Mean First Passage Time and Stochastic Resonance in a Transcriptional Regulatory System with Non-Gaussian Noise

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The mean first passage time (MFPT) in a phenomenological gene transcriptional regulatory model with non-Gaussian noise is analytically investigated based on the singular perturbation technique. The effect of the non-Gaussian noise on the phenomenon of stochastic resonance (SR) is then disclosed based on a new combination of adiabatic elimination and linear response approximation. Compared with the results in the Gaussian noise case, it is found that bounded non-Gaussian noise inhibits the transition between different concentrations of protein, while heavy-tailed non-Gaussian noise accelerates the transition. It is also found that the optimal noise intensity for SR in the heavy-tailed noise case is smaller, while the optimal noise intensity in the bounded noise case is larger. These observations can be explained by the heavy-tailed noise easing random transitions.

Keywords: Non-Gaussian colored noise; mean first passage time; stochastic resonance; singular perturbation technique.

1. Introduction

The first passage time (FPT) is defined as the time that a walker or a particle spends before crossing a given position for the first time [1, 2], and is a value that fluctuates

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with every trial. The mean first passage time (MFPT), or the statistical mean of the FPT, is an important quantity in stochastic processes and statistical mechanics, with wide applications ranging from the lifespan of electron devices [3] and neural firing dynamics [4] to the spread of diseases [5] and stochastic resonance (SR) [6, 7].

In gene regulation models, the FPT is referred to as the time for the protein concentration to transition from a lower level to a higher level or vice versa. As an important quantity that characterizes gene transcriptional regulation, the MFPT has begun to attract more and more attention [8–10]. For example, Zheng *et al.* investigated the effect of the maximal transcriptional rate and the noise correlation on the MFPT in an auto-activating positive-feedback loop [9], and Qiu *et al.* disclosed the dependence of the FPT distribution on the type of unstable attractor crossed by stochastic trajectories on the separatrix [10]. In particular, we note that the fluctuations involved in the existing investigations are modeled by Gaussian noise. Nevertheless, growing evidence suggests that transport in biological and chemical processes tends to be an anomalous process of long range correlation or long term memory [11–14]. Thus, in this paper, we prefer to model the fluctuation in gene regulation with a more appropriate kind of noise, namely non-Gaussian noise [15–20]. Our purpose is to analytically deduce the MFPTs of a gene transcriptional regulatory system driven by non-Gaussian noise. As an application of the derived MFPTs, we further explore the effect of non-Gaussian noise on SR based on a new combination of adiabatic elimination [6, 21, 22] and linear response approximation [23–28].

The paper is organized as follows. In Sec. 2, following a brief introduction to the model, the exact expressions for the MFPTs in the gene regulatory system are deduced based on the singular perturbation analysis. In Sec. 3, the effect of non-Gaussian noise on SR in the gene transcriptional regulatory system is disclosed and discussed. Finally, conclusions are given in Sec. 4.

2. MFPT under Non-Gaussian Colored Noise

We consider a simple regulatory model [29, 30] that captures the salient features of transcription factor dimerization, binding, and phosphorylation-dependent regulation of transcription. As shown in Fig. 1, a single transcriptional activator TF-A is taken as part of the pathway mediating the cellular response to a stimulus, and the transcription factor TF-A forms a homodimer by phosphorylation that can bind to responsive elements (TF-REs). The *tf-a* gene then incorporates one of these responsive elements so that the TF-A transcription is enhanced when homodimers bind to the elements.

Assume that the transcription rate of *tf-a* saturates hyperbolically with TF-A dimer concentration and that the concentration of the homodimer is proportional to the square of the TF-A monomer concentration [29, 30]. Then, using a non-Gaussian noise term $u(t)$ to model the abnormal fluctuation occurring in transcriptional regulation, we acquire a simplified stochastic model for the ν concentration of the

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

TF-A monomer:

$$\frac{d\nu}{dt} = \frac{k_f \nu^2}{\nu^2 + K_d} - k_d \nu + R_{bas} + u(t), \quad (1)$$

where k_f is the maximal transcription rate of the *tf-a* gene, K_d denotes the dissociation constant of the TF-A dimer from TF-Res, k_d is a linear degradation constant, and R_{bas} is the basal rate of synthesis at a negligible dimer concentration. The evolution of $u(t)$ is governed by the nonlinear Ornstein–Uhlenbeck process [15, 17]

$$\frac{du(t)}{dt} = -\frac{1}{\tau_0} \frac{dV_p(u)}{du} + \frac{1}{\tau_0} \zeta(t), \quad (2)$$

