Sufficient and necessary conditions for Lyapunov stability of genetic networks with SUM regulatory logic

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Abstract In this paper, a nonlinear model for genetic regulator networks (GRNs) with SUM regulatory logic is presented. Four sufficient and necessary conditions of global asymptotical stability and global exponential stability for the equilibrium point of the GRNs are proposed, respectively. Specifically, three weak sufficient conditions and corresponding corollaries are derived by using comparing theorem and Dini derivative method. Then, a famous GRN model is used as the example to illustrate the effectiveness of our theoretical results. Comparing to the results in the previous literature, some novel ideas, study methods and interesting results are explored.

Keywords Genetic regulator networks · Asymptotical stability · Exponential stability · Comparing theorem · Dini derivative

Introduction

In recent years, GRNs have become an important area of research in system biology as it explains the interactions between gene (mRNA) and its products (proteins) to form a

complex system that performs complicated biology functions (Jacob and Monod 1961; Smolen et al. 2000; Yuh et al. 1998). It is also expected that the study may lead to engineering developments of circuits and systems such as biotechnological design principles of synthetic GRNs (Gardner et al. 2000; Elowitz and Leibler 2000), and new kinds of integrated circuits like neurochips learnt from biological neural networks. GRNs are biochemically dynamic systems to describe highly complex interactions among two main species of gene products: mRNA and proteins, in the interactive transcription and translation process, and they are always modeled by using dynamic systems. Several computational models have been applied to investigate the behaviors of GRNs: Boolean models (Somogyi and Sniegowski 1996; Weaver et al. 1999), Bayesian network models (Friedman et al. 2000; Hartemink et al. 2002), Petri net models (Hardy and Robillard 2004; Chaouiya et al. 2008), and the differential equation models (Smolen et al. 2000; Bolouri and Davidson 2002; Chen and Aihara 2002; Chesi and Hung 2008).

From the GRN models proposed, the differential equation models have been widely used to investigate the GRNs, and many quantitative results have been obtained (Chen and Aihara 2002; Chesi and Hung 2008; Chesi 2011, 2009; Yu et al. 2009; Li et al. 2010; Ren and Cao 2008; Hu et al. 2013; Wang et al. 2010; Wu 2011; Li and Lin 2013; Pan et al. 2010; Luo et al. 2010). In differential equation models, the variables describe the concentrations of gene products, such as mRNA and proteins, as continuous values of dynamic systems. Each concentration of the systems is expressed by a function, this function consists of two parts: a linear part which defines the natural decay rate of the concentration itself, and a nonlinear part which defines the influence by other concentrations. The nonlinear part is usually described via sum of saturation functions (i.e.,

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SUM logic) (Chen and Aihara 2002; Chesi and Hung 2008), or product of saturation functions (i.e., PROD logic) (Chesi 2009).

Since the genetic regulatory process is a dynamic process of transcription, translation and translocation, the stability of GRNs is naturally of great importance, and it has attracted many researchers' attention (Yu et al. 2009; Li et al. 2010; Ren and Cao 2008; Hu et al. 2013; Wang et al. 2010; Wu 2011; Li and Lin 2013; Pan et al. 2010; Luo et al. 2010). Different GRN models and different methods are considered in the literature. Chen and Aihara (2002) studied local stability and the bifurcation of GRNs, Chesi and Hung studied robust stability of uncertain GRNs with SUM logic (Chesi and Hung 2008; Chesi 2011). Chen and Aihara (2002), Li et al. (2010) studied stability of GRNs with time-delay by using LMI methods. Ren and Cao (2008), Hu et al. (2013) and Wang et al. (2010) studied the stability for a class of GRNs with time delays and noise perturbations. Wu (2011) studied global and robust stability for GRNs with time-variant delays and parameter uncertainties. Li and Lin (2013) and Pan et al. (2010) studied monostability or multistability with different regulatory functions. Luo et al. (2010) proposed some results of unconditional global exponential stability in sense of Lagrange for GRNs with time-variant delays and SUM logic. Some studies are about the stability in sense of Lyapunov (Yu et al. 2009; Li et al. 2010; Ren and Cao 2008; Hu et al. 2013; Wang et al. 2010; Wu 2011), while some other researches are about the stability in sense of Lagrange (Luo et al. 2010; Liao and Yu 2008). Nevertheless, they are mostly sufficient condition, and the linear matrix inequalities (LMIs) are mainly used. As is known to all, for the linear matrix inequalities solver, although you can make full use of the computer, any one-dimensional matrix will meet a higher dimensional linear matrix inequality, results are conservative because of the strong conditions. So far, we can't look out the sufficient and necessary conditions of the Lyapunov stability of GRNs.

Since GRN is actually a Lurie system, which is a linear system plus nonlinear feedback term, and sufficient and necessary conditions for absolute stability of Lurie system are proposed [see references in Liao and Yu (2008)], people always raise the question whether the sufficient and necessary conditions for stability of GRNs exist, unlike the existing literature of sufficient conditions. By analyzing, GRNs with SUM logic are just with the excellent properties which Lurie systems have. Therefore, we can take advantage of the core idea of reference (Liao and Yu 2008), and aim to study the GRNs with SUM logic.

Based on the definition of Lyapunov stability, differential mean value theorem, some sufficient and necessary conditions for global asymptotical stability and global exponential stability of the GRNs will be proposed,

respectively. Especially, some weak sufficient conditions for global asymptotical stability and global exponential stability of the GRNs will be presented by imposing comparing theorem and Dini derivation method (Liao 2010). Then, a general model is used as the example to illustrate the effectiveness of our theoretical results. Comparing to the results in the previous literature, some novel idea, study methods and interesting results are included in this paper.

The rest of this paper is organized as follows. In the “**Problem formulation and preliminaries**” section, the GRN considered in this paper is presented, some definitions and main problems are given. In “**Sufficient and necessary conditions for global stability of GRNs**” section, some sufficient and necessary conditions for global asymptotic stability and global exponential stability are proposed. The “**Sufficient conditions for global stability of GRNs**” section presents some sufficient conditions for global stability. In “**Illustrative example**” section, one numerical example is given to demonstrate the effectiveness of the theoretical results. The final “**Conclusion**” section is about the conclusions.

Problem formulation and preliminaries

In this paper, we consider the GRNs consisting of n mRNAs and n proteins, it can be described by the following equations (Chen and Aihara 2002; Chesi and Hung 2008):

$$\begin{cases} \frac{dm_i}{dt} = -a_i m_i(t) + b_i(p_1(t), p_2(t), \dots, p_n(t)) \\ \frac{dp_i}{dt} = -c_i p_i(t) + d_i m_i(t), \quad i = 1, 2, \dots, n \end{cases} \quad (1)$$

where $m_i(t), p_i(t)$ are the concentrations of mRNA and protein of the i th node, respectively. The parameters $a_i > 0, c_i > 0$ are the decay rates of mRNA and protein, respectively. d_i is a constant, which is the translation rate. b_i is the regulation function of the i th gene, and it is generally a nonlinear function of variables $(p_1(t), p_2(t), \dots, p_n(t))$, but has a form of monotonicity with each variable. Genetic regulatory function b_i may be very complicated and we will investigate the model of GRNs where each transcription factor acts additively to regulate i th gene. That is, the regulatory function can be described as follows:

$$b_i(p_1(t), p_2(t), \dots, p_n(t)) = \sum_{j=1}^n b_{ij}(p_j(t))$$

it is also called SUM logic Chesi and Hung (2008), Luo et al. (2010). $b_{ij}(p_j(t))$ is expressed by a monotonic function of Hill form:

$$b_{ij}(p_j(t)) = \begin{cases} \alpha_{ij} \frac{(p_j(t)/\beta_j)^{H_j}}{1 + (p_j(t)/\beta_j)^{H_j}}, & \text{if transcription factor } j \text{ is an activator of gene } i \\ \alpha_{ij} \frac{1}{1 + (p_j(t)/\beta_j)^{H_j}}, & \text{if transcription factor } j \text{ is a repressor of gene } i \end{cases}$$

where H_j is Hill coefficient, β_j is a positive constant, α_{ij} is the dimensionless transcription rate of the transcription factor j to gene i , which is a bounded constant. Note that

$$\frac{1}{1 + (p_j(t)/\beta_j)^{H_j}} = 1 - \frac{(p_j(t)/\beta_j)^{H_j}}{1 + (p_j(t)/\beta_j)^{H_j}},$$

we define $g_j(x) = \frac{(x/\beta_j)^{H_j}}{1 + (x/\beta_j)^{H_j}}$. Let $\omega_{ij} = 0$, if there is no link from node j to node i ; $\omega_{ij} = \alpha_{ij}$, if transcription factor j is an activator of gene i ; $\omega_{ij} = -\alpha_{ij}$, if transcription factor j is a repressor of gene i . I_i is defined as a basal rate with $I_i = \sum_{j \in V_i} \alpha_{ij}$, in which V_i is the set of repressors of gene i .

