MONOTONE INPUT/OUTPUT SYSTEMS, AND APPLICATIONS TO BIOLOGICAL SYSTEMS

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A dissertation submitted to the

Graduate School—New Brunswick

Rutgers, The State University of New Jersey

in partial fulfillment of the requirements

for the degree of

Doctor of Philosophy

Graduate Program in Mathematics

Written under the direction of

Eduardo Sontag

and approved by

New Brunswick, New Jersey

October, 2005

ABSTRACT OF THE DISSERTATION

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Monotone systems in abstract Banach spaces have strong stability and convergence properties and have been studied in various contexts, especially since the work of Hirsch in the 1980's [48, 49]. In this dissertation we generalize a framework to study the global attractivity of certain abstract, non-monotone systems via monotone systems methods, by considering the concept of a monotone system with inputs and outputs. This method is applied to various quantitative models from molecular biology, in the finite dimensional case as well as in the case of systems with time delays. We develop and implement an algorithm to decompose non-monotone systems as the negative feedback loop of controlled monotone systems which fit into this framework.

The concept of inputs and outputs is also used in the positive feedback case to study the stability of arbitrary monotone systems. We establish an algorithm to determine the number of equilibria of finite dimensional strongly monotone systems as well as to determine the stability behavior of these equilibria. Using the properties of monotone systems, we then generalize these results to the case of delay and reaction diffusion systems. The result is a graphic approach useful for the study of the dynamics of complex positive feedback models.

We also study the generic convergence to equilibrium of abstract strongly monotone

systems, give a self-contained presentation of the subject of monotone systems, consider several other topics related to the subject of monotone systems, and present possible further work.

Preface: From Tycho Brahe To Microarrays

How does mathematics fit into modern biology research? Long gone are the frog dissections and the classification of birds. The new biology establishment, with an army of white-lab-coated experts and billions of dollars in funding from enormous funding agencies such as the NIH and the NSF, has found formidable opponents in the form of microscopic bacteria, transparent worms and fruit flies. The challenge: to understand, at the molecular level, the very mechanisms that allow such organisms to function. New technologies such as mRNA microarrays, as well as the increasing sophistication of older ones like X-ray crystallography, have made increasingly feasible what seemed far-fetched just a few years ago. Recent efforts are made towards an integrative approach, modeling quantitatively the entire molecular process once the key players have been identified and once the basic interactions have been found. Classic examples of such molecular processes are the digestion of lactose in *E. Coli* bacteria, and the way that a protein binding to the membrane of skin cells triggers cell division. Some of the effects that are observed lie outside of the expertise of the biologist, and fall within that of the control theorist, physicist or engineer. An abstraction of some of these models and problems can also become the field of study for a mathematician.

A parallel problem of a more philosophical nature is the following. There are obvious structural similarities among different gene networks (as these 'molecular processes' are also called), for instance the facts that they are usually based on the expression of proteins and use mRNA molecules as intermediaries (being often regulated through so-called transcription factors, etc). But the dynamics produced by these systems seems to be quite varied depending on the task at hand, and the way that Nature has chosen to solve a given problem sometimes appears to be quite arbitrary. The problem is whether gene networks are biased towards a certain underlying structure, beyond that provided by their physical implementation. This is very related to a more practical question, namely what mathematical tools can be best used for a formal analysis of gene network models; this is also why a mathematician may have a useful point of view to address that question.

There is a common metaphor comparing modern biology with astronomy. During the late 16th century, the Danish astronomer Tycho Brahe spent much of his life making the most accurate astronomical measurements of his time. After his death, Johannes Kepler spent many years studying these measurements, and he finally proposed three simple laws according to which the motion of the planets could be predicted. Later on, Newton would be able to provide general physical laws that imply Kepler's as a particular case. In the same way in biology, a challenge for a mathematician can be to participate in the search for such an 'underlying order', at the same time as obtaining inspiration from biology to create new mathematics with an interest of their own.

It is important to realize that in spite of the new tools and the available information, quantitative modeling continues to be a controversial undertaking in mainstream biology. The reason: only the dynamics of the simplest and very best understood processes can be reliably predicted quantitatively at this point. The mainstream biologist still concentrates on the foundations: what genes and proteins participate in what processes, what is the overall effect of the over- or underexpression of a protein, and so on. The same sobering comment can be said about the search for some underlying order in the dynamics of molecular systems: we may well still be in Tycho Brahe's time rather than in Kepler's (let alone Newton's) and many physicists and biologists are skeptic about whether such general principles exist at all.

On the other hand, one can argue that the reason why quantitative modeling doesn't replicate the behavior of most systems is not that it is fundamentally the wrong tool, but rather that we don't have the necessary information to incorporate into the models. Thus as a theoretician one can nevertheless prepare the ground by finding general tools and algorithms, to be applied when the time is ripe in a few decades. Such a strategy doesn't sound nearly as misguided if one considers that the average drug takes about 15 years to develop from the lab into the market.

This dissertation addresses one possible modeling tool, namely measuring a given gene network by the extent to which it differs from a monotone system. This approach is successful to the extent to which the structure of gene networks is compatible with that point of view; in that respect, this work is but one possible answer to both problems stated above.

Acknowledgements

I would like to thank Dimacs for their continuing Summer and Winter support and their excellent conferences, the teaching assistant program at the Math department, and my advisor's funding agencies whose sources are ultimately traced to the American government in its different guises. At the administration of the department Diane Apadula, Lynn Braun, Carla Ortiz for her contagious smile, and especially Pat Barr at the mailbox office who made it great fun to pick your mail. Stephen Greenfield and Chuck Weibel are the best grad directors one can possibly imagine, and they were extremely helpful and enthusiastic throughout the program.

I was happy to find the help of excellent professors such as Yanyan Li, Terence Butler, and Richard Lyons, in matters academic and otherwise. Special thanks to Roger Nussbaum for his patience and explanations, and to Fred Roberts for his vision and organization skills. I have also received immense help from Hal Smith, who shows great interest in the work of our group and has shared his expertise in monotone systems every time, even when the answer was later found to hide in some part of his textbook. I also want to thank Arnold Levine for his interest and his invitations to talk at the IAS, and especially his postdoctoral student Gareth Bond. Talking to Gareth has given me an opportunity to look into a working biologist's world, and collaborating with him has been eye-opening and great fun.

I want to thank many friends along the way: Anna Sykes, Karen Ludke, Jeremy Pronchik, Liz Kuhns, Peter Kay, Aleidria Lichau, Elvia Valencia, Jerry Chen, Raif Rustamov, Sandrine Anthoine, Stefan von der Mark and Sabine Doermann, my Colombian friends in the US Juan Manuel Pedraza, Juan Gabriel Restrepo, Ana Maria Rey and many others: thanks for being there, for many times spent together, and for your inspiration.

Thanks in our group to Madalena Chaves, Liming Wang, David Angeli in Firenze, and Patrick de Leenheer for sharing ideas, talking and working together, and to Thomas Gedeon and Michael Malisoff who are starting to be interested in the subject.

I cannot find the words to express my gratitude to my advisor Eduardo Sontag: finding him was probably the singe best thing that happened to me academically during the program. He is an outstanding mathematician and a sympathetic human being, and he has always had time to spend with his students – on top of the numerous things he is doing at any given time. His energy to work, teach, publish and communicate is contagious, and he knows just the right way to explain something in clear and simple terms. This rare combination of human and mathematical abilities, as well as availability, single him out as the great advisor that he is. I also want to thank him for his effort to advertise me when I was in the job market.

Finally, I want to thank very especially my parents: for their unconditional selfless support, and for always wishing the best for me.

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Chapter 1

Introduction

1.1 Monotonicity and Biological Systems

The dynamical systems that arise in models of molecular biology have several characteristics that distinguish them from more traditional models, say, from classical mechanics.

1. They tend to have a very large number of variables, in the order of a dozen for the simplest realistic models, up to several hundreds (or more) for the more ambitious ones that may encompass all proteins and genes involved, as well as metabolites, different types of RNA molecules, etc. This factor alone makes most of these systems quite intractable from a formal viewpoint, even when the form of the functions involved and the values of all parameters are fixed.

2. For all their complexity, these systems tend to present remarkably simple dynamics: global attractivity towards one or multiple equilibria seems the most common behavior, followed by generically attractive periodic orbits. One reason may be that most of these models are quite simplified compared with their real-world counterparts. But there is reason to believe that such stable behavior is actually encouraged by natural selection, so that molecular processes can work reliably under different circumstances.

3. A third property that characterizes biological systems is that the direct effect that one given variable in the model has over another is often either consistently inhibitory or consistently promoting. Thus, if protein A binds to the promoter region of gene B, it usually does so either to consistently prevent the transcription of the gene or to consistently facilitate it.

Consider an ordinary differential equation

$$\dot{x} = F(x) \tag{1.1}$$

(in the biological interpretation, $x = x(t)$ is a vector each of whose components $x_i(t)$ indicates the concentration of compound i at time t). Then Condition 3 amounts to requiring that for every $i, j = 1 \ldots n$, $i \neq j$, the partial derivative $\partial F_i / \partial x_j$ be either ≥ 0 at all states or ≤ 0 at all states. Note that this nevertheless doesn't prevent protein A from having an indirect influence (through other molecules) that can ultimately lead to the opposite effect on gene B.

One way to exploit Conditions 2 and 3, as will be seen below, is by using the concept of monotonicity. Consider a partial order $\leq$ defined on $\mathbb{R}^n$. System (1.1) is said to be *monotone with respect to* $\leq$ if $x_0 \leq y_0$ implies $x(t) \leq y(t)$ for every $t \geq 0$ (where $x(t)$, $y(t)$ are the solutions of (1.1) with initial conditions x_0, y_0, respectively). Of course, a system may be monotone or not depending on the partial order at hand. It will be said to be simply *monotone* if the order is clear from the context.

Positive and Negative Feedback

Monotonicity (with respect to nontrivial orders) is a strong condition to ask from a dynamical system. It turns out to restrict the possible dynamics of the system substantially. It provides a large amount of information about its stability behavior: attractive periodic orbits are ruled out, for instance, and under different types of circumstances most or all solutions converge towards some equilibrium – see [101] and Chapter 3. Monotonicity is therefore also appealing in light of the Condition 2 for molecular processes described above, since it may be possible to describe the relatively tame behavior of such systems in terms of their monotonicity or the monotonicity of closely related systems.

Nevertheless, most large systems arising in biology (or elsewhere) are likely not to be monotone with respect to any orthant order. In order to address this we consider *controlled* dynamical systems, which are systems with an additional parameter $u \in \mathbb{R}^m$, and which have the form

$$\dot{x} = f(x, u). \tag{1.2}$$

The values of u over time are specified by means of a function $t \to u(t) \in \mathbb{R}^m$, $t \geq 0$, called an *input*. Thus each input defines a time-dependent dynamical system in the usual sense. The consideration of systems with inputs is key to the understanding of cascades of systems and, more generally, the study of large-scale systems as interconnections of smaller systems. (Indeed, it would be impossible to even define the notion of "interconnection" if inputs, and outputs, were not considered in the formalism.) Moreover, the study of responses (input/output behavior in the sense of control theory, see [106]) requires such a formalism as well.

To system (1.2), we often associate a *feedback function* $h : \mathbb{R}^n \to \mathbb{R}^m$, which is usually used to create the *closed loop system* $\dot{x} = f(x, h(x))$.

Given orders $\leq_p$ and $\leq_q$ for $\mathbb{R}^n$ and $\mathbb{R}^m$ respectively, we say that a feedback function h is *positive* if $x \leq_p y$ implies $h(x) \leq_q h(y)$, and that it is *negative* if $x \leq_p y$ implies $h(y) \leq_q h(x)$. It can be shown (Chapter 6) that the closed loop of a monotone system with a positive feedback function is actually itself monotone, so that no system can be produced in this way that was not monotone already. Nevertheless writing a monotone system as the positive feedback loop of a controlled monotone system turns out to be of use when studying its long-term behavior, as will be described in Chapters 6 and 7. On the other hand, writing a non-monotone system as the closed loop of a monotone controlled system under negative feedback opens the possibility to apply some of the arguments from monotone systems theory to such systems. This will be the framework of Chapter 2 (implicitly) as well as Chapters 4 and 5.

In the remainder of this introduction, an outline of each of the chapters will be given.

1.2 Testosterone Dynamics

Chapter 2 is a self contained discussion of a delay dynamical system, which uses many of the ideas that will be treated more rigorously in Chapters 4 and 5. Any explicit mention of monotone systems has been intentionally left out for this introductory discussion.

The material in this chapter (see [32]) is also interesting because of its relationship to the classic textbook by J. Murray *Mathematical Biology* [77]. One of the sections of this book considers this model and concludes the existence of periodic solutions for certain choices of the parameter values. The main conclusion of Chapter 2 is that in fact the system is globally attractive to equilibrium for all parameter values, in what apparently was an error that went unnoticed since the first edition of this book in 1989.

1.3 Monotone Systems

Chapter 3 is a self contained introduction to monotone systems, which may appear at first unnecessary in the presence of standard references such as [101], [10] but is done for two reasons. The first reason is to expose the reader to what are arguably some of the most important results of the theory in a survey-like manner. Special attention is given to those results that will appear in the subsequent chapters. At the same time, part of the material in this chapter actually generalizes the results from these references, or else it is devoted to proving the results in a concise and clear manner while filling a few gaps in between.

Section 3.1 gives a formal introduction to cones, monotonicity, and the various classes of matrices involved. Section 3.3 introduces the omnipresent Perron Frobenius and Krein Rutman theorems, and it discusses their relationship to monotone systems by providing statements and (our own) proofs for quasimonotone matrices and operators. These latter theorems are very useful but hard to find in the literature in general form. Section 3.2 discusses the so called Volkmann condition, which is a useful way to verify the monotonicity of a system with respect to an abstract cone. Section 3.5 is a very short introduction to convergence results, which are perhaps the specialty of the field, and which were pioneered by M. Hirsch in the 1980's. Section 3.6 is a discussion of the sobering argument by Smale, which provides many counterexamples to conjectures in the theory. Sections 3.7 and 3.8 have the objective to discuss two key facts, namely that in a certain sense the stability of an equilibrium in a monotone system doesn't change after adding or eliminating diffusion or delays. The argument in Section 3.7 is given for abstract cones, as opposed to the cooperative cone assumed in [101] (definition in Section 3.1), although such a result is also found in [58]. Section 3.8 presents a very similar properly for equilibria after adding or eliminating diffusion, which is here generalized to abstract cones and general monotone (as opposed to strongly monotone) systems.

1.4 The Small Gain Theorem

The subject of the stability and global attractivity of dynamical systems has been extensively studied since the end of the 19th century, and it has grown into a vast theory with branches and applications in numerous disciplines. The last few years have seen the ever increasing appearance of large scale dynamical systems (for instance in biological applications), often in the form of complex systems of equations spanning over dozens of variables. Many of these systems are not realistically tractable using traditional approaches like phase plane analysis and Lyapunov functions. The difficulty is compounded when the system in question has delay or diffusion components built into it. Usually the tools used are linearization around the equilibria to study local stability, and more often numerical simulation with the computer. But the former tool doesn't provide conclusive evidence at the global level, and the latter may not provide enough insight into the inner workings of the model.

The paper Angeli and Sontag [6] introduced an approach for establishing sufficient conditions under which certain dynamical systems (1.1), described by ordinary differential equations, are guaranteed to have a globally attractive equilibrium. Consider a controlled dynamical system (1.2) which is monotone with respect to cones in the input and state spaces U, X (see Section 1.1). Let $h : X \to U$ be a negative feedback function, that is, $x \leq y$ implies $h(x) \geq h(y)$. Let $k^X : U \to X$ be such that for every fixed value of u_0, the associated autonomous system $\dot{x} = f(x, u_0)$ is globally attractive towards $k^X(u_0)$. Define $k(u) := h(k^X(u))$, and consider the discrete system

$$u_{n+1} = k(u_n). \tag{1.3}$$

Angeli and Sontag showed in the scalar input case (see Theorem 3 of [6] for details) that if this discrete system is globally attractive towards $\bar{u}$, then the closed loop system

$$\dot{x} = f(x, h(x)) \tag{1.4}$$

converges globally towards $k^X(\bar{u})$.

Note that even though the ideas of monotone system theory are used, this result involves the stability of a system which is *not* monotone.

Chapters 4 and 5 of this dissertation address this method to prove the global attractivity to equilibrium of other non-monotone dynamical systems. Also, recall from above that Chapter 2 itself contains many of the ideas in a self contained manner for a first reading.

The results of Angeli and Sontag [6] are generalized in several directions: (i) we address the stability of the closed loop system, which was not done in [6]; (ii) we prove results which are novel even in the finite-dimensional case, in particular allowing the consideration of systems with multiple inputs and outputs; and (iii) we extend considerably the class of systems to which the theory can be applied and the above characterization holds, by formulating our definitions and theorems in an abstract Banach space setting. The extension to Banach space forces us to develop very different proofs, but it permits the treatment of delay-differential and other infinite-dimensional systems. In addition, we work out a number of interesting examples, exploit a useful necessary and sufficient condition for monotonically decreasing discrete systems to be globally attractive, which leads to sufficient tests for stability of our negative feedback loops, and study a procedure for decomposing a system as the negative feedback closed loop of a monotone controlled system (Section 5.3). We rely on basic results from the theory of monotone systems, all of which are included in Chapter 3.

There has been previous work that remarked upon special cases of the relationship in asymptotic behavior between continuous systems and associated discrete systems of the type discussed above (which is not to be confused with, for instance, a Poincare map associated to the system). Indeed, in [100], Smith studied a cyclic gene model with repression, and observed how a certain discrete system seemed to mirror the continuous model's dynamics, both at the local and the global level. The setup of feedback loops around monotone control systems provides one appealing formalization of this remark, and the repression model in question will be used as an illustration of our main result. Related work has been carried out by Chow and Mallet-Paret, and surveyed by Tyson and Othmer [16, 110].

The organization of these two chapters is as follows. In Section 4.1, the general framework is built, and the hypotheses are discussed. In Section 4.2, the main result is proven in an abstract framework, and in Section 4.3 the stability of the closed loop system is addressed. In Section 5.1 an introduction to delay controlled systems is given at length, and sufficient conditions are given for such a system to satisfy the general hypotheses. Two applications of the main result are also given. Section 5.2 is the main application, a discussion of a delay model of the lac operon in *E. Coli* from a paper by Mahaffy [69]. The stability results from that paper are re-derived and extended as a corollary of the main results of our Section 4.2.

Section 5.3 is a self contained section which formalizes the algorithm given in Section 1.1 in finite dimensions, to decompose an autonomous system as the negative feedback loop of a monotone controlled system.

1.5 Multistability under Positive Feedback

A major long term objective of the program of this dissertation is to study complex dynamical systems by decomposing them in terms of controlled monotone systems. Therefore it is important to consider complex monotone systems themselves as a starting point and to decompose them to gain as much understanding as possible. As we have seen, it is not necessary for all interactions to be positive in order for a system to be monotone with respect to some well-chosen order. Intuitively speaking, one can think of a (strongly) monotone system as being such that all (or most) solutions converge towards one or more equilibria (positive feedback is widely understood to be related to multistability). Therefore the number and stability of the equilibria is a determining factor, which will be essential in what follows.

Chapters 6 and 7 are devoted to considering an autonomous strongly monotone system (1.1) and writing it as the feedback loop of a controlled monotone system (1.2) under a *positive* feedback function $h : X \to U$. The single most important insight of these two chapters is that *one can obtain information about the number of equilibria of (1.1) and their stability by looking at a graph such as in Figure 1.5 c)*. This graph,

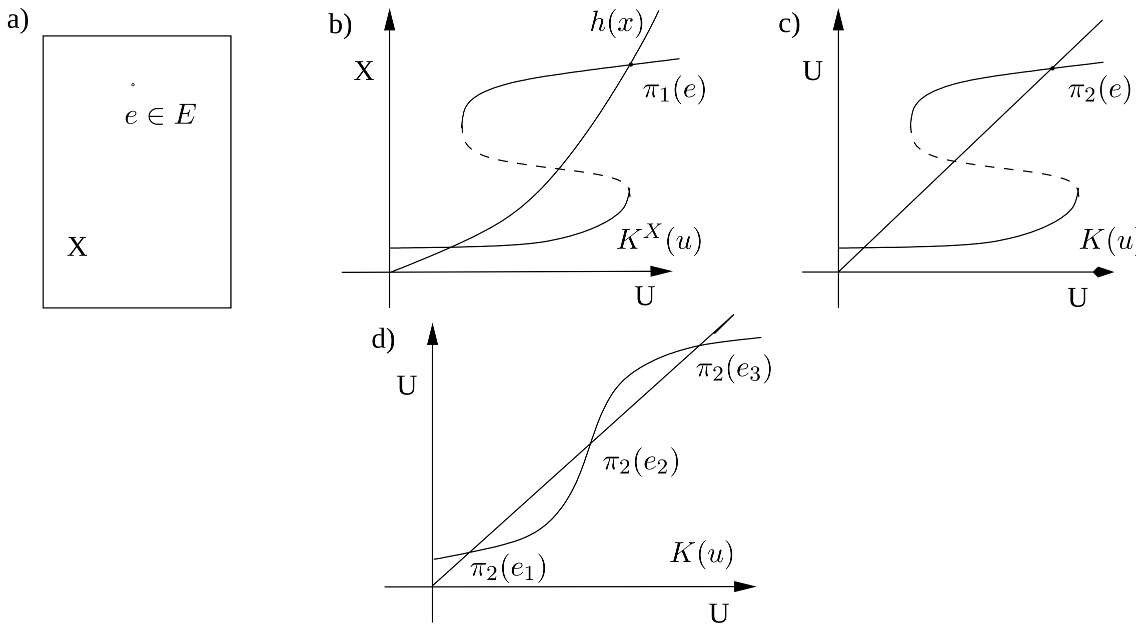

Figure 1.1: Interpreting the stability of equilibria in (1.1) by using the graphs of $K^X(u)$ and $K(u)$. Each equilibrium e in a) corresponds to a point $\pi_1(e) = (h(e), e)) \in \operatorname{graph} K^X \cap \operatorname{graph} h$ in b), and to a point $\pi_2(p) = (h(e), h(e)$ in c). The first correspondence is always a bijection, whereas the second correspondence is a bijection provided condition (H) is satisfied, see Section 6.2. The point e is guaranteed to be exponentially unstable if $\pi_i(e)$ lies on an exponentially unstable branch, but it may be exponentially unstable even if it is on a stable branch, such as $\pi_2(e_2)$ in d). Sufficient and necessary conditions for a hyperbolic point e to be exponentially stable are that both $\pi_2(e)$ lies on a stable branch and $\operatorname{Red}(e)$ is exponentially stable (see the definition of $\operatorname{Red}(e)$ below).

a radiography of the system of sorts, is displayed either on the plane or in a higher-dimensional space depending on the number of inputs used in the decomposition. To construct it, consider the multivalued function defined as

$$K^X(u) = \{x \in X \mid f(x,u) = 0\}$$

and imagine the point (u, x) as being 'stable' if x is an exponentially stable equilibrium of $\dot{z} = f(x, u)$, and 'unstable' otherwise. The former points form what can be informally referred to as the stable branches of $K^X(u)$, and the latter the unstable branches. (Since there is a certain ambiguity involved in these definitions, they won't be used in the formal discussion — but see the end of Section 6.4.) Then one can build the function

$$K(u) = \{h(x) \,|\, x \in K^X(u)\},$$

with the branch coding inherited from K^X.

It is not difficult to see that the function $\pi_1(e) = (h(e), e)$ forms a bijection between the set E of equilibria of the closed loop system and the intersection of the graphs of K^X and h (Lemma 29). If a mild additional condition (H) is satisfied, then in fact the function $\pi_2(e) = (h(e), h(e))$ is a bijection between E and the fixed points of K (Lemma 30). See once again Figure 1.5 and Section 6.2.

Let $e \in E$, and let $\mathrm{Red}(e)$ be the linearization of $K(u) - u$ around $(h(e), h(e))$ in Figure 1.5 c) (provided this is well defined). Writing the linearization of system (1.2) around $(h(e), h(e))$ in the form $\dot{x} = Ax + Bu$, $C = h'(e)$, one can show that $\mathrm{Red}(e) = -CA^{-1}B - I$ (see Section 6.2).

In the scalar case $m = 1$, $\mathrm{Red}(e)$ is none other than $k'(h(e)) - 1$, where $k(u)$ is the branch of $K(u)$ where $(h(e), h(e))$ is located. Therefore $\mathrm{Red}(e)$ is exponentially stable if and only if $k'(u) < 1$ at $h(e)$. See Figure 1.5 d).

This notation allows us to go further in the description of the closed loop system, by characterizing the *stability* of the equilibria in terms of features of Figure 1.5 c). A crucial assertion is that *the exponentially stable points in E are in bijective correspondence with the points on a stable branch of $K(u)$ and such that* $\mathrm{Red}(e)$ *is exponentially stable* (assuming the condition (H); see Corollary 11). If E is countable and all equilibria in E are either exponentially stable or exponentially unstable, then this implies that almost all solutions of the system converge towards such points (see also Theorem 21).

It remains to consider the case in which there are equilibria in E which are neither exponentially stable nor exponentially unstable. To account for these points on the graph of $K(u)$ we make further use of a standing assumption in this chapter, namely the *strong* monotonicity of the closed loop system. This is closely related to the strong connectivity of the digraph associated to the system [101]. Therefore one way to ensure this condition is by writing the system as a cascade of smaller, strongly connected subsystems, and by studying these systems separately. By assuming that most linearizations of the closed loop system around equilibria are strongly monotone, one is able to extend the stability correspondence between the equilibria of the closed loop system and the fixed points of $K(u)$; see Theorems 19 and 20, and Proposition 6.

At this point we also stress another standing assumption so far, namely that the set E of equilibria is countable. This allows us to eliminate exponentially unstable equilibria from the picture, since the countable union of basins of attraction with measure zero has itself measure zero. This assumption is commonly satisfied after eliminating constraints such as mass conservation laws, but it is interesting in its own right (and for applications) to consider the case of a general set E. The subject of the generic convergence to equilibria in strongly monotone systems became a topic of its own in this thesis and is treated in Chapter 8. One of the main results gives sufficient mild conditions so that, in a strongly monotone system, most solutions converge towards an equilibrium whose spectrum lies on the closed left hand side of the complex plane. This allows us, once again, to characterize the dynamics of the system in terms of the stability of its equilibria, which is in turn described by the function $K(u)$ (Theorem 22).

1.6 Applications

Chapter 6 gives several detailed examples relevant to the theory developed in the previous chapter. In the last two sections, it also shows how to generalize the ideas from the main results to delay and diffusion systems, using two very strong properties of monotone systems detailed in Chapter 3. The first application considers a core 3-variable gene regulation system, involving a gene and its self-promoting protein. It is shown under realistic Michaelis-Menten reaction functions how this simple system can present multistability, using the function K described above. The second system is a 4-variable two-protein regulation model, which is decomposed using two inputs. This example illustrates the case in which the function $K(u) = k(u)$ is single valued for every

u. In this case, one can interpret $\mathrm{Red}(e)$ as the linearization of the system

$$\dot{u} = k(u) - u \tag{1.5}$$

around the point $h(e)$. It also holds under weak hypotheses that $k(u)$ is a stable branch, and that the condition (H) above holds. The arguments described above therefore guarantee that the stability of e in the closed loop system is the same as that for $h(e)$ in system (1.5), and that the equilibria of both systems are in bijective correspondence. The reduced system (1.5) associated to the two-protein model is displayed in Figure 7.5.

Since only the stable branches of the function $K(u)$ are relevant for the interpretation of the dynamics of the closed loop system, Section 7.2 is devoted to finding this new multivalued function in an efficient manner. Given an open cascade of monotone systems, it is shown that to build this 'stable branch' function (also known as *stable equilibrium descriptor*, or SED) it is enough to consider that of each step of the cascade and compose them in a natural way (Lemma 37). This procedure is an iteration of the so-called *convergent input, convergent state (CICS)* property, which is in fact another interesting property of monotone systems since it doesn't need to hold in the non-monotone case (see [93]).

In Section 7.3, a larger-scale nine-variable model is considered using three coupled systems of the core form studied in Section 7.1. The subsystems are coupled by letting two proteins be transcription factors of each gene, and they still include Michaelis-Menten kinetic terms to describe the reactions. This system is studied to verify several technical hypotheses (condition (H), strong monotonicity of equilibria), and then it is written as a closed cascade of smaller subsystems using the framework from Section 7.2. Finally, a Matlab implementation is included, in which particular sets of parameters are chosen and the graphs of $K(u)$ are given for the analysis of the system. This underscores the fact that computer algorithms are useful and welcome for this analysis, especially as the systems themselves become increasingly complex.

Section 7.4 is essential because it generalizes the results of these two chapters to the case of delay and reaction diffusion equations. Recall that in Section 3.7 it is established (see also [101, 58]) that an equilibrium of a monotone delay system has the same stability as that of its corresponding equilibrium in the associated undelayed system. This means that the function $K(u)$ associated to the undelayed version of a delay monotone system yields just as much information about the equilibria of the delay system as about the system without delay. Using generic convergence results from Chapter 8 for infinite dimensional strongly monotone systems, this implies statements similar to the main results in Chapter 6 in the delay case.

The same ideas apply again for the reaction diffusion case in the second part of Section 7.4, using the fact that the stability of a spatially homogeneous equilibrium in a monotone reaction diffusion system is the same as that of the corresponding equilibrium in the undiffused system (Section 3.8). A result by Kishimoto et al. [59] states that in a convex domain Ω, and given a strongly cooperative system, a spatially inhomogeneous equilibrium must necessarily be exponentially unstable. Therefore these equilibria, which do not have a corresponding associated vector in the finite dimensional system, don't play a role in the behavior of the generic solution of the system, in light of the results from Chapter 8. Similar results such as in Chapter 6 follow for the reaction diffusion case.

In Section 7.5 it is pointed out that simple low pass filters are monotone and have a single-valued input to output characteristic; this fact is used to generalize some special results from Chapter 6 to cascades that include such filters. In Section 7.6 another computer implementation is included to illustrate how the equilibria of delay systems have the same stability as their undelayed counterparts, but that it is possible for their respective basins of attraction to be very different from each other.

1.7 Generic Convergence

In the chapters of this dissertation devoted to multistability and positive feedback, an approach is proposed to study the dynamics of strongly monotone systems by determining the number and stability of each of its equilibria. This approach is based on the assumption that most if not all solutions of the system are convergent towards one of the equilibria whose spectrum lies on the closed left hand side of the complex plane.

In Chapter 8, this assumption is considered and studied in detail in the infinite dimensional case. Indeed, Chapter 8 grew out of the problem of generalizing the results from Chapter 6 to delay and reaction diffusion systems. Applications of it are given in the end of Chapter 7, but the subject is of theoretical interest of its own.

Genericity

By the Smale argument that is described in Section 3.6, it is easy to see that any nontrivial statement about the convergence of *all* solutions in a strongly monotone system is bound to be false. Therefore one must talk about the convergence of a *generic* solution of the system. There are several results in the literature [101, 89] that guarantee that the set of convergent points has a dense interior – thus treating the word *generic* in a topological sense. In that chapter, the efforts are concentrated in a *measure-theoretic* kind of genericity, namely the concept of prevalence addressed by Yorke et al. [51], and previously by Christensen [17]. Recall that a subset W of a Banach space B (the notation $\mathbb{B}$ is used in that chapter) is *shy* if there exists a compactly supported Borel measure μ on B, such that $\mu(W + x) = 0$ for every $x \in B$. A set is said to be *prevalent* if its complement is shy. This simple concept turns out to provide a very fitting framework to the arguments given by Hirsch in his classic papers [48, 49].

In Section 8.1, a transfer result is proven showing that if the set C of convergent points is dense (weak topological genericity), then it must be prevalent (measure-theoretic genericity). Combined with the current results in the literature about topological genericity of C, this result gives mild sufficient conditions for C to be prevalent in a strongly monotone system.

In Section 8.2, the set of equilibria is classified as $E = E_s \dot{\bigcup} E_u$, where E_u is the set of exponentially unstable equilibria. Then sufficient regularity conditions are given for the generic solution of the system (in the sense of prevalence) to be convergent towards a point in E_s. These conditions involve mostly the differentiability and compactness of the time evolution operators, and therefore they hold in many interesting cases such as reaction diffusion and delay systems (in the latter case, possibly after making minor changes to the statements and proofs).

In Section 8.3, applications are provided to the specific case of reaction diffusion systems. One basic result used is that in Kishimoto et al. [59] described above, stating that if the domain Ω is convex in a strongly cooperative reaction diffusion system, then any nonhomogeneous equilibrium must lie on E_u. One can therefore conclude that the generic solution (in the sense of prevalence) converges towards a *homogeneous* equilibrium in E_s.

In Section 8.4, an application is given to a class of chemical reactions which are strongly monotone, but which may lose their monotonicity properties after using conservation laws to reduce the system. The result given shows that the generic solution (in the sense of prevalence) converges towards a unique equilibrium.

The Appendix of this chapter, Section 8.5, considers the measurability of different sets appearing in the proof of the main results.

1.8 Monotone Decompositions

Chapter 9 is an in-depth look at a simple algorithm to decompose non-monotone systems into the negative feedback loop of a controlled monotone system, using a minimal number of input variables. The algorithm turns out to be NP-hard to compute, which is a problem in the case of large scale networks, but suitable approximations can be given via semidefinite programming.

In Section 9.1, the decomposition algorithm from Section 5.3 is reviewed and a second algorithm with the same purpose is introduced. Several combinatorial results are given to provide a more clear picture of the framework. In Section 9.2, the first algorithm is implemented using Matlab and based on an idea by Prof. Bhaskar DasGupta to relate this problem to the classical MAX-CUT problem from computer science. An implementation is given in Section 9.3 to a 13-variable, 20-edge system from a *Drosophila* segment polarity network model. The minimum number of necessary inputs is found, using an argument that combines both theory and the Matlab implementation results. A linearly coupled row of networks is also considered, and corresponding extensions are given for that case. The second model (Section 9.4 is a large-scale network related to the EGF receptor, with several hundred variables and nodes. A report is given with the minimum number of inputs found by the implementation. Finally, two ideas are considered which may reduce the number of inputs substantially, namely the possibility of a change of variables and an extension of the implemented algorithm.

1.9 Further Topics

Two topics are addressed in Chapter 10 that have as background motif the theory of monotone systems.

In the paper [6], Sontag and Angeli find conditions called *weak (strong) excitability* and *weak (strong) transparency*, with the following property: a controlled monotone system under positive feedback which is weakly excitable and weakly transparent has strongly monotone closed loop provided that it is also either strongly excitable or strongly transparent. But this property doesn't hold for cascades of monotone systems under the given definitions. Thus, a closed cascade of weakly transparent and weakly excitable systems may not necessarily be strongly monotone, even if some of the transparency or excitability conditions are strong. In Section 10.1, the conditions of partial excitability and partial transparency are defined, which make up for this deficiency. These definitions also become important for the discussion in Section 6.3.

In Section 10.2, it is pointed out that the stability analysis of a quasimonotone matrix is substantially simpler to carry out than that of an ordinary matrix, and that it can be meaningful to study the stability of an arbitrary matrix by comparing it to a quasimonotone matrix with similar entries. The simple concept of monotone envelopes is then defined and used for this purpose. Also, several results are provided about monotone envelopes for their own sake.

1.10 Future Work

The two sections on future work concern possible generalizations of the previous results for the negative feedback closed loop of monotone controlled systems. The first section considers the ‘embedding’ of the n-dimensional closed loop system into a certain $2n$-dimensional monotone system. such an embedding has been considered before by Gouze [39], by Cosner et al. [18], and more recently by Enciso, Smith and Sontag [29]. It is discussed how one could potentially conclude the convergence of all solutions of the closed loop system towards one out of two or more equilibria, by showing this property for the monotone embedding itself.

On the contrary, showing the existence of periodic solutions for the closed loop system seems to require tools away from the domain of monotone systems. In the following section of that chapter, a background is given as to the plausibility and usefulness of such a result. A tentative approach is also illustrated via the socalled ejective fix point theory, which has been succesfully used by Nussbaum, Mallet-Paret and several others to prove such results in a general one-dimensional delay framework.

1.11 The Appendix

The short monograph in Section 12.1 addresses the following question: given a reaction diffusion system

$$\dot{u} = \Delta u + f(u) \tag{1.6}$$

under Neumann boundary conditions, and assuming that the n-dimensional reaction system $\dot{u} = f(u)$ is globally attractive to an equilibrium, can there be spatially nonhomogeneous equilibria of the original system? Can there be a continuum of such nonhomogeneous equilibria? The answer to both questions turns out to be yes, and this is relevant to the material in Chapters 8 and 7: using the Smale argument, such a function as that built in this section can be extended to a 3-dimensional strongly monotone system with a continuum of non-homogeneous (and quite possibly exponentially unstable, see Kishimoto [59]) equilibria.

On a different note, Section 12.2 closely follows Chapter 8 of the book [113] by Volpert, Volpert and Volpert. This text is concerned with chemical reactions under mass action kinetics, and in particular it considers when these systems are monotone after reduction using conservation laws. Our section first describes and reviews the ideas from that chapter, then offers an extension to invertible reactions. This section therefore arguably addresses the basic material on monotonicity as applied to chemical reactions.

Section 12.3 is an appendix to Section 5.1, where the basics of controlled delay systems are reviewed. In this section, sufficient conditions are provided for a system of the form (5.4) to have unique maximally defined solutions (Theorem 14 in Chapter 5). It also provides a proof that the semiflow condition is satisfied for such systems.

1.12 Publications Associated to this Work

Many portions of this dissertation have been published or submitted for publication. These publications are all self contained, and the reader is invited to look at them for discussions that are independent of the rest of the material, and in particular (crucially!) much shorter.

- The material in Chapter 2 was published in the Journal of Mathematical Biology [32], as joint work with Eduardo Sontag.
- Chapters 4 and 5 were submitted together as a paper and accepted for publication in the journal Discrete and Continuous Dynamical Systems [30], jointly with Eduardo Sontag. A very related work that includes applications to reaction diffusion systems has been accepted for publication in the Journal of Differential Equations [29], in joint work with Hal Smith and Eduardo Sontag.
- Chapters 6 and 7 are the result of combining three different papers, the first two published in Systems and Control Letters [31] and in the proceedings for the 2004 IEEE conference on Decision and Control. The third paper covers the remaining material, and it will be submitted presently. All three are coauthored with Eduardo Sontag.
- The material in Chapter 8 is the subject of a paper that will presently be submitted to a theoretical journal, coauthored with Hal Smith.
- Chapter 9 will become part of a joint paper that is being prepared for submission coauthored with Bhaskar DasGupta, Eduardo Sontag, and Yi Zhang.

1.13 Stability Notation

We close this introductory chapter with some remarks on our notation for the stability of matrices and linear operators, some of which has already been used above. An $n \times n$ matrix A is said to be *Hurwitz* or *exponentially stable* if $\Re(\lambda) < 0$ for every eigenvalue λ of A. It is said to be *exponentially unstable* if there exists some eigenvalue λ of A such that $\Re(\lambda) > 0$. We denote by $\mathcal{N}$ the class of matrices A such that $\Re(\lambda) \leq 0$ for every eigenvalue λ of A. It is well known in the literature that a system $\dot{x} = Ax$ is globally attractive to the origin if A is exponentially stable, and that it is dynamically unstable if A is exponentially unstable. It is also well known that this system can be dynamically unstable even when A is in the class $\mathcal{N}$, as exemplified in the case

$$A = \begin{bmatrix} 0 & 1 \\ 0 & 0 \end{bmatrix}.$$

(The instability is not exponentially fast, hence the name in the other cases.)

In the infinite dimensional case, one must take into account that the spectrum of a linear operator is divided into the point spectrum, the continuous spectrum and the residual spectrum, which are pairwise disjoint from each other. For simplicity's sake we give the three definitions above in terms of the point spectrum alone. Nevertheless in Chapter 3 it will be shown that for quasimonotone operators the element of the spectrum with the largest real part (if it exists) is generally part of the point spectrum. This would render several alternative definitions of stability equivalent for such operators.

Given a dynamical system, we denote by E the associated set of equilibria. Let $e \in E$, and let L be the linearization of the system around e in the appropriate context. We say that e is *exponentially stable* if L is an exponentially stable operator. We similarly define when e is *exponentially unstable*. Finally, we define the set E_s to be the set of equilibria e whose associated linearization L is in the class $\mathcal{N}$.

Chapter 2

A First Tour: Testosterone Dynamics

2.1 Introduction

In this chapter we give a self-contained introduction to the main ideas that will be formalized in Chapters 4 and 5. Although the set of differential equations is of interest in its own right, it is described here in the context of a specific biological application. No explicit mention is made here of monotone systems – rather, the reader should take this discussion as a motivation for how monotonicity can be of use.

The concentration of testosterone in the blood of a healthy human male is known to oscillate periodically with a period of a few hours, in response to similar oscillations in the concentrations of the luteinising hormone (LH) secreted by the pituitary gland, and the luteinising hormone releasing hormone (LHRH), normally secreted by the hypothalamus (see [14],[104]). In his influential textbook *Mathematical Biology* [77], J.D. Murray presents this process as an example of a biological oscillator, and proposes a model to describe it (pp. 244-253 in this edition). To obtain periodic oscillations in an otherwise globally attractive model, he introduces a delay in one of the variables, and by linearizing around the unique equilibrium point, he presents an argument to find conditions for the existence of such oscillations. This section in his book has remained virtually unchanged since the first edition of 1989, up to the recent publication of the third edition in 2002.

The study of delayed models is one of great interest for its relevance in biological applications (consider for instance the delay between the moment a protein is transcribed, and the moment the folded and translated protein gets to act as a transcription factor back in the nucleus). But the introduction of delays often comes at the expense of a higher sophistication in mathematical treatment.

As a “case study” for a method for proving stability in a class of dynamical systems with delays, we show here that *Murray’s model in fact does not exhibit oscillations.* The biological model itself, while simplified, is still interesting in its own right, and belongs to a commonly recurring class of models of negative feedback proposed (in undelayed form) by Goodwin [38], and illustrated in Goldbeter [37]. In what follows, we first study the linearized system around the unique equilibrium, establishing local stability, and then proceed to show the global stability of the system. We also propose an explanation for the confusion in [77].

2.2 The Model and its Linearization

The presence of LHRH in the blood is assumed in this simple model to induce the secretion of LH, which induces testosterone to be secreted in the testes. The testosterone in turn causes a negative feedback effect on the secretion of LHRH. Denoting LHRH, LH, and testosterone by R, L, and T respectively, and assuming first order degradation and a delay τ in the response of the testes to LH, we arrive to the dynamical system

$$\begin{aligned} \dot{R} &= f(T) - b_1 R \\ \dot{L} &= g_1 R - b_2 L \\ \dot{T} &= g_2 L(t-\tau) - b_3 T. \end{aligned} \tag{2.1}$$

Here $f(x) = A/(K+x)$, $b_1, b_2, b_3, g_1, g_2, A, K$ are positive constants, and $\tau \geq 0$. Other positive, monotone decreasing functions could be employed as well, for instance such as $f(x) = A/(K+x^n)$ for $n > 1$ (see Murray [77], p. 246 and below).

Several comments are at hand. First, one could introduce arbitrary delays in the first summands of each of the three equations above, since a simple change of variables would reduce such a system to the form (2.1). Second, this simple feedback system is of interest independent of its interpretation as that of a testosterone dynamics model. Third, the terms $g_1 R$ and $g_2 L(t-\tau)$ could be replaced by monotone increasing functions $g_1(R)$ and $g_2(L(t-\tau))$ without undermining the discussion that follows.

By setting the left hand sides equal to zero, it is straightforward to show that there are as many equilibrium points of (2.1) as there are solutions of

$$f(T) - \frac{b_1 b_2 b_3 T}{g_1 g_2} = 0, \tag{2.2}$$

namely for each such solution T_0 of (2.2), one has the equilibrium

$$L_0 = \frac{b_3 T_0}{g_2},\ R_0 = \frac{b_3 b_2 T_0}{g_1 g_2},\ T_0. \tag{2.3}$$

By the assumption of positivity and monotonicity of f there always exists a unique solution of (2.2), thus a unique equilibrium point of (2.1). Linearizing around that point we obtain the system

$$\begin{aligned}
\dot{x} &= f'(T_0)z - b_1 x \\
\dot{y} &= g_1 x - b_2 y \\
\dot{z} &= g_2 y(\cdot - \tau) - b_3 z.
\end{aligned} \tag{2.4}$$

The characteristic polynomial of (2.4), which determines all solutions of (2.4) of the form $\mathbf{v}(t) = \mathbf{v_0} e^{\lambda t}$, is

$$(\lambda + b_1)(\lambda + b_2)(\lambda + b_3) + de^{-\lambda\tau} = 0, \quad d = -f'(T_0) g_1 g_2 > 0. \tag{2.5}$$

Proposition 1 *The linear system (2.4) is exponentially stable, for all values of* b_1, b_2, b_3, g_1, g_2, τ *and* $f(x) = A/(K + x)$.

Proof. For the statement to be false, there must be a solution λ of (2.5) such that $\mathrm{Re}\,\lambda \geq 0$. Assuming that this is the case, we have

$$d \geq |-de^{-\lambda\tau}| = |\lambda + b_1||\lambda + b_2||\lambda + b_3| \geq |b_1||b_2||b_3| = b_1 b_2 b_3\,. \tag{2.6}$$

But on the other hand, using the choice for $f(T)$ above, we have $f'(T_0) = -A/(K + T_0)^2 = -f(T_0)/(K + T_0)$, and

$$d = -f'(T_0) g_1 g_2 = \frac{f(T_0)}{K + T_0} g_1 g_2 = b_1 b_2 b_3 \frac{T_0}{K + T_0} < b_1 b_2 b_3\,, \tag{2.7}$$

which is a contradiction. ∎

2.3 Global Asymptotic Stability of the Model

Even with the addition of only one simple delay, it is probably best to view (2.1) as a dynamical system with states in the space X of continuous functions from $[-\tau, 0]$ into the closed positive quadrant $(\mathbb{R}^+)^3$. The right hand side of (2.1) defines a function $F : X \to (\mathbb{R}^+)^3$ in the natural way, and given an initial state $\phi \in X$, the solution of the system is the unique absolutely continuous function $x : [-\tau, \infty) \to (\mathbb{R}^+)^3$ such that

$$x_{(0)} = \phi \text{ and } \dot{x}(t) = F(x_{(t)}),\ t \geq 0. \tag{2.8}$$

Here, $x_{(t)}$, or simply x_t, is the state defined by $x_t(s) = x(t+s),\ s \in [-\tau, 0]$. The function $\Phi(t, \phi) = x_t$ will be from now on formally identified with system (2.1). For proofs of the fact that Φ is well-defined, and more details, the reader is referred to the next chapter.

Cutting the Loop

We define a function $G : X \times \mathbb{R}^+ \to (\mathbb{R}^+)^3$ in a very similar manner to F: for $\phi(s) = (R(s), L(s), T(s))$, let

$$G(\phi, w) = (w - b_1 R(0),\ g_1 R(0) - b_2 L(0),\ g_2 L(-\tau) - b_3 T(0))\,.$$

Given a piecewise continuous function $u : \mathbb{R}^+ \to \mathbb{R}^+$, called an *input* [1], we define $\Psi(t, \phi, u) = x_t$, where $x : [-\tau, \infty) \to (\mathbb{R}^+)^3$ is the unique absolutely continuous function such that

$$x_{(0)} = \phi \text{ and } \dot{x}(t) = G(x_t, u(t)),\ t \geq 0. \tag{2.9}$$

In effect, we are thus cutting the feedback loop induced by T upon R, and replacing it with an arbitrary input $u(t)$. The resulting controlled system has therefore the form

$$\begin{aligned}
\dot{R} &= f(u) - b_1 R \\
\dot{L} &= g_1 R - b_2 L \\
\dot{T} &= g_2 L(t-\tau) - b_3 T.
\end{aligned} \tag{2.10}$$

[1] The more general control-theoretic definition is more elaborate, and it will be used starting in the following chapter. See also [6]

Notation: given $x, y \in \mathbb{R}^3$, let $x \leq y$ denote $x_i \leq y_i,\ i = 1,2,3$. For $\phi, \psi \in X$, let $\phi \leq \psi$ denote $\phi(s) \leq \psi(s),\ \forall s \in [-\tau, 0]$.

Theorem 1 *The dynamical system with input $\Psi(t, \phi, u)$ satisfies the following properties:*

1. *If the input $u(t)$ converges to $w \in \mathbb{R}^+$, then $\Psi(t, \phi, u)$ converges as t tends to ∞ towards the constant state*

$$k(w) \;=\; \left(\frac{w}{b_1}, \frac{g_1 w}{b_2 b_1}, \frac{g_1 g_2 w}{b_1 b_2 b_3}\right),$$

   for any initial state $\phi \in X$.

2. *Let u_1, u_2 be inputs, and pick any two initial states $\phi, \psi \in X$. If $u_1(t) \leq u_2(t)\ \forall t$ and $\phi \leq \psi$, then $\Psi(t, \phi, u_1) \leq \Psi(t, \psi, u_2)\ \forall t$.*

Proof. Suppose that $u(t)$ converges towards $w \in \mathbb{R}^+$. Let $\phi \in X$ be arbitrary. The dynamics of the component $R(t)$ of the solution $x(t)$ is determined by the equation $\dot{R}(t) = u(t) - b_1 R(t)$, and so $R(t)$ converges towards w/b_1. Applying a very similar argument to $L(t)$ and $T(t)$ in this order, we obtain the first result.

The proof of the second statement follows by the "Kamke condition" (see [101]): if $w_1 \leq w_2,\ \phi \leq \psi$, and $\phi(0)_i = \psi(0)_i$ (that is, the ith components of ϕ and ψ are equal), then $G(\phi, w_1)_i \leq G(\psi, w_2)_i$. For instance, if $\phi = (R_1, L_1, T_1),\ \psi = (R_2, L_2, T_2),\ \phi \leq \psi$, and $R_1(0) = R_2(0)$, then $w_1 - b_1 R_1(0) \leq w_2 - b_1 R_2(0)$. This can be checked for L and T in the same way. The fact that the Kamke condition implies the desired property follows from the results in [101]; however, in the interest of exposition and since the proof is so short, we provide it next.

Let $x(t)$ be the solution of (2.9) with input u_1 and initial condition ϕ, and let $G_\epsilon = G + (\epsilon, \epsilon, \epsilon)$, for $\epsilon > 0$. Let $y_\epsilon(t)$ be the solution of $\dot{y}(t) = G_\epsilon(y_t, u_2)$ with initial condition ψ. Suppose that at some point t_1, $x(t_1) \not\leq y_\epsilon(t_1)$, and so there exists a component i (that is, R, L or T) and t_0 such that $x_{t_0} \leq y_{\epsilon t_0},\ x(t_0)_i = y_\epsilon(t_0)_i$ and $\dot{x}(t_0)_i \geq \dot{y}_\epsilon(t_0)_i$. But then

$$\dot{x}(t_0)_i = G(x_{t_0}, u_1(t_0))_i \leq G(y_{\epsilon t_0}, u_2(t_0))_i < G_\epsilon(y_{\epsilon t_0}, u_2(t_0))_i = \dot{y}_\epsilon(t_0)_i$$

which is a contradiction. We thus conclude that $x(t) \leq y_\epsilon(t),\ \forall t \geq 0$. Now, it can be shown ([45],[101]) that as $\epsilon \to 0$ $y_\epsilon(t)$ converges pointwise to $y(t)$, the solution of (2.9) with input u_2 and initial condition ψ, and from here the conclusion follows. ∎

Definition 1 *For an arbitrary continuous function $x : [-\tau, \infty) \to (\mathbb{R}^+)^3$, we say that $z \in (\mathbb{R}^+)^3$ is a* lower hyperbound of $x(t)$ *if there is $z_1, z_2, \ldots \to z$ and $t_1 < t_2 < t_3 \ldots \to \infty$ such that for all $t \geq t_i,\ z_i \leq x(t)$. If for all $t \geq t_i,\ z_i \geq x(t)$, we say that z is an* upper hyperbound of $x(t)$.

For instance, z is a lower hyperbound of the trajectory x if it bounds from below $x(t)$ for every t. Similar definitions are given for inputs $u(t)$. The previous Theorem is the basis for the following result.

Theorem 2 *Let $v \in \mathbb{R}^+$ be a lower hyperbound of the input $u(t)$, and let $\phi \in X$ be arbitrary. Then $k(v)$ is a lower hyperbound of the solution $x(t)$ of the system (2.9). If v is, instead, an upper hyperbound of $u(t)$, then $k(v)$ is an upper hyperbound of $x(t)$.*

Proof. Suppose that v is a lower hyperbound of $u(t)$, the other case being similar, and let $v_1, v_2, \ldots \to v$ and $t_1 < t_2 < \ldots \to \infty$ be as above.

For every $i \geq 1$, let $V_i \subset (\mathbb{R}^+)^3$ be a neighborhood of $k(v_i)$ that is open in $(\mathbb{R}^+)^3$, and let $y_i \in (\mathbb{R}^+)^3$ be such that $y_i \leq V_i$ componentwise. Without loss of generality we will assume that $|y_i - k(v_i)| \leq 1/i$. Also, let

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

Let $T_1 < T_2 < \ldots \infty$ be defined by induction as follows: $T_1 = 0$, and if T_{i-1} is defined, let T_i be chosen such that $T_i \geq T_{i-1} + 1,\ T_i \geq t_i$, and for all $t \geq T_i :\ x_i(t) = \Psi(t, \phi, u_i)$ is contained in V_i. By the previous theorem, $x_i(t) \leq x(t) \forall t$, and so $y_i \leq x(t),\ \forall t \geq T_i$. As $y_i \to k(v)$, the conclusion follows. ∎

The following simple Lemma is standard in the literature on discrete iterations (and is used in a similar context in [4]); we provide a proof for expository purposes.

Lemma 1 *Let $S : \mathbb{R}^+ \to \mathbb{R}^+$ be a continuous, nonincreasing function. Then the discrete system $u_{n+1} = S(u_n)$ has a unique, globally attractive equilibrium if and only if the equation $S(S(x)) = x$ has a unique solution.*

Proof. If the system has a unique, globally attractive equilibrium $\bar{u}$, then this point is a solution of the equation $S^2(x) = S(S(x)) = x$. Any other point u cannot be a solution of this equation, as $S^n(u)$ must converge to $\bar{u}$. This proves the 'only if' part of the lemma.

Conversely, suppose that the equation $S^2(x) = x$ has a unique solution. Let $u \in \mathbb{R}^+$ be arbitrary, and consider the sequence $u_n = S^n(u)$. If $u \leq u_2$, then since S^2 is a nondecreasing function, we have $u_2 \leq u_4$, and so

$$u \leq u_2 \leq u_4 \leq u_6 \leq \ldots .$$

But the sequence $u_2, u_4 \ldots$ is bounded (by $S(0)$), and so u_{2n} must converge to some point v_0. The same argument applies if $u_2 < u$, and also for the sequence $u_1, u_3, u_5, \ldots$, which must converge to some point v_1. But the continuity of S implies that both v_0 and v_1 are solutions of $S^2(x) = x$, so $v_0 = v_1$ are both equal to our unique solution, and u^n thus converges to this point, independent of the choice of u. ∎

Consider for instance $S(x) = p/(q + x)$, where p, q are positive real numbers. If x satisfies $S^2(x) = x$, then it holds that

$$x = \frac{p}{q + S(x)},$$

which can be rearranged as $x^2 + qx - p = 0$. Using the quadratic formula, it becomes clear that there is always exactly one *positive* solution.

