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GLOBAL ATTRACTIVITY, I/O MONOTONE SMALL-GAIN THEOREMS, AND BIOLOGICAL DELAY SYSTEMS

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Abstract. This paper further develops a method, originally introduced by Angeli and the second author, for proving global attractivity of steady states in certain classes of dynamical systems. In this approach, one views the given system as a negative feedback loop of a monotone controlled system. An auxiliary discrete system, whose global attractivity implies that of the original system, plays a key role in the theory, which is presented in a general Banach space setting. Applications are given to delay systems, as well as to systems with multiple inputs and outputs, and the question of expressing a given system in the required negative feedback form is addressed.

1. **Introduction.** In their paper, Angeli and Sontag [2] introduced an approach for establishing sufficient conditions under which a dynamical system Φ, described by ordinary differential equations, is guaranteed to have a globally stable equilibrium. The method may be applied whenever Φ can be decomposed as a negative feedback loop around a monotone controlled system. A discrete system is associated to Φ, and its global attractivity toward an equilibrium implies that of Φ.

In this paper, we generalize the results of Angeli and Sontag [2] in several directions: (i) we address the stability of the closed loop system, which was not done in [2], (ii) we prove results which are novel even in the finite-dimensional case, in particular allowing the consideration of systems with multiple inputs and outputs, and (iii) we extend considerably the class of systems to which the theory can be applied and the above characterization holds, by formulating our definitions and theorems in an abstract Banach space setting. The extension to Banach space forces us to develop very different proofs, but it permits the treatment of delay-differential and other infinite-dimensional systems. In addition, we work-out a number of interesting examples, exploit a useful necessary and sufficient condition for monotonically decreasing discrete systems to be globally attractive which leads to sufficient tests for stability of our negative feedback loops, and provide a procedure for decomposing a system as the negative feedback closed loop of a monotone controlled system (Appendix 1). We rely on basic results from the theory of monotone systems, but most necessary concepts will be defined in the text. The reader is encouraged to consult Smith [32] for further references on this topic.

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There has been previous work that remarked upon special cases of the relationship in asymptotic behavior between continuous systems and associated discrete systems. Indeed, in [31], Smith studied a cyclic gene model with repression, and observed how a certain discrete system seemed to mirror the continuous model's dynamics, both at the local and the global level. The setup of feedback loops around monotone control systems provides one appealing formalization of this remark, and the repression model in question will be used as an illustration of our main result. Related work has been carried out by Chow, Mallet-Paret and Nussbaum, and surveyed by Tyson and Othmer [6, 23, 37]. See also [10] for an application by the authors to a model of testosterone dynamics, and [3, 9, 19] for related work in the positive feedback case.

The topic of monotone and related positive systems is a very active current area of research, especially in biological applications; see e.g. [1, 5, 12, 11, 27]. Nevertheless the results in this paper are meant to be applied to systems that are *not* monotone. Given an autonomous system, the idea is to *decompose it as the negative feedback loop of a monotone controlled system*, and to apply the main result to this controlled system. Hence, the global attractivity of the original system will follow from the main result. To carry out this preliminary step, we provide in the appendix a systematic description on how to decompose an autonomous system, under relatively few constraints, as the negative feedback loop of a monotone controlled system with a comparatively small number of inputs and outputs.

The organization of this paper is as follows. In Section 2 we define the most important concepts involved, such as monotonicity and the existence of a characteristic, and we state the general hypotheses that will be assumed. In Section 3 we prove the main result in an abstract framework, and in Section 4 we address the stability of the closed loop system. In Section 5 we specialize to delay systems, and after a general introduction we show how to apply the abstract results in this scenario. We conclude in Section 6 with our main application, re-deriving and extending, as a corollary of our main theorem, the global attractivity results of an autonomous model of the lac operon published by Mahaffy and Savev [24]. In the Appendix I, we describe how to decompose an autonomous system as the negative feedback loop of a monotone controlled system. In the Appendix II we provide a proof of existence and uniqueness for controlled delay systems, including the semiflow property.

2. **Preliminaries.** Let B be a real Banach space, and let $\mathcal{K} \subseteq B$ be a *cone*, that is, a nonempty, convex set that is closed under multiplication by a positive scalar and pointed (i.e. $\mathcal{K} \cap (-\mathcal{K}) = \{0\}$). Assume also that $\mathcal{K}$ is closed and has nonempty interior. The cone $\mathcal{K}$ induces the following order relations in B:

$$\begin{aligned} x \le y \quad &\Leftrightarrow y - x \in \mathcal{K}, \\ x < y \quad &\Leftrightarrow x \le y \text{ and } x \ne y, \\ x \ll y \quad &\Leftrightarrow y - x \in \text{ int } \mathcal{K}. \end{aligned}$$

The pair (B, K) is referred to as an *ordered* Banach space. The following notation will be used: $[x, y] = \{z |\, x \le z \le y\}$, $(x, y) = \{z |\, x \ll z \ll y\}$. These sets will be denoted as *intervals* or *boxes*. The cone $\mathcal{K}$ is called *normal* if $0 \le x \le y$ implies $|x| \le M\,|y|$ for some constant $M > 0$, called a *normality constant* for $\mathcal{K}$. Also, a set $A \subset B$ will be said to be *bounded from above* if there is some $x \in B$ such that $a \le x$, for all $a \in A$. If B_1, B_2 are two ordered Banach spaces, $\gamma : B_1 \to B_2$ is said to be $\le$*-increasing* if $x \le y$ implies $\gamma(x) \le \gamma(y)$, and it is said to be $\le$*-decreasing* if $x \le y$

implies $\gamma(x) \geq \gamma(y)$ (similarly with the other order relations). In the case $B = \mathbb{R}^n$, a tuple $(s_1, \ldots s_n),\ s_i :=$'+','−', defines the *orthant cone* $\mathcal{K} := \mathbb{R}^{s_1} \times \ldots \times \mathbb{R}^{s_n}$. The canonic orthant cone defined by $s = (+ \ldots +)$ is called the *cooperative cone*.

The following lemmas are standard exercises in convex analysis. For convenience, proofs are provided in the appendix.

Lemma 1. *A cone $\mathcal{K}$ has nonempty interior if and only if the unit ball is bounded from above.*

Lemma 2. *Let $\mathcal{K} \subseteq \mathbb{R}^n$. Then $\mathcal{K}$ is normal.*

Dynamical Systems. Let B_X, B_U be two arbitrary Banach spaces, and pick Borel measurable subsets $X \subseteq B_X$, $U \subseteq B_U$. The set U is referred to as the set of *input values*, and an *input* is defined as a function $u : \mathbb{R}^+ \to U$ that is Borel measurable and locally bounded. The set of all inputs taking values in U will be denoted as U_∞. The set of all constant inputs $\hat{u}(t) \equiv u \in U$ is denoted by $\hat{U} \subseteq U_\infty$, and is considered to have the topology induced by U.

Definition 1. *A* controlled dynamical system *is a function*

$$\Phi : \mathbb{R}^+ \times X \times U_\infty \to X$$

which satisfies the following hypotheses:

1. Φ *is continuous on its first two variables, and the restriction of* Φ *to the set* $\mathbb{R}^+ \times X \times \hat{U}$ *is continuous.*
2. *For every* $u, v \in U_\infty$ *such that* $u(s) = v(s)$ *for almost every* s, $x(t, x_0, u) = x(t, x_0, v)$ *for all* $x_0 \in X,\ t \geq 0$.
3. $x(0, x_0, u) = x_0$ *for any* $x_0 \in X,\ u \in U_\infty$.
4. *(Semigroup Property) if* $\Phi(s, x, u) = y$ *and* $\Phi(t, y, v) = z$, *then by appending* $u|_{[0,s]}$ *to the beginning of* v *to form the input* w, *it holds that* $\Phi(s+t, x, w) = z$.

See also Sontag [33]. The functions $x(\cdot) = \Phi(\cdot, x_0, u)$ can be regarded as trajectories in time for every x_0, u. We often refer to $\Phi(t, x_0, u)$ as $x(t, x_0, u)$ or simply $x(t)$ if the context is clear. As a simple remark, note that the properties above imply that if $u, w \in U_\infty$ and $u|_{[0,s]} = w|_{[0,s]}$, then $\Phi(s, x, u) = \Phi(s, x, w)$. This can be seen simply by letting $t = 0$ in Property 4.

Output and Feedback Functions. Given a controlled dynamical system (1), a Banach space B_Y and a measurable set $Y \subseteq B_Y$, an *output function* is any continuous function $h : X \to Y$. In that case, the pair (Φ, h) consisting of

$$\Phi : \mathbb{R}^+ \times X \times U_\infty \to X, \qquad h : X \to Y \tag{2.1}$$

will be referred to as a *dynamical system with input and output.* Unless explicitly stated, *we will assume throughout this paper that* $B_Y = B_U,\ Y = U$, in which case h is also called a *feedback function. It will also be assumed that* h *is* $\leq$*-decreasing*, in which case (2.1) is said to be under *negative feedback.*

Monotonicity and Characteristic. Given cones $\mathcal{K}_X \subseteq B_X,\ \mathcal{K}_U \subseteq B_U$, a dynamical system (1) is said to be *monotone with respect to* $\mathcal{K}_X, \mathcal{K}_U$ if the following property is satisfied: for any two inputs $u, v \in U_\infty$ such that $u(t) \leq v(t)$ for almost every t, and any two initial conditions $x_1 \leq x_2$ in X, it holds that

$$x(t, x_1, u) \leq x(t, x_2, v),\ \forall t \geq 0.$$

The partial orders are interpreted here as $\leq_U$ or $\leq_X$ in the obvious manner. If there is no input space, i.e. if the system is autonomous, then the system is monotone if $x_1 \leq x_2$ implies $x(t, x_1) \leq x(t, x_2)$ for all t. The cones will usually be omitted if they are clear from the context. We observe also that if $x_1 \leq x_2$, $u_1, u_2 \in U_\infty$ and $u_1(t) \leq u_2(t)$ on $[0, s]$, then $x(s, x_1, u_1) \leq x(s, x_2, u_2)$. To see this, let $\bar{u}_i(t) = u_i(t), 0 \leq t \leq s$, and $\bar{u}_i(t) = a$ otherwise, for fixed $a \in U$. Then $\bar{u}_1 \leq \bar{u}_2$, and by monotonicity $x(s, x_1, \bar{u}_1) \leq x(s, x_2, \bar{u}_2)$. The conclusion follows by the remark after Definition 1.

A dynamical system (1) is said to have an *input to state (I/S) characteristic* $k^X : U \to X$ if for every constant input $\hat{u}(t) \equiv u \in U$, $x(t, x_0, u)$ converges[3] to $k^X(u) \in X$ as $t \to \infty$, for every initial condition $x_0 \in X$. Given a system with input and output (2.1) with $Y = U$, the function $k := h \circ k^X$ will be called the *feedback characteristic* of the system. (This function has been called *input to output characteristic* in previous work, where U and Y are not necessarily equal.) It can be easily shown that if (1) is monotone then k^X is a $\leq$-increasing function, see Angeli and Sontag [2].

Closed Loop Trajectories. Consider a system (2.1) and assume that $B_Y = B_U$, $Y = U$. Given a vector $x_0 \in X$, and a continuous function $x : \mathbb{R}^+ \to X$, it will be said that $x(t)$ is a *closed loop trajectory of (2.1) with initial condition* x_0 if $x(0) = x_0$ and $x(t) = \Phi(t, x_0, h \circ x(\cdot))$, for all $t \geq 0$.

Definition 2. *Suppose that (2.1) is such that, for each $x_0 \in X$, there is a unique continuous closed loop trajectory $x(t)$ so that $x(0) = x_0$. The function*

$$\Psi : \mathbb{R}^+ \times X \to X, \ \Psi(t, x_0) := x(t) \tag{2.2}$$

will be called the closed-loop behavior *associated to* (Φ, h). *If this function itself constitutes a dynamical system, then it is denoted as the* closed loop system associated to (Φ, h).

The semiflow condition for Ψ is actually guaranteed by the unique closed loop trajectory assumption. To see this, let $x(t)$ be an absolutely continuous closed loop trajectory, and $y_0 = x(t_0)$. Then the function $w(t) = x(t + t_0)$ can be shown to be itself an absolutely continuous closed loop trajectory, by using the semiflow condition for Φ. Therefore $w(t) = \Psi(t, y_0)$, and $\Psi(s_0, y_0) = z_0$ implies $x(t_0 + s_0) = w(s_0) = z_0$. To prove the continuity of Ψ on its second argument, one may nevertheless need to assume stronger continuity conditions than are stated in Definition 1. While the main result will not assume the existence or uniqueness of closed loop trajectories for any $x_0 \in X$, the fact that the closed loop system Ψ is well defined will be guaranteed in all our applications, since we will start off with an autonomous dynamical system in the first place (see the introduction).

The General Assumptions. A subset A of an ordered metric space $(T, \leq)$ is said to satisfy the *ϵ-box property* if for every $\epsilon > 0$ and $x \in A$, there are $y, z \in A$ such that diam $[y, z] < \epsilon$ and $[y, z] \cap A$ is a neighborhood of x (with respect to the relative topology on A). A simple example of a set that does *not* satisfy this property is $A := \{(x, y) \in \mathbb{R}^2 \mid x + y \geq 0\}$, under the usual positive orthant order for $\mathbb{R}^2$.

Let B_X, B_U be arbitrary Banach spaces ordered by cones $\mathcal{K}_X, \mathcal{K}_U$, and let (1) be a controlled dynamical system with states in $X \subseteq B_X$ and input values in $U \subseteq B_U$. Let $h : X \to U$ be a given feedback function. The following general hypotheses will be used throughout this paper:

H1: $\mathcal{K}_X$ and $\mathcal{K}_U$ are closed, normal cones with nonempty interior.

