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Analysis of a Gene Regulatory Network Model With Time Delay Using the Secant Condition

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ABSTRACT A cyclic model for gene regulatory networks with time delayed negative feedback is analyzed using an extension of the so-called secant condition, which is originally developed for systems without time delays. It is shown that sufficient conditions obtained earlier for delay-independent local stability can be further improved for homogenous networks to obtain delay-dependent necessary and sufficient conditions, which are expressed in terms of the parameters of the Hill-type nonlinearity.

INDEX TERMS Gene regulatory networks (GRNs), local stability, negative feedback, secant condition, time delay systems.

I. INTRODUCTION

ONE of the widely studied gene regulatory network (GRN) models is the cyclic nonlinear time delayed feedback system described by n cascaded subsystems as shown in Fig. 1, where each x_i, $i = 1, \ldots, n$, represents a physical quantity that is nonnegative [1]. The feedback is

$$x_{n+1}(t) := x_1(t - \tau) \tag{1}$$

where the time delay $\tau \in \mathbb{R}_+$ is assumed to be known.

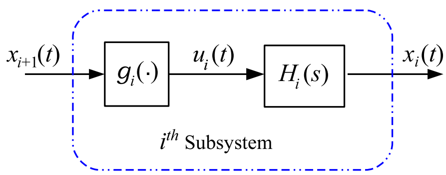

FIGURE 1. Subsystems of the GRN model.

In this model, the linear time-invariant systems represented by $H_i(s)$ (where s is the Laplace transform variable) are bounded analytic functions in $\mathbb{C}_+$. In the sequel, the cascade connections of n subsystems shown in Fig. 1 under feedback (1) will be called the GRN model; specific forms of g_i and H_i considered in this letter are discussed in the following.

The nonlinear functions $g_i : \mathbb{R}_+ \to \mathbb{R}_+$ are bounded, and they satisfy $g_i'(x) > 0$ or $g_i'(x) < 0$ for all $x \in \mathbb{R}_+$. Moreover, it is assumed that the Schwarzian derivative of each g_i is negative, which means that g_i is at least three times continuously differentiable on $\mathbb{R}_+$ and

$$\frac{g_i'''(x)}{g_i'(x)} - \frac{3}{2}\left(\frac{g_i''(x)}{g_i'(x)}\right)^2 < 0 \quad \forall\, x \in \mathbb{R}_+.$$

The left-hand side of the above inequality is the Schwarzian derivative of g_i. Typically, in biological systems, g_i is a Hill function satisfying the above conditions.

An interesting biological example of the GRN defined above is the *repressilator* [8], where three subsystems, in the form of Fig. 1, are connected in cascade, i.e., $n = 3$, with x_i representing mRNA concentrations. The protein concentration at each stage appears as a state variable of $H_i(s)$. It should be noted that a *homogenous network* is proposed in [8] (see also [11, Sec. II-C] for the justification of this model) where

$$H_i(s) = \frac{1}{(1+s)(1+(s/\beta))}$$

and $g_i(x) = \alpha_0 + \alpha/(1+x^m)$, for all $i = 1, 2, 3$. In this letter, α_0 will be taken as zero, and a more general structure for the Hill function is considered

$$g_i(x) = \frac{a}{b + x^m} =: h(x)$$

where $a, b \in \mathbb{R}_+$ and the Hill exponent m is a positive integer, greater or equal to two. The parameter $\beta > 0$ denotes the ratio of the protein decay rate to the mRNA decay rate [8]. In Section III, a similar homogenous network is considered for the special case corresponding to $\beta \to \infty$, i.e., $H_i(s) = (s+1)^{-1}$. This is also consistent with the model studied [6]. Note that in [6], [8], and [11], time delay is ignored. The main objective of this letter is to derive stability conditions of such a network in terms of the network parameters a, b, m, and n, and the feedback delay τ.

