

## Monotone bifurcation graphs

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In recent work by Angeli and the authors, it was shown that the stability and global behaviour of strongly monotone dynamical systems may be profitably studied using a technique that involves feedback decompositions into ‘well-behaved’ subsystems. The present paper generalizes the approach, so that it applies to a far larger class of systems. As an illustration, the techniques are used in the analysis of a nine-variable autoregulatory transcription network. Also, extensions to delay and reaction diffusion systems are considered.

**Keywords:** monotone systems; multistability; gene regulatory networks; reaction diffusion equations; delay equations

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### 1. Introduction

The work of Hal Smith on monotone systems constitutes a deep and beautiful contribution to pure mathematics, as well as to mathematical biology and specifically the analysis of biochemical networks. In this paper, written on the occasion of Hal’s 60th birthday, we present new theoretical results regarding the detection of multiple stable states in a class of monotone feedback systems, and we illustrate our results with an application to a model of a transcriptional gene and protein network.

#### 1.1. Monotone systems

Monotone dynamical systems have been present in the mathematical literature for many years, in systems of ordinary and partial differential equations. The simplest example of a monotone system is that of a differentiable *cooperative* dynamical system

$$\dot{x} = g(x), \tag{1}$$

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51 which is characterized by the property that  $\partial g_i(x)/\partial x_j \geq 0$  for all  $i \neq j$  and all  $x$  in the domain  
 52 of definition. More generally, monotone systems are associated with *positive feedback* among  
 53 the variables  $x_1, \dots, x_n$ , a property that can be verified by looking at a simple signed digraph  
 54 associated to the system (see Section 2).

55 During 1980's, M. Hirsch performed a general study of monotone dynamical systems in papers  
 56 such as [20, 21]. In what is arguably the most important result available for abstract monotone  
 57 systems, he showed that almost all bounded solutions of a strongly monotone system (definitions  
 58 below) are convergent towards the set of equilibria [21]. Under mild additional smoothness and  
 59 boundedness assumptions, almost every solution of the system (1) converges towards one of its  
 60 equilibria. The book by Smith [36] is the standard introduction to the study of monotone dynamical  
 61 systems.

## 62 63 1.2. *Multistability*

64 A multistable system is one that admits several discrete, alternative stable steady-states. Multi-  
 65 stable systems, and associated phenomena of hysteresis and oscillations, are central to molecular  
 66 systems biology. Indeed, it has been frequently noted that even relatively simple gene and pro-  
 67 tein signaling networks have the potential to produce multistability [5, 17–19, 27, 34, 38, 43, 44].  
 68 Among the earlier works are those using bistable system models as a mechanism to explain  
 69 the lambda phage lysis-lysogeny switch as well as the hysteretic *lac* repressor system [30, 32].  
 70 In the current systems biology literature, one finds bistability in studies of the production of  
 71 self-sustaining biochemical memories of transient stimuli [28, 45], the generation of switch-  
 72 like biochemical responses, especially in MAPK cascades in animal cells [3, 4, 8, 16] the rapid  
 73 lateral propagation of receptor tyrosine kinase activation [33], the establishment of cell cycle  
 74 oscillations and mutually-exclusive cell cycle phases in organisms such as *Xenopus* and *S.*  
 75 *cerevisiae* [11, 31, 35], models of *Drosophila* development based on steady states of morphogen  
 76 expression [24], and many other processes.

## 77 78 79 80 1.3. *Monotone decompositions*

81 A general strategy for the detection of multistability, advanced by one of the authors and Angeli  
 82 in [1, 2], is the analysis of gene regulatory networks that either are themselves monotone or can be  
 83 studied using monotone systems ideas. The present paper will be solely concerned with monotone  
 84 dynamical systems themselves. In [2], the authors consider a monotone dynamical system (1),  
 85 and inspired by concepts from control theory, they carry out a decomposition procedure which  
 86 is akin to replacing one of the variables in the expression for  $g(x)$  by a real parameter  $u$  (see the  
 87 definitions below, and the example in Section 6). The study of the resulting parametrized system  
 88

$$90 \quad \dot{x} = f(x, u) \quad (2)$$

91 then allows them to derive conclusions about the *original* system (1).

92 More precisely, [2] considers a parametrized system (2), together with a function  $h(x)$ , such  
 93 that  $\dot{x} = f(x, h(x)) = g(x)$  forms the original system (1). Several monotonicity conditions are  
 94 assumed, which are satisfied *e.g.* if  $\partial f_i/\partial x_j \geq 0$  for all  $i \neq j$ ,  $\partial f_i/\partial u \geq 0$  for all  $i$ , and  $h'_i(u) \geq 0$   
 95 for all  $i$ . Furthermore, it is assumed that Equation (2) satisfies a steady state response property:  
 96 for every fixed value  $v$ , the system  $\dot{x} = f(x, v)$  converges globally towards some state  $X(v)$ .  
 97 Then a plot of the function  $k(u) = h(X(u))$  is sufficient to establish the number of equilibria  
 98 of the original system (1) and whether each equilibrium is stable or unstable. Namely, to each  
 99 equilibrium  $e$  of Equation (1) there corresponds an associated fixed point  $u_e$  of  $k(u)$ , and  $e$  is  
 100

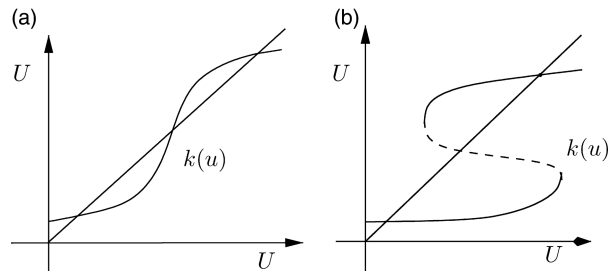


Figure 1. (a) The steady state response curve  $k(u)$  and its fixed points. It follows from this graph that there are two stable equilibria and one unstable equilibrium of Equation (1). (b) In this case, the steady state response function is not well defined, and it is interpreted instead as a bifurcation curve. The dotted line represents an unstable branch of this curve (see Section 3). For the corresponding monotone system there are, once again, two stable equilibria and one unstable equilibrium (Theorem 4.6).

linearly stable if and only if  $k'(u_e) < 1$ ; see Figure 1a. These results were generalized in the paper [13] to allow for a multidimensional input vector  $u$ .

The contribution of the current paper is to provide a generalization of these results to the case where a single-valued steady state response  $X(u)$  does not necessarily exist. Thus, we consider an arbitrary monotone dynamical system (1), under mild regularity and boundedness conditions often satisfied for gene regulatory networks, and we provide an analysis of the number of its equilibria and their stability properties in terms of a graph such as that given in Figure 1b. The steady state response ‘functions’  $X(u)$  and  $k(u)$  are now interpreted as bifurcation graphs on the parameter  $u$ . The multivalued function  $k(u)$  is assumed to be locally differentiable around certain points, and in fact it can be regarded informally as a collection of branches, which may be stable or unstable depending on the local stability of the system (Figure 1b).

Our main result is Theorem 4.6, which essentially states that the linearly stable equilibria  $e$  of Equation (1) correspond to the fixed points  $u_e$  of the multivalued function  $k(u)$  such that both  $k'(u_e) < 1$  and  $(u_e, u_e)$  lies on a stable branch of  $k(u)$ . Using generic convergence results, almost every solution of the system (1) converges towards one of its stable equilibria – therefore the type of information obtained by this argument constitutes a general analysis of the dynamical behaviour of this system. Thus our main result, Theorem 4.6, is in effect a statement about linear control systems, and its application to nonlinear monotone systems is straightforward in the context of the current literature.

A recent result by Malisoff and de Leenheer [29] has been previously published which extends the negative feedback results of [1] to multivalued functions, in a similar way as we extend the positive feedback results of the paper [2].

#### 1.4. Robustness and uncertainty

A most important feature of our approach is that, as illustrated above, one may deduce the number and location of equilibria, and their stability, from the analysis of the fixed points (and slopes) of multivalued bifurcation graphs. This means that *the system’s asymptotic behaviour is preserved under changes of parameters and even the general form of the vector field*, as long as the number of fixed points is unchanged and their slopes remain within appropriate bounds.

