Multi-valued characteristics and Morse decompositions

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Abstract

A theory of monotone input-output systems is one of a few mathematical approaches that has been successfully applied to complex models of biological and chemical interactions. Replacing some dynamic interactions between variables by a set of static inputs and characterizing the resulting open loop system by an input-output characteristic, the theory establishes convergence results for the original closed loop system.

We significantly extend the theory to the situation when the open loop system has multiple stable equilibria and hence a multi-valued characteristic. We show that the information embedded in the characteristic can be used to construct a Morse decomposition of the invariant set of the closed loop system. These results can be used to predict bistability as well as suggest existence of periodic orbits for the closed loop system. The previous theory on global convergence is shown to apply locally to individual Morse sets and is seamlessly incorporated into our global theory.

We apply our tools to a previously studied model of cell cycle maintenance. Our results show that changing the strength of the negative feedback loop can lead to cessation of cell cycle in two different ways: it can either lead to globally attracting equilibrium or to a pair of equilibria that attract almost all solutions.

1 Introduction

One of the most important issues facing system biologists in the post-genomic era is to understand how the cell behavior emerges from the properties of complex networks of genes and proteins. The challenge for mathematical biologists is to develop mathematical techniques that would allow meaningful analysis of the corresponding mathematical models. Even the simplest models involve a number of coupled nonlinear differential equations and more realistic models include significant delays, spatial dependence and noise. The differential equations models arise from mass action kinetics, often augmented by Michealis-Menten nonlinearities. An important observation is that such nonlinearities are monotone in their arguments. Although they are biologically well founded exceptions to this monotonicity [12], it also reflects the prevailing paradigm in the design and evaluation of biochemical experiments. The effect of knocking out a particular gene on the activity of another gene is usually characterized in binary terms as either positive or negative.

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Consequently, each interaction is labeled as either positive or negative, which is reflected in the choice of either a monotonically increasing, or monotonically decreasing nonlinearity in the model.

An important set of analytical tools applicable to models with monotone nonlinearities arise from the theory of *monotone dynamical systems* [24]. If, maybe after a change of variables, all interactions can be made positive, the system is *monotone* and almost all solutions converge to a set of equilibria [24]. In the last 6 years Sontag and collaborators [1, 2, 4, 8, 9, 10, 3, 26], using insights from the control theory, extended the monotone systems theory to input-output systems. The main idea is to simulate an approach an experimentalist would take to interrogate an unknown complex system. For the sake of exposition we imagine that we can control the expression level of a certain gene. This expression level is our control variable u and we can measure the behavior of the system with u fixed in terms of an output y. The input and output variables are chosen in such a way that by setting $u = cy$ (or $u = -cy$) for some constant c we recover the original system. The collection of systems parameterized by different values of u is called an *open loop system*, while the original system with is the corresponding *closed loop system.* We assume that we understand sufficiently well the dynamics of the systems with $u = u_0$ fixed, for all relevant values of u_0. The key assumptions are placed on the open loop system: namely, that each system with a fixed $u = u_0$ **(1.)** is a monotone; and **(2.)** almost all solutions converge to a unique equilibrium E_{u_0}. The second assumption assures the existence of a mapping $u_0 \to E_{u_0}$, called an *input-state (I/S) characteristic.* The function which maps u_0 to the value of the output y on the equilibrium E_{u_0} is an *input-output (I/O) characteristic.* The basic results of the theory [2, 4] predicts convergence of the trajectories of the closed-loop system based on the properties of the input-output characteristic.

This theory presents an alternative to the standard dynamical system approach to the analysis of complex systems which proved to be successful in the applications [3, 26]. When the feedback is slowly varying ($u = \pm\epsilon y$ for a small ϵ) it reduces to a particular case of a singular perturbation analysis of slow-fast systems [13], where the open loop system is a fast flow parameterized by a set of constant inputs u. When the feedback is not slowly varying, the monotone input-output theory is a tool to construct numerical assisted proof of global convergence to a single equilibrium. The numerical assistance is (usually) needed to compute the I/O characteristic. In spite of these undeniable advantages, there are limitations to the applicability of the theory. The most serious is the assumption **(2.)** that all solutions of the open loop system with $u = u_0$ converge to a unique equilibrium E_{u_0}. This requirement is motivated by the desire to prove a global convergence to an equilibrium for the closed loop system.

We wish to simultaneously generalize and broaden the scope of the theory for *single-input single-output* (SISO) systems. We will not require convergence to a unique equilibrium and instead assume that almost all initial condition converge to one of a finite number of equilibria. Apart for the finiteness part, this assumption follows from the monotonicity assumption **(1.)** . We will broaden the theory by asking for not just for the convergence to an equilibrium, but also broader characterization of the dynamics of the closed loop system. To do this we will invoke the notion of a *Morse decomposition* [6] of the invariant set. The Morse decomposition consists of a finite number of compact invariant sets, called Morse sets, and a partial ordering of these sets. The Morse sets capture the recurrent dynamics, while the dynamics outside these sets is gradient-like and consistent with the ordering. We will use the multi-valued I/O characteristic to define a Morse decomposition for an open loop system. From such Morse decomposition we then construct a Morse decomposition of the invariant set for the closed loop system, that attracts generic (i.e. countable intersection of open and dense sets) set of initial data.

We show that the previous global results on convergence to equilibria [2, 4] apply locally inside the individual Morse sets. Our theory is thus *recursive*: it establishes a decomposition of the invariant set to individual Morse sets, and then it can be applied again within the Morse sets to further refine the Morse decomposition.

We will apply our results to the cell cycle oscillator in bacteria. We analyze the effect of changing the strength of the negative feedback and show how our theory implies bistability rather then oscillations for certain range of parameters.

We now review our main results in greater detail. The assumptions for our theoretical results are formulated for the SISO open loop system, which is a one-dimensional family of monotone systems parameterized by the input $u \in \mathbb{R}$. Under a natural dissipativity assumption we establish the existence of a compact interval $[p_1, p_2] \subset \mathbb{R}$ such that for all solutions of the closed loop system the output $y = h(x(t))$ satisfies

$$p_1 \leq \liminf_{t\to\infty} h(x(t)) \leq \limsup_{t\to\infty} h(x(t)) \leq p_2.$$

Since we can assume without loss of generality that $u(t) = \pm y(t)$, this result provides bounds on u-projection of the invariant sets of the closed loop dynamics. Therefore the subsequent analysis of the open loop system can be restricted to $u \in [p_1, p_2]$. Another important observation for the applications is that the interval $[p_1, p_2]$ can be explicitly constructed using I/O characteristic of the open loop system.

For our second result we assume existence of a Morse decomposition for the open loop system over the interval $[p_1, p_2]$. This means that for any $u, v \in [p_1, p_2]$ the Morse decompositions $\mathcal{M}(u)$ and $\mathcal{M}(v)$ are isomorphic and ordered with respect to the order cone of the monotone system. Based on this information we construct a Morse decomposition of the closed loop system.

We will illustrate these concepts on a simple example. Assume that the I/O characteristic is multi-valued and is a solution of $u = f(y)$ where u is an input, y is an output and f is a cubic function, see Figure 1. Let (b_1, b_2) be an interval of u's for which this equation has three solutions. One of the key insights of this paper is the importance of mutual position of (b_1, b_2) and $[p_1, p_2]$ for the dynamics of the closed loop system. If (b_1, b_2) contains the interval $[p_1, p_2]$ then the open loop system admits a Morse decomposition over $[p_1, p_2]$ containing three Morse sets (Figure 1.A); in the opposite case the only Morse decomposition over the entire interval contains just a single Morse set- the entire attractor, Figure 1.B. These two cases have distinctly different behavior for the closed loop system. In the first case there will be two stable equilibria in the closed loop system, while the second case with negative feedback $u = -y$ is compatible with the existence of a periodic orbit [13]. Details, obviously, depend on the particular function f.

In order to prove the latter results we need to use the recursive character of our theory. We will show that to each Morse set $M(u)$ we can associate a branch of a *multi-valued I/O characteristic*, which naturally generalizes the (single-valued) I/O characteristic. If this branch itself is single-valued then the global results of Sontag and collaborators [1, 2, 4, 8, 9, 10] apply for initial conditions in a restricted set associated to $M(u)$; if the branch is still multi-valued our theory can be applied again to find a finer Morse decomposition of the Morse set $M(u)$.

There have been few attempts to remove the global convergence to equilibrium assumption. Angeli *et.al.* [4] extended the small gain theorem of Angeli and Sontag [1] to the situation where they assume that almost all solutions converge to a unique equilibrium. Another attempt to generalize the monotone input-output theory was by DeLenheer and Malisoff [7]. They introduced the notion of the multi-valued I/O characteristic and found quite restrictive conditions on multi-valued characteristic under which convergence to a unique equilibrium still holds. Our results significantly generalize these results. In fact, in can be shown that the assumptions imposed on I/O characteristic in [7] imply $p_1 = p_2$ and a trivial Morse decomposition at $u = p_1 = p_2$.

We finish the introduction with a brief overview of the organization of the paper. In section 2 we review the necessary background in the monotone systems theory, provide the key assumptions and formulate our main results. In section 3 we apply the theory to a model of the cell cycle engine [22, 23, 20]. We start our proofs in section 4 where we construct $[p_1, p_2]$, which we follow by the proof of a Morse decomposition in section 5. Finally, our results concerning recursiveness of our theory can be found in section 6.

2 Main results

The basic framework for our results is a finite dimensional, single-input, single output controlled system

$$\dot{x} = f(x, u), \quad y = h(x) \tag{1}$$

where $u(t) \in U \subseteq \mathbb{R}$ is the input, $y(t) \in Y \subseteq \mathbb{R}$ is the output, f, h are C^2, and the state space variable $x(t) \in X \subseteq \mathbb{R}^n$. We assume that U, Y, X lie in the closure of their interiors. Together with the *open loop system* (1) we will also study a *closed loop system*, where, in addition to (1), we set $u = g(y)$. The most important set of questions concerns the predictability of the closed loop dynamics

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

based on the properties of the open loop system (1). Since the function h is arbitrary, we can assume without loss of generality that $g(y) = \pm y$. The system (1) with $g(y) = y$ ($g(y) = -y$) is a closed loop system with a positive (negative) feedback.

Our main motivation is the study of gene regulatory networks [3, 5], where systems of the form (1) have usually an additional structure of *monotone systems.* We now recall essential definitions in this area and refer the reader for a more thorough background to [1, 24].

A *cone* is a closed, convex set with nonempty interior and with $\alpha K \subset K$ for $\alpha \in \mathbb{R}^+$ and $K \cap (-K) = \{0\}$. If a space Z is endowed with a cone K_z we will write

$$x \succeq y \text{ if, and only if, } x - y \in K_z \quad \text{and} \quad x \succ y \text{ if, and only if, } x - y \in \text{int } K_z.$$

We assume that the input space U, the state space X and the output space Y each has a distinguished cone $K_u \subset U$, $K_x \subset X$ and $K_y \subset Y$. For $U \subset \mathbb{R}$ and $Y \subset \mathbb{R}$ this amounts to a choice of either a positive, or a negative half-line.

We say that the controlled system (1) is a *monotone system with outputs* if

$$u_1(t) \succeq u_2(t) \ \forall t, \quad \text{and } x_1 \succeq x_2 \quad \Longrightarrow \quad \varphi(t, x_1, u_1) \succeq \varphi(t, x_2, u_2) \ \forall t \geq 0, \quad \text{and } h(x_1) \succeq h(x_2)$$

where φ is the flow generated by (1), and the $\succeq$ is the order with respect to the appropriate cones. We say that the controlled system is *strongly monotone* if it is monotone, and

$$u_1(t) \succeq u_2(t) \ \forall t, \text{ and } x_1 \succ x_2 \quad \Longrightarrow \quad \varphi(t, x_1, u_1) \succ \varphi(t, x_2, u_2) \ \forall t \geq 0.$$

Infinitesimal characterizations of monotonicity, which are more suitable for verification, can be found in [1] and [24]. We say that two points $x, y \in Z$ are *order related* if either $x \succ y$ or $y \succ x$ with respect to cone $K_z \subset Z$. If $x \prec y$ then $[x, y] := \{z \in Z \mid x \preceq z \preceq y\}$ is the *order interval* generated by x and y. If $U, V \subset X$ are two disjoint subsets of X, we write $U \prec V$ if for all $x \in U$ and $y \in V$ we have $x \prec y$; we define $[U, V] := \{z \in Z \mid x \preceq z \preceq y, \forall x \in U \text{ and } \forall y \in V\}$.

Definition 2.1 We say that the controlled system (1) is endowed with an *input-state characteristic* $k_x(u) : U \to X$ if for each constant input $u(t) \equiv \bar{u}$ there exists a (necessary unique) globally asymptotically stable equilibrium $k_x(\bar{u})$ of system (1).

The system (1) is endowed with a *multi-valued input-state characteristic* $k_x(u) : U \to X$ if for each constant input $u(t) \equiv \bar{u}$ there are finitely many equilibria $k_x(\bar{u})$ of system (1), such that a set of initial conditions that contains an open and dense set of X converge to one of these equilibria.

