A Remark on Multistability for Monotone Systems

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Abstract— A recent paper by Angeli and Sontag presented a stability criterium for feedback loops involving single input, single output models which admit a well-defined I/O characteristic and satisfy a monotonicity condition. This paper extends the result to systems with multiple inputs and outputs and delays, and introduces a continuous-time reduction of such systems that preserves some of their stability properties.

Keywords: monotone systems, feedback, stability

I. Introduction

This paper is a follow-up to the article [2]. That work presented a reduction principle for feedback loops involving single input, single output models which admit a well-defined I/O characteristic and satisfy a monotonicity condition, and here we extend the result to the multivariable case. We also consider the introduction of delays, as well as the preservation of the result under cascading and pseudodelays.

The setup is as follows. Consider subsets $X \subseteq \mathbb{R}^n$ and $U \subseteq \mathbb{R}^m$, and a system

$$\dot{x} = f(x,u), \; y = h(x) \tag{1}$$

with input-value and output-value space U, and state space X. We are interested in the global stability properties (location and stability of equilibria) of the closed loop system

$$\dot{x} = f(x,h(x)) \tag{2}$$

which arises under unity feedback.

The main assumptions are that the open-loop system (1) is monotone with respect to cones $\mathcal{K}_m$, $\mathcal{K}_n$, and $\mathcal{K}_m$ in the input-value, state, and output-value spaces, and it admits a nondegenerate I/S characteristic $k^X : U \to X$ (definitions of monotonicity and characteristics are reviewed below). We denote the corresponding I/O characteristic as $k = h \circ k^X : U \to U$. In our main result we will establish a connection between (1) and the reduced system:

$$\dot{u} = k(u) - u \tag{3}$$

as follows:

Theorem 1: Let (1) be a monotone system that admits a nondegenerate I/S characteristic k^X and an I/O characteristic k with nondegenerate fixed points, and assume that the closed loop system (2) is strongly monotone. Then the function $\bar{u} \to k^X(\bar{u})$ forms a bijective correspondence between the locally asymptotically stable points of the monotone system (3) and those of (2). Furthermore, almost all bounded solutions of (2) converge to one of these asymptotically stable points.

This reduction allows one to study the global stability properties of the full system (1) in terms of the reduced system, which has, in general, much lower dimensionality than (1).

In [2], a result was proved that is equivalent to this one for the special case of scalar inputs and outputs ($m = 1$). This scalar result was formulated in terms of a discrete-time condition involving derivatives of k. One of the main contributions of the present paper is the re-interpretation of that condition in terms of the reduced-order continuous-time system (3). This re-interpretation is crucial to the generalization that we gave in Theorem 1.

The above theorem is of use in a number of applications by writing autonomous systems as the closed loop of suitable controlled systems, especially in biological networks with multiple steady states and/or presenting hystheresis effects. The reader is referred to [1], [2], [3] for the proof of the result in the special case of scalar inputs and outputs.

One of the most interesting implications of this methodology lies in the fact that the mapping k can be often obtained from experimental data, even when knowledge of the system (1) is poor because of uncertainty in the form of reactions, or unknown or unmeasurable parameters. Provided that general qualitative knowledge about the system is available (insuring the appropriate assumptions for the system to apply), one can then mathematically conclude stability from this input/output data. This is discussed in detail in the paper [3].

The organization of this paper is as follows. After stating some basic definitions, we first establish a number of preliminary results about positive matrices, followed by the local version of the result (linear systems). In Section IV we prove the theorem, and follow in Section V with an example. Section VI is concerned with cascading and strong monotonicity, as well as the introduction of pseudodelays. We conclude in Section VII with a generalization to systems with true delays. For many proofs we refer the reader to [6].

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II. Definitions

Let $\mathcal{K} \subseteq \mathbb{R}^n$ be a cone, by which we mean a set that is nonempty, convex, closed under multiplication by positive scalars, and pointed (i.e. $\mathcal{K} \cap (-\mathcal{K}) = \{0\}$). We will also assume that $\mathcal{K}$ is closed and has nonempty interior (it is "proper"). The cone $\mathcal{K}$ induces the partial order given by: $x \leq y$ iff $y - x \in \mathcal{K}$, and the stronger order $x \ll y$ iff $y - x \in \operatorname{int} \mathcal{K}$. We also say that $x < y$ if $x \leq y$ and $x \neq y$.

