On the Transient and Steady-State Estimates of Interval Genetic Regulatory Networks

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***Abstract*—This paper is concerned with the transient and steady-state estimates of a class of genetic regulatory networks (GRNs). Some sufficient conditions, which do not only present the transient estimate but also provide the estimates of decay rate and decay coefficient of the GRN with interval parameter uncertainties (interval GRN), are established by means of linear matrix inequality (LMI) and Lyapunov–Krasovskii functional. Moreover, the steady-state estimate of the proposed GRN model is also investigated. Furthermore, it is well known that gene regulation is an intrinsically noisy process due to intracellular and extracellular noise perturbations and environmental fluctuations. Then, by utilizing stochastic differential equation theory, the obtained results are extended to the case with noise perturbations due to natural random fluctuations. All the conditions are expressed within the framework of LMIs, which can easily be computed by using standard numerical software. A three-gene network is provided to illustrate the effectiveness of the theoretical results.**

***Index Terms*—Exponential estimate, genetic regulatory network (GRN), interval system, steady-state estimate, stochastic perturbation.**

I. Introduction

GENES are the units of heredity in living organisms and play an important role in the control of cellular processes, such as the response of a cell to external signals, the differentiation of cells in the unfolding of developmental programs, and the replication of the deoxyribonucleic acid preceding cell division [1]. As systems biology emerges in the postgenomic era, one of its main challenges has been to understand the gene functions and regulations at the system level, e.g., how proteins are synthesized from genes as transcription factors binding to regulatory sites of other genes and how they interact with each other and with other substances in the cell to perform complicated biological functions. These molecules and their interactions compose a complex network that is known as genetic regulatory network (GRN).

Recent years have witnessed tremendous developments in the research field of genetic regulatory systems, and the development of modeling techniques has made it possible to introduce computational and mathematical methods for investigating the GRNs [2]–[4]. Until now, a large variety of formalisms have been proposed to model, analyze, and simulate GRNs, such as directed graphs, Bayesian networks, Boolean networks, Petri nets, and differential equations (see [3], [4], and the references therein for a wider categorization of gene network models). Mathematical modeling of genetic networks as dynamic systems provides a powerful tool for studying gene regulation processes in living organisms since genetic networks are biochemically dynamic [5]. The most frequently chosen mathematical models of developmental processes have been those described by differential equations where the variables represent concentrations of messenger ribonucleic acids (mRNAs), proteins, or small molecules, which can better show the accurate status of the gene products and understand the dynamic behavior of biological systems in detail [6]. In addition, since GRNs are high-dimensional and nonlinear systems, it is necessary to investigate the network dynamics from the viewpoint of the nonlinear system theory [7]–[9].

On the other hand, it is well known that cells are intrinsically noisy biochemical reactors, and even a small number of reactants can lead to significant statistical fluctuations in molecule numbers and reaction rates [10], [11]. Indeed, gene regulation is an intrinsically noisy process due to intracellular and extracellular noise perturbations and environmental fluctuations [11]–[18]. It is observed that a given gene-expression state may generate more than one successive gene-expression state, which implies that different cells of the same population could follow different gene-expression paths [19]. As a result of these considerations, a stochastic model more accurately describes the dynamics of gene regulation than a deterministic model. To study the origins of noise in gene expression, McAdams and Arkin proposed a stochastic model for gene expression in prokaryotes [14], and stochastic differential equations have been applied in stochastic simulations based on the chemical master equation [20]. Recently, Xu and Tao investigated the steady-state statistics of a single-gene auto-regulatory genetic network with additive external Gaussian white noises and showed that the negative (positive) feedback will result in the mRNA noise having a positive (negative) contribution to the protein noise [18]. The fuzzy approximation method was applied to investigate the stability and noise-filtering schemes of gene networks under stochastic molecular noises in [21]. The filtering problem from gene-expression time-series data with variance constraints was investigated in [22], and the stochastic modeling of GRNs from gene time-series data was proposed by applying the expectation maximization algorithm in [23].

Recently, by extracting functional information from observable data, significant advances on discovering the structure of the genetic network have been made, and deeper insights have been gained on both the static and dynamic behaviors of genetic networks. Similar to other dynamic systems [24]–[26], stability is a natural requirement for GRNs with clear biological

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significance [27]. On the other hand, it is also observed that time delays are present during the slow reaction process, such as transcription, translation, and translocation involving multistage reactions in genetic networks [28]. It has been shown in [29], by mathematically modeling observation data, that the oscillatory expression of three proteins is likely to be the consequence of transcriptional delays. In fact, delay is often the key factor to the instability of a given system and plays an important role in the analysis of gene regulation dynamics. The theoretical results obtained for gene networks with or without time delays are scattered in the literature. To mention a few, a simple gene circuit has been designed and studied for testing the role of negative feedback in the stability analysis of gene networks, which consists of a regulator and transcriptional repressor modules in *Escherichia coli* [30]. Considering the fact that a genetic network is composed of a number of molecules that interact and regulate the expression of other genes by proteins, the authors presented a GRN model described by a delay differential equation and studied the local stability by using the characteristic equation analysis in [8]. A nonlinear model for GRNs with SUM regulatory functions was proposed in the form of the Lur'e system, and sufficient conditions for ensuring the stability of the gene networks were also derived in terms of linear matrix inequalities (LMIs) in [9]. Moreover, it has been well known in the area of cancer therapy that the increase in drug dosage and concentration will increase the rate of exponential decay of the cell population (or concentration) in [31], which is desirable in practical applications; in addition, from the viewpoint of potential applications, the study of exponential stability is more important and meaningful since the dynamic process of a gene network can more clearly be characterized once the decay rate is determined, which could provide better understanding of the mechanism of the interactions between biochemical molecules. To the best of the authors' knowledge, this is the first time to investigate the stability of the GRN model with exponential estimates proposed in this paper.

In addition, it is generally assumed that the numerical values of system parameters, such as kinetic reaction rate constants, are precisely known. However, given the fact that GRNs are modeled from the real-world gene-expression time-series data, as well as the current limitations of experimental techniques, it has been well recognized that the modeling error and parameter fluctuation are unavoidable, which may result in instability and poor performance of the real genetic network. Specifically, it is very likely that the parameters of the model identified from the experimental data will vary from time to time, and such variations may be bounded but unknown. In other words, "parameter uncertainties" should exist in those models that are constructed from real-time data. However, unfortunately, the stability analysis for GRNs with interval uncertainties has not been studied yet and still remains an open research problem.

Moreover, when investigating the robust stability of the genetic network and some other networks, such as neural networks, the following approach is usually applied, for a given network model, one usually shifts the equilibrium to the origin, and obtains the new model with zero point as its equilibrium, then studies the robust stability of the transformed system [32], [33]. However, such a methodology is not precise due to the fact that the equilibrium of the network should heavily be dependent on the parameter uncertainties, which means that the parameter uncertainties of the GRN will result in variation of the equilibrium. Thus, a natural but important question we should ask is the following: when the perturbed network eventually achieves the steady state, how far is it from the steady state of the nominal network?

Motivated by the preceding discussions, in this paper, we deal with the problem of robust stability analysis for the interval GRN model, in which the values of the parameters are not exactly known but bounded in given compact sets. Several criteria are presented to ensure the robust exponential stability of the proposed model with/without noise perturbation, and the estimates of decay rate and decay coefficient are established for the first time by means of LMI techniques. Furthermore, the steady-state estimate of the GRNs with parameter uncertainties is also analyzed. Note that the obtained results are formulated in terms of LMIs, which can easily be checked by standard software (such as Matlab), and no tuning of parameters is required [34]. A numerical example is provided to show the effectiveness of the proposed conditions.

Notations: $\mathbb{R}^n$ and $\mathbb{R}^{m\times n}$ denote the n-column vectors and the set of all $m \times n$ real matrices, respectively. For any real symmetric matrices P and Q, the notation $P \geq Q$ ($P > Q$) means that matrix $P - Q$ is positive semidefinite (positive definite). $|\cdot|$ denotes the Euclidean norm for vectors, and $\|\cdot\|$ denotes the spectral norm for matrices; $\lambda_{\max}(M)$ and $\lambda_{\min}(M)$ denote the maximal and minimal eigenvalues of real matrix M, respectively. Superscript "T" represents the matrix transpose, and the asterisk $*$ is used to denote a matrix that can be inferred by symmetry. $\mathcal{C}([-\tau, 0], \mathbb{R}^n)$ denotes the family of continuous functions ϕ from $[-\tau, 0]$ to $\mathbb{R}^n$ with norm $|\phi|_\tau = \sup_{-\tau\leq s\leq 0} |\phi(s)|$. Matrix dimensions, if not explicitly stated, are assumed to be compatible for algebraic operations.

II. Model Description and Preliminaries

Being arguably the most widespread formalism for modeling dynamic systems in science and engineering, ordinary differential equations have extensively been applied to analyze genetic regulatory systems. Cherry and Adler investigated a single-gene auto-regulatory genetic network in the following form [35]:

$$\begin{cases} \frac{dm(t)}{dt} = -\gamma m(t) + f(p) \\ \frac{dp(t)}{dt} = -\gamma' p(t) + k' m(t) \end{cases}$$

where $m(t)$ and $p(t)$ are the concentrations of mRNA and protein at time t, respectively; γ and γ' are the rates of degradation of mRNA and protein, respectively; k' is the translation rate; and function $f(p)$ represents the feedback regulation of the protein on transcription. Considering the existence of transmission delays in the process of biological reactions, Monk studied the following model [36]:

$$\begin{cases} \frac{dm(t)}{dt} = -\gamma m(t) + \beta f(p - t_m) \\ \frac{dp(t)}{dt} = -\gamma' p(t) + k' m(t - t_p) \end{cases}$$

and numerically presented that the observed oscillatory expression and activity of the proteins was most likely to be driven by transcriptional delays. Moreover, it is well known that a genetic network is composed of a number of molecules that interact and regulate the expression of other genes by proteins; thus, in this paper, we consider the GRN model with n

mRNAs and proteins described by delay differential equations (1) shown at the bottom of the page, where $m_i(t)$ and $p_i(t)$ denote the concentrations of mRNA and protein of the ith gene at time t, respectively; a_i and c_i are the degradation rates of mRNA and protein, respectively; d_i represents the translation rate; and f_i is the feedback regulation of the protein on the transcription, which is usually a nonlinear function but has a form of monotonicity with each variable [2], [37]. Generally, f_i could be complicated, depending on the biological reactions in the process of gene expression. Here, we assume that the regulation function is of the form $f_i(p_1(t), p_2(t), \ldots, p_n(t)) = \sum_{j=1}^{n} f_{ij}(p_j(t))$, which is also called the SUM logic, i.e., each transcription factor additively acts to regulate the ith gene [9].

