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Determining the structural properties of a class of biological models

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***Abstract*— A property for a class of systems is said to be structural if it is met by any system in the class regardless of the adopted parameters. In this paper we investigate the structural nature of oscillatory behaviors, adaptation and monotonicity in a class of sign–invariant systems, capturing a wide variety of biological models.**

We employ standard robustness analysis tools, suitably tailored to the category of sign definite dynamics, i.e. in which terms are monotonic with respect to all arguments. In particular, our results are based on Jacobian analysis and invariant sets, and we are able to provide simple criteria to determine whether a system structurally admits Hopf-type bifurcations, perfect adaptation or monotonic behavior. Such criteria are easily verified numerically on a set of examples.

I. Introduction

A big challenge in biological network analysis is represented by parametric uncertainty: even for simple systems, extensive simulation campaigns are often the preferred choice to find out whether certain properties are *robust* or not with respect to variability of the parameters [1], [2]. Notable exceptions are advanced mathematical techniques providing strong, parameter-independent conclusions on the dynamic behavior of specific classes of biochemical systems; for instance, Lyapunov methods, [3], the deficiency theory, [4], [5], and the theory of monotone systems, [6].

An alternative approach is that of investigating the dynamics of molecular systems with qualitative modeling techniques [7], [8], [9]. We have shown that focusing only on sign, trends and boundedness of molecular interactions, we can often establish *structurally* the dynamic outcomes, and rule out behaviors that cannot be achieved. Here, we propose a systematic methodology, based on Jacobian analysis, to determine when a class of biological system models can yield oscillations, adaptation or monotonicity. Our main result is given by a series of simple criteria (easy to verify numerically) to check if a given model can or cannot structurally yield a certain behavior, for some parametric realization. These results are built on classical and well-known control theoretic methods [10], in particular on invariant sets theory [11].

Structural analysis of oscillators has been recently considered in [12], [13]: using the formalism of mass-action kinetics, the authors provide necessary conditions based on the underlying graph structure of the network. A graph-based approach has been also followed in [14], to establish monotonicity of chemical reaction network models. Perfect adaptation [2], a fundamental feature for gradient sensing, has also been explored analytically highlighting its link with integral feedback [15] and with the presence of zeros in the system transfer function [16].

The key feature of our approach is that we focus only on positivity and monotonicity of reaction rates. Thus, the conclusions of our analysis can be considered structural, in the sense that they are independent of specific choices for reaction parameters [7]. We propose structural criteria to establish the following properties:

1) potential oscillatory behavior (Section III);
2) adaptation (Section IV)
3) monotone behavior (Section V).

Finally, in the Discussion section we provide some additional remarks on the relationship of our work with other known results in the robustness literature, including the mapping theorem and the D–stability problem.

II. Structural analysis of biological networks

We consider biological dynamics that are successfully captured by the following class of models:

$$\dot{x} = Sg(x) + Vu, \tag{1}$$

where $x \in \mathbb{R}^n_+$ is a state representing the concentration of each biological species in the system, and u is a vector of constant influxes or outfluxes. Vector $g(x) \in \mathbb{R}^m$ is a vector of reaction rates: we assume that each reaction rate is a positive function, monotonic in each argument. Matrix S corresponds to the system's *stoichiometry* matrix in the literature of chemical reaction networks theory [17].

The following example, a biochemical reaction network, will illustrate our setup. Throughout this paper, we will denote chemical species with capital letters, and their concentrations with the corresponding small letter: for example, X_1 indicates a species, while x_1 is its concentration.