Then, one obtains:

$$\begin{cases} \frac{dm_i}{dt} = -a_i m_i(t) + \sum_{j=1}^n \omega_{ij} g_j(p_j(t)) + I_i \\ \frac{dp_i}{dt} = -c_i p_i(t) + d_i m_i(t), i = 1, 2, \dots, n. \end{cases} \quad (2)$$

It is easy to see that $g_j(x)$ is a monotonically increasing function and valued between $[0, 1]$. Furthermore, $g_j(x)$ is a sigmoid type and continuous derivative function if $H_j > 1$. Obviously, there exists a positive constant $k > 0$ such that $0 \leq \dot{g}_i(\cdot) \leq k$. Without loss of generality, let $\ell_{ij} = \sup |\omega_{ij} \dot{g}_j(\cdot)|$ and it will be used all over this paper.

Let $m = [m_1, m_2, \dots, m_n]^T$, $p = [p_1, p_2, \dots, p_n]^T$, by the well known Brouwer fixed point theorem (Granas and Dugundji 2003), there exists some equilibrium point (m^*, p^*) for system (2) such that

$$\begin{cases} -a_i m_i^* + \sum_{j=1}^n \omega_{ij} g_j(p_j^*) + I_i = 0 \\ -c_i p_i^* + d_i m_i^* = 0, \quad i = 1, 2, \dots, n. \end{cases} \quad (3)$$

Now, we shift the equilibrium point (m^*, p^*) to the origin by letting $\tilde{m} = m - m^*$, $\tilde{p} = p - p^*$, it is easy to obtain that

$$\begin{cases} \frac{d\tilde{m}_i}{dt} = -a_i \tilde{m}_i + \sum_{j=1}^n \omega_{ij} [g_j(p_j) - g_j(p_j^*)] \\ \frac{d\tilde{p}_i}{dt} = -c_i \tilde{p}_i + d_i \tilde{m}_i(t), \quad i = 1, 2, \dots, n. \end{cases} \quad (4)$$

Then, we introduce some necessary definitions (Liao 2010).

Definition 1 The zero solution of system (4) (i.e., the corresponding equilibrium point (m^*, p^*) of system (2)) is globally asymptotically stable if

- (I) $\forall \varepsilon > 0, \exists \delta(\varepsilon) > 0, \forall t \geq t_0$, when $\|\tilde{m}_0\| = \|\tilde{m}(t_0; t_0, \tilde{m}_0, \tilde{p}_0)\| < \delta(\varepsilon)$, $\|\tilde{p}_0\| = \|\tilde{p}(t_0; t_0, \tilde{m}_0, \tilde{p}_0)\| < \delta(\varepsilon)$, it holds that
- $$\|\tilde{m}(t; t_0, \tilde{m}_0, \tilde{p}_0)\| < \varepsilon, \|\tilde{p}(t; t_0, \tilde{m}_0, \tilde{p}_0)\| < \varepsilon;$$
- (II) $\forall \tilde{m}_0 \in \mathbb{R}^n, \tilde{p}_0 \in \mathbb{R}^n$, it holds that $\lim_{t \rightarrow +\infty} \tilde{m}(t; t_0, \tilde{m}_0, \tilde{p}_0) = 0, \lim_{t \rightarrow +\infty} \tilde{p}(t; t_0, \tilde{m}_0, \tilde{p}_0) = 0$.

Definition 2 The zero solution of system (4) (i.e., the corresponding equilibrium point (m^*, p^*) of system (2)) on partial variable $\tilde{m}$ or $\tilde{p}$ is globally asymptotically stable if

- (I) $\forall \varepsilon > 0, \exists \delta(\varepsilon) > 0, \forall t \geq t_0$, when $\|\tilde{m}_0\| < \delta(\varepsilon)$, and $\|\tilde{p}_0\| < \delta(\varepsilon)$, it holds that
- $$\|\tilde{m}(t; t_0, \tilde{m}_0, \tilde{p}_0)\| < \varepsilon \text{ or } \|\tilde{p}(t; t_0, \tilde{m}_0, \tilde{p}_0)\| < \varepsilon;$$
- (II) $\forall \tilde{m}_0 \in \mathbb{R}^n, \tilde{p}_0 \in \mathbb{R}^n$, it holds that
- $$\lim_{t \rightarrow +\infty} \tilde{m}(t; t_0, \tilde{m}_0, \tilde{p}_0) = 0 \text{ or } \lim_{t \rightarrow +\infty} \tilde{p}(t; t_0, \tilde{m}_0, \tilde{p}_0) = 0.$$

Definition 3 The zero solution of system (4) (i.e., the equilibrium point (m^*, p^*) of system (2)) is globally exponentially stable if the solution of system (4) has the following estimation.

$$\|\tilde{m}(t; t_0, \tilde{m}_0, \tilde{p}_0), \tilde{p}(t; t_0, \tilde{m}_0, \tilde{p}_0)\| \leq M(\tilde{m}_0, \tilde{p}_0) e^{-\lambda(t-t_0)}$$

where $M(\tilde{m}_0, \tilde{p}_0) > 0$ and $\lambda > 0$ are positive constants.

Definition 4 The zero solution of system (4) (i.e., the equilibrium point (m^*, p^*) of system (2)) is globally exponentially stable on the partial variable $\tilde{m}$ or $\tilde{p}$ if the partial variable $\tilde{m}$ or $\tilde{p}$ has the following estimation.

$$\begin{aligned} \|\tilde{m}(t; t_0, \tilde{m}_0, \tilde{p}_0)\| &\leq K(\tilde{m}_0, \tilde{p}_0) e^{-\lambda(t-t_0)} \text{ or} \\ \|\tilde{p}(t; t_0, \tilde{m}_0, \tilde{p}_0)\| &\leq K(\tilde{m}_0, \tilde{p}_0) e^{-\lambda(t-t_0)} \end{aligned}$$

where $K(\tilde{m}_0, \tilde{p}_0) > 0$ and $\lambda > 0$ are positive constants.

sufficient and necessary conditions for global stability of GRNs

In this section, we will propose some sufficient and necessary conditions for global asymptotical stability, global exponential stability of the zero solution of system (4).

Theorem 1 *The sufficient and necessary condition for global asymptotical stability of the zero solution of system (4) is that $\tilde{m}$ or $\tilde{p}$ is globally asymptotically stable.*

Proof *Necessity.* Since the zero solution of system (4) is globally asymptotically stable, any partial variable is globally asymptotically stable. Thus, the necessary condition obviously holds.

Sufficiency. The proof consists of two cases.

