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RESEARCH ARTICLE

Fixed points and convergence in monotone systems under positive or negative feedback

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In this paper a theorem is discussed that unifies two lines of work in I/O monotone control systems. Under a generalized small gain hypothesis, it is shown that almost all solutions of closed loops of MIMO monotone systems are convergent, regardless of whether the feedback is positive or negative. This result is based on a topological argument showing that any monotonically decreasing n-dimensional map that has convergent iterations must have a unique fixed point. The paper also generalizes the standard small gain theorem by replacing the small gain condition with a weaker hypothesis. An example and simulations are given involving a simple cyclic system under arbitrary feedback.

Keywords: I/O monotone systems; systems biology; fixed point; degree theory

1 Introduction

A class of autonomous and control systems that has been studied extensively for potential applications in biological systems is that of monotone systems. The simplest form of such system is a *cooperative dynamical system*, an n-dimensional ODE of the form

$$x' = f(x), \tag{1}$$

with the property that $\frac{\partial f_i}{\partial x_j}(x) \geq 0$ for every $x \in X \subseteq \mathbb{R}^n$ and $i \neq j$. Although one can define monotone systems in more generality as systems that have exclusively positive feedback interactions, they can be brought to this form after a change of variables (see Section 4 for details). The solutions of monotone systems preserve a partial order defined on the state space (18). Regarding their qualitative dynamical behavior, the key result shown by Hirsch in the 1980's states that under mild irreducibility assumptions almost every bounded solution of a monotone system converges towards a steady state (16). The use of *almost* is meant in the sense of measure, i.e. the set of exceptional initial conditions has measure zero.

The reason monotone systems can be useful in biological applications is that often the amount of information given about biological systems is very limited and of a qualitative rather than quantitative nature. If it is known that all interactions between different variables in the system are positive, then much can be deduced about the qualitative dynamics of the system as described above. For instance, if all solutions are bounded and there are only two stable steady states, then one can conclude that almost all solutions converge towards one of these two steady states and rule out chaotic behavior, stable periodic oscillations, etc. (18).

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The theory of monotone systems was extended to systems with inputs and outputs by Sontag and Angeli in a series of papers (2, 3). Again in the simplest case, an input/output (I/O) system

$$x' = f(x, u), \quad y = h(x) \tag{2}$$

is *cooperative* if $\frac{\partial f_i}{\partial x_j}(x, u) \geq 0$, $\frac{\partial f_i}{\partial u_k}(x, u) \geq 0$ for every $i, j = 1 \ldots n$, $i \neq j$, $k = 1 \ldots m$, and every $x \in X \subseteq \mathbb{R}^n, u \in U \subseteq \mathbb{R}^m$. Assume for simplicity that X, U are box sets i.e. Cartesian products of bounded or unbounded intervals. Two different types of feedback are considered. In *positive feedback* I/O systems it is assumed that $\frac{\partial h_k}{\partial x_i}(x) \geq 0$ for all k, i and all $x \in X$, and in *negative feedback* systems $\frac{\partial h_k}{\partial x_i}(x) \leq 0$ for all k, i and all x. The *closed loop* of an I/O cooperative system is an autonomous control system defined as

$$x' = f(x, h(x)). \tag{3}$$

In the positive feedback case the closed loop is itself a cooperative system (2) and can therefore be studied using techniques from monotone systems theory. This is not the case in nontrivial systems under negative feedback. System (2) is assumed to converge globally towards a unique equilibrium $g^X(u)$ under any constant input $u \in U$, and the function $g(u) = h(g^X(u))$ is called the *I/O characteristic* of the system. We make the standing assumption that if $g(e) = e$, then $g'(e)$ has no eigenvalue of magnitude 1 (nondegeneracy).

The I/O characteristic $g(u)$ can be potentially measured experimentally, and it provides an amount of quantitative information complementing the qualitative assumptions. Specifically, it was shown that the stable steady states of the cooperative closed loop $x' = f(x, h(x))$ are in bijective correspondence with the stable fixed points of $g(u)$. Therefore in the positive feedback case, one can determine whether the system is multistable or monostable by examining $g(u)$ alone. Originally described in (2), this result has been generalized and applied to various specific models in (8, 12), among others.

In the negative feedback case, the literature has focused around nonlinear small gain results. Specifically, it was shown (3) that if all solutions of the system

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

converge towards a unique fixed point $\bar{u}$, then the closed loop (3) has a globally attractive steady state $g^X(\bar{u})$. This seminal result, known as the *small gain theorem* for I/O monotone control systems, enables an analysis of many non-monotone dynamical systems using ideas from monotone systems theory. It was generalized, expanded, or applied in several references including (9, 10, 15, 17).

Notice that although the positive and negative feedback frameworks are very similar, the growing literature has focused on one case or the other, with largely no unifying results. (A different approach for unification in mixed feedback systems is being pursued in the manuscript (21).)

Contributions of this paper

An idea originally proposed by Eduardo Sontag (22) is to alter the hypothesis that (4) has a unique globally attractive fixed point, and to assume instead that almost every solution converges towards some fixed point which may depend on the initial condition. One can call this the *generalized small gain condition, GSGC*. If there are multiple locally stable fixed points of (4), Sontag conjectured that the solutions of the closed loop may converge towards one of multiple stable steady states, an important improvement over the original result. Condition GSGC was also devised as a way to unify the negative and positive feedback frameworks. Another interesting effort to generalize the small gain theorem is the work by Malisoff and de Leenheer (17), where the I/O characteristic was allowed to be multivalued and the authors consider an associated discrete inclusion corresponding to (4).

In this paper, the open conjecture is resolved in a negative sense. Assuming the generalized small gain condition GSGC, along with irreducibility and mild regularity assumptions, it is proved that $g(u)$ can only have one fixed point. This means that the generalized small gain theorem collapses into the standard theorem, as GSGC is equivalent to the standard convergence of all solutions of (4) towards a unique fixed point. It is shown that monotonically decreasing, irreducible m-dimensional maps with convergent iterations can only have one fixed point (Theorem 3.3), which is surprising and of interest by itself. Its proof makes use of topological degree theory and various linear algebra tools.

