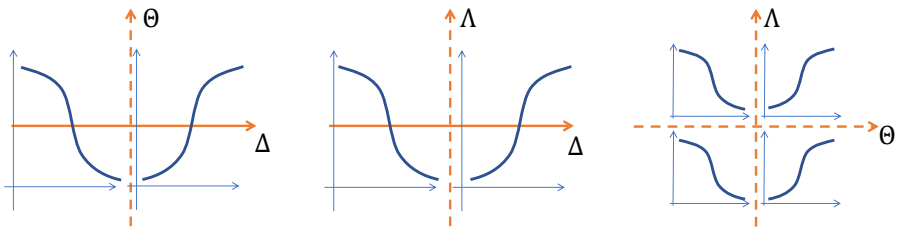

Figure 3. The dynamic behaviors of $m(t)$ when the point $(\Delta, \Theta, \Lambda)$ lies in three coordinate planes. The monotonicity of $m(t)$ is determined by the plane that the point $(\Delta, \Theta, \Lambda)$ lies in. There is no point $(\Delta, \Theta, \Lambda)$ which will lie on Λ-axis except the Origin $(0, 0, 0)$.

From Proposition 3.1, we find that when $(\Delta, \Theta, \Lambda)$ lies in the second or the eighth octant, the mean level $m(t)$ has a unique local minimum or maximum value. At this moment, the stationary point is determined by solving $m'(t) = 0$, that is,

$$t_p = \frac{1}{\delta_1 - \lambda_1 - \gamma_1} \ln \left(\frac{\delta_1 m^*(\delta_1 - \lambda_1 - \gamma_1) + \nu_1(\lambda_1 - \delta_1 P_E^*)}{\nu_1[\lambda_1 - (\lambda_+ \gamma_1) P_E^*]} \right).$$

Since t_p is the unique stationary point, the critical value $m(t_p)$ is the global minimum value with $(\Delta, \Theta, \Lambda) \in$ II or the global maximum value with $(\Delta, \Theta, \Lambda) \in$ VIII.

3.2. The noise

To determine how the numbers of mRNA molecules measured in individual cells deviate from the mean, we compute the ratio of the variance and the square of the mean, or the noise. By definition (1.1), we first give the analytical form of the second moment $\mu(t)$ in the following theorem.

Theorem 3.2. *Under the same condition of Theorem 3.1, the second moment* $\mu(t) = \mathbf{E}[M^2(t)]$ *of the mRNA copy number* $M(t)$ *takes the form*

$$\mu(t) = \mu_0 + \mu_1 e^{-\delta_1 t} + \mu_2 e^{-2\delta_1 t} + \mu_3 e^{-(\lambda_1+\gamma_1)t} + \mu_4 e^{-(\delta_1+\lambda_1+\gamma_1)t}, \tag{3.8}$$

with the coefficients given by

$$\mu_0 = \frac{\nu_1^2 \lambda_1(\delta_1 + \lambda_1) + \nu_1 \lambda_1 \delta_1(\delta_1 + \lambda_1 + \gamma_1)}{\delta_1^2(\lambda_1 + \gamma_1)(\delta_1 + \lambda_1 + \gamma_1)},$$

$$\mu_1 = \frac{(2\nu_1\lambda_1 + \delta_1\lambda_1 + \delta_1\gamma_1)[(\lambda_1+\gamma_1-\delta_1)\delta_1 m^* - \nu_1(\lambda_1 - \delta_1 P_E^*)]}{\delta_1^2(\lambda_1+\gamma_1)(\lambda_1+\gamma_1-\delta_1)},$$

$$\mu_2 = \mu^* - m^* + \frac{2\nu_1\delta_1(\lambda_1+\gamma_1-2\delta_1)(\delta_1 m_E^* - \lambda_1 m^*) + \nu_1^2(\lambda_1-\delta_1)(\lambda_1-2\delta_1 P_E^*)}{\delta_1^2(\lambda_1+\gamma_1-\delta_1)(\lambda_1+\gamma_1-2\delta_1)},$$