where $V_p(u) = D \ln(1 + \tau_0(p-1)u^2/2D/(\tau_0(p-1)))$ with the extensive index p , the Gaussian white noise $\zeta(t)$ satisfies $\langle \zeta(t) \rangle = 0$ and $\langle \zeta(t)\zeta(t') \rangle = 2D\delta(t-t')$, and the noise correlation time τ_0 is a small parameter. According to [15, 19], the non-Gaussian process governed by Eq. (2) has a stationary distribution for $p \in (-\infty, 3)$. In fact, when $p \in (1, 3)$ the stationary distribution has a Tsallis-exponential asymptotic form, i.e., $P_p^{as}(u) \propto u^{-2/(p-1)}$ as $|u| \rightarrow \infty$, and when $p \in (-\infty, 1)$, it is a cut-off distribution with critical value $u_0 = \left[\frac{(1-p)\tau_0}{2D} \right]^{-1/2}$. The linear Ornstein-Uhlenbeck process, namely the Gaussian colored noise process, can also be recovered from Eq. (2) when $p = 1$. It is the fact that Eq. (2) covers bounded noise, Gaussian colored noise, and power-law heavy-tailed distributed noise when the extensive index $p \in (-\infty, 3)$ varies that motivates us to model the non-Gaussian fluctuation in such a way.

With linear stability analysis in mind, it is easy to find when the parameters satisfy

$$|K_d(k_f + R_{bas})/(6k_d) - |(k_f + R_{bas})/(3k_d)|^3 - K_d/(2k_d)|^2 + |K_d/3 - |(k_f + R_{bas})/(3k_d)|^2|^3 < 0,$$

Fig. 2. The schema of the bistable potential $U(v) = -\int |k_f v^2/(v^2 + K_d) - k_d v + R_{\text{bas}}| dv$ with $k_f = 6, K_d = 10, k_d = 1, R_{\text{bas}} = 0.4$. In this case, the stable equilibrium points are $v_- \approx 0.6268$ and $v_+ \approx 4.2834$, and the unstable equilibrium point is $v_0 \approx 1.4897$.

the deterministic counterpart of Eq. (1) has two stable equilibrium states that indicate different levels of protein concentration, namely

$$v_+ = 2\sqrt{p_1/3} \cos(\theta_1) + (R_{\text{bas}} + k_f)/(3k_d)$$

and

$$v_- = 2\sqrt{p_1/3} \cos(\theta_1 + 2\pi/3) + (R_{\text{bas}} + k_f)/(3k_d),$$

and one unstable equilibrium state

$$v_0 = 2\sqrt{p_1/3} \cos(\theta_1 + 4\pi/3) + (R_{\text{bas}} + k_f)/(3k_d),$$

with

$$p_1 = [(R_{\text{bas}} + k_f)/k_d]^2/3 - K_d,$$

$$q_1 = K_d(k_f - 2R_{\text{bas}}/(3k_d) - 2[(R_{\text{bas}} + k_f)/k_d]^3),$$

and

$$\theta_1 = \arccos(-q_1/(2\sqrt{p_1^3/27}/3)).$$

Hence, in this case system (1) has two potential wells at v_+ and v_- , separated by a potential barrier at v_0 when the noise level is low.

We now aim to deduce exact expressions for the MFPTs between different protein concentration states. Using the path integral technique [15], we can use the

approximation $\frac{1}{\tau_0} \frac{dV_p u}{du} \approx \frac{u}{\tau_1}$ with $\tau_1 = \frac{2(2-p)}{(5-3p)}\tau_0$ when $|p-1| \ll 1$ to rewrite Eq. (2) as

$$\frac{du(t)}{dt} = -\frac{1}{\tau_1}u(t) + \frac{1}{\tau_1}\xi(t), \quad (3)$$

where the Gaussian white noise $\xi(t)$ satisfies $\langle \xi(t) \rangle = 0$ and $\langle \xi(t)\xi(t') \rangle = 2D_1\delta(t-t')$ with $D_1 = (2(2-p)/(5-3p))^2 D$. Substituting of Eq. (3) into Eq. (1) yields

$$\begin{cases} \frac{d\nu}{dt} = f(\nu) + \varepsilon^{-1}\sqrt{D_1}z(t) \\ \frac{dz}{dt} = -\varepsilon^{-2}z + \sqrt{2}\varepsilon^{-1}\xi(t), \end{cases} \quad (4)$$

where $\tau_1 = \varepsilon^2$ and $f(\nu) = U'(\nu)$. According to singular perturbation analysis [31–33], we can take ε to be a small parameter. Let $P(\nu, z, t)$ be the solution of the Fokker–Planck equation

