THE MEAN AND NOISE OF FPT MODULATED BY PROMOTER ARCHITECTURE IN GENE NETWORKS

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Abstract. Increasing experimental evidences suggest that cell phenotypic variation often depends on the accumulation of some special proteins. Recently, a lot of studies have shown that the complexity of promoter architecture plays a major role in regulating transcription and controlling expression dynamics and further phenotype. One unanswered question is why the organism chooses such a complex promoter architecture and how the promoter architecture affects the timing of proteins amount up to a given threshold. To address this issue, we study the effect of promoter architecture on the first-passage time (FPT) by formulating a multi-state gene model, that may reflect the complexity of promoter architecture. We derive analytical formulae for FPT moments in each case of irreversible promoter and reversible promoter regulation, which is the first time to give these analytical results in the existing literature. We show that the mean and noise of FPT increase with the state number of promoter architecture if the mean residence time at \textit{off} states is not fixed. Inversely, if the mean residence time at \textit{off} states is fixed, then complex promoter architecture will not vary the mean of FPT but will tend to decrease the noise of FPT. Our results show that, in the same inactive promoter states, the noise of FPT with promoters in irreversible case is always less than that in reversible case. In conclusion, our results reveal the effect of the promoter architecture on FPT and enhance understanding of the regulation mechanism of gene expression.

1. Introduction. Gene expression undergoes a series of complex biochemical processes, involving transcription of deoxyribonucleic acid (DNA) into messenger ribonucleic acid (mRNA), translation of mRNA into protein, transcriptional regulation, recruitment of transcription factors and polymerase, transitions between promoter active and inactive states, and chromatin remodeling, etc. [4, 27, 36, 45, 58]. These biochemical processes and complex promoter architecture inevitably lead to stochastic fluctuation in the number of gene expression products [4, 30, 52, 53]. As a

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result, after initiation of gene expression, the first-passage time FPT, is stochastic as well. As soon as the amount of protein hits a critical threshold, a series of cellular events (such as E.coli cell lysis [15,60,71]; cell division [19]) will be triggered. Thus, FPT in gene regulatory networks has attracted more and more attention in recent years. For instance, lysis timing is closely related to bacteriophage fitness [1, 6, 20, 21, 55, 69, 70]. Singh and Dennehy revealed how holin transcription and translation efficiencies independently modulate the mean and variation of lysis time [60]. The authors in [19] proposed a simple yet elegant model to explain key experimental findings and suggested a mechanism for regulating both the mean and fluctuations in cell-division timing for controlling size. The impact of different burst ways on the mean of FPT was discussed in [57]. However, it is barely understood how complex promoter architecture affects the mean and noise of FPT and this is a great challenge in molecular biology. Here we devote ourselves to studying the mechanism of FPT on the promoter architecture.

The promoter is a portion of DNA sequences that can recognise and recruit some particular functional RNA polymerases. The promoter architecture is greatly complex. It has been demonstrated that there are many factors leading to the complex structure of promoters. These factors include the presence or absence of proximal nucleosome binding sites, the presence of a TATA box with variable strength, and the number of transcription factor binding sites as well as their strength and their locations on the promoter, etc. [52]. Recently, biologists have done a great deal of experiments and research works focusing on the regulation mechanism of the complex promoter architecture on cell plasticity and fate [63], bacteriophage λ fitness [28,56], fluctuation of production of gene expression [12,17,18,29,33,34,37,39,46,48,51,65,67,68,73–77], phenotypic diversity [5,7,23,50], cell-to-cell variability of gene expression [8,10,13,22,53], energy consumption of gene expression [24,25] etc. These studies have contributed greatly to revealing the effects of complex promoter architecture on the biological functions of cells and exploring the biological mechanisms. Nevertheless, the function of complex promoter architecture needs to be fully understood, e.g., how the promoter architecture affects the mean and noise of FPT is still unclear. Cellular function and cell fate are linked closely with stochasticity on FPT. For example, lysis time for an E. coli cell infected by a λ phage virus is stochastic [6,20,21,55,63,69,70]. Lysis of the cell takes place when holin, the protein responsible for lysis, reaches a critical threshold [15,60,71]. Therefore, many scientists have been being interested in the study of FPT and have shown that phenotypic diversity and cell fate decision often mainly rely on the number of the particular protein [1, 2, 6, 11, 15–19,21,31,32,38,55,57,60,69–71]. More concretely, the noise at timing of cell cycle start may be suppressed independently by multiple pathways [2]. Cell-to-cell lysis time differences arise due to the stochastic transcription and translation of the lysis timekeeper protein [60]. The noise in cell-division time increases with size at birth [19]. Mean FPT depending on transcriptional and translational bursts monotonically decreases with bursty [57].

