Estimating Stable Uncertainty Sets for Genetic Regulatory Networks with Guaranteed Disturbance Attenuation

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***Abstract*- It is well-known that models of genetic regulatory networks (GRNs) are unavoidably affected by uncertainties. This paper addresses the problem of estimating stable uncertainty sets of uncertain GRNs with guaranteed disturbance attenuation. Specifically, the GRNs are assumed to be affected by disturbances in the form of Wiener processes, and by uncertainties in the form of a parameter vector that determines the coefficients of the model via given functions. It is shown that estimates of the sought stable uncertainty sets can be obtained through a recursive strategy based on parameter-dependent Lyapunov functions and convex optimization. Some examples with fictitious and real biological models illustrate the use of the proposed strategy.**

Keywords- Uncertain Genetic Regulatory Networks; Stability Regions; Disturbance Attenuation; Semidefinite Programming

I. INTRODUCTION

As a fundamental research area in systems biology, the study of GRNs has become a major challenge which helps us to better understand the gene regulation process at the holistic level [1]. For example, one need to know how proteins are synthesized from genes that are affected by other genes, and how DNA, RNA and proteins interact with each other in order to form a complicated system which performs multiple biological functions [2-4]. Within the scope of the researches in systems biology, one significant objective of the study on GRNs is to have a deeper insight of the inter-gene interactions and relationships on a system level which will facilitate the diagnosis of disease [5].

Currently, with the development of the modeling techniques in systems biology, by using different mathematical tools, it is possible to describe the network structure and predict potential mechanisms of GRNs more accurately [6-9]. Nowadays, in order to model, analyze and simulate GRNs, many different mathematical models have been proposed, such as Bayesian networks, Boolean networks, differential equation models. See for example [10-15] and references therein for a wider categorization of GRNs models.

In the researches of GRNs, the major challenge is not specifying the gene network structure only, but finding and understanding the network dynamics and working mechanisms also. As far as we know, there are some main characteristics of GRNs which play a key role in establishing the mathematical model [16-21]. Firstly, GRNs are typically considered as biochemical dynamic systems which are nonlinear and high dimensional. Secondly, gene regulation is an intrinsically noisy process which owns to random births and deaths of individual molecules intracellularly and environment fluctuations extracellularly. Furthermore, the whole system is characterized with significant time delays in the processes of transcription, translation, diffusion and translocation. Finally, it is also found that gene expression levels tend to be continuous [25]. Motivated by the above characteristics, a mathematical model is required to better describe both the network structure and potential mechanisms of GRNs. In the case of differential equation model, the concentrations of the gene products such as mRNAs, proteins and other small molecules in the whole gene regulation system are described by positive real values governed by differential equations [22-24]. According to the main characteristics of GRNs and different equation models, the advantage of using such model is that one can take into account the detailed network dynamics and gene regulation mechanisms, such as individual kinetics and the interactions among mRNAs and proteins.

On the other hand, since the mathematical model of GRNs is derived from real-world gene expression data, it is well known that the unavoidable modeling error brings the uncertainty to the whole system. Moreover, it is noted that, some of the fluctuations in GRNs are not entirely random, which also makes the mathematical model uncertain. Therefore, it is essential and important to consider parameter uncertainties during the constructing of the network models. Among the research aspects in GRNs, “stability analysis” is one of the most attractive research areas. Other than simply considering the stability conditions of GRNs, one problem arises here is the estimation of the stable uncertainty sets of uncertain GRNs. To the best of the authors' knowledge, up to now, little effort has been made towards such topics in GRNs, which motivates the present study.

In this paper, we focus on the GRNs described by differential equation models and affected by both stochastic noise and parametric uncertainties [26-29]. Specifically, the GRNs are assumed to be affected by disturbances in the form of Wiener processes, and by uncertainties in the form of a parameter vector that determines the coefficients of the model via given functions. It is shown that estimates of the sought stable uncertainty sets can be obtained through a recursive strategy based on parameter-dependent Lyapunov functions

and convex optimization problem with linear matrix inequalities (LMIs).