Due to the observation of rapid changes in many biochemical networks when a threshold parameter is exceeded, regulatory function $f_{ij}(p_j(t))$ can usually be described in the Hill form, which has been found to adequately represent the experimental results as follows [37]:

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

where H_j is the Hill coefficient, $\beta_j > 0$ is a scalar, and $\alpha_{ij} > 0$ denotes the transcriptional rate of transcription factor j to gene i. Noting the fact

$$\frac{1}{1+(p_j(t)/\beta_j)^{H_j}} = 1 - \frac{(p_j(t)/\beta_j)^{H_j}}{1+(p_j(t)/\beta_j)^{H_j}} \tag{3}$$

then system (1) can be rewritten as (4) shown at the bottom of the page, where $g_j(s)=(s/\beta_j)^{H_j}/(1+(s/\beta_j)^{H_j})$, $B=(b_{ij})_{n\times n}$ is known as the coupling matrix of the genetic network defined by

$$b_{ij} = \begin{cases}\alpha_{ij}, & \text{if transcription factor } j \\ & \text{is an activator of gene } i \\ 0, & \text{if there is no connection} \\ & \text{between } j \text{ and } i \\ -\alpha_{ij}, & \text{if transcription factor } j \\ & \text{is a repressor of gene } i\end{cases} \tag{5}$$

and $u_i = \sum_{j\in V_i}\alpha_{ij} = -\sum_{j\in V_i} b_{ij}$, where V_i denotes the set of transcription factors, which are the repressors of gene i (see [8], [9], and the references therein for details and illustrations of the modeling mechanism of this gene network).

For simplicity, assume $\tau_1 = \cdots = \tau_n = \tau$ and $\sigma_1 = \cdots = \sigma_n = \sigma$; then, system (4) can be described by the following compact matrix form:

$$\begin{cases}\frac{dm(t)}{dt} = -Am(t) + Bg\left(p(t-\tau)\right) + u_B \\ \frac{dp(t)}{dt} = -Cp(t) + Dm(t-\sigma)\end{cases} \tag{6}$$

where $m(t) = [m_1(t), m_2(t), \ldots, m_n(t)]^T$, $p(t) = [p_1(t), p_2(t), \ldots, p_n(t)]^T$, $A = \mathrm{diag}(a_1, a_2, \ldots, a_n)$, $C = \mathrm{diag}(c_1, c_2, \ldots, c_n)$, $D = \mathrm{diag}(d_1, d_2, \ldots, d_n)$, $g(p(t)) = [g_1(p_1(t)), g_2(p_2(t)), \ldots, g_n(p_n(t))]^T$, and $u_B = [u_1, u_2, \ldots, u_n]^T$.

Remark 1: A three-gene network modeling the repressilator in *Escherichia coli* has been proposed in [38], which can be viewed as a special case of model (6). Such kind of model has also been studied in [9], [17], and [27]. In addition, we wish to point out that the main results of this paper can easily be extended to the case where time delays are different from each other.

The initial condition of the GRN in (6) is assumed to be

$$m(t) = \varphi(t) \quad p(t) = \psi(t), \qquad -\rho \le t \le 0;\ \rho \triangleq \max(\sigma, \tau)$$

where φ and ψ are positive continuous functions. Here, matrices A, B, C, and D are unknown but bounded, which are assumed to satisfy

$$A \in A_I \quad B \in B_I \quad C \in C_I \quad D \in D_I \tag{7}$$

where

$$\begin{aligned} A_I &= \{A \,|\, 0 < \underline{a}_i \le a_i \le \overline{a}_i, \qquad i = 1, 2, \ldots, n\} \\ B_I &= \{B \,|\, \underline{b}_{ij} \le b_{ij} \le \overline{b}_{ij}, \qquad i, j = 1, 2, \ldots, n\} \\ C_I &= \{C \,|\, 0 < \underline{c}_i \le c_i \le \overline{c}_i, \qquad i = 1, 2, \ldots, n\} \\ D_I &= \{D \,|\, \underline{d}_i \le d_i \le \overline{d}_i, \qquad i = 1, 2, \ldots, n\}. \end{aligned}$$

Let (m^*, p^*) be an equilibrium point of system (6), i.e., they satisfy

$$\begin{cases} -Am^* + Bg(p^*) + u_B = 0 \\ -Cp^* + Dm^* = 0. \end{cases} \tag{8}$$

Then, we have $|\varphi - m^*|_\rho^2 = \sup_{s\in[-\rho,0]} |\varphi(s) - m^*|^2$ and $|\psi - p^*|_\rho^2 = \sup_{s\in[-\rho,0]} |\psi(s) - p^*|^2$.

If there are no parameter uncertainties in GRN model (6), then the system in (6) will reduce to the nominal case, and the corresponding system is called the nominal system of (6).

$$\begin{cases}\frac{dm_i(t)}{dt} = -a_i m_i(t) + f_j\left(p_1(t-\tau_1), p_2(t-\tau_2), \ldots, p_n(t-\tau_n)\right) \\ \frac{dp_i(t)}{dt} = -c_i p_i(t) + d_i m_i(t-\sigma_i), \qquad i = 1, 2, \ldots, n\end{cases} \tag{1}$$

$$\begin{cases}\frac{dm_i(t)}{dt} = -a_i m_i(t) + \sum_{j=1}^{n} b_{ij} g_j\left(p_j(t-\tau_j)\right) + u_i \\ \frac{dp_i(t)}{dt} = -c_i p_i(t) + d_i m_i(t-\sigma_i), \qquad i = 1, 2, \ldots, n\end{cases} \tag{4}$$

Definition 1: The nominal system of (6) is said to be globally exponentially stable if there exist two constants, $\lambda > 0$ and $\mu \geq 1$, such that

$$|m(t)-m^*|^2+|p(t)-p^*|^2 \leq \mu e^{-\lambda t}\left(|\varphi-m^*|_\rho^2+|\psi-p^*|_\rho^2\right)$$

where λ and μ are called the decay rate and decay coefficient of system (6), respectively. In addition, the nominal system of (6) is said to be globally λ-exponentially stable if it is globally exponentially stable with a decay rate not less than λ.

Definition 2: The uncertain system in (6) is said to be globally robustly λ-exponentially stable if system (6) is globally λ-exponentially stable for all admissible uncertainties (7).

In the following, we will shift the equilibrium (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

$$\begin{cases} \frac{dx(t)}{dt} = -Ax(t) + Bh\left(y(t-\tau)\right) \\ \frac{dy(t)}{dt} = -Cy(t) + Dx(t-\sigma) \end{cases} \tag{9}$$

where $h(y(t)) = [h_1(y_1(t)), h_2(y_2(t)), \ldots, h_n(y_n(t))]^T$, with $h_i(y_i(t)) = g_i(y_i(t) + p_i^*) - g_i(p_i^*)$.

Since g_i is a monotonically increasing and differentiable function with saturation, it satisfies $0 \leq dg_i(s)/ds \leq k_i$, which is equivalent to

$$0 \leq \frac{g_i(s_1) - g_i(s_2)}{s_1 - s_2} \leq k_i, \qquad i = 1, 2, \ldots, n$$

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

$$h_i(s)(h_i(s) - k_i s) \leq 0, \qquad i = 1, 2, \ldots, n \tag{10}$$

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

Remark 2: It should be noted that condition (10) is more general than those in [9] and [17], where the derivative of each regulatory function is assumed to be bounded by a scalar k. However, from the viewpoint of gene expression, the regulation function of each protein g_i may be different from each other; thus, the assumption in [9] and [17] may not be valid, which implies that the results obtained in this paper are more general.

Our goals are to present some sufficient criteria to ensure the global robust stability and give the exponential and steady-state estimates of the proposed GRN model in the form of LMIs. To this end, we shall give the following notations and lemma, which will be applied in the following:

$$\begin{aligned}
&\underline{A} = \mathrm{diag}(\underline{a}_1, \underline{a}_2, \ldots, \underline{a}_n) \quad \overline{A} = \mathrm{diag}(\overline{a}_1, \overline{a}_2, \ldots, \overline{a}_n) \\
&\underline{B} = (\underline{b}_{ij})_{n\times n} \quad \overline{B} = (\overline{b}_{ij})_{n\times n} \\
&\underline{C} = \mathrm{diag}(\underline{c}_1, \underline{c}_2, \ldots, \underline{c}_n) \quad \overline{C} = \mathrm{diag}(\overline{c}_1, \overline{c}_2, \ldots, \overline{c}_n) \\
&\underline{D} = \mathrm{diag}(\underline{d}_1, \underline{d}_2, \ldots, \underline{d}_n) \quad \overline{D} = \mathrm{diag}(\overline{d}_1, \overline{d}_2, \ldots, \overline{d}_n) \\
&A_0 = \frac{1}{2}(\overline{A} + \underline{A}) \quad B_0 = \frac{1}{2}(\overline{B} + \underline{B}) \\
&A_1 = \frac{1}{2}(\overline{A} - \underline{A}) \triangleq \mathrm{diag}(\tilde{a}_1, \tilde{a}_2, \ldots, \tilde{a}_n) \\
&C_0 = \frac{1}{2}(\overline{C} + \underline{C}) \quad D_0 = \frac{1}{2}(\overline{D} + \underline{D})
\end{aligned}$$

$$\begin{aligned}
&B_1 = \frac{1}{2}(\overline{B} - \underline{B}) \triangleq (\tilde{b}_{ij})_{n\times n} \\
&C_1 = \frac{1}{2}(\overline{C} - \underline{C}) \triangleq \mathrm{diag}(\tilde{c}_1, \tilde{c}_2, \ldots, \tilde{c}_n) \\
&D_1 = \frac{1}{2}(\overline{D} - \underline{D}) \triangleq \mathrm{diag}(\tilde{d}_1, \tilde{d}_2, \ldots, \tilde{d}_n).
\end{aligned}$$

