Bifurcation and Oscillatory Dynamics of Delayed Cyclic Gene Networks Including Small RNAs

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***Abstract*—It has been demonstrated in a large number of experimental results that small RNAs (sRNAs) play a vital role in gene regulation processes. Thus, the gene regulation process is dominated by sRNAs in addition to messenger RNAs and proteins. However, the regulation mechanism of sRNAs is not well understood and there are few models considering the effect of sRNAs. So it is of realistic biological background to include sRNAs when modeling gene networks. In this paper, sRNAs are incorporated into the process of gene expression and a new differential equation model is put forward to describe cyclic genetic regulatory networks with sRNAs and multiple delays. We mainly investigate the stability and bifurcation criteria for two cases: 1) positive cyclic genetic regulatory networks and 2) negative cyclic genetic regulatory networks. For a positive cyclic genetic regulatory network, it is revealed that there may exist more than one equilibrium and the multistability can appear. Sufficient conditions are established for the delay-independent stability and fold bifurcations. It is found that the dynamics of positive cyclic gene networks has no bearing on time delays, but depends on the biochemical parameters, the Hill coefficient and the equilibrium itself. For a negative cyclic genetic regulatory network, it is proved that there exists a unique equilibrium. Delay-dependent conditions for the stability are derived, and the existence of Hopf bifurcations is examined. Different from the delay-independent stability of positive gain networks, the stability of equilibrium is determined not only by the biochemical parameters, the Hill coefficient and the equilibrium itself, but also by the total delay. At last, three illustrative examples are provided to validate the major results.**

***Index Terms*—Bifurcation, cyclic gene networks, multiple delays, oscillations, stability.**

I. Introduction

RHYTHMIC phenomena play a crucial role to maintain various biological functions of living organisms and one of the best studied rhythmic phenomena so far is circadian rhythms with a period of 24 h [1], [2]. It has long been suggested that circadian rhythms are produced by limit cycle oscillators at the molecular level from the genetic regulatory feedback loops [3]. Besides periodic oscillators, the other important feature in the process of gene representation is the stable steady state [4]. Thus, it is desirable to explore the conditions of the stability and the existence of oscillations in gene networks. It should be noted that Hopf bifurcations can induce the transitions between stable states and periodic oscillations [5]. Therefore, apart from the stability and periodic oscillations, the investigation of Hopf bifurcations is also crucial for gene networks.

Gene networks are composed of a great number of gene nodes, interrelating and interacting with each other. The study of dynamics of gene networks has become very important in describing the interaction mechanism between gene nodes in gene expression [6]–[8]. Hence, dynamical behaviors of gene networks have attracted growing attention from many scholars and numerous results have been reported [9]–[23].

It has been confirmed by considerable experimental evidence that the cyclic structure is a general feature in genetic networks [24], [25]. In recent years, many scholars have probed the influence of the cyclic structure on the dynamics of stability, Hopf bifurcations as well as periodic oscillations in gene networks. For example, the asymptotical behaviors were extensively examined for a ring-structured genetic model with repression. It was found that multiple stable states may be coexistent if the number of genes is even, while periodic oscillations may exist if the number of genes is odd [26]. A cyclic repressilatory network model was designed and constructed in *Escherichia coli* [4]. This inhibition network contains three genes, namely, *lacl, cl*, and *tetR*, while every gene is repressed by its upstream node. It should be mentioned that the negative cyclic gene network with three nodes generated oscillatory phenomena for the first time. The dynamical features of ring-structured gene networks with only positive loops [27] or K-repressive and K-inducible groups [28] were investigated by applying the theory of monotone dynamical systems. In [29], a class of ring-structured networks with n genes and time delays were discussed. The delay-independent stability of the equilibrium state was examined, and then the existence of Hopf bifurcations was determined. In [30], a class of $2n$-dimensional gene networks with ring structure and mixed delays were considered. The specific conditions to ensure the stability and Hopf bifurcations were deduced in positive and negative gain networks. In [31], a dual-ring genetic network with delays

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was put forward. The multistability and bifurcation analysis was conducted. By applying control theoretic tools, a general framework to formulate negative cyclic gene networks was proposed, and some conditions that ensure the stability and oscillation existence were derived in [32] and [33].

It is noteworthy that in addition to the ring structure, the hub structure is also a common topology in intracellular networks [34], [35]. Different from the ring-structured network models considered in the previous works, in [36], a class of hub-structured gene network models of arbitrary dimension were put forward, and sufficient conditions for the stability and bifurcating oscillations were given using the Hopf bifurcation theory.

In the last few years, it has been demonstrated by experimental evidence that RNAs play crucial roles in the regulation and control of genetic events (see a recent review in [37]). A large quantity of RNA is transcribed from the genome, of which only a small fraction is messenger RNAs (mRNAs) that will be translated into proteins. Many other small RNAs (sRNAs), microRNAs, or noncoding RNAs are also transcribed, ranging in size over several orders of magnitude from several kilobases down to around 20 nucleotides. These sRNAs appear to be dominant operation in a number of genetic processes and are guardians of an organism's genome [38]–[41]. sRNAs play an important role in gene regulation processes, including the regulation of transcription and translation, the modification of chromatin structure, and the processing, modification and stability of RNA and protein molecules [42], [43]. Fig. 1 shows that produced in parallel with mRNAs, sRNAs play a number of roles involved in the regulation of transcription and translation events. Hence, it is natural to assume that sRNAs will have a significant impact on the dynamical performances of genetic networks. However, previous models of gene regulation processes in cells involve only the interaction between mRNAs and proteins [4], [6]–[30], [32], [33], [36]. To better understand the regulation mechanism of sRNAs, this paper is to explore dynamical behaviors for cyclic gene networks mediated by sRNAs.

Although there have been some studies on Hopf bifurcations and oscillations for gene networks mediated by sRNAs in the past few years, it should be noticed that only the simplified genetic network models with a few delays and a few nodes have been considered. For instance, sRNA was incorporated into gene expression in [44] and the investigation on stability as well as Hopf bifurcations was carried out for a single-gene model with sRNAs. But only two time delays were considered in such simplified model. The effect of sRNAs on dynamical behaviors was addressed in detail [45]. The conditions that ensure the stability and existence of Hopf bifurcations were established for a two-gene network model including four delays and sRNAs. A single-gene model mediated by microRNA (sRNA) with time delays and reaction-diffusion terms was studied in [46]. Some conditions for local stability and Hopf bifurcations were derived, and the direction and stability of bifurcating oscillations were determined by applying the normal form theory and center manifold reduction. This paper will propose a class of n-gene network models with ring structure and sRNAs. Then the stability, oscillations and Hopf bifurcations will be investigated for delayed cyclic gene networks with sRNAs.

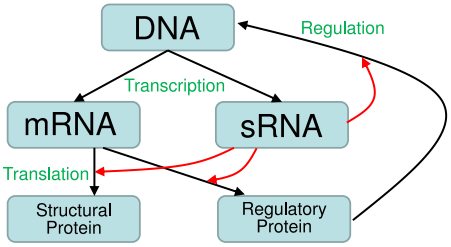

Fig. 1. sRNA regulation.

Besides Hopf bifurcations, it has been proved that there also exist fold bifurcations in genetic regulatory networks without sRNAs [29], [30], [36]. A fold bifurcation is a local bifurcation indicating that a dynamical system has the ability to present the change of the number of equilibria. This can help us to determine the number of equilibria by regulating the biochemical parameters for genetic regulatory networks. Different from [29], [30], and [36], we will take the effect of sRNAs into account and establish the existence condition of fold bifurcations for cyclic genetic regulatory networks mediated by sRNAs in this paper.

This paper is arranged as follows. Section II introduces the model under study, together with relevant notations. Section III discusses when positive equilibria are existent, and derives the characteristic equation around any equilibrium point. Section IV analyzes the stability and Hopf bifurcations of delayed cyclic gene networks including sRNAs. Section V provides three numerical examples to demonstrate the obtained results. Section VI illustrates general biological insights. Lastly, Section VII concludes this paper.

II. Model Description and Notation

Gene networks are often described by a differential equation model [24], [25]. In a ring-structured network with n genes, each gene contains products of mRNA, sRNA, and protein. It should be noted that the ith gene only receives information from the previous gene with delay τ_{pi-1}. We can express such network by the following equations [29], [30], [44], [45]:

$$\begin{aligned}\dot{m}_i(t) &= -c_i m_i(t) - d_i s_i(t) m_i(t) + g_i\big(p_{i-1}\big(t-\tau_{pi-1}\big)\big)\\ \dot{s}_i(t) &= e_i - d_i s_i(t) m_i(t) - f_i s_i(t)\\ \dot{p}_i(t) &= -b_i p_i(t) + a_i m_i(t-\tau_{mi})\end{aligned} \tag{1}$$

where i is the node number; when $i=1$, let $i-1=n$. m_i, s_i, and p_i represent, respectively, the concentrations of mRNA, sRNA, and protein of node i. c_i, f_i, and b_i denote, respectively, the degradation rates of mRNA, sRNA, and protein of node i. a_i stands for the synthesis rate with which protein i is generated by mRNA i in the ribosome. d_i denotes the paring rate of sRNA i with mRNA i. e_i represents the transcription rate of sRNA i. All of the above parameters are positive. τ_{pi} and τ_{mi} are known, respectively, as the discrete time delays for mRNA i and protein i. In addition, $g_i(\cdot)$ is the positive function that reflects the synthesis mechanism of mRNA i from protein $i-1$.

In network (1), the third equation depicts the process of translation. In addition to the linear degradation of protein i, $a_i m_i(t-\tau_{mi})$ represents the linear translational activity of mRNA i to protein i, which reflects the fact that one protein is produced from one mRNA only in network (1). The first two equations of network (1) describe the process of transcription. Besides the linear degradation of mRNA i and sRNA i, $d_i s_i(t) m_i(t)$ denotes the nonlinear degradation of mRNA i and sRNA i, which is induced by the association of two RNAs. Due to the ring structure of (1), the mRNA of node i is regulated by the protein produced from the previous node $i-1$ indicated in the expression of $g_i(p_{i-1}(t-\tau_{pi-1}))$. The protein, as a transcription factor, can directly promote the transcriptional process of mRNA by binding its activator to the mRNA's promoters, while the transcriptional process of sRNA can be indirectly influenced by the protein through mRNA. sRNAs directly affect the level of mRNA transcription by accelerating its degradation rates. This is achieved through binding of sRNA by partial nucleotide sequence complementarity to its target mRNA sequences.

