

Local Bifurcation Analysis of a Fractional-Order Dynamic Model of Genetic Regulatory Networks with Delays

Qingshan Sun¹ · Min Xiao¹ · Binbin Tao¹

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Abstract In this paper, we propose a delayed fractional-order gene regulatory network model. Firstly, the sum of delays is chosen as the bifurcation parameter, and the conditions of the existence for Hopf bifurcations are achieved through analyzing its characteristic equation. Secondly, it is shown that the fractional order can be effectively manipulated to control the dynamics of such network, and the stability domain can be changed with different fractional orders. The fractional-order genetic network can generate a Hopf bifurcation (oscillation appears) as the sum of delays passes through some critical values. Therefore, we can achieve some desirable dynamical behaviors by choosing the appropriate fractional order. Finally, numerical simulations are carried out to illustrate the validity of our theoretical analysis.

Keywords Time delays · Hopf bifurcation · Fractional-order · Genetic regulatory networks

Mathematics Subject Classification 34C23 · 34K18 · 37G15

1 Introduction

As we know, fractional calculus is a common generalization of an arbitrary, which was originally proposed in the late seventeenth century. In recent years, the fractional-order derivatives and integrals have been widely used in numerous branches of science and engineering. It has been found that dynamical equations using fractional derivatives are useful and more accurate in the mathematical modeling of real world phenomena arising from several fields, such as colored noises [1], diffusion and wave propagation [2], electromagnetic wave [3], control [4], biological systems [5], and so on. In fact, many real-world physical systems can

✉ Min Xiao
candymanxm2003@aliyun.com

¹ College of Automation, Nanjing University of Posts and Telecommunications,
Nanjing 210003, China

be more accurately described by fractional-order differential equations than integer-order ones.

Numbers of genes and gene products consist of a genetic regulatory network with regulatory interactions. Its dynamical systems are extremely complicated, which can represent the interaction functions in gene expression [6, 7]. The Genetic regulatory network describes interactions between DNAs, RNAs, proteins and small molecules in an organism [8]. So it is necessary and important to investigate the dynamics of gene regulatory networks to get insight to its mechanism.

Time delays are inevitably in many real dynamical systems, such as biological systems, neural networks and so on. In [9], a mathematical model was proposed to describe the interaction of inducible defenses and herbivore outbreak. It was proved that time delays play a pivotal role in the persistence of herbivore populations. In [10], the effect of periodic sub-threshold pacemaker activity and time-delayed coupling on stochastic resonance over scale-free neuronal networks was considered. It was shown that finite delays in coupling can significantly affect the stochastic resonance on scale-free neuronal networks. Time delays can lead to complex dynamical behaviors for systems, and an appropriate delay can also improve the stability of systems. Therefore, it is necessary to investigate the effect that time delays cause on dynamical behaviors of complex systems theoretically and practically.

Hopf bifurcation analysis is an efficient tool to acquire more information around the equilibrium point of complex dynamical networks [11–15]. It is well known that the Hopf bifurcation in delayed inter-order systems has been extensively studied, and numerous valuable results have been obtained. Due to the development of fractional calculus, the study of Hopf bifurcations of fractional-order models has attracted an increasing interest in recent years [16–19]. Unfortunately, the impact of time delays on these fractional-order models are rarely taken account to.

The integer-order calculus is only determined by the local character of the function, while the fractional-order calculus can accumulate the global information of the function in the weighted form, which is also called the memory. The integer-order calculus is a special case of fractional calculus, and almost all physical systems can be described with fractional-order models. In the last decade, fractional-order models have been an active field of research both from a theoretical and applied perspective. For instance, the resistance-capacitance-inductance (RLC) interconnect model of a transmission line is a fractional-order model [20]. Heat conduction can be more adequately modeled by fractional-order models than by their integer-order counterparts [21].

Recently, quite a few studies have been conducted on the Hopf bifurcation analysis of genetic regulatory networks [22–26]. However, most of these results have only considered integer-order genetic regulatory networks. Magin [27] argued that the activities of the organism can be accurately described by using the fractional-order derivative. In [28], a new approach based on fractional differential equations to build the genetic regulatory networks from time series data was proposed. It was revealed that the proposed mathematical model is more suitable to model genetic regulatory mechanism. In [29], a class of fractional-order gene regulatory networks was studied. Some criteria on the Mittag–Leffler stability and generalized Mittag–Leffler stability were established by using the fractional Lyapunov method for these networks. In [30], a fractional gene regulatory algorithm by extended fractional Kalman filter was proposed to estimate the hidden states as well as the unknown static parameters of the model. The mathematical model based on the fractional-order differential equation can describe the dynamic response of the actual system more accurately, and further improve the design, characterization and control of dynamical systems.

