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A Note on a Monotone Small Gain Theorem, with Applications to Delay Systems

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ABSTRACT

We consider the problem of showing the stability of a dynamical system by writing it as the negative feedback closed loop of a controlled monotone system. We associate to this continuous system a discrete one in a lower dimensional state space, whose global attractivity to an equilibrium implies that of the continuous system to some state. The proofs are given in an abstract setting, and the main application is given to a lac operon model with time delay.

1 Introduction

The present paper describes an approach to provide sufficient conditions for a system to have a globally stable equilibrium, based on the results of Angeli and Sontag [2]. The main result is a small gain theorem as in [2], which essentially consists in associating to any monotone controlled system with a well defined characteristic (definitions below) a reduced discrete system, whose global attractivity implies that of the original system. The result proven in this text will be stated on an abstract Banach space setting, which allows one to apply it to systems with multiple inputs and outputs, as well as to delayed systems and reaction-diffusion equations.

We review a useful sufficient and necessary condition for this system to be globally attractive, and also consider the question of asymptotic stability, which is proven at least for single input, single output systems. We further provide a systematic description on how to write an autonomous model, under relatively few constraints, as a monotone controlled system under negative unity feedback loop with a relatively small number of inputs and outputs, and provide sufficient conditions for the existence of a characteristic. We also apply the main theorem to an example from the literature, showing that it precisely mirrors the global stability results of a model of lac operon dynamics due to Mahaffy [11]. 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 [13] for further reference on this topic.

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, in which case it is called a *proper cone*. The cone $\mathcal{K}$ induces the following order relations in B:

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

We say that $\mathcal{K}$ is *normal* if $0 \leq x \leq y$ implies $|x| \leq M\,|y|$ for some constant $M > 0$. The following lemmas are standard excercises in convex analysis. For convenience, we provide proofs 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 $\mathcal{K} \subseteq \mathbb{R}^n$ be a closed cone. Then C is normal.*

Now let B_X, B_U be two arbitrary Banach spaces, and pick subsets $X \subseteq B_X$ and $U \subseteq B_U$. We refer to U as the set of *input values*, and we define an *input* to be a function $u : \mathbb{R}^+ \to U$ that is measurable and locally bounded. A *dynamical system* in this context is a function $\Phi(t, x, u)$ with arguments in $\mathbb{R}_0^+, X$ and the set of inputs respectively, and values in X, such that the functions (thought of as trajectories) $x(t) = \Phi(t, x_0, u)$ are continuous in t for any 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. It should hold that $x(t, x_0, u) =$

$x(t, x_0, v)$ for all t if $u(s) = v(s)$ for almost every s, and that $x(0, x_0, u) = x_0$ for any x_o, u. Finally, the semigroup property should hold: 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 w, we have $\Phi(s + t, x, w) = z$ (see Sontag [15]).

Monotonicity and Characteristic Given proper cones $\mathcal{K}_X \subseteq B_X$, $\mathcal{K}_U \subseteq B_U$, we say that a dynamical system $\Phi(t, x, u)$ is *monotone with respect to* $\mathcal{K}_X, \mathcal{K}_U$ if the following property is satisfied: for any two inputs u, v 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. the system is autonomous, then it is monotone if $x_1 \leq x_2$ implies $x(t, x_1) \leq x(t, x_2)$ for all t.

We say that $\Phi(t, x, u)$ has *input to state (I/S) characteristic* $k^X : U \to X$ if for every constant input $u(t) \equiv u \in U$, $x(t, x_0, u)$ converges to $k^X(u) \in X$ for every initial condition $x_0 \in X$, and $k^X(u)$ is globally asymptotically stable[1]. If there is an output function $h : X \to Y \subset \mathbb{R}^l$ associated to the system, then we refer to $k = h \circ k^X$ as the *input to output characteristic*. If $\Phi(t, x, u)$ is monotone then it is understood, unless explicitly stated otherwise, that h is a monotone function, that is, $x_1 \leq x_2$ implies $h(x_1) \leq h(x_2)$, and that it sends bounded sets to bounded sets. It can also be easily shown that if $\Phi(t, x, u)$ is monotone then k is a monotone function as well, see Angeli and Sontag [2].

The General Assumptions Let B_X, B_U be arbitrary Banach spaces ordered by the cones $\mathcal{K}_X, \mathcal{K}_U$, and let $\Phi(t, x, u)$ be a controlled dynamical system with states in $X \subseteq B_X$ and input values in $U \subseteq B_U$. Let also be given an output function $h : X \to Y = U$ – note that the input and output spaces are assumed to coincide. 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 $\text{diam}[y, z] < \epsilon$ and $[y, z] \cap A$ is a neighborhood of x (with respect to the relative topology on A).

We will make the following general hypotheses throughout this monograph:

H1 $\mathcal{K}_X$ and $\mathcal{K}_U$ are proper, normal cones.

H2 For every bounded $C \subseteq U$, there exist a, b 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, and the output h is a continuous function.

H5 The system $u_{n+1} = k(u_n)$ has bounded orbits for any initial condition $u_0 \in U$.

We recall that $[y, z] = \{w \in B_X |\ y \leq w \leq z\}$, and that a map $T : B \to B$ is completely continuous iff it is continuous and $\overline{T(A)}$ is compact, for every bounded set $A \subseteq B$. Note that H4 implies that $k = h \circ k^X$ is completely continuous as well. A similar definition as H3 was proposed by H. Smith in [13]: $x \in X$ *can be approximated from below* if there exists a sequence $\{x_n\}$ in X such that $x_1 < x_2 < \ldots \to x$. It is easy to see that H3 doesn't imply boundedness from below, for

[1]This definition coincides with that in Angeli and Sontag [2], but in fact global attractivity would be sufficient for the proofs in this paper.

instance with $X = [0, 1],\ x = 0$ and the usual order. It also holds that approximability from both below and above doesn't imply H3. 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 $K = \mathbb{R}^{\pm} \times \ldots \times \mathbb{R}^{\pm}$, 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 $\text{int}K \neq \emptyset$.

Property H3 can also be compared with the definition in Hirsch [7] of the *order topology* in a Banach space B, namely the topology generated by the order intervals $(x - \lambda e, x + \lambda e)$, where $x \in B, \lambda > 0$ arbitrary, and $e \in B,\ e \gg 0$ is fixed. The fact that the cones are normal actually implies throughout this monograph that both the usual topology and the order topology are the same. To see this, let $x - \lambda e \ll y \ll x + \lambda e$. Then by normality $|y - x + \lambda e| \leq M 2\lambda |e|$, and so $|y - x| \leq 2M\lambda |e| - \lambda |e|$. By making λ small enough we can fit an order interval inside any open ball in B. The assertion follows.

It may be useful to point out that if $B_U = \mathbb{R}^m, B_X = \mathbb{R}^n$, $\mathcal{K}_U, \mathcal{K}_X$, are orhant cones, U is a closed box (not necessarily bounded), and X is either an open set or an interval (bounded or not) that contains some or all of its sides, then conditions H1,H2,H3,H4 are automatically satisfied for any monotone system $\dot{x} = f(x, t, u), y = h(x)$ for all f continuous and locally Lipschitz on x, and continuous h - see [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 $k^X(\bar{u})$, for any arbitrary initial condition x_0.*

Proof. Let $u(t) \to \bar{u}$. For $\epsilon > 0$, let $\delta > 0$ such that $|v - \bar{u}| < \delta \Rightarrow \left|k^X(v) - k^X(\bar{u})\right| < \epsilon$. We use H3 on U to construct a "δ-box" around $\bar{u}$, in other words, to find $a, b \in U$ such that $\text{diam}[a, b] < \delta$ and $[a, b] \cap U$ is a neighborhood of $\bar{u}$. In particular since $\bar{u} \in [a, b]$, $\left|k^X(v) - k^X(\bar{u})\right| < \epsilon$ for every $v \in [a, b]$, and $\left|k^X(a) - k^X(b)\right| \leq 2\epsilon$.

