Interaction sign patterns in biological networks: from qualitative to quantitative criteria

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Abstract— **In stable biological and ecological networks, the steady-state influence matrix gathers the signs of steady-state responses to step-like perturbations affecting the variables. Such signs are difficult to predict a priori, because they result from a combination of direct effects (deducible from the Jacobian of the network dynamics) and indirect effects. For stable monotone or cooperative networks, the sign pattern of the influence matrix can be qualitatively determined based exclusively on the sign pattern of the system Jacobian. For other classes of networks, we propose criteria to assess whether the influence matrix is fully positive: we show that a semi-qualitative approach yields sufficient conditions for Jacobians with a given sign pattern to admit a fully positive influence matrix, and we also provide quantitative conditions for Jacobians that are translated eventually nonnegative matrices. We present a computational test to check whether the influence matrix has a constant sign pattern in spite of parameter variations, and we apply this algorithm to quasi-Metzler Jacobian matrices, to assess whether positivity of the influence matrix is preserved in spite of deviations from cooperativity. When the influence matrix is fully positive, we give a simple vertex algorithm to test robust stability. The devised criteria are applied to analyse the steady-state behaviour of ecological and biomolecular networks.**

I. Introduction

A vast class of biological and ecological systems can be modelled as networks, where the nodes correspond to species concentrations and the edges to their direct interactions (transcription factor and binding site interactions for gene networks, protein-protein bindings for protein networks, predator-prey, mutualistic or competitive interactions for ecological networks, etc.). Assuming that the network is at equilibrium, and the equilibrium is stable, a common way to gain insight into its steady-state behaviour is to perform perturbation experiments in which the concentration of a species is permanently altered (due to stability, perturbations that are only transient may leave the equilibrium point unchanged). In a gene regulatory network, this corresponds for instance to a knock-down or silencing experiment on a gene [30]. In the ecological network literature, these experiments are widely used in field studies and known under the name of press perturbations [3], [26], [32]. When the density of a species is permanently changed, the network settles to a new equilibrium, where some (or all) of the species concentrations are changed. Such changes in response to step-like perturbations are normally difficult to predict, even when the network topology is available. Indeed, even if the Jacobian of the network dynamics at the original equilibrium point (or the adjacency matrix of the network graph) is available, the effect on the state vector of a step perturbation at one of the nodes is due to the interplay of direct and indirect feedback interactions, where only the former can be deduced from the network "wiring". As these direct and indirect feedback effects are highly entangled, even assessing the sign of the steady-state change of the ith species induced by a step perturbation in the jth species is a challenging task and the outcome often changes with the numerical entries of the Jacobian. The problem is well-known in the context of ecological networks, where it has been formulated and investigated for more than 40 years [20], [21], [22].

The *steady-state influence matrix* (SSIM), i.e., the sensitivity matrix describing the changes in the equilibrium state vector induced by step-like perturbations of the state variables [16], is related to the inverse of the Jacobian matrix at the equilibrium [10], [11], [12], [19]. Since the dynamics of biological/ecological networks are poorly known, it is useful to approach the problem from a *qualitative* (parameter-free) perspective and determine the sign pattern of the SSIM, regardless of the numerical values of the Jacobian entries; early attempts to provide qualitative methods in the ecological networks literature rely on the so-called *loop analysis*, which expands the terms of the Jacobian determinant into products of disjoint *elementary circuits* [20], [21].

In this paper, we discuss novel criteria, ranging from qualitative to quantitative, to assess the sign of interactions in biological and ecological networks. Section III deals with criteria to determine when a given stable Jacobian J can admit a SSIM $M = \text{sgn}(-J^{-1})$ that is fully positive, or is the *gauge transformation* [13] of a positive matrix (i.e., is similar to a positive matrix through a diagonal signature matrix). As pointed out in Section III-A, the SSIM can be computed in a purely *qualitative* way when the Jacobian is a Metzler matrix, or a gauge transformation of a Metzler matrix (hence, when the system is either cooperative, or monotone); in particular, for cooperative systems, the SSIM is fully nonnegative. When the system is not monotone, we provide *semi-qualitative* conditions to identify sign patterns of the Jacobian that admit a fully positive SSIM for some numerical values (Section III-B). In Section III-C, we show that Jacobians that are translated *eventually nonnegative matrices* (matrices with some negative entries that however

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"disappear" when taking powers) admit a positive SSIM: we provide a *quantitative* condition, which requires the knowledge of the numerical values of the Jacobian entries.

For Jacobian matrices affected by parametric uncertainty, Section IV proposes an algorithm, which generalises that in [16] and relies on the so-called BDC-decomposition [6], [7], [16], to check whether the entire polytope of Jacobian matrices preserves the *nominal* sign pattern of the SSIM.

As shown in Section V, this algorithm can be applied to quasi-Metzler Jacobian matrices (Metzler matrices perturbed by a few negative off-diagonal entries) so as to assess whether the SSIM remains fully positive even when cooperativity is lost, provided that the deviation from cooperativity is bounded. Whenever the SSIM is fully positive, we propose a simple vertex algorithm (Section V-A) to robustly test the initial assumption of stability of the considered equilibrium, and guarantee stability of the whole polytope of matrices.

Section VI illustrates how the proposed criteria can be effectively employed to gain a deeper insight into the steady-state behaviour of ecological and biomolecular networks.

II. Background Concepts and Definitions

A. Linear algebraic notations

Given the real square matrix A, $\mathcal{G}(A)$ denotes the digraph with adjacency matrix A. The *qualitative class* $Q[A]$ of all matrices having the same sign pattern as A always contains a signature matrix $S = \text{sgn}(A)$, with entries in $\{0, -1, +1\}$. Clearly, $\mathcal{G}(A)$, $\mathcal{G}(S)$ and $\mathcal{G}(F)$ $\forall\, F \in Q[A]$ have the same topology, but possibly different numerical weights.

Matrix A is *irreducible* if there is no permutation matrix P such that $P^\top AP$ is block triangular; equivalently, $\mathcal{G}(A)$ is strongly connected. If A is irreducible, any matrix $F \in Q[A]$ is irreducible as well.

Given A, we denote A^+ the *nonnegative part* of A (such that $A^+_{ij} = A_{ij}$ if $A_{ij} \geq 0$, $A^+_{ij} = 0$ if $A_{ij} < 0$) and $\hat{A}$ the following "*lifting*" of A to $\mathbb{R}^{2n\times 2n}$ (see e.g. [8]):

$$\hat{A} = \begin{bmatrix} 0 & A \\ -A^\top & 0 \end{bmatrix}^+.$$

Matrix A is *fully indecomposable* if there are no permutation matrices P_1, P_2 such that P_1AP_2 is block triangular; equivalently, for some permutation matrix P, PA is irreducible and has nonzero diagonal entries [4, p. 56].

We denote by $\sigma(A)$ the *spectrum* of matrix A, by λ^* its *dominant eigenvalue* $\lambda^* = \arg\max_{\lambda\in\sigma(A)} \Re(\lambda)$, having the largest real part, and by $\text{index}_\lambda(A)$ the multiplicity of its eigenvalue λ as a root of the minimal polynomial (*i.e.*, the dimension of the largest Jordan block associated with λ).

