Bifurcation Analysis and Fractional PD Control of Gene Regulatory Networks with sRNA

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Abstract: This paper investigates the problem of bifurcation analysis and bifurcation control of a fractional-order gene regulatory network with sRNA. Firstly, the process of stability change of system equilibrium under the influence of the sum of time delay is discussed, the critical condition of Hopf bifurcation is explored, and the effect of fractional order on the system stability domain. Secondly, aiming at the system’s instability caused by a large time delay, we design a controller to improve the system’s stability and derive the parameter conditions that satisfy the system’s stability. It is found that changing the parameter values of the controller within a certain range can control the system’s nonlinear behaviours and effectively expand the stability range. Then, a numerical example is given to illustrate the results of this paper.

Keywords: fractional-order; time delay; gene regulatory network; Hopf bifurcation; PD control

1. Introduction

Gene regulatory networks (GRNs) are biological networks that represent the complex regulatory relationships between genes and are one of the most important means of understanding gene function [1]. Small RNA, a vital gene-regulatory protein, is essential for many physiological activities in plants and animals, including growth and development, gene silencing, and viral defense. Studying gene regulatory networks can help understand genes’ interactions and regulatory mechanisms. It can realize the overall understanding of gene function, which is of great significance for the research on finding and identifying human pathogenic factors [2].

The study of fractional calculus focuses on integral and differential problems of arbitrary order. Fractional calculus has recollection and heredity [3]. So it is fit for describing systems with recollection and historical dependence processes and can represent and simulate natural objects more precisely. As an arbitrary extension of integral calculus on order, fractional calculus has shown substantial advantages and broad application background in many fields such as power systems [4,5], biological systems [6,7], secure communication [8,9], finance [10,11] and physics [12,13]. The development and application of fractional calculus theory have injected new vitality into studying gene regulatory networks. Researchers have found that fractional-order models are capable of describing the activity rules of organisms with exceptional accuracy and is more suitable for describing the regulatory mechanisms between genes within organisms [14]. In biological systems, the transmission, transcription and translation of proteins is a slow biochemical change.
process, so there may be a time delay in the GRNs. It may exhibit complicated dynamic behavior due to time delay [15].

The bifurcation theory can help study the parameter stability of dynamic nonlinear systems. There have many achievements in the study of Hopf bifurcation related to mRNA and protein gene regulation networks. Song et al. respectively studied gene networks with strong and weak kernel distributed time delays, took the time-delay averaging as component bifurcation parameters, the network's bifurcation characteristics and local stability are analyzed [16]. Yue et al. used the eigenvalue analysis method to derive the local stability conditions of equilibrium points related to biochemical parameters and coupling delay. The results showed that, under different biological parameters, coupling delay would induce the system to generate dynamic behavior of stable or stable and unstable phase switch [17]. Zhou et al. discussed the stability of indeterministic systems with variable delays, which took into account both biochemical parameter uncertainty and generalized activation effect [18]. Wang et al. obtained the bifurcation characteristics by studying the positive equilibrium point of the two-gene four-delay gene regulatory network model [19]. Ling et al. discussed the coupled ring gene network model with positive and negative drivers and gave the stability discrimination conditions of all equilibrium points. The results showed that the coupled ring gene network with positive drivers has multiple stability.

In contrast, Ling et al. analyzed a coupled ring gene network model. As the time delay varies, the model may exhibit Hopf bifurcation [20]. Xiao et al. investigated the dynamical behavior of a Hub-Like gene regulatory network model with delays and two-way coupling [21]. Yu et al. considered Hopf bifurcation caused by changes in biochemical parameters and used normal form theory and central prevailing theorem to describe a periodic bifurcation solution’s stability and direction [22].

There has been progress in the research on Hopf bifurcation of fractional GRNs. Yue et al. studied fractional order GRNs with diffusion, analyzed the number of equilibrium points in the system, and analyzed equilibrium points' local stability and the oscillation behavior under the condition of with or without diffusion, and found that compared with integer-order systems, fractional-order systems have a wider stable parameter range [23]. Liu et al. investigated the stability of the asymmetric fractional delay gene regulatory network, the system’s Hopf bifurcation conditions have been presented, and a positive equilibrium point exists and is unique under those conditions. Then a state feedback controller was developed to handle the system’s Hopf bifurcation efficiently [24]. Tao et al. extended the gene network containing two gene vibrators to fractional order, chose the total time delay as the bifurcation parameter to study the bifurcation behavior of the system at the positive equilibrium point, and presented the mathematical expression of critical time lag [25]. However, as math progressed and the discovery of sRNA, the basic 2-D model alone cannot adequately to describe the GRNs model with complex relationships. sRNA can bind with mRNA or protein to promote or inhibit gene expression [26]. Much experimental evidence shows that the regulatory effects of sRNA can be found in most cell activities in organisms. Ambros et al. proved that sRNA could adjust many biological pathways from an experimental perspective [27]. Liu et al. studied an integer-order gene regulatory network model containing mRNA, sRNA and protein. They found that the nonlinear solution generated by the binding of sRNA and mRNA could effectively reduce the concentration of translated protein, thus generating periodic oscillation behavior [28].

So far, there are some research on applying fractional order controllers in biological systems. Balasaheb et al. proposed a novel SIEP algorithm-based FAPID controller to adjust the system parameters [29]. Coronel-Escamilla et al. investigated the effects of using a fractional-order PID controller for a model of deep brain stimulation [30]. Guo et al. investigate the bifurcation of stochastic delayed biradical oscillators with fractional order derivatives [31].

Because sRNAs are smaller molecules than proteins and are not translated, so they use less energy to express genes than proteins. So far, most of the studies on fractional
gene regulatory networks focused on the model containing only mRNA and protein, and few results studied the gene network model with sRNA.

