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Box invariance in biologically-inspired dynamical systems☆

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ABSTRACT

A dynamical system is box invariant if there exists a box-shaped positively invariant region. We show that box invariance can be checked in cubic time for linear and affine systems, and that it remains decidable for classes of nonlinear systems of interest (with polynomial structure). We present results on the robustness of box invariance for linear systems using spectral properties of Metzler matrices. We also present sufficient conditions for establishing box invariance of switched and hybrid systems. In general, we argue that box invariance is a characteristic of many biologically-inspired dynamical models.

1. Introduction

An *invariant* set is a subset of the state space of a dynamical system with the property that, if the system state is in this set at some time, then it will stay in the set indefinitely in the future (Blanchini, 1999). An invariant set is extremely useful from the perspective of formal analysis and verification (Clarke, Grumberg, & Peled, 2000). The task in formal verification is to show that none of the trajectories of a given dynamical system violate a given property, such as a liveness or safety property, or in the opposite instance to find "witnesses" that do not abide by such properties. *Safety* specifications form an important class of properties, which encode the condition that a system can never reach a given subset of "unsafe" or "bad" states. Direct verification of safety properties is difficult because computing the set of reachable states is often infeasible. However, an invariant set can be used to verify a safety property by showing that it encloses all reachable states, but none of the unsafe states. From a dual perspective, invariants can be used to look at *reachability* properties, where the objective is to verify if any trajectory of the system, starting from a region of the state space, will reach a target set (which is again a subset of the state space). The concept of invariance can also be related to certain notions of stability (Podelski & Wagner, 2006). This motivates the need to develop effective and constructive approaches to discover invariant sets for dynamical systems—and especially invariant sets with simple shapes.

Positively invariant sets can be obtained by exploiting the property that their boundaries may correspond to level surfaces of a proper Lyapunov-like function. This approach has been the source of several results on the existence of positively invariant sets (Blanchini, 1999; Kiendl, Adamy, & Stelzner, 1992). However, this is quite restrictive in general, since systems that are not stable can still have useful invariant sets.

In this paper, we focus on positively invariant sets that are in the form of a box, that is, a hyper-rectangular region specified by giving (upper and lower) bounds for each state variable. The concept of box invariance is related to a number of studies in the literature (Blanchini, 1999) (see Section 2.1). For instance, Kiendl et al. (1992) look at the use of vector norms to study stability. The notions that are developed in the present study are related to that of component-wise stability (Pastravanu & Voicu, 2003; Voicu, 1984), as well as to the concepts of practical stability and Lagrange stability (Passino, Burgess, & Michel, 1995).

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The study of several systems, especially models drawn from the domain of systems biology, has suggested that they frequently admit box-shaped, positively invariant sets. This seems natural in retrospect since state variables often correspond to physical quantities that are naturally constrained and tend to either degrade, or remain conserved. In this paper, we are interested in the practical aspects of the notion of box invariance. In particular, we focus on how complex it is to check for box invariance of a dynamical model, as well as to construct a particular box, whenever possible. More precisely, we show that it is computationally feasible to check if a dynamical system is invariant with respect to a box set, and to explicitly find out box invariant sets for a large class of dynamical systems (in particular, biological ones). Because of the discussed connections with other notions in systems theory, it is then argued that box invariance is an ideal concept for building analysis and verification tools to investigate such systems.

Outline. We formally define the notion of box invariance in Section 2. Next, we present necessary and/or sufficient characterizations of this notion for linear (Section 3), affine (Section 3.3), and classes of nonlinear systems (Section 4) that are especially meaningful for models of biological systems. Box invariance of linear systems is strongly related to the theory of Metzler matrices, as explained in Section 3.1. Using this connection, we perform robustness analysis of box invariant systems in Section 3.2. In Section 5, we extend the study to the more general case of switched and hybrid systems. All throughout, we will present computational complexity results and illustrate the introduced concepts using examples from systems biology.

2. The concept of box invariance

We consider general and uncontrolled dynamical systems of the form $\dot{\boldsymbol{x}} = f(\boldsymbol{x}), \boldsymbol{x} \in \mathbb{R}^n$. We assume the basic boundedness and Lipschitz properties that ensure the existence of a unique solution of the vector field, given any possible initial condition. A rectangular box around a point $\boldsymbol{x}_0$ is specified using two diagonally opposite points $\boldsymbol{l}$ and $\boldsymbol{u}$, where $\boldsymbol{l} < \boldsymbol{x}_0 < \boldsymbol{u}$ (interpreted component-wise) and is defined as $Box(\boldsymbol{l}, \boldsymbol{u}) := \{\boldsymbol{x} \mid \boldsymbol{l} \leq \boldsymbol{x} \leq \boldsymbol{u}\}$. Such a box has $2n$ faces consisting of n lower and n upper faces. The jth lower face is defined as $Face\,L^j(\boldsymbol{l}, \boldsymbol{u}) := \{\boldsymbol{x} \in Box(\boldsymbol{l}, \boldsymbol{u}) \mid x_j = l_j\}$ and the jth upper face is defined as $Face\,U^j(\boldsymbol{l}, \boldsymbol{u}) := \{\boldsymbol{x} \in Box(\boldsymbol{l}, \boldsymbol{u}) \mid x_j = u_j\}$, for $j \in \{1, \dots, n\}$.

Definition 1 (*Box Invariant System*). A dynamical system $\dot{\boldsymbol{x}} = f(\boldsymbol{x})$ is said to be *box invariant* around an equilibrium point $\boldsymbol{x}_0$ if there exists a finite rectangular box $Box(\boldsymbol{l}, \boldsymbol{u})$ around $\boldsymbol{x}_0$ such that $f(\boldsymbol{y})_j \leq 0$ whenever $\boldsymbol{y} \in Face\,U^j(\boldsymbol{l}, \boldsymbol{u})$ and $f(\boldsymbol{y})_j \geq 0$ whenever $\boldsymbol{y} \in Face\,L^j(\boldsymbol{l}, \boldsymbol{u})$. The system is said to be *strictly box invariant* if the inequalities hold strictly.

An equivalent definition of box invariant system can be given as a system that admits a box as a positively invariant set. In the case of multiple equilibria, either finite or infinite in cardinality, we require the existence of (possibly different) boxes for each of them.

Note that the existence of a box is unaffected by the reordering of state variables and by rotations by multiples of $\pi/2$. It also displays invariance under independent stretches of the coordinates. Nevertheless, it is not invariant under general linear transformations.

Definition 2 (*Symmetrical Box Invariance*). A system $\dot{\boldsymbol{x}} = f(\boldsymbol{x})$ is said to be *symmetrically box invariant* around the equilibrium $\boldsymbol{x}_0$ if there exists a point $\boldsymbol{u} > \boldsymbol{x}_0$ (interpreted component-wise) such that the system $\dot{\boldsymbol{x}} = f(\boldsymbol{x})$ is box invariant with respect to the box $Box(2\boldsymbol{x}_0 - \boldsymbol{u}, \boldsymbol{u})$.

2.1. Box invariance through vector norms

The boundary of a box can be seen as a level surface of a function defined by a vector norm. Let $\|\boldsymbol{x}\|_\infty = \max\{|x_i|, i = 1, \dots, n\}$ denote the infinity norm on an n-dimensional Euclidean space. Let D be an $n \times n$ positive diagonal matrix. Any level set of the positive real-valued function $\|D\boldsymbol{x}\|_\infty$ coincides with a hyper-rectangle in $\mathbb{R}^n$ that is symmetric around the origin. Specifically, for any positive constant $c \in \mathbb{R}$, $\{\boldsymbol{x} \mid \|D\boldsymbol{x}\|_\infty \leq c\} = Box(-cD^{-1}\mathbf{1}, cD^{-1}\mathbf{1})$, where $\mathbf{1}$ is the n-dimensional unity vector. Accordingly, symmetrical box invariance has in part already, though not explicitly, been studied in the literature by exploring when $\|D\boldsymbol{x}\|_\infty$ is a Lyapunov function for a dynamical system (Pastravanu & Voicu, 2003; Voicu, 1984). For linear systems, a sufficient condition for this to hold is the existence of a matrix Q of proper size, with $\mu(Q) < 0$, such that $WA = QW$ (Kiendl et al., 1992). Here $\mu(Q)$ is a matrix measure defined as $\mu(Q) = \lim_{\Delta \to 0^+} \frac{\|I + \Delta Q\|_\infty - 1}{\Delta}$.

Whereas the existence of box invariants is closely related to Lyapunov stability under infinity vector norms for linear systems (see Theorems 2 and 3), this is not so for more general nonlinear and hybrid systems. Invariants are also not easy to compute in general. This motivates the search for invariants of a simple form, such as a box. As we show in the present work, box invariants can be easily *computed* using simple constraint-solving techniques.