This example will be useful in what follows.

Theorem 3 *All solutions of the system (2.8), with $f = A/(K + x)$, converge towards the unique equilibrium, for any choice of the parameters $b_1, b_2, b_3, g_1, g_2, \tau, A, K$.*

Proof. Consider any initial condition $\phi \in X$, and the corresponding solution $x(t) = (R(t), L(t), T(t))$ of (2.8). Defining the input $u(t) = f(T(t))$, and using it to solve the system (2.9) with initial condition ϕ, we arrive of course at exactly the same solution $x(t)$.

Let v bound $u(t)$ from below for all t – for instance, $v = 0$ will do. Then by Theorem 2, $k(v)$ is a lower hyperbound of $x(t)$. In particular,

$$Qv = \frac{g_1 g_2}{b_1 b_2 b_3} v$$

is a lower hyperbound of $T(t)$. But, since f is a nonincreasing function, this implies that $f(Qv)$ is an upper hyperbound of $f(T(t)) = u(t)$. Defining $v_1 = f(Qv)$, we apply the same theorem once again to show that $k(v_1)$ is an upper hyperbound of $x(t)$, $v_2 = f(Qv_1)$ is a lower hyperbound of $u(t)$, etc. But

$$f(Qx) = \frac{A}{K + Qx} = \frac{p}{q + x} = S(x)$$

for $p = A/Q$, $q = K/Q$. Thus we see that $v_n = S^n(v)$ is a convergent sequence of numbers that are alternating upper and lower hyperbounds of $u(t)$. This easily implies that $u(t)$ itself converges to the unique solution $\bar{u}$ of the equation $S^2(x) = x$. By Theorem 1, $x(t)$ converges towards $k(\bar{u})$, independently of the choice of the initial condition ϕ.

Finally, this implies that $k(\bar{u})$ is the unique equilibrium of the system, otherwise one could reach a contradiction by taking this equilibrium as constant initial condition. ∎

2.3.1 Discussion

Several remarks are in order: first, the actual value of the delay τ was never used, and indeed can be arbitrarily large or small. In fact, we can introduce different delays, large or small, in all of the first terms at the right hand sides of (2.1), and the results will apply with almost no variation. If delays are introduced in the second terms, the system will not be *monotone*, that is, won't satisfy the second property of Theorem 1, which is essential for this argument. But then again, introducing a delay in the degradation terms wouldn't be very biologically meaningful.

As for the conclusions in pp. 244-253 of *Mathematical Biology*, we may venture to suggest that in eq 7.49, p. 247, Murray writes the characteristic equation (2.5) of the linearized system (2.4) as

$$\lambda^3 + a\lambda^2 + b\lambda + c + de^{-\lambda\tau} = 0, \tag{2.11}$$

where a, b, c, d are all written in terms of the original parameters of the system: $a = b_1 + b_2 + b_3$, etc. From here on the efforts are concentrated in finding a root λ of this equation with Re $\lambda = 0$, for some well-chosen coefficients a, b, c, d. But the author seems to disregard in the remaining argument the fact that a, b, c, d cannot be chosen arbitrarily and independently, *but rather that their values are determined from choosing arbitrarily* $b_1, b_2, b_3, g_1, g_2, \tau$. Thus for instance, it is assumed in the last line of p.251 that $d > c$, without justification from the original variables. It turns out that the former assumption cannot be satisfied for the particular choice of f, as seen in the proof of Proposition 1.

We point out that a simple modification can make oscillatory behavior possible. In p. 246 of [77], the author discusses varying cooperativity coefficients of $f(x) = A/(K+x^m)$, then settles for $m = 1$ for the delayed model. If indeed m is increased, then it is very possible to have $d > c$ and the remaining argument in the section will be valid. One example of this is when parameters are picked as follows:

$$m = 2,\ A = 10,\ K = 2,\ b_1 = 1,\ b_2 = 1,\ b_3 = 1,\ g_1 = 10,\ g_2 = 10.$$

Another interesting contribution to the modeling of testosterone dynamics is the paper [91] by Ruan et al., where sufficient conditions are found for globally attractive and oscillatory behavior in a neighborhood of an equilibrium. We would like to describe the relationship between [91] and our own result, given the similarity of the hypotheses and the potentially conflicting conclusions: global stability in our results vs. Hopf bifurcations in [91]. Moreover, we will simplify the statement of that result. In that paper, several new quantities are introduced in order to state the main result, Theorem 3.1. In terms of the original variables of the system (b_1, b_2, b_3, etc.), these are as follows:

$$\begin{aligned}
p &= b_1^2 + b_2^2 + b_3^2 \geq 0 \\
q &= b_1^2 b_2^2 + b_2^2 b_3^2 + b_1^2 b_3^2 \geq 0 \\
\Delta &= p^2 - 3q = \frac{1}{2}((b_1^2 - b_2^2)^2 + (b_2^2 - b_3^2)^2 + (b_1^2 - b_3^2)^2) \geq 0
\end{aligned}$$

$$z_1 = \frac{1}{3}(-p + \sqrt{\Delta}).$$

Theorem 3.1 holds under the assumption that

$$(b_1 + b_2)(b_1 + b_3)(b_3 + b_2) < d \tag{2.12}$$

and deals essentially with the following three special cases:

1. $b_1 b_2 b_3 \geq d$ and $\Delta < 0$,
2. $b_1 b_2 b_3 \geq d$ and $z_1 > 0$,
3. $b_1 b_2 b_3 < d$.

In case 1, (local) asymptotic stability is guaranteed for arbitrary delay lengths (part (i) of the Theorem), while in cases 2 and 3, and under some additional conditions (parts (ii) and (iii) of the Theorem), stability holds for small enough delays, but a Hopf bifurcation occurs at some critical value of this delay length. In light of the above computation, case 1 can never be satisfied (for variables p, q, r generated from the original set of parameters b_1, b_2, b_3, etc.). Similarly, the condition $z_1 > 0$ will never be satisfied since

$$z_1 > 0 \Leftrightarrow \Delta > p^2 \Leftrightarrow 3q < 0,$$

so case 2 cannot hold either. One is only left with case 3, which is actually a consequence of (2.12). On the other hand, for the particular choice of $f(x)$ made in [77] and the present discussion, Proposition 1 shows that we always have $b_1 b_2 b_3 > d$. Thus Theorem 3.1 does not apply for the present model, as well as for any choice of the function f and any set of parameters such that $b_1 b_2 b_3 > d$.

Chapter 3

An Overview of Monotone Systems

3.1 Cones and Monotonicity

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

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

The pair $(\mathbb{B}, K)$ is referred to as an *ordered* Banach space. The following notation will be used: $[x, y] = \{z | \, x \leq z \leq y\}$, $(x, y) = \{z | \, x \ll z \ll y\}$. These sets will be denoted as *intervals* or *boxes*. The cone $\mathcal{K}$ is called *normal* if $0 \leq x \leq y$ implies $|x| \leq M \, |y|$ for some constant $M > 0$, called a *normality constant* for $\mathcal{K}$. Also, a set $A \subset \mathbb{B}$ will be said to be *bounded from above* if there is some $x \in \mathbb{B}$ such that $a \leq x$, for all $a \in A$. If $\mathbb{B}_1, \mathbb{B}_2$ are two ordered Banach spaces, $\gamma : \mathbb{B}_1 \to \mathbb{B}_2$ is said to be $\leq$-*increasing* if $x \leq y$ implies $\gamma(x) \leq \gamma(y)$, and it is said to be $\leq$-*decreasing* if $x \leq y$ implies $\gamma(x) \geq \gamma(y)$ (similarly with the other order relations). In the case $\mathbb{B} = \mathbb{R}^n$, consider a tuple $(s_1, \ldots s_n)$, where $s_i = 1$ or -1 for every i. This tuple defines the order $x \leq_s y$ if and only if $s_i x_i \leq s_i y_i$ for every i. The cones $\mathcal{K}_s = \{x \in \mathbb{R}^n \, | \, x \geq_s 0\}$ are denoted as *orthant cones*. The canonic orthant cone defined by $s = (1 \ldots 1)$ is called the *cooperative cone*.

For convenience of the reader, we review the following standard facts from convex analysis.

Lemma 2 *A cone $\mathcal{K}$ has nonempty interior if and only if the unit ball is bounded from above.*

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

Lemma 3 *Let $\mathcal{K} \subseteq \mathbb{R}^n$. Then $\mathcal{K}$ is normal.*

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

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

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

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

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

∎

Let $\mathbb{B}$ be a Banach space, and let A be a linear operator on $\mathbb{B}$. Let the linear system

$$\dot{x} = Ax \tag{3.1}$$

have well defined solutions (see Section 3.3 for more precise terminology in the infinite dimensional case). In the following definition we will avoid the use of the abstract term 'positive' given in Berman and Plemmons [10] (which has ambiguous associations), but otherwise we will use the terminology from the literature.

Definition 2 *Let $\mathcal{K} \subseteq \mathbb{B}$ be a cone. With respect to $\mathcal{K}$, a linear operator $A : \mathbb{B} \to \mathbb{B}$ is said to be:*

i) monotone, *if $A\mathcal{K} \subseteq \mathcal{K}$.*

ii) quasimonotone *if the system $\dot{x} = Ax$ has monotone evolution operators.*

iii) strongly monotone *if $A(\mathcal{K} - \{0\}) \subseteq int\, \mathcal{K}$.*

iv) strongly quasimonotone *if the system $\dot{x} = Ax$ has strongly monotone evolution operators (after positive time).*

In the case that the choice of the underlying cone $\mathcal{K}$ is not clear from the context, one can use the more explicit terms $\mathcal{K}$-monotone and so on. The following equivalence is very useful throughout this dissertation in order to have an intuition for these different definitions. In the context of finite dimensional spaces, we associate to any matrix A a digraph G, where $1, \ldots n$ are nodes, and (i, j) is an arc iff $a_{ji} \neq 0$ — see also Section 3.4. We say that a matrix is *irreducible* if its associated digraph G is strongly connected. See Figure 3.1 for a compact description of this information.

Lemma 4 *Let $\mathbb{B} = \mathbb{R}^n$, and let A be an $n \times n$ matrix. With respect to the cooperative cone $\mathcal{K} = (\mathbb{R}^+)^n$,*

i) *A is monotone iff it has only nonnegative entries.*

ii) *A is quasimonotone iff it has only nonnegative entries except possibly on the diagonal.*

iii) *A is strongly monotone iff it has only positive entries.*

iv) *A is strongly quasimonotone iff it is quasimonotone and irreducible.*

Proof. The first statement is obvious: if all the entries of A are nonnegative, then $Ax \geq 0$ for $x \geq 0$. But if $a_{ij} < 0$, then $Ae_j \ngeq 0$. The second statement is proven for instance in [21]. The third statement is proven similarly as the first; the fourth is proven in [101], Section 4.1. ∎

Definition 3 *We say that a linear system $\dot{x} = Ax$ is* monotone *if $x_0 \leq y_0$ implies $x(t, x_0) \leq x(t, y_0)$ for all $t \geq 0$. Similarly, a system $\dot{x} = Ax$ will be called* strongly monotone *if $x_0 < y_0$ implies $x(t, x_0) \ll x(t, y_0)$ for all $t > 0$.*

Degrees of Monotonicity		Degrees of Quasimonotonicity	
monotone	$a_{ij} \geq 0\ \forall i,j$	quasimonotone	$a_{ij} \geq 0\ \forall i \neq j$
mon. irreducible	$a_{ij} \geq 0\ \forall i,j$ + Irr.	—	—
strongly monotone	$a_{ij} > 0\ \forall i,j$	strongly q.m.	$a_{ij} \geq 0\ \forall i \neq j$ + Irr.

Figure 3.1: The left two columns represent the different types of monotone matrices (1st column) and their equivalent definition in the cooperative case (2nd column). The 3rd and 4th columns describe their quasimonotone counterparts. The abbreviation *Irr.*, for *irreducible*, simply states that the signed digraph associated to the matrix is strongly connected. The second row in the quasimonotone matrix columns is empty: if a matrix A is such that the time evolution operators of $\dot{x} = Ax$ are monotone irreducible for $t > 0$, then these operators are automatically strongly monotone.

Thus a linear system is monotone if and only if its associated operator is *quasi*monotone, and it is strongly monotone if and only if its associated operator is strongly *quasi*monotone.

3.2 The Volkmann Condition

Consider a finite dimensional system

$$\dot{x} = f(x). \tag{3.2}$$

A useful condition to verify that this system is monotone with respect to a cone $\mathcal{K}$ is the so called *Volkmann* or *Vidyasagar* condition, introduced in the reference [112] (and [98] in the linear case). Given a cone $\mathcal{K}$ in an abstract Banach space $\mathbb{B}$, let $\mathcal{K}^*$ consist of all linear functionals $\sigma : B \to \mathbb{R}$ such that $\sigma(v) \geq 0$, for all $v \in \mathcal{K}$. System (3.2) (or the function f) is said to satisfy the Volkmann condition if for every $x \leq y$ and $\sigma \in \mathcal{K}^*$, it holds that

$$\sigma(x) = \sigma(y) \Rightarrow \sigma(f(x)) \leq \sigma(f(y)).$$

In the cooperative case, this condition can be easily seen to be equivalent to the so called Kamke condition

$$\frac{\partial f_i}{\partial x_j} \geq 0, \text{ for all } i \neq j.$$

Lemma 5 *Let $\mathcal{K}$ be a closed cone with nonempty interior, and let $f, g \in C^1(\mathbb{R}^n, \mathbb{R}^n)$ be such that $f \leq g$ and at least one of the functions f and g satisfy the Volkmann* *condition. Then for any pair of solutions $x(t)$, $y(t)$ of $\dot{x} = f(x)$, $\dot{x} = g(x)$ respectively, such that $x(0) \leq y(0)$, it holds that $x(t) \leq y(t)$ for every t.*

Proof. Let $p \gg 0$, and fix $\epsilon > 0$. Define $g_\epsilon(w) := g(w) + \epsilon p$ and let $y_\epsilon(t)$ be the solution of $\dot{x} = g_\epsilon(x)$ with initial condition $y(0)$. We show the statement for the functions $x(t), y_\epsilon(t)$. Once this is shown, one can let ϵ tend to zero, and the result follows by the continuity of the solutions.

Define $z(t) := y_\epsilon(t) - x(t)$. Clearly $z(t)$ is a differentiable function such that $z(0) \geq 0$. We show that for every $t \geq 0$ and every $\sigma \in \mathcal{K}^*$ such that $z(t) \geq 0$, $\sigma(z(t)) = 0$, it holds $\sigma(\dot{z}(t)) = \sigma(g_\epsilon(y(t))) - \sigma(f(x(t))) > 0$, whence the statement follows. Assume by contradiction that there exists some fixed t_0 and $\sigma \in \mathcal{K}^*$ such that $x_0 \leq y_0$, $\sigma(x_0) = \sigma(y_0)$ and $\sigma(f(x_0)) \geq \sigma(g_\epsilon(y_0))$, $x_0 := x(t_0)$, $y_0 := y_\epsilon(t_0)$. Using the Volkmann condition for f, it follows that

$$\sigma(f(x_0)) \leq \sigma(f(y_0)) \leq \sigma(g(y_0)) < \sigma(g_\epsilon(y_0)),$$

which is a contradiction. In case that g satisfies the Volkmann condition instead of f, a similar argument is used. ∎

Lemma 6 *Let $\mathcal{K}$ be a closed cone with nonempty interior, and let $f : \mathbb{R}^n \to \mathbb{R}^n$ be C^1. Then system (3.2) is monotone with respect to K if and only if it satisfies the Volkmann condition.*

Proof. The proof of one of the two directions follows directly from the previous lemma. To prove the other direction, let $x_0 \leq y_0$ and $\sigma \in \mathcal{K}^*$ such that $\sigma(x_0) = \sigma(y_0)$. Define $x(t), y(t)$ as the solutions of (3.2) with initial conditions x_0, y_0 respectively, and $r(t) := \sigma(x(t))$, $s(t) := \sigma(y(t))$. By monotonicity $x(t) \leq y(t)$ for every t, hence $r(t) \leq s(t)$, $t \geq 0$. Since also $r(0) = s(0)$, it follows $r'(0) \leq s'(0)$. Noting that $r'(t) = \sigma(f(x(t)))$, $s'(t) = \sigma(f(y(t)))$, the Volkmann condition follows. ∎

Corollary 1 *Let $f : \mathbb{R}^n \to \mathbb{R}^n$ be C^1. Then system (3.2) is cooperative if and only if it satisfies the Kamke condition.*

3.3 The Perron-Frobenius and Krein-Rutman Theorems

Perhaps the most important result one should know for any application of monotone operators is the Perron-Frobenius theorem for finite dimensional systems or Krein-Rutman theorem (for abstract Banach spaces). These theorems give information about the spectrum and the eigenvectors of a monotone operator. There are several possible ways in which these theorems are stated, depending on which properties of monotone operators want to be stressed by each author and on which ones are left out for the sake of clarity. For the Perron-Frobenius Theorem, see for instance Theorem 4.3.1 [101] and Theorems 1.3.2, 1.3.23, 1.3.26 of [10]. For the Krein-Rutman theorem see Theorem 2.4.1 [101], Theorems 19.2 and 19.3 of [25], Exercise (I-9) of Chapter 7 in [41], or the original 1950 paper [62] (in Russian). All of these theorems have in common a certain core statement for general monotone operators, together with stronger conclusions for operators satisfying stronger monotonicity properties.

For cones that are not cooperative (or orthant, see below), there are several equivalent ways to define the concept of irreducibility. We will say here that a monotone operator is *irreducible* if for any number $\alpha > 0$ and vector $x > 0$, $Ax \leq \alpha x$ implies $x \gg 0$. Theorem 1.3.20 in [10] shows that this definition generalizes the one given above for the cooperative case, and that any strongly monotone operator is monotone irreducible.

Theorem 4 (Perron-Frobenius) *Let $\mathcal{K} \subseteq \mathbb{R}^n$ be a closed cone with nonempty interior, and let $A\mathcal{K} \subseteq \mathcal{K}$. Then $\rho(A)$ is an eigenvalue of A, and there exists a positive eigenvector (i.e. $v > 0$) associated to $\rho(A)$.*

If A is monotone and irreducible, then $v \gg 0$. Also in this case, if $u > 0$ is an eigenvalue of A associated to any eigenvector, then $u = \alpha v$ for some real $\alpha > 0$.

If A is a strongly monotone matrix, then all conclusions above hold, and $|\lambda| < \rho(A)$ for any eigenvalue $\lambda \neq \rho(A)$ of A.

Proof. See the references in Berman and Plemmons [10] above for a discussion. ∎

One may wonder how this theorem can be used in the case of a monotone system

$\dot{x} = Ax$, since the underlying matrix A is only quasimonotone. Through the use of the spectral mapping theorem we obtain a completely equivalent result, which we call the Perron-Frobenius theorem for quasimonotone matrices. The concept corresponding to $\rho(A)$ is that of the *leading eigenvalue* of A, that is,

$$\operatorname{leig}(A) = \sup\{\operatorname{Re}\lambda \mid \lambda \in \sigma(A)\}.$$

Theorem 5 (Perron-Frobenius for quasimonotone matrices) *Let $\mathcal{K} \subseteq \mathbb{R}^n$ be a closed cone with nonempty interior, and let A be quasimonotone with respect to $\mathcal{K}$. Then $\operatorname{leig}(A)$ is an eigenvalue of A, and there exists a positive eigenvector (i.e. $v > 0$) associated to $\rho(A)$.*

If A is strongly quasimonotone, then $v \gg 0$. Also in this case, if $u > 0$ is an eigenvalue of A associated to any eigenvector, then $u = \alpha v$ for some real $\alpha > 0$. Furthermore, Re $\lambda < \operatorname{leig}(A)$ for any $\lambda \neq \operatorname{leig}(A)$ eigenvalue of A.

Proof. Let A be quasimonotone, and consider the time t evolution operator $T(t)$ of the system $\dot{x} = Ax$. It is well known that $T(t) = e^{tA}$ in operator notation. By the spectral mapping theorem, it holds that $\sigma(T(t)) = \exp(t\sigma(A))$. Now, $T(t)$ is monotone with respect to K by hypothesis, and therefore we can apply the Perron-Frobenius theorem. Since $\rho(T(t)) \in \sigma(T(t))$, there exists a real $\lambda \in \sigma(A)$ such that $e^{t\lambda} = \rho(T(t))$. We may require for this that $t > 0$ be small enough that no eigenvalue of A has imaginary part $2\pi m$, for any nonzero integer m. Since $\rho(T(t))$ has maximal radius in $\sigma(T(t))$, then λ has maximal real part in $\sigma(A)$. Therefore $\lambda = \operatorname{leig}(A)$.

For the remaining part of the first statement, recall that if v is an eigenvector of A with eigenvalue μ then v is an eigenvector of $T(t)$ with eigenvalue $e^{t\mu}$ (by expanding the exponential function as a Mc Laurin series). But this is not necessarily true in the opposite direction. We note instead that $\sigma(T(t)) = \{1\}$ if $t = 0$ and that there exists $t > 0$ small enough that $\sigma(T(t))$ is contained in a ball around 1 with radius $1/2$. Then we can define the operator $S = \ln(T(t))/t$, which is well defined since $z \to (\ln z)/t$ is holomorphic in a neighborhood of $\sigma(T(t))$. Thus the eigenvalue $\ln(\rho(T(t)))/t$ of S has an eigenvector $v > 0$. But it is easy to see that in fact $S = A$, and also $\ln(\rho(T(t)))/t = \operatorname{leig}(A)$. This completes the first part of the proof.

Let now A be strongly quasimonotone. The fact that there is an eigenvector $v \gg 0$ of A with eigenvalue leig(A) is proved similarly as above. Furthermore, after carrying out the same construction, let $u > 0$ be an eigenvector of A. Then u is also an eigenvector of $T(t)$, and by the Perron-Frobenius theorem, $Tu = \rho(T(t))u$ and $u = \alpha v$. The last statement follows also from the spectral mapping theorem and the last statement in Theorem 4. ∎

A very elegant extension of the Perron-Frobenius theorem for abstract compact operators is the Krein-Rutman theorem, which we state now.

Theorem 6 (Krein-Rutman Theorem) *Let $\mathbb{B}$ be a Banach space, and let $\mathcal{K}$ be a closed cone with nonempty interior. If $A \in L(\mathbb{B}, \mathbb{B})$ is a compact monotone operator, and if $\rho(A) > 0$, then $\rho(A)$ is an eigenvalue of A, and there exists a positive eigenvector $v > 0$ associated to $\rho(A)$.*

If $A \in L(\mathbb{B}, \mathbb{B})$ is a compact, strongly monotone operator, then $\rho(A) \in \sigma(A)$ with an eigenvector $v \gg 0$. In this case, if $u > 0$ is an eigenvalue of A associated to any eigenvector, then $u = \alpha v$ for some real $\alpha > 0$.

Proof. See the references given above to Deimling [25] for a discussion. ∎

Notes:

For the first statement it may be assumed that $\mathcal{K}$ is merely closed and *total*, that is $\overline{\mathcal{K} - \mathcal{K}} = \mathbb{B}$. Note that the conclusions of the second statement correspond to the case "A is monotone and irreducible" in the Perron-Frobenius theorem, and therefore assumes a stronger hypothesis than the latter theorem. This may be simply a matter of usage – see for instance the statement of the reference given in [41].

In the same way as for the finite dimensional case, the spectral mapping theorem can be of use to prove a Krein-Rutman theorem for quasimonotone operators. Such a result appears in the literature for particular cases, for instance in Section 7.6 of [101] in the case of strongly monotone reaction diffusion equations. The statement is very similar to that of Theorem 5, but its proof is substantially more subtle. For instance, in the abstract case the spectral mapping theorem requires us to consider the point spectrum, continuous spectrum and residual spectrum of an operator separately. Also, the proof of the more general result holds through for systems that are *eventually monotone (eventually strongly monotone)*, that is, when the time evolution operators $T(t)$ are monotone (strongly monotone) only for $t \geq t_0$. This is especially useful in the case of delay systems. For the argument that follows the most important reference used is Pazy [87].

Consider a Banach space X, as well as linear operator $L : X \to X$ which defines an abstract dynamical system

$$\dot{x} = Lx. \tag{3.3}$$

That is, (3.3) generates a C_0 semigroup of bounded operators $T(t) : X \to X$, $t > 0$. It is important that we do not assume that L itself is bounded, or even that it is defined in all of X, since this is not the case for applications such as in delay or reaction diffusion systems.

Theorem 7 (Krein-Rutman theorem for quasimonotone operators) *Let $\mathbb{B}$ be a Banach space, $\mathcal{K}$ a closed cone with nonempty interior, and (3.3) generate a C_0 semigroup of compact time evolution operators $T(t)$, $t > 0$.*

If (3.3) is a monotone system and $\sigma(L) \neq \emptyset$, then $\operatorname{leig}(L) \in \sigma(L)$*, and* $\operatorname{leig}(L)$ *has an associated eigenvector $v > 0$.*

If (3.3) is a strongly monotone system, then $\operatorname{leig}(L)$ *has an associated eigenvector $v \gg 0$. Furthermore, any positive eigenvector $u > 0$ of L is a multiple of v, and Re $\lambda <$* $\operatorname{leig}(L)$*, for every $\lambda \neq$* $\operatorname{leig}(L)$ *eigenvalue of L.*

Proof. Let L generate a monotone semigroup. We first show that $\operatorname{leig}(L) \in \sigma_p(L)$. Let $t > 0$, and note that by Theorem 2.2.3 of [87] $exp(t\sigma(L)) \subseteq \sigma(T(t))$. Since $\sigma(L) \neq \emptyset$, it follows that $\rho(T(t)) > 0$. We can therefore apply the Krein-Rutman theorem to the compact monotone operator $T(t)$ to find that $\rho(T(t)) \in \sigma_p(T(t)) \subseteq \sigma(T(t))$. Now, by another result in Section 2.2 of [87],

$$e^{t\sigma_p(L)} \subseteq \sigma_p(T(t)) \subseteq e^{t\sigma_p(L)} \cup \{0\},$$

and thus $\rho(T(t)) \in \exp(t\sigma_p(L))$. This inequality also means, by compactness of T, that $\sigma_p(A)$ is enumerable and that

$$\mathrm{leig}_p(L) := \sup\{\mathrm{Re}\ \lambda \,|\, \lambda \in \sigma_p(L)\} < \infty.$$

It is also clear that $\rho(T) = \exp(t\mathrm{leig}_p(L))$. The fact that $\rho(T(t)) \in \exp(t\ \sigma_p(L))$ doesn't quite imply yet that $\mathrm{leig}_p(L) \in \sigma_p(L)$, but rather that there exists $m = m(t)$ such that

$$\mathrm{leig}_p(L) + 2\pi i m/t \in \sigma_p(L).$$

Suppose by contradiction that $m(t) \neq 0$ for every $t > 0$. Then there would be an uncountable number of eigenvalues in the point spectrum of L which have real part equal to $\mathrm{leig}_p(L)$. This would contradict the enumerability of $\sigma_p(L)$ shown above; therefore $\mathrm{leig}_p(L) \in \sigma_p(L)$ after all.

Finally, by Theorem 2.2.5 of [87] and the discussion above, there cannot be any eigenvalues in the residual spectrum of L with real part larger than $\mathrm{leig}_p(L)$. The same applies to the continuous spectrum of L, by Theorem 2.2.6 of [87]. We conclude that $\mathrm{leig}_p(L) = \mathrm{leig}(L)$, and thus finish the proof that $\mathrm{leig}(L) \in \sigma(L)$.

From the above argument, it holds that $L - \mu I$ is Hurwitz, for some μ large enough. The equalities

$$-I = \int_0^\infty \frac{\mathrm{d}}{\mathrm{d}t} e^{-\mu t} T(t)\,\mathrm{d}t = (L - \mu I) \int_0^\infty e^{-\mu t} T(t)\,\mathrm{d}t = (L - \mu I)C,$$

show that $C = -(L - \mu I)^{-1}$ is monotone. From Pazy [87], Theorem 2.3.3, it follows that C is a compact operator. Note also that since $\sigma(L - \mu I) = \sigma(L) - \mu$ is a nonempty set contained in the left side of the complex plane, it holds $\rho(L - \mu I) > 0$ and $\rho(C) > 0$. This is used to obtain, by the Krein-Rutman theorem, an eigenvector of C $v > 0$ associated to $\rho(C)$, and therefore to obtain an eigenvalue $\lambda_0 = -1/\rho(C)$ of $L - \mu I$ with eigenvector v. Note that λ_0 is the largest negative real eigenvalue of $L - \mu I$. On the other hand, $L - \mu I$ is Hurwitz, and it therefore has no nonnegative real eigenvalues. It follows that λ_0 is the largest real eigenvalue of $L - \mu I$, that is, $\lambda_0 = \mathrm{leig}(L - \mu I)$. Therefore $v > 0$ is an eigenvector of L with eigenvalue $\lambda_0 + \mu = \mathrm{leig}(L)$, and we thus finish the first part of the theorem.

To prove the second part, let it be assumed that the system (3.11) is strongly monotone. Then the operator C constructed above is strongly monotone as well, and therefore we can assume $v \gg 0$ by the Krein-Rutman theorem. If $u > 0$ is an eigenvector of L with eigenvalue λ, then u is an eigenvector of $T(t)$ with eigenvalue $e^{t\lambda}$ by the spectral mapping theorem. Therefore $u = \alpha v$ by the Krein-Rutman theorem. The fact that $\mathrm{Re}\,\lambda < \mathrm{leig}(L)$, for every $\lambda \in \sigma(L), \lambda \neq \mathrm{leig}(L)$, follows directly from Theorems 2.2.4, 2.2.5 and 2.2.6 of [87]. ∎.

A very thorough reference on the behavior of abstract positive semigroups is [8]. The result above can therefore be seen as a short compendium of the results in this reference (although it was developed independently).

The Krein-Rutman Theorem has been studied and generalized in many different directions over time, for instance by providing more information about the setup given above for C_0 semigroups (e.g. [80]). Another possible direction is to consider a normal and reproducing cone and a bounded positive operator (not necessarily compact), and to conclude that the spectral radius is in the (not necessarily point) spectrum of the operator [12, 96, 42, 81]. Finally, note that by dividing the linear operator A by its spectral radius, one can see the main conclusion of Theorem 6 as guaranteeing that there exists a positive, nonzero fixed point of A. This observation allows to study generalizations of this theorem for nonlinear operators [79, 82]. See also [46, 83, 96, 97, 101].

3.4 Orthant Monotone Systems

Consider a finite-dimensional nonlinear system (3.2). As it was mentioned above, one way to define partial orders in $\mathbb{R}^n$ is as follows. Given a tuple $s = (s_1, \ldots s_n)$, with $s_i = 1$ or -1 for every i, we say that $x \leq_s y$ if $s_i x_i \leq s_i y_i$ for every i. We call $\leq_s$ the *orthant order generated by s*. The following characterization of monotonicity for orthant monotone systems is a direct consequence of the arguments in Lemma 6 and Corollary 1 (or see Corollary III.3 in [6] for a direct proof).

Lemma 7 *Consider an orthant order $\leq_s$ generated by $s = (s_1, \ldots, s_n)$. A system*

$\dot{x} = f(x)$ defined on $\mathbb{R}^n$ is monotone with respect to $\leq_s$ if and only if

$$s_i s_j \frac{\partial f_j}{\partial x_i} \geq 0,\ i,j = 1 \dots n,\ i \neq j. \tag{3.4}$$

Another characterization of monotonicity with respect to orthant orders is given by looking at the signed graph associated to (3.2) in the natural way: given nodes i, j, draw an arc signed '+' (or $+1$) from i to j if $\partial f_j/\partial x_i \geq 0$ and $\partial f_j/\partial x_i \not\equiv 0$. Similarly for '$-$' (or -1), and finally assign no arc if $\partial f_j/\partial x_i \equiv 0$. The signed, undirected graph associated to (3.2) is defined from the directed graph simply by ignoring the directions of the arcs. Note that this definition generalizes that which is given for linear systems in Section 3.1. It is important to note that not every dynamical system has an associated (di)graph; we restrict our attention in this section to systems that satisfy this condition, and we call such systems *sign definite*.

Given p, we say that an edge (i, j) is *consistent with respect to* p if $p(i)p(j)\mathrm{sign}(i, j) = 1$. Then the following analog of Lemma 7 holds.

Lemma 8 *Consider a system (3.2) and an orthant cone $\leq_p$. Then (3.2) is monotone with respect to $\leq_p$ if and only if every edge is consistent with respect to p.*

Proof. Note that $p(i)p(j)\partial f_i/\partial x_j = 0$ if $(i, j) \notin E(G)$. For $(i, j) \in E(G)$, it holds that $p(i)p(j)\partial f_i/\partial x_j \geq 0$ if and only if $p(i)p(j)\mathrm{sign}(i, j) = 1$. The result follows from Lemma 7. ∎

Let the *parity* of a chain in G be the product of the signs $(+1, -1)$ of its individual edges. We will consider in the next result closed *undirected chains*, that is, sequences $x_{i_1}, \dots, x_{i_r}$ such that $x_{i_1} = x_{i_r}$, and such that for every $\lambda = 1 \dots r-1$ either $(x_{1,\lambda}, x_{1,\lambda+1}) \in E(G)$ or $(x_{1,\lambda+1}, x_{1,\lambda}) \in E(G)$.

The following lemma is analogous to the fact from vector calculus that there exists a potential function for a vector field $f(x)$ if and only if all closed path integrals along $f(x)$ vanish.

Lemma 9 *Consider a dynamical system (3.2) with associated directed graph G. Then (3.2) is monotone with respect to some orthant order if and only if all closed undirected chains of G have parity* 1.

Proof. Suppose that the system is monotone with respect to $\leq_p$, that is, $p(i)p(j)\text{sign}(i,j) = 1$ for all $i, j,\ i \neq j$ (by Lemma 8). Let $V(G) = A \cup B$, where $i \in A$ if $p(i) = 1$, and $i \in B$ otherwise. Note that by hypothesis $\text{sign}(i,j) = 1$ if $x_i, x_j \in A$ or if $x_i, x_j \in B$. Also, $\text{sign}(i,j) = -1$ if $x_i \in A$, $x_j \in B$ or vice versa. Noting that every closed chain in G must cross an even number of times between A and B, it follows that every closed chain has parity 1.

Conversely, let all closed chains in G have parity 1. We define a function p as follows: consider the partition of $V(G)$ induced by letting $i \sim j$ if there exists an undirected open chain joining i and j. Pick a representative i_k of every equivalence class, and define $p(i_k) = 1$, $k = 1, \ldots, K$. Next, given an arbitrary vertex i and the representative i_k of its connected component, define $p(i)$ as the parity ($+1$ of -1) of any undirected open chain joining i_k with i. To see that this function is well defined, note that any two chains joining i and j can be put together into a closed chain from i_k to itself, which has parity 1 by hypothesis. Thus the value of $p(i)$ is independent of the choice of the chain.

Let now i, j be arbitrary different vertices. If $\partial F_j/\partial x_i \equiv 0$, then (3.4) is satisfied for i, j; otherwise there is an edge joining i with j. By construction of the 'potential' function p, it holds that if $p(i) = p(j)$ then $\text{sign}(i,j) = 1$, i.e. $\partial F_j/\partial x_i \geq 0$, and so (3.4) holds as well. If $p(i) \neq p(j)$, then $\text{sign}(i,j) = -1$, i.e. $\partial F_j/\partial x_i \leq 0$. In that case (3.4) also holds, and the proof is complete. ∎

3.5 Convergence to Equilibria

As it was shown above, monotonicity is related with positive feedback – and positive feedback is associated in the literature with multiple stable equilibria. We will see in this section some concrete statements that embody this assertion.

The first result is due to Dancer [19] in its discrete form; the continuous version given below is a straightforward generalization.

Lemma 10 (Dancer 1998) *Let $\mathbb{B}$ be a Banach space and $\mathcal{K}$ a closed normal cone. Let $X \subseteq \mathbb{B}$ be such that for every compact $A \subseteq X$, there exists $a \in X$ which bounds A*

from above (below). Consider a monotone dynamical system $x(x_0, t)$ defined on X, and assume that 1) the system has completely continuous evolution operators, and 2) the system has precompact orbits in X. Then every omega limit set $\omega(x)$ is bounded from above (below) by an equilibrium.

Proof. Let $x_0 \in X$, and consider the set $\omega(x_0)$, which is nonempty by condition 2). Let $u \in X$ be such that $\omega(x_0) \leq u$. Given $w \in \omega(x_0)$ and $t > 0$, let $q \in \omega(x_0)$ be such that $x(q, t) = w$. Such an element can be found, again using condition 2). Since $q \leq u$, it follows by monotonicity that $w \leq x(u, t)$; since w, t are arbitrary, it must hold that $\omega(x_0) \leq \omega(u)$ pointwise.

Now let $z \in X$ be such that $z \geq \omega(u)$. By the same procedure as above, we have $\omega(u) \leq \omega(z)$ pointwise. Let

$$S := \{y \in X \,| \omega(x_0) \leq y \leq \omega(z)\}.$$

Since $\omega(u) \subseteq S$, it holds that S is nonempty. It also holds that S is convex, closed, and bounded (the latter from the normality of $\mathcal{K}$) and that S is an invariant subset of system $x(\cdot, t)$. Thus, for any time $t > 0$, and letting $T(t)$ be the time-evolution operator of the system, we have that $T(t)$ is a compact function such that $T(t)S \subseteq S$. By the Schauder fixed point theorem, the set $E_t := \{e \in S \,|\, T(t)(e) = e\}$ is nonempty. It is easy to see that each set E_t is a compact set, by compactness of $T(t)$ and the boundedness of S, and that

$$E_1 \supseteq E_{\frac{1}{2}} \supseteq E_{\frac{1}{4}} \supseteq E_{\frac{1}{8}} \supseteq \ldots$$

Therefore the intersection of all these sets must be nonempty. But this intersection is none other than E, the set of equilibria of $x(\cdot, t)$ in S. It follows that there exists $e \in E$ such that $\omega(x) \leq e$.

Finding an equilibrium that bounds $\omega(x)$ from below follows a similar argument. ∎

Corollary 2 *Under the hypotheses of the previous lemma, if there exists a unique equilibrium e, then every solution must converge towards e.*

The second result is by now a classic statement proven by Hirsch [48, 49]. A detailed proof will be given in Chapter 8 as part of a generic convergence study. We state this result in finite dimensions for simplicity.

Theorem 8 *Let $\mathcal{K} \subseteq \mathbb{R}^n$ be a closed cone with nonempty interior. If (3.2) is strongly monotone with respect to $\mathcal{K}$, then almost every bounded solution $x(t)$ of (3.2) is such that $\omega(x(t)) \subseteq E$.*

Recall that periodic solutions are generally associated with negative feedback. The following result precludes the existence of attractive periodic solutions for monotone systems. See [48].

Theorem 9 *Let $\mathcal{K} \subseteq \mathbb{R}^n$ be a closed cone with nonempty interior. If (3.2) is monotone with respect to $\mathcal{K}$, then (3.2) has no attractive periodic solutions.*

3.6 Smale's Argument

The reader has seen in the previous section what strong stability properties hold for monotone and strongly monotone systems. Theorem 8 in effect precludes the possibility for chaotic behavior, and Theorem 9 rules out even the more tame attractive periodic behavior. One is therefore tempted to go further, and make many other possible conjectures: given a monotone system, can it be that there aren't any periodic solutions at all? (This can be seen to be true for $n = 2$.) Can one say that in fact *all* bounded solutions of a strongly monotone system converge to the equilibrium set?

The following remarkably simple argument puts a stop to both conjectures above, and in fact it negates just about any nontrivial conjecture of the form "In a strongly monotone system, *all* bounded solutions are such that ...". It is due to Smale in the 1976 paper [99], and it seems to have been dubbed since "Smale's argument" or "Smale's construction". See also [50]. Even though Smale proved this result originally in terms of strongly competitive systems, we will provide it in the setup of this chapter. See also Section 8.3 for a generalization to reaction-diffusion systems.

Theorem 10 *Let* $\Sigma = \{x \in \mathbb{R}^n \mid \sum_i x_i = 0\}$*, and let* $f : \Sigma \to \Sigma$ *be an arbitrary compactly supported* C^1 *function. Then there exists a strongly monotone system* $\dot{x} = F(x)$ *defined on* $\mathbb{R}^n$*, and such that* $F(x) = f(x)$ *on* Σ*.*

Proof. Let $S(x) := \sum_i x_i$. Let $p : \mathbb{R} \to [0,1]$ be a smooth, compactly supported function such that $p \equiv 1$ on a neighborhood of 0. Let $Q > 0$ be a fixed number to be determined. Finally, let $v := (1/n, \ldots, 1/n)$, and note that $S(x - S(x)v) = S(x) - S(x)S(v) = 0$. Using this fact, we can extend the domain of definition of f to all $\mathbb{R}^n$ by letting $f(x) := f(x - S(x)v),\ x \notin \Sigma$. We will still call this function $f(x)$ for simplicity, and it can be verified that $f : \mathbb{R}^n \to \Sigma$ is still a C^1 function. Define

$$F_i(x) = QS(x) + p(S(x))f_i(x), \quad i = 1 \ldots n,$$

so that for any $j = 1 \ldots n$,

$$\frac{\partial F_i}{\partial x_j} = Q + p'(S(x))f_i(x) + p(S(x))\frac{\partial f_i}{\partial x_j}.$$

Note that if $F = (F_1, \ldots F_n)$, then $F = f$ on Σ. The functions $p'(S(x)), p(S(x))$ are supported inside a set of the form $\{x \in \mathbb{R}^n \mid d(x, \Sigma) < \epsilon\}$, and $f_i, \partial f_i/\partial f_j$ are supported inside one of the form $\{x \in \mathbb{R}^n \mid d(x, \mathbb{R}\mathbf{1}) < \epsilon\}$. Therefore the continuous functions $p'(S(x))f_i$ and $p(S(x))\partial f_i/\partial x_j$ are compactly supported, and one can find Q which is large enough so that $\partial F_i/\partial x_j > 0$ for all i, j. The statement follows. ∎

The use of Theorem 10 for building counterexamples is clear. For instance, to show that there exists a strongly monotone system with periodic solutions simply consider a function $\hat{f} : \mathbb{R}^{n-1} \to \mathbb{R}^{n-1}$ whose associated system $\dot{x} = \hat{f}(x)$ has periodic solutions. Then use an isomorphism $\pi : \Sigma \to \mathbb{R}^{n-1}$ to define $f(x) := \pi^{-1}\hat{f}(\pi(x))$. The system $\dot{x} = f(x)$ has therefore the exact same properties as its $n-1$-dimensional counterpart. The resulting system $\dot{x} = F(x)$ after applying the theorem is strongly monotone, but has a periodic solution on Σ by construction.

It is important to observe that, by definition, Σ is a repelling (though invariant) set of the system. Indeed,

$$S(F(x)) = S(\mathbf{Q}S(x) + p(S(x))f(x)) = S(x)S(\mathbf{Q}) + p(S(x))S(f(x)) = S(x)nQ.$$

The geometrical interpretation of this is that $F(x)$ points away from Σ, for every $x \notin \Sigma$. Moreover, in every counterexample using this construction, the set of bounded solutions itself has measure zero – and in fact is contained in Σ.

One can therefore escape the threat of Smale's argument by asking "Let the system have bounded solutions, and let every compact set $A \subseteq X$ be bounded from below and above by some element in X." This is exactly what was done in Theorem 10.

3.7 Stability for Delay Systems

In the following two sections we will prove two statements that further illustrate the strong stability properties implied by monotonicity. Roughly speaking, *the stability of a steady state in a monotone system doesn't change after adding or eliminating delays or diffusion terms.* More precisely, given an equilibrium $\hat{e}$ of a monotone delay system, or a spatially homogeneous equilibrium $\hat{e}$ of a monotone reaction diffusion system, then

$$\mathrm{sign}(\mathrm{leig}(\hat{e})) = \mathrm{sign}(\mathrm{leig}(e)),$$

where e is the canonical equilibrium associated to $\hat{e}$ in the finite dimensional system associated to the original system. It is important to note that the original system (delay or reaction diffusion) must be a well defined monotone system in its own right – not every delay system with an associated monotone undelayed system is itself monotone. These two sections attempt to form concise, clear presentations of these results, and they require some familiarity with the subjects at hand - a formal introduction to delay or reaction diffusion systems is out of the question. Nevertheless, in Section 5.1 a self-contained overview of delay systems is given at length. The following two sections are based on the discussions given in the corresponding sections of Smith [101] for the cooperative case.

Consider a general linear delay system on $\mathbb{R}^n$, that is a system of the form

$$\dot{x} = Lx_t,\ x_{(0)} = \phi. \tag{3.5}$$

Here $x_t(s) = x(t+s)$ for $s \in [-r, 0]$, $\phi : [-r, 0] \to \mathbb{R}^n$ is a continuous function, and L is an $n \times n$ matrix of real signed Borel measures L_{ij} on $[-r, 0]$ for each $i, j = 1 \ldots n$. The formal multiplication by a continuous function x_t, $(x_t)_j : [-r, 0] \to \mathbb{R}$ for $j = 1 \ldots n$, is understood in the obvious sense.

Suppose that (3.5) is monotone with respect to a closed cone $K \subseteq \mathbb{R}^n$ with nonempty interior. By this it is meant that the dynamical system in $X = C([-r, 0], \mathbb{R}^n)$ induced by (3.5) is monotone with respect to the cone $\hat{\mathcal{K}} = \{\phi \in X | \, \phi(s) \geq 0, \ \forall s\}$. This is equivalent to the following property: for every state $\phi \geq 0$ and every $\sigma \in K^*$, $\sigma(\phi(0)) = 0$, it holds that $\sigma(L\phi) \geq 0$ (the so-called Volkmann property). see [101], Section 5.1 for the cooperative case, and [50] for the general case.

The spectrum associated with the operator L in (3.5) satisfies $\sigma(L) = \sigma_p(L)$ and consists of the complex numbers λ such that

$$\det(\lambda I - A(\lambda)) = 0, \tag{3.6}$$

where $A(\lambda)_{ij} := L_{ij} e^{\lambda t}$ (see [44], Lemma 7.2.1).

Lemma 11 *Let (3.5) be monotone with respect to K. Then $A(\lambda)$ is quasimonotone with respect to K, for all $\lambda \in \mathbb{R}$.*

Proof. The matrices $A(\lambda)$ are defined in such a way that for $x_0 \in \mathbb{R}^n$ and $\phi := x_0 e^{\lambda t}, t \in [-r, 0]$, it holds that $L\phi = L x_0 e^{\lambda t} = A(\lambda) x_0$. Let $x_0 \geq 0$, and let $\sigma \in K^*$ with $\sigma(x_0) = 0$. The Volkmann property for L implies that $\sigma(L\phi) \geq 0$. But this is $\sigma(A(\lambda)x_0) \geq 0$, which proves the (finite dimensional) Volkmann property for $A(\lambda)$. ∎

The function $\lambda \to \mathrm{leig}(A(\lambda))$ is clearly continuous on λ. In the cooperative case discussion in [101], Section 5.5, $\lambda_1 \leq \lambda_2$ implies $A(\lambda_1)_{ij} \geq A(\lambda_2)_{ij}$ for all i, j, and therefore $\mathrm{leig}(A(\lambda_1)) \geq \mathrm{leig}(A(\lambda_2))$ This is used in [101] to show that the graph of $\mathrm{leig}(A(\lambda))$ intersects the diagonal at exactly one point, and it is critical in the proof of Corollary 5.5.2. The intersections of this function with the diagonal are important since they are associated with real eigenvalues in the spectrum of (3.5): $\lambda - \mathrm{leig}(A(\lambda)) = 0$ implies that $\lambda \in \sigma(A(\lambda))$ and (3.6) holds.

Lemma 12 *Let (3.5) be monotone with respect to $\mathcal{K}$. Then $\lambda \to \mathrm{leig}(A(\lambda))$ intersects the diagonal at least at one point. If (3.5) is eventually strongly monotone, then there* *is exactly one intersection.*

Proof. Suppose by contradiction that there are no intersections. In the first scenario, we have $\lambda < \text{leig}(A(\lambda))$ for all λ. Now, for $\lambda > 0$, the functions $e^{\lambda t},\ t \in [-r, 0]$ are bounded between zero and one, and thus every A_{ij} is similarly bounded. This implies that there is a uniform upper bound for $\|A(\lambda)\|,\ \lambda > 0$, which is a contradiction since

$$\text{leig}(A(\lambda)) \leq \rho(A(\lambda)) \leq \|A(\lambda)\| .$$

Suppose then that $\lambda > \text{leig}(A(\lambda))$ for all λ. Let $\lambda_0 := \text{leig}(L) \in \mathbb{R}$. We have that $\lambda_0 \in \sigma(A(\lambda_0))$, and so $\lambda_0 \leq \text{leig}(A(\lambda_0)) < \lambda_0$, another contradiction.

Let now (3.5) be eventually strongly monotone. In the same way as in the proof of Theorem 7, we can use the spectral theorem to write the spectrum of (3.5) in terms of the spectrum of the evolution operator $T(t)$ for t large enough, that is

$$\sigma(T(t)) = \{0\} \cup \{e^{\lambda t} \mid \lambda \text{ eigenvalue of } (3.5)\}.$$

This operator can be assumed to be strongly monotone for t large enough, and it can be shown to be compact. Every real λ such that $\lambda = \text{leig}(A(\lambda))$ has, by Theorem 4, an associated eigenvector $v > 0$ such that $A(\lambda)v = \lambda v$. It is easy to verify that $x = ve^{\lambda t}$ is a solution of (3.5) and therefore generates an eigenvector $ve^{\lambda t} > 0$ of $T(t)$. But by the Krein-Rutman theorem such eigenvectors are uniquely associated to the eigenvalue $\text{leig}(T(t)) = e^{\text{leig}(L)}$. Thus $\lambda = \text{leig}(L)$, and the intersection must be unique. ∎

To system (3.5) we can associate an undelayed system by letting $\hat{L}x = L(\hat{x})$ and considering

$$\dot{x} = \hat{L}(x). \tag{3.7}$$

We now conclude that the stability of (3.5) is tied with that of (3.7).

Corollary 3 *Let (3.5) be eventually strongly monotone. Then it is exponentially stable (exponentially unstable) if and only if (3.7) is exponentially stable (exponentially unstable).*

Proof. Let λ_0 be the unique real value such that $\lambda_0 = \text{leig}(A(\lambda_0))$. We show that $\lambda_0 < 0$ ($\lambda_0 > 0$) if and only if $\text{leig}(A(0)) < 0$ ($\text{leig}(A(0)) > 0$): if $\lambda_0 < 0$, then necessarily $\text{leig}(A(0)) < 0$, since otherwise by the previous lemma $\lambda < \text{leig}(A(\lambda))$ for all $\lambda > 0$, which is a contradiction. All other implications are very similar to prove.

Note that

$$\hat{L}x = L(\hat{x}) = L(e^{0t}x) = A(0)x,$$

that is $\hat{L} = A(0)$, and recall from the previous proof that λ_0 is the leading eigenvalue of L. Since the exponential stability or instability of a system at an equilibrium is determined by the sign of the leading eigenvalue, the statement follows. ∎

The question remains as to how one can identify a delay monotone system (3.5) as being eventually strongly monotone. Smith and Thieme [102, 101] propose practical conditions (I), (R) for the cooperative case, which can also be used for any orthant cone. In the case of general cones, the reader is referred to Section 4.3 of [50] for a condition (called (STD)) which is very related to strong monotonicity for a monotone delay system, and which is a direct generalization of a corresponding condition for the ODE case (called (ST) in this reference).

Finally, note that the previous corollary can be used on any nonlinear delay system

$$\dot{x} = f(x_t), \tag{3.8}$$

by letting $\hat{f}(x) := f(\hat{x})$ and considering its associated finite dimensional system

$$\dot{x} = \hat{f}x. \tag{3.9}$$

Corollary 4 *Let (3.8) be a nonlinear delay system which is eventually strongly monotone with respect to $\mathcal{K}$, and let $\phi = \hat{e}$ be an equilibrium of this system. Then $\hat{e}$ is exponentially stable (exponentially unstable) in this system if and only if e is exponentially stable (exponentially unstable) in the system (3.9).*

Proof. The proof follows simply by linearizing both systems around their respective equilibria $\hat{e}, e$. ∎

In particular, if $f'(\hat{x})$ is nonsingular, then either exponential stability or exponential instability must follow, simply by looking at the linearization of the corresponding undelayed system around the appropriate fixed point.

3.8 Stability for Reaction Diffusion Equations

Consider a cone $K \subseteq \mathbb{R}^n$, closed and with nonempty interior, and a reaction diffusion system

$$\dot{x} = D\Delta x + f(q, x). \tag{3.10}$$

The state space of this system is the space of continuous functions $z : \Omega \to \mathbb{R}^n$ defined on a bounded domain $\Omega \subseteq \mathbb{R}^m$ with smooth boundary, under the supremum norm. D is an elliptic matrix (the typical case is $D = I$), the vector Δx stands for $(\Delta x_1, \ldots \Delta x_n)^t$, $f : \Omega \times \mathbb{R}^n \to R^n$, and suitable boundary conditions are defined (Neumann, Dirichlet, Robin). See Mora [76] for details on the existence and uniqueness of solutions of such equations under this framework. We say that system (3.10) is monotone with respect to $\mathcal{K} \subseteq \mathbb{R}^n$ if $x(q) \leq y(q)$ pointwise implies that the solutions $x(t, q), y(t, q)$ of the system satisfy

$$x(t, q) \leq y(t, q), \text{ for every } q \in \Omega, t \geq 0.$$

This is equivalent to asking that the dynamical system induced in $X = C(\Omega, \mathbb{R}^n)$ be monotone with respect to the cone

$$\hat{\mathcal{K}} := \{x \in X \,|\, x(q) \geq_{\mathcal{K}} 0 \text{ for every } q\}.$$

For a thorough introduction to the subject of monotonicity for cooperative reaction diffusion systems, see [101].

Now, if D is such that the system $\dot{x} = D\Delta x$ is monotone with respect to $\hat{K}$ (which is often the case by comparison principles), and if $\dot{x} = f(q, x)$ is monotone for every $q \in \Omega$, then (3.10) is a monotone system as well (see [101], Chapter 7). It will also be assumed later on that (3.10) is strongly monotone, for which suitable sufficient conditions (such as $\dot{x} = f(q_0, x)$ strongly monotone for some q_0) can be found.

It can be verified that the linear case for system (3.10) is of the form

$$\dot{x} = D\Delta x + M(q)x, \tag{3.11}$$

for $M(q)$ an $n \times n$ matrix for every q. In the general case, linearizing the system in the state space around an equilibrium $y(q)$ generates a system as in (3.10) with

$M(q) = \partial f/\partial x(q, y(q))$. The generator of this system in state space is the unbounded operator

$$L : X \to X,\ Lu = D\Delta x + M(q)x.$$

The eigenvalues of L are the solutions of the elliptic system

$$\lambda\omega = D\Delta w + M(q)\omega$$

under the given boundary conditions.

