Monotone Bifurcation Graphs

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In recent work by Angeli and the authors, it was shown that the stability and global behavior 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.

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.

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

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

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 of definition. More generally, monotone systems are associated with *positive feedback* among the variables $x_1, \ldots, x_n$, a property that can be verified by looking at a simple signed digraph associated to the system (see Section 2).

During the 1980's, M. Hirsch performed a general study of monotone dynamical systems in papers such as [18,19]. In what is arguably the most important result available for abstract monotone systems, he showed that almost all bounded solutions of a strongly monotone system (definitions below) are convergent towards the set of equilibria [19]. Under mild additional smoothness and boundedness assumptions, almost every solution of the system (1) converges towards one of its equilibria. The book by H. Smith [36] is the standard introduction to the study of monotone dynamical systems.

Multistability

A multistable system is one that admits several discrete, alternative stable steady-states. Multistable systems, and associated phenomena of hysteresis and oscillations, are central to molecular systems biology. Indeed, it has been frequently noted that even relatively simple gene and protein signaling networks have the potential to produce multistability [5, 16, 17, 24, 27, 34, 38, 43, 44]. Among the earlier works are those using bistable system models as a mechanism to explain the lambda phage lysis-lysogeny switch as well as the hysteretic *lac* repressor system [30, 32]. In the current systems biology literature, one finds bistability in studies of the production of self-sustaining biochemical memories of transient stimuli [28, 45], the generation of switch-like biochemical responses, especially in MAPK cascades in animal cells [3, 4, 8, 23] the rapid lateral propagation of receptor tyrosine kinase activation [33], the establishment of cell cycle oscillations and mutually-exclusive cell cycle phases in organisms such as *Xenopus* and *S. cerevisiae* [11, 31, 35], models of *Drosophila* development based on steady states of morphogen expression [22], and many other processes.

Monotone Decompositions

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

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

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

More precisely, [2] considers a parametrized system (2), together with a function $h(x)$, such that $\dot{x} = f(x, h(x)) = g(x)$ forms the original system (1). Several monotonicity conditions are 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 $h_i'(u) \geq 0$ for all i. Furthermore, it is assumed that (2) satisfies a steady state response property: for every fixed value v, the system $\dot{x} = f(x, v)$ converges globally towards some state $X(v)$. Then a plot of the function $k(u) = h(X(u))$ is sufficient to establish the number of equilibria of the original system (1) and whether each equilibrium is stable or unstable. Namely, to each equilibrium e of (1) there corresponds an associated fixed point u_e of $k(u)$, and e is linearly stable if and only if $k'(u_e) < 1$; see Figure 1a. These results were generalized in the paper [14] 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 steady state response $X(u)$ necessarily exists. 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 (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 behavior 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
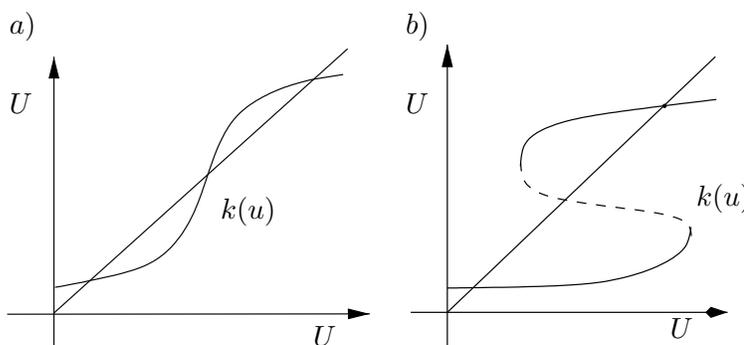
of the paper [2].

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 (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).

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 behavior 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 modeling of receptor-ligand interactions.

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 non-monotone 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 $y - x \in \operatorname{int} \mathcal{K}$. 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 $s = (s_1, \ldots s_n)$, 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 $s = (1, \ldots, 1)$.