The function $g_i(p_{i-1}(t))$ stands for the repressor or activator action of protein $i-1$ to mRNA i, and it can be expressed in the following Hill form as:

$$g_i(p_{i-1}(t)) = \begin{cases} \dfrac{\alpha_i (p_{i-1}(t)/\beta_i)^{h_i}}{1+(p_{i-1}(t)/\beta_i)^{h_i}} \\ \quad \text{if gene } i-1 \text{ is an activator of gene } i \\ \dfrac{\alpha_i}{1+(p_{i-1}(t)/\beta_i)^{h_i}} \\ \quad \text{if gene } i-1 \text{ is a repressor of gene } i \end{cases}$$

where α_i, β_i are positive constants, and the Hill coefficient $h_i > 0$ represents the degree of cooperativity. It is easy to see that the activator function and repressor function are strictly increasing and strictly decreasing, respectively, and they are both bounded.

Let ν_i be a class of structure variables, and denote $\nu_i = 1$ when gene $i-1$ is an activator of gene i; otherwise, $\nu_i = 0$. Then we can express $g_i(p_{i-1})$ in the unified form as follows:

$$g_i(p_{i-1}) = \frac{(-1)^{\nu_i}\alpha_i \beta_i^{h_i}}{\beta_i^{h_i} + (p_{i-1})^{h_i}} + \nu_i \alpha_i. \tag{2}$$

It is obvious that the total number ν of repressors in the whole cyclic network can be written as

$$\nu = n - \sum_{i=1}^{n} \nu_i.$$

If ν is odd, then the cyclic genetic regulatory network is topologically the same as a negative gain network and it can be called a negative cyclic gene network; if ν is even, then it can be called a positive cyclic gene network [30].

Remark 1: Due to the complexity of bifurcation analysis, most of pioneering works have been only limited to low-dimensional models of genetic networks with a few nodes as well as a few delays [21], [23], [47]–[49]. In this paper, we will investigate the stability, oscillations, and Hopf bifurcations in a class of high-dimensional genetic networks with a large number of nodes and multiple time delays.

Remark 2: The previous models of cyclic genetic regulatory networks involve only the interaction between mRNAs and proteins of node i [4], [24]–[33], which can be expressed by the first and third equations of model (1), respectively. The second equation of network (1) depicts the regulation process of sRNA of node i. The presence of sRNAs makes the analytical work much harder since it not only makes the network structure more complex but also extends the dimension of the system from $2n$ to $3n$. This paper will consider a class of ring-structured gene networks mediated by sRNAs.

III. Equilibrium and Characteristic Equation

A. Existence of Equilibria

Assume that network (1) has a possible equilibrium (M^*, S^*, P^*), where $M^* = (m_1^*, m_2^*, \ldots, m_n^*)$, $S^* = (s_1^*, s_2^*, \ldots, s_n^*)$ and $P^* = (p_1^*, p_2^*, \ldots, p_n^*)$. An equilibrium is the solution of the equations given below:

$$0 = -c_i m_i^* - d_i s_i^* m_i^* + g_i\big(p_{i-1}^*\big) \tag{3a}$$

$$0 = e_i - d_i s_i^* m_i^* - f_i s_i^* \tag{3b}$$

$$0 = -b_i p_i^* + a_i m_i^*, \qquad i = 1, 2, \ldots, n. \tag{3c}$$

Substituting (3b) and (3c) into (3a) yields $\mathcal{F}_i(p_{i-1}^*, p_i^*) = 0$, where

$$\mathcal{F}_i(\xi, \eta) = \frac{b_i c_i}{a_i}\eta + \frac{b_i d_i e_i \eta}{b_i d_i \eta + a_i f_i} - g_i(\xi). \tag{4}$$

Lemma 1: There exist a neighborhood B of p_{i-1}^* in $\mathbb{R}$, and a unique function $F_i : B \to \mathbb{R}$ such that

$$p_i^* = F_i\big(p_{i-1}^*\big), \ \ \mathcal{F}_i(\xi, F_i(\xi)) = 0, \ \text{ for all } \xi \in \mathbb{B}$$

and this function F_i is continuously differentiable with

$$\frac{dF_i(\xi)}{d\xi} = g_i'(\xi) \Bigg/ \left[\frac{b_i c_i}{a_i} + \frac{a_i b_i d_i e_i f_i}{(b_i d_i \eta + a_i f_i)^2}\right].$$

Proof: Calculating the partial derivative gives

$$\left.\frac{\partial \mathcal{F}_i(\xi, \eta)}{\partial \eta}\right|_{\left(p_{i-1}^*, p_i^*\right)} = \frac{b_i c_i}{a_i} + \frac{a_i b_i d_i e_i f_i}{\left(b_i d_i p_i^* + a_i f_i\right)^2} > 0.$$

It can be seen by the implicit function theorem that the function F_i is continuously differentiable and satisfies that $p_i^* = F_i(p_{i-1}^*)$ and $\mathcal{F}_i(\xi, F_i(\xi)) = 0$. In addition,

$$\begin{aligned} \frac{dF_i(\xi)}{d\xi} &= -\frac{\partial \mathcal{F}_i}{\partial \xi} \Bigg/ \frac{\partial \mathcal{F}_i}{\partial \eta} \\ &= g_i'(\xi) \Bigg/ \left[\frac{b_i c_i}{a_i} + \frac{a_i b_i d_i e_i f_i}{(b_i d_i \eta + a_i f_i)^2}\right]. \end{aligned}$$

The conclusion follows. ∎

Theorem 1: There exists an odd number of positive equilibria for the cyclic gene network (1). In particular, there exists a unique positive equilibrium for a negative cyclic gene network.

Proof: Let

$$\Psi(u) = u - F_n(F_{n-1}(\cdots(F_1(u))))$$

where the implicit function $F_i(u)$ is as defined in Lemma 1. Each zero p_n^* of $\Psi(u)$ determines an equilibrium of network (1).

Notice that $g_i(u)$ is positive and bounded. It is straightforward to obtain

$$\Psi(0) = -F_n(F_{n-1}(\cdots(F_1(0)))) < 0$$
$$\Psi(+\infty) = \lim_{u\to+\infty}\left[u - F_n(F_{n-1}(\cdots(F_1(u))))\right] = +\infty.$$

So, for network (1), there is surely a positive number p_n^* satisfying $\Psi(p_n^*) = 0$, which together with geometric properties of $\Psi(u)$ implies that $\Psi(u)$ has an odd number of positive zeroes.

It follows from (2) that:

$$\frac{dg_i(u)}{du} = \frac{(-1)^{1+\nu_i}h_i\alpha_i\beta_i^{h_i}}{\left(\beta_i^{h_i}+u^{h_i}\right)^2}u^{h_i-1} = \frac{(-1)^{1-\nu_i}h_i\alpha_i\beta_i^{h_i}}{\left(\beta_i^{h_i}+u^{h_i}\right)^2}u^{h_i-1}.$$

Thus, $\operatorname{sign}(dg_i(u)/du) = (-1)^{1-\nu_i}$. Furthermore, from Lemma 1, we obtain

$$\operatorname{sign}\left(\frac{dF_i(u)}{du}\right) = \operatorname{sign}\left(\frac{dg_i(u)}{du}\right) = (-1)^{1-\nu_i}$$
$$\operatorname{sign}\left(\frac{dF_n(F_{n-1}(\cdots(F_1(u))))}{du}\right) = \prod_{i=1}^{n}(-1)^{1-\nu_i} = (-1)^{\nu}.$$

If ν is odd, then we have $\Psi'(u) > 0$, which means that the function $\Psi(u)$ is strictly increasing in $[0, +\infty)$. So, $\Psi(u)$ has a unique positive zero p_n^*. The conclusion follows. ■

Remark 3: Theorem 1 reveals that cyclic gene networks mediated by sRNAs may have more than one positive equilibrium. Furthermore, the number of positive equilibria must be odd.

B. Characteristic Equation

Let $x_i(t) = m_i(t) - m_i^*$, $y_i(t) = s_i(t) - s_i^*$ and $z_i(t) = p_i(t) - p_i^*$. Then the linearized system of (1) around the equilibrium (M^*, S^*, P^*) takes the following form:

$$\begin{aligned}\dot{x}_i(t) &= -\left(c_i + d_i s_i^*\right)x_i(t) - d_i m_i^* y_i(t) \\ &\quad + g_i'\left(p_{i-1}^*\right)z_{i-1}\left(t - \tau_{pi-1}\right) \\ \dot{y}_i(t) &= -d_i s_i^* x_i(t) - \left(f_i + d_i m_i^*\right)y_i(t) \\ \dot{z}_i(t) &= a_i x_i(t - \tau_{mi}) - b_i z_i(t). \end{aligned} \tag{5}$$

