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Technical Report No. UCB/EECS-2006-185
http://www.eecs.berkeley.edu/Pubs/TechRpts/2006/EECS-2006-185.html

December 18, 2006

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***Abstract*— In this paper we introduce a special notion of Invariance Set for certain classes of dynamical systems: the concept has been inspired by our experience with models drawn from Biology. We claim that *Box Invariance*, that is, the existence of "boxed" invariant regions, is a characteristic of many biologically-inspired dynamical models, especially those derived from stoichiometric reactions. Moreover, box invariance is quite useful for the verification of safety properties of such systems. This paper presents effective characterization of this notion for linear and affine systems, the study of the dynamical properties it subsumes, computational aspects of checking for box invariance, and a comparison with related concepts in the literature. The concept is illustrated using two models from biology.**

I. INTRODUCTION

Stability analysis of dynamical models is of utmost importance in understanding the behavior of systems. The literature on System Theory has offered many notions of stability, depending on the structure and characteristics of the models. Focusing on a particular notion of "convergent behavior" of trajectories needs therefore to be justified. The main motivation for this work comes from the many biological case studies that have been investigated by the authors. The structure of the models under study has naturally raised the following question: is the concept of Lyapunov stability always rightful and descriptive in the biological realm, which is often characterized by complicated models endowed with imprecisely known parameters? As a viable alternative, would it not make sense to look for "bounded behavior in the closeness of an equilibrium"? Intuitively, it may be legitimate to consider a notion of stability defined "within certain limits", or "bounds", rather than abstractly on neighborhoods of equilibria. In other words, we may be interested in the existence of a region, around the equilibrium, within which a trajectory would indefinitely dwell once it intersects it. Hence, the notion of Invariant Set comes handy. We shall focus on the simplest possible shape for this region, that of a box. Empirically, we have found that models of many biological systems have box shaped regions as invariant sets. This seems natural in retrospect since state variables often correspond to physical quantities that are naturally bounded.

Research supported by the grants CCR-0225610 and DAAD19-03-1-0373, and in part by NSF CCR-0311348 and DARPA DE-AC03-765F00098.

From the perspective of formal verification of such models, a box invariant set can be used to verify safety properties. As an added advantage, box invariance is computationally easy to check for a large class of systems, and hence it is an ideal concept for proving strong safety properties of such systems.

We compare in some detail the notion with other related concepts in the literature and try to establish connections between them.

In this manuscript we shall formally introduce and define the notion of Box Invariance, starting with the simplest instance of linear and affine dynamical systems; we will also stress how to practically compute an actual box. The strong connection of the notion with the theory of Metzler matrices will highlight a procedure to study the dynamical properties of these invariant systems. The focus will then switch to a robustness study, through the use of the theory of Metzler matrices from Linear Algebra. Furthermore, possible extensions to more general vector fields will be sketched. We shall discuss some applicative example drawn from the biology world to illustrate the results.

II. THE CONCEPT OF BOX INVARIANCE

In this work, we shall consider general, autonomous 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 for 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 will be said to be *strictly box invariant* if the last equalities hold strictly.

***Remark** 1:* The concept of box invariance requires the existence of an *invariant set* for a dynamical system with a special polyhedral shape. In the case of linear systems, we shall see that this invariant set is also an ω-*limit set* (or a *domain of attraction*); thus, the existence of a box invariant set will be shown to imply the stability of the trajectories of the system towards the equilibrium: hence, a notion of *box stability*. 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 reordering of state variables and rotations by multiples of $\pi/2$; we shall also display its 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 *symmetrical 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 $(2\boldsymbol{x}_0 - \boldsymbol{u})$.

III. CHARACTERIZATION OF BOX INVARIANCE.

In this section we investigate the problem of characterizing the notion of box invariance for two simple classes of systems. Moreover, we propose efficient computational ways to find such a box. This is followed by a study of robustness properties and comparison to related concepts in the literature. The important extension to more general vector fields (in particular, multi-affine [1], which are fundamental for reaction networks) will be presented in future works.

A. *Linear Systems.*

Given a linear system and a box around its equilibrium point, the problem of checking if 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 all the faces 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 $\boldsymbol{u} \in \mathbb{R}^{+n}$ and $\boldsymbol{l} \in \mathbb{R}^{-n}$ such that for each point $\boldsymbol{c}$, with $c_i \in \{u_i, l_i\}, \forall i$, we have $A\boldsymbol{c} \ \sim \ \boldsymbol{0}$, where $\sim_i$ is $\leq$ if $c_i = u_i$ and $\sim_i$ is $\geq$ if $c_i = l_i$.

