Disturbance Analysis of Nonlinear Differential Equation Models of Genetic SUM Regulatory Networks

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Abstract—Noise disturbances and time delays are frequently met in cellular genetic regulatory systems. This paper is concerned with the disturbance analysis of a class of genetic regulatory networks described by nonlinear differential equation models. The mechanisms of genetic regulatory networks to amplify (attenuate) external disturbance are explored, and a simple measure of the amplification (attenuation) level is developed from a nonlinear robust control point of view. It should be noted that the conditions used to measure the disturbance level are delay-independent or delay-dependent, and are expressed within the framework of linear matrix inequalities, which can be characterized as convex optimization, and computed by the interior-point algorithm easily. Finally, by the proposed method, a numerical example is provided to illustrate how to measure the attenuation of proteins in the presence of external disturbances.

Index Terms—Disturbance attenuation, asymptotic stability, genetic regulatory network, systems biology, time delay.

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1 INTRODUCTION

Since the days of Nobert Wiener, system-level understanding has been a recurrent theme in biological sciences [1]. Traditionally, the different phases involved in the cellular processes were analyzed and characterized in isolation by using biochemical techniques, leading to the view that they operate independently. As systems biology emerges in the postgenomic era, one of the major challenges in contemporary systems biology has been to understand the gene regulation and function at the system level, for instance, how proteins are synthesized from genes as transcription factors binding to other genes, how DNA, RNA, and proteins interact with each other and other small molecules to coordinate multiple biological functions. These molecules and their interactions compose a complex network, known as *genetic regulatory network* (or simply, gene network).

Meanwhile, the development of modeling techniques has made it possible to apply mathematical methods to describe the network structure and predict the dynamic behavior of the genetic regulatory networks [2], [3], [4], and a large variety of formalisms have been proposed to model, analyze, and simulate genetic regulatory networks, such as directed graphs, Bayesian networks, Boolean networks, differential equations, and Petri nets (see also [5] and references therein for a wider categorization of gene network models). Although many approaches have been proposed to specify the gene network structure, it is generally accepted that finding the network topology is not sufficient to understand the network dynamics. In the case of differential equation models, the variables represent the concentrations of gene products, such as mRNAs, proteins, and other small molecules, as time-dependent values of the gene networks. Moreover, it is observed that genes spend a lot of time at intermediate values, which implies that gene expression levels tend to be continuous rather than binary [6]. The advantage of the description with differential equation networks is

that one can take into account detailed information about genetic regulatory mechanisms such as individual kinetics and interactions among mRNAs and proteins. In addition, it is also indispensable to study the genetic regulatory systems from the viewpoint of nonlinear system theory due to the fact that GRNs are strongly nonlinear and high dimensional.

In addition, it is recognized that it is system dynamics and internal structures of the biological phenomena that give rise to the functioning and function of cells [7]. In fact, stability is a fundamental requirement of biological systems, with obvious biological significance, see [8], [9] and references therein. In [10], the authors investigated a simple genetic circuit model in Escherichia coli to test the role of negative feedback in the stability analysis of gene networks. Also, an important issue in modeling gene expression is the fact that individual processes need a certain amount of time to be finished [11], [12]. This motivates to consider the effect of delay on dynamic behaviors of gene network, it has been well known that delay is often the key factor to instability of a given system, and thus, plays an important role in the dynamic analysis of gene regulation [13]. A nonlinear model of genetic regulatory networks with time delays was proposed, and sufficient conditions were also obtained in the form of linear matrix inequality in [14], where the transcription functions are assumed to act additively to regulate a gene. Such a regulatory function is known to be SUM logic [15], [16], which was first proposed in [17]. Sufficient conditions for the stochastic stability of the genetic networks with disturbance attenuation were also derived in [18], [19].

On the other hand, due to the fact that a realistic gene network model should be identified from real-world gene expression time-series data, it is well known that the modeling error is unavoidable in practice, which makes the mathematical model uncertain. Moreover, one of the objectives of modeling is to obtain information about the input of the genetic regulatory networks, such as physical and chemical stimuli, and environmental changes [20]. It should be noted that the nature of these inputs and their corresponding values may not be fully known or measurable due to the complexity of biological processes [21]. When referring to modeling genetic regulatory networks, it is very difficult to fully detect the extrinsic signals, not to mention the fact that it is impossible to completely know the intrinsic inputs affecting each components of the gene network.

Motivated by the aforementioned reasons, in this paper, we propose a genetic regulatory network model with time delays and external disturbances, and investigate the dynamic performances of genetic regulatory networks. To be specific, the effects due to delays and external disturbances on the stability of gene networks are studied, sufficient conditions, which are delay-dependent or delay-independent, are established to measure the external disturbance level by means of nonlinear control theory. Moreover, an LMI optimization problem is further established to minimize the attenuation level of disturbances. It should be noted that the conditions obtained in this paper are expressed in a unified linear matrix inequality framework, and can be verified easily by existing standard software.

The remaining portion of this paper is organized as follows: Section 2 gives a system-level description on GRNs and presents the problem formulation. Section 3 is devoted to the stability analysis of the gene network in the presence of both time delays and external disturbances. A three-gene network is provided to show the effectiveness and applicability of the theoretical results in Section 4. In Section 5, we summarize our results.