$$\partial_t P(\nu, z, t) = [\varepsilon^{-2}\partial_z(z + \partial_z) - \varepsilon^{-1}\sqrt{D_1}z\partial_\nu - \partial_\nu f(\nu)]P(\nu, z, t), \quad (5)$$

under an initial condition $P(\nu, z, t)|_{t=0} = \delta(\nu - \nu_-)\mu(z)$ with $\mu(z) = e^{-z^2/2}/\sqrt{2\pi}$ and a half-absorbing boundary condition [31–33] at $\nu = \nu_0$. Then, the survival probability for a protein molecule that starts from $\nu = \nu_-$ at $t_0 = 0$ and still stays in the left well at time t reads $S(t|\nu_-) = \int_0^{\nu_0} \int_{-\infty}^{+\infty} P(\nu, z, t) dz d\nu$. As a result, the MFPT for the molecule moving from ν_- to ν_0 can be defined as $\langle T_- \rangle = \int_0^{\nu_0} \int_{-\infty}^{+\infty} \int_0^{+\infty} P(\nu, z, t) dt dz d\nu$. With $G(\nu, z) = \int_0^{+\infty} P(\nu, z, t) dt$ denoting the mean residence time at a point (ν, z) before crossing the potential barrier at $\nu = \nu_0$ [33], the MFPT can be rewritten as

$$\langle T_- \rangle = \int_0^{\nu_0} \int_{-\infty}^{+\infty} G(\nu, z) dz d\nu. \quad (6)$$

Integrating both sides of Eq. (5) with respect to t from 0 to $+\infty$ leads to

$$(\varepsilon^{-2}L_0 + \varepsilon^{-1}L_1 + L_2)G(\nu, z) = -\delta(\nu - \nu_-)\mu(z), \quad (7)$$

where the differential operators are defined by $L_0 = \partial(z + \partial_z)$, $L_1 = -\sqrt{D_1}z\partial_\nu$ and $L_2 = -\partial_\nu f(\nu)$. If we seek a solution for Eq. (7) in the ansatz

$$G(\nu, z) = G_0(\nu, z) + \varepsilon G_1(\nu, z) + \varepsilon^2 G_2(\nu, z) + \cdots, \quad (8)$$

then substitution of the ansatz into Eq. (7) yields a set of embedded equations:

$$L_0 G_0 = 0, \quad (9a)$$

$$L_0 G_1 = -L_1 G_0, \quad (9b)$$

$$L_0 G_2 = -L_1 G_1 - L_2 G_0 - \delta(\nu - \nu_-)\mu(z), \quad (9c)$$

$$L_0 G_3 = -L_1 G_2 - L_2 G_1. \quad (9d)$$

The embedded system can be iteratively solved by means of the integrability condition and the Hermite functions.

Let $\rho_n(z) = e^{-z^2/2}/\sqrt{2\pi}\text{He}_n(z)$ denote the n th Hermite function, with $\text{He}_n(z) = (-1)^n e^{z^2/2} \left(\frac{d^n}{dz^n} e^{-z^2/2} \right)$. Then $\rho_n(z)$ satisfies

$$L_0 \rho_n(z) = -n \rho_n(z) \quad (10)$$

and the recurrence relation $z \rho_n(z) = \rho_{n+1}(z) + n \rho_{n-1}(z)$. Considering that $G_0(\nu, z)$ belongs to the null space of the operator L_0 , we substitute $G_0(\nu, z) = \rho_0(z) r_0(\nu)$ into Eq. (9b) to obtain

$$L_0 G_1 = \sqrt{D_1} \rho_1(z) \partial_\nu r_0(\nu). \quad (11)$$

With Eqs. (10) and (11) in mind, by setting $G_1(\nu, z) = \rho_0(z) r_1(\nu) - \sqrt{D_1} \rho_1(z) \partial_\nu r_0(\nu)$ and repeating the above deduction, we obtain

$$\begin{aligned} L_0 G_2 = & \rho_0(z) (-\delta(\nu - \nu_-) - D_1 \partial_\nu^2 r_0(\nu) + \partial_\nu f(\nu) r_0(\nu)) \\ & + \sqrt{D_1} \rho_1(z) \partial_\nu r_1(\nu) - D_1 \rho_2(z) \partial_\nu^2 r_0(\nu). \end{aligned} \quad (12)$$

Because L_0 is only reversible in the subspace spanned by $\rho(z) (n \geq 1)$, the coefficient of $\rho_0(z)$ in Eq. (12) must vanish, which leads to

$$-D_1 \partial_\nu^2 r_0(\nu) + \partial_\nu f(\nu) r_0(\nu) = \delta(\nu - \nu_-). \quad (13)$$