The paper is organized as follows. Section II introduces some preliminaries about uncertain GRNs. Section III provides the stability condition of uncertain GRN with disturbance attenuation, representation of polynomials and the description of the proposed strategy for estimating stable uncertainty sets. Section IV presents some illustrative examples with fictitious and real biology models. Finally, Section V provides some concluding remarks.

II. PROBLEM FORMULATION

Notation: 0_n denotes the origin of $\mathbb{R}^n$, A^T denotes the transpose of a matrix A, I denotes the identity matrix, $A>0$ $(A\geq 0)$ denotes a real symmetric positive definite (semi-definite) matrix A, $A\otimes B$ denotes the Kronecker product of matrices A and B, $E(\cdot)$ represents the expectation operator, $L_2[0,\infty)$ is the space of square-integrable vector functions over $[0,\infty)$, $\|\cdot\|$ and $\|\cdot\|_{L_2}$ denote the Euclidean vector norm and the usual $L_2[0,\infty)$ norm. Matrices, if their dimensions are not explicitly stated, are assumed to have compatible dimensions for algebraic operations.

An uncertain GRN described by differential equations can be described with the model

$$\begin{cases}\dfrac{dm(t)}{dt}=A(\theta)m(t)+G(\theta)g(p(t))+l(\theta)\\ \dfrac{dp(t)}{d(t)}=C(\theta)p(t)+D(\theta)m(t)\end{cases} \tag{1}$$

where $m(t)=(m_1(t),\, m_2(t),...,\, m_n(t))^T\in\mathbb{R}^n$ and $p(t)=(p_1(t),\, p_2(t),...,\, p_n(t))^T\in\mathbb{R}^n$ are vectors containing the concentrations of mRNA and protein, $\theta\in\mathbb{R}^r$ is a time-invariant uncertainty vector, $A(\theta), C(\theta)\in\mathbb{R}^{n\times n}$ are negative definite diagonal matrices which contain the degradation rates, $D(\theta)\in\mathbb{R}^{n\times n}$ is a positive definite diagonal matrix which contains the translation rate, $G(\theta)\in\mathbb{R}^{n\times n}$ defines the coupling topology, and $l(\theta)\in\mathbb{R}^n$ is the basal rate.

We select an activation function $g(\cdot)$ which is monotonically increasing and ranges from 0 to 1 which satisfies

$$0\leq\frac{g(a)-g(b)}{a-b}\leq\xi,\ \forall a,b\geq 0,\ a\neq b \tag{2}$$

for some ξ.

One special case of the activation function $g(\cdot)$ is with Hill form, in such case the ith entry of $g(\cdot)$ is given by

$$g_i(p(t))=\frac{p_i(t)^H}{\beta^H+p_i(t)^H},\ \beta>0,\ p_i(t)>0\ \ \forall i \tag{3}$$

where H is the Hill coefficient.

Let $(m^*(\theta), p^*(\theta))$ be an equilibrium point of the system (1), i.e., a solution of the equations

$$\begin{cases}A(\theta)m^*(\theta)+G(\theta)g(p^*(\theta))+l(\theta)=0_n\\ C(\theta)p^*(\theta)+D(\theta)m^*(\theta)=0_n.\end{cases} \tag{4}$$

Let us shift the origin to the unknown equilibrium point $(m^*(\theta), p^*(\theta))$ by defining $x=m-m^*(\theta)$, $y=p-p^*(\theta)$ and by letting $f(y(t))=g(y(t)+p^*(\theta))-g(p^*(\theta))$. The system (1) becomes

$$\begin{cases}\dfrac{dx(t)}{dt}=A(\theta)x(t)+G(\theta)f(y(t))\\ \dfrac{dy(t)}{d(t)}=C(\theta)y(t)+D(\theta)x(t).\end{cases} \tag{5}$$

In order to study stochastic stability, we write the system (5) into

$$\begin{cases}dx(t)=(A(\theta)x(t)+G(\theta)f(y(t)))dt\\ \qquad +\varphi(x(t),y(t))d\omega_1(t)+v(t)d\omega_2(t)\\ dy(t)=(C(\theta)y(t)+D(\theta)x(t))dt\end{cases} \tag{6}$$

where $\varphi(x(t),y(t))\in\mathbb{R}^n$ is the noise intensity vector, $v(t)\in\mathbb{R}^n$ belongs to $L_2[0,\infty)$, and $\omega_1(t)$ and $\omega_2(t)$ are two independent one-dimensional Wiener processes.

