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Research Article

Robust Genetic Circuit Design: A Mixed $\mathscr{H}_\infty$ and IQC Analysis

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This paper considers the problem of designing a genetic circuit which is robust to noise effect. To achieve this goal, a mixed $\mathscr{H}_\infty$ and Integral Quadratic Constraints (IQC) approach is proposed. In order to minimize the effects of external noise on the genetic regulatory network in terms of $\mathscr{H}_\infty$ norm, a design procedure of Hill coefficients in the promoters is presented. The IQC approach is introduced to analyze and guarantee the stability of the designed circuit.

1. Introduction

Genetic regulatory network (GRN) is subjected to noise disturbances that may occur at transcription, translation, transport, chromatin remodeling, and pathway specific regulation. The GRN diagrams that resemble complex electrical circuits are generated by the connectivity of mRNAs and proteins [1]. Mathematical and computational tools have been utilized to develop the genetic circuits and systems using biotechnological design principles of synthetic GRN, which involves new kinds of integrated circuits like neurochips inspired by the biological neural networks [2]. This method leads to a large-scale system composed of several interconnected subsystems. The previous work [3] performs a hierarchical analysis by propagating the IQC characterization of each uncertain subsystem through their interaction channels. More specifically, both plant states and the IQC dynamic states are used as feedback information in the closed-loop system model, and then the robust l_2 stability analysis is performed via dynamic IQCs. Thereby, the synthesis conditions for the proposed full-information feedback controller are derived for the linear matrix inequality (LMI) systems [4].

Therefore, stability analysis of uncertain GRN is a prerequisite for any design issue. From the perspectives of control engineering, H_∞ is a key performance index to evaluate the noise rejection/attenuation capability. Unlike the external control inputs used in the conventional robust control theory [5], the feedback regulation mechanism is embedded in the GRN. We construct a genetic circuit by introducing a Hill function type feedback loop from proteins (mostly from transcription process) to regulate the expression of target genes. By binding to promoter domain, the GRN is mean square asymptotically stable with a given noise attenuation level γ.

The paper is organized as follows. Section 2 introduces the mathematical model of GRN. A design procedure for the Hill coefficients is proposed in Section 3. We provide an example to illustrate the developed design method in Section 4. The concluding remark is given in Section 5.

2. Problem Formulation

The activities of a gene are regulated by other genes through their interactions, that is, the transcription and translation factors [6, 7]. The underlying dynamics can be modeled as a gene $i = 1, 2, \ldots, n$,

$$\begin{aligned} \frac{dm_i(t)}{dt} &= -l_i m_i(t) + \sum_{j=1}^{n} G_{ij} h_j\left(p_j(t)\right) + e_i(t), \\ \frac{dp_i(t)}{dt} &= -c_i p_i(t) + d_i m_i(t), \end{aligned} \tag{1}$$

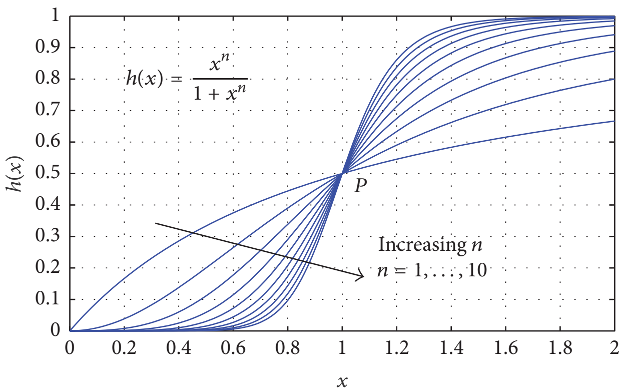

Figure 1: Positive Hill function.