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 [13], 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. Thus for instance, the system associated with the digraph in Figure 2 is monotone, and it would still be monotone if both arcs $p_1 \to r_2$, $p_2 \to r_3$ 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 (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

(i) $g(x) = f(x, h(x))$
(ii) $\dot{x} = f(x, u)$ is monotone, for every fixed u (D)
(iii) $u_1 \leq u_2$ implies $f(x, u_1) \leq f(x, u_2)$, for every fixed x
(iv) $h : X \to U$ 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 Sontag and Angeli [1]:

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:

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

and define the function k_s so that it captures the 'stable' points of the graph,

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

Note that k and k_s are set-valued functions, $k, k_s : U \to \mathcal{P}(U)$. 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 (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 (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 Theorem 6 of [2] 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:

For every $x_1, \ x_2 \in E, \ x_1 \neq x_2$, it holds that $h(x_1) \neq h(x_2)$. $\hspace{2em} (H)$

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 $x \to h(x)$ is a surjective correspondence between equilibria of (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 $x \to h(x)$ 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 neighborhoods 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 that the bifurcation graph k is single valued around its fixed points (y, y).*

Lemma 3.3 Let e be an equilibrium of (4) such that $\det A \neq 0$, and let k be single valued and differentiable in a neighborhood 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 $\sigma : S \to X$ defined on an open neighborhood S of v, such that $\sigma(v) = e$ and $f(\sigma(u), u) = 0$ for all $u \in S$. The function $u \to h(\sigma(u))$ 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 $A\sigma'(v) + B = 0$, hence $\sigma'(v) = -A^{-1}B$.

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

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

$$-x_0 = \int_0^\infty x'(t)\,\mathrm{d}t = A \int_0^\infty x(t)\,\mathrm{d}t.$$

∎

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 $s(A + B) > s(A)$.

Proof. This follows e.g. by Theorem 1.1 of Thieme [42]. ∎

The following proposition is essentially a reference to Theorem 2 in [14], in this more general context. Recall that a matrix is called *Hurwitz* if all its eigenvalues have strictly negative real part.

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

Proof. Let $A + BC$ be Hurwitz, so that A is Hurwitz as well since $s(A) \leq S(A + BC)$ — this inequality is a standard result for the cooperative cone, and it follows e.g. from Theorem 1.1 of [42] in the abstract

cone case. Then $-CA^{-1}B - I$ is nonsingular by Lemma 4.1, and therefore Hurwitz by Theorem 2 of [14]. Conversely, let A and $-CA^{-1}B - I$ be Hurwitz. Then in particular $-CA^{-1}B - I$ is nonsingular. By Theorem 2 of [14] once again, $A + BC$ is Hurwitz. ∎

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

The following proposition establishes a general relationship between the two matrices $A + BC$ and $-CA^{-1}B - I$, eliminating the nonsingularity condition in [14].

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

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

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

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

$$\text{s}(A + BC) \leq 0 \quad \leftrightarrow \quad \text{s}(-CA^{-1}B - I) \leq 0,$$

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

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

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

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

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

Proof. We can apply Theorem 7 of [12], which in this context states that given a C^1 strongly monotone system with bounded orbits and strongly monotone linearizations, almost every solution converges towards an equilibrium e in E_s (e is dependent on the initial condition). Now let A, B, C be A_e, B_e, C_e respectively. Given an equilibrium e of the system, if $\text{s}(A) > 0$ then $\text{s}(A + BC) > 0$ by Lemma 4.3 in the Appendix. If $\text{s}(A) < 0$, then A is Hurwitz and it follows that $\text{s}(A + BC) \leq 0$ if and only if $\text{s}(-CA^{-1}B - I) \leq 0$ by Proposition 4.5. This is equivalent to $\text{s}(C(-A^{-1})B) \leq 1$ by definition. ∎

Several remarks concerning the above result are at hand.

Remark 0: in the case $m = 1$, by Lemma 3.3, the conclusion is equivalent to the almost-everywhere convergence towards the equilibria e such that $h(e)$ is a fixed point of k_s and $k_s'(h(e)) \leq 1$. This geometric interpretation is probably the most useful aspect of this theorem.

Remark 1: The assumption that the system has strongly monotone linearizations is used to conclude that a generic solution converges towards some element of E_s (as opposed to merely towards the set of equilibria E_s). The same conclusion follows from assuming that the system has countably many equilibria.

