A dichotomy for a class of cyclic delay systems

Germán Andrés Enciso

February 5, 2008

Abstract: Two complementary analyses of a cyclic negative feedback system with delay are considered in this paper. The first analysis applies the work by Sontag, Angeli, Enciso and others regarding monotone control systems under negative feedback, and it implies the global attractiveness towards an equilibrium for arbitrary delays. The second one concerns the existence of a Hopf bifurcation on the delay parameter, and it implies the existence of nonconstant periodic solutions for special delay values. A key idea is the use of the Schwarzian derivative, and its application for the study of Michaelis-Menten nonlinearities. The positive feedback case is also addressed.

Key Words: delay systems, Schwarzian derivative, Michaelis-Menten functions, negative feedback, Hopf bifurcation.

Consider the cyclic nonlinear system

\[ \begin{align*} 
\dot{x}_i &= g_i(x_{i+1}) - \mu_i x_i, \quad i = 1 \ldots n - 1, \\
\dot{x}_n &= g_n(x_1(t-\tau)) - \mu_n x_n, 
\end{align*} \]

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

\[ \mu_i > 0, \quad \delta_i g_i'(x) \geq 0, \quad \delta_i \in \{1, -1\}, \quad i = 1 \ldots n, \text{ and } \delta_1 \ldots \delta_n = -1. \]
This system can be considered a generalization of classical models, by Goldbeter [1] and Goodwin [2], 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 [3, 4], 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 Michaelis-Menten form

\[
\begin{align*}
  f(x) &= \frac{ax^m}{b + x^m} + c, \quad \text{or} \quad f(x) = \frac{a}{b + x^m} + c, & a, b > 0, & c \geq 0, & m = 1, 2, \ldots. \quad (3)
\end{align*}
\]

A recent (though undelayed) model within this framework is that of the so-called repressilator, see Elowitz and Leibler [5]. We will give especial attention below to this type of nonlinearity.

The dynamics of the bounded solutions of system (1) under assumptions (2) is governed by a Poincare-Bendixson result, proved by Mallet-Paret and Sell in 1996 [6]. 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 [7, 8].

The work of Sontag and Angeli [9] can be used to establish a relationship between the system (1) and the one-dimensional discrete system

\[
  u_{k+1} = g(u_k),
\]

where

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

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 \( \tau \); see also [10 11 12 13 14], and Hale and Ivanov [15].
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 [16], Hadeler and Tomiuk [17], Hale and Ivanov [15], and Ivanov and Lani-Wayda [18], among others.

In the present paper, both approaches are unified to give a more complete picture of the relationship between system (11) (under assumptions (2)) and system (4). A Hopf bifurcation approach is considered to prove that \(|g'(x_0)| > 1\) implies the existence of periodic solutions of (1) for certain values of \(\tau\). Also, an important class of nonlinearities \(g_i\) is shown to be such that the following conditions are a dichotomy:

1. The system (11) is globally attractive towards \(x_0\).
2. \(|g'(x_0)| > 1\).

The main result of this paper is the following theorem, where \(Sg\) denotes the Schwarzian derivative of the function \(g\); see for instance [19].

**Theorem 1** Consider a system (11) under assumptions (2), and let the function \(g(x)\) defined by (5) be bounded. Suppose that all nonlinear functions \(g_i(x)\) are of Michaelis-Menten form (3), \(m \geq 1\), or that \(Sg < 0\). Then exactly one of the following holds:

1. System (11) is globally attractive to a unique equilibrium, and (1) is also globally attractive to a unique equilibrium, for all values of the delay \(\tau\).
2. System (4) contains nonconstant periodic solutions, and system (11) is subject to a Hopf bifurcation on the delay parameter \(\tau\). In particular, (11) contains nonconstant periodic solutions for some values of \(\tau\).

