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Authors
Hara, Shinji
Iwasaki, Tetsuya
Hori, Yutaka

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Robust Stability Analysis for LTI Systems with Generalized Frequency Variables and Its Application to Gene Regulatory Networks [1]

Shinji Hara [a], Tetsuya Iwasaki [b], Yutaka Hori [c],

[a] *Research and Development Initiative, Chuo University, 1-13-27 Kasuga, Bunkyo-ku, Tokyo 112-8551, Japan*

[b] *Mechanical and Aerospace Engineering, University of California, 420 Westwood Plaza, Los Angeles, CA 90095*

[c] *Applied Physics and Physico-Informatics, Keio University, 3-14-1 Hiyoshi, Kohoku-ku, Yokohama, Kanagawa 223-8522, Japan*

Abstract

A class of networked dynamical systems with multiple homogeneous agents can be represented by a linear system with a generalized frequency variable. This paper is concerned with robust stability analysis of such class of systems under perturbations in the dynamics of agents. The perturbed agents no longer share the same dynamics and thus the analysis encompasses heterogeneous multi-agent systems consisting of slightly different agents. We first present nominal stability conditions for the system of interconnected MIMO agents. We then focus on robust stability, where we consider three types of perturbations, leading to homogeneous agents, heterogeneous agents with and without uncertain interconnections. For each case, we show that a necessary and sufficient condition for robust stability is given by an $\mathcal{H}_\infty$-norm bound on a set of transfer functions parametrized by the eigenvalues of the interconnection matrix, provided the nominal interconnections have a certain structure. The robust stability condition is interpreted as the requirement that the eigenvalues of the interconnection matrix be located in a particular region on the complex plane. The usefulness of the results is demonstrated through an application to robust stability analysis for gene regulatory networks.

Key words: Large-scale systems, Linear control systems, Robust stability, Biomedical systems, Networks

1 Introduction

Recently, much attention has been paid to large scale or complex dynamical systems in a variety of science and engineering fields including control. One of the main issues in control is to systematically design decentralized cooperative controllers for multi-agent networked dynamical systems. There are many research results addressing this issue in the form of proposing a specific approach within a particular problem formulation (see e.g., [8,28] and references therein). However, very few results are available so far to provide a unifying theoretical framework along this line of research.

To establish a unified framework for the analysis and synthesis of multi-agent networked dynamical systems, our research group recently proposed a linear time-invariant (LTI) system with a generalized frequency variable as one of the unifying expressions for multi-agent dynamical systems [10,11]. Specifically, the transfer function $\mathcal{G}(s)$ representing the overall dynamics of a multi-agent system with homogeneous agent dynamics $h(s)$ is described by simply replacing s by a rational function $\phi(s) := 1/h(s)$ in a transfer function $G(s)$, i.e., $\mathcal{G}(s) := G(\phi(s))$. We call $\phi(s)$ the generalized frequency variable, because s in a continuous-time transfer function represents the frequency variable.

The system description has a potential to provide a theoretical foundation for analyzing and designing homogeneous large-scale networked dynamical systems in a variety of areas including central pattern generators (CPGs) [18] , gene-protein regulatory networks [3,7], and automobile platoons [34] as well as consensus and for-

Email addresses: Shinji_Hara@ipc.i.u-tokyo.ac.jp (Shinji Hara), tiwasaki@ucla.edu (Tetsuya Iwasaki), yhori@appi.keio.ac.jp (Yutaka Hori).
[1] Corresponding author S. Hara. Tel. +81-3-3817-1602. Fax. +81-3-3817-1677.

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mation problems as surveyed in [28]. The very fundamental properties on LTI multi-agent systems including controllability/observability [10,11], graphical stability tests [28,30], an algebraic and LMI conditions for Hurwitz stability [14,32], and $\mathcal{H}_2$-norm and $\mathcal{H}_\infty$-norm computations [13,24,25] have been investigated. However, most of those researches treat homogeneous multi-agent systems, while agents in practical applications in general do not share common dynamics and the communication time delay may be different. Hence the results can not be directly applied to those problems in which the assumption on homogeneity of the agent dynamics is unrealistic.

To relax the assumption accordingly and cope with such practical situations, reference [22] considered symmetric networks of heterogeneous agents with an unstructured uncertainty in the interconnections, and provided scalable robust stability conditions exploiting the symmetry. The idea was also used to address consensus problems [23]. References [19,20] considered systems of heterogeneous agents with interconnections specified by a class of normal matrices with uncertain eigenvalues, and provided scalable robust stability conditions exploiting the normality. All these results are focused on single-input-single-output (SISO) agents. Reference [33] considered uncertain multi-input-multi-output (MIMO) multi-agent systems and proposed robustly synchronizing dynamic protocols under heterogeneous (resp. homogeneous) perturbations in the agent dynamics with symmetric (resp. asymmetric) interconnections.

Here we provide a unified perspective on the robust stability analysis of MIMO multi-agent systems exploiting the framework of LTI systems with generalized frequency variables [14]. We consider several classes of uncertain multi-agent systems containing cases that have not been addressed in the previous works. In particular, we consider three types of perturbations, leading to (a) uncertain homogeneous agents with arbitrary interconnections, (b) uncertain heterogeneous agents with diagonally normalizable interconnections (a precise definition will be given later), and (c) heterogeneous agents and arbitrary interconnections that are uncertain but nominally homogeneous and normal, respectively. Case (b) captures one of realistic situations of the multi-agent system consisting of the same type of agents with independent uncertainties such as multi-robot systems and multi-wheel electric vehicles [5]. Case (a) represents the fully idealized situation for homogeneous multi-agent system with uncertain dynamics of the agent, which is mainly introduced for deriving the results for Case (b). Case (c) allows uncertainties in the interaction among agents due to the change of environments.

For each case, we show that a necessary and sufficient condition for robust stability is given by an $\mathcal{H}_\infty$-norm bound on a set of transfer functions parametrized by the eigenvalues of the interconnection matrix. It should be emphasized that the classes of interconnections specified in Cases (b) and (c) are not so restrictive in practice. We have at least two real applications which meet the class specified for Case (b), namely cyclic gene regulatory networks [16] and multi-wheel electric vehicles [5], as will be shown in Section 3.2. Any networked system with undirected interconnection graph satisfies the condition specified for Case (c).

The robust stability condition is interpreted as the requirement that the eigenvalues of the interconnection matrix be located in a particular region on the complex plane. The computational issues are also discussed by investigating the case of normalized coprime factor perturbations, which can take both the sensitivity and complementary sensitivity functions into account. While a state space formulation captures the general case of MIMO agents, a transfer function formulation provides an analytical characterization of the robust stability region for the SISO case. We then demonstrate robust stability analysis for gene regulatory networks as a biological application to show the effectiveness of the theoretical results to get the analytical formula of the robust stability condition.

A preliminary investigation on the robust stability analysis was done for SISO agents with multiplicative perturbations in the authors' conference paper [12]. The present paper treats MIMO agents with general class of perturbations and provides necessary and sufficient robust stability conditions with complete proofs. The application to gene regulatory networks is also new in this paper, which clearly shows the effectiveness of the theoretical results to get an analytical condition for the robustness that leads to new biological insights.

This paper is organized as follows. In Section 2, we briefly review (nominal) stability conditions for LTI systems with generalized frequency variables as a preliminary study, where previous SISO results are generalized to the MIMO case in a straightforward manner. Section 3 is devoted to robust stability analysis. We first introduce three different types of perturbations which correspond to three typical situations for multi-agent systems consisting of slightly different dynamic agents with communication time delays. We then derive necessary and sufficient conditions for the robust stability. The computational issues are discussed in Section 4. Section 5 demonstrates the usefulness of the robust stability conditions by an application to gene regulatory networks. Finally, we make concluding remarks in Section 6.

We use the following notation. The sets of real, complex and natural numbers, are denoted by $\mathbb{R}$, $\mathbb{C}$, and $\mathbb{N}$, respectively. The complex conjugate of $z \in \mathbb{C}$ is denoted by $\bar{z}$. For a matrix A, its transpose and complex conjugate transpose are denoted by A^T and A^*, respectively. For a square matrix A, the set of eigenvalues is denoted by $\sigma(A)$. The symbols $\mathbf{S}_n$ and $\mathbf{S}_n^+$ stand for the sets of $n \times n$ real symmetric matrices and its positive definite

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subsets. For matrices A and B, $A \otimes B$ means their Kronecker product. The open left-half complex plane and the closed right-half complex plane are denoted by $\mathbb{C}_-$ and $\mathbb{C}_+$, respectively. The upper and lower linear fractional transformations (LFTs) are denoted by $\mathcal{F}_u$ and $\mathcal{F}_\ell$, respectively. The set of $p \times m$ proper stable real rational functions is denoted by $\mathbb{R}\mathbf{H}_\infty^{p\times m}$.

Summary of symbols: Matrix A represents the general interconnections of homogeneous MIMO agents $H(s)$ with $(\mathsf{B}, \mathsf{C}, \mathsf{D})$ specifying the input-output structure. Matrix A specifies an instance of the interconnection structure by $\mathsf{A} = A \otimes I_q$, on which our analysis focuses. For robust stability analysis, the uncertain agent $\tilde{H}_i(s)$ is expressed as the LFT of $G(s)$ and $\Delta_i(s)$, and their block-diagonal assembly is denoted by $\tilde{\mathbf{H}}(s)$, which is the LFT of $\mathbf{G}(s)$ and $\Delta(s)$. The generalized plant $G(s)$ under the influence of the interconnections by A is denoted by $\mathcal{G}_\lambda$ where λ is an eigenvalue of A.