For the equilibrium analysis, consider the case where $u_i(t)$ and $x_i(t)$ converge to constant values u_i^e and x_i^e, respectively. Then, from the steady-state analysis of the systems $H_i(s)$, we must have $x_i^e = H_i(0)u_i^e$, where $H_i(0) = k_i$. Therefore, the following function plays a crucial role in the equilibrium and stability analysis of the GRN model defined above:

$$g := (k_1\, g_1) \circ (k_2\, g_2) \circ \cdots \circ (k_n\, g_n). \tag{2}$$

In this letter, the GRN is assumed to be under *negative feedback*

$$g'(x) < 0 \quad \forall x \in (0, \infty). \tag{3}$$

It has been shown that (see [1], [3], [9], and the references therein), in the negative feedback case, g has a unique fixed point $x_1^e \in \mathbb{R}_+$, satisfying $g(x_1^e) = x_1^e$, and hence the GRN has a unique equilibrium point $x_{eq} = [x_1^e, \ldots, x_n^e]^\top$ in $\mathbb{R}_+^n$, where $x_i^e = k_i g_i(x_{i+1}^e)$, $i = 2, \ldots, n$, with $x_{n+1}^e := x_1^e$. Moreover, g is a function with negative Schwarzian derivative, and (3) implies that $|g'(x_1^e)| \neq 1$ (see [1] for a formal proof).

The global asymptotic stability of the GRN is guaranteed by the following sufficient condition:

$$\left|g'\left(x_1^e\right)\right| < 1. \tag{4}$$

Note that inequality (4) is a small gain condition, and it implies stability independent of delay, that is, all solutions $x(t) = [x_1(t) \cdots x_n(t)]^\top$ converge to x_{eq} as $t \to \infty$, for all values of $\tau > 0$. See [1] and [9] for more details.

On the other hand, what happens when $|g'(x_1^e)| > 1$ is an interesting question. In this case, it can be shown that there are some values of $\tau > 0$ leading to periodic solutions (generically); these correspond to locally unstable response around the equilibrium point, x_{eq}. However, the condition $|g'(x_1^e)| > 1$ does not rule out stability: in this case, the system may be locally stable for sufficiently small values of τ. With some additional assumptions on the system, it can be shown that delay-dependent local asymptotic stability implies global asymptotic stability; see [7] and its references where homogeneity is assumed, and [14] where integral quadratic constraints are used.

In this letter, the case $|g'(x_1^e)| > 1$ is revisited. A necessary and sufficient condition is derived for the local stability of the system for the *homogenous network case*. For this purpose, the so-called *secant condition* is used. It has been shown that the secant condition can be very useful in the analysis of cyclic systems with no delays; see [4], [5], and the references therein for further discussions. Briefly, the secant condition gives a less conservative bound on the gain of the feedback system than the bound determined by the small gain condition, for local stability of a cyclic feedback system formed by first-order stable linear time-invariant filters. Recently, a delay-dependent local stability condition for the GRN model considered here has been obtained in [2]; see also [15] for a similar sufficient condition for local asymptotic stability.

In the next section, the secant condition is stated and its relation to GRN model is illustrated. The main result is given in Section III. The repressilator network for a finite β is studied in Section IV.

II. SECANT CONDITION

Let us consider a feedback system formed by a cascade connection of $n \geq 2$ linear time-invariant stable systems

$$\dot{z}_i(t) = -\lambda_i\, z_i(t) + \rho_i\, z_{i+1}(t) \tag{5}$$

for $i = 1, \ldots, n$, under time delayed feedback

$$z_{n+1}(t) = z_1(t - \tau) \tag{6}$$

where $\lambda_i \in \mathbb{R}_+$, $\rho_i \in \mathbb{R}$ for all $i = 1, \ldots, n$, and $\tau \geq 0$. The characteristic equation of this feedback system is

$$\chi(s) := \prod_{i=1}^{n} \left(\frac{s}{\lambda_i} + 1 \right) + k e^{-\tau s} = 0 \tag{7}$$

where

$$k := -\prod_{i=1}^{n} \frac{\rho_i}{\lambda_i} \tag{8}$$

is the dc gain of the system. By definition, the feedback system is under negative feedback if $k > 0$, and it is under positive feedback if $k < 0$.

The feedback systems (5) and (6) are stable if and only if the roots of the characteristic equation (7) are in $\mathbb{C}_-$. There are many different techniques to check if all the roots of $\chi(s)$ are in $\mathbb{C}_-$, or not (see [12] and [10]). The Nyquist test implies that when $k < 0$, i.e., under positive feedback, the system is stable if and only if $-1 < k < 0$. The negative feedback case is more interesting and will be considered in the rest of this letter. When $k > 0$, the feedback system is stable if $|k| \leq 1$ (small gain condition) independent of the values of $\lambda_1, \ldots, \lambda_n$ and the time delay $\tau \geq 0$. On the other hand, the small gain condition is conservative: for $k > 1$, there exist (k, τ) pairs leading to feedback system stability, depending on the values of $\lambda_1, \ldots, \lambda_n$. When λ_i's are distinct, analytic computation of the exact stability region in the (k, τ)-plane may not be possible; in this case, graphical or numerical tools are used. For each fixed k and $\lambda_1, \ldots, \lambda_n$, these numerical tools help us compute the critical value of the time delay, τ_c, such that the feedback system is stable for all $\tau < \tau_c$ and unstable for $\tau \geq \tau_c$.

