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Parameter identification of genetic regulatory network with time-varying delays via adaptive synchronization method

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Abstract

In this paper, the parameter identification of gene regulatory network with time-varying delay is studied. Firstly, we introduce the differential equation model of gene regulatory network with unknown parameters and time delay. Secondly, for the unknown parameters in the time-varying model, a corresponding system with adaptive parameters and adaptive controller is introduced, and the parameter identification problem of the original model is transformed into the synchronization problem of the two systems. Thirdly, we design an effective adaptive controller and an adaptive law for parameters and construct a Lyapunov functional. Then we give a strict theoretical proof that the adaptive parameters can converge to unknown parameters by Barbalat's lemma. Finally, a numerical example is given to verify the validity of the theoretical results.

Keywords: Parameter identification; Genetic regulatory network; Adaptive synchronization

1 Introduction

As a complex system, genetic regulatory networks (GRNs) could describe the complicated regulatory mechanism in living cells, which consist of DNA, RNA (especially mRNA), proteins, and some other micro-molecules [1, 2]. In the past decades, GRNs have attracted many researchers from some different fields, such as applied mathematics, systems biology, molecular biology, etc. Several kinds of models have been proposed and investigated, for example, Boolean networks model [3], Bayesian networks model [4], weighted matrices model [5], differential equation model [6], and so on.

Among those models, the differential equation models could describe the change in concentration of proteins and mRNA, which could reflect the nonlinear dynamical behaviors of biological process, thus, the differential equation models have been discussed widely in recent years. The differential equation models were modeled to describe gene expression process in [7] at first. Then, many results about dynamic analysis about GRNs have been published. For example, stability [8–10], stabilization [11–14], bifurcation [15–17], state estimation [18–20], and so on.

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In the above results, the models are known. In many real world GRNs, one can determine the structure of the differential equation model according to some indetermination. However, the parameters of models may be unknown or different in various cells. Consequently, parameter identification of unknown GRNs is an interesting and important work. The common strategy of parameter identification is translating it into an optimization problem, in which the unknown parameters could be regarded as decision variables, while minimizing the error between pseudo state and real state could be regarded as optimization objective. Then, the problem could be solved by intelligent optimization algorithms. For example, Zhao and Yin have studied the parameter identification problem in geomechanics by particle swarm optimization and support vector machine methods [21]. Parameter identification of solar cell models according to artificial bee swarm optimization algorithm has been investigated in [22]. More recently, parameter identification of photovoltaic models using an improved JAYA optimization algorithm has been discussed in [23]. As for the GRNs, Tang and Wang have considered the problem of parameter identification of unknown delayed GRNs by a switching particle swarm optimization algorithm [24].

There were also some results about parameter identification problem for differential equations via adaptive synchronization method. In which, an auxiliary system would be constructed as a response system. Then, the adaptive laws would be designed to synchronize the auxiliary system to the unknown system. Meanwhile, the parameters in the auxiliary system were also updated with some adaptive laws. When the synchronization was achieved, the adaptive parameters were supposed to approach the unknown parameters. This significant method was proposed by Chen and Lv in [25]. Then, some related results have also been published, one can see [26–30]. For different models, the adaptive laws would be designed in different forms, which brings difficulties and challenges to this method.
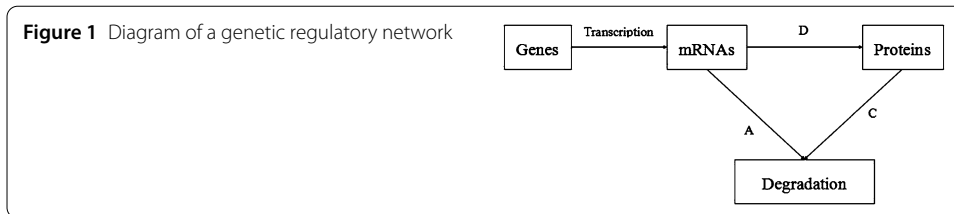
Time delay often occurs due to transportation lag. And the existence of delays is a frequently result in instability, bifurcation, and chaos for dynamical systems. Therefore, there are many results about time delay systems [31–35]. Inspired by the above analysis, this paper studies the parameter identification problem of GRNs with time delay. We design some effective adaptive laws of linear feedback controllers and parameters in an auxiliary system. According to rigorous theoretical analysis, the synchronization could be achieved between the auxiliary system and the unknown system. Meanwhile, all the unknown parameters in the time-delayed GRNs could be estimated. The rest of the paper is organized as follows: In Sect. 2, we introduce the models of GRNs at first, and then the parameter identification problem is converted into a synchronization problem, some useful lemmas are also given in this section. The main results about synchronization and parameter identification are presented in Sect. 3. Then, some examples are given to demonstrate the effectiveness of our results in Sect. 4. Conclusions are finally drawn in Sect. 5.

2 Preliminaries

2.1 Basic model of GRN

In this paper, we consider the following GRN model with time-varying delay, which has been proposed in [6]:

$$\begin{cases} \dot{m}(t) = -Am(t) + Wf(p(t - \tau_1(t))) + L, \\ \dot{p}(t) = -Cp(t) + Dm(t - \tau_2(t)), \end{cases} \tag{1}$$

Figure 1 Diagram of a genetic regulatory network

where $m(t) = [m_1(t), m_2(t), \ldots, m_n(t)]^T \in \mathbb{R}^n$, $p(t) = [p_1(t), p_2(t), \ldots, p_n(t)]^T \in \mathbb{R}^n$, and $m_i(t)$, $p_i(t)$ are concentrations of ith mRNA and ith protein at the time t, respectively. Based on the central dogma, a simplified dynamic system of gene regulation can be described as Fig. 1. $A = \text{diag}\{a_1, a_2, \ldots, a_n\} > 0$ and $C = \text{diag}\{c_1, c_2, \ldots, c_n\} > 0$ are the degradation rates of the mRNAs and proteins, respectively. The nonlinear function $f(\cdot)$ denotes feedback regulation from protein to transcription factor with $f(\cdot) = [f_1(\cdot), f_2(\cdot), \ldots, f_n(\cdot)] \in \mathbb{R}^n$, and $f_i(x)$ is a monotonic increasing function with a Hill form:

$$f_i(x) = \frac{(x/\beta_i)^{H_i}}{1 + (x/\beta_i)^{H_i}},$$

where H_i called the Hill coefficients, β_i are positive constants, $i = 1, 2, \ldots, n$. $D = \text{diag}\{d_1, d_2, \ldots, d_n\}$, and d_i is the translation rate of ith protein. $\tau_1(t)$ and $\tau_2(t)$ are time-varying delays, which denote the translation delay and the feedback regulation delay, respectively. $L = [l_1, l_2, \ldots, l_n]^T \in \mathbb{R}^n$, where $l_i = \sum_{j \in I_i} \alpha_{ij}$, in which I_i is the set of all the repressors of gene i. $W = (w_{ij}) \in \mathbb{R}^{n \times n}$ with
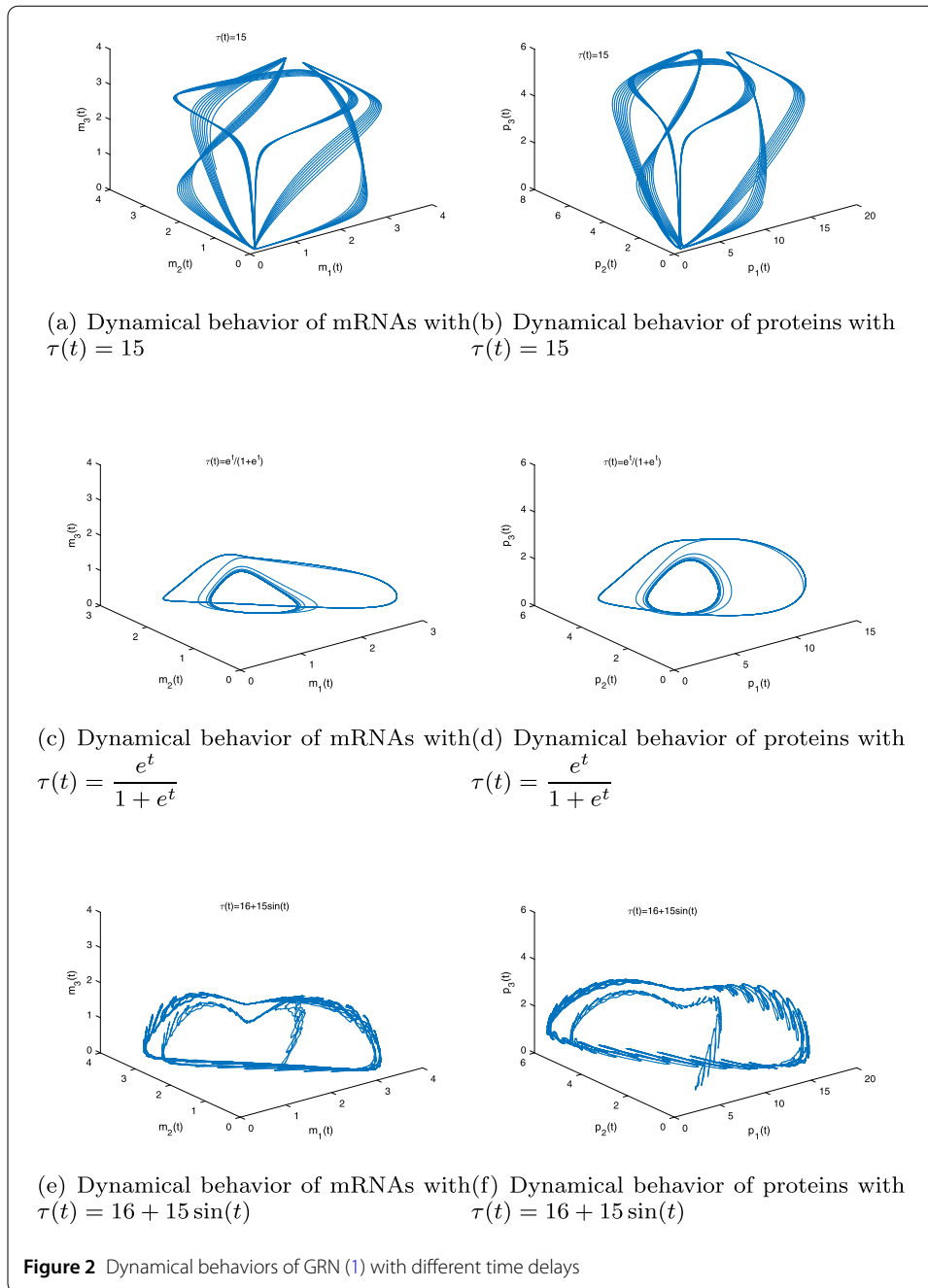
$$w_{ij} = \begin{cases} \alpha_{ij}, & \text{if transcription factor } j \text{ is an activator of gene } i, \\ 0, & \text{if there is no link from node } j \text{ to } i, \\ -\alpha_{ij}, & \text{if transcription factor } j \text{ is a repressor of gene } i. \end{cases}$$

Assumption 1 We assume that the time-varying delays $\tau_1(t)$ and $\tau_2(t)$ are satisfied: $\dot{\tau}_i(t) \leq \mu_i < 1$, $i = 1, 2$.

Assumption 2 It is obvious that the function $f_i(\cdot)$ satisfies the Lipschitz condition, we assume that there are constants $h_i \geq 0$, $i = 1, 2, \ldots, n$, such that, for any $x, y \in \mathbb{R}$, one has $|f_i(y) - f_i(x)| \leq h_i|y - x|$, $i = 1, 2, \ldots, n$.

Remark 1 The above two assumptions are very common. Clearly, Assumption 1 is certainly ensured if the transmission delay is constant, and many results have the same assumption, see for example [36–39] and the references therein. In addition, Assumption 2 can guarantee the existence and uniqueness of the solution for system (1); thus, the proof of the existence and uniqueness of the solution for system (1) is omitted here.

Remark 2 Time-varying delays have been considered in the above GRN model. Time delays are unavoidable in real world. Indeed, systems with time delays exhibit much more complicated dynamical behaviors than ordinary differential equations without time delays. Figure 2 shows some different dynamical behaviors under different time delays for GRN (1). In which, let $\tau_1(t) = \tau_2(t) = \tau(t)$, the other parameters are the same as the ones in the simulation part.

(a) Dynamical behavior of mRNAs with (b) Dynamical behavior of proteins with $\tau(t) = 15$ $\tau(t) = 15$

(c) Dynamical behavior of mRNAs with (d) Dynamical behavior of proteins with
$\tau(t) = \dfrac{e^t}{1 + e^t}$ $\tau(t) = \dfrac{e^t}{1 + e^t}$

(e) Dynamical behavior of mRNAs with (f) Dynamical behavior of proteins with
$\tau(t) = 16 + 15\sin(t)$ $\tau(t) = 16 + 15\sin(t)$

Figure 2 Dynamical behaviors of GRN (1) with different time delays

2.2 Description of parameter identification and transformation

Noting that in many real situations the parameter matrices A, C, W, and D maybe unknown, we identify those unknown parameters by adaptive synchronization method in this paper. Model (1) could be regarded as a driven system. We construct the following response system:

$$\begin{cases} \dot{\hat{m}}(t) = -\hat{A}(t)\hat{m}(t) + \hat{W}(t)f(\hat{p}(t - \tau_1(t))) + L + u_1(t), \\ \dot{\hat{p}}(t) = -\hat{C}(t)\hat{p}(t) + \hat{D}(t)\hat{m}(t - \tau_2(t)) + u_2(t), \end{cases} \tag{2}$$

where $\hat{m}(t) = [\hat{m}_1(t), \hat{m}_2(t), \ldots, \hat{m}_n(t)]^T \in \mathbb{R}^n$, $\hat{p}(t) = [\hat{p}_1(t), \hat{p}_2(t), \ldots, \hat{p}_n(t)]^T \in \mathbb{R}^n$, $\hat{A}(t) = (\hat{a}_{ij}(t))_{n \times n}$, $\hat{W}(t) = (\hat{w}_{ij}(t))_{n \times n}$, $\hat{C}(t) = (\hat{c}_{ij}(t))_{n \times n}$, and $\hat{D}(t) = (\hat{d}_{ij}(t))_{n \times n}$ are the estimations of unknown parameters A, W, C, and D, respectively. $u_1(t)$ and $u_2(t)$ are the feedback controllers to be designed later. Because there are unknown parameters A, W, C, and D in the driven system, we cannot construct an identical system. In addition, the complete synchronization between (1) and (2) cannot be achieved by the static linear feedback control method. Therefore, the adaptive control strategy is used in this manuscript; meanwhile, the parameters $\hat{A}(t)$, $\hat{W}(t)$, $\hat{C}(t)$, and $\hat{D}(t)$ are also assumed to be time-varying.