Notations. Denote $\mathbb{Z}_n \triangleq \{1, 2, \ldots, n\}$; let $\mathbb{R}$ be the set of real numbers; $\mathbb{R}^n$ denotes the n-column vectors; $\mathbb{R}^{m \times n}$ is the set of $m \times n$ matrices for which all components belong to $\mathbb{R}$. For any real symmetric matrices P and Q, the notation $P \geq Q$ (respectively, $P > Q$) means that the matrix $P - Q$ is positive

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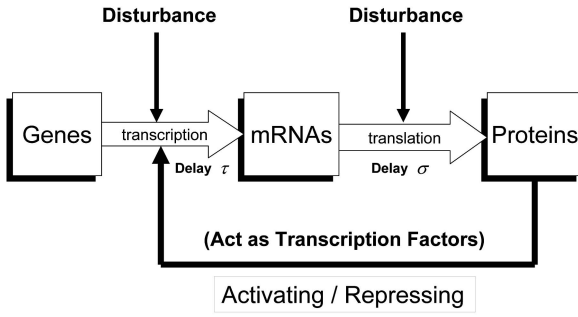*E-mail: {pingli, james.lam}@hku.hk.*

Fig. 1. System-level approach to GRNs.

semidefinite (respectively, positive definite). $|\cdot|$ denotes the euclidean norm for vectors and $\|\cdot\|$ denotes the spectral norm for matrices. $\mathcal{C}([-\tau, 0], \mathbb{R}^n)$ and $\mathcal{C}([-\tau, 0], \mathbb{R}^n_+)$ denote the family of continuous functions ϕ from $[-\tau, 0]$ to $\mathbb{R}^n$ and $\mathbb{R}^n_+$, with norm $|\phi|_\tau = \sup_{-\tau \leq s \leq 0} |\phi(s)|$. $\mathrm{diag}(\ldots)$ stands for a block-diagonal matrix. The superscript "T" denotes matrix transpose and the symbol $\#$ is used to represent a matrix which can be inferred by symmetry. Matrices, if their dimensions are not explicitly stated, are assumed to have compatible dimensions for algebraic operations.

2 GENETIC REGULATORY NETWORK AND MODEL DESCRIPTION

2.1 Genetic Regulatory network

In living organisms, gene expression is regulated by genetic regulatory networks with interactions among DNA, RNA, proteins, and small molecules. In general, the term gene refers to those segments of one strand of DNA where genetic information can be transferred to mRNAs in a process called transcription. mRNA is then used as a template to synthesize proteins in a process called translation. In turn, some of proteins, acting as transcription factors, regulate the transcription process.

In addition, time delays and noise disturbances are common and substantial in the signal transmission along the pathway of gene networks. It is well known that gene transcription and mRNA translation must take some time to generate the corresponding product. Also, noise disturbances are always present during the process of gene expression, which are usually generated by its external environment. The whole scenario is shown from a system level point of view in Fig. 1.

2.2 Problem Formulation

The following differential equations have been used recently to describe the genetic regulatory networks [8], [22]:

$$\begin{cases} \dfrac{dm_i(t)}{dt} = -a_i m_i(t) + f_i(p_1(t-\tau), p_2(t-\tau), \\ \qquad\qquad \ldots, p_n(t-\tau)) + u_i, \\ \dfrac{dp_i(t)}{dt} = -b_i p_i(t) + d_i m_i(t-\sigma),\ i \in \mathbb{Z}_n, \end{cases} \quad (1)$$

where $m_i(t)$ and $p_i(t)$ are the concentrations of the ith mRNA and protein, and $a_i > 0$ and $b_i > 0$ are constant numbers, representing the degradation rate of the ith mRNA and protein, respectively. $d_i > 0$ is the production constant, and u_i is defined as a basal rate, which may be considered as the "leakiness" of the promoter. In this paper, the function f_i is taken as $f_i(p_1(t), p_2(t), \ldots, p_n(t)) = \sum_{j=1}^n f_{ij}(p_j(t))$, which is called SUM logic, since each transcription factor acts additively to regulate the gene i. Here, $f_{ij}(\cdot)$ is a monotonic function of the Hill form, that is,

$$f_{ij} = \begin{cases} \alpha_{ij} \dfrac{(x/\beta_j)^{H_j}}{1 + (x/\beta_j)^{H_j}}, & \text{if transcription factor } j \\ & \text{is an activator of gene } i, \\ \alpha_{ij} \dfrac{1}{1 + (x/\beta_j)^{H_j}}, & \text{if transcription factor } j \\ & \text{is a repressor of gene } i, \end{cases} \quad (2)$$

where H_j is the Hill coefficient, $\beta_j > 0$ is a scalar, and α_{ij} is a bounded constant, which denotes the dimensionless transcriptional rate of transcription factor j to gene i. Such a SUM logic is indeed exhibited in many natural gene networks [15], [16], [23], [24]. Note that when $n = 1$, (1) degenerates into a single-gene network model, which has been proposed and investigated in [13]. Note

$$\alpha_{ij} \frac{(x/\beta_j)^{H_j}}{1 + (x/\beta_j)^{H_j}} = \alpha_{ij} \left(1 - \frac{1}{1 + (x/\beta_j)^{H_j}} \right), \quad (3)$$

then, based on (2) and (3), the gene network in (1) can be rewritten as

$$\begin{cases} \dfrac{dm_i(t)}{dt} = -a_i m_i(t) + \sum_{j=1}^n w_{ij} g_j(p_j(t-\tau)) + l_i, \\ \dfrac{dp_i(t)}{dt} = -b_i p_i(t) + d_i m_i(t-\sigma),\ i \in \mathbb{Z}_n, \end{cases} \quad (4)$$

where

$$g_j(x) = \frac{(x/\beta_j)^{H_j}}{1 + (x/\beta_j)^{H_j}} (j \in \mathbb{Z}_n), l_i = u_i + \sum_{j \in \mathcal{V}_i} \alpha_{ij}$$

with $\mathcal{V}_i$ being the set of all the transcription factor j which is a repressor of gene i; $W = (w_{ij})_{n \times n}$ is defined as follows: if transcription factor j is an activator of gene i, $w_{ij} = \alpha_{ij}$; if there is no connection between j and i, $w_{ij} = 0$; if transcription factor j is a repressor of gene i, $w_{ij} = -\alpha_{ij}$.