Proof: The points $\boldsymbol{u}$ and $\boldsymbol{l}$ are the two vertices in the positive and negative quadrants of the n-dimensional space the box lies on. The inequalities just state that the vector field points inwards on these 2^n vertices. Moreover, the value of the vector field on other points of the surface of the box is bounded by the expressions at the vertices, thus the inequalities on the surface points hold *a fortiori*. ■

***Remark** 2:* Proposition 1 shows that box invariance of linear systems can be checked by testing satisfiability of 2^n linear inequality constraints (over $2n$ unknowns given by $\boldsymbol{l}$ and $\boldsymbol{u}$). In two steps (Thms. 1, 2), we will show that these 2^n constraints are subsumed by just n linear inequality constraints (over n unknowns).

***Assumption** 1:* In the following, we shall focus on system matrices *with non positive diagonal elements*, unless otherwise stated. This condition often holds in models obtained from stoichiometric reactions; in fact, the diagonals represent degradation rates of the various species.

In the following statement we suggest box invariance can be equivalently checked on a new matrix that is obtained from the system matrix A.

***Theorem** 1:* An n-dimensional linear system $\dot{\boldsymbol{x}} = A\boldsymbol{x}$ is symmetrical box invariant iff there exists a positive vector $\boldsymbol{c} \in \mathbb{R}^{+n}$ such that $A^m\boldsymbol{c} \leq \boldsymbol{0}$, where $a_{ii}^m = a_{ii} (< 0)$ and $a_{ij}^m = |a_{ij}|$ for $i \neq j$. This is equivalent to checking if the linear system defined by A^m is symmetrical box invariant.

Proof: Consider the following 2^{n-1} constraints:

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

where $c_i \in \{u_i, -u_i\}$. We know that $a_{11} \leq 0$ and $u_1 > 0$. Hence, these 2^{n-1} constraints are subsumed by the one of them, which is the strongest inequality constraint, and is given by,

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

This way the $n2^{n-1}$ constraints are equivalent to satisfiability of n constraints, which can be succinctly written as $A^m\boldsymbol{u} \leq \boldsymbol{0}$, where A^m is as defined in the statement of the Theorem and $\boldsymbol{u}$ is a positive vector. ■

Surprisingly, the notion of box invariance and symmetrical box invariance are equivalent for linear systems:

***Theorem** 2:* A linear system $\dot{\boldsymbol{x}} = A\boldsymbol{x}$, where $A \in \mathbb{R}^{n \times n}$, is box invariant iff it is symmetrical box invariant.

Proof: The proof follows the same argument used in the proof of Thm. 1. If the linear system is symmetrical box invariant, then it is clearly also box invariant. To prove the converse, assume that the linear system is box invariant. Let the box be defined by the diagonally opposite points $\boldsymbol{l} \in \mathbb{R}^{-n}$ and $\boldsymbol{u} \in \mathbb{R}^{+n}$. We will show that the linear system is also box invariant with respect to the (symmetrical) box defined by $(\boldsymbol{u} - \boldsymbol{l})$ and $-(\boldsymbol{u} - \boldsymbol{l})$. By Thm. 1, box invariance of $\dot{\boldsymbol{x}} = A\boldsymbol{x}$ is equivalent to the satisfiability of the $n2^n$ inequality constraints. Consider the following 2^{n-1} constraints:

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

where $c_i \in \{u_i, l_i\}$. We know that $a_{11} \leq 0$ and $u_1 > 0$. Hence, these 2^{n-1} constraints are subsumed by the one of them which is the strongest inequality constraint, and is given by,

$$a_{11}u_1 + a_{12}d_2 + a_{13}d_3 + \cdots + a_{1n}d_n \leq 0, \tag{1}$$

where $d_i = l_i$ if $a_{1i} < 0$ and $d_i = u_i$ if $a_{1i} > 0$. Similarly, the 2^{n-1} constraints given by

$$a_{11}l_1 + a_{12}c_2 + a_{13}c_3 + \cdots + a_{1n}c_n \geq 0,$$

where $c_i \in \{u_i, l_i\}$, can be replaced by just one constraint

$$a_{11}l_1 + a_{12}d'_2 + a_{13}d'_3 + \cdots + a_{1n}d'_n \geq 0, \tag{2}$$

where $d'_i = l_i$ if $a_{1i} > 0$ and $d'_i = u_i$ if $a_{1i} < 0$. Using Inequality (1) and Inequality (2), we get

$$a_{11}(u_1 - l_1) + a_{12}e_2 + a_{13}e_3 + \cdots + a_{1n}e_n \leq 0, \tag{3}$$

where $e_i = u_i - l_i$ if $a_{1i} > 0$ and $e_i = l_i - u_i$ if $a_{1i} < 0$. Inequality (3) subsumes the 2^{n-1} other constraints,

$$a_{11}(u_1 - l_1) + a_{12}e'_2 + a_{13}e'_3 + \cdots + a_{1n}e'_n \leq 0,$$

where $e'_i \in \{l_i - u_i, u_i - l_i\}$. We can thus conclude that on all vertices of the box defined by $(\boldsymbol{u}-\boldsymbol{l})$ and $(\boldsymbol{l}-\boldsymbol{u})$, the vector field points inwards. Hence, the linear system is symmetrical box invariant with respect to box defined by $(\boldsymbol{u}-\boldsymbol{l})$ (and $-(\boldsymbol{u}-\boldsymbol{l})$). ■