Till now, there are few results with regard to fractional-order genetic regulatory networks. The existing work on the dynamics of fractional-order genetic regulatory networks pays little attention to the effect of time delays. The time delay is an essential factor when modeling genetic networks due to slow biochemical processes such as gene transcription, translation and transportation. Motivated by those facts, the problem of the bifurcation for delayed fractional-order genetic regulatory networks is investigated in the present paper.

The rest of this paper is organized as follows. In Sect. 2, some definitions are recalled and the delayed fractional-order genetic network model is presented. In Sect. 3, the stability and bifurcation of the delayed fractional-order genetic regulatory network is analyzed. In Sect. 4, the simulation examples are given to illustrate the results. Finally, the conclusions are drawn in Sect. 5.

2 Preliminaries and Model Description

Generally speaking, there are three definitions of fractional derivatives: the Grunwald–Letnikov fractional derivative, Riemann–Liouville fractional derivative, and Caputo fractional derivative [31]. The Caputo derivative only requires initial conditions given by means of integer-order derivative, which has well understood physical meanings and has more applications in engineering. The Caputo derivative will be used in this paper.

The Caputo fractional-order derivative is defined as follows:

$${}^C D_t^\alpha f(t) = \frac{1}{\Gamma(m-\alpha)} \int_a^t (t-\tau)^{m-\alpha-1} f^{(n)}(\tau) d\tau, \quad (2.1)$$

where $m-1 < \alpha < m$, $m \in \mathbb{N}$, and $\Gamma(\cdot)$ is the Gamma function. The symbol α denotes the value of the fractional order that is usually chosen in the range $0 < \alpha \leq 1$.

The Laplace transform of the Caputo fractional-order derivative is represented by:

$$L\{{}^C D_t^\alpha f(t)\} = s^\alpha F(s) - \sum_{k=0}^{m-1} s^{\alpha-k-1} f^{(k)}(0). \quad (2.2)$$

If $f^{(k)}(0) = 0$, $k = 0, 1, \dots, m-1$, then $L\{{}^C D_t^\alpha f(t)\} = s^\alpha F(s)$.

Lewis [32] proposed a single-gene regulatory network model with time delays described by the following equations:

$$\begin{aligned} \dot{m}(t) &= -cm(t) + g(p(t - \tau_1)), \\ \dot{p}(t) &= -bp(t) + am(t - \tau_2), \end{aligned} \quad (2.3)$$

where $m(t)$ and $p(t)$ are the concentrations of the mRNA and protein, respectively, $c > 0$ and $b > 0$ are the degradation rates of the mRNA and protein, respectively, and $a > 0$ is the synthesis rate of the protein. The time delay τ_1 elapses between the initiation of transcription and the arrival of the mature mRNA molecule in the cytoplasm, and τ_2 elapses between the initiation of translation and the emergence of a complete functional protein molecule. In addition, $g(p(t))$ is the rate of the production of the mRNA, and $g(x)$ can be expressed with a sigmoid function, $\in \tanh(x)$ or a function of the Hill form, $\sigma/(x^n + \epsilon)$, where ϵ and σ are positive numbers and n is the Hill coefficient denoting the degree of cooperativity [33].

In this paper, we are interested in the dynamics of the following delayed fractional-order model of genetic regulatory networks:

$$\begin{aligned} D^q m(t) &= -cm(t) + g(p(t - \tau_1)), \\ D^q p(t) &= -bp(t) + am(t - \tau_2), \end{aligned} \tag{2.4}$$

where $q \in (0, 1]$, $m(t), p(t), g(x), c, b, a, \tau_1$ and τ_2 have the same meanings as those defined in (2.3), and the notation D^q is chosen as the Caputo fractional derivative (2.1).

Obviously, when $q = 1$, network (2.4) degenerates to network (2.3). (m^*, p^*) is an equilibrium point of the fractional-order genetic regulatory network (2.4) if and only if

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

Clearly, network (2.3) and (2.4) possess the same equilibrium point.

3 Stability and Bifurcation Analysis

In this section, we investigate the stability of the fractional-order genetic regulatory network (2.4), then some conditions of Hopf bifurcations are established.

Let $x(t) = m(t) - m^*, y(t) = p(t) - p^*$. Then the linearized network (2.4) is:

$$\begin{cases} x^q(t) = -cx(t) + g'(p^*)y(t - \tau_1), \\ y^q(t) = -by(t) + ax(t - \tau_2), \end{cases} \tag{3.1}$$

with the characteristic equation:

$$\begin{vmatrix} s^q + c & -g'(p^*)e^{-s\tau_1} \\ -ae^{-s\tau_2} & s^q + b \end{vmatrix} = 0. \tag{3.2}$$

That is:

$$s^{2q} + A_1s^q + A_2 - A_3e^{-s\tau} = 0, \tag{3.3}$$

where

$$A_1 = b + c, \quad A_2 = bc, \quad A_3 = ag'(p^*), \quad \tau = \tau_1 + \tau_2.$$

In the following, the total delay τ is regarded as the bifurcation parameter to investigate the distribution of roots of the characteristic equation (3.3).