Case 1. Suppose that the zero solution of system (4) on partial variable $\tilde{m}$ is globally asymptotically stable. Then,

$\forall \varepsilon > 0$, $\exists \delta(\varepsilon) = \frac{\varepsilon}{2} > 0$, let $\varepsilon_1 > 0$ with $\frac{|d_i|}{c_i} \varepsilon_1 \leq \frac{\varepsilon}{2}$, when

$\|\tilde{m}_0\| < \delta(\varepsilon)$, $\|\tilde{p}_0\| < \delta(\varepsilon)$, it holds that

$$\|\tilde{m}(t; t_0, \tilde{m}_0, \tilde{p}_0)\| < \varepsilon_1,$$

and for any $\tilde{m}_0 \in \mathbb{R}^n$, $\tilde{p}_0 \in \mathbb{R}^n$, it holds that

$$\begin{aligned} \lim_{t \rightarrow +\infty} \tilde{m}(t; t_0, \tilde{m}_0, \tilde{p}_0) \\ = \lim_{t \rightarrow +\infty} [\tilde{m}_1(t; t_0, \tilde{m}_0, \tilde{p}_0), \tilde{m}_2(t; t_0, \tilde{m}_0, \tilde{p}_0), \dots, \\ \{\tilde{m}_n(t; t_0, \tilde{m}_0, \tilde{p}_0)\}^T] = 0. \end{aligned}$$

From the second equation of system (4), one obtains that

$$\begin{aligned} |\tilde{p}_i(t; t_0, \tilde{m}_0, \tilde{p}_0)| &\leq e^{-c_i(t-t_0)} |\tilde{p}_i(t_0; t_0, \tilde{m}_0, \tilde{p}_0)| \\ &\quad + \int_{t_0}^t e^{-c_i(t-\tau)} |d_i \tilde{m}_i(\tau; t_0, \tilde{m}_0, \tilde{p}_0)| d\tau \\ &\leq e^{-c_i(t-t_0)} |\tilde{p}_i(t_0; t_0, \tilde{m}_0, \tilde{p}_0)| \\ &\quad + e^{-c_i t} \int_{t_0}^t e^{c_i \tau} |d_i| \varepsilon_1 d\tau \\ &= \delta(\varepsilon) + \frac{|d_i| \varepsilon_1}{c_i} e^{-c_i t} (e^{c_i t} - e^{c_i t_0}) \\ &= \delta(\varepsilon) + \frac{|d_i| \varepsilon_1}{c_i} (1 - e^{-c_i(t-t_0)}) \\ &\leq \frac{\varepsilon}{2} + \frac{|d_i| \varepsilon_1}{c_i} \\ &\leq \frac{\varepsilon}{2} + \frac{\varepsilon}{2} = \varepsilon, \quad i = 1, 2, \dots, n. \end{aligned} \quad (5)$$

Accordingly, the zero solution of system (4) on partial variable $\tilde{p}$ is stable in sense of Lyapunov.

Now, we prove the global attractivity of system (4). By using Hospital's rule, one has

$$\begin{aligned} \lim_{t \rightarrow +\infty} \tilde{p}_i(t; t_0, \tilde{m}_0, \tilde{p}_0) &= \lim_{t \rightarrow +\infty} e^{-c_i(t-t_0)} \tilde{p}_i(t_0; t_0, \tilde{m}_0, \tilde{p}_0) \\ &\quad + \lim_{t \rightarrow +\infty} \frac{\int_{t_0}^t e^{c_i \tau} d_i \tilde{m}_i(\tau; t_0, \tilde{m}_0, \tilde{p}_0) d\tau}{e^{c_i t}} \\ &= 0 + \lim_{t \rightarrow +\infty} \frac{e^{c_i t} d_i \tilde{m}_i(t; t_0, \tilde{m}_0, \tilde{p}_0)}{c_i e^{c_i t}} \\ &= \frac{d_i}{c_i} \lim_{t \rightarrow +\infty} \tilde{m}_i(t; t_0, \tilde{m}_0, \tilde{p}_0) = 0, \\ &\quad i = 1, 2, \dots, n. \end{aligned} \quad (6)$$

Therefore, global asymptotical stability on partial variable $\tilde{m}$ of system (4) implies global asymptotical stability on partial variable $\tilde{p}$, and thus, all variables of system (4) are globally asymptotically stable.

Case 2. Suppose the zero solution of system (4) on partial variable $\tilde{p}$ is globally asymptotically stable. Then,

$\forall \varepsilon > 0$, let $0 < \varepsilon_2 < 1$, such that $\sum_{j=1}^n \frac{\ell_{ij} \varepsilon_2}{a_i} \leq \frac{\varepsilon}{2}$. Let $0 <$

$\delta(\varepsilon) < \frac{\varepsilon}{2}$, when $\|\tilde{m}_0\| < \delta(\varepsilon)$, $\|\tilde{p}_0\| < \delta(\varepsilon)$, it holds that

$$\|\tilde{p}(t; t_0, \tilde{m}_0, \tilde{p}_0)\| < \varepsilon_2,$$

and for any $\tilde{m}_0 \in \mathbb{R}^n$, $\tilde{p}_0 \in \mathbb{R}^n$, one has

$$\begin{aligned} \lim_{t \rightarrow +\infty} \tilde{p}(t; t_0, \tilde{m}_0, \tilde{p}_0) \\ = \lim_{t \rightarrow +\infty} [\tilde{p}_1(t; t_0, \tilde{m}_0, \tilde{p}_0), \tilde{p}_2(t; t_0, \tilde{m}_0, \tilde{p}_0), \dots, \\ \tilde{p}_n(t; t_0, \tilde{m}_0, \tilde{p}_0)]^T = 0. \end{aligned}$$

From the first equation of system (4), and by using Differential Mean-value Theorem, one has

$$\begin{aligned} |\tilde{m}_i(t; t_0, \tilde{m}_0, \tilde{p}_0)| &= e^{-a_i(t-t_0)} |\tilde{m}_i(t_0; t_0, \tilde{m}_0, \tilde{p}_0)| \\ &\quad + e^{-a_i t} \int_{t_0}^t e^{a_i \tau} \sum_{j=1}^n |\omega_{ij}(g_j(p_j(\tau)) \\ &\quad - g_j(p_j^*))| d\tau \\ &= e^{-a_i(t-t_0)} |\tilde{m}_i(t_0; t_0, \tilde{m}_0, \tilde{p}_0)| \\ &\quad + e^{-a_i t} \int_{t_0}^t e^{a_i \tau} \sum_{j=1}^n |\omega_{ij} \dot{g}_j(\xi) \\ &\quad \times \|\tilde{p}_j(\tau; t_0, \tilde{m}_0, \tilde{p}_0)\| d\tau \\ &\leq \delta(\varepsilon) + e^{-a_i t} \int_{t_0}^t e^{a_i \tau} \sum_{j=1}^n \ell_{ij} \varepsilon_2 d\tau \\ &= \frac{\varepsilon}{2} + e^{-a_i t} \sum_{j=1}^n \ell_{ij} \varepsilon_2 \frac{e^{a_i t} - e^{a_i t_0}}{a_i} \\ &\leq \frac{\varepsilon}{2} + \sum_{j=1}^n \frac{\ell_{ij} \varepsilon_2}{a_i} \\ &\leq \frac{\varepsilon}{2} + \frac{\varepsilon}{2} = \varepsilon, \quad i = 1, 2, \dots, n. \end{aligned} \quad (7)$$

Therefore, the zero solution of system (4) on partial variable $\tilde{m}$ is stable in sense of Lyapunov.

Since $\lim_{t \rightarrow +\infty} \tilde{p}_i(t; t_0, \tilde{m}_0, \tilde{p}_0) = 0, \forall (\tilde{m}_0, \tilde{p}_0) \in \mathbb{R}^{2n}$, consider the first equation of system (4), and using Hospital's rule, one has

$$\begin{aligned} \lim_{t \rightarrow +\infty} |\tilde{m}_i(t; t_0, \tilde{m}_0, \tilde{p}_0)| &\leq \lim_{t \rightarrow +\infty} e^{-a_i(t-t_0)} |\tilde{m}_i(t_0; t_0, \tilde{m}_0, \tilde{p}_0)| \\ &\quad + \lim_{t \rightarrow +\infty} \int_{t_0}^t e^{-a_i(t-\tau)} \\ &\quad \times \sum_{j=1}^n |\omega_{ij}(g_j(p_j(\tau)) - g_j(p_j^*))| d\tau \\ &= \lim_{t \rightarrow +\infty} e^{-a_i(t-t_0)} |\tilde{m}_i(t_0; t_0, \tilde{m}_0, \tilde{p}_0)| \\ &\quad + \lim_{t \rightarrow +\infty} e^{-a_i t} \int_{t_0}^t e^{a_i \tau} \\ &\quad \times \sum_{j=1}^n |\omega_{ij} \dot{g}_j(\xi)| |\tilde{p}_j(\tau; t_0, \tilde{m}_0, \tilde{p}_0)| d\tau \\ &\leq 0 + \lim_{t \rightarrow +\infty} \frac{e^{a_i t} \sum_{j=1}^n \ell_{ij} |\tilde{p}_j(t; t_0, \tilde{m}_0, \tilde{p}_0)|}{a_i e^{a_i t}} \\ &= \lim_{t \rightarrow +\infty} \frac{\sum_{j=1}^n \ell_{ij} |\tilde{p}_j(t; t_0, \tilde{m}_0, \tilde{p}_0)|}{a_i} = 0. \end{aligned}$$

