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# Robust estimation of stochastic gene-network systems

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## ABSTRACT

**Gene networks in biological systems are highly complicated because of their nonlinear and stochastic features. Network dynamics typically involve cross-talk mechanism and they may suffer from corruption due to intrinsic and extrinsic stochastic molecular noises. Filtering noises in gene networks using biological techniques accompanied with a systematic strategy is thus an attractive topic. However, most states of biological systems are not directly accessible. In practice, these immeasurable states can only be predicted based on the measurement output. In the lab experiment, green fluorescent protein (GFP) is commonly adopted as the reporter protein since it is able to reflect intensity of the gene expression. On this basis, this study considers a nonlinear stochastic model to describe the stochastic gene networks and shows that robust state estimation using Kalman filtering techniques is possible. Stability of the robust estimation scheme is analyzed based on the Ito's theorem and Lyapunov stability theory. Numerical examples *in silico* are illustrated to confirm performance of the proposed design.**

**Keywords:** Biological System; Stochastic Model; Stability; Estimation

## 1. INTRODUCTION

The gene network in biological systems plays an important role in recent diagnoses of diseases such as cancer and autoimmune diseases. Because this network is highly complicated and extremely nonlinear, investigating related problems using a systematic strategy is highly desirable.

Systems biology aims to understand the internal behaviors of biological systems from a system level view. It is different from traditional biology, which focuses on individual cellular components [1-3]. Researchers have recently designed and constructed biological models using molecular biology techniques and engineering approaches. For example, microarray technology uses high-throughput methods to measure a large amount of gene expression states, and is a useful tool in biotechnology. Measured data makes it possible to reconstruct the structures of gene networks, perform qualitative and quantitative analyses, systematically control biological states and design desired biological process, and ultimately examine dynamic behavior using computational simulations.

Biological models describing the behavior of biological systems can be classified into a logical model in the discrete-time domain and a differential equation set in the continuous-time domain [4-6]. Unlike the deterministic case, the gene networks of real biological systems are generally non-ideal and invariably noisy. These molecular noises generally involve the intrinsic noises resulting from molecular birth and death, and extrinsic noises caused by environmental influences such as changes in temperature, PH, or nutrient levels and may affect the quantitative and qualitative characteristics of biological systems [7-9]. To ensure modeling accuracy, the influence of noise contamination should not be ignored. The parameters of gene network are estimated to reconstruct its model form noisy measured data [10].

The robustness of biological systems is defined as the capability of the system to resist noise corruption while ensuring satisfactory performance or stability [11]. Disease and malfunction represent a decay in robustness and the noise filtering ability of the corresponding biological networks. Drug design is an effective way to improve the robustness and filtering ability of biological networks to resist fluctuation and noise, much like the robust control design in engineering problems. Nonlinear feedback control methods have also been used to regulate the steady state of biological systems [12]. Other issues that have directed greater attention to stochastic biological systems include the development of control strategies when ensuring robust stability and filtering ability. Chen and Wu proposed a robust filtering circuit design based on $H_\infty$-control theory by regulating kinetic parameters [13].

Before performing any feedback control designs, all biological state information should be available. However, most of the internal states of these systems can only

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be observed partially. In this situation, a state estimator is appropriate to reconstruct full states, especially in noisy environments. The Kalman filter (KF) has been adopted to estimate full states in engineering for decades [14,15]. Liang and Lam designed a linear state estimator to estimate the concentrations of mRNA and protein for stochastic gene regulatory networks by considering parameter uncertainties [16]. However, there are relatively few applications of the extended KF (EKF) in state estimation for nonlinear biochemical networks [17,18]. Moreover, a state estimator was implemented based on the fluorescence probe, a dynamic state model of the plant cell bioreactor and online GFP fluorescence measurement [19].

Although a few papers discuss state estimation for biological networks, most approaches are based on the traditional Kalman filtering theory. This theory assumes that noise covariances, including process noise and measurement noise, are known a priori. The KF can identify optimal state estimation against noise using Gaussian distributions. However, noise distribution may not be Gaussian in biological systems; its autocorrelation may not be known exactly, or may be difficult to model precisely [7-9]. Chuang and Lin proposed a robust EKF to handle gene network systems with uncertain process noises [20].

This paper extends the design to a more general class of perturbative gene networks with uncertain extrinsic noise, process noise, and multiple intrinsic noise sources. A state estimator for this class of gene networks is designed based on a generalized robust EKF. This study also presents quantitative error analysis for the robust EKF based on Ito derivatives and Lyapunov stability theory. After this analysis is completed, establishing the convergence condition for estimation error, which is expressed in terms of the linearization error of the given gene network and the amplification factors of intrinsic noises, is then possible. Numerical experiments for an *in silico* example verify the theoretical results obtained.

## 2. PRELIMINARIES

To clarify the notation in the derivations, let the vector norm of $x \in \mathbb{R}^n$, denoted by $\|x\|$, be defined as $\|x\| = \sqrt{x^{\mathrm{T}} x}$. Some preliminary lemmas are introduced a priori.

The following lemma provides the covariance propagation equation for stochastic linear systems.

**Lemma 1 [21].** For the following linear stochastic system:

$$dx(t) = Ax(t)\,dt + Dx(t)\,dW(t),$$
$$E\left[\left|W(t) - W(\tau)\right|^2\right] = \sigma_w^2 |t - \tau|$$

where $x(t)$ is state, $E(\cdot)$ denotes expectation, and $W(t)$ is the zero mean Gaussian white noise. The covariance propagation for $x(t)$ is governed by

$$\dot{X}(t) = AX(t) + X(t)A^{\mathrm{T}} + \sigma_w^2 DX(t)D^{\mathrm{T}}$$

where the state covariance is $X(t) = E\left(x(t)x^{\mathrm{T}}(t)\right)$.

The following lemma is known as the Ito Lemma for the differential of the given stochastic process.