Without further delay, the following is the stability result that is the main purpose of this section. The key to this result is a 'sandwich' argument very common in a monotone setting. This proposition simplifies the argument carried out in Remark 7.6.1 of [101], and in fact generalizes it to the monotone (as opposed to strongly monotone) case.

Proposition 2 *Consider a monotone system (3.10) under the cone K, and let f be independent of q. Then a constant equilibrium $\hat{e}$ of (3.10) is locally attractive (exponentially unstable) if and only if e is a locally attractive (exponentially unstable) equilibrium of the system $\dot{x} = f(x)$.*

Proof.

Observe that the finite dimensional system

$$\dot{x} = f(x) \tag{3.12}$$

is contained in the system (3.10), in the sense that any solution $x(t)$ of (3.12) is also a solution $x(t, q) \equiv x(t)$ of (3.10). Thus in particular, if system (3.12) is exponentially unstable, then there is a solution $x(t)$ that tends exponentially to infinity, and the same solution shows that (3.10) is exponentially unstable.

Let now the finite dimensional system

$$\dot{x} = Mx \tag{3.13}$$

be locally attractive towards e. Let $\epsilon > 0$ be such that $|y - e| < \epsilon$ implies that the solution $x(t)$ of (3.12) starting at y will converge towards e. Since $\mathcal{K}$ has nonempty interior, there exists $p \gg 0$ such that the unit ball in $\mathbb{R}^n$ around the origin is bounded from above by p.

Consider an initial condition $x(0, q)$ of system (3.11) such that

$$e - \frac{\epsilon}{2\,|p|}p \leq x(0, q) \leq e - \frac{\epsilon}{2\,|p|}p$$

for every $q \in \Omega$. It is easy to see that any $x(q, 0)$ contained in a small enough ball around e satisfies this condition. By monotonicity, the solution $x(t, q)$ of (3.10) is bounded from above and below by the solutions at time t of (3.12) starting at $x_1 = e - \frac{\epsilon}{2|p|}p$ and $x_2 = e + \frac{\epsilon}{2|p|}p$ respectively. Since these solutions converge towards e, so does $x(q, t)$ by normality of $\mathcal{K}$ – see the proof of Theorem 11. ∎

We can use the Krein-Rutman theorem for quasimonotone operators in order to strengthen the statement of Proposition 2 in the linear case.

Corollary 5 *Consider a monotone linear system (3.11) with* $M(q) = M$*, for all* q*. Then* $\mathrm{leig}(M) \leq \mathrm{leig}(L)$*. If the system (3.11) is strongly monotone, then* $\mathrm{leig}(M) = \mathrm{leig}(L)$*.*

Proof. Note that any eigenvalue λ of the associated, finite dimensional system (3.13) with eigenvector y, is also an eigenvalue of (3.11) with the corresponding constant eigenvector $\hat{y}$. In particular, $\sigma(M) \subseteq \sigma(L)$ and $\mathrm{leig}(M) \leq \mathrm{leig}(L)$.

Let now (3.11) be strongly monotone. (This implies that (3.13) is also strongly monotone by definition.) By the Perron-Frobenius theorem, there is an eigenvector $\omega > 0$ of M associated to the eigenvalue $\mathrm{leig}(M)$. But then $\hat{\omega} > 0$ is also an eigenfunction of L, with eigenvalue $\mathrm{leig}(M)$. From Theorem 7, the uniqueness of a positive eigenfunction implies that $\mathrm{leig}(L) = \mathrm{leig}(M)$. ∎

Chapter 4

The Small Gain Theorem

4.1 Preliminaries

Controlled Dynamical Systems

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

Definition 4 *A* controlled dynamical system *is a function*

$$\Phi : \mathbb{R}^+ \times X \times U_\infty \to X \tag{4.1}$$

which satisfies the following hypotheses:

1. *Φ is continuous on its first two variables, and the restriction of Φ to the set $\mathbb{R}^+ \times X \times \hat{U}$ is continuous.*

2. *For every $u, v \in U_\infty$ such that $u(s) = v(s)$ for almost every s, $x(t, x_0, u) = x(t, x_0, v)$ for all $x_0 \in X,\ t \geq 0$.*

3. *$x(0, x_0, u) = x_0$ for any $x_0 \in X,\ u \in U_\infty$.*

4. *(Semigroup Property) if $\Phi(s, x, u) = y$ and $\Phi(t, y, v) = z$, then by appending $u|_{[0,s]}$ to the beginning of v to form the input w, it holds that $\Phi(s + t, x, w) = z$.*

See also Sontag [106]. The functions $x(\cdot) = \Phi(\cdot, x_0, u)$ can be regarded as trajectories in time for every x_0, u. We often refer to $\Phi(t, x_0, u)$ as $x(t, x_0, u)$ or simply $x(t)$ if the context is clear. As a simple remark, note that the properties above imply that if $u, w \in U_\infty$ and $u|_{[0,s]} = w|_{[0,s]}$, then $\Phi(s, x, u) = \Phi(s, x, w)$. This can be seen simply by letting $t = 0$ in Property 4.

Output and Feedback Functions

Given a controlled dynamical system (4.1), a Banach space B_Y and a measurable set $Y \subseteq B_Y$, an *output function* is any continuous function $h : X \to Y$. In that case, the pair (Φ, h) consisting of

$$\Phi : \mathbb{R}^+ \times X \times U_\infty \to X, \qquad h : X \to Y \tag{4.2}$$

will be referred to as a *dynamical system with input and output.* Unless explicitly stated, *we will assume throughout this chapter that* $B_Y = B_U,\ Y = U$, in which case h is also called a *feedback function. It will also be assumed that* h *is* $\leq$*-decreasing*, in which case (4.2) is said to be under *negative feedback.*

Monotonicity and Characteristic

Given cones $\mathcal{K}_X \subseteq B_X,\ \mathcal{K}_U \subseteq B_U$, a controlled dynamical system (4.1) is said to be *monotone with respect to* $\mathcal{K}_X, \mathcal{K}_U$ if the following property is satisfied: for any two inputs $u, v \in U_\infty$ such that $u(t) \leq v(t)$ for almost every t, and any two initial conditions $x_1 \leq x_2$ in X, it holds that

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

The partial orders are interpreted here as $\leq_U$ or $\leq_X$ in the obvious manner. If there is no input space, i.e. if the system is autonomous, then we recover the definition of monotonicity from Chapter 3. The cones will usually be omitted if they are clear from the context. We observe also that if $x_1 \leq x_2,\ u_1, u_2 \in U_\infty$ and $u_1(t) \leq u_2(t)$ on $[0, s]$, then $x(s, x_1, u_1) \leq x(s, x_2, u_2)$. To see this, let $\bar{u}_i(t) = u_i(t), 0 \leq t \leq s$, and

$\bar{u}_i(t) = a$ otherwise, for fixed $a \in U$. Then $\bar{u}_1 \leq \bar{u}_2$, and by monotonicity $x(s, x_1, \bar{u}_1) \leq x(s, x_2, \bar{u}_2)$. The conclusion follows by the remark after Definition 1.

A dynamical system (4.1) is said to have an *input to state (I/S) characteristic* $k^X : U \to X$ if for every constant input $\hat{u}(t) \equiv u \in U$, $x(t, x_0, u)$ converges[1] to $k^X(u) \in X$ as $t \to \infty$, for every initial condition $x_0 \in X$. Given a system with input and output (4.2) with $Y = U$, the function $k := h \circ k^X$ will be called the *feedback characteristic* of the system. (This function has been called *input to output characteristic* in previous work, where U and Y are not necessarily equal.) It can be easily shown that if (4.1) is monotone then k^X is a $\leq$-increasing function, see Angeli and Sontag [6]. By invoking Theorem 10, we can prove the following result.

Proposition 3 *Let system (4.1) be monotone with respect to cones $\mathcal{K}_X$, $\mathcal{K}_X$. Suppose that for every constant input $\hat{u}(t) \equiv u \in U$, the system $x(t, x_0, u)$ has 1) precompact orbits, 2) completely continuous time-evolution operators, and 3) a unique equilibrium $k^X(u)$. Then the function $k^X : U \to X$ is an I/S characteristic.*

Proof. This result follows immediately by Theorem 10. ∎

Closed Loop Trajectories

Consider a system (4.2) and assume that $B_Y = B_U$, $Y = U$. Given a vector $x_0 \in X$, and a continuous function $x : \mathbb{R}^+ \to X$, it will be said that $x(t)$ is a *closed loop trajectory of (4.2) with initial condition* x_0 if $x(0) = x_0$ and $x(t) = \Phi(t, x_0, h \circ x(\cdot))$, for all $t \geq 0$.

Definition 5 *Suppose that (4.2) is such that, for each $x_0 \in X$, there is a unique continuous closed loop trajectory $x(t)$ so that $x(0) = x_0$. The function*

$$\Psi : \mathbb{R}^+ \times X \to X, \ \ \Psi(t, x_0) := x(t) \tag{4.3}$$

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

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[1]This definition differs slightly with that in Angeli and Sontag [6], in that stability of the attractor $k^X(u)$ is not assumed. Nevertheless see the comments after Theorem 11.

The semiflow condition for Ψ is actually guaranteed by the unique closed loop trajectory assumption. To see this, let $x(t)$ be an absolutely continuous closed loop trajectory, and $y_0 = x(t_0)$. Then the function $w(t) = x(t + t_0)$ can be shown to be itself an absolutely continuous closed loop trajectory, by using the semiflow condition for Φ. Therefore $w(t) = \Psi(t, y_0)$, and $\Psi(s_0, y_0) = z_0$ implies $x(t_0 + s_0) = w(s_0) = z_0$. To prove the continuity of Ψ on its second argument, one may nevertheless need to assume stronger continuity conditions than are stated in Definition 4. While the main result will not assume the existence or uniqueness of closed loop trajectories for any $x_0 \in X$, the fact that the closed loop system Ψ is well defined will be guaranteed in all our applications, since we will start off with an autonomous dynamical system in the first place (see the introduction).

The General Assumptions

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

Let B_X, B_U be arbitrary Banach spaces ordered by cones $\mathcal{K}_X, \mathcal{K}_U$, and let (4.1) be a controlled dynamical system with states in $X \subseteq B_X$ and input values in $U \subseteq B_U$. Let $h : X \to U$ be a given feedback function. The following general hypotheses will be used throughout this chapter:

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

H2 U is closed and convex. Moreover, for every bounded set $C \subseteq U$, there exist $a, b \in U$ such that $a \leq C \leq b$.

H3 $X \subseteq B_X$ and $U \subseteq B_U$ satisfy the ϵ-box property.

H4 $\Phi(t, x_0, u)$ is monotone, with a *completely continuous* I/S characteristic k^X. Furthermore, h is a $\leq$-decreasing feedback function that sends bounded sets to bounded sets.

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

A notion related to H3 is proposed in Smith [101]: $x \in X$ *can be approximated from below* if there exists a sequence $\{x_n\}$ in X such that $x_1 < x_2 < x_3 < \ldots$ and x_n converges towards x as n tends to infinity. It is easy to see that H3 doesn't imply boundedness from below for every $x \in X$, for instance considering $X = [0, 1],\ x = 0$ and the usual order. It also holds that approximability from both below and above for all $x \in X$ doesn't imply the ϵ-property for X. An example for this is

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

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

Property H3 can also be compared with the definition in Hirsch [49] of the *order topology* in a Banach space B, namely the topology generated by the order intervals $(x - \lambda e, x + \lambda e)$, where $x \in B, \lambda > 0$ arbitrary, and $e \in B,\ e \gg 0$ is fixed. But under the hypothesis that the underlying cone $\mathcal{K}_B$ is normal, it holds that the usual topology and the order topology are the same. To see this, let $x - \lambda e \ll y \ll x + \lambda e$. Then by normality of $\mathcal{K}_B$, $|y - x + \lambda e| \leq M 2\lambda\, |e|$, and so $|y - x| \leq 2M\lambda\, |e| + \lambda\, |e|$. By making λ small enough one can fit an order interval inside any open ball in B. The assertion follows.

In particular, consider $B_U = \mathbb{R}^m, B_X = \mathbb{R}^n$, $\mathcal{K}_U$ and $\mathcal{K}_X$ orthant cones. Let U be a closed box (not necessarily bounded), and let X be either an open set or an interval (bounded or not) that contains some or all of its sides. Given a monotone system $\dot{x} = f(x, u),\ u = h(x)$ with characteristic, f continuous and locally Lipschitz on x, and h $\leq$-decreasing and continuous, conditions H1,H2,H3,H4 are necessarily satisfied. Indeed, the only condition that still needs verification is that k^X is (completely) continuous; this has been done in [6].

4.2 The Small Gain Theorem

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

Theorem 11 (CICS) *Consider a monotone system $\Phi(x,t,u)$ with a continuous I/S characteristic k^X, under hypotheses H1,H3. If $u(t)$ converges to $\bar{u} \in U$ as $t \to \infty$, then $x(t,x_0,u)$ converges to $\bar{x} := k^X(\bar{u})$, for any arbitrary initial condition x_0.*

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

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

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

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

it follows that

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

where M is a normality constant for C_X. Thus

$$|x(t,x_1,u_1) - \bar{x}| \leq (4M+2)\epsilon,$$

for all $t \geq T_2$. This proves the assertion. ∎

Several remarks are in order. First, this theorem is an infinite-dimensional generalization of Proposition V5, number 2) in [6]. In addition, even in the finite dimensional case, it holds using weaker assumptions on the characteristic (in [6], an additional stability property is imposed on $k^X(u)$, for every fixed $u \in U$). See [92] for a counterexample showing that, in the absence of stability or monotonicity, systems with characteristics may fail to exhibit the CICS property. Conclusion 1) in Proposition V5 of [6], namely the stability of the system $x(t, x, u)$ for fixed $u(t) \to \bar{u}$, may not hold here in general. Nevertheless it holds under relatively weak additional hypotheses: if a, b are such that $a \ll \bar{u} \ll b$, and k^X is $\ll$-increasing, then $(k^X(a), k^X(b))$ is an open neighborhood of $\bar{x}$, and by monotonicity $x(t, x_0, v) \in (k^X(a), k^X(b))$ for any $t \geq 0$, whenever $x_0 \in (k^X(a), k^X(b))$ and $v(t) \in (a, b)$ for all t. Thus stability holds for instance if U is open and k^X is $\ll$-increasing. A similar argument shows that stability holds if k^X is an open function. CICS is a strong property of systems with both characteristic and monotonicity, and it will be used frequently in what follows.

The Small Gain Theorem

Monotone systems have very useful global convergence properties (see Theorem 10 and Theorem 8, but many gene and protein interaction networks are not themselves monotone. We will consider the closed loop of a monotone controlled system (when it is defined), forming an autonomous system in which nevertheless the monotonicity will be of use.

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

Lemma 13 *Suppose given a system (4.1) under hypotheses H3,H4. Let $u \in U_\infty$, and let v be a lower (upper) hyperbound of u. Then for any arbitrary initial condition $x_0 \in X$, $k^X(v)$ is a lower (upper) hyperbound of $x(\cdot) = \Phi(\cdot, x_0, u)$.*

Proof. Suppose v is a lower hyperbound of $u(\cdot)$, the other case being similar, and let $v_1, v_2, \ldots \to v$ and $t_1 < t_2 < \ldots \to \infty$ be as above. For every positive integer n, let

$y_n, z_n \in X$ be such that $\mathrm{diam}(y_n, z_n) < 1/n$ and $V_n := [y_n, z_n] \cap X$ is a neighborhood of $k^X(v_n)$ (such y_n, z_n exist by H3).

For $n \geq 1$ let

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

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

We use a result from Dancer [19], slightly adapted to our setup, which will provide a simple criterion to study the global attractivity of discrete systems

$$x_{n+1} = T(x_n) \tag{4.4}$$

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

Lemma 14 *Let K be a closed, normal cone with nonempty interior defined on a Banach space B, and let $M \subseteq B$ satisfy axiom H2 (i.e. with U replaced by M). Let $T : M \to M$ be $\leq$-increasing and completely continuous. Suppose also that the system (4.4) has bounded forward orbits, and that there is a unique fixed point $\bar{x}$ of T. Then all solutions of (4.4) converge towards $\bar{x}$.*

Proof. It is easy to see that a set $C \subseteq B$ is order-bounded (in the sense of Dancer [19]) if and only if it is bounded in B. Since T sends bounded sets to precompact sets, it also holds that the orbits of (4.4) are precompact in M.

The same argument can now be used as in Lemma 1 of Dancer [19]: given $x \in M$, let $\omega(x) \leq u$ for some $u \in U$, using H2. It then holds that $\omega(x) \leq \omega(u)$ pointwise. Let similarly $\omega(u) \leq \omega(z)$, for $z \in M$, and let

$$S = \{y \in M \,|\, \omega(x) \leq y \leq \omega(z)\}.$$

Then S is nonempty, closed, and convex, again using H2. By the Schauder fixed point, one finds $f \in S$ such that $T(f) = f$. But necessarily $f = \bar{x}$. One similarly concludes $\bar{x} \leq \omega(x) \leq \bar{x}$, and thus that $\omega(x) = \{\bar{x}\}$.

∎

It is a well-known result that if $T : \mathbb{R} \to \mathbb{R}$ is a continuous, bounded, nonincreasing function, then system (4.4) is globally attractive towards its unique fixed point $\bar{x}$ if and only if the equation $T^2(x) = T(T(x)) = x$ has only the trivial solution $\bar{x}$. The following consequence of the above lemma generalizes this result to an arbitrary space (see also Kulenovic and Ladas [64]).

Lemma 15 *Assume the same hypotheses of Lemma 14, except that $T : M \to M$ is $\leq$-decreasing instead of $\leq$-increasing. Then system (4.4) is globally attractive towards $\bar{x}$ if and only if the equation $T^2(x) = x$ has only the trivial solution $\bar{x}$.*

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

Definition 6 *We say that a system (4.2) with I/S characteristic k^X satisfies the* small gain condition *if the following properties hold:*

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

The terminology "small gain" arises from control theory. Classical small-gain theorems (cf. [26, 94, 95, 116]) show stability based on the assumption that the closed-loop gain (meaning maximal amplification factor at all frequencies) is less than one, hence the name. These results are formulated in terms of appropriate Banach spaces of causal and bounded signals, and amount to the fact that the open-loop operator $I + F$ is invertible, and thus solutions exist in these spaces, provided that the closed-loop operator F has operator norm < 1. The characteristic k in the current setup plays an analogous role to F; observe that, for linear k, norm < 1 would guarantee stability. Versions with "nonlinear gains" were introduced in [74], and the most useful ones were developed by [56] on the basis of the notion of "input to state stability" from [105]; see also the related paper [52, 107]. The current formulation is from [6].

The main result of this chapter, denoted as the *small gain theorem* or SGT for short, gives sufficient conditions for the bounded closed loop trajectories of a system (Φ, h), under negative feedback, to converge globally to an equilibrium. Observe that in view of Lemma 15, and under the hypotheses H1,H4, a system (4.2) satisfies the small gain condition if and only if the system $u_{n+1} = k(u_n)$ is globally attractive to an equilibrium. The two statements will be used interchangeably in the applications.

Theorem 12 (SGT) *Let (4.2) be a system satisfying the assumptions H1, H2, H3, H4, and suppose that the small gain condition is satisfied. Then all bounded closed loop trajectories of (4.2) converge towards $\bar{x} = k^X(\bar{u})$.*

Proof. Let $x_0 \in X$ be an arbitrary initial condition, and let $x(\cdot)$, $u = h \circ x$ be a bounded closed loop trajectory and its corresponding feedback, respectively. Let α be a lower hyperbound of $u(\cdot)$. Such an element always exists: by H3 the range of $u(\cdot)$ is bounded, and by H2 there exist $\alpha, \beta \in U$ that bound the bounded function u entirely from below and above, respectively. Then by Lemma 13, $k^X(\alpha)$ and $k^X(\beta)$ are lower and upper hyperbounds of x, respectively. Since h is a continuous, $\leq$-decreasing function, it is easy to see that $k(\alpha)$, $k(\beta)$ are upper and lower hyperbounds of u respectively. Similarly, one concludes that $k^2(\alpha)$, $k^2(\beta)$ are lower and upper hyperbounds of u respectively, by using Lemma 13 once more. By repeating this procedure twice at a time, it is deduced that $k^{2n}(\alpha)$, $k^{2n}(\beta)$ are also lower and upper hyperbounds of $x(t)$, for every natural n.

Now, $k^{2n}(v)$ converges as $n \to \infty$ towards $\bar{u}$ for all $v \in U$ by H4, the small gain condition and Lemma 14. But this implies that u converges to $\bar{u}$. This is proven as follows: given $\epsilon > 0$, there is n large enough so that

$$\left|k^{2n}(\alpha) - \bar{u}\right| < \epsilon, \ \left|k^{2n}(\beta) - \bar{u}\right| < \epsilon.$$

By definition of lower and upper hyperbound, there are $a, b \in U$ and $T \geq 0$ large enough such that $\left|a - k^{2n}(\alpha)\right| < \epsilon$, $\left|b - k^{2n}(\beta)\right| < \epsilon$ and for every $t \geq T: \ a \leq u(t) \leq b$. The normality of the cone $\mathcal{K}_U$ is used in the same way as in the proof of CICS: for M a normality constant of $\mathcal{K}_U$, it holds that

$$|u(t) - a| \leq M\,|b - a| < 4\epsilon M,$$

and so $|u(t) - \bar{u}| \leq 4\epsilon M + 2\epsilon$, for all $t \geq T$.

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

Corollary 6 *Let (4.2) be a system satisfying assumptions H1,H2,H3,H4 and the small gain condition. If the closed loop system $\Psi(t,x)$ is well defined and has bounded solutions, and the if equation $k^2(u) = u$ has a unique solution, then $\Psi(t,x)$ has a unique globally attractive equilibrium $\bar{x}$.*

Proof. It is sufficient to observe that every solution $x(t)$ of the closed loop system $\Psi(t,x)$ is in particular a closed loop trajectory, and to invoke Theorem 12. ∎

The statement of Theorem 12 in [6] is restricted to single input, single output systems in finite dimensions and doesn't address the equivalence provided by Lemma 15.

Finally, the same proof as above can be carried out for the case in which h is $\leq$-increasing (rather than $\leq$-decreasing), assuming simply that there is a unique fixed point $\bar{u}$ of k. Nevertheless this latter result is not very strong, since it follows from weaker hypotheses. See for instance Ji Fa [55], and de Leenheer, Angeli and Sontag [22].

4.3 Stability in the Small Gain Theorem

In this section we turn to the question of stability for the closed loop trajectories considered in Theorem 12. Given a vector $x_0 \in X$, we say that a system (4.2) has *stable closed loop trajectories around* x_0 if for every $\epsilon > 0$ there is $\delta > 0$ such that $|z_0 - x_0| < \delta$ implies $|z(t) - x_0| < \epsilon$, $t \geq 0$, for any closed loop trajectory $z(t)$ with initial condition z_0. Of course, if the closed loop system $\Psi(t,x)$ is well defined, then this is equivalent to the stability of $\Psi(t,x)$ at x_0. The basic idea is given by the following lemma.

Lemma 16 *Let (4.2) be a monotone system with characteristic k^X and a $\leq$-decreasing feedback function h. Let $y \ll z$ in X be such that $k^X h(y), k^X h(z) \in (y,z)$. Then any closed loop trajectory $x(t)$ of (4.2), with initial condition $x_0 \in [k^X h(z), k^X h(y)]$, satisfies $x(t) \in (y,z),\ t \geq 0$.*

Proof. Let $k^X h(z) \leq x_0 \leq k^X h(y)$, and let $x(t)$ be a closed loop trajectory of (4.2) with initial condition x_0. Suppose that the conclusion doesn't hold, and let by contradiction

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

It is stressed that as $x(0) \in (y,z)$, $x(\cdot)$ is continuous, and the interval (y,z) is open, it holds that $x(t_0) \notin (y,z)$. Nevertheless $u(\cdot) = h \circ x(\cdot)$ satisfies $h(z) \leq u(t) \leq h(y)$ for $t < t_0$, and therefore also $h(z) \leq u(t_0) \leq h(y)$ by continuity. Then by monotonicity

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

for all $t \leq t_0$, and in particular,

$$y \ll k^X h(z) \leq x(t_0) \leq k^X h(y) \ll z,$$

which is a contradiction. ∎

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

Define $\gamma(x) := k^X h(x)$. The result in Lemma 16 is applied systematically in the following proposition to guarantee the stability of the closed loop.

Lemma 17 *Under the hypotheses of Theorem 12, let $\bar{x} = k^X(\bar{u})$, and let $\{y_n,\}, \{z_n\}$ be sequences in X such that $y_n, z_n \to \bar{x}$ as $n \to \infty$. Assume also that for every n, $\gamma(z_n) \ll \bar{x} \ll \gamma(y_n)$ and $\gamma(y_n), \gamma(z_n) \in (y_n, z_n)$. Then (4.2) has stable closed loop trajectories around $\bar{x}$.*

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

The following lemma provides a simple criterion for the application of Lemma 17.

Lemma 18 *Under the hypotheses of Theorem 12, suppose that k^X is $\ll$-increasing and h is $\ll$-decreasing. Suppose that there exists $z \in$ int X such that $\bar{x} \ll k^2(z) \ll z$. Then (4.2) has stable closed loop trajectories around $\bar{x}$.*

Proof.

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

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

It is easy to see how this implies that

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

using the fact that γ^2 is $\ll$-increasing. By Lemma 15, $y_n := \gamma^{2n}(y)$ and $z_n := \gamma^{2n}(z)$ converge to $\bar{x}$, and thus these sequences satisfy the hypotheses of Lemma 17. ∎

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

Theorem 13 *Under the hypotheses of Theorem 12, let $B_U = \mathbb{R}$ or $B_U = \mathbb{R}^2$, and let $U \subseteq B_U$ be a (not necessarily bounded) closed interval with positive measure. If k^X is $\ll$-increasing and h is $\ll$-decreasing, then (4.2) has stable closed loop trajectories around $\bar{x}$.*

Proof. Recall the notation $k(u) = hk^X(u)$. It is only needed to prove in both cases that there exists $z \in X$ such that $\bar{x} \ll k^2(z) \ll z$, by Lemma 18. In the case $B_U = \mathbb{R}$, let $c \in \operatorname{int} U$, $c > \bar{u}$. Then necessarily $\gamma^2(c) < c$, since otherwise the sequence $c \leq \gamma^2(c) \leq \gamma^4(c) \leq \ldots$ would not converge towards $\bar{u}$. Using the fact that k^X is $\ll$-increasing, it follows that $z := k^X(c)$ satisfies $\bar{x} \ll \gamma^2(z) \ll z$.

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

We want to find $c \gg_{(1,1)} 0$ such that $\kappa^2(c) \ll_{(1,1)} c$, since then the vector $z := k^X \phi^{-1} c$ will satisfy $\bar{u} \ll \gamma^2(z) \ll z$. Suppose by contradiction that there is no such point. By global attractivity, for any $u \gg_{(1,1)} 0$ it must hold $\kappa^2(u) \not\gg_{(1,1)} u$. Then the function $\alpha(u) := \kappa^2(u) - u$ is such that

$$\alpha(\mathbb{R}^+ \times \mathbb{R}^+) \subseteq (\mathbb{R}^+ \times \mathbb{R}^-) \cup (\mathbb{R}^- \times \mathbb{R}^+).$$

But if there existed $v, w >_{(1,1)} 0$ such that $\alpha(v) \in \mathbb{R}^+ \times \mathbb{R}^-$, $\alpha(w) \in \mathbb{R}^- \times \mathbb{R}^+$, then by joining the points v and w with a line one would find a point $q >_{(1,1)} 0$ such that $\alpha(q) = 0$ by continuity, that is, a nonzero fixed point of $\kappa^2 u = u$. This contradicts attractivity. Assume therefore that $\kappa^2(u)_1 \leq u_1,\ \kappa^2(u)_2 \geq u_2$ holds for all $u \gg_{(1,1)} 0$, the other case being similar. Then $0 < u_2 \leq \kappa^2(u)_2 \leq \kappa^4(u)_2 \leq \ldots$, which also violates attractivity. The conclusion is that $0 \ll \kappa^2(c) \ll_{(1,1)} c$ for some c. ∎

The following corollary of Lemma 18 strengthens the hypotheses of Theorem 12 to imply the stability of the closed loop in arbitrary input spaces. Thus, instead of assuming that the function $u \to k(u)$ defines a globally attractive system and is $\leq$-decreasing, we will assume that its *linearization* T around $\bar{u}$ defines a globally attractive system and that $u < v$ implies $T(u) \gg T(v)$. The linearization is taken here in the usual sense of Frechet differentiation.

Corollary 7 *Under the hypotheses of Theorem 12, suppose that k^X is $\ll$-increasing and h is $\ll$-decreasing. Assume that the linear operator $T = k'(\bar{u})$ is well defined* *and compact, and that i)* $u_{n+1} = T(u_n)$ *is a globally attractive discrete system, ii)* $T(K_U - \{0\}) \subseteq -int\ K_U$*. Then (4.2) has stable closed loop trajectories around* $\bar{x}$*.*

Proof. By i), the operator $T^2 u = (k^2)'(u)$ defines a globally attractive discrete system. Hence the point spectrum of T^2 is contained in the open complex unit ball. By ii), it holds that T^2 is a strongly monotone operator, and in particular $\lambda := \rho(T) > 0$. By the Krein Rutman theorem, there is $v \gg 0$ such that $T^2(v) = \lambda v$. But since $0 < \lambda < 1$, it holds that $0 \ll T^2(v) \ll v$. Let $|v| = 1$ and $\epsilon > 0$ be such that

$$0 \ll B(\epsilon, T^2(v)) \ll B(\epsilon, v)$$

pointwise in U. Letting $\delta > 0$ be small enough that $\left|k^2(\bar{u} + u) - T^2(u) - \bar{u}\right| < \epsilon\,|u|$ whenever $|u| < \delta$, it follows that

$$\bar{u} \ll k^2(u + \lambda\delta v) \ll \bar{u} + \delta v.$$

The conclusion follows from Lemma 18. ∎

An Application of Theorem 13

The local stability of finite-dimensional systems can usually be verified by calculating the eigenvalues of the linearized system around the equilibrium. Nevertheless further understanding of the stability of the system is difficult to extract in this way, especially in the case of large-scale systems and variable (or unknown) parameters. One finite-dimensional illustration of Theorem 13 can be found in Section VII of [6], where global attractivity is proven for a model of MAP kinase cascade dynamics. We prove here that this system is actually asymptotically stable. The fact that the model satisfies the hypotheses of Theorem 12 is mostly guaranteed from the last paragraph of Section 4.1 of this chapter. It will be assumed here, since later examples will treat these hypotheses at length.

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

$$\begin{aligned}
\dot{x} &= \theta_1(1-x) - u\theta_2(x) \\
\dot{y} &= \theta_3(1-y-z) - (1-x)\theta_4(y) \\
\dot{z} &= (1-x)\theta_5(1-y-z) - \theta_6(z) \qquad h(x,y,z,Y,Z) = \frac{K}{1+\frac{g_1+Z}{g_2+Z}}, \\
\dot{Y} &= \theta_7(1-Y-Z) - z\theta_8(Y) \\
\dot{Z} &= z\theta_9(1-Y-Z) - \theta_{10}(Z),
\end{aligned} \tag{4.5}$$

where $\theta_i(x) := a_i x/(b_i + x)$, for positive constants a_i, b_i, $K > 0$, and $g_2 > g_1 > 0$. It is shown in [6] that (4.5) is monotone with respect to the cones $\mathbb{R}^+$ for the input, and $\mathbb{R}^- \times \mathbb{R}^- \times \mathbb{R}^+ \times \mathbb{R}^- \times \mathbb{R}^+$ for the states. It is only needed to verify that k^X is $\ll$-increasing and h is $\ll$-decreasing, the latter of which can be easily checked. To verify the former, note that the system is a cascade of three subsystems $x \to (y,z) \to (Y,Z)$ with characteristic, and that it is enough to verify that each of the characteristic functions is $\ll$-increasing. This is done for the third subsystem, the other two being very similar.

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

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

and all θ_j are strictly increasing, then Y cannot decrease without Z increasing, and vice versa. Putting all together, one concludes that $z_1 < z_2$ implies $Z_1 < Z_2,\ Y_1 > Y_2$, so that in particular $k^{(Y,Z)}$ is $\ll$-increasing. A similar argument for the remaining subsystems shows that the characteristic of (4.5) is $\ll$-increasing, as desired, and stability of (4.5) follows.

Chapter 5

Applications

5.1 Delay Systems: An Overview

The abstract treatment we have followed allows us to specialize to situations that generalize the single input, single output setup considered in [6]. From now on, we will rather consider the introduction of delay terms in finite-dimensional systems of ODEs. One example of such systems is

$$\dot{x}(t) = Ax(t-r) + Bx(t), \tag{5.1}$$

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

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

$$\dot{x}(t) = f(x_t),\ x_0 = \phi, \tag{5.2}$$

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

Similar comments apply to the controlled system

$$\dot{x} = f(x_t, \alpha(t)), \tag{5.3}$$

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

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

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

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

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

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

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

the function f cannot have as argument an input value

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

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

Definition 7 *A* delay dynamical system *consists of a tuple (X, U, f), $f : X \times U \to \mathbb{R}^n$, and X, U as above for some $X_0 \subseteq \mathbb{R}^n$, $U_0 \subseteq \mathbb{R}^m$, with the following property: for any initial condition $\phi \in X$ and any measurable, locally bounded $\alpha : \mathbb{R}^+ \to U$, there is a unique maximally defined, absolutely continuous function x such that*

$$\dot{x}(t) = f(x_t, \alpha(t)) \text{ for almost every } t,\ x_0 = \phi. \tag{5.4}$$

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

In the case that $U = C([-r_{\text{input}}, 0], U_0)$, note that for a discontinuous input

$$u : \mathbb{R}^+ \to U_0,$$

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

Lemma 19 *Let $u : [-r_{\text{input}}, \infty) \to U_0$ be a continuous function. If*

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

or if

$$B_U = C([-r_{\text{input}}, 0], \mathbb{R}^m),$$

then the function $\alpha : [0, \infty) \to B_U$, defined as $\alpha(t) := u_t$, is a well defined input in U_∞.

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

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

To prove the second statement, and assuming without loss of generality that the τ_i are pairwise distinct, consider a continuous partition of unity

$$\nu_1 \ldots \nu_k : [-r_{\text{input}}, 0] \to [0, 1]$$

such that $\nu_j(\tau_j) = 1$ for all $j = 1 \ldots k$ and $\nu_j(\tau_i) = 0$, $i \neq j$. Let

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

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

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

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

∎

The second statement of the above lemma is useful when considering a system (5.3) in which $f(\phi, \alpha)$ only depends on the values of ϕ at discrete times $\tau_1, \ldots, \tau_k$, that is, in the case of point delays. In this case, given an input u in U_0, the function u_t can be replaced by the input α in Lemma 19 for all practical purposes.

In the Appendix II the question is addressed as to which functions $f : X \times U \to \mathbb{R}^n$ generate a well defined delay dynamical system. The main result is the following theorem, where X_0, U_0, X, U are as described in the end of Section 4.1.

Theorem 14 *Let $f : X \times U \to \mathbb{R}^n$ be continuous and locally Lipschitz on X, locally uniformly on U. Let also $f(\phi, C)$ be bounded, for any $\phi \in X$, $C \subseteq U$ closed and bounded. Then the system (5.4) has a unique maximally defined, absolutely continuous solution $x(t)$, for every input $\alpha(t)$ and every initial condition $\phi \in X$.*

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

Lemma 20 *Let U_0 be a closed box (possibly unbounded), and let X_0 be open or, in the case of $\mathcal{K}_{X_0}$ being an orthant cone, a box including some or all of its faces. Let $\mathcal{K}_{U_0} \subseteq \mathbb{R}^m, \mathcal{K}_{X_0} \subseteq \mathbb{R}^n$ be closed cones with nonempty interior, $r_{\text{input}}, r_{\text{state}} \geq 0$, B_X, B_U as in Definition 7, and let $\mathcal{K}_X := \{\phi \in B_X |\ \phi(s) \in \mathcal{K}_{X_0}\ \forall s\}$, $\mathcal{K}_U := \{\alpha \in B_U |\ \alpha(s) \in \mathcal{K}_{U_0}$ a.e. $s\}$. Then conditions H1,H2 and H3 in the general hypotheses are satisfied for $X, U, \mathcal{K}_X, \mathcal{K}_U$.*

Proof. By Lemmas 2 and 3, $\mathcal{K}_{X_0}, \mathcal{K}_{U_0}$ are normal. Let M, N be normality constants for $\mathcal{K}_{X_0}, \mathcal{K}_{U_0}$ respectively. If $0 \leq \phi \leq \psi$ in X, that is $0 \leq \phi(s) \leq \psi(s)$ in X_0 for every s, then it holds that $|\phi(s)| \leq M\,|\psi(s)|$, for every s. This asserts the normality of $\mathcal{K}_X$ with normality constant M. One proves similarly that $\mathcal{K}_U$ is normal.

Let $a \in \mathbb{R}^m$ bound the unit ball from above (see Section 4.1). Then the constant function $\hat{a}$ bounds the unit ball in B_U. This implies that $\mathcal{K}_U$ has nonempty interior. For $\alpha \in B_U$, the function

$$d(\alpha) := \text{ess sup}\,\{\text{dist}(\alpha(s), \mathcal{K}_{U_0})|\; s \in [-r_{\text{input}}, 0]\}$$

is continuous, which implies that $\mathcal{K}_U = d^{-1}(0)$ is closed. The same argument applies to $\mathcal{K}_X$.

If X_0 is open, Range ϕ will remain a finite distance away from X_0^c, for every $\phi \in X$. Thus there is an open neighborhood around ϕ contained in X, which shows that X is open and satisfies the ϵ-box property. Let $s = (s_1, \dots s_n)$, $s_i = \pm 1$ for all i, defining an orthant cone in a natural way as in Section 4.1. Let X be a box containing some or all of its sides. Consider a given state $\phi \in X$ and $\epsilon > 0$, and let

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

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

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

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

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

Given $\phi \in X$, let $\phi_i(s) := \pi_i(x(s)),\; i = 1, 2.$. See Figure 5.1 for an illustration of these two functions. It is clear that π_1 and π_2 are both continuous functions. Then $(y =)\phi_1,\; (z =)\phi_2 \in X$ by construction, and

$$\text{diam}[\phi_1, \phi_2] = |\phi_2 - \phi_1| \leq |2\eta(1 \dots 1)| = 2\eta\sqrt{n} < 3\eta\sqrt{n} \leq \epsilon.$$

Also, it is easy to see that

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

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

In the case $B_U = C([-r_{\text{input}}, 0], \mathbb{R}^m)$, the same proof above applies to prove H3 for U, even if some or all of its sides are missing. However, if $B_U = L^\infty([-r_{\text{input}}, 0], \mathbb{R}^m)$,

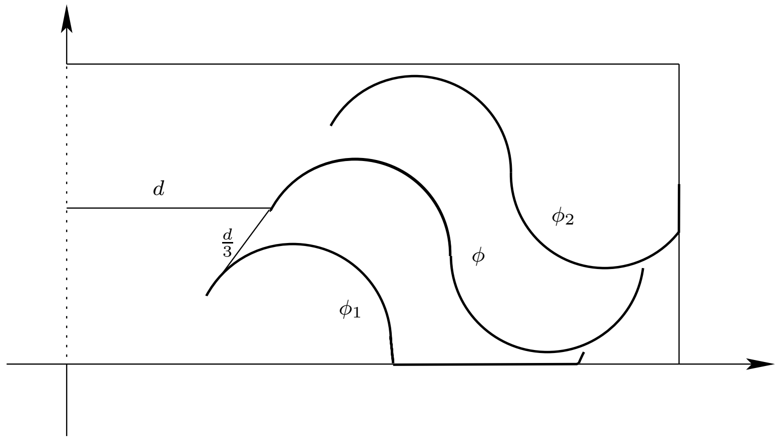

Figure 5.1: Shown in the picture is the box X_0 with one open and three closed faces, and $\phi_1 \leq \phi \leq \phi_2$ in bold. Here $d = \text{dist}(\text{Range } \phi, \partial X - X_0)$, and $\eta = d/(3\sqrt{2})$. Note that $|\phi(0) - \phi_1(0)| = |\eta(1,1)| = d/3$.

then for a given $\alpha \in U$ the distance between the range of α and $\partial U \setminus U$ may well be zero. One uses the fact that U is closed to show that for $\eta = \frac{1}{2\sqrt{m}}\epsilon$, $\pi_1, \pi_2 : U_0 \to U_0$ are well defined. Since the π_i are continuous, $\alpha_i(s) = \pi_i(\alpha(s))$ are measurable functions. The rest of the proof that U satisfies H3 follows similarly as above.

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

We give a convenient criterion to check for monotonicity in the orthant cone case, which is based on Theorem 1.1 of Smith [101]. Refer to Figure 5.2 for an illustration of this criterion. We give only a sketch of the proof, which is along the same lines as that for Lemma 5.

Proposition 4 (Monotonicity Criterion) *Let (5.3) be a delay system, and let* $\mathcal{K}_X$

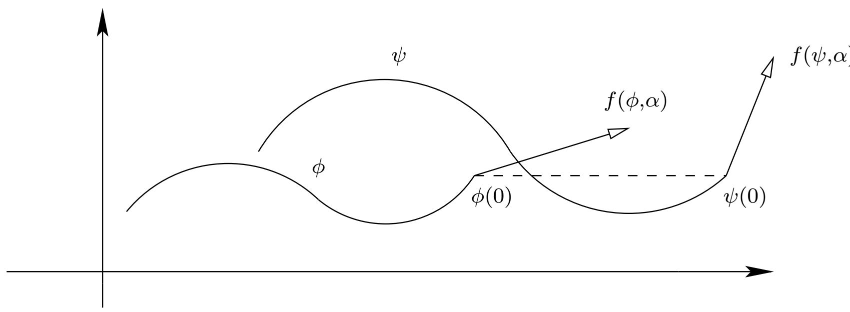

Figure 5.2: Monotonicity Criterion. Illustrated are two states $\phi, \psi : [-r_{\text{state}}, 0] \to \mathbb{R}^2$ with $\phi \leq \psi$ and $\phi_2(0) = \psi_2(0)$. In the cooperative case, the criterion requires that $f_2(\phi, \alpha) \leq f_2(\psi, \alpha)$.

be the orthant cone defined by the tuple $s = (s_1 \dots s_n)$. Assume that i) $\alpha \to f(\phi, \alpha)$ is an increasing function, for every $\phi \in X$, and that ii) for every $\alpha \in U$, $\phi \leq \psi$, and if $\phi_i(0) = \psi_i(0)$ for some i, it holds that $s_i f_i(\phi, \alpha) \leq s_i f_i(\psi, \alpha)$. Then system (5.3) is monotone with respect to its underlying cones.

Sketch of Proof. Let α, β be two inputs, and assume $\alpha(t) \leq \beta(t)$ for every t (if this only holds a.e. t, one can change the value of these functions at a set of measure zero). Let $h_1(t, \phi) := f(\phi, \alpha(t))$, $h_2(t, \phi) := f(\phi, \beta(t))$. Theorem 5.1.1 of Smith [101] cannot be applied directly, even in the cooperative case, since the functions h_i are not necessarily continuous on t. Nevertheless by writing the absolutely continuous solution $x(t, \phi; h_i)$ of $\dot{x} = h_i(t, x_t)$ as an integral (see Bensoussan et al. [9]) one shows that, for $e \gg 0$ in X and $h_i^{\epsilon}(\phi, t) := \epsilon e + h_i(\phi, t)$, $x(t_0, \phi; h_i^{\epsilon})$ converges towards $x(t_0, \phi; h_i)$ as $\epsilon \to 0$ for each t_0. The rest of the argument is as in [101] or Lemma 5: define $e := (s_1, s_2, \dots s_n) \gg 0$. Show by contradiction that $x(t, \phi; h_1) \ll x(t, \phi; h_2^{\epsilon})$ for all t and small ϵ, and let ϵ tend to zero. ∎.

Suppose that the delay system (X, U, f) allows an I/S characteristic $k^X : U \to X$. Note that $\phi = \Phi(t, k^X(\alpha), \hat{\alpha})$ is constant over t, and thus that any solution of (5.3) with constant input $\hat{\alpha}$ starting at $k^X(\alpha)$ must satisfy $x_t = k^X(\alpha)$ for all $t \geq 0$. This easily implies that $k^X(\alpha)$ is a constant function, for every α. Hence, since k^X has a finite dimensional range, it is easy to verify when it is completely continuous, namely the image of every bounded set should be bounded. One can also think of k^X as having values in X_0, and when evaluating $u_{n+1} = k(u_n)$ it is sufficient to consider constant initial conditions.

In the applications of this chapter the feedback function $h : X \to U$ will be defined as $h(\phi)(s) = h_0(\phi(s))$, for some $h_0 : X_0 \to U_0$. In such case, it holds that $\bar{u}$ is itself a constant vector. Also note that if $z \in \mathbb{R}^m$ is such that $\bar{u} \ll k^2(z) \ll z$, then the constant function $\hat{z}$ has this property in U. Therefore one can apply Theorem 13 to prove stability in the context of delay systems.

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

As a first example of SGT for delay systems consider the following toy model, from Stepan [108]. It is linear, so that many different (and more comprehensive) approaches are available. It is included here only in order to illustrate how to use the small gain theorem for delay systems in practice.

Example 1:

Consider the system

$$\begin{aligned} \dot{x}_1(t) &= -a_{11}x_1(t) - a_{12}x_2(t-\xi) \\ \dot{x}_2(t) &= a_{21}x_1(t-\tau) - a_{22}x_2(t), \end{aligned} \tag{5.5}$$

where $a_{11}, a_{12}, a_{21}, a_{22}$ are positive real numbers, $\xi, \tau \geq 0$. Define for instance $X_0 = (\mathbb{R}^+)^2$. If $x_t \leq z_t$ componentwise, and $x_2(t) = z_2(t)$, then certainly

$$\dot{z}_2(t) - \dot{x}_2(t) = a_{21}z_1(t-\tau) - a_{22}z_2(t) - a_{21}x_1(t-\tau) + a_{22}x_2(t) \geq 0.$$

If the same were true for x_1, z_1, then one could conclude that (5.5) is cooperative, by Theorem 4. Since this is not the case, consider the controlled system

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

whose closed-loop system is (5.5). A natural choice for the delays is $r_{\text{state}} = \tau$, $r_{\text{input}} = \xi$. This system satisfies the hypotheses of Proposition 4, provided that the cone in

$B_U = C([-r_{\text{input}}, 0], \mathbb{R})$ is defined as $\mathcal{K}_U = \{\phi | \, \phi(s) \leq 0 \ \forall s\}$. All hypotheses of Lemma 20 are satisfied, so that assumptions H1,H2,H3 hold. The I/S characteristic of the system can be easily seen to exist and be defined by $k^X(u) = (\hat{x}_1, \hat{x}_2)$, where

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

for any $u \in \mathbb{R}$. Since it is continuous and sends bounded sets to bounded sets, H4 is satisfied. We are left with the hypothesis H5 and the discrete convergence condition, which hold together for the function $k(u) = \frac{a_{21}}{a_{22}} \frac{a_{12}}{a_{11}} u$ if and only if $a_{12}a_{21} < a_{11}a_{22}$. In this latter case, Theorem 12 can then be applied, showing that the closed loop (5.5) is globally attractive towards its equilibrium point. Theorem 13 shows that this equilibrium is in fact globally asymptotically stable.

Example

The following system corresponds to the cyclic gene model with repression studied in [100]. Let y_1 be a messenger RNA, which produces an enzyme y_2, which produces another enzyme y_3, and so on for $p \geq 2$ steps. Let y_p in turn inhibit the production of y_1, closing the cycle and inducing the repression. The system is modeled as

$$\begin{aligned} \dot{y}_1 &= F(L_p y_p^t) - a_1 y_1(t) \\ \dot{y}_i &= L_{i-1} y_{i-1}^t - a_i y_i(t), \quad 2 \leq i \leq p, \end{aligned} \tag{5.6}$$

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

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

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

$$\begin{aligned} \dot{y}_1 &= F(L_p \alpha(t)) - a_1 y_1(t) \\ \dot{y}_i &= L_{i-1} y_{i-1}^t - a_i y_i(t), \qquad 2 \leq i \leq p, \end{aligned} \qquad h(y^t) = y_p^t = \alpha(t), \tag{5.7}$$

will fit the setup of our results. Indeed, letting $U = L^{\infty}([-r,0],\mathbb{R}^+)$,[1] the system satisfies the hypotheses of Theorem 14. It also fulfills the monotonicity criterion using the cones

$$\mathcal{K}_X = C([-r,0],(\mathbb{R}^+)^p),\ \mathcal{K}_U = L^{\infty}([-r,0],\mathbb{R}^-)$$

(note the negative sign). Lemma 20 is also satisfied, thus guaranteeing hypotheses H1-H3. Fixing $\alpha \in U$, the controlled system can now be shown to converge towards the constant function $(\hat{y}_1,\dots \hat{y}_p)$, where

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

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

$$\dot{y}_2 = \beta - a_2y_2(t),$$

where $\beta(t) := L_1y_1^t$, and by noting that $\beta(t)$ must converge. Inductively, the existence of the characteristic follows. Noting that k^X sends bounded sets to bounded sets, it follows that H4 holds. The item 1 in the small gain condition holds clearly, since F is bounded (see below). To see that any solution $y(t)$ of (5.6) is bounded, let $z_1(t)$ be a solution of $z' = F(0) - a_1z$, with initial condition $z_1(0) = y_1(0)$. Then $y_1(t) \leq z_1(t)$ for all $t \geq 0$: to see this, note that the function $w(t) = z_1(t) - y_1(t)$ satisfies the equation

$$w'(t) = F(0) - F(L_p\alpha(t)) - a_1w,$$

where $F(0)-F(L_p\alpha(t)) \geq 0$ and $w(0) = 0$. Now, since $z_1(t)$ is monotonic and converges towards $F(0)/a_1$, $y_1(t)$ is eventually bounded from above by $F(0)/a_1 + \epsilon$, for any $\epsilon > 0$. In fact, $F(0)/a_1$ is an upper hyperbound of $y_1(t)$ under the usual order. The boundedness of $y_1(t)$ is used to carry out a very similar argument in order to show that $y_2(t)$ is also eventually bounded, and the same holds for all other variables. This shows that all the solutions of the closed loop system are bounded.

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

By Theorem 12, system (5.6) is globally attractive whenever the discrete system

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

is globally attractive. Note that even if u_1 is a function, still $u_2, u_3, \ldots$ can be assumed to be constants, so that one can further reduce the system to be 1-dimensional. Whenever the hypotheses of Theorem 12 apply, the stability of the system is ensured by Theorem 13, the remaining hypotheses being trivially verified (especially since $L_p(u) = L_p(\widehat{L_p(u)}/\nu_p([-r, 0]))$ for $u \in U$). The same procedure can be applied throughout to the coupled system of an odd number of repressions of the form (5.6), as done in Smith [100]. This is in accord with the comments in p. 188 of that article:

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

An example of a system (5.1) which is globally attractive is given by the function $F(x) := A/(K + x)$, for $A, K > 0$ arbitrary (the division by the constants $a_1 \ldots a_p$ is here irrelevant). By Lemma 15, one only needs to show that the equation $F(F(x)) = x$ has a unique solution. Such a solution would satisfy $x = A/(K + F(x))$, that is

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

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

5.2 A model of the lac operon

The following dynamical system was proposed by Mahaffy and Savev [69] to describe the dynamics of lactose metabolism in *E. Coli*, which is orchestrated by the genes known as the lac operon. Some of the main results in [69] concern the global stability of the system; we will apply the small gain theorem in its delay form to prove and extend these results.

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

$$\begin{aligned}
\dot{x}_1(t) &= g(x_4(t-\tau)) - b_1 x_1(t) \\
\dot{x}_2(t) &= x_1(t) - b_2 x_2(t) \\
\dot{x}_3(t) &= r x_1(t) - b_3 x_3(t) \\
\dot{x}_4(t) &= S x_2(t) - x_3(t) x_4(t).
\end{aligned} \tag{5.8}$$

Here $g(\theta) := (1 + K\theta^\rho)/(1 + \theta^\rho)$, $K > 1$, all other constants are positive, and all variables are nonnegative. We will illustrate our main result by writing this system as the negative feedback loop of a controlled monotone system, in the way illustrated by Figure 5.3. The resulting system, which is modeled with $r_{\text{state}} = \tau, r_{\text{input}} = 0$, is

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

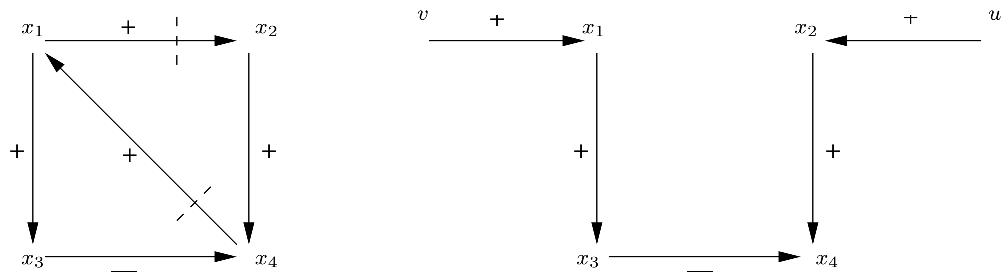

Figure 5.3: On the left, the digraph associated with equation (5.8). The dotted arrows are replaced by inputs on the right digraph, making the system into a controlled monotone one. Setting $u = x_1,\ v = x_4$ closes the loop back to (5.8).

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

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

using our monotonicity criterion. (In fact, monotonicity with respect to some orthant cone is equivalent to the property that the associated digraph doesn't have any undirected closed loop with an odd number of '$-$' signs.) See [6] for details, and Appendix I for a more systematic treatment in the finite dimensional case. It is clear that the closed feedback loop of this system is (5.8).