where $m_i(t), p_i(t) \in \mathbf{R}$ are concentrations of mRNA and protein of the ith gene at time t, respectively, $l_i, c_i \in \mathbf{R}^+$ are the degradation rates of the mRNA and protein, $d_i \in \mathbf{R}^+$ is the translation rate, $e_i(t)$ is the external noise, and

$$h_j(x) = \frac{\beta_j \left(x/k_j\right)^{n_j}}{1 + \left(x/k_j\right)^{n_j}}, \quad j = 1, \ldots, n, \tag{2}$$

is a monotonically increasing function [8] in which n_j is the Hill coefficient, β_j is a positive constant, and k_j is the apparent dissociation constant derived from the law of mass action, which equals the ratio of the dissociation rate of the ligand-receptor complex to its association rate. The family of positive Hill functions is shown in Figure 1. In this paper, the Hill function assumes that protein j is an activator of gene i [6, 7]. The matrix $\mathbf{G} = (G_{ij}) \in \mathbf{R}^{n\times n}$ is the coupling matrix of the GRN and e_i is defined as a base rate. System (1) can be written into the compact matrix form:

$$\begin{aligned} \frac{dm(t)}{dt} &= Lm(t) + \mathbf{G}h(p(t)) + e(t), \\ \frac{dp(t)}{dt} &= Cp(t) + Dm(t), \end{aligned} \tag{3}$$

where $m(t) = [m_1(t), \ldots, m_n(t)]^T$, $p(t) = [p_1(t), \ldots, p_n(t)]^T$, $L = \operatorname{diag}\{-l_1, \ldots, -l_n\}$, $C = \operatorname{diag}\{-c_1, \ldots, -c_n\}$, $D = \operatorname{diag}\{d_1, \ldots, d_n\}$, $e(t) = [e_1(t), \ldots, e_n(t)]^T$, and $h(p(t)) = [h_1(p_1(t)), \ldots, h_n(p_n(t))]^T$. To simplify our exposition, we use a more general set of notations and shift the equilibrium point of the noiseless system to P; then model (3) can be expressed as

$$\frac{dx(t)}{dt} = Ax(t) + BH(x(t)) + E(t), \tag{4}$$

where

$$A = \begin{bmatrix} L & 0 \\ D & C \end{bmatrix}, \quad B = \begin{bmatrix} 0 & \mathbf{G} \\ * & 0 \end{bmatrix}, \tag{5}$$

with $*$ being an arbitrary matrix such that $|B| \neq 0$,

$$x(t) = \begin{bmatrix} m(t) \\ p(t) \end{bmatrix}, \quad H(x(t)) = \begin{bmatrix} 0 \\ h(p(t)) \end{bmatrix}, \quad E(t) = \begin{bmatrix} e(t) \\ 0 \end{bmatrix}. \tag{6}$$

In this model, the system states of mRNAs and proteins play different roles in regulation, for example, activators, repressers, or other factors. We name $x(\cdot) = [x_1(\cdot), \ldots, x_n(\cdot), x_{n+1}(\cdot), \ldots, x_{2n}(\cdot)]^T \in \mathbb{R}^{2n}$ as the deviation of concentration from the equilibrium point of (3). The rate of change in x_i denoted by $\dot{x}_i$ represents the concentration changes of the variables due to production or degradation. $H(\cdot) = [0, \ldots, 0, h_1(\cdot), \ldots, h_n(\cdot)]^T$ represents the regulation function on the ith variable, which is generally a nonlinear or linear function on the variables $[x_1(\cdot), \ldots, x_n(\cdot), x_{n+1}(\cdot), \ldots, x_{2n}(\cdot)]^T$, but has a form of monotonicity with each variable. The degradation parameters matrix A has zero elements on its nondiagonal plane; the matrix B defines the coupling topology, direction, and the transcriptional rate of the GRN. When the input is $u(t) \triangleq H(x(t))$, the system model (4) can be rewritten as

$$\begin{aligned} \dot{x}(t) &= Ax(t) + Bu(t) + E(t), \\ u(t) &= H(x(t)), \end{aligned} \tag{7}$$

where $E(t)$ is the vector of zero-mean white Gaussian noise.

In this paper, we aim to address the following problem.

Problem 1. Given the system represented by model (7) and parameters A, B, the purpose of robust genetic circuit design is to determine the parameters in $H(\cdot)$ such that

(i) the whole system is stable;

(ii) $\mathscr{H}_\infty$ norm of the noise $e(t)$ in the measurement channel $x(t)$ is minimized (we assume full observation).

In the following section, we propose a mixed H_∞ and IQC approach to tackle Problem 1. The objective of this approach is to promote $\mathscr{H}_\infty$ method in the design of Hill function for GRN. We will give the theoretical analysis to underpin this technique.

