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On the asymptotic behavior of a cyclic biochemical system with delay

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Abstract— The study of the effects of feedback in biochemical circuits is central to the understanding of complex molecular processes such as signal transduction. In this paper, a simple cyclic system with delay is considered, whose nonlinearities are assumed to have a form common in the theory of mass action kinetics. Two possible consequences of this assumption are then discussed, namely either the global convergence to equilibrium, or the existence of periodic solutions for large delay. The work on monotone controlled systems by Sontag and Angeli is central to this discussion, as is the application of Schwarzian derivatives to Michaelis-Menten and Hill nonlinearities.

As a relatively simple example of a biochemical dynamical system with feedback, the following cyclic system with delay is considered in this paper:

$$\begin{aligned} \dot{x}_i &= g_i(x_{i+1}) - \mu_i x_i,\ i = 1 \dots n-1, \\ \dot{x}_n &= g_n(x_1(t-\tau)) - \mu_n x_n, \end{aligned} \tag{1}$$

for $n \geq 1$. Assume that each function g_i is either increasing or decreasing and that the system is subject to negative feedback. More formally, let

$$\mu_i > 0,\ \delta_i g_i'(x) \geq 0,\ \delta_i \in \{1, -1\},\ i = 1 \dots n, \prod_{i=1}^{n} \delta_i = -1. \tag{2}$$

This system can be considered a generalization of classical models, by Goldbeter [10] and Goodwin [11], of autoregulated biochemical networks under negative feedback. Delay systems with this general structure can also be found in the modeling of neural networks, for instance in [19], [28], using $g_i(x) = \alpha_i \tanh(\beta_i x)$ as nonlinearities. It should also be noted that different delays can be introduced in the nonlinear terms of each equation without loss of generality, since all but one of them can be removed with a simple change of variables.

An important special case in biochemical models is that in which those functions $g_i(x)$ which are not linear have the Hill function form

$$f(x) = \frac{ax^m}{b + x^m} + c, \quad \text{or} \quad f(x) = \frac{a}{b + x^m} + c,\ a, b > 0,\ c \geq 0, \tag{3}$$

$m = 1, 2, \dots$. A recent (though undelayed) model within this framework is that of the so-called repressilator, see Elowitz and Leibler [6]. We will give special attention below to this type of nonlinearity.

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The dynamics of the bounded solutions of system (1) under assumptions (2) is governed by a Poincaré-Bendixson result, proved by Mallet-Paret and Sell in 1996 [23]. Informally speaking, for every initial condition the solution of the system approaches either an equilibrium, a periodic orbit, or a homoclinic chain of orbits. In particular, any chaotic behavior is ruled out. In the positive feedback case $\delta_1 \cdot \ldots \cdot \delta_n = 1$, system (1) is monotone and also falls within the framework of Mallet-Paret and Sell. A large number of results are known in that case, the most important one perhaps being that the generic solution is convergent towards an equilibrium [15], [26].

The work of Sontag and Angeli [3] can be used to establish a relationship between the system (1) and the one-dimensional discrete system

$$u_{k+1} = g(u_k), \tag{4}$$

where

$$g(u) := \frac{1}{\mu_1} g_1 \circ \frac{1}{\mu_2} g_2 \circ \ldots \circ \frac{1}{\mu_n} g_n. \tag{5}$$

Namely, if the discrete system (4) is globally attractive towards its unique equilibrium x_0, then the original system (1) is globally attractive towards its unique equilibrium, for all values of the delay τ; see also [8], [7], [9], [2], [27], and Hale and Ivanov [13].

A second branch of study for systems analogous to (1) is the search for nonconstant periodic oscillations. This usually involves a different kind of assumption, namely that the system (1) is 'ejective' around its unique equilibrium for large enough delay. Such arguments usually require the hypothesis $|g'(x_0)| > 1$, which in particular rules out the global attractiveness of (4). See Nussbaum [22], Hadeler and Tomiuk [12], Hale and Ivanov [13], and Ivanov and Lani-Wayda [17], among others.

