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Hybrid Control of Hopf Bifurcation in a Single-Gene Expression Model with Small RNAs and Delays

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***Abstract*—In this paper, we study the bifurcation and bifurcation control of a single-gene expression model mediated by small RNAs (sRNAs) with two delays. We first show the effect of sRNAs on the stability and bifurcation of the single-gene expression model. Then we control the Hopf bifurcation by using a hybrid control strategy. Under the control, the onset of the critical value of the undesirable Hopf bifurcation is postponed, and thus the model can remain stable for a larger delay. Finally, we verify the correctness of the theoretical results through the numerical simulations.**

Keywords- single-gene expression model, small RNAs, Hopf bifurcation, Bifurcation control.

I. INTRODUCTION

As we know, the studies on genetic regulatory networks not only involve a discussion of stability properties [1]–[3], but also involve other dynamic behaviors, such as periodic oscillatory behaviors [4], chaos and bifurcation [5]–[7]. The bifurcations, which involve the emergence of oscillatory behaviors, may provide an explanation for the parameter sensitivity observed in practice in many realistic genetic regulatory networks. On the other hand, if we understand more about the bifurcation behaviors of genetic regulatory networks, we can apply the bifurcation control methods to achieve some desirable behaviors that benefit the networks. Thus, the study of bifurcations on genetic regulatory networks is quite important.

In general, bifurcation control refers to the control of bifurcation properties of nonlinear dynamic systems, thereby resulting in some desired output behaviors of the systems, such as delaying the onset of an inherent bifurcation, stabilizing an unstable bifurcated solution or branch, and changing the critical values of an existing bifurcation [8]. Various bifurcation control approaches have been proposed in the literature [9]–[13]. Particularly, for the problem of relocating an inherent Hopf bifurcation, a dynamic state feedback control law incorporating a washout filter was proposed [9]. Later, the state feedback scheme was successfully developed to control Hopf bifurcations of autonomous systems [10], [11]. It should be noted that the state feedback scheme was first proposed to realize the control of the Hopf bifurcation for time-delayed systems [13], [14]. However, much less is known in the case of applying the hybrid to control bifurcations arising from time-delayed systems.

To motivate our present study in this area, we recall that the gene regulation process in cells is governed not only by mRNAs and proteins, but also by small RNA (sRNA) molecules [18], [22]. There has been considerable experimental evidence that sRNAs can play a major role in gene regulation processes [17], [24]. The sRNAs are transcripts of an organism's genome, similar to the mRNAs that encode proteins. Unlike mRNAs, however, the main function of sRNAs is to regulate the expression of other genes, which they accomplish by binding to target mRNAs or by interacting with proteins. The sRNAs act as guides to direct mRNAs degradation, translational repression, hetero-chromatin formation and DNA elimination [16], [20]. It would be logical to suppose that the sRNAs in gene regulatory networks could have a significant impact on network dynamics.

To our knowledge, the first gene regulatory model mediated by sRNAs was proposed by Shen et al. [15]. They derived the theoretical results of the globally asymptotic stability and provided the sufficient conditions for the oscillation. In this paper, we illustrate the effect of sRNAs on the gene regulation by a comparison analysis of the dynamics between a single-gene regulatory network without and with sRNAs firstly. Then a new method is presented to control the Hopf bifurcation of a delayed single-gene expression model. Finally, through the numerical simulations we verify the correctness of the theoretical results.

II. SINGLE-GENE EXPRESSION MODEL WITHOUT OR WITH SRNAS

In this section, we introduce a single-gene regulatory network without or with sRNAs. This network is an important class of genetic regulatory networks. Its mathematical model has been derived and has been experimentally and/or theoretically investigated in [15], [19]. Then we give the effect of sRNAs on the stability and Hopf bifurcation of the single-gene regulatory network model.

