# Fluctuations-induced switch in the gene transcriptional regulatory system

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Based on the kinetic model of genetic regulation system proposed by Smolen *et al.* [Am. J. Physiol. **274**, c531 (1998)], the effects of fluctuations in the degradation reaction rate and the synthesis reaction rate of the transcription factor have been investigated through numerical computation and analysis theory. In the case of uncorrelated noises, it is shown that only the fluctuation of degradation reaction rate can induce a switch process, and the mean first passage time (MFPT) from the high concentration state to the low concentration one is decreased when the noise intensity of degradation reaction rate is increased. In the case of correlations between noises, a switch process can also be induced by the cross-correlation intensity between noises and by the fluctuation of the synthesis reaction rate in the genetic regulatory system. It is found that, under large cross-correlation intensity, a successive switch process (i.e., "on"→"off"→"on," which we call the reentrance transition or twice switch ) occurs with an increase of noise intensities, and a critical noise intensity exists at which the MFPT of the switch process is the largest. While the system is initially in the high concentration state with an increase of the cross correlation, the stationary probability distribution (SPD) of the transcription factor activator monomer concentration at the low concentration state is increased, yet the MFPT is increased due to the decreasing of the SPD of the transient states between the two steady stable states.

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## I. INTRODUCTION

The effects of noise on nonlinear dynamical systems have been extensively studied from both theoretical and experimental points of view [1]. Particulary, the noise-induced transition [2], the nonequilibrium fluctuation-induced transport [3], and the stochastic resonance phenomena [4] have been intensively investigated in a large variety of physical, chemical, and biological systems. On the other hand, many systems require considering various noise sources. Moreover, in certain situations, noises may be correlated with each other. Recently, the effects of correlated noises on nonlinear dynamical systems have attracted attention in the field of stochastic processes [5–7].

Regulation of gene expression by signals from outside and within the cell plays important roles in many biological processes. As the basic principles of genetic regulation have been characterized, it has become increasingly evident that nonlinear interactions, positive and negative feedback within signaling pathways, time delays, protein oligomerization, and crosstalk between different pathways need to be considered to fully understand genetic regulation [8–10]. However, cells are intrinsically noisy biochemical reactors: low reactant numbers can lead to significant statical fluctuations in molecule numbers and reaction rates [11]. It has been found that the stability against fluctuations is essential for the case of a gene regulatory cascade controlling cell differentiation in a developing embryo [12], moreover, these fluctuations are intrinsic: they are determined by structure, reaction rates, and species concentrations of the underlying biochemical networks.

To examine the capability of genetic regulatory systems for complex dynamic activity, Smolen *et al.* [8] developed simple kinetic models that incorporate known features of these systems. These features include autoregulation and stimulus-dependent phosphorylation of transcription factors (TFs), dimerization of TFs, crosstalk, and feedback. The simplest kinetic model of genetic regulation proposed by Smolen *et al.* [8] can be described by Fig. 1. A single transcriptional activator (TF-A) is considered as part of a pathway mediating a cellular response to a stimulus. The TF forms a homodimer that can bind to responsive elements

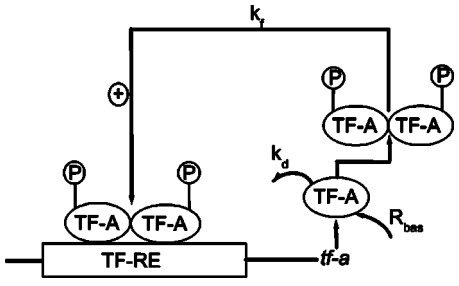


FIG. 1. Model of genetic regulation with a positive autoregulatory feedback loop. The transcription factor activator (TF-A) activates transcription with a maximal rate $k_f$ when phosphorylated ($P$) and binds as a dimer to specific responsive-element DNA sequences (TF-REs). TF-A is decomposed with rate $k_d$ and synthesized with rate $R_{\mathrm{bas}}$.

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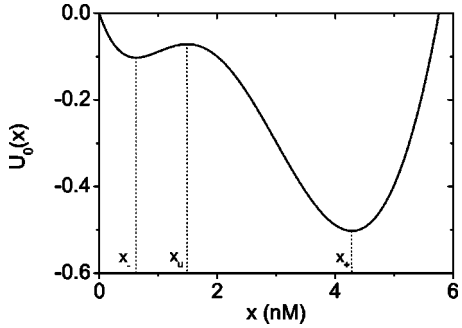


FIG. 2. The bistable potential of Eq. (3). The parameter values are $k_f=6\ \mathrm{min}^{-1}$, $K_d=10$, $k_d=1\ \mathrm{min}^{-1}$, and $R_{\mathrm{bas}}=0.4\ \mathrm{min}^{-1}$. The steady table states are $x_-\approx 0.62685nM$ and $x_+\approx 4.28343nM$, and the unstable steady state is $x_u\approx 1.48971nM$.