In view of these studies, we conduct bifurcation research on fractional-order GRNs with sRNA. Contributions of this paper include:

1. A fractional GRNs with sRNA is obtained by introducing Caputo fractional derivative, and the GRNs model incorporates time delays.
2. The fractional-order GRNs model’s dynamic behavior is investigated, and the Hopf bifurcation criteria and the network model’s stability are obtained. The influence of the total time delay and fractional order on system stability are thoroughly discussed.
3. For controlling the model’s bifurcation behavior, a fractional order controller is proposed. The system’s nonlinear behavior can be controlled by changing the controller’s parameters, and the system’s stability range can be expanded effectively.

Other parts of the thesis: The differential equation of a fractional delay GRNs with sRNA is given in Section 2. Section 3 discusses Hopf bifurcation and gene network stability at positive equilibrium. Section 4 introduces a fractional PD controller to boost dynamic performance and revisits Hopf bifurcation and system stability. The theoretical derivation is verified by numerical simulations in Section 5. Section 6 summarizes the whole paper and gives some conclusions.

2. Model Description

In general, fractional calculus can be expressed in several ways: Caputo fractional, Grunwald-Letnikov fractional and Riemann-Liouville fractional [32]. In engineering, we use Caputo’s fractional derivative’s Laplace transform derivative to examine the dynamic behavior of linked models.

Definition 1 ([24]). For fractional-order integrals \( f(t) \), the following definition applies:

\[
I^\alpha f(t) = \frac{1}{\Gamma(\alpha)} \int_0^t (t-\tau)^{\alpha-1} f(\tau) \, d\tau,
\]

where \( \alpha > 0 \), \( \Gamma(z) \) is Gamma function.

Definition 2 ([24]). Following is the Caputo fractional-order derivative \( f(t) \) definition:

\[
\frac{\partial^\alpha}{\partial t^\alpha} f(t) = \frac{1}{\Gamma(n-\alpha)} \int_0^t (t-\tau)^{n-\alpha-1} f^{(n)}(\tau) \, d\tau,
\]

where \( n-1 < \alpha \leq n(n \in \mathbb{Z}^+) \), In practical engineering, \( \alpha \in (0,1] \) is usually taken, and the following inferences are drawn:

\[
\frac{\partial^\alpha}{\partial t^\alpha} f(t) = \frac{1}{\Gamma(1-\alpha)} \int_0^t f^{(\tau)}(\tau) \, d\tau.
\]

Definition 3 ([25]). Caputo fractional-order derivatives have the following Laplace transforms:

\[
L\left\{ \frac{\partial^\alpha}{\partial t^\alpha} f(t) \right\} = s^{\alpha} F(s) - \sum_{k=0}^{m-1} s^{\alpha-k} f^{(k)}(0),
\]

Especially, when \( f^{(k)}(0) = 0, k = 0,1, \ldots, m-1 \), then \( L\left\{ \frac{\partial^\alpha}{\partial t^\alpha} f(t) \right\} = s^{\alpha} F(s) \).
Definition 4 ([33]). A fractional order delayed system:

\[ ^{0}D_{t}^{\alpha}x_{j}(t) = f_{j}(x_{1}(t), \ldots, x_{n}(t); \tau), \ j = 1, 2, \ldots, n, \]

where \( 0 < \alpha \leq 1, \tau \geq 0 \). If the following three conditions are true, Hopf bifurcation will occur, when \( \tau = \tau_{0} \), thus producing limit cycle and periodic oscillation behavior:

When \( \tau = 0 \), linearized System (5) has all eigenvalues \( \lambda_{j}(j = 1, 2, \ldots, n) \) in matrix A meet:

\[ \arg(\lambda_{j}) > g\pi/2. \]

When \( \tau = \tau_{0} \), there are two pure imaginary roots \( \pm i\omega_{0} \) in the linearized System (5)'s characteristic equation.

Satisfy \( \text{Re}[ds(\tau)/d\tau]|_{\tau=\tau_{0},\omega=\omega_{0}} > 0. \)

Because sRNA binding with mRNA or protein can promote or inhibit gene expression, the following gene network model with sRNA is considered [26]:

\[
\begin{align*}
\dot{m}(t) &= -cm(t) - ds(t)m(t) + g\left(p(t - \tau_{m})\right), \\
\dot{s}(t) &= e - ds(t)m(t) - fs(t), \\
\dot{p}(t) &= -bp(t) + am\left(t - \tau_{p}\right),
\end{align*}
\]

(6)

where \( m(t) \) represents the mRNA concentration of the GRNs, \( s(t) \) represents the corresponding sRNA concentration, and \( p(t) \) represents the corresponding translation protein concentration. The parameters \( c, f, b \) were numbers, which are mRNA, sRNA, and translated protein degradation rates. Parameter \( a > 0 \) represents mRNA translation rate, \( d > 0 \) represents pairing rate between mRNA and sRNA, \( e > 0 \) transcription rate of DNA into sRNA, \( \tau_{m} > 0 \) represents the transcription delay of genes, \( \tau_{p} > 0 \) represents the translation delay of genes, \( g(p(t - \tau_{m})) \) is a nonlinear regulatory function, represents the rate of mRNA gene generation. Specifically, it is expressed as \( g(p) = u / (1 + (p / p_{0})^{H}) \), where \( H \) represents Hill’s constant, which is related to the molecular binding mechanism; The dimensionless gene transcription rate can be represented by a number \( u \geq 0 \); The inhibition threshold is represented by a number \( p_{0} > 0 \).

Based on the above model, we analyze Hopf bifurcations for gene networks with discrete delay and Caputo fractional derivative form. The model is expressed as:

\[
\begin{align*}
D^{\alpha}m(t) &= -cm(t) - ds(t)m(t) + g\left(p(t - \tau_{m})\right), \\
D^{\alpha}s(t) &= e - ds(t)m(t) - fs(t), \\
D^{\alpha}p(t) &= -bp(t) + am\left(t - \tau_{p}\right),
\end{align*}
\]

(7)

where \( m(t), s(t), p(t) \), \( a, b, c, d, e, f, \tau_{m}, \tau_{p} \) is consistent with the meaning in model (6), and \( \alpha \in (0, 1) \) represents fractional order of system.