Accordingly, we have

$$\lim_{t \rightarrow +\infty} \tilde{m}_i(t; t_0, \tilde{m}_0, \tilde{p}_0) = 0, i = 1, 2, \dots, n. \quad (8)$$

Therefore, global asymptotical stability of system (4) on variable $\tilde{p}$ implies global asymptotical stability on variable $\tilde{m}$, and thus, all variables of system (4) are globally asymptotically stable. That is, the equilibrium point (m^*, p^*) of system (2) is globally asymptotically stable. The sufficiency holds. $\square$

Theorem 2 *The sufficient and necessary condition for global exponential stability of the zero solution of system (4) is that the zero solution of system (4) on partial variable $\tilde{m}$ or $\tilde{p}$ is globally exponentially stable.*

Proof Necessity. Since the zero solution of system (4) on all variable is globally exponentially stable, any partial variable is globally exponentially stable. Thus, the necessity condition obviously holds. Specially,

$$\|\tilde{m}(t; t_0, \tilde{m}_0, \tilde{p}_0), \tilde{p}(t; t_0, \tilde{m}_0, \tilde{p}_0)\| \leq K(\tilde{m}_0, \tilde{p}_0) e^{-\lambda(t-t_0)} \quad (9)$$

where $K(\tilde{m}_0, \tilde{p}_0) > 0, \lambda > 0$ are constants.

Sufficiency. The proof consists of two cases.

Case1. Suppose the zero solution of system (4) on partial variable $\tilde{m}$ is globally exponentially stable, then,

there exist two positive constants $K_1(\tilde{m}_0, \tilde{p}_0) > 0, \lambda_1 > 0$, such that

$$|\tilde{m}_i(t; t_0, \tilde{m}_0, \tilde{p}_0)| \leq K_1(\tilde{m}_0, \tilde{p}_0) e^{-\lambda_1(t-t_0)}, i = 1, 2, \dots, n. \quad (10)$$

Consider the second equation of system (4), it holds that

$$\begin{aligned} |\tilde{p}_i(t; t_0, \tilde{m}_0, \tilde{p}_0)| &\leq e^{-c_i(t-t_0)} |\tilde{p}_i(t_0; t_0, \tilde{m}_0, \tilde{p}_0)| \\ &\quad + \int_{t_0}^t e^{-c_i(t-\tau)} |d_i \tilde{m}_i(\tau; t_0, \tilde{m}_0, \tilde{p}_0)| d\tau \\ &\leq e^{-c_i(t-t_0)} |\tilde{p}_i(t_0; t_0, \tilde{m}_0, \tilde{p}_0)| \\ &\quad + \int_{t_0}^t e^{-c_i(t-\tau)} |d_i| K_1(\tilde{m}_0, \tilde{p}_0) e^{-\lambda_1(\tau-t_0)} d\tau \\ &= e^{-c_i(t-t_0)} |\tilde{p}_i(t_0; t_0, \tilde{m}_0, \tilde{p}_0)| \\ &\quad + |d_i| K_1(\tilde{m}_0, \tilde{p}_0) e^{-(c_i-\lambda_1)t} e^{-\lambda_1(t-t_0)} \\ &\quad \times \int_{t_0}^t e^{(c_i-\lambda_1)\tau} d\tau \\ &= e^{-c_i(t-t_0)} |\tilde{p}_i(t_0; t_0, \tilde{m}_0, \tilde{p}_0)| \\ &\quad + \frac{|d_i| K_1(\tilde{m}_0, \tilde{p}_0)}{c_i - \lambda_1} (1 - e^{-(c_i-\lambda_1)(t-t_0)}) \\ &\quad \times e^{-\lambda_1(t-t_0)} \end{aligned}$$

Without loss of generality, assuming $c_i > \lambda_1, i = 1, 2, \dots, n$, it yields

$$\begin{aligned} |\tilde{p}_i(t; t_0, \tilde{m}_0, \tilde{p}_0)| &\leq e^{-c_i(t-t_0)} |\tilde{p}_i(t_0; t_0, \tilde{m}_0, \tilde{p}_0)| \\ &\quad + \frac{|d_i| K_1(\tilde{m}_0, \tilde{p}_0) e^{-\lambda_1(t-t_0)}}{c_i - \lambda_1} \\ &\leq \left(|\tilde{p}_i(t_0; t_0, \tilde{m}_0, \tilde{p}_0)| + \frac{|d_i| K_1(\tilde{m}_0, \tilde{p}_0)}{c_i - \lambda_1} \right) e^{-\lambda_1(t-t_0)} \\ &\leq H_1(\tilde{m}_0, \tilde{p}_0) e^{-\lambda_1(t-t_0)} \end{aligned} \quad (11)$$

where

$$H_1(\tilde{m}_0, \tilde{p}_0) = \max_{1 \leq i \leq n} \left\{ |\tilde{p}_i(t_0; t_0, \tilde{m}_0, \tilde{p}_0)| + \frac{|d_i| K_1(\tilde{m}_0, \tilde{p}_0)}{c_i - \lambda_1} \right\}.$$

Therefore, the zero solution of system (4) on partial variable $\tilde{p}_i$ is globally exponentially stable, so the zero solution of (4) on all variables are globally exponentially stable.

Case2. Now, suppose the zero solution of system (4) on partial variable $\tilde{p}$ is globally exponentially stable, then there exist two positive constants $K_2(\tilde{m}_0, \tilde{p}_0) > 0, \lambda_2 > 0$, such that

$$|\tilde{p}_i(t; t_0, \tilde{m}_0, \tilde{p}_0)| \leq K_2(\tilde{m}_0, \tilde{p}_0) e^{-\lambda_2(t-t_0)}, i = 1, 2, \dots, n. \quad (12)$$

Consider the second equation of system (4), one has

$$\begin{aligned}
& |\tilde{m}_i(t; t_0, \tilde{m}_0, \tilde{p}_0)| \\
& \leq e^{-a_i(t-t_0)} |\tilde{m}_i(t_0; t_0, \tilde{m}_0, \tilde{p}_0)| \\
& \quad + \int_{t_0}^t e^{-a_i(t-\tau)} \sum_{j=1}^n |w_{ij}(g_j(p_j(\tau)) - g_j(p_j^*))| d\tau \\
& \leq e^{-a_i(t-t_0)} |\tilde{m}_i(t_0; t_0, \tilde{m}_0, \tilde{p}_0)| \\
& \quad + e^{-a_i t} \int_{t_0}^t e^{a_i \tau} \sum_{j=1}^n |w_{ij} \dot{g}_j(\xi)| |\tilde{p}_j(\tau; t_0, \tilde{m}_0, \tilde{p}_0)| d\tau \\
& \leq e^{-a_i(t-t_0)} |\tilde{m}_i(t_0; t_0, \tilde{m}_0, \tilde{p}_0)| \\
& \quad + e^{-a_i t} \int_{t_0}^t e^{a_i \tau} \sum_{j=1}^n \ell_{ij} K_2(\tilde{m}_0, \tilde{p}_0) e^{-\lambda_2(\tau-t_0)} d\tau \\
& = e^{-a_i(t-t_0)} |\tilde{m}_i(t_0; t_0, \tilde{m}_0, \tilde{p}_0)| \\
& \quad + e^{-(a_i-\lambda_2)t} e^{-\lambda_2(t-t_0)} K_2(\tilde{m}_0, \tilde{p}_0) \sum_{j=1}^n \ell_{ij} \int_{t_0}^t e^{(a_i-\lambda_2)\tau} d\tau \\
& = e^{-a_i(t-t_0)} |\tilde{m}_i(t_0; t_0, \tilde{m}_0, \tilde{p}_0)| \\
& \quad + K_2(\tilde{m}_0, \tilde{p}_0) \sum_{j=1}^n \ell_{ij} \frac{1 - e^{-(a_i-\lambda_2)(t-t_0)}}{a_i - \lambda_2} e^{-\lambda_2(t-t_0)}.
\end{aligned}$$

Without loss of generality, assuming $a_i > \lambda_2, i = 1, 2, \dots, n$, then, it yields

$$\begin{aligned}
& |\tilde{m}_i(t; t_0, \tilde{m}_0, \tilde{p}_0)| \\
& \leq e^{-a_i(t-t_0)} |\tilde{m}_i(t_0; t_0, \tilde{m}_0, \tilde{p}_0)| + \frac{K_2(\tilde{m}_0, \tilde{p}_0)}{a_i - \lambda_2} \sum_{j=1}^n \ell_{ij} e^{-\lambda_2(t-t_0)} \\
& \leq \left(|\tilde{m}_i(t_0; t_0, \tilde{m}_0, \tilde{p}_0)| + \frac{K_2(\tilde{m}_0, \tilde{p}_0)}{a_i - \lambda_2} \sum_{j=1}^n \ell_{ij} \right) e^{-\lambda_2(t-t_0)} \\
& \leq H_2(\tilde{m}_0, \tilde{p}_0) e^{-\lambda_2(t-t_0)}
\end{aligned} \tag{13}$$

where $H_2(\tilde{m}_0, \tilde{p}_0) = \max_{1 \leq i \leq n} \{ |\tilde{m}_i(t_0; t_0, \tilde{m}_0, \tilde{p}_0)| + \frac{K_2(\tilde{m}_0, \tilde{p}_0)}{a_i - \lambda_2} \sum_{j=1}^n \ell_{ij} \}$.

