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Robust filtering of extended stochastic genetic regulatory networks with parameter uncertainties, disturbances, and time-varying delays

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ABSTRACT

This paper addresses robust H_∞ filtering problem for a nonlinear genetic regulatory network (GRN), which is extended to include noise and disturbances, parameter uncertainties, and time-varying delays simultaneously. It is assumed that the nonlinear function that describes the feedback regulation satisfies the sector-bounded condition, the stochastic state perturbation is in the form of a scalar Brownian motion, and the time-varying delays enter into both the translation process and the feedback regulation process. To account for the unavoidable modeling errors and parameter fluctuations, the network parameters are assumed to be time-varying but norm-bounded values. We aim to estimate the true concentrations of mRNAs and proteins by designing a linear filter such that, for all admissible uncertainties, nonlinearities, stochastic perturbations and time delays, the dynamics of the filtering error is guaranteed to be robustly asymptotically stable in the mean square sense while achieving the prescribed H_∞ disturbance attenuation level. By using the Lyapunov stability theory and Itô formula, sufficient conditions for the existence of the filter are obtained in the form of a linear matrix inequality (LMI). Then, explicit expressions for the desired filter gains are provided. Finally, a simulation example is given in order to illustrate the effectiveness of the proposed design procedure.

1. Introduction

In a living cell, the encoded information contained in a gene has an important role for an organism to develop within a changing environment. Genetic Regulatory Networks (GRNs) are the mechanisms to regulate gene expression. Many questions about gene functions, expression mechanisms, and global integration of individual mechanisms remain open. It is widely believed that the gene expression data contains rich information that could discover the higher order structures of an organism and even interpret its behavior [1]. With the development of DNA microarray technology [2], it has become possible to measure the gene expression levels on a genomic scale, and furthermore to analyze the gene regulatory network. The theoretical analyses and experimental investigations on GRNs show the dynamical behavior of these networks [3,4].

In practice, for identifying the genes of interest and developing proper drugs, biologists need to know the steady-state values of the GRN states, which are the concentrations of the mRNAs and proteins. Unfortunately, due to the existence of state delay and state-depended noises, the network measurements are far from the accurate network state values. The filtering goal is to estimate the network states such that the estimation error asymptotically converges to zero in the mean square sense for a GRN that contains transmission varying delays, intrinsic fluctuations, and parameter uncertainties. Although the filtering problem has been extensively studied in the control and signal processing communities in general, it still remains a challenging issue for the specific structure of GRNs because of the complex structure of these networks.

In biological systems or artificial genetic networks, time delays exist primarily due to the slow process of transcription and translation [5,6]. Therefore, without properly addressing the delay effects in the design of GRNs, mathematical models may provide wrong predictions of the concentrations of mRNAs and proteins. Moreover, in these networks, the delays of translation and regulation are time-varying, and one may not have exact information about the amount of delay bounds [7].

On the other hand, the noisy fluctuations of gene expression data are an important issue to be considered when modeling GRNs. In general, the stochastic noise appears in gene expression either due to internal or external noise. The internal random fluctuations in the GRNs are due to probabilistic view of chemical reactions, and the external noise originates from the random variation of one or more of the externally-set control parameters.

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Moreover, a mathematical model can by no means exactly represent the real GRN. It is very likely that the parameters of the model identified from the experimental data varies from time to time, and such variations are unknown but with known bounds. Therefore, when modeling GRNs, beside stochastic perturbations, norm-bounded parameter uncertainties should also be taken into account.

In recent works, the filtering problem has been studied for GRNs while ignoring some actual characteristics of GRNs. In [2], the parameter uncertainties and the nonlinear character of GRN are ignored in the filtering design. In [8,9], the nonlinear filtering problem is addressed but without considering parameter uncertainties and time-varying delays. In [10,11], parameter uncertainties of the GRN have been considered in the filtering design; however, the delays are assumed constant.

In general, filter design for stochastic time–delay systems are classified into two categories: delay-dependent and delay independent approaches. The former makes use of the bound of delays and is thus less conservative than the latter especially when the delays are small. However, when the bound of delay is not known, one needs to adopt a delay-independent technique [23].

In this paper, we first offer an extended GRN model for the first time, containing most actual characteristics of GRNs such as uncertainties, time-varying delays, and stochastic disturbances, simultaneously. We then design two robust filters, one without and one with considering H_∞ criterion, for the extended nonlinear GRNs with state-depended stochastic disturbances and parameter uncertainties as well as time-varying state delays. The feedback regulation is described by a sector-like nonlinear function, the stochastic perturbation is a scalar Brownian motion, and the time delays enter into both the translation process and the feedback regulation process. We aim to estimate the true concentrations of the mRNAs and proteins by designing an augmented filtering system. Using linear matrix inequality (LMI) technique, we derive the sufficient conditions for ensuring asymptotic mean square stability of the extended GRN, and then, we find the corresponding filter gains in terms of the solution of the LMI parameters.

This paper is organized as follows: Section 2 introduces some preliminary backgrounds and the problem statement of the extended GRN model as well as its conditions. In Section 3, a robust filter and a robust H_∞ filter are designed for accurate estimation of mRNAs and proteins concentrations. In Section 4, a numerical example is given to demonstrate the correctness of the presented result for the gene expression model. Finally, conclusions are given in Section 5.

Notation: Throughout this paper, $L_2[0,\infty)$ is the space of square-integrable vector function over $[0,\infty)$, $\|.\|$ stands for the usual $L_2[0,\infty)$ norm, $(\Omega,F,\{F_t\}_{t\in R},P)$ is a complete probability space with filtration $\{F_t\}_{t\in R}$ satisfying the usual conditions (i.e., the filtration contains all P-null sets and is right continuous). The symbol * is used as an ellipsis for terms induced by symmetry.