The Hopf bifurcation in the second case is not shown to be supercritical, although this seems to be the case from numerical simulations. Bounded decreasing functions with negative Schwarzian derivative include \(-\tan^{-1}(x)\), \(-\tanh(x)\), and \(e^{-x}\) (on \(\mathbb{R}^+\)), as well as their decreasing compositions. They also include the Michaelis-Menten functions above for \(m > 1\), as is shown here in Lemma 2.
Figure 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 $|g'(x_0)| = 1/1.1 < 1$. 
Figure 2: The same system is considered as in Figure 1 except that the value of $\mu_1$ 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.
It is important to note that this information is not provided \textit{a priori} by the Poincare-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 \cite{20}).

A corresponding theorem will be stated and proved in the positive feedback case $\delta_1 \cdot \ldots \cdot \delta_n = 1$, simplifying a result from Angeli and Sontag \cite{9} in the case without delays, and from Enciso and Sontag \cite{21} in the delay case.

System (4) is one-dimensional and doesn’t contain delays, which makes it much more tractable than (1). The assumption of the negative Schwarzian is a common simplifying hypothesis in the discrete systems literature; see for instance \cite{22} for an application to continuous systems. A Hopf bifurcation approach has also been proposed in the Poincare-Bendixson context in \cite{23}.

The direct contributions of the present paper are i) to show that for an important class of nonlinearities the two alternative cases form a dichotomy; ii) to formally establish a relationship between the discrete and the continuous system, which has already been conjectured by Smith \cite{24} 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 Michaelis-Menten functions.

In Section 1 the concept of the Schwarzian derivative is briefly introduced and applied to Michaelis-Menten functions. In Section 2 the discrete system and its relationship with (1) are described. In Section 3 the Hopf bifurcation argument is developed, and in Section 4 the positive feedback case is considered. Finally, in Section 5 the relationship with the general results in \cite{9} and \cite{10} is shortly discussed, and a conjecture is described from numerical simulations.

\section{Sg and Michaelis-Menten Functions}

An important concept related to the stability of discrete dynamical systems is the so-called \textit{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 [19], 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 cooperative Michaelis-Menten 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

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

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

$$f''(x) = -\frac{m}{x^2} y(y - 1)(2my - (m - 1))$$

$$f'''(x) = \frac{m}{x^3} y(1 - y)[6m^2 y^2 + (6m - 6m^2)y + (m - 1)(m - 2)].$$
We calculate the Schwarzian derivative

\[ S_f(x) = \frac{f'''(x)}{f'(x)} - \frac{3}{2} \left( \frac{f''(x)}{f'(x)} \right)^2 \]

\[ = \frac{1}{x^2} \left[ 6m^2y^2 - 6m(m-1)y + (m-1)(m-2) \right] - \frac{3}{2} \frac{1}{x^2} \left[ 4m^2y^2 - 4m(m-1)y + (m-1)^2 \right] \]

\[ = \frac{1}{x^2} \left[ (m-1)(m-2) - \frac{3}{2} (m-1)^2 \right] = \frac{m^2 - 1}{2x^2}. \]

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

\[ Sg(x) = S(f \circ \kappa) = Sf(\kappa(x))\kappa'(x)^2 + S\kappa(x) = -\frac{m^2 - 1}{2x^4} + 0 = -\frac{m^2 - 1}{2x^2}. \]

## 2 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 [25] 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 \( u_{k+1} = g(u_k) \) 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 **fix 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 fix point. For instance, it was shown in [12] that the functions 

\[
g(x) = \frac{A}{K + x}, \quad x \geq 0,
\]

form fix 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 fix point determined is

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

This function has the unique fix 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 fix 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 fix 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 fix point determined functions is not necessarily fix 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 fix 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 must follow 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 \( y < x < z \). We use here the fact that \( SG < 0 \), by Lemma 4. Suppose first that \( G(x) = x \) on some interval containing \( x_0 \). Then in the interior of this interval it would hold \( G''(x) = G'''(x) = 0 \) and thus \( SG = 0 \) for these points, a contradiction. It is easy to conclude, using the mean value theorem, that there exist constants \( y_1, z_1 \) such that \( y < y_1 < x_0 < z_1 < z \) and \( G'(y_1) > 1, \ G'(z_1) > 1 \). Now consider the function \( G'(x) \) on the interval \([y_1, z_1]\). The results above imply that 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 Michaelis Menten form for $m \geq 1$, then $g$ is fix 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 fix point determined by Lemma 4. The same holds if some of the $g_i$ are of Michaelis-Menten form with $n > 1$, by Lemma 2. If some but not all of these functions are of Michaelis Menten form for $m = 1$, 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 [13] and Enciso, Smith, and Sontag [11] for an abstract formal treatment, as well as Sontag [14] 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 [26] 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 [26], but a variation for continuous systems is straightforward). Consider the extended $2n$-dimensional system