Therefore, the zero solution of system (4) on partial variable $\tilde{m}$ is globally exponentially stable, and thus, the zero solution of system (4) is globally exponentially stable. The sufficiency holds. $\square$

Theorem 3 *The sufficient and necessary condition for global asymptotical stability of the zero solution of system (4) is that each of the following conditions holds.*

- (I) $\tilde{m}_1, \tilde{m}_2, \dots, \tilde{m}_{[\frac{n}{2}]+1}, \tilde{p}_{[\frac{n}{2}]+2}, \dots, \tilde{p}_n$ are globally asymptotically stable;
- (II) $\tilde{p}_1, \tilde{p}_2, \dots, \tilde{p}_{[\frac{n}{2}]+1}, \tilde{m}_{[\frac{n}{2}]+2}, \dots, \tilde{m}_n$ are globally asymptotically stable.

Proof Necessity. The necessity is obvious, and it is omitted here.

Sufficiency. The proof consists of two cases.

Case 1. If condition (I) holds, then, $\forall(\varepsilon) > 0, \exists \delta(\varepsilon) = \frac{\varepsilon}{2} > 0$, let $\varepsilon_3 > 0$ with $\frac{|d_i|\varepsilon_3}{c_i} \leq \frac{\varepsilon}{2}$, when $\|\tilde{m}_0\| < \delta(\varepsilon)$, $\|\tilde{p}_0\| < \delta(\varepsilon)$, it holds that

$$|\tilde{m}_i(t, t_0, \tilde{m}_0, \tilde{p}_0)| < \varepsilon_3, i = 1, 2, \dots, \left[\frac{n}{2}\right] + 1,$$

and for any $\tilde{m}_0 \in \mathbb{R}^n, \tilde{p}_0 \in \mathbb{R}^n$, it holds that

$$\lim_{t \rightarrow +\infty} \tilde{m}_i(t, t_0, \tilde{m}_0, \tilde{p}_0) = 0, i = 1, 2, \dots, \left[\frac{n}{2}\right] + 1.$$

From the second equation of system (4), one obtains that

$$\begin{aligned}
& |\tilde{p}_i(t, t_0, \tilde{m}_0, \tilde{p}_0)| \leq e^{-c_i(t-t_0)} |\tilde{p}_i(t_0, t_0, \tilde{m}_0, \tilde{p}_0)| \\
& \quad + \int_{t_0}^t e^{-c_i(t-\tau)} |d_i \tilde{m}_i(\tau, t_0, \tilde{m}_0, \tilde{p}_0)| d\tau \\
& \leq e^{-c_i(t-t_0)} |\tilde{p}_i(t_0, t_0, \tilde{m}_0, \tilde{p}_0)| \\
& \quad + e^{-c_i t} \int_{t_0}^t e^{c_i \tau} |d_i| \varepsilon_3 d\tau \\
& \leq \delta(\varepsilon) + \frac{|d_i|\varepsilon_3}{c_i} e^{-c_i t} (e^{c_i t} - e^{c_i t_0}) \\
& = \delta(\varepsilon) + \frac{|d_i|\varepsilon_3}{c_i} (1 - e^{-c_i(t-t_0)}) \\
& \leq \frac{\varepsilon}{2} + \frac{|d_i|\varepsilon_3}{c_i} \leq \frac{\varepsilon}{2} + \frac{\varepsilon}{2} = \varepsilon, \\
& \quad i = 1, 2, \dots, \left[\frac{n}{2}\right] + 1.
\end{aligned} \tag{14}$$

Accordingly, the zero solution of system (4) on partial variable $\tilde{p}_i, i = 1, 2, \dots, \left[\frac{n}{2}\right] + 1$, is stable in sense of Lyapunov. And thus, $\tilde{p}_i, i = 1, 2, \dots, n$, is stable in sense of Lyapunov.

Now, by using Hospital's rule, one has

$$\begin{aligned}
& \lim_{t \rightarrow +\infty} \tilde{p}_i(t, t_0, \tilde{m}_0, \tilde{p}_0) = \lim_{t \rightarrow +\infty} e^{-c_i(t-t_0)} \tilde{p}_i(t_0, t_0, \tilde{m}_0, \tilde{p}_0) \\
& \quad + \lim_{t \rightarrow +\infty} \frac{\int_{t_0}^t e^{c_i \tau} d_i \tilde{m}_i(\tau, t_0, \tilde{m}_0, \tilde{p}_0) d\tau}{e^{c_i t}} \\
& = 0 + \lim_{t \rightarrow +\infty} \frac{e^{c_i t} d_i \tilde{m}_i(t, t_0, \tilde{m}_0, \tilde{p}_0)}{c_i e^{c_i t}} \\
& = \frac{d_i}{c_i} \lim_{t \rightarrow +\infty} \tilde{m}_i(t, t_0, \tilde{m}_0, \tilde{p}_0) = 0, \\
& \quad i = 1, 2, \dots, \left[\frac{n}{2}\right] + 1.
\end{aligned} \tag{15}$$

Therefore, global asymptotical stability of system (4) on variable $\tilde{m}_i, i = 1, 2, \dots, \left[\frac{n}{2}\right] + 1$, implies global asymptotical stability on variable $\tilde{p}_i, i = 1, 2, \dots, \left[\frac{n}{2}\right] + 1$. Thus, $\tilde{p}_i, i = 1, 2, \dots, n$, is globally asymptotically stable. By using Theorem 1 proved previously, the zero solution of system (4) is globally asymptotically stable.

Case 2. If condition (II) holds, then, $\forall \varepsilon > 0$, $\exists \delta(\varepsilon) = \frac{\varepsilon}{2} > 0$, let $\varepsilon_4 > 0$ with $\frac{|d_i|\varepsilon_4}{c_i} \leq \frac{\varepsilon}{2}$, when $\|\tilde{m}_0\| < \delta(\varepsilon)$, $\|\tilde{p}_0\| < \delta(\varepsilon)$, it holds that

$$|\tilde{m}_i(t, t_0, \tilde{m}_0, \tilde{p}_0)| < \varepsilon_4, i = \left[\frac{n}{2}\right] + 2, \dots, n,$$

and for any $\tilde{m}_0 \in \mathbb{R}^n, \tilde{p}_0 \in \mathbb{R}^n$, one has

$$\lim_{t \rightarrow +\infty} \tilde{m}_i(t, t_0, \tilde{m}_0, \tilde{p}_0) = 0, i = \left[\frac{n}{2}\right] + 2, \dots, n.$$

From the second equation of system (4), one obtains that

$$\begin{aligned} |\tilde{p}_i(t, t_0, \tilde{m}_0, \tilde{p}_0)| &\leq e^{-c_i(t-t_0)} |\tilde{p}_i(t_0, t_0, \tilde{m}_0, \tilde{p}_0)| \\ &\quad + \int_{t_0}^t e^{-c_i(t-\tau)} |d_i \tilde{m}_i(\tau, t_0, \tilde{m}_0, \tilde{p}_0)| d\tau \\ &\leq e^{-c_i(t-t_0)} |\tilde{p}_i(t_0, t_0, \tilde{m}_0, \tilde{p}_0)| \\ &\quad + e^{-c_i(t)} \int_{t_0}^t e^{c_i\tau} |d_i| \varepsilon_4 d\tau \\ &\leq \delta(\varepsilon) + \frac{|d_i|\varepsilon_4}{c_i} e^{-c_i t} (e^{c_i t} - e^{c_i t_0}) \\ &= \delta(\varepsilon) + \frac{|d_i|\varepsilon_4}{c_i} (1 - e^{-c_i(t-t_0)}) \\ &\leq \frac{\varepsilon}{2} + \frac{|d_i|\varepsilon_4}{c_i} \leq \frac{\varepsilon}{2} + \frac{\varepsilon}{2} = \varepsilon, \\ i &= \left[\frac{n}{2}\right] + 2, \dots, n. \end{aligned} \quad (16)$$

Accordingly, the zero solution of system (4) on partial variable $\tilde{p}_i, i = \left[\frac{n}{2}\right] + 2, \dots, n$, is stable in sense of Lyapunov. And thus, $\tilde{p}_i, i = 1, 2, \dots, n$, is stable in sense of Lyapunov.

