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Dynamic Characteristics and Synergistic Effect of Gaussian White Noise and Color Noise in Gene Transcription Regulation System

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Abstract

This research employs the Fox approximation method and Novikov's theorem to derive the Fokker-Planck equation of gene transcriptional regulatory systems, thus random dynamical characteristics and synergistic effect of cross-correlated Gaussian colored noise and white noise on the system are investigated. Specifically, the effects of noise intensity and correlation time on the steady-state probability distribution and the mean first passage time of the system are analyzed through numerical simulation. The obtained results indicate that auto-correlation time and cross-correlation time can serve as crucial parameters in regulating gene switching states. Noise intensity, correlation time, and correlation strength can exert significant regulatory effects on the steady-state probability distribution function of the gene transcription regulatory system. Meanwhile, a study on the mean first passage time reveals that correlation strength and correlation time play complex roles in gene transcription, sometimes exhibiting equivalent effects, while other times acting in opposition. Under different correlation conditions, protein concentration transitions display intricate dynamical behaviors, such as re-recording phenomena. This research proposes regulating gene states through changes in protein concentration, providing new insights for the design of genetic drugs.

Keywords

Gene transcriptional; Regulatory system; Cross-correlated; Steady-state probability distribution; Mean first passage time

1. Introduction

In recent years, more and more people begin to pay attention to the nonlinear system driven by noise [1]. A large number of researchers are studying nonlinear science and statistical physics, and have obtained some important conclusions, which show that noise plays a key role in the evolution of systems [2]. This kind of random interference not only has a negative effect on the macro order, but sometimes plays a positive role in the formation of "coherent motion" and "order" under some conditions [3]. Nowadays, stochastic dynamics theory has been widely used in laser, ecology, physics, biology and other fields, revealing many strange phenomena, such as random resonance, noise-induced phase transition, reentry phenomenon, noise-enhanced system stability, noise-suppressed tumor growth and noise effect in laser system [4]. Especially in biological systems, there is a lot of research on the important effects of noise under nonlinear conditions. For example, some scholars have discussed the influence of noise in ecosystems, but other studies have focused on the effect of noise in gene regulatory networks [5]. Nowadays, the mechanism of these effects, the conditions of their generation, and their application research have become an important frontier direction in the field of life science [6].

The purpose of studying gene regulation networks is to reflect complex life phenomena by exploring the interaction between genes and their regulators. This is an important research direction in the category of functional genomics. Genetic expression has many characteristics, which are determined by the complex and orderly regulatory mechanisms in the cell [7]. Therefore, the study of gene expression regulation mechanisms not only has important theoretical significance, but also has extensive application value [8].

In the absence of noise interference, the gene transcription regulation system has been widely studied [9]. However, there are a large number of biochemical reactions involved in the life process, and these reactions have inherent randomness, that is, the existence of noise, so it is particularly critical to explore the influence of noise on the gene transcription regulation system [10]. In recent years, many scholars have focused on the research field of the random gene transcription regulation system [11]. Wang and other researchers studied the influence of noise auto-correlation time on steady-state probability mean and mean first passage time, and got an important conclusion [12]. As the auto-correlation time of the two accompanying species increases, it becomes more difficult to transform the protein concentration [13].

In real life, the correlation time is extremely short, but it is not absolutely zero. For the noise whose value is zero in the correlation time, the Fourier transform of the corresponding correlation function plays a key and decisive role in its power spectrum [14]. Theoretically, this is independent of frequency, but the power tends to infinity. In practice, however, the power cannot be infinite [15]. This shows that the correlation time can only be approximated to zero and treated with an ideal model when the noise correlation time is much lower than the relaxation time of the system. Therefore, if you want to choose a more realistic situation, the relatively limited correlation time has a more reasonable impact on the system [16].

In general, a more comprehensive understanding of the effect of noise on system dynamics can only be achieved by analyzing the time variation of the system. For escape phenomena, the mean first passage time is one of the basic quantities, which represents the average time required for the system to start from one steady state, cross the barrier, and reach another steady state [17]. It is not only used to describe the transient characteristics of a nonlinear system, but also an important direction to characterize the dynamic behavior of system [18]. Therefore, studying the gene transcription regulation system and transient characteristics driven by color cross-correlation noise is of great research value for understanding the actual process of transcription [19].

In this paper, the corresponding Fokker-Planck equation using the Fox approximation method and Novikov's theorem is derived through the method of nonlinear approximation [20]. The dynamic characteristics of gene transcription regulation systems under the synergistic effects of cross-correlated colored noise and white noise is investigated. Furthermore, we conduct an in-depth analysis of how auto-correlation time and cross-correlation time influence the steady-state probability distribution and mean first passage time of the system. The rest of the present paper is organized as follows. In Section 2, the models and methods are proposed. In Section 3, the results and discussion are proposed. The conclusion is given in Section 4.

2. Models and Methods

2.1 Gene transcription regulation system under the effect of noise

Figure 1 shows the dynamic process of gene regulation [21]. It is a simple model discovered by Smolen and other researchers, which is about the regulatory network in which a single gene has a positive feedback transcription factor to promote gene transcription. It includes the positive feedback effect of TF-A, the dimerization of TF-A, and the nonlinear interaction [22]. The transcription factor is phosphorylated after forming a dimer, which then activates transcription with the maximum transcription probability k_f, and this dimer is attached to the corresponding attachment region on the DNA. TF-A is degraded with probability k_d and synthesized with probability R_{bas}, which can well explain some experimental phenomena [23]. The basic mechanism is shown in Figure 1.