Although GSGC may not lead to multistable systems in the negative feedback case, it does satisfy the more general intended purpose to unify the positive and negative feedback frameworks in the I/O monotone literature. Given such a system under either positive or negative feedback, under GSGC and mild irreducibility conditions almost every solution of the closed loop converges towards a stable steady state (Theorem 4.2). In the negative feedback case this equilibrium is unique, but in the positive feedback case the system can be multistable.

While the main idea for this unified statement is simple, the additional technical assumptions of the positive and negative feedback results are different, and a nontrivial part of the work is to find a common set of additional assumptions that fit both frameworks. In particular, the negative feedback result makes irreducibility assumptions on the I/O characteristic, while the positive feedback results in the literature tend to assume irreducibility of the closed loop system. It is shown here that assuming irreducibility of the closed loop is sufficient for both cases.

In Section 2 linear I/O cooperative systems under positive or negative feedback are considered, and it is shown that if the closed loop is irreducible, then the I/O characteristic is also irreducible. Section 3 uses topological tools to show that under GSGC, the I/O characteristic of a system under negative feedback must have a unique fixed point. Section 4 describes and proves a theorem that unifies both the positive and negative feedback frameworks for multiple input, multiple output (MIMO) systems. Section 5 discusses a simple example of a cyclic feedback loop of arbitrary sign, together with simulations illustrating the use of Theorem 4.2. Section 6 discusses a case when the same system can be decomposed as a positive or negative feedback loop.

2 Irreducibility of I/O characteristics

This section is concerned with linear cooperative systems, with or without inputs. A linear system $x' = Ax$ can be seen to be cooperative if and only if all non-diagonal entries of A are nonnegative. In this case the matrix A itself is called cooperative. Given any linear system $x' = Ax$ on $\mathbb{R}^n$, associate to it the directed graph G with nodes $x_1, \ldots, x_n$ and a directed edge from x_i to x_j if and only if $A_{ji} \neq 0$. Each edge can be labeled as positive or negative depending on the sign of a_{ji}. If G is strongly connected, the linear system is said to be *irreducible*. A *path* on the directed graph is meant in the usual sense, and it consists of a set of edges of the form $(x_{i_1}, x_{i_2}), (x_{i_2}, x_{i_3}), \ldots, (x_{i_{p-1}}, x_{i_p})$. Also, a few standard notations are used involving order relations in multiple dimensions. Given two vectors $x, y \in \mathbb{R}^k$, define

$$x \leq y \text{ if } x_i \leq y_i \text{ for all } i = 1 \dots k,$$

$$x \ll y \text{ if } x_i < y_i \text{ for all } i = 1 \dots k,$$

$$x < y \text{ if } x \leq y,\ x \neq y.$$

Similarly for $\geq, \gg, >$. Using this notation, a cooperative system satisfies that if $x(t), y(t)$ are two solutions and $x(0) \leq y(0)$, then $x(t) \leq y(t)$ for every $t \geq 0$ (18). The first lemma is standard but it is included for the sake of completeness. Recall that a square matrix A is *Hurwitz* if all its eigenvalues have negative real part.

Lemma 2.1 Suppose that the matrix A is cooperative and Hurwitz. Then all entries of $P := -A^{-1}$ are nonnegative. Moreover for every $i, j, i \neq j$, there exists a path from x_i to x_j on the graph of A if and only if $P_{ji} > 0$.

Proof Consider a solution $x(t)$ of the system $x' = Ax$. Then

$$A \int_0^\infty x(t)\, dt = \int_0^\infty x'(t)\, dt = -x(0)$$

and $Px(0) = -A^{-1}x(0) = \int_0^\infty x(t)\, dt$. If $x(0) \geq 0$, then $x(t) \geq 0$ for all $t > 0$ by cooperativity, so that $Px(0) \geq 0$ and all entries of P are nonnegative. Also, setting $x(0) = e_i$ we have

$$P_{ji} = [Pe_i]_j = \int_0^\infty x_j(t)\, dt.$$

If there exists a path from x_i to x_j on the graph of A, then $x_j(t) > 0$ for every $t > 0$ by cooperativity of $x' = Ax$, and therefore $P_{ji} > 0$. Conversely if there is no path from x_i to x_j, then a solution with initial condition e_i satisfies $x_j(t) = 0$, hence $P_{ji} = 0$. □

Consider a cooperative I/O control system under positive feedback

$$x' = Ax + Bu, \quad y = Cx. \tag{5}$$

That is, all off-diagonal entries of A and all entries of B, C are nonnegative. Assuming that A is Hurwitz, one can easily show that the I/O characteristic of the system is well defined by the matrix $-CA^{-1}B$. Also, the closed loop of the system is given by the matrix $A + BC$. The following lemma relates the irreducibility of this matrix with that of the closed loop system.

Lemma 2.2 Consider a Hurwitz cooperative linear control system (5) under positive feedback. Assume that all the columns of B, and all the rows of C, are nonzero. If $A + BC$ is irreducible, then $-CA^{-1}B$ is irreducible.

Proof

Consider the graph G of the closed loop matrix $A + BC$, and the graph G' of the matrix A. Due to the cooperativity assumptions, G' is a subgraph of G. If there is a directed path in G' from the variable x_k to x_l, then the lk-entry of $P := -A^{-1}$ is positive by the above lemma (and vice versa). Define for any input variable u_i the set of nodes in the graph $R_i := \{x_k \,|\, [B]_{ki} \neq 0\}$, and for y_i the set of nodes $S_i := \{x_l \,|\, [C]_{il} \neq 0\}$. By the assumptions in the statement, these sets are nonempty for every u_i and y_i.

We have that

$$[-CA^{-1}B]_{ij} = [CPB]_{ij} = \sum_{k,l=1\dots n} c_{il} p_{lk} b_{kj}, \tag{6}$$

where $i \neq j$, $b_{ij} = [B]_{ij}$, $c_{ij} = [C]_{ij}, p_{ij} = [P]_{ij}$. By cooperativity, $c_{il}p_{lk}b_{kj} \geq 0$ for each k, l. Therefore, $[-CA^{-1}B]_{ij} \neq 0$ if and only if there exist k, l such that $c_{il} \neq 0$, $p_{lk} \neq 0$, $b_{kj} \neq 0$. From the discussion above and the previous lemma, it follows that $[-CA^{-1}B]_{ij} \neq 0$ if and only if there exist $x_k \in R_j$ and $x_l \in S_i$ such that there is a directed path from x_k to x_l in G'.

