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Robust Stability Analysis of Gene-protein Regulatory Networks with Cyclic Activation-inhibition Interconnections

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Abstract

This paper studies analytic robust stability criteria for large-scale cyclic gene-protein regulatory network systems with unstructured or parametric uncertainties. We first consider a class of gene expressions, which is described as uncertain Linear Transcription-Translation Models (LTTMs) with not only feedback loops from translation products to transcription but also degradation properties of proteins and mRNAs. Next, we show that such uncertain models belong to a class of large-scale dynamical linear network systems with a generalized frequency variable. Then, based on the above system description approach, considerably simple analytic robust stability analysis methods are developed. The proposed schemes require less computational burden, and hence can be readily applied to the analysis of large-scale genetic regulatory networks.

Keywords: Gene-protein regulatory networks; Matrices with cyclic structure; Robust stability; Generalized frequency variable

1 Introduction

In biological sciences, stability could negatively be interpreted; e.g., a biosystem which is stable in the sense of insensitivity or lack of flexibility to changes in the environments is threatened in its existence. However, the

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stability has positive meanings in many cases; e.g., in biological science and technologies, and in medicine, it may have meaning of a disease coming to a rest (or recovering), etc. [13]. This paper has a contribution to mathematical robust stability analysis applied to large-scale uncertain gene-protein regulatory networks with cyclic activation-repression interconnections.

The process by which gene information is converted for producing cell structures and cell functions is called gene (or protein) expression. There are two main process events: transcription and translation. During transcription, some special blocks of DNA, called genes, are copied into messenger RNA (mRNA), a molecule which serves as a template for the production of proteins. The last part of the process is called translation. Due to the fact that DNA already includes the information, from which protein can be made, one says that DNA encodes proteins. The transcription of a gene can be repressed or activated by regulatory proteins, called transcription factors [4].

For such genetic regulatory networks, Chen and Aihara [3] presented a dynamic system model with functional differential equations, and analyzed the nonlinear properties of the model in terms of local stability and bifurcation. The developed model transforms the original interaction network into several simple transcendental equations at an equilibrium, thereby significantly reducing the computational complexity and making analysis of stability and bifurcation tractable for even large-scale networks. However, their method cannot be applied to the case that the genetic regulatory network model has various uncertainties. In order to overcome the above problem, Wang *et al.* [14] proposed a stability analysis scheme for genetic regulatory networks. They represented genetic regulatory networks by a differential equation model with polytopic uncertainties, and then presented that its robust stability can be easily confirmed via LMIs. However, the size of matrices in LMIs becomes considerably large when the regulatory network is composed of many genes, which may be intractable because of computational complexities; i.e., their method may not be applied to large-scale genetic regulatory networks.

On the other hand, Arcak [1] and Sontag [10] studied a cyclic interconnection structure in biological networks where the first subsystem of a cascade is driven by a negative feedback from the last subsystem downstream. Besides the engineering and mathematical interest of the study of cyclic negative feedback systems, there is a biological science motivation as well, which arises from the field of genetic regulatory networks [6], cellular signaling pathways [9], and metabolic pathways [11], etc..

This paper is concerned with analytic methods of *robust* stability analysis for *large-scale* gene-protein regulatory networks with cyclic activation-inhibition connections from a control-theoretic viewpoint. Here, we first consider

a class of gene expressions, which is described as a Linear Transcription-Translation Model (LTTM) with not only feedback loops from translation products to transcription but also degradation properties of proteins and mRNAs. Then, we consider the following four types of LTTMs

(i) homogeneous gene dynamics + unstructured uncertainty,

(ii) heterogeneous gene dynamics + unstructured uncertainty,

(iii) homogeneous gene dynamics + parametric uncertainty,

(iv) heterogeneous gene dynamics + parametric uncertainty,

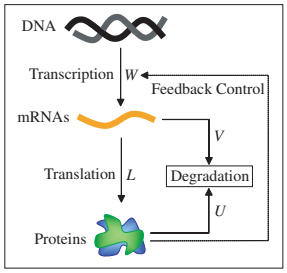
and define the robust stability problems rigorously for each case. We develop simple analytic methods of robust stability check for those biological uncertain systems based on the diagrammatic stability analysis scheme for large-scale systems proposed by Hara *et al.* [5, 12]. To this end, we first show that an LTTM belongs to a class of large-scale dynamical linear network systems with a generalized frequency variable [12], and then present a diagrammatic stability criterion briefly. Next, we explicitly explain how to handle LTTMs for cases (i), (ii) and (iii) within the above framework, and then present analytic robust stability criteria for those cases. The developed methods are considerably simple (e.g., they require less computational burden), and further can be readily applied to large-scale genetic regulatory networks. Finally, we briefly remark on the difficulty of robust stability analysis for the case (iv).

2 Gene-protein regulatory network system model description

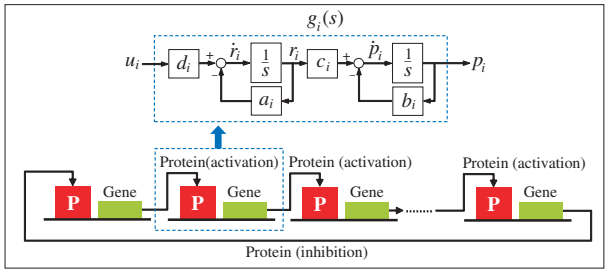
Consider a simplified dynamic system of gene regulation with feedback on transcription in Figure 1(a). Genes on the DNA are transcribed into mRNA, which consists of nearly the same bases. An mRNA is translated into one or multiple copies of corresponding proteins, which can further affect the transcription of other genes. It means that the transcription of a gene can be repressed or activated by regulatory proteins, called transcription factors. As shown in Samad *et al.* [8], the system in Figure 1(a) can be modeled by a linearized dynamical system at an equilibrium point, which is called as a Linear Transcription-Translation Model (LTTM):

$$\begin{aligned} \dot{\mathbf{r}}(t) &= W\mathbf{p}(t) - V\mathbf{r}(t), \\ \dot{\mathbf{p}}(t) &= L\mathbf{r}(t) - U\mathbf{p}(t), \end{aligned} \tag{1}$$

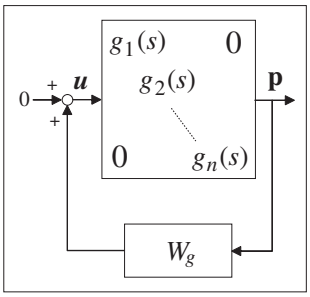
where n is the number of genes in the genome, $\mathbf{r} := [r_1, r_2, \cdots, r_n]^T \in \mathbb{R}^n$ is mRNA concentrations, $\mathbf{p} := [p_1, p_2, \cdots, p_n]^T \in \mathbb{R}^n$ is protein concentrations, $L := \mathrm{diag}\{c_1, c_2, \cdots, c_n\} \in \mathbb{R}^{n\times n}$, $c_i > 0$, is translation constants, $V := \mathrm{diag}\{a_1, a_2, \cdots, a_n\} \in \mathbb{R}^{n\times n}$, $a_i > 0$, is degradation rates of mRNAs, and



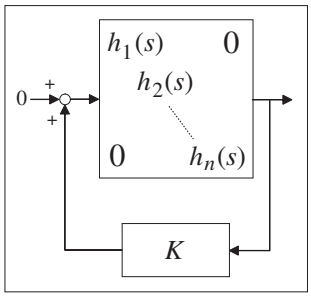
(a) Simplified genetic regulatory network



(b) Dynamic gene-protein regulatory network system with cyclic feedback interconnection



(c) Control-oriented system description



(d) Equivalent block diagram of one in Figure 1(c)

Figure 1: Dynamic gene-protein regulatory network system and its control theory-oriented block diagram representation.

