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RESEARCH ARTICLE

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Stability of genetic networks with hybrid regulatory mechanism

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Abstract A dynamical system model is presented in this paper for genetic regulatory networks with hybrid regulatory mechanism. The sufficient conditions for the stability of the proposed model are established based on the Lyapunov functional method and linear matrix inequality techniques. To test the effectiveness and correctness of our theoretical results, illustrative examples regarding modified repressilator and modified 5-node genetic network models are also presented.

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الملخص

يتم في هذه الورقة تقديم نموذج لنظام ديناميي لشبكات الوراثة التنظيمية مع ميكانيكية تنظيمية مهجنة. يتم ترسيخ شروط كافية لاستقرار النموذج المقترح بناءً على طريقة ليابونوف الدالية وتقنيات متراجحات مصفوفات خطية. لفحص فعالية وصحة نتائجنا النظرية، يتم أيضاً تقديم أمثلة توضيحية بالنسبة لكابح معدل ونموذج لشبكات وراثية خماسية العقدة.

1 Introduction

Synthetic biology is an emerging field that aims to design and synthesize biological networks or devices that perform a desired function in a predictable manner. Achieving this goal requires a combination of in silico and in vivo analyses, and combines approaches from the field of biology, engineering, and mathematics [1,16,23,29,30]. The study of genetic regulatory networks (GRNs) has received a major impetus from the recent development of experimental techniques allowing the measurement of patterns of gene expression in a massively parallel way [10], and becomes a fundamental challenge in synthetic biology as it explains the interactions between genes and proteins to form a complex system that performs complicated biological functions [7,35]. Mathematical models often found in the literature describing GRNs can be roughly divided into three classes [19], or classified into two types [9,21]. No matter which classification is used, the differential equation or dynamic system model is similar. Genetic networks are biochemically dynamical systems and it is natural to model them by using dynamical system models which provide a powerful tool for studying gene

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regulation processes in living organisms [13,20]. The dynamic system model describes the concentrations of gene products, such as mRNAs and proteins, as continuous values of the gene regulation systems, which are more accurate and can provide detailed understanding of the nonlinear dynamical behavior exhibited by biological systems. Terms in differential equations describe how gene expression rates are modified by changes in the levels of transcription factors (TFs) or other effector molecules. In this paper, we consider the differential equation model of genetic networks.

Computational models of regulatory networks are expected to provide insights into mechanisms underlying behaviors of more complex gene networks, affected by many TFs and not amenable to intuitive understanding [19,35]. In the absence of a time delay, a desired function, for example, toggle switch in [12], oscillation in [11] and stability in [3,8,19], can be generated by the ordinary differential equation (ODE) model. Taking into the consideration the slow processes of transcription, translation, and translocation or the finite switching speed of amplifiers, the study of GRNs model incorporating time delay (transcriptional delay and translational time [24]) have attracted some attentions [5,6,15,27,28,31,36,37]. In fact, for most genetic regulatory systems, there are two types of reactions [9]: fast reaction and slow reaction. Fast reaction, such as RNA annealing, dimerization, binding reactions, and other medical modification reactions, we can assume that this reaction is immediate and that time delay is reduced to zero. While transcription and translation involve a number of multi-stage reactions, there is a time lag in the peaks between mRNA molecules and proteins of gene. On the other side, mRNA and proteins may be synthesized at different locations (i.e., nucleus and cytoplasm, respectively), thus transportation or diffusion of mRNA and proteins between these two locations results in sizeable delays. The mechanisms of combinational transcription activation are relatively unexplored [4,17]. So it is reasonable to study the dynamical properties of a general dynamical model for GRNs with some terms incorporating transcription delay and some that do not, simultaneously. In this paper, we call the term incorporating transcription delay as 'indirect' regulatory while the opposite one as 'direct' regulatory. The GRNs model with 'indirect' and 'direct' regulatory term is called here as *GRNs with hybrid regulatory mechanism* (see Fig. 1).

Stability has positive meanings in biological science and technologies, and in medicine. For example, it may have meaning of a disease coming to a rest (or recovering). The applications of GRNs heavily depend on the dynamic behavior of the equilibrium point. If an equilibrium of a neural network is globally, asymptotically stable, it means that the domain of attraction of the equilibrium point is the whole space, and convergence is in real time. Thus, it is of both theoretical and practical importance to study the stability of GRNs. Moreover, the gene regulation is an intrinsically noisy process; this is always subject to intracellular and extracellular noise perturbations, which are caused by the random births and deaths of individual molecules, along with extrinsic noise due to fluctuations in the environment. Due to the fact that such cellular noises undoubtedly affect the dynamics of networks both quantitatively and qualitatively, it is also important to investigate the stochastic GRNs [20,32,36,38–40].

Motivated by the above discussion, we are concerned with the stability of GRNs with hybrid regulatory mechanism, which is first proposed to be applied to GRNs. By using the Lyapunov functional method and the linear matrix inequality techniques, stability conditions are established in terms of LIMs that can be readily solved by using standard numerical software (such as Matlab).

