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Abstract

This paper investigates robustness properties of gene regulatory networks with cyclic interconnections. In particular, we treat the heterogeneity of the gene's dynamics using a framework of robustness analysis, and derive necessary and sufficient conditions for robust stability. To this end, we first present a mathematical formulation of the gene regulatory network where dynamics of gene expression has a certain degree of uncertainty. Then, graphical and analytic criteria for robust stability are derived based on a robustness analysis scheme for large-scale multi-agent systems. These conditions are easily applicable to large-scale gene regulatory networks, which involve many components. Finally, the results are interpreted from a biological viewpoint, and they are verified by numerical simulations.

1 Introduction

Robustness of biochemical network has been recognized as one of the outstanding properties of living systems, and it has been widely investigated in the last decades (see [13] and references therein). It is often argued that robustness comes from diversity, or heterogeneity, of each component of the large-scale biological networks as well as complex biochemical pathways [13]. Detailed mechanisms of the robustness is, however, still open to be solved, since the large-scale nature of biochemical network often becomes an obstacle to examine the properties of the systems. Hence, this paper aims

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to present a systematic analysis method of robust stability for large-scale uncertain gene-protein regulatory networks, and provide biological insight based on the proposed method.

Gene expression refers to the biochemical process that produces protein from genetic information, and consists of two steps, transcription and translation. In transcription process, a block of DNA sequence is converted to a messenger RNA (mRNA), the molecule which carries the information of protein coding. Then, protein is produced based on the information of mRNA in the translation process. In living cells, this protein production process is regulated in the way that some protein species chemically activate and repress the transcription process. Therefore, the schematic diagram of the regulatory network can be illustrated as in Fig. 1, in which a cyclically regulated network is considered.

As for robustness analysis, many analysis problems have been considered to tackle various types of uncertainty [2, 10, 11, 17]. In [11], it was presented that μ-analysis can be a powerful tool to analyze the robustness of gene regulatory networks. Henceforth, classical robust control theory was extensively applied to find critical pathways [10], and to deal with kinetic perturbations [17]. In most works, however, highly structured uncertainties of the regulatory network prevented them to obtain analytic conditions for robust stability, which help us discover general principle of the biological systems.

One of possible approaches to such analytic conditions was recently presented for unperturbed systems in [8], where analytic existence conditions of periodic oscillations were considered based on local stability analysis. In their formulation, a key assumption is that genes have a common expression dynamics. This assumption, however, is considered as restrictive for practical gene regulatory networks. Thus, it is desirable to relax this assumption to obtain more useful conditions.

In this paper, we generalize the formulation introduced in [8] to the case where genes have different expression dynamics. Specifically, gene's expression dynamics is represented by a nominal dynamics, which is shared with all the genes, and multiplicative disk uncertainty, which accounts for the heterogeneity of the dynamics between genes as well as uncertainty of the dynamics. We here consider the class of gene regulatory network that is cyclically regulated as illustrated in Fig. 1, which has been focused on by many previous works [1, 4, 9, 15, 16] so far. Then, we conduct robust stability analysis for the large-scale uncertain systems, and derive necessary and sufficient analytic condition for robust stability.

This paper is organized as follows. In Section 2, we introduce a dynamical model of cyclic gene regulatory network with uncertainty considered in this paper. Then, in Section 3, we present the graphical condition for robust stability based on a result in [6]. The analytic robust stability condition

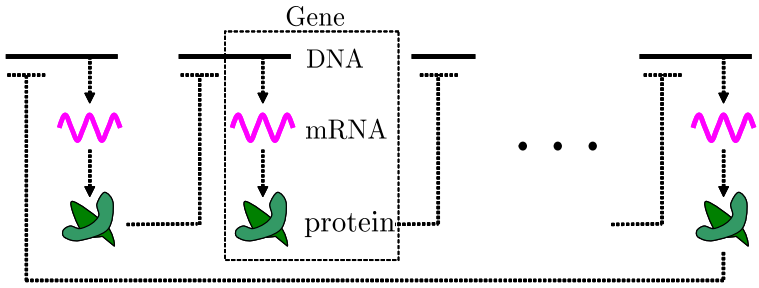

Figure 1: Schematic diagram of cyclic gene regulatory networks.

and its biological interpretations are derived in Section 4. Then, the results are confirmed with illustrative numerical simulations in Section 5. Finally, Section 6 concludes the paper.

