Box Invariance for biologically-inspired dynamical systems

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***Abstract*— In this paper, motivated in particular by models drawn from biology, we introduce the notion of *box invariant* dynamical systems. We argue that box invariance, that is, the existence of a box-shaped positively invariant region, is a characteristic of many biologically-inspired dynamical models. Box invariance is also useful for the verification of stability and safety properties of such systems. This paper presents effective characterization of this notion for some classes of systems, computational results on checking box invariance, the study of the dynamical properties it subsumes, and a comparison with related concepts in the literature. The concept is illustrated using models derived from different case studies in biology.**

I. Introduction

A *positively 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 this set in the future [1]. A positively invariant set is extremely useful from the perspective of formal analysis and verification. It can be used to verify *safety* properties of a system, that is, properties that specify that a system can never be in a given subset of "unsafe" or "bad" states, as well as stability specifications [2]. This motivates the need for an effective and constructive approach to compute positively invariant sets for dynamical systems.

Positively invariant sets can be obtained by noticing that their boundaries correspond with level surfaces of a Lyapunov-like function. This approach has been a source of several results about positively invariant sets. However, this is quite restrictive in general, since systems that are not stable (and hence that do not admit a Lyapunov function) 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 region specified by giving bounds for each state variable. The investigation of several models, especially from the domain of systems biology, has revealed 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. We show in this paper that it is computationally feasible to construct box invariant sets for a large class of dynamical systems and hence that this is an ideal concept for building analysis and verification tools.

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In this manuscript we introduce and define the notion of box invariance. We start with the simplest instances of linear dynamical systems and move to more general nonlinear systems, study their dynamical properties and perform robustness analysis of box invariant systems. We present computational complexity results on finding box invariant sets. The proofs of the claims, all originally derived, can be found in [3]. Some examples from systems biology are presented to argue for the significance of the notion.

II. The concept of Box Invariance

In this work, we shall 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 continuity 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 $\boldsymbol{x}_0$ can be specified using two diagonally opposite points $\boldsymbol{x}_{lb}$ and $\boldsymbol{x}_{ub}$, where $\boldsymbol{x}_{lb} < \boldsymbol{x}_0 < \boldsymbol{x}_{ub}$ (interpreted component-wise). Such a box has $2n$ surfaces $S^{j,k}(1 \leq j \leq n, k \in \{l,u\})$, where $S^{j,k} = \{\boldsymbol{y} : x_{lb,i} \leq y_i \leq x_{ub,i}$ for $i \neq j; y_j = x_{lb,j}$ if $k = l; y_j = x_{ub,j}$ if $k = u\}$.

***Definition** 1:* 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 around $\boldsymbol{x}_0$, specified by $\boldsymbol{x}_{lb}$ and $\boldsymbol{x}_{ub}$, such that for any point $\boldsymbol{y}$ on any surface $S^{j,k}(1 \leq j \leq n, k \in \{l,u\})$ of this rectangular box, it is the case that $f(\boldsymbol{y})_j \leq 0$ if $k = u$ and $f(\boldsymbol{y})_j \geq 0$ if $k = l$. The system is said to be *strictly box invariant* if the last inequalities hold strictly. □

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:* 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 defined by $\boldsymbol{u}$ and $(2\boldsymbol{x}_0 - \boldsymbol{u})$. □

***Vector Norms**:* The boundary of a box can be seen as a level surface of a vector norm. Let $\|\boldsymbol{x}\|_\infty = \max\{|x_i|, i = 1,\dots,n\}$ denote the infinity norm. Let D be a $n \times n$ positive diagonal matrix. The level set of $\|D\boldsymbol{x}\|_\infty$ is a hyper-rectangle in $\mathbb{R}^n$ that is symmetric around the origin.

Symmetrical box invariance has been indirectly already studied in the literature by exploring when $\|D\boldsymbol{x}\|_\infty$ is a

Lyapunov function for a dynamical system. The notion of *component-wise (exponential) asymptotic stability* of a linear system is characterized by $\|D\boldsymbol{x}\|_\infty$ being a strong Lyapunov function [4], [5], [6].

More generally, for a linear system $\dot{\boldsymbol{x}} = A\boldsymbol{x}$, a vector norm $\|W\boldsymbol{x}\|$, where W is of rank n, will be a Lyapunov function if $\mu(Q) < 0$, where $WA = QW$ [7]. Here $\mu(Q)$ is a matrix measure defined by $\lim_{\Delta\to 0^+} \frac{\|I+\Delta Q\|-1}{\Delta}$. This condition is also sufficient for quadratic and infinity norms [8].

III. Characterization of Box Invariance.

We investigate the notion of box invariance for several classes of systems, propose efficient computational ways to find such boxes, and study their robustness properties.