The organization of the paper is as follows: In Sect. 2, we present a model for GRNs with hybrid regulatory mechanism by introducing a parameter θ for measuring the relative contribution rate of direct regulatory. In Sect. 3, we derive the sufficient conditions for the stability of the proposed model without stochastic per-

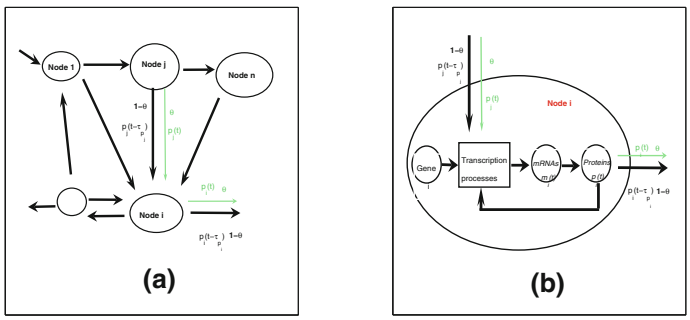

Fig. 1 Genetic regulatory networks with hybrid regulatory mechanism for transcription. **a** Genetic regulatory networks. **b** Structure of node i with hybrid regulatory mechanism, where there exists one output but multiple inputs for the ith node or gene

turbation and with stochastic perturbation, respectively. Illustrative examples are shown to support the theory results in Sect. 4. The paper is completed with a conclusion in Sect. 5.

Notations: The notations used throughout the paper are fairly standard. A^{T} stands for the transpose of a matrix A. The notation $M > (<)0$ is used to define a real symmetric positive definite (negative definite) matrix. R^n denotes the n-dimensional Euclidean space; $R^{n\times m}$ denotes the set of all $n \times m$ real matrices and I_n represents n-order identity matrix. In the sequel, if not explicitly stated, matrices are assumed to have compatible dimensions. $\lambda_{\max}(P)$ denotes the maximal eigenvalue of a square matrix P.

2 Model for GRNs with hybrid regulatory mechanism

We propose a mathematical model for GRNs with hybrid regulatory mechanism by exploiting the structure of the genome–proteome networks and by representing mRNAs and proteins with different variable. Figure 1 schematically shows our model for GRNs with considering simultaneously the indirect feedback (black line) effects on transcription and the direct feedback (blue line) of metabolites on transcription, where the latter feedback effect is ignored in the model proposed in Ref. [6]. Based on the structure of the GRNs (shown in Fig. 1), the genetic networks containing of n nodes with hybrid regulatory mechanism can be described as follows:

$$\begin{aligned}\dot{m}_i(t) =& -a_i m_i(t) + \theta b_i(p_1(t), p_2(t), \ldots, p_n(t)) \\ &+ (1-\theta)\bar{b}_i(p_1(t-\tau_{p_1}), p_2(t-\tau_{p_2}), \ldots, p_n(t-\tau_{p_n})) \\ \dot{p}_i(t) =& -c_i p_i(t) + d_i m_i(t-\tau_{m_i}), \quad i = 1, 2, \ldots, n\end{aligned} \tag{1}$$

where $m_i(t)$, $p_i(t) \in R$ are the concentration of *mRNA* and protein of the ith node, respectively. In (1), a_i and c_i are the degradation rates of the *mRNA* and protein, respectively. d_i is the rate at which protein i is produced from *mRNA* i, and b_i, $\bar{b}_i$ are the regulatory functions of the ith gene, which are generally nonlinear functions of the variables $(p_1, p_2, \ldots, p_n)$ but have a form monotonicity with each variable. In this paper, we take the SUM logic function [20] $b_i(p_1(t), p_2(t), \ldots, p_n(t)) = \sum_{j=1}^{n} b_{ij}(p_j)$ and $\bar{b}_i(p_1(t-\tau_{p_1}), p_2(t-\tau_{p_2}), \ldots, p_n(t-\tau_{p_n})) = \sum_{j=1}^{n} \bar{b}_{ij}(p_j-\tau_{p_j})$, where τ_{p_i} indicating the time delay for ith protein. Parameter $\theta \in [0, 1]$ is used to measure the relative contribution of direct effects of gene products to the activation/inactivation of TFs.

Remark 2.1 The genetic networks (1) with hybrid regulatory mechanism is the extension of some previous GRNs. Two extreme cases are (*i*) the model investigated in [6,31] when $\theta = 0$ and (*ii*) the basic GRNs model studied in [20] when $\theta = 1$ and $\tau_{m_i} = 0$ for all i.