Observe that if an edge (x_l, x_k) is in G but not in G', then necessarily $[BC]_{kl} \neq 0$. This is because in that case $[A]_{kl} = 0$ but $[A + BC]_{kl} \neq 0$. Therefore there must exist i such that $b_{ki} \neq 0$, $c_{il} \neq 0$, in other words $x_k \in R_i$, $x_l \in S_i$.

Now consider two fixed input nodes u_i, u_j, $i \neq j$, and suppose that $A + BC$ is irreducible. To prove irreducibility of CPB we find as follows a sequence $u_i = u_{h_0}, \dots, u_{h_{N+1}} = u_j$, such that $[-CA^{-1}B]_{h_\lambda h_{\lambda+1}} \neq 0$, $\lambda = 0 \dots N$. Let $x_k \in R_i$, $x_l \in S_j$, and consider a directed path in G from x_k to x_l. Denote all edges on this path that are not on G' as $(x_{f_1}, x_{g_1}), \dots (x_{f_N}, x_{g_N})$. Now for each $\lambda = 1, \dots, N$, let h_λ be such that $x_{f_\lambda} \in S_{h_\lambda}$, $x_{g_\lambda} \in R_{h_\lambda}$. Since $x_k \in R_i = R_{h(0)}$, $x_{f_1} \in S_{h_1}$, and there is a path from x_k to x_{f_1} along G', then $[CPB]_{h(0)h(1)} \neq 0$. Similarly by construction, it holds that $[CPB]_{h_\lambda h_{\lambda+1}} \neq 0$, for $\lambda = 1 \dots N$. □

Observe that if one of the columns of B (or one of the rows of C) is zero, then $CA^{-1}B$ may not be irreducible. However these assumptions are mild - if a column of B is zero, then one can simply eliminate the unused input from the system without any change in the dynamics. Similarly for unused outputs.

For the sake of completeness, the following proposition is stated and proved, which gives sufficient conditions for the equivalence of the irreducibility of $A + BC$ and $-CA^{-1}B$. The key concepts used here are known as weak excitability/transparency and were defined in (2). Consider the directed graph defined by the open loop system using the nodes x_i, u_i, y_i. We say that *there exists a path from u_i to x_j* if there is k such that $B_{ki} \neq 0$ and $-A^{-1}_{jk} > 0$ (see Lemma 2.1. Similarly with paths from a state variable to an output variable. We say that a system is *weakly excitable and weakly transparent* if every input (state) variable has a path leading to some state (output) variable, and every output (state) variable has a path leading to it from some state (input) variable.

Proposition 2.3 Consider a Hurwitz, cooperative linear control system (5). Assume also that the system is weakly excitable and weakly transparent. Then $A + BC$ is irreducible if and only if $-CA^{-1}B$ is irreducible.

Proof Following up on the proof of Lemma 2.2, note that if for some variables x_k, x_l and u_i it holds that $x_l \in R_i$, $x_k \in S_i$, then necessarily $[BC]_{lk} \neq 0$, and therefore (x_k, x_l) is an edge in G.

The assumptions of weak excitability and weak transparency imply the remaining hypotheses of the previous result. They also allow us to assume the following statement: for every x_l, there exist u_i and $x_k \in R_i$ ($x_k \in S_i$) such that there is a path on G' from x_k to x_l (from x_l to x_k). Assume that $-CA^{-1}B$ is irreducible. Given any x_k, x_l, $k \neq l$, find a path from x_k to $x_{k'} \in S_i$ and from $x_{l'} \in R_j$ to x_l. Find a sequence $u_i = u_{h_1}, \dots, u_{h_N} = u_j$, such that $[-CA^{-1}B]_{h_{\lambda+1}h_\lambda} \neq 0$, $\lambda = 1 \dots N - 1$, and use the equivalence after equation (6) and the paragraph above to find a directed path from x_k to x_l. □

Having proved Lemma 2.2 for the positive feedback case, the corresponding result for negative feedback control systems is surprisingly simple. A cooperative system (5) under negative feedback is of the form

$$x' = Ax + Bu, \quad y = -Cx, \tag{7}$$

under the same assumptions for the matrices A, B, C.

Theorem 2.4 Consider a Hurwitz cooperative linear control system under positive (5) or negative (7) feedback. Assume that all the columns of B, and all the rows of C, are nonzero. If the closed loop matrix $A \pm BC$ is irreducible, then the I/O characteristic matrix $\mp CA^{-1}B$ is also irreducible.

Proof The positive feedback case was proved in Lemma 2.2. For the remaining negative feedback case, recall that the closed loop matrix is $A - BC$, and the I/O characteristic matrix is $CA^{-1}B$.

We prove that the (unsigned) interaction graph for $A - BC$ is a subgraph of that for $A + BC$. Suppose that $[A - BC]_{ij} \neq 0$ for $i \neq j$. In case that $A_{ij} > 0$, then also $[A + BC]_{ij} > A_{ij}$ is nonzero. Since A is cooperative, the only other alternative is $A_{ij} = 0$, in which case $[A + BC]_{ij} = -[A - BC]_{ij} \neq 0$. Thus by irreducibility of the matrix $A - BC$, the matrix $A + BC$ is also irreducible.

By Lemma 2.2 it follows that $-CA^{-1}B$ is irreducible. But then $CA^{-1}B$ is also irreducible since it has the same nonzero entries. □

3 Convergent monotonically decreasing maps

In this section we prove an interesting topological property of monotonically decreasing maps $g : U \to U$, $U \subseteq \mathbb{R}^m$, that is, functions with the property that if $u \leq v$ then $g(u) \geq g(v)$. Assuming that the generic iteration of this map converges towards a fixed point, it is shown that under regularity and nondegeneracy assumptions g can only have a unique fixed point.

Lemma 3.1 For $U \subseteq \mathbb{R}^m$, let $g : U \to int\ U$ be a C^2 monotonically decreasing map. Let $g'(e)$ be irreducible for any fixed point $e \in U$, and assume that a.e. solution of (4) is convergent. Then g cannot have any exponentially unstable fixed point.