According to experimental results and theoretical models above, complex promoter architecture is one of the most important sources of noise in gene expression and FPT provides a frame-work for studying the time for cellular functions conversion caused by crossing a threshold. In order to gain more insight into regulation mechanism of promoter architecture on FPT, we discuss the effects of multiple-state promoter architecture on FPT.
Quantifying the effects of complex promoter architecture modulation on FPT is an important step towards understanding cellular functional variability. In order to make up the lack that the previous studies ([1, 2, 15, 20, 21, 38, 55, 60, 69–71]) did not consider the influence of promoter structure on FPT moments, we are going to investigate the mechanism of FPT in the case of promoter architecture regulation by using gene expression model, where the gene activity proceeds sequentially through the on state (only here burst of protein can occur) and multiple off states (here no proteins are produced) and then returns to the on state, forming a loop; see Figure 1. To be consistent with experimental observation, we assume proteins are stable as the lysis protein in λ phage, i.e. holin, is stable [56] and protein synthesis is almost in a bursting manner [9, 35, 44, 57, 72]. Further research [16] revealed that the total number of proteins produced in a single burst event follows a geometric distribution. The main results of this paper are as follows. Firstly, analytical calculations of FPT moments are derived respectively for both irreversible and reversible promoter. This is the first time to obtain these analytical results in the existing literature. In addition, for a given protein threshold, compared with two-state (promoter transition only between on and off) model, our numerical results show that adding promoter states tends to increase the mean and noise of FPT; if we fix the residence time at off states, our numerical results reveal that the mean of FPT is invariable, but complex promoter architecture tends to reduce the noise of FPT. Our results also indicate that, in the same inactive promoter states, the noise of FPT with promoters in irreversible case is always less than that in reversible case. Given the prevalence of complex promoter architecture, illuminating the effects of complex promoter architecture on FPT can enhance understanding of its regulatory roles in biological processes.

2. Analytical expression for the mean and noise of FPT. In order to clearly reveal the mechanism of how promoter architecture modulates FPT, we establish a representative gene model with multi-state promoter architecture (See Figure 1). The gene activity proceeds sequentially through the on state and several off states and then returns to the on state, with the indicated rates, forming a loop; protein synthesizes in burst manner. In the light of the model, we will make some detailed introductions to parameters based on complex promoter architecture. \( \lambda_0 \) is the rate of gene inactivation; \( \lambda_L \) is the rate of gene activation; \( \lambda_k \) is the transition rate from the \( k^{th} \) off state to the \( (k+1)^{th} \) off state with \( (k = 1, 2, \cdots, L - 1) \); \( \lambda'_k \) is the transition rate from the \( (k+1)^{th} \) off state to the \( k^{th} \) off state with \( (k = 1, 2, \cdots, L - 1) \); \( k_m \) is the arrival rate of protein burst synthesis. Note that if \( L = 1 \), the corresponding model will become familiar two-state model. In addition, for the sake of convenience, we call the promoter architecture process is a irreversible loop if \( \lambda'_k = 0 \) (Figure 1A) and a reversible loop if \( \lambda'_k \neq 0 \) (Figure 1B). During processes of gene expression, active genes are transcribed into mRNAs which are then translated into proteins. Here, to simplify our analysis, we further integrate transcription and translation into a single-step process. This simplification has been extensively made [23, 43, 54]. In fact, it has been shown that the half-life of protein is in general much longer than that of mRNA [43, 54]. For example, Shahrezaei and Swain [54] did a survey for about 2000 genes in budding yeast and found that the expressions of most of these genes satisfy this condition. Osella and Lagomarsino [40] indicated that the loss of highly stable proteins is mainly due to dilution through cell growth and cell division. For this reason, we don’t consider the factor on degradation of protein. Our models are as follows:
Figure 1. Simplified sketch of complex promoter architecture for a gene expression model. Where the gene activity proceeds sequentially through \(\text{on}\) state and several \(\text{off}\) states and then returns to \(\text{on}\) state, with the indicated rates: \(\lambda_0\) is the rate of gene inactivation; \(\lambda_L\) is the rate of gene activation; \(\lambda_k\) is the transition rate from the \(k^{th}\) \(\text{off}\) state to the \((k+1)^{th}\) \(\text{off}\) state with \((k = 1, 2, \cdots, L - 1)\); \(\lambda'_k\) is the transition rate from the \((k+1)^{th}\) \(\text{off}\) state to the \(k^{th}\) \(\text{off}\) state with \((k = 1, 2, \cdots, L - 1)\); \(k_m\) is the rate of protein synthesis. To investigate the effects of promoter architecture on FPT, we divide promoters into two categories: A: Irreversible promoter structure; B: Reversible promoter structure.

Consistent with experimental observation and relative studies, the time interval between two burst events is exponentially distributed with the parameter \(k_m\) \([26, 60, 61, 64]\); the proteins are not degradative as the lysis protein in \(\lambda\) phage, i.e. holin, is stable \([56]\); the burst size follows a geometric distribution with mean \(b\) \([9, 16, 66, 72]\).

Our model focuses on effects of complex promoter architecture on FPT. Complexity of promoter structure is reflected by dynamic transitions between active and inactive states and by dynamic transitions among inactive states. How dynamic transitions among states of these promoters affect randomness of proteins has been observed in various gene regulation networks \([3, 4, 45, 52, 56, 60]\). Meanwhile, a number of studies also have been paying attention to the influences of promoter structure on regulated-gene product \([13, 23, 75–77]\). Furthermore, the time at which proteins reach a special threshold has been widely concerned \([6, 15, 20, 21, 41, 55, 60, 63, 69, 70]\). But the effect of complex promoter architecture on FPT is still elusive. Our main purpose is to quantify the effect of complex promoter architecture on FPT. In the following, we will drive the analytical expression for FPT on the basis of the gene regulation model (Figure 1).

