On the estimation of robustness and filtering ability of dynamic biochemical networks under process delays, internal parametric perturbations and external disturbances

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Abstract

Inherently, biochemical regulatory networks suffer from process delays, internal parametrical perturbations as well as external disturbances. Robustness is the property to maintain the functions of intracellular biochemical regulatory networks despite these perturbations. In this study, system and signal processing theories are employed for measurement of robust stability and filtering ability of linear and nonlinear time-delay biochemical regulatory networks. First, based on Lyapunov stability theory, the robust stability of biochemical network is measured for the tolerance of additional process delays and additive internal parameter fluctuations. Then the filtering ability of attenuating additive external disturbances is estimated for time-delay biochemical regulatory networks. In order to overcome the difficulty of solving the Hamilton Jacobi inequality (HJI), the global linearization technique is employed to simplify the measurement procedure by a simple linear matrix inequality (LMI) method. Finally, an example is given in silico to illustrate how to measure the robust stability and filtering ability of a nonlinear time-delay perturbative biochemical network. This robust stability and filtering ability measurement for biochemical network has potential application to synthetic biology, gene therapy and drug design.

1. Introduction

In living cells, the interactions of genes and proteins build up of dynamic genetic regulatory networks. In these networks, the internal parameter perturbations include kinetic parameter variations in molecular processes of transcriptional control, alternative splicing, translation, diffusion and chemical modification. In contrast, the external molecular disturbances come from the transmitted noise from upstream genes and the global noise affecting the expression of all genes. These processes also bring about the effect of process delays. A mixed integer linear programming framework has been discussed for inferring time delay in gene regulatory networks [1], and the stability of gene regulatory network with time delay has also been discussed [2,3]. Despite the process delays, intrinsic kinetic parameter variations and external disturbances, most cellular events are ordered and precisely regulated [4–9]. For example, development of *Caenorhabditis elegans* (C. elegans) is so regular that we can trace the differentiated states of nearly every cell [10]. In *Drosophila melanogaster* embryos, the transition from disorder to order has been measured [11]. Although the anterior-to-posterior gradient of the maternal morphogen bicoid in *D. melanogaster* embryo displays significant variability, the profile of the hunchback gap gene, which is regulated by bicoid, is precise. The need for order has led to the proposal that robust stability and filtering ability are inherent properties of biochemical networks [6–10,12,13].

Robust stability is a fundamental property of biological systems [8]. Given the importance of robustness in understanding the function principles of biochemical networks and their medical implications, it is important to formulate a mathematically solid and possibly unified theory for biological robustness that might serve as a basic organizational principle of biological systems. Such a unified theory could be a bridge between the fundamental principles of life, medical practice, engineering, physics and chemistry [8]. It is a difficult challenge in which a number of issues have to be solved for establishment of mathematically well-founded theories. However, the impact could be enormous [8].

In the last decade, robustness in bacterial chemotaxis, hox genes, neuron-genetic networks, circadian rhythms and biochemical networks has been widely discussed under kinetic parameter variation due to intracellular fluctuations [14]. Recently, the filtering ability of genetic networks to attenuate the effect of external disturbances has also been an important topic of signal...
transmission in systems biology [12–15]. Although examples of robust cellular process abound, how cells are able to function under process delays and biochemical fluctuations remains unclear [12,13]. These questions present one of the most challenging and fascinating problems for systems biologists, as they raise questions in physiology, development and evolutionary biology [7–9]. In order for biochemical networks to maintain their functions, they must be able to cope with these types of internal fluctuations, external noise and the effects of time delay [3,8,16,17]. The robustness is shown to arise from the systematic properties of regulatory networks rather than from a single mechanism [8,14,17]. Apparently, both the robustness against process delays and intrinsic parameter perturbations as well as the filtering ability against external disturbances arise from complex mechanisms involving multiple feedback loops. Recently, stability robustness of biochemical networks without time-delay has been investigated from the frequency domain perspective based on the linearized models [1–3,9,18] and from the steady state perspective based on S-system model [5,19,20].

In this study, new measures of robust stability and filtering ability are proposed for biochemical networks. Based on dynamic system models, we can estimate the robustness for linear and nonlinear time-delay biochemical regulatory networks. The kinetic parameter variations due to internal molecular fluctuations are modeled as additive state-dependent noise, which will influence the stability of the biochemical regulatory network. The environmental and extrinsic noises are modeled as additive external disturbances, which have fluctuation effects on the performance of biochemical regulatory network. The robustness to tolerate the process delays and intrinsic parameter perturbations is analyzed by Lyapunov (energy-like) stability theory [21], while the filtering ability to attenuate the effect of external disturbances on biochemical networks is examined by nonlinear robust filtering theory. Both linear and nonlinear time-delay biochemical perturbative regulatory networks are discussed in this study. The techniques of nonlinear stabilization, nonlinear filtering and constrained optimization are employed to efficiently measure the robust stability and the filtering ability of biochemical time-delay regulatory networks.

Because of the nonlinearity of the time-delay biochemical networks, estimations of both the robust stability and filtering ability need to be done by solving a nonlinear Hamilton-Jacobi inequality (HJI), which can not be easily solved except in some special cases. In this study, global linearization [22,23] is employed to simplify the measurement procedure by solving the corresponding linear matrix inequalities (LMIs) instead. Estimations of both the robust stability and filtering ability in a time-delay perturbative biochemical network are potential for robust designs of synthetic gene networks [4,8,16,17,20,24–26] and for therapeutic drug designs [15]. For example, a prescribed robust stability and a desired filtering ability must be specified before designing a synthetic gene network which is suffered from intrinsic parameter variation due to DNA mutation and evolution and from external disturbance due to the context in the host cells, and a prescribed robust stability and a desired filtering ability must be specified before synthesis circuit design [4,8,17,27]. Besides, a cause of diseases can be considered as the loss of robust stability and the reduction of filtering ability of biochemical networks. In this way, the stability of the biochemical network is violated by intrinsic parameter perturbations, the external disturbances such as pathogens cannot be efficiently attenuated, and the performance of the biochemical network is deteriorated [28,29]. Therefore, by the estimation method in this study, the designer could complete their genetic therapy and drug designs by filling in the blanks of how the robust stability and filtering ability of the corresponding biochemical networks can be improved [15,28,29]. Finally, a time-delay perturbative biochemical network example is given in silico to estimate the robust stability to parameter fluctuation and the filtering ability to external disturbance.

2. Preliminaries of time-delay perturbative biochemical networks

For simplicity of analysis, the robust stability of linear time-delay perturbative biochemical network is discussed first. It is also useful to highlight the global linearization approach for the robustness measure of nonlinear time-delay biochemical system in the sequel. The linear biochemical network with process delays can be suitably modeled by the following dynamic system [1,20]

\[
X(t) = A_0 X(t) + \sum_{i=1}^l A_{di} X(t - \tau_i), \quad X(t) = X_0(t), \quad \forall t \in [-\tau, 0]
\]

(1)

In (1), the state vector \(X(t)\) denotes the expression vector of the concentrations of the molecules, e.g. mRNAs, proteins, or other chemical complexes in the biochemical network at time \(t\). \(A_0\) and \(A_{di}\) denote the real-time and delay-time interactive matrices among these molecules (see Fig. 1). The index \(i\) indicates that these regulations are associated with time delays of \(\tau_i\) for \(l = 1 \ldots L\) due to the time needed for transcription, translation, post-translation, signal transduction or molecular diffusion in the biochemical process while the maximum time delay is \(\tau = \max(\tau_i, i \in \{1, L\})\). In real dynamic biochemical processes, process delays always exist and will influence the stability of the biochemical network [4]. In this situation, the process delays should be considered in a dynamic biochemical model to mimic the real biochemical process. Suppose the biochemical network consists of \(n\) molecules with stoichiometric matrices as follows

\[
X(t) = \begin{bmatrix} x_1(t) \\ x_2(t) \\ \vdots \\ x_{n-1}(t) \\ x_n(t) \end{bmatrix}, \quad A_0 = \begin{bmatrix} 0_{0,11} & a_{0,12} & \cdots & \cdots & 0_{0,1n} \\ a_{0,21} & \ddots & \cdots & \cdots & \cdots \\ \vdots & \ddots & \ddots & \cdots & \cdots \\ 0_{0,n1} & \cdots & \cdots & \cdots & a_{0,nn} \end{bmatrix}
\]

\[
A_{di} = \begin{bmatrix} a_{di,11} & a_{di,12} & \cdots & \cdots & a_{di,1n} \\ a_{di,21} & \ddots & \cdots & \cdots & \cdots \\ \vdots & \ddots & \ddots & \cdots & \cdots \\ a_{di,n1} & \cdots & \cdots & \cdots & a_{di,nn} \end{bmatrix}
\]

(2)

where \(x_i(t)\), \(i = 1 \ldots n\) are the concentrations of different molecules (mRNAs, proteins and other complexes) in the biochemical network; the diagonal component \(a_{0,ii}\) of \(A_0\) denotes the degradation of biochemical process of the \(i\)th molecule; the kinetic parameter \(a_{ij}\) means the interaction from molecule \(j\) to molecule \(i\). So does the term of \(a_{di,ij}\).

Remark 0. For a linear biochemical network, the interactive parameter \(a_{0ij} > 0\) means that molecule \(j\) activates the biochemical process of molecule \(i\); the interactive parameter \(a_{0ij} < 0\) means that molecule\(j\) inhibits the biochemical process of molecule \(i\); the kinetic parameter \(a_{0ij} = 0\) means that there is no interaction between molecule \(j\) and molecule \(i\); and so does the term of \(a_{di,ij}\).

Suppose the kinetic parameters of a biochemical network are affected by the following real-time and delay-time intrinsic perturbations (see Fig. 1)
\[ \dot{X}(t) = (A_0 + \Delta A)X(t) + \sum_{i=1}^{l} (A_{dl} + \Delta A_{dl})X(t - \tau_i) \]  

where \( \Delta A_0 = \begin{bmatrix} \Delta a_{0,11} & \Delta a_{0,12} & \cdots & \Delta a_{0,1n} \\ \Delta a_{0,21} & \cdots & \cdots & \cdots \\ \vdots & \cdots & \cdots & \cdots \\ \Delta a_{0,ni} & \cdots & \cdots & \Delta a_{0,nn} \end{bmatrix} \) and

\[ \Delta A_{dl} = \begin{bmatrix} \Delta a_{dl,11} & \Delta a_{dl,12} & \cdots & \Delta a_{dl,1n} \\ \Delta a_{dl,21} & \cdots & \cdots & \cdots \\ \vdots & \cdots & \cdots & \cdots \\ \Delta a_{dl,ni} & \cdots & \cdots & \Delta a_{dl,nn} \end{bmatrix} \]

i.e. \( \Delta A_0 \) and \( \Delta A_{dl} \) may individually be the combination of several kinds of intrinsic perturbations with real-time and time-delay, for example, due to thermal fluctuation, alternative splicing, DNA mutation, or molecular diffusion etc. In order to establish a solid quantitative index of robustness and to equate with experimentally measurable quantities, the perturbation matrices \( \Delta A_0 \) and \( \Delta A_{dl} \) are assumed to be arbitrary but bounded as follows

\[ \| \Delta A_0 \|_2 \leq \alpha_0, \quad \text{or} \quad \| \Delta A_0 \|_2 \leq \alpha_0 \| A_0 \|_2 \]

\[ \| \Delta A_{dl} \|_2 \leq \alpha_l, \quad \text{or} \quad \| \Delta A_{dl} \|_2 \leq \alpha_l \| A_{dl} \|_2 \]

for some constants \( \alpha_0 \) and \( \alpha_l \), where the matrix norm \( \| A \|_2 = \mu_{max}(A^T A)^{1/2} \) is denoted as the largest singular value [30]. In other words, the intrinsic parameter perturbations are all bounded and finite as (4).