A. *Linear 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 checking the condition only at the 2^n vertices of the box (instead of on all points of the surface of the box):

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 $\boldsymbol{c}$, with $c_i \in \{u_i, l_i\}$, we have $A\boldsymbol{c} \sim \boldsymbol{0}$, where $\sim_i$ is $\leq$ if $c_i = u_i$ and $\sim_i$ is $\geq$ if $c_i = l_i$. □

Remark 1: Proposition 1, which is a simple consequence of linearity, shows 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 $\boldsymbol{u}$). Theorem 1 and Theorem 2 will allow us to simplify this to testing n linear inequalities over n variables. □

The notion of box invariance and symmetrical box invariance are equivalent for linear systems:

Theorem 1: A linear system $\dot{\boldsymbol{x}} = A\boldsymbol{x}$, where $A \in \mathbb{R}^{n\times n}$, is box invariant iff it is symmetrically box invariant. □
As a result of Theorem 1, we can now use results obtained using infinity vector norms as Lyapunov functions [7], [5]. The following result can be easily obtained using a direct proof based on simplifying the $n2^n$ inequality constraints.

Theorem 2: An n-dimensional linear system $\dot{\boldsymbol{x}} = A\boldsymbol{x}$ is symmetrically box invariant iff there exists a positive vector $\boldsymbol{c} \in (\mathbb{R}^+)^n$ such that $A^m\boldsymbol{c} \leq \boldsymbol{0}$, where $a^m_{ii} = a_{ii}(< 0)$ and $a^m_{ij} = |a_{ij}|$ for $i \neq j$. This is equivalent to checking if the system defined by A^m is symmetrically box invariant. □

Putting together Theorem 1 and 2, we conclude that in order to check whether a linear system $\dot{\boldsymbol{x}} = A\boldsymbol{x}$ is box invariant, we only need to test if there exists a positive vector $\boldsymbol{c}$ such that $A^m\boldsymbol{c} \leq 0$. This can be solved using linear programming in *polynomial* time. However, we can do much better. Since A^m has negative diagonal terms and non-negative off-diagonal terms, it is immediate that the Fourier-Motzkin procedure can be used to solve the n linear inequality constraints $A^m\boldsymbol{c} \leq 0$ for positive $\boldsymbol{c}$ in $O(n^3)$ time.

In fact, we can exactly characterize when the Fourier-Motzkin 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 [9]. A matrix A is said to be a *P-matrix* if all of its principal minors are positive.

Theorem 3: Let A be a $n \times n$ matrix such that $a_{ii} < 0$ and $a_{ij} \geq 0$ for all $i \neq j$. 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) For every $i = 1, 2, \ldots, n$, the determinant of the top left $i \times i$ submatrix of $-A$ is positive. □

Remark 2: Theorem 3 shows that box invariance of linear systems can also be tested by checking if the modified matrix $-A^m$ is a P-matrix. It is known that the problem of deciding if a given matrix is a P-matrix is co-NP-hard [10]. But in our case, due to the special form of A^m, we can determine if $-A^m$ is a P-matrix using a simple $O(n^3)$ Fourier-Motzkin elimination procedure. □

In the language of infinite vector norms, the existence of a positive vector $\boldsymbol{c}$ such that $A^m\boldsymbol{c} \leq 0$ is equivalent to $\mu(D^{-1}A^mD) \leq 0$, where D is the positive diagonal matrix $\mathtt{diag}(\boldsymbol{c})$. This connection was known [5], [7], but we now have the following new complexity result.

Theorem 4: Let $A \in \mathbb{Q}^{n\times n}$ be any matrix and let A^m denote a $n\times n$ rational matrix such that $a^m_{ii} < 0$ and $a^m_{ij} \geq 0$ for $i \neq j$ (e.g., the one obtained from A). The following problems can be solved in $O(n^3)$ time:

- Is the linear system $\dot{\boldsymbol{x}} = A\boldsymbol{x}$ (strictly) box invariant?
- Are the constraints $A^m\boldsymbol{z} \leq 0,\ \boldsymbol{z} > 0$ satisfiable?
- Does there exist a positive diagonal matrix D s.t. $\mu(D^{-1}A^mD) \leq 0$ (in the infinity norm)?
- Is $-A^m$ a P-matrix? □

Remark 3: Theorem 4 is stated for rational matrices since irrational real numbers are computationally difficult to represent and manipulate. □

We can not only decide box invariance, but also find box invariant sets by generating solutions for the above linear constraint satisfaction problem. Indeed, with 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 $\mathcal{C} = \{\boldsymbol{x} \in {\mathbb{R}^+}^n : A^m\boldsymbol{x} \leq \boldsymbol{0}\}$. Any choice of a single vertex in $\mathcal{C}$, or a couple of different points in $\mathcal{C}$ and its origin-symmetric, determine respectively a symmetric and a non-symmetric box for the system described by A (see Fig. 1). For linear systems, box invariance is a stronger concept than stability, see also [5], [7], [8].