Let now T_1 be such that $u(t) \in [a, b]$ for all $t \geq T_1$. Let $x_1 = x(T_1, x_0, u(t))$ – now we can restrict our attention to the input $u_1(t) = u(t + T_1)$ with the initial condition x_1, which has the same limit behavior as before but with the added advantage that now all input values correspond to globally attractive equilibria that are very close to $k^X(\bar{u})$.

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 we have

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

we get

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

where M is the normality constant of C_X. Thus $\left|x(t, x_1, u_1) - k^X(\bar{u})\right| \leq (4M + 2)\epsilon$, for all $t \geq T_2$. ∎

In general, the CICS property might fail when the speed at which the solutions approach the globally attractive equilibrium, under constant input, varies for different constant inputs in a non-uniform manner - see for instance Sontag [**?**]. In this case, the speed of convergence under each input $v(t)$, $a \leq v(t) \leq b$, is governed by that under the constant inputs a, b, by monotonicity.

The Small Gain Theorem Monotone systems have very useful properties (see Hirsch [7], Smith [13]), but many gene and protein interaction networks are not themselves monotone. We will consider interconnections of controlled monotone systems forming an autonomous system in which nevertheless the monotonicity of the subsystems will be of use.

Let u be a bounded input. We say that $v \in U$ is 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 $t \geq t_k$, $v_k \leq u(t)$. A similar difinition is given if for every $t \geq t_k, v_k \geq u(t)$, and we say that v is an *upper hyperbound of* u. Identical definitions are given for the state space.

Lemma 3 *Let u be a bounded input, 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 $y_n, z_n \in X$ 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).

Let $T_1 < T_2 < \ldots \infty$ be defined by induction as follows: let $T_0 = 0$, and for $n \geq 1$ let

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

Given T_{n-1}, let T_n be chosen such 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 $y_n \to k^X(v)$, $T_n \to \infty$, and so $k^X(v)$ is a lower hyperbound of $x(\cdot)$. ∎

We quote a result from Dancer [5], slightly adapted to our setup, which will provide a simple criterion to study the global attractivity of discrete systems

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

when the function $T : B \to B$ is monotone.

Lemma 4 *Let K be a proper, normal cone defined on a Banach space B, and let $T : B \to B$ be monotone and completely continuous. Suppose also that the system $x_{n+1} = T(x_n)$ has bounded forward orbits, and that there is a unique fixed point $\bar{x}$ of T. Then all solutions of (1) converge towards $\bar{x}$.*

Proof. By normality of the cone, T maps order intervals into precompact sets. Since the cone has nonempty interior, the forward orbits of (1) are order-bounded. Therefore Lemma 1 in [5] applies, and for any $x \in B$, $\omega(x)$ is bounded from below and from above by a fixed point. But since this fixed point is unique, $\bar{x} \leq \omega(x) \leq \bar{x}$ and the result follows. ∎

It is a well-known result (see for instance [1] for an application in a context similar to ours) that if $T : \mathbb{R} \to \mathbb{R}$ is a continuous, bounded, nonincreasing function, then system (1) is globally attractive towards its unique fixed point $\bar{x}$ iff 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 [8]). We say that a function $T : B \to B$ is *antimonotone* if $x \leq y$ implies $T(x) \geq T(y)$.

Lemma 5 *Assume the same hypotheses of Lemma 4, except that instead $T : B \to B$ is antimonotone. Then system (1) is globally attractive towards $\bar{x}$ iff 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 monotone, satisfies all hypotheses of the above lemma, and therefore for any $x \in B$ we have that $T^{2n}(x)$ converges to $\bar{x}$. But so does $T^{2n+1}(x)$, too. The conclusion follows. ∎

Given an output function $h : X \to Y = U$, assume that for every $x_0 \in X$ there exists a unique trajectory $x : \mathbb{R}^+ \to X$ such that $x(t) = \Phi(t, x_0, h \circ x(\cdot))$, for all $t \geq 0$. We say that the autonomous system $\Psi(t, x_0) = x(t)$ is the *closed-loop system associated with* Φ, h - note that we are only concerned with unity feedback here. We will for now assume that the closed-loop system is well posed (i.e. satisfies the condition above) and has bounded solutions, and it will be clear in the applications when these conditions are met. For instance, if the system is defined via a differential equation $\dot{x}(t) = f(x(t), u(t))$, then the closed-loop system is well posed if and only if the autonomous system $\dot{x} = f(x(t), h(x(t))$ has unique well defined solutions.

Theorem 2 (SGT) *Let (X, U, Φ) be a system satisfying the assumptions H1,H2,H3, H4, H5, and let $h : X \to U$ be antimonotone. If the equation $k^2(u) = u$ has a unique solution $u = \bar{u}$, then the closed loop system $\Psi(t, x_0)$ has a unique attractive equilibrium $k^X(\bar{u})$.*

Proof. Let $x_0 \in X$ be an arbitrary initial condition, and let $x(\cdot)$, $y = h \circ x$ be the solution of the closed loop system and its corresponding output respectively, and $u = y$ as above. Let α be a lower hyperbound of $u(\cdot)$. Such an element always exists: by H2 in the general assumptions 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. Also, $k(\alpha),\ k(\beta)$ are upper and lower hyperbounds of u respectively. Similarly, we conclude that $k^2(\alpha),\ k^2(\beta)$ are lower and upper hyperbounds of u respectively, and by induction the same can be deduced for $k^{2n}(\alpha),\ k^{2n}(\beta)$, respectively.

Now, $k^{2n}(u)$ converges as $n \to \infty$ towards $\bar{u}$ for all $u \in U$, by H4, H5 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 that $|k^{2n}(\alpha) - \bar{u}| < \epsilon/2,\ |k^{2n}(\beta) - \bar{u}| < \epsilon/2$. By definition of lower and upper hyperbound, there is $a, b \in U$ and $T \geq 0$ large enough such that $|a - k^{2n}(\alpha)| < \epsilon/2,\ |b - k^{2n}(\beta)| < \epsilon/2$ and for every $t \geq T :\ a \leq u(t) \leq b$. The normality of U is used in the same way as in the proof of CICS: $|u(t) - a| \leq M_U\,|b - a| < 2\epsilon M_U$, and so $|u(t) - \bar{u}| \leq 2\epsilon M_U + \epsilon$ 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 $(k^X(\bar{u})$ in X. ∎

We want to stress the fact that in view of Lemma 5, the fact that $k^2(u) = u$ has no nontrivial solutions is equivalent to the global attractivity of the system $u_{n+1} = k(u_n)$. This equivalence explains why the theorem is referred with the name "small gain theorem"; the two statements will be used interchangeably in the applications. Finally, the same proof as above can be carried out for the case in which h is monotone, 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 [**?**], Sontag and de Leenheer [**?**].

We now turn to the stability of the closed loop considered in SGT.