2 Problem Formulation

2.1 Dynamical Model of Cyclic Gene Regulatory Networks

The gene regulatory networks, where each protein activates or represses another transcription in a cyclic way as illustrated in Fig. 1, are called cyclic gene regulatory networks. The dynamics of mRNA and protein concentrations in the cyclic gene regulatory networks consisting of N genes is modeled by the following differential equations [3]:

$$\begin{aligned} \dot{r}_i(t) &= -a_i r_i(t) + \beta_i f_i(p_{i-1}(t)), \\ \dot{p}_i(t) &= c_i r_i(t) - b_i p_i(t), \end{aligned} \tag{1}$$

for $i = 1, 2, \cdots, N$, where $r_i \in \mathbb{R}_+ (:= \{x \in \mathbb{R} \mid x \geq 0\})$ and $p_i \in \mathbb{R}_+$ denote the concentrations of the i-th mRNA and its corresponding protein synthesized by the i-th gene, respectively. Let the subscript 0 be replaced by N throughout this paper for the sake of notational simplification. The kinetic constants a_i, b_i, c_i and β_i represent the followings: a_i and b_i denote the degradation rates of the i-th mRNA and protein, respectively; c_i and β_i denote the translation and transcription rates, respectively. The nonlinear function $f_i(\cdot) : \mathbb{R}_+ \to \mathbb{R}_+$ stands for the effect of either activation or repression of the transcription, and it is a monotone function satisfying $f_i(0) = 1$ and $f_i(\infty) = 0$, thus a monotone decreasing function for repression, and $f_i(0) = 0$ and $f_i(\infty) = 1$, thus a monotone increasing function for activation.

It is known that dynamical behavior of the system (1) is characterized by

$$\delta := \prod_{i=1}^{N} Z_i, \text{ where } Z_i = \begin{cases} +1 & (f_i(\cdot) \text{ is increasing}) \\ -1 & (f_i(\cdot) \text{ is decreasing}) \end{cases}. \tag{2}$$

Specifically, the protein concentrations asymptotically converge to one of equilibria when $\delta > 0$, while they exhibit oscillatory behaviors as well as convergence when $\delta < 0$ [3,12]. Therefore, it is important to study the case of $\delta < 0$.

Assumption 1. *For given $f_i(\cdot)$ $(i = 1, 2, \cdots, N)$, $\delta < 0$.*

This assumption implies that a given cyclic gene regulatory network has an odd number of repressive interactions between genes, which means an odd number of decreasing $f_i(\cdot)$,

Then, the overall dynamics of gene regulatory network systems defined by (1) can be formulated by a transfer matrix $G(s)$ and a static vector nonlinearity function $\mathbf{f}$ as shown in Fig. 2 (Left), where

$$G(s) := \mathrm{diag}(g_1(s), g_2(s), \cdots, g_N(s)), \tag{3}$$

$$\mathbf{f} := [f_1(\cdot), f_2(\cdot), \cdots, f_N(\cdot)]^T \tag{4}$$

with

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

$$R_i := \frac{\sqrt{c_i\beta_i}}{\sqrt{a_i b_i}}.\ \ (i = 1, 2, \cdots, N). \tag{6}$$

The dimensionless quantity R_i $(i = 1, 2, \cdots, N)$ in (6) is pointed out as one of biologically essential quantities that determine the dynamical behavior of the cyclic gene regulatory network systems (see [8] for details).

It was shown in [8] that the equilibrium point of the system (1) is unique, and local instability of the equilibrium leads to oscillations of protein levels in gene regulatory networks. This motivates us to put our attention on local stability analysis of the system (1) in the vicinity of the unique equilibrium point.

Let p_i^* denote the unique equilibrium concentration of the i-th protein p_i $(i = 1, 2, \cdots, N)$, and the linearized gain of $f_i(\cdot)$ be defined by $\xi_i := f_i'(p_{i-1}^*)$. The linearized system of (1) can be obtained by replacing $\mathbf{f}$ in Fig. 2 (Left) with the corresponding Jacobian matrix K, where

$$K := \begin{bmatrix} 0 & 0 & 0 & \cdots & \xi_1 \\ \xi_2 & 0 & 0 & \cdots & 0 \\ 0 & \xi_3 & 0 & \cdots & 0 \\ \vdots & \vdots & \ddots & \ddots & \vdots \\ 0 & 0 & \cdots & \xi_N & 0 \end{bmatrix}. \tag{7}$$

Note that the value of ξ_i $(i = 1, 2, \cdots, N)$ depends on the equilibrium point, which is determined from the system's parameters.

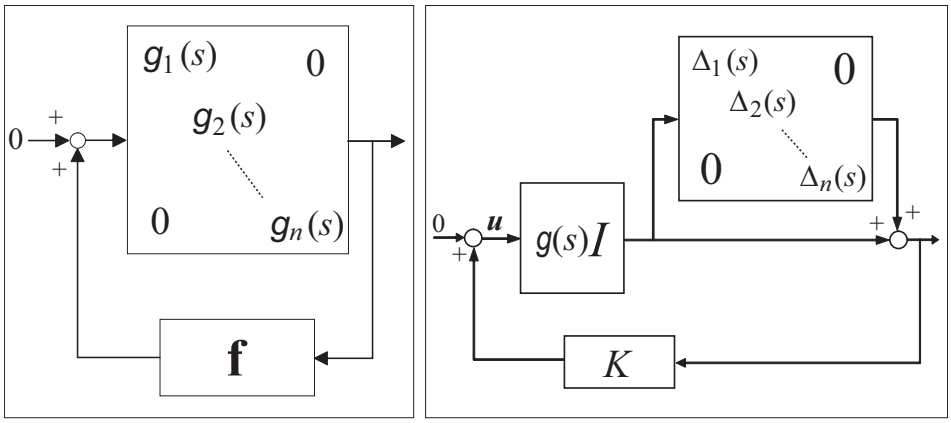

Figure 2: (Left) Block diagram of cyclic gene regulatory networks. (Right) Block diagram of the linearized gene regulatory network system with uncertainty, $\mathcal{G}(s)$.