3. Box invariant linear and affine systems

Given a linear system and a box around its equilibrium point, the problem of checking whether the system is box invariant with respect to the given box can be solved by verifying the related condition only at the 2^n vertices of the box (rather than on all the points of the surface of the box). The set of vertices, $Vert(\boldsymbol{l}, \boldsymbol{u})$, of the box $Box(\boldsymbol{l}, \boldsymbol{u})$ is defined as $Vert(\boldsymbol{l}, \boldsymbol{u}) = \{\boldsymbol{x} \mid x_i = l_i \vee x_i = u_i, \forall i\}$.

Proposition 1. *A linear system $\dot{\boldsymbol{x}} = A\boldsymbol{x}, \boldsymbol{x} \in \mathbb{R}^n$, is box invariant if there exist two points $\boldsymbol{l} \in (\mathbb{R}^-)^n$ and $\boldsymbol{u} \in (\mathbb{R}^+)^n$ such that for each point $\boldsymbol{c} \in Vert(\boldsymbol{l}, \boldsymbol{u})$, we have $A\boldsymbol{c} \sim \mathbf{0}$, where $\sim_i$ is $\leq$ if $c_i = u_i$ and $\sim_i$ is $\geq$ if $c_i = l_i$.*

The proof follows the observation that the inequalities state that the vector field points inwards on the 2^n vertices in $Vert(\boldsymbol{l}, \boldsymbol{u})$, and that it is possible to extend by linearity the value of the vector field at other points on the faces of the box. Proposition 1 claims that box invariance of linear systems can be checked by testing the satisfiability of $n2^n$ linear inequality constraints, over $2n$ unknowns (given by $\boldsymbol{l}$ and $\boldsymbol{u}$). Lemmas 1 and 2 will allow us to simplify this requirement to testing n linear inequalities over n variables. Observe that the notion of box invariance and symmetrical box invariance are equivalent for linear systems:

Lemma 1. *A linear system $\dot{\boldsymbol{x}} = A\boldsymbol{x}$, where $A \in \mathbb{R}^{n \times n}$, is box invariant if and only if it is symmetrically box invariant.*

Proof. If the linear system is symmetrically box invariant, then it is clearly also box invariant. To prove the converse, assume that the linear system is box invariant with respect to the box $Box(\boldsymbol{l}, \boldsymbol{u})$, where $\boldsymbol{l} \in (\mathbb{R}^-)^n$ and $\boldsymbol{u} \in (\mathbb{R}^+)^n$. We will show that the linear system is also box invariant with respect to the (symmetrical) box $Box(-\boldsymbol{c}, \boldsymbol{c})$, where $c_i = min(|l_i|, |u_i|)$. Consider first $i = 1$ and the case when $u_1 \leq -l_1$ so that $c_1 = u_1$. On the face $Face\,U^1(\boldsymbol{l}, \boldsymbol{u})$ of the $x_1 = u_1$ hyper-surface, by definition of $\boldsymbol{c}$, we have $Face\,U^1(-\boldsymbol{c}, \boldsymbol{c}) \subseteq Face\,U^1(\boldsymbol{l}, \boldsymbol{u})$. Hence, $(A\boldsymbol{x})_1 \leq 0, \forall \boldsymbol{x} \in Face\,U^1(-\boldsymbol{c}, \boldsymbol{c})$. Since $A(-\boldsymbol{x}) = -A\boldsymbol{x}$, we also get $(A\boldsymbol{x})_1 \geq 0$ for all $\boldsymbol{x} \in Face\,L^1(-\boldsymbol{c}, \boldsymbol{c})$. The opposite case when $-l_1 < u_1$ is similar. Repeating this argument for $i = 2, 3, \dots, n$, completes the proof. □

The following result shows that box invariance can be equivalently checked on a new matrix that is obtained from the original system matrix A. The proof is again based on the simplification of the $n2^n$ inequality constraints.

Lemma 2. *An n-dimensional linear system $\dot{\boldsymbol{x}} = A\boldsymbol{x}$ is symmetrically box invariant if and only if there exists a positive vector $\boldsymbol{c} \in (\mathbb{R}^+)^n$ such that $A^\star\boldsymbol{c} \le \boldsymbol{0}$, where the components $a^\star_{ii} = a_{ii}$ and $a^\star_{ij} = |a_{ij}|$ for $i \ne j$; $i, j \in \{1, \dots, n\}$. This is equivalent to checking if the system defined by the matrix $A^\star$ is symmetrically box invariant.*

Proof. By Proposition 1, box invariance of $\dot{\boldsymbol{x}} = A\boldsymbol{x}$ is equivalent to the satisfiability of $n2^n$ inequality constraints. Out of these $n2^n$ constraints, consider the following subset of 2^{n-1} constraints:

$$a_{11}u_1 + a_{12}c_2 + a_{13}c_3 + \dots + a_{1n}c_n \le 0,$$

where $c_i \in \{u_i, -u_i\}$. These 2^{n-1} constraints are subsumed by one of them, which is the strongest constraint:

$$a_{11}u_1 + |a_{12}|u_2 + |a_{13}|u_3 + \dots + |a_{1n}|u_n \le 0.$$

This way the $n2^{n-1}$ constraints are equivalent to satisfiability of n constraints, which can be succinctly written as $A^\star\boldsymbol{u} \le \boldsymbol{0}$, where $A^\star$ is as defined in the statement and $\boldsymbol{u}$ is a positive n-dimensional vector. Notice that, because of symmetry ($\boldsymbol{l} = -\boldsymbol{u}$), we do not need to consider the remaining $n2^{n-1}$ constraints. □

Putting together Lemmas 1 and 2 we conclude that checking whether an n-dimensional linear system $\dot{\boldsymbol{x}} = A\boldsymbol{x}$ is box invariant reduces to existence of a positive n-dimensional vector $\boldsymbol{c} \in (\mathbb{R}^+)^n$ such that $A^\star\boldsymbol{c} \le 0$. This can be generically solved using linear programming in *polynomial* time. However, we can do much better. Since $A^\star$ has non-negative off-diagonal terms, it is immediate that the Fourier–Motzkin procedure (Dantzig & Eaves, 1973) can be used to solve the n linear inequality constraints $A^\star\boldsymbol{c} \le 0$ for positive $\boldsymbol{c}$ in $O(n^3)$ time.

In fact, we can exactly characterize when the Fourier–Motzkin elimination procedure would succeed in finding a solution using the notion of *principal minors*. A principal minor of a matrix A is the determinant of the submatrix of A formed by removing certain rows and the corresponding columns from A (Berman & Plemmons, 1994). A matrix A is said to be a *P-matrix* if all of its principal minors are positive (Berman & Plemmons, 1994; Horn & Johnson, 1991). Lemma 3 formally recapitulates the above claims.

Lemma 3. *Let A be an $n \times n$ matrix such that $a_{ij} \ge 0$ for all $i \ne j$. Then, the following statements are equivalent:*

(1) *The linear system $\dot{\boldsymbol{x}} = A\boldsymbol{x}$ is strictly symmetrically box invariant.*
(2) *$-A$ is a P-matrix.*
(3) *$\forall\, i = 1, 2, \dots, n$, the determinant of the top left $i \times i$ submatrix of $-A$ is positive.*

Proof. Using Lemma 2, we know that Condition 1 is equivalent to the existence of a point $\boldsymbol{u} \in (\mathbb{R}^+)^n$ such that $-A\boldsymbol{u} > \boldsymbol{0}$. We apply the well-known Fourier–Motzkin elimination procedure (Dantzig & Eaves, 1973) to $-A\boldsymbol{u} > \boldsymbol{0}$. Due to the form of A, this procedure reduces to Gaussian reduction/elimination procedure for converting $-A$ to upper triangular form. A positive $\boldsymbol{u}$ exists iff all diagonals in the triangular form of $-A$ are positive. This shows Condition 1 is equivalent to Condition 3. Repeating this argument using different permutations of the rows and columns of $-A$, we infer the equivalence to Condition 2. □

If A is nonsingular, then box invariance is equivalent to *strict* box invariance, and results of Lemma 3 apply to box invariance.

Remark 1. Lemma 3 shows that box invariance of a linear system characterized by matrix A can also be tested by checking if the modified matrix $-A^\star$ is a P-matrix. It is known that the problem of deciding if a given matrix is a P-matrix is co-NP-hard (Coxson, 1994). But in our case, due to the special form of $A^\star$, we can determine if $-A^\star$ is a P-matrix using the simple $O(n^3)$ Fourier–Motzkin elimination procedure. □

In the language of vector norms (see Section 2.1), the existence of a positive vector $\boldsymbol{c}$ such that $A^\star\boldsymbol{c} \le 0$ is equivalent to the verification of the inequality $\mu(D^{-1}A^\star D) \le 0$, where D is the positive diagonal matrix $D = \mathtt{diag}(\boldsymbol{c})$. This connection was known (Kiendl et al., 1992; Pastravanu & Voicu, 2003), but we now additionally have the following new complexity result—notice that it is effectively stated for rational-valued matrices since irrational numbers are computationally difficult to represent.