The gene activity is tightly controlled in a cell, and gene regulation function b_i, $\bar{b}_i$ play a crucial role in the dynamics [26]. The regulation functions $b_{ij}(p_j(t))(\bar{b}_{ij}(p_j(t-\tau_{p_j})))$ are generally expressed by the monotonic function of the Hill form [20]

$$b_{ij}(p_j(t)) \quad (\bar{b}_{ij}(p_j(t-\tau_{p_j}))) = \begin{cases} \alpha_{ij}\frac{(p_j(t)/\beta)^H}{1+(p_j(t)/\beta)^H} & \left(\bar{\alpha}_{ij}\frac{(p_j(t-\tau_{p_j})/\beta)^H}{1+(p_j(t-\tau_{p_j})/\beta)^H}\right), \\ & \text{if TF } j \text{ is an activator of gene } i \\ \frac{\alpha_{ij}}{1+(p_j(t)/\beta)^H} & \left(\frac{\bar{\alpha}_{ij}}{1+(p_j(t-\tau_{p_j})/\beta)^H}\right), \\ & \text{if TF } j \text{ is an repressor of gene } i \end{cases} \tag{2}$$

where H is the Hill coefficient, β is a positive constant, and the bounded constants α_{ij}, $\bar{\alpha}_{ij}$ are the dimensionless transcriptional rate of TF j to gene i under direct and indirect feedback, respectively. Note that

$$\frac{1}{1+x^H} = 1 - \frac{x^H}{1+x^H}$$

Hence, Equation (1) can be rewritten into the following form:

$$\begin{aligned}\dot{m}_i(t) &= -a_i m_i(t) + \theta \textstyle\sum_j G_{ij} g(p_j(t)) + (1-\theta)\sum_j \bar{G}_{ij} g(p_j(t-\tau_{p_j})) + l_i \\ \dot{p}_i(t) &= -c_i p_i(t) + d_i m_i(t-\tau_{m_i}), \quad i = 1, 2, \ldots, n\end{aligned} \tag{3}$$

where $g(x) = (x/\beta)^H/[1+(x/\beta)^H]$ is a monotonically increasing function. $G_1 = (G_{ij})$, $G_2 = (\bar{G}_{ij}) \in R^{n\times n}$ are the coupling matrix of genetic network, which is defined as follows:

$$G_{ij}(\bar{G}_{ij}) = \begin{cases} 0, & \text{if there is no connection between } i \text{ and } j \\ \alpha_{ij}(\bar{\alpha}_{ij}), & \text{if TF } j \text{ is an activator of gene } i \\ -\alpha_{ij}(-\bar{\alpha}_{ij}), & \text{if TF } j \text{ is an repressor of gene } i \end{cases}$$

and l_i is the basal rate, which have the similar definition as in [20]. In compact matrix form, (3) can be rewritten as

$$\begin{aligned} \dot{m}(t) &= Am(t) + \theta G_1 g(p(t)) + (1-\theta)G_2 g(p(t-\tau_p)) + l \\ \dot{p}(t) &= Cp(t) + Dm(t-\tau_m) \end{aligned} \tag{4}$$

where $m(t) = (m_1(t), m_2(t), \ldots, m_n(t))^{\mathrm{T}}$, $p(t) = (p_1(t), p_2(t), \ldots, p_n(t))^{\mathrm{T}}$, $A = \mathrm{diag}(-a_1, -a_2, \ldots, -a_n)$, $C = \mathrm{diag}(-c_1, -c_2, \ldots, -c_n)$, $D = \mathrm{diag}(d_1, d_2, \ldots, d_n)$, $l = (l_1, l_2, \ldots, l_n)^{\mathrm{T}}$ and nonlinear function $g(z(t)) = (g(z_1(t)), g(z_2(t)), \ldots, g(z_n(t)))^{\mathrm{T}}$. In this paper, for simplicity, the time delay is assumed to be same for different nodes. In model (4), delay $\tau_p(t) > 0$ and $\tau_m(t) > 0$ are time-varying delays satisfied $\dot{\tau}_p(t) \le d_p < 1$ and $\dot{\tau}_m(t) \le d_m < 1$.

Assume that $(\bar{m}, \bar{p})$ is an equilibrium point of (4). Letting $x(t) = m(t) - \bar{m}$ and $y(t) = p(t) - \bar{p}$, we can shift the equilibrium point $(\bar{m}, \bar{p})$ to the origin and have

$$\begin{aligned} \dot{x}(t) &= Ax(t) + \theta G_1 f(y(t)) + (1-\theta)G_2 f(y(t-\tau_p(t))) \\ \dot{y}(t) &= Cy(t) + Dx(t-\tau_m(t)) \end{aligned} \tag{5}$$

where $f(y(t)) = g(y(t) + \bar{p}) - g(\bar{p})$ and $f(y(t-\tau_p(t))) = g(y(t-\tau_p(t)) + \bar{p}) - g(\bar{p})$. Since g is a monotonically increasing function with saturation, it satisfies, for all $a, b \in R$ with $a \neq b$

$$0 \le \frac{g(a) - g(b)}{a - b} \le k$$

when g is differentiable, the above inequality is equivalent to $0 \le \mathrm{d}g(a)/\mathrm{d}a \le k$. From the relationship of $f(\cdot)$ and $g(\cdot)$, we know that $f(\cdot)$ satisfies the following condition:

$$f(a)(f(a) - ka) \le 0 \tag{6}$$

Remark 2.2 Equation (5) is derived from GRNs with hybrid regulatory mechanism. In analyzing the stability of an equilibrium point in (1), it is equivalent to study the stability of origin point in (5). Therefore, we will study the system (5) directly in the rest of this paper.