The intrinsic randomness of biochemical reactions leads to the fact that the protein count \(P(t)\) at time \(t\) with \(P(0) = 0\) is a stochastic process. Accordingly, for a given threshold \(X\), FPT should be the time when \(P(t)\) firstly reaches \(X\). Therefore, we have

\[
\text{FPT} = \inf\{t : P(t) \geq X\}. \tag{1}
\]

Since the protein count changes only when a burst occurs, we can calculate the minimum times of burst events, \(N\), taking for the protein count to reach the threshold \(X\). Let \(P_n\) be the protein count after \(n^{th}\) gene expression events. Then

\[
N = \inf\{n : P_n \geq X\}. \tag{2}
\]

Further, let the interval time between \((i - 1)^{th}\) and \(i^{th}\) protein burst events be denoted by the random variable \(T_i\). Then \(T_i \ (i = 1, 2, \cdots, N)\) are independent
identical distributions. We have

\[ \text{FPT} = \sum_{i=1}^{N} T_i. \]  

(3)

Next, we bend ourselves to find the mean, variance and noise of FPT. The basic idea is to elaborate the properties of conditional expectation, and then based on Laplace Transform, we solve the master equation. The overall procedure for finding such random characters is technical.

Let \( \text{Pr}(D) \) represent the probability of event \( D \), and \( \langle R \rangle, \text{Var}(R) \) and \( \text{CV}(R) \) respectively denote mean, variance and noise of \( R \). Since \( T_i \ (i = 1, 2, 3, \cdots, N) \) are independent identical distributions and each of \( T_i \) is independent of \( N \), using standard results from probability theory \([47, 49]\), we obtain

\[
\langle \text{FPT} \rangle = \langle \sum_{i=1}^{N} T_i \rangle \\
= \langle \langle \sum_{i=1}^{N} T_i | N \rangle \rangle \\
= \sum_{n=1}^{\infty} \left( \sum_{i=1}^{n} T_i | N = n \right) \text{Pr}(N = n) \\
= \sum_{n=1}^{\infty} \langle \sum_{i=1}^{n} T_i \rangle \text{Pr}(N = n) \\
= \langle T_i \rangle \langle N \rangle, 
\]  

(4)

and

\[
\text{Var}(\text{FPT}) = \langle (\sum_{i=1}^{N} T_i)^2 \rangle - \langle \sum_{i=1}^{N} T_i \rangle^2 \\
= \sum_{n=1}^{\infty} [\text{Var}(\sum_{i=1}^{n} T_i) + \langle \sum_{i=1}^{n} T_i \rangle^2] \text{Pr}(N = n) - \langle \sum_{i=1}^{n} T_i \rangle^2 \langle N \rangle^2 \\
= \sum_{n=1}^{\infty} [n \text{Var}(T_i) + n^2 \langle T_i \rangle^2] \text{Pr}(N = n) - \langle T_i \rangle^2 \langle N \rangle^2 \\
= \text{Var}(T_i) \langle N \rangle + \langle T_i \rangle^2 \text{Var}(N). 
\]  

(5)

That is

\[
\langle \text{FPT} \rangle = \langle N \rangle \langle T_i \rangle, 
\]  

(6)

\[
\text{Var}(\text{FPT}) = \langle N \rangle \text{Var}(T_i) + \text{Var}(N) \langle T_i \rangle^2. 
\]  

(7)

Then, the noise of FPT can be written as

\[
\text{CV}(\text{FPT}) = \frac{\text{Var}(\text{FPT})}{\langle \text{FPT} \rangle^2} = \frac{\text{Var}(T_i)}{\langle T_i \rangle^2 \langle N \rangle} + \frac{\text{Var}(N)}{\langle N \rangle}. 
\]  

(8)
In order to determine the mean, variance and noise of FPT in Eq.(6)-(8), we need to derive expressions for the first two moments of $T_i$ and $N$, which we calculate as follows.

2.1. The mean and variance of $N$. In order to calculate the first two moments of the minimum times of burst events $N$ for protein count to reach the threshold $X$, we need to derive the distribution for protein population firstly.

Let us denote the size of $i^{th}$ burst by random variable $B_i$ and the parameter of its distribution by $\mu$. The probability mass function, therefore, can be written as

$$Pr(B_i = k) = \mu(1 - \mu)^k, \mu \in (0, 1], k \in \{0, 1, 2, \cdots\}. \quad (9)$$

The mean burst size, $b$, can be expressed as

$$\langle B_i \rangle = b = \frac{1 - \mu}{\mu}. \quad (10)$$

Further, protein count after $n^{th}$ burst events $P_n$ can be expressed as the sum of random variables $B_i$,

$$P_n = \sum_{i=1}^{n} B_i. \quad (11)$$

As the sum of independent and identically distributed geometric random variables, $P_n$ has a negative binomial distribution with parameters $n$ and $\mu$. The probability mass function of $P_n$, denoted as $f_{P_n}(j)$, can be expressed as

$$f_{P_n}(j) = Pr(\sum_{i=1}^{n} B_i = j) = \binom{n+j-1}{n-1}\mu^n(1-\mu)^j. \quad (12)$$

Also, the cumulative distribution function is given by

$$Pr(\sum_{i=1}^{n} B_i \leq j) = 1 - I_{1-\mu}(j+1, n), \quad (13)$$

where $I_{1-\mu}(j+1, n)$ is the incomplete beta function,

$$I_{1-\mu}(j+1, n) = \sum_{l=j+1}^{n+j} \binom{n+j}{l} (1-\mu)^l \mu^{n+j-l}, \quad (14)$$

which satisfies the following property

$$I_{1-\mu}(j+1, n) = 1 - I_\mu(n, j+1). \quad (15)$$

We have determined the distribution for protein population $P_n$. Next, in line with the definition of random variable $N$ in Eq.(2), the cumulative distribution function for $N$ can be written as

$$Pr(N \leq n) = Pr(P_n \geq X) = 1 - Pr(P_n \leq X - 1), \quad (16)$$

since $P_n$ is a negative binomial distribution, we have

$$Pr(N \leq n) = 1 - (1 - I_{1-\mu}(X, n)) = I_{1-\mu}(X, n), \quad (17)$$

using the property of incomplete beta function mentioned in Eq.(15), we get

$$Pr(N \leq n) = 1 - I_\mu(n, X). \quad (18)$$
Comparing with Eq.(12) and Eq.(13), the probability mass function corresponding to Eq.(18) can be written as

\[ f_N(n) = \binom{n+X-2}{n-1} \mu^{n-1}(1-\mu)^X, \quad n \in \{1, 2, \ldots\}, \quad X \geq 1. \]  