3. Analysis and Design

We take point P as the equilibrium position due to the special shape of Hill functions in Figure 1. The intuitive way to address such an issue would be firstly to design a static feedback $u = F_{\text{opt}}x$ by which the closed-loop system can achieve the minimum $\gamma_{\min}$. Then we prove the stability of the system with the nonlinearity involved by analysis methods [9]. However, the optimal performance with $u = F_{\text{opt}}x$ for the linear system does not necessarily guarantee the optimal

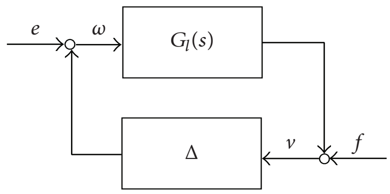

Figure 2: The feedback system model structure.

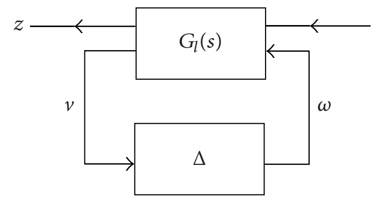

Figure 3: The transferred system model structure.

performance for the nonlinear system with $u = H(x)$. In some cases, the nonlinearity of $u = H(x)$ might even worsen the system performance to a degree which is far from optimal. Therefore, robust performance has rarely been considered for the nonlinear system. In the following subsections, we resolve this difficulty.

3.1. Preliminaries. We first recall some preliminary results in the system analysis via IQCs from [10]. Let $\mathbf{RH}_{\infty}^{m\times n}$ be the set of real proper rational function matrices without right-half plane poles and let $\mathbf{L}_{\mathbf{2e}}^{\mathbf{l}}[0,\infty)$ be the set of functions $f : [0,\infty) \to \mathbf{R}^l$ that have finite energy on the interval $[0,T]$, $\forall T > 0$; that is,

$$\|f\|_2^2 = \int_0^T \|f(t)\|^2\, dt < \infty, \quad \forall T > 0. \tag{8}$$

The Fourier transform for an $\mathbf{R}^l$-valued function $f : [0,\infty) \to \mathbf{R}^l$ is denoted as $\widehat{f}(j\omega)$. Consider the feedback configuration in Figure 2,

$$\begin{aligned} v &= Gw + f, \\ w &= \Delta v + e, \end{aligned} \tag{9}$$

where $f \in \mathbf{L}_{2e}^{m}[0,\infty)$, $e \in \mathbf{L}_{2e}^{n}[0,\infty)$, and G and Δ are two causal operators. Note that G is stable and Δ is bounded but could be nonlinear, time-varying, or uncertain. Δ is said to satisfy the IQC defined by Π if the two vectors of signal v, w fulfill

$$\int_{-\infty}^{+\infty} \begin{bmatrix} \widehat{v}(j\omega) \\ \widehat{w}(j\omega) \end{bmatrix}^{*} \Pi(j\omega) \begin{bmatrix} \widehat{v}(j\omega) \\ \widehat{w}(j\omega) \end{bmatrix} d\omega \geq 0, \tag{10}$$

in which $\Pi : j\mathbf{R} \to \mathbf{C}^{(m+n)\times(m+n)}$ can be any measurable Hermitian-valued function defined on the imaginary axis and the superscript $*$ denotes the complex conjugate transpose.

Lemma 2 (see [10]). *Let $G(s) \in \mathbf{RH}_{\infty}^{\mathbf{m}\times\mathbf{n}}$ and Δ be a bounded causal operator. If the following assumptions hold,*

(i) *for every $\tau \in [0,1]$, the interconnection of G and $\tau\Delta$ is well-posed;*

(ii) *for every $\tau \in [0,1]$, the IQC defined by Π is satisfied by $\tau\Delta$;*

(iii) *there exists $\epsilon > 0$ such that*

$$\begin{bmatrix} G(j\omega) \\ I \end{bmatrix}^{*} \Pi(j\omega) \begin{bmatrix} G(j\omega) \\ I \end{bmatrix} \leq -\epsilon I, \quad \forall\omega; \tag{11}$$

then the feedback interconnection of G and Δ is stable.