In the present paper, both approaches are unified to give a more complete picture of the relationship between system (1) (under assumptions (2)) and system (4). A Hopf bifurcation approach is used to prove that $|g'(x_0)| > 1$ implies the existence of periodic solutions of (1) for certain values of τ. Also, an important class of nonlinearities g_i is shown to be such that the following conditions are a dichotomy:

1) The system (4) is globally attractive towards x_0.
2) $|g'(x_0)| > 1$.

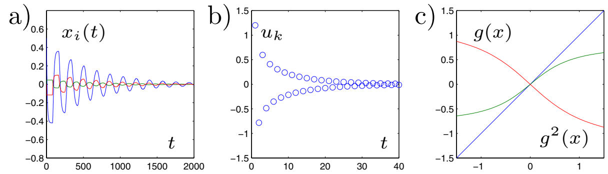

Fig. 1. Typical solutions of a) system (1) and b) system (4), where $n = 3$, $g_1 = g_2 = g_3 = tan^{-1}(x)$, $\mu_1 = 0.11$, $\mu_2 = 2.5$, $\mu_3 = 4$, and $\tau = 80$. c) The induced decreasing function $g(x)$ and the increasing function $g^2(x) = g(g(x))$ (see Lemma 3). Here $|g'(x_0)| = 1/1.1 < 1$.

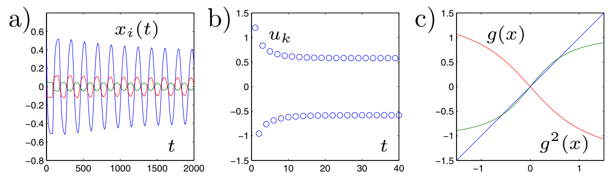

Fig. 2. The same system is considered as in Figure 1, except that the value of μ_1 has been changed to 0.09. The typical solutions of a) system (1) and b) system (4) now appear to be limit oscillations and periodic 2-cycles. c) In this case $|g'(x_0)| = 1/0.9 > 1$ and $g^2(x) = x$ has several solutions.

The main result of this paper is the following theorem, which combines the results from [3], [7] with a Hopf bifurcation approach on the parameter τ.

Theorem 1: Consider system (1) under assumptions (2). Suppose that every nonlinear function $g_i(x)$ is of Hill function form (3), $m \geq 1$. Then exactly one of the following holds:

1) $|g'(x_0)| \leq 1$, system (4) is globally attractive to a unique equilibrium, and system (1) is also globally attractive to a unique equilibrium, for all values of the delay τ.
2) $|g'(x_0)| > 1$, the discrete system (4) has nonconstant periodic solutions, and the continuous system (1) has nonconstant periodic solutions for some values of τ.

The same result holds if, instead of assuming a Hill function form, every nonlinear function $g_i(x)$ is assumed to be of one of the forms $\pm a \tan^{-1}(bx)$, $\pm a \tanh(bx)$, which are used in neural networks applications. A key ingredient is the use of the so-called Schwarzian derivative, see Section I and [24].

The Hopf bifurcation which is present in the second case of Theorem 1 is not shown to be supercritical, although this seems to be the case as suggested by numerical simulations. In fact, simulations suggest that oscillations in system (1) for the case 2. are present for all sufficiently large τ.

It is important to note that this information is not provided a priori by the Poincaré-Bendixson theorem itself, which doesn't give conditions for the different possible outcomes. Even knowing that the equilibrium of (1) is unstable doesn't guarantee the existence of periodic oscillations, since for instance homoclinic orbits need to be ruled out (possibly using Morse decomposition theory [21]).

System (4) is one-dimensional and doesn't contain delays, which makes it much more tractable than (1). The use of the Schwarzian derivative to simplify the behavior of a model is common in the discrete systems literature; see for instance [20] for an application to continuous systems. A Hopf bifurcation approach has also been proposed in the Poincaré-Bendixson context in [30].

The direct contributions of the present paper are i) to show that for an important class of nonlinearities the two alternative cases of this model form a dichotomy; ii) to formally establish a relationship between the discrete and the continuous system, which has already been conjectured by Smith [25] in the undelayed case; iii) to carry out a direct Hopf bifurcation analysis of the linear system associated to (1) (which is new to my knowledge), and iv) to illustrate the usefulness of the Schwarzian derivative in the context of Hill functions.

