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Desired clustering of genetic regulatory networks with mixed delays

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Abstract

In this study, we propose two techniques for clustering genetic regulatory networks with mixed delays. Laws for identifying coupling parameters are designed, and the Lyapunov theorem and Lipschitz condition are employed to achieve the desired stability and to identify the coupling parameters. Using our proposed methods, the value of a cluster or the sum of clusters can approach the expected values. Numerical examples verify the feasibility and effectiveness of this method.

Keywords: Desired clustering; Genetic regulatory network; Stability theory; Lyapunov function

1 Introduction

After the double helix structure of DNA was discovered by Watson and Crick in 1953, we entered a new era of molecular biology, and many subsequent studies have shown that physiological functions are controlled by biological networks instead of several molecules and genes. Biological networks include metabolic networks, protein interaction networks, and genetic regulatory networks (GRNs), where the latter are significant for studies of the interactions between mRNA and proteins at the molecular level. GRNs have been elucidated increasingly in the last 30 years due to great progress in genome sequencing and gene recognition, thereby attracting considerable attention from researchers in the areas of biology, computer science, physics, and mathematics; and thus GRNs is a focus of interdisciplinary research. Various models have been proposed to describe the transcription and translation of DNA, e.g., Boolean networks [1–3] and differential equation models [4–12], where the latter can depict the continuous dynamic behavior of mRNA and protein.

Time delays are ubiquitous in biology [13], physics [14], chemistry [15], optics [16], and complex networks [17, 18]. Thus, time delays need to be considered in GRNs because of the finite speeds of the slow processes of transcription, translation, and translocation [7–10, 12]. Furthermore, inappropriate considerations of time delays can lead to incorrect predictions of the behavior of GRNs.

Stability is essential for the design or control of GRNs because it ensures that an organism can robustly regulate its functions even if the state of the organism moves away from the equilibrium points. Zhang et al. used the improved integral inequality to conduct stability analysis for a GRN with interval time-varying delays [19]. Wang et al. performed exponential convergence analysis for an uncertain GRN with time-varying delays [20].

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Zhang et al. established globally asymptotic stability criteria for a GRN with time-varying discrete and unbounded distributed delays [21]. Liu and Wu analyzed the global asymptotical stability of a GRN with time-varying delays via a convex combination method [22].

These previous studies considered the stability of GRNs but not clustering phenomena. In general, cells can communicate with neighboring cells via quorum sensing because the genetic signals transmitted from genes can support different physiological functions [23]. Therefore, clustering is a common phenomenon in interacting populations, and clustering is an important aspect of biological control [24]. Recently, some studies have investigated the clustering of GRNs, such as how the influence of coupling or noise can generate cluster patterns in an ensemble of cellular oscillators [25], how individual GRNs are divided into different clusters by cluster synchronization [23, 24, 26], and how temporal control is introduced to cluster mammalian signaling modules [27]. In this study, we investigate the desired clustering of GRNs where clusters of GRNs could have different features according to two proposed strategies. In particular, we impose no limitations on the number of nodes in each cluster, the division of the clusters of GRNs, and the time delay for feedback regulation. Comparing with the previous research of GRNs, we not only analyze the stability of GRNs, but also make the concentrations of protein and mRNA approach the desired values through our tactics. Linear matrix inequality (LMI) method is often used to obtain the stability criteria for GRNs, but the computation of LMI is complex. In this paper, stability criterion is given by a Lyapunov function.

The real genetic regulatory network is over complex, and the number of nodes is huge. Since "network motifs" [28, 29] were proposed by Alon et al. in 2002, few node genetic regulatory networks have become research hotspots. It is hoped that the real genetic regulatory network can be understood gradually by the research of such network motifs. In 2000, Elowitz et al. used three transcriptional repressor systems to build a synthetic oscillating network in Escherichia coli [30]. Gardner et al. used two transcriptional repressors to construct a synthetic toggle switch genetic regulatory network in Escherichia coli also in 2000 [31]. Therefore, 7 or 20 genes with clustering as numerical examples in Sect. 4 are significant.

2 Model of GRNs

GRNs with mixed delays [12] are described by Eq. (1):

$$
\begin{cases}
\dot{m}_i(t) = -a_i m_i(t) + \sum_{j=1}^{N} \omega_{ij}(t) f_j(p_j(t - \tau(t))) + l_i(t), \\
\dot{p}_i(t) = -c_i p_i(t) + d_i m_i(t - \sigma(t)), \quad i \in \{1, 2, \ldots, n\},
\end{cases}
\tag{1}
$$

where $m(t) = [m_1(t) \cdots m_n(t)] \in R^n$ and $p(t) = [p_1(t) \cdots p_n(t)] \in R^n$ are the concentrations of mRNA and protein for node i at the time t, respectively, the parameters a_i and c_i are the degradation rates of the mRNA and protein, and d_i is the translation rate. The feedback regulation delays $\tau(t)$, $\sigma(t)$ are both positive, and $f_i(x)$ is the Hill form regulatory function, which represents the feedback regulation of the protein on transcription, and it is described by Eq. (2):

$$
f_j(x) = \frac{\left(\frac{x}{v_j}\right)^{H_j}}{1 + \left(\frac{x}{v_j}\right)^{H_j}},
\tag{2}
$$

$$\underbrace{m_1, m_2, \ldots, m_{q_1}}_{c_1}, \ldots, \underbrace{m_{q_{k-1}+1}, m_{q_{k-1}+2}, \ldots, m_{q_k}}_{c_k}, \ldots$$

Figure 1 Cluster of GRNs where $q_k - q_{k-1}$ represents the number of nodes in the kth cluster and $\{q_{k-1} + 1, \ldots, q_{k-1} + \gamma, \ldots, q_k\}$ represents the index set of all the nodes in the kth cluster. We find that $m_i = m_{q_{k-1}+\gamma}$, when the index of the ith gene is the γth gene in the kth cluster
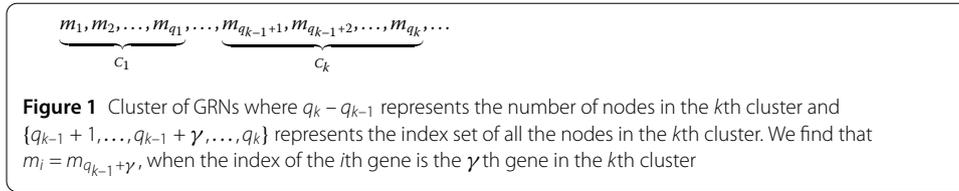
where H_i is the Hill coefficient, v_j is a positive constant, and we propose that $f_j(x)$ is positive. $l_i(t) = \sum_{j \in I_i} \alpha_{ij}(t)$ and I_i is the set of all j, which is a repressor of gene i. The coupling matrix $W = \omega_{ij} \in R^{n \times n}$ is described as follows:

$$\omega_{ij}(t) = \begin{cases} \alpha_{ij}(t) & \text{if } j \text{ is an activator of gene } i, \\ 0 & \text{if there is no link from node } j \text{ to } i, \\ -\alpha_{ij}(t) & \text{if } j \text{ is an repressor of gene } i. \end{cases} \tag{3}$$

As shown in Fig. 1, we assume that there are M clusters in the GRNs (1) ($M \geq 1$), which are denoted by $C_1, C_2, \ldots, C_m$, where $C_k = \{q_{k-1} + 1, q_{k-1} + 2, \ldots, q_k\}$, with $k = 1, 2, \ldots, m, q_0 = 0$, and $q_m = N$.