3 Main results

3.1 The design of adaptive laws

Let $x(t) = \hat{m}(t) - m(t) = [x_1(t), x_2(t), \ldots, x_n(t)]^T \in \mathbb{R}^n$, $y(t) = \hat{p}(t) - p(t) = [y_1(t), y_2(t), \ldots, y_n(t)]^T \in \mathbb{R}^n$. The adaptive controllers

$$u_1(t) = E_1(t)x(t) \quad \text{and} \quad u_2(t) = E_2(t)y(t),$$

where $E_1(t) = \mathrm{diag}\{\varepsilon_1^x(t), \varepsilon_2^x(t), \ldots, \varepsilon_n^x(t)\}$ and $E_1(t) = \mathrm{diag}\{\varepsilon_1^y(t), \varepsilon_2^y(t), \ldots, \varepsilon_n^y(t)\}$ are dynamical feedback control gain matrices. Then, it is easy to get the error system as follows:

$$\begin{cases} \dot{x}(t) = -Ax(t) + W\tilde{f}(y(t - \tau_1(t))) + \tilde{A}(t)\hat{m}(t) - \tilde{W}(t)f(\hat{p}(t - \tau_1(t))) + E_1(t)x(t), \\ \dot{y}(t) = -Cy(t) + Dx(t - \tau_2(t)) + \tilde{C}(t)\hat{p}(t) - \tilde{D}(t)\hat{m}(t - \tau_2(t)) + E_2(t)y(t), \end{cases} \quad (3)$$

where $\tilde{f}(y)(t - \tau_1(t)) = f(y(t - \tau_1(t)) + p(t - \tau_1(t))) - f(p(t - \tau_1(t)))$, $\tilde{A}(t) = A - \hat{A}(t)$, $\tilde{W}(t) = W - \hat{W}(t)$, $\tilde{C}(t) = C - \hat{C}(t)$ and $\tilde{D}(t) = D - \hat{D}(t)$.

In this paper, we design the adaptive laws as follows:

$$\begin{cases} \dot{\varepsilon}_i^x(t) = -\eta_i^x x_i^2(t), \\ \dot{\varepsilon}_i^y(t) = -\eta_i^y y_i^2(t), \\ \dot{\hat{a}}_i(t) = \sigma_i^x x_i(t)\hat{m}_i(t), \\ \dot{\hat{c}}_i(t) = \sigma_i^x y_i(t)\hat{p}_i(t), \\ \dot{\hat{w}}_{ij}(t) = -\gamma_{ij}^x x_i(t)\tilde{f}_j(\hat{p}_j(t - \tau_1(t))), \\ \dot{\hat{d}}_{ij}(t) = -\gamma_{ij}^y y_i(t)(\hat{m}_j(t - \tau_2(t))), \quad i, j = 1, 2, \ldots, n, \end{cases} \quad (4)$$

where $\eta_i^x > 0$, $\eta_i^y > 0$, $\sigma_i^x > 0$, $\sigma_i^y > 0$, $\gamma_{ij}^x > 0$, $\gamma_{ij}^y > 0$ are arbitrary constants for $i, j = 1, 2, \ldots, n$.

3.2 The main theorem

Theorem 1 *Under Assumptions* 1, 2 *and controllers* $u_1(t) = E_1(t)x(t)$ *and* $u_2(t) = E_2(t)y(t)$ *with adaptive laws* (4), *the synchronization can be achieved between* (1) *and* (2). *Furthermore, the unknown parameters can be estimated, that is,* $\lim_{t \to +\infty}(a_i - \hat{a}_i(t)) = 0$, $\lim_{t \to +\infty}(w_{ij} - \hat{w}_{ij}(t)) = 0$, $\lim_{t \to +\infty}(c_i - \hat{c}_i(t)) = 0$, $\lim_{t \to +\infty}(d_{ij} - \hat{d}_{ij}(t)) = 0, j = 1, 2, \ldots, n$.

Proof Construct a Lyapunov function:

$$V(t) = \frac{1}{2}x^T(t)x(t) + \frac{1}{2}y^T(t)y(t) + \frac{1}{2}\sum_{i=1}^{n}\frac{1}{\sigma_i^x}\hat{a}_i^2(t) + \frac{1}{2}\sum_{i=1}^{n}\frac{1}{\sigma_i^y}\hat{c}_i^2(t)$$

$$+ \frac{1}{2}\sum_{i=1}^{n}\sum_{j=1}^{n}\frac{1}{\gamma_{ij}^x}\hat{w}_{ij}^2(t) + \frac{1}{2}\sum_{i=1}^{n}\sum_{j=1}^{n}\frac{1}{\gamma_{ij}^y}\hat{d}_{ij}^2(t)$$

$$+ \frac{1}{2}\sum_{i=1}^{n}\frac{1}{\eta_i^x}\left(\varepsilon_i^x(t) + l\right)^2 + \frac{1}{2}\sum_{i=1}^{n}\frac{1}{\eta_i^y(t)}\left(\varepsilon_i^y(t) + l\right)^2$$

$$+ \frac{1}{2(1-\mu_1)}\int_{t-\tau_1(t)}^{t} x^T(\theta)x(\theta)\,d\theta + \frac{1}{2(1-\mu_2)}\int_{t-\tau_2(t)}^{t} y^T(\theta)y(\theta)\,d\theta,$$

where $l > \max(\lambda_{\max}(\frac{1}{2}WW^T - A + \frac{1}{2(1-\mu_1)}LI), \lambda_{\max}(\frac{1}{2}DD^T - C + \frac{1}{2(1-\mu_2)}I)) + 1 > 0$ is a constant.
Although the parameters W, A, D, C are unknown, one can select l to be a sufficiently large
constant to guarantee the above inequality.