The characteristic equation of network (1) is given by

$$\Delta(\lambda) = \det\begin{pmatrix} \lambda I_n + A & E & -N \\ D & \lambda I_n + B & 0 \\ -M & 0 & \lambda I_n + C \end{pmatrix} = 0 \tag{6}$$

where I_n is an $n \times n$ identity matrix. And

$$\begin{aligned} A &= \operatorname{diag}\left(c_1 + d_1 s_1^*, c_2 + d_2 s_2^*, \ldots, c_n + d_n s_n^*\right) \\ B &= \operatorname{diag}\left(f_1 + d_1 m_1^*, f_2 + d_2 m_2^*, \ldots, f_n + d_n m_n^*\right) \\ C &= \operatorname{diag}(b_1, b_2, \ldots, b_n) \\ D &= \operatorname{diag}\left(d_1 s_1^*, d_2 s_2^*, \ldots, d_n s_n^*\right) \\ E &= \operatorname{diag}\left(d_1 m_1^*, d_2 m_2^*, \ldots, d_n m_n^*\right) \\ M &= \operatorname{diag}\left(a_1 e^{-\lambda\tau_{m1}}, a_2 e^{-\lambda\tau_{m2}}, \ldots, a_n e^{-\lambda\tau_{mn}}\right) \end{aligned}$$

are all $n \times n$ diagonal matrices. $N = (n_{ij})$ is an $n \times n$ matrix, where $n_{ij} = g_i'(p_{i-1}^*)e^{-\lambda\tau_{pi-1}}$ if $j = i - 1$, and otherwise $n_{ij} = 0$. Let $\mathbb{C}$ represents the set of all complex numbers. Then a solution λ of the characteristic equation (6) is in $\mathbb{C}$. It can be seen by the definition of (1) that $n \times n$ matrices $\lambda I_n + A$, $I_n + B$, $\lambda I_n + C$, D, E, and M are all diagonal. With some calculation, (6) becomes

$$\begin{aligned}\Delta(\lambda) &= \det\Big((\lambda I_n + A) - N(\lambda I_n + A)^{-1}M - E(\lambda I_n + B)^{-1}D\Big) \\ &\quad \times \det(\lambda I_n + B) \times \det(\lambda I_n + C) \\ &= \prod_{i=1}^{n}(\lambda + b_i)\Big[\left(\lambda + f_i + d_i m_i^*\right)\left(\lambda + c_i + d_i s_i^*\right) - d_i^2 s_i^* m_i^*\Big] \\ &\quad - e^{-\lambda\tau}\prod_{i=1}^{n} a_i\left(\lambda + f_i + d_i m_i^*\right)g_i'\left(p_{i-1}^*\right) = 0 \end{aligned} \tag{7}$$

where

$$\tau = \sum_{i=1}^{n}\left(\tau_{mi} + \tau_{pi}\right).$$

Denote

$$L(\lambda) = \prod_{i=1}^{n}(\lambda + b_i)\Big[\left(\lambda + f_i + d_i m_i^*\right)\left(\lambda + c_i + d_i s_i^*\right) - d_i^2 s_i^* m_i^*\Big]$$
$$Q(\lambda) = \prod_{i=1}^{n} a_i\left(\lambda + f_i + d_i m_i^*\right)g_i'\left(p_{i-1}^*\right).$$

Then (7) is expressible as

$$\begin{aligned}\Delta(\lambda) &= L(\lambda) - Q(\lambda)e^{-\lambda\tau} \\ &= \lambda^{3n} + l_1\lambda^{3n-1} + \cdots + l_{3n-1}\lambda + l_{3n} \\ &\quad - \Big[q_0\lambda^n + q_1\lambda^{n-1} + \cdots + q_{n-1}\lambda + q_n\Big]e^{-\lambda\tau} \\ &= 0 \end{aligned} \tag{8}$$

where

$$l_{3n} = \prod_{i=1}^{n} b_i\left(f_i c_i + f_i d_i s_i^* + c_i d_i m_i^*\right) > 0$$
$$q_n = \prod_{i=1}^{n} a_i\left(f_i + d_i m_i^*\right)g_i'\left(p_{i-1}^*\right).$$

Let

$$\gamma = \frac{l_{3n}}{q_n} = \frac{\prod_{i=1}^{n} b_i\left(f_i c_i + f_i d_i s_i^* + c_i d_i m_i^*\right)}{\prod_{i=1}^{n} a_i\left(f_i + d_i m_i^*\right)g_i'\left(p_{i-1}^*\right)}$$

be the product of biochemical parameters and the concentration level of a certain equilibrium.

Remark 4: The distribution of roots of the characteristic equation is not dependent on each single delay, instead it relies upon the total of multiple delays. Moreover, the characteristic equation is influenced by a multiplication of each function between different gene nodes rather than a single function. Thus, the size of cyclic gene networks plays a vital role in the characteristic equation.

Remark 5: The sign of q_n is related closely to the quantity of repressors instead of activators. Specifically, the sign of q_n is decided by the quantity of repressors in terms of whether it is odd or even.

IV. Stability and Bifurcation Analysis

As we know, the distribution of characteristic roots determines whether equilibria in the cyclic gene network (1) involving sRNAs are stable or not. The equilibrium of network (1) is asymptotically stable if the real parts of the roots of the characteristic equations are all negative, while the equilibrium of network (1) is unstable if there is at least one characteristic root whose real part is positive [50]. In general, network (1) may suffer a loss of stability through two ways. Either the characteristic equation (7) has a pair of purely imaginary eigenvalues $\lambda = \pm i\omega$, or has a simple real eigenvalue $\lambda = 0$, with regard to certain value of the parameter. These two cases correspond to a Hopf bifurcation when $\lambda = \pm i\omega$ and a fold bifurcation when $\lambda = 0$, respectively [51].

A. Positive Cyclic Gene Networks

For a positive cyclic gene network, the total number ν of repressors is even and the network may have more than one equilibrium. Note that $q_n > 0$ and $\gamma > 0$.

Theorem 2: For the positive cyclic gene network (1), the following results hold.

1) If $\gamma < 1$, then an arbitrary equilibrium of network (1) is unstable for any time delay $\tau \geq 0$.
2) If $\gamma > 1$, then an arbitrary equilibrium of network (1) is locally asymptotically stable for any time delay $\tau \geq 0$.
3) When $\gamma = 1$, network (1) undergoes a fold bifurcation.

Proof: The value of γ decides the distribution of the characteristic roots of (7).

1) If $\gamma < 1$, then we have

$$\begin{aligned}\Delta(0) &= \prod_{i=1}^{n} b_i\Big[\big(f_i + d_i m_i^*\big)\big(c_i + d_i s_i^*\big) - d_i^2 m_i^* s_i^*\Big] \\ &\quad - \prod_{i=1}^{n} a_i\big(f_i + d_i m_i^*\big) g_i'\big(p_{i-1}^*\big) \\ &< 0.\end{aligned}$$

Moreover, note that $\Delta(+\infty) = \lim_{\lambda\to+\infty}\Delta(\lambda) = +\infty$. Due to the continuity of function $\Delta(\lambda)$, there is at least a root $\lambda_0 > 0$ satisfying $\Delta(\lambda_0) = 0$ for any $\tau \geq 0$. Thus, the conclusion follows.

2) Denote by C_+ the open right-half of the complex plane and by $\overline{C}_+$ its closure. Obviously, we have two analytic functions $L(\lambda)$ and $Q(\lambda)$ in $\overline{C}_+$. Thus,

$$|G(\lambda)| = \big|Q(\lambda)e^{-\lambda\tau}/L(\lambda)\big|, \ \forall\tau \geq 0$$

is subharmonic in $\overline{C}_+$ [52]. Based on the theory on subharmonic functions [52], we can get the $\sup_{\lambda\in\overline{C}_+}|G(\lambda)|$ shown at the top of the next page.

Thus, if $\gamma > 1$, then we have

$$|G(\lambda)| \leq \sup_{\lambda\in\overline{C}_+}|G(\lambda)| = \frac{1}{\gamma} < 1.$$

For any $\lambda \in \overline{C}_+$ and for any $\tau \geq 0$

$$|\Delta(\lambda)| = \big|L(\lambda) - Q(\lambda)e^{-\lambda\tau}\big| \geq |L(\lambda)| - \big|Q(\lambda)e^{-\lambda\tau}\big| > 0$$

which implies that (7) has no roots with non-negative real parts. So the conclusion follows immediately.

3) It is clearly seen that the characteristic equation (7) has a root $\lambda = 0$ when $\gamma = 1$. Hence, a fold bifurcation appears in network (1), which completes the proof. ■

Remark 6: Theorem 2 indicates that the stability of positive cyclic gene networks is delay-independent. The value of γ consisting of the equilibrium itself and biochemical factors decides whether an equilibrium has the local stability or instability for a positive cyclic gene network.

B. Negative Cyclic Gene Networks

For a negative cyclic gene network, there is an odd total number ν of repressors. A unique equilibrium is existent for this type of genetic format, and $q_n < 0$, $\gamma < 0$.

Let $i\omega(\omega > 0)$ be a root of (8). Then

$$L_R + iL_I - (Q_R + iQ_I)e^{-i\omega\tau} = 0 \tag{10}$$

where $L_R = \mathrm{Re}(L(i\omega))$, $Q_R = \mathrm{Re}(Q(i\omega))$, $L_I = \mathrm{Im}(L(i\omega))$, and $Q_I = \mathrm{Im}(Q(i\omega))$. So the following relations hold:

$$\begin{aligned}Q_R(\omega)\cos(\omega\tau) - Q_I(\omega)\sin(\omega\tau) &= L_R(\omega) \\ Q_R(\omega)\sin(\omega\tau) + Q_I(\omega)\cos(\omega\tau) &= L_I(\omega).\end{aligned} \tag{11}$$

Hence, ω satisfies the following equation:

$$L_R^2(\omega) + L_I^2(\omega) - Q_R^2(\omega) - Q_I^2(\omega) = 0. \tag{12}$$

Let

$$\begin{aligned}H(\omega) &= L_R^2(\omega) + L_I^2(\omega) - Q_R^2(\omega) - Q_I^2(\omega) \\ &= \omega^{6n} + r_2\omega^{6n-2} + \cdots + r_{6n-2}\omega^2 + r_{6n}\end{aligned}$$

where $r_{6n} = l_{3n}^2 - q_n^2$. Denote

$$h(z) = z^{3n} + r_2 z^{3n-1} + \cdots + r_{6n-2}z + r_{6n}. \tag{13}$$

Lemma 2: If $-1 < \gamma < 0$, then there exists at least one positive root for (12).

