

A Secant Condition for Cyclic Systems with Time Delays and its Application to Gene Regulatory Networks

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Abstract: A stability condition is derived for cyclic systems with time delayed negative feedback. The result is an extension of the so-called secant condition, which is originally developed for systems without time delays. This extension of the secant condition gives a new local stability condition for a model of GRNs (Gene Regulatory Networks) under negative feedback. Stability robustness of homogenous networks is also investigated.

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1. INTRODUCTION

Let us consider an n th order linear time invariant plant consisting of cascade connections of n stable first order filters whose DC gains are normalized to unity and pole locations are $s = -\lambda_i, i = 1, \dots, n$. Assume that this plant is in negative feedback with a static controller whose gain is $k > 0$, and let $\tau > 0$ be the time delay in the feedback loop. Then, the characteristic polynomial of this feedback system is

$$\chi(s) = \prod_{i=1}^n \left(\frac{s}{\lambda_i} + 1 \right) + ke^{-\tau s}. \quad (1)$$

Clearly, by the small-gain theorem, the feedback system is stable independent of time delay if $k < 1$. However, it is well known that the small-gain condition is conservative in general. In other words, there are (k, τ) pairs with $k > 1$, and $\tau \geq 0$, for which the feedback system is stable. For the case where λ_i 's are distinct, analytic computation of the exact stability region may not be possible, and one resorts to graphical/numerical methods such as Nyquist or Bode plots, see e.g. Özbay (1999) and Michiels and Niculescu (2007).

For the delay-free systems the secant condition, see e.g. Sontag (2006), is less conservative than the small-gain condition. Accordingly, when $\tau = 0$, the feedback system is stable if the following condition holds:

$$k \leq \left(\sec \frac{\pi}{n} \right)^n. \quad (2)$$

The inequality (2) is known as the secant condition. Note that when $n = 1$ or $n = 2$, under $\tau = 0$, the system is stable for all $k \in \mathbb{R}_+$. So, the problem of finding a stability

range for k becomes more interesting when $n \geq 3$. On the other hand, $\left(\sec \frac{\pi}{n} \right)^n > 1$ for $n \geq 3$, so the secant condition is less conservative than the small gain condition: 8 to 2 times less conservative for n between 3 and 7, respectively, see Figure 1.

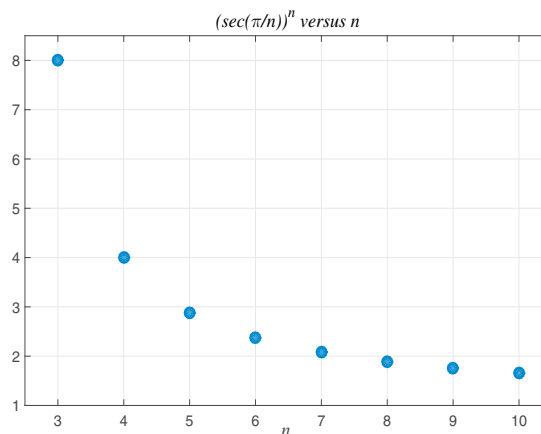


Fig. 1. The secant condition is less conservative than the small gain condition.

In this paper, the secant condition is extended to include time delays. That leads to a condition on stability of the feedback system whose characteristic equation is in the form (1). Moreover, this result is applied to a time-delayed cyclic dynamical network representing Gene Regulatory Networks (GRNs) under negative feedback, to derive conditions regarding local stability of the network. This problem was considered earlier in Ahsen et al. (2014a). Due to a sign mistake in Ahsen et al. (2014a) the local stability condition presented there (Lemma 6) is *valid only for the*

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positive feedback case. Here we correct this mistake and provide a local stability analysis for the *negative feedback case.* Further discussion on this topic can be found in the recent book Ahsen et al. (2015). Another problem investigated in the present paper is stability robustness for homogenous GRNs under negative feedback. A stability condition was derived in Ahsen et al. (2015) for homogenous networks with a special Hill type of nonlinearity. Here we examine how much deviation from homogeneity can be tolerated.