2 LTI System with Generalized Frequency Variable

2.1 System Representation

Consider the linear time-invariant system described by an upper LFT representation

$$\mathsf{G}(s) = \mathcal{F}_u\left(\begin{bmatrix} \mathsf{A} & \mathsf{B} \\ \mathsf{C} & \mathsf{D}\end{bmatrix}, I_n \otimes H(s)\right), \qquad (1)$$

where $\mathsf{A} \in \mathbb{R}^{nq\times nq}$, $\mathsf{B} \in \mathbb{R}^{nq\times m}$, $\mathsf{C} \in \mathbb{R}^{p\times nq}$, $\mathsf{D} \in \mathbb{R}^{p\times m}$, and $H(s)$ is a MIMO square strictly proper rational transfer function matrix with q inputs and q outputs, of which a minimal realization is given by (A_h, B_h, C_h), where $A_h \in \mathbb{R}^{\nu\times\nu}$, $B_h \in \mathbb{R}^{\nu\times q}$, $C_h \in \mathbb{R}^{q\times\nu}$, and ν is the McMillan degree of $H(s)$.

The system $\mathsf{G}(s)$ can be viewed as an interconnection of n identical agents, each of which has the common internal dynamics $H(s)$, and the interconnection structure is specified by A, and the input-output structure for the whole system is specified by B, C, and D. The assumption on the squareness of $H(s)$ is not quite restrictive, since $H(s)$ represents not necessarily the original agent dynamics but a locally modified agent. One of typical and fairly general form of the modified agent is given by

$$H(s) = \mathcal{F}_u\left(\begin{bmatrix} F_{fb}(s) & F_{pre}(s) \\ F_{pst}(s) & 0\end{bmatrix}, P(s)\right), \qquad (2)$$

where $P(s)$ denotes the possibly non-square original agent transfer function, and $F_{fb}(s)$, $F_{pre}(s)$ and $F_{post}(s)$ respectively correspond to the local feedback controller, and the pre- and post- filters for adjustments of before and after communications.

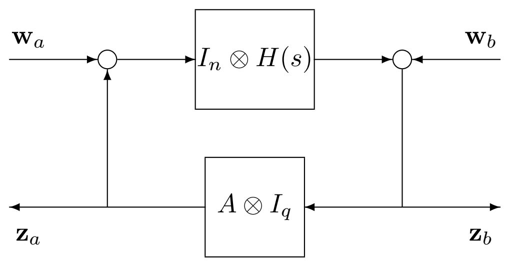

Fig. 1. Feedback system $\Sigma(I_n \otimes H(s), A \otimes I_q)$

Let us consider the SISO case where $q = 1$ and define a transfer function

$$\mathsf{G}_o(s) = \mathsf{C}(sI_n - \mathsf{A})^{-1}\mathsf{B} + \mathsf{D}, \qquad (3)$$

then system $\mathsf{G}(s)$ can be expressed as

$$\mathsf{G}(s) = \mathsf{G}_o(\phi(s)), \quad \phi(s) := 1/H(s). \qquad (4)$$

Note that the variable "s" in (3) characterizes frequency properties of the continuous-time transfer function $\mathsf{G}_o(s)$ and that $\mathsf{G}(s)$ is generated by simply replacing s by $\phi(s)$ in G_o. Hence, we call system $\mathsf{G}(s)$ represented by (4) an *LTI system with generalized frequency variable* $\phi(s)$ [10,11].

2.2 Stability Analysis

We here show that our previous results for the SISO case [32] can be extended to the MIMO case. In order to investigate the internal stability of $\mathsf{G}(s)$, we will focus on the feedback system $\Sigma(I_n \otimes H(s), A \otimes I_q)$ depicted in Fig. 1. [2] We say that $\Sigma(I_n \otimes H(s), A \otimes I_q)$ is *Hurwitz stable* if all the roots of its characteristic polynomial belong to $\mathbb{C}_-$, i.e., $\det(I_{nq} - A \otimes H(s)) = 0$ has no roots in the closed right half complex plane.

We can derive stability conditions similar to those obtained in [32] for the SISO case.

Theorem 1 *Let a matrix $A \in \mathbb{R}^{n\times n}$, and a strictly proper rational function $H(s)$ with a minimal realization (A_h, B_h, C_h) be given and define $p(\lambda, s)$ by*

$$p(\lambda, s) := \det(sI_\nu - A_h - \lambda B_h C_h). \qquad (5)$$

Then, the following five statements are equivalent, where the positive integer $\ell_k \in \mathbb{N}$ and $\Phi_k \in \mathbf{S}_{\ell_k}$ for $k =$

[2] A more general interconnection structure of the form $A \otimes K$ with an arbitrary $q \times q$ matrix K can be reformulated as in Fig. 1 with $A \otimes I_q$ by absorbing K into $H(s)$. Hence, the essential restriction is only to share, among agents, common weighted outputs for information exchanges.

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$1, 2, \dots, \nu$ *are specified by applying the Hurwitz-type stability test for polynomials with complex coefficients to the corresponding closed-loop characteristic polynomial* $p(\lambda, s)$ *in the same way as Theorem 1 with Appendixes B and C in [14]:*

(i) $\Sigma(I_n \otimes H(s), A \otimes I_q)$ *is Hurwitz stable.*
(ii) $\sigma(A) \subset \mathbf{\Lambda}_s := \{ \lambda \in \mathbb{C} \mid p(\lambda, s) \text{ is Hurwitz} \}$.
(iii) *For each* $\lambda \in \sigma(A)$, *all the eigenvalues of* $A_h + \lambda B_h C_h$ *belong to the open left-half complex plane.*
(iv) $\sigma(A) \subset \mathbf{\Lambda}_s$, *where* $\mathbf{\Lambda}_s = \bigcap_{k=1}^{\nu} \{ \lambda \in \mathbb{C} \mid l_{\ell_k}(\lambda)^* \Phi_k l_{\ell_k}(\lambda) > 0 \}$.
(v) *For each* $k = 1, 2, \dots, \nu$, *there exists* $X_k \in \mathbf{S}_n^+$ *such that*

$$L_{\ell_k}(A)^T (\Phi_k \otimes X_k) L_{\ell_k}(A) > 0. \tag{6}$$

Here $l_\ell(\lambda)$ *and* $L_\ell(A)$ *are defined by*

$$l_\ell(\lambda) := \begin{bmatrix} 1 \\ \lambda \\ \vdots \\ \lambda^{\ell-1} \end{bmatrix}, \; L_\ell(A) := \begin{bmatrix} I \\ A \\ \vdots \\ A^{\ell-1} \end{bmatrix}.$$

Proof. Let T be an $n \times n$ non-singular matrix so that TAT^{-1} is an upper triangular matrix and λ_i $(i = 1, 2, \dots n)$ be eigenvalues of A. Then we have

$$\begin{aligned} &\det(I_n \otimes I_q - A \otimes H(s)) = 0 \\ \Leftrightarrow &\det((TI_nT^{-1}) \otimes I_q - (TAT^{-1}) \otimes H(s)) = 0 \\ \Leftrightarrow &\prod_{i=1}^{n} \det(I_q - \lambda_i H(s)) = 0 \end{aligned} \tag{7}$$

In other words, we can check the stability of the MIMO LTI system with generalized frequency variable by checking the stability of n independent feedback systems consisting of $H(s)$ and the eigenvalues of A, or $\Sigma(H(s), \lambda_i I)$ for $i = 1, \dots, n$. Standard determinant formulas [3] can be used to express the condition in terms of state space matrices:

$$\begin{aligned} &\det(I_q - \lambda H(s)) = \det(I_q - \lambda C_h (sI_\nu - A_h)^{-1} B_h) = 0 \\ \Leftrightarrow &\det(\begin{bmatrix} sI_\nu - A_h & B_h \\ \lambda C_h & I_q \end{bmatrix}) = 0 \\ \Leftrightarrow &\det(sI_\nu - A_h - \lambda B_h C_h) = 0. \end{aligned}$$

This clearly shows the equivalence of (i), (ii), and (iii). The equivalence with (iv) and (v) can be proved by the same technique as in Theorem 1 in [14] for the SISO case. □

[3] $\det\left(\begin{bmatrix} A & B \\ C & D \end{bmatrix}\right) = 0$ is equivalent to $D - CA^{-1}B = 0$ or $A - BD^{-1}C = 0$ assuming non-singularity of A or D, respectively (See e.g., [4]).

Conditions (iv) and (v) in Theorem 1 provide two types of systematic ways of checking the stability, namely an algebraic stability test and a numerical method (LMI feasibility problem), respectively. Note that $p(\lambda, s)$ is a polynomial with respect to s and λ and that the degrees with respect to s and λ are ν and r, respectively, where

$$r := \operatorname{rank}(B_h C_h) \le \min\{\operatorname{rank}(B_h), \operatorname{rank}(C_h)\} \le q.$$

It should be noticed that the degree with respect to λ is essentially irrelevant for computational complexity for the stability test as seen in Theorem 1.

3 Robust Stability Analysis

3.1 Analysis Problems

This section is devoted to setting up appropriate robust stability problems which properly capture the nature of multi-agent networked dynamical systems. We first introduce three classes of perturbations in multi-agent dynamical systems, which correspond to three different situations. Among the three cases we will mainly focus on the case where the same type of agents with slightly different dynamics are connected to each other through slightly different communication time delays, since it is most fit to practical situations.