Theorem 5: If a linear dynamical system is box invariant, then it is stable. □
In other words, the invariant set is also a *domain of attraction* and its existence will imply stability (towards the enclosd equilibrium). The opposite is not true (see Cor. 1).

B. *Connections with Metzler Matrices*

Matrices with the shape of those in Theorem 3 (or, equivalently, of A^m in Theorem 2) are known under the appellative of *Metzler* matrices. Metzler matrices are in fact, by definition, *matrices with non-negative off-diagonal terms*. In particular, the known *positive matrices* form a subset of them. *Stochastic matrices* (or rates matrices, which can be obtained from probability transition matrices) are another

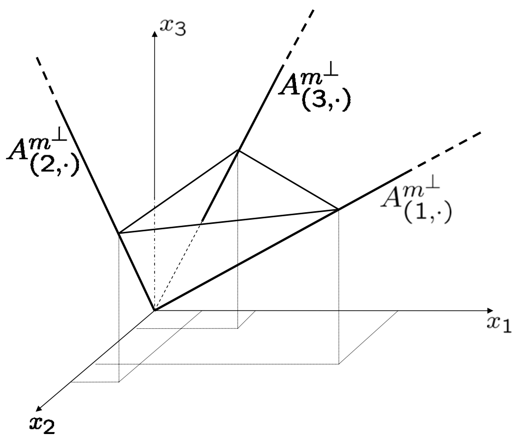

Fig. 1. A three-dimensional conic region $\mathcal{C}$ describing the set of possible choices for the positive vertex of an invariant box.

instance of Metzler matrices, with an additional constraint on the row sum.The properties of Metzler matrices can be reconducted to those of positive matrices, or at least to those of non-negative matrices. In fact, for every $A^m \in \mathbb{R}^{n\times n}$ that is Metzler, there exists a positive number c such that A^m+cI is non-negative. For instance, pick $c \geq \max_{i\in\{1,\ldots,n\}} |a_{ii}|$.

Perron and Frobenius were the first to study positive matrices. Many results can be extended to the Metzler case provided a structural property, that of *irreducibility*, holds. This property is also used in the theory of Markov Chains, and assumes that there is a connectivity chain between each pair of elements of the matrix, i.e. a sequence of links that brings from the first term of the couple to the second one, along the underlying connection graph that is associated with the matrix. In practice this assumption is not restrictive, as its lack of validity would imply a certain level of decoupling between parts of the dynamical system; this would then advocate a separate study of these different parts in the first place, therefore solving the issue at its root. [3, Example 2] shows this explicitly. Similar, slightly slacker results, can in any case be derived for the general case. The following holds (cf. [11]):

***Proposition** 2:* Suppose $A^m \in \mathbb{R}^{n\times n}$ is Metzler; then it has an eigenvalue τ which verifies the following statements:

1) τ is real;
2) $\tau > Re(\lambda)$, where λ is any other eigenvalue of A^m different from τ;
3) τ has single algebraic and geometric multiplicity;
4) τ is associated with a unique (up to multiplicative constant) positive (right) eigenvector (equivalently, considering the transpose of A^m, also with a positive left eigenvector);
5) $\tau \leq 0$ iff $\exists \boldsymbol{c} > \boldsymbol{0}$, such that $A^m\boldsymbol{c} \leq \boldsymbol{0}$; $\tau < 0$ iff there is at least one strict inequality in $A^m\boldsymbol{c} \leq \boldsymbol{0}$;
6) $\tau < 0$ iff all the principal minors of $-A^m$ are positive;
7) $\tau < 0$ iff $-(A^m)^{-1} > 0$. □

Such a special τ is generally known as the *Perron-Frobenius eigenvalue* of the matrix. We can prove the following theorem:

***Theorem** 6:* Suppose A^m is Metzler and has negative diagonal terms; then all the points of the previous fact hold but 5), which needs to be modified as:

5) $\tau \leq 0$ iff $\exists \boldsymbol{c} > \boldsymbol{0}$, such that $A^m\boldsymbol{c} \leq \boldsymbol{0}$; $\tau < 0$ iff $\exists \boldsymbol{c} > \boldsymbol{0}$, such that $A^m\boldsymbol{c} < \boldsymbol{0}$. □

The following two results will be used in the remainder:

***Theorem** 7:* If A and B are two Metzler matrices and $a_{ij,i\neq j} \leq b_{ij,i\neq j}$, while $a_{ii} = b_{ii}, \forall i \in \{1,\ldots,n\}$; then $\tau_A \leq \tau_B$, where τ_A, τ_B are the two Perron-Frobenius eigenvalues of, respectively, A and B. □