This robustness of conclusions makes the combination of graphical and theoretical approach, as used here and in [1, 2], a very useful tool for sensitivity analysis, akin to the use of graphical tools in classical control theory. It also allows one to address the ‘data-rich/data-poor’ dichotomy [39, 40] pervasive in systems biology: while, on one hand, fairly good qualitative network, graph-theoretic, knowledge is frequently available for signaling, metabolic, and gene regulatory networks, on the

other hand, little of this knowledge is quantitative at the level of precision demanded by most mathematical tools of analysis. It is often hard to experimentally validate the form of the nonlinearities used in reaction terms, and even when such forms are known, to accurately estimate coefficients (parameters). Therefore, analysis techniques that use relatively small amounts of quantitative information are especially useful in that context. This is especially so when the quantitative information is the ‘response’ to possible constant inputs. In biological problems, a constant input may represent, for example, the concentration of a certain extracellular ligand in a signaling system, or the level of expression of a constitutively expressed gene. Steady-state responses (dose response curves, activity plots, etc.) are very frequently available from experimental data, especially in molecular biology and pharmacology, for instance, in the modelling of receptor-ligand interactions.

### 1.5. Outline of the rest of the paper

In Section 2, we provide definitions of various general concepts involved. In Section 3, we formally define the functions referred to as monotone bifurcation graphs, and we introduce their relevance to the stability of a given dynamical system. Section 4 contains the proof of the main result, Theorem 4.6. Section 5 considers a particular case of this framework, in which a one-dimensional reduction of the system is possible. In Section 6, these results are applied to a nine-dimensional cooperative gene network. Section 7 addresses the generalization of Theorem 4.6 to reaction diffusion and time delay systems. The Appendix contains a technical result on cascades of nonmonotone systems.

## 2. Definitions

Let  $\mathcal{K} \subseteq \mathbb{R}^n$  be a *cone*, by which is meant a set that is nonempty, convex, closed under multiplication by positive scalars, and pointed (*i.e.*  $\mathcal{K} \cap (-\mathcal{K}) = \{0\}$ ). It will also be assumed that  $\mathcal{K}$  is closed and has nonempty interior. The cone  $\mathcal{K}$  induces the partial order given by:  $x \leq y$  iff  $y - x \in \mathcal{K}$ , and the stronger order  $x \ll y$  iff  $y - x \in \text{int } \mathcal{K}$ . It will also be said that  $x < y$  if  $x \leq y$  and  $x \neq y$ . A commonly used order is that induced by a tuple  $s = (s_1, \dots, s_n)$ , where  $s_i = \pm 1$  for every  $i$ , and defined by  $x \leq_s y$  iff  $s_i x_i \leq s_i y_i$  for every  $i$ . These cones are referred to as *orthant cones*. The *cooperative cone* is defined by the tuple  $s = (1, \dots, 1)$ .

An autonomous system  $\dot{x} = f(x)$  is said to be *monotone with respect to*  $\leq$  if  $x \leq y$  implies  $x(t) \leq y(t)$  for all  $t$ , where  $x(t), y(t)$  are the solutions of the system with initial conditions  $x, y$ , respectively. It is *strongly monotone* if  $x < y$  implies  $x(t) \ll y(t)$  for all  $t > 0$ .

A matrix  $A \in M_{n \times n}$  is said to be *monotone* with respect to the order  $\leq$  if  $x \geq 0$  implies  $Ax \geq 0$ . We also say  $A \geq 0$  as a shorthand notation. The matrix  $A$  is *strongly monotone* if  $x > 0$  implies  $Ax \gg 0$ . The matrix  $A$  is (*strongly*) *quasimonotone* with respect to  $\leq$  if the linear system  $\dot{x} = Ax$  is (*strongly*) monotone with respect to this order. The *leading eigenvalue* of  $A$ , or  $s(A)$ , is the eigenvalue with the largest real part among all eigenvalues of  $A$ . If  $A$  is quasimonotone, then the Perron–Frobenius theorem guarantees that  $s(A)$  is a real number and that there exists an eigenvector  $v > 0$  of  $A$  associated to  $s(A)$ . For a full statement of this theorem for quasimonotone matrices, see [12], and for the classic statements for monotone systems, see for instance [36].

One can form the *digraph associated to*  $\dot{x} = f(x)$  by writing a positive (negative) arc from  $x_i$  to  $x_j$  if  $\partial f_i / \partial x_j \geq 0$  ( $\partial f_i / \partial x_j \leq 0$ ), with the strong inequality holding at least at some state  $x$ . We write no arc if  $\partial f_i / \partial x_j \equiv 0$ . Note that not every system allows for the construction of such a digraph – if it does, we call it a *sign-definite system*. A system is monotone with respect to some orthant cone if and only if the digraph of the system has no closed chains with negative parity.

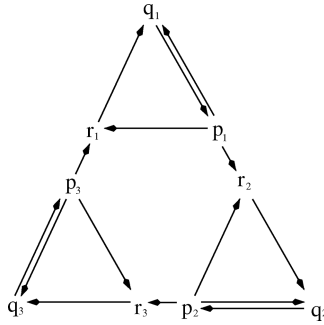


Figure 2. The signed digraph associated to system (7) in the case  $N = 3$ .

Thus for instance, the system associated with the digraph in Figure 2 is monotone, and it would still be monotone if both arcs  $p_1 \rightarrow r_2, p_2 \rightarrow r_3$  had a negative sign. In the case of orthant cones, a sufficient condition for strong monotonicity is that the Jacobian be an irreducible matrix, for all  $x$ . This happens, in particular, provided that the partial derivatives  $\partial f_i / \partial x_j(x)$ , for all  $i \neq j$  all have a constant sign (everywhere zero, everywhere positive, or everywhere negative) and the adjacency graph is strongly connected.

We denote by  $E$  the set of equilibria of Equation (1), and by  $E_s \subseteq E$  the set of equilibria whose linearization has all eigenvalues on the closed left half of the complex plane.

### 3. Monotone decompositions

Consider a given  $C^1$  dynamical system  $\dot{x} = g(x)$  over the state space  $X \subseteq \mathbb{R}^n$ . A *monotone decomposition* of the system is a tuple  $(f, h)$ , where the  $C^1$  function  $f$  defines a parametrized dynamical system on the state space  $X$ ,

$$\dot{x} = f(x, u), \tag{3}$$

$u$  is a parameter which may take values on  $U \subseteq \mathbb{R}^m$ , and there exist cones  $K_X \subseteq \mathbb{R}^n, K_U \subseteq \mathbb{R}^m$  generating orders  $\leq_X, \leq_U$  on  $\mathbb{R}^n$  and  $\mathbb{R}^m$ , such that

- 1  $g(x) = f(x, h(x))$
- 2  $\dot{x} = f(x, u)$  is monotone, for every fixed  $u$  (D)
- 3  $u_1 \leq u_2$  implies  $f(x, u_1) \leq f(x, u_2)$ , for every fixed  $x$
- 4  $h : X \rightarrow U$  is a  $C^1$  function such that  $x_1 \leq x_2$  implies  $h(x_1) \leq h(x_2)$ .

The last three conditions are defined with respect to the orders  $\leq_X, \leq_U$ .

As stated in Angeli and Sontag [1] the following lemma holds.

LEMMA 3.1 *If  $\dot{x} = g(x)$  allows for a monotone decomposition, then it is monotone with respect to  $K_X$ .*

We will, without loss of generality, refer to the original system as

$$\dot{x} = f(x, h(x)). \tag{4}$$

### 3.1. Bifurcation graphs

We define now the *bifurcation graphs* associated with a decomposition (3) (under the further assumptions 1.– 4.). They constitute a portrait of the equilibria of this parametrized system for every given value of  $u$ , reminiscent of a bifurcation analysis (see, for instance, the bifurcation diagrams in Strogatz [41], Chapter 3). For each  $u \in U$ , let:

$$k(u) = \{h(x) \mid f(x, u) = 0\},$$

and define the function  $k_s$ , so that it captures the ‘stable’ points of the graph,

$$k_s(u) = \{h(x) \mid f(x, u) = 0, \quad s(\partial_x f(x, u)) \leq 0\}$$

Note that  $k$  and  $k_s$  are set-valued functions,  $k, k_s : U \rightarrow \mathcal{U}$ . The function  $k$  generalizes the steady state response function  $h(X(u))$  described in the introduction. A *fixed point* of  $k$  is a value  $y$  such that  $y \in k(y)$ , i.e.  $f(x, y) = 0$  and  $y = h(x)$  for some  $x$  (similarly for  $k_s$ ). The *bifurcation graphs* of the system are the graphs of the functions  $k$  and  $k_s$  in  $U \times U$ , seen as relations.