When $\tau = 0$, the secant condition

$$k \leq \left(\sec \frac{\pi}{n} \right)^n \tag{9}$$

implies feedback system stability under negative feedback. Note that when $n = 2$, inequality (9) is satisfied for all $k \in \mathbb{R}_+$. Furthermore, the right-hand side of (9) is strictly greater than 1 for all $n \geq 3$; more specifically, it takes decreasing values between 8 and 2 as n increases from 3 to 7. Also note that (9) is equivalent to

$$\frac{\pi}{n} > \arccos(\sqrt[n]{1/k}). \tag{10}$$

For time delay systems, i.e., when $\tau > 0$ in (6), earlier analysis shows that (see [1], [2]) the secant condition (9) together with a small delay condition constitutes a sufficient condition for stability of the feedback system. The result is formally stated as follows.

Proposition 1: Consider systems (5) and (6), with $\lambda_i > 0$ for $i = 1, \ldots, n$; assume that τ and k defined in (8) are positive. If $k \leq 1$, then the feedback system is stable independent of delay τ and the parameters $\lambda_1, \ldots, \lambda_n$. Suppose now $k > 1$ and define $\lambda := \max_i \lambda_i$ and $\widetilde{\lambda} := (\prod_{i=1}^n \lambda_i)^{1/n}$. Then, if

$$k < \left(\sec \frac{\pi}{n} \right)^n \tag{11}$$

and

$$\tau < \max\{\tau_m, \widetilde{\tau}_m\} \tag{12}$$

where

$$\tau_m := \frac{\pi - n\arccos(\sqrt[n]{1/k})}{\lambda\sqrt{k^{2/n}-1}} \tag{13}$$

$$\widetilde{\tau}_m := \frac{\pi - n\arccos(\sqrt[n]{1/k})}{\widetilde{\lambda}\sqrt[2n]{k^2-1}} \tag{14}$$

then systems (5) and (6) are stable. Note that by equivalence (10), inequality (11) implies $\tau_m > 0$ and $\widetilde{\tau}_m > 0$. Moreover, when $\lambda_i = \lambda$ for all $i = 1, \ldots, n$, then conditions (11) and (12) are necessary as well, and in this case, $\max\{\tau_m, \widetilde{\tau}_m\} = \tau_m = \tau_c$.

Proof: See [1], [2] and also [14] for a similar result. □

Remark: For a fixed $k > 1$, we have that

$$\sqrt{k^{2/n}-1} \leq \sqrt[2n]{k^2-1}$$

for all integers $n \geq 2$. Thus, $\tau_m \geq \widetilde{\tau}_m$ for the homogenous GRNs, where $\lambda_i = \lambda_j$ for all i, j, in which case $\lambda = \widetilde{\lambda}$. On the other hand, when λ_i's are not uniform, we have $\lambda > \widetilde{\lambda}$, which implies that we *may* have $\tau_m \leq \widetilde{\tau}_m$. □

Let us now consider a GRN model where $H_i(s) = (1/(s+\lambda_i))$. Its linearization around the equilibrium point $x_{eq} = [x_1^e, \ldots, x_n^e]^\top$ leads to a system in the form of (5) and (6) where $z_i(t) = x_i(t) - x_i^e$, $\rho_i = g_i'(x_{i+1}^e)$, for $i = 1, \ldots, n-1$, and $\rho_n = g_n'(x_1^e)$. The characteristic equation of the linearized system around x_{eq} is in the form of (7), where

$$k = -\prod_{i=1}^{n}\frac{\rho_i}{\lambda_i} = -g'\left(x_1^e\right) > 0. \tag{15}$$