Theorem 1. *Let $A \in \mathbb{Q}^{n\times n}$ be any rational matrix, and let $A^\star$ denote the matrix obtained from A so that $a^\star_{ii} = a_{ii}$ and $a^\star_{ij} = |a_{ij}|$ for $i \ne j$. The following problems are all equivalent and can be solved in $O(n^3)$ time:*

- *Is the linear system $\dot{\boldsymbol{x}} = A\boldsymbol{x}$ strictly box invariant?*
- *Is the linear system $\dot{\boldsymbol{x}} = A^\star\boldsymbol{x}$ strictly box invariant?*
- *Is there a $\boldsymbol{z} > \boldsymbol{0}$ such that $A^\star\boldsymbol{z} < \boldsymbol{0}$?*
- *Does there exist a positive diagonal matrix D s.t. $\mu(D^{-1}A^\star D) < 0$ (in the infinity norm)?*
- *Is $-A^\star$ a P-matrix?*

Proof. The theorem follows immediately from Lemmas 1–3 and the remarks on the use of the Fourier–Motzkin procedure (Dantzig & Eaves, 1973). □

It is important to underline that it is not only possible to "decide" box invariance, but also to find box invariant sets by generating solutions for the described linear constraint satisfaction problem. Indeed, for a linear system, $\dot{\boldsymbol{x}} = A\boldsymbol{x}$, we can associate a *cone* in the positive $(2^n)^{th}$-ant described by the set

$$\mathcal{C} = \{\boldsymbol{x} \in (\mathbb{R}^+)^n : A^\star\boldsymbol{x} \le \boldsymbol{0}\}.$$

Any choice of a single vertex in the cone $\mathcal{C}$ and its origin-symmetric, or of a pair of points in $\mathcal{C}$, determine respectively a symmetric and a non-symmetric box for the system described by A.

We next show that, for linear systems, box invariance is a stronger concept than stability (see also related results in Kiendl et al. (1992), Loskot, Polanski, and Rudnicki (1998) and Pastravanu and Voicu (2003)).

Theorem 2. *If a linear dynamical system is box invariant, then it is stable. The converse is not true.*

Proof. For a linear system, if $Box(-\boldsymbol{c}, \boldsymbol{c})$ is a box-shaped invariant, then so is $Box(-\alpha\boldsymbol{c}, \alpha\boldsymbol{c})$ for *any* $\alpha > 0$. Thus, given any neighborhood of the equilibrium point, call it $\mathcal{B}$, there exists an $\alpha^* > 0$ that defines a box small enough to be contained in $\mathcal{B}$ and, by its invariant property, all the trajectories starting within this box will stay in it, and thus also in $\mathcal{B}$. The converse is not true as the system $\dot{x}_1 = -x_1 + 10x_2$, $\dot{x}_2 = -10x_1 - x_2$ is stable, but not box invariant. □

3.1. Connections with Metzler Matrices

Matrices with *non-negative off-diagonal terms*, such as $A^\star$ are known as *Metzler* matrices. Metzler matrices are related to non-negative matrices (Berman & Plemmons, 1994; Seneta, 1973), first

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studied by Frobenius (1908) and Perron (1907). Many results for Metzler matrices can be shown provided a structural property, which we will assume henceforth, holds:

Definition 3 (*Irreducible Matrix*). An $(n \times n)$-matrix A, indexed by $\{1, \ldots, n\}$, is said to be irreducible if for every pair $i, k \in \{1, \ldots, n\}$ of indices, there is a sequence of indices $\{j_1, j_2, \ldots, j_l\}$, $l \leq n-2$, such that the elements $A(i, j_1), A(j_1, j_2), \ldots, A(j_l, k)$ are all non-zero.

In practice, the irreducibility assumption is not restrictive, as violation of irreducibility implies a certain level of decoupling between parts of the dynamical system, which suggests a separate study of these different parts. Example 2 illustrates this fact. We will use the following properties of Metzler matrices.

Proposition 2 (*From Seneta (1973)*). *Suppose $A^\star \in \mathbb{R}^{n\times n}$ is Metzler and irreducible. Then it has an eigenvalue τ which verifies the following statements:*

(1) *τ is real; furthermore, $\tau > Re(\lambda)$, where λ is any other eigenvalue of $A^\star$ different from τ;*
(2) *τ is associated with a unique (up to multiplicative constant) positive (right) eigenvector $\boldsymbol{x}^\tau$;*
(3) *$\tau \leq 0$ iff $\exists \boldsymbol{c} > \boldsymbol{0}$, such that $A^\star \boldsymbol{c} \leq \boldsymbol{0}$; $\tau < 0$ iff there is at least one strict inequality in $A^\star \boldsymbol{c} \leq \boldsymbol{0}$;*
(4) *$\tau < 0$ iff all the principal minors of $-A^\star$ are positive;*
(5) *$\tau < 0$ iff $-(A^\star)^{-1} > 0$.*

This special τ is known as the *Perron–Frobenius eigenvalue* of the matrix. It is of interest to modify point (3) as follows (the proof can be directly adapted).

Proposition 3. *Suppose $A^\star$ is Metzler, irreducible, and has negative diagonal terms. Then all the points of the previous fact hold but (3), which needs to be modified as:*

(3) *$\tau \leq 0$ iff $\exists \boldsymbol{c} > \boldsymbol{0}$, such that $A^\star \boldsymbol{c} \leq \boldsymbol{0}$; $\tau < 0$ iff $\exists \boldsymbol{c} > \boldsymbol{0}$, such that $A^\star \boldsymbol{c} < \boldsymbol{0}$.*

The following result will be used later.

Proposition 4 (*From Seneta (1973)*). *Given a Metzler matrix $A^\star$, with Perron–Frobenius eigenvalue τ and a positive vector $\boldsymbol{x}$, the following holds, for $i \in \{1, \ldots, n\}$:*

$$\min_i \frac{1}{x_i} \sum_{j=1}^n x_j a^\star_{ij} \leq \tau \leq \max_i \frac{1}{x_i} \sum_{j=1}^n x_j a^\star_{ij}.$$

Using the Perron eigenvector $\boldsymbol{x}^\tau$ in place of $\boldsymbol{x}$ turns both inequalities into equalities.

The results described in Propositions 2–4 are interesting because they provide alternative proofs of Lemma 3 and Theorem 2. In particular, we can go beyond Theorem 2 and argue that strict box invariance is *equivalent* to asymptotic stability for linear systems specified by Metzler matrices.

Theorem 3. *Let A be Metzler, irreducible and with negative diagonal elements. The system $\dot{\boldsymbol{x}} = A\boldsymbol{x}$ is strictly box invariant if and only if it is asymptotically stable.*

Proof. Observe that the system is strictly box invariant iff there exists $\boldsymbol{c} > 0$ s.t. $A\boldsymbol{c} < \boldsymbol{0}$ (by Lemmas 1 and 2). The existence of such a $\boldsymbol{c}$ is equivalent, by Point (3) of Proposition 3, to $\tau < 0$. The negativity of the Perron–Frobenius eigenvalue is equivalent to asymptotic stability (by Point (1) of Proposition 2). □

The use of Metzler matrices has wide applications in biological models, for instance in the study of positive systems (Farina & Rinaldi, 2000) and compartmental systems (Sorensen, 1985). In particular, the negativity of the diagonal elements of a matrix may denote a class of reactions with decay, or be related to models with some forms of loss or dissipation.

3.2. Robust properties of box invariance

The issue of *robustness* arises in biological models when some parameters of the system are not exactly measured and may be only known to lie within some bounds. These parameters can represent rates of reactions that are often subject to intrinsic or measurement noise (McAdams & Arkin, 1999), especially for models describing environments with only a few interacting species (Gillespie, 1977).

We divide the study of robustness within three cases.