For $\nu_- < \nu \leq \nu_0$, integration of Eq. (13) from ν to ν_0 gives

$$D_1 \partial_\nu r_0(\nu) - f(\nu) r_0(\nu) = C_1, \quad (14)$$

where C_1 is the constant of integration. We further integrate Eq. (14) to obtain

$$r_0(\nu) = \left(A_1 - \frac{C_1}{D_1} \int_\nu^{\nu_0} \exp \left(-\frac{1}{D_1} \int_u^{\nu_0} f(\nu') d\nu' \right) du \right) \exp \left(-\frac{1}{D_1} \int_\nu^{\nu_0} f(\nu') d\nu' \right).$$

The constant of integration A_1 is found to be zero from the absorbing boundary condition $r_0(\nu_0) = 0$, and thus $r_0(\nu)$ can be reduced to

$$r_0(\nu) = -\frac{C_1}{D_1} \int_\nu^{\nu_0} \exp \left(-\frac{1}{D_1} \int_u^{\nu_0} f(\nu') d\nu' \right) du \exp \left(-\frac{1}{D_1} \int_\nu^{\nu_0} f(\nu') d\nu' \right). \quad (15)$$

Similarly, for $\nu < \nu_-$ integrating Eq. (13) twice over 0 to ν gives

$$r_0(\nu) = \left[\frac{C_1}{D_1} \int_0^\nu \exp \left(-\frac{1}{D_1} \int_0^u f(\nu') d\nu' \right) du + A_2 \right] \exp \left(\frac{1}{D_1} \int_0^\nu f(\nu') d\nu' \right).$$

Note that the kinetic term $f(\nu)$ in Eq. (4) satisfies $f(0) > 0$, which means that the deterministic dynamics cannot drive the concentration of the TF-A monomer from the nonnegative range. Certainly, it is equally desirable that the weak noise should not make the concentration negative. As a result, we have to impose an absorbing boundary at $\nu = 0$ to guarantee the nonnegativity of the concentration [34]. Because the absorbing boundary directly leads to $A_2 = 0$, we have

$$r_0(\nu) = \frac{C_2}{D_1} \int_0^\nu \exp \left(-\frac{1}{D_1} \int_0^u f(\nu') d\nu' \right) du \exp \left(\frac{1}{D_1} \int_0^\nu f(\nu') d\nu' \right). \quad (16)$$

According to Eq. (13), the continuity of $r_0(\nu)$ holds at $\nu = \nu_-$, namely $r_0(\nu_- -) = r_0(\nu_- +)$, which means that

$$\begin{aligned} & -C_1 \int_{\nu_-}^{\nu_0} \exp\left(-\frac{1}{D_1} \int_u^{\nu_0} f(\nu') d\nu'\right) du \\ & = C_2 \int_0^{\nu_-} \exp\left(-\frac{1}{D_1} \int_0^u f(\nu') d\nu'\right) du \exp\left(\frac{1}{D_1} \int_0^{\nu_0} f(\nu') d\nu'\right), \end{aligned} \quad (17)$$

and that the derivative $\partial_\nu r_0(\nu)$ has a jump discontinuity,

$$D_1 \partial_\nu r_0(\nu_- +) - D_1 \partial_\nu r_0(\nu_- -) = -1,$$

which can be simplified to

$$C_1 - C_2 = -1. \quad (18)$$

Simultaneously solving Eqs. (17) and (18) yields

$$C_1 = \frac{-\int_0^{\nu_-} \exp\left(-\frac{1}{D_1} \int_0^u f(\nu') d\nu'\right) du \exp\left(\frac{1}{D_1} \int_0^{\nu_0} f(\nu') d\nu'\right)}{C}$$

and

$$C_2 = \frac{\int_{\nu_-}^{\nu_0} \exp\left(-\frac{1}{D_1} \int_u^{\nu_0} f(\nu') d\nu'\right) du}{C}$$

with $C = \int_{\nu_-}^{\nu_0} \exp\left(-\frac{1}{D_1} \int_u^{\nu_0} f(\nu') d\nu'\right) du + \int_0^{\nu_-} \exp\left(-\frac{1}{D_1} \int_0^u f(\nu') d\nu'\right) du \times \exp\left(\frac{1}{D_1} \int_0^{\nu_0} f(\nu') d\nu'\right)$. We finally obtain $r_0(\nu)$ by substituting C_1 and C_2 into Eqs. (15) and (16).