Now, by using Hospital's rule, one has

$$\begin{aligned} \lim_{t \rightarrow +\infty} \tilde{p}_i(t, t_0, \tilde{m}_0, \tilde{p}_0) &= \lim_{t \rightarrow +\infty} e^{-c_i(t-t_0)} \tilde{p}_i(t_0, t_0, \tilde{m}_0, \tilde{p}_0) \\ &\quad + \lim_{t \rightarrow +\infty} \frac{\int_{t_0}^t e^{c_i\tau} d_i \tilde{m}_i(\tau, t_0, \tilde{m}_0, \tilde{p}_0) d\tau}{e^{c_i t}} \\ &= 0 + \lim_{t \rightarrow +\infty} \frac{e^{c_i t} d_i \tilde{m}_i(t, t_0, \tilde{m}_0, \tilde{p}_0)}{c_i e^{c_i t}} \\ &= \frac{d_i}{c_i} \lim_{t \rightarrow +\infty} \tilde{m}_i(t, t_0, \tilde{m}_0, \tilde{p}_0) = 0, \\ i &= \left[\frac{n}{2}\right] + 2, \dots, n. \end{aligned} \quad (17)$$

Therefore, global asymptotic stability of system (4) on variable $\tilde{m}_i, i = \left[\frac{n}{2}\right] + 2, \dots, n$, implies global asymptotic stability on variable $\tilde{p}_i, i = \left[\frac{n}{2}\right] + 2, \dots, n$. Thus, $\tilde{p}_i, i = 1, 2, \dots, n$, is globally asymptotically stable. By using Theorem 1 proved previously, the zero solution of system (4) is globally asymptotically stable. $\square$

Theorem 4 The sufficient and necessary condition for global exponential stability of the zero solution of system (4) is that each of the following conditions holds.

- (I) $\tilde{m}_1, \tilde{m}_2, \dots, \tilde{m}_{\left[\frac{n}{2}\right]+1}, \tilde{p}_{\left[\frac{n}{2}\right]+2}, \dots, \tilde{p}_n$, are globally exponentially stable;
- (II) $\tilde{p}_1, \tilde{p}_2, \dots, \tilde{p}_{\left[\frac{n}{2}\right]+1}, \tilde{m}_{\left[\frac{n}{2}\right]+2}, \dots, \tilde{m}_n$, are globally exponentially stable.

Proof The necessity is obvious.

The sufficiency can follow Theorems 2 and Theorem 3, for simplicity, the proof process is omitted here. $\square$

Sufficient conditions for global stability of GRNs

Some sufficient conditions for global asymptotic stability, global exponential stability of the zero solution of system (4) will be proposed in this section.

Theorem 5 If there are constants $\xi_i, \eta_i > 0, i = 1, 2, \dots, n$, which satisfy

$$(I) \quad \xi_i a_i > \eta_i d_i, \eta_i c_i \geq \sum_{j=1}^n \xi_j |\ell_{ji}|, i = 1, 2, \dots, n, \quad (18)$$

or

$$(II) \quad \xi_i a_i \geq \eta_i d_i, \eta_i c_i > \sum_{j=1}^n \xi_j |\ell_{ji}|, i = 1, 2, \dots, n. \quad (19)$$

Then, condition (I) (or condition (II)) implies that the zero solution of system (4) is globally asymptotically stable.

Proof Construct a radially unbounded Lyapunov function as follows:

$$V = \sum_{i=1}^n \xi_i |\tilde{m}_i| + \sum_{i=1}^n \eta_i |\tilde{p}_i| \quad (20)$$

Taking upper-right-hand Dini derivative along the solution of system (4), one obtains that

$$\begin{aligned} D^+ V &\leq \sum_{i=1}^n (-\xi_i a_i + \eta_i d_i) |\tilde{m}_i| \\ &\quad + \sum_{i=1}^n (-\eta_i c_i + \sum_{j=1}^n \xi_j |\omega_{ji} \dot{g}_i(\varsigma)|) |\tilde{p}_i| \\ &\leq \sum_{i=1}^n (-\xi_i a_i + \eta_i d_i) |\tilde{m}_i| + \sum_{i=1}^n (-\eta_i c_i + \sum_{j=1}^n \xi_j \ell_{ji}) |\tilde{p}_i| \end{aligned} \quad (21)$$

If condition (I) holds, and $\sum_{i=1}^n |\tilde{m}_i| \neq 0$, we have

$$D^+V \leq \sum_{i=1}^n (-\xi_i a_i + \eta_i d_i) |\tilde{m}_i| < 0 \quad (22)$$

Similarly, if condition (II) holds, and $\sum_{i=1}^n |\tilde{p}_i| \neq 0$, we also have $D^+V < 0$.

If condition (I) holds, by LaSalle invariant theorem (Liao and Yu 2008), the zero solution of system (4) on the partial variable $\tilde{m}$ is globally asymptotically stable. Similarly, if condition (II) holds, the zero solution of system (4) on the partial variable $\tilde{p}$ is globally asymptotically stable. And thus, by utilizing Theorem 1, each of the conditions implies that the zero solution of system (4) on all variables is globally asymptotically stable. $\square$

Corollary 1 *The zero solution of system (4) is globally exponentially stable if there are constants $\xi_i, \eta_i > 0$, $i = 1, 2, \dots, n$, such that*

$$\xi_i a_i > \eta_i d_i, \eta_i c_i > \sum_{j=1}^n \xi_j |\ell_{ji}|, i = 1, 2, \dots, n.$$

Proof The proof can follow Theorem 5, it is omitted here. $\square$

Corollary 2 *The zero solution of system (4) is globally exponentially stable if matrix A is a M-matrix.*

$$A = \begin{bmatrix} \text{diag}(a_i)_{n \times n} & (-\ell_{ij})_{n \times n} \\ \text{diag}(-d_i)_{n \times n} & \text{diag}(c_i)_{n \times n} \end{bmatrix}$$

Proof Since A is a M-matrix, A^T is a M-matrix. Furthermore, there exists a positive constant vector $\varsigma = [\xi_1, \xi_2, \dots, \xi_n, \eta_1, \eta_2, \dots, \eta_n]^T > 0$, such that $A^T \varsigma > 0$ (Liao and Yu 2008). So, it holds that

$$\xi_i a_i > \eta_i d_i, \eta_i c_i > \sum_{j=1}^n \xi_j |\ell_{ji}|, i = 1, 2, \dots, n.$$

Then, referring to Corollary 1, the zero solution of system (4) is globally exponentially stable. $\square$

Theorem 6 *If there exist positive constants $\xi_i, \eta_i > 0$, $i = 1, 2, \dots, n$, it holds that*

$$(I) \xi_i a_i > \eta_i d_i, \quad i = 1, 2, \dots, \left\lfloor \frac{n}{2} \right\rfloor + 1,$$

$$\eta_i c_i > \sum_{j=1}^n \xi_j \ell_{ji}, \quad i = \left\lfloor \frac{n}{2} \right\rfloor + 2, \dots, n,$$

$$\xi_i a_i \geq \eta_i d_i, \quad i = \left\lfloor \frac{n}{2} \right\rfloor + 2, \dots, n,$$

$$\eta_i c_i \geq \sum_{j=1}^n \xi_j \ell_{ji}, \quad i = 1, 2, \dots, \left\lfloor \frac{n}{2} \right\rfloor + 1;$$

or

$$(II) \xi_i a_i \geq \eta_i d_i, \quad i = 1, 2, \dots, \left\lfloor \frac{n}{2} \right\rfloor + 1,$$

$$\eta_i c_i \geq \sum_{j=1}^n \xi_j \ell_{ji}, \quad i = \left\lfloor \frac{n}{2} \right\rfloor + 2, \dots, n,$$

$$\xi_i a_i > \eta_i d_i, \quad i = \left\lfloor \frac{n}{2} \right\rfloor + 2, \dots, n,$$

$$\eta_i c_i > \sum_{j=1}^n \xi_j \ell_{ji}, \quad i = 1, 2, \dots, \left\lfloor \frac{n}{2} \right\rfloor + 1.$$

Then, condition (I) (or condition (II)) implies that the zero solution of system (4) is globally asymptotically stable.