(19)

First two statistical moments of the distribution in Eq.(19) are given by [42]

\[ \langle N \rangle = \frac{\mu X}{1-\mu} + 1 = \frac{X}{b} + 1, \]  

(20)

\[ \text{Var}(N) = \langle N^2 \rangle - \langle N \rangle^2 = \frac{\mu X}{(1-\mu)^2} = \frac{X}{b} \left(1 + \frac{b}{b} \right). \]  

(21)

2.2. The mean and variance of \( T_i \). For the sake of gaining the mean and variance of inter arrival time \( T_i \) between \((i-1)\)th and \( i\)th protein burst events, we consider the gene model (Figure 1) regulated by promoter architecture as the following \((L+2)\)-state Markov chain shown in Figure 2, where 1, 2, \ldots, \( L \) mean that the promoter is in the first inactive state, the second inactive state, \ldots, the \( L\)th inactive state respectively and no protein burst events occur. 0 means that the promoter is in the active state but no protein has been produced. Finally, \( L+1 \) is an absorbing state meaning that the promoter is in the active state and one burst event is occurred. Transition rates between these states are the corresponding rates in Figure 1. We assume that the system is in initial state at \( t = 0 \). Let \( p_i(t), i = 0, 1, 2, \ldots, L \) denote the probability that the system is in the \( i\)th state at time \( t \). Then, based on the model (see Figure 2), we obtain the following equations

\[ \frac{dp_0(t)}{dt} = - (\lambda_0 + k_m)p_0(t) + \lambda_L p_L(t), \]
\[ \frac{dp_1(t)}{dt} = \lambda_0 p_0(t) - \lambda_1 p_1(t) + \lambda_1' p_2(t), \]
\[ \frac{dp_2(t)}{dt} = \lambda_1 p_1(t) - (\lambda_1' + \lambda_2) p_2(t) + \lambda_2' p_3(t), \]
\[ \frac{dp_3(t)}{dt} = \lambda_2 p_2(t) - (\lambda_2' + \lambda_3) p_3(t) + \lambda_3' p_4(t), \]
\[ \ldots \]
\[ \frac{dp_L(t)}{dt} = \lambda_{L-1} p_{L-1}(t) - (\lambda_{L-1}' + \lambda_L) p_L(t), \]
\[ p_0(0) = 1, p_1(0) = 0, p_2(0) = 0, \ldots, p_L(0) = 0. \]  

(22)

Note that the above equations are all linear differential equations, by using Laplace Transforms of \( p_i(t) \),

\[ \tilde{p}_i(s) = \mathcal{L}p_i(t) = \int_0^\infty e^{-st}p_i(t)dt, \quad i = 0, 1, 2, \ldots, L, \]
we obtain the following algebraic equations
\[
(s + \lambda_0 + k_m)p_0(s) - \lambda_L \tilde{p}_L(s) = 1,
-\lambda_0 \tilde{p}_0(s) + (s + \lambda_1) \tilde{p}_1(s) - \lambda'_1 \tilde{p}_2(s) = 0,
-\lambda_1 \tilde{p}_1(s) + (s + \lambda'_1 + \lambda_2) \tilde{p}_2(s) - \lambda'_2 \tilde{p}_3(s) = 0,
-\lambda_2 \tilde{p}_2(s) + (s + \lambda_2 + \lambda_3) \tilde{p}_3(s) - \lambda'_3 \tilde{p}_4(s) = 0,
\ldots
-\lambda_{L-1} \tilde{p}_{L-1}(s) + (s + \lambda'_{L-1} + \lambda_L) \tilde{p}_L(s) = 0.
\] (23)

Note that the probability that the system reaches \( L + 1 \) in the infinitesimal time interval \((t, t+dt)\) is \( k_m p_0(t) dt \). Thus, the burst’s arrival time distribution is \( k_m p_0(t) \), and we can calculate the mean and variance for the inter arrival time by the following formulae
\[
\langle T_i \rangle = \int_0^\infty k_m t p_0(t) dt = -k_m \left. \frac{d \tilde{p}_0(s)}{ds} \right|_{s=0},
\]
\[
\langle T_i^2 \rangle = \int_0^\infty k_m t^2 p_0(t) dt = k_m \left. \frac{d^2 \tilde{p}_0(s)}{ds^2} \right|_{s=0}. \tag{24}
\]