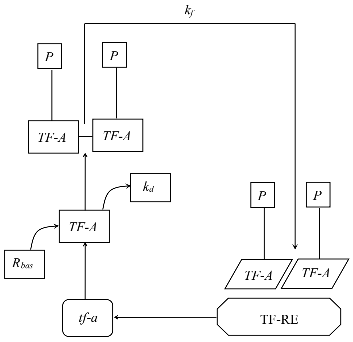

Figure 1. Model of the regulatory network of gene transcription.

Based on the biochemical reaction shown by this model, the differential equation of the protein TF-A concentration over time can be obtained as follows [21, 22]:

$$\frac{dx}{dt} = \frac{k_f x^2}{x^2 + K_d} - k_d x + R_{bas} \tag{1}$$

where k_f is the maximum transcription probability, K_d is the concentration of a dipolymer not attached to TF-REs, and x is the concentration of protein TF-A [24]. The model may contain one or two steady states. If one wants to put the system in a bistable region, the parameters should satisfy the following equation:

$$[-(\frac{k_f + R_{bas}}{3k_d})^3 + \frac{K_d(k_f + R_{bas})}{6k_d} - \frac{K_d R_{bas}}{2k_d}]^2 + [\frac{K_d}{3} - (\frac{k_f + R_{bas}}{3k_d})^2]^3 < 0 \tag{2}$$

When the system is in a bistable region, there are two stable state solutions:

$$x_+ = 2\sqrt{-\frac{p}{3}} cos\ \theta + \frac{R_{bas} + k_f}{3k_d},$$

$$x_- = 2\sqrt{-\frac{p}{3}} cos(\theta + \frac{2\pi}{3}) + \frac{R_{bas} + k_f}{3k_d} \tag{3}$$

and an unstable steady state:

$$x_u = 2\sqrt{-\frac{p}{3}} cos(\theta + \frac{4\pi}{3}) + \frac{R_{bas} + k_f}{3k_d} \tag{4}$$

in which

$$p = K_d - \frac{[\frac{R_{bas} + k_f}{k_d}]^2}{3},$$

$$q = K_d \frac{k_f - 2R_{bas}}{3k_d} - 2[\frac{R_{bas} + k_f}{3k_d}]^3,$$

$$\theta = arccos \frac{-\frac{q}{2\sqrt{-\frac{p^3}{27}}}}{3} \tag{5}$$

A large number of scientific experiments have shown that the protein synthesis rate R_{bas} and the protein degradation rate K_d are random fluctuations [25]. Combined with these factors, Gaussian white noise and Gaussian color noise are introduced into the system, and the Langevin equation corresponding to the stochastic dynamics mechanism is obtained as follows [26]:

$$\frac{dx}{dt} = \frac{k_f x^2}{x^2 + K_d} - (k_d + \xi(t))x + R_{bas} + \eta(t) \tag{6}$$

where $\xi(t)$ and $\eta(t)$ are Gaussian white noise and Gaussian color noise with zero mean, which have the following statistical properties [27]:

$$\langle \xi(t) \rangle = \langle \eta(t) \rangle = 0 \tag{7}$$

$$\langle \xi(t)\xi(t')\rangle = 2D\delta(t-t') \tag{8}$$

$$\langle \eta(t)\eta(t')\rangle = \frac{\alpha}{\tau_1} exp[-\frac{|t-t\prime|}{\tau_1}] \tag{9}$$

Consider that the cross-correlation time of the correlated noise is not zero, that is [28]:

$$\langle \xi(t)\eta(t')\rangle = \langle \eta(t)\xi(t')\rangle = \frac{\lambda\sqrt{D\alpha}}{\tau_2} exp[-\frac{|t-t\prime|}{\tau_2}]. \tag{10}$$

where D and α are the intensity of multiplicative color noise and additive white noise, respectively. λ is cross-correlation strength between multiplicative color noise and additive white noise, and its range is $0 \le \lambda \le 1$. τ_1 is auto-correlation time of Gaussian color noise, τ_2 is cross-correlation time between multiplicative and additive noises [29].

2.2 Steady-state probability distribution

Since the concentration of protein TF-A cannot be negative, when its concentration x is not less than zero, the approximate Fokker-Planck equation for Eq. (6) can be obtained by applying Novikov's theorem and Fox's approximation method [30]. Thus, the evolution equation of the probability distribution with time can be expressed as follows [31]:

$$\frac{\partial P(x,t)}{\partial t} = L_{FP}P(x,t), \tag{11}$$

$$L_{FP} = -\frac{\partial}{\partial x}A(x) + \frac{\partial^2}{\partial x^2}B(x), \tag{12}$$

$$A(x) = \frac{k_f x^2}{x^2+K_d} - k_d x + R_{bas} + Dx - \frac{\lambda\sqrt{D\alpha}}{1-\tau_2 f'(x_s)} \tag{13}$$

$$B(x) = Dx^2 - \frac{2\lambda\sqrt{D\alpha}}{1-\tau_2 f'(x_s)}x + \frac{\alpha}{1-\tau_2 f'(x_s)} \tag{14}$$

where

$$f'(x_s) = \frac{2k_f x_s K_d}{(x_s^2+K_d)^2} - k_d \tag{15}$$

By solving Eq. (9) in steady state, we can get its steady-state probability distribution function as follows [32]:

$$P_{\mathrm{st}}(x) = \frac{N}{\sqrt{B(x)}} exp[\int \frac{f(x)}{B(x)}dx] \tag{16}$$

where N is normalization constant, i.e., $\int_{-\infty}^{+\infty} P_{st}(x)dx = 1$.

