Differentiation of Induced Transformation in Gene Transcription Regulation System with Cross-correlated White Noise and Colored Noise

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Abstract: Considering the random fluctuation of protein synthesis rate and protein degradation rate in the gene transcription control system, the steady and transient properties of protein concentration are analyzed. The Gauss white noise and color noise are introduced respectively in the gene transcription control system, and the mean first-passage-time(MFPT) are studied in different cases. By comparing the two cases, the induction of noise in the gene transcription control system of protein concentration are analyzed. Significant conclusions are drawn from the influence of transformation.

1. Introduction

Gene expression regulation is the core issue of molecular biology and the basis of gene engineering theory. With the development of biological experimental technology, more and more experimental results show that there are a lot of randomness in the process of gene transcription regulation. Therefore, gene transcription regulation system is a typical non-linear random system, and the role of noise in this system can not be ignored. When the noise source is independent, with the increase of multiplicative noise intensity, the protein concentration undergoes a transformation, and the protein concentration undergoes two transformations.

Gene transcription regulation is a very important process in living cells. At present, many mathematical models about gene transcription regulation have been developed. Most models describe transcription regulation quantitatively, and predict the steady distribution of transcription regulation through models. Usually cells are always observed in a steady state, so this is a very useful feature. Due to environmental disturbance and gene instability, gene transcription regulation can usually be transformed between different states, so it is necessary to establish a transcription model to predict the steady-state behavior of the system. Most chemical reactions can be expressed mathematically by differential equation of protein product concentration. But in fact, the noise caused by the instability of the external environment and the fluctuation of the number of intracellular molecules will have a crucial impact on gene expression. The effects of noise on non-linear biological systems have been studied extensively. More and more experimental and theoretical results show that there is a large amount of randomness in every regulation process of gene expression. Noise is of great significance to gene regulation. In general, the random terms in transcription and translation in biochemistry are called "internal noise". The noise caused by the concentration fluctuation of protein products and the change of environmental temperature is defined as "external noise". In addition, the different parameters in biological system will also cause certain fluctuations in the system.

In order to qualitatively describe the randomness of gene expression, biologists have given a variety of quantification methods, such as noise, noise intensity (Fano factor). For a given random variable, people usually call the square ratio of variance to mean noise. It can describe the fluctuation of gene expression well, and the noise intensity is the ratio of variance to mean.

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According to the different sources of noise, noise can be divided into internal noise and external noise. Internal noise originates from the dynamic structure of the system. Gene expression changes between different states, while the states are irregularly segregated, and the internal noise is usually relatively small in numerical expression. External noise is caused by environmental factors.

However,it is considered that the correlation time between noise sources is zero in their work. Although the correlation time of noise is very small, it is not strictly equal to zero in reality. Therefore, the influence of color cross-correlation noise on the transient properties of gene transcription regulation system has been further studied in the literature. Stochastic resonance (SR) in gene transcription regulation systems with linear time delay and cross-correlation noise has been studied in the literature.

2. Model Construction

Smolen et al. first proposed the model of transcription factor promoted gene transcription regulatory network in 1986. In this simplified model, protein transcription factor(TF-A) dimerization, TF-A positive feedback and non-linear interaction are included. TF-A forms dimer and binds to response element (TF-RE)， then TF-A gene transcription is enhanced, and phosphorylated TF-A can activate gene transcription. The principle of the model can explain many experimental phenomena well. The basic mechanism of the model feedback is shown in Figure 1. In Figure 1, protein transcription factor TF-A is phosphorylated after forming a dimer, and then activates the transcription with the maximum transcription probability. This dipolymer is the corresponding attachment region TF-RE attached to DNA，and TF-A is degraded by probability k_d and synthesized by probability R_{bas}. Based on the series of biochemical reactions proposed by this model, the differential equation (Langevin equation) of the protein TF-A concentration evolution with time can be written out.

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

This model includes the dimerization of transcription factor (TF-A), the positive feedback of TF-A and the non-linear interaction. It can explain some experimental phenomena very well. The basic mechanism is shown in Figure 1. κ_D represents the concentration of protein TF-A, which is not attached to TF-REs. x represents the concentration of protein TF-A.The model can contain two stable states or one stable state.

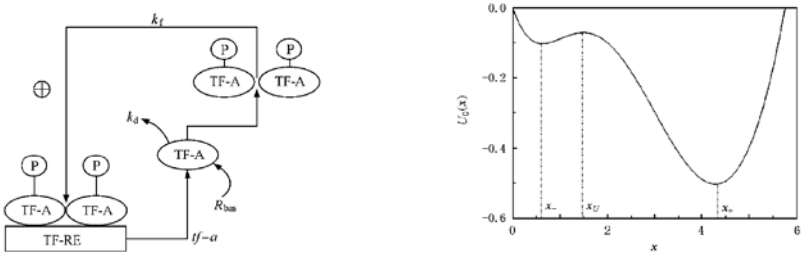

Figure 1 The model of gene regulating loop based on positive feedback and the bistable potential of gene transcription regulatory system.