Matrix A is *eventually nonnegative* (*eventually positive*) if $\exists\ p_0 \in \mathbb{N}$ such that, $\forall\ p \geq p_0$, $A^p \geq 0$ (resp. $A^p > 0$) elementwise; equivalently, its spectral radius $\rho(A) = \max_{\lambda_i\in\sigma(A)} |\lambda_i|$ is a real, positive eigenvalue of A, called Perron-Frobenius eigenvalue, and the associated left and right eigenvectors are elementwise nonnegative (resp. positive).

Matrix A is *eventually exponentially positive* if $\exists\ t_0 \in \mathbb{R}$ such that, $\forall\ t \geq t_0$, $e^{At} > 0$ elementwise; equivalently, its spectral abscissa $\eta(A) = \max_{\lambda_i\in\sigma(A)} \Re(\lambda_i)$ is a real eigenvalue of A and the corresponding left and right eigenvectors are elementwise positive.

B. Monotone and cooperative systems

Consider the nonlinear dynamical system

$$\dot{x}(t) = f(x(t)), \tag{1}$$

and denote by $x(t) \in \mathbb{R}^n$ its solution at time t with initial condition $x(0)$. Given a partial order for the axes of $\mathbb{R}^n$ represented by vector $\sigma = (\sigma_1, \dots, \sigma_n)$, with $\sigma_i \in \{\pm 1\}$, and the associated *gauge matrix* $\Sigma = \text{diag}(\sigma)$ (as defined in [13]), system (1) is *monotone* w. r. t. σ if, for all $x_1(0)$, $x_2(0)$ such that $\Sigma x_1(0) \leqslant \Sigma x_2(0)$, it is $\Sigma x_1(t) \leqslant \Sigma x_2(t)$ $\forall\, t \geqslant 0$ [27], [28], [29]. The ordering is strict if, in addition, strict inequality holds for at least one of the coordinates of x_1, x_2. System (1) is *strongly monotone* w. r. t. σ if, for all initial conditions $x_1(0)$, $x_2(0)$ such that $\Sigma x_1(0) \leq \Sigma x_2(0)$, $x_1(0) \neq x_2(0)$, it is $\Sigma x_1(t) < \Sigma x_2(t)$ $\forall\, t > 0$. When $\sigma_i = +1$ for all i, the system is *cooperative*: system (1) is cooperative if and only if its Jacobian $J(x) = \partial f(x)/\partial x$ is Metzler (i.e., it has nonnegative off-diagonal entries); in terms of $S = \text{sgn}[J(x)]$,

$$S_{ij} \geqslant 0 \qquad \forall\, i,j = 1,\dots,n \quad i \neq j. \tag{2}$$

In view of the Kamke condition [27, Lemma 2.1], system (1) is monotone w. r. t. σ if and only if $\Sigma J(x)\Sigma$ is Metzler $\forall\, x \in \mathbb{R}^n$. Equivalently, in terms of S,

$$\sigma_i\sigma_j S_{ij} \geqslant 0 \qquad \forall\, i,j = 1,\dots,n \quad i \neq j. \tag{3}$$

The conditions (2)-(3) admit a graph-theoretical reformulation: system (1) is *cooperative* iff all the edges of $\mathcal{G}(S)$ (excluding self-loops) are positive, and is *monotone* with respect to some order iff all directed cycles of length > 1 in $\mathcal{G}(S)$ are positive. Monotonicity, combined with irreducibility of $J(x)$ at all x, implies strong monotonicity of system (1).

C. Step perturbations and steady-state influence matrix

Let system (1) represent the evolution of a biochemical (or ecological) system with n-species, where the ith component of vector $x(t) = [x_1(t) \dots x_n(t)]^\top$ represents the concentration (resp. population density) of species i and the ith component of the continuously differentiable vector function $f(x(t)) = [f_1(x(t)) \dots f_n(x(t))]^\top$ is the corresponding overall reaction rate (resp. growth rate).

Assumption 1: System (1) admits an asymptotically stable equilibrium point $\bar{x}$: $f(\bar{x}) = 0$. $\diamond$

The entry $[J]_{ij}$ of the system Jacobian matrix

$$J = \left.\frac{\partial f(x)}{\partial x}\right|_{x=\bar{x}} \tag{4}$$

expresses the direct effect of species j on the growth rate of species i. Depending on the sign pattern $S = \text{sgn}(J)$, each species has a positive/negative direct influence, or no direct influence, on each of the other species. This is visually represented in the associated graph $\mathcal{G}(S)$ by a positive/negative edge, or no edge, between the two corresponding nodes.

Assumption 2: The diagonal entries of J are negative. $\diamond$ This is typically true in biological and ecological systems.

While J includes direct effects only, the net steady-state influence, combining all direct and indirect feedback effects, is given by the *steady-state influence matrix* (SSIM) M, whose entry M_{ij} predicts the signed steady-state response of species i to a positive step perturbation on species j: at the new equilibrium, $\bar{x}_i$ will be higher if $M_{ij} > 0$, lower if $M_{ij} < 0$ and unchanged if $M_{ij} = 0$. To compute M, following the approach in [16], we consider the system

$$\dot{x}(t) = f(x(t)) + E_j u(t), \tag{5}$$
$$y(t) = H_i x(t), \tag{6}$$

where u is a scalar persistent input, E_j is a column vector with a single non-zero entry, equal to 1, in the jth position and H_i is a row vector with a single non-zero entry, equal to 1, in the $i$the position (hence y is one of the state variables).

We assume that there exists an asymptotically stable equilibrium point $\bar{x}$, corresponding to $\bar{u}$, such that $f(\bar{x})+E\bar{u} = 0$, and that the perturbing input is small enough to ensure that the stability of $\bar{x}(u)$ is preserved. Then, based on the implicit function theorem and on the system linearisation in a neighbourhood of the equilibrium $\bar{x}$, as discussed in [16], the influence M_{ij} can be computed as the sign of

$$\frac{\partial \bar{y}}{\partial \bar{u}} = H_i(-J)^{-1}E_j = \frac{n_{ij}(0)}{d(0)}, \tag{7}$$

where $n_{ij}(0)$ and $d(0)$ are the numerator and the denominator of the *transfer function* $F_{ij}(s) = n_{ij}(s)/d(s) = H_i(sI-J)^{-1}E_j$ of the linearised system, computed at $s = 0$. Asymptotic stability guarantees that $d(0) = \det(-J) > 0$, hence the influence is determined by the sign of $n_{ij}(0)$:

$$M_{ij} = \text{sgn}[n_{ij}(0)] = \text{sgn}\left(\det \begin{bmatrix} -J & -E_j \\ H_i & 0 \end{bmatrix}\right). \tag{8}$$

Equivalently, as discussed in the ecological literature [10], [11], [12], [19], [20], [21], [22], the SSIM is

$$M = \text{sgn}[\text{adj}(-J)].$$

Since $\det(-J) > 0$, J is invertible and we can equivalently consider the sign pattern of $-J^{-1}$ [3], [26], [32]:

$$M = \text{sgn}[(-J)^{-1}\det(-J)] = \text{sgn}[(-J)^{-1}].$$

The steady-state influence M_{ij} is *qualitatively signed* if it always has the same sign (positive, negative, or zero), for any choice of parameter values in the system [16]; otherwise, it is indeterminate (it can have a different sign depending on the chosen parameter values).

