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Nonmonotone systems decomposable into monotone systems with negative feedback

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Abstract

Motivated by the work of Angeli and Sontag [Monotone control systems, IEEE Trans. Automat. Control 48 (2003) 1684–1698] and Enciso and Sontag [On the global attractivity of abstract dynamical systems satisfying a small gain hypothesis, with applications to biological delay systems, Discrete Continuous Dynamical Systems, to appear] in control theory, we show that certain finite and infinite dimensional semi-dynamical systems with "negative feedback" can be decomposed into a monotone "open-loop" system with "inputs" and a decreasing "output" function. The original system is reconstituted by "plugging the output into the input". Employing a technique of Gouzé [A criterion of global convergence to equilibrium for differential systems with an application to Lotka–Volterra systems, Rapport de Recherche 894, INRIA] and Cosner [Comparison principles for systems that embed in cooperative systems, with applications to diffusive Lotka–Volterra models, Dynam. Cont., Discrete Impulsive Systems 3 (1997) 283–303] of imbedding the system into a larger symmetric monotone system, we are able to obtain information on the asymptotic behavior of solutions, including existence of positively invariant sets and global convergence.

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1. Introduction

In [1], Angeli and Sontag construct a theory of monotone control systems of the form

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

where the state space is partially ordered, the function space of controls $u = u(t)$ is partially ordered, and the output space is partially ordered. Monotonicity of this input–output system means that increasing the input control function and/or the initial conditions leads to a larger output. The property of monotonicity is preserved under cascades of such systems whereby the output of one system is the input of the next system. Angeli and Sontag say that system (2) has an input-to-state characteristic if for each constant input u, there is a steady state $x = k_x(u)$ of the system which is globally attracting; we will use this terminology simply to mean that there exists a unique steady state $x = k_x(u)$, adding the modifier "globally stable" in that case. Angeli and Sontag use the theory of monotone control systems to show that certain (uncontrolled) systems of nonlinear ordinary differential equations

$$v' = F(v), \tag{2}$$

not necessarily monotone (see [23,12]), can sometimes be decomposed into two monotone control subsystems, each with scalar inputs and scalar outputs,

$$x' = f_1(x,w), \quad y = h_1(x), \quad z' = f_2(z,y), \quad w = h_2(z), \tag{3}$$

where $v = (x, y)$. If each subsystem has globally stable input-to-state characteristics k_i, $i = 1, 2$ with certain monotonicity properties and the output functions h_i have certain monotonicity properties, then the original system is globally convergent provided that the scalar, discrete dynamical system $u_{k+1} = (K_2 \circ K_1)(u_k)$ has a globally attracting fixed point, where $K_i = h_i \circ k_i$. See [1] for further details of this result, referred to as the Small Gain Theorem. This theorem, and its extension in [8], have remarkable applications [26,2,13,14,7] to biological and chemical models. The recent work of Enciso and Sontag [8] extends the theory to abstract dynamical systems, including certain infinite dimensional systems such as delay-differential equations, and relaxes the restriction to scalar inputs and outputs. They also give a nice strategy for decomposing systems into subsystems of the required type.

Inspired by this work, we consider the input–output system (2) as a tool to study the asymptotic behavior of the closed-loop system

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

where we make the following assumptions: (1) for each fixed $u \in U \subset \mathbb{R}^m$, $x' = f(x,u)$ generates a monotone system in the usual sense [23,12], (2) $f(x,u)$ is increasing in u, relative to an order relation $\leqslant_U$, for each fixed x, and (3) h is a decreasing mapping of the state space into the input space U. These conditions will be made more precise in the following section. We stress that these conditions do not mean that (4) is a monotone system; in fact, it is not because of the negative feedback $u = h(x)$. Following Gouzé [9] and Cosner [5], we imbed (4) into the symmetric monotone system

$$
\begin{aligned}
x' &= f(x, h(y)),\\
y' &= f(y, h(x)),
\end{aligned}
\tag{5}
$$

which reduces to (4) on the invariant diagonal $x = y$. This trick allows us to obtain information, such as the existence of invariant regions and conditions for global convergence, for the dynamics of (4) without assuming that (2) has an input-to-state characteristic. In some of our results, we do assume that a characteristic $x = k_x(u)$ exists for (2) but we do not assume that $k_x(u)$ is a globally attracting equilibrium for the open-loop system (2), nor do we require conditions assuring continuity of k_x. Furthermore, our analog of a Small Gain-type theorem, which gives global convergence, requires only that the mapping $k = h \circ k_x$ has no strict, order-related, period-two points. Remarkably, the existence and uniqueness of the globally attracting equilibrium comes as a consequence of the result, not as part of the hypotheses. Our framework, using systems (2) and (4), includes (4) as a special case as follows:

$$
\begin{aligned}
x' &= f_1(x, w),\\
z' &= f_2(z, h_1(x)),\\
W &= h_2(z).
\end{aligned}
\tag{6}
$$

More precisely, the input is w, the state of the system is (x,z) and the output is W. It has the input-to-state characteristic $(x,z) = (k_1(w), (k_2 \circ h_1)(x))$ and input-to-output characteristic $K_2 \circ K_1$.

As a simple example of the kinds of results obtained, consider the classical "Goodwin Model" of a negative feedback, gene regulatory system modeled by the equations

$$
\begin{aligned}
x_1' &= g(x_n) - \alpha_1 x_1, \qquad (7)\\
x_j' &= x_{j-1} - \alpha_j x_j, \quad 2 \leqslant j \leqslant n,
\end{aligned}
$$

where $\alpha_j > 0$ and $g : \mathbb{R}_+ \to \mathbb{R}_+$ is continuously differentiable and satisfies $g(0) > 0$ and $g' < 0$. See Smith [22] for references. The open-loop system is given by

$$
\begin{aligned}
x_1' &= u - \alpha_1 x_1,\\
x_j' &= x_{j-1} - \alpha_j x_j, \quad 2 \leqslant j \leqslant n,\\
y &= h(x) := g(x_n).
\end{aligned}
$$

Let $k : [0, g(0)] \to [0, g(0)]$ be defined by

$$k(u) = g(\beta u), \quad \beta = (\alpha_1 \alpha_2 \dots \alpha_n)^{-1}.$$

It is readily seen that k has a unique fixed point $\bar{u}$. Our main result for (8) is the following, which also follows from methods developed in [26].

Proposition 1. *If k has no period-two point other than $\bar{u}$, then* (20) *has a globally attracting equilibrium. In particular, this holds if*

$$\max \left\{ -g'(u) : 0 \leqslant u \leqslant g(0) \Bigg/ \prod_{i=1}^{n} \alpha_i \right\} < \prod_{i=1}^{n} \alpha_i \ . \tag{8}$$

Sharper results are obtained in [29] in case f is of Hill type. See [16] for a more complete treatment of the dynamics of (8).

The theory extends as well to delay differential equations, to reaction–diffusion systems, and to discrete dynamical systems, although we treat the latter case elsewhere. For example, Proposition 1 holds if delayed arguments are introduced into the first terms on the right-hand side of (8) and diffusion is included. We develop the theory for ordinary differential equations, delay differential equations, and reaction–diffusion systems in the following sections.

2. Ordinary differential equations

Let $\mathbb{R}^n$ be ordered by $\leqslant$ generated by a cone K with nonempty interior. Recall that $x \leqslant y$ means $y - x \in K$. Denote by K^* the cone dual to K. If $a, b \in \mathbb{R}^n$, we let $[a, b] = \{x \in \mathbb{R}^n : a \leqslant x \leqslant b\}$ denote the order interval. It is well known that order intervals in finite dimensional spaces are bounded (see [6]). Let $X \subset \mathbb{R}^n$.

Our focus is on the asymptotic behavior of the system

$$x' = f(x, h(x)) \equiv F(x), \tag{9}$$

which we view as the closed-loop system obtained from the open-loop, input/output system

$$\begin{aligned} x' &= f(x, u), \quad u \in U, \\ y &= h(x) \end{aligned} \tag{10}$$

by identifying input and output: $y = u$.