In Section I the concept of the Schwarzian derivative is briefly introduced and applied to Hill functions. In Section II, the discrete system and its relationship with (1) are described. In Section III the Hopf bifurcation argument is developed. Finally, in Section IV, the relationship with the general results in [3] and [8] is shortly discussed, and a conjecture is described from numerical simulations.

I. Sg and Hill Functions

An important concept related to the stability of discrete dynamical systems is the so-called Schwarzian derivative Sf of a real function f, defined by

$$Sf(x) = \frac{f'''(x)}{f'(x)} - \frac{3}{2}\left(\frac{f''(x)}{f'(x)}\right)^2 .$$

The properties of Sf that will be useful here are summarized in the following lemma; see [24], Section 2B for proofs and details. Intuitively, the condition $Sf < 0$ restricts the form of the function f so that the dynamics of $u_{k+1} = f(u_k)$ is more easily determined.

Lemma 1: Let f, g be C^3 real functions on a real interval. Then the following hold:

1) If $Sf < 0$, then f' cannot have positive local minima or negative local maxima.
2) $S(f \circ g)(x) = Sf(g(x))g'(x)^2 + Sg(x)$.
3) $Sf < 0$, $Sg < 0$ imply $S(f \circ g) < 0$.

It is now shown that the class of functions with negative Schwarzian derivative includes the Hill functions with $m > 1$, and that $S(x/(b + x)) = 0$.

Lemma 2: Let $a, b > 0$, $c \geq 0$, and $m = 1, 2, \ldots$, and define

$$f(x) = \frac{ax^m}{b + x^m} + c, \;\; g(x) = \frac{a}{b + x^m} + c.$$

Then $Sf(x) = Sg(x) = -\frac{m^2 - 1}{2}\frac{1}{x^2}$.

Proof: Noting that the Schwarzian derivative doesn't change after multiplication by or addition of a constant, we can assume that $a = 1,\ c = 0$. Using the quotient rule we compute

$$f'(x) = \frac{mx^{m-1}}{b+x^m} - \frac{mx^{2m-1}}{(b+x^m)^2} = \frac{m}{x}(y-y^2) = \frac{m}{x}y(1-y),$$

where $y = f(x)$. Similarly we compute

$$\begin{aligned} f''(x) &= -\frac{m}{x^2}y(y-1)(2my-(m-1)) \\ f'''(x) &= \frac{m}{x^3}y(1-y)[6m^2y^2+(6m-6m^2)y \\ &\quad +(m-1)(m-2)]. \end{aligned}$$

We calculate the Schwarzian derivative

$$\begin{aligned} Sf(x) &= \frac{f'''(x)}{f'(x)} - \frac{3}{2}\left(\frac{f''(x)}{f'(x)}\right)^2 \\ &= \frac{1}{x^2}[6m^2y^2 - 6m(m-1)y + (m-1)(m-2)] \\ &\quad - \frac{3}{2}\frac{1}{x^2}[4m^2y^2 - 4m(m-1)y + (m-1)^2] \\ &= \frac{1}{x^2}[(m-1)(m-2) - \frac{3}{2}(m-1)^2] = -\frac{m^2-1}{2}\frac{1}{x^2}. \end{aligned}$$

To compute $Sg(x)$, it is easy to see that $g = b^{-1}f\circ\kappa$, where $\kappa(x) = b^{1/m}/x$. A simple computation shows that $S\kappa = S(1/x) = 0,\ x \neq 0$. Therefore

$$\begin{aligned} Sg(x) &= S(f\circ\kappa) = Sf(\kappa(x))\kappa'(x)^2 + S\kappa(x) \\ &= -\frac{m^2-1}{2}x^2\frac{1}{x^4} + 0 = -\frac{m^2-1}{2}\frac{1}{x^2}. \end{aligned}$$

■

II. The Discrete System

Consider a continuous, bounded, decreasing function $g : I \to I$, where $I = \mathbb{R}$ or $I = [a,\infty),\ a \in \mathbb{R}$. It can be easily seen that there is a unique fixed point x_0 of g. The study of the discrete system (4) becomes straightforward by relating its dynamics to that of the system $u_{k+1} = g^2(u_k)$, since the function $g^2(x) = g(g(x))$ is bounded and increasing. We state the following lemma for convenience; see also Angeli and de Leenheer [1] for an extended discussion.