Assume given a system (1), where the state space $X \subseteq \mathbb{R}^n$ is the closure of an open set, the input- and output-value set U is also the closure of an open set, and f and h are continuously differentiable. We also assume given two proper cones $\mathcal{K}_n \subset \mathbb{R}^n$ and $\mathcal{K}_m \subseteq \mathbb{R}^m$. By an input we mean a measurable essentially bounded map $u : \mathbb{R}^+ \to U$ and write "$u \leq v$" for two inputs provided that $u(t) \leq v(t)$ for almost all t. (We abuse notation and use letters such as u to denote both an input value –element of U– or an input, depending on the context.)

The system (1) is monotone with respect to $\mathcal{K}_n, \mathcal{K}_m$ if h is a monotone function, that is $x \leq y$ implies $h(x) \leq h(y)$, and the flow preserves the order, i.e., the following property is satisfied:

> For any two inputs u, v such that $u \leq v$, and any two initial conditions $x_1, x_2 \in X$ such that $x_1 \leq x_2$, it holds that $x(t, x_1, u) \leq x(t, x_2, v)$ for all $t \geq 0$.

Here, $x(t, x_0, u)$ is the solution of the system (1) with initial condition x_0, evaluated at time t, and the relations $\leq$ are defined as in the previous section for each cone, and interpreted as $\leq_U$ or $\leq_X$ in the obvious manner. Systems with no inputs can be seen as a particular case (using an input value space consisting of just one point); such a system is monotone if $x_1 \leq x_2$ implies $x(t, x_1) \leq x(t, x_2)$ for all t. We will always understand "for all t" to mean for all times t belonging to the common domain of definition of the solutions involved.

A system of the form (1) is said to be strongly monotone if $u \leq v$, $x_1 < x_2$ implies $x(t, x_1, u) \ll x(t, x_2, v)$ $\forall t$. We also assume in this case that $x \ll y$ implies $h(x) \ll h(y)$ (we say that h itself is strongly monotone).

A. Characteristics

We say that (1) has a well-defined input to state characteristic $k^X : U \to X$ if for every constant input $u(t) \equiv u \in U$, $x(t, x_0, u)$ converges to $k^X(u)$ for every initial condition $x_0 \in X$. In that case we refer to $k = h \circ k^X$ as the system's input to output characteristic. We will also assume throughout in this text that the characteristic k^X is nondegenerate, that is, $\det f_x(k^X(u), u) \neq 0$ for every $u \in U$.

We say that k has nondegenerate fixed points if $\det(k'(\bar{u}) - I) \neq 0$ (i.e., $k'(u)$ has no eigenvalues equal to one) for each $\bar{u}$ fixed point of k (not to confuse with the previous definition).

Suppose given a system (1) which is both monotone and admits an I/O characteristic k. Then k is a monotone function. This is proved as follows. Pick any two elements $u \leq v$ in U, and consider the corresponding constant inputs $u(t) \equiv u$ and $v(t) \equiv v$ as well as an arbitrary initial state x_0. By monotonicity, $x(t, x_0, u) \leq x(t, x_0, v)$. Letting t tend to infinity, we conclude that $k(u) \leq k(v)$.

It can be shown that system (3) has unique, maximally defined solutions under the given circumstances. The reader is referred to [6] for details.

III. Linear Systems

Consider a linear system $\dot{x} = Ax + Bu$, $y = Cx$ that is monotone and admits well defined (and necessarily nondegenerate) I/S and I/O characteristics. We close the system by unity feedback, letting $u = y = Cx$, thus forming an autonomous dynamical system $\dot{x} = (A + BC)x$. It is easy to compute the I/O characteristic from the equation $Ax + Bu = 0$ for a fixed $u \in U$, namely $k(u) = -CA^{-1}Bu$. Thus $k'(0) = -CA^{-1}B$; this will be important for the statement of the following theorem, which is equivalent to Lemma 6.6 in [2], and whose proof can be found in [6].