**Lemma 2 [22].** For the following nonlinear time-varying stochastic system:

$$dx(t) = f\left(x(t),t\right)dt + h\left(x(t),t\right)dW(t)$$

and the differential of a given stochastic process $V\left(x(t),t\right)$ is

$$dV\left(x(t),t\right) = \frac{\partial V\left(x(t),t\right)}{\partial t}dt$$
$$+\left[\frac{\partial V\left(x(t),t\right)}{\partial x(t)}\right]^{\mathrm{T}}\left[f\left(x(t),t\right)dt + h\left(x(t),t\right)dW(t)\right]$$
$$+\frac{1}{2}\left[h^{T}\left(x(t),t\right)\frac{\partial^2 V\left(x(t),t\right)}{\partial x^2(t)}h\left(x(t),t\right)\right]$$
$$+\frac{1}{2}\frac{\partial^2 V\left(x(t),t\right)}{\partial t^2}(dt)^2$$
$$+\left[\frac{\partial^2 V\left(x(t),t\right)}{\partial x(t)\partial t}\right]^{\mathrm{T}}\left[f\left(x(t),t\right)dt + h\left(x(t),t\right)dW(t)\right]dt$$

where $f\left(x(t),t\right)$ and $h\left(x(t),t\right)$ are time-varying nonlinear function vectors, and $dW(t)$ is a Brownian motion.

### 2.1. Problem Description

To explain this problem, consider a stochastic nonlinear synthetic gene network of a cascade loop of transcriptional inhibitions built in *E. coli* with 4 genes (*tetR*, *lacI*, *cI*, and *eyfp*), 3 repressor proteins (TetR, LacI, and CI), and the fluorescent protein EYFP as the output (shown in **Figure 1**). The fluorescence of the system resulting from EYFP is the only measured output, and other gene products $(tetR, lacI, cI)$ are not accessible. By considering the disturbance effect, the dynamic response of the system can be described by the following equations [23]:

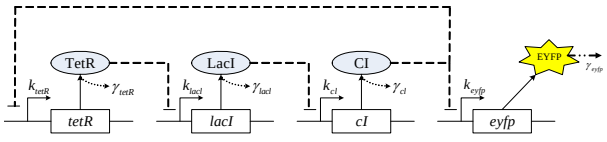


**Figure 1.** Example of a synthetic gene network. The dashed line and the solid line represent, respectively, the repression effect and the activation effect.

 

$$\begin{aligned}
&\dot{x}_{tetR}(t) = \kappa_{tetR,0} + \left(\kappa_{tetR} + \Delta\kappa_{tetR} n_1(t)\right) r_{tetR}\left(x_{cI}\right) \\
&-\left(\gamma_{tetR} + \Delta\gamma_{tetR} n_1(t)\right) x_{tetR}(t) + w_1(t), \\
&\dot{x}_{lacI}(t) = \kappa_{lacI,0} + \left(\kappa_{lacI} + \Delta\kappa_{lacI} n_2(t)\right) r_{lacI}\left(x_{tetR}\right) \\
&-\left(\gamma_{lacI} + \Delta\gamma_{lacI} n_2(t)\right) x_{lacI}(t) + w_2(t), \\
&\dot{x}_{cI}(t) = \kappa_{cI,0} + \left(\kappa_{cI} + \Delta\kappa_{cI} n_3(t)\right) r_{cI}\left(x_{lacI}\right) \\
&-\left(\gamma_{cI} + \Delta\gamma_{cI} n_3(t)\right) x_{cI}(t) + w_3(t), \\
&\dot{x}_{eyfp}(t) = \kappa_{eyfp,0} + \left(\kappa_{eyfp} + \Delta\kappa_{eyfp} n_4(t)\right) r_{eyfp}\left(x_{cI}\right) \\
&-\left(\gamma_{eyfp} + \Delta\gamma_{eyfp} n_4(t)\right) x_{eyfp}(t) + w_4(t),
\end{aligned} \tag{1}$$

where the initial state is

$$x_0 = E\left[x_{tetR}(0) \quad x_{lacI}(0) \quad x_{cI}(0) \quad x_{eyfp}(0)\right]^{\mathrm{T}},$$

the production rate parameters of the corresponding proteins is $\kappa_i$, $i = tetR, lacI, cI, eypf$, the decay rate parameters of the corresponding proteins is $\gamma_i, i = tetR, lacI, cI, eypf$, $n_i$, $i = 1, \cdots, 4$ represent the intrinsic parameter fluctuations with uncertain magnitudes $\Delta\kappa_i$ and $\Delta\gamma_i$, $\kappa_{i,0}$ and $\gamma_{i,0}$ are the basal production and decay rates, and $w_i$, $i = 1, \cdots, 4$ reflect the effect of environmental noises. The stochastic molecular noises in the host cells are assumed uncertain but bounded. The Hill function for the repressors is

$$r_k(x) = \frac{\beta_r}{1 + \left(\dfrac{x}{K_r}\right)^n}, \; k = tetR, lacI, cI, eyfp$$

with $\beta_r$ being the maximal expression level of the promoter and $K_r$ the repression coefficient. The EYFP protein, a green fluorescent protein (GFP), is a useful reporter protein consisting of several amino acid residues. The EYFP protein exhibits bright green fluorescence when exposed to blue light. Based on this feature, it is possible to obtain information about the concentration variations of other proteins and mRNAs by measuring the fluorescent intensity generated by GFP. According to the Beer-Lambert law [19], the measurement model can be expressed as follows:

$$y_{eyfp}(t) = F_0\left(1 - \mathrm{e}^{-l\varepsilon x_{eyfp}}\right) + v(t) \tag{2}$$

where $y_{eyfp}(t)$ denotes the measurement output of GFP, $v(t)$ is the measurement noise, $F_0$ is the basal light intensity, $l$ is path length of light, and absorption coefficient $\varepsilon$ with $l\varepsilon x_{eyfp} < 0.05$.

This study discusses an approach for estimating the gene concentration of a class of stochastic gene networks in the form of (1)-(2) with multiple intrinsic noises when their states are not directly accessible. In this situation, estimating state information based on measurement output is a key issue.

Mathematical models provide a platform for the systematic analysis of various gene networks. One type of ordinary differential equation (ODEs) is the stoichiometric model, which is known for representing biochemical reactions. Gene networks often suffer from intrinsic noises resulting from molecular birth and death, but also from extrinsic noises caused by environmental perturbations. The dynamical variation of concentrations for biological systems shown in (1)-(2) can be applied to a more general perturbative gene network using the following nonlinear stochastic differential equation, which incorporates intrinsic and extrinsic noises:

$$\dot{x}(t) = f\left(x(t)\right) + \sum_{i=1}^{M} g_i\left(x(t)\right) n_i(t) + w(t) \tag{3}$$

where $M$ represents the number of intrinsic noise sources,

$$x_0 = E\left[x(0)\right], \; P_{x_0} = E\left[\left(x(0) - x_0\right)\left(x(0) - x_0\right)^{\mathrm{T}}\right],$$

