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Monostability, bistability, periodicity and chaos in gene regulatory network

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Abstract. This letter gives a general review on the monostability, bistability, periodicity and chaos in gene regulatory network. Some simple motifs that generate monostability, bistability, periodicity and chaos are analytically and numerically reported. Further research directions of the nonlinear dynamics of gene regulatory network are discussed.

1 Introduction

Gene regulatory network is a group of molecular regulators and their connections which controls the gene expression levels of mRNAs and proteins in the cell. The regulators can be deoxyribonucleic acid (DNA), ribonucleic acid (RNA), messenger ribonucleic acid (mRNA), protein and other substances involved in regulation process. Their connections are very diverse and dynamically evolving. The gene expression commonly has two important processes: transcription and translation. The genes on DNA are first transcribed into mRNAs, and then mRNAs are translated into proteins. For deeply understanding the mechanism of gene expression, scholars incline to study the gene regulatory network rather than focusing on a single gene. The gene regulatory network is widely known as the key factor in determining the morphogenesis and phylogenesis of living organisms [1–3]. More and more studies have been emphasised on gene regulatory network to reveal the nature of biodiversity, leading to the great prosperity of evolutionary developmental biology [4,5].

As a strongly nonlinear complex system, gene regulatory network often produces various types of amazing dynamic properties, such as multistability [6], synchronization [7], periodic oscillation [8], bifurcation [9], chaos [10], etc. In the past few decades, a large number of valuable research results on nonlinear dynamics of gene regulatory network have been constantly reported. The asymptotic stability

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conditions of gene regulatory networks with time delay, noise perturbation, impulsive, reaction-diffusion factor, parameter uncertainty and Markovian switching were established by applying the classic Lyapunov stability theory and linear matrix inequality approach [11–15]. The robust stability criteria of stochastic genetic regulatory networks were analytically and numerically presented [16–18]. The fractional order gene regulatory network was constructed and its Mittag–Leffler stability criterion was derived via the fractional Lyapunov method [19]. The bifurcation of delayed gene regulatory networks were investigated by analyzing the corresponding characteristic equations and taking time delay as the bifurcation parameter [20–22]. With the time delay crossing a certain critical value, the network yielded bifurcation and became unstable. The periodic oscillation of gene regulatory networks were investigated as well [23,24]. Hori et al. established the graphical results for the generation of periodic oscillations of cyclic gene regulatory networks and claimed that the local instability of an equilibrium indicates the existence of periodic oscillations [25]. Some achievements on the study of chaos of gene regulatory networks were presented by statistical analysis and numerical verification [26,27]. Much attention has also been paid to the research of multistability of gene regulatory network in recent years [28–30]. Ozbudak et al. discovered the bistability of lactose utilization network of Escherichia coli by using the phase diagram [6]. Pan et al. analytically verified the existence of multiple stable states in gene regulatory network with time delays and multivariable regulation functions [31]. In a nutshell, the study of dynamic properties of gene regulatory networks is an important issue that attracts a wide range of research interests. It is of great significance for the understanding of regulatory mechanism and the interpretation of biodiversity.

In order to study the gene regulatory network, a mathematical model which quantitatively describes the regulating action between genes should be constructed. The commonly used model of gene regulatory network with n coupled nodes is described by the following ordinary differential equations [32–34]

$$\dot{x}_i(t) = -a_i x_i(t) + (1 - b_i) f_i(\mathbf{x}) + b_i, \tag{1}$$

where $\mathbf{x} = (x_1, x_2, \ldots, x_n)$, $x_i > 0$ $(i = 1, 2, \ldots, n)$ is the protein concentration of the ith node, $a_i > 0$ denotes the decay rate, $b_i > 0$ represents the leakage transcription rate in the absence of activator and the presence of repressor. The function $f_i(\mathbf{x})$ is given as follows

$$f_i(\mathbf{x}) = \begin{cases} p_i(\mathbf{x}), & \text{Active regulation,} \\ r_i(\mathbf{x}), & \text{Repressive regulation,} \\ p_i(\mathbf{x}) r_i(\mathbf{x}), & \text{Joint regulation,} \end{cases} \tag{2}$$