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 the set of n linear inequality constraints for the corresponding matrix A^m, succinctly written as $A^m\boldsymbol{c} \leq 0$ (over the n unknowns embedded in $\boldsymbol{c}$) has feasible solution. This can be done in *polynomial* time. In fact, we can even find a box by generating solutions for the above linear constraint satisfaction problem. Indeed, it is possible to associate with a linear dynamical system, characterized by a system matrix $A \in \mathbb{R}^{n\times n}$, 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).

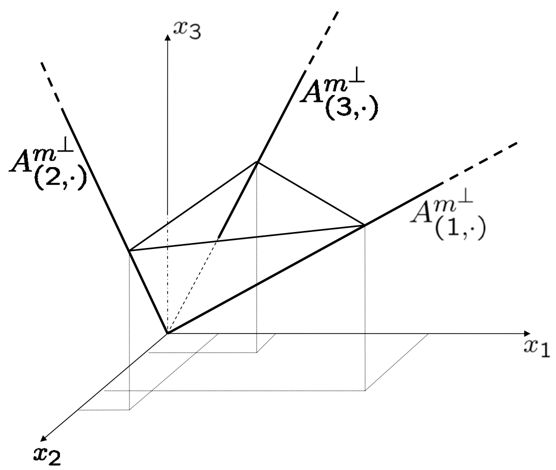

Fig. 1. A three-dimensional conic region $\mathcal{C}$ containing possible vertices for the box.

Box Invariance is a sharp and characterizing notion; for instance, the following can be of interest:

***Theorem** 3:* If a linear dynamical system is box invariant, then it is stable.

Proof: If a symmetric box determined by the diagonal $\boldsymbol{c}$ exists, then any other symmetric box determined by $\alpha\boldsymbol{c}, \alpha > 0$ is also an invariant set for the system. Thus, given any neighborhood of the equilibrium point $\mathcal{B}$, there exists an α^* 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 $\mathcal{B}$. ■

In the following we propose another computationally tractable methodology to check for the box invariance property of a linear dynamical system endowed with a state matrix of the special form that we introduced in Assumption 1. We exploit the notion of principal minor of a matrix A, which is the determinant of the submatrix of A formed by removing certain rows and the same columns from A, (cf. [2]). In particular, the diagonal elements of A are its principal minors and the determinant of A is also a principal minor. As we shall see later, a matrix A is said to be positive, or a *P-matrix* if all of its principal minors are positive.

***Theorem** 4:* Let A be a $n \times n$ matrix such that $a_{ii} \leq 0$ 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 symmetrical 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.

Proof: 1) ⇒ 2): Using Theorem 1 we know that 1) implies that there exists a point $\boldsymbol{c} \in \mathbb{R}^+$ in the positive quadrant such that $-A\boldsymbol{c} \geq \boldsymbol{0}$. Let $I = \{1, \ldots, n\}$ be the set of indices. Let $I' \subset I$ be *any* nonempty subset of the index set. We need to show that the determinant $|-A'|$ of the submatrix $(A'_{ij})_{i,j\in I'}$ of A (A' contains only those rows and columns of A whose indices are in I') is non-negative. To show this, we apply the well-known Fourier-Motzkin elimination procedure to the system $-A'\boldsymbol{c} \geq \boldsymbol{0}$. We observe that Fourier-Motzkin elimination procedures reduces to Guassian reduction/elimination procedure for converting $-A'$ to upper triangular form. (To see this note that all non-diagonal elements remain non-positive because of the assumptions on the signs of a_{ij}'s, and the diagonal entries are forced to be positive by the existence of $\boldsymbol{c}$.) The determinant of the triangular matrix, which is a product of its diagonal entries, therefore, is forced to be positive. But the determinant of the original $-A'$ is a positive multiple of the determinant of the triangular matrix (since the Gaussian elimination steps use only positive multiplication factors on rows). This shows that the chosen principal minor is positive.

2) ⇒ 3): Since $-A$ is a P-matrix, it follows that all principal minors are positive. In particular, the the determinant of the top left $i \times i$ submatrix of $-A$ will be positive (for every $i = 1, 2, \ldots, n$).