(TF-REs). The TF-A gene incorporates a TF-RE, and when homodimers bind to this element, TF-A transcription is increased. Binding to the TF-REs is independent of dimer phosphorylation. Only phosphorylated dimers can activate transcription. The fraction of dimers phosphorylated is dependent on the activity of kinases and phosphatases whose activity can be regulated by external signals. Thus, this model incorporates both signal-activated transcription and positive feedback on the rate of TF synthesis. It is assumed that the transcription rate saturates with TF-A dimer concentration to maximal rate $k_f$, which is proportional to TF-A phosphorylation. At negligible dimmer concentration, the synthesis rate is $R_{\mathrm{bas}}$. TF-A is eliminated with a rate constant $k_d$, binding processes are considered comparatively rapid, so the concentration of dimmer is proportional to the square of TF-A monomer concentration $x$. These simplifications gives a model with a single ordinary differential equation for the concentration of the TF-A:

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

where $K_d$ is the dissociation concentration of the TF-A dimer from TF-REs. Under the following condition of parameters:

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

the potential

$$U_0(x)=k_f\sqrt{K_d}\arctan\frac{x}{\sqrt{K_d}}+\frac{k_d}{2}x^2-(R_{\mathrm{bas}}+k_f)x \tag{3}$$

corresponding to Eq. (1) has two steady stable states $x_+=2\sqrt{-p/3}\cos(\theta)+(R_{\mathrm{bas}}+k_f)/(3k_d)$, $x_-=2\sqrt{-p/3}\cos(\theta+2\pi/3)+(R_{\mathrm{bas}}+k_f)/(3k_d)$, and one unstable steady state $x_u=2\sqrt{-p/3}\cos(\theta+4\pi/3)+(R_{\mathrm{bas}}+k_f)/(3k_d)$, where $p=K_d-[(R_{bas}+k_f)/k_d]^2/3$, $q=K_d(k_f-2R_{\mathrm{bas}})/(3k_d)-2[(R_{\mathrm{bas}}+k_f)/(3k_d)]^3$, and $\theta=\arccos[-q/(2\sqrt{-p^3/27})]/3$. A bistable potential of $U_0(x)$ is plotted in Fig. 2.

The simplest model of Eq. (1) manifests two stable steady states, and it was shown that [8] the brief manipulations of $k_f$ could switch the model between these states when $R_{\mathrm{bas}}$ and $k_d$ are treated as constants. Such transitions might explain how a brief pulse of hormone or neurotransmitter could elicit a long-lasting cellular response. However, all these simple kinetic models proposed by Smolen *et al.* [8] are deterministic, and the intrinsic fluctuations are not considered there. Recently, some experiments showed that $R_{\mathrm{bas}}$ and $k_d$ are affected by the biochemical reactions, mutations, and the concentrations of other proteins, and are also fluctuant [13]. Based on the simplest kinetic model, we will investigate the emergent noise properties of genetic regulatory systems in this paper.

Our goal is to quantify the properties of the switch between stable states when the reaction rates of synthesis and degradation of proteins are fluctuations. For simplicity, the two fluctuations considered here are assumed as Gaussian white noises, with variances independent of other model parameters. On the other hand, when fluctuations in the reaction rates of synthesis and degradation of the same proteins (i.e., TFs) are simultaneously considered, the two noises would be independent of each other. In some situations [5–7], however, both noises may have a common origin and thus not be independent, physically it would mean that the noises are of the same origin. Although we have not found a biological rationale for the correlation between the fluctuations in the reaction rates of synthesis and degradation of TF-As so far, it seems interesting to check what effects would result from such a correlation between the two fluctuations. Therefore, two cases have been considered in this paper: there is no correlation between the noise of the synthesis rate and that of the degradation rate, and there is correlation between the two noises. Here the mean first passage time is used to characterize the switch between states in the genetic regulatory systems.