It is worth mentioning that each diagonal entry of $G(s)$, *i.e.*, $g_i(s)$, stands for each gene's dynamics, and the matrix K specifies the interactions between genes.

2.2 Uncertainty in gene's dynamics

It is often the case that dynamics of gene expression is slightly different between cells, and the resulting dynamical behaviors are deviated from one another. In this section, a robustness analysis framework is introduced to deal with such regulatory networks with uncertainty.

We consider that the dynamics of the uncertain gene expression $\tilde{g}_i(s)$ $(i = 1, 2, \cdots, N)$ is represented with a common nominal dynamics of each gene, $g(s)$, and the heterogeneous uncertainty $\delta_i(s)$ as

$$\tilde{g}_i(s) := g(s)(1 + \delta_i(s)), \tag{8}$$

where

$$\begin{aligned} &g(s) := \frac{R^2}{(T_a s + 1)(T_b s + 1)} \text{ with } T_a := \frac{1}{a}, T_b := \frac{1}{b}, R^2 := \frac{c\beta}{ab}, \\ &\text{and } \delta_i(s) \in \{\delta(s) \mid \|\delta\|_\infty \leq \gamma_i\}. \end{aligned} \tag{9}$$

The constants a, b, c and β represent common nominal values of a_i, b_i, c_i and β_i $(i = 1, 2, \cdots, N)$, respectively. The uncertainty $\delta_i(s)$ $(i = 1, 2, \cdots, N)$ takes account of the following three uncertainties:

(1) uncertainty of each gene's dynamics.

(2) heterogeneity of the gene expression dynamics between genes.

(3) variation of the linearized gain ξ_i ($i = 1, 2, \cdots, N$) due to the variation of the equilibrium point.

It should be noted that we can merge ξ_i into $\tilde{g}_i(s)$ by using the cyclic structure of the system, though ξ_i originally appeared in the matrix K defined in (7).

Consequently, the gene regulatory network system where each gene's dynamics has a certain degree of uncertainty is obtained as depicted in Fig. 2 (Right). In the sequel, this system is defined by

$$\mathcal{G}(s) := \tilde{G}(s)\left(I - K\tilde{G}(s)\right)^{-1}, \tag{10}$$

where $\tilde{G}(s) := \mathrm{diag}(\tilde{g}_1(s), \tilde{g}_2(s), \cdots, \tilde{g}_N(s))$. The transfer matrix $\tilde{G}(s)$ can be equivalently written as $\tilde{G}(s) = g(s)(I + \Delta(s))$, where $\Delta(s) \in \mathbf{\Delta}_\gamma$ with

$$\mathbf{\Delta}_\gamma := \{\Delta(s) := \mathrm{diag}(\delta_1(s), \delta_2(s), \cdots, \delta_N(s)) \mid \|\delta_i\|_\infty \leq \gamma_i\}.$$

The subscript γ of $\mathbf{\Delta}_\gamma$ is defined by $\gamma := \max_i \gamma_i$. We see that each entry of the diagonal transfer matrix $\tilde{G}(s)$ stands for the dynamics of gene expression with uncertainty, of which $\mathcal{H}_\infty$ norm is bounded by γ_i, and the matrix K specifies the interaction structure between genes.

Therefore, the problem of the robust stability analysis of cyclic gene regulatory networks can be posed as follows.

Problem. *Consider the cyclic gene regulatory network system with multiplicative dynamic uncertainty, i.e., $\mathcal{G}(s)$ in (10). For given $\mathbf{\Delta}_\gamma$, derive the condition that $\mathcal{G}(s)$ is robustly stable for all $\Delta \in \mathbf{\Delta}_\gamma$.*

3 Graphical robust stability condition

In this section, we first show an existing robust stability result for the class of systems presented in the previous section. Then, the simple algorithm, which allows us to check the robust stability in a graphical way, is derived based on the result. The developed graphical condition can be further used to obtain the analytic condition for robust stability, which is the main result of this paper.

In [5] and [14], the nominal system, *i.e.,* $\mathcal{G}(s)$ with $\Delta(s) = 0$, was designated as *linear system with generalized frequency variables*, and its properties have been extensively studied. In particular, various types of robust stability conditions were obtained for the class of systems formulated in the previous section [6]. We first introduce one of the robust stability conditions.

Theorem 1. [6] *Consider the system $\mathcal{G}(s)$ defined by (10). Suppose the nominal system is stable and there exists a diagonal matrix D such that*

DKD^{-1} becomes a normal matrix. Then, $\mathcal{G}(s)$ is robustly stable for all $\Delta(s) \in \mathbf{\Delta}_\gamma$, if and only if

$$\left| \frac{\lambda}{\phi(j\omega) - \lambda} \right| < \frac{1}{\gamma} \tag{11}$$

for all $\lambda \in \mathrm{spec}(K)$ and all $\omega \in \mathbb{R}$, where

$$\phi(s) := \frac{1}{g(s)}. \tag{12}$$

This theorem gives a robust stability condition for $\mathcal{G}(s)$ under the assumption of existence of the diagonal matrix D stated in Theorem 1. It should be emphasized that the robust stability is characterized by $g(s)$ and the matrix K, which represent a nominal dynamics of each gene and the structure of the regulatory network, respectively.