Lemma 6 *Let $\Phi(t, x, u)$ be a monotone system with characteristic k^X and antimonotone output h. Let $y \ll z$ in X such that $k^X h(y), k^X h(z) \in (y, z)$. Then all solutions $x(t, x_0)$ of the closed loop system with initial condition $x_0 \in [k^X h(z), k^X h(y)]$ are contained in (y, z), for all $t \geq 0$.*

Proof. Let $k^X h(z) \ll x_0 \ll k^X h(y)$, and let $x(t)$ be the solution of the closed-loop system with initial condition x_0. Suppose that the conclusion doesn't hold, and let by contradiction

$$t_0 = \min\{t \geq 0 \,|\, x(t) \notin (y, z)\}.$$

We stress the fact that as $x(0) \in (y, z)$, $x(\cdot)$ is continuous and the interval (y, z) is open, $x(t_0) \notin (y, z)$. 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 we have

$$k^X(h(z)) = x(t, k^X(h(z)), h(z)) \leq x(t, x_0, u) \leq x(t, k^X(h(y)), h(y)) = k^X(h(y)),\ \forall t \leq t_0$$

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 monotone the lemma also holds. One may interchange "$h(y)$" and "$h(z)$" in the above proof to obtain the corresponding stability result.

Proposition 1 (SGT Stability Criterion) *In the context of Theorem 2, let $\bar{x} = k^X(\bar{u})$, and suppose that there exist sequences $\{y_n\}$, $\{z_n\}$ in X such that, for every n, $y_n \ll \bar{x} \ll z_n$ and $\bar{x} \in (k^X h(z_n), k^X h(y_n)) \subseteq (y_n, z_n)$. Assume further that $y_n, z_n \to \bar{x}$. Then $\bar{x}$ is a stable steady state of the closed-loop system $\Psi(t, x_0)$.*

Proof. Let V be an open neighborhood V of $\bar{x}$. For $\epsilon > 0$, let y_n, z_n be within distance ϵ of $\bar{x}$ for some n large enough. For $x \in (y_n, z_n)$, we have $|x - y_n| \leq 2M_X\epsilon$ and $|x - \bar{x}| \leq 2M_X\epsilon + \epsilon$ by normality. Thus for ϵ small enough, $(y_n, z_n) \subseteq V$. We know that $(k^X h(z_n), k^X h(y_n))$ is nonempty by hypothesis, and that all forward orbits with initial condition in this set are contained in V by the previous lemma. ∎

We consider an application of this criterion for single input, single output systems. Let a function $g : U \to X$ be called $\ll$-*increasing* if $u \ll v$ implies $g(u) \ll g(v)$. For instance, this condition holds trivially if g is the identity function and U is contained in X. Define similarly a $\ll$-*decreasing* function, and allow U and X above to be interchanged.

Proposition 2 *Under the hypotheses of Theorem 2, let $B_U = \mathbb{R}$. If k^X is $\ll$-increasing, and h is $\ll$-decreasing, then $\bar{x}$ is a stable steady state of the closed-loop system $\Psi(t, x_0)$.*

Proof. We will carry out a construction as in the hypothesis of Theorem 1, first on $\mathbb{R}$ and then on X by taking its image under k^X. Recall that by Lemma 5, the iteration $u_{n+1} = k(u_n)$ is globally attractive towards $\bar{u}$, and note that the function $k : \mathbb{R} \to \mathbb{R}$ is also $\ll$-decreasing by hypothesis. Let $u > \bar{u}$, so that $k(u) < \bar{u}$. We have necessarily $k^2(u) < u$, since otherwise $k^2(u) = u$ giving rise to a second fixed point, or else $k^2(u) > u$, from which $k^{2i}(u) > u$ for all $i > 0$, a contradiction by the convergence hypothesis. From $k^2(u) < u$ we deduce $k^3(u) > k(u)$, $k^4(u) < k^2(u)$ and so on. Thus we can define $(a_0, b_0) = (k(u), u)$, and more generally $(a_n, b_n) = (k^{2n+1}u, k^{2n}u)$, and we have

$$a_0 < a_1 < \ldots \to \bar{u} \leftarrow \ldots b_1 < b_0,\ k(a_n, b_n) \subset (a_n, b_n).$$

Defining $y_n = k^X(a_n),\ z_n = k^X(b_n)$ we can use Proposition 1 since k^X is continuous and $\ll$-increasing, and stability thus follows. ∎

In the positive feedback case, a very similar argument implies stability as well.

4 Finding Monotone Systems with Negative Feedback

Are the above conditions ever satisfied, let alone useful in practice? We will show in this section that under rather general conditions, one can write an autonomous, not necessarily monotone system as the negative feedback closed-loop of a monotone controlled system, which has a well defined characteristic. Let

$$\dot{x} = f(x, u),\ x \in X = (\mathbb{R}^+)^n, u \in U \subseteq R^m \tag{2}$$

be a given autonomous system, $f(x, u) = (f_1(x, u), \ldots f_n(x, u))$. Fix a set $S \subseteq \{1, \ldots n\}$. Any vector $(x_i)_{i=1\ldots n}$ defines a vector $x^S = (x_i)_{i \in S}$. Letting z stand for a vector $(z_i)_{i \in S^C}$, we define a 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

$$\dot{x^S} = f^S(x^S; z, u), \tag{3}$$

with $n-s+m$–dimensional control (z, u). Finally, note that if $\pi = \{S_1, \ldots S_\Lambda\}$ is a partition of $\{1 \ldots n\}$, then the coupled system

$$\dot{x^{S_\lambda}} = f^{S_\lambda}(x^{S_\lambda}; x^{S_\lambda^C}, u),\ \lambda = 1 \ldots \Lambda \tag{4}$$

is equivalent to (2).

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

$$\dot{x} = g(x),\ x \in X = (\mathbb{R}^+)^n, \tag{5}$$

we let the variables $x_1 \ldots x_n$ be the vertices, and write a positive arc from x_i to x_j, $i \neq j$, if $\frac{\partial}{\partial x_i} g_j(x) > 0$ for all $x \in X$. Similarly, we write a negative arc from x_i to x_j if $\frac{\partial}{\partial x_i} g_j(x) < 0$

throughout, and no arc if $\frac{\partial}{\partial x_i} g_j(x) = 0$, for all $x \in X$. Note that not every system satisfies this trichotomy for all its variables; we will restrict ourselves in this section to such systems, which we can refer to as *sign definite*. We will assume here that $X = (\mathbb{R}^+)^n$ for simplicity.

If system (5) is sign definite with associated digraph G, then we can find an n-dimensional monotone system, with respect to some orthant cone, with input and output

$$\dot{x} = f(x, u), \;\; x \in X, \;\; u \in U \subseteq \mathbb{R}^m, \;\; h : U \to X \tag{6}$$

whose closed loop system under negative unity feedback is (5). We do this as follows, trying to minimize the number of inputs and outputs involved so as to make the reduced model in SGT as simple as possible. Let $A \subseteq \{x_1, \ldots x_n\}$ be an arbitrary set of variables, called *agonists*. These variables can 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 among themselves.

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

$$D_j = \{x_i | \text{ there is a discordant arc from } x_i \text{ to } x_j\},$$

and let $D = \bigcup_j D_j$, $m = |D|$ and $U = (\mathbb{R}^+)^m$. Now enumerate the elements of D as $\{x_{l_1}, \ldots x_{l_m}\}$. We 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 $x_{l_i} \in D_j$. We set $u_i = h_i(x) = x_{l_i}$, and we define cones in $\mathbb{R}^n$ and $\mathbb{R}^m$ as

$$K_X = K^1 \times \ldots \times K^n \qquad K^i = \begin{cases} \mathbb{R}^+ \text{ if } x_i \in A \\ \mathbb{R}^- \text{ if } x_i \notin A \end{cases}$$
$$K_U = (-K^{l_1}) \times \ldots \times (-K^{l_m}).$$

This controlled system has a state digraph G' that can be described as the result of removing all discordant arcs from G. See Figure 1 and the model (12) in Section 6, for an illustration of these definitions.