SINGLE-GENE EXPRESSION MODEL WITHOUT SRNAS

Lewis [19] has proposed a single-gene regulatory network model with time delays described by the following equations

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$$\begin{cases} \dot{m}(t) = -cm(t) + g(p(t-\tau_1)), \\ \dot{p}(t) = -bp(t) + am(t-\tau_2), \end{cases} \tag{2.1}$$

where and $p(t)$ are the concentrations of the mRNA and protein, respectively, $a > 0$ and $b > 0$ are the degradation rates of the mRNA and protein, respectively, and $a > 0$ is the synthesis rate of the protein. Then a significant time, τ_1 elapses between the initiation of transcription and the arrival of the mature mRNA molecule in the cytoplasm. Likewise, there is a delay, τ_2 between the initiation of translation and the emergence of a complete functional protein molecule. In addition, $g(p(t-\tau))$ is the rate of the production of the mRNA, and $g(x)$ is a function in the Hill form as follows:

$$g(x) = \frac{\beta}{1+(\frac{x}{p_0})^n},$$

where the Hill coefficient representing the degree of cooperation is $n(n > 0)$, and β, p_0 are positive constants. It is shown in [19] that model (2.1) can exhibit Hopf bifurcations as the sum of delays passes through some critical values.

SINGLE-GENE EXPRESSION MODEL WITH SRNAS

The sRNAs are often shown to act as inhibitors of the translation by base pairing with mRNAs in the ribosome binding site [17]. Shen et al. [15] incorporated the sRNA into the single-gene network (2.1) to study the regulatory effects of the sRNA. The corresponding differential equation model is described as follows

$$\begin{cases} \dot{m}(t) = -cm(t) - ds(t)m(t) + g(p(t-\tau_1)), \\ \dot{s}(t) = e - ds(t)m(t) - fs(t), \\ \dot{p}(t) = -bp(t) + am(t-\tau_2), \end{cases} \tag{2.2}$$

where $m(t)$, $s(t)$ and $p(t)$ are the concentrations of the mRNA, sRNA and protein, respectively, $c > 0$, $f > 0$ and $b > 0$ are the degradation rates of the mRNA, sRNA and protein, respectively, $a > 0$ is the synthesis rate of the protein, $e > 0$ is the transcription rate of the sRNA, $d > 0$ is the rate of the sRNA pairing with the mRNA and $g(x)$ is the sigmoid function or the function of the Hill form. In network (2.2), $s(t)$, $m(t)$ represents the effect of base pairing between $s(t)$ and $m(t)$. Shen et al. [15] have proved that there are periodic solutions for model (2.2) when the total delay $\tau = \tau_1 + \tau_2$ exceeds the critical value τ_0 and the gene oscillation is also robust in the model.

THE EFFECT OF SRNAS ON THE STABILITY AND HOPF BIFURCATION OF THE SINGLE-GENE EXPRESSION MODEL

In this subsection, the comparison of the stability between network (2.1) without sRNAs and network (2.2) with sRNAs is given by some numerical examples, and the effect of sRNAs on the stability of the single-gene regulatory network model is shown.

In [19], Lewis took the biologically meaningful values of parameters in network (2.1) without sRNAs as $a = 4.5$, $b = c = 0.23$, and $g(x) = \frac{33' 40^2}{x^2 + 40^2}$. He estimated the values of the total delay $\tau = \tau_1 + \tau_2$ and the period of the oscillation which are far from the results observed in a real-life zebra fish. In [23], under this group of data, Wu accurately predicted $\tau = 7.55$ min. It can be seen from Theorem 4.3 in [23] that the equilibrium $(m^*, p^*) = (8.27, 161.76)$ of network (2.1) is asymptotically stable when $\tau < \tau_0$ (see Fig. 2.1). On the other hand, as τ passes through the critical value $\tau_0 = 7.55$ min, the equilibrium loses its stability and a Hopf bifurcation occurs, i.e. a periodic oscillation bifurcates from the equilibrium (see Fig. 2.2).

For a consistent comparison, we consider the special case of network (2.2) with sRNAs: $a = 4.5$, $b = c = 0.23$, and $g(x) = \frac{33' 40^2}{x^2 + 40^2}$, $e = 1$, $d = 0.1$ and $f = 0.2$, where the values of parameters a, b, c, and $g(x)$ are same as those of network (2.1) without sRNAs used in [19], [23]. It follows from Equation (2.10) in [15] that $\tau = 4.965$ min. Note that the equilibrium $(m^*, s^*, p^*) = (7.23, 1.08, 141.39)$ of network (2.2) is different as that of network (2.1), and the critical value τ_0 for network (2.2) decreases from 7.55 min to 4.965 min, implying that the onset of the Hopf bifurcation is advanced.