### 3.2. Linearization of the system

Given an equilibrium  $e$  of Equation (4), we linearize the decomposition (3) around this point to create the system

$$\dot{x} = Ax + Bu, \tag{5}$$

where  $A = \partial_x f(e, h(e))$ ,  $B = \partial_u f(e, h(e))$ , and we also introduce the matrix  $C = h'(e)$ . It follows from the chain rule that  $\dot{x} = (A + BC)x$  is the linearization of Equation (4) around  $e$ . To highlight the dependence of the matrices  $A, B, C$  on  $e$ , they will be denoted as  $A_e, B_e, C_e$  when necessary. It can be verified that this system is a monotone decomposition of  $\dot{x} = (A + BC)x$  in the sense above. In particular,  $A$  is a quasimonotone matrix, and  $B \geq 0, C \geq 0$ ; see [2, Theorem 6] of for details.

### 3.3. Fixed points of $k$ and equilibria

A key component in the argument that follows is the next lemma. We will say that the system has property (H) if,

$$\text{For every } x_1, x_2 \in E, x_1 \neq x_2, \text{ it holds that } h(x_1) \neq h(x_2). \tag{H}$$

The following simple remark will be used often and is stated here as a lemma.

**LEMMA 3.2** *Consider a monotone decomposition (3). Then the function  $x \rightarrow h(x)$  is a surjective correspondence between equilibria of Equation (4) and fixed points of  $k$ . If condition (H) is satisfied, then this is a bijective correspondence.*

*Proof* If  $e$  is such that  $f(e, h(e)) = 0$ , and letting  $v = h(e)$  then  $v \in k(v)$  by definition of  $k$ . It is also clear that this correspondence must be surjective. Condition (H) says that the map  $x \rightarrow h(x)$  is injective on equilibria; thus the result holds. ■

We close this section with an analysis of the Jacobian of  $k$  around equilibria. Given a point  $(a, b)$  such that  $b \in k(a)$ , we say that  $k$  is *single valued around*  $(a, b)$  if there exist open neighbourhoods  $S, T$  around  $a, b$ , respectively, such that  $\text{graph}(k) \cap (S \times T)$  is the graph of a single valued

function. From now on, we will always assume that the bifurcation graph  $k$  is single valued around its fixed points  $(y, y)$ .

LEMMA 3.3 *Let  $e$  be an equilibrium of Equation (4) such that  $\det A \neq 0$ , and let  $k$  be single valued and differentiable in a neighbourhood of  $(v, v)$ ,  $v := h(e)$ . Then  $k'(v) = -CA^{-1}B$  at this point.*

*Proof* Define  $v := h(e)$ . Since  $\det A \neq 0$ , the implicit function theorem yields a function  $\sigma : S \rightarrow X$  defined on an open neighbourhood  $S$  of  $v$  such that  $\sigma(v) = e$  and  $f(\sigma(u), u) = 0$  for all  $u \in S$ . The function  $u \rightarrow h(\sigma(u))$  can be thought of as a branch of  $k$  that intersects  $(v, v)$ . Let  $A, B, C$  be as above. It follows by the chain rule that  $A\sigma'(v) + B = 0$ , and hence  $\sigma'(v) = -A^{-1}B$ .

The assumption that  $k$  is single valued around  $(v, v)$  allows us to conclude that  $k(u) = h(\sigma(u))$  in a neighbourhood of this point. Hence locally  $k'(v) = h'(\sigma(v))\sigma'(v) = -CA^{-1}B$ . ■

In the case  $m = 1$ , note that  $k$  is locally a scalar function, and  $-CA^{-1}B$  is a real number.

In the following section, we study the relationship between  $-CA^{-1}B$  and  $A + BC$  in this context, in order to draw conclusions about the stability of the equilibria of the original system (4) by looking at the functions  $k$  and  $k_s$ .

#### 4. Stability of equilibria

We begin by stating several results which are standard, at least in the cooperative case, and we provide two short proofs for the sake of clarity. Consider matrices  $A \in M_{n \times n}$ ,  $B \in M_{n \times m}$ ,  $C \in M_{m \times n}$ , where  $M_{k \times l}$  is the space of all matrices with  $k$  rows and  $l$  columns.

LEMMA 4.1 *Assume that  $A$  is nonsingular. Then  $A + BC$  is nonsingular if and only if  $CA^{-1}B + I$  is nonsingular.*

*Proof* Recall that for  $P \in M_{n \times m}$  and  $Q \in M_{m \times n}$  arbitrary, it holds  $\det(I + PQ) = \det(I + QP)$ . Then  $\det(A + BC) = \det(A) \det(I + A^{-1}BC) = \det(A) \det(I + CA^{-1}B)$ , and the conclusion follows. ■

For the following result, see also [2, Lemma 6.6], and the book by Bellman [6].

LEMMA 4.2 *Let  $A$  be a quasimonotone, Hurwitz matrix. Then  $-A^{-1} \geq 0$ .*

*Proof* Consider  $x_0 \geq 0$ , and let  $x(t)$  be the solution of the dynamical system  $\dot{x} = Ax$  such that  $x(0) = x_0$ . By quasimonotonicity it holds  $x(t) \geq 0$ , for every  $t \geq 0$ . The result follows from the equation

$$-x_0 = \int_0^\infty x'(t) dt = A \int_0^\infty x(t) dt.$$

The following lemma will also be used below. For an excellent resource on this general subject for the cooperative case, we recommend the book by Berman and Plemmons [7].

LEMMA 4.3 *Let  $A$  be strongly quasimonotone with respect to  $\mathcal{K}$ , and let  $B \geq 0$  with respect to  $\mathcal{K}$ ,  $B \neq 0$ . Then  $s(A + B) > s(A)$ .*

351 *Proof* This follows *e.g.* by Theorem 1.1 of Thieme [42]. ■

352 The following proposition is essentially a reference to Theorem 2 in [13], in this more general  
353 context. Recall that a matrix is called *Hurwitz* if all its eigenvalues have strictly negative real part.

354 PROPOSITION 4.4 *Let  $B \geq 0$ ,  $C \geq 0$ , and  $A$  quasimonotone. Then  $A + BC$  is Hurwitz if and*  
355 *only if  $A$  is Hurwitz and  $-CA^{-1}B - I$  is Hurwitz.*

356 *Proof* Let  $A + BC$  be Hurwitz, so that  $A$  is Hurwitz as well since  $s(A) \leq S(A + BC)$  – this  
357 inequality is a standard result for the cooperative cone, and it follows *e.g.* from Theorem 1.1  
358 of [42] in the abstract cone case. Then  $-CA^{-1}B - I$  is nonsingular by Lemma 4.1, and therefore  
359 Hurwitz by Theorem 2 of [13]. Conversely, let  $A$  and  $-CA^{-1}B - I$  be Hurwitz. Then, in particular,  
360  $-CA^{-1}B - I$  is nonsingular. By Theorem 2 of [13] once again,  $A + BC$  is Hurwitz. ■

361 See Section 2 of [7] for more information about the stability of quasimonotone matrices of  
362 similar form, and see also the book by Farina and Rinaldi [15].

363 The following proposition establishes a general relationship between the two matrices  $A + BC$   
364 and  $-CA^{-1}B - I$ , eliminating the nonsingularity condition in [13].

365 PROPOSITION 4.5 *Let  $B \geq 0$ ,  $C \geq 0$ , and let  $A$  be quasimonotone and Hurwitz. Then*

$$366 \text{sign } s(A + BC) = \text{sign } s(-CA^{-1}B - I).$$

367 *Proof* By Lemma 4.2 it holds  $-A^{-1} \geq 0$ , and therefore  $-CA^{-1}B - I$  is a quasimonotone  
368 matrix. Thus  $s(-CA^{-1}B - I)$  is a well-defined real number.

369 Given that  $A$  is Hurwitz, it follows by Proposition 4.4 that  $s(A + BC) < 0$  if and only if  
370  $s(-CA^{-1}B - I) < 0$ . We will show that it also holds that

$$371 s(A + BC) \leq 0 \iff s(-CA^{-1}B - I) \leq 0,$$

372 which immediately implies that  $s(A + BC) = 0 \iff s(-CA^{-1}B - I) = 0$ . Hence  $s(A + BC) >$   
373  $0$  if and only if  $s(-CA^{-1}B - I) > 0$ , and this will complete the proof.

374 Let  $s(A + BC) \leq 0$ , and let  $\epsilon > 0$ . Define  $A_\epsilon = A - \epsilon I$ , so that  $A_\epsilon + BC$  is Hurwitz. Applying  
375 Proposition 4.4 with  $A$  replaced by  $A_\epsilon$ , it holds that  $-CA_\epsilon^{-1}B - I$  is a Hurwitz matrix. As  $\epsilon$   
376 tends towards zero,  $A_\epsilon^{-1}$  converges to  $A^{-1}$ , using the nonsingularity of these matrices. Therefore  
377  $s(-CA_\epsilon^{-1}B - I)$  converges towards  $s(-CA^{-1}B - I)$ , so that  $s(-CA^{-1}B - I) \leq 0$ .