In this paper, we introduce external disturbances to model (4) and consider the following gene network model in a vector-matrix form:

$$\begin{cases} \dfrac{dm(t)}{dt} = -Am(t) + Wg(p(t-\tau)) + l + G_1 \omega(t), \\ \dfrac{dp(t)}{dt} = -Bp(t) + Dm(t-\sigma) + G_2 \omega(t), \\ \tilde{z}(t) = \begin{bmatrix} C_1 m(t) \\ C_2 p(t) \end{bmatrix}, \end{cases} \quad (5)$$

where $m(t) = [m_1(t), m_2(t), \ldots, m_n(t)]^T$, $p(t) = [p_1(t), p_2(t), \ldots, p_n(t)]^T$, the system parameters $A = \mathrm{diag}(a_1, a_2, \ldots, a_n) > 0$, $B = \mathrm{diag}(b_1, b_2, \ldots, b_n) > 0$, and $D = \mathrm{diag}(d_1, d_2, \ldots, d_n) > 0$ are diagonal matrices, $g(p(t)) = [g_1(p_1(t)), g_2(p_2(t)), \ldots, g_n(p_n(t))]^T$, and $l = [l_1, l_2, \ldots, l_n]^T$. $\omega(t)$ is the disturbance input which cannot be fully measured and are not completely known beforehand. We assume that $\omega(t)$ belongs to $L_2[0, +\infty)$, which implies that it is a function of finite energy. G_1 and G_2 are the input matrices, C_1 and C_2 are the output matrices, and $\tilde{z}(t)$ represents the concentration of mRNAs and proteins we are interested in.

Remark 1. It is worth pointing out that the theory developed in this paper can be generalized to the case when the time delays in (5) are different from each other. However, it is anticipated that the introduction of multiple time delays will result in more complicated notations, whereas no essential difficulty will be added.

Remark 2. The disturbance input $\omega(t)$ can be viewed as additive intrinsic and extrinsic signals that are not able to be detected. The output $\tilde{z}(t)$ can be thought as responses, if we are only interested in mRNAs or proteins, then we can let $[C_1, C_2] = [I, 0]$ or $[C_1, C_2] = [0, I]$, respectively. Particularly, if we are only interested in discussing the effect of disturbances on protein i,

then we can just let $[C_1, C_2] = [0, e_i]$, where e_i is the unit vector with every element of e_i being 0 except 1 at the ith element.

Let (m^*, p^*) be the equilibrium point (steady state) of (5), that is, it is a solution of the following equations:

$$\begin{cases} 0 = -Am^* + Wg(p^*) + l, \\ 0 = -Bp^* + Dm^*. \end{cases} \quad (6)$$

The aim of this paper is to investigate the influence of disturbance $\omega(t)$ on the stability of gene network (5). To achieve this, we will shift the steady state (m^*, p^*) to the origin by using the transformation $x(t) \triangleq [x_1(t), x_2(t), \ldots, x_n(t)]^T = m(t) - m^*$ and $y(t) \triangleq [y_1(t), y_2(t), \ldots, y_n(t)]^T = p(t) - p^*$, then we have

$$\begin{cases} \dfrac{dx(t)}{dt} = -Ax(t) + Wh(y(t-\tau)) + G_1\omega(t), \\ \dfrac{dy(t)}{dt} = -By(t) + Dx(t-\sigma) + G_2\omega(t), \\ z(t) = \begin{bmatrix} C_1 x(t) \\ C_2 y(t) \end{bmatrix}, \end{cases} \quad (7)$$

where

$$h(y(t)) = [h_1(y_1(t)), h_2(y_2(t)), \ldots, h_n(y_n(t))]^T$$

with $h_j(y_j(t)) = g_j(y_j(t) + p_j^*) - g_j(p_j^*)$.

We assume the initial condition of the genetic regulatory network in (7) to be

$$x(t) = \varphi_x(t), \quad y(t) = \psi_y(t), \quad -\varsigma \le t \le 0, \quad \varsigma = \max\{\tau, \sigma\}.$$

where φ_x and ψ_y both belong to $\mathcal{C}([-\varsigma, 0], \mathbb{R}^n)$. Since g_i is a monotonically increasing and differentiable function with saturation, it satisfies

$$0 \le \dfrac{g_j(s_1) - g_j(s_2)}{s_1 - s_2} \le k_j, \quad k_j > 0, j \in \mathbb{Z}_n, \quad (8)$$

for any different $s_1, s_2 \in \mathbb{R}$. From the relationship between g and h, we obtain the following condition:

$$h_j(s)(h_j(s) - k_j s) \le 0, \quad j \in \mathbb{Z}_n, \quad (9)$$

for any $s \in \mathbb{R}$.

For convenience, we denote $K \triangleq \mathrm{diag}(k_1, k_2, \ldots, k_n)$ throughout the paper. In the following, we give the definition of disturbance-level measurement from a nonlinear robust control point of view.

Definition 1. *Network (7) is said to have attenuation level ρ, if it is globally asymptotically stable for $w(t) = 0$, and under zero initial conditions $\varphi_x(t) = \psi_y(t) = 0$, $t \in [-\varsigma, 0]$, it holds that*

$$\int_0^T |z(s)|^2 \, ds \le \rho^2 \int_0^T |w(s)|^2 \, ds, \quad (10)$$

for any $T > 0$ and nonzero input disturbance $w(t)$.

3 DISTURBANCE ATTENUATION OF GENETIC REGULATORY NETWORK

The problem to be addressed in this section is to study the effect of external disturbances on the stability of gene networks (5) theoretically. Based on the analysis in Section 2, we study the stability of network (7) equivalently and present the main result in the following theorem:

Theorem 1. *If there exist matrices $Q_1 > 0$, $Q_2 > 0$, $Q_3 > 0$, $Q_4 > 0$, $Q_5 > 0$, a diagonal matrix $\Gamma = \mathrm{diag}(\gamma_1, \gamma_2, \ldots, \gamma_n) > 0$, and matrices P_{11}, P_{12}, P_{22}, X_1, X_2, Y_1, Y_2, such that the following LMIs hold:*

$$\Upsilon(\bar{\tau}, \bar{\sigma}) = \begin{bmatrix} \Upsilon_{11} & \Upsilon_{12} & \Upsilon_{13} & \Upsilon_{14} \\ \# & \Upsilon_{22} & \Upsilon_{23} & \Upsilon_{24} \\ \# & \# & \Upsilon_{33} & \Upsilon_{34} \\ \# & \# & \# & \Upsilon_{44} \end{bmatrix} < 0, \quad (11)$$