In the next section, some notation and preliminary results are given. An extension of the secant condition to systems with time delays is presented in Section 3. Applications of this result to local stability of the GRNs are the subject of Section 4. Homogenous GRNs and stability robustness to perturbations in the nonlinear functions is considered in Section 5. Concluding remarks are made in Section 6.

2. NOTATION AND PRELIMINARY RESULTS

The GRNs considered here are cyclic connection of n stable first order filters whose inputs are subject to a static nonlinearity. Typically, in biological systems, these nonlinear functions are Hill type nonlinearities. In this work we will consider a more general class, where the nonlinear functions are assumed to have negative Schwarzian derivatives. In order to set-up the notation for the rest of the paper, in this section, we provide the definition of functions with negative Schwarzian derivatives, see Chapter 3 of Ahsen et al. (2015) for more detailed discussion on relevant properties of such functions.

Let f^m denote the function obtained by m compositions of a given function f . For a function f , the point x is a fixed point if $f(x) = x$. Let a function f be defined from \mathbb{R}_+ to \mathbb{R}_+ . Suppose it is at least three times continuously differentiable. Then, the Schwarzian derivative of the function f , denoted as $Sf(x)$, is given by the following expression, see Sedaghat (2003),

$$Sf(x) = \begin{cases} -\infty & \text{if } f'(x) = 0 \\ \frac{f'''(x)}{f'(x)} - \frac{3}{2} \left(\frac{f''(x)}{f'(x)} \right)^2 & \text{if } f'(x) \neq 0. \end{cases} \quad (3)$$

Some immediate results can be deduced from the above definition as follows.

Lemma 1. Let $I \subseteq \mathbb{R}$ be an interval and suppose $f, h \in D^3(\mathbb{R}_+)$ such that the function $f \circ h$ is well-defined. Suppose also that we have

$$f'(x) \neq 0 \quad \forall x \in (0, \infty), \quad (4)$$

then the following properties hold:

- (1) For any $c \in \mathbb{R}$ and $d \in \mathbb{R} \setminus \{0\}$, $Sf(x) = S(f(x) + c)$ and $Sf(x) = S(df(x))$.
- (2) $S(f \circ h)(x) = Sf(h(x)) \cdot h'(x)^2 + Sh(x)$.
- (3) If $Sf(x) \leq 0$, $Sh(x) < 0$ then $S(f \circ h)(x) < 0$.
- (4) If $Sf(x) < 0 \quad \forall x \in \text{int}(I)$, then $f'(x)$ cannot have positive local minima nor negative local maxima. \square

The proofs of the properties mentioned in Lemma 1 can be found in Sedaghat (2003). From (3), one can

calculate Schwarzian derivatives of some functions that are frequently used in the analysis of biological systems:

$$S\left(\frac{a}{b+x^m}\right) = S\left(\frac{ax^m}{b+x^m}\right) = -\frac{(m^2-1)}{x^2} \quad (5)$$

$$S(p \tanh(qx)) = -2q^2 \quad a, b, p, q \geq 0 \quad m \in \mathbb{N}. \quad (6)$$

We can see that Hill functions, given in equation (5), have negative Schwarzian derivatives for $m \geq 2$. Moreover, tangent hyperbolic functions appearing frequently in neural networks also have negative Schwarzian derivatives.