We consider a general representation of unstructured perturbations for the common nominal (modified) agent $H(s)$. Note that $H(s)$ may include a factor associated with the nominal communication time delay τ_c, or the Pade approximation of the time delay say $(2 - \tau_c s)/(2 + \tau_c s)$, and the $\Delta_i(s)$ captures the gap between the actual system with time delay and $H(s)$ in a certain way.

As seen in Fig. 2, the perturbed i-th agent $(i = 1, 2, \dots, n)$ is described by

$$\tilde{H}_i(s) = \mathcal{F}_u\left(\begin{bmatrix} G_{11}(s) & G_{12}(s) \\ G_{21}(s) & H(s) \end{bmatrix}, \Delta_i(s)\right), \tag{8}$$

where $G_{11}(s) \in \mathbb{R}\mathbf{H}_\infty^{\tilde{p} \times \tilde{m}}$, $G_{12}(s) \in \mathbb{R}\mathbf{H}_\infty^{\tilde{p} \times q}$, $G_{21}(s) \in \mathbb{R}\mathbf{H}_\infty^{q \times \tilde{m}}$, and $\Delta_i(s) \in \mathbb{R}\mathbf{H}_\infty^{\tilde{m} \times \tilde{p}}$ represents the unstructured norm-bounded perturbations for the i-th agent. We may consider a variety of classes of perturbations by setting $G_{11}(s)$, $G_{12}(s)$, and $G_{21}(s)$ appropriately. For examples,

- **Additive Perturbations:** Setting $G_{11}(s) = 0$, $G_{12}(s) = W_2(s)$, and $G_{21}(s) = W_1(s)$ leads to $\tilde{H}_i(s) = H(s) + W_1(s)\Delta_i(s)W_2(s)$.

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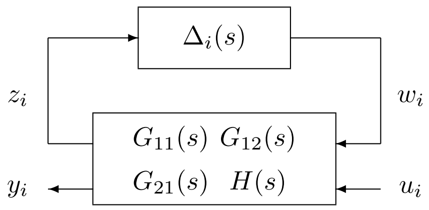

Fig. 2. Perturbed agent $\tilde{H}_i(s)$

- **Multiplicative Perturbations:** Setting $G_{11}(s) = 0$, $G_{12}(s) = W_2(s)$, and $G_{21}(s) = H(s)W_1(s)$ leads to $\tilde{H}_i(s) = H(s)(I_q + W_1(s)\Delta_i(s)W_2(s))$. In order to make $G_{21}(s) = H(s)W_1(s)$ stable for unstable $H(s)$, $W_1(s)$ should have a form $W_1(s) = D_H(s)\hat{W}_1(s)$ with a certain $\hat{W}_1(s) \in \mathbb{R}\mathbf{H}_\infty^{q\times\tilde{m}}$, where $D_H(s)$ is the denominator of a right coprime factorization of $H(s)$ over $\mathbb{R}\mathbf{H}_\infty$, i.e., $H(s) = N_H(s)D_H(s)^{-1}$.
- **Multiple Perturbations:** There are several other popular classes of perturbations. One of typical examples of multiple perturbations is a combination of multiplicative and feedback perturbations, which respectively correspond to the numerator and the denominator perturbations, as seen later in (37) for the application of gene regulatory networks in Section 5 . Another example is so called normalized coprime factor perturbations, which relates to the loop shaping $\mathcal{H}_\infty$ design. This case will be investigated in Section 4.2. Note that the same technique for the multiplicative perturbations for unstable $H(s)$ using $D_H(s)$ is also available for these cases.

Then, the overall perturbed system without interconnection can be expressed as

$$\tilde{\mathbf{H}}(s) := \mathcal{F}_u\left(\mathbf{G}(s), \Delta(s)\right), \quad \Delta(s) := \mathrm{diag}(\Delta_i(s)), \tag{9}$$

where

$$\mathbf{G}(s) := \begin{bmatrix} I_n \otimes G_{11}(s) & I_n \otimes G_{12}(s) \\ I_n \otimes G_{21}(s) & I_n \otimes H(s) \end{bmatrix}. \tag{10}$$

In addition to the class of block diagonal perturbations above, we will treat two additional classes of perturbations, namely *full perturbations* and *identical/repeated perturbations*. More precisely, we will investigate robust stability conditions for $\tilde{\mathbf{H}}(s)$ in (9) with the following three different classes of perturbations:

$$\boldsymbol{\Delta}_\gamma := \{\ \Delta(s) \in \boldsymbol{\Delta}_p \mid \ \|\Delta\|_\infty \le 1/\gamma\ \}, \tag{11}$$
$$\boldsymbol{\Delta}_{d\gamma} := \{\ \Delta(s) \in \boldsymbol{\Delta}_\gamma \mid \Delta(s) = \mathrm{diag}(\Delta_i(s))\ \}, \tag{12}$$
$$\boldsymbol{\Delta}_{I\gamma} := \{\ \Delta(s) \in \boldsymbol{\Delta}_\gamma \mid \Delta(s) = I_n \otimes \delta(s)\ \}, \tag{13}$$

where $\boldsymbol{\Delta}_p$ denotes the class of proper stable rational functions, i.e., $\Delta_p(s) \in \mathbb{R}\mathbf{H}_\infty^{\tilde{m}\times\tilde{p}}$.

The total feedback system $\Sigma(\tilde{\mathbf{H}}(s), A \otimes I_q)$, with interconnection specified by A, is then expressed as $\mathcal{F}_\ell(\mathcal{F}_u\left(\mathbf{G}(s), \Delta(s)\right), A \otimes I_q)$.

Clearly,

$$\boldsymbol{\Delta}_{I\gamma} \subset \boldsymbol{\Delta}_{d\gamma} \subset \boldsymbol{\Delta}_\gamma.$$

The set $\boldsymbol{\Delta}_{I\gamma}$ represents a class of homogeneous diagonal perturbations, and the robust stability was investigated in [30]. It should be noticed that the agents still share the same dynamics even if it includes perturbation, or the perturbation as well as the nominal dynamics should be coincident among all the agents. This assumption is too strong for many practical applications, and hence we have introduced another class $\boldsymbol{\Delta}_{d\gamma}$ which represents a class of heterogeneous diagonal perturbations with common nominal dynamics to address the practical situations. The main purpose of this paper is to investigate the robust stability for this class. On the other hand, $\boldsymbol{\Delta}_\gamma$ corresponds to the full perturbation, where the existence of off-diagonal perturbations implies that multiple agents may physically interact with each other in an uncertain manner. The robust stability conditions for full perturbations were derived when A is a normal matrix, i.e., $AA^* = A^*A$, in [12].

We are now ready to define a notion of robust stability investigated in this paper.

Definition 1 *Consider the interconnected system $\Sigma(\tilde{\mathbf{H}}(s), A \otimes I_q)$, where the nominal system $\Sigma(I_n \otimes H(s), A \otimes I_q)$ consists of n agents with identical dynamics $H(s)$ interconnected by an $n \times n$ real matrix A and we have the perturbations $\Delta(s)$ in a class $\boldsymbol{\Delta}_\#$ ($= \boldsymbol{\Delta}_{I\gamma}$, $\boldsymbol{\Delta}_{d\gamma}$, $\boldsymbol{\Delta}_\gamma$). We assume that the nominal system is Hurwitz stable. Then, the perturbed interconnected system $\Sigma(\tilde{\mathbf{H}}(s), A \otimes I_q)$ is said to be robustly Hurwitz stable against $\boldsymbol{\Delta}_\#$ if it is Hurwitz stable against all perturbations $\Delta(s) \in \boldsymbol{\Delta}_\#$.*

3.2 Robust Stability Conditions

The following theorem provides necessary and sufficient conditions for the robust stability with three different types of perturbations, namely $\boldsymbol{\Delta}_{I\gamma}$, $\boldsymbol{\Delta}_{d\gamma}$, and $\boldsymbol{\Delta}_\gamma$.

Theorem 2 *We consider the following three cases:*

(a) $\Delta(s) \in \boldsymbol{\Delta}_{I\gamma}$ *and* $A \in \mathbb{R}^{n\times n}$,
(b) $\Delta(s) \in \boldsymbol{\Delta}_{d\gamma}$ *and* $A \in \mathbb{R}^{n\times n}_{DN} \subset \mathbb{R}^{n\times n}$,
(c) $\Delta(s) \in \boldsymbol{\Delta}_\gamma$ *and* $A \in \mathbb{R}^{n\times n}$ *is normal, i.e.,* $AA^* = A^*A$,

where

$$\mathbb{R}^{n\times n}_{DN} := \{A \in \mathbb{R}^{n\times n} \mid \exists \text{ a diagonal matrix } D \in \mathbb{R}^{n\times n} \text{ such that } DAD^{-1} \text{ is normal}\}, \tag{14}$$

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and we assume that the nominal system $\Sigma(I_n \otimes H(s), A \otimes I_q)$ is Hurwitz stable. Then for all three cases (a), (b), and (c), the perturbed interconnected system $\Sigma(\tilde{\mathbf{H}}(s), A \otimes I_q)$ is robustly Hurwitz stable for the corresponding classes of perturbations $\mathbf{\Delta}_{\#}$, if and only if

$$\|\mathcal{G}_\lambda\|_\infty < \gamma \tag{15}$$

holds for all $\lambda \in \sigma(A)$, where

$$\mathcal{G}_\lambda(s) := \mathcal{F}_\ell\left(\begin{bmatrix} G_{11}(s) & G_{12}(s) \\ G_{21}(s) & H(s) \end{bmatrix}, \lambda I_q\right). \tag{16}$$