2. The problem statement and preliminaries

Extending the GRN model in [8] to include both parameter uncertainties [12], time-varying delays [2,13], and exogenous disturbances [14], we introduce the following compact matrix from nonlinear GRN model:

$$\begin{aligned}
&dx_m(t)=[(A_1+\Delta A_1(t))x_m(t)+(B+\Delta B(t))g(x_p(t-\tau_1(t)))+(G_1+\Delta G_1(t))v(t)]dt+(E+\Delta E(t))x_m(t)d\omega_1(t),\\
&dx_p(t)=[(A_2+\Delta A_2(t))x_p(t)+(D+\Delta D(t))x_m(t-\tau_2(t))+(G_2+\Delta G_2(t))v(t)]dt+(F+\Delta F(t))x_p(t)d\omega_2(t),\\
&y_m(t)=(C_1+\Delta C_1(t))x_m(t)+(G_3+\Delta G_3(t))v(t),\\
&y_p(t)=(C_2+\Delta C_2(t))x_p(t)+(G_4+\Delta G_4(t))v(t),\\
&x_m(t)=\varphi_m(t),\quad x_p(t)=\varphi_p(t),\quad \forall t<0,
\end{aligned}\tag{1}$$

where $x_m(t)=\begin{bmatrix}x_{m1}(t) & x_{m2}(t) & \cdots & x_{mn}(t)\end{bmatrix}^T\in R^n$, and $x_p(t)=\begin{bmatrix}x_{p1}(t) & x_{p2}(t) & \cdots & x_{pn}(t)\end{bmatrix}^T\in R^n$ denote the concentrations of mRNAs and proteins at time t for a GRN with n nodes, respectively; $y_m(t)=\begin{bmatrix}y_{m1}(t) & y_{m2}(t) & \cdots & y_{mr}(t)\end{bmatrix}^T\in R^r$, and $y_p(t)=\begin{bmatrix}y_{p1}(t) & y_{p2}(t) & \cdots & y_{pr}(t)\end{bmatrix}^T\in R^r$ represent the expression levels of mRNAs and proteins at time t, respectively; ϕ_m, and ϕ_p are the initial functions of $x_m(t)$ and $x_p(t)$ for $t<0$, respectively; the time-varying scalars $\tau_1(t)>0$, and $\tau_2(t)>0$ denote the feedback regulation delay and the translation delay, respectively, satisfying $0\le\dot\tau_1(t)\le\bar d_1<1$ and $0\le\dot\tau_2(t)\le\bar d_2<1$; and monotone function $g(x_p)=\begin{bmatrix}g_1(x_p) & g_2(x_p) & \cdots & g_n(x_p)\end{bmatrix}^T\in R^n$ represents the feedback regulation of the protein on the transcription, whose elements are generally nonlinear functions in the form of SUM logic: $g_i(x_{p1},x_{p2},\ldots,x_{pn})=\sum_{j=1}^n g_{ij}(x_{pj})$ where g_{ij} is a monotonic function of the Hill form. If transcription factor j is an activator of gene i, then:

$$g_{ij}(x_{pj})=\rho_{ij}\frac{x_{pj}^{H_j}}{\beta^{H_j}+x_{pj}^{H_j}},\tag{2}$$

where β is a positive constant, H_j is the Hill coefficient, and dimensionless bounded constant ρ_{ij} is the transcriptional rate of transcription factor j to i. On the other hand, if transcription factor j is a repressor of gene i , then:

$$g_{ij}(x_{pj})=\rho_{ij}\frac{\beta^{H_j}}{\beta^{H_j}+x_{pj}^{H_j}}=\rho_{ij}\left(1-\frac{x_{pj}^{H_j}}{\beta^{H_j}+x_{pj}^{H_j}}\right).\tag{3}$$

Moreover, it is assumed that $A_1=diag\{-a_{11},-a_{12},\ldots,-a_{1n}\}$, $A_2=diag\{-a_{21},-a_{22},\ldots,-a_{2n}\}$ and $D=diag\{d_1,d_2,\ldots,d_n\}$ are diagonal matrices with $a_{1i}>0$, $a_{2i}>0$, $d_i>0$ $(i=1,\ldots,n)$ being the rate of degradation of mRNA, the rate of degradation of protein, and the translation rate of the i-th node, respectively. Moreover, A_1, B, E, G_1, A_2, D, F, G_2, C_1, G_3, C_2, and G_4 in (1) are known real constant matrices with appropriate dimensions, while $\Delta A_1(t)$, $\Delta B(t)$, $\Delta E(t)$, $\Delta G_1(t)$, $\Delta A_2(t)$, $\Delta D(t)$, $\Delta F(t)$, $\Delta G_2(t)$, $\Delta C_1(t)$, $\Delta G_3(t)$, $\Delta C_2(t)$, and $\Delta G_4(t)$ are unknown matrices representing time-varying uncertainties, which are assumed to satisfy the following conditions:

$$\begin{bmatrix}\Delta A_1 & \Delta B\\ \Delta D & \Delta A_2\\ \Delta C_1 & \Delta C_2\\ \Delta E & \Delta F\end{bmatrix}=\begin{bmatrix}M_1\\M_2\\M_3\\M_4\end{bmatrix}Q(t)\begin{bmatrix}N_1 & N_2\end{bmatrix},\quad \begin{bmatrix}\Delta G_1 & \Delta G_2 & \Delta G_3 & \Delta G_4\end{bmatrix}^T=\begin{bmatrix}M_5 & M_6 & M_7 & M_8\end{bmatrix}^TQ(t)N_3,\tag{4}$$