Correspondingly, in the irreversible case with \( L = 2 \), we obtain
\[
\langle T_i \rangle = \frac{1}{k_m} + \frac{\lambda_0}{k_m} \left( \frac{1}{\lambda_2} + \frac{1}{\lambda_1} \right), \tag{25}
\]
\[
\langle T_i^2 \rangle = \frac{A}{k_m^2 \lambda_1^2 \lambda_2^2}, \tag{26}
\]
where \( A = 2(\lambda_1 \lambda_2^2 + k_m \lambda_0 \lambda_1^2 + \lambda_1^2 \lambda_2 + 2 \lambda_0 \lambda_1 \lambda_2^2 + 2 \lambda_0 \lambda_1 \lambda_2^2 + 2 \lambda_0 \lambda_1 \lambda_2^2 + k_m \lambda_0 \lambda_1 \lambda_2 + \lambda_0^2 \lambda_2^2 + \lambda_1^2 \lambda_2^2 + \lambda_0 \lambda_1 \lambda_2^2) \). Further, we can get
\[
\text{Var}(T_i) = \langle T_i^2 \rangle - \langle T_i \rangle^2 = \frac{B}{k_m^2 \lambda_1^2 \lambda_2^2}, \tag{27}
\]
where \( B = 2k_m \lambda_0 \lambda_1^2 + k_m \lambda_0 \lambda_2^2 + 2 \lambda_0^2 \lambda_1 \lambda_2 + 2 \lambda_0 \lambda_1 \lambda_2^2 + 2 \lambda_0 \lambda_1 \lambda_2 + 2 \lambda_0 \lambda_1 \lambda_2^2 + 2k_m \lambda_0 \lambda_1 \lambda_2 + \lambda_0^2 \lambda_1^2 + \lambda_0^2 \lambda_2^2 + \lambda_1^2 \lambda_2^2 \).

Similarly, in the reversible case with \( L = 2 \), we have
\[
\langle T_i \rangle = \frac{1}{k_m} + \frac{\lambda_0}{k_m} \left( \frac{1}{\lambda_1} + \frac{1}{\lambda_2} + \frac{\lambda'_1}{\lambda_1 \lambda_2} \right), \tag{28}
\]
\[
\langle T_i^2 \rangle = \frac{C}{k_m^2 \lambda_1^2 \lambda_2^2}, \tag{29}
\]
where \( C = k_m \lambda_0 \lambda_1^2 + k_m \lambda_0 \lambda_2^2 + k_m \lambda_0 (\lambda'_1)^2 + 2 \lambda_0 \lambda_1 \lambda_1' + 2 \lambda_0 \lambda_2 \lambda_2' + 2 \lambda_0 \lambda_1 \lambda_2 + 2 \lambda_0 \lambda_2 \lambda_2' + 2 \lambda_0 \lambda_1 \lambda_2' + 2 \lambda_0 \lambda_1 \lambda_2' + 2 \lambda_0 \lambda_1 \lambda_2' + 2 \lambda_0 \lambda_1 \lambda_2' + 2 \lambda_0 \lambda_1 \lambda_2' + 2 \lambda_0 \lambda_1 \lambda_2' \), and
\[
\text{Var}(T_i) = \langle T_i^2 \rangle - \langle T_i \rangle^2. \tag{30}
\]

In the irreversible case with \( L = 3 \),
\[
\langle T_i \rangle = \frac{1}{k_m} + \frac{\lambda_0}{k_m} \left( \frac{1}{\lambda_3} + \frac{1}{\lambda_2} + \frac{1}{\lambda_1} \right), \tag{31}
\]
\[
\text{Var}(T_i) = \frac{D}{k_m^2 \lambda_1^2 \lambda_2^2 \lambda_3^2}, \tag{32}
\]
where \( D = \lambda_0^2 \lambda_1^2 + \lambda_0^2 \lambda_2^2 + \lambda_0^2 \lambda_3^2 + \lambda_1^2 \lambda_2^2 + \lambda_1^2 \lambda_3^2 + 2k_m \lambda_0 \lambda_1^2 + 2k_m \lambda_0^2 \lambda_2^2 + 2k_m \lambda_0^2 \lambda_3^2 + 2k_m \lambda_0 \lambda_2^2 \lambda_3 + 2k_m \lambda_0 \lambda_1^2 \lambda_3 + 2k_m \lambda_0 \lambda_1 \lambda_2^2 \lambda_3 + 2k_m \lambda_0 \lambda_1 \lambda_2 \lambda_3^2 + 2k_m \lambda_0 \lambda_1 \lambda_2 \lambda_3 + 2k_m \lambda_0 \lambda_1 \lambda_2 \lambda_3^2 + 2k_m \lambda_0 \lambda_1 \lambda_2 \lambda_3 + \lambda_0 \lambda_1 \lambda_2 \lambda_3 \).

In the reversible case with \( L = 3 \),

\[
\langle T_i \rangle = \frac{1}{k_m} + \frac{\lambda_0}{k_m^2} \left( \sum_{k=1}^{L} 1 \right),
\]

\[
Var(T_i) = \frac{E}{k_m^2 \sum_{k=1}^{L} \lambda_k^2},
\]

where \( E \) is the function of parameters \( k_m, \lambda_0, \lambda_1, \lambda_2, \lambda_3 \), and in the reversible case

\[
\langle T_i \rangle = \frac{1}{k_m} + \frac{\lambda_0}{k_m^2} \left( \sum_{k=1}^{L} 1 \right) + \frac{1}{\lambda_k} \sum_{k=1}^{L-1} \frac{\lambda_k'}{\lambda_k \lambda_{k+1}} + \cdots + \frac{\lambda_1 \lambda_2 \cdots \lambda_{L-1}}{\lambda_1 \lambda_2 \cdots \lambda_L},
\]

\[
Var(T_i) = \frac{G}{k_m^2 \sum_{k=1}^{L} \lambda_k^2},
\]

where \( G \) is the function of parameters \( k_m, \lambda_0, \lambda_1, \lambda_2, \cdots, \lambda_L, \lambda_1', \cdots, \lambda_{L-1}' \).