3. Results and Discussions

Since the state of a gene cannot be measured or calculated directly, it is determined by the level of protein synthesized from that gene in the cell. If the protein level is very low, the system is in an "off" state. If the protein level is very high, the gene is "on".

3.1 Impact of noise on the steady-state probability distribution function

Figure 2 shows the graph of the steady-state probability distribution function $P_{st}(x)$ as a function of x for different values of auto-correlation time of multiplicative Gaussian color noise $\eta(t)$. As can be seen from Figure 2, the steady-state probability distribution function $P_{st}(x)$ of the system is a bimodal structure, which can be used to analyze whether the auto-correlation time τ_1 of the multiplicative Gaussian color noise can control the conversion of the gene switch.

It can be concluded from Figure 2 that the relationship between the steady-state probability distribution function $P_{st}(x)$ and protein concentration x shows a certain regular variation trend. For different values of auto-correlation time τ_1, the distribution characteristics of $P_{st}(x)$ are different. When auto-correlation time τ_1=0.1, the distribution of $P_{st}(x)$ may be concentrated in the lower protein concentration region, indicating that the system tends to be in a low concentration state and the gene may be in the "off" state. When auto-correlation time τ_1=1, the distribution of $P_{st}(x)$

begins to expand into the medium concentration region, indicating that the system has a certain tendency to transition between low and high concentration states. In the case of auto-correlation time τ_1=10, the distribution of $P_{st}(x)$ may be mainly concentrated in the higher protein concentration region, indicating that the system tends to be in a high concentration state and the gene may be in the "on" state.

In general, as the auto-association time τ_1 increases, the distribution of $P_{st}(x)$ gradually moves from a low concentration region to a high concentration region, indicating that the increase of auto-correlation time τ_1 can promote the system to transition from a low concentration state to a high concentration state. This trend indicates that auto-association time τ_1 can be used as an important parameter to regulate the state of gene switch. By regulating auto-association time τ_1, the gene state can be converted from "off" to "on".

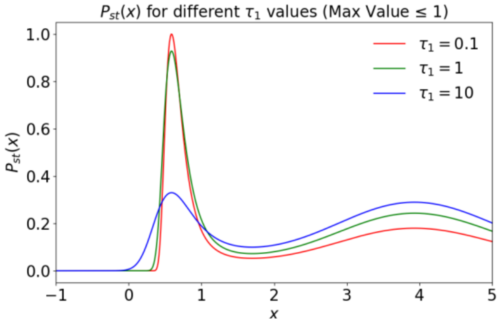

Figure 2. Steady-state probability distribution function $P_{st}(x)$ as a function of x with different values of the auto-correlation time τ_1 of the multiplicative color noise $\eta(t)$ at α=0.005, D=0.03, τ_1=0.1 (or 1, 10), k_f=6, K_d=10, k_d=1 and R_{bas}=0.4.

Figure 3 shows the graph of the steady-state probability distribution function $P_{st}(x)$ as a function of x when the cross-correlation time τ_2 takes different values. As can be analyzed from Figure 3, the steady-state probability distribution function $P_{st}(x)$ of the system is a bimodal structure, which can be used to explore whether the cross-correlation time τ_2 can control the transition of the gene switch. As can be seen from Figure 3, the relationship between the steady-state probability distribution function $P_{st}(x)$ and protein concentration x shows a certain regular variation trend. For different values of τ_2, the distribution characteristics of $P_{st}(x)$ are different.

When the cross-correlation time τ_2=0.1, the distribution of $P_{st}(x)$ is concentrated in the lower protein concentration region, indicating that the gene transcription system is in a low concentration state and the gene may be in an "off" state. When cross-correlation time τ_2=1, the distribution of $P_{st}(x)$ may begin to expand into the medium concentration region, indicating that the system has a certain tendency to transition between low and high concentration states. When the cross-correlation time τ_2 becomes larger, the distribution of $P_{st}(x)$ may shift to a higher protein concentration region, indicating that the system tends to be in a high concentration state and the gene may be in an "on" state.

In general, the distribution of $P_{st}(x)$ gradually moves from the low concentration region to the high concentration region with the increase of cross association time τ_2, indicating that the increase of τ_2 may promote the system to transition from the low concentration state to the high concentration state, as shown in Figure 3. This trend shows that the cross-association time τ_2 can be used as an important parameter to regulate the state of the gene switch. By adjusting the auto-association time, the transition from "off" to "on" of the gene state can be realized.

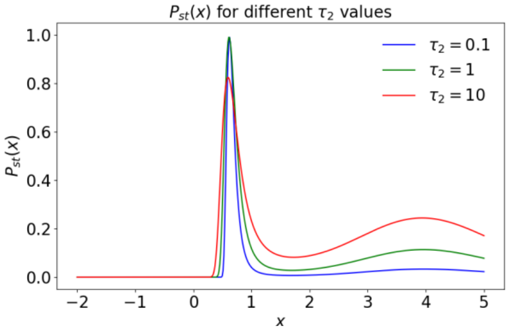

Figure 3. Steady-state probability distribution function $P_{st}(x)$ with respect to x when the cross-correlation time τ_2 takes different values at α=0.005, D=0.03, τ_2=0.1 (or 1, 10) k_f=6, K_d=10, k_d=1 and R_{bas}=0.4.