[3]This definition differs slightly with that in Angeli and Sontag [2], in that stability of the attractor $k^X(u)$ is not assumed. Nevertheless see the comments after Theorem 1.

H2: U is closed and convex. Moreover, for every bounded set $C \subseteq U$, there exist $a, b \in U$ such that $a \leq C \leq b$.
H3: $X \subseteq B_X$ and $U \subseteq B_U$ satisfy the ϵ-box property.
H4: $\Phi(t, x_0, u)$ is monotone, with a *completely continuous* I/S characteristic k^X. Furthermore, h is a $\leq$-decreasing feedback function that sends bounded sets to bounded sets.

Recall that a map $T : D \subseteq B_1 \to B_2$ is completely continuous if and only if it is continuous and $\overline{T(A)}$ is compact, for every bounded set $A \subseteq D$. Note that H4 implies that $k = h \circ k^X$ is completely continuous as well.

A notion related to H3 is proposed in Smith [32]: $x \in X$ *can be approximated from below* if there exists a sequence $\{x_n\}$ in X such that $x_1 < x_2 < x_3 < \ldots$ and x_n converges towards x as n tends to infinity. It is easy to see that H3 doesn't imply boundedness from below for every $x \in X$, for instance considering $X = [0, 1],\ x = 0$ and the usual order. It also holds that approximability from both below and above for all $x \in X$ doesn't imply the ϵ-property for X. An example for this is

$$X = \{(x_1, x_2) \in \mathbb{R}^2 |\ x_1 x_2 < 0\} \cup \{x_2 = 0\},\ x = (0, 0)$$

with the usual positive cone. Note that for orthant cones $K = \mathbb{R}^{s_1} \times \ldots \times \mathbb{R}^{s_n}$ ($s_i =$ '+' or '−'), any box (a, b) together with some or all of its faces satisfies condition H3. So does also any open X in an arbitrary Banach space ordered with a cone K with $\operatorname{int} K \neq \emptyset$.

In particular, consider $B_U = \mathbb{R}^m, B_X = \mathbb{R}^n$, $\mathcal{K}_U$ and $\mathcal{K}_X$ orthant cones. Let U be a closed box (not necessarily bounded), and let X be either an open set or an interval (bounded or not) that contains some or all of its sides. Given a monotone system $\dot{x} = f(x, u),\ u = h(x)$ with characteristic, f continuous and locally Lipschitz on x, and h $\leq$-decreasing and continuous, conditions H1,H2,H3,H4 are necessarily satisfied. Indeed, the only condition that still needs verification is that k^X is (completely) continuous; this has been done in [2].

3. **The Small Gain Theorem.**

Our first result is referred to as the Converging Input Converging State property, or CICS for short.

Theorem 1 (CICS)**.** *Consider a monotone system $\Phi(x, t, u)$ with a continuous I/S characteristic k^X, under hypotheses H1,H3. If $u(t)$ converges to $\bar{u} \in U$ as $t \to \infty$, then $x(t, x_0, u)$ converges to $\bar{x} := k^X(\bar{u})$, for any arbitrary initial condition x_0.*

Proof. Let $u(t) \to \bar{u}$. For $\epsilon > 0$, let $\delta > 0$ be such that $|v - \bar{u}| < \delta \Rightarrow \left|k^X(v) - \bar{x}\right| < \epsilon$. The assumption H3 can be used on U to construct a "δ-box" around $\bar{u}$, that is, to find $a, b \in U$ such that $\operatorname{diam}[a, b] < \delta$ and $[a, b] \cap U$ is a neighborhood of $\bar{u}$. In particular, it holds that $\left|k^X(v) - \bar{x}\right| < \epsilon$ for every $v \in [a, b] \cap U$, and that $\left|k^X(a) - k^X(b)\right| \leq 2\epsilon$.

Let now T_1 be such that $u(t) \in [a, b]$ for all $t \geq T_1$, and let $x_1 := x(T_1, x_0, u(t))$. Now the attention can be restricted to the input $u_1(t) := u(t + T_1)$ with the initial condition x_1. This trajectory has the same limit behavior as before but with the added advantage that now all input values correspond to globally attractive equilibria that are close to $\bar{x}$.

Let T_2 be large enough so that $\left|x(t, x_1, a) - k^X(a)\right| < \epsilon$ and $\left|\phi(t, x_1, b) - k^X(b)\right| < \epsilon$, for all $t \geq T_2$. Since by monotonicity

$$x(t, x_1, a) \leq x(t, x_1, u_1) \leq x(t, x_1, b), \quad \forall t \geq 0,$$

it follows that

$$|x(t, x_1, u_1) - x(t, x_1, a)| \leq M\,|x(t, x_1, b) - x(t, x_1, a)| \leq 4M\epsilon,\ \forall t \geq T_2,$$

where M is a normality constant for C_X. Thus $|x(t, x_1, u_1) - \bar{x}| \leq (4M + 2)\epsilon$, for all $t \geq T_2$. This proves the assertion. □

Several remarks are in order. First, this theorem is an infinite-dimensional generalization of Proposition V5, number 2) in [2]. In addition, even in the finite dimensional case, it holds using weaker assumptions on the characteristic (in [2], an additional stability property is imposed on $k^X(u)$, for every fixed $u \in U$). See [28] for a counterexample showing that, in the absence of stability or monotonicity, systems with characteristics may fail to exhibit the CICS property. Conclusion 1) in Proposition V5 of [2], namely the stability of the system $x(t, x, u)$ for fixed $u(t) \to \bar{u}$, may not hold here in general. Nevertheless it holds under relatively weak additional hypotheses: if a, b are such that $a \ll \bar{u} \ll b$, and k^X is $\ll$-increasing, then $(k^X(a), k^X(b))$ is an open neighborhood of $\bar{x}$, and by monotonicity $x(t, x_0, v) \in (k^X(a), k^X(b))$ for any $t \geq 0$, whenever $x_0 \in (k^X(a), k^X(b))$ and $v(t) \in (a, b)$ for all t. Thus stability holds for instance if U is open and k^X is $\ll$-increasing. A similar argument shows that stability holds if k^X is an open function. CICS is a strong property of systems with both characteristic and monotonicity, and it will be used frequently in what follows.

The Small Gain Theorem. Monotone systems have very useful global convergence properties (see Hirsch [14], Smith [32]), but many gene and protein interaction networks are not themselves monotone. We will consider the closed loop of a monotone controlled system (when it is defined), forming an autonomous system in which nevertheless the monotonicity will be of use.

Let $u \in U_\infty$ be an input. An element $v \in U$ will be called a *lower hyperbound of* u if there exist sequences $v_1, v_2, \ldots \to v$ and $t_1 < t_2 < \ldots \to \infty$ such that for all $k \geq 1$ and $t \geq t_k,\ v_k \leq u(t)$. A similar definition is given if for every $t \geq t_k,\ v_k \geq u(t)$, and v is said to be an *upper hyperbound of* u. Identical definitions are given for the state space.

Lemma 3. *Suppose given a system (1) under hypotheses H3,H4. Let* $u \in U_\infty$*, and let* v *be a lower (upper) hyperbound of* u*. Then for any arbitrary initial condition* $x_0 \in X$*,* $k^X(v)$ *is a lower (upper) hyperbound of* $x(\cdot) = \Phi(\cdot, x_0, u)$*.*

Proof. Suppose v is a lower hyperbound of $u(\cdot)$, the other case being similar, and let $v_1, v_2, \ldots \to v$ and $t_1 < t_2 < \ldots \to \infty$ be as above. For every positive integer n, let $y_n, z_n \in X$ be such that $\mathrm{diam}(y_n, z_n) < 1/n$ and $V_n := [y_n, z_n] \cap X$ is a neighborhood of $k^X(v_n)$ (such y_n, z_n exist by H3).

For $n \geq 1$ let

$$u_n(t) := \begin{cases} u(t), & 0 \leq t < t_n \\ v_n, & t \geq t_n. \end{cases}$$

The numbers $T_1 < T_2 < \ldots \infty$ are defined by induction as follows: let $T_0 := 0$, and given T_{n-1}, let T_n be chosen so that $T_n \geq T_{n-1} + 1$, $T_n \geq t_n$ and for all $t \geq T_n$: $x(t, x_0, u_n) \in V_n$. By monotonicity, $y_n \leq x(t, x_0, u)$ for every $t \geq T_n$. Finally, by construction, $y_n \to k^X(v)$ as $T_n \to \infty$, and so $k^X(v)$ is a lower hyperbound of $x(\cdot)$. □

We use a result from Dancer [7], slightly adapted to our setup, which will provide a simple criterion to study the global attractivity of discrete systems

$$x_{n+1} = T(x_n) \tag{3.3}$$

when the function T is $\leq$-increasing.

Lemma 4. *Let K be a closed, normal cone with nonempty interior defined on a Banach space B, and let $M \subseteq B$ satisfy axiom H2 (i.e. with U replaced by M). Let $T : M \to M$ be $\leq$-increasing and completely continuous. Suppose also that the system (3.3) has bounded forward orbits, and that there is a unique fixed point $\bar{x}$ of T. Then all solutions of (3.3) converge towards $\bar{x}$.*

Proof. It is easy to see that a set $C \subseteq B$ is order-bounded (in the sense of Dancer [7]) if and only if it is bounded in B. Since T sends bounded sets to precompact sets, it also holds that the orbits of (3.3) are precompact in M.

The same argument can now be used as in Lemma 1 of Dancer [7]: given $x \in M$, let $\omega(x) \leq u$ for some $u \in U$, using H2. It then holds that $\omega(x) \leq \omega(u)$ pointwise. Let similarly $\omega(u) \leq \omega(z)$, for $z \in M$, and let $S = \{y \in M \,|\, \omega(x) \leq y \leq \omega(z)\}$. Then S is nonempty, closed, and convex, again using H2. By the Schauder fixed point, one finds $f \in S$ such that $T(f) = f$. But necessarily $f = \bar{x}$. One similarly concludes $\bar{x} \leq \omega(x) \leq \bar{x}$, and thus that $\omega(x) = \{\bar{x}\}$. □

It is a well-known result that if $T : \mathbb{R} \to \mathbb{R}$ is a continuous, bounded, non increasing function, then system (3.3) is globally attractive towards its unique fixed point $\bar{x}$ if and only if the equation $T^2(x) = T(T(x)) = x$ has only the trivial solution $\bar{x}$. The following consequence of the above lemma generalizes this result to an arbitrary space (see also Kulenovic and Ladas [21]).

Lemma 5. *Assume the same hypotheses of Lemma 4, except that $T : M \to M$ is $\leq$-decreasing instead of $\leq$-increasing. Then system (3.3) is globally attractive towards $\bar{x}$ if and only if the equation $T^2(x) = x$ has only the trivial solution $\bar{x}$.*

Proof. Any solution of $T^2(x) = x$ other than $x = \bar{x}$ would contradict the global attractivity towards $\bar{x}$, since it would imply the existence of a two cycle $T(x) = y$, $T(y) = x$ (if $x \neq y$) or of another fixed point of T (if $x = y$). Conversely, assume that the only solution of $T^2(x) = x$ is $\bar{x}$. Then T^2, being $\leq$-increasing, satisfies all hypotheses of the above lemma, and therefore for any $x \in B$ it holds that $T^{2n}(x)$ converges to $\bar{x}$. But so does $T^{2n+1}(x)$, too, for any fixed $x \in B$. The conclusion follows. □

Definition 3. *We say that a system (2.1) with I/S characteristic k^X satisfies the* small gain condition *if the following properties hold:*

1. *The system $u_{n+1} = k(u_n)$ has bounded orbits for every initial condition $u_0 \in U$.*
2. *The equation $k^2(u) = u$ has a unique solution $\bar{u} \in U$.*

The terminology "small gain" arises from control theory. Classical small-gain theorems (cf. [8, 29, 30, 38]) show stability based on the assumption that the closed-loop gain (meaning maximal amplification factor at all frequencies) is less than one, hence the name. These results are formulated in terms of appropriate Banach spaces of causal and bounded signals, and amount to the fact that the open-loop operator $I+F$ is invertible, and thus solutions exist in these spaces, provided that the closed-loop operator F has operator norm < 1. The characteristic k in the current setup plays an analogous role to F; observe that, for linear k, norm < 1 would guarantee stability. Versions with "nonlinear gains" were introduced in [25], and the most useful ones were developed by [17] on the basis of the notion of "input to state stability" from [34]; see also the related paper [15, 36]. The current formulation is from [2].

The main result of this paper, denoted as the *small gain theorem* or SGT for short, gives sufficient conditions for the bounded closed loop trajectories of a system (Φ, h), under negative feedback, to converge globally to an equilibrium. Observe that in view of Lemma 5, and under the hypotheses H1,H4, a system (2.1) satisfies the small gain condition if and only if the system $u_{n+1} = k(u_n)$ is globally attractive to an equilibrium. The two statements will be used interchangeably in the applications.

Theorem 2 (SGT). *Let (2.1) be a system satisfying the assumptions H1,H2,H3, H4, and suppose that the small gain condition is satisfied. Then all bounded closed loop trajectories of (2.1) converge towards* $\bar{x} = k^X(\bar{u})$.