### 2.3. The mean, variance and noise of FPT

We now have expressions for the first two moments of \( T_i \), and \( N \) in irreversible and reversible cases. The expressions for the first two moments of FPT in terms of irreversible promoter architecture model parameters can, therefore, be written as

\[
\langle \text{FPT} \rangle = \left( \frac{X}{b} + 1 \right) \frac{1}{k_m} (1 + \lambda_0 \sum_{k=1}^{L} \frac{1}{\lambda_k}),
\]

\[
Var(\text{FPT}) = \left( \frac{X}{b} + 1 \right) \frac{F}{k_m^2 \sum_{k=1}^{L} \lambda_k^2} + \left( \frac{X}{b} + 1 \right) \frac{1}{k_m^2} \left( 1 + \lambda_0 \sum_{k=1}^{L} \frac{1}{\lambda_k} \right)^2.
\]

Thus, we get an analytical expression for noise of FPT, that is

\[
CV(\text{FPT}) = \frac{Var(\text{FPT})}{(\text{FPT})^2}.
\]

The expressions for first two moments of FPT in terms of reversible promoter architecture model parameters can, therefore, be written as

\[
\langle \text{FPT} \rangle = \left( \frac{X}{b} + 1 \right) \frac{1}{k_m} \left[ 1 + \lambda_0 \left( \sum_{k=1}^{L} \frac{1}{\lambda_k} + \sum_{k=1}^{L-1} \frac{\lambda_k'}{\lambda_k \lambda_{k+1}} + \cdots + \frac{\lambda_1 \lambda_2 \cdots \lambda_{L-1}'}{\lambda_1 \lambda_2 \cdots \lambda_L} \right) \right],
\]
\[ \text{Var}(\text{FPT}) = \left( \frac{X}{b} + 1 \right) \frac{G}{b^2} \prod_{k=1}^{L} \frac{\lambda_k^2}{k_m^2} + \frac{X}{b} \frac{1 + b}{k_m^2} \times \left[ 1 + \lambda_0 \left( \sum_{k=1}^{L} \frac{\lambda_k}{\lambda_k \lambda_{k+1}} + \cdots + \frac{\lambda_1 \lambda_2 \cdots \lambda_{L-1}}{\lambda_1 \lambda_2 \cdots \lambda_L} \right) \right]^2. \quad (43) \]

Further, the analytical expression for noise of FPT is
\[ \text{CV}(\text{FPT}) = \frac{\text{Var}(\text{FPT})}{\langle \text{FPT} \rangle^2}. \quad (44) \]

3. The average residence time at off states. Residence time is very interesting in various actual applications including stochastic process, physics, chemistry, finance, bank and aviation. In particular, in biology, it is a common quantity [75–77], which proved that if keep residence time at inactive states of promoter the same in each of the three cases (irreversible, reversible, classical on-off), then the mean of gene expression is invariant, nevertheless, the noise intensity in the irreversible case is less than that in the reversible case and the noise intensity in reversible case is further smaller than that in the classical on-off model. For our stochastic model of bursty gene expression, which considers promoter architecture, a natural question is as follows: with fixed residence time at off states, how can the residence time at multiple off states affect the mean and noise of FPT? So, we devote ourselves to deriving the residence-time distribution at off states.

First, we state a method of computing residence time and its distribution for the gene model [76]. Consider a gene model with the transition matrix among promoter activity states, denoted by
\[ H = \begin{pmatrix} H_{00} & H_{10} \\ H_{01} & H_{11} \end{pmatrix}, \]
where \( H_{00} \) describes the internal transitions between on states and the transitions from some off state to on state; \( H_{10} \) and \( H_{01} \) describe transitions from some off state to on state and from some on state to off state, respectively; and \( H_{11} \) describes the internal transitions between off states and the transitions from some on state to off state. Then, the distribution functions for the mean time at on states and off states are given by
\[ f_{\text{on}}(\tau) = U_L H_{01} \exp(H_{00} \tau) H_{10} U_L^T, \quad (45) \]
\[ f_{\text{off}}(\tau) = U_K H_{10} \exp(H_{11} \tau) H_{01} U_K^T. \quad (46) \]

Moreover, the mean residence time at off and on states are given by
\[ \langle \tau_{\text{on}} \rangle = \frac{1}{U_L H_{10} U_L^T} U_L H_{01} (H_{00})^{-2} H_{10} U_L^T, \quad (47) \]
\[ \langle \tau_{\text{off}} \rangle = \frac{1}{U_K H_{01} U_K^T} U_K H_{10} (H_{11})^{-2} H_{01} U_K^T, \quad (48) \]

where \( L \) and \( K \) are the order of \( H_{00} \) and \( H_{11} \), respectively, \( U_L = (1, 1, \cdots, 1)_{1 \times L} \) and \( U_K = (1, 1, \cdots, 1)_{1 \times K} \). The above formulae indicate that the mean time at on states and at off states distributions are easily computed as long as the transition matrix \( H \) is determined. Thus, for the gene model shown in Figure 1 where the promoter has \( L \) off states and one on state that together constitute a loop, we
have

\[ \langle \tau_{\text{on}} \rangle = -\frac{1}{a_{11}}, \]
\[ \langle \tau_{\text{off}} \rangle = -\frac{1}{a_{11}} \frac{c_2 + c_3 + \cdots + c_{L+1}}{c_1}, \]

where \( c_i \) is the algebraic complement of the diagonal element \( a_{ii} \) (\( i = 1, 2, \cdots, L+1 \)) of the transition matrix \( H \). For example, in the irreversible case with \( L = 2 \),

\[ \langle \tau_{\text{on}} \rangle = -\frac{1}{a_{11}} = \frac{1}{\lambda_0}, \]
\[ \langle \tau_{\text{off}} \rangle = -\frac{1}{a_{11}} \frac{c_2 + c_3}{c_1} = \frac{1}{\lambda_1} + \frac{1}{\lambda_2}. \]