378 Similarly, let  $s(-CA^{-1}B - I) \leq 0$ . Given  $\epsilon > 0$ , it holds that  $-CA^{-1}B - I - \epsilon I =$   
379  $-CA^{-1}B - (1 + \epsilon)I$  is Hurwitz. So is therefore the matrix  $-C[(1 + \epsilon)A]^{-1}B - I$ . Applying  
380 Proposition 4.4 as before, we obtain that  $(1 + \epsilon)A + BC$  is Hurwitz, for every  $\epsilon > 0$ . By the  
381 same continuity argument,  $s(A + BC) \leq 0$ . ■

382 For the remainder of this section, we assume that the set  $X$  is *order convex*, *i.e.* if  $a \in X$ ,  $b \in X$ ,  
383 and  $a \leq c \leq b$ , then  $c \in X$ . We assume also that the cone  $K$  has nonempty interior.

384 THEOREM 4.6 *Consider a  $C^1$  strongly monotone system with bounded orbits, which is decom-*  
385 *posed in the form of Equation (3) under assumptions 1.–4. For every equilibrium  $e$  of Equation (4),*  
386 *let the linearization around  $e$  be strongly monotone, and assume  $s(A_e) \neq 0$ . Then almost*  
387 *every solution of the system converges towards an equilibrium  $e$  such that  $s(A_e) < 0$  and*  
388  *$s(-C_e A_e^{-1} B_e) \leq 1$ .*

389 *Proof* We can apply Theorem 7 of [14], which in this context states that given a  $C^1$  strongly  
390 monotone system with bounded orbits and strongly monotone linearizations, almost every solution  
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400

401 converges towards an equilibrium  $e$  in  $E_s$  ( $e$  is dependent on the initial condition). Now let  $A$ ,  $B$ ,  $C$   
 402 be  $A_e$ ,  $B_e$ ,  $C_e$ , respectively. Given an equilibrium  $e$  of the system, if  $s(A) > 0$  then  $s(A + BC) > 0$   
 403 by Lemma 4.3 in the Appendix. If  $s(A) < 0$ , then  $A$  is Hurwitz and it follows that  $s(A + BC) \leq 0$   
 404 if and only if  $s(-CA^{-1}B - I) \leq 0$  by Proposition 4.5. This is equivalent to  $s(C(-A^{-1})B) \leq 1$   
 405 by definition. ■

406  
 407 Several remarks concerning the above result are at hand.

408  
 409 *Remark 1* In the case  $m = 1$ , by Lemma 3.3, the conclusion is equivalent to the almost-  
 410 everywhere convergence towards the equilibria  $e$  such that  $h(e)$  is a fixed point of  $k_s$  and  
 411  $k'_s(h(e)) \leq 1$ . This geometric interpretation is probably the most useful aspect of this theorem.

412  
 413 *Remark 2* The assumption that the system has strongly monotone linearizations is used to  
 414 conclude that a generic solution converges towards some element of  $E_s$  (as opposed to merely  
 415 towards the set of equilibria  $E_s$ ). The same conclusion follows from assuming that the system has  
 416 countably many equilibria.

417  
 418 *Remark 3* Another variation can be given for systems in which some equilibria satisfy  $s(A) = 0$ .  
 419 This is conceivable in applications, for instance, in the event of the diagonal in the bifurcation  
 420 graph intersecting the boundary between a stable and an unstable branch. Also, one could have  
 421  $s(A) = 0$  at the origin, although this is unlikely in systems with linear decay terms. In either case,  
 422 one can allow for such equilibria in the result by concluding that almost every solution converges  
 423 towards an equilibrium  $e$  such that *either*  $s(A) = 0$  *or*  $s(A(e)) < 0$ ,  $s(C(-A^{-1})B) \leq 1$ . Moreover,  
 424 one can rule out that  $s(A + BC) \leq 0$  for some of those equilibria: if it holds that  $BC \neq 0$  and  
 425  $A + BC$  has strongly monotone linearization, then  $0 = s(A) < s(A + BC)$  by Lemma 4.3 in the  
 426 Appendix.

427  
 428 *Remark 4* An important variation of this result concerns the case in which the only equilibrium  
 429 without a strongly monotone linearization is zero. This case is encountered, for instance, in  
 430 cooperative gene regulatory network models with Hill function nonlinearities. To get around this  
 431 problem in the cooperative case (assuming one might have uncountably many equilibria), one  
 432 can prove that the improved limit set dichotomy is still satisfied for this system, by following the  
 433 same argument as in the proof of Theorem 2.16 of [20], observing that the origin cannot be part  
 434 of any omega limit set with more than one element by the limit set nonordering property. Then  
 435 the same proof of Theorem 7 in [14] can still be verified to hold for this system, and the same  
 436 conclusion in Theorem 4.6 above holds.

437  
 438 Theorem 7 of [14] is only one of several results strengthening the original argument by Hirsch  
 439 [20]. It differs from other results in that it does not make assumptions on the countability of  $E$ ,  
 440 that it concludes the generic convergence towards a point in  $E_s$  (as opposed to  $E$ ), and that it can  
 441 be generalized to infinite dimensions (which will be essential in later sections of this paper).

## 442 443 444 445 **5. System reduction**

446  
 447 We now come to the subject of defining a new system which preserves some of the properties of  
 448 the original one, while being in some sense simpler to study. In the case of strongly monotone  
 449 systems, the relevant properties are the number and location of the equilibria, as well as their  
 450 stability properties.

451 Consider the particular case in which the bifurcation function  $k(u)$  on  $\mathbb{R}^m$  is single-valued,  
 452  $s(A) < 0$  around each equilibrium, and condition (H) is satisfied. Then the equilibria of the  
 453 system

$$454 \quad \dot{u} = k(u) - u$$

455  
 456 are in bijective correspondence with those of the original system, by Lemma 3.2. Moreover, the  
 457 linear stability of the equilibria is preserved under this correspondence, by Proposition 4.5. It  
 458 follows in this sense that this  $m$ -dimensional system is a reduction of the original system – see  
 459 [13] for a more detailed discussion of this particular case.

460 Even for general set-valued  $k$ , a different, stronger reduction is sometimes possible, in the  
 461 sense that the reduced system is one-dimensional. We say that a set function  $\gamma$  is *injective\** if  
 462  $\gamma(x_1) \cap \gamma(x_2) = \emptyset$  whenever  $x_1 \neq x_2$ . Notice that if  $\gamma$  is injective\*, then the inverse  $\gamma^{-1}$  is a well  
 463 defined single-valued function. If the set function  $\gamma$  is single valued around a point  $(a, b)$ , then  
 464 its differentiability can be naturally defined locally around that point.

465  
 466 LEMMA 5.1 *Let  $\gamma : U \subseteq \mathbb{R} \rightarrow \mathcal{P}\mathbb{R}$  be an injective\* set function, which is both locally single*  
 467 *valued and differentiable around its fixed points. Define  $g(x) := x - \gamma^{-1}(x)$ . Then:*

- 468  
 469 (1) *the function  $g$  is single-valued.*  
 470 (2)  *$x \in \gamma(x)$  if and only if  $g(x) = 0$ .*  
 471 (3) *consider a fixed point  $x \in \gamma(x)$  such that  $\gamma'(x) \neq 0$ . Then  $g'(x) \leq 0$  if and only if*  
 472  *$0 < \gamma'(x) \leq 1$ .*

473  
 474 *Proof* The proofs of the first two statements are evident by definition. To see the third statement,  
 475 note that  $(\gamma^{-1})'(x)$  is locally well defined around  $(x, x)$  by the inverse function theorem. It holds  
 476  $g'(x) \leq 0$  iff  $1 \leq (\gamma^{-1})'(x)$ , and  $(\gamma^{-1})'(x) = 1/\gamma'(x)$  using the chain rule and the expression  
 477  $\gamma^{-1}(\gamma(z)) = z$ . Finally,  $1 \leq 1/\gamma'(x)$  iff  $0 < \gamma'(x) \leq 1$ . ■

478  
 479 We will see below how the injectivity of bifurcation functions for strongly monotone systems  
 480 is satisfied.