Proof

Suppose that g does have an exponentially unstable fixed point $e \in U$. Since $g'(e)$ is irreducible, the cooperative matrix $-g'(e)$ is also irreducible and therefore strongly cooperative (18). By the Perron-Frobenius theorem, there exists $\lambda > 1$ and $v \gg 0$ such that $g'(e)v = -\lambda v$. Define $u := e + \epsilon v$, where ϵ is small enough that $u \in \text{int}\ U$. Then

$$g(u) = g(e + \epsilon v) = g(e) + g'(e)\epsilon v + o(\epsilon) = e - \lambda \epsilon v + o(\epsilon),$$

$$g^{(2)}(u) = g(g(u)) = g(e - \lambda\epsilon v + o(\epsilon)) = g(e) + g'(e)(-\lambda\epsilon v + o(\epsilon)) + o(\epsilon) = e + \lambda^2 \epsilon v + o(\epsilon).$$

Therefore for sufficiently small ϵ

$$u - g(u) = (1 + \lambda)\epsilon v + o(\epsilon) \gg 0,$$

$$g^{(2)}(u) - u = \epsilon(\lambda^2 - 1)v + o(\epsilon) \gg 0.$$

This implies the inequality

$$g(u) < u < g(g(u)) \tag{8}$$

for some $u \in int\ U$. We will show now that this inequality is inconsistent with the assumption of generic convergence towards a fixed point, which implies a contradiction. The following inequality follows directly from (8) and antimonotonicity, again using $g^{(p)}$ to denote the p-th iteration of g:

$$\ldots g^{(5)}(u) \leq g^{(3)}(u) \leq g(u) < u < g^{(2)}(u) \leq g^{(4)}(u) \leq \ldots.$$

In particular, the sequence $g^{(i)}(u)$ cannnot converge. Let z be such that $u \ll z$. Then $g^{(2)}(u) \leq g^{(2)}(z)$, and more generally $g^{(2k)}(u) \leq g^{(2k)}(z)$ for all $k = 1, 2, \ldots$. Also $g^{(2k+1)}(z) \leq g^{(2k+1)}(u)$ for all $k = 0, 1, 2, \ldots$. Therefore $g^{(i)}(z)$ does not converge either. Since $u \in \text{int}\ U$, the set of such z has nonzero measure, which violates the a.e. convergence condition. □

The following lemma uses a topological argument to ensure that if a discrete system defined on the unit ball B in $\mathbb{R}^m$ has two stable fixed points, then it must also have one exponentially unstable fixed point. For details on the background of degree theory in $\mathbb{R}^m$, the reader is referred to (7) and (20).

Lemma 3.2 Suppose that $g : B \to B$ is a C^2 function, $g(x) \neq x$ on ∂B, and that 1 is not an eigenvalue of the matrix $g'(e)$ whenever $g(e) = e$ (nondegeneracy). Suppose also that g has two Lyapunov stable fixed points. Then g must have at least one exponentially unstable fixed point.

Proof
Define $f : B \to \mathbb{R}^m$ by $f(x) = g(x) - x$. Then f has no zeros on ∂B, and any zero of $f(x)$ in B has nonsingular linearization. Moreover, the system $x' = f(x)$ has two exponentially stable steady states in B, and each has degree $(-1)^m$ with respect to the function $f(x)$ ((7), Theorem 2.11.5). The degree $deg(f, B)$ is also equal to $(-1)^m$ ((7), proof of Theorem 2.11.4). Since

$$deg(f, B) = \sum_{y \in f^{-1}(0)} deg(f, y),$$

there must exist another zero x_0 of f in B such that $deg(f, x_0) \neq (-1)^m$. Clearly x_0 cannot be exponentially stable, therefore there is an eigenvalue λ of $f'(x_0)$ such that $\text{Re}\,\lambda \geq 0$, $\lambda \neq 0$. But then $\lambda + 1$ is eigenvalue of $g'(x_0)$, and $|\lambda + 1| > 1$. This shows that g has an exponentially unstable fixed point. □

Theorem 3.3 Suppose $U \subseteq \mathbb{R}^m$ is a box set and $g : U \to int\ U$ is a C^2, bounded, nondegenerate, monotonically decreasing function such that system (4) has a.e. convergent solutions. Also assume that for every fixed point e, $g'(e)$ is irreducible. Then g has a unique fixed point.

Proof Since g is bounded, we can restrict it to a bounded invariant subset, $g : \hat{U} \to \hat{U}$, where $\hat{U} \subseteq U$ is homeomorphic to the closed unit ball, and all fixed points of g are contained within int $\hat{U}$.

It follows from Lemma 3.1 that g cannot have an exponentially unstable fixed point. On the other hand, the result in the last lemma transfers to the nondegenerate function $g : \hat{U} \to \hat{U}$ by homeomorphism with the unit ball. So if g had two stable fixed points, it would also have an exponentially unstable fixed point, leading again to a contradiction. It follows from nondegeneracy that g cannot have weakly unstable fixed points. Hence it only has one fixed point, and this fixed point is exponentially stable. □

As a corollary, a generalization of the small gain theorem in (10) is proved. It is a more general result because it replaces the standard small gain condition with the weaker condition GSGC. On the other hand this can be considered a negative answer to the conjecture, since no multistability for the closed loop can be obtained.

Corollary 3.4 Consider a C^2 cooperative MIMO control system (2) under negative feedback, and let the I/O characteristic $g : U \to int\ U$ be bounded and nondegenerate. If GSGC holds, then the solutions of the closed loop of system (2) converge globally towards a unique steady state.

Proof As a direct consequence of Theorem 3.3, the I/O characteristic function $g(u)$ has a unique fixed point $\bar{u}$. Therefore by GSGC almost every solution of (4) must converge towards $\bar{u}$. In fact *every* solution must converge towards this fixed point, since every $u \in U$ can be bound from above and below by converging states, $v \leq u \leq w$. Therefore the standard small gain condition in Theorem 2 of (10) is satisfied, and the conclusion follows. □

4 Unified Positive/Negative Feedback Theorem

Having proved the preliminary results, in order to state the main result a more general definition for monotoncity is discussed. An I/O control system (2) is called *orthant monotone* if there exist $\delta_i \in \{-1, 1\}$ for $i = 1 \ldots n$, and $\tau_k \in \{-1, 1\}$ for $k = 1 \ldots m$, such that

$$\delta_i \delta_j \frac{\partial f_i}{\partial x_j}(x, u) \geq 0, \quad \delta_i \tau_k \frac{\partial f_i}{\partial u_k}(x, u) \geq 0$$

for every $i, j = 1 \ldots n$, $i \neq j$, $k = 1 \ldots m$, $x \in X$, and $u \in U$. It is said to be under *positive feedback* if

$$\delta_i \tau_k \frac{\partial h_k}{\partial x_i}(x) \geq 0,$$

and under *negative feedback* if

$$\delta_i \tau_k \frac{\partial h_k}{\partial x_i}(x) \leq 0,$$

again for every $i = 1 \ldots n$, $k = 1 \ldots m$, $x \in X$. An I/O control system is orthant monotone if and only if the signed digraph of the system including the states and the inputs contains no unordered closed loops of negative parity (2). On the other hand the following result holds.