Analogously, setting

$$G_2(\nu, z) = \rho_0(z) r_2(\nu) - \sqrt{D_1} \rho_1(z) \partial_\nu r_1(\nu) + D_1 \rho_2(z) \partial_\nu^2 r_0(\nu)/2$$

and substituting $G_1(\nu, z)$ and $G_2(\nu, z)$ into Eq. (9d) yields

$$\begin{aligned} L_0 G_3(\nu, z) &= \sqrt{D_1} z \partial_\nu (\rho_0(z) r_2(\nu) - \sqrt{D_1} \rho_1(z) \partial_\nu r_1(\nu) + D_1 \rho_2(z) \partial_\nu^2 r_0(\nu)/2) \\ &+ \partial_\nu f(\nu) (\rho_0(z) r_1(\nu) - \sqrt{D_1} \rho_1(z) \partial_\nu r_0(\nu)) \end{aligned} \quad (19)$$

and annihilation of the coefficient of $\rho_0(z)$ leads to

$$-\partial_\nu f(\nu) r_1(\nu) + D_1 \partial_1^2 r_1(\nu) = 0. \quad (20)$$

A direct integration of Eq. (20) yields $r_1(\nu) = B \exp(-U(\nu)/D_1)$, where the constant B can be determined by the half boundary condition $r(\nu_0) = \varepsilon \sqrt{D_1} \lambda_M r'(\nu_0)$ with $\lambda_M = -\zeta(1/2) \approx 1.460354$ [31–33], where $\zeta(\cdot)$ denotes the Riemann zeta

function. Substitution of $r(\nu_0) = r_0(\nu_0) + \varepsilon r_1(\nu_0) + \dots$ into the boundary condition immediately gives $B = (\lambda_M / \sqrt{D_1}) \exp(U(\nu_0)/D_1)$, and thus we have

$$r_1(\nu) = \lambda_M / \sqrt{D_1} \exp((U(\nu_0) - U(\nu))/D_1). \quad (21)$$

With the above expressions for $r_0(\nu)$ and $r_1(\nu)$ available, the MFPT can be calculated as

$$\begin{aligned} \langle T_- \rangle &= \int_0^{\nu_0} r_0(\nu) d\nu + \varepsilon \int_0^{\nu_0} r_1(\nu) d\nu \\ &= \frac{C_2}{D_1} \int_0^{\nu_-} \exp\left(-\frac{U(\nu)}{D_1}\right) d\nu \int_0^{\nu} \exp\left(\frac{U(u)}{D_1}\right) du \\ &\quad - \frac{C_1}{D_1} \int_{\nu_-}^{\nu_0} \exp\left(-\frac{U(\nu)}{D_1}\right) d\nu \int_{\nu}^{\nu_0} \exp\left(\frac{U(u)}{D_1}\right) du + \varepsilon \int_0^{\nu_0} r_1(\nu) d\nu. \end{aligned} \quad (22)$$

We emphasize that the result in Eq. (22) is exact in the sense of discarding the higher-order terms in ε . To avoid involved calculation of integrals, we can simplify the above results by the steepest descent method [1] as follows:

$$\begin{aligned} &\frac{C_2}{D_1} \int_0^{\nu_-} \exp\left(\frac{U(u)}{D_1}\right) du \int_u^{\nu_-} \exp\left(-\frac{U(\nu)}{D_1}\right) d\nu \\ &\quad \approx C_2 \pi \exp\left(\frac{U(\nu_0) - U(\nu_-)}{D_1}\right) |U''(\nu_0)U''(\nu_-)|^{-\frac{1}{2}}, \\ &\frac{C_1}{D_1} \int_{\nu_-}^{\nu_0} \exp\left(\frac{U(u)}{D_1}\right) du \int_{\nu}^{\nu_0} \exp\left(-\frac{U(\nu)}{D_1}\right) d\nu \\ &\quad \approx C_1 \pi \exp\left(\frac{U(\nu_0) - U(\nu_-)}{D_1}\right) |U''(\nu_0)U''(\nu_-)|^{-\frac{1}{2}}, \\ &\varepsilon \int_0^{\nu_0} r_1(\nu) d\nu \approx \sqrt{2\pi\varepsilon\lambda_M} |U''(\nu_-)|^{-\frac{1}{2}} \exp\left(\frac{U(\nu_0) - U(\nu_-)}{D_1}\right). \end{aligned}$$

Now Eq. (22) becomes

$$\begin{aligned} \langle T_- \rangle &= \pi(|U''(\nu_0)U''(\nu_-)|)^{-\frac{1}{2}} \exp\left(\frac{U(\nu_0) - U(\nu_-)}{D_1}\right) \\ &\quad + \sqrt{2\pi\varepsilon\lambda_M} |U''(\nu_-)|^{-\frac{1}{2}} \exp\left(\frac{U(\nu_0) - U(\nu_-)}{D_1}\right). \end{aligned} \quad (23)$$