$$P = \begin{bmatrix} P_{11} & P_{12} \\ \# & P_{22} \end{bmatrix} > 0, \quad (12)$$

where

$$\Upsilon_{11} = \begin{bmatrix} M_1 & P_{12}D + X_1 + X_2^T & -AP_{12} - P_{12}B \\ \# & -Q_1 - X_2 - X_2^T & DP_{22} \\ \# & \# & M_3 \end{bmatrix},$$

$$\Upsilon_{12} = \begin{bmatrix} 0 & 0 & P_{11}W \\ D\Gamma & 0 & 0 \\ 0 & Y_1 + Y_2^T & P_{12}^T W \end{bmatrix},$$

$$\Upsilon_{13} = \begin{bmatrix} \bar{\sigma}X_1 & 0 & P_{11}G_1 + P_{12}G_2 \\ -\bar{\sigma}X_2 & 0 & 0 \\ 0 & \bar{\tau}Y_1 & P_{12}^T G_1 + P_{22}G_2 \end{bmatrix},$$

$$\Upsilon_{14} = \begin{bmatrix} \bar{\sigma}AQ_4 & 0 \\ 0 & -\bar{\tau}DQ_5 \\ 0 & \bar{\tau}BQ_5 \end{bmatrix},$$

$$\Upsilon_{22} = \mathrm{diag}\big(-2K^{-1}\Gamma B + Q_3, -Q_2 - Y_2 - Y_2^T, -Q_3 \big),$$

$$\Upsilon_{23} = \begin{bmatrix} 0 & 0 & \Gamma G_2 \\ 0 & -\bar{\tau}Y_2 & 0 \\ 0 & 0 & 0 \end{bmatrix},$$

$$\Upsilon_{24} = \begin{bmatrix} 0 & 0 \\ 0 & 0 \\ -\bar{\sigma}W^T Q_4 & 0 \end{bmatrix},$$

$$\Upsilon_{33} = \mathrm{diag}\big(-\bar{\sigma}Q_4, \quad -\bar{\tau}Q_5, \quad -\rho^2 I \big),$$

$$\Upsilon_{34} = \begin{bmatrix} 0 & 0 \\ 0 & 0 \\ -\bar{\sigma}G_1^T Q_4 & -\bar{\tau}G_2^T Q_5 \end{bmatrix},$$

$$\Upsilon_{44} = \mathrm{diag}\big(-\bar{\sigma}Q_4, \quad -\bar{\tau}Q_5 \big),$$

with

$$M_1 = -P_{11}A - AP_{11} - X_1 - X_1^T + Q_1 + C_1^T C_1,$$
$$M_3 = -P_{22}B - BP_{22} - Y_1 - Y_1^T + Q_2 + C_2^T C_2,$$

then the attenuation level ρ of the perturbed genetic regulatory network in (7) is guaranteed for any (τ, σ) satisfying $\tau \le \bar{\tau}$ and $\sigma \le \bar{\sigma}$.

From Theorem 1, one can see that we develop a sufficient condition under which the genetic regulatory network in (5) with $w(t) = 0$ is globally asymptotically stable, and explore the mechanisms of gene networks to measure the disturbance level from the L_2 gain point of view. Also, for a preassigned disturbance level ρ, the condition in Theorem 1 is delay-dependent, which further implies that we can discuss the effect of time delays on the kinetics of gene networks and estimate the maximal delay pair (τ, σ) to ensure that the attenuation level ρ of the perturbed genetic regulatory network in (7) is guaranteed by means of Theorem 1. This will be of importance in revealing the impact of delays on the analysis of gene networks and introducing more flexibility in the design of delay-tolerant genetic circuit.

Remark 3. Under conditions (11) and (12), one may prove the uniqueness of the equilibrium point by using a contradiction argument. To be specific, if there exists another equilibrium point $(\bar{m}, \bar{p})$ different from (m^*, p^*), then by following the same analysis in Theorem 1, one can prove that $(\bar{m}, \bar{p})$ is also globally asymptotically stable. Note that the conditions in Theorem 1 are independent of the equilibrium point; thus, there exist two globally asymptotically stable equilibria, which is impossible.

Remark 4. For fixed delay pair $(\bar{\tau}, \bar{\sigma})$, we may optimize the disturbance level ρ by solving the following constrained optimization:

$$\rho_0 \stackrel{\triangle}{=} \min_S \rho$$

subject to (11) and (12),

where $S = \{\rho > 0, Q_i > 0, i = 1, \ldots, 5, \Gamma = \mathrm{diag}(\gamma_1, \gamma_2, \ldots, \gamma_n) > 0, P_{11}, P_{12}, P_{22}, X_1, X_2, Y_1, Y_2\}$. Note that the optimized value ρ_0 can be attained by a simple bisection algorithm [25].

Remark 5. In a real gene network, the output $z(t)$ may not be composed entirely of network state, but also be corrupted by the external disturbance $w(t)$. From the proof of Theorem 1, it can be seen that this will not add significant difficulty and similar results can also be obtained. In addition, one can show that if the initial condition $\varphi_x(t)$ and $\psi_y(t)$ are not zero, then an extra term should be added as follows:

$$\int_0^T |z(s)|^2 \, \mathrm{d}s \le \rho^2 \int_0^T |w(s)|^2 \, \mathrm{d}s + V(0),$$

for some positive-definite function $V(t)$.

Meanwhile, it is sometimes also the case that we may not know how long it will take for an individual process to be finished during the process of gene regulation. That is, we have no information about the magnitude of time delays in the signaling pathway, an interesting question one may raise is that whether we can still obtain a bit conservative condition, under which the attenuation level ρ of the perturbed genetic regulatory network in (5) is guaranteed for any $\tau > 0$ and $\sigma > 0$. Similar to Theorem 1, we can obtain the so-called delay-independent condition on the disturbance analysis of gene networks (the proof is omitted here).