481  
 482  
 483 LEMMA 5.2 *Under the assumptions of Theorem 4.6, (H), and  $m = 1$ , let it also hold that*

- 484  
 485 (1)  *$k$  is injective\**  
 486 (2)  *$k$  is locally single valued and differentiable around its fixed points*  
 487 (3)  *$k'(x) \neq 0$  for any fixed point  $x$*   
 488 (4)  *$k'(x) < 0$  for every fixed point  $x$  such that  $x \notin k_s(x)$ .*

489  
 490 *Then there is a bijective correspondence between the equilibria of the system (3) and those of*

$$491 \quad \dot{u} = u - k^{-1}(u). \quad (6)$$

492  
 493 *Moreover, the local stability of the equilibria is preserved under this correspondence.*

494  
 495  
 496 *Proof* The correspondence between the equilibria of the closed loop and Equation (6) is clear  
 497 by Lemmas 3.2 and 5.1. By Theorem 4.6 and its interpretation for one-dimensional systems  
 498 (Remark 1), the locally stable equilibria are those corresponding to fixed points  $u$  of  $k(u)$  for  
 499 which  $0 < k'(u)$  (by assumption 3.) and  $k'(u) \leq 1$ . These are exactly those points which are  
 500 linearly stable in Equation (6), by Lemma 5.1. ■

## 6. An autoregulatory transcription network

We consider as an application the following gene network, where we apply our arguments with  $m = 1$ . Consider a cycle of  $N$  proteins  $p_1, \dots, p_N$ , each of which with its respective messenger RNA  $r_i$ . We denote the extranuclear concentration of the protein  $p_i$  by  $q_i$ . Let each protein promote the transcription of its own mRNA, as in the model proposed in [9] in the case of nitrogen catabolism. Let also each protein  $p_i$  promote the transcription of  $p_{i+1}$ , or that of  $p_1$  in the case of  $p_N$ . The full system has the form

$$\begin{aligned}\dot{p}_i &= K_{\text{imp},i}(q_i) - K_{\text{exp},i}(p_i) - a_{2i}p_i \\ \dot{q}_i &= T(r_i) - K_{\text{imp},i}(q_i) + K_{\text{exp},i}(p_i) - a_{3i}q_i, \quad i = 1, \dots, N, \\ \dot{r}_i &= H(p_i, p_{i-1}) - a_{1i}r_i,\end{aligned}\tag{7}$$

where all constants involved are positive, and  $p_0$  is identified with  $p_N$  throughout. See Figure 2 for an illustration. The model in [9] lets the transcription factors  $w, y$  be inhibitory, and hence does not fit the present analysis from here on. Nevertheless note that by replacing  $(p_1, q_1, r_1)$ ,  $(p_2, q_2, r_2)$  and  $(p_3, q_3, r_3)$  by  $(y, \psi, Y)$ ,  $(z, \zeta, Z)$ ,  $(w, \omega, W)$ , respectively, one obtains a very similar structure as in Equation (7) for the main downstream subsystem of that model.

The exact form of the functions  $H, T, K$  is relatively unimportant, as long as each of their partial derivatives are positive (except possibly at the origin). For the sake of the argument, we use the following functions, including a multivariate Hill function  $H(x, y)$ :

$$H(x, y) = \frac{A_1 x^m + A_2 y^n}{A_1 x^m + A_2 y^n + B_1}, \quad T(r) = \frac{A_4 r}{B_2 + r}, \quad K_{\text{imp}}(q) = K_i q, \quad K_{\text{exp}}(p) = K_e p.$$

Note that the double use of  $A_1$  and  $A_2$  is necessary for  $H$  to be increasing with respect to  $x, y$ . It is also a consequence of a quasi steady state analysis as in [25].

The decomposition considered uses the input variable  $\lambda$ :

$$\begin{aligned}\dot{p}_i &= K_{\text{imp},i}(q_i) - K_{\text{exp},i}(p_i) - a_{2i}p_i, \quad i = 1, \dots, N, \\ \dot{q}_i &= T(r_i) - K_{\text{imp},i}(q_i) + K_{\text{exp},i}(p_i) - a_{3i}q_i, \quad i = 1, \dots, N, \\ \dot{r}_i &= H(p_i, p_{i-1}) - a_{1i}r_i, \quad i = 2, \dots, N, \\ \dot{r}_1 &= H(p_1, \lambda) - a_{11}r_1,\end{aligned}\tag{8}$$

A routine verification shows that this decomposition satisfies the conditions 1.– 4. in the definition, using the standard cooperative orders in  $\mathbb{R}^n$  and  $\mathbb{R}^m$ .

Recall that  $A, B, C$  denote the matrices which linearize the open system, in this case of Equation (8).

**PROPOSITION 6.1** *Almost every solution of Equation (7) converges towards those equilibria  $e$  such that  $s(A) < 0$ ,  $s(C(-A^{-1})B) \leq 1$ .*

*Suppose (H) holds. Then almost every solution of Equation (7) converges towards the equilibria  $e$  corresponding to fixed points  $h(e)$  of  $k_s$  such that  $k'_s(h(e)) \leq 1$ .*

*Proof* We prove the first statement. The boundedness of the solutions of Equation (7) follows by a straightforward argument, using the boundedness of the Hill nonlinearities (proof: the values of each of the variables  $p_i$  converge towards an interval  $[0, M]$  for some large enough  $M$  regardless of initial condition, due to the boundedness of the function  $K_{\text{imp},i}$  and the decay rate  $a_{2i}p_i$ . Use this information to bound the values of the variable  $q_i$ . Bound the values of  $r_i$  in a similar way).

551 Also, every equilibrium  $e \gg 0$  of the system has a strongly monotone linearization: each of  
 552 the nonlinearities of the system has positive derivative given positive arguments, therefore the  
 553 digraph associated to the linearization around  $e$  is still given by Figure 2.

554 Furthermore, it holds that  $e \gg 0$  implies  $e = 0$ . For instance, if  $e$  is an equilibrium such that  $q_i =$   
 555  $0$  for some  $i$ , then necessarily  $r_i = p_i = 0$ . If  $r_i = 0$ , then either  $p_i = 0$  or  $p_{i-1} = 0$ . Similarly,  
 556 if  $p_i = 0$ , then  $q_i = 0$ ,  $r_i = 0$  and  $r_{i+1} = 0$ . By iterating these arguments the claim follows.

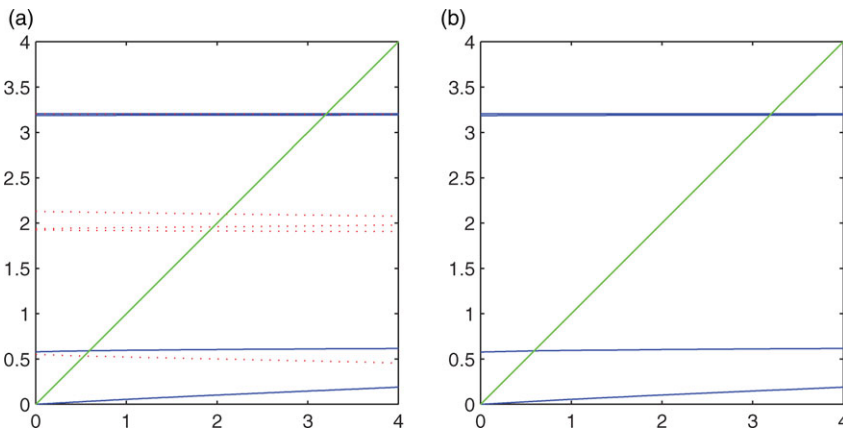
557 In particular, it follows that every nonzero equilibrium has a strongly monotone linearization.  
 558 If  $s(A_e) \neq 0$  at every equilibrium  $e$  and if the linearization around  $e = 0$  is strongly monotone  
 559 (or not an equilibrium), then the result follows from Theorem 4.6.

560 If the linearization around the origin is strongly monotone but  $s(A_e) = 0$  for some equilibria  
 561  $e$ , notice that linearizing around each such equilibrium it holds  $BC \neq 0$  – otherwise  $A = A +$   
 562  $BC$  and  $A$  would also be strongly quasimonotone, a contradiction by construction. It follows  
 563  $s(A + BC) > 0$ , by Lemma 4.3. Therefore almost no solution converges towards  $e$  (see, [37,  
 564 Lemma 2.1]). The conclusion of Theorem 4.6 follows as in Remark 3.

565 In the case that the origin  $e = 0$  does not have a strongly monotone linearization, it holds  
 566  $s(A_e) < 0$  at this point, as is clear by looking at the linearization around the origin. The result  
 567 follows using Remark 4, given after the proof of Theorem 4.6.