Remark 2.3 Parameter $\theta \in [0, 1]$ introduced in (5) for reflecting the hybrid regulatory mechanism, intuitively should have the ability to control its dynamics, which has similar role as that of [14,25]. Further study will be published elsewhere. We note that one may model another alternative regulatory by using the nonlinear combination $Gf(\theta(y(t)) + (1-\theta)y(t-\tau_p(t)))$ instead of $\theta G_1 f(y(t)) + (1-\theta)G_2 f(y(t-\tau_p(t)))$ in the equation for $\dot{x}$ in Equation (5).

3 Stability analysis

In this section, we analyze the stability of GRNs with hybrid regulatory mechanism described by (5) by using the Lyapunov stability theorem. The sufficient condition for the stability of system (5) and the case with noise perturbation are given in the following two subsections, respectively.

3.1 Stability conditions of genetic networks

Theorem 3.1 *If there exist matrices $P_{11} > 0$, $P_{12} > 0$, $P_{22} > 0$, $Q > 0$, $R > 0$ and a diagonal matrix $\Lambda = \mathrm{diag}(\lambda_1, \lambda_2, \ldots, \lambda_n) > 0$, such that the following linear matrix inequalities hold:*

$$M_1 < 0, \quad P = \begin{pmatrix} P_{11} & P_{12} \\ P_{12}^T & P_{22} \end{pmatrix} > 0 \tag{7}$$

where

$$M_1 = \begin{pmatrix} 2P_{11}A + R & P_{12}C + A^{\mathrm{T}}P_{12} & P_{12}D & \theta P_{11}G_1 & (1-\theta)P_{11}G_2 \\ P_{12}^{\mathrm{T}}A + C^{\mathrm{T}}P_{12}^{\mathrm{T}} & 2P_{22}C & P_{22}D & k\Lambda + \theta P_{12}^{\mathrm{T}}G_1 & (1-\theta)P_{12}^{\mathrm{T}}G_2 \\ D^{\mathrm{T}}P_{12}^{\mathrm{T}} & D^{\mathrm{T}}P_{22}^{\mathrm{T}} & -(1-d_m)R & 0 & 0 \\ \theta G_1^{\mathrm{T}}P_{11}^{\mathrm{T}} & k\Lambda + \theta G_1^{\mathrm{T}}P_{12} & 0 & Q - 2\Lambda & 0 \\ (1-\theta)G_2^{\mathrm{T}}P_{11}^{\mathrm{T}} & (1-\theta)G_2^{\mathrm{T}}P_{12} & 0 & 0 & -(1-d_p)Q \end{pmatrix}$$

Then the origin of the genetic network (5) is the unique equilibrium point, and it is globally, asymptotically stable.

Proof Consider the following Lyapunov–Krasovskii functional:

$$V(x, y, t) = \left(x(t)^{\mathrm{T}}, y(t)^{\mathrm{T}}\right) P \begin{pmatrix} x(t) \\ y(t) \end{pmatrix} + \int_{t-\tau_p(t)}^{t} f^{\mathrm{T}}(y(s))Qf(y(s))\mathrm{d}s + \int_{t-\tau_m(t)}^{t} x^{T}(s)Rx(s)\mathrm{d}s$$

Calculating the time derivative of $V(x, y, t)$ along the solutions to (5), we have,

$$\begin{aligned} \dot{V}(x, y, t) = {} & 2x^{\mathrm{T}}(t)P_{11}Ax(t) + 2x^{\mathrm{T}}(t)(A^{\mathrm{T}}P_{12} + P_{12}C)y(t) + 2x^{\mathrm{T}}(t)P_{12}Dx(t-\tau_2)) \\ & +2\theta x^{\mathrm{T}}(t)P_{11}G_1 f(y(t)) + 2(1-\theta)x^{\mathrm{T}}(t)P_{11}G_2 f(y(t-\tau_p(t))) \\ & +2y^{\mathrm{T}}(t)P_{22}Cy(t) + 2y^{\mathrm{T}}(t)P_{22}Dx(t-\tau_m(t)) + 2\theta y^{\mathrm{T}}(t)P_{12}^{\mathrm{T}}G_1 f(y(t)) \\ & +2(1-\theta)y^{\mathrm{T}}(t)P_{12}^{\mathrm{T}}G_2 f(y(t-\tau_p(t))) + f^{\mathrm{T}}(y(t))Qf(y(t)) \\ & -(1-\dot{\tau}_1(t))f^{\mathrm{T}}(y(t-\tau_p(t)))Qf(y(t-\tau_p(t))) \\ & +x^{\mathrm{T}}(t)Rx(t) - (1-\dot{\tau}_2(t))x^{\mathrm{T}}(t-\tau_m(t))Rx(t-\tau_m(t)) \end{aligned} \tag{8}$$