In both cases we define the *(multi-valued) input-output characteristic* as

$$k(u) := g(h(k_x(u))), \quad k : U \to U.$$

Before we introduce our main results we illustrate some of these concepts on a simple example. Consider an open loop system

$$\begin{aligned} \dot{x} &= u - 8x(x^2 - \frac{3}{4}) + \frac{y}{4} =: g_1(x, y, u) \\ \dot{y} &= \epsilon(x - \frac{y}{2}) =: g_2(x, y) \end{aligned} \tag{3}$$

with an output function $h(x, y) = y$ and negative feedback $u = -y$. Using an intermediate value theorem for $\varphi(t, x_1, u) - \varphi(t, x_2, u)$ it is easy to verify that the monotonicity of g_1 and g_2 with respect to y and x respectively

$$dg_1/dy > 0 \quad \text{and} \quad dg_2/dx > 0$$

imply that (3), for a fixed u, is a monotone system with respect to the positive orthant. Furthermore for each fixed u the open loop system has either one, two, or three equilibria that are intersections of

$$y = 2x \quad \text{and} \quad u = 8x(x^2 - \frac{3}{4}) - \frac{y}{4}.$$

The value of multi-valued input-state characteristic $k_x(u)$ at each u is this set of equilibria. To compute the input-output characteristic, we first combine these two equations to express y as an (implicit) function of u

$$u = 4y(\frac{y^2}{4} - \frac{3}{4}) - \frac{y}{4} = y(y^2 - \frac{13}{4}).$$

This represents implicitly the composition $y = h(k_x(u))$. Finally, taking the composition with the function g, which in this case represents a negative feedback $u = -y$, we obtain the multi-valued input-output characteristic $k : U \to U$ given implicitly by

$$u = -k(u)((-k(u))^2 - \frac{13}{4}). \quad (4)$$

This multi-valued characteristic is depicted in Figure 1.A.

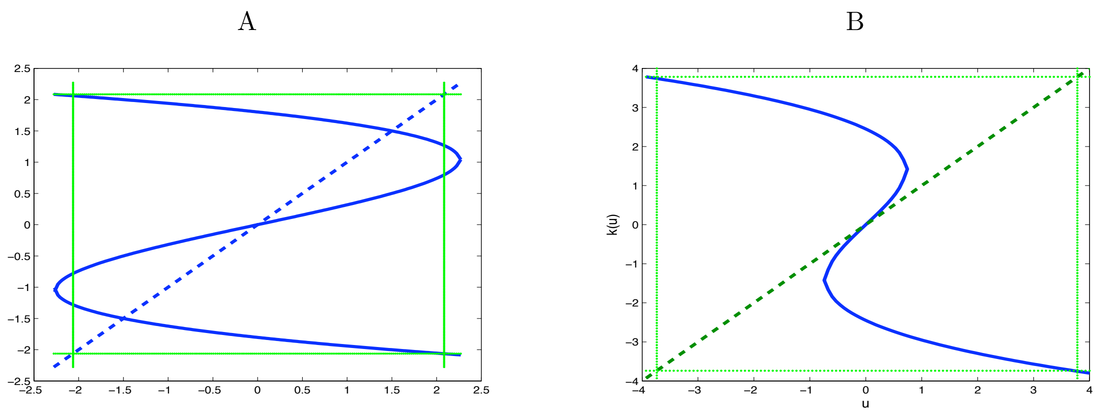

Figure 1: (A) I/O characteristic (solid line) given by (4); (B) I/O characteristic given by (12). The region $[p_1, p_2] \times [p_1, p_2]$ is marked as a dotted square, the diagonal is the dashed line.

This finishes the example and we proceed by formulating a set of *standing assumptions*. We assume that

1. the open loop system (1) is monotone;
2. there is a compact set $C \subset U$ such that for each $v \in C$ the system (1) with $u(t) = v$;
   - **a.** is dissipative, i.e. all solutions eventually enter a fixed compact set K_v;
   - **b.** there is an exceptional set $\mathcal{B}_v$ such that all solutions starting in a generic set $X \setminus \mathcal{B}_v$ converge to one of finitely many equilibria.
   - **c.** the equilibria are ordered with respect to the cone K_x.

Note that we only assume finiteness in (2b): for monotone dissipative systems all solutions starting in $X \setminus \mathcal{B}_v$ converge to a set of equilibria, and the set $X \setminus \mathcal{B}_v$ contains an open and dense set of initial data [24].

Our first result below shows that the open-loop SISO system, the information encoded into the input-output characteristic is sufficient to bound the attractor of the closed loop system (2).

We start by finding the maximum and minimum of the I/O characteristic at each u.

Definition 2.2 Assume (1) is SISO system, i.e. $U \subset \mathbb{R}$. If k is a multi-valued input-output characteristic, we set

$$K_{min}(u) = min\{k(u)\} \quad \text{and} \quad K_{max}(u) = max\{k(u)\}. \quad (5)$$

For the function in Figure 1.A the function $K_{min}(u)$ is continuous, except at the value of u corresponding to the left turning point, and $K_{max}(u)$ is continuous except for u corresponding to the right turning point.

Positive and negative feedback systems differ in the general direction of their characteristic. We will not prove this fact until later, but for large $|u|$ the I/O characteristic for positive feedback is increasing and for negative feedback it is decreasing. Indeed, if we had positive feedback $u = y$ in the example (3) then the graph of the I/O characteristic satisfying $u = k(u)((k(u))^2 - \frac{9}{4})$ would be that in Figure 1.A, but flipped around the y-axis.

Even though we assume in (2a) dissipativity for each fixed input $u(t) = v$, we need a global notion of dissipativity for the entire open loop system. In order to express such a dissipativity assumption for an open loop system in the same language for both negative and positive feedbacks we define non-decreasing functions $B(u)$ (for "bottom") and $T(u)$ (for "top"). For a positive feedback system

$$B(u) := K_{min}(u), \qquad T(u) := K_{max}(u) \tag{6}$$

and for a negative feedback system we set

$$B(u) := K_{min}(K_{max}(u)), \qquad T(u) := K_{max}(K_{min}(u)). \tag{7}$$

We can express dissipativity in terms of functions B and T.

Definition 2.3 We say that an open loop system (1) is *dissipative* if there is a constant A such that

$$T(u) < u \text{ for } u \geq A \text{ and } B(u) > u \text{ for } u \leq -A. \tag{8}$$

The dissipativity assumption is equivalent to a sub-linear growth of the input-output characteristic as $u \to \pm\infty$. Indeed, it is easy to check that for a negative feedback system it is equivalent to

$$K_{max}(u) < -u \text{ for } u \leq -A, \quad \text{ and } \quad K_{min}(u) > -u \text{ for } u \geq A.$$

Our first major result is the following.

Theorem 2.4 *Assume the standing assumptions and that the open loop system (1) is dissipative. Define* $p_1 := \sup\{a : B(u) > u, \; \forall\, u < a\}$ *and* $p_2 := \inf\{b : T(u) < u, \; \forall\, u > b\}$. *Then for a generic set of initial conditions* $\xi \in X$ *and all* $u(t) \in U$ *for which solution* $x(t, \xi, u(t))$ *is bounded,*

$$p_1 \leq \liminf_{t\to\infty} h(x(t)) \leq \limsup_{t\to\infty} h(x(t)) \leq p_2.$$

The values p_1 and p_2 were computed for the example above and are represented by the dotted square in Figure 1.A. As we will see in Lemma 4.8 and in Lemma 4.9 the characterization of p_1 and p_2 in terms of $B(u)$ and $T(u)$ implies that the interval $[p_1, p_2]$ is an attracting fixed point of a multi-valued map that maps intervals to intervals, and whose graph is the convex hull of the I/O characteristic. Therefore the values p_1, p_2 can be computed by iterating the functions $B(u)$ and $T(u)$.

Our second result describes the structure of the global attractor of the closed loop system (2) by defining its Morse decomposition. The Morse decomposition is defined using a parameterized Morse decomposition of the open loop system (1).

Definition 2.5 A Morse decomposition $\mathcal{M}(\mathcal{A}) = \{M(p) \mid p \in (\mathcal{P}, \geq)\}$ of a compact invariant set $\mathcal{A}$ is a decomposition of $\mathcal{A}$ into a finite number of disjoint compact invariant subsets $M(p)$, called *Morse sets*, indexed by a partially ordered set $(\mathcal{P}, \geq)$, such that if $x \in \mathcal{A}$ one of the following holds:

1. there exist $p, q \in \mathcal{P}$ such that $q \geq p$, $\omega(x) \in M(p)$ and $\alpha(x) \in M(q)$.

2. there exists $p \in \mathcal{P}$ such that $\varphi(t, x) \in M(p)$ for all t, where $\varphi : \mathcal{A} \times R \to \mathcal{A}$ denotes the flow.

We specialize this general definition to Morse decompositions that occur in monotone dynamical systems satisfying our standing assumptions. Since our monotone system (1) is dissipative for each $u(t) = u \in C$, there is a compact attractor $\mathcal{A}_u$, and a generic set of initial conditions $X \setminus \mathcal{B}_u$ that converge to one of finitely many, ordered equilibria with open basins of attraction [24]. Each of these equilibria forms an individual Morse set. All the other recurrent sets in $\mathcal{A}$ must belong to some Morse set as well. We now look more closely at some such sets. Assume e_1 and e_3 are two equilibria with open basins of attraction and that $e_1 \prec e_3$. Since the basins of attraction of e_1 and e_3 are open, there must be a point q with $e_1 \prec q \prec e_3$ which does not belong to any of the two basins. Monotonicity now implies that the solution $\varphi(t, q, u)$ of (1) stays in the compact set $\{z \in X \mid e_1 \preceq z \preceq e_3\}$ for all $t \geq 0$. This implies that $\omega(q)$ lies in some invariant set S with $e_1 \prec S \prec e_3$. Let M_2 be the smallest invariant set such that any q with $e_1 \prec q \prec e_3$ with $\omega(q) \neq \{e_1, e_3\}$ we have $\omega(q) \in M_2$. We say that M_2 *separates the basins* of e_1 and e_3. In many applications the set M_2 will also be an equilibrium. In the example (3) when $u \in [p_1, p_2]$, there are two stable equilibria e_1 and e_3 that lie on the bottom and the top branches of the input-state characteristic; their basins of attraction are separated by the stable manifold of the equilibrium e_2 that lies on the middle branch. So in this case $M_2 = e_2$.

An immediate generalization of the example (3) has an input-output characteristics defined implicitly by $u = H(k(u))$ where H is $2L+1$ degree polynomial. Then the I/O characteristic $k(u)$ can have up to $2L+1$ branches. This discussion motivates the following definition.

Definition 2.6 (Morse decomposition for the monotone open loop system) We assume that for each $u \in [p_1, p_2]$ there is a compact invariant set $\mathcal{A}_u$ which attracts a generic set of initial conditions in X. The set $\mathcal{A}_u$ admits a Morse decomposition $\mathcal{M}(u) = \{M_i(u) \mid i = 1, \ldots, 2L+1\}$, where each odd numbered Morse set $M_{2i+1}(u), i = 0, \ldots L$ has an open basin of attraction $B_{2i+1}(u)$. We assume that a generic set of initial conditions belongs to one of the sets B_{2i+1}, $i = 1, \ldots, L$. The even numbered Morse sets $M_{2i}(u)$, $i = 1, \ldots, 2L$, are minimal invariant sets that separate basins $B_{2i-1}(u)$ and $B_{2i+1}(u)$. We assume that the Morse sets are ordered for each u

$$M_1(u) \prec M_2(u) \ldots \prec M_{2L+1}(u). \tag{9}$$

Furthermore we assume a that the Morse sets are uniformly ordered in the output

$$\bigcup_{u\in[p_1,p_2]} h(M_1(u)) \prec \bigcup_{u\in[p_1,p_2]} h(M_2(u)) \prec \bigcup_{u\in[p_1,p_2]} h(M_3(u)) \prec \ldots \prec \bigcup_{u\in[p_1,p_2]} h(M_{2L+1}(u)). \tag{10}$$

As we have mentioned before, in the example (3) we can define a Morse decomposition with three sets $M_j(u), j = 1, 2, 3$. The Morse sets $M_1(u)$ and $M_3(u)$ have open basins of attraction, while the stable manifold of $M_2(u)$ separates these basins. The condition (9) is readily satisfied. Since $h(x, y) = y$, the uniform output order condition (10) also holds. We illustrate the interplay between the interval $[p_1, p_2]$ and the interval (b_1, b_2), on which the I/O characteristic is multi-valued, on another example. Consider a negative feedback open loop system

$$\begin{aligned} \dot{x} &= u - x(x^2 - 1) + \frac{y}{4} \\ \dot{y} &= \epsilon(x - \frac{y}{2}) \end{aligned} \tag{11}$$

with an output function $h(x, y) = y$, and $u = -y$. As in the example (3), for a fixed u this is a monotone system with respect to the positive orthant and has either one, two, or three equilibria. The input-output characteristic is (see Figure 1.B)

$$u = \frac{-k(u)}{2}((\frac{k(u)}{2})^2 - 3/2). \tag{12}$$

In this case the interval $[p_1, p_2]$ contains the region of bistability (b_1, b_2). Since the Definition 2.6 requires that the Morse decomposition $\mathcal{M}(u)$ is the same for all $u \in [p_1, p_2]$ we cannot define a Morse decomposition with three Morse sets each corresponding to one equilibrium. The only Morse decomposition that continues across $[p_1, p_2]$ is a trivial Morse decomposition with only one Morse set $M_1(u) = \mathcal{A}_u$, that is, the entire attractor. The fundamental reason why we cannot consider the Morse sets on the three branches as separate, is that the closed loop system has a periodic orbit for all $\epsilon > 0$ sufficiently small. Indeed, the equations (11) describe a *relaxation oscillator* [14, 15, 16]. One of the consequences of the following Theorem is that such a periodic orbit cannot exist in the closed loop system for a three set Morse decomposition in the example (3).