Under these values of parameters, we choose $\tau = 4.8$ min $< \tau_0$. According to Theorem 1 in [15], trajectories of network (2) converge to the equilibrium (m^*, s^*, p^*), as shown in Fig. 2.3.

Under these values of parameters, we choose $\tau = 5.2$ min $> \tau_0$, which is the same value as that used in Fig. 2.1. From Theorem 1 in [15], we conclude that instead of having a stable equilibrium, the equilibrium of network (2.2) becomes unstable and a Hopf bifurcation occurs, as shown in Fig. 2.4.

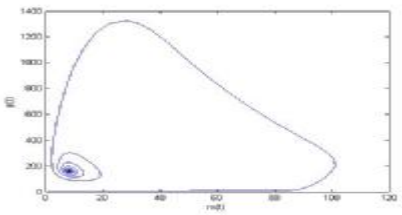

Fig. 2.1 Phase portrait of system (2.1). The equilibrium point (m^*, p^*) is asymptotically stable, where $\tau = \tau_1 + \tau_2 = 1.5 + 4 = 5.5 < \tau_0 = 7.55$.

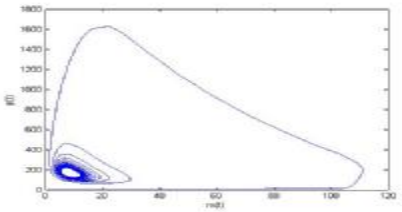

Fig. 2.2. Phase portrait of system (2.1). The equilibrium point (m^*, p^*) is unstable, where $\tau = \tau_1 + \tau_2 = 1.5 + 6.2 = 7.7 > \tau_0 = 7.55$.

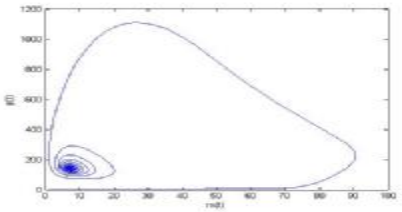

Fig. 2.3 Phase portrait of system (2.2). The equilibrium point (m^*, s^*, p^*) is asymptotically stable, where $\tau = \tau_1 + \tau_2 = 1.5 + 3 = 4.5 < \tau_0 = 4.965$.

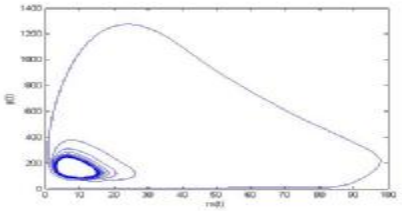

Fig. 2.4. Phase portrait of system (2.2). The equilibrium point (m^*, s^*, p^*) is unstable, where $\tau = \tau_1 + \tau_2 = 1.5 + 4 = 5.5 > \tau_0 = 4.965$.

III. HOPF BIFURCATION CONTROL OF SINGLE-GENE EXPRESSION MODEL WITH SRNAS AND TWO DELAYS VIA HYBRID

In this section, we design a hybrid law to the original single-gene system (2.2) for controlling the Hopf bifurcation.

It is well known that time delays cannot change the number and location of equilibriums of system (2). Let (m^*, s^*, p^*) be the equilibrium of (2.2), which is the solution of the following equation

$$\begin{cases} -cm^* - ds^*m^* + g(p^*) = 0, \\ e - ds^*m^* - fs^* = 0, \\ -bp^* + am^* = 0. \end{cases}$$

The controlled system will be assumed as the follows

$$\begin{cases} \dot{m}(t) = -cm(t) - ds(t)m(t) + g(p(t-\tau_1)), \\ \dot{s}(t) = e - ds(t)m(t) - fs(t), \\ \dot{p}(t) = (1-\alpha)(-bp(t) + am(t-\tau_2)) + \alpha(p(t) - p^*), \end{cases} \tag{3.1}$$

where the feedback gain parameter α is negative.

Remark 3.1: The hybrid controller can keep the equilibrium (m^*, s^*, p^*) of system (2.2) unchanged. Thus, the bifurcation control can be realized without destroying the properties of the original system (2.2).

Remark 3.2: The hybrid scheme has been successfully used to control the Hopf bifurcation in various autonomous systems. However, we first apply this scheme to the time-delayed genetic regulatory network.