Diagonal perturbations. Given a box invariant Metzler matrix $A^\star$, consider the matrix $A^\star_\epsilon$, where $a^\star_{\epsilon,ij} = a^\star_{ij}, i \neq j$, while $a^\star_{\epsilon,ii} = a^\star_{ii}(1+\epsilon)$. In other words, $A^\star_\epsilon = A^\star + \epsilon\, \mathtt{diag}(a^\star_{ii})$. If $\epsilon > 0$, then the perturbed system remains box invariant. If $\epsilon < 0$, then the Perron–Frobenius eigenvalue τ_ϵ of $A^\star_\epsilon$ may still be negative for some ϵ. Using the Perron–Frobenius eigenvector $\boldsymbol{x}^\tau$ of $A^\star$ in Proposition 4, we get $\tau^\epsilon \leq \max_i \frac{1}{x_i^\tau} \sum_{j=1}^n x_j^\tau a^\star_{\epsilon,ij}$, which simplifies to $\tau^\epsilon \leq \max_i(\tau + \epsilon a^\star_{ii})$. Since $\epsilon < 0$, it follows that $\tau_\epsilon \leq \tau + \epsilon \min_i a^\star_{ii}$. Hence, a lower bound for the allowable (negative) perturbation that maintains box invariance is given by the inequality $\epsilon > -\frac{\tau}{\min_i a^\star_{ii}}$.

Off-diagonal perturbations. Consider a perturbed matrix $A^\star_\epsilon$, where $a^\star_{\epsilon,ij} = a^\star_{ij}(1+\epsilon_{ij}), \forall i, j \neq i$ and $a^\star_{\epsilon,ii} = a^\star_{ii}$. We are interested in finding how much we can perturb the off-diagonal elements of the matrix $A^\star$, while preserving its box invariance. We solve this problem by separately considering it for each of the n components. Specifically, along direction i, using Proposition 4, we formulate the following problem:

$$\max_{\boldsymbol{\epsilon}_i \geq 0} \|\boldsymbol{\epsilon}_i\|_2^2 \quad \text{s.t.} \sum_{j=1}^n a^\star_{\epsilon,ij} < 0, \epsilon_{ii} = 0,$$

where the vector $\boldsymbol{\epsilon}_i = [\epsilon_{ij}]_{j=1,\ldots,n}$. The choice of the norm is arbitrary here. Note that we focus on positive perturbations for the off-diagonal terms, because only those can negatively affect box invariance. (The reader should notice that, while negative perturbations do not affect box invariance, they may interfere with the Metzler structure of the matrix—in particular, its irreducibility.) The optimization problem can be solved by introducing two Lagrange multipliers (respectively $\lambda > 0$ and ν), one for each constraint. Direct calculations show that the solution has the following form, $\forall j \neq i$:

$$\epsilon_{ii} = 0; \qquad \epsilon_{ij} = \frac{1}{2}\left(\frac{a^\star_{ij}}{\sum\limits_{j=1, j\neq i}^n a^\star_{ij}} + \frac{a^\star_{ii} a^\star_{ij}}{\sum\limits_{j=1, j\neq i}^n (a^\star_{ij})^2}\right).$$

For each i, we can thus get a bound for the off-diagonal perturbations ϵ_{ij}.

General perturbations. We can tackle the problem more generally, albeit at the expense of renouncing to closed-form solutions. Let $A^\star$ be a Metzler matrix that describes a box invariant linear system. Consider the perturbed matrix $A^\star_\epsilon = A^\star + E = A^\star + \sum_{i,j=1}^n \epsilon_{ij}[\Delta_{(i,j)}]$, where $\Delta_{(i,j)}$ is an $n \times n$ matrix that has a 1 in position (i, j), and 0 elsewhere, and $\epsilon_{ij} \geq 0, \forall i, j \in \{1, \ldots, n\}$. It then makes sense, in order to understand what the worst (in some sense) perturbation is that does not affect the box invariance property, to set up the following problem:

$$\max_E f(E), \quad \text{s.t.} \ (A^\star_\epsilon \boldsymbol{1} < \boldsymbol{0}) \vee (\boldsymbol{1}^T A^\star_\epsilon < \boldsymbol{0}), E \geq \boldsymbol{0}.$$

Here $f(E)$ is a measure of the "perturbation level" introduced in the model. For instance, we may choose $f(E) = \sum_{i,j=1}^n \epsilon_{ij}$, or $f(E) = \|E\|_p, p \geq 1$. For the 2-norm ($p = 2$), interpreting E as a

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function of its elements ϵ_{ij}, introducing an epigraph and resorting to the Schur complement, we can reformulate the problem as the following linear matrix inequality (LMI):

$$\max_{\substack{\epsilon_{ij}\geq 0\\ s\geq 0}} s, \quad \text{s.t.} \begin{cases} \begin{bmatrix} -sI & -E(\epsilon) \\ E(\epsilon) & sI \end{bmatrix} \succeq 0, \\ \min\left\{A^{\star}_{\epsilon}\mathbf{1}, \mathbf{1}^T A^{\star}_{\epsilon}\right\} < \mathbf{0}, \end{cases}$$

where the last inequality is interpreted component-wise.

3.3. *Affine systems*

We now consider an n-dimensional affine system $\dot{\boldsymbol{x}} = A\boldsymbol{x} + \boldsymbol{b}$. We can relate the box invariance of such a system to the condition that the equilibrium point $\boldsymbol{x}_0$ of the model lies in the positive quadrant, $\boldsymbol{x}_0 > \mathbf{0}$ (component-wise). The idea is again to exploit a Metzler matrix $A^{\star}$ that corresponds to A, to deduce possible box properties of the original system around $\boldsymbol{x}_0$. Note that the condition that $\boldsymbol{x}_0$ belongs to the positive quadrant is naturally satisfied in biological models where state variables often represent concentrations of species or reactants. We give an alternate proof of the following result known in the literature (Farina & Rinaldi, 2000).

Lemma 4. *If the affine system $\dot{\boldsymbol{x}} = A\boldsymbol{x} + \boldsymbol{b}$ is characterized by a Metzler matrix A and $\boldsymbol{b} > \mathbf{0}$, then its equilibrium point $\boldsymbol{x}_0 > \mathbf{0}$ if and only if the system is box invariant.*

Proof. "⇒": Consider the Perron–Frobenius eigenvalue τ^A of A and the corresponding positive left eigenvector $\boldsymbol{x}^{\tau}$. Multiplying by this eigenvector, we have

$$0 = (\boldsymbol{x}^{\tau})^T(A\boldsymbol{x}_0 + \boldsymbol{b}) = (\boldsymbol{x}^{\tau})^T(\tau\boldsymbol{x}_0 + \boldsymbol{b}),$$

which, given the positivity of the involved terms, implies that $\tau < 0$. Using Proposition 2, we conclude that the affine system is box invariant.
"⇐": The box invariant property of the Metzler matrix A allows us to use the last point of Proposition 2. The equilibrium $\boldsymbol{x}_0 : A\boldsymbol{x}_0 + \boldsymbol{b} = \mathbf{0}$, will be $\boldsymbol{x}_0 = -A^{-1}\boldsymbol{b} > \mathbf{0}$. □

The assumptions of the previous theorem can be relaxed to having a non-negative $\boldsymbol{b} \geq \mathbf{0}$, $\boldsymbol{b} \neq \mathbf{0}$ at the expense of the necessity of the claim (the proof follows similarly).

Theorem 4. *If the affine system $\dot{\boldsymbol{x}} = A\boldsymbol{x} + \boldsymbol{b}$ is characterized by a Metzler matrix and its equilibrium point $\boldsymbol{x}_0 > \mathbf{0}$, then the positivity of its drift term $\boldsymbol{b} > \mathbf{0}$ implies that the system is box invariant. The converse is not true.*

Notice that the converse does not hold, as the following counter-example shows:

$$A = \begin{pmatrix} -1 & 1.5 \\ 1 & -2 \end{pmatrix}; \qquad \boldsymbol{x}_0 = \begin{bmatrix} 1 \\ 1 \end{bmatrix}; \qquad \boldsymbol{b} = \begin{bmatrix} -0.5 \\ 1 \end{bmatrix}.$$

Theorem 5. *Assume $\boldsymbol{b} \neq \mathbf{0}$. Given an n-dimensional affine dynamical system $\dot{\boldsymbol{x}} = A\boldsymbol{x} + \boldsymbol{b}$, consider the modified system $\dot{\boldsymbol{x}} = A^{\star}\boldsymbol{x} + \boldsymbol{b}^P$, where we substituted A with its Metzler correspondent $A^{\star}$ and, additionally, we introduced $\boldsymbol{b}^P$, made up of the absolute values of the components of $\boldsymbol{b}$. The original system is box invariant if and only if the modified system has a positive equilibrium.*

The proof follows from Lemma 4, after performing coordinate shifts according to the respective equilibria.

