Chemical Networks with Inflows and Outflows: A Positive Linear Differential Inclusions Approach

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Certain mass-action kinetics models of biochemical reaction networks, although described by nonlinear differential equations, may be partially viewed as state-dependent linear time-varying systems, which in turn may be modeled by convex compact valued positive linear differential inclusions. A result is provided on asymptotic stability of such inclusions, and applied to a ubiquitous biochemical reaction network with inflows and outflows, known as the futile cycle. We also provide a characterization of exponential stability of general homogeneous switched systems which is not only of interest in itself, but also plays a role in the analysis of the futile cycle. © 2009 American Institute of Chemical Engineers *Biotechnol. Prog.,* 25: 632–642, 2009
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Introduction

The study of positive systems, systems whose state is confined to the closed positive orthant, naturally arises in many different disciplines, including mathematical biology, chemistry, economics, and telecommunications engineering. The implications of positivity constraints on the dynamics are often nontrivial. For instance, in the case of positive linear systems, the dynamical behavior is strongly constrained by the Perron-Frobenius theory.[1] Likewise, the dynamics of nonlinear cooperative systems—where the variational equation associated to the system turns out to be positive—is also limited, as shown in the theory of monotone systems.[2]

Linear systems are positive when they are described by differential equations of the type $\dot{x} = Ax$, where A is a square matrix having non-negative off-diagonal entries. In the literature such matrices are commonly referred to as a Metzler matrices. Only recently, the study of such systems in conjunction with switching has attracted some attention in engineering and mathematics.[3,4] In particular, Ref. 4 provides an algebraic criterion for the existence of a common linear Lyapunov function for switched positive linear systems with 2 modes.

We relax the notion of a common linear Lyapunov function introduced in Ref. 4 and allow for nonstrict decrescence along solutions of the system. The existence of such a function, combined with the assumption that all matrices describing the switched system are Hurwitz, leads to a Lasalle-like criterion which allows one to conclude asymptotic stability of the switched system, or equivalently, of the associated differential inclusion.

Indeed, although such kinds of criteria have been widely studied in the past literature for general-purpose switched systems (see for instance Refs. 5 and 6), the additional structure provided by the positivity constraint allows for easily checkable and tight conditions (indeed necessary and sufficient for the considered class of systems).

We also revisit the problem of characterizing exponential stability of switched homogeneous systems (not necessarily positive). The main result concerning this problem seems to have been part of the collective memory in the switched systems literature; yet, it is hard to cite an article or text where a proof can be found. Moreover, the proof presented here is new, as it does not require notions from the theory of differential inclusions. We will see how it is useful in establishing our main result regarding stability of positive linear differential inclusions, and also as a tool in showing that solutions of biochemical networks with inputs remain bounded. At first glance, the latter statement appears to be trivial; yet, perhaps surprisingly, it turns out that solutions to open biochemical reaction networks may grow unbounded. We will illustrate this by means of a case study of an important example arising in systems biology, known as the 2-step futile cycle.[7–11] In fact, the study of this particular example triggered the development of our main theoretical results. The 2-step futile cycle is one of the basic building blocks of various biochemical networks, for instance as a 2-step phosphorylation-dephosphorylation reaction. We have

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previously studied the futile cycle in isolation,[7–9] and despite the fact that it is governed by a relatively large system of nonlinear differential equations for which traditional techniques such as the quasi-steady state approximation only yield partial results (as they are based on simpler approximations), its global dynamical behavior is now fairly well understood, mainly because of monotonicity properties, see Refs. 7 and 8. Of course, in reality the futile cycle is not isolated, and thus it makes sense to study it with time-varying inputs and outputs. As already mentioned, we will discover that very basic properties, such as boundedness of solutions, are not as easy to establish, or even worse, may fail to hold.

The rest of this article is structured as follows. In "Problem Formulation and Main Result" Section, we state the main result concerning asymptotic stability of positive linear differential inclusions, as well as an example that illustrates the necessity of some of our assumptions. We will also provide a characterization of exponential stability of homogeneous switched systems. "Application to Some Chemical Networks" Section provides an application of our main result. For the sake of readability technical proofs are deferred to the Appendix.

Problem Formulation and Main Result

Let $\Omega \subset \mathbb{R}^{n\times n}$ be a nonempty, closed set of real $n \times n$ matrices, for some integer $n > 0$. For $x \in \mathbb{R}^n$ we say that $v \in \Omega\, x$, if there exists a matrix $A \in \Omega$ such that $v = Ax$. With this notation, we define a *linear differential inclusion* (LDI) in the following way:

$$\dot{x}(t) \in \Omega x(t) \tag{1}$$

and we call an absolutely continuous function x: $\mathbb{R} \to \mathbb{R}^n$ a solution to (1) if and only if $\dot{x}(t) \in \Omega x(t)$ for almost all $t \in \mathbb{R}$. For each $x_0 \in \mathbb{R}^n$ we define the set of solutions with initial condition at x_0 as the following set:

$$\mathcal{S}(x_0) \doteq \{x(\cdot) \text{ is a solution of } (1) : x(0) = x_0\}.$$

Basic results about general differential inclusions are covered in several texts, such as the introductory work.[12]

Hereby, it is worth recalling that, due to the set-valued nature of the right-hand side of (1), the set $\mathcal{S}(x_0)$ has usually infinite cardinality (and in particular is not a singleton). To a certain extent (which can be made rigorous by selection theorems), a linear differential inclusion can be seen as a way of simultaneously considering all possible measurable signals $A(\cdot)$: $\mathbb{R} \to \Omega$, and the associated time-varying linear systems $\dot{x}(t) = A(t)x(t)$. In the particular case of piecewise constant signals $A(\cdot)$, moreover, one ends up dealing with a so-called *switched system*.

Although general LDIs typically give rise to solutions evolving in Euclidean space, when one is considering systems whose variables are naturally confined to the positive orthant (as in the case of concentrations of chemical compounds) it makes sense to restrict the class of systems under investigation, by taking into account this additional requirement. We make this mathematically precise by means of the following definitions.

We say that a differential inclusion is *positive* if for all $x_0 \in \mathbb{R}^n_+$ and all $x(\cdot) \in \mathcal{S}(x_0)$ it holds that $x(t) \in \mathbb{R}^n_+$ for all $t \geq 0$ (viz. the positive orthant is a positively invariant set for the inclusion).

It is well known that a closed set K is positively invariant for all solutions of a Lipschitz differential inclusion $\dot{x} \in F(x)$ iff $F(x) \in TC_x(K)$ for all $x \in K$, where $TC_x(K)$ denotes the Bouligand's tangent cone to the set K at the point x (this property is usually referred to as strong invariance of K, see Refs. 13 or 14). Hence, in our case, (1) is positive iff $Ax \in TC_x(\mathbb{R}^n_+)$ for all $A \in \Omega$ and all $x \in \mathbb{R}^n_+$. In turn, for a single linear time invariant system, it is well known that $Ax \in TC_x(\mathbb{R}^n_+)$ for all $x \in \mathbb{R}^n_+$ iff A is a Metzler matrix. (See for instance Ref. 15 for an exposition of positive linear systems theory.) In view of these two facts, (1) is positive if and only if:

$$A_{ij} \geq 0,\ \forall i \neq j \in \{1, 2, \ldots, n\},\ \forall A \in \Omega. \tag{2}$$

In words, Ω consists of Metzler matrices. We say that a (positive) linear differential inclusion is *asymptotically stable* if (for all $x_0 \in \mathbb{R}^n_+$) for all $x_0 \in \mathbb{R}^n$, $x(t) \to 0$ as $t \to +\infty$ for all $x(\cdot)$ in $\mathcal{S}(x_o)$. When Ω is a singleton, then (1) amounts to a differential equation, and asymptotic stability is equivalent to the matrix $A \in \Omega$ being Hurwitz (viz. all of its eigenvalues have negative real part). In general, checking asymptotic stability of a linear differential inclusion is a difficult task; its characterization in algebraic terms has long been sought for. Although it is known that a necessary condition for asymptotic stability is that all matrices A in Ω should be Hurwitz, it is also well known that in general this condition is not sufficient. The purpose of this article is to provide a sufficient condition for asymptotic stability of positive linear differential inclusions. Before stating our main result, we introduce some additional notation. We say that a (row or column) vector v satisfies $v \succ 0$ if $v \in \mathbb{R}^n_+$ and $v \neq 0$. Accordingly, we write $v_1 \succ v_2$ when $v_1 - v_2 \succ 0$. If $v \in \text{int}\,(\mathbb{R}^n_+)$, we denote this fact by $v \gg 0$.