Remark 2: Another variation can be given for systems in which some equilibria satisfy $\text{s}(A) = 0$. This is conceivable in applications, for instance in the event of the diagonal in the bifurcation graph intersecting the boundary between a stable and an unstable branch. Also, one could have $\text{s}(A) = 0$ at the origin, although this is unlikely in systems with linear decay terms. In either case, one can allow for such

equilibria in the result by concluding that almost every solution converges towards an equilibrium e such that *either* $s(A) = 0$ *or* $s(A(e)) < 0$, $s(C(-A^{-1})B) \le 1$. Moreover, one can rule out that $s(A + BC) \le 0$ for some of those equilibria: if it holds that $BC \ne 0$ and $A + BC$ has strongly monotone linearization, then $0 = s(A) < s(A + BC)$ by Lemma 4.3 in the Appendix.

Remark 3: An important variation of this result concerns the case in which the only equilibrium without a strongly monotone linearization is zero. This case is encountered for instance in cooperative gene regulatory network models with Hill function nonlinearities. To get around this problem in the cooperative case (assuming one might have uncountably many equilibria), one can prove that the Improved Limit Set Dichotomy is still satisfied for this system, by following the same argument as in the proof of Theorem 2.16 of [20], observing that the origin cannot be part of any omega limit set with more than one element by the Limit Set Nonordering Property. Then the same proof of Theorem 7 in [12] can still be verified to hold for this system, and the same conclusion in Theorem 4.6 above holds.

Theorem 7 of [12] is only one of several results strengthening the original argument by Hirsch [18]. It differs from other results in that it doesn't make assumptions on the countability of E, that it concludes the generic convergence towards a point in E_s (as opposed to E), and that it can be generalized to infinite dimensions (which will be essential in later sections of this paper).

5. System Reduction

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

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

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

are in bijective correspondence with those of the original system, by Lemma 3.2. Moreover, the linear stability of the equilibria is preserved under this correspondence, by Proposition 4.5. It follows in this sense that this m-dimensional system is a reduction of the original system — see [14] for a more detailed discussion of this particular case.

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

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

(i) The function g is single-valued.
(ii) $x \in \gamma(x)$ if and only if $g(x) = 0$.
(iii) Consider a fixed point $x \in \gamma(x)$, such that $\gamma'(x) \ne 0$. Then $g'(x) \le 0$ if and only if $0 < \gamma'(x) \le 1$.

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

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

Lemma 5.2 Under the assumptions of Theorem 4.6, (H), and $m = 1$, let it also hold that

(i) k is injective*

(ii) k is locally single valued and differentiable around its fixed points

(iii) $k'(x) \neq 0$ for any fixed point x

(iv) $k'(x) < 0$ for every fixed point x such that $x \notin k_s(x)$.

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

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

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

Proof. The correspondence between the equilibria of the closed loop and (6) is clear by Lemmas 3.2 and 5.1. By Theorem 4.6 and its interpretation for one dimensional systems (Remark 0), the locally stable equilibria are those corresponding to fixed points u of $k(u)$ for which $0 < k'(u)$ (by assumption 3.) and $k'(u) \leq 1$. These are exactly those points which are linearly stable in (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 $p_1, \ldots, p_N$, 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

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

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 doesn't 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, ψ, Y), (z, ζ, Z), (w, ω, W) respectively, one obtains a very similar structure as in (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 $H(x, y)$:

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

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 λ:

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

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 (8).
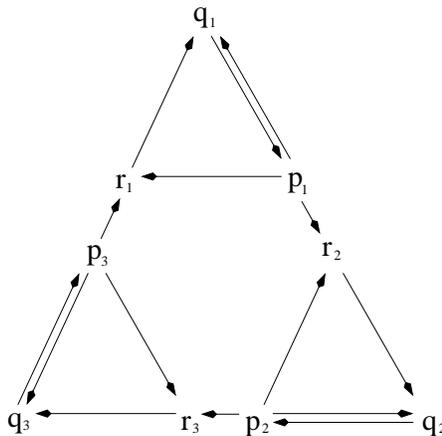
G.A. Enciso and E.D. Sontag

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

Proposition 6.1 Almost every solution of (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 (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 (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 $K_{imp,i}$ 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).

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

Furthermore, it holds that $e \not\gg 0$ implies $e = 0$. For instance, if e is an equilibrium such that, $q_i = 0$ 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, if $p_i = 0$, then $q_i = 0, r_i = 0$ and $r_{i+1} = 0$. By iterating these arguments the claim follows.