Along any trajectory of the error system, the derivative is

$$\dot{V}(t) = x^T(t)\dot{x}(t) + y^T(t)\dot{y}(t) - \sum_{i=1}^{n}\hat{a}_i(t)x_i(t)m_i(t) - \sum_{i=1}^{n}\hat{c}_i(t)y_i(t)p_i(t)$$

$$+ \sum_{i=1}^{n}\sum_{j=1}^{n}\hat{w}_{ij}(t)x_i(t)f_j\left(\hat{p}_j\left(t - \tau_1(t)\right)\right) + \sum_{i=1}^{n}\sum_{j=1}^{n}\hat{d}_{ij}(t)y_i(t)\hat{m}_j\left(t - \tau_2(t)\right)$$

$$- \sum_{i=1}^{n}\left(\varepsilon_i^x(t) + l\right)x_i^2(t) - \sum_{i=1}^{n}\left(\varepsilon_i^y(t) + l\right)y_i^2(t) + \frac{1}{2(1-\mu_1)}\tilde{f}^T\left(x(t)\right)\tilde{f}\left(x(t)\right)$$

$$- \frac{1-\dot{\tau}_1(t)}{2(1-\mu_1)}\tilde{f}^T\left(x\left(t - \tau_1(t)\right)\right)\tilde{f}\left(x\left(t - \tau_1(t)\right)\right) + \frac{1}{2(1-\mu_2)}y^T(t)y(t)$$

$$- \frac{1-\dot{\tau}_2(t)}{2(1-\mu_2)}y^T\left(t - \tau_2(t)\right)y\left(t - \tau_2(t)\right)$$

$$= -x^T(t)Ax(t) + x^T(t)W\tilde{f}\left(y\left(t - \tau_1(t)\right)\right) + x^T(t)\tilde{A}(t)\hat{m}(t)$$

$$- x^T(t)\tilde{W}(t)f\left(\hat{p}\left(t - \tau_1(t)\right)\right) + x^T(t)E_1(t)x(t)$$

$$- y^T(t)Cy(t) + y^T(t)Dx\left(t - \tau_2(t)\right) + y^T(t)\tilde{C}(t)\hat{p}(t) - y^T(t)\tilde{D}(t)\hat{m}\left(t - \tau_2(t)\right)$$

$$+ y^T(t)E_2(t)y(t)$$

$$- \sum_{i=1}^{n}\hat{a}_i(t)x_i(t)m_i(t) - \sum_{i=1}^{n}\hat{c}_i(t)y_i(t)p_i(t) + \sum_{i=1}^{n}\sum_{j=1}^{n}\hat{w}_{ij}(t)x_i(t)f_j\left(\hat{p}_j\left(t - \tau_1(t)\right)\right)$$

$$+ \sum_{i=1}^{n}\sum_{j=1}^{n}\hat{d}_{ij}(t)y_i(t)\hat{m}_j\left(t - \tau_2(t)\right) - \sum_{i=1}^{n}\left(\varepsilon_i^x(t) + l\right)x_i^2(t) - \sum_{i=1}^{n}\left(\varepsilon_i^y(t) + l\right)y_i^2(t)$$

$$+ \frac{1}{2(1-\mu_1)}\tilde{f}^T\left(x(t)\right)\tilde{f}\left(x(t)\right) + \frac{1}{2(1-\mu_2)}y^T(t)y(t)$$

$$- \frac{1-\dot{\tau}_2(t)}{2(1-\mu_2)}y^T\left(t - \tau_2(t)\right)y\left(t - \tau_2(t)\right) - \frac{1-\dot{\tau}_1(t)}{2(1-\mu_1)}\tilde{f}^T\left(x\left(t - \tau_1(t)\right)\right)\tilde{f}\left(x\left(t - \tau_1(t)\right)\right).$$

By Assumption 1, we know that $\dot{\tau}_i(t) \le \mu_i < 1$, $i = 1, 2$, and hence $-\frac{1-\dot{\tau}_i(t)}{1-\mu_i} \le -1$, then

$$
\begin{aligned}
\dot{V}(t) \le {} & -x^T(t)Ax(t) + x^T(t)W\tilde{f}\big(y\big(t - \tau_1(t)\big)\big) + x^T(t)\tilde{A}\hat{m}(t) - x^T(t)\tilde{W}f\big(\hat{p}\big(t - \tau_1(t)\big)\big) \\
& + x^T(t)E_1(t)x(t) \\
& - y^T(t)Cy(t) + y^T(t)Dx\big(t - \tau_2(t)\big) + y^T(t)\tilde{C}\hat{p}(t) - y^T(t)\tilde{D}\hat{m}\big(t - \tau_2(t)\big) \\
& + y^T(t)E_2(t)y(t) \\
& - \sum_{i=1}^n \hat{a}x_i(t)m_i(t) - \sum_{i=1}^n \hat{c}y_i(t)p_i(t) + \sum_{i=1}^n \sum_{j=1}^n \hat{w}_{ij}x_i(t)f_j\big(\hat{p}_j\big(t - \tau_1(t)\big)\big) \\
& + \sum_{i=1}^n \sum_{j=1}^n \hat{d}_{ij}y_i(t)\hat{m}_j\big(t - \tau_2(t)\big) - \sum_{i=1}^n \big(\varepsilon_i^x + l\big)x_i^2(t) - \sum_{i=1}^n \big(\varepsilon_i^y + l\big)y_i^2(t) \\
& + \frac{1}{2(1-\mu_1)}\tilde{f}^T\big(x(t)\big)\tilde{f}\big(x(t)\big) - \frac{1}{2}\tilde{f}^T\big(x\big(t - \tau_1(t)\big)\big)\tilde{f}\big(x\big(t - \tau_1(t)\big)\big) \\
& + \frac{1}{2(1-\mu_2)}y^T(t)y(t) - \frac{1}{2}y^T\big(t - \tau_2(t)\big)y\big(t - \tau_2(t)\big).
\end{aligned}
$$

According to (4), one has

$$
\begin{cases}
x^T(t)\tilde{A}(t)\hat{m}(t) = \sum_{i=1}^n \tilde{a}_i(t)x_i(t)m_i(t), \\
y^T(t)\tilde{C}(t)\hat{p}(t) = \sum_{i=1}^n \tilde{c}_i(t)y_i(t)p_i(t), \\
x^T(t)\tilde{W}(t)\tilde{f}(\hat{p}(t - \tau_1(t)))) = \sum_{i=1}^n \sum_{j=1}^n \tilde{w}_{ij}(t)x_i(t)\tilde{f}_j(p_j(t - \tau_1(t))), \\
y^T(t)\tilde{D}(t)\hat{m}(t - \tau_2(t))) = \sum_{i=1}^n \sum_{j=1}^n \tilde{d}_{ij}(t)y_i(t)m_j(t - \tau_2(t)), \\
x^T(t)E_1(t)x(t) = \sum_{i=1}^n \varepsilon_i^x x_i^2(t), \\
y^T(t)E_2(t)y(t) = \sum_{i=1}^n \varepsilon_i^y y_i^2(t).
\end{cases}
$$