Definition 2.1. We say that $V(x) = c'x$ is a *linear copositive weak Lyapunov function* for (1) if $c \gg 0$ and

$$c'A \leq 0 \quad \forall A \in \Omega.$$

Notice that, in the case in which $c'A = 0$ for all $A \in \Omega$, $c'x$ has a clear physical interpretation as a conserved quantity of the system, along its solutions; indeed, $c'\dot{x}(t) = c'A(t)x(t)$ for some $A(t) \in \Omega$, and therefore $c'\dot{x}(t) = 0$. Similarly, if $x(t) \geq 0$ and $c'A \leq 0$ for all $A \in \Omega$, $c'\dot{x}(t) \leq 0$, thus showing that the quantity $c'x(t)$ is actually dissipated by the system. This may occur, for instance, when adding outflows to a closed reaction network; as it is intuitive, in such case some of the conserved moieties become quantities which actually decrease along solutions.

Observe that, in the special case in which Ω consists of nonsingular matrices (and in particular, if each matrix in Ω is Hurwitz), then a linear copositive weak Lyapunov function satisfies the stronger property:

$$c'A \prec 0 \quad \forall A \in \Omega.$$

Definition 2.2. We say that $V(x) = c'x$ is a *uniform linear copositive weak Lyapunov function* for (1) if $c \gg 0$ and

$$\exists \varepsilon > 0 :\ \forall A \in \Omega,\ \exists i_A \in \{1, 2, \ldots, n\} : \qquad c'A \prec -\varepsilon e'_{i_A}$$

with e_i denoting the i-th vector of the canonical basis of $\mathbb{R}^n$.

We have the following simple remark (see Appendix for the proof).

Lemma 2.3. Consider a positive, linear differential inclusion (1), and let $\Omega \subset \mathbb{R}^{n\times n}$ be compact. Suppose that every element of Ω is nonsingular. Then, any linear copositive weak Lyapunov function for (1) is also a *uniform* linear copositive weak Lyapunov function. □

We will need the following result, also proved in the Appendix.

Lemma 2.4. Consider a positive linear differential inclusion (1) and assume that $\Omega \subset \mathbb{R}^{n\times n}$ is compact. Let $x(t)$, $t \geq 0$ be a forward solution of (1). If $x_i(0) > 0$, then $x_i(t) > 0$ for all $t > 0$. □

Our main result is stated next, and proved in the Appendix.

Theorem 1. *Consider a positive linear differential inclusion (1), and assume that* Ω *is* compact *and* convex. *Suppose that*:

(1) *There exists a linear copositive weak Lyapunov function* $V(x) = c'x$ *for (1).*

(2) *Each* $A \in \Omega$ *is nonsingular.*

Then, (1) is asymptotically stable. □

Remark 2.5. As remarked in the proof, in view of condition 1 and Condition 2 of Theorem 1 could be replaced by the statement that "Each $A \in \Omega$ is Hurwitz", which is a necessary condition for asymptotic stability of (1). Hence, Theorem 1 could be stated equivalently by saying that for positive linear differential inclusions, admitting a linear copositive weak Lyapunov function, asymptotic stability of the inclusion is equivalent to Hurwitzianity of the individual matrices $A \in \Omega$. Such an equivalence is far from being true in more general set-ups, for instance, if existence of a linear weak Lyapunov function is not assumed. Indeed article[3] is devoted to showing that Hurwitzianity of all matrices in Ω is equivalent to asymptotic stability for positive differential inclusions in the plane, and to building a counter-example to the above in higher dimension. Conditions relating existence of common Lyapunov functions to Hurwitzianity of the frozen systems, viz. of matrices A in Ω, are not new in the literature. See for instance article Ref. 21, where results are established for existence of quadratic common Lyapunov functions in terms of Hurwitzianity of matrix pencils (an analog of convex hulls). More in general, the idea of proving stability of differential inclusions on the basis of stability of frozen linear systems is indeed at the core of the well-known Aizerman conjecture, which, though false in its original formulation, has triggered a rich line of research starting with the circle and Popov's criteria (see for instance Ref. 22). □

A counter-example

We remark that the assumptions of Theorem 1 cannot be weakened by only requiring that Ω be a closed set. As we show in the subsequent example, this is not possible even if Assumption 2 is strengthened to the existence of a *uniform* linear copositive weak Lyapunov function, which, in the noncompact case, is in general a stronger assumption than existence of a mere linear copositive weak Lyapunov function.

Consider the following linear time-varying differential equation:

$$\dot{x}(t) = \begin{bmatrix} -1 - n(t) & 1 \\ n(t) & -1 \end{bmatrix} x(t) \tag{3}$$

where $n(t)$ is a measurable, locally essentially bounded function of t, taking values in $[0,+\infty)$. Notice that:

$$[1,1]\begin{bmatrix} -1 - n(t) & 1 \\ n(t) & -1 \end{bmatrix} = [-1,0] \prec 0 \tag{4}$$

Thus $x_1 + x_2$ is a uniform linear copositive weak Lyapunov function for (3). Moreover, each of the matrices in

$$\Omega : = \{A \in \mathbb{R}^{2\times 2} : \exists n \geq 0 : A_{11} = -1 - n, A_{12} = 1, A_{21} = n, A_{22} = -1\}$$

is Hurwitz. Hence, by the Theorem 1, asymptotic stability follows provided that $n(t)$ is bounded from above. On the other hand, let $x_2(0) > 1$ and let $n(t) = 1/x_1(t)$ for all $t \geq 0$. Substituting in (3) the following equations are obtained:

$$\begin{aligned} \dot{x}_1(t) &= -x_1(t) + x_2(t) - 1 \\ \dot{x}_2(t) &= -x_2(t) + 1 \end{aligned} \tag{5}$$

Hence, $x_2(t) \searrow 1$ as $t \to +\infty$. Consequently $x_2(t) - 1 \to 0$ and $x_1(t) \to 0$ by the first equation in (5). In particular then $n(t) \geq 0$ for all t and $n(t) \to +\infty$ as $t \to +\infty$. Thus we have found a solution of (3) for which convergence to 0 does not hold.

Switched homogeneous systems

The proof of Theorem 1 given in the Appendix relies upon Theorem 2, which is stated in this section. As discussed in Remark A.1, one could alternatively have appealed to a more special result in the theory of switched linear systems. However, the statement and proof that we provide applies to a larger class of systems, namely all switched homogeneous systems.

The study of switched systems is a rapidly growing area of research in control theory. Informally, a switched system is a dynamical system which is able to commute between different behaviors according to some external input variable, which we will call the switching signal. The practical relevance of this wide class of systems has been often emphasized, see for instance Refs. 23 and 24 for recent surveys on the subject. On the other hand, many challenging theoretical questions which arise in this area are still waiting for an answer.

From a mathematical point of view, a switched system is a nonlinear system of the following form

$$\dot{x} = f(x, \sigma) \tag{6}$$

with state x evolving in $\mathbb{R}^n$ and with exogenous inputs σ (the *switching signal*), taking values in a compact set Σ. In this context, we think of $\sigma(\cdot) : \mathbb{R}_{\geq 0} \to \Sigma$ as a time-varying uncertain parameter of the system. In order to guarantee existence of solutions, one assumes that $\sigma(\cdot)$ is a measurable function, and that f is continuous and satisfies a local Lipschitz property on x, uniformly on inputs (see e.g. Ref. 25). The homogeneity assumption refers to the dependence of f on x, meaning that f satisfies

$$\forall \lambda > 0, \forall x \in \mathbb{R}^n, \forall \sigma \in \Sigma : \qquad f(\lambda x, \sigma) = \lambda f(x, \sigma). \tag{7}$$

We will also assume that f satisfies a uniform Lipschitz condition:

$$|f(x_1,\sigma)-f(x_2,\sigma)| \leq M|x_1-x_2| \quad \forall x_1,x_2 \in \mathbb{R}^n,\ \forall \sigma \in \Sigma \tag{8}$$

We remark that, because of compactness of Σ and homogeneity of f this is not stronger than the usual local Lipschitzianity condition used in order to guarantee existence and uniqueness of classical solutions for (6).