with

$$\begin{aligned} p_i(\mathbf{x}) &= \frac{\varphi_i^{h_i}(\mathbf{x})}{\varphi_i^{h_i}(\mathbf{x}) + K_i^{h_i}}, \; r_i(\mathbf{x}) = \frac{K_i^{h_i}}{\phi_i^{h_i}(\mathbf{x}) + K_i^{h_i}}, \\ \varphi_i(\mathbf{x}) &= \sum_{j=1}^{n} c_{ij} x_j, \; \phi_i(\mathbf{x}) = \sum_{j=1}^{n} d_{ij} x_j, \; j = 1, 2, \ldots n, \end{aligned} \tag{3}$$

where $\varphi_i(\mathbf{x})$ and $\phi_i(\mathbf{x})$ respectively denote the sum of active and repressive transcriptional factors, $h_i > 0$ is the Hill coefficient that implies the degree of cooperative binding, $K_i > 0$ represents the concentration of activator (repressor) for defining the regulation half-maximal, c_{ij} and d_{ij} respectively denote the strength of the node

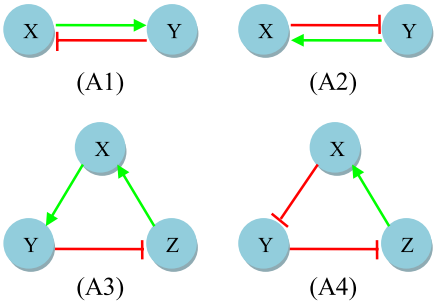

Fig. 1. Monostable motifs coupled by two or three nodes, where the red "⊣" and green "→" respectively denote the repressive and active regulation.

j that activate and repress the node i. The model (1) directly shows the relationships between different regulating nodes in the network with respect to their protein concentrations. It takes into account the active regulation, repressive regulation and joint regulation in the process of gene expression. Also it is more consistent with the general complex network model that can be used in many biological networks. Thus many scholars consider the dynamic properties of the gene network based on this model. In order to facilitate the analysis, we usually let the leakage transcription rate $b_i = 0$ and assume all the nodes have homogeneous parameter distributions with $a_i = a$, $h_i = h$, $K_i = K$, $c_{ij} = d_{ij} = 1$ for any $i = 1, 2, \ldots, n$. In the following part, we will discuss the monostability, bistability, periodicity and chaos of gene regulatory network based on the mathematical model (1).

2 Monostability

Stability is the prerequisite for the normal operation of gene regulatory network. It determines whether the network can maintain a steady state for a long time. The monostability which refers to the existence of a unique stable state can be observed in gene regulatory network with negative feedback loops. From this point of view, we can discover many gene regulatory networks with different structures and functions that exhibit monostability. The motifs of gene regulatory network shown in Figure 1 are introduced as typical examples of monostability. These motifs coupled by two or three nodes have the only negative feedback loop. Based on the motifs, a large number of monostable gene regulatory networks with more nodes and more complex structures can be produced in cells.

The stability of the motifs can be studied based on the mathematical model (1) and the classic stability theory. From the equations (1)–(3), we can write the model of motif (A1) as the following simplified differential equations

$$\begin{cases} \dot{x}(t) = -ax(t) + r(y(t)), \\ \dot{y}(t) = -ay(t) + p(x(t)), \end{cases} \tag{4}$$

where $x(t)$, $y(t)$ denote the protein concentration of the nodes, The functions $r(y)$, $p(x)$ represented the active and repressive regulations are given as follows

$$r(y) = \frac{1}{1+y^h}, \; p(x) = \frac{x^h}{1+x^h}. \tag{5}$$

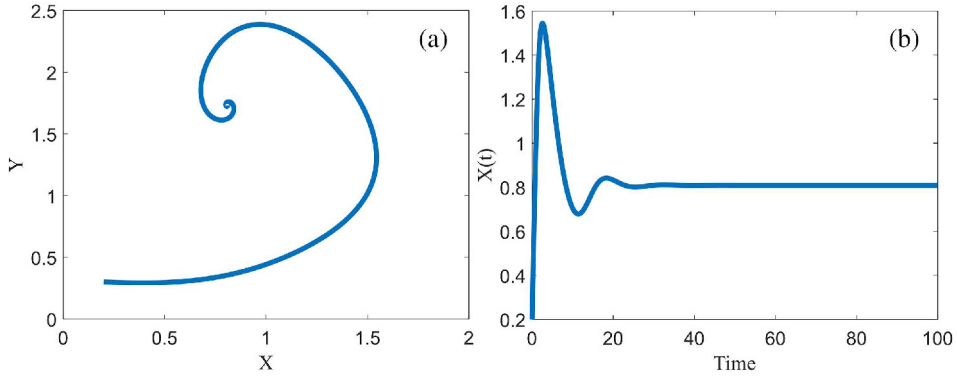

Fig. 2. Monostability of system (4) with $a = 0.2$, $h = 3$: (a) phase portrait on $x(t) - y(t)$; (b) time series of $x(t)$.