Therefore, a sufficient condition for the local asymptotic stability around the unique equilibrium x_{eq} is given by Proposition 1. In particular, for homogenous GRNs, conditions (16) and (17) are necessary and sufficient

$$\sqrt[n]{1/\left|g'\left(x_1^e\right)\right|} =: \kappa > \cos\left(\frac{\pi}{n}\right) \tag{16}$$

$$\frac{\pi - n\arccos(\kappa)}{\lambda\sqrt{\kappa^{-2}-1}} =: \tau_m > \tau. \tag{17}$$

III. HOMOGENOUS GRNS WITH HILL-TYPE NONLINEARITIES

In this section, we consider the homogeneous GRN

$$\begin{cases} \dot{x}_1(t) = -x_1(t) + g_1(x_2(t)) \\ \quad\vdots \\ \dot{x}_n(t) = -x_n(t) + g_n(x_1(t-\tau)) \end{cases} \tag{18}$$

with each $g_i(x)$ being a Hill function of the form

$$g_i(x) := h(x) = \frac{a}{b + x^m} \;:\; \mathbb{R}_+ \to \mathbb{R}_+ \tag{19}$$

where $a > 0$, $b > 0$, and $m \in \mathbb{N}$ with $m \geq 2$ are common constants for each of the nonlinearities. Note that $h'(x) < 0$ for all $x > 0$, and hence the homogeneous network is under negative feedback if and only if n is an odd number.

A local stability condition is derived for (18); it depends only on the parameters a, b, m, τ, and n. This generalizes an earlier result on the delay-independent local stability presented in [1], that is, if $m > 1$ and

$$\left(\frac{a}{m}\right)^m < \left(\frac{b}{m-1}\right)^{m+1} \tag{20}$$

then the homogeneous GRN (18) is locally stable around its unique equilibrium point, independent of delay. The main result given in the following considers the case where (20) is not satisfied.

Proposition 2: Consider the homogenous GRN defined by the set of equations (18) and (19). Let x_1^e be the unique positive root of the polynomial $q(x) = x^{m+1} + bx - a$, and

$$\kappa = \frac{a}{m\left(a - bx_1^e\right)}. \tag{21}$$

If $m > \sec(\pi/n)$ and

$$\left(\frac{b}{m-1}\right)^{m+1} < \left(\frac{a}{m}\right)^m < \left(\frac{b}{m-\sec(\frac{\pi}{n})}\right)^{m+1}\sec\left(\frac{\pi}{n}\right) \tag{22}$$

then the homogenous GRN (18) is locally stable around its unique fixed point for all $\tau < \tau_m$ and it is locally unstable for all $\tau \geq \tau_m$, where

$$\tau_m = \frac{\pi - n\arccos(\kappa)}{\sqrt{\kappa^{-2}-1}} \tag{23}$$

with κ defined in (21). Furthermore, if

$$\left(\frac{a}{m}\right)^m > \left(\frac{b}{m-\sec(\frac{\pi}{n})}\right)^{m+1}\sec\left(\frac{\pi}{n}\right) \tag{24}$$

then systems (18) and (19) are locally unstable independent of the value of τ.

Proof: Since the equilibrium point is unique in $\mathbb{R}_+^n$ [1], in the homogenous case (18), it must be in the particular form $x_{eq} = [x_1^e \cdots x_1^e]^T$, where

$$x_1^e = \frac{a}{b + \left(x_1^e\right)^m}. \tag{25}$$

From Proposition 1, the homogenous GRN (18) exhibits delay-dependent stability around x_{eq} if

$$\left|g'\left(x_1^e\right)\right| < \left(\sec\left(\frac{\pi}{n}\right)\right)^n \iff \left|h'\left(x_1^e\right)\right| < \sec\left(\frac{\pi}{n}\right) \tag{26}$$

where $g(x) = h^n(x)$. The inequalities (26) hold if and only if

$$\begin{aligned} |h'(x_1^e)| \quad &= \quad m\frac{\left(x_1^e\right)^{m+1}}{a} < \sec\left(\frac{\pi}{n}\right) \\ &\iff \frac{a}{bm}\left(m - \sec\left(\frac{\pi}{n}\right)\right) < x_1^e. \end{aligned} \tag{27}$$

Let us define $q(x) = x^{m+1} + bx - a$. Note that $q(x_1^e) = 0$ and $q'(x) > 0$ for all $x \in \mathbb{R}_+$. Therefore, (27) holds if and only if

$$q\left(\frac{a}{bm}\left(m - \sec\left(\frac{\pi}{n}\right)\right)\right) < 0$$

which holds if and only if

$$\left(\frac{a}{m}\right)^m < \left(\frac{b}{m-\sec\left(\frac{\pi}{n}\right)}\right)^{m+1}\sec\left(\frac{\pi}{n}\right).$$