In addition, we can verify that the matrix K can always be converted by a diagonal matrix to the circulant matrix, which is normal.

Lemma 1. *Consider the matrix K defined by (7). There exists a diagonal matrix $D := \mathrm{diag}(d_1, d_2, \cdots, d_N) \in \mathbb{C}^{N\times N}$ such that DKD^{-1} is a normal matrix. In particular, d_i is given by*

$$d_i = \frac{d_{i-1}\xi_1}{d_N \xi_i} \quad (i = 1, 2, \cdots, N-1) \tag{13}$$

with $d_N = \xi_1 \prod_{i=1}^{N} (\xi_i)^{-\frac{1}{N}}$.

Proof: We will show that there exists a diagonal matrix D such that DKD^{-1} is normal. Let D be defined as

$$D = \mathrm{diag}(d_1, d_2, \cdots, d_N), \;\; d_i \neq 0. \tag{14}$$

Then, we have

$$\begin{aligned} V &:= DKD^{-1} \\ &= \begin{bmatrix} 0 & \cdots & \cdots & \frac{d_1}{d_N}\xi_1 \\ \frac{d_2}{d_1}\xi_2 & \ddots & \ddots & 0 \\ \vdots & \ddots & \ddots & \vdots \\ 0 & \cdots & \frac{d_N}{d_{N-1}}\xi_N & 0 \end{bmatrix}. \end{aligned}$$

Note that V is normal if and only if $V^*V = VV^*$ holds. Setting d_i as

$$\begin{aligned} d_i &= \frac{d_{i-1}\xi_1}{d_N \xi_i} \quad (i = 1, 2, \cdots, N-1), \\ d_N &= \xi_1 \prod_{i=1}^{N} (\xi_i)^{-\frac{1}{N}}, \end{aligned}$$

we see that DKD^{-1} is a circulant matrix, thus normal.

□

This lemma allows us to apply Theorem 1 to our system, and we have the following result.

Proposition 1. *Consider the cyclic gene regulatory network system with uncertainty, $\mathcal{G}(s)$. The system $\mathcal{G}(s)$ is robustly stable for all $\Delta \in \mathbf{\Delta}_\gamma$, if and only if*

$$|\phi(j\omega) - \lambda| > \gamma|\lambda| \tag{15}$$

holds for all $\lambda \in \mathrm{spec}(K)$ and all $\omega \in \mathbb{R}$.

We see that the condition is characterized by $g(s), K$ and γ, and is easily checked from the each gene's nominal dynamics, the interconnection structure of the network and the uncertainty bound.

The equation (15) implies that the distance between the vector locus $\phi(j\omega)$ and the eigenvalues of K, λ, is greater than $\gamma|\lambda|$. In particular, we see from the cyclic structure of the matrix K that the eigenvalues $\{\lambda_i\}_{i=1}^N$ of K can be written as

$$\lambda_i = \prod_{k=1}^{N} |\xi_k|^{\frac{1}{N}} e^{j\frac{(2i-1)\pi}{N}}. \tag{16}$$

This implies that the eigenvalues are located on a circle with center at the origin and radius $L := \prod_{k=1}^{N} |\xi_k|^{\frac{1}{N}}$. Therefore, the condition provided in Proposition 1 can be graphically checked as follows.

Procedure: graphical condition

1. Plot the eigenvalues of the matrix K, $\mathrm{spec}(K)$, in the complex plane, which are uniformly located on the circle.
2. Draw the vector locus of $\phi(j\omega)$.
3. Draw circles with center at each point on the vector locus $\phi(j\omega)$ and radius γL. We hereafter denote the region inside this circles by
$$\mathcal{C} := \{z \in \mathbb{C} \mid \exists \omega \in \mathbb{R},\ |z - \phi(j\omega)| \leq \gamma L\}. \tag{17}$$
4. The system $\mathcal{G}(s)$ is robustly stable if and only if $\mathrm{spec}(K) \cap \mathcal{C} = \emptyset$, *i.e.,* the domain $\mathcal{C}$ includes none of the eigenvalues of K.

Following the above procedure, we can easily confirm robust stability of the cyclic gene regulatory networks. Figure 3, which shall be explained in details in Section 5, shows an example of our graphical condition.

4 Main Result

4.1 Analytic robust stability condition

In this section, we derive an analytic robust stability condition by geometric consideration of the graphical criterion presented in the previous section. Then, we reveal the relation of the biological parameters and robustness of the system.

The robust stability condition in the previous section can be graphically characterized by the vector locus $\phi(j\omega)$, the eigenvalues of K and the norm bound γ of uncertainty. Thus, we approach to an analytic condition by obtaining explicit form of them, and computing the condition that at least one eigenvalue goes inside $\mathcal{C}$.