Theorem 2.7 *For (1), assume the standing assumptions, dissipativity and that it admits a Morse decomposition described in Definition 2.6.*

Then there is an invariant set $\mathcal{A}$ of the closed loop system (2), that attracts a generic set of solutions, and which admits a Morse decomposition $\mathcal{M}^* = \{M^*_{2i+1} \mid i = 0, \ldots, L\} \cup M^*_0$, with the ordering $M^*_0 \succ M^*_{2i+1}$ for all $i = 1, \ldots, L$.

The Morse set M^*_{2i+1} is the maximal invariant set in $B^*_{2i+1} := \bigcap_{u\in[p_1,p_2]} B_{2i+1}(u)$ and M^*_0 is the maximal invariant set in $X \setminus \bigcup_{i=1,\ldots,L} B^*_{2i+1}$.

Our final result shows that our theory is recursive and it can be applied iteratively. If the restriction of the input-output characteristic $u \to M_{2l+1}(u)$ for $u \in [p_1, p_2]$ is multi-valued then we can apply the Theorem 2.4 and the Theorem 2.7 to this restriction. In this way we may discover a finer Morse decomposition of the invariant set corresponding to M_{2l+1} in the open loop system. If, on the other hand, the restriction of the input-output characteristic $u \to M_{2l+1}(u)$ for $u \in [p_1, p_2]$ is single valued, then, as we will show next, we can apply the standard theory [2, 4] of single valued characteristics. We first recall these results using our notation.

Theorem 2.8 *[4, Theorem 1] Consider the open loop system (1) with a negative feedback $u = -y$. Suppose that X and $Y = U$ are ordered with respect to their cones K_z and $K_y = K_u$ respectively, and that they are closed under component-wise maximization and minimization. Assume that the input-state characteristic k_x is single-valued and continuous (thus, the I/O characteristic k is single-valued and exists, too). Finally, assume that all solutions of the closed-loop system (2) is precompact. Then the system (2) has a unique equilibrium $k_x(\bar{u})$ that attracts almost all solutions in X, provided that the following discrete dynamical system, evolving on U:*

$$u^n = -k^n(u^0)$$

has a unique globally attractive equilibrium $\bar{u}$.

Theorem 2.9 *[2, Theorem 3] Consider an SISO open-loop system (1) with $u = y$ and single-valued input-output characteristic k. Then the equilibria of the closed-loop system (2) are in 1-1 correspondence with the fixed points of the input-output characteristic k. Furthermore, stable fixed points of k correspond to stable equilibria of (2) and unstable fixed points of k correspond to stable equilibria of (2).*

We are ready for our final result. Assume that some Morse set $M_{2i+1}(u) = e_{2i+1}(u)$ consists of a single equilibrium for each $u \in [p_1, p_2]$. In such case the branch $k_{x,2i+1} : [p_1, p_2] \to X$ of the multi-valued I/S characteristic k_x given by $k_{x,2i+1}(u) = e_{2i+1}(u)$ is well defined and single-valued. We denote by $k_{2i+1} : [p_1, p_2] \to [p_1, p_2]$ the corresponding single valued branch of the I/O characteristic k.

Theorem 2.10 *Let i be such $M_{2i+1}(u) = e_{2i+1}(u)$ is an equilibrium for each $u \in [p_1, p_2]$ and let $k_{x,2i+1} : [p_1, p_2] \to X$ and $k_{2i+1} : [p_1, p_2] \to [p_1, p_2]$ be the corresponding single-valued branches of the I/S and I/O characteristics. Then for a positive feedback system the Theorem 2.9 holds with k replaced by k_{2i+1} and X replaced by B^*_{2i+1}. For a negative feedback system the Theorem 2.8 holds with k replaced by k_{2i+1} and X replaced by B^*_{2i+1}. In particular, there is at least one fixed point e^*_{2i+1} of the I/O characteristic in M^*_{2i+1} and if for any initial condition $u \in [p_1, p_2]$ the iterations $k^n_{2i+1}(u)$ of the I/O branch converge to e^*_{2i+1}*

$$\lim_{n\to\infty} k^n_{2i+1}(u) = e^*_{2i+1} \quad \textit{for each } u \in [p_1, p_2]$$

then the Morse set M^*_{2i+1} consists of the unique equilibrium $E_{2i+1} := k_x(e^*_{2i+1})$ and all solutions starting in B^*_{2i+1} converge to E_{2i+1}.

3 A cell cycle model

We illustrate our theory on a biochemical model of the cell cycle control in *Xenopus* embryos. Over the last 15 years both the biology [21] and the modeling [22, 23, 20, 27] of the cell cycle oscillator made great strides towards understanding of generation and control of the cell cycle oscillator. One of the most striking features of this oscillation is the abrupt change that signals entry into the M-phase of the cycle. Several experimental papers [22, 23] suggest that the presence of the positive feedback loops is responsible for the switch-like behavior, and the negative feedback loop for generating the periodic oscillations. Ultimately, however, the presence of both is needed for the proper function of the cell cycle. At the center of the cell cycle engine is a heterodimer Cdc2-cyclin. Its activity is regulated by synthesis and degradation of cyclin and by phosporylation and dephosporylation of Cdc2. There are two major feedback loops: Cdc2-cyclin modulates kinases and phospatases that in turn modulate its own activity in a positive feedback loop; and Cdc2-cyclin stimulates proteolytic machinery that degrades cyclin in a negative feedback loop.

The activity of Cdc2-cyclin is regulated by three phosporylation sites: activation site Thr161, and two inhibitory phosporylation sites Thr14 and Tyr15. Since the latter sites are always dephosporylated simultaneously, it is sufficient to track the state of Tyr15. In *Xenopus* Thr161 is phosporylated by CAK and dephosporylated by PP2c; the kinase that phosporylates Tyr15 is Wee1 and the corresponding phosphatase is Cdc25. The active form of Cdc2-cyclin is phosporylated on Thr161, but not on Tyr15. The rapid onset of the M-phase transition is brought on by rapid conversion of the doubly phosporylated Cdc2-cyclin to its Thr161 phosporylated active form. There are two positive feedback loops: Cdc2-cyclin up-regulates activity of the phosphatase Cdc25 and down-regulates activity of the kinase Wee1. Since phosphatase Cdc25 promotes the active form of Cdc2-cyclin and the kinase promotes the inactive form of Cdc2-cyclin, both of these constitute positive feedback loops.

Cdc2-cyclin dimers are broken up by cyclin degradation, which is promoted by APC (anaphase-promoting complex). Since Cdc2-cyclin activates APC, this forms a negative feedback loop. It is very likely that the activation of the APC is done through an intermediary, since the effect is significantly delayed.

A model incorporating these ingredients was proposed and numerically analyzed by Novak and Tyson [20] and used later by Pommering *et. al.* [22, 23]. In order to apply our theory we simplify the model to six differential equations (for details on the derivation of this model see [11])

$$
\begin{aligned}
\dot{q} &= k_{synth} - k_{dest} q z - k_{wee1} u q - k_{wee1basal}(wee1_{tot} - u) q + k_{cdc25} w y + k_{cdc25basal}(cdc25_{tot} - w) y \\
\dot{y} &= k_{synth} - k_{dest} y z \\
\dot{w} &= k_{cdc25on} \frac{q^{n_{cdc25}}}{e_{cdc25}^{n_{cdc25}} + q^{n_{cdc25}}}(cdc25_{tot} - w) - k_{cdc25off} w \\
\dot{u} &= -k_{wee1off} \frac{q^{n_{wee1}}}{e_{wee1}^{n_{wee1}} + q^{n_{wee1}}} u + k_{wee1on}(wee1_{tot} - u) \\
\dot{v} &= k_{plxon} \frac{q^{n_{plx}}}{e_{plx}^{n_{plx}} + q^{n_{plx}}}(plx_{tot} - v) - k_{plxoff} v \\
\dot{z} &= k_{apcon} \frac{v^{n_{apc}}}{e_{apc}^{n_{apc}} + v^{n_{apc}}}(apc_{tot} - z) - k_{apcoff} z
\end{aligned}
\tag{13}
$$

where we track the total Cdc2-cyclin (y), the active Cdc2-cyclin (q), the active Cdc25 (w), active Wee1 (u), active plx (putative APC intermediary) (v) and APC (z). The constants and their values (taken from Supplement of Pommering [23]) are described in Table 1.

$k_{synth} = 0.4$	cyclin synthesis rate	$k_{dest} = 0.006$	cyclin destruction rate
$k_{wee1} = 0.05$	active Wee1 phosp. rate	$k_{wee1basal} = 0.0033$	basal Wee1 phosp. rate
$k_{cdc25} = 0.1$	active Cdc25 dephosp. rate	$k_{cdc25basal} = 0.0066$	basal Cdc25 dephosp. rate
$k_{cdc25on} = 1.75$	Cdc25 activation rate	$k_{cdc25off} = 0.2$	Cdc25 deactivation rate
$k_{wee1on} = 0.2$	Wee1 activation rate	$k_{wee1off} = 1.75$	Wee1 deactivation rate
$k_{plxon} = 1$	Plx activation rate	$k_{plxoff} = 0.15$	Plx deactivation rate
$k_{apcon} = 1$	APC activation rate	$k_{apcoff} = 0.15$	APC deactivation rate
$wee1_{tot} = 15$	total Wee1 concentration	$cdc25_{tot} = 15$	total Cdc25 concentration
$plx_{tot} = 50$	total Plx concentration	$apc_{tot} = 50$	total APC concentration
$n_{cdc25} = 4$	Cdc25 Hill coefficient	$n_{wee1} = 4$	Wee1 Hill coefficient
$n_{apc} = 3$	APC Hill coefficient	$n_{plx} = 3$	Plx Hill coefficient
$e_{cdc25} = 40$	Cdc25 half-activation	$e_{wee1} = 40$	Wee1 half-activation
$e_{apc} = 40$	APC half-activation	$e_{plx} = 40$	Plx half-activation

The system (13) is amenable to the analysis using input-output characteristic. The only negative feedback in the system is the degradation of the Cdc2-cyclin by APC. Therefore we consider an open loop system, where we replace z in the first two equations by an input parameter $\alpha := -z$, with $\alpha \leq 0$.

The system with the input α fixed is a monotone open loop system and thus [24] almost all solutions converge to the set of equilibria. The (multi-valued) input state characteristic is the function that associates to each fixed α the corresponding set of equilibria of the system. The input-output characteristic is the value of the variable $z = h(y, q, w, u, v, z)$ on the set of equilibria. We recover the closed loop system (13) by setting $\alpha = -z$, which indicates a negative feedback in the loop.

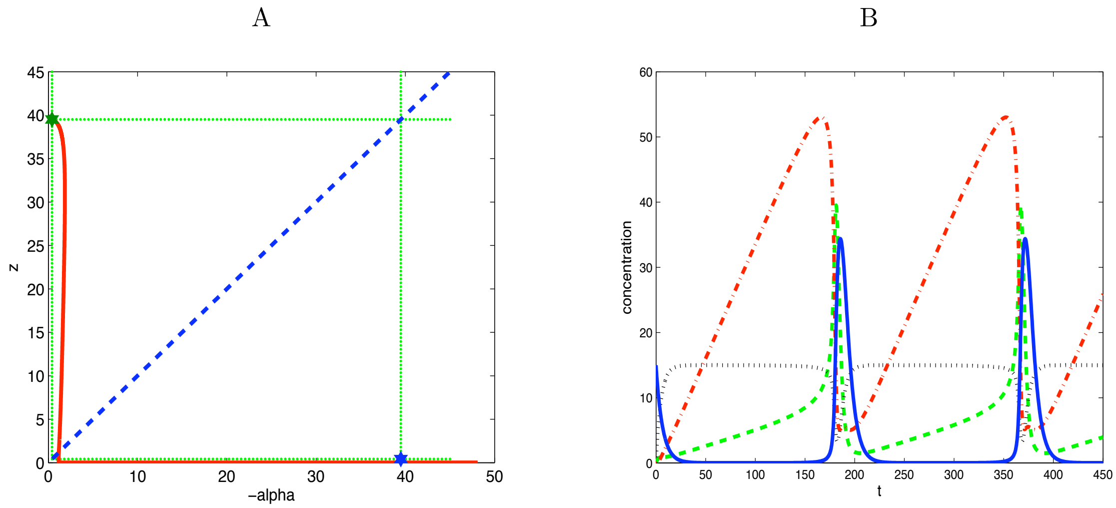

Figure 2: (A) The input-output characteristic (solid curve) for (13) with parameters from Table 1; The attracting region $[p_1, p_2]$ is a dotted square and the dashed curve is the diagonal (B). Dynamics of (13) with the same parameter values as in (A). Legend: solid curve $= z$, dotted curve $= u$, dashed curve $= q$, and dash-dot curve $= y - q$

We investigate how the strength of the negative feedback connection from APC to Cdc2-cyclin affects the dynamics of the system. To compute the I/O characteristic we set the left-hand side of the equations in (13) to zero and solve the resulting system for z as a function of α.

The input-output characteristic is multi-valued (solid line in Figure 2.A) in the region approximately $\alpha \in (b_1, b_2) := (1.17, 1.85)$. Since the values of z on the upper branch are greater then 35, the characteristic is a very narrow curve. The dotted square denotes the region $[p_1, p_2] \times [p_1, p_2]$ where p_1 and p_2 are described in Theorem 2.4. The output (z) values of all solutions of the closed loop system will eventually enter $[p_1, p_2]$. Since the multi-stability region $(b_1, b_2) = (1.17, 1.85)$ is clearly a subset of the interval $[p_1, p_2]$, the only Morse decomposition that continues across this interval is a trivial decomposition that consist of only one set - the entire attractor of the open loop system at different values of α. The conclusion (rather trivial) of the Theorem 2.7 is that there exists one Morse set for the closed loop system and as the simulation of the closed loop system in Figure 2.B indicates, this Morse set contains a periodic orbit of the cell cycle. Observe that the range of $z(t)$ solution (solid line in Figure 2.B) matches the range of the characteristic, which suggests that the cell cycle periodic orbit may arise as a relaxation oscillator associated to the characteristic. This is theoretically justified by Gedeon and Sontag [13] in the presence of slow feedback, which is, however, not the case here. A detailed analysis of this example is forthcoming [11].