3. AN EXTENSION OF THE SECANT CONDITION FOR SYSTEMS WITH TIME DELAYS

Consider a linear plant with the following state space representation:

$$\dot{x}(t) = A_0x(t) + Bu(t),$$

$$y(t) = Cx(t)$$

where

$$A_0 = \begin{bmatrix} -\lambda_1 & b_1 & 0 & \cdots & 0 \\ 0 & -\lambda_2 & b_2 & 0 & \cdots & \vdots \\ 0 & 0 & \ddots & \ddots & & 0 \\ \vdots & & \ddots & \ddots & & b_{n-1} \\ 0 & \cdots & \cdots & 0 & & -\lambda_n \end{bmatrix}$$

$$B = [0 \quad \cdots \quad 0 \quad 1]^T$$

$$C = [1 \quad 0 \quad \cdots \quad 0].$$

It is assumed that $\lambda_i > 0$ for $i = 1, \dots, n$, and $b_i \in \mathbb{R}$ for $i = 1, \dots, n-1$. Suppose now we apply a delayed static output feedback control in the form

$$u(t) = b_n y(t - \tau),$$

where b_n is the constant controller gain. Then, the feedback system is described by state space equation

$$\dot{x}(t) = A_0x(t) + A_1x(t - \tau), \quad (7)$$

where $A_1 = b_nCB$. The characteristic polynomial of the feedback system, $\det(sI - A_0 - A_1e^{-\tau s})$, can be computed to be in the form

$$\chi(s) = \left(\prod_{i=1}^n (s + \lambda_i) \right) - \beta e^{-\tau s} \quad (8)$$

$$\beta = \prod_{i=1}^n b_i. \quad (9)$$

In this paper, we assume that the system is under negative feedback, which means that $\beta < 0$. Accordingly, define

$$k := -\frac{\beta}{\prod_{i=1}^n \lambda_i}$$

which is positive. The characteristic function $\chi(s)$ defined in (8) has all its roots in \mathbb{C}_- if and only if the transfer function

$$T(s) := G(s)(1 + G(s))^{-1} \quad (10)$$

is stable, where

$$G(s) = \frac{ke^{-\tau s}}{\prod_{i=1}^n (1 + s/\lambda_i)}$$

is the open loop transfer function. Cyclic systems of the form (7) (where A_0 and A_1 have special structures given above) are frequently encountered in modeling of biological processes such as gene regulation, which is a motivation for the current work, see Ahsen et al. (2014a), Enciso (2007), Hori et al. (2013) and their references for specific examples.

When $k > 0$ and $\tau = 0$, i.e. there is no time delay, the secant condition states that if

$$k < \left(\sec \frac{\pi}{n}\right)^n = \frac{1}{\left(\cos \frac{\pi}{n}\right)^n}, \quad (11)$$

then, the transfer function $T(s)$ is stable.

Next result extends the secant condition for systems with a time delay, i.e. $\tau > 0$. It is also included in our recent book Ahsen et al. (2015).

Proposition 1. Consider the system given by (7), with $\lambda_i > 0$ for $i = 1, \dots, n$, and assume that $k > 1$ (clearly, if $0 < k \leq 1$ then, the feedback system stable for all $\tau \geq 0$). Suppose now τ is fixed and let $\lambda := \max_i \lambda_i$. If

$$k < \left(\sec \frac{\pi}{n}\right)^n, \quad (12)$$

and

$$\tau < \frac{\pi - n \arccos\left(\sqrt[n]{1/k}\right)}{\omega_m} =: \tau_m, \quad (13)$$

where $\omega_m = \lambda \sqrt[n]{k^2} - 1$, then the system (7) is stable.

Proof: The proof is included here for completeness and for setting up the notation for the next section. It is taken from Chapter 5 of Ahsen et al. (2015) with slight modification on the notation.

Let $p_\tau(\omega)$ and $q_\tau(\omega)$ be

$$\begin{aligned} p(\omega) &= \prod_{i=1}^n \sqrt{\left(\frac{\omega}{\lambda_i}\right)^2 + 1}, \\ q_\tau(\omega) &= \sum_{i=1}^n \arctan\left(\frac{\omega}{\lambda_i}\right) + \tau\omega. \end{aligned} \quad (14)$$