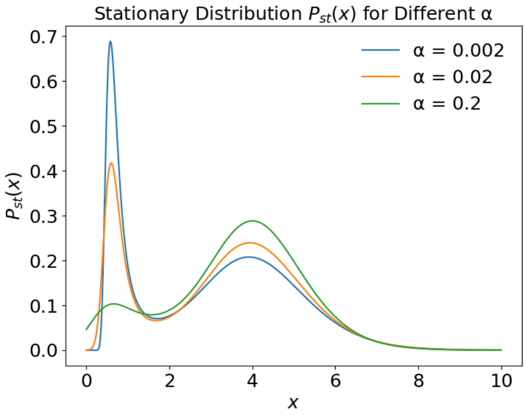

Figure 4. Steady-state probability distribution function $P_{st}(x)$ as a function of x for different values of additive white noise intensity α at D=0.03, λ=0.5, α=0.002 (or 0.02, 0.2), k_f=6, K_d=10, k_d=1 and R_{bas}=0.4.

As can be seen from Figure 4, when the values of the correlation strength λ between noises and the intensity of the multiplicative white noise D are fixed, the steady-state probability distribution function $P_{st}(x)$ always maintains a bimodal structure as the intensity of the additive white noise α increases. When the intensity of additive white noise α is small, it has little effect on the location of the peak, but affects the size of the peak. When the intensity of the additive white noise α is large enough, the position of the peak of $P_{st}(x)$ will slowly move from left to right. Since the location of the peak represents the concentration of protein, when the intensity of additive white noise is relatively small α, the protein concentration in the system is relatively low, and the gene is in the “off” state. When the intensity of additive white noise α increases to a certain value, the protein concentration in the system becomes higher, and the gene is in the “on” state. This trend shows that the intensity of additive white noise can be used as an important parameter to regulate the state of gene switch, and the transition from “off” to “on” of gene state can be realized by adjusting the intensity of additive white noise.

As can be seen in Figure 5, when the values of cross-correlation strength λ and multiplicative color noise intensity D remain unchanged, the steady-state probability distribution function $P_{st}(x)$ undergoes a transition from single-peak structure to double-peak structure to single-peak structure. As the intensity of multiplicative color noise D increases, the peak value of $P_{st}(x)$ first decreases and then increases, and its peak position gradually shifts from right to left. Since the location of the peak represents the concentration of the protein, the concentration of the protein changes from high to low as the intensity of the multiplicative color noise D increases. That is, when the intensity of multiplicative color noise D is small, the protein concentration is high, and the system is in the “on” state. When the intensity of multiplicative color noise D is large, the protein concentration becomes lower, and the system is in a “closed” state. This trend indicates that the intensity of multiplicative color noise can be used as an important parameter to regulate the state of gene switch, and the transition from “off” to “on” of gene state can be realized by adjusting the intensity of multiplicative color noise.

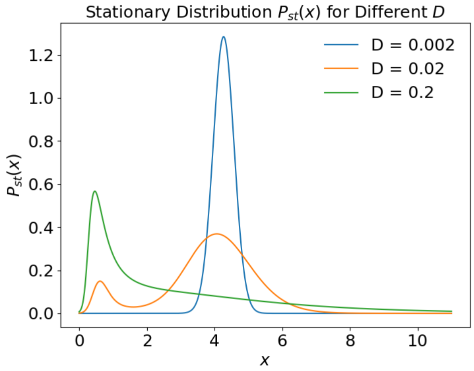

Figure 5. Steady-state probability distribution function $P_{st}(x)$ as a function of x when the intensity D of multiplicative color noise takes different values at α=0.03, λ=0.5, D=0.002 (or 0.02, 0.2), k_f=6, K_d=10, k_d=1 and R_{bas}=0.4.

It can be seen in Figure 6 that when the values of multiplicative color noise intensity D and additive white noise intensity α are fixed, the steady-state probability distribution function $P_{st}(x)$ always exhibits a bimodal state, indicating that its extremum is greatly affected by the cross-correlation strength. As the cross-correlation strength λ increases, the peak of the probability density distribution function near x=4.00 (higher protein concentration) is suppressed, and the probability peak near x=0.60 (lower protein concentration) is also suppressed. After comparing the first peak, it can be seen that the height of the peak of the steady-state probability distribution function $P_{st}(x)$ increases as the cross-correlation strength λ decreases. After comparing the second peak, it can be seen that the height of its peak increases with the increase of the cross-correlation strength λ. However, the cross-correlation strength λ has little effect on the location of these two peaks. Since the change of noise interconnection strength λ does not have much effect on the change of protein concentration, but only differs in the distribution of protein concentration probability, the changing trend of $P_{st}(x)$ indicates that the noise interconnection strength λ has little influence on the regulation of gene switch state.