Proof. Let $x_0 \in X$ be an arbitrary initial condition, and let $x(\cdot)$, $u = h \circ x$ be a bounded closed loop trajectory and its corresponding feedback, respectively. Let α be a lower hyperbound of $u(\cdot)$. Such an element always exists: by H3 the range of $u(\cdot)$ is bounded, and by H2 there exist $\alpha, \beta \in U$ that bound the bounded function u entirely from below and above, respectively. Then by Lemma 3, $k^X(\alpha)$ and $k^X(\beta)$ are lower and upper hyperbounds of x, respectively. Since h is a continuous, $\leq$-decreasing function, it is easy to see that $k(\alpha)$, $k(\beta)$ are upper and lower hyperbounds of u respectively. Similarly, one concludes that $k^2(\alpha)$, $k^2(\beta)$ are lower and upper hyperbounds of u respectively, by using Lemma 3 once more. By repeating this procedure twice at a time, it is deduced that $k^{2n}(\alpha)$, $k^{2n}(\beta)$ are also lower and upper hyperbounds of $x(t)$, for every natural n.

Now, $k^{2n}(v)$ converges as $n \to \infty$ towards $\bar{u}$ for all $v \in U$ by H4, the small gain condition and Lemma 4. But this implies that u converges to $\bar{u}$. This is proven as follows: given $\epsilon > 0$, there is n large enough so that $\left|k^{2n}(\alpha) - \bar{u}\right| < \epsilon$, $\left|k^{2n}(\beta) - \bar{u}\right| < \epsilon$. By definition of lower and upper hyperbound, there are $a, b \in U$ and $T \geq 0$ large enough such that $\left|a - k^{2n}(\alpha)\right| < \epsilon$, $\left|b - k^{2n}(\beta)\right| < \epsilon$ and for every $t \geq T :\ a \leq u(t) \leq b$. The normality of the cone $\mathcal{K}_U$ is used in the same way as in the proof of CICS: for M a normality constant of $\mathcal{K}_U$, it holds that $|u(t) - a| \leq M\,|b - a| < 4\epsilon M$, and so $|u(t) - \bar{u}| \leq 4\epsilon M + 2\epsilon$, for all $t \geq T$.

By CICS, the solution $x(\cdot)$ converges to $k^X(\bar{u})$. This shows the global attractivity towards the point $\bar{x} = k^X(\bar{u})$. □

Corollary 1. *Let (2.1) be a system satisfying assumptions H1,H2,H3,H4 and the small gain condition. If the closed loop system* $\Psi(t, x)$ *is well defined and has bounded solutions, and the if equation* $k^2(u) = u$ *has a unique solution, then* $\Psi(t, x)$ *has a unique globally attractive equilibrium* $\bar{x}$.

Proof. It is sufficient to observe that every solution $x(t)$ of the closed loop system $\Psi(t, x)$ is in particular a closed loop trajectory, and to invoke Theorem 2. □

The statement of Theorem 2 in [2] is restricted to single input, single output systems in finite dimensions and doesn't address the equivalence provided by Lemma 5.

Finally, the same proof as above can be carried out for the case in which h is $\leq$-increasing (rather than $\leq$-decreasing), assuming simply that there is a unique fixed point $\bar{u}$ of k. Nevertheless this latter result is not very strong, since it follows from weaker hypotheses. See for instance Ji Fa [16], and de Leenheer, Angeli and Sontag [22].

4. **Stability in the Small Gain Theorem.** In this section we turn to the question of stability for the closed loop trajectories considered in Theorem 2. Given a vector $x_0 \in X$, we say that a system (2.1) has *stable closed loop trajectories around* x_0 if for every $\epsilon > 0$ there is $\delta > 0$ such that $|z_0 - x_0| < \delta$ implies $|z(t) - x_0| < \epsilon$, $t \geq 0$, for any closed loop trajectory $z(t)$ with initial condition z_0. Of course, if the closed loop system $\Psi(t, x)$ is well defined, then this is equivalent to the stability of $\Psi(t, x)$ at x_0. The basic idea is given by the following lemma.

Lemma 6. *Let (2.1) be a monotone system with characteristic k^X and a $\leq$-decreasing feedback function h. Let $y \ll z$ in X be such that $k^X h(y), k^X h(z) \in (y, z)$. Then any closed loop trajectory $x(t)$ of (2.1), with initial condition $x_0 \in [k^X h(z), k^X h(y)]$, satisfies $x(t) \in (y, z)$, $t \geq 0$.*

Proof. Let $k^X h(z) \leq x_0 \leq k^X h(y)$, and let $x(t)$ be a closed loop trajectory of (2.1) with initial condition x_0. Suppose that the conclusion doesn't hold, and let by contradiction
$$t_0 := \min\{t \geq 0 \,|\, x(t) \notin (y, z)\}.$$
It is stressed that as $x(0) \in (y, z)$, $x(\cdot)$ is continuous, and the interval (y, z) is open, it holds that $x(t_0) \notin (y, z)$. Nevertheless $u(\cdot) = h \circ x(\cdot)$ satisfies $h(z) \leq u(t) \leq h(y)$ for $t < t_0$, and therefore also $h(z) \leq u(t_0) \leq h(y)$ by continuity. Then by monotonicity
$$k^X(h(z)) = x(t, k^X(h(z)), h(z)) \leq x(t, x_0, u) \leq x(t, k^X(h(y)), h(y)) = k^X(h(y)),$$
for all $t \leq t_0$, and in particular,
$$y \ll k^X h(z) \leq x(t_0) \leq k^X h(y) \ll z,$$
which is a contradiction. □

In the case in which h is $\leq$-increasing the lemma also holds. One may interchange "$h(y)$" and "$h(z)$" in the above proof to obtain the corresponding stability result.

Define $\gamma(x) := k^X h(x)$. The result in Lemma 6 is applied systematically in the following proposition to guarantee the stability of the closed loop.

Lemma 7. *Under the hypotheses of Theorem 2, let $\bar{x} = k^X(\bar{u})$, and let $\{y_n, \}, \{z_n\}$ be sequences in X such that $y_n, z_n \to \bar{x}$ as $n \to \infty$. Assume also that for every n, $\gamma(z_n) \ll \bar{x} \ll \gamma(y_n)$ and $\gamma(y_n), \gamma(z_n) \in (y_n, z_n)$. Then (2.1) has stable closed loop trajectories around $\bar{x}$.*

Proof. Let V be an open neighborhood of $\bar{x}$. For $\epsilon > 0$, let y_n, z_n be within distance ϵ of $\bar{x}$, for some n large enough. For $x \in (y_n, z_n)$, one has $|x - y_n| \leq 2M_X\epsilon$ and $|x - \bar{x}| \leq 2M_X\epsilon + \epsilon$, by normality. Thus for ϵ small enough, $(y_n, z_n) \subseteq V$. It follows that $(\gamma(z_n), \gamma(y_n))$ is a neighborhood of $\bar{x}$ with the property that all closed loop trajectories with initial condition in this set are contained in V (by the previous lemma). □

The following lemma provides a simple criterion for the application of Lemma 7.

Lemma 8. *Under the hypotheses of Theorem 2, suppose that k^X is $\ll$-increasing and h is $\ll$-decreasing. Suppose that there exists $z \in$ int X such that $\bar{x} \ll k^2(z) \ll z$. Then (2.1) has stable closed loop trajectories around $\bar{x}$.*

Proof.
Recall that $\bar{x}$ is a fixed point of γ. Let $y := \gamma(z) - \nu$, where $\nu \gg 0$ is small enough that $\gamma(y) \ll z$; this is possible by continuity of γ. It holds that

$$y \ll \gamma(z) \ll \bar{x} \ll \gamma(y) \ll z.$$

It is easy to see how this implies that

$$\gamma^2(y) \ll \gamma^4(y) \ll \ldots \ll \bar{x} \ll \ldots \ll \gamma^4(z) \ll \gamma^2(z),$$

using the fact that γ^2 is $\ll$-increasing. By Lemma 5, $y_n := \gamma^{2n}(y)$ and $z_n := \gamma^{2n}(z)$ converge to $\bar{x}$, and thus these sequences satisfy the hypotheses of Lemma 7. □

The following theorem will ensure the stability of the closed loop in the case that the input space is one or two-dimensional. Note that this can be the case even if X is infinite dimensional.

Theorem 3. *Under the hypotheses of Theorem 2, let $B_U = \mathbb{R}$ or $B_U = \mathbb{R}^2$, and let $U \subseteq B_U$ be a (not necessarily bounded) closed interval with positive measure. If k^X is $\ll$-increasing and h is $\ll$-decreasing, then (2.1) has stable closed loop trajectories around $\bar{x}$.*

Proof. Recall the notation $k(u) = hk^X(u)$. It is only needed to prove in both cases that there exists $z \in X$ such that $\bar{x} \ll k^2(z) \ll z$, by Lemma 8. In the case $B_U = \mathbb{R}$, let $c \in \text{int}\, U$, $c > \bar{u}$. Then necessarily $\gamma^2(c) < c$, since otherwise the sequence $c \leq \gamma^2(c) \leq \gamma^4(c) \leq \ldots$ would not converge towards $\bar{u}$. Using the fact that k^X is $\ll$-increasing, it follows that $z := k^X(c)$ satisfies $\bar{x} \ll \gamma^2(z) \ll z$.

If $B_U = \mathbb{R}^2$, let A be a 2×2 matrix such that $A\mathcal{K}_U = (\mathbb{R}^+)^2$, and define $\phi(u) = A(u - \bar{x})$, $\kappa(u) = \phi k \phi^{-1}(u)$. Note that $u \ll v$ if and only if $Au \leq_{(1,1)} Av$, and that the system $u_{n+1} = \kappa(u_n)$ is $\ll$-decreasing in the cooperative order $(1,1)$ and converges globally towards 0.

We want to find $c \gg_{(1,1)} 0$ such that $\kappa^2(c) \ll_{(1,1)} c$, since then the vector $z := k^X \phi^{-1} c$ will satisfy $\bar{u} \ll \gamma^2(z) \ll z$. Suppose by contradiction that there is no such point. By global attractivity, for any $u \gg_{(1,1)} 0$ it must hold $\kappa^2(u) \not\gg_{(1,1)} u$. Then the function $\alpha(u) := \kappa^2(u) - u$ is such that $\alpha(\mathbb{R}^+ \times \mathbb{R}^+) \subseteq (\mathbb{R}^+ \times \mathbb{R}^-) \cup (\mathbb{R}^- \times \mathbb{R}^+)$. But if there existed $v, w >_{(1,1)} 0$ such that $\alpha(v) \in \mathbb{R}^+ \times \mathbb{R}^-$, $\alpha(w) \in \mathbb{R}^- \times \mathbb{R}^+$, then by joining the points v and w with a line one would find a point $q >_{(1,1)} 0$ such that $\alpha(q) = 0$ by continuity, that is, a nonzero fixed point of $\kappa^2 u = u$. This contradicts attractivity. Assume therefore that $\kappa^2(u)_1 \leq u_1$, $\kappa^2(u)_2 \geq u_2$ holds for all $u \gg_{(1,1)} 0$, the other case being similar. Then $0 < u_2 \leq \kappa^2(u)_2 \leq \kappa^4(u)_2 \leq \ldots$, which also violates attractivity. The conclusion is that $0 \ll \kappa^2(c) \ll_{(1,1)} c$ for some c. □

The following corollary of Lemma 8 strengthens the hypotheses of Theorem 2 to imply the stability of the closed loop in arbitrary input spaces. Thus, instead of assuming that the function $u \to k(u)$ defines a globally attractive system and is $\leq$-decreasing, we will assume that its *linearization* T around $\bar{u}$ defines a globally attractive system and that $u < v$ implies $T(u) \gg T(v)$. The linearization is taken here in the usual sense of Frechet differentiation.

Corollary 2. *Under the hypotheses of Theorem 2, suppose that k^X is $\ll$-increasing and h is $\ll$-decreasing. Assume that the linear operator $T = k'(\bar{u})$ is well defined and compact, and that i) $u_{n+1} = T(u_n)$ is a globally attractive discrete system, ii) $T(K_U - \{0\}) \subseteq -int\ K_U$. Then (2.1) has stable closed loop trajectories around $\bar{x}$.*

Proof. By i), the operator $T^2 u = (k^2)'(u)$ defines a globally attractive discrete system. Hence the point spectrum of T^2 is contained in the open complex unit ball. By ii), it holds that T^2 is a strongly monotone operator, and in particular $\lambda := \rho(T) > 0$. By the Krein Rutman theorem, there is $v \gg 0$ such that $T^2(v) = \lambda v$. But since $0 < \lambda < 1$, it holds that $0 \ll T^2(v) \ll v$. Let $|v| = 1$ and $\epsilon > 0$ be such that $0 \ll B(\epsilon, T^2(v)) \ll B(\epsilon, v)$ pointwise in U. Letting $\delta > 0$ be small enough that $\left|k^2(\bar{u} + u) - T^2(u) - \bar{u}\right| < \epsilon\,|u|$ whenever $|u| < \delta$, it follows that $\bar{u} \ll k^2(u + \lambda\delta v) \ll \bar{u} + \delta v$. The conclusion follows from Lemma 8. □

An Application of Theorem 3. The local stability of finite-dimensional systems can usually be verified by calculating the eigenvalues of the linearized system around the equilibrium. Nevertheless further understanding of the stability of the system is difficult to extract in this way, especially in the case of large-scale systems and variable (or unknown) parameters. One finite-dimensional illustration of Theorem 3 can be found in Section VII of [2], where global attractivity is proven for a model of MAP kinase cascade dynamics. We prove here that this system is actually asymptotically stable. The fact that the model satisfies the hypotheses of Theorem 2 is mostly guaranteed from the last paragraph of Section 2 of this paper. It will be assumed here, since later examples will treat these hypotheses at length.