Let $s = \omega(\cos \frac{\pi}{2} + i \sin \frac{\pi}{2})(\omega > 0)$. Then (3.3) becomes

$$\begin{aligned} \omega^{2q} \cos q\pi + A_1\omega^q \cos \frac{q\pi}{2} + A_2 - A_3 \cos \omega\tau + i(\omega^{2q} \sin q\pi \\ + A_1\omega^q \sin \frac{q\pi}{2} + A_3 \sin \omega\tau) = 0. \end{aligned}$$

Separating the real and imaginary parts gives

$$\begin{cases} \phi_1 \cos \omega\tau = \mu_1, \\ -\phi_1 \sin \omega\tau = \eta_1, \end{cases} \tag{3.4}$$

where

$$\phi_1 = A_3, \quad \mu_1 = \omega^{2q} \cos q\pi + A_1\omega^q \cos \frac{q\pi}{2} + A_2, \quad \eta_1 = \omega^{2q} \sin q\pi + A_1\omega^q \sin \frac{q\pi}{2}.$$

It can be obtained from (3.4) that

$$\begin{cases} \cos \omega \tau = \mu_1 / \phi_1, \\ \sin \omega \tau = -\eta_1 / \phi_1. \end{cases} \tag{3.5}$$

Hence

$$\omega^{4q} + D_1 \omega^{3q} + D_2 \omega^{2q} + D_3 \omega^q + D_4 = 0, \tag{3.6}$$

where

$$\begin{aligned} D_1 &= 2A_1 \cos \frac{q\pi}{2}, & D_2 &= A_1^2 + 2A_2 \cos q\pi, \\ D_3 &= 2A_1 A_2 \cos \frac{q\pi}{2}, & D_4 &= A_2^2 - A_3^2. \end{aligned}$$

Denote

$$h(\omega) = \omega^{4q} + D_1 \omega^{3q} + D_2 \omega^{2q} + D_3 \omega^q + D_4.$$

The following lemma examines the distribution of the roots of the characteristic equation (3.3).

Lemma 3.1 For (3.3), the following results hold:

- i) If $D_k > 0, k = 1, 2, 3, 4, A_2 - A_3 \neq 0$, then (3.3) has no root with zero real parts for all $\tau \geq 0$.
- ii) If $D_4 < 0$, and $D_k > 0, k = 1, 2, 3$, then (3.3) has a pair of purely imaginary roots $\pm \omega_0$ when $\tau = \tau_j, j = 0, 1, \dots$, where

$$\tau_j = \frac{1}{\omega_0} \arccos \left(\frac{\mu_1}{\phi_1} + 2j\pi \right), \quad j = 0, 1, 2, \dots, \tag{3.7}$$

in which ω_0 is the unique positive zero of the function $h(\omega)$.

Proof i) From $D_k > 0, k = 1, 2, 3, 4$, we can derive

$$h(0) = D_4 > 0,$$

and

$$h'(\omega) = 4q\omega^{4q-1} + D_1 3q\omega^{3q-1} + D_2 2q\omega^{2q-1} + D_3 q\omega^{q-1} > 0, \quad \text{for } \omega > 0.$$

Combining $q > 0$ and $D_k > 0, k = 1, 2, 3, 4$, we claim that (3.6) has no real root, and hence (3.3) has no purely imaginary root. Provided that $A_2 - A_3 \neq 0, \lambda = 0$ is not a root of (3.3). This ends the proof of i).

- ii) By means of $D_4 < 0$, it is easy to see that $h(0) = D_4 < 0$. By $\lim_{\omega \rightarrow +\infty} h(\omega) = +\infty$, and $h'(\omega) > 0$ for $\omega > 0$, there exists a unique positive number ω_0 such that $h(\omega) = 0$. Then ω_0 is a root of (3.6). Hence, for τ_j as defined in (3.7), (ω_0, τ_j) is a root of (3.4). It can be seen that $\pm \omega_0$ is a pair of purely imaginary roots of (3.3) when $\tau = \tau_j, j = 0, 1, \dots$. This completes the proof of ii). □