Obviously, each element of A_1, B_1, C_1, and D_1 is nonnegative, then, we denote

$$\begin{aligned}
E_A &= \mathrm{diag}\left(\sqrt{\tilde{a}_1}, \sqrt{\tilde{a}_2}, \ldots, \sqrt{\tilde{a}_n}\right) \\
E_B &= \left[\sqrt{\tilde{b}_{11}}e_1, \ldots, \sqrt{\tilde{b}_{1n}}e_1, \ldots, \sqrt{\tilde{b}_{n1}}e_n, \ldots, \sqrt{\tilde{b}_{nn}}e_n\right]_{n\times n^2} \\
F_B &= \left[\sqrt{\tilde{b}_{11}}e_1, \ldots, \sqrt{\tilde{b}_{1n}}e_n, \ldots, \sqrt{\tilde{b}_{n1}}e_1, \ldots, \sqrt{\tilde{b}_{nn}}e_n\right]^T_{n^2\times n} \\
E_C &= \mathrm{diag}\left(\sqrt{\tilde{c}_1}, \sqrt{\tilde{c}_2}, \ldots, \sqrt{\tilde{c}_n}\right) \\
E_D &= \mathrm{diag}\left(\sqrt{\tilde{d}_1}, \sqrt{\tilde{d}_2}, \ldots, \sqrt{\tilde{d}_n}\right)
\end{aligned}$$

where $e_i \in \mathbb{R}^n$ is the column vector with the ith element 1 and 0 elsewhere. Furthermore, let

$$\begin{aligned}
\mathbf{\Delta} &= \left\{\Delta \in \mathbb{R}^{n\times n} \,|\, \Delta = \mathrm{diag}(\delta_1, \delta_2, \ldots, \delta_n), \quad |\delta_i| \leq 1\right\} \\
\mathbf{\Omega} &= \Big\{\Omega \in \mathbb{R}^{n^2\times n^2} | \Omega = \mathrm{diag}(\omega_{11}, \ldots, \omega_{1n}, \ldots, \omega_{n1}, \ldots, \omega_{nn}), \\
&\qquad\qquad |\omega_{ij}| \leq 1 \qquad \forall\, i, j = 1, 2, \ldots, n\Big\}.
\end{aligned}$$

Then, through simple manipulations, we deduce that

$$\begin{aligned}
A_I &= \{A = A_0 + E_A\Delta_A E_A \,|\, \Delta_A \in \mathbf{\Delta}\} \\
B_I &= \{B = B_0 + E_B\Omega_B F_B \,|\, \Omega_B \in \mathbf{\Omega}\} \\
C_I &= \{C = C_0 + E_C\Delta_C E_C \,|\, \Delta_C \in \mathbf{\Delta}\} \\
D_I &= \{D = D_0 + E_D\Delta_D E_D \,|\, \Delta_D \in \mathbf{\Delta}\}.
\end{aligned}$$

Lemma 1 [39]: Assume that H, D, and E are real matrices with appropriate dimensions and $F(t)$ is a real matrix function satisfying $F^T(t)F(t) \leq I$. Then

1) $H + DF(t)E + (DF(t)E)^T < 0$ holds if and only if there exists a scalar $\epsilon > 0$ satisfying $H + \epsilon DD^T + (1/\epsilon)E^TE < 0$.
2) For $\varepsilon > 0$, we have $DF(t)E + (DF(t)E)^T \leq \varepsilon DD^T + (1/\varepsilon)E^TE$.

III. Main Results

In this section, we first present the exponential estimates of GRN model (6) by using Lyapunov functional methods and give the estimates of the steady states between the nominal and perturbed networks; furthermore, based on the preceding analysis, we introduce noise perturbations to model (9) and obtain some sufficient criteria to ensure the exponential stability of the proposed GRN model by virtue of stochastic functional differential equation theory.

A. Exponential and Steady-State Estimates of GRNs Without Noise Perturbations

In this section, we shall first investigate the global exponential stability of GRN model (6) and then reduce it to the

case when there are no parameter uncertainties of system (6), a sufficient condition is summarized in Theorem 1.

Theorem 1: For a prescribed $\lambda > 0$, if there exist matrices $P_1 > 0$, $P_2 > 0$, $Q_1 > 0$, and $Q_2 > 0$; a diagonal matrix $\Gamma = \mathrm{diag}(\gamma_1, \gamma_2, \ldots, \gamma_n) > 0$; and scalars $\varepsilon_i > 0$, $i = 1, \ldots, 5$, satisfying the LMI in (11), shown at the bottom of the page, where

$$\Phi_{11} = \lambda P_1 - P_1 A_0 - A_0 P_1 + P_2 + \varepsilon_1 E_A^T E_A \tag{12}$$
$$\Phi_{22} = -e^{-\lambda\overline{\sigma}} P_2 + \varepsilon_3 E_D^T E_D \tag{13}$$
$$\Phi_{33} = \lambda Q_1 - Q_1 C_0 - C_0 Q_1 + \varepsilon_4 E_C^T E_C + 2\lambda K\Gamma \tag{14}$$
$$\Phi_{44} = -2K^{-1}\Gamma C_0 + Q_2 + \varepsilon_5 E_C^T E_C \tag{15}$$
$$\Phi_{55} = -e^{-\lambda\overline{\tau}} Q_2 + \varepsilon_2 F_B^T F_B \tag{16}$$

then the interval genetic network in (6) is globally robustly λ-exponentially stable for any σ and τ satisfying $0 < \sigma \le \overline{\sigma}$ and $0 < \tau \le \overline{\tau}$.

Proof: It can be seen from (11) and the Schur complement in [34] that

$$\begin{bmatrix} H_{11} & 0 & 0 & 0 & P_1 B_0 \\ * & \Phi_{22} & D_0^T Q_1 & D_0^T \Gamma & 0 \\ * & * & H_{33} & 0 & 0 \\ * & * & * & H_{44} & 0 \\ * & * & * & * & \Phi_{55} \end{bmatrix} + \begin{pmatrix} 0 \\ 0 \\ Q_1 E_D \\ \Gamma E_D \\ 0 \end{pmatrix} \varepsilon_3^{-1} \begin{pmatrix} 0 & 0 & E_D^T Q_1 & E_D^T \Gamma & 0 \end{pmatrix} < 0 \tag{17}$$

where

$$H_{11} = \Phi_{11} + \varepsilon_1^{-1} P_1 E_A E_A^T P_1 + \varepsilon_2^{-1} P_1 E_B E_B^T P_1$$
$$H_{33} = \Phi_{33} + \varepsilon_4^{-1} Q_1 E_C E_C^T Q_1$$
$$H_{44} = \Phi_{44} + \varepsilon_5^{-1} K^{-1}\Gamma E_C E_C^T \Gamma K^{-1}.$$

By Lemma 1, it is easy to have

$$-P_1 E_A \Delta_A E_A - (E_A \Delta_A E_A)^T P_1 \le \varepsilon_1 E_A^T E_A + \varepsilon_1^{-1} P_1 E_A E_A^T P_1 \tag{18}$$
$$-Q_1 E_C \Delta_C E_C - (E_C \Delta_C E_C)^T Q_1 \le \varepsilon_4 E_C^T E_C + \varepsilon_4^{-1} Q_1 E_C E_C^T Q_1 \tag{19}$$
$$-K^{-1}\Gamma E_C \Delta_C E_C - (E_C \Delta_C E_C)^T \Gamma K^{-1} \le \varepsilon_5 E_C^T E_C + \varepsilon_5^{-1} K^{-1}\Gamma E_C E_C^T \Gamma K^{-1} \tag{20}$$

$$\begin{bmatrix} 0 & P_1 E_B \Omega_B F_B \\ (E_B \Omega_B F_B)^T P_1 & 0 \end{bmatrix} \le \begin{bmatrix} \varepsilon_2^{-1} P_1 E_B E_B^T P_1 & 0 \\ 0 & \varepsilon_2 F_B^T F_B \end{bmatrix} \tag{21}$$

$$\begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & (E_D \Delta_D E_D)^T Q_1 & (E_D \Delta_D E_D)^T \Gamma & 0 \\ 0 & * & 0 & 0 & 0 \\ 0 & * & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix} = \xi_{11}^T \Delta_D \xi_{22} + \left(\xi_{11}^T \Delta_D \xi_{22}\right)^T \le \varepsilon_3 \xi_{11}^T \xi_{11} + \varepsilon_3^{-1} \xi_{22}^T \xi_{22} \tag{22}$$

where

$$\xi_{11} = \begin{pmatrix} 0 & E_D & 0 & 0 & 0 \end{pmatrix}$$
$$\xi_{22} = \begin{pmatrix} 0 & 0 & E_D^T Q_1 & E_D^T \Gamma & 0 \end{pmatrix}.$$

Then, it follows from (17)–(22) that

$$\Pi(\overline{\sigma}, \overline{\tau}) = \begin{bmatrix} S_{11} & 0 & 0 & 0 & P_1 B \\ * & -e^{-\lambda\overline{\sigma}} P_2 & D^T Q_1 & D^T \Gamma & 0 \\ * & * & S_{33} & 0 & 0 \\ * & * & * & -2K^{-1}\Gamma C + Q_2 & 0 \\ * & * & * & * & -e^{-\lambda\overline{\tau}} Q_2 \end{bmatrix} < 0 \tag{23}$$

with

$$S_{11} = \lambda P_1 - P_1 A - A P_1 + P_2$$
$$S_{33} = \lambda Q_1 - Q_1 C - C Q_1 + 2\lambda K\Gamma.$$

Consider the following Lyapunov–Krasovskii functional candidate for system (9):

$$V(t, x(t), y(t)) = V_1(t, x(t), y(t)) + V_2(t, y(t)) + V_3(t, x(t), y(t)) \tag{24}$$

where

$$V_1(t, x(t), y(t)) = e^{\lambda t} x^T(t) P_1 x(t) + e^{\lambda t} y^T(t) Q_1 y(t)$$
$$V_2(t, y(t)) = 2e^{\lambda t} \sum_{i=1}^{n} \gamma_i \int_0^{y_i(t)} h_i(s) ds$$

$$M = \begin{bmatrix} \Phi_{11} & 0 & 0 & 0 & P_1 B_0 & P_1 E_A & P_1 E_B & 0 & 0 & 0 \\ * & \Phi_{22} & D_0^T Q_1 & D_0^T \Gamma & 0 & 0 & 0 & 0 & 0 & 0 \\ * & * & \Phi_{33} & 0 & 0 & 0 & 0 & Q_1 E_D & Q_1 E_C & 0 \\ * & * & * & \Phi_{44} & 0 & 0 & 0 & \Gamma E_D & 0 & K^{-1}\Gamma E_C \\ * & * & * & * & \Phi_{55} & 0 & 0 & 0 & 0 & 0 \\ * & * & * & * & * & -\varepsilon_1 I & 0 & 0 & 0 & 0 \\ * & * & * & * & * & * & -\varepsilon_2 I & 0 & 0 & 0 \\ * & * & * & * & * & * & * & -\varepsilon_3 I & 0 & 0 \\ * & * & * & * & * & * & * & * & -\varepsilon_4 I & 0 \\ * & * & * & * & * & * & * & * & * & -\varepsilon_5 I \end{bmatrix} < 0 \tag{11}$$

$$V_3(t,x(t),y(t)) = \int_{t-\sigma}^{t} e^{\lambda s} x^T(s) P_2 x(s) ds + \int_{t-\tau}^{t} e^{\lambda s} h^T(y(s)) Q_2 h(y(s)) ds.$$