We consider the vector locus $\phi(j\omega)$ first. Let Q be defined by

$$Q := \frac{\sqrt{T_a T_b}}{(T_a + T_b)/2}. \tag{18}$$

Then, we see from the definition that the vector locus $\phi(j\omega)$ can be written as

$$x(\omega) = -\frac{1}{4}Q^2R^2y(\omega)^2 + \frac{1}{R^2}, \tag{19}$$

where $x(\omega)$ and $y(\omega)$ are defined by $\phi(j\omega) =: x(\omega) + jy(\omega)$. Note that (19) implies that the vector locus $\phi(j\omega)$, which the circles $\mathcal{C}$ are drawn around, becomes a parabolic curve (see Fig. 3).

Our next goal is to find the critical eigenvalue, which makes the system unstable for the first time as γ gets large. It is clear that such an eigenvalue is given by the closest one to the parabolic curve since the region $\mathcal{C}$ is obtained by drawing circles with center at each point of the parabolic curve. Then, we define $J(y, \theta)$ that stands for a distance between the circle where the eigenvalues of K are located and the vector locus given by (19). Specifically,

$$J(y,\theta) := \left\{ -\frac{1}{4}Q^2R^2y^2 + \frac{1}{R^2} - L\cos\theta \right\}^2 + (y - L\sin\theta)^2 \tag{20}$$

with θ specifying an angular position on the circle. Note that y and θ in $J(y, \theta)$ specify a point on the parabolic curve (19) and a point on the circle with radius L, respectively. Since $\phi(j\omega)$ and the eigenvalues are symmetric to the real axis, the function $J(y, \theta)$ is defined only for $y \geq 0$ and $0 \leq \theta \leq \pi$ in the following. Therefore, the robust stability analysis problem can be summarized as the following minimization problem.

$$\text{Find} \quad \min_{y,\theta} J(y, \theta) \tag{21}$$

subject to $\theta \in \{\pi/N, 3\pi/N, \cdots, (2i-1)\pi/N, \cdots, (2N-1)\pi/N\}$. The maximum allowable γ for robust stability is obtained from the minimum value of the above problem, and the corresponding critical eigenvalue is located at $\mathrm{argmin}_\theta\ J(y,\theta)$.

Though $J(y,\theta)$ becomes fourth-order with respect to y, the above minimization problem can be efficiently solved because of some monotone properties shown below. We first show uniqueness of an extremum with respect to y (see Appendix A for the proof).

Lemma 2. *Consider $J(y,\theta)$ defined in (20). For any given $\theta \in (0,\pi)$, $J(y,\theta)$ has a unique minimum value y^* in $y > 0$. In particular,*

$$y^* = \sqrt[3]{\frac{4L\sin\theta}{Q^4R^4}}T \tag{22}$$

with

$$T := \sqrt[3]{1+\sqrt{1+k}} + \sqrt[3]{1-\sqrt{1+k}},$$
$$k := \frac{4\left(2 - Q^2(1-LR^2\cos\theta)\right)^3}{27L^2Q^4R^4\sin^2\theta}.$$

We see from the above lemma that the minimum value of $J(y,\theta)$ for given θ becomes

$$J(y^*,\theta) = \frac{2-(1-LR^2\cos\theta)Q^2}{4}y^{*2} - \frac{3}{2}L\sin\theta y^* + L^2 - \frac{2L\cos\theta}{R^2} + \frac{1}{R^4}. \tag{23}$$

It should be noted that (23) is second-order with respect to y, though (20) is fourth-order, because it can be eliminated by using the relation

$$\frac{\partial J}{\partial y} = \frac{1}{4}Q^4R^4y^3 + (2-(1-LR^2\cos\theta)Q^2)y - 2L\sin\theta = 0. \tag{24}$$

The last step to obtain an analytic condition is to find θ minimizing $J(y^*,\theta)$. Here, we show a certain monotone property of $J(y^*,\theta)$, which greatly simplifies the analysis.

Lemma 3. *Consider $J(y^*,\theta)$ defined by (20). $J(y^*,\theta)$ monotonically increases for θ such that $0 \le \theta \le \pi$ and $L(\cos\theta + j\sin\theta) \in \Omega_+^c$, where $\Omega_+^c := \{\lambda \in \mathbb{C} \mid \phi(s) \neq \lambda \text{ for } \forall s \in \mathbb{C}_+\}$.*

The proof can be found in Appendix B. Lemma 3 implies that the eigenvalue λ_1 in (16), *i.e.*, $\theta = \pi/N$, always achieves the minimum of $J(y^*,\theta)$. Thus, the analytic robust stability condition can be obtained from $J(y^*,\pi/N)$, which represents the square distance of the eigenvalue at π/N and the vector locus (see Fig. 3).