Lemma 3: System (4) is globally attractive if and only if the equation $g(g(x)) = x$ has the unique solution x_0.

Proof: All solutions of the system $u_{k+1} = g(g(u_k))$ are monotonic increasing or decreasing, and each converges towards some fixed point by boundedness and continuity. Furthermore, this system is globally attractive to x_0 if and only if (4) is globally attractive to x_0. The conclusion follows immediately. ■

Let $I = \mathbb{R}$ or $I = [a,\infty)$ and let $g : I \to I$ be differentiable, bounded and decreasing. We say that system (4) is fixed point determined if

$$|g'(x_0)| \leq 1 \Leftrightarrow \text{system (4) is globally attractive towards } x_0.$$

Thus, the global attractiveness of (4) is determined by the slope of $g(x)$ at its unique fixed point. For instance, it was shown in [9] that the functions $g(x) = A/(K+x)$, $x \geq 0$, form fixed point determined systems for every $A, K > 0$, since for such functions system (4) is globally attractive and $|g'(x_0)| < 1$; see also Corollary 1.

An example of a (discontinuous) function which is not fixed point determined is

$$g(x) = \begin{cases} 1, & x < -0.5, \\ 0, & -0.5 \leq x \leq 0.5, \\ -1, & x > 0.5. \end{cases} \qquad (6)$$

This function has the unique fixed point $x_0 = 0$ and $g'(0) = 0$, but there is the obvious stable cycle $g(1) = -1,\ g(-1) = 1$. To obtain a proper example of a differentiable function which is not fixed point determined, it is sufficient to smoothen $g(x)$ above with an appropriate convolution operator.

The reader will have noticed the importance of g being fixed point determined from the discussion leading to the statement of Theorem 1. Nevertheless g is only defined in terms of the functions g_i, and the composition of fixed point determined functions is not necessarily fixed point determined (nor is the composition of merely sigmoidal functions necessarily sigmoidal). This is why the Schwarzian derivative becomes useful at this point.

Lemma 4: Let $g : I \to I$ be C^3, decreasing and bounded, and such that $Sg < 0$. Then g is fixed point determined.

Proof: Consider the increasing function $G = g^2 = g\circ g$, and note that $G'(x_0) = g'(x_0)^2$. If $|g'(x_0)| > 1$, hence $G'(x_0) > 1$, then by boundedness it follows that $G(z) = z$ for some $z > x_0$. Therefore (4) has a nontrivial cycle of period 2, since $g(z) \neq z$.

Conversely, let $G'(x_0) \leq 1$, and assume that $G(z) = z$ for some $z \neq x_0$. Without loss of generality we can assume that $G(y) = y,\ G(z) = z$, for some y, z such that $y < x_0 < z$. We show that there exists y_1 such that $y < y_1 < x_0$ and $G'(y_1) > 1$: otherwise one would have

$$x_0 = G(x_0) = G(y) + \int_y^{x_0} G'(x)\,\mathrm{d}x \leq y + (x_0 - y) = x_0,$$

and in particular $G'(x) = 1$ on $[y, x_0]$. But this would imply $SG = 0$ on that interval, a contradiction. Similarly there exists z_1 such that $x_0 < z_1 < z$ and $G'(z_1) > 1$. Now consider the function $G'(x)$ on the interval $[y_1, z_1]$. Since $G'(x_0) \leq 1$, this function has a minimum w_1 on the interior of this interval, and that therefore $G''(w_1) = 0,\ G'''(w_1) \geq 0$. Thus $SG(w_1) \geq 0$, a contradiction. ■

Corollary 1: Let $I = \mathbb{R}$ or $I = [a,\infty)$, and let $g : I \to I$ be decreasing and bounded. If $g(x)$ is the composition of functions each of which either i) has negative Schwarzian derivative, or ii) is of Hill function form for $m \geq 1$, then g is fixed point determined.