and the measurement model is given by

$$y(t) = h\left(x(t)\right) + v(t) \tag{4}$$

where $x(t) \in R^n$ denotes a concentration vector that indicates the concentration of mRNA and protein. $y(t) \in \mathbb{R}^r$ denotes the measurement output. The terms $f(\cdot)$, $g_i(\cdot)$, $i = 1, 2, \cdots, M$ and $h(\cdot)$ are nonlinear functions that respectively denote the interactions of gene networks, coupling vectors of intrinsic noises, and the function of sensors. The intrinsic noises $n_i(t)$, $i = 1, 2, \cdots, M$, the extrinsic noise $w(t)$, and the measurement noise $v(t)$ are uncorrelated and assumed to be zero-mean Gaussian white noise processes:

$$E\left[w(t)\right] = E\left[v(t)\right] = E\left[n_i(t)\right] = 0, \; \forall t \tag{5}$$

and

$$E\left\{\begin{bmatrix} w(t) \\ v(t) \\ n_1(t) \\ \vdots \\ n_M(t) \end{bmatrix}\begin{bmatrix} w(t) \\ v(t) \\ n_1(t) \\ \vdots \\ n_M(t) \end{bmatrix}^{\mathrm{T}}\right\} = \begin{bmatrix} Q & 0 & 0 & \cdots & 0 \\ 0 & R & 0 & \cdots & 0 \\ 0 & 0 & \sigma_1^2 & \cdots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \cdots & \sigma_M^2 \end{bmatrix} \tag{6}$$

The noise uncertainties satisfy

$$\left\|Q - Q_0\right\| \le \varepsilon_1, \; \left\|R - R_0\right\| \le \varepsilon_2, \; \left|\sigma_i - \sigma_{i0}\right| \le \varepsilon_{3i} \tag{7}$$

where $Q = Q^{\mathrm{T}} > 0$, $R = R^{\mathrm{T}} > 0$ and $\sigma_i^2 > 0$, $\forall i$ are positive definite matrices, $Q_0, R_0$ and $\sigma_{i0}$, $\forall i$ are their corresponding nominal parts, and $\varepsilon_1, \varepsilon_2$ and $\varepsilon_{3i}$, $\forall i$ are positive constants.

***Remark* 1.** Equations (3) and (4) can be rewritten as the following Ito stochastic equations:

$$dx(t) = f\left(x(t)\right)dt + \sum_{i=1}^{M} g_i\left(x(t)\right) dN_i(t) + dW(t)$$

 

and

$$dz(t) = h(x(t))dt + dV(t)$$

where $y(t) = \dot{z}(t)$, $N_i(t)$, $W(t)$ and $V(t)$ are standard Wiener processes or Brownian motions with

$$dN_i(t) = n_i(t)dt,\ dW(t) = w(t)dt$$

and $v(t)dt = dV(t)$. This formulation is widely applicable to general nonlinear gene networks with $M$ intrinsic noise sources.

## 2.2. Estimator Design

Biological processes for gene networks include DNA to mRNA transcription and mRNA to protein translation, and generated protein regulates other genes. However, the internal states of most biological systems are not directly accessible.

As described, gene networks in the real world are always noisy. The corresponding dynamic model is thus stochastic. To tackle the situation, this study presents a design approach for robust estimation with the estimator given in the following form:

$$\begin{aligned}\dot{\hat{x}}(t) &= f(\hat{x}(t)) + K(t)(y(t) - \hat{y}(t)),\ \hat{x}(0) = x_0\\ \hat{y}(t) &= h(\hat{x}(t))\end{aligned} \tag{8}$$

where $\hat{x}(t) \in R^n$ is the estimated state vector, $\hat{y}(t) \in R^r$ is the estimated output, and $K(t) \in R^{n\times r}$ is the estimator gain. The computational algorithm (8) is implemented in a computer to conduct state integration with $y(t)$ obtained from the GFP expression while filtering measurement noises. **Figure 2** shows the system configuration. The sensor measures GFP fluorescence intensity and converts it into electrical signals for further processing on the computer. The green fluorescence intensity per cell can be measured using a flow cytometer. The computer computes an appropriate estimation gain $K(t)$ using the measured data. The process of propagating the estimation error to further determine $K(t)$ is independent of the gene network. The following derivations are given to determine the estimation gain so that the estimated states will track the noise-free states.

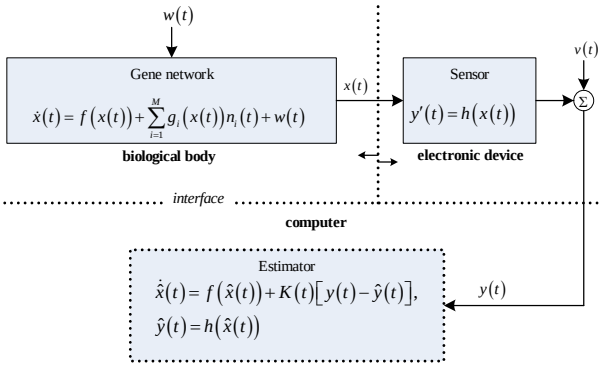


**Figure 2.** System structure for realization of the state estimator.

Let the estimation error state be $\tilde{x}(t) = x(t) - \hat{x}(t)$ then

$$\begin{aligned}\dot{\tilde{x}}(t) = {} & f(x(t)) - f(\hat{x}(t)) - K(t)\left[h(x(t)) - h(\hat{x}(t))\right]\\ & + \sum_{i=1}^{M} g_i(x(t))n_i(t) + w(t) - K(t)v(t)\end{aligned} \tag{9}$$

The augmented system can then be constructed as

$$\begin{aligned}\dot{\xi}(t) = {} & A(t)\xi(t) + L(t)\Delta A(x(t), \hat{x}(t))\\ & + \sum_{i=1}^{M}\left[B_i\xi(t) + \Delta B_i(x(t))\right]n_i(t) + L(t)\eta(t)\end{aligned} \tag{10}$$

where

$$\xi(t) = \begin{bmatrix} x^{\mathrm{T}}(t) & \tilde{x}^{\mathrm{T}}(t)\end{bmatrix}^{\mathrm{T}},\ \eta(t) = \begin{bmatrix} w^{\mathrm{T}}(t) & v^{\mathrm{T}}(t)\end{bmatrix}^{\mathrm{T}},$$

$$A(t) = \begin{bmatrix} F & 0\\ 0 & F - K(t)H\end{bmatrix}, B_i = \begin{bmatrix} G_i & 0\\ G_i & 0\end{bmatrix},$$

$$L(t) = \begin{bmatrix} I & 0\\ I & -K(t)\end{bmatrix},\ \Delta B_i(x(t)) = \begin{bmatrix} I\\ I\end{bmatrix}\Delta G_i(x(t)),$$

$$\Delta A(x(t), \hat{x}(t)) = \begin{bmatrix}\Delta F(x(t), \hat{x}(t))\\ \Delta H(x(t), \hat{x}(t))\end{bmatrix}$$