Note that both p and q_τ are increasing functions of ω . Let ω_c be the gain-crossover frequency such that $p(\omega_c) = k$. By using the Nyquist criteria for stability, we conclude that $T(s)$ is stable if

$$q_\tau(\omega_c) < \pi. \quad (15)$$

Now assume that (12) holds so the delay free system is asymptotically stable by the secant condition. Let

$$\theta_i = \arctan\left(\frac{\omega_c}{\lambda_i}\right).$$

Since each θ_i is positive, by the definition of tangent inverse function we have $\theta_i \in (0, \pi/2)$ for all i . The system remains stable if

$$\tau\omega_c < \pi - \sum_{i=1}^n \theta_i.$$

Note that

$$\cos(\theta_i) = \sqrt{\frac{\lambda_i^2}{\lambda_i^2 + \omega_c^2}},$$

so we have

$$\frac{1}{\prod_{i=1}^n \cos(\theta_i)} = k.$$

Similar to Sontag (2006), we use the fact that

$$\prod_{i=1}^n \cos(\theta_i) \leq \left(\cos\left(\frac{\sum_{i=1}^n \theta_i}{n}\right)\right)^n, \quad (16)$$

so we have

$$k = \frac{1}{\prod_{i=1}^n \cos(\theta_i)} \geq \frac{1}{\left(\cos\left(\frac{\theta_1 + \dots + \theta_n}{n}\right)\right)^n}.$$

The above equation implies that

$$\sum_{i=1}^n \theta_i \leq n \arccos\left(\sqrt[n]{1/k}\right). \quad (17)$$

Therefore,

$$\pi - n \arccos\left(\sqrt[n]{1/k}\right) \leq \pi - \sum_{i=1}^n \theta_i.$$

Hence, if $\tau\omega_c < \pi - n \arccos\left(\sqrt[n]{1/k}\right)$, then the system is stable. Let $\lambda = \max_i \lambda_i$, and define

$$\omega_m = \lambda \sqrt[n]{k^2} - 1.$$

Note that, $\omega_c \leq \omega_m$. Therefore, if

$$\tau < \frac{\pi - n \arccos\left(\sqrt[n]{1/k}\right)}{\omega_m} = \tau_m \quad (18)$$

then the system is stable, which concludes the proof. \square

Note that the necessary and sufficient condition for stability of the system (10) is

$$\tau < \frac{\pi - \sum_{i=1}^n \theta_i}{\omega_c} =: \tau_c. \quad (19)$$

Clearly, $\tau_m \leq \tau_c$, in general. The computation of τ_c can be done numerically; what is preventing us to find an analytical expression like τ_m , (18), is that for a given k , the crossover frequency ω_c can only be determined using numerical tools. On the other hand, when $\lambda_i = \lambda$ for all $i = 1, \dots, n$, the gain crossover frequency ω_c can be computed analytically as $\omega_c = \omega_m$. Moreover, in this case the inequality (16) becomes equality which implies that $\tau_c = \tau_m$. In other words, for the case $\lambda_i = \lambda$ for all i , the secant condition derived in Proposition 1 becomes necessary and sufficient for feedback system stability. See e.g. Arcak and Sontag (2006), Arcak and Sontag (2008), Sontag (2006), and references therein for further discussions on the interpretations of the secant condition. It should also be pointed out that a different version of the secant condition obtained here was derived in Wagner and Stolovitzky (2008). This point is discussed in the next section with an example.

4. A MATHEMATICAL MODEL REPRESENTING GENE REGULATORY NETWORKS

The cyclic feedback model we study in this paper is given as:

$$\begin{cases} \dot{x}_1(t) = -\lambda_1 x_1(t) + g_1(x_2(t)) \\ \dot{x}_2(t) = -\lambda_2 x_2(t) + g_2(x_3(t)) \\ \vdots \\ \dot{x}_n(t) = -\lambda_n x_n(t) + g_n(x_1(t - \tau)). \end{cases} \quad (20)$$

We assume that $\lambda_i > 0$ for all $i = 1, \dots, n$, and the nonlinear functions g_i satisfy the following properties for

all i ; $g_i(x)$ is a bounded function defined on \mathbb{R}_+ ; $g'_i(x) < 0$ or $g'_i(x) > 0$, and $Sg_i(x) < 0$ for all $x \in (0, \infty)$. Note that, in general, there may be time delays between each cascade connection above. But they can be handled by a state transformation, and the system can be put in the form (20), where there is a single delay, which is equivalent to total delay in the feedback loop, see Chapter 4 of Ahsen et al. (2015).