Example 1: Consider the chemical reactions:

$$\emptyset \xrightarrow{u_1} X_1 \xrightarrow{g_1(x_1)} X_2 \xrightarrow{g_2(x_2)} X_3 \xrightarrow{g_3(x_3)} X_4$$
$$pX_1 + X_4 \xrightarrow{g_{14}(x_1, x_4)} \emptyset$$

X_1 is supplied to the system with a constant influx u_1, and a chain of reactions generates X_4; a negative feedback loop is introduced by the reaction between X_1 and X_4. We write

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the dynamics of this system as:

$$\begin{aligned}\dot{x}_1 &= u_1 - g_1(x_1) - p\, g_{14}(x_1, x_4)\\ \dot{x}_2 &= g_1(x_1) - g_2(x_2)\\ \dot{x}_3 &= g_2(x_2) - g_3(x_3)\\ \dot{x}_4 &= g_3(x_3) - g_{14}(x_1, x_4).\end{aligned}$$

We assume that $g_1(x_1)$, $g_2(x_2)$, $g_3(x_3)$ are smooth, strictly increasing functions and zero at the origin. We also assume that function $g_{14}(x_1, x_4)$ is smooth, strictly increasing in both arguments and zero when either x_1 or x_4 are zero.
We write the dynamics in the general form of Equation (1):

$$\begin{bmatrix}\dot{x}_1\\ \dot{x}_2\\ \dot{x}_3\\ \dot{x}_4\end{bmatrix} = \begin{bmatrix}-1 & 0 & 0 & -p\\ 1 & -1 & 0 & 0\\ 0 & 1 & -1 & 0\\ 0 & 0 & 1 & -1\end{bmatrix}\begin{bmatrix}g_1(x_1)\\ g_2(x_2)\\ g_3(x_3)\\ g_{14}(x_1, x_4)\end{bmatrix} + \begin{bmatrix}1\\0\\0\\0\end{bmatrix} u_1 \tag{2}$$

We will now focus on the properties of the Jacobian of the general class of systems (1). First, denote Col_j^S as the jth column of matrix S; then, the Jacobian of (1) can be written as

$$J = \sum \mathrm{Col}_j^S \nabla g_j, \qquad \nabla g_j = \begin{bmatrix}\frac{\partial g_j}{\partial x_1} & \dots & \frac{\partial g_j}{\partial x_n}\end{bmatrix},$$

where now for simplicity we associate a general index $j = 1, ..., q$ to the partial derivatives. It is worth remarking that there are only few non-zero elements in the reaction rates partial derivatives vector. Therefore, we can rewrite each term of the above sum as a sum of terms corresponding to all non-zero derivatives. For example, the last term of the sum in the case of (2) would be

$$\begin{bmatrix}-p\\0\\0\\-1\end{bmatrix}\frac{\partial g_{14}}{\partial x_1}\begin{bmatrix}1 & 0 & 0 & 0\end{bmatrix} + \begin{bmatrix}-p\\0\\0\\-1\end{bmatrix}\frac{\partial g_{14}}{\partial x_4}\begin{bmatrix}0 & 0 & 0 & 1\end{bmatrix}.$$

Then we may rewrite J as the product of three matrices:

$$J = B\, D\, C,$$

where B selects (and possibly duplicates) columns of J; therefore, B is a matrix having n rows and q columns, with $q \geq m$ (where m is the number of nonzero reaction rates), and $q \geq n$ (where n is the number of states). D is a $q \times q$ diagonal matrix, whose diagonal elements d_k, $k = 1, ..., q$ are all the nonzero partial derivatives. C is a matrix having q rows and n columns, whose elements are $c_{ij} = 1$ if the ith derivative affects the jth column of J, and $c_{ij} = 0$ otherwise.

For Example 1, we find:

$$J = \begin{bmatrix}-1 & 0 & 0 & -p & -p\\ 1 & -1 & 0 & 0 & 0\\ 0 & 1 & -1 & 0 & 0\\ 0 & 0 & 1 & -1 & -1\end{bmatrix} D \begin{bmatrix}1 & 0 & 0 & 0\\ 0 & 1 & 0 & 0\\ 0 & 0 & 1 & 0\\ 1 & 0 & 0 & 0\\ 0 & 0 & 0 & 1\end{bmatrix},$$

$$D = \mathrm{diag}\left\{\frac{\partial g_1(x_1)}{\partial x_1}, \frac{\partial g_2(x_2)}{\partial x_2}, \frac{\partial g_3(x_3)}{\partial x_3}, \frac{\partial g_{14}(x_1,x_4)}{\partial x_1}, \frac{\partial g_{14}(x_1,x_4)}{\partial x_4}\right\}.$$

The compact notation: $D = \mathrm{diag}\{d_1, \dots, d_k, \dots, d_q\}$ will be adopted for clarity. Our monotonicity assumption implies that all the above partial derivatives, hence the d_k, are sign-definite. Without loss of generality, we assume:

Assumption 1: The diagonal elements of matrix D are positive.