We now analyze different values of feedback. First, we weaken the negative feedback by decreasing the destruction rate of cyclin 100 times and set $k_{dest} = 0.00006$. The I/O characteristic shifts to the right (Figure 3.A, compare the range of $-\alpha$). The diagonal (dashed line) intersects only the upper branch of the I/O characteristic. In this case $p_1 = p_2 = z = -\alpha$ at this intersection. Theorem 2.4 implies that the values of the output $z(t)$ for any initial condition in an open and dense set will converge to $p_1 = p_2$. The long term behavior of the closed loop system is governed by the open loop system with constant $\alpha = p_1 = p_2$. Since this system is monotone and has a unique equilibrium, almost all solutions of this system, and thus all solutions of the closed loop system, converge to this equilibrium. The numerical simulations (Figure 3.B) confirm this. Note that $z(t)$ (solid line in Figure 3.B) converges to a high value about 40 which is the value of $p_1 = p_2 = z$.

Finally we will show that by modifying few other parameters almost all solutions of the system (13) converge to one of two stable equilibria. We will increase synthesis rate from $k_{synth} = 0.4$ to $k_{synth} = 0.9$. At the same time we weaken the negative feedback by decreasing the destruction rate of cyclin 10 fold to $k_{dest} = 0.0006$; we also change cooperativity constants to $n_{apc} = 2$ and $n_{plx} = 1$ (from $n_{apc} = n_{plx} = 3$).

All remaining parameters including all rate constants remain the same. The resulting input-output

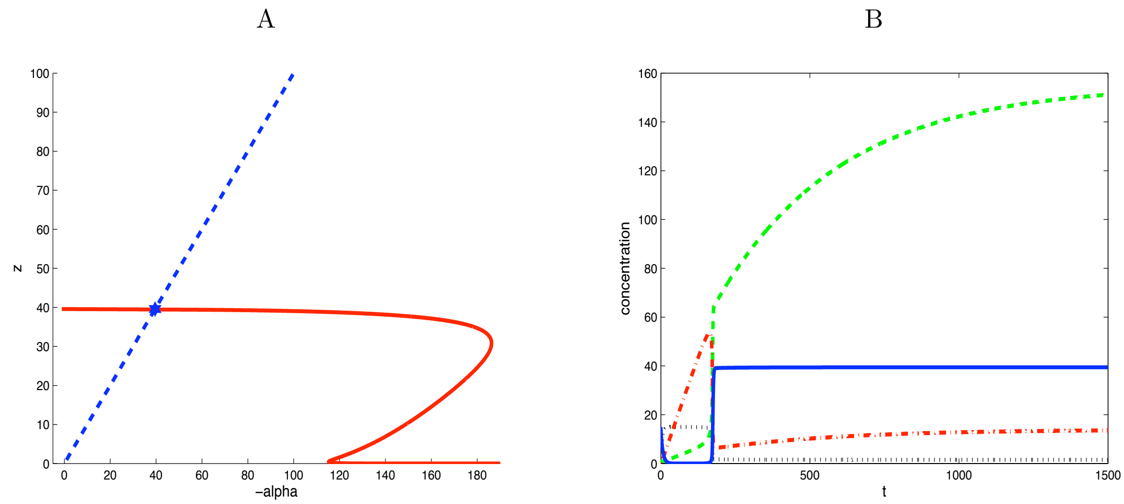

Figure 3: (A) The input-output characteristic of (13) with $k_{dest} = 0.00006$; and (B) its dynamics. The legend is the same as in Figure 2.

characteristic is in Figure 4.A, where we again plot the region $[p_1, p_2] \times [p_1, p_2]$ as a dotted square. Both the upper and lower branches of the characteristic intersect the diagonal and the interval of multi-stability (b_1, b_2) contains $[p_1, p_2]$. Therefore there is a Morse decomposition of the open loop system that contains three ordered Morse sets $M_1(u) \prec M_2(u) \prec M_3(u)$ where $M_1(u), M_2(u), M_3(u)$ correspond to the equilibria on the bottom, middle and top branches respectively. Theorem 2.7 shows the existence of the Morse decomposition with sets M_1^*, M_3^* and M_0^* with $M_0^* \prec M_3^*, M_0^* \prec M_1^*$ for the closed loop system. Let e_1^* be the intersection of the bottom branch and e_3^* the intersection of the top branch with the diagonal. Since e_1^* is a stable fixed point under the iterations of the function given by the lower branch, and of e_3^* is a stable fixed point under the iterations of the upper branch of the I/O characteristic, by Theorem 2.10 there are corresponding stable equilibria E_1 and E_3 of the closed loop system (13). Numerical simulation shows that for different initial conditions solutions converge to both the equilibrium E_1 (Figure 4.B) and the equilibrium E_3 (Figure 4.C). Note the widely different values of the active Cdc2-cyclin (dashed curve representing $y(t)$) and the inactive Cdc2-cyclin (dashed-dot curve representing $q(t) - y(t)$). The closed loop system is bistable.

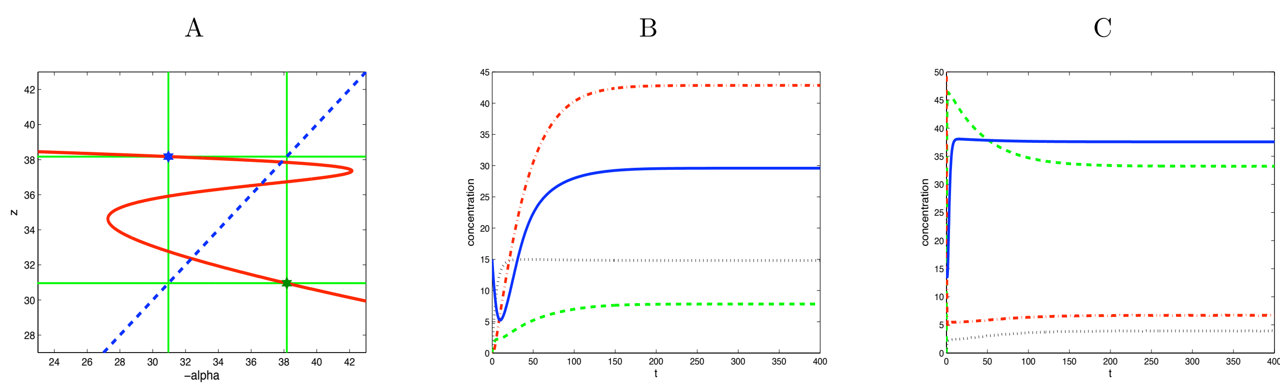

Figure 4: (A) Input-output characteristic for the bistable system. (B) Convergence to the low equilibrium E_1 for the system (13) with the initial data $y = q = w = u = v = 0, z = 15$; (C) Convergence to the high equilibrium E_3 for the system (13) with the initial data $q = u = v = 0, y = 50, w = 30, z = 15$. The legend is the same as in Figure 2.

4 Attractor of the closed loop system

The goal of this section is to prove Theorem 2.4. Although many results in this section hold for systems with inputs of arbitrary dimension, we will assume throughout that the open loop system is a SISO system.

4.1 Multi-valued maps

The first definition generalizes monotonicity to multi-valued maps.

Definition 4.1 (Definition 2.3 [7]) Let Z_1 and Z_2 be partially ordered Euclidean spaces and $F : Z_1 \to Z_2$ be a set valued map. We say that F is *weakly non-increasing (weakly non-decreasing)* provided that the following holds for all $p, q \in Z_1$ such that $q \succ p$ ($p \succ q$): For each $x_p \in F(p)$ and $x_q \in F(q)$ there exist $y_p \in F(p)$ and $y_q \in F(q)$ such that $y_p \succeq x_q$ and $x_p \succeq y_q$.

We now relate the weak monotonicity of the multi-valued I/O characteristic to the regular monotonicity of functions K_{max} and K_{min}.

Lemma 4.2 *The input-output characteristic k in a SISO system is weakly non-increasing (non-decreasing) if, and only if, the functions K_{min} and K_{max} defined in (5) are non-increasing (non-decreasing).*

Proof. We first observe, that in SISO system the input-output characteristic $k : \mathbb{R} \to \mathbb{R}$ and thus the order inequality $\succeq$ with respect to $\mathbb{R}^+$ is given by $\geq$.

Assume $q > p$. Assume first that K_{min} and K_{max} are non-increasing. Given $x_p \in k(p)$ and $x_q \in k(q)$ we set $y_p := K_{max}(p)$ and $y_q := K_{min}(q)$. Since K_{max} is non-increasing, our choice of y_p and y_q implies $y_p \geq K_{max}(q)$ and $K_{max}(q) \geq x_q$ by the definition of K_{max}. Thus $y_p \geq x_q$. A similar argument shows that $x_p \geq y_q$. Therefore k is weakly non-increasing.

Now we assume that the input-output characteristic k is weakly non-increasing and K_{min} is not non-increasing, i.e decreasing. Then there are values $q_0 > p_0$ such that $K_{min}(q_0) > K_{min}(p_0)$. Select $x_{p_0} := K_{min}(p_0)$. Then for all $y_{q_0} \in k(q_0)$ we have

$$y_{q_0} > K_{min}(q_0) > K_{min}(p_0).$$

This is a contradiction to the fact that the input-output characteristic k is weakly non-increasing.

The argument for K_{max} is analogous. □

Lemma 4.3 (Lemma 2.4 [7]) *An input-state characteristic k_x of a monotone open loop system is weakly non-decreasing.*

We use the previous Lemma to show that the monotonicity of K_{max} and K_{min} are determined by the type of feedback. However, since we defined functions $B(u)$ and $T(u)$ differently for negative and positive feedback, they will always be non-decreasing.

Corollary 4.4 *1. The functions K_{min} and K_{max} are non-increasing for any negative feedback system ($u = -y$) and they are non-decreasing for any positive feedback system ($u = y$).*

2. $B(u)$ and $T(u)$ are non-decreasing functions of u for both types of feedback.

Proof. **1.** The input-output characteristic k of (1) is a composition of an input-state characteristic k_x, a non-decreasing output function h and the function $g(u) = \pm u$ where the sign depends on whether the feedback is negative or positive. Since k_x is weakly non-decreasing by Lemma 4.3 and the composition of a weakly non-decreasing function and a non-decreasing function h results in a weakly non-decreasing function, the composition $h \circ k_x$ is weakly non-decreasing. The composition with $g = \pm u$ causes k to be weakly non-decreasing for positive and weakly non-increasing for negative feedback. Lemma 4.2 now finishes the argument.

2. Recall (see (7)) that for a negative feedback system we defined $B(u) := K_{min}(K_{max}(u))$ and $T(u) := K_{max}(K_{min}(u))$; for a positive feedback system (see (6)) we set $B(u) := K_{min}(u)$, and $T(u) := K_{max}(u)$. The proof now follows from the part 1. □

Definition 4.5 We define a multi-valued map $\bar{k}(a) = [K_{min}(a), K_{max}(a)]$ where the value of each point is a closed interval in $\mathbb{R}$. If $a < b$ and $I = [a, b]$ is an interval, then we set

$$\bar{k}(I) = \cup_{u \in I} \bar{k}(u).$$

We now characterize the images of an interval under the multi-valued map $\bar{k}$. This is the key point where the SISO assumption (that is both input and output $u, y \in \mathbb{R}$) is used.

Lemma 4.6 *Consider a SISO system with a multi-valued input-output characteristic k. Then for a negative feedback system and any $a \leq b$, $a, b \in \mathbb{R}$*

$$\bar{k}([a, b]) = [K_{min}(b), K_{max}(a)].$$

On the other hand, for a positive feedback

$$\bar{k}([a, b]) = [K_{min}(a), K_{max}(b)].$$

Proof. Consider first a SISO system with a negative feedback. Take $x \in \bar{k}([a, b])$. Then $x \in \bar{k}(s)$ for some s satisfying $a < s < b$. Since both K_{min} and K_{max} are non-increasing by Corollary 4.4.1, we have

$$K_{max}(a) > K_{max}(s) > x > K_{min}(s) > K_{min}(b).$$

Hence $x \in [K_{min}(b), K_{max}(a)]$.

Now we prove the other inclusion. Take x such that $K_{min}(b) < x < K_{max}(a)$. Since both $K_{min}(b) \in k(b)$ and $K_{max}(a) \in k(a)$ and the set $\bigcup_{x \in [a,b]} k(x)$ is connected, there is $c \in [a, b]$ such that $x \in k(c)$.

The argument for the positive feedback case is analogous. □

The Next Lemma relates the multi-valued function $\bar{k}$ to the functions $B(u)$ and $T(u)$. Since the definition of functions B and T for the negative feedback has already built-in the composition of K_{min} and K_{max}, the formulas for $\bar{k}$ in the positive feedback case, and $\bar{k}^2$ in the negative feedback case, are identical.