In general, the interactions of biochemical networks are nonlinear in real biochemical systems. In this situation, (3) should be modified as follows [1,20]

\[ \dot{X}(t) = f_0(X(t)) + \sum_{i=1}^{l} f_{dl}(X(t - \tau_i)), \quad X(0) = X_0, \quad \forall t \in [-\tau, 0] \]

where \( f_0(X(t)) = [f_{0,1}(X(t)) \cdots f_{0,ni}(X(t))]^T \) and \( f_{dl}(X(t - \tau_i)) = [f_{dl,1}(X(t - \tau_i)) \cdots f_{dl,ni}(X(t - \tau_i))]^T \) denote the nonlinear interactions among \( n \) molecules in real-time and delay-time, respectively.

Suppose the biochemical system suffers from nonlinear intrinsic perturbations as follows

\[ \dot{X}(t) = f_0(X(t)) + \Delta f_0(X(t)) + \sum_{i=1}^{l} (f_{dl}(X(t - \tau_i)) + \Delta f_{dl}(X(t - \tau_i))), \]

\[ X(t) = X_0(t), \quad \forall t \in [-\tau, 0] \]

where \( \Delta f_0(X(t)) = [\Delta f_{0,1}(X(t)) \cdots \Delta f_{0,ni}(X(t))]^T \) and \( \Delta f_{dl}(X(t - \tau_i)) = [\Delta f_{dl,1}(X(t - \tau_i)) \cdots \Delta f_{dl,ni}(X(t - \tau_i))]^T \) denote the combinations of the several kinds of intrinsic perturbations with real-time and time-delay, respectively. The perturbation vectors \( \Delta f_0(X(t)) \) and \( \Delta f_{dl}(X(t - \tau_i)) \) in the nonlinear biochemical network (6) are arbitrary but bounded by the following inequality

\[ \| \Delta f_0(X(t)) \|_2 \leq \beta_0 \| X(t) \|_2, \quad \| \Delta f_{dl}(X(t - \tau_i)) \|_2 \leq \beta_1 \| X(t - \tau_i) \|_2 \]

(7)

or

\[ \Delta f_0^{T}(X(t))\Delta f_0(X(t)) \leq \beta_0^2 X^T(t)X(t), \]

\[ \Delta f_{dl}^{T}(X(t - \tau_i))\Delta f_{dl}(X(t - \tau_i)) \leq \beta_1^2 X^T(t - \tau_i)X(t - \tau_i), \quad \forall i = 1 \cdots L \]

for some positive constants \( \beta_0 \) and \( \beta_1 \), where the vector norm is defined as \( \| X(t) \|_2 = \left( x_1^2(t) + \cdots + x_n^2(t) \right)^{1/2} \). The implication of (7) is that the nonlinear perturbations are within a sector with slopes \( \pm \beta_0 \) and \( \pm \beta_1 \), respectively.
Before further analysis of robust stability, the definition about the ‘stability’ should be given firstly.

**Definition 1.** [31]

The equilibrium point $X = 0$ is said to be stable if, for any $\epsilon > 0$, there exists $\delta > 0$, such that if $\|X(0)\| < \delta$, then $\|X(t)\| < \epsilon$ for all $t \geq 0$. Otherwise, the equilibrium point is unstable.

**Definition 2.** [32,33]

Given an equilibrium point $X = 0$ in an uncertain biochemical system with perturbations such as (3) or (6), the equilibrium point is said to be robustly stable if the equilibrium point is still stable under the effects of intrinsic perturbations.

**Definition 3.** [21,23,34]

If there exists a symmetric positive definite matrix $P$ for the equilibrium point $X = 0$ with a positive Lyapunov function $V(X) > 0$ with $dV(X)/dt \leq 0$ along every nonzero trajectory, then we say the equilibrium point of the system is Lyapunov stable.

We employed these concepts of stability from system and signal processing viewpoints for the following measurement of robust stability and filtering ability of linear and nonlinear time-delay biochemical regulatory networks. In this study, we assume that the equilibrium point of interest (i.e. the phenotype of biochemical network is near this equilibrium point with which we are concerned) is at the origin $X = 0$. If the equilibrium point of interest is not at the origin, for the convenience of analysis and estimation, it should be shifted to the origin.

### 3. Robust stability estimation in biochemical networks under time-delays and intrinsic parameter perturbations

Based on Lyapunov stability theory [21], we could obtain the following robust stability proposition for a dynamic linear/nonlinear biochemical network with process delays and intrinsic parameter perturbations.

**Proposition 1.** For the nonlinear perturbative biochemical network in (6), if the following Hamilton-Jacobi inequality (HJI) holds for a Lyapunov function $V(X(t)) > 0$, and two scale values $\gamma_1 > 0$ and $\gamma_2 > 0$

\[
\left( \frac{\partial V(X(t))}{\partial X(t)} \right)^T \left( f(X(t)) + \sum_{i=1}^{n} \left( \frac{\partial V(X(t))}{\partial X(t)} \right)^T f_{d,i}(X(t) - \tau_i) \right)
+ \frac{1}{2} \gamma_1 \left( \frac{\partial V(X(t))}{\partial X(t)} \right)^T \left( \frac{\partial V(X(t))}{\partial X(t)} \right) + \frac{1}{2} \gamma_1 \beta_2 X^T(t) X(t)
+ \frac{1}{2} \gamma_2 \sum_{i=1}^{n} \beta_i^2 X^2(t - \tau_i) X(t - \tau_i) \leq 0
\]
then the nonlinear time-delay biochemical network is robustly stable under bounded parameter perturbations in (7).

**Proof.** see Appendix A. □

**Remark 1.** In order to guarantee the stability of a nonlinear time-delay biochemical network in (5) or (6), we need to find a Lyapunov function $V(X(t))$ to satisfy the inequality (8). In general, it is not easy to solve the HJI and at present there is no systematic method to find a Lyapunov function $V(X(t))$ for a nonlinear time-delay biochemical network such that (8) holds to guarantee the robust stability. For the convenience of analysis and estimation, the global linearization method [22,23] is employed for robust stabilization and filtering ability estimation in the following sections. Consider the following global linearization of nonlinear system (6) [22,23]

\[
\frac{\partial}{\partial X} [f_0(X(t)) f_{d,1}(X(t - \tau_1)) \ldots f_{d,k}(X(t - \tau_k))] \in \Omega \quad \text{for all} \quad X
\]

where the polytope $\Omega \subseteq \mathbb{R}^{(l+c) \times n}$. For example, if $f_0(X(t)) = g_0(X(t)) X(t), f_{d,1}(X(t - \tau_1)) = g_{d,1}(X(t - \tau_1)) X(t - \tau_1)$ then $[g_0(X(t)) g_{d,1}(X(t - \tau_1)) \ldots g_{d,k}(X(t - \tau_k))] \in \Omega$. Suppose $A_{d,j}$ and $A_{d,k}$ for $j = 1 \ldots M, k = 1 \ldots L$ denote the vertices of the convex hull of $\Omega$, i.e. [22,23]

\[
\Omega \subset \text{Co} \left\{ \begin{bmatrix} A_{d,1} & A_{d,2} & \ldots & A_{d,M} \\ A_{d,1,L} & A_{d,2,L} & \ldots & A_{d,M,L} \end{bmatrix} \right\}
\]

where (10) denotes a convex hull of $\Omega$, consisting of $M$ vertices via the real-time linearization matrices $A_{d,1}, \ldots A_{d,M}$, and the delay-time linearization matrices $A_{d,1,L}, \ldots A_{d,M,L}, l = 1 \ldots L$. Then the stability property of the trajectory of the nonlinear time-delay biochemical system (6) could be represented by the stability properties of the following linearized systems at vertices [22,23]

\[
X = A_{d,j} X(t) + \sum_{l=1}^{M} A_{d,1,L} X(t - \tau_l) + \Delta f_0(X(t)) + \sum_{l=1}^{L} \Delta f_{d,l}(X(t - \tau_l)),
\]

\[
X(t) = X_0(t), \quad \forall t \in [-\tau, 0], \quad j = 1 \ldots M
\]

and the nonlinear biochemical network in (6) can be interpolated by the linearized biochemical systems at $M$ vertices in (10) as follows [22,23]

\[
\begin{align*}
X(t) &= f_0(X(t)) + \sum_{l=1}^{M} f_{d,l}(X(t - \tau_l)) + \Delta f_0(X(t)) + \sum_{l=1}^{L} \Delta f_{d,l}(X(t - \tau_l)) \\
&= \sum_{j=1}^{M} \zeta_j(X(t)) \left[ A_{d,j} X(t) + \sum_{l=1}^{M} A_{d,1,L} X(t - \tau_l) \right] \\
&\quad + \Delta f_0(X(t)) + \sum_{l=1}^{L} \Delta f_{d,l}(X(t - \tau_l)),
\end{align*}
\]

\[
X(t) = X_0(t), \quad \forall t \in [-\tau, 0], \quad j = 1 \ldots M
\]

where $\zeta_j(X(t))$ are some normalized interpolation functions with $0 \leq \zeta_j(X(t)) \leq 1$ and $\sum_{j=1}^{M} \zeta_j(X(t)) = 1$ [35]. This means that the nonlinear biochemical network could be represented by interpolating $M$ linearized biochemical networks at the vertices of the convex hull [23]. If the set of the above linearized time-delay biochemical systems in (11) is stable, then the nonlinear time-delay biochemical network in (6) is stable. Theoretically, the interpolation via the global linearization method can approach a nonlinear time-delay network. In practice, it is still difficult to efficiently choose an appropriate polytope for the global approximation of complex nonlinear time-delay network. At present, it is still not easy to answer the questions that how many vertices we picked up is reasonable and how the polytope encloses the convex hull without trial and error. The more vertices we choose, the more exact polytope we could get. However, huge number of vertices would make our method too complex to get the reasonable solution. Furthermore, the convex hull may not be interpolated by a polytope with finite vertices exactly. In order to efficiently solve the global linearization problems above, we introduce the approximation errors for finite vertices selection and denote them as follows.
\[
\dot{f}_0(X) = f_0(X(t)) - \sum_{j=1}^{M} \xi_j(X(t)) A_{0,j} X(t) \\
\dot{f}_i(X) = \dot{f}_i(X(t - \tau_i)) - \sum_{j=1}^{M} \xi_j(X(t)) A_{i,j} X(t - \tau_i) \quad \text{for } i = 1 \cdots L
\]