A major example from the previous class of systems is a linear switched system

$$\dot{x} = \Phi_\sigma x, \quad \sigma \in \Sigma. \tag{9}$$

with $x \in \mathbb{R}^n$ and Φ_σ a square matrix, typically σ dependent, of compatible dimension. In the area of robust control, the stability of a family of linear systems is usually studied employing common quadratic Lyapunov functions whose expression can be determined solving an LMI. It is well known that the existence of a common Lyapunov function is a necessary and sufficient condition for stability of (6) under arbitrary switchings[26] however, quadratic Lyapunov functions are not universal, not even for linear systems, meaning that there might be stable families of linear systems for which no common quadratic Lyapunov function exists.[27] Nevertheless, it was shown in Ref. 20 that a Lyapunov function of the following kind always exists

$$V(x) = \max_i (v_i'x)^2 \tag{10}$$

where $v_i \in \mathbb{R}^n$ are constant vectors, but the question of how to build such Lyapunov functions in general is still open.

Here we will investigate the stability properties of homogeneous, switched systems; in particular, a new proof is presented that does not rely on differential inclusion techniques, showing equivalence of exponential stability and attractivity. In the following $x(t,\xi,\sigma)$ will denote the response at time t, to the input signal σ and initial condition ξ at time $t=0$. It is straightforward to see from (8) that (6) is forward complete and hence solutions are unique and maximally defined over $[0,+\infty)$.

Definition 2.6. We say that system (6) is *exponentially stable* if there exist positive constants M and λ such that

$$|x(t,\xi,\sigma)| \leq Me^{-\lambda t}|\xi| \quad \forall t \geq 0,\ \forall \xi \in \mathbb{R}^n, \forall \sigma \in \mathcal{M}_\Sigma. \tag{11}$$

Definition 2.7. We say that system (6) is *uniformly globally asymptotically stable* if there exists a $\mathcal{KL}$ function β such that the following estimate holds

$$|x(t,\xi,\sigma)| \leq \beta(|\xi|,t) \quad \forall t \geq 0, \forall \xi \in \mathbb{R}^n, \forall \sigma \in \mathcal{M}_\Sigma. \tag{12}$$

Both stability notions are uniform with respect to σ, in the sense that the switching signal does not affect the speed of convergence of the system to 0. The following notions of attractivity are also of interest.

Definition 2.8. We say that system (6) is *attractive* if

$$\forall \xi \in \mathbb{R}^n,\ \forall \sigma \in \mathcal{M}_\Sigma, \quad \lim_{t\to+\infty} |x(t,\xi,\sigma)| = 0 \tag{13}$$

Definition 2.9. We say that system (6) is *weakly attractive* if

$$\forall \xi \in \mathbb{R}^n,\ \forall \sigma \in \mathcal{M}_\Sigma, \quad \liminf_{t\to+\infty} |x(t,\xi,\sigma)| = 0 \tag{14}$$

With these definitions, we are ready to state the main result concerning switched homogeneous systems. It was conjectured [for the part relative to items (1),(2) and (3)] in Ref. 27; as a matter of fact, an even stronger result holds.

Theorem 2. *Consider the family of switched systems in Eq.* 6, *and assume that* (7) *is satisfied, Then, the following facts are equivalent*:

(1) *System (6) is exponentially stable*,
(2) *System (6) is uniformly globally asymptotically stable*,
(3) *System (6) is attractive*,
(4) *System (6) is weakly attractive*. □

Remark 2.10. We remark that by virtue of (7), local stability properties are equivalent to global ones. In particular then, by the previous theorem weak local attractivity in a neighborhood of the origin is equivalent to global exponential stability.

By shifting the initial time from 0 to an arbitrary initial time s, we obtain the following simple Corollary to Theorem 2 which is used in the following section.

Corollary 2.11. Let $\Phi(t,s)$ denote a fundamental matrix solution of system (9). Then system (9) is attractive if and only if there are positive constants M and λ such that

$$|\Phi(t,s)| \leq Me^{-\lambda(t-s)} \quad \forall t \geq s.$$

□

An example of transition from stability to instability

To see how the result in the previous section is not obvious even for very simple switched systems, consider the following parameterized family of linear switched systems:

$$\dot{x} = \Phi_\sigma(\theta)x, \quad \sigma \in \{1,2\} \tag{15}$$

with

$$\Phi_1(\theta) = \begin{bmatrix} -1 & \theta \\ 0 & -1 \end{bmatrix} \quad \Phi_2(\theta) = \begin{bmatrix} -1 & 0 \\ \theta & -1 \end{bmatrix}. \tag{16}$$

where θ is a parameter varying in [0,2]. Both systems are asymptotically stable. Moreover, for all θ in [0,2) we have:

$$\Phi_1'(\theta) + \Phi_1(\theta) = \Phi_2'(\theta) + \Phi_2(\theta) < 0. \tag{17}$$

Hence, $\Phi_1(\theta)$ and $\Phi_2(\theta)$ admit the identity as a common Lyapunov function and the resulting switched system is quadratically stable. For $\theta = 2$, however, it is not difficult to see that the system (15) fails to be exponentially stable; a necessary condition for exponential stability is in fact that all convex combinations of the Φ'_is be such.[28] In this case instead

$$\frac{1}{2}\Phi_1 + \frac{1}{2}\Phi_2 = \begin{bmatrix} -1 & 1 \\ 1 & -1 \end{bmatrix}, \tag{18}$$

which has a zero eigenvalue, corresponding to the eigenvector $v_0 = [1,1]'$. Therefore, there exist nonconvergent relaxed solutions of (15) for $\theta = 2$. It is not obvious instead, without making use of Theorem 2, how to show that the system is not attractive. As a matter of fact, taking as a Lyapunov function $V(x) = x'x$ one easily obtains

$$\dot{V}(x) = 2x'\Phi_i x = -2([1,-1]x)^2 \leq 0 \quad i = 1,2. \tag{19}$$

Thus $x(t)'x(t) \le x(0)'x(0)$ and $[1, -1]x \in L_2$. As x is bounded, so is $([1 - 1]x)^2$ is uniformly continuous and thus it follows from Barbalat's Lemma 16 that $[1, -1]x \to 0$.

One might even be brought to think, by the above considerations, that (15) be attractive; the only source of instability comes from the fact that solutions of the linear system $\dot{x} = (\Phi_1 + \Phi_2)x/2$ can be approximated, arbitrarily close on finite time intervals, by switching rapidly between Φ_1 and Φ_2, for equally long time intervals. Theorem 2 clearly indicates that this is not the case and that nonconvergent trajectories of (15) exist also taking into account only classical solutions.

Application to Some Chemical Networks

It turns out that a very important class of systems, which can be often described by linear positive differential inclusions of the type that we are considering in this note, arises in the modeling of *chemical reaction networks* (CRNs). As a matter of fact, the study of their dynamics was the main motivation that triggered this research.

From a mathematical point of view, a chemical network is just a list of chemical reactions, viz. objects of the following type:

$$\sum_{j \in \mathcal{S}} \alpha_{ij} S_j \;\to\; \sum_{j \in \mathcal{S}} \beta_{ij} S_j$$

for i ranging over a set $\mathcal{R}$ of chemical reactions. $\mathcal{S}$ is the set of chemical species $\{\mathcal{S}_1, \mathcal{S}_2, \ldots, \mathcal{S}_N\}$, whereas the α_{ij}'s and β_{ij}'s are non-negative integers, called the stoichiometry coefficients of the reaction network. Assuming that reactions happen continuously in time, with a rate proportional to the concentration of the reactants (this is the so-called mass-action kinetics hypothesis), we can associate to a chemical reaction network a differential equation, which keeps track of the time evolution of the concentrations of the different chemical species. As reactions may involve more than one reactant at a time, the corresponding reaction rates will be polynomial functions in the chemical species, and this determines overall a nonlinear system of differential equations whose analysis is often nontrivial. Moreover, external inputs and outputs can also be included in this model, in particular, if one is considering *open* systems, rather than closed ones. To apply our results to the analysis of such systems, it is first necessary to rewrite the nonlinear system as a linear differential inclusion.