Lemma 4.1 Given an orthant monotone system (2) under positive or negative feedback, define the new variables $z_i := \delta_i x_i$, $v_k := \tau_k u_k$. With respect to these new variables, system (2) is I/O cooperative, under positive or negative feedback respectively.

Proof
For given i and k, one can replace x_i by $\delta_i z_i$ and u_k by $\tau_k v_k$ in the equation to obtain the new system

$$z_i' = \delta_i x_i' = \delta_i f_i(\delta z, \tau v), \quad v_k = \tau_k h(\delta z), \tag{9}$$

where δz is shorthand notation for $(\delta_1 z_1, \ldots, \delta_n z_n)$ and similarly for τv. One can verify that

$$\frac{\partial}{\partial z_j} \delta_i f_i(\delta z, \tau v) = \delta_i \delta_j f_i(\delta z, \tau v) \geq 0, \quad \frac{\partial}{\partial v_k} \delta_i f_i(\delta z, \tau v) = \delta_i \tau_k f_i(\delta z, \tau v) \geq 0.$$

Also

$$\frac{\partial}{\partial z_i} \tau_k h_k(\delta z) = \delta_i \tau_k h_k(\delta z) \geq 0$$

in the positive feedback case, and similarly in the negative feedback case. □

In that sense, much of what can be proved for cooperative I/O systems generalizes to arbitrary orthant monotone systems.

Consider an I/O orthant monotone control system (2) with a well defined I/O characteristic $g : U \to U$, and its corresponding closed loop system (3). In the positive feedback case, and under conditions of nondegeneracy and irreducibility, it has been established that almost every solution of the closed loop (3) converges towards a stable steady state, and that these stable steady states are in bijective correspondence with the stable fixed points of (4). See (12) and the included references for various forms of this result. In the negative feedback case, if all solutions of (4) converge towards a unique equilibrium, then (3) is globally attractive towards one steady state (2, 3).

The topological argument in Section 3 and the irreducibility results from Section 2 are used now to address both positive and negative feedback systems in the same framework. An I/O control system (2) is said to be *sign-definite* if the sign of each of $\partial f_i/\partial x_j$, $\partial f_i/\partial u_k$, $\partial h_k/\partial x_j$ (positive, negative, or zero) does not change as a function of x or u. Such a system has a well defined signed, directed graph G after linearization around any point.

Theorem 4.2 Consider a C^2 sign-definite, orthant monotone control system (2) under either positive or negative feedback. Assume that the Jacobian of the closed loop (3) is nonsingular at steady states and irreducible at every $x \in X$. Also assume that there is a well defined, bounded I/O characteristic $g : U \to \text{int}\, U$. Finally, suppose that the system satisfies the generalized small gain condition GSGC.
Then almost every bounded solution of the closed loop (3) converges towards a (not necessarily unique) stable equilibrium. Moreover, the stable equilibria of (3) are in bijection with the stable fixed points of (4) via the map $x \to h(x)$.

Proof

Notice that all the assumptions on the I/O control system, including irreducibility, nonsingularity, nondegeneracy and the convergence of the iterations of the I/O characteristic, are preserved after making the simple change of variables described in Lemma 4.1. Also, the qualitative behavior of the new system is the same as that of the original system. Thus one can without loss of generality assume that the original system is cooperative, i.e. $\delta_i = 1$, $\tau_k = 1$ for all i, k.

In the positive feedback case, the closed loop is strongly cooperative since the Jacobian is irreducible (19). Therefore almost every bounded solution converges towards the set of equilibria, as stated in the Hirsch generic convergence theorem (16). A strengthening of that result is Theorem 7 of (13), which uses the smoothness of the system to guarantee in this context that the generic bounded solution converges towards a stable steady state. The bijection between the stable equilibria of the closed loop and those of the discrete system (4) is established in Theorem 4.6 of (12).

In the negative feedback case, the aim is to prove the hypotheses of Theorem 3.3. The I/O characteristic function $g : U \to \mathit{int}\ U$ is C^2 by the implicit function theorem and the fact that $\det(\frac{\partial}{\partial x} f(x,u)) \neq 0$ for the function $f(x,u)$ (nondegeneracy). This function is monotonically decreasing by construction, see also Sontag and Angeli (3).

Consider a fixed point $e \in U$ of g, and its corresponding steady state $z \in X$. One can linearize around these points to obtain the system (7), where $A = \partial f/\partial x(z,e)$, $B = \partial f/\partial u(z,e)$, and $C = -h'(z)$. Then $g'(e) = CA^{-1}B$ and $A - BC$ is the linearization of the closed loop at $x = z$. The linearization is itself a Hurwitz cooperative I/O system under negative feedback. One can assume that the columns of B and rows of C are nonzero from the fact that the system (2) is sign-definite: if any such row or column was equal to zero, then it would remain equal to zero under linearization of (2) around any $u \in U$, $x \in X$, in which case that input or output could be removed without loss of generality. By hypothesis $A - BC$ is irreducible, hence by Theorem 2.4 $g'(e)$ is also irreducible. Therefore the linearization of $-g$ around e is strongly cooperative.

It follows from Sylvester's determinant formula (1) that

$$\det(A - BC) = \det(A)\det(I - A^{-1}BC) = \det(A)\det(I + C(-A^{-1})B)$$

$$= \det(A)(-1)^n \det(CA^{-1}B - I).$$

By hypothesis, $\det(A - BC) \neq 0$. Therefore $\lambda = 0$ is not an eigenvalue of $CA^{-1}B - I$, i.e. $\lambda = 1$ is not an eigenvalue of $CA^{-1}B = g'(e)$, and g is nondegenerate.

Having satisfied all assumptions of Theorem 3.3, one can conclude that $g(u)$ has a unique fixed point $e \in U$.