It will be shown that this controlled system has a well defined characteristic, by appealing to Figure 5.3 and by noting that one can write the system as a cascade of asymptotically stable, one-dimensional systems. In fact, in the notation of (5.3), it holds in this example that $f(x_t, \alpha) = f(x(t), \alpha)$, and that the delay is only used for defining the feedback function. If the delay in the state is ignored and the controlled system is viewed as a strictly finite dimensional system, it becomes obvious that a fixed control (u, v) will induce a globally asymptotically stable equilibrium, which is calculated to be

$$x_1 = \frac{g(v)}{b_1},\ x_2 = \frac{u}{b_2},\ x_3 = \frac{r}{b_1 b_3} g(v),\ x_4 = \frac{S b_1 b_3 u}{r b_2 g(v).}$$

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

$$k(u, v) = \left(\frac{1}{b_1} g(v), \frac{S b_1 b_3}{r b_2} \frac{u}{g(v)} \right). \tag{5.9}$$

To guarantee that this open loop system satisfies the hypotheses of the main result, let $X_0 = (\mathbb{R}^+)^4,\ U_0 = (\mathbb{R}^+)^2$, and note that Lemma 20 can be directly applied to prove H1,H2,H3. The monotonicity and existence of the characteristic was shown above, and since k^X sends bounded sets to bounded sets ($g(\theta)$ is bounded from above by K and from below by 1), condition $H4$ also holds. Since the first component of $k(u,v)$ is bounded from below and above by $1/b_1$ and K/b_1 respectively, it is easy to see that the orbits of the discrete system (5.9) are uniformly bounded after two steps. Therefore item 1 in the small gain condition is satisfied. To see that a solution $x(t)$ of system (5.8) is bounded, let $z_1(t), z_2(t)$ be the solutions of the systems $z' = 1 - b_1 z$ and $z' = K - b_1 z$ respectively, with initial conditions $z_i(0) = x_1(0)$. It is easy to see that $z_1(t) \leq x_1(t) \leq z_2(t)$ for all $t \geq 0$, see the previous example. Since $z_1(t)$ ($z_2(t)$) converges towards $1/b_1$ (K/b_1), it holds that $x_1(t)$ is eventually bounded from below and above by fixed positive constants $1/b_1 - \epsilon$ and $K/b_1 + \epsilon$ respectively. In fact, $1/b_1$ (K/b_1) is a lower (upper) hyperbound of $x_1(t)$ in the usual order. Using this fact, the same procedure is used to show that x_2, x_3 are bounded, and this in turn implies that x_4 is also bounded (see also [69]). This shows that all the solutions of the closed loop system are bounded.

Note that $k(u,v)$ has a unique fixed point

$$u = \frac{1}{b_1} g(\frac{Sb_3}{rb_2}),\ \ v = \frac{Sb_3}{rb_2}.$$

For any choice of the parameters such that the discrete system $(u_{n+1}, v_{n+1}) = k(u_n, v_n)$ is globally attractive to this equilibrium, it follows from Theorem 12 that the original model (5.8) is globally attractive to its unique equilibrium. In those cases, the stability of (5.8) will be ensured by Theorem 3 and by the strict monotonicity of k^X and h. For the remainder of this example, we will concentrate on finding sufficient conditions for the global attractivity of the discrete system.

In the global analysis of model (5.8), Mahaffy and Savev [69] restrict their attention to the case $\rho = 1$, and they prove three results that provide sufficient conditions for global attractivity. We will come to the exact same conclusions, by writing the system associated to (5.9) as a scalar discrete system of second order, and by appealing to the attractivity results known for such systems. For arbitrary ρ we will also prove a new result, concerning global attractivity for any choice of the parameters b_1, b_2, b_3, S and r, provided that an inequality holds for ρ, K. Let $\rho = 1$, and consider the discrete system

$$(u_{n+1}, v_{n+1}) = k(u_n, v_n). \tag{5.10}$$

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

$$u_{n+2} = \frac{1}{b_1} g\left(\frac{Sb_1b_3}{rb_2}\frac{u_n}{g(v_n)}\right) = \frac{1}{b_1} g\left(\frac{Sb_3}{rb_2}\frac{u_n}{u_{n+1}}\right) = \frac{\beta u_{n+1} + \gamma u_n}{Bu_{n+1} + Cu_n}, \tag{5.11}$$

where here $\rho = 1$ in $g(\theta)$, and

$$\beta := \frac{1}{b_1}, \gamma := K\frac{Sb_3}{rb_1b_2}, B := 1, C := \frac{Sb_3}{rb_2}.$$

If the parameters of (5.11) are such that this discrete system has a globally attractive equilibrium for all initial conditions $u_0, u_1 > 0$, then (5.10) has globally attractive solutions for any initial condition $u, v \geq 0$. (If $u = 0$ or $v = 0$, simply iterate (5.9) a few times and the states will become strictly positive.) The global attractivity of (5.10) clearly also implies that of (5.11).

The book by Kulenovic and Ladas [64] deals exclusively with rational discrete systems of second order. It follows from their treatment of equation (5.11) that for $p := \beta/\gamma, q := B/C$, and $p < q$, global attractivity holds (that is, with respect to arbitrary real initial conditions for which the iterations are well defined, including $(u_0, u_1) \in (0,\infty) \times (0,\infty)$) if $q < pq + 1 + 3p$. Furthermore, instability occurs if $q > pq + 1 + 3p$ (see Theorem 6.9.1 in [64]).

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

$$0 < q^2 + 3q - Kq + K, \quad q := \frac{rb_2}{Sb_3}. \tag{5.12}$$

For instance, if $q < 1$ then $0 < K - qK$ and thus (5.12) follows. This corresponds to Proposition 4.1 in [69]. Similarly, convergence follows whenever $q > K$, since then $0 < q^2 - qK$ (Proposition 4.2 in [69]). Finally, for $q > 1$ equation (5.12) is equivalent to $K < q(q+3)/(q-1)$, and the right hand side of this equation is bounded from below by 9. Thus for $1 \leq K < 9$ stability also follows. The remaining hypotheses in Theorem 4.3 of [69] can be shown to be equivalent to

$$K < q(q+3)/(q-1), \ q > 1.$$

We summarize the three main global stability results of [69] in the following statement.

Theorem 15 *For $\rho = 1$, the system (5.8) is globally attractive to a unique equilibrium, provided that $0 < q^2 + 3q - Kq + K$, $q := \frac{rb_2}{Sb_3}$. In particular, this holds if $q < 1$, if $q > K$ or if $q > 1$ and $K < q(q+3)/(q-1)$. Whenever this condition is satisfied, system (5.8) is stable around this equilibrium.*

The stability part of the above theorem is a direct consequence of Theorem 13, after noting that k^X is $\ll$-increasing and h is $\ll$-decreasing, both of which are straightforward to check.

Note that the delay τ was almost never used, and indeed can be arbitrarily large or small. In fact, one can introduce different delays, large or small, in all of the first terms of the right hand sides of (5.8), and the results will apply with almost no variation. (If delays are introduced in the second terms, the systems will not be monotone anymore.) If no delays are assumed, substantially stronger attractivity conditions hold; see [69].

Note that one can associate a second order, scalar discrete system to the original two-dimensional system for any value of ρ, in the same way as above. One correspondence that can be easily verified by using equation (5.11) repeatedly is the following: if $u_0 = u > 0$ and $u_1 = v > 0$, and if u_0, u_1 and (u, v) are taken as initial conditions of the systems (5.11) and (5.10) respectively, then $u_0, u_1, u_2, \ldots$ generates a two cycle in (5.11) if and only if (u, v) forms a two cycle in (5.10). Thus there exist nontrivial two-cycles in (5.10) if and only if there exist nontrivial two cycles in (5.11). For $u = 0$ or $v = 0$, similar comments apply as before. Recall that the existence of nontrivial two-cycles in (5.10) is equivalent to the global attractivity of system (5.10), by Lemma 15 and the fact that this system is $\leq$-decreasing under some orthant cone. By the above arguments, the same is true for system (5.11). Using the main result, the following proposition follows:

Proposition 5 *The system (5.8) is globally attractive to its equilibrium whenever the only solution $u > 0, v > 0$ of the system of equations*

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

is $u = v = (\beta+\gamma)/(B+C)$*, for*

$$\beta = \frac{1}{b_1}, \gamma = \frac{K}{b_1}\left(\frac{Sb_3}{rb_2}\right)^{\rho}, B = 1, C = \left(\frac{Sb_3}{rb_2}\right)^{\rho}.$$

This is a good point to comment on decomposing the same model as the negative feedback loop of a monotone system *in other ways* – after all, one can see that replacing x_3 by "u" in the fourth equation of (5.8), the resulting SISO system is monotone as well. Indeed, in that way a characteristic $k(u)$ can also be shown to exist, but it can be expressed only indirectly as the solution of a certain algebraic equation, since a directed loop remains in the digraph of the controlled system. To check that there are no nontrivial two-cycles for the discrete system, it is necessary to solve the system of equations $u = k(v), v = k(u)$, which turns out to be equivalent and very similar to the system of equations in Proposition 5. Thus, there is more than one way to decompose autonomous systems as closed loops of monotone controlled systems and use Theorem 12.

Next we provide sufficient conditions on K, ρ for system (5.8) to be globally attractive, for any choice of the remaining parameters. We transform $k(u,v) = (\zeta v, \xi u/g(v))$ into logarithmic coordinates. That is, consider

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

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

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

Note that the iterations of this function converge globally to an equilibrium if and only if those of $k(u,v)$ do. To the former system one can associate the second order system $\sigma_{n+2} = \Delta(c + \sigma_n - \sigma_{n+1})$ as was done in equation (5.11).

Lemma 21 *Consider a discrete system* $\sigma_{n+2} = \Delta(c+\sigma_n-\sigma_{n+1})$*, where* c *is an arbitrary constant and* Δ *is a bounded, non-decreasing, Lipschitz function with Lipschitz constant* $\alpha < 1/2$*. Then the system is globally attractive to its unique equilibrium* $\sigma = \Delta(c)$*.*

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

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

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

Define inductively

$$a_{i+1} := \Delta(a_i - b_i + c),\ b_{i+1} := \Delta(b_i - a_i + c).$$

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

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

and the conclusion follows. ∎

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

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

and that ρ arbitrary if $K = 1$. The following corollary follows by the previous lemma and Theorem 12:

The following corollary follows by using the previous lemma and Theorem 12:

Corollary 8 *The lac operon model (5.8) has a unique, globally attractive equilibrium for any choice of the positive parameters $b_1, b_2, b_3, r, S, \tau$, provided that*

$$\rho < \frac{\sqrt{K}+1}{K-1}.$$

5.3 Decomposing Autonomous Systems as Negative Feedback Loops of Monotone Controlled Systems

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

$$\dot{x} = f(x,u),\ x \in X = (\mathbb{R}^+)^n, u \in U = (\mathbb{R}^+)^m, \tag{5.13}$$

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

$$\dot{x}^S = f^S(x^S; z, u) \tag{5.14}$$

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

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

$$\dot{x}^{S_\lambda} = f^{S_\lambda}(x^{S_\lambda}; x^{S_\lambda^C}, u),\ \lambda = 1 \ldots \Lambda \tag{5.15}$$

is equivalent to (5.13).

Sign Definite Systems

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

$$\dot{x} = g(x),\ x \in X = (\mathbb{R}^+)^n, \tag{5.16}$$

let the variables $x_1 \ldots x_n$ be vertices, and write a positive arc from x_i to x_j, $i \neq j$, if $\frac{\partial}{\partial x_i} g_j(x) \geq 0$ for all $x \in X$ and the strict inequality holds at least at some state.

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

If the system (5.16) is sign definite with associated digraph G, then one can find an n-dimensional controlled system

$$\dot{x} = f(x,u), \ \ x \in X = (\mathbb{R}^+)^n, \ \ u \in U = (\mathbb{R}^+)^m, \ \ h : X \to U, \tag{5.17}$$

which is i) monotone with respect to some orthant cones in the inputs and the states; ii) such that the function h is $\leq$-decreasing; and iii) such that its closed loop system is well defined and is (5.16). This will be done as follows, trying to minimize the number of inputs and outputs involved so as to make the reduced model in Theorem 12 as simple as possible.

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

An arc in G will be called *discordant* if it is positive and joins an agonist with an antagonist, or if it is negative and joins two agonists or two antagonists. Let $D_j := \{x_i |$ there is a discordant arc from x_i to $x_j\}$, and let

$$D := \bigcup_j D_j, \ \ m := |D|, \ \ U := (\mathbb{R}^+)^m.$$

Now enumerate the elements of D as $x_{l_1}, \ldots, x_{l_m}$. Define $f_j(x,u)$ as the result of replacing in $g_j(x)$ all appearances of x_{l_i} by u_i, for each $x_{l_i} \in D_j$. The controlled system (5.17) thus defined has a state digraph G' that can be described as the result of removing all discordant arcs from G.

Now define the output function $h : X \to U$ as

$$h_k(x) := x_{l_k}, \ \ k = 1 \ldots p,$$

and close the loop by letting $u(t) = h(x(t))$. Let

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

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

Example

Equation (5.8) and Figure 5.3 form a good example of these definitions. In this model, one can consider as agonists the variables x_1, x_3 and as antagonists x_2, x_4. There are only two discordant arcs and it holds that $D_1 = \{x_4\},\ D_2 = \{x_1\},\ D_3 = D_4 = \emptyset$; thus $D = \{x_1, x_4\}$. The variables x_1 and x_4 are replaced by u and v in the functions g_2, g_1 to form the functions $f_2(x, u)$, $f_1(x, v)$, respectively.

An important consideration in making the choice of the agonist set is to minimize the number of inputs. See Figure 5.4 for an example of a system in which the agonist set is chosen in two different ways.

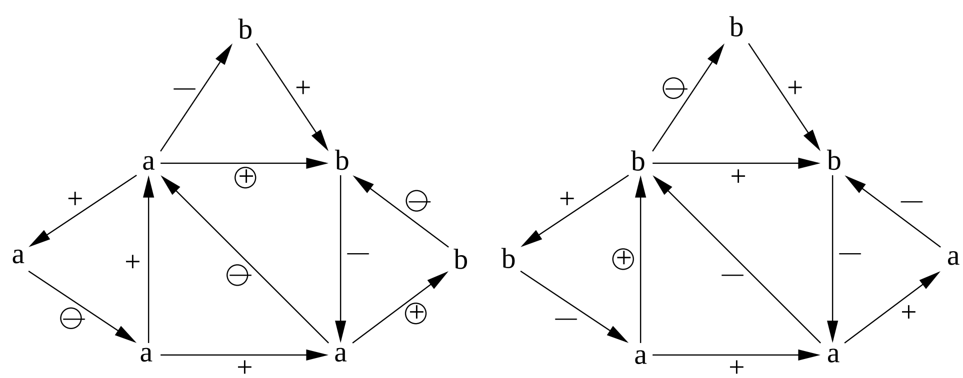

Figure 5.4: Network Splitting. The nodes in the digraphs above have been labeled "a" for agonist and "b" for antagonist in two different ways, and the discordant arrows have been circled in each case. The nodes at the base of these arrows will form the set D of inputs of the controlled system (four inputs in the first digraph, and two in the second). Note that by choosing the agonists and antagonists in an educated way one can substantially reduce the number of inputs.

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

Lemma 22 *Let H be an acyclic digraph. Then there exists a bijection $b : V(H) \to \{1, \dots |V(H)|\}$ such that $(v_1, v_2) \in A(H)$ implies $b(v_1) < b(v_2)$.*

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

Theorem 16 *The controlled system (5.17) described above is monotone, and h is a $\leq$-decreasing function. The closed loop system of (5.17) is well defined and equal to system (5.16). Furthermore, if for each strongly connected component of G' with vertices $S \subseteq \{1 \dots n\}$ the system (5.14) has a well defined I/S characteristic, then (5.17) allows an I/S characteristic.*

Proof. The Kamke monotonicity criterion for controlled systems will be used: given orthant cones $\mathcal{K}_X$ and $\mathcal{K}_U$ generated by the tuples $(s_1, \dots s_n)$ and $(p_1, \dots p_m)$ respectively, a system (5.17) is monotone with respect to these cones if and only if

$$s_j s_i \frac{\partial f_j}{\partial x_i} \geq 0, \ \forall i \neq j \ \text{ and } s_j p_k \frac{\partial f_j}{\partial u_k} \geq 0, \ \forall i, k, \tag{5.18}$$

where $i, j = 1 \dots n$ and $k = 1 \dots m$; see [101, 6]. To prove the first assertion in 5.18, let $i \neq j$ be such that there is an arc from x_i to x_j in G' (otherwise there is nothing to prove). Then either both variables are agonists and the arc is positive, or both are antagonists and the arc is also positive, or else one is agonist, one is antagonist and the arc is negative. In all these cases, the first statement in (5.18) is satisfied. As to the second statement, if k, j are such that $\partial f_j / \partial u_k \not\equiv 0$, then by construction the arc from x_{l_k} to x_j in G is discordant, so that $s_{l_k} s_j \partial g_j / \partial x_{l_k} \leq 0$. Also by construction,

$$\text{sign } \frac{\partial g_j}{\partial x_i} = \text{sign } \frac{\partial f_j}{\partial u_k}.$$

Therefore $s_j p_k \partial f_j / \partial u_k \geq 0$ as expected.

Recall that $p_k = -s_{l_k}$, $h_k(x) = x_{l_k}$ to see that h is $\leq$-decreasing. Replacing each u_k in $f_j(x, u)$ back with $h_k(x) = x_{l_k}$ will form back $g_j(x)$. This proves that the closed loop system is the same as (5.16).

For the last assertion write (5.17) as a cascade of controlled monotone systems on the state spaces $X_\lambda := (\mathbb{R}^+)^{|S_\lambda|}$, $\lambda = 1 \dots \Lambda$, where $S_1, \dots, S_\Lambda$ are the strongly connected components (s.c.c.) of G'. Let H be the acyclic digraph with vertices $S_1 \dots D_\Lambda$ which is naturally induced by the digraph G', i.e. $(S_\lambda, S_\mu) \in A(H)$ if and only if $(x, y) \in A(G')$ for some $x \in S_\lambda, y \in S_\mu$. Now use Lemma 22 to relabel the s.c.c's in such a way that if $x_i \in S_{\lambda_1}$, $x_j \in S_{\lambda_2}$, and there is an arc from x_i to x_j, then $\lambda_1 \leq \lambda_2$.

Consider the function $f^{S_1}(x^{S_1}; z, u)$, where $z = (z_i)_{i \in S_1^C}$ is given. By the choice of S_1, it holds that f^{S_1} doesn't actually depend on z, and it can be written as $f^{S_1}(x^{S_1}, u)$. Similarly one can write $f^{S_\lambda}(x^{S_\lambda}; x^{S_\lambda^C}, u)$ in (5.15) as

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

and thus system (5.17) is written as a cascade as desired, using equation (5.15).

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

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

can be seen to satisfy (5.18), since some of the variables have now been simply relabeled as inputs. Also, this system has a well-defined characteristic by hypothesis. Thus the property CICS holds, and since (x^{S_1}, u) converges to $(\bar{x}^{S_1}, u)$, then x^{S_2} converges to $\bar{x}^{S_2}$. The same argument holds to show that all the cascade converges, thus proving that system (5.17) has an I/S characteristic. ∎

Corollary 9 *If the digraph G' associated to system (5.17) is acyclic, and for every $i = 1 \dots n$ the 1-dimensional system*

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

with controls $\hat{x}_j, j \neq i$, has a well defined I/S characteristic, then (5.17) allows an I/S characteristic.

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

Discussion

The reader will notice a tradeoff in the number of variables chosen to form the input: the more variables are included in D, the more complex is the resulting discrete system in SGT, but the less connected is G' and the easier to show the existence of a characteristic. Note that D is completely determined by the set A of agonists, which is arbitrary and allows for some choice. The results in this section make SGT robust to possible changes in the model. If a new participating gene is discovered as part of a gene network, one can simply keep the previous agonists, introduce the new gene either as agonist or antagonist, and obtain a monotone system (5.17) that has a similar topology as the previous one. The second condition in Theorem 16, regarding the existence of the characteristic, also needs to be checked only locally if a new node or a new arrow is introduced.

Chapter 6

Multistability and the Reduced Model

6.1 Quasimonotone Matrices, Revisited

We begin this discussion with some results on the leading eigenvalue of a quasimonotone matrix. This section therefore builds on the general results of Chapter 3. Although the present chapter is concerned exclusively with finite-dimensional systems, the results of this section hold through for abstract Banach spaces after replacing matrices by suitable linear operators.

We assume throughout that A is an $n \times n$ matrix, and that $\mathcal{K} \subseteq \mathbb{R}^n$ is an arbitrary closed cone.

Lemma 23 *Let A be quasimonotone with respect to $\mathcal{K}$. Then*

$$\mathrm{leig}(A) = \max\{\lambda \in \mathbb{R} \,|\, \textit{there exists } v > 0 \textit{ such that } Av \geq \lambda v\}.$$

Proof. Let $S = \{\lambda \in \mathbb{R} \,|$ there exists $v > 0$ such that $Av \geq \lambda v\}$, and let $\bar{\lambda} = \mathrm{leig}(A)$. Consider first a given real number $\lambda \leq \bar{\lambda}$. By the Perron-Frobenius theorem for quasimonotone matrices there exists a vector $v_0 > 0$ such that $Av_0 = \bar{\lambda} v_0$. Since clearly $\bar{\lambda} v_0 \geq \lambda v_0$, it holds that $\lambda \in S$. Thus $\sup(S) \geq \bar{\lambda}$.

Now let $\lambda > \bar{\lambda}$, and suppose by contradiction that $\lambda \in S$. Then $B = A - \lambda I$ is a Hurwitz, quasimonotone matrix. By hypothesis, $Bv = Av - \lambda v \geq 0$ for some $v > 0$. Consider the system $\dot{x} = Bx$. Since $Bv \geq 0$, the set $v + \mathcal{K} = \{v + x \,|\, x \in \mathcal{K}\}$ is positively invariant (see Smith [101]). But since all solutions converge towards zero, it must hold that $0 \in \overline{v + \mathcal{K}} = v + \mathcal{K}$. Hence $-v > 0$, which is a contradiction. One concludes that $\lambda \notin S$, so that $S = (-\infty, \bar{\lambda}]$ and the statement of the lemma follows. ∎

Lemma 24 *Let A be a quasimonotone matrix with respect to $\mathcal{K}$, $\alpha \in \mathbb{R}$ an arbitrary real number, and B a monotone matrix with respect to $\mathcal{K}$. Then $A+B$, $A+\alpha I$ are quasimonotone,* $\operatorname{leig}(A+B) \geq \operatorname{leig}(A)$, *and* $\operatorname{leig}(A+\alpha I) = \operatorname{leig}(A) + \alpha$.

Proof. To prove that $A+B$ is quasimonotone, we use the Vidyasagar condition for quasimonotonicity — see Chapter 3. Let $\phi \in \mathcal{K}^*$, and let $x > 0$ be such that $\phi(x) = 0$. By quasimonotonicity of A, the Vidyasagar condition implies that $\phi(Ax) \geq 0$. But therefore also $\phi((A+B)x) = \phi(Ax) + \phi(Bx) \geq 0$. This constitutes the Vidyasagar condition for the quasimonotonicity of $A+B$ as expected. The fact that $A+\alpha I$ is quasimonotone is proven similarly.

Let $\lambda \in \mathbb{R}$ be such that $Av \geq \lambda v$ for some $v > 0$. Then obviously $(A+B)v \geq \lambda v$. It holds that $S_A \subseteq S_{A+B}$ (using the notation for S above), so that $\operatorname{leig}(A) \leq \operatorname{leig}(A+B)$ by the previous lemma. The last statement of the lemma follows from the fact that the spectra of A and $A+\alpha I$ are related by $\sigma(A+\alpha I) = \sigma(A) + \alpha$. ∎

The next lemma will also be used in the main results below. The additional strong quasimonotonicity hypothesis on A allows for the stronger conclusion.

Lemma 25 *Let A be strongly quasimonotone with respect to $\mathcal{K}$, and let B be a monotone matrix with respect to $\mathcal{K}$, $B \neq 0$. Then* $\operatorname{leig}(A+B) > \operatorname{leig}(A)$.

Proof. Consider a the time t evolution operators $T_1(t), T_2(t) : X \to X$ associated with A and $A+B$ respectively. Both T_1 and T_2 are strongly monotone, by hypothesis. By Lemma 5, $T_1 \leq T_2$ on the set $\mathcal{K}$. Moreover, since there exists $x_0 > 0$ such that $Bx_0 > 0$, it follows that $T_1(x_0) < T_2(x_0$. By Theorem 1.3.28 and Corollary 1.3.29 of Berman and Plemmons [10], it holds that $\rho(T_1) < \rho(T_2)$. By the spectral mapping theorem, it holds that $\rho(T_1) = \exp(t\operatorname{leig}(A))$, $\rho(T_2) = \exp(t \operatorname{leig}(A+B))$. The result thus follows. ∎

The following lemma will be useful below. It has implicity been already put to use in the abstract case for the proof of Theorem 7.

Lemma 26 *Let A be Hurwitz and quasimonotone with respect to $\mathcal{K}$. Then $-A^{-1}$ is monotone with respect to $\mathcal{K}$.*

Proof. Let $T(t)$ be the time t evolution operator of the system $\dot{x} = Ax$, that is, $T(t) = \exp(tA)$. The equalities

$$-I = \int_0^\infty \frac{\mathrm{d}}{\mathrm{d}t} T(t)\,\mathrm{d}t = A \int_0^\infty T(t)\,\mathrm{d}t$$

show that $-A^{-1} = \int_0^\infty T(t)\,\mathrm{d}t$, and that in particular $-A^{-1}$ is monotone. ∎

We now introduce a new definition, which will be useful in the proof of the main results. Refer to [10] for a more thorough treatment (and where these matrices are called $\mathcal{K}$-*monotone*).

Definition 8 *The matrix A is called* inverse-positive with respect to $\mathcal{K}$ *if it satisfies the property $Ax \geq 0 \Rightarrow x \geq 0, \quad \forall x \in \mathbb{R}^n$.*

We first note that an inverse-positive matrix A must be invertible: if $Ax = 0$, then also $A(-x) = 0$, which implies $x \in \mathcal{K}$, $-x \in \mathcal{K}$, and $x = 0$. Also, it is easy to see that $A^{-1}\mathcal{K} \subseteq \mathcal{K}$, and that these two conditions imply inverse-positivity.

We quote the following result without proof from Plemmons [10], pp 113. (That reference also calls inverse positive matrices $\mathcal{K}$-*monotone*.)

Lemma 27 *Let $A = \alpha I - B, \ \alpha > 0$, and assume B*
$K \subseteq \mathcal{K}$. The following conditions:

1. *A is inverse-positive.*

2. *$\rho(B) < \alpha$*

3. *$-A$ is Hurwitz*

are equivalent.

The following result is from [10], p. 10. We include here a simple proof for the reader's convenience.

Lemma 28 *Let $A = \alpha I - B, \ \alpha > 0$, B*
$K \subseteq \mathcal{K}$, and suppose that A is invertible and $Ax > 0$ for some $x \gg 0$. Then A is inverse-positive.

Proof. Recall that for any norm $|\cdot|$ on $\mathbb{R}^n$, and any $n\times n$ matrix M, we have $\rho(M) \leq |M|$, where $|M|$ is the usual induced operator norm. For any fixed x as in the statement of the Lemma, we define a norm $|\cdot|_x$ on $\mathbb{R}^n$ as follows:

$$|y|_x = \inf\{t > 0| \ -tx \leq y \leq tx\}\,.$$

Using B

$K \subseteq \mathcal{K}$, we prove next that $|B|_x = |Bx|_x$, where the left-hand side indicates the induced operator norm. Trivially $|B|_x \geq |Bx|_x$, and if $|y|_x = 1$, the condition $-tx \leq Bx \leq tx$ implies

$$\begin{aligned} tx - By = tx - Bx + B(x-y) &\geq 0 \\ tx + By = tx - Bx + B(y+x) &\geq 0\,, \end{aligned}$$

and hence $|By|_x \leq |Bx|_x$.

Further, it is easy to see that $0 \leq y_1 \leq y_2$ implies $|y_1|_x \leq |y_2|_x$. In particular, $Ax = \alpha x - Bx \geq 0$ implies $|Bx|_x \leq |\alpha x|_x$.

Putting all together we have

$$\rho(B) \leq |B|_x = |Bx|_x \leq \alpha\,|x|_x = \alpha\,.$$

But if $\rho(B) = \alpha$, then 0 would be an eigenvalue of A, which would contradict our hypotheses. Thus $\rho(B) < \alpha$, and by the previous lemma the result follows. ∎

6.2 The Reduced System

Consider a C^1 dynamical system

$$\dot{x} = f(x,u),\ \ u = h(x) \tag{6.1}$$

defined on the input and state spaces $U \subseteq R^m$, $X \subseteq R^n$. Assume that X (U) is the closure of open sets in $\mathbb{R}^n$ ($\mathbb{R}^m$), and let $\mathcal{K}_X \subseteq \mathbb{R}^n$, $\mathcal{K}_U \subseteq \mathbb{R}^m$ be the cones with respect to which the system is monotone. In contrast with the previous chapters, in this chapter we will assume that h is a *positive feedback function*, that is, $x \leq y$ implies $h(x) \leq h(y)$ (or, using our notation, h is $\leq$-increasing). In particular, the closed loop system

$$\dot{x} = f(x, h(x)) \tag{6.2}$$

can be shown to be monotone [7]. We prove this using the Vidyasagar condition from Chapter 3: let $x \leq y$ and $\sigma \in \mathcal{K}_X^*$ be such that $\sigma(x) = \sigma(y)$. Using the Vidyasagar condition on the quasimonotone function $f(\cdot, h(x))$ we conclude that

$$\sigma(f(x, h(x))) \leq \sigma(f(y, h(x))) \leq \sigma(f(y, h(y))),$$

the last inequality holding since $f(y, h(\cdot))$ is increasing.

Corollary 10 *The closed loop of a controlled monotone system under a positive feedback function is monotone with respect to $\mathcal{K}_X$.*

Consider the set function $K^X : U \to \mathcal{P}(X)$ defined by

$$K^X(u) = \{x \in X \mid f(x, u) = 0\}.$$

For each fixed $u \in U$, and in the particular case that (6.1) is strongly monotone, Hirsch's theorem implies that almost all bounded solutions of $\dot{x} = f(x, u)$ converge towards the set $K^X(u)$. In this way the present setup generalizes the concept of *characteristic* proposed in Chapter 4. The idea of generalizing characteristic functions as set characteristics was also used by de Leenheer et al. [23] for a similar setup in the negative feedback case. In the case that K is a single-valued function, and if it holds that i) $\det f_x(K(u), u) \neq 0$ for every u, and ii) for every fixed point $\bar{u}$ of K, $\det(K'(\bar{u}) - I) \neq 0$, we say that K is a *strong characteristic*; this definition corresponds to that of a 'characteristic' in [31].

The equilibria of the closed loop system (6.2) are in bijective correspondence with the intersection between graph K^X and the transpose of graph h. We state this in the following lemma, whose proof should be self-evident.

Lemma 29 *Given a controlled system (6.1), a state $x \in X$ is an equilibrium of (6.2) if and only if $x \in K^X(h(x))$. The function $x \to (h(x), x)$ is a bijective correspondence between equilibria of (6.2) and points (u, x) such that $x \in K^X(u)$, $u = h(x)$.*

Given the function K^X above, consider the set function $K : U \to \mathcal{P}(U)$, defined by $K(u) = \{h(x) \,|\, x \in K^X(u)\}$. The following lemma relates to K as Lemma 29 relates to K^X. We will say that the system has property (H) if

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

Lemma 30 *Let condition (H) be satisfied. Then the function $x \to h(x)$ forms a bijective correspondence between the equilibria of (6.2) and the points $u \in U$ such that $u \in K(u)$.*

Proof. By Lemma 29 an equilibrium of (6.2) satisfies $x \in K^X(h(x))$. Therefore such an equilibrium satisfies $h(x) \in K(h(x))$, by definition. If $u \in K(u)$, then there is $x \in K^X(u)$ such that $h(x) = u$. Therefore $x \in K^X(h(x))$, that is, x is an equilibrium of (6.2) by Lemma 29. The injectivity of the correspondence is guaranteed by the assumption in the statement. ∎

Note that if K^X is a strong characteristic, then the assumption of this lemma is satisfied automatically, since $h(x_1) = h(x_2)$ implies $x_1 = K^X(h(x_1)) = K^X(h(x_2)) = x_2$.

Consider now an equilibrium point $\bar{x} \in K^X(h(\bar{x}))$ of (6.2). Let

$$\dot{x} = Ax + Bu,\ y = Cx \tag{6.3}$$

be the linearization of (6.1) around $(\bar{u}, \bar{x}),\ \bar{u} = h(\bar{x})$. Let $k^X : S \to X$ be a C^1 function defined on an open neighborhood of $\bar{u}$, and such that $f(k^X(u), u) = 0$ for all $u \in S$ (thus k^X can be thought of as a 'branch' of K^X). From this equation one can find the derivative $(k^X)'(\bar{u})$ by using the chain rule, namely $(k^X)'(\bar{u}) = -A^{-1}B$. Then the C^1 function $k : S \to U$ given by $k(u) = h(k^X(u))$ is such that $k(\bar{u}) = \bar{u}$ and $k'(\bar{u}) = -CA^{-1}B$. The input value $\bar{u}$ is also an equilibrium of the dynamical system

$$\dot{u} = k(u) - u. \tag{6.4}$$

This system is defined as the *reduced system associated to (6.1) at $\bar{x}$*. It is important to note that this system is only locally defined (unless k is single-valued) and only whenever

k^X is a uniquely defined function in a neighborhood of $\bar{u}$. We will show presently that the latter is the case if A is a Hurwitz matrix. The linearization of system (6.4) around $\bar{u}$ is associated with the matrix $Red(\bar{x}) := -CA^{-1}B - I$. In the following section we will study the relationship between this matrix and the matrix $A + BC$, which is the linearization of (6.2) at $\bar{x}$.

6.3 Results for Linear Systems

Consider a controlled monotone system (6.1). Given $u_0 \in U, x_0 \in X$, let $A(u_0, x_0) = f_x(u_0, x_0)$, $B(u_0, x_0) = f_u(u_0, x_0)$, and $C(x_0) = h_x(x_0)$. We will refer to these matrices as A, B, C if the point (u_0, x_0) is clear from the context. Thus the linearization of (6.1) around (u_0, x_0) has the form (6.3). By linearizing at equilibrium points, we will derive information about the stability of the closed loop system (6.2) by looking at the matrix $-CA^{-1}B - I$.

We begin by stating and proving a theorem which relates the stability properties of the matrices $A + BC$ and $-CA^{-1}B - I$, given a Hurwitz monotone linear system (6.3).

Theorem 17 *Let (6.3) be a monotone controlled system with respect to the cones $\mathcal{K}_X$, $\mathcal{K}_U$ on X, U respectively, and such that A is a Hurwitz matrix. Assume that* $\det\left(I + CA^{-1}B\right) \neq 0$. *Then $A + BC$ is exponentially stable (exponentially unstable) if and only if $-(I + CA^{-1}B)$ is exponentially stable (exponentially unstable).*

Proof.

Recall from Chapter 4 that the monotonicity of the linear controlled system (6.3) is equivalent to the following conditions:

1. the positivity cone $\mathcal{K}_X$ is positively invariant for the system $\dot{x} = Ax$,

2. $B\mathcal{K}_U \subseteq \mathcal{K}_X$, and

3. $C\mathcal{K}_X \subseteq \mathcal{K}_Y$.

It holds that $-CA^{-1}B$ is a monotone matrix, since it can be written as the product $C(-A^{-1})B$ of monotone matrices (by Lemma 26). This implies in particular that

$-(I+CA^{-1}B)$ is a quasimonotone matrix, by Lemma 24. The fact that $A+BC$ is also quasimonotone follows similarly. We define $\lambda := \mathrm{leig}(A+BC)$ and $\mu := \mathrm{leig} - (I + CA^{-1}B)$. We must therefore prove that

$$\lambda < 0 \leftrightarrow \mu < 0,\ \ \lambda > 0 \leftrightarrow \mu > 0.$$

Let $v > 0$ be such that $(A+BC)v = \lambda v$. By multiplying on both sides by CA^{-1} we obtain : $(I + CA^{-1}B)Cv = \lambda CA^{-1}v$. We prove that $\lambda \neq 0$: if λ were zero, then $\det\big(I + CA^{-1}B\big) \neq 0$ would imply $Cv = 0$ and $Av = (A+BC)v = 0$, contradicting the fact that A is a Hurwitz matrix. Note also that $Cv \geq 0$ and $CA^{-1}v = -\int_0^\infty Ce^{At}v\,\mathrm{d}t \leq 0$.

Suppose first that $Cv \gg 0$, and that therefore $Ce^{At}v \gg 0$ on $[0,\delta]$ for some small $\delta > 0$. Since the convex hull of $\{Ce^{At} \,|\, 0 \leq t \leq \delta\}$ is in the interior of the open convex set int $\mathcal{K}_X$, it follows that $\int_0^\delta Ce^{At}v\,\mathrm{d}t \gg 0$. Therefore

$$CA^{-1}v = -\int_0^\delta Ce^{At}v\,\mathrm{d}t - \int_\delta^\infty Ce^{At}v\,\mathrm{d}t \ll 0.$$

If $\lambda < 0$, we can apply Lemma 28 (with "α" $= 1$, "B" $= -CA^{-1}B$, "A" $= I + CA^{-1}B$, and "x" $= Cv$) to conclude that $I + CA^{-1}B$ is inverse-positive, and therefore, by Lemma 27, that $-\big(I + CA^{-1}B\big)$ is Hurwitz, that is, $\mu < 0$.

Conversely, if $-\big(I + CA^{-1}B\big)$ is Hurwitz, then, once again appealing to Lemma 27, we know that $I + CA^{-1}B$ is inverse-positive. Then, from $(I + CA^{-1}B)(-\lambda^{-1})Cv = -CA^{-1}v$, we conclude that $(-\lambda^{-1})Cv > 0$ or $\lambda < 0$.

Now let us consider the general case, $Cv \geq 0$. We show the existence of an $m \times n$ matrix P with $Px \gg 0$ for each $x > 0$: since $\mathcal{K}_X$ is closed and pointed, there must be some $(n-1)$–dimensional hyperplane $H \subseteq \mathbb{R}^n$ whose intersection with $\mathcal{K}_X$ is $\{0\}$. Letting $w \in \mathbb{R}^n$ have norm equal to 1 and be perpendicular to H, we have without loss of generality $x \cdot w > 0$, for every $x > 0$. Let now $\mathcal{B}$ be a basis of $\mathbb{R}^n$ consisting of an orthonormal basis of H, together with w. Then $\mathcal{B}$ itself is orthonormal.

We can define a linear transformation $P : \mathbb{R}^n \to \mathbb{R}^m$ by freely defining the value of P at each of the elements of $\mathcal{B}$, and we do so by setting $P(w) \gg 0$ and $P(b) = 0$ for all other $b \in \mathcal{B}$. Given $x > 0$, one can write x as linear combination of the base elements, and the coefficient associated with each $b \in \mathcal{B}$ is $b \cdot x$. Since $P(b) = 0$ except for $b = w$, our assertion follows from

$$P(x) = P((x \cdot w)w) = (x \cdot w)P(w) \gg 0.$$

Let now $C_\epsilon = C + \epsilon P$, for $\epsilon > 0$ small enough so that $\det\left(I + C_\epsilon A^{-1}B\right) \neq 0$. Thus we can repeat the procedure above with this new matrix, and we have, for λ_ϵ, μ_ϵ denoting the stability modulus of $A + BC_\epsilon$ and $-(I + C_\epsilon A^{-1}B)$ respectively, that $\lambda_\epsilon < 0$ if and only if $\mu_\epsilon < 0$. By continuity of eigenvalues on both sides of the equivalence under continuous changes in matrix entries, the result follows, taking into account that $\lambda \neq 0, \mu \neq 0$.

Finally, since $\lambda \neq 0, \mu \neq 0$, and $\lambda < 0$ iff $\mu < 0$, it must hold that $\lambda > 0$ iff $\mu > 0$. ∎

Observe that a regularity condition in the hypotheses of the Theorem above is that $\det(I + CA^{-1}B) \neq 0$. We proceed to prove that $\det A + BC \neq 0$ could be used just as well.

Lemma 31 *Consider matrices $A \in M_{n\times n}$, $B \in M_{n\times m}$, $C \in M_{m\times n}$, and assume that A is nonsingular. Then $A+BC$ is nonsingular if and only if $CA^{-1}B+I$ is nonsingular.*

Proof. The proof that $CA^{-1}B + I$ is nonsingular implies $A + BC$ is nonsingular can be derived from the proof of the theorem above. To prove the opposite direction, suppose that $\det -CA^{-1}B - I = 0$. Let $v \neq 0$ be such that $-CA^{-1}Bv - v = 0$. Multiply by B from the left, and let $w = A^{-1}Bv$. After simplifying we have $(A + BC)w = 0$. If $A + BC$ were nonsingular, it would follow that $w = 0$, which implies that $Bv = 0$. But from this follows that $-v = 0$ in the first equation, which is a contradiction. ∎

The following corollary incorporates this information into Theorem 17 in order to eliminate some of the hypotheses in the applications.

Corollary 11 *Consider a arbitrary linear monotone controlled system (6.3. 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 by Lemma 24. Then $-CA^{-1}B - I$ is nonsingular by Lemma 31, and therefore Hurwitz by Theorem 17. Conversely, let

A and $-CA^{-1}B-I$ be Hurwitz. Then in particular $-CA^{-1}B-I$ is nonsingular. By Theorem 17 once again, $A+BC$ is Hurwitz. ∎

The following theorem relaxes the nonsingularity condition altogether, and imposes a strong monotonicity condition instead.

Theorem 18 *Let (6.3) be a monotone controlled system, and let A be Hurwitz. If $A+BC$ and $-CA^{-1}B-I$ are strongly quasimonotone, then*

$$\textit{sign}\ \mathrm{leig}(A+BC) = \textit{sign}\ \mathrm{leig}(-CA^{-1}B-I).$$

Proof. It remains only to consider the case $\det -CA^{-1}B-I=0$, or equivalently, $\det A+BC=0$. Define $\lambda := \mathrm{leig} A+BC$ and $\mu := \mathrm{leig} -CA^{-1}B-I$, and note that in particular $\lambda \geq 0,\ \mu \geq 0$. We show that $\lambda>0$ if and only if $\mu>0$, which will complete the result.

Suppose first that $\mu>0$. The key observation is that if $\lambda=0$, then there exists a unique vector $\sigma \gg 0$ (modulo multiplication by constant) such that $(A+BC)\sigma = 0$, by strong quasimonotonicity and the Perron-Frobenius theorem for quasimonotone matrices. Let $\tau \neq 0$ be such that $-CA^{-1}B\tau - \tau = 0$. Multiply by B from the left, and let w be such that $Aw=B\tau$. After simplifying, it holds that $-BCw-Aw=0$, or

$$(A+BC)w=0. \tag{6.5}$$

Note that $B\tau \neq 0$, since otherwise $0=-CA^{-1}B\tau-\tau=-\tau$. Therefore also $w \neq 0$. If it were true that $\lambda=0$, then by our observation above, $w=\alpha\sigma$, $\alpha \neq 0$. Now, after multiplying (6.5) from the left by CA^{-1} and canceling, we get

$$(-I-CA^{-1}B)C\sigma=0,\ Cu>0,$$

which is a contradiction, since by the Perron-Frobenius theorem for q.m. matrices the only eigenvalue of $-I-CA^{-1}B$ that can have positive eigenvectors is $\mu \neq 0$. Thus $\lambda>0$.

Conversely, let $\lambda>0$, and assume by contradiction $\mu=0$. Let $\sigma \gg 0$ be such that

$$-CA^{-1}B\sigma-\sigma=0. \tag{6.6}$$

Let τ be such that $B\sigma = A\tau$. Note that since $\sigma \gg 0$, it holds that $B\sigma > 0$, and therefore $\tau \neq 0$. In the same fashion as above, we have $(A+BC)\tau = 0$. Now, since A is quasimonotone and Hurwitz, it holds that for any $x > 0$,

$$A^{-1}x = -\int_0^\infty e^{tA}\, x \,\mathrm{d}t < 0,$$

see for instance [31], in the proof of Theorem 2. Therefore $\tau = A^{-1}Bu < 0$. The fact that $-\tau > 0$ is an eigenvector of the eigenvalue $0 \neq \lambda$ of $A + BC$ violates the Perron-Frobenius theorem, by strong quasimonotonicity. ∎

We say that an autonomous system

$$\dot{x} = g(x) \tag{6.7}$$

is an *orthant monotone system* if it is monotone with respect to an orthant cone $\mathcal{K} \subseteq \mathbb{R}^n$. In the following result we prove that in orthant monotone systems, the strong quasimonotonicity of $-CA^{-1}B - I$ is guaranteed by that of $A+BC$. This will eliminate an important assumption in the main results.

Theorem 19 *Consider a Hurwitz linear system (6.3) which is orthant monotone. Assume that all the columns of B, and all the rows of C, are nonzero. If $A + BC$ is strongly quasimonotone, then $-CA^{-1}B - I$ is strongly quasimonotone.*

Proof. Recall that by stability $Pv := -A^{-1}v = \int_0^\infty T(t)v\,\mathrm{d}t$, $v \in \mathbb{R}^n$, where $T(t)$ is the time t evolution operator of the system $\dot{x} = Ax$. Consider the graph G of the closed loop matrix $A+BC$, and the subgraph G' of the matrix A. If there is a directed path in G' from the variable x_k to x_l, then the l-th component of $T(t)e_k$ becomes (and remains) nonzero for $t > 0$; see Theorem 4 of [6] for a more complete discussion. That is, $e_l \cdot \int_0^\infty T(t)e_k\,\mathrm{d}t \neq 0$, or $p_{lk} \neq 0$. One can similarly verify the opposite statement, that is, if $p_{kl} = 0$, then there is no directed path from x_k to x_l.

Define for any input variable u_i the sets $R(u_i) := \{x_k \,|\, [B]_{ki} \neq 0\}$, $S(u_i) := \{x_l \,|\, [C]_{il} \neq 0\}$. By the assumptions in the statement, these sets are nonempty for every u_i.

We have that

$$[-CA^{-1}B]_{ij} = [CPB]_{ij} = \sum_{k,l=1\ldots n} c_{il}p_{lk}b_{kj}, \tag{6.8}$$

where $i \neq j$, $b_* = [B]_*$, $c_* = [C]_*, p_* = [P]_*$. By monotonicity, $\tau_i\tau_j c_{il}p_{lk}b_{kj} \geq 0$ for each k, l (otherwise one could arrive to a contradiction by deleting all remaining entries in the i-th row of C and j-th column of B). Therefore, $[-CA^{-1}B]_{ij} \neq 0$ if and only if there exist k, l such that $c_{il} \neq 0,\ p_{lk} \neq 0,\ b_{kj} \neq 0$. From the discussion above, it follows that $[-CA^{-1}B]_{ij} \neq 0$ if and only if there exist $x_k \in R(u_i)$ and $x_l \in S(u_j)$ such that there is a directed path from x_k to x_l.

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

Now consider two fixed inputs nodes u_i, u_j, $i \neq j$. To prove strong quasimonotonicity we find as follows a sequence $u_i = u_{h_1}, \ldots, u_{h_N} = u_j$, such that $[-CA^{-1}B]_{h_\lambda h_{\lambda+1}} \neq 0$, $\lambda = 1 \ldots N-1$. Let $x_k \in R(u_i)$, $x_l \in S(u_j)$, and consider a directed path in G from x_k to x_l. For every edge $(x_{f_\lambda}, x_{g_\lambda})$ that is on this path but not in G', let h_λ be such that $x_{g_\lambda} \in R(u_{h_\lambda})$, $x_{f_\lambda} \in S(u_{h_\lambda})$. The $u_{h_1} \ldots u_{h_N}$ satisfy the required criteria. ∎

Observe that if one of the columns of B (or one of the rows of C) is zero, then $CA^{-1}B$ may not be strongly quasimonotone, and neither can $-CA^{-1}B - I$.

For the sake of completeness, the following proposition is stated and proved, which gives sufficient conditions for the equivalence of the strong quasimonotonicity for $A+BC$ and $-CA^{-1}B$. The definitions of partial transparency and partial excitability are given in Section 10.1

Proposition 6 *Consider a Hurwitz linear system (6.3) which is monotone with respect to some orthant cones in $\mathbb{R}^n$, $\mathbb{R}^m$. Assume further that the system is partially excitable and partially transparent. Then $A+BC$ is strongly quasimonotone if and only if $-CA^{-1}B - I$ is strongly quasimonotone.*

Proof. Following up on the proof of Lemma 19, note that if for some variables x_k, x_l and u_i it holds that $x_l \in R(u_i)$, $x_k \in S(u_i)$, then necessarily $[BC]_{lk} \neq 0$ by definition, and therefore (x_k, x_l) is an arc in G.

The assumptions of partial excitability and partial transparency (other than implying the remaining hypotheses in the previous result) allow us to assume the following statement: for every x_l, there exist u_i and $x_k \in R(u_i)$ ($x_k \in S(u_i)$) such that there is a path on G' from x_k to x_l (from x_l to x_k). Assume that $-CA^{-1}B - I$ is strongly quasimonotone. Given any $x_k,\ x_l,\ k \neq l$, find a path from x_k to $x_{2k} \in S(u_i)$ and from $x_{2l} \in R(u_j)$ to x_l. Find a sequence $u_i = u_{h_1}, \ldots, u_{h_N} = u_j$, such that $[-CA^{-1}B]_{h_\lambda h_{\lambda+1}} \neq 0$, $\lambda = 1 \ldots N-1$, and use the equivalence after equation (6.8) and the paragraph above to find a directed path from x_k to x_l. ∎

6.4 The Main Results

Recall that $\mathcal{N}$ is the class of all matrices whose set of eigenvalues is contained in the closed left half of the complex plane. Given an autonomous dynamical system, E_s denotes the set of equilibria e such that the linearization of the system around e is in $\mathcal{N}$. Also recall that we use the terms 'Hurwitz' and 'exponentially stable' interchangeably. We denote the set of $x \in X$ with bounded orbit in (6.2) as B. A state $x \in X$ is called *reducible* if either $BC = 0$ or $A + BC$ is not strongly quasimonotone.

Consider a monotone controlled system (6.1), and the set function K^X defined in Section 6.2. The following proposition will help determine when an equilibrium $x \in K^X(h(x))$ is stable or exponentially unstable in the closed loop.

Proposition 7 *Let $p = (u_0, x_0) \in U \times X$, and let f in system (6.1) be a C^1 function. Then the following statements hold:*

1. *If x_0 is a limit point of $K^X(u_0)$, then* $\det A(p) = 0$.

2. *If $A(p)$ is Hurwitz, then there exists a C^1 function $k^X : S \to X$ defined on an open neighborhood S of u_0 such that $f(k^X(u), u) = 0$ on S. This function is unique except for extensions or restrictions of the domain S.*

3. *If the point p is non-reducible, and if all solutions of $\dot{x} = f(x, u_0)$ converge towards x_0, then $A(p)$ is Hurwitz.*

Proof. Since f is C^1, it can by definition be extended to an open set containing $U \times X$. Suppose first that x_0 is a limit point of $K^X(u_0)$. If $\det A(p) \neq 0$, then by the inverse function theorem the function $f(\cdot, u_0)$ would be injective in a neighborhood of p, which is a contradiction. This proves the first assertion.

The second assertion is a direct consequence of the implicit function theorem: since $A(p)$ is Hurwitz, then in particular $\det A(p) \neq 0$. Thus there exist open neighborhoods $S \subseteq \mathbb{R}^m$, $T \subseteq \mathbb{R}^n$ of u_0, x_0 respectively, and a C^1 function $k^X : S \to T$ such that

$$\text{graph } k^X = (S \times T) \cap \text{graph } K^X.$$

This implies the second statement of the Proposition.

To prove the third statement, note that by the convergence hypothesis it must hold $\text{leig} A + BC \leq 0$. Let $\epsilon > 0$ be small enough that $A + (1-\epsilon)BC$ is strongly quasimonotone. (In finite dimensions, the strong quasimonotonicity of a matrix M is determined by the strong monotonicity of e^{Mt} for any $t > 0$. This in turn is determined by whether the image of $\{x > 0 \mid |x| = 1\}$ under e^{Mt} is contained in int $\mathcal{K}$. Thus if M is strongly quasimonotone, a sufficiently small perturbation of its entries preserves this property.) Then by Lemma 25,

$$\text{leig} A \leq \text{leig} A + (1-\epsilon)BC < \text{leig} A + BC \leq 0,$$

and the conclusion follows. See also the proof of Theorem 20.

∎

Note that in the proof above one can conclude without loss of generality that $A(k^X(u))$ is Hurwitz, for each $u \in S$. This assertion follows after possibly restricting the domain of definition of k^X so that $A(u, k(u))$ is Hurwitz for all $u \in \text{Dom } k$, which is possible by continuity of the eigenvalues. Such a function can be referred to as a *stable branch* of the function K^X.

Example Consider the system

$$\begin{cases} \dot{x} = uy - x \\ \dot{y} = x - y, \end{cases} \quad x, y \geq 0, \; u \geq 0. \tag{6.9}$$

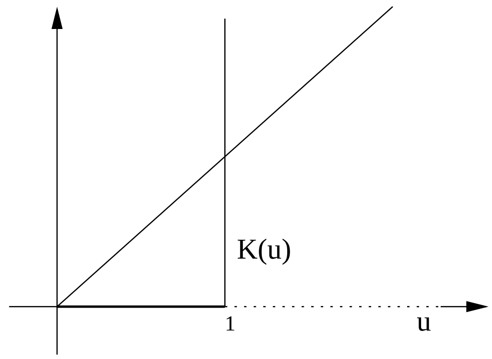

Figure 6.1: The function $K(u)$ for the system (6.9).

For $u < 1$ ($u > 1$), this system has a unique equilibrium at the origin, which is Hurwitz (exponentially unstable). Therefore $K^X(u) = \{0\}$ for such u. But $K^X(1) = \{(x, x) \,|\, x \in \mathbb{R}\}$. If we set $h(x, y) = x$, we can draw the set function K as in Figure 6.1. Note that condition (H) is not satisfied in this example, since for instance the vectors $(1, 0)$ and $(1, 1)$ are equilibria with the same output value. There are two points u such that $u \in K(u)$: $u = 0$, associated to the (reducible) equilibrium $(x, y) = (0, 0)$, and $u = 1$, associated to the (non-reducible) equilibria $(1, y)$, y arbitrary.

Assume that the set of equilibria of the strongly monotone closed loop system (6.2) is countable. By Hirsch's theorem, almost all bounded solutions converge towards some point in E. We are now able to state the main result, which discriminates among the equilibrium points those that are stable from those that are exponentially unstable. Not surprisingly, all Hurwitz points turn out to be on stable branches, but even here stability is not guaranteed.

Theorem 20 *Consider a system (6.1) which is monotone with respect to an orthant cone, and whose closed loop (6.2) is strongly monotone. Assume that the set of equilibria of (6.2) is countable. Then almost all bounded solutions of (6.2) converge towards those equilibrium points $x_0 \in E$ that are either reducible (if any), or such that $A(h(x_0), x_0)$ is Hurwitz and $-CA^{-1}B - I$ is in $\mathcal{N}$.*

Proof. As mentioned above, Hirsch's theorem [49] guarantees that almost all states $x \in X$ with bounded orbit satisfy $\omega(x) \subseteq E$. Since any such omega limit set is nonempty and connected, and E is countable, it follows that $w(x)$ is a singleton for almost every

$x \in X$ with bounded orbit. That is, the solution of almost every $x \in B$ converges towards some equilibrium point $x_0 \in E$. Furthermore, By Corollary 4.5 in [48] (which uses the enumerability of E), almost every $x \in B$ has a solution which converges towards an equilibrium $x_0 \in E_s$.

Consider an equilibrium x_0 of the closed loop (6.2), and the linearization (6.3) of the open loop system around $p = (h(x_0), x_0)$. The linearization of the closed loop around this point has the form

$$\dot{x} = (A + BC)x. \tag{6.10}$$

We observe first that if $A(p)$ is exponentially unstable, then $A + BC$ is itself exponentially unstable by Lemma 25. By the Perron Frobenius theorem, the leading eigenvalue of $A(p)$ is real and positive, and by Lemma 24 the leading eigenvalue of $A + BC$ is also positive.

