Impact of time delay in a stochastic gene regulation network

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A B S T R A C T

In this paper, stationary probability distribution (SPD), mean first passage time (MFPT) and stochastic resonance (SR) phenomenon of an abstract model of the Myc/E2F/MiR-17-92 network with time delay and cross-correlation noise sources are investigated. The impacts of time delay τ, additive and multiplicative noise intensities Q and D, and cross-correlation intensity λ between noises on the SPD, MFPT, and SNR are discussed, respectively. Research results show that: (i) the high protein level (or ON) state is enhanced (or weaken) by the τ (or λ); (ii) the MFPT as a function of Q or D exhibits a maximum, which is the signature of the noise enhanced stability (NES) of the ON state. The stability of the ON state can also enhance (or weaken) by the λ (or τ); (iii) the existence of a maximum and a minimum in the signal-to-noise ratio (SNR) is identifying the characteristics of the SR and stochastic reverse-resonance (SRR) phenomenon, τ and λ enhance the SR and weaken the SRR phenomenon for SNR as a function of Q, while τ (or λ) weakens (or enhances) the SR phenomenon for SNR as a function of D; and (iv) the time delay weakens the SR, and causes the SR phenomenon to disappear for SNR as a function of λ.

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1. Introduction

In recent years, there has been increasing evidence for studying the effects of time delay in the nonlinear dynamical system [1–4]. In most practically relevant cases, the state of the system can exhibit temporal long range correlations and should be affected in the first place by its immediate past, with additional correction arising from the time delays. On the level of a nonlinear stochastic differential equation description of a system, the presence of time delay changes the dynamics properties of the system, and brings a series of interesting and significant results, for example, time delay induced traveling wave solutions [5], coherence resonance [6,7], excitability [8], periodically oscillate synchronously [9], transitions [10] and resonance [11,12].

Over the past decade, there is considerable experimental evidence that the gene regulation should be augmented with noise terms [13–16]. In Ref. [17], Hasty et al. considered the roles of the additive noise and multiplicative noise in engineered gene networks. Based on the model in Ref. [18], Liu and Jia considered the effects of fluctuations in the degradation and the synthesis reaction rate of the transcription factor, including the case of uncor-

related and correlated noises [19]. The microscopic realisation of correlated noise processes has been discussed [20,21]. Meanwhile, it appears that the correlation of internal and external fluctuations is ubiquitous in nature and often fundamentally changes the dynamics of a system [22,23].

Recently, Aguda et al. [24] presented an abstract model of the coupling between the E2F/Myc positive feedback loops and the E2F/Myc/miR- 17-92 negative feedback loop. They showed that the transcription factors E2F and Myc participate in the control of cell proliferation and apoptosis, and positive feedback loops in the regulation of these factors leads to bistability, which is a phenomenon characterized by the existence of low (OFF state) and high (ON state) protein levels. For the same model, Li et al. [25] found that the switching behaviors of the network involving miR-17-92 is both sensitive to stimuli and resistant to fluctuations in stimulus. Subsequently, Zhang et al. [26] showed that the role of the feedback loop on extrinsic colored noise effects is found to depend on the dynamic properties of the system. These important studies have provided many valuable insights, yet little work has been directed toward realistic time delay, which appears in the linear term, coupled with intrinsic and extrinsic noises in an abstract model of the Myc/E2F/miR-17-92 network presented by Aguda et al. (2008). In order to characterize further the dynamics of the gene regulation network, the effect of the time de-

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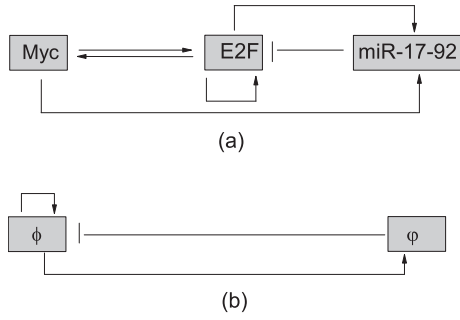
Fig. 1. An abstract model of the reducing process in cancer networks involving miR-17-92, E2F, and Myc. (a) Model of the coupling between E2F/Myc and E2F/Myc/miR-17-92; (b) the reduced abstract model.

lay coupled with intrinsic and extrinsic noises on the stochastic resonance (SR) in an abstract model of the Myc/E2F/miR-17-92 network need to be investigated. SR is a noise-induced effect demonstrating the phenomenon of signal amplification, which has been extensively investigated in the past two decades [27–34]. The mechanism is such that an external forcing injected on a nonlinear system can be amplified under a proper dose of noise. The concept of SR was originally proposed to explain periodic recurrences of the earth's ice age [35–38], it has attracted researchers interests, and it has been studied in geophysical, biological, chemical systems, and other fields [39–41] to manifest the constructive role of noises. Noise-induced resonance phenomena include doubly stochastic resonance [42], SR on bone loss [43], SR in excitable systems [44], coherence resonance [45] and array-enhanced coherence resonance [46].

The present paper is organized as follows. In Section 2, the abstract model of the Myc/E2F/miR-17-92 network with time delay and noises is presented, and then the effects of time delay and noise parameters on the SPD, MFPT and SR are discussed, respectively. Finally, results and discussions are given in Section 3.