Theorem 2: Let $\dot{x} = Ax + Bu,\ y = Cx$, with $A \in \mathbb{R}^{n \times n}$, $B \in \mathbb{R}^{n \times m}$, $C \in \mathbb{R}^{m \times n}$, be a linear system that admits an I/O characteristic k and is monotone with respect to cones $\mathcal{K}_n$ and $\mathcal{K}_m$ in the input-value and state spaces. Assume that

$$\det\left(I + CA^{-1}B\right) \neq 0\,.$$

Then $A + BC$ is Hurwitz iff $-\left(I + CA^{-1}B\right)$ is Hurwitz. In other words, the closed loop system is exponentially stable iff the linear system $\dot{u} = k(u) - u$ is exponentially stable.

Recall that if a linear system is asymptotically stable, then all of its eigenvalues must have negative real part, and the system is therefore exponentially stable. A similar property holds for monotone systems, which we explicitly state below (see [6] for a proof).

Lemma 1: Let $\dot{x} = F(x)$ be a monotone system under some proper cone, $F(\bar{x}) = 0$, and $\det \frac{\partial F}{\partial x}(\bar{x}) \neq 0$. Then $\bar{x}$ is asymptotically stable if and only if it is exponentially stable.

IV. Proof of Theorem 1

Now we are ready to prove the main result. In the case that $m = 1$, the condition that $\bar{u}$ be a stable equilibrium of the reduced system (3) is equivalent to asking that $k(\bar{u}) = \bar{u}$ and $k'(\bar{u}) - 1 < 0$, since by nondegeneracy $k'(\bar{u}) - 1 \neq 0$. This is just the condition $k'(\bar{u}) < 1$ used in [2].

Proof: Given an equilibrium point $\bar{u}$ of (3), that is $k(\bar{u}) = \bar{u}$, let the linearization of the open system around $\bar{u}$ and $k^X(\bar{u})$ be denoted as $\dot{x} = Ax + Bu,\ y = Cx$. The hypotheses of Lemma 1 are satisfied both for $\bar{u}$ in the reduced system and for $\bar{x} = k^X(\bar{u})$ in the closed loop system, by nondegeneracy of fixed points in the former, and since $\det A + BC \neq 0$ in the latter. We therefore have by Theorem 2 and Lemma 1:

$\bar{u}$ is asymptotically stable in the reduced system
iff $\bar{u}$ is exponentially stable in the reduced system
iff $\bar{x}$ is exponentially stable in the closed loop system
iff $\bar{x}$ is asymptotically stable in the closed loop system

This shows that there is a direct correspondence between those asymptotically stable points of the closed loop system and those of the reduced system.

The important generic convergence result proven by Hirsch in the late 1980's can be stated in our framework as follows: given an autonomous system that is strongly monotone with respect to some proper cone, almost every initial condition with bounded solution has a limit set contained in the set of equilibria; see Theorem 7.8 in [8]. In the case that the set of equilibria is discrete, as it is here, we can conclude that almost every bounded solution converges to an equilibrium point.

Let $\lambda \in \mathbb{R}$ be the Perron-Frobenius eigenvalue associated with $A + BC$ after linearizing around an unstable equilibrium point $\bar{x}$. By unstability and since we know $\lambda \neq 0$, we have $\lambda > 0$; thus $\bar{x}$ is a hyperbolically unstable equilibrium of the closed loop system, and it follows (see [2] and de la Llave et al. [9]) that the set of initial conditions that converge toward $\bar{x}$ in the closed loop system has measure zero.

Thus almost all bounded solutions converge to one of the equilibria corresponding to a locally exponentially stable steady state of the reduced system, as stated. ■

Note that under the present hypotheses merely asymptotic stability is actually ruled out: an equilibrium point is either exponentially stable, or unstable with some eigenvalue with positive real part.

This theorem provides a way to describe the behavior of a complex monotone system in terms of a potentially much simpler, associated system. For $m = 2$ a graphical analysis as in [2], [3] is also possible, by plotting the vector field $k(u) - u$ on the input space, and observing which equilibria appear to be stable (see example below).