The partial derivative matrices evaluated at the estimated state are given by

$$F = \left.\frac{\partial f(x(t))}{\partial x(t)}\right|_{x(t)=\hat{x}(t)},\ H = \left.\frac{\partial h(x(t))}{\partial x(t)}\right|_{x(t)=\hat{x}(t)},$$

$$G_i = \left.\frac{\partial g_i(x(t))}{\partial x(t)}\right|_{x(t)=\hat{x}(t)}$$

and

$$\begin{aligned}\Delta F(x(t), \hat{x}(t)) &= \Delta F(x(t)) - \Delta F(\hat{x}(t)),\\ \Delta H(x(t), \hat{x}(t)) &= \Delta H(x(t)) - \Delta H(\hat{x}(t))\end{aligned}$$

where $\Delta F(x(t)) = f(x(t)) - Fx(t)$ and $\Delta H(x(t)) = h(x(t)) - Hx(t)$ denote the linearization errors. The errors are assumed to be bounded as follows:

$$\begin{aligned}& E\left[\Delta F^{\mathrm{T}}(x(t), \hat{x}(t))\Delta F(x(t), \hat{x}(t))\right]\\ & \le \rho_1 E\left[\tilde{x}^{\mathrm{T}}(t)\tilde{x}(t)\right],\ \forall x(t), \hat{x}(t)\\ & E\left[\Delta H^{\mathrm{T}}(x(t), \hat{x}(t))\Delta H(x(t), \hat{x}(t))\right]\\ & \le \rho_2 E\left[\tilde{x}^{\mathrm{T}}(t)\tilde{x}(t)\right],\ \forall x(t), \hat{x}(t)\\ & E\left[\Delta G_i^{\mathrm{T}}(x(t))\Delta G_i(x(t))\right]\\ & \le \delta_i E\left[x^{\mathrm{T}}(t)x(t)\right],\ \forall x(t), \forall i\end{aligned} \tag{11}$$

 

where $\rho_1, \rho_2$, and $\delta_i$ are finite constants.

For the EKF design, consider the nominal case with the linearization error ignored. In this case, the augmented system becomes

$$\dot{\xi}(t) = A(t)\xi(t) + \sum_{i=1}^{M} B_i \xi(t) n_i(t) + L(t)\eta(t) \quad (12)$$

First consider a case in which all noise covariances are exactly measured so that $\varepsilon_1 = \varepsilon_2 = \varepsilon_{3i} = 0, \forall i$. By defining the augmented covariance matrix

$$\Sigma(t) = E\left[\xi(t)\xi^{\mathrm{T}}(t)\right]$$

and applying Lemma 1, the error propagation equation with the Kalman gain $K(t) = \Sigma_{22}(t) H^{\mathrm{T}} R^{-1}$ can be determined by solving the stochastic Riccati equation:

$$\begin{aligned}\dot{\Sigma}(t) &= A\Sigma(t) + \Sigma(t)A^{\mathrm{T}} + \sum_{i=1}^{M} B_i E\left[n_i^2(t)\xi(t)\xi^{\mathrm{T}}(t)\right] B_i^{\mathrm{T}} \\ &\quad + LE\left[\eta(t)\eta^{\mathrm{T}}(t)\right] L^{\mathrm{T}} \\ &= A\Sigma(t) + \Sigma(t)A^{\mathrm{T}} + \sum_{i=1}^{M} \sigma_i^2 B_i \Sigma(t) B_i^{\mathrm{T}} + L \cdot \mathrm{diag}(Q, R) L^{\mathrm{T}}\end{aligned} \quad (13)$$

Next, consider the case with noise uncertainties presented in (7). Based on results obtained by [24], and taking the least favorable noise covariances of $Q_0 + \varepsilon_1 I, R_0 + \varepsilon_2 I$, and $\sigma_{i0} + \varepsilon_{3i}, i = 1, 2, \cdots, M$ into consideration, the robust Kalman gain $K$ can be determined by solving the following Riccati equation:

$$\begin{aligned}\dot{\Sigma}(t) &= A\Sigma(t) + \Sigma(t)A^{\mathrm{T}} \\ &\quad + \sum_{i=1}^{M} \left(\sigma_{i0} + \varepsilon_{3i}\right)^2 B_i \Sigma(t) B_i^{\mathrm{T}} + L\hat{Q}L^{\mathrm{T}}\end{aligned} \quad (14)$$

where $\hat{Q} = \mathrm{diag}\left(Q_0 + \varepsilon_1 I, R_0 + \varepsilon_2 I\right)$ and

$$K(t) = \Sigma_{22}(t) H^{\mathrm{T}} \left(R_0 + \varepsilon_2 I\right)^{-1} \quad (15)$$

Equation (15) indicates that $K(t)$ is closely related to the amount of measurement noise reflected by the magnitude of $R_0$ and the extent of the uncertain noise covariance specified by $\varepsilon_2$.

When $F$ is time-invariant, it is easy to verify the stability of the linearized system (12) with the Kalman gain $K = \Sigma_{22} H^{\mathrm{T}} \left(R_0 + \varepsilon_2 I\right)^{-1}$. Stability can be analyzed by observing that the Riccati matrix equation (14) is reduced to the algebraic Riccati equation

$$0 = A\Sigma + \Sigma A^{\mathrm{T}} + \sum_{i=1}^{M} \left(\sigma_{i0} + \varepsilon_{3i}\right)^2 B_i \Sigma B_i^{\mathrm{T}} + L\hat{Q}L^{\mathrm{T}}$$

and

$$A\Sigma + \Sigma A^{\mathrm{T}} + \sum_{i=1}^{M} \sigma_i^{\,2} B_i \Sigma B_i^{\mathrm{T}} + L \cdot \mathrm{diag}(Q, R) L^{\mathrm{T}} < 0$$

for all $Q, R$, and $\sigma_i$ satisfying (7). Based on the result given in [13], the above inequality represents a Lyapunov inequality guaranteeing the stability of the system (12).

However, if one considers a system disturbed not only by noises with uncertain covariances, but also by linearization errors, the KF presented in this study is possibly not robust. To make the estimation scheme robust and stable, more constraints must be imposed on linearization errors and intrinsic noises. Thus, advanced analysis of the augmented system (10) with linearization errors is required.