Remark 3. From Lemma 2, an important conclusion on IQC stability analysis can be drawn: if Δ satisfies several IQCs, it also satisfies all nonnegative linear combinations of IQCs. For example, if v, w satisfy the IQC defined by Π_1 and the IQC defined by Π_2, they will also satisfy the IQC defined by $\lambda_1\Pi_1 + \lambda_2\Pi_2$ for all $\lambda_1, \lambda_2 \geq 0$. In other words, the set of IQCs that Δ satisfies forms a "description" for the block Δ, and the more IQCs we know that Δ satisfies, the more precisely that we can describe the uncertainty of Δ.

Lemma 4 (KYP lemma, [11]). *Suppose $\mathscr{M}(s) = C_{cl}(sI - A_{cl})^{-1}B_{cl} + D_{cl}$. Assume (A_{cl}, B_{cl}) is stabilizable and A_{cl} has no eigenvalues on the imaginary axis. Then the following conditions are equivalent:*

(i) *The system $\mathscr{M}$ is stable, and $\|\mathscr{M}\|_{\infty} < \gamma$.*

(ii) *We have $\forall\omega \in [0,\infty)$,*

$$\begin{aligned} &\begin{bmatrix} \left(j\omega - A_{cl}^{-1}\right) B_{cl} \\ I \end{bmatrix}^{*} \\ &\quad \cdot \begin{bmatrix} C_{cl}^{T}C_{cl} & C_{cl}^{T}D_{cl} \\ D_{cl}^{T}C_{cl} & D_{cl}^{T}D_{cl} - \gamma I \end{bmatrix} \begin{bmatrix} \left(j\omega - A_{cl}^{-1}\right) B_{cl} \\ I \end{bmatrix} < 0; \end{aligned} \tag{12}$$

(iii) *There exists a symmetric matrix $P > 0$, such that*

$$\begin{bmatrix} A_{cl}^{T}P + PA_{cl} & PB_{cl} \\ B_{cl}^{T}P & -\gamma I \end{bmatrix} + \begin{bmatrix} C_{cl}^{T} \\ D_{cl}^{T} \end{bmatrix} \begin{bmatrix} C_{cl} & D_{cl} \end{bmatrix} < 0. \tag{13}$$

Lemma 5 (see [11]). *By using linear fraction transformation, we convert the system configuration from Figure 2 to Figure 3. Let $e \in \mathbf{L}_{2e}^{n}[0,\infty)$, $G_l(s) \in \mathbf{RH}_{\infty}$ with corresponding dimension, and let the system $\mathbf{L}_2$-gain be the performance measurement.*

Assume that Δ satisfies an IQC defined by Π having the following block structure:

$$\Pi = \begin{bmatrix} \Pi_{11} & \Pi_{12} \\ \Pi_{12}^{*} & \Pi_{22} \end{bmatrix}; \tag{14}$$

then the system in Figure 3 is stable and has robust $\mathbf{L}_2$*-gain* γ, *if*

(i) *for every* $\tau \in [0,1]$, *the interconnection of* G_l *and* $\tau\Delta$ *is well-posed;*

(ii) *for every* $\tau \in [0,1]$, *the IQC defined by* Π *is satisfied by* $\tau\Delta$*;*

(iii) *the frequency domain inequality,*

$$\begin{bmatrix} G_l(j\omega) \\ I \end{bmatrix}^* \Gamma \begin{bmatrix} G_l(j\omega) \\ I \end{bmatrix} < 0, \tag{15}$$

holds for all $\omega \in [0,\infty)$, *where*

$$\Gamma = \left[\begin{array}{cc|cc} I & 0 & 0 & 0 \\ 0 & \Pi_{11}(j\omega) & 0 & \Pi_{12}(j\omega) \\ \hline 0 & 0 & -\gamma^2 I & 0 \\ 0 & \Pi_{12}^*(j\omega) & 0 & \Pi_{22}(j\omega) \end{array}\right]. \tag{16}$$

3.2. Design Procedure. The algorithm for the design of Hill function considering both the stability and performance of the nonlinear system will be proposed.