Theorem 2. *Consider the gene regulatory network system with uncertainty $\mathcal{G}(s)$ defined by (10). Then, the system is robustly stable for all $\mathbf{\Delta}_\gamma$, if and only if*

$$\gamma < \frac{\sqrt{J^*}}{L}, \tag{25}$$

where

$$\begin{aligned}
J^* =& \frac{2-(1-LR^2\cos\theta_0)Q^2}{4}y^{*2} - \frac{3}{2}L\sin\theta_0 y^* + L^2 - \frac{2L\cos\theta_0}{R^2} + \frac{1}{R^4},\\
y^* =& \sqrt[3]{\frac{4L\sin\theta_0}{Q^4R^4}}T,\ T = \sqrt[3]{1+\sqrt{1+k}} + \sqrt[3]{1-\sqrt{1+k}},\\
k =& \frac{4\left(2-Q^2(1-LR^2\cos\theta_0)\right)^3}{27L^2Q^4R^4\sin^2\theta_0} \text{ and } \theta_0 = \frac{\pi}{N}.
\end{aligned}$$

The above theorem is a direct consequence of Lemma 2 and Lemma 3. Since $J(y^*, \pi/N)$ is the square distance between $\phi(j\omega)$ and the eigenvalues at π/N, $\gamma L > \sqrt{J(y^*, \pi/N)}$ is the necessary and sufficient condition for robust stability (see Fig. 3).

Theorem 2 analytically provides the maximum uncertainty bound that the system remains robustly stable. It is remarkable that the condition is analytically written in terms of the three parameters N, L, R and Q, and thus, we can easily see the relation of the biological quantities and robustness of the cyclic gene regulatory network systems. In the next section, we shall see biological insight obtained from the above theorem.

4.2 Interpretation of the analytic condition

In this section, the analytic robust stability condition is interpreted from a biological viewpoint.

It can be easily verified that J^* in Theorem 2 monotonically decreases as the number of genes consisting of the regulatory network increases. Thus, assuming L does not depend on N, we can conclude that the cyclic gene regulatory network becomes less robust as the number of genes gets large.

It is also the case that J^* in Theorem 2 monotonically decreases with respect to R^2. Thus, the system becomes less robust as R^2 gets large. The quantity R^2 is the ratio of production and degradation rates of mRNA and protein as defined in (9). It is related to the equilibrium point of the system, and large R^2 implies large equilibrium concentrations. Thus, the system can be less robust if its equilibrium concentration is large.

Similarly, J^* monotonically decreases as Q gets large. Thus, the system with $Q = 1$ gives the least robust system when all the other parameters

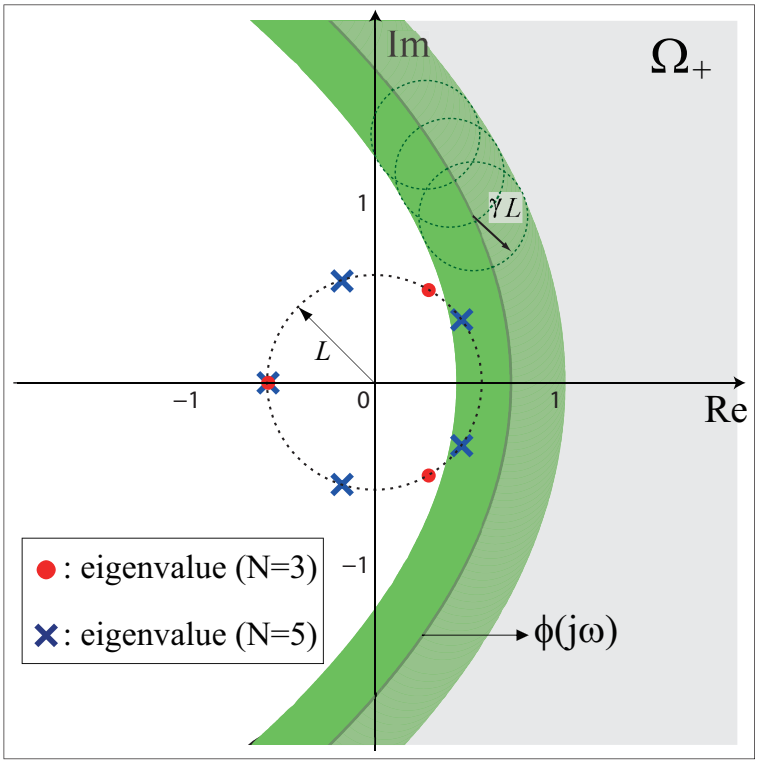

Figure 3: Graphical stability conditions. The system is robustly stable for $N = 3$, but not for $N = 5$.

are fixed. Note that $0 < Q \leq 1$ holds because Q is defined as the ratio of geometric and arithmetic means of the degradation rates (see (18)). In particular, Q gets large as the degradation rates of mRNA and protein get close to each other. Hence, it is inferred that robust gene regulatory networks tend to have large difference between mRNA and protein degradation rates.

It can also be seen from (25) that the system becomes less robust as the linearized gain L gets large. Note that the value of L depends on the equilibrium point of the system (1), which is nonlinear. The dependence of the equilibrium point on the system's parameters can be numerically obtained with the bisection algorithm (see Section 2 in [7]).

5 Numerical examples

In this section, we confirm the graphical and the analytic conditions (see the box in Section 3 and Theorem 2 in Section 4, respectively) through illustrative numerical simulations.