Calculating the derivative of $V(t,x(t),y(t))$ along the trajectory of system (9) with respect to t, one has

$$\begin{aligned}\dot{V}_1(t) =& e^{\lambda t}\left[x^T(t)\lambda P_1 x(t) + 2x^T(t)P_1\dot{x}(t) + y^T(t)\lambda Q_1 y(t) + 2y^T(t)Q_1\dot{y}(t)\right] \\ =& e^{\lambda t}\left[x^T(t)(\lambda P_1 - P_1 A - A P_1)x(t) + 2x^T(t)P_1 B h(y(t-\tau)) + y^T(t)(\lambda Q_1 - Q_1 C - C Q_1)y(t) + 2y^T(t)Q_1 D x(t-\sigma)\right] \quad (25)\\ \dot{V}_2(t) =& 2\lambda e^{\lambda t}\sum_{i=1}^{n}\gamma_i \int_0^{y_i(t)} h_i(s)ds + 2e^{\lambda t}h^T(y(t))\Gamma\dot{y}(t) \\ \le& e^{\lambda t}\left[-2h^T(y(t))\Gamma C y(t) + 2h^T(y(t))\Gamma D x(t-\sigma) + 2\lambda h^T(y(t))\Gamma y(t)\right] \quad (26)\\ \dot{V}_3(t) =& e^{\lambda t}\left[x^T(t)P_2 x(t) - e^{-\lambda\sigma}x^T(t-\sigma)P_2 x(t-\sigma) + h^T(y(t))Q_2 h(y(t)) - e^{-\lambda\tau}h^T(y(t-\tau))Q_2 h(y(t-\tau))\right]. \quad (27)\end{aligned}$$

In addition, condition (10) yields

$$\begin{aligned}-2h^T(y(t))\Gamma C y(t) \le& -2h^T(y(t))\Gamma C K^{-1} h(y(t)) \quad (28)\\ 2\lambda h^T(y(t))\Gamma y(t) \le& 2\lambda y^T(t) K \Gamma y(t). \quad (29)\end{aligned}$$

The relations from (25) to (29) lead to

$$\begin{aligned}\dot{V}(t) =& \dot{V}_1(t) + \dot{V}_2(t) + \dot{V}_3(t) \\ \le& e^{\lambda t}\left[x^T(t)\left(\lambda P_1 - P_1 A - A P_1 + P_2\right)x(t) + 2x^T(t)P_1 B h(y(t-\tau)) + y^T(t)(\lambda Q_1 - Q_1 C - C Q_1)y(t) + 2y^T(t)Q_1 D x(t-\sigma) + h^T(y(t))\left(-2\Gamma C K^{-1} + Q_2\right)h(y(t)) + 2h^T(y(t))\Gamma D x(t-\sigma) + 2\lambda y^T(t)K\Gamma y(t) - e^{-\lambda\sigma}x^T(t-\sigma)P_2 x(t-\sigma) - e^{-\lambda\tau}h^T(y(t-\tau))Q_2 h(y(t-\tau))\right] \\ =& e^{\lambda t}\eta^T(t)\Pi(\sigma,\tau)\eta(t) \quad (30)\end{aligned}$$

where

$$\eta(t) = \left[x^T(t), x^T(t-\sigma), y^T(t), h^T(y(t)), h^T(y(t-\tau))\right]$$

and

$$\Pi(\sigma,\tau) = \begin{bmatrix} S_{11} & 0 & 0 & 0 & P_1 B \\ * & -e^{-\lambda\sigma}P_2 & D^T Q_1 & D^T\Gamma & 0 \\ * & * & S_{33} & 0 & 0 \\ * & * & * & -2\Gamma C K^{-1} + Q_2 & 0 \\ * & * & * & * & -e^{-\lambda\tau}Q_2 \end{bmatrix}. \quad (31)$$

Since $\Pi(\sigma,\tau) \le \Pi(\overline{\sigma},\overline{\tau})$ for any $0 < \sigma \le \overline{\sigma}$ and $0 < \tau \le \overline{\tau}$, (30) and (31), together with (23), yield $\dot{V}(t) \le 0$.

On the other hand, from the definition of $V(t,x(t),y(t))$, it is not difficult to obtain the following inequalities:

$$\begin{aligned}&V_1(t,x(t),y(t)) \le e^{\lambda t}\left(\|P_1\|\,|x(t)|^2 + \|Q_1\|\,|y(t)|^2\right) \\ &V_2(t,x(t),y(t)) \le 2e^{\lambda t}y^T(t)\Gamma h(y(t)) \le 2e^{\lambda t}\|\Gamma K\|\,|y(t)|^2 \\ &V_3(t,x(t),y(t)) \le \|P_2\|\cdot\sup_{t-\sigma\le s\le t}|x(s)|^2\int_{t-\sigma}^{t}e^{\lambda s}ds + \|Q_2\|\cdot\sup_{t-\tau\le s\le t}|h(y(s))|^2\int_{t-\tau}^{t}e^{\lambda s}ds \\ &= e^{\lambda t}\left[\frac{1-e^{-\lambda\sigma}}{\lambda}\|P_2\|\cdot\sup_{t-\sigma\le s\le t}|x(s)|^2 + \frac{1-e^{-\lambda\tau}}{\lambda}\|Q_2\|\|K\|^2\cdot\sup_{t-\tau\le s\le t}|y(s)|^2\right].\end{aligned}$$

Thus, we obtain

$$\begin{aligned}V(t,x(t),y(t)) \le& V(0) \le \|P_1\|\,|x(0)|^2 + \|Q_1\|\,|y(0)|^2 + 2\|\Gamma K\|\,|y(0)|^2 + \frac{1-e^{-\lambda\sigma}}{\lambda}\|P_2\|\sup_{-\sigma\le s\le 0}|x(s)|^2 + \frac{1-e^{-\lambda\tau}}{\lambda}\|Q_2\|\|K\|^2\sup_{-\tau\le s\le 0}|y(s)|^2 \\ \le& \mu_1|\varphi - m^*|_\rho^2 + \mu_2|\psi - p^*|_\rho^2 \quad (32)\end{aligned}$$

where

$$\mu_1 = \left(\|P_1\| + \frac{1-e^{-\lambda\sigma}}{\lambda}\|P_2\|\right)$$
$$\mu_2 = \left(\|Q_1\| + 2\|\Gamma K\| + \frac{1-e^{-\lambda\tau}}{\lambda}\|Q_2\|\|K\|^2\right).$$

Inequality (32), together with $e^{\lambda t}(\lambda_{\min}(P_1)|x(t)|^2 + \lambda_{\min}(Q_1)|y(t)|^2) \le V(t,x(t),y(t))$, yields

$$|m(t) - m^*|^2 + |p(t) - p^*|^2 \le \mu e^{-\lambda t}\left(|\varphi - m^*|_\rho^2 + |\psi - p^*|_\rho^2\right)$$

where

$$\mu = \frac{\max\{\mu_1,\mu_2\}}{\min\{\lambda_{\min}(P_1),\lambda_{\min}(Q_1)\}}. \quad (33)$$

Therefore, the interval genetic network (6) is globally robustly stable with decay rate λ. This completes the proof. ■

Assume that the nominal system of (6) takes the following form:

$$\begin{cases}\frac{dm(t)}{dt} = -A_0 m(t) + B_0 g(p(t-\tau)) + u_{B_0} \\ \frac{dp(t)}{dt} = -C_0 p(t) + D_0 m(t-\sigma),\end{cases} \quad (34)$$

For the nominal system in (34), according to Theorem 1, it is easy to obtain the following sufficient condition on global λ-exponential stability.

Theorem 2: For a prescribed $\lambda > 0$, if there exist matrices $P_1 > 0$, $P_2 > 0$, $Q_1 > 0$, and $Q_2 > 0$, and a diagonal matrix $\Gamma = \mathrm{diag}(\gamma_1, \gamma_2, \ldots, \gamma_n) > 0$, such that the following LMI holds:

$$M = \begin{bmatrix} \Xi_{11} & 0 & 0 & 0 & P_1 B_0 \\ * & -e^{-\lambda\overline{\sigma}} P_2 & D_0^T Q_1 & D_0^T \Gamma & 0 \\ * & * & \Xi_{33} & 0 & 0 \\ * & * & * & \Xi_{44} & 0 \\ * & * & * & * & -e^{-\lambda\overline{\tau}} Q_2 \end{bmatrix} < 0 \tag{35}$$

where

$$\begin{aligned} \Xi_{11} &= \lambda P_1 - P_1 A_0 - A_0 P_1 + P_2 \\ \Xi_{33} &= \lambda Q_1 - Q_1 C_0 - C_0 Q_1 + 2\lambda K \Gamma \\ \Xi_{44} &= -2K^{-1}\Gamma C_0 + Q_2 \end{aligned}$$

then the genetic network in (34) is globally λ-exponentially stable for any σ and τ satisfying $0 < \sigma \le \overline{\sigma}$ and $0 < \tau \le \overline{\tau}$.

By shifting the equilibrium of the network (34) to the origin and choosing the same Lyapunov–Krasovskii functional candidate (24) for system (34), one can obtain Theorem 2 in a way similar to Theorem 1. As the proof is straightforward, it is omitted.

Remark 3: To the best of our knowledge, it is the first time to investigate the global exponential stability of interval GRNs; the condition obtained in Theorem 1 is in the form of LMI, which can easily be checked by utilizing standard software. In addition, for any σ and τ satisfying $0 < \sigma \le \overline{\sigma}$ and $0 < \tau \le \overline{\tau}$, the maximal decay rate λ^* of gene network (6) can be estimated by using a simple bisection algorithm [40]. Furthermore, the decay rate was usually a fixed value computed by solving a transcendental equation in previous studies of dynamic systems, whereas the decay rate in Theorem 1 could be a free value that is equal to a preassigned constant, which can be selected according to different practical requirements. This will be of importance in understanding the mechanism of the regulatory, as well as introducing more flexibility in the analysis of genetic network.