Theorem 2. *If there exist matrices $Q_1 > 0$, $Q_2 > 0$, a diagonal matrix $\Gamma = \mathrm{diag}(\gamma_1, \gamma_2, \ldots, \gamma_n) > 0$, and matrices P_{11}, P_{12}, P_{22}, such that the following LMIs hold:*

$$\Sigma = \begin{bmatrix} \Sigma_{11} & \Sigma_{12} \\ \# & \Sigma_{22} \end{bmatrix} < 0, \tag{13}$$

$$P = \begin{bmatrix} P_{11} & P_{12} \\ \# & P_{22} \end{bmatrix} > 0, \tag{14}$$

where

$$\Sigma_{11} = \begin{bmatrix} N_{11} & P_{12}D & -AP_{12} - P_{12}B \\ \# & -Q_1 & DP_{22} \\ \# & \# & N_{33} \end{bmatrix},$$

$$\Sigma_{12} = \begin{bmatrix} 0 & P_{11}W & P_{11}G_1 + P_{12}G_2 \\ D\Gamma & 0 & 0 \\ 0 & P_{12}^T W & P_{12}^T G_1 + P_{22}G_2 \end{bmatrix},$$

$$\Sigma_{22} = \begin{bmatrix} -2K^{-1}\Gamma B + Q_2 & 0 & \Gamma G_2 \\ \# & -Q_2 & 0 \\ \# & \# & -\rho^2 I \end{bmatrix},$$

with

$$N_{11} = -P_{11}A - AP_{11} + Q_1 + C_1^T C_1,$$
$$N_{33} = -P_{22}B - BP_{22} + C_2^T C_2,$$

then the attenuation level ρ of the perturbed genetic regulatory network in (7) is guaranteed.

4 APPLICATION TO THREE-GENE NETWORKS

In this section, we illustrate the application of the proposed results to a biological network, which has been adopted as a mathematical model, and experimentally studied in Escherichia coli [22]. The network is a cyclic negative feedback loop with three repressor genes ($lacl$, $tetR$, and cl) and their corresponding promoters. Here, we incorporate time delays and external disturbances to the repressor system in [22] to check the stability of the steady state. Consider the following gene network described by six coupled differential equations:

$$\begin{cases} \dfrac{\mathrm{d}m_i(t)}{\mathrm{d}t} = -m_i(t) + \alpha_i \dfrac{1}{1 + p_j^H(t - \tau)} + \alpha_0 + G_{1i}\omega(t), \\ \dfrac{\mathrm{d}p_i(t)}{\mathrm{d}t} = -\beta_i p_i(t) + \gamma_i m_i(t - \sigma) + G_{2i}\omega(t), \end{cases} \tag{15}$$

where i and j have the following three pairs of values: $(i = 1, j = 2), (i = 2, j = 3), (i = 3, j = 1)$. β_i denotes the ratio of the protein decay rate to the mRNA decay rate and H is the Hill coefficient. From (15), we have

$$\begin{cases} \dfrac{\mathrm{d}m_i(t)}{\mathrm{d}t} = -m_i(t) + (-\alpha_i) \dfrac{p_j^H(t - \tau)}{1 + p_j^H(t - \tau)} + \alpha_i \\ \qquad + \alpha_0 + G_{1i}\omega(t), \\ \dfrac{\mathrm{d}p_i(t)}{\mathrm{d}t} = -\beta_i p_i(t) + \gamma_i m_i(t - \sigma) + G_{2i}\omega(t). \end{cases}$$

Then, by selecting

$$m(t) = [m_1(t), m_2(t), m_3(t)]^T, p(t) = [p_1(t), p_2(t), p_3(t)]^T,$$

and $g_j(x) = x^2/(1 + x^2)$ for any j, we obtain network (5) with the following parameters:

$$A = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}, \quad W = \begin{bmatrix} 0 & 0 & -\alpha_1 \\ -\alpha_2 & 0 & 0 \\ 0 & -\alpha_3 & 0 \end{bmatrix},$$

$$B = \mathrm{diag}(\beta_1, \beta_2, \beta_3), \quad D = \mathrm{diag}(\gamma_1, \gamma_2, \gamma_3),$$

$$l = \begin{bmatrix} \alpha_1 + \alpha_0 \\ \alpha_2 + \alpha_0 \\ \alpha_3 + \alpha_0 \end{bmatrix}, \quad G_1 = \begin{bmatrix} G_{11} \\ G_{12} \\ G_{13} \end{bmatrix} \quad G_2 = \begin{bmatrix} G_{21} \\ G_{22} \\ G_{23} \end{bmatrix}.$$

For numerical simulation, we choose the Hill coefficient $H = 2$, then we have $K = \mathrm{diag}(0.65, 0.65, 0.65)$. Moreover, we assume that $\tau = 1$ and $\sigma = 2$, and the other parameters are taken as

$$\alpha_1 = 0.8, \quad \alpha_2 = 0.6, \quad \alpha_3 = 0.6, \quad \alpha_0 = 0,$$
$$\beta_1 = \beta_2 = \beta_3 = 1,$$
$$\gamma_1 = 0.6, \quad \gamma_2 = 0.4, \quad \gamma_3 = 0.5,$$
$$G_{11} = G_{13} = 1, \quad G_{12} = 0,$$
$$G_{21} = G_{22} = 1, \quad G_{23} = 0.$$

By means of Theorem 1, it is easy to check that the genetic regulatory network in (15) is globally asymptotically stable when there are no external disturbances ($\omega(t) = 0$); thus, the steady state $m^* = (0.7389, 0.5014, 0.5766)^T$, $p^* = (0.4435, 0.2008, 0.2880)^T$ is a stable and unique equilibrium. Figs. 2 and 3 show the trajectory of the system state $m(t)$ and $p(t)$ with the initial state chosen as
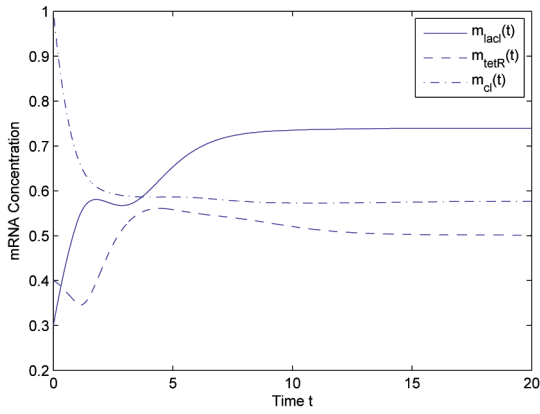
Fig. 2. State response of $m(t)$ of genetic regulatory network in (15) with $w(t) = 0$.