It is easy to verify that $r(y)$ is monotonically decreasing for $y \in (0, +\infty)$ and $p(x)$ is monotonically increasing for $x \in (0, +\infty)$. Let $O(\bar{x}, \bar{y})$ is a positive equilibrium of system (4), then it satisfies the equations $a\bar{x} = r(\bar{y})$, $a\bar{y} = p(\bar{x})$. It follows that $G(\bar{x}) = -a\bar{x} + r(p(\bar{x})/a) = 0$. Since $G(\bar{x})$ is monotonically decreasing and $G(0) = 1 > 0$, $G(+\infty) < 0$, then there exists only one $\bar{x} > 0$ such that $G(\bar{x}) = 0$. It implies that system (4) has only one positive equilibrium.

Linearizing the system (4) at $O(\bar{x}, \bar{y})$ and by some simple calculations, the corresponding characteristic equation can be obtained as follows

$$\lambda^2 + 2a\lambda + a^2 - r'(\bar{y})p'(\bar{x}) = 0. \tag{6}$$

Since $a > 0$ and $r'(\bar{y}) < 0, p'(\bar{x}) > 0$ for $\bar{x}, \bar{y} > 0$, then $a^2 - r'(\bar{y})p'(\bar{x}) > 0$. It follows that all the roots of equation (6) have negative real parts. Thus the equilibrium $O(\bar{x}, \bar{y})$ is asymptotically stable. The monostability of the motif (A1) is determined. We also can verify that the motifs (A2)–(A4) have only one stable positive equilibrium that leads to the appearance of monostability.

Let $a = 0.2$, $h = 3$, the only positive equilibrium of system (4) can be calculated as $O(0.8089, 1.7305)$. The eigenvalues $\lambda_{1,2} = -0.04 \pm 0.4855i$ of equation (6) imply that $O(0.8089, 1.7305)$ is asymptotically stable. Solving the system (4) via the fourth-fifth-order Runge–Kutta method with time step size $\Delta t = 0.01$ and time interval $t \in [0, 100]$ on Matlab 8.0, we can obtain the phase portrait on $x(t) - y(t)$ and time series of $x(t)$ as shown in Figure 2. Clearly, the system (4) exhibits stable state with $a = 0.2$, $h = 3$.

3 Bistability

The coexistence of multiple steady states in gene regulatory network plays an important role in the emergence of biodiversity. It enables organisms to have diverse functions that respond to different internal and external environments. The bistability has been widely discovered in gene regulatory networks. The existing results have shown that the gene regulatory network with positive feedback loops is prone to yield bistability [35,36]. Here, we give some coupled networks that generate bistability, as shown in Figure 3. The bistability of networks (B1) and (B2) in Figure 3 have been verified in literature [37,38]. The networks (B3) and (B4) are special motifs with simple cyclic symmetry. However, their bistability is mainly due to the existence of positive feedback loops, not the cyclic symmetry. Any other networks with

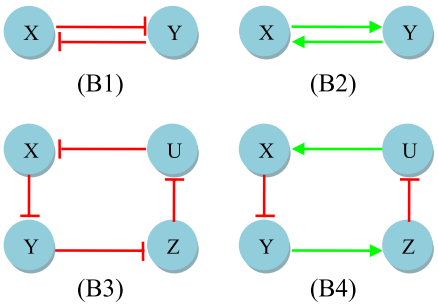

Fig. 3. Bistable motifs coupled by two or four nodes, where the red "⊣" and green "→" respectively denote the repressive and active regulation.