The system in question can be written as the closed loop system of the following controlled dynamical system (after a simple change of variables):

$$\begin{aligned} \dot{x} &= \theta_1(1-x) - u\theta_2(x) \\ \dot{y} &= \theta_3(1-y-z) - (1-x)\theta_4(y) \\ \dot{z} &= (1-x)\theta_5(1-y-z) - \theta_6(z) \\ \dot{Y} &= \theta_7(1-Y-Z) - z\theta_8(Y) \\ \dot{Z} &= z\theta_9(1-Y-Z) - \theta_{10}(Z), \end{aligned} \qquad h(x,y,z,Y,Z) = \frac{K}{1 + \frac{g_1+Z}{g_2+Z}}, \tag{4.4}$$

where $\theta_i(x) := a_i x/(b_i + x)$, for positive constants a_i, b_i, $K > 0$, and $g_2 > g_1 > 0$. It is shown in [2] that (4.4) is monotone with respect to the cones $\mathbb{R}^+$ for the input, and $\mathbb{R}^- \times \mathbb{R}^- \times \mathbb{R}^+ \times \mathbb{R}^- \times \mathbb{R}^+$ for the states. It is only needed to verify that k^X is $\ll$-increasing and h is $\ll$-decreasing, the latter of which can be easily checked. To verify the former, note that the system is a cascade of three subsystems $x \to (y,z) \to (Y,Z)$ with characteristic, and that it is enough to verify that each of the characteristic functions is $\ll$-increasing. This is done for the third subsystem, the other two being very similar.

For every fixed input z of the third subsystem, the state converges towards the globally attractive state $(Y,Z) = k^{(Y,Z)}(z)$. By monotonicity, if $z_1 < z_2$ and $(Y_i, Z_i) = k^X(z_i)$, $i = 1,2$, it follows that $Z_1 \leq Z_2$, $Y_1 \geq Y_2$. But by definition $z_i = \theta_7(1 - Y_i - Z_i)/\theta_8(Y_i)$, and thus one cannot have both $Z_1 = Z_2$ and $Y_1 = Y_2$. On the other hand, since also by definition it holds that

$$\theta_8(Y)\theta_{10}(Z) = \theta_7(1-Y-Z)\theta_9(1-Y-Z),$$

and all θ_j are strictly increasing, then Y cannot decrease without Z increasing, and vice versa. Putting all together, one concludes that $z_1 < z_2$ implies $Z_1 < Z_2$, $Y_1 > Y_2$, so that in particular $k^{(Y,Z)}$ is $\ll$-increasing. A similar argument for the remaining subsystems shows that the characteristic of (4.4) is $\ll$-increasing, as desired, and stability of (4.4) follows.

5. **Delay Systems.** The abstract treatment we have followed allows us to specialize to situations that generalize the single input, single output setup considered in [2]. Apart from including multiple inputs and outputs, one possible generalization consists of allowing diffusion terms in the equations, and thus transforming them into a weakly coupled system of PDEs. This is out of the scope of this paper, and it will be discussed elsewhere. From now on, we will rather consider the introduction of delay terms in finite-dimensional systems of ODEs. One example of such systems is

$$\dot{x}(t) = Ax(t-r) + Bx(t), \tag{5.5}$$

where A, B are $n \times n$ constant matrices. Note that the initial condition of such a system would have to include not only $x(-r)$ and $x(0)$, but also all $x(s)$ for $-r < s < 0$.

Given $r \geq 0$ (the delay of the system), $a \leq \infty$, $x : [-r, a) \to \mathbb{R}^n$ and $0 \leq t < a$, define $x_t \in X$ as $x_t(s) = x(t+s),\ s \in [-r, 0]$. A general autonomous delay system can be thus written as

$$\dot{x}(t) = f(x_t),\ x_0 = \phi, \tag{5.6}$$

where $\phi : [-r, 0] \to \mathbb{R}^n$, and f has values in $\mathbb{R}^n$. The state of the system at time t is considered to be x_t (as opposed to just $x(t)$). Thus even though the equation is defined in a finite dimensional context, the proper dynamical system $\Phi(t, \phi) = x_t$ is defined in a suitable state space of such functions.

Similar comments apply to the controlled system

$$\dot{x} = f(x_t, \alpha(t)), \tag{5.7}$$

which defines a dynamical system $\Phi(t, \phi, \alpha) = x_t$, for every input $\alpha : [0, \infty) \to U$. The set U of input values will be allowed to consist itself of functions, in order to include delays in the inputs. The delay r_{input} used for input values will nevertheless be allowed to be different from that used for states, which will be referred to as r_{state}. Thus if α is an input, then for every $t \geq 0$, $\alpha(t) : [-r_{\text{input}}, 0] \to U_0$ is a function $\alpha(t)(s)$ (though not necessarily of the form $\alpha(t) = u_t$ for some $u : \mathbb{R}^+ \to X_0$, see below). It will be clear from the context when α is an *input* ($\alpha \in U_\infty$), and when it is an *input value* ($\alpha \in U$).

Let $U_0 \subseteq \mathbb{R}^m$ be a closed box (possibly unbounded), and $X_0 \subseteq \mathbb{R}^n$ be open or, in the case of $\mathcal{K}_{X_0}$ being an orthant cone, a box including some or all of its faces. Define

$$B_X := C([-r_{\text{state}}, 0], \mathbb{R}^n),\ X := C([-r_{\text{state}}, 0], X_0)$$

under the supremum norm. The tentative choice of the function space

$$B_U = L^\infty([-r_{\text{input}}, 0], \mathbb{R}^n)$$

carries with it a problem: for a delay system such as

$$\dot{x} = f(x_t, u_t) = u(t-1) - u(t) + x(t-1) - x(t),$$

the function f cannot have as argument an input value $\alpha \in L^\infty([-r_{\text{input}}, 0], \mathbb{R}^n)$, since such functions are not defined pointwise. Thus in the case of discrete delays, the input space will be restricted to $B_U := C([-r_{\text{input}}, 0], \mathbb{R}^m)$, $U = C([-r_{\text{input}}, 0], U_0)$. In the case of distributed delays, this problem disappears; for this reason B_U will be allowed to be either $L^\infty([-r_{\text{input}}, 0], \mathbb{R}^n)$ or $C([-r_{\text{input}}, 0], \mathbb{R}^m)$, and U will be defined accordingly.

Definition 4. *A* delay dynamical system *consists of a tuple* (X, U, f)*,* $f : X \times U \to \mathbb{R}^n$*, and* X*,* U *as above for some* $X_0 \subseteq \mathbb{R}^n$*,* $U_0 \subseteq \mathbb{R}^m$*, with the following property: for any initial condition* $\phi \in X$ *and any measurable, locally bounded* $\alpha : \mathbb{R}^+ \to U$*, there is a unique maximally defined, absolutely continuous function* x *such that*

$$\dot{x}(t) = f(x_t, \alpha(t)) \text{ for almost every } t,\ x_0 = \phi. \tag{5.8}$$

The lowercase greek letters ϕ, ψ will be used to refer to elements of X, that is, $\phi, \psi : [-r, 0] \to X_0$ continuous, and α, β will be used for elements in U as well as for inputs in U_∞.

In the case that $U = C([-r_{\text{input}}, 0], U_0)$, note that for a discontinuous input $u : \mathbb{R}^+ \to U_0$, the function $t \to u_t$ is not a well defined input in U_0. The following lemma will provide a source of allowed inputs for each choice of the space B_U. (Recall that an input $u \in U_\infty$ is any locally bounded, measurable function $u : \mathbb{R}^+ \to U$.)

Lemma 9. *Let* $u : [-r_{input}, \infty) \to U_0$ *be continuous. If* $B_U = L^\infty([-r_{input}, 0], \mathbb{R}^m)$*, or if* $B_U = C([-r_{input}, 0], \mathbb{R}^m)$*, then the function* $\alpha : [0, \infty) \to B_U$*, defined as* $\alpha(t) := u_t$*, is a well defined input in* U_∞*.*

Let B_U *be any of the two spaces above, and consider* $\tau_1, \tau_2, \ldots \tau_k$*, where* $\tau_i \in [-r_{input}, 0]$ *for all* i*. If* $u \in (U_0)_\infty$*, and if* U_0 *is convex, then there exists an input* $\alpha \in U_\infty$ *such that* $\alpha(t)(\tau_i) = u_t(\tau_i)$*, for all* i *and* $t \geq 0$*.*

Proof. A continuous function $u : [-r_{\text{input}}, \infty) \to U_0$ is uniformly continuous on every closed bounded interval. This implies that $\|u_s - u_t\|_\infty \to 0$ if $s \to t$, and therefore that the function $\alpha(t) = u_t$ is continuous, for both choices of the space B_U. The local boundedness of α follows directly from that of u.

To prove the second statement, and assuming without loss of generality that the τ_i are pairwise distinct, consider a continuous partition of unity $\nu_1 \ldots \nu_k : [-r_{\text{input}}, 0] \to [0, 1]$ such that $\nu_j(\tau_j) = 1$ for all $j = 1 \ldots k$ and $\nu_j(\tau_i) = 0$, $i \neq j$. Let

$$\alpha(t)(s) := \nu_1(s)u(t + \tau_1) + \ldots + \nu_k(s)u(t + \tau_k).$$

For every $t \geq 0$, $\alpha(t)$ is a linear combination of continuous functions, and therefore $\alpha(t) \in B_U$. To prove measurability, note that each function $\nu_i(s)u(t + \tau_i)$ is measurable by writing it as the composition of

$$\mathbb{R}^+ \xrightarrow{\zeta} C([-r_{\text{input}}, 0], [0, 1]) \times \mathbb{R}^m \xrightarrow{\xi} B_U,$$

where $\zeta(t) := (\nu_i, u(t))$, $\xi(\phi, q) := q\,\phi$, ζ is measurable and ξ is continuous. It holds that Range $\alpha(t) \subseteq U_0$ for every t, by convexity of U_0. The local boundedness of α follows from that of u, and the fact that $\alpha(t)(\tau_i) = u_t(\tau_i)$ for all t and i can be easily verified. $\square$

The second statement of the above lemma is useful when considering a system (5.7) in which $f(\phi, \alpha)$ only depends on the values of ϕ at discrete times $\tau_1, \ldots, \tau_k$, that is, in the case of point delays. In this case, given an input u in U_0, the function u_t can be replaced by the input α in Lemma 9 for all practical purposes.

In the Appendix II the question is addressed as to which functions $f : X \times U \to \mathbb{R}^n$ generate a well defined delay dynamical system. The main result is the following theorem, where X_0, U_0, X, U are as described in the end of Section 2.

Theorem 4. *Let $f : X \times U \to \mathbb{R}^n$ be continuous and locally Lipschitz on X, locally uniformly on U. Let also $f(\phi, C)$ be bounded, for any $\phi \in X$, $C \subseteq U$ closed and bounded. Then the system (5.8) has a unique maximally defined, absolutely continuous solution $x(t)$, for every input $\alpha(t)$ and every initial condition $\phi \in X$.*

We give conditions on X_0, U_0 and the underlying cones in $\mathbb{R}^n, \mathbb{R}^m$ that guarantee that the general hypotheses H1,H2,H3 are satisfied.

Lemma 10. *Let U_0 be a closed box (possibly unbounded), and let X_0 be open or, in the case of $\mathcal{K}_{X_0}$ being an orthant cone, a box including some or all of its faces. Let $\mathcal{K}_{U_0} \subseteq \mathbb{R}^m, \mathcal{K}_{X_0} \subseteq \mathbb{R}^n$ be closed cones with nonempty interior, r_{input}, $r_{state} \geq 0$, B_X, B_U as in Definition 4, and let $\mathcal{K}_X := \{\phi \in B_X |\ \phi(s) \in \mathcal{K}_{X_0}\ \forall s\}$, $\mathcal{K}_U := \{\alpha \in B_U |\ \alpha(s) \in \mathcal{K}_{U_0}$ a.e. $s\}$. Then conditions H1,H2 and H3 in the general hypotheses are satisfied for $X, U, \mathcal{K}_X, \mathcal{K}_U$.*

Proof. By Lemmas 1 and 2, $\mathcal{K}_{X_0}, \mathcal{K}_{U_0}$ are normal. Let M, N be normality constants for $\mathcal{K}_{X_0}, \mathcal{K}_{U_0}$ respectively. If $0 \leq \phi \leq \psi$ in X, that is $0 \leq \phi(s) \leq \psi(s)$ in X_0 for every s, then it holds that $|\phi(s)| \leq M\,|\psi(s)|$, for every s. This asserts the normality of $\mathcal{K}_X$ with normality constant M. One proves similarly that $\mathcal{K}_U$ is normal.

Let $a \in \mathbb{R}^m$ bound the unit ball from above (see Section 2). Then the constant function $\hat{a}$ bounds the unit ball in B_U. This implies that $\mathcal{K}_U$ has nonempty interior. For $\alpha \in B_U$, the function $d(\alpha) :=$ ess sup$\{\mathrm{dist}(\alpha(s), \mathcal{K}_{U_0})|\ s \in [-r_{\mathrm{input}}, 0]\}$ is continuous, which implies that $\mathcal{K}_U = d^{-1}(0)$ is closed. The same argument applies to $\mathcal{K}_X$.

If X_0 is open, Range ϕ will remain a finite distance away from X_0^c, for every $\phi \in X$. Thus there is an open neighborhood around ϕ contained in X, which shows that X is open and satisfies the ϵ-box property. Let $s = (s_1, \ldots s_n)$, $s_i = \pm 1$ for all i, defining an orthant cone in a natural way as in Section 2. Let X be a box containing some or all of its sides. Consider a given state $\phi \in X$ and $\epsilon > 0$, and let

$$\eta := \frac{1}{3\sqrt{n}} \min(\epsilon, \mathrm{dist}(\mathrm{Range}(\phi), \partial X_0 - X_0).$$

Define $\pi_1, \pi_2 : X_0 \to X_0$ as

$$\pi_1(x) := \inf\{x + q \cdot s \,|\, q \in (-\eta, \eta),\ x + q \cdot s \in X\},$$
$$\pi_2(x) := \sup\{x + q \cdot s \,|\, q \in (-\eta, \eta),\ x + q \cdot s \in X\},$$

where the infimum and supremum are taken with respect to the order $\leq_s$.