To derive the transversality condition of the Hopf bifurcation, we make the following hypothesis:

$$(H_1) \quad \frac{P_1 Q_1 + P_2 Q_2}{Q_1^2 + Q_2^2} > 0,$$

where

$$\begin{aligned}
 P_1 &= -\omega_0 A_3 \sin \omega_0 \tau_0, \\
 P_2 &= -\omega_0 A_3 \cos \omega_0 \tau_0, \\
 Q_1 &= 2q\omega_0^{2q-1} \cos \frac{(2q-1)}{2}\pi + A_1 q \omega_0^{q-1} \cos \frac{(2q-1)}{2}\pi + A_3 \tau_0 \cos \omega_0 \tau_0, \\
 Q_2 &= \omega_0^{2q-1} \sin \frac{(2q-1)}{2}\pi + A_1 q \omega_0^{q-1} \sin \frac{(2q-1)}{2}\pi - A_3 \tau_0 \sin \omega_0 \tau_0.
 \end{aligned}$$

Lemma 3.2 *Let $s(\tau) = \zeta(\tau) + i\omega(\tau)$ be the root of system (3.3) near $\tau = \tau_j$ satisfying $\zeta(\tau_j) = 0, \omega(\tau_j) = \omega_0$. If H_1 holds, then we have*

$$\operatorname{Re} \left[\frac{ds}{d\tau} \right]_{\omega=\omega_0, \tau=\tau_0} > 0.$$

Proof Differentiating (3.3) implicitly with respect to τ , we obtain

$$\frac{ds}{d\tau} = \frac{-s A_3 e^{-s\tau}}{2q s^{2q-1} + q A_1 s^{q-1} + A_3 \tau e^{-s\tau}}. \tag{3.8}$$

Hence, from (3.8), we deduce that

$$\operatorname{Re} \left[\frac{ds}{d\tau} \right]_{\omega=\omega_0, \tau=\tau_0} = \frac{P_1 Q_1 + P_2 Q_2}{Q_1^2 + Q_2^2}.$$

Obviously, the hypothesis (H_1) implies that transversality condition is satisfied. This ends the proof. □

Theorem 3.3 *For the fractional-order genetic regulatory network (2.4), the following results hold:*

- i) *If $D_4 < 0, D_k > 0, k = 1, 2, 3, A_2 - A_3 > 0$, and $A_1 > 0$, then the equilibrium (m^*, p^*) of network (2.4) is locally asymptotically stable for $\tau \in [0, \tau_0)$, and unstable when $\tau > \tau_0$.*
- ii) *If all the conditions as stated in (ii) hold, then network (2.4) undergoes a Hopf bifurcation at (m^*, p^*) when $\tau = \tau_j, j = 0, 1, \dots$, where $\tau = \tau_j$ as defined in (3.7).*

Proof Observing that when $\tau = 0$, the characteristic equation (3.3) becomes:

$$s^{2q} + A_1 s^q + A_2 - A_3 = 0. \tag{3.9}$$

- i) According to the fractional Routh–Hurwitz criterion, it is easy to see that all the roots of (3.9) have negative real parts when $A_2 - A_3 > 0$, and $A_1 > 0$. From the conclusion ii) of Lemma 3.1, the definition of τ_0 implies that all the roots of (3.3) have negative real parts for $\tau \in [0, \tau_0)$. The conclusion in Lemma 3.2 indicates that (3.3) has at least a root with positive real parts when $\tau > \tau_0$. Hence, the conclusion i) holds.
- ii) The conclusion in Lemma 3.2 implies that the transversality condition for Hopf bifurcations is satisfied under the given assumption. So the Hopf bifurcation occurs at $\tau = \tau_j, j = 0, 1, \dots$. We complete the proof of Theorem 3.3. □

4 Simulation Examples

In this section, we present some numerical results to illustrate the analytical results obtained in the previous section, and display the Hopf bifurcation phenomenon of the delayed fractional-order model (2.4) of genetic regulatory networks.

We choose the same parameters used in [34]: $a = 5, b = 2, c = 1.5, g(x) = 4/(1 + x^2)$, and the fractional order is chosen as $q = 0.92$, then system (enumerate) becomes:

$$\begin{aligned} D^{0.92}m(t) &= -1.5m(t) + 4/(1 + (p(t - \tau_1))^2), \\ D^{0.92}p(t) &= -2p(t) + 5m(t - \tau_2), \end{aligned} \tag{4.1}$$

which has a positive equilibrium $(m^*, p^*) = (0.6822, 1.7055)$. From (3.7), we can obtain $\tau_0 = 2.1585$. From Theorem 3.3, the positive equilibrium point (m^*, p^*) of the fractional-order genetic regulatory network (2.4) is asymptotically stable when $\tau = 2.1 < \tau_0 = 2.1585$ as illustrated in Figs. 1 and 2. When $\tau = 2.3 > \tau_0 = 2.1585$, the positive equilibrium point (m^*, p^*) of the fractional-order genetic regulatory network (2.4) becomes unstable, and a Hopf bifurcation occurs, as shown in Figs. 3 and 4.