positive feedback loops are likely to produce bistability. We will show our discussion on the bistability of network (B3). The model of the network (B3) derived from equations (1)–(3) is described by the following simplified differential equations:

$$\begin{cases} \dot{x}(t) = -ax(t) + r(u(t)), \\ \dot{y}(t) = -ay(t) + r(x(t)), \\ \dot{z}(t) = -az(t) + r(y(t)), \\ \dot{u}(t) = -au(t) + r(z(t)), \end{cases} \tag{7}$$

where $x(t), y(t), z(t), u(t)$ are the protein concentration of the nodes. The positive equilibrium $S(\bar{x}, \bar{y}, \bar{z}, \bar{u})$ satisfies $a\bar{x} = r(\bar{u})$, $a\bar{y} = r(\bar{x})$, $a\bar{z} = r(\bar{y})$, $a\bar{u} = r(\bar{z})$. Accordingly we have

$$H(\bar{x}) = -a\bar{x} + r(r(r(r(\bar{x})/a)/a)/a) = 0. \tag{8}$$

Thus we can determine the existence of positive equilibrium of the system (7) by discussing the equation (8). Since $H(0) > 0, H(+\infty) = -\infty$, then equation (8) has at least one positive root. As the function $H(\bar{x})$ is not monotonous for $\bar{x} \in (0, +\infty)$, then equation (8) may exist multiple positive roots. It implies that the system (7) may exist multiple positive equilibria.

The characteristic equation at the equilibrium $S(\bar{x}, \bar{y}, \bar{z}, \bar{u})$ can be written as follows

$$(\lambda + a)^4 - \beta = 0, \tag{9}$$

where $a > 0$, $\beta = r'(\bar{x})r'(\bar{y})r'(\bar{z})r'(\bar{u}) > 0$. It is easy to verify that S is asymptotically stable as long as $a > \sqrt[4]{\beta}$. If the system (7) has multiple equilibria, then the condition $a > \sqrt[4]{\beta}$ can guarantee the stability of all the equilibria and the multistability may appear in system (7).

Let the parameters $h = 2$, $a = 0.2$ of system (7), then we can get that system (7) has the following three positive equilibria

$$\begin{aligned} &S(1.516, 1.516, 1.516, 1.516), \\ &S_1(0.2087, 4.7913, 0.2087, 4.7913), \\ &S_2(4.7913, 0.2087, 4.7913, 0.2087). \end{aligned}$$

By computing the corresponding eigenvalues of the equilibria, we can determine that S_1, S_2 are stable and S is unstable. The numerical simulations in Figure 4 discover

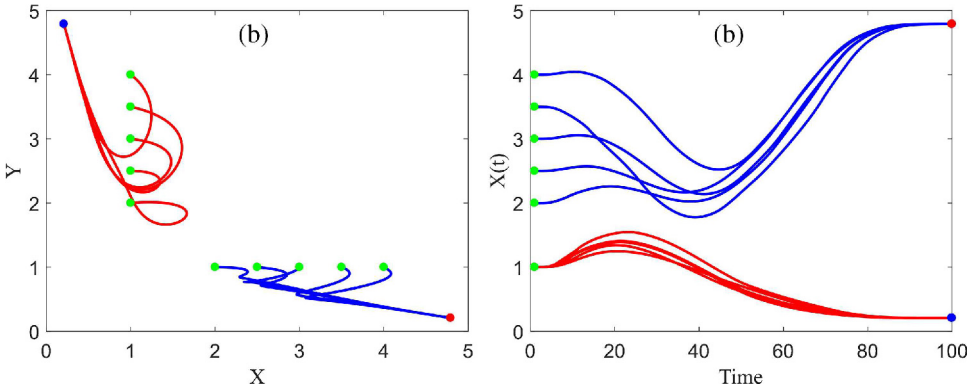

Fig. 4. Bistability of system (7) with $a = 0.2$, $h = 2$: (a) phase portrait on $x(t) - y(t)$; (b) time series of $x(t)$.

that system (7) has two stable states as the trajectories from different initial values finally tend to the equilibria S_1 and S_2.