Assume that $f : X \times U \to \mathbb{R}^n$ and $h : X \to U$ are continuous and satisfy

(a) $\forall u \in U,\ x \to f(x,u)$ is quasimonotone in the sense of condition (QM).

(b) $\forall x \in X,\ u_1 \leqslant_U u_2 \Rightarrow f(x,u_1) \leqslant f(x,u_2)$.

(c) $x_1 \leqslant x_2 \Rightarrow h(x_2) \leqslant_U h(x_1)$.

Vector field $f(x,u)$ satisfies the *quasimonotone condition* in X if for all $x, y \in X$, all $u \in U$, and $\phi \in K^*$ we have

(QM) $x \leqslant y$ and $\phi(x) = \phi(y)$ implies $\phi(f(x,u)) \leqslant \phi(f(y,u))$.

See the reviews by Hirsch and Smith [11,12]. A consequence of the quasimonotonicity assumption is that the open-loop system (11) gives rise to an order preserving, or monotone system in the sense that, with constant input, larger initial data give rise to larger states at time $t > 0$. The closed-loop system (9) does not have this property since the input is not constant. In fact, the input is a nonincreasing function of the output. In this sense, (9) is decomposable into the monotone open-loop system with negative feedback.

We assume that solutions of initial value problems for (9) are unique and write $x(t,x_0)$ for the maximally defined solution of the associated initial value problem $x(0) = x_0$. Denote by $\omega_F(A)$ the omega limit set of set $A \subset X$ in case it exists.

The closed-loop system (9) can be imbedded in the larger symmetric system

$$\begin{aligned} x' &= f(x, h(y)),\\ y' &= f(y, h(x)). \end{aligned} \tag{11}$$

We assume unique solutions of initial value problems in $X \times X$, write $z = (x, y)$ and use the notation $z(t, z_0) = (x(t), y(t))$ for the solution satisfying $z(0, z_0) = z_0$. Symmetry ensures that $(x(t), y(t))$ is a solution if and only if $(y(t), x(t))$ is a solution. By uniqueness of solutions, the diagonal

$$D = \{(x,x) : x \in X\}$$

is invariant under (11). If $z_0 = (x_0, x_0)$, then $z(t, z_0) = (x(t,x_0), x(t,x_0))$ where $x(t,x_0)$ satisfies (9) and $x(0,x_0) = x_0$.

The larger system (11) generates a monotone system on $X \times X \subset \mathbb{R}^n \times \mathbb{R}^n$ with respect to the cone $C := K \times (-K)$ as we will show below. C gives rise to the order relation

$$(x,y) \leqslant_C (\bar{x}, \bar{y}) \iff x \leqslant \bar{x} \text{ and } \bar{y} \leqslant y.$$

The dual cone C^* can be represented as $K^* \times (-K^*)$ where $(\phi, -\psi)(x,y) = \phi(x) - \psi(y)$ holds for $x, y \in \mathbb{R}^{2n}$ and $\phi, \psi \in K^*$.

Lemma 2. (11) *generates a monotone system on* $X \times X$ *with respect to* $\leqslant_C$.

Proof. We need only verify the quasimonotone condition for the vector field $G(x, y) := (f(x, h(y)), f(y, h(x)))$ relative to the cone C; see [12]. Given $(x, y) \leqslant_C (\bar{x}, \bar{y})$ and $(\lambda, -\mu) \in C^*$ with $(\lambda, -\mu)(x, y) = (\lambda, -\mu)(\bar{x}, \bar{y})$, we must verify that

$$(\lambda, -\mu)G(x, y) \leqslant (\lambda, -\mu)G(\bar{x}, \bar{y}). \tag{12}$$

Now, $(\lambda, -\mu)(x, y)=(\lambda, -\mu)(\bar{x}, \bar{y})$ and $\lambda, \mu \in K^*$ imply that $0 \leqslant \lambda(\bar{x}-x)=\mu(\bar{y} - y) \leqslant 0$ so $\lambda(\bar{x}) = \lambda(x)$ and $\mu(\bar{y}) = \mu(y)$. As $x \leqslant \bar{x}$ and $\bar{y} \leqslant y$, we have

$$\begin{aligned}
(\lambda, -\mu)G(x, y) &= \lambda(f(x, h(y))) - \mu(f(y, h(x))) \\
&\leqslant \lambda(f(x, h(\bar{y}))) - \mu(f(y, h(\bar{x}))) \\
&\leqslant \lambda(f(\bar{x}, h(\bar{y}))) - \mu(f(\bar{y}, h(\bar{x}))) = (\lambda, -\mu)G(\bar{x}, \bar{y}).
\end{aligned}$$

where the second line follows from monotonicity of f and h and the third line follows from the quasimonotonicity assumption (QM) for f. □

Lemma 2 may also be proved by appealing to the theory of monotone input/output systems [1]: the composition of monotone input/output systems is monotone.

We now return to the closed-loop system (9). In the following, we give conditions on the open-loop system that have important implications for the asymptotic behavior of the closed-loop system.

Proposition 3. *Let* $u_0, v_0 \in U$ *satisfy* $u_0 \leqslant_U v_0$ *and suppose there exist* x_0, y_0 *satisfying* $x_0 \leqslant y_0$, $f(y_0, v_0) \leqslant 0 \leqslant f(x_0, u_0)$ *with* $[x_0, y_0] \subset X$ *and*

$$u_0 \leqslant_U h(y_0) \leqslant_U h(x_0) \leqslant_U v_0. \tag{13}$$

Then $[x_0, y_0]$ *is positively invariant for* (9). *There exist* $x_*, y_* \in [x_0, y_0]$ *with* $x_* \leqslant y_*$ *such that* $\omega_F([x_0, y_0]) \neq \emptyset$ *is compact, invariant and*

$$\omega_F([x_0, y_0]) \subset [x_*, y_*]. \tag{14}$$

Moreover, $f(x_*, h(y_*)) = 0 = f(y_*, h(x_*))$.

Proof. Inequality $x_0 \leqslant y_0$ implies that $(x_0, y_0) \leqslant_C (y_0, x_0)$. Define the C-order interval

$$I := \{(x, y) : (x_0, y_0) \leqslant_C (x, y) \leqslant_C (y_0, x_0)\} = \{(x, y) : x_0 \leqslant x, y \leqslant y_0\}$$

and observe that

$$I \cap D = \{(x, x) : x \in [x_0, y_0]\}.$$

Using (13), we have

$$f(x_0, h(y_0)) \geqslant f(x_0, u_0) \geqslant 0$$

and

$$f(y_0, h(x_0)) \leqslant f(y_0, v_0) \leqslant 0.$$

This implies that

$$(f(y_0, h(x_0)), f(x_0, h(y_0))) \leqslant_C (0, 0) \leqslant_C (f(x_0, h(y_0)), f(y_0, h(x_0))),$$

which, together with quasimonotonicity of G, imply that the order interval I is positively invariant for (11) (see [12, Section 3, Proposition 3.3]). Moreover, because of monotonicity of (11) and $(x_0, y_0) \leqslant_C \bar{z} \leqslant_C (y_0, x_0)$ if $\bar{z} \in I$, we have

$$(x_0, y_0) \leqslant_C z(t, (x_0, y_0)) \leqslant_C z(t, \bar{z}) \leqslant_C z(t, (y_0, x_0)) \leqslant_C (y_0, x_0)$$

for all $t \geqslant 0$ and for all $\bar{z} \in I$. Furthermore, $z(t, (x_0, y_0)) \nearrow (x_*, y_*)$ and $z(t, (y_0, x_0)) \searrow (y_*, x_*)$, where the monotonicity implied by the inclination of the arrows is relative to $\leqslant_C$, and $(x_*, y_*), (y_*, x_*)$ are equilibria of (11). See Fig. 1. Put $\bar{z} = (\bar{x}, \bar{x})$ where $\bar{x} \in [x_0, y_0]$, write $z(t, (x_0, y_0)) = (x(t, x_0, y_0), y(t, x_0, y_0))$ so $z(t, (y_0, x_0)) = (y(t, x_0, y_0), x(t, x_0, y_0))$, to obtain

$$\begin{aligned}(x_0, y_0) &\leqslant_C (x(t, x_0, y_0), y(t, x_0, y_0)) \leqslant_C (x(t, \bar{x}), x(t, \bar{x})) \\ &\leqslant_C (y(t, x_0, y_0), x(t, x_0, y_0)) \leqslant_C (y_0, x_0)\end{aligned}$$

or, on taking the first components,

$$x_0 \leqslant x(t, x_0, y_0) \leqslant x(t, \bar{x}) \leqslant y(t, x_0, y_0) \leqslant y_0,$$

where $x(t, x_0, y_0) \nearrow x_*$ and $y(t, x_0, y_0) \searrow y_*$ relative to $\leqslant$. This implies the positive invariance of $[x_0, y_0]$ for (9) and the remaining assertions. □