When \( \alpha = 1 \), System (7) is System (6), they have an equilibrium point, satisfying the following equations:

\[
\begin{align*}
-cm_{0} - ds_{0}m_{0} + g(p_{0}) &= 0, \\
e - ds_{0}m_{0} - f_{0} &= 0, \\
-bp_{0} + am_{0} &= 0.
\end{align*}
\]

3. Stability and Bifurcation Analysis

The regular operation of a system requires stability as a prerequisite. If the system is subjected to external interference, it will likely lose its stable state. Therefore, in many cases, examining the influence degree of interference parameters on stability is essential,
obtaining the critical conditions for the system’s instability and seeking effective control methods.

Only the positive equilibrium \((m_0, s_0, p_0)\) of the system is analyzed for stability. In order to facilitate subsequent derivation, let \(x_i(t) = m(t) - m_0, x_i(t) = s(t) - s_0,\)
\(x_i(t) = p(t) - p_0\) move the equilibrium point to the origin and derive the system’s origin-linearized equation:

\[
\begin{align*}
D^\alpha x_i(t) &= -(c + ds_0)x_i(t) - dm_0x_i(t) + g'(p_0)x_i(t - \tau_m), \\
D^\alpha x_i(t) &= -ds_0x_i(t) - (dm_0 + f)x_i(t), \\
D^\alpha x_i(t) &= ax_i(t - \tau_p) - bx_i(t).
\end{align*}
\] (9)

After Laplace changes, the characteristic equation corresponding to the linearized equation is obtained:

\[
\begin{vmatrix}
 s^\alpha + c + ds_0 & dm_0 & -g'(p_0)e^{-\tau_m} \\
 ds_0 & s^\alpha + dm_0 + f & 0 \\
 -ae^{-\tau_p} & 0 & s^\alpha + b
\end{vmatrix} = 0.
\] (10)

Equation (10) can be further converted into:

\[
s^{3\alpha} + L_3s^{2\alpha} + L_2s^\alpha + L_1s + L_0s^{\alpha - \tau} + L_0s^{\alpha - \tau} - L_\gamma = 0,
\] (11)

where

\[
\begin{align*}
 L_1 &= b + c + f + d(m_0 + s_0), \\
 L_2 &= b(c + f + d(m_0 + s_0))(ds_0 + c)(dm_0 + f), \\
 L_3 &= b(d(m_0 + c)(dm_0 + f), \\
 L_4 &= -ag'(p_0), \\
 L_5 &= -a(dm_0 + f)g'(p_0), \\
 L_6 &= d^2m_0s_0, \\
 L_7 &= bd^2m_0s_0, \\
 \tau &= \tau_m + \tau_p.
\end{align*}
\]

Then, taking the system the sum of time delay \((\tau = \tau_m + \tau_p)\) as the bifurcation parameter. The stability condition at the positive equilibrium point can be deduced according to time delay:

(1) If the System (9) is without time delay \((\tau = 0)\), Equation (11) becomes:

\[
s^{3\alpha} + L_3s^{2\alpha} + (L_2 + L_4 - L_6)s^\alpha + L_1s + L_0s^{\alpha - \tau} - L_\gamma = 0.
\] (12)

According to the Routh stability criterion, if

\[
\begin{align*}
 \Delta_1 &= L_1 > 0, \\
 \Delta_2 &= L_2 + L_4 - L_6 > 0, \\
 \Delta_3 &= L_1 + L_5 - L_7 > 0, \\
 \Delta_4 &= L_1(L_2 + L_4 - L_6) - L_1 - L_3 + L_7 > 0.
\end{align*}
\]

The roots of Equation (12) have no positive real parts, and the system does not contain positive real part roots, that is, \(\arg(\lambda_k) > \pi / 2(k = 1, 2, ..., 6)\). Obviously, \(\arg(\lambda_k) > \alpha \pi / 2\), and local asymptotic stability exists at the positive equilibrium point \((m_0, s_0, p_0)\).
If the system has time delay (immediate), Hopf bifurcation analysis is carried out based on the linearized characteristic equation.

If Equation (11) has a root \( s = i\omega = \omega(\cos(\pi/2) + i\sin(\pi/2)) (\omega > 0) \), it is substituted into Equation (11), and then we have separated parts:

\[
\begin{align*}
M_1\cos\omega\tau + N_1\sin\omega\tau &= R_i, \\
N_1\cos\omega\tau - M_1\sin\omega\tau &= S_i,
\end{align*}
\]

where

\[
\begin{align*}
M_1 &= L_4\omega^\alpha\cos(\pi\alpha/2) + L_5, \\
N_1 &= L_4\omega^\alpha\sin(\pi\alpha/2), \\
R_i &= -(\omega^\alpha\cos(3\pi\alpha/2) + L_4\omega^\alpha\cos(\pi\alpha) + (L_2 - L_7)\omega^\alpha\cos(\pi\alpha/2) + L_3 - L_7), \\
S_i &= -(\omega^\alpha\sin(3\pi\alpha/2) + L_4\omega^\alpha\sin(\pi\alpha) + (L_2 - L_7)\omega^\alpha\sin(\pi\alpha/2)).
\end{align*}
\]

From Equation (13) and \( \sin^2(\omega\tau) + \cos^2(\omega\tau) = 1 \), it can be obtained

\[
\begin{align*}
\cos\omega\tau &= (R_iM_1 + S_iN_1) / (M_1^2 + N_1^2), \\
\sin\omega\tau &= (R_iN_1 - S_iM_1) / (M_1^2 + N_1^2).
\end{align*}
\]

and

\[
\omega^\alpha + D_1\omega^{5\alpha} + D_2\omega^{4\alpha} + D_3\omega^{3\alpha} + D_4\omega^{2\alpha} + D_5\omega^\alpha + D_6 = 0,
\]

where

\[
\begin{align*}
D_1 &= 2L_4\cos(\pi\alpha/2), \\
D_2 &= L_1^2 + 2(L_2 - L_7)\cos(\pi\alpha), \\
D_3 &= 2(L_4L_7 - L_5)L_3\cos(\pi\alpha/2), \\
D_4 &= (L_2 - L_7)^2 - L_7^2 - 2L_4(L_2 - L_7)\cos(\pi\alpha), \\
D_5 &= 2L_4L_7(L_2 - L_7) - L_2L_3\cos(\pi\alpha/2), \\
D_6 &= (L_3 - L_7)^2 - L_2^2.
\end{align*}
\]