Proof: Obviously, if $-1 < \gamma < 0$, then we have that

$$\begin{aligned}H(0) = r_{6n} &= \left[\prod_{i=1}^{n} b_i\big(f_i c_i + f_i d_i s_i^* + c_i d_i m_i^*\big)\right]^2 \\ &\quad - \left[\prod_{i=1}^{n} a_i\big(f_i + d_i m_i^*\big) g_i'\big(p_{i-1}^*\big)\right]^2 \\ &< 0.\end{aligned}$$

Considering the continuity of $H(\omega)$ and $\lim_{\omega\to+\infty}H(\omega) = +\infty$, there thus exists at least one positive root for (12). ■

Assume that there exist positive roots for (12). Without loss of generality, we suppose that for (12) there are at most $3n$ positive roots, denoted by $\omega_k, k = 1, 2, \ldots, 3n$. From (11), we have

$$\cos(\omega_k\tau) = \frac{L_R(\omega_k)Q_R(\omega_k) + L_I(\omega_k)Q_I(\omega_k)}{Q_R^2(\omega_k) + Q_I^2(\omega_k)}.$$

Thus, if we define

$$\tau_j^{(k)} = \frac{1}{\omega_k}\left(\arccos\frac{L_R(\omega_k)Q_R(\omega_k) + L_I(\omega_k)Q_I(\omega_k)}{Q_R^2(\omega_k) + Q_I^2(\omega_k)} + 2j\pi\right) \tag{14}$$

$$\begin{aligned}\sup_{\lambda\in\overline{C}_+}|G(\lambda)| &= \sup_{\omega\geq 0}|G(i\omega)| = \sup_{\omega\geq 0}\left|\frac{Q(i\omega)e^{-i\omega\tau}}{L(i\omega)}\right| \\ &= \sup_{\omega\geq 0}\frac{\left|\prod_{i=1}^{n}a_i\left(i\omega+f_i+d_im_i^*\right)g_i'\left(p_{i-1}^*\right)\right|}{\left|\prod_{i=1}^{n}(i\omega+b_i)\left[\left(i\omega+f_i+d_im_i^*\right)\left(i\omega+c_i+d_is_i^*\right)-d_i^2s_i^*m_i^*\right]\right|} \\ &= \sup_{\omega\geq 0}\frac{\prod_{i=1}^{n}a_i\sqrt{\omega^2+\left(f_i+d_im_i^*\right)^2}g_i'\left(p_{i-1}^*\right)}{\prod_{i=1}^{n}\sqrt{\omega^2+b_i^2}\sqrt{\omega^4+\left[\left(f_i+d_im_i^*\right)^2+\left(c_i+d_is_i^*\right)^2+2d_i^2m_i^*s_i^*\right]\omega^2+\left(f_ic_i+f_id_is_i^*+c_id_im_i^*\right)^2}} \\ &= \frac{\prod_{i=1}^{n}a_i\left(f_i+d_im_i^*\right)g_i'\left(p_{i-1}^*\right)}{\prod_{i=1}^{n}b_i\left(f_ic_i+f_id_is_i^*+c_id_im_i^*\right)} \\ &= \frac{1}{\gamma} \end{aligned} \tag{9}$$

where $j=0,1,\ldots;k=1,2,\ldots,3n$, then there are a pair of purely imaginary roots $\pm i\omega_k$ for (7) when $\tau=\tau_j^{(k)}$. Denote

$$\tau_0=\tau_0^{(k_0)}=\min_{k\in\{1,2,\ldots,3n\}}\{\tau_0^{(k)}\},\quad \omega_0=\omega_{k_0}. \tag{15}$$

Next, we discuss (7) based on a result in [53].

Lemma 3 [53]: Introduce the exponential polynomial

$$\begin{aligned}&P\left(\lambda,e^{-\lambda\tau_1},\ldots,e^{-\lambda\tau_m}\right)\\ &\quad=\lambda^n+p_1^{(0)}\lambda^{n-1}+\cdots+p_{n-1}^{(0)}\lambda+p_n^{(0)}\\ &\qquad+\left[p_1^{(1)}\lambda^{n-1}+\cdots+p_{n-1}^{(1)}\lambda+p_n^{(1)}\right]e^{-\lambda\tau_1}+\cdots\\ &\qquad+\left[p_1^{(m)}\lambda^{n-1}+\cdots+p_{n-1}^{(m)}\lambda+p_n^{(m)}\right]e^{-\lambda\tau_m}\end{aligned}$$

where $\tau_i\geq 0$ $(i=1,2,\ldots,m)$, and $p_j^{(i)}$ $(i=0,1,\ldots,m;j=1,2,\ldots,n)$ are known coefficients. When $(\tau_1,\tau_2,\ldots,\tau_m)$ changes, the total of the order of the zeros of $P(\lambda,\ e^{-\lambda\tau_1},\ldots,e^{-\lambda\tau_m})$ on C_+ will vary only if there is a zero occurring on or crossing the imaginary axis.

Suppose that (7) has the root $\lambda(\tau)=\alpha(\tau)+i\omega(\tau)$ which satisfies $\alpha(\tau_j^{(k)})=0$ and $\omega(\tau_j^{(k)})=\omega_k$. Then, we have the transversality condition stated as follows.

Lemma 4: If $z_k=\omega_k^2$ and $h'(z_k)\neq 0$, in which $h(z)$ is as given in (13), then we have

$$\left[\frac{d(\mathrm{Re}\lambda(\tau))}{d\tau}\right]_{\tau=\tau_j^{(k)}}\neq 0$$

with the sign of $[(d(\mathrm{Re}\lambda(\tau)))/d\tau]_{\tau=\tau_j^{(k)}}$ being in agreement with that of $h'(z_k)$.

The proof of Lemma 4 follows the same steps as the proof of [34, Lemma 2], and thus is skipped here.

If $\tau=0$, then (7) turns into

$$\Delta(\lambda)=\lambda^{3n}+u_{3n-1}\lambda^{3n-1}+\cdots+u_1\lambda+u_0=0 \tag{16}$$

where $u_{3n-1}=l_1,u_{3n-2}=l_2,\ldots,u_{n+1}=l_{2n-1}$, and $u_n=l_{2n}-q_0,u_{n-1}=l_{2n+1}-q_1,\ldots,u_1=l_{3n-1}-q_{n-1},u_0=l_{3n}-q_n$.

Define $T_1,T_2,T_3,\ldots,T_{3n}$ as shown at the bottom of the next page, where $u_i=0$ for $i<0$.

Theorem 3: If $-1<\gamma<0$, $h'(z_0)>0$, $u_i>0$ $(i=0,1,\ldots,3n-1)$, and $T_i>0$ $(i=1,2,\ldots,3n)$, then the unique equilibrium (M^*,S^*,P^*) of the negative cyclic gene network (1) is locally asymptotically stable for $\tau\in[0,\tau_0)$, a Hopf bifurcation occurs at the critical value $\tau=\tau_0$, and the equilibrium becomes unstable when $\tau>\tau_0$, with τ_0 being as defined in (15).

Proof: If all the coefficients, u_i $(i=0,1,\ldots,3n-1)$ of the characteristic equation (16), and T_i $(i=1,2,\ldots,3n)$ are positive, then it follows from the Routh–Hurwitz criterion [54] that the real parts of the eigenvalues of (16) are all negative. That is to say, the real parts of the eigenvalues of (7) are all negative when $\tau=0$. It is also evident from Lemma 2 that if $-1<\gamma<0$, then (12) has at least one positive eigenvalue. This implies that there exist purely imaginary roots $\pm i\omega_k$ for (7) when $\tau=\tau_j^{(k)}$. Clearly, τ_0 is the smallest value of $\tau_j^{(k)}$ to ensure that there exist a pair of complex roots $\pm i\omega_0$ for (7) when $\tau=\tau_0$. It can be seen from Lemma 3 that the number of the roots with positive real parts of (7) is the same as the one of (16) when $\tau\in[0,\tau_0)$. Thus, the real parts of the roots of (7) are all negative when $\tau\in[0,\tau_0)$, which indicates that the equilibrium of network (1) is stable.

It is obvious from Lemma 4 that $[(d(\mathrm{Re}\lambda(\tau)))/d\tau]_{\tau=\tau_0}>0$ if $h'(z_0)>0$. This implies that there exist at least a couple of roots with positive real parts for (7) when $\tau>\tau_0$. Therefore, the equilibrium of (1) is unstable.

From Lemma 4, the transversality condition of Hopf bifurcations is reached under the given conditions. Thereby, network (1) undergoes a Hopf bifurcation when $\tau=\tau_0$. ■

Remark 7: Theorem 3 indicates that the stability of negative cyclic gene networks is delay-dependent.

V. Numerical Simulations

Two specific cyclic networks with three gene nodes are provided to verify the theoretical findings given in the preceding sections. One is a synthetic positive cyclic gene network [30], and the other is a synthetic negative cyclic gene network, which is called the "repressilator" [4], [25], [29]. Fig. 2 shows the schematic of tri-node cyclic structure, where the symbol "$\rightarrow$" stands for the activation of one node to another, while the symbol "$\dashv$" means the inhibition of one node to another.

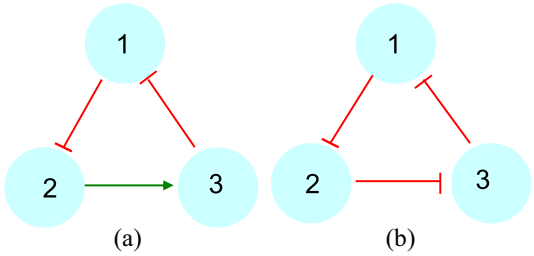

Fig. 2. Schematic of tri-node ring structure. (a) Positive cyclic genetic regulatory network. (b) Negative cyclic genetic regulatory network.