D. *BDC-decomposition*

System (1) admits a *BDC-decomposition* [6], [7], [16] if, for any x in the domain, $J(x) = \partial f(x)/\partial x$ can be written as the positive linear combination of rank-one matrices:

$$J(x) = \sum_{h=1}^{q} R_h D_h(x) = \sum_{h=1}^{q} B_h D_h(x) C_h^\top = BD(x)C, \tag{9}$$

where B_h and $C_h^\top$ are column and row vectors, respectively, so that $R_h = [B_h C_h^\top]$ are constant rank-one matrices, while $D_h(x)$, $h = 1, \dots, q$, are positive scalar functions depending on x; $D(x)$ is a diagonal matrix with positive diagonal entries $D_h(x)$, B is the matrix formed by the columns B_h and C is the matrix formed by the rows $C_h^\top$.

The class of systems that admit a BDC-decomposition includes, as a particular case, systems with a sign-definite Jacobian. For all systems admitting a BDC-decomposition, M_{ij} can be evaluated based on a qualitative vertex algorithm [16] that yields "+1" if the influence is always positive *regardless of the parameters* (i.e., for any choice of $D_h > 0$), "-1" if it is always negative, "0" if its always zero, and "?" if the behaviour is *parameter-dependent*.

III. Positive Steady-State Influence Matrices

Can a system admit a SSIM that is positive, or is the gauge transformation of a positive matrix?

A. *Qualitative criteria*

The SSIM is elementwise nonnegative for all **cooperative systems**, whose Jacobian is Metzler, and is elementwise positive if, in addition, the Metzler Jacobian is irreducible.

The following theorems are suitable reformulations, in a novel context, of results already available in the literature.

Theorem 1: (See [14], [16]) If the Jacobian matrix (4) associated with system (1) is stable and Metzler, then $M_{ij} \in \{0, +1\}$ for all $i, j \in \{1, \dots, n\}$. If the Jacobian is also irreducible, then $M_{ij} = +1$ for all $i, j \in \{1, \dots, n\}$. $\square$

The result in Theorem 1 admits a graph-based reformulation.

Theorem 2: Given S Metzler with $S_{ii} < 0$ for all i, any stable $J \in Q[S]$ has SSIM M such that $M_{ij} \in \{0, +1\}$ for all $i, j \in \{1, \dots, n\}$. If $\mathcal{G}(S)$ is also strongly connected, then $M_{ij} = +1$ for all $i, j \in \{1, \dots, n\}$. $\square$

The converse is not true: as shown in [16], some systems can yield a fully positive SSIM, even though their Jacobian matrix is not Metzler. The results are qualitative: they do not require information about parameter values.

Since the Jacobian of any monotone system becomes Metzler after a gauge transformation, Theorems 1 and 2 can be generalised to **monotone systems** [27], [28], [29].

Theorem 3: If system (1) is monotone and, given a gauge transformation Σ, matrix $\Sigma J \Sigma$ is stable and Metzler, then $M = \Sigma \hat{M} \Sigma$, where $\hat{M}_{ij} \in \{0, +1\}$ for all $i, j \in \{1, \dots, n\}$. If the Jacobian is also irreducible (i.e., the system is strongly monotone), then $\hat{M}_{ij} = +1$ for all $i, j \in \{1, \dots, n\}$. $\square$

Theorem 4: Given S such that $\Sigma S \Sigma$ is Metzler for a gauge transformation Σ and $S_{ii} < 0$ for all i, any stable $J \in Q[S]$ has SSIM $M = \Sigma \hat{M} \Sigma$, where $\hat{M}_{ij} \in \{0, +1\}$ for all $i, j \in \{1, \dots, n\}$. If $\mathcal{G}(S)$ is also strongly connected (i.e., the system is strongly monotone), then $\hat{M}_{ij} = +1$ for all $i, j \in \{1, \dots, n\}$. $\square$

B. *Semi-qualitative criteria*

If the system is not monotone, purely qualitative conditions cannot be provided. To assess whether a Jacobian matrix $J \in Q[S]$ can yield a positive SSIM for some choice of the parameter values, we give *semi-qualitative* graph-based conditions that rely on the sign pattern of $\mathcal{G}(S)$ only. We build on the following result from [15].

Theorem 5: [15] Given a fully indecomposable signature matrix S, the following are equivalent:

1) there exists a matrix $F \in Q[S]$ such that $F^{-1} > 0$;
2) matrix $\hat{S} = \begin{bmatrix} 0 & S \\ -S^\top & 0 \end{bmatrix}^+$ is irreducible;
3) S cannot be expressed in the form $P_1 \begin{bmatrix} S_{11} & S_{12} \\ S_{21} & S_{22} \end{bmatrix} P_2$, where S_{11} need not be square, P_1 and P_2 are permutation matrices, $S_{12} \geqslant 0$ and $S_{21} \leqslant 0$, with at least one of these two blocks being nonvoid. □

Then, we can show that the qualitative class $Q[S]$ contains a Jacobian with a positive SSIM if the subgraph $\mathcal{G}(S^+)$, obtained by removing the negative edges from $\mathcal{G}(S)$, forms a network-wide strongly connected component, which can be seen as a **strongly connected cooperative backbone**.

Theorem 6: Given an irreducible matrix S, with $S_{ii} = -1$ $\forall\, i = 1, \ldots, n$, if matrix S^+ is irreducible, then there exists a matrix $J \in Q[S]$ such that $-J^{-1} > 0$. □

Proof: Matrix $-S$ is irreducible and $-S_{ii} > 0$ $\forall$ i, hence $-S$ is fully indecomposable. Consider then its lifting

$$\hat{S}_{neg} = \begin{bmatrix} 0 & -S \\ S^\top & 0 \end{bmatrix}^+.$$

Since by construction the upper right block of $\hat{S}_{neg}$ has all nonzero diagonal entries, in the bipartite graph $\mathcal{G}(\hat{S}_{neg})$ there exists a direct edge from each node $n+i$ to node i, with $i \in \{1, \ldots, n\}$. If S^+ is irreducible, then $(S^\top)^+$ is irreducible as well and there exists a path in $\mathcal{G}(\hat{S}_{neg})$ between each pair of nodes j and $n+i$, with $i, j \in \{1, \ldots, n\}$. Hence, for any pair $i, j \in \{1, \ldots, n\}$, there exists a path $n+j \to j \to n+i \to i$, which means that the graph $\mathcal{G}(\hat{S}_{neg})$ is strongly connected, thus $\hat{S}_{neg}$ is irreducible. Therefore, in view of Theorem 5, for some $F \in Q[-S]$ it must be $F^{-1} > 0$. If we choose $J = -F$, then $J \in Q[S]$ and $-J^{-1} = F^{-1} > 0$. ■

The converse is not true, as the following example shows.

Example 1: Consider the irreducible signature matrix

$$S = \begin{bmatrix} -1 & -1 & -1 & 1 \\ -1 & -1 & 1 & -1 \\ -1 & 1 & -1 & -1 \\ 1 & 0 & -1 & -1 \end{bmatrix}.$$

The corresponding S^+ is clearly reducible, but the corresponding matrix $\hat{S}$ is irreducible. Therefore, although Theorem 5 still holds, Theorem 6 cannot be applied. ⋄

Theorem 6 can be extended to systems that have a **strongly monotone backbone**, i.e., such that $\mathcal{G}\big((\Sigma S \Sigma)^+\big)$ is strongly connected, where Σ is a gauge transformation matrix.