Proof: If g is the composition of functions all of which have negative Schwarzian derivative, then this must be true of g as well, and g is fixed point determined by Lemma 4. The same holds if some of the g_i are of Hill function form with $n > 1$, by Lemma 2. If some but not all of these functions are of Hill function form for

$m = 1$ (or Michaelis-Menten form), then still $Sg(x) < 0$ by the derivation formula in Lemma 1.

Finally, if all the functions are of the form $(\alpha+\beta x)/(\gamma+\delta x)$, $\alpha, \beta, \gamma, \delta \geq 0$, then g and g^2 are also of this form. It is then easy to show that the (bounded, increasing) function $g^2(x)$ is concave down on I, and that it has a unique fixed point x_0 which further satisfies $g'(x_0)^2 = (g^2)'(x_0) \leq 1$. The result follows from Lemma 3. ■

The relationship between the nonlinear system (1) and the discrete system (4) becomes clear in the proof sketch of the following well-studied result. See Angeli and Sontag [2] and Enciso, Smith, and Sontag [7] for an abstract formal treatment, as well as Sontag [27] for a discussion of the embedding argument. The use of the lemma by Dancer in this context is new.

Proposition 1: Consider a system (1) under assumption (2), and let $g(x)$ be defined by (5). If (4) is globally attractive towards x_0, then (1) is globally attractive towards a unique equilibrium.

Sketch of Proof: An elegant result of Dancer [5] shows that in an abstract monotone system with bounded solutions and a unique equilibrium, all solutions must converge towards this equilibrium (the result is stated for discrete systems in [5], but a variation for continuous systems is straightforward). Consider the extended $2n$-dimensional system

$$\begin{aligned} \dot{x}_i &= g_i(x_{i+1}) - \mu_i x_i,\ i = 1 \ldots n-1, \\ \dot{x}_n &= g_n(z_1(t-\tau)) - \mu_n x_n, \\ \dot{z}_i &= g_i(z_{i+1}) - \mu_i z_i,\ i = 1 \ldots n-1, \\ \dot{z}_n &= g_n(x_1(t-\tau)) - \mu_n z_n. \end{aligned} \tag{7}$$

It is not difficult to see that a trajectory $(x_1(t) \ldots x_n(t))$ is a solution of (1) if and only if $(x_1(t) \ldots x_n(t), x_1(t) \ldots x_n(t))$ is a solution of (7). Moreover, this system is now subject to positive feedback, since $\delta_1 \cdot \ldots \delta_n \cdot \delta_1 \cdot \ldots \cdot \delta_n = 1$. Thus this system is monotone with respect to a certain partial order; see [26], Chapter 5, and [4]. Finally, the equilibria of this system are in bijective correspondence with the solutions of $g(g(x)) = x$. The conclusion follows from the result by Dancer and Lemma 3.

III. Hopf Bifurcation

In this section we consider the linearization

$$\begin{aligned} \dot{x}_i &= k_i x_{i+1} - \mu_i x_i,\ i = 1 \ldots n-1, \\ \dot{x}_n &= k_n x_1(t-\tau) - \mu_n x_n, \end{aligned} \tag{8}$$

of system (1) around its unique equilibrium point $(\overline{x}_1, \ldots \overline{x}_n)$. It is easy to see that

$$\begin{aligned} k_i &= g_i'(\overline{x}_{i+1}),\ i = 1 \ldots n-1, \\ k_n &= g_n'(\overline{x}_1). \end{aligned} \tag{9}$$

We will show in the negative feedback case $k_1 \ldots k_n < 0$ that for $|k_1 \cdot \ldots \cdot k_n| > \mu_1 \cdot \ldots \cdot \mu_n$, a Hopf bifurcation exists on the parameter τ. The characteristic polynomial associated to the linear system (8) is

$$g(z, \tau) := (z + \mu_1)(z + \mu_2) \cdot \ldots \cdot (z + \mu_n) + Ke^{-\tau z}, \tag{10}$$

where $K := -k_1 \cdot \ldots \cdot k_n > 0$. See Lemma 3 of Hofbauer and So [16].