Proposition 6. *After shifting the equilibrium point P (Figure 1) to the origin, Hill function* $h(x)$ *takes the following form:*

$$h(x) = \frac{\beta(x+k)^n}{k^n + (x+k)^n} - \frac{\beta}{2}, \tag{17}$$

and there exist real scalars $\alpha_1 \geq \alpha_2 \geq 0$, *such that* $h(x)$ *satisfies the IQCs defined by*

$$\pi_1 = \begin{bmatrix} -2\alpha_1\alpha_2 & (\alpha_1+\alpha_2) \\ (\alpha_1+\alpha_2) & -2 \end{bmatrix},$$
$$\pi_2 = \begin{bmatrix} \left(\frac{\beta}{2}\right)^2 z & y \\ -y & -z \end{bmatrix}, \tag{18}$$

where $z \geq 0$.

Proof. π_1 is from a sector bound condition $\alpha_2 v^2 \leq h(v)v \leq \alpha_1 v^2$; to see this we notice that in the time domain

$$\begin{bmatrix} v \\ h(v) \end{bmatrix}^T \pi_1 \begin{bmatrix} v \\ h(v) \end{bmatrix} = 2(\alpha_1 v - h(v))(h(v) - \alpha_2 v) \geq 0. \tag{19}$$

The derivation of π_2 involves an approximation, in which $h(v(t)) = \delta(v(t))v(t)$ with a scalar function $\delta \in \mathbf{L}_\infty$ with $\|\delta\|_\infty \leq \beta/2$; then

$$\begin{bmatrix} v \\ h(v) \end{bmatrix}^T \pi_2 \begin{bmatrix} v \\ h(v) \end{bmatrix} = v^T\left(\left(\frac{\beta}{2}\right)^2 z - \delta^2 z + \delta(y-y)\right)v \geq 0. \tag{20}$$

This ends the proof. □

Remark 7. From Proposition 6, we should know that the set of IQCs is a sufficient condition for stability; therefore, it is conservative. Yet the challenge for nonlinear system stability is significant, because all the existing methods, including Lyapunov theory and IQCs, are conservative.

In Proposition 6, π_1 and π_2 are for the case of scalar x and $h(x)$. Here we consider the case of vectors x and $h(x)$.

Corollary 8. *When* $x = [x_1,\ldots,x_i,\ldots,x_n,x_{n+1},\ldots,x_{2n}]^T$ *and* $H(x) = [0,\ldots,0,h_1(x_1),\ldots,h_i(x_i),\ldots,h_n(x_n)]^T$, *then IQCs for* $H(x)$ *take the following forms:*

$$\Pi_1 = \left[\begin{array}{c|c} \Pi_{1-11} & \Pi_{1-12} \\ \hline \Pi_{1-21} & \Pi_{1-22} \end{array}\right], \tag{21}$$

where

$$\begin{aligned} \Pi_{1-11} &= \operatorname{diag}(-2\alpha_{11}\alpha_{21},\ldots,-2\alpha_{1i}\alpha_{2i},\ldots,-2\alpha_{1n}\alpha_{2n}), \\ \Pi_{1-12} &= \operatorname{diag}((\alpha_{11}+\alpha_{21}),\ldots,(\alpha_{1i}+\alpha_{2i}),\ldots, \\ &\quad (\alpha_{1n}+\alpha_{2n})), \\ \Pi_{1-21} &= \Pi_{1-12}^T, \\ \Pi_{1-22} &= \operatorname{diag}(-2,\ldots,-2,\ldots,-2), \\ \Pi_2 &= \left[\begin{array}{c|c} \Pi_{2-11} & \Pi_{2-12} \\ \hline \Pi_{2-21} & \Pi_{2-22} \end{array}\right], \end{aligned} \tag{22}$$

where

$$\begin{aligned} \Pi_{2-11} &= \operatorname{diag}(z_1,\ldots,z_i,\ldots,z_n), \\ \Pi_{2-12} &= \operatorname{diag}(y_1,\ldots,y_i,\ldots,y_n), \\ \Pi_{2-21} &= -\Pi_{2-12}^T, \\ \Pi_{2-22} &= \operatorname{diag}(-z_1,\ldots,-z_i,\ldots,-z_n), \end{aligned} \tag{23}$$