We can get τ_k^j after we linearize system (3.1)

$$\tau_k = \frac{1}{\omega_k}\arccos\left[\frac{(k_5 - k_1k_4)\omega^4 + (k_1k_6 + k_3k_4 - k_2k_5)\omega^2 - k_3k_6}{k_4^2\omega^4 + (k_5^2 - 2k_4k_6)\omega^2 + k_6^2}\right] + \frac{2j\pi}{\omega_k}, k = 0,1,2,....$$

$\tau = \tau_1 + \tau_2$,

$k_1 = c + f + b - \alpha + ds^* + dm^*$,

$k_2 = cf + cdm^* + fds^* + (b - \alpha)(c + f + ds^* + dm^*)$,

$k_3 = (b - \alpha)(cf + fds^* + cdm^*)$,

$k_4 = \alpha$,

$k_5 = \alpha(c + f + ds^* + dm^*) - ag'(p^*)$,

$k_6 = \alpha(cf + fds^* + cdm^*) - ag'(p^*)(dm^* + f)$.

The method of calculation is same as [15].

Theorem 1: For (3.1), the following results hold.

(i) System (3.1) is stable when $\tau \in (0, \tau_0)$ and it is unstable when $\tau > \tau_0$.

(ii) System (3.1) undergoes a Hopf bifurcation at the equilibrium when $\tau = \tau_0$.

IV. NUMERICAL SIMULATION

Now we illustrate the effectiveness of the state feedback control strategy through the numerical simulation. We put into the same parameters as [21]

$$a = 4.5, b = c = 0.23, d = 0.1, e = 1, f = 0.2, \quad g(x) = \frac{33 \times 40^2}{x^2 + 40^2},$$

then system (3.1) is

$$\begin{cases} \dot{m}(t) = -0.23m(t) - 0.1s(t)m(t) + \dfrac{52800}{1600 + p(t-\tau_1)^2}, \\ \dot{s}(t) = 1 - 0.1s(t)m(t) - 0.2s(t), \\ \dot{p}(t) = (1-\alpha)(-0.23p(t) + 4.5m(t-\tau_2)) + \alpha(p(t) - p^*), \end{cases} \tag{4.1}$$

where the equilibrium point (m^*, s^*, p^*) of the system (3.1) is $(7.23, 1.08, 141.39)$.

When $a = 0$, system (4.1) is the non-controlled system (2.2). From [21], we can get $w_0 = 0.278, t_0 = 4.965$. When $t \in [0, 4.965)$, the equilibrium point (m^*, s^*, p^*) is asymptotically stable. When $t > 4.965$, the equilibrium point (m^*, s^*, p^*) becomes unstable, and the Hopf bifurcation appears (see Fig. 3.1).

Now, we choose an appropriate to control the bifurcation. We take $a = -0.1$. We can get $w_0 = 0.256, t_0 = 5.967$. The controlled system (4.1) has the same equilibrium point as that of the non-controlled system (2.2), but the critical value t_0 has increased from 4.965 to 5.967, which means that the onset of the bifurcation is delayed. Under the state feedback control with $a = -0.1$, we take $t = s_1 + s_2 = 3.5 + 1.5 < t_0 = 5.967$, which is the same value as that used in Fig. 3.1. We can see the equilibrium (m^*, s^*, p^*) of the controlled model (4.1) is stable, as shown in Fig. 3.2.

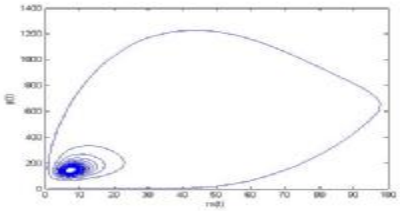

Fig. 3.1. Phase portrait of the non-controlled system (2.2) with $a = 0$. The equilibrium point (m^*, s^*, p^*) is unstable, where $t = t_1 + t_2 = 3.5 + 1.5 = 5 > t_0 = 4.965$.

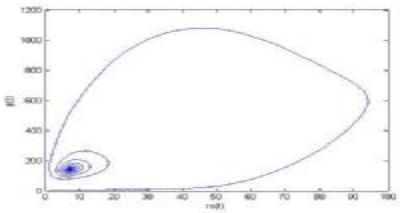

Fig. 3.2. Phase portrait of the controlled system (3.13) with $a = -0.1$. The equilibrium point (m^*, s^*, p^*) is asymptotically stable, where $t = t_1 + t_2 = 3.5 + 1.5 = 5 < t_0 = 5.976$.

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