Proof. We here assume that the matrix A is diagonalizable just for notational simplicity, because any small perturbation to A preserves the robustness property due to the continuity of eigenvalues and we can find a small perturbation which makes the perturbed A diagonalizable. Then, there exists an $n \times n$ non-singular matrix T satisfying

$$\Lambda := TAT^{-1} = \mathrm{diag}\{\lambda_i\},$$

and this leads to

$$(T \otimes I_q)\ (A \otimes I_q)\ (T^{-1} \otimes I_q) = \mathrm{diag}\{\lambda_i I_q\}. \tag{17}$$

In order to adopt this transformation T, we define

$$\mathbf{G}_T(s) := \mathrm{diag}\{T \otimes I_{\tilde{p}}, T \otimes I_q\} \times \mathbf{G}(s) \times \mathrm{diag}\{T^{-1} \otimes I_{\tilde{m}}, T^{-1} \otimes I_q\}$$

and

$$\Delta_T(s) := (T \otimes I_{\tilde{m}})\Delta(s)(T^{-1} \otimes I_{\tilde{p}}). \tag{18}$$

We can see that $\mathbf{G}_T(s) = \mathbf{G}(s)$, and hence we have

$$\begin{aligned}&(T \otimes I_q)\ \mathcal{F}_u(\mathbf{G}(s), \Delta(s))\ (T^{-1} \otimes I_q)\\ &= \mathcal{F}_u(\mathbf{G}_T(s), \Delta_T(s)) = \mathcal{F}_u(\mathbf{G}(s), \Delta_T(s)).\end{aligned} \tag{19}$$

This together with (17) implies that the original robust stability problem is equivalent to that of an interconnected system consisting of $\mathcal{F}_u(\mathbf{G}(s), \Delta_T(s))$ and $\mathrm{diag}\{\lambda_i I_q\}$ or equivalently consisting of $\Delta_T(s)$ and $\mathcal{F}_\ell(\mathbf{G}(s), \mathrm{diag}\{\lambda_i I_q\})$.

• Proof for Case (a):

If $\Delta(s)$ belongs to $\mathbf{\Delta}_{I\gamma}$, then we have $\Delta_T(s) := T\Delta(s)T^{-1} = \Delta(s) = I_n \otimes \delta(s)$. Hence, the interconnected system $\Sigma(\tilde{\mathbf{H}}(s), A \otimes I_q)$ can be equivalently transformed into $\Sigma(\mathcal{F}_u(\mathbf{G}(s), I_n \otimes \delta(s)), \mathrm{diag}\{\lambda_i I_q\})$, of which the robust stability is equivalent to that of $\Sigma(I_n \otimes \delta(s), \mathcal{F}_\ell(\mathbf{G}(s), \mathrm{diag}\{\lambda_i I_q\})$. Note that both the components of the system are block diagonal, and hence checking the component-wise robust stability condition, i.e., robust stability condition for $\Sigma(\delta(s), \mathcal{G}_{\lambda_i})$ for all $i = 1, 2, \ldots, n$ gives the robust stability condition for the total system. Since the nominal system is stable and $\|\delta(s)\|_\infty \le 1/\gamma$, we can apply the small gain theorem (e.g., Theorem 9.1 in [35]) which shows that the $\mathcal{H}_\infty$-norm condition given by (15) is the necessary and sufficient condition for robust stability. This is the proof for case (a) and the same technique was used in [30] for the similar problem.

• Proof for Case (b):

We need more investigation for the proof of case (b), although the necessity is obvious due to $\mathbf{\Delta}_{I\gamma} \subset \mathbf{\Delta}_{d\gamma}$. We will prove the sufficiency by introducing a class of transformations T represented by

$$\begin{aligned}\mathcal{T}_{UD} := \{\ T = UD \in \mathbb{C}^{n\times n} \mid U \in \mathbb{C}^{n\times n}\ :\ \text{unitary},\\ D \in \mathbb{R}^{n\times n}\ :\ \text{nonsingular \& diagonal}\ \}.\end{aligned} \tag{20}$$

We readily see that $A \in \mathbb{R}^{n\times n}_{DN}$ is equivalent to the existence of $T \in \mathcal{T}_{UD}$ so that TAT^{-1} is diagonal. If T is chosen as $T = UD$, then

$$\begin{aligned}&(T \otimes I_{\tilde{m}})\Delta(s)(T^{-1} \otimes I_{\tilde{p}})\\ &= (U \otimes I_{\tilde{m}})(D \otimes I_{\tilde{m}})\ \mathrm{diag}\{\Delta_i(s)\}(D^{-1} \otimes I_{\tilde{p}})(U^* \otimes I_{\tilde{p}})\\ &= (U \otimes I_{\tilde{m}})\ \mathrm{diag}\{\Delta_i(s)\}\ (U^* \otimes I_{\tilde{p}})\end{aligned}$$

holds for $\Delta(s) \in \mathbf{\Delta}_{d\gamma}$ with any nonsingular diagonal matrix $D \in \mathbb{R}^{n\times n}$. Also note that

$$\|U\Delta_i(s)U^*\|_\infty = \|\Delta_i(s)\|_\infty \le 1/\gamma\ \ (i = 1, 2, \ldots, n)$$

or equivalently

$$\|(U \otimes I_{\tilde{m}})\ \mathrm{diag}\{\Delta_i(s)\}\ (U^* \otimes I_{\tilde{p}})\|_\infty \le 1/\gamma \tag{21}$$

holds for $\Delta(s) \in \mathbf{\Delta}_{d\gamma}$ with any unitary matrix $U \in \mathbb{C}^{n\times n}$. This shows that the $\mathcal{H}_\infty$-norm of the perturbation block of the system transformed by $T = UD$ is bounded by $1/\gamma$. We need to evaluate the $\mathcal{H}_\infty$-norm of the nominal system, which is represented by $\mathcal{F}_\ell\{\mathbf{G}_T, (T \otimes I_q)\ (A \otimes I_q)\ (T^{-1} \otimes I_q)\ \}$ in order to apply the small gain theorem (Theorem 9.1 in [35]). Since $TAT^{-1} = \mathrm{diag}\{\lambda_i\}$ or (17) holds, we have

$$\begin{aligned}&\mathcal{F}_\ell\{\mathbf{G}_T, (T \otimes I_q)\ (A \otimes I_q)\ (T^{-1} \otimes I_q)\ \}\\ &= \mathcal{F}_\ell\{\mathbf{G}, \mathrm{diag}\{\lambda_i I_q\}\}\\ &= \mathrm{diag}\left\{\mathcal{F}_\ell\left(\begin{bmatrix} G_{11}(s) & G_{12}(s) \\ G_{21}(s) & H(s) \end{bmatrix}, \lambda_i I_q\right)\right\}.\end{aligned}$$

Hence, we can see from the small gain theorem (Theorem 9.1 in [35]) that the robust stability is guaranteed if (15) is satisfied. This completes the proof of sufficiency.

• Proof for Case (c):

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The proof for case (c) is similar to that for case (b). The necessity is again obvious due to $\mathbf{\Delta}_{I\gamma} \subset \mathbf{\Delta}_\gamma$. The sufficiency can be proved by choosing a unitary matrix U as a candidate of T which makes A diagonal and applying the small gain theorem (Theorem 9.1 in [35]) to the transformed interconnected system. □

There are three remarks on Theorem 2.

- The theorem shows that the robust stability conditions for the three cases (a), (b), and (c) are the same. This implies for instance that one of the worst case perturbations is an identical diagonal perturbation when A is normal or A belongs to $\mathbb{R}_{DN}$.
- It should be noticed that the class of normal matrices includes Hermitian, skew-Hermitian, unitary, and circulant matrices, and hence the results in Theorem 2 would address practical applications for which the interconnections have such particular structures including undirected graph structure.
- Although the meaning of class $\mathbb{R}_{DN}$ is not clear, there are at least two classes of matrices that are not normal but belong to $\mathbb{R}_{DN}$, which fit to some practical applications. One is a class of cyclic matrices with nonuniform entries, which corresponds to any multi-agent system with cyclic graph structure such as cyclic gene regulatory networks [16,17] as seen in Section 5. The other is a class of rank one matrices of the form $\mathbf{a}\mathbf{1}^T$ or $\mathbf{1}\mathbf{a}^T$, where $\mathbf{a}$ is an n dimensional vector with all positive entries and $\mathbf{1}$ is an n dimensional vector of which all the elements are 1. This situation appears in hierarchical networked systems having physical and/or communication interactions based on the average or sum of the lower level variables such as multi-wheel electric vehicles [5], See below for the proper choices of D for those two cases.

1) A class of cyclic matrices: Let A be an $n\times n$ real matrix such that all the elements are zero except $a_{i+1,i} := \alpha_i$, $(i = 1, 2, \ldots, n-1)$ and $a_{1,n} := \alpha_n$. Suppose α_i are all nonzero, and the product $\alpha_1\alpha_2\cdots\alpha_n$ is positive if n is even. Define a diagonal matrix D by its diagonal entries d_i $(i = 1, 2, \ldots, n)$, where

$$d_1 = 1, \quad d_i = \frac{\alpha_o^{i-1}}{\alpha_1\alpha_2\cdots\alpha_{i-1}} \quad (i = 2, \ldots, n)$$

with

$$\alpha_o := \sqrt[n]{|\alpha_1\alpha_2\cdots\alpha_n|}.$$

Then we have

$$(DAD^{-1})(DAD^{-1})^T = \alpha_o^2 I_n = (DAD^{-1})^T(DAD^{-1}),$$

i.e., DAD^{-1} is normal. It should be emphasized that we do not need to know the exact values of α_i $(i = 1, 2, \ldots, n)$, because showing $A \in \mathbb{R}_{DN}$ is enough to apply Theorem 2.