## 3. STABILITY ANALYSIS

This section analyzes stability of the stochastic gene system based on the Ito Lemma and Lyapunov stability theory. Stability condition derivation is developed on the basis of the following definition.

**Definition 1 [15].** Given a stochastic process denoted by $\xi(t)$, assume that there is a stochastic process $V(\xi(t))$ and real numbers $V_{\min}$, $V_{\max}$, $\mu, \gamma > 0$ such that

$$V_{\min} \left\|\xi(t)\right\|^2 \le V(\xi(t)) \le V_{\max} \left\|\xi(t)\right\|^2, \ \forall t$$

and

$$\dot{V}(\xi(t)) \le -\gamma V(\xi(t)) + \mu$$

are fulfilled. In this case, $\xi(t)$ is exponentially bounded in mean square with $\gamma$ determining its decaying rate.

To proceed the stability analysis, we choose a Lyapunov candidate function as [15]

$$V(\xi(t), t) = \xi^{T}(t)\Theta(t)\xi(t)$$

where $\Theta(t) = \Sigma^{-1}(t)$ and $\Sigma(t)$ is the solution of (14). Taking the time derivative of $V(\xi(t), t)$ by Lemma 2 and ignoring the higher order terms gives

$$\begin{aligned}E\left[\dot{V}(\xi(t), t)\right] &= E\left\{\frac{\partial V(\xi(t), t)}{\partial t}\right. \\ &+ \left[\frac{\partial V(\xi(t), t)}{\partial \xi(t)}\right]^{\mathrm{T}} \left[A(t)\xi(t) + L(t)\Delta A(x(t), \hat{x}(t))\right. \\ &\left. + \sum_{i=1}^{M} \left(B_i \xi(t) + \Delta B_i(x(t))\right) n_i(t) + L(t)\eta(t)\right] \\ &+ \frac{1}{2}\sum_{i=1}^{M} \left[n_i^2 \left(B_i \xi(t) + \Delta B_i(x(t))\right)^{\mathrm{T}} \left(\frac{\partial V^2(\xi(t), t)}{\partial \xi^2(t)}\right)\right. \\ &\left.\left. \cdot \left(B_i \xi(t) + \Delta B_i(x(t))\right)\right] + \frac{1}{2}\eta^{\mathrm{T}}(t) L^{\mathrm{T}} \left(\frac{\partial V^2(\xi(t), t)}{\partial \xi^2(t)}\right) L\eta(t)\right\}\end{aligned}$$

Then, using (5) and (6) yields

 

$$
\begin{aligned}
&E\left[\dot{V}\left(\xi(t),t\right)\right] \le \xi^{\mathrm{T}}(t)\dot{\Theta}(t)\xi(t)\\
&+\xi^{\mathrm{T}}(t)\left[A^{\mathrm{T}}(t)\Theta(t)+\Theta(t)A(t)\right]\xi(t)\\
&+E\left[2\xi^{\mathrm{T}}(t)\Theta(t)L(t)\Delta A\left(x(t),\hat{x}(t)\right)\right]\\
&+\sum_{i=1}^{M}\left(\sigma_{i0}+\varepsilon_{3i}\right)^{2}\left(\xi^{\mathrm{T}}(t)B_i^{\mathrm{T}}\Theta(t)B_i\xi(t)\right.\\
&\left.+E\left[\Delta B_i^{\mathrm{T}}\left(x(t)\right)\Theta(t)\Delta B_i\left(x(t)\right)\right]\right)\\
&+\mathrm{trace}\left(L(t)\hat{Q}L^{\mathrm{T}}(t)\Theta(t)\right)
\end{aligned}
$$

Using

$$\dot{\Theta}(t) = -\Theta(t)\dot{\Sigma}(t)\Theta(t)$$

then

$$
\begin{aligned}
&E\left[\dot{V}\left(\xi(t),t\right)\right] \le -\xi^{\mathrm{T}}(t)\Theta(t)\dot{\Sigma}(t)\Theta(t)\xi(t)\\
&+\xi^{\mathrm{T}}(t)\left[A^{T}(t)\Theta(t)+\Theta(t)A(t)\right]\xi(t)\\
&+E\left[2\xi^{\mathrm{T}}(t)\Theta(t)L(t)\Delta A\left(x(t),\hat{x}(t)\right)\right]\\
&+\sum_{i=1}^{M}\left(\sigma_{i0}+\varepsilon_{3i}\right)^{2}\left(\xi^{\mathrm{T}}(t)B_i^{\mathrm{T}}\Theta(t)B_i\xi(t)\right.\\
&\left.+E\left[\Delta B_i^{\mathrm{T}}\left(x(t)\right)\Theta(t)\Delta B_i\left(x(t)\right)\right]\right)\\
&+\mathrm{trace}\left(L(t)\hat{Q}L^{\mathrm{T}}(t)\Theta(t)\right)\Big\}
\end{aligned}
\tag{16}
$$

Substituting (14) into (16) gives

$$
\begin{aligned}
&E\left[\dot{V}\left(\xi(t),t\right)\right] \le -\xi^{\mathrm{T}}(t)\Big\{\Theta(t)\Big[A(t)\Sigma(t)+\Sigma(t)A^{\mathrm{T}}(t)\\
&+\sum_{i=1}^{M}\left(\sigma_{i0}+\varepsilon_{3i}\right)^{2}B_i\Sigma(t)B_i^{\mathrm{T}}+L(t)\hat{Q}L^{\mathrm{T}}(t)\Big]\Theta(t)\Big\}\xi(t)\\
&+\xi^{\mathrm{T}}(t)\left[A^{\mathrm{T}}(t)\Theta(t)+\Theta(t)A(t)\right]\xi(t)\\
&+E\left[2\xi^{\mathrm{T}}(t)\Theta(t)L(t)\Delta A\left(x(t),\hat{x}(t)\right)\right]\\
&+\sum_{i=1}^{M}\left(\sigma_{i0}+\varepsilon_{3i}\right)^{2}\left(\xi^{\mathrm{T}}(t)B_i^{\mathrm{T}}\Theta(t)B_i\xi(t)\right.\\
&\left.+E\left[\Delta B_i^{\mathrm{T}}\left(x(t)\right)\Theta(t)\Delta B_i\left(x(t)\right)\right]\right)\\
&+\mathrm{trace}\left(L(t)\hat{Q}L^{\mathrm{T}}(t)\Theta(t)\right)\Big\}
\end{aligned}
$$

