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Emergent bimodality and switch induced by time delays and noises in a synthetic gene circuit

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HIGHLIGHTS

- Fluctuations enhance bimodality of probability distribution.
- Time delay weakens switch of ON state, and enhances stability of the ON state.
- Physical mechanisms for switch can be explained from effective potential.

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ABSTRACT

Based on the kinetic model for obtaining emergent bistability proposed by Tan et al. (2009), the effects of the fluctuations of protein synthesis rate and maximum dilution rate, the cross-correlation between two noises, and the time delay and the strength of the feedback loop in the synthetic gene circuit have been investigated through theoretical analysis and numerical simulation. Our results show that: (i) the fluctuations of protein synthesis rate and maximum dilution rate enhance the emergent bimodality of the probability distribution phenomenon, while the cross-correlation between two noises(λ), the time delay(τ) and the strength of the feedback loop(K) cause it to disappear; and (ii) the mean first passage time(MFPT) as functions of the noise strengths exhibits a maximum, this maximum is called noise-delayed switching (NDS) of the high concentration state. The NDS phenomenon shows that the noise can modify the stability of a metastable system in a counterintuitive way, the system remains in the metastable state for a longer time compared to the deterministic case. And the τ and the K enhances the stability of the ON state. The physical mechanisms for the switch between the ON and OFF states can be explained from the point of view of the effective potential.

1. Introduction

As a fundamental behavior of biological system, bistability has been studied extensively through experiments, theoretical analysis and numerical simulations [1,2]. There is experimental evidence that bistability has been obtained in a wide

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range of biological systems, for instance, the induction of the *lac* operon in *E. coli* results in the synthesis of the protein *β-galactosidase* required for breaking up sugar molecules and releasing energy to the cell [3], the lysis–lysogeny genetic circuit in bacteriophage λ [4], and the network of coupled positive feedback loops governing the transition to the mitotic phase of the eukaryotic cell cycle [5]. Recently, the example of a new mechanism biological system model exhibits emergent bistability, in which a noncooperative positive feedback circuit combined with circuit-induced growth retardation of the embedding cell give rise to two stable expression states [6]. In the actual system, the production of protein X has a retarding effect on the growth of the host cell so that the circuit function is linked to cellular growth. The protein decay rate has, in general, two components, the natural degradation rate and the dilution rate due to cell growth [7].

There is considerable experimental evidence that noise can play a major role in gene regulation dynamics [8–11]. Isaacs et al. [12] studied the dynamics of an isolated genetic module in an *in vivo* autoregulatory gene network. Jia et al. [13] considered the effects of fluctuations in the gene transcriptional regulatory system. 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 [14–20]. 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 [21–26]. On the other hand, these investigations on the dynamic properties of the gene network may neglect the possible effects induced by time-delayed feedback. In many physical as well as biological systems, the time-delayed feedback plays a significant role in the dynamics, and brings a series of interesting and significant results [27–32]. For example, time delay induced traveling wave solutions [33], coherence resonance [34], excitability [35], and periodically oscillate synchronously [36]. Time delay has a significant impact on the controls and the operation flexibility of chemical process and it should not be ignored. Furthermore, it appears that the combination of noises and time-delayed feedback is fairly ubiquitous in nature and often change fundamentally dynamics of the system [37–44]. So, in this paper, a challenging question is how the switching behavior between the high concentration state and the low concentration state are affected by multiplicative and additive noises, and time-delayed feedback. Our investigation is a significant try towards understanding the basic mechanisms of the delay-induced stochastic gene switch, and will motivate further the experimental research for stochastic gene expression system.

The paper is organized as follows. In Section 2, the basic model subject to noises and delayed feedback is presented, and then the impacts of the noises and time-delayed feedback on the probability distribution in Section 3 and MFPT in Section 4 are discussed, respectively. Finally, the conclusions are given in Section 5.

2. The basic model

Tan et al. [6] developed a mathematical kinetic model to capture the essential dynamics of the system of two positive feedback loops and showed that in a region of parameter space bistable gene expression is possible. The rate equation governing the dynamics of the system is given by

$$\frac{\mathrm{d}x}{\mathrm{d}t} = \frac{\delta + \alpha x}{1 + x} - \frac{\phi x}{1 + \gamma x} - x, \tag{1}$$

where the variables and the parameters are nondimensionalized with x being a measure of the protein amount. The parameter δ is the rate constant associated with basal gene expression, α represents the effective rate constant for protein synthesis, ϕ denotes the maximum dilution rate due to cell growth, and γ is a parameter denoting the metabolic burden.

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-delayed feedback [34]. To explore the optimal solution of control variables, it is necessary to understand the relations between state variables and control variables in the process system with time delays. The time delay has a significant impact on the controls and the operation flexibility of chemical process and it should not be ignored. Similar to the cases of Refs. [45–47], we introduce a delayed feedback loop into the model, so Eq. (1) can be rewritten as:

$$\frac{\mathrm{d}x}{\mathrm{d}t} = \frac{\delta + \alpha x}{1 + x} - \frac{\phi x}{1 + \gamma x} - x + K(x_\tau - x), \tag{2}$$

here K is the strength of a feedback loop of time delay $\tau > 0$, while x_τ denotes the delayed variable $x(t - \tau)$. In chemical reaction process, time delays often take place in the mass transmission in serial reactors, recycles, intermediate storage tanks, or in the heat transmission and measurement.

In order to simulate the stochastic effects of biochemical reaction rates, we consider two types of multiplicative noise associated with the rate constants α (rate constant for protein synthesis) and ϕ (the maximum dilution rate). Now we firstly consider the fluctuations of α by a stochastic parameter, i.e., the control parameter α from Eq. (2) is not constant, but fluctuates in time. Then, the control parameter α is replaced by $\alpha \to \alpha + \varepsilon_1(t)$, where $\varepsilon_1(t)$ is the Gaussian multiplicative white noise. Thus the stochastic differential equation under the Stratonovich form (or Langevin equation) corresponding to Eq. (2) can be rewritten as:

$$\frac{\mathrm{d}x}{\mathrm{d}t} = \frac{\delta + \alpha x}{1 + x} - \frac{\phi x}{1 + \gamma x} - x + K_1(x_{\tau_1} - x) + \frac{x}{1 + x}\varepsilon_1(t) + \eta_1(t). \tag{3}$$