If any of the partial derivatives is negative, we can simply change the corresponding coefficients in matrices C or B.
In the remainder of this paper, we will consider systems whose Jacobian can be written in the form we just described, and in particular:

$$J = B\, D\, C = \sum_{k=1}^{q} \mathrm{Col}_k^B \mathrm{Row}_k^C d_k = \sum_{k=1}^{q} M_k d_k, \quad d_k > 0 \tag{3}$$

Remark 1: It is worth noting that for all k

$$\mathrm{rank}[M_k] = 1.$$

A. Remarks on boundedness and stability

Boundedness is a fundamental property in biological system analysis. Generally speaking, boundedness of the solutions of molecular systems often follows naturally from mass conservation constraints and degradation reactions. For brevity, we will assume that

Assumption 2: The solutions of (1) are globally bounded.

The next step is discussing conditions that robustly assure or exclude stability. Two examples will clearly illustrate our approach.

Example 2: The following reactions:

$$\emptyset \xrightarrow{u_1} X_1 \xrightarrow{g_1(x_1)} X_2 \xrightarrow{g_2(x_2)} X_3 \xrightarrow{g_3(x_3)} \emptyset,$$
$$X_1 + X_3 \xrightarrow{g_{13}(x_1, x_3)} \emptyset,$$

generate dynamics having the following Jacobian matrix:

$$J = \begin{bmatrix}-(\alpha+\epsilon) & 0 & -\delta\\ \alpha & -\beta & 0\\ -\epsilon & \beta & -(\gamma+\delta)\end{bmatrix},$$

we indicate the partial derivatives with the compact notation α, β, γ, δ and ϵ, which are all positive parameters (e.g. $\alpha = \frac{\partial g_1(x_1)}{\partial x_1}$).
The characteristic polynomial of this system has positive coefficients for any choice of the parameters and corresponding equilibria. Thus, the Jacobian cannot have positive real eigenvalues.

Example 3: We slightly modify the reactions at Example 2:

$$\emptyset \xrightarrow{u_1} X_1 \xrightarrow{g_1(x_1)} X_2 \xrightarrow{g_2(x_2)} X_3 \xrightarrow{g_3(x_3)} \emptyset,$$
$$X_1 + X_3 \xrightarrow{g_{13}(x_1, x_3)} X_3.$$

The above reactions generate the following Jacobian:

$$J = \begin{bmatrix} -(\alpha+\epsilon) & 0 & -\delta \\ \alpha & -\beta & 0 \\ 0 & \beta & -\gamma \end{bmatrix},$$

where again all the elements (partial derivatives) α, β, γ, δ and ϵ are positive. As in the previous example, the characteristic polynomial of J has positive coefficients for any choice of the parameters and corresponding equilibria. Thus, the Jacobian cannot have positive real eigenvalues.

Claim: In Examples 2 and 3, instability of equilibria can only arise in association with pairs of complex eigenvalues having positive real part.

It turns out that the system of Example 2 is unconditionally stable. Conversely, example 3 may become unstable for very large δ.

In the remainder of this paper, we adopt a similar analysis setup for detecting the structural oscillatory behavior, adaptability and monotonicity.

III. Revealing potential oscillators

Consider the general model (1) under Assumption 2. Suppose its Jacobian

$$J = \sum_{k=1}^{q} M_k d_k, \quad \text{rank}[M_k] = 1,$$

can be an unstable matrix, for some choice of the parameters. Instability could be exponential (nonnegative, real eigenvalues) or "oscillatory" (complex eigenvalues with nonnegative real part). We want to find structural conditions that *exclude* exponential instability for J. Thus, any choice of parameters destabilizing J yields oscillatory dynamics.