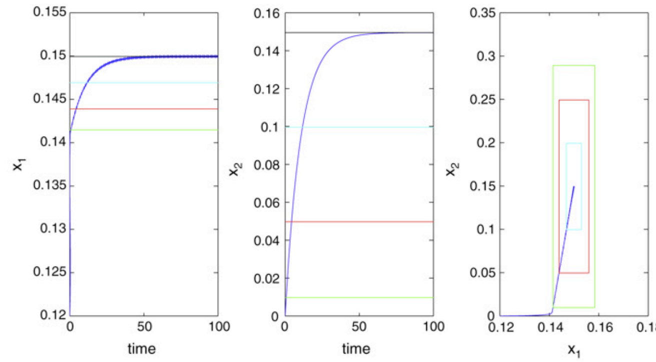

Fig. 1. Blood Glucose Concentration: simulation of a trajectory, and computation of some boxes.

Example 1 (*A Model for Glucose Concentration*). The following model describes a physiological compartment, the human brain, and focuses on the dynamics of the blood glucose concentration. In Sorensen (1985), this compartment is part of a larger model of all the organs of the body (each organ is modeled as a single compartment), which interact via some conservation laws. The mass balance equations are:

$$V_B\dot{C}_{Bo} = Q_B(C_{Bi} - C_{Bo}) + (C_I - C_{Bo})V_I/T - r_{RBC}$$
$$V_I\dot{C}_I = (C_{Bo} - C_I)V_I/T - r_T,$$

where the variables C_{Bo}, C_I and C_{Bi} denote solute concentrations, V_B and V_I fluid volumes, Q_B a volumetric flow rate, r_{RBC} and r_T removal rates, and T a diffusion time. This last value is chosen to be $T = 10$ [min]. By applications of the conditions described in Theorem 5, the system is box invariant. Fig. 1 plots a trajectory and some concentric boxes with aligned vertices. □

V_B	0.04 (l)	V_I	0.45 (l)
Q_B	0.7 (l/min)	C_{Bi}	0.15 (kg/l)
r_T	2×10^{-6} (kg/min)	r_{RBC}	10^{-5} (kg/min)

Example 2 (*EGFR and HER2 Trafficking Model*). This model is taken from Hendriks, Orr, Wells, Wiley, and Lauffenburger (2005). It is affine in its variables, which make up the six-dimensional vector $\boldsymbol{x} = (R_s, C_s, H_s, R_i, C_i, H_i)$, and presents a positive constant drift. The parameter L, which in general assumes three possible values, is held fixed in this instance.

$$\dot{R}_s = S_R - k_f LR_s + k_{er}C_s - k_{er}R_s + k_{xr}f_{xr}R_i$$
$$\dot{C}_s = k_f LR_s - k_r C_s - k_{ec}C_s + k_{xc}f_{xc}C_i$$
$$\dot{H}_s = S_H - k_{eh}H_s + k_{xh}f_{xh}H_i$$
$$\dot{R}_i = k_{er}R_s - k_{xr}R_i$$
$$\dot{C}_i = k_{ec}C_s - k_{xc}C_i$$
$$\dot{H}_i = k_{eh}H_s - k_{xh}H_i.$$

The system matrix verifies the structural conditions on the signs of its elements, as per Lemma 3. Noticing that the system matrix is explicitly Metzler and that the constant drift is positive, we may apply Lemma 4 and conclude that the system is box invariant. A calculation of its eigenvalues shows that they are, as expected, all negative (and so is, in particular, the Perron–Frobenius one). However, the computation of the Perron–Frobenius eigenvector yields a non-positive solution, thus going against the equivalent condition 2) in Proposition 2. The reason for this is that the system matrix is not *irreducible*. In fact, the third and the sixth coordinates are decoupled from all the others. Fortunately, as discussed in Section 3, we can carry on a separate study of these two separate components of the system. Splitting $\boldsymbol{x}$ into $\boldsymbol{x}_1 = (R_s, C_s, R_i, C_i) \in \mathbb{R}^4$ and $\boldsymbol{x}_2 = (H_s, H_i) \in \mathbb{R}^2$, we can set up two reduced models. The two new reduced-size system matrices are irreducible, and, as expected, are Metzler and verify all the equivalent conditions for box invariance of Proposition 2. □

4. Box invariant nonlinear systems

In this Section, we extend the study of box invariance to nonlinear systems. While for the linear and the affine cases box invariance can be characterized with necessary and sufficient conditions, in the more general nonlinear case we will present only sufficient conditions. Again, our focus will be on the computational aspects.

Polynomial systems. Dynamical models in biology, especially those drawn from biochemical relations, commonly take the form of polynomial systems, $\dot{\boldsymbol{x}} = \boldsymbol{p}(\boldsymbol{x})$, where $\boldsymbol{p}(\boldsymbol{x})$ is a vector of polynomials over the n-dimensional variable $\boldsymbol{x}$. For polynomial systems, the condition for box invariance (Definition 1) can be written out as the following formula:

$$\exists \boldsymbol{l}, \boldsymbol{u}. \forall \boldsymbol{x}. \bigwedge_{1 \le j \le n} \Big((\boldsymbol{x} \in Face\, L^j(\boldsymbol{l}, \boldsymbol{u}) \Rightarrow \boldsymbol{p}_j(\boldsymbol{x}) \ge 0) \wedge (\boldsymbol{x} \in Face\, U^j(\boldsymbol{l}, \boldsymbol{u}) \Rightarrow \boldsymbol{p}_j(\boldsymbol{x}) \le 0) \Big), \qquad (1)$$

Since $\boldsymbol{p}_j(\boldsymbol{x})$ is a polynomial and the conditions $x \in Face\, L^j(\boldsymbol{l}, \boldsymbol{u})$ and $x \in Face\, U^j(\boldsymbol{l}, \boldsymbol{u})$ can also be written as (conjunctions of) polynomial inequalities, it follows that Formula (1) is a formula in the first-order theory of reals (Tarski, 1948). Since this theory is decidable (Tarski, 1948), the following result holds.

Proposition 5. *Box invariance of polynomial systems is decidable.*

While this is a useful theoretical result, it is not very practical due to the high complexity of the decision procedure for real-closed fields. A subclass of polynomial systems, called *multi-affine systems*, naturally arises when modeling biochemical reaction networks (Belta, Habets, & Kumar, 2002; Lincoln & Tiwari, 2004). In these systems, the polynomials are restricted so that every monomial has degree at most one in each of its variables. Multi-affine systems are endowed with several properties that have been exploited for building efficient analysis and verification tools (Batt, Ropers, de Jong, Geiselmann, Page, & Schneider, 2005; Belta et al., 2002). We generalize the definition of multi-affine systems in Belta et al. (2002) and call an n-dimensional system $\dot{\boldsymbol{x}} = \boldsymbol{p}(\boldsymbol{x})$ *multi-affine* if every variable x_j has degree at most one in each monomial in p_i *for all* $j \neq i; i, j \in \{1, \ldots, n\}$. We next show that for multi-affine systems, the universal quantifiers in Formula (1) can be eliminated and the formula can be simplified to a conjunction of $n2^n$ (existentially quantified) constraints using the following generalization of Proposition 1 (the proofs are identical).

Proposition 6. *A multi-affine system $\dot{\boldsymbol{x}} = \boldsymbol{p}(\boldsymbol{x}), \boldsymbol{x} \in \mathbb{R}^n$ is box invariant iff there exist two points $\boldsymbol{l}, \boldsymbol{u} \in \mathbb{R}^n$ such that for each point $\boldsymbol{c} \in Vert(\boldsymbol{l}, \boldsymbol{u})$, we have $\boldsymbol{p}(\boldsymbol{c}) \sim \boldsymbol{0}$, where $\sim_i$ is $\le$ if $c_i = u_i$ and $\sim_i$ is $\ge$ if $c_i = l_i$.*

Proposition 6 still requires checking the satisfiability of an exponential number of (nonlinear) constraints. The following result shows that we cannot hope to obtain polynomial time algorithms for checking if a multi-affine system is box invariant with respect to a *given* box.

Theorem 6. *The problem of determining if a multi-affine system is box invariant with respect to a given box is co-NP-hard.*

Proof. Given a clause ϕ, say $b_1 \vee \bar{b}_2 \vee \bar{b}_3$, let $poly(\phi)$ denote the polynomial $(1-x_1)x_2x_3$. Given a formula ϕ consisting of the clauses ϕ_i, let $poly(\phi)$ denote the polynomial $\Sigma_i poly(\phi_i)$. Suppose ϕ is an instance of 3-SAT with n Boolean variables. Consider the following multi-affine system (note that this system is multi-affine even in the sense of Belta et al. (2002)),

$$\dot{x}_i = -x_i, \ (i = 1, \ldots, n); \qquad \dot{x}_{n+1} = x_{n+1}(1 - poly(\phi)),$$

and the box $Box(\boldsymbol{0}, \boldsymbol{1})$. It can be shown that this box is positively invariant for the multi-affine system iff ϕ is unsatisfiable. □

Despite the preceding result, for a very useful subclass of multi-affine systems, we can reduce the number of constraints (from $n2^n$) to $2n$. Let us introduce the notion of *directional* monotonicity. A function $f : \mathbb{R}^n \mapsto \mathbb{R}$ is monotonic with respect to a variable x_j if $f(\ldots, x_j, \ldots) \le f(\ldots, x_j', \ldots)$ (or $f(\ldots, x_j, \ldots) \ge f(\ldots, x_j', \ldots)$) whenever $x_j < x_j'$. Notice the difference between this notion and a graph-theoretical version of monotonicity, as discussed in Sontag (2007).