4 Periodicity

The periodic oscillations are ubiquitous in gene regulatory networks. When the periodic oscillation occurs, the concentration of proteins will remain in a bounded range and do regular reciprocating movements as time goes on. It is widely believed that the periodic oscillations of gene regulatory networks play an important role in maintaining the rhythmic behaviors of living organisms. Many scholars have shown great interest in the study of periodic oscillations of gene regulatory networks. Some existing results indicated that the gene regulatory networks with time delays or negative feedback loops are more likely to produce periodic oscillation [39–41]. That is to say, the time delays or negative feedback loops have the positive effect on yielding the periodic oscillation in the networks. Time delay which causes by the slow biochemical reactions is inevitable in gene regulatory network. It can easily drive the network to lose stability and produce bifurcation leading to periodic oscillation.

We will take the motif (A1) in Figure 1 as the example for illustrating the periodic oscillation. By introducing the time delays τ_1, τ_2 to the system (4), we can rewrite the system (4) as follows

$$\begin{cases} \dot{x}(t) = -ax(t) + r(y(t-\tau_1)), \\ \dot{y}(t) = -ay(t) + p(x(t-\tau_2)). \end{cases} \tag{10}$$

The characteristic equation of system (10) at the equilibrium $O(\bar{x}, \bar{y})$ is given by

$$\lambda^2 + 2a\lambda + a^2 - \mu e^{-\tau} = 0, \tag{11}$$

where $\tau = \tau_1 + \tau_2 > 0$, $\mu = r'(\bar{y})p'(\bar{x}) < 0$. Since $a^2 - \mu > 0$, then $\lambda = 0$ is not a root of equation (11). Assume $\lambda = \pm\sigma i$, $\sigma > 0$ is a pair of pure imaginary roots of equation (11), we have

$$\begin{cases} \mu \sin(\sigma\tau) = -2a\sigma, \\ \mu \cos(\sigma\tau) = a^2 - \sigma^2. \end{cases}$$

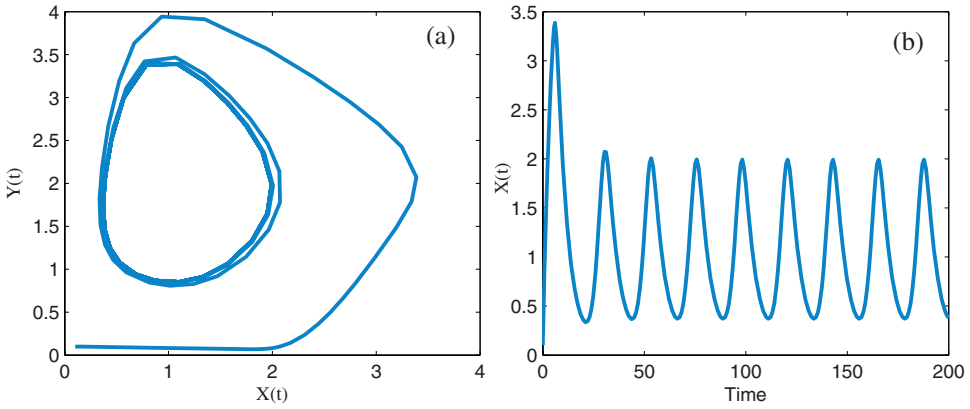

Fig. 5. Periodic oscillation of system (10) with $a = 0.2$, $h = 3$, $\tau_1 = \tau_2 = 2$: (a) phase portrait on $x(t) - y(t)$; (b) time series of $x(t)$.

It follows that $\sigma = \sigma_0 = \sqrt{-\mu - a^2} > 0$ if $\mu + a^2 < 0$. It means that equation (11) has pure imaginary roots $\lambda = \pm\sigma_0 i$. We can compute the critical value $\tau = \tau_0 = \min\{\tau_k, k = 0, 1, 2, \ldots\}$, where τ_k is given by

$$\tau_k = \frac{1}{\sigma_0} \arccos\left(\frac{a^2 - \mu}{\mu}\right) + \frac{2k\pi}{\sigma_0}, \; k = 0, 1, 2, \ldots \tag{12}$$

By establishing the transversability condition $\mathrm{Re}(d\lambda/d\tau)\,|_{\sigma=\sigma_0,\tau=\tau_0} \neq 0$, we can confirm the generation of Hopf bifurcation of system (10) which leads to periodic oscillation at the equilibrium O. The periodic oscillation of system (10) is illustrated in Figure 5 by fixing the parameters $h = 3$, $a = 0.2$, $\tau_1 = \tau_2 = 2$.