Remark 4. Proposition 3 could be stated more concisely by replacing the assumptions concerning x_0, y_0, u_0, v_0 including (13) by the existence of $x_0 \leqslant y_0$ such that $f(y_0, h(x_0)) \leqslant 0 \leqslant f(x_0, h(y_0))$. This amounts to taking $u_0 = h(y_0)$ and $v_0 = h(x_0)$. However in applications, it may be easier to identify x_0, y_0, u_0, v_0 satisfying the hypotheses of Proposition 3 than to determine such x_0, y_0.

We observe that the positive invariance of $[x_0, y_0]$ for (9) asserted in Proposition 3 implies the existence of an equilibrium for (9) in $[x_*, y_*]$. See e.g. Hale [10, Chapter 1, Theorem 8.2].

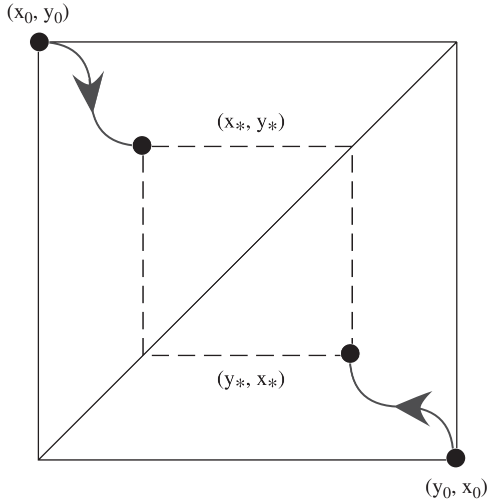

Fig. 1. Converging orbits $z(t,(x_0,y_0))\nearrow(x_*,y_*)$ and $z(t,(y_0,x_0))\searrow(y_*,x_*)$ and their limits; $\omega_F([x_0,y_0])$ belongs to the dashed box.

An immediate consequence of the final assertion of Proposition 3 is the following result.

Corollary 5. *Let the hypotheses of Proposition* 3 *hold and suppose that*

$$a, b \in [x_0, y_0], \quad a \leqslant b, \quad f(a, h(b)) = 0 = f(b, h(a)) \Rightarrow a = b \tag{15}$$

holds. Then $x_* = y_*$, $F(x_*) = 0$ *and*

$$\omega_F([x_0, y_0]) = \{x_*\}.$$

Symmetry dictates that equilibria of (11) come in pairs (a, b) and (b, a); if $a = b$, we say the equilibrium is symmetric. Since $a \leqslant b$ if and only if $(a, b) \leqslant_C (b, a)$, hypothesis (15) just says that (11) does not have a C-ordered, nonsymmetric pair $(a, b), (b, a)$ of equilibria in the order interval $I := [(x_0, y_0), (y_0, x_0)]_C$.

Remark 6. Hypothesis (13) is key: we require that corresponding to two ordered inputs u_0, v_0 there are corresponding ordered sub- and super-equilibria x_0, y_0 of (11) with the restriction that the corresponding outputs $h(x_0), h(y_0)$ should fall between the given inputs. This requirement is trivially satisfied in case that $U = [u_0, v_0]_U = \{u \in \mathbb{R}^m : u_0 \leqslant_U u \leqslant_U v_0\}$ since $h(X) \subset U$ and h is decreasing.

The open-loop system is said to have an input-to-state characteristic if to each $u \in U$, $f(x,u) = 0$ has a unique solution $x := k_x(u) \in X$. In that case, $k : U \to U$ defined by $k(u) = h(k_x(u))$ is called the input-to-output characteristic.

Corollary 7. *Suppose that* $U = [u_0, \infty) := \{u \in \mathbb{R}^m : u_0 \leqslant_U u\}$ *and that* (11) *has an input-to-state characteristic* k_x *satisfying* $k_x(u_0) \leqslant k_x(u)$ *for* $u \geqslant u_0$, *and* $X_0 := \cup_{u \geqslant u_0} [k_x(u_0), k_x(u)] \subset X$. *If the input-to-output characteristic* $k : U \to U$ *has no pair* $u, v \in U$, $u <_U v$ *such that* $k(u) = v$, $k(v) = u$, *then* (9) *has an equilibrium* $x_* \in [k_x(u_0), k_x(h(x_0))]$ *and*

$$\omega_F(x) = x_*, \quad x \in X_0.$$

Proof. The assertion follows from Proposition 3 and Corollary 5 applied to $[u_0, v_0]_U$ for each v_0 chosen as follows: put $x_0 = k_x(u_0)$ and let v_0 satisfy $h(x_0) \leqslant_U v_0$. Recall that h is assumed to map X into U so $u_0 \leqslant_U h(x_0)$. If $y_0 = k_x(v_0)$, then $y_0 \geqslant x_0$ because $v_0 \geqslant u_0$ and $u_0 \leqslant_U h(y_0) \leqslant_U h(x_0) \leqslant_U v_0$. Therefore, the hypotheses of Proposition 3 are satisfied. If $a, b \in [x_0, y_0]$, $a < b$, and $f(a, h(b)) = 0 = f(b, h(a))$ then $a = k_x(h(b))$ and $b = k_x(h(a))$ and consequently $h(a) \neq h(b)$ so $h(b) <_U h(a)$ by hypothesis (c). Applying h, we have $h(a) = k(h(b))$ and $h(b) = k(h(a))$, contradicting our hypothesis. Thus, Corollary 5 implies the result. $\square$

Remark 8. The assumption that h is decreasing gives a negative feedback character to the closed-loop system (9). One could instead modify (c) to assume that h is increasing, i.e., that $x_1 \leqslant x_2$ implies that $h(x_1) \leqslant_U h(x_2)$. However, in this case, the closed-loop system (9) satisfies the quasimonotone condition (QM) and therefore generates a monotone system in its own right. As there is already a well-developed theory for monotone systems, especially regarding convergence to equilibria, we do not pursue this direction here.

A simple family of examples of the theory is given by systems of the form

$$x' = Ax + h(x) \tag{16}$$

on $\mathbb{R}^n_+$, where A is a Hurwitz stable, quasipositive matrix ($a_{ij} \geqslant 0$, $i \neq j$). In that case, it is well-known that $-A^{-1} = \int_0^\infty e^{At}\, dt \geqslant 0$ in the sense that all entries are nonnegative. In case that A is irreducible, which we do not assume, then $e^{At} \gg 0$, $t > 0$ so $-A^{-1} \gg 0$ (all entries positive). Let $s(A)$ denote the stability modulus of matrix A, the maximum real part of any eigenvalue; $s(A)$ is the dominant eigenvalue of A in case A is quasipositive. Assume that $h : \mathbb{R}^n_+ \to \mathbb{R}^n_+$ is continuously differentiable and decreasing: $x \leqslant \bar{x}$ implies $h(\bar{x}) \leqslant h(x)$ (so $Dh(x) \leqslant 0$). With these hypotheses, $\mathbb{R}^n_+$ is positively invariant for (16).