$U := \mathrm{diag}\{b_1, b_2, \cdots, b_n\} \in \mathbb{R}^{n\times n}$, $b_i > 0$, is degradation rates of proteins. $W \in \mathbb{R}^{n\times n}$ contains transcription constants, by which the transcription of a gene can be repressed or activated.

Following the many existing works[1, 8, 10], we assume that a gene-protein regulatory network system in (1) has a cyclic feedback structure as shown in Figure 1(b), which is one of the simplest and essential arrangements observed in many living cells. In addition, we hereafter consider the case where cyclic gene regulatory networks have an odd number of repressive interactions, because protein concentrations can exhibit both periodic oscillations and convergence to an equilibrium point only if there are an odd number of

repressive interactions [8]. Then, $W \in \mathbb{R}^{n\times n}$ can be defined as

$$W := \begin{bmatrix} 0 & 0 & 0 & \cdots & -d_1 \\ d_2 & 0 & 0 & \cdots & 0 \\ 0 & d_3 & 0 & \cdots & 0 \\ \vdots & \vdots & \ddots & \ddots & \vdots \\ 0 & 0 & \cdots & d_n & 0 \end{bmatrix} \tag{2}$$

where d_i denotes a transcription rate and $d_i > 0$ for $\forall i$, and positive and negative entries in matrix W mean activation and repression of other genes, respectively. It should be noted that an odd number of repressions can be equivalently expressed as one negative sign as shown in (2) because of the cyclic structure and linearity. Also, note that the LTTM in (1) is obtained via linearization, and hence, in fact, d_i depends on the values of other parameters a_i, b_i and c_i for $\forall i$. Then, we obtain from (1) and (2) that

$$\begin{bmatrix} \dot{r}_i \\ \dot{p}_i \end{bmatrix} = \begin{bmatrix} -a_i & 0 \\ c_i & -b_i \end{bmatrix} \begin{bmatrix} r_i \\ p_i \end{bmatrix} + \begin{bmatrix} d_i \\ 0 \end{bmatrix} u_i, \quad y_i = \begin{bmatrix} 0 & 1 \end{bmatrix} \begin{bmatrix} r_i \\ p_i \end{bmatrix} \tag{3}$$

where $i = 1, 2, \cdots, n$ and

$$u_i(t) = \begin{cases} -p_n(t), & \text{for } i = 1 \\ p_{i-1}(t), & \text{for } i = 2, 3, \cdots, n. \end{cases} \tag{4}$$

From (1), (2) and (3), we can see that $-d_1 p_n(t)$ represses a transcription of a gene, but $d_i p_{i-1}(t)$ activates a transcription. This cyclic feedback structure is ubiquitous not only in gene regulatory networks, but also in cellular signaling pathways and metabolic pathways [1, 2].
The transfer functions from u_i to $y_i (= p_i)$ is derived from (3)-(4) as

$$g_i(s) = \frac{c_i d_i}{(s + a_i)(s + b_i)} =: \frac{R_i^2}{(T_{a_i} s + 1)(T_{b_i} s + 1)}, \tag{5}$$

where

$$R_i := \frac{\sqrt{c_i d_i}}{\sqrt{a_i b_i}} = \frac{\text{Geometric mean of translation and transcription rates}}{\text{Geometric mean of degradation rates}},$$

$$T_{a_i} := \frac{1}{a_i} (> 0), \quad T_{b_i} := \frac{1}{b_i} (> 0).$$

Note that $g_i(s)$ is stable because $a_i > 0$ and $b_i > 0$. Therefore, the overall gene-protein regulatory network system with cyclic activation-repression connections is composed as depicted in Figure 1(c) where $\boldsymbol{u}(t) = W_g \mathbf{p}(t)$, $\boldsymbol{u} := [u_1, u_2, \cdots, u_n]^T \in \mathbb{R}^n$, with

$$W_g := \begin{bmatrix} 0 & 0 & 0 & \cdots & -1 \\ 1 & 0 & 0 & \cdots & 0 \\ 0 & 1 & 0 & \cdots & 0 \\ \vdots & \vdots & \ddots & \ddots & \vdots \\ 0 & 0 & \cdots & 1 & 0 \end{bmatrix}. \tag{6}$$

Since the feedback gain matrix W_g has a very special structure, we can readily see that the gains R_i^2 in $g_i(s)$ can be merged into the corresponding unity feedback gains in W_g. In other words, the feedback system shown in Figure 1(c) can be equivalently transformed into a feedback system depicted in Figure 1(d), where $h_i(s)$ and K are defined as

$$h_i(s) = \frac{1}{(T_{a_i}s+1)(T_{b_i}s+1)}, \tag{7}$$

and

$$K := \begin{bmatrix} 0 & 0 & 0 & \cdots & -R_1^2 \\ R_2^2 & 0 & 0 & \cdots & 0 \\ 0 & R_3^2 & 0 & \cdots & 0 \\ \vdots & \vdots & \ddots & \ddots & \vdots \\ 0 & 0 & \cdots & R_n^2 & 0 \end{bmatrix}. \tag{8}$$

Note that the perturbations in R_i should take account of the both perturbations due to the changes of d_i which may be affected by changes of an equilibrium point.

Here, we can see that if the number of genes n becomes very large, the derivation of an analytic stability condition for the gene-protein regulatory network system in Figure 1(d) based on the conventional schemes is considerably difficult. It is important to note that if $h_1(s) = h_2(s) = \cdots = h_n(s) = h(s)$ (homogeneous gene dynamics case without uncertainties), the system illustrated in Figure 1(d) belongs to a class of large-scale multi-agent dynamical systems defined by Hara *et al.* [5, 12]. They proposed a considerably simple *diagrammatic* method to judge the nominal stability of such systems, which is briefly described as follows: First, define the generalized frequency variable $\phi(s)$ as

$$\phi(s) := \frac{1}{h(s)} = (T_a s+1)(T_b s+1). \tag{9}$$

Next, the following two domains are defined based on $\phi(s)$:

$$\Omega_+ := \phi(\mathbb{C}_+), \quad \Omega_+^c := \mathbb{C}\backslash\Omega_+, \tag{10}$$

where $\mathbb{C}_+ = \{s \in \mathbb{C} : \mathrm{Re}[s] \geq 0\}$. Since $\Omega_+ = \{\lambda \in \mathbb{C} : \exists s \in \mathbb{C}_+ \text{ such that } \phi(s) = \lambda\}$, it follows that Ω_+^{c} can be alternatively expressed as $\Omega_+^{\mathrm{c}} = \{\lambda \in \mathbb{C} : \forall s \in \mathbb{C}_+,\ \phi(s) \neq \lambda\}$. Then, a diagrammatic stability criterion is stated as follows: all poles of the system in Figure 1(d) are located in the left-half complex plane, if and only if all eigenvalues of matrix K belong to the domain Ω_+^{c}. Note that systematic ways of checking the condition are found in [12], and that Polyak and Tsypkin [7] presented a similar result for uncertain uniform systems.