Theorem 3 *The controlled system (6) described above is monotone, and h is an antimonotone function, thus forming a negative feedback loop whose associated closed system is (5). Furthermore, if for each strongly connected component of G' with vertices $S \subseteq \{1 \ldots n\}$ the system (3) has a well defined I/S characteristic, then (6) allows an I/S characteristic.*

Proof. Consider variables x_i, x_j in (6). Then either $\frac{\partial}{\partial x_i} f_j(x, u) > 0$ and both variables are agonists or both are antagonists, or $\frac{\partial}{\partial x_i} f_j(x, u) < 0$ and x_i agonist, x_j antagonist or viceversa, or else $\frac{\partial}{\partial x_i} f_j(x, u) = 0$. In any case, increasing the value of x_i (in the direction given by K_i) will either leave $f_j(x)$ untouched or increase its value as well (in the direction given by K^j). This is known as the Kamke condition for monotonicity, see [2, 13] for details.

Further, if $\frac{\partial}{\partial u_i} f_j(x, u) \neq 0$, then there must necessarily be a discordant edge in G from x_{l_i} to x_j. But the cone in U has been inverted with respect to K_X, so a similar argument as above will ensure that (6) is monotone with respect to inputs as well, using the Kamke condition for monotonicity of controlled systems [2].

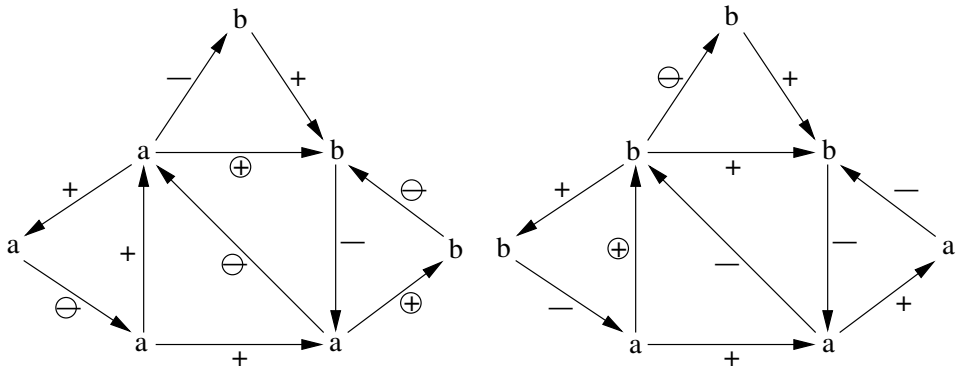

Figure 1: Network Splitting. The nodes in the digraphs above have been labeled "a" for agonist, and "b" for antagonist in two different ways, and the discordant arrows have been circled in each case. The nodes at the base of these arrows together will form the set D of inputs of the controlled system (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

The function h is antimonotone by construction. Finally, replacing each u_i in $f_j(x,u)$ back with $h_i(x) = x_{l_i}$ will bring back $g_j(x)$ - this proves that the closed loop system is the same as (5).

For the last assertion we will write (6) 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'. We index the s.c.c.'s in the following way: we know that the s.c.c. reduction of G' is an acyclic digraph, and that therefore there exists a strongly connected component of G' with no incoming arcs from other s.c.c.'s. Let one such component be S_1. Now eliminate the vertices in S_1 from $G' = G_0$ to form the digraph G_1. It is easy to see that the s.c.c.'s of G_1 are the same as those of G' minus S_1. Let S_2 be an s.c.c. of G_2 with no incoming arcs - thus in particular S_2 is also a s.c.c. of $G_0 = G'$. Continuing in this manner, we index all strongly connected components of G' 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 $f^{S_1}(x^{S_1}; z, u)$ using the notation above, where $z = (z_i)_{i \in S_1^C}$. By the choice of S_1, we know that f^{S_1} doesn't actually depend on z, and we can write it as $f^{S_1}(x^{S_1}, u)$. Similarly we can write $f^{S_\lambda}(x^{S_\lambda}; x^{S_\lambda^C}, u)$ in (4) as

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

and thus system (6) is written as a cascade as desired, using equation (4).

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. Now, it can be verified using the Kamke condition in [2] that each of the controlled systems in the cascade is monotone, and thus satisfies the CICS property. Thus the system $\dot{x}^{S_2} = f^{S_2}(x^{S_2}; x^{S_1}, u)$ converges globally towards some vector $(\bar{x}_i)_{i \in S_2}$. The same arguent follows by induction for all coupled subsystems in the cascade, which thus converges globally towards $(\bar{x}_i)_{i \in \{1 \dots n\}} = k^X(u)$.

∎

Corolary 1 *If the digraph G' associated to system (6) is acyclic, and for every $i = 1 \dots n$ the 1-dimensional system*

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

with controls $\hat{x}_j, \rfloor \neq i$, has a well defined I/S characteristic, then (6) also allows an I/S characteristic.

Proof.

Recall that the two expressions $g_i(x)$ and $f_i(x,u)$ are the same except possibly for some or several $x_{l_j}, j \neq i$ in the former that are replaced in the latter by some or several controls u_l. Our hypothesis thus implies that the system

$$\dot{x}_i = f_i(x_i; z, u)$$

has a characteristic, $z = (z_j)_{j \neq i}$. The graph G' is acyclic, therefore its strongly connected components are exactly the singletons $\{1\}, \ldots, \{n\}$ - by the previous theorem, the result follows. ∎

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 an amount of choice. Finally, note that this result makes SGT more 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 (6) that has a similar form to the previous one.

5 Delayed 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 possibility is to allow diffusion terms in the equations, and thus transform it into a weakly coupled system of PDEs – this is out of the scope of this paper, and will be discussed elsewhere. From now on we will rather consider the introduction of delay terms in the system. One example of such systems is

$$\dot{x}(t) = Ax(t-\tau) + Bx(t) \tag{7}$$

where A, B are $n \times n$ constant matrices. At first sight this might still look like a finite dimensional problem, but we point out that the initial condition of such system would have to include not only $x(-\tau)$ and $x(0)$, but also all $x(s)$ for $-\tau < s < 0$.

Given $r \geq 0$ (the delay of the system), $a \leq \infty$, a function $x : [-r, a) \to \mathbb{R}^n$, and $0 \leq t < a$, we 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

$$\dot{x}(t) = f(x_t),\ x_0 = \phi \tag{8}$$

where $\phi : [-r, 0] \to \mathbb{R}^n$. We consider the state of the solution at time t to be x_t (as opposed to just $x(t)$), and 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. In what follows we will refer to a continuous function $\phi : [-r, 0] \to \mathbb{R}^n$ as a *worm*.

Similar comments apply to the controlled system

$$\dot{x} = f(x_t, \alpha(t)), \tag{9}$$

which defines a dynamical system $\Phi(\phi, t, \alpha) = x_t$, for every input $\alpha : [0, \infty) \to U$. We will allow for the set U of input values to consist itself of functions, in order to include delays in the inputs. That is, for every $t \geq 0$, $\alpha(t) : [-r, 0] \to U_0$ is a function $\alpha(t)(s)$. It will be clear from the context when α is an *input*, and when it is an *input value*.

Let thus $X_0 \subseteq R^n, U_0 \subseteq R^m$, and let $B_X = C([-r, 0], \mathbb{R}^n)$, $X = C([-r, 0], X_0)$ under the supremum norm. The tentative choice of the function space $B_U = L^\infty([-r, 0], \mathbb{R}^n)$ 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 $\alpha \in L^\infty([-r, 0], \mathbb{R}^n)$, since such functions are not defined pointwise. Thus in the case of discrete delays, we restrict the input space to $B_U = C([-r, 0], \mathbb{R}^m)$, $U = C([-r, 0], U_0)$. In the case of integral delays, this problem disappears; for this reason we allow B_U to be either $L^\infty([-r, 0], \mathbb{R}^n)$ or $C([-r, 0], \mathbb{R}^m)$, and define U accordingly. In the latter case, note that if $u : \mathbb{R}^+ \to U_0$ is measurable and locally bounded, then $t \to u_t$ is in general not a well defined input in U_0; nevertheless (provided U_0 is connected) there exists an input α in B_U such that $u_t(s) = \alpha(t)(s)$ for every t and $s = -\tau_1, \ldots, -\tau_k$, and for $f(\phi, \beta) = f(\phi, \beta(-\tau_1, \ldots, -\tau_k)$, u_t can be replaced by α for practical purposes.