Our assumptions imply that any solution $x(t)$ of (16) with $x(0) \geqslant 0$ satisfies

$$x' \leqslant Ax + h(0)$$

so by standard comparison theorems, $0 \leqslant x(t) \leqslant y(t)$, where $y(t)$ satisfies the linear inhomogeneous differential equation and $y(0) = x(0)$. As A is a stable matrix, $y(t) \to -A^{-1}h(0)$ and hence the omega limit set of $x(t)$ belongs to $X := [0, -A^{-1}h(0)]$. We may as well restrict (16) to X.

The open-loop system, given by

$$\begin{aligned} x' &= f(x, u) := Ax + u, \\ y &= h(x), \end{aligned} \tag{17}$$

where we may as well restrict u to belong to $U := [0, h(0)]$. The open-loop system has a globally stable, nondecreasing input-to-state characteristic $k_x : U \to X$ defined by $k_x(u) := -A^{-1}u$. We employ the standard ordering generated by $\mathbb{R}^n_+$ on both X and U.

In order to apply Corollary 7 we let $u_0 = 0$ and observe that input-to-output characteristic $k : U \to U$ is defined by

$$k(u) = h(-A^{-1}u).$$

Proposition 9. *Suppose that there does not exist $u, v \in U$, $u < v$ such that $k(u) = v$ and $k(v) = u$. Then* (16) *has a globally attracting equilibrium in $\mathbb{R}^n_+$.*

Alternatively, we could apply Lemma 3 and Corollary 5 to obtain the following result.

Proposition 10. *Suppose that whenever $a, b \in X$ satisfy $a < b$ and $h(b) < h(a)$, then $A - \int_0^1 Dh(sb + (1-s)a)\,ds$ is irreducible and*

$$s\left[A - \int_0^1 Dh(sb + (1-s)a)\,ds\right] \neq 0. \tag{18}$$

Then (16) *has a globally attracting equilibrium in $\mathbb{R}^n_+$.*

Proof. Choose $x_0 = u_0 = 0$ and let $v_0 = h(0)$, $y_0 = -A^{-1}v_0$. Then the hypotheses of Proposition 3 are satisfied: $f(x_0, u_0) = 0 = f(y_0, v_0)$ and $u_0 \leqslant h(y_0) \leqslant h(x_0) = v_0$. But we would like to conclude global stability. Corollary 5 requires consideration of $a, b \in [0, y_0]$ satisfying $a \leqslant b$ and $f(a, h(b)) = 0 = f(b, h(a))$. Equivalently, $Aa + h(b) = 0 = Ab + h(a)$ or, if $v := b - a$, then

$$0 = Av - [h(b) - h(a)] = \left[A - \int_0^1 Dh(sb + (1-s)a)\,ds\right]v.$$

If $v \neq 0$, then $h(b) \neq h(a)$ by the equality above since A is nonsingular so $v > 0$. Since $A - \int_0^1 Dh(sb + (1-s)a)\,ds$ is irreducible by hypothesis, it follows that the quasipositive matrix $[A - \int_0^1 Dh(sb + (1-s)a)\,ds]$ is singular and that its stability modulus (eigenvalue of largest real part) is zero by the Perron–Frobenius theory [4]. But this contradicts (18). □

A particular example of (16), treated in [22], is the gene regulatory system modeled by the equations

$$\begin{aligned} x_1' &= g(x_n) - \alpha_1 x_1, \\ x_j' &= x_{j-1} - \alpha_j x_j, \quad j \geqslant 2, \end{aligned} \tag{19}$$

where $\alpha_j > 0$ and $g : \mathbb{R}_+ \to \mathbb{R}_+$ is continuously differentiable and satisfies $g(0) > 0$ and $g' < 0$. The matrix A is clearly stable and quasipositive. Since the open-loop system, obtained by replacing $g(x_n)$ by u, has scalar input and scalar output, we modify slightly our notation from the general case. Let $h(x) := g(x_n)$ denote the output. The open-loop system has input-to-state characteristic given by

$$k_x(u) = u\left(\alpha_1^{-1}, (\alpha_1\alpha_2)^{-1}, \ldots, (\alpha_1\alpha_2\ldots\alpha_n)^{-1}\right)^T$$

for $u \in U = [0, g(0)]$. We may take $X := [0, -A^{-1}(g(0), 0, \ldots, 0)^T] = [0, k_x(g(0))]$. The input-to-output characteristic $k = h \circ k_x : U \to U$ is given by

$$k(u) = g(\beta u), \quad \beta = (\alpha_1\alpha_2\ldots\alpha_n)^{-1}.$$

Obviously, k has a unique fixed point $\bar{u} > 0$ since it is strictly decreasing. The unique equilibrium of (20) is

$$\bar{x} = k_x(\bar{u}).$$

Applying Proposition 9 we get the following result.

Proposition 11. *Assume that $k \circ k(u) = u$ for $u \in [0, g(0)]$ implies that $u = \bar{u}$. Then $\bar{x}$ is globally attracting for* (20).

Proof. Follows from Corollary 7. □

A necessary condition that k has a nontrivial period-two point is that $k'(u) = -1$ for some $u \in [0, g(0)]$. Since $k : [0, g(0)] \to [0, g(0)]$ satisfies $k(0) = g(0)$ and $k(g(0)) > 0$, by the Mean Value Theorem $k'(u) > -1$ for some u. Therefore, if we assume that $k'(u) > -1$ for all $u \in [0, g(0)]$ then k has no nontrivial period-two points. As $k'(u) = \beta g'(\beta u)$, Proposition 11 implies Proposition 1.

Alternatively, we may apply Proposition 10 to get Proposition 1 of the introduction. For this, we need to revert to the notation of the general case and take

$h(x) = (g(x_n), 0, \dots, 0)$. Indeed, using the mean value theorem to evaluate the integral, consider the matrix

$$A - \int_0^1 Dh(sb + (1-s)a)\,ds = \begin{bmatrix} -\alpha_1 & 0 & \cdots & 0 & -g'(\eta) \\ 1 & -\alpha_2 & \cdots & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \cdots & 1 & -\alpha_n \end{bmatrix}, \tag{20}$$

where $\eta \in [0, g(0)\beta]$. It is quasipositive so its dominant eigenvalue is real; its characteristic equation is given by

$$(\alpha_1 + \lambda)(\alpha_2 + \lambda) \dots (\alpha_n + \lambda) + g'(\eta) = 0.$$

If $-g'(\eta) \neq \prod_{i=1}^n \alpha_i$ holds, then the stability modulus of the above matrix cannot vanish.

2.1. An alternative formulation

The effect of our assumptions (a)–(c) is that $f(x, h(y))$ is quasimonotone in x for fixed y and nonincreasing in y for fixed x. Consequently, we may remove the control theoretic aspects of our theory by simply considering

$$x' = F(x) := f(x, x), \tag{21}$$

where $f : X \times X \to X$ satisfies

(i) $\forall y \in X,\ x \to f(x, y)$ is quasimonotone in the sense of condition (QM).
(ii) $\forall x \in X,\ y_1 \leqslant y_2 \Rightarrow f(x, y_2) \leqslant f(x, y_1)$.

In that case, the symmetric system

$$x' = f(x, y),$$
$$y' = f(y, x)$$

is quasimonotone with respect to the ordering $\leqslant_C$ and a somewhat more elegant version of Proposition 3 holds

Proposition 12. *Suppose there exist x_0, y_0 satisfying $x_0 \leqslant y_0$, $[x_0, y_0] \subset X$, and*

$$f(y_0, x_0) \leqslant 0 \leqslant f(x_0, y_0). \tag{22}$$

Then $[x_0, y_0]$ is positively invariant for (21). There exist $x_*, y_* \in [x_0, y_0]$ with $x_* \leqslant y_*$ such that $\omega_F([x_0, y_0]) \neq \emptyset$ is compact, invariant and

$$\omega_F([x_0, y_0]) \subset [x_*, y_*]. \tag{23}$$

Moreover, $f(x_*, y_*) = 0 = f(y_*, x_*)$.