Proof The proof can follow Theorem 3 and Theorem 5, it is omitted here. $\square$

Now, consider system (4) again, it is easy to obtain the following inequalities.

$$\begin{cases} \frac{d\tilde{m}_i}{dt} \leq -a_i \tilde{m}_i + \sum_{j=1}^n |\omega_{ij} \dot{g}_j(\cdot)| |\tilde{p}_j| \leq -a_i \tilde{m}_i + \sum_{j=1}^n \ell_{ij} |\tilde{p}_j| \\ \frac{d\tilde{p}_i}{dt} \leq -c_i \tilde{p}_i + d_i |\tilde{m}_i|, \quad i = 1, 2, \dots, n. \end{cases} \quad (23)$$

Then, the comparing equations of (23) is given by

$$\begin{cases} \frac{d\bar{m}_i}{dt} = -a_i \bar{m}_i + \sum_{j=1}^n \ell_{ij} \bar{p}_j \\ \frac{d\bar{p}_i}{dt} = d_i \bar{m}_i - c_i \bar{p}_i, \quad i = 1, 2, \dots, n. \end{cases} \quad (24)$$

Assume that the standard solution matrix of system (24), also known as Cauchy matrix, is as follows:

$$G_{2n \times 2n}(t, t_0) = \begin{bmatrix} G_{11} & G_{12} \\ G_{21} & G_{22} \end{bmatrix} \quad (25)$$

where

$$\begin{aligned} G_{11} &= \begin{bmatrix} h_{11}(t, t_0) & h_{12}(t, t_0) & \cdots & h_{1n}(t, t_0) \\ h_{21}(t, t_0) & h_{22}(t, t_0) & \cdots & h_{2n}(t, t_0) \\ \vdots & \vdots & \ddots & \vdots \\ h_{n1}(t, t_0) & h_{n2}(t, t_0) & \cdots & h_{nn}(t, t_0) \end{bmatrix} \\ G_{12} &= \begin{bmatrix} h_{1 \cdot (n+1)}(t, t_0) & h_{1 \cdot (n+2)}(t, t_0) & \cdots & h_{1 \cdot 2n}(t, t_0) \\ h_{2 \cdot (n+1)}(t, t_0) & h_{2 \cdot (n+2)}(t, t_0) & \cdots & h_{2 \cdot 2n}(t, t_0) \\ \vdots & \vdots & \ddots & \vdots \\ h_{n \cdot (n+1)}(t, t_0) & h_{n \cdot (n+2)}(t, t_0) & \cdots & h_{n \cdot 2n}(t, t_0) \end{bmatrix} \\ G_{21} &= \begin{bmatrix} h_{(n+1) \cdot 1}(t, t_0) & h_{(n+1) \cdot 2}(t, t_0) & \cdots & h_{(n+1) \cdot n}(t, t_0) \\ h_{(n+2) \cdot 1}(t, t_0) & h_{(n+2) \cdot 2}(t, t_0) & \cdots & h_{(n+2) \cdot n}(t, t_0) \\ \vdots & \vdots & \ddots & \vdots \\ h_{2n \cdot 1}(t, t_0) & h_{2n \cdot 2}(t, t_0) & \cdots & h_{2n \cdot n}(t, t_0) \end{bmatrix} \end{aligned}$$

$$G_{22} = \begin{bmatrix} h_{(n+1) \cdot (n+1)}(t, t_0) & h_{(n+1) \cdot (n+2)}(t, t_0) & \cdots & h_{(n+1) \cdot 2n}(t, t_0) \\ h_{(n+2) \cdot (n+1)}(t, t_0) & h_{(n+2) \cdot (n+2)}(t, t_0) & \cdots & h_{(n+2) \cdot 2n}(t, t_0) \\ \vdots & \vdots & \ddots & \vdots \\ h_{2n \cdot (n+1)}(t, t_0) & h_{2n \cdot (n+2)}(t, t_0) & \cdots & h_{2n \cdot 2n}(t, t_0) \end{bmatrix}$$

The partial variable solutions $\bar{m}(t, t_0)$ or $\bar{p}(t, t_0)$ with the initial value $(\bar{m}(t_0, t_0), \bar{p}(t_0, t_0))$ can be expressed as

That is, $G_{2n \times 2n}$ satisfies (24), and $G_{2n \times 2n}(t_0, t_0) = E_{2n \times 2n}$ is a unit matrix.

Let

$$G_{n \times 2n}^{(1)} = \begin{bmatrix} h_{11}(t, t_0) & h_{12}(t, t_0) & \cdots & h_{1n}(t, t_0) & h_{1 \cdot (n+1)}(t, t_0) & \cdots & h_{1 \cdot 2n}(t, t_0) \\ \vdots & \vdots & \ddots & \vdots & \vdots & \ddots & \vdots \\ h_{n1}(t, t_0) & h_{n2}(t, t_0) & \cdots & h_{nn}(t, t_0) & h_{n \cdot (n+1)}(t, t_0) & \cdots & h_{n \cdot 2n}(t, t_0) \end{bmatrix},$$

and

$$G_{n \times 2n}^{(2)} = \begin{bmatrix} h_{(n+1) \cdot 1}(t, t_0) & h_{(n+1) \cdot 2}(t, t_0) & \cdots & h_{(n+1) \cdot n}(t, t_0) & h_{(n+1) \cdot (n+1)}(t, t_0) & \cdots & h_{(n+1) \cdot 2n}(t, t_0) \\ \vdots & \vdots & \ddots & \vdots & \vdots & \ddots & \vdots \\ h_{2n \cdot 1}(t, t_0) & h_{2n \cdot 2}(t, t_0) & \cdots & h_{2n \cdot n}(t, t_0) & h_{2n \cdot (n+1)}(t, t_0) & \cdots & h_{2n \cdot 2n}(t, t_0) \end{bmatrix}.$$

$G_{n \times 2n}^{(1)}$ and $G_{n \times 2n}^{(2)}$ are called the truncated matrix of Cauchy matrix.

Theorem 7 The zero solution of system (4) is globally exponentially stable if there exists a negative exponential estimation in the truncated matrix of Cauchy matrix $G_{n \times 2n}^{(1)}$ or $G_{n \times 2n}^{(2)}$, i.e., there exist two positive constants $K > 0$, $\lambda > 0$, such that

$$\|G_{n \times 2n}^{(1)}\| \leq K e^{-\lambda(t-t_0)} \quad \text{or} \quad \|G_{n \times 2n}^{(2)}\| \leq K e^{-\lambda(t-t_0)} \quad (26)$$

Proof For the initial value $(\bar{m}(t_0, t_0), \bar{p}(t_0, t_0))$ with $\|(\bar{m}(t_0, t_0), \bar{p}(t_0, t_0))\| \leq M$ (M is a positive constant), any solution of system (24) with the initial value $(\bar{m}(t_0, t_0), \bar{p}(t_0, t_0))$ can be expressed as

$$\begin{bmatrix} \bar{m}_1(t, t_0) \\ \vdots \\ \bar{m}_n(t, t_0) \\ \bar{p}_1(t, t_0) \\ \vdots \\ \bar{p}_n(t, t_0) \end{bmatrix} = G_{2n \times 2n}(t, t_0) \begin{bmatrix} \bar{m}_1(t_0, t_0) \\ \vdots \\ \bar{m}_n(t_0, t_0) \\ \bar{p}_1(t_0, t_0) \\ \vdots \\ \bar{p}_n(t_0, t_0) \end{bmatrix}. \quad (27)$$

$$\begin{bmatrix} \bar{m}_1(t, t_0) \\ \vdots \\ \bar{m}_n(t, t_0) \end{bmatrix} = G_{n \times 2n}^{(1)} \begin{bmatrix} \bar{m}_1(t_0, t_0) \\ \vdots \\ \bar{m}_n(t_0, t_0) \\ \bar{p}_1(t_0, t_0) \\ \vdots \\ \bar{p}_n(t_0, t_0) \end{bmatrix},$$

$$\begin{bmatrix} \bar{p}_1(t, t_0) \\ \vdots \\ \bar{p}_n(t, t_0) \end{bmatrix} = G_{n \times 2n}^{(2)} \begin{bmatrix} \bar{m}_1(t_0, t_0) \\ \vdots \\ \bar{m}_n(t_0, t_0) \\ \bar{p}_1(t_0, t_0) \\ \vdots \\ \bar{p}_n(t_0, t_0) \end{bmatrix}.$$