Defining function

\[
h(\omega) = \omega^\alpha + D_1\omega^{5\alpha} + D_2\omega^{4\alpha} + D_3\omega^{3\alpha} + D_4\omega^{2\alpha} + D_5\omega^\alpha + D_6.
\]

**Lemma 1.** For Equation \( h(\omega) = 0 \), has the following lemma:

1. If \( D_j > 0 (j = 1, 2, \ldots, 6) \), \( h(\omega) = 0 \) does not have a positive root, and Equation (11) does not have a pure imaginary root.
2. If \( D_j > 0 (j = 1, 2, \ldots, 5) \) and \( D_6 < 0 \), there is at least one positive root in \( h(\omega) = 0 \), then Equation (11) contains two pure imaginary roots.

**Proof.** Fractional derivative of \( h(\omega) \):

\[
h'(\omega) = 6\alpha\omega^{\alpha-1} + 5\alpha D_1\omega^{5\alpha-1} + 4\alpha D_2\omega^{5\alpha-1} + 3\alpha D_3\omega^{3\alpha-1} + 2\alpha D_4\omega^{2\alpha-1} + \alpha D_5\omega^{\alpha-1}.
\]
(1) According to $D_j > 0 (j = 1, 2, ..., 6)$, it can be concluded that $h'(\omega) > 0, \omega \in (0, +\infty)$ and $h(w)$ is a mono-increasing function. $h(0) = D_k > 0$, so $h(\omega) = 0$ has not positive root at $(0, +\infty)$.

(2) From $D_j > 0 (j = 1, 2, ..., 5)$ and $D_k < 0$ and $\lim_{z \to +\infty} h(w) > 0$. From the zero-point theorem, a positive number $\omega_0$ must exist to meet $h(\omega) = 0$. In this case, there are two pure imaginary roots in Equation (11), satisfying the Hopf bifurcation crossing conditions.

A positive root of $h(\omega) = 0$ indicates a crossover frequency $\omega_0$. To satisfy the generalization, we suppose that there are six positive real roots $\omega_m (m = 1, 2, ..., 6)$ in $h(\omega) = 0$. According to Equation (14), the delay parameter is expressed as follows:

$$\tau_k^* = \frac{1}{\omega_k} \left[ \arcsin \left( \frac{R_n N_k - S_k M_k}{M_k^2 + N_k^2} \right) + 2n\pi \right], k = 1, 2, ..., 6; n = 0, 1, 2, ...$$  \hspace{1cm} (18)

Then, it has value $\tau_0 = \min \left\{ \tau_k^* \right\}, \omega_0 = \omega_{e - \tau_0}$.

**Remark 1.** Formula (17) defines parameters the critical bifurcation delay and the critical bifurcation frequency. Where $\tau_0 = \min \left\{ \tau_k^* \right\}$ is the minimum critical bifurcation delay, and $\omega_0 = \omega_{e - \tau_0}$ is the corresponding frequency at this time, we can also call it the critical bifurcation frequency.

When Hopf bifurcation occurs in the system, its equilibrium point will lose stability. At this time, the system’s characteristic root just crosses from the left side of the imaginary axis to the right side of the imaginary axis. Therefore, a derivative of the characteristic root is obtained at the critical bifurcation point. The real part of the derivative is greater than zero. To further verify Hopf bifurcation crossing conditions, assumed that:

$$\text{HI} \quad \delta(\omega_0, \tau_0) > 0.$$  \hspace{1cm}

**Lemma 2.** If Equation (11) has a root $s(\tau) = \xi(\tau) + i\omega(\tau)$, so $\lim_{\tau \to \tau_0} \xi(\tau) = 0$ and $\lim_{\tau \to \tau_0} \omega(\tau) = \omega_0$. The cross-conditions apply if assumption (HI) holds:

$$\text{Re} \left[ \frac{ds}{d\tau} \right]_{\omega=\omega_0, \tau=\tau_0} > 0.$$  \hspace{1cm} (19)

**Proof.** Here is a derivation of Equation (11) with respect to $\tau$,

$$\frac{ds}{d\tau} = \frac{-s \left( -L_s s_3 + L_3 \right) e^{-\tau s}}{3\alpha s^{2s-1} + 2\alpha L_s s_3^{2s-1} + \alpha \left( L_2 - L_3 \right) s^{s-1} - \left( \alpha L_s s_3^{s+1} - \tau L_3 s^{s+1} - \tau L_3 \right) e^{-\tau s}}.$$  \hspace{1cm} (20)

Equation (19) yields

$$\text{Re} \left[ \frac{ds}{d\tau} \right]_{\omega=\omega_0, \tau=\tau_0} = \frac{A_i B_i + A_i B_i}{B_i^2 + B_i^2} = \frac{\delta(\omega_0, \tau_0)}{B_i^2 + B_i^2},$$  \hspace{1cm} (21)

where
\[A_i = a_i \left( L_i \omega_0^\alpha \cos \frac{\alpha \pi}{2} + L_i \right) \sin \omega_0 \tau_0 - L_i \omega_0^{\alpha+1} \sin \frac{\alpha \pi}{2} \cos \omega_0 \tau_0,\]
\[A_2 = a_0 \left( L_4 \omega_0^\alpha \cos \frac{\alpha \pi}{2} + L_0 \right) \cos \omega_0 \tau_0 + L_4 \omega_0^{\alpha+1} \sin \frac{\alpha \pi}{2} \cos \omega_0 \tau_0,\]
\[B_i = 3a_0 \omega_0^{\alpha+1} \cos \frac{(3\alpha - 1)\pi}{2} + 2a L_i \omega_0^{\alpha+1} \cos \frac{(2\alpha - 1)\pi}{2} + \alpha \left( L_2 - L_0 \right) \omega_0^{\alpha+1} \cos \frac{(\alpha - 1)\pi}{2} + \alpha \omega_0 \tau_0 - \tau_0 L_i \cos \omega_0 \tau_0,\]
\[B_2 = 3a_0 \omega_0^{\alpha+1} \sin \frac{(3\alpha - 1)\pi}{2} + 2a L_i \omega_0^{\alpha+1} \sin \frac{(2\alpha - 1)\pi}{2} + \alpha \left( L_2 - L_0 \right) \omega_0^{\alpha+1} \sin \frac{(\alpha - 1)\pi}{2} + \alpha \omega_0 \tau_0 - \tau_0 L_i \sin \omega_0 \tau_0.\]

Therefore, under the assumption that (HI) is true, the value of the denominator is always greater than zero according to calculation, which can prove that the Hopf bifurcation crossing condition is satisfied.

\[\square\]

The model’s stability condition and Lemmas 1 and 2 yield the following theorem.