In fact, the two formulations are equivalent. As noted above, if f and h satisfy (a)–(c), then $\hat{f}(x, y) := f(x, h(y))$ satisfies (i) and (ii). Conversely, if f satisfies (i)–(ii), let $U = -X$ with $K_U = K$, define $g : X \times U \to X$ by $g(x, u) := f(x, -u)$ and $h : X \to U$ by $h(x) = -x$. Then g and h satisfy (a)–(c) and $F(x) = g(x, h(x))$. It is a matter of taste which approach to take.

3. Functional differential equations

As in the previous section, let K be a cone in $\mathbb{R}^n$ with nonempty interior generating a partial order $\leqslant$ on $\mathbb{R}^n$ and let K^* denote the dual cone. The cone K induces a cone $\mathcal{C}_K$ in the Banach space $\mathcal{C} := C([-r, 0], \mathbb{R}^n)$, where $r > 0$, defined by

$$\mathcal{C}_K = \{\phi \in \mathcal{C} : \phi(\theta) \geqslant 0,\ \ -r \leqslant \theta \leqslant 0\}.$$

We use the same notation $\leqslant$ for the order relation in $\mathbb{R}^n$ and $\mathcal{C}$ since no confusion should result. Let K_U be a cone in $\mathbb{R}^m$ generating the partial order $\leqslant_U$. K_U induces a cone $\mathcal{CU}_{K_U}$ in the Banach space $\mathcal{CU} := C([-r, 0], \mathbb{R}^m)$ in the same way. Again, we use the notation $\leqslant_U$ for both order relations generated by K_U. It will be convenient to have notation for the natural imbedding of $\mathbb{R}^n$ into $\mathcal{C}$ ($\mathbb{R}^m$ into $\mathcal{CU}$). If $x \in \mathbb{R}^n$, let $\hat{x} \in \mathcal{C}$ be the constant function equal to x for all values of its argument. Let $\mathcal{X} \subset \mathcal{C}$ and $\mathcal{U} \subset \mathcal{CU}$ and let $X = \{x \in \mathbb{R}^n : \hat{x} \in \mathcal{X}\}$ and $U = \{u \in \mathbb{R}^m : \hat{u} \in \mathcal{U}\}$.

We consider the closed-loop system

$$x' = f(x_t, \mathbf{h}(x_t)) \equiv F(x_t) \tag{24}$$

obtained from the open-loop system

$$\begin{aligned} x' &= f(x_t, \psi), \quad \psi \in \mathcal{U}, \\ y &= \mathbf{h}(x_t) \end{aligned} \tag{25}$$

by identifying input and output: $\psi = \mathbf{h}(x_t)$.

Assume that $f : \mathcal{X} \times \mathcal{U} \to \mathbb{R}^n$ and $\mathbf{h} : \mathcal{X} \to \mathcal{U}$ are continuous and satisfy

(a) $\forall \psi \in \mathcal{U},\ \phi \to f(\phi, \psi)$ is quasimonotone in sense of (QMD).
(b) $\forall \phi \in \mathcal{X},\ \psi_1 \leqslant_U \psi_2 \Rightarrow f(\phi, \psi_1) \leqslant f(\phi, \psi_2)$.
(c) $\forall x \in X, \exists u := h(x) \in U$ such that $\mathbf{h}(\hat{x}) = \hat{u}$; $\phi_1 \leqslant \phi_2 \Rightarrow \mathbf{h}(\phi_2) \leqslant_U \mathbf{h}(\phi_1)$.

Hypothesis (c) says that $\mathbf{h}$ maps constant functions into constant functions and is decreasing.

The quasimonotone condition is:

(QMD) $\phi, \chi \in \mathcal{X},\ \psi \in \mathcal{U},\ \phi \leqslant \chi$ and $\eta(\phi(0)) = \eta(\chi(0))$ for some $\eta \in K^*$, implies $\eta(f(\phi, \psi)) \leqslant \eta(f(\chi, \psi))$.

This assumption implies that for each fixed ψ, the open-loop system (26) is monotone.

We assume that solutions of initial value problems associated with (24) are unique and write $x(t,\phi)$ $(x_t(\phi))$ for the maximally extended solution (state) of the associated initial value problem $x_0=\phi$. Denote by $\omega_F(A)$ the omega limit set of set $A\subset\mathcal{X}$ in case it exists.

As for ODEs, we imbed (24) into the symmetric delay system

$$\begin{aligned} x' &= f(x_t,\mathbf{h}(y_t)),\\ y' &= f(y_t,\mathbf{h}(x_t)). \end{aligned} \tag{26}$$

We assume unique solutions of initial value problems in $\mathcal{X}\times\mathcal{X}$, write $z=(x,y)$, $z_t=(x_t,y_t)$ and use the notation $z(t,\eta)=(x(t,\eta),y(t,\eta))$ for the solution satisfying $z_0(\eta)=\eta=(\phi,\psi)\in\mathcal{X}\times\mathcal{X}$. Assume also that $G(\phi,\psi):=(f(\phi,h(\psi)),f(\psi,h(\phi)))$, the right-hand side of (26), is completely continuous. Symmetry of (26) ensures that $(x(t,\eta),y(t,\eta))$ is a solution with initial value $\eta=(\phi,\psi)$ if and only if $(y(t,\eta),x(t,\eta))$ is a solution with initial value $\xi=(\psi,\phi)$. Uniqueness of solutions implies that the diagonal

$$D=\{(\phi,\phi):\phi\in\mathcal{X}\}$$

is invariant under (26). If $\eta=(\phi,\phi)$, then $z(t,\eta)=(x(t,\phi),x(t,\phi))$ where $x(t,\phi)$ satisfies (9).

The symmetric system (26) generates a monotone system on $\mathcal{X}\times\mathcal{X}\subset\mathcal{C}\times\mathcal{C}$ with respect to the cone $\mathcal{P}:=\mathcal{C}_K\times(-\mathcal{C}_K)$, generated by the cone $K\times(-K)$ on $\mathbb{R}^{2n}$, as we will show below. $\mathcal{P}$ gives rise to the order relation

$$(\phi,\psi)\leqslant_P(\bar\phi,\bar\psi)\iff\phi\leqslant\bar\phi\text{ and }\bar\psi\leqslant\psi.$$

Lemma 13. (26) *generates a monotone system on $\mathcal{X}\times\mathcal{X}$ with respect to $\leqslant_P$. More precisely, if $\eta,\xi\in\mathcal{X}\times\mathcal{X}$ satisfy $\eta\leqslant_P\xi$, then $z_t(\eta)\leqslant_P z_t(\xi)$ for all $t\geqslant0$ for which both solutions are defined.*

Proof. We need only verify the quasimonotone condition for

$$G(\phi,\psi):=(f(\phi,h(\psi)),f(\psi,h(\phi)))$$

relative to the cone P; see [12, Section 4]. Given $(\phi,\psi)\leqslant_P(\bar\phi,\bar\psi)$ and $(\lambda,-\mu)\in K^*\times(-K^*)$ with $(\lambda,-\mu)(\phi(0),\psi(0))=(\lambda,-\mu)(\bar\phi(0),\bar\psi(0))$, we must verify that

$$(\lambda,-\mu)G(\phi,\psi)\leqslant(\lambda,-\mu)G(\bar\phi,\bar\psi). \tag{27}$$

Now, $(\lambda,-\mu)(\phi(0),\psi(0))=(\lambda,-\mu)(\bar\phi(0),\bar\psi(0))$ and $\lambda,\mu\in K^*$ imply that $0\leqslant\lambda(\bar\phi(0)-\phi(0))=\mu(\bar\psi(0)-\psi(0))\leqslant0$ so $\lambda(\bar\phi(0))=\lambda(\phi(0))$ and $\mu(\bar\psi(0))=\mu(\psi(0))$. As $\phi\leqslant\bar\phi$

and $\bar{\psi} \leqslant \psi$, we have

$$\begin{aligned}(\lambda, -\mu)G(\phi, \psi) &= \lambda(f(\phi, \mathbf{h}(\psi))) - \mu(f(\psi, \mathbf{h}(\phi)))\\ &\leqslant \lambda(f(\phi, \mathbf{h}(\bar{\psi}))) - \mu(f(\psi, \mathbf{h}(\bar{\phi})))\\ &\leqslant \lambda(f(\bar{\phi}, \mathbf{h}(\bar{\psi}))) - \mu(f(\bar{\psi}, \mathbf{h}(\bar{\phi}))) = (\lambda, -\mu)G(\bar{\phi}, \bar{\psi}).\end{aligned}$$

where the second line follows from monotonicity of f and $\mathbf{h}$ and the third line follows from the quasimonotonicity assumption (QMD) for f. □

We now return to the closed-loop system (24).