If the approximation error is bounded and small enough, then we could replace the global linearization method with infinite vertices by one with finite vertices. After finding the system matrices \(A_{0,j}\) and \(A_{i,j}\) via global linearization with suitable finite vertices, we could easily find the bounds \(\epsilon_i\) on the interpolation errors for \(i = 0, 1, \ldots, L\) as follows
\[
\|\dot{f}_0(X)\|_2 \leq \epsilon_0 \|X(t)\|_2, \quad \|\dot{f}_i(X)\|_2 \leq \epsilon_i \|X(t - \tau_i)\|_2, \quad \text{for } i = 1 \cdots L
\]

or
\[
\dot{f}_0^2(X) \leq \epsilon_0^2 X^2(t), \quad \dot{f}_i^2(X) \leq \epsilon_i^2 X^2(t - \tau_i) X(t - \tau_i)
\]

In this situation, the representation of nonlinear perturbative biochemical system in (6) could be rewritten as follows
\[
X(t) = f_0(X(t)) + \sum_{i=1}^{L} \dot{f}_i(X(t - \tau_i)) + \Delta f_0(X(t)) + \sum_{i=1}^{L} \Delta f_i(X(t - \tau_i))
\]

\[
= \sum_{i=1}^{M} \xi_j(X) \left[ A_{0,j} X(t) + \sum_{i=1}^{L} A_{i,j} X(t - \tau_i) \right] + \Delta f_0(X(t))
\]

\[
+ \sum_{i=1}^{L} \Delta f_i(X(t - \tau_i)) + \sum_{i=0}^{L} \dot{f}_i(X)
\]

\[
X(t) = X_0(t), \quad \forall t \in [-\tau, 0]
\]

Further, the robust stability and filtering ability techniques of a linear biochemical network in (3) could be extended to discuss the robust stability and filtering ability problem of nonlinear biochemical network under time-delays, intrinsic parameter perturbations and external disturbances with approximation errors.

First, let us choose Lyapunov function \(V(X(t)) > 0\) as the following quadratic function from the energy point of view
\[
V(X(t)) = X^T(t) P X(t) + \sum_{i=1}^{L} \int_{0}^{\tau_i} X^T(t - s) P X(t - s) ds
\]

for some symmetric positive definite matrices \(P\) and \(P_i > 0\). If we can obtain \(\dot{V}(X(t)) \leq 0\), then the dynamic time-delay biochemical network in (3) or (15) is defined as quadratically stable \([21,34]\), i.e. the energy of the biochemical network is not increasing. If this is the case, the biochemical network could tolerate these parameter perturbations and be robustly stable.

**Proposition 2.** Suppose the linear dynamic time-delay biochemical network in (3) suffers from parameter perturbations bounded by (4). Then the linear perturbative time-delay biochemical network in (3) is robustly stable if the following inequality has symmetric positive definite solutions \(P = P^T > 0, P_i = P_i^T > 0, \gamma_1 > 0, \gamma_2 > 0\)
\[
\begin{bmatrix}
A_{0,j}^T P + P A_{0,j} + \gamma_1 e_0^2 I + \sum_{i=1}^{L} P_i & P & P A_{0,1,j} & \cdots & P A_{0,L,j} \\
\vdots & \ddots & \ddots & \ddots & \vdots \\
P & \cdots & \cdots & \cdots & \cdots \\
A_{1,j}^T P & 0 & \cdots & \cdots & \cdots \\
A_{L,j}^T P & 0 & \cdots & \cdots & \cdots \\
\end{bmatrix} \leq 0
\]

or equivalent to the following inequality by Schur Complements \([23]\)
\[
A_{0,j}^T P + P A_{0,j} + \gamma_1 e_0^2 I + \sum_{i=1}^{L} P_i + (\gamma_1^2 + \gamma_2^2) L P P
\]

\[
- \sum_{i=1}^{L} P A_{0,j}(\gamma_2 e_1^2 I - P_i)^{-1} A_{0,j}^T P \leq 0
\]

**Proof.** see Appendix B. \(\square\)

Similarly, using the global linearization technique, we could get the following robust stability result for nonlinear time-delay biochemical network.

**Proposition 3.** The interpolated time-delay biochemical network in (6) or (15) is stable under parametric perturbation if the following inequalities have common solutions \(P = P^T > 0, P_i = P_i^T > 0, \gamma_1 > 0, \gamma_2 > 0\)
\[
\begin{bmatrix}
A_{0,j}^T P + P A_{0,j} + \gamma_1 e_0^2 I + \sum_{i=1}^{L} P_i & P & P A_{0,1,j} & \cdots & P A_{0,L,j} \\
\vdots & \ddots & \ddots & \ddots & \vdots \\
P & \cdots & \cdots & \cdots & \cdots \\
A_{1,j}^T P & 0 & \cdots & \cdots & \cdots \\
A_{L,j}^T P & 0 & \cdots & \cdots & \cdots \\
\end{bmatrix} \leq 0
\]

**Proof.** see Appendix C. \(\square\)

**Remark 2.**

(i) If the linear biochemical network in (3) is free of process delays and intrinsic perturbation, the stability condition in (18) is reduced to the following inequality
\[
A_{0,j}^T P + P A_{0,j} \leq 0
\]

i.e. if the eigenvalues of \(A_0\) are all in the left half complex \(s\)-domain (or the real parts of eigenvalues \(\leq 0\)), then the linear biochemical network is stable.
(b) If the linear biochemical network in (3) is free of time-delays, then the robust stability condition in (18) is reduced to
\[ A_0^T P + PA_0 + \gamma_1 z_1^2 I + \gamma_1^{-1} PP \leq 0 \]  \tag{21}

The last two terms of robust stability condition in (21) are needed to tolerate the parameter perturbation \( \Delta A_0 \). Therefore, the eigenvalues of \( A_0 \) should be more far in the complex \( s \)-domain than that in (20) to guarantee the robust stability against the parameter perturbation \( \Delta A_0 \).

(c) If the linear biochemical network in (3) is only free of intrinsic parameter perturbation, the stability condition in (18) becomes the following inequality
\[ A_0^T P + PA_0 + \sum_{l=1}^{L} \sum_{i=1}^{l} P_l + \sum_{l=1}^{L} PA_l P_l^{-1} A_0^T P \leq 0 \]  \tag{22}
i.e. in order to overcome the effects of process delays, two additional terms with respect to (20) are needed for robust stability. Therefore, the eigenvalues of \( A_0 \) should be all far in the left half complex \( s \)-domain [21] to guarantee the more negative inequality in (22) than that in (20) of the non-delay system. Clearly, the process delays will influence the system stability. If many delay processes or long time delays are involved, a biochemical network may be unstable or oscillate when these delay processes cannot be tolerated by the robust stability of the biochemical network [36]. From (18), in order to bear large \( \gamma_1 \) and \( \gamma_2 \), \( P_l \) must be large enough so that \( \gamma_1 z_1^2 I - P_l < 0 \) for \( l = 1 \cdots L \). In this situation, the fourth term \( \sum_{l=1}^{L} P_l \) in (18) would become much more positive. It is also important to tolerate the other extra terms, \( (\gamma_1^{-1} + \gamma_2^{-1} L) PP + \gamma_1 z_1^2 I \) due to parameter perturbations. Thus the locations of the eigenvalues of \( A_0 \) must be far away in the left hand side of the \( s \)-domain than that in any of (20), (21), or (22), i.e. the real parts of eigenvalues must be more negative (or with larger stability margin) [32].

(d) The specifications of two positive values \( \gamma_1 \) and \( \gamma_2 \) in (17) and (18) will influence the conservation of the robust stability solution. With appropriate choice of \( \gamma_1 \) and \( \gamma_2 \) to (17) and (18), the tolerances \( \zeta_0 \) and \( \zeta_1 \) of parameter perturbations in (4) will be increased.

(ii) The physical meaning of the results in (19) is that if the linearized time-delay biochemical systems at the vertices of the globally linearized systems in (15) are all stable, then the nonlinear system (6) is stable. In general, using the LMI toolbox in Matlab [37], it is easier to check the LMIs in (19) than to solve the nonlinear inequality in (8) directly.

(iii) By the global linearization theory [23], the quadratic stability of nonlinear perturbative time-delay biochemical network can be equivalent to the quadratic stability of the set of globally linearized systems. Obviously, we use M LMIs in (19) of linearized systems at M vertices to replace the HJI in (8) of nonlinear system. With the help of global linearization method, we could extend all the robust stability characteristics in a linear biochemical network to the robust stability characteristics of the set of the globally linearized systems of a nonlinear biochemical network, i.e. \( A_{0,j} \) would play the role as \( A_0 \).

(iv) By Shur Complement [23], the LMIs in (19) are equivalent to the following inequalities
\[
\begin{align*}
(\gamma_1^{-1} + \gamma_2^{-1} L) PP + \gamma_1 (\beta_0^2 + \epsilon_0^2) I + \sum_{l=1}^{L} P_l \hfill \\
&- \sum_{l=1}^{L} P_l A_{0,l} (\beta_1^2 + \epsilon_1^2) I - P_l - A_{0,l}^T P_l A_{0,l} < \gamma_1^{-1} (A_{0,j}^T P + PA_{0,j})
\end{align*}
\]  \tag{23}

for \( j = 1 \cdots M \), i.e. all the eigenvalues of each linearized system \( A_{0,j} \) should be far enough in the left hand plane of the complex \( s \)-domain (i.e. the real parts of eigenvalues of \( A_{0,j} \) are more negative) so that robust stability inequality in the right hand side of (23) is guaranteed to be large enough to tolerate those terms in the left hand side due to parameter perturbations and time-delays in (6). In this situation, negative feedback loops in a biochemical network are favored by natural selection in the evolution process to move these eigenvalues to the far left-hand \( s \)-domain to increase the right terms of (23). Further, redundancy, multiple heterogeneous components and decoupling are also favored by natural selection in biochemical networks in order to make \( \beta_0, \beta_1 \) and \( L \) as small as possible to decrease the left hand side of (23) not to violate the robust stability [38,39].