Then one can obtain

$$
\begin{aligned}
\dot{V}(t) \le {} & -x^T(t)Ax(t) - y^T(t)Cy(t) + x^T(t)W\tilde{f}\big(y\big(t - \tau_1(t)\big)\big) + y^T(t)Dx\big(t - \tau_2(t)\big) \\
& - l\sum_{i=1}^n \big(x_i^2(t) + y_i^2(t)\big) + \frac{1}{2(1-\mu_1)}\tilde{f}^T\big(x(t)\big)\tilde{f}\big(x(t)\big) \\
& - \frac{1}{2}\tilde{f}^T\big(x\big(t - \tau_1(t)\big)\tilde{f}\big(x\big(t - \tau_1(t)\big) \\
& + \frac{1}{2(1-\mu_2)}y^T(t)y(t) - \frac{1}{2}y^T\big(t - \tau_2(t)\big)y\big(t - \tau_2(t)\big) \\
\le {} & -x^T(t)Ax(t) - y^T(t)Cy(t) + \frac{1}{2}x^T(t)WW^Tx(t) \\
& + \frac{1}{2}y^T(t)DD^Ty(t) - l\sum_{i=1}^n \big(x_i^2(t) + y_i^2(t)\big) \\
& + \frac{1}{2(1-\mu_1)}\tilde{f}^T\big(x(t)\big)\tilde{f}\big(x(t)\big) + \frac{1}{2(1-\mu_2)}y^T(t)y(t).
\end{aligned}
$$

Based on Assumption 2, we know

$$\tilde{f}^T\big(x(t)\big)\tilde{f}\big(x(t)\big) \le \sum_{i=1}^{n} h_i^2 x_i^2(t) \le h\sum_{i=1}^{n} x_i^2(t),$$

where $h = \max\{h_i^2 | i = 1, 2, \ldots, n\}$.

According to the above inequations, we get

$$\dot{V}(t) \le x^T(t)\left(\frac{1}{2}WW^T - A - lI + \frac{1}{2(1-\mu_1)}LI\right)x(t)$$
$$+ y^T(t)\left(\frac{1}{2}DD^T - C - lI + \frac{1}{2(1-\mu_2)}I\right)y(t), \tag{5}$$

where I is a unit matrix, $\lambda_{\max}(M)$ is an eigenvalue of the maximum of M. Based on the definition of l, we know that

$$\dot{V}(t) \le -x^T(t)x(t) - y^T(t)y(t) \le 0.$$

It is obvious that $\dot{V}(t) = 0$ if and only if $x(t) = 0$ and $y(t) = 0$. Under the conditions $x(t) = 0$ and $y(t) = 0$, one can get the largest invariant $\mathbb{E} = \{\hat{A}(t) = A, \hat{C} = C, \hat{W} = W, \hat{D} = D, E_1(t) = \hat{E}_1, E_2(t) = \hat{E}_2\}$, where the feedback control gains $\hat{E}_1$ and $\hat{E}_2$ depend on the initial value of error system (3). Then, based on the well-known Lyapunov–LaSalle type theorem for functional differential equations (Theorem 3.1, p. 119 [40]), the trajectories of error dynamical system (3) will converge into the largest invariant $\mathbb{E}$ as $t \to +\infty$, which implies that the synchronization can be achieved between (1) and (2). Moreover, $\lim_{t\to+\infty}(a_i - \hat{a}_i) = \lim_{t\to+\infty}(w_{ij} - \hat{w}_{ij}) = \lim_{t\to+\infty}(c_i - \hat{c}_i) = \lim_{t\to+\infty}(d_{ij} - \hat{d}_{ij}) = 0$ ($\forall i, j = 1, 2, \ldots, n$). This completes the proof of this theorem.   □
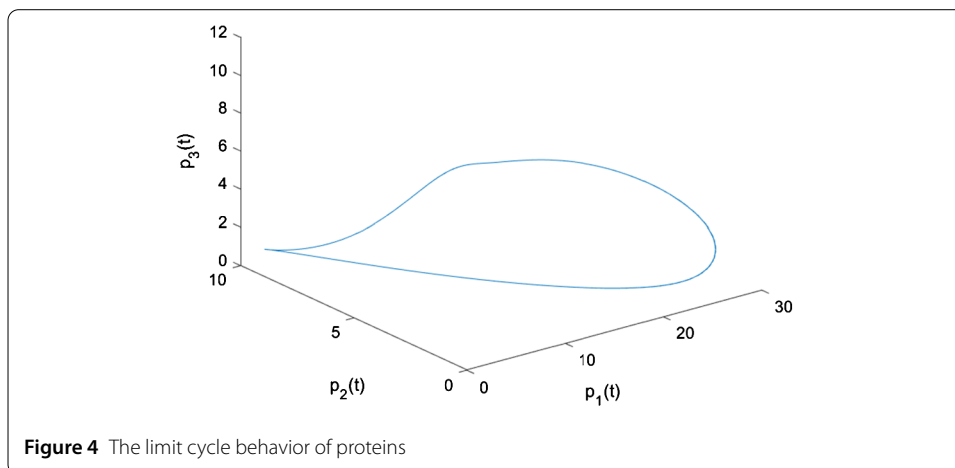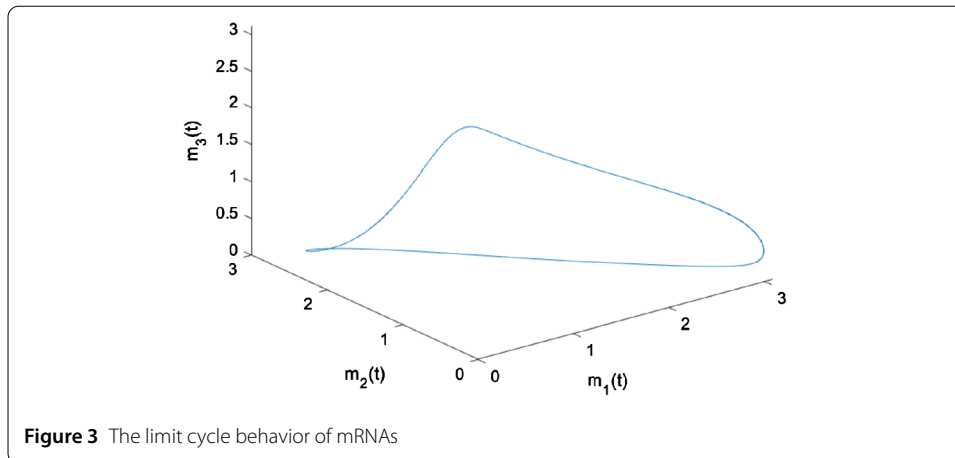
4 Numerical simulations
In this section, a numerical example is given to show the effectiveness of the proposed results.