Proposition 14. *Let $u_0, v_0 \in U$ satisfy $u_0 \leqslant_U v_0$ and suppose there exist x_0, y_0 satisfying $x_0 \leqslant y_0$, $f(\hat{y}_0, \hat{v}_0) \leqslant 0 \leqslant f(\hat{x}_0, \hat{u}_0)$ with $[\hat{x}_0, \hat{y}_0] \subset \mathcal{X}$, and*

$$u_0 \leqslant_U h(y_0) \leqslant_U h(x_0) \leqslant_U v_0. \tag{28}$$

Then $[\hat{x}_0, \hat{y}_0]$ is positively invariant for (24). *There exist $x_*, y_* \in [x_0, y_0]$ with $x_* \leqslant y_*$ such that $\omega_F(\phi) \neq \emptyset$ satisfies*

$$\omega_F(\phi) \subset [\hat{x}_*, \hat{y}_*], \quad \phi \in [\hat{x}_0, \hat{y}_0]. \tag{29}$$

Moreover, $f(\hat{x}_*, \mathbf{h}(\hat{y}_*)) = 0 = f(\hat{y}_*, \mathbf{h}(\hat{x}_*))$.

Proof. Inequality $x_0 \leqslant y_0$ implies that $(\hat{x}_0, \hat{y}_0) \leqslant_P (\hat{y}_0, \hat{x}_0)$. Define the $\mathcal{P}$-order interval

$$\begin{aligned}I &= [(\hat{x}_0, \hat{y}_0), (\hat{y}_0, \hat{x}_0)]_P := \{(\phi, \psi) : (\hat{x}_0, \hat{y}_0) \leqslant_P (\phi, \psi) \leqslant_P (\hat{y}_0, \hat{x}_0)\}\\ &= \{(\phi, \psi) : \hat{x}_0 \leqslant \phi, \psi \leqslant \hat{y}_0\}\end{aligned}$$

and observe that

$$I \cap D = \{(\phi, \phi) : \phi \in [\hat{x}_0, \hat{y}_0]\}.$$

Using (28), we have

$$f(\hat{x}_0, \mathbf{h}(\hat{y}_0)) \geqslant f(\hat{x}_0, \hat{u}_0) \geqslant 0$$

and

$$f(\hat{y}_0, \mathbf{h}(\hat{x}_0)) \leqslant f(\hat{y}_0, \hat{v}_0) \leqslant 0.$$

This implies that

$$(f(\hat{y}_0, \mathbf{h}(\hat{x}_0)), f(\hat{x}_0, \mathbf{h}(\hat{y}_0))) \leqslant_P (0,0) \leqslant_P (f(\hat{x}_0, \mathbf{h}(\hat{y}_0)), f(\hat{y}_0, \mathbf{h}(\hat{x}_0))),$$

which, together with quasimonotonicity of G, implies that the order interval I is positively invariant for (26) (see [12, Section 4, Theorem 4.2]). Moreover, because of monotonicity, we have

$$(\hat{x}_0, \hat{y}_0) \leqslant_P z_t(\hat{x}_0, \hat{y}_0) \leqslant_P z_t(\eta) \leqslant_P z_t(\hat{y}_0, \hat{x}_0) \leqslant_P (\hat{y}_0, \hat{x}_0)$$

for all $t \geqslant 0$ and for all $\eta \in I$. Furthermore, $z_t(\hat{x}_0, \hat{y}_0) \nearrow (x_*, y_*)$ and $z_t(\hat{y}_0, \hat{x}_0) \searrow (y_*, x_*)$, where the monotonicity implied by the inclination of the arrows is relative to $\leqslant_P$, and $(\hat{x}_*, \hat{y}_*)$, $(\hat{y}_*, \hat{x}_*)$ are equilibria of (26). Put $\eta = (\bar{\phi}, \bar{\phi})$ where $\bar{\phi} \in [\hat{x}_0, \hat{y}_0]$, write $z(t, (\hat{x}_0, \hat{y}_0)) = (x(t, \hat{x}_0, \hat{y}_0), y(t, \hat{x}_0, \hat{y}_0))$ and $z(t, (\hat{y}_0, \hat{x}_0)) = (y(t, \hat{x}_0, \hat{y}_0), x(t, \hat{x}_0, \hat{y}_0))$, to obtain

$$(x_t(\hat{x}_0, \hat{y}_0), y_t(\hat{x}_0, \hat{y}_0)) \leqslant_P (x_t(\bar{\phi}), x_t(\bar{\phi})) \leqslant_P (y_t(\hat{x}_0, \hat{y}_0), x_t(\hat{x}_0, \hat{y}_0))$$

or, on taking the first components,

$$\hat{x}_0 \leqslant x_t(\hat{x}_0, \hat{y}_0) \leqslant x_t(\bar{\phi}) \leqslant y_t(\hat{x}_0, \hat{y}_0) \leqslant \hat{y}_0,$$

where $x_t(\hat{x}_0, \hat{y}_0) \nearrow \hat{x}_*$ and $y_t(x_0, y_0) \searrow \hat{y}_*$. This implies the positive invariance of $[\hat{x}_0, \hat{y}_0]$ for (9) and the remaining assertions. □

An immediate consequence of the final assertion of Lemma 14 is the following result.

Corollary 15. *Let the hypotheses of Lemma* 14 *hold and suppose that*

$$a, b \in [x_0, y_0], \;\; a \leqslant b, \;\; f(\hat{a}, \mathbf{h}(\hat{b})) = 0 = f(\hat{b}, \mathbf{h}(\hat{a})) \Rightarrow a = b \tag{30}$$

holds. Then $x_* = y_*$ *and*

$$\omega_F(\phi) = \{\hat{x_*}\}, \;\; \phi \in [\hat{x}_0, \hat{y}_0].$$

An especially simple example is given by the delayed negative feedback equation

$$x'(t) = -x(t) + h\left(\int_{-r}^{0} x(t+\theta)\, d\nu(\theta)\right), \tag{31}$$

where ν is a probability measure (a positive Borel measure with $\nu([-r,0]) = 1$), $h(0) = 0$ and $h' < 0$. In this case $X = \mathbb{R}$ and $U = \mathbb{R}$ with the usual ordering on X and U. A special case of (31) is, after a simple change of variable, the equation introduced by Mackey for red blood cell dynamics [15]. The corresponding open-loop equation is given by

$$x' = \psi(0) - x, \quad \psi \in \mathcal{CU},$$
$$y = \mathbf{h}(x_t) := \hat{h}\left(\int_{-r}^{0} x(t+\theta)\, d\nu(\theta)\right).$$

Note that $\mathbf{h}$ maps into the constant functions in $\mathcal{CU}$ and that (a)–(c) hold where $f(\phi,\psi) := \psi(0) - \phi(0)$. Our hypotheses guarantee that 0 is the unique equilibrium of (31).

Proposition 16. *Assume that there exist sequences* $0 < a_n, b_n \to \infty$ *such that* $h([-a_n, b_n]) \subset [-a_n, b_n]$ *for all* $n \geqslant 1$ *and that* $h \circ h(x) = x \in \mathbb{R}$ *implies* $x = 0$. *Then* $x = 0$ *is globally attracting for* (31).