## II. GENE TRANSCRIPTIONAL REGULATORY SYSTEM WITH UNCORRELATED NOISES

In order to simulate the stochastic effects of biochemical reaction rates $R_{\mathrm{bas}}$ and $k_d$, it is assumed that the stochasticity is added to the reaction rates as $R_{\mathrm{bas}}\rightarrow R_{\mathrm{bas}}+\xi(t)$ and $k_d\rightarrow k_d+\zeta(t)$, where $\zeta(t)$ and $\xi(t)$ are the Gaussian white noise. Thus, Eq. (1) becomes a Langevin equation

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

and the statistical properties of $\zeta(t)$ and $\xi(t)$ are given by

$$\langle\xi(t)\rangle=0,\ \langle\xi(t)\xi(t')\rangle=2\alpha\delta(t-t'), \tag{5}$$

$$\langle\zeta(t)\rangle=0,\ \langle\zeta(t)\zeta(t')\rangle=2D\delta(t-t'), \tag{6}$$

$\alpha$ and $D$ are the intensity of noises. It is well know that $\zeta(t)$ is a multiplicative noise and $\xi(t)$ is an additive one. To investigate effects of these noises on the genetic regulatory systems, in this section we consider that the noises $\zeta(t)$ and $\xi(t)$ in Eq. (4) are independent of each other, that is,

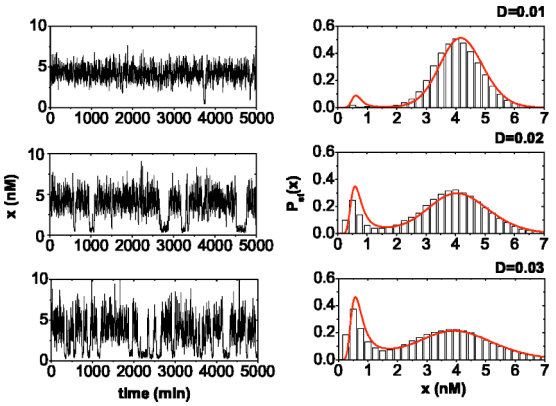


FIG. 3. Sample paths and probability distribution of $x(t)$ for different noise intensity $D$. From top to bottom $D=0.01$, 0.02, and 0.03. The additive noise intensity $\alpha=0.005$. The sold curve in right is the SPD by using of Eq. (9). The other parameter values are the same as those in Fig. 2.

$$\langle \xi(t)\zeta(t')\rangle = \langle \zeta(t)\xi(t')\rangle = 0. \tag{7}$$

Then, the Fokker-Planck equation can be derived from Eq. (4) with Eqs. (5)–(7):

$$\frac{\partial P(x,t)}{\partial t} = -\frac{\partial}{\partial x}\left(\frac{k_f x^2}{x^2+K_d} - k_d x + R_{\text{bas}} + Dx\right)P(x,t) + \frac{\partial^2}{\partial x^2}(Dx^2+\alpha)P(x,t). \tag{8}$$

The stationary probability distribution (SPD) corresponding to Eq. (8) is given by

$$P_{\text{st}}(x) = \frac{N}{\sqrt{Dx^2+\alpha}}\exp\left(-\frac{\phi(x)}{D}\right), \tag{9}$$

where $N$ is the normalization constant and the modified potential $\phi(x)$ is

$$\phi(x) = \frac{k_f D\sqrt{K_d}}{\alpha - DK_d}\arctan\left[\frac{x}{\sqrt{K_d}}\right] - \left(\frac{k_f\alpha}{\alpha - DK_d} + R_{\text{bas}}\right) \times \sqrt{\frac{D}{\alpha}}\arctan\left[\sqrt{\frac{D}{\alpha}}x\right] + \frac{k_d}{2}\ln(Dx^2+\alpha). \tag{10}$$

In the region of bistable, the time course of TF-A monomer concentration $x(t)$ and the probability distribution are plotted by directly simulating the stochastic differential equation (4) and by using the theoretical formula (9) for different noise intensities of degradation rate $D$ in Fig. 3, respectively. It is shown that the TF-A monomer concentration $x$ concentrates on the high concentration state when the intensity of the multiplicative noise $D$ is small, that is, we begin the switch in the "on" position by tuning the multiplicative noise intensity to a very low value. However, increasing of the multiplicative noise intensity causes the low concentration state to become populated, corresponding to a decrease of the concentration of the TF-A monomer and a flipping of the switch to the "off" position. The above result indicates that a switch process can be induced by the fluctuation of degradation reaction rate of the TF-A (i.e., the multiplicative noise) in the genetic regulatory systems, which usually realizes by the manipulations of $k_f$ in the previous investigations [8]. It should be pointed out that the fluctuation of the synthesis reaction rate of the TF-A (i.e., the additive noise) cannot cause switch phenomena (data not shown here).