***Theorem** 8:* Given a Metzler matrix A^m, with Perron-Frobenius eigenvalue τ, the following holds:

$$\min_i \sum_{j=1}^{n} a^m_{ij} \leq \tau \leq \max_i \sum_{j=1}^{n} a^m_{ij}, \;\; i \in \{1,\ldots,n\}. \qquad (1)$$

If the equality holds, then it does in both cases. □

***Remark** 4:* A similar result holds calculating along the columns of the matrix A^m. □

The previous results are interesting because they allow us to reinterpret the conditions we found beforehand (Thm. 2) within a new perspective. In particular, this gives a new proof of Theorem 3. If our original state matrix A^m is already Metzler, then we can infer some dynamical properties of the linear system associated to it. For instance,

***Corollary** 1:* Strict box invariance for a linear system $\dot{\boldsymbol{x}} = A^m\boldsymbol{x}$, with A^m Metzler, implies asymptotic stability. The converse is not true. □

The following result, anticipated in the introduction, is interesting from a robustness study perspective.

***Corollary** 2:* Given a Metzler matrix A^m, its box invariance is not affected by pre- or post-multiplications by positive diagonal matrices. □

Although the connection with the theory of Metzler matrices appears quite promising, the reader should notice that in general it is not possible to directly translate results obtained for a Metzler matrix A^m to its ancestor A, which may not be Metzler. The results outlined for the Metzler correspondent of a system matrix can be instead fully exploited for robustness analysis, as explained in the next section.

***Example** 1:* **A Model for Blood Glucose Concentration.** The following model is taken from [12]. It is a model of a physiologic compartment, specifically the human brain, and focuses on the dynamics of the blood glucose concentration. In general, this compartment is part of a larger model of glucose concentration in all organs of the body that interact via some conservation laws. The mass balance equations are the following:

$$\begin{aligned} V_B\dot{C}_{Bo} &= Q_B(C_{Bi}-C_{Bo}) + PA(C_I - C_{Bo}) - r_{RBC} \\ V_I\dot{C}_I &= PA(C_{Bo}-C_I) - r_T, \end{aligned}$$

where V_B describes the capillary volume, V_I the interstitial fluid volume, Q_B the volumetric blood flow rate, PA the permeability-area product, C_{Bi} the arterial blood solute concentration, C_{Bo} the capillary blood solute concentration, C_I the interstitial fluid solute concentration, r_{RBC} the rate of red blood cell uptake of solute, and r_T models the tissue cellular removal of solute through cell membrane. The quantity PA can be expressed as the ratio V_I/T, where T is the transcapillary diffusion time. For this last value, which may in general vary, we choose the value $T = 10$ [min].

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]

By applications of the conditions described above, the system is box invariant. Figure 2 plots a trajectory and some boxes. In [13], an extension of the model is studied. □

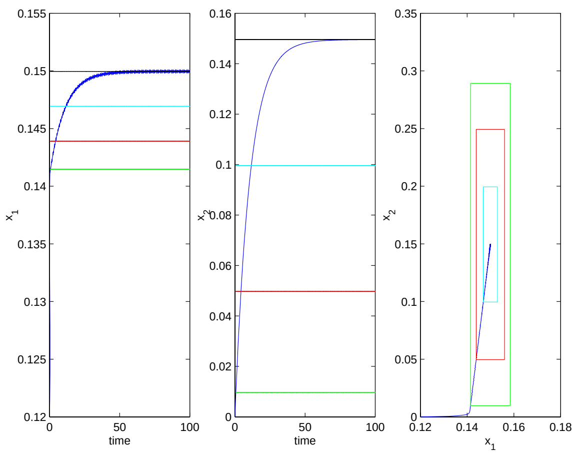

Fig. 2. Blood Glucose Concentration: simulation of a trajectory, and computation of some boxes.

C. Robust Properties of Box Invariance

The issue of *robustness* arises in biological models when some parameters of the system are not known exactly and thus may be thought to lie within specified bounds. These parameters can represent rates of reactions that are often unknown or subject to noise.

The theory of Metzler matrices allows us to exploit some results on the spectral properties of this class of matrices to study robustness of box invariance of linear systems. Consider Theorems 7 and 8. As discussed above, the positive Perron eigenvector $\boldsymbol{x}^\tau$ defines (one vertex of) the actual box. This knowledge can be exploited to obtain stricter bounds for the Perron eigenvalue τ.