Based on the above result, we derive *analytic robust* stability conditions for large-scale gene-protein regulatory network systems with *unstructured* and *parametric uncertainties* in this paper. Next, we explicitly formulate four types of robust stability problems.

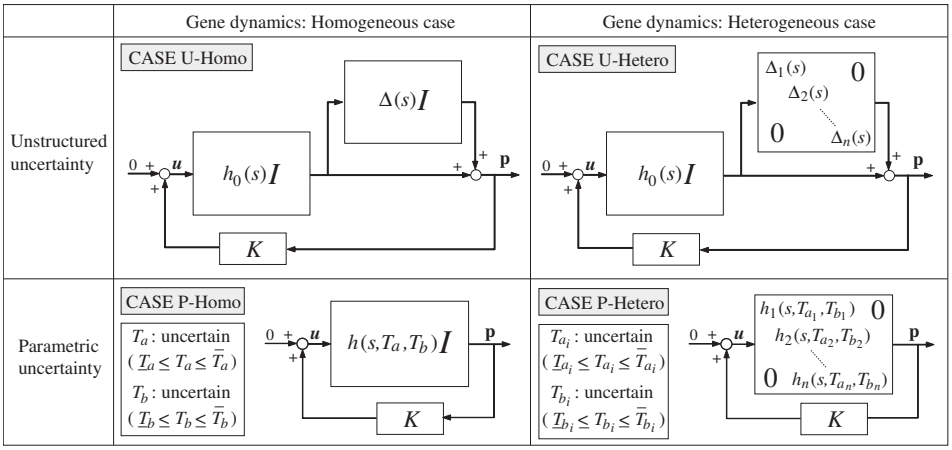


Figure 2: Classification of gene-protein regulatory network systems with uncertainties.

3 Robust stability problems

In this paper, we investigate the following four types of robust stability problems for cyclic gene-protein regulatory networks introduced in Section 2 (see Figure 2)[1]

• Problem U-Homo (see Figure 2 CASE U-Homo): The homogeneous gene dynamics $h(s)$ having identical multiplicative uncertainties is written as

$$h(s) = h_0(s)(1 + \Delta(s)) \tag{11}$$

where a nominal gene dynamics $h_0(s)$ is defined for given by

$$h_0(s) = \frac{1}{(T_{a_0}s + 1)(T_{b_0}s + 1)}, \tag{12}$$

where $T_{a_0}(= 1/a_0)$ and $T_{b_0}(= 1/b_0)$, and $\Delta(s)$ satisfies

$$\Delta(s) \in \mathcal{RH}_\infty, \quad \|\Delta\|_\infty \le \gamma \ (< 1). \tag{13}$$

Let $\mathcal{F}_{\rm ho}(s)$ denote the transfer function of the systems in Figure 2 CASE U-Homo. Then, for the gene-protein regulatory network system with *homogeneous* gene dynamics and *identical* multiplicative uncertainties, the robust stability problem is formulated as follows:

[1]Unstructured uncertainty refers to the one in each gene dynamics $h_i(s)$ (see (11) or (14)). Note that the overall system takes a form of Figure 2 CASE U-Homo or CASE U-Hetero with a diagonal structured perturbation, since the genetic regulatory network in Figure 1(d) has $h_i(s)$ in its diagonal entries.

Problem U-Homo: Find the necessary and sufficient robust stability condition for the following large-scale uncertain system described in Figure 2 CASE U-Homo:

$$\mathcal{F}_{\rm ho}(s) = (I + \mathbf{\Delta}_{\rm ho}(s)) \left(\frac{1}{h_0(s)} I - K(I + \mathbf{\Delta}_{\rm ho}(s)) \right)^{-1},$$

where $h_0(s)$ is defined in (12), $\mathbf{\Delta}_{\rm ho}(s) := {\rm diag}(\Delta(s), \Delta(s), \cdots, \Delta(s))$ with $\Delta(s)$ satisfying the conditions in (13), and the exact value R_i in the matrix K is unknown but its positive upper and lower bounds satisfying $\underline{R}_i \le R_i \le \bar{R}_i$ for $\forall i$ are given.

• Problem U-Hetero (see Figure 2 CASE U-Hetero): The heterogeneous gene dynamics $h_i(s)$ having nonidentical multiplicative uncertainties is defined as

$$h_i(s) = h_0(s)(1 + \Delta_i(s)) \tag{14}$$

where $\Delta_i(s)$ satisfies $\Delta_i(s) \in \mathcal{RH}_\infty$ and $\|\Delta_i\|_\infty \le \gamma_i$ (< 1). Let $\mathcal{F}_{\rm he}(s)$ denote the transfer function of the systems in Figure 2 CASE U-Hetero. Then, for the gene-protein regulatory network system with *heterogeneous* gene dynamics and *nonidentical* multiplicative uncertainties, the robust stability problem is formulated as follows:

Problem U-Hetero: Find the necessary and sufficient robust stability condition for the following large-scale uncertain system described in Figure 2 CASE U-Hetero:

$$\mathcal{F}_{\rm he}(s) = (I + \mathbf{\Delta}_{\rm he}(s)) \left(\frac{1}{h_0(s)} I - K(I + \mathbf{\Delta}_{\rm he}(s)) \right)^{-1}$$

where $h_0(s)$ is defined in (12), $\mathbf{\Delta}_{\rm he}(s) := {\rm diag}(\Delta_1(s), \Delta_2(s), \cdots, \Delta_n(s))$ with $\Delta_i(s) \in \mathcal{RH}_\infty$ and $\|\Delta_i\|_\infty \le \gamma_i$ (< 1), and the exact value R_i in the matrix K is unknown, but its positive upper and lower bounds satisfying $\underline{R}_i \le R_i \le \bar{R}_i$ for $\forall i$ are given.