Let $\overline{m}_k(t) = (m_{q_{k-1}+1}, m_{q_{k-1}+2}, \ldots, m_{q_k})$, $\overline{p}_k(t) = (p_{q_{k-1}+1}, p_{q_{k-1}+2}, \ldots, p_{q_k})$.

Definition 1 $X(t) \in R^n$ will approach the desired values $\hat{X} \in R^n$ if $\lim_{t \to \infty} |X(t) - \hat{X}| = 0$.

3 Desired clustering of GRNs

In this section, the GRNs (1) are clustered using two techniques.

3.1 Method 1

In this method, the concentrations of mRNA and protein within a cluster have the same desired values $\hat{m}_k$ and $\hat{p}_k$, and the desired values of the nodes vary in different clusters.

Theorem 1 *The desired clustering of GRNs with mixed delays will be achieved when the law for identifying the coupling parameters ω_{ij}, a_i, $c_i \beta_i$ ($i \in \{q_{k-1} + 1, q_{k-1} + 2, \ldots, q_k\}, j \in \{1, \ldots, N\}$) and $\hat{p}_k$ is taken as follows, respectively*:

$$\dot{\omega}_{ij}(t) = \alpha(\hat{m}_k(t) - m_i), \tag{4}$$

$$a_i + \delta - \varepsilon_i > 0, \tag{5}$$

$$c_i > 0, \tag{6}$$

$$\beta_i = \frac{a_i \hat{m}_k}{\sum_{j=1}^n \hat{\omega}_{ij}} > 0, \tag{7}$$

$$\hat{p}_k = \lim_{t \to \infty} \theta_k m_i(t - \sigma(t)), \tag{8}$$

where the real numbers δ and ε_i are positive; the estimated identification of the uncertain adjustment parameters ω_{ij} is $\hat{\omega}_{ij}$ and α is an adjustment parameter; $\theta_k = d_k/c_k$ is a scale factor that represents the proportional relationship between $\hat{p}_k$ and $\hat{m}_k$, $c_k = c_{q_{k-1}+1} = \cdots = c_{q_k}$, and $d_k = d_{q_{k-1}+1} = \cdots = d_{q_k}$.

Proof For $i \in C_k$, the error between m_i and $\hat{m}_k$ and the error between p_i and $p_i(t - \sigma(t))$ are defined by Eq. (9).

$$
\begin{cases}
e_{1i}(t) = m_i(t) - \hat{m}_k, \\
e_{2i}(t) = p_i(t) - \hat{p}_k.
\end{cases} \tag{9}
$$

We establish the Lyapunov function as follows.

$$
\begin{aligned}
V(t) &= \frac{1}{2}\left(\sum_{i=1}^{N} e_{1i}^{\mathrm{T}}(t)e_{1i}(t) + \sum_{i=1}^{N} e_{2i}^{\mathrm{T}}(t)e_{2i}(t) + \frac{\beta_i}{\alpha} \sum_{i=1}^{N}\sum_{j=1}^{N} \left(\hat{\omega}_{ij} - \omega_{ij}(t)\right)^{\mathrm{T}}\left(\hat{\omega}_{ij} - \omega_{ij}(t)\right) \right) \\
&= \frac{1}{2}\sum_{k=1}^{M}\sum_{i=q_{k-1}+1}^{q_k}\left(e_{1i}^{\mathrm{T}}(t)e_{1i}(t) + e_{2i}^{\mathrm{T}}(t)e_{2i}(t) \right. \\
&\quad \left. + \frac{\beta_i}{\alpha}\sum_{j=1}^{N}\left(\hat{\omega}_{ij} - \omega_{ij}(t)\right)^{\mathrm{T}}\left(\hat{\omega}_{ij} - \omega_{ij}(t)\right) \right).
\end{aligned} \tag{10}
$$

The derivative form of $V(t)$ can be described as follows:

$$
\begin{aligned}
\dot{V}(t) &= \sum_{k=1}^{M}\sum_{i=q_{k-1}+1}^{q_k}\left[e_{1i}^{\mathrm{T}}(t)\left(-a_i m_i(t) + \sum_{j=1}^{N}\omega_{ij}f_j\left(p_j\left(t - \tau(t)\right)\right) + l_i(t) + \beta_i\sum_{j=1}^{N}(\hat{\omega}_{ij} - \omega_{ij}) \right) \right. \\
&\quad \left. + e_{2i}^{\mathrm{T}}(t)\left(-c_i p_i(t) + d_i m_i\left(t - \sigma(t)\right) \right) \right] \\
&= \sum_{k=1}^{M}\sum_{i=l_{k-1}+1}^{q_k}\left[e_{1i}^{\mathrm{T}}(t)(-(a_i + \delta)m_i(t) + (a_i + \delta)\hat{m}_k + F_i\left(m_i(t)\right) - H_i(\hat{m}_k) \right. \\
&\quad \left. + \beta_i\sum_{j=1}^{N}\hat{\omega}_{ij} - a_i\hat{m}_k + e_{2i}^{\mathrm{T}}(t)\left(-c_i p_i(t) + c_i\hat{p}_k + d_i m_i\left(t - \sigma(t)\right) - c_i\hat{p}_k \right) \right],
\end{aligned} \tag{11}
$$

where

$$
F_i = \delta_i^m(t) + \sum_{j=1}^{N}\omega_{ij}\left[f_j\left(p_j\left(t - \tau(t)\right)\right) - \beta_i\right] + l_i(t), \tag{12}
$$

$$
H_i(\hat{m}_k) = (a_i + \delta)\hat{m}_k. \tag{13}
$$

For the real number $\varepsilon_i > 0$, the following relationship is obtained using the Lipschitz condition:

$$
\left\| F_i\left(m_i(t)\right) - H_i(\hat{m}_k) \right\| \leq \varepsilon_i \left\| m_i(t) - \hat{m}_k \right\|, \tag{14}
$$

and Eq. (10) can be simplified as follows:

$$
\dot{V}(t) \leq \sum_{k=1}^{M}\sum_{i=q_{k-1}+1}^{q_k}\left\{ (\varepsilon_i - a_i - \delta)e_{1i}^{\mathrm{T}}(t)e_{1i}(t) + e_{1i}^{\mathrm{T}}(t)\left(\beta_i\sum_{j=1}^{N}\hat{\omega}_{ij} - a_i\hat{m}_k \right) - c_i e_{2i}^{\mathrm{T}}(t)e_{2i}(t) \right.
$$

$$+ e_{2i}^{\mathrm{T}}(t)\big[d_i m_i\big(t - \sigma(t)\big) - c_i \hat{p}_k\big]\bigg\}. \tag{15}$$