***Corollary** 3:* Given a Metzler matrix A^m, with Perron-Frobenius eigenvalue τ and a positive vector $\boldsymbol{x}$, the following holds:

$$\min_i \frac{1}{x_i}\sum_{j=1}^n x_j a_{ij}^m \le \tau \le \max_i \frac{1}{x_i}\sum_{j=1}^n x_j a_{ij}^m, i \in \{1,\ldots,n\}. \square$$

***Remark** 5:* The substitution of $\boldsymbol{x}^\tau$ in place of $\boldsymbol{x}$ turns the inequality into equality, in both directions. Thus, due to the continuous dependence of the eigenvalues of a matrix on its elements, the use of $\boldsymbol{x} = \boldsymbol{x}^\tau$ for bounding the value of τ of a matrix A^m will definitely yield better results than the use of $\boldsymbol{x} = \mathbf{1}$, as in Thm. 8. □

If the Perron-Frobenius eigenvector is unknown, we can obtain improved bounds for the Perron-Frobenius eigenvalue regardless of the computation of any vector. We skip the details, but refer the reader to the results for positive matrices in [14] for simple adaptation to the Metzler case.

We start with two cases in our study of robustness. The first deals with uncertainty on the diagonal terms, while the second with uncertainty on the off-diagonal terms. It is clear that, for a matrix with Metzler form, the effect of these two sets towards box invariance is dichotomic: while the first contributes to it, the second can be disruptive.

*1) **Diagonal Perturbations**:* For the first instance, let us refer to a matrix of the form A^m_ϵ, where $a^m_{\epsilon,ij} = a^m_{ij}, i \neq j$, while $a^m_{\epsilon,ii} = a^m_{ii}(1+\epsilon)$. In other words, $A^m_\epsilon = A^m + \epsilon\ \mathtt{diag}(a^m_{ii})$. If $\epsilon > 0$, then the perturbed system remains box invariant. If $\epsilon < 0$, then the Perron-Frobenius eigenvalue τ_ϵ of A^m_ϵ may still be negative for some ϵ. The eigenvalues of A^m_ϵ are known to be a convex function of the entries of the diagonal matrix $\epsilon\ \mathtt{diag}(a^m_{ii})$. In particular, from Corollary 3 and by the convexity of the max function, it follows that $\tau_\epsilon \le \tau + \epsilon \max_i a^m_{ii}$. Hence, a lower bound to the minimum allowed (negative) perturbation that maintains box invariance is given by the inequality $\epsilon > -\frac{\tau}{\max_i a^m_{ii}}$.

*2) **Off-diagonal Perturbations**:* In the second case, more complex in general than the first, we can again exploit the upper bounds described in either Thm. 8 or Cor. 3 to make sure that the box invariance condition is retained if some of the off-diagonal terms vary. Introducing a new perturbed matrix A^m_ϵ, where $a^m_{\epsilon,ij} = a^m_{ij}(1+\epsilon_{ij}), \forall i, j \neq i$ and $a^m_{\epsilon,ii} = a^m_{ii}$, we are interested in finding how much we can perturb the off-diagonal elements of the matrix A^m, while preserving box invariance. Along direction i, introducing the vector $\boldsymbol{\epsilon}^i = [\epsilon_{ij}]_{j=1,\ldots,n}$ and a vector $\boldsymbol{v}^i = [\delta_{ij}]_{j=1,\ldots,n}$, where δ_{ij} is the Kronecker delta, we state the problem as follows:

$$\max_{\boldsymbol{\epsilon}^i \ge 0} \|\boldsymbol{\epsilon}^i\|_2^2, \quad \text{s.t. } \sum_{j=1}^n A^m_{\boldsymbol{\epsilon}^i}|_{(i,j)} < 0,\ (\boldsymbol{v}^i)^T\boldsymbol{\epsilon}^i = 0.$$

The choice of the norm is arbitrary at this level. Moreover, 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 first constraint comes from Thm 8. In general, as discussed, it can be substituted by $(X^\tau)^{-1} A^m_{\boldsymbol{\epsilon}^i} X^\tau|_{(i,j)} \le 0, \forall i = 1,\ldots,n$, where X^τ is a diagonal matrix formed with the elements of the Perron (right) eigenvector $\boldsymbol{x}^\tau$ of A^m. The second constraint forces the diagonal terms of A^m to stay unperturbed, and bounds the solution of the problem. The optimization problem can be restated by introducing two Lagrange multipliers (respectively $\lambda > 0$ and ν), one for each constraint. Let us denote the i^{th} row of $A^m_{\boldsymbol{\epsilon}^i}$ as $A^m_i(\mathbf{1}+\boldsymbol{\epsilon}^i)$. Calculations show that the solution has the form, $\boldsymbol{\epsilon}^i = \frac{1}{2}(\lambda A^{m^T} + \gamma \boldsymbol{v}^i)$, where

$$\lambda = \frac{1}{\sum_{j=1,j\neq i}^n a^m_{ij}} + \frac{a^m_{ii}}{\sum_{j=1,j\neq i}^n (a^m_{ij})^2};$$

$$\nu = -\frac{a^m_{ii}}{\sum_{j=1,j\neq i}^n a^m_{ij}} - \frac{(a^m_{ii})^2}{\sum_{j=1,j\neq i}^n (a^m_{ij})^2} = -\lambda a^m_{ii}.$$