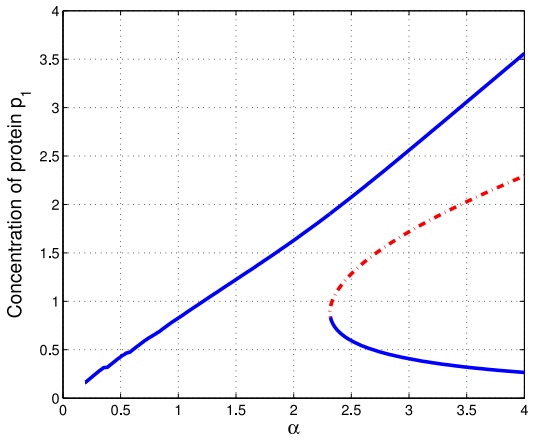

Fig. 3. Fold bifurcation diagram of equilibria of the positive cyclic gene network (17) with $c = 1, b = 0.2, a = 0.2, d = 0.3, e = 0.5, f = 0.6, h = 2$ and the transcription coefficient α as the bifurcation parameter.

Example 1: Consider the following positive cyclic gene network with three nodes depicted in Fig. 2(a):

$$\begin{aligned}
\dot{m}_1(t) &= -cm_1(t) - ds_1(t)m_1(t) + \frac{\alpha}{1+p_3^h(t-\tau_{p3})}\\
\dot{m}_2(t) &= -cm_2(t) - ds_2(t)m_2(t) + \frac{\alpha}{1+p_1^h(t-\tau_{p1})}\\
\dot{m}_3(t) &= -cm_3(t) - ds_3(t)m_3(t) + \frac{\alpha p_2^h(t-\tau_{p2})}{1+p_2^h(t-\tau_{p2})}\\
\dot{s}_i(t) &= e - ds_i(t)m_i(t) - fs_i(t)\\
\dot{p}_i(t) &= -bp_i(t) + am_i(t-\tau_{mi}), \quad i = 1,2,3. \qquad (17)
\end{aligned}$$

In this positive cyclic gene network, $c_i = c$, $d_i = d$, $e_i = e$, $f_i = f$, $b_i = b$, $a_i = a$, $h_i = h$, and $\alpha_i = \alpha$, $i = 1, 2, 3$. From Theorem 1, it is known that the positive tri-gene cyclic network (17) has more than one positive equilibrium, and there must be an odd number of equilibria.

It should be mentioned that the existence of fold bifurcations was examined for positive cyclic gene networks without sRNAs in [29], [30], and [36]. We will illustrate that the fold bifurcation may also occur in positive cyclic gene networks with sRNAs. Take $c = 1$, $b = 0.2$, $a = 0.2$, $d = 0.3$, $e = 0.5$, $f = 0.6, h = 2$ and choose the transcription coefficient α as the bifurcation parameter. Fig. 3 displays the fold bifurcation diagram of equilibria in terms of the parameter α for network (17), in which blue solid curves stand for the stable concentration of protein p_1, while red dashed-dotted curves stand for the unstable concentration of protein p_1.

Fig. 3 illustrates the effect of the transcription coefficient α on the equilibrium of protein p_1. For small values of α, only a stable positive equilibrium exists, and the equilibrium concentration of protein p_1 is increasing with α. When α increases and passes through the critical value $\alpha_0 = 2.3195$, a fold bifurcation will appear. Meanwhile, three positive equilibria emerge for the positive tri-gene cyclic network (17), with two stable equilibria and one unstable equilibrium, for sufficiently big values of α. It should be pointed out that the maximum number of equilibria for positive cyclic gene networks depends on the size of networks (the number of gene nodes). The greater the size of the network is, the higher chance there occur multiple equilibria. Each equilibrium may have different stability features, and the multistability occurs for positive gene cyclic networks.

Let $\alpha = 2 < \alpha_0$, and all the other parameters are fixed. A positive equilibrium (M^*, S^*, P^*) uniquely exists for network (17), where $m_1^* = 1.6291$, $m_2^* = 0.4547$, $m_3^* = 0.2811$, $s_1^* = 0.4592$, $s_2^* = 0.679$, $s_3^* = 0.7306$, $p_1^* = 1.6291$, $p_2^* = 0.4547$, $p_3^* = 0.2811$. It follows that the parameter γ for the equilibrium (M^*, S^*, P^*) is $\gamma = 2.3864 > 1$. By Theorem 2, the unique equilibrium (M^*, S^*, P^*) of network (17) is delay-independently stable. Dynamical trajectories under different initial conditions with random values eventually approach the positive equilibrium (M^*, S^*, P^*), which can be observed in Fig. 4.

When $\alpha = 2.5 > \alpha_0$, there are three positive equilibria for network (17)

$$\begin{aligned}
\left(M^{1*}, S^{1*}, P^{1*}\right) &= (2.0757, 0.3894, 0.2698, 0.4089, 0.6975\\
&\quad 0.7343, 2.0757, 0.3894, 0.2698)\\
\left(M^{2*}, S^{2*}, P^{2*}\right) &= (0.593, 1.6254, 1.592, 0.6428, 0.4597\\
&\quad 0.464, 0.593, 1.6254, 1.592)\\
\left(M^{3*}, S^{3*}, P^{3*}\right) &= (1.2832, 0.8015, 0.8311, 0.5076, 0.5949\\
&\quad 0.5887, 1.2832, 0.8015, 0.8311)
\end{aligned}$$

where $(M^{i*}, S^{i*}, P^{i*}) = (m_1^{i*}, m_2^{i*}, m_3^{i*}, s_1^{i*}, s_2^{i*}, s_3^{i*}, p_1^{i*}, p_2^{i*}, p_3^{i*})$, $i = 1, 2, 3$. For these three equilibria, the parameters γ are $\gamma_1 = 2.2476 > 1$, $\gamma_2 = 2.0841 > 1$, and $\gamma_3 = 0.707 < 1$, respectively. By Theorem 2, the equilibria (M^{1*}, S^{1*}, P^{1*}) and (M^{2*}, S^{2*}, P^{2*}) of network (17) are locally delay-independently stable, while the equilibrium (M^{3*}, S^{3*}, P^{3*}) is unstable. Different initial conditions determine the ultimate convergence of network (17) to which

$$T_1 = u_{3n-1},\ T_2 = \begin{vmatrix} u_{3n-1} & 1 \\ u_{3n-3} & u_{3n-2} \end{vmatrix},\ T_3 = \begin{vmatrix} u_{3n-1} & 1 & 0 \\ u_{3n-3} & u_{3n-2} & u_{3n-1} \\ u_{3n-5} & u_{3n-4} & u_{3n-3} \end{vmatrix}, \ldots, T_{3n} = \begin{vmatrix} u_{3n-1} & \cdots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \cdots & u_0 \end{vmatrix}$$

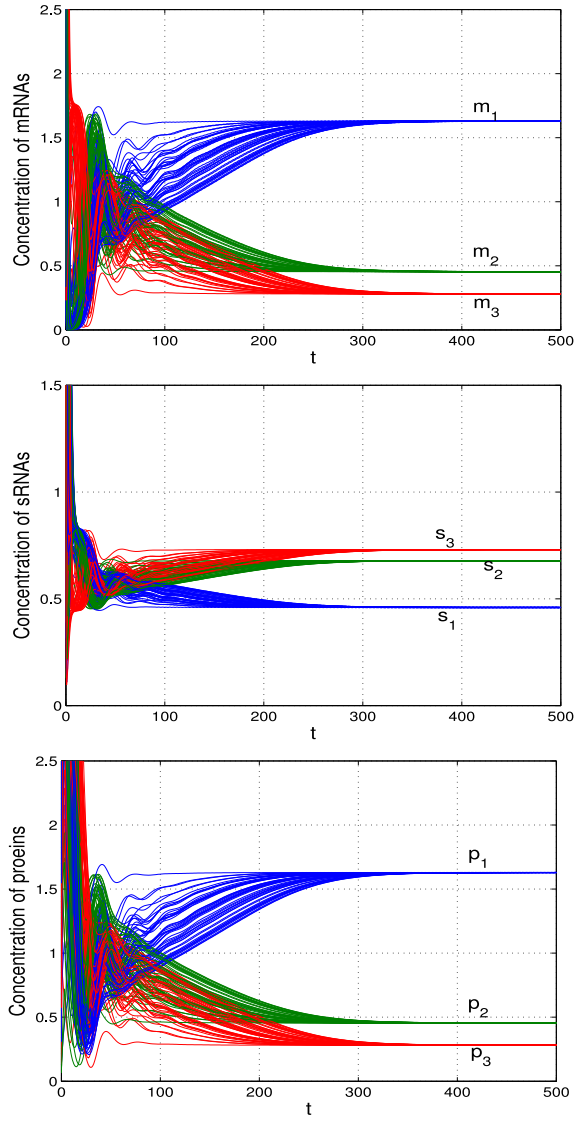

Fig. 4. Waveform plots of the positive cyclic gene network (17) with $c = 1, b = 0.2, a = 0.2, d = 0.3, e = 0.5, f = 0.6, h = 2$, $\tau_{p1} = \tau_{p2} = \tau_{p3} = 2, \tau_{m1} = \tau_{m2} = \tau_{m3} = 3$, and $\alpha = 2 < \alpha_0$. Network (17) has local delay-independent stability around the equilibrium (M^*, S^*, P^*). Initial conditions are $(M_0, S_0, P_0) = i \times (\zeta_1, \zeta_2, \ldots, \zeta_9), i = 1, 2, \ldots, 50$, where $\zeta_j (i = 1, 2, \ldots, 9)$ are the random numbers between 0 and 1.