When we choose $q = 0.8$, it can be obtained from (3.7) that $\tau_0 = 3.2449$. The positive equilibrium point (m^*, p^*) is asymptotically stable when $\tau = 3.0 < \tau_0 = 3.2499$ as

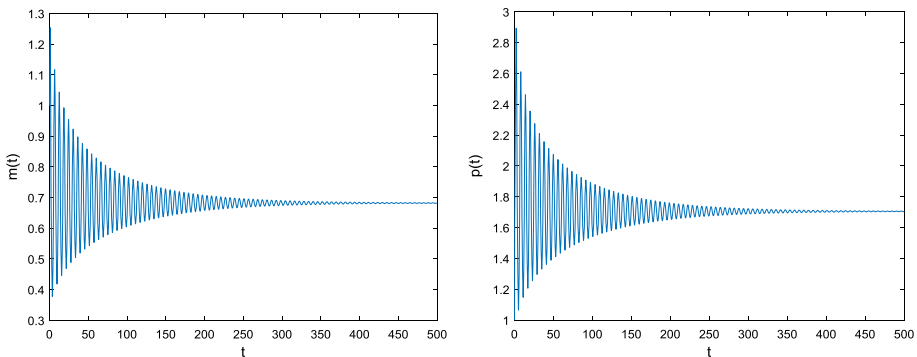
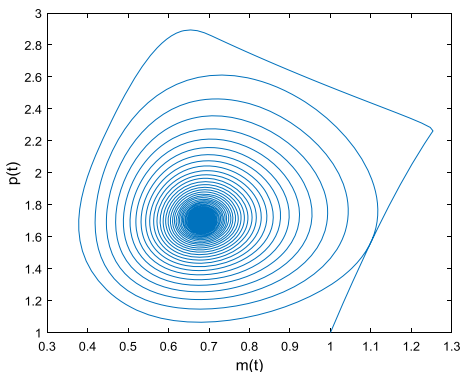


Fig. 1 Waveform plots of the fractional-order network (2.4) with $a = 5, b = 2, c = 1.5, g(x) = 4/(1 + x^2), q = 0.92$ and initial values (1, 1). The equilibrium (0.6822, 1.7055) is asymptotically stable when $\tau = 2.1 < \tau_0 = 2.1585$.

Fig. 2 Phase portrait of the fractional-order network (2.4) with $a = 5, b = 2, c = 1.5, g(x) = 4/(1 + x^2), q = 0.92$ and the initial value (1, 1). The equilibrium (0.6822, 1.7055) is asymptotically stable when $\tau = 2.1 < \tau_0 = 2.1585$



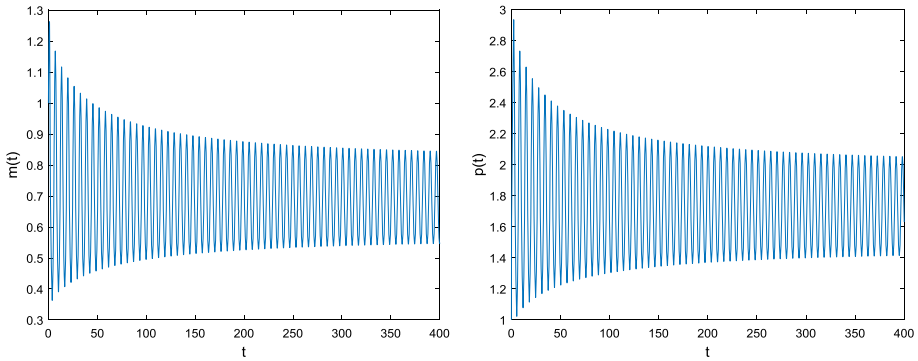


Fig. 3 Waveform plots of the fractional-order network (2.4) with $a = 5, b = 2, c = 1.5, g(x) = 4/(1 + x^2), q = 0.92$ and the initial value (1, 1). A periodic oscillation bifurcates from the equilibrium (0.6822, 1.7055), where $\tau = 2.3 > \tau_0 = 2.1585$

Fig. 4 Phase portrait of the fractional-order network (2.4) with $a = 5, b = 2, c = 1.5, g(x) = 4/(1 + x^2), q = 0.92$ and the initial value (1, 1). A periodic oscillation bifurcates from the equilibrium (0.6822, 1.7055), where $\tau = 2.3 > \tau_0 = 2.1585$.