3) ⇒ 1): To show that there is a positive vector $\boldsymbol{c}$ such that $-A\boldsymbol{c} \geq 0$, we apply Fourier-Motzkin procedure and eliminate variables in the order $1, 2, \ldots, n$. It is now easy to see that condition 3) guarantees that this procedure would not lead to an inconsistent state, and that the final saturated set of constraints (defined by the upper triangular matrix) will be satisfiable. ■

***Remark** 3:* Theorem 4 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 (see [3], [4]). Our case is special though, since we know that only the diagonal entries in $-A^m$ are positive. As a result, we can determine if $-A^m$ is a P-matrix using a simple *polynomial* time algorithm. For example, Fourier-Motzkin elimination method will run in polynomial time here and it can determine satisfiability and even generate the solution cone $\mathcal{C}$.

Matrices with the shape of those in Theorem 4 (or, equivalently, of A^m in Theorem 1) are known under the appellative of *Metzler* matrices[1]. 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 instance of Metzler matrices, with an additional constraint on the row sum; similarly for *doubly stochastic matrices*.

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 (see refs. [5], [6]) were the first to study positive matrices; many results can be extended to the Metzler case provided a structural property, that of *irreducibility*, holds[2]. This property is also used in the theory of Markov Chains, and assumes that there's 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 practical instances, 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. Example 3 will show this explicitly. Similar, slightly slacker results, can in any case be derived for the general case.

The following holds, (cf. [7]):

***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 $\exists \boldsymbol{c} > \mathbf{0}$, such that $A^m\boldsymbol{c} \leq \mathbf{0}$; $\tau < 0$ iff there is at least one strict inequality in $A^m\boldsymbol{c} \leq \mathbf{0}$;
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** 5:* 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 $\exists \boldsymbol{c} > \mathbf{0}$, such that $A^m\boldsymbol{c} \leq \mathbf{0}$; $\tau < 0$ iff $\exists \boldsymbol{c} > \mathbf{0}$, such that $A^m\boldsymbol{c} < \mathbf{0}$.

Proof: The first part of the statement is shown by point 5) above. For the second part, observe that if all the diagonal terms are negative, then $d = \max_{i\in\{1,\ldots,n\}} |m_{ii}| > 0$. Defining the positive matrix $P = A^m + dI$, the condition $A^m\boldsymbol{c} < \mathbf{0}$ on a vector $\boldsymbol{c} > \mathbf{0}$ can be expressed as $P\boldsymbol{c} < d\boldsymbol{c}$, which, by the Subinvariance theorem (see, for instance, [7], Ch. 1), is tantamount to $\tau^P < d$, where τ^P is the positive Perron-Frobenius eigenvalue of P. From this follows that $\tau < 0$. Conversely, if $\tau < 0$, consider the corresponding strictly positive left Perron eigenvector $\boldsymbol{x}^\tau$, and we have that $(\boldsymbol{x}^\tau)^T A^m \boldsymbol{c} = \tau(\boldsymbol{x}^\tau)^T\boldsymbol{c} < 0$, by the strict positivity of $\boldsymbol{c}$. ■

The following are two interesting results which will be useful in the sequel:

***Theorem** 6:* 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.

Proof: Consider the corresponding non-negative matrices $A+cI$ and $B+cI$, where again $c = \max_{i\in\{1,\ldots,n\}} a_{ii} = \max_{i\in\{1,\ldots,n\}} b_{ii}$. Then $A + cI \leq B + cI$. Furthermore, it can be shown by hand that $(A+cI)^k \leq (B+cI)^k, \forall k > 0$, and that $\|(A+cI)^k\|^{1/k} \leq \|(B+cI)^k\|^{1/k}, \forall k > 0$. Taking the limit, we obtain that $\tau_{A+cI} \leq \tau_{B+cI}$, and the conclusion is direct. ■

***Theorem** 7:* Given a Metzler matrix A^m, with Perron-Frobenius eigenvalue τ, the following holds:

$$\min_i \sum_{j=1}^{n} a_{ij}^m \leq \tau \leq \max_i \sum_{j=1}^{n} a_{ij}^m, \ \ i \in \{1,\ldots,n\}. \qquad (4)$$

If the equality holds, then it happens so in both directions.

Proof: It can be shown that a similar result holds for the corresponding non-negative matrix $(A^m + \max_{i\in\{1,\ldots,n\}} a_{ii}^m I)$ (see, for instance, [2]). A trivial simplification extends the inequality to the one in the statement. ■

***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. 1) within a new perspective. In particular, this sheds some light on Theorem 4, and proves it. 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.

Proof: The implication follows from points 2) of Prop. 2 and 5) of Thm. 5. Conversely, consider:

$$\dot{\boldsymbol{x}} = \begin{pmatrix} -1 & 10 \\ -10 & -1 \end{pmatrix} \boldsymbol{x}.$$

■

***Remark** 5:* This point can also be proven by arguments based on the idea of dynamically varying the size of the box with the trajectory.

[1]Metzler matrices are also known as *essentially non-negative* matrices.