Theorem 7: For any irreducible matrix S with $S_{ii} = -1$ $\forall\, i \in \{1, \ldots, n\}$, if a gauge transformation Σ exists such that matrix $(\Sigma S \Sigma)^+$ is irreducible, then a matrix $J \in Q[S]$ exists such that $-(\Sigma J \Sigma)^{-1} = \Sigma(-J^{-1})\Sigma > 0$. □

C. Quantitative criteria

Other matrices J that yield a positive SSIM M, but are not associated with cooperative systems, can be found based on a quantitative approach: this is the case of eventually nonnegative matrices [23], [24] with a proper diagonal shift.

Given an irreducible and **eventually nonnegative matrix** F, there exists an interval $(\rho(F), \beta)$ of the real line, where $\rho(F)$ is the spectral radius of F, such that for all $\alpha \in (\rho(F), \beta)$, matrix $J = F - \alpha I$ is stable and such that $(-J)^{-1} > 0$, implying that $M > 0$. In $J = F - \alpha I$, the diagonal term αI plays the same role as the diagonal of a Metzler matrix: it guarantees Hurwitz stability of J, which in turn ensures that $\det(-J) > 0$. Since $\alpha > \rho(F)$, stability holds regardless of the values on the diagonal of F.

The following result is adapted from [18, Theorem 4.2].

Theorem 8: Consider $J = F - \alpha I$, where $F \in \mathbb{R}^{n \times n}$ is irreducible and eventually nonnegative, with $\operatorname{index}_0(F) \leqslant 1$. Then, $\exists\, \beta > \rho(F)$ such that $\forall\, \alpha \in (\rho(F), \beta)$, $-J = \alpha I - F$ has a positive inverse. □

Then, if $\exists\, \alpha$ such that $J + \alpha I = F$ is eventually nonnegative and satisfies Theorem 8, we have $(-J)^{-1} > 0$, hence the SSIM M derived from J is elementwise positive. Note that the converse of Theorem 8 is not true.

Remark 1: The condition $\operatorname{index}_0(F) \leqslant 1$ is generically verified if F is irreducible: when the coefficients of F are drawn randomly, all eigenvalues (including 0) are simple. ⋄

Other, similar, cases are described in [25]. For instance, if we consider the closely related class of **eventually positive matrices**, then we can obtain qualitative conditions on the sign pattern that forbid a certain qualitative class of matrices to have a representative that is eventually positive. A first necessary condition for a qualitative class $Q[S]$ to contain an eventually positive matrix is that S is irreducible [5]; another is given by the following theorem.

Theorem 9: ([5], Thm. 5.2) Consider an irreducible signature matrix S. If S has the block sign pattern

$$\begin{bmatrix} S_{11} & S_{12} \\ S_{21} & S_{22} \end{bmatrix}$$

with S_{11} and S_{22} square matrices and $S_{12} = S_{12}^+$, $-S_{21} = (-S_{21})^+$, then no $F \in Q[S]$ can be eventually positive. □

The following result, adapted from [23, Theorem 2.2], [1, Lemma 2], links eventual positivity with **eventual exponential positivity** and clarifies the role of α in $J = F - \alpha I$.

Theorem 10: A matrix $A \in \mathbb{R}^{n \times n}$ is eventually exponentially positive if and only if $A + \alpha I$ is eventually positive for some $\alpha \geq 0$. □

Remark 2: (A **graph-theoretical interpretation** of Theorem 8.) If F is the adjacency matrix of a (weighted) directed graph ($F_{ij} \neq 0$ if an edge connects nodes i and j, $F_{ij} = 0$ otherwise), then F^k_{ij} is equal to the (weighted) number of paths of length k that connect nodes i and j. Let F be eventually positive and $F_{ii} = 0$ (self-loops are not relevant). Then

$$F^k_{ij} = \sum_{h_1, h_2, \ldots, h_{k-1}} F_{i,h_1} F_{h_1,h_2} \ldots F_{h_{k-1},j}$$

is the sum of all possible (weighted) edge products that correspond to paths of length k in the graph. Hence, *when F is eventually positive, the sum of all possible paths of length k becomes positive for large k*. In the expression of the exponential matrix of $J = F - \alpha I$, therefore,

$$e^{(F-\alpha I)t} = e^{Ft} e^{-\alpha I t} = \sum_{k=0}^{\infty} \frac{F^k t^k}{k!} e^{-\alpha I t},$$

where $e^{-\alpha I t}$ is a diagonal matrix with positive diagonal entries; in the infinite sum, the terms with powers F^k give a positive contribution for $k > k_o$, since the sum of all possible paths of length $k > k_o$ is positive in the graph. $\diamond$

IV. Robust Influence Matrix Computation

Following the approach in [16], we consider system

$$\dot{x}(t) = f(x(t)) + Eu(t), \quad y(t) = Hx(t), \qquad (10)$$

where $x \in \mathbb{R}^n$, $f(\cdot)$ is continuously differentiable, $u \in \mathbb{R}$ is an input, $y \in \mathbb{R}$ is an output, and we assume that there exists an asymptotically stable equilibrium point $\bar{x}$. Then, both the state asymptotic value $\bar{x}(u)$ and the output asymptotic value $\bar{y}(u) = H\bar{x}$ are functions of u. The *steady-state input-output influence* [16] is the ensuing variation of the steady state of the system output y, upon a variation in the input u (a relevant variable or parameter). We assume that the considered input perturbation is small enough to ensure that the stability of $\bar{x}(u)$ is preserved. Different variables of interest for the system may respond with a steady-state variation that has the same sign as the input variation, the opposite sign, or is zero. The steady-state input-output influence is *qualitatively signed* if it always has the same sign (positive, negative, or zero), regardless of the choice of parameter values. As shown in [16], denoting by J the Jacobian matrix, the steady-state input-output influence can be expressed based on the implicit function theorem as

$$\frac{\partial \bar{y}}{\partial \bar{u}} = H(-J)^{-1}E = \frac{\det \begin{bmatrix} -J & -E \\ H & 0 \end{bmatrix}}{\det(-J)} \doteq \frac{n(J,E,H)}{\det(-J)}, \quad (11)$$

where $\det(-J) > 0$, in view of stability. Entry M_{ij} of the SSIM can be computed by evaluating the sign of $n(J,E,H)$ in (11) when $E = E_j$ and $H = H_i$ have a single non-zero entry (the $j$the and the ith, respectively) equal to 1.

To evaluate the *qualitative* input-output influence, [16] proposes a vertex algorithm, applicable to any system that admits a BDC-decomposition, to assess if increasing the input always results in an *increase* in the output steady-state value, if it always results in a *decrease*, if the steady-state output is *unchanged*, *regardless of the choice of parameter values*, or if the behaviour is *parameter-dependent*. Along the same lines, we can apply a vertex algorithm to **uncertain Jacobian matrices admitting a BDC-decomposition** $J = BDC$, where $D \succ 0$ is a diagonal matrix whose diagonal entries lie within known intervals, $D_{ii} \in [D_{ii}^-, D_{ii}^+]$. This more general setup includes, as a particular case, uncertain Jacobians where each entry **belongs to a known (possibly bounded) interval**, $J_{ij} \in [J_{ij}^-, J_{ij}^+]$: for instance, if the nominal value J_{ij}^* of the (i,j) entry is affected by an uncertainty of amplitude δ_{ij}, $J_{ij} \in [J_{ij}^* - \delta_{ij}, J_{ij}^* + \delta_{ij}]$.