3. Protein synthesis rate and degradation rate fluctuate randomly

The Gauss white noises are lead into the Langevin equation (1), and the noises have the following statistical properties

$$<\xi(t)>=<\eta(t)>=0 \qquad <\xi(t)\xi'(t)>=2D\delta(t-t') \tag{2}$$

$$< \eta(t)\eta'(t) >= 2Q\delta(t-t') \qquad < \xi(t)\eta'(t) >=< \eta(t)\xi'(t) >= 2DQ\delta(t-t') \tag{3}$$

A large number of experiments show that there are random fluctuations in protein synthesis R_{bas} and degradation rate k_d in the specific gene expression and gene regulation system. In the process of gene transcription regulation, the external environmental factors which affect the protein synthesis and degradation rate contain electromagnetic radiation, seasonal changes and solar terms. So the Gauss noise is introduced into the system to represent the fluctuation, and then replace $k_d + \xi(t)$ with k_d in the system, the Langevin equation (1) can be written as

$$\frac{dx}{dt} = \frac{k_f x^2}{x^2 + K_d} - [k_d + \xi(t)]x + [R_{bas} + \eta(t)] \tag{4}$$

Considering that the range of protein TF-A concentration x does not contain negative values, we can know that $x \geq 0$ through the analysis. Under this circumstance, the corresponding Fokker-Planck equation of the system is obtained as follows by using Novikov principle and Fox approximation method.

$$\frac{\partial P(x,t)}{\partial t} = L_{FP}P(x,t) \quad \text{and} \quad L_{EP} = -\frac{\partial}{\partial} A(x) + \frac{\partial^2}{\partial x^2} B(x) \tag{5}$$

Among them, $A(x) = \frac{k_f x^2}{x^2 + K_d} + k_d x + R_{bas} + Dx + \frac{\lambda\sqrt{QD}}{1+c(\tau)}$, $B(x) = Dx^2 + \frac{2\lambda\sqrt{DQ}}{1+c(\tau)}x + Q$ (6)

And there are $c(\tau) = -\tau[\frac{k_f x}{x^2 + K_d} - \frac{2k_f x^3}{(x^2 + K_d)^2}] - \frac{R_{bas}}{x}$ (7)

The steady-state probability distribution function of the system is obtained by solving the above equation under steady-state conditions.

$$P_i(x) = N_i B(x)^{-1/2} exp[-\frac{U_i(x)}{D}], i = 1,2 \tag{8}$$

4. Protein synthesis and maximum conversion are affected by correlated color noise

Considering that the additions of $\xi(t)$ and $\eta(t)$ are both Gauss colored noise, and we have the following statistical properties

$$< \xi(t) >=< \eta(t) >= 0 \qquad < \xi(t)\xi'(t) >= \frac{D}{\tau_1}\exp[-\frac{|t-t'|}{\tau_1}] \tag{9}$$

$$< \eta(t)\eta'(t) >= \frac{Q}{\tau_2}\exp[-\frac{-|t-t'|}{\tau_2}] \qquad < \xi(t)\eta'(t) >=< \eta(t)\xi'(t) >= 2DQ\delta(t-t') \tag{10}$$

Through theoretical calculation, the Fokker-Planck equation for the above equation pair and the steady-state probability density distribution function of the system are obtained.

5. Conclusion

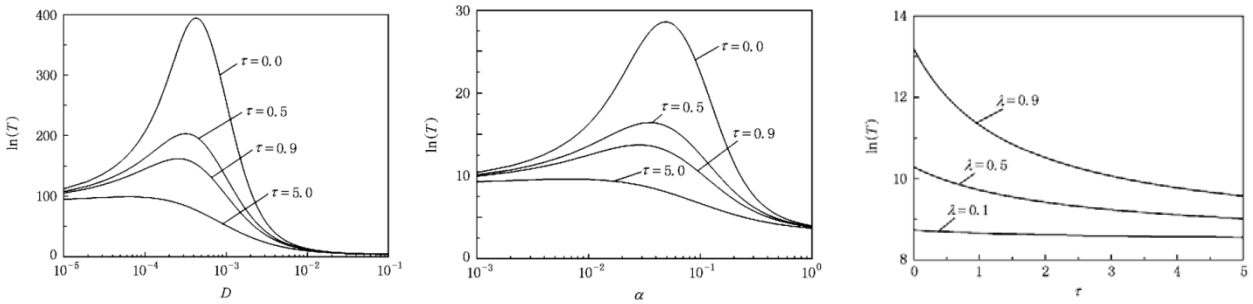

Figure 2 The mean first passage time of the system.