[2]For the sake of completeness, it has to be reported that another stronger assumption, that of *primitivity*, is also introduced to strengthen the results obtained for the irreducibility case; we shall skip the details given the sufficient generality and practical applicability of the irreducibility assumption.

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.

Proof: If A^m is box invariant, then also $A^m_\epsilon = E^1 A^m E^2$ shall be, where $E^i = diag\{\epsilon^i_j\}, i \in \{1, 2\}, j = 1, \ldots, n, \epsilon^i_j > 0$. ■

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. In fact, the system associated with matrix A^m is not always an upper bound for the original system associated with A; in particular, this setback happens for some combinations of the signs of the elements of the matrix, and, correspondingly, in some of the quadrants of the state space. Of course, if we pose restrictions on the signs of the variables (which may derive from the particular instances we may be considering), we may be allowed to exploit these bounds. The results outlined for the Metzler correspondent of a system matrix can be instead fully exploited for robustness analysis, as in the next section.

B. Robust Properties of Box Invariance – Linear Systems

The issue of *robustness* arises in biological models when some of the parameters of the system are not known exactly and thus may be thought to vary within specified bounds. This fact is particularly urgent in the case of biological systems, where the coefficients of the model are often roughly measured, or they are known to be subject to noise.

The interpretation of the concept of box invariance through the theory of Metzler matrices allows us to exploit some results on the spectral properties of this class of matrices. Let us look back to Theorems 6 and 7. As discussed above, the knowledge of the positive Perron eigenvector $\boldsymbol{x}^\tau$ encompasses that of the actual box; this knowledge can be exploited for defining stricter bounds for the Perron eigenvector τ, as the following result presents:

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

$$\min_i \frac{1}{x_i} \sum_{j=1}^{n} x_j a^m_{ij} \leq \tau \leq \max_i \frac{1}{x_i} \sum_{j=1}^{n} x_j a^m_{ij}, i \in \{1, \ldots, n\}. \tag{5}$$

Proof: The eigenvalues of A^m are those of $X^{-1} A^m X$, where X is a full rank diagonal matrix formed with the components of $\boldsymbol{x}$. Direct calculations lead to the result. ■

***Remark** 6:* 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 $\boldsymbol{x} = \boldsymbol{1}$, as in Thm. 7.

If the Perron-Frobenius eigenvector is unknown, an alternative is to exploit improved bounds for the Perron-Frobenius eigenvalue that are independent of the computation of any vector. Without getting in lengthy details, the reader is referred to the results for positive matrices in [8] for simple adaptation to the Metzler case.

To begin with the study, let us single out two notable cases: 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, $A^m_\epsilon = A^m + \epsilon \mathrm{diag}(a^m_{ii})$. 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 $\epsilon \mathrm{diag}(a^m_{ii})$. In particular, from Corollary 3 and by the convexity of the max function, it follows that $\tau_\epsilon \leq \tau + \epsilon \max_i a^m_{ii}$. 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. 7 or Cor. 3 to make sure 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, in some sense, the off diagonal elements of the matrix A^m, while preserving box invariance. For 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:

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

We arbitrarily chose a particular norm, due to its intuitive meaning. Moreover, we focus on positive perturbations for the off-diagonal terms, because only those can actually 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 above comes from Thm 7. In general, as discussed, it can be substituted by $(X^\tau)^{-1} A^m_{\boldsymbol{\epsilon}^i} X^\tau|_{(i,j)} \leq 0, \forall i = 1, \ldots, n$, 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 bound the solution of the problem. The optimization problem can be restated introducing two Lagrange multipliers (respectively $\lambda > \boldsymbol{0}$ and ν), one for each constraint. Let us denote the i^{th} row of $A^m_{\boldsymbol{\epsilon}^i}$ as $A^m_i(1 + \boldsymbol{\epsilon^i})$. Calculations show that the solution has the following form:

$$\boldsymbol{\epsilon}^i = \frac{1}{2}(\lambda A^{m^T} + \gamma \boldsymbol{v}^i),$$

where $\quad \lambda = \frac{1}{\sum_{j=1,j\neq i}^n a_{ij}^m} + \frac{a_{ii}^m}{\sum_{j=1,j\neq i}^n (a_{ij}^m)^2};$

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

This can be rewritten as follows:

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

3) General case: At the cost of not obtaining closed form solutions, we can tackle the problem more generally. 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 is the worst (in some sense) perturbation that does not affect the box invariance property, to set up the following problem:

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

Here $f(E)$ is a measure of the "perturbation level"; for instance, we may choose $f(E) = \sum_{i,j=1}^n e_{i,j} = \sum_{i,j=1}^n \epsilon_{ij}$, or $f(E) = \|E\|_p, p \geq 1$. The first constraint codifies the condition of Thm. 7. 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:

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

where the last inequality ought to be interpreted componentwise.