Example 1. We first consider one of the pioneering examples of synthetic gene regulatory network named Repressilator [4], which is a cyclic

gene regulatory network consisting of $N = 3$ genes. Let the parameter of nominal dynamics be obtained as $a = 3.0$, $b = 1.0$, $c = 1.0$, $\beta = 4.0$ and $\xi_1 = \xi_2 = \xi_3 = -0.592$. We suppose each gene's dynamics has uncertainty up to 51% from nominal dynamics, *i.e.* $\gamma = 0.51$.

Let us confirm the graphical condition. Following the algorithm presented in Section 3, we first plot the eigenvalues of the matrix A, which are located on a circle as illustrated in Fig. 3. Then, the vector locus of $\phi(j\omega)$, which is defined from the nominal dynamics $g(s) = 4/(s+1)(s+3)$ by $\phi(j\omega) = 1/g(j\omega)$, is drawn for $\omega \in \mathbb{R}$. Finally, the circle region $\mathcal{C}$ is hatched with $L = 0.592$. We see from Fig. 3 that Repressilator with the above parameters is stable for $\gamma = 0.51$ because no eigenvalue is included in $\mathcal{C}$.

Next, the analytic condition, Theorem 2, is confirmed. It is easily computed from the definition that $Q = 0.866$. Then, we have $J^* = 0.140$ from Theorem 2, and

$$\frac{\sqrt{J^*}}{L} = 0.631. \tag{26}$$

Therefore, we conclude that the system is stable for $\gamma = 0.51$, and it is stable for all Δ satisfying $\|\Delta\|_\infty < 0.631$.

Example 2. We consider the cyclic gene regulatory network consisting of $N = 5$ genes in the next to compare with the previous example. Let the parameters be set to the same as the previous example. That is, $a = 3.0$, $b = 1.0$, $c = 1.0$, $\beta = 4.0$ and $\xi_1 = \xi_2 = \cdots = \xi_5 = -0.592$. We again suppose $\gamma = 0.51$.

Since the nominal dynamics $g(s)$ and the uncertainty bound γ are the same as the previous example, we have the same vector locus and the circle region $\mathcal{C}$. The only difference is the location of the eigenvalues, which is illustrated in Fig. 3. We see that two eigenvalues are included by $\mathcal{C}$, thus the gene regulatory network is no longer robustly stable.

In fact, J^* is computed from Theorem 2 as 0.0561, and

$$\frac{\sqrt{J^*}}{L} = 0.400. \tag{27}$$

Thus, the maximum allowable γ for robust stability is 0.400.

6 Conclusion

In this paper, we have considered the cyclic gene regulatory network where each gene's dynamics has a certain degree of uncertainty, then the robust stability conditions have been derived. First, the graphical condition has been presented, and it has been shown that robust stability can be easily

checked by eigenvalues of a matrix representing the interconnection structure and a contour determined from nominal dynamics and norm bound of the uncertainty. Then, the analytic condition, which is the main result of this paper, has been derived based on the graphical condition. Since the condition is explicitly obtained in terms of biological parameters, it is easy to gain biological insight on how each parameter relates to robustness of the system. The obtained insight has been presented in Section 4.2, and it has been confirmed with illustrative numerical simulations.

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A Proof of Lemma 2

We first show that (24) has a unique positive solution when $0 < \theta < \pi$. To this end we consider the following third-order polynomial equation:

$$t^3 + pt + q = 0. \tag{28}$$

Letting $t = u+v$ yields $u^3+v^3+q+(3uv+p)(u+v) = 0$, which is equivalent to (28). It is clear that the equality holds when the following relations are satisfied.

$$\begin{cases} u^3 + v^3 + q = 0, \\ 3uv + p = 0, \end{cases} \tag{29}$$

We will next show that there exist three different types of $t = u + v$ which satisfies (29). Substituting the second equation of (29) into the first equation of (29) to eliminate v, we obtain $u^6 + qu^3 - \frac{p^3}{27} = 0$, which leads to

$$u^3 = \frac{-q \pm\sqrt{q^2 + \frac{4p^3}{27}}}{2} \ , \ v^3 = \frac{-q \mp\sqrt{q^2 + \frac{4p^3}{27}}}{2}. \tag{30}$$

Since u and v have a relation $t = u + v$, the possible combinations of (u, v) are given by

$$u^3 = \frac{-q +\sqrt{q^2 + \frac{4p^3}{27}}}{2} \ , \ v^3 = \frac{-q -\sqrt{q^2 + \frac{4p^3}{27}}}{2}. \tag{31}$$

Without loss of generality we assume $q < 0$ and consider the following three cases depending on the sign of $q^2 + \frac{4p^3}{27}$:

(i) $\alpha^2 := q^2 + \frac{4p^3}{27} > 0$:

This case corresponds to $u^3 > 0$ and the situation where $p = -3uv$ is real is represented by

$$\begin{cases} u = \kappa^k \sqrt[3]{\dfrac{-q+\alpha}{2}} \\ \\ v = \kappa^{3-k} \sqrt[3]{\dfrac{-q-\alpha}{2}} \end{cases} \quad (k = 0, 1, 2), \tag{32}$$

where $\kappa = e^{j\frac{2\pi}{3}}$. We can see that $k = 0$ is possible only when $t = u + v$ is positive, since $|u| > |v|$.