Through the comparison of data in the articles, it is found that, the correlation strength λ and cross correlation time τ have opposite effects on the mean first-passage-time T. With the increase of λ, the transformation of protein concentration states becomes difficult, and double-switch phenomenon appears. On the contrary, with the increase of τ, the transformation of protein concentration states becomes easier, and there is only on-off phenomenon. It is noteworthy that the concentration of protein undergoes on-off-on under strong correlation and small correlation time conditions, while the concentration of protein undergoes on-off under weak correlation and large correlation time conditions. This is a re-entry phenomenon.

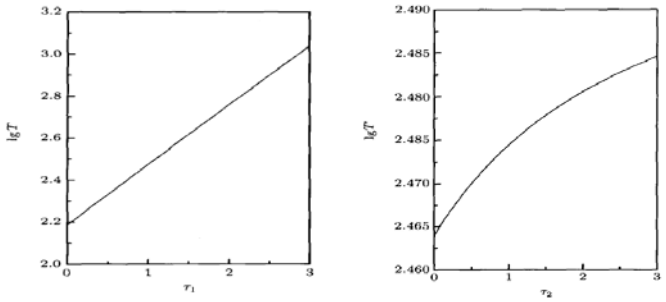

Figure 3 The mean first passage time of the system.

According to the theoretical expression of the mean first-passage-time of the gene transcription regulation system, the mean first passage time is obtained with the self-correlation time τ_1 and τ after numerical treatment. As shown in the figure, the left-hand figure shows the mean first-passage-time as the self-correlation time of the multiplicative noise. As you can see from the figure, the mean first passage time increases linearly monotonously with the increase of self-correlation time of the multiplicative noise. It means that the time required to convert protein concentration from high concentration to low concentration increases, and the transition from "on" to "off" becomes difficult. The right figure shows image of the mean first-passage-time T as the function of self-correlation time of the additive noise τ_2. As you can see from the figure, the mean first-passage-time increases monotonously with the increasing of τ_2, and the conversion from "on" to "off" becomes difficult. Comparing to the left figure, the trend of change is relatively slow. It is because the multiplicative noise intensity is very sensitive to the state transition of the system.

6. Discussion

Understanding the transformation law of protein concentration in gene regulation system and the influence of fluctuation intensity (noise parameter) on the system can provide a train of thought for the research of gene pharmacology and achieve the desired purpose by controlling the corresponding parameters.

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References

[1] Finkenstädt B, Dan J W, Komorowski M, et al. Quantifying intrinsic and extrinsic noise in gene transcription using the linear noise approximation: An application to single cell data[J].

Annals of Applied Statistics, 2013, 7(4):1960-1982.

[2] Wang C J，Mei D C. Effect of colored cross-correlated noise on the gene transcriptional regulatory system[J]. Acta Physica Sinica, 2008, 57(7):3983-3988.

[3] Wang C J. Colored noise induced switch in the gene transcriptional regulatory system[J]. Acta Physica Sinica, 2012, 61(1):013110.

[4] Tang M. The mean and noise of stochastic gene transcription[J]. Journal of Theoretical Biology, 2008, 253(2):271-280.

[5] Dattani J, Barahona M. Stochastic models of gene transcription with upstream drives: exact solution and sample path characterization[J]. Journal of the Royal Society Interface, 2017, 14(126):20160833.

[6] Feng T Q, Yi M. Stochastic multiresonance induced by correlated noise from a gene transcriptional regulatory system driven by amplitude-modulated signal[J]. Scientia Sinica, 2015, 45(9):098701.

[7] Feng T, Ming Y I. Stochastic multiresonance induces by additive amplitude modulation signal and noise in a gene transcriptional regulatory model[J]. Journal of Biological Systems, 2015, 23(02):1550015.

[8] Liu X M. Effects of Additive and multiplicative noises on gene transcription regulation[J]. Journal of South China University of Technology, 2009, 37(7):132-134.

[9] Simpson M L, Cox C D, Sayler G S. Frequency domain chemical Langevin analysis of stochasticity in gene transcriptional regulation.[J]. Journal of Theoretical Biology, 2004, 229(3):383-394.

[10] Raser J M, O'Shea E K. Noise in gene expression: origins, consequences, and control[J]. Science, 2005, 309(5743):2010-2013.