Systems of the form (20) is observed in biological systems. Examples arise in the construction of genetic toggle switches, Gardner et al. (2000), and in the repressilator gene networks that generate circadian rhythms, Buse et al. (2010), Elowitz and Liebler (2000). The most important of such networks that can be modeled in the form of (20) are the GRNs; see Ahsen et al. (2014a), Chen and Aihara (2002), Hori et al. (2013) Ma et al. (2005), Morarescu and Niculescu (2008) for the justification of the model and literature survey. Accurate modeling of GRN can help us understand the underlying mechanism of the biological processes; thus, it can provide researchers new tools to control cellular processes, which may lead to better treatments of diseases.

Now define a new function

$$g = \left(\frac{1}{\lambda_1}g_1\right) \circ \left(\frac{1}{\lambda_2}g_2\right) \circ \dots \circ \left(\frac{1}{\lambda_n}g_n\right). \quad (21)$$

An important point to note is that by Lemma 1, $g(x)$ has negative Schwarzian derivative, i.e. $Sg(x) < 0$ holds.

Definition 1. The gene regulatory network (20) is said to be under *negative feedback* if

$$g'(x) < 0 \quad \forall x \in (0, \infty)$$

and it is under *positive feedback* if

$$g'(x) > 0 \quad \forall x \in (0, \infty).$$

In this work we consider the negative feedback case, as in Ahsen et al. (2014a). The positive feedback case has been studied in Ahsen et al. (2014b). Next, we briefly present an equilibrium analysis from Ahsen et al. (2014a), and using the results of the previous section we derive a local stability condition. Due to a sign mistake in Ahsen et al. (2014a) the local stability condition presented there (Lemma 6) is valid only for the positive feedback case. Here we correct this mistake and provide an analysis for the negative feedback case.

The following result illustrates the relation between the equilibrium points of (20) and the fixed points of (21).

Lemma 2. Let $h(x) : \mathbb{R}_+^n \rightarrow Y \subseteq \mathbb{R}_+^n$ be defined as

$$h(x_1, x_2, \dots, x_n) = \begin{pmatrix} \frac{g_1(x_2)}{\lambda_1} \\ \vdots \\ \frac{g_{n-1}(x_n)}{\lambda_{n-1}} \\ \frac{g_n(x_1)}{\lambda_n} \end{pmatrix},$$

where

$$g_i(z_i) : \mathbb{R}_+ \rightarrow Y_i \subseteq \mathbb{R}_+ \quad \forall i = 1, 2, \dots, n.$$

At any equilibrium point x_{eq} of (20), we have $h(x_{eq}) = x_{eq}$. Then, there is a bijection between the fixed

points of the functions h and g . In particular, if g has a unique fixed point, then the system (20) has a unique equilibrium point.

Proof: See Ahsen et al. (2014a). \square

Note that each $g_i(x) > 0$ for $x > 0$, so in order to have an equilibrium in the positive cone \mathbb{R}_+^n , we need $g(0) > 0$. But then, under negative feedback, $g'(x) < 0$ for all $x > 0$; so we have a unique equilibrium point in this case. Let $x_{eq} = [x_1, \dots, x_n]^T$ be the unique equilibrium point of the GRN. Then, the linearization of the GRN around x_{eq} results in a system in the form (7), with

$$b_1 = g'_1(x_2), \dots, b_{n-1} = g'_{n-1}(x_n), b_n = g'_n(x_1).$$

Thus, the characteristic equation of the linearized system is of the form (8) where