Remark 4: The local stability criteria of biological and genetic networks have been established in [8] by the linearization technique, which involves the solvability of some transcendental equations. It has been well known that it will become more difficult to solve these equations with the increase in system dimensions, not to mention the fact that a GRN is usually a high-dimensional system and the introduction of parameter uncertainties may make the characteristic equation unsolvable. On the other hand, LMI is a pretty powerful and versatile tool for system analysis and design in the area of control theory and applications [34], and can efficiently be solved by existing algorithms.

Remark 5: It was pointed out in [9] that one can prove the uniqueness of equilibrium point (m^*, p^*) by using a contradiction argument. However, in this paper, we deal with the global exponential stability of the genetic network, which, in turn, implies the uniqueness of the equilibrium point of the GRN.

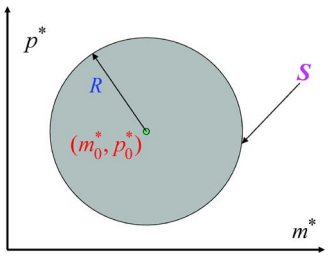

Fig. 1. Profile of the steady-state estimate of network (6).

It should be noted that the equilibrium (m^*, p^*) of the network is, in general, dependent on parameter uncertainties, which implies that, for different uncertainties, the equilibrium should be different from each other. Let (m_0^*, p_0^*) be the equilibrium of the nominal network (34), which represents the concentration of mRNA and the protein in the steady state, i.e.,

$$\begin{cases} -A_0 m_0^* + B_0 g(p_0^*) + u_{B_0} = 0 \\ -C_0 p_0^* + D_0 m_0^* = 0. \end{cases} \tag{36}$$

Therefore, there must be some variations between the equilibriums (m^*, p^*) and (m_0^*, p_0^*). An interesting question that one may raise is the following: when the network with parameter uncertainties achieves the steady state (m^*, p^*), how will it be drifted from the steady state (m_0^*, p_0^*) of the nominal genetic network (see Fig. 1)? Note the fact that the stability of the gene regulatory network in (6) will naturally ensure the stability of network (34), which means that, if (m^*, p^*) is stable, then (m_0^*, p_0^*) must also be stable. In the remaining portion of the section, we try to establish the steady-state estimate between the GRN (6) and (34) under condition (11).

Consider the GRN (6) and (34), let $e_1(t) = m(t) - m_0^*$ and $e_2(t) = p(t) - p_0^*$, then we obtain the following equation:

$$\begin{cases} \frac{de_1(t)}{dt} = -Ae_1(t) + Bh(e_2(t-\tau)) + I(m_0^*, p_0^*) \\ \frac{de_2(t)}{dt} = -Ce_2(t) + De_1(t-\sigma) + J(m_0^*, p_0^*) \end{cases} \tag{37}$$

in which $I(m_0^*, p_0^*) = -E_A \Delta_A E_A m_0^* + E_B \Omega_B F_B g(p_0^*) + u_B - u_{B_0}$, where the ith element of $u_B - u_{B_0} = -\sum_{j \in V_i}(b_{ij} - b_{ij}^0)$, and $J(m_0^*, p_0^*) = -E_C \Delta_C E_C p_0^* + E_D \Delta_D E_D m_0^*$. We present the steady-state estimates in Theorem 3.

Theorem 3: If condition (11) holds, then, for σ and τ satisfying $0 < \sigma \le \overline{\sigma}$ and $0 < \tau \le \overline{\tau}$, the equilibrium point (m^*, p^*) of the network (6) will be located in set S, which is defined by

$$S = \left\{ (m^*, p^*) : \left| \begin{pmatrix} m^* - m_0^* \\ p^* - p_0^* \end{pmatrix} \right| \le R \right\}$$

where

$$\begin{aligned} R &= 2\frac{\|P_1\| v_1 + (\|Q_1\| + \|K\Gamma\|) v_2}{\lambda \cdot \min(\lambda_{\min}(P_1), \lambda_{\min}(Q_1 + 2K\Gamma))} \\ v_1 &= \|E_A\| \, |E_A m_0^*| + \|E_B\| \, |F_B g(p_0^*)| \\ &\quad + \left(\sum_{i=1}^{n} \left(\sum_{j \in V_i} \frac{\overline{b}_{ij} - \underline{b}_{ij}}{2} \right)^2 \right)^{1/2} \\ v_2 &= \|E_C\| \, |E_C p_0^*| + \|E_D\| \, |E_D m_0^*| . \end{aligned}$$

Proof: Consider the following Lyapunov–Krasovskii functional candidate for system (37):

$$V(t,e_1(t),e_2(t)) = V_1(t,e_1(t),e_2(t)) + V_2(t,e_2(t)) + V_3(t,e_1(t),e_2(t))$$

where

$$V_1(t,e_1(t),e_2(t)) = e_1^T(t)P_1e_1(t) + e_2^T(t)Q_1e_2(t)$$

$$V_2(t,e_2(t)) = 2\sum_{i=1}^{n}\gamma_i\int_0^{e_{2i}(t)} h_i(s)ds$$

$$V_3(t,e_1(t),e_2(t)) = \int_{t-\sigma}^{t} e_1^T(s)P_2e_1(s)ds + \int_{t-\tau}^{t} h^T(e_2(s))Q_2h(e_2(s))ds.$$

Calculating the derivative of $V(t,e_1(t),e_2(t))$ along the trajectories of system (37) with respect to t, with the similar techniques employed in Theorem 1, one has

$$\begin{aligned}
\dot V(t) =& \dot V_1(t) + \dot V_2(t) + \dot V_3(t)\\
\le& e_1^T(t)(-P_1A - AP_1 + P_2)e_1(t)\\
&+ 2e_1^T(t)P_1[Bh(e_2(t-\tau)) + I(m_0^*,p_0^*)]\\
&+ e_2^T(t)(-Q_1C - CQ_1)e_2(t)\\
&+ 2e_2^T(t)Q_1[De_1(t-\sigma) + J(m_0^*,p_0^*)]\\
&+ h^T(e_2(t))(-2\Gamma CK^{-1} + Q_2)h(e_2(t))\\
&+ 2h^T(e_2(t))\Gamma De_1(t-\sigma)\\
&+ 2h^T(e_2(t))\Gamma J(m_0^*,p_0^*)\\
&- e_1^T(t-\sigma)P_2e_1(t-\sigma)\\
&- h^T(e_2(t-\tau))Q_2h(e_2(t-\tau))\\
=& \eta^T(t)\Pi(\sigma,\tau)\eta(t)\\
&+ e_1^T(t)[-\lambda P_1e_1(t) + 2P_1I(m_0^*,p_0^*)]\\
&+ e_2^T(t)[(-\lambda Q_1 - 2\lambda K\Gamma)e_2(t) + 2Q_1J(m_0^*,p_0^*)]\\
&+ 2h^T(e_2(t))\Gamma J(m_0^*,p_0^*)\\
\le& \eta^T(t)\Pi(\sigma,\tau)\eta(t)\\
&- \lambda\cdot\min(\lambda_{\min}(P_1),\lambda_{\min}(Q_1+2K\Gamma))\left|\left(e_1^T,e_2^T\right)^T\right|^2\\
&+ 2(\|P_1\|\upsilon_1 + (\|Q_1\| + \|K\Gamma\|)\upsilon_2)\left|\left(e_1^T,e_2^T\right)^T\right| \quad (38)
\end{aligned}$$

where

$$\eta(t) = \left[e_1^T(t), e_1^T(t-\sigma), e_2^T(t), h^T(e_2(t)), h^T(e_2(t-\tau))\right]$$

and $\Pi(\sigma,\tau)$ is defined in (31). On the other hand, define a set $\tilde S = \{(e_1,e_2) : |(e_1^T,e_2^T)^T| \le R\}$. For $(e_1,e_2)\notin\tilde S$, we have

$$\left|\left(e_1^T,e_2^T\right)^T\right| > 2\frac{\|P_1\|\upsilon_1 + (\|Q_1\| + \|K\Gamma\|)\upsilon_2}{\lambda\cdot\min(\lambda_{\min}(P_1),\lambda_{\min}(Q_1+2K\Gamma))}$$

which is equivalent to

$$-\lambda\cdot\min(\lambda_{\min}(P_1),\lambda_{\min}(Q_1+2K\Gamma))\left|\left(e_1^T,e_2^T\right)^T\right|^2 + 2(\|P_1\|\upsilon_1 + (\|Q_1\| + \|K\Gamma\|)\upsilon_2)\left|\left(e_1^T,e_2^T\right)^T\right| < 0.$$

This, together with (38), gives $\dot V(t) < 0$ for any $(e_1,e_2)\notin\tilde S$; then, we can conclude that there exists $T > 0$ such that $(e_1,e_2)\in\tilde S$ for any $t \ge T$. According to condition (11), it can easily be obtained that the steady state (m^*,p^*) of the network (6) will be located in set S. This completes the proof. ■

Remark 6: Theorem 3 shows that the steady state of mRNAs and proteins in the genetic network varies under the condition that there exist uncertainties on system parameters. The minimization of R can be achieved via the following convex optimization:

$$\min_{\mathcal{S}} R$$

$$\text{s.t.}\quad \begin{cases} (11)\text{ holds}\\ 0 < \vartheta I \le P_1 \le p_1 I\\ 0 < Q_1 \le q_1 I\\ 0 < K\Gamma \le q_2 I\\ \vartheta I \le Q_1 + 2K\Gamma\\ 2(p_1\upsilon_1 + (q_1+q_2)\upsilon_2) \le \lambda\vartheta R \end{cases}$$

where $\mathcal{S} = \{P_1>0, P_2>0, Q_1>0, Q_2>0, \Gamma = \mathrm{diag}(\gamma_1,\gamma_2,\ldots,\gamma_n) > 0, \varepsilon_i > 0, i = 1,\ldots,5, \vartheta > 0, p_1 > 0, q_1 > 0, q_2 > 0\}$. In fact, we convert the original "feasible solution" condition to a generalized eigenvalue minimization problem, which paves a way to estimate the range of concentrations of the variables. Due to the page length restriction, here we only present a rough estimate of the steady state, and one may use some other techniques, such as the introduction of free matrices and the optimization theory in [41], to reduce the conservatism of this estimate.

B. Exponential Estimates of GRNs With Noise Perturbations

Genetically identical cells and organisms exhibit remarkable diversity even when they have identical histories of environmental exposure. Noise, in the process of gene expression, may contribute to this phenotypic variability [16]. It is suggested that this noise has multiple sources, including the stochastic or inherently random nature of the biochemical reactions of gene expression, and undoubtedly affects the kinetics of the networks [15], [17]. Since we often know little about the noise in the genetic network, different from the method in [13] and [42], where the stochastic properties are supposed to be known or the external noise are used to control a single gene autoregulatory network in the concentration of protein, we assume here that the noise perturbations are unknown and additively perturb the network. By means of the stochastic functional differential equation theory, we study the exponential stability of the randomized genetic network and investigate the impact on both parameter uncertainties and noise perturbations.