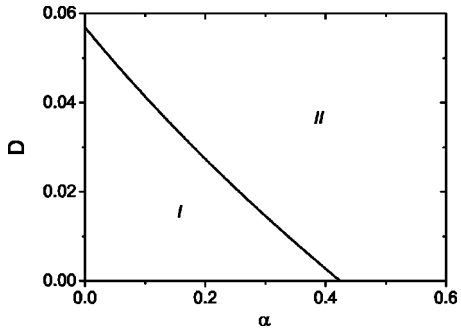


FIG. 4. The valid region $I$ of Eq. (11) in the $D$-$\alpha$- parameter plane. The other parameter values are the same as those in Fig. 2.

Now the question is how do we quantify the effects of noises on the switch between the steady stable states? When the system is stochastically bistable, a quantity of interest is the time from one state to the other state. This time is a random variable and is often referred to as the first passage time. Here we consider the mean first passage time (MFPT). The MFPT $\tau$ of the process $x(t)$ to reach the low concentration state $x_-$ with initial condition $x(t=0)=x_+$ (the high concentration state) can be given by the Kramers time [14]

$$\tau = 2\pi|U_0''(x_+)U_0''(x_u)|^{-1/2}\exp\left[\frac{\phi(x_u)-\phi(x_+)}{D}\right]. \tag{11}$$

Note that Eq. (11) is valid only when the intensities of two types of noise, measured by $D$ and $\alpha$, is small in comparison with the energy barrier height [15], that is,

$$D,\alpha < \phi(x_u) - \phi(x_+). \tag{12}$$

These provide a restriction on the noise intensities $D$ and $\alpha$. In Fig. 4 we display the valid region in the $D$-$\alpha$ parameter plane, and following results of MFPT are restricted in the valid region.

Figure 5 shows the MFPT as a function of noise intensity $D$ of the degradation reaction rate for different noise intensity $\alpha$ of synthesis reaction rate. It is shown that the MFPT is decreased when the noise intensity $D$ of degradation reaction rate is increased. Therefore, the transition between the high concentration state and the low concentration one for the large fluctuation of the degradation reaction rate is faster than that for the small fluctuation of the degradation reaction rate. In fact, the effect of the stochastic degradation reaction rate on the MFPT of the switch process can be easily understood through the SPD of the genetic regulatory system. Because the SPD is shifted from a high concentration state to a low concentration one when $D$ is increased as shown in Fig. 3, therefore, the MFPT defined by the stochastic process to reach the low concentration state with an initial condition at high concentration is decreased with $D$ increasing.

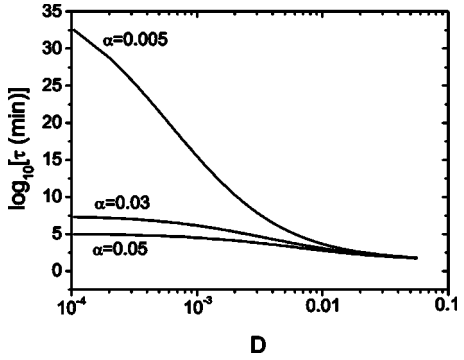


FIG. 5. The MFPT as a function of noise intensity $D$ of degradation reaction rate for different noise intensity $\alpha$. The other parameter values are the same as those in Fig. 2.

## III. GENE TRANSCRIPTIONAL REGULATORY SYSTEM WITH CORRELATED NOISES

In this section, consider the stochastic genetic regulatory system (4) with correlations between multiplicative and additive noises, and the correlation form between the two noises is assumed to be as follows [5–7]:

$$\langle \xi(t)\zeta(t')\rangle = \langle \zeta(t)\xi(t')\rangle = 2\lambda\sqrt{D\alpha}\,\delta(t-t'), \tag{13}$$

where λ is the cross-correlation intensity. The Fokker-Planck equation corresponding to Eq. (4) with Eqs. (5), (6), and (13) can be written as

$$\frac{\partial P(x,t)}{\partial t} = -\frac{\partial}{\partial x}\left(\frac{k_f x^2}{x^2+K_d} - k_d x + R_{\mathrm{bas}} + Dx - \lambda\sqrt{D\alpha}\right)P(x,t) + \frac{\partial^2}{\partial x^2}(Dx^2 - 2\lambda\sqrt{D\alpha}x + \alpha)P(x,t). \tag{14}$$