2) A class of rank one matrices of the form $\mathbf{a}\mathbf{1}^T$: Let A be represented by $\mathbf{a}\mathbf{1}^T$, where $\mathbf{a} = [a_1, a_2, \ldots, a_n]^T$ and $a_i > 0$ $(i = 1, 2, \ldots, n)$. It can be seen that our choice of

$$d_1 = 1, \quad d_i = \sqrt{a_1/a_i} \quad (i = 2, \ldots, n)$$

makes DAD^{-1} symmetric, and hence DAD^{-1} is normal. Note again that we do not need to know the exact values of $a_i > 0$ $(i = 1, 2, \ldots, n)$ to apply Theorem 2.

Before closing this section we here provide a straightforward generalization of Theorem 2. As seen in the proof in the Appendix, D for case (b) corresponds to the D-scaling in the μ-analysis. In fact, the class of A for each case is specified so that DAD^{-1} is normal for some scaling matrix D of the structure commuting with $\mathbf{\Delta}_\#$. This observation immediately leads to the result for a general case where $\Delta(s)$ has a special block-diagonal structure represented by

$$\Delta(s) = \begin{bmatrix} \Delta_{homo} & 0 & 0 \\ 0 & \Delta_{hetero} & 0 \\ 0 & 0 & \Delta_{full} \end{bmatrix}, \quad \begin{array}{l} \Delta_{homo} \in \mathbf{\Delta}_{I\gamma} \\ \Delta_{hetero} \in \mathbf{\Delta}_{d\gamma} \\ \Delta_{full} \in \mathbf{\Delta}_\gamma \end{array} \tag{22}$$

with appropriate dimensions of diagonal blocks. We readily see that the corresponding class of D-scaling matrices is given by

$$\mathcal{D}_{gen} := \{D \in \mathbb{R}^{n\times n} \mid D = \begin{bmatrix} D_{homo} & 0 & 0 \\ 0 & D_{hetero} & 0 \\ 0 & 0 & I \end{bmatrix}\} \tag{23}$$

with symmetric $D_{homo} > 0$ and diagonal $D_{hetero} > 0$. Consequently, we have a generalization of Theorem 2 as follows: If $\Delta(s)$ is in the class defined by (22) and A belongs to a subclass of $\mathbb{R}^{n\times n}$ defined by

$$\mathbb{R}^{n\times n}_{DgN} := \{A \in \mathbb{R}^{n\times n} \mid \exists\, D \in \mathcal{D}_{gen} \text{ such that } DAD^{-1} \text{ is normal }\}, \tag{24}$$

then we have the same robust stability condition as in Theorem 2. This simple extension was made explicit in [21] based on our previous conference publication [12].

4 Robust Stability Region

We define the robust stability region $\mathbf{\Lambda}$ such that the $\mathcal{H}_\infty$-norm condition $\|\mathcal{G}_\lambda(s)\|_\infty < \gamma$ is satisfied if and only if $\lambda \in \mathbf{\Lambda}$. The main purpose of this section is to characterize $\mathbf{\Lambda}$ and translate the robust stability condition (15) into a condition on the eigenvalues of the interconnection matrix A.

4.1 General case

The following result states that the robust stability region can be characterized in terms of polynomial inequal-

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ities. The constructive proof that follows show how such inequalities can be obtained.

Proposition 3 *Let a positive number γ and transfer function $\mathcal{G}_\lambda(s)$ in (16) be given. Suppose $\mathcal{G}_\lambda(s)$ is stable and $H(s)$ is strictly proper. Then robust stability condition (15) holds if and only if all the eigenvalues λ of the interconnection matrix A lie in a region $\mathbf{\Lambda}$ on the complex plane characterized by polynomial inequalities of the following form:*

$$\mathbf{\Lambda} = \bigcap_{k=1}^{r} \{ \lambda \in \mathbb{C} \mid l_{\ell_k}(\lambda)^* \Psi_k l_{\ell_k}(\lambda) > 0 \}$$

where Ψ_k are Hermitian matrices and $l_{\ell_k}(\lambda)$ is defined in Theorem 1.

Proof. First note that there exists a minimal state space realization $\mathcal{G}_\lambda(s) = \mathsf{C}_\lambda(sI_{\tilde{n}} - \mathsf{A}_\lambda)^{-1}\mathsf{B}_\lambda + \mathsf{D}_\lambda$ with coefficient matrices affine in λ. The $\mathcal{H}_\infty$-norm condition in (15) holds if and only if the associated Hamiltonian matrix defined by

$$\mathsf{H}_\lambda := \begin{bmatrix} \mathsf{A}_\lambda + \mathsf{B}_\lambda\mathsf{R}^{-1}\mathsf{D}_\lambda^*\mathsf{C}_\lambda & \mathsf{B}_\lambda\mathsf{R}^{-1}\mathsf{B}_\lambda^* \\ -\mathsf{C}_\lambda^*(I + \mathsf{D}_\lambda\mathsf{R}^{-1}\mathsf{D}_\lambda^*)\mathsf{C}_\lambda & -(\mathsf{A}_\lambda + \mathsf{B}_\lambda\mathsf{R}^{-1}\mathsf{D}_\lambda^*\mathsf{C}_\lambda)^* \end{bmatrix}$$

with $\mathsf{R} := \gamma^2 I_{\tilde{m}} - \mathsf{D}_\lambda^*\mathsf{D}_\lambda$ has no eigenvalues on the imaginary axis [35]. That is, $\det(j\omega I_{2\tilde{n}} - \mathsf{H}_\lambda) \neq 0$ or

$$\det \begin{bmatrix} j\omega I_{\tilde{n}} - \mathsf{A}_\lambda & 0 & \mathsf{B}_\lambda & 0 \\ 0 & j\omega I_{\tilde{n}} + \mathsf{A}_\lambda^* & 0 & \mathsf{C}_\lambda^* \\ 0 & \mathsf{B}_\lambda^* & \gamma I_{\tilde{m}} & \mathsf{D}_\lambda^* \\ -\mathsf{C}_\lambda & 0 & \mathsf{D}_\lambda & \gamma I_{\tilde{p}} \end{bmatrix} \neq 0, \quad \forall\, \omega \in \mathbb{R}. \tag{25}$$

This requirement can be reduced to a polynomial inequality (sign definite) condition with respect to λ (and its complex conjugate $\bar{\lambda}$), which is required to be satisfied for all $\omega \in \mathbb{R}$. Such reduction is possible because $\mu \in \sigma(j\omega I - H)$ implies $-\bar{\mu} \in \sigma(j\omega I - H)$ for any Hamilatonian matrix H and hence the determinant always takes a real value. We can then apply symbolic computation methods such as quantifier elimination (QE) [2] to remove the quantifier "$\forall\omega$," resulting in polynomial inequality conditions of the form indicated above. See [9] for the details. □

The robust stability region $\mathbf{\Lambda}$ is the set of $\lambda \in \mathbb{C}$ satisfying condition (25). As shown in the above proof, $\mathbf{\Lambda}$ can be analytically characterized, in principle, in terms of polynomial inequalities with variables (x, y) where $\lambda = x + jy$, allowing for graphical visualization of $\mathbf{\Lambda}$ on the complex plane. The stability requirement of A_λ being Hurwitz is equivalent to the polynomial condition $\lambda \in \mathbf{\Lambda}_s$ in statement (iv) of Theorem 1. Similarly to the stability condition, we can get the corresponding equivalent LMIs by applying the generalized Lyapunov inequality formula in terms of A [14].

4.2 A special case: normalized coprime factor perturbations

In the previous section, we considered the general case and provided a rather conceptual characterization of the robust stability region $\mathbf{\Lambda}$ in terms of polynomial inequalities, which can yield a set of LMIs in terms of A. Here, we focus on a special case related to normalized coprime factor perturbations in order to illustrate the idea clearly and concretely. Other special cases have been studied and reported in [13].

Consider the feedback system depicted in Fig. 1, which consists of a number of $H(s) = C_h(sI_\nu - A_h)^{-1}B_h$ interconnected through a constant matrix specified by A. We assume that perturbations Δ_{a_i} and Δ_{b_i} enter the system as $\mathbf{w}_{a_i} = \Delta_{a_i}\mathbf{z}_{a_i}$ and $\mathbf{w}_{b_i} = \Delta_{b_i}\mathbf{z}_{b_i}$. This type of feedback system is used for the $\mathcal{H}_\infty$ loop shaping design, and is recognized as one of typical settings in robust control. The reasons are (i) it is related to the normalized coprime factor perturbations, and (ii) it includes both the sensitivity and complementary sensitivity functions.

Suppose that the interconnection matrix A satisfies the assumption in Theorem 2. Then we see from Theorem 2 that the perturbed feedback system $\Sigma(\tilde{\mathbf{H}}(s), A \otimes I_q)$ is robustly stable against $\mathbf{\Delta}_\#$ if and only if (15) holds for all $\lambda \in \sigma(A)$, where

$$\mathcal{G}_\lambda(s) = \begin{bmatrix} \lambda I_q \\ I_q \end{bmatrix} (I_q - \lambda H(s))^{-1} \begin{bmatrix} H(s) & I_q \end{bmatrix}. \tag{26}$$

When $H(s)$ is a scalar transfer function, the robust stability region $\mathbf{\Lambda}$ can be plotted without relying on symbolic computations. The following result characterizes the robust stability region $\mathbf{\Lambda}$ for the scalar case and gives a graphical test for the $\mathcal{H}_\infty$-norm condition.