We assume that $\varphi(x(t),y(t))$ satisfies

$$\varphi^T(x(t),y(t))\varphi(x(t),y(t))\leq x^T(t)H_1x(t)+y^T(t)H_2y(t) \tag{7}$$

for some positive definite matrices H_1 and H_2.

Definition: The system (6) is said to be stochastically stable with disturbance attenuation γ if the system (6) is asymptotically stable in mean-square for $v(t)=0$, and under zero initial conditions, we have

$$\|z(t)\|_{E_2}<\gamma\|v(t)\|_{L_2} \tag{8}$$

for all nonzero $v(t)$, where $z(t)=(x(t)^T, y(t)^T)^T$ and $\|z(t)\|_{E_2}=(E(\int_0^\infty\|z(t)\|^2dt))^{1/2}$.

Problem: Estimate the stable uncertainty set with disturbance attenuation $\Theta_{stable}(\gamma)$, where

$$\Theta_{stable}(\gamma)=\{\theta\in\mathbb{R}^r:(6)\ \text{is stochastically stable with disturbance attenuation}\ \gamma\}. \tag{9}$$

III. ESTIMATION

Here we describe the proposed estimation scheme of the stable uncertainty sets for GRNs with guaranteed disturbance attenuation. Specifically, we provide a stability condition for GRNs with disturbance attenuation for a candidate estimate of the sought set in Section III-A. Then, we explain how this condition can be checked through convex optimization in Section III-B. Finally, we provide the algorithm in Section III-C to estimate the stable uncertainty sets for GRNs with guaranteed disturbance attenuation.

A. Stability Condition

In this section, we propose a condition for establishing stability with guaranteed disturbance attenuation for a candidate estimate based on Lyapunov functions and sum of squares of matrix polynomials (SOS).

First of all, we parameterize the uncertainty set as

$$\Theta = \{\theta \in \mathbb{R}^r : t_i(\theta) \geq 0, \forall i = 1,...,r\} \tag{10}$$

where $t_i(\theta)$ are polynomials.

Hence, we consider the system (6) with θ constrained into Θ, i.e.,

$$\begin{cases} dx(t) = (A(\theta)x(t) + G(\theta) f(y(t)))dt \\ \qquad + \varphi(x(t), y(t))d\omega_1(t) + v(t)d\omega_2(t) \\ dy(t) = (C(\theta)y(t) + D(\theta)x(t))dt \\ \theta \in \Theta. \end{cases} \tag{11}$$

We have the following result.

Theorem 1: Given a scalar $\gamma > 0$, suppose that there exist matrix polynomials $P(\theta)$, $\Lambda(\theta)$, $U_i(\theta)$, a polynomial $\rho(\theta)$, and a positive scalar ε, such that

$$\begin{cases} -M(\theta) - \sum_{i=1}^{r} t_i(\theta)U_i(\theta) - \varepsilon I \ \ is\ SOS \\ P(\theta) - \varepsilon I \ \ is\ SOS \\ \rho(\theta)I - P_{11}(\theta) - \varepsilon I \ \ is\ SOS \\ \Lambda(\theta) \ \ is\ SOS \\ U_i(\theta) \ \ is\ SOS \end{cases} \tag{12}$$

where

$$\begin{cases} M(\theta) = \begin{pmatrix} M_{11} & M_{12} & M_{13} \\ M_{12}^T & M_{22} & M_{23} \\ M_{13}^T & M_{23}^T & M_{33} \end{pmatrix} \\ P(\theta) = \begin{pmatrix} P_{11}(\theta) & P_{12}(\theta) \\ P_{12}^T(\theta) & P_{22}(\theta) \end{pmatrix} \\ \Lambda(\theta) = diag(\lambda_1(\theta),...,\lambda_n(\theta)) \end{cases} \tag{13}$$