Correspondingly, in the reversible case with \( L = 2 \), we can get

\[ \langle \tau_{\text{on}} \rangle = \frac{1}{\lambda_0}, \]
\[ \langle \tau_{\text{off}} \rangle = -\frac{1}{a_{11}} \frac{c_2 + c_3}{c_1} = \frac{1}{\lambda_1} + \frac{1}{\lambda_2} + \frac{\lambda'_1}{\lambda_1 \lambda_2}. \]

Similarly, in the irreversible case with \( L = 3 \),

\[ \langle \tau_{\text{on}} \rangle = \frac{1}{\lambda_0}, \]
\[ \langle \tau_{\text{off}} \rangle = -\frac{1}{a_{11}} \frac{c_2 + c_3 + c_4}{c_1} = \frac{1}{\lambda_1} + \frac{1}{\lambda_2} + \frac{1}{\lambda_3}. \]

and in the reversible case with \( L = 3 \),

\[ \langle \tau_{\text{on}} \rangle = \frac{1}{\lambda_0}, \]
\[ \langle \tau_{\text{off}} \rangle = \frac{1}{\lambda_1} + \frac{1}{\lambda_2} + \frac{1}{\lambda_3} + \frac{\lambda'_1}{\lambda_1 \lambda_2} + \frac{\lambda'_2}{\lambda_2 \lambda_3} + \frac{\lambda'_1 \lambda'_2}{\lambda_1 \lambda_2 \lambda_3}. \]

By induction, we have in the irreversible case

\[ \langle \tau_{\text{on}} \rangle = \frac{1}{\lambda_0}, \]
\[ \langle \tau_{\text{off}} \rangle = \sum_{k=1}^{L} \frac{1}{\lambda_k}, \]

and in the reversible case,

\[ \langle \tau_{\text{on}} \rangle = \frac{1}{\lambda_0}, \]
\[ \langle \tau_{\text{off}} \rangle = \sum_{k=1}^{L} \frac{1}{\lambda_k}, \]

4. **Main results.** The above analytical results in principle show how the complex promoter architecture impacts the mean, variance and noise of FPT. Here, we perform some numerical calculations to give some intuitive results.
4.1. Increasing the state number of promoter architecture always raises the mean and noise of FPT in the case where the average residence time at off states is not fixed. Here, we numerically show that promoter architecture has unneglectable effects on FPT. More specially, in the case where the mean residence time at off states is not fixed, the more the promoter states, the greater both the mean and noise of FPT are, as shown in Figure 3 A and B.

In our numerical calculations, we find that if the state number of promoters is much more, then the structure of the promoter is becoming much more complex. This phenomenon leads to the fact that the mean of FPT is greater, as well as the noise of FPT, in both irreversible and reversible case. Ulteriorly, compared with reversible promoter modulation, irreversible promoter tends to decrease the mean and noise of FPT under the condition that the amount of promoter states is the same. These results provide theoretical guidance for studies of cell fate decision caused by protein level up to the critical threshold, such as lysis time of bacteriophage $\lambda$ and latency of HIV and so on. It reveals that both lysis time of bacteriophage $\lambda$ and latency of HIV with irreversible promoter architecture may become smaller and stabler than those with reversible promoter architecture.

4.2. Complex promoter architecture tends to reduce the noise of FPT under the condition that the mean residence time at off states is immobilized. Next, we will perform numerical calculations to further reveal quantitative effects of promoter architecture on the mean and the noise of FPT shown in Figure 4. Here, let the promoter architecture be more and more complex (as shown in Figure 4, the states of promoter architecture are from 2 to 6 in order), but keep the average residence time at off states fixed, and classify the promoter architecture into two cases: irreversible promoter modulation (Figure 4A) and reversible promoter modulation (Figure 4B). From Figure 4A and Figure 4B, we observe that in the case where the mean residence time at off states is immobilized, the noise of FPT is a monotonically decreasing function of the states of promoter architecture.
The average residence time at off states

CV(FPT)

Irreversible promoter modulation

2 states
3 states
4 states
5 states
6 states

Reversible promoter modulation

2 states
3 states
4 states
5 states
6 states

Figure 4. Effects of promoter architecture on the noise of FPT. The dependence of the noise intensity on the promoter architecture in the case where the residence time at off state is immobilized. (A) The noise intensity of FPT regulated by irreversible promoter; (B) The noise intensity of FPT modulated by reversible promoter. Showing the noise intensity is always a monotonically decreasing function of promoter state for both irreversible promoter regulation and reversible promoter regulation. Here, $X = 1500, b = 3, \lambda_0 = 1/50, k_m = 10$ (see [12]), we fix the average residence time at off state, and take a 5 state model as an example, the residence time at off state is 30 min, the transition rates among inactive promoters in the irreversible case are $\lambda_1 = 1/6, \lambda_2 = 1/9, \lambda_3 = 1/7, \lambda_4 = 1/8$; the transition rate among inactive promoters in the reversible case are $\lambda_1 = 1/3, \lambda_1' = 1/5, \lambda_2 = 1, \lambda_2' = 1/3, \lambda_3 = 1/2, \lambda_3' = 1/4, \lambda_4 = 53/670$.