Given $J = BDC$, with $D \succ 0$ diagonal, the vertex algorithm relies on multiaffinity of $n(J,E,H)$ with respect to the diagonal entries of D, as per the following result.

Theorem 11: Denote by $J^{(v)} = BD^{(v)}C$, $v = 1, \ldots, 2^{n^2}$, the matrices corresponding to all possible choices of the diagonal matrix D with $D_{ii} \in \{D_{ii}^-, D_{ii}^+\}$. Then, for all matrices $J = BDC$ with $D \succ 0$ and $D_{ii} \in (D_{ii}^-, D_{ii}^+)$,

(i) $n(J,E,H) = 0$ iff $n(J^{(v)},E,H) = 0$ for all v;
(ii) $n(J,E,H) > 0$ iff $n(J^{(v)},E,H) \geq 0$ for all v and $n(J^{(v)},E,H) > 0$ for some v;
(iii) $n(J,E,H) < 0$ iff $n(J^{(v)},E,H) \leq 0$ for all v and $n(J^{(v)},E,H) < 0$ for some v. $\square$

Proof: Necessity is immediate in view of continuity. Sufficiency relies on the multiaffinity of $n(J,E,H)$ with respect to the entries of J. A multiaffine function defined on a hypercube reaches its minimum and maximum on a vertex of the hypercube [2, Lemma 14.5.5]. We provide a sufficiency proof for claim (ii) (the other cases are similar). Being the function multiaffine, it must be $n(BDC,E,H) \geq 0$ in the whole hypercube. Assume by contradiction that there is an internal point of the hypercube with $n(BDC,E,H) = 0$. Then, for variations along the direction $D_{11}^- \leq D_{11} \leq D_{11}^+$, the restricted function is linear and nonnegative: if it is zero at one point, it must be zero at both the extrema, $n(BD_{(1)}^-C,E,H) = n(BD_{(1)}^+C,E,H) = 0$. If we fix $D_{11} = D_{11}^+$ ($D = D_{(1)}^+$) and $D_{11} = D_{11}^-$ ($D = D_{(1)}^-$), in both cases we can repeat the same argument along the direction of all the other diagonal entries of D, to conclude that it must be $n(BDC,E,H) = 0$ for all the vertices. However, this contradicts the assumption that $n(BD^{(v)}C,E,H) > 0$ for some v. Hence, it must be $n(BDC,E,H) > 0$ for all internal points of the hypercube. $\blacksquare$

Theorem 11 of course particularises to the case of interval Jacobian matrices, whose entries are bounded within given intervals $J_{ij} \in [J_{ij}^-, J_{ij}^+]$.

In the worst case, when all the entries are uncertain, the number of Jacobian matrices to be tested is 2^{n^2}, but it reduces to 2^q if just q of the entries are uncertain. The computational effort is paid back by a very strong knowledge: if the test provides a qualitative answer for an entry of M, then the steady-state response has the same sign **for all possible Jacobians J in the uncertainty polytope**.

V. Influence Matrix of Quasi-Metzler Jacobians and Robust Stability Results

As previously highlighted, there can be non-Metzler Jacobians that yield a fully positive SSIM. We consider **quasi-Metzler Jacobian matrices**, namely, Metzler matrices perturbed by few negative off-diagonal entries. For the sake of generality, we describe a quasi-Metzler matrix using the BDC-decomposition as

$$J = J_0 + BDC \in \mathbb{R}^{n \times n}, \qquad (12)$$

where J_0 is Metzler and BDC accounts for q possibly negative off-diagonal entries of J (identified by the corresponding column of $B \in \mathbb{R}^{n\times q}$ and row of $C \in \mathbb{R}^{q\times n}$), bounded in magnitude because the diagonal entries of $D \in \mathbb{R}^{q\times q}$ lie within given intervals. Denote by $\tilde{J}_{ij}$ the entries of J that can be negative for some choice of D and assume $|\tilde{J}_{ij}| \leq \varepsilon$.

Example 2: Matrix $J = J_0 + BDC$, with

$$J_0 = \begin{bmatrix} -1 & 0 & 1 \\ 0 & -2 & 3 \\ 4 & 1 & -6 \end{bmatrix}, B = \begin{bmatrix} -1 & 0 \\ 0 & -1 \\ 0 & 0 \end{bmatrix}, C = \begin{bmatrix} 0 & 1 & 0 \\ 1 & 0 & 0 \end{bmatrix}$$

and $D = \text{diag}[\varepsilon_1, \varepsilon_2]$, is a quasi-Metzler matrix, with $|\tilde{J}_{12}| \leq \varepsilon$ and $|\tilde{J}_{21}| \leq \varepsilon$ for $\varepsilon = \max\{\varepsilon_1, \varepsilon_2\}$. ◇

The parameter ε quantifies the maximum deviation from cooperativity: if $\varepsilon = 0$, the Jacobian J yields a SSIM that is fully nonnegative (positive if J is irreducible). How much shall we perturb J_0 in order to alter the sign of its SSIM?

We can look for the maximum value ε^* of ε such that, when $\varepsilon \leq \varepsilon^*$, all entries of $(-J)^{-1}$ are positive for any choice of the entries $|\tilde{J}_{ij}| \leq \varepsilon$, and observe which entries of $(-J)^{-1}$ are the first to become negative when $\varepsilon > \varepsilon^*$.

To this aim, we can apply the algorithm for the robust computation of the SSIM presented in Section IV, and check if the sign pattern of the SSIM obtained for the Metzler Jacobian J_0 is preserved for all perturbed quasi-Metzler Jacobians $J = J_0 + BDC$ with $\tilde{J}_{ij} \in [-\varepsilon, \varepsilon]$.

A. A vertex algorithm for checking robust stability

Throughout the paper, we have assumed stability of the equilibrium, to assess the system steady-state behaviour. For any polytope $\mathcal{P}$ of Jacobians such that all $J \in \mathcal{P}$ yield a fully positive SSIM $M = \text{adj}(-J)$, we can provide a simple vertex algorithm that actually checks if the stability assumption is robustly verified for all the Jacobians in $\mathcal{P}$.

First, we give the following preliminary results.

Proposition 1: Given the Hurwitz matrix J, assume $M = (-J)^{-1} > 0$. Then, J has a real dominant eigenvalue. □

Proof: Since M is a positive matrix, it has a positive real dominant eigenvalue λ^*. If $\lambda \in \sigma(M)$, then $-\lambda^{-1} \in \sigma(J)$. In view of Hurwitz stability, J has just eigenvalues with negative real part. Therefore, the dominant eigenvalue of J is $(-\lambda^*)^{-1}$, hence it is real (and negative). ■

Remark 3: In general, requiring Hurwitz stability of J limits the spectrum of its SSIM $M = (-J)^{-1}$, which must have positive-real-part eigenvalues only. Indeed, if λ_i were an eigenvalue of M with nonpositive real part, then $-\lambda_i^{-1}$ would be an eigenvalue of J with nonnegative real part, and this would contradict the Hurwitz stability assumption.