$$\mu_3 = -\frac{[\lambda_1-(\lambda_1+\gamma_1)P_E^*][2\nu_1^2(\delta_1-\gamma_1)+\nu_1\delta_1(2\delta_1-\lambda_1-\gamma_1)]}{\delta_1(\lambda_1+\gamma_1)(\delta_1-\lambda_1-\gamma_1)(2\delta_1-\lambda_1-\gamma_1)},$$

$$\mu_4 = \frac{2\nu_1\big[\delta_1(\delta_1+\lambda_1+\gamma_1)(\gamma_1 m_E^* - \lambda_1 m_O^*) + \nu_1\gamma_1[\lambda_1-(\delta_1+\lambda_1+\gamma_1)P_E^*]\big]}{\delta_1(\lambda_1+\gamma_1)(\delta_1+\lambda_1+\gamma_1)(\delta_1-\lambda_1-\gamma_1)}.$$

And the steady form of $\mu(t)$ is

$$\mu^{**} = \frac{\nu_1^2\lambda_1(\delta_1+\lambda_1) + \nu_1\lambda_1\delta_1(\delta_1+\lambda_1+\gamma_1)}{\delta_1^2(\lambda_1+\gamma_1)(\delta_1+\lambda_1+\gamma_1)}. \tag{3.9}$$

Proof. By the definition of noise (1.1), to acquire the analytical form of noise, we only need to calculate the second moment. Since the transcription system has reached a dynamic equilibrium before parameter changes, we will derive the analytical form of the second moment (3.8) by solving (2.14) with the initial condition (2.15) through the Laplace transform.

By applying the Laplace transform to (2.14), we have

$$s\mathcal{L}(\mu) - \mu^* = 2\nu_1\mathcal{L}(m_E) + \nu_1\mathcal{L}(P_E) + \delta_1\mathcal{L}(m) - 2\delta_1\mathcal{L}(\mu).$$

Solving this algebra equation gives

$$\mathcal{L}(\mu) = \frac{2\nu_1\mathcal{L}(m_E) + \nu_1\mathcal{L}(P_E) + \delta_1\mathcal{L}(m) + \mu^*}{s+2\delta_1}.$$

Since the Laplace transforms of $m_E(t)$ and $P_E(t)$ have been obtained, and the Laplace transform of $m(t)$ can be given by summing $\mathcal{L}(m_O)$ and $\mathcal{L}(m_E)$ up, we derive

$$\begin{aligned}\mathcal{L}(\mu) = {} & \frac{1}{s(s+\delta_1)(s+2\delta_1)(s+\lambda_1+\gamma_1)(s+\delta_1+\lambda_1+\gamma_1)} \\ & \times\Big[\nu_1(sP_E^*+\lambda_1)(s+2\delta_1)(s+\delta_1+\lambda_1+\gamma_1) \\ & +[m^*\delta_1(s+\delta_1+\lambda_1+\gamma_1)+2\nu_1 m_E^*(s+\delta_1+\lambda_1)+2\nu_1\lambda_1 m_O^*]s(s+\lambda_1+\gamma_1) \\ & +2\nu_1^2(s+\delta_1+\lambda_1)(sP_E^*+\lambda_1)+\mu^* s(s+\delta_1)(s+\lambda_1+\gamma_1)(s+\delta_1+\lambda_1+\gamma_1)\Big].\end{aligned}$$

The application of the inverse Laplace transform to $\mathcal{L}(\mu)$ gives the analytical form of $\mu(t)$ as shown in (3.8). The steady form of $\mu(t)$ can be obtained by taking a limit on it. What has mentioned above establishes the proof. □

By using the definition (1.1), combined with the analytical expression (3.4) for the stationary mean transcription level, and (3.9) for the second moments, we derive the noise of mRNA copy numbers at steady state, that is,

$$\eta^{2**} = \frac{1}{m^{**}} + \frac{\delta_1\gamma_1}{\lambda_1(\delta_1+\lambda_1+\gamma_1)},$$

which is also independent of the initial state.