Lemma 4.7 *Consider a SISO system with a multi-valued input-output characteristic k. Then for a negative feedback system*

$$\bar{k}^2(u) = [B(u), T(u)] \quad \textit{and} \quad \bar{k}^2[a, b] = [B(a), T(b)].$$

For a positive feedback system

$$\bar{k}(u) = [B(u), T(u)] \quad \textit{and} \quad \bar{k}[a, b] = [B(a), T(b)].$$

Proof. For the negative feedback system we have from the Lemma 4.6

$$\bar{k}^2(u) = \bar{k}([K_{min}(u), K_{max}(u)]) = [K_{min}(K_{max}(u)), K_{max}(K_{min}(u))] = [B(u), T(u)].$$

For a positive feedback system by definition 4.5

$$\bar{k}(u) = [K_{min}(u), K_{max}(u)] = [B(u), T(u)].$$

The second equality in both cases follows from the first equality and Corollary 4.4.2. □

Next Lemma provides an important characterization of the points p_1 and p_2.

Lemma 4.8 *The points p_1 and p_2, defined in Theorem 2.4, are fixed points of $B(u)$ and $T(u)$ respectively:*

$$p_1 = \min\{p : p \textit{ is a fixed point of } B(u)\}, \quad p_2 = \max\{p : p \textit{ is a fixed point of } T(u)\}.$$

Proof. We prove the first statement. The definition of p_1 and Lemma 4.7 imply $p_1 := \sup\{a : B(u) > u,\ \forall\, u < a\}$. Therefore we have

$$B(p_1) \leq p_1. \tag{14}$$

We now prove the opposite inequality. Since $B(u)$ is non-decreasing we have $\lim_{n\to\infty} B(x_n) \leq B(p_1)$ for any sequence $\{x_n\}_{n=1}^{\infty}$ with $x_n < p_1$ and $x_n \to p_1$. Therefore

$$B(p_1) \geq \lim_{n\to\infty} B(x_n) \geq \lim_{n\to\infty} x_n = p_1. \tag{15}$$

Now (14) and (15) show that p_1 is a fixed point of $B(u)$. If z satisfies $B(z) = z$ then by definition of p_1 we must have $u \geq p_1$. This shows that p_1 is the smallest fixed point of $B(u)$.

The second result is analogous to the first. □

The following Lemma shows that for the SISO negative feedback system p_1 and p_2 form an "almost" period 2 point of the input-output characteristic.

Lemma 4.9 *For a SISO negative feedback system, the values p_1 and p_2 satisfy*

$$p_1 = K_{min}(p_2), \quad p_2 = K_{max}(p_1).$$

Proof. Take $\alpha(u) := K_{min}(u)$ and $\beta(u) := K_{max}(u)$. For a negative feedback system, both K_{min} and K_{max} are non-increasing functions of u. By Lemma 4.8 and the definition of p_1 and p_2 we get $p_1 = B(p_1) = K_{min}(K_{max}(p_1))$ and $p_2 = T(p_2) = K_{max}(K_{min}(p_2))$. We apply K_{max} to the first equation to get $K_{max}(p_1) = K_{max}(K_{min}(K_{max}(p_1)))$. Observe that this implies that $K_{max}(p_1)$ is a fixed point of $K_{max} \circ K_{min} = T$. Since by Lemma 4.8 p_2 is the largest fixed point of T , it follows that

$$K_{max}(p_1) \leq p_2. \tag{16}$$

Similarly, applying K_{min} to the second equation and applying Lemma 4.8, we get

$$K_{min}(p_2) \geq p_1. \tag{17}$$

Since K_{min} is non-increasing, (16) implies

$$K_{min}(p_2) \leq K_{min}(K_{max}(p_1)) = p_1.$$

This, together with (17), implies $K_{min}(p_2) = p_1$. A similar argument show that $K_{max}(p_1) = p_2$. □

In the final result of this section we will show that the iterations of the multi-valued map $\bar{k}$ will converge to the interval $[p_1, p_2]$. Since the functions $B(u)$ and $T(u)$ are constructed from the multi-valued characteristic the following lemma provides an explicit construction of this interval.

Lemma 4.10 *Consider a SISO system with multi-valued input-output characteristic k. Then for any $u \leq p_1$, and both a positive and negative feedback systems we have*

$$\lim_{m\to\infty} \min \bar{k}^{2m}(u) = p_1 = \lim_{n\to\infty} B^n(u),$$

and for any $u \geq p_2$,

$$\lim_{m\to\infty} \max \bar{k}^{2m}(u) = p_2 = \lim_{n\to\infty} T^n(u).$$

Proof. We consider a SISO system with a positive feedback. Then by Lemma 4.7 the minimum $\min \bar{k}(u) = B(u)$. By induction we assume that for $l = n-1$ we have $\min \bar{k}^{n-1}(u) = B^{n-1}(u)$. Then

$$\begin{aligned} \min \bar{k}^n(u) &= \min \bar{k}(\bar{k}^{n-1}(u)) \\ &= \min \bar{k}(\min \bar{k}^{n-1}(u)) \\ &= \min \bar{k}(B^{(n-1)}(u)) \\ &= B^n(u). \end{aligned} \tag{18}$$

Therefore for a positive feedback system $\min \bar{k}^n(u) = B^n(u)$.

For the negative feedback system Lemma 4.7 implies that $\min \bar{k}^2(u) = B(u)$. By induction we can get as above that in this case $\min \bar{k}^{2n}(u) = B^n(u)$. In either positive or negative feedback case the first result now follows from the fact that for all $u < p_1$ we have $B(u) > u$ and thus the sequence $\{B^k(u)\}_{k=1}^{\infty}$ is monotone increasing and converges to p_1.

To prove the second result, we first observe that in analogy to (18)

$$\max \bar{k}^{2n}(u) = T^n(u) \quad \text{and} \quad \max \bar{k}^n(u) = T^n(u) \tag{19}$$

for negative and positive feedback systems, respectively. The second result now follows from the fact that for all $u \leq p_2$ we have $T(u) < u$ and thus the sequence $\{T^k(u)\}_{k=1}^{\infty}$ is monotone decreasing and converges to p_2. □

4.2 From open to closed loop system

In the previous section we observed a key roles the functions $B(u)$ and $T(u)$ play in open loop system. We will now show that the these functions bound the projection of the trajectories of the closed loop system into the output variable y. We consider the closed loop system (2), which we write in the form

$$\dot{x} = f(x,u),\ y = h(x),\ u = \pm y,\ \ x \in X,\ u \in U,\ y \in Y. \tag{20}$$

Here again $u = +y$ ($u = -y$) correspond to a positive (negative) feedback, respectively. The corresponding open loop system is

$$\dot{x} = f(x,u),\ y = h(x),\ \ x \in X,\ u \in U,\ y \in Y. \tag{21}$$

Definition 4.11 Consider the system (20) and assume that the control function $u(t)$ is bounded. Let $u^- := \liminf_{t\to\infty} u(t)$, $u^+ := \limsup_{t\to\infty} u(t)$ and let

$$y^- := \liminf_{t\to\infty} y(t) = h(x(t)),\ y^+ := \limsup_{t\to\infty} y(t) = h(x(t)).$$

Lemma 4.12 *Consider a closed loop system (20) and assume that the corresponding open loop system (21) satisfies the standing assumptions.*

Then there exists a generic set $\mathcal{X} \subset X$ such that for each initial condition $\xi \in \mathcal{X}$ and each bounded input $u(t)$ with the property that the solution $\varphi(t, \xi, u(t))$ of (20) is defined for all $t \geq 0$, we have

$$B(y^-) \leq y^- \leq y^+ \leq T(y^+).$$

Proof. Our proof combines the argument of DeLeenheer and Malisoff [7] and Angeli and Sontag [4]. In a SISO system a cone $U \subset \mathbb{R}$ must be a half-line. Then by Lemma A.3 of Angeli and Sontag [4] there are sequences v_n^+ and v_n^- in U such that given any compact set $K \subset U$, there exists a sufficiently large $n = n(K)$ such that $v_n^- \leq K \leq v_n^+$. It follows from standing assumptions that for each constant $u(t) = q$ there is an exceptional set $\mathcal{B}_q$ of the set of initial conditions that do not converge to an equilibrium in open loop system (21). Recall that the monotonicity assumption implies that the set $X \setminus \mathcal{B}_q$ contains an open and dense set i.e. it is generic. Following ([4]) define

$$\mathcal{B} := \bigcup_{n,k\in N, \sigma=\pm, q\in U_0} \varphi(-n, \mathcal{B}_q, v_k^\sigma), \tag{22}$$

where U_0 is a countable and dense subset of U and $\varphi(t, x_0, u_0)$ is the flow generated by (20). Since flow defined maps are diffeomorphisms and $X \setminus \mathcal{B}_q$ is generic, each set $X \setminus \varphi(-n, \mathcal{B}_q, v_k^\sigma)$ is generic. Thus

$$\mathcal{X} := X \setminus \mathcal{B} = \bigcap_{n,k\in N, \sigma=\pm, q\in U_0} (X \setminus \varphi(-n, \mathcal{B}_q, v_k^\sigma))$$

is generic, as a countable intersection of generic sets is generic.

We first prove that for $\xi \in \mathcal{X}$

$$\min k_x(u^-) \preceq \liminf_{t\to\infty} \varphi(t,\xi,u(t)) \preceq \limsup_{t\to\infty} \varphi(t,\xi,u(t))) \preceq \max k_x(u^+) \tag{23}$$

Take an arbitrary $\xi \in X \setminus \mathcal{B}$. By the definition of the lim inf there is an increasing sequence of integer times $n_j \to \infty$ and a sequence of constant-valued controls $u_j \in U_0$ such that $u_j \to u^-$ and $u(t) \geq u_j$ for all $t \geq n_j$. Then

$$\begin{aligned} \varphi(t,\xi,u) &= \varphi(t-n_j, \varphi(n_j,\xi,u(\cdot)), u(\cdot + n_j)) \\ &\succeq \varphi(t-n_j, \varphi(n_j,\xi,u), u_j) \end{aligned} \tag{24}$$

Let $\zeta \in \omega(\xi)$ which implies that there is a sequence $s_i \to \infty$ such that $\varphi(s_i,\xi,u) \to \zeta$. Let $t = s_i$ in (24)

$$\varphi(s_i,\xi,u) \succeq \varphi(s_i - n_j, \varphi(n_j,\xi,u), u_j)$$

So

$$\lim_{i\to\infty} \varphi(s_i,\xi,u) \succeq \lim_{i\to\infty} \varphi(s_i - n_j, \varphi(n_j,\xi,u), u_j) =: v_j \tag{25}$$

where the last limit exists because $\xi \notin \mathcal{B}$ which implies $\varphi(t-n_j, \varphi(n_j,\xi,u), u_j) \notin \mathcal{B}_{u_j}$ and therefore $\lim_{t\to\infty} \varphi(t-n_j, \varphi(n_j,\xi,u), u_j)$ converges to the set of equilibria. By the standing assumption all equilibria are order-related, and so $\lim_{t\to\infty} \varphi(t-n_j, \varphi(n_j,\xi,u), u_j)$ is a unique equilibrium v_j [24]. We can apply (25) for every value of j thereby getting a sequence of such v_j's. There must be a subsequence of the v_j's which converges to, say, v (since there are an infinite number of them and they are bounded). We also know that along each branch, k_x is continuous and so $k_x(u_j) \to k_x(u^-)$. Therefore the subsequence of v_j must converge to some value of $k_x(u^-)$. In particular $v \succeq \min k_x(u^-)$. So we have

$$\limsup_{t\to\infty} \varphi(t,\xi,u(t))) \preceq \liminf_{t\to\infty} \varphi(t,\xi,u(t))) \preceq \min k_x(u^-)$$

The rest of the inequality in (23) follows by the similar argument.

Now we apply non-decreasing function h to the equation (23) to get

$$\min h(k_x(u^-)) \leq \liminf_{t\to\infty} y(t) \leq \limsup_{t\to\infty} y(t) \leq \max h(k_x(u^+)). \tag{26}$$

Recall, that for the positive feedback we have $y = u$ and hence $u^- = y^-$ and $u^+ = y^+$. Therefore in this case (26) reads

$$[y^-, y^+] \subset [K_{min}(y^-), K_{max}(y^+)] = [B(y^-), T(y^+)]$$

which proves the Lemma when $y = u$.

In the negative feedback case we have $y = -u$ and hence $u^- = y^+$ and $u^+ = y^-$ and therefore (26) reads $K_{min}(y^+) \preceq y^- \preceq y^+ \preceq K_{max}(y^-)$. In other words,

$$[y^-, y^+] \subset [K_{min}(y^+), K_{max}(y^-)]. \tag{27}$$

We now repeat the above argument starting with equation (23) with $u^- = K_{min}(y^+)$ and $u^+ = K_{max}(y^-)$. In analogy to the equation (27) we obtain

$$[K_{min}(y^+), K_{max}(y^-)] \subset [K_{min}(K_{max}(y^-)), K_{max}(K_{min}(y^+))]. \tag{28}$$

Combining equations (27) and (28) with the definition (7) of $B(u)$ and $T(u)$ in the negative feedback case yields

$$[y^-, y^+] \subset [B(y^-), T(y^+)].$$

□

Proof of Theorem 2.4. In the view of Definition 4.11 it is enough to show

$$[y^-, y^+] \subset [p_1, p_2].$$

By Lemma 4.12 $[y^-, y^+] \subset [B(y^-), T(y^+)]$.

Since $u(t) = \pm y(t)$ this implies that $u(t) \subset [B(y^-), T(y^+)]$ for all t. We apply Lemma 4.12 to $u^- := B(y^-)$ and $u^+ := T(y^+)$ to get with

$$[y^-, y^+] \subset [B^2(y^-), T^2(y^+)].$$

By induction it follows that

$$[y^-, y^+] \subset [B^n(y^-), T^n(y^+)] \tag{29}$$

for all n.