Proposition 2: Given the matrix polytope

$$\mathcal{P} = \{J = BDC \in \mathbb{R}^n : D = \text{diag}[D_{11} \dots D_{qq}] \succ 0 \text{ with } D_{ii} \in [D_{ii}^-, D_{ii}^+]\}, \quad (13)$$

assume that matrix $J_0 = BD_0C \in \mathcal{P}$ is Hurwitz stable and that all the matrices in $\mathcal{P}$ have a real dominant eigenvalue. Then, robust Hurwitz stability of $\mathcal{P}$ (namely, stability of all $J \in \mathcal{P}$) is equivalent to robust non-singularity of $\mathcal{P}$ (namely, nonsingularity of all $J \in \mathcal{P}$). □

Proof: If some $J \in \mathcal{P}$ is singular, then $\mathcal{P}$ is not robustly Hurwitz stable. Since the eigenvalues of a matrix are continuous functions of the matrix entries, if we continuously alter the entries of the stable matrix J_0 in order to obtain any other matrix $J \in \mathcal{P}$, the only possible transition to instability is due to the real dominant eigenvalue of J_0 crossing the imaginary axis and changing sign from negative to positive. Hence, if J_0 is Hurwitz stable and all matrices $J \in \mathcal{P}$ are nonsingular, any $J \in \mathcal{P}$ is Hurwitz stable as well. ■

In view of Propositions 1 and 2, and of continuity arguments analogous to those adopted in the proof of Proposition 2, we can state the following robust stability result.

Theorem 12: Given the matrix polytope $\mathcal{P}$ as in (13), assume that $\text{adj}(-J) > 0$ for all $J = BDC \in \mathcal{P}$ and that $J_0 = BD_0C \in \mathcal{P}$ is Hurwitz stable. Then, robust Hurwitz stability of $\mathcal{P}$ is equivalent to robust non-singularity of $\mathcal{P}$. □

Remark 4: For a polytope of matrices admitting a BDC-decomposition $J = BDC$, where $D \succ 0$ is a diagonal matrix and $D_{ii}^- \leq D_{ii} \leq D_{ii}^+$, robust non-singularity is equivalent to robust non-singularity of all the vertices obtained by picking $D_{ii} \in \{D_{ii}^-, D_{ii}^+\}$, hence it can be checked by means of a simple vertex algorithm. ◇

The above results hold for any Jacobian matrix that admits a BDC-decomposition, hence in particular for signed Jacobians whose entries are bounded within given intervals, $J_{ij} \in [J_{ij}^-, J_{ij}^+]$. Again, for a polytope of interval matrices J, with entries $J_{ij}^- \leq J_{ij} \leq J_{ij}^+$, robust non-singularity is equivalent to robust non-singularity of all the vertices, and can be simply checked by means of a vertex algorithm.

We have therefore shown that, for all matrices that admit a BDC-decomposition and yield a positive influence matrix, a simple **vertex algorithm** can be employed to **robustly check the stability assumption** in the presence of uncertainties.

VI. Examples

We demonstrate in this section how the proposed results can give more insight into real models of ecological and biomolecular networks.

Example 3: The ecological network describing a **plankton-bacteria-protozoa community** that is presented in [31], [10] has a Jacobian matrix with nominal value [31]

$$\bar{J} = \begin{bmatrix} -1 & 0.6 & 0 & 0 & 0 \\ -0.6 & -1 & 0.6 & 0.1 & 0 \\ 0.6 & -0.6 & -1 & -0.5 & 0.2 \\ 0 & 0 & 0.5 & -1 & -0.2 \\ 0 & 0 & 0 & 0.2 & -1 \end{bmatrix}, \quad (14)$$

associated with the interaction graph $\mathcal{G}(J)$ shown in Fig. 1(a). The corresponding SSIM is

$$M = \begin{bmatrix} 1 & 1 & 1 & -1 & 1 \\ -1 & 1 & 1 & -1 & 1 \\ 1 & -1 & 1 & -1 & 1 \\ 1 & -1 & 1 & 1 & -1 \\ 1 & -1 & 1 & 1 & 1 \end{bmatrix}. \quad (15)$$

If matrix (14) is uncertain, the vertex algorithm described in the previous section (see Theorem 11) allows us to certify that the sign pattern in (15) is preserved, *no matter how the Jacobian entries vary within bounded intervals* $J_{ij} \in [\bar{J}_{ij} - \delta_{ij}, \bar{J}_{ij} + \delta_{ij}]$, with $\delta_{11} = \delta_{22} = 0.15$, $\delta_{12} = \delta_{21} =$

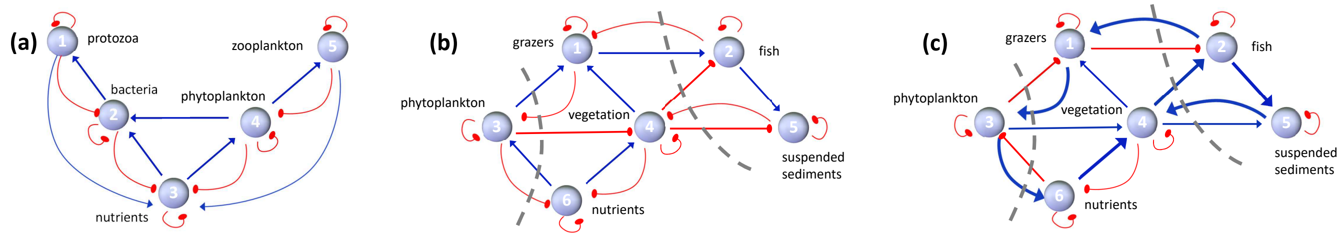

Fig. 1. Interaction graphs associated with ecological networks in the literature: (a) the plankton-bacteria-protozoa community [31], [10]; (b) the shallow lake community in [17]; (c) graph of the same shallow lake community after a gauge transformation.

$\delta_{23} = \delta_{24} = \delta_{31} = \delta_{35} = \delta_{43} = \delta_{44} = \delta_{55} = 0.1$, $\delta_{32} = \delta_{33} = \delta_{34} = \delta_{45} = \delta_{54} = 0.01$.

The SSIM (15) is not fully positive. However, if we consider the sign pattern $S = \text{sgn}(J)$, the graph $\mathcal{G}(S^+)$ is strongly connected, as can be seen from Fig. 1(a). Hence, in view of Theorem 6, some other choice of the parameters (with the same sign pattern) must yield a fully positive SSIM. For instance, we can choose

$$J_{pos} = \begin{bmatrix} -0.6 & 0.6 & 0 & 0 & 0 \\ -0.6 & -0.6 & 0.6 & 1 & 0 \\ 1 & -0.8 & -0.6 & -0.6 & 1 \\ 0 & 0 & 0.6 & -0.6 & -1 \\ 0 & 0 & 0 & 0.6 & -0.6 \end{bmatrix}, \qquad (16)$$

for which $-J_{pos}^{-1} > 0$ elementwise. To show robustness of this parameter choice, the vertex algorithm certifies that the SSIM remains fully positive, *no matter how the entries d_i vary within the intervals* with $\delta_{34} = \delta_{44} = \delta_{54} = \delta_{55} = 0.05$, $\delta_{21} = \delta_{22} = \delta_{23} = \delta_{24} = 0.04$, $\delta_{11} = 0.03$, $\delta_{12} = \delta_{31} = \delta_{35} = 0.02$, $\delta_{32} = \delta_{33} = \delta_{43} = \delta_{45} = 0.01$. These intervals are fairly small because we want to guarantee positivity *simultaneously* for all variations; typically, just some of the parameters are uncertain.