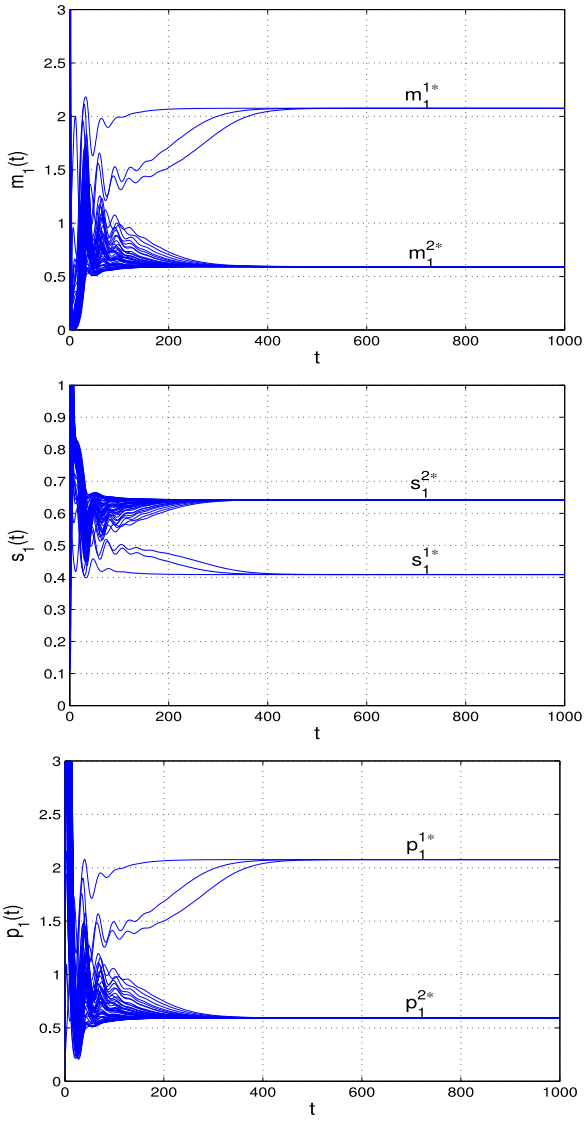

Fig. 5. Waveform plots of the positive cyclic genetic regulatory network (17) with $c = 1, b = 0.2, a = 0.2, d = 0.3, e = 0.5, f = 0.6, h = 2$, $\tau_{p1} = \tau_{p2} = \tau_{p3} = 2, \tau_{m1} = \tau_{m2} = \tau_{m3} = 3$, and $\alpha = 2.5 > \alpha_0$. Network (17) has local delay-independent stability around the equilibria (M^{1*}, S^{1*}, P^{1*}) and (M^{2*}, S^{2*}, P^{2*}). Initial conditions are $(M_0, S_0, P_0) = i \times (\zeta_1, \zeta_2, \ldots, \zeta_9), i = 1, 2, \ldots, 50$, where $\zeta_j (i = 1, 2, \ldots, 9)$ are the random numbers between 0 and 1.

equilibrium, (M^{1*}, S^{1*}, P^{1*}) or (M^{2*}, S^{2*}, P^{2*}). Under different initial conditions with random values, the tri-gene positive cyclic network (17) presents the phenomenon of bistability as illustrated in Fig. 5. The trajectories of network (17) with different initial conditions converge to either (M^{1*}, S^{1*}, P^{1*}) or (M^{2*}, S^{2*}, P^{2*}).

Example 2: Consider the negative cyclic gene network (repressilator) with three nodes illustrated in Fig. 2(b)

$$\begin{aligned} \dot{m}_i(t) &= -cm_i(t) - ds_i(t)m_i(t) + \frac{\alpha}{1 + p_{i-1}^h\big(t - \tau_{pi-1}\big)} \\ \dot{s}_i(t) &= e - ds_i(t)m_i(t) - fs_i(t) \\ \dot{p}_i(t) &= -bp_i(t) + am_i(t - \tau_{mi}), \quad i = 1, 2, 3. \end{aligned} \tag{18}$$

The repressilator network (18) is cyclically symmetrical, where $c_i = c$, $d_i = d$, $e_i = e$, $f_i = f$, $b_i = b$, $a_i = a$, $h_i = h$, and $\alpha_i = \alpha$, $i = 1, 2, 3$. According to Theorem 1, we can see that a positive equilibrium (M^*, S^*, P^*) is uniquely existent for the repressilator network (18) and it satisfies that $m_1^* = m_2^* = m_3^*$, $s_1^* = s_2^* = s_3^*$, and $p_1^* = p_2^* = p_3^*$.

We choose the total delay τ as the bifurcation parameter and take $c = 2, b = 2.5, d = 1, e = 1, f = 0.5, a = 1, h = 2$, and $\alpha = 10$. Next, we explore the Hopf bifurcation in the repressilatory network (18). In this case, for network (18), there exists a unique positive equilibrium given by

$$\begin{aligned} \big(M^*, S^*, P^*\big) = (&2.2987, 2.2987, 2.2987, 0.3573, 0.3573 \\ &0.3573, 0.9195, 0.9195, 0.9195). \end{aligned}$$

By calculation, the real parts of the roots of (16) are all negative. So the repressilator network (18) has local stability when $\tau = \sum_{i=1}^{3}(\tau_{mi} + \tau_{pi}) = 0$. It should be mentioned

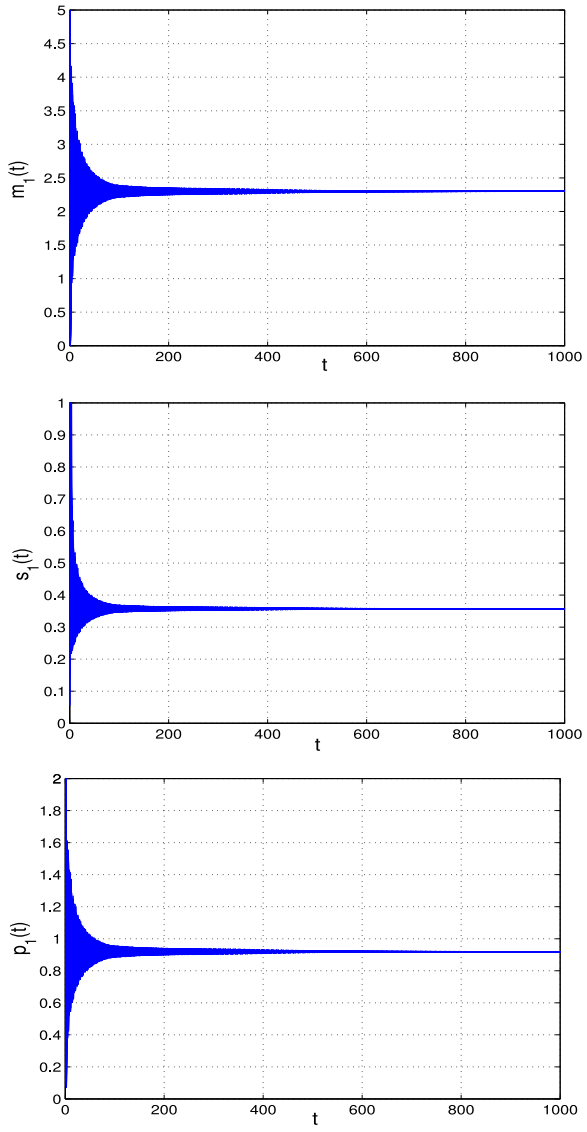

Fig. 6. Waveform plots of the negative cyclic genetic regulatory network (18) with $c = 2, b = 2.5, d = 1, e = 1, f = 0.5, a = 1, h = 2, \alpha = 10$, and the initial condition $(M_0, S_0, P_0) = i \times (\zeta_1, \zeta_2, \ldots, \zeta_9), i = 1, 2, \ldots, 50$, where $\zeta_j (i = 1, 2, \ldots, 9)$ are the random numbers between 0 and 1. Network (18) is asymptotically stable at the unique equilibrium (M^*, S^*, P^*), where $\tau = \sum_{i=1}^{3}(\tau_{mi} + \tau_{pi}) = 2.1 < \tau_0 = 2.2496$.

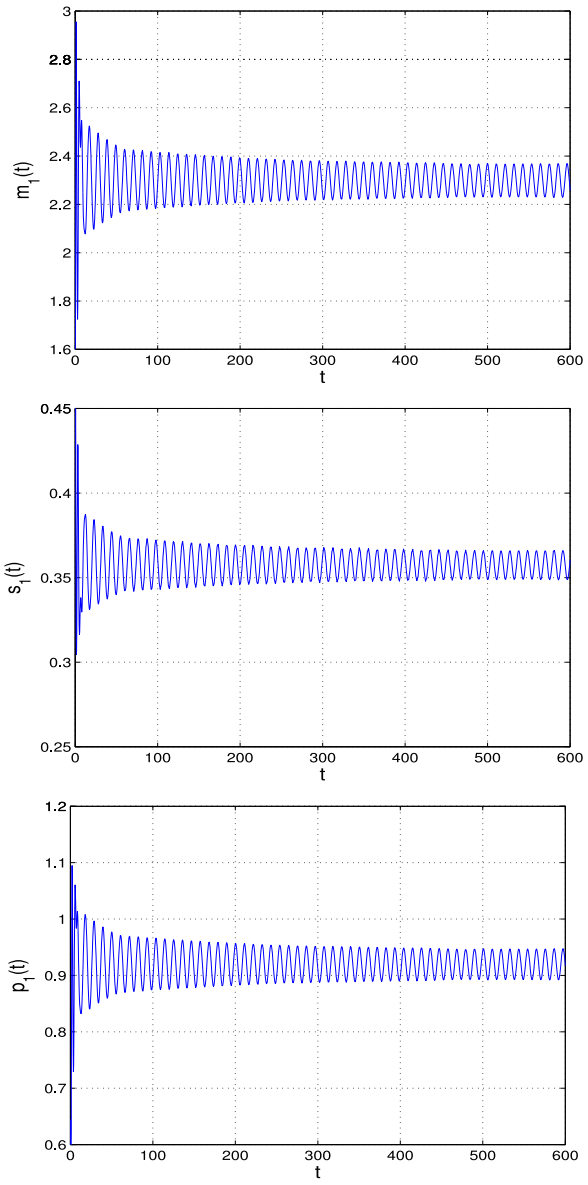

Fig. 7. Waveform plots of the negative cyclic genetic regulatory network (18) with $c = 2, b = 2.5, d = 1, e = 1, f = 0.5, a = 1, h = 2, \alpha = 10$, and the initial condition $(M_0, S_0, P_0) = (\zeta_1, \zeta_2, \ldots, \zeta_9)$, where $\zeta_j (i = 1, 2, \ldots, 9)$ are the random numbers between 0 and 1. The periodic oscillations occur, where $\tau = \sum_{i=1}^{3}(\tau_{mi} + \tau_{pi}) = 2.6 > \tau_0 = 2.2496$.

that network (18) is not locally delay-independently stable, but is delay-dependently stable. It can be calculated that $\gamma = -0.8725 \in (-1, 0)$, which satisfies the condition stated in Lemma 2. Then there is the positive root $\omega_0 = 0.4405$ for (12), which is also unique. From (14), the critical value is given by $\tau_0 = 2.2496$. It can be seen from Theorem 3 that network (18) is locally stable at the equilibrium (M^*, S^*, P^*) for $\tau \in [0, \tau_0)$, but unstable for $\tau \in (\tau_0, +\infty)$. Figs. 6 and 7 illustrate the transition between the stable equilibrium and periodic oscillation as the total delay τ varies. The trajectories of (18) converge to (M^*, S^*, P^*) when $\tau = 2.1 < \tau_0$ as shown in Fig. 6. A Hopf bifurcation occurs for network (18) when $\tau = \tau_0$. The oscillator trajectories of (18) are displayed when $\tau = 2.6 > \tau_0$ in Fig. 7. It can be found from Fig. 8 that the amplitudes of oscillators increase evidently with the total delay τ.