**Theorem 1.** For a fractional-order delayed GRNs with sRNA:

1. If \( D_j > 0 \) (\( j = 1, 2, \ldots, 6 \)) and \( \Delta_i > 0 \) (\( i = 1, 2, 3 \)), then \( \forall \tau \geq 0 \), it is asymptotically stable at its positive equilibrium \((m_0, s_0, p_0)\).

2. If \( D_j > 0 \) (\( j = 1, 2, \ldots, 5 \)), \( D_k < 0 \) and \( \Delta_i > 0 \) (\( i = 1, 2, 3 \)), when \( 0 \leq \tau < \tau_0 \), it is asymptotically stable at its positive equilibrium point \((m_0, s_0, p_0)\). When \( \tau = \tau_0 \), Hopf bifurcation will occur at its positive equilibrium point \((m_0, s_0, p_0)\). When \( \tau > \tau_0 \), the system loses stability at its positive equilibrium point \((m_0, s_0, p_0)\), resulting in the phenomenon of limit cycles and periodic oscillations.

### 4. Bifurcation Control

In this section, in order to eliminate or retard the occurrence of Hopf bifurcation, and extend the stability range of a delay systems, a fractional PD control is applied to gene networks with sRNA. The system equation after adding the controller is expressed as follows:

\[
\begin{align*}
D^\alpha m(t) &= -cm(t) - ds(t)m(t) + g(p(t - \tau_m)), \\
D^\alpha s(t) &= e - ds(t)m(t) - fs(t), \\
D^\alpha p(t) &= -hp(t) + am(t - \tau_p) + kp(p(t) - p_0) + kd[D^\alpha (p(t) - p_0)].
\end{align*}
\]  

(22)

The meanings of biochemical parameters in System (21) are the same as those in System (7). \( kp \) represent the proportional gain coefficient and \( kd \) represent differential gain coefficient in the fraction-order PD controller. Similar to the derivation process when the controller is not applied, we study stability at positive equilibrium points \((m_0, s_0, p_0)\).

In order to facilitate theoretical derivation, move the equilibrium point to the origin and derive the system’s origin-linearized equation:

\[
\begin{align*}
D^\alpha \bar{m}(t) &= -\bar{m}(t) - g(p(t - \tau_m)), \\
D^\alpha \bar{s}(t) &= e, \\
D^\alpha \bar{p}(t) &= -hp(t) + am(t - \tau_p) + kp(p(t) - p_0) + kd[D^\alpha (p(t) - p_0)].
\end{align*}
\]
\[
D^\alpha x_1(t) = -(c + ds_0)x_1(t) - dm_0x_2(t) + g'(p_0)\left(t - \tau_m\right), \\
D^\alpha x_2(t) = -ds_0x_1(t) - (dm_0 + f)x_2(t), \\
D^\alpha x_3(t) = \frac{1}{1 - kd}\left[ax_3(t - \tau_p) + (-b + kp)x_3(t)\right].
\]  

(23)

Its characteristic equation is as follows:

\[
\begin{vmatrix}
\alpha + c + ds_0 & dm_0 & -g'(p_0)e^{-\tau_m} \\
d s_0 & s^\alpha + dm_0 + f & 0 \\
& -\alpha e^{-\tau_p} & \frac{b - kp}{1 - kd} \\
\end{vmatrix} = 0.
\]  

(24)

It can be further deduced from (23) that:

\[
s^{3\alpha} + F_1s^{2\alpha} + F_2s^\alpha + F_3 + F_4s^{\alpha + \tau} + F_6e^{-\tau_m}F_7s^\alpha - F_7s^\alpha - F_7 = 0,
\]  

(25)

where

\[
F_1 = \frac{b - kp}{1 - kd} + c + f + d(m_0 + s_0), \\
F_2 = \frac{(b - kp)(c + f + d(m_0 + s_0)) + (ds_0 + c)(dm_0 + f)}{1 - kd}, \\
F_3 = \frac{(b - kp)(ds_0 + c)(dm_0 + f)}{1 - kd}, \\
F_4 = \frac{-ag'(p_0)}{1 - kd}, \\
F_5 = \frac{-a(dm_0 + f)g'(p_0)}{1 - kd}, \\
F_6 = d^2m_0s_0, \\
F_7 = \frac{(b - kp)d^2m_0s_0}{1 - kd}, \\
\tau = \tau_m + \tau_p.
\]

The stability of the system and the Hopf bifurcation properties are investigated by taking the sum of time delay of the system under fractional PD control as the bifurcation parameter. There are also two situations:

1. If System (22) is without time delay (\(\tau = 0\)), Equation (24) becomes:

\[
s^{3\alpha} + F_1s^{2\alpha} + (F_2 - F_6)s^\alpha + F_3 + F_4s^{\alpha - \tau} - F_7s^\alpha - F_7 = 0.
\]  

(26)

The fractional-order Routh-Hurwitz stability criteria states that when \(\tau = 0, kp < b\) and \(kd < 1\) are true, then

\[
\Lambda_1 = F_1 > 0, \\
\Lambda_2 = F_2 + F_4 - F_6 > 0, \\
\Lambda_3 = F_3 + F_4 - F_7 > 0, \\
\Lambda_4 = F_1\left(F_2 + F_4 - F_6\right) - (F_3 + F_4 - F_7) > 0.
\]
In this case, the roots of Equation (25) have no positive real parts, and the system does not contain positive real part roots, that is, \( \arg(\lambda_k) > \pi / 2 \) \((k = 1, 2, ..., 6)\), then obviously \( \arg(\lambda_k) > \alpha \pi / 2 \), and local asymptotic stability exists at the positive equilibrium \((m_0, s_0, p_0)\).