568 The second statement follows directly from the first, together with Lemmas 3.2 and  
 569 Lemma 3.3. ■

570  
 571  
 572 See Figure 3 for a numerical example of this result. This figure shows a numerical computation  
 573 of  $k$  and  $k_s$  for some specific values of the parameters. The theorem predicts that most solutions of  
 574 the closed-loop system (7) should converge to one of the states that correspond to the intersection  
 575 of the green and the blue curves (given that the slopes of the blue curves have value less than one  
 576 in the graph). Note that there are four such intersections (one at zero, one at an intermediate value,  
 577 and two on the two almost-overlapping branches), and hence there are four stable steady states.  
 578 Moreover, and this is a most important feature of our approach, this conclusion persists even if  
 579 the very special parameter values used in the example are varied across broad ranges, as long as  
 580 the qualitative graphical picture (*i.e.* the number of blue fixed points and their slopes) remains  
 581 unchanged. This robustness of conclusions makes our combination of graphical and theoretical  
 582



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 Figure 3. A numerical computation of  $k$ ,  $k_s$  for Equation (7) in the case  $N = 2$ , using the parameters  $m_1 = m_2 = 4$ ;  $n_1 = n_2 = 1$ ;  $K_{i1} = K_{i2} = 1/6$ ;  $K_{e1} = 1/15$ ;  $K_{e2} = 1/12$ ;  $a_{11} = a_{12} = 1$ ;  $a_{21} = 1/10$ ;  $a_{22} = 1/12$ ;  $a_{31} = a_{32} = 1/6$ ;  $A_{11} = A_{12} = 1$ ;  $A_{21} = A_{22} = 1$ ;  $A_{41} = A_{42} = 10$ ;  $B_{11} = B_{12} = 16$ ;  $B_{21} = B_{22} = 10$ . (a) The function  $k$ , with the unstable branches in red. (b) The function  $k_s$  after removing unstable branches.

601 approach a very useful tool for sensitivity analysis, akin to the use of graphical tools in classical  
602 control theory.

603 In the rest of this section, we will take a closer look at the bifurcation curve  $k(\lambda)$  and how to  
604 determine its stable branches and to ensure property (H), the main results being Proposition 6.5  
605 and Corollary 6.7. We will also show that for  $N = 1$ , a one dimensional reduction of the system  
606 is possible.

607 Note that this system is a cascade of  $N$  three-dimensional subsystems with a single input each.  
608 Let us concentrate on one of these subsystems, which we write as

$$\begin{aligned} 609 \quad \dot{p} &= K_i q - K_e p - a_2 p \\ 610 \quad \dot{q} &= T(r) - K_i q + K_e p - a_3 q \\ 611 \quad \dot{r} &= H(p, \lambda) - a_1 r. \end{aligned} \quad (9)$$

612 In order to study this ‘core’ system, we consider  $\lambda$  to be a fixed constant, rather than an input. To  
613 compute the bifurcation graph of this system, note that it is itself a strongly monotone system,  
614 and that it can be studied using the previous results by decomposing it as the closed loop of

$$\begin{aligned} 615 \quad \dot{p} &= K_i u - K_e p - a_2 p \\ 616 \quad \dot{q} &= T(r) - K_i q + K_e p - a_3 q, \quad h(p, q, r) = q, \\ 617 \quad \dot{r} &= H(p, \lambda) - a_1 r. \end{aligned} \quad (10)$$

618 which contains the single input  $u$ .

619 LEMMA 6.2 *Let  $\lambda$  be a fixed constant. Then the system (9), when decomposed according to*  
620 *Equation (10), satisfies property (H).*

621 *Proof* Suppose that  $(p_1, q_1, r_1)$ ,  $(p_2, q_2, r_2)$  are two equilibria of the system (9) such that  $q_1 =$   
622  $q_2$ . From the first equation in Equation (9) we deduce that  $p_1 = p_2$ , and therefore also  $r_1 = r_2$ .  
623 This implies the statement. ■

624 Note that for every value of  $u$  there exists a unique equilibrium of Equation (10). Let  $\hat{k}(u)$   
625 denote the concentration of the variable  $q$  at this equilibrium. Thus  $\hat{k}(u)$  is the bifurcation graph  
626 of the system (9) decomposed as in Equation (10), given a constant value of  $\lambda$ . One can compute

$$627 \quad \hat{k}(u) = c_1 T(c_2 H(c_3 u, \lambda)) + c_3 c_4 u,$$

628 where  $c_1 = 1/K_i + a_3$ ,  $c_2 = 1/a_1$ ,  $c_3 = K_i/K_e + a_2$ ,  $c_4 = K_e/K_i + a_3$ .

629 LEMMA 6.3 *Let  $\lambda$  be a fixed constant. The equilibria of the system (9) are in bijective corre-*  
630 *spondence with the fixed points of  $\hat{k}(u)$ . The exponentially stable (resp. exponentially unstable)*  
631 *equilibria of Equation (9) correspond to the fixed points  $\hat{k}(u) = u$  such that  $\hat{k}'(u) < 1$  (resp.*  
632  *$\hat{k}'(u) > 1$ ).*

633 *Proof* The correspondence of the equilibria follows by Lemma 3.2. The correspondence of their  
634 stability follows after linearizing around each equilibrium by Proposition 4.5 and Lemma 3.3. ■

635 Having studied the core system (9) for a fixed value of  $\lambda$ , we let now  $\lambda$  vary over a range of  
636 values to compute the bifurcation graph  $k(\lambda)$  of the open loop of Equation (8). In the case  $N = 1$ ,  
637 this can be done by setting equal to zero the LHS of system (9), obtaining

$$638 \quad C_1 p = T\left(\frac{1}{a_1} H(p, \lambda)\right), \quad (11)$$

639 for  $C_1 := (K_e + a_2)(K_i + a_3)/K_i - K_e > 0$ . Then  $k(\lambda)$  is the set of  $p$  satisfying this equation.

651 For general  $N$ ,  $k(\lambda)$  consists of the steady state values of  $p_N$  in Equation (8) given the constant  
 652 value  $\lambda$ . Thus while  $\hat{k}(u)$  is single valued and typically sigmoidal,  $k(\lambda)$  may be multivalued and  
 653 have stable and unstable branches.

654  
 655 LEMMA 6.4 For  $N = 1$ , the function  $k(\lambda)$  is injective\*.

656  
 657 *Proof* Note that  $\partial\hat{u}/\partial\lambda > 0$ , and that therefore for every fixed  $u$ , there can be at most one  $\lambda$  such  
 658 that  $\hat{k}_\lambda(u) = u$ . The injectivity follows by definition of  $k(\lambda)$ . ■

659  
 660 PROPOSITION 6.5 System (8) satisfies condition (H) for general  $N \geq 1$ .

661  
 662 *Proof* This is a direct consequence of Lemmas 6.2 and 6.4: let  $(p_i^1, q_i^1, r_i^1)$ ,  $(p_i^2, q_i^2, r_i^2)$  be  
 663 two different equilibria such that  $p_N^1 = p_N^2$ . Let  $j$  be the least index such that  $(p_j^1, q_j^1, r_j^1) \neq$   
 664  $(p_j^2, q_j^2, r_j^2)$ . We can view the system associated to  $H_i$  as a closed loop of the form of Equation (10),  
 665 and use as constant  $\lambda$  the value  $p_{i-1}^1 = p_{i-1}^2$ , or  $p_N^1 = p_N^2$  if  $i = 1$ . From Lemma 6.2 it follows that  
 666  $p_j^1 \neq p_j^2$ . But from Lemma 6.4 it follows that  $p_{i+1}^1 \neq p_{i+1}^2$ . Inductively, it must follow  $p_N^1 \neq p_N^2$ ,  
 667 which is a contradiction. ■

668  
 669 Using the bifurcation graph  $k(\lambda)$  in the case  $N = 1$ , one can create the bifurcation graph of the  
 670 open loop (8) for general  $N$  by composing the (multivalued) graphs  $k_i(\lambda)$  of every subsystem.  
 671 This is further detailed in the appendix, where it is proved that the stable branches of  $k(\lambda)$  are  
 672 the compositions of the stable branches of the  $k_i(\lambda)$ . Recall that we denote by  $k_s(\lambda)$  the stable  
 673 bifurcation graph of the system.

674 We now show that for  $N = 1$  there exists a one-dimensional reduction of the three-dimensional  
 675 system (7).

676  
 677 LEMMA 6.6 For  $N = 1$ , the stable (resp. unstable) branches of  $k(\lambda)$  are strictly increasing (resp.  
 678 decreasing).