Interestingly, matrix J_{pos} in (16) is eventually exponentially positive. Hence, in view of Theorem 10, there exists $\alpha \geq 0$ such that $J_{pos} = F - \alpha I$, with F eventually positive. Indeed, for $\alpha = 2$, $F = J_{pos} + \alpha I$ is eventually positive, irreducible and $\text{index}_0(F) \leqslant 1$, with $\rho(F) \approx 1.91$. Theorem 8 guarantees the existence of $\beta > \rho(F)$ such that $\forall\, \alpha \in (\rho(F), \beta)$, $\alpha I - F$ has a positive inverse: in this case, $\beta \approx 2.05$. Clearly, $\alpha = 2 \in (1.91, 2.05) = (\rho(F), \beta)$. $\diamond$

Example 4: The ecological network describing the **shallow lake community** in [17] has a Jacobian with sign pattern

$$S = \begin{bmatrix} -1 & -1 & 1 & 1 & 0 & 0 \\ 1 & -1 & 0 & -1 & 0 & 0 \\ -1 & 0 & -1 & 0 & 0 & 1 \\ 0 & 0 & -1 & -1 & -1 & 1 \\ 0 & -1 & 0 & -1 & -1 & 0 \\ 0 & 0 & -1 & -1 & 0 & -1 \end{bmatrix}, \qquad (17)$$

corresponding to the interaction graph $\mathcal{G}(S)$ shown in Fig. 1(b). The gauge transformation $\Sigma = \text{diag}\begin{bmatrix} -1 & 1 & 1 & -1 & 1 & -1 \end{bmatrix}$ leads to the new sign pattern $S' = \Sigma S \Sigma$, which satisfies the assumptions of Theorem 6: if we consider only the positive edges of the associated graph $\mathcal{G}(S')$, shown in Fig. 1(c), the resulting graph $\mathcal{G}(S'^+)$ is strongly connected. Hence, there must be a fully positive SSIM corresponding to some choice of the parameters having the sign pattern S'. Indeed, the choice

$$J'_{pos} = \begin{bmatrix} -0.6 & 0.6 & -0.6 & 0.6 & 0 & 0 \\ -0.6 & -0.6 & 0 & 0.6 & 0 & 0 \\ 0.6 & 0 & -0.6 & 0 & 0 & -0.6 \\ 0 & 0 & 0.6 & -1 & 0.6 & 1 \\ 0 & 0.7 & 0 & 0.6 & -1 & 0 \\ 0 & 0 & 1 & -0.6 & 0 & -0.8 \end{bmatrix} \qquad (18)$$

yields $-(J'_{pos})^{-1} > 0$ elementwise.

The sign pattern of the SSIM for the original graph can be achieved from the all-ones matrix O by applying the same gauge transformation Σ: $M = \Sigma O \Sigma$.

Note that J'_{pos} in (18) is eventually exponentially positive. Therefore, in view of Theorem 10, there exists $\alpha \geq 0$ such that $J'_{pos} = F - \alpha I$, with F eventually positive. Indeed, for $\alpha = 1.5$, $F = J'_{pos} + \alpha I$ is eventually positive, irreducible and $\text{index}_0(F) \leqslant 1$, with $\rho(F) \approx 1.47$. Theorem 8 thus ensures that there exists $\beta > \rho(F)$ such that $\forall\, \alpha \in (\rho(F), \beta)$, $\alpha I - F$ has a positive inverse: in this case, $\beta \approx 1.52$. Clearly $\alpha = 1.5$ belongs to the interval $(\rho(F), \beta)$. $\diamond$

Example 5: (**The presence of titration confers robustness to the steady-state response.**) An inhibited module and an activated module are suitably interconnected in the synthetic biomolecular circuits proposed in [9], so as to induce by design oscillatory and bistable behaviours in minimal network models with monomeric regulators.

After a sign change to the third variable, the Jacobian $J^{(I)}$ of the system describing the **inhibited module** has the form

$$\begin{bmatrix} -(a+b) & d & e \\ a-c & -(c+d+h) & k \\ b & h & -(e+f+k) \end{bmatrix}, \qquad (19)$$

where (consistently with the reasonable parameter values for the system that are given in [9]) we can choose as nominal values $\bar{a} = 4 \cdot 10^{-3}$, $\bar{b} = 3 \cdot 10^{-3}$, $\bar{c} = 2 \cdot 10^{-3}$, $\bar{d} = 3 \cdot 10^{-2}$, $\bar{e} = 6 \cdot 10^{-3}$, $\bar{f} = 1 \cdot 10^{-3}$, $\bar{k} = 4 \cdot 10^{-3}$ and $\bar{h} = 3 \cdot 10^{-3}$. Parameters h and k represent the effect of titration reactions.

Matrix $J^{(I)}$ is quasi-Metzler, since $J^{(I)}(2,1)$ can be negative if $a < c$. Whenever $a \geq c$, the SSIM $(-J^{(I)})^{-1}$ is fully positive. The Jacobian is not a signed matrix, but it admits a BDC-decomposition. Hence, based on the results in Section V, we can apply the vertex algorithm described in Section IV and discover that positivity of the SSIM is preserved no matter how all the parameter values vary within the intervals $p \in [\bar{p} \pm 1.2 \cdot 10^{-3}]$, where p stands for any of the parameters and $\bar{p}$ for the corresponding nominal value.

Our analysis highlights the robustness effect (in terms of preserving the steady-state behaviour after step-like perturbations) conferred by the presence of titration. Indeed, if $k = h = 0$ (no titration), tightest intervals $[\bar{p} \pm 1 \cdot 10^{-3}]$ (for which the Jacobian is actually Metzler) are necessary to make sure that the SSIM is positive within the whole matrix polytope. Conversely, the presence of titration allows the SSIM to remain positive even when $J^{(I)}$ is not Metzler.

The system describing the **activated module**, after a sign change in the second variable, has a Jacobian $J^{(A)}$ of the same form (19), where now reasonable nominal values [9] are $\bar{a} = 3 \cdot 10^{-3}$, $\bar{b} = 80 \cdot 10^{-3}$, $\bar{c} = 2 \cdot 10^{-3}$, $\bar{d} = 3 \cdot 10^{-2}$, $\bar{e} = 6 \cdot 10^{-3}$, $\bar{f} = 1 \cdot 10^{-3}$, $\bar{k} = 4 \cdot 10^{-3}$ and $\bar{h} = 3 \cdot 10^{-3}$. Also in this case, h and k represent the effect of titration.

For the quasi-Metzler matrix $J^{(A)}$, the SSIM $(-J^{(A)})^{-1}$ is fully positive when $a \geq c$. If, in view of the results in Section V, we apply the vertex algorithm described in Section IV, we discover that positivity of the SSIM is preserved no matter how all the parameter values vary within the intervals $[\bar{p} \pm 2 \cdot 10^{-3}]$.