or

$$
\begin{aligned}
&E\left[\dot{V}\left(\xi(t),t\right)\right] \le -\xi^{T}(t)\Big\{\Theta(t)\Big[\sum_{i=1}^{M}\left(\sigma_{i0}+\varepsilon_{3i}\right)^{2}B_i\Sigma(t)B_i^{\mathrm{T}}\\
&+L(t)\hat{Q}L^{\mathrm{T}}(t)\Big]\Theta(t)\Big\}\xi(t)\\
&+E\left[2\xi^{\mathrm{T}}(t)\Theta(t)L(t)\Delta A\left(x(t),\hat{x}(t)\right)\right]\\
&+\sum_{i=1}^{M}\left(\sigma_{i0}+\varepsilon_{3i}\right)^{2}\left(\xi^{\mathrm{T}}(t)B_i^{\mathrm{T}}\Theta(t)B_i\xi(t)\right.\\
&\left.+E\left[\Delta B_i^{\mathrm{T}}\left(x(t)\right)\Theta(t)\Delta B_i\left(x(t)\right)\right]\right)\\
&+\mathrm{trace}\left(L(t)\hat{Q}L^{\mathrm{T}}(t)\Theta(t)\right)\Big\}
\end{aligned}
$$

It is easy to see that

$$
\begin{aligned}
&E\left[2\xi^{\mathrm{T}}(t)\Theta(t)L(t)\Delta A\left(x(t),\hat{x}(t)\right)\right]\\
&\le \frac{1}{\alpha_1}\xi^{\mathrm{T}}(t)\Theta(t)L(t)L^{\mathrm{T}}(t)\Theta(t)\xi(t)\\
&+\alpha_1 E\left[\Delta^{\mathrm{T}}A\left(x(t),\hat{x}(t)\right)\Delta A\left(x(t),\hat{x}(t)\right)\right]\\
&\le \xi^{T}(t)\left[\frac{1}{\alpha_1}\Theta(t)L(t)L^{\mathrm{T}}(t)\Theta(t)+\alpha_1\max\left(\rho_1,\rho_2\right)I\right]\xi(t)
\end{aligned}
\tag{17}
$$

and

$$
\begin{aligned}
&E\left[\Delta B_i^{\mathrm{T}}\left(x(t)\right)\Theta(t)\Delta B_i\left(x(t)\right)\right]\\
&=2E\left[\Delta G_i^{\mathrm{T}}\left(x(t)\right)\Theta(t)\Delta G_i\left(x(t)\right)\right]\\
&\le 2\lambda_{\max}\left(\Theta(t)\right)E\left[\Delta G_i^{\mathrm{T}}\left(x(t)\right)\Delta G_i\left(x(t)\right)\right]\\
&\le 2\lambda_{\max}\left(\Theta(t)\right)\delta_i\xi^{\mathrm{T}}(t)\xi(t)
\end{aligned}
\tag{18}
$$

According to (17) and (18), and by using the Lyapunov stability theory, it is possible to obtain

$$
\begin{aligned}
&E\left[\dot{V}\left(\xi(t),t\right)\right] \le -\xi^{\mathrm{T}}(t)\Big\{\Theta(t)\Big(\sum_{i=1}^{M}\left(\sigma_{i0}+\varepsilon_{3i}\right)^{2}B_i\Sigma(t)B_i^{\mathrm{T}}\\
&+L(t)\left(\hat{Q}-\frac{1}{\alpha_1}I\right)L^{\mathrm{T}}(t)\Big)\Theta(t)-\alpha_1\max\left(\rho_1,\rho_2\right)I\\
&-\lambda_{\max}\left(\Theta(t)\right)\sum_{i=1}^{M}\left(\sigma_{i0}+\varepsilon_{3i}\right)^{2}\left(2\delta_i I+B_i^{\mathrm{T}}B_i\right)\Big\}\xi(t)\\
&+\mathrm{trace}\left(C(t)\hat{Q}C^{\mathrm{T}}(t)\Theta(t)\right)\\
&\le -\gamma\xi^{\mathrm{T}}(t)\Theta(t)\xi(t)+\mu
\end{aligned}
$$

where $\mu = \mathrm{trace}\left(L(t)\hat{Q}L^{\mathrm{T}}(t)\Theta(t)\right) < \infty$ (from the non-singularity of the last term of (14) we know that $\Sigma(t)$ is singular and $\Theta(t)$ is bounded) and $\gamma > 0$ provided that

$$
\begin{aligned}
&\min\lambda_i\Big(\Theta(t)\Big\{\sum_{i=1}^{M}\left(\sigma_{i0}+\varepsilon_{3i}\right)^{2}B_i\Sigma(t)B_i^{\mathrm{T}}\\
&+L(t)\left(\hat{Q}-\frac{1}{\alpha_1}I\right)L^{\mathrm{T}}(t)-\left[\alpha_1\max\left(\rho_1,\rho_2\right)I\right.\\
&\left.+\lambda_{\max}\left(\Theta(t)\right)\sum_{i=1}^{M}\left(\sigma_{i0}+\varepsilon_{3i}\right)^{2}\left(2\delta_i I+B_i^{\mathrm{T}}B_i\right)\Sigma^{2}(t)\right\}\Big) > 0, \forall t \ge 0
\end{aligned}
\tag{19}
$$

Equation (19) was obtained by applying the Rayleigh principle and algebraic manipulations, where $\lambda$ denotes the eigenvalue.

According to Definition 1, the stochastic gene network becomes exponentially more stable with the exponentially decaying rate $\gamma$. This means that the estimation error never diverges if noises do not force the gene network to diverge when the stability condition is satisfied.