Noting that $\dot{\tau}_1(t) \le d_p < 1$, $\dot{\tau}_2(t) \le d_m < 1$ and $-2\sum_{i=1}^{n}\lambda_i f(y_i(t))(f(y_i(t)) - ky_i(t)) \ge 0$, we have,

$$\dot{V}(x, y, t) \le \eta^{\mathrm{T}}(t)M_1\eta(t) < 0$$

where $\eta(t) = (x^{\mathrm{T}}(t), y^{\mathrm{T}}(t), x^{\mathrm{T}}(t-\tau_m(t)), f^{T}(y(t)), f^{\mathrm{T}}(y(t-\tau_p(t))))^{\mathrm{T}}$. It is easy to see that $\dot{V}(t) = 0$ if and only if both $x(t) = 0$ and $y(t) = 0$. It follows from the Lyapunov–Krasovskii stability theorem that the genetic networks (5) with the hybrid regulatory mechanism are globally, asymptotically stable.

Notice that the condition (7) is independent of the equilibrium point, so it is easy to prove the uniqueness of the equilibrium point by using the contradiction method which is similar to the proof of Theorem 1 in [20]. □

3.2 Stability conditions of genetic networks with noise perturbations

Along the line in [20,21], we consider genetic networks (5) with additive noise perturbations:

$$\begin{aligned} \dot{x}(t) &= Ax(t) + \theta G_1 f(y(t)) + (1-\theta)G_2 f(y(t-\tau_p(t))) + \sigma(y(t), y(t-\tau_p(t)))n(t) \\ \dot{y}(t) &= Cy(t) + Dx(t-\tau_m(t)) \end{aligned} \tag{9}$$

where $n(t) = [n_1(t), \ldots, n_m(t)]^{\mathrm{T}}$ with $n_i(t)$ as a scalar zero mean Gaussian white noise process, and $n_i(t)$ is independent of $n_j(t)$ for all $i \ne j$. where $\sigma(y(t), y(t-\tau_p(t))) \in R^{n\times m}$ is called the noise intensity matrix and it is estimated by:

$$\begin{aligned} & \mathrm{trace}(\sigma(y(t), y(t-\tau_p(t)))\sigma^{\mathrm{T}}(y(t), y(t-\tau_p(t)))) \\ & \le y^{\mathrm{T}}(t)H_1y(t) + y^{\mathrm{T}}(t-\tau_p(t))H_2y(t-\tau_p(t)) \end{aligned} \tag{10}$$

where $H_1, H_2 \geq 0$. Recall that the time derivative of a Wiener process is a white noise process. We have $\mathrm{d}\omega(t) = n(t)\mathrm{d}t$, where $\omega(t)$ is an m-dimensional Wiener process. Hence, genetic networks (9) can be rewritten as the following stochastic differential equations:

$$\begin{aligned} \mathrm{d}x(t) &= (Ax(t) + \theta G_1 f(y(t)) + (1-\theta)G_2 f(y(t-\tau_p(t))))\mathrm{d}t + \sigma(y(t), y(t-\tau_p(t)))d\omega(t) \\ \mathrm{d}y(t) &= (Cy(t) + Dx(t-\tau_m(t)))\mathrm{d}t \end{aligned} \tag{11}$$

Then we have the following theorem:

Theorem 3.2 *If there exist matrices* $P_{11} > 0, P_{12} > 0, P_{22} > 0, Q > 0, R > 0, S > 0, \Lambda = \mathrm{diag}(\lambda_1, \lambda_2, \ldots, \lambda_n) > 0$, *and a constant* $\rho > 0$ *such that the following linear matrix inequalities hold:*

$$M_2 < 0, \quad P = \begin{pmatrix} P_{11} & P_{12} \\ P_{12}^{\mathrm{T}} & P_{22} \end{pmatrix} > 0, \quad P_{11} \leq \rho I \tag{12}$$

where

$$M_2 = \begin{pmatrix} 2P_{11}A + R & P_{12}C + AP_{12} & P_{12}D & \theta P_{11}G_1 & (1-\theta)P_{11}G_2 & 0 \\ * & 2P_{22}C & P_{22}D & k\Lambda + \theta P_{12}^{\mathrm{T}}G_1 & (1-\theta)P_{12}^{\mathrm{T}}G_2 & 0 \\ * & * & 0 & 0 & 0 & \\ * & * & * & Q - 2\Lambda & 0 & 0 \\ * & * & * & * & -(1-d_p)Q & 0 \\ * & * & * & * & * & M_{66} \end{pmatrix}$$

where $M_{66} = \rho H_2 - (1-d_p)S$. *Then the origin of the genetic network* (11) *is asymptotically stable in the mean square.*