with $z_i \geq 0$. *Combining* Π_1 *and* Π_2, *we obtain the following IQCs for* $H(x)$:

$$\begin{aligned} \Pi = &\left[\begin{array}{c|c} \Lambda_1\Pi_{1-11} & \Lambda_1\Pi_{1-12} \\ \hline \Lambda_1\Pi_{1-21} & \Lambda_1\Pi_{1-22} \end{array}\right] \\ &+ \left[\begin{array}{c|c} \Lambda_2\Pi_{2-11} & \Lambda_2\Pi_{2-12} \\ \hline \Lambda_2\Pi_{2-21} & \Lambda_2\Pi_{2-22} \end{array}\right], \end{aligned} \tag{24}$$

for any $n \times n$ *nonnegative diagonal matrices* Λ_1 *and* Λ_2.

Example 9. Take $n = 1$, $n_1 = 3$, $k = 1$, and $\beta = 1$ as an example; therefore,

$$h(x) = \frac{(x+1)^3}{1+(x+1)^3} - 0.5. \tag{25}$$

Assume that the evolution of x is within a limited a range $[-1,1]$; then a sector condition of $\alpha_1 = 0.84$, $\alpha_2 = 0.35$ with $\delta \in [-0.5, 0.5]$ can form a good bound on $h(x)$, which is shown in Figure 4.

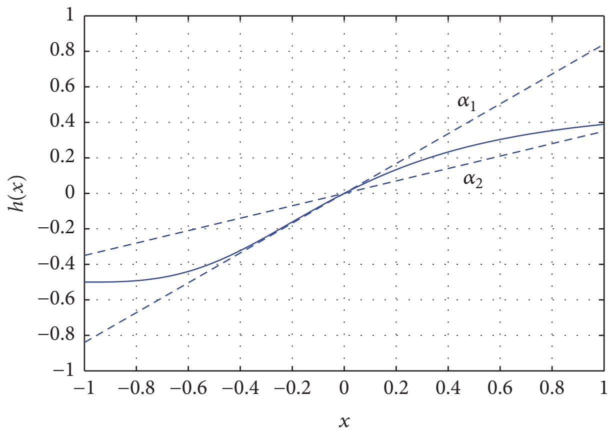

FIGURE 4: Hill function $h(x)$ and its bounds. In this picture, the solid line is the considered Hill function and dashed lines are the corresponding bounds.

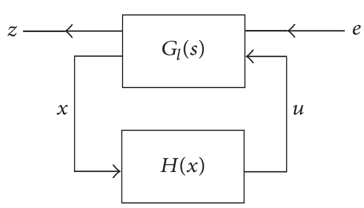

FIGURE 5: The system with Hill feedback model structure.

Proposition 10. *Consider the system configuration in Figure 5, let $e \in \mathbf{L}_{2e}^m[0,\infty)$, $G_l(s) \in \mathbf{RH}_\infty$ be the genetic network, and $x(\cdot) = [x_1(\cdot),\ldots,x_n(\cdot),x_{n+1}(\cdot),\ldots,x_{2n}(\cdot)]^T$ and $H(x) = [0,\ldots,0,h_1(x_1),\ldots,h_i(x_i),\ldots,h_n(x_n)]^T$ represent the designed feedback Hill function. We denote with Δ_H the uncertainty derived from $H(x)$, which satisfies the IQCs in (24).*

Then the system in Figure 5 is stable and has robust $\mathbf{L}_2$-gain γ, if

(i) *for every $\tau \in [0,1]$, the interconnection of G_l and $\tau\Delta_H$ is well-posed;*

(ii) *for every $\tau \in [0,1]$, the IQC defined by Π is satisfied by $\tau\Delta_H$;*

(iii) *the frequency domain inequality,*

$$\begin{bmatrix} G_l(j\omega) \\ I \end{bmatrix}^* \Gamma \begin{bmatrix} G_l(j\omega) \\ I \end{bmatrix} < 0, \tag{26}$$

holds for all $\omega \in [0,\infty]$, where

$$\Gamma = \left[\begin{array}{cc|cc} I & 0 & 0 & 0 \\ 0 & \Pi_{11}(j\omega) & 0 & \Pi_{12}(j\omega) \\ \hline 0 & 0 & -\gamma^2 I & 0 \\ 0 & \Pi_{12}^*(j\omega) & 0 & \Pi_{22}(j\omega) \end{array}\right], \tag{27}$$

and Π_{ij}s take the form in (24).