Given $\phi \in X$, let $\phi_i(s) := \pi_i(x(s)),\ i = 1, 2..$ See Figure 1 for an illustration of these two functions. It is clear that π_1 and π_2 are both continuous functions. Then $(y =)\phi_1,\ (z =)\phi_2 \in X$ by construction, and diam$[\phi_1, \phi_2] = |\phi_2 - \phi_1| \leq |2\eta(1 \ldots 1)| = 2\eta\sqrt{n} < 3\eta\sqrt{n} \leq \epsilon$. Also, it is easy to see that

$$[\phi_1, \phi_2] = X \cap [\phi - \eta s, \phi + \eta s].$$

This implies that $[\phi_1, \phi_2] \subseteq X$ is a neighborhood of ϕ, and H3 thus holds for X.

In the case $B_U = C([-r_{\mathrm{input}}, 0], \mathbb{R}^m)$, the same proof above applies to prove H3 for U, even if some or all of its sides are missing. However, if $B_U = L^\infty([-r_{\mathrm{input}}, 0], \mathbb{R}^m)$, then for a given $\alpha \in U$ the distance between the range of α and $\partial U \setminus U$ may well be zero. One uses the fact that U is closed to show that for $\eta = \frac{1}{2\sqrt{m}}\epsilon$, $\pi_1, \pi_2 : U_0 \to U_0$ are well defined. Since the π_i are continuous, $\alpha_i(s) = \pi_i(\alpha(s))$ are measurable functions. The rest of the proof that U satisfies H3 follows similarly as above.

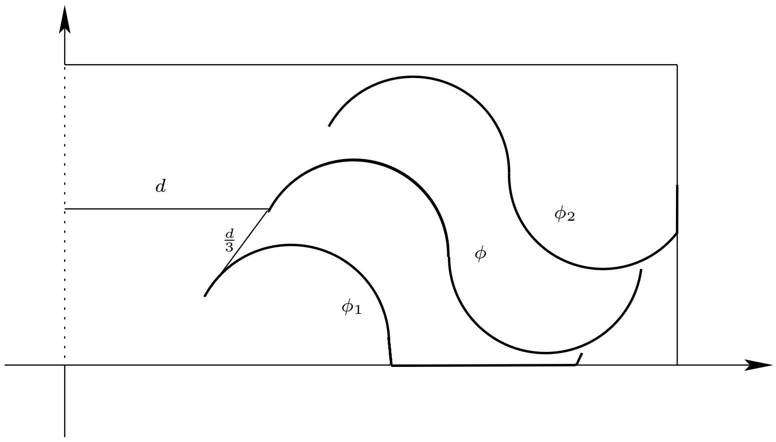

FIGURE 1. Shown in the picture is the box X_0 with one open and three closed faces, and $\phi_1 \leq \phi \leq \phi_2$ in bold. Here $d = \mathrm{dist}(\mathrm{Range}\, \phi, \partial X - X_0)$, and $\eta = d/(3\sqrt{2})$. Note that $|\phi(0) - \phi_1(0)| = |\eta(1,1)| = d/3$.

It will be proved that U satisfies H2. It is clear that U is closed and convex. In the case $B_U = C([-r_{\text{input}}, 0], \mathbb{R}^m)$, and given a bounded set $A \subseteq U$, consider the bounded set A_0 defined as the union of all the images of the functions in A. Use H2 on A_0 to find $a, b \in U_0$ such that $a \leq A_0 \leq b$. Then the constant functions $\hat{a}, \hat{b}$ do the same on the set A. In the case $B_U = L^\infty([-r_{\text{input}}, 0], \mathbb{R}^m)$, the axiom of choice allows to define A_0, by picking a particular point-by-point defined function for each $u \in A$. After possibly changing the values of each function at sets of measure zero to ensure that A_0 is bounded, the result follows as before. $\square$

We give a convenient criterion to check for monotonicity in the orthant cone case, which is based on Theorem 1.1 of Smith [32]. Refer to Figure 2 for an illustration of this criterion.

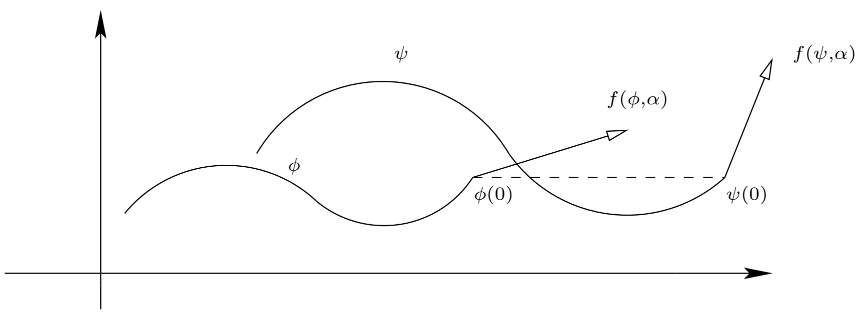

FIGURE 2. Monotonicity Criterion. Illustrated are two states $\phi, \psi : [-r_{\text{state}}, 0] \to \mathbb{R}^2$ with $\phi \leq \psi$ and $\phi_2(0) = \psi_2(0)$. In the cooperative case, the criterion requires that $f_2(\phi, \alpha) \leq f_2(\psi, \alpha)$.

Proposition 1 (Monotonicity Criterion)**.** *Let (5.7) be a delay system, and let* $\mathcal{K}_X$ *be the orthant cone defined by the tuple* $s = (s_1 \dots s_n)$*. Assume that i)* $\alpha \to f(\phi, \alpha)$ *is an increasing function, for every* $\phi \in X$*, and that ii) for every* $\alpha \in U$*,* $\phi \leq \psi$*, and if* $\phi_i(0) = \psi_i(0)$ *for some* i*, it holds that* $s_i f_i(\phi, \alpha) \leq s_i f_i(\psi, \alpha)$*. Then system (5.7) is monotone with respect to its underlying cones.*

Proof. See the appendix for a sketch of the proof. □.

Suppose that the delay system (X, U, f) allows an I/S characteristic $k^X : U \to X$. Note that $\phi = \Phi(t, k^X(\alpha), \hat{\alpha})$ is constant over t, and thus that any solution of (5.7) with constant input $\hat{\alpha}$ starting at $k^X(\alpha)$ must satisfy $x_t = k^X(\alpha)$ for all $t \geq 0$. This easily implies that $k^X(\alpha)$ is a constant function, for every α. Hence, since k^X has a finite dimensional range, it is easy to verify when it is completely continuous, namely the image of every bounded set should be bounded. One can also think of k^X as having values in X_0, and when evaluating $u_{n+1} = k(u_n)$ it is sufficient to consider constant initial conditions.

In the applications of this paper the feedback function $h : X \to U$ will be defined as $h(\phi)(s) = h_0(\phi(s))$, for some $h_0 : X_0 \to U_0$. In such case, it holds that $\bar{u}$ is itself a constant vector. Also note that if $z \in \mathbb{R}^m$ is such that $\bar{u} \ll k^2(z) \ll z$, then the constant function $\hat{z}$ has this property in U. Therefore one can apply Theorem 3 to prove stability in the context of delay systems.

To prove that $\Phi(t, \phi, \alpha)$ is a dynamical system, it is important to verify that the semiflow condition is satisfied. To avoid confusion, this is best done for an abstract input space U; a short proof will be given in the appendix.

Example. The following system corresponds to the cyclic gene model with repression studied in [31]. Let y_1 be a messenger RNA, which produces an enzyme y_2, which produces another enzyme y_3, and so on for $p \geq 2$ steps. Let y_p in turn inhibit the production of y_1, closing the cycle and inducing the repression. The system is modeled as

$$\begin{aligned} \dot{y}_1 &= F(L_p y_p^t) - a_1 y_1(t) \\ \dot{y}_i &= L_{i-1} y_{i-1}^t - a_i y_i(t), \qquad 2 \leq i \leq p, \end{aligned} \tag{5.9}$$

where $a_1, \dots, a_p > 0$, $F : [0, \infty) \to (0, \infty)$ is a strictly decreasing continuous function, and y_i^t stands for the delay term y_t used above, with superscripts to allow indexing. The delay is assumed to be $r > 0$ for all y_i for simplicity. The operators L_i are of the form

$$L_i \phi = \int_{-r}^{0} \phi(s)\ \mathrm{d}\nu_i(s),$$

for positive Borel measures ν_i on $[-r, 0]$, $0 < \nu_i([-r, 0]) < \infty$. Set $X = C([-r, 0], (\mathbb{R}^+)^p)$. Since F is decreasing, this system is not monotone. Nevertheless the induced control system

$$\begin{aligned} \dot{y}_1 &= F(L_p \alpha(t)) - a_1 y_1(t) \\ \dot{y}_i &= L_{i-1} y_{i-1}^t - a_i y_i(t), \qquad 2 \leq i \leq p, \\ h(y^t) &= y_p^t = \alpha(t), \end{aligned} \tag{5.10}$$

will fit the setup of our results. Indeed, letting $U = L^\infty([-r, 0], \mathbb{R}^+)$,[4] the system satisfies the hypotheses of Theorem 4. It also fulfills the monotonicity criterion

[4]Here it is assumed that $\nu_i(E) = 0$ whenever the Lebesgue measure of $E \subseteq [-r, 0]$ is zero. In the case of point delays, one would set $U = C([-r, 0], \mathbb{R}^+)$ as before.

using the cones $\mathcal{K}_X = C([-r,0],(\mathbb{R}^+)^p)$, $\mathcal{K}_U = L^\infty([-r,0],\mathbb{R}^-)$ (note the negative sign). Lemma 10 is also satisfied, thus guaranteeing hypotheses H1-H3. Fixing $\alpha \in U$, the control system can now be shown to converge towards the constant function $(\hat{y}_1,\dots \hat{y}_p)$, where

$$y = \left(\frac{F(L_p\alpha)}{a_1},\dots,\frac{F(L_p\alpha)}{a_1\cdots a_p}\right).$$

To see this, note first that the convergence of y_1 towards the constant function $F(L_p\alpha)/a_1$ is elementary. The convergence of y_2^t towards (the constant function) $F(L_p\alpha)/(a_1a_2)$ is also evident, by considering the controlled linear system

$$\dot{y}_2 = \beta - a_2 y_2(t),$$

where $\beta(t) := L_1 y_1^t$, and by noting that $\beta(t)$ must converge. Inductively, the existence of the characteristic follows. Noting that k^X sends bounded sets to bounded sets, it follows that H4 holds. The item 1 in the small gain condition holds clearly, since F is bounded (see next paragraph). To see that any solution $y(t)$ of (5.9) is bounded, let $z_1(t)$ be a solution of $z' = F(0) - a_1 z$, with initial condition $z_1(0) = y_1(0)$. Then $y_1(t) \le z_1(t)$ for all $t \ge 0$: to see this, note that the function $w(t) = z_1(t) - y_1(t)$ satisfies the equation $w'(t) = F(0) - F(L_p\alpha(t)) - a_1 w$, where $F(0) - F(L_p\alpha(t)) \ge 0$ and $w(0) = 0$. Now, since $z_1(t)$ is monotonic and converges towards $F(0)/a_1$, $y_1(t)$ is eventually bounded from above by $F(0)/a_1 + \epsilon$, for any $\epsilon > 0$. In fact, $F(0)/a_1$ is an upper hyperbound of $y_1(t)$ under the usual order. The boundedness of $y_1(t)$ is used to carry out a very similar argument in order to show that $y_2(t)$ is also eventually bounded, and the same holds for all other variables. This shows that all the solutions of the closed loop system are bounded.

By Theorem 2, system (5.9) is globally attractive whenever the discrete system

$$u_{n+1} = k(u_n) = \frac{F(L_p u_n)}{a_1\cdot \ldots \cdot a_p}$$

is globally attractive. Note that even if u_1 is a function, still $u_2, u_3, \dots$ can be assumed to be constants, so that one can further reduce the system to be 1-dimensional. Whenever the hypotheses of Theorem 2 apply, the stability of the system is ensured by Theorem 3, the remainding hypotheses being trivially verified. The same procedure can be applied throughout to the coupled system of an odd number of repressions of the form (5.9), as done in Smith [31]. This is in accord with the comments in p. 188 of that article:

> The remarkable fact is that the dynamics of the two systems [discrete and continuous] appear to correspond both at the level of local stability analysis and at the level of global dynamics. This is potentially a very useful fact, both for model construction and for analysis of particular models.

An example of a system (5) which is globally attractive is given by the function $F(x) := A/(K+x)$, for $A, K > 0$ arbitrary (the division by the constants $a_1 \dots a_p$ is here irrelevant). By Lemma 5, one only needs to show that the equation $F(F(x)) = x$ has a unique solution. Such a solution would satisfy $x = A/(K + F(x))$, that is

$$A = Kx + \frac{Ax}{K+x}.$$

The right hand side is an increasing function that starts at the origin and grows to infinity; thus x is the unique intersection of this function with $y = A$, and the statement follows.

6. **A model of the lac operon.** The following dynamical system was proposed by Mahaffy and Savev [24] to describe the dynamics of lactose metabolism in *E.Coli*, which is orchestrated by the genes known as the lac operon. Some of the main results in [24] concern the global stability of the system; we will apply the small gain theorem in its delay form to prove and extend these results.