Now we use the framework established for the small gain theorem for negative feedback systems in (10). It needs to be proved that *every* solution of (4) converges towards the unique steady state e. Since $g : U \to int\ U$, it is sufficient to consider a given initial condition $u_0 \in int\ U$. By generic convergence towards equilibria, there exist $a < u_0 < b$ such that $g^k(a) \to e, g^k(b) \to e$. Using the reverse order property of the map g, it follows easily that $u_k = g^k(u_0) \to e$.

All assumptions H1-H4 in (10) are satisfied. By Theorem 2 in that paper it follows that every bounded solution of the closed loop converges towards the state $z \in X$ associated with e. The bijection between the unique steady state and the unique fixed point of g still holds, thus completing the proof.

□

5 Example

As a simple application to illustrate this result, consider the cyclic system

$$\begin{aligned} x_1' &= g_1(x_n) - \alpha_1 x_1, \\ x_i' &= g_i(x_{i-1}) - \alpha_i x_i, \quad i = 2, \dots, n, \end{aligned} \tag{10}$$

where $g_i(x) : [0, \infty) \to (0, \infty)$ are C^2, bounded nonlinear functions such that $g_i'(s) \neq 0$ for all s (i.e. each g_i is increasing or decreasing), and $\alpha_i > 0$ for $i = 1, \dots n$. Assume that this system is defined on the state space $X = [0, \infty)^n$. This system can be easily seen to be the closed loop of the following control system:

$$\begin{aligned} x_1' &= g_1(u) - \alpha_1 x_1, \\ x_i' &= g_i(x_{i-1}) - \alpha_i x_i, \quad i = 2, \dots, n, \quad h(x) = x_n. \end{aligned} \tag{11}$$

The I/O characteristic $g(u)$ of this open loop system is well defined, see also below. In the negative feedback case (e.g. when an odd number of g_i are decreasing), this system has been studied e.g. in (11). In the positive feedback case it is a simple example of a monotone dynamical system. In the current unified framework we don't need to worry about the sign of the feedback but can state and prove the following result.

Proposition 5.1 Suppose that the Jacobian of (10) is nonsingular at steady states, and that almost every solution of the discrete system $u_{k+1} = g(u_k)$ is convergent. Then almost every solution of (10) is also convergent. Moreover, the map $x \to x_n$ is a bijection between the steady states of (10) and the fixed points of $g(u)$.

Proof

We need to prove that the assumptions of Theorem 4.2 are satisfied. First, the open loop system (11) must be shown to be orthant monotone. This is obvious in light of the loop representation

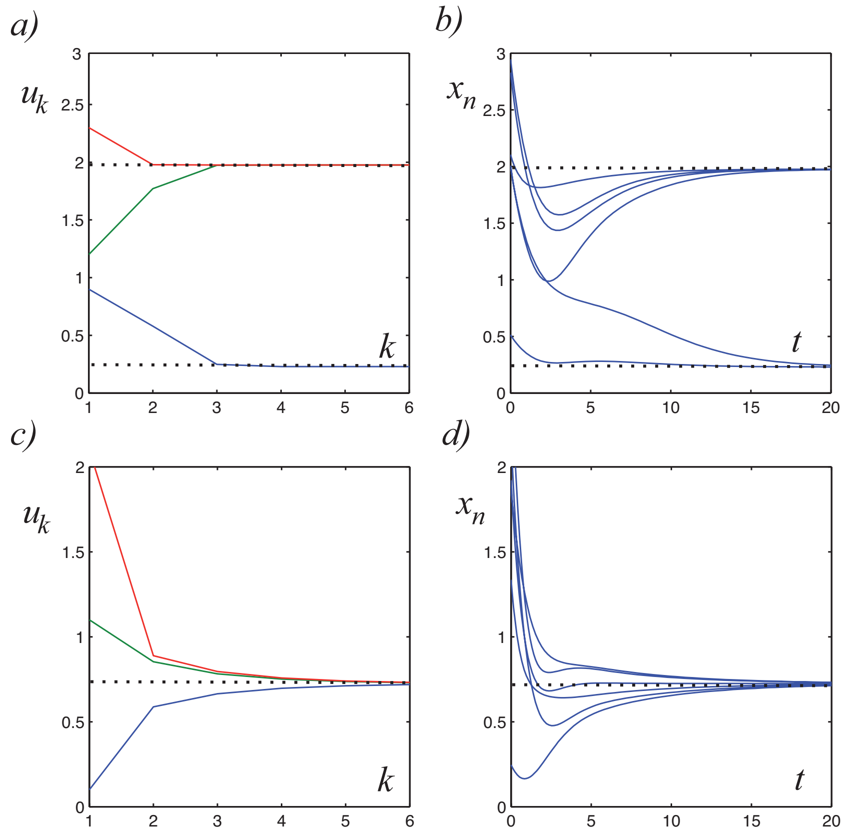

Figure 1. Simulations of the cyclic system (10) for $n = 4$ (positive feedback). Several sample solutions of the 1D discrete system $u_{k+1} = g(u_k)$ (a,c) are compared with sample solutions of the corresponding continuous dynamical system (b,d). Horizontal dotted lines indicate the fixed points and steady states of the system, respectively.

of the system since the open loop system has no actual feedback loops, but for illustration let us find the corresponding δ_i, and τ. For $i = 1 \dots n$, let $\pi_i \in \{-1, 1\}$ be defined such that $\pi_i g_i'(s) > 0$. Then define the product $\delta_i := \pi_1 \dots \pi_i$, for $i = 1 \dots n$. Notice that $\delta_i \delta_{i-1} = \pi_i$, for $i = 2 \dots n$. So

$$\delta_i \delta_{i-1} g_i'(x_{i-1}) = \pi_i g_i'(x_{i-1}) > 0, \quad i = 2 \dots n.$$

Setting $\tau = 1$, notice also that $\tau \delta_1 g_1'(u) = \pi_1 g_1'(u) > 0$. In this way (2) is an orthant monotone I/O system. Finally, given that $h(x) = x_n$, $\delta_n \tau \partial h / \partial x_n = \delta_n$, which has the same sign as the overall feedback of the system.