and

$$\begin{aligned} M_{11} &= P_{11}(\theta)A(\theta) + A^T(\theta)P_{11}(\theta) + P_{12}(\theta)D(\theta) \\ &\quad + D(\theta)P_{12}^T(\theta) + \rho(\theta)H_1 + (\rho(\theta)/\gamma^2)I \\ M_{12} &= D(\theta)P_{22}(\theta) + A^T(\theta)P_{12}(\theta) + P_{12}(\theta)C(\theta) \\ M_{13} &= P_{11}(\theta)G(\theta) \\ M_{22} &= P_{22}(\theta)C(\theta) + C^T(\theta)P_{22}(\theta) + \rho(\theta)H_2 \\ &\quad + (\rho(\theta)/\gamma^2)I \\ M_{23} &= P_{12}^T(\theta)G(\theta) + \xi\Lambda(\theta) \\ M_{33} &= -2\Lambda(\theta). \end{aligned} \tag{14}$$

Then, $\Theta \subseteq \Theta_{stable}(\gamma)$.

Proof: Let us observe that, whenever the constraints in (12) hold, for all $\theta \in \mathbb{R}^r$ one has that

$$\begin{cases} -M(\theta) - \sum_{i=1}^{r} t_i(\theta)U_i(\theta) - \varepsilon I \geq 0 \\ P(\theta) - \varepsilon I \geq 0 \\ \rho(\theta)I - P_{11}(\theta) - \varepsilon I \geq 0 \\ \Lambda(\theta) \geq 0 \\ U_i(\theta) \geq 0. \end{cases} \tag{15}$$

Since $\varepsilon > 0$, it follows that

$$\begin{cases} -M(\theta) - \sum_{i=1}^{r} t_i(\theta)U_i(\theta) > 0 \\ P(\theta) > 0 \\ \rho(\theta)I - P_{11}(\theta) > 0 \\ \Lambda(\theta) \geq 0 \\ U_i(\theta) \geq 0. \end{cases} \tag{16}$$

Consider any $\theta \in \Theta$. Since $t_i(\theta) \geq 0$ and $U_i(\theta) \geq 0$, it follows that

$$\begin{cases} -M(\theta) > 0 \\ P(\theta) > 0 \\ \rho(\theta)I - P_{11}(\theta) > 0 \\ \Lambda(\theta) \geq 0. \end{cases} \tag{17}$$

From [27], we conclude that the system (11) is stochastically stable with disturbance attenuation γ.

B. SOS Matrix Polynomials

In this section we explain how the condition of Theorem 1 can be checked with convex optimization. First of all, let $Q(\theta) \in \mathbb{R}^{n \times n}$ be a matrix polynomial of degree $2m$ in $\theta \in \mathbb{R}^r$. We can express $Q(\theta)$ according to the square matrix representation (SMR) as

$$Q(\theta) = \Delta(\bar{Q} + L(\alpha), \theta^{\{m\}}, I) \tag{18}$$

where $\Delta(\bar{Q}+L(\alpha),\theta^{\{m\}},I)$ denotes the notation

$$\Delta(\bar{Q}+L(\alpha),\theta^{\{m\}},I)=(\theta^{\{m\}}\otimes I)^T(\bar{Q}+L(\alpha))\cdot(\theta^{\{m\}}\otimes I), \tag{19}$$

$\bar{Q}=\bar{Q}^T\in\mathbb{R}^{n\sigma(q,m)\times n\sigma(q,m)}$ is such that

$$Q(\theta)=\Delta(\bar{Q},\theta^{\{m\}},I), \tag{20}$$

$L(\alpha)=L(\alpha)^T$ is a linear parametrization of

$$\mathcal{L}=\{L=L^T\in\mathbb{R}^{n\sigma(q,m)\times n\sigma(q,m)}:\ \Delta(L,\theta^{\{m\}},I)=0,\ \ \forall\theta\in\mathbb{R}^r\} \tag{21}$$

and $\alpha\in\mathbb{R}^{\mu(q,n,m)}$ is a free vector with dimension

$$\mu(q,n,m)=\frac{1}{2}n(\sigma(q,m)(n\sigma(q,m)+1)-(n+1)\sigma(q,2m)). \tag{22}$$

The SMR allows one to establish whether $Q(\theta)$ is SOS, i.e.,

$$Q(\theta)=\sum_i N_i(\theta)^T N_i(\theta) \tag{23}$$

for some matrix polynomials $N_i(\theta)$. Indeed, $Q(\theta)$ is SOS if and only if there exists α and satisfying the LMI

$$\bar{Q}+L(\alpha)\geq 0 \tag{24}$$

which can be established by solving a convex optimization problem.