In this particular case, we have

$$k = |h'(x_1^e)|^n = \left(m\frac{a(x_1^e)^{m-1}}{\left(b+(x_1^e)^m\right)^2}\right)^n = \left(m\frac{a-bx_1^e}{a}\right)^n.$$

Thus, $\kappa = \sqrt[n]{1/k}$ is as defined in (21), and the result regarding the delay follows from Proposition 1. Finally, if (24) holds, then the secant condition (11) is violated. Since (11) is necessary for local stability in the homogenous case, inequality (24) leads to local instability independent of delay. □

IV. LOCAL STABILITY ANALYSIS FOR THE REPRESSILATOR

The repressilator model of [8], where $g_i(x) = h(x) = \alpha/(1+x^m)$ and $H_i(s) = H(s) = (1/((s+1)((s/\beta)+1)))$ for all $i = 1, 2, 3$, fits into the framework of (18) when $\beta \to \infty$. Nevertheless, for finite $\beta > 0$, it is still possible to perform a local stability analysis around the unique equilibrium point $x_{eq} = [x_e,\ x_e,\ x_e]^{\mathrm{T}}$, where x_e is the unique positive root of $x^{m+1} + x - \alpha = 0$. Let $\rho = h'(x_e)$, which can be computed as $\rho = m(((x_e)/\alpha) - 1) < 0$. Define

$$k = -\rho = m\left(1 - \frac{x_e}{\alpha}\right) > 0.$$

Then, the linearized system around the equilibrium has the following characteristic equation:

$$1 + k^3(H(s))^3 e^{-\tau s} = 0.$$

If $k < 1$, then the small gain condition is in effect and we have delay-independent stability. Thus, assume now $k > 1$. In this case, local stability condition depends on time delay τ. The gain cross-over frequency ω_c is determined from the equation $|H(j\omega_c)| = 1/k$ as

$$\omega_c = \sqrt{-\frac{\beta^2+1}{2} + \sqrt{\left(\frac{\beta^2+1}{2}\right)^2 + \beta^2(k^2-1)}}.$$

Using the Nyquist criterion, it can be shown that the system is locally stable if and only if

$$\tau < \frac{\pi - 3\theta}{\omega_c} =: \tau_{max} \qquad (28)$$

where $\theta \in (0\ ,\ (\pi/2))$ satisfies

$$\cos(\theta) = \frac{1 - \omega_c^2/\beta}{k}.$$

Note the similarity between (17) and (28). We have $\tau_{max} > 0$ if and only if $\theta < (\pi/3)$. After some algebraic manipulations, it can be shown that $\theta < (\pi/3)$ is equivalent to

$$\frac{1}{2}\left(\beta + \frac{1}{\beta}\right) > \frac{3}{2}\left(\frac{(k/2)^2}{1-(k/2)}\right) - 1. \qquad (29)$$

The special case $\beta = 1$ is interesting because the left-hand side of (29) becomes minimum at this value. When $\beta = 1$ for $k > 1$, we have $\omega_c = (k-1)^{1/2}$, and (29) holds if and only if $k < 4/3$. Note that the condition $k < 4/3$ depends on the parameters α and m: for $m = 2$, $m = 3$, and $m = 4$, the largest allowable α values are 4.23, 1.67, and 1.26, respectively. Accordingly, the largest allowable time delay, τ_{max}, can be computed for the allowable range of α (see Fig. 2) where $m = 2$ and $\beta \to \infty$ case is computed from (23).

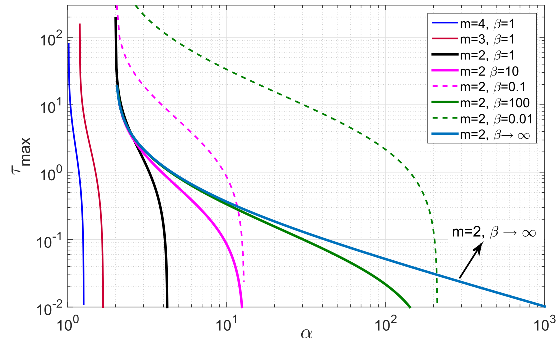

FIGURE 2. τ_{max} **versus** α **for various values of** m **and** β**.**

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