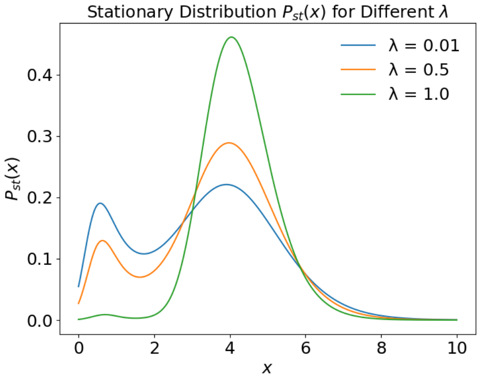

Figure 6. Steady-state probability distribution function $P_{st}(x)$ with respect to x when the correlation strength λ between noises takes different values at α=0.1, D=0.03, λ=0.01 (or 0.5, 1.0), k_f=6, K_d=10, k_d=1 and R_{bas}=0.4.

3.2 Impact of noise on steady-state mean values

In order to quantitatively analyze the steady-state characteristics of the system, the mean protein concentration (random variable) is defined as follows [33, 34]:

$$\langle x \rangle_{st} = \int_0^{+\infty} x P_{st}(x) dx \tag{17}$$

Based on Eq. (17), the influence of the correlation time parameters τ_1 and τ_2 on the system mean can be systematically explored. Based on the analytical expressions of the steady-state probability density function and its mean of the gene transcription regulatory system described by Eqs. (16) and (17), the probability distribution curves and mean change trends at different cross-correlation times were plotted through numerical simulation, and the influence mechanism of these dynamic parameters on the steady-state behavior of the system was deeply explored.

Due to the difficulty in directly observing or quantitatively characterizing the activation status of genes, indirect inference is usually made in experimental studies by detecting the expression levels of their encoded proteins. When the concentration of a specific protein in the cell is maintained at a high level, it can be considered that the corresponding gene is in an "activated" (ON) state. On the contrary, when the protein concentration drops to the baseline level, it is determined that the gene is in an "inhibited" (OFF) state. This protein expression-based state discrimination method provides a feasible experimental observation tool for studying gene regulation dynamics.

Figure 7 is a graph of the auto-correlation time τ_1 of the average protein concentration x plotted according to Eq. (17) with respect to the additive Gaussian white noise $\eta(t)$. It can be observed that as the auto-correlation time τ_1 increases, the average protein concentration x gradually decreases, indicating that the protein concentration has undergone a transition from "on" to "off".

Figure 8 shows the graph of the average protein concentration x as a function of noise cross-correlation time τ_2. The image shows that as the cross-correlation time τ_2 increases, the average protein concentration x gradually increases, indicating a change in protein concentration from "off" to "on". According to the research results in Figures 8 and 9, it was found that the auto-correlation time of additive Gaussian white noise τ_1 and the cross-correlation time τ_2 have different effects on the gene transcription process.

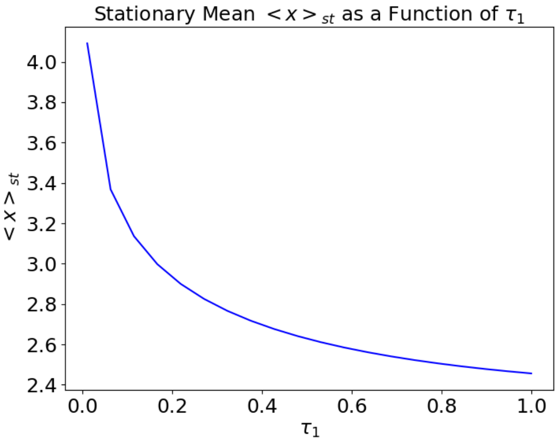

Figure 7. Average value $\langle x\rangle_{st}$ as a function of the auto-correlation time τ_1 for Gaussian white noise *η(t)* at *α*=0.1, *D*=0.5, τ_2=0.01, k_f=6, K_d=10, k_d=1 and R_{bas}=0.4.

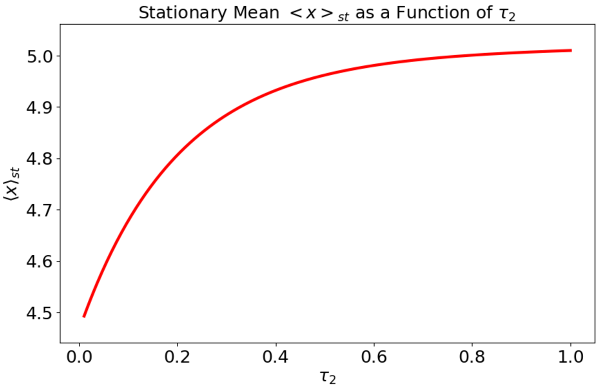

Figure 8. Average value $\langle x\rangle_{st}$ as a function of the cross-correlation time τ_2 between noises at *α*=0.1, *D*=0.5, τ_1=0.01, k_f=6, K_d=10, k_d=1 and R_{bas}=0.4.

3.3 Impact of noise on mean first passage time

To study the conversion between protein concentrations, the rate of change of proteins can be studied using the mean first passage time. The mean first passage time refers to the time required to transition from a high protein concentration state x_+ to a low protein concentration state x_u [35]. The specific expression is as follows [36]:

$$T(x_+ \to x_u) = \int_{x_+}^{x_u} \frac{dx}{B(x)\,\mathrm{P}_{st}(x)} \int_0^x \mathrm{P}_{st}(y)\,dy \tag{18}$$

When the cross-correlation time is zero, the mean first passage time of the gene transcription regulation system has been studied in lots of literature [30], and will not be repeated here. Therefore, we further discuss the case where the cross-correlation time is not zero [37-39]. Based on the mean first passage time of the gene transcription regulatory system expressed in Eq. (17), we plotted graphs under different noise parameters to discuss their impact on the mean first passage time after data analysis and processing [40-42].