Similarly, we can obtain the MFPT from ν_+ to ν_0 :

$$\begin{aligned} \langle T_+ \rangle &= \pi(|U''(\nu_0)U''(\nu_+)|)^{-\frac{1}{2}} \exp\left(\frac{U(\nu_0) - U(\nu_+)}{D_1}\right) \\ &\quad + \sqrt{2\pi\varepsilon\lambda_M} |U''(\nu_+)|^{-\frac{1}{2}} \exp\left(\frac{U(\nu_0) - U(\nu_+)}{D_1}\right). \end{aligned} \quad (24)$$

The theoretical results based on Eqs. (23) and (24) are shown in Figs. 3 and 4. As seen from Fig. 3, there is a good agreement between the theoretical and the

Fig. 3. Dependence of $\langle T_- \rangle$ and $\langle T_+ \rangle$ on noise intensity with $\tau_0 = 0.1$ and $p = 1.2$: theoretical (green smooth) and simulated (blue coarse). The other parameters are same as Fig. 2.

Fig. 4. Dependence of $\langle T_+ \rangle$ on the noise intensity D with (a) different deviation parameters p under $\tau_0 = 0.1$; (b) different correlation time τ_0 under $p = 0.9$. The smooth curves stand for theoretical results and coarse curves correspond to direct simulations. The other parameters are same as Fig. 2.

simulated results, but the discrepancy between them grows as the noise intensity increases, which is more obvious for $\langle T_- \rangle$ than for $\langle T_+ \rangle$. We remark that this discrepancy does not contradict the singular perturbation analysis, but rather it is a result of the steepest descent approximation, which can produce better accuracy for higher relative potential barriers (see Fig. 2). At the same time, we emphasize that the dependence of $\langle T_- \rangle$ on the extensive index p and the correlation time τ_0 is similar to that of $\langle T_+ \rangle$, so from Fig. 4 we can conclude that when τ_0 and D are fixed, the MFPT of the system under study is a decreasing function of the extensive index p , while with p and D fixed, the MFPT is a slowly increasing function of the

correlation time τ_0 . Obviously, our observations generalize existing insights for the gene regulatory model.

3. Effect of Non-Gaussian Noise on Stochastic Resonance

According to [35, 36], an intrinsic cellular process can involve oscillation in the production of certain proteins, so the genetic circuits might also be modulated periodically by this protein. Based on this consideration, we introduce an external weak periodic signal $\kappa e^{-i\Omega t}$ of amplitude κ and periodic Ω on the right-hand side of Eq. (1) to modulate gene regulation. As an application of the MFPTs derived above, in this section we investigate the effect of non-Gaussian noise on SR in the gene regulatory system.

Suppose that $\kappa \ll 1$ and that $\Omega \ll 1$. Then, the coherent signal can be approximated as constant in the sense of adiabatic elimination [6, 21, 22], and thus Eqs. (23) and (24) can be modified into

$$\begin{aligned} \langle T_- \rangle = & \pi(|U''(\nu_0)|U''(\nu_-))^{-\frac{1}{2}} \exp\left(\frac{\hat{U}(\nu_0, t) - \hat{U}(\nu_-, t)}{D_1}\right) \\ & + \sqrt{2\pi\epsilon}U''(\nu_-)^{-\frac{1}{2}}\lambda_M \exp\left(\frac{\hat{U}(\nu_0, t) - \hat{U}(\nu_-, t)}{D_1}\right) \end{aligned} \quad (25)$$

and

$$\begin{aligned} \langle T_+ \rangle = & \pi(|U''(\nu_0)|U''(\nu_+))^{-\frac{1}{2}} \exp\left(\frac{\hat{U}(\nu_0, t) - \hat{U}(\nu_+, t)}{D_1}\right) \\ & + \sqrt{2\pi\epsilon}U''(\nu_+)^{-\frac{1}{2}}\lambda_M \exp\left(\frac{\hat{U}(\nu_0, t) - \hat{U}(\nu_+, t)}{D_1}\right) \end{aligned} \quad (26)$$

with $\hat{U}(\nu, t) = -\int |k_f \nu^2 / (\nu^2 + K_d) - k_d \nu + R_{\text{bas}} + \kappa e^{-i\Omega t}| d\nu$.