$$\beta = g'_1(x_2) \cdots g'_{n-1}(x_n) \cdot g'_n(x_1).$$

It is a simple exercise to check that

$$k = -\frac{\beta}{\prod_{i=1}^n \lambda_i} = -g'(x_1).$$

By the negative feedback assumption, $g'(x_1) < 0$, so, we have $k > 0$, and thus the result of Proposition 1 is applicable for this system. More precisely, (20) is locally stable around its equilibrium $x_{eq} = [x_1, \dots, x_n]^T$ independent of delay, if $|g'(x_1)| < 1$. Furthermore, (20) is locally stable around its equilibrium if

$$\kappa := \sqrt[n]{|g'(x_1)|} < \sec \frac{\pi}{n} \quad (22)$$

and

$$\tau < \frac{\pi - n \arccos(1/\kappa)}{\lambda \sqrt{\kappa^2 - 1}} =: \tau_m \quad (23)$$

where $\lambda = \max\{\lambda_1, \dots, \lambda_n\}$.

It is clear that (22) is equivalent to

$$\cos \frac{\pi}{n} < 1/\kappa,$$

so, $\arccos(1/\kappa) < \pi/n$. Hence $\tau_m > 0$ when (22) holds.

Note that we only provide a local stability result around the unique equilibrium point of the GRN (20). Our results are inconclusive about the global behavior of the system. Nevertheless, in Ahsen et al. (2014a) it is shown that if $|g'(x_1)| < 1$ then the system is *globally stable* around its unique equilibrium point. The small gain condition $|g'(x_1)| < 1$ also implies delay independent stability of the linearized network. However, when $|g'(x_1)| > 1$, we can not make any conclusions regarding the global stability of the system. Our extensive simulations suggest that the local stability of the system also implies the global stability of the network. The proof of such a result would most likely require a modified version of the Poincaré-Bendixson type of result obtained in Mallet-Paret and Sell (1996). See also Ahsen et al. (2015) for further discussions.

Example. See also Exercise Problems at the end of Chapter 5 of Ahsen et al. (2015). Consider the cyclic system:

$$\dot{x}_1(t) = -\lambda_1 x_1(t) + g_1(x_2(t)) \quad (24)$$

$$\dot{x}_2(t) = -\lambda_2 x_2(t) + g_2(x_1(t - \tau)), \quad (25)$$

where $\lambda_1 = 2$ and $\lambda_2 = 0.5$, $g_1(x) = \frac{6}{2+x^2}$, $g_2(x) = \frac{4x^2}{1+x^2}$ and $\tau > 0$. The unique equilibrium point of (24)–(25) is

$x_e = [0.55, 1.86]^T$, so we define $x_1 = 0.55$ and $x_2 = 1.86$. It is easy to verify that the fixed point of $g = (\frac{1}{\lambda_1}g_1) \circ (\frac{1}{\lambda_2}g_2)$ is $x_1 = 0.55$ and $g'(x) < 0$ for all $x > 0$, i.e. the cyclic system is under negative feedback. In particular,

$$k = -\frac{g'_1(x_2) \cdot g'_2(x_1)}{\lambda_1 \cdot \lambda_2} = 1.9447 = -g'(x_1).$$

Hence $\kappa = \sqrt{1.9447} = 1.3945$. Since $\sec(\pi/2) = \infty$, the inequality (22) is automatically satisfied. By using (23) we compute $\tau_m = 0.8227$; whereas the exact delay bound τ_c for local stability around x_e is calculated numerically from the delay margin of the feedback system whose open loop transfer function is $G(s) = \frac{k}{(1+s/\lambda_1)(1+s/\lambda_2)}$ by using the Bode plots and `allmargin` command of Matlab: $\tau_c = 2.3585$. The conservatism introduced here is due to the fact that λ_1 and λ_2 differ by a factor of 4; in this case $\tau_c/\tau_m = 2.87$. We expect that as λ_1 and λ_2 get closer to each other, τ_m increases to τ_c .