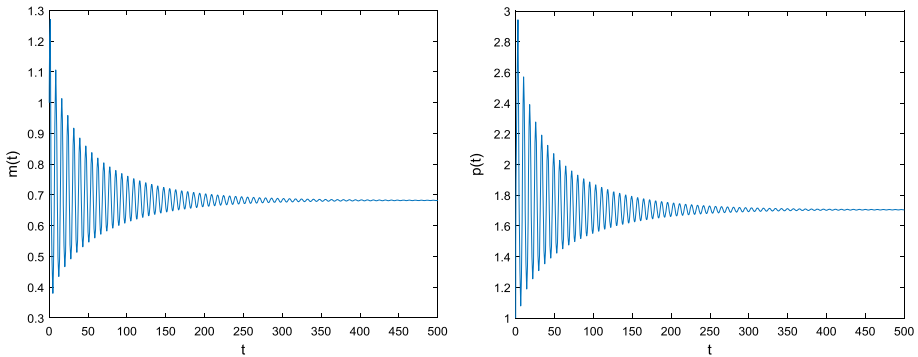
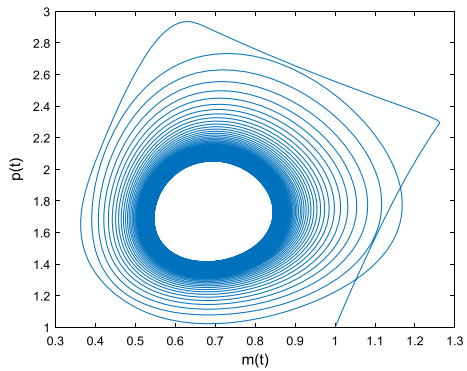


Fig. 5 Waveform plots of the fractional-order network (2.4) with $a = 5, b = 2, c = 1.5, g(x) = 4/(1 + x^2), q = 0.8$ and the initial value (1, 1). The equilibrium (0.6822, 1.7055) is asymptotically stable when $\tau = 3.0 < \tau_0 = 3.2449$

Fig. 6 Phase portrait of the fractional-order network (2.4) with $a = 5, b = 2, c = 1.5, g(x) = 4/(1 + x^2), q = 0.8$ and the initial value $(1, 1)$. The equilibrium $(0.6822, 1.7055)$ is asymptotically stable when $\tau = 3.0 < \tau_0 = 3.2449$

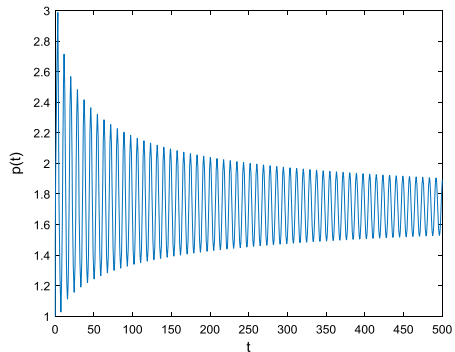
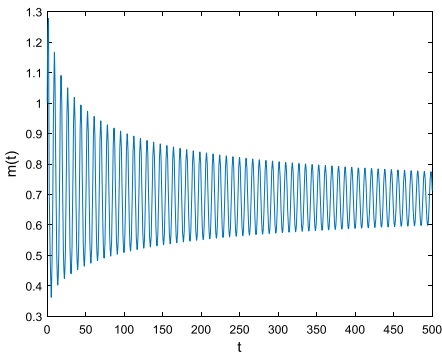
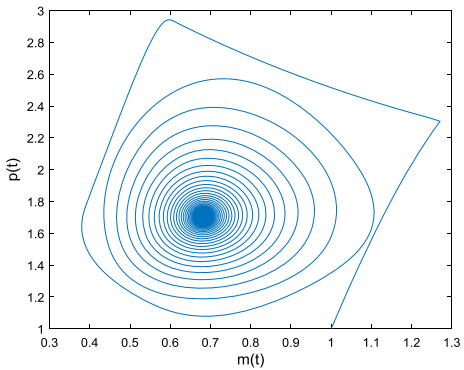
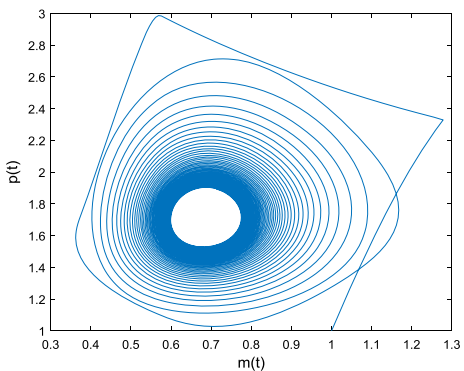