C. Sensitivity Properties

Given the Perron eigenvalue τ of the matrix A^m knowing both left and right Perron eigenvectors $\boldsymbol{x}^\tau$ and $\boldsymbol{y}^\tau$, it would be interesting to calculate what is its sensitivity with respect to the elements of $A_\epsilon^m = A^m + \epsilon D$. Here D is a fixed matrix of disturbances that are parameterized by ϵ. It can be stated that (cf. [2])

$$\left.\frac{d\tau}{d\epsilon}\right|_{\epsilon=0} = \frac{\boldsymbol{y}^{\tau^T} D \boldsymbol{x}^\tau}{\boldsymbol{y}^{\tau^T} \boldsymbol{x}^\tau}.$$

It also holds that

$$\frac{d\tau}{d(a_\epsilon^m)_{ij}} = \frac{\boldsymbol{y}_i^\tau \boldsymbol{x}_j^\tau}{\boldsymbol{y}^{\tau^T} \boldsymbol{x}^\tau}.$$

D. *Box Invariance and Lyapunov Functions.*

The concept of box invariance, which is closely related to that of classical stability in the linear case, can also be studied via Lyapunov arguments. In our particular instance, to prove box invariance we want to find a Lyapunov functional which is defined (at least) inside a certain boxed region of the state space. Clearly, this function will not be smooth. We can obtain it by intersecting proper ellipsoidal functions that have been adequately stretched to the limit. The following calculations deal with the two dimensional case; the generalization to higher dimensions is only a matter of algebraic manipulations. Although the Lyapunov argument seems more awkward than the geometrical ones outlined above, it is quite inspiring in the case of hybrid and switched systems; we shall report some results on this topic in a future publication.

***Example** 1:* Consider the linear system $\dot{\boldsymbol{x}} = A\boldsymbol{x} = \begin{pmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{pmatrix} \boldsymbol{x}, \boldsymbol{x} \in \mathbb{R}^2$; the possible Lyapunov function $V(\boldsymbol{x}) = \boldsymbol{x}^T D \boldsymbol{x}$, where $D = \begin{pmatrix} 1/a^2 & 0 \\ 0 & 1/b^2 \end{pmatrix}$ describes a quadratic ellipsoidal expression (the ellipsis has radii (a, b)). The time derivative of the functional is

$$\begin{aligned} \dot{V}(\boldsymbol{x}) &= \frac{\partial V}{\partial \boldsymbol{x}} A\boldsymbol{x} = \boldsymbol{x}^T (DA + A^T D)\boldsymbol{x} \\ &= \boldsymbol{x}^T \begin{pmatrix} 2a_{11}/a^2 & a_{12}/a^2 + a_{21}/b^2 \\ a_{12}/a^2 + a_{21}/b^2 & 2a_{22}/b^2 \end{pmatrix} \boldsymbol{x}. \end{aligned}$$

The condition of negative definiteness can be stated with regards to the negativity of the eigenvalues of this last matrix; in order to define it on a box of positive vertex (a, b), let us consider the intersection of the two limit functions $V(\boldsymbol{x})|_{b\uparrow\infty}$ and $V(\boldsymbol{x})|_{a\uparrow\infty}$. Calculations yield the following condition on the coefficients: $(a_{11} < 0 \wedge |a_{12}| < a_{11}a_{22}) \wedge (a_{22} < 0 \wedge |a_{21}| < a_{11}a_{22})$; it is equivalent to the condition $(a_{11}, a_{22}) < 0 \wedge |a_{12}||a_{21}| < a_{11}a_{22}$ that comes from Theorem 4.

Throughout the manuscript we shall stick with the geometrical interpretation for box invariance, rather than the dynamical one which is based on Lyapunov arguments, since it is easier to handle and generalize.

E. *Affine Systems.*

Consider the 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 lies in the positive quadrant, $\boldsymbol{x}_0 > \mathbf{0}$. The idea is to exploit the corresponding Metzler matrix A^m to deduce possible box properties of the system around $\boldsymbol{x}_0$. The assumption of $\boldsymbol{x}_0$ being in the positive quadrant is justified both from a technical standpoint and from our applications.

***Theorem** 8:* If the affine system $\dot{\boldsymbol{x}} = A\boldsymbol{x} + \boldsymbol{b}$ has Metzler matrix and $\boldsymbol{b} > \mathbf{0}$, then its equilibrium point $\boldsymbol{x}_0 > \mathbf{0}$ iff the system is box invariant.