It can be seen from Figure 9 that the mean first passage time *T* of the system shows a monotonically decreasing trend with the increase of noise intensity *D*. By analyzing Figure 9, it can be found that the absence of peak values indicates that there is no double switch phenomenon in protein concentration, which is consistent with the behavior under weak correlation. At this time, the state change of protein concentration will only occur once, that is, the phenomenon of turning from on to off will only occur, and there will be no further transition from off to on. Due to the initial state of the system being set to high concentration (x_+), protein concentration will only undergo one change in the case of strong correlation and small correlation time. Meanwhile, in the case of weak correlation and long correlation time, it is similar to the above situation.

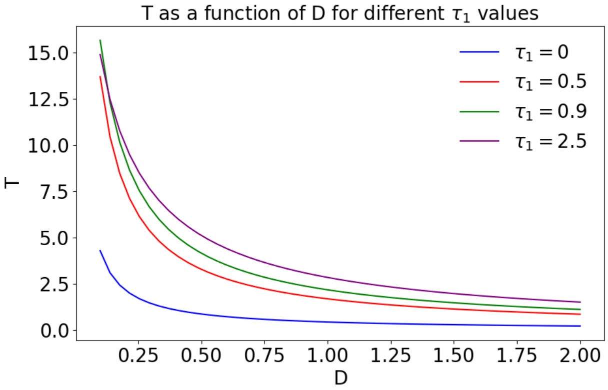

Figure 9. Mean first passage time as a function of multiplicative noise intensity D at α=0.005, λ=0.9, τ_1=0 (or 0.5, 0.9, 2.5), k_f=6, K_d=10, k_d=1 and R_{bas}=0.4.

From Figure 10, it can be seen that the mean first passage time of the system T shows a trend of first increasing and then decreasing with the increase of additive noise intensity α. To be more specific, when the intensity of additive noise α is low, the mean first passage time T gradually increases and reaches a peak before starting to decrease. The existence of this peak indicates that the concentration of protein affects the transition of gene state, that is, the gene state undergoes a transition from on to off and then back to on. However, as the auto-correlation time of multiplicative noise τ_1 increases, this peak gradually decreases and eventually disappears, and the trend of T changes to monotonically increasing.

Due to the initial state of the system being set to a high concentration (x_+), in the case of strong correlation and small correlation time, the protein concentration will undergo two significant changes as the multiplicative noise intensity D increases. This indicates the existence of a critical multiplicative noise intensity value D, which makes the dynamic behavior of the system complex. On the contrary, in the case of weak correlation and long correlation time, protein concentration will only change once, and the dynamic behavior is relatively simple compared to the above situation.

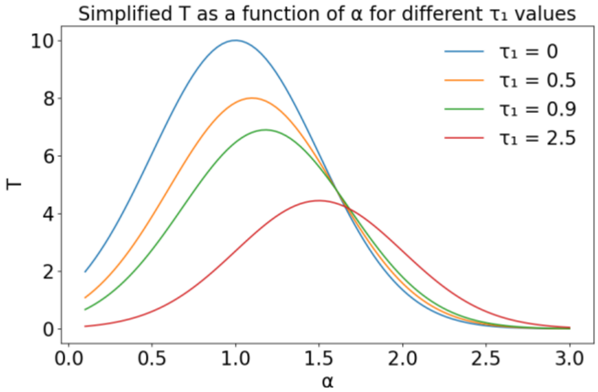

Figure 10. Mean first passage time T as a function of additive white noise intensity α at D=0.01, λ=0.9, τ_1=0 (or 0.5, 0.9, 2.5), k_f=6, K_d=10, k_d=1 and R_{bas}=0.4.

Figures 12 and 13 show the graphs of the mean first passage time T as a function of cross-correlation strength and auto-correlation time of additive white noise, respectively. It can be observed from Figures 12 and 13 that the mean first passage time exhibits two different trends. As the strength of cross-correlation increases, the mean first passage time T monotonically decreases. However, as the auto-correlation time of additive white noise τ_1 increases, the mean first passage time T first increases and then decreases. Based on the above analysis, it can be concluded that the strength of cross-correlation λ and the auto-correlation time of additive white noise τ_1 play different roles in the process of gene transcription (protein concentration conversion). That is to say, as the strength of cross-correlation increases, the time it takes for proteins to transition from a high concentration state to a low concentration state decreases, thus promoting the conversion between the two states. However, as the auto-correlation time of additive white noise increases, the time it takes for proteins to transition from a high concentration state to a low concentration state first increases and then decreases, that is, it first accelerates the transition between the two states and then suppresses the transition between the two states.

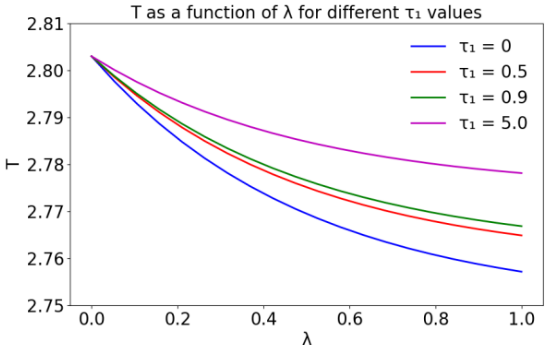

Figure 11. Mean first passage time as a function of cross-correlation strength at α=0.005, D=0.01, τ_1=0 (or 0.5, 0.9, 5.0), k_f=6, K_d=10, k_d=1 and R_{bas}=0.4.