Definition 1 *A* delayed dynamical system *consists of a tuple (X_0, U_0, f), $f : X \times U \to \mathbb{R}^n$, such that 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*

$$\dot{x}(t) = f(x_t, \alpha(t)) \text{ for almost every } t, \ x_0 = \phi. \tag{10}$$

We use ϕ, ψ to refer to elements of X, that is, worms in X_0, and α, β for elements in U as well as for inputs. One common example of an input in U will be $\alpha(t) = u_t$, where $u(t) : [-r, \infty) \to U_0$ is measurable and locally bounded, in the case that $B_U = L^\infty([-r, 0], \mathbb{R}^n)$. To see this, note that this input is a well defined function since for every $t \geq 0$, u_t is measurable and bounded except for a set of measure zero. Also, the function $t \to u_t$ is locally bounded, since $t \to u(t)$ is. Finally, $t \to u_t$ is measurable (?!). In the case that $B_U = C([-r, 0], \mathbb{R}^m)$, the functions $\alpha(t) = u_t$, for $u(t) : [-r, \infty) \to U_0$ continuous, are inputs in U. Nevertheless it is important to point out that, in both cases, not every input of U is of this form.

We address in the appendix the question of which functions $f : X \times U \to \mathbb{R}^n$ generate a well defined delay dynamical system. The main result is the following theorem:

Theorem 4 *Let $f : X \times U \to \mathbb{R}^n$ be continuous, and locally Lipschitz on U locally uniformly on X. Let also $f(\phi, C)$ be bounded for any $\phi \in X$, $C \subseteq U$ closed and bounded. Then the system (10) has a unique maximally defined, absolutely continuous solution $x(t)$ for every input $\alpha(t)$ and every initial condition $\phi \in X$.*

We consider 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 7 *Let $C_{U0} \subseteq \mathbb{R}^m, C_{X0} \subseteq \mathbb{R}^n$ be closed cones with nonempty interior, and let $C_X = \{\phi \in B_X |\ \phi(s) \in C_{X0} \ \forall s\}$, $C_U = \{\alpha \in B_U |\ \alpha(s) \in C_{U0} \text{ a.e. } s\}$. Let U_0 be a closed box (possibly unbounded), and X_0 be open or, in the case of C_{X0} being an orthant cone, let X_0 be a box including some or all of its faces. Then C_X, C_U are proper and normal. Also, U, X satisfy hypotheses H2,H3.*

Proof. By Lemmas 1 and 2, C_{X0}, C_{U0} are normal, say with normality constants M, N respectively. But if $0 \leq \phi \leq \psi$ in X, then $0 \leq \phi(t) \leq \psi(t)$ for every t, and so $|\phi(t)| \leq M\,|\psi(t)|$, for every t – this asserts the normality of C_X with constant M. One proves similarly that C_U is normal.

Let $a \in \mathbb{R}^m$ bound the unit ball from above. Then the constant function $\hat{a}$ bounds the unit ball in B_U - this implies that C_U has nonempty interior. The function $d(\alpha) = sup\{\text{dist}(\alpha(s), C_{U_0})|\ s \in [-r, 0]\}$ is continuous, which implies that $C_U = d^{-1}(0)$ is closed. The same arguments apply to C_X.

If X_0 is open, any worm ϕ taking values in X_0 will remain a finite distance away from X_0^c, and thus there is an open neighborhood around ϕ contained in X, showing that X is open, too. In the positive orthant case (the general orthant case being almost identical) let $\epsilon > 0$ be given, and let

$$\eta = \frac{1}{2\sqrt{n}}\,\min(\epsilon, \text{dist}(Im(\phi), \partial X_0 - X_0)$$

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

$$\pi_1(x) = \inf\{x + q \cdot (1 \ldots 1)\,|\,q \in (-\eta, \eta),\ x + q \cdot (1 \ldots 1) \in X\},$$

$$\pi_2(x) = \sup\{x + q \cdot (1 \ldots 1)\,|\,k \in (-\eta, \eta),\ x + q \cdot (1 \ldots 1) \in X\}.$$

(In the case of a different orthant cone, one would take $q \cdot (\pm 1, \ldots \pm 1)$ accordingly.)

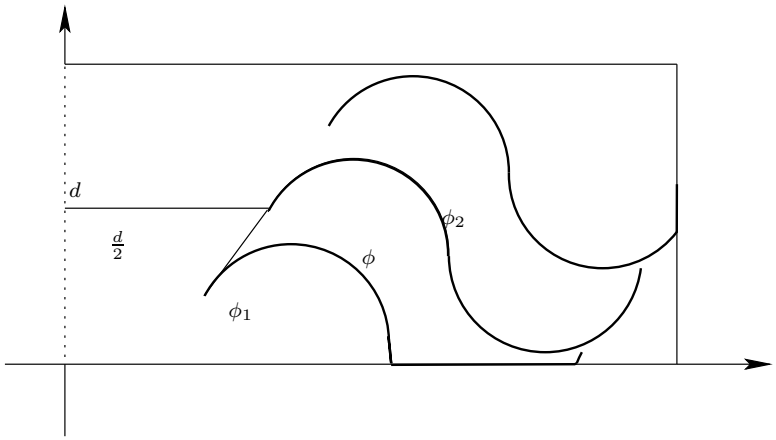

Figure 2: Shown in the picture are the box X_0 with one open and three closed sides, and $\phi_1 \leq \phi \leq \phi_2$ in bold. After computing $d = \min(\epsilon, \text{dist}(Im(\phi), \partial X_0 - X_0))$, the latter argument is in this case the smaller number.

Given $\phi \in X$, let $\phi_i(s) = \pi_i(x(s)),\ i = 1, 2$. Then $(y =)\phi_1,\ (z =)\phi_2 \in X$ by construction, and $\text{diam}[\phi_1, \phi_2] = |\phi_2 - \phi_1| < \epsilon$. Also,

$$[\phi_1, \phi_2] = X \cap \{\psi \in B_X|\ \phi - \eta(1 \ldots 1) \leq \psi \leq \phi + \eta(1 \ldots 1)\}.$$

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

In the case $B_U = C([-r, 0], \mathbb{R}^m)$, the same proof as for X applies to prove H3 for U even if some or all of its sides are missing. However, if $B_U = L^\infty([-r, 0], \mathbb{R}^m)$, then for a given $\alpha \in U$ the distance between the image of α and $\partial U - U$ may well be zero. Thus we use the fact that

U is an interval and contains its boundary, 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, $\alpha_1(s) = \pi_i(\alpha(s))$ are measurable functions. The rest of the proof follows as before.

We prove that U satisfies H2: in the case $B_U = C([-r, 0], \mathbb{R}^m)$, given $A \subseteq U$ bounded, 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 $B_U = L^\infty([-r, 0], \mathbb{R}^m)$, the axiom of choice allows to define A_0 by picking a particular pointwise 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.

■

We give a convenient criterion to check for monotonicity in the case of orthant cones, based on Theorem 1.1 of Smith [13]. If $\mathcal{K} \subseteq \mathbb{R}^n$ is an orthant cone, we can write it as $\mathcal{K} = \mathbb{R}^{\sigma(s_1)} \times \ldots \times \mathbb{R}^{\sigma(s_n)}$, where $s_i \in \{1, -1\}$ for each i and $\sigma(1) =$'+', $\sigma(-1)=$'−'.