5 Chaos

Chaos in gene regulatory network has been reported before [42–45], but the corresponding studies are still scarce. The main reason for the limitation of chaos research of gene regulatory network is that the restricted availability of gene expression data and the existence of gene expression noise greatly increased the difficulty of quantitatively describing chaos, and chaos itself is rare in gene regulatory network. However, this does not mean that chaos is not important for gene regulatory network. On the contrary, it plays an important role in the realization of some special biological functions. Sevim et al. claimed that the gene regulatory networks with strong robustness to mutations and noise are more likely to generate chaos, and the chaos is of great significance to hold stable gene expression patterns [46]. Zhang et al. presented a conclusion that the formation of chaos in gene regulatory networks is mainly the result of competitions between different oscillatory modes with rivaling intensities, and they proposed many chaotic network motifs with three or four nodes [47]. Here, we show two chaotic network motifs with autoregulations in Figure 6 proposed by Zhang et al. as examples of analysis. The mathematical model of motif (C1) in Figure 6 can be described as follows

$$\begin{cases} \dot{x}(t) = -ax(t) + \widehat{r}(z(t)), \\ \dot{y}(t) = -ay(t) + \widehat{r}(x(t))\widehat{p}(y(t)), \\ \dot{z}(t) = -az(t) + \widehat{r}(y(t))\widehat{p}(x(t)), \end{cases} \tag{13}$$

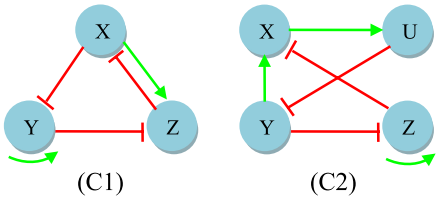

Fig. 6. Chaotic motifs coupled by three or four nodes, where the red "⊣" and green "→" respectively denote the repressive and active regulation.