The following inequation is obtained while Eq. (7) is substituted into Eq. (15):

$$\dot{V}(t) \leq \sum_{k=1}^{M} \sum_{i=q_{k-1}+1}^{q_k} \big\{ (\varepsilon_i - a_i - \delta) e_{1i}^{\mathrm{T}}(t) e_{1i}(t) - c_i e_{2i}^{\mathrm{T}}(t) e_{2i}(t)$$

$$+ e_{2i}^{\mathrm{T}}(t)\big[d_i m_i\big(t - \sigma(t)\big) - c_i \hat{p}_k\big]\big\}. \tag{16}$$

Clearly, when (5), (6), (8) are satisfied, we find that $\lim_{t \to \infty} \dot{V}(t) \leq 0$. According to stability theory and Definition 1, $m_i(t) \in \overline{m}_k(t)$ and $p_i(t) \in \overline{p}_k(t)$ will approach the desired values, where $\hat{p}_k = \lim_{t \to \infty} \theta_k m_i(t - \sigma(t)) = \theta_k \hat{m}_k$ ($i \in \{q_{k-1} + 1, q_{k-1} + 2, \ldots, q_k\}$). □

3.2 Method 2

In this method, the GRNs is clustered by summing, which means that the sums of $\overline{m}_k(t)$ and $\overline{p}_k(t)$ have the desired values $\hat{S}_{1k}$ and $\hat{S}_{2k}$, respectively, and the desired values of the sum of the various clusters are different. The sums of the mRNAs and proteins in the kth cluster are defined as follows:

$$S_{1k}(t) = \sum_{i=q_{k-1}+1}^{q_k} m_i(t), \tag{17}$$

$$S_{2k}(t) = \sum_{i=q_{k-1}+1}^{q_k} p_i(t). \tag{18}$$

The error between $S_{1k}(t)$ and $\hat{S}_{1k}$ and the error between $S_{2k}(t)$ and $\hat{S}_{2k}$ are defined as follows:

$$E_{1k}(t) = S_{1k}(t) - \hat{S}_{1k}, \tag{19}$$

$$E_{2k}(t) = S_{2k}(t) - \hat{S}_{2k}. \tag{20}$$

Theorem 2 *The desired cluster of GRNs with mixed delays will be achieved when the law for identifying the coupling parameters ω_{ij}, a_i, c_i, β_i ($i \in \{q_{k-1} + 1, q_{k-1} + 2, \ldots, q_k\}, j \in \{1, \ldots, N\}$), and $\hat{S}_{2k}$ is taken as follows, respectively:*

$$\dot{\omega}_{ij}(t) = \alpha\big(\hat{S}_{1k} - S_{1k}(t)\big) \tag{21}$$

$$a_k + \xi - \mu_k > 0 \tag{22}$$

$$c_k > 0 \tag{23}$$

$$\beta_k = \frac{a_k \hat{S}_{1k}}{\sum_{i=q_{k-1}+1}^{q_k} \sum_{j=1}^{N} \hat{\omega}_{ij}} > 0 \tag{24}$$

$$\hat{S}_{2k} = \lim_{t \to \infty} \vartheta_k S_{1k}\big(t - \sigma(t)\big), \tag{25}$$

where the real numbers ξ and μ_k are positive; $\vartheta_k = d_k/c_k$ is a scale factor that represents the proportional relationship between $\hat{S}_{2k}$ and $\hat{S}_{1k}$; $a_k = a_{q_{k-1}+1} = \cdots = a_{q_k}$, $c_k = c_{q_{k-1}+1} = \cdots = c_{q_k}$, and $d_k = d_{q_{k-1}+1} = \cdots = d_{q_k}$.

Proof The Lyapunov function is established as follows:

$$
V(t) = \frac{1}{2} \left(\sum_{k=1}^{M} E_{1k}^{\mathrm{T}}(t) E_{1k}(t) + \sum_{k=1}^{M} E_{2k}^{\mathrm{T}}(t) E_{2k}(t) \right.
$$

$$
\left. + \frac{\beta_k}{\alpha} \sum_{k=1}^{M} \sum_{i=q_{k-1}}^{q_k} \sum_{j=1}^{N} (\hat{\omega}_{ij} - \omega_{ij})^{\mathrm{T}} (\hat{\omega}_{ij} - \omega_{ij}) \right). \tag{26}
$$

The derivative form of $V(t)$ can be described as follows:

$$
\dot{V}(t) = \sum_{k=1}^{M} E_{1k}^{\mathrm{T}}(t) \dot{E}_{1k}(t) + \sum_{k=1}^{M} E_{2k}^{\mathrm{T}}(t) \dot{E}_{2k}(t) - \frac{\beta_k}{\alpha} \sum_{k=1}^{M} \sum_{i=q_{k-1}}^{q_k} \sum_{j=1}^{N} (\hat{\omega}_{ij} - \omega_{ij})^{\mathrm{T}} \dot{\omega}_{ij}
$$

$$
= \sum_{k=1}^{M} \left(E_{1k}^{\mathrm{T}}(t) \sum_{i=q_{k-1}+1}^{q_k} \dot{m}_{i\gamma}(t) + E_{2k}^{\mathrm{T}}(t) \sum_{i=q_{k-1}+1}^{q_k} \dot{p}_i(t) + \beta_k E_{1k}^{\mathrm{T}}(t) \sum_{i=q_{k-1}+1}^{q_k} \sum_{j=1}^{N} (\hat{\omega}_{ij} - \omega_{ij}) \right)
$$

$$
= \sum_{k=1}^{M} \left\{ E_{1k}^{\mathrm{T}}(t) \left[\sum_{i=q_{k-1}+1}^{q_k} \left(-a_i m_i(t) + \sum_{j=1}^{N} \omega_{ij} f_j \big(p_j \big(t - \tau(t) \big) \big) + l_i(t) \right. \right. \right.
$$

$$
\left. \left. + \beta_k \sum_{j=1}^{N} (\hat{\omega}_{ij} - \omega_{ij}) \right) \right]
$$

$$
\left. + E_{2k}^{\mathrm{T}}(t) \sum_{i=q_{k-1}+1}^{q_k} \left[-c_i p_i(t) + d_i m_i \big(t - \sigma(t) \big) \right] \right\}. \tag{27}
$$

