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Delays-based protein switches in a stochastic single-gene network

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HIGHLIGHTS

- We study the protein switch in a single-gene network with time delays and noises.
- Noises and delays can induce the protein switch between the ON state and OFF one.
- It is shown that noises and delays can enhance stability of the OFF state in a single-gene network.

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ABSTRACT

In this paper, the protein switch in a single-gene network with time delays is investigated, where the gene expression is assumed to be disturbed by multiplicative and additive noises. The impacts of time delays τ_d and τ_s in degradation and synthesis processes, time delay τ_g in global process and cross-correlation between two noises (λ_i, and $i = d, s, g$) on the probability distribution and switch time (ST) from low protein level (OFF state) to high one (ON state) are discussed, respectively. Our results show that (1) the increase of the cross-correlation between two noises (λ_i) can induce protein switches from ON state to OFF one; (2) for $\lambda_i \geqslant 0$, the increase of τ_d can induce protein switches from OFF state to ON one, while τ_s (or τ_g) can induce protein switches from the ON state to the OFF one, but for $\lambda_i < 0$, the τ_d (or τ_s) can induce protein switches from the OFF state to the ON one, while τ_g can induce protein switches from the ON state to the OFF one; (3) the ST as functions of the noise intensities exhibits a maximum, which is the signature of the noise enhanced stability (NES) of the OFF state, while the increase of τ_d can cause the NES phenomenon to disappear; and (4) τ_d and τ_s play opposing roles in the ST, i.e., the impacts of the time delays τ_d and τ_s on ST can be canceled each other out.

1. Introduction

In recent years, plenty of researches show that noises play a positive role in many fields of physics, chemistry and biology [1–5]. In particular, there is considerable experimental evidence that noise can play a major role in gene regulation

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Table 1
Fast and slow reactions in single-gene network.

Fast reactions	Slow reactions
$2X \rightleftharpoons X_2$	$D_1 + P \rightarrow D_1 + P + nX$
$D + X_2 \rightleftharpoons D_1$	$D_2D_1 + P \rightarrow D_2D_1 + P + nX$
$D_1 + X_2 \rightleftharpoons D_2D_1$	$X \rightarrow \phi$
$D_2D_1 + X_2 \rightleftharpoons D_3D_2D_1$	$X_2 \rightarrow \phi$

dynamics [6–10]. Isaacs et al. studied the dynamics of an isolated genetic module in an *in vivo* autoregulatory gene network [11]. Liu and Jia [12] considered the effects of fluctuations in the gene transcriptional regulatory system. On the other hand, time delay sources are commonly encountered in nature and have been recently studied numerically, such as biophysiological controls [13], signal transmissions in biological and artificial neuronal networks [14], and laser dynamics in optical cavities [15,16], etc. Meanwhile, it appears that the combination of noise and time delay is ubiquitous in nature and often change fundamental dynamics of the system [17–21]. In the field of pure statistical physics, the bistable systems with noise and time delay simultaneously have been investigated in detail [22,23].

The quantitative model, a single-gene network derived from bacteriophage λ and construct a two-parameter deterministic model describing the temporal evolution of the concentration of λ repressor protein. This system is a DNA plasmid consisting of a promoter region P_{RM} that regulates the *cI* gene. The promoter region contains the three operator sites known as O_{R1}, O_{R2}, and O_{R3}. The ensuing increase in protein concentration brings to the binding to O_{R3} that switches off transcription, acting as a negative feedback loop [24]. The biochemical reactions that control λ phage are very well characterized [25,26]. They are, naturally, divided into fast and slow categories (Table 1) [27].

This defines the concentrations of network components as dynamical variables, $x = [X]$, $x_2 = [X_2]$, $d_0 = [D]$, $d_1 = [D_1]$, $d_2 = [D_2D_1]$, and $d_3 = [D_3D_2D_1]$, it is possible to write a rate equation describing the evolution of the concentration of repressor,

$$\dot{x} = -2k_1x^2 + 2k_{-1}x_2 + nk_tp_0(d_0 + d_1 + \alpha d_2) - k_xx, \tag{1}$$

where the concentration of RNA polymerase, p_0, remains constant during time. $K_i = k_i/k_{-i}$ are equilibrium rate constants ($i = 1, \ldots, 4$). To accurately model the evolution of the chemical species x, we can sum x and x_2 to consider the total number of biomolecules, and obtain the dimensionless variables $\tilde{x} = x\sqrt{K_1K_2}$ and $\tilde{t} = t(k_tp_0d_Tn\sqrt{K_1K_2})$ [24]. Upon substitution into Eq. (1), one obtains

$$\dot{x} = \frac{m(1 + x^2 + \alpha\sigma_1x^4)}{1 + x^2 + \sigma_1x^4 + \sigma_1\sigma_2x^6} - \gamma x, \tag{2}$$

in which x is the concentration of the repressor. The parameter m represents the number of plasmids per cell. The parameters γ determine the steady-state concentration of repressor and is directly proportional to the protein degradation rate, and it can be utilized as a tunable parameter, in the construction of artificial networks. For the operator region of λ phage, we have to fix the other parameters at $\sigma_1 \sim 2$, $\sigma_2 \sim 0.08$, and $\alpha \sim 11$ [24,28]. The nonlinearity of Eq. (2) leads to a bistable regime in steady-state concentration of repressor and its deterministic potential $V(x)$ shown in Fig. 1. The bistability (two stable states x_1 and x_2) in the system arises due to competition between production of x along with dimerization and its degradation. The final concentration of x is determined by the initial concentration of repressor.

Furthermore, gene regulation is an intrinsical noisy process, which is driven by intracellular and extracellular noise perturbations and environment fluctuations [29,30]. Such cellular noises will undoubtedly affect the dynamics of networks both quantitatively and qualitatively. Therefore, the chemical reaction of the model under ambient noise is given by [31]

$$\dot{x} = \frac{m(1 + x^2 + \alpha\sigma_1x^4)}{1 + x^2 + \sigma_1x^4 + \sigma_1\sigma_2x^6} - \gamma x + \eta(t), \tag{3}$$

where $\eta(t)$ is the additive Gaussian white noise. Amit et al. [31] consider only a single (additive) noise, but real systems are simultaneously disturbed by multiplicative and additive noises. In some situations, both noises may have a common origin and thus are not independent; physically this would mean that the noises are of the same origin [32–37]. Presently, the effects of cross-correlations between additive and multiplicative noises, either on a stationary state or on dynamics of the bistable potential system, have been widely studied [38–43]. In addition, these investigations on the dynamic properties of the gene network may neglect the possible effects induced by time delay. In many physical as well as biological systems, time delay plays a significant role in the dynamics, and brings a series of interesting and significant results [44–48]. Time delay has a significant impact on the controls and the operation flexibility of chemical process and it should not be ignored. In most practically relevant cases, the state of the system should be affected in the first place by its immediate past, with additional correction arising from the time delay [49]. In this paper, the protein switches between ON and OFF states in a single-gene network with time delay in three different cases are explored for cross-correlation between multiplicative and