Now, let x_0 be non-reducible and such that $\mathrm{leig}(A(p)) = 0$. We cannot directly apply Lemma 25, since A is not necessarily strongly quasimonotone. But we know that $A + BC$ is strongly quasimonotone. Therefore there must exist a small number $\epsilon > 0$ such that $A + (1 - \epsilon)BC$ is strongly quasimonotone. By Lemma 24, $0 = \mathrm{leig}(A) \leq \mathrm{leig}(A + (1 - \epsilon)BC)$. Since also $\epsilon BC > 0$, we apply Lemma 25 to conclude that $\mathrm{leig}(A + BC) > 0$. Thus this equilibrium is also exponentially unstable. This shows how the exponential stability of $A(p)$ is a necessary condition for a non-reducible point p to have a closed loop linearization in $\mathcal{N}$.

Finally, let $A(p)$ be a Hurwitz matrix and let p be non-reducible. By Theorem 19, and using the assumption that the monotonicity is with respect to orthant cones, we conclude that $A + BC$ is in $\mathcal{N}$ (Hurwitz) if and only if $-CA^{-1}B - I$ is in $\mathcal{N}$ (Hurwitz). This completes the result. ∎

Note that the non-reducible points x_0 such that A is Hurwitz and $-CA^{-1}B - I$ is Hurwitz are guaranteed to have a basin of attraction with nonempty interior. Conversely, note that if x_0 is reducible, then it only potentially has a nontrivial basin. For instance, if A is exponentially unstable for this point, then $A + BC$ is also exponentially unstable and the basin has measure zero.

The following lemma serves as a criterion for ruling out the exponential stability of certain equilibria.

Lemma 32 *Under the hypotheses of Theorem 20, let $x_0 \in K^X(h(x_0))$ be an equilibrium of (6.2). Assume that x_0 is non-reducible, and that it is an accumulation point of $K^X(h(x_0))$. Then almost no solutions of (6.2) converge towards x_0.*

Proof.

Since by Proposition 7 $\det A(p) = 0$, it holds that $\mathrm{leig}(A(p)) \geq 0$. Since $B, C \neq 0$, it follows that $BC > 0$. The same argument as was done in the proof of Theorem 20 shows that $\mathrm{leig}(A + BC) > 0$ and $A + BC$ is an exponentially unstable matrix. Therefore in the context of Corollary 4.5 of [48], x_0 cannot be a 'trap', and therefore almost no bounded solutions converge towards x_0. Evidently no unbounded solution can converge towards x_0 either. ∎

If it is assumed that the equilibria of (6.2) are nonsingular, then both the hypotheses and the conclusion of the statement can be simplified. Note that the statement allows for monotonicity with respect to abstract cones (as opposed to merely orthant cones).

Theorem 21 *Consider a controlled monotone system (6.1) such that the closed loop system (6.2) is strongly monotone and has nonsingular equilibria. Then almost all bounded solutions of (6.2) converge towards those equilibrium points corresponding to vectors p which are on a stable branch and such that $-CA^{-1}B - I$ is exponentially stable.*

Proof. Since the equilibria of the closed loop system are nonsingular, the inverse function theorem can be invoked at every equilibrium $e \in E$. This implies that g is injective in a neighborhood of e and that therefore E is discrete and countable. Let $p \in U \times X$ correspond to an equilibrium of (6.2). Since by the Perron-Frobenius theorem the leading eigenvalue of $A + BC$ is real, nonsingularity in particular implies that $A + BC$ is hyperbolic. If $\mathrm{leig}A \geq 0$, then $\mathrm{leig}A + BC > 0$ by hyperbolicity, and therefore almost no initial condition will converge towards p. Thus almost all solutions converge to those points p with $\mathrm{leig}A(p) < 0$. Now suppose that p is such a point. Since $A + BC$

is nonsingular, it holds by Lemma 31 that $-CA^{-1}B - I$ is nonsingular. Thus by Theorem 17, exponential stability holds if and only if $-CA^{-1}B - I$ is Hurwitz. ∎

The following corollary is equivalent to the main theorem in [31].

Corollary 12 *Consider a controlled monotone system (6.1) with strongly monotone closed loop, and such that for every $u \in U$, $K^X(u) = k^X(u)$ is a singleton. Assume also that $A(u, k^X(u))$ is nonsingular for every u, and that the fixed points of the reduced system (6.4) are also nonsingular.*

Then almost all bounded solutions of (6.2) converge towards those equilibrium points corresponding to vectors p such that $-CA^{-1}B - I$ is Hurwitz.

Proof. To apply the previous theorem, we only need to verify that the equilibria of the closed loop (6.2) are nonsingular. But this follows from Lemma 31, and the fact that the equilibria of the reduced system are nonsingular.

Since $k^X(u)$ attracts all solutions of $\dot{x} = f(x, u)$ for every fixed u by monotonicity, it follows in particular that $\text{leig}(A) \not> 0$. By nonsingularity of A, it must hold that A is a Hurwitz matrix, for every u. Therefore the graph of K^X is one single stable branch. The conclusion of the corollary follows. ∎

The next corollary assumes the stronger condition of hyperbolicity instead of nonsingularity. This may be useful in experimental applications, where a log plot of the dynamics over time can potentially distinguish between exponential and asymptotic stability.

Corollary 13 *Consider an orthant monotone system (6.1) with strongly monotone closed loop and hyperbolic equilibria. Assume that the set of equilibria is discrete. Then the conclusion of Theorem 20 holds.*

Proof. The necessity of the exponential stability of $A(p)$ follows as in the proof of Theorem 21. The remainder of the proof is as in that of Theorem 20. ∎

The following theorem is the result of current unpublished work inspired by these results, in the case that the set of equilibria E is not assumed to be discrete. Recall that C is the set of states whose solution is convergent towards an equilibrium.

Proposition 8 *Consider a system $\dot{x} = f(x)$ which is strongly monotone with respect to a closed cone with nonempty interior. Assume that every set of reducible equilibria $\hat{E} \subseteq E$ which is totally ordered with respect to $\ll$ is at most countable. Assume also that the set C has dense interior in X. Then almost all bounded solutions converge towards an equilibrium in E_s.*

See chapter 2 of [101] for relatively weak conditions under which C has dense interior. This result gives rise to the following variant of the main theorem, which does not assume the discreteness of E.

Theorem 22 *Consider a C^1 system (6.1) defined on a closed orthant X of $\mathbb{R}^n$, and whose closed loop (6.2) is strongly monotone with respect to an orthant cone. Let the system have bounded solutions, and let all reducible equilibria of the system lie in ∂X. Then almost all bounded solutions of (6.2) converge towards those equilibrium points $x_0 \in E$ that are either reducible (if any), or such that $A(h(x_0), x_0)$ is Hurwitz and $-CA^{-1}B - I$ is in $\mathcal{N}$.*

Proof. Since all reducible equilibria are contained in ∂X, there cannot be two such equilibria ordered by $\ll$. The fact that int C is dense in X can be argued as follows: consider the C^1 system $\dot{x} = f(x)$ restricted to int X, which has uniformly bounded solutions by hypothesis. In this system int C is dense in int X, by the theorems in pp. 19-23 of [101]. The conclusion then follows for C in the original system.

By Proposition 8, we know that almost all bounded solutions converge towards some equilibrium in E_s. The same argument as in Theorem 20 can then be used to show that if an equilibrium $e \in X$ is non-reducible, then e is in E_s if and only if $A(h(x_0), x_0)$ is Hurwitz and $-CA^{-1}B - I$ is in $\mathcal{N}$. ∎

Branches

Consider an open and connected set $S \subseteq U$ (open in U) and a C^1 function $k^X : S \to X$, such that for all $u \in S$, $k^X(u) \in K^X(u)$. If $A(u, k^X(u))$ is Hurwitz for each $u \in S$, the graph of k^X is called a *stable branch of* K^X. Similarly, if $A(u, k^X(u))$ is exponentially unstable for each $u \in S$, then the graph of k^X is an *unstable branch of*

K^X. Finally, given $u \in U$, if the set L of limit points of $K^X(u)$ is nonempty, then L is called a *vertical branch* of K^X.

Multiple Branching As seen in the Example 6.9, it is possible for a point (u_0, x_0) to be adjacent to multiple branches simultaneously. Although in this example $(1, (0, 0))$ is only a part of the vertical branch, it is a priori possible for a point to be part of more than one branch simultaneously, or to none at all. We can rule out some possibilities: for instance, a single point p cannot be part of both a stable and an unstable branch, since the former would imply that $A(p)$ is Hurwitz, and that latter that it is exponentially unstable. But a single point may a priori be part of, say, two different branches of the same type. Under this light, Proposition 7 can be viewed as stating that 1) a vertical branch does not intersect any stable or unstable branches; 2) if $A(p)$ is Hurwitz, then p is part of exactly one branch, and this branch is stable. In particular, the only branches that can intersect other branches are the unstable ones.

Chapter 7

Applications and Further Results

7.1 Two Simple Autoregulatory Transcription Networks

The following example will be extended in the following section, but it will be useful to provide it here as a first simple case. In a study of nitrogen catabolism, Mischaikow et al. [11] consider an eucaryotic unicellular organism (specifically, yeast) which produces a protein that crosses the nuclear membrane and promotes the further production of its own messenger RNA. Let another protein also influence the transcription of the messenger RNA, and denote its (for now fixed) concentration by λ. Denote by r, p and q the concentrations of the mRNA, the intranuclear protein, and the extranuclear protein respectively, and describe the system by the equations

$$\begin{aligned} \dot{p} &= K_i q - K_e p - a_2 p \\ \dot{q} &= T(r) - K_i q + K_e p - a_3 q \\ \dot{r} &= H(p, \lambda) - a_1 r. \end{aligned} \tag{7.1}$$

Here the functions H, T are such that $\partial H/\partial p > 0,\ \partial H/\partial \lambda > 0,\ T'(r) > 0$ and represent the transcription and translation rate, respectively. The constants $a_1,\ a_2,\ a_3$ are dilution/degradation coefficients, and the constants $K_i,\ K_e$ represent the rates of import and export of protein through the nuclear membrane, respectively. (The original model in [11] uses more arbitrary increasing functions $K_i(x),\ K_e(x)$.) In order to study the stability of this model, we write it as the closed loop of the controlled system

$$\begin{aligned} \dot{p} &= K_i u - K_e p - a_2 p \\ \dot{q} &= T(r) - K_i q + K_e p - a_3 q \qquad h(p, q, r) = q, \\ \dot{r} &= H(p, \lambda) - a_1 r. \end{aligned} \tag{7.2}$$

It can be easily verified that this controlled system is monotone, and that for every value of u there exists a unique equilibrium of the system with fixed control u. In particular, the variable q converges globally to the value

$$q(u) = c_1 T(c_2 H(c_3 u, \lambda)) + c_3 c_4 u,$$

where $c_1 = \frac{1}{K_i + a_3}$, $c_2 = \frac{1}{a_1}$, $c_3 = \frac{K_i}{K_e + a_2}$, $c_4 = \frac{K_e}{K_i + a_3}$. The function $q(u)$ corresponds to the set characteristic $k(u) = K(u)$ from the previous chapter.

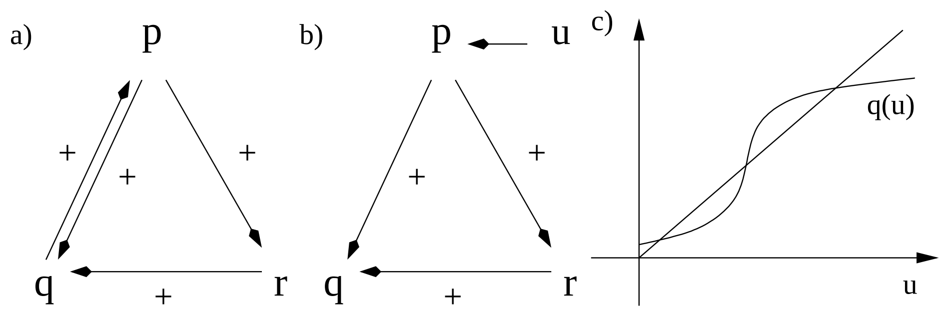

Figure 7.1: System (7.1) has the associated digraph a). Item b) illustrates that of the open loop system (7.2), and Item c) its associated function $q(u) = K(u) = k(u)$.

We verify that this open loop system contains no reducible points. First, note that the linearization of the closed loop system at any point has the associated digraph in Figure 7.1 a), since all functions involved have positive derivative. Therefore the matrices $A + BC$, in the notation of the previous chapter, are all irreducible. Second, note that the derivative of the right hand side of (7.2) with respect to u is a nonzero matrix at every point, as is also ∇h. It is easy to verify that the multiplication of these two matrices is nonzero, and the conclusion follows.

By Theorem 20, one can determine the set E_s in (7.1) for every fixed value of λ simply by looking at the fixed points of the function $K(u) = k(u)$ (such as on Figure 7.1 c)) and the respective slopes. That is, the equilibria in E_s correspond to the intersections $(\bar{u}, \bar{u})$ of $q(u)$ with the diagonal for which $q'(\bar{u}) \leq 1$, and the Hurwitz equilibria to those points such that $q'(\bar{u}) < 1$. The fact that this correspondence is a bijection is guaranteed by the following Lemma, which will also be useful below.

Lemma 33 *System (7.1) satisfies property (H).*

Proof. Suppose that (p_1, q_1, r_1), (p_2, q_2, r_2) are two equilibria of (7.1) such that $q_1 = q_2$. From the first equation in (7.1) we deduce that $p_1 = p_2$, and therefore also $r_1 = r_2$. This implies the statement. ∎

We conclude by the lemma above that the equilibria of the system are in bijective correspondence with the fixed points of $q(u)$. Furthermore, since there are no reducible equilibria, we can apply Theorem 20, to conclude that almost all (bounded) solutions converge towards the points corresponding to fixed points $\bar{u}$ of $q(u)$ with $q'(\bar{u}) \leq 1$.

Using λ as a Control

After studying the stability of system (7.1) for fixed λ, we now consider this system *itself* as a monotone controlled system with control λ. The previous discussion becomes useful to study the resulting new characteristic function $k^X(\lambda)$. Letting now $h(x) = p$ *for this new system*, one can find the values p_λ towards which p may converge given a fixed value of λ. These values form the *set characteristic* $k(\lambda)$.

The following technical Lemma will be used in the next section. We say that a set function f is *injective** if $y \in f(x_1)$, $y \in f(x_2)$ implies $x_1 = x_2$. This is the same as requiring that $f(x_1) \cap f(x_2) = \emptyset$ whenever $x_1 \neq x_2$.

Lemma 34 *The function $K(\lambda)$ is injective*.*

Proof. Simply note that $\partial q / \partial \lambda > 0$, and that therefore for every fixed u, there can be at most one λ such that $q(u, \lambda) = u$. The result follows by definition of $K(\lambda)$. ∎

Most often $K(\lambda)$ consists of two stable branches and one unstable branch, which are joined together as in Figure 7.2 d). In the end of the following section, we will provide a third and final layer of complexity for this case study.

Switch-like Behavior Observe in Figure 7.2 that system (7.1) may behave like a switch: for values of λ in a high (low) range, there is a unique equilibrium which has a high (low) output. If one maintains a high value of λ, one can after some time return to a medium range and the state still tends to converge towards the high equilibrium, and vice versa. Bistable behavior plays a central role in differentiation and other biological

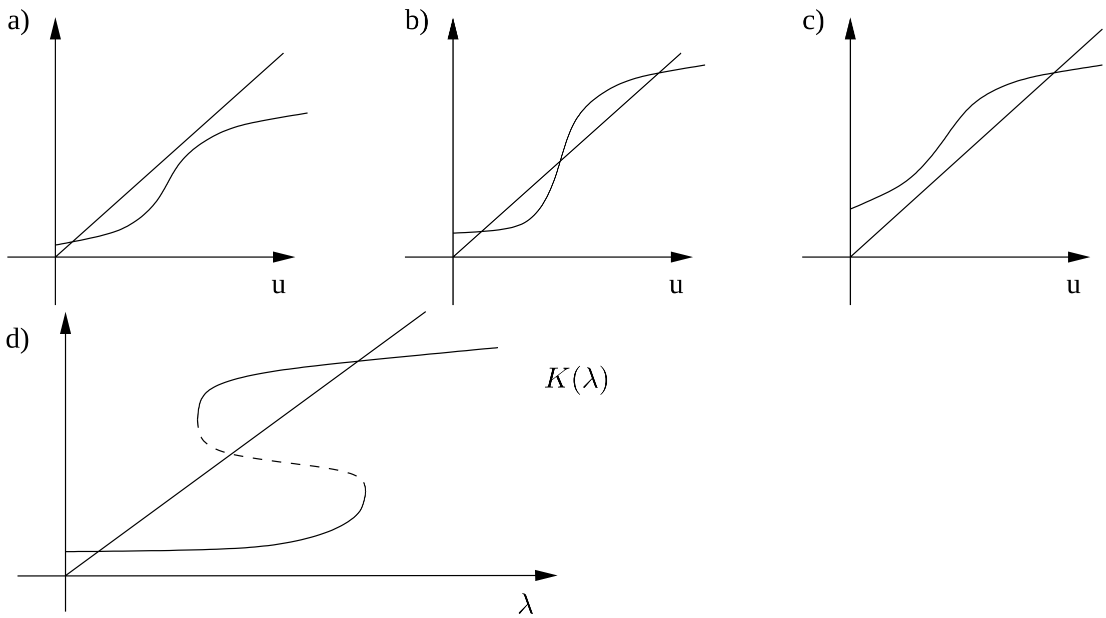

Figure 7.2: The function $k(u)$ for a) low, b) medium, and c) high values of the constant λ. Using the main results, one can conclude which equilibria are Hurwitz for every fixed value of lambda, and therefore draw the function $K(\lambda)$ for the (now) open loop system (7.1), $h(p, q, r) = q$.

forms of memory, as has been recognized in classical work on the lambda phage lysis-lysogeny switch and the hysteretic *lac* repressor system [78, 90] as well as the current literature. See for instance Thattai [85] for a more recent treatment.

7.1.1 A Second Application

Consider a strongly monotone system (6.2) and its associated reduced system (6.4). In the case that (6.4) is itself strongly monotone and has bounded solutions, one can apply Hirsch's theorem and deduce that almost all trajectories converge toward one of the Hurwitz steady states. The question arises as to whether the analogy between the two systems could be carried further: if the output function h were surjective, does it hold that $x(t, x_0)$ converges to $\bar{x}$ in (6.2) if and only if $u(t, h(x_0))$ converges to $h(\bar{x})$ in (6.4)? In other words, do the basins of attraction of each stable point correspond to each other, as the stable points do? Unfortunately this is not true, as the example below will illustrate.

Our second application of the main results in the previous chapter is an example of a coupled biological circuit. An important class of proteins, referred to as *transcription factors*, regulate transcription of messenger RNA by promoting (or inhibiting) the binding of the enzyme RNA polymerase to the DNA sequence. An autoregulatory transcription factor regulates the production of its own messenger RNA. Transcription factors are very common, and often more than one is necessary for RNA polymerase to initiate transcription. For a mathematical analysis of the simple autoregulatory circuit, see Smith [101][1].

Let p_1, p_2 be two autoregulatory transcription factors, and r_1, r_2 their corresponding messenger RNAs. We will couple the circuits by assuming that the proteins are also needed to regulate each other's transcription. The dynamics of the circuit is thus expressed as follows:

$$\begin{aligned} \dot{p}_i &= a_i r_i - b_i p_i \\ \dot{r}_i &= g_i(p_1, p_2) - c_i r_i, \end{aligned} \qquad i = 1, 2. \tag{7.3}$$

We assume that both $g_1(p_1, p_2)$ and $g_2(p_1, p_2)$ are increasing functions of both p_1 and p_2, as well as positive and bounded. The interconnections are illustrated in Figure 7.3. Note that all the solutions of this system are bounded: the boundedness of the functions g_i bounds the values of r_i as $t \to \infty$, and this in turns bounds the values of the variables p_i.

We analyze the dynamics of this system by cutting the loop as indicated in the figure, and we arrive to the following controlled system with two inputs:

$$\begin{aligned} \dot{p}_i &= a_i u_i - b_i p_i \\ \dot{r}_i &= g_i(p_1, p_2) - c_i r_i, \end{aligned} \qquad i = 1, 2. \tag{7.4}$$

which is monotone under the usual positive orthant cone. If we fix the input (u_1, u_2), the system converges toward the point

$$p_i = \frac{a_i}{b_i} u_i, \quad r_i = \frac{1}{c_i} g_i \left(\frac{a_1}{b_1} u_1, \frac{a_2}{b_2} u_2 \right),$$

[1] The standard model in p. 58 of [101] is in fact another interesting application of Theorem 20: by cutting the arc $x_n \to x_1$ as explained in our example, the results in Section 4.2, [101], follow by looking at the fixed points of $k(u) = \alpha_1^{-1} \ldots \alpha_n^{-1} g(u)$. Furthermore, the local stability of each equilibrium is determined by the slope of $k(u)$ at each corresponding fixed point.

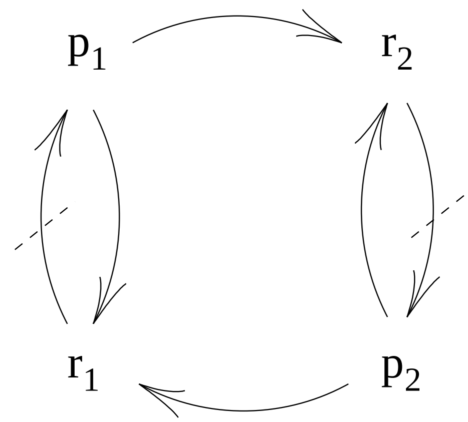

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Figure 7.3: Interconnections for system (7.3). The dotted lines indicate where the interconnections will be cut and replaced by inputs.

which constitutes the value of k^X at the point (u_1, u_2). In order for the closed loop to be (7.3), we need

$$h(p_1, p_2, r_1, r_2) = (r_1, r_2),$$

which when composed with k^X yields

$$k(u, v) = \left(\frac{1}{c_1} g_1\left(\frac{a_1}{b_1} u_1, \frac{a_2}{b_2} u_2\right), \frac{1}{c_2} g_2\left(\frac{a_1}{b_1} u_1, \frac{a_2}{b_2} u_2\right)\right).$$

Under mass action kinetics assumptions, a quasi-steady state analysis (see [57]) yields for the g_i the general form

$$g_i = \hat{\sigma}_i \frac{p_1^{m_i} p_2^{n_i}}{\hat{K}_i + p_1^{m_i} p_2^{n_i}}. \tag{7.5}$$

The coefficients m_i, n_i describe the cooperativity with which the proteins bind to the DNA sequence. For instance, if two p_1 proteins bind to each other (forming a *dimer*) before acting on the DNA sequence of p_i, then $m_i = 2$. It is a reasonable assumption that the cooperativity of a given protein is the same as it bind to any of the two DNA sequences, that is $m_1 = m_2 = m, n_1 = n_2 = n$. We set for the sake of the argument $m = 2, n = 1$. The remaining coefficients $\hat{K}_i, \hat{\sigma}_i$ are determined by the way the proteins bind to the particular DNA sequence and how they aid the polymerase enzyme. We have

$$k(u_1, u_2) = \left(\sigma_1 \frac{u_1^2 u_2}{K_1 + u_1^2 u_2}, \sigma_2 \frac{u_1^2 u_2}{K_2 + u_1^2 u_2}\right),$$

where $\sigma_i = \hat{\sigma}_i c_i^{-1},\ K_i = \hat{K}_i a_1^{-2} b_1^{-2} a_2^{-1} b_2^{-1}$.

Stability Analysis

This system will now be studied in the framework of the main results in the previous chapter. First, recall that since the system has a well defined characteristic function k^X, then the property (H) is satisfied and the set E is in bijective correspondence with the fixed points of k.

Now the degeneracy of the equilibria in E is discussed.

Lemma 35 *The only reducible equilibrium of system (7.3), using the form of the functions g_i given by (7.5), is the trivial equilibrium* 0*. This equilibrium is stable.*

Proof. Note that for every fixed point $e \in E$ it holds $C \neq 0$ and $B \neq 0$. In fact, given the different digraphs associated to the open and closed loops around a given fixed point, and given that they are given by the matrices A and $A+BC$ respectively, it must follow $BC \neq 0$. Also note that if (u_1, u_2) is a fixed point of k and $u_1 = 0$, then necessarily $u_2 = 0/K_2 = 0$. Similarly for u_2. Therefore if $k(u) = u$, then either $u = 0$ or $u \gg 0$. One can similarly see that for $e \in E$, either $e = 0$ or $e \gg 0$. But for $e \gg 0$, the Jacobian matrix associated to the closed loop system around e is given by Figure 7.3, and e is therefore a non-reducible point. We conclude that the only reducible equilibrium is 0. It can be verified by hand that $\mathrm{leig} A + BC < 0$ at this reducible equilibrium, thus completing the proof of the statement. ∎

We have therefore successfully 'reduced' the four dimensional system (7.3) to the simpler, two dimensional system (6.4), as the following corollary concludes.

Corollary 14 *The stability of every equilibrium in (7.3) corresponds to that of its associated equilibrium in the reduced system (6.4)*

Proof. For the exponentially stable equilibrium 0 of the closed loop system, this follows from Theorem 17. The remaining equilibria are on stable branches by Proposition 7, item 3. The conclusion follows by Theorem 20. ∎

Observe that for the reduction argument above we have used relatively little information about the reduced system itself. In the paragraphs below, we proceed to actually find its equilibria and illustrate their stability.

Finding the Solutions of the Reduced Model

Apart from the trivial solution $(0,0)$, the equation $k(u_1,u_2) = (u_1,u_2)$ can be rewritten as

$$K_1 + u_1^2 u_2 = \sigma_1 u_1 u_2, \quad K_2 u_2 + u_1^2 u_2^2 = \sigma_2 u_1^2 u_2. \tag{7.6}$$

We solve for u_1 in the first equation of (7.6) and replace in the second equation, obtaining

$$K_1 u_1^2 = (\sigma_2 u_1^2 - K_2)(\sigma_1 - u_1)u_1\,. \tag{7.7}$$

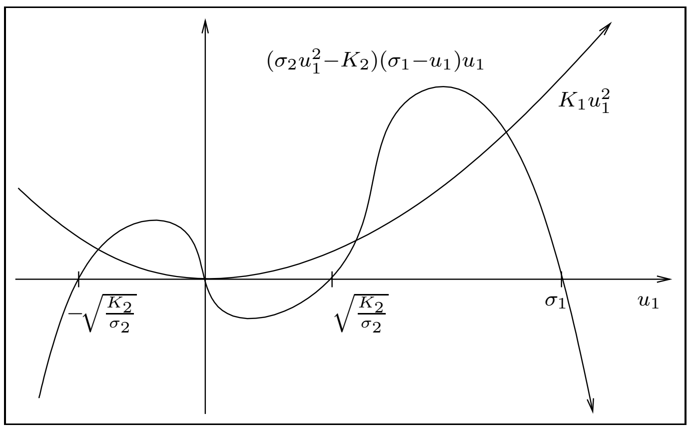

Figure 7.4: The solutions of the system of equations (7.7)

From Figure 7.4 we see that there might be only one nonnegative solution of (7.6) (i.e., the trivial solution $u_1 = 0$), or there may be three nonnegative solutions, in the case that K_1, K_2 are comparatively small. In Figure 7.5 one can see an example in which the reduced system has one exponentially unstable and two exponentially stable equilibria. Therefore the same is true for the original system (7.3). Note that additional solutions may appear outside of the positive quadrant.

Given the simple form of the output function $h(x) = (r_1, r_2)$, any basin of attraction of $\dot{u} = k(u) - I$ will correspond in X (under h^{-1}) to a rather rigid set, namely that of every (p_1, p_2, r_1, r_2) such that (r_1, r_2) is in the basin. It is clear that the basins of attraction of (7.3) don't have this form — this limits the analogy between (7.3) and its reduced system.

On the other hand, the same procedure can be applied for cones that are not necessarily the positive orthant: for instance if, in the above example, each protein promoted its own growth and *inhibited* each other's growth, then $\mathcal{K}_X = \mathbb{R}^+ \times \mathbb{R}^- \times \mathbb{R}^+ \times \mathbb{R}^-$ would make (7.3) strongly monotone.

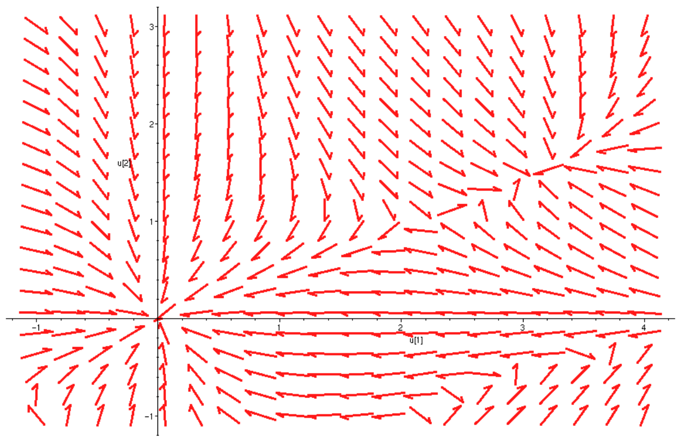

Figure 7.5: The vector field $\gamma(u) = k(u) - u$, using parameter values $\sigma_1 = 4, \sigma_2 = 2, K_1 = 4, K_2 = 5$.

7.2 Stable Equilibrium Descriptors

In this section we illustrate a way to apply systematically the main results in order to carry out an analysis of a more complex monotone system.

Consider an autonomous, monotone dynamical system

$$\dot{x} = f(x) \tag{7.8}$$

which allows a representation by the signed digraph G. It will be assumed for the sake of simplicity that $X = (\mathbb{R}^+)^n$ throughout this section. The definition that follows is quite general, and it doesn't necessarily require monotonicity (but we do it given what follows).

Let H be a proper subdigraph of G, not necessarily generated by a proper subset of the vertices of G. Let

$$\mathrm{In}(H) = \{x_i \in V(G) \,|\, \text{there exists } x_j \in V(H) \text{ such that } (x_i, x_j) \in E(G) - E(H)\}$$
$$\mathrm{Out}(H) = \{x_i \in V(H) \,|\, \text{there exists } x_j \in V(G) \text{ such that } (x_i, x_j) \in E(G) - E(H)\}$$

Note that the elements of $\mathrm{In}(H)$ may or may not lie on $V(H)$.

Enumerate $\mathrm{In}(H)$ as $\{x_{\alpha_1}, \ldots, x_{\alpha_m}\}$ and $\mathrm{Out}(H)$ as $\{x_{\omega_1}, \ldots, x_{\omega_l}\}$. If the variables are denoted in a different way (for instance $p_1 \ldots p_2, q_1 \ldots q_s$ as below), the definition can be adapted slightly in the natural way. Then one can define a controlled dynamical system with $U = (\mathbb{R}^+)^m,\ Y = (\mathbb{R}^+)^l$ by

$$\dot{x} = f_H(x, u), \quad y = h(x), \tag{7.9}$$

Here the nodes of H are used as the variables of the system, and the function f_H is formed by replacing x_{α_i} with u_i on every function f_j such that $x_j \in V(H),\ (x_{\alpha_i}, x_j) \in E(G) - E(H)$. The output function $h : X \to Y$ is defined as $h(x) = (x_{\omega_1}, \ldots, x_{\omega_l})$.

We define the set function $S_H : U \to \mathcal{P}(Y)$ in the following manner: for every $u \in U$, let

$$S_H(u) = \{h(x_0) \,|\, f_H(x_0, u) = 0 \text{ and } \frac{\partial f_H}{\partial x}(x_0, u) \text{ is Hurwitz}\}.$$

We refer to the function S_H as the *stable equilibrium descriptor* associated to H, or *SED(H)* for short.

The Case $\mathbf{V(H) = V(G)}$ Special consideration is given to the case in which $V(H) = V(G)$, that is when H is the result of merely eliminating a number of arcs from G. In that case (7.9) is simply a canonical decomposition of (7.8) as a monotone control system under positive feedback. It holds by definition that $In(H) = Out(H)$, and it is further imposed in this case that the same enumeration be used for these sets, that is $\alpha_i = \omega_i$ for all i. Under these conditions, the closed loop of the system is simply (7.8). Furthermore, the graph of S_H consists precisely of the 'stable branches' of the set characteristic function K^X.

Cascades of SEDs

Given a cascade of controlled systems

$$\dot{z}_i = g_i(z_1, \ldots, z_i),\ i = 1 \ldots k, \tag{7.10}$$

it is easy to see that the equilibria of (7.10) are in one to one correspondence with tuples $(\bar{z}_1, \ldots, \bar{z}_k)$ of equilibria z_i of each cascade step. The following lemma gives a similar statement involving the stability of the equilibria.

Lemma 36 *Consider a (not necessarily monotone) cascade (7.10). Then a tuple of vectors* $(\bar{z}_1, \ldots, \bar{z}_k)$ *is an exponentially stable equilibrium if and only if for every* i, $\bar{z}_i$ *is an exponentially stable equilibrium of*

$$\dot{z}_i = g_i(\bar{z}_1, \ldots, \bar{z}_{i-1}, z_i). \tag{7.11}$$

Proof. The proof is obvious from the fact that the characteristic polynomial of the cascade is the product of that for $B_i i$, for $i = 1, \ldots, n$. ∎

The following lemma will allow the streamlined use of the main results in applications, and it can be thought of as a nonlinear version of the result above. Let H be a subdigraph of a signed digraph G, and let $H_1, \ldots H_k$ be subdigraphs of H. We say that the H_i form a *cascade decomposition* of H if:

1. The sets $V(H_i)$ form a partition of $V(H)$.
2. $\mathrm{In}(H) = \mathrm{In}(H_1)$, and $\mathrm{Out}(H) = \mathrm{Out}(H_k)$.
3. $\mathrm{Out}(H_i) = \mathrm{In}(H_{i+1})$ for $i = 1 \ldots k-1$.

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

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

Lemma 37 *Consider an orthant monotone system (7.8). Let* $H \leq G$*, and let* $H_1, \ldots H_k$ *be a cascade decomposition of* H*. Then* $S_H = S_{H_k} \circ \ldots \circ S_{H_1}$.

Proof.

System (7.9) can be written as a cascade

$$\dot{x}^i = f_H^i(x^1, \ldots, x^i, u), \quad i = 1 \ldots k.$$

Since (7.8) is orthant monotone, there exists a function $V(g) \to \{-1, 1\}$ which is consistent with G - see Section 3.4. The same function can be used to show that the systems induced by $H, H_1, \dots H_k$ are (orthant) monotone as well. Let u be a fixed input for this system, and let $y \in S_H(u)$. That is, let the vector tuple $\bar{x} = (\bar{x}^1, \dots, \bar{x}^k)$ be an exponentially stable equilibrium of this cascade, and $y = h(\bar{x})$. By the previous lemma, it holds that for every $i = 1 \dots k$ the vector $\bar{x}^i$ is an exponentially stable equilibrium of

$$\dot{x}^i = f_H^i(\bar{x}^1, \dots, \bar{x}^{i-1}, x^i, u). \tag{7.12}$$

Now consider for each i the system

$$\dot{x}^i = f_{H_i}(x^i, u^i), \tag{7.13}$$

with output $h_i(x^i)$. We show that for $y^i := h_i(\bar{x}^i)$ for all i, it holds that

1. $y^1 \in S_{H_1}(u)$
2. $y^i \in S_{H_i}(y^{i-1})$, $i = 2 \dots k$, and
3. $y_k = y$.

This will imply that $y \in S_{H_k} \circ \dots \circ S_{H_1}(u)$.

To see 1. note that $f_H^1(x^1, u) = f_{H_1}(x^1, u)$ by $\mathrm{In}(H) = \mathrm{In}(H_1)$, and that therefore $\bar{x}^1$ is an exponentially stable equilibrium of $\dot{x}^1 = f_{H_1}(x^1, u)$ by (7.12). Therefore $y^1 = h_1(\bar{x}^1) \in S_{H_1}(u)$ by definition. Statement 3. follows directly from the fact that $\mathrm{Out}(H) = \mathrm{Out}(H_k)$.

We show that for every $i = 2, \dots k$, $\bar{x}^i$ is an exponentially stable equilibrium of

$$\dot{x}^i = f_{H_i}(x^i, y^{i-1})$$

(from which 2. follows by definition). To see this, note that since $y^{i-1} = h_{i-1}(\bar{x}^{i-1})$, $f_{H_i}(x^i, y^{i-1})$ is the result of replacing all variables in f_j that are not in $V(H_i)$ with the corresponding values from $\bar{x}^{i-1}$. That is, $f_{H_i}(x^i, y^{i-1}) = f_H^i(\bar{x}^1, \dots, \bar{x}^{i-1}, x^i)$. The statement follows once again by (7.12).

The other direction of the proof consists of letting $y \in S_{H_k} \circ \dots \circ S_{H_1}(u)$, and showing that $y \in S_H(u)$. By definition, there exist vectors y_i, $i = 1 \dots k$, such that the statements 1., 2., 3. above hold. Define $\bar{x}^i$ to be some exponentially stable equilibrium of (7.13), which must exist by definition of S_{H_i}, $i = 1 \ldots k$. By the same argument as before one can show that $\bar{x} = (\bar{x}^1, \ldots, \bar{x}^k)$ is an exponentially stable equilibrium of (7.9), using the previous lemma. After observing that $y = y^k = h(\bar{x})$, the conclusion follows to imply that $S_H(u) = S_{H_k} \circ \ldots \circ S_{H_1}(u)$. ∎

Note: one can generalize this statement to the case where $\dot{x} = f(x)$ is not orthant monotone, but each individual H_i is. This is more general than assuming that H is orthant monotone: the interconnections between H_i and H_{i+1} may not be consistent if $|\mathrm{Out}(H_i)| > 1$.

7.3 A Larger Example

Now we are ready for the analysis of a medium scale, monotone dynamical system. Consider a cycle of k proteins $p_1, \ldots, p_k$, each of which with its respective messenger RNA. Let each protein promote the transcription of its own mRNA, as documented for example in [11] 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_k. The full system therefore looks like

$$\begin{aligned} \dot{p}_i &= K_{imp,i}(q_i) - K_{exp,i}(p_i) - a_{2i} p_i \\ \dot{q}_i &= T(r_i) - K_{imp,i}(q_i) + K_{exp,i}(p_i) - a_{3i} q_i \;\; i = 1 \ldots k, \\ \dot{r}_i &= H(p_1, p_{i-1}) - a_{1i} r_i, \end{aligned} \tag{7.14}$$

where p_0 is identified with p_k throughout. (The model in [11] lets certain inter-protein transcription factors be inhibitory, and doesn't fit the present analysis from here on). Let all constant parameters of this system be positive. As to the nonlinear functions T_i, H_i, assume that they are nonnegative, and that

$$\begin{aligned} &T(0) = 0,\ T_i'(\theta) > 0, K_{s,i}(0) = 0, \mathcal{K}_{s,i}'(\theta) > 0,\ i = 1 \ldots k,\ s = \text{‘imp’}, \text{‘exp’},\ \theta \geq 0, \\ &H_i(0,0) = H_i(0,\phi) = H_i(\theta,0) = 0,\ \nabla H_i(\theta,\phi) \gg 0,\ i = 1 \ldots k,\ \theta, \phi > 0. \end{aligned} \tag{7.15}$$

See Figure 7.6 for an illustration. In order to best visualize the behavior of this complex system, only one input will be introduced, and the multi-valued function $K(u)$

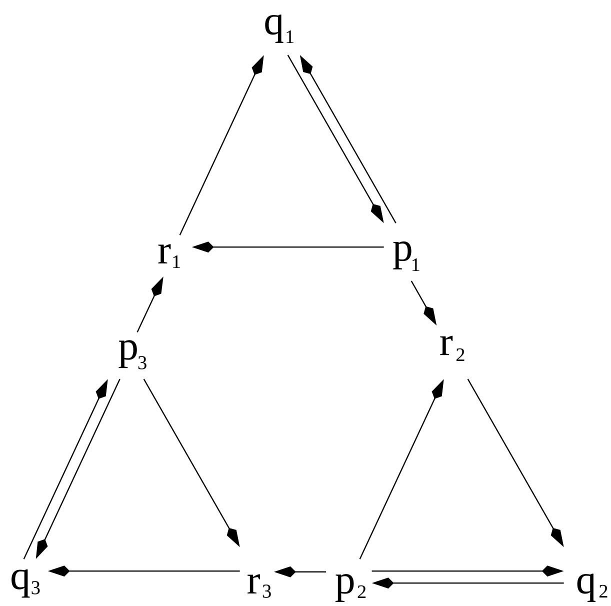

Figure 7.6: The digraph associated to system (7.14) in the case $k = 3$.

will be computed using the tools from digraph decompositions. The open loop system considered is

$$\begin{aligned}
\dot{p}_i &= K_{imp,i}(q_i) - K_{exp,i}(p_i) - a_{2i}p_i, \ i = 1 \dots k, \\
\dot{q}_i &= T(r_i) - K_{imp,i}(q_i) + K_{exp,i}(p_i) - a_{3i}q_i, i = 1 \dots k, \\
\dot{r}_i &= H(p_1, p_{i-1}) - a_{1i}r_i, \ i = 2 \dots k, \\
\dot{r}_1 &= H(p_1, u) - a_{1i}r_1,
\end{aligned} \quad , \quad h(p_i, q_i, r_i) = p_k. \tag{7.16}$$

Lemma 38 *The only reducible equilibrium of system (7.16) is the trivial equilibrium* 0.

Proof. The fact that the origin is an equilibrium is an immediate consequence of the hypotheses. Since $\nabla H_i(0, 0) = 0$ for all i, this equilibrium has a Jacobian which is not irreducible, and it is therefore a reducible equilibrium.

If e is an equilibrium such that, say, $q_i = 0$ 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 $r_{i+1} = 0$. Using such arguments, it follows that if $e \not\gg 0$, then $e = 0$.

If $e \gg 0$, on the other hand, then the hypotheses on the partial derivatives in (7.14) ensure that the Jacobian at the point e has the associated digraph in Figure 7.6. Also for such an equilibrium, the associated matrices B and C are nonzero, and in fact $BC \neq 0$ by the argument given above. It follows that e is a non-reducible equilibrium.

∎

The exponential stability of the origin itself can be readily verified by directly computing the Jacobian.

We find an efficient way to compute the function $K(u)$ as well as its stable branches. In order to do this, we apply the results on cascade decompositions above.

Let H consist of the same nodes and arcs of G except for the arc (p_k, r_1), so that in effect S_H consists of the stable branches of K. Consider the subdigraph H_i of G generated by the nodes r_i, p_i, q_i, for each $i = 1 \ldots k$. It holds that $\mathrm{In}(H_i) = \{p_{i-1}\}$ and that $\mathrm{Out}(H_i) = \{p_i\}$. If K_i is the characteristic function of the i-th system of the form (7.2), then it clearly follows that $K = K_k \circ \ldots \circ K_1$. This decomposition of (7.14) is used for the following result.

Lemma 39 *System (7.16) satisfies condition (H).*

Proof. This is a direct consequence of Lemmas 33 and 34: let (p_1^i, q_1^i, r_1^i), (p_2^i, q_2^i, r_2^i) be two different equilibria such that $p_1^k = p_2^k$. Let j be the least index such that $(p_1^j, q_1^j, r_1^j) \neq (p_2^j, q_2^j, r_2^j)$. We can view the system associated to H_i as a closed loop of the form (7.2), and use as constant λ the value $p_1^{i-1} = p_2^{i-1}$, or $p_1^k = p_2^k$ if $i = 1$. From Lemma 33 it follows that $p_1^j \neq p_2^i$. But from Lemma 34 it follows that $p_1^{i+1} \neq p_2^{i+1}$. Inductively, it must follow $p_1^k \neq p_2^k$, which is a contradiction. ∎

This lemma can be generalized to abstract closed cascades as follows: if every component of the cascade satisfies condition (H) and has injective* characteristic, then the closed loop of the cascades also satisfies (H).

Corollary 15 *Every nonzero equilibrium $e \in E_s$ in (7.14) corresponds bijectively to a fixed point on a stable branch of the real, multivalued function $K(u)$, with slope less or equal than 1.*

Proof. Follows from the fact that every nonzero equilibrium in E_s is non-reducible, Theorem 22, Lemma 30, and Lemma 39. ∎

It is easy to see that $H_1, \ldots, H_k$ form a cascade decomposition of the graph H. By Lemma 37, S_H can be written as the composition of all the functions S_{H_i}, $i = 1 \ldots k$. We write this in the following corollary.

Corollary 16 *Every nonzero equilibrium $e \in E_s$ in (7.14) corresponds bijectively to a fixed point on the graph of $S_{H_1} \circ \ldots \circ S_{H_k}$, with slope less or equal than 1.*

We implemented these ideas on Matlab, using the functions

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

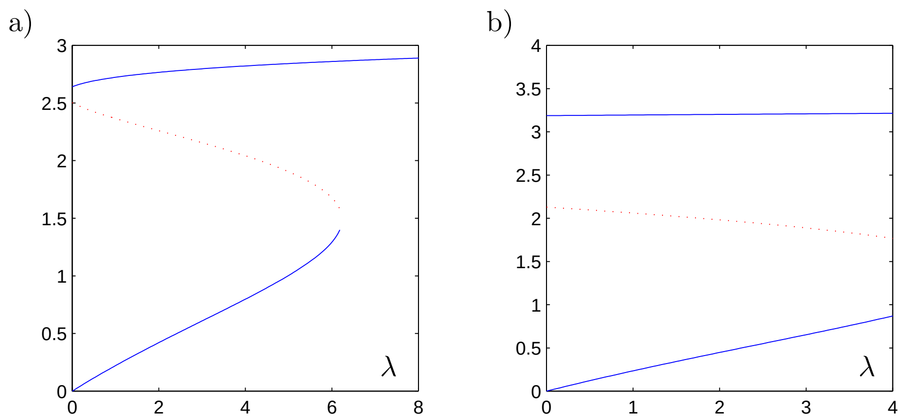

Figure 7.7: The multivalued characteristic graphs for system (7.1), using the parameters sets from (7.17). Stable branches are solid, and unstable branches are dotted.

The function H can be derived using Michaelis-Menten kinetics (quasi steady state analysis, see [57]) in the case of the gene regulation of two proteins that form m- and n-mers before binding to the mRNA protein (resp.) and which complement each other in the sense that either of the two can facilitate the transcription process without the other's help. For simplicity, we will assume $m = 4,\ n = 1$ throughout (albeit in the case of cascades of two subsystems, it would be more realistic to let $m = 1,\ n = 4$ for the second subsystem, etc). The function $T(r)$ is another Hill-type function with saturation, and the functions K_{imp}, K_{exp} are assumed to be linear.

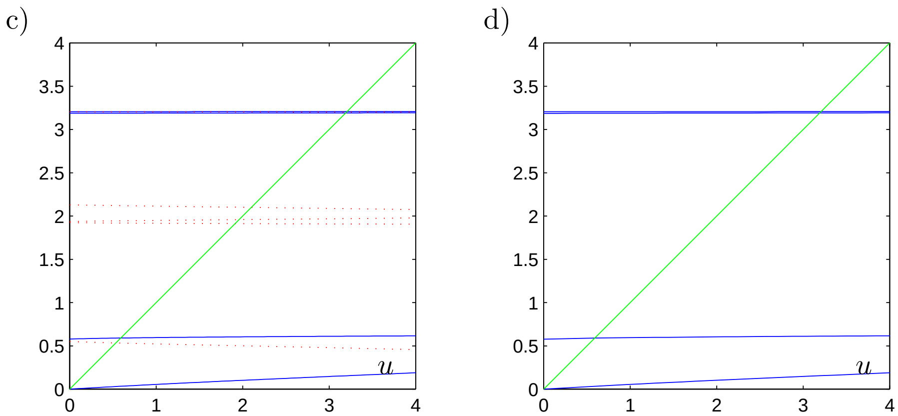

Figure 7.8: In chart c), the function $K(u)$ for system (7.14), $k = 2$, using the systems from Figure 7.7 a) and b) as first and second components, respectively, by composing the functions in these two charts. In chart d), the stable branches are isolated, thus forming the function $S_H(u) = S_{H_2} \circ S_{H_1}$.

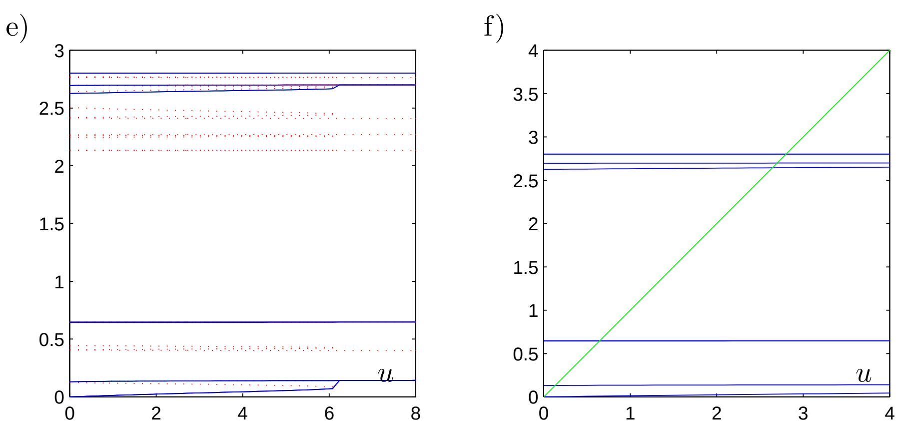

Figure 7.9: In e) and f), the same procedure as in Figure 7.8 is carried out for a system (7.14), $k = 3$, using the systems from Figure 7.7 a), b) and a) as first, second and third components, respectively.

Consider two subsystems of the form (7.1), with parameters

$$
\begin{aligned}
&\text{First System: } K_i = 1/6;\ K_e = 1/15;\ a_1 = 1;\ a_2 = 1/10;\ a_3 = 1/6;\\
&A_1 = 1;\ A_2 = 1;\ A_4 = 10;\ B_1 = 16;\ B2 = 10,\\
&\text{Second System: } K_i = 1/6;\ K_e = 1/12;\ a_1 = 1;\ a_2 = 1/12;\ a_3 = 1/6;\\
&A_1 = 1;\ A_2 = 1;\ A_4 = 10;\ B_1 = 16;\ B_2 = 10,
\end{aligned}
\tag{7.17}
$$

and coupled in the form (7.14), $k = 2$. Let the system be opened in the form (7.16), and write its associated digraph as a cascade of the subsystems H_1, H_2 as given above. In Figure 7.7 a),b) are illustrated the functions $K(\lambda)$ of the two subsystems in the sense of Section 7.1. Recall that the output of those systems was $h = q$, and that the output of the subsystems here should rather be p. To avoid confusion, the constants K_i, K_e, a_2 are chosen throughout so that $p = q$ for any equilibrium of a system (7.1). The characteristic function $K(u)$ of system (7.14) can therefore be seen as the composition of these two functions, and it is depicted in Figure 7.8 c). (Note that the resolution of the graph can present a problem in the upper right corner.) By Lemma 37, the stable branches of $K(u)$ are the composition of those of the two subsystems – they are illustrated as solid lines throughout the Figure, and separately on Figure 7.8 d).

Every one of the intersections of the graph in Figure 7.8 c) with the diagonal represents an equilibrium in system (7.14). But only a few of those are stable, and they correspond to those points in Figure 7.8 d) on a stable branch (and whose slope is less or equal than one).

In Figure 7.9, a nine-variable system is considered as in Figure 7.6. By composing the function in Figure 7.8 c) with that in Figure 7.7 a), the associated set valued characteristic is given in Figure 7.9 e), and its associated stable branches (i.e. the function S_H) in Figure 7.9 f).

7.4 Introducing Diffusion or Delay Terms

The discussion of the previous and present chapters has been carried out exclusively for finite dimensional systems. Given a strongly monotone system, the problem has been to find the equilibria towards which almost all of the solutions converge, and the strategy to do this has been to root out all the exponentially unstable equilibria of the system. It turns out that the results given have a very direct application to the case of delay or reaction diffusion strongly monotone systems. To do this one will use the two properties of monotone systems described in Sections 3.7 and 3.8: a strongly monotone delay (reaction diffusion) system can have its delay (diffusion) term removed without changing the general stability properties around an equilibrium (see these sections for details). We will also make use of the results from Chapter 8, for the reaction-diffusion case.

7.4.1 Delay Systems

It is not uncommon for biological systems to involve delays. For instance, in the above example, it is known that cells can take a few minutes, or more, creating and folding a protein from the moment that the messenger RNA is present. This will lead to a delay τ_i to appear in the first equation of (7.4), $i = 1, 2$. Another common source of delays is given by the transport of molecules, say, through the blood flow, an example of which is the delay in the system of Chapter 2. It is possible for a delay to be detected experimentally, yet not to be able to identify its cause, for instance if additional protein and transcription interactions are unknown.

Let $\hat{\mathcal{K}} \subseteq \mathbb{R}^n$ be a closed cone with nonempty interior. Consider a delay system

$$\dot{x} = f(x_t) \tag{7.18}$$

defined on the state space $X \subseteq C([-\tau, 0], \mathbb{R}^n)$, which is strongly monotone with respect to

$$\mathcal{K} := \{\phi \in C([-\tau, 0], \mathbb{R}^n) \mid \phi(t) \in \hat{\mathcal{K}} \text{ for every } t\},$$

and which has a countable set of equilibria E. We can associate to this system the finite dimensional system

$$\dot{x} = \hat{f}(x), \tag{7.19}$$

where $\hat{f}(x) = f(\hat{x})$. See Section 5.1. This system is strongly monotone with respect to $\mathcal{K}$ (see comments before Corollary 5.5.2 in [101]). The fact that any equilibrium of (7.18) is a constant function means that there is a natural correspondence between the equilibria of (7.18) and (7.19). In the case of reaction-diffusion equations, a similar correspondence doesn't hold; see Section 12.1.

The key result is Corollary 4, which ensures that an equilibrium $\hat{e}$ of (7.18) is exponentially unstable if and only if the corresponding equilibrium e of (7.19) is exponentially unstable.

In order to generalize the results of the previous chapter to infinite-dimensional systems, we will use the following convenient concept of 'sparseness' due to Yorke et al. and Christensen [51, 17]. A Borel measurable subset A of a Banach space $\mathbb{B}$ is said to be *shy* if there exists a compactly supported Borel measure μ on $\mathbb{B}$ such that $\mu(A + x) = 0$ for every $x \in \mathbb{B}$. See also Chapter 8. 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.

Define the sets

$$B = \{\phi \in X \,|\, O(\phi) \text{ has compact closure in } X\}$$
$$C = \{\phi \in X \mid \lim_{t\to\infty} x(t, \phi) = \{e\} \text{ for some } e \in E\}$$
$$C_s = \{\phi \in X \mid \lim_{t\to\infty} x(t, \phi) = \{e\} \text{ for some } e \in E_s\}$$

The strong monotonicity theorem by Hirsch still applies to system (7.18), i.e. the set of elements in B whose solution doesn't converge to the set of equilibria is shy (Theorem 26). Since E is countable, any solution that converges to the set of equilibria actually converges towards some equilibrium. Moreover, the set of states that converge towards an exponentially unstable equilibrium is shy - see Lemma 45. Using the fact that a countable union of shy sets is shy we obtain the following result.