• Problem P-Homo (see Figure 2 CASE P-Homo): In this case, the following homogeneous gene dynamics is considered:

$$h_1(s) = h_2(s) = \cdots = h(s) = \frac{1}{(T_a s + 1)(T_b s + 1)}. \tag{15}$$

Note that this is a plausible assumption because genes on the DNA consist of nearly the same bases. Here, we assume that the exact values of T_a, T_b in (15) and R_i in the matrix K are unknown but their upper and lower bounds satisfying $\underline{T}_a \le T_a \le \overline{T}_a$, $\underline{T}_b \le T_b \le \overline{T}_b$ and $\underline{R}_i \le R_i \le \overline{R}_i$ are given. Let

$\mathcal{G}_{\rm ho}(s)$ denote the transfer function of the system in Figure 2 CASE P-Homo. Then, for the gene-protein regulatory network system with *homogeneous* gene dynamics and *identical* parametric uncertainties, the robust stability problem is formulated as follows:

Problem P-Homo: Find the necessary and sufficient robust stability condition for the following large-scale uncertain system described in Figure 2 CASE P-Homo:

$$\mathcal{G}_{\rm ho}(s) = \left(\frac{1}{h(s)}I - K\right)^{-1}$$

where the exact values of T_a, T_b and R_i are unknown, but their positive upper and lower bounds are given as follows: $\underline{T}_a \le T_a \le \overline{T}_a$, $\underline{T}_b \le T_b \le \overline{T}_b$, and $\underline{R}_i \le R_i \le \overline{R}_i$.

• Problem P-Hetero (see Figure 2 CASE P-Hetero): In this case, we assume that gene-protein regulatory network system consists of heterogeneous gene dynamics $h_i(s)$ defined in (7); i.e., the condition $h_1(s) = h_2(s) = \cdots = h_n(s)$ in (15) is not assumed. Also, T_{a_i}, T_{b_i} and R_i are assumed to be uncertain parameters. Then, the robust stability problem is formulated as follows:

Problem P-Hetero: Find the necessary and sufficient robust stability condition for the system presented in Figure 2 CASE P-Hetero with uncertain parameters T_{a_i}, T_{b_i} of $h_i(s)$ in (7) and R_i in K where $i = 1, 2, \cdots, n$.

Note that it is well known that an analytic robust stability analysis for this class of large-scale network systems is one of the considerably difficult problems.

4 Robust stability for unstructured uncertainties

The robust stability criterion for large-scale *homogeneous* gene-protein regulatory network systems with *identical* multiplicative uncertainties in Figure 2 CASE U-Homo can be derived based on the zero exclusion principle in Polyak and Tsypkin [7]. Hence, in this section, we mainly focus on an analytic robust stability condition for gene-protein regulatory network system with *heterogeneous* gene dynamics and *nonidentical* multiplicative uncertainties in Figure 2 CASE U-Hetero (see "Problem U-Hetero" given in Section 3 for details). It should be noticed that an analytic robust stability condition for the system in Figure 2 CASE U-Homo, which is equivalent to that of Polyak and Tsypkin [7], can also be derived based on the similar manner, which is briefly mentioned at the end of this section.

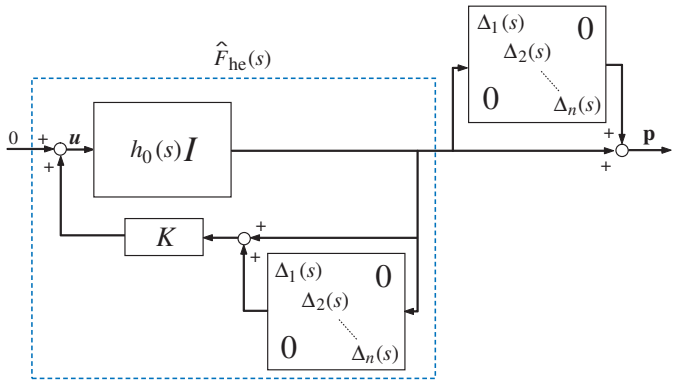


Figure 3: The equivalent form of the block diagram "CASE U-Hetero" in Figure2.

To this end, we first derive an equivalent block diagram representation in Figure 3 to the system $\mathcal{F}_{\mathrm{he}}(s)$ in Figure 2 U-Hetero. Then, the transfer function $\hat{\mathcal{F}}_{\mathrm{he}}(s)$ illustrated in Figure 3 is defined as

$$\hat{\mathcal{F}}_{\mathrm{he}}(s) := \left(\frac{1}{h_0(s)}I - \Psi_{\mathrm{he}}\right)^{-1}, \quad \Psi_{\mathrm{he}} := K(I + \boldsymbol{\Delta}_{\mathrm{he}}), \tag{16}$$

where

$$\Psi_{\mathrm{he}} := K(I + \boldsymbol{\Delta}_{\mathrm{he}}) = \begin{bmatrix} 0 & 0 & \cdots & -R_1^2(1+\Delta_n(s)) \\ R_2^2(1+\Delta_1(s)) & 0 & \cdots & 0 \\ \vdots & \ddots & \ddots & \vdots \\ 0 & \cdots & R_n^2(1+\Delta_{n-1}(s)) & 0 \end{bmatrix}.$$

Here, we can see that the overall system $\mathcal{F}_{\mathrm{he}}(s)$ is robustly stable if and only if $\hat{\mathcal{F}}_{\mathrm{he}}(s)$ is robustly stable. Thus, in the following, we derive a robust stability condition for $\hat{\mathcal{F}}_{\mathrm{he}}(s)$.

We first characterize the domain Ω_+^{c} of the considered gene-protein regulatory network systems. Let $x(\omega) := \mathrm{Im}[\phi(j\omega, T_{a_0}, T_{b_0})]$ and $y(\omega) := -\mathrm{Re}[\phi(j\omega, T_{a_0}, T_{b_0})]$, where $\phi(\cdot)$ has an identical form with (9) and the x-y axis is set as denoted in Figure 4. Then, $\phi(j\omega, T_{a_0}, T_{b_0})$ can be rewritten by using $x(\omega)$ and $y(\omega)$ as

$$y = \frac{1}{4}Q^2x^2 - 1, \tag{17}$$

where

$$Q := \frac{\sqrt{T_{a_0}T_{b_0}}}{(T_{a_0} + T_{b_0})/2} \left(= \frac{\sqrt{a_0b_0}}{(a_0 + b_0)/2}\right). \tag{18}$$

Let $x =: r\sin\theta$ and $y =: -r\cos\theta$ where $0 \le \theta < \pi$. Then, we have

$$r = \frac{-\cos\theta + \sqrt{\cos^2\theta + Q^2\sin^2\theta}}{\frac{1}{2}Q^2\sin^2\theta}. \tag{19}$$

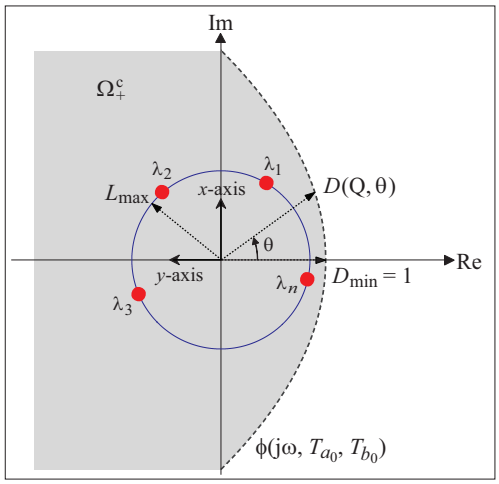


Figure 4: The domain Ω_+^c and the positions of eigenvalues λ_i $(i = 1, 2, \cdots, n)$ of Ψ in the system $\hat{\mathcal{F}}_{\rm he}(s)$.