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

If the linearization around the origin is strongly monotone but $s(A_e) = 0$ for some equilibria e, notice that linearizing around each such equilibrium it holds $BC \neq 0$ — otherwise $A = A + BC$ and A would also be strongly quasimonotone, a contradiction by construction. It follows $s(A + BC) > 0$, by Lemma 4.3. Therefore almost no solution converges towards e (see Lemma 2.1 of [37]). The conclusion of Theorem 4.6 follows as in Remark 2.

In the case that the origin $e = 0$ doesn't have a strongly monotone linearization, it holds $s(A_e) < 0$ at this point, as is clear by looking at the linearization around the origin. The result follows using Remark 3, given after the proof of Theorem 4.6.

The second statement follows directly from the first, together with Lemma 3.2 and Lemma 3.3. ∎

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

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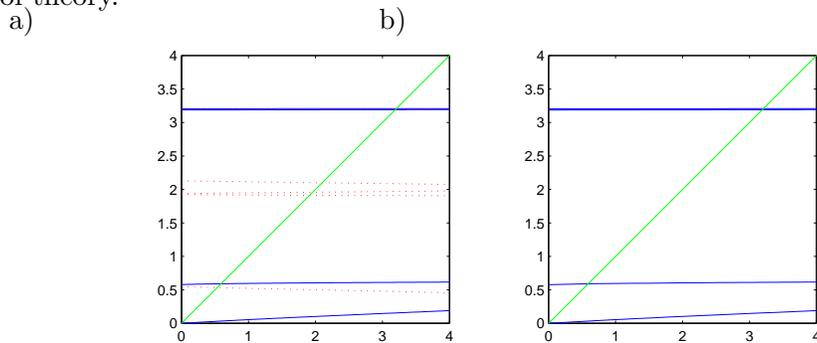

Figure 3.   A numerical computation of k, k_s for (7) in the case $N = 2$, using the parameters $m_1 = m_2 = 4$; $n_1 = n_2 = 1$; $K_{i1} = K_{i2} = 1/6$; $K_{e1} = 1/15$; $K_{e2}1/12$; $a_{11} = a_{12} = 1$; $a_{21} = 1/10$; $a22 = 1/12$; $a_{31} = a_{32} = 1/6$; $A_{11} = A_{12} = 1$; $A_{21} = A_{22} = 1$; $A_{41} = A_{42} = 10$; $B_{11} = B_{12} = 16$; $B_{21} = B_{22} = 10$. a) The function k, with the unstable branches in red. b) the function k_s after removing unstable branches.

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

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

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

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

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

which contains the single input u.

Lemma 6.2 Let λ be a fixed constant. Then the system (9), when decomposed according to (10), satisfies property (H).

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

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

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

where $c_1 = \frac{1}{K_i + a_3}$, $c_2 = \frac{1}{a_1}$, $c_3 = \frac{K_i}{K_e + a_2}$, $c_4 = \frac{K_e}{K_i + a_3}$.

Lemma 6.3 Let λ be a fixed constant. The equilibria of the system (9) are in bijective correspondence with the fixed points of $\hat{k}(u)$. The exponentially stable (resp. exponentially unstable) equilibria of (9) correspond to the fixed points $\hat{k}(u) = u$ such that $\hat{k}'(u) < 1$ (resp. $\hat{k}'(u) > 1$).

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

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

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

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.

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

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

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

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

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 two different equilibria such that $p_N^1 = p_N^2$. Let j be the least index such that $(p_j^1, q_j^1, r_j^1) \neq (p_j^2, q_j^2, r_j^2)$. We can view the system associated to H_i as a closed loop of the form (10), and use as constant λ 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 $p_j^1 \neq p_i^2$. But from Lemma 6.4 it follows that $p_{i+1}^1 \neq p_{i+1}^2$. Inductively, it must follow $p_N^1 \neq p_N^2$, which is a contradiction.   ∎

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

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

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

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

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

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

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

Proof. Follows from Lemma 5.2, using Proposition 6.5 and Lemmas 6.4, 6.6.   ∎

We define now an expression for the function $k^{-1}(\lambda)$, in the case $N = 1$. Recall that for a given λ, $k(\lambda)$ is the set of p satisfying (11). Evidently for a fixed λ, $k(\lambda)$ can have several values — but given a fixed

value of p, one can find an expression for λ by expanding and solving this equation, obtaining