The compounds involved in the system are the lac operon mRNA, the proteins β-galactoside permease, β-galactosidase (β-gal for short) and lactose, which are denoted respectively by x_1, x_2, x_3, x_4. (Actually it is isolactose that regulates the operon, but lactose and isolactose are considered identical in this model.) All substances degrade at a fixed rate except for the lactose, which is actively digested by the enzyme β-gal. The gene is activated whenever lactose is present in the system; more energetic sources of food, like glucose, are assumed not to be present. The mRNA then induces the production of permease and β-gal, and the permease makes the cell membrane more permeable to lactose, so that it can more efficiently enter the cell. Mahaffy et al. assume that the production of mRNA has a natural saturation point, with Michaelis-Menten dynamics. This amounts to the presence of, say, a constant number of RNA polymerase molecules. After introducing an arbitrary delay τ_1 as a result of the transcription of x_1, as well as a delay τ_2 as a result of the translation of x_2, x_3, one can make a change of variables and arrive to the system with a single delay

$$\begin{aligned}
\dot{x}_1(t) &= g(x_4(t-\tau)) - b_1 x_1(t) \\
\dot{x}_2(t) &= x_1(t) - b_2 x_2(t) \\
\dot{x}_3(t) &= r x_1(t) - b_3 x_3(t) \\
\dot{x}_4(t) &= S x_2(t) - x_3(t) x_4(t).
\end{aligned} \tag{6.11}$$

Here $g(\theta) := (1 + K\theta^\rho)/(1 + \theta^\rho)$, $K > 1$, all other constants are positive, and all variables are nonnegative. We will illustrate our main result by writing this system as the negative feedback loop of a controlled monotone system, in the way illustrated by Figure 3. The resulting system, which is modeled with $r_{\text{state}} = \tau, r_{\text{input}} = 0$, is

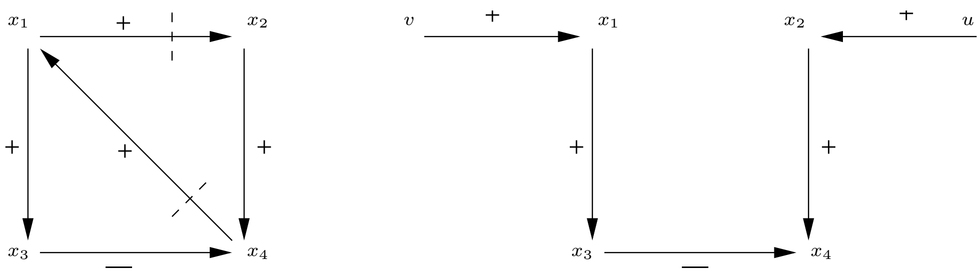

Figure 3. On the left, the digraph associated with equation (6.11). The dotted arrows are replaced by inputs on the right digraph, making the system into a controlled monotone one. Setting $u = x_1,\ v = x_4$ closes the loop back to (6.11).

$$\begin{aligned}\dot{x}_1(t) &= g(v(t)) - b_1x_1(t)\\ \dot{x}_2(t) &= u(t) - b_2x_2(t)\\ \dot{x}_3(t) &= rx_1(t) - b_3x_3(t)\\ \dot{x}_4(t) &= Sx_2(t) - x_3(t)x_4(t),\end{aligned} \qquad h(x(t)) = (x_1(t), x_4(t-\tau)).$$

This model can be verified to be monotone with respect to the cones

$$\mathcal{K}_X = C([-r_{\text{state}}, 0], \mathbb{R}^+ \times \mathbb{R}^- \times \mathbb{R}^+ \times \mathbb{R}^-),\ K_U = \mathbb{R}^- \times \mathbb{R}^+$$

using our monotonicity criterion. (In fact, monotonicity with respect to some orthant cone is equivalent to the property that the associated digraph doesn't have any undirected closed loop with an odd number of '$-$' signs.) See [2] for details, and Appendix I for a more systematic treatment in the finite dimensional case. It is clear that the closed feedback loop of this system is (6.11).

It will be shown that this controlled system has a well defined characteristic, by appealing to Figure 3 and by noting that one can write the system as a cascade of stable, one-dimensional systems. In fact, in the notation of (5.7), it holds in this example that $f(x_t, \alpha) = f(x(t), \alpha)$, and that the delay is only used for defining the feedback function. If the delay in the state is ignored and the controlled system is viewed as a strictly finite dimensional system, it becomes obvious that a fixed control (u, v) will induce a globally asymptotically stable equilibrium, which is calculated to be

$$x_1 = \frac{g(v)}{b_1},\ x_2 = \frac{u}{b_2},\ x_3 = \frac{r}{b_1b_3}g(v),\ x_4 = \frac{Sb_1b_3u}{rb_2g(v).}$$

After proving this, it is evident that the state $k^X(u, v) = (\hat{x}_1, \hat{x}_2, \hat{x}_3, \hat{x}_4)$ is a globally asymptotically stable state. This proves the existence of the I/S characteristic. The feedback characteristic of the system is

$$k(u, v) = \left(\frac{1}{b_1}g(v), \frac{Sb_1b_3}{rb_2}\frac{u}{g(v)}\right). \tag{6.12}$$

To guarantee that this open loop system satisfies the hypotheses of the main result, let $X_0 = (\mathbb{R}^+)^4$, $U_0 = (\mathbb{R}^+)^2$, and note that Lemma 10 can be directly applied to prove H1,H2,H3. The monotonicity and existence of the characteristic was shown above, and since k^X sends bounded sets to bounded sets ($g(\theta)$ is bounded from above by K and from below by 1), condition $H4$ also holds. Since the first component of $k(u, v)$ is bounded from below and above by $1/b_1$ and K/b_1 respectively, it is easy to see that the orbits of the discrete system (6.12) are uniformly bounded after two steps. Therefore item 1 in the small gain condition is satisfied. To see that a solution $x(t)$ of system (6.11) is bounded, let $z_1(t), z_2(t)$ be the solutions of the systems $z' = 1 - b_1z$ and $z' = K - b_1z$ respectively, with initial conditions $z_i(0) = x_1(0)$. It is easy to see that $z_1(t) \leq x_1(t) \leq z_2(t)$ for all $t \geq 0$, see the previous example. Since $z_1(t)$ ($z_2(t)$) converges towards $1/b_1$ (K/b_1), it holds that $x_1(t)$ is eventually bounded from below and above by fixed positive constants $1/b_1 - \epsilon$ and $K/b_1 + \epsilon$ respectively. In fact, $1/b_1$ (K/b_1) is a lower (upper) hyperbound of $x_1(t)$ in the usual order. Using this fact, the same procedure is used to show that x_2, x_3 are bounded, and this in turn implies that x_4 is also bounded (see also [24]). This shows that all the solutions of the closed loop system are bounded.

Note that $k(u, v)$ has a unique fixed point $u = \frac{1}{b_1}g(\frac{Sb_3}{rb_2})$, $v = \frac{Sb_3}{rb_2}$. For any choice of the parameters such that the discrete system $(u_{n+1}, v_{n+1}) = k(u_n, v_n)$ is globally attractive to this equilibrium, it follows from Theorem 2 that the original model (6.11) is globally attractive to its unique equilibrium. In those cases, the stability of (6.11) will be ensured by Theorem 3 and by the strict monotonicity of k^X and h. For the remainder of this example, we will concentrate on finding sufficient conditions for the global attractivity of the discrete system.

In the global analysis of model (6.11), Mahaffy and Savev [24] restrict their attention to the case $\rho = 1$, and they prove three results that provide sufficient conditions for global attractivity. We will come to the exact same conclusions, by writing the system associated to (6.12) as a scalar discrete system of second order, and by appealing to the attractivity results known for such systems. For arbitrary ρ we will also prove a new result, concerning global attractivity for any choice of the parameters b_1, b_2, b_3, S and r, provided that an inequality holds for ρ, K. Let $\rho = 1$, and consider the discrete system

$$(u_{n+1}, v_{n+1}) = k(u_n, v_n). \tag{6.13}$$

It holds that $u_{n+1} = \frac{1}{b_1} g(v_n)$, and

$$u_{n+2} = \frac{1}{b_1} g\left(\frac{Sb_1b_3}{rb_2}\frac{u_n}{g(v_n)}\right) = \frac{1}{b_1} g\left(\frac{Sb_3}{rb_2}\frac{u_n}{u_{n+1}}\right) = \frac{\beta u_{n+1} + \gamma u_n}{Bu_{n+1} + Cu_n}, \tag{6.14}$$

where here $\rho = 1$ in $g(\theta)$, and $\beta := \frac{1}{b_1}, \gamma := K\frac{Sb_3}{rb_1b_2}, B := 1, C := \frac{Sb_3}{rb_2}$. If the parameters of (6.14) are such that this discrete system has a globally attractive equilibrium for all initial conditions $u_0, u_1 > 0$, then (6.13) has globally attractive solutions for any initial condition $u, v \geq 0$. (If $u = 0$ or $v = 0$, simply iterate (6.12) a few times and the states will become strictly positive.) The global attractivity of (6.13) clearly also implies that of (6.14).

The book by Kulenovic and Ladas [21] deals exclusively with rational discrete systems of second order. It follows from their treatment of equation (6.14) that for $p := \beta/\gamma, q := B/C$, and $p < q$, global attractivity holds (that is, with respect to arbitrary real initial conditions for which the iterations are well defined, including $(u_0, u_1) \in (0, \infty) \times (0, \infty)$) if $q < pq + 1 + 3p$. Furthermore, instability occurs if $q > pq + 1 + 3p$ (see Theorem 6.9.1 in [21]).

In our case $p = \frac{rb_2}{KSb_3} < \frac{rb_2}{Sb_3} = q$, and attractivity holds if and only if

$$0 < q^2 + 3q - Kq + K, \quad q := \frac{rb_2}{Sb_3}. \tag{6.15}$$

For instance, if $q < 1$ then $0 < K - qK$ and thus (6.15) follows. This corresponds to Proposition 4.1 in [24]. Similarly, convergence follows whenever $q > K$, since then $0 < q^2 - qK$ (Proposition 4.2 in [24]). Finally, for $q > 1$ equation (6.15) is equivalent to $K < q(q+3)/(q-1)$, and the right hand side of this equation is bounded from below by 9. Thus for $1 \leq K < 9$ stability also follows. The remaining hypotheses in Theorem 4.3 of [24] can be shown to be equivalent to $K < q(q+3)/(q-1)$ for $q > 1$. We summarize the three main global stability results of [24] in the following statement.

Theorem 5. *For $\rho = 1$, the system (6.11) is globally attractive to a unique equilibrium, provided that $0 < q^2 + 3q - Kq + K$, $q := \frac{rb_2}{Sb_3}$. In particular, this holds if $q < 1$, if $q > K$ or if $q > 1$ and $K < q(q+3)/(q-1)$. Whenever this condition is satisfied, system (6.11) is stable around this equilibrium.*

The stability part of the above theorem is a direct consequence of Theorem 3, after noting that k^X is $\ll$-increasing and h is $\ll$-decreasing, both of which are straightforward to check.

Note that the delay τ was almost never used, and indeed can be arbitrarily large or small. In fact, one can introduce different delays, large or small, in all of the first terms of the right hand sides of (6.11), and the results will apply with almost no variation. (If delays are introduced in the second terms, the systems will not be monotone anymore.) If no delays are assumed, substantially stronger attractivity conditions hold; see [24].

Note that one can associate a second order, scalar discrete system to the original two-dimensional system for any value of ρ, in the same way as above. One correspondence that can be easily verified by using equation (6.14) repeatedly is the following: if $u_0 = u > 0$ and $u_1 = v > 0$, and if u_0, u_1 and (u, v) are taken as initial conditions of the systems (6.14) and (6.13) respectively, then $u_0, u_1, u_2, \ldots$ generates a two cycle in (6.14) if and only if (u, v) forms a two cycle in (6.13). Thus there exist nontrivial two-cycles in (6.13) if and only if there exist nontrivial two cycles in (6.14). For $u = 0$ or $v = 0$, similar comments apply as before. Recall that the existence of nontrivial two-cycles in (6.13) is equivalent to the global attractivity of system (6.13), by Lemma 5 and the fact that this system is $\leq$-decreasing under some orthant cone. By the above arguments, the same is true for system (6.14). Using the main result, the following proposition follows:

Proposition 2. *The system (6.11) is globally attractive to its equilibrium whenever the only solution $u > 0, v > 0$ of the system of equations*

$$u = \frac{\beta v^\rho + \gamma u^\rho}{Bv^\rho + Cu^\rho},\ v = \frac{\beta u^\rho + \gamma v^\rho}{Bu^\rho + Cv^\rho}$$

is $u = v = (\beta + \gamma)/(B + C)$, for $\beta = \dfrac{1}{b_1}, \gamma = \dfrac{K}{b_1}\left(\dfrac{Sb_3}{rb_2}\right)^\rho, B = 1, C = \left(\dfrac{Sb_3}{rb_2}\right)^\rho$.

This is a good point to comment on decomposing the same model as the negative feedback loop of a monotone system *in other ways* – after all, one can see that replacing x_3 by "u" in the fourth equation of (6.11), the resulting SISO system is monotone as well. Indeed, in that way a characteristic $k(u)$ can also be shown to exist, but it can be expressed only indirectly as the solution of a certain algebraic equation, since a directed loop remains in the digraph of the controlled system. To check that there are no nontrivial two-cycles for the discrete system, it is necessary to solve the system of equations $u = k(v), v = k(u)$, which turns out to be equivalent and very similar to the system of equations in Proposition 2. Thus, there is more than one way to decompose autonomous systems as closed loops of monotone controlled systems and use Theorem 2.