Example 3: In this example, we apply our theoretical results to large-scale cyclic networks consisting of a large number of genes and study the effect of the network size (the number of genes) on the dynamics of cyclic gene regulatory networks. Consider the following general high-dimensional negative cyclic gene network with n genes:

$$\begin{aligned} \dot{m}_i(t) &= -cm_i(t) - ds_i(t)m_i(t) + \frac{\alpha}{1 + p_{i-1}^h(t - \tau_p)} \\ \dot{s}_i(t) &= e - ds_i(t)m_i(t) - fs_i(t) \\ \dot{p}_i(t) &= -\mu p_i(t) + \mu m_i(t - \tau_m), \quad i = 1, 2, \ldots, n \end{aligned} \tag{19}$$

where n is an odd number. To investigate the essential dynamical properties of large-scale cyclic genetic regulatory networks, we make a simplification that $c_i = c$, $d_i = d$, $e_i = e$,

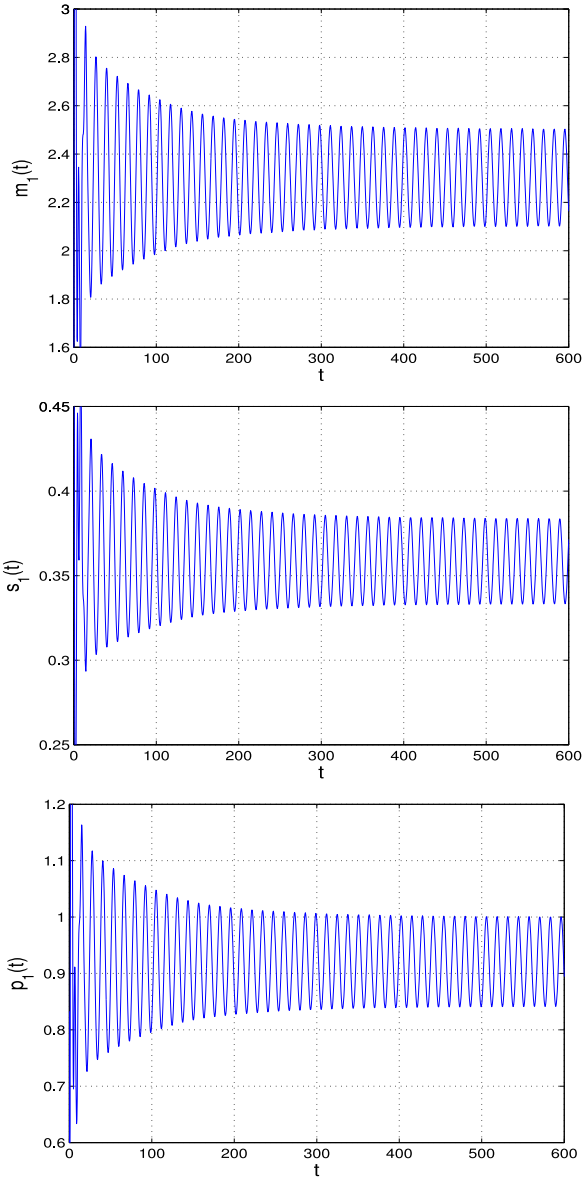

Fig. 8. Waveform plots of the negative cyclic genetic regulatory network (18) with $c = 2, b = 2.5, d = 1, e = 1, f = 0.5, a = 1, h = 2, \alpha = 10$, and the initial condition $(M_0, S_0, P_0) = (\zeta_1, \zeta_2, \ldots, \zeta_9)$, where $\zeta_j (i = 1, 2, \ldots, 9)$ are the random numbers between 0 and 1. The large-amplitude oscillations occur, where $\tau = \sum_{i=1}^{3}(\tau_{mi} + \tau_{pi}) = 3.7 > \tau_0 = 2.2496$.

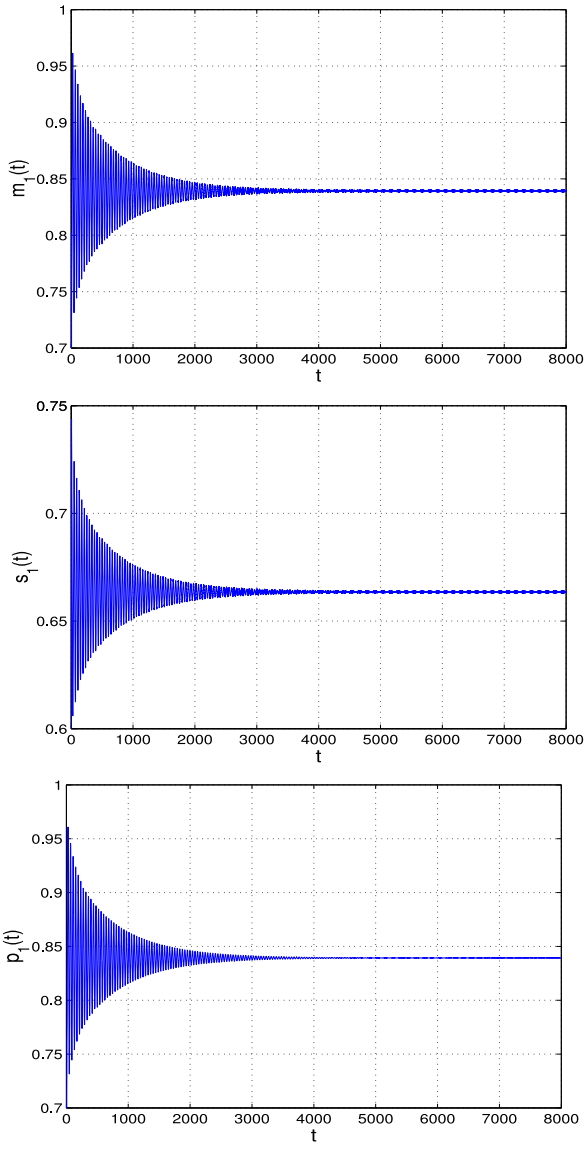

Fig. 9. Waveform plots of the negative cyclic gene regulatory network (19) with $n = 9, c = 1, \mu = 1, e = 0.5, d = 0.6, f = 0.25, h = 2, \alpha = 2$, and the initial condition $(M_0, S_0, P_0) = (\zeta_1, \zeta_2, \ldots, \zeta_9)$, where $\zeta_j (i = 1, 2, \ldots, 9)$ are the random numbers between 0 and 1. Network (19) is asymptotically stable at the unique equilibrium (M^*, S^*, P^*), where $\tau = 9 \times (\tau_m + \tau_p) = 1.8 < \tau_0 = 8.2858$.

$f_i = f$, $a_i = b_i = \mu$, $h_i = h$, $\alpha_i = \alpha$, $\tau_{mi} = \tau_m$, and $\tau_{pi} = \tau_p$, $i = 1, 2, \ldots, n$ in (1). Noted that such a simplification is natural and standard for exploring qualitative properties of biochemical systems [4], [55], [56]. It can be seen that network (19) considered in this example is a generalization of the repressilator network with $n = 3$ genes [4], the pentilator network with $n = 5$ genes [55], and the negative cyclic network with $n = 7$ genes [32]. However, the network model in the previous literatures did not consider the function effect of sRNAs in gene regulation processes.

We set the parameters as follows: $c = 1, \mu = 1, e = 0.5, d = 0.6, f = 0.25, h = 2$, and $\alpha = 2$. The number of genes is $n = 9$. The unique positive equilibrium of network (19) is then calculated as (M^*, S^*, P^*), where $m_i^* = 0.8393$, $s_i^* = 0.6635$ and $p_i^* = 0.8393$, $i = 1, 2, \ldots, 9$. Note that the condition $\gamma = -0.8306 \in (-1, 0)$ in Lemma 2 is reached. Therefore, we know that (12) has at least one positive root. By calculation, one can find that the unique positive solution of (12) is $\omega_0 = 0.113$. Thus, the critical value defined in (14) is $\tau_0 = 8.2858$. According to Theorem 3, we can see that the positive equilibrium (M^*, S^*, P^*) of the negative cyclic genetic network (19) with $n = 9$ is asymptotically stable when $\tau < \tau_0 = 8.2858$ and unstable when $\tau > \tau_0$. A Hopf bifurcation occurs, i.e., a periodic oscillation bifurcates from the positive equilibrium (M^*, S^*, P^*) when τ crosses through the critical values as shown in Figs. 9 and 10.