Proof. Apply Proposition 14 with $u_0 = -a_n, v_0 = b_n$ and $x_0 = u_0, y_0 = v_0$. Our hypotheses regarding the sequences a_n, b_n ensure that (28) holds. The hypothesis forbidding nontrivial period-two points of h ensures that (30) of Corollary 15 holds. Indeed, $0 = f(\hat{a}, \mathbf{h}(\hat{b})) = h(b) - a$ and $0 = f(\hat{b}, \mathbf{h}(\hat{a})) = h(a) - b$ imply $h(h(b)) = b$ so $b = 0$ and similarly for a. The latter result implies that $\omega_F([-\hat{a}_n, \hat{b}_n]) = \{\hat{0}\}$ for every n. □

The hypotheses of the proposition are equivalent to the requirement that $x = 0$ is globally attracting for the difference equation $x_n = h(x_{n-1})$.

Remark 17. In the special case that $\nu = \delta_{-r}$ is the Dirac measure with unit mass at $-r$, the equation is $x'(t) = -x(t) + h(x(t-r))$. In this case, we could take $f(\phi,\psi) = -\phi(0) + \psi(-r)$ and $\mathbf{h}(\phi) = h \circ \phi$, $\phi \in \mathcal{CU}$. Thus, $f(\phi, \mathbf{h})(\phi) = -\phi(0) + h(\phi(-r))$ and hypotheses (a)–(c) hold.

The open-loop system is said to have an input-to-state characteristic if to each $u \in U$, $f(\hat{x}, \hat{u}) = 0$ has a unique solution $x := k_x(u) \in X$. The following result is proved exactly as Corollary 7.

Corollary 18. *Suppose that* $\mathcal{U} = [\hat{u}_0, \infty) := \{\psi : \hat{u}_0 \leqslant_U \psi\}$, *for each* v_0 *with* $u_0 \leqslant_U v_0$, $k_x(u_0) \leqslant k_x(v_0)$, *and* $\mathcal{X}_0 := \cup_{v_0 \geqslant u_0} [\hat{k}_x(u_0), \hat{k}_x(v_0)] \subset \mathcal{X}$. *If* $k : U \to U$ *defined by* $k(u) = h(k_x(u))$ *has no pair* $u, v \in U$, $u <_U v$ *such that* $k(u) = v$, $k(v) = u$, *then* (24) *has an equilibrium* $\hat{x}_* \in [\hat{k}_x(u_0), \hat{k}_x(h(u_0))]$ *such that*

$$\omega_F(\phi) = \{\hat{x}_*\}, \quad \phi \in X_0.$$

Consider the delayed gene regulatory system

$$x_1' = g(L_n x_n^t) - \alpha_1 x_1,$$
$$x_j' = L_{j-1} x_{j-1}^t - \alpha_j x_j, \quad 2 \leqslant j \leqslant n, \tag{32}$$

where $\alpha_j > 0$ and $g : \mathbb{R}_+ \to \mathbb{R}_+$ is continuously differentiable and satisfies $g(0) > 0$ and $g' < 0$. See [22] for details of model interpretation. Let

$$L_i x_i^t = \int_{-r}^{0} x_i(t+\theta)\, dv_i(\theta), \quad 1 \leqslant i \leqslant n,$$

where each v_i is a positive Borel measure on $[-r, 0]$ such that $v_i([-r, 0]) = 1$. We employ the notation $x_t = (x_1^t, \ldots, x_n^t)$ for the state of the system as time t.

Define the open-loop system by

$$x_1' = \psi(0) - \alpha_1 x_1, \quad \psi \in \mathcal{CU},$$
$$x_j' = L_{j-1} x_{j-1}^t - \alpha_j x_j, \quad j \geqslant 2,$$
$$y = \mathbf{h}(x_t) := \hat{g}(L_n x_n^t). \tag{33}$$

It may be useful to stress that $\mathcal{CU} = C([-r, 0], \mathbb{R}_+)$, $\mathcal{X} = C([-r, 0], \mathbb{R}_+^n)$ and that $\mathbf{h} : \mathcal{X} \to \mathcal{CU}$ is defined by $\mathbf{h}(\phi) = \hat{g}(L_n \phi_n)$, that is, $\mathbf{h}(\phi)$ is a constant function.

We note that (a)–(c) hold with, as in the case without delays,

$$k_x(u) = u\left(\alpha_1^{-1}, (\alpha_1\alpha_2)^{-1}, \ldots, (\alpha_1\alpha_2 \ldots \alpha_n)^{-1}\right)^T.$$

Indeed, the open-loop system is affine and its solutions, which may be solved recursively beginning with x_1, can be shown to satisfy $x(t, \phi, \psi) \to k_x(\psi(0))$ as $t \to \infty$. The same differential inequality argument that we used in the nondelay case shows that limit sets belong to $X = [0, k_x(g(0))]$. We may take $U = [0, g(0)]$ with the usual ordering on X and U. Thus, $k : [0, g(0)] \to [0, g(0)]$ is given by

$$k(u) = h(k_x(u)) = g(\beta u), \quad \beta = (\alpha_1\alpha_2 \ldots \alpha_n)^{-1}.$$

k has a unique fixed point $\bar{u} > 0$ and the unique equilibrium of (32) is

$$\bar{x} = k_x(\bar{u}).$$

Proposition 19. *Assume that $k \circ k(u) = u$ implies $u = \bar{u}$. Then $\bar{x}$ is globally attracting for* (32).

Proof. Follows from Corollary 18 and the fact that $\mathcal{X}_0 = \mathcal{X}$. □

Proposition 19 affirms that Proposition 1 remains true when delays are introduced.

Bélair and Buono [3], extending work of Siegel and Pitt [21], consider a system of delay differential equations modeling the controlled delivery of a drug from a chamber partially bounded by a semi-permeable membrane whose permeability depends on the concentration of a product produced in the chamber via an enzyme catalyzed reaction using substrate. The strategy is to choose product and membrane such that the permeability of the membrane to drug oscillates with a controlled period so that the drug delivery can be pulsatile. This may be achieved if the product negatively effects permeability so that when product is low the permeability increases allowing substrate from the exterior to diffuse into the chamber and form product which then reduces permeability and so on. The equations for substrate x and product y are given by

$$\begin{aligned} x'(t) &= \Phi(y(t-r))(1-x(t)) - x(t), \\ y'(t) &= x(t) + \Psi(y(t-r))(Y - y(t)), \end{aligned} \tag{34}$$

where Y and 1 denote the constant external concentrations of product and substrate, respectively, and r is the delay in the response of permeability to product. $Y, r \geqslant 0$, $\Phi, \Psi : \mathbb{R}_+ \to \mathbb{R}_+$ are positive with $\Phi' < 0$, $\Psi' \leqslant 0$. In order to simplify the algebra, we assume, as in [21], that $\Psi \equiv c > 0$ is constant. The domain $X := [0,1] \times [Y, \infty) \subset \mathbb{R}^2$ is positively invariant and attracts all solutions with nonnegative initial data.

The open-loop system can be chosen to be the linear system without delays given by

$$\begin{aligned} x'(t) &= \psi(-r)(1-x(t)) - x(t), \\ y'(t) &= x(t) + c(Y - y(t)), \\ z &= h(y_t) := \Phi(y_t(-r)). \end{aligned} \tag{35}$$

One see that (a)–(c) holds with $U = [0, \infty)$ and X with the usual orderings. For each $u \geqslant 0$ (35) has a unique equilibrium

$$x = k_x(u) = \left(\frac{u}{u+1}, \frac{1}{c} \frac{u}{u+1} + Y \right).$$

The map $k : U \to U$ defined by $k(u) = h \circ k_x(u)$ is given by

$$k(u) = \Phi\left(\frac{1}{c} \frac{u}{u+1} + Y \right)$$

is monotone decreasing and has a unique fixed point $\bar{u} > 0$.

We have the following conditions for the failure of oscillatory drug release.