In the following, we consider genetic networks with both parameter uncertainties and noise perturbation described by

$$\begin{cases} \frac{dx(t)}{dt} = -Ax(t) + Bh(y(t-\tau)) + G_1(t,x(t),y(t-\tau))\xi(t)\\ \frac{dy(t)}{dt} = -Cy(t) + Dx(t-\sigma) + G_2(t,x(t-\sigma),y(t))\xi(t) \end{cases} \quad (39)$$

where $G_1, G_2 : \mathbb{R}\times\mathbb{R}^n\times\mathbb{R}^n \to \mathbb{R}^{n\times l}$ are called the noise intensity function, which are both Borel measurable and assumed

to satisfy

$$\begin{aligned}&\text{trace}\left(G_1^T\left(t,x(t),y(t-\tau)\right)G_1\left(t,x(t),y(t-\tau)\right)\right)\\&\quad\le\rho_1\left|x(t)\right|^2+\rho_2\left|y(t-\tau)\right|^2 \qquad (40)\\&\text{trace}\left(G_2^T\left(t,x(t-\sigma),y(t)\right)G_2\left(t,x(t-\sigma),y(t)\right)\right)\\&\quad\le\rho_3\left|x(t-\sigma)\right|^2+\rho_4\left|y(t)\right|^2. \qquad (41)\end{aligned}$$

$\xi(t)$ is the l-dimensional Gaussian white noise, and the other system parameters are defined to be the same as those in (9).

Recall that l-dimensional Gaussian white noise can be viewed as the derivative (in the generalized function sense) of the l-dimensional Wiener process (or Brown motion); then, we can rewrite (39) in the form of

$$\begin{cases}dx(t)=\left[-Ax(t)+Bh\left(y(t-\tau)\right)\right]dt\\\qquad\quad+G_1\left(t,x(t),y(t-\tau)\right)dW(t)\\dy(t)=\left[-Cy(t)+Dx(t-\sigma)\right]dt\\\qquad\quad+G_2\left(t,x(t-\sigma),y(t)\right)dW(t)\end{cases}\qquad(42)$$

where $W(t)=(w_1(t),w_2(t),\ldots,w_l(t))$ is an l-dimensional Brown motion defined on a complete probability space $(\Omega,\mathcal{F},\{\mathcal{F}\}_{t\ge o},P)$. The initial condition associated with the network (42) is given in the following form:

$$x(t)=\varphi_x(t)\quad y(t)=\psi_y(t),\qquad -\rho\le t\le 0;\ \rho\triangleq\max(\sigma,\tau)$$

for any $\varphi_x,\psi_y\in L^2_{\mathcal{F}}([-\rho,0],\mathbb{R}^n)$, where $L^2_{\mathcal{F}}([-\rho,0],\mathbb{R}^n)$ is the family of all $\mathcal{F}_0$-measurable $\mathcal{C}([-\tau,0],\mathbb{R}^n)$-valued random variables satisfying $\mathbf{E}|\varphi_x(s)|^2_\rho\triangleq\sup_{-\rho\le s\le 0}\mathbf{E}|\varphi_x(s)|^2<\infty,\mathbf{E}|\psi_y(s)|^2_\rho\triangleq\sup_{-\rho\le s\le 0}\mathbf{E}|\psi_y(s)|^2<\infty$. For the stochastic functional differential equation, we discuss the global exponential stability of the proposed model (42) in the mean square.

Theorem 4: For a prescribed $\lambda>0$, if there exist matrices $P_1>0$, $P_2>0$, $Q_1>0$, $Q_2>0$, and $R>0$; a diagonal matrix $\Gamma=\text{diag}(\gamma_1,\gamma_2,\ldots,\gamma_n)>0$; and scalars $\varepsilon_i>0, i=1,\ldots,8$, satisfying the LMIs in (43) and (44), shown at the bottom of the page, where

$$\begin{aligned}\Psi_{11}&=\lambda P_1-P_1A_0-A_0P_1+P_2+\varepsilon_1E_A^TE_A+\varepsilon_6\rho_1I\\\Psi_{22}&=-e^{-\lambda\overline{\sigma}}P_2+\varepsilon_3E_D^TE_D+(\varepsilon_7+\varepsilon_8)\rho_3I\\\Psi_{33}&=\lambda Q_1-Q_1C_0-C_0Q_1+R+2\lambda K\Gamma\\&\quad+\varepsilon_4E_C^TE_C+(\varepsilon_7+\varepsilon_8)\rho_4I\\\Psi_{44}&=\Phi_{44}=-2K^{-1}\Gamma C_0+Q_2+\varepsilon_5E_C^TE_C\\\Psi_{55}&=\Phi_{55}=-e^{-\lambda\overline{\tau}}Q_2+\varepsilon_2F_B^TF_B\end{aligned}$$

then the interval genetic network (42) is globally robustly λ-exponentially stable in the mean square for any σ and τ satisfying $0<\sigma\le\overline{\sigma}$ and $0<\tau\le\overline{\tau}$.

Proof: Consider the following Lyapunov–Krasovskii functional candidate for system (9):

$$\begin{aligned}V\left(t,x(t),y(t)\right)&=V_1\left(t,x(t),y(t)\right)\\&\quad+V_2\left(t,y(t)\right)+V_3\left(t,x(t),y(t)\right)\end{aligned}\qquad(45)$$

where

$$\begin{aligned}V_1\left(t,x(t),y(t)\right)&=e^{\lambda t}x^T(t)P_1x(t)+e^{\lambda t}y^T(t)Q_1y(t)\\V_2\left(t,y(t)\right)&=2\sum_{i=1}^{n}e^{\lambda t}\gamma_i\int_0^{y_i(t)}h_i(s)ds\\V_3\left(t,x(t),y(t)\right)&=\int_{t-\sigma}^{t}e^{\lambda s}x^T(s)P_2x(s)ds\\&\quad+\int_{t-\tau}^{t}e^{\lambda s}y^T(s)Ry(s)ds\\&\quad+\int_{t-\tau}^{t}e^{\lambda s}h^T\left(y(s)\right)Q_2h\left(y(s)\right)ds.\end{aligned}$$

The weak infinitesimal operator $\mathcal{L}V$ along (42) is given by [43]

$$\begin{aligned}\mathcal{L}V\left(t,x(t),y(t)\right)&=\mathcal{L}V_1\left(t,x(t),y(t)\right)\\&\quad+\mathcal{L}V_2\left(t,y(t)\right)+\mathcal{L}V_3\left(t,x(t),y(t)\right)\end{aligned}$$

where

$$\begin{aligned}&\mathcal{L}V_1\left(t,x(t),y(t)\right)\\&\quad=e^{\lambda t}\left[x^T(t)\lambda P_1x(t)+y^T(t)\lambda Q_1y(t)\right.\\&\qquad+2x^T(t)P_1\left(-Ax(t)+Bh\left(y(t-\tau)\right)\right)\\&\qquad\left.+\,2y^T(t)Q_1\left(-Cy(t)+Dx(t-\sigma)\right)\right]\\&\qquad+e^{\lambda t}\Big[\text{trace}\big(G_1^T\left(t,x(t),y(t-\tau)\right)\\&\qquad\quad\times P_1G_1\left(t,x(t),y(t-\tau)\right)\big)\\&\qquad+\text{trace}\big(G_2^T\left(t,x(t-\sigma),y(t)\right)\\&\qquad\quad\times Q_1G_2\left(t,x(t-\sigma),y(t)\right)\big)\Big]\end{aligned}$$

$$M=\begin{bmatrix}\Psi_{11}&0&0&0&P_1B_0&P_1E_A&P_1E_B&0&0&0\\*&\Psi_{22}&D_0^TQ_1&D_0^T\Gamma&0&0&0&0&0&0\\*&*&\Psi_{33}&0&0&0&0&Q_1E_D&Q_1E_C&0\\*&*&*&\Psi_{44}&0&0&0&\Gamma E_D&0&K^{-1}\Gamma E_C\\*&*&*&*&\Psi_{55}&0&0&0&0&0\\*&*&*&*&*&-\varepsilon_1I&0&0&0&0\\*&*&*&*&*&*&-\varepsilon_2I&0&0&0\\*&*&*&*&*&*&*&-\varepsilon_3I&0&0\\*&*&*&*&*&*&*&*&-\varepsilon_4I&0\\*&*&*&*&*&*&*&*&*&-\varepsilon_5I\end{bmatrix}<0\qquad(43)$$

$$P_1\le\varepsilon_6I\quad Q_1\le\varepsilon_7I\quad\varepsilon_6\rho_2I\le e^{-\lambda\overline{\tau}}R\quad\Gamma K\le\varepsilon_8I\qquad(44)$$

$$
\begin{aligned}
&\mathcal{L}V_2\left(t,y(t)\right)\\
&\quad=2\lambda\sum_{i=1}^{n}e^{\lambda t}\gamma_i\int_0^{y_i(t)}h_i(s)ds\\
&\qquad+e^{\lambda t}\left[2h^T\left(y(t)\right)\Gamma\left(-Cy(t)+Dx(t-\sigma)\right)\right.\\
&\qquad\quad+\text{trace}\big(G_2^T\left(t,x(t-\sigma),y(t)\right)\\
&\qquad\qquad\times\ \text{diag}\left(\gamma_1h_1',\gamma_2h_2',\ldots,\gamma_nh_n'\right)\\
&\qquad\qquad\left.\times\ G_2\left(t,x(t-\sigma),y(t)\right)\big)\right]\\
&\mathcal{L}V_3\left(t,x(t),y(t)\right)\\
&\quad=e^{\lambda t}\left[x^T(t)P_2x(t)-e^{-\lambda\sigma}x^T(t-\sigma)P_2x(t-\sigma)\right.\\
&\qquad+h^T\left(y(t)\right)Q_2h\left(y(t)\right)\\
&\qquad-e^{-\lambda\tau}h^T\left(y(t-\tau)\right)Q_2h\left(y(t-\tau)\right)\\
&\qquad\left.+y^T(t)Ry(t)-e^{-\lambda\tau}y^T(t-\tau)Ry(t-\tau)\right].
\end{aligned}
$$