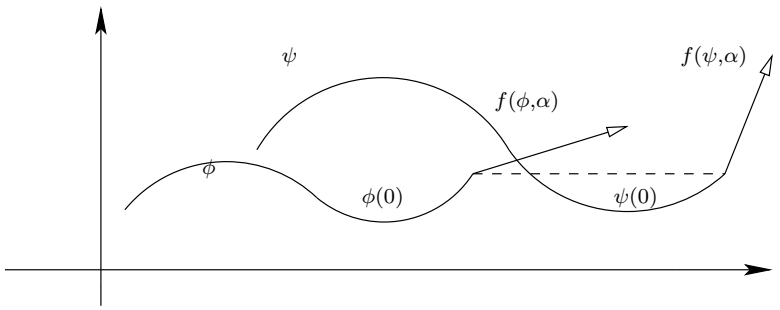

Figure 3: Monotonicity Criterion. Illustrated are two worms $\phi, \psi \in X$ with $\phi \leq \psi$, and $\phi_2(0) = \psi_2(0)$. In the cooperative case, it needs to hold that $f_2(\phi, \alpha) \leq f_2(\psi, \alpha)$.

Proposition 3 (Monotonicity Criterion) *Let (9) be a delayed system, and let $\mathcal{K}_X$ be an orthant cone. 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 $s_i f_i(\phi, u) \leq s_i f_i(\psi, \alpha)$. Then system (9) is monotone with respect to its underlying cones.*

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

Suppose that the delay system (X_0, U_0, f) allows an I/S characteristic $k^X : U \to X$. Note that $\phi = \Phi(t, k^X(\alpha), \alpha)$ is constant over t, and thus any solution of (9) with constant input α starting at $k^X(\alpha)$ must have $x_t = k^X(\alpha)$ 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 . We 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.

To prove that $\Phi(t, \phi, \alpha)$ is a dynamical system, we need 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.

As a first example of SGT for delayed systems we use the following toy model, from Stepan [16]. It is linear, so that many different (and more comprehensive) approaches are available. We include it to illustrate how to use the small gain theorem for delay systems in practice.

Example 1: Consider the system

$$\begin{aligned} \dot{x}_1(t) &= -a_{11}x_1(t) - a_{12}x_2(t-\xi) \\ \dot{x}_2(t) &= a_{21}x_1(t-\tau) - a_{22}x_2(t), \end{aligned} \tag{11}$$

where $a_{11}, a_{12}, a_{21}, a_{22}$ are positive real numbers, $\xi, \tau \geq 0$. We let the delay of the system be $r = max(\tau, \xi)$, and define for instance $X_0 = (\mathbb{R}^+)^2$. If $x_t \leq z_t$ componentwise, and $x_2(t) = z_2(t)$, then certainly $\dot{z}_2(t) - \dot{x}_2(t) = a_{21}z_1(t-\tau) - a_{22}z_2(t) - a_{21}x_1(t-\tau) + a_{22}x_2(t) \geq 0$. If the same were true for x_1, z_1, then we could conclude that (11) is cooperative, by Theorem 3. Since this is not the case, we consider the controlled system

$$\begin{aligned} \dot{x}_1(t) &= -a_{11}x_1(t) - a_{12}u(t-\xi) \\ \dot{x}_2(t) &= a_{21}x_1(t-\tau) - a_{22}x_2(t) \end{aligned}, \quad u(t) = h(x(t)) = x_2(t),$$

whose closed-loop system is (11). This system does satisfy the hypotheses of Theorem 3, provided that we define the cone in $B_U = \mathbb{R}$ as $\mathcal{K}_U = \mathbb{R}^-$. Letting further $U_0 = R$, we satisfy all hypotheses of Lemma 6, so that assumptions H1,H2,H3 are satisfied. The I/S characteristic of the system can be easily seen to exist and be defined by

$$x_1 = \frac{a_{12}}{a_{11}}u, \quad x_2 = \frac{a_{21}}{a_{22}}\frac{a_{12}}{a_{11}}u$$

for any $u \in \mathbb{R}$. Since it is continuous and sends bounded sets to bounded sets, H4 is satisfied. We are left with condition H5 and the discrete convergence, which hold together for the function $k(u) = \frac{a_{21}}{a_{22}}\frac{a_{12}}{a_{11}}u$ if and only if $a_{12}a_{21} < a_{11}a_{22}$

6 A model of the lac operon

The following dynamical system was proposed by J.M. Mahaffy and E.S. Savev [11] to describe the dynamics of lactose metabolism in *E.Coli*, orchestrated by the genes known as the lac operon. Some of the main results in [11] concern the global stability of the system; we will apply the small gain theorem in its delayed variant to prove and extend these results.

The species involved in the system are the lac operon mRNA, the proteins β-galactoside permease, β-galactosidase (β-gal for short) and lactose, which we denote respectively by y_1, y_2, y_3, y_4. (Actually it is isolactose that regulates the operon, but we will identify lactose and isolactose here.) All concentrations degrade at a fixed rate, except for the lactose, which is actively digested by the enzyme β-gal. The mRNA is activated when lactose is present in the system — more enegetic souces of food, like glucose, are assumed not to be present. The mRNA proceeds to be transcribed into equal quantities permease and β-gal, and the permease makes the cell membrane more permeable to lactose so that it can enter the system (often β-gal and permease are described by the same variable). Mahaffy et al. assume that the production of mRNA has a natural saturation point, with Michaelis-Menten dynamics, which amounts to, say, the presence of a constant amount

of RNA polymerase. An arbitrary delay is introduced as a result of translation — perhaps the most interesting feature of the following approach is that it allows to introduce more delays if so desired, without affecting the result. The model in question is the following, where $k > 1$ and all other constants are assumed positive and arbitrary:

$$\begin{aligned}
\dot{y}_1(t) &= g(y_4(t-\tau)) - b_1 y_1(t) \\
\dot{y}_2(t) &= y_1(t) - b_2 y_2(t) \\
\dot{y}_3(t) &= r y_1(t) - b_3 y_3(t) \\
\dot{y}_4(t) &= S y_2(t) - y_3(t) y_4(t),
\end{aligned} \qquad g(\theta) = \frac{1 + k\theta^\rho}{1 + \theta^\rho}. \tag{12}$$

We will illustrate our main result by writing this system as the negative feedback loop of a controlled monotone system, using the tools from Section 4. We define as agonists the variables y_1, y_2, and as antagonists y_2, y_4. There is only two discordant arcs, as seen in Figure **??**, and we have $D_1 = \{y_4\},\ D_2 = \{y_1\},\ D_3 = D_4 = \emptyset$, and thus $D = \{y_1, y_4\}$. The associated controlled system is then

$$\begin{aligned}
\dot{y}_1(t) &= g(v(t)) - b_1 y_1(t) \\
\dot{y}_2(t) &= u(t) - b_2 y_2(t) \\
\dot{y}_3(t) &= r y_1(t) - b_3 y_3(t) \\
\dot{y}_4(t) &= S y_2(t) - y_3(t) y_4(t)
\end{aligned} \qquad g(x) = \frac{1 + kx^\rho}{1 + x^\rho}, \quad h(y(t)) = (y_1(t), y_4(t-\tau)).$$

which is monotone with respect to the cones $K_Y = \mathbb{R}^+ \times \mathbb{R}^- \times \mathbb{R}^+ \times \mathbb{R}^-,\ K_U = \mathbb{R}^- \times \mathbb{R}^+$, and whose closed feedback loop digraph is shown in Figure **??**. Note that we might as well have written $\dot{y}_1(t) = g(v(t-\tau)) - b_1 y_1(t),\ h(y(t)) = (y_1(t), y_4(t)$, and the treatment would be quite similar in our setup.