Recall from the proof of Proposition 1 that the system is locally stable if

$$\tau < \frac{\pi - n \arccos(1/\kappa)}{\omega_c} \quad (26)$$

where $\kappa = \sqrt[n]{k}$ and ω_c is the solution of the equation

$$k^2 = \left(1 + \frac{\omega_c^2}{\lambda_1^2}\right) \cdots \left(1 + \frac{\omega_c^2}{\lambda_n^2}\right). \quad (27)$$

As mentioned before, analytical computation of ω_c is typically impossible especially when $n \geq 3$ and λ_i 's are distinct. This is the reason why ω_m is determined as an upper bound and it has been used in (18). However, it is possible to determine another bound by re-writing (27) as

$$k^2 - 1 = \frac{\omega_c^{2n}}{\lambda_1^2 \cdots \lambda_n^2} + R(\omega_c)$$

where $R(\omega_c) \geq 0$ for all $\omega_c \in \mathbb{R}_+$, and $R(\omega_c)$ is an increasing function of ω_c . This motivates the definition of $\tilde{\omega}_m$ as the solution of

$$k^2 - 1 = \frac{\tilde{\omega}_m^{2n}}{\lambda_1^2 \cdots \lambda_n^2}$$

that is

$$\tilde{\omega}_m = \tilde{\lambda} \sqrt[2n]{k^2 - 1} \quad \text{where} \quad \tilde{\lambda} = \sqrt[n]{\lambda_1 \cdots \lambda_n}.$$

Clearly, $\omega_c \leq \tilde{\omega}_m$. Thus another estimate of τ_c is

$$\tau < \frac{\pi - n \arccos(1/\sqrt[n]{k})}{\tilde{\lambda} \sqrt[2n]{k^2 - 1}} =: \tilde{\tau}_m, \quad (28)$$

and we have $\tilde{\tau}_m \leq \tau_c$. In conclusion, for finding an estimate of ω_c , rather than taking the maximum of λ_i 's, it may be preferable to use their geometric mean. See Wagner and Stolovitzky (2008) where a similar analysis is conducted.

Returning to the numerical example, we see that $\tilde{\lambda} = 1$, and $\tilde{\omega}_m = 1.2915$; these give $\tilde{\tau}_m = 1.2383$. This represents an improvement in the estimate of τ_c : we now have $\tau_c/\tilde{\tau}_m = 1.9$.

However, we should point out that it is not always possible to compare τ_m and $\tilde{\tau}_m$ as illustrated by the following example. In (24)–(25) let us now take $\lambda_1 = 2$ and $\lambda_2 = 1$. Then, the equilibrium point shifts to $x_1 = 0.7441$, $x_2 = 1.4254$; linearization around this point gives the gain $k = 1.2975$. Then, we compute $\tau_c = 3.1035$, with $\omega_c = 0.7052$; the estimates are $\tau_m = 1.9646$ and $\tilde{\tau}_m =$

1.666. In this particular case using (28) over (18) is not preferable. In conclusion, these two analytical bounds should be computed side by side and the larger one should be used as a lower bound of τ_c .

5. ROBUSTNESS ANALYSIS OF THE HOMOGENEOUS NETWORK

In this section we consider the following homogeneous network

$$\begin{cases} \dot{x}_1(t) = -x_1(t) + g_1(x_2(t)) \\ \dot{x}_2(t) = -x_2(t) + g_2(x_3(t)) \\ \vdots \\ \dot{x}_n(t) = -x_n(t) + g_n(x_1(t - \tau)), \end{cases} \quad (29)$$

with each $g_i(x)$ is given as

$$g_i(x) = \epsilon_i \frac{a}{b + x^m}, \quad (30)$$

where $a > 0$, $b > 0$, and $m \in \mathbb{N}$ with $m \geq 2$, are common constants for each of the nonlinearities; the variables ϵ_i can be seen as perturbations from homogeneity of the network. Note that in order to have negative feedback n should be an odd number. The dependence of the global stability of the network on the parameters ϵ_i is determined by the following.