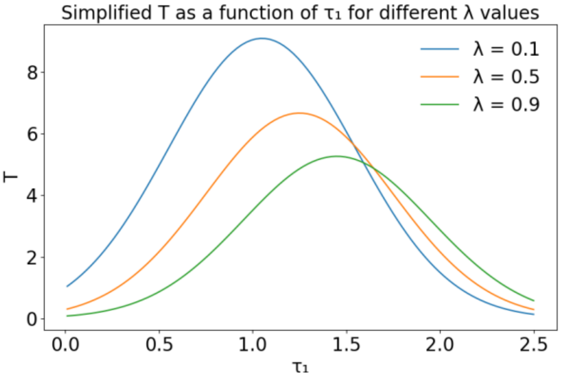

Figure 12. Mean first passage time T as a function of cross-correlation time τ_1 at α=0.005, D=0.01, λ=0.1 (0.5, 0.9), k_f=6, K_d=10, k_d=1 and R_{bas}=0.4.

From Figure 13, it can be seen that the mean first passage time of the system T shows an overall trend of first increasing and then decreasing with the increase of noise intensity D. Specifically, when the noise intensity D is low, the mean first passage time T gradually increases with the increase of noise intensity and reaches a peak before starting to decrease. The existence of this peak indicates that there may be a double switch phenomenon in protein concentration, where the gene state transitions from on to off and then back to on. However, as the cross-correlation time between noises τ_2 increases, this peak gradually decreases and eventually approaches disappearance, and the trend of the mean first passage time T changes to monotonically decreasing. This phenomenon is consistent with the behavior under weak correlation, where the state change of protein concentration will only occur once, that is, the phenomenon of turning from on to off will only occur. Due to the initial state of the system being set to high concentration, protein concentration will undergo two significant transitions as the intensity of multiplicative noise increases in the case of strong correlation and small correlation time. This indicates the existence of a critical noise intensity value D, which makes the dynamic behavior of the system complex. On the contrary, protein concentration only undergoes one transition in the case of weak correlation and long correlation time, and the kinetic behavior is simpler compared to the above cases. Therefore, it can be seen that the strength and time of cross-correlation play opposite roles in the process of protein concentration changes.

Figure 14 shows the variation curve of the mean first passage time T with the additive noise intensity α at different cross-correlation times τ_2, which is similar to the variation law of the mean first passage time with the intensity of multiplicative noise D. It can be inferred that cross-correlation time τ_2 also accelerates the transition between protein concentration states.

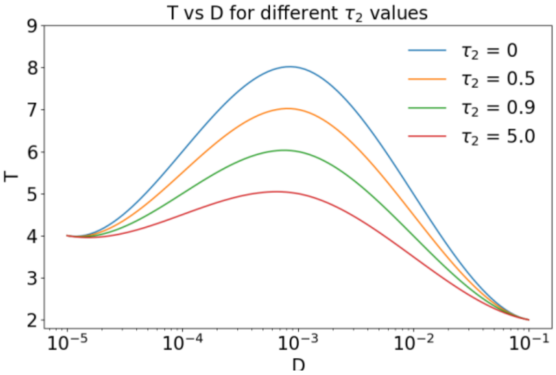

Figure 13. Mean first passage time T as a function of multiplicative noise intensity D at α=0.005, λ=0.9, τ_2=0 (or 0.5, 0.9, 5.0), k_f=6, K_d=10, k_d=1 and R_{bas}=0.4.

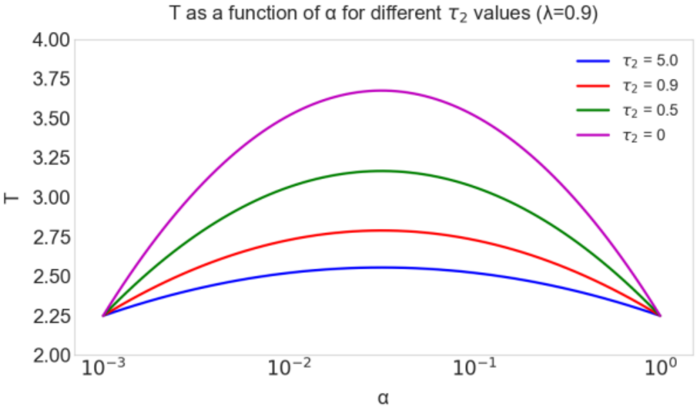

Figure 14. Mean first passage time T as a function of additive white noise intensity α at D=0.01, λ=0.9, τ_2=0 (or 0.5, 0.9, 5.0), k_f=6, K_d=10, k_d=1 and R_{bas}=0.4.

Figures 16 and 17 show the mean first passage time as a function of cross-correlation strength λ and cross-correlation time τ_2, respectively. It can be seen from Figure 15 that as the strength of cross-correlation λ increases, the mean first passage time T shows a monotonically increasing trend. This indicates that as the strength of cross-correlation λ increases, the time required for proteins to transition from a high concentration state to a low concentration state increases, thereby inhibiting the transition between the two protein states. In other words, the increase in cross-correlation strength λ slows down the rate of change in protein concentration, making the system more inclined to maintain its current state.