Lemma 5: Let $g(\lambda, \tau_0) = 0$ for $\lambda = \sigma + \omega i$, $\tau_0 > 0$, and assume that $\sigma \geq 0$. Then there exists an open neighborhood U of τ_0, and a differentiable function $\rho : U \to \mathbb{C}$, such that $g(\rho(\tau), \tau) = 0$ on U. If $\sigma = 0$, then Re $\rho'(\tau_0) > 0$.

Proof: Define $f(z) := \prod_i (z + \mu_i)$. The proof of the first statement follows by the implicit function theorem for the function $g(z, \tau)$ at the point (λ, τ_0), after verifying that $\partial_1 g(\lambda, \tau_0) \neq 0$:

$$\begin{aligned} \tfrac{\partial g}{\partial z}(\lambda, \tau_0) &= f(\lambda) \textstyle\sum_j \frac{1}{\lambda + \mu_j} - \tau_0 K e^{-\lambda \tau_0} \\ &= -Ke^{-\lambda \tau_0} Q(\lambda, \tau_0), \end{aligned}$$

where

$$Q(\lambda, \tau_0) := \sum_j \frac{1}{\lambda + \mu_j} + \tau_0.$$

Using the fact that $\mu_j \geq 0$ for every j, it is easy to see that Re $Q(\lambda, \tau_0) > 0$ and the proof is complete.

To prove the second statement, let $\sigma = 0$. Note that necessarily $\omega \neq 0$, since $g(z, \tau) > 0$ whenever $z \geq 0$. Assume $\omega > 0$, the other case being similar. Multiplying on both numerator and denominator by $\lambda - \mu_j$, it follows that

$$\text{Im } Q(\lambda, \tau_0) = -\omega \sum_j \frac{1}{\omega^2 + \mu_j^2} < 0.$$

By the implicit function theorem,

$$\rho'(\tau_0) = -\partial_2 g(\lambda, \tau_0)(\partial_1 g(\lambda, \tau_0))^{-1} = -\omega i Q(\lambda, \tau_0)^{-1}.$$

It follows that Re $\rho'(\tau_0) > 0$ as stated. ■

Theorem 2: If $K > \mu_1 \cdot \ldots \cdot \mu_n$ and (1) is not exponentially unstable for $\tau = 0$, then system (1) has a Hopf bifurcation with respect to the parameter τ.

Proof:

We show that there exists $\tau_0 \geq 0$ such that

i) $g(\omega i, \tau_0) = 0$ for some $\omega > 0$,

ii) $g(\lambda, \tau_0) \neq 0$, for all $\lambda \in \mathbb{C}$ with Re $\lambda > 0$,

iii) for some $\omega_0 > 0$, it holds that both $g(\omega_0 i, \tau_0) = 0$ and $g(m\omega_0 i, \tau_0) \neq 0$ for all integer $m \neq 1, -1$.

Together with Lemma 5, this will directly imply the existence of a Hopf bifurcation at the point $\tau = \tau_0$; see Theorem 11.1.1 of Hale [14].

We start with the case in which $g(\omega i, 0) = 0$ for some $\omega \in \mathbb{R}$. Then necessarily $\omega \neq 0$ by definition of g, and without loss of generality $\omega > 0$. Thus i) and ii) are satisfied for $\tau_0 = 0$, by hypothesis. To see iii), simply recall that $g(\omega i, \tau_0) = 0$ implies $|\omega i| < M$, and pick $\omega_0 > 0$ so that $\omega_0 i$ is a root with maximal norm.