The I/O characteristic of (11) is

$$g(u) = \frac{1}{\alpha_n} g_n \circ \frac{1}{\alpha_{n-1}} g_{n-1} \circ \dots \circ \frac{1}{\alpha_1} g_1(u),$$

and it is increasing or decreasing depending on the sign of δ_n.

Now we can verify the remaining assumptions of Theorem 4.2. The Jacobian of (10) is clearly irreducible , and it is nonsingular at steady states by assumption. The Jacobian of the open loop system (11) is an upper diagonal matrix with nonzero diagonal entries and it is therefore nonsingular, hence the characteristic g is nondegenerate. The characteristic function $g : [0, \infty) \to (0, \infty)$ is also bounded.

By Theorem 4.2, every bounded solution of the closed loop (10) is convergent. The map $x \to h(x) = x_n$ establishes a bijection between steady states of (10) and the fixed points of $g(u)$. □

Several simulations were carried out to further illustrate this result. In system (10), set for the sake of the argument

$$g_i(s) = \frac{K_i^{h_i}}{K_i^{h_i} + x^{h_i}},$$

a classical sigmoidal, decreasing regulatory function. Then the system is under negative feedback for odd n and under positive feedback for even n. For simplicity the parameters were chosen for this system as $K_i = 1$, $h_i = 3$ for all i. However the degradation terms α_i were varied. In Figure 1 the case $n = 4$ is considered. In Figure 1a), setting $a_i = 0.5$ for all i, several sample solutions of the discrete system $u_{k+1} = g(u_k)$ are shown, illustrating that there are two fixed points towards which the solutions converge. For Figure 1b), several random initial conditions for the closed loop (10) are chosen, showing only the values of $x_n(t)$ over time for each simulation. Depending on the initial condition, x_n converges towards one of two possible steady state values. Notice the correspondence in the values of the steady states in Figure 1a,b). In Figure 1c,d) a similar situation is shown for $a_i = 1$, $i = 1 \ldots n$. The solutions of the discrete system converge towards a unique fixed point, and in the simulations of the cyclic system $x_n(t)$ converges towards this same value.

In Figure 2, the case $n = 5$ is considered using exactly the same parameters. In Figure 2a), using the values $a_i = 0.5$, one can see a single typical simulation of the discrete system, showing that the solutions of the system do not converge towards a steady state. In Figure 2b) a single sample solution of the closed loop (10) with the same parameters is displayed, showing the formation of periodic oscillations. For Figure 2c,d), the parameters a_i were set to 1 for all i. Figure 2c) shows three separate simulations of the discrete system, and these solutions are convergent towards a single fixed point. In Figure 2d) a single generic simulation of the system is produced showing all system variables. Once again notice the correspondence between the value of the fixed point in c) and the steady state in d). If the parameters K_i, α_i, h_i were varied for different i, the correspondence would only hold for the steady state value of the variable x_n. Overall, Proposition 5.1 applies in three out of the four simulations, and the remaining simulation illustrates what can happen when the assumptions don't hold.

6 Feedback Ambivalence

It is interesting that sometimes the same system can be described as a positive feedback or a negative feedback of I/O monotone systems. Consider two single input, single output (SISO), cooperative negative feedback systems

$$x_1' = f_1(x_1, u_1), \quad x_2' = f_2(x_2, u_2), \quad y_1 = h_1(x_1), \quad y_2 = h_2(x_2), \tag{12}$$

with decreasing I/O characteristic functions $g_1(u_1)$, $g_2(u_2)$ respectively. Setting $u_1 = y_2, u_2 = y_1$ results in the closed loop system

$$x_1' = f_1(x_1, h_2(x_2)), \quad x_2' = f_2(x_2, h_1(x_1)). \tag{13}$$

System (13) is also the closed loop of the I/O system

$$x_1' = f_1(x_1, u_1), \quad x_2' = f_2(x_2, h_1(x_1)), \quad u_1 = h_2(x_2), \tag{14}$$

which is orthant monotone by setting $\delta_1 = 1,\ \delta_2 = -1,\ \tau = 1$. This open loop is under positive feedback, since the output satisfies $\delta_2 \tau \partial h_2/\partial x_2 \geq 0$. Viewing (13) as a closed loop in this

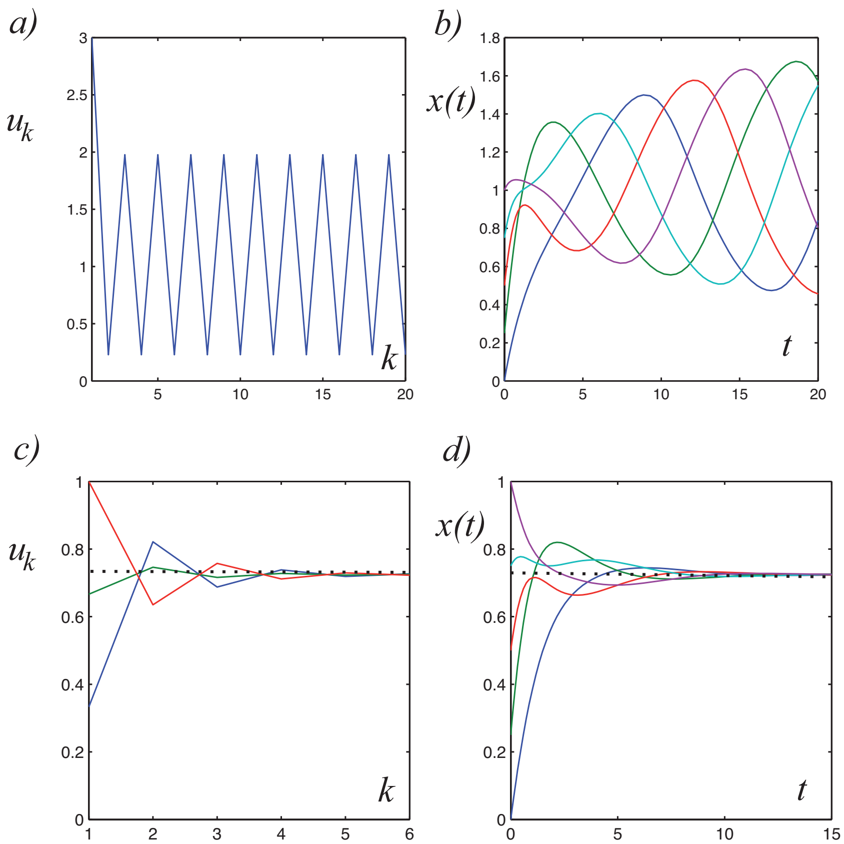

Figure 2. Simulations of the cyclic system (10) for $n = 5$ (negative feedback). Sample solutions of the 1D discrete system $u_{k+1} = g(u_k)$ (a,c) are compared with a single solution of the corresponding continuous system (b,d).

way, with an increasing I/O function $g(u_1) = g_2(g_1(u_1))$, Theorem 4.2 guarantees under mild hypotheses that the solutions of the system converge a.e. to the steady states corresponding to the fixed points of g.