The SPD corresponding to Eq. (14) can be obtained as follows:

$$P_{\mathrm{st}}(x) = \frac{N}{\sqrt{\mathcal{D}(x)}}\exp\left(-\frac{\phi(x)}{D}\right), \tag{15}$$

where $N$ is normalization constant, $\mathcal{D}(x) = Dx^2 - 2\lambda\sqrt{D\alpha}x + \alpha$, and the modified potential $\phi(x)$ is

$$\phi(x) = -\frac{ADk_f}{2}\ln(x^2+K_d) - \frac{BDk_f}{\sqrt{K_d}}\arctan\frac{x}{\sqrt{K_d}} - \frac{mk_f - k_d}{2}\ln(Dx^2 - 2\lambda\sqrt{D\alpha}x + \alpha) - \frac{(nk_f + R_{\mathrm{bas}})\sqrt{D/\alpha} + \lambda(mk_f - k_d)}{\sqrt{1-\lambda^2}} \times \arctan\frac{\sqrt{D/\alpha}x - \lambda}{\sqrt{1-\lambda^2}}, \tag{16}$$

with $B = K_d(DK_d - \alpha)/[(4\lambda^2 - 2)DK_d\alpha + D^2K_d^2 + \alpha^2]$, $n = -\alpha B/K_d$, $m = 2\alpha\sqrt{D\alpha}DB/(DK_d - \alpha)$, $A = -m/D$.

The time course of TF-A monomer concentration $x(t)$ and the probability distribution are plotted by directly simulating of the stochastic differential equation (4) with Eq. (13) and by using of the theoretical formula (15) with Eq. (16) for different cross-correlation intensities λ in Figs. 6 and 7, respectively. It is shown that the TF-A monomer concentration $x$ concentrates on the high concentration state when the cross-correlation intensity λ is small, that is, we begin the switch in the "on" position by tuning the cross-correlation intensity to a very low value. However, increasing the cross-correlation intensity causes the low concentration state to become populated, corresponding to a concentration of TF-A monomer decrease and a flipping of the switch to the "off" position. Therefore, a switch process can also be induced by the correlation between two noises, and the cross-correlation intensity between noises can be used as a control parameter of the switch process in the genetic regulatory system. In the case of uncorrelated noises, the fluctuation of the synthesis

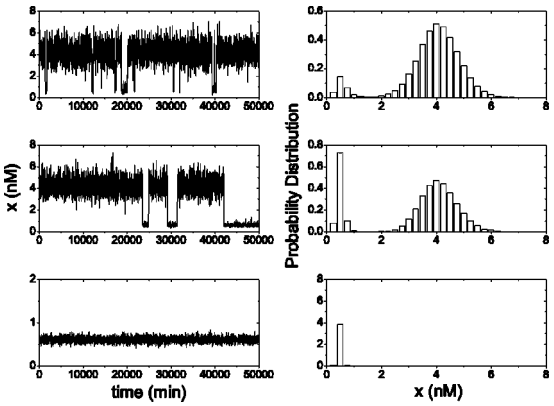


FIG. 6. Sample paths and probability distribution of $x(t)$ for different cross-correlation intensities. From top to bottom: λ = 0.1, 0.7, and 0.9. $D = 0.01$ and $\alpha = 0.005$. The other parameter values are the same as those in Fig. 2.

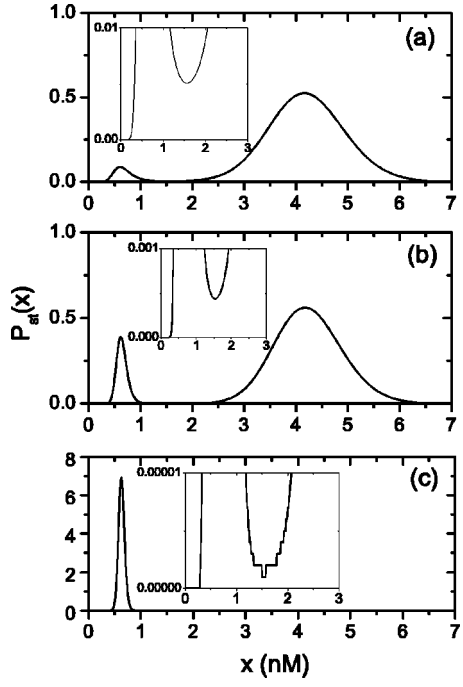


FIG. 7. The SPD of Eq. (15). (a) λ = 0.1, (b) λ = 0.7, (c) λ = 0.9. The other parameter values are the same as those in Fig. 6.