Next we provide sufficient conditions on K, ρ for system (6.11) to be globally attractive, for any choice of the remaining parameters. We transform $k(u, v) = (\zeta v, \xi u/g(v))$ into logarithmic coordinates. That is, consider

$$\kappa(\sigma, \tau) := \ln(k(e^\sigma, e^\tau)).$$

The initial condition (σ, τ) of the resulting discrete system is allowed to be an arbitrary vector in $\mathbb{R}^2$. Then

$$\kappa(\sigma, \tau) = (\Delta(\tau), \sigma + c - \Delta(\tau)),\quad \Delta(\tau) := \ln\ \zeta g(e^\tau),\ c := \ln \zeta\xi.$$

Note that the iterations of this function converge globally to an equilibrium if and only if those of $k(u,v)$ do. To the former system one can associate the second order system $\sigma_{n+2} = \Delta(c + \sigma_n - \sigma_{n+1})$ as was done in equation (6.14).

Lemma 11. *Consider a discrete system $\sigma_{n+2} = \Delta(c + \sigma_n - \sigma_{n+1})$, where c is an arbitrary constant and Δ is a bounded, non-decreasing, Lipschitz function with Lipschitz constant $\alpha < 1/2$. Then the system is globally attractive to its unique equilibrium $\sigma = \Delta(c)$.*

Proof. It is clear that a constant sequence $\sigma_{-1}, \sigma_0, \sigma_1 \ldots = \sigma$ is a solution of the discrete system if and only if $\sigma = \Delta(c)$, since $\sigma_0 = \sigma_1$ implies $\sigma_2 = \Delta(c + \sigma_0 - \sigma_1) = \Delta(c)$ and so on for all $n \geq 2$ (the converse direction is evident). Let $a_0 := \inf\ \text{Range}\ \Delta,\ b_0 := \sup\ \text{Range}\ \Delta$. Then it holds that $\sigma_n \in [a_0, b_0],\ n \geq 1$, for any initial conditions σ_{-1}, σ_0. Thus for all $n \geq 1$,

$$\sigma_n - \sigma_{n+1} + c \in [a_0 - b_0 + c, b_0 - a_0 + c],$$

and by calling $a_1 := \Delta(a_0 - b_0 + c),\ b_1 := \Delta(b_0 - a_0 + c)$, it follows that $\sigma_n \in [a_1, b_1],\ n \geq 3$.

Define inductively $a_{i+1} := \Delta(a_i - b_i + c),\ b_{i+1} := \Delta(b_i - a_i + c)$. Then for any $n \geq 2i+1$, $\sigma_n \in [a_i, b_i]$, by induction on i as above. If one shows that $|b_i - a_i|$ tends to 0 as i increases, then the discrete system will be shown to be globally attractive towards $\Delta(c)$, since $a_i \leq \Delta(c) \leq b_i$ for all i. Using the Lipschitz condition on Δ, it holds that

$$\begin{aligned} |b_i - a_i| &= |\Delta(b_{i-1} - a_{i-1} + c) - \Delta(a_{i-1} - b_{i-1} + c)| \\ &\leq \alpha\, |b_{i-1} - a_{i-1} + c - (a_{i-1} - b_{i-1} + c)| \\ &= 2\alpha\, |b_{i-1} - a_{i-1}| \leq \ldots \leq (2\alpha)^i\, |b_0 - a_0|\,, \end{aligned}$$

and the conclusion follows. $\square$

In the particular case in question, it follows from the definitions of $\Delta(x)$ and $g(\theta)$ that $\Delta(x) = \ln\zeta + \ln(1 + ke^{\rho x}) - \ln(1 + e^{\rho x})$. By derivating twice, it is shown that $\Delta(x)$ has a unique inflexion point at $x_0 = -\frac{1}{2\rho}\ln K$, and that

$$\Delta'(x_0) = \frac{(K-1)\rho}{2(\sqrt{K}+1)} < \frac{1}{2} \Leftrightarrow \rho < \frac{\sqrt{K}+1}{K-1},$$

and that ρ arbitrary if $K = 1$. The following corollary follows by the previous lemma and Theorem 2:

The following corollary follows by using the previous lemma and Theorem 2:

Corollary 3. *The lac operon model (6.11) has a unique, globally attractive equilibrium for any choice of the positive parameters b_1, b_2, b_3, r, S, provided that $\rho < (\sqrt{K}+1)/(K-1)$.*

7. **Appendix I: Decomposing Autonomous Systems into Negative Feedback Loops of Monotone controlled Systems.** It will be shown in this section that, under rather general conditions, one can decompose an autonomous (not necessarily monotone) system into the negative feedback loop of a monotone controlled system. Sufficient conditions will also be found for the controlled system to have a well defined characteristic. This appendix is solely concerned with finite dimensional systems, where the ideas are most simply presented, but a generalization to delay systems is straightforward. Consider the controlled system

$$\dot{x} = f(x,u),\ x \in X = (\mathbb{R}^+)^n, u \in U = (\mathbb{R}^+)^m, \tag{7.16}$$

and fix a set $S \subseteq \{1, \dots n\}$. Any vector $(x_i)_{i=1\dots n}$ defines a vector $x^S = (x_i)_{i \in S}$. Letting z stand for a fixed vector $(z_i)_{i \in S^C}$, define the function $f^S(x^S; z, u) := f(x^S, z, u)^S$, where $f(x^S, z, u)$ is meant in the obvious sense. This vector field defines a controlled $|S|$-dimensional dynamical system

$$\dot{x}^S = f^S(x^S; z, u) \tag{7.17}$$

with $n-|S|+m$–dimensional control (z, u).

Finally, denote by S^C the complement {1,. . . , n} - S of S. If $\pi = \{S_1, \dots S_\Lambda\}$ is a partition of $\{1 \dots n\}$, then the coupled system

$$\dot{x}^{S_\lambda} = f^{S_\lambda}(x^{S_\lambda}; x^{S_\lambda^C}, u), \ \lambda = 1 \dots \Lambda \tag{7.18}$$

is equivalent to (7.16).

Sign Definite Systems. Many dynamical systems arising from gene and protein models can be associated with a signed digraph. Given an autonomous system

$$\dot{x} = g(x), \ x \in X = (\mathbb{R}^+)^n, \tag{7.19}$$

let the variables $x_1 \dots x_n$ be vertices, and write a positive arc from x_i to x_j, $i \neq j$, if $\frac{\partial}{\partial x_i} g_j(x) \geq 0$ for all $x \in X$ and the strict inequality holds at least at some state. Similarly, write a negative arc from x_i to x_j if $\frac{\partial}{\partial x_i} g_j(x) \leq 0$ (with strict inequality at some state), and no arc if $\frac{\partial}{\partial x_i} g_j(x) \equiv 0$. Note that not every system satisfies this trichotomy for all its variables. The attention will be restricted in this appendix to such systems, which will be denoted as *sign definite*.

If the system (7.19) is sign definite with associated digraph G, then one can find an n-dimensional controlled system

$$\dot{x} = f(x, u), \ \ x \in X = (\mathbb{R}^+)^n, \ u \in U = (\mathbb{R}^+)^m, \ h : X \to U, \tag{7.20}$$

which is i) monotone with respect to some orthant cones in the inputs and the states; ii) such that the function h is $\leq$-decreasing; and iii) such that its closed loop system is well defined and is (7.19). This will be done as follows, trying to minimize the number of inputs and outputs involved so as to make the reduced model in Theorem 2 as simple as possible.

Let $A \subseteq \{x_1, \dots x_n\}$ be an arbitrary set of variables, called *agonists*. These variables may be unrelated to each other, but it is best (and most meaningful) to choose them so that their dynamics are positively correlated, i.e. most arrows connecting two nodes from A are positive. The remaining variables will be referred to as *antagonists*, and they will also be thought of as being mostly positively correlated to each other.

An arc in G will be called *discordant* if it is positive and joins an agonist with an antagonist, or if it is negative and joins two agonists or two antagonists. Let $D_j := \{x_i |$ there is a discordant arc from x_i to $x_j\}$, and let $D := \bigcup_j D_j$, $m := |D|$ and $U := (\mathbb{R}^+)^m$. Now enumerate the elements of D as $x_{l_1}, \dots, x_{l_m}$. Define $f_j(x, u)$ as the result of replacing in $g_j(x)$ all appearances of x_{l_i} by u_i, for each $x_{l_i} \in D_j$. The controlled system (7.20) thus defined has a state digraph G' that can be described as the result of removing all discordant arcs from G.

Now define the output function $h : X \to U$ as $h_k(x) := x_{l_k}$, $k = 1 \dots p$, and close the loop by letting $u(t) = h(x(t))$. Let

$$s(i) := \begin{cases} 1 & \text{if } x_i \in A \\ -1 & \text{if } x_i \notin A \end{cases}$$

and let K_X be the orthant cone induced by s. Let $p_k := -s_{l_k}$, $k = 1 \dots m$, and let K_U be the orthant cone defined by p.

Example. Equation (6.11) and Figure 3 form a good example of these definitions. In this model, one can consider as agonists the variables x_1, x_3 and as antagonists x_2, x_4. There are only two discordant arcs and it holds that $D_1 = \{x_4\}$, $D_2 = \{x_1\}$, $D_3 = D_4 = \emptyset$; thus $D = \{x_1, x_4\}$. The variables x_1 and x_4 are replaced by u and v in the functions g_2, g_1 to form the functions $f_2(x, u)$, $f_1(x, v)$, respectively.

An important consideration in making the choice of the agonist set is to minimize the number of inputs. See Figure 4 for an example of a system in which the agonist set is chosen in two different ways.

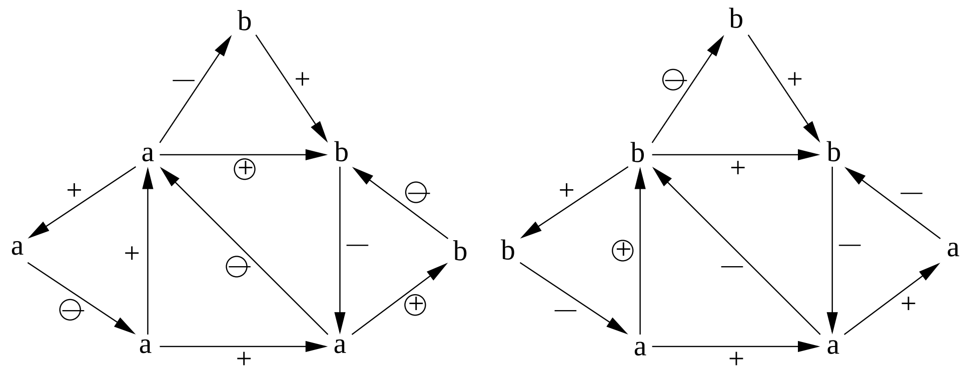

FIGURE 4. Network Splitting. The nodes in the digraphs above have been labelled "a" for agonist and "b" for antagonist in two different ways, and the discordant arrows have been circled in each case. The nodes at the base of these arrows will form the set D of inputs of the controlled system (four inputs in the first digraph, and two in the second). Note that by choosing the agonists and antagonists in an educated way one can substantially reduce the number of inputs.

Before providing our construction leading to i),ii),iii), the following simple result is stated and proved for convenience. Given a digraph H, we denote by $V(H)$ the set of vertices of H, and by $A(H)$ the set of arcs of H.

Lemma 12. *Let H be an acyclic digraph. Then there exists a bijection $b : V(H) \to \{1, \dots |V(H)|\}$ such that $(v_1, v_2) \in A(H)$ implies $b(v_1) < b(v_2)$.*

Proof. The proof proceeds by induction on the number of vertices. If there is only one vertex, the bijection is trivial. Assuming the statement true for graphs of at most n vertices, let H have $n + 1$ vertices. There exists at least one vertex v with no incoming arcs. Remove it and apply the statement on the remaining digraph H' to form a bijection $b : V(H') \to \{2, \dots n + 1\}$. Finally, define $b(v) := 1$. The result follows. □

Theorem 6. *The controlled system (7.20) described above is monotone, and h is a $\leq$-decreasing function. The closed loop system of (7.20) is well defined and equal to system (7.19). Furthermore, if for each strongly connected component of G' with* *vertices $S \subseteq \{1 \dots n\}$ the system (7.17) has a well defined I/S characteristic, then (7.20) allows an I/S characteristic.*

Proof. The Kamke monotonicity criterion for controlled systems will be used: given orthant cones $\mathcal{K}_X$ and $\mathcal{K}_U$ generated by the tuples $(s_1, \dots s_n)$ and $(p_1, \dots p_m)$ respectively, a system (7.20) is monotone with respect to these cones if and only if

$$s_j s_i \frac{\partial f_j}{\partial x_i} \geq 0, \ \forall i \neq j \ \text{ and } s_j p_k \frac{\partial f_j}{\partial u_k} \geq 0, \ \forall i, k, \tag{7.21}$$

where $i, j = 1 \dots n$ and $k = 1 \dots m$; see [32, 2]. To prove the first assertion in 7.21, let $i \neq j$ be such that there is an arc from x_i to x_j in G' (otherwise there is nothing to prove). Then either both variables are agonists and the arc is positive, or both are antagonists and the arc is also positive, or else one is agonist, one is antagonist and the arc is negative. In all these cases, the first statement in (7.21) is satisfied. As to the second statement, if k, j are such that $\partial f_j / \partial u_k \not\equiv 0$, then by construction the arc from x_{l_k} to x_j in G is discordant, so that $s_{l_k} s_j \partial g_j / \partial x_{l_k} \leq 0$. Also by construction, sign $\partial g_j / \partial x_i =$ sign $\partial f_j / \partial u_k$. Therefore $s_j p_k \partial f_j / \partial u_k \geq 0$ as expected.

Recall that $p_k = -s_{l_k}$, $h_k(x) = x_{l_k}$ to see that h is $\leq$-decreasing. Replacing each u_k in $f_j(x, u)$ back with $h_k(x) = x_{l_k}$ will form back $g_j(x)$. This proves that the closed loop system is the same as (7.19).