In the case that (3) is itself strongly monotone and has bounded solutions, one can actually apply Hirsch's theorem to it and deduce that almost all trajectories converge toward one of the stable steady states. The question arises as to whether the analogy between the two systems could be carried further: if the output function h were surjective, does it hold that $x(t, x_0)$ converges to $\bar{x}$ if and only if $u(t, h(x_0))$ converges to $h(\bar{x})$? In other words, do the basins of attraction of each stable point correspond to each other, as the stable points do? Unfortunately this is not true, as the example below will illustrate.

V. An Example

We illustrate the main result with an example of a coupled biological circuit. An important class of proteins, referred to as transcription factors, regulate transcription of messenger RNA by promoting (or inhibiting) the binding of the enzyme RNA polymerase to the DNA sequence. An autoregulatory transcription factor regulates the production of its own messenger RNA. Transcription factors are very common, and often more than one is necessary for RNA polymerase to initiate transcription. For a mathematical analysis of the simple autoregulatory circuit, see Smith [14][1].

Let p_1, p_2 be two autoregulatory transcription factors, and r_1, r_2 their corresponding messenger RNAs. We will couple the circuits by assuming that the proteins are also needed to regulate each other's transcription. The dynamics of the circuit is thus expressed as follows:

$$\begin{array}{l} \dot{p}_i = a_i r_i - b_i p_i \\ \dot{r}_i = g_i(p_1, p_2) - c_i r_i \end{array} \qquad i = 1, 2. \tag{4}$$

We assume that both $g_1(p_1, p_2)$ and $g_2(p_1, p_2)$ are increasing functions of both p_1 and p_2, as well as positive and bounded. The interconnections are illustrated in Figure 1. In particular, note that all the solutions of this system are bounded.

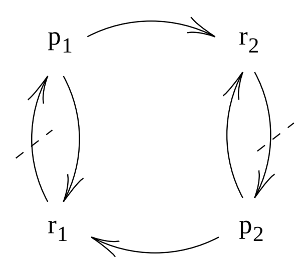

Fig. 1. Interconnections for system 4. The dotted lines indicate where the interconnections will be cut and replaced by inputs.

We analyse the dynamics of this system by cutting the arcs as indicated in the figure, and we arrive to the following controlled system with two inputs:

$$\begin{array}{l} \dot{p}_i = a_i u_i - b_i p_i \\ \dot{r}_i = g_i(p_1, p_2) - c_i r_i \end{array} \qquad i = 1, 2. \tag{5}$$

which is monotone under the usual positive orthant cone. If we fix the input (u_1, u_2), the system converges

[1] The standard model in p. 58 of [14] is in fact another interesting application of Theorem 1: by cutting the arc $x_n \to x_1$ as explained in our example, the results in Section 4.2, [14], follow by looking at the fixed points of $k(u) = \alpha_1^{-1} \dots \alpha_n^{-1} g(u)$. Furthermore, the local stability of each equilibrium is determined by the slope of $k(u)$ at each corresponding fixed point.

toward the point

$$p_i = \frac{a_i}{b_i}u_i, \quad r_i = \frac{1}{c_i} g_i\left(\frac{a_1}{b_1}u_1, \frac{a_2}{b_2}u_2\right)$$

which constitutes the value of k^X at the point (u_1, u_2). Note that the arcs cut in Figure 1 are chosen so as to leave the digraph with no directed loops in order for the characteristic to be well defined, while minimizing the number of inputs. Also, two cuts are the minimum since there are two disjoint, directed loops in the digraph. Since we want the closed loop to be (4), we need $h(p_1, p_2, r_1, r_2) = (r_1, r_2)$, which when composed with k^X yields

$$k(u, v) = \left(\frac{1}{c_1} g_1\left(\frac{a_1}{b_1}u_1, \frac{a_2}{b_2}u_2\right), \frac{1}{c_2} g_2\left(\frac{a_1}{b_1}u_1, \frac{a_2}{b_2}u_2\right)\right).$$

Under mass action kinetics assumptions, a quasi-steady state analysis (see [11]) yields for the g_i the general form

$$g_i = \hat{\sigma}_i \frac{p_1^{m_i} p_2^{n_i}}{\hat{K}_i + p_1^{m_i} p_2^{n_i}}.$$