Proof. The result follows from applying the IQCs defined by (24) in Corollary 8. □

Proposition 11. *Let the Hill coefficients* **Hc** *be the set of proper values of (β,k) for a Hill function; given any $(\beta,k) \in$* **Hc** *and n, a Hill function can be uniquely defined and hence a set of IQCs in the form of (24) can be formulated. Then the design of Hill function feedback can be reformulated into the following linear matrix inequality (LMI) problem:*

$$\inf_{\Lambda_{1,2}>0,\mathbf{Hc},\omega} \gamma, \tag{28}$$

such that (26) is satisfied.

The frequency-dependent inequality in (26) can be resolved by using YALMIP (https://users.isy.liu.se/johanl/yalmip/). Since the linear matrix inequality (28) has to be solved simultaneously for all frequencies in the frequency domain, the basic strategy is to start with a small set of points and then check whether the solution satisfies all ω. If it does not, add one or more frequency points to the previous set and solve LMI again. Another more efficient way to solve the LMI is to transform (26) into the time domain by using the KYP lemma of Lemma 4 if the state-space realizations of G_l and Π have been obtained.

4. Biologically Inspired Example

In this section, we provide an example to illustrate the algorithm and design procedures developed in Section 3. Consider the following GRN:

$$\begin{aligned} \dot{x}(t) &= Ax(t) + Bu(t) + E(t), \\ u(t) &= H(x(t)), \end{aligned} \tag{29}$$

in which

$$\begin{gathered} A = \begin{bmatrix} -0.1 & 0 & 0 & 0 \\ 0 & -0.5 & 0 & 0 \\ a_1 & 0 & -0.1 & 0 \\ 0 & a_2 & 0 & -0.5 \end{bmatrix}, \\ B = \begin{bmatrix} 0 & \mathbf{G} \\ \widetilde{B} & 0 \end{bmatrix}, \\ \mathbf{G} = \begin{bmatrix} 0 & 1 \\ 1 & 0 \end{bmatrix}, \end{gathered} \tag{30}$$

where a_1, a_2, and $\widetilde{B}$ are randomly generated in MATLAB and a_1, a_2, and the elements in matrix $\widetilde{B}$ follow the even distribution on the interval $[0,1]$. In this simulation, the generated data are $a_1 = 0.8$, $a_2 = 0.1$,

$$\widetilde{B} = \begin{bmatrix} 0.7 & 0.9 \\ 0.1 & 1 \end{bmatrix}. \tag{31}$$

The system gain of the original system $\mathbf{G}_0 = (sI - A)^{-1}B$ is 94.2653. Although the system is originally stable, its performance is far from satisfactory. In order to further investigate the effects of noise e on u, the procedure of designing $H(x)$ is slightly modified in this example. Specifically, it is an undesirable result if a small e causes a large u. Therefore, rather than minimizing $\mathscr{H}_\infty$ norm from e to x, we minimize $\mathscr{H}_\infty$ norm from e to $[x, \alpha u]$, where α is a constant. With $\mathbf{Hc} = \{(\beta, k) \mid \beta \in [0.01, 100],\ k \in [1, 100]\}$ ([8]) and $\alpha = 2$, $n = 2$, we solve the LMI problem stated in (28), resulting in the feedback Hill function with $(\beta_1, \beta_2) = [10, 100]$, $(k_1, k_2) = [1, 10]$. As a result, $\mathscr{H}_\infty$ norm of the closed-loop system is upper bounded by $\gamma_1 = 72.3593$. Compared with γ_0, a distinct improvement has been made for the system performance in terms of $\mathscr{H}_\infty$ norm.

5. Conclusion

This paper tackles the problem of designing robust genetic circuit via constructing parameters of the Hill function. Targeting to minimize the noise effect in the genetic regulatory network, a design procedure is proposed. With the help of IQC approach, stability and performance of the designed circuit are guaranteed.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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