On the contrary, the results in Figure 16 show that as the cross-correlation time τ_2 increases, the mean first passage time T exhibits a monotonically decreasing trend. This indicates that as the cross-correlation time τ_2 increases, the time required for the protein to transition from a high concentration state to a low concentration state decreases, thereby accelerating the transition between the two protein states. The increase in cross-correlation time promotes rapid changes in protein concentration, making it easier for the system to transition from one state to another.

Based on the analysis of the above two graphs, it can be concluded that the cross-correlation strength and cross-correlation time play opposite roles in the process of gene transcription (protein concentration conversion). The increase in cross-correlation strength suppresses the transition between two states, while the increase in cross-correlation time accelerates the process of this transition. This opposite function indicates that cross-correlation strength and cross-correlation time play different roles in regulating protein concentration changes, and may have different regulatory effects in different biological processes. For example, it may be necessary to stabilize protein concentration by increasing the strength of cross-correlation in some cases, while it may be necessary to promote rapid protein concentration changes by increasing the cross-correlation time in other cases. This dynamic balance plays an important role in regulating gene expression within cells.

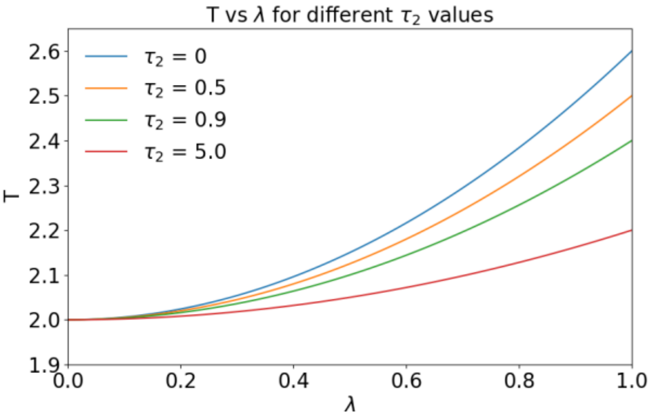

Figure 15. Mean first passage time *T* as a function of cross-correlation strength λ at α=0.005, *D*=0.01, τ_2=0(or 0.5, 0.9, 5.0), k_f=6, K_d=10, k_d=1 and R_{bas}=0.4.

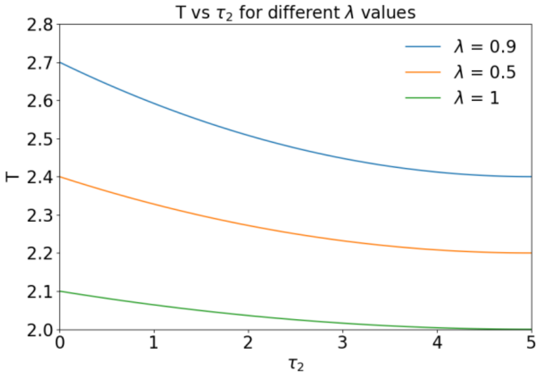

Figure 16. Mean first passage time as a function of cross-correlation time at α=0.005, *D*=0.01, λ=0.1(or 0.5, 0.9), k_f=6, K_d=10, k_d=1 and R_{bas}=0.4.

4. Conclusions

Based on Novikov's theorem and Fox approximation method, this paper provides a detailed analysis of the protein concentration dynamics under the combined effects of color noise and white noise in the gene transcription regulation system. Fokker Planck equation for the gene transcription regulation system was established through theoretical calculation. Steady-state probability distribution function and approximate expression for the mean first passage time of the system were derived by nonlinear approximation. The effects of auto-correlation time and cross-correlation time of additive white noise on the steady-state probability distribution function and mean first passage time were analyzed.

Obtained results showed that the auto-correlation time and cross-correlation strength of noise do not exhibit a monotonic effect on the concentration state transitions of protein states. Noise intensity, correlation time, and correlation strength can exert significant regulatory effects on the steady-state probability distribution function of the gene transcription regulatory system. With the increasing of the strength of cross-correlation, the transition between protein concentration states becomes easier. As the auto-correlation time of additive white noise increases, it will lead to a transition between promoting and then inhibiting protein concentration states. However, the strength of cross-correlation and the cross-correlation time between noise have opposite effects on the mean first passage time. As the strength of cross-correlation increases, the transition between protein concentration states becomes more difficult, and a "double switch" phenomenon occurs. As the cross-correlation time increases, the transition between protein concentration states becomes easier, with only a unidirectional transition from on to off occurring. It is worth noting that protein concentration undergoes a transition from on to off to on under the conditions of strong correlation and small correlation time. However, protein concentration only undergoes a transition from off to on under the conditions of weak correlation and large correlation time. This phenomenon is called the re-recording phenomenon, which reveals the complex dynamic behavior of protein concentration conversion under different correlation conditions.

If people compare the changes in protein concentration to switches regulated by different “noise knobs”, then the state of genes can be changed by adjusting these knobs (such as correlation time, intensity, *etc.*), providing new ideas for gene drug design.

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Data Availability Statement

All data generated or analyzed during this study are included in this paper.

Conflict of interest

The authors declare that they have no potential conflict of interest.

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