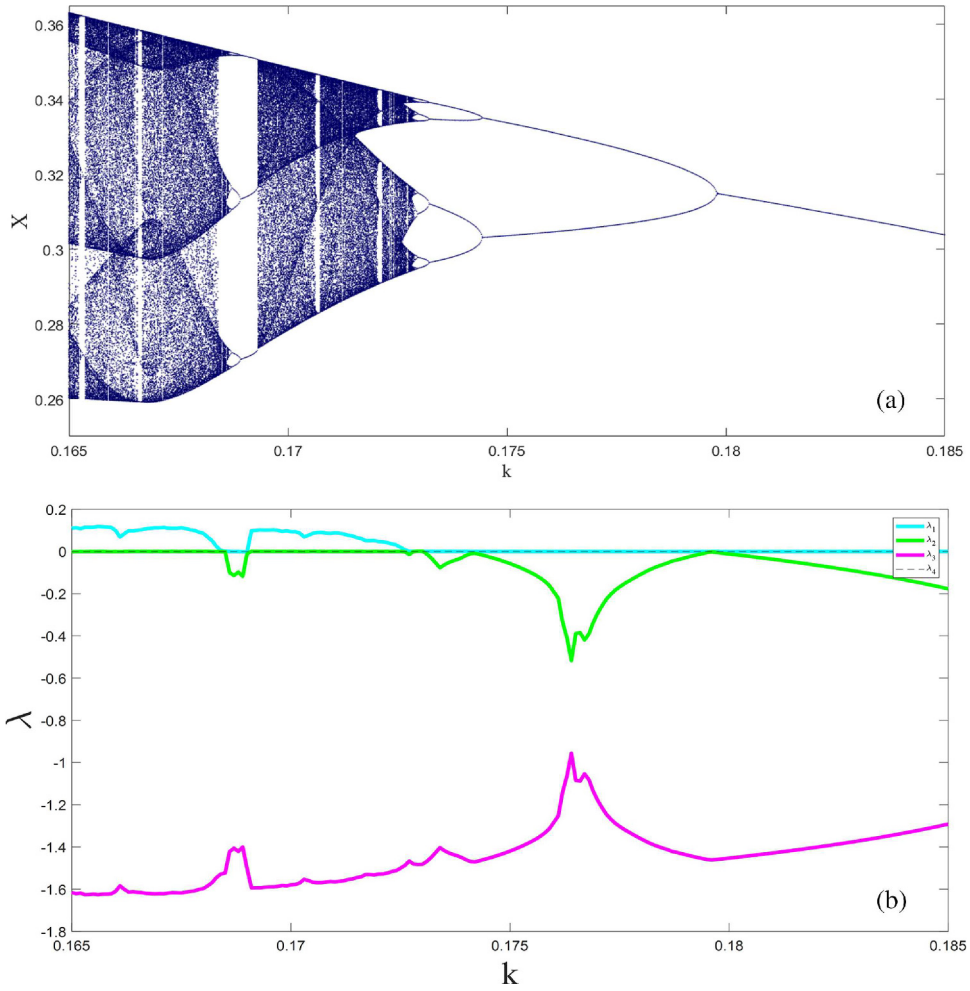

Fig. 7. The bifurcation diagram and finite time Lyapunov exponents with $a = 1, h = 3$ and $K \in [0.165, 0.185]$ of system (13).

with the simplified functions

$$\widehat{r}(x) = \frac{K^h}{K^h + x^h}, \ \widehat{p}(x) = \frac{x^h}{K^h + x^h}. \tag{14}$$

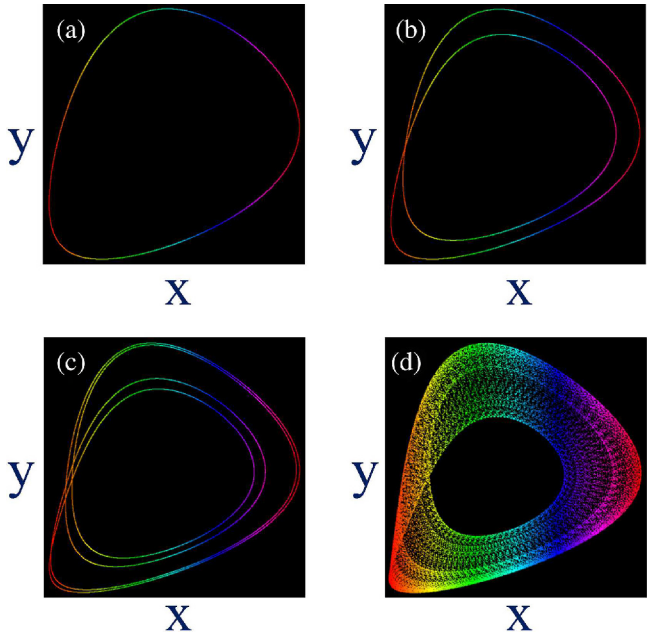

Fig. 8. The phase portraits on $x - y$ of the periodic-1, periodic-2, periodic-4, and chaotic attractors of system (13) with $K = 0.183, 0.178, 0.174$, and 0.170.

By plotting the bifurcation diagram and finite time Lyapunov exponents of system (13) with $a = 1, h = 3$ and $K \in [0.165, 0.185]$, we can numerically determine the existence of chaos. As shown in Figure 7, the system (13) generates chaos via reverse period-doubling bifurcation. It can be illustrated visually by presenting the phase portraits of the periodic-1, periodic-2, periodic-4 and chaotic attractors with parameter $K = 0.183, 0.178, 0.174, and 0.170$, as shown in Figure 8. The notable feature of chaos is the extreme sensitivity to the initial condition. By comparing the trajectories starting from initial values $(0.4, 0.4, 0.5)$ (blue solid line) and $(0.401, 0.4, 0.5)$ (red dash line) in Figure 9, we can know that the small change $(\Delta x = 0.001)$ in initial values causes the big difference of the final trajectories with the evolution of time. It means that system (13) with $K = 1.70$ is sensitive dependence on initial conditions and the chaotic motion is determined. The chaotic behavior of motif (C2) can be detected by numerical experiments as well.