Example 1 Consider the following the GRN with several unknown parameters:

$$\begin{cases} \dot{m}(t) = -Am(t) + Wf(p(t - \tau_1(t))) + L, \\ \dot{p}(t) = -Cp(t) + Dm(t - \tau_2(t)), \end{cases} \tag{6}$$

where

$$A = \begin{pmatrix} 0.46 & 0 & 0 \\ 0 & 0.36 & 0 \\ 0 & 0 & 0.48 \end{pmatrix}, \qquad C = \begin{pmatrix} 0.2 & 0 & 0 \\ 0 & 0.5 & 0 \\ 0 & 0 & 0.6 \end{pmatrix},$$

$$W = \begin{pmatrix} 0 & 0 & -1.5 \\ -1.5 & 0 & 0 \\ 0 & -1.5 & 0 \end{pmatrix}, \qquad D = \begin{pmatrix} 2 & 0 & 0 \\ 0 & 2 & 0 \\ 0 & 0 & 2 \end{pmatrix}, \qquad L = \begin{pmatrix} 1.5 \\ 1.5 \\ 1.5 \end{pmatrix},$$

Figure 3 The limit cycle behavior of mRNAs

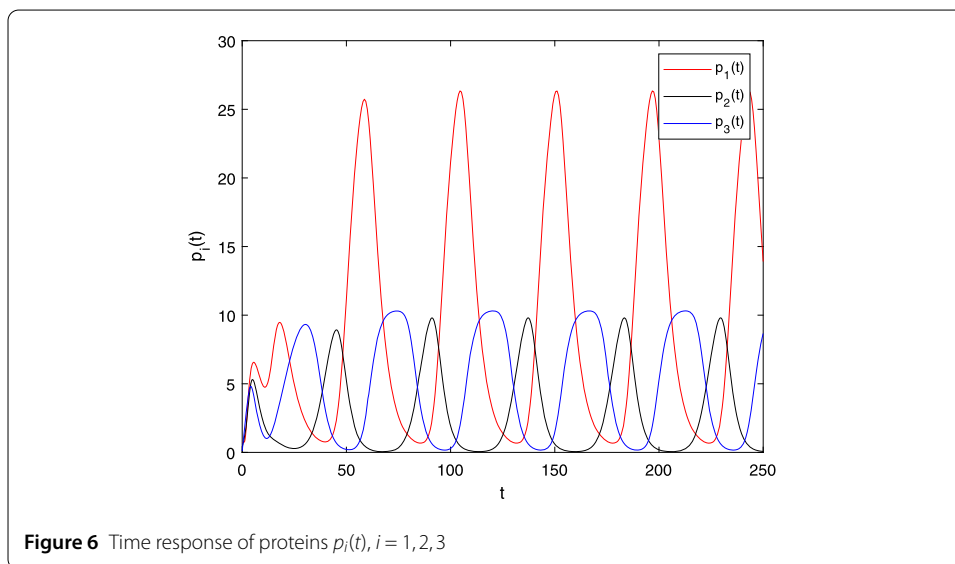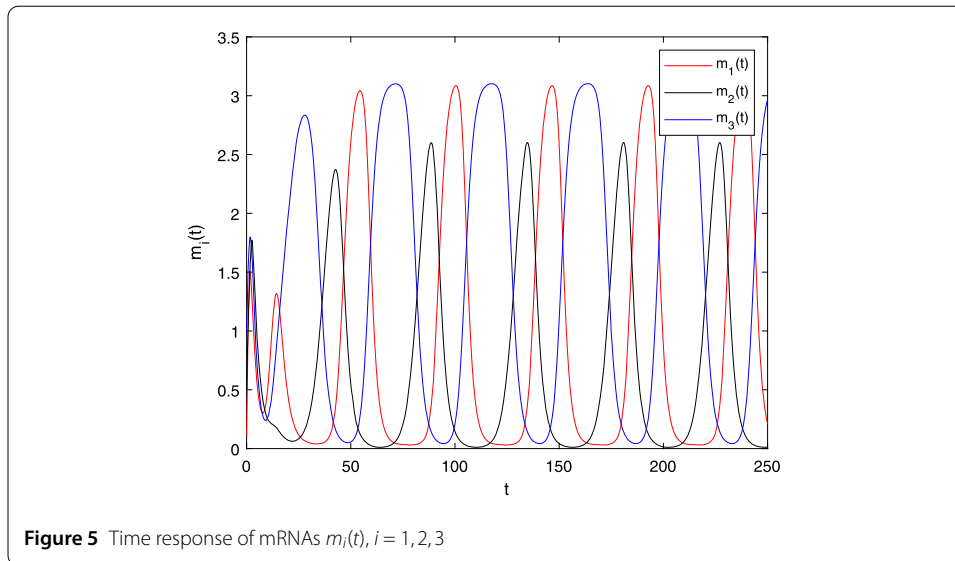

Figure 4 The limit cycle behavior of proteins

and $\tau_1(t) = \tau_2(t) = 1$, there are limit cycles among mRNAs and proteins under those parameters, respectively. One can see in Fig. 3 and Fig. 4. The time-response of $m_i(t)$ and $p_i(t)$ can be seen in Fig. 5 and Fig. 6, respectively. Indeed, for different parameters, the GRN may be stable, unstable, period, or even chaotic. However, synchronization between two stable or unstable systems maybe meaningless. Consequently, we selected the above parameters to get a period orbit. Note that this dynamical behavior is sensitive to the parameters. For example, if we let $w_{21} = -1.4$, other parameters are the same as above, without any control, one can see the time response between (6) and (7) in Fig. 7 and Fig. 8, respectively.

We construct the following response GRN four unknown parameters a_{33}, c_{22}, w_{21}, d_{33}:

$$
\begin{cases}
\dot{\hat{m}}(t) = -\hat{A}(t)\hat{m}(t) + \hat{W}(t)\hat{f}(p(t - \tau_1(t))) + L + \varepsilon^1(t)(\hat{m}(t) - m(t)), \\
\dot{\hat{p}}(t) = -\hat{C}(t)\hat{p}(t) + \hat{D}(t)\hat{m}(t - \tau_2(t)) + \varepsilon^2(t)(\hat{p}(t) - p(t)),
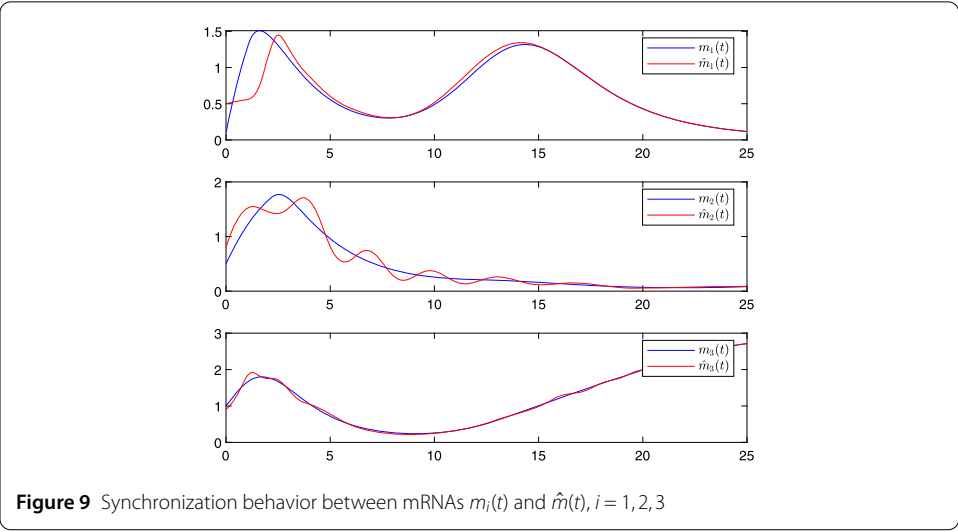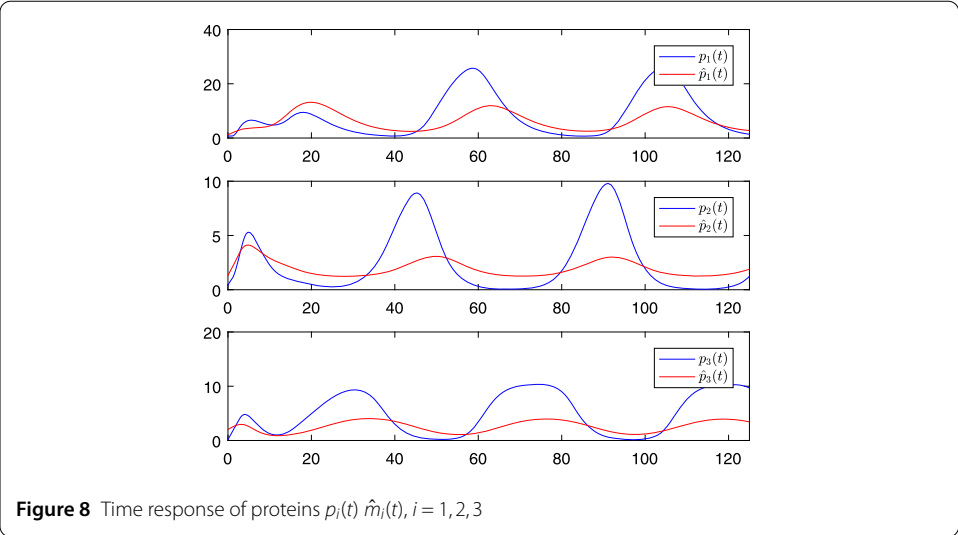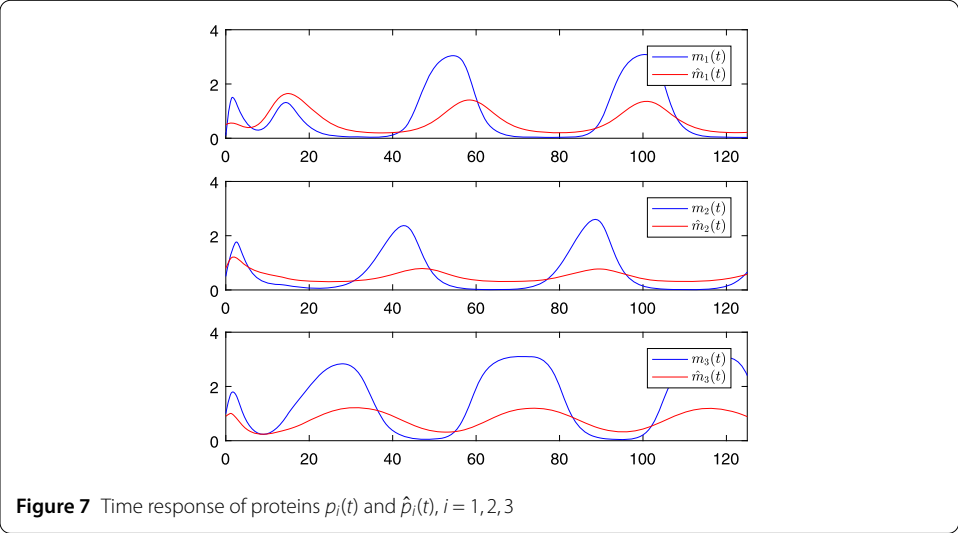\end{cases} \tag{7}
$$

with

$$
\hat{A}(t) = \begin{pmatrix} 0.46 & 0 & 0 \\ 0 & 0.36 & 0 \\ 0 & 0 & \hat{a}_{33}(t) \end{pmatrix}, \qquad \hat{C}(t) = \begin{pmatrix} 0.2 & 0 & 0 \\ 0 & \hat{c}_{22}(t) & 0 \\ 0 & 0 & 0.6 \end{pmatrix},
$$