2. The model with time delay and noises

The abstract model of the Myc/E2F/miR-17-92 network is illustrated in Fig. 1, and the basic principles of $\phi(\hat{t})$ and $\varphi(\hat{t})$ can be expressed as [24–26]

$$\frac{d\phi}{d\hat{t}} = \sigma + \left(\frac{k_1\phi^2}{\Gamma_1 + \Gamma_2\varphi + \phi^2}\right) - \rho\phi, \tag{1}$$

$$\frac{d\varphi}{d\hat{t}} = \chi + k_2\phi - \theta\varphi, \tag{2}$$

here $\phi(\hat{t})$ and $\varphi(\hat{t})$ denote the protein level (Myc and E2F) and miRNA cluster level, respectively. The parameter σ describes the constitutive protein expression from the signal transduction pathway in the extracellular medium, and χ depicts the ϕ-independent constitutive transcription of φ. The parameter k_1 stands for the protein module's autocatalytic process that is a positive feedback loop, and Γ_2 stands for the protein that is inhibited by the miRNAs. Simultaneously, the protein level ϕ induces the transcription of miRNAs φ, which is denoted by k_2. ρ and θ are the rate coefficients of degradation ϕ and φ, respectively. Γ_1 is the coefficient of protein expression, and Γ_2 is a measure of the miRNA inhibition of protein expression.

In most practically relevant cases, the state of the gene regulation network can exhibit temporal long range correlations and should be affected in the first place by its immediate past, with additional correction arising from the time delays. In practice, time delays always exist and play a significant role in the dynamics, for example, time delays can be used to introduce oscillations [47–50].

We consider the mammalian G1-S regulatory network. It can simplify an abstract model of the coupling between the E2F/Myc positive feedback loops and the E2F/Myc/miR-17-92 negative feedback loop and the essential abstract structure of the E2F/Myc/miR-17-92 network is illustrated in Fig. 1. It is well known that the transcription and translation processes involve compound multistage reactions and the sequential assembly of long molecules [51]. Therefore, time delay is very relevant in this system and should be considered explicitly in the stochastic gene expression dynamic. In the most practical relevant cases, the state of the system can exhibit temporal long range correlations and should be affected in the first place by its immediate past, with additional correction arising from the time delay. Similar to the cases of Refs. [52–54], we introduce a time delay into the linear term and it can also induce oscillatory behaviour here, then the linear term including time delay is $\rho\phi_\tau$, where ϕ_τ denotes the time-delayed variable with $\phi_\tau = \phi(\hat{t} - \tau)$. So the Eq. (1) can be written as

$$\frac{d\phi}{d\hat{t}} = \sigma + \left(\frac{k_1\phi^2}{\Gamma_1 + \Gamma_2\varphi + \phi^2}\right) - \rho\phi_\tau. \tag{3}$$

To more accurately describe our model, a stochastic description is then required. In this paper, we are more interested in how the dynamics of protein level (Myc and E2F) is affected by the intrinsic and extrinsic noises due to the existence of a range of Myc and E2F levels with increased probability of inducing cancer between levels associated with normal cell cycles and apoptosis. We take into account that the intrinsic noise $\epsilon(\hat{t})$, alters protein production, i.e., $\sigma = \sigma + \epsilon(\hat{t})$. Then fluctuations of the degradation of protein is considered, i.e., let $\rho = \rho + \eta(\hat{t})$. According to the above definitions about $\epsilon(\hat{t})$ and $\eta(\hat{t})$, the Langevin equation corresponding to Eq. (3) is given by

$$\frac{d\phi}{d\hat{t}} = \sigma + \left(\frac{k_1\phi^2}{\Gamma_1 + \Gamma_2\varphi + \phi^2}\right) - [\rho + \eta(\hat{t})]\phi_\tau + \epsilon(\hat{t}), \tag{4}$$

here the $\epsilon(\hat{t})$ and $\eta(\hat{t})$ are additive and multiplicative Gaussian zero mean noises and have the following statistical properties:

$$\langle\epsilon(\hat{t})\rangle = \langle\eta(\hat{t})\rangle = 0,$$
$$\langle\epsilon(\hat{t})\epsilon(t')\rangle = 2Q\delta(\hat{t} - t'), \langle\eta(\hat{t})\eta(t')\rangle = 2D\delta(\hat{t} - t'),$$

where Q and D are intensities of the Gaussian white noises $\epsilon(\hat{t})$ and $\eta(\hat{t})$, respectively. Here a natural question is whether the intrinsic and extrinsic noises are statistically correlated. However we could imagine the correlation arising from the feedback regulation, i.e., the protein degradation (affected by noise) is chemically coupled to its production (also affected by noise). We define that the cross-correlation of $\epsilon(\hat{t})$ and $\eta(\hat{t})$ is

$$\langle\eta(\hat{t})\epsilon(t')\rangle = \langle\epsilon(\hat{t})\eta(t')\rangle = 2\lambda\sqrt{DQ}\delta(\hat{t} - t'). \tag{5}$$

and λ denote the intensity of cross-correlation between $\epsilon(\hat{t})$ and $\eta(\hat{t})$. In practice, for the cross-correlation between intrinsic noise $\epsilon(\hat{t})$ and extrinsic noise $\eta(\hat{t})$, we have no experimental evidence that indicate that the parameter λ should be positive, or negative. We also noticed that in a previous model developed by authors of Refs. [25,26], they only consider the effect of extrinsic white (or colored) noise. However the effect of cross-correlation between intrinsic and extrinsic noises in a gene regulation network is ignored. Therefore, for the effect of λ we will only provide some theoretical possibilities.

For the sake of simplicity, the Eqs. (2) and (4) can be rewritten as follows by a series of nondimensionalizing processes [24]

$$\frac{dx}{dt} = \mu + \left(\frac{kx^2}{\gamma_1 + \gamma_2\zeta + x^2}\right) - [1 + \tilde{\eta}(t)]x_\tau + \tilde{\epsilon}(t), \tag{6}$$

$$\frac{d\zeta}{dt} = \varepsilon[1 + x - \zeta], \tag{7}$$