The coefficients m_i, n_i describe the cooperativity with which the proteins bind to the DNA sequence. For instance, if two p_1 proteins bind to each other (forming a dimer) before acting on the DNA sequence of p_i, then $m_i = 2$. It is a reasonable assumption that the cooperativity of a protein is the same for both DNA sequences, that is $m_1 = m_2 = m, n_1 = n_2 = n$. We set for simplicity $m = 2, n = 1$. The remaining coefficients $\hat{K}_i, \hat{\sigma}_i$ are determined by the way the proteins bind to the particular DNA sequence and how they aid the polymerase enzyme. We have

$$k(u_1, u_2) = \left(\sigma_1 \frac{u_1^2 u_2}{K_1 + u_1^2 u_2}, \sigma_2 \frac{u_1^2 u_2}{K_2 + u_1^2 u_2}\right),$$

where $\sigma_i = \hat{\sigma}_i c_i^{-1}$, $K_i = \hat{K}_i a_1^{-2} b_1^{-2} a_2^{-1} b_2^{-1}$. Apart from the trivial solution $(0, 0)$, the equation $k(u_1, u_2) = (u_1, u_2)$ can be rewritten as

$$K_1 + u_1^2 u_2 = \sigma_1 u_1 u_2, \quad K_2 u_2 + u_1^2 u_2^2 = \sigma_2 u_1^2 u_2 \qquad (6)$$

We solve for u_1 in the first equation of (6) and replace in the second equation, obtaining

$$K_1 u_1^2 = (\sigma_2 u_1^2 - K_2)(\sigma_1 - u_1)u_1\,. \qquad (7)$$

From Figure 2 we see that there might be only one nonnegative solution of (6) (i.e., the trivial solution $u_1 = 0$), or there may be three nonnegative solutions, in the case that K_1, K_2 are comparatively small. Theorem 1 can be used here to establish a correspondence between these points and the equilibrium points of (4), which sends stable states (of the system $\dot{u} = k(u) - I$) to stable states of (4). Thus, by verifying that there are two stable points and one unstable point in $\dot{u} = k(u) - I$, we will have shown that the same holds for (4). See Figure 3 for an illustration of this in the particular case

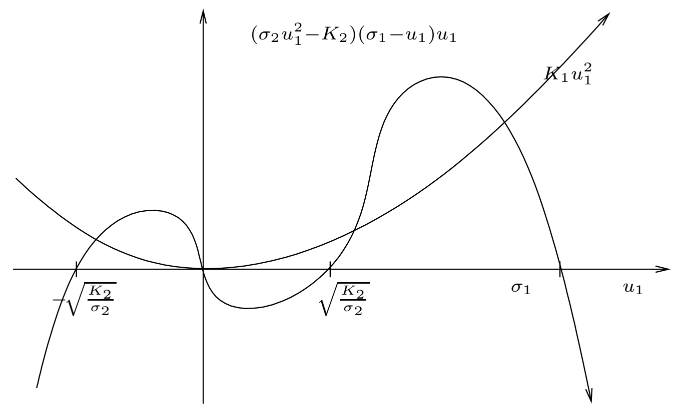

Fig. 2. The solutions of the system of equations (7)

$\sigma_1 = 4, \sigma_2 = 2, K_1 = 4, K_2 = 5$; note that additional solutions may appear outside of the positive quadrant.

Given the simple form of the output function $h(x) = (r_1, r_2)$, any basin of attraction of $\dot{u} = k(u) - I$ will correspond in X (under h^{-1}) to a rather rigid set, namely that of every (p_1, p_2, r_1, r_2) such that (r_1, r_2) is in the basin. It is clear that the basins of attraction of (4) don't have this form — this limits the analogy between (4) and its reduced system.

On the other hand, the same procedure can be applied for cones that are not necessarily the positive orthant: for instance if, in the above example, each protein promoted its own growth and inhibited each other's growth, then $\mathcal{K}_n = \mathbb{R}^+ \times \mathbb{R}^- \times \mathbb{R}^+ \times \mathbb{R}^-$ would make (4) strongly monotone.