This can be rewritten as follows, $\forall j \neq i$:

$$\epsilon_i^i = 0; \quad \epsilon_j^i = \frac{1}{2}\left(\frac{a_{ij}^m}{\sum_{j=1,j\neq i}^n a_{ij}^m} + \frac{a_{ii}^m a_{ij}^m}{\sum_{j=1,j\neq i}^n (a_{ij}^m)^2}\right).$$

*3) **General Perturbations:*** We can tackle the problem more generally, albeit trading off the obtainment of closed form solutions. Let A^m be a Metzler matrix that describes a box invariant linear system. Consider the perturbed matrix $A_\epsilon^m = A^m + E = A^m + \sum_{i,j=1}^n \epsilon_{ij}[\Delta_{(i,j)}]$, 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 is clear that adding positive terms to a Metzler Matrix may disrupt its box invariance. 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:

$$\max_E f(E), \quad \text{s.t. } (A_\epsilon^m \mathbf{1} < \mathbf{0}) \vee (\mathbf{1}^T A_\epsilon^m < \mathbf{0}),\ E \geq 0.$$

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 $f(E) = \|E\|_p, p \geq 1$. The first constraint codifies the condition of Thm. 8. For the 2-norm ($p = 2$), interpreting E as a function of its elements ϵ_{ij}, introducing an epigraph and resorting to the Schur complement, we can reformulate the problem as the following LMI:

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

where the last inequality is to be interpreted componentwise.

D. *Polynomial Systems*

Dynamical models in biology are often in the form of polynomial systems, $\dot{\boldsymbol{x}} = \boldsymbol{p}(\boldsymbol{x})$, where $\boldsymbol{p}(\boldsymbol{x})$ is a vector of polynomials over $\boldsymbol{x}$. The condition for box invariance for polynomial systems can be written as a formula in the first-order theory of reals

$$\exists \boldsymbol{l},\boldsymbol{u}.\forall \boldsymbol{x}. \quad \textstyle\bigwedge_{1\leq j\leq n} \quad ((\boldsymbol{x} \in S^{j,l} \Rightarrow \boldsymbol{p}_j(\boldsymbol{x}) \geq 0) \ \wedge \ (\boldsymbol{x} \in S^{j,u} \Rightarrow \boldsymbol{p}_j(\boldsymbol{x}) \leq 0)), \quad (2)$$

where, as mentioned earlier, $S^{j,k}$ are the $2n$ faces of the box defined by $\boldsymbol{l}$ and $\boldsymbol{u}$. Since this theory is decidable [15], [16], the following result follows.

***Theorem** 9:* 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 [17], naturally arise in modeling biochemical reaction networks [17], [18]. In these systems, the polynomials are restricted so that each variable has at most degree one in each monomial. Multi-affine systems have several nice properties that have been exploited for building efficient analysis tools. We generalize the definition of multi-affine systems and call a system $\dot{\boldsymbol{x}} = \boldsymbol{p}(\boldsymbol{x})$ *multi-affine* if each variable x_j has degree at most one in each monomial in p_i *for all* $j \neq i$. In fact, the universal quantifiers in Formula (2) can be eliminated and Formula (2) can be simplified for multi-affine systems to a conjunction of $n2^n$ (existentially quantified) constraints using the following analogue of Proposition 1.

***Proposition** 3:* 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 $\boldsymbol{c}$, with $c_i \in \{u_i, l_i\}$, we have $\boldsymbol{p}(\boldsymbol{c}) \sim \mathbf{0}$, where $\sim_i$ is $\leq$ if $c_i = u_i$ and $\sim_i$ is $\geq$ if $c_i = l_i$. □

Proposition 3 still requires checking satisfiability of an exponential number of (nonlinear) constraints. The following result shows that we cannot hope to obtain polynomial time algorithms for checking box invariance of multi-affine systems for the case when the box is given.

***Theorem** 10:* The problem of determining if a multi-affine system is box invariant with respect to a given box is co-NP-hard. □

However, for a very useful subclass of multi-affine systems, we can reduce the number of constraints (from $n2^n$) to $2n$. We use the notion of monotonicity. A function $f : \mathbb{R}^n \mapsto \mathbb{R}$ is monotonic with respect to a variable x_j if $f(\ldots,x_j,\ldots) \leq f(\ldots,x_j',\ldots)$ (or $f(\ldots,x_j,\ldots) \geq f(\ldots,x_j',\ldots)$) whenever $x_j < x_j'$.

***Proposition** 4:* Let $\dot{\boldsymbol{x}} = \boldsymbol{p}(\boldsymbol{x})$ be a 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 3 are equivalent to some subset of $2n$ constraints. □

We illustrate the ideas and the utility of Proposition 4 in the following example.