The robustness effect due to the presence of titration is even more evident for the activated module. Indeed, if $k = h = 0$ (no titration), a very tight interval $[\bar{p} \pm 0.5 \cdot 10^{-3}]$ (tight enough to guarantee that any Jacobian in the polytope is Metzler) is necessary to make sure that the SSIM is positive within the whole matrix polytope. The presence of titration reactions, instead, allows the SSIM to remain positive even when $J^{(A)}$ is not Metzler. $\diamond$

VII. Conclusions

We have proposed criteria to evaluate the sign pattern of the steady-state influence matrix SSIM, which gathers the steady-state responses to step-like perturbations affecting the variables, in stable biological and ecological systems. We have provided criteria to assess when the SSIM is fully positive, and vertex algorithms that allow to robustly compute the SSIM in the presence of parametric uncertainties. For systems whose SSIM is fully positive, we have also given a vertex algorithm to robustly test the stability assumption.

References

[1] C. Altafini and G. Lini, "Predictable dynamics of opinion forming for networks with antagonistic interactions," *IEEE Transactions on Automatic Control*, vol. 60, no. 2, pp. 342–357, 2015.

[2] B. R. Barmish. *New tools for robustness of linear systems*. McMillan, 1994.

[3] E. A. Bender, T. J. Case, and M. E. Gilpin, "Perturbation experiments in community ecology: Theory and practice," *Ecology*, vol. 65, no. 1, pp. 1–13, 1984.

[4] A. Berman and R. Plemmons, *Nonnegative Matrices in the Mathematical Sciences*, ser. Classics in Applied Mathematics. Society for Industrial and Applied Mathematics, 1994.

[5] A. Berman, M. Catral, L. M. Dealba, A. Elhashash, F. J. Hall, L. Hogben, I.-J. Kim, D. D. Olesky, P. Tarazaga, M. J. Tsatsomeros, and P. van den Driessche, "Sign patterns that allow eventual positivity." *El. Journal of Linear Algebra*, vol. 19, pp. 108–120, 2009.

[6] F. Blanchini, E. Franco, and G. Giordano, "Determining the structural properties of a class of biological models," in *Proc. IEEE Conference on Decision and Control*, Maui (HI), USA, 2012, pp. 5505–5510.

[7] F. Blanchini and G. Giordano, "Piecewise-linear Lyapunov functions for structural stability of biochemical networks," *Automatica*, vol. 50, no. 10, pp. 2482–2493, 2014.

[8] R. Brualdi and B. Shader, *Matrices of Sign-Solvable Linear Systems*. Cambridge Univ. Press, 1995.

[9] C. Cuba Samaniego, G. Giordano, J. Kim, F. Blanchini, and E. Franco, "Molecular titration promotes oscillations and bistability in minimal network models with monomeric regulators," *ACS Synthetic Biology*, vol. 5, no. 4, pp. 321–333, 2016.

[10] J. Dambacher, H. Li, and P. Rossignol, "Relevance of community structure in assessing indeterminacy of ecological predictions," *Ecology*, vol. 83, no. 5, pp. 1372–1385, 2002.

[11] J. Dambacher, H. Li, and P. Rossignol, "Qualitative predictions in model ecosystems," *Ecological Modelling*, vol. 161, no. 1-2, pp. 79–93, 2003.

[12] J. M. Dambacher and R. Ramos Jiliberto, "Understanding and predicting effects of modified interactions through a qualitative analysis of community structure," *The Quarterly Review of Biology*, vol. 82, no. 3, pp. 227–250, 2007.

[13] G. Facchetti, G. Iacono, and C. Altafini, "Computing global structural balance in large-scale signed social networks," *PNAS*, vol. 108, no. 52, pp. 20 953–20 958, 2011.

[14] L. Farina and S. Rinaldi, *Positive Linear Systems: Theory and Applications*. Wiley, New York, 2000.

[15] M. Fiedler and R. Grone, "Characterizations of sign patterns of inverse-positive matrices," *Linear Algebra and its Applications*, vol. 40, pp. 237 – 245, 1981.

[16] G. Giordano, C. Cuba Samaniego, E. Franco, and F. Blanchini, "Computing the structural influence matrix for biological systems," *Journal of Mathematical Biology*, vol. 72, no. 7, pp. 1927–1958, 2016.

[17] G. R. Hosack, H. W. Li, and P. A. Rossignol, "Sensitivity of system stability to model structure," *Ecological Modelling*, vol. 220, no. 8, pp. 1054 – 1062, 2009.

[18] H. T. Le and J. J. McDonald, "Inverses of M-type matrices created with irreducible eventually nonnegative matrices," *Linear Algebra and its Applications*, vol. 419, pp. 668 – 674, 2006.

[19] R. Levins, *Evolution in changing environments: some theoretical explorations*. Princeton University Press, 1968.

[20] R. Levins, "The qualitative analysis of partially specified systems," *Annals New York Academy of Science*, vol. 231, pp. 123–138, 1974.

[21] R. Levins, "Evolution in communities near equilibrium," in *Ecology and evolution of communities*, M. Cody and J. M. Diamond, Eds. Harvard University Press, 1975, pp. 16–50.

[22] R. M. May, *Stability and Complexity in Model Ecosystems, 2nd ed.* Princeton University Press, 1974.

[23] D. Noutsos, "On Perron-Frobenius property of matrices having some negative entries," *Linear Algebra and its Applications*, vol. 412, pp. 132 – 153, 2006.

[24] D. Noutsos and M. J. Tsatsomeros, "Reachability and holdability of nonnegative states," *SIAM Journal on Matrix Analysis and Applications*, vol. 30, no. 2, pp. 700–712, 2008.

[25] D. D. Olesky, M. J. Tsatsomeros, and P. van den Driessche, "M_v matrices: a generalization of m-matrices based on eventually nonnegative matrices," *El. Journal of Linear Algebra*, vol. 18, p. 339351, 2009.

[26] O. J. Schmitz, "Press perturbations and the predictability ofecological interactions in a food web," *Ecology*, vol. 78, no. 1, pp. 55–69, 1997.

[27] H. L. Smith, "Systems of ordinary differential equations which generate an order preserving flow. A survey of results," *SIAM Rev.*, vol. 30, no. 1, pp. 87–113, 1988.

[28] H. L. Smith, *Monotone Dynamical Systems: An Introduction to the Theory of Competitive and Cooperative Systems*, ser. Mathematical Surveys and Monographs. AMS, 1995, vol. 41.

[29] E. D. Sontag, "Monotone and near-monotone biochemical networks," *Syst. Synth. Biol.*, vol. 1, no. 2, pp. 59–87, 2007.

[30] N. Soranzo, G. Bianconi, and C. Altafini, "Comparing association network algorithms for reverse engineering of large-scale gene regulatory networks: synthetic versus real data," *Bioinformatics*, vol. 23, no. 13, p. 1640, 2007.

[31] L. Stone, "Phytoplankton-bacteria-protozoa interactions: a qualitative model portraying indirect effects," *Marine Ecology Progress Series*, vol. 64, no. 1-2, pp. 137 – 145, 1990.

[32] P. Yodzis, "The indeterminacy of ecological interactions as perceived through perturbation experiments," *Ecology*, vol. 69, no. 2, pp. 508–515, 1988.