It is quite clear that fixing an input (u, v) will make the system converge to a fixed value independent of initial conditions, which can be calculated to be

$$y_1 = \frac{g(v)}{b_1},\ y_2 = \frac{u}{b_2},\ y_3 = \frac{r}{b_1 b_3} g(v),\ y_4 = \frac{S b_1 b_3 u}{r b_2 g(v)}$$

and thus the I/O characteristic of the system is

$$k(u, v) = \left(\frac{1}{b_1} g(v), \frac{S b_1 b_3}{r b_2} \frac{u}{g(v)} \right). \tag{13}$$

Note that $k(u, v)$ has a unique steady state $u = \frac{1}{b_1} g(\frac{S b_3}{r b_2}),\ v = \frac{S b_3}{r b_2}$. For any choice of the parameters such that the discrete system $(u_{n+1}, vn + 1) = k(u_n, v_n)$ is globally attractive to this equilibrium, we can conclude from Theorem 2 that the original model 12 is globally attractive to its unique equilibrium.

In the global analysis of model (12), Mahaffy and Savev [11] restrict their attention to the case $\rho = 1$, and prove three results that provide sufficient conditions for global attractiveness. We will come to the exact same conclusions by writing the system associated to (13) as a scalar discrete system of second order, and borrowing the stability results known for this system. Then we will

prove global stability for any choice of the parameters b_1, b_2, b_3, S, r provided an inequality holds for ρ, K.

Consider the discrete system $(u_{n+1}, v_{n+1}) = k(u_n, v_n)$. We have $u_{n+1} = \frac{1}{b_1} g(v_n)$, and

$$u_{n+2} = \frac{1}{b_1} g\left(\frac{Sb_1b_3}{rb_2}\frac{u_n}{g(v_n)}\right) = \frac{1}{b_1} g\left(\frac{Sb_3}{rb_2}\frac{u_n}{u_{n+1}}\right) = \frac{\beta u_n + \gamma u_{n-1}}{Bu_n + Cu_{n-1}}, \tag{14}$$

where here $\rho = 1$ in $g(x)$, and $\beta = \frac{1}{b_1}, \gamma = K\frac{Sb_3}{rb_1b_2}, B = 1, C = \frac{Sb_3}{rb_2}$. The book by Kulenovic and Ladas [8] deals exclusively with rational discrete systems of second order, and we find from their treatment of this equation that for $p = \beta/\gamma, q = B/C$, and $p < q$, global attractivity holds if and only if $q < pq + 1 + 3p$. In our case $p = \frac{rb_2}{KSb_3} < \frac{rb_2}{Sb_3} = q$, and attractivity holds if and only if

$$0 < q^2 + 3q - Kq + K, \quad q = \frac{rb_2}{Sb_3}. \tag{15}$$

For instance, if $q < 1$ then $0 < K - qK$ and convergence follows - this corresponds to Proposition 4.1 in [11]. Similarly, convergence follows whenever $q > K$, since $0 < q^2 - qK$. (Proposition 4.2). Finally, for $q > 1$ equation (15) is equivalent to $K < q(q+3)/(q-1)$, and this function is bounded from below by 9. Thus for $1 \leq K < 9$ stability also follows. The remainding assertions in Theorem 4.2 of [11] follow similarly. We summarize this in the following theorem.

Theorem 5 *The system (12) 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* $q < 1$, $q > K$, *or if* $q > 1$ *and* $K < q(q+3)/(q-1)$.

Note that the delay τ was almost never used, and indeed can be arbitrarily large or small. In fact, we can introduce different delays, large or small, in all of the first summands of the right hand sides of (12), and the results will apply with almost no variation (if delays are introduced in the second summands, the systems will not be monotone anymore). If no delays are assumed, substantially stronger stability conditions hold - see [11].

The association above of a second order, scalar discrete system to the original two-dimensional system can be carried out for any value of ρ in the same way, and global attractiveness of (12) follows whenever this discrete system has no nontrivial 2-cycles. We write this in the following proposition.

Proposition 4 *The system (12) 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 splitting the same model as the negative feedback loop of a monotone system *in other ways* – after all, one can see that having y_1, y_2, y_4 as agonists and y_3 as antagonist will yield a such a system with the need to cut only one arrow, that is, with only one scalar input and output. Indeed, 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 loop remains in the controlled system). To check that there are no nontrivial 2-cycles for the discrete system, we need 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 the proposition above. Thus, there are several ways to apply the tools of Section 4 and Theorem 2.

In what follows, we transform $k(u, v) = (\zeta v, \xi u/g(v))$ into logarithmic coordinates, that is, we consider

$$\hat{k}(\sigma, \tau) = \ln(k(e^\sigma, e^\tau)),$$

where here $\ln(x, y) = (\ln x, \ln y)$. We compute

$$\hat{k}(\sigma, \tau) = (\gamma(\tau), \sigma + c - \gamma(\tau)), \quad \gamma(\tau) = \ln\ \zeta g(e^\tau),\ c = \ln \zeta\xi.$$

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 we associate the second order system $\sigma_{n+2} = \gamma(c + \sigma_n - \sigma_{n+1})$ as above.

Lemma 8 *Consider a discrete system $\sigma_{n+2} = \gamma(c + \sigma_n - \sigma_{n+1})$, where c is an arbitrary constant and γ is a bounded, non-decreasing, Lipschitz function with Lipschitz constant $\alpha < 1/2$. Then the system is globally attractive to its unique equilibrium $\sigma = \gamma(c)$.*

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 $\sigma = \gamma(c)$, since $\sigma_0 = \sigma_1$ implies $\sigma_2 = \gamma(c + \sigma_0 - \sigma_1) = \gamma(c)$ and so on. Let $a_0 = \inf\ \mathrm{Im}\ \gamma,\ b_0 = \sup\ \mathrm{Im}\ \gamma$. Then it holds that for any initial conditions σ_{-1}, σ_0 we have $\sigma_n \in [a_0, b_0],\ n \geq 1$. Thus for any $n \geq 1$,

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

and by calling $a_1 = \gamma(a_0 - b_0 + c),\ b_1 = \gamma(b_0 - a_0 + c)$, we have $\sigma_n \in [a_1, b_1],\ n \geq 3$.

We define inductively $a_{i+1} = \gamma(a_i - b_i + c),\ b_{i+1} = \gamma(b_i - a_i + c)$, and have that for any $n \geq 2i+1$, $\sigma_n \in [a_i, b_i]$, by induction on i as above. If we show that $|b_i - a_i|$ tends to 0 as i increases, then the discrete system will be globally attractive towards $\gamma(c)$, since $a_i \leq \gamma(c) \leq b_i$ for all i. Using the Lipschitz condition on γ, we have

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

and the conclusion follows.

∎

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

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

or ρ arbitrary if $K = 1$. We conclude thus by using the previous lemma and our main result:

Corolary 2 *The lac operon model (12) 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

7.1 Existence and Uniqueness

Theorem 6 *Let $X_0 \subseteq \mathbb{R}^n$ be an open set, or in the orthant case, a box (not necessarily bounded) containing some or all of its sides. Let B_U be a Banach space, and $U \subseteq B_U$. 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 $C \subseteq U$, $D \subseteq X$ closed and bounded, there exists $M > 0$ such that*

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

ii) *For every $\phi \in X, C \subseteq U$ closed and bounded, the set $f(\phi, C)$ is bounded.*

Then the system (10) has a unique, maximally defined, absolutely continuous solution $x(t)$ for every input α and initial condition $\phi \in X$.