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

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

which, given the positivity of the known terms involved puts the following condition on the sign of τ: $\tau < 0$. But,

remembering the fact that the matrix is Metzler, we can resort to the sixth point of Theorem 2, which ensures that the conditions for box invariance are verified.
"$\Leftarrow$": The fact that the Metzler matrix A is box invariant enables us to use the last point of Proposition 2. The equilibrium $\boldsymbol{x}_0 : A\boldsymbol{x}_0 + \boldsymbol{b} = \boldsymbol{0}$ will be $\boldsymbol{x}_0 = -A^{-1}\boldsymbol{b} > \boldsymbol{0}$. ■

***Remark** 7:* The assumptions of the previous theorem can be relaxed to having a non-negative $\boldsymbol{b} \geq \boldsymbol{0}, \boldsymbol{b} \neq \boldsymbol{0}$.

***Theorem** 9:* If the affine system $\dot{\boldsymbol{x}} = A\boldsymbol{x} + \boldsymbol{b}$ has Metzler matrix and its equilibrium point $\boldsymbol{x}_0 > \boldsymbol{0}$, then the positivity of its drift term $\boldsymbol{b} > \boldsymbol{0}$ implies that the system is box invariant. The converse is not true.

Proof: The proof of the sufficiency comes from the previous Theorem. The converse does not hold, as the following counter-example shows:

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

■

The following result is an attempt to get condition for box invariance for an affine system looking at a properly modified correspondent, as we did in the linear case:

***Theorem** 10:* Assume $\boldsymbol{b} \neq 0$. Given an affine dynamical system $\dot{\boldsymbol{x}} = A\boldsymbol{x} + \boldsymbol{b}$, consider the correspondent modified system $\dot{\boldsymbol{x}} = A^m\boldsymbol{x} + \boldsymbol{b}^P$, where we substituted the Metzler correspondent of A and, additionally, we introduced $\boldsymbol{b}^P$, composed of the absolute values of the components of $\boldsymbol{b}$. The original system is Box-invariant iff the modified system has a positive equilibrium.

Proof: Naming $\boldsymbol{x}_0$ and $\boldsymbol{x}_0^m$ respectively the equilibria of the two systems, we shall perform two shifts according to the new variables $\boldsymbol{y} = \boldsymbol{x} - \boldsymbol{x}_0$ and $\boldsymbol{y} = \boldsymbol{x} - \boldsymbol{x}_0^m$ and infer the property for the first system through those of the second. The necessary and sufficient condition on the equilibrium of the modified system from Theorem 8 then ensure its Box-invariance and, by extension, that of the the system $\dot{\boldsymbol{x}} = A\boldsymbol{x} + \boldsymbol{b}$. ■

F. *Robust Properties of Box Invariance – Affine Systems*

The results on box invariance for affine systems, in particular Thm. 10, show that this property is again intrinsically dependent on the Metzler correspondent of the system matrix. If we consider a perturbed version of the dynamical system $\dot{\boldsymbol{x}} = A\boldsymbol{x} + \boldsymbol{b}$, say $\dot{\boldsymbol{x}} = A_\epsilon\boldsymbol{x} + \boldsymbol{b}_\epsilon$, its box invariance will be checked on the modified system $\dot{\boldsymbol{x}} = A_\epsilon^m\boldsymbol{x} + \boldsymbol{b}_\epsilon^P$. As long as A_ϵ^m will remain box invariant the perturbed system will be as well, regardless of the values assumed by vector $\boldsymbol{b}_\epsilon^P$.

G. *Box Invariance and Related Concepts in the Literature.*

It has already been stressed how the concept of Box Invariance ties itself with many results from special topics in Linear Algebra, such as that of Positive Matrices for instance. It is likewise important to highlight some connections with other notions from Systems Theory. The concept of *practical stability*, [9], is a Lyapunov-like concept introduced for controlled models; it is not defined on neighborhoods of an equilibrium point, but for specific sets in the state space. The notion of *ultimate boundedness*, [10], introduced for controlled dynamical systems, looks at conditions for ensuring that the trajectories enter a specified invariant set (usually, a polyhedron) in a finite time (stabilizability problem). It will be interesting in perspective to look at the application of such techniques, mostly based on computational methods to derive a polynomial Lyapunov function, and relate them to the Box Invariant set, especially in the nonlinear case. The strongly related notion of *Lagrange stability*, [9], looks at executions that stay bounded within a specific set; it is defined a-la-Lyapunov, without referring to neighborhoods of the equilibrium point but rather at specific sets. It is related to the concept of Box Invariance (usually, the set does not have a particular structure or shape). Conditions to obtain Lagrange stability are derived through the existence of Lyapunov or La Salle-like functionals, hence they may be computationally unattractive. *Positive systems* are (controlled) dynamical systems that, starting in the positive quadrant, evolve within its bounds. In the linear case and in the absence of control, they are described by Metzler matrices (in continuous time), and positive ones (in discrete time). Literature on this topic, [11], focuses on the controllability and stabilizability problems, and analyzes the dynamical properties of these systems, mostly via frequency arguments. From our perspective, we see possibilities, through the extension of the Box Invariance idea to non linear systems, to give some insight on the positivity notion for systems that are multi-affine (and which, as discussed, are important for biological models).