Proposition 7. *Let $\dot{\boldsymbol{x}} = \boldsymbol{p}(\boldsymbol{x})$ be an n-dimensional multi-affine system such that each multi-affine polynomial $\boldsymbol{p}_i(\boldsymbol{x})$ is monotonic with respect to every variable x_j, for $j \neq i$. Then, the $n2^n$ constraints of Proposition 6 are equivalent to a subset of the $2n$ constraints.*

Proof. Consider any one of the $n2^n$ inequalities, say $\boldsymbol{p}_1(\boldsymbol{c}) \ge 0$, where $\boldsymbol{v} \in Vert(\boldsymbol{l}, \boldsymbol{u})$ is a vertex s.t. $v_1 = l_1$. Consider the vertex $\boldsymbol{v}^*$ defined by $v_1^* = v_1$ and for all $i > 1$, $v_i^* = l_i$ if $\boldsymbol{p}_1(\boldsymbol{x})$ is monotonically increasing with respect to the variable x_i, and $v_i^* = u_i$ if $\boldsymbol{p}_1(\boldsymbol{x})$ is monotonically decreasing with respect to the variable x_i. By definition of monotonicity, $\boldsymbol{p}_1(\boldsymbol{v}) \ge \boldsymbol{p}_1(\boldsymbol{v}^*)$ and hence $\boldsymbol{p}_1(\boldsymbol{v}^*) \ge 0$ would imply $\boldsymbol{p}_1(\boldsymbol{v}) \ge 0$. Thus, we can remove the constraint $\boldsymbol{p}_1(\boldsymbol{v}) \ge 0$ and only keep $\boldsymbol{p}_1(\boldsymbol{v}^*) \ge 0$. In fact, the same argument shows that $\boldsymbol{p}_1(\boldsymbol{v}^*) \ge 0$ subsumes 2^{n-1} other such constraints (obtained by considering all possibilities for $v_2, v_3, \ldots, v_n$). This shows that the $n2^n$ original constraints are eventually subsumed by a subset of $2n$ constraints. □

We illustrate the utility of Proposition 7 in the following example.

Example 3 (*Phytoplankton Growth Model*). Consider the following model (Bernard & Gouze, 2002):

$$\dot{x}_1 = 1 - x_1 - \frac{x_1 x_2}{4}, \qquad \dot{x}_2 = (2x_3 - 1)x_2, \qquad \dot{x}_3 = \frac{x_1}{4} - 2x_3^2,$$

where the positive variable x_1 denotes the substrate, x_2 the phytoplankton biomass, and x_3 the intracellular nutrient per biomass. This system is not multi-affine in the sense of Belta et al. (2002) (see the third dynamical relation), but it is multi-affine in our weaker sense. Moreover, it satisfies the monotonicity condition. (Technically, $(2x_3 - 1)x_2$ is not monotonic with respect to x_3, but when restricted to the positive quadrant, it is indeed monotonic. This is more formally developed in Tiwari (2008).) Hence, by Proposition 7, its box invariance is equivalent to the existence of $\boldsymbol{l}, \boldsymbol{u}$ such that the following six constraints (that subsume the $3 \cdot 2^3 = 24$ constraints) are satisfied:

$$1 - u_1 - \frac{u_1 l_2}{4} \le 0, \qquad u_2(2u_3 - 1) \le 0, \qquad \frac{u_1}{4} - 2u_3^2 \le 0,$$

$$1 - l_1 - \frac{l_1 u_2}{4} \ge 0, \qquad l_2(2l_3 - 1) \ge 0, \qquad \frac{l_1}{4} - 2l_3^2 \ge 0.$$

One possible solution for these constraints is given by $\boldsymbol{l} = (0, 0, 0)$ and $\boldsymbol{u} = (2, 1, 1/2)$, indicating that the box formed by these two points as diagonally opposite vertices is a positive invariant set. □

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Nonlinear systems as perturbations of linear systems. In this Section we employ ideas from the robustness study in Section 3.2 to *efficiently* check box invariance (using only a sufficient characterization) of polynomial systems in which the degree of each polynomial is at most two, thus slightly generalizing the results presented in the previous Section. As argued before, dynamical models derived from stoichiometric reactions can often be included in this class (Lincoln & Tiwari, 2004). In particular, this assumption is natural for models of biochemical reactions where second-order polynomials can describe both homo- and hetero-dimerizations. (A trimerization can in fact be expressed as two rapidly succeeding dimerizations.) Consider a general degree-2 polynomial system $\dot{\boldsymbol{x}} = f(\boldsymbol{x}), \boldsymbol{x} \in \mathbb{R}^n$. The structure of the vector field allows expressing the model as

$$\dot{\boldsymbol{x}} = A\boldsymbol{x} + g(\boldsymbol{x}) = A\boldsymbol{x} + B(\boldsymbol{x})\boldsymbol{x} = \Gamma(\boldsymbol{x})\boldsymbol{x}.$$

where A is a constant $n \times n$ matrix, while $B(\boldsymbol{x})$ is made up of terms that are now linear in the variables. Let us assume for the moment that $f_i(\boldsymbol{x})$ does not contain the term x_i^2. This assumption is satisfied in models of biochemical reaction networks because dimerization of an element cannot yield that same element. This assumption allows us to choose $B(\boldsymbol{x})$ so that $b(\boldsymbol{x})_{ii} = 0$.[1]

Let us now assume that system corresponding to the linear part ($\dot{\boldsymbol{x}} = A\boldsymbol{x}$) is box invariant, i.e. there exists a nonempty (conical) set $\mathcal{C}$ in $\mathbb{R}^n$ that defines all the possible locations of the symmetric vertices of the invariant hyper-rectangle. Let us introduce a matrix $\Gamma^\star(\boldsymbol{x}) \doteq A^\star + B^\star(\boldsymbol{x})$, where $b^\star(\boldsymbol{x})_{ij} = |b(\boldsymbol{x})_{ij}|$. It is then possible to refer back to Section 3.2 and interpret $\Gamma^\star(\boldsymbol{x}) = A^\star_\epsilon$, where the nonlinear part $B^\star(\boldsymbol{x})$ is perceived as an additional term that may disrupt the box invariance of the linear system. Clearly this is a worst-case scenario, which comes from the positivity of the terms $b^\star(\boldsymbol{x})_{ij}$. By the application of the results derived in Section 3.2, a set of upper bounds for the values of the "allowed perturbations" is obtained. These bounds define some hyperplanes which, when intersected with the cone $\mathcal{C}$, define the new reduced feasible region $\mathcal{C}'$ for the vertices of the box:

$$\mathcal{C}' = \{\boldsymbol{c} \mid A^\star \boldsymbol{c} \leq \boldsymbol{0}, b^\star_{ij}(\boldsymbol{c}) \leq \epsilon_{ij}/a^\star_{ij}\}$$

where ϵ_{ij} is the maximum allowed perturbation obtained in Section 3.2, and $b^\star_{ij}(\boldsymbol{c})$ is computed as $\sum_k |\beta_k||c_k|$ if $b_{ij}(\boldsymbol{x})$ is $\sum_k \beta_k x_k$. Notice that this procedure can also be extended to include the presence of a constant drift term, according to Section 3.3, as well as to disregard the assumption on matrix B raised in this paragraph.