We can therefore assume that $g(\lambda, 0) = 0$ implies Re $\lambda < 0$. Let

$$S := \{\tau \geq 0 \,|\, g(\lambda, \tau) = 0 \text{ for some } \lambda \in \mathbb{C} \text{ s.t. Re } \lambda \geq 0\}.$$

so that in particular $0 \notin S$. To see that S is nonempty, first note that whenever $\omega > 0$ and $|f(\omega i)| = K$, one can find $\tau > 0$ such that $e^{-\omega i \tau} = -f(\omega i)/K$ and so $g(\omega i, \tau) = 0$. Noting that $|f(0)| = \mu_1 \cdot \ldots \cdot \mu_n < K$ and $|f(\omega i)| \to \infty$ as $\omega \to \infty$, it follows by the intermediate value theorem that $|f(\omega i)| = K$ for some ω; therefore $S \neq \emptyset$.

Let $\tau_0 := \inf\ S$; it is shown now that $\tau_0 \in S$. Let $\sigma_1 > \sigma_2 > \ldots \to \tau_0$, and let $\lambda_1, \lambda_2, \ldots$ be such that Re $\lambda_i \geq 0$ and $g(\lambda_i, \sigma_i) = 0$ for every i. Let $M > 0$ be such that $|f(z)| > 2K$ for $|z| \geq M$. Then $\left|e^{-\lambda_i \tau}\right| < 1$, and therefore necessarily $|\lambda_i| < M$, for every i. There exists thus a subsequence of $\{\lambda_i\}$ which converges towards $\lambda_0 \in \mathbb{C}$, Re $\lambda_0 \geq 0$. By continuity $g(\lambda_0, \tau_0) = 0$, and $\tau_0 \in S$. In particular $\tau_0 > 0$.

To complete the proof of i) and ii), it suffices to show that $g(\lambda, \tau_0) = 0$, Re $\lambda \geq 0$ imply Re $\lambda = 0$. But this follows directly from Lemma 5, by the minimality of $\tau_0 > 0$.

The proof of iii) follows now in the same way as above. ■

Note that this result is proved in the context of Theorem 11.1.1 of [14]. The existence of periodic solutions for certain values $\tau > \tau_0$ follows, but no assertion is made regarding their stability. This may nevertheless be shown using the above proof, if the asymptotic stability of the equilibrium of (1) is established for $\tau = \tau_0$.

In the particular case $\tau = 0$, it is known [29] that system (8) is asymptotically stable provided that $K/(\mu_1 \cdot \ldots \cdot \mu_n) < \sec^n(\pi/n) = 1/(cos^n(\pi/n))$. Therefore necessarily $\tau_0 > 0$ in those cases.

The following proposition establishes a global stability result for the linear system (8). Let τ_0 be as in the proof of Theorem 2.

Proposition 2: Let $K > \mu_1 \cdot \ldots \cdot \mu_n$ and assume that (1) is not exponentially unstable for $\tau = 0$. Then the linear system (8) is exponentially unstable if and only if $\tau > \tau_0$.

Proof: Recall from Theorem 2 that $0 < \tau_0 = \inf S$, so that for $\tau < \tau_0$, $g(\cdot, \tau)$ can have no root λ with Re $\lambda \geq 0$. Similarly, $g(\cdot, \tau_0)$ can have no root λ with Re $\lambda > 0$, by Lemma 5. Therefore for $\tau \leq \tau_0$, the exponential instability of (8) is ruled out.

Let $S' \subseteq (\tau_0, \infty)$ be the set of $\tau \geq 0$ such that system (8) is exponentially unstable. It follows from $g(i\omega, \tau_0) = 0$, $\mathrm{Re}\, \rho'(\tau_0) > 0$ (Theorem 2, Lemma 5) that $(\tau_0, \tau_0 + \epsilon) \subseteq S'$ for some $\epsilon > 0$. Assume by contradiction that $S' \neq (\tau_0, \infty)$, and let τ_1 be the infimum of $(\tau_0, \infty) - S'$. In particular, it holds that $\tau_1 \geq \tau_0 + \epsilon > \tau_0$. It holds nevertheless that $\tau_1 \in S$ (see the proof of Theorem 2), therefore $g(i\omega_1, \tau_1) = 0$ for some $\omega_1 \geq 0$. Applying Lemma 5 to construct a corresponding function ρ_1 on a neighborhood of τ_1 such that $\mathrm{Re}\, \rho_1'(\tau_1) > 0$, a contradiction follows from $(\tau_0, \tau_1) \subseteq S'$. ■

The following lemma, which addresses the undelayed system in the unstable case, will be used in the proof of the main result.