The basic idea is as follows. One may always rewrite (in many alternative ways) a dynamics $\dot{x} = f(x)$ in the "state-dependent" form $\dot{x} = A(x)x$, provided that the origin is an equilibrium and the vector field f is differentiable. This approach is often useful in optimization and other feedback control problems, see for instance.[29] Since many chemical reactions are defined by quadratic nonlinearities, it is often the case that $A(x)$ will be an affine (and therefore convex) function of its arguments, and, because chemical species are non-negative, often $A(x)$ can be picked to be a Metzler matrix (for each possible state x). Linear copositive weak Lyapunov functions are then suggested by mass conservation laws. An even more general case is that in which *some* of the equations can be rewritten in this fashion, but the remaining equations are comparatively easy to analyze. Rather than providing an abstract theorem for the general systems, we illustrate this procedure through a very important example arising in biochemistry.[7–11]

We will study the following chemical reaction network:

$$\begin{array}{ccccccccc} E+S_0 & \leftrightarrow & ES_0 & \to & E+S_1 & \leftrightarrow & ES_1 & \to & E+S_2 \\ F+S_2 & \leftrightarrow & FS_2 & \to & F+S_1 & \leftrightarrow & FS_1 & \to & F+S_0 \\ u & \to & S_0 & & S_2 & \to & \emptyset & & \end{array} \tag{20}$$

where $\leftrightarrow$ denotes reversible reactions, viz. reactions that can happen in both directions (this notation is used to avoid having to write two reactions, respectively the forward and backward reaction); moreover $A \to B \to C$ is short-hand notation for $A \to B$, $B \to C$. Notice that the last two reactions represent, respectively, the fact that an inflow of substrate S_0 occurs through the input u (basically u will denote in the model the inflow rate of the compound S_0) and that a degradation of S_2 occurs spontaneously (it is customary, in degradation reactions, to use the symbol $\emptyset$, to denote the fact that we are not interested in keeping track of the products of such reactions). We denoted u in lower-case because it is not a state variable, but plays the role of an exogenous signal (which is assumed to be non-negative at all times). The chemical reaction network (20) can also be graphically represented as a Petri Net, with chemical species represented as places and reactions as transitions, see Figure 1. The resulting system of polynomial differential equations (assuming mass-action kinetics) is given below:

$$\begin{aligned} \dot{S}_0 &= -k_1 E \cdot S_0 + k_{-1} ES_0 + k_8 FS_1 + u \\ \dot{S}_1 &= -k_3 E \cdot S_1 + k_{-3} ES_1 - k_7 F \cdot S_1 \\ &\quad + k_{-7} FS_1 + k_2 ES_0 + k_6 FS_2 \\ \dot{S}_2 &= -k_5 F \cdot S_2 + k_{-5} FS_2 + k_4 ES_1 - k_9 S_2 \\ \dot{ES}_0 &= k_1 E \cdot S_0 - k_{-1} ES_0 - k_2 ES_0 \\ \dot{ES}_1 &= k_3 E \cdot S_1 - k_{-3} ES_1 - k_4 ES_1 \\ \dot{FS}_2 &= k_5 F \cdot S_2 - k_{-5} FS_2 - k_6 FS_2 \\ \dot{FS}_1 &= k_7 F \cdot S_1 - k_{-7} FS_1 - k_8 FS_1 \\ \dot{E} &= -k_1 E \cdot S_0 + k_{-1} ES_0 + k_2 ES_0 \\ &\quad - k_3 E \cdot S_1 + k_{-3} ES_1 + k_4 ES_1 \\ \dot{F} &= -k_5 F \cdot S_2 + k_{-5} FS_2 + k_6 FS_2 \\ &\quad - k_7 F \cdot S_1 + k_{-7} FS_1 + k_8 FS_1, \end{aligned} \tag{21}$$

where the various constants k_i's and k_{-i}'s are the reaction rate constants of the forward, respectively, backward ith reaction.

We can study the nonlinear system (21) by considering the following pseudolinear system:

$$\begin{bmatrix} \dot{S}_0 \\ \dot{S}_1 \\ \dot{S}_2 \\ \dot{ES}_0 \\ \dot{ES}_1 \\ \dot{FS}_2 \\ \dot{FS}_1 \end{bmatrix} = A(E,F) \begin{bmatrix} S_0 \\ S_1 \\ S_2 \\ ES_0 \\ ES_1 \\ FS_2 \\ FS_1 \end{bmatrix} + \begin{bmatrix} 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} u(t). \tag{22}$$

where $A(E,F)$ denotes the following matrix:

$$\begin{bmatrix} -k_1E & 0 & 0 & k_{-1} & 0 & 0 & k_8 \\ 0 & -k_3E-k_7F & 0 & k_2 & k_{-3} & k_6 & k_{-7} \\ 0 & 0 & -k_5F-k_9 & 0 & k_4 & k_{-5} & 0 \\ k_1E & 0 & 0 & -k_{-1}-k_2 & 0 & 0 & 0 \\ 0 & k_3E & 0 & 0 & -k_{-3}-k_4 & 0 & 0 \\ 0 & 0 & k_5F & 0 & 0 & -k_{-5}-k_6 & 0 \\ 0 & k_7F & 0 & 0 & 0 & 0 & -k_{-7}-k_8 \end{bmatrix}. \tag{23}$$

Equation 22 is then coupled together with the following nonlinear equations:

$$\begin{aligned}\dot{E} &= -k_1E\cdot S_0 + k_{-1}ES_0 + k_2ES_0 - k_3E\cdot S_1 \\ &\quad + k_{-3}ES_1 + k_4ES_1 \\ \dot{F} &= -k_5F\cdot S_2 + k_{-5}FS_2 + k_6FS_2 - k_7F\cdot S_1 \\ &\quad + k_{-7}FS_1 + k_8FS_1. \end{aligned} \tag{24}$$

Of course, the only meaningful initial conditions are in the positive orthant. We prove below that the system enjoys *Bounded Input Bounded State (BIBS) Stability* for sufficiently small input signals. This is a nontrivial conclusion, because nothing a priori guarantees that the only outflow present in the system (viz. the reaction $S_2 \to \emptyset$) will yield boundedness of all chemical species; indeed there needs to be an adequate balance between the inflow of S_0 [through the input signal $u(t)$] and degradation of S_2. The proof exploits in a crucial way Theorem 1 of the previous Section.

Proof of BIBS Stability with small inputs for (21)

To apply our main result, and infer BIBS stability for sufficiently small input signals of the considered chemical reaction network (21), we will, first of all, establish that after some finite time, all solutions are confined to a region where the assumptions of the theorem are fulfilled. In particular, we will establish positive upper and lower bounds for $E(t)$ and $F(t)$. To this end, notice that the closed positive orthant is positively invariant for (21). Moreover, (21) admits the two linear first integrals $E(t) + ES_0(t) + ES_1(t) =$ const. and $F(t) + FS_1(t) + FS_2(t) =$ const.. The combination of these two considerations is already enough to guarantee boundedness of E, ES_0, ES_1, F, FS_1, FS_2. We want to show now that also $S_0(t)$, $S_1(t)$ and $S_2(t)$ are bounded functions of time provided $u(t)$ takes values in $[0, \overline{u}]$ for some sufficiently small

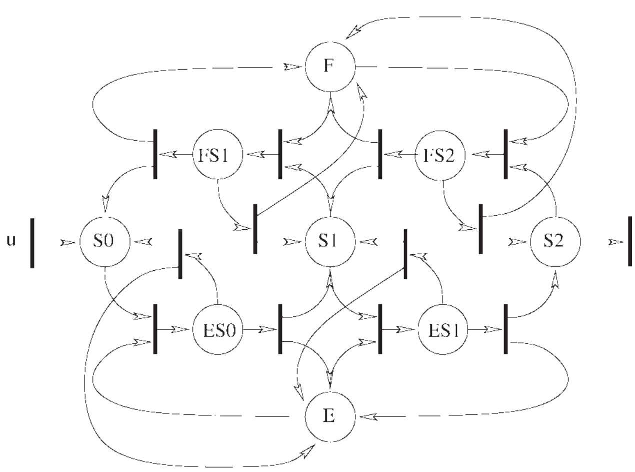

Figure 1. Petri Net representation of CRN (20).