***Example** 2:* Consider the following Phytoplankton Growth Model (see [19] and references therein):

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

where 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 [17], but it is multi-affine in our weaker sense. Moreover, it satisfies the monotonicity condition, and hence by Proposition 4, its box invariance is equivalent to the existence of $\boldsymbol{l},\boldsymbol{u}$ s.t. the following 6 constraints (that subsume the $3 \cdot 2^3 = 24$ constraints) are satisfied:

$$\begin{array}{lll} 1 - u_1 - \frac{u_1 l_2}{4} \leq 0, & u_2(2u_3 - 1) \leq 0, & \frac{u_1}{4} - 2u_3^2 \leq 0, \\ 1 - l_1 - \frac{l_1 u_2}{4} \geq 0, & l_2(2l_3 - 1) \geq 0, & \frac{l_1}{4} - 2l_3^2 \geq 0. \end{array}$$

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. □

E. *Extensions to a class of NonLinear Systems*

In this section we use ideas from the previous robustness study to *efficiently* check box invariance (using only a sufficient, but not necessary, characterization) of a subclass of multi-affine systems in which the degree of each polynomial is at most two. This assumption is natural for models of biochemical reactions in which every reaction can have at most two reactants. We shall tackle the study of these systems leveraging two different perspectives.

NonLinear Systems as perturbations of Linear Systems: Consider a general non linear, multi-affine model $\dot{\boldsymbol{x}} = f(\boldsymbol{x}), \boldsymbol{x} \in \mathbb{R}^n$. The structure of the vector field allows to express 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, and in particular can be chosen to have the form $b(\boldsymbol{x})_{ii} = 0, b(\boldsymbol{x})_{ij} = \beta x_i + \gamma x_k; i \neq k \neq j \in \{1, 2, \ldots, n\}; \beta, \gamma \in \mathbb{R}$. The nullity of the values on the diagonal is justified in biological instances by observing that a dimerization of an element cannot yield that element. Notice that in the off-diagonal positions we could in principle also accomodate second order homogeneous terms ($b(\boldsymbol{x})_{ij} = \beta x_i + \gamma x_k + \delta x_j$, which would incidentally disrupt the multi-affine structure as defined in [17]).
Let us now assume that system corresponding to the linear part ($\dot{\boldsymbol{x}} = A\boldsymbol{x}$) is box-invariant, i.e. that there exists a nontrivial (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 $\Gamma^m(\boldsymbol{x}) \doteq A^m + B^m(\boldsymbol{x})$, where $b^m(\boldsymbol{x})_{ij} = |b(\boldsymbol{x})_{ij}|$. It is then possible to refer back to section III-C.2 and think of $\Gamma^m(\boldsymbol{x}) = A^m_\epsilon$, where $b^m(\boldsymbol{x})_{ij} = \epsilon_{ij}/a^m_{ij}$. In other words, the non-linear part can be conceived as an additional term that may disrupt the box invariance of the linear system. Clearly this is a pessimistic take, which comes from the positivity assumption on the terms $b^m(\boldsymbol{x})_{ij}$. By the application of the results derived in III-C.2, a set of upper bounds for the values of the "allowed perturbations" is obtained. Furthermore, these bounds define some hyperplanes which, when intersected, reduce the feasible region for the vertices of the box: $b^m(\boldsymbol{x})_{ij} = |\beta x_i + \gamma x_k| \leq |\beta||x_i| + |\gamma||x_k| \leq \epsilon_{ij}/a^m_{ij}$, where ϵ_{ij} is here the maximum allowed perturbation, solution of the optimization problem. Notice that these inequalities on halfspaces are all satisfiable on the positive quadrant, and when intersected with the cone $\mathcal{C}$ define a new set of possible vertices for the invariant hyper-rectangle.

Overvaluing Dynamical Systems: A second method to compute invariant regions, closely related to the first in its outcomes, is based on the definition of an *overvaluing system* [20], [21], which depends on the choice of a particular (vector) norm [7]. 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 II, in our study, we are interested in a real valued, infinity vector norm $p(\boldsymbol{x}) = \|\boldsymbol{x}\|_\infty$ or possibly in a scaled version thereof, $p^W(\boldsymbol{x}) = \|W\boldsymbol{x}\|_\infty$, where W is a diagonal, positive $n \times n$ matrix. The right-derivative of $p(\boldsymbol{x})$ [7], $D^+p(\boldsymbol{x})$, can be upper-bounded, within a given limited region $\mathcal{S} \subset \mathbb{R}^n$, by a value $m \in \mathbb{R}$ as follows: $D^+p(\boldsymbol{x}) \leq mp(\boldsymbol{x})$. Results in [20] allow to claim that, whenever the inequality $D^+p(\boldsymbol{x}) \leq mp(\boldsymbol{x})$ holds in $\mathcal{S}$ with $m < 0$, then the region defined as