See also [29] for further details on SOS polynomials and the SMR.

Hence, the condition of Theorem 1 can be checked with a system of LMIs by imposing that the matrix polynomials in (12) are SOS with the SMR according to (24).

C. Estimation Algorithm

Now, let us consider the estimation of the stable uncertainty set with disturbance attenuation $\Theta_{stable}(\gamma)$. The idea is to use Theorem 1 to check the stability of the GRN with disturbance attenuation over hyperrectangles. Specifically, if stability with disturbance attenuation γ can be ensured over a given hyperrectangle, then such hyperrectangle is guaranteed to belong to $\Theta_{stable}(\gamma)$. Otherwise, the hyperrectangle is divided into a number of smaller hyperrectangles, and the procedure is recursively performed for each hyperrectangle.

Hence, let us denote with S the generic hyperrectangle with extremes $\theta^-,\theta^+\in\mathbb{R}^r$, i.e.,

$$S=\{\theta\in\mathbb{R}^r:\theta_i\in[\theta_i^-,\theta_i^+],i=1,...,r\}. \tag{25}$$

Let us observe that Θ coincides with S by choosing

$$t_i(\theta)=(\theta_i-\theta_i^-)(\theta_i^+-\theta_i),\ i=1,...,r. \tag{26}$$

Let us denote with $LMI(S)$ the system of LMIs built for checking the condition of Theorem 1 with such a choice for $t_i(\theta)$. Let l be a nonnegative integer, and define the sought algorithm $E=EST(S,l)$ as follows:

Step 1: If $l=0$, set $E=\varnothing$ and exit.

Step 2: If $LMI(S)$ holds, set $E=S$ and exit.

Step 3: Divide S into disjoint hyperrectangles $S_1,...,S_k$.

Step 4: Set $E=\bigcup_{i=1}^{k}EST(S_i,l-1)$ and exit.

The above algorithm is started with an initial hyperrectangle S_{INI}, chosen sufficiently large in order to contain $\Theta_{stable}(\gamma)$ if possible. In fact, the estimate returned by the algorithm is a inner estimate of S_{INI}, i.e.

$$E\subseteq S_{INI}. \tag{27}$$

The parameter l is an integer that defines the accuracy of the estimate. In particular, the larger l the more accurate is the estimate.

IV. EXAMPLES

In this section we present some numerical examples in order to demonstrate the main steps of the proposed algorithm.

A. Example 1

Let us consider system (6) with $H=2$, $\beta=1$, $n=2$, $r=2$ and

$$A(\theta)=\begin{bmatrix}-0.9+0.5\theta_1 & 0\\ 0 & -1\end{bmatrix}$$

$$C(\theta)=\begin{bmatrix}-0.8-0.3\theta_1 & 0\\ 0 & -1+0.4\theta_1\end{bmatrix}$$

$$D(\theta)=\begin{bmatrix}0.9+0.2\theta_1 & 0\\ 0 & 1+0.3\theta_1\end{bmatrix}$$

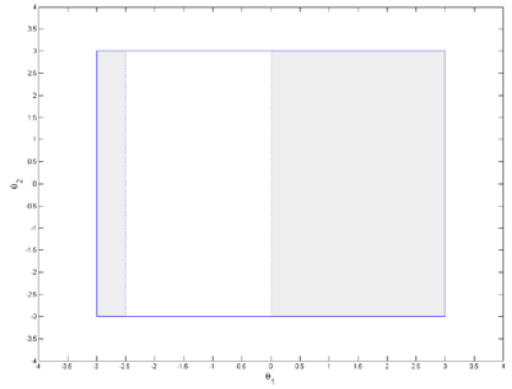
$$G(\theta)=\begin{bmatrix}0 & -0.1-0.4\theta_2\\ -0.9+0.5\theta_2 & 0\end{bmatrix}.$$