$\overline{u} > 0$ (possibly depending on the initial condition). Let $E_{\max}$ and $F_{\max}$ be upper bounds for $E(t)$ and $F(t)$. Specifically, we pick $E_{\max} = E(0) + ES_0(0) + ES_1(0)$ and $F_{\max} = F(0) + FS_1(0) + FS_2(0)$. Pick $\tau > 0$ sufficiently small so that:

$$K_E := \int_0^{\tau} e^{-[(k_1+k_3)(c'x(0)+\tau+1)+\min\{k_{-1}+k_2,k_{-3}+k_4\}]s}\min\{k_{-1}+k_2, k_{-3}+k_4\}ds < 1$$

and

$$K_F := \int_{\tau}^{0} e^{-[(k_5+k_7)(c'x(0)+\tau+1)+\min\{k_{-5}+k_6,k_{-7}+k_8\}]s}\min\{k_{-5}+k_6, k_{-7}+k_8\}ds < 1.$$

We let $E_{\min} := K_E E_{\max}$ and $F_{\min} := K_F F_{\max}$ so that we have that $0 < E_{\min} < E_{\max}$, $0 < F_{\min} < F_{\max}$. Next, define Ω as the following compact and convex set:

$$\Omega = \{A(E,F) : E \in [E_{\min}, E_{\max}] \text{ and } F \in [F_{\min}, F_{\max}]\}.$$

For such Ω, we may consider the associated forced linear differential inclusion:

$$\dot{x}(t) \in \Omega x(t) + e_1 u(t) \tag{25}$$

where e_1 is the first vector of the canonical basis of $\mathbb{R}^7$ and the above sum of a set and a vector denotes as usual the corresponding set shift. Notice that $c'x := [1,1,1,1,1,1,1]'x$ is a linear copositive weak Lyapunov function for $\dot{x}(t) \in \Omega x(t)$, which, together with irreducibility of each A in Ω, implies that Ω consists of Hurwitz matrices. (To see this, let $d \gg 0$ be such that $d'A \prec 0$. As A is irreducible, it has a real dominant Perron-Frobenius[1] eigenvalue λ with corresponding eigenvector $z \gg 0$. Then $Az = \lambda z$ and $d'A \prec 0$ with $z,d \gg 0$ implies that $\lambda < 0$, and thus A is Hurwitz.)

The Fillipov Selection Lemma and the variation of parameters formula says that solutions of (25) with initial condition $x(0) = x^0$ have the form:

$$x(t) = \Phi(t,0)x^0 + \int_t^0 \Phi(t,s)e_1u(s)\,ds$$

for a fundamental solution matrix associated to the selected solution of the inclusion. Now, applying Theorem 1 together with Corollary 2.11 which states that $|\Phi(t,s)|$ decreases exponentially, we conclude that there exists a positive scalar K such that for positive t, all solutions $x(\cdot)$ of (25) satisfy:

$$c'x(t) \le c'x(0) + K\overline{u}, \tag{26}$$

provided that inputs $u(\cdot)$ take values in $[0, \overline{u}]$.

We show next that every solution of (21) is also a solution of (24) and (25) for all $t \geq \tau$. To this end, notice first of all the following dissipation inequality which holds along solutions of (22) as well as (25):

$$c'\dot{x}(t) \leq u(t). \tag{27}$$

This implies that $c'x(t) \leq c'x(0) + t\bar{u}$, as long as $u(t) \in [0, \bar{u}]$. Let us now consider Eq. (24) and exploit the fact that the signals $S_0(t)$, $S_1(t)$ and $S_2(t)$ satisfy

$$S_i(t) \leq c'x(t) \leq c'x(0) + t\bar{u} \quad i = 0, 1, 2. \tag{28}$$

Let in the following k_m denote $\min\{k_{-1} + k_2, k_{-3} + k_4\}$. For all $t \geq 0$, there holds that

$$\begin{aligned}\dot{E}(t) &\geq -(k_1 + k_3)(c'x(0) + t\bar{u})E(t) + (k_{-1} + k_2)ES_0(t) \\ &\quad + (k_{-3} + k_4)ES_1(t) \\ &\geq -(k_1 + k_3)(c'x(0) + t\bar{u})E(t) + k_m(ES_0(t) + ES_1(t)) \\ &= -(k_1 + k_3)(c'x(0) + t\bar{u})E(t) + k_m(E_{\max} - E(t)) \\ &= -((k_1 + k_3)(c'x(0) + t\bar{u}) + k_m)E(t) + k_m E_{\max}.\end{aligned} \tag{29}$$

By a standard comparison principle and exploiting that $E(0) \geq 0$, we have indeed:

$$E(t) \geq \int_0^t e^{-\int_s^t ((k_1+k_3)(c'x(0)+\theta\bar{u})+k_m)d\theta} k_m E_{\max}\, ds \tag{30}$$

which for $t = \tau$ and assuming that $\bar{u} \leq 1$, yields

$$E(\tau) \geq k_m E_{\max} \int_0^\tau e^{-((k_1+k_3)(c'x(0)+\tau)+k_m)\tilde{s}} d\tilde{s} > E_{\min} \tag{31}$$

after exploiting the fact that the integration variable θ which belongs to $[s,t]$ always fulfills $\theta \leq \tau$ and changing variables in the integral by letting $\tilde{s} = t - s$.

A similar argument can be carried out for $F(t)$ to show that $F(\tau) > F_{\min}$. Hence, by continuity of solutions, every solution of (21) is a solution of (25) and (24) at least for some interval $[\tau, \tau + \varepsilon)$. Let $\tau_E := \inf\{t \geq \tau : E(t) < E_{\min}\}$ and, respectively, $\tau_F := \inf\{t \geq \tau : F(t) < F_{\min}\}$. We claim that $\tau_E, \tau_F = +\infty$. To see this, we remark that by (26), with initial time translated to $t = \tau$, we have for all subsequent $t \in [\tau, \tau_E)$:

$$c'x(t) \leq c'x(\tau) + K\bar{u} \tag{32}$$

In fact, for all $t \in [\tau, \tau_E)$ we derive, provided that $\bar{u} < \min\{1, 1/K\}$:

$$\begin{aligned}\dot{E}(t) &\geq -(k_1 + k_3)(c'x(\tau) + K\bar{u})E(t) + (k_{-1} + k_2)ES_0(t) \\ &\quad + (k_{-3} + k_4)ES_1(t) \\ &> -(k_1 + k_3)(c'x(0) + \tau + 1)E(t) + k_m(ES_0(t) \\ &\quad + ES_1(t)) \\ &= -(k_1 + k_3)(c'x(0) + \tau + 1)E(t) + k_m(E_{\max} - E(t)) \\ &= -((k_1 + k_3)(c'x(0) + \tau + 1) + k_m)E(t) + k_m E_{\max}.\end{aligned} \tag{33}$$

Notice that:

$$K_E \leq k_m \int_0^{+\infty} e^{-[(k_1+k_3)(c'x(0)+\tau+1)+k_m]s} ds = \frac{k_m}{[(k_1 + k_3)(c'x(0) + \tau + 1) + k_m]}$$

so that, for $E(t) = K_E E_{\max} = E_{\min}$ we have by virtue of (33), that $\dot{E}(t) \geq 0$. This indeed shows that $E(t) \geq E_{\min}$ is positively invariant.

It follows by BIBS stability of (25) [i.e., using the estimate in Eq. (26)] that $S_0(t)$, $S_1(t)$, and $S_2(t)$ are bounded. This completes the proof.

Global BIBS stability

One may wonder whether the result can be strengthened to BIBS stability for all bounded inputs $u(\cdot)$, rather than just for sufficiently small ones. Simulations, reported in Figure 2, however, show that unbounded solutions corresponding to constant input signals are possible. In particular we picked all kinetic constants equal to 1 and $u(t) \equiv 1$. Initial conditions were selected as follows:

$$[S_0(0), S_1(0), S_2(0), ES_0(0), ES_1(0), FS_2(0), FS_1(0), E(0), F(0)] = [1, 1, 1, 1, 1, 1, 1, 1, 1].$$

Notice, in particular, that $S_0(t) \to +\infty$ as $t \to +\infty$ and that, $E(t) \to 0$ as $t \to +\infty$, which explains why Theorem 1 cannot be applied: Indeed, for $E_{\min} = 0$ the matrices contained in Ω do not fulfill the second assumption as they are singular in that case. From a physical point of view, fast inflow of S_0 leads to a sharp decrease in the number of molecules of E, since they are almost all bound to S_0 molecules in the complex ES_0. Asymptotically, there would not be any free molecules of E left. In turn, this shuts off the transformation of S_0 into S_1 and, similarly, of S_1 into S_2, preventing degradation of S_2 to happen at a sufficient rate to keep the overall state bounded. This shows the criticality of the assumption that Ω should be a compact set, even in practical applications.