(2) If the system has time delay \((\tau > 0)\), Hopf bifurcation analysis is carried out based on the linearized characteristic equation.

If Equation (24) has a root \( s = i\omega = \omega(\cos(\pi / 2) + i\sin(\pi / 2)) (\omega > 0) \), it is substituted into Equation (24), and then we have separated parts:

\[
\begin{align*}
M_2 \cos \omega \tau + N_2 \sin \omega \tau &= R_2, \\
N_2 \cos \omega \tau - M_2 \sin \omega \tau &= S_2,
\end{align*}
\]

where

\[
\begin{align*}
M_2 &= F_4 \omega^2 \cos(\pi \alpha / 2) + F_4, \\
N_2 &= F_4 \omega^2 \sin(\pi \alpha / 2), \\
R_2 &= -(\omega^3 \cos(3\pi \alpha / 2) + F_1 \omega^2 \cos(\pi \alpha) + (F_2 - F_6) \omega \cos(\pi \alpha / 2) + F_1 - F_3), \\
S_2 &= -(\omega^3 \sin(3\pi \alpha / 2) + F_1 \omega^2 \sin(\pi \alpha) + (F_2 - F_6) \omega \sin(\pi \alpha / 2)).
\end{align*}
\]

From Equation (26) and \( \sin^2(\omega \tau) + \cos^2(\omega \tau) = 1 \), it can be obtained

\[
\begin{align*}
\cos \omega \tau &= (R_2 M_2 + S_2 N_2) / (M_2^2 + N_2^2), \\
\sin \omega \tau &= (R_2 N_2 - S_2 M_2) / (M_2^2 + N_2^2),
\end{align*}
\]

and

\[
\omega^{6\alpha} + E_1 \omega^{5\alpha} + E_2 \omega^{4\alpha} + E_3 \omega^{3\alpha} + E_4 \omega^{2\alpha} + E_5 \omega^\alpha + E_6 = 0, \tag{29}
\]

Where

\[
\begin{align*}
E_1 &= 2F_1 \cos(\pi \alpha / 2), \\
E_2 &= F_1^2 + 2(F_2 - F_6) \cos(\pi \alpha), \\
E_3 &= 2(F_1(F_2 - F_6) \cos(\pi \alpha / 2) + (F_2 - F_6) \cos(3\pi \alpha / 2)), \\
E_4 &= (F_2 - F_6) F_3^2 + 2F_1(F_2 - F_6) \cos(\pi \alpha), \\
E_5 &= 2((F_2 - F_6)(F_3 - F_7) - F_1 F_6) \cos(\pi \alpha / 2), \\
E_6 &= (F_1 - F_3) F_2^2 - F_4^2.
\end{align*}
\]

Defining function

\[
f(\omega) = \omega^{6\alpha} + E_1 \omega^{5\alpha} + E_2 \omega^{4\alpha} + E_3 \omega^{3\alpha} + E_4 \omega^{2\alpha} + E_5 \omega^\alpha + E_6 = 0. \tag{30}
\]

**Lemma 3.** For Equation (29) \( f(\omega) = 0 \), has the following lemma:

(1) If \( E_j > 0 (j = 1, 2, ..., 6) \), \( f(\omega) = 0 \) has not positive root, then Equation (24) has no pure imaginary root.

(2) If \( E_j > 0 (j = 1, 2, ..., 5) \) and \( E_6 < 0 \), then \( kd < 1 \) and \( a_1'(p^*) / c + b < kp < b \), there is at least a positive root in \( f(\omega) = 0 \), there are two pure imaginary roots in Equation (24).
Proof. Fractional derivative of \( f(\omega) \):
\[
f'(\omega) = 6\alpha\omega^{\alpha-1} + 5\alpha E_\alpha \omega^{\alpha-1} + 4\alpha E_2 \omega^{\alpha-1} + 3\alpha E_\alpha \omega^{\alpha-1} + 2\alpha E_2 \omega^{\alpha-1} + \alpha E_\alpha \omega^{\alpha-1}.
\]
When \( kd < 1 \) and \( ag' (\rho^*)/c + b < kp < b \), for \( \omega \in [0, +\infty) \), \( f'(\omega) > 0 \) is constant, that is, \( f(\omega) \) increases monotonically. And \( f(0) = E_\alpha < 0 \) is greater than 0, and we can be sure that \( \lim_{\omega \to +\infty} f(\omega) = +\infty \). From the zero-point theorem, we can judge that there must be a positive number \( \omega \), which makes \( f(\omega_0') = 0 \), that is, \( \omega_0' \) is the solution of function \( f(\omega) \).

Similarly, A positive root of \( f(\omega) = 0 \) indicate a crossover frequency \( \omega_0' \). In general, if there are 6 positive roots of \( f(\omega) = 0 \), then the corresponding traverse frequency \( \omega_0' \) also has 6 positive values, namely \( \omega_0'(m = 1, 2, \ldots, 6) \). At this time, the expression of critical bifurcation delay can be solved by Equation (27), namely:
\[
\tau^*_e = \frac{1}{\omega_0'[\arcsin(\frac{R_2 N_1 - S M_2}{M_2 + N_1}) + 2n\pi], k = 1, 2, \ldots; n = 0, 1, 2, \ldots} \quad (31)
\]
Then, it has value \( \tau_0' = \min \{ \tau^*_e \} \), \( \omega_0' = \omega_{e-\tau_0'} \).