When $a_k = a_{q_{k-1}+1} = \cdots = a_{q_k}$, $c_k = c_{q_{k-1}+1} = \cdots = c_{q_k}$, and $d_k = d_{q_{k-1}+1} = \cdots = d_{q_k}$, Eq. (27) is simplified as follows:

$$
\dot{V}(t) = \sum_{k=1}^{M} \left\{ E_{1k}^{\mathrm{T}}(t) \left[-a_k S_{1k}(t) + \sum_{i=q_{k-1}+1}^{q_k} \left(\sum_{j=1}^{N} \omega_{ij} \big(f_j \big(p_j \big(t - \tau(t) \big) \big) - \beta_k \big) + l_i(t) \right. \right. \right.
$$

$$
\left. \left. + \beta_k \sum_{j=1}^{N} \hat{\omega}_{ij} \right) \right]
$$

$$
\left. + E_{2k}^{\mathrm{T}}(t) \big[-c_k S_{2k}(t) + d_k S_{1k} \big(t - \sigma(t) \big) \big] \right\}
$$

$$
= \sum_{k=1}^{M} \left\{ E_{1k}^{\mathrm{T}}(t) \left[-(a_k + \xi) S_{1k}(t) + (a_k + \xi) \hat{S}_{1k} + \Lambda_k(S_{1k}) - \Psi_k(\hat{S}_{1k}) \right. \right.
$$

$$
\left. + \beta_k \sum_{i=q_{k-1}+1}^{q_k} \sum_{j=1}^{N} \hat{\omega}_{ij} - a_k \hat{S}_{1k} \right]
$$

$$
\left. + E_{2k}^{\mathrm{T}}(t) \big[-c_k S_{2k}(t) + c_k \hat{S}_{2k} + d_k S_{1k} \big(t - \sigma(t) \big) - c_k \hat{S}_{2k} \big] \right\}, \tag{28}
$$

where

$$\Lambda_k\big(S_{1k}(t)\big) = \xi S_{1k}(t) + \sum_{i=q_{k-1}+1}^{q_k}\left(\sum_{j=1}^{N}\omega_{ij}\big(f_j\big(p_j\big(t-\tau(t)\big)\big)-\beta_k\big)+l_i(t)\right), \qquad (29)$$

$$\Psi_k(\hat{S}_{1k}) = (a_k+\xi)\hat{S}_{1k}. \qquad (30)$$

For the real number $\mu_k > 0$, the following relationship can be obtained using the Lipschitz condition:

$$\big\|\Lambda_k\big(S_{1k}(t)\big)-\Psi_k(\hat{S}_{1k})\big\| \le \mu_k\big\|\Lambda_{1k}(t)-\hat{S}_{1k}\big\|, \qquad (31)$$

and Eq. (28) can be simplified as follows:

$$\dot{V}(t) \le \sum_{k=1}^{M}\Bigg\{(\mu_k-a_k-\xi)E_{1k}^{\mathrm{T}}(t)E_{1k}+E_{1k}^{\mathrm{T}}(t)\Bigg[\beta_k\sum_{i=q_{k-1}+1}^{q_k}\sum_{j=1}^{N}\hat{\omega}_{ij}f_j\big(p_j\big(t-\tau(t)\big)\big)-a_k\hat{S}_{1k}\Bigg]$$
$$-c_kE_{2k}^{\mathrm{T}}(t)E_{2k}+E_{2k}^{\mathrm{T}}(t)\big[d_kS_{1k}\big(t-\sigma(t)\big)-c_k\hat{S}_{2k}\big]\Bigg\}. \qquad (32)$$

The following inequation is obtained while Eq. (24) is substituted into Eq. (32):

$$\dot{V}(t) \le \sum_{k=1}^{M}\big\{(\mu_k-a_k-\xi)E_{1k}^{\mathrm{T}}(t)-c_kE_{2k}^{\mathrm{T}}(t)E_{2k}+E_{2k}^{\mathrm{T}}(t)\big[d_kS_{1k}\big(t-\sigma(t)\big)-c_k\hat{S}_{2k}\big]\big\}. \qquad (33)$$

Based on (22), (23), (25), one can deduce $\lim_{t\to\infty}\dot{V}(t) \le 0$. According to stability theory and Definition 1, $S_{1k}(t)$ and $S_{2k}(t)$ will approach the desired values, where $\hat{S}_{2k} = \lim_{t\to\infty}\vartheta_k S_{1k}(t-\sigma(t)) = \vartheta_k\hat{S}_{1k}$. □

4 Numerical simulation

Example 1 In the numerical simulation of Example 1, the number of the nodes is fixed as $n = 7$; the parameters are fixed as $a_i = 2$ ($i = 1, \ldots, 7$), $c_k = 1$, and $d_k = c_k\hat{p}_k/\hat{m}_k$ ($k = 1, \ldots, M$); and the adjustment parameter $\alpha = 0.5$.

We assume that there are two clusters in the GRNs, $M = 2$, where

$$\begin{pmatrix}\overline{m}_1\\\overline{p}_1\end{pmatrix} = \left\{\begin{pmatrix}m_1(t)\\p_1(t)\end{pmatrix}, \begin{pmatrix}m_2(t)\\p_2(t)\end{pmatrix}, \begin{pmatrix}m_3(t)\\p_3(t)\end{pmatrix}\right\},$$

$$\begin{pmatrix}\overline{m}_2\\\overline{p}_2\end{pmatrix} = \left\{\begin{pmatrix}m_4(t)\\p_4(t)\end{pmatrix}, \begin{pmatrix}m_5(t)\\p_5(t)\end{pmatrix}, \begin{pmatrix}m_6(t)\\p_6(t)\end{pmatrix}, \begin{pmatrix}m_7(t)\\p_7(t)\end{pmatrix}\right\},$$

$$\begin{pmatrix}\hat{m}_1\\\hat{p}_1\end{pmatrix} = \begin{pmatrix}1.5\\3\end{pmatrix}, \begin{pmatrix}\hat{m}_2\\\hat{p}_2\end{pmatrix} = \begin{pmatrix}3\\6\end{pmatrix}.$$

The temporal evolution of m_i ($i = 1, \ldots, 7$) and p_i is shown in Fig. 2. Figure 2 clearly indicates that the concentrations of m_i and p_i at equilibrium approach the desired values. In addition, m_i, p_i ($i = 1, 2, 3$) belong to the first cluster and the concentration of m_i, p_i ($i = 4, 5, 6, 7$) belongs to the second cluster.

Figure 2 Time trajectories of $m_i(t)$ and $p_i(t)$, $(i = 1, \ldots, 7)$, and identification process for the uncertain parameter ω_{1j} $(j = 1, \ldots, 7)$
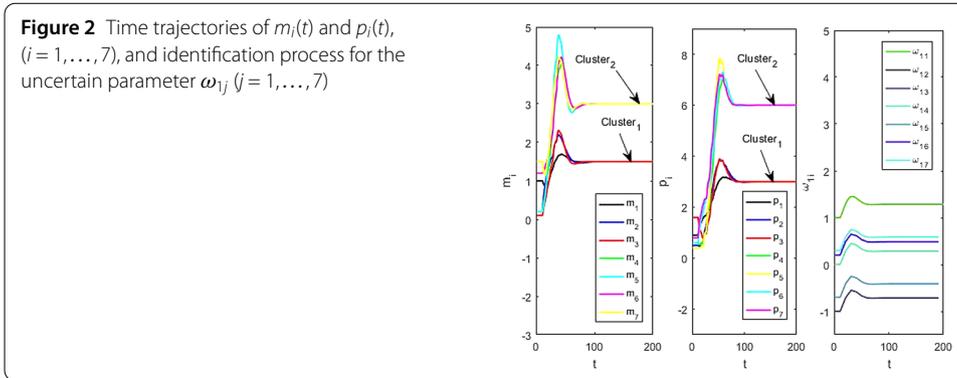
According to Figs. 2 and 3, the curves for identifying ω_{ij} $(i = 1, 2, \ldots, 7; j = 1, 2, \ldots, 7)$ gradually tend toward the fixed values as follows:

$$\hat{W} = \begin{pmatrix} 1.28 & 0.48 & -0.71 & 0.28 & -0.41 & 0.48 & 0.58 \\ -1.98 & 1.31 & 0.21 & 0.02 & -0.28 & -0.28 & 1.41 \\ 1.51 & 0.01 & 0.01 & 0.31 & 1.01 & 0.31 & -0.28 \\ 1.21 & 1.01 & 1.01 & -0.68 & 1.01 & 1.41 & 0.71 \\ 0.56 & 3.01 & 0.31 & 0.61 & 0.81 & 0.51 & 0.61 \\ 1.64 & 0.64 & 2.14 & 0.71 & 0.64 & -0.45 & 0.64 \\ 2.31 & 0.71 & 0.31 & 1.01 & 0.31 & 1.01 & 0.71 \end{pmatrix},$$

where $\hat{W}$ is the identification estimates for the uncertain coupling matrix W;

$$\beta_1 = \frac{a_1 \hat{m}_1}{\sum_{j=1}^{7} \hat{\omega}_{1j}} = 1.50, \qquad \beta_2 = \frac{a_2 \hat{m}_1}{\sum_{j=1}^{7} \hat{\omega}_{2j}} = 6.82,$$

$$\beta_3 = \frac{a_3 \hat{m}_1}{\sum_{j=1}^{7} \hat{\omega}_{3j}} = 1.03, \qquad \beta_4 = \frac{a_4 \hat{m}_2}{\sum_{j=1}^{7} \hat{\omega}_{4j}} = 1.05,$$

$$\beta_5 = \frac{a_5 \hat{m}_2}{\sum_{j=1}^{7} \hat{\omega}_{5j}} = 0.94, \qquad \beta_6 = \frac{a_6 \hat{m}_2}{\sum_{j=1}^{7} \hat{\omega}_{6j}} = 1.00, \qquad \beta_7 = \frac{a_7 \hat{m}_2}{\sum_{j=1}^{7} \hat{\omega}_{7j}} = 0.93.$$

Clearly, the value of β_i, $(i = 1, \ldots, 7)$ is positive, and thus inequation (7) is satisfied.

Furthermore, when we expand the number of nodes of GRNs to 20 and assume that there are three clusters in the GRNs, where $a_i = 3$ $(i = 1, \ldots, 20)$, $c_k = 1$, $d_k = c_k \hat{p}_k / \hat{m}_k$ $(k = 1, \ldots, M)$; $M = 3$; $\alpha = 0.3$;

$$\begin{pmatrix} \overline{m}_1 \\ \overline{p}_1 \end{pmatrix} = \left\{ \begin{pmatrix} m_1(t) \\ p_1(t) \end{pmatrix}, \ldots, \begin{pmatrix} m_{10}(t) \\ p_{10}(t) \end{pmatrix} \right\}, \qquad \begin{pmatrix} \overline{m}_2 \\ \overline{p}_2 \end{pmatrix} = \left\{ \begin{pmatrix} m_{11}(t) \\ p_{11}(t) \end{pmatrix}, \ldots, \begin{pmatrix} m_{15}(t) \\ p_{15}(t) \end{pmatrix} \right\},$$

$$\begin{pmatrix} \overline{m}_3 \\ \overline{p}_3 \end{pmatrix} = \left\{ \begin{pmatrix} m_{16}(t) \\ p_{16}(t) \end{pmatrix}, \ldots, \begin{pmatrix} m_{20}(t) \\ p_{20}(t) \end{pmatrix} \right\},$$

$$\begin{pmatrix} \hat{m}_1 \\ \hat{p}_1 \end{pmatrix} = \begin{pmatrix} 1 \\ 2 \end{pmatrix}, \begin{pmatrix} \hat{m}_2 \\ \hat{p}_2 \end{pmatrix} = \begin{pmatrix} 2 \\ 4 \end{pmatrix}, \begin{pmatrix} \hat{m}_3 \\ \hat{p}_3 \end{pmatrix} = \begin{pmatrix} 3.5 \\ 7 \end{pmatrix}$$

The temporal evolution of m_i $(i = 1, \ldots, 7)$ and p_i is shown in Fig. 4. According to Fig. 4, $m_i(t)$ and $p_i(t)$ reach equilibrium at the desired values and the concentrations of m_i and

Figure 3 Identification process for the uncertain parameters ω_{ij} ($i = 2, \ldots, 7; j = 1, \ldots, 7$)

Figure 4 State trajectories of $m_i(t)$ and $p_i(t)$ ($i = 1, 2, \ldots, 20$)