679  
 680 *Proof* If  $(p, q, r)$  is an equilibrium of (9) for a fixed  $\lambda$ , then  $q = cp$  for a positive constant  $c$   
 681 by the first equation of Equation (9). It holds in general that  $\hat{k}_\lambda(ck(\lambda)) = ck(\lambda)$  by definition of  
 682  $\hat{k}(u)$ ,  $k(\lambda)$ . By the chain rule it holds

$$683 \quad \frac{\partial}{\partial\lambda} \hat{k}_\lambda(ck(\lambda)) = ck'(\lambda) \left( 1 - \frac{\partial}{\partial u} \hat{k}_\lambda(ck(\lambda)) \right).$$

684  
 685 The left-hand side is positive as mentioned above. Thus if  $\partial/\partial u \hat{k}_\lambda(ck(\lambda)) > 1$  (i.e. on an unstable  
 686 branch of  $k(\lambda)$ ), it holds that  $k'(\lambda) < 0$ . Similarly on a stable branch. ■

687  
 688 COROLLARY 6.7 For  $N = 1$ , there exists a bijective correspondence between the equilibria of  
 689 Equation (7) and those of  $\dot{\lambda} = \lambda - k^{-1}(\lambda)$ , which preserves local stability properties.

690  
 691 *Proof* Follows from Lemma 5.2, using Proposition 6.5 and Lemmas 6.4 and 6.6. ■

692  
 693 We define now an expression for the function  $k^{-1}(\lambda)$ , in the case  $N = 1$ . Recall that for a given  
 694  $\lambda$ ,  $k(\lambda)$  is the set of  $p$  satisfying Equation (11). Evidently for a fixed  $\lambda$ ,  $k(\lambda)$  can have several  
 695 values – but given a fixed value of  $p$ , one can find an expression for  $\lambda$  by expanding and solving  
 696 this equation, obtaining

$$697 \quad \lambda = [C_1(B_2A_1 + A_1/a_1)p^{m+1} - A_1A_4p^m + B_1B_2C_1p]^{1/n} [A_2 - C_1(B_2A_2 + A_2/a_1)p]^{-1/n}.$$

698  
 699 This expression is none other than  $k^{-1}(p)$ .  
 700

## 7. Introducing diffusion or delay terms

Because of the strong structure imposed by the monotonicity conditions, the stability properties of monotone systems are preserved after the addition of delay or diffusion terms. This phenomenon is made precise in [36], and it is used here to extend Theorem 4.6 to such cases.

In order to address statements about ‘almost every’ state in infinite-dimensional systems, we will use the following measure-theoretic concept of ‘sparseness’ due independently to Christensen and Yorke *et al.* [10, 23]. A Borel measurable subset  $A$  of a Banach space  $\mathbb{B}$  is said to be *shy* if there exists a compactly supported (nonzero) Borel measure  $\mu$  on  $\mathbb{B}$  such that  $\mu(A + x) = 0$  for every  $x \in \mathbb{B}$ . In finite dimensions, the concepts of shyness and zero Lebesgue measure coincide. Given a set  $W \subseteq \mathbb{B}$ , we also say that a set  $A$  is *prevalent in  $W$*  if  $W - A$  is shy.

For both the delay and reaction diffusion systems, denote by  $\Phi_t$  the time evolution operator after time  $t$ . Fix  $t_0 > 0$ , and assume that  $t_0 > r$  in the delay case, where  $r$  is the maximum delay in the system. Define  $\tilde{E}_s$  as the set of equilibria  $e$  such that  $\rho(\Phi'_r(e)) \leq 1$ . It is a standard result that this definition does not depend on the specific value of  $t_0$ .

We will continue to denote by  $E_s$  the set of equilibria  $e$  of the finite-dimensional system (3) for which  $s(A + BC) \leq 0$ . Once again, we assume that the set  $X$  is *order convex* and that the cone  $K$  has nonempty interior.

### 7.1. Reaction diffusion systems

Let Equation (3) be a strongly cooperative system with strongly monotone linearizations around equilibria, defined on  $X_0 = \mathbb{R}^n$  or  $X_0 = (\mathbb{R}^+)^n$ . Consider the reaction diffusion system with Neumann boundary conditions

$$v_t = D\Delta v + f(v, h(v)). \quad (12)$$

Here  $D$  is a diagonal matrix with non-negative entries, the domain  $\Omega \subseteq \mathbb{R}^p$  is convex with smooth boundary, and the state space used is  $X = C(\Omega, X_0)$ . We use the variable  $v$  instead of the usual  $u$  to prevent confusion with the input notation (we will nevertheless use  $x$  as the space variable in this section). For details on the existence and uniqueness of solutions for this system, see, for instance, Theorem 7.3.1 in Smith [36].

If the state  $e$  is an equilibrium of Equation (3), then the constant function  $\hat{e}$  is an equilibrium of Equation (12). But, unlike the delay case (see below), there may be equilibria of Equation (12) which do not correspond to equilibria of Equation (3), *i.e.* which are not uniform in space. A theorem by Kishimoto and Weinberger [26] guarantees, for strongly cooperative reaction diffusion systems on a convex domain, that a spatially nonuniform equilibrium must be linearly unstable. This is a key ingredient in the following result, which uses the notation following equation (5).

**THEOREM 7.1** *Let Equation (3) be a strongly cooperative system with bounded solutions, and such that every equilibrium  $e$  has a strongly monotone linearization, and  $s(A(e)) \neq 0$ . Then almost every solution of the reaction diffusion system (12) converges towards the spatially uniform equilibria  $\hat{e}$  such that  $s(A(e)) < 0$  and  $s(C(-A^{-1})B) \leq 1$ .*

*Proof* By Corollary 7.3.2 and Theorem 7.4.1 of [36], system (12) is well defined on  $X$  and strongly monotone. Consider the following independent statements.

First, by the proof of Theorem 9 in [14], for almost every initial condition  $v(x) \in X$  (in the sense of prevalence) there exists  $\bar{v}(x) \in \tilde{E}_s$  such that  $\Phi_t(v) \rightarrow \bar{v}$  as  $t \rightarrow \infty$  (under the supremum norm).

751 Second, by the main result in [26], every element of  $\check{E}_s$  is of the form  $\hat{e}$ , for some equilibrium  
 752  $e$  of Equation (3). Moreover, by Remark 7.6.1 of Smith [36], an equilibrium  $\hat{e}$  of Equation (12) is  
 753 in  $\check{E}_s$  if and only if  $e$  is in  $E_s$ . Therefore the function  $e \rightarrow \hat{e}$  is a bijection between  $\check{E}_s$  and  $E_s$ .

754 Third, the argument in the proof of Theorem 4.6 applies for system (3) to conclude that  $E_s$   
 755 consists of the equilibria  $e$  such that  $s(A(e)) < 0$  and  $s(C(-A^{-1})B) \leq 1$ .

756 The conclusion follows by combining the results of the last three paragraphs. ■

757  
 758 Given the modularity of this proof, any of the remarks after the proof of Theorem 4.6, which be  
 759 used to provide a slight generalization of that theorem, can in turn be used to prove an analogue  
 760 generalization of the result above. For instance, in the case  $m = 1$ , the equilibria of Equation (12)  
 761 correspond to the fixed points  $u_0$  of  $k_s(u)$  such that  $k'_s(u_0) \leq 1$ , etc.

762  
 763 *Example.* Consider the gene network from our previous application with the addition of diffusion  
 764 terms for each variable. The system has the form

$$\begin{aligned} 766 \quad \dot{p}_i &= d_{pi} \Delta p_i + K_{\text{imp},i}(q_i) - K_{\text{exp},i}(p_i) - a_{2i} p_i \\ 767 \quad \dot{q}_i &= d_{qi} \Delta q_i + T(r_i) - K_{\text{imp},i}(q_i) + K_{\text{exp},i}(p_i) - a_{3i} q_i \\ 768 \quad \dot{r}_i &= d_{ri} \Delta r_i + H(p_i, p_{i-1}) - a_{1i} r_i, \end{aligned} \quad (13)$$

769  
 770 where all diffusion coefficients are non-negative. A realistic biological example might assume  
 771  $d_{qi} > 0$  for some  $i$ , all other diffusion coefficients having value zero. Assume for simplicity that the  
 772 derivatives at zero of all nonlinearities involved are larger than zero, so that the linearization around  
 773 the origin of Equation (7) is strongly monotone. Also assume for simplicity that  $s(A(e)) \neq 0$  for  
 774 every equilibrium  $e$  in (7). Then Theorem 7.1 can be used to describe the dynamics of the reaction  
 775 diffusion system. Using the correspondence  $\hat{e} \rightarrow e \rightarrow h(e)$  between equilibria of the reaction  
 776 diffusion system and fixed points of the bifurcation graph  $k$ , we further have:

777  
 778  
 779  
 780 **COROLLARY 7.2** *Almost every solution of the reaction diffusion system (13) converges towards*  
 781 *the equilibria  $\hat{e}$  corresponding to fixed points  $h(e)$  of  $k_s$ , such that  $k'_s(h(e)) \leq 1$ .*

## 782 7.2. Delay systems

783 Consider a  $C^1$  delay system

$$784 \quad \dot{x} = F(x_t) \quad (14)$$

785 defined in the set  $X$  of states  $\phi \in C([-r, 0], X_0)$ , where  $X_0 = \mathbb{R}^n$  or  $X_0 = (\mathbb{R}^+)^n$  for simplicity.  
 786 The usual definitions of monotonicity can be made using the cooperative cone  $K = \{\phi \in X \mid \phi(s) \in$   
 787  $(\mathbb{R}^+)^n \text{ for all } s\}$ . Practical conditions for characterizing strong monotonicity with respect to  $K$  are  
 788 the assumptions (I), (R), (M) described in detail in Chapter 5 of [36].