Lemma 6: Under the assumptions of Theorem 1, assume that (1) is exponentially unstable for $\tau = 0$. Then there exist nonconstant periodic solutions of (1), $\tau = 0$.

Proof: The undelayed cyclic system (1) has been considered extensively in the literature. To prove this result we apply Theorem 4.1 b) of Mallet-Paret and Smith [18]. In order satisfy its hypotheses, we note that any root of $g(*, 0)$ with positive real part cannot be real, therefore at least two roots with positive real part are present. Second, we note that $\bar{x}_1 > 0, \ldots \bar{x}_n > 0$ under the present hypotheses, and that therefore $U_{k_0} \neq \emptyset$ in that result. ■

A similar argument can be given for $g_i(x) = \pm a \tan^{-1}(bx)$, $g_i(x) = \pm a \tanh(bx)$ using a suitable change of variables so that $(\mathbb{R}^+)^n$ is invariant for (1).

A. Proof of Theorem 1

Now the proof of the main result can be completed, as well as the remark which follows it.

Proof: It is a standard result that the functions $a \tan^{-1}(bx)$, $a \tanh(bx)$, $a \in \mathbb{R}$, $b > 0$, have negative Schwarzian derivative at every point, see [24].

Let x_0 be the unique fixed point of $g(x)$. The first case corresponds to the situation in which $|g'(x_0)| \leq 1$. Since (4) is fixed point determined by Corollary 1 and Lemma 4, it holds that (4) is globally attractive to equilibrium. By Proposition 1, system (1) is also globally attractive towards a unique equilibrium.

Assuming now $|g'(x_0)| > 1$, system (4) must have a periodic solution since it is fixed point determined. Evaluating $g'(x)$ using the chain rule yields that $K > \mu_1 \cdot \ldots \cdot \mu_n$. If (1) is exponentially unstable around its equilibrium for $\tau = 0$, there exist periodic solutions of (1) for $\tau = 0$, by Lemma 6. Otherwise, one can use Theorem 2 to conclude that a Hopf bifurcation occurs with respect to the parameter τ. ■

IV. Future Work

The framework of Angeli and Sontag [3] and Enciso, Smith and Sontag [7] describes quite general dynamical systems as the negative feedback loop of controlled monotone systems. Sufficient conditions are then given for the system to be globally attractive to equilibrium, even in the presence of delays or diffusion terms. Theorem 1 can potentially be used to extend these results to the case of periodic oscillations, as well as to show that the original results are sharp in some sense. It is not the first time that this is suggested. For instance, Angeli and Sontag [2] have pointed out that if the associated discrete system has a 2-cycle, then large enough delays would create the appearance of oscillatory behavior (or pseudooscillations), which in a biological system might be as meaningful as proper periodic oscillations.

The analysis of the asymptotic behavior of the system considered in this paper is far from complete. If the system falls into the second case of the main theorem, simulations suggest that for $\tau > \tau_0$ the system is in fact globally attractive towards a unique nonconstant periodic solution. Work towards such a result would most likely include the use of the Poincaré-Bendixson result, for example by finding a Morse decomposition of the system and ruling out the existence of homoclinic orbits.

Finally, note that the need for the assumption $Sg < 0$ can be traced back to the particular approach used to prove the existence of periodic oscillations (Hopf bifurcation), in the following sense: if one could prove the existence of periodic oscillations of (1) based solely on the existence of a stable periodic 2-cycle of (4), then the proof of the main theorem wouldn't have to require that g is fixed point determined, and the assumption $Sg < 0$ could be dropped. Indeed, it has been observed in numerical simulations that whenever there is a stable 2-cycle of (4), then there is also a limit cycle of (1) for large enough τ — even when $Sg \not< 0$. This has been numerically observed to be also true in more complex noncyclic systems in the framework of [7]. Note that the proof of the existence of periodic solutions would require to abandon any obvious use of Hopf bifurcation or ejective fixed point methods, since it could not be required that $|g'(x_0)| > 1$.

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