4. Simulation

We take advantage of a set of experimental data to explain the conclusions. By means of the smFISH (single molecule fluorescence in situ hybridization) method, Skinner et al [35] measured nascent and mature Oct4 mRNAs in mouse embryonic stem cells. It was observed that the average OFF duration in the transcription of Oct4 is about 108 min, and the average ON duration is about 56 min before the gene replication. The mRNA synthesis rate is 114 hr^{-1} during each ON state, and the average lifetime for mature mRNA is about 7.14 hr. As a result, the four parameters that govern gene transcription before gene replication are given as

$$\nu_0 = 114\ \text{hr}^{-1},\ \delta_0 = 0.14\ \text{hr}^{-1},\ \lambda_0 = 0.5556\ \text{hr}^{-1}\ \text{ and }\ \gamma_0 = 1.0714\ \text{hr}^{-1}.$$

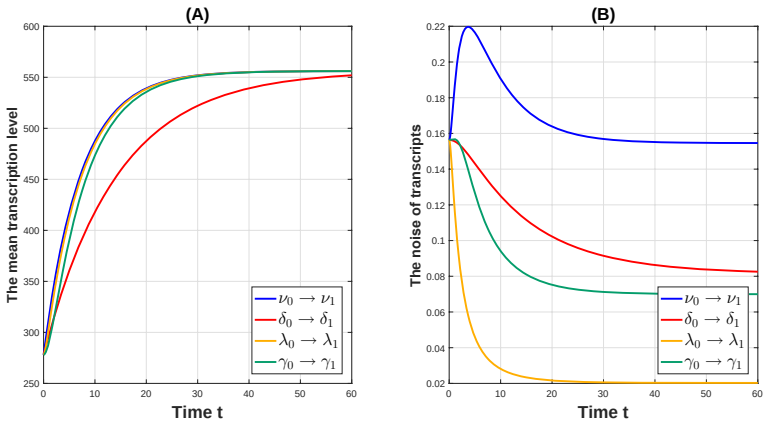

Figure 4. The temporal profiles of the mean transcription level $m(t)$ and the noise $\eta^2(t)$ after the occurrence of the variation in transcription kinetics. In order to double the mRNA number, we can accelerate the synthesis rate, or delay the degradation rate, or increase the transcription frequency. (A) The dynamic behavior of the mean level $m(t)$. (B) The dynamic behavior of the noise $\eta^2(t)$.

As stated in Proposition 3.1, we discover that the mean transcription level $m(t)$ displays a very simple behavior. Especially, when only one parameter changes, the point $(\Delta, \Theta, \Lambda)$ lies in one coordinate plane and the level $m(t)$ is increasing or decreasing on the interval $(0, +\infty)$. For instance, when the synthesis rate changes from ν_0 to ν_1 and other parameters are maintained, the level $m(t)$ can be simplified to

$$m_\nu(t) = \frac{\nu_1\lambda_0}{\delta_0(\lambda_0+\gamma_0)} + \frac{(\nu_0-\nu_1)\lambda_0}{\delta_0(\lambda_0+\gamma_0)}e^{-\delta_0 t}. \tag{4.1}$$

From Proposition 3.1 and Equation (4.1), it is easy to find that $m_\nu(t)$ is increasing when $\nu_1 > \nu_0$ and decreasing when $\nu_1 < \nu_0$.

From the expression (3.3), we learn that the mean transcription level will approach a stationary value m^{**} after several transcription cycles. We explore the dynamic behaviors of the mean level $m(t)$ and the noise $\eta^2(t)$ by assuming that the level m^{**} is twice as much as m^*. There are three simple strategies that can help us achieve the goal of doubling the mRNA number: accelerating the synthesis rate to 2 fold ($\nu_1 = 2\nu_0$), doubling the lifespan of mRNAs ($\delta_1 = \delta_0/2$), or increasing

transcription frequency to 2 fold ($P_E^{**} = 2P_E^*$). To improve the transcription frequency, we could increase the duration of the ON state or decrease the duration of the OFF state.