Proposition 4 *Let a positive number γ, complex number λ, and scalar transfer function $H(s)$ be given. Define the generalized frequency variable $\phi(s)$ by $\phi(s) := 1/H(s)$. Then the system $\mathcal{G}_\lambda(s)$ represented by (26) satisfies $\|\mathcal{G}_\lambda(s)\|_\infty < \gamma$ if and only if $\lambda \in \mathbf{\Lambda}$, where $\mathbf{\Lambda}$ is the set of complex numbers λ such that $p(\lambda, s)$ in (5) is Hurwitz and*

$$\begin{cases} (1-\alpha)(|\lambda - c_\phi|^2 - r_\phi^2) > 0, & (\text{if } \alpha \neq 1) \\ 1 + |\lambda|^2 < |\phi - \lambda|^2, & (\text{if } \alpha = 1), \end{cases} \tag{27}$$

hold for all $\phi \in \mathbf{\Phi}$, where

$$\mathbf{\Phi} := \{\phi(j\omega) \mid \omega \in \mathbb{R}\}, \quad \alpha := (1 + |\phi|^2)/\gamma^2,$$

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$$c_\phi := \frac{\phi}{1-\alpha}, \quad r_\phi := \sqrt{\frac{\alpha}{1-\alpha}\left(\frac{|\phi|^2}{1-\alpha}+1\right)}.$$

Proof. Assuming nominal stability (i.e. A_λ Hurwitz), some straightforward calculations show that condition (15) is satisfied if and only if

$$\begin{bmatrix} H_\omega & I_q \end{bmatrix} (\Psi_\lambda \otimes I_q) \begin{bmatrix} H_\omega^* \\ I_q \end{bmatrix} < 0 \qquad (28)$$

holds for all $\omega \in \mathbb{R}$, where $H_\omega := H(j\omega)$ and

$$\Psi_\lambda := \begin{bmatrix} 1+(1-\gamma^2)|\lambda|^2 & \gamma^2\lambda \\ \gamma^2\bar{\lambda} & 1+|\lambda|^2-\gamma^2 \end{bmatrix}. \qquad (29)$$

When $H(s)$ is a scalar, (28) can be written as

$$\frac{(1+|\lambda|^2)(1+|\phi|^2)}{|\phi-\lambda|^2} < \gamma^2, \quad \forall\, \phi \in \mathbf{\Phi}. \qquad (30)$$

The result then follows directly from this inequality. □

When $\alpha < 1$, the corresponding inequality condition holds if and only if λ is outside of the circle of radius r_ϕ centered at c_ϕ. When $\alpha > 1$, the inequality holds if and only if λ is inside of the circle. It can be shown using $\gamma > 1$ that the radius r_ϕ is always well defined (i.e., real positive) unless $\alpha = 1$. When $\alpha = 1$, the set of λ satisfying the corresponding inequality is the half plane not containing ϕ with the boundary specified as the straight line, orthogonal to the line connecting the origin and ϕ, passing through the point $\phi(1-1/|\phi|^2)/2$.

Now consider a SISO numerical example with $H(s) = \frac{1}{s^2+s+1}$. Figures 3 and 4 respectively illustrate the robust stability region $\mathbf{\Lambda}$ for $\gamma = 3$ and 4. In each figure, the black curve is the Nyquist plot of $\phi(s)$ and the region to the left of the curve is $\mathbf{\Lambda}_s$. The blue and the red circles represent the conditions for $\alpha < 1$ and $\alpha > 1$ respectively, i.e., $\mathbf{\Lambda}_r$ is the region outside of the blue circles and inside of the red circles. Hence, $\|\mathcal{G}_\lambda(s)\|_\infty < \gamma$ holds if and only if λ lies in the intersection of $\mathbf{\Lambda}_s$ and $\mathbf{\Lambda}_r$, which is the white region including the origin. This is exactly the robust stability region $\mathbf{\Lambda}$ in which all the eigenvalues of A should lie to ensure the robust stability.

We now try to get the analytical formula of the boundary of the robust stability region. In principle, it can be done by using the QE, one of the effective symbolic computation methods, as seen in [9]. Here, we only show the exact interval(s) of real axis which guarantee the robust stability. We first see that the robust stability region is empty if $\gamma \le \sqrt{2}$. We also see that exact interval on the

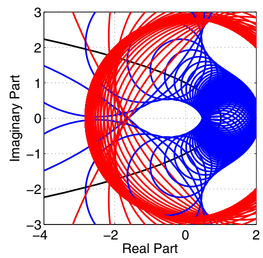

Fig. 3. Robust stability region ($\gamma = 3$)

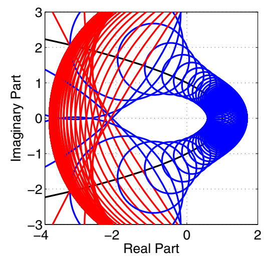

Fig. 4. Robust stability region ($\gamma = 4$)

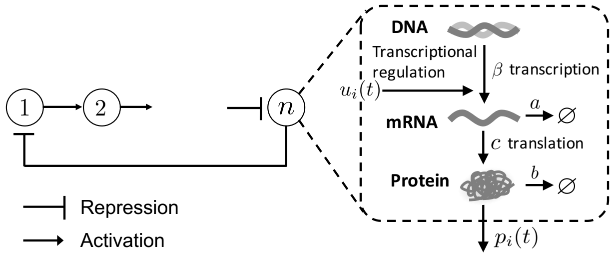

Fig. 5. Cyclic gene regulatory network

eigenvalues of A for guaranteeing the robust stability for specified $\gamma > \sqrt{2}$ is given by

$$x_m < \lambda < x_M\,;\ \sqrt{2} < \gamma < \sqrt{4+2\sqrt{2}}\,,$$
$$x_m < \lambda < \frac{\gamma^2 - 2\sqrt{\gamma^2-1}}{\gamma^2-2}\,;\ \gamma > \sqrt{4+2\sqrt{2}}\,,$$

where x_m and x_M are respectively the minimum and maximum real roots of

$$f(x) = (4\gamma^2-7)x^4 - 4\gamma^2x^3 + 14(\gamma^2-1)x^2 + 4(\gamma^4-\gamma^2)x - 3\gamma^4 + 10\gamma^2 - 7.$$

Note that the two numbers $\sqrt{2}$ and $\sqrt{4+2\sqrt{2}}$ are the best achievable control performances respectively for single and double integrators in the $\mathcal{H}_\infty$ loop shaping design.

5 Application to Gene Regulatory Networks

Robustness is one of the distinctive properties of biological systems. This section is concerned with robustness analysis of cyclic gene regulatory networks. In particular, we apply the robust stability result in Section 3.2 to analyze the robustness of the system systematically.

5.1 Model of Uncertain Gene Regulatory Networks

We consider biomolecular reactions for protein production in Fig. 5, where mRNA and protein molecules are produced by genetic transcription and translation, and

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the proteins activate or repress the transcription of other genes to form a network of gene regulation called gene regulatory network. The nominal dynamics of transcription and translation are modeled by the following differential equations

$$\frac{d}{dt}\begin{bmatrix} r_i(t) \\ p_i(t) \end{bmatrix} = \begin{bmatrix} -a & 0 \\ c & -b \end{bmatrix}\begin{bmatrix} r_i(t) \\ p_i(t) \end{bmatrix} + \begin{bmatrix} \beta \\ 0 \end{bmatrix} u_i(t) \quad (31)$$

where r_i and p_i are the concentrations of mRNA and protein associated with the i-th gene, respectively ($i = 1, 2, \ldots, n$), and the constants a, b, c and β denote the degradation rate of mRNA and protein, and the rate of translation and transcription, respectively [6,7,16,17]. The variable $u_i(t)$ represents the effect of transcriptional regulation by proteins.

We consider gene regulatory networks with cyclic feedback regulation, or cyclic gene regulatory networks, illustrated in Fig. 5. For this class of networks, the variable $u_i(t)$ is modeled by the Hill function

$$u_i(t) = f_i(p_{i-1}(t)) = \begin{cases} \dfrac{K^\varrho}{K^\varrho + p_{i-1}^\varrho} & \text{repression} \\ \dfrac{p^\varrho}{K^\varrho + p_{i-1}^\varrho} & \text{activation,} \end{cases} \quad (32)$$

where ϱ and K represent a Hill coefficient and a Michaelis-Menten constant, respectively [1], and $p_0(t) := p_n(t)$. Note that $f_i(\cdot)$ is a monotone function of p_{i-1}.

The protein concentrations in cyclic gene regulatory networks converge to either a limit cycle or a constant at steady state depending on the sign of the loop gain of the network $\kappa := \prod_{i=1}^n df_i/dp_{i-1}$ and the stability of equilibrium points. When $\kappa > 0$, the system has multiple stable equilibria, *i.e.,* multi-stable, and the concentrations always converge to one of equilibria [31]. When $\kappa < 0$, on the other hand, the system has a unique equilibrium, and the local instability of the equilibrium leads to periodic oscillations of molecular concentrations [16]. A necessary and sufficient condition for local stability was previously obtained in an analytic form with the reaction rate parameters in (31) [16]. The condition was experimentally tested by building cyclic gene regulatory networks with $n = 3$ and $n = 5$ genes and tuning their parameters [27].