In order to estimate the robust stability characteristically, a new measure of robust stability (or stability margin) of the linear time-delay biochemical network (3) is proposed as the following
\[
\alpha = \max_{\gamma_1 \geq 0} \min_{P > 0} \left( \frac{\max_{P > 0} \lambda_i} {\max_{\gamma_1 > 0} \lambda_i} \right)
\]

subject to \( P > 0, P_l > 0, \gamma_1 > 0, \gamma_2 > 0 \), \( l = 1 \cdots L \) \tag{24}

Similarly, the robust stability of the nonlinear time-delay biochemical network (6) could be measured as follows
\[
\beta = \max_{\gamma_1 \geq 0} \min_{P > 0} \left( \frac{\max_{P > 0} \lambda_i} {\max_{\gamma_1 > 0} \lambda_i} \right)
\]

subject to \( P > 0, P_l > 0, \gamma_1 > 0, \gamma_2 > 0 \), and \( l = 1 \cdots L \) i.e. \( \alpha \) and \( \beta \) are the largest tolerance abilities to parameter perturbation without violation of stability of the time-delay biochemical network in (3) and (6), respectively. The robust stability measure problems in (24) and (25) could be easily solved by the LMI tools which will be introduced in (iii) of Remark 5.

**Remark 3.**

(i) If the linear system in (3) is free of time-delays, then the measure of robust stability is reduced to
\[
\alpha = \max_{\gamma_1 \geq 0} \min_{P > 0} \left( \frac{\max_{P > 0} \lambda_i} {\max_{\gamma_1 > 0} \lambda_i} \right)
\]

subject to \( P > 0, \gamma_1 > 0, \gamma_2 > 0 \). \tag{26}

(ii) Based on the steady state of the S-system model, a measure of robust stability of biochemical network has been introduced [19]. Further, based on transfer function in frequency domain, a robust stability of linear biochemical network without time-delays is also discussed [9]. However, this study considers the dynamic system of time-delay biochemical network from a more general perspective.

(iii) Since robust stability is only a sufficient condition, any measure of robust stability derived from the conditions might underestimate robust stability, i.e. systems that violate these conditions may be robustly stable.

4. Filtering ability in biochemical networks under time-delays, intrinsic parameter perturbations, and environmental noises.

In addition to the process delays and intrinsic kinetic parameter perturbations, the biochemical network also suffers from external disturbance as follows (see Fig. 1)
\[
\dot{X}(t) = (A_0 + \Delta A_0)X(t) + \sum_{l=1}^{L} (A_{0,l} + \Delta A_{0,l})X(t - \tau_l) + B_0 v(t)
\]

\[
Z(t) = C_0 X(t)
\]

\[
Y(t) = C_0 X(t)
\]
or
\[ X(t) = f_0(X(t)) + \Delta f_0(X(t)) + \sum_{i=1}^{L} \left( f_i(X(t - \tau_i)) + \Delta f_i(X(t - \tau_i)) \right) + g(X(t)) \eta(t) \]
\[ Z(t) = C_2 X(t) \]
(28)

where \( \eta(t) = [\eta_1(t) \cdots \eta_{i}(t) \cdots \eta_{n}(t)]^T \) denotes the environmental and extrinsic disturbances with the linear and nonlinear coupling matrix \( B_2 \) and \( g(X(t)) \) to the network; \( Z(t) \) denotes the molecules in the biochemical network we want to observe. For example, if we want to observe the effect of molecular disturbance \( \eta(t) \) on a molecule of interest \( i \), then \( C_2 = [0 \ 0 \ \cdots \ 1 \ 0 \ \cdots \ 0] \), i.e. all elements of \( C_2 \) are zero except 1 at the ith component. If we want to observe the effect of disturbances on all the molecules in the biochemical network, then \( C_2 = I_{\text{num}} \), which is an identity matrix.

The external disturbances include the environmental disturbances and the extrinsic disturbances, which consist of the disturbances from other biochemical networks and the intracellular disturbances from cellular communications or interactions [40]. For instance, the disturbance from the upstream transcription factor concentrations is the former; the various social behaviors of bacteria, macromolecular transport fluctuations between neighboring cells within the plasmodesmata, and the undefined interactions with cellular context between host cells are part of the latter [40–42].

The day–night cycle is a famous example for environmental disturbance. We then want to discuss the robust stability to tolerate parameter fluctuations and the filtering ability to attenuate the effects of external molecular disturbance \( \eta(t) \) on molecules \( Z(t) \) in the perturbative time-delay biochemical network (27) and (28).

In a dynamic biochemical network with process delays, intrinsic parameter fluctuations and external disturbances, the biochemical network needs not only to tolerate the process delays and intrinsic fluctuations (i.e. robust stability) but also to filter the effect of external molecular disturbances (i.e. noise filtering) so that it can function properly. Let us denote a measure of molecular signal \( X(t) \) as follows
\[
\|X(t)\|_{L_2} = \left( \int_0^{\infty} X^T(t) X(t) dt \right)^{1/2}
\]
(29)

We call \( X(t) \) is \( L_2 \) if \( \|X(t)\|_{L_2} < \infty \). Then the effect of external disturbance \( \eta(t) \) on \( Z(t) \) is said to be less than a positive value \( \rho \) if the following inequality holds [34]
\[
\frac{\|Z(t)\|_{L_2}^2}{\|\eta(t)\|_{L_2}^2} \leq \rho^2 \quad \text{or} \quad \|Z(t)\|_{L_2} \leq \rho \|\eta(t)\|_{L_2}
\]
(30)

for all \( \eta(t) \in L_2 \), \( \eta(t) \neq 0 \), and \( X(T) = 0 \) for \( T \leq 0 \); i.e. the effect of external disturbance \( \eta(t) \) on the molecular concentration of interest does not exceed a prescribed attenuation value \( \rho \) or the disturbance attenuation is \( \rho \) at the interested molecule of the biochemical network.

If \( X(T) \neq 0 \) for \( T \leq 0 \), then inequality (30) should be modified as [34]
\[
\|Z(t)\|_{L_2}^2 \leq V(X(0)) + \rho^2 \|\eta(t)\|_{L_2}^2
\]
(31)

The attenuation level \( \rho_0 \) is defined as the smallest \( \rho \) in (30) and denoted as follows
\[
\rho_0 \equiv \min \rho
\]
(32)
i.e. the effect of all possible external disturbance on the interested molecule is less than \( \rho_0 \). The concentration \( Z(t) \) is attenuated by the disturbance \( \eta(t) \) if \( \rho_0 < 1 \), and is amplified by this disturbance if \( \rho_0 > 1 \). A larger \( \rho_0 \) means that a biochemical network is more sensitive to external disturbance, i.e. the sensitivity is proportional to \( \rho_0 \) and the filtering ability is inversely proportional to \( \rho_0 \). If a biochemical network is affected by the external disturbances easily (large \( \rho_0 \)), then the network is said to have a high sensitivity or to be with a weak structure. Based on the definition of attenuation level \( \rho_0 \) on external disturbance, we could gain more insight into the effect of environmental and extrinsic disturbances on individual molecules of the time-delay biochemical network. When diseases are considered as a perturbed biochemical network problem due to pathway dysfunctions (internal parameter fluctuations) and pathogens (external molecular disturbances) [15,28,29], our study has potential for genetic therapy and drug design by improving the robust stability and filtering ability.

**Remark 4.** \( \rho \) in (30) can be consider as the upper bound of disturbance attenuation level \( \rho_0 \), which is defined as
\[
\rho_0 = \max_{\|\eta(t)\|_{L_2} \neq 0} \frac{\|Z(t)\|_{L_2}}{\|\eta(t)\|_{L_2}}, \text{ i.e. the worst case signal to disturbance ratio at } \eta(t) \\
\]

some molecule of the biochemical network. Therefore, the minimization in (32) is to minimize its upper bound to achieve the disturbance attenuation level \( \rho_0 \). That is to say, we do not solve the attenuation level \( \rho_0 \) from the optimization problem \( \max_{\|\eta(t)\|_{L_2} \neq 0} \frac{\|Z(t)\|_{L_2}}{\|\eta(t)\|_{L_2}} \)

directly, but solve this problem from (30) and (32) from the suboptimal perspective.

Based on the analysis above, the following results can be obtained to study the filtering ability in a time-delay biochemical network.

**Proposition 4.** Suppose the linear time-delay biochemical network in (27) suffers from the intrinsic parameter perturbations \( \Delta A_0 \) and \( \Delta A_{ij} \) as (4) and external disturbance \( \eta(t) \). If there exists symmetric positive definite matrices \( P \), \( P_\epsilon \), and \( g_1 > 0 \), \( g_2 > 0 \) such that the following inequality holds for a prescribed filtering value \( \rho \)

\[
\begin{bmatrix}
A_0^T P + P A_0 + \gamma_1 g_1^2 I + \sum_{i=1}^{L} P_i + C_2^T C_2 & P & P & P A_{d1} & \cdots & P A_{dL} & P B P \\
-\gamma_1 I & 0 & \cdots & 0 & \cdots & 0 & 0 \\
0 & -L^{-1} \gamma_2 I & 0 & \cdots & 0 & \cdots & 0 \\
A_{d1}^T P & 0 & 0 & g_2 g_1^2 I - P_1 & 0 & \cdots & 0 \\
\vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\
A_{dL}^T P & 0 & 0 & \cdots & \cdots & \cdots & \cdots \\
B_i^T P & 0 & 0 & \cdots & \cdots & \cdots & -\rho^2 I \\
\end{bmatrix} \leq 0
\]
(33)

then the effect of \(v(t)\) on \(Z(t)\) is less than or equal to \(\rho\), i.e. the desired filtering of disturbance in (30) or (31) holds.

**Proof.** see Appendix D.

Similarly, to discuss the robust stability and the filtering ability on external molecular disturbance \(v(t)\) at molecules \(Z(t)\) in the nonlinear perturbative time-delay biochemical network (28), the following result can be derived

**Proposition 5.** If the following inequality holds for a Lyapunov function \(V(X(t)) > 0\) and a prescribed attenuation value \(\rho\) with \(\gamma_1 > 0, \gamma_2 > 0\)

\[
\begin{align*}
&\left(\frac{\partial V(X(t))}{\partial X(t)}\right)^T f_0(X(t)) + \sum_{i=1}^{L} \left(\frac{\partial V(X(t))}{\partial X(t)}\right)^T f_{ai}(X(t - \tau_i)) \\
&+ \frac{1}{2} \sum_{i=1}^{L} \left(\frac{\partial V(X(t))}{\partial X(t)}\right)^T \frac{\partial V(X(t))}{\partial X(t)} + \frac{1}{2} \gamma_1 \rho^2 g^T(t) X(t) \\
&+ \frac{1}{2} \sum_{i=1}^{L} \gamma_2 \sum_{j=1}^{m} b_{ij}^T X(t - \tau_i) X(t - \tau_j) \\
&+ \frac{1}{2} \sum_{i=1}^{L} \frac{\partial V(X(t))}{\partial X(t)} g(X(t)) g^T(t) \frac{\partial V(X(t))}{\partial X(t)} \\
&+ \frac{1}{2} Z^T(t) Z(t) \leq 0
\end{align*}
\]

then the nonlinear perturbative time-delay biochemical network in (28) with bounded parameter perturbations in (7) is robustly stable and the effect of external disturbance \(v(t)\) on \(Z(t)\) is less than \(\rho\); i.e. the robust filtering with a desired attenuation value \(\rho\) in (30) or (31) is achieved for the nonlinear time-delay biochemical network in (28).