Figure 5 Identification process for adjustment parameter ω_{ij}, ($i = 1, \ldots, 20; j = 1, \ldots, 20$)
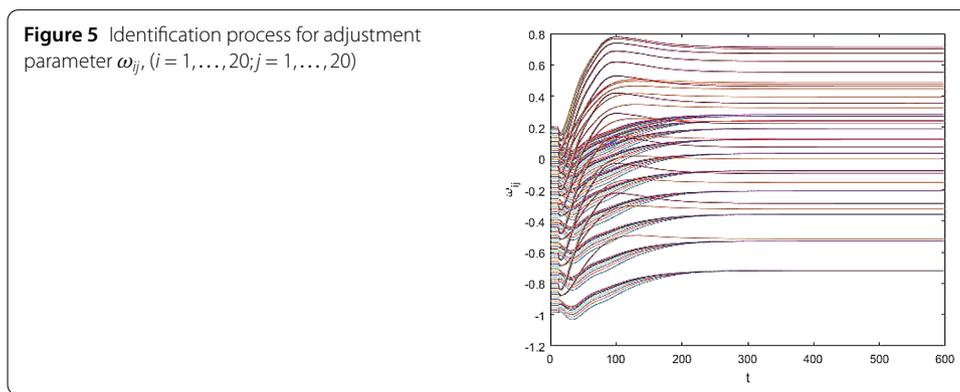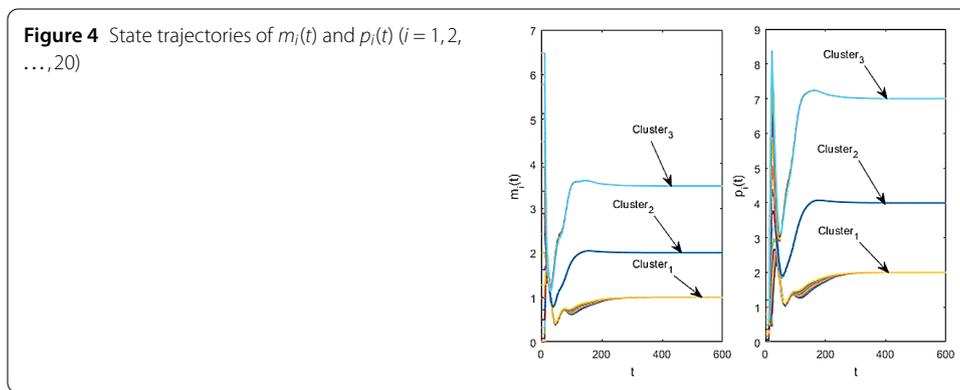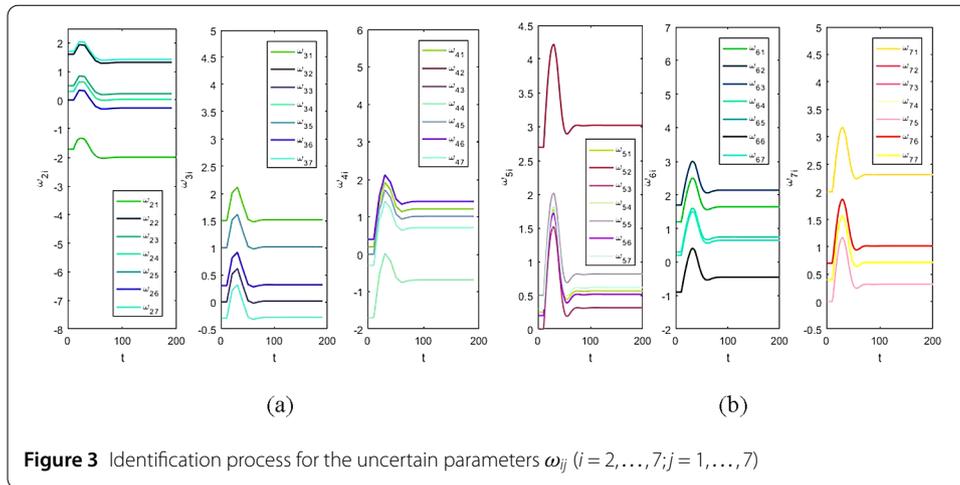
p_i ($i = 1, \ldots, 10$) belong to the first cluster, the concentrations of m_i and p_i ($i = 11, \ldots, 15$) belong to the second cluster, and the concentrations of m_i, p_i ($i = 16, \ldots, 20$) approach the third cluster.

According to Fig. 5, the curves for identifying ω_{ij} ($i = 1, 2, \ldots, 20; j = 1, 2, \ldots, 20$) gradually tend to the fixed values. Based on Fig. 6, inequation (7) is satisfied.

Example 2 In the numerical simulation of Example 2, the number of the nodes is fixed as $n = 7$, and it is assumed that there are two clusters in the GRNs, where $a_i = 2$ ($i = 1, \ldots, 7$),

Figure 6 Value of β_i, $(i = 1, \ldots, 20)$

Figure 7 State trajectory of $m_i(t)$ $(i = 1, 2, \ldots, 7)$, and identification process for the uncertain parameter ω_{1j} $(j = 1, \ldots, 7)$
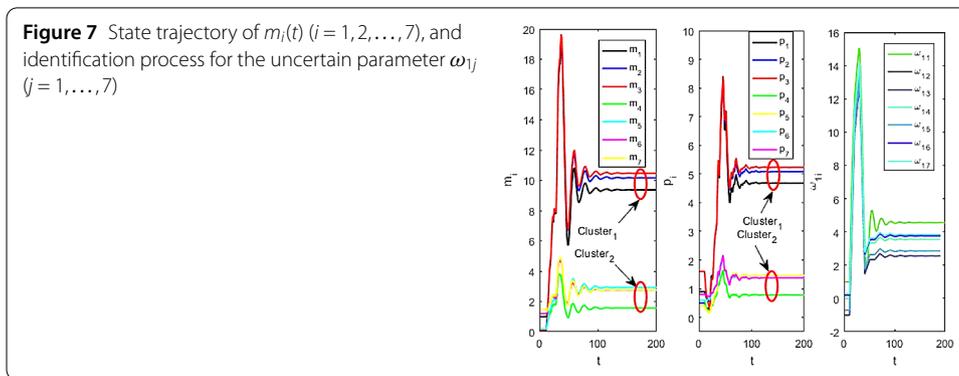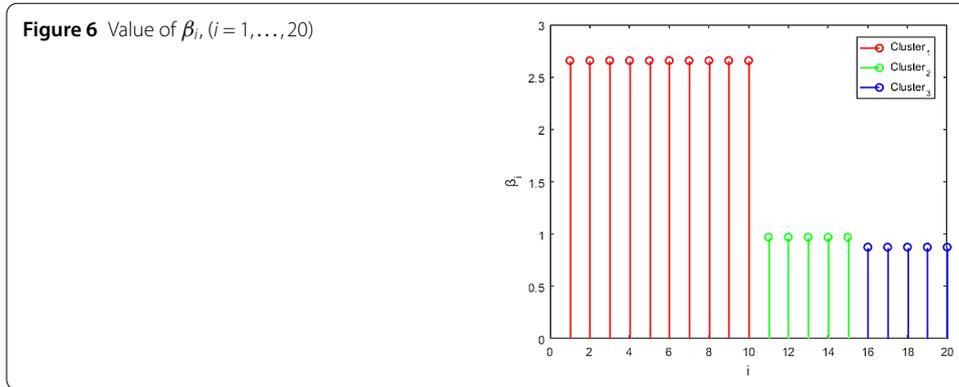
$c_k = 2$, $d_k = c_k \hat{S}_{2k}/\hat{S}_{1k}$ $(k = 1, \ldots, M)$; $M = 2$; $\alpha = 0.5$.

$$\begin{pmatrix} \overline{m}_1 \\ \overline{p}_1 \end{pmatrix} = \left\{ \begin{pmatrix} m_1(t) \\ p_1(t) \end{pmatrix}, \begin{pmatrix} m_2(t) \\ p_2(t) \end{pmatrix}, \begin{pmatrix} m_3(t) \\ p_3(t) \end{pmatrix} \right\},$$

$$\begin{pmatrix} \overline{m}_2 \\ \overline{p}_2 \end{pmatrix} = \left\{ \begin{pmatrix} m_4(t) \\ p_4(t) \end{pmatrix}, \begin{pmatrix} m_5(t) \\ p_5(t) \end{pmatrix}, \begin{pmatrix} m_6(t) \\ p_6(t) \end{pmatrix}, \begin{pmatrix} m_7(t) \\ p_7(t) \end{pmatrix} \right\};$$

where $S_{11} = m_1(t) + m_2(t) + m_3(t)$ and $S_{12} = m_4(t) + m_5(t) + m_6(t) + m_7(t)$; $S_{21} = p_1(t) + p_2(t) + p_3(t)$ and $S_{22} = p_4(t) + p_5(t) + p_6(t) + p_7(t)$ and the desired values of S_{11}, S_{12}, S_{21}, S_{22} are fixed at $\hat{S}_{11} = 30$, $\hat{S}_{12} = 10$, $\hat{S}_{21} = 15$, $\hat{S}_{22} = 5$, respectively.