Similarly, to further verify Hopf bifurcation crossing conditions, assumed that:

\( (H2) \quad \partial(\omega_0, \tau_0) > 0. \)

Lemma 4. If Equation (24) has a root \( s(\tau) = \xi(\tau) + i\omega(\tau) \), so \( \lim_{\tau \to 0} \xi(\tau) = 0 \) and \( \lim_{\tau \to 0} \omega(\tau) = \omega_0' \). The cross-conditions apply if assumption \( (H1) \) holds:
\[
\text{Re}\left\{ \frac{d s}{d \tau} \right\}_{\tau = \omega_0', \tau = \tau_0'} > 0. \quad (32)
\]

The proof of Hopf bifurcation crossing condition of the corresponding model under fractional PD control is similar to that without controller, so we will not go into details here.

Theorem 2. For the fractional gene regulatory network under the action of fractional PD controller, the following conclusions are valid:

1. If \( E_j > 0 \) (\( j = 1, 2, \ldots, 6 \)) and \( \Lambda_i > 0 \) (\( i = 1, 2, 3 \)), then \( \forall \tau \geq 0 \), the system is asymptotically stable at its positive equilibrium point \( (m_0, s_0, p_0) \).
2. If \( E_j > 0 \) (\( j = 1, 2, \ldots, 5 \)), \( E_\alpha < 0 \) and \( \Lambda_i > 0 \) (\( i = 1, 2, 3 \)), when \( 0 \leq \tau < \tau_0' \), the system is asymptotically stable at its positive equilibrium point \( (m_0, s_0, p_0) \). When \( \tau = \tau_0' \), Hopf bifurcation will occur at its positive equilibrium point \( (m_0, s_0, p_0) \). When \( \tau > \tau_0' \), the system loses stability at its positive equilibrium point \( (m_0, s_0, p_0) \), resulting in the phenomenon of limit cycles and periodic oscillations.

5. Simulation Examples

In this section, fractional order predictive correction algorithm is used for numerical simulation [34]. Firstly, the stability and bifurcation analysis of the system are simulated, and then the bifurcation control of the system is simulated, so as to verify the control effect of fractional PD controller on the instability of the system caused by large time delay.
5.1. Stability and Bifurcation Analysis

To verify the correctness of theoretical analysis results, the parameter involved in System (7) is set as [26]:

\[ a = 1, \ b = 0.1, \ c = 0.2, \ d = 1, \ e = 1, \ f = 0.25, \ g(p) = \frac{200}{100 + p^2}. \]

Through calculation, it can be known that the positive equilibrium point \( (m_0, s_0, p_0) \) of the system at this time is \( (1, 0.8, 10) \).

Set fractional order \( \alpha = 0.98 \), fix other parameters, and draw the single-parameter bifurcation diagram of variables with respect to time delay, as shown in Figure 1. The red solid line and black dashed line represent the equilibrium point of stability and instability of the system respectively, while the green dotted line represents the stable periodic solution generated by Hopf. At this point, the system’s critical bifurcation delay \( \tau_0 \approx 8.251 \), and when \( \tau = 7.2 < \tau_0 \), the system is asymptotically stable at the equilibrium point, as shown in Figure 2. When \( \tau = 9.2 > \tau_0 \) is taken, Hopf bifurcation occurs at the equilibrium point of the system, resulting in a limit cycle, as shown in Figure 3.

![Bifurcation diagram](image)

**Figure 1.** Bifurcation diagram of \( m(t), s(t), p(t) \) with respect to time delay with \( \alpha = 0.98 \). In Figs (a) - (c), when the parameter \( \tau \) is valued on the red solid line segment, the equilibrium point of the system is stable. When the parameter \( \tau \) is taken on the black dotted line, the equilibrium point of the system is unstable; when the parameter \( \tau \) is valued on the green dotted line, the equilibrium point of the system will have a stable limit cycle, where \( \tau_0 \) is the critical bifurcation point of time delay.
Figure 2. (a): Phase portrait and (b): Waveform plot with $\alpha = 0.98, \tau = 7.2 < \tau_0$.

Figure 3. (a): Phase portrait and (b): Waveform plot with $\alpha = 0.98, \tau = 9.2 > \tau_0$.

Change the fractional order to $\alpha = 0.94$, and draw the single-parameter bifurcation diagram of system variables with respect to time delay again, as shown in Figure 4. At this time, the system’s critical bifurcation delay $\tau_0 \approx 9.997$, compared with the time when order $\alpha = 0.98$, the bifurcation point has a delay. When $\tau = 9.2 < \tau_0$ is taken, the system is asymptotically stable at the equilibrium point, as shown in Figure 5. When $\tau = 11.2 > \tau_0$ is taken, there is a Hopf bifurcation at the system’s equilibrium, and a stable limit cycle and periodic oscillation are generated, as shown in Figure 6.
Figure 4. Bifurcation diagram of $m(t), s(t), p(t)$ with respect to time delay with $\alpha = 0.94$. In Figs (a) - (c), when the parameter $\tau$ is valued on the red solid line segment, the equilibrium point of the system is stable. When the parameter $\tau$ is taken on the black dotted line, the equilibrium point of the system is unstable; when the parameter $\tau$ is valued on the green dotted line, the equilibrium point of the system will have a stable limit cycle, where $\tau_0$ is the critical bifurcation point of time delay.

Figure 5. (a): Phase portrait and (b): Waveform plot with $\alpha = 0.94, \tau = 9.2 < \tau_0$.

Figure 6. (a): Phase portrait and (b): Waveform plot with $\alpha = 0.94, \tau = 11.2 > \tau_0$.

Next, in order to fully consider the impact of system order variation on its critical bifurcation point, the fractional order changes constantly, and then the corresponding cross frequency $\omega_0$ and critical bifurcation delay $\tau_0$ are obtained respectively according to Equations (16) and (17). The data records are shown in Table 1. According to Table 1, the relationship curve between critical delay $\tau_0$ and fractional order $\alpha$, as shown in
Figure 7. The results show that the critical bifurcation delay $\tau_0$ of the system declines as the order $\alpha$ increases. It is proved again that the fractional order system has a wider stability range than the integer order system, and the lower the order, the wider the stability range. This is also the significance of investigating systems with fractional orders, that is, constantly breaking the bounds of previous integer order systems, seeking the possibility of differences in system dynamics behavior.