Fig. 4. State response of $p(t)$ of perturbed genetic regulatory network in (15).

$\varphi(t) = [0.3 + 0.5 \sin t, 0.2 + 0.2 \cos t, 1.0 - 0.6 \sin t]^T$ a n d $\psi(t) = [0.5 + 0.5 \cos t, 0.4 - 0.2 \sin t, 0.8 - 0.4 \cos t]^T$.

Furthermore, if we are interested in the effects of additive disturbance $\omega(t)$ on individual protein p_1, p_2, and p_3, then we can let C in (5) be $[1, 0, 0]$, $[0, 1, 0]$, and $[0, 0, 1]$, respectively. By Remark 4, we solve the LMIs in (11) and (12) to calculate the attenuation level and obtain the optimal attenuation level ρ_0 of protein p_1, p_2, and p_3, as 0.7432, 0.4684, and 0.4630 via Yalmip [26], respectively, which further implies that the disturbance attenuation levels of these proteins cannot exceed these corresponding scalars. Equivalently, we have

$$\int_0^T |p_1(s) - p_1^*|^2 \, ds \le 0.5523 \int_0^T |w(s)|^2 \, ds,$$

$$\int_0^T |p_2(s) - p_2^*|^2 \, ds \le 0.2194 \int_0^T |w(s)|^2 \, ds,$$

$$\int_0^T |p_3(s) - p_3^*|^2 \, ds \le 0.2143 \int_0^T |w(s)|^2 \, ds.$$

Therefore, in this gene network, it can be concluded that the disturbances at p_1, p_2, and p_3 are all attenuated by the network, which was verified by the proposed theory. For numerical simulation, we assume that $w(t) = 2/(1 + 0.5t)$, and the initial condition as $\varphi(t) = [0.5, 0.2, 0.4]^T$ and $\psi(t) = [0.1, 0.2, 0.3]^T$. Fig. 4 depicts the dynamic response of the perturbed genetic regulatory network in (15), where the solid lines show the state trajectory of protein under the excitation of external disturbances, and the dashed lines illustrate the steady state of the undisturbed gene network.
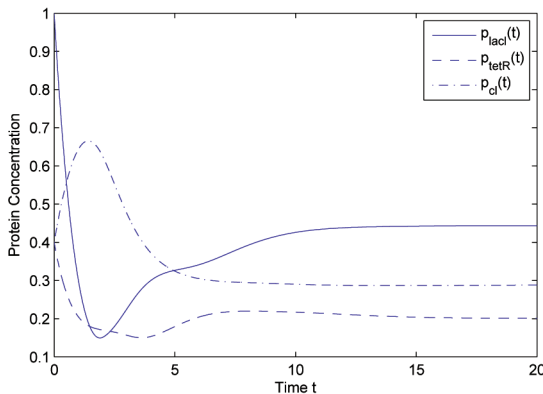
5 CONCLUSION

In this study, a nonlinear differential equation model of delayed genetic regulatory network was proposed, and the dynamic behaviors of such a class of networks were investigated. To be precise, we presented the stability conditions for gene networks with both time delays and external disturbances, and explored the mechanisms of gene networks to measure the disturbance level from the signal processing perspective. Moreover, we presented a convex optimization algorithm to minimize the disturbance level by virtue of L_2 control theory. To verify the obtained theoretical results, a three-gene network example was used for numerical illustration.

APPENDIX

PROOF OF THEOREM 1

According to Definition 1, we show that the attenuation level ρ of the perturbed genetic regulatory network in (7) is guaranteed in two steps. First, we prove that the genetic regulatory network in (7) with $w(t) = 0$ is globally asymptotically stable under the condition (11), and then, we show that (10) is satisfied under zero initial conditions.

Step I. It follows from (11) that

$$\Omega(\bar{\tau}, \bar{\sigma}) = \begin{bmatrix} \Omega_{11} & \Omega_{12} \\ \# & \Omega_{22} \end{bmatrix} < 0, \tag{16}$$

where

$$\Omega_{11} = \begin{bmatrix} \Omega_{111} & \Omega_{112} \\ \# & \Omega_{113} \end{bmatrix},$$

$$\Omega_{111} = \begin{bmatrix} \tilde{M}_1 & P_{12}D + X_1 + X_2^T & -AP_{12} - P_{12}B \\ \# & -Q_1 - X_2 - X_2^T & DP_{22} \\ \# & \# & \tilde{M}_3 \end{bmatrix},$$

$$\Omega_{112} = \begin{bmatrix} 0 & 0 & P_{11}W \\ D\Gamma & 0 & 0 \\ 0 & Y_1 + Y_2^T & P_{12}^T W \end{bmatrix},$$

$$\Omega_{113} = \text{diag}\big(-2K^{-1}\Gamma B + Q_3, -Q_2 - Y_2 - Y_2^T, -Q_3\big),$$

$$\Omega_{12} = \begin{bmatrix} \bar{\sigma}X_1 & 0 & \bar{\sigma}AQ_4 & 0 \\ -\bar{\sigma}X_2 & 0 & 0 & -\bar{\tau}DQ_5 \\ 0 & \bar{\tau}Y_1 & 0 & \bar{\tau}BQ_5 \\ 0 & 0 & 0 & 0 \\ 0 & -\bar{\tau}Y_2 & 0 & 0 \\ 0 & 0 & -\bar{\sigma}W^T Q_4 & 0 \end{bmatrix},$$

$$\Omega_{22} = \text{diag}(-\bar{\sigma}Q_4, -\bar{\tau}Q_5, -\bar{\sigma}Q_4, -\bar{\tau}Q_5),$$

Fig. 3. State response of $p(t)$ of genetic regulatory network in (15) with $w(t) = 0$.