Conclusions

We have discussed a set of mathematical tools to address questions of stability with respect to exogenous inflows in open chemical reaction networks. The key idea is to embed an ODE describing the dynamics of a chemical network into a positive linear differential inclusion, preserving the conservation laws of the original system. Although stability of such class of dynamical models can be tested in a rather straightforward way (thanks to one of the main results of this article), a crucial assumption turns out to be compact-valuedness of the associated differential inclusion. This assumption is in turn tightly linked to the particular embedding chosen and, for general reactions, can only be established provided the systems state is a priori known to be bounded (which is instead what we actually wish to prove). This circularity in the arguments makes it difficult to isolate classes of chemical reaction networks for which I-O stability can be concluded by applying the theory, and, to be sorted out, typically requires some additional and non trivial extra

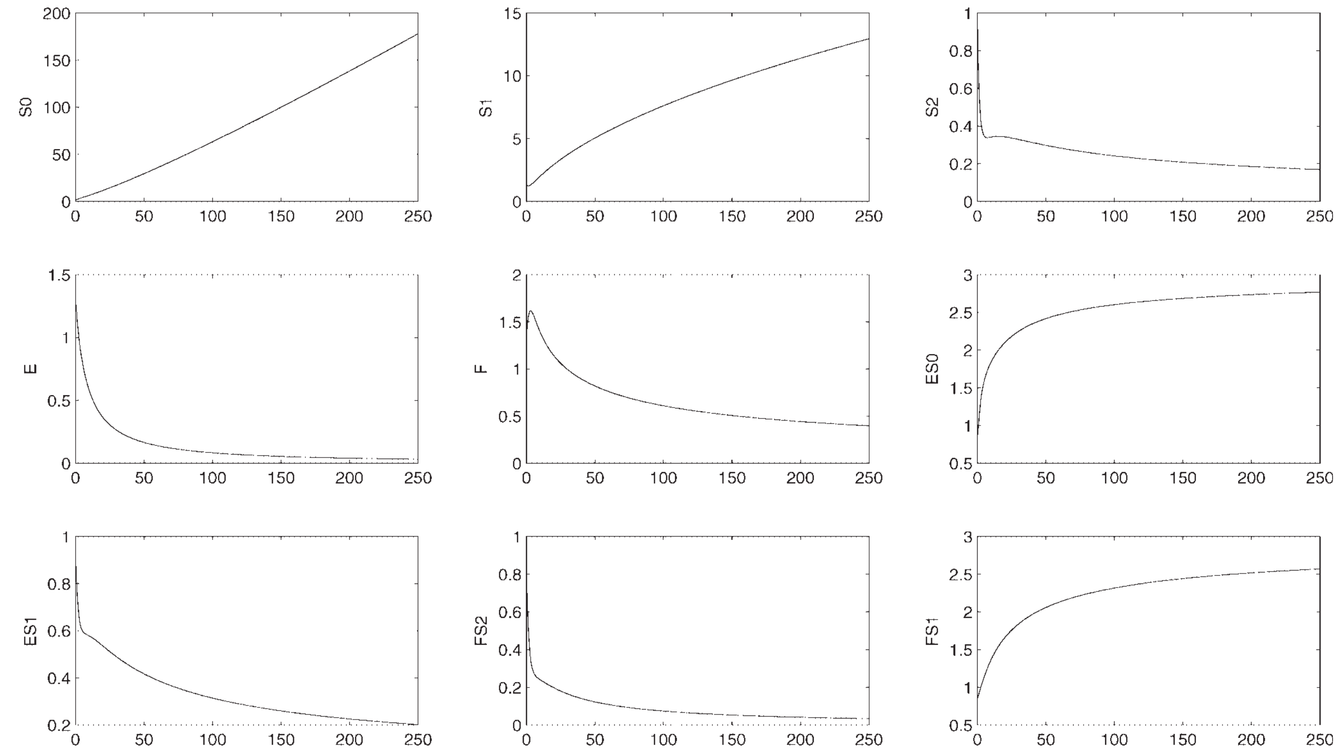

Figure 2. Simulation of system (21) with constant inflow.

Parameter values and initial conditions are given it the text.

work to be performed in an ad hoc manner, see the example in the previous Section. Nevertheless, we still believe that the tools hereby developed are appropriate in many examples of interest, due to the broad applicability of the linear embedding techniques. It is worth mentioning that such I-O stability properties are not as common as one may expect in chemical reaction networks; even when some intuitive necessary conditions for the property to hold are fulfilled: namely that for each chemical compound which is an inflow of the reaction, there should be at least one or more outflows where chemical compounds are dissipated and which contain the corresponding inflow up to possible recombination and decompositions. Indeed, simulations show that, especially at high inflow rates, certain paths along the reaction may shut off, and lead to accumulation of compounds which cannot be drained to their corresponding sinks. This is a further reason to estimate the usefulness of such tools: to have a theoretically sound derivation of an important qualitative property of chemical reaction networks.

Acknowledgments

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Appendix A: Main Technical Proofs

Proof of Lemma 2.3: Let $V(x) = c'x$ be the linear copositive weak Lyapunov function in question. By nonsingularity, $c'A \prec 0$ for every $A \in \Omega$. Consider the mapping $F : \Omega \to \mathbb{R}^n_+$ given by $A \to -c'A$. As this mapping is continuous and Ω is compact, the image is compact, and therefore closed. As the point 0 is not in the closed set $F(\Omega)$, there is some $\varepsilon > 0$ such that the rectangle $[0,\varepsilon]^n$ doesn't intersect $F(\Omega)$. This means that, for each A in Ω, there is some i such that

$$c'A \prec -\varepsilon e_i$$

and therefore the same c gives a strong function. □

Proof of Lemma 2.4: By the Filippov Selection Lemma[14] there is some $\Omega(t)$, measurable, which is in Ω for all t, such that $\dot{x}(t) = \Omega(t)x(t)$ for almost all t. Thus, for almost all $t \geq 0$:

$$\dot{x}_i(t) = \Omega_{ii}(t)x_i(t) + b(t) \geq \Omega_{ii}(t)x_i(t),$$

where the latter inequality holds since $b(t) := \sum_{i\neq j}\Omega_{ij}(t)x_j(t) \geq 0$ and $\Omega_{ij}(t) \geq 0$ for $i \neq j$ and $x_j(t) \geq 0$ for all j and $t \geq 0$. Therefore, since $x_i(0) > 0$ and by compactness of Ω, it follows from a comparison argument that

$$x_i(t) \geq x_i(0)e^{\int_0^t \Omega_{ii}(s)ds} > 0,\ \forall t > 0.$$

□

Proof of Theorem 1: Without loss of generality, using Lemma 2.3, we assume given a V which is a uniform linear copositive weak Lyapunov function. Note that each matrix A in Ω is Hurwitz because existence of a weak Lyapunov function yields λ_{PF} $(A) \leq 0$ and in turn, by nonsingularity, λ_{PF} $(A) < 0$ (λ_{PF} denotes here the dominant eigenvalue of A).

We prove the result by induction. Notice first of all that the result is trivial in dimension 1. Indeed, for $n = 1$, it follows from assumption 2. that Ω is of the form $\Omega = [a,b]$ for some negative reals a and b. In this case, for any positive c, cx is a strictly decreasing common copositive Lyapunov function and the result follows trivially.