**Proof.** see Appendix E.

**Remark 5.**

(i) Since the LMI in (33) implies the LMI in (17), the robust stability (against the delays \(\tau_i\) and parameter fluctuations \(\Delta A_{0}, \Delta A_{kl}\) bounded by (4)) and the desired disturbance attenuation value \(\rho\) (below which external disturbance \(v(t)\) is attenuated) are both achieved in Propositions 4. Furthermore, the LMI in (33) is more constrained than the LMI in (17) because in addition to robust stability, the time-delay biochemical network still needs to filter external disturbance \(v(t)\) to a prescribed value \(\rho\). That is to say, the eigenvalues of \(A_0\) should be sufficiently far to the left hand side of s-domain to avoid being perturbed easily by parameter variation and external disturbance to the right hand side of s-domain.

(ii) According to the definition of attenuation level \(\rho_0\) in (32), a measure of attenuation level for a linear time-delay biochemical network in (27) can be obtained by solving the following constrained optimization problem

\[
\rho_0 = \min_{P_{\gamma_1, \gamma_2}} \rho \\
\text{subject to } \rho > 0, P > 0, P_{\gamma_1} > 0, \gamma_1 > 0, \gamma_2 > 0, \text{ and } (33)
\]

In general, smaller attenuation level \(\rho_0\) means better filtering ability or lower sensitivity to external molecular disturbance, whereas larger attenuation level \(\rho_0\) means worse filtering ability or more sensitive to external molecular disturbance.

(iii) The constrained optimization in (35) can be easily solved with the LMI toolbox in MATLAB [23,37], SeDuMi in MATLAB [43], LMI-tool in SCILAB [44] through the interior-point methods [45,46], or SDPA methods implemented in C++ [47,48] through the Generalized Augmented Lagrangian Method [49]. These two methods can reduce \(\rho\) until no positive definite \(P > 0\) and \(P_1 > 0\) are solved in (35).

(iv) By Schur complements [23], the LMI in (33) is equivalent to

\[
\begin{align*}
&\gamma_1 \rho^2 I + \frac{1}{\rho^4} P B_2 B_2^T P - \sum_{l=1}^{L} P A_{li}(\gamma_2^2 I - P_l^{-1}) A_{lj}^T P_l \\
&+ \sum_{l=1}^{L} P_l + C_l^T C_l + (\gamma_1^2 + L_2^2) P P \leq -(A_0^T P + P A_0)
\end{align*}
\]

From the right hand side of (36), it can be seen that the robustness of the biochemical network is related to the negative real part of the eigenvalues of \(A_0\). The left hand side of (36) is related to time delays, intrinsic parameter perturbations and external disturbances. The physical meaning of (36) is that if the eigenvalues of system matrix \(A_0\) are far in the left hand complex s-domain (i.e. the real part of the eigenvalues of \(A_0\) is more negative), then the biochemical network will be more robust to tolerate the parameter perturbations and process time-delays, thus filtering more external disturbances. Obviously, for a fixed robustness (i.e. the location of eigenvalues of \(A_0\) are fixed or the right hand side of (36) is fixed), if the biochemical network wants to tolerate large intrinsic parameter variations (large \(\alpha_0\) and \(\chi_0\)), \(\rho\) should be large enough (less filtering or more sensitive to external disturbance) in order to let the second term \(\frac{1}{\rho^4} P B_2 B_2^T P\) in (36) be small. Similarly, if we want the linear time-delay biochemical network in (27) to filter more external disturbances (i.e. less sensitivity or smaller \(\rho\)), then the first and third term in (36) should be small (i.e. small \(\rho\) in (24) or less robust stability). Therefore we could conclude that robust stability against intrinsic parameter perturbations and filtering ability against external disturbances are in a trade-off relationship [18,50].

(v) In order to maintain robust stability and filtering ability in (33) or (36) in evolution, two strategies are employed to achieve the robust stability and filtering ability of biochemical networks [38,39]. The first is to increase the right hand side of (36) and the other is to decrease the left hand side of (36). Negative feedback loops is the first strategy which could shift eigenvalues of \(A_0\) to be more negative (stable) to increase the right hand side of (36). Together with redundancy, multiple heterogeneous components, modularity and decoupling structures, which could reduce time-delay and attenuate the parameter variation and external noises to decrease the left hand side of (36), are the second one. Both of them are the more favored structures of biochemical networks by natural selection. As pointed out by Kitano [8], robust stability is a fundamental property of biological systems. It facilitates evolvability, and evolution selects robust traits [8]. These statements could be confirmed by our propositions about biochemical networks from the mathematical perspective.

(vi) In general, it is not easy to solve the Hamilton-Jacobi inequality (HJI) in (34) for the robust disturbance filtering problem. In the nonlinear time-delay biochemical system
Based on the vertices of the convex hull of the linearization of the nonlinear biochemical network in (28), if there are common solutions $P > 0$, $P_1 > 0$, $\gamma_1 > 0$ and $\gamma_2 > 0$ for the following LMIs,

$$
\begin{bmatrix}
\Xi & P & P A_{d,1,2} & \ldots & P A_{d,1,L} & P B_j \\
P & -\gamma_1 I & 0 & \ldots & 0 \\
P & 0 & -L^{-1} \gamma_2 I \\
A_{d,1,j}^T P & \gamma_2 (\beta_i^2 + \epsilon_i^2) I - P_1 & \ldots \\
\vdots & \vdots & \vdots \\
A_{d,1,j}^T P & \gamma_2 (\beta_i^2 + \epsilon_i^2) I - P_L & 0 \\
B_j^T P & 0 & \ldots & -\rho^2 I
\end{bmatrix} \leq 0
$$

(38)

where $\Xi = A_{d,1}^T P + P A_{d,1} + \gamma_1 (\beta_0^2 + \epsilon_0^2) I + C_2^T C_2 + \sum_{l=1}^L P_l$, and $j = 1 \ldots M$, then the robust stability to tolerate parameter perturbations with perturbation bounds $\beta_0$ and $\beta_l$ in (7) as well as the robust filtering with a prescribed attenuation value $\rho$ in (30) are all achieved for the nonlinear perturbative time-delay biochemical network in (28). We need to solve $M$ LMIs in (38) instead of solving the HJI in (34).

(vii) The LMIs in (38) are equivalent to

$$
\gamma_1 (\beta_0^2 + \epsilon_0^2) I + \frac{1}{\rho^2} P B_j^T P - \sum_{l=1}^L P A_{d,1,j} (\gamma_2 (\beta_i^2 + \epsilon_i^2) I - P_l) A_{d,1,j}^T P + (\gamma_1^{-1} + \gamma_2^{-1}) L P + C_2^T C_2 + \sum_{l=1}^L P_l \leq - (A_{d,1}^T P + P A_{d,1})
$$

(39)

Thus, following the inference from (iv) in linear case, robust stability and filtering ability are held in a trade-off relationship for a nonlinear perturbative biochemical network [85-53].

(viii) Similar to (ii) in the linear case, the attenuation level $\rho_0$ in a nonlinear time-delay biochemical network, defined as the minimum $\rho$ to solve HJI in (34), could be replaced by minimizing $\rho$ via the following constrained optimization problem

$$
\rho_0 = \min_{\rho, P, \gamma_1, \gamma_2} \rho
$$

subject to $P > 0$, $P_1 > 0$, $\gamma_1 > 0$, $\gamma_2 > 0$, and (38)

which could be easily solved by LMI toolbox in Matlab and other software as in (iii).
The *E. coli* lactose operon biochemical network includes the processes of transcription, translation, transport, mRNA decay, mRNA synthesis, protein decay, protein synthesis and so on. The constant term in the first equation denotes the spontaneous rate of mRNA concentration. Since our study focuses on the analysis of robust stability and filtering ability, the further details of this biochemical network could be referred to [54].

Suppose we want to measure the robust stability of the following perturbative biochemical network

\[
\begin{align*}
\dot{M} &= \frac{9.97 \times 10^{-1}(1 + 25,086A^2(t - 0.1))}{7200 + 25,086A^2(t - 0.1)} + 7.25 \times 10^{-7} \\
&\quad - 0.4336M(t) + \left(\frac{9.97 \times 10^{-1}(1 + 25,086A^2(t - 0.1))}{7200 + 25,086A^2(t - 0.1)}\right)p_1 \\
&\quad + (7.25 \times 10^{-7} - 0.4336M(t))p_0 \\
\dot{B} &= 0.01586B(t - 2) - 0.02343B(t) + (0.01586B(t - 2))p_2 \\
&\quad - 0.02343B(t)p_0 \\
\dot{A} &= 17,600 \frac{B(t)L(t)}{0.97 + L(t)} - 21,500 \frac{B(t)A(t)}{1.95 + A(t)} - 0.5426A(t) \\
&\quad + \left(17,600 \frac{B(t)L(t)}{0.97 + L(t)} - 21,500 \frac{B(t)A(t)}{1.95 + A(t)} - 0.5426A(t)\right)p_0
\end{align*}
\]

where \(p_0, p_1, p_2, \) and \(p_3\) are supposed different intrinsic parameter fluctuations due to alternative splicing transcription, fluctuations in translational processing, thermal fluctuations, and molecule diffusion. In this study, we assume that the intrinsic perturbations \(p_i\) would vary with time but be bounded with a positive constant \(M_i\) for \(i = 0, 1, 2, 3\) as follows

\[
|p_0| \leq M_0, \quad |p_1| \leq M_1, \\
|p_2| \leq M_2, \quad |p_3| \leq M_3
\]

Based on (28), the perturbative biochemical network (42) can be rewritten as follows

\[\hat{L} = 716.66P(t) - 2650 \frac{P(t)L(t)}{1.81 + L(t)} - 7614 \frac{B(t)L(t)}{0.972 + L(t)} + 1.6266L(t) + \left(\frac{716.66P(t) - 2650}{1.81 + L(t)}\right)p_1 \\
- 7614 \frac{B(t)L(t)}{0.972 + L(t)} - 1.6266L(t)\]

\[\hat{P} = 9.38M(t - 2.83) - 0.6726P(t) + (9.38M(t - 2.83))p_3 - 0.6726P(t)p_0\]
We employ the global linearization technique for the nonlinear dynamic time-delay biochemical system and estimate the robust stability of the biochemical system in two ways: (i) how large internal fluctuation $\beta$ in (25) could the system tolerate? and (ii) if the biochemical network suffers from internal perturbations, how small could the filtering level be for the biochemical network to attenuate the external disturbances?