789 Let  $\hat{x} \in X$  denote the constant function with value  $x$ , for  $x \in X_0$ . One can associate to the delay  
 790 system the finite-dimensional system  $\dot{x} = \hat{F}(x)$ , where  $\hat{F}(x) = F(\hat{x})$ . This system is strongly  
 791 cooperative whenever Equation (14) is (in the sense of Theorem 5.3.4 of Smith [36]), and it will  
 792 be written in the form of Equation (3) to apply the results from the previous sections. It is a  
 793 basic result from the theory of delay systems that  $e \rightarrow \hat{e}$  is a bijective correspondence between  
 794 equilibria of Equation (3) and those of Equation (14).

795 The key result is Corollary 5.2 of [36], which ensures that an equilibrium  $\hat{e}$  of Equation (14) is  
 796 exponentially unstable if and only if the corresponding equilibrium  $e$  of its undelayed system (3)  
 797 is exponentially unstable.  
 798  
 799  
 800

801 THEOREM 7.3 *Let Equation (14) be a  $C^1$  strongly cooperative system with bounded solutions and*  
 802 *strongly monotone linearizations around equilibria, and for every equilibrium  $\hat{e}$  let  $s(A(e)) \neq 0$*   
 803 *in Equation (3). Then almost every solution of the delay system converges towards an equilibrium*  
 804  *$\hat{e}$  such that  $s(A(e)) < 0$  and  $s(C(-A^{-1})B) \leq 1$ .*

805  
 806 *Proof* Consider the following independent statements below.

807 First, it can be verified that the delay system satisfies the hypotheses of Theorem 7 in [14].  
 808 Therefore for almost every initial condition  $\phi$  (in the sense of prevalence) there exists  $e \in \check{E}_s$  such  
 809 that  $\Phi_t(\phi) \rightarrow e$  as  $t \rightarrow \infty$  (using the supremum norm).

810 Second, by Corollary 5.2 of Smith [36], the function  $e \rightarrow \hat{e}$  is a bijection between  $E_s$  and  $\check{E}_s$ .

811 Third, given the hypotheses on Equation (14), it follows that the undelayed system (3) is  
 812 also strongly monotone with strongly monotone linearizations around equilibria. We use the  
 813 argument in Theorem 4.6 to conclude that  $E_s$  consists of the equilibria  $e$  such that  $s(A(e)) < 0$   
 814 and  $s(C(-A^{-1})B) \leq 1$ .

815 The conclusion follows by combining the results of the last three paragraphs. ■

816  
 817 *Example.* Consider the gene network from our previous application with the addition of tran-  
 818 scriptional and translational delays for each protein, which we denote by  $\sigma_i$  and  $\tau_i$  respectively.  
 819 The system has the form

$$\begin{aligned} 820 \dot{p}_i &= K_{\text{imp},i}(q_i) - K_{\text{exp},i}(p_i) - a_{2i}p_i \\ 821 \dot{q}_i &= T(r_i(t - \tau_i)) - K_{\text{imp},i}(q_i) + K_{\text{exp},i}(p_i) - a_{3i}q_i \quad i = 1, \dots, N, \\ 822 \dot{r}_i &= H(p_i(t - \sigma_i), p_{i-1}(t - \sigma_i)) - a_{1i}r_i, \end{aligned} \quad (15)$$

823  
 824  
 825 Assume for simplicity that the derivatives at zero of all nonlinearities involved are larger than  
 826 zero, so that the linearization of Equation (7) around the origin is strongly monotone. Also  
 827 assume for simplicity that  $s(A(e)) \neq 0$  for every equilibrium  $e$  in Equation (7). Then we can  
 828 use Theorem 7.3 to characterize the dynamics of the delay system. Using the correspondence  
 829  $\hat{e} \rightarrow e \rightarrow h(e)$  between equilibria of the delay system and fixed points of the bifurcation graph  
 830  $k$ , we further have the following.

831  
 832 COROLLARY 7.4 *Almost every solution of the delay system (15) converges towards the equilibria*  
 833  *$\hat{e}$  corresponding to fixed points  $h(e)$  of  $k_s$  such that  $k'_s(h(e)) \leq 1$ .*

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## 906 Appendix Stable equilibrium descriptors

907  
 908 LEMMA A1 Consider a (not necessarily monotone) cascade

$$909 \dot{z}_i = g_i(z_1, \dots, z_i), \quad i = 1, \dots, N. \quad (\text{A1})$$

910 Then a tuple of vectors  $(\bar{z}_1, \dots, \bar{z}_N)$  is an exponentially stable equilibrium if and only if for every  $i$ ,  $\bar{z}_i$  is an exponentially  
 911 stable equilibrium of

$$912 \dot{z}_i = g_i(\bar{z}_1, \dots, \bar{z}_{i-1}, z_i). \quad (\text{A2})$$

913  
 914 *Proof* The proof is obvious from the fact that the characteristic polynomial of the cascade is equal to  
 915  $\prod_{i=1}^n \text{charpoly}(\partial g_i / \partial z_i)$ . ■

916 Consider now a series of  $N$  single input, single output systems

$$917 \dot{z}_i = f_i(z_i, u_i), \quad i = 1, \dots, N, \quad (\text{A3})$$

$$918 y_i = h_i(z_i) \in \mathbb{R}, \quad i = 1, \dots, N,$$

919 which are coupled as a cascade by  $u_i = y_{i-1}$ ,  $i = 2, \dots, N$ . Define as before the set functions  $S_i(u) := \{h_i(\bar{z}_i) | \bar{z}_i \text{ is an}$   
 920 exponentially stable equilibrium of  $\dot{z}_i = f_i(z_i, u)\}$ .

921 Given functions  $f : A \rightarrow \mathcal{P}(B)$ ,  $g : B \rightarrow \mathcal{P}C$ , we compose in the natural way to form the function  $g \circ f : A \rightarrow \mathcal{P}C$ :

$$922 (g \circ f)(a) = \{c \in C | \text{there exists } b \in B \text{ such that } b \in f(a), c \in g(b)\}.$$

923  
 924 LEMMA A2 Define for the cascade above the output  $h(z_1, \dots, z_N) := h_N(z_N)$  and the stable output set function  $S$ . Then  
 925  $S = S_N \circ \dots \circ S_1$ .

926  
 927 *Proof* Consider a fixed  $\bar{u}_1 \in \mathbb{R}$ . Given a vector  $(\bar{z}_1, \dots, \bar{z}_N)$ , define  $\bar{y}_i := h_i(\bar{z}_i)$ ,  $i = 1, \dots, N$ ,  $\bar{u}_i := \bar{y}_{i-1}$ ,  $i =$   
 928  $2, \dots, N$ . Then  $h(\bar{z}_1, \dots, \bar{z}_N) = \bar{y}_N \in S$  if and only if  $(\bar{z}_1, \dots, \bar{z}_N)$  is an exponentially stable equilibrium of the cascade.  
 929 But by Lemma A1, this is equivalent to the exponential stability of  $\bar{z}_i$  in Equation (A2) for every  $i$ , where

$$930 g_1(z_1) := f_1(z_1, \bar{u}_1),$$

$$931 g_i(z_1, \dots, z_i) := f_i(z_i, h_{i-1}(z_{i-1})), \quad i = 2, \dots, N.$$

932 This is in turn equivalent to  $\bar{y}_i \in S_i(\bar{u}_i)$ ,  $i = 1, \dots, N$ , which is equivalent by definition of composition to  $\bar{y}_N \in$   
 933  $S_N \circ \dots \circ S_1(\bar{u}_1)$ . ■

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