From the comparison theorem and assumptions, we have

$$\left\| \begin{bmatrix} \tilde{m}_1(t, t_0) \\ \tilde{m}_2(t, t_0) \\ \vdots \\ \tilde{m}_n(t, t_0) \end{bmatrix} \right\| \leq \left\| \begin{bmatrix} \bar{m}_1(t, t_0) \\ \bar{m}_2(t, t_0) \\ \vdots \\ \bar{m}_n(t, t_0) \end{bmatrix} \right\| \leq \|G_{n \times 2n}^{(1)}\| \left\| \begin{bmatrix} \bar{m}_1(t_0, t_0) \\ \vdots \\ \bar{m}_n(t_0, t_0) \\ \bar{p}_1(t_0, t_0) \\ \vdots \\ \bar{p}_n(t_0, t_0) \end{bmatrix} \right\|$$

$$\leq MKe^{-\lambda(t-t_0)} \quad (28)$$

or

$$\left\| \begin{bmatrix} \tilde{p}_1(t, t_0) \\ \tilde{p}_2(t, t_0) \\ \vdots \\ \tilde{p}_n(t, t_0) \end{bmatrix} \right\| \leq \left\| \begin{bmatrix} \bar{p}_1(t, t_0) \\ \bar{p}_2(t, t_0) \\ \vdots \\ \bar{p}_n(t, t_0) \end{bmatrix} \right\| \leq \|G_{n \times 2n}^{(2)}\| \left\| \begin{bmatrix} \bar{m}_1(t_0, t_0) \\ \vdots \\ \bar{m}_n(t_0, t_0) \\ \bar{p}_1(t_0, t_0) \\ \vdots \\ \bar{p}_n(t_0, t_0) \end{bmatrix} \right\|$$

$$\leq MKe^{-\lambda(t-t_0)}. \quad (29)$$

Therefore, the zero solution of system (4) is globally exponentially stable. $\square$

Illustrative example

For the purpose to illustrate the effectiveness of our theoretical results in the previous sections, we present a famous GRNs model composed of three nodes. The gene repressitory network, which consists of three repressor-protein concentrations p_i and their mRNA concentrations m_i (where i is *lacl*, *tetR*, *cl*), has been theoretically predicted and experimentally verified on *Escherichia coli* (Gardner et al. 2000; Elowitz and Leibler 2000). The dynamic model is described by

$$\begin{cases} \frac{dm_i}{dt} = -m_i(t) + \frac{\alpha}{1+p_j^h} \\ \frac{dp_i}{dt} = -c_i p_i(t) + d_i m_i(t), \quad i = lacl, tetR, cl; j = cl, lacl, tetR \end{cases} \quad (30)$$

where $m_i \in \mathbb{R}, p_i \in \mathbb{R}, h > 0$ is a Hill coefficient, $c_i > 0$ denotes the protein decay rate, d_i represents the translation rate of i th gene.

For convenience of our discussion, we introduce some parameters into system (30) and rewrite it as follows:

$$\begin{cases} \frac{dm_i}{dt} = -a_i m_i(t) + \sum_{j=1}^n \omega_{ij} \frac{p_j^h}{1+p_j^h} + I_i \\ \frac{dp_i}{dt} = -c_i p_i(t) + d_i m_i(t), \quad i = lacl, tetR, cl; j = cl, lacl, tetR \end{cases} \quad (31)$$

where $A = \begin{bmatrix} 2 & 0 & 0 \\ 0 & 2 & 0 \\ 0 & 0 & 2 \end{bmatrix}$, $W = \begin{bmatrix} 0 & 2.5 & 0 \\ 0 & 0 & 2.5 \\ 2.5 & 0 & 0 \end{bmatrix}$, $C = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}$,
 $D = \begin{bmatrix} 0.8 & 0 & 0 \\ 0 & 0.8 & 0 \\ 0 & 0 & 0.8 \end{bmatrix}$, $I = [2.5, 2.5, 2.5]^T$, $h = 2$.

For simplicity of expression, let $lacl = 1, tetR = 2, cl = 3$. The equilibrium point can be computed as (m^*, p^*) , where $m_1^* = m_2^* = m_3^* = 0.8529, p_1^* = p_2^* = p_3^* = 0.6823$. For the initial states $m_0 = [1, 0.8, 0.6]^T, p_0 = [0.6, 0.4, 0.2]^T$. The trajectories of mRNA and protein concentrations in system (31) with $a_1 = a_2 = a_3 = 2$ are plotted in Fig. 1. It indicates that this system is stable on all variables $m(t)$ and $p(t)$ with the given parameters. If we only change one parameter $a_1 = 2$ to $a_1 = -0.1$, we can obtain Fig. 2. One can see that $m_1(t)$ and $p_1(t)$ are unstable.

It is easy to confirm that $|\dot{g}_j(\cdot)| < 0.65$ (Ren and Cao 2008), let $\ell_{11} = \ell_{13} = \ell_{21} = \ell_{22} = \ell_{32} = \ell_{33} = 0, \ell_{12} = \ell_{23} = \ell_{31} = 1.625$, then

$$\begin{aligned} |\omega_{11}g_1| &= 0 = \ell_{11}, |\omega_{12}g_2| < 2.5 \times 0.65 = \ell_{12}, \\ |\omega_{13}g_3| &= 0 = \ell_{13}, \\ |\omega_{21}g_1| &= 0 = \ell_{21}, |\omega_{22}g_2| = 0 = \ell_{22}, \\ |\omega_{23}g_3| &< 2.5 \times 0.65 < \ell_{23}, \\ |\omega_{31}g_1| &= 2.5 \times 0.65 \leq \ell_{31}, |\omega_{32}g_2| = 0 = \ell_{32}, \\ |\omega_{33}g_3| &= 0 = \ell_{33}. \end{aligned}$$

Let $\xi_1 = \xi_2 = \xi_3 = 0.5, \eta_1 = \eta_2 = \eta_3 = 1$, then

$$\begin{aligned} -\xi_1 a_1 + \eta_1 d_1 &= -0.2 < 0, -\xi_2 a_2 + \eta_2 d_2 = -0.2 < 0, \\ -\xi_3 a_3 + \eta_3 d_3 &= -0.2 < 0, \\ -\eta_1 c_1 + \sum_{j=1}^3 \xi_j \ell_{j1} &= -0.1875 < 0, \\ -\eta_2 c_2 + \sum_{j=1}^3 \xi_j \ell_{j2} &= -0.1875 < 0, \\ -\eta_3 c_3 + \sum_{j=1}^3 \xi_j \ell_{j3} &= -0.1875 < 0, \end{aligned}$$

By Corollary 1, the equilibrium of system (31) is globally exponentially stable. If we change one parameter $a_1 = 2$ to $a_1 = -0.1$, there exist no positive constants $\xi_1, \eta_1 > 0$

Fig. 1 The trajectory of the mRNA and protein concentrations of system (31) with $a_1 = a_2 = a_3 = 2$

Fig. 2 The trajectory of the mRNA and protein concentrations of system (31) with $a_1 = -0.1, a_2 = a_3 = 2$

such that $\xi_1 a_1 + \eta_1 d_1 < 0$ since $a_1 < 0, d_1 > 0$. Therefore, if a_1 is changed from 2 to -0.1 , the system is not stable anymore.

Conclusion

In this paper, we studied global stability of GRNs with SUM regulatory Logic. Four sufficient and necessary conditions for global asymptotic stability and global exponential stability, together with three sufficient conditions for global asymptotical stability and global exponential stability of GRNs are proposed. Then, a famous example is used to illustrate our proposed results such as global asymptotic stability, global exponential stability and instability.

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