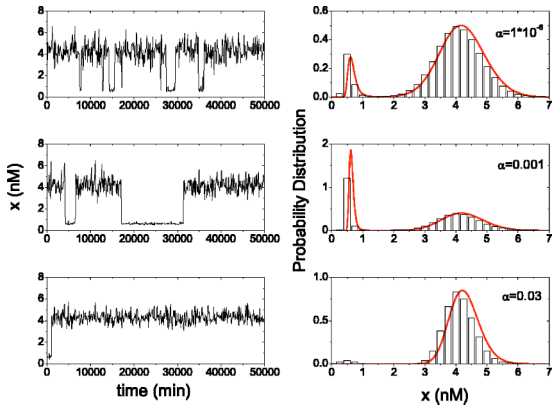


FIG. 8. Sample paths and probability distribution of $x(t)$ for different additive noise intensity $\alpha$. From top to bottom: $\alpha=10^{-6}$, 0.001, and 0.03. The sold curve in right is the SPD by using Eq. (15). $D=0.01$ and $\lambda=0.9$. The other parameter values are the same as those in Fig. 2.

reaction rate of TF-A (i.e., the additive noise) cannot cause switch phenomena to occur as mentioned in the above section. In the case of correlated noises, however, the correlation between noises causes the fluctuation of the synthesis reaction rate to induce a switch process as shown in Fig. 8. When the cross-correlation intensity $\lambda$ is large (e.g., $\lambda=0.9$ in Fig. 8), it is interesting that the probability distribution of $x(t)$ is shifted from the high concentration state to the low concentration state first, and then shifted from the low concentration state to the high concentration state with the increase of additive noise intensity $\alpha$. The same transition process can also occur for the variation of multiplicative noise intensity if $\lambda$ is large (data not shown here). Our result indicates that, when the cross-correlation intensity is large, there is a successive switch process with the increase of noise intensities, i.e. "on"→"off"→"on," and we call this phenomenon the reentrance transition or twice switch.

To character the switch process between states, the theoretical formula of the MFPT for the case of correlated noises is the same as that for the case of uncorrelated noises [i.e., Eq. (11) with Eq. (12)] instead of the modified potential $\phi(x)$. In Fig. 9, we display the valid regions in the $\lambda$-$D$ and $\lambda$-$\alpha$ planes, respectively. The following results of the MFPT are restricted in these valid regions.

Figure 10 shows the MFPT as a function of noise intensity $D$ and as a function of noise intensity $\alpha$ for different cross-correlation intensity $\lambda$ of noises, respectively. When the cross-correlation intensity $\lambda$ is small (e.g., $\lambda=0.1$ in Fig. 10), it is shown that the MFPT is monotonic and decreased with the increasing of $D$, which corresponds to once switch process occurring (i.e., "on"→"off"). However, when the cross-correlation intensity $\lambda$ is larger (e.g., $\lambda=0.7$ or 0.9 in Fig. 10), the MFPT first increases, reaches a maximum, and then decreases with the increasing of $D$, which corresponds to twice switch processes occurring (i.e., "on"→"off" →"on") in the genetic regulatory system. Moreover, the maximum of MFPT is increased with the increasing of the cross-correlation intensity $\lambda$. Our result showed that, under large cross-correlation intensity $\lambda$, a critical noise intensity $D$

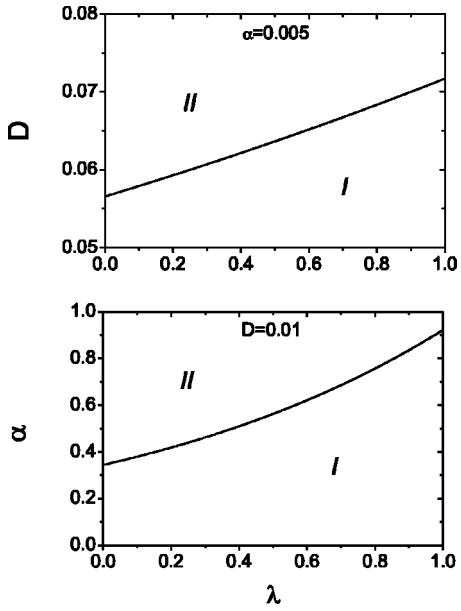


FIG. 9. The valid region $I$ in the $D$-$\lambda$ and $\alpha$-$\lambda$ parameter planes, respectively. The other parameter values are the same as those in Fig. 2.

or $\alpha$ exists at which the MFPT of the switch process induced by noises is the largest.