We take five vertices of the system convex hull to come to a compromise and to interpolate the nonlinear biochemical system via the five linearized systems through the following suitable interpolation functions

$$
\xi_j(X(t)) = \frac{1}{|X_j - X(t)|^2} \sum_{i=1}^M \frac{1}{|X_j - X(t)|^2}, \quad j = 1 \cdots M
$$

with $M = 5$ by the metric interpolation method [35]. Through bringing the all possible $X_j$ into (45) and (13) to find the minimum approximation errors, the least errors bounds in (14) could be obtained as follows

$$
e_0 = 2.5 \times 10^{-2}, \quad e_1 = 3.2 \times 10^{-3}, \quad e_2 = 3.9 \times 10^{-3}, \quad e_3 = 2.4 \times 10^{-2}
$$

Suppose the intrinsic perturbations $\Delta f_0(X(t))$ and $\Delta f_{01}(X(t - t_1))$ could be bounded as (7) i.e.

$$
\|\Delta f_0(X(t))\| \leq 3.08 \times 10^{-2} M_0 \|X(t)\| \leq \beta_0 \|X(t)\|
$$

$$
\|\Delta f_{01}(X(t - t_1))\| \leq 7.37 \times 10^{-4} M_1 \|X(t - t_1)\| \leq \beta_1 \|X(t - t_1)\|
$$

$$
\|\Delta f_{02}(X(t - t_2))\| \leq 2.69 \times 10^{-5} M_2 \|X(t - t_2)\| \leq \beta_2 \|X(t - t_2)\|
$$

$$
\|\Delta f_{03}(X(t - t_3))\| \leq 1.59 \times 10^{-2} M_3 \|X(t - t_3)\| \leq \beta_3 \|X(t - t_3)\|
$$

where the relationship between $\beta_i$ and $M_i$ comes from the inherent character of this E. coli biochemical network. With suitable $\gamma_1$ and $\gamma_2$ in (19), the individual perturbation bounds of intrinsic perturbations which could tolerated are estimated as follows

$$
[M_0, M_1, M_2, M_3] = [7.08 \times 10^{-3}, 2.4 \times 10^{-1}, 7.01 \times 10^{0}, 1.18 \times 10^{-2}]
$$

with $[\beta_0 \beta_1 \beta_2 \beta_3] = [2.18 \times 10^{-4}, 1.77 \times 10^{-4}, 1.89 \times 10^{-4}, 1.89 \times 10^{-4}].$ From (25), the robust stability (robustness or stability margin) is estimated as $\beta = 1.77 \times 10^{-4}$. The simulations of nonlinear biochemical network with nominal, stable, and unstable time responses are given in Fig. 3(a)-(c) with free parameter perturbations, stable and unstable parameter perturbations $[p_0 \ p_1 \ p_2 \ p_3]$ with perturbation bounds $[M_0, M_1, M_2, M_3]$ as $[0 \ 0 \ 0 \ 0], [1 \times 10^{-4} \ 1 \times 10^{-2} \ 1 \times 10^{-1} \ 1 \times 10^{-3}], \text{and} [7 \times 10^{-4} \ 1 \times 10^{0} \ 5 \times 10^{-1} \ 1 \times 10^{-1}],$ respectively. For more insight into the system properties of a biochemical network, we also measure the robust stability without delay process and delay-time parameter perturbations. When the network is free of delays and delay-time perturbations, the robust stability $\beta = \beta_0 = 6.95 \times 10^{-4}$ and it is larger than $1.77 \times 10^{-4}$ of the contaminated biochemical network. In other words, the time-delay process and intrinsic perturbations could influence the robust stability explicitly.

Furthermore, suppose the operator network also suffers from external disturbances $\nu(t) = 0.15 \sin(0.01 \pi t) + 0.15 \cos(0.05 \pi t) + 0.1$, we could rewrite the network as follows

$$
A = 17.600 \begin{bmatrix}
B(t)L(t) & 0.97 + L(t) \\
0.97 + L(t) & 1.95 + A(t)
\end{bmatrix} + 21.500 \begin{bmatrix}
B(t)L(t) & 0.97 + L(t) \\
0.97 + L(t) & 1.95 + A(t)
\end{bmatrix} - 0.5426A(t)
$$

$$
\times p_0 + 0.1\nu(t)
$$

$$
L = 716.66P(t) - 2650 \begin{bmatrix}
P(t)L(t) & 0.97 + L(t) \\
0.97 + L(t) & 1.95 + A(t)
\end{bmatrix} - 1.62699L(t)
$$

$$
\times p_0 + 0.1\nu(t)
$$
with the other equations same as (42). In this case, we get the following parameter matrices $B_{pJ} = \begin{bmatrix} 0 & 0 & 0.1 & 0 \\ 0 & 0 & 0.1 & 0 \end{bmatrix}$, and $C_Z = \begin{bmatrix} 0 & 0 & 0 & 0 \end{bmatrix}$.

For the biochemical network with parameter fluctuations and external disturbances in (47), we could estimate the robust stability and filtering ability by solving (40). The solutions of $P$, $P_1$, $P_2$, and $P_3$ are given by

\[
\]

\[
P_1 = \begin{bmatrix} 814,227 & 723 & 0.1485 & 145 & -396 \\ 22,604,706 & -14,345 & 4,550,991 & -7,901,661 \\ 10,645 & -14,978 & 5061 \\ 930,111 & -1,591,934 \\ 5,514,582 & 740 & 0.4336 & 148 & -402 \\ 22,598,589 & -14,326 & 4,549,739 & -7,899,521 \\ 10,645 & -14,974 & 5053 \\ 929,855 & -1,591,496 \\ 2,770,433 \end{bmatrix}
\]

Meanwhile, the theoretical robust stability is measured as $\beta = 1.21 \times 10^{-5}$ where the related bounds of intrinsic perturbations are estimated as follows

\[
[M_0 M_1 M_2 M_3] = [3.94 \times 10^{-4} 1.64 \times 10^{-2} 4.85 \times 10^{-1} 8.21 \times 10^{-4}]
\]

and

\[
[\beta_0 \beta_1 \beta_2 \beta_3] = [1.21 \times 10^{-5} 1.21 \times 10^{-5} 1.31 \times 10^{-5} 1.31 \times 10^{-5}].
\]

The time response of the biochemical network under intrinsic parameter perturbations and external disturbances is shown in Fig. 3(d). Obviously, these bounds of intrinsic perturbations are all smaller than that without external disturbances.
By the proposed measurement method, the theoretical result of attenuation level is estimated as $\rho_0 = 0.1915$, but the realistic system attenuation value is measured as $\rho \approx 0.1440$ by practical simulation under the perturbation bounds $|M_4, M_1, M_2, M_3| = [3.9 \times 10^{-4} 1.6 \times 10^{-2} 4.8 \times 10^{-1} 8.2 \times 10^{-4}]$. Clearly, the lactose operon system could attenuate more external disturbance under the same intrinsic parameter fluctuations than the theoretical estimations. This is mainly due to the conservative nature of both Lyapunov stability and LMIs in the robust filtering estimation procedure.

The benchmark in silico example of E. coli operon biochemical network illustrates that our method could not only measure the robust stability of a nonlinear dynamic time-delay biochemical network to tolerate process delays and intrinsic parameter perturbations but also estimate the filtering ability when suffering external disturbances. The emergence of a disease could be considered as a process in which the biochemical network suffers from genetic perturbation and/or pathological environmental disturbance such as infectious agents or chemical carcinogens. Based on the proposed measure methods, the robust stability and filtering ability on a biochemical network can be analyzed and a drug design could be developed to improve the robust stability and filtering ability of some corresponding biochemical networks [28,52,55].

### 6. Discussion and conclusion

Robustness (or the robust stability) is an essential property which permits a biochemical network to maintain its routine functions under process delays, internal perturbations and environmental disturbances. It is not only a basic but also a ubiquitously system-level phenomenon. Thus a study of robustness is simply a study of why, when and how systems do or do not function properly [18,27,29]. In this study, based on robust system theory, we have estimated not only the robust stability against process delays and intrinsic perturbations from the Lyapunov stability perspective, but also the filtering ability to attenuate or amplify external disturbances from the signal filtering perspective, no matter whether the biochemical system is linear or nonlinear. To simplify the estimation method, we replaced the HJI in (34), which is not easy to solve, with a set of linear matrix inequalities (LMIs) in (38) via the global linearization method. The robust stability and filtering ability could gain more insight into the effect of process delays, intrinsic parameter perturbations, and environmental/extrinsic disturbances on individual molecules of the biochemical network.

In our simulation example as Fig. 3(a), the free-perturbative nonlinear dynamic time-delay biochemical networks are stable, but it is not easy to gain more insight into their robust stability for process delays, intrinsic parameter perturbations and filtering ability to attenuate external disturbances. By our robust stabilization and filtering analysis method, the nonlinear dynamic time-delay biochemical networks could be interpolated by a set of linearized biochemical networks with the global linearization technique to simplify the measurement procedure. We could efficiently measure the intrinsic parameter perturbation bound $b$ in (25) to inspect the robust stability of these biochemical networks by checking the existence of the symmetric positive definite matrices $P$ and $P_i$ of LMIs. We also used MATLAB, SDPA, SCILAB and so on. In time-delay biochemical network systems, if the robust stability is violated, then the cell behavior may be changed, resulting in another phenotype (see Fig. 3(b) and Fig. 3(c)). The simulation results in Fig. 3(c) show that when the perturbation bounds $M_6$, $M_1$, $M_2$, and $M_3$ (stability margins) of kinetic parameter fluctuations are violated, these kinetic parameter fluctuations can not be tolerated by the biochemical network again and would shift the interested equilibrium point of the biochemical network to another one. The simulation results also verify that the more delay-time process and parameter perturbations a system suffers the less robust stability the system has.

In biochemical networks, ‘robustness’ is the antonym of ‘sensitivity’. If a system is so robust that it could not adapt itself to a new environmental condition, then it would be eliminated by natural selection. On the contrary, a biochemical network which lost its robustness will blow up or shift to another equilibrium point (another phenotype). In this study, we define the sensitivity (fragility) as the attenuation level which is inversely proportional to the filtering ability.