Fig. 7 Waveform plots of the fractional-order network (2.4) with $a = 5, b = 2, c = 1.5, g(x) = 4/(1 + x^2), q = 0.8$ and the initial value $(1, 1)$. The equilibrium $(0.6822, 1.7055)$ is asymptotically stable when $\tau = 3.4 > \tau_0 = 3.2449$

Fig. 8 Phase portrait of the fractional-order network (2.4) with $a = 5, b = 2, c = 1.5, g(x) = 4/(1 + x^2), q = 0.8$ and the initial value $(1, 1)$. The equilibrium $(0.6822, 1.7055)$ is asymptotically stable when $\tau = 3.4 > \tau_0 = 3.2449$

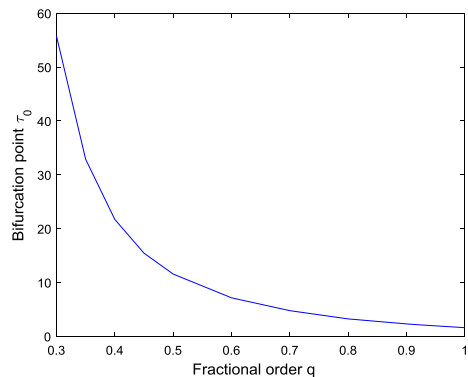


illustrated in Figs. 5 and 6. When $\tau = 3.4 > \tau_0 = 3.2449$, the positive equilibrium point (m^*, p^*) becomes unstable, and a Hopf bifurcation occurs, as shown in Figs. 7 and 8.

The effect of the order q on the values of τ_0 and ω_0 for network (2.4) is shown in Table 1 and Fig. 9. It is found that the critical value τ_0 decreases clearly with the order q , which means that the value of τ_0 is sensitive to the change of the order q .

Table 1 Bifurcation point τ_0 versus fractional order q for network (2.4)

Fractional order q	Critical frequency ω_0	Bifurcation point τ_0
0.1	6.5526e-005	4.7076e+004
0.2	0.0095	318.9563
0.3	0.0531	55.7920
0.4	0.1331	21.7197
0.5	0.2426	11.5750
0.6	0.3782	7.1601
0.7	0.5405	4.7775
0.8	0.7455	3.2449
0.9	0.9524	2.3173
0.92	0.9994	2.1585
1.0	1.1937	1.6179

Fig. 9 Bifurcation point τ_0 versus the fractional-order q for network (2.4)

5 Conclusions

In this paper, we have extended a delayed fractional-order model of genetic regulatory networks, and have considered the stability and bifurcations of the network. A stability criterion has been established, and some conditions of Hopf bifurcations have been proposed for the delayed fractional-order genetic network model. The delayed fractional-order genetic network model may generate a Hopf bifurcation (i.e., periodic oscillations appear) as the total delay passes through some critical values which can be determined exactly. It is observed that an increase in the order may lead to a decrease of the critical value of delay. The observations allow us to design the Hopf bifurcation with the desired bifurcation point by adjusting the delays and the order for genetic networks. It should be pointed out that the method proposed in this paper can be extended to deal with the bifurcation of 3-dimensional or multidimensional fractional-order systems.

It has been demonstrated by experimental evidence that small RNAs play crucial roles in the regulation and control of genetic events [35]. Thus, our future work will incorporate small RNAs and other small molecules into gene expressions to establish more accurate models and then address the effect of small RNAs on dynamics of gene regulatory networks. On the

other hand, we will adopt a fractional-order Proportion-Integral-Derivative scheme to control the bifurcation embedded in fractional-order genetic regulatory networks.