The SPD of the TF-A monomer concentration $x$ is shifted from the high concentration state to the low concentration one with the increasing of the cross-correlation intensity $\lambda$ (as shown in Figs. 6 or 7). However, Fig. 11 (also Fig. 10) shows another fact that the MFPT, defined as the mean escape time from the high concentration state to the low con-

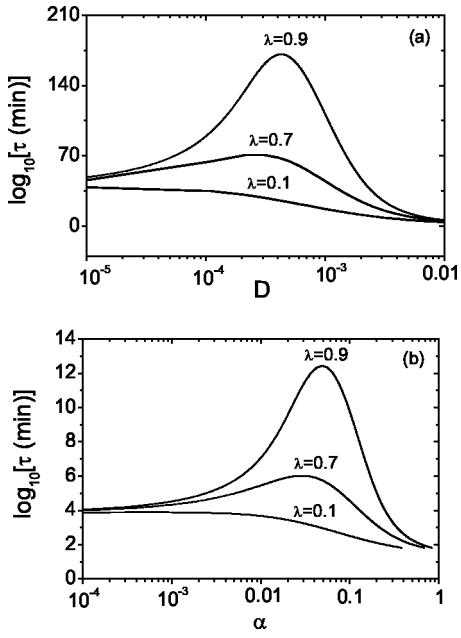


FIG. 10. The MFPT as a function of the multiplicative noise intensity $D$ (a) and the additive noise intensity $\alpha$ (b) for different cross-correlation intensities $\lambda$. $\alpha=0.005$ in (a) and $D=0.01$ in (b). The other parameter values are the same as those in Fig. 2.

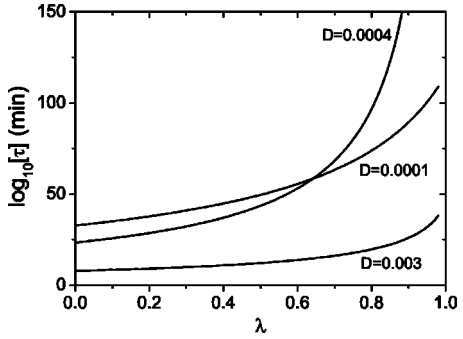


FIG. 11. The MFPT as a function of cross-correlation intensity λ for different multiplicative noise intensities *D*. The other parameter values are the same as those in Fig. 2.

centration one, is increased when λ is increased. That is, the transition from the high concentration state to the low concentration one becomes more and more slow with the increasing of the cross-correlation intensity λ. It seems indigestible. How can we understand this phenomenon? In fact, if all the states between two steady stable states are transient states, the system will go through these transient states when the system transition from the high concentration state to the low concentration one occurs, and the transition process could be imagined as the system through a "channel." The probability of these transient states strongly affects the transition. The smaller the probability of these transient states, the less the transition occurrence will be. From the inset of Fig. 7 (note the vertical scales of the inset), it can be seen that the SPD of the transient states dramatically decreases with the increase of the cross-correlation intensity λ. Therefore, when the system is initially at the high concentration state, with the increase of the cross-correlation intensity λ, although the SPD of the TF-A monomer concentration *x* in the low concentration state increases, yet the transition from the high concentration state to the low concentration one becomes more and more difficult due to the decrease of the SPD of the transient states (or the narrowing of the "channel"), thus, the MFPT increases with the increase of the cross-correlation intensity λ.

## IV. CONCLUSION AND DISCUSSION

Transcriptional regulation is an inherently noisy process. One origin of this stochastic behavior can be traced to finite number fluctuations in the biochemical reactions for the synthesis and degradation of protein [10–13]. In this paper, a kinetic model of a single genetic regulation system with fluctuations in both the degradation reaction rate and synthesis reaction rate of TF-As has been investigated through the numerical computation and the analysis theory. Our results indicate that noises and correlated noises can induce switch processes in the gene transcriptional regulatory system, which is implemented by the brief manipulations of $k_f$ in a previous study [8]. In the case of uncorrelation between the noises of synthesis rate and degradation rate, the switch process can only be induced by the fluctuation of degradation