We consider next the n-dimensional case. Let x_0 be an arbitrary initial condition in $\mathbb{R}^n_+$, and $x(\cdot) \in \mathcal{S}(x_0)$. The function $V(x(t))$ is absolutely continuous and, for almost all $t \in \mathbb{R}$ it satisfies:

$$\dot{V}(x(t)) = c'\dot{x}(t) \leq -\varepsilon \min_i x_i(t)$$

for some $\varepsilon > 0$ as in Definition 2.2. Hence, integrating the previous inequality between 0 and $+\infty$, we obtain that $\int_0^{+\infty} \min_i x_i(t)\, dt < +\infty$. Then Barbalat's lemma[16] implies —by uniform continuity of $x(t)$ and $\min_i x_i(t)$— that $\min_i x_i(t) \to 0$ as $t \to +\infty$. In particular, we have that the omega limit set $\omega(x_0)$ of $x(\cdot)$ [i.e., the set of limit points of $x(t)$] is a subset of $\partial\mathbb{R}^n_+$. As Ω is convex and compact, $\omega(x_0)$ is compact and control invariant, i.e., for all $x_1 \in \omega(x_0)$ there exists $\tilde{x}(\cdot) \in \mathcal{S}(x_1)$ such that $\tilde{x}(t) \in \omega(x_0)$ for all $t \in \mathbb{R}$ (two other names for this property are "weakly invariant" or "viable"); see Ref. 17, Lemma 6.2.

To complete the proof we need some additional notation. For an arbitrary set $Z \subset \{1,2,\ldots,n\}$ we let L_Z denote $\{x \in \mathbb{R}^n_+ : x_i = 0,\ \forall\, i \in Z \text{ and } x_i > 0,\ \forall\, i \notin Z\}$. Clearly $\mathbb{R}^n_+ = \bigcup_{Z\subset\{1,2,\ldots,n\}} L_Z$ and $\partial\mathbb{R}^n_+ = \bigcup_{\emptyset\neq Z\subset\{1,2,\ldots,n\}} L_Z$. Hence there exists $Z \neq \emptyset$ such that $\omega(x_0) \cap L_Z$ is nonempty. In fact, we may assume that Z is minimal, i.e., there is no nonempty, proper subset Z' of Z with the property that $\omega(x_0) \cap L_{Z'}$ is nonempty.

We claim that $\omega(x_0) \cap L_Z$ is also forward control invariant, that is, control invariant for non-negative times. To see this, we choose for each $\tilde{x}0$ in $\omega(x_0) \cap L_Z$, a solution $\tilde{x}(t) \in \mathcal{S}(\tilde{x}_0)$ which remains in $\omega(x_0)$ for all $t \geq 0$ [this is possible by control invariance of $\omega(x_0)$]. To finish the proof, it is enough to show that $\tilde{x}(t) \in L_Z$ for $t > 0$. Suppose this were not the case, then there would exist some $\tau > 0$ such that $\tilde{x}(\tau) \notin L_Z$. Then there are two possibilities:

(1) There is some index $i \notin Z$ such that $\tilde{x}_i(0) > 0$, but $\tilde{x}_i(\tau) = 0$.
(2) There is some index $j \in Z$ such that $\tilde{x}_j(0) > 0$, but $\tilde{x}_j(\tau) = 0$.

The first scenario is impossible by Lemma 2.4. In other words, all components of $\tilde{x}(t)$ that are initially positive, remain positive for all forward times. As the second scenario must occur, this implies that $\tilde{x}(t)$ has entered a set $L_{Z'}$ at time τ, where Z' is a proper subset of Z. If $Z' = \emptyset$, then the solution has entered the interior of $\mathbb{R}^n_+$ at time τ, contradicting that $\tilde{x}(t)$ remains in $\partial\mathbb{R}^n_+$ for all $t \geq 0$. If Z' is a nonempty, proper subset of Z, then we have a contradiction to the fact that Z is minimal. Thus, $\omega(x_0) \cap L_Z$ is forward control invariant, as claimed.

We fix some $\tilde{x}_0 \in \omega(x_0) \cap L_Z$. By the above, for some $\tilde{x}(t) \in \mathcal{S}(\tilde{x}_0)$, we have that $\tilde{x}(t) \in \omega(x_0) \cap L_Z$ for all $t \geq 0$. Notice that $\tilde{x}(t)$ can be seen as embedded in a positive orthant of lower dimension, (indeed $\tilde{x}_i(t) = 0$ for all $i \in Z$). Let, for an arbitrary $\mathbb{R}^{n\times n}$ matrix A, A_Z be the $\mathbb{R}^{n-|Z|\times n-|Z|}$ principal submatrix obtained by removing the columns and rows corresponding to indices contained in Z. We define Ω_Z as follows

$$\Omega_Z := \{\tilde{A} : \exists A \in \Omega : \tilde{A} = A_Z\}.$$

Clearly, the nonzero components of $\tilde{x}$, (if any), are a solution of

$$\dot{\hat{x}}(t) \in \Omega_Z \hat{x}(t). \quad (34)$$

It is well known that principal submatrices of Metzler Hurwitz matrices are again Hurwitz[1] (obviously they are also Metzler matrices), hence Ω_Z is again a compact, convex set of Hurwitz matrices. Moreover, the components of c corresponding to the elements of $\{1,2,\ldots,n\} \setminus Z$, (let us denote them by $c_{\overline{Z}}$,) act as a linear copositive weak Lyapunov function for (34), (indeed, it is trivial to see that $c'_{\overline{Z}} A_Z \preceq 0$ for all $A_Z \in \Omega_Z$; the fact that $c'_Z A_Z \neq 0$ follows because A_Z is Hurwitz and hence nonsingular). Remarkably then, system (34) satisfies the assumptions of our Theorem. Hence, by total induction, (34) is asymptotically stable, and consequently $\omega(\tilde{x}_0) = \{0\}$. Since $\tilde{x}(t) \in \omega(x_0)$, for all $t \geq 0$, and since $\omega(x_0)$ is compact, it follows that $0 \in \omega(x_0)$.

By the Filippov Selection Lemma and Theorem 2, this proves the stability result. Alternatively, we can derive the conclusion as follows. Note that V is constant on $\omega(x_0)$. Indeed, were this not the case, then we could find $p, q \in \omega(x_0)$ with $p \neq q$ and $V(p) \neq V(q)$. Moreover, by continuity of V and $x(\cdot)$, there would then be two increasing sequences $t_n \to \infty$ and $s_n \to \infty$ such that $V(x(t_n)) \to V(p)$ and $V(x(s_n)) \to V(q)$ as $t_n, s_n \to \infty$. As $V(p) \neq V(q)$, this would contradict that $V(x(t))$ is nonincreasing. It follows that $V(x) = 0$ for all $x \in \omega(x_0)$, and therefore $\omega(x_0) = 0$. □

Remark A.1. An alternative proof of the above can be obtained by arguing as follows. Let e_i denote the i-th element of the canonical basis. As $c'x$ is a weak Lyapunov function, for each $x_i(t) \in \mathcal{S}(e_i)$ we have $c'x_i(t) \leq c'e_i$. Pick next ξ arbitrary in $\mathbb{R}^n$ (not necessarily positive initial condition). Clearly $\xi = \sum_i \xi_i e_i$ and by linearity and Filippov's Selection Lemma, for each $x(t) \in \mathcal{S}(\xi)$ there exists $x_i(t) \in \mathcal{S}(e_i)$ so that $x(t) = \sum_i \xi_i x_i(t)$. Let us now evaluate the function $c'|x|$ along the considered solution (here $|\cdot|$ denotes entrywise absolute values of a vector). Clearly:

$$c'|x(t)| = c'\left|\sum_i \xi_i x_i(t)\right| \leq \sum_i c'|\xi_i x_i(t)| = \sum_i |\xi_i| c' x_i(t) \leq \sum_i |\xi_i| c' e_i = c'|\xi|.$$

Hence, denoting $\|x\| := c'|x|$, we have shown $\|x(t)\| \leq \|x(0)\|$. Notice, further that $\|x\| = 0$ iff $x = 0$ and $\|x + y\| \leq \|x\| + \|y\|$. Hence, $\|\cdot\|$ is what in [20] is called an *a priori polytope norm* for the differential inclusion (1). Under existence of such an a priori polytope norm, asymptotic stability of (1) is equivalent to nonsingularity of all matrices in Ω, by virtue of Theorem 2.1 in Ref. 18. The proof technique in Ref. 18 is different and is built on an auxiliary linear discrete difference inclusion for which existence of an apriori norm implies validity of the so-called Finiteness Conjecture. We feel that the alternative proof given here, though limited to the special case of positive systems, is of independent interest since it uses an induction argument and indeed rather different tools from differential inclusions theory. □

Appendix B: Proof of Theorem 2

The proof of Theorem 2, which we discuss next, heavily relies on a powerful technical lemma which was proved in Ref. 19.