On the other hand, it follows from (40) and (41) that

$$
\begin{aligned}
&\text{trace}\left(G_1^T\left(t,x(t),y(t-\tau)\right)P_1G_1\left(t,x(t),y(t-\tau)\right)\right)\\
&\quad\le\text{trace}\left(G_1^T\left(t,x(t),y(t-\tau)\right)\varepsilon_6IG_1\left(t,x(t),y(t-\tau)\right)\right)\\
&\quad\le\varepsilon_6\left[\rho_1\left|x(t)\right|^2+\rho_2\left|y(t-\tau)\right|^2\right]\\
&\text{trace}\left(G_2^T\left(t,x(t-\sigma),y(t)\right)Q_1G_2\left(t,x(t-\sigma),y(t)\right)\right)\\
&\quad\le\text{trace}\left(G_2^T\left(t,x(t-\sigma),y(t)\right)\varepsilon_7IG_2\left(t,x(t-\sigma),y(t)\right)\right)\\
&\quad\le\varepsilon_7\left[\rho_3\left|x(t-\sigma)\right|^2+\rho_4\left|y(t)\right|^2\right].
\end{aligned}
$$

By (10), it is clear that

$$
\begin{aligned}
&\text{trace}\left(G_2^T\left(t,x(t-\sigma),y(t)\right)\text{diag}\left(\gamma_1h_1',\gamma_2h_2',\ldots,\gamma_nh_n'\right)\right.\\
&\qquad\left.\times\ G_2\left(t,x(t-\sigma),y(t)\right)\right)\\
&\quad\le\text{trace}\left(G_2^T\left(t,x(t-\sigma),y(t)\right)\right.\\
&\qquad\left.\times\,\text{diag}(\gamma_1k_1,\gamma_2k_2,\ldots,\gamma_nk_n)G_2\left(t,x(t-\sigma),y(t)\right)\right)\\
&\quad\le\varepsilon_8\left[\rho_3\left|x(t-\sigma)\right|^2+\rho_4\left|y(t)\right|^2\right].
\end{aligned}
$$

Then, following a similar process as that in the proofs of Theorem 1, we have

$$
\begin{aligned}
&\mathcal{L}V\left(t,x(t),y(t)\right)\\
&\quad\le e^{\lambda t}\eta^T(t)\Xi(\sigma,\tau)\eta(t)\\
&\qquad+y^T(t-\tau)\left[-e^{-\lambda\tau}R+\varepsilon_6\rho_2I\right]y(t-\tau)\\
&\quad\le 0
\end{aligned}
$$

where

$$
\eta(t)=\left[x^T(t),x^T(t-\sigma),y^T(t),h^T\left(y(t)\right),h^T\left(y(t-\tau)\right)\right]
$$

$$
\Xi(\sigma,\tau)=\begin{bmatrix}T_{11}&0&0&0&P_1B\\*&T_{22}&D^TQ_1&D^T\Gamma&0\\*&*&T_{33}&0&0\\*&*&*&T_{44}&0\\*&*&*&*&-e^{-\lambda\tau}Q_2\end{bmatrix}<0
$$

with

$$
\begin{aligned}
T_{11}&=\lambda P_1-P_1A-AP_1+P_2+\varepsilon_6\rho_1I\\
T_{22}&=-e^{-\lambda\sigma}P_2+(\varepsilon_7+\varepsilon_8)\rho_3I\\
T_{33}&=\lambda Q_1-Q_1C-CQ_1+R+2\lambda K\Gamma+(\varepsilon_7+\varepsilon_8)\rho_4I\\
T_{44}&=-2\Gamma CK^{-1}+Q_2.
\end{aligned}
$$

It is noted that $\Xi(\sigma,\tau)<0$ because of (43) with the similar method used in Theorem 1. By taking the mathematical expectation, it can easily be obtained that

$$
\begin{aligned}
\mathbf{E}V\left(t,x(t),y(t)\right)&\le\mathbf{E}V(0)+\int_0^t\mathcal{L}V\left(s,x(s),y(s)\right)ds\\
&\le\mu_1\mathbf{E}|\varphi_x|_\rho^2+\mu_2\mathbf{E}|\psi_y|_\rho^2
\end{aligned}
\tag{46}
$$

where

$$
\begin{aligned}
\mu_1&=\left(\|P_1\|+\frac{1-e^{-\lambda\sigma}}{\lambda}\|P_2\|\right)\\
\mu_2&=\left(\|Q_1\|+2\|\Gamma K\|+\frac{1-e^{-\lambda\tau}}{\lambda}\cdot\left[\|Q_2\|\|K\|^2+\|R\|\right]\right).
\end{aligned}
$$

Inequality (46) implies that

$$
\mathbf{E}\left|x(t)\right|^2+\mathbf{E}\left|y(t)\right|^2\le\mu e^{-\lambda t}\left(\mathbf{E}|\varphi_x|_\rho^2+\mathbf{E}|\psi_y|_\rho^2\right)
$$

where

$$
\mu=\frac{\max\{\mu_1,\mu_2\}}{\min\left\{\lambda_{\min}(P_1),\lambda_{\min}(Q_1)\right\}}.
$$

This completes the proof. ■

Remark 7: Theorems 1–4 can easily be extended to the GRNs with time-varying delays. For the lucidity of exposition, we only discuss the GRN with time-invariant delays and focus more on the impact of parameter uncertainties and noise perturbations.

Remark 8: Although the asymptotic stability of GRNs has been investigated in [9], the exponential stability and its estimates, which provide a more accurate characterization on the transient process of GRNs, have not been well considered. Moreover, parameter uncertainties when modeling the GRNs are fully neglected in [9]. In contrast, the result in Theorem 4 provides the exponential stability condition of GRNs where both parameter uncertainties and random noise are taken into account. It will be shown in the subsequent example that the GRNs, under certain conditions, can withstand a certain level of uncertainties and noises, which provides a further step for understanding signal fidelity in gene networks and designing robust noise-tolerant gene circuits.

According to Theorem 4, we can easily obtain Theorem 5. (To avoid unnecessary duplication, the proof is omitted here.)

Theorem 5: For a prescribed $\lambda>0$, if there exist matrices $P_1>0$, $P_2>0$, $Q_1>0$, $Q_2>0$, and $R>0$; a diagonal

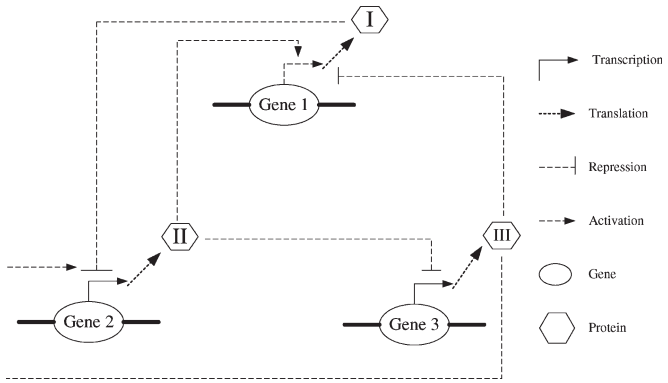

Fig. 2. Gene regulation network comprising three genes (6).

matrix $\Gamma = \mathrm{diag}(\gamma_1, \gamma_2, \ldots, \gamma_n) > 0$; and scalars $\varepsilon_1 > 0$, $\varepsilon_2 > 0$, $\varepsilon_3 > 0$, such that the following LMIs holds:

$$M = \begin{bmatrix} \Theta_{11} & 0 & 0 & 0 & P_1 B_0 \\ * & \Theta_{22} & D_0^T Q_1 & D_0^T \Gamma & 0 \\ * & * & \Theta_{33} & 0 & 0 \\ * & * & * & \Theta_{44} & 0 \\ * & * & * & * & -e^{-\lambda\overline{\tau}} Q_2 \end{bmatrix} < 0$$

$$P_1 \le \varepsilon_1 I \quad Q_1 \le \varepsilon_2 I \quad \varepsilon_1 \rho_2 I \le e^{-\lambda\overline{\tau}} R \quad \Gamma K \le \varepsilon_3 I$$

where

$$\Theta_{11} = \lambda P_1 - P_1 A_0 - A_0 P_1 + P_2 + \varepsilon_1 \rho_1 I$$

$$\Theta_{22} = -e^{-\lambda\overline{\sigma}} P_2 + (\varepsilon_2 + \varepsilon_3)\rho_3 I$$

$$\Theta_{33} = \lambda Q_1 - Q_1 C_0 - C_0 Q_1 + R + 2\lambda K\Gamma + (\varepsilon_2 + \varepsilon_3)\rho_4 I$$

$$\Theta_{44} = -2K^{-1}\Gamma C_0 + Q_2$$

then the nominal system of network (42) is globally robustly λ-exponentially stable in the mean square for any σ and τ satisfying $0 < \sigma \le \overline{\sigma}$ and $0 < \tau \le \overline{\tau}$.

IV. Three-Gene Network

To show the effectiveness of the theoretical results obtained, we employ a synthetic oscillatory network of transcriptional regulators in *Escherichia coli*, which has been presented as the mathematical model of the repressilator and experimentally investigated in [38]. In this section, we generalize the model proposed in [38] by introducing time delays and random noises, and consider the GRN shown in Fig. 2, which describes the gene, mRNA, and protein interactions. These genes are regulated by other genes; they are then expressed through transcription to obtain mRNA (which is not shown for simplicity) and then through translation to produce their products, i.e., proteins. These proteins could then act as the transcription factors of other genes to regulate the expressions of others. From the structure of the network in Fig. 2, one can obtain the adjacency matrix as

$$G = \begin{bmatrix} 0 & 1 & -1 \\ -1 & 0 & 1 \\ 0 & -1 & 0 \end{bmatrix}.$$

In addition, we assume that regulatory function $g_i(s)$ is $g_i(s) = ((s^2/i)/(1 + s^2/i)) = (s^2/i + s^2)$ $(i = 1, 2, 3)$ in network (6), i.e., the Hill coefficient is 2, with the derivative of $g(s)$ satisfying $K = \mathrm{diag}(0.65, 0.46, 0.38)$. Two cases will be discussed to investigate the dynamics of the genetic network.