 

## 4. DEMONSTRATIVE EXPERIMENTS

Consider the nonlinear stochastic gene network illustrated in **Figure 1**. The system model can be mathematically described by (1), and the values of the parameters are taken from [23]:

$$\begin{aligned}
&\left(\kappa_{tetR,0},\kappa_{tetR},\gamma_{tetR}\right)=\left(150,2000,1.98\right),\\
&\left(\Delta\kappa_{tetR},\Delta\gamma_{tetR}\right)=\left(50,0.3\right),\\
&\left(\kappa_{lacI,0},\kappa_{lacI},\gamma_{lacI}\right)=\left(587,2000,0.05\right),\\
&\left(\Delta\kappa_{lacI},\Delta\gamma_{lacI}\right)=\left(200,0.3\right),\\
&\left(\kappa_{cI,0},\kappa_{cI},\gamma_{cI}\right)=\left(210,2000,0.7\right),\\
&\left(\Delta\kappa_{cI},\Delta\gamma_{cI}\right)=\left(50,0.3\right),\\
&\left(\kappa_{eyfp,0},\kappa_{eyfp},\gamma_{eyfp}\right)=\left(3487,15000,0.57\right),\\
&\left(\Delta\kappa_{eyfp},\Delta\gamma_{eyfp}\right)=\left(200,0.3\right)
\end{aligned} \tag{20}$$

The initial state is assumed to be $x_0=\begin{bmatrix}200 & 40000 & 200 & 20000\end{bmatrix}^{\mathrm{T}}$ and the Hill function takes the Hill coefficient $n=2$, the repression coefficient $K_r=1000$, and the maximal expression level of the promoter $\beta_r=1$. The extrinsic noise, intrinsic noise, and measurement noise are zero-mean white Gaussian noises with the standard deviations of $0.5^2$, $0.1^2$, and 1, respectively. For the measurement model in (2), the basal light intensity $F_0=10^5$, and $l\varepsilon=10^{-6}$.

**Figure 3** shows the dynamic simulation of the noisy states. For this synthetic gene network, the protein CI inhibits gene *eyfp* and gene *tetR*, the protein TetR inhibits gene *lacI*, and the protein LacI inhibits gene *cI*. However, one only possesses the measurement output response depicted in **Figure 4**.

These linearized matrices can obtain the following bounds on linearization errors using the remainder formula of the Taylor approximation [25]:

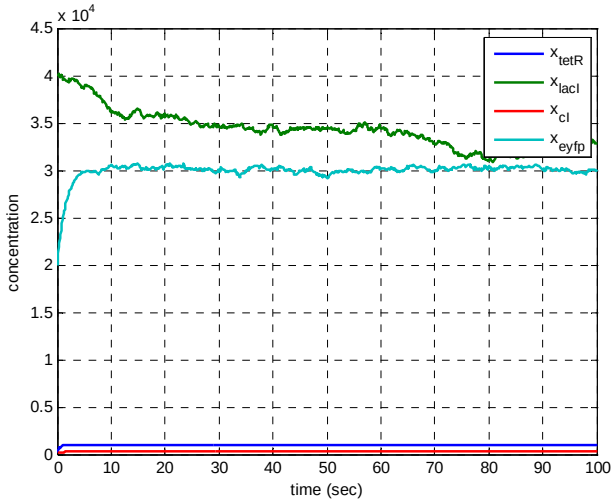


**Figure 3.** Dynamic simulation of the noisy states.

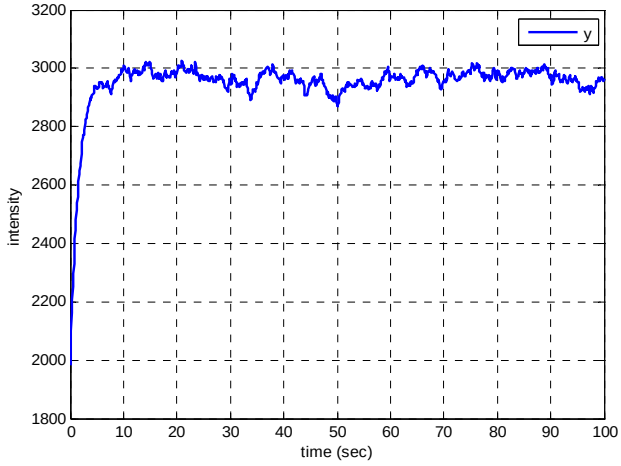


**Figure 4.** Dynamic simulation of the measurement output.

$$F=\begin{bmatrix}
-1.98 & 0 & \dfrac{-\hat{x}_{cI}}{250\left(1+\dfrac{\hat{x}_{cI}^2}{10^6}\right)^2} & 0\\
\dfrac{-\hat{x}_{tetR}}{250\left(1+\dfrac{\hat{x}_{tetR}^2}{10^6}\right)^2} & -0.05 & 0 & 0\\
0 & \dfrac{-\hat{x}_{lacI}}{250\left(1+\dfrac{\hat{x}_{lacI}^2}{10^6}\right)^2} & -0.7 & 0\\
0 & 0 & \dfrac{-3\hat{x}_{cI}}{100\left(1+\dfrac{\hat{x}_{cI}^2}{10^6}\right)^2} & -0.57
\end{bmatrix},$$

$$G_1=\begin{bmatrix}
-0.3 & 0 & \dfrac{-\hat{x}_{1cI}}{10^4\left(1+\dfrac{\hat{x}_{cI}^2}{10^6}\right)^2} & 0\\
0 & 0 & 0 & 0\\
0 & 0 & 0 & 0\\
0 & 0 & 0 & 0
\end{bmatrix},$$

$$G_2=\begin{bmatrix}
0 & 0 & 0 & 0\\
\dfrac{-\hat{x}_{tetR}}{2500\left(1+\dfrac{\hat{x}_{tetR}^2}{10^6}\right)^2} & -0.3 & 0 & 0\\
0 & 0 & 0 & 0\\
0 & 0 & 0 & 0
\end{bmatrix},$$

$$G_3=\begin{bmatrix}
0 & 0 & 0 & 0\\
0 & 0 & 0 & 0\\
0 & \dfrac{-\hat{x}_{lacI}}{10^4\left(1+\dfrac{\hat{x}_{lacI}^2}{10^6}\right)^2} & -0.3 & 0\\
0 & 0 & 0 & 0
\end{bmatrix},$$

 

$$G_4 = \begin{bmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & \dfrac{-\hat{x}_{cI}}{2500\left(1+\dfrac{\hat{x}_{cI}^2}{10^6}\right)^2} & -0.3 \end{bmatrix}$$

and

$$H = \begin{bmatrix} 0 & 0 & 0 & 0.1e^{-10^{-6}\hat{x}_{eyfp}} \end{bmatrix}$$

These linearized matrices reveal that the bounds on the linearization errors are as follows:

$$E\left[\Delta F^{\mathrm{T}}(x,\hat{x})\Delta F(x,\hat{x})\right] \le 237E\left[(x-\hat{x})^{\mathrm{T}}(x-\hat{x})\right],$$

$$E\left[\Delta H^{\mathrm{T}}(x,\hat{x})\Delta H(x,\hat{x})\right] \le 0.2642E\left[(x-\hat{x})^{\mathrm{T}}(x-\hat{x})\right],$$

$$E\left[\Delta G_3^{\mathrm{T}}(x)\Delta G_3(x)\right] = E\left[\Delta G_1^{\mathrm{T}}(x)\Delta G_1(x)\right] \le 0.0025E\left[x^{\mathrm{T}}x\right],$$

$$E\left[\Delta G_4^{\mathrm{T}}(x)\Delta G_4(x)\right] = E\left[\Delta G_2^{\mathrm{T}}(x)\Delta G_2(x)\right] \le 0.04E\left[x^{\mathrm{T}}x\right]$$

for all $x,\ \hat{x} \in \mathbb{R}^4$.