Now assume that $y^- < p_1$. Since by Lemma 4.10 $\lim_{n\to\infty} B^n(y^-) = p_1$, there exists N such that for all $n \geq N$ we have $B^n(y^-) > y^-$. This, however, contradicts (29) and therefore we must have $y^- \geq p_1$. Similar argument shows that $y^+ \leq p_2$. This shows that $[y^-, y^+] \subset [p_1, p_2]$ and thus proves the Theorem. □

5 Morse decomposition for the closed loop system

In this section we prove Theorem 2.7 that provides a construction of a Morse decomposition of a closed loop system based on a Morse decomposition of an the corresponding open loop system.

Our first observation is that since $u(t) = \pm y(t)$ and by Theorem 2.4 $[y^-, y^+] \subset [p_1, p_2]$, we may assume without loss of generality that $u(t) \in [p_1, p_2]$ for all $t \geq 0$. Further, we assume all assumptions of Theorem 2.7. In particular, in addition to the standing assumptions, we assume that for each fixed $u(t) = u \in [p_1, p_2]$ the open loop system

$$\dot{x} = f(x, u) \tag{30}$$

admits a Morse decomposition $\mathcal{M}(u) = \{M_i(u) \mid i = 1, \ldots, 2L+1\}$ described in Definition 2.6.

Definition 5.1 Let $B_{2k+1}(u)$ be a basin of attraction of the Morse set $M_{2k+1}(u)$, $k = 1, \ldots, L$ and let

$$B^*_{2k+1} := \bigcap_{u \in [p_1, p_2]} B_{2k+1}(u) \qquad \text{for } k = 0, \ldots, L.$$

Let $B_{2k}(u)$ be the basin of attraction of $M_{2k}(u)$.

Let $W_{2k}(u)$ be defined as

$$W_{2k}(u) := \text{cl}\, B_{2k+1}(u) \cap \text{cl}\, B_{2k-1}(u). \tag{31}$$

Recall, that $\mathcal{B}_u$ is the exceptional set of initial conditions which do not converge to the set of equilibria in the open loop system with the constant input $u(t) = u$. We now characterize the boundary of the basins of attraction of B_{2k+1}, $k = 0, \ldots, L$.

Lemma 5.2 *For each fixed u and $k = 1, \ldots, L-1$, the set $B_{2k+1}(u)$ is bounded by $W_{2k}(u)$ and $W_{2k+2}(u)$*

$$\partial B_{2k+1}(u) = W_{2k}(u) \cup W_{2k+2}(u),$$

while for $k = 0$ and $k = L$

$$\partial B_1(u) = W_2(u), \quad \partial B_{2L+1} = W_{2L}.$$

Furthermore,

$$W_{2k}(u) \subset B_{2k} \cup \mathcal{B}_u$$

consists of points ξ such that either $\lim_{t\to\infty} \varphi(t, \xi, u) = M_{2k}(u)$ or $\xi \in \mathcal{B}_u$.

Proof. Since the value of u is fixed in this Lemma, will will drop the reference to u from our notation. Recall, that $[\cdot, \cdot]$ denotes the order interval. Observe that since $M_{2k-1} \subset B_{2k-1}$ and $M_{2k+1} \subset B_{2k+1}$, both $B_{2k-1} \cap [M_{2k-1}, M_{2k+1}] \neq \emptyset$ and $B_{2k+1} \cap [M_{2k-1}, M_{2k+1}] \neq \emptyset$. Therefore $\partial B_{2k-1} \cap [M_{2k-1}, M_{2k+1}] \neq \emptyset$ and $\partial B_{2k+1} \cap [M_{2k-1}, M_{2k+1}] \neq \emptyset$ for every k.

Take $x_0 \in \partial B_{2k+1} \cap [M_{2k-1}, M_{2k+1}]$. Then for all $z \in M_{2k-1}$ and all $w \in M_{2k+1}$ we have $z \prec x_0 \prec w$. It follows from the monotonicity of (1) that

$$z_0 := \lim_{t\to\infty} \varphi(t, z, u) \preceq \lim_{t\to\infty} \varphi(t, x_0, u) \preceq \lim_{t\to\infty} \varphi(t, w, u) =: w_0. \tag{32}$$

Note that by the invariance of the Morse sets $z_0 \in M_{2k-1}$ and $w_0 \in M_{2k+1}$. Since x_0 is in the boundary of B_{2k+1}, $\lim_{t\to\infty} \varphi(t, x_0, u) \notin M_{2k+1}$; since B_{2k-1} is open, $x_0 \notin B_{2k-1}$ and thus $\lim_{t\to\infty} \varphi(t, x_0, u) \notin M_{2k-1}$. Therefore either $\varphi(t, x_0, u) \to M_{2k}$ or $x_0 \in \mathcal{B}_u$. A similar argument shows that if $x_0 \in \partial B_{2k+1} \cap [M_{2k+1}, M_{2k+3}]$ then either $\varphi(t, x_0, u) \to M_{2k+2}$ or $x_0 \in \mathcal{B}_u$.

Now we deal with the general case. Assume $x_0 \in \partial B_{2k+1}$, but not necessarily that $x_0 \in [M_{2k-1}, M_{2k+1}]$. Since $B_{2i+1}, i = 0, \ldots, L$ is a collection of disjoint open sets, $x_0 \notin B_{2i+1}$ for any $i = 0, \ldots, L$. Therefore either $x_0 \in \mathcal{B}_u$ or $\lim_{t\to\infty} \varphi(t, x_0, u) \in M_{2s}$ for some $s = 1, \ldots, L$. We will now show that either $s = k$ or $s = k + 1$. Since $x_0 \in \partial B_{2k+1}$ and B_{2k+1} is open, for any neighborhood N of x_0 there is an open set $V_N \subset B_{2k+1} \cap N$. Assume now that $\lim_{t\to\infty} \varphi(t, x_0, u) \subset M_{2s}$, for some $s < k$. Since the Morse sets are ordered by the assumption, there exist a T such that $\varphi(T, x_0, u) \in [M_{2s+1}, M_{2s-1}]$ and almost all solutions in a neighborhood $\bar{V}$ of $\varphi(T, x_0, u)$ converge to either M_{2s+1}, M_{2s-1} or M_{2s}. By the continuous dependence on initial condition there is a neighborhood $\bar{U}$ of x_0 such that $\varphi(T, \bar{U}, u) \subset \bar{V}$ and thus almost all solutions in $\bar{U}$ converge to either M_{2s+1}, M_{2s-1} or M_{2s}. This is a contradiction to the fact that there is an open set of points $V_{\bar{U}} \subset B_{2k+1} \cap \bar{U}$ that converge to M_{2k+1}. The assumption $s > k+1$ leads to a similar contradiction. Therefore $s = k$ or $s = k+1$ and $x_0 \in \partial B_{2k+1}(u)$ implies $\varphi(t, x_0, u) \to M_{2k}$, $\varphi(t, x_0, u) \to M_{2k+2}$ or $x_0 \in \mathcal{B}_u$. This proves the second statement of the Lemma.

Our argument also shows that all points in the neighborhood of x_0 are either in $B_{2k+1}(u)$ and $B_{2k-1}(u)$, which implies $x_0 \in W_{2k}(u)$; or in $B_{2k+1}(u)$ and $B_{2k+3}(u)$ which implies $x_0 \in W_{2k+2}(u)$. This proves the first statement of the Lemma. □

In the next two Lemmas we show that the basins of attraction for the open loop system are ordered even for different values of constant input u and v. Recall that $[p_1, p_2] \subset U$ is the interval over which the Morse decomposition $\mathcal{M}(u)$ of the open loop system is defined.

Lemma 5.3 *Assume the standing assumptions and the existence of Morse decomposition for an open loop system. Then for all $u \leq v$, $u, v \in [p_1, p_2]$ and all $k < s$*

$$B_k(v) \cap B_s(u) = \emptyset.$$

Proof. Assume to the contrary that there is $\zeta \in B_k(v) \cap B_s(u)$. Then by the monotonicity $\varphi(t, \zeta, u) \prec \varphi(t, \zeta, v)$ for all t and $z := \lim_{t\to\infty} \varphi(t, \zeta, u) \preceq \lim_{t\to\infty} \varphi(t, \zeta, v) =: w$. By definition $z \in M_s(u)$ and $w \in M_k(v)$. By the monotonicity of the output function h, $z \preceq w$ implies $h(z) \leq h(w)$ for $z \in M_s(u)$ and $w \in M_k(v)$ with $k < s$. This contradicts the assumption (10). □

Lemma 5.4 *Assume the standing assumptions and the existence of open loop Morse decomposition. Then for any $u \in [p_1, p_2]$, and any fixed k*

$$\bigcup_{l\geq k} B_l(p_1) \subset \bigcup_{l\geq k} B_l(u) \cup \mathcal{B}_u, \qquad \bigcup_{l\leq k} B_l(p_2) \subset \bigcup_{l\leq k} B_l(u) \cup \mathcal{B}_u.$$

Proof. Take any $u \leq v$, $u, v \in [p_1, p_2]$. Since by Lemma 5.3 $B_s(u) \cap B_l(v) = \emptyset$ for all $s < l$, and

$$X = \bigcup_{s<l} B_s(v) \cup \bigcup_{s\geq l} B_s(v) \cup \mathcal{B}_v,$$

it follows that $B_l(u) \subset \bigcup_{s\geq l} B_s(v) \cup \mathcal{B}_v$. Taking union over all $l \geq k$ we get

$$\bigcup_{l\geq k} B_l(u) \subset \bigcup_{l\geq k} \bigcup_{s\geq l} B_s(v) \cup \mathcal{B}_v = \bigcup_{l\geq k} B_l(v) \cup \mathcal{B}_v.$$

Finally, taking $u = p_1$ and $v = u$ we obtain the first statement above.

Similarly, Lemma 5.3 and the fact that $X = \bigcup_{s\leq l} B_s(u) \cup \bigcup_{s>l} B_s(u) \cup \mathcal{B}_u$, implies

$$B_l(v) \subset \bigcup_{s\leq l} B_s(u) \cup \mathcal{B}_u. \tag{33}$$

Taking union over $l \leq k$ yields $\bigcup_{l\leq k} B_l(v) \subset \bigcup_{l\leq k}\bigcup_{s\leq l} B_s(u) \cup \mathcal{B}_u = \bigcup_{l\leq k} B_l(u) \cup \mathcal{B}_u$, and taking $v = p_2$ we get the second statement above. □

As we will show next, the ordering of basins for the open loop systems implies that the boundaries of their intersections B^*_{2k+1} have a particularly simple form. We will use these to check the positive invariance of the sets B^*_{2k+1} in the closed loop system, which is the key step in the proof of Theorem 2.7.

Proposition 5.5 *For each $k = 0, \ldots, L$, the boundary of B^*_{2k+1} satisfies*

$$\partial B^*_{2k+1} \subset W_{2k+2}(p_2) \cup W_{2k}(p_1) \cup \mathcal{B}_{p_1} \cup \mathcal{B}_{p_2}.$$

Proof. We write

$$B_{2k+1}(u) = \left(\bigcup_{l\geq 2k+1} B_l(u)\right) \cap \left(\bigcup_{l\leq 2k+1} B_l(u)\right). \tag{34}$$

From the definition of B_{2k+1} and using (34) we get

$$\begin{aligned} B^*_{2k+1} &= \bigcap_{u\in[p_1,p_2]} B_{2k+1}(u) \\ &= \bigcap_{u\in[p_1,p_2]} \left((\bigcup_{l\geq 2k+1} B_l(u)) \cap (\bigcup_{l\leq 2k+1} B_l(u)) \right) \\ &= \left(\bigcap_{u\in[p_1,p_2]} \bigcup_{l\geq 2k+1} B_l(u)\right) \cap \left(\bigcap_{u\in[p_1,p_2]} \bigcup_{l\leq 2k+1} B_l(u)\right). \end{aligned}$$

We will show that

$$\bigcup_{l\geq 2k+1} B_l(p_1) = \bigcap_{u\in[p_1,p_2]} \bigcup_{l\geq 2k+1} B_l(u), \text{ and } \bigcup_{l\leq 2k+1} B_l(p_2) = \bigcap_{u\in[p_1,p_2]} \bigcup_{l\leq 2k+1} B_l(u). \tag{35}$$

The one inclusion follows from Lemma 5.4

$$\bigcup_{l\geq 2k+1} B_l(p_1) \subset \bigcap_{u\in[p_1,p_2]} \bigcup_{l\geq 2k+1} B_l(u), \quad \bigcup_{l\leq 2k+1} B_l(p_2) \subset \bigcap_{u\in[p_1,p_2]} \bigcup_{l\leq 2k+1} B_l(u). \tag{36}$$

The opposite inclusions follow from the fact that the set on the left side of each of the expressions in (36) is one of the intersected sets on the right side of these expressions. Therefore we proved (35) and thus

$$B^*_{2k+1} = \left(\bigcup_{l\geq 2k+1} B_l(p_1)\right) \cap \left(\bigcup_{l\leq 2k+1} B_l(p_2)\right). \tag{37}$$

We can write the right hand side in (37) as

$$B_{2k+1}(p_1) \cap B_{2k+1}(p_2) \cup \bigcup_{s>r} \left(B_s(p_1) \cap B_r(p_2)\right).$$

Taking $u = p_1$ and $v = p_2$ in Lemma 5.3 we get that $B_s(p_1) \cap B_r(p_2) = \emptyset$ if $s > r$. Therefore

$$B^*_{2k+1} = B_{2k+1}(p_1) \cap B_{2k+1}(p_2).$$

We will use this expression to find the boundary of B^*_{2k+1}. Observe that

$$\begin{aligned}\partial B^*_{2k+1} &= \partial(B_{2k+1}(p_1) \cap B_{2k+1}(p_2)) \\ &\subset \partial(B_{2k+1}(p_1)) \cup \partial(B_{2k+1}(p_2)) \\ &= W_{2k}(p_1) \cup W_{2k+2}(p_1) \cup W_{2k}(p_2) \cup W_{2k+2}(p_2), \end{aligned} \tag{38}$$

where we used Lemma 5.2 in the last line. We wish to further simplify the right hand side of (38). Since $W_{2k}(p_2) \subset cl(B_{2k-1}(p_2))$, it follows from (33) with $v = p_2$, $u = p_1$ and $l = 2k-1$ that

$$W_{2k}(p_2) \subset cl(\bigcup_{s \leq 2k-1} B_s(p_1)) \cup \mathcal{B}_{p_1},$$

where we used that by ([24], Theorem 4.3), $\mathcal{B}_{p_1}$ is closed. Now we select some $x \in W_{2k}(p_2)$ and consider two complementary cases: either $x \in \text{int}\left(\bigcup_{s\leq 2k-1} B_s(p_1)\right)$ or $x \in \partial\left(\bigcup_{s\leq 2k-1} B_s(p_1)\right)$.