Overvaluing dynamical systems. A second method to compute invariant regions is based on the definition of an *overvaluing system* (Borne, Richard, & Radhy, 1996; Erdem & Alleyne, 2002), which depends on the choice of a particular (vector) norm (Kiendl et al., 1992). Consider the multi-affine model already introduced: $\dot{\boldsymbol{x}} = A\boldsymbol{x} + g(\boldsymbol{x}) = A\boldsymbol{x} + B(\boldsymbol{x})\boldsymbol{x} = \Gamma(\boldsymbol{x})\boldsymbol{x}, \boldsymbol{x} \in \mathbb{R}^n$. As shown in Section 2, we are interested in the infinity vector norm $V(\boldsymbol{x}) = \|\boldsymbol{x}\|_\infty$ (or similarly in a scaled version thereof, $V^W(\boldsymbol{x}) = \|W\boldsymbol{x}\|_\infty$, where W is a diagonal, positive $n \times n$ matrix). If the right-derivative of $V(\boldsymbol{x})$ (Kiendl et al., 1992), $D^+V(\boldsymbol{x})$, can be upper-bounded (within a given limited region $\mathcal{S} \subset \mathbb{R}^n$) as follows: $D^+V(\boldsymbol{x}) \leq mV(\boldsymbol{x})$, where m is a negative real number, then the region defined as

$$B \doteq \{\boldsymbol{x} \in \mathbb{R}^n : V(\boldsymbol{x}) \leq c, c \in \mathbb{R}_+\} \subseteq \mathcal{S}$$

is positively invariant for the original nonlinear system (Borne et al., 1996). The right-derivative $D^+V(\boldsymbol{x})$ can be upper-bounded by a set of inequalities: given the matrices A and $B(\boldsymbol{x})$ as in the preceding paragraph, notice that

$$D^+V(\boldsymbol{x}) \leq \max_{1 \leq i \leq n} \left(a_{ii} + \sum_{j \neq i} (|a_{ij}| + |b_{ij}(\boldsymbol{x})|) \right) V(\boldsymbol{x}).$$

This expression can yield a bound for m. Here we have not used any assumption on the existence of a box.

5. Box invariance for hybrid systems

We extend the notion of box invariance to models, known as hybrid or switched, which are compositions of different dynamical systems. As in the case of the preceding nonlinear studies, we will only derive sufficient conditions.

Definition 4 (*Hybrid System, (Lygeros, Johansson, Simic, Zhang, & Sastry, 2003)*). A *hybrid system* is a tuple $\mathscr{H} = (Q, E, D, G, R, F)$, where

- $Q = \{1, \ldots, m\}$ is a finite set of *discrete states*
- $E \subset Q \times Q$ is a set of *edges*, where $e = (e(1), e(2)) \in E$
- $D = \{D_i\}_{i \in Q}$ is a set of *domains*, where $D_i \subset \mathbb{R}^n$
- $G = \{G_e\}_{e \in E}$ is a set of *guards*, where $G_e \subseteq D_{e(1)}$
- $R = \{R_e\}_{e \in E}$ is a set of identity *reset maps*
- $F = \{f_i\}_{i \in Q}$ is a set of Lipschitz *vector fields* on D_i.

The *hybrid state space* of $\mathscr{H}$ is $\bigcup_{q \in Q} \{q\} \times D_q$, i.e. the disjoint union of the domains associated to each mode. A hybrid trajectory (evolving in the hybrid state space), starting from an initial condition $(q_0, \boldsymbol{x}_0) \in \bigcup_{q \in Q} \{q\} \times D_q$, evolves continuously according to the vector field in $f_q \in F$ until it intersects a guard set in G (this last condition is called an "event"). The guard set is associated with an edge in E, which determines the new domain the trajectory jumps to. Furthermore, the specific point in the guard set is mapped, according to a function in R (in this work, the identity function), to an initial condition within the new domain, from which the continuous motion restarts. Hybrid models allow for a plethora of possible dynamical behaviors. We refer the reader to Lygeros et al. (2003) for further details on their dynamical properties.

In contrast, *switched systems* specify jumping conditions in time, rather than in state.

Definition 5 (*Switched System*). A *switched system* is a tuple $\mathscr{S} = (Q, E, D, G, R, F)$, where

- Q, E, R, F are as in Definition 4
- $D = \{D_i\}_{i \in Q}$ is a set of *domains* where $D_i = \mathbb{R}^n$
- $G = \{0, \tau_1, \tau_2, \ldots\}$ is a possibly infinite set of *guards* in time, where $\tau_i \in \mathbb{R}^+$ are increasing in $i : \tau_0 = 0 \leq \tau_1 \leq \tau_2 \ldots$ Each τ_i is mapped to a state by a function $g : G \to Q$ such that $(g(\tau_{i-1}), g(\tau_i)) \in E, \forall i > 0$.

The state space of $\mathscr{S}$ is then $\bigcup_{q \in Q} \{q\} \times \mathbb{R}^n$. Trajectories of $\mathscr{S}$ are defined similarly to those of $\mathscr{H}$, where the "events" are now simply time-dependent, rather than being determined by spatial conditions.

An *invariant set* of a hybrid or a switched system is a subset of the hybrid state space such that every trajectory originating in this set or intersecting it continues to dwell inside it. The notion of box invariance for hybrid and switched systems is defined so as to allow for jumps between the different domains, as well as for the possibility of having a number of different equilibria in each separate domain (recall Definition 1 and ensuing comments).

[1] The nonlinear part, which is made up of products of two different monomials, can be ordered into possibly different $B(\boldsymbol{x})$ matrices. Thus the choice of $B(\boldsymbol{x})$ is not unique.

Definition 6 (*Hybrid Box Invariance*). A hybrid system $\mathscr{H}$ (a switched system $\mathscr{S}$) is said to be hybrid box invariant if there exists a subset $Q' \subset Q$ of states and boxed regions $B_q \subset D_q, q \in Q'$ around the corresponding equilibria, such that $\bigcup_{q \in Q'} \{q\} \times B_q$ is an invariant set for $\mathscr{H}$ (or $\mathscr{S}$).

As for the dynamics, we restrict ourselves to the instance where the components of F are either linear or affine vector fields. An important classification in our analysis hinges on whether multiple domains share an equilibrium point and whether equilibria belong to guard sets.

Reduction to pure dynamical systems. We first consider the case for the hybrid system $\mathscr{H}$ when there is a discrete state, say $i \in Q$, such that (i) the dynamical system of state i is box invariant with respect to a box $B \subseteq D_i$, (ii) none of the guard sets G_i intersect B, i.e., $B \cap \left(\bigcup_{e \in E, e(1)=i} G_e\right) = \varnothing$, and (iii) B is contained in the domain of state i, i.e., $B \subseteq D_i$. Existence of a mode i with such properties implies hybrid box invariance for $\mathscr{H}$. This case occurs frequently in models of genetic regulatory pathways. This happens, for example, in the hybrid model of the Delta-Notch lateral inhibition mechanism of Ghosh and Tomlin (2001). A second example is given below. The reader should realize that, as in the *nonlinear* case, the existence of a box for a single discrete state does not imply the existence of boxes of different sizes: expanding a box may in fact cause it to intersect a guard, which may disrupt the invariance property.

Example 4 (*Tetracycline Antibiotics Resistance*). Tetracyclines are a group of broad-spectrum antibiotics whose general usefulness has been reduced with the onset of bacterial resistance. The dynamics of tetracycline antibiotic in a bacteria which develops resistance to this drug (by turning on genes *tet A* and *tet R*) can be described by the following hybrid system with multi-affine dynamics, where x_1, x_2, x_3, x_4 are the cytoplasmic concentrations of Tet R protein, the Tet R-Tc complex, Tetracycline, and Tet A protein respectively, and u_0 is the extracellular concentration of Tetracycline (Rubin, Kumar, & Sokolsky, 2006):

$$\dot{x}_1 = f - \frac{x_3 x_1}{3} + \frac{5x_2}{40\,000}, \qquad \dot{x}_2 = \frac{15u_0}{1000} - \frac{35x_3x_4}{10},$$

$$\dot{x}_3 = \frac{x_3x_1}{3} - \frac{16x_2}{40\,000}, \qquad \dot{x}_4 = f - \frac{11x_4}{40\,000}.$$

Here f is the transcription rate of genes, which are inhibited by Tet R, $f = 1/2000$ if $x_1 > 2/10\,0000$ and $f = 1/40$ otherwise. In the mode when the genes are "on" (i.e., $f = 1/2000$), if u_0 is fixed to 200, then we can compute a positive invariant box $3/2 \le x_4 \le 2$, $2/5 \le x_3 \le 3/5$, $3/1000 \le x_1 \le 8/1000$, $1 \le x_2 \le 4$ by focusing solely on this mode and using Proposition 7. □

Hybrid domains sharing an equilibrium point. Let us first observe that a hybrid dynamical system can be over-approximated by a switched system that allows transitions at all possible time instants. This over-approximation can be used to check properties of the original system.