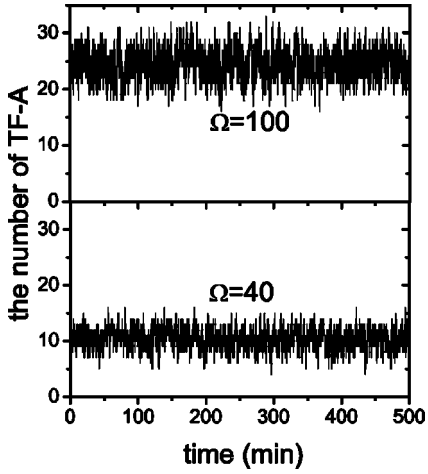


FIG. 12. The time series of the number of TF-As with different molecule noise intensities. The parameter Ω controls the number of molecules present in the system, which denotes the molecular noise. When Ω=100, i.e., the intensity of the molecular noise is low, the state of the TF-A is in the high concentration state. When Ω is decreased to 10, i.e., the intensity of the molecular noise is high, the state shifts to the low concentration state.

reaction rate of TF-A, and the transition time from the high concentration state to the low concentration one (i.e., the MFPT) is decreased and monotonic when the noise intensity of the degradation reaction rate is increased.

In the case of correlations between the noise of synthesis rate and that of the degradation rate, the switch process can also be induced both by the correlation between two noises and by the fluctuation in the synthesis reaction rate in addition to the fluctuation in degradation reaction rate. It has been shown that, under large cross-correlation intensity λ, a successive switch process, that is, "on" →"off" →"on" which we call the reentrance transition or twice switch, occurs with the increase of noise intensities, and a critical noise intensity *D* or $\alpha$ exists at which the MFPT of the switch process is the largest. However, when the cross-correlation intensity λ is small, there is only once switch process (i.e., "on" →"off") occurring with the increase of noise intensities, and the MFPT is monotonic and decreases with the

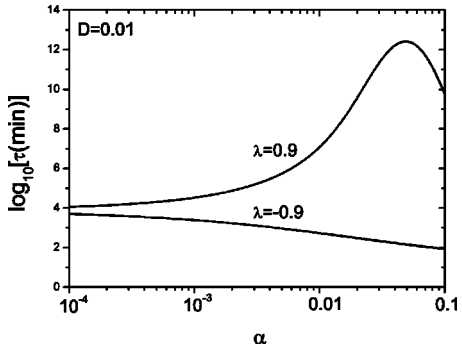


FIG. 13. The MFPT as a functional of additive noise intensity $\alpha$ with λ=0.9 and λ=−0.9. The other parameter values are the same as those in Fig. 2.

noise intensities. When the system is initially in the high concentration state, with increasing cross-correlation intensity $\lambda$, the SPD of the TF-A monomer concentration $x$ at the low concentration state is increased, yet the MFPT increases due to the decrease of the SPD of the transient states between the two steady stable states.

The above results show that noises and correlated noises play important roles in the genetic regulatory switch processes. It should be pointed out that the stochastic kinetic equation [i.e., Eq. (4), a nonlinear Langevin equation] considered here is valid when the molecule numbers (or the concentrations) of proteins are large (or high). Indeed, if the concentrations of TF-As are very low, then the discrete nature of the factors might become important, and a Markov chain might serve as a better model. Can the fluctuations in molecule numbers induce genetic switches with small numbers of molecular species? To assess the effects of molecular noise, we simulated the genetic regulatory processes according to the biochemical reaction processes, and the numerical simulations of the temporal evolution of molecule numbers of TF-As are performed by means of the Gillespie method [17]. Figure 12 shows that the molecular noise can also induce switch in the gene transcriptional regulatory system.

In the case of correlated noises, the correlation intensity $\lambda$ was restricted on positive values in this paper, that is, positive correlation between noises. However, physically it might be negative values (i.e., the case of negative correlation between noises) [5–7]. Now a question is how would the results look when $\lambda$ is negative? When we compared the MFPT for $\lambda=-0.9$ with that for $\lambda=0.9$ in Fig. 13, it was found that the negative correlation between noise could not bring any new physics.

Genetic regulation is a topic of central importance in biology. The nature of transcriptional regulation dictates that stochasticity is explicitly treated and understood in the basic models. Our contention is buttressed by the existence of several macroscopic gene-regulatory phenomena in which stochastic effects play a major role [16]. The fluctuation-induced switch process we discuss here is one important property of the stochasticity in the gene transcriptional regulatory system. In addition, the stochastic dynamic approach can identify key physiological control parameters to which the behavior of specific genetic regulatory systems is particularly sensitive. Such parameters might provide targets for pharmacological intervention. Thus, it would be highly interesting to investigate if similar experimental techniques could be used to bring out the noise- or correlated-noise-induced switch in the gene transcriptional regulatory process.

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