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

is positively invariant for the original nonlinear system. As a side result, the original non linear system will be asymptotically stable, as expected. The right-derivative $D^+p(\boldsymbol{x})$ can be upper-bounded by a set of inequalities: given the matrices A and $B(\boldsymbol{x})$ as in the preceding paragraph, notice that $D^+p(\boldsymbol{x}) \leq \max_{i=1,\ldots,n}\{a_{ii} + \sum_{j\neq k\neq i}|a_{ij}| + |\beta||x_i| + |\gamma||x_k|\}p(\boldsymbol{x})$. This condition is in fact similar to the one used for the robustness study in section III-C.2 and exploited above. Here no prior assumption on the existence of an invariant box is raised. The approach is similar, accounting for the rescaling factors, for the case of $p^W(\boldsymbol{x})$. The above region $B \subseteq \mathcal{S}$ is an n-dimensional hypercube with side of length $2c$. The vector norm $p^W(\boldsymbol{x})$ would instead single out a symmetric hyper rectangle with a vertex lying on the vector $[w_{11}, \ldots, w_{nn}]^T$.

References

[1] F. Blanchini, "Set invariance in control," *Automatica*, vol. 35, pp. 1747–1767, 1999.
[2] A. Podelski and S. Wagner, "Model checking of hybrid systems: from reachabilty towards stabilty," in *Hybrid Systems: Computation and Control*, ser. LNCS 3927. Springer Verlag, Apr 2006.
[3] A. Abate, A. Tiwari, and S. Sastry, "The concept of box invariance for biologically-inspired dynamical systems," EECS Dept., UC Berkeley, Tech. Rep., 2006.
[4] M. Voicu, "Componentwise asymptotic stability of linear constant dynamical systems," *IEEE Transactions on Automatic Control*, vol. 29, pp. 937–939, 1984.
[5] O. Pastravanu and M. Voicu, "Norm-based approach to componentwise asymptotic stability," in *Proc. 11th IEEE Mediterranean Conf. on Control and Automation*, 2003.
[6] ——, "Necessary and sufficient conditions for componentwise stability of interval matrix systems," *IEEE Transactions on Automatic Control*, vol. 49, pp. 1016–1021, 2004.
[7] H. Kiendl, J. Adamy, and P. Stelzner, "Vector norms as lyapunov functions for linear systems," *IEEE Transactions on Automatic Control*, vol. 37, pp. 839–842, 1992.
[8] K. Loskot, A. Polanski, and R. Rudnicki, "Further comments on "vector norms as Lyapunov functions for linear systems"," *IEEE Trans. on Automatic Control*, vol. 43, no. 2, 1998.
[9] R. Horn and C. Johnson, *Matrix Analysis*. Cambridge University Press, 1985.
[10] G. Coxson, "The p-matrix problem is co-np-complete," *Mathematical Programming*, vol. 64, pp. 173–178, 1994.
[11] E. Seneta, *Nonnegative Matrices*. Wiley, New York, 1973.
[12] J. Sorensen, "A physiologic model of glucose metabolism in man and its use to design and assess improved insulin therapies for diabetes," Ph.D. dissertation, MIT, 1985.
[13] A. Abate and A. Tiwari, "Box invariance for hybrid and switched systems," in *Proceedings of the 2nd IFAC Conference on Analysis and Design of Hybrid Systems*, 2006.
[14] H. Minc, *Nonnegative Matrices*. Wiley, New York, 1988.
[15] A. Tarski, *A Decision Method for Elementary Algebra and Geometry*. University of California Press, 1948, second edition.
[16] G. E. Collins, "Quantifier elimination for the elementary theory of real closed fields by cylindrical algebraic decomposition," in *Proc. 2nd GI Conf. Automata Theory and Formal Languages*, ser. LNCS, vol. 33. Springer, 1975, pp. 134–183.
[17] C. Belta, L. Habets, and V. Kumar, "Control of multi-affine systems on rectangles with applications to hybrid biomolecular networks," in *Proc. 41st Conf. on Decision and Control*. IEEE, 2002, pp. 534–539.
[18] P. Lincoln and A. Tiwari, "Symbolic systems biology: Hybrid modeling and analysis of biological networks," in *Hybrid Systems: Computation and Control*, ser. LNCS 2993. Springer, 2004, pp. 660–672.
[19] O. Bernard and J.-L. Gouze, "Global qualitative description of a class of nonlinear dynamical systems," *Artificial Intelligence*, vol. 136, pp. 29–59, 2002.
[20] P. Borne, J. Richard, and N. Radhy, "Stability, stabilization, regulation using vector norms," *J. Fossard and D. Normand-Cyrot eds., Nonlinear Systems, Stability and Stabilization*, vol. 2, pp. 45–90, 1996.
[21] E. Erdem and A. Alleyne, "Estimation of stability regions of sdre controlled systems using vector norms," in *Proceedings of the American Control Conference*, 2002, pp. 80–85.