Corollary 17 *Let the strongly monotone system (7.18) have enumerably many equilibria. Then C_s is prevalent in B.*

The proof of Theorem 20 consists of rooting out the exponentially unstable equilibria e of a dynamical system (7.19), which correspond to the exponentially unstable equilibria $\hat{e}$ of (7.18). A consequence is the following corollary.

Corollary 18 *Consider a finite dimensional system (6.1) which is monotone with respect to an orthant cone, and whose closed loop (6.2) is strongly monotone. Then every equilibrium $e \in E_s$ of (6.1) is either reducible, or such that $A(h(e), e)$ is Hurwitz and $-CA^{-1}B - I$ is in $\mathcal{N}$.*

We have the following theorem, whose proof follows by combining the two previous corollaries.

Theorem 23 *Let $\hat{\mathcal{K}}$ be an orthant cone, and let (7.18) be a strongly monotone system with respect to $\mathcal{K}$ with countable equilibria. Then almost all bounded solutions of (7.18) converge towards those equilibrium points $\hat{e}$ such that the corresponding equilibrium e of (7.19) is either reducible (if any), or such that A is Hurwitz and $-CA^{-1}B - I$ is in $\mathcal{N}$.*

Notes: The words 'almost every' are given here in the context of prevalence. See Section 6.4 for the terminology A, B, C, given an equilibrium e of (7.19).

Example

Consider the delay system

$$\begin{aligned} \dot{p}_i &= a_i r_i(t - \tau_i) - b_i p_i \\ \dot{r}_i &= g_i(p_1, p_2) - c_i r_i, \end{aligned} \qquad i = 1, 2, \tag{7.20}$$

corresponding to the finite dimensional system (7.3) with the introduction of one transcription delay. It is important to verify that this delay system is strongly monotone with respect to some well chosen state space — this can be done by verifying the conditions (M), (I), (R) from Chapter 5 of [101] in the cooperative case. See also Section 3.7. Once this has been verified, by the argument above almost all solutions (in the prevalence sense) of the system converge towards one of the equilibria in E_s of (7.3), which was studied in Section 7.1. These equilibria correspond in turn to those of the two dimensional, strongly monotone system (6.4), by Corollary 14). A vector field for this system is displayed in Figure 7.5.

7.4.2 Reaction-Diffusion Systems

Consider a convex bounded domain $\Omega \subseteq \mathbb{R}^m$ with smooth boundary, and a reaction diffusion system under Neumann boundary conditions

$$\dot{x} = \Delta x + f(x) \tag{7.21}$$

which is strongly monotone with respect to

$$\mathcal{K} := \{x \in C(\Omega, \mathbb{R}^n) \,|\, x(q) \in \hat{\mathcal{K}} \text{ for every } q\},$$

for $\hat{\mathcal{K}}$ an orthant cone. Useful sufficient conditions for the strong monotonicity of this system are given in Chapter 7 of [101] in the cooperative case; see also Chapter 8.

To this system we associate the finite-dimensional system

$$\dot{x} = f(x). \tag{7.22}$$

If the state e is an equilibrium of (7.22), then the constant function $\hat{e}$ is an equilibrium of (7.21). But, unlike in the delay case, there may be equilibria of (7.21) which do not correspond to equilibria of (7.22), i.e. which are not uniform in space. Moreover, assuming the existence of only countably many equilibria of (7.21) can be difficult to enforce, see Corollary 22. The material in Chapter 8 can be seen in fact as a generalization of Corollary 17 to the case of more abstract spaces. In the case of reaction-diffusion systems, Theorem 29 provides the result that we need to extend the ideas from Chapter 6.

Let system (7.22 be written as the closed loop of a controlled monotone system $\dot{x} = g(x, u)$, $u = h(x)$, and for a given equilibrium $e \in E$ define as before $A = g_x(e, h(e))$, $B = g_u(e, h(e))$, $C = h_x(e)$.

Theorem 24 *Let (7.21) be such that f is C^1 and system (7.22) is strongly cooperative, $f'(x)$ is irreducible for all x, the solutions of (7.21) are uniformly bounded, and Ω is convex. Then almost all bounded solutions of (7.21) converge towards those equilibrium points $\hat{e}$ such that the corresponding equilibrium e of (7.22) is either reducible (if any), or such that A is Hurwitz and $-CA^{-1}B - I$ is in $\mathcal{N}$.*

Proof. By the proof of Theorem 29, C_s is prevalent in X for the system (7.21). We know from Kishimoto et al. [59] that in the case that $\partial f_i/\partial x_j > 0$ for all $i \not= j$, E_s is contained in the set of uniform equilibria. It can be verified by following the proof in that reference that the same result is true in the general strongly cooperative case, as long as every element of E_s is irreducible. Therefore almost all states in B converge towards some uniform, equilibrium in E_s (in the sense of prevalence). But by Proposition 2, these equilibria are in bijective correspondence with the equilibria in E_s of (7.22). Corollary 18 provides a criterion for finding these equilibria, and using it the statement of this theorem follows. ∎

Example

Consider the system (7.14), under the functions given by (7.15), except that

$$\nabla H_i(\theta, \phi) \gg 0, \; i = 1 \ldots k, \; \theta, \phi \geq 0,$$

instead of only for $\theta, \phi > 0$. Then one can verify that system (7.14) has no reducible equilibria, following a very similar argument as under the original assumptions in Section 7.3, and that therefore the assertion in Corollary 15) holds for every equilibrium $e \in E_s$ of (7.14) including $e = 0$. Consider the reaction-diffusion system

$$\begin{aligned} \dot{p}_i &= d_{pi}\Delta p_i + K_{imp,i}(q_i) - K_{exp,i}(p_i) - a_{2i}p_i \\ \dot{q}_i &= d_{qi}\Delta q_i + T(r_i) - K_{imp,i}(q_i) + K_{exp,i}(p_i) - a_{3i}q_i \\ \dot{r}_i &= d_{ri}\Delta r_i + H(p_1, p_{i-1}) - a_{1i}r_i. \end{aligned} \tag{7.23}$$

By establishing the usual correspondence $\hat{e} \to e \to (h(e), h(e))$ between uniform equilibria of (7.23) and the fixed points of the multivalued function $K(u)$, we reach the following conclusion.

Corollary 19 *The set of states that converge towards a equilibrium in E_s of (7.23) is prevalent in X. Every such equilibrium corresponds bijectively to a fixed point on a stable branch of the real, multivalued function $K(u)$, with slope less or equal than 1.*

Proof. Follows from Theorem 7.21, the uniform boundedness of (7.14) following from the fact that (7.14) has bounded solutions, and using the monotonicity hypothesis for the diffusion system. The proof that the correspondence is a bijection follows as in Corollary 15. ∎

7.5 Low Pass Filters

It turns out that the controlled systems considered in the main results of Chapter 6 allow for certain kinds of subsystems to be introduced downstream, without changing the quantitative values of their I/O characteristic, their steady states, or the stability of each of their steady states. An important example will be the introduction of *low pass filters*, which are subsystems that imitate the introduction of delays in a finite dimensional setting (see below).

Consider a controlled monotone system

$$\dot{x} = f(x,u),\ y = h(x)\,, \tag{7.24}$$

whose closed loop is strongly monotone with respect to a closed cone with nonempty interior. For the sake of simplicity, let the function $K^X = k^X$ be single valued, and assume that 1) for every u, $k(u)$ is an exponentially stable, globally attractive equilibrium of $\dot{x} = f(x,u)$, and that 2) every equilibrium of E is nonsingular. In particular, k^X is a strong I/S characteristic, see [31].

Consider a second controlled monotone system with I/O characteristic, which is an extension of (7.24) of the form

$$\begin{aligned} &\dot{x} = f(x,u),\ y = h(x), \\ &\dot{z} = g(z,v),\ v = y,\ w = H(z)\,. \end{aligned} \tag{7.25}$$

Here $Y = V$ and $W = U$, and $g(z,v)$ and H are chosen so that, in an appropriate technical sense, and for large classes of inputs v, the second system satisfies

$$H(z(t)) \simeq v(t-\tau)$$

independent of initial conditions. A simple example is of course $\tau\dot{z} = v - z$ (and, more generally, a linear system $\dot{z} = Az + Bv$, $w = Cz$ which is a state-space model of a Padé approximation of the delay $e^{\tau s}$ in the frequency domain) or a cascade of such systems. We will give sufficient conditions to ensure that the closed loop of the extended system (7.25) can be reduced to the closed loop of (7.24) in a similar fashion as it was done in Section 7.4.

We will say that a system of the form (7.25) *reduces* to its corresponding system (7.24) if both have the same I/O characteristic, and if the points in E_s (the exponentially stable points) of their corresponding (unity-feedback) closed loops are in canonical correspondence.

Theorem 25 *Consider monotone systems (7.25.1) and (7.25.2) with I/O characteristics $k_1(u)$ and $k_2(v) = v$ respectively. Assume that the closed loop systems of (7.24) and (7.25) are strongly monotone. Then system (7.25) has a I/O characteristic, and it reduces to system (7.24).*

Proof.

We linearize the controlled system (7.25), around a fixed input value u and a fixed state (x, z), and the resulting linear system has the form

$$\begin{pmatrix} x \\ z \end{pmatrix}' = \begin{pmatrix} f_x(x,u) & 0 \\ g_v(z,h(x))h_x(x) & g_z(z,h(x)) \end{pmatrix} \begin{pmatrix} x \\ z \end{pmatrix} + \begin{pmatrix} f_u(x,u) \\ 0 \end{pmatrix} u,$$

$$w = \begin{pmatrix} 0 & H'(z) \end{pmatrix} \begin{pmatrix} x \\ z \end{pmatrix}.$$

Since (7.25.2) is monotone and has a well defined I/S characteristic, fixing an input value u and letting $h(t) = v(t)$ converge to $k_1(u)$ will make $z(t)$ converge to $k^Z(k_1(u))$. This follows from the converging input, converging state property, see [6]. Thus $H(t)$ converges towards $Hk^Z(k_1(u)) = k_2(k_1(u)) = k_1(u)$. This means that the extended system (7.25) has a well defined I/O characteristic which is equal to that of (7.24). In particular, it has nondegenerate fixed points (using the notation of [31]). We verify that $k(u) = (k^X(u), k^Z k_1(u))$ is also nondegenerate:

$$\det \begin{pmatrix} f_x(x,u) & 0 \\ g_v(z,h(x))h_x(x) & g_z(z,h(x)) \end{pmatrix} = \det f_x(x,u)\ \det g_z(z,h(x))$$

and evaluating at $x = k^X(u)$, $z = k^Z k_1(u)$, by nondegeneracy of k_1 and k_2 we have $\det f_x(k^X(u), u) \neq 0$, $\det g_z(k^Z k_1(u), k_1(u)) \neq 0$ and nondegeneracy of the new characteristic follows.

The exponentially stable equilibria of (7.25) are in canonical correspondence with those of $\dot{u} = h(k_1(u)) - u$ by Theorem 20, and these correspond to those of (7.24), again by Theorem 20. ∎

See also Lemma 36. As a sufficient condition for the strong monotonicity of the system (7.25), one can assume their partial or strong excitability and transparency. See Section 10.1.

For the specific case of orthant cones, the following result can be used to apply one or more different delays while guaranteeing the strong monotonicity of the closed loop of (7.25). Consider a sign definite monotone system with multiple outputs

$$\begin{aligned} &\dot{x} = f(x, u),\ y_\ell = h_\ell(x), \\ &\dot{z}_\ell = g_\ell(z_\ell, v_\ell),\ v_\ell = y_\ell,\ w_\ell = H_\ell(z_\ell),\ \ell = 1 \ldots p \end{aligned} \tag{7.26}$$

In this case we have $Y_\ell = V_\ell = W_\ell$, $U = \prod_{\ell=1}^{p} Y_\ell$. Note that it would be rather unrealistic to suppose even the excitability or transparency of each of the systems $\dot{x} = f(x, u)$, $y_\ell = h_\ell(x)$, because the inputs and outputs might have been picked rather artificially in order to study the effects of delays in a particular variable. Instead, we assume that the closed loop system $\dot{x} = f(x, y_1, \ldots y_p)$ has a strongly connected digraph, and that it is therefore strongly monotone, see [7]. We also assume that $\dot{x} = f(x, u)$, $y_\ell = h_\ell(x)$ has *non-idle inputs and outputs.* A sign definite controlled system (7.24) has non-idle inputs (outputs) if for every input variable u_i (output variable y_i) in the digraph there exists some state variable x_j s.t. there is a directed path from u_i to x_j (a directed path from x_j to y_i). As for the systems $\dot{z}_\ell = g_\ell(z_\ell, v_\ell)$, $w_\ell = H_\ell(z_\ell)$, we will assume that for every input variable $v_{\ell j}$ there is a directed path from $v_{\ell j}$ to the output $w_{\ell j} = v_{\ell j}$, and that there is one such path passing through each state variable $z_{\ell i}$.

Proposition 9 *Consider a monotone system (7.26) under the hypotheses in the paragraph above, and let k_0, k_ℓ be I/O characteristics of $\dot{x} = f(x, u)$, $\dot{z}_\ell = g_\ell(z_\ell, v_\ell)$ respectively, $\ell = 1 \ldots p$. Let $k_\ell(v_\ell) = v_\ell$ for all ℓ. Then (7.26) reduces to system (7.24).*

Proof. As in the proof of the previous theorem, it is easy to show that the characteristic of system (7.26) is equal to that of (7.24), and so it has nondegenerate fixed points. To check for nondegeneracy of the characteristic itself, we need to compute the determinant of the linearization matrix, which is equal to

$$\det \frac{\partial}{\partial x} f(x,u) \cdot \det \frac{\partial}{\partial z_1} g_1(z_1, h_1(x)) \cdot \ldots \cdot \det \frac{\partial}{\partial z_p} g_p(z_p, h_p(x)).$$

Evaluating at $x = k^X(u),\ z_\ell = k^{Z_\ell}(k_0(x)), \ell = 1 \ldots p$ and using nondegeneracy of each subsystem's characteristic, this implies this property for the cascade's characteristic.

We argue now that the digraph associated with the cascade is strongly monotone. Consider two state variables x_i, x_j. Since $\dot{x} = f(x, y_1, \ldots y_p)$ is strongly connected, there exists a path from x_i to x_j that may cross through output variables $y_{\ell_1 j_1}, \ldots y_{\ell_p j_p}$ and the corresponding input variables $u_{\ell_1 j_1}, \ldots u_{\ell_p j_p}$. Given our assumption on the controlled systems $\dot{z}_\ell = g_\ell(z_\ell, v_\ell),\ w_\ell = H_\ell(z_\ell)$, we can naturally extend this path so as to lead from x_i to x_j in the closed loop of the cascade system. To go from x_i to a state $z_{\ell q}$, find a path from some input $v_{\ell p}$ to $z_{\ell q}$, and then by non-idleness of outputs find a path from some x_j to $v_{\ell p}$. Finally, find a path from x_i to x_j as described above. To find a path from a state $z_{\ell q}$ to other states in the digraph, follow a path from $z_{\ell q}$ to some output $w_{\ell p} = u_j$, and from u_j to some x_i by non-idleness of inputs; then proceed as before.

The last statement of the proposition is proved as in the preceeding theorem. ∎

This result can be directly applied to insert pseudo-delays $\tau_1, \ldots \tau_p$ in the system, as in the following corollary.

Corollary 20 *Consider a monotone sign definite system $\dot{x} = F(x)$ whose digraph is strongly connected. Let $x_{i_1}, \ldots x_{i_p}, x_{j_1}, \ldots x_{j_p}$ be states s.t. $\frac{\partial}{\partial x_{i_\ell}} F_{j_\ell}(x) \neq 0,\ \ell = 1 \ldots p$, and replace all appearances of x_{i_ℓ} in $f_{j_\ell}(x)$ by u_ℓ, to form the controlled system $\dot{x} = f(x,u),\ y_\ell = h_\ell(x) = x_{i_\ell},\ \ell = 1 \ldots p$. Suppose that this system admits an I/O characteristic k_0. Then the cascade (7.26) reduces to (7.24), where*

$$\begin{aligned} \tfrac{\tau_\ell}{L} \dot{z_{\ell 1}} &= -z_{\ell 1} + v_\ell \\ \tfrac{\tau_\ell}{L} \dot{z_{\ell i}} &= -z_{\ell i} + z_{\ell(i-1)} \end{aligned} \qquad i = 2 \ldots L,\ H_\ell(z_\ell) = z_{\ell L},\ \ell = 1 \ldots p,$$

and $\tau_\ell \dot{z}_\ell = -z_\ell + v_\ell,\ H_\ell(z_\ell) = z_\ell$ *in the case* $L = 1$.

Proof. The system $\dot{x} = f(x,u)$ has non-idle outputs by definition, and non-idle inputs since $\frac{\partial}{\partial u_\ell} f_{j\ell}(x,u) \neq 0$. The subsystems $\dot{z}_\ell = g_\ell(z_\ell, v_\ell)$ are linear cascades with a single input and a single output, and so they satisfy the condition imposed in the paragraph above Proposition 9. Their I/S characteristic $k^{Z_\ell}(v) = (v, \ldots, v)$ is nondegenerate, and their I/O characteristic is $k_\ell(v) = v$. The results follow by applying Proposition 9. ∎

7.6 Another Example

In order to illustrate the effect of delays inserted in the feedback loop, we study the simplified Cdc2-cyclin B/Wee1 cell cycle model system from [5][2]. This is just a two-dimensional model, which may also be analyzed by routine phase plane techniques, and it was used in that paper in order to relate input/output analysis based on monotone systems to such more standard techniques. The equations are as follows:

$$
\begin{aligned}
\dot{x}_1 &= \alpha_1(1-x_1) - \frac{\beta_1 x_1 u^{\gamma_1}}{K_1 + u^{\gamma_1}} \\
\dot{x}_2 &= \alpha_2(1-x_2) - \frac{\beta_2 x_2 x_1^{\gamma_2}}{K_2 + x_1^{\gamma_2}} \\
x_2 &= y \;=\; u
\end{aligned}
\tag{7.27}
$$

with the constants:

$$\alpha_1 = \alpha_2 = 1,\ \beta_1 = 200,\ \beta_2 = 10,\ \gamma_1 = \gamma_2 = 4,\ K_1 = 30,\ K_2 = 1\,.$$

This system is monotone, has a well-defined characteristic, and is strongly monotone in closed loop. The characteristic is plotted in Figure 7.10, together with the diagonal $u = y$. To find the steady states under unity feedback, we intersect the characteristic and the diagonal $u = y$, and we find that there are two exponentially stable states in closed loop, corresponding to $u = y \approx 0.168$ and $u = y \approx 0.997$. Associated to these values there are the respective internal states

$$\xi_1 = (0.995, 0.168) \quad \text{and} \quad \xi_2 \approx (0.136, 0.997)$$

[2] Section 5.6 of [101] can also be studied, at least in pseudo-delayed form, using Theorem 25.

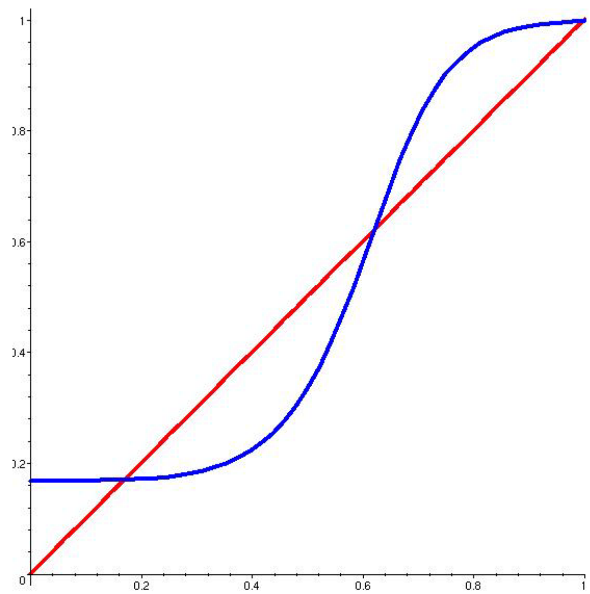

Figure 7.10: Characteristic for Cdc2-Wee1 Example, and Diagonal

to which all trajectories (except for those lying in a separatrix, the stable manifold of the saddle point $\xi_3 \approx (0.506, 0.619)$ associated to the intersection $u = y \approx 0.619$) converge. As an illustration, we show in Figure 7.11 the closed-loop trajectories (using $u = y$ in Equation (7.27) corresponding to initial conditions $x_1(0) = 0.8$, $x_2(0) = 0.95$. Next,

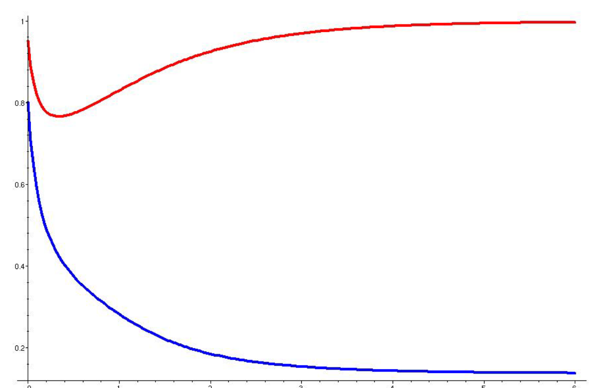

Figure 7.11: Closed-Loop Solution for Cdc2-Wee1 Example, $x_1(0) = 0.8$, $x_2(0) = 0.95$

we study the effect of adding to the feedback loop a cascade of simple one-dimensional systems, which might represent delays due to unmodeled reactions. Thus, after closing the loop under unity feedback, but now introducing these additional systems (so $u = z_2$), we are led to consider the following *four*-dimensional system:

$$\dot{x}_1 = \alpha_1(1-x_1) - \frac{\beta_1 x_1 z_2^{\gamma_1}}{K_1 + z_2^{\gamma_1}}, \quad \dot{x}_2 = \alpha_2(1-x_2) - \frac{\beta_2 x_2 x_1^{\gamma_2}}{K_2 + x_1^{\gamma_2}}$$

$$\frac{\tau}{2}\dot{z}_1 = -z_1 + y\,, \quad \frac{\tau}{2}\dot{z}_2 = -z_2 + z_1\,,$$

where, for definiteness, we picked the same constants as earlier, and took the time-constants as $\tau = 20$. Notice that the system was still monotone before closing the loop with $u = z_2$, and the characteristic is unchanged. Thus there should be exactly two steady states of this system, corresponding to ξ_1 and ξ_2, of the form $(0.995, 0.168, z_1^1, z_1^2)$ and $(0.136, 0.997, z_2^1, z_2^2)$, which attract all trajectories except those starting from a set of measure zero. As an illustration, we show in Figure 7.12 the closed-loop trajectories of this extended system corresponding to initial conditions $x_1(0) = 0.8$, $x_2(0) = 0.95$, $z_1(0) = z_2(0) = 0$ (we do not show the plots of the z_i variables). The theory predicts

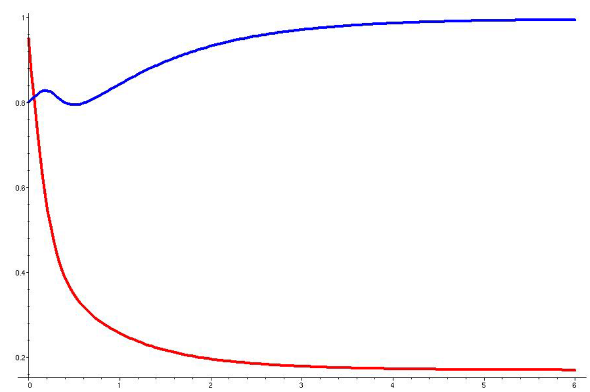

Figure 7.12: Closed-Loop Solution for "Delayed" Cdc2-Wee1 Example, $x_1(0) = 0.8$, $x_2(0) = 0.95$, $z_1(0) = z_2(0) = 0$.

almost-global convergence to the same states ξ_1, ξ_2 as in the original system. However, it is interesting to see that a different final state is reached asymptotically, for the same initial conditions, compared to that shown in Figure 7.11. Instead of converging towards ξ_2 as in the case without delay, the solution converges now towards ξ_1 due to the "delay" imposed by the two z-systems.

Chapter 8

Prevalence of Convergence

Let $\mathbb{B}$ be a separable Banach space, and consider a dynamical system

$$\Phi(x,t) \tag{8.1}$$

which is strongly monotone with respect to a closed cone K with nonempty interior. In the paper [48], M. Hirsch addresses the question of the convergence of solutions towards the set of equilibria E. Denote for this discussion the sets

$$\begin{aligned} B &= \{x \in X \,|\, \text{the orbit } x(t) \text{ has compact closure in } X\} \\ Q &= \{x \in X \,|\, \omega(x) \subseteq E\} \\ C &= \{x \in X \,|\, \omega(x) = \{e\} \text{ for some } e \in E\}. \end{aligned}$$

The elements of C are said to be *convergent* or to have *convergent solution*, and those of Q are said to be *quasiconvergent*.

It was established in [48] that the generic element of B is quasiconvergent, where the word 'generic' is made specific in two different senses: the topologic sense ($B - Q$ is meagre), and the measure theoretic sense ($\mu(B - Q) = 0$ for any gaussian measure μ).

In the case that the set E is discrete, Hirsch's theorem trivially implies the following results: 1) the set C is also generic in B (since omega limit sets are connected and therefore $Q = C$), and 2) if $\mathbb{B} = R^n$, the generic solution converges towards an equilibrium which is not exponentially unstable (since the basin of attraction of every exponentially unstable equilibrium has measure zero and E is countable).

In the following writeup these two statements are generalized to the case of an arbitrary equilibrium set (and arbitrary separable $\mathbb{B}$). We have found the concept of prevalence due to Yorke et al and Christensen [51, 17] to be a convenient measure-theoretic way of formalizing the term 'generic' – see below for details. For the problem

1) there is already a wealth of literature, especially a result proved first in [102] showing that under relatively mild regularity conditions on the system, the set C has dense interior. We show in Section 8.1 that if C is dense in B (topological genericity), then C is prevalent in B (measure-theoretical genericity).

Let $T_t : X \to X$ be the time-t evolution operators of the system (8.1). We will use the following stability notation in this chapter: let $e \in E$ be an equilibrium of this system, and let $\rho(e,t)$ be the spectral radius of $T_t'(e)$. We say that e is *linearly stable* if $\rho(e,t) < 1$ for all $t > 0$, *linearly unstable* if $\rho(e,t) > 1,\ t > 0$, and *neutrally stable* if $\rho(e,t) = 1,\ t > 0$. Standard stability results imply that every equilibrium in E satisfies one of these three conditions. Finally, define $E_s \subseteq E$ as the set of equilibria that are either linearly stable or neutrally stable. Without making any assumptions on topological genericity, we show in Section 8.2 that the set of states that converge to a point in E_s is prevalent in C.

8.1 C is Prevalent in B

In the context of autonomous strongly monotone systems, we say that an equilibrium point $e \in E$ is *irreducible* if for every $t > 0$, $T_t'(e)$ is a strongly monotone operator (i.e. $x > 0$ implies $T_t'(e)x \gg 0$). The point e is said to be *non-irreducible* otherwise.

A basic tool in abstract monotone systems theory is the so called *limit set dichotomy* for strongly monotone systems: if $x, y \in B$ and $x \ll y$, then either i) $\omega(x) \ll \omega(y)$, or ii) $\omega(x) = \omega(y) \subseteq E$. See Theorem 1.3.7 in [101]. In [102], Smith and Thieme found sufficient conditions in Banach space for a strongly monotone system with precompact orbits to satisfy a strengthened limit set dichotomy: if $x, y \in B$ and $x \ll y$, then either $\omega(x) \ll \omega(y)$ or $\omega(x) = \omega(y) = \{e\}$ for some $e \in E$. The sufficient conditions for the stronger dichotomy are reviewed in [101] pp. 19-23, and involve the continuous differentiability of the time evolution operators $T(t)$, the nonexistence of non-irreducible equilibria, and the compactness of the operators $T'(t)$.

Smith and Thieme then use this stronger dichotomy to show that int C is dense in X, using additional hypotheses, such as the complete continuity of the operators $T(t)$, the boundedness of $O(R)$ for compact sets R, and the approximability of any state from above or below by other states in X. See Theorem 2.4.7 of [101] for details and for a more general set of hypotheses, in particular regarding the so-called condition (C).

One possible drawback of this result is that closed, nowhere dense subsets of X may still be quite large in terms of measure. In fact, it is well known that one can partition $\mathbb{R}^n$ into a set of measure zero and an countable collection of such sets (see for instance Section 8 of [35]).

On the other hand, asking for a set to have measure zero in an infinite dimensional space $\mathbb{B}$ is difficult to formalize, since there doesn't exist a measure with the basic properties of the Lebesgue measure in finite dimensions. A definition of 'sparseness' that turns out to be very useful in infinite dimensions is that of prevalence [51, 17]: a set $W \subseteq \mathbb{B}$ is *shy* if there exists a compactly supported Borel measure μ on $\mathbb{B}$, such that $\mu(W + x) = 0$ for every $x \in \mathbb{B}$. A set is said to be *prevalent* if its complement is shy. Given $A \subseteq \mathbb{B}$, we also say here that a set W is *prevalent in* A if $A - W$ is shy. Useful properties of the idea of prevalence are given in [51]. Most importantly in the current paper, a shy set has empty interior, and in finite dimensions W is shy if and only if W has Lebesgue measure zero.

Define for any set $A \subset X$ the *strict basin of attraction*

$$SB(A) := \{x_0 \in X \,|\, \omega(x_0) = A \text{ and } x \in B\,\}.$$

Note the difference with the usual basin of attraction of A, $\mathcal{B}(A) = \{x \in X \,|\, \omega(x) \subseteq A\}$. Given $v \in B, v \neq 0$, we define the Borel measure $\mu(v)$ on B to be the uniform measure supported in the set $\{tv \,|0 \leq t \leq 1\}$. That is, $\mu(v)(A) = m\{t \in [0, 1] \,|tv \in A\}$, where m is the Lebesgue measure in $[0, 1]$. The proof of Hirsch's generic convergence theorem as stated in terms of prevalence becomes clear at this point. See Theorem 4.4 of [48], and [49].

Theorem 26 *Let $\mathbb{B}$ be a separable Banach space, and consider a strongly monotone system defined on $X \subseteq \mathbb{B}$. Then Q is prevalent in B.*

Proof. Let N be the set of states $x \in B$ such that $\omega(x) \nsubseteq E$. Let $L \subseteq X$ be a straight line that is ordered under $\ll$. Note that if $x, y \in L \cap N$, $x \ll y$, then $\omega(x) \ll \omega(y)$, since otherwise $\omega(x) = \omega(y) \subseteq E$ by the limit set dichotomy. Also, $\omega(x)$ must have more than one element (otherwise x must converge towards this element, which would necessarily be an equilibrium).

We can apply an argument as in Theorem 7.3 c) of Hirsch [49] to conclude that $N \cap L$ is countable: consider the set $Y = \cup_{x \in N \cap L} \omega(x)$ with the topology inherited by $\mathbb{B}$. Since no point in an omega limit set $\omega(x)$ can bound $\omega(x)$ from below or above (Theorem 6.2 in [49]), no point in $\omega(x)$ can be the limit of elements in $\omega(y)$, $y \neq x$. Therefore $\omega(x)$ is open in Y, for every $x \in N \cap L$. The result follows by the separability of Y.

Consider now $v \gg 0$ and the uniform measure $\mu(v)$ supported in $S_v = \{tv \,|\, 0 \leq t \leq 1\}$. Let $L = \mathbb{R}v - x$ for an arbitrary $x \in \mathbb{B}$. Then

$$(N + x) \cap S_v \subseteq (N + x) \cap \mathbb{R}v = (N \cap L) + x.$$

Therefore clearly $\mu(v)(N + x) = 0$, and we have proven that N is shy with respect to $\mu(v)$. ∎

Theorem 27 *Let $\mathbb{B}$ be a separable Banach space, and let X be the closure of a convex open set. If C is dense in B, then C is prevalent in B.*

Proof. Let K be the set of the states $x \in B$ such that $|\omega(x)| > 1$, and $SB(\omega(x))$ has empty interior. We will show that K is shy with respect to the measure $\mu(v)$, for every $v \gg 0$.

Let L be a strongly ordered straight line on X, and consider the function $\gamma : L \cap K \to \mathcal{P}(X)$ defined by $\gamma(x) = \omega(x)$. Then this function is injective: indeed, if $x, y \in L \cap K$, $x \ll y$, where such that $\gamma(x) = \gamma(y) = W$, then $W \subseteq E$ and $\omega(z) = W$ for any $z \in (x, y) \cap X$ by the limit set dichotomy. But this implies that W has nonempty interior, which is a contradiction with the fact that $SB(\omega(x))$ is shy.

Note also that the image of γ is a strongly ordered collection of sets, again by the limit set dichotomy. That is, if $x \ll y$ then $\gamma(x) \ll \gamma(y)$. Following the same argument as in the proof of Theorem 26, one proves that K is shy with respect to $\mu(v)$, for any $v \gg 0$.

Let $x \in B$ be such that $|\omega(x)| > 1$. Then $SB(\omega(x))$ has empty interior, from the fact that C is dense in B. Therefore x belongs to the shy set K. ∎

On the more technical side, it needs to hold that the sets N and K involved in the proofs of the theorems above are Borel measurable in $\mathbb{B}$. For the sake of completeness this is done in the appendix.

Note that one can write the set K in the above proof in the form

$$K = \dot{\bigcup} \{SB(A) \mid |A| > 1,\ SB(A) \text{ nonempty with empty interior}\}. \tag{8.2}$$

From the fact that K is shy, one may be tempted to conclude that such sets A must be relatively sparse in X. But it is possible even in finite dimensions for a strongly monotone system to have a continuum of pairwise disjoint sets A_i whose union is connected, and each of which satisfies the condition in equation (8.2). To see this, simply build a (not necessarily monotone) 3-dimensional system with such property, and apply on this system Smale's construction to form a strongly monotone 4-dimensional system with the same property; see [50]. Even in this case the basin $\mathcal{B}(\bigcup_i A_i)$ is a shy set, since it is contained in K.

The following lemma helps to visualize the behavior of nonconverging bounded orbits.

Lemma 40 *Let $A \subseteq X$ be such that $|A| > 1$ and $SB(A) \neq \emptyset$. Then the following hold:*

1. *No two different elements in A are comparable under $\leq$.*

2. *No two different elements $a \in A,\ x \in BS(A)$ are comparable under $\leq$.*

3. *If $SB(A)$ has nonempty interior, then $A \subseteq E$.*

In the finite dimensional case, if $m(SB(A)) > 0$, then the set $SB(S)$ has nonempty interior in X and $\lim_{x\to\infty} x'(t) = 0$, $x(t) = x(t, x_0)$.

Proof. Item 1. follows from Theorem 6.2 b) in [49]. If $a \in A$ and $x \in BS(A)$, then $a \neq x$, since otherwise $\omega(x) = \{a\} \neq A$. If $x > a$, then $x(1, a) \gg a$ and a contradiction follows easily using the limit set dichotomy. Item 3 also follows directly from the dichotomy.

To show the last statements, we find $x, y \in SB(A)$ such that $x \ll y$. Suppose that no such two elements exist, and let L be a strongly ordered straight line in $\mathbb{R}^n$. Then $L \cap SB(A)$ has at most one element. By Fubini's theorem it follows that $m(SB(A)) = 0$, which is a contradiction. As for the last assertion, we observe that for any $x_0 \in SB(A)$

$$\lim_{t\to\infty} \operatorname{dist}(x(t, x_0), A) = 0,$$

and we use the continuity of the function f, together with the fact that $A \subseteq E$. ∎

8.2 C_s is Prevalent in C

paragraphHypotheses In this section we will assume that $\mathbb{B}$ is a separable Banach space, that system (8.1) is a strongly monotone C^0 semigroup, and that its time evolution operators are compact and (Frechet) C^1, and that their derivatives are compact. As to the underlying cone $\mathcal{K}$, we assume that it is closed and has nonempty interior. Regarding the set X, we will assume that every element can be approximated from below and above by elements of X in the sense of [101], and that for every $x, y \in X,\ x \ll y$, it holds that $X \cap (x, y)$ has nonempty interior.

We turn our attention to the convergence of solutions towards equilibria in E_s for arbitrary E. More precisely, defining

$$C_s = \{x \in C \mid \lim_{t\to\infty} x(t) \in E_s\},$$

we will show that under an irreducibility condition, it holds that C_s is prevalent in C. If the set of equilibria E is discrete, this follows in finite dimensions from the fact that in a neighborhood of the equilibrium, its basis of attraction is a manifold with dimension at most n-1, together with the principle of nonintersecting orbits.

This section is independent of the previous one, but a natural conclusion will follow from the two in Corollary 21.

Let $x \in X$ and let $C, D \subseteq X$. The relation $x \ll D$ will denote that $x \ll d$ for every $d \in D$, and the relation $C \ll D$ will denote $c \ll d$ for all $c \in C,\ d \in D$. We state first two general lemmas which are not specific to monotone systems.

Lemma 41 *Let $T : X \to X$ be a continuous (nonlinear) operator. Let $e \in X$ be a fixed point of T, and assume that the Frechet derivative $T'(e) : T \to T$ exists and is compact. Assume also that there exists a sequence $e_1,\ e_2,\ \dots$ of fixed points of T, $e_k \neq e$, such that $e_k \to e$ as $n \to \infty$.*

Then the unit vectors $v_k := (e_k - e)/\left|e_k - e\right|$ have a subsequence that converges towards a unit vector $w \in \mathbb{B}$, and $T'(0)w = w$.

Proof. Let $\epsilon > 0$, and let $A := T'(e)$. We will show that there exists a subsequence (v_{k_j}) such that

$$|v_{k_i} - Av_{k_i}| < \epsilon, \quad \left|v_{k_i} - v_{k_j}\right| < 3\epsilon, \text{ for all } i, j.$$

Once this has been shown, by setting $\epsilon = 1/n,\ n = 1, 2, 3\dots$ and following a diagonal argument, it follows that there exists a subsequence (u_i) of (v_k) which is Cauchy, and such that $|u_i - Au_i| \to 0$. Letting $w = \lim u_i$, clearly w is a unit vector, and it must follow that $Aw = w$.

In order to prove the statement above, let N be such that

$$|T(e_n) - T(e) - A(e_n - e)| < \epsilon \left|e_n - e\right|,\ n \geq N.$$

Such a number can be found using the definition of the Frechet derivative of T at e. Using the fact that e, e_n are fixed points of T, and dividing on both sides by $|e - e_n|$, we obtain

$$|v_n - Av_n| < \epsilon,\ n \geq N. \tag{8.3}$$

By compactness of A, it holds that the sequence $Av_N,\ Av_{N+1},\ Av_{N+2}\dots$ is precompact, and therefore it has a Cauchy subsequence Av_{k_1}, Av_{k_2}, etc. We can assume without loss of generality that in fact $\left|Av_{k_i} - Av_{k_j}\right| < \epsilon$, for all i, j. Using the triangle inequality and (8.3), it follows that $\left|v_{k_i} - v_{k_j}\right| < 3\epsilon$. This completes the proof. ∎

Lemma 42 *Let $S \subseteq X$ be uncountable. Then there exists $a \in S$ that is an accumulation point of S.*

Proof. Suppose that the statement is false. Then for every $a \in S$ there exists an open ball of radius $r(a)$ around a which doesn't intersect any other point of S. By surrounding each $a \in S$ with an open ball of radius $r(a)/2$, we find a uncountable collection of open balls that are pairwise disjoint, a contradiction by the separability of $\mathbb{B}$. ∎

The following two results will lead up to Theorem 28 on the convergence of solutions towards unstable equilibria, which is similar to Theorem 4.4 in [48] in finite dimensions, and to a lesser extent to Theorem 10.1 in [49]. It drops the assumptions of finiteness or discreteness for the set E. We will use the following property in what follows.

(P) Every set of equilibria $\hat{E} \subseteq E$ which is totally ordered by $\ll$ has at most enumerably many non-irreducible points.

For instance, this condition holds if all equilibria in X are irreducible (condition (S) in [101], p. 19). It also holds if every totally $\ll$-ordered subset of X has at most enumerably many non-irreducible points. A common example is also the case $X = (\mathbb{R}^+)^n$, ordered by an orthant cone, when all non-irreducible points are in ∂X.

Lemma 43 *If $(e_k)_{k\in\mathbb{N}}$ is a sequence of equilibria of the system (8.1) such that $e_k \gg e_{k+1}$ ($e_k \ll e_{k+1}$) for all k, and if the sequence (e_k) converges towards a irreducible equilibrium $e \in E$, then $e \in E_s$.*

Proof. Let $T = T_1$ be the time evolution operator of the system after one unit of time. Then T satisfies the hypotheses of Lemma 41, so that defining $v_k = (e_k - e)/\,|e_k - e|$, there exists a subsequence v_{k_i} which converges to a unit vector $w \in \mathbb{B}$. Furthermore, $T'(e)w = w$. From the fact that $e \ll e_k$ for every k, we conclude that $v_k \gg 0$ for all k, and that therefore $w > 0$.

By the nondegeneracy of the point e, the linear operator $T'(e)$ is strongly monotone. By the Krein Rutman theorem, the fact that $T'(e)$ has a positive eigenvector with eigenvalue 1 implies that in fact $\rho(T'(e)) = 1$. By the spectral mapping theorem for C^0 semigroups (see [87], Theorem 2.2.4), the stability modulus of $L'(e)$ is equal to zero. In particular, $e \in E_s$, and this concludes the proof.

The case $e_{k+1} \ll e_k$ for every $k \in \mathbb{N}$ can be treated similarly. ∎

Lemma 44 *Let property (P) be satisfied. If $\hat{E} \subseteq E$ is totally ordered by $\ll$, and if every element of $\hat{E}$ is linearly unstable, then $\hat{E}$ is countable.*

Proof. Suppose that $\hat{E}$ is not countable. Then the set $\tilde{E} \subseteq \hat{E}$ of irreducible elements in $\hat{E}$ is also uncountable, by property (P). Let $e \in \tilde{E}$ be an accumulation point of $\tilde{E}$, which exists by Lemma 42. Then there exists a monotone sequence of elements in $\tilde{E}$ which converges towards e. By the previous lemma it holds that $e \in E_s$, thus violating the assumptions. ∎

Lemma 45 *Let $\mathbb{B}$ be a separable Banach space, and let system (8.1) be strongly monotone. Let $e \in E$ be a linearly unstable equilibrium such that T_t is C^1 in a neighborhood U_t of e and $T_t'(e)$ is compact, $t > 0$. Then the basin of attraction of e is shy.*

Proof. The proof follows the same argument as Lemma 2.1 in [103]: suppose that there exist $x, y \in \mathcal{B}(e)$ with $x < y$. Then $(x(t), y(t))$ is a nonempty open set contained in $\mathcal{B}(e)$ for every $t > 0$ by strong monotonicity. But locally around e, $\mathcal{B}(e)$ has the form of a manifold with codimension larger or equal than 1, which is a contradiction (see Lemma 2.1 in [103] for details). It follows that no two elements in $\mathcal{B}(e)$ can be ordered by $<$, which implies that this set is shy with respect to $\mu(v)$ for every $v > 0$. ∎

Theorem 28 *Let property (P) be satisfied, and let system (8.1) have C^1, compact time operators with compact derivatives. Let X be the closure of a convex open set. Then C_s is prevalent in C.*

Proof. We follow a very similar argument as in the proof of Theorem 26. Let N be the set of $x_0 \in C$ such that x_0 converges towards a linearly unstable equilibrium. Let $v \gg 0$, $x \in \mathbb{B}$ be fixed, and let $L = \{rv + x \,|\, r \in \mathbb{R}\}$. Then we can define the function $\sigma : L \cap N \to X$ by $\sigma(x_0) = \lim_{t\to\infty} \Phi(x_0, t)$. If $x_1, x_2 \in L \cap N$, $x_1 \ll x_2$, then necessarily $\sigma(x_1) \neq \sigma(x_2)$, since otherwise $[x_1, x_2] \cap X \subseteq SB(\sigma(x_1))$, thus violating that the basin of attraction of $\sigma(x_1)$ has nonempty interior by Lemma 45. Also note that $\hat{E} = \text{range } \sigma$ is totally ordered by $\ll$. Therefore by Lemma 44 $\hat{E}$ is countable, and so is $L \cap N$ by injectivity. The rest of the argument follows as in Theorem 26 and Theorem 27. ∎

See also Theorem 4.4 and Theorem 4.1 of [48].

Corollary 21 *Let system (8.1) have C^1, compact time operators with compact derivatives. Let $O(R)$ be bounded for every bounded $R \subseteq B$. Let also $B = X$, and let all the equilibria of the system be irreducible. Then C_s is prevalent in X.*

Proof. From the discussion in [101], pp 19-23, it follows that int C is dense in $B = X$. The result then follows from Theorem 27 and Theorem 28. ∎

8.3 Applications to Reaction-Diffusion Systems

Consider a reaction-diffusion system of equations

$$\dot{u} = D\Delta u + f(u) \tag{8.4}$$

under Neumann boundary conditions, defined on the state space $C(\Omega, \mathbb{R}^n)$. Kishimoto and Weinberger [59] showed that if Ω is a convex domain, and assuming that $\partial f_i/\partial x_j > 0$ for all i, j, then any nonconstant equilibrium $\overline{u}$ is linearly unstable. A careful reading of the proof in that paper will show that in fact it is sufficient that $\partial f_i/\partial x_j > 0$ for all i, j and every equilibrium $e \in E$ is irreducible. By making a change of variables, the same is true for any system which is strongly monotone with respect to an orthant cone and in which all equilibria are irreducible.

On the other hand, elliptic systems such as $D\Delta u + f(u) = 0$ are known for having multiple and sometimes unexpected solutions. Not only is it possible for a strongly monotone reaction diffusion system to have several non-uniform equilibria, but it is in fact possible that there is a continuum of them. In Section 12.1, we consider this question at length by providing a two-dimensional reaction diffusion system with a continuum of nonhomogeneous equilibria, but whose associated undiffused system converges globally towards an equilibrium. The question arises as to whether the basin of attraction of the set of all unstable equilibria can possibly have a basin of attraction, say, with nonempty interior.

Lemma 46 *Let $W \subseteq \mathbb{R}^n$ be a vector space, and let $u : \Omega \to \mathbb{R}^n$ be twice differentiable and such that Im $u \subseteq W + p$ for some $p \in \mathbb{R}^n$. Then $\Delta u(x) \in W$, for every $x \in \Omega$.*

Proof. The proof of this lemma is an exercise in change of variables. Let B_1 be the standard basis in $\mathbb{R}^n$, and let B_2 be a second basis. Let M be their associated change of basis matrix, so that if $[s]_{B_1},\ [s]_{B_2}$ are the representations of $s \in \mathbb{R}^n$ with respect to the indicated basis, it holds that $[s]_{B_2} = M[s]_{B_1}$. Define $v(x) := [u(x)]_{B_2} = Mu(x)$. To see that Δu is independent of the choice of basis, observe that it can be written as $\Delta u = u \cdot (1, \ldots, 1) \cdot \partial^2$, where $\partial^2 = (\partial^2/\partial x_1^2, \ldots \partial^2/\partial x_m^2)^t$. Thus $\Delta(v) = \Delta(Mu) = (Mu) \cdot (1, \ldots, 1) \cdot \partial^2 = M\Delta(u)$.

Choose the basis B_2 in such a way that the first $\dim W$ basis vectors are a basis of W. Clearly v is a constant function in its last $n - \dim W$ entries, so that $\Delta v = 0$ in these entries. Since $\Delta u = M^{-1}\Delta v$, the conclusion follows that $\Delta(u)(x) \in W$ for all x.

∎

The following proposition is an adaptation of Smale's argument (see [50]) for reaction diffusion systems.

Proposition 10 *Let $\Sigma := \{x \in \mathbb{R}^n \mid \sum_i x_i = 0\}$, and let $f : \Sigma \to \Sigma$ be a compactly supported C^1 function. Then there exists a strongly cooperative reaction-diffusion system*

$$\dot{u} = \Delta u + F(u) \tag{8.5}$$

in which Σ is an invariant subset, and such that $F|_\Sigma = f$.

Proof. Define $S(x) := \sum_i x_i$, $x \in \mathbb{R}^n$. Let Q be a fixed constant to be determined later on. Let $p : \mathbb{R} \to [0, 1]$ be a smooth function supported on $[-1, 1]$, and such that $p \equiv 1$ on a neighborhood of 0. Define

$$F_i(x) := QS(x) + p(S(x))f_i(x),\ \ i = 1 \ldots n.$$

Then for every $i, j = 1 \ldots n$,

$$\frac{\partial F_i}{\partial x_j} = Q + p'(S(x)f_i(x) + p(S(x)\frac{\partial f_i}{\partial x_j}.$$

It is also clear that $F_i = f_i$ on Σ for every i. Now, note that $\frac{\partial F_i}{\partial x_j}$ is a continuous function which is compactly supported, for every i, j. Therefore one can choose Q to be large enough so that $\frac{\partial F_i}{\partial x_j} > 0$ for all i, j, thus making (8.5) into a strongly cooperative system.

Since for every $u : \Omega \to \Sigma$, it holds that $\Delta u + F(u) = \Delta u + f(u) \in \Sigma$, by Lemma 46, it follows that Σ is an invariant subset of system (8.5). ∎

Armed with this proposition, one can build the example given above: let $f : \mathbb{R}^{n-1} \to \mathbb{R}^{n-1}$ be a function, not necessarily monotone, whose associated system (8.4), with $D = I$ and under Neuman boundary conditions, has a continuum of non-uniform equilibria. Redefine f so that its domain is Σ, via a rigid linear transformation $\mathbb{R}^{n-1} \to \Sigma$, and extend it using Proposition 10. An argument similar to that in Lemma 46 will guarantee that the solutions of the system are in fact identical to those of system (8.5) in Σ. We write this result in the following

Corollary 22 *There exists a strongly cooperative reaction diffusion system (8.4) with a continuum of non-uniform equilibria.*

Even in this case, it is hard a priori to tell whether the set of states that converge towards an unstable equilibrium – or to a set of equilibria containing a non-uniform equilibrium – is sparse (note that for instance u may cross Σ in one or several places). The following application of Corollary 21 resolves this question in the general case.

Theorem 29 *Let (8.4) be such that f is C^1, $\partial f_i / \partial x_j > 0$ for every i, j, the solutions of (8.4) are uniformly bounded, and Ω is convex. Then the set of initial conditions that converge towards a uniform equilibrium is prevalent in $C(\Omega, \mathbb{R}^n)$.*

Proof. We need to show that all the general assumptions of the previous section are satisfied, as well as the hypotheses of Corollary 21. Clearly $C(\Omega, \mathbb{R}^n)$ is a separable Banach space under the uniform norm. The fact that the time evolution operators form a C^0 semigroup of compact operators with compact derivatives is well known in the literature; see for instance [87]. The assumptions on the cone $\mathcal{K} = (\mathbb{R}^+)^n$ in question are easily seen to be satisfied. Similarly for the set $X = B = C(\Omega, \mathbb{R}^n)$. The fact that $B = X$ follows for instance from Theorem 7.3.1 in [101]. To see that the system has no non-irreducible equilibria, let $\hat{u}$ be an equilibrium of the system, and recall that the linearization around $\hat{u}$ is of the form

$$\dot{u} = D\Delta u + M(x)u,$$

where $M(x) = \partial f/\partial u(\hat{u}(x))$. According to Theorem 7.4.1 of [101], to prove that this system is strongly monotone it is enough to verify that the associated finite-dimensional system with no diffusion is monotone for every fixed value of $x \in \Omega$, and strongly monotone for at least one value of x. But by hypothesis $M(x)$ has only positive entries, and therefore this condition holds.

By Corollary 21, it holds that C_s is prevalent in $B = X$. But by the main theorem in [59], any initial condition in C_s has a solution which converges towards an equilibrium which is uniform in space. This completes the proof. ∎

8.4 An Application: Monomial Chemical Reactions

As an application of Corollary 21 we consider the class of *monomial* chemical reactions. Let $A_1, \ldots, A_n$ be n chemical compounds (also known as *species*), and consider a set of reactions of the form

$$\alpha_{ij} A_i \xrightarrow{k_{ij}} \beta_{ij} A_j.$$

That is, we let one compound react and transform itself into another, possibly after making α_{ij}-mers of itself and/or splitting itself into β_{ij} equal parts. Assuming mass action kinetics, the reaction rate of each such reaction is $k_{ij} A_i^{\alpha_{ij}}$. We will also assume that the reaction diagram (using the compounds as nodes and $A_i \to A_j$ if this reaction takes place) is strongly connected. *Note that we don't assume that the reaction diagram doesn't contain closed cycles, nor that every reaction must be reversible.* For an excellent treatment of chemical reactions from a mathematical viewpoint, the reader is referred to [113], Chapter 8. For similar results to the ones here, see [75].

The associated dynamical system is strongly monotone, and if we view it as taking place in the state space $(0, \infty)^n$, it holds that the Jacobian matrices associated to each state are irreducible. The associated vector field is C^1, and all states can be approximated from above or below in the sense of pp. 19-23 [101]. Furthermore, the solutions can be shown to be bounded - in fact, each orbit can be shown to have compact closure in $(0, \infty)^n$. We can therefore conclude that the set C has dense interior in $(0,\infty)^n$, by the discussion in [101]. If we now extend the state space to $X = (R^+)^n$, this property certainly continues to hold. We can now invoke Corollary 21 to conclude the following result:

Lemma 47 *Given a strongly connected monomial reaction, and for almost every initial condition $x \in (\mathbb{R}^+)^n$, the solution of the system converges to an equilibrium.*

Thus if a chemical reaction is modeled with such a system in the laboratory, no non-converging solutions are ever likely to be observed.

Now, chemical reactions often have so-called conservation laws, i.e. linear relationships between the different species that are preserved by the dynamics. In other words, there are r-dimensional hyperplanes whose intersection with X is invariant for the system. We will assume that r is minimal with this property, i.e. that there are $n-r$ independent conservation laws.

It is common to reduce the system by making a change of variables so that only r variables are left — but after making this reduction it is not guaranteed that monotonicity will be preserved. Our approach here is to use the monotonicity properties of the reaction *before* carrying out the reduction.

Let $\Delta \subseteq \mathbb{R}^n$ be an r-dimensional linear subspace such that $\Delta_t := (\Delta + (t, t, \ldots t)) \cap X$ is invariant for every $t \geq 0$. It can be shown that for every $t \geq 0$, Δ_t is a bounded set, and that no two elements in Δ_t are comparable under $\leq$.

Theorem 30 *Consider a strongly connected monomial reaction. Then for every $t \geq 0$, there exists a unique equilibrium $e_t \in \Delta_t$. Moreover, for almost every $t \geq 0$, almost every solution in Δ_t converges towards e_t.*

Proof. Let $S = C^C$. By Fubini's theorem it holds that

$$\int_X \chi(S)\,\mathrm{d}m = \int_0^\infty \int_{\Delta_t} \chi(S \cap \Delta_t)\,\mathrm{d}t.$$

Since the left hand side is equal to zero, this implies that for almost every $t \geq 0$, $S \cap \Delta_t$ has measure zero in the r-dimensional sense. Therefore for almost every $t \geq 0$, almost every state in Δ_t has a solution which converges to an equilibrium.