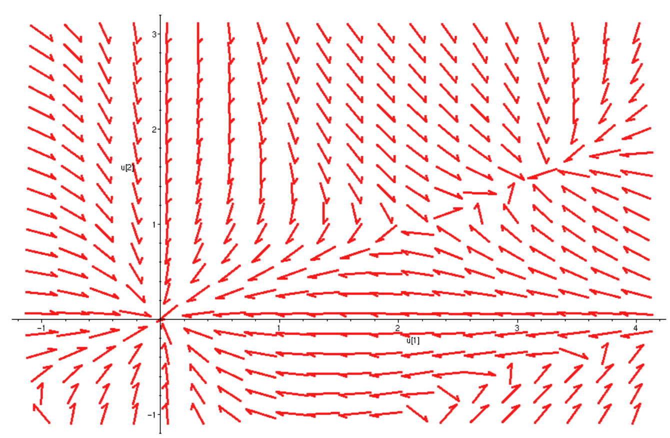

Fig. 3. The vector field $\gamma(u) = k(u) - I$, using parameter values $\sigma_1 = 4, \sigma_2 = 2, K_1 = 4, K_2 = 5$.

VI. Cascades and Systems with Pseudodelays

In this section we will extend Theorem 1 to cascades of monotone systems with characteristic. One possible application is the introduction of pseudodelays, as we will briefly discuss below.

We say that a monotone system (1) is partially excitable if for any $x_1 \leq x_2$, arbitrary inputs u_1, u_2, and any $t_0 > 0$, the following properties hold: 1) $u_1 < u_2$ a.e. on $(0, t_0)$ implies $x(t, x_1, u_1) < x(t, x_2, u_2),\ t \in (0, t_0)$, and 2) $u_1 \ll u_2$ a.e. on $(0, t_0)$ implies $x(t, x_1, u_1) \ll x(t, x_2, u_2),\ t \in (0, t_0)$. We also say that (1) is strongly excitable if $u_1 < u_2$ a.e. on $(0, t_0)$ implies $x(t, x_1, u_1) \ll x(t, x_2, u_2),\ t \in (0, t_0)$. Further, we will say that (1) is partially transparent if for arbitrary inputs $u_1 \leq u_2$ and initial conditions x_1, x_2 one has 1) $x_1 < x_2$ implies $h(x(t, x_1, u_1)) < h(x(t, x_2, u_2))$, and 2) $x_1 \ll x_2$ implies $h(x(t, x_1, u_1)) \ll h(x(t, x_2, u_2))$. It is strongly transparent if $x_1 < x_2$ implies $h(x(t, x_1, u_1)) \ll h(x(t, x_2, u_2))$, for all $t > 0$ for which the solutions $x(t, x_i, u_i)$ are defined. Note that the first condition for partial excitability and the second condition for partial transparency correspond to the notions of weak excitability and weak transparency, respectively, in the terminology of [2] (borrowed from [10]). These definitions are further discussed in [6], where for instance infinitesimal characterizations are provided in the orthant case.

Now consider, instead of system (1), a cascade of the form

$$\dot{x}^i = f_i(x^i, u^i),\ u^{i+1} = h_i(x^i),\ i = 1 \ldots N \qquad (8)$$

We will refer to the subsystem $\dot{x}^i = f_i(x^i, u^i),\ u^{i+1} = h_i(x^i)$, as $(8.i)$.

The usefulness of the concepts of partial transparency and excitability is illustrated in the following proposition, proved at length in [6]. The corresponding assertion with 'weak' instead of 'partial' transparency and excitability would not hold.

Proposition 1: Let the system (8) be such that each $(8.i)$ is monotone, partially excitable and partially transparent. Let one of these two conditions be also strong, for some $(8.i)$, and suppose that $U_{N+1} \subseteq U_1$. Then the closed loop system obtained by setting $u^1 = u^{N+1}$ in (8) is strongly monotone.

Theorem 3: Let every subsystem $(8.i)$ of (8) be monotone and have a nondegenerate characteristic $k_i,\ i = 1 \ldots N$. Let $U_{N+1} \subseteq U_1$, and let every $(8.i)$ be partially transparent and partially excitable, with one of these conditions being strong, for some $(8.i)$. Also assume that $k = h_N k_n \ldots h_1 k_1$ has nondegenerate fixed points. Then the function $u \to (k_1(u), k_2 h_1 k_1(u), \ldots)$ forms a correspondence between the stable points of (3) and those of (8). Also, almost all solutions of (8) converge towards one of these points.