I. Assume first that $x \in \text{int}\left(\bigcup_{s\leq 2k-1} B_s(p_1)\right)$. Then there is a neighborhood $N(x)$ such that $N(x) \subset \bigcup_{s\leq 2k-1} B_s(p_1)$. Since $B_{2k+1}(p_1) \cap \bigcup_{s\leq 2k-1} B_s(p_1) = \emptyset$ and these sets are both open, $x \notin \partial B_{2k+1}(p_1)$.

II. Consider now the case when $x \in \partial\left(\bigcup_{s\leq 2k-1} B_s(p_1)\right)$. Recall that

$$\bigcup_{s\leq 2k-1} B_s(p_1) \quad = \quad B_1(p_1) \cup B_2(p_1) \cup \ldots \cup B_{2k-1}(p_1)$$

Since all these sets are disjoint

$$\text{cl}(\bigcup_{s\leq 2k-1} B_s(p_1)) = \text{cl}(B_1(p_1)) \cup \text{cl}(B_2(p_1)) \cup \ldots \cup \text{cl}(B_{2k-1}(p_1)).$$

By Lemma 5.2 and Definition 31 $\text{cl}(B_{2k-1}) \cap \text{cl}(B_{2k+1}) = W_{2k} \subset B_{2k} \cup \mathcal{B}_{p_1}$. Since B_{2k} is closed we have

$$\begin{aligned}\text{cl}(B_{2k-1}) \cup \text{cl}(B_{2k+1}) &= B_{2k-1} \cup B_{2k+1} \cup \partial B_{2k-1} \cup \partial B_{2k+1} \\ &= B_{2k-1} \cup B_{2k+1} \cup W_{2k-2} \cup W_{2k} \cup W_{2k+2} \\ &\subset B_{2k-1} \cup B_{2k+1} \cup B_{2k} \cup W_{2k-2} \cup W_{2k+2} \cup \mathcal{B}_{p_1}.\end{aligned}$$

Therefore $\text{cl}(\bigcup_{s\leq 2k-1} B_s(p_1)) \subset \left(\bigcup_{s\leq 2k-1} B_s(p_1)\right) \cup W_{2k}(p_1) \cup \mathcal{B}_{p_1}$, and thus

$$\partial\left(\bigcup_{s\leq 2k-1} B_s(p_1)\right) \subset W_{2k}(p_1) \cup \mathcal{B}_{p_1}.$$

We conclude that if $x \in \partial\left(\bigcup_{s\leq 2k-1} B_s(p_1)\right)$ then $x \in W_{2k}(p_1)$ or $x \in \mathcal{B}_{p_1}$.

We now put **I.** and **II.** together. We have shown that if $x \in W_{2k}(p_2) \cap cl(\bigcup_{s\leq 2k-1} B_s(p_1))$ then either $x \notin \partial B_{2k+1}(p_1)$ or $x \in W_{2k}(p_1) \cup \mathcal{B}_{p_1}$. Therefore if $x \in W_{2k}(p_2) \cap \partial B_{2k+1}(p_1)$, then $x \in W_{2k}(p_1) \cup \mathcal{B}_{p_1}$. Therefore

$$W_{2k}(p_2) \cap \partial B_{2k+1}(p_1) \subset W_{2k}(p_1) \cup \mathcal{B}_{p_1}.$$

Similar argument shows that if $x \in W_{2k+2}(p_1) \cap \partial B_{2k+1}(p_2) \cup \mathcal{B}_{p_2}$, then $x \in W^s_{2k+2}(p_2)$ and therefore

$$W_{2k+2}(p_1) \cap \partial B_{2k+1}(p_2) \subset W_{2k+2}(p_2) \cup (\mathcal{B}_{p_2} \cap \partial B_{2k+1}(p_2)) \subset W_{2k+2}(p_2) \cup \mathcal{B}_{p_2}.$$

These two facts imply that (38) can be rewritten $\partial B^*_{2k+1} \subset W_{2k}(p_1) \cup W_{2k+2}(p_2) \cup \mathcal{B}_{p_1} \cup \mathcal{B}_{p_2}$. □

The following is the key result in this section, where we show the positive invariance of the sets B^*_{2k+1} in the closed loop system.

Theorem 5.6 *Assume the standing assumptions and the existence of a Morse decomposition for the monotone open loop system (1). Then for all $k = 0, \dots, L$ the set B^*_{2k+1} is positively invariant under the closed loop flow (2).*

Proof. In the proof of this Theorem we will distinguish between the flow $\phi(t, x_0)$ of the closed loop system (2) and the flow of the open loop $\varphi(t, x_0, u(t))$. Note that we can always represent the flow $\phi(t, x_0)$ as $\varphi(t, x_0, u(t))$ with $u(t)$ defined by $u(t) = g(h(\phi(t, x_0)))$.

We now take $x \in B^*_{2k+1}$ and assume there is a $T > 0$ such that $\phi(x, T) \in \partial B^*_{2k+1}$. By Lemma 5.5 either

$$\phi(T, x) \in W_{2k+2}(p_2) \cup \mathcal{B}_{p_2} \qquad \text{or} \qquad \phi(T, x) \in W_{2k}(p_1) \cup \mathcal{B}_{p_1}.$$

In order to simplify the notation we set $x(T) := \phi(T, x)$. Assume the first case and consider the flow $\phi(t, x(T))$ in the open flow form $\varphi(t, x(T), u(t))$. Since $u(t) \le p_2$ for all t, we have

$$\varphi(t, x(T), u(t)) \prec \varphi(t, x(T), p_2) \qquad \text{for all } t \tag{39}$$

By Lemma 5.2 $\varphi(t, x(T), p_2)$ either converges to $M_{2k}(p_2)$ or belongs to $\mathcal{B}_{p_2}$. In either case we have $\varphi(t, x(T), p_2) \not\subset \bigcup_{l>2k+1} B_l(p_2)$. Therefore by monotonicity

$$\phi(t, x(T)) = \varphi(t, x(T), u(t)) \in \bigcup_{l \le 2k+1} B_l(p_2) \cup \mathcal{B}_{p_2} \text{ for all } t \ge 0. \tag{40}$$

On the other hand if $\phi(x(T), t) \in W_{2k}(p_1) \cup \mathcal{B}_{p_1}$ we again write $\phi(t, x(T)) = \varphi(t, x(T), u(t))$ for the appropriate $u(t)$. Since $u(t) \ge p_1$ for all t we have

$$\varphi(t, x(T), u(t)) \succ \varphi(t, x(T), p_1) \qquad \text{for all } t \ge 0. \tag{41}$$

Again by Lemma 5.2 $\varphi(t, x(T), p_1) \not\subset \bigcup_{l<2k+1} B_l(p_1)$ and therefore

$$\varphi(t, x(T), u(t)) \in \bigcup_{l \ge 2k+1} B_l(p_1) \cup \mathcal{B}_{p_1}. \tag{42}$$

Combining (40) and (42) we see that an arbitrary trajectory $\varphi(t, x, u(t))$ starting at $x \in B^*_{2k+1}$ has to stay in the intersection

$$\varphi(t, x, u(t)) \subset \left(\bigcup_{l \ge 2k+1} B_l(p_1) \cup \mathcal{B}_{p_1} \right) \cap \left(\bigcup_{l \le 2k+1} B_l(p_2) \cup \mathcal{B}_{p_2} \right).$$

The latter set (see (37)) is

$$B^*_{2k+1} \cup \left(\bigcup_{l \le 2k+1} B_l(p_2) \cap \mathcal{B}_{p_1} \right) \cup \left(\bigcup_{l \le 2k+1} B_l(p_1) \cap \mathcal{B}_{p_2} \right) \cup (\mathcal{B}_{p_2} \cap \mathcal{B}_{p_1}). \tag{43}$$

We now note that $B^*_{2k+1} \cap (\mathcal{B}_{p_1} \cup \mathcal{B}_{p_2}) = \emptyset$. Indeed, $B^*_{2k+1} \subset B_{2k+1}(p_1)$ which is disjoint from $\mathcal{B}_{p_1}$. A similar argument applies to $\mathcal{B}_{p_2}$, proving the assertion. This implies that in (43) $\varphi(t, x_0, u(t))$ is either a subset of B^*_{2k+1} for all t, or a subset of the latter three sets for all t.

Since $x_0 \in B^*_{2k+1}$ it must be that

$$\varphi(t, x, u(t)) \in B^*_{2k+1} \quad \text{ for all } t.$$

□

Proof of Theorem 2.7. Recall that each Morse set $M^*_{2i+1}, i = 1, \dots, L$ is defined as the maximal invariant set in $B^*_{2i+1} := \bigcap_{u \in [p_1, p_2]} B_{2i+1}(u)$ and M^*_0 is the maximal invariant set in $\mathcal{X} \setminus \bigcup_{i=0,\dots,L} B^*_{2i+1}$. Then by Theorem 2.4 all the ω-limit set of arbitrary initial conditions $\xi \in \mathcal{X}$ lies in one of the set sets M^*_0 or M^*_{2i+1}, $i = 0, \dots, L$.

We now show that B^*_{2i+1} is open for all $i = 0, \ldots, L$. Since the solutions of the system (1) depend continuously on the parameter u, the open sets $B_{2i+1}(u)$ vary continuously with u. Therefore for each $x \in B_{2i+1}(u)$ there is an open neighborhood $U_{2i+1}(u)$ of x such that $U_{2i+1}(u) \subset B_{2i+1}(v)$ for all $v \in N(u)$, a neighborhood of u. Since $[p_1, p_2]$ is compact it admits a finite cover by neighborhoods $N(u_1), \ldots, N(u_k)$. Hence the set $\bigcap_{j=1}^k U_{2i+1}(u_j)$ is an open neighborhood of x in B^*_{2i+1}.

Since the Morse sets $M^*_{2i+1}, i = 1, \ldots, L$ lie in an open positively invariant set B^*_{2i+1}, there cannot be any solution with $\alpha(x) \subset M^*_{2i+1}$ and $\omega(x) \subset M^*_0$. This proves the existence of the order advertised in the Theorem.

6 Convergence inside the Morse sets

In this section we show that our theory can be applied iteratively. If the restriction of the input-output characteristic $u \to M_{2l+1}(u)$ for $u \in [p_1, p_2]$ is multi-valued (see Example 11) then we can apply the Theorem 2.4 and the Theorem 2.7 to this characteristic. If, on the other hand, the restriction of the input-output characteristic $u \to M_{2l+1}(u)$ for $u \in [p_1, p_2]$ is single valued, then, as we will show next, we can apply the standard theory of single valued characteristics. Note that the assumption that $u \to M_{2l+1}(u)$ for $u \in [p_1, p_2]$ is single valued is equivalent to the assumption that $M_{2l+1}(u) = e_{2l+1}(u)$ is a unique equilibrium for all $u \in [p_1, p_2]$. We have the following definition.

Definition 6.1 Let $k_{x,2l+1} : [p_1, p_2] \to X$ be the $2l+1$-th branch of the I/S characteristic k_x defined by $k_{x,2l+1}(u) = e_{2l+1}(u)$. Let k_{2l+1} be the corresponding $2l+1$-th branch of the I/O characteristic $k : [p_1, p_2] \to \mathbb{R}$ defined by $k(u) = h(e_{2l+1}(u))$. Notice that the requirement that the domain of these maps is an entire interval $[p_1, p_2]$ is essential. If $u \to M_{2l+1}(u)$ for $u \in [p_1, p_2]$ is single valued for some l then $k_{x,2l+1}$ and k_{2l+1} are well defined. We will call them *single-valued branches* of the multi-valued characteristic and l a *single-valued index.*

Lemma 6.2 *Let l be a single valued index and let $\xi \in B^*_{2l+1}$. Let $\varphi(t, \xi, u(t))$ be a solution starting at ξ with an arbitrary input $u(t)$ in the open loop system (1). Let $y^- := \liminf_{t\to\infty} y(t) = h(x(t))$, $y^+ := \limsup_{t\to\infty} y(t) = h(x(t))$, $u^- := \liminf_{t\to\infty} u(t)$, and $u^+ := \limsup_{t\to\infty} u(t)$. Then*

$$[y^-, y^+] \subset [k^2_{2l+1}(y^-), [k^2_{2l+1} y^+)].$$

Proof. Observe that since B^*_{2l+1} is positively invariant by Theorem 5.6 the solution $\varphi(t, \xi, u(t))$ exists for all $t \geq 0$ and $u^-, u^+ \subset [p_1, p_2]$. Further, by the assumption on l the restriction of the input-state characteristics to the set B^*_{2l+1} is the branch $k_{x,2l+1}$

$$k_x([p_1, p_2]) \cap B^*_{2l+1} = k_{x,2l+1}.$$

The remainder of proof is completely analogous to the proof of Lemma 4.12 were we use $k_{x,2l+1}$ instead of k_x and k_{2l+1} instead of k. We will indicate the main steps in the proof.