We restrict our attention again to the state space $(0,\infty)^n$, and we let $\Delta'_t := \Delta \cap (0,\infty)^n$, which are also invariant sets under the system as mentioned above. Let $t > 0$, and consider $E_t = E \cap \Delta_t$. By the strong monotonicity of the system, no equilibrium can lie on $\partial\Delta_t$, so that $E_t \subseteq \Delta'_t$.

Consider an equilibrium $e \in E_t$ which is an accumulation point of E_t. Using an argument like that in Lemma 7 and Lemma 9, it follows that there exists a nonzero vector $v \in \Delta$ such that $f'(e)v = 0$. But this is a contradiction by the Perron Frobenius theorem since the only eigenvector of $f'(e)$ modulo renormalization must be $\gg 0$. We conclude that the set E_t is discrete in Δ_t.

Now, suppose that $|E_t| > 1$ and let $e_1, e_2 \in E_t$ be two different discrete equilibria of E_t. Then there must exist at least one equilibrium in Δ'_t which is unstable in $\Delta'(t)$. But this is a contradiction since 0 is the leading eigenvalue of each equilibrium. Therefore $|E_t| \leq 1$ for all $t > 0$. But $|E_t| > 0$ for almost every $t > 0$ by the argument above. Therefore by continuity of the vector field $|E_t| = 1$ for every $t > 0$. ∎

Example

Consider a molecule A which dimerizes to form B, which in turn forms a trimer C. Let C transform into either D or E via, say, the binding of one out of two different residues at the same site. See Figure xxx for a diagram. We will assume that the inverse transformations $D \to C$, $E \to C$, $C \to 2B$ and $B \to 3A$ also take place. The resulting equations are of the form

$$\begin{aligned}
\dot{a} &= 2k_1 b - 2\alpha(a) \\
\dot{b} &= -k_1 b + \alpha(a) - 3\gamma(b) + 3k_2(c) \\
\dot{c} &= \gamma(b) - k_2(c) + k_3 d - \eta(c) + k_4 e - \tau(c) \\
\dot{d} &= -k_3 d + \eta(c) \\
\dot{e} &= -k_4 e + \tau(c),
\end{aligned}$$

where a, b, c, d, e stand for the concentrations of the respective compounds, $k_1 \ldots k_4$ are positive constants, and $\alpha(a) = \text{const}.a^2$, $\gamma(b) = \text{const}.b^3$, $\eta(c) = \text{const}.c$ and $\tau(c) = \text{const}.c$. We reduce the system by defining the new variables $x = \frac{1}{6}a$, $y = \frac{1}{6}a + \frac{1}{2}b$,

$z = \frac{1}{6}a + \frac{1}{2}b + c$, $p = \frac{1}{6}a + \frac{1}{2}b + c + d$, $q = \frac{1}{6}a + \frac{1}{2}b + c + d + e = \text{const}$. In terms of the new variables, the system takes the form

$$\begin{aligned}
\dot{x} &= \tfrac{k_1}{3}(y - x) - \tfrac{1}{3}\alpha(x) \\
\dot{y} &= -\tfrac{1}{2}\gamma(y - x) + \tfrac{k_2}{2}(z - y) \\
\dot{z} &= -\eta(z - y) + k_3(p - z) - \tau(z - y) + k_4(q - p) \\
\dot{p} &= -\tau(z - y) + k_4(q - p).
\end{aligned} \tag{8.6}$$

This system is not monotone with respect to any orthant cone, for any positive choice of the constants, because of the (undirected) chain between y, p and z which has negative parity (in fact, this system may not even be sign definite — see for instance [6] or [30] for details). Note that every given value of the constant q will fix a hyperplane for the dynamics of the system. Now, after setting (8.6) equal to zero, and assuming without loss of generality that $k_1 = 1, \ldots, k_4 = 1$ (otherwise one can redefine $\alpha(a)$, etc.), one can write

$$\begin{aligned}
y &= \alpha(x) + x \\
z &= \alpha(x) + x + \gamma(\alpha(x)) \\
p &= \alpha(x) + x + \gamma(\alpha(x)) + \eta(\gamma(\alpha(x))) \\
\tau(\gamma(\alpha(x))) &= q - (\alpha(x) + x + \gamma(\alpha(x)) + \eta(\gamma(\alpha(x)))).
\end{aligned}$$

It is easy to see from the fourth equation (using the monotonicity of the functions $\alpha, \gamma, \eta, \tau$) that for every fixed q there exists a unique value of x that satisfies it, and therefore a unique tuple x, y, z, p that is an equilibrium of the reduced system. This was in fact predicted by the previous theorem. We can conclude that for almost every q, almost all solutions of (8.6) converge towards the unique equilibrium, *even though (8.6) is not itself a monotone system.*

8.5 Regarding Measurability

It is worth noting that in order to apply measure-theoretic arguments on the different main results, one needs to prove first that the sets in question are Borel measurable. One way to do this is as follows: let $D \subseteq X$ be a closed set in X and $r \in R^+$, and consider the set

$$W(D,r) = \{x \in X \,|\, x(t) \in D, \text{ for all } t \geq r\} = \bigcap_{q \in Q,\ q > r} T(q)^{-1}(D),$$

where $T(t)$ is the time t evolution operator of system (8.1). The equality holds clearly from the continuity of the solutions. Since each operator $T(q)$ is continuous, it holds that $W(D,r)$ is a measurable set.

We can use these sets to describe the set of solutions having a certain behavior. For instance, $\cup_{k \in \mathbb{N}} W(B(k) \cap X, 0)$ is the set of states with bounded solutions, where $B(k)$ is the closed ball or radius k around the origin. Given a set $A \subseteq X$ and $\epsilon > 0$, let

$$A_\epsilon = \{x \in X \,|\, d(A,x) \leq \epsilon\},$$

which is a closed set by continuity of the function $d(\cdot, A)$. Then we can write

$$C(A) = \{x \in X \,|\, \lim_{t \to \infty} d(x(t), A) = 0\} = \bigcap_{m \in \mathbb{N}} \bigcup_{k \in \mathbb{N}} W(A_{\frac{1}{m}}, k).$$

Finally, note that for any closed set $D \subseteq X$ and for any $x \in X$, it holds that

$$\omega(x) \subseteq D \Leftrightarrow \lim_{t \to \infty} d(x(t), D) = 0.$$

Thus since the set E of equilibria of (8.1) is closed, it holds that

$$Q = \{x \in X \,|\, \omega(x) \subseteq E\} = C(E)$$

is a measurable set. If B is itself Borel measurable, it follows that $N = B - Q$ is measurable.

Let $A \subseteq B$ be compact. In order to show that $SB(A)$ is Borel measurable, recall that for every $\epsilon > 0$, there exists a finite collection of open balls of radius ϵ which cover A. Let $\{R_i\}_{i \in I}$ be the union of such collections, for $\epsilon = 1/n, n = 1, 2, 3 \ldots$. Then the set $\bigcup_{i \in I} W(R_i^C, 0)$ consists of the vectors $x \in X$ such that $a \notin \omega(x)$ for some $a \in A$. Consequently,

$$SB(A) = C(A) - \bigcup_{i \in I} W(R_i^C, 0),$$

and this set is also Borel measurable.

Chapter 9

Monotone Decompositions

9.1 Decompositions Revisited, and Consistent Sets

In Section 5.3, it was described how an arbitrary sign-definite dynamical system can be decomposed as the negative feedback loop of a monotone controlled system under negative feedback. To do this, the associated signed digraph G was considered, and a minimal number of edges was removed so that the remaining digraph didn't contain any (undirected) loops with negative parity. A systematic way of doing this was to partition the set of nodes into two antagonistic sets via a function $p : V(G) \to \{-1, 1\}$ and to eliminate exactly those edges $(i, j) \in G$ that were 'inconsistent' or 'discordant', i.e. such that $\mathrm{sign}(i, j)p(i)p(j) = -1$. The main objective was therefore to find a partition p so that as few as possible discordant edges are present (since each discordant edge will become an input in the reduced system). The second objective was to do so in such a way that as few as possible positive loops remain (so that the open loop system will be easy to study for each fixed value of the input).

It is useful to recall as an example at this point the model considered in Chapter 2, in non-delayed form (the delay system can be treated similarly for the purpose of this argument):

$$\begin{aligned}
\dot{x}_1 &= \frac{A}{K + x_3} - b_1 x_1 \\
\dot{x}_2 &= c_1 x_1 - b_2 x_2 \\
\dot{x}_3 &= c_2 x_2 - b_3 x_3.
\end{aligned} \tag{9.1}$$

By drawing the digraph of this system, it is easy to see that it is not monotone with respect to any orthant order, by Lemma 9. But replacing x_3 in the first equation by u, we obtain a system that is monotone with respect to the orders $\leq_{(1,1,1)}$, $\leq_{(-1)}$ for state and input respectively. Defining $h(x) = x_3$, the closed loop system of this controlled system is none other than (9.1).

We recall the procedure for an arbitrary system (1.1) with a directed graph G: given a set E of edges in G, enumerate the edges in E^C as $(i_1, j_1), \ldots (i_m, j_m)$. For every $k = 1 \ldots m$, replace all appearances of x_{i_k} in the function F_{j_k} by the variable u_k, to form the function $f(x, u)$. Define $h(x) = (x_{i_1}, \ldots x_{i_m})$. It is easy to see that this controlled system (1.2) has closed loop (1.1) (Theorem 16).

Note that the controlled system (1.2) generated by the set E as above has, as associated digraph, the subdigraph of G generated by E. This is because for every k, one has $\partial f_{j_k}(x, u)/\partial x_{i_k} \equiv 0$, i.e. the edge from i_k to j_k has been 'erased'.

If $\mathbb{R}^n, \mathbb{R}^m$ are ordered by orthant orders $\leq_p,\ \leq_q$ respectively, a controlled system

$$\dot{x} = f(x, u),\ y = h(x) \tag{9.2}$$

is monotone with respect to $\leq_p,\ \leq_q$ if and only if

$$p(i)p(j)\frac{\partial f_i}{\partial x_j} \geq 0$$

for every $i \neq j$ (see Section 3.2) and

$$q(k)p(j)\,\frac{\partial f_j}{\partial u_k} \geq 0,\ \text{for every } k, j. \tag{9.3}$$

The latter equation simply ensures that the function $u \to f(x, u)$ is increasing on u for every fixed x.

Let the set E be called *consistent* if the undirected subgraph of G generated by E has no closed chains with parity -1. Note that this is equivalent to the existence of a function p with respect to which every edge in E is consistent, by Lemma 48 applied to the open loop system (1.2). If E is consistent, then the associated system (1.2) itself can also be shown to be monotone: to verify condition (9.3), simply define each $q(k)$ so that (9.3) is satisfied for k, j_k. Since $\partial f_{j_k}/\partial u_k = \partial F_{j_k}/\partial x_{i_k} \not\equiv 0$, this choice is in fact unambiguous. Conversely, if (1.2) is monotone with respect to the orthant orders $\leq_p,\ \leq_q$, then in particular it is monotone for every fixed constant u, so that E is consistent by Lemma 9. We thus have the following result[1].

[1] A natural problem is therefore the following. Given a dynamical system (1.1) that admits a digraph

Lemma 48 *Let E be a set of edges of the digraph G. Then E is consistent if and only if the corresponding controlled system (1.2) is monotone with respect to some orthant orders.*

The following proposition describes a way to write a sign definite system as the closed loop of a controlled monotone system with a negative feedback function. Let $(\mathcal{C}, \subseteq)$ be the class of consistent subsets of $E(G)$, ordered under inclusion.

Proposition 11 *Let E be a consistent set. Then E is maximal in $(\mathcal{C}, \subseteq)$ if and only if h is a negative feedback function for every p such that E is consistent with respect to p.*

Proof. Suppose that E is maximal, and let p be such that E is consistent with respect to p. Given any edge $(i_k, j_k) \in E^C$, it holds that $f(i_k, j_k) = -1$. Otherwise one could extend E by adding (i_k, j_k), thus violating maximality. That is, $p(i_k)p(j_k)\text{sign}(i_k, j_k) = -1$. By monotonicity, it holds that $q(k)p(j_k)\partial f_{j_k}/\partial u_k \geq 0$, and since $\partial f_{j_k}/\partial u_k = \partial F_{j_k}/\partial x_{i_k}$, it follows necessarily that $q(k)p(j_k)\text{sign}(i_k, j_k) = 1$. Therefore it must hold that $q(k) = -p(i_k)$ for each k, which implies that h is a negative feedback function.

Conversely, if p is such that E is consistent with respect to p and h is a negative feedback function, then $q(k) = -p(i_k)$. By the same argument as above, $q(k)p(j_k)\text{sign}(i_k, j_k) = 1$ for all k by monotonicity. Therefore no edge in E^C is consistent with respect to p. Repeating this for all admissible p, maximality follows. ∎

There is a second, slightly more sophisticated way of writing a system (1.1) as the feedback loop of a system (1.2) using an arbitrary set of edges E, which can potentially lead to the use of fewer input variables. Given any such E, define

$$S(E^c) = \{i \,|\, \text{there is some } j \text{ such that } (i,j) \in E^c\}.$$

Now enumerate $S(E^c)$ as $\{i_1, \ldots i_m\}$, and for each k label the set $\{j \,|\, (i_k, j) \in E^c\}$ as $j_{k1}, j_{k2}, \ldots$. Then for each k, l, one can replace each appearance of x_{i_k} in $F_{j_{kl}}$ by u_k,

---

G, use the procedure above to decompose it as the closed loop of a monotone controlled system (1.2), while minimizing the number $|E^C|$ of inputs. An implementation of this problem is discussed in Section 9.1.

to form the function $f(x,u)$. Then one lets $h(x) = (x_{i_1}, \ldots, x_{i_m})$ as above. The closed loop of this system (1.2) is also (1.1) as before but with the advantage that there are $|S(E^c)|$ inputs, and of course $|S(E^c)| \leq |E^c|$.

If E is a consistent and *maximal* set, then one can make (1.2) into a monotone system as follows. By letting p be such that E is consistent with respect to p, we define the order $\leq_p$ on $\mathbb{R}^n$. For every i_k, j_{kl} such that $(i_k, j_{kl}) \in E^C$, it must hold that $p(i_k)p(j_{kl})\mathrm{sign}(i_k, j_{kl}) = -1$. Otherwise $E \cup \{(i_k, j_{kl})\}$ would be consistent, thus violating maximality. By choosing $q(k) = -p(i_k)$, equation (9.3) is therefore satisfied. See the proof of Proposition 11. Conversely, if the system generated by E using this second algorithm is monotone with respect to orthant orders, and if h is a negative function, then it is easy to verify that E must be both consistent and maximal.

9.2 A Semidefinite Programming Approach

For the remainder of this chapter, we will concentrate our attention on the first problem described in the previous section, namely decomposing non-monotone systems as the negative feedback loop of controlled monotone systems by finding a partition p of the nodes and cutting all non-consistent edges forming an open loop system. We can refer to the problem of finding a partition p that minimizes the number of non-consistent edges as the *undirected labeling problem*, or *ULP*.

Professor Bhaskar DasGupta from the University of Illinois pointed out that this problem is very similar to a classic problem in graph theory known as the MAX-CUT problem: given an unsigned, undirected graph, find a partition p of the nodes into two sets, such that the number of edges that connect both partition sets is maximized. In fact, ULP reduces to MAX-CUT in the case where only negative edges are present in G. An efficient algorithm is well known for the MAX-CUT problem, whose core computational part can be reduced to a problem in *semidefinite programming* (SDP) ([36]; see also [111]). Professor DasGupta and his graduate student Yi Zhang then generalized the algorithm in a straightforward manner so that it addresses the present problem. The algorithm and the subsequent implementation are described below - the computer implementation and the analysis of two networks that follows was carried out by myself. See also our article [20].

Recall that the subject of the field of *linear programming* is to find maxima or minima of a scalar linear function $s : D \subset \mathbb{R}^k \to \mathbb{R}$ defined on a polyhedral domain D. A common description of the domain D is

$$D = \{x \in \mathbb{R}^k \,|\, x \geq 0,\ Ax = b\},$$

where $\leq$ is the standard cooperative cone, and A, b are given.

The simplicity of the setup is misleading: many interesting and computationally difficult (i.e. NP hard) problems can be rephrased into this framework, and if that is the case they can be solved with a stunning computational efficiency.

Let $x \in \mathbb{R}^{n^2}$, and let $mat(x)$ be the $n \times n$ matrix composed by distributing the entries of x in an $n \times n$ box in some fixed order. Let K be the cone of all $x \in \mathbb{R}^{n^2}$ such that $mat(x)$ is a symmetric, positive semidefinite matrix. In *semidefinite programming (SDP)*, a problem consists of maximizing or minimizing a scalar linear function $s : D \subseteq \mathbb{R}^{n^2} \to \mathbb{R}$, where the domain D is described as

$$D = \{x \in \mathbb{R}^k \,|\, x \geq_K 0,\ Ax = b\},$$

for some given matrix A and vector b. Thus the domain of the linear functional can be thought of as a restriction of the set of symmetric positive semidefinite matrices.

The following idea relates symmetric, positive semidefinite (psd) matrices to our setup. It is a standard linear algebra result that a matrix Y is symmetric and psd if and only if it can be written as $Y = B^t B$, for some matrix B. Furthermore, the matrix B in question consists of unit vectors if and only if all entries of the diagonal of Y are equal to 1. Given a signed graph G with n vertices, let the unitary vectors $v_i, \dots v_n \in \mathbb{R}^n$ represent each of the vertices $1, \dots n$ of G. We try to choose the v_i so that v_i, v_j are far apart if $\mathrm{sign}(i,j) = -1$ and close together if $\mathrm{sign}(i,j) = 1$. This allows us to cluster the vectors geometrically into two groups, which induces naturally a partition of $V(G)$. Maximizing the function

$$s(v_1, \dots v_n) = \sum_{\mathrm{sign}(i,j)=1} v_i \bullet v_j \quad - \quad \sum_{\mathrm{sign}(i,j)=-1} v_i \bullet v_j$$

over all collections of unitary vectors $v_1 \dots v_n$ in $\mathbb{R}^n$ (or in any other $\mathbb{R}^m$, for that matter) will do. (The function for the MAX-CUT case involves only the second sum.) Let B be formed by the column vectors $v_1, \dots v_n$. The equivalence mentioned above shows that this is can be rephrased as the problem of maximizing

$$s(Y) = \sum_{\text{sign}(i,j)=1} a_{ij} \quad - \sum_{\text{sign}(i,j)=-1} a_{ij}$$

over all symmetric, positive definite matrices Y with diagonal entries equal to 1. For some suitably chosen matrix A and vector b, this is a problem of the kind treated in the SDP setup.

Once the vectors $v_1 \dots v_n$ have been found, this standard algorithm calls for separating them into two groups by choosing a random hyperplane that passes through the origin. After doing this last step several times, the partition is chosen which induces the least number of inconsistent edges.

9.3 Drosophila Segment Polarity

The SDP-based algorithm was implemented using Matlab, and it is illustrated with two applications to biological systems. The first application concerns the relatively small-scale 13-variable digraph of a model of the Drosophila segment polarity network. The second application involves a digraph with 300+ variables associated to the human Epidermal Growth Factor Receptor (EGFR) signaling network (this latter model was published recently and built using information from 242 published papers).

An important part of the development of the early Drosophila (fruit fly) embryo is the differentiation of cells into several stripes (or *segments*), each of which eventually gives rise to an identifiable part of the body such as the head, the wings, the abdomen, etc. Each segment then differentiates into a posterior and an anterior part, in which case the segment is said to be *polarized*. (This differentiation process continues up to the point when all identifiable tissues of the fruit fly have developed.) Differentiation at this level starts with differing concentrations of certain key proteins in the cells; these proteins form striped patterns by reacting with each other and by diffusion through the cell membranes.

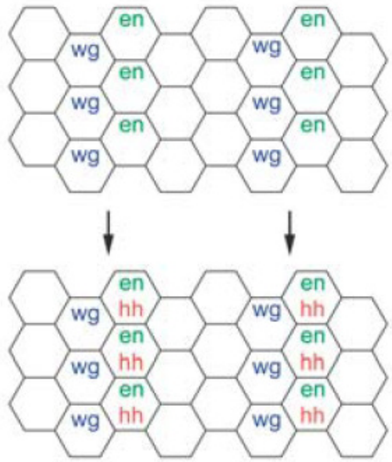

Figure 9.1: A digram of the Drosophila embryo during early development. A part of the segment polarization process is displayed. Courtesy of N. Ingolia and PLoS [53]

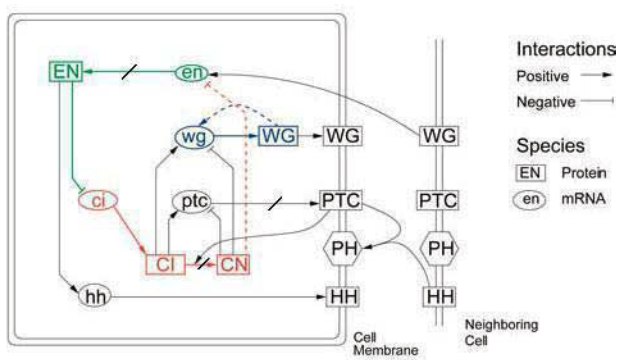

Figure 9.2: The network associated to the Drosophila segment polarity, as proposed in [114], Courtesy of N. Ignolia and PLoS. The three edges that have been crossed have been chosen in order to let the remaining edges form an orthant monotone system.

A model for the network that is responsible for segment polarity [114] is illustrated on Figure 9.2. As explained above, this model is best studied when multiple cells are present interacting with each other. But it is interesting at the one-cell level in its own right — and difficult enough to study that analytic tools seem mostly unavailable. The arrows with a blunt end are interpreted as having a negative sign in our notation. Furthermore, the concentrations of the membrane-bound and inter-cell traveling compounds PTC, PH, HH and WG(membrane) on all cells have been identified in the one-cell model (so that, say, HH$\rightarrow$ PH is now in the digraph). Finally, PTC acts on the reaction CI$\rightarrow$ CN itself by promoting it without being itself affected, which in our notation means PTC$\stackrel{+}{\rightarrow}$ CN *and* PTC$\stackrel{-}{\rightarrow}$CI.

The Implementation

The Matlab implementation of the algorithm on this digraph with 13 nodes and 20 edges produced several partitions with as many as 17 consistent edges. One of these possible partitions simply consists of placing the three nodes ci, CI and CN in one set and all other nodes in the other set, whereby the only inconsistent edges are CL$\stackrel{+}{\rightarrow}$ wg, CL$\stackrel{+}{\rightarrow}$ ptc, and PTC$\stackrel{+}{\rightarrow}$ CN. But note that it is desirable for the resulting open loop system to have as simple remaining loops as possible after eliminating all inconsistent edges. In this case, the remaining directed loops

$$\text{EN}\stackrel{-}{\rightarrow}\text{ci}\stackrel{+}{\rightarrow}\text{CI}\stackrel{+}{\rightarrow}\text{CN}\ \stackrel{-}{\rightarrow}\text{en}\stackrel{+}{\rightarrow}\text{EN}$$

$$\text{EN}\stackrel{-}{\rightarrow}\text{ci}\stackrel{+}{\rightarrow}\text{CI}\ \stackrel{+}{\rightarrow}\text{CN}\ \stackrel{-}{\rightarrow}\text{wg}\stackrel{+}{\rightarrow}\text{WG}\ \stackrel{+}{\rightarrow}\text{WG(membrane)}\ \stackrel{+}{\rightarrow}\text{en}\stackrel{+}{\rightarrow}\text{EN}$$

can still cause difficulties.

A second partition which generated 17 consistent edges is that in which EN, hh, CN, and the membrane compounds PTC, PH, HH are on one set, and the remaining compounds on the other. The edges cut are ptc$\stackrel{+}{\rightarrow}$ PTC, CI$\stackrel{+}{\rightarrow}$ CN and en$\stackrel{+}{\rightarrow}$ EN, each of which eliminates one or several positive loops. By writing the remaining consistent digraph in the form of a cascade, it is easy to see that the only loop whatsoever remaining is wg $\leftrightarrow$ WG; this makes the analysis proposed in Chapter 4 much easier.

In this relatively low dimensional case we can prove that in fact OPT=17, as the results below will show.

Lemma 49 *Any partition of the nodes in the digraph in Figure 9.2 generates at most 17 consistent edges.*

Proof. From Lemma 9, a simple way to prove this statement is by showing that there are three disjoint cycles with negative parity in the network associated to Figure 9.2 (disjoint in the sense that no edge is part of more than one of the cycles). Such three disjoint cycles exist in this case, and they are CI-CN-wg, CI-ptc-PTC, CN-en-EN-hh-HH-PH-PTC. ∎

9.3.1 Multiple Copies

It was mentioned above that the purpose of this network is to create striped patterns of protein concentrations along multiple cells. In this sense, it is most meaningful to consider a *coupled* collection of networks as it is given originally in Figures 9.1 and 9.2. Consider a row of k cells, each of which has independent concentration variables for each of the compounds, and let the cell-to-cell interactions be as in Figure 9.2 with cyclic boundary conditions (that is, the k-th cell is coupled with the first in the natural way). We show that the results can be extended in a very similar manner as before.

Given a partition p of the 1-cell network considered above, let $\hat{p}$ be the partition of the k-cell network defined by $\hat{p}(\mathrm{en}_i) := p(\mathrm{en})$ for every i, etc. Thus $\hat{p}$ consists of k copies of the partition p in a natural way.

Lemma 50 *Let p be a partition of the nodes of the 1-cell network with n consistent edges. Then with respect to the partition $\hat{p}$, there are exactly kn consistent edges for the k-cell coupled model.*

Proof. Consider the network consisting of k *isolated* copies of the network, that is, k groups of nodes each of which is connected exactly as in the 1-cell case. Under the partition $\hat{p}$, this network has exactly kn consistent edges. To arrive to the coupled network, it is sufficient to replace all edges of the form $(\mathrm{HH}_i, \mathrm{PH}_i)$ by $(\mathrm{HH}_{i+1}, \mathrm{PH}_i)$ and $(\mathrm{WG}_i, \mathrm{en}_i)$ by $(\mathrm{WG}_{i+1}, \mathrm{en}_i)$, $i = 1 \ldots k$ (where we identify $k+1$ with 1). Since by definition $\hat{p}(\mathrm{HH}_{i+1}) = \hat{p}(\mathrm{HH}_i)$ and $\hat{p}(\mathrm{WG}_{i+1}) = \hat{p}(\mathrm{WG}_i)$, the consistency of these edges doesn't change, and the number of consistent edges therefore remains constant. ∎

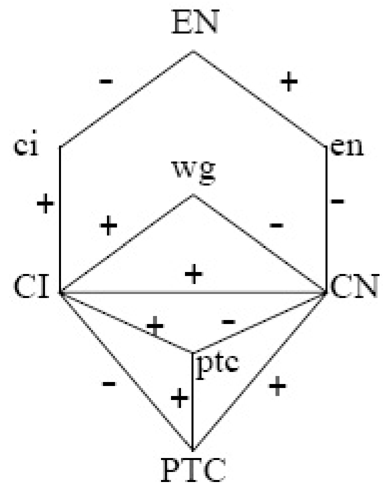

Figure 9.3: A subdigraph of the network in Figure 9.2, using the notation defined in the previous sections. Note that this subdigraph doesn't include any of the two edges (WGmem,en) and (HH,PH), which connect the networks of different cells in Figure 9.2; this will be important in the proof of Lemma 51.

In particular, OPT$\geq 17k$ for the coupled system. The following result will establish an upper bound for OPT.

Lemma 51 *Any partition of the nodes in the digraph in the k-cell coupled network generates at most $17k$ consistent edges.*

Proof. Consider the signed graph in Figure 9.3, which is a subdigraph of the network associated to Figure 9.2. Since the inter-cell edges (WGmem,en) and (HH,PH) are not in this graph, it follows that there are k identical copies of it in the k-cell model. If it is shown that at least three edges need to be cut in each of these k subdigraphs, the result follows immediately.

Consider the negative cycle ci-CI-wg-CN-en-EN, which must contain at least one inconsistent edge for any given partition. The remaining edges of the subgraph form a tetrahedron with four negative parity triangles, which cannot all be cut by eliminating any single edge. If follows that no two edges can eliminate all negative parity cycles in this signed graph, and that therefore $20k - 3k = 17k$ is an upper bound for the number of consistent edges in the k-cell network. ∎

Corollary 23 *For the k-cell linearly coupled network described in Figure 9.2, it holds $OPT=17k$.*

Proof. Follows from the previous two results. ∎

9.4 EGFR Signaling

9.4.1 EGFR Signaling

The protein called *epidermal growth factor* is frequently stored in epitelial tissues such as skin, and it is released when rapid cell division is needed (for instance, it is mechanically triggered after an injury). Its function is to bind to a receptor on the membrane of the cells, aptly called the *epidermal growth factor receptor.* The EGFR, on the inner side of the membrane, has the appearance of a scaffold with dozens of docks to bind with numerous agents, and it starts a reaction of vast proportions at the cell level that ultimately induces cell division.

In their May 2005 paper [84], Oda et al. integrate the information that has become available about this process from multiple sources, and they define a network with 330 known molecules under 211 chemical reactions. The network itself is available from the supplementary material in SBML format (*Systems Biology Markup Language, www.sbml.org*), and will most likely be subject to continuous updates.

The Implementation

Each reaction in the network classifies the molecules as reactants, products, and/or modifiers (enzymes). We imported this information into Matlab using the Systems Biology Toolbox, and constructed a digraph G in our notation by letting $\text{sign}(i, j) = 1$ if there exists a reaction in which j is a product and i is either a reactant or a modifier. We let $\text{sign}(i, j) = -1$ if there exists a reaction in which j is a reactant, and i is also either a reactant or a modifier. Similarly $\text{sign}(i, j) = 0$ if the nodes i, j are not simultaneously involved in any given reaction, and $\text{sign}(i, j)$ is undefined (NaN) if the first two conditions above are both satisfied.

An undefined edge can be thought of as an edge that is *both* positive and negative, and it can be dealt with, given an arbitrary partition, by deleting exactly one of the two signed edges so that the remaining edge is consistent. Thus, in practice, one can consider undefined edges as edges with sign 0, and simply add the number of undefined edges to the number of inconsistent edges in the end of each procedure, in order to form the total number of inputs. This is the approach followed here; there are exactly 7 such entries in the digraph G.

The Results

After running the algorithm 100 times for this problem, and choosing that partition which produced the highest number of consistent edges, the induced consistent set contained 633 out of 852 edges (ignoring the edges on the diagonal and the 7 undefined edges). Contrary to the previous application, many of the reactions involve several reactants and products in a single reaction. This induces a denser amount of negative and positive edges: even though there are 211 reactions, there are 852 (directed) edges in the 330×330 graph G. It is very likely that this substantially decreases OPT for this system.

The approximation ratio of the SDP algorithm is guaranteed to be at least 0.87 for some r, which gives the estimate OPT$\leq\approx 633/0.87 \approx 728$ (valid to the extent that r has sampled the right areas of the 330-dimensional sphere, but reasonably accurate in practice). The 'reduction' of the model using 852-633+7=226 variables instead of 330 is of debatable usefulness in this case, and possibly at this scale in general unless further steps are taken.

Two Possible Improvements

One possible way to drastically reduce the number of inputs necessary to write this system as the negative closed loop of a controlled monotone system is by making suitable changes of variables using the mass conservation laws. Such changes of variables are discussed in many places, for example in [113] and [6]. In terms of the associated digraph, the result of the change of variables is often the elimination of one of the closed chains. The simplest target for a suitable change of variables is a set of three nodes that form part of the same chemical reaction, for instance two reactants and one product, or one reactant, one product and one modifier. It is easy to see that such nodes are connected in the associated digraph by a negative parity triangle of three edges.

In order to estimate the number of inputs that can potentially be eliminated by suitable changes of variables, we counted pairwise disjoint, negative parity triangles in the digraph of the EGFR network. Using a greedy algorithm to find and tag disjoint negative feedback triangles, we found a maximal number of them in the subgraph associated to each of the 211 chemical reactions. Special care was taken so that any two triangles from different reactions were themselves disjoint. After carrying out this procedure we found 196 such triangles in the EGFR network. This is a surprisingly high number, considering that each of these triangles must have been opened in the ULP algorithm implementation above and that therefore each triangle must contain one of the 226 edges cut.

A second procedure that was carried out to lower the number of inputs was a hybrid algorithm involving *out-hubs*, that is, nodes with an abnormally high out-degree. Recall from the description of the DLP algorithm that all the out-edges of a node x_i can be potentially cut at the expense of only one input u, by replacing all the appearances of x_i in $f_j(x)$, $j \neq i$, by u. We considered the k nodes with the highest out-degrees, and eliminated all the out-edges associated to these hubs from the reaction digraph to form the graph G_1. Then we run the ULP algorithm on G_1 to find a partition p of the nodes and a set of edges that can be cut to eliminate all remaining negative closed chains. Finally, we put back on the digraph those edges that were taken in the first step, and which are consistent with respect to the partition p. The result is a decomposition of the system as the negative feedback loop of a controlled monotone system, using at most $k + m$ edges.

An implementation of this algorithm with $k = 60$ yielded a total maximum number of inputs $k + m = 137$. This is, once again, a significant improvement over the 226 inputs in the original algorithm.

Chapter 10

Further Topics

In this chapter, several topics are addressed that have as background motif the theory of monotone systems. Section 10.1 introduces concepts that can be helpful to determine when a cascade of monotone systems under positive feedback can be strongly monotone. Section 10.2 considers the possibility of studying the stability of a non-quasimonotone matrix by comparing it to a similar matrix which is quasimonotone (in case there is such a matrix).

10.1 Transparency and Excitability

In this section we further ellaborate on the ideas presented in [7] to give sufficient conditions on a monotone controlled system so that its closed loop under unity feedback is strongly monotone. These conditions are chosen in such a way that, in the orthant-cone case, they can be routinely verified by looking at the digraph of the system. More precisely, we study conditions under which a *cascade* of monotone systems is strongly monotone.

In what follows, we say that a monotone system (9.2) is *partially excitable* if for any $x_1 \leq x_2$, arbitrary inputs u_1, u_2, and any $t_0 > 0$:

$$\begin{aligned} &u_1 < u_2 \text{ a.e. on } (0,t_0) \Rightarrow x(t,x_1,u_1) < x(t,x_2,u_2),\ \ t \in (0,t_0) \\ &u_1 \ll u_2 \text{ a.e. on } (0,t_0) \Rightarrow x(t,x_1,u_1) \ll x(t,x_2,u_2),\ \ t \in (0,t_0). \end{aligned} \tag{10.1}$$

We also say that (9.2) is *strongly excitable* if

$$u_1 < u_2 \text{ a.e. on } (0,t_0) \Rightarrow x(t,x_1,u_1) \ll x(t,x_2,u_2),\ \ t \in (0,t_0).$$

Further, we will say that (9.2) is *partially transparent* if for arbitrary inputs $u_1 \leq u_2$

and initial conditions x_1, x_2 one has

$$\begin{aligned} x_1 < x_2 &\Rightarrow h(x(t, x_1, u_1)) < h(x(t, x_2, u_2)) \\ x_1 \ll x_2 &\Rightarrow h(x(t, x_1, u_1)) \ll h(x(t, x_2, u_2)), \end{aligned} \tag{10.2}$$

and *strongly transparent* if

$$x_1 < x_2 \Rightarrow h(x(t, x_1, u_1)) \ll h(x(t, x_2, u_2)),$$

for all $t > 0$ for which the solutions $x(t, x_i, u_i)$ are defined.

Note that the first equation in (10.1) and the second equation in (10.2) correspond to the notions of weak excitability and weak transparency, respectively, in the terminology of [7] (borrowed from [88]).

In particular partial excitability (transparency) implies weak excitability (transparency). But the converse is not true: in the cooperative case, if there are arcs from a fixed input to every single state, but no arcs from other inputs whatsoever, then the system is weakly excitable but not partially excitable since $u_1 < u_2$ doesn't imply $x(t, \xi, u_1) < x(t, \xi, u_2)$. Similarly for transparency. The valid implication allows us nevertheless to quote Theorem 2 from [7] in our present terminology:

Proposition 12 *A monotone system (9.2) that is partially excitable and partially transparent has strongly monotone feedback loop provided that it is also either strongly excitable or strongly transparent.*

It has also been shown that in the case of orthant cones and sign definite systems, there are simple conditions on the digraph of the system that imply transparency and excitability statements. For instance, if there exists a directed path from every input variable (from every state variable) to every state variable (to every output variable), then the system is strongly excitable (strongly transparent). (See Theorems 4 and 5 of [7]). We show a similar result for the definitions above.

Lemma 52 *Let (9.2) be a sign definite controlled system that is monotone with respect to some orthant cone. If from every input (from every state) there exists a path towards some state (towards some output), and if towards every state (towards every output)* *there exists a path from some input (from some state), then the system is partially excitable (partially transparent).*

Proof.

These results follow from a revision of the proofs of Theorems 4 and 5 in Appendix A of [7]. Consider first partial excitability: by Case 2 of Lemma A1 of [7], since every input variable u_j reaches some x_i through a directed path (we will say that the inputs are *non-idle*), $u_1 < u_2$ a.e. on $(0, t_0)$ implies that $x(t, \xi, u_1) < x(t, \xi, u_2)$ for any $\xi,\ t \in (0, t_0)$. By monotonicity,

$$x(t, x_1, u_1) \leq x(t, x_2, u_1) < x(t, x_2, u_2)\,.$$

As to the second assertion, the proof given for Theorem 4 in [7] actually shows that if every x_i is reachable from some u_j, then for any ξ:

$$u_1 \ll u_2 \Rightarrow x(t, \xi, u_1) \ll x(t, \xi, u_2)\,.$$

The statement for $x_1 \leq x_2$ follows by monotonicity. A similar argument is valid for transparency: given an input u and assuming $\xi_1 < \xi_2$, there is i such that $\{t \geq 0 \,|\, x_i(t, \xi_1, u) < x_i(t, \xi_2, u)\} \cap [0, \epsilon)$ has nonzero measure for every $\epsilon > 0$, see sketch of proof of Theorem 5 in [7]. If y_i is reachable from x_i, then $h_j(x(t, \xi_1, u)) < h_j(x(t, \xi_2, u)),\ t > 0$. The statement for $u_1 \leq u_2$ follows by monotonicity, and from the fact that every x_i reaches some y_j. By the same token, since every y_j is reached by some x_i (we will say the outputs are *non-idle*), $x_1 \ll x_2$ implies $h_j(x(t, x_1, u_1)) \ll h_j(x(t, x_2, u_2)),\ t > 0$.

∎

Now consider, instead of system (9.2), a cascade one of the form

$$\begin{aligned} \dot{x} &= f(x, u),\ y = h(x), \\ \dot{z} &= g(z, v),\ v = y,\ w = H(z)\,, \end{aligned} \tag{10.3}$$

where $Y = V$ and $W = U$. We will refer to the controlled subsystems $\dot{x} = f(x, u),\ y = h(u)$, and $\dot{z} = g(z, v),\ w = H(z)$ as (10.3.1) and (10.3.2) respectively.

Lemma 53 *Suppose that the cascade system (10.3) is monotone, and that (10.3.1) and (10.3.2) are both partially excitable and partially transparent. Then (10.3) is partially excitable and partially transparent, and*

1. *If (10.3.1) is strongly excitable, then (10.3) is strongly excitable.*

2. *If (10.3.2) is strongly transparent, then (10.3) is strongly transparent.*

Proof. Consider any pair of initial conditions $(x_1, z_1) < (x_2, z_2)$ of the closed loop system, and let $x_i(t), z_i(t), u_i(t), y_i(t) = v_i(t), w_i(t)$ be their induced inputs and outputs on a maximally defined interval, $i = 1, 2$ (from now on we will restrict ourselves to this interval). In particular, note that $x_i(t)$ is the solution of the open system $\dot{x} = f(x, u_i)$ with initial condition x_i and input $u_i(\cdot)$, and similarly for $z_i(t)$. The monotonicity of (10.3) is clear since it is the closed loop of a cascade of monotone systems, under positive feedback. By monotonicity we thus have $x_1(t) \leq x_2(t)$ and $z_1(t) \leq z_2(t)$, and consequently all other functions are ordered as well, for every $t \geq 0$.

We prove the partial excitability of the cascade: if $u_1 < u_2$ on some interval $(0, t_0)$, then $x_2 < x_2$ on that interval by partial excitability of (10.3.1), $y_1 < y_2$ i.e. $v_1 < v_2$ by partial transparency of (10.3.1), and $z_1 < z_2$ by partial excitability of (10.3.2). The other half of partial excitability for (10.3), as well as the proof of partial transparency, are very similar.

Now suppose that (10.3.1) is strongly excitable, and let $u_1 < u_2$. By strong transparency we have $x_1 \ll x_2$, and by partial transparency and excitability $z_1 \ll z_2$, as expected. Item (2) is proven in a similar way. ∎

Corollary 24 *Let the system (10.3) be monotone and let both (10.3.1) and (10.3.2) be partially excitable and partially transparent, with one of these four conditions being also strong. Then the closed loop system obtained by setting $u = w$ in (10.3) is strongly monotone.*

Proof. By the previous lemma, the cascade (10.3) is itself partially excitable and partially transparent. If (10.3.1) is strongly excitable or if (10.3.2) is strongly transparent, the conclusion follows by the previous lemma and the previous proposition. In the other two cases, simply invert the order of the two systems in the cascade, note that the closed loop system remains the same, and apply the previous argument. ∎

A straightforward generalization applies, of course, for cascades of more than two subsystems.

10.2 Monotone Envelopes

Monotone matrices have very strong stability properties, in particular thanks the Perron Frobenius theorem (see Chapter 3). Suppose that a matrix is not quasimonotone, but that it would be if a few of its entries changed sign. Then it would make sense to study the stability of this matrix by looking at its monotone counterpart. This is the idea behind the present section. There are plenty of such results in the literature: a classic theorem of McKenzie states that if a matrix M has negative diagonal entries, and

$$|m_{ii}| > \sum_{j\neq i} |m_{ij}|\,,\ i = 1\ldots n,$$

then M must be exponentially stable. This result can be thought of not quite as a test for the stability of M, but rather for the matrix that results by replacing m_{ij} by $|m_{ij}|$, $i \neq j$.

Given an arbitrary $n \times n$ matrix M, let the *monotone envelope* $\overline{M}$ *of* M *with respect to* $\leq$ be defined by

$$\overline{m}_{ij} = \begin{cases} m_{ij}, & i = j \\ |m_{ij}|\,, & i \neq j. \end{cases}$$

Let $M_- = (\overline{M} - M)/2$, and let $M_+ = M - M_-$. Then $M = M_+ - M_-$, $\overline{M} = M_+ + M_-$. Note that M_+ is quasimonotone, and $M_- \geq 0$. The following lemma shows a sense in which this is a canonical decomposition of M, and it can be used to define the monotone envelope of M for more general cones.

Lemma 54 *$\overline{M} \leq A + P$, for any A quasimonotone and $P \geq 0$ such that $M = A - P$.*

Proof. Since all the off-diagonal entries of A are nonnegative, it must follow that $P \geq M_-$. But

$$M_+ - M_- = M = A - P \leq A - M_-,$$

so that $M_+ \leq A$. Therefore $\overline{M} = M_+ + M_- \leq A + P$. ∎

In the non-orthogonal case, one can define $\overline{M}$ as follows. Let $A \leq B$ if and only if $B - A$ is a positive matrix, i.e. $(B - A)\mathcal{K} \subseteq \mathcal{K}$. Assume that the cone defined by this order has nonempty interior and that for any nonempty set of matrices S that is bounded from below there exists the matrix $\inf S$. Then one can let

$$S = \{A + P \,|\, A \text{ quasimonotone },\ P\mathcal{K} \subseteq \mathcal{K},\ M = A - P\}.$$

The set S is necessarily nonempty, since there exists $A \gg 0$ large enough that $A \leq M$; for $P := A - M$ the existence of a point in S is assured. A lower bound for S is M itself. Defining $\overline{M} := \inf(S)$, Lemma 54 guarantees that this matrix coincides with that previously defined in the cooperative case.

We call $M = A - P$ a *monotone decomposition* of the matrix M if A is quasimonotone and $P \geq 0$. Thus $\overline{M}$ is the minimum of $A + P$ over all monotone decompositions of M. If $A + P$ is irreducible, then we call it a *strongly monotone decomposition* of M.

Consider the monotone controlled system under negative feedback

$$\dot{x} = Ax + Bu, \quad u = -Cx \tag{10.4}$$

(A is not assumed here to be a stable matrix). The closed loop system associated to (10.4) is therefore

$$\dot{x} = (A - BC)x. \tag{10.5}$$

The following lemma is the linear version of a result in [29].

Lemma 55 *Assume that there are $a, b \in \mathbb{R}^n$, $a \leq b$, such that*

$$Aa - BCb \geq 0,\ Ab - BCa \leq 0. \tag{10.6}$$

Then $[a, b]$ is an invariant set for (10.5). The solution $a(t)$ ($b(t)$) of (10.4) with initial condition a (b) and constant control $-Cb$ ($-Ca$) is monotonically increasing (decreasing) and converges towards $a_1 = A^{-1}BCb$ ($b_1 = A^{-1}BCa$). Furthermore, $\omega([a, b]) \subseteq [a_1, b_1]$.

Proof. See the proof for the general nonlinear case in [29]. ∎

In the simple case $BC = 0$, equation (10.6) implies $a \leq 0, b \geq 0$, by monotonicity of $-A^{-1}$. Then using a lemma from [101] the functions $a(t), b(t)$ are monotonic and bounded (by monotonicity) and must therefore converge to the unique equilibrium $a_1 = b_1 = 0$.

The following Lemma is related to McKenzie's result stated above. For simplicity, we still consider only the cooperative case.

Lemma 56 *If $\overline{M}$ is exponentially stable, then M is exponentially stable.*

Proof. Let D be defined by $p_{ij} = 1$ for all i, j. Let $A = M_+ + \epsilon D$ and $B = M_- + \epsilon D$, $C = I$, where $\epsilon > 0$ is small enough that $A + BC$ is still exponentially stable. Since $A + BC$ is quasimonotone irreducible, there exists a Perron-Frobenius eigenvalue $b \gg 0$ such that $(A + BC)b = \lambda b \gg 0$ (see Chapter 3). Let $a := -b$. Then $a \ll 0 \ll b$, and

$$Aa - BCb = \lambda b \gg 0, Ab - BCa = -\lambda b \ll 0. \tag{10.7}$$

By Lemma 55, $[a, b]$ is invariant for (10.5). Since this set has nonempty interior, it follows that $M = A - BC$ is Lyapunov stable.

The proof that M is actually exponentially stable follows by a perturbation argument, and by the fact that $\overline{M + \delta I} = \overline{M} + \delta I$. If M were only Lyapunov stable, then one could consider $M' = M + \delta I$ for $\delta > 0$ small enough that $\overline{M}'$ is still exponentially stable, and reach a contradiction by the above argument. ∎

Notes

It is clear from the proof that if $\overline{M}$ is Lyapunov stable, then M is also Lyapunov stable. Also, it is not true that if M is exponentially stable, then $\overline{M}$ is exponentially stable, even for irreducible M. But it follows from the proof that if $\overline{M}$ is exponentially stable then there exists a strongly monotone decomposition $M = A - BC$ and $a \ll 0 \ll b$ such that

$$Aa - BCb \gg 0, \;\; Ab - BCa \ll 0. \tag{10.8}$$

The following result shows that a converse also holds.

Lemma 57 *Let M be an arbitrary $n \times n$ matrix, and let $M = A - P$ be a strongly monotone decomposition of M. Then $A + P$ is Lyapunov stable (exponentially stable) if and only if there exist a, b, $a \ll 0 \ll b$ such that (10.6) ((10.8)) holds.*

Proof.

Let $A + P$ be Lyapunov stable, and let q be the Perron-Frobenius eigenvalue of $A + P$; define $b := q$, $a := -q$. Then in the same way as in the previous proof, $Aa - Pb = \lambda b \geq 0, Ab - Pa = -\lambda b \leq 0$. If $A + P$ is exponentially stable, then equation (10.7) holds. This shows one direction of the statement.

To see the converse result, let $a \ll 0 \ll b$ be such that the weaker inequality (10.6) holds, and suppose that leig $A + P > 0$. Let $q \gg 0$ be the Perron-Frobenius eigenvalue associated to $A+P$, and let $p := -q$. By possibly rescaling p, q using a positive constant, we can assume that $[p, q] \subseteq [a, b]$ and either $p \in \partial[a, b]$ or $q \in \partial[a, b]$. Assume the first case (the other being very similar). Since $p \ll 0 \ll b$, it is impossible that $p \in \partial(b - K)$. Therefore it must hold $p \in \partial(a + K)$. Using the Volkmann condition, let $\lambda \in K^*$ be such that $\lambda(p - a) = 0$, so that by monotonicity $\lambda(Ap) \geq \lambda(Aa)$. But then

$$\lambda(Ap - Pq) \geq \lambda(Aa - Pq) \geq \lambda(Aa - Pb) \geq 0,$$

which is a contradiction since $Ap - Pq = -(A + P)q \ll 0$. Therefore one concludes that leig $A + P \leq 0$.

If a, b are such that the stronger inequality (10.8) holds, define $A' = A + \epsilon I$ for $\epsilon > 0$ small enough that (10.8) still holds for A replaced by A'. Then by the previous argument $A' + P$ is Lyapunov stable, hence $A + P$ is exponentially stable. ∎

The following simple lemma addresses some properties relating monotone decompositions and irreducibility.

Lemma 58 *Let M be a $n \times n$ matrix. The following conditions are equivalent:*

1. *M is irreducible.*

2. *$\overline{M}$ is irreducible.*

3. *Every monotone decomposition of M is strongly monotone.*

Proof. The equivalence of the first two conditions is obvious, since M and $\overline{M}$ have nonzero entries at the same coordinates. If $\overline{M}$ is irreducible, and $M = A - P$ is a monotone decomposition, then by Lemma 54 $\overline{M} \leq A + P$. Since both matrices have nonnegative off diagonal entries, $A + P$ is also irreducible. Finally, if every monotone decomposition of M is strongly monotone, then in particular $M = M_+ - M_-$ is strongly monotone, that is, $\overline{M} = M_+ + M_-$ is irreducible. ∎

The following corollary shows how the condition in Lemma 55 is in a sense a test for stability, not for M, but rather for $\overline{M}$.

Corollary 25 *Let M be an irreducible arbitrary matrix, and let $A = M_+$, $B = M_-$, $C = I$. Then $\overline{M}$ is Lyapunov stable (exponentially stable) if and only if there exist a, b, $a \ll 0 \ll b$ such that (10.6) ((10.8)) holds.*

Proof. Follows directly from Lemma 57 and Lemma 58. ∎

Chapter 11

Future Work

In several chapters of this dissertation the negative feedback closed loop of a monotone controlled system is considered, and sufficient conditions are given for global attractivity towards a unique equilibrium. It was also shown how in a very general setting a non-monotone system can be decomposed as such a negative feedback loop. It is therefore natural to ask whether the same setup can provide sufficient conditions for other kinds of behavior, namely global attractivity towards two or more equilibria (i.e. *multistability*) or the existence of periodic solutions. The present chapter is a discussion how such results could be addressed.

11.1 Monotone Embeddings and Multistability for Non-Monotone Systems

Recall that given a strongly monotone system in $\mathbb{R}^n$ with precompact orbits, almost all solutions must converge towards the set of equilibria E. If this set is discrete, or under other relatively mild hypotheses [101, 28], then almost all solutions are in fact convergent towards some equilibrium (which depends on the initial condition). See Section 3.5 and Chapter 8 for a thorough discussion of these ideas.

It is a direct consequence of Dancer's Theorem 10 that a stronger stability conclusion can be reached for a general monotone system provided that no two equilibria are comparable under $\leq$, namely that *all* solutions of the monotone system are convergent. In this section, it is illustrated how the convergence of all solutions to equilibrium on a monotone system implies the convergence of all solutions to equilibrium for another, non-monotone system in a potentially quite general context. The possible relevance of the input-output approach is described as well.

Lemma 59 *Let $K \subseteq \mathbb{R}^n$ be a cone, and let $X \subseteq \mathbb{R}^n$ be such that for every bounded $A \subseteq X$, there exist $a, b \in X$ that bound A from below and above. Let $\dot{x} = f(x)$ be a monotone system on X with precompact orbits, and let no two equilibria in E be comparable under $\leq$. Then all solutions of the system converge towards some equilibrium.*

Proof. This is a direct consequence of Dancer's lemma in [19]: given $x \in X$, there exist equilibria e_1, e_2 such that $e_1 \leq \omega(x) \leq e_2$. But then it follows $e := e_1 = e_2$ by hypothesis, and therefore $\omega(x) = e$. ∎

A particular case of interest is that in which all equilibria are included in the diagonal, as will be shown below. It will be essential that *every* solution is convergent, since we will concentrate our attention on the convergence of solutions on a set of measure zero.

Let $\mathcal{K}_X \subseteq \mathbb{R}^n$, $\mathcal{K}_U \subseteq \mathbb{R}^m$ be orthant cones, and let $X \subseteq \mathbb{R}^n$, $U \subseteq \mathbb{R}^m$ be closed orthants for simplicity. Consider a controlled monotone system under negative feedback

$$\dot{x} = f(x, u), \;\; u = h(x). \tag{11.1}$$

Closing the loop we obtain the system that is the actual target of our study, namely

$$\dot{x} = f(x, h(x)). \tag{11.2}$$

In Sections 5.3 and 9.1, it is shown how any sign-definite system can be written as the negative feedback loop of a controlled monotone system in this way.

Following an argument similar to that given by Gouze [39] and Cosner et al. [18], we extend this system by considering the $2n$-dimensional system

$$\begin{aligned} \dot{x} &= f(x, h(z)) \\ \dot{z} &= f(z, h(x)). \end{aligned} \tag{11.3}$$

This system is defined on the set $X \times X$, and it is monotone with respect to the cone $K \times (-K)$ — see [29]. The system extends (11.2) in the sense that the diagonal $D = \{(x, x) \,|\, x \in X\}$ is invariant for (11.3), and a trajectory of the form $(x(t), x(t))$ is a solution of (11.3) in D if and only if $x(t)$ is a solution of (11.2) in X.

In the paper [29], this embedding is exploited to replicate many of the results of this dissertation's chapters on negative feedback, by considering the particular case in which the extended monotone system has a unique equilibrium. This promising and simple approach was considered only after the results of Chapters 4 and 5 were in the press for the Journal of Discrete and Continuous Dynamical Systems. Nevertheless the ideas in these chapters are of value in their own right; see also the subsection on periodic solutions in the present chapter.

On the other hand, any condition on the monotone embedding system that guarantees that every solution converges towards an equilibrium can be used to conclude the convergence of every solution of (11.2) to an equilibrium. For instance, consider the following corollary.