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

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

7. Introducing Diffusion or Delay Terms

Because of the strong structure imposed by the monotoncity 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, 21]. 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 μ 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 Φ_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 $_s$ as the set of equilibria e such that $\rho(\Phi'_r(e)) \leq 1$. It is a standard result that this definition doesn't 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 (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

$$v_t = D\Delta v + f(v, h(v)). \tag{12}$$

Here D is a diagonal matrix with nonnegative 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 (3), then the constant function $\hat{e}$ is an equilibrium of (12). But, unlike the delay case (see below), there may be equilibria of (12) which do not correspond to equilibria of (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 (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 [12], for almost every initial condition $v(x) \in X$ (in the sense of prevalence) there exists $\bar{v}(x) \in_s$ such that $\Phi_t(v) \to \bar{v}$ as $t \to \infty$ (under the supremum norm).

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

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

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

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

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

$$\dot{p}_i = d_{pi}\Delta p_i + K_{imp,i}(q_i) - K_{exp,i}(p_i) - a_{2i}p_i$$
$$\dot{q}_i = d_{qi}\Delta q_i + T(r_i) - K_{imp,i}(q_i) + K_{exp,i}(p_i) - a_{3i}q_i \tag{13}$$
$$\dot{r}_i = d_{ri}\Delta r_i + H(p_i, p_{i-1}) - a_{1i}r_i,$$

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

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

7.2. *Delay Systems*

Consider a C^1 delay system

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

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. The usual definitions of monotonicity can be made using the cooperative cone $K = \{\phi \in X \,|\, \phi(s) \in (\mathbb{R}^+)^n \text{ for all } s\}$. Practical conditions for characterizing strong monotonicity with respect to K are the assumptions (I), (R), (M) described in detail in Chapter 5 of [36].

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

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

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

Proof. Consider the following independent statements below.

First, it can be verified that the delay system satisfies the hypotheses of Theorem 7 in [12]. Therefore for almost every initial condition ϕ (in the sense of prevalence) there exists $e \in_s$ such that $\Phi_t(\phi) \to e$ as $t \to \infty$ (using the supremum norm).

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

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

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

Example. Consider the gene network from our previous application with the addition of transcriptional and translational delays for each protein, which we denote by σ_i and τ_i respectively. The system has the form

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

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

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

Appendix: Stable Equilibrium Descriptors

Lemma 7.5 Consider a (not necessarily monotone) cascade

$$
\dot{z}_i = g_i(z_1, \ldots, z_i), \; i = 1 \ldots N.
\tag{16}
$$

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

$$
\dot{z}_i = g_i(\bar{z}_1, \ldots, \bar{z}_{i-1}, z_i).
\tag{17}
$$

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

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

$$\dot{z}_i = f_i(z_i, u_i), \ i = 1 \ldots N,$$
$$y_i = h_i(z_i) \in \mathbb{R}, \ i = 1 \ldots N, \tag{18}$$

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

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

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

Lemma 7.6 Define for the cascade above the output $h(z_1, \ldots, z_N) := h_N(z_N)$ and the stable output set function S. Then $S = S_N \circ \ldots S_1$.

Proof.

Consider a fixed $\bar{u}_1 \in \mathbb{R}$. Given a vector $(\bar{z}_1, \ldots, \bar{z}_N)$, define $\bar{y}_i := h_i(\bar{z}_i), \ i = 1 \ldots N, \ \bar{u}_i := \bar{y}_{i-1}, \ i = 2 \ldots N$. Then $h(\bar{z}_1, \ldots, \bar{z}_N) = \bar{y}_N \in S$ if and only if $(\bar{z}_1, \ldots, \bar{z}_N)$ is an exponentially stable equilibrium of the cascade. But by Lemma 7.5, this is equivalent to the exponential stability of $\bar{z}_i$ in (17) for every i, where

$$g_1(z_1) := f_1(z_1, \bar{u}_1),$$
$$g_i(z_1, \ldots, z_i) := f_i(z_i, h_{i-1}(z_{i-1})), \ i = 2 \ldots N.$$

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

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