Proof. We will show that all hypotheses are met to apply Theorem 4.3.1, p. 207 of Bensoussan et al. [4] in a systematic manner. Consider a fixed input β of the input space U, and let $\Omega_0 \subseteq X_0$ be a given compact set. Let $C_1 \subseteq C_2 \subseteq C_3 \subseteq \ldots \subseteq U$ a sequence of bounded sets such that $\bigcup_i C_i = U$, by letting C_i be the intersection of the ball $B(0, i)$ with U. For every C_i, there is M_i such that $f(\cdot, \alpha)$ is M_i-Lipschitz on Ω_0, for all $\alpha \in C_i$. 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_0, for all α, and that m is measurable. Indeed, if each M_i was chosen to be as small as possible, then $M_1 \leq M_2 \leq \ldots$, and m is a step function on each C_i.

Now for every fixed $\alpha \in U$, extend the function $\phi \to f(\phi, \alpha)$ from Ω_0 to all of B_X, in such a way that the extension is also $m(\alpha)$-Lipschitz. That is, let

$$F(\phi, \alpha) = \inf_{\psi \in \Omega_0} f(\psi, \alpha) + m(\alpha) \, |\phi - \psi| \,,$$

where the infimum is taken componentwise, i.e. with respect to the cooperative cone $(\mathbb{R}^+)^n$. It is straightforward to verify that for a fixed α, $F(\cdot, \alpha)$ is well defined, coincides with $f(\cdot, \alpha)$ on Ω_0, and is itself $m(\alpha)$-Lipschitz.

Define now $g(t, \phi) = F(\phi, \beta(t))$. It is on this function that we apply Theorem 4.3.1 of [4]. We need to verify a few conditions: $F(\phi, \alpha)$ is the infimum of measurable functions (in fact F is piecewise continuous on each set $X \times C_i$) and thus measurable, which implies that $g(t, \phi)$ is also measurable. By setting $n(t) = m(\beta(t)$, we have that $n(t)$ is measurable and locally bounded (since each $\beta|_{[0,T]}$ is contained in some C_i), and thus locally integrable. Finally, by using our second hypothesis on some ϕ_0 in Ω_0, we see that $F(\phi, C_i)$ is bounded in $\mathbb{R}^n$, and thus $t \to g(t, 0)$ 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, absolutely continuous solution defined for all $t \geq 0$ and every initial condition $\phi \in B_X$.

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

$$\Omega_j = \mathrm{Im}(\phi) \cap \{x \in X_0 \,|\, \mathrm{dist}(x, \mathrm{Im}(\phi)) \leq j \text{ and } \mathrm{dist}(x, \partial X - X) \geq 1/j\}.$$

We extend f from Ω_j to all $\mathbb{R}^n$ to form F_n, applying the main step. 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 unicity within Ω_k, to form an absolutely continuous solution $x(t)$. Finally, $x(t)$ must agree with and be defined wherever any other solution $x_1(t)$ of (2) is defined. This shows that x(t) is unique and maximally defined. ∎

7.2 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 is identical. ∎

Proof of Lemma 2: Let $C_1 = \{x \in \mathcal{K} |\ |x| = 1\}$. Let $f : C_1 \times C_1 \to \mathbb{R}, f(x, y) = x \cdot y$. Now, 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 $\mathcal{K} \cap (-\mathcal{K}) = \{0\}$. We conclude that there is $\theta < 1$ such that $x \cdot y \geq -\theta\,|x|\,|y|$ for every $x, y \geq 0$.

Now let $0 \leq x \leq y$. We have $(y - x) \cdot x \geq -\theta\,|x|\,|y - x|$, 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 $|x|$, we find that

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

∎

7.3 Monotonicity Criterion and Semiflow Property

Sketch of proof for Proposition 3 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 in 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 [13] 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 [13]: 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 for the semiflow condition for the function $\Phi(t, \phi, \alpha) = x_t$ to satisfy the semiflow property. 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 $f : X \times U \to \mathbb{R}^n$.

Lemma 9 *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 (9), 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 (9) with input $\gamma(t)$ 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) absolutely continuous, as it is built from absolutely continuous parts. Further,

$$w'(t + t_0) = z'(t) = f(\gamma(t), z_t) = f(v(t + t_0), w(t + t_0)), \forall t \geq 0.$$

Thus $w(t)$ is a solution of (9) with input $v(t)$ (recall $u(t) = v(t), -r \leq t \leq t_0$), and initial condition ϕ_0, that is, $w = y$. The conclusion follows.

Lemma 10 (Semiflow Property) *Let (X_0, U_0, f) be a delayed system. Let $u_1(t)$, $u_2(t)$ inputs, and $x(t), y(t)$ solutions of (9) with inputs $u_1(t), u_2(t)$ respectively, and initial conditions ϕ_0 and $\phi_1 = x_{s_0}$ respectively. Finally, let $z(t)$ solution of (9) with initial condition ϕ_0 and input $v(t) = u_1(t), 0 \leq t \leq s_0, v(t) = u_2(t - s_0), t > s_0$.*

Then $y_{t_0} = z_{s_0+t_0}$.

Proof. By the previous Lemma, $z_{s_0} = x_{s_0} = \phi_1$. Note that $w(t) = z(s_0 + t)$ is a solution of (9) with input u_2 and initial condition ϕ_1:

$$w'(t) = z'(s_0 + t) = f(v(s_0 + t), z(s_0 + t) = f(u_2(t), w(t)), \forall t \geq 0.$$

Thus $w = y$ by unicity. In particular, $y_{t_0} = w_{t_0} = z_{s_0+t_0}$. ∎

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References

[1] D. Angeli, P. de Leenheer, E. Sontag, 2002. On predator-prey systems and small gain theorems, submitted.

[2] D. Angeli, E.D. Sontag, 2003. Monotone control systems. IEEE Trans. Autom. Control, 48: 1684-1698.

[3] D. Angeli, E.D. Sontag, 2004. Multistability in monotone input/output systems. Systems and Control Letters **51**: 185–202.

[4] A. Bensoussan, G. Prato, M.C. Delfour, and S.K Mitter, 1992. Representation and Control of Infinite Dimensional Systems. Boston, Birkhauser.

[5] E.N. Dancer, 1998. Some remarks on a boundedness assumption for monotone dynamical systems. Proc. of the AMS 126:801-807.

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

[7] M.W. Hirsch, 1989. Stability and convergence in strongly monotone dynamical systems. Reine und Angew. Math. 383:1-53.

[8] M.R.S. Kulenovic, G. Ladas, 2002. Dynamics of Second Order Rational Difference Equations. New York, Chapman & Hall/CRC.

[9] J. Keener, J. Sneyd, 1998. Mathematical Physiology. New York, Springer.

[10] V.L. Kocic, G. Ladas, Global Behavior of Nonlinear Difference Equations of Higher Order with Applications. Boston, Kluwer Academic, 1993.

[11] J.M. Mahaffy, E.S. Savev, 1999. Stability analysis for a mathematical model of the *lac* operon. Quarterly of Appl. Math, LVII,1:37-53.

[12] J.D. Murray, 2002. Mathematical Biology, I: An introduction. New York, Springer.

[13] H.L. Smith, 1995. Monotone Dynamical Systems. Providence, R.I., AMS.

[14] H. Smith, 1987. Oscillations and multiple steady states in a cyclic gene model with represion. Journal of Math. Biology, 25:169-190.

[15] E. Sontag, 1998. Mathematical Control Theory. New York, Springer.

[16] G. Stepan, 1989. Retarded Dynamical Systems: Stability and Characteristic Functions. New York, Wiley.