with

$$\tilde{M}_1 = -P_{11}A - AP_{11} - X_1 - X_1^T + Q_1,$$
$$\tilde{M}_3 = -P_{22}B - BP_{22} - Y_1 - Y_1^T + Q_2.$$

For convenience, we denote $x(t - \sigma)$ and $y(t - \tau)$ as $x_\sigma(t)$ and $y_\tau(t)$, respectively. Choose the Lyapunov functional candidate of the form

$$V(t) = \sum_{i=1}^{4} V_i(t, x(t), y(t)), \tag{17}$$

where

$$V_1(t, x(t), y(t)) = \begin{bmatrix} x(t) \\ y(t) \end{bmatrix}^T P \begin{bmatrix} x(t) \\ y(t) \end{bmatrix}, \tag{18}$$

$$V_2(t, x(t), y(t)) = 2 \sum_{i=1}^{n} \gamma_i \int_0^{y_i(t)} h_i(\alpha) \, d\alpha, \tag{19}$$

$$V_3(t, x(t), y(t)) = \int_{t-\sigma}^{t} x^T(\alpha) Q_1 x(\alpha) \, d\alpha$$
$$+ \int_{t-\tau}^{t} y^T(\alpha) Q_2 y(\alpha) \, d\alpha$$
$$+ \int_{t-\tau}^{t} h^T(y(\alpha)) Q_3 h(y(\alpha)) \, d\alpha, \tag{20}$$

$$V_4(t, x(t), y(t)) = \int_{-\sigma}^{0} \int_{t+\beta}^{t} \dot{x}^T(\alpha) Q_4 \dot{x}(\alpha) \, d\alpha \, d\beta$$
$$+ \int_{-\tau}^{0} \int_{t+\gamma}^{t} \dot{y}^T(\alpha) Q_5 \dot{y}(\alpha) \, d\alpha \, d\gamma. \tag{21}$$

For techniques on the choice of Lyapunov functional, we refer the readers to [27] for details. To facilitate the stability analysis of gene network (7), we first calculate the time derivative of $V_i(t, x(t), y(t))$ along the trajectory of network (7), we have

$$\dot{V}_1(t, x, y) = 2(x^T(t)P_{11} + y^T P_{12}^T)\dot{x}(t)$$
$$+ 2(x^T(t)P_{12} + y^T(t)P_{22})\dot{y}(t), \tag{22}$$

$$\dot{V}_2(t, x, y) = 2h^T(y(t))\Gamma \dot{y}(t)$$
$$= -2h^T(y(t))\Gamma By(t) + 2h^T(y(t))\Gamma D x_\sigma(t), \tag{23}$$

$$\dot{V}_3(t, x, y) = x^T(t)Q_1 x(t) - x_\sigma^T(t)Q_1 x_\sigma(t)$$
$$+ y^T(t)Q_2 y(t) - y_\tau^T(t)Q_2 y_\tau(t)$$
$$+ h^T(y(t))Q_3 h(y(t)) - h^T(y_\tau(t))Q_3 h(y_\tau(t)), \tag{24}$$

$$\dot{V}_4(t, x, y) = \int_{-\sigma}^{0} [\dot{x}^T(t)Q_4 \dot{x}(t) - \dot{x}^T(t+\beta)Q_4 \dot{x}(t+\beta)] \, d\beta$$
$$+ \int_{-\tau}^{0} [\dot{y}^T(t)Q_5 \dot{y}(t) - \dot{y}^T(t+\gamma)Q_5 \dot{y}(t+\gamma)] \, d\gamma$$
$$= \int_{t-\sigma}^{t} [x^T(t)AQ_4 Ax(t) - 2x^T(t)AQ_4 Wh(y_\tau(t))$$
$$+ h^T(y_\tau(t))W^T Q_4 Wh(y_\tau(t)) - \dot{x}^T(\beta)Q_4 \dot{x}(\beta)] \, d\beta$$
$$+ \int_{t-\tau}^{t} [y^T(t)BQ_5 By(t) - 2y^T(t)BQ_5 D x_\sigma(t)$$
$$+ x_\sigma^T(t)DQ_5 D x_\sigma(t) - \dot{y}^T(\gamma)Q_5 \dot{y}(\gamma)] \, d\gamma. \tag{25}$$

Considering the relationship in (9) and noting $\Gamma > 0$, we can deduce

$$- 2h^T(y(t))\Gamma By(t) \leq -2h^T(y(t))\Gamma BK^{-1}h(y(t)). \tag{26}$$

In addition, for any matrices X_1 and X_2, we have

$$2x^T(t)X_1 \int_{t-\sigma}^{t} \dot{x}(\beta) \, d\beta$$
$$= 2x^T(t)X_1 x(t) - 2x^T(t)X_1 x_\sigma(t), \tag{27}$$

$$2x_\sigma^T(t)X_2 \int_{t-\sigma}^{t} \dot{x}(\beta) \, d\beta$$
$$= 2x_\sigma^T(t)X_2 x(t) - 2x_\sigma^T(t)X_2 x_\sigma(t). \tag{28}$$

Likewise, for any matrices Y_1 and Y_2, we have

$$2y^T(t)Y_1 \int_{t-\tau}^{t} \dot{y}(\gamma) \, d\gamma$$
$$= 2y^T(t)Y_1 y(t) - 2y^T(t)Y_1 y(t - \tau), \tag{29}$$

$$2y_\tau^T(t)Y_2 \int_{t-\tau}^{t} \dot{y}(\gamma) \, d\gamma$$
$$= 2y_\tau^T(t)Y_2 y(t) - 2y_\tau^T(t)Y_2 y_\tau(t). \tag{30}$$