Figure 5 Time response of mRNAs $m_i(t)$, $i = 1, 2, 3$

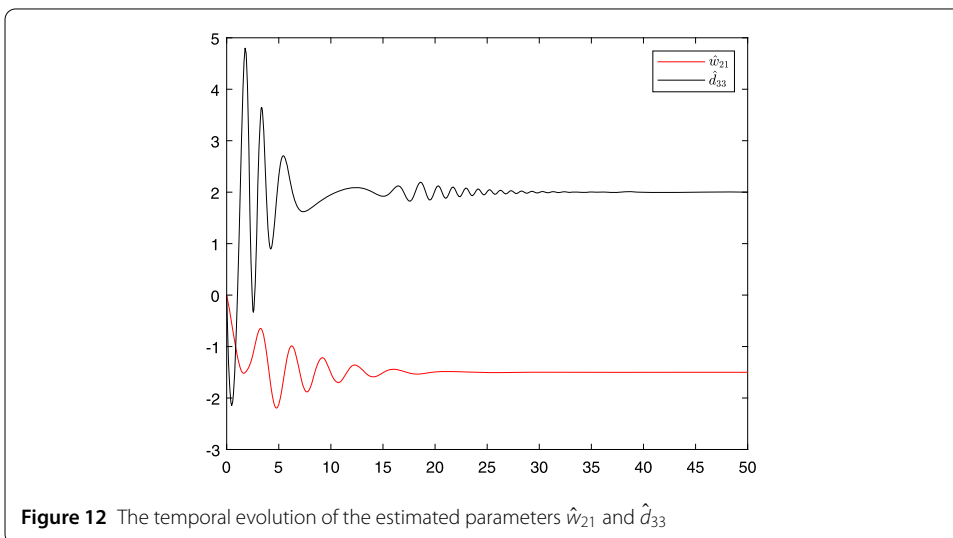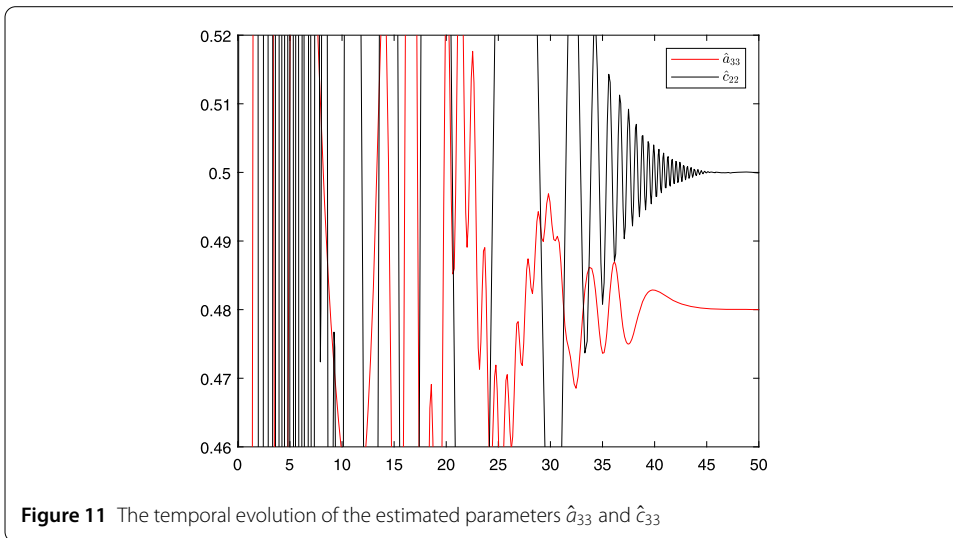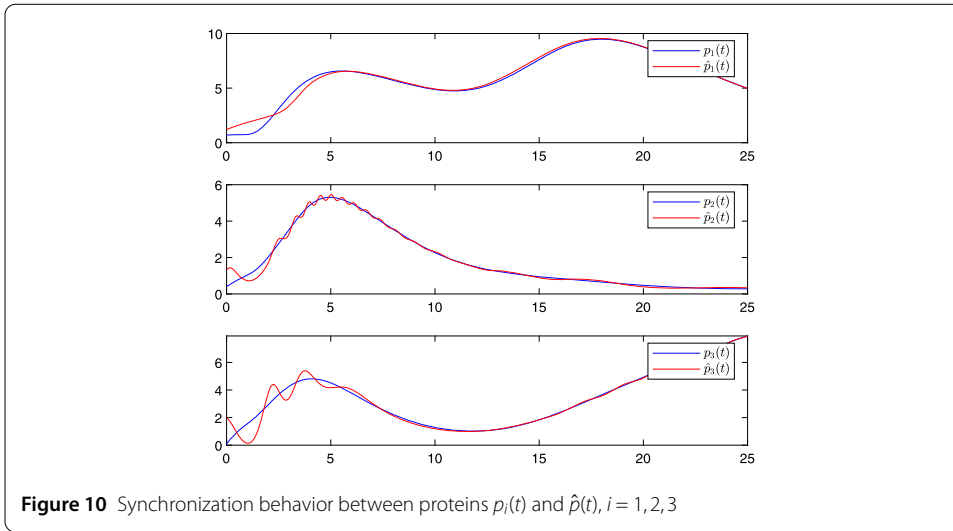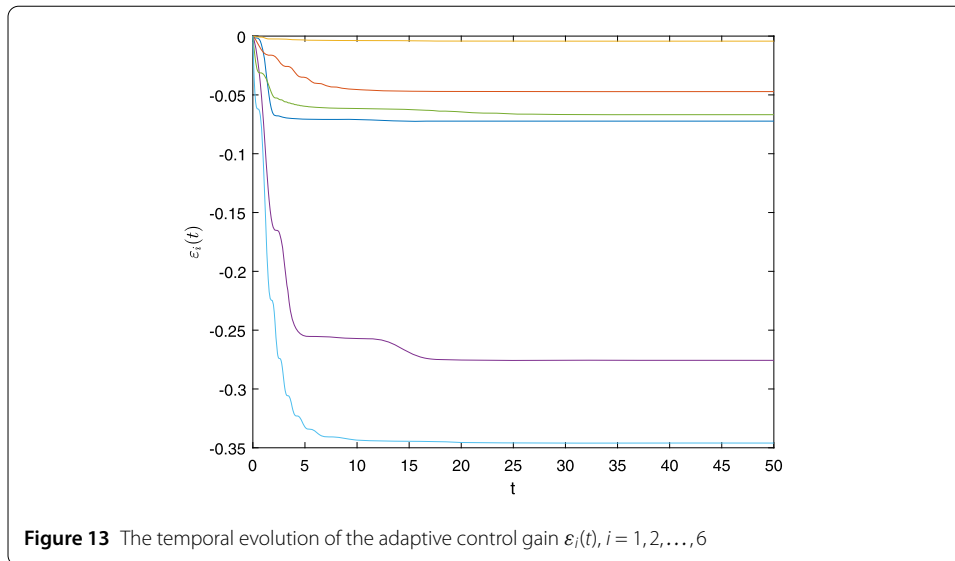**Figure 6** Time response of proteins $p_i(t)$, $i = 1, 2, 3$

$$\hat{W}(t) = \begin{pmatrix} 0 & 0 & -1.5 \\ \hat{w}_{21}(t) & 0 & 0 \\ 0 & -1.5 & 0 \end{pmatrix}, \qquad \hat{D}(t) = \begin{pmatrix} 2 & 0 & 0 \\ 0 & 2 & 0 \\ 0 & 0 & \hat{d}_{33}(t) \end{pmatrix},$$

$$E_1(t) = \mathrm{diag}\{\varepsilon_1^x(t), \varepsilon_2^x(t), \varepsilon_3^x(t)\}, \qquad E_2(t) = \mathrm{diag}\{\varepsilon_1^y(t), \varepsilon_2^y(t), \varepsilon_3^y(t)\}.$$

In the following simulations, we take $m(s) = [0.1, 0.5, 1]^T$, $p(s) = [0.7, 0.4, 0.1]^T$, $\hat{m}(s) = [0.5, 0.8, 0.9]^T$, $\hat{p}(s) = [1.2, 1.3, 2]^T$ when $s \in [-1, 0]$, and $a_{33}(0) = c_{22}(0) = w_{21}(0) = d_{33}(0) = \varepsilon_i^x(0) = \varepsilon_i^y(0) = 0$, $i = 1, 2, 3$, the updated gains are set as $\eta_i^x = \eta_i^y = 0.1$, $\sigma_i^x = \sigma_i^y = 5$, $\gamma_{ij}^x = \gamma_{ij}^y = 5$, $i, j = 1, 2, 3$. Then, one can get the following results. The synchronization between (6) and (7) can be obtained, one can see in Figs. 9 and 10. In addition, the unknown parameters can be estimated, which has been shown in Figs. 11 and 12, respectively. Finally, the adaptive control gain $\varepsilon_i(t)$, $i = 1, 2, \ldots, 6$, can be see in Fig. 13.

Figure 7 Time response of proteins $p_i(t)$ and $\hat{p}_i(t)$, $i = 1, 2, 3$

Figure 8 Time response of proteins $p_i(t)$ $\hat{m}_i(t)$, $i = 1, 2, 3$

Figure 9 Synchronization behavior between mRNAs $m_i(t)$ and $\hat{m}(t)$, $i = 1, 2, 3$

Figure 10 Synchronization behavior between proteins $p_i(t)$ and $\hat{p}(t)$, $i = 1, 2, 3$

Figure 11 The temporal evolution of the estimated parameters $\hat{a}_{33}$ and $\hat{c}_{33}$

Figure 12 The temporal evolution of the estimated parameters $\hat{w}_{21}$ and $\hat{d}_{33}$

Figure 13 The temporal evolution of the adaptive control gain $\varepsilon_i(t)$, $i = 1, 2, \ldots, 6$

5 Conclusion

In this paper, the adaptive synchronization method has been applied to identify the unknown parameters of a time-delayed GRN. A dynamical linear feedback controller and adaptive parameters updated laws have been designed to synchronize the auxiliary system to the unknown GRN. Then, based on the Lyapunov stability theorem and Barbalat's lemma, the synchronization results could be guaranteed, the unknown parameters could also be identified. An example is given to show the effectiveness of the theoretical results.

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