Notwithstanding our method is useful and efficient, the estimation in this study is limited to the additive delay-time systems. The polypeptide of biochemical systems may be of multi-delay process, i.e. the non-additive interactions between variables at different delays in (5) may appear. In this study, the robust stability problem of non-additive interactions between variables at different delays is not within the scope and our method can not be applied directly. Hence, in order to avoid these difficulties, we only confine our study to the biochemical networks with additive interactions. The conservation of LMIs techniques is also another shortage of our method about the robust stability and filtering ability. Any measurement derived from LMIs might be underestimated.

In the evolutionary process of biochemical networks, because they are the backbone of physiological systems and need to function properly, there are two ways to improve the robustness against parameter fluctuation and environmental noise: (i) one scheme is to make the real parts of the real-time eigenvalues of the biochemical network as negative as possible, and negative feedback loops are of these kinds of schemes in biochemical network; and (ii) the other scheme is to make the parameter variation as small as possible [15], and multiple loop, redundancy, modularity and decoupling structures are of these schemes in biochemical networks. Under these aspects, in the future, the robustness and the filtering ability could potentially be used for drug design with gene therapy, since the drug design can be considered as the development of new drugs to enhance the robust stability for disease-perturbed biochemical networks to tolerate genetic fluctuations or to improve the filtering ability to attenuate some external disturbances from the pathogenic environment [15,28].

Recently, synthetic biology is to engineer artificial biological systems to investigate natural biological phenomena and for a variety of applications. However, the development of synthetic biological networks is still difficult and most newly created biological networks are non-functioning due to parameter perturbations and external disturbances on the host cell [56]. At present, how to design robust synthetic biological network to work properly under these parameter perturbations and disturbances is the most important topic of synthetic biology. The proposed method can help biological engineers estimate the robust stability and measure the filtering ability of synthetic biological networks before engineering these biological networks. Therefore, the proposed methods are useful for the design of robust synthetic biological networks in future.

### 7. Appendix

The following lemma is necessary for the proof of the propositions.

**Lemma 1.** [23]:

\[ a^T b + b^T a \leq \gamma a^T R a + \gamma^{-1} b^T R^{-1} b \]  

(A.1)

for any vector or matrix $a$, $b$, scalar $\gamma > 0$ and any $R = R^T > 0$. In the following proofs, we define $R = I$. For simplicity of notation, we repre-
sent \( X(t), X(t - \tau_1), Z(t) \) and \( v(t) \) as \( X, X_{d1}, Z, v \) respectively in the following proof.

Appendix A. Proof of Propositions 1

For the nonlinear dynamic time-delay biochemical network with nonlinear parametric fluctuation in (7), the robust stability theory based on Lyapunov function will be employed to discuss its robust stability. For Lyapunov function \( V(X) > 0 \), by chain rule, we have

\[
V = \left( \frac{\partial V(X)}{\partial X} \right)^T \frac{\partial X}{\partial t} \\
= \left( \frac{\partial V(X)}{\partial X} \right)^T \left( f_0(X) + \Delta \theta_0(X) + \sum_{i=1}^{l} \left( f_{d1}(X_{d1}) + \Delta \theta_{d1}(X_{d1}) \right) \right) \\
= \left( \frac{\partial V(X)}{\partial X} \right)^T f_0(X) + \sum_{i=1}^{l} \left( \frac{\partial V(X)}{\partial X} \right)^T f_{d1}(X_{d1}) + \frac{1}{2} \Delta \theta_0(X) \left( \frac{\partial V(X)}{\partial X} \right)^T + \frac{1}{2} \Delta \theta_{d1}(X_{d1}) \left( \frac{\partial V(X)}{\partial X} \right)^T + \frac{1}{2} \Delta \theta_{d1}(X_{d1}) \left( \frac{\partial V(X)}{\partial X} \right)^T f_{d1}(X_{d1}) \\
= \left( \frac{\partial V(X)}{\partial X} \right)^T f_0(X) + \sum_{i=1}^{l} \frac{1}{2} \Delta \theta_{d1}(X_{d1}) \left( \frac{\partial V(X)}{\partial X} \right)^T f_{d1}(X_{d1}) \\
+ \frac{1}{2} \gamma_1^{1-1} \left( \frac{\partial V(X)}{\partial X} \right)^T \left( \frac{\partial V(X)}{\partial X} \right) + \frac{1}{2} \gamma_1 \left( \frac{\partial V(X)}{\partial X} \right)^T \frac{\partial V(X)}{\partial X} \\
+ \frac{1}{2} \gamma_2 \left( \frac{\partial V(X)}{\partial X} \right)^T \frac{\partial V(X)}{\partial X} + \frac{1}{2} \gamma_2 \left( \frac{\partial V(X)}{\partial X} \right)^T f_{d1}(X_{d1}) \\
(\text{by (A.1)}) \\
\leq \left( \frac{\partial V(X)}{\partial X} \right)^T f_0(X) + \sum_{i=1}^{l} \frac{1}{2} \left( \frac{\partial V(X)}{\partial X} \right)^T f_{d1}(X_{d1}) \\
+ \frac{1}{2} \gamma_1^{1-1} \left( \frac{\partial V(X)}{\partial X} \right)^T \left( \frac{\partial V(X)}{\partial X} \right) + \frac{1}{2} \gamma_1 \left( \frac{\partial V(X)}{\partial X} \right)^T \frac{\partial V(X)}{\partial X} \\
+ \frac{1}{2} \gamma_2 \left( \frac{\partial V(X)}{\partial X} \right)^T \frac{\partial V(X)}{\partial X} + \frac{1}{2} \gamma_2 \left( \frac{\partial V(X)}{\partial X} \right)^T f_{d1}(X_{d1}) \\
(\text{by (7)})
\]

If the inequality in (8) holds, then \( V < 0 \) and the nonlinear perturbative biochemical network is robustly stable.

Appendix B. Proof of Propositions 2

Recall the linear time-delay perturbative biochemical network (3)

\[
\dot{X}(t) = \left( A_0 + \Delta A_0 \right) X(t) + \sum_{i=1}^{l} \left( A_{d1} + \Delta A_{d1} \right) X(t - \tau_i)
\]

\[
= \left( A_0 + \Delta A_0 \right) X(t) + \sum_{i=1}^{l} \left( A_{d1} + \Delta A_{d1} \right) X(t - \tau_i)
\]

where the \( A_0 \) and \( A_{d1} \) denote the real-time and delay-time interactive matrices among these molecules, and \( \Delta A_0, \Delta A_{d1} \) denote the relative intrinsic parameter perturbations with \( l \) process delays.

By choosing a Lyapunov quadratic function as

\[
V(X(t)) = X^T(t) P X(t) + \sum_{i=1}^{l} \int_{0}^{\tau_i} X^T(t - s) P X(t - s) \, ds > 0
\]

\[
= X^T P X + \sum_{i=1}^{l} \int_{0}^{\tau_i} X^T(t - s) P X(t - s) \, ds > 0
\]

then we have

\[
\frac{d}{dt} V = X^T P X + X^T P + \sum_{i=1}^{l} X^T P A_{d1} + \Delta A_{d1} X_{d1} + \sum_{i=1}^{l} X^T P X - \sum_{i=1}^{l} X^T P X_{d1}
\]

\[
= X^T \left( A_0^T + \Delta A_0^T \right) P X + \sum_{i=1}^{l} X^T P A_{d1} + \Delta A_{d1} X_{d1} + X^T P A_0 + \Delta A_0 X
\]

\[
+ \sum_{i=1}^{l} X^T P A_{d1} + \Delta A_{d1} X_{d1} + \sum_{i=1}^{l} X^T P X - \sum_{i=1}^{l} X^T P X_{d1}
\]

\[
= X^T \left( A_0^T P + \Delta A_0^T + \sum_{i=1}^{l} \Delta A_{d1} \right) P X + \sum_{i=1}^{l} X^T P A_{d1} + \Delta A_{d1} X_{d1}
\]

\[
+ \sum_{i=1}^{l} X^T P A_{d1} + \Delta A_{d1} X_{d1} + X^T P A_0 + \Delta A_0 X
\]

\[
+ \sum_{i=1}^{l} X^T P A_{d1} + \Delta A_{d1} X_{d1} + \sum_{i=1}^{l} X^T P X - \sum_{i=1}^{l} X^T P X_{d1}
\]

By Lemma 1 and (4), we could get the following inequality by choosing suitable \( \gamma_1 \) and \( \gamma_2 \) for \( \Delta A_0 \) and \( \Delta A_{d1} \), respectively

\[
\frac{d}{dt} V \leq X^T \left( A_0^T P + \sum_{i=1}^{l} \Delta A_{d1} \right) P X + \sum_{i=1}^{l} X^T P A_{d1} + \Delta A_{d1} X_{d1} + \sum_{i=1}^{l} P_i \right) X
\]

\[
+ \sum_{i=1}^{l} X^T P A_{d1} + \Delta A_{d1} X_{d1} + \sum_{i=1}^{l} X^T P A_0 + \Delta A_0 X
\]

\[
+ \sum_{i=1}^{l} X^T P A_{d1} + \Delta A_{d1} X_{d1} + \sum_{i=1}^{l} X^T P X - \sum_{i=1}^{l} X^T P X_{d1}
\]

\[
\leq X^T \left( A_0^T P + \sum_{i=1}^{l} \Delta A_{d1} + \gamma_1 \sum_{i=1}^{l} P_i \right) X + \sum_{i=1}^{l} X^T P A_{d1} + \Delta A_{d1} X_{d1}
\]

\[
+ \sum_{i=1}^{l} X^T P A_0 + \Delta A_0 X + \sum_{i=1}^{l} P_i \right) X
\]

\[
+ \sum_{i=1}^{l} X^T P A_{d1} + \Delta A_{d1} X_{d1} + \sum_{i=1}^{l} X^T P X - \sum_{i=1}^{l} X^T P X_{d1}
\]

which is equivalent to the following inequality

\[
\begin{bmatrix}
X
tilde{X}_{d1}
X_{d1}
\end{bmatrix}
\begin{bmatrix}
A_0^T P + \sum_{i=1}^{l} \Delta A_{d1} + \gamma_1 \sum_{i=1}^{l} P_i + \gamma_1 \gamma_2 \sum_{i=1}^{l} P_i \right) & \cdots & PA_{d1} \\
PA_{d1}^T & \cdots & PA_{d1} \\
\vdots & \ddots & \vdots \\
\cdots & \cdots & \gamma_2 \sum_{i=1}^{l} P_i \\
A_{d1}^T P & \cdots & \gamma_2 \sum_{i=1}^{l} P_i \\
\end{bmatrix}
X
\end{bmatrix} + \begin{bmatrix}
X
tilde{X}_{d1}
X_{d1}
\end{bmatrix}
\begin{bmatrix}
P_{d1} & \cdots & X_{d1} \\
\vdots & \ddots & \vdots \\
\cdots & \cdots & P_{d1} \\
\end{bmatrix}
\begin{bmatrix}
X
tilde{X}_{d1}
X_{d1}
\end{bmatrix}
\leq 0, \text{ by (17)}.
\]

By Lyapunov stability theory [21], the perturbed time-delay biochemical network in (3) is robustly stable.

Appendix C. Proof of Propositions 3

Since the trajectory of nonlinear dynamic time-delay biochemical network could be represented by the interpolation system of the linearized systems at vertices in (15). By the global linearization theory [22,23], the stability of nonlinear dynamic time-delay biochemical system in (6) could be guaranteed by the stability of
the corresponding interpolatory system in (15). By the Lyapunov stability theory, we want to prove condition (19) is the sufficient condition for the stability of time-delay biochemical system in (6). Suppose we choose Lyapunov function as $V(X) = X^TPX + \sum_{i=1}^{l} \int_{0}^{\tau_i} X^T(t-s)P_X(t-s)ds$ and

$$V(X) = X^TPX + X^TPX + \sum_{i=1}^{l} X^T(t)P_X(t-s)ds - \sum_{i=1}^{l} X^T(t-s)P_X(t-s)ds.$$ 

Then, through a similar procedure in Appendix B with the bounded noise in (7) and bounded approximation error in (14), the differentiation of $V(X)$ could be proved as the following inequality

$$V'(X) \leq \sum_{j=1}^{M} \delta_j(X) + \left[ \begin{array}{c}
X^T(A_{ij}^TP + PA_{ij} + \sum_{i=1}^{l} P_X(t-s)ds) \\
+ \frac{1}{2} \sum_{i=1}^{l} X^T(t-s)P_X(t-s)ds \\
+ \sum_{i=1}^{l} X^T(t-s)P_X(t-s)ds \\
\end{array} \right] + \left( \frac{dV(X)}{dt} \right) \left( I - \sum_{i=1}^{l} \Delta_0(X) + \sum_{i=1}^{l} \Delta_d(X) \right)$$

i.e. if the condition in (19) holds, then the biochemical system in (6) is stable.

**Appendix D. Proof of Proposition 4**

Suppose we choose the Lyapunov function as follows

$$V(X(t)) = X^TPX(t) + \sum_{i=1}^{l} \int_{0}^{\tau_i} X^T(t-s)P_X(t-s)ds > 0$$

$$= X^TPX + \sum_{i=1}^{l} \int_{0}^{\tau_i} X^T(t-s)P_X(t-s)ds > 0$$

By the fact of (4) and with a similar procedure in Appendix B, if the following inequality holds,

$$X^T(A_{ij}^TP + PA_{ij} + \gamma_i \alpha_i I + (\gamma_i^2 + \gamma_i^2) I)X + v^T B_{ij}^TPX + X^T v + Z^T Z$$

$$- \rho^2 v^T v + \sum_{i=1}^{l} X^T A_{ij}^TPX + \sum_{i=1}^{l} X^T P_X(t-s)ds + \sum_{i=1}^{l} X^T(t-s)P_X(t-s)ds < 0$$

(A.2)

then

$$V \leq - (Z^T Z - \rho^2 v^T v)$$

for every $X$, $Z$, and $v$ satisfying (4) and (27).

So we integrate the above inequality on both sides from 0 to $T$ with the initial condition $X(0) = 0$, then we have $V(X(t)) - V(X(0)) \leq - \int_{0}^{T} (Z^T Z - \rho^2 v^T v) dt$ for every $T \geq 0$. The inequality can be written as follows

$$V(X(T)) - V(X(0)) \leq \int_{0}^{T} (Z^T Z - \rho^2 v^T v) dt \leq 0$$

(A.3)

Since $V(X(t)) \geq 0$, if the initial condition $X(0) = 0$ and $V(X(0)) = 0$, then we can get $\int_{0}^{T} (Z^T Z - \rho^2 v^T v) dt \leq 0$, which can be rewritten as (30), i.e.

$$\|Z\|_{L_2}^2 \leq \rho^2 \|v\|_{L_2}^2$$

If $V(X(0)) \neq 0$, the inequality in (A.3) should be modified as

$$\|Z\|_{L_2}^2 \leq V(X(0)) + \rho^2 \|v\|_{L_2}^2$$

The above results hold only when the inequality (A.2) holds, i.e. when the following inequality holds

$$X^T(A_{ij}^TP + PA_{ij} + \gamma_i \alpha_i I + (\gamma_i^2 + \gamma_i^2) I)X + v^T B_{ij}^TPX$$

$$+ X^T v + Z^T Z - \rho^2 v^T v + \sum_{i=1}^{l} X^T A_{ij}^TPX + \sum_{i=1}^{l} X^TP_X(t-s)ds + \sum_{i=1}^{l} X^T(t-s)P_X(t-s)ds < 0$$

(A.2)

then

$$V \leq - (Z^T Z - \rho^2 v^T v)$$

for every $X$, $Z$, and $v$ satisfying (4) and (27).

$$\begin{bmatrix} X \\ X_{d_1} \\ \vdots \\ X_{d_l} \\ v \end{bmatrix}^T \begin{bmatrix}
A_{ij}^TP + PA_{ij} + \sum_{i=1}^{l} P_X(t-s)ds + (\gamma_i^2 + \gamma_i^2) I & PA_{ij} & \cdots & 0 \\
A_{ij}^TP & \gamma_i \alpha_i I - P_i & 0 & \cdots & 0 \\
\vdots & \vdots & \ddots & \vdots & \vdots \\
A_{ij}^TP & 0 & \cdots & \gamma_i \alpha_i I - P_i & -\rho^2 I \\
B_{ij}^TP & 0 & \cdots & \gamma_i \alpha_i I - P_i & -\rho^2 I \end{bmatrix} \begin{bmatrix} X \\ X_{d_1} \\ \vdots \\ X_{d_l} \\ v \end{bmatrix} \leq 0$$

which is equivalent to the following inequality
or equivalent to the following LMI by Schur Complements [23]

\[
\begin{bmatrix}
P A_0 + \gamma_1 x_1^2 I + \sum_{l=1}^L P_l + C_l^T C_l & P & P & \cdots & P A_{d1} & \cdots & P A_{dL} & PB_v
\end{bmatrix}
\begin{bmatrix}
P 
\end{bmatrix}
\begin{bmatrix}
P
1
\end{bmatrix}
\begin{bmatrix}
\gamma_2 x_1^2 I - P_1 & \cdots & \cdots & \cdots \n
\end{bmatrix}
\begin{bmatrix}
\gamma_2 x_1^2 I - P_k
\end{bmatrix}
\begin{bmatrix}
\cdots \n
\end{bmatrix}
\begin{bmatrix}
\rho^2 I
\end{bmatrix}
\leq 0
\]

then the robust filtering in (30) or (31) holds.

**Appendix E. Proof of Propositions 5**

By choosing the Lyapunov function \( V(X) \) suitably and with (A.1), we can get

\[
V = \left( \frac{\partial V(X)}{\partial X} \right)^T X
\]

\[
= \left( \frac{\partial V(X)}{\partial X} \right)^T \left( f_0(X) + \Delta f_0(X) + \sum_{l=1}^L (f_{d1}(X_{d1}) + \Delta f_{d1}(X_{d1})) + g(X) v \right)
\]

\[
= \left( \frac{\partial V(X)}{\partial X} \right)^T \left( f_0(X) \right) + \sum_{l=1}^L \left( \frac{\partial V(X)}{\partial X} \right)^T \left( f_{d1}(X_{d1}) \right)
\]

\[
+ \frac{1}{2} \left( \frac{\partial V(X)}{\partial X} \right)^T \Delta f_0(X) + \frac{1}{2} \left( \frac{\partial V(X)}{\partial X} \right)^T \Delta f_{d1}(X_{d1})
\]

\[
+ \frac{1}{2} \left( \frac{\partial V(X)}{\partial X} \right)^T \left( g(X) v + \frac{1}{2} \left( \frac{\partial V(X)}{\partial X} \right)^T \left( g(X) v \right) \right)
\]

\[
\leq \left( \frac{\partial V(X)}{\partial X} \right)^T \left( f_0(X) \right) + \sum_{l=1}^L \left( \frac{\partial V(X)}{\partial X} \right)^T \left( f_{d1}(X_{d1}) \right)
\]

\[
+ \frac{1}{2} \gamma_1 \left( \frac{\partial V(X)}{\partial X} \right)^T \left( \frac{\partial V(X)}{\partial X} \right) + \frac{1}{2} \gamma_1 \beta_0^2 x_1^2 X
\]

\[
+ \frac{1}{2} \gamma_2 \left( \frac{\partial V(X)}{\partial X} \right)^T \left( \frac{\partial V(X)}{\partial X} \right) + \frac{1}{2} \gamma_2 \sum_{l=1}^L \beta_1^2 X_{d1}^2 X_{d1}
\]

\[
+ \frac{1}{2} \rho^2 \left( \frac{\partial V(X)}{\partial X} \right)^T \left( \frac{\partial V(X)}{\partial X} \right) g(X) g(X) \left( \frac{\partial V(X)}{\partial X} \right) + \frac{1}{2} \rho^2 v^T v + \frac{1}{2} (Z^2 - Z^2) Z
\]

(by (A.1) and (7))

If the following inequality holds,

\[
\left( \frac{\partial V(X)}{\partial X} \right)^T \left( f_0(X) \right) + \sum_{l=1}^L \left( \frac{\partial V(X)}{\partial X} \right)^T \left( f_{d1}(X_{d1}) \right)
\]

\[
+ \frac{1}{2} \gamma_1 \left( \frac{\partial V(X)}{\partial X} \right)^T \left( \frac{\partial V(X)}{\partial X} \right) + \frac{1}{2} \gamma_1 \beta_0^2 X^T X
\]

\[
+ \frac{1}{2} \gamma_2 \left( \frac{\partial V(X)}{\partial X} \right)^T \left( \frac{\partial V(X)}{\partial X} \right) + \frac{1}{2} \gamma_2 \sum_{l=1}^L \beta_1^2 X_{d1}^2 X_{d1}
\]

\[
+ \frac{1}{2} \rho^2 \left( \frac{\partial V(X)}{\partial X} \right)^T \left( \frac{\partial V(X)}{\partial X} \right) + \frac{1}{2} \rho^2 v^T v + \frac{1}{2} (Z^2 - Z^2) Z \leq 0
\]

then we have

\[
V \leq \frac{1}{2} (Z^2 + \rho^2 v^T v).
\]

Since we can integrate the above inequality as Appendix 4, from 0 to \( T \), the system robust stability and a desired attenuation value \( \rho \) if (A.4) or (34) holds for the nonlinear biochemical network in (28).

**References**