Note that in particular, if $k_i = id,\ i = 2, \ldots N$, and $h_1 = id,\ i = 1 \ldots N$, then $k = k_1$ and the stable points of (8) correspond with those of $\dot{x}^1 = f_1(x^1, u^1)$.

Proof: By the previous Proposition, we see that the closed loop system is strongly monotone. We linearize the controlled system (8) around a fixed input value u^1 and a fixed state $x = (x^1, \ldots, x^N)$, and the resulting linear system has the form $\dot{x} = Ax + Bu$, where A is a lower triangular matrix. Thus the determinant of A is the product of the determinants of its diagonal elements, that is $\det f_{1x^1} \cdot \ldots \cdot \det f_{1x^N}$, which is nonzero by nondegeneracy of each subsystem. The caracteristic of the cascade as a whole can be shown to exist, by the Converging Input, Converging State property, see [1] and work to appear by the authors. It has the form $(k_1(u), k_2 h_1 k_1(u), \ldots)$, and thus the input to output characteristic is $k = h_N k_n \ldots h_1 k_1$. Thus we can apply Theorem 1, and the conclusions follow. ∎

An example of this result can be seen by defining (8) with $\frac{\tau}{N-1}\dot{x}^i = -x^i + x^{i-1}$, $i = 2, \ldots N$, and $h_i = id$ for all i. This will have the effect of roughly delaying the output by τ units; the previous Theorem guarantees that the stability properties of this new system are unchanged, compared with the system without the "pseudodelay".

VII. Systems with (True) Delays

For a final motivation for the use of monotone systems and the application of the main theorem, we quote a stability result from Smith [14] for systems with true delays (as opposed to the pseudodelays from the previous section). A similar application for reaction diffusion systems is valid and given in Section 7.6 of [14].

Given a fixed $r \geq 0$ (delay length), any function $x : [-r, \infty) \to \mathbb{R}^n$, and any $t \geq 0$, we denote by x_t the function $x_t(s) = x(t + s),\ s \in [-r, 0]$. A general autonomous delay system can then be written as

$$\dot{x}(t) = F(x_t),\ x_0 = \phi \qquad (9)$$

where $\phi : [-r, 0] \to \mathbb{R}^n$, and F is an $\mathbb{R}^n$-valued function defined on an apropiate domain of such functions. System (9) is said to be monotone with respect to a given cone $\mathcal{K} \subseteq \mathbb{R}^n$ if for any $\sigma \in \mathcal{K}^*$, $\phi \leq \psi$ pointwise, and $\sigma(\phi(0) = \sigma(\psi(0))$, it holds that $\sigma(F(\psi) - F(\phi)) \geq 0$. This definition becomes condition (Q) (Smith [14], p.78) in the cooperative case, and it generalizes, for delay systems, a related concept used by H. Schneider and M. Vidyasagar (see [17]). It can be shown to be equivalent to the monotonicity of (9) as a dynamical system in the state space of functions ϕ, with respect to the cone of states ϕ that are pointwise nonnegative, using an argument very similar to that in Theorem 5.1.1 of Smith [14] for the nontrivial direction.

One can associate to (9) the finite dimensional system $\dot{x} = g(x),\ g(x) = F(\hat{x})$ where $\hat{x}$ is the function with constant value x. It is easy to see that an equilibrium ϕ of system (9) must be a constant function $\hat{v}$ – but its stability may in general well differ from that of v in $\dot{x} = g(x)$. The next lemma is a rephrasing of [14], Corollary 5.5.2, and will allow us to extend the main result to include certain delays. Also, we will say that an autonomous delay system has uniformly bounded solutions if for every compact set $A \subseteq \mathbb{R}^n$ there exists a bounded $B \subseteq \mathbb{R}^n$ that contains all solutions of the system with initial conditions contained in A.

Lemma 2: If (9) is cooperative, then $v \in \mathbb{R}^n$ is an exponentially stable (unstable) equilibrium of $\dot{x} = g(x)$ if and only if $\hat{v}$ is an exponentially stable (unstable) equilibrium of (9).