Proof of Theorem 2: Some of the implications, in particular $1 \Rightarrow 2 \Rightarrow 3 \Rightarrow 4$, are straightforward from the definition. The homogeneity assumption clearly comes in when proving the converse implications. Let us start from the easier one, $2 \Rightarrow 1$, which was already stated without proof in Ref. 20. Let $\xi \in \mathbb{R}^n$ be such that $|\xi| = 1$ and β be as in (12). By definition of class $\mathcal{KL}$ function there exists $\overline{T}$ such that $\beta(1,\overline{T}) \leq 1/2$. Let $M = 2\,\beta(1,0)$ and $\lambda = \log(2)/\overline{T}$. We claim that (11) holds with M and λ defined earlier. To see this, recall that for homogeneous systems $x(t, \lambda\xi, \sigma) = \lambda x(t,\xi,\sigma)$, for all $\lambda > 0$. As all estimates hold independently of the particular switching signal and in order to keep the notation simple we drop the dependence of x on σ. Hence, for arbitrary $k \in \mathbb{N}$ we have,

$$|x(k\overline{T}, \xi)| = |x(\overline{T}, x((k-1)\overline{T}, \xi))| \leq |x((k-1)\overline{T}, \xi)|\beta(1,\overline{T}) \leq |x((k-1)\overline{T}, \xi)|/2. \quad (35)$$

By induction, $|x(k\overline{T},\xi)| \leq |\xi|/2^k = e^{-\lambda k\overline{T}}|\xi|$. Then, letting t belong to $[(k-1)\overline{T}, k\overline{T})$ for some $k \in \mathbb{N}$, we have

$$|x(t, \xi)| = |x(t-(k-1)\overline{T}, x((k-1)\overline{T}, \xi))| \leq |x((k-1)\overline{T}, \xi)|\beta(1,0) \leq e^{-\lambda(k-1)\overline{T}} \times \beta(1,0)|\xi| \leq 2\beta(1,0)e^{-\lambda t}|\xi|.$$

We now turn to the most interesting implication, $4 \Rightarrow 2$. We define the set of reachable states in time T, starting from initial conditions in some compact $K \subset \mathbb{R}_n$ as

$$\mathcal{R}^T(K) = \{x \in \mathbb{R}^n : \exists \xi \in K, \exists \sigma \in \mathcal{M}_\Sigma, \exists \bar{t} \in [0,T] : x = x(\bar{t}, \xi, \sigma)\}.$$

Further, we let $\mathcal{R}(K)$ be the set of states reachable from K for arbitrary time, viz.

$$\mathcal{R}(K) = \bigcup_{T \geq 0} \mathcal{R}^T(K). \quad (36)$$

It is again a consequence of (7) that $\mathcal{R}^T(\lambda K) = \lambda \mathcal{R}^T(K)$ for any positive λ. For a given set $\mathcal{S}$ and input u one may consider the "first crossing time",

$$\tau(\xi, \mathcal{S}, u) = \inf\{t > 0 : x(t, \xi, u) \in \mathcal{S}\}. \quad (37)$$

Let $\varepsilon > 0$ be arbitrary; we define the set $\mathcal{C}_\varepsilon$ as

$$\mathcal{C}_\varepsilon = \{x \in \mathbb{R}^n : \varepsilon \leq |x| \leq 2\varepsilon\}. \quad (38)$$

and $\mathcal{B}_\varepsilon$ the closed ball of radius ε. Clearly, if $\mathcal{R}(\mathcal{C}_\varepsilon)$ is bounded, $\mathcal{R}(\mathcal{B}_\varepsilon)$ is also bounded; as a matter of fact we have $||\mathcal{R}(\mathcal{B}_\varepsilon)|| \leq ||\mathcal{R}(\mathcal{C}_\varepsilon)||$, where $||\mathcal{S}||$ denotes the norm of a set $\mathcal{S}$, which is defined as $\sup_{s \in \mathcal{S}} |s|$. We will show next that, for weakly attractive systems, $\mathcal{R}(\mathcal{C}_\varepsilon)$ is bounded. In particular, by virtue of weak attractivity, we have:

$$\forall \xi \in \mathcal{C}_\varepsilon,\ \forall \sigma \in \mathcal{M}_\Sigma \quad \exists t \geq 0 : x(t, \xi, \sigma) \in \mathcal{B}_\varepsilon. \quad (39)$$

By Corollary III.3 of Ref. 19, we have

$$T_\varepsilon \doteq \sup_{\xi \in \mathcal{C}_\varepsilon, \sigma \in \mathcal{M}_\Sigma} \tau(\xi, \mathcal{B}_\varepsilon, \sigma) < +\infty. \quad (40)$$

Since, for a forward complete family of systems, the set of reachable states in bounded time from bounded initial conditions is bounded (Ref. 19 Fact III.1), we have that

$$\|\mathcal{R}(\mathcal{B}_\varepsilon)\| \leq \|\mathcal{R}(\mathcal{C}_\varepsilon)\| = \left\|\mathcal{R}^{T_\varepsilon}(\mathcal{C}_\varepsilon)\right\| \doteq \delta_\varepsilon < +\infty. \qquad (41)$$

It is worth pointing out how the equality above follows by contradiction; indeed, in case $||\mathcal{R}^{T_\varepsilon}(\mathcal{C}_\varepsilon)||<||\mathcal{R}(\mathcal{C}_\varepsilon)||$, there would exist $t > T_\varepsilon$, $\sigma \in \mathcal{M}_\Sigma$ and $\xi \in \mathcal{C}_\varepsilon$ such that $|x(t, \xi, \sigma)| > |w|$ for all $w \in \mathcal{R}^{T_\varepsilon}(\mathcal{C}_\varepsilon)$ and, a fortiori, for all $w \in \mathcal{R}^{T_\varepsilon}(\mathcal{B}_\varepsilon)$. However, by definition (40) there exists $\tau \leq T_\varepsilon$ such that $x(\tau, \xi, \sigma) \in \mathcal{B}_\varepsilon \bigcap \mathcal{C}_\varepsilon$. Let us, without loss of generality take $\tau \leq t$ to be the maximum real such that $x(\tau, \xi, \sigma) \in \mathcal{B}_\varepsilon \bigcap \mathcal{C}_\varepsilon$. Clearly, $t - \tau \leq T_\varepsilon$ [again by (40)], so that $x(t, \xi, \sigma) \in \mathcal{R}^{T_\varepsilon}(\mathcal{B}_\varepsilon)$, thus contradicting our previous conclusion.

Notice that, without using assumption (7), we already proved that weak attractivity implies uniform Lagrange stability, viz.

$$\forall \varepsilon > 0,\ \exists \delta_\varepsilon : |\xi| \leq \varepsilon \Rightarrow |x(t, \xi, \sigma)| \leq \delta_\varepsilon, \quad \forall t \geq 0,\ \forall \sigma(\cdot). \qquad (42)$$

For homogeneous systems this is equivalent to uniform Lyapunov stability. In fact,

$$\forall \varepsilon > 0,\ |\xi| \leq \varepsilon \Rightarrow |x(t, \xi, \sigma)| = |\xi||x(t, \xi/|\xi|, \sigma)| \leq \varepsilon\delta_1 \quad \forall t \geq 0,\ \forall \sigma(\cdot)$$

and hence,

$$\forall \varepsilon > 0, \exists \tilde{\delta}_\varepsilon = \varepsilon/\delta_1 : |\xi| \leq \tilde{\delta}_\varepsilon \Rightarrow |x(t, \xi, \sigma)| \leq \varepsilon, \quad \forall t \geq 0,\ \forall \sigma(\cdot).$$

Weak attractivity and Lyapunov stability imply attractivity and Lyapunov stability, see Theorem 1 in Ref. 19. The main result now follows from Theorem 2 in Ref. 19, where equivalence of uniform Lyapunov stability plus attractivity and uniform global asymptotic stability is shown. □

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