\[
\begin{align*}
\dot{x}_i &= g_i(x_{i+1}) - \mu_i x_i, \quad i = 1 \ldots n - 1, \\
\dot{x}_n &= g_n(z_1(t - \tau)) - \mu_n x_n, \\
\dot{z}_i &= g_i(z_{i+1}) - \mu_i z_i, \quad i = 1 \ldots n - 1, \\
\dot{z}_n &= g_n(x_1(t - \tau)) - \mu_n z_n.
\end{align*}
\]
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 \( \delta_1 \cdot \ldots \delta_n \cdot \delta_1 \cdot \ldots \delta_n = 1 \).

Thus this system is monotone with respect to a certain partial order; see [8], Chapter 5, and [27]. Finally, the equilibria of this system are in bijective correspondence with the solutions of \( g(g(x)) = x \). The conclusion follows by the result by Dancer and Lemma 3.

3 Hopf Bifurcation

In this section we consider the linearization

\[
\begin{align*}
\dot{x}_i &= k_i x_{i+1} - \mu_i x_i, \quad i = 1 \ldots n - 1, \\
\dot{x}_n &= k_n x_1(t - \tau) - \mu_n x_n,
\end{align*}
\]

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

\[
\begin{align*}
k_i &= g'_i(\bar{x}_{i+1}), \quad i = 1 \ldots n - 1, \\
k_n &= g'_n(\bar{x}_1).
\end{align*}
\]

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

\[
g(z, \tau) := (z + \mu_1)(z + \mu_2) \cdots (z + \mu_n) + Ke^{-\tau z},
\]

where \( K := -k_1 \cdot \ldots k_n > 0 \). See Lemma 3 of Hofbauer and So [28].

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 \( \tau_0 \), 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 \( (\lambda, \tau_0) \), after verifying that \( \partial g/\partial z \neq 0 \) at that point:

\[
\frac{\partial g}{\partial z}(\lambda, \tau_0) = f(\lambda) \sum_j \frac{1}{\lambda + \mu_j} - \tau_0 Ke^{-\lambda \tau_0} = -Ke^{-\lambda \tau_0} Q(\lambda, \tau_0),
\]
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
\[ \Im Q(\lambda, \tau_0) = -\omega \sum_j \frac{1}{\omega^2 + \mu_j^2} < 0. \]

By the implicit function theorem,
\[ \rho'(\tau_0) = -\frac{\partial g}{\partial \tau}(\lambda, \tau_0) \left( \frac{\partial g}{\partial \tau}(\lambda, \tau_0) \right)^{-1} = -\omega i Q(\lambda, \tau_0)^{-1}. \]

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

**Theorem 2** If \( K > \mu_1 \cdot \ldots \cdot \mu_n \), then system (\ref{eq:1}) has a Hopf bifurcation on the parameter \( \tau \).

**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 \( g(\omega_0, \tau_0) = 0 \) and that if \( g(\lambda, \tau_0) = 0 \), \( \lambda = m\omega_0 \) for integer \( m \) then \( \lambda = \pm \omega_0 i \).

Together with Lemma\[1\] this will directly imply the existence of a Hopf bifurcation at the point \( \tau = \tau_0 \); see Theorem 11.1.1 of Hale\[29\].