It is easy to know that ξ is less than 0.65 in the sector condition (2), and we set the noise intensity $\varphi(x(t),y(t))$ as

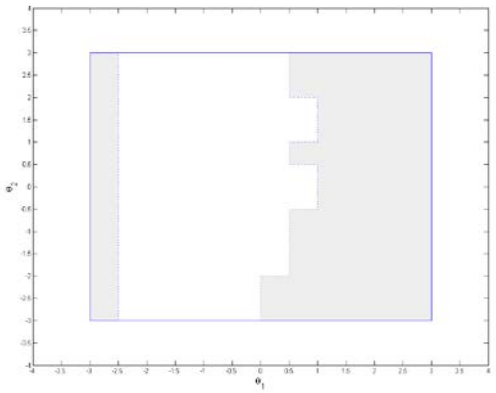
$$\varphi_i(x(t),y(t))=0.05[x_i(t)+\sum_{j=1}^{2}y_j(t)]\ \ \forall i. \tag{28}$$

Then, let us consider the proposed algorithm in Section III. We select a guaranteed disturbance attenuation $\gamma=5$, and

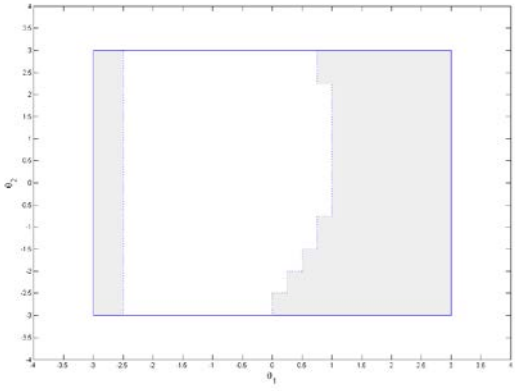
choose $H_1 = H_2 = 0.1I$. Since $r = 2$, we have $\theta_i \in \mathbb{R}^2$. With $l = 1$, let us check the stability condition $LMI(S)$ within the area $\theta_1 \in [-4,4]$, $\theta_2 \in [-4,4]$, i.e., S_{INI} , then the stable uncertainty set E we get in this step is shown in Figure 1a. With $l = 2$, we divide the rectangle S into smaller rectangles S_i , and the stable uncertainty set E we get in this step is shown in Figure 1b. Proceeding in this way, with $l = 3$ we continue to divide the rectangles into smaller ones, and the stable uncertainty set E we get in this step is shown in Figure 1c.



(a)



(b)



(c)

Figure 1. Example 1: With γ=5, estimates of the steady states with (a): l=1, (b): l=2, (c): l=3. Within the rectangle: white-stable area, gray-undecided area (maybe stable or may not). Outside the rectangle: unstable area.

B. Example 2

In this example we illustrate the application of the proposed algorithm to a real biological system, specifically the repressilator which has been investigated in *Escherichia coli* [30]. In this system, the repressilator is a cyclic negative-feedback loop comprising three repressor genes (*lacl*, *tetR* and *cl*) and their promoters and has the form

$$\begin{cases} \dfrac{dm_i(t)}{dt} = -m_i(t) + \alpha_i^{rep}(1 - f(p_i(t))) \\ \dfrac{dp_i(t)}{dt} = -\beta_i^{rep}(p_i(t) - m_i(t)) \\ i = lacl, tetR, cl \\ j = cl, lacl, tetR \end{cases} \tag{29}$$

where the activation function $f(\cdot)$ is with Hill form

$$f_i(p(t)) = \frac{p_i(t)^H}{1 + p_i(t)^H}. \tag{30}$$

In (29) $m_i(t)$ and $p_i(t)$ are the concentrations of the three mRNAs and repressor-proteins. Now, let us consider the network parameters α_i^{rep} and β_i^{rep} over a set of possible coefficients, in particular

$$\begin{aligned} \alpha_1^{rep} &= 0.8 + 0.3\theta_1 - 0.4\theta_2 \qquad \beta_1^{rep} = 0.5 \\ \alpha_2^{rep} &= 0.5 + 0.3\theta_1 + 0.2\theta_2 \qquad \beta_2^{rep} = 1 \\ \alpha_3^{rep} &= 1 - 0.5\theta_1 + 0.2\theta_2 \qquad \beta_3^{rep} = 1.5. \end{aligned} \tag{31}$$