Proof Consider the same Lyapunov function as one used in the proof of Theorem 3.1. By Ito's formula [2], we obtain the following stochastic differential:

$$\mathrm{d}V(x, y, t) = LV(x, y, t)\mathrm{d}t + 2(x^{\mathrm{T}}(t)P_{11} + y^{\mathrm{T}}(t)P_{12}^{\mathrm{T}})\sigma(y(t), y(t-\tau_p(t)))\mathrm{d}\omega(t)$$

where L is the diffusion operator, and

$$\begin{aligned} LV(x, y, t) &= 2x^{\mathrm{T}}(t)P_{11}Ax(t) + 2x^{\mathrm{T}}(t)AP_{12}y(t) + 2\theta x^{\mathrm{T}}(t)P_{11}G_1 f(y(t)) \\ &\quad + 2(1-\theta)x^{\mathrm{T}}(t)P_{11}G_2 f(y(t-\tau_p(t))) + 2y^{\mathrm{T}}(t)P_{22}Cy(t) \\ &\quad + 2y^{\mathrm{T}}(t)P_{22}Dx(t-\tau_m(t)) + 2\theta y^{\mathrm{T}}(t)P_{12}^{\mathrm{T}}G_1 f(y(t)) \\ &\quad + 2(1-\theta)y^{\mathrm{T}}(t)P_{12}^{\mathrm{T}}G_2 f(y(t-\tau_p(t))) + f^{\mathrm{T}}(y(t))Qf(y(t)) \\ &\quad - (1-\dot{\tau}_1(t))f^{\mathrm{T}}(y(t-\tau_p(t)))Qf(y(t-\tau_p(t))) \\ &\quad + x^{\mathrm{T}}(t)Rx(t) - (1-\dot{\tau}_2(t))x^{\mathrm{T}}(t-\tau_m(t))Qx(t-\tau_m(t)) \\ &\quad + \mathrm{trace}(\sigma(y(t), y(t-\tau_p(t)))P_{11}\sigma^{\mathrm{T}}(y(t), y(t-\tau_p(t)))) \end{aligned}$$

By (10) and (12), we have:

$$\begin{aligned} &\mathrm{trace}(\sigma(y(t), y(t-\tau_p(t)))P_{11}\sigma^{\mathrm{T}}(y(t), y(t-\tau_p(t)))) \\ &\quad \leq \lambda_{\max}(P_{11})\mathrm{trace}(\sigma(y(t), y(t-\tau_p(t)))\sigma^{\mathrm{T}}(y(t), y(t-\tau_p(t)))) \\ &\quad \leq \rho y^{\mathrm{T}}(t)H_1 y(t) + \rho y^{\mathrm{T}}(t-\tau_p(t))H_2 y(t-\tau_p(t)) \end{aligned}$$

and taking $-2\sum_{i=1}^{n}\lambda_i f(y_i(t))(f(y_i(t)) - ky_i(t)) \geq 0$ into account, we have:

$$LV(x, y, t) \leq \eta^{\mathrm{T}}(t)M_2\eta(t)$$

where $\eta(t) = (x^{\mathrm{T}}(t), y^{\mathrm{T}}(t), x^{\mathrm{T}}(t-\tau_m(t)), f^{\mathrm{T}}(y(t)), f^{\mathrm{T}}(y(t-\tau_p(t))))^{\mathrm{T}}$. Therefore, it follows from $M_2 < 0$ that $\mathbf{E}(\mathrm{d}V(t, x, y)) = \mathbf{E}(LV(t, x, y)\mathrm{d}t) < 0$, where $\mathbf{E}$ is the mathematical expectation operator. Therefore, the genetic network (11) is asymptotically stable in the mean square. □

4 Numerical examples

In this section, three illustrative examples are given to demonstrate the effectiveness and correctness of our theoretical results.

4.1 Example 1

The repressilator is a cyclic negative-feedback loop composed of three repressor genes ($lacl$, $tetR$, and cl) and their promoters, which has been theoretically predicted and experimentally investigated in *E. coli* [11]. We consider here the dynamics of the modified repressilator with hybrid regulatory mechanism (Fig. 2a), which are determined by the following differential equations:

$$\begin{aligned} \dot{m}_i(t) &= -m_i(t) + \theta \frac{\alpha}{1+p_j^n(t)} + (1-\theta)\frac{\alpha}{1+p_j^n(t-\tau_p(t))} \\ \dot{p}_i(t) &= -\beta(p_i(t) - m_i(t-\tau_m(t))) \\ i &= lacl, tetR, cl; \quad j = cl, lacl, tetR \end{aligned} \tag{13}$$