Proposition 2. Consider the homogenous GRN model given in (29). Let $x_{eq} = [x_1, \dots, x_n]^T$ denote the unique equilibrium point of the system. If for each i we have

$$a \epsilon_i < b \sqrt[m]{\frac{b}{m-1}}, \quad (31)$$

then the system is globally stable around its unique equilibrium point x_{eq} .

Proof: In the light of Proposition 2 of Ahsen et al. (2014a), it is sufficient to show that (31) implies $|g'(x_1)| < 1$. Note that the following equalities hold at the equilibrium point

$$x_i = \epsilon_i \frac{a}{b + x_{i+1}^m} \quad i = 1, \dots, n \quad (32)$$

with $x_{n+1} := x_1$. We can calculate $|g'(x_1)|$ as

$$\begin{aligned} |g'(x_1)| &= \prod_{i=1}^n \frac{\epsilon_i a m x_{i+1}^{m-1}}{(b + x_{i+1}^m)^2} \\ &= \frac{x_1 m x_2^{m-1}}{b + x_2^m} \cdots \frac{x_{n-1} m x_n^{m-1}}{b + x_n^m} \cdot \frac{x_n m x_1^{m-1}}{b + x_1^m} \\ &= \prod_{i=1}^n \frac{m x_i^m}{b + x_i^m} \end{aligned} \quad (33)$$

Now, if the following inequality holds for each i

$$\frac{m x_i^m}{b + x_i^m} < 1 \quad (34)$$

then $|g'(x_1)| < 1$. So, it is sufficient to check that (34) is satisfied for each i . Note that the function $f(x) = \frac{x^m}{b+x^m}$ is monotonically increasing for all $x > 0$. Also, from (32) we have

$$x_i < \epsilon_i a/b.$$

Therefore, if $m f(\epsilon_i a/b) < 1$ then (34) holds. In other words,

$$m \frac{(\epsilon_i a/b)^m}{b + (\epsilon_i a/b)^m} < 1 \quad \forall i = 1, \dots, n \quad (35)$$

implies $|g'(x_1)| < 1$. By re-arranging the terms in the above inequality, it is easy to see that (35) is equivalent to having

$$\epsilon_i a < b \sqrt[m]{\frac{b}{m-1}}, \quad \forall i = 1, \dots, n,$$

which completes the proof. \square

Recall from Ahsen et al. (2014a) that

$$a < \frac{m}{m-1} b \sqrt[m]{\frac{b}{m-1}}$$

is a sufficient condition for $|g'(x_1)| < 1$, when $\epsilon_i = 1$ for all $i = 1, \dots, n$. Therefore, we have introduced some conservatism in order to derive a sufficient condition for global stability when the system deviates from homogeneity. The conservatism comes from the use of the inequality $x_i < \epsilon_i a/b$. In fact, if we use the exact value given in (32), then the above arguments lead to the following result: $|g'(x_1)| < 1$ holds if

$$\epsilon_i a < (b + x_{i+1}^m) \sqrt[m]{\frac{b}{m-1}}, \quad \forall i = 1, \dots, n.$$

Clearly, the above inequality is less conservative than (31), but it involves the values of x_1, \dots, x_n (the coordinates of equilibrium point).

6. CONCLUSIONS

The secant condition derived earlier for delay-free cyclic systems is revisited for the case where there is time delay in the feedback loop. The negative feedback case is considered here, and the result is applied to gene regulatory networks to derive an analytic sufficient condition for the local stability, when the small gain is inconclusive.

The small gain condition for the homogenous GRNs leads to a global stability condition which can be checked by verifying an inequality depending on the parameters of the Hill function defining the nonlinear couplings, Ahsen et al. (2014a). In the present work we have also extended this result by discussing how much we can increase the gain of the Hill function without violating the small gain condition.

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