(I) There are parameter uncertainties in GRN model (6) with parameters as

$$\underline{A} = \overline{A} = \begin{bmatrix} 2.85 & 0 & 0 \\ 0 & 2.73 & 0 \\ 0 & 0 & 2.81 \end{bmatrix}$$

$$\underline{C} = \overline{C} = \begin{bmatrix} 2.11 & 0 & 0 \\ 0 & 2.47 & 0 \\ 0 & 0 & 2.07 \end{bmatrix}$$

$$\underline{B} = \begin{bmatrix} 0 & 0.91 & -1.18 \\ -1.10 & 0 & 0.96 \\ 0 & -0.92 & 0 \end{bmatrix}$$

$$\overline{B} = \begin{bmatrix} 0 & 0.95 & -1.08 \\ -1.10 & 0 & 1.17 \\ 0 & -0.88 & 0 \end{bmatrix}$$

$$\underline{D} = \begin{bmatrix} 0.88 & 0 & 0 \\ 0 & 0.95 & 0 \\ 0 & 0 & 0.92 \end{bmatrix}$$

$$\overline{D} = \begin{bmatrix} 0.96 & 0 & 0 \\ 0 & 1.03 & 0 \\ 0 & 0 & 1.00 \end{bmatrix}.$$

For $\lambda = 0.8$ and maximal delays $\overline{\tau} = 1.8$ and $\overline{\sigma} = 2$, by using standard software, it can be verified that there exists a feasible solution to the LMI in (11), and the estimate of μ can be calculated by (33), with $\mu = 16.5848$. Therefore, according to Theorem 1, the GRN is globally 0.8-exponentially robustly stable for any σ and τ satisfying $0 < \tau \le 1.8$ and $0 < \sigma \le 2$, denote $\rho = \max(\tau, \sigma)$, and the solutions of the network satisfy

$$|m(t) - m^*|^2 + |p(t) - p^*|^2 \le 16.5848 e^{-0.8t} \left(|\varphi - m^*|_\rho^2 + |\psi - p^*|_\rho^2 \right).$$

Figs. 3 and 4 are numerical illustrations of the trajectories of network with $B = B_0 + E_B \Omega_B F_B$ and $D = D_0 + E_D \Delta_D E_D$, where the diagonal elements of Ω_B and Δ_D are generated by uniformly distributed random numbers from the interval $[-1, 1]$. The time delays are $\sigma = 1.8$ and $\tau = 2$, respectively. The initial state is chosen to be $\varphi(t) = [0.4 + 0.05\cos t, 0.4 - 0.05\cos t, 0.4 + 0.05\sin t]^T$, $\psi(t) = [0.2 - 0.05\cos t, 0.2 + 0.05\cos t, 0.2 - 0.05\sin t]^T$ for $t \in [-2, 0]$, and the simulation results indicate that the equilibrium of the genetic network is $(m^* = [0.3820, 0.3948, 0.3122]^T, p^* = [0.1664, 0.1575, 0.1466]^T)$, which is globally robustly exponentially stable.

For the steady-state estimate, it can be checked that the unique equilibrium of the nominal network (34) is $(m_0^* = [0.3977, 0.3939, 0.3163]^T$, $p_0^* = [0.1634, 0.1579, 0.1467]^T)$; here, we focus on the variation of (m^*, p^*) in the network (6).

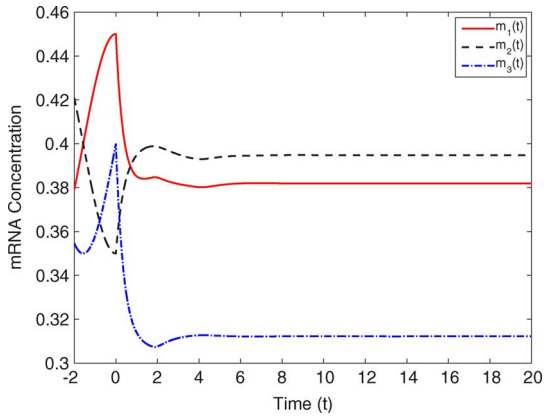

Fig. 3. State response of $m(t)$ of the genetic network (6).

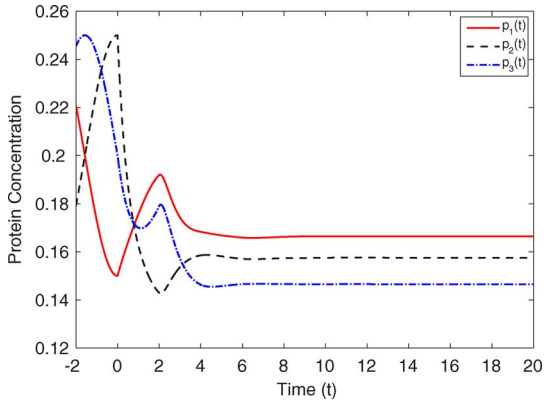

Fig. 4. State response of $p(t)$ of the genetic network (6).

From Theorem 3, the steady state of the mRNAs and proteins in the network (m^*, p^*) satisfies

$$\left|\begin{pmatrix} m^* - m_0^* \\ p^* - p_0^* \end{pmatrix}\right| \leq 0.1773. \tag{47}$$

Fig. 5 shows the trajectories of state variable $m_1(t)$, where the red dashed line represents the state trajectory of the nominal network and the ten blue real lines denote the state trajectories of the perturbed network. Here, all the blue trajectories are generated by randomly choosing the system matrices B and D of the perturbed network in the same way previously mentioned, and the initial conditions of the gene network (6) are chosen to be constant, which are all randomly produced from the interval [0, 1]. The simulation result in Fig. 5 indicates that all the steady states of the perturbed network are within the range between the upper and lower bounds, which was calculated according to (47).

(II) There are random noises incorporated to the genetic network with parameter uncertainties.

Since we are interested in the stability of the equilibrium $(m^* = [0.3820, 0.3948, 0.3122]^T, \quad p^* = [0.1664, 0.1575, 0.1466]^T)$ under both parameter and noise perturbations, the equilibrium should be shifted to the origin, and the GRN should be rewritten under coordinate shift (see (42)). We assume the noise intensity functions as $G_1(t, x(t), y(t-\tau)) = (\sqrt{2}/4)[x(t) + \sqrt{3}y(t-\tau), \sqrt{3}x(t) - y(t-\tau)]$ and $G_2(t, x(t-\sigma), y(t)) = (1/2)[x(t-\sigma)+y(t), x(t-\sigma)-y(t)]$. Then, it can easily be obtained that $\rho_1 = \rho_2 = \rho_3 = \rho_4 = 1/2$, and

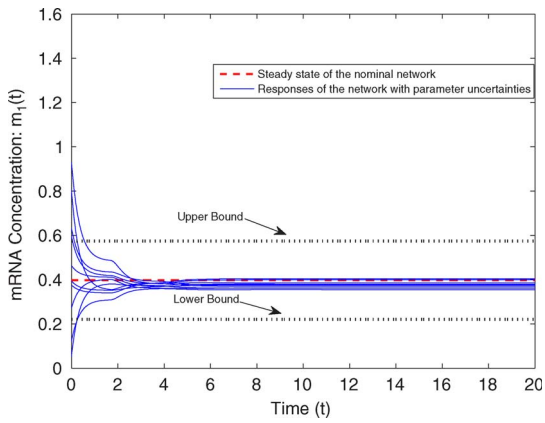

Fig. 5. Steady-state estimate of the genetic network (6).

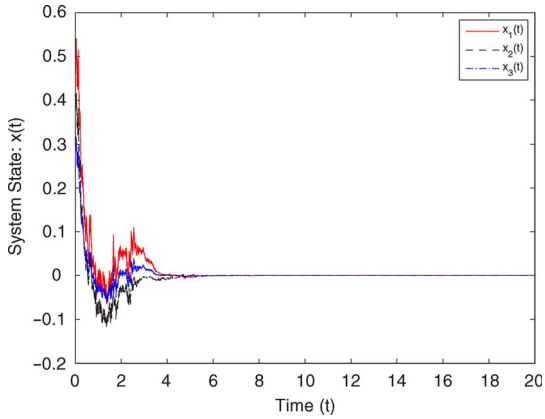

Fig. 6. State response of $x(t)$ of the genetic network (42).

$W(t)$ is a 2-D Brown motion. The other system parameters are chosen to be the same as those in Case I. For the maximal time delays $\overline{\sigma} = 0.9$ and $\overline{\tau} = 1.2$, we compute the maximal decay rate λ with bisection method proposed in Remark 3 and obtain $\lambda = 0.6677$. By referring to standard software, one can easily find the feasible solution of the LMIs (43) and (44) in Theorem 4, which implies that the uncertain system (42) is globally robustly 0.6677-exponentially stable in the mean square for any σ and τ satisfying $0 < \sigma \leq 0.9$ and $0 < \tau \leq 1.2$.

For the numerical simulation, we set $\sigma = 0.9$ and $\tau = 1.2$, and take the initial condition of system (42) as $\varphi_x(t) = [0.5, 0.4, 0.3]^T$, $\psi_y(t) = [0.4, 0.3, 0.2]^T$ for $t \in [-1.2, 0]$, and apply the well-known Euler–Maruyama scheme with step size 10^{-4}. The trajectories of variables $x(t)$ and $y(t)$ are shown in Figs. 6 and 7, respectively, which imply that the network is globally robustly stable in the mean square with the incorporation of noises.

V. Conclusion

In this paper, we have proposed and dealt with the transient and steady-state estimate problem of a class of interval genetic network models. Based on the Lyapunov functional method and matrix inequality techniques, some criteria have been established to ensure the global robust stability of the network model with the estimate of decay rate and decay coefficient given. Furthermore, the steady-state estimate of the proposed gene network model has been analyzed. The obtained results have

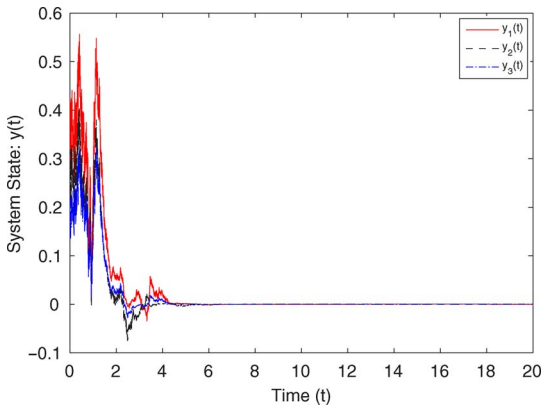

Fig. 7. State response of $y(t)$ of the genetic network (42).

also been extended to the case with noise perturbations based on the stochastic functional differential equation theory. These results, which are in terms of LMIs, can easily be solved by standard software. A simple three-gene network model has been used to demonstrate the usefulness of the theoretical results. As we stated in this paper, how to more accurately establish the steady-state estimate of GRNs is an interesting problem for our further exploration in the future.

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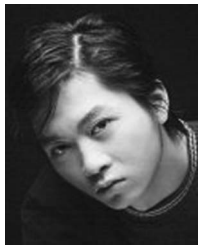

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