Hence, the distance from the origin of the complex plane to the boundary of $\phi(j\omega, T_{a_0}, T_{b_0})$ can be obtained as

$$D(Q,\theta) = \begin{cases} 1, & \text{for } \theta = 0 \\ \dfrac{-\cos\theta + \sqrt{\cos^2\theta + Q^2\sin^2\theta}}{\frac{1}{2}Q^2\sin^2\theta}, & \text{otherwise.} \end{cases} \tag{20}$$

Furthermore, it is easily verified that for given T_{a_0} and T_{b_0}, $D(Q,\theta)$ achieves the minimum at $\theta = 0$ and monotonically increases with respect to θ.

Next, we investigate the eigenvalue distribution of $\Psi_{\rm he}$ in (16). The i-th eigenvalue of $\Psi_{\rm he}$ can be obtained as

$$\lambda_i = \Pi_{k=1}^n |R_k^2(1 + \Delta_{k-1}(s))|^{\frac{1}{n}} e^{j\left(\frac{\pi}{n}(2i-1)+\varphi\right)} \tag{21}$$

with $\varphi = \arg\left(\Pi_{\ell=1}^n R_\ell^2(1 + \Delta_{\ell-1}(s))\right)$, where $\Delta_n(s) := \Delta_0(s)$. It means that the eigenvalues are equiangularly spaced on the circle of radius $\Pi_{k=1}^n |R_k^2(1 + \Delta_{k-1}(s))|^{\frac{1}{n}}$ whose center at the origin. In particular, we can see that the maximum radius of the circle becomes

$$L_{\max} := (\Pi_{k=1}^n \bar{R}_k^2(1 + \gamma_{k-1}))^{\frac{1}{n}} \tag{22}$$

(see Figure 4). Then, we explicitly characterize the perturbation of eigenvalues due to uncertainties $\Delta_i(s)$ $(i = 1, 2, \cdots, n)$. Note that φ can be rewritten as

$$\varphi = \varphi_1 + \varphi_2 + \cdots + \varphi_n, \quad \varphi_i := \arg\left(R_i^2(1 + \Delta_{i-1}(s))\right). \tag{23}$$

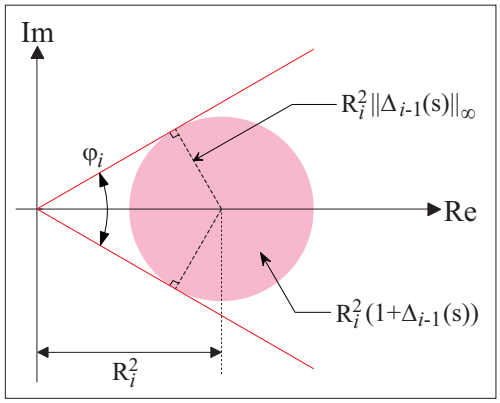


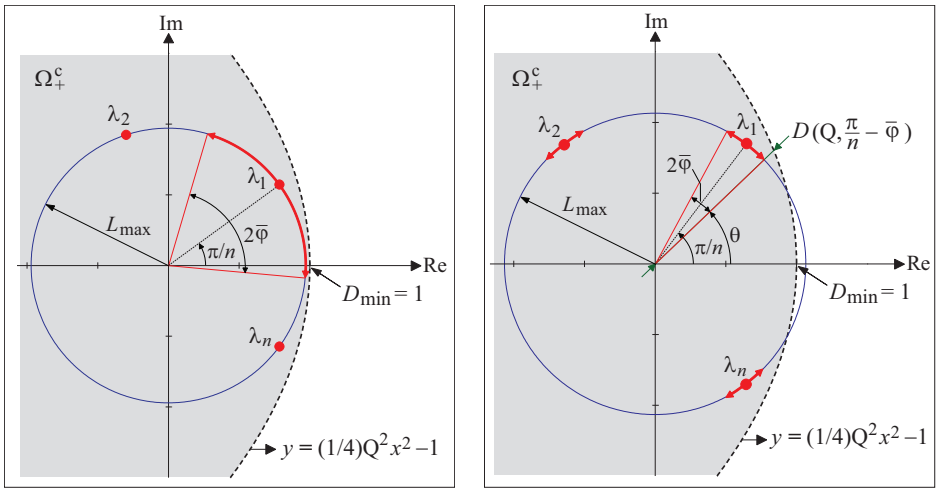
Figure 5: The schematic diagram showing how to determine the upper bound of angle φ_i. (A positive φ_i denotes the counterclockwise angle from the positive real axis)

We have $|\varphi_i| \leq \arccos\left(\sqrt{1-\|\Delta_{i-1}(s)\|_\infty^2}\right)$ from Figure 5, which does not depend on R_i. Therefore, the upper bound of $|\varphi|$ (i.e., $|\varphi| \leq \bar{\varphi}$) is obtained as

$$\bar{\varphi} := \sum_{k=1}^{n} \arccos\left(\sqrt{1-\gamma_k^2}\right). \tag{24}$$

The two types of eigenvalue distribution of Ψ_{he} depending on the uncertain φ are illustrated in Figure 6. Note that, as mentioned before, $D(Q,\theta)$ in (20) achieves the minimum at $\theta = 0$ (i.e., $D_{\min} := D(Q,0)(=1)$), and monotonically increases as θ increases. Therefore, a diagrammatic robust stability criterion for $\hat{\mathcal{F}}_{he}(s)$ should be developed for two cases in Figures 6(a) and 6(b). In Case U-Hetero-A of Figure 6(a), the robust stability of $\hat{\mathcal{F}}_{he}(s)$ is guaranteed, if and only if the maximum disk radius $L_{\max}$ in (22) is less than a unity, which can be easily derived from the diagrammatic stability criterion presented in Section 2. On the other hand, in Case U-Hetero-B of Figure 6(b), the robust stability of $\hat{\mathcal{F}}_{he}(s)$ is guaranteed, if and only if the disk radius $L_{\max}$ is less than a certain distance $D(Q,\theta)$, where θ depends on both the number of genes n and $\bar{\varphi}$ in (24).

From the above observation, the analytic robust stability condition for the gene-protein regulatory network system with *heterogeneous* gene dynamics and *nonidentical* multiplicative uncertainties in Figure 2 CASE U-Hetero is stated as follows:



(a) Case U-Hetero-A (b) Case U-Hetero-B

Figure 6: The schematic diagram showing the eigenvalue location of $\hat{\mathcal{F}}_{he}(s)$.