Proposition 20. *Assume that $k \circ k(u) = u$ implies $u = \bar{u}$. Then $\bar{x} := k_x(\bar{u})$ is globally attracting for* (34).

Proof. Follows from Corollary 18 and the fact that $\mathcal{X}_0 = \mathcal{X}$. □

We remark that (a)–(c) continue to hold without the assumption that $\Psi \equiv c$. However, the characteristic is difficult to express.

4. Reaction–diffusion systems

Rather than give the most general results possible, we specialize to the case that $\mathbb{R}^n$ is given the standard ordering generated by the cone $\mathbb{R}^n_+$. Other orthant cones may be substituted for this one and general polyhedral cones may be used following [19,20]. We assume (a)–(c) of the ODE section holds for $f : X \times U \to \mathbb{R}^n$ and $h : X \to U$. The ordering on $U \subset \mathbb{R}^m$ may be given by a general cone K_U as in that section. Let $\Omega \subset \mathbb{R}^k$ be a bounded domain with smooth boundary and $\mathcal{C} := C(\overline{\Omega}, \mathbb{R}^n)$ ordered in the usual way by $w_1 \leqslant w_2$ if and only if $w_1(x) \leqslant w_2(x)$ for all $x \in \overline{\Omega}$. Let $\mathcal{X} = \{w \in \mathcal{C} : w(x) \in X,\ x \in \overline{\Omega}\}$. For $a \in \mathbb{R}^n$, we write $\hat{a}$ for the element of $\mathcal{C}$ satisfying $\hat{a}(x) = a,\ x \in \overline{\Omega}$.

The reaction–diffusion system of interest is given by

$$\begin{aligned} &w_t = D\triangle w + f(w, h(w)), \quad x \in \Omega, \\ &\frac{\partial w}{\partial n} = 0,\ \ x \in \partial\Omega, \end{aligned} \tag{36}$$

where D is a positive diagonal matrix. Given $w_0 \in \mathcal{X}$, denote by $w(t, x, w_0)$ the solution of (36) satisfying $w(0, x, w_0) = w_0(x),\ x \in \overline{\Omega}$. We assume that (36) generates a completely continuous local semi-flow on $\mathcal{X}$. Let $\omega_F(w_0)$ be the omega limit set of $w_0 \in \mathcal{X}$ if it exists.

System (36) can be imbedded into the symmetric system

$$\begin{aligned} &w_t = D\triangle w + f(w, h(W)), \quad x \in \Omega, \\ &W_t = D\triangle W + f(W, h(w)), \\ &\frac{\partial w}{\partial n} = \frac{\partial W}{\partial n} = 0, \quad x \in \partial\Omega. \end{aligned} \tag{37}$$

We assume (37) has unique solutions of initial value problems in $\mathcal{X} \times \mathcal{X}$, write $z = (w, W)$ and use the notation $z(t, x, z_0) = (w(t, x), W(t, x))$ for the solution satisfying $z(0, x, z_0) = z_0(x)$. Symmetry ensures that $(w(t, x), W(t, x))$ is a solution if and only if $(W(t, x), w(t, x))$ is a solution. By uniqueness of solutions, the diagonal

$$D = \{(w_0, w_0) : w_0 \in \mathcal{X}\}$$

is positively invariant under (37) and

$$z(t, x, z_0) = (w(t, x, w_0), w(t, x, w_0)), \quad z_0 = (w_0, w_0),$$

where $w(t, x, w_0)$ satisfies (36).

When z_0 is a constant function $z_0 = \hat{z} = (\hat{w}, \hat{W})$, then $z(t, x, \hat{z})$ is independent of x so we drop the x and write $z(t, \hat{z})$ for the solution of the ordinary differential equation (11).

The symmetric system (37) generates a monotone system on $\mathcal{X} \times \mathcal{X}$ with respect to the order relation

$$(w, W) \leqslant_P (\bar{w}, \bar{W}) \iff w(x) \leqslant \bar{w}(x) \quad \text{and} \quad \bar{W}(x) \leqslant W(x), \quad x \in \overline{\Omega}.$$

Lemma 21. (37) *generates a monotone system on $\mathcal{X} \times \mathcal{X}$ with respect to $\leqslant_P$. More precisely, if $z_0 \leqslant_P \bar{z}_0$, then $z(t, \bullet, z_0) \leqslant_P z(t, \bullet, \bar{z}_0)$ for all $t \geqslant 0$ for which both solutions exist.*

Proof. We need only verify the quasimonotone condition for the vector field $G(x, y) := (f(x, h(y)), f(y, h(x)))$ relative to the cone C defined in the ODE section. See e.g. [23, Proposition 1.3, Chapter 8]. But this was done in Lemma 2. □

As in the previous sections, our main result is stated in terms of the input/output system which, in this section, we have omitted. Notice that the hypotheses of the result are precisely those of Proposition 3 with only a change of notation. Thus, Proposition 3 remains true when diffusion is added.

Proposition 22. *Let $u_0, v_0 \in U$ satisfy $u_0 \leqslant_U v_0$ and suppose that there exist w_0, W_0 satisfying $w_0 \leqslant W_0$, $f(W_0, v_0) \leqslant 0 \leqslant f(w_0, u_0)$ with $[w_0, W_0] \subset X$ and*

$$u_0 \leqslant_U h(W_0) \leqslant_U h(w_0) \leqslant_U v_0. \tag{38}$$

Then $[\hat{w}_0, \hat{W}_0]$ is positively invariant for (36). *There exist $w_*, W_* \in [w_0, W_0]$ with $w_* \leqslant W_*$ such that for each $w \in [\hat{w}_0, \hat{W}_0]$, $\omega_F(w) \neq \emptyset$ is compact, invariant and*

$$\omega_F(w) \subset [\hat{w}_*, \hat{W}_*]. \tag{39}$$

Moreover, $f(w_*, h(W_*)) = 0 = f(W_*, h(w_*))$.

Proof. By Proposition 3, the solutions $z(t, (w_0, W_0)) = (w(t), W(t))$ and $z(t, (W_0, w_0)) = (W(t), w(t))$ satisfy

$$(w_0, W_0) \leqslant_C z(t, (w_0, W_0)) \leqslant_C z(t, (W_0, w_0)) \leqslant_C (W_0, w_0)$$

and $z(t, (w_0, W_0)) \nearrow (w_*, W_*)$ and $z(t, (W_0, w_0)) \searrow (W_*, w_*)$, the monotonicity relative to $\leqslant_C$. By Lemma 21, for $z_0 \in [(\hat{w}_0, \hat{W}_0), (\hat{W}_0, \hat{w}_0)]$, we have

$$z(t, (w_0, W_0)) \leqslant_P z(t, x, z_0) \leqslant_P z(t, (W_0, w_0)), \quad x \in \Omega, \ t \geqslant 0.$$

Putting $z_0 = (\bar{w}, \bar{w})$ with $\bar{w} \in [\hat{w}_0, \hat{W}_0]$ and taking only the first components, we find that

$$w(t) \leqslant w(t, x, \bar{w}) \leqslant W(t), \quad t > 0, \ x \in \overline{\Omega}.$$

The result follows immediately since $w(t) \nearrow w_*$ and $W(t) \searrow W_*$. $\square$

Corollary 23. *Let the hypotheses of Proposition* 22 *hold and suppose that*

$$a, b \in [w_0, W_0], \quad a \leqslant b, \quad f(a, h(b)) = 0 = f(b, h(a)) \Rightarrow a = b \tag{40}$$

holds. Then $w_* = W_*$, $f(w_*, h(w_*)) = 0$ *and*

$$\omega_F(w) = \{w_*\}, \quad w \in [\hat{w}_0, \hat{W}_0].$$

The obvious analog of Corollary 7 holds. Furthermore, this result implies that Proposition 1 holds even when diffusion is added to the Goodwin system to (8).

The ideas here may be extended to reaction–diffusion systems with more general elliptic part and to systems with time delays. See [17,18].

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