In what follows, we further analyze the robustness of the unique equilibrium of cyclic gene regulatory networks with $\kappa < 0$. We denote the unique equilibrium by $x^* := [r_1^*, p_1^*, r_2^*, p_2^*, \ldots, r_n^*, p_n^*]^T$ and consider a linearized system of (31) at x^*. The linearized system can be formulated by an LTI system with generalized frequency variable as

$$H(s) = \frac{1}{(T_a s + 1)(T_b s + 1)}, \quad (33)$$

$$A = \begin{bmatrix} 0 & 0 & 0 & \cdots & R^2\zeta_1 \\ R^2\zeta_2 & 0 & 0 & \cdots & 0 \\ 0 & R^2\zeta_3 & 0 & \cdots & 0 \\ \vdots & \vdots & \ddots & \ddots & \vdots \\ 0 & 0 & \cdots & R^2\zeta_n & 0 \end{bmatrix} \quad (34)$$

where

$$T_a := \frac{1}{a}, \quad T_b := \frac{1}{b}, \quad R := \frac{\sqrt{c\beta}}{\sqrt{ab}}, \quad (35)$$

and for $i = 1, 2, \ldots, n$

$$\zeta_i := \frac{df_i}{dp}(p_{i-1}^*). \quad (36)$$

It should be emphasized that we can readily see that A defined in (34) belongs to $\mathbb{R}_{DN}^{n\times n}$ due to its cyclic nature as seen in the the third remark on Theorem 2. Hence, we can apply Theorem 2 to the robust stability analysis for the gene regulatory networks.

We investigate the case where the dynamics of each gene has heterogeneous uncertainty and the i-th perturbed system is represented by

$$\tilde{H}_i(s) := \frac{1 + w_{\text{mul}}\Delta_{\text{mul},i}(s)}{1 + w_{\text{fb}}\Delta_{\text{fb},i}(s)} H(s) \quad (37)$$

The uncertainties $\Delta_{\text{mul},i}$ and $\Delta_{\text{fb},i}$ are multiplicative to the numerator and denominator of $H(s)$, respectively. Note that $\Delta_{\text{mul},i}(s)$ and $\Delta_{\text{fb},i}(s)$ account for different types of uncertainties. $\Delta_{\text{mul},i}(s)$ mainly accounts for (i) uncertainty and heterogeneity of each gene's gain, (ii) variation of the linearized gain ζ_i due to perturbation of the equilibrium point, and (iii) time delay in the interactions between genes. On the other hand, $\Delta_{\text{fb},i}$ mainly accounts for (i) heterogeneity and uncertainty of the degradation time constants $T_a := 1/a$ and $T_b := 1/b$, and (ii) unmodeled dynamics associated with the transcription and translation processes.

The block diagram of the closed-loop system is depicted in Fig. 6, where $\Delta_{\text{mul}} := \text{diag}[\Delta_{\text{mul},1}, \Delta_{\text{mul},2}, \ldots \Delta_{\text{mul},n}]$, $\Delta_{\text{fb}} := \text{diag}[\Delta_{\text{fb},1}, \Delta_{\text{fb},2}, \cdots, \Delta_{\text{fb},n}]$ and the overall perturbation is expressed as

$$\Delta := \text{blockdiag}\{[\Delta_{\text{mul},i}, -\Delta_{\text{fb},i}]\}.$$

We hereafter assume that Δ and $[\Delta_{\text{mul},i}(s), \Delta_{\text{fb},i}(s)]$ respectively belong to the following sets:

$$\boldsymbol{\Delta} := \text{diag}(\boldsymbol{\delta}, \ldots, \boldsymbol{\delta})$$
$$\boldsymbol{\delta} := \{[\delta_{\text{mul}}, \delta_{\text{fb}}] \in \mathbb{R}\mathbf{H}_\infty^{1\times 2} \mid \|[\delta_{\text{mul}}, \delta_{\text{fb}}]\|_\infty \leq 1\}$$

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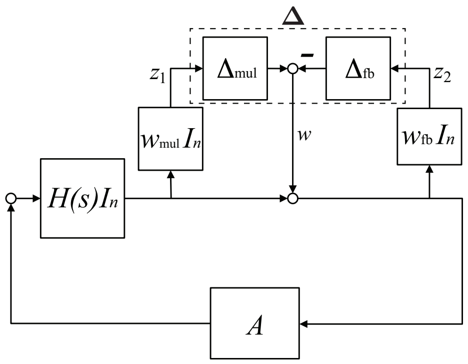

Fig. 6. Block diagram of the system with uncertainty.

where the norm bound is normalized since the constants $w_{\mathrm{mul}} \in [0,1)$ and $w_{\mathrm{fb}} \in [0,1)$ weigh the magnitude of the uncertainty.

We can readily see that the heterogeneous gene regulatory network system depicted in Fig. 6 belongs to $\Sigma(\tilde{\mathbf{H}}(s), A)$ with $G(s)$ of the form

$$G_{11}(s) = \begin{bmatrix} 0 \\ w_{\mathrm{fb}} \end{bmatrix}, \; G_{12}(s) = \begin{bmatrix} w_{\mathrm{mul}} \\ w_{\mathrm{fb}} \end{bmatrix} H(s), \; G_{21}(s) = 1.$$

This leads to

$$\mathcal{G}_\lambda(s) = \begin{bmatrix} w_{\mathrm{mul}}\lambda H(s) \\ w_{\mathrm{fb}} \end{bmatrix} /(1-\lambda H(s)). \tag{38}$$

5.2 *Graphical Robust Stability Condition*

Applying robust stability condition (15) in Theorem 2 to $\mathcal{G}_\lambda(s)$ represented by (38) with $\gamma = 1$ yields the following robust stability condition:

$$\left\| \begin{bmatrix} w_{\mathrm{mul}}\lambda H(s) \\ w_{\mathrm{fb}} \end{bmatrix} /(1-\lambda H(s)) \right\|_\infty < 1 \;\; ; \;\; \forall\, \lambda \in \sigma(A), \tag{39}$$

or equivalently

$$\frac{w_{\mathrm{fb}}^2|\phi(j\omega)|^2 + w_{\mathrm{mul}}^2|\lambda|^2}{|\phi(j\omega)-\lambda|^2} < 1 \;\; ; \;\; \forall\, \lambda \in \sigma(A), \tag{40}$$

hold for $\forall\, \omega \in \mathbb{R}$, where $\phi(s) := 1/H(s)$.

Moreover, we can specifically write the robust stability condition using the structure of A and the property of $\phi(s) = 1/H(s)$. The set of eigenvalues of the matrix A can be analytically written in the following form.

$$\lambda_i = Le^{j\frac{(2i-1)}{n}\pi} \;\; (i = 1, 2, \ldots, n), \quad L := \prod_{i=1}^{n} |R^2\zeta_i|^{\frac{1}{n}}. \tag{41}$$

This implies that the eigenvalues of the matrix A are located on a circle with radius L, which means that $|\lambda| = L$. Regarding $\phi(s)$ we introduce a normalization of the frequency variable s by $\tilde{s} := \sqrt{T_a T_b}\, s$, which leads to

$$\tilde{\phi}(s) := s^2 + \frac{2}{Q}s + 1\,, \quad Q := \frac{\sqrt{T_a T_b}}{(T_a+T_b)/2}. \tag{42}$$

Note that this normalization does not change the inequality condition, i.e., condition (40) can be written as

$$r_\omega < |\tilde{\phi}(j\omega) - \lambda_i|, \tag{43}$$

where $r_\omega > 0$ is defined by

$$\begin{aligned} r_\omega^2 &:= w_{\mathrm{fb}}^2|\tilde{\phi}(j\omega)|^2 + w_{\mathrm{mul}}^2 L^2 \\ &= w_{\mathrm{fb}}^2\left(\omega^4 + 2\left(\frac{2}{Q^2}-1\right)\omega^2 + 1\right) + w_{\mathrm{mul}}^2 L^2. \end{aligned}$$

Thus, the robust stability region is obtained as the intersection of the regions outside of the circle at center $\tilde{\phi}(j\omega)$ with radius r_ω, parametrized by $\omega \in \mathbb{R}$. When $w_{\mathrm{fb}} = 0$, the perturbation can be regarded as the multiplicative perturbation of the form $H(s)(1 + w_{\mathrm{mul}}\Delta_{\mathrm{mul}})$ with $\|\Delta_{\mathrm{mul}}\|_\infty \le 1$. In fact, the robust stability condition for the case of $w_{\mathrm{fb}} = 0$ agrees with the one derived in [29].

The condition (43) implies that the robust stability condition is determined by five parameters $(Q, L, n, w_{\mathrm{mul}}, w_{\mathrm{fb}})$, where $Q \in [0,1]$ is the criterion of the discrepancy between the mRNA and protein degradation time constants T_a and T_b, and Q approaches 1 as T_a and T_b become closer. In the following subsections, we further analyze this condition to reveal how these parameters affect the robustness of cyclic gene regulatory networks.

5.3 *Analytic Robust Stability Condition*

The graphical stability test developed in the previous subsection is useful for examining given biochemical systems but requires numerical computations for each set of parameter values. To gain deeper insights into the robustness of cyclic gene regulatory networks, we derive analytic conditions for the robust stability using the reaction rate parameters.