Theorem 1. (CASE: U-Hetero) *Consider the gene-protein regulatory network system with heterogeneous gene dynamics and multiplicative uncertainties in Figure 2 CASE U-Hetero. It is assumed that T_{a_0} and T_{b_0} in $h_0(s)$ of (12) are given in advance, and $\Delta_i(s)$ satisfies the conditions in (13). Then, $\mathcal{F}_{\rm he}(s)$ is robustly stable, if and only if one of the following conditions is satisfied:*

$$\begin{cases} L_{\max} < D\left(Q, \dfrac{\pi}{n} - \bar{\varphi}\right), & \text{if } \dfrac{\pi}{n} > \bar{\varphi}\ (\geq 0) \quad \text{[see Figure 6(b)]} \\ L_{\max} < 1, & \text{otherwise} \quad \text{[see Figure 6(a)]} \end{cases} \tag{25}$$

From the viewpoint of systems biology, the above theorem informs the following key facts:

1. Note that $L_{\max}$ depends on the upper bound of $R_i(=\sqrt{c_i d_i}/\sqrt{a_i b_i})$. Thus, the above condition implies that the higher values of degradation rates can be related with a much easier occurrence of a stability phenomenon in gene-protein regulatory networks.

2. The above analytic criterion is considerably simple, and further is applicable to the system with any number of genes. Therefore, we can readily judge the stability of gene-protein regulatory networks composed of very large numbers of genes.

3. In large-scale gene-protein regulatory networks (i.e., it has a large number of genes), the condition $\frac{\pi}{n} \leq \bar{\varphi}$ is highly probable, which can easily be convinced from (24). It implies that the stability of most practical gene-protein regulatory networks composed of a large number of genes could be checked simply by $L_{\max} < 1$.

Example 1. Suppose that the number of genes is five, or $n = 5$, and their nominal gene dynamics is given by

$$h_0(s) = \frac{1}{(s+1)(0.5s+1)}, \quad T_{a_0} = 1, \quad T_{b_0} = 0.5. \tag{26}$$

We assume that R_i(unknown) in (8) and its upper bound $\overline{R}_i$(known) are as follows: $R_1 = 0.5477 \leq \overline{R}_1 = 0.6426$, $R_2 = 0.6325 \leq \overline{R}_2 = 0.7131$, $R_3 = 0.6325 \leq \overline{R}_3 = 0.7191$, $R_4 = 0.4472 \leq \overline{R}_4 = 0.5327$, and $R_5 = 0.7071 \leq \overline{R}_5 = 0.8020$. The heterogeneous $\Delta_i(s)$ for $i = 1, 2, \cdots, 5$ is set as

$$\begin{aligned}
\Delta_1(s) &= \frac{0.1195s^2 - 0.07032s - 0.3266}{s^2 + 0.8517s + 0.6501}, && \|\Delta_1(s)\|_\infty = 0.6347, \\
\Delta_2(s) &= \frac{0.5198s^2 + 2.085s - 0.8862}{s^2 + 6.76s + 2.08}, && \|\Delta_2(s)\|_\infty = 0.5198, \\
\Delta_3(s) &= \frac{-0.2803s^2 - 0.2014s + 0.09407}{s^2 + 2.095s + 1.093}, && \|\Delta_3(s)\|_\infty = 0.2803, \\
\Delta_4(s) &= \frac{-0.2875s^2 - 0.3915s - 0.2355}{s^2 + 1.379s + 0.2968}, && \|\Delta_4(s)\|_\infty = 0.7936, \\
\Delta_5(s) &= \frac{0.7065s^2 + 1.039s + 0.3247}{s^2 + 1.913s + 0.6795}, && \|\Delta_5(s)\|_\infty = 0.7065.
\end{aligned}$$

The upper bound γ_i of $\|\Delta_i(s)\|$ is assumed to be $\|\Delta_1(s)\|_\infty \leq \gamma_1 = 0.7547$, $\|\Delta_2(s)\|_\infty \leq \gamma_2 = 0.6998$, $\|\Delta_3(s)\|_\infty \leq \gamma_3 = 0.4303$, $\|\Delta_4(s)\|_\infty \leq \gamma_4 = 0.9236$, and $\|\Delta_5(s)\|_\infty \leq \gamma_5 = 0.8765$.

In this case, $\bar{\varphi}$ in (24) is $\bar{\varphi} = 4.3213$ ($> \pi/5 = 0.6283$(rad)), which is the case of Figure 6(a). Then, we can see from (25) in Theorem 1 that

$$L_{\max} = \left(\Pi_{k=1}^{5} \bar{R}_k^2 (1 + \gamma_{k-1})\right)^{\frac{1}{5}} = 0.7886 < 1,$$

which denotes that the gene-protein regulatory network system $\mathcal{F}_{\text{he}}$ defined in "Problem U-Hetero" of Section 3 is robustly stable. The above fact can be verified from Figure 7, where the initial protein concentrations are $p_1(0) = 1.5334$, $p_2(0) = 1.0103$, $p_3(0) = 1.1712$, $p_4(0) = 1.0340$, and $p_5(0) = 0.8813$. It illustrates the time response of $p_i(t)$ ($i = 1, 2, \cdots, 5$) converging to an equilibrium point. □

In the following, we briefly show that "Problem U-Homo" in Section 3 can be considered in a similar manner, except that $\mathbf{\Delta}(s)$ is defined by $\mathbf{\Delta}(s) =$

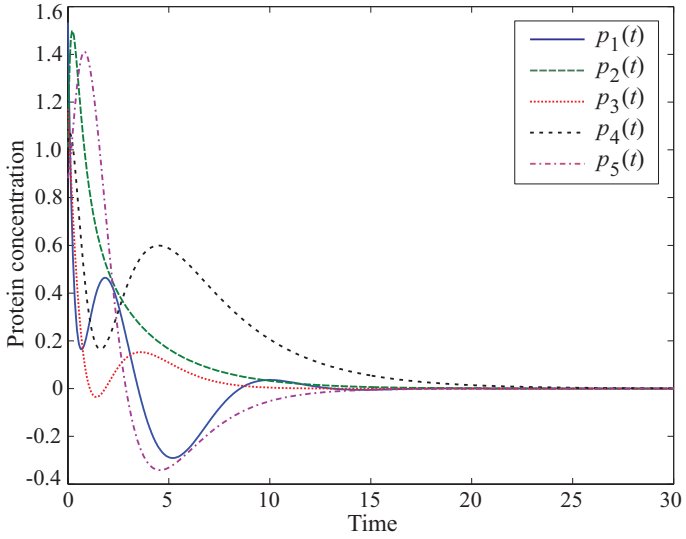


Figure 7: Time plot of protein concentration $p_i(t)$ in Example 1.

diag$(\Delta(s), \Delta(s), \cdots, \Delta(s))$. Therefore, in this case, the maximum radius of circumference where all eigenvalues are located is obtained as

$$L'_{\max} := (1+\gamma)\left(\Pi_{k=1}^{n}\bar{R}_k^2\right)^{\frac{1}{n}}. \tag{27}$$