The following Theorem is the conclusion of this section.

Theorem 4: Let the cone $\mathcal{K}_n$ be the positive orthant, and $r \geq 0$. Suppose that the assumptions of Theorem 1 hold. Consider the system

$$\dot{x}(t) = f(x(t), h(x(t-r))) \tag{10}$$

viewed as a delay system (9) with $F(\phi) = f(\phi(0), h(\phi(-r)))$, and suppose that (9) has uniformly bounded solutions. Then the function $\bar{u} \to \widehat{k^X(\bar{u})}$ forms a bijective correspondence between the locally exponentially stable points of the monotone system $\dot{u} = k(u) - u$ and those of (10). Furthermore, almost all bounded solutions of (10) converge to one of these exponentially stable points.

Proof: We show first that the autonomous delay system (10) is monotone. Let $\sigma \in \mathcal{K}^*$, $\phi \leq \psi$, and $\sigma(\phi(0) = \sigma(\psi(0))$. Using the notation in Section 2 of [6], let 'x'$= \phi(0)$, 'h'$= \psi(0) - \phi(0)$, 'u'$= h(\phi(-r))$, 'v'$= h(\psi(-r) - h(\phi(-r))$. By hypothesis it holds that $h \geq 0$, $v \geq 0$ and $\sigma(h) = 0$. Thus by monotonicity of system (1), it holds that $\phi(f(x+h, u+v) - f(x, u)) \geq 0$, or $\sigma(F(\psi) - F(\phi)) \geq 0$, and the conclusion follows.

Consider $\bar{u} \in \mathbb{R}^m$. By monotonicity and Lemma 1, $\bar{u}$ is exponentially stable in $\dot{u} = k(u) - u$ iff it is asymptotically stable in this system. By Theorem 1, this holds iff $k^X(u)$ is asymptotically stable in (2), iff it is exponentially stable, again by monotonicity and Lemma 1. But this holds iff the constant function $\widehat{k^X(u)}$ is an exponentially stable equilibrium of (10), by Lemma 2 and monotonicity.

To show the convergence of almost all bounded solutions of (10) to one of these equilibria, we use Hirsch's theorem and verify that this system is eventually strongly monotone. Smith ([14], pp. 85-91) provides as sufficient criteria for strong monotonicity the conditions called there (K),(I),(R),(T). (K) and (R) are easy to show, the former by monotonicity; (T) holds for this function since f is assumed to be continuous, and using the uniform boundedness of the system. Finally, (I) holds since it is equivalent to the irreducibility of the undelayed closed loop (2), which holds by hypothesis. Now, any equilibrium of the undelayed closed loop must be either exponentially stable or exponentially unstable, since $\lambda \neq 0$ for any of its equilibria (see the proof of Theorem 2). By Lemma 2, the same holds for (9). The last statement follows from the last section of [8]. ■

Example: We consider the same model as before, with a delay introduced to simulate the time necessary for translation and folding of the proteins:

$$\begin{array}{l} \dot{p}_i = a_i r_i(t-r) - b_i p_i \\ \dot{r}_i = g_i(p_1, p_2) - c_i r_i \end{array} \quad i = 1, 2. \tag{11}$$

The previous theorem then guarantees that the analysis we carried out in the previous section applies equally for this system, to find which equilibria are locally stable. Note that nevertheless the basins of attraction of the two systems don't necessarily correspond to each other.

Finally, we remark that for a general monotone controlled delay system $\dot{x} = f(x_t, \alpha)$, $x_0 = \phi$, $y_t(s) = h(x_t(s))$ (see [1]), we can also characterize the locally stable equilibria of its closed loop as follows: if we assume that the associated, undelayed system $\dot{x} = f(\hat{x}, \hat{u}), y = h(\hat{x})$ satisfies the hypotheses of Theorem 1, then $u \to \widehat{k^X(u)}$ forms a correspondence between the locally exponentially stable equilibria of the delayed closed loop system, and those of $\dot{u} = k(u) - u$. The proof is exactly like that of the corresponding statement in Theorem 4. This result allows for delays to be introduced in places other than the output, as well as multiple different delays or integral delays.

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