The temporal evolution of m_i $(i = 1, \ldots, 7)$ and p_i are shown in Fig. 7, respectively. Figure 8(c) clearly indicates that the values of S_{1k} and S_{2k} $(k = 1, 2)$ approach those of $\hat{S}_{1k}$ and $\hat{S}_{2k}$. It is important to note that the GRNs are divided into two clusters, where the concentrations of m_i, p_i $(i = 1, 2, 3)$ belong to the first cluster and the concentrations of m_i, p_i $(i = 4, 5, 6, 7)$ belong to the second cluster.

Figure 8 **(a)**, **(b)**: Identification process for the adjustment parameter ω_{ij} $(i, j = 2, \ldots, 7)$; **(c)**: state trajectories of $S_{1k}(t)$ and $S_{2k}(t)$ $(k = 1, 2)$
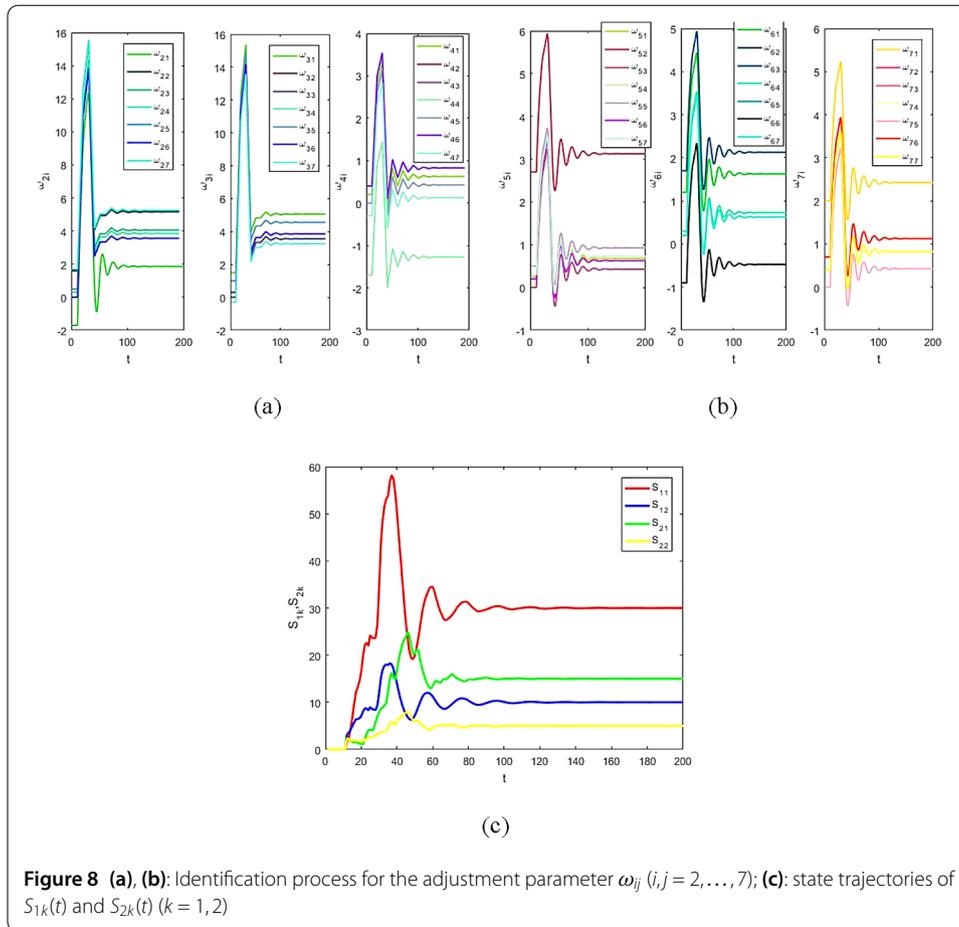
According to Figs. 7 and 8(a)–(b), the curves for identifying ω_{ij} $(i = 1, 2, \ldots, 7; j = 1, 2, \ldots, 7)$ gradually tend toward the fixed values as follows:

$$\hat{W} = \begin{pmatrix} 4.56 & 3.76 & 2.56 & 3.56 & 2.86 & 3.76 & 3.86 \\ 1.86 & 5.16 & 4.06 & 3.86 & 3.56 & 3.56 & 5.26 \\ 5.06 & 3.56 & 3.56 & 3.86 & 4.56 & 3.86 & 3.26 \\ 0.63 & 0.43 & 0.43 & -1.27 & 0.43 & 0.83 & 0.12 \\ 0.68 & 3.13 & 0.43 & 0.73 & 0.93 & 0.63 & 0.72 \\ 1.63 & 0.63 & 2.13 & 0.73 & 0.63 & -0.47 & 0.63 \\ 2.43 & 0.83 & 0.43 & 1.13 & 0.43 & 1.13 & 0.83 \end{pmatrix},$$

where $\hat{W}$ is the identification estimates for the uncertain coupling matrix W.

$$\beta_1 = \frac{a_1 \hat{S}_{11}}{\sum_{i=1}^{3} \sum_{j=1}^{7} \hat{\omega}_{ij}} = 0.75, \qquad \beta_2 = \frac{a_2 \hat{S}_{12}}{\sum_{i=4}^{7} \sum_{j=1}^{7} \hat{\omega}_{ij}} = 0.91.$$

Clearly, the value of β_k $(k = 1, 2)$ is positive, and thus inequation (24) is satisfied.