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References

1. Cottone G, Paola MD, Santoro R (2010) A novel exact representation of stationary colored gaussian processes (fractional differential approach). *J Phys A Math Theor* 43(8):085002
2. Henry B, Wearne S (2002) Existence of turing instabilities in a two-species fractional reaction-diffusion system. *SIAM J Appl Math* 62(3):870–887
3. Engheta N (1997) On the role of fractional calculus in electromagnetic theory. *IEEE Antennas Propag Mag* 39(4):35–46
4. Baleanu D (2012) *Fractional dynamics and control*. Springer, Berlin
5. Djordjević VD, Jarić Fabry B, Fredberg JJ, Stamenovi D (2003) Fractional derivatives embody essential features of cell rheological behavior. *Ann Biomed Eng* 31(6):692–699
6. Elowitz MB, Leibler S (2000) A synthetic oscillatory network of transcriptional regulators. *Nature* 403(6767):335–338
7. Bar YY, Harmon D, Bivort B (2009) Attractors and democratic dynamics. *Science* 323(5917):1016–1017
8. Hidde DJ (2002) Modeling and simulation of genetic regulatory systems: a literature review. *J Comput Biol* 9(1):67–103
9. Sun GQ, Wang SL, Ren Q, Jin Z, Wu YP (2015) Effects of time delay and space on herbivore dynamics: linking inducible defenses of plants to herbivore outbreak. *Sci Rep* 5:11246
10. Wang QY, Perc M, Duan ZS, Chen GR (2009) Delay-induced multiple stochastic resonances on scale-free neuronal networks. *Chaos* 19(2):023112
11. Verdugo A, Rand R (2008) Hopf bifurcation in a DDE model of gene expression. *Commun Nonlinear Sci Numer Simul* 13(2):235–242
12. Wan AY, Zou XF (2009) Hopf bifurcation analysis for a model of genetic regulatory system with delay. *J Math Anal Appl* 356(2):464–476
13. Xu CJ, Zhang QM, Wu YS (2016) Bifurcation analysis in a three-neuron artificial neural network model with distributed delays. *Neural Process Lett* 44(2):343–373
14. Tian XH, Xu R (2016) Hopf bifurcation analysis of a reaction-diffusion neural network with time delay in leakage terms and distributed delays. *Neural Process Lett* 43(1):173–193
15. Xu CJ, Shao YF, Li PL (2015) Bifurcation behavior for an electronic neural network model with two different delays. *Neural Process Lett* 42(3):541–561
16. Abdelouhab MS, Hamri NE, Wang JW (2012) Hopf bifurcation and chaos in fractional-order modified hybrid optical system. *Nonlinear Dyn* 69(1):275–284
17. Li X, Wu RC (2014) Hopf bifurcation analysis of a new commensurate fractional-order hyperchaotic system. *Nonlinear Dyn* 78(1):279–288
18. Tian JL, Yu YG, Wang H (2014) Stability and bifurcation of two kinds of three-dimensional fractional Lotka–Volterra systems. *Math Probl Eng* 2014:695871
19. Xiao M, Zheng WX, Jiang GP, Cao JD (2015) Undamped oscillations generated by hopf bifurcations in fractional-order recurrent neural networks with caputo derivative. *IEEE Trans Neural Netw Learn Syst* 26(12):3201–3214
20. Chen GQ, Friedman EG (2005) An RLC interconnect model based on fourier analysis. *IEEE Trans Comput Aided Des Integr Circuits Syst* 24(2):170–183
21. Jenson V, Jeffreys G (1977) *Mathematical methods in chemical engineering*. Academic Press, New York
22. Wu X, Eshete M (2011) Bifurcation analysis for a model of gene expression with delays *Commun. Nonlinear Sci Numer Simul* 16:1073–1088
23. Zhang T, Song Y, Zhang H (2012) The stability and Hopf bifurcation analysis of a gene expression model. *J Math Anal Appl* 395:103–113
24. Cao J, Jiang H (2013) Hopf bifurcation analysis for a model of single genetic negative feedback autoregulatory system with delay. *Neurocomputing* 99:381–389
25. Song Y, Han Y, Zhang Y (2014) Stability and Hopf bifurcation in a model of gene expression with distributed time delays. *Appl Math Comput* 243:398–412

26. Zang H, Zhang T, Zhang Y (2015) Bifurcation analysis of a mathematical model for genetic regulatory network with time delays. *Appl Math Comput* 260:204–226
27. Magin RL (2010) Fractional calculus models of complex dynamics in biological tissues. *Comput Math Appl* 59(5):1586–1593
28. Ji RR, Ding L, Yan XM, Xin M (2010) Modelling gene regulatory network by fractional order differential equations. In: *IEEE fifth international conference on BIC-TA*, pp 431–434
29. Ren FL, Cao F, Cao JD (2015) Mittag-leffler stability and generalized mittag-leffler stability of fractional-order gene regulatory networks. *Neurocomputing* 160:185–190
30. Zhang YQ, Pu YF, Zhang HS, Cong Y, Zhou JL (2014) An extended fractional Kalman filter for inferring gene regulatory networks using time-series data. *Chemom Intell Lab* 138:57–63
31. Podlubny I (1999) *Fractional differential equations*. Academic Press, New York
32. Lewis J (2003) Autoinhibition with transcriptional delay: a simple mechanism for the zebrafish somito genesis oscillator. *Curr Biol* 13:1398–1408
33. Chen L, Aihara K (2002) Stability of genetic regulatory networks with time delay delay. *IEEE Trans Circuits Syst I Fundam Theory Appl* 49:602–608
34. Xiao M, Cao JD (2008) Genetic oscillation deduced from Hopf bifurcation in a genetic regulatory network with delays. *Math Biosci* 215:55–63
35. Zamore P, Haley B (2005) Ribo-gnome: the big world of small RNAs. *Science* 309:1519–1524