Corollary 26 *Let (11.2) be such that system (11.3) has bounded solutions and has all its equilibria in the diagonal D. Then all the solutions of (11.2) converge towards an equilibrium.*

Proof. Note that the cone $K \times (-K)$ as well as the state space $X \times X$ are closed orthant sets, and that therefore the boundedness hypothesis in Lemma 59 is satisfied. Furthermore, in the closed set $X \times X$ the precompactness of the solutions is equivalent to their boundedness (in open state spaces this is not guaranteed). Clearly any two elements of the diagonal are unordered: if $(x, x) \leq (y, y)$, then $x \leq y$ and $y \leq x$, and therefore $x = y$ and $(x, x) = (y, y)$. Lemma 59 can be applied, to conclude in particular that all solutions of (11.3) on D converge towards an equilibrium. By the equivalence between systems (11.3) on the diagonal and (11.2), the conclusion follows. ∎

Proving that a monotone system $\dot{x} = g(x)$ has only bounded solutions can be done by finding arbitrarily large vectors x such that $g(x) \leq 0$, $g(-x) \geq 0$ (at least in the case $X = \mathbb{R}^n$); see [101].

A characterization for the second hypothesis in Corollary 26 is given now. We define the *set characteristics* K^X, K of the open loop (11.1) as elsewhere:

$$\begin{aligned} K^X(u) &= \{x \,|\, f(x, u) = 0\} \\ K(u) &= \{h(x) \,|\, f(x, u) = 0\} \end{aligned} \tag{11.4}$$

Now consider the discrete inclusion system

$$u_{n+1} \in K(u_n) \tag{11.5}$$

which can potentially yield useful information about the original system. For instance, it follows from Theorem 12 that if K^X is a single-valued function and the discrete system (11.5) is globally attractive towards $\bar{u}$, then (11.2) converges globally towards $\mathcal{K}(\bar{u})$.

Another common behavior of this discrete system is the convergence towards two cycles; the following lemma provides a simple description of such cycles in terms of the monotone embedding.

Lemma 60 *A point (x, z) is an equilibrium of (11.3) if and only if $(h(x), h(z))$ is a two-cycle of the discrete inclusion (11.5).*

Proof. Simply note that (x, z) is an equilibrium if and only if $x \in K^X(h(z))$, $z \in K^X(h(x))$, and that this is equivalent to $h(x) \in K(h(z)$, $h(z) \in K(h(x))$. ∎

Lemma 61 *Suppose that whenever e_1, e_2 are two different equilibria of (11.2), it holds that $h(e_1) \neq h(e_2)$. Then all equilibria of (11.3) are on the diagonal D if and only if system (11.5) has no nontrivial two-cycles.*

Proof. Let u, v be two different input values such that $u \in K(v)$, $v \in K(u)$. By definition of K, there must exist $x, z \in X$ such that $u = h(x), v = h(z)$. Clearly $x \neq z$. By the previous lemma, (x, z) is an off-diagonal equilibrium of (11.3).

Let now $(x, z) \notin D$ be an equilibrium of (11.3), so that $u = h(x), v = h(z)$ form a two-cycle of the discrete inclusion. Assume by contradiction that $u = v$; then $0 = f(x, h(z)) = f(x, h(x))$ and x is an equilibrium of (11.2). Similarly for z. Since $x \neq z$, then by the stated assumption it must hold $u = v$, which is a contradiction. ∎

Corollary 27 *Let h be injective in the set E of equilibria of (11.2), and let (11.3) have bounded solutions. Then all solutions of (11.2) converge to an equilibrium, provided that the discrete inclusion (11.5) has no nontrivial two-cycles.*

The injectiveness of h in E is particularly common in the case that the digraph of (11.2) is strongly connected. The condition on the discrete inclusion holds in particular when all solutions of the discrete inclusion are convergent.

The work of de Leenheer and Malisoff [24] should be mentioned at this point, in which they consider the original paper by Angeli and Sontag [6], and weaken the small gain condition by considering set characteristics and a discrete inclusion very much like in equation (11.4). They conclude that all solutions of the closed loop system (11.2) are convergent to an equilibrium, provided that all solutions of the discrete inclusion are convergent, which is consistent with the argument provided above.

The following negative result is the reason why this argument is not in the main text — namely, the hypotheses of Corollary 26 turn out only to be satisfied in the case considered in the paper [29].

Lemma 62 *Consider a system $\dot{x} = g(x)$ defined on $\mathbb{R}^n$ which i) is monotone with respect to a cone with nonempty interior, ii) has bounded solutions, and iii) is such that $|E| > 1$. Then there exist two different equilibria e_1, e_2 such that $e_1 < e_2$.*

Proof. Suppose that all equilibria are pairwise unordered. By the Dancer result above, the boundedness of the solutions and the monotonicity imply that every solution converges towards an equilibrium. Let $x(t)$ and $y(t)$ be solutions such that $x(t) \to e_1$ and $y(t) \to e_2$, $e_1 \neq e_2$. Since the underlying cone has nonempty interior, there exists $z = z(0)$ which bounds $x(0)$ and $y(0)$ from above. Let the corresponding solution $z(t)$ converge to e_3. Then necessarily $e_1 \leq e_3$ and $e_2 \leq e_3$ by monotonicity. But one of these two inequalities must be strict, since otherwise $e_1 = e_2$. ∎

The problem that nevertheless remains is *to find other conditions on the open loop system (11.1) such that* all *solutions of the monotone system (11.3) are convergent to equilibrium*, regardless of the existence of off-diagonal equilibria. Any such conditions, which will likely use more of the structure of the particular monotone system (11.3), will yield sufficient conditions for the *non-monotone* system (11.2) to have only convergent solutions.

11.2 Inverse SGT and Ejective Fix Points

Consider once again a monotone controlled dynamical system under negative feedback (11.1) assuming $X = \mathbb{R}^n,\ U = R^m$, and consider the corresponding closed loop system (11.2). Assume also the existence of single-valued characteristic functions $k^X : U \to X,\ k : U \to U$ as in Chapter 4. In the simplest case of the small gain theorem (Theorem 12, or SGT for short), the small gain condition (namely that all solutions of the discrete system $u_{n+1} = k(u_n)$ are convergent towards a point $\bar{u}$) implies that system (11.2) is globally attractive to an equilibrium. In Chapter 5, it is described how one can in fact introduce delays of arbitrary length in the open loop system (11.1), without changing the functions $k^X,\ k$, and still preserve the global attractivity of the closed loop system. (Essentially, the only condition necessary after the introduction of the delay is that the monotonicity of the open loop system is preserved.)

To evaluate the usefulness of the SGT one must ask the question of how strong the underlying assumptions are. Indeed, often in an application the open loop system (11.1) has a unique equilibrium for each constant value of the control u, but this value is not globally attractive and the solutions are unbounded; in this case the characteristic functions k^X, k are not well defined.

But an interesting case which will occupy us in this section is that in which the characteristic functions exist but the small gain condition is not satisfied. The question we want to ask is: under which conditions does it hold that if the small gain condition fails, then the continuous system is not globally attractive for *some* value of the chosen delay? In particular, when does a violation of the small gain condition result in the existence of periodic solutions for some value of the delay? A general solution to this problem would go a long way towards showing the strength of the small gain theorem, and it would provide a more complete picture of the relationship between the closed loop system and its associated discrete system.

In the absence of delays, a violation of the small gain condition doesn't generally imply that the continuous system is not globally attractive, for example in the case $\dot{x} = -x + u, u = -2x$. But even in this case, there seems to be a relationship between closed loop and discrete system, as it was noted by Smith in 1987 [100] for the case of the cyclic gene expression model — see the quote in Section 5.1. If the discrete system is globally attractive to equilibrium, Smith notes, the continuous system is globally attractive as well (i.e. SGT). But if the discrete system globally approaches a two-cycle, then the continuous system, as simulated numerically, often approaches a periodic cycle. In 1990, Mallet-Paret and Smith [73] proved a Poincare-Bendixon theorem for a class of undelayed systems containing this example, and thus proved that convergence to equilibrium or to a periodic solution are the only possible behaviors of such a system. But the relationship to an associated discrete system does not seem to be studied in this work. The corresponding result for cyclic delay systems was published in 1996 by Mallet-Paret and Sell [72]. Once again, no relationship with a discrete system appears to be given — and this relationship could prove very illuminating, since the Poincare-Bendixon theorem per se does not provide information as to when, say, periodic behavior arises as opposed to global attraction to equilibrium.

A clue to the solution of the stated question is provided in a one-dimensional delay setup by the work of Nussbaum, Mallet-Paret, and others [15, 43, 70]. Consider a delay differential equation

$$\dot{x} = g(x(t-\tau)) - x(t),$$

where $g : \mathbb{R} \to \mathbb{R}$ is a decreasing bounded function such that $g(0) = 0$, $|g'(0)| > 1$ (the work in the quoted references assumes $xg(x) < 0,\ x \neq 0$ instead of decreasingness, but the simpler framework is appropriate for this presentation). One can decompose this system as the closed loop of the delay controlled system

$$\dot{x} = u - x(t),\ u = g(x(t-\tau)).$$

Note that this system is monotone with negative feedback using the standard orders, and that the characteristic functions are well defined and have the value $k^X(u) = u, k(u) = g(u)$. Therefore the condition $|g'(0)| > 1$ can be thought of as ensuring the linear instability of the fix point 0 of the discrete system $u_{n+1} = k(u_n) = g(u_n)$.

It is proven in [43, 70] that for large enough τ, there exists a periodic solution of this system. Thus the question asked above is answered affirmatively, at least for this one-dimensional framework. The strategy used to prove this is roughly as follows: after a straightforward change of variables, the system is brought into the equivalent form

$$\epsilon\dot{x} = g(x(t-1)) - x(t) \tag{11.6}$$

where $\epsilon = 1/\tau$. Consider the set K of functions $\phi : [-1, 0] \to \mathbb{R}^+$ such that $\phi(-1) = 0$ (an additional condition is actually further imposed, see Hadeler and Tomiuk [43]), and define (for $\phi \neq 0$) $S(\phi) = x_{t_0}$, where $x(t)$ is the solution of (11.6) with initial condition ϕ, and where t_0 is the least $t \geq 0$ such that $x_t \geq 0$. Define further $S(0) = 0$. Now it is shown that $S(\phi) \in K$, and that $S : K \to K$ is a completely continuous function.

After noting that K has a closed and bounded invariant subset, the Schauder fix point theorem ensures that there exists a fix point of the function S, which strictly speaking guarantees the existence of a periodic solution of system (11.6). But there is a problem: the fix point $S(0) = 0$ induces the solution $x(0) \equiv 0$, which is 'periodic', but which should be ruled out if one wants to find a nontrivial periodic trajectory of this system. This is where the so-called ejective fix point theory becomes useful.

Let $P : Y \to Y$ be a completely continuous function defined on a closed, bounded subset Y of an infinite dimensional Banach space. A fix point x of P is said to be *ejective* if there exists an open neighborhood U of x such that for every $z \in U - \{x\}$, $P^n(z) \notin U$ for some n. Browder [13] proved that in this setup, which is the same of the Schauder fix point theorem, there always exists a fix point which is *not* ejective. It is interesting that this result is false in finite dimensions: the complex function $P(re^{\theta i}) = \sqrt{r}e^{(\theta+\pi/2)i}$ is an example for the two-dimensional closed disc.

Back to equation (11.6): by proving that the trivial fix point $\phi = 0$ of P is ejective and noting that the domains in question are infinite dimensional, it follows by Browder's theorem that there must be *another* fix point, which therefore must correspond to a nonzero periodic solution of the delay equation.

The future work proposed in this section is therefore to carry out a similar proof for a multidimensional delay system. In order to make it compatible with the results of the Poincare-Bendixon theorem in [72], a similar framework can be chosen as in that paper; this framework could eventually be generalized to other non-cyclic systems. The difficulties involved are to choose the set K appropriately, to prove that the function P is continuous (especially at 0), and to show that the trivial fix point of P is ejective. It should be mentioned that similar work has recently been done in that context by Ivanov and Lani-Wayda [54], in which the authors explicitly avoid the ejective fix point approach.

Chapter 12

Appendix

12.1 On Nonhomogeneous Equilibria of RD Systems

Consider a finite dimensional system

$$\dot{u} = f(u) \tag{12.1}$$

which is globally attractive towards a point $e \in \mathbb{R}^n$. If diffusion is added to the system to form the reaction diffusion system

$$\dot{u} = \Delta u + f(u), \tag{12.2}$$

under Neumann boundary conditions, does it follow that this system is globally attractive towards the constant function $\hat{e}$?

The following counterexample should illustrate why this conclusion doesn't hold. Let $\Omega = [-\pi/2, \pi/2]$ and $X = C(\Omega, \mathbb{R}^2)$. Let the function $\phi \in X$ be defined by

$$\phi(x) := (\sin(x), \frac{1}{2}\cos(2x) + \frac{1}{2}),\ x \in \Omega.$$

Then $\phi'(-\pi/2) = \phi'(\pi/2) = 0$, and $\Delta\phi = \phi''(x) = (-sin(x), -2cos(2x))$. The image of ϕ is a dome not unlike the upper half of the unit sphere in $\mathbb{R}^2$, and $\Delta\phi$ points towards the inside of this dome throughout. The idea is to construct a function $f : \mathbb{R}^2 \to \mathbb{R}^2$ such that $f(\phi(x)) = -\Delta\phi(x)$ for every $x \in \Omega$, so that ϕ becomes a non-homogeneous equilibrium of (12.2). In order to do this, let $\gamma : \mathbb{R} \times \mathbb{R}^+ - \{0\} \to A$ be the radial projection function towards $A = \text{Im } \phi$. Define $\alpha : \mathbb{R}^2 - (\{0\} \times \mathbb{R}^-) \to \mathbb{R}^2$ by

$$\alpha(u) := \begin{cases} -(\Delta\phi)(\phi^{-1}(\gamma(u)), & \text{if } u \in \text{Dom } \gamma \\ (1, 0), & \text{if } u_2 < 0,\ u_1 > 0 \\ (-1, 0), & \text{if } u_2 < 0,\ u_1 < 0. \end{cases}$$

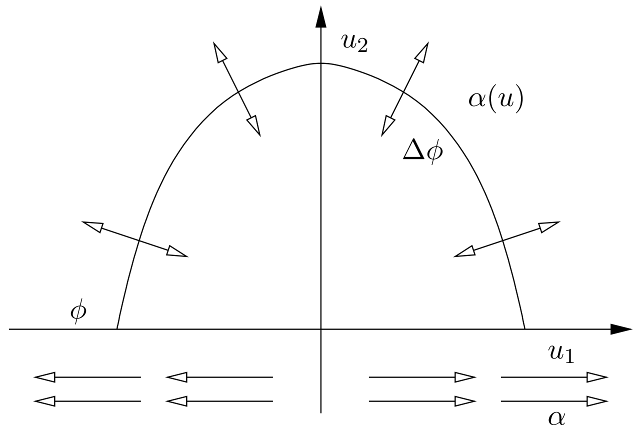

Figure 12.1: The arc on this figure represents the image A of the function $\phi : [-\pi/2, \pi/2] \to \mathbb{R}^2$. The functions $\Delta\phi(x)$ and $\alpha(\phi(x))$ cancel each other on A. The function α is further defined on $\mathbb{R}^2 - \{0\} \times \mathbb{R}^-$ as shown.

It is easy to see that α is a Lipschitz continuous function, and that $\alpha(\phi(x)) = -\Delta\phi(x)$ for $x \in \Omega$. Define now $\beta : \mathbb{R}^2 \to \mathbb{R}^2$ as $\beta(e) := 0$, and

$$\beta(u) := \frac{|e-u|}{1+|e-u|}\frac{(e-u)}{|e-u|}$$

for $u \neq e$, where $e = (0,3)$. Thus clearly β is a continuous function and the system $\dot{u} = \beta(u)$ converges globally towards e.

Finally, let $\eta : \mathbb{R}^2 \to [0,1]$ be a C^1 function such that $\eta(u) = 1$ if $d(u, A) \leq 1/3$, $\eta(u) = 0$ if $d(u, A) \geq 2/3$, and $0 < \eta(u) < 1$ otherwise. Define $f : \mathbb{R}^2 \to \mathbb{R}^2$, by

$$f(u) = \eta(u)\alpha(u) + (1 - \eta(u))\beta(u).$$

To verify that ϕ is an equilibrium of (12.2), note that $f(\phi(x)) = \alpha(\phi(x)) = -\Delta\phi(x)$ on Ω. Also, $\partial\phi/\partial n = 0$ on $\partial\Omega$ as shown above.

It only remains to show that (12.1) is still globally attractive towards e. The following lemma should be of help.

Lemma 63 *Consider a dynamical system (12.1) defined on $\mathbb{R}^2$ with bounded solutions. Let $a \in \mathbb{R}$, and $S := \{x \in \mathbb{R}^2 \,|\, x_2 \leq a\}$. If (12.1) has no equilibria in S, and if $f_2(x) \geq 0$ in S, then for every solution $x(t)$, it holds that $x(t) > a$ for some t.*

Proof. Consider a solution $x(t)$ of (12.1), $x_0 = x(0)$. Let $b := \sup\{x_2(t) \,|\, t > 0\}$, and suppose by contradiction that $b \leq a$. From $x_2'(t) \geq 0$, it follows that $\omega(x_0) \subseteq \{x \in \mathbb{R}^2 \,|\, x_2 = b\}$. Since $\omega(x_0)$ is a compact, connected set, we have $\omega(x_0) = [c,d] \times \{b\}$ for some $c \leq d$. Let now $z \in \omega(x_0)$, and let $z(t)$ be the solution of (12.1) with initial condition z. Since it also holds that $\omega(x_0)$ is an invariant subset under (12.1), and since $z_1(t)$ is monotonic on t, it follows that $z(t)$ converges towards an equilibrium in $\omega(x_0)$, which is a contradiction. ∎

In our particular case, we observe that the solutions of (12.1) are bounded, since $f(u) = \beta(u)$ except on a bounded set. Note that $\alpha_2(u) \geq 0$ whenever defined, and that $\beta_2(u) \geq 0$ for $u_2 \leq e_2 = 3$. Therefore letting $a = 2$ it holds that $f_2(u) \geq 0$ on S. To check that there are no equilibria in S, suppose by contradiction that $f(\hat{u}) = 0$ for $\hat{u} \in S$. Since $\beta_2(\hat{u}) > 0$, it must in particular hold that $\eta(\hat{u}) = 1$ and $d(\hat{u}, A) \leq 1/3$. Noting that $\alpha_2(u) > 0$ whenever $u_2 > 0$, it follows that $\hat{u}_2 \leq 0$. But in this case $\alpha_1(\hat{u}) = 1$ or -1, and thus $\hat{u}$ cannot be an equilibrium. By the lemma above, all solutions of (12.1) satisfy $x_2(t) > 2$, for some t. But in this (invariant) set $f(u) = \beta(u)$, and thus all solutions converge towards e.

A Continuum of Nonhomogeneous Equilibria

A similar argument as the one given above can be provided to guarantee the existence of not only one equilibrium ϕ, but of a continuum of nonhomogeneous equilibria ϕ_δ, while preserving the fact that the undiffused system (12.1) has a unique globally attractive equilibrium. Given the functions defined above, let $\phi_\delta(x) = \delta\phi(x)$, for $\delta > 0$. Since $\phi_\delta'(x) = \delta\phi'(x)$ and $\phi_\delta''(x) = \delta\phi''(x)$, it can be easily checked that any of these functions satisfies the Neumann boundary condition. Moreover, for every $u \in \mathbb{R} \times \mathbb{R}^+ - \{0\}$ there exists a unique pair $(\delta, x) = (\bar{\delta}(u), \bar{x}(u))$ such that $\phi_\delta(x) = u$. We can therefore redefine the function α as

$$\alpha(u) = \begin{cases} -\Delta\phi_{\bar{\delta}(u)}(\bar{x}(u)), & u \in \mathbb{R} \times \mathbb{R}^+ - \{0\} \\ (u_1, 0), & u_2 < 0,\ u_1 \neq 0. \end{cases}$$

We show that α is continuous: note that $\phi_\delta(\pi/2) = (\delta, 0)$, $\phi_\delta(-\pi/2) = (-\delta, 0)$; from this it follows that $\bar{\delta}(u_1, 0) = |u_1|$, $u_1 \neq 0$, and $\bar{x}(u_1, 0) = \mathrm{sign}(u_1)\pi/2$. Therefore for

$u = (u_1, 0)$, it holds

$$\Delta\phi_{\bar{\delta}(u)}(\bar{x}(u)) = \Delta\phi_{|u_1|}(\mathrm{sign}(u_1)\pi/2) = |u_1|\,(\mathrm{sign}(u_1), 0) = (u_1, 0),$$

and thus the continuity of α is guaranteed.

It is also clear by construction that for every $\delta > 0$, $\alpha(\phi_\delta(x)) = -\Delta\phi_\delta(x)$. Therefore by defining the function f as before, ϕ_δ is a nonhomogeneous equilibrium of (12.2) for all δ in a neighborhood of 1.

Finally, it is easy to verify that f still satisfies the hypotheses of Lemma 63 for $a = 2$, by following the same argument as above. We have thus proven the following corollary.

Corollary 28 *There exists a function $f : \mathbb{R}^2 \to \mathbb{R}^2$ such that system (12.1) is globally attractive to an equilibrium, but such that the associated reaction diffusion system (12.2) has a continuum of nonhomogeneous equilibria.*

12.2 A Note on Monotonicity for Chemical Reactions

It is appealing to apply the ideas of monotone systems to the theory of chemical reactions. After all, the interactions between compounds seem to be consistently promoting (though we will see shortly that this is not necessarily true). Also, the behavior of many reactions is like that of monotone systems in that every solution converges towards some equilibrium.

In Chapter 8 of the book by A.I. Volpert, V.A. Volpert and V.A. Volpert [113], the authors consider a general chemical reaction under mass action assumptions, and they give a sufficient condition for the underlying dynamical system to be monotone, after eliminating mass conservation constraints. In the beginning of the chapter, the authors give a useful account of the basic setup for chemical reactions. For both of these reasons, it is worthwhile to give this short self-contained description of the beginning of that chapter.

Consider a set of n chemical reactions on m chemical species $A_1 \ldots A_n$: [1]

$$\sum_{k=1}^{m} \alpha_{ki} A_k \longrightarrow \sum_{k=1}^{m} \beta_{ki} A_k, \;\; i = 1 \ldots n.$$

Define the number $\gamma_{ki} := \beta_{ki} - \alpha_{ki}$, that is the net number of molecules of species A_k that appear each time that reaction i is carried out; it can be interpreted as the 'stake' of molecule A_k in the reaction i. Forming the matrix Γ with these components, called the *stoichiometry matrix* of the system, one can write the dynamical system associated to the reactions as

$$\frac{\mathrm{d}A}{\mathrm{d}t} = \Gamma \omega.$$

Here ω_i is the rate at which reaction i is taking place at a particular state, $i = 1 \ldots n$, and it is given by

$$\omega_i = K A_1^{\alpha_{1i}} \cdot \ldots \cdot A_m^{\alpha_{mi}}$$

in the mass action case. This is generalized in equation (1.3) of [113] where the exponents are allowed to vary from α_{ki} and K is allowed to depend on the temperature[2]. An additional function $g_i(A)$ is introduced but never used in this argument, and it will be ignored here by defining $g_i(A) := 1$.

Notice that even though all the reactions are superficially 'promoting each other', in fact many compounds can influence each other in an inhibitory manner. The simplest case for this is that in which A and B bind to form C, in which case A and B influence C positively, but A influences B negatively and vice versa.

One important property of this system is that there are often planes that are invariant under it. If $\sigma \in R^m$ is a vector such that

$$\Gamma^t \sigma = 0,$$

then $\Gamma\omega \cdot \sigma = \omega^t \Gamma^t \sigma = 0$, and so every plane $\sigma \cdot A =$ const. is invariant under system (12.2). In applications, the vectors σ can be interpreted as mass conservation laws. It is

[1] In the book 'a_{ik}' stands throughout for the i-th *column*, j-th *row*, of a matrix A. See for instance equation (1.6) in V^3. I have therefore switched the order of all such double indices here for the sake of clarity.

[2] This last dependence is interesting since it can provide the framework for a dependence on a control u, but assumptions are then made for the temperature that make the setup unlikely for other controls.

a standard result from linear algebra for arbitrary matrices that Rank $\Gamma+$Null $\Gamma^t = m$. Therefore we can form a basis $\sigma_1, \ldots, \sigma_{m-r}$ of Ker Γ^t, where r is the rank of Γ. After intersecting all corresponding hyperplanes to form the r-dimensional subspace $\mathbb{R}_0^r \subseteq \mathbb{R}^m$, we see that all planes of the form $\mathbb{R}_0^r + A_0$ are invariant under (12.2). Since all solutions are also restricted to the positive orthant of $\mathbb{R}^m$, every state A_0 defines an invariant polyhedron $\Pi = (\mathbb{R}_0^r + A_0) \cap (R^+)^m$.

Fixing such a plane $\mathbb{R}_0^r + A_0$, and defining an affine transformation $A = Pu + A_0$ for any nonsingular $P : \mathbb{R}^r \to \mathbb{R}_0^r$, one can view the system as taking place in an r-dimensional polyhedron in $\mathbb{R}^r$. The particular choice of P will make the system in R^r look in various ways, but one canonical choice for P is as follows: since every column γ_i of Γ is orthogonal with all $\sigma_l,\ l = 1 \ldots m-r$, it follows that each column γ_i is in R_0^r, and therefore one can choose for P the first r columns of Γ, which can be assumed without loss of generality to be linearly independent and generate the remaining columns of Γ. Letting

$$\gamma_k = \lambda_{k1}\gamma_1 + \ldots + \lambda_{kr}\gamma_r,\ k = r+1 \ldots n,$$

one calculates after carrying out the change of variables that the new system takes the form

$$\frac{\mathrm{d}u_i}{\mathrm{d}t} = \omega_i + \sum_{k=r+1}^{n} \lambda_{ki}\omega_k,\ i = 1 \ldots r,$$

where each ω_i must be written in terms of the u_i's by replacing the A_i's using the affine transformation. The authors restrict their attention here to the case where Γ has full rank, in which case the sum above disappears and the system is particularly simple. By differentiating each ω_i with respect to $u_j,\ i \neq j$, and assuming no temperature dependence, the following sufficient condition for cooperativity holds:

$$\alpha_{ki}\gamma_{kj} \geq 0,\ k = 1 \ldots m,\ i,j = 1, \ldots r,\ i \neq j.$$

In the case that Γ doesn't have full rank, the sufficient condition is (12.2), together with the condition

$$\lambda_{li}\alpha_{kl}\gamma_{kj},\ i,j = 1 \ldots r,\ i \neq j,\ l = r+1 \ldots n,\ k = 1 \ldots m. \tag{12.3}$$

The Invertible Reactions Case

We consider the case of m species and n' linearly independent reactions, each of which is reversible to form a total of $n = 2n'$ reactions. If Γ' is the $m \times n'$ stoichiometry matrix associated to the nonreversible case, we therefore have that $\Gamma = (\Gamma'; -\Gamma')$. The assumption on independence means that Γ' has full rank, that is, $r = n'$. Clearly it holds in this case that $\lambda_{r+i,i} = -1$ for $i = 1 \ldots r$, and that $\lambda_{li} = 0$ otherwise. The criterion for monotonicity in this case is (12.2), together with

$$-\alpha_{k,r+i}\gamma_{kj} \geq 0,\ \ i,j = 1 \ldots r,\ \ i \neq j,\ \ k = 1 \ldots m,$$

that is,

$$\beta_{ki}\gamma_{kj} \leq 0,\ \ i,j = 1 \ldots r,\ \ i \neq j,\ \ k = 1 \ldots m, \tag{12.4}$$

Example:

The simple system

$$A + B \leftrightarrow C$$

consisting of two reactions, with reaction rates $\omega_1 = \mu AB,\ \omega_2 = \nu C$, has the associated reaction matrices

$$\text{Alpha} = \begin{pmatrix} 1 & 0 \\ 1 & 0 \\ 0 & 1 \end{pmatrix},\quad \text{Beta} = \begin{pmatrix} 0 & 1 \\ 0 & 1 \\ 1 & 0 \end{pmatrix},\quad \Gamma = \begin{pmatrix} -1 & 1 \\ -1 & 1 \\ 1 & -1 \end{pmatrix}.$$

It can be put in the above setup as follows. After setting $\gamma_1 = (-1,-1,1)^t,\ \gamma_2 = (1,1,-1)^t$, one finds that there are two independent vectors $\sigma_1 = (1,0,1)^t, \sigma_2 = (0,1,1)^t$, indicating that the system moves along the planes $A + C = c_1,\ B + C = c_2$, for any given constants c_1, c_2. The rank of Γ is one, and clearly $\lambda = \lambda_{21} = -1$. After considering an initial point, say $A_0 = (c_1, c_2, 0)$, and choosing $P = \gamma_1$, one makes the change of variables to obtain

$$\dot{u} = \mu(c_1 - u)(c_2 - u) - \nu u.$$

This system is not globally attractive as a whole, but after restricting the attention to the appropriate interval $[0, min(c_1, c_2)]$, it is not difficult to see that u converges globally to an equilibrium. The same must therefore be true of the original system restricted to its polyhedron Π, for any starting condition.

Interpretation

The sufficient condition (12.2) for the case $r = n$ can be interpreted as follows (in the entries in which $\alpha_{ki} = 0$, there is nothing to prove, and it holds by construction that all entries of Alpha are nonnegative). Given a species A_k, if there is a reaction i in which $\alpha_{ki} > 0$, then *for all other reactions $j \neq i$ A_k must be produced or at least not consumed (ie $\gamma_{ki} \geq 0$).* Equivalently, if A_k is consumed in some reaction i, then it cannot appear as an input in any other reaction $j \neq i$ in order to satisfy the sufficient condition. In particular, if A_k is an input of at least two reactions, then it can't be consumed in any single reaction. Nevertheless note that the presence of enzymes doesn't directly violate the condition, since such compounds have zero stoichiometry by definition.

In the case of invertible reactions considered above, the second condition (12.4) can be interpreted similarly considering the species that appear as outputs: given a species A_k, if there is a reaction i in which $\beta_{ki} > 0$, then *for all other reactions $j \neq i$ A_k must be consumed or at least not produced (ie $\gamma_{ki} \leq 0$).*

As a strategy for studying the monotonicity of other systems, it would be interesting to consider other choices for the matrix P, which are chosen in such a way that the resulting system on u is monotone.

12.3 Well-Definiteness of Delay Controlled Systems

Consider a controlled delay system

$$\dot{x}(t) = f(x_t, \alpha(t)) \; x_0 = \phi, \tag{12.5}$$

defined on the state space $X \subseteq B_X = C([-r, 0], \mathbb{R}^n)$, and with controls from an abstract input space $U \subseteq B_U$. An introduction to such systems is given at length in Section 5.1, but it is assumed that the system is well defined in the sense that it has unique maximally defined solutions for every initial condition, and that it satisfies the semiflow property. See Definition 7 for details. The following results establish sufficient conditions for these properties to hold.

The following theorem is referred to as Theorem 14 in Section 5.1.

Theorem 31 *Let $X_0 \subseteq \mathbb{R}^n$ be an open set, or in the orthant cone case, a box (not necessarily bounded) containing some or all of its sides. Let B_U be a Banach space, and let $U \subseteq B_U$ be an arbitrary Borel measurable set. Let $X = C([-r, 0], X_0)$, and let $f : X \times U \to \mathbb{R}^n$ be a continuous function. Assume that*

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

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

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

Then the system (12.5) has a unique maximally defined, absolutely continuous solution $x(t)$ for every input $\beta \in U_\infty$ and every initial condition $\phi \in X$.

Proof. It will be shown that all hypotheses are met so as to apply Theorem 4.3.1, p. 207 of Bensoussan et al. [9]. Let $\Omega_0 \subseteq X_0$ be a given compact set, and let $\Omega = C([-r, 0], \Omega_0)$. Let $C_i := B(0, i) \cap U$, where $i = 1, 2, 3 \ldots$ and $B(0, i)$ is the open ball in B_U with radius i. For every C_i, there is a constant M_i such that $f(\cdot, \alpha)$ is M_i-Lipschitz on Ω, for all $\alpha \in C_i$. For any $\alpha \in U$, let $m(\alpha) := \inf\{M_i \,|\, i \text{ such that } \alpha \in C_i\}$. Note that $f(\cdot, \alpha)$ is $m(\alpha)$-Lipschitz on Ω for each α and that m is measurable. Indeed, each M_i can be chosen to be as small as possible, and then m becomes a step function on each C_i.

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

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

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

Fix now $\beta \in U_\infty$, and define $g(t, \phi) := F(\phi, \beta(t))$. It is to this function that Theorem 4.3.1 of [9] is applied. A few conditions need to be verified: F is continuous on each set $X \times (C_i - C_{i-1})$) and therefore measurable, which implies that $g(t, \phi)$ is also measurable. By setting $n(t) = m(\beta(t))$, it follows that $n(t)$ is measurable and locally bounded (since each $\beta|_{[0,T]}$ is contained in some C_i), and thus locally integrable. Finally, note that $F(\phi_0, C_i)$ is bounded in $\mathbb{R}^n$ for every i, and that therefore $t \to g(t, \phi_0)$ is locally integrable.

By Theorem 4.3.1 in [9], the system $\dot{x} = g(t, x_t) = F(x_t, \beta(t))$ has a unique maximally defined, absolutely continuous solution defined for every initial condition $\phi \in B_X$.

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

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

Extend f from Ω_j to all $\mathbb{R}^n$ to form F_j, applying the main step above. The solutions of the systems $\dot{x} = F_j(x_t, \beta(t)),\ j = k, k+1, \ldots$, using the same initial condition ϕ, must agree with each other by uniqueness. If $x_1(t), x_2(t)$ are both solutions of (12.5) with initial condition ϕ and are defined on $[0, T]$, let j be such that $x_1|_{[-r,T]} \cup x_2|_{[-r,T]} \subseteq \Omega_j$. Then $x_1 = x_2$ on $[-r, T]$ by the argument above. This shows that x(t) is unique. The fact that it is maximally defined follows similarly. ∎

The following two lemmas give a proof that the function $\Phi(t, \phi, \alpha) = x_t$ generated by system (12.5) satisfies the semiflow property. The proof is straightforward, but it is included because the result might seem counterintuitive for delay systems. Let B_U be an abstract Banach space here, and $U \subseteq B_U$. Consider $X_0 \subseteq \mathbb{R}^n,\ X = C([-r, 0], \mathbb{R}^n)$ as before, and $f : X \times U \to \mathbb{R}^n$ such that the triple (X,U,f) forms a well defined delay dynamical system as in Definition 7.

Lemma 64 *Let u, v be inputs in U such that $u(t) = v(t), 0 \leq t \leq t_0$. Then the solutions $x(t), y(t)$ of the system (12.5), with initial condition ϕ_0 and inputs u and v respectively, satisfy $x(t) = y(t), -r \leq t \leq t_0$.*

Proof: Let $\gamma(t) := v(t + t_0)$, and let $z(t)$ be the solution of (12.5) with input γ and starting condition $\phi_1 = x_{t_0}$. Let $w(t) := x(t)$ for $-r \leq t \leq t_0$, $w(t) := z(t - t_0)$ for $t > t_0$. It is easy to see that $w(t)$ is absolutely continuous, as it is built from absolutely continuous parts. Furthermore,

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

Thus $w(t)$ is a solution of (12.5) with input $v(t)$ (recall $u(t) = v(t), -r \leq t \leq t_0$), and initial condition ϕ_0. By uniqueness, it must hold that $w = y$, and the conclusion follows.

Lemma 65 (Semiflow Property) *Given $s, t \geq 0$, and inputs $u(\tau), v(\tau)$, let $x(\tau), y(\tau)$ be the solutions of (12.5) with inputs $u_1(\tau), u_2(\tau)$ respectively, and initial conditions ϕ and x_s respectively. Let $z(\tau)$ be the solution of (12.5) with initial condition ϕ and input $v(\tau) := u_1(\tau), 0 \leq \tau \leq s, v(\tau) := u_2(\tau - s), \tau > s$. Then $z_{s+t} = y_t$.*

Proof. By the previous Lemma, $z_s = x_s$. Note that $w(t) := z(s + t)$ is a solution of (12.5) with input u and initial condition x_s:

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

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

References

[1] D. Aeyels and P. de Leenheer. Stability for homogeneous cooperative systems. *Proc. IEEE Conf. Decision and Control*, pages 5241–5242, 1999.

[2] J. D. Allwright. A global stability criterion for simple control loops. *J. Math Biol.*, 4:363–373, 1977.

[3] H. Amman. Fixed point equations and nonlinear eigenvalue problems in ordered Banach spaces. *SIAM Rev.*, 18:620–709, 1976.

[4] D. Angeli, P. de Leenheer, and E.D. Sontag. On predator-prey systems and small-gain theorems. *Mathematical Biosciences and Engineering*, 2:25–42, 2005.

[5] D. Angeli, J.E. Ferrell, Jr., and E.D. Sontag. Detection of multi-stability, bifurcations, and hysteresis in a large class of biological positive-feedback systems. *Proceedings of the Nat. Acad. of Sciences*, 101:1822–1827, 2004.

[6] D. Angeli and E.D. Sontag. Monotone controlled systems. *IEEE Trans. Autom. Control*, 48:1684–1698, 2003.

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

[8] W. Arendt, A. Grabosch, G. Greiner, U. Groh, H.P. Lotz, U. Moustakas, R. Nagel, F. Neubrander, and U. Schlotterbeck. *One-parameter Semigroups of Positive Operators*. Springer, 1980.

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

[10] A. Berman and R.J. Plemmons. *Nonnegative Matrices in the Mathematical Sciences*. Academic Press, New York, 1979.

[11] E. Boczko, T. Cooper, T. Gedeon, K. Mischaikow, D. Murdock, S. Pratap, and S. Wells. Structure theorems and the dynamics of nitrogen catabolite repression in yeast. *Proc. Nat. Acad. Sci*, 102:5647–5652, 2005.

[12] F.F. Bonsall. Linear operators in complete positive cones. *Proc. London Math. Soc.*, 8(3):53–75, 1958.

[13] F.E. Browder. A further generalization of the schauder fixed point theorem. *Duke Math. J.*, 32(4):575–578, 1965.

[14] M. Cartwright and M.A. Husain. A model for the control of testosterone secretion. *J. of Theor. Biology*, 123:239–250, 1986.

[15] S-N. Chow. Existence of periodic solutions of autonomous functional differential equations. *J. Differential Equations*, 15:350–378, 1974.

[16] S.N. Chow and J. Mallet-Paret. Singularly perturbed differential equations. In *Coupled Nonlinear Oscillators*, page . North-Holland, Amsterdam, 1983.

[17] J.P.R. Christensen. On sets of haar measure zero in abelian Polish groups. *Israel J. Math.*, 13:255–260, 1972.

[18] C. Cosner. Comparison principles for systems that embed in cooperative systems, with applications to diffusive lotka-volterra models. *Dynam. Contin., Discrete & Impulsive Systems*, 3:283–303, 1997.

[19] E.N. Dancer. Some remarks on a boundedness assumption for monotone dynamical systems. *Proc. of the AMS*, 126(3):801–807, March 1998.

[20] G. DasGupta, G.A. Enciso, E.D. Sontag, and Y. Zheng. On approximate consistent labeling of biological dynamical systems. In preparation, 2005.

[21] P. de Leenheer and D. Aeyels. Stabilization of positive linear systems. *Systems and Control Letters*, 44:259–271, 2001.

[22] P. de Leenheer, D. Angeli, and E.D. Sontag. A tutorial on monotone systems with an application to chemical reaction networks. In *Proc. 16th Int. Symp. Mathematical Theory of Networks and Systems (MTNS)*, 2004.

[23] P. de Leenheer and M. Malisoff. A small gain theorem for monotone systems with multi-valued input-state characteristics. to appear in the IEEE Transactions on Automatic Control, 2005.

[24] P. de Leenheer and M. Malisoff. A small-gain theorem for monotone systems with multi-valued input-state characteristics. to appear in IEEE Transactions on Automatic Control, 2005.

[25] K. Deimling. *Nonlinear Functional Analysis*. Springer, New York, 1980.

[26] C.A. Desoer and M. Vidyasagar. *Feedback Synthesis: Input-Output Properties*. Academic Press, New York, 1975.

[27] S.N. Elaydi. *An Introduction to Difference Equations*. Undergraduate Texts in Mathematics. Springer, New York, 1991.

[28] G.A. Enciso and H. Smith. Prevalence of convergence in strongly monotone systems. manuscript in preparation, 2005.

[29] G.A. Enciso, H.L. Smith, and E.D. Sontag. Non-monotone systems decomposable into monotone systems with negative feedback. to appear in the Journal of Differential Equations.

[30] G.A. Enciso and E.D. Sontag. Global attractivity, I/O monotone small-gain theorems, and biological delay systems. To appear in Discrete and Continuous Dynamical Systems.

[31] G.A. Enciso and E.D. Sontag. Monotone systems under positive feedback: multistability and a reduction theorem. *Systems and Control Letters*, 7:34–76, 2004.

[32] G.A. Enciso and E.D. Sontag. On the stability of a model of testosterone dynamics. *Journal of Mathematical Biology*, 49:627–634, 2004.

[33] G.A. Enciso and E.D. Sontag. A remark on multistability for monotone systems. *Proceedings of the 43rd IEEE Conference on Decision and Control (CDC)*, pages 249–254, 2004.

[34] L. Farina and S. Rinaldi. *Positive Linear Systems: Theory and Applications*. John Wiley & Sons, New York, 2000.

[35] B.R. Gelbaum and J.M.H. Olmsted. *Counterexamples in Analysis*. Holden-Day, San Francisco, 1964.

[36] M. Goemans and D. Williamson. Improved approximation algorithms for maximum cut and satisfiability problems using semidefinite programming. *Journal of the ACM*, 42(6):1115–1145, 1995.

[37] A. Goldbeter. *Biochemical Oscillations and Cellular Rythms. The Molecular Basis of Periodic and Chaotic Behaviour*. Cambridge Univ. Press, Cambridge, 1996.

[38] B.C. Goodwin. Oscillatory behaviour in enzymatic control processes. *Adv. in Enzyme Regulation*, 3:425–438, 1965.

[39] J.-L. Gouze. Global stabilization of n-dimensional population models by a positive control. Technical report, INRIA, BP 93, 06902 Sophia-Antipolis Cedex, France.

[40] J.-L. Gouze. Differential systems with positive variables. In L. Benvenuti, A. De Santis, and L. Farina, editors, *First Multidisciplinary International Symposium on Positive Systems: Theory and Applications (Posta 2003, Rome)*, pages 151–158, Heidelberg, August 2003. Springer.

[41] A. Granas and J. Dugundji. *Fixed Point Theory*. Springer, New York, 2003.

[42] G. Greiner, J. Voigt, and M. Wolff. On the spectral bound of the generator of semigroups of positive operators. *J. Operator Theory*, 5:245, 1981. 256.

[43] K.P. Hadeler and J. Tomiuk. Periodic solutions of difference differential equations. *Arch. Rat. Mech. Anal.*, 65:87–95, 1977.

[44] J. Hale. *Theory of Functional Differential Equations*, volume 3 of *Applied Mathematical Sciences*. Springer, New York, 1977.

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

[46] E. Hille and R. Phillips. *Functional Analysis and Semigroups*. Amer. Math. Soc., Rhode Island, 1957.

[47] M. Hirsch. Systems of differential equations which are competitive or cooperative I: limit sets. *SIAM J. Appl. Math*, 13:167–179, 1982.

[48] M. Hirsch. Systems of differential equations which are competitive or cooperative II: convergence almost everywhere. *SIAM J. Math. Anal.*, 16(3):423–439, 1985.

[49] M.W. Hirsch. Stability and convergence in strongly monotone dynamical systems. *Reine und Angew. Math*, 383:1–53, 1988.

[50] M.W. Hirsch and H.L. Smith. Monotone dynamical systems. Unpublished, 2004.

[51] B. Hunt, T. Sauer, and J. Yorke. Prevalence: a translation-invariant 'almost every' on infinite-dimensional spaces. *Bull. Amer. Math. Soc.*, 27:217–238, 1992. Addendum, Bull. Amer. Math. Soc. 28 (1993), 306-307.

[52] B. Ingalls and E.D. Sontag. A small-gain theorem with applications to input/output systems, incremental stability, detectability, and interconnections. *J. Franklin Institute*, 339:211–229, 2002.

[53] N. Ingolia. Topology and robustness in the *drosophila* segment polarity network. *Public Library of Science*, 2(6):0805–0815, 2004.

[54] A.F. Ivanov and B. Lani-Wayda. Periodic solutions for three-dimensional systems with time-delays. *Discrete Contin. Dyn. Syst.*, 2:667–692, 2004.

[55] J. Ji-Fa. On the global stability of cooperative systems. *Bull. London Math. Soc.*, 26:455–458, 1994.

[56] Z.P. Jiang, A. Teel, and L. Praly. Small-gain theorem for ISS systems and applications. *Mathematics of Control, Signals, and Systems*, 7:95–120, 1994.

[57] J. Keener and J. Sneyd. *Mathematical Physiology.* Springer, New York, 1998.

[58] W. Kerscher and R. Nagel. Asymptotic behavior of one-parameter semigroups of positive operators. *Acta Applicandae Math.*, 2:297–309, 1984.

[59] K. Kishimoto and H. Weinberger. The spacial homogeneity of stable equilibria of some reaction-diffusion systems on convex domains. *J. Diff. Eqns*, 58:15–21, 1985.

[60] T. Kobayashi, L. Chen, and K. Aihara. Modeling genetic switches with positive feedback. *J.Theor.Biol*, 221:379–399, 2003.

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

[62] M.G. Krein and M.A. Rutman. Linear operators leaving invariant a cone in a Banach space. *Uspekhi Mat. Nauk*, 3:3–95, 1948. (In Russian). Translation in English: AMS Translation No. 26, AMS, Providence, RI, 1950.

[63] S.G. Krein. *Linear Differential Equations in Banach Space*, volume 29 of *Translations of Mathematical Monographs.* AMS, 1971.

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

[65] Leslie Lamport. *LaTeX: A Document Preparation System.* Addison-Wesley, 1986.

[66] J.P. LaSalle. *The Stability and Control of Discrete Processes*, volume 62 of *Applied Mathematical Sciences.* Springer, New York, 1986.

[67] A.W. Leung. *Systems of Nonlinear Partial Differential Equations.* Kluwer Academic Publishers, Boston, 1989.

[68] A.M. Lyapunov. *Stability of Motion.* Academic Press, 1966.

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

[70] J. Mallet-Paret and R.D. Nussbaum. Global continuation and asymptotic behavior for periodic solutions of a differential-delay equation. *Ann. Mat. Pura. App.*, IV:33–128, 1986.

[71] J. Mallet-Paret and R.D. Nussbaum. Global continuation and asymptotic behavior for periodic solutions of a differential-delay equation. *Ann. Mat. Pura. App.*, CXLV(IV):33–128, 1986.

[72] J. Mallet-Paret and G. Sell. The Poincare-Bendixson theorem for monotone cyclic feedback systems with delay. *Journal of Differential Equations*, 125:441–489, 1996.

[73] J. Mallet-Paret and H. Smith. The Poincare-Bendixon theorem for monotone cyclic feedback systems. *J. Dynamics and Diff. Eqns*, 2:367–421, 1990.

[74] I.M.Y. Mareels and D.J. Hill. Monotone stability of nonlinear feedback systems. *J. Math. Systems, Estimation and Control*, 2:275–291, 1992.

[75] J. Mierczynski. Strictly cooperative systems with a first integral. *SIAM J. of Math. Analysis*, 18(3):642–646, 1987.

[76] X. Mora. Semilinear parabolic problems define semiflows on C^k spaces. *Trans. of the AMS*, 278:21–55, 1983.

[77] J.D. Murray. *Mathematical Biology, I: An Introduction.* Springer, New York, 2002.

[78] A. Novick and M. Wiener. Enzyme induction as an all-or-none phenomenon. *Proc. Natl. Acad. Sci. USA*, 43:553–566, 1957.

[79] R.D. Nussbaum. Eigenvalues of nonlinear operators and the linear Krein-Rutman theorem. In *Fixed Point Theory*, volume 886 of *Lecture Notes in Mathematics*, pages 309–331. Springer, Berlin, 1981.

[80] R.D. Nussbaum. A folk theorem in the spectral theory of C_0-semigroups. *Pacific Journal of Mathematics*, 113(2):433–449, 1984.

[81] R.D. Nussbaum. Positive operators and elliptic eigenvalue problems. *Math. Z.*, 186:247–264, 1984.

[82] R.D. Nussbaum and J. Mallet-Paret. Eigenvalues for a class of homogeneous cone maps arising from max-plus operators. *Discrete and Continuous Dynamical Systems*, 8(3):519–562, July 2002.

[83] R.D. Nussbaum and B. Walsh. Approximation by polynomials with nonnegative coefficients and the spectral theory of positive operators. *Transactions of the Amer. Math. Soc.*, 350(6):2367–2391, June 1998.

[84] K. Oda, Y. Matsuoka, A. Funahashi, and H. Kitano. A comprehensive pathway map of epidermal growth factor receptor signaling. *Molecular Systems Biology*, 2005. doi:10.1038/msb4100014.

[85] E. M. Ozbudak, M. Thattai, H. N. Lim, B. I. Shraiman, and A. van Oudenaarden. Multistability in the lactose utilization network of *escherichia coli*. *Nature*, 427:737, 2004.

[86] C.V. Pao. *Nonlinear Parabolic and Elliptic Equations.* Plenum Press, New York, 1992.

[87] A. Pazy. *Semigroups of Linear Operators and Applications to PDEs.* Springer, New York, 1983.

[88] C. Piccardi and S. Rinaldi. Remarks on excitability, stability, and sign of equilibria in cooperative systems. *Systems and Control Letters*, 46:153–163, 2002.

[89] P. Polacik. Parabolic equations: Asymptotic behavior and dynamics on invariant manifolds. In *Handbook of Dynamical Systems*, volume 2, chapter 16, pages 835–884. Elsevier, handbook of dynamical systems edition, 2002.

[90] M. Ptashne. *A Genetic Switch: Phage λ and Higher Organisms.* Cell Press and Blackwell Scientific Publications, Cambridge, MA, 1992.

[91] S. Ruan and J. Wei. On the zeros of a third degree exponential polynomial with applications to a delayed model for the control of testosterone secretion. *IMA Journal of Mathematics Applied in Medicine and Biology*, 18:41–52, 2001.

[92] E.P. Ryan and E. Sontag. A counterexample on steady state responses and the converging-input converging-state property. Submitted, 2005.

[93] E.P. Ryan and E.D. Sontag. Well-defined steady-state response does not imply cics. submitted.

[94] M. Safonov. *Stability and Robustness of Multivariable Feedback Systems.* MIT Press, Cambridge, Massachusetts, 1980.

[95] I.W. Sandberg. On the L_2-boundedness of solutions of nonlinear functional equations. *Bell System Technical Journal*, 43:1581–1599, 1964.

[96] H.H. Schaefer. Halbgeordnete lokalkonvexe vektorraeume ii. *Math. Ann.*, 138:259–286, 1959.

[97] H.H. Schaefer. *] Lattices and Positive Operators.* Springer, New York, 1974.

[98] H. Schneider and M. Vidyasagar. Cross-positive matrices. *SIAM J. Numer. Anal.*, 7:508–519, 1970.

[99] S. Smale. On the differential equations of species in competition. *J. Math. Bio*, 3:5–7, 1976.

[100] H.L. Smith. Oscillations and multiple steady states in a cyclic gene model with repression. *J. Math. Biol.*, 25:169–190, 1987.

[101] H.L. Smith. *Monotone Dynamical Systems.* AMS, Providence, RI, 1995.

[102] H.L. Smith and H. Thieme. Quasi convergence for strongly order preserving semiflows. *SIAM J. Math. Anal.*, 21:673–692, 1990.

[103] H.L. Smith and H. Thieme. Stable coexistence and bistability for competitive systems on ordered banach spaces. *J. Diff. Eqns*, 176:195–212, 2001.

[104] W.R. Smith. Hypothalamic regulation of pituitary secretion of luteinizing hormone. II. Feedback control of gonadotropin secretion. *Bull Math. Biol.*, 42:57–78, 1980.

[105] E.D. Sontag. Smooth stabilization implies coprime factorization. *IEEE Trans. Automatic Control*, 34:435–443, 1989.

[106] E.D. Sontag. *Mathematical Control Theory.* Springer, New York, 1998.

[107] E.D. Sontag. Asymptotic amplitudes and cauchy gains: A small-gain principle and an application to inhibitory biological feedback. *Systems and Control Letters*, 47:167–179, 2002.

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

[109] William Strunk, Jr. and E. B. White. *The Elements of Style.* Macmillan, third edition, 1979.

[110] J.J. Tyson and H.G. Othmer. The dynamics of feedback control circuits in biochemical pathways. In *Progress in Theoretical Biology.* Academic Press, New York, 1978.

[111] V.V. Varizani. *Aproximation Algorithms.* Springer, Berlin, 2001.

[112] P. Volkmann. Gewoehnliche Differentialgleichungen mit quasimonoton wachsenden Funktionen in topologischen Vektorraeumen. *Math. Z.*, 127:157–164, 1972.

[113] A.I. Volpert, V.A. Volpert, and V.A. Volpert. *Traveling Wave Solutions of Parabolic Systems*, volume 140 of *Translations of Mathematical Monographs.* AMS, 2000.

[114] G. von Dassaw, E. Meir, E.M. Munro, and G.M. Odell. The segment polarity network is a robust developmental module. *Nature*, 406:188–192, 2000.

[115] K. Yosida. *Functional Analysis.* Springer, Berlin, 1980.

[116] G. Zames. On the input-output stability of time-varying nonlinear feedback systems. part I: Conditions using concepts of loop. *IEEE Trans. Autom. Control*, 11:228–238, 1966.

[117] E. Zeidler. *Nonlinear Functional Analysis and its Applications I, Fixed Point Theorems.* Springer, New York, 1985.

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2. G. Enciso, E. Sontag, On the stability of a model of testosterone dynamics, Journal of Mathematical Biology 49:627-634, 2004
3. G. Enciso, E. Sontag, Monotone systems under positive feedback: multistability and a reduction theorem, Systems and Control Letters 51(2):185-202, 2005
4. G. Enciso, E. Sontag, On the global attractivity of abstract dynamical systems satisfying a small gain hypothesis, with applications to biological delay systems, to appear in the Journal of Discrete and Continuous Dynamical Systems.
5. G. Enciso, H. Smith, E. Sontag, Non-monotone systems decomposable into monotone systems with negative feedback, to appear in the Journal of Differential Equations.
6. G. Enciso, E. Sontag, Monotone systems under positive feedback: multistability and a reduction theorem II, submitted.
7. B. DasGupta, G. Enciso, E. Sontag, Y. Zhang, On approximate consistent labeling of biological dynamical systems, submitted.
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9. G. Bond, G. Enciso, Modeling cancer incidence at the MDM2 SNP309 locus, manuscript in preparation.

Other Publications

10. G. Enciso, La Fuerza de Elección del Teorema de Hahn-Banach, Undergraduate Thesis, Universidad de los Andes, Bogotá, 2000

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12. G. Enciso, E. Sontag, A remark on multistability for monotone systems, to appear in the proceedings of the 43rd IEEE Conference on Decision and Control, Bahamas, 2004

13. G. Enciso, E. Sontag, A remark on multistability for monotone systems II, to appear in the proceedings of the 44rd IEEE Conference on Decision and Control, Seville, Spain, 2005