As shown in Figure 4 (A) and described in Proposition 3.1, the dynamic behavior of the level $m(t)$ is monotonously increasing. In fact, when we set $\nu_1 = 2\nu_0$ or $\delta_1 = \delta_0/2$ and maintain other parameters, $\Delta > 0, \Theta = 0$ and $(\Delta, \Theta, \Lambda)$ lies in the $\Delta\Lambda$-plane. Figure 4 (A) also tells us that, compared to the other three parameters, the change in degradation rate makes the mean level $m(t)$ increase slowly and eventually tend to a stable value. From Figure 4 (B), we find that the dynamic behaviors of the noises manifest a large difference. When the synthesis rate doubles, the noise $\eta^2(t)$ increases very abruptly and attains the maximum value 0.22, then decays to 0.155, as shown by the blue curve in Figure 4 (B). However, when the other three parameters change respectively, the noise decreases sharply and approaches smaller stable values. The variation in the inactivation rate produces the smallest noise, as shown by the orange curve in Figure 4 (B).

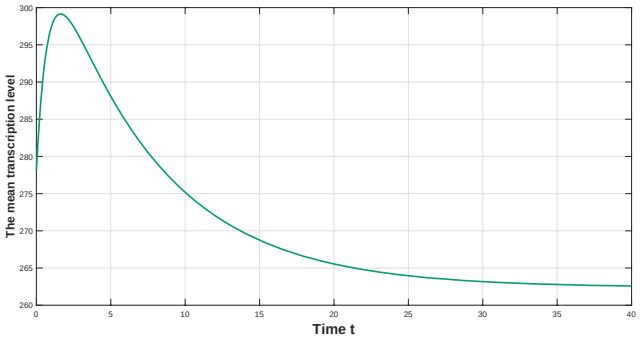

Figure 5. The temporal profile of the mean transcription level $m(t)$ when $(\Delta, \Theta, \Lambda) = (814.3, -0.1804, -58.9184) \in$ VIII. The level $m(t)$ increases from its initial value 278.1 and reaches its maximum level 299.1 at time $t = 1.6$ hr, and subsequently decays to a stationary value 262.4, which is smaller than its initial value.

Owing to the variation of multiple parameters, the average level $m(t)$ may display a non-monotonous behavior. For example, at time $t = 0$, the synthesis rate ν varies from 114 hr^{-1} to 228 hr^{-1}, and the inactivation rate λ varies from 0.5556 hr^{-1} to 0.2058 hr^{-1}, then the point $(\Delta, \Theta, \Lambda)$ will lie in the eighth octant. As shown by the curve in Figure 5, $m(t)$ increases sharply in the beginning and peaks at $t = 1.6$ hr, with maximum value of 299.1. After the plunge, $m(t)$ steadily decays to a smaller stationary value 263.4 than its initial value. The maximum value is 7.55% higher than its initial value and 14% than its stationary value.

5. Conclusion

For living organisms in the stable environment, the mRNAs and proteins in their bodies are generally in dynamic balances. When the internal or external environment changes, the response mechanism of the organism is induced to respond to the changes in the environment.

At first, we assumed that the transcription system resides on one equilibrium state. The changes of environment led to a variation in the transcription kinetics.

By means of using the two-state transcription model, we derived the analytical expressions of the mean level $m(t)$ and the noise $\eta^2(t)$. Simultaneously, we defined three quantities Δ, Θ and Λ. The three coordinate planes $\Delta = 0, \Theta = 0$, and $\Lambda = 0$ divide space into eight octants. Via using the location where the point $(\Delta, \Theta, \Lambda)$ lies, we could easily determine the monotonicity of $m(t)$. With the method of varying the four parameters respectively in simulation, we found that the behavior of $m(t)$ is similar, but the noise takes on different forms.

The study of this article tells us that when regulating gene expression, we need to pay special attention to the existence of thresholds of expression outputs. Especially, when the outputs approach a threshold, any variable is very robust to perturbations of a homeostatic state [11, 13, 25]. These values may touch the potential thresholds, thereby altering the fate of cells [18]. For instance, Mukherji et. al [29] established a threshold level of target messenger RNA via regulation by microRNAs, such as addition of miR-20 binding sites or modulation of miR-20 abundance. Below this threshold, protein production is highly repressed. Near the threshold, protein expression responds sensitively to target mRNA input. When it comes to regulation of gene transcription, we not only have to consider the variation of the transcription level, but also pay special attention to the existence of local extremum in the meantime. This exerts a significant impact on researching gene expression regulation.

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