where m_i and p_i are the concentrations of the three mRNAs and repressor-proteins, and $\beta > 0$ denotes the ratio of the protein decay rate to the mRNA decay rate. Obviously, when $\theta = 1$ and $\tau_m = 0$, model (13) becomes the one in [11]. We select a set of biologically plausible parameters as $n = 2, \alpha = 1.4, \beta = 1$ and parameter $\theta = 0.5$. By calculating, the unique steady state of (13) is $\bar{m}_i = \bar{p}_i = 0.8294$ for all i, which is globally, asymptotically stable. We can rewrite the above Equations (13) into vector form (5) by shifting the equilibrium to the origin point, where $A = C = -D = -I_3, l = [1.4, 1.4, 1.4]^{\mathrm{T}}$,

$$G_1 = G_2 = \begin{pmatrix} 0 & 0 & -1.4 \\ -1.4 & 0 & 0 \\ 0 & -1.4 & 0 \end{pmatrix}$$

and $f(x) = \frac{x^2}{1+x^2}$. Calculating the derivative of $f(x)$, we have $\max(\frac{\mathrm{d}f(x)}{\mathrm{d}x}) = \frac{3\sqrt{3}}{8} \leq k = 0.65$. In this example and the following two examples, we select time-varying delay $\tau_p(t) = 1 + 0.1\sin(t)$ and $\tau_m(t) = 0.5 + 0.1\sin(t)$, then it is easy to check that the conditions $d_p < 1$ and $d_m < 1$ are satisfied. According to Theorem 3.1, the feasible solutions to the linear matrix inequalities (7) can be obtained by using the MATLAB LMI Toolbox, which indicates that the genetic networks with hybrid regulatory mechanism are globally, asymptotically stable. The simulation result of the trajectories of the protein $p_i(t)$ is shown in Fig. 3.

Remark 4.1 Notice that the linear matrix inequalities (7) is sufficient condition for the stability of genetic networks (13), but it is too strong. In Example 1, if we take $\alpha = 2.5$ which is used in [20] and all the other parameters do not change except for θ, there are no feasible solutions to linear matrix inequalities (7) for any $\theta \in [0, 1]$. Computational simulations found that genetic networks (13) show robust oscillatory behavior when $\theta \longrightarrow 0$ while converges to its stable steady-state when $\theta \longrightarrow 1$. Contraction theory [33,34] may be relevant for future research aimed at obtaining less conservative conditions for the GRNs (5) with hybrid regulatory mechanism.

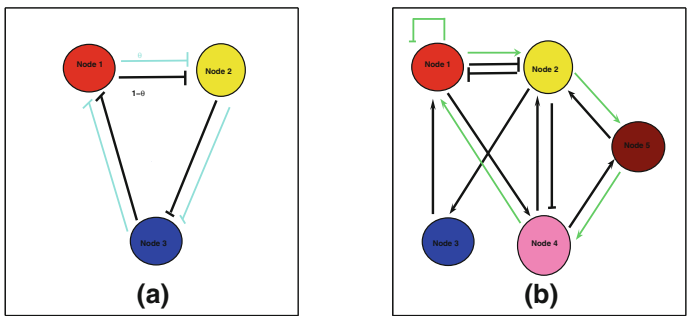

Fig. 2 Genetic network model with hybrid regulatory mechanism. **a** Scheme of the modified repressilator and **b** scheme of the modified 5-node genetic network model used in [20]. *Arrow line* represents activation and *blunt-ended line* represents repression/inactivation. *Black line* denotes indirect effect and the *green line* denotes direct effect on gene products to the TFs

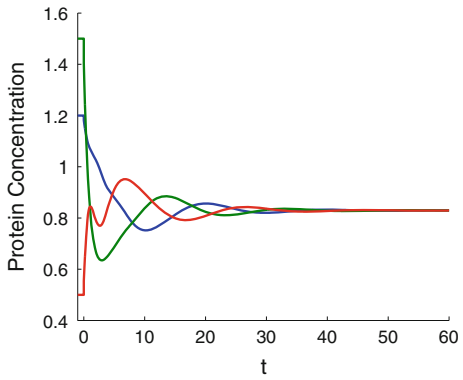

Fig. 3 Time evolution of the three protein concentrations of the modified repressilator with $\theta = 0.5$

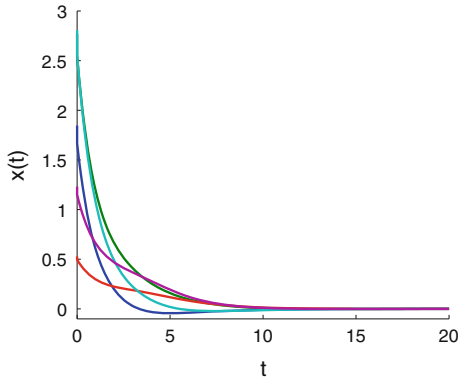

Fig. 4 Time evolution of $x(t)$ of the modified 5-node genetic networks with hybrid regulatory mechanism, where, $\theta = 0.5$