Furthermore, when we expand the number of nodes of GRNs to 20 and assume that there are three clusters in the GRNs, where $a_i = 3$ $(i = 1, \ldots, 20)$, $c_k = 0.5$, $d_k = c_k \hat{S}_{2k} / \hat{S}_{1k}$ $(k =$
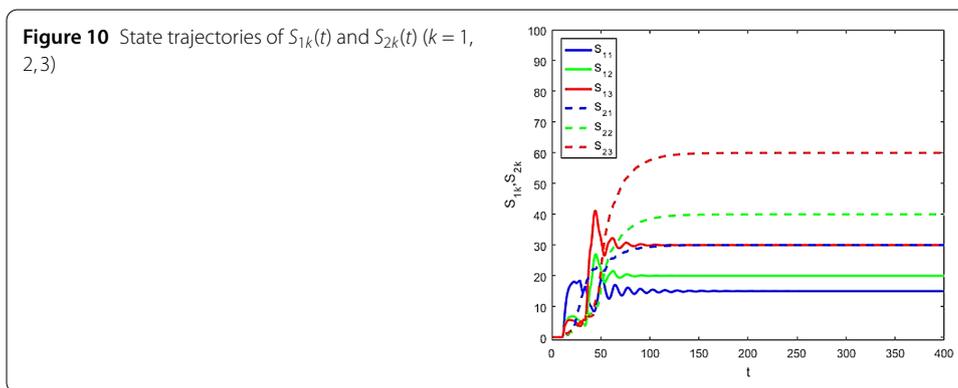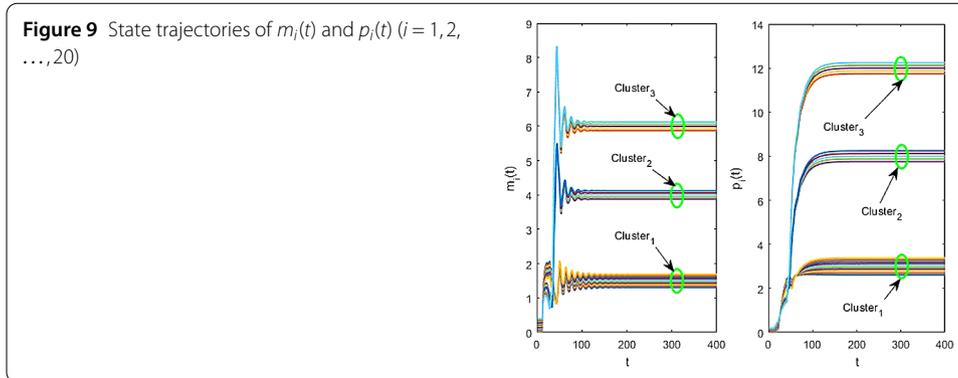
Figure 9 State trajectories of $m_i(t)$ and $p_i(t)$ ($i = 1, 2, \ldots, 20$)

Figure 10 State trajectories of $S_{1k}(t)$ and $S_{2k}(t)$ ($k = 1, 2, 3$)

$1, \ldots, M$); $M = 3$; $\alpha = 0.2$,

$$\begin{pmatrix} \overline{m}_1 \\ \overline{p}_1 \end{pmatrix} = \left\{ \begin{pmatrix} m_1(t) \\ p_1(t) \end{pmatrix}, \ldots, \begin{pmatrix} m_{10}(t) \\ p_{10}(t) \end{pmatrix} \right\},$$

$$\begin{pmatrix} \overline{m}_2 \\ \overline{p}_2 \end{pmatrix} = \left\{ \begin{pmatrix} m_{11}(t) \\ p_{11}(t) \end{pmatrix}, \ldots, \begin{pmatrix} m_{15}(t) \\ p_{15}(t) \end{pmatrix} \right\},$$

$$\begin{pmatrix} \overline{m}_3 \\ \overline{p}_3 \end{pmatrix} = \left\{ \begin{pmatrix} m_{16}(t) \\ p_{16}(t) \end{pmatrix}, \ldots, \begin{pmatrix} m_{20}(t) \\ p_{20}(t) \end{pmatrix} \right\},$$

such that $S_{11} = \sum_{i=1}^{10} m_i(t), S_{12} = \sum_{i=11}^{15} m_i(t), S_{13} = \sum_{i=16}^{20} m_i(t); S_{21} = \sum_{i=1}^{10} p_i(t), S_{22} = \sum_{i=11}^{15} p_i(t), S_{23} = \sum_{i=16}^{20} p_i(t)$.

The desired values of $S_{11}, S_{12}, S_{13}, S_{21}, S_{22}, S_{23}$ are fixed at $\hat{S}_{11} = 15, \hat{S}_{12} = 20, \hat{S}_{13} = 30,$ $\hat{S}_{21} = 30, \hat{S}_{22} = 40, \hat{S}_{23} = 60$, respectively.

The temporal evolution of m_i and p_i ($i = 1, \ldots, 20$) is shown in Fig. 9. According to Fig. 10, the values of S_{1k} and S_{2k} ($k = 1, 2, 3$) clearly approach those of $\hat{S}_{1k}$ and $\hat{S}_{2k}$. It is important to note that the GRNs are divided into three clusters, where the concentrations of m_i, p_i ($i = 1, \ldots, 10$) belong to the first cluster, the concentrations of m_i, p_i ($i = 11, \ldots, 15$) belong to the second cluster, and the concentrations of m_i, p_i ($i = 16, \ldots, 20$) belong to the third cluster.

Figure 11 Identification process for the uncertain parameter ω_{ij}, $(i = 1, \ldots, 20; j = 1, \ldots, 20)$
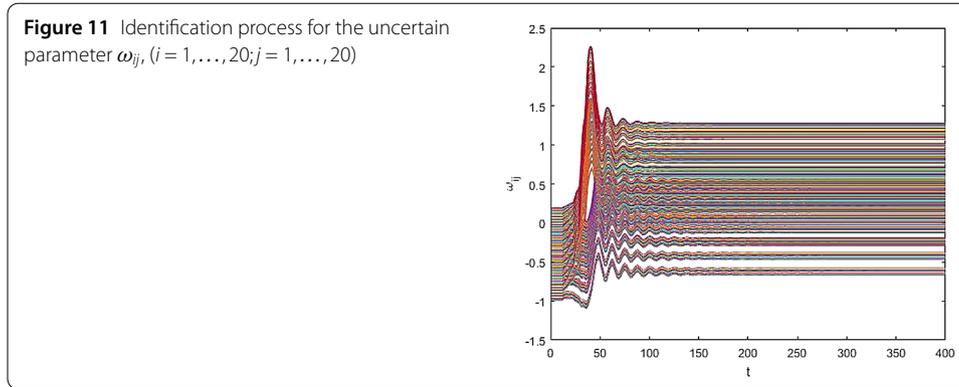
According to Fig. 11, the curves for identifying ω_{ij} $(i = 1, 2, \ldots, 20; j = 1, 2, \ldots, 20)$ gradually tend toward the fixed values.

$$\beta_1 = \frac{a_1 \hat{S}_{11}}{\sum_{i=1}^{10} \sum_{j=1}^{7} \hat{\omega}_{ij}} = 1.47, \qquad \beta_2 = \frac{a_2 \hat{S}_{12}}{\sum_{i=11}^{15} \sum_{j=1}^{7} \hat{\omega}_{ij}} = 0.95,$$

$$\beta_3 = \frac{a_3 \hat{S}_{13}}{\sum_{i=16}^{20} \sum_{j=1}^{7} \hat{\omega}_{ij}} = 0.95.$$

Clearly, the value of β_k $(k = 1, 2, 3)$ is positive, and thus inequation (24) is satisfied.

5 Conclusions

In this study, we investigated desired clusters of GRNs with fixed time lags based on the Lyapunov theorem and Lipschitz condition. GRNs can be clustered using the two proposed strategies. In the first method, the concentrations of mRNAs in the same cluster approach the unique desired value. In the second method, the sums of clusters tend toward the desired value. Numerical examples were provided to demonstrate the effectiveness of the proposed clustering techniques. The results showed that the number of possible clusters in the GRNs does not affect the targeted stability of the cluster. In addition, not limiting the number of nodes in each cluster enhances the practicality and flexibility of these methods.

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