In the other words, the noise of FPT always decreases with the increase of the promoter states. This implies that the complexity of promoter architecture plays a role of attenuating the noise in the first passage time of proteins crossing a given value, no matter what the promoter architecture is (irreversible or reversible). Interestingly, for fixed residence time at off states, the mean of FPT is not relevant to promoter architecture, that is, whatever the states of promoter architecture is, only if the residence time at off state is fixed, the mean of FPT is invariant. However, if both the states of promoter architecture and mean residence time at off states are fixed, what properties do the noise of FPT irreversible promoters and reversible promoters have? See the following content for interpretation.

4.3. Irreversible promoter architecture can result in less noise of FPT than reversible one at the same promoter states. As is well known, the noise of gene expression products is regulated by the complexity of promoter architecture. Some examples have shown that even if the mean residence time at off states and the states of promoter structure are fixed, the noise modulated by the structure of irreversible promoter is less than that regulated by irreversible promoter structure [75–77]. However, it is unclear whether the noise of FPT in the irreversible case has the similar property as that in reversible case? It is still unclear. Here, we will carry out numerical calculations to give a positive answer as shown in Figure 5. We numerically calculate the noise of FPT for four diverse promoter states, namely, 3 states (Figure 5A), 4 states (Figure 5B), 5 states (Figure 5C), 6 states (Figure 5D). It can be observed that under conditions of fixed average residence time at off states and the same states of promoter architecture, the noise of FPT regulated
The average residence time at off states
CV(FPT)

Comparison of the noise intensity of FPT of irreversible promoter modulation (solid green line) and reversible promoter modulation (solid red line) at the same promoter state. (A), (B), (C), (D) represent the promoter state of 3, 4, 5, 6 respectively. The noise intensity regulated by irreversible promoter is always smaller than that regulated by reversible promoter. The parameter values are the same as those for Figure 4.

Figure 5.

by irreversible promoter is always less than that modulated by reversible promoter. Further, we observe that the noise of FPT is a monotonically increasing function of the mean residence time at off states regulated by both irreversible promoter and reversible promoter. At last, what needs to be explained is whether it has the same result when the promoter states are bigger. In conclusion, the noise of FPT modulated by irreversible promoter is smaller than that by reversible promoter. These conclusions may explain commendably that both lysis time (the time when holin, the protein responsible for lysis, reaches a critical threshold) of λ phage and latency of HIV in the case of irreversible promoter modulation may be stabler than that in the case of reversible promoter modulation.

5. Discussion. The complex promoter architecture can cause the time of proteins crossing a given threshold to be stochastic and the randomness of time further results in cell-to-cell variability in several cellular functions. To capture the effects of promoter structure on expression noise, many gene models have been proposed such as those with simple promoter structures [23,54] or with a DNA loop [75,77] or with a more complex promoter structure [76]. Recently, more and more experiments confirm that the stochasticity of the time of the special proteins reaching a given value can lead genetically identical cells to different cell fates [1,45,52,59] and play a critical role in cell’s fitness [2,6,15,20,21,38,55,69–71], and the noise of the time needs to be minimized [21,38,55,60]. However, the previous studies did not take effects of complex promoter architecture on FPT into consideration. To investigate the impact of promoter architecture on the timing of cellular key events,
we consider the first-passage time of proteins up to a given threshold. Here, we have systematically analyzed a representative gene expression model regulated promoter architecture. Our analysis leads to the following main results,

a) Analytical expressions for FPT moments, either irreversible or reversible promoter regulation, are derived.

b) Increasing the number of promoter states always increase the mean and noise of FPT in the case where the residence time at off states is not fixed.

c) Compared with two-state model, with fixed residence time at off states, complex promoter architecture can not vary the mean of FPT but tends to cut down the noise of FPT. Therefore, the most organisms have such a complex promoter architecture.

d) With fixed the residence time at off states, the noise of FPT modulated by irreversible promoter architecture is always less than that regulated by reversible one at the same promoter states.

The analytical and numerical method used in this paper allowed us to explore how dynamic promoter architecture affects FPT and can be further extended to more generalized gene expression models wherein the promoters can also transit arbitrarily among multi-active and multi-inactive promoter states [76]. Moreover, our study would have biological implications. First, our results can provide a guideline for biologists who can design looping circuits to probe the relationship between real time and cell-to-cell variability. Second, promoter architecture in cell is actually far more complex than classical on-off model and several cellular functions (such as cell lysis [60], cell division [19], cell cycle [2] and its fitness [69]) are inevitable to be controlled by it. Our proposed model based on complex promoter architecture is much closer to biological reality. Thus, introducing the complex promoter architecture to the gene model to explore regulation mechanism of FPT would be more in line with the real time and be more effective in understanding cellular biological functions. Third, our results would imply that with fixed residence time at off states, complex promoter architecture always decreases the noise of FPT and irreversible promoter structure give less noise of FPT than reversible one at the same promoter states in vivo organisms, which indicates that the organism with irreversible promoter structure have more evolutionary advantage than those with reversible promoter structure in biology.

6. Conclusions. The complexity of promoter architecture is an unneglectable factor in gene expression and plays an important role of controlling FPT. Specifically, promoter architecture (1) always prolongs the mean and noise of FPT ; (2) fixed residence time at off states, complex promoter architecture tends to reduce the noise of FPT; (3) the noise of FPT modulated by irreversible promoter architecture is always less than that regulated by reversible one. These principles not only provide a different view of point for understanding gene expression dynamics, but also imply that promoter architecture may be taken as a strategy of efficiently controlling FPT.

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