A condition that *excludes* exponential instability is:

$$\det(\lambda I - \sum_{k=1}^{q} M_k d_k) \neq 0, \quad \text{for} \quad \lambda \in \mathbb{R}^+.$$

Since d_k are arbitrary, positive scalars, we normalize them as $0 < \underline{d}_k \leq 1$. In addition, we want to exclude zero eigenvalues, so our condition becomes:

$$\det(\lambda I - \sum_{k=1}^{q} M_k \underline{d}_k) \neq 0 \tag{4}$$

$$\text{s.t.} \quad \epsilon \leq \lambda \in \mathbb{R}^+, \epsilon > 0, \quad 0 < \underline{d}_k \leq 1. \tag{5}$$

We can divide everything by λ:

$$\det\left(I - \sum_{k=1}^{q} M_k \frac{\underline{d}_k}{\lambda}\right), \quad \lambda \geq \epsilon.$$

Now, take $\bar{d}_k = \frac{\underline{d}_k}{\lambda}$, $0 < \bar{d}_k \leq \frac{1}{\epsilon}$. Therefore, our problem is equivalent to analyzing function:

$$f(\bar{d}) = \det\left(I - \sum_{k=1}^{q} M_k \bar{d}_k\right). \tag{6}$$

Proposition 1: Consider the cube:

$$\mathcal{C}_{\bar{d}} = \{\bar{d}_k : \quad 0 < \bar{d}_k \leq \Theta\}, \qquad \Theta = \frac{1}{\epsilon}. \tag{7}$$

Function $f(\bar{d}_k)$ in (6) is nonzero in the cube $C_{\bar{d}}$ if and only if $f(\bar{d})$ is positive on each vertex of $C_{\bar{d}}$.

Proof: Because matrices M_k have rank one, function $f(\bar{d})$ is multiaffine in $\bar{d}_k$ [10]. It is known that an affine function defined on a cube reaches its minimum (and maximum) on a vertex of the cube (7).

It is trivial to verify that $f(0) = 1$, (0 is the zero vector). Take $\bar{d}^* = \Theta\, b$, where b is a binary vector of length q defining a vertex selection. If for some value of $\bar{d}$, we find $f(\bar{d}) = 0$, then there must be a vertex in which $f(\bar{d}^*) \leq 0$. Conversely, if there is a vertex in which $f(\bar{d}^*) \leq 0$, by continuity it must be that $f(\theta) = 0$ for some θ on the segment joining the origin with the vertex. ■

Therefore, Proposition 1 provides a criterion to detect a potential oscillatory system.

Lemma 1: If the determinant function (4) is positive on all the vertices of the parameter cube (7), then system (1) under Assumption 2 can exhibit only oscillatory unstable linearized dynamics.

Consider Example 1: in this case our determinant function is simply:

$$f = \det \begin{bmatrix} 1+(\alpha+p\delta) & 0 & 0 & p\epsilon \\ -\alpha & 1+\beta & 0 & 0 \\ 0 & -\beta & 1+\gamma & 0 \\ \delta & 0 & -\gamma & 1+\epsilon \end{bmatrix}$$

We numerically verified that the determinant is positive on all the 32 vertices. The values of $\bar{d}_k$ were varied between zero (which is a strict lower bound) and $\Theta = 10^{15}$; this high value was chosen as a very conservative upper bound. Therefore, this system is a potential oscillator because instability is necessarily associated with complex, unstable eigenvalues.

Remark 2: If vector $\bar{d}$ has q components, then we have to check 2^q vertices. Thus, an algorithm exploring the sign of $f(\bar{d})$ on all vertices has exponential complexity.