Let
\[ S := \{ \tau \geq 0 \mid g(\lambda, \tau) = 0 \text{ for some } \lambda \in \mathbb{C} \text{ such that } \Re \lambda \geq 0 \}. \]
To see that $S$ is nonempty, first note that whenever $\omega > 0$ and $|f(\omega i)| = K$, one can find $\tau > 0$ such that $e^{-\omega \tau} = -f(\omega i)/K$ and so $g(\omega i, \tau) = 0$. Noting that $|f(0)| = \mu_1 \cdots \mu_n < K$ and $|f(\omega i)| \to \infty$ as $\omega \to \infty$, it follows by the intermediate value theorem that $|f(\omega i)| = K$ for some $\omega$; 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 $|e^{-\lambda_i \tau}| < 1$, 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 $\tau_0 \in S$.

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 $\tau_0$.

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.

Note that this result is proved in the context of Theorem 11.1.1 of [29]. 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 [30] that system (8) is asymptotically stable provided that $K/((\mu_1 \cdots \mu_n) < \sec^n(\pi/n) = 1/(\cos^n(\pi/n)))$. Therefore necessarily $\tau_0 > 0$ in those cases.

The following proposition establishes a global stability result for the linear system (8).

**Proposition 2** Let $K > \mu_1 \cdots \mu_n$. Let $\tau_0 \geq 0$ be the Hopf bifurcation point as in Theorem 2, and let $\tau \geq 0$. Then the linear system (8) is exponentially unstable if and only if $\tau > \tau_0$.

**Proof.** It was shown in the proof of Theorem 2 that if $\tau < \tau_0$ ($\tau = \tau_0$), then $g(\cdot, \tau)$ could have no root $\lambda$ with Re $\lambda \geq 0$ (Re $\lambda > 0$). Therefore for $\tau \leq \tau_0$, the exponential stability of (8) is ruled out.

Let $S'$ be the set of $\tau \geq 0$ such that system (8) is exponentially unstable. It follows from Lemma 5 and the proof of Theorem 2 that $(\tau_0, \tau_0 + \epsilon) \subseteq S'$ for some $\epsilon > 0$. Assume by contradiction that $S' \neq (\tau_0, \infty)$, and let $\tau_1$ be the infimum of $(\tau_0, \infty) - S'$. In particular, it holds that $\tau_1 \geq \tau_0 + \epsilon > \tau_0$. But this is once again a violation of Lemma 5. 

\[ 13 \]
3.1 Proof of Theorem 1

Now the proof of the main result is complete.

Proof. Let $x_0$ be the unique fix point of $g(x)$. The first case corresponds to the situation in which $|g'(x_0)| \leq 1$. Since (4) is fix 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.

In the case $|g'(x_0)| > 1$, system (4) must have a periodic solution since it is fix point determined. Evaluating $g'(x)$ using the chain rule yields that $K > \mu_1 \cdots \mu_n$, and therefore by Theorem 2, a Hopf bifurcation occurs on the parameter $\tau$.

4 The Positive Feedback Case

We state and prove the corresponding statement in the positive feedback case, which follows from the material in [9] and [21]. Given a system (1), consider the positive feedback hypotheses

$$\mu_i > 0, \delta_i g_i(x) \text{ strictly increasing, } \delta_i \in \{1, -1\}, \ i = 1 \ldots n, \text{ and } \delta_1 \cdots \delta_n = 1.$$  \hfill (11)

It is easy to see, by setting the RHS of (1) equal to zero, that the function $x \in \mathbb{R} \rightarrow \phi(x) = (x_1, \ldots x_n)$ defined by $x_n := \mu_n^{-1} g_n(x), \ x_{n-1} := \mu_{n-1}^{-1} g_{n-1}(x_n), \ldots, x_1 := \mu_1^{-1} g_1(x_2)$ is a bijection between equilibria of (4) and equilibria of (1). In the following result, ‘almost every’ is meant in the sense of measure, more precisely in the sense of prevalence in [31]. For other notation used in the proof, refer to [21].

Theorem 3 Consider the system (1) under (11), and let $g$ be bounded and have countable equilibria. Then almost every solution of (4) converges towards some equilibrium $x$ such that $g'(x) \leq 1$. Also, almost every solution of (1) converges towards some equilibrium $\phi(x)$ such that $g'(x) \leq 1$.