6 Discussions

A general presentation of nonlinear dynamics of gene regulatory network was given in this letter. By introducing some typical motifs, the monostability, bistability, periodicity and chaos of gene regulatory network were analytically and numerically investigated. Although the dynamic properties of gene regulatory networks have been studied for many years, there are still many problems to be further explored. On the one hand, more research needs to focus on the dynamic analysis of more complex large-scale gene regulatory networks. Many kinetic study results have been limited to small-scale gene regulatory networks with fixed topology and can not well explain the biological phenomena since the actual gene regulatory network consists of many different nodes and complex, multiple, uncertain interaction relationships. On the other hand, many unknown and strange dynamic properties of gene regulatory network should be detected to understand the law of gene expression comprehensively,

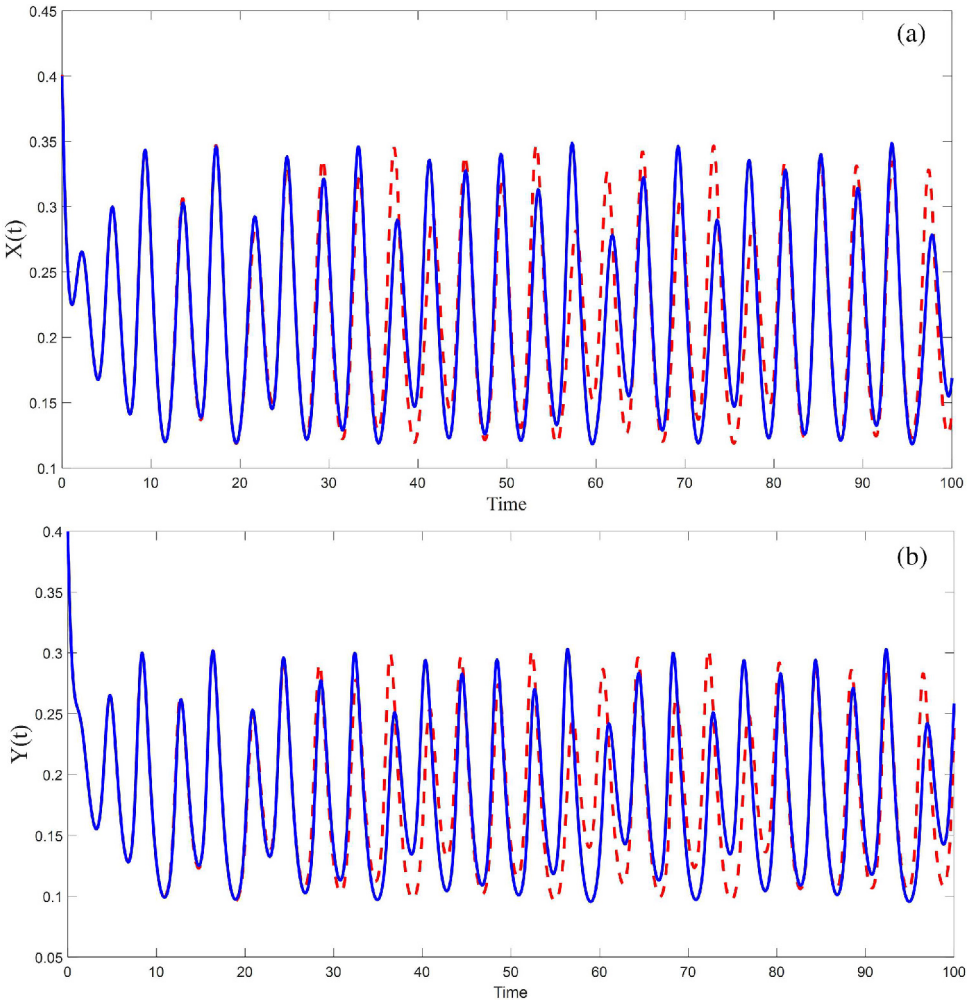

Fig. 9. Sensitive dependence on initial conditions: (a) time series of $x(t)$; (b) time series of $y(t)$.

such as the study of hidden attractors and coexisting attractors. The study of hidden attractors and coexisting attractors has been a hot research topic in recent years which has received widespread attention [48–51]. The hidden attractors and coexisting attractors are ubiquitous in nonlinear systems. Actually the multistability is an important manifestation of coexisting attractors. The bistability has been widely discovered in gene regulatory network. However, the multistability with three or more steady states has not been well addressed. Thus the study of hidden attractors and coexisting attractors of gene regulatory network and their biological insights will be an interesting research work. Furthermore, the control of gene regulatory network has been of recent interest [52–54]. The control of gene regulatory network has two research aspects: the understanding of internal control function of gene regulatory network itself and the design of external control input. The control design can improve the performance of gene regulatory network and obtain the desired dynamic behaviors. Especially the control of multistability is of great significance [55]. More research results on gene regulatory network will be reported in our forthcoming paper.

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