IV. Revealing perfect adaptation

Consider a system in the form (1), with output $y = Nx(t)$. Suppose we introduce a constant perturbation on the input (with respect to the equilibrium input value). Our goal is to determine if, after a transient, the system responds by returning to the equilibrium prior to the perturbation. We indicate this behavior as perfect adaptation. The linearized system is:

$$\dot{z} = Jz + Vv \tag{8}$$

$$w = Nz. \tag{9}$$

It is well known that a linear, time invariant dynamical system has perfect adaptation if and only if its transfer function has a zero at the origin. This is equivalent to

requiring that:

$$\det \begin{bmatrix} J & V \\ N & 0 \end{bmatrix} = \det H = 0.$$

Assume that every nonzero term of J, d_k, $k = 1, ..., q$, can be normalized as: $0 \leq \bar{d}_k \leq 1$. The tools introduced in the previous section allow us to easily prove the following:

Proposition 2: Function $f(\bar{d}) = \det H$ is identically zero if and only if it is zero at each vertex of the cube $\mathcal{C}_{\bar{d}}$, defined consistently with expression (7).

A zero at the origin assures zero response to a step input, but clearly we have to require that there is no cancellation, i.e. there is no pole at the origin:

$$\det J \neq 0.$$

Also this condition can be checked as done in the previous section. Assume that all nonzero terms of J, d_k, can be normalized as: $\epsilon \leq \bar{d}_k \leq 1$, $\epsilon > 0$. Then, our goal is to find if $f(\bar{d}) = \det J(\bar{d})$ is sign definite on the cube defined by the possible values of $\bar{d}_k$.

Proposition 3: Function $f(\bar{d})$ is nonzero inside the cube $\epsilon \leq \bar{d}_k \leq 1$ if and only if it has the same sign (either positive or negative) on all the vertices.

We provide another example.

Example 4: Consider the chemical reactions:

$$\emptyset \xrightarrow{u_1} X_1 \qquad \emptyset \xrightarrow{u_2} X_2$$
$$X_1 + X_2 \xrightarrow{g_{12}(x_1, x_2)} X_3 \xrightarrow{g_3(x_3)} X_1 \xrightarrow{g_1(x_1)} \emptyset.$$

We assume that u_1 and u_2 are constant positive functions, and that $g_1(x_1)$, $g_3(x_3)$ and $g_{12}(x_1, x_2)$ are smooth, strictly increasing in each argument and zero when either argument is zero. We write the dynamics of this system as:

$$\begin{aligned} \dot{x}_1 &= u_1 - g_{12}(x_1, x_2) + g_3(x_3) - g_1(x_1) \\ \dot{x}_2 &= u_2 - g_{12}(x_1, x_2) \\ \dot{x}_3 &= g_{12}(x_1, x_2) - g_3(x_3). \end{aligned}$$

The Jacobian is:

$$J = \begin{bmatrix} \alpha + \eta & \beta & -\gamma \\ \alpha & \beta & 0 \\ -\alpha & -\beta & \gamma \end{bmatrix}$$

We verified that $\det J > 0$, exploring the sign of the determinant function on a cube where each $\bar{d}_k$ varied between 10^{-3} and 10^{15}; therefore this network admits perfect adaptation. If we consider perturbations on input u_1, and we take x_3 as the system's output, we have to check the condition:

$$\det \begin{bmatrix} \alpha + \eta & \beta & -\gamma & 1 \\ \alpha & \beta & 0 & 0 \\ -\alpha & -\beta & \gamma & 0 \\ 0 & 0 & 1 & 0 \end{bmatrix} = 0.$$

It is easy to verify that this condition is always satisfied, thus the system admits perfect adaptation to perturbations in u_1.

V. Revealing monotonicity

We begin this section with an example, which is taken from [9] and represents part of an overall set of reactions defining an oscillator. As a standalone system, we are interested in exploring its monotonicity properties.