It then follows from (22)-(30) that

$$\dot{V}(t) = \sum_{i=1}^{4} \dot{V}_i(t, x(t), y(t))$$
$$\leq \frac{1}{\tau\sigma} \int_{t-\tau}^{t} \int_{t-\sigma}^{t} \eta^T(t, \beta, \gamma) \Xi(\tau, \sigma) \eta(t, \beta, \gamma) \, d\beta \, d\gamma,$$

where

$$\eta(t, \beta, \gamma) = [x^T(t), x_\sigma^T(t), y^T(t), h^T(y(t)), y_\tau^T(t),$$
$$h^T(y_\tau(t)), \dot{x}^T(\beta), \dot{y}^T(\gamma)]^T,$$
$$\Xi(\tau, \sigma) = \begin{bmatrix} \Omega_{11} & \sigma\varrho_1^T & \tau\varrho_2^T \\ \# & -\sigma Q_4 & 0 \\ \# & \# & -\tau Q_5 \end{bmatrix}$$
$$+ \sigma\chi_1^T Q_4^{-1}\chi_1 + \tau\chi_2^T Q_5^{-1}\chi_2,$$

and

$$\varrho_1 = \begin{bmatrix} X_1^T & -X_2^T & 0 & 0 & 0 & 0 \end{bmatrix},$$
$$\varrho_2 = \begin{bmatrix} 0 & 0 & Y_1^T & 0 & -Y_2^T & 0 \end{bmatrix},$$
$$\chi_1 = \begin{bmatrix} Q_4 A & 0 & 0 & 0 & 0 & 0 & -Q_4 W & 0 & 0 \end{bmatrix},$$
$$\chi_2 = \begin{bmatrix} 0 & -Q_5 D & Q_5 B & 0 & 0 & 0 & 0 & 0 \end{bmatrix}.$$

Define

$$\kappa_1 = \begin{bmatrix} X_1^T & -X_2^T & 0 & 0 & 0 & 0 \\ Q_4 A & 0 & 0 & 0 & 0 & -Q_4 W \end{bmatrix},$$
$$\kappa_2 = \begin{bmatrix} 0 & 0 & Y_1^T & 0 & -Y_2^T & 0 \\ 0 & -Q_5 D & Q_5 B & 0 & 0 & 0 \end{bmatrix},$$

then

$$\Omega_{11} + \sigma\kappa_1^T \text{diag}(Q_4^{-1}, Q_4^{-1})\kappa_1 + \tau\kappa_2^T \text{diag}(Q_5^{-1}, Q_5^{-1})\kappa_2$$

is a monotonic increasing matrix function with respect to σ and τ, respectively. Moreover, based on Schur Complement equivalence in [28] and (16), we have $\Xi(\tau, \sigma) < 0$, which further indicates that $\dot{V}(t, x(t), y(t)) < 0$ for any nonzero $\eta(t, \beta, \gamma)$ in (31). Thus, it follows from [29] that the genetic regulatory network in (7) with $w(t) = 0$ is globally asymptotically stable.

Step II. We show that $z(t)$ in (7) satisfies $\int_0^\infty |z(t)|^2 \, dt \leq \rho^2 \int_0^\infty |w(t)|^2 \, dt$. For $\rho > 0$ and $T > 0$, we define

$$J(T) \triangleq \int_0^T [|z(t)|^2 - \rho^2 |w(t)|^2] \, dt.$$

Observing the fact that

$$0 = \int_0^T \frac{\mathrm{d}V(t)}{\mathrm{d}t}\, \mathrm{d}t + V(0) - V(T),$$

where $\frac{\mathrm{d}V(s)}{\mathrm{d}s}$ is the time derivative along the trajectory of network (7), we have

$$
\begin{aligned}
J(T) &= \int_0^T \left[|z(t)|^2 - \rho^2 |w(t)|^2\right]\, \mathrm{d}t \\
&\quad + \int_0^T \frac{\mathrm{d}V(t)}{\mathrm{d}t}\, \mathrm{d}t + V(0) - V(T) \\
&= \int_0^T \left[|z(t)|^2 - \rho^2 |w(t)|^2\right]\, \mathrm{d}t \\
&\quad + \int_0^T \left[2\left(x^T(t)P_{11} + y^T(t)P_{12}^T\right)\right. \\
&\quad \times \left(-Ax(t) + Wh(y_\tau(t)) + G_1\omega(t)\right)]\, \mathrm{d}t \\
&\quad + \int_0^T \left[2\left(x^T(t)P_{12} + y^T(t)P_{22}\right)\right. \\
&\quad \times \left(-By(t) + Dx_\sigma(t) + G_2\omega(t)\right)]\, \mathrm{d}t \\
&\quad + \int_0^T \left[-2h^T(y(t))\Gamma By(t) + 2h^T(y(t))\Gamma Dx_\sigma(t)\right. \\
&\quad + 2h^T(y(t))\Gamma G_2\omega(t)]\, \mathrm{d}t \\
&\quad + \int_0^T \left[x^T(t)Q_1 x(t) - x_\sigma^T(t)Q_1 x_\sigma(t)\right]\, \mathrm{d}t \\
&\quad + \int_0^T \left[y^T(t)Q_2 y(t) - y_\tau^T(t)Q_2 y_\tau(t)\right]\, \mathrm{d}t \\
&\quad + \int_0^T \left[h^T(y(t))Q_3 h(y(t)) - h^T(y_\tau(t))Q_3 h(y_\tau(t))\right]\, \mathrm{d}t \\
&\quad + \int_0^T \int_{t-\sigma}^t \left[\dot{x}^T(t)Q_4 \dot{x}(t) - \dot{x}^T(\beta)Q_4 \dot{x}(\beta)\right]\, \mathrm{d}\beta\, \mathrm{d}t \\
&\quad + \int_0^T \int_{t-\tau}^t \left[\dot{y}^T(t)Q_5 \dot{y}(t) - \dot{y}^T(\gamma)Q_5 \dot{y}(\gamma)\right]\, \mathrm{d}\gamma\, \mathrm{d}t \\
&\quad + V(0) - V(T).
\end{aligned}
$$

Since the initial values φ_x and ψ_y are assumed to be zero, then $V(0) = 0$. In addition, $V(T) \geq 0,\ \forall\ T > 0$. Using a similar method in Step I, we obtain from (11) that $J(T) < 0,\ \forall\ T > 0$. That is, the attenuation level ρ of perturbed genetic regulatory network in (7) is guaranteed, and the proof is thus completed.

ACKNOWLEDGMENTS

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