For the last assertion write (7.20) as a cascade of controlled monotone systems on the state spaces $X_\lambda := (\mathbb{R}^+)^{|S_\lambda|}$, $\lambda = 1 \dots \Lambda$, where $S_1, \dots, S_\Lambda$ are the strongly connected components (s.c.c.) of G'. Let H be the acyclic digraph with vertices $S_1 \dots D_\Lambda$ which is naturally induced by the digraph G', i.e. $(S_\lambda, S_\mu) \in A(H)$ if and only if $(x, y) \in A(G')$ for some $x \in S_\lambda, y \in S_\mu$. Now use Lemma 12 to relabel the s.c.c's in such a way that if $x_i \in S_{\lambda_1}$, $x_j \in S_{\lambda_2}$, and there is an arc from x_i to x_j, then $\lambda_1 \leq \lambda_2$.

Consider the function $f^{S_1}(x^{S_1}; z, u)$, where $z = (z_i)_{i \in S_1^C}$ is given. By the choice of S_1, it holds that f^{S_1} doesn't actually depend on z, and it can be written as $f^{S_1}(x^{S_1}, u)$. Similarly one can write $f^{S_\lambda}(x^{S_\lambda}; x^{S_\lambda^C}, u)$ in (7.18) as

$$f^{S_\lambda}(x^{S_\lambda};\ x^{S_1}, \dots x^{S_{\lambda-1}}, u),$$

and thus system (7.20) is written as a cascade as desired, using equation (7.18).

Given a fixed input $u \in U$, the system $\dot{x}^{S_1} = f^{S_1}(x^{S_1}; u)$ converges globally towards a vector $(\bar{x}_i)_{i \in S_1}$, by hypothesis. Using $u_1, \dots u_m$ and the variables in S_1 as inputs, the system

$$\dot{x}^{S_2} = f^{S_2}(x^{S_2}; x^{S_1}, u)$$

can be seen to satisfy (7.21), since some of the variables have now been simply relabelled as inputs. Also, this system has a well-defined characteristic by hypothesis. Thus the property CICS holds, and since (x^{S_1}, u) converges to $(\bar{x}^{S_1}, u)$, then x^{S_2} converges to $\bar{x}^{S_2}$. The same argument holds to show that all the cascade converges, thus proving that system (7.20) has an I/S characteristic. $\square$

Corollary 4. *If the digraph G' associated to system (7.20) is acyclic, and for every $i = 1 \dots n$ the 1-dimensional system*

$$\dot{x}_i = g_i(\hat{x}_1, \dots, \hat{x}_{i-1}, x_i, \hat{x}_{i+1}, \dots, \hat{x_n})$$

with controls $\hat{x}_j, j \neq i$, has a well defined I/S characteristic, then (7.20) allows an I/S characteristic.

Proof. The graph G' is acyclic, therefore its strongly connected components are exactly the singletons $\{1\}, \ldots, \{n\}$. By the previous theorem, the result follows. □

Discussion. The reader will notice a tradeoff in the number of variables chosen to form the input: the more variables are included in D, the more complex is the resulting discrete system in SGT, but the less connected is G' and the easier to show the existence of a characteristic. Note that D is completely determined by the set A of agonists, which is arbitrary and allows for some choice. The results in this section make SGT robust to possible changes in the model. If a new participating gene is discovered as part of a gene network, one can simply keep the previous agonists, introduce the new gene either as agonist or antagonist, and obtain a monotone system (7.20) that has a similar topology as the previous one. The second condition in Theorem 6, regarding the existence of the characteristic, also needs to be checked only locally if a new node or a new arrow is introduced.

8. Appendix II.

8.1. Existence and Uniqueness.

Theorem 7. *Let $X_0 \subseteq \mathbb{R}^n$ be an open set, or in the orthant cone case, a box (not necessarily bounded) containing some or all of its sides. Let B_U be a Banach space, and let $U \subseteq B_U$ be an arbitrary Borel measurable set. Let $X = C([-r, 0], X_0)$, and let $f : X \times U \to \mathbb{R}^n$ be a continuous function. Assume that*

i): *f is locally Lipschitz on X, locally uniformly on U: for any $C \subseteq U$ and $D \subseteq X$ closed and bounded, there exists $M > 0$ such that*

$$|f(\phi, \alpha) - f(\psi, \alpha)| \leq M\,|\phi - \psi|\,, \forall \phi, \psi \in D, \forall \alpha \in C.$$

ii): *There exists $\phi_0 \in X$ such that for all $C \subseteq U$ closed and bounded, the set $f(\phi, C)$ is bounded.*

Then the system (5.8) has a unique maximally defined, absolutely continuous solution $x(t)$ for every input $\beta \in U_\infty$ and every initial condition $\phi \in X$.

Proof. It will be shown that all hypotheses are met so as to apply Theorem 4.3.1, p. 207 of Bensoussan et al. [4]. Let $\Omega_0 \subseteq X_0$ be a given compact set, and let $\Omega = C([-r, 0], \Omega_0)$. Let $C_i := B(0, i) \cap U$, where $i = 1, 2, 3 \ldots$ and $B(0, i)$ is the open ball in B_U with radius i. For every C_i, there is a constant M_i such that $f(\cdot, \alpha)$ is M_i-Lipschitz on Ω, for all $\alpha \in C_i$. For any $\alpha \in U$, let $m(\alpha) := \inf\{M_i \,|\, i \text{ such that } \alpha \in C_i\}$. Note that $f(\cdot, \alpha)$ is $m(\alpha)$-Lipschitz on Ω for each α and that m is measurable. Indeed, each M_i can be chosen to be as small as possible, and then m becomes a step function on each C_i.

Now for every fixed $\alpha \in U$, extend the function $\phi \mapsto f(\phi, \alpha)$ from Ω to all of B_X, in such a way that the extension is also $m(\alpha)$-Lipschitz. For this, let

$$F_i(\phi, \alpha) := \inf_{\psi \in \Omega_0} f_i(\psi, \alpha) + m(\alpha)\,|\phi - \psi|\,,$$

for each i, and let $F = (F_1, \ldots, F_n)$. It is a simple exercise in analysis to verify that for a fixed α, $F(\cdot, \alpha)$ is well defined, coincides with $f(\cdot, \alpha)$ on Ω, and is itself $\sqrt{n}m(\alpha)$-Lipschitz.

Fix now $\beta \in U_\infty$, and define $g(t, \phi) := F(\phi, \beta(t))$. It is to this function that Theorem 4.3.1 of [4] is applied. A few conditions need to be verified: F is continuous on each set $X \times (C_i - C_{i-1})$) and therefore measurable, which implies that $g(t, \phi)$ is also measurable. By setting $n(t) = m(\beta(t))$, it follows that $n(t)$ is measurable and locally bounded (since each $\beta|_{[0,T]}$ is contained in some C_i), and thus locally integrable. Finally, note that $F(\phi_0, C_i)$ is bounded in $\mathbb{R}^n$ for every i, and that therefore $t \to g(t, \phi_0)$ is locally integrable.

By Theorem 4.3.1 in [4], the system $\dot{x} = g(t, x_t) = F(x_t, \beta(t))$ has a unique maximally defined, absolutely continuous solution defined for every initial condition $\phi \in B_X$.

Next define for a fixed initial condition $\phi \in X$, and $j = 1, 2, 3, \ldots$:

$$\Omega_j := \mathrm{Range}(\phi) \cup \{x \in X_0 \,|\, \mathrm{dist}(x, \mathrm{Range}(\phi)) \leq j \text{ and } \mathrm{dist}(x, \partial X \setminus X) \geq 1/j\}.$$

Extend f from Ω_j to all $\mathbb{R}^n$ to form F_j, applying the main step above. The solutions of the systems $\dot{x} = F_j(x_t, \beta(t)),\ j = k, k+1, \ldots$, using the same initial condition ϕ, must agree with each other by uniqueness. If $x_1(t), x_2(t)$ are both solutions of (5.8) with initial condition ϕ and are defined on $[0, T]$, let j be such that $x_1|_{[-r,T]} \cup x_2|_{[-r,T]} \subseteq \Omega_j$. Then $x_1 = x_2$ on $[-r, T]$ by the argument above. This shows that x(t) is unique. The fact that it is maximally defined follows similarly. □

8.2. **Proof of Lemmas 1 and 2.**

Proof of Lemma 1: Let $\mathcal{K}$ have nonempty interior, that is $0 \leq B_\epsilon(x_0)$ for some $x_0 > 0$ and some real $\epsilon > 0$. Then $0 \leq B_1(\epsilon^{-1}x_0)$, which is equivalent by definition to $B_1(0) \leq \epsilon^{-1}x_0$. The converse result follows by the same argument. □

Proof of Lemma 2: Let $C_1 := \{x \in \mathcal{K} |\ |x| = 1\}$. Let $f : C_1 \times C_1 \to \mathbb{R},\ f(x, y) := x \cdot y$. C_1 is compact, therefore f must have a minimum at some (x_0, y_0). But $f(x_0, y_0) > -1$, since otherwise $x_0 = -y_0$ and a contradiction would follow from $\mathcal{K} \cap (-\mathcal{K}) = \{0\}$. If follows that there is $\theta < 1$ such that $x \cdot y \geq -\theta\,|x|\,|y|$, for every $x, y \geq 0$.

Now let $0 \leq x \leq y$. Then $(y - x) \cdot x \geq -\theta\,|x|\,|y - x|$, so

$$|x|^2 \leq \theta\,|x|\,|y - x| + x \cdot y \leq |x|\,(\theta\,|x| + \theta\,|y| + |y|),$$

and after cancelling $|x|$ on both sides (if $x = 0$ there is nothing to prove) and solving for $|x|$, one has

$$|x| \leq \frac{\theta + 1}{\theta - 1}\,|y|\,.$$

□

8.3. **Monotonicity Criterion and Semiflow Property.**

Sketch of Proof for Proposition 1. Let α, β be two inputs, and assume $\alpha(t) \leq \beta(t)$ for every t (if this only holds a.e. t, one can change the value of these functions at a set of measure zero). Let $h_1(t, \phi) := f(\phi, \alpha(t)),\ h_2(t, \phi) := f(\phi, \beta(t))$. Theorem 1.1 of Smith [32] cannot be applied directly, even in the cooperative case, since the functions h_i are not necessarily continuous on t. Nevertheless by writing the absolutely continuous solution $x(t, \phi; h_i)$ of $\dot{x} = h_i(t, x_t)$ as an integral (see Bensoussan et al. [4]) one shows that, for $e \gg 0$ in X and $h_i^\epsilon(\phi, t) := \epsilon e + h_i(\phi, t)$, $x(t_0, \phi; h_i^\epsilon)$ converges towards $x(t_0, \phi; h_i)$ as $\epsilon \to 0$ for each t_0. The rest of the argument is as in [32]: define $e := (s_1, s_2, \ldots s_n) \gg 0$. Show by contradiction that $x(t, \phi; h_1) \ll x(t, \phi; h_2^\epsilon)$ for all t and small ϵ, and let ϵ tend to zero. □

The following two lemmas give a proof that the function $\Phi(t, \phi, \alpha) = x_t$ satisfies the semiflow property. The proof is straightforward, but it is included because the result might seem counterintuitive for delay systems. Let B_U be an abstract Banach space here, and $U \subseteq B_U$. Consider $X_0 \subseteq \mathbb{R}^n$, $X = C([-r,0],\mathbb{R}^n)$ as before, and $f : X \times U \to \mathbb{R}^n$ such that the triple (X,U,f) forms a well defined delay dynamical system as in Definition 4.

Lemma 13. *Let u, v be inputs in U such that $u(t) = v(t), 0 \leq t \leq t_0$. Then the solutions $x(t), y(t)$ of the system (5.7), with initial condition ϕ_0 and inputs u and v respectively, satisfy $x(t) = y(t), -r \leq t \leq t_0$.*

Proof: Let $\gamma(t) := v(t + t_0)$, and let $z(t)$ be the solution of (5.7) with input γ and starting condition $\phi_1 = x_{t_0}$. Let $w(t) := x(t)$ for $-r \leq t \leq t_0$, $w(t) := z(t - t_0)$ for $t > t_0$. It is easy to see that $w(t)$ is absolutely continuous, as it is built from absolutely continuous parts. Further,

$$w'(t + t_0) = z'(t) = f(\gamma(t), z_t) = f(v(t + t_0), w(t + t_0)), \text{ a.e. } t \geq 0.$$

Thus $w(t)$ is a solution of (5.7) with input $v(t)$ (recall $u(t) = v(t), -r \leq t \leq t_0$), and initial condition ϕ_0. By uniqueness, it must hold that $w = y$, and the conclusion follows.

Lemma 14 (Semiflow Property)**.** *Given $s, t \geq 0$, and inputs $u(\tau), v(\tau)$, let $x(\tau), y(\tau)$ be the solutions of (5.7) with inputs $u_1(\tau), u_2(\tau)$ respectively, and initial conditions ϕ and x_s respectively. Let $z(\tau)$ be the solution of (5.7) with initial condition ϕ and input $v(\tau) := u_1(\tau), 0 \leq \tau \leq s, v(\tau) := u_2(\tau - s), \tau > s$. Then $z_{s+t} = y_t$.*

Proof. By the previous Lemma, $z_s = x_s$. Note that $w(t) := z(s + t)$ is a solution of (5.7) with input u and initial condition x_s:

$$w'(\tau) = z'(s + \tau) = f(v(s + \tau), z(s + \tau) = f(u_2(\tau), w(\tau)), \forall \tau \geq 0.$$

Thus $w = y$ by uniqueness. In particular, $y_t = w_t = z_{s+t}$. □

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