Example 5: Consider the chemical system:

$$X_1 + X_2 \xrightarrow{g_{12}(x_1, x_2)} X_1^*, \qquad X_3 + X_1^* \xrightarrow{g_{13}(x_1, x_3)} X_1 + X_2^*$$
$$X_2^* \xrightarrow{g_2(x_2^*)} X_2, \qquad \emptyset \xrightarrow{u_3} X_3$$
$$x_1 + x_1^* = x_{tot}, \quad x_2 + x_2^* = x_2^{tot}$$

The ODEs below already account for the mass conservation constraints:

$$\begin{aligned} \dot{x}_1 &= g_{13}(x_1, x_3) - g_{12}(x_1, x_2) \\ \dot{x}_2 &= g_2(x_1 - x_2) - g_{12}(x_1, x_2) \\ \dot{x}_3 &= u_3 - g_{13}(x_1, x_3), \end{aligned}$$

where we substituted $x_2^* = x_2^{tot} - x_1^{tot} - x_1 - x_2$. Function g_{13} is decreasing in x_1, increasing in x_3 and zero for $x_1 = 0$; g_{12} is increasing in both variables, and zero for zero arguments; finally $g_2(x_1 - x_2)$ is increasing in x_1 and decreasing in x_2. The Jacobian is:

$$J = \begin{bmatrix} -(\alpha + \beta) & -\gamma & \delta \\ \epsilon - \beta & -(\epsilon + \gamma) & 0 \\ \alpha & 0 & -\delta \end{bmatrix}, \tag{10}$$

where $\alpha = \frac{\partial g_{13}(x_1, x_3)}{x_1}$ etc. This system is not monotone, and cannot be rendered monotone by a simple order change in the domain of any variable; in particular, because the sign of entry $(2, 1)$ is undetermined.

We recast the problem of determining monotonicity into the problem of showing the existence of a simplicial cone:

$$\mathcal{K} = \{z : \ z = T\tau, \quad \text{with} \quad \tau \in R^n_+, \} \tag{11}$$

($\tau \in R^n_+$ means $\tau_i \geq 0$) with T square invertible, which is a robustly invariant set for the system

$$\dot{z} = Jz = \left(\sum_{k=1}^{q} M_k d_k \right) z.$$

It is well known that finding such cone is a linear programming problem [18], [11].

Proposition 4: Cone (11) is robustly positive invariant if and only if there exist matrices $H^{(k)}$ with nonnegative non–diagonal entries, $H^{(k)}_{ij} \geq 0$, for $i \neq j$, such that

$$M_k T = T H^{(k)}$$

A dual proposition holds for cones of the form

$$\mathcal{K} = \{z : \ Qz \leq 0\}, \qquad QM_k = H^{(k)} Q \tag{12}$$

again with $H^{(k)}_{ij} \geq 0$, for $i \neq j$. For a given T, the condition is a linear programming problem since the inequalities are linear and we have linear inequalities on the non–diagonal coefficient of $H^{(k)}$. However, if T (or Q) is an unknown of the problem, then these equations become bilinear.

We can find a candidate cone starting from expression (3).

$$J = \sum_{k=1}^{q} M_k d_k = \sum_{k=1}^{q} \left(\text{Col}_k^B \text{Row}_k^C\right) d_k.$$

We propose to choose the columns of T as a selection of the columns of B_k. For simplicity, take the first n columns:

$$T = [\text{Col}_1^B \ \text{Col}_2^B \ \dots \ \text{Col}_n^B]$$

Then, in general we find:

$$M_k \text{Col}_j^B = \text{Col}_k^B \text{Row}_k^C \text{Col}_j^B = \text{Col}_k^B \, \theta_{kj}. \qquad (13)$$

T defines a cone of type (11) if $\theta_{kj} \geq 0$ for $j \neq k$. If $j = k$, then $M_j \text{Col}_j^B$ is a vector that lies in the same direction as Col_j^B; therefore, it still belongs to the cone regardless of the sign of $\theta_{jj} = \text{Row}_j^C \text{Col}_j^B$.

Proposition 5: The cone generated by T, chosen as a selection of n columns of B, is robustly positive invariant if and only if θ_{kj} defined in equation (13) is nonnegative for any k and j for which $\text{Col}_j^B \neq \text{Col}_k^B$.