Proposition 8. *Let $\mathscr{H}$ be a hybrid system and let $\mathscr{S}$ be the corresponding switched system made up of the same tuple, except that the domains are now $D_i = \mathbb{R}^n$ and the set of guards is given by a symbolic, non-decreasing sequence $G = \{0, \tau_1, \tau_2, \ldots\}$ that allows for all possible switchings. For any (universal) property $\mathscr{P}$, if $\mathscr{P}$ holds for (all the possible trajectories of) $\mathscr{S}$, then $\mathscr{P}$ holds for $\mathscr{H}$.*

Proof. Given an initial condition $(q_0, \boldsymbol{x}_0), \boldsymbol{x}_0 \in D_{q_0}, q_0 \in Q$ for $\mathscr{H}$, the determinism of $\mathscr{H}$ (Lygeros et al., 2003) allows us to state that the (unique) hybrid trajectory can be related to a unique sequence of switching times $\{0, \tau_1, \tau_2, \ldots\}$ (possibly infinite in cardinality). Clearly, this sequence belongs to the set G of $\mathscr{S}$. Hence, proving a (universal) property (for instance, stability) for all possible switching sequence G for $\mathscr{S}$, will *a fortiori* prove the property for $\mathscr{H}$ (and for any of its executions). □

The following result deals with the case of switched linear systems that share the origin as a common equilibrium.

Theorem 7. *A switched linear system $\mathscr{S}$, characterized by a set of vector fields of the form*

- $F = \{f_i\}_{i \in Q} = A_i \boldsymbol{x}, \boldsymbol{x} \in \mathbb{R}^n, \ i \in Q$

is hybrid box invariant around the origin if there exists a single hybrid box $\bigcup_{i \in Q} \{i\} \times B, B \subset \mathbb{R}^n$, such that the dynamical system in each domain is box invariant with respect to B. Thus, recalling the definition in Section 3 of the cones $\mathcal{C}_i$ for each mode $i \in Q$, a sufficient condition for box invariance is that $\bigcap_{i \in Q} \mathcal{C}_i \neq \varnothing$, which can be tested in polynomial time.

Proof. In each domain $i \in Q$, the corresponding dynamical system characterized by matrix A_i is related, via the Metzler correspondent $A_i^\star$, to a cone $\mathcal{C}_i$. The non-emptiness of the intersection $\bigcap_{i \in Q} \mathcal{C}_i$ allows choosing points that define a common box, and thus directly specify a hybrid box. With reference to the notations in Section 3, in order to find a box for all the discrete domains, the objective is to find a positive $\boldsymbol{c} \in \mathbb{R}^n$, such that $A_i^\star \boldsymbol{c} \le 0$ for all $i \in \mathcal{Q} = \{1, \ldots, m\}$. This is a set of linear constraints that can be efficiently solved in polynomial time. □

The condition for a common box, as in Theorem 7, is analogous to the search for a common Lyapunov function for the stability of switched systems (Branicky, 1994; Liberzon, 2003).

It is well known that the composition of two stable systems can be unstable (Branicky, 1994). Similarly, Example 5 shows that hybrid systems made up of box invariant linear systems need not be box invariant—in fact, they can show divergent behavior.

Example 5. Consider the following two-dimensional hybrid system, characterized by two modes with domains coinciding with the whole space, $D_1 = D_2 = (\mathbb{R}^+)^2$, and endowed with the following vector fields:

$$A_1 = \begin{pmatrix} -1 & 5 \\ -0.1 & -1 \end{pmatrix}; \qquad A_2 = \begin{pmatrix} -1 & -0.2 \\ 4 & -1 \end{pmatrix}.$$

Assume that there are two edges $(1, 2), (2, 1)$, with the following guards in $\mathbb{R}^2$: $G_{(1,2)}(x_1, x_2) = \{\boldsymbol{x} \in \mathbb{R}^2 : x_1 - 5x_2 = 0\}$, $G_{(2,1)}(x_1, x_2) = \{\boldsymbol{x} \in \mathbb{R}^2 : 4x_1 - x_2 = 0\}$. Assume again identity reset maps, and initial condition $(x_1(0), x_2(0)) = (0.1, 0.1) \in D_1$. In isolation, both linear systems are box invariant and indeed have spiraling convergent trajectories towards the origin. The hybrid model though is unstable (e.g., for initial conditions on the bisector of the first quadrant). Incidentally, notice that

$$\mathcal{C}_1 = \{(x_1, x_2) : x_1 - 5x_2 \ge 0 \wedge x_2 \ge 0\};$$
$$\mathcal{C}_2 = \{(x_1, x_2) : 4x_1 - x_2 \le 0 \wedge x_1 \ge 0\};$$

and that $\mathcal{C}_1 \cap \mathcal{C}_2 = \varnothing$. □

Affine hybrid systems. We finally consider the case of affine hybrid and switched systems. Unlike the linear case, the different modes in an affine hybrid system need not share their equilibrium

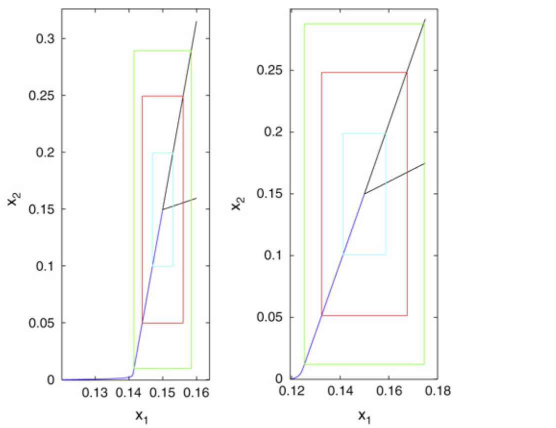

Fig. 2. Simulation of a trajectory for the first (left) and second (right) system, and computation of some symmetrical boxes.

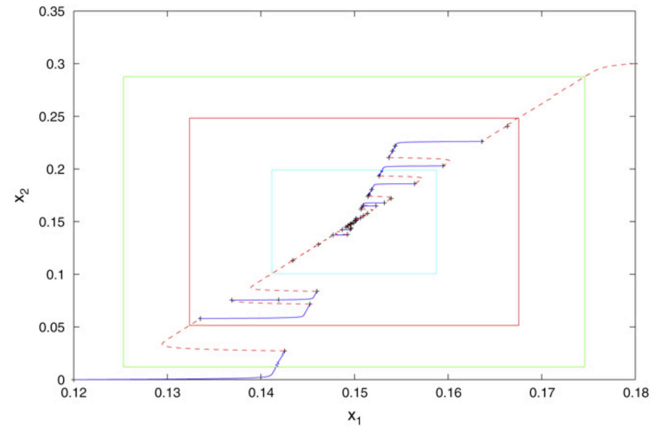

Fig. 3. Two realizations of the switched system composed by the two dynamical systems, with a few global boxes.

point. However, we can still derive a sufficient condition for the existence of a "common box" (the proof directly follows that in Theorem 7).

Theorem 8. *Consider an affine hybrid system $\mathscr{H}$, where each domain has an equilibrium point $\boldsymbol{x}_o^i$, $i \in Q$, and all variables are bound to be positive. $\mathscr{H}$ is box invariant if the following condition holds: $\bigcap_{i \in Q} (\mathcal{C}_i + \boldsymbol{x}_o^i) \neq \varnothing$.*

Example 6 (*A Model for Glucose Concentration*). The following model is an extension of Example 1 and its dynamics are given there. We allow T to assume two different values (10 and 3 min), which correspond to different physiological conditions. Furthermore, we assume that the switch between these two conditions can happen at any time. This calls for the introduction of a bimodal switched model, composed of the following two dynamics: $\dot{\boldsymbol{x}} = \begin{cases} A_1 \boldsymbol{x} + b, & \text{if } T = 10 \text{ [min]}; \\ A_2 \boldsymbol{x} + b, & \text{if } T = 3 \text{ [min]}. \end{cases}$

Both models, considered in isolation, are box invariant. They therefore are stable around two different equilibria. In Fig. 2 we plot trajectories for these two systems, and draw some boxes. Additionally, the cones are shown, centered around the equilibria. Notice that the intersection of the two cones is not empty. The smaller one was thus chosen to define the "global" box. Two different simulations, with random switching, starting from opposite initial conditions, are shown in Fig. 3. The new box is indeed an invariant for the switched system. This box yields a bound on the values of $\boldsymbol{x}$, which in the model represents the blood glucose concentration in the brain. □

6. Conclusions

With a focus on computational aspects related to the characterization of box invariance, this paper has obtained necessary and sufficient conditions for linear system, and sufficient conditions for classes of nonlinear (in particular, monotone multi-affine) and hybrid systems. We observed that the Metzler structure helps in obtaining efficient computational procedures for analyzing dynamical systems.

Since robustness is a central issue for biological systems, we also presented results on robustness of box invariance for linear systems. The concept of box invariance is stronger than that of asymptotic stability (for linear systems), but it is still not fully compositional in the hybrid and switched cases: box invariance of dynamical systems is not necessarily preserved when these systems are composed into a hybrid or switched system.

The notion of box invariance is intuitive, rather descriptive, and computationally attractive. It was shown and it is argued that several models of biological systems are box invariant.

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