To simplify the stochastic differential equation model to a two-state discrete model, let A and B represent the left and right potential wells. Noting that $R_{AB} = 1/\langle T_- \rangle$ and $R_{BA} = 1/\langle T_+ \rangle$ are the probability transition rates between the two stable states, we immediately obtain the two-state master equation

$$\begin{cases} \frac{dp_A(t)}{dt} = -R_{AB}(t)p_A(t) + R_{BA}(t)p_B(t) \\ \frac{dp_B(t)}{dt} = R_{AB}(t)p_A(t) - R_{BA}(t)p_B(t), \end{cases} \quad (27)$$

where p_A and p_B are the dwelling probabilities in the respective potential wells at time t .

Within a linear response range [25–28], we seek the long term solution of Eq. (27) in the form

$$p_A^{(\text{as})}(t) = p_{10} + p_{11}\kappa e^{-i\Omega t}, \quad p_B^{(\text{as})}(t) = p_{20} + p_{21}\kappa e^{-i\Omega t}, \quad (28)$$

where p_{i0} and $p_{i1}(i = 1, 2)$ are coefficients to be determined. Correspondingly, we set

$$R_{AB} = R_{10} + R_{11}\kappa e^{-i\Omega t}, \quad R_{BA} = R_{20} + R_{21}\kappa e^{-i\Omega t} \quad (29)$$

with

$$R_{10} = \frac{1}{\pi(|U''(\nu_0)|U''(\nu_-))^{-\frac{1}{2}} + \sqrt{2\pi\varepsilon}U''(\nu_-)^{-\frac{1}{2}}\lambda_M} \exp\left(\frac{U(\nu_-) - U(\nu_0)}{D_1}\right),$$

$$R_{20} = \frac{1}{\pi(|U''(\nu_0)|U''(\nu_+))^{-\frac{1}{2}} + \sqrt{2\pi\varepsilon}U''(\nu_+)^{-\frac{1}{2}}\lambda_M} \exp\left(\frac{U(\nu_+) - U(\nu_0)}{D_1}\right),$$

$R_{11} = \frac{(\nu_0 - \nu_-)}{D_1} R_{10}$ and $R_{21} = \frac{(\nu_0 - \nu_+)}{D_1} R_{20}$. Substitution of Eqs. (28) and (29) into Eq. (27) yields

$$\begin{aligned} -\kappa i\Omega e^{-i\Omega t} p_{11} = & -(R_{10} + R_{11}\kappa e^{-i\Omega t})(p_{10} + p_{11}\kappa e^{-i\Omega t}) \\ & + (R_{20} + R_{21}\kappa e^{-i\Omega t})(p_{20} + p_{21}\kappa e^{-i\Omega t}), \end{aligned} \quad (30a)$$

$$\begin{aligned} -\kappa i\Omega e^{-i\Omega t} p_{21} = & -(R_{10} + R_{11}\kappa e^{-i\Omega t})(p_{10} + p_{11}\kappa e^{-i\Omega t}) \\ & + (R_{20} + R_{21}\kappa e^{-i\Omega t})(p_{20} + p_{21}\kappa e^{-i\Omega t}). \end{aligned} \quad (30b)$$

Comparison of the coefficients of κ^0 and κ^1 yields

$$R_{10}p_{10} - R_{20}p_{20} = 0, \quad (31)$$

$$-i\Omega p_{11} = -R_{10}p_{11} + R_{20}p_{21} - R_{11}p_{10} + p_{20}R_{21}. \quad (32)$$

With the requirement of conservation of probability in mind, namely

$$p_{10} + p_{20} = 1, \quad p_{11} + p_{21} = 0,$$

the solutions of Eqs. (31) and (32) can be written as

$$p_{10} = \frac{R_{20}}{R_{10} + R_{20}}, \quad p_{20} = \frac{R_{10}}{R_{10} + R_{20}} \quad (33)$$

and

$$\begin{aligned} p_{11} &= \frac{1}{R_{10} + R_{20}} \frac{R_{10}R_{21} - R_{11}R_{20}}{(R_{10} + R_{20}) - i\Omega}, \\ p_{21} &= \frac{1}{R_{10} + R_{20}} \frac{R_{11}R_{20} - R_{10}R_{21}}{(R_{10} + R_{20}) - i\Omega}, \end{aligned} \quad (34)$$

respectively. Substituting Eqs. (33) and (34) into Eq. (28), we obtain the long term average of the output response of the two-state model as

$$EX = \nu_- p_{10} + \nu_+ p_{20} + (\nu_- p_{11} + \nu_+ p_{21})\kappa e^{-i\Omega t}, \quad (35)$$

and consequently the spectral amplification factor is

$$|\chi|^2 = \kappa^{-2} |\nu_- p_{11} + \nu_+ p_{21}|^2.$$

In Fig. 5, the nonmonotonic dependence of the SAF via the noise intensity signifies the occurrence of SR in the gene regulatory systems. From this figure, we see that

Fig. 5. Dependence of the spectral amplification factor on the noise intensity with $\Omega = 0.1$, $\kappa = 0.3$ and (a) $\tau_0 = 0.1$; (b) $p = 0.9$. The other parameters are same as Fig. 2.

the peak SR is almost constant for different extensive indices, but that the optimal noise intensity lessens as the extensive index increases (Fig. 5(a)). We also observe that the resonant peak becomes weak when the noise correlation time is prolonged (Fig. 5(b)), and thus it can be concluded that the correlation time of the non-Gaussian noise has the same tendency in its effect on SR as that of Gaussian colored noise [37, 38].