Proposition 5 *Consider the linearized cyclic gene regulatory network system $\Sigma(\tilde{\mathbf{H}}(s), A)$ depicted in Fig. 6. Suppose the nominal system $\Sigma(I_n \otimes H(s), A)$ is stable. Then, $\Sigma(\tilde{\mathbf{H}}(s), A)$ is stable for all $\Delta \in \mathbf{\Delta}$ if and only if*

$$w_{\mathrm{mul}}^2 < \frac{\bar{w}_{\mathrm{fb}}^2}{L^2}\left(p\omega_*^2 + 3q\omega_* + 1 - \frac{2L\cos(\frac{\pi}{n})}{\bar{w}_{\mathrm{fb}}^2} + \frac{L^2}{\bar{w}_{\mathrm{fb}}^2}\right) \tag{44}$$

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where

$$\bar{w}_{\mathrm{fb}}^2 := 1 - w_{\mathrm{fb}}^2,$$

$$p := \frac{2}{Q^2} - 1 + \frac{L\cos(\pi/n)}{\bar{w}_{\mathrm{fb}}^2}, \quad q := -\frac{L\sin(\pi/n)}{Q\bar{w}_{\mathrm{fb}}^2},$$

$$\omega_* := \sqrt[3]{\frac{-q + \sqrt{q^2 + 4p^3/27}}{2}} + \sqrt[3]{\frac{-q - \sqrt{q^2 + 4p^3/27}}{2}}.$$

Proposition 5 is an analytic condition for robust stability of $\Sigma(\tilde{\mathbf{H}}(s), A)$. This analytic condition allows for checking the robust stability by just substituting the given parameters into (44). In the next subsection, we demonstrate the robust stability condition using an illustrative example and numerically investigate the effect of parameters on robust stability.

5.4 Numerical Simulations and Biological Insights

We consider a cyclic gene regulatory network consisting of $n = 5$ genes. Suppose the parameters of the nominal dynamics are $a = 3.0$, $b = 1.0$, $c = 1.0$, $\beta = 4.0$, and $\varrho = 2.0$. Given these parameters, the linearized gains can be computed as $\zeta_i = -0.592$ for all $i = 1, 2, \cdots, 5$. The nominal dynamics of each gene is written as

$$H(s) = \frac{1}{(\frac{1}{3}s + 1)(s + 1)}, \quad R^2 = \frac{4}{3},$$

thus $T_a = 1/3, T_b = 1, Q = 0.866$ and $L = 0.789$.

We first consider the case where $w_{\mathrm{mul}} = w_{\mathrm{fb}} = 0.141 (\simeq 0.2/\sqrt{2})$, and apply the graphical robust stability test. We see that the robust stability region $\mathbf{\Lambda}$ is the white region containing the origin. Since all the eigenvalues of A plotted by red points are in $\mathbf{\Lambda}$ as seen in Fig. 7 (left), we conclude that the cyclic gene regulatory network system is robustly stable. This can be also confirmed by the analytic condition of (44), of which the right-hand side is calculated as $0.123 > w_{\mathrm{mul}}^2 = 0.02$. We can prove that $Le^{\pm j\pi/5}$ is the critical eigenvalue for robust stability, no matter how we increase w_{mul} and w_{fb}. Hence, the painted region eventually includes the eigenvalues as we increase the amplitude of uncertainty (see Figure 7 (right) for the case of $(w_{\mathrm{mul}}, w_{\mathrm{fb}}) = (0.567, 0.567) \simeq (0.8/\sqrt{2}, 0.8/\sqrt{2})$).

The analytic robust stability condition in Proposition 5 enables in-depth investigation of the robustness of the cyclic gene regulatory networks with respect to the reaction rate parameters. Figure 8 illustrates the square root value of the right-hand side of (44), the admissible maximum value of w_{mul} for robust stability, for the parameters n, Q and w_{fb}. These figures provide two guidelines for the design of robustly stable synthetic biomolecular systems: (i) the number of genes in the network, n,

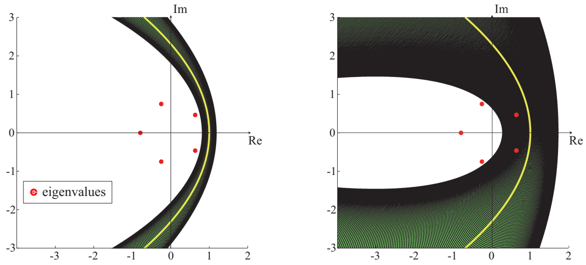

Fig. 7. The graphical robust stability tests.

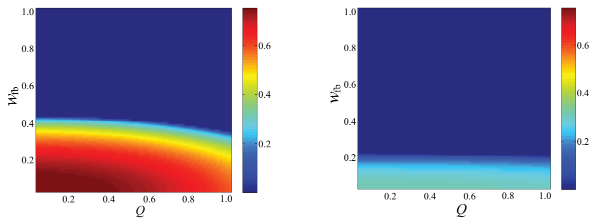

Fig. 8. The right-hand side of (44), (Left) $n = 3$, (Right) $n = 10$.

should not be too large, and (ii) the dimensionless parameter $Q \in (0, 1]$, which is interpreted as the difference of the two degradation rates a and b, should be as small as possible especially when w_{fb} is small. The parameter was previously introduced in [16] in the context of the instability analysis of nominal systems, and it was shown that the nominal stability also tends to be lost with increasing Q. Thus, decreasing Q enhances both nominal and robust stability of cyclic gene regulatory networks.

6 Conclusion

In this paper, we have investigated robust stability conditions for linear time-invariant systems with generalized frequency variables. After a brief review of the stability analysis with an extension to the MIMO case, we have treated three different types of perturbations and derived necessary and sufficient conditions for the robust stability. We then provided several methods of checking the derived robust stability conditions by investigating the case of normalized coprime factor perturbations as a typical example. Finally we have shown an example of robust stability analysis for gene regulatory networks to confirm the utility of the theoretical results by getting the exact analytical formula of the robustness condition.

The future research may include to extend the class of interconnections to be handled and to analyze control performances such as $\mathcal{H}_2$ and$\mathcal{H}_\infty$ norms [13] .

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A Proof of Proposition 5

The robust stability condition (40) can be equivalently written as $F(\omega, \lambda_i) > 0$ for all $\omega \in \mathbb{R}$ and $i = 1, 2, \cdots, n$, where $F(\omega, \lambda)$ is defined by

$$F(\omega, \lambda) := \omega^4 + 2p_\lambda \omega^2 + 4q_\lambda \omega + \frac{\bar{w}_{\rm fb}^2 + \bar{w}_{\rm mul}^2 L^2 - 2{\rm Re}[\lambda]}{\bar{w}_{\rm fb}^2}$$

with

$$\bar{w}_{\rm mul}^2 := 1 - w_{\rm mul}^2,\ p_\lambda := \frac{2}{Q^2} - 1 + \frac{{\rm Re}[\lambda]}{\bar{w}_{\rm fb}^2} \text{ and } q_\lambda := -\frac{{\rm Im}[\lambda]}{Q\bar{w}_{\rm fb}^2},$$

and λ_i $(i = 1, 2, \cdots, n)$ is defined in (41). In what follows, we show $\min_{\omega,i} F(\omega, \lambda_i) = F(\omega_*, \lambda_1)$ with ω_* defined in Proposition 5, and thus, $F(\omega_*, \lambda_1) > 0$ is the necessary and sufficient condition for the robust stability of $\Sigma(\tilde{\mathbf{H}}(s), A)$ for all $\Delta \in \mathbf{\Delta}$.

It should be first noticed that $F(\omega, \lambda_i) = F(-\omega, \lambda_{n-i+1})$ holds, and the robust stability of $\Sigma(\tilde{\mathbf{H}}(s), A)$ is equivalent to $F(\omega, \lambda_i) > 0$ for all $\omega \geq 0$ and $i = 1, 2, \cdots, \lceil n/2 \rceil$. Thus, in what follows, we consider to find the minimum of $F(\omega, \lambda_i)$ for $\omega \geq 0$ and $i = 1, 2, \cdots, \lceil n/2 \rceil$. For each fixed value of λ_i, $F(\omega, \lambda_i)$ is minimized at the frequency ω that satisfies

$$\frac{\partial F(\omega, \lambda_i)}{\partial \omega} = \omega^3 + p_{\lambda_i}\omega + q_{\lambda_i} = 0. \tag{A.1}$$

It follows that there is a single positive solution to (A.1) since $\partial F/\partial \omega < 0$ at $\omega = 0$, and the two roots of

$$\frac{\partial^2 F(\omega, \lambda_i)}{\partial \omega^2} = 3\omega^2 + p_{\lambda_i} = 0 \tag{A.2}$$

are either real with opposite signs or a pair of complex conjugates for $i = 1, 2, \cdots, \lceil n/2 \rceil$. Thus, the minimum of $F(\omega, \lambda_i)$ is achieved by one of the pairs (ω_i, λ_i), where ω_i is the positive solution of (A.1). Substituting the definition (41) of λ_i into $F(\omega, \lambda_i)$, we have $\min_{\lambda,i} F(\omega_i, \lambda_i) = F(\omega_1, \lambda_1)$ since ${\rm Re}[\lambda_1] = {\rm Re}[Le^{j\frac{\pi}{n}}] > {\rm Re}[Le^{j\frac{(2i-1)\pi}{n}}]$ for $i = 2, \cdots, \lceil n/2 \rceil$.

Finally, we substitute $i = 1$ into (A.1) and calculate the solution to the cubic equation to obtain $\omega_1 = \omega_*$. The inequality (44) is obtained by simplifying $F(\omega_*, \lambda_1) > 0$ using $\omega_*^3 = -p_{\lambda_1}\omega_* - q_{\lambda_1}$ and defining $p := p_{\lambda_1}$ and $q := q_{\lambda_1}$. □

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