Table 1. Effect of fractional order on critical bifurcation delay

<table>
<thead>
<tr>
<th>Order $\alpha$</th>
<th>Cross frequency $\omega_b$</th>
<th>Bifurcation delay $\tau_0$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.189</td>
<td>7.497</td>
</tr>
<tr>
<td>0.98</td>
<td>0.177</td>
<td>8.251</td>
</tr>
<tr>
<td>0.96</td>
<td>0.168</td>
<td>9.081</td>
</tr>
<tr>
<td>0.94</td>
<td>0.157</td>
<td>9.997</td>
</tr>
<tr>
<td>0.92</td>
<td>0.148</td>
<td>11.012</td>
</tr>
<tr>
<td>0.90</td>
<td>0.138</td>
<td>12.142</td>
</tr>
<tr>
<td>0.88</td>
<td>0.129</td>
<td>13.402</td>
</tr>
<tr>
<td>0.86</td>
<td>0.120</td>
<td>14.815</td>
</tr>
<tr>
<td>0.84</td>
<td>0.111</td>
<td>16.406</td>
</tr>
<tr>
<td>0.82</td>
<td>0.103</td>
<td>18.205</td>
</tr>
<tr>
<td>0.80</td>
<td>0.094</td>
<td>20.250</td>
</tr>
<tr>
<td>0.78</td>
<td>0.087</td>
<td>22.586</td>
</tr>
</tbody>
</table>

Figure 7. The relationship between critical bifurcation delay $\tau_0$ and fractional order $\alpha$.

5.2. Bifurcation Control

To further enhance the dynamic performance of the system and broaden the system’s stability range, a fractional PD controller is implemented for the system.

Set the proportional gain coefficient of the controller as $kp = -0.1$ and the differential gain coefficient as $kd = 0.4$. When the fractional order $\alpha = 0.94$, the critical bifurcation delay $\tau_0' \approx 17.603$ can be obtained according to Equations (29) and (30), which is significantly improved compared with the critical bifurcation delay $\tau_0 \approx 9.997$ before the controller is applied. This means that the system is able to approach an asymptotic steady state again in the original unstable position after control is applied to the system, it is shown that the adopted controller is able to retard the occurrence of Hopf bifurcation in the system, allowing the system to remain stable in a larger time delay region, as shown in Figure 8.
Figure 8. (a): Phase portrait (b): Waveform plot with $\alpha = 0.94, kp = -0.1, kd = 0.4, \tau = 11.2 < \tau_o$.

With a fixed controller parameter value of $kp = -0.1, kd = 0.4$, as fractional order $\alpha$ changes, the critical bifurcation delay of the system still decreases with the increase of the order. The relationship between critical bifurcation delay $\tau_o'$ and fractional order $\alpha$ of the system is shown in Figure 9.

![Figure 9](image)

Figure 9. The relationship between critical bifurcation delay $\tau_o'$ and fractional order $\alpha$.

With fixed differential gain coefficient $kd = 0.4$, the proportional gain coefficient $kp$ is changed to study its effect of $kp$ on the critical point of bifurcation. It is observed that as $kp$ increases, $\tau_o'$ (the crucial delay of bifurcation) decreases, there is a faster deceleration when the fractional order is lower, as shown in Figure 10.
Similarly, the fixed proportional gain coefficient $kp = -0.1$ changes the size of the differential gain coefficient $kd$, and the influence of $kd$ on critical point of bifurcation is studied. It is found that as $kd$ increases, $\tau_0'$ (the critical delay of bifurcation) decreases, there is a faster deceleration when the fractional order is lower, as shown in Figure 11.

![Figure 11](image)

Figure 11. The relationship diagram between proportional gain coefficient $kd$ and critical delay of bifurcation $\tau_0'$ with $kp = -0.1$.

6. Conclusions

A class of delay GRNs with sRNA is investigated in this paper. Firstly, the characteristic equation of the linearized system at the origin is obtained. Then, according to Routh-Hurwitz’s fractional-order stability criteria and the Hopf bifurcation theory of fractional system, the local stability of the system at positive equilibrium is discussed according to whether the delay exists in two cases. Finally, sufficient conditions for Hopf bifurcation are derived. The simulation results indicate that the system undergoes Hopf bifurcation and produces a stable periodic state when the system delay increases to the critical
bifurcation point. The corresponding critical bifurcation frequency and critical bifurcation delay are obtained by constantly changing the fractional order. It was discovered that the creation of bifurcation points could be postponed by decreasing the system’s order; i.e., a fractional order system has a broader stability domain than its integer order counterpart.

In addition, in view of the instability of the equilibrium point caused by the large time delay of the system, a fractional-order PD controller is applied to the system to enhance its dynamic performance. The conditions for the control parameters to meet the system’s stability are deduced through theoretical analysis. It provides the possibility to control the dynamic behavior of nonlinear systems, and the stability range of the system can be effectively expanded by changing the parameter values of the controller within a certain range.

Fractional order nonlinear systems are commonly studied by introducing terms into the controller to counteract nonlinear effects in the original system. This results in complex controllers that are difficult to implement and costly to control. Therefore, how to design simple and easy-to-implement controllers to achieve general forms of fractional-order nonlinear system stability has become a hot issue in current research.

Traditional control theory is linear control theory. It assumes the system is linear, i.e., a linear relationship exists between the output and the system’s input. In contrast, bifurcation-based dynamics control is a nonlinear control theory that considers the system’s nonlinear characteristics, i.e., a nonlinear relationship exists between the output and the system’s input. Therefore, bifurcation-based dynamics control can better describe and control nonlinear systems. Nonlinear dynamical systems are studied using bifurcation theory, which focuses on the system’s stability when parameters change and the bifurcation phenomena.

In this paper, we study the bifurcation analysis and control problems of low-dimensional systems, single-node network systems, which are relatively easy to solve; however, in reality, natural network systems are complex multi-dimensional systems formed by multi-node interactions and mutual coupling, and we will study the dynamics analysis and control problems of such multi-node coupled complex network systems in the future.

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