IV. Application Instances in Biology

***Example** 2:* **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 network of different parts, which model the concentration in other organs of the body, and which follow some conservation laws that account for the exchange of matter between different compartments. 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 for this system.

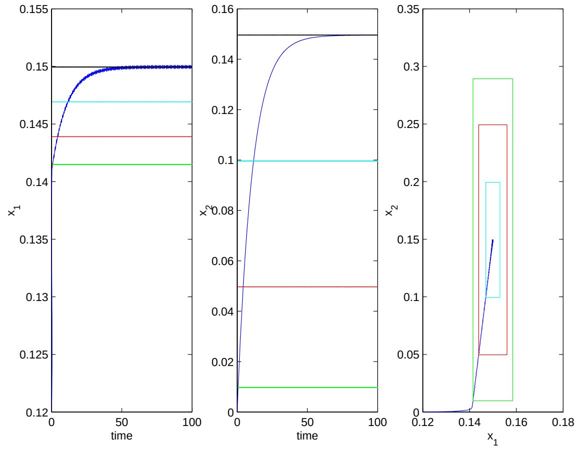

Fig. 2. Blood Glucose Concentration: simulation of a trajectory, and computation of some boxes.

***Example** 3:* **The global trafficking model for EGFR and HER2.** The following model is taken from [13]. It is affine in its variables, 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 assumes three possible values, thus we shall just consider its possible different realizations separately. In this particular study, we refer to the instance where the quantity of EGF is $L = 10^{-12}$ [ng/ml].

$$\frac{dR_s}{dt} = S_R - k_f L R_s + k_{er} C_s - k_{er} R_s + k_{xr} f_{xr} R_i$$
$$\frac{dC_s}{dt} = k_f L R_s - k_r C_s - k_{ec} C_s + k_{xc} f_{xc} C_i$$
$$\frac{dH_s}{dt} = S_H - k_{eh} H_s + k_{xh} f_{xh} H_i$$
$$\frac{dR_i}{dt} = k_{er} R_s - k_{xr} R_i$$
$$\frac{dC_i}{dt} = k_{ec} C_s - k_{xc} C_i$$
$$\frac{dH_i}{dt} = k_{eh} H_s - k_{xh} H_i$$

The system matrix verifies the structural conditions on the signs of its elements, as of Thm. 4; given their values, the application of the results above shows the existence of a box. Furthermore, noticing that the system matrix is explicitly Metzler and that the constant drift is positive, we may apply Thm. 8 and conclude that the system is box invariant. A calculation of its eigenvalues shows that they are, as expected, all negative (in particular, the Perron-Frobenius one). Nevertheless, the computation of the Perron-Frobenius eigenvector yields a non positive solution, thus going against the equivalent condition 4) in Prop. 2. Why does that happen? The reason is that the system matrix is not *irreducible*. In fact, the third and the sixth coordinates are decoupled from all the others; thus, the underlying graph associated with the matrix is not strongly connected. Fortunately, as discussed in Sec. III-A, we can carry on single studies of these two separate components of the system. Introducing $\boldsymbol{x}_1 = (R_s, C_s, R_i, C_i) \in \mathbb{R}^4$ and $\boldsymbol{x}_2 = (H_s, H_i) \in \mathbb{R}^2$, we can set up the following reduced models:

$$\dot{\boldsymbol{x}}_1 = \begin{pmatrix} -k_f L - k_{er} & k_r & k_{xr} f_{xr} & 0 \\ k_f L & -k_r & 0 & k_{xc} f_{xc} \\ k_{er} & 0 & -k_{xr} & 0 \\ 0 & k_{ec} & 0 & -k_{xc} \end{pmatrix} \boldsymbol{x}_1 + \begin{pmatrix} S_R \\ 0 \\ 0 \\ 0 \end{pmatrix};$$
$$\dot{\boldsymbol{x}}_2 = \begin{pmatrix} -k_{eh} & k_{xh} f_{xh} \\ k_{eh} & -k_{xh} \end{pmatrix} \boldsymbol{x}_2 + \begin{pmatrix} S_H \\ 0 \end{pmatrix}.$$

The two new reduced-size system matrices are irreducible, Metzler, and verify all the equivalent conditions for Box Invariance of Prop. 2. This example should advise the reader about the applicability of the conditions derived for Metzler matrices. The instances where they do not completely hold suggest ways to structurally simplify the analysis of the problem.

V. Conclusions and Future Work

This paper introduced the notion of Box Invariance for single-domain linear and affine systems. The notion of box invariance is rather intuitive, quite descriptive, and computationally attractive. We claim it is particularly distinguishing when applied on models derived from biology. Extension of the study to non linear vector fields (in particular multi-affine ones (see [1])) and to hybrid and switched models, has not been reported for space reasons, and will be discussed in future publications.

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