Proof: Sufficiency: first, note that

$$M_k[\text{Col}_1^B \ \text{Col}_2^B \ \dots \ \text{Col}_n^B] = [\text{Col}_1^B \ \text{Col}_2^B \ \dots \ \text{Col}_n^B]\Theta$$

where each column of Θ has a single non–zero element. If $j = k$, the unique nonnegative entry is on the diagonal of Θ; otherwise the entry is off-diagonal and is nonnegative by assumption. Thus, invariance of the cone is guaranteed.
Necessity: we need to invoke the theory of tangent cones by Nagumo (1943) [19]. Consider specific points on the cone, defined by the columns (generators) of T: $z_i = \text{Col}_i^T = T\,\tau_i$, $i = 1, \dots, n$. Without loss of generality assume that $M_2 z_1 = z_2 \theta_{12}$ taking *ab absurdo* $\theta_{21} < 0$. Recall that the *tangent cone* to the cone defined by T at a point $z_i = \text{Col}_i^T$ is given by all vectors of the form

$$v = a_i z_i + \sum_{j \neq i} a_j z_j \qquad (14)$$

with arbitrary a_i and arbitrary but nonnegative a_j, $j \neq i$. We want to check that the cone generated by T is an invariant set for the local dynamics of the system. In a neighborhood of z_i, the dynamics are:

$$\dot{z} = \left(\sum_{k=1}^{q} M_k d_k\right) z_i.$$

For the cone to be invariant, the derivative at the cone generators must be directed "inside" the cone. Thus, as remarked earlier, if $M_k z_i$ lies in the same direction as z_i, then the coefficient θ_{ki} is just a scaling factor which can be either positive or negative. Conversely if $M_k z_i$ lies along the direction of a different generator, say, $M_k z_k$, then θ_{ki} must be positive otherwise it would point outside the cone.
Robust invariance implies that we must have invariance taking, without loss of generality, $z_i = z_1$, for $d_2 > 0$ and $d_k = 0$, $\forall k \neq 2$. Unfortunately

$$\dot{z} = M_2 d_2 z_1 = d_2 \theta_{12} z_2 = a_2 z_2, \quad \text{with} \quad a_2 < 0.$$

Thus, with reference to expression (14), locally we have that $v = \dot{z} = a_2 z_2$, $a_2 < 0$. Therefore, the derivative does not belong to the tangent cone, and this is a contradiction. ■

Let us now go back to Example (10) and consider its Jacobian. Matrices M_k are found by first "ordering" the partial derivatives, e.g. $d_1 = \alpha$, $d_2 = \beta$, etc.; then, we simply set all entries of the Jacobian to zero, except elements where the partial d_k appears. For example, choosing $d_1 = \alpha$, means:

$$M_1 = \begin{bmatrix} -1 & 0 & 0 \\ 0 & 0 & 0 \\ 1 & 0 & 0 \end{bmatrix}.$$

We pick matrix T as:

$$T = [\text{Col}_1^T \ \text{Col}_2^T \ \text{Col}_3^T] = \left[\begin{array}{c|c|c} 1 & -1 & 0 \\ 1 & 0 & -1 \\ 0 & 1 & 0 \end{array}\right].$$

The following table reports the evaluated products $M_k \text{Col}_j^T$:

	M_1	M_2	M_3	M_4	M_5
Col_1^T	$\widehat{\text{Col}_2^T}$	$-\text{Col}_1^T$	$-\text{Col}_1^T$	0	0
Col_2^T	$-\text{Col}_2^T$	$\widehat{\text{Col}_1^T}$	0	$-\text{Col}_2^T$	$\widehat{\text{Col}_3^T}$
Col_3^T	0	0	$\widehat{\text{Col}_1^T}$	0	$-\text{Col}_3^T$

The table entries marked with a $\widehat{\ }$ symbol correspond to a positive θ_{kj} coefficient. We recall that those are the critical products $M_k \text{Col}_k^T = \text{Col}_j^T \theta_{kj}$, with $k \neq j$, highlighted in equation (13).