Proof. The first part of this theorem is straightforward: every solution of (4) is monotone increasing or decreasing, and it is bounded since $g$ is bounded. Therefore each solution must converge towards an equilibrium. But if $x$ is an equilibrium of (4) such that $g'(x) > 1$, then it is repelling and no strictly
The second statement follows from Theorem 6 of [21], which is a consequence of results in [9, 7]. It follows from the results in [10], or from Chapter 5 of [8] after a change of variables, that (1) is monotone with respect to an orthant cone. The strong monotonicity follows using the strict monotonicity of the functions $g_i(x)$ in (11); see the proof of Theorem 1.3 in [32]. The boundedness of $g$ implies that one of the functions $g_i$ is bounded, and therefore all solutions of the system are also bounded.

We write system (1) as the closed loop of a control monotone system by replacing $g_n(x_1(t - \tau))$ on the right hand side by $g_n(u)$ and by letting $h(x_i) = x_1(t - \tau)$. Theorem 6 of [21] implies in this case that almost all solutions converge towards equilibrium points $e = (x_1, \ldots, x_n) = \phi(x)$ such that either the linearization (8) is not irreducible, $g_n'(x_1) = 0$, or else $g_i'(x) \leq 1$. But any of the first two conditions imply that in the linearization (8) it holds $k_i = 0$ for some $i$, and that therefore

$$g'(x) = k_1 \cdot \ldots \cdot k_n / (\mu_1 \cdot \ldots \cdot \mu_n) = 0 \leq 1.$$ 

Thus almost every solution converges to an equilibrium $e = \phi(x)$ such that $g'(x) \leq 1$.

5 Future Work

The framework of Angeli and Sontag [9] and Enciso, Smith and Sontag [11] 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 [13] 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 Poincare-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 (1), then the proof of the main theorem wouldn’t have to require that $g$ is fix 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 (1), then there is also a limit cycle of (1) for large enough $\tau$ — even when $Sg \neq 0$. This has been numerically observed to be also true in more complex noncyclic systems in the framework of [11]. 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 $|g'(x_0)| > 1$.

Acknowledgments: The author would like to thank his former advisor Eduardo Sontag for many helpful discussions and comments. Also to be thanked are David Angeli, Tomas Gedeon, Benjamin Kennedy and Roger Nussbaum, for their friendly input and correspondence.

References

[1] A. Goldbeter. Biochemical Oscillations and Cellular Rythms. The Molecular Basis of Periodic and Chaotic Behaviour. Cambridge Univ. Press, Cambridge, 1996.

[2] B.C. Goodwin. Oscillatory behaviour in enzymatic control processes. Adv. in Enzyme Regulation, 3:425–438, 1965.

[3] C. Grotta-Ragazzo O. Arino J.-F. Vibert K. Pakdaman, C.P. Malta. Transient oscillations in continuous-time excitatory ring neural networks with delay. Physical Review E, 55:3234–3248, 1997.
[4] S. Townley, A. Ilchmann, M. G. Weiss, W. Mcclements, A.C. Ruiz, D.H. Owens, and D. Praetzel-Wolters. Existence and learning of oscillations in recurrent neural networks. *IEEE Trans. on Neural Networks*, 11(1):205–214, 2000.

[5] M.B. Elowitz and S. Leibler. A synthetic oscillatory network of transcriptional regulators. *Nature*, 403:335–338, 2000.

[6] J. Mallet-Paret and G. Sell. The Poincare-Bendixson theorem for monotone cyclic feedback systems with delay. *Journal of Differential Equations*, 125:441–489, 1996.

[7] M.W. Hirsch. Stability and convergence in strongly monotone dynamical systems. *Reine und Angew. Math*, 383:1–53, 1988.

[8] H.L. Smith. *Monotone Dynamical Systems*. AMS, Providence, RI, 1995.

[9] D. Angeli and E.D. Sontag. Monotone controlled systems. *IEEE Trans. Autom. Control*, 48:1684–1698, 2003.

[10] G.A. Enciso and E.D. Sontag. Global attractiveness, I/O monotone small-gain theorems, and biological delay systems. To appear in Discrete and Continuous Dynamical Systems.