One first shows that

$$k_{x,2l+1}(u^-) \preceq \liminf \varphi(t, \xi, u(t)) \preceq \limsup \varphi(t, \xi, u(t)) \preceq k_{x,2l+1}(u^+) \tag{44}$$

and then applying h we get

$$h(k_{x,2l+1}(u^-)) \leq \limsup y(t) \leq \liminf y(t) \leq h(k_{x,2l+1}(u^+)). \tag{45}$$

As in Lemma 4.12 this implies for the positive feedback system with $u(t) = y(t)$ that

$$k_{2l+1}(y^-) \preceq \liminf y(t) \preceq \limsup y(t) \preceq k_{2l+1}(y^+).$$

In other words,

$$[y^-, y^+] \subset [k_{2l+1}(y^-), k_{2l+1}(y^+)]. \tag{46}$$

If we apply the argument one more time starting with equation (23) and with $u^- = k_{2l+1}(y^-)$ and $u^+ = k_{2l+1}(y^+)$ we get

$$[k_{2l+1}(y^-), k_{2l+1}(y^+)] \subset [k^2_{2l+1}(y^-), k^2_{2l+1}(y^+)].$$

This, together with (46) proves the Lemma for the positive feedback case.

For the negative feedback $u = -y$ equation (45) can be written as

$$[y^-, y^+] \subset [k_{2l+1}(y^+), k_{2l+1}(y^-)]. \quad (47)$$

We now repeat the above argument with $u^- = k_{2l+1}(y^+)$ and $u^+ = k_{2l+1}(y^-)$ and get

$$[k_{2l+1}(y^+), k_{2l+1}(y^-)] \subset [k^2_{2l+1}(y^-), k^2_{2l+1}(y^+)]. \quad (48)$$

Equations (47) and (48) imply the result for the negative feedback. □

Lemma 6.3 *The input-output characteristic k maps the interval $[p_1, p_2]$ into itself $k : [p_1, p_2] \to [p_1, p_2]$. Therefore the graph of every single valued branch k_{2l+1} intersects the diagonal in $[p_1, p_2] \times [p_1, p_2]$.*

Proof. By Corollary 4.4 for the negative feedback system both $K_{min}(u)$ and $K_{max}(u)$ are non-increasing functions of u. Therefore the graph of the input-output characteristic k satisfies $K_{min}(p_2) \leq k(u) \leq K_{max}(p_1)$ for all $u \in [p_1, p_2]$. By Lemma 4.9 $K_{max}(p_1) = p_2$ and $K_{min}(p_2) = p_1$ and hence the graph satisfies $p_1 \leq k(u) \leq p_2$.

By Corollary 4.4 for the positive feedback system functions $K_{min}(u)$ and $K_{max}(u)$ are non-decreasing functions of u and thus the graph of k satisfies $K_{min}(p_1) \leq k(u) \leq K_{max}(p_2)$ for all $u \in [p_1, p_2]$. By Lemma 4.8 $K_{min}(p_1) = B(p_1) = p_1$ and $K_{max}(p_2) = T(p_2) = p_2$ and thus again the graph of k satisfies $p_1 \leq k(u) \leq p_2$. Therefore for both the negative and positive feedback systems $k([p_1, p_2]) \subset [p_1, p_2]$.

Since each single valued branch k_{2l+1} is defined for all $u \in [p_1, p_2]$ the second result follows from the continuity of k_{2l+1}. □

Lemma 6.3 implies that the following is well defined.

Definition 6.4 For each single-valued index l let e^*_{2l+1} be an intersection of the branch k_{2l+1} and the line $y = u$. Let $E_{2l+1} := k_{x,2l+1}(e^*_{2l+1})$ be the corresponding equilibrium of the closed loop system in the state space.

Proof of Theorem 2.10.

The first two results follow directly from the invariance (Theorem 5.6) of the B^*_{2l+1} under the closed loop system (2) and the original papers [2, 4].

The second statement is a special case of the results [2, 4] which applies to both positive and negative feedback systems. Take $\xi \in B^*_{2l+1}$ and let $\varphi(t, \xi, u(t))$ be a solution starting at ξ with arbitrary $u(t)$. Let y^-, y^+, u^- and u^+ be defined as in Lemma 6.2. Then by that Lemma $[y^-, y^+] \subset [k^2_{2l+1}(y^-), k^2_{2l+1}(y^+)]$.

Since $u(t) = \pm y(t)$ this implies that $u(t) \subset [k^2_{2l+1}(y^-), k^2_{2l+1}(y^+)]$ for all $t \geq 0$. We apply Lemma 6.2 to $u^- := k^2_{2l+1}(y^-)$ and $u^+ := k^2_{2l+1}(y^+)$ to get

$$[y^-, y^+] \subset [k^4_{2l+1}(y^-), k^4_{2l+1}(y^+)].$$

By induction it follows that

$$[y^-, y^+] \subset [k^{2n}_{2l+1}(y^-), k^{2n}_{2l+1}(y^+)] \quad (49)$$

for all n.

By assumption $k^{2n}_{2l+1}(u) \to e^*_{2l+1}$ for all $u \in [p_1, p_2]$ and since $u = \pm y$, then $k^{2n}_{2l+1}(y^-) \to e^*_{2l+1}$ and $k^{2n}_{2l+1}(y^+) \to e^*_{2l+1}$ as well. By (49) $y^- = y^+ = e^*_{2l+1}$ and thus $u^- = u^+ = e^*_{2l+1}$. Therefore $u(t)$ converges to e^*_{2l+1}. The Converging inputs-Converging state Theorem 1 of [25] implies

$$\lim_{t\to\infty} \varphi(t, \xi, u(t)) \to E_{2l+1}.$$

□

7 Conclusions

Monotone input-output systems have proved to be a successful paradigm in analyzing complex models of biochemical regulatory networks. Starting with a (closed loop) system of equations with nonlinearities monotone in each of their arguments, we first identify the negative feedback connections. We then replace these connections by a set of constant inputs and study the dynamics of the open loop system parameterized by this set of inputs. This approach has two potential advantages. First, the open loop system is often simpler to analyze and, second, since we replaced all negative feedback connections, the open loop system is monotone. The monotone systems have relatively simple dynamics - almost all solutions converge to the set of equilibria. To realize these potential advantages we must have a theory that links the dynamics of the original closed loop system with the properties of the open loop system.

If we radically simplify the situation further and assume that for every fixed set of inputs almost all solutions converge to a unique equilibrium then one can define an *input-output* characteristic for the open loop system. The properties of the characteristic, considered as a map from the space of inputs to itself, are closely related to the global convergence to equilibria for the original closed loop system.

In this paper we broaden the link between the dynamics of the open and closed loop systems. We only assume finiteness and a very general structure of the set of equilibria in the single-input, single-output system. We allow coexistence of multiple equilibria in the open loop system which results in a multi-valued characteristic. We have shown how such multi-valued function constrains the dynamics of the closed loop system. First, the multi-valued characteristic determines an interval $[p_1, p_2]$ of inputs, which bounds the projection into the input variables of the generic set of closed loop solutions. The interplay between $[p_1, p_2]$ and the interval where the characteristic is multi-valued is key to the overall dynamics of the closed loop system. One way to express this dependence and describe the global dynamics is through the notion of the Morse decomposition. We show that if the open loop system admits a Morse decomposition over $[p_1, p_2]$, there is a Morse decomposition of the closed loop system, which is valid for a generic set of solutions. In other words, if a branch of the characteristic continues across $[p_1, p_2]$, then it is a Morse set in a Morse decomposition and there is a corresponding non-empty Morse set for the closed loop system. In fact, we show that the previous results on single-valued input-output characteristic are directly applicable to single valued branches of the multi-valued characteristic and can be used to determine the character of this Morse set. On the other hand, if a branch does not continue across $[p_1, p_2]$ it has to be combined with other branches to form a Morse set of the open loop system. Again, once such a collection of branches does cross $[p_1, p_2]$, it forms a Morse set of the open loop system and there is a corresponding non-empty Morse set for the closed loop system. We show on an example that such a set can be a periodic orbit.

We apply our theory to a model of the cell cycle. We investigate how the strength of the negative feedback loop affects the existence of the periodic orbit. Not surprisingly, if we weaken the negative feedback loop the periodic orbit disappears and we show that almost all solutions converge to a stable equilibrium. On the other hand, if we change the cooperativity constants in the negative feedback loop, we can find a bistable regime, where solutions converge to one of two different stable equilibria. Our approach provides an alternative to a bifurcation analysis by Tyson and collaborators [27, 20]. While our approach relies on numerically computed input-output characteristic, it can provide proofs of convergence for (almost) all initial conditions.

References

[1] D. Angeli and E.D. Sontag, Monotone control systems, *IEEE Trans. Automatic Control*, vol. 48, No. 10, pp. 1684-1698, (2003)

[2] D. Angeli and E.D. Sontag, Multi-stability in monotone input/output systems, *Systems & Control Letters* **51**, 185-202, (2004).

[3] D. Angeli, J.E. Ferrell Jr. and E. Sontag, Detection of multi-stability, bifurcations, and hysteresis in a large class of biological positive-feedback systems, *Proc. Natl. Acad. Sci.* vol. 101, no. 7, 1822-1827, (2004).

[4] D. Angeli, P. De Leenheer and E.D. Sontag, A small-gain theorem for almost global convergence of monotone systems, *Systems and Control Letters* **52**, 407–414, (2004).

[5] E. Boczko, T.G. Cooper, T. Gedeon, K. Mischaikow, D. Murdock, S. Pratap and S. Wells, Structure theorems and the dynamics of nitrogen catabolite repression in yeast, *Proc. Natl. Acad. Sci.* **102**, 5647-5652, (2005).

[6] C. Conley, *Isolated invariant sets and the Morse index*, CBMS reg. conf. ser. on Mathematics No. 38, AMS Providence 1978.

[7] P. DeLenheer and M. Malisoff, A small gain Theorem for monotone systems with multi-valued input-state characteristics, *IEEE Transactions on Automatic Control* 41 (2), pp 287-292, 2006.

[8] G. Enciso and E.D. Sontag, Monotone systems under positive feedback: Multi-stability and a reduction theorem, *Systems and Control Letters* **54** 159–168, (2005).

[9] G. Enciso and E.D. Sontag, Global attractivity, I/O monotone small-gain theorems, and biological delay systems, *Discrete Contin. Dyn. Syst.*, 14(3):549-578, 2006.

[10] G. Enciso, H.L. Smith and E.D. Sontag, Non-monotone systems decomposable into monotone systems with negative feedback, *J. Diff. Equations*, 224:205-227, 2006.

[11] T. Gedeon, Negative and positive feedback loops in cell cycle engine, in preparation 2008.

[12] T. Gedeon, K. Mischaikow, K. Patterson and E. Traldi, When activators repress and repressors activate: a qualitative analysis of Shea-Ackers model, *Bull. Math. Biol.* in press (2008).

[13] T. Gedeon and E. Sontag, Oscillations in multi-stable monotone systems with slowly varying feedback, *J. Diff. Eq.*,239:2, p. 273-295,(2007).

[14] J. Hale, *Ordinary Differential Equations*, John Wiley & Sons Inc., 2nd edition, 1980.

[15] C.K.R.T. Jones, *A geometric approach to applied dynamics and differential equations*, Lecture Notes 1996.

[16] S. Lefchetz, *Differential Equations: Geometric Theory*, Dover 1977.

[17] J. Mallet-Paret and H. Smith, The Poincaré-Bendixson theorem for monotone feedback systems, *J. Dynam. Differential Equations* **2** (1990), 367-421.

[18] J. Mallet-Paret and G. Sell, The Poincaré-Bendixson theorem for monotone cyclic feedback systems with delay, *J. Differential Equations* 125 (1996), no. 2, 441–489.

[19] R. Milo, S. Shen-Orr, S. Itzkovitz, N. Kashtan, D. Chklovskii and U. Alon, Network Motifs: Simple Building Blocks of Complex Networks *Science*, 298:824-827 (2002).

[20] B. Novak and J.J. Tyson, Numerical analysis of a comprehensive model of M-phase control in *Xenopus* oocyte extracts and intact embryos, *J. Cell Science* 106, 1153-1168, (1993).

[21] P. Nurse, Universal control mechanism regulating the onset of the M-phase, *Nature* 344, 503-508, (1990).

[22] J. R. Pomering, E. D. Sontag and J.E. Ferrell Jr., Building a cell cycle oscillator: hysteresis and bistability in the activation of Cdc2, *Nature Cell Biology* 5, 346-351 (2003).

[23] J. R. Pomering, Sun Young Kim and J.E. Ferrell Jr., Systems-level dissection of the cell-cycle oscillator: bypassing positive feedback produces damped oscillations, *Cell*, vol. 122, 565-578, Aug. 26 (2005).

[24] H. Smith, *Monotone Dynamical Systems*, AMS Mathematical Surveys and Monographs 41, 1995.

[25] E.D. Sontag, A Remark on the Converging-Input Converging-State Property, *IEEE Trans. Automatic Control*, vol. 48, No. 2, 313-314, (2003).

[26] E.D. Sontag, Some new directions in control theory inspired by systems biology, *IEEE Systems Biology* **1**, 9-18 (2004).

[27] J.J. Tyson, A. Csikasz-Nagy and B. Novak, The dynamics of cell cycle regulation, *BioEssays* 24:1095-1109 (2002).