Suppose that the nominal covariance matrices are $Q_0 = 0.5^2 I_4$, $R_0 = 1$ and $\sigma_{i0} = 0.1^2$, $\forall i$, and the initial state of the estimator is $\hat{x}_0 = \begin{bmatrix} 300 & 20000 & 100 & 40000 \end{bmatrix}^{\mathrm{T}}$. For the initial covariance of $\Sigma(0) = 100 I_8$, **Figure 5** shows the simulation results of the noise-free state response and the case of state estimation using the proposed method for the stochastic gene network without noise uncertainties. The steady-state KF gain is

$$K(\infty) = \begin{bmatrix} 0.0536 & -0.142 & -0.0929 & 1.1602 \end{bmatrix}^{\mathrm{T}}$$

It's seen that the estimator tracked the noise-free state well when there were intrinsic, extrinsic, and measurement noises.

Next, consider the existence of uncertainty regarding extrinsic noise, measurement noise, and intrinsic noise with $\varepsilon_1 = 0.05$, $\varepsilon_2 = 0.1$, and $\varepsilon_{3i} = 0.01$, $\forall i$. **Figure 6** shows the results of dynamic simulation of the noise-free state response and the case of state estimation using the proposed method for the stochastic gene network with noise uncertainties. For the case, the steady-state KF gain is obtained as

$$K(\infty) = \begin{bmatrix} 0.0536 & -0.1422 & -0.0929 & 1.1616 \end{bmatrix}^{\mathrm{T}}$$

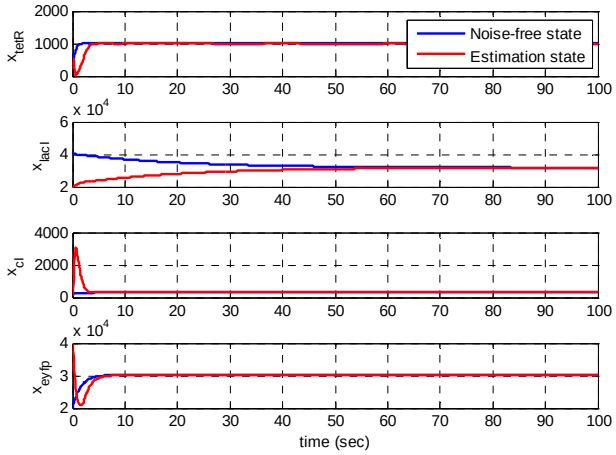


**Figure 5.** Dynamic simulation of the noise-free state response and the cases of state estimation using the proposed method for the stochastic gene network without noise uncertainties.

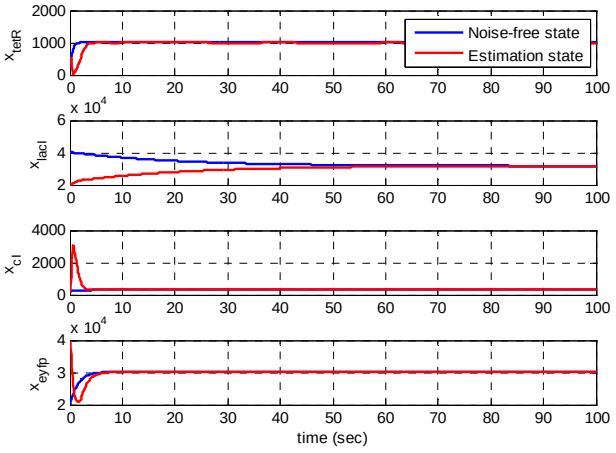


**Figure 6.** Dynamic simulation of the noise-free state response and the case of state estimation using the proposed method for the stochastic gene network with noise uncertainties.

For comparison, we define the estimation error as

$$\text{error} = \sqrt{\frac{\int_0^{t_f}\left(\hat{x}(t)-x_f(t)\right)^2 \mathrm{d}t}{\int_0^{t_f} x_f^2(t)\,\mathrm{d}t}}$$

where $x_f(t)$ is the state of the noise-free system, and $t_f$ is the final time. **Table 1** has compared the error percentage of the estimation error under the noise-free environment and the estimated states of the system with and without noise uncertainties via the traditional EKF design and our proposed method. Under the same initial conditions and settings, the dynamic simulation of the noise-free state response and the case of state estimation using the traditional EKF for the stochastic gene network with noise uncertainties yield larger estimation error.

## 5. DISCUSSION

Previous literature indicates that the state variables of

 

**Table 1.** Comparison of the estimation error for the stochastic gene network.

| estimation error | state | | | |
|---|---|---|---|---|
| | $x_{tetR}$ | $x_{lacI}$ | $x_{cI}$ | $x_{eyfp}$ |
| system without noise uncertainties under the proposed EKF design | 0.0918 | 0.1784 | 0.8145 | 0.0372 |
| system with noise uncertainties under the proposed EKF design | 0.0918 | 0.1784 | 0.8143 | 0.0373 |
| system with noise uncertainties by the traditional EKF design | 0.0981 | 0.1780 | 0.8466 | 0.0453 |

experimental systems in the field of biological frameworks cannot be fully acquired [23]. For the steady gene concentration tracking problem, fluorescent proteins (with red, green, and cyan color) can be used to observe gene expressions. This experimental design makes it possible to determine whether all state variables can approach desired states. However, this approach does not solve the problem of noise corruption because the observed state variables can still be noisy and seriously deteriorate the accuracy of state information. Nevertheless, a robust state estimator based on the EKF is a useful design for predicting network states when there are various noise sources. The resulting state information can next be used to analyze and track gene concentration.

## 6. CONCLUSION

This paper proposes a robust estimation scheme to acquire state information for a class of gene networks that are suffered from uncertain extrinsic and intrinsic noise corruption. Quantitative performance and stability analyses based on the Ito Theorem and Lyapunov stability theory for state estimation are presented. *In silico* experiments confirm the proposed method for designing the estimator. Simulation results demonstrate the potential of the presented design method in bridging engineering approaches and specific biological problems.

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