VI. Biological Insights

In this section, from a biological viewpoint, we reveal the effects of parameters and structures on the dynamics of genetic

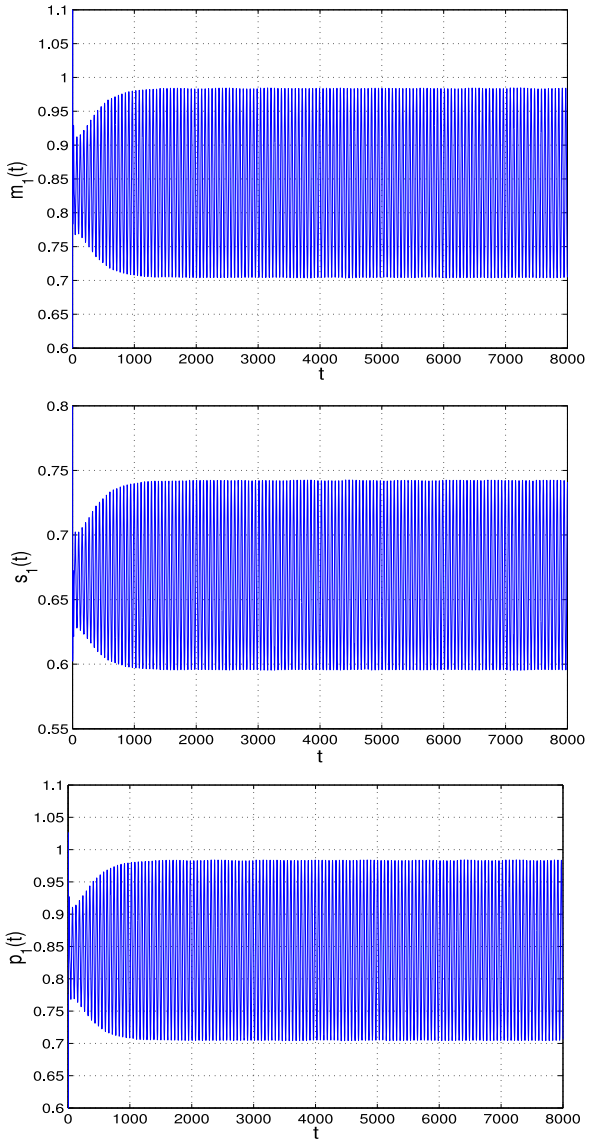

Fig. 10. Waveform plots of the negative cyclic gene regulatory network (19) with $n = 9, c = 1, \mu = 1, e = 0.5, d = 0.6, f = 0.25, h = 2, \alpha = 2$, and the initial condition $(M_0, S_0, P_0) = (\zeta_1, \zeta_2, \ldots, \zeta_9)$, where $\zeta_j (i = 1, 2, \ldots, 9)$ are the random numbers between 0 and 1. The periodic oscillations occur, where $\tau = 9 \times (\tau_m + \tau_p) = 8.46 > \tau_0 = 8.2858$.

regulatory networks with sRNAs. This provides a guideline for the design of experiments and the construction of gene oscillators.

A. Existence of Equilibria

The analytic conditions of Theorem 1 indicate that cyclic genetic regulatory networks including sRNAs tend to have an odd number of equilibria.

The parameter ν is an original quantity that denotes the number of repressors, and it plays important roles for not only the existence of equilibria but also the profiles of bifurcations. In practice, when ν is odd, the cyclic genetic regulatory network with sRNAs has a unique equilibrium; when ν is even, the cyclic genetic regulatory network with sRNAs has an odd number of equilibria and there may be more than one equilibrium.

TABLE I
VALUES OF ω_0 AND τ_0 FOR (19) WITH $c = 1$, $\mu = 1$, $e = 0.5$, $d = 0.6$, $f = 0.25$, $h = 2$, $\alpha = 2$ AND DIFFERENT VALUES OF n: $n = 1$, 3, 5, 7, AND 9

Number of genes	ω_0	τ_0
n=1	0.5314	28.2963
n=3	0.1137	21.1201
n=5	0.1138	16.7536
n=7	0.1137	12.4169
n=9	0.113	8.2858

The number of genes, n, represents the size of gene networks, which has an important influence on the number of equilibria and dynamical behaviors of positive cyclic genetic networks with sRNAs. The parameter n is associated with the degree of nonlinearity $\Psi(\cdot)$. A large n means the high nonlinearity. In particular, a large n implies more equilibria for positive cyclic genetic networks with sRNAs.

The large Hill coefficient, h_i, indicates the high nonlinearity of $g_i(\cdot)$. The gene networks with a relatively large Hill coefficient are more likely to have more equilibria.

B. Fold Bifurcation

The parameter γ is a synthetic quantity proposed in this paper, which has a significant impact on the stability and fold bifurcation of positive cyclic gene networks with sRNAs. It can be concluded from Theorem 2 that the large γ actually implies a more stable equilibrium.

The positive cyclic genetic network mediated by sRNAs may have more equilibria as the parameters n and h_i get larger. This means that the positive network consisting of a large number of genes and bigger Hill coefficients are more likely to generate fold bifurcations.

C. Hopf Bifurcation

As a result of cyclic structure, the total delay τ plays a key role rather than the individual delays among each gene. The large n and τ mean that the cyclic network has a large delay in the loop. This coincides with the intuition that the closed-loop network with a large loop delay tends to become unstable.

Table I shows the effect of the number of genes on the values of ω_0 and τ_0. It is obvious that the critical value τ_0 decreases clearly with the number n of genes increasing, implying that the value of τ_0 is sensitive to the change of the number of genes. We can conclude from Table I that the networks consisting of a large number of genes are difficult to maintain stable in the presence of a larger total delay, and are more likely to have a Hopf bifurcation when the total delay τ varies. This also means that the networks with a large number of genes tend to have periodic oscillations.

Moreover, Figs. 11 and 12 reflect the effect of τ on the amplitude and frequency of $p_i(t)$ for the negative cyclic gene regulatory network (19) with $n = 9$, respectively. To be specific, the amplitude increases with the delay τ, while the frequency gets smaller with the delay τ becoming bigger. This

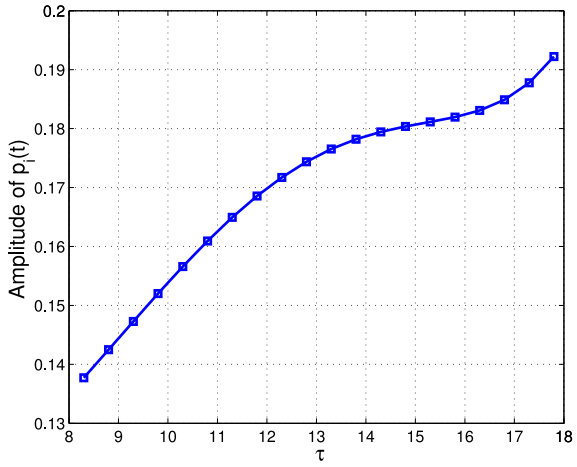

Fig. 11. Amplitude of $p_i(t)$ depending on τ for the negative cyclic gene regulatory network (19) with $n = 9, c = 1, \mu = 1, e = 0.5, d = 0.6, f = 0.25, h = 2$, and $\alpha = 2$.

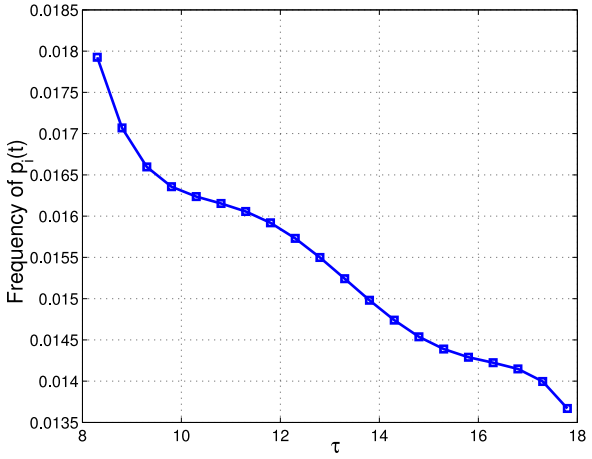

Fig. 12. Frequency of $p_i(t)$ depending on τ for the negative cyclic gene regulatory network (19) with $n = 9, c = 1, \mu = 1, e = 0.5, d = 0.6, f = 0.25, h = 2$, and $\alpha = 2$.

suggests that one may choose the appropriate value of τ to obtain the desired oscillation of the Hopf bifurcation.

VII. Conclusion

It has been proved by experiments that sRNAs take a significant role in gene regulation processes. Thus, it is very important to introduce sRNAs to regulate gene expressions in real gene networks. In this paper, sRNAs have been incorporated into a new dynamical model for cyclic gene networks, which is described by high-dimensional delay differential equations. The existence of equilibria has been verified and the stability and bifurcations have been investigated by analyzing the distribution of characteristic roots. It has been demonstrated that the dynamics of cyclic gene networks mainly depends on the number of repressors, the multiplication of functions, and the sum of delays.

For a positive cyclic gene network with an even number of repressors, more than one equilibrium probably exists, and the value of γ composed of the Hill coefficient, the biochemical parameters, and the equilibrium itself decides the stability of each equilibrium. Moreover, the stability of the equilibrium is delay-independent. When the positive cyclic gene network has more than one equilibrium, the multistability may occur.

For a negative cyclic gene network with an odd number of repressors, there exists a unique equilibrium. Unlike the delay-independent stability of positive cyclic gene networks, the stability of the equilibrium is delay-dependent for negative cyclic gene networks. Therefore, the stability of the equilibrium is decided not only by the biochemical parameters, the Hill coefficient and the equilibrium itself, but also by multiple delays. The total delay can switch the negative cyclic gene networks between the stable states and unstable states and a Hopf bifurcation may occur when the stability of the equilibrium changes.

Moreover, some biological insights have been derived. With increasing the number of genes, the critical value of the total delay decreases clearly. Furthermore, the amplitude of bifurcating oscillations grows apparently along the total delay, while the frequency of oscillations decreases with the increase of the total delay. These insights can be a useful guidance in constructing synthetic gene circuits and designing experiments.

It is worth noting that the global stability of the equilibrium and stability of periodic oscillations are very important for gene networks which are not involved in this paper. Thus, our future work will be devoted to the global stability analysis and the direction and stability of the bifurcating periodic oscillations for gene networks.

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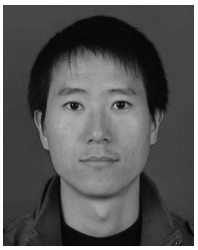

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