On the other hand, (13) is the closed loop of the cooperative open system (12) with negative feedback output $(x_1, x_2) \to (h_2(x_2), h_1(x_1))$. One would think that Theorem 4.2 might apply here and lead to a proof of the convergence of the solutions of (13) towards one of several steady states. The I/O characterstic of that system is $G(u_1, u_2) = (g_2(u_2), g_1(u_1))$, and the associated discrete system is

$$u^{k+1} = (g_2(u_2^k), g_1(u_1^k)). \tag{15}$$

If the increasing function g has a single fixed point, then Proposition 5.1 might apply equally to both scenarios and imply the global attractivity of (13) towards a unique steady state. But suppose g has three fixed points, $a_1, a_2, a_3 \in \mathbb{R}$. For *any* $i, j = 1 \ldots 3$, the pair $(a_i, g_1(a_j))$ is a 2-cycle of (15):

$$G(a_i, g_1(a_j)) = (g_2(g_1(a_j)), g_1(a_i)) = (g(a_j), g_1(a_i)) = (a_j, g_1(a_i)),$$

and similarly $G(a_j, g_1(a_i)) = (a_i, g_1(a_j))$. In fact if, say, a_1 and a_3 are stable fixed points of the system $u_{k+1} = g(u_n)$, then the 2-cycle $(a_1, g_1(a_3)), (a_3, g_1(a_1))$ above can be seen to be stable for the system (15). In this way, the negative feedback system cannot satisfy the condition GSGC. That is, the same multistable system can be described in terms of positive or negative feedback, but while the positive feedback formulation applies, the negative feedback formulation does not satisfy the hypotheses of the theorem.

7 Conjectures on Delay and Reaction Diffusion Equations

The main result in this paper, Therorem 4.2, could open the door to further generalizations of the theory of monotone systems, since it allows to compare the positive and negative feedback cases in the same context. One immediate extension of the results would be their generalization to infinite dimensional systems such as systems with delays and reaction-diffusion equations. In this section two results are stated as conjectures, the details of the proofs will be left for future work. One difficulty in writing complete proofs lies in determining additional regularity assumptions that are compatible with existing results for both positive and negative feedback systems.

Consider first the case of delay equations, in particular the system

$$x' = f(x(t), u), \quad y = h(x(t-\tau)), \tag{16}$$

for fixed $\tau \geq 0$, and such that for $\tau = 0$ the system is a monotone I/O system under positive or negative feedback.

Conjecture 7.1 Suppose that system (16) satisfies the assumptions of Theorem 4.2 when $\tau = 0$. Then almost every bounded solution of $x' = f(x(t), h(x(t-\tau)))$ converges towards a stable equilibrium. Moreover, the stable equilibria of this system are in bijection with the stable fixed points of g via the map $x \to h(x)$.

Proof Sketch: In the positive feedback case, the local stability of the closed loop delay system around a steady state is the same as that of the same system with delay $\tau = 0$, i.e. system (3) (Corollary 5.5.2 of (18)). It is also known that under certain hypotheses the 'typical' solution of a strongly monotone delay system is convergent (13, 19)). One can conclude that the typical solution converges towards a state corresponding to a stable steady state of (3). But these are also the steady states corresponding to a stable fixed point of g, by Theorem 4.2. Regarding the negative feedback case, in the same way as in the proof of Theorem 4.2, the generalized small gain condition for the (finite dimensional) map g implies the stronger small gain hypothesis. A generalization of the traditional small gain theorem to delay systems was developed in a paper by Smith, Sontag and the author (9), which could be pursued in this context. ∎

In the case of reaction diffusion equations, one can state the following conjecture. Consider a system with variables $w_i = w_i(x, t)$ given by equations

$$\frac{\partial w_i}{\partial t} = d_i \Delta w_i + f_i(w, u(t, x)), \quad i = 1, \ldots m, x \in \Omega, \; t > 0, \; y(x, t) = h(w(x, t)), \tag{17}$$

defined on a smooth convex domain Ω under Neumann boundary conditions, such that the corresponding ODE (2) is monotone under positive or negative feedback. This ODE can be defined by simply setting all $d_i = 0$ and fixing x. A framework for showing that (17) itself satisfies monotonicity conditions was developed in (13), based on maximum principles for systems of parabolic equations.

Conjecture 7.2 Suppose that system (17) satisfies the assumptions of Theorem 4.2 when $d_i = 0$, $i = 1 \ldots n$. Then almost every bounded solution of

$$\frac{\partial w_i}{\partial t} = d_i \Delta w_i + f_i(w, h(w(t, x))), \quad i = 1, \ldots m, \tag{18}$$

converges towards a spatially uniform equilibrium. Moreover, the stable equilibria of this system are in bijection with the stable fixed points of g via the map $x \to h(x)$.

Proof Sketch: It was shown in (13) that if an irreducible cooperative system

$$\frac{\partial z_i}{\partial t} = d_i \Delta z_i + f_i(z), \quad i = 1, \dots m, t > 0, \tag{19}$$

is defined on a smooth convex domain Ω under Neumann boundary conditions, then the generic solution (in the sense of *prevalence* (13)) converges towards a spatially uniform equilibrium. Here a system is understood as irreducible and cooperative if the corresponding ODE system (3) has these properties. Since such uniform equilibria are in bijective correspondence with the steady states of the ODE, determining the stable steady states of the ODE allows to determine the dynamics of the generic solution of an irreducible cooperative reaction diffusion system. In the negative feedback case, once again (9) develops a framework to prove the small gain theorem for cooperative reaction diffusion systems, which could be further generalized using GSGC as a hypothesis. Notice that the inputs are now functions of space and time, so that the I/O characteristic is infinite dimensional and does not immediately fit the framework of Section 3. ■

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