By rewriting this repressilator in the form of the system (6): we have $H = 2$, $n = 3$, $r = 2$ and

$$A(\theta) = \begin{bmatrix} -1 & 0 & 0 \\ 0 & -1 & 0 \\ 0 & 0 & -1 \end{bmatrix}$$

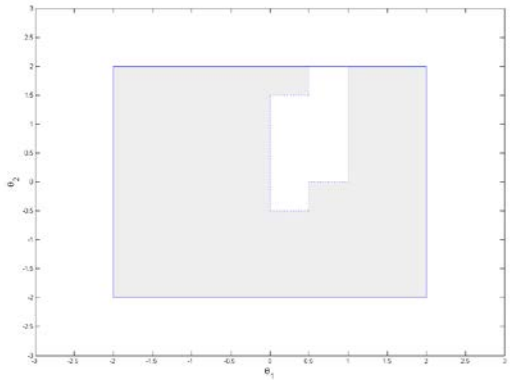
$$C(\theta) = \begin{bmatrix} -0.5 & 0 & 0 \\ 0 & -1 & 0 \\ 0 & 0 & -1.5 \end{bmatrix}$$

$$D(\theta) = \begin{bmatrix} 0.5 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1.5 \end{bmatrix}$$

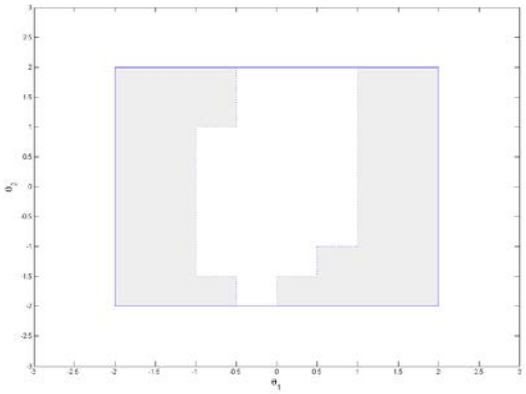
$$G(\theta)_{i,j} = \begin{cases} -0.8 - 0.3\theta_1 + 0.4\theta_2 & if\ (i,j) = (1,3) \\ -0.5 - 0.3\theta_1 - 0.2\theta_2 & if\ (i,j) = (2,1) \\ -1 + 0.5\theta_1 - 0.2\theta_2 & if\ (i,j) = (3,2) \\ 0 & otherwise. \end{cases}$$

Then, let us consider the proposed algorithm in Section III. Let us select $H_1 = H_2 = 0.1I$ and $r = 2$. With $l = 1$, let us check the stability conditions $LMI(S)$ within S_{INI} ($\theta_1 \in [-3,3]$, $\theta_2 \in [-3,3]$) with different guaranteed

disturbance attenuation γ . By choosing $\gamma = 1.2$, the estimated stable uncertainty set E is shown in Figure 2a. By choosing $\gamma = 1.3$, the estimated stable uncertainty set E is shown in Figure 2b. We hence conclude that, with the same size of the rectangle S , by choosing different guaranteed disturbance attenuation γ, we will have different estimated stable uncertainty set E .



(a)



(b)

Figure 2. Example 2: With l=1, estimates of the steady states with different guaranteed disturbance attenuation γ. (a): γ=1.2. (b): γ=1.3. Within the rectangle: white-stable area, gray-undecided area (maybe stable or may not). Outside the rectangle: unstable area.

V. CONCLUSION

This paper has addressed the problem of the estimation of stable uncertainty sets with guaranteed disturbance attenuation for uncertain GRNs. Specifically, it has been shown that estimates of the sought stable uncertainty sets can be obtained through a recursive strategy based on parameter-dependent Lyapunov functions and convex optimization. Some examples with fictitious and real biological models have been used to illustrate the use of the proposed strategy.

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