(ii) $-\alpha^2 = q^2 + \frac{4p^3}{27} < 0$:

Similarly to the case (i), we have

$$u = \kappa^k \sqrt[3]{\frac{-q+\alpha j}{2}} \ , \ v = \kappa^{3-k} \sqrt[3]{\frac{-q-\alpha j}{2}}. \tag{33}$$

Again we can see that $k = 0$ is possible only when $t = u+v$ is positive, since (u, v) belongs to the first and second orthants.

(iii) $q^2 + \frac{4p^3}{27} = 0$:

Similarly, we have

$$u = \kappa^k \sqrt{\frac{-q}{2}} \ , \ v = \kappa^{3-k} \sqrt{\frac{-q}{2}}. \tag{34}$$

These yield $t = u + v = (\kappa^k + \kappa^{3-k}) \sqrt[3]{\frac{-q}{2}}$, and we can show that only $k = 0$ gives a possible solution.

Consequently, we can conclude that the third-order polynomial equation (28) has a unique positive solution

$$t = \sqrt[3]{\frac{-q + \sqrt{q^2 + \frac{4p^3}{27}}}{2}} + \sqrt[3]{\frac{-q - \sqrt{q^2 + \frac{4p^3}{27}}}{2}}, \tag{35}$$

when $q < 0$. Setting t, p, and q as

$$t = y^*, \tag{36}$$

$$p = \frac{8 - 4Q^2(1 - LR^2 \cos\theta)}{Q^4 R^4}, \tag{37}$$

$$q = -\frac{8L \sin\theta}{Q^4 R^4} \tag{38}$$

completes the proof of Lemma 2.

□

B Proof of Lemma 3

Note first that $J(y^*, \theta)$ is a function of y^* and θ, and we see from Lemma 2 that y^* is the solution of $\frac{\partial J}{\partial y} = 0$ and hence it is a function of θ. Therefore, we can characterize $J(y^*, \theta)$ as the optimal solution of the following constrained minimization problem:

$$\min\ J(y, \theta) \quad \text{s.t. } f(y, \theta) := \frac{\partial J}{\partial y} = 0. \tag{39}$$

This problem can be solved by introducing the corresponding Lagrange function $W(y, \theta, \mu)$ which is defined by

$$W(y, \theta, \mu) := J(y, \theta) - \mu f(y, \theta). \tag{40}$$

Then a necessary condition for the optimality can be written as

$$\begin{cases} \frac{\partial W}{\partial y} = \frac{\partial J}{\partial y} - \mu \frac{\partial f}{\partial y} = -\mu \frac{\partial f}{\partial y} = 0 \\ \frac{\partial W}{\partial \theta} = \frac{\partial J}{\partial \theta} - \mu \frac{\partial f}{\partial \theta} = 0 \\ \frac{\partial W}{\partial \mu} = -f(y, \theta) = 0 \end{cases} \tag{41}$$

We see from the first equation of (41) that $\mu = 0$ or $\frac{\partial f}{\partial y} = 0$. We now assume that $\frac{\partial f}{\partial y} = \frac{3}{4}Q^4R^4y^2 + 2 - (1 - LR^2\cos\theta)Q^2 = 0$ holds. Multiplying y by this equation and using the third condition, we have $\frac{\partial f}{\partial y}y = \frac{1}{2}Q^4R^4y^3 + 2L\sin\theta = 0$. This contradicts $y > 0,\ 0 < \theta < \pi$, and hence we can conclude that $\mu = 0$. The second condition with $\mu = 0$ is written by

$$\begin{aligned} \frac{\partial J}{\partial \theta} &= -2L\sin\theta\left(\frac{1}{4}Q^2R^2y^2 - \frac{1}{R^2} + L\cos\theta\right) \\ &\quad -2L\cos\theta(y - L\sin\theta) \\ &= -2L(-x\sin\theta + y\cos\theta) = 0, \end{aligned} \tag{42}$$

where we use the fact that the locus of $\phi(j\omega)$ is given by

$$x = -\frac{1}{4}Q^2R^2y^2 + \frac{1}{R^2} \tag{43}$$

to derive the last equality. This leads to $\frac{y}{x} = \tan\theta$ and implies that one of the candidates for the optimal point is the intersection of the straight line passing at the origin with angle θ and the boundary of robust stability region. We can also see from the vector locus that

$$x^2 + y^2 = \left(x - \frac{2}{Q^2R^2}\right)^2 - \frac{4(1 - Q^2)}{Q^4R^4} \tag{44}$$

holds. Hence, the distance from the origin to the parabolic curve is monotonically increasing with respect to x due to $x \le 1$ and $Q^2 \le 1$. Consequently,

we can conclude that the distance between the corresponding points on the circle and parabolic curve, i.e., $\left|\sqrt{x^2+y^2}-L\right|^2$, has no extreme in the interval of θ which satisfies both $(L\sin\theta, L\cos\theta) \in \Omega_+^c$ and $0 < \theta < \pi$. This together with a fact that the distance at $\theta = 0$ is smaller than that at $\theta = \pi$ leads to Lemma 3.

□