On the other hand, $\bar{\varphi}'$ $(\geq |\varphi'|)$ of the form (23) is calculated as follows:

$$\bar{\varphi}' := n \cdot \arccos\left(\sqrt{1-\gamma^2}\right). \tag{28}$$

Then, we obtain the following robust stability result:

Theorem 2. (CASE: U-Homo) *Consider the gene-protein regulatory network system with homogeneous gene dynamics and identical multiplicative uncertainties in Figure 2 CASE U-Homo. We assume that T_{a_0} and T_{b_0} in $h_0(s)$ of (12) are given in advance and that $\Delta(s)$ satisfies the conditions in (13). Then, $\mathcal{F}_{\rm ho}(s)$ is robustly stable, if and only if one of the following conditions is satisfied:*

$$\begin{cases} L'_{\max} < D\left(Q, \dfrac{\pi}{n} - \bar{\varphi}'\right), & \text{if } \dfrac{\pi}{n} > \bar{\varphi}' \ (\geq 0) \\ L'_{\max} < 1, & \text{otherwise} \end{cases} \tag{29}$$

Note that the above analytic robust stability condition is equivalent to that of Polyak and Tsypkin [7] derived based on the zero exclusion principle.

Example 2. Consider $n = 5$ genes which have an identical nominal dynamics such as (26). Here, the homogeneous uncertain dynamics $\Delta(s)$ is set as

$$\Delta(s) = \frac{0.09845s^2 - 0.00772s - 0.3722}{s^2 + 8.554s + 7.195}, \quad \|\Delta(s)\|_\infty = 0.0984.$$

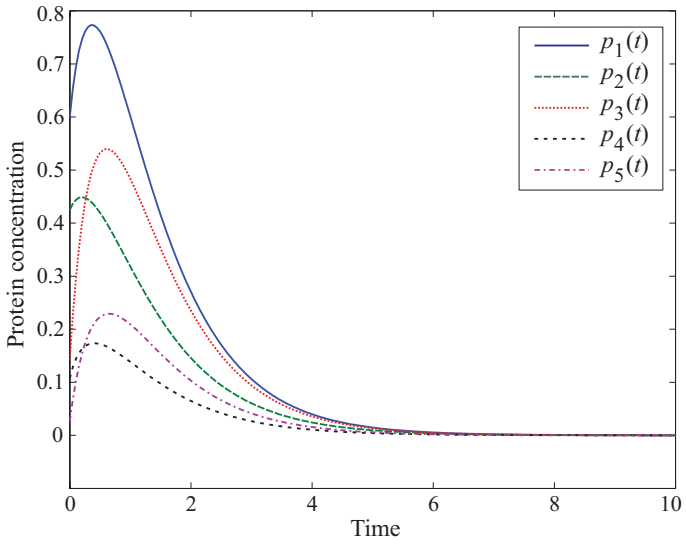


Figure 8: Time plot of protein concentration $p_i(t)$ in Example 2.

The upper bound γ of $\|\Delta(s)\|$ is assumed as $\|\Delta(s)\|_\infty \leq \gamma = 0.1234$. The parameter R_i in (8) and its upper bound $\overline{R}_i$ are identical to those of Example 1. In this case, $\bar{\varphi}' = 0.6188(\text{rad})$ which is less than $\pi/5 = 0.6283(\text{rad})$. Therefore, we can conclude that the considered gene-protein regulatory network system $\mathcal{F}_{\text{ho}}$ defined in "Problem U-Homo" of Section 3 is robustly stable, since the condition in (29),

$$L'_{\max} = 0.5128 < D\left(Q, \frac{\pi}{5} - \bar{\varphi}'\right) = 1.1175.$$

is satisfied. The above fact is confirmed by Figure 8, where the initial protein concentrations are $p_1(0) = 0.5999$, $p_2(0) = 0.4252$, $p_3(0) = 0.1429$, $p_4(0) = 0.1075$, and $p_5(0) = 0.0266$. □

5 Robust stability for parametric uncertainties

In this subsection, we derive a necessary and sufficient robust stability condition for large-scale *homogeneous* gene-protein regulatory network system with *identical* parametric uncertainties in Figure 2 CASE P-Homo (see "Problem P-Homo" given in Section 3 for details). To this end, we first investigate the eigenvalue locations of the matrix K in (8): the eigenvalues λ_i of K are determined as

$$\lambda_i = \left(\Pi_{k=1}^n R_k^2\right)^{\frac{1}{n}} e^{j\left(\frac{\pi}{n}(2i-1)\right)}, \quad i = 1, 2, \cdots, n. \tag{30}$$

It means that all eigenvalues are located on a circle of radius $L := \left(\Pi_{k=1}^n R_k^2\right)^{\frac{1}{n}}$ whose center is at the origin of the complex plane. Further, if the number

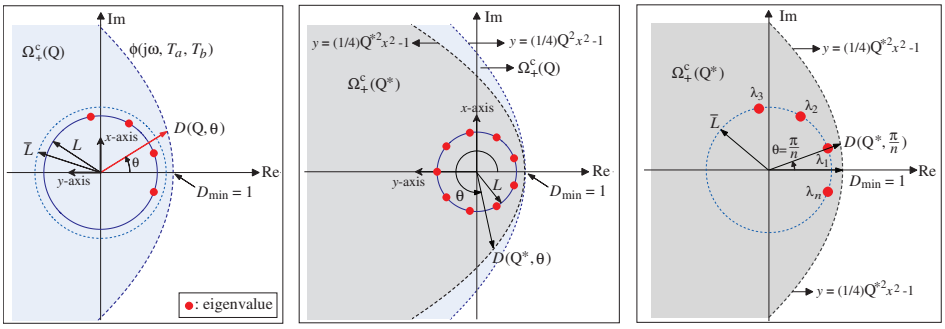


Figure 9: The domains $\Omega_+^c(Q)/\Omega_+^c(Q^*)$ and the positions of eigenvalues λ_i $(i = 1, 2, \cdots, n)$ of K in the system $\mathcal{G}_{\text{ho}}(s)$.

of genes, n, is given, the angle θ_i between the positive real axis and the line connecting the origin to the i-th eigenvalue can be determined by (30) (see Figure 9(left)). In this case, the upper and lower bounds of L such that

$$\underline{L} := \left(\Pi_{k=1}^n \underline{R}_k^2\right)^{\frac{1}{n}} \leq L \leq \bar{L} := \left(\Pi_{k=1}^n \bar{R}_k^2\right)^{\frac{1}{n}} \tag{31}$$

are known, since $\underline{R}_i \leq R_i \leq \bar{R}_i$. The domain Ω_+^c in (10) can be redefined by using Q defined in (18) as follows:

$$\Omega_+^c(Q) := \left\{(x, y) \in \mathbb{R}^2 |\ y > \frac{1}{4}Q^2x^2 - 1\right\}. \tag{32}$$