Finally, the state transformation introduced by T, which defines the cone in the positive orthant, yields a positive linear system, i.e.:

$$MT = T\hat{M}$$

with

$$\hat{M} = \begin{bmatrix} -(\gamma+\beta) & \beta & \gamma \\ \alpha & -(\alpha+\delta) & 0 \\ 0 & \epsilon & -\epsilon \end{bmatrix}, \qquad (15)$$

which is a Metzler matrix. Thus, the system is input-to-state monotone.
It is worth noting that this state transformation yields monotonicity also in the *nonlinear* system in the sense that the transformation $\tilde{x} = T^{-1}x$ yields the following input-to-state monotone nonlinear system:

$$\begin{aligned} \dot{\tilde{x}}_1 &= -g_{12}(\tilde{x}_1 - \tilde{x}_2, \tilde{x}_1 - \tilde{x}_3) + u_3 \\ \dot{\tilde{x}}_2 &= -g_{13}(\tilde{x}_1 - \tilde{x}_2, \tilde{x}_2) + u_3 \\ \dot{\tilde{x}}_3 &= -g_2(\tilde{x}_3 - \tilde{x}_2) + u_3 \end{aligned}$$

whose Jacobian is given in equation (15).

VI. Discussion and final remarks

We have investigated structural properties to detect potential oscillators, perfect adaptation and monotonicity with respect to the partial order induced by a given cone. Here, we are marginally concerned with stability *per se*. In our

results, stability (or instability) has an important role when investigating:

- Potential oscillatory behaviors: oscillations cannot be achieved if the system does not transition to instability with complex modes.
- Potential perfect adaptation: the system must be asymptotically stable.

Since the Jacobian of system (1) can be written as the sum of rank–one matrices, as in expression (3), then the coefficients of the characteristic polynomial are multi–affine functions of the Jacobian elements. Thus, that the famous mapping theorem [10] applies, providing a sufficient condition for stability.

It is also worth mentioning the relationship of our results with D-stability. We recall the Jacobian decomposition (3): $J = BDC$. Assume $q \geq n$, which is a necessary condition for J to be invertible (otherwise we would structurally lose asymptotic stability with an eigenvalue at the origin). Consider the matrix obtained from J by permuting its factors

$$J^* = C\ B\ D = N\ D$$

The dimension of J^* is q. So for $q \geq n$, the spectral set of J is included in the spectral set of J^*.

Proposition 6: If $q \geq n$, then the eigenvalues of J^* are those of J plus the eigenvalue $\lambda = 0$ with multiplicity $q-n$. The problem of analyzing robust stability of a matrix of the form $J^* = N\ D$ where D is a positive diagonal is known as D-stability problem [20]. Note that this is a "special" version of the problem, since 0 is usually present in J^*, but this is not a problem since one can use an ϵ perturbation $\epsilon I + J^*$. The D–stability property has been proven equivalent to a μ–type of condition [21]. This implies that for large scale biological systems, this type of investigation might become highly complex. In large scale problems, a probabilistic approach [22] might be more effective.

As a final remark, we point out that we have focused on how to exclude the presence of real positive eigenvalues, ruling out exponential transition to instability (through the origin). But we have not considered the problem of ruling out oscillatory transitions to instability. It is well known that if a system is monotone, instability can happen only with real unstable eigenvalues. More in general, if we wish to exclude oscillatory bifurcations, then we need to assure that

$$\det(j\omega I - J(d)) \neq 0$$

for $\omega > 0$. We can normalize the expression to $\omega = 1$ and multiply the expression by its conjugate, getting the condition:

$$h(\bar{d}) = \det(jI - J(\bar{d}))\det(-jI - J(\bar{d})) \neq 0$$

Function $h(\bar{d})$ is a real polynomial in the variables d_k, $k = 1, ..., q$. Then the problem reduces to determining if the polynomial $h(\bar{d})$ is copositive (i.e. positive for $d_k > 0$). Unfortunately, $h(\bar{d})$ in this case is not a multi–affine function of d_k. As a consequence we cannot rely on vertex results such as Propositions 1 and 2 and more sophisticated algorithms are required. Stability analysis by means of positive polynomials has been considered in the literature for many years [23] (see [24] for more recent results and references).

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