Theoretically, we have determined the effect of non-Gaussian noise on SR in the gene regulatory model from the viewpoint of two-state approximation. Nevertheless, because the probability transition rates used in the two-state model is an approximate outcome from the steepest descent method and especially the two-state model captures the nonlocal interwell random jumps but omits the local intrawell motion, we have to adopt stochastic simulation to check whether the above discussion on SR can characterize the real effect of non-Gaussian noise on SR in the original gene regulatory model. To clarify this point, we exhibit some typical time history in Fig. 6. From the picture, it is clear that there occur two different motions in the bistable system, at the weak noise level, the intrawell fluctuation is dominated, while on the strong noise level, the interwell jump is intertwined with the intrawell motion. This suggests us that the negligence of the intrawell motion might cause certain quantitative deviations. Actually, we show the dependence of the spectral amplification factor on noise intensity in Fig. 7. Here, the spectral amplification factor is captured from the long time quasi-stationary dynamics which is obtained by discarding the transient response over the first several periods. By comparing Fig. 6 with Fig. 7, it is easy to observe evident quantitative differences in the resonant

Fig. 6. The simulation on the evolution of the model (1) with weak periodic signal with $p = 1$ and $\tau_0 = 0.1$. From the top to the bottom, the noise intensity denotes $D = 0.1$, $D = 0.5$ and $D = 0.9$, respectively. The other parameters are same as Fig. 5. Here the nonnegativity of the concentration is guaranteed by imposing an absorbing boundary condition to the model (1), as treated in Sec. 2. That is to say, when the concentration variable is crossing zero from above, it will be reset to zero.

Fig. 7. Simulation for the dependence of the spectral amplification factor on the noise intensity with $\Omega = 0.1$, $\kappa = 0.3$ and (a) $\tau_0 = 0.1$; (b) $p = 0.9$. The other parameters are same as Fig. 5.

curves between the two methods. Fortunately, the effect of the extensive index and the correlation time of non-Gaussian noise on SR between the two methods is similar. That is, changing the extensive index almost only shifts the location of the resonant peak while increasing the correlation time weakens the resonant effects. Undoubtedly, this qualitative agreement confirms our theoretical observations to some extent.

4. Discussion and Conclusion

We have derived an explicit formula for the MFPT for a phenomenological gene transcriptional regulatory model with non-Gaussian colored noise using singular perturbation analysis and the steepest descent approximation. When the extensive index is close to 1, we found that the MFPT is a decreasing function of the extensive index of the non-Gaussian noise. Noting that as the extensive index increases, the non-Gaussian noise changes from bounded noise ($p < 1$) to Gaussian colored noise ($p = 1$) and then heavy-tailed distribution noise ($p > 1$), we conclude from our investigation that heavy-tailed distribution noise is more helpful for protein concentration transition than bounded noise. This characteristic reflects the universal fact

that the heavy-tailed distribution noise easily induces more large random jumps than bounded noise.

We have also demonstrated the phenomenon of SR in the gene regulatory model. Adiabatic elimination and linear response theory are two fundamental mathematical techniques established for SR, and we have deduced a connection between them for the first time. By altering the extensive index, it is found that the peak SR does not vary obviously as the extensive index increases, but that the optimal noise intensity for SR is a decreasing function of the index. Compared with the case of Gaussian colored noise, the optimal noise intensity is smaller in the case of heavy-tailed non-Gaussian noise, but larger in the case of bounded non-Gaussian noise. Because SR is a synchronization effect between a noise-induced switch and weak signal modulation in the time-modulated bistable model [39], the weaker optimal noise intensity for heavy-tailed distribution noise is most likely because it easily induces more random jumps.

Additionally, as with the time correlation of Gaussian noise [37, 38], our investigation demonstrates that the time correlation for heavy-tailed or bounded non-Gaussian noise has an inhibitive effect on SR. Again, this observation depends on the ease of noise-induced random switches. The qualitative characteristic of these results has been confirmed by simulations and should be useful in gene circuit design.

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