4.2 Example 2

For further demonstrating our theoretical results, a modified 5-node genetic network [20] with hybrid regulatory mechanism (Fig. 2b) is used in this example. We assume that the dimensionless transcription rates are all 0.5. According to the definition of links in (2), we can obtain the coupling matrix:

$$G_1 = 0.5 \times \begin{pmatrix} 0 & -1 & 1 & 0 & 0 \\ -1 & 0 & 0 & 1 & 1 \\ 0 & 1 & 0 & 0 & 0 \\ 1 & -1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \end{pmatrix}, \quad G_2 = 0.5 \times \begin{pmatrix} -1 & 0 & 0 & 1 & 0 \\ 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 \\ 0 & 1 & 0 & 0 & 0 \end{pmatrix}$$

and $l = 0.5 \times [1, \theta, 0, \theta, 0]^{\mathrm{T}}$ in (4). Let $A = C = -I_5$, $D = 0.8I_5$, $\theta = 0.5$ and $f(x)$ is same as example 1. The unique equilibrium point of this network is $\bar{m} = (0.4698, 0.2613, 0.0105, 0.2706, 0.0217)^{\mathrm{T}}$ and $\bar{p} = (0.3758, 0.2090, 0.0084, 0.2164, 0.0173)^{\mathrm{T}}$. We shift the equilibrium point to the origin. According to Theorem 3.1, if the LMIs linear matrix inequalities (7) hold, then the genetic network is globally, asymptotically stable. By using the MATLAB LMI Toolbox, we can easily obtain feasible solutions to the linear matrix inequalities (7). Thus, the network is globally, asymptotically stable. The simulation result of the trajectories of the variables $x(t)$ is shown in Fig. 4, which indicates that the network considered in this example is indeed stable.

Remark 4.2 In this example, node 1 has dual effects on node 2: direct activation and indirect repression (see Fig. 2b), which have been known to exist in practice. For example, gene tfdS is proposed to activate and repress the expression of the gene tfdB in the bacterium Alcaligenes eutrophus JMP134 [18], and E2Fs are known to activate and repress the same gene in different phases [22]. However, previous theoretical research on GRNs has not adequately considered this phenomenon.

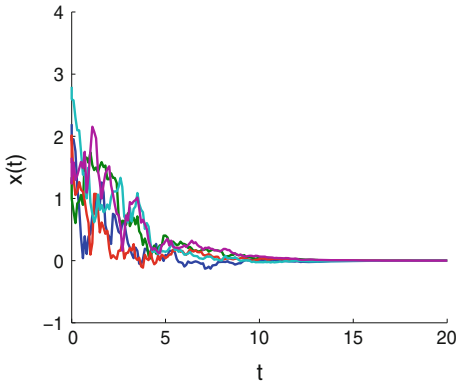

Fig. 5 Time evolution of $x(t)$ of the modified 5-node genetic networks with stochastic perturbation with hybrid regulatory mechanism, where $\theta = 0.5$

4.3 Example 3

We consider the genetic networks in Fig. 2b with additive noise perturbation. All the parameters are same as example 2 except that $D = I_5, n(t)$ is a scalar zero mean Gaussian white noise process, and $\sigma(y(t), y(t - t_p)) = (\sigma_1(y(t)), \sigma_2(y(t)), \ldots, \sigma_5(y(t)))^{\mathrm{T}}$ with $\sigma_i(y(t)) = 0.3\sum_{j=1}^{5} y_j(t)$ for all i. The unique equilibrium point of this network without stochastic perturbation is $\bar{m} = (0.4578, 0.2681, 0.0168, 0.2768, 0.0346)^{\mathrm{T}}$ and $\bar{p} = (0.4578, 0.2681, 0.0168, 0.2768, 0.0346)^{\mathrm{T}}$. We also shift the equilibrium point to the origin. By using the MATLAB LMI Toolbox, we can easily find feasible solutions to the linear matrix inequalities (12), which indicate that the network with stochastic perturbation is asymptotically stable in mean square. We show the simulation result of the trajectories of the variables $x(t)$ in Fig. 5, which indicates that the network considered in this example is indeed stable in the mean square.

Remark 4.3 Since the genetic network (5) and (11) used in the three examples includes the direct and indirect regulatory functions, the stability derived in [20,31] cannot be applied to Example 2 and 3.

5 Conclusions

In this paper, we modeled a general genetic network with hybrid regulatory mechanism, which includes some existing as special case, and then analyzed global stability issues of the GRNs. The method combining Lyapunov stability theory and Lur'e system approach was adopted to study these issues. All the sufficient conditions were given in terms of linear matrix inequalities, which are easy to be verified. Three genetic networks modified from existing literature [11,20] were also given to show the effectiveness and correctness of our theoretical results. The parameter θ which was adopted to measure relative contribution of direct effects of gene products to the activation/inactivation of TFs is an important control parameter like in [14,25]. This is probably an interesting issue for further study in the future. The GRNs with hybrid regulatory mechanism can also be used for synthetic biological applications when we design or engineer biomolecular regulatory circuits such that fast and slow reactions are taken into consideration simultaneously.

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