[11] G.A. Enciso, H.L. Smith, and E.D. Sontag. Non-monotone systems decomposable into monotone systems with negative feedback. to appear in the Journal of Differential Equations.

[12] G.A. Enciso and E.D. Sontag. On the stability of a model of testosterone dynamics. *Journal of Mathematical Biology*, 49:627–634, 2004.

[13] D. Angeli and E. D. Sontag. Interconnections of monotone systems with steady-state characteristics. In M. Malisoff de Queiroz, M. and P. Wolenski, editors, *Optimal Control, Stabilization, and Nonsmooth Analysis*, pages 135–154. Springer Verlag, Heidelberg, 2004.

[14] E.D. Sontag. A remark on monotone i/o systems. [arXiv:math.OC/0503311v1], March 2005.

[15] J. Hale and A. Ivanov. On a high order differential delay equation. *Journal of Mathematical Analysis and Applications*, 173:505–514, 1993.
[16] J. Mallet-Paret and R.D. Nussbaum. Global continuation and asymptotic behavior for periodic solutions of a differential-delay equation. *Ann. Mat. Pura. App.*, IV:33–128, 1986.

[17] K.P. Hadeler and J. Tomiuk. Periodic solutions of difference differential equations. *Arch. Rat. Mech. Anal.*, 65:87–95, 1977.

[18] A.F. Ivanov and B. Lani-Wayda. Periodic solutions for three-dimensional systems with time-delays. *Discrete Contin. Dyn. Syst.*, 2:667–692, 2004.

[19] H. Sedaghat. *Nonlinear Difference Equations*. Kluwer Academic Publishers, 2003.

[20] J. Mallet-Paret. Morse decompositions for delay differential equations. *J. Diff. Eq.*, 72:270–315, 1988.

[21] G.A. Enciso and E.D. Sontag. A characterization of the stability of strongly monotone systems. submitted.

[22] E. Liz, M. Pinto, G. Robledo, S. Trofimchuk, and V. Tkachenko. Wright type delay differential equations with negative schwarzian. *Discrete and Continuous Dynamical Systems*, 9(2):309–321, 2003.

[23] R. Wang, Z. Jing, and L. Chen. Modelling periodic oscillation in gene regulatory networks by cyclic feedback systems. *Bull. Math. Bio.*, 67:339–367, 2005.

[24] H.L. Smith. Oscillations and multiple steady states in a cyclic gene model with repression. *J. Math. Biol.*, 25:169–190, 1987.

[25] D. Angeli, P. de Leenheer, and E.D. Sontag. On predator-prey systems and small-gain theorems. *Mathematical Biosciences and Engineering*, 2:25–42, 2005.

[26] E.N. Dancer. Some remarks on a boundedness assumption for monotone dynamical systems. *Proc. AMS*, 126(3):801–807, March 1998.

[27] D. Angeli and E.D. Sontag. Multistability in monotone input/output systems. *Systems and Control Letters*, 51:185–202, 2004.
[28] J. Hofbauer and J. W.-H. So. Diagonal dominance and harmless off-diagonal delays. *Proc. AMS*, 128(9):2675–2682, 2000.

[29] J.K. Hale. *Introduction to Functional Differential Equations*. Springer, New York, 1993.

[30] J.J. Tyson and H.G. Othmer. The dynamics of feedback control circuits in biochemical pathways. In F.M. Snell R. Rosen, editor, *Progress in Theoretical Biology*, volume 5, pages 1–62. Academic Press, New York, 1978.

[31] B. Hunt, T. Sauer, and J. Yorke. Prevalence: a translation-invariant 'almost every' on infinite-dimensional spaces. *Bull. Amer. Math. Soc.*, 27:217–238, 1992. Addendum, Bull. Amer. Math. Soc. 28 (1993), 306-307.

[32] M. Hirsch and H.L. Smith. Competitive and cooperative systems: a mini-review. In Alberto De Santis Luca Benvenuti and Lorenzo Farina, editors, *Positive Systems. Proceedings of the First Multidisciplinary Symposium on Positive Systems (POSTA 2003).*, Heidelberg, 2003. Springer Verlag.