Note that the value of Q depends on uncertain parameters (T_a, T_b). However, we can easily see that, for any T_a and T_b satisfying $\underline{T}_a \leq T_a \leq \overline{T}_a$ and $\underline{T}_b \leq T_b \leq \overline{T}_b$,

$$\Omega_+^c(Q^*) \subseteq \Omega_+^c(Q) \tag{33}$$

is guaranteed (see Figure 9(center)), where Q^* is defined as

$$Q^* = \begin{cases} \dfrac{\sqrt{\underline{T}_a \overline{T}_b}}{(\underline{T}_a + \overline{T}_b)/2}, & \text{if } \underline{T}_a > \overline{T}_b \\ \dfrac{\sqrt{\overline{T}_a \underline{T}_b}}{(\overline{T}_a + \underline{T}_b)/2}, & \text{else if } \underline{T}_b > \overline{T}_a \\ 1, & \text{otherwise} \end{cases} \tag{34}$$

It means that the domain $\Omega_+^c(Q^*)$ corresponds to the worst case when the parameters $T_a(= 1/a)$ and $T_b(= 1/b)$ of gene dynamics $h(s)$ are uncertain. Note that the minimum length $D_{\min}$ of $D(Q^*, \theta)$ is $1(= D(Q^*, 0))$.

Based on the above observation, we obtain the following key result - an analytic robust stability condition mentioned in Problem P-Homo (CASE P-Homo, Figure 2) in Section 3:

Theorem 3. (CASE: P-Homo) *Consider the gene-protein regulatory network system $\mathcal{G}_{\rm ho}(s)$ in Figure 2 CASE P-Homo. We assume that only the upper and lower bounds of T_a and T_b in $h(s)$ and R_i in a matrix K are given. Then, $\mathcal{G}_{ho}(s)$ is robustly stable, if and only if the following condition is satisfied (see Figure 9(right)):*

$$D\left(Q^*, \frac{\pi}{n}\right) > \bar{L} = \left(\Pi_{k=1}^{n} \bar{R}_k^2\right)^{\frac{1}{n}} \tag{35}$$

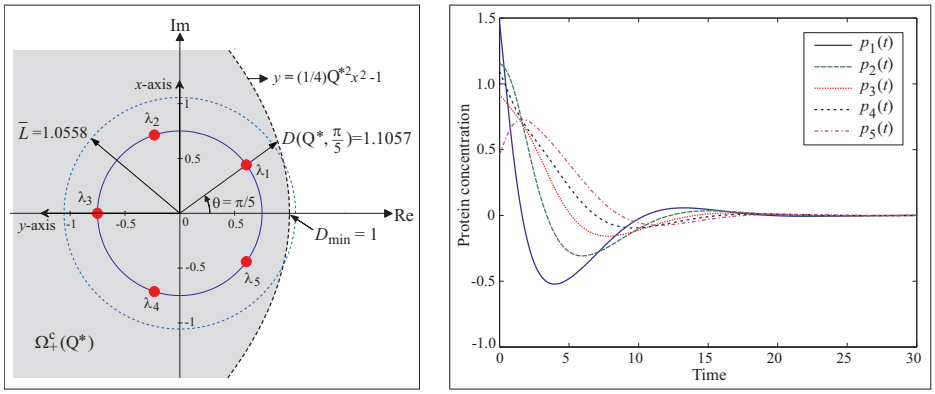
This theorem means that all the poles of uncertain system $\mathcal{G}_{\rm ho}(s)$ are located in the left-half complex plane, if and only if the condition (35) is satisfied. Furthermore, we can see from (35) and a biological viewpoint that the higher values of degradation rates can be related with a much easier occurrence of a stability phenomenon in gene-protein regulatory networks, which is similar to that of Theorems 1 and 2.

Example 3. Consider $n = 5$ genes whose identical dynamics $h(s)$ is given as (15) with $T_a = 1$ and $T_b = 0.5$. Here, we assume the known upper and lower bounds of T_a and T_b are given by $\underline{T}_a = 0.75 \leq T_a \leq \overline{T}_a = 1.2$ and $\underline{T}_b = 0.4 \leq T_b \leq \overline{T}_b = 0.7$. Thus, we have $Q^* = 0.9994$. Here, R_i(unknown) in (8) and its upper bound $\overline{R}_i$(known) are set as follows: $R_1 = 0.9487 \leq \overline{R}_1 = 1.0536$, $R_2 = 0.8367 \leq \overline{R}_2 = 0.9315$, $R_3 = 0.7746 \leq \overline{R}_3 = 1.0763$, $R_4 = 0.8367 \leq \overline{R}_4 = 1.0603$, and $R_5 = 0.9287 \leq \overline{R}_5 = 1.0228$. Then, it follows from (35) that

$$D\left(Q^*, \frac{\pi}{5}\right) = 1.1057 > \bar{L} = \left(\Pi_{k=1}^{5} \bar{R}_k^2\right)^{\frac{1}{5}} = 1.0558,$$

which means that the gene-protein regulatory network system $\mathcal{G}_{\rm ho}$ defined in "Problem P-Homo" in Section 3 is robustly stable. The above fact can be confirmed by Figure 10(a), which shows that all eigenvalues of K belong to the domain $\Omega_+^c(Q^*)$. The Figure 10(b) verifies the convergence properties of $p_i(t)$ $(i = 1, 2, \cdots, 5)$, where the initial protein concentrations are set as $p_1(0) = 1.4607$, $p_2(0) = 1.1571$, $p_3(0) = 0.9177$, $p_4(0) = 1.0936$, and $p_5(0) = 0.4632$. □

Finally, we briefly remark on a robust stability problem for large-scale *heterogeneous* gene-protein regulatory network system with *nonidentical* parametric uncertainties in Figure 2 CASE P-Homo. If we only consider a special case $n = 2$ (two genes), a robust stability criterion could be derived analytically. However, such a condition has not been obtained at current stage for the case $n \geq 3$. Hence, the derivation of an analytic robust stability criterion for general case remains as one of the future research works.



(a) The domain $\Omega_+^c(Q^*)$ and eigenvalue distribution.

(b) Time plot of $p_i(t)$ for $i = 1, 2, \cdots, 5$.

Figure 10: Simulation results of Example 3.

6 Conclusion

In this paper, we have developed analytic robust stability criteria for large-scale cyclic gene-protein regulatory network systems with unstructured or parametric uncertainties from a control-theoretic viewpoint. Here, we first considered a class of gene expressions, which is described as uncertain LTTMs with not only feedback loops from translation products to transcription but also degradation properties of proteins and mRNAs. We then showed that such uncertain LTTMs belong to a class of large-scale dynamical linear network systems with a generalized frequency variable. Finally, we proposed considerably simple analytic robust stability analysis methods, which require less computational burden and can be readily applied to large-scale genetic regulatory networks. The future research is